ORIGINAL RESEARCH

Impact of Antecedent Aspirin Use on Infarct Size, Bleeding and Composite Endpoint in Patients with de Novo Acute Myocardial Infarction

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Background: The study aimed to evaluate the impact of antecedent aspirin use on infarct size, bleeding and composite endpoint in patients with de novo acute myocardial infarction.

Patients and Methods: A total of 562 consecutive patients with de novo acute myocardial infarction were included in this prospective cohort study. Patients were assigned into two groups based on presence (n=212) and absence (n=350) of prior aspirin use. Primary endpoint was myocardial infarct size, as estimated by troponin I peak. In-hospital mortality, bleeding and composite clinical endpoint including cardiogenic shock, stroke, in-hospital mortality and major bleeding were also evaluated.

Results: Although GRACE and CRUSADE scores were higher, troponin I peak was lower in prior aspirin users. This result was maintained after adjustment for baseline ischemic risk profile and other major confounders including MI type and location. Despite high CRUSADE score, there was no increase in major and minor bleeding. Minimal bleeding was higher in antecedent aspirin users. When it was adjusted for the CRUSADE score, a similar risk was reported.

Conclusion: Patients with de novo acute myocardial infarction using aspirin for primary prevention have an unexpectedly smaller infarct size and similar bleeding rates.

Keywords: acute myocardial infarction, aspirin, infarct size, primary prevention

Introduction

Aspirin has proven evidence of benefit and is guideline recommended as a treatment option for secondary prevention of cardiovascular events.[1] However, a promising decrease in adverse cardiovascular events was offset by an increase in bleeding complications for primary prevention.[1] The occurrence of an arterial thrombotic event despite aspirin therapy is defined as aspirin resistance. Possible mechanisms are incomplete suppression of thromboxane A2 generation, stress-induced cyclooxygenase-2 expression in platelets and increased platelet sensitivity to adenosine diphosphate and collagen. Twenty years ago, the main explanation for patients who had an acute coronary syndrome despite antecedent aspirin therapy was 'aspirin resistance'.[2] Contemporary use of aspirin for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) has been widely accepted, as the benefits linked to the reduction of clinical events outweigh the risk of major bleeding. However, the potential of aspirin to reduce atherothrombotic events, its overall efficacy

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441

and safety in primary ASCVD prevention remains unclear, despite being used for this purpose for decades.[3]

Current myocardial infarction (MI) therapy has evolved from the conservative approach to early invasive strategies and the combination of more potent antiplatelet and statin therapy.[4] MI event rates and in-hospital case fatalities declined in 1985–2010 in almost all populations analysed due to the rapidly expanding number of hospitals that were capable of performing percutaneous coronary interventions (PCIs).[5] However, the increased incidence of obesity and diabetes in the overall population has resulted in a modest increase in morbidity. Prior aspirin use has recently been shown to decrease serious vascular events, including MI and stroke, in diabetics without cardiovascular disease.[6] Additionally, aspirin pretreatment has been associated with similar primary endpoints, including death, MI and stroke, in patients at moderate cardiovascular risk.[7]

Bleeding risk with aspirin prescribed for primary prevention should be taken into consideration while interpreting these results. Very low dose aspirin (< 100 mg) was found to be related to increased major gastrointestinal bleeding.[8] Hence, the findings of A Study of Cardiovascular Events in Diabetes (ASCEND) demonstrated a 12% reduction in the incidence of major adverse cardiac events in diabetic patients; however, this was outweighed by a 29% increase in the risk of major bleeding complications.[6] The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial has consistently verified this complication.[7]

Possible explanations for increased bleeding might be that chronic aspirin users usually have established ASCVD[9] and are generally older.[9] The recommendation for aspirin use as primary prevention has been downgraded over the years. Recent guidelines restricted the use of aspirin to 40–70 year-old-adults who are at higher risk of cardiovascular events.[10] It should not be used among adults older than 70 or any person who is at increased risk of bleeding.[10]

A decrease in nonfatal infarction in chronic aspirin users has been demonstrated recently.[6] It was put forward that this decrease could translate into a reduction in fatal MI with randomized trials with long-term follow-up.

One of the most consequential determinants of outcome in MI is infarct size, which is important for therapeutic interventions.[11] Cardiac troponins (Tn) provide quantitative estimations of infarct size.[12] Omura et al

reported a close relationship between TnT and infarct size in acute MI.[13] The trends for TnT and TnI assays were remarkably similar in the same population.[14] Measurements of Tn, including area under curve (AUC) and peak, have consistently verified that the correlations between Tn and different imaging modalities of infarct size are 0.6 and 0.75.[14] Single-point measures and 24 hour onwards were found to be equally effective.[15] Although aspirin therapy is a cornerstone in the treatment of MI and reduces mortality and hospitalization after ischemic attack,[16] there are not enough investigations about effects of aspirin pretreatment on infarct size. Wu et al postulated in his 2002 study that acute infarct size was a stronger predictor of cardiac death, nonfatal reinfarction and symptomatic heart failure than ejection fraction and end-systolic volume index.[17] In the contemporary era, we tried to investigate the role of aspirin pretreatment for primary prevention prior to MI in a PCI-capable tertiary center. This center could perform primary PCI systematically on a 24/7 basis for all patients.

The Global Registry of Acute Coronary Events (GRACE) and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) scores are among the most frequently used risk assessment tools.[18,19] GRACE was primarily developed to predict in-hospital mortality in patients with both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). CRUSADE was developed from a cohort of NSTEMI patients, with a primary focus on bleeding. Both scores are currently used in broad acute coronary syndrome populations to assess the risk of both mortality and bleeding. In concordance with previous studies, GRACE scores were used to assess clinical risk and CRUSADE scores to assess bleeding risk in this study.

Cardiovascular disease prevention is defined as a combination of actions aimed at minimizing or eliminating the deleterious effect of cardiovascular disease at individual or population level. Modification of lifestyle is the primary focus of interventions. Moreover, lipid-lowering with statins[20,21] and antihypertensive therapy in conjunction with this primary focus are considered as two components of prevention if targeted at individuals at high risk.[22] Antiplatelet therapy including aspirin is not recommended in individuals without cardiovascular disease.[23] In this study, we investigated the effect of aspirin use for primary

prevention prior to MI on myocardial infarct size, which was evaluated by TnI peak value and in-hospital bleeding.

Patients and Methods
Study Patients
This prospective, single-center study was conducted at Bezmialem University between September 10, 2018 and March 8, 2020; 562 patients with de novo MI (both STEMI and NSTEMI) were enrolled. Patients were assigned into two groups based on presence (n=212) and absence (n=350) of prior aspirin use.

Inclusion criteria were: (1) age > 18 years; (2) duration of pain onset to hospital admission of 72 hours;[24] (3) MI denotes acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper range limit and at least one of the following: (a) symptoms of myocardial ischemia; (b) new ischemic electrocardiographic changes; (c) development of pathological Q waves;[25] and (4) pretreatment with aspirin at least 30 days before admission.

Exclusion criteria were: (1) history of previous MI; (2) pretreatment with antiplatelets other than aspirin, such as clopidogrel, prasugrel or others; and (3) severe physical disability or inability to comprehend the study.

Study was approved by Bezmialem University Ethics Committee (number 71306642) on May 21, 2018 and the study was conducted in accordance with ethical principles described by the Declaration of Helsinki. All participants signed written informed consent forms before study enrollment.

Study Design
Case report forms which included compliance and duration of antecedent aspirin use were given to each patient. A minimum duration of 30 days until index event was accepted as antecedent aspirin use.

Demographic details, clinical characteristics and laboratory findings were recorded, respectively. Measurement of TnI (Beckman Coulter, Fullerton, California, USA) was repeated at serial time intervals until 24 hours after reaching the peak value. Cardiac Tn provides quantitative estimation of infarct size.[12] Admission Tn values are also predictive of future risk, but their correlation with infarct size is poor.[14] The trends for TnT and TnI assays were remarkably similar in the same population.[14] Measurements of Tn, including

area under curve (AUC) and peak, have consistently verified that the correlations between Tn and different imaging modalities of infarct size are 0.6 and 0.75.[14] Single-point measures and 24 hour onwards were found to be equally effective.[15] Echocardiography was performed within 24 hours of hospital admission. Ejection fraction was calculated using a modified Simpson's method.

GRACE score was used to assess clinical risk and improved the selection of patients for clinical and interventional procedures following an acute coronary event.[18] CRUSADE score was used to determine bleeding risk.[19] GRACE and CRUSADE scores were applied to both STEMI and NSTEMI patients.

The Thrombolysis In Myocardial Infarction (TIMI) bleeding classification of major, minor and minimal was applied to in-hospital adverse events. Our intention in using the TIMI bleeding classification was only to describe bleeding complications in detail, not to assess bleeding risk or ischemic risk. It concluded that major bleeding was an intracranial hemorrhage or a ≥ 5 g/dl decrease in hemoglobin concentration or a $\geq 15\%$ absolute decrease in hematocrit.[26] Minor bleeding was described as a ≥ 3 g/dl decrease in hemoglobin concentration or a $\geq 10\%$ absolute decrease in hematocrit.[26] Minimal bleeding was described as a < 3 g/dl decrease in hemoglobin concentration or a $< 10\%$ decrease in hematocrit.[27]

TIMI flow grade before and after PCI was evaluated using a standard method.[28] Current guidelines were taken into consideration while giving optimal medical treatment and providing coronary revascularization for all patients.[4,24]

Infarct size was the primary endpoint of the study. It was estimated by TnI peak value. STEMI and NSTEMI subcategorizations were performed for infarct size (Tables 1 and 2). Additionally, the secondary endpoint was in-hospital bleeding. STEMI and NSTEMI subcategorizations were also performed for bleeding (Tables 3 and 4). Stroke was defined as a new neurological deficit of more than 24 hours duration. Cardiogenic shock, stroke, in-hospital mortality and major bleeding were considered as a composite endpoint.

Statistical Analysis
A sample size of 504 patients was calculated under the assumption of a 5 ng/mL difference in mean TnI peak value between two groups. This sample size allowed an 80% statistical power to be deemed significant (α error of 0.05).

Table 1 Multiple Linear Regression Analysis for Infarct Size in STEMI Subgroups

	Infarct Size			
	BETA (Non-standard Coefficient)	95% CI for BETA	BETA (Standard Coefficient)	p-value
Prior aspirin treatment	14.752	10.927–18.578	0.335	< 0.001
GRACE score	0.266	0.175–0.356	0.288	< 0.001
AMI location (anterior vs nonanterior)	20.611	16.533–24.710	0.477	< 0.001
Smoking status	6.030	2.034–10.026	0.133	0.003
Prior beta-blocker treatment	2.669	−4.583–9.920	0.032	0.469
Prior statin treatment	1.892	−2.449–6.233	0.038	0.391

Abbreviations: AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; STEMI, ST-elevation myocardial infarction.

Table 2 Multiple Linear Regression Analysis for Infarct Size in NSTEMI Subgroups

	Infarct Size			
	BETA (Non-standard Coefficient)	95% CI for BETA	BETA (Standard Coefficient)	p-value
Prior aspirin treatment	2.593	1.470–3.716	0.250	< 0.001
GRACE score	0.007	−0.030–0.045	0.022	0.695
AMI location (anterior vs nonanterior)	−0.074	−1.306–1.158	−0.007	0.906
Smoking status	2.859	1.366–4.351	0.212	< 0.001
Prior beta-blocker treatment	0.221	−2.213–2.655	0.010	0.858
Prior statin treatment	1.687	0.341–3.033	0.136	0.014

Abbreviations: AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-elevation myocardial infarction.

Table 3 Univariate and Multivariate Logistic Regression Analysis for Bleeding in STEMI Subgroup

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Prior aspirin treatmen	1.962 (0.949–4.055)	0.066		
Age	1.010 (0.971–1.051)	0.608		
Hypertension	1.376 (0.627–3.020)	0.436		
CRUSADE score	1.115 (1.072–1.158)	< 0.001	1.113 (1.071–1.158)	< 0.001
Clopidogrel treatment	1.372 (0.641–2.936)	0.406		
Ticagrelor treatment	1.348 (0.570–3.187)	0.496		
Glycoprotein IIB/IIIA inhibitor treatment	2.879 (1.309–6.333)	0.009	2.984 (1.204–7.400)	0.018

Abbreviations: CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines; STEMI, ST-elevation myocardial infarction.

Table 4 Univariate and Multivariate Logistic Regression Analysis for Bleeding in NSTEMI Subgroup

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Prior aspirin treatment	1.475 (0.677–3.210)	0.328		
Age	0.999 (0.950–1.050)	0.958		
Hypertension	0.368 (0.161–0.843)	0.018	1.228 (0.473–3.187)	0.673
CRUSADE score	1.156 (1.102–1.212)	< 0.001	1.149 (1.094–1.207)	< 0.001
Clopidogrel treatment	5.529 (1.869–16.356)	0.002	0.169 (0.041–0.690)	0.013

Abbreviations: CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines; NSTEMI, non-ST-elevation myocardial infarction.

Data analysis was performed using SPSS 17 software (SPSS Inc., Chicago, Illinois, USA). The Shapiro–Wilk test was used for assessing whether or not the variables follow normal distributiont. Continuous variables were expressed as mean ± standard deviation (SD). Variables with a skewed distribution were presented as median and interquartile range (IQR). Categorical variables were expressed as number and percentage. Differences between independent groups were assessed by unpaired Student's *t*-test for quantitative variables with normal distribution and Mann–Whitney's *U*-test for quantitative variables without normal distribution. Chi-square tests and Fisher's exact tests were performed for qualitative variables. Pearson's correlation analysis was performed for correlation between TnI peak value and GRACE score.

To identify variables that were associated with infarct size, a linear regression analysis was performed. TnI peak value was the dependent variable and GRACE score, type of myocardial infarction, smoking, antecedent medications, acute total occlusion and culprit vessel were integrated into analysis as independent variables. Additionally, linear regression analysis was repeated with the same variables for STEMI and NSTEMI subgroups for detailed analysis.

Moreover, univariate and multivariate logistic regression analyses were conducted to determine independent predictors of bleeding. Univariate analyses were performed for prior aspirin treatment, age, hypertension, CRUSADE score and intraprocedural medications including clopidogrel, ticagrelor and glycoprotein IIB/IIIA inhibitors. Variables found to be significant in univariate analysis were integrated into multivariate analysis. Logistic regression analyses were repeated for STEMI and NSTEMI subgroups for detailed analysis of bleeding.

To determine the independent predictive role of prior aspirin use for minimal, minor and major bleeding, univariate logistic regression analyses were conducted. The results were adjusted according to CRUSADE score. A p-value of < 0.05 was considered statistically significant. All p-values were two-sided.

Results

The study population consisted of 562 consecutive patients with a mean age of 69.1 ± 9.0 years. Patients with NSTEMI (n=302) and STEMI (n=260) were included in this prospective cohort. Data for prior aspirin use was available for all patients; 212 (37.7%) patients were taking aspirin at least 30 days before admission. Among these, 78 patients (36.7%) were taking aspirin prescribed by a clinician and 134 patients (63.3%) were taking aspirin bought over the counter.

Baseline demographic characteristics of the study group are presented in Table 5. Although age, gender, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, smoking status and glomerular filtration rate were similar, GRACE and CRUSADE scores were higher in prior aspirin users (Figure 1). There was no significant difference between the two groups in terms of type and location of MI and reperfusion time.

Table 6 summarizes complications which occurred during hospitalization. Cardiogenic shock, stroke, in-hospital mortality and major bleeding were defined as a composite endpoint. In-hospital mortality and this composite endpoint were similar. Although GRACE and CRUSADE score were higher, prior aspirin users had lower infarct sizes as estimated by lower TnI peak. A significant correlation was found between TnI peak and GRACE score in all patients (Figure 2).

Table 5 Baseline Characteristics of Study Patients According to Prior Aspirin Use

	Prior Aspirin (+) (n=212)	Prior Aspirin (-) (n=350)	p-value
Age, years	68.7 ± 8.6	69.3 ± 9.3	0.497
Male sex, n (%)	114 (53.8)	190 (54.3)	0.906
Body weight (kg)	78.0 ± 9.7	77.3 ± 9.4	0.436
Height (cm)	167.3 ± 6.9	167.8 ± 6.8	0.444
Hypertension, n (%)	126 (59.4)	214 (61.1)	0.688
Diabetes mellitus, n (%)	60 (28.3)	98 (28.0)	0.938
Hyperlipidemia, n (%)	78 (36.8)	128 (36.6)	0.958
Smokers, n (%)	52 (24.5)	86 (24.6)	0.991
LVEF (%)	49.2 ± 6.7	48.9 ± 8.2	0.686
STEMI, n (%)	100 (47.2)	160 (45.7)	0.737
Culprit vessel (LAD), n (%)	74 (34.9)	122 (34.9)	0.991
Time to reperfusion (hours)	4.2 ± 2.4	4.1 ± 2.1	0.567
GRACE score	124.2 ± 18.8	120.2 ± 19.8	0.007
CRUSADE score	30.4 ± 10.7	28.6 ± 11.9	0.082
Laboratory values at hospital admission			
WBC (x10³/l)	8.0 ± 1.9	8.6 ± 2.1	0.002
Hemoglobin (gr/dl)	13.2 ± 1.6	13.4 ± 1.5	0.367
Platelet (x10³/l)	242.6 ± 60.4	247.4 ± 59.3	0.188
Blood glucose (mg/dl)	114.2 ± 47.7	114.4 ± 43.7	0.699
Serum creatinine (mg/dl)	0.9 ± 0.1	0.9 ± 0.2	0.480
Troponin I (ng/mL)	0.82 (0.07–7.40)	0.94 (0.14–8.92)	0.420
Total cholesterol (mg/dl)	207.0 ± 34.6	204.1 ± 42.7	0.150
LDL (mg/dl)	129.1 ± 29.9	125.0 ± 33.0	0.130
HDL (mg/dl)	44.2 ± 6.6	42.9 ± 9.3	0.002
Triglycerides (mg/dl)	166.0 ± 66.0	166.8 ± 76.7	0.518
Medication before AMI			
ACE inhibitors/ARB, n (%)	88 (41.5)	142 (40.6)	0.826
Beta-blockers, n (%)	12 (5.7)	6.3 (6.3)	0.763
Statins, n (%)	50 (23.6)	78 (22.3)	0.722
In-hospital antiplatelet use			
Clopidogrel, n (%)	176 (83.0)	294 (84.0)	0.761
Ticagrelor, n (%)	24 (11.3)	40 (11.4)	0.969
Prasugrel, n (%)	12 (5.7)	18 (5.1)	0.791
Glycoprotein IIB/IIIA inhibitor, n (%)	20 (9.4)	28 (8.0)	0.556
In-hospital procedures			
PCI, n (%)	188 (88.7)	302 (86.3)	0.411
CABG, n (%)	16 (7.5)	32 (9.1)	0.512
Medically managed (%)	8 (4.7)	16 (4.6)	0.912
TIMI flow before PCI, n (%)			
0	72 (33.9)	124 (35.4)	0.724
I	14 (6.6)	14 (6.6)	0.467
TIMI flow after PCI, n (%)			
0-I	3 (1.4)	5 (1.4)	0.990
II–III	209 (98.6)	345 (98.6)	0.990

Note: Data is presented as mean ± SD or n (%).
Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; APT, antiplatelet therapy; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending coronary artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.
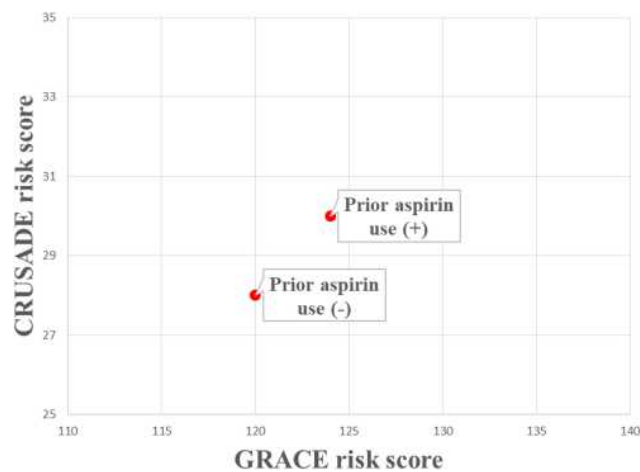
Figure 1 Comparison of GRACE and CRUSADE scores in patients with and without antecedent aspirin use. GRACE: Mean Global Registry of Acute Coronary Events; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines.

Statistical stability of prior aspirin use to reduce infarct size was maintained after integration of GRACE score, MI location (anterior vs non-anterior),

MI type (STEMI vs NSTEMI), prior beta blocker and statin use and smoking status in the multiple linear regression analysis (Table 7). This finding has been consistently verified in both STEMI and NSTEMI subgroups (Tables 1 and 2).

CRUSADE score (OR 1.131, 95% CI 1.097–1.167; p < 0.001), clopidogrel treatment (OR 2.691, 95% CI 1.334–5.429; p = 0.038) and glycoprotein IIB/IIIA inhibitors (OR 4.462, 95% CI 1.815–10.973; p = 0.001) were found to be significant independent predictors of bleeding in multivariate analysis (Table 8). However, prior aspirin use was not associated with bleeding in either STEMI or NSTEMI subgroups (Tables 3 and 4).

Despite major bleeding and minor bleeding being similar in the two groups, minimal bleeding was higher in prior aspirin users (Table 6). When minimal bleeding was adjusted for CRUSADE score in the multiple logistic regression analysis, the difference between the two groups in terms of minimal bleeding disappeared (Figure 3).

Table 6 In-Hospital Adverse Events and Troponin I Peak Value of Study Patients According to Antecedent Aspirin Use

	Prior ASA (+) (n=212)	Prior ASA (-) (n=350)	p-value
Death, n (%)	4 (1.9)	6 (1.7)	0.881
Cardiogenic shock, n (%)	10 (4.7)	8 (2.3)	0.113
APE, n (%)	14 (6.6)	16 (4.6)	0.299
MV, n (%)	8 (3.8)	10 (2.9)	0.550
Atrial fibrillation, n (%)	16 (7.5)	26 (7.4)	0.959
AV block, n (%)	6 (2.8)	10 (2.9)	0.985
VT/VF, n (%)	16 (7.5)	20 (5.7)	0.390
Minimal bleeding, n (%)	24 (11.3)	22 (6.3)	0.039
Minor bleeding, n (%)	7 (3.3)	12 (3.4)	0.696
Major bleeding, n (%)	4 (1.9)	6 (1.7)	0.881
AKI requiring hemodialysis, n (%)	18 (8.5)	34 (9.7)	0.627
Hemorrhagic stroke, n (%)	0 (0)	0 (0)	1.000
Ischemic stroke, n (%)	2 (0.9)	4 (1.1)	0.824
Composite endpoint, n (%)	19 (9.0)	20 (5.7)	0.142
Troponin I peak value (ng/mL)	11.0 (4.5–31.9)	14.7 (6.7–42.9)	0.002

Note: Data is presented as median ± interquartile range (IQR) or n (%).
Abbreviations: AKI, acute kidney injury; APE, acute pulmonary edema; APT, antiplatelet therapy; AV, atrioventricular; DAPT, dual antiplatelet therapy; MV, mechanical ventilation; VT/VF, ventricular tachycardia/ventricular fibrillation; Composite endpoint, composite of in-hospital mortality, stroke, cardiogenic shock and major bleeding.
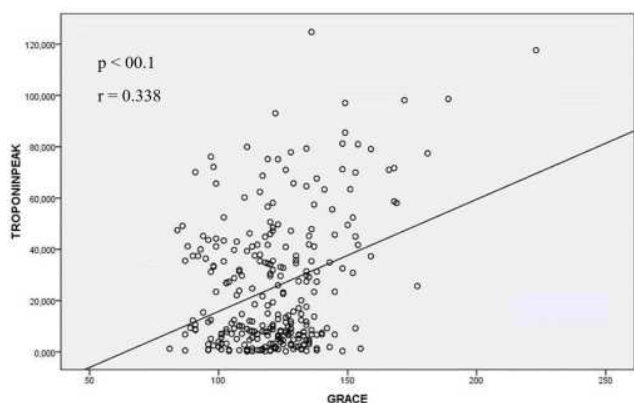
Figure 2 The close relation between Troponin I peak value and GRACE score in all patients. GRACE: Mean Global Registry of Acute Coronary Events.

Discussion

The main findings of the present study were as follows. (1) Although patients with prior aspirin use had a higher GRACE score, smaller infarct size, which was determined by TnI peak value, was reported. (2) There was no difference between those who used aspirin and those who did not in terms of occurrence of major and minor bleeding. Minimal bleeding was more frequently seen in antecedent aspirin users. However, when minimal bleeding was integrated into regression analysis with CRUSADE score, a similar odds ratio was reported. (3) A composite endpoint including in-hospital mortality, cardiogenic shock, stroke and major bleeding was similar between the two groups.

The clinical utility of aspirin, particularly in MI, has always been attributed to its antiplatelet effect. Recent studies have shown that it might reduce infarct size by cardioprotective mechanisms.[29,30] It is still unclear whether antecedent aspirin use is beneficial or harmful.

Chronic aspirin users had a worse baseline cardiovascular risk profile than those who did not. GRACE score, in particular, was higher in those using aspirin. Despite the higher basal ischemic risk, chronic aspirin users had a lower TnI peak in our study. In concordance with this study, Campodonico et al found smaller infarct size in chronic MI patients receiving antiplatelet treatment.[31] It is noteworthy to emphasize that patients were assigned to one of three groups based on the number of antiplatelet agents used (no, single and dual antiplatelet groups) in their study. Weidmann et al concluded that pre-existing treatment with aspirin and/or statins, particularly in combination, decreased infarct size.[30] Additionally, Marenzi et al reported that sole statin pretreatment was associated with smaller infarct size in STEMI.[32] The net effect of aspirin was found to be significantly higher than statin pretreatment for infarct size in our study. However, only 20% of the total study population was using antecedent statin therapy and this study was not designed to determine the net effect of statin pretreatment.

Chronic aspirin use was shown to be associated with increased major bleeding in primary prevention.[8] Additionally the use of low dose aspirin in older adults

Table 7 Multiple Linear Regression Analysis for Infarct Size

	Infarct Size			
	BETA (Non-standard Coefficient)	**95% CI for BETA**	**BETA (Standard Coefficient)**	**p-value**
Prior aspirin treatment	8.346	6.207–10.485	0.160	< 0.001
GRACE score	0.214	0.156–0.271	0.165	< 0.001
AMI location (anterior vs nonanterior)	10.889	8.605–13.174	0.205	< 0.001
AMI type (STEMI vs NSTEMI)	36.393	34.213–38.572	0.718	< 0.001
Smoking status	6.976	4.501–9.451	0.119	< 0.001
Prior beta-blocker treatment	0.740	−3.610–5.089	0.007	0.738
Prior statin treatment	0.626	−1.869–3.120	0.010	0.622

Abbreviations: AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 8 Univariate and Multivariate Logistic Regression Analysis for Bleeding

Variables	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Prior aspirin treatment	1.176 (0.701–1.970)	0.531		
Age	1.001 (0.973–1.029)	0.959		
Hypertension	1.954 (1.108–3.447)	0.021	0.940 (0.492–1.798)	0.852
CRUSADE score	1.129 (1.096–1.162)	< 0.001	1.131 (1.097–1.167)	< 0.001
Clopidogrel treatment	2.038 (1.127–3.687)	0.018	2.691 (1.334–5.429)	0.038
Ticagrelor treatment	2.302 (1.194–4.439)	0.013	0.624 (0.153–2.543)	0.510
Glycoprotein IIB/IIIA inhibitor treatment	2.726 (1.341–5.544)	0.006	4.462 (1.815–10.973)	0.001

Abbreviation: CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines.

(> 70 years) resulted in major hemorrhage.[33] Gastrointestinal bleeding accounts for up to half of major bleeding.[6] The absolute benefits of aspirin pretreatment were largely counterbalanced by the bleeding hazard. We also investigated the relationship between chronic aspirin use and in-hospital bleeding. Contrary to expectations, there was no difference in the occurrence of major and minor bleeding events between those using aspirin and those who did not. Minimal bleeding was more frequent in prior aspirin users. However, when the risk of bleeding due to aspirin was adjusted according to the CRUSADE score, there was no significant bleeding in terms of minimal bleeding. While most previous studies investigating the role of antecedent aspirin therapy were large retrospective analyses with limited inclusion criteria, our study was established to specifically prospectively
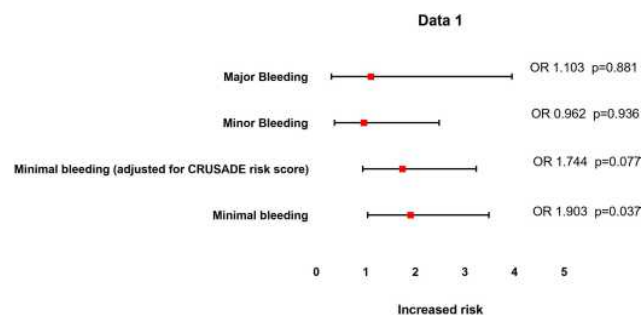

Figure 3 Comparison of bleeding in patients with and without antecedent aspirin use. Patients without prior aspirin use were accepted as the reference point. Minimal bleeding and CRUSADE score were integrated in multiple regression analysis. CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines.

evaluate consecutive de novo AMI patients using inclusion criteria in accordance with current practice.[34–37] The strength of our study is evaluating bleeding complications using standardized bleeding classifications.[26]

Time from presentation to intervention has a substantial impact on infarct size. Primary PCI is the treatment of choice in STEMI within 12 hours of symptom onset.[24] Time from presentation to intervention was approximately 4 hours in this study. It included 2 hours European Society of Cardiology-mandated door to balloon time.[24] It was an acceptable duration for a 7/24 PCI-capable hospital. An early invasive strategy is defined as coronary angiography performed within 24 hours of hospital admission in NSTEMI,[4] which is recommended in high-risk patients.[4] All patients were taken to the angiography laboratory as soon as possible in this study. However, it cannot be denied that 4 hours is not achievable in ordinary conditions for NSTEMI. All patients received an aspirin 300 mg loading dose on arrival at hospital, irrespective of prior aspirin use. Inhibition of the cyclooxygenase and attenuation of thromboxane A2 were achieved within minutes with a loading dose of 250–500 mg. The rapid action of aspirin might decrease infarct size.

Cardiovascular magnetic resonance (CMR) imaging allows noninvasive assessment of myocardial function and viability with high spatial resolution and is superior to single-photon emission computed tomography (SPECT) for the identification of MI.[38,39] Furthermore, the technique is highly sensitive and permits quantification of small areas of myocardial injury attributable to native coronary artery disease and/or PCI.[40,41] It was considered to be the most

reliable indicator of infarct size. Tn was also shown to be closely related to infarct size after STEMI.[42] Peak values, in particular, correlated well with infarct size.[43] Low cost and high availability favor TnI instead of imaging modalities for identifying infarct size in current practice.

Some limitations should be taken into consideration while interpreting our data. First, confounding factors including creatinine clearance and slow or incomplete reperfusion could not be totally eliminated while showing the direct relationship between antecedent aspirin use and infarct size. Second, patients' self-reported prior aspirin use was subjective. Third, many factors, including access site and anticoagulants, might cause serious bleeding rather than those identified by CRUSADE score. Finally, large prospective trials should be conducted to find associations between prior aspirin use and long-term mortality in acute MI.

Conclusions

Patients who were hospitalized with de novo MI and were chronic aspirin users had an unexpectedly lower TnI peak level and similar bleeding compared to those who did not use aspirin, despite having a higher initial ischemic and bleeding risk profile. These findings may shed light on the contemporary preventive role of aspirin in acute MI.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Disclosure

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The authors have had full control of all primary data and they agree to allow the journal to review their data if requested.

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