

# Influence of Antiplatelet Drugs on the Outcome of Subarachnoid Hemorrhage Differs with Age

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*Background:* The aim of this study was to examine the risk factor profiles and functional outcomes of subarachnoid hemorrhage (SAH) in different age groups, focusing on the effect of antiplatelet drugs when used before stroke. *Methods:* A total of 5344 patients with SAH were included in a multicenter, hospital-based registration study involving 95 Japanese institutes from 2000 to 2012. Patients' profiles and use of antithrombotic agents were retrospectively reviewed. A modified Rankin Scale score of 4 or more at discharge was defined as poor outcome. *Results:* The frequency of antithrombotic agent use increased with age; it reached its peak (10.9%) among patients in their 80s and remained constant at 7.5% for those 90 years or older. Poorer outcomes were evident as age increased. The frequency of hypertension increased with age, whereas current smoking and heavy drinking reached its peak among patients in their 40s and 50s, respectively. The use of antiplatelet agents significantly improved outcome in patients younger than 60 years ( $P = .04$ ). In contrast, in the older group ( $\geq 60$  years), the use of antiplatelet agents tended to worsen the outcome; patients aged 70-79 years who had used these agents had a significantly worse outcome compared with those who had not ( $P = .03$ ). *Conclusions:* In the present study, the influence of antiplatelet agents was different among age groups. The potential beneficial effects of antiplatelet agents must be weighed against their potential adverse effects in the context of SAH, considering the differences in age-related outcomes. **Key Words:** Age stratification—subarachnoid hemorrhage—antiplatelet drugs—Japanese.

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## Introduction

Subarachnoid hemorrhage (SAH) accounts for 5.5% of all strokes in Japan,<sup>1</sup> but its relative impact is significant. The incidence of SAH in Japan has been reported to be one of the highest in the world.<sup>2</sup> In the past, SAH was

considered a potentially fatal disease that mainly affected middle-aged patients (<60 years).<sup>3</sup> Because of better general health and improved life expectancy, however, the number of elderly patients with SAH is increasing. Compared with younger age groups, older age groups have different stroke risk profiles and clinical features, but only a few studies on SAH have compared different age groups.<sup>4,5</sup> Furthermore, the influence of antiplatelet drugs before onset of SAH has not been clearly determined—some studies have indicated that aspirin protected brain from cerebral aneurysm rupture,<sup>6-8</sup> whereas another showed it increased rebleeding rates.<sup>9</sup> The aim of the present study was to examine the risk factor profiles and functional outcomes of SAH among different age groups using the Japan Standard Stroke Registry Study database.<sup>1</sup> Particular focus was placed on the effect of antiplatelet drug use before onset of SAH.

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## Methods

The Japan Standard Stroke Registry Study is an ongoing multicenter stroke registration study based on a computerized database involving 95 Japanese institutes.<sup>1</sup> From January 2000 to December 2012, 101,164 patients with acute stroke were registered. Among them, 5334 patients with SAH were enrolled in the present study.

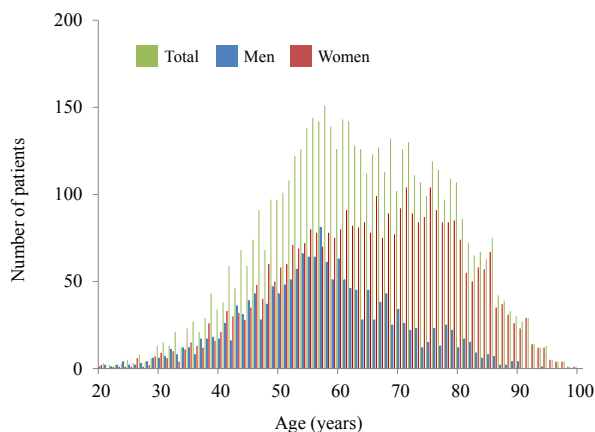
Data on patients' characteristics (age and sex) and underlying risk factors, such as hypertension, current smoking, and heavy drinking (>46 g of alcohol/d), were retrospectively reviewed. Use of antithrombotic (antiplatelet and/or anticoagulant) agents before stroke was also assessed. Patients were assessed according to a modified Rankin Scale at discharge and those with a score of 4 or more were defined as having a poor outcome. Data obtained during the study period were analyzed and compared among different age groups.

Outcomes in antiplatelet users and nonusers were compared using the chi-square tests or Fisher exact tests when sample sizes were limited. Probability values were considered statistically significant at *P* values less than .05.

## Results

Of the 5344 enrolled patients, 1772 were men and 3572 were women. Their sex and age distributions are shown in Figure 1. The peak age of stroke onset was higher for women than for men ( $65.2 \pm 14.3$  and  $57.0 \pm 13.1$  years, respectively). The female/male ratio increased from 1.2:1 in patients younger than 60 years to 3.3:1 in those older than 60 years.

Figure 2 shows the frequencies of hypertension, current smoking, heavy drinking, and use of antithrombotic agents in different age groups. The frequency of hypertension increased with age (Fig 2, A). In contrast, the fre-



**Figure 1.** Age and sex distribution of Japanese patients with subarachnoid hemorrhage (SAH). The occurrence of SAH peaked in the 50s for men and 70s for women.

quency of current smoking decreased with age (Fig 2, B). The frequency of heavy drinking reached its peak among patients in their 50s and decreased thereafter (Fig 2, C). The frequency of antithrombotic agent use increased with age; peak use (10.9%) occurred among patients in their 80s, and it remained constant at 7.5% in patients older than 90 years (Fig 2, D).

Figure 3 shows the percentage of poor functional outcomes at discharge by age group, depicting outcome comparisons among patients who used antiplatelet agents before stroke and those who did not. Poorer outcomes were evident with an increase in age. In the younger than 60-year age group, the use of antiplatelet agents significantly improved the prognosis (*P* = .04). In contrast, in the older group ( $\geq 60$  years), the use of antiplatelet agents tended to make the prognosis worse: patients aged 70-79 years who had used antiplatelet agents had a significantly worse outcome compared with patients who had not used antithrombotic drugs (*P* = .03).

## Discussion

This was a nationwide, multicenter registration study investigating how age affects the characteristics and functional outcomes of Japanese patients with SAH. In the present study, the younger patients taking antiplatelet agents had a significantly improved outcome compared with those who did not, whereas older patients taking antiplatelet agents were more likely to have poorer outcome.

Consistent with the results from this study, increasing age is a known risk factor for poor outcome after aneurysmal SAH.<sup>4,5</sup> One study has also demonstrated that anticoagulant therapy is associated with a worse outcome.<sup>10</sup> However, the influence of antiplatelet use on outcome after SAH is less clear. For instance, a few studies failed to reveal any significant impact of pre-hemorrhage aspirin use on outcome after aneurysmal SAH.<sup>8,9</sup> In the present study, the influence of antiplatelet agents was found to differ among age groups.

This is the first study to report that pre-hemorrhage antiplatelet use significantly improved prognosis, albeit only in younger patients (<60 years). In previous studies, the trend toward reduced risk of SAH was particularly pronounced in patients receiving aspirin.<sup>6-8</sup> The underlying mechanisms associated with reduced risk were attributed to a possible inhibitory effect of aspirin on the inflammatory cascade implicated in intracranial aneurysmal formation<sup>11</sup>—the cause of SAH in approximately 85% of cases.<sup>12</sup> These data suggested that aspirin may potentially be used as therapeutic agent to prevent intracranial aneurysm growth and rupture.<sup>13</sup> Based on the available data, one hypothesis that merits testing is that aspirin, when taken in advance, may also ameliorate symptoms in cases where it cannot be prevented.

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