



# Safety and efficacy of high-dose versus low-dose aspirin in individuals with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention: A randomized clinical trial

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## Abstract

**Introduction:** Aspirin is the most frequently used antiplatelet therapy after percutaneous coronary intervention (PCI). Yet, the optimal daily dose of aspirin is unanswered.

**Objectives:** We aimed to compare the effect of high-dose versus low-dose aspirin in a randomized trial of patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI.

**Patients and Methods:** In a double-blind randomized trial, 175 patients with STEMI were randomly assigned to high-dose or low-dose aspirin. The primary efficacy outcome was major adverse cardiovascular events (MACE) as a composite endpoint of death, myocardial infarction, stroke and revascularization procedures. The primary safety endpoint was major bleeding.

**Results:** Totally 90 and 85 patients were assigned to high-dose and low-dose aspirin, respectively. The incidence rate of MACE was 13.1 and 10.1 per 100 person year in high-dose and low dose aspirin, respectively. There was no significant difference between high-dose and low-dose aspirin in terms of efficacy (Adjusted hazard ratio: 0.85, 95% CI=0.29-2.45) and safety outcome (Adjusted hazard ratio: 1.65, 95% CI=0.41-6.69).

**Conclusion:** Efficacy and safety outcomes were not significantly different between high-dose and low-dose aspirin.

**Trial registration:** The trial protocol was registered in the Iranian registry of clinical trial (#IRCT2014122220392N1; <https://en.irct.ir/trial/18085>, ethical code; IR.GUMS.REC.1920141901).

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## Introduction

Antiplatelet therapy is the cornerstone of pharmacotherapy after percutaneous coronary intervention (PCI) for long-term success of revascularization procedure (1). Among several drugs, aspirin has been widely accepted in PCI with a history that goes back to 1988 with a significant reduction of the risk of re-infarction (2,3). Nonetheless, the optimal daily dose of aspirin is still unanswered and in practice, the daily maintenance dose is ranged between 75 and 325 mg (4). Most observational studies have shown similar efficacy of high-dose and low dose aspirin. However, in terms of safety, some complications especially increased risks of bleeding from gastrointestinal tract have been reported for higher dose of aspirin (5-10). Meanwhile, there is scant randomized trial to compare the safety and efficacy of different aspirin doses in patients with ST-

## Key point

In a double-blind randomized trial with one year complete follow-up, results revealed that patients in low-dose aspirin had similar long-term major adverse cardiovascular events compared to high-dose group.

segment elevation myocardial infarction (STEMI) who underwent PCI (11). There is also obvious geographical variation in prescribing dose between countries while most physicians prefer to prescribe higher doses due to concerns of increased risk for subacute ischemic event that outweigh the bleeding complications (4).

## Objectives

In the current study we sought to compare high-dose versus low dose aspirin in a randomized trial of patients with myocardial infarction undergoing primary PCI to



provide the best evidence for choosing the suitable dose of aspirin.

## Patients and Methods

### Study population

This is a double-blind parallel randomized clinical trial designed to compare the long-term safety and efficacy of high versus low-dose aspirin. Study subjects are patients with STEMI who underwent primary PCI. STEMI was defined as typical chest pain lasting for >30 min and ST-segment elevation >1 mm in >2 contiguous electrocardiographic leads. Patients with a history of gastrointestinal bleeding and hemorrhagic stroke, major surgeries within 6 weeks, opium and alcohol abusers, patients with coagulopathies or history of anticoagulant therapy, platelet <100 000/ $\mu$ L, hematocrit <25%, and creatinine >4 mg/dL were excluded from the study.

All patients were given a loading dose of 325 mg aspirin orally and 5000 U intravenous bolus of heparin before transportation to the PCI. PCI procedure was performed with a standard femoral approach. One hundred seventy-five eligible patients were then randomly allocated to receive 325 mg daily as high-dose or 81 mg daily as low-dose aspirin for days 2 to 30. Drugs were provided in similar boxes labeled as A or B. Both patients and researchers who assessed the outcome events were blinded about the type of enclosed drugs. At discharge, patients were prescribed for clopidogrel 75 mg/d for one month or one year, which depended on the type of stent. A checklist including baseline variables, conventional cardiovascular risk factors and laboratory test results were collected for all patients. Transthoracic echocardiography was performed in all patients within 48 hours after PCI and left ventricular ejection fraction was measured based on modified Simpson's method (12).

Patients were assessed daily until the date of discharge from the hospital and then followed-up through telephone contacts. The research staff was blinded to the treatment groups. The primary efficacy endpoint was defined as a composite measure of major adverse cardiovascular events (MACE). The outcomes included in MACE were all-cause mortality, revascularization procedures, myocardial infarction (MI), and stroke. All-cause mortality defined as any post-procedural death and was considered of cardiac origin unless there was documentation for another cause. Revascularization procedures defined as subsequent percutaneous intervention or surgery after PCI. Stroke was defined as any ischemic neurologic deficit lasting more than 24 hours. MI defined as prolonged chest pain. The primary safety endpoint was defined as major bleeding event including gastrointestinal (GI) bleeding and bleeding not related to GI system.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. This paper was extracted from the residential

thesis of Mohadeseh Poursadeghi, Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences. Moreover, the study protocol was registered in the Iranian Registry of Clinical Trials (#IRCT2014122220392N1; <https://en.irct.ir/trial/18085>). The study was approved by the ethics committee of the Guilan University of Medical Sciences (#IR.GUMS.REC.1920141901). Accordingly, informed consent was obtained from all the patients.

### Statistical analysis

The analyses were based on intention to treat approach in which all patients are analyzed according to randomization assignment. Baseline variables were compared using t-test or  $\chi^2$  test. The outcome of interest is the time to endpoint events. The cumulative hazards for each group were estimated using Kaplan-Meier method and were compared using log-rank test. Cox proportional hazard model was used to investigate hazard ratio with 95% confidence interval of aspirin dosing groups adjusted for potential confounders. For multivariate adjustment, those variables with *P* value less than 0.1 in univariate analysis were included in the model. Proportional hazard assumption was assessed using graphical approach and goodness of fit test. The global goodness of fit of the model was assessed using likelihood ratio test. All statistical analyses were performed using Stata/SE version (13).

## Results

Patient enrollment was begun in May 2011. Of 200 patients enrolled in the trial, three patients did not meet inclusion criteria, three patients did not accept to participate and 184 patients were randomly allocated to treatment. These patients were divided into two groups of 92 persons. Of these, 9 were excluded and 175 remained. The remaining patients were divided into two groups of 85 (received 81 mg dose), 90 (received 325 mg dose). Of 9 patients excluded from the study, one person died the first day after PCI. Eight patients did not receive allocated intervention. The flowchart of the patients included in the study is shown in [Figure 1](#).

The mean age of the patients was 57.8 years (SD = 12.4) with predominant percentage of male patients (74%). Baseline characteristic of patients is illustrated in [Table 1](#). The prevalence of conventional risk factors was similar in the two groups. One hundred thirteen patients received stent, as either Bare-metal stent (n = 72) or drug-eluting stent (n = 41). Only two patients received elective PCI. The time from randomization to PCI was the only variable with significant difference between the two groups. Though, the mean time from randomization to PCI in both groups was less than standard time of 90 minutes. Left anterior descending (LAD) followed by ramus was the most frequent vessels treated in both groups. The mean number of vessels treated in low-dose aspirin was significantly lower than high-dose aspirin ([Table 1](#)).

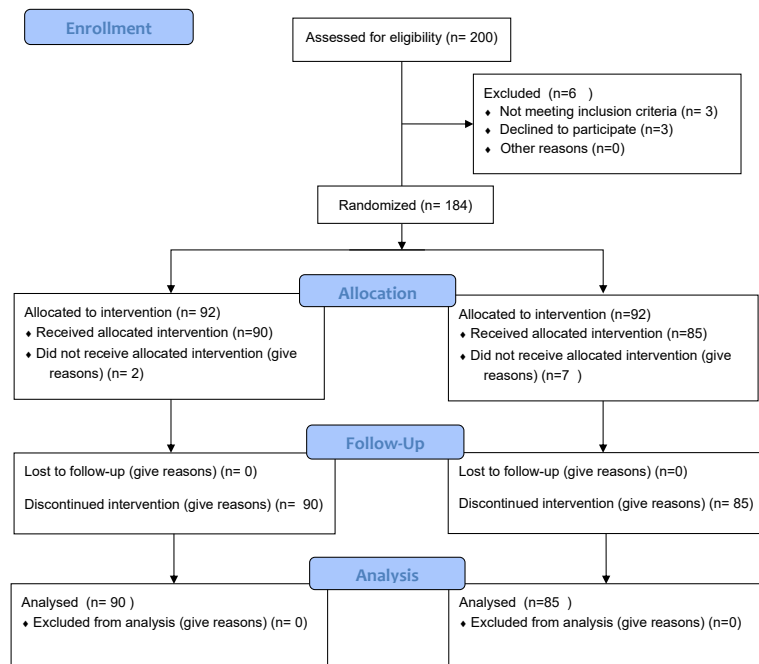


Figure 1. Flow diagram of the study.

Table 1. Baseline characteristic of patients randomized to high and low dose aspirin

	High-dose aspirin (n=90)	Low-dose aspirin (n=85)	P value
Age (y)	59.6 (1.29)	55.9 (1.35)	0.05
Male gender	64 (71)	65 (76)	0.42
Current smoking	30 (33)	40 (47)	0.06
Pack-year	23 (3)	25 (1.8)	0.64
Hypertension	36 (40)	31 (36)	0.63
Diabetes mellitus	20 (22)	25 (29)	0.28
Dyslipidemia	32 (35)	34 (40)	0.54
BMI (kg/m <sup>2</sup> )	27.1 (0.61)	26.9 (0.58)	0.81
History of MI	4 (4)	3 (3)	0.75
History of stroke	2 (2)	3 (3.5)	0.60
Ejection fraction <30	4 (5.5)	5 (6.7)	0.76
Troponin	51 (69)	41 (67)	0.83
Stent type			
DES	22 (39)	19 (34)	0.61
BMS	35 (61)	37 (66)	
No. of vessel treated	1.97 (0.11)	1.62 (0.1)	0.02
Vessels treated			
Left main	11 (13)	4 (4.9)	0.15
LAD	60 (67)	52 (61)	0.45
LCX	37 (43)	24 (29)	0.17
RCA	42 (49)	35 (43)	0.36
Ramus	2 (2.3)	2 (2.4)	0.92
Time from randomization to PCI (min)	65 (3.9)	80 (4.65)	0.02

Values are mean (SD) or No. (%).

BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, Left anterior descending; LCX, circumflex branch of the left coronary artery; RCA, right coronary artery, Ramus= A branch or subdivision arising from the division (bifurcation) of a blood or lymphatic vessel or a nerve.

A total of 175 person years were followed during one year, which major cardiovascular events (MACEs) occurred among 18 individuals of them. The median duration of follow-up was one year and the incidence rate of MACE was 13.07 per 100 person year in high-dose and 10.1 per 100 person year in low-dose aspirin (RR = 1.29, 95% CI = 0.51-3.28). The cumulative failure estimates of MACE during one year follow-up were 12% in high-dose aspirin compared to 9% in low-dose aspirin. Regarding safety outcomes, the incidence rate of bleeding was 6.5 and 5.2 per 100 person year in high-dose and low-dose aspirin, respectively (RR = 1.26, 95% = 0.34-4.69). There was no significant difference in cumulative failure rate between the two groups (Log rank P value = 0.77). Table 2 shows the frequency of efficacy and safety outcomes in the two groups. Most of the bleeding complications were related to GI bleeding. There were only three cases of genitourinary and skin bleeding occurred in high-dose and low-dose aspirin, respectively.

Multivariate adjustment for potential confounders showed no significant difference in the hazard of MACE between high-dose and low-dose aspirin (adjusted HR). The hazard of bleeding in high-dose group was not significantly different from low-dose aspirin (Table 2).

## Discussion

The finding of current double-blind randomized trial with one year complete follow-up revealed that patients in low-dose aspirin had similar long-term MACE compared to the high-dose group. This finding is in accordance with most of the previous observational studies and a randomized clinical trial which showed no significant

**Table 2.** Efficacy and safety outcome of patients randomized to high-dose and low-dose aspirin

	High dose aspirin n=90	Low dose aspirin n=85	Unadjusted HR 95% CI	Adjusted HR 95% CI
<b>MACE</b>	10 (11.2)	8 (9.4)	1.26 (0.49-3.19)	0.85 (0.29-2.45)
Death	6 (6.7)	3 (3.5)		
MI	0	1 (1.2)		
Stroke	0	1 (1.2)		
<b>Revascularization</b>				
CABG	3 (3.4)	2 (2.3)		
Stent	1 (1.1)	1 (1.2)		
<b>Major bleeding</b>	5 (5.6)	4 (4.7)	1.22 (0.33-4.53)	1.65 (0.41-6.69)

Values are No. (%).

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

reduction in cardiac outcome for high-dose compared to low dose aspirin (4-11).

Although aspirin is considered as the most frequent antiplatelet therapy in the setting of PCI for patients with acute coronary syndrome, there are scant randomized trials that compared different doses of aspirin directly. Previous randomized trial studies had the primary objective to compare different regimens of antithrombotic agents and assessed the efficacy and safety of aspirin (9,11,14-17). To our knowledge, this is the first randomized trial with primary goal to compare high-dose versus low-dose aspirin. All patients in this study received clopidogrel.

Regarding safety outcome in the present study, there was no difference in the rate of major bleeding. Previous studies showed inconsistent findings on the rate of bleeding as the major complication. Some observational studies assessing different aspirin doses found increased risk of major bleeding associated with higher dose of aspirin (6,7,18). There is also inconsistent finding on the rate of major bleeding as the safety outcome in two previous randomized trial studies (9,11). Some of discrepancies between studies regarding bleeding outcome might be explained by different types of bleeding definition. In this study we excluded occurrence of hematoma during surgery or recovery period. Yu et al found a significant difference in major bleeding between high-dose and low-dose aspirin in a non-randomized study (7). They considered access site hematoma as major bleeding while aspirin side effects might not be initiated immediately after consumption. However, our study is too small to detect significant differences if any, in the rate of bleeding outcome between the two groups.

Despite the consistent finding on similar efficacy outcome between high-dose and low-dose aspirin, there are still variations in recommended guidelines for patients with primary PCI at discharge. There are also regional disparities between clinicians in prescribing practice. Concerns of reduced efficacy for low-dose aspirin at the cost of higher bleeding complication for high-dose aspirin are the two major ambiguities for clinicians to prescribe a suitable dosage. Although this randomized trial with primary randomization of patients based on aspirin

dosage found no difference in efficacy and safety outcome, we recommend further randomized trials with larger sample size to detect any difference between the groups, with adequate power.

Though, due to low rate of events, it is estimated that over 11 000 patients would be required to show a benefit of high-dose over low-dose aspirin with adequate power (5). We also had about 20% lost to follow-up in each group. However, the distribution of baseline characteristics and conventional cardiovascular risk factors were not significantly different between lost to follow-up and complete follow-up patients.

### Conclusion

Efficacy and safety outcomes were not significantly different between high-dose and low-dose aspirin.

### Study limitations

The major limitation of current study is small sample size and limited number of available patients used for randomization.

### Authors' contribution

Study concept and design; AES and MP. Acquisition of data; FM and SFM. Statistical analysis; FM. Drafting of the manuscript; SFM and FM. Critical revision of the manuscript for important intellectual content by all authors. All authors read and approved the final version.

### Conflicts of interest

There is no conflict of interest in this study.

### Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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