# To Load or Not to Load? Aspirin Loading in Acute Ischemic Stroke: A Study of Clinical Outcomes

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*Background and purpose:* Aspirin is known to reduce mortality and recurrent vascular events. However, there are no reports about the dose–response of loading aspirin in treating acute ischemic stroke. The objective of this study was to compare the effectiveness of different loading doses of aspirin in acute ischemic stroke presenting within 48 hours of symptom onset. *Methods:* This was a retrospective, hospital-based cohort study. Patients were classified as high dose (160-325 mg) or low dose (<160 mg) based on the initial loading dose of aspirin at the emergency department. The primary outcome measure was a favorable modified Rankin Scale (mRS) score of 1 or lower on discharge. Secondary outcomes included in-hospital mortality, stroke progression during admission, and bleeding events. A propensity score with 1:3 matching was used to balance baseline characteristics, and stepwise multiple logistic regression was performed for variable adjustment. *Results:* From a total of 7738 available patients, 3802 patients were included. Among them, 750 patients were in the high-dose group. Multiple logistic regression after matching revealed that the high-dose group was significantly associated with a favorable clinical outcome on discharge (odds ratio: 1.49, 95% confidence interval: 1.17-1.89, $P < .01$), but not mortality or stroke progression. The high-dose group also experienced more minor bleeding events. *Conclusions:* A higher loading dose of aspirin (160-325 mg) can be beneficial in treating acute ischemic stroke, although there is an increased risk of minor bleeding. **Key Words:** Aspirin—acute stroke—treatment—loading dose—observational study.


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## Introduction

Aspirin, through its antiplatelet effects, can reduce mortality and risk of recurrent vascular events in the secondary prevention of ischemic stroke.[1,2] Current guidelines recommend loading of aspirin between 160 and 325 mg for acute ischemic stroke patients within 48 hours from symptom onset.[3-6] However, while the side effects of aspirin (e.g., gastrointestinal [GI] upset or bleeding events) are dose dependent, a wide range of aspirin doses seem equally effective in exerting its antithrombotic effect.[7,8] Although different loading doses of aspirin have been studied for the antithrombotic effect in laboratory settings,[9-11] to our knowledge, there have been no investigations of the effect on clinical outcomes. It is unknown whether administering a lower loading dose of aspirin for acute ischemic stroke could provide the same beneficial effects as the higher loading dose, but with fewer side effects.

The aim of the present study was to compare the clinical outcomes of patients with acute ischemic stroke who received different loading doses of aspirin, using a propensity score method.

## Methods

### *Data Collection and Patient Selection*

The present study was a retrospective analysis of prospectively registered data in the Chang Gung Memorial Hospitals from 2008 to 2012. We identified all hospitalizations through the emergency department (ED) indicating an initial diagnosis of ischemic stroke (the *International Classification of Disease-Ninth Revision* codes: 433, 434, 436, and 437.1) from the Stroke Registry in Chang Gung Healthcare System (SRICHS). SRICHS is an electronic chart-based registry system that, since 2007, has prospectively recorded clinical information, stroke-associated risk factors, disease severity scales, and etiologies of stroke on the basis of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[12] Details of SRICHS were published previously.[13]

In the present study, patients older than 20 years old were included if they presented to the ED within 48 hours of symptom onset. Patients were excluded if they were not prescribed aspirin or if they received thrombolytic agents, other anticoagulants, or dual antiplatelet agents in the ED. Patients with missing outcome records or patients enrolled in clinical trials were also excluded. For patients with multiple admission records that met our inclusion criteria, only the first admission was included in the analysis.

### *Clinical Profiles, Risk Factors, and Treatment Group Definitions*

Patients were classified into 2 groups based on the initial aspirin loading dosage at the ED: the high-dose group received 160-325 mg and the low-dose group received less than 160 mg. Both groups were given aspirin orally. The maintenance dose of aspirin was prescribed according to clinical guidelines and the physician's discretion, and was recorded as the aspirin mean daily maintenance dose (in milligram per day).

Baseline information, including age, sex, initial body temperature (BT), heart rate, blood pressure, Glasgow Coma Scale score, and body mass index, was recorded on admission. Stroke etiology by TOAST classification and stroke-associated risk factors and comorbidities were also recorded, the latter including history of diabetes mellitus (DM), hypertension, atrial fibrillation, dyslipidemia, previous stroke, chronic kidney disease, previous GI bleeding, cardiovascular disease including ischemic heart disease and congestive heart failure, and history of cigarette smoking. The diagnosis of DM was defined by either medical history, prior use of antidiabetic medication, or elevated in-hospital blood glucose (fasting glucose level ≥126 mg/dL, random glucose level ≥200 mg/dL, or glycosylated hemoglobin [Hb] level ≥6.5%). Hypertension was considered to be presented when a patient has known hypertension history, prior use of antihypertensive medications, or if blood pressure is 140/90 mmHg or above on the average of 2 measurements. Atrial fibrillation was recorded if there were positive findings on baseline electrocardiography or 24-hour Holter monitor. Dyslipidemia would be recorded by positive history, associated medications, or abnormal lipid profile routinely checked during admission. Previous stroke, GI bleeding, or cardiovascular disease would be recorded by positive history or associated drug prescriptions. Chronic kidney disease would be identified by routinely checked renal function during admission or by medical history. Prior antiplatelet or statin use was determined by prescription history up to 6 months before the incidence of stroke. Laboratory results, including hemograms and biochemistry data, were recorded if collected within 24 hours of admission. Fasting serum glucose level and lipid profiles including total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein levels were measured on the first working morning after the patients were admitted to the hospital.

### *Outcomes*

The primary outcome measure of the present study was a favorable clinical outcome, defined as a modified Rankin Scale (mRS) score of 1 or lower on discharge. The secondary outcomes included in-hospital mortality, stroke progression during admission, and bleeding events. Stroke progression was defined as an increase of at least 4 points on the National Institutes of Health Stroke Scale (NIHSS) score on discharge compared with the initial score on admission. Both the mRS and the NIHSS scores were assessed by trained physicians or neurologists.