Impact of aspirin on the prognosis in patients with coronary spasm without significant atherosclerotic stenosis

Masanobu Ishii [a], Koichi Kaikita [a,*], Koji Sato [a], Kenshi Yamanaga [a], Takashi Miyazaki [a], Tomonori Akasaka [a], Noriaki Tabata [a], Yuichiro Arima [a], Daisuke Sueta [a], Kenji Sakamoto [a], Eiichiro Yamamoto [a], Kenichi Tsujita [a], Megumi Yamamuro [a], Sunao Kojima [a], Hirofumi Soejima [a], Seiji Hokimoto [a], Kunihiko Matsui [b], Hisao Ogawa [a]

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[b] Department of General and Community Medicine, Kumamoto University Hospital, Kumamoto, Japan

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ABSTRACT

Background: Coronary spasm is one of the mechanisms of myocardial infarction with nonobstructive coronary arteries (MINOCA). The aim of this study was to investigate the effects of aspirin on future cardiovascular events in patients with coronary vasospastic angina (VSA) with non-significant atherosclerotic stenosis.
Methods: This was the retrospective analysis of the 640 VSA patients with non-significant atherosclerotic stenosis (≤50% stenosis) among 1,877 consecutive patients who underwent acetylcholine (ACh)-provocation testing between January 1991 and December 2010. The patients were divided into 2 groups treated with ($n = 137$) or without ($n = 503$) low-dose aspirin (81–100 mg/day). We evaluated major adverse cardiac events (MACE), defined as cardiac death, nonfatal myocardial infarction, and unstable angina.
Results: In the study population, 24 patients (3.8%) experienced MACE; there were 6 cases in VSA patients with aspirin and 6 in those without aspirin. Multivariate Cox hazards analysis for correlated factors of MACE indicated that use of statin (HR: 0.11; 95% CI: 0.02 to 0.84; $P = 0.033$), ST-segment elevation during attack (HR: 5.28; 95% CI: 2.19–12.7; $P < 0.001$), but not the use of aspirin as a significant predictor of MACE. After propensity score matching ($n = 112$, each), Kaplan–Meier survival analysis indicated almost identical rate of 5-year survival free from MACE in those with aspirin, compared to those without aspirin in the entire and matched cohort ($P = 0.640$ and $P = 0.541$, respectively).
Conclusions: Low-dose aspirin might not reduce future cardiovascular events in VSA patients with non-significant stenosis.

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1. Introduction

Coronary spasm is involved in the pathogenesis of variant angina and ischemic heart disease (IHD), which is one of the particular causes of myocardial infarction with nonobstructive coronary arteries (MINOCA) [1,2]. Previous reviews showed that patients with MINOCA were more likely to be younger females, less likely to have dyslipidemia, and had identical prevalence of other cardiovascular risk factors compared to MI with obstructive coronary artery disease (CAD), and that 27% of those were caused by coronary spasms [1]. In the pathogenesis of MI with obstructive CAD, coronary spasm is also involved. Although vulnerable plaques, such as plaque rupture, plaque erosion, and calcified nodules, play a major role in the pathogenesis of MI with obstructive CAD [3], coronary spasm is suspected as one of the causes of plaque rupture [4] and plaque erosion [5]. In addition to the above mechanism, thrombus formation is a crucial mechanism of MI with or without obstructive CAD. Low-dose aspirin reduces the production of thromboxane A2 by inhibiting cyclooxygenase-1, resulting in the prevention of thrombosis, and is widely used in management of patients with ischemic stroke [6], chronic stable angina [7], acute coronary syndrome [8,9], and secondary prevention of MI with obstructive CAD [10]. However, it is not clear whether aspirin therapy suppresses future cardiovascular events in patients with coronary vasospastic angina (VSA). The purpose of the present study was to investigate the prognosis in VSA patients with non-significant atherosclerotic stenosis treated with or without low-dose aspirin.

2. Methods

2.1. Study population and acetylcholine provocation test

This retrospective analysis was a sub-analysis of our previous studies [11–14]. Briefly, we enrolled 1,877 consecutive Japanese patients who had angina-like chest discomfort

* Corresponding author at: Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
E-mail address: kaikitak@kumamoto-u.ac.jp (K. Kaikita).

and underwent acetylcholine (ACh)-provocation testing at Kumamoto University Hospital between January 1991 and December 2010. After exclusion of 475 patients (obstructive CAD; $n = 358$, acute MI; $n = 20$, cardiomyopathy; $n = 75$, Brugada syndrome; $n = 10$, and others; $n = 12$), we analyzed 640 VSA patients (Fig. 1) from the remaining 1,402 patients with non-significant atherosclerotic stenosis (≤50% stenosis defined by the American Heart Association classification [15]), and divided them into 2 groups treated with or without low-dose aspirin (81–100 mg/day). We performed ACh-provocation testing as described previously in the VSA Guideline by the Japanese Circulation Society [16], and defined coronary spasm as total or subtotal obstruction within the borders of a single isolated coronary segment, or severe diffuse vasoconstriction observed in more than 2 adjacent coronary segments associated with transient myocardial ischemia, as evidenced by ischemic ST-segment changes on the electrocardiogram, as described previously [11–14].

The study protocol was approved by the Human Ethics Review Committee of Kumamoto University and a signed consent form was obtained from each subject.

2.2. Follow-up and endpoints

Follow-up data were collected from the information available on the medical records, the patients, their families, and their family physicians. We defined the primary endpoint as major adverse cardiac events (MACE), including cardiac death, non-fatal acute myocardial infarction (AMI), and unstable angina, and the secondary endpoint as all-cause death during the follow-up period (from the date of diagnosis to the date of the first event or until December 2012) as previously described [11–14].

2.3. Statistical analysis

To reduce the effect of treatment-selection bias and possible confounders, we performed a propensity score-matched analysis. The predicted probability of use of aspirin was calculated by fitting a logistic regression model, using all clinically relevant variables as age, gender, current smoking, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, diffuse spasm, chest pain at rest only, low-density lipoprotein cholesterol, and statins use. One patient with aspirin was matched to one patient without aspirin using nearest-neighbor matching within a caliper width of 0.01 without replacement. Variables were compared with the chi-square test of Fisher's exact test, the unpaired t test or Mann–Whitney U test, and the log-rank test for MACE-free survival curves, as appropriate. Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95%

confidence intervals (CI) as estimates for the endpoint. The HRs were adjusted for clinical characteristics, angiographic findings, and medication according to the univariate analysis for the endpoint. Aspirin use and variables with $P < 0.05$ on the univariate analysis were entered into the multivariate model using the stepwise backward selection and forced entry method. A two-tailed P-value of <0.05 denoted the presence of a statistically significant difference. All statistical analyses were performed with The Statistical Package for Social Sciences software version 23.0 (IBM Corporation, Armonk, New York).

3. Results

In the study population, 137 of 640 VSA patients were treated with aspirin for primary and secondary prevention of cardio-cerebral-vascular disease, and 503 of those were not. The patients with aspirin were older, more likely to have diabetes, hypertension, dyslipidemia, CKD, ACE inhibitor use, ARB use, and statin use, and less likely to have diffuse spasm, compared to those without aspirin (Table 1). Twenty-four patients (3.8%) experienced the primary endpoints, which were 2 cases of cardiac death and 4 of unstable angina in VSA patients with aspirin, and 1 of cardiac death, 2 of non-fatal MI, and 15 of unstable angina in those without aspirin (Table 2). Multivariate Cox proportional hazards analyses for correlated factors of MACE indicated that use of statin as a significant negative correlate of MACE (HR: 0.11; 95% CI: 0.02 to 0.84; $P = 0.033$) and ST-segment elevation during angina attack as a significant positive correlate of MACE (HR: 5.28; 95% CI: 2.19–12.7; $P < 0.001$) in stepwise selection model (Table 3). However, aspirin was not a significant correlated factor of MACE in each model (Table 3).

After propensity score matched analysis, 112 matched pairs of patients were identified. For the logistic regression model to estimate propensity score, Hosmer–Lemeshow goodness of fit chi-square was 9.414 with a P value of 0.309 and area under the curve of receiver operating characteristic curve was 0.711. There were no significant
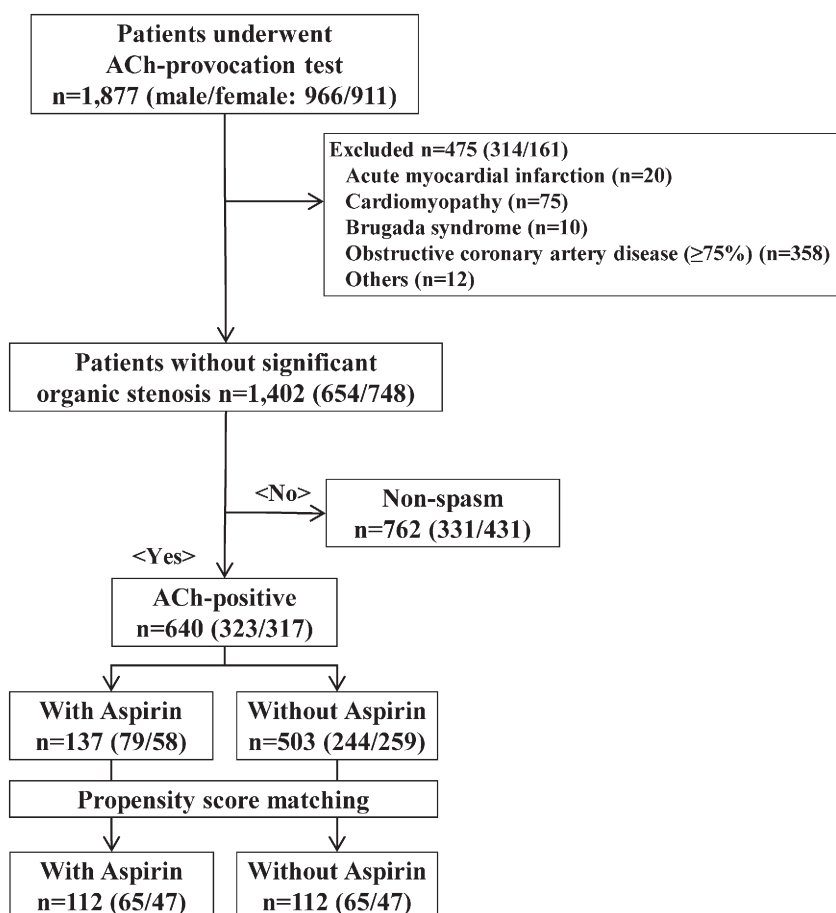
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┌─────────────────────────────────┐
│    Patients underwent           │
│    ACh-provocation test         │
│ n=1,877 (male/female: 966/911)  │
└─────────────────────────────────┘
        │
        │        ┌────────────────────────────────────────────────┐
        │───────▶│ Excluded n=475 (314/161)                       │
        │        │    Acute myocardial infarction (n=20)          │
        │        │    Cardiomyopathy (n=75)                       │
        │        │    Brugada syndrome (n=10)                     │
        │        │    Obstructive coronary artery disease         │
        │        │    (≥75%) (n=358)                              │
        │        │    Others (n=12)                               │
        │        └────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────┐
│ Patients without significant    │
│ organic stenosis n=1,402 (654/748) │
└─────────────────────────────────┘
        │
        │   <No>   ┌──────────────────┐
        │─────────▶│  Non-spasm       │
        │          │ n=762 (331/431)  │
        │ <Yes>    └──────────────────┘
        ▼
┌─────────────────────────────────┐
│      ACh-positive               │
│    n=640 (323/317)              │
└─────────────────────────────────┘
    │                    │
    ▼                    ▼
┌──────────────┐  ┌──────────────────┐
│ With Aspirin │  │ Without Aspirin  │
│ n=137 (79/58)│  │ n=503 (244/259)  │
└──────────────┘  └──────────────────┘
        │                 │
        ▼                 │
┌─────────────────────────────────┐
│    Propensity score matching    │
└─────────────────────────────────┘
    │                    │
    ▼                    ▼
┌──────────────┐  ┌──────────────────┐
│ With Aspirin │  │ Without Aspirin  │
│ n=112 (65/47)│  │ n=112 (65/47)    │
└──────────────┘  └──────────────────┘
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Fig. 1. Flow chart of the patient recruitment process. The chart shows enrollment criteria and flow of patients.