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Safety and Efficacy of High- Versus Low-Dose Aspirin After Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction

The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial

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Objectives This study sought to examine the relationship between the aspirin dose prescribed at hospital discharge and long-term outcomes after ST-segment elevation myocardial infarction in patients treated with primary percutaneous coronary intervention (PCI).

Background Patients with ST-segment elevation myocardial infarction who undergo primary PCI are prescribed maintenance aspirin doses that vary between 75 and 325 mg daily. Whether the dose of aspirin affects long-term patient outcomes is unknown.

Methods We compared 3-year outcomes in patients who were prescribed high-dose (>200 mg daily) versus low-dose (≤200 mg daily) aspirin from the large-scale HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial.

Results Among 2,851 patients, 2,289 patients (80.3%) were discharged on low-dose aspirin and 562 patients (19.7%) were discharged on high-dose aspirin. Patients discharged on high-dose rather than low-dose aspirin were more likely to have a history of hypertension, hyperlipidemia, family history of premature coronary disease, prior treatment with PCI or coronary artery bypass surgery, and to be enrolled in the United States. Patients discharged on high-dose aspirin had higher 3-year rates of major adverse cardiovascular events, reinfarction, ischemic target vessel revascularization, major bleeding, and stent thrombosis. After multivariable analysis, discharge on high-dose aspirin was an independent predictor of major bleeding (hazard ratio: 2.80; 95% confidence interval: 1.31 to 5.99; $p = 0.008$), but not of adverse ischemic events.

Conclusions In patients with ST-segment elevation myocardial infarction undergoing primary PCI, discharge on high-dose rather than low-dose aspirin may increase the rate of major bleeding without providing additional ischemic benefit. (J Am Coll Cardiol Intv 2012;5:1231–8) © 2012 by the American College of Cardiology Foundation

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Whereas the efficacy of aspirin for primary and secondary prevention in patients with coronary artery disease and acute coronary syndromes (ACS) is well established (1–3), there is uncertainty regarding the optimal dose of aspirin. Currently, daily maintenance doses range between 75 and 325 mg. Maximal inhibition of thromboxane-mediated platelet activation is achieved with aspirin doses as low as 30 mg (4), whereas higher doses of aspirin may result in increased bleeding risk, especially from the gastrointestinal tract, in part due to dose-dependent inhibition of gastroprotective prostaglandin synthesis (5,6). The question regarding aspirin maintenance dose is of renewed significance in the context of the long-term requirement for dual antiplatelet therapy following percutaneous coronary intervention (PCI), the increased bleeding propensity of newer, more potent adenosine diphosphate antagonists, and possible drug-to-drug interactions (7–9). Recent ACS studies have not shown benefits with higher maintenance aspirin doses (9,10). However, the optimal long-term maintenance dose of aspirin in patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) has not been studied.

Therefore, we assessed 3-year outcomes from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial according to the discharge dose of aspirin, with the aim to examine the impact of aspirin dose on late outcomes in patients with STEMI.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass graft

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Methods

Patient population. The design of the HORIZONS-AMI trial has been described elsewhere (11,12). In brief, HORIZONS-AMI was a prospective, large-scale, multicenter, 2 × 2 factorial randomized trial. Patients with STEMI undergoing primary PCI who presented within 12 h of symptom onset were randomly assigned to receive bivalirudin versus heparin (unfractionated heparin) plus a glycoprotein IIb/IIIa inhibitor in a 1:1, open-label fashion.

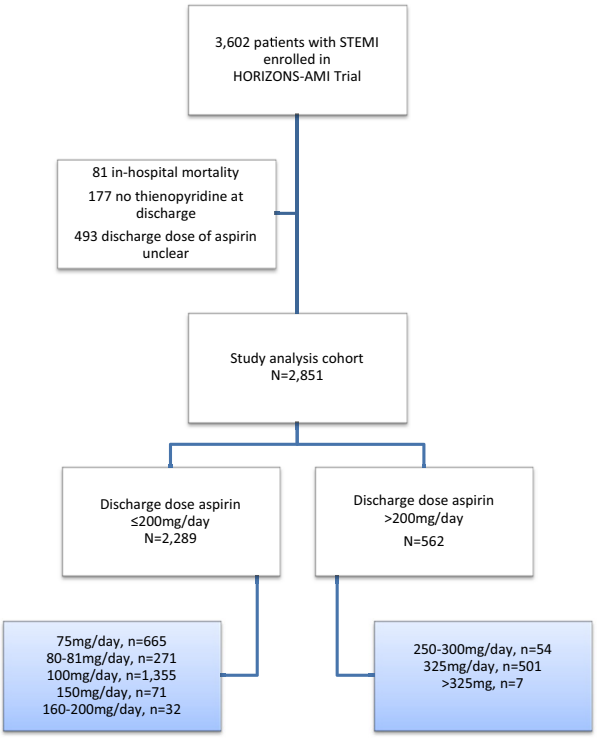

Figure 1. Study Flow Chart

HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; STEMI = ST-segment elevation myocardial infarction.

After diagnostic coronary angiography, eligible patients underwent a secondary 3:1 randomization to the Taxus Express paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts) versus the Express bare-metal stent (Boston Scientific).

Patients were given a loading dose of aspirin (324 mg chewable or 500 mg intravenous) in the emergency department, a daily dose of 300 to 325 mg/day while in hospital, and an indefinite maintenance dose ≥75 mg/day at discharge at the discretion of the treating physician. A 300- or 600-mg clopidogrel loading dose was given per physician preference, followed by 75 mg daily for a minimum of 6 months (≥12 months recommended).

The institutional review board or ethics committee of all participating centers approved the trial protocol and all patients provided written informed consent.

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Clinical endpoints and definitions. The primary endpoints of HORIZONS-AMI have been reported (11,12). Major bleeding not related to coronary artery bypass graft (CABG) included: intracranial or intraocular hemorrhage; access site hematoma with diameter ≥5 cm, or one requiring intervention; overt bleeding with hemoglobin decrease ≥3 g/dl, or any hemoglobin decrease ≥4 g/dl; bleeding requiring reoperation; and blood transfusion. Net adverse clinical events were a composite of non-CABG–related major bleeding and major adverse cardiovascular events, including death, reinfarction, target vessel revascularization for ischemia, and stroke. Stent thrombosis was defined as definite or probable by Academic Research Consortium criteria (13). All events were adjudicated by an independent clinical events committee blinded to treatment assignment.

Present analysis. For the current study, high-dose aspirin was defined as a discharge dose >200 mg daily. Low-dose aspirin was defined as a discharge dose ≤200 mg daily. Of the 3,602 patients enrolled in the HORIZONS-AMI trial, we excluded 81 patients due to in-hospital mortality, 95 patients who were discharged on no aspirin, 177 patients discharged on no thienopyridine, and 398 patients for whom the aspirin discharge dose was uncertain. The baseline characteristics and out-of-hospital outcomes in the remaining 2,851 patients were examined according to the prescription of high-dose versus low-dose aspirin at discharge (Fig. 1).

Table 1. Baseline Patient Characteristics

Characteristic	Aspirin Discharge Dose ≤200 mg (n = 2,289)	Aspirin Discharge Dose >200 mg (n = 562)	p Value
Age, yrs	59.9 [52.6, 69.2]	58.8 [50.8, 68.5]	0.03
Male sex	76.3 (1,747/2,289)	79.4 (446/562)	0.11
Enrollment in the United States (vs. outside the United States)	10.4 (238/2,289)	81.9 (460/562)	<0.0001
Race			
White	96.0 (2,197/2,289)	84.3 (474/562)	<0.0001
Black	0.7 (16/2,289)	7.3 (41/562)	<0.0001
Asian	0.7 (16/2,289)	0.7 (4/562)	0.99
Hispanic	2.5 (57/2,289)	6.8 (38/562)	<0.0001
Other	0.1 (3/2,289)	0.9 (5/562)	0.01
BMI, kg/m^2	27.0 [24.5, 30.0]	27.9 [25.0, 31.5]	0.0002
Medical history			
Hypertension	50.6 (1,158/2,289)	58.2 (327/562)	0.001
Hyperlipidemia	42.3 (968/2,289)	47.9 (269/562)	0.02
Current smoker	65.0 (1,482/2,280)	63.5 (357/562)	0.13
Diabetes mellitus	16.6 (380/2,289)	15.8 (89/562)	0.66
Treated with insulin	4.7 (107/2,289)	4.4 (25/562)	0.82
Prior MI	10.6 (243/2,289)	11.0 (62/562)	0.77
Prior PCI	10.0 (228/2,289)	13.2 (74/562)	0.03
Prior CABG	2.5 (57/2,289)	4.1 (23/562)	0.04
Family history of premature	29.1 (667/2,289)	33.8 (190/562)	0.03
CAD			
Angina	24.3 (556/2,289)	14.9 (84/562)	<0.0001
CHF	2.5 (58/2,289)	2.8 (16/562)	0.68
Atrial fibrillation or flutter	1.7 (38/2,289)	1.4 (8/562)	0.69
Peripheral vascular disease	4.5 (103/2,288)	2.8 (16/562)	0.08
Chronic kidney disease on dialysis	0.2 (4/2,288)	0.0 (0/562)	0.99
Characteristics at presentation			
Killip class >1	8.3 (189/2,286)	7.3 (41/562)	0.45
Anemia*	10.2 (219/2,148)	12.4 (69/555)	0.13
Creatinine clearance <60†	14.9 (315/2,108)	16.6 (89/536)	0.34
LVEF—site reported, %	50 [45, 60]	50 [40, 55]	<0.0001
LVEF <40%—site reported	12.9 (255/1,973)	17.7 (86/487)	0.007

Values are % (n/N) or median [IQR]. *Anemia is defined as baseline hematocrit <39 for men, <36 for women. †Creatinine clearance was calculated by the Cockroft-Gault formula.

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Statistical analyses. All analyses are by intention to treat. Categorical variables were compared using chi-square or Fisher exact test, and continuous variables were compared using the Wilcoxon rank-sum test. A propensity score was developed using a logistic regression model with high- versus low-aspirin discharge dose as a dependent variable and the following factors as independent variables: age; sex; race; enrollment in versus outside the United States; body mass index; hypertension; current smoking; diabetes; anemia; platelet count; white cell count; creatinine clearance; post-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 versus <3 flow; pre-randomization heparin; assignment to bivalirudin versus unfractionated heparin + glycoprotein IIb/IIIa inhibitor; radial versus femoral access; discharge prescription of beta blockers, angiotensin converting enzyme-inhibitors or angiotensin receptor blockers, and statins; and thienopyridine discontinuation within the first 6 months, 1, 2, or 3 years. A set of significant variables was selected using an entry and exit level of significance of 0.10, and a propensity score was determined. Cox proportional hazard models were used to predict time-to-event outcomes using high- versus low-aspirin discharge dose and the propensity score as covariates, and compared with the log-rank test. These models were used to determine the predicted survival rates at the actual event times in each group and to generate the adjusted time-to-event curves. All statistical analyses were performed with SAS (version 9.2, SAS Institute Inc., Cary, North Carolina).

Table 2. Procedural Data, Medications, and In-Hospital Events

	Aspirin Discharge Dose ≤200 mg (n = 2,289)	Aspirin Discharge Dose >200 mg (n = 562)	p Value
Assignment to bivalirudin (vs. UFH + GPI)	51.2 (1,172/2,289)	49.1 (276/562)	0.37
Radial access	8.1 (185/2,289)	0.5 (3/562)	<0.0001
Primary management strategy			
Primary PCI	97.6 (2,235/2,289)	98.2 (552/562)	0.41
Deferred PCI	0.0 (1/2,289)	0.0 (0/562)	0.99
CABG without PCI (through 30 days)	0.4 (9/2,289)	0.2 (1/562)	0.70
Medical management only (through 30 days)	1.9 (43/2,289)	1.6 (9/562)	0.66
PCI cohort			
Assignment to Taxus PES (vs. BMS)	75.2 (1,558/2,073)	75.3 (368/489)	0.96
Total stent length implanted, mm	24.0 [18.0, 36.0]	28.0 [20.0, 40.0]	0.002
Multiple vessels treated	4.2 (94/2,213)	3.5 (19/546)	0.42
Multiple lesions treated	9.8 (216/2,213)	10.8 (59/546)	0.47
Total fluoroscopy time, min	11.0 [7.0, 16.0]	13.0 [9.0, 19.0]	<0.0001
Total amount of contrast, ml	224.0 [178.0, 288.0]	240.0 [190.0, 300.0]	<0.0001
LAD infarct-related artery (per vessel)	40.6 (983/2,422)	37.1 (219/590)	0.12
Post-PCI TIMI flow grade 3 (per vessel)	92.7 (2,241/2,417)	93.6 (552/590)	0.48
Symptom onset to first balloon inflation, min	225.0 [162.0, 335.0]	206.5 [148.0, 310.0]	0.001
Door-to-balloon time, min	102.0 [75.0, 138.0]	89.0 [70.0, 124.0]	<0.0001
Length of hospitalization, days	5.0 [4.0, 7.0]	3.0 [3.0, 5.0]	<0.0001
In-hospital events			
Reinfarction	1.0 (22/2,289)	1.4 (8/562)	0.34
Ischemic TVR	1.4 (33/2,289)	1.6 (9/562)	0.78
Stroke	0.3 (8/2,289)	0.5 (3/562)	0.46
Major bleeding (non-CABG related)	5.3 (121/2,289)	10.3 (58/562)	<0.0001
Stent thrombosis	1.3 (29/2,188)	1.1 (6/534)	0.71
Discharge medications			
Beta blockers	91.9 (2,104/2,289)	92.2 (518/562)	0.84
Coumadin	3.1 (71/2,288)	3.9 (22/562)	0.33
ACE-I or ARB	85.6 (1,958/2,288)	68.5 (385/562)	<0.0001
Statin	96.6 (2,210/2,288)	92.9 (522/562)	<0.0001

Values are % (n/N) or median [IQR].

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMS = bare-metal stents; GPI = glycoprotein IIb/IIIa inhibitor; LAD = left anterior descending artery; PES = paclitaxel-eluting stents; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; UFH = unfractionated heparin; other abbreviations as in Table 1.

Table 3. Antiplatelet Use Following Discharge

	Low-Dose Aspirin	High-Dose Aspirin	p Value
30 days			
Aspirin	98.7 (2,198/2,228)	99.1 (539/544)	0.42
Thienopyridine	98.6 (2,197/2,229)	98.2 (535/545)	0.49
6 months			
Aspirin	97.8 (2,130/2,177)	98.2 (504/513)	0.56
Thienopyridine	91.5 (1,993/2,179)	92.4 (474/513)	0.49
1 year			
Aspirin	97.4 (2,111/2,168)	96.1 (470/489)	0.13
Thienopyridine	69.2 (1,502/2,171)	76.9 (376/489)	0.0007
2 years			
Aspirin	96.8 (2,073/2,142)	95.1 (462/486)	0.06
Thienopyridine	32.1 (690/2,148)	61.5 (299/486)	<0.0001
3 years			
Aspirin	96.2 (2,004/2,083)	94.7 (443/468)	0.13
Thienopyridine	23.0 (480/2,089)	56.2 (263/468)	<0.0001

Values are % (n/N).

Results

Patient characteristics and treatment. Among 2,851 patients, 2,289 (80.3%) were discharged on low-dose aspirin (≤200 mg/day) and 562 patients (19.7%) were discharged on high-dose aspirin (>200 mg/day) (Fig. 1). Patients discharged on high-dose versus low-dose aspirin were more likely to have a history of hypertension, hyperlipidemia, prior PCI or CABG, family history of premature coronary disease, and to be enrolled in the United States (Table 1). Treatment assignments were similar between the 2 groups (Table 2). With respect to PCI variables, patients on high-dose compared with low-dose aspirin had more femoral (vs. radial) access, longer total stent length, longer fluoroscopy time, and more contrast volume, but also had shorter symptom-onset- and door-to-first-balloon inflation time. The proportion of patients who had final TIMI flow grade 3 following PCI was similar in the 2 groups. Patients maintained on high-dose aspirin were, however, less likely to have an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or statin prescribed on discharge, and had a higher incidence of major bleeding before discharge. The use of Coumadin was balanced between the 2 groups.

Post-discharge antiplatelet therapy and clinical outcomes. From 1-year follow-up, patients on high-dose aspirin were more likely to continue with thienopyridine therapy than were patients on low-dose aspirin (Table 3). There was no significant difference in the rates of aspirin use between the 2 groups during the 3-year follow-up. Patients discharged on high-dose aspirin had significantly higher rates of major adverse cardiovascular events, reinfarction, target vessel revascularization, non-CABG–related major bleeding, net adverse clinical events, and definite or probable stent thrombosis (Table 4).

After propensity score–adjusted multivariable analysis, high-dose aspirin was an independent predictor of non-CABG–related major bleeding, but not of adverse ischemic outcomes (Table 5, Fig. 2A). The increase in major bleeding in patients treated with high-dose rather than low-dose aspirin emerged in the first 2 months after hospital discharge, although excess events continued to accrue in the high-dose aspirin group over the entire 3-year follow-up period (Fig. 2B). There was no significant interaction between enrollment within versus outside the United States and aspirin dose on adverse ischemic and bleeding endpoints (Table 6). Formal interaction testing also showed no significant effect of the duration of thienopyridine use on the increased risk of major bleeding with high-dose versus low-dose aspirin (p = 0.63).

Additional sensitivity analyses showed consistent results. Comparing 3-year outcomes in 262 propensity-matched pairs led to no qualitative changes in the study results (data not shown). In addition, the results remained essentially unchanged when: 1) the propensity score–adjusted multivariable analysis was repeated with a new propensity score that did not include thienopyridine use duration; and when 2) additional variables (thienopyridine discontinuation as a

Table 4. Post-Discharge 3-Year Clinical Outcomes

	Aspirin Discharge Dose ≤200 mg (n = 2,289)	Aspirin Discharge Dose >200 mg (n = 562)	p Value
MACE	17.5 (391)	23.8 (125)	0.0009
Mortality	4.1 (92)	5.0 (26)	0.39
Cardiac mortality	1.8 (39)	2.1 (11)	0.58
Reinfarction	5.7 (124)	8.6 (44)	0.01
Ischemic TVR	11.3 (249)	15.4 (80)	0.01
Stroke	1.2 (26)	1.7 (9)	0.31
Ischemic	1.1 (23)	1.7 (9)	0.18
Hemorrhagic	0.1 (3)	0.0 (0)	0.40
Major bleeding (non-CABG related)	1.6 (34)	6.5 (33)	<0.0001
NACE	18.3 (408)	26.4 (139)	<0.0001
TIMI bleeding			
Major	0.8 (18)	2.3 (12)	0.003
Minor	0.4 (8)	1.1 (6)	0.02
Major or minor	1.2 (26)	3.5 (18)	0.0002
GUSTO bleeding			
Severe/life-threatening	0.3 (7)	0.6 (3)	0.37
Moderate	1.2 (26)	5.3 (27)	<0.0001
Mild	0.3 (6)	1.1 (6)	0.01
Definite or probable stent thrombosis	63 (3.0)	27 (5.4)	0.007

Values are Kaplan-Meier estimated % (n).

GUSTO = Global Use of Strategies to Open Occluded Arteries; MACE = major adverse cardiovascular events, including death, reinfarction, TVR for ischemia, stroke; NACE = net adverse clinical events, including MACE or major bleeding; other abbreviations as in Tables 1 and 2.

Table 5. Hazard of Post-Discharge Outcomes With High- vs. Low-Dose Aspirin

	Unadjusted		Adjusted*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
MACE	1.41 (1.15–1.72)	0.0009	1.14 (0.83–1.56)	0.41
Mortality	1.20 (0.78–1.89)	0.39	0.85 (0.43–1.69)	0.64
Reinfarction	1.54 (1.09–2.17)	0.01	0.92 (0.55–1.55)	0.76
Mortality or reinfarction	1.39 (1.05–1.82)	0.02	0.89 (0.58–1.37)	0.61
Ischemic TVR	1.39 (1.08–1.79)	0.01	1.18 (0.81–1.72)	0.39
Stroke	1.49 (0.69–3.13)	0.31	1.07 (0.32–3.53)	0.92
Major bleeding (non-CABG–related)	4.17 (2.63–6.67)	<0.0001	2.80 (1.31–5.99)	0.008
NACE	1.52 (1.25–1.85)	<0.0001	1.21 (0.90–1.62)	0.22
Definite or probable stent thrombosis	1.85 (1.18–2.94)	0.007	1.23 (0.64–2.37)	0.54

*Propensity score–adjusted. C-statistic for the propensity score discrimination of aspirin dose groups was 0.9.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1, 2, and 4.

time-dependent covariate, prior MI or CABG and Killip class at presentation) were included along with the propensity score in the Cox model.

Discussion

In the present analysis from the HORIZONS-AMI trial, after adjustment for baseline and procedural differences, patients undergoing primary PCI for STEMI discharged on and maintained chronically on high-dose aspirin had similar long-term rates of adverse ischemic events but significantly more major bleeding than did patients on low-dose aspirin. Therefore, this analysis contributes to an increasing literature that suggests that patients with ACS (both STEMI and non-STEMI) and those undergoing PCI should be maintained on low-dose rather than high-dose aspirin.

Most, but not all prior studies support the results of the present analysis. Post-hoc analyses from the CURE (Clopidogrel in Unstable Angina To Prevent Recurrent Events) and the BRAVO (Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion) trials showed increased rates of bleeding rates in patients taking higher versus lower aspirin maintenance dose at long-term follow-up, without concordant reductions in their respective primary study endpoint, composite ischemic events (14,15). A similar result was reported in a meta-analysis by Serebruany et al. (16). However, other meta-analyses showed no difference in bleeding rates whether higher or lower aspirin maintenance doses were used (1,17). In the CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Symptoms) trial, in which patients with ACS were randomized to high-dose (300 to 325 mg) versus low-dose (75 to 100 mg) aspirin, there were no significant differences in the 30-day rates of major bleeding or the composite endpoint of cardiac death, MI, or stroke (10). However, all patients in this trial received a ≥300-mg loading dose of aspirin, which may have diminished the ability for differences to emerge given the short follow-up duration. In light of these conflicting results, the recent 2011 consensus guidelines for PCI give a new class IIa recommendation, that it is reasonable to use 81 mg/day maintenance aspirin dose instead of higher doses (18).

In the present study, there were numerous differences in baseline demographics and treatments between patients discharged on high-dose versus low-dose aspirin. Importantly, most patients maintained on high-dose aspirin were enrolled in the United States. This is consistent with

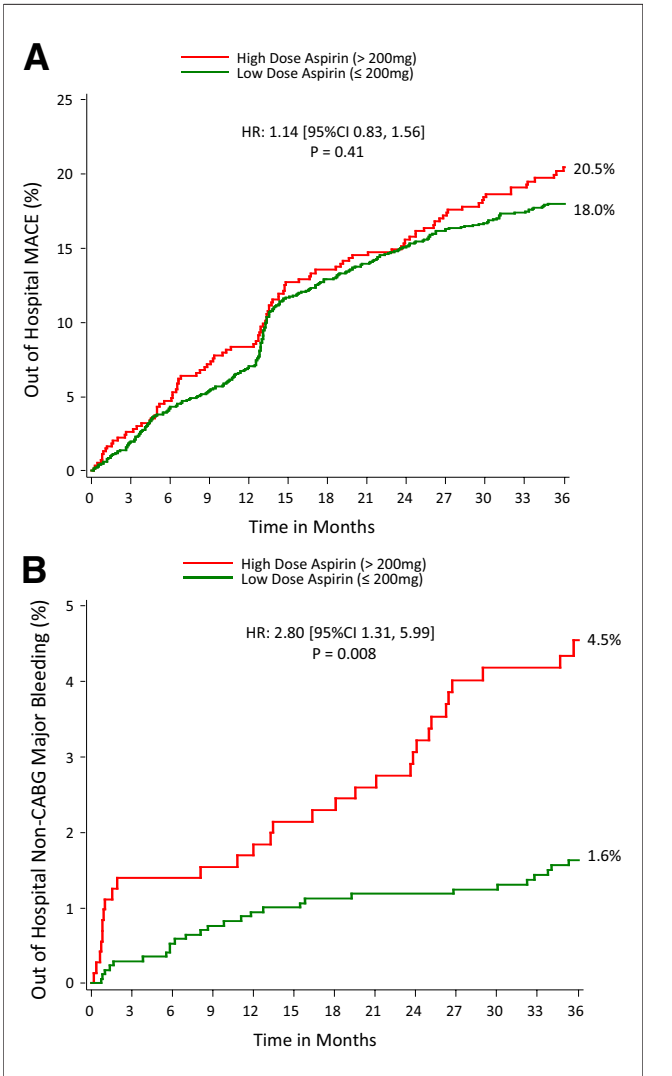

Figure 2. 3-year Clinical Outcomes

Three-year, propensity score–adjusted time-to-event curves for out-of-hospital **(A)** major adverse cardiovascular events (MACE) and **(B)** major bleeding. CABG = coronary artery bypass graft; CI = confidence interval; HR = hazard ratio.

Table 6. Post-Discharge 3-Year Outcomes According to Aspirin Dose and Region of Enrollment

	Region	Aspirin ≤200 mg	Aspirin >200 mg	HR (95% CI)	p Value	p Interaction
MACE	US	21.7%	23.9%	0.88 (0.63–1.23)	0.45	0.62
	OUS	16.9%	23.2%	0.76 (0.50–1.15)	0.20	
Mortality	US	7.4%	5.6%	1.34 (0.72–2.48)	0.35	0.44
	OUS	3.9%	4.5%	0.87 (0.35–2.14)	0.76	
Reinfarction	US	7.2%	9.7%	0.72 (0.40–1.27)	0.25	0.12
	OUS	5.4%	2.7%	1.99 (0.63–6.26)	0.23	
Mortality or reinfarction	US	13.5%	14.2%	0.93 (0.61–1.43)	0.75	0.49
	OUS	8.9%	7.2%	1.25 (0.61–2.53)	0.54	
Stroke	US	2.2%	2.2%	0.98 (0.33–2.86)	0.97	0.82
	OUS	1.2%	0.9%	1.27 (0.17–9.41)	0.81	
TVR	US	11.0%	14.4%	0.75 (0.47–1.19)	0.22	0.89
	OUS	10.9%	15.4%	0.69 (0.42–1.12)	0.13	
Stent thrombosis	US	4.2%	5.9%	0.70 (0.31–1.56)	0.38	0.62
	OUS	2.9%	3.1%	0.90 (0.28–2.88)	0.86	
Major bleeding	US	3.5%	7.0%	0.50 (0.23–1.09)	0.07	0.26
(Not related to CABG)	OUS	1.4%	4.8%	0.30 (0.11,–0.76)	0.008	
NACE	US	23.4%	26.7%	0.84 (0.61–1.16)	0.29	0.60
	OUS	17.5%	23.2%	0.73 (0.49–1.09)	0.12	

Values are Kaplan-Meier estimated.

OUS = outside the United States; US = United States; other abbreviations as in Tables 1, 2, 4, and 5.

previously reported geographic trends in aspirin prescribing (19) and reflects discrepancies in local treatment guidelines (20–23). Notably, patients in the high-dose aspirin group also had a less favorable cardiovascular risk profile and (for unclear reasons) lower prescription rates of statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. They were also more likely to continue with a thienopyridine beyond 1 year after STEMI. Again, regional patient characteristics and prescribing patterns may in part explain these differences.

After adjusting for these differences, discharge aspirin dose did not affect long-term ischemic endpoints in this high-risk population, a finding that is consistent with most prior studies in which aspirin was combined with clopidogrel (1,14,24). However, in the PLATO (Platelet Inhibition and Patient Outcomes) trial (9), the lowest 1-year rates of cardiovascular death, MI, or stroke were noted in patients with ACS treated with ticagrelor and low-dose aspirin, whereas the highest rates occurred in those treated with ticagrelor and high-dose aspirin. Ischemic event rates were intermediate in patients discharged on clopidogrel and either low-dose or high-dose aspirin, with no significant differences between these groups. Thus, the PLATO results are consistent with the present analysis, in which almost all patients were discharged on clopidogrel (a few on ticlopidine, but none on prasugrel or ticagrelor). Whether there truly is an interaction between aspirin dose and ticagrelor deserves further study.

In the current analysis, high-dose aspirin was an independent predictor of major bleeding. In contrast, in PLATO there was no significant difference in bleeding rates between patients enrolled within versus outside the United States (9), nor according to aspirin dose, with either concomitant clopidogrel or ticagrelor treatment (25). In part, this disparity may be explained by differences in patient selection criteria, bleeding definitions, or rates between the 2 trials. Also, the high-dose aspirin group in PLATO was quite small, and in neither trial was aspirin dose randomized, leading to the possibility for unmeasured confounders or chance findings. In CURRENT-OASIS 7, there was no significant difference in the secondary endpoint of 30-day major bleeding between the high- and low-dose aspirin arms in the overall cohort of 25,000 patients or in the pre-specified subgroup of patients treated with PCI (10,24). Rates of cardiovascular events were numerically lower among patients on high- versus low-dose aspirin, but this was not significant (4.2% vs. 4.4%, p = 0.61) (10). However, significant increases in major gastrointestinal bleeding and minor bleeding were observed in the higher dose aspirin group in this trial (10), adding credence to the hypothesis that high-dose aspirin indeed increases the risk of bleeding in patients with ACS and in those undergoing PCI, without providing additional protection from adverse ischemic events.

Study limitations. As a post-hoc analysis, the findings from the present study are exploratory and should be considered hypothesis-generating. Data regarding changes in aspirin dose after discharge, use of enteric-coated formulations of aspirin and coprescription of nonsteroidal anti-inflammatory agents were not collected in the case report form. Even

propensity-adjusted analyses cannot correct for unmeasured confounders. Whereas the present study supports the use of low-dose maintenance aspirin after PCI in ACS, only a large-scale, randomized trial can definitively address this issue.

Conclusions

In the current study, we found no difference in ischemic endpoints between high- and low-dose aspirin used in combination with clopidogrel, but high-dose aspirin was an independent predictor for higher rates of major bleeding. Thus, absent a demonstrated benefit of high-dose aspirin in patients on dual antiplatelet therapy with clopidogrel following PCI, and given the concern of potential harm of high-dose aspirin used with more potent $P2Y_{12}$ inhibitors (i.e., prasugrel and ticagrelor), these data support the routine use of low-dose aspirin (<200 mg daily) at discharge following primary PCI in STEMI.

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