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Clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis; a propensity score-matched analysis

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ABSTRACT

Background: High-dose aspirin has been reported to exacerbate coronary artery spasm in patients with vasospastic angina. We investigated clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis.

Methods: We included patients without significant coronary artery stenosis on coronary angiography (CAG) and with positive results on intracoronary ergonovine provocation test between January 2003 and December 2014. A total of 777 patients were divided into two groups according to prescription of low-dose aspirin at discharge: aspirin group (n = 321) and non-aspirin group (n = 456). The major adverse cardiovascular events (MACE), defined as composite outcomes of cardiac death, acute myocardial infarction, revascularization, or rehospitalization requiring CAG or medication change due to recurrent angina were compared.

Results: The aspirin group had significantly higher incidence of MACE (22.8% versus 12.1%; p = 0.04) and had higher tendency for rehospitalization (20.6% versus 11.2%; p = 0.08). All-cause mortality and cardiac death were similar between the two groups. After propensity score matching, the aspirin group had greater risk of MACE (hazard ratio [HR] 1.54; 95% confidence interval [CI], 1.04–2.28; p = 0.037) and rehospitalization requiring CAG (HR, 1.33; 95% CI, 1.13–4.20; p = 0.03), and a higher tendency for rehospitalization (HR, 1.40; 95% CI, 0.94–2.09; p = 0.12).

Conclusion: In vasospastic angina without significant coronary artery stenosis, patients taking low-dose aspirin are at higher risk of MACE, driven primarily by tendency toward rehospitalization. Low-dose aspirin might be used with caution in vasospastic angina patients without significant coronary artery stenosis.

1. Introduction

Aspirin is widely used in patients with cardiovascular disease. Although new P2Y12 inhibitors have been used for acute coronary syndromes, aspirin is still essential for the management of significant coronary artery diseases including stable angina [1,2], acute coronary syndrome [3,4] as well as ST-elevation myocardial infarction [5,6]. For primary prevention, however, the efficacy and safety of aspirin is substantially uncertain in patients without vascular disease [7]. In addition, high-dose aspirin could aggravate coronary artery spasm in patients with vasospastic angina [8–11]. Recent study also proposed that low-dose aspirin was associated with frequent coronary artery spasm in patients with vasospastic angina [12]. However, there are limited data about long-term outcomes of the use of low-dose aspirin in patients with vasospastic angina [13]. Therefore, we sought to investigate the clinical implications of low-dose aspirin on vasospastic angina patients without significant coronary artery stenosis.

2. Methods

2.1. Study population

Fig. 1 is a flow chart of this study. A total of 1198 patients with positive results on intracoronary ergonovine provocation testing at Samsung Medical Center between January 2003 and December 2014 were enrolled. Among them, patients who had history of

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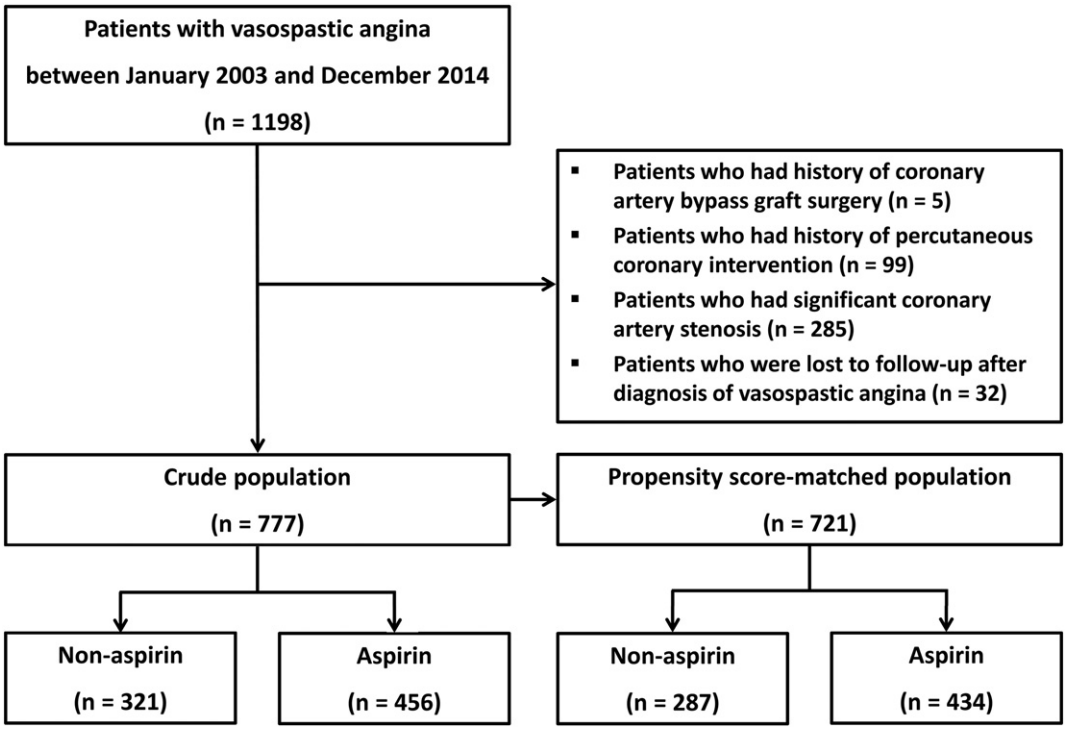

Fig. 1. Study population.

bypass graft surgery (n = 5) or percutaneous coronary intervention (n = 99) were excluded. Patients who had significant coronary artery stenosis defined as more than 50% diameter stenosis in major epicardial coronary arteries by visual estimation on coronary angiography (CAG) (n = 285) were excluded. Thirty-two patients who were refused to follow-up after diagnosis of vasospastic angina were also excluded. The remaining 777 patients were divided into two groups according to prescription of low-dose aspirin at discharge. This study was approved by the Samsung Medical Center Institutional Review Board, and was conducted according to the Declaration of Helsinki. A waiver of consent was granted, given the retrospective nature of the project.

2.2. Provocation test and definition for vasospastic angina

A spasm provocation test was performed with intracoronary ergonovine injection after baseline CAG. Incremental doses of 20, 40, and 80 μg were injected into the left coronary artery and 10, and 20 μg were injected into the right coronary artery. If coronary spasm was induced, intracoronary nitrate was injected. Vasoactive drugs including nitrates, nicorandil and calcium channel blockers were withheld at least 48 h before CAG.

Vasospastic angina was diagnosed if patients had a significant vasospasm, defined as transient, total or subtotal occlusion (>90% diameter stenosis) of the coronary arteries after intracoronary ergonovine injection in addition to ischemic symptoms and/or electrocardiographic changes. An electrocardiographic change was defined as ST-segment elevation, depression (≥1 mm), or T-wave inversion in at least two consecutive leads. Multivessel spasm was defined as coronary artery spasm in more than two major epicardial coronary arteries, and spontaneous spasm was defined as >90% diameter stenosis on baseline CAG and relieved after intracoronary nitrate injection. The degree of coronary artery stenosis was evaluated by visual estimation.

2.3. Study outcomes

The primary outcome was major adverse cardiovascular events (MACE), defined as cardiac death, acute myocardial infarction, revascularization, or rehospitalization due to recurrent angina. All deaths were considered cardiac unless a definite non-cardiac cause could be established. Myocardial infarction was defined as both elevation of cardiac biomarkers above the 99th percentile upper reference limit and at least one of the following: ischemic symptoms, new significant ST-T changes, new left bundle branch block, development of pathologic Q on electrocardiography, imaging evidence of loss of viable myocardium or regional wall motion abnormality, and identification of a thrombus by CAG [14]. Revascularization was defined as any revascularization of an epicardial coronary artery by percutaneous coronary intervention or bypass graft surgery. Rehospitalization was defined as any hospitalization after the index hospital discharge due to recurrent angina including any of the following symptoms: typical chest pain, atypical chest pain, dyspnea, syncope, palpitations, and aborted cardiac arrest [2]. Rehospitalization was classified based on whether or not patients required CAG or medication adjustment only during rehospitalization. The incidence of all-cause death was analyzed as a secondary outcome.

2.4. Statistical analysis

Continuous variables are shown as median (25th–75th percentiles), and categorical variables as numbers and percentages. Group comparisons were performed using the chi-square test, Fisher's exact test or Student's t-test as appropriate. Univariate and multivariate Cox proportional hazard models were used to compare the prevalence of adverse events between the aspirin and non-aspirin groups. Event-free survival was determined by the Kaplan–Meier method and compared using the log-rank test. For multiple risk factor analysis, initially considered covariates included previous aspirin treatment, sex, age, initial presentation of cardiac arrest, diabetes, hypertension, current smoking, dyslipidemia, coronary stenosis in spasm-positive vessels, statin, calcium channel blockers, nitrates or nicorandil, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Hazard ratios (HR) and 95% confidence intervals (CI) were also calculated. We used propensity score matching to balance intergroup differences. Upon matching propensity scores, we created 434 patients in the aspirin group and 287 patients in the non-aspirin group. The adequacy of the propensity matching method was evaluated by the overall balance achieved in terms of a less than 0.1 standardized mean difference. We also assessed the overall discrepancy score between groups (chi-square = 3.25, df = 8.0, and p = 0.918). Since balance was achieved, the matched data set was analyzed using a univariate Cox regression model for each clinical outcome, resulting HR and 95% CI. All tests were two sided, and p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using R 3.2.0 (R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Among the 777 patients enrolled, 456 patients (58.7%) were treated with aspirin. Table 1 shows baseline characteristics of patients with vasospastic angina according to prescription of low-dose aspirin. There were no significant differences in coronary risk factors or laboratory findings between the two groups. Patients in cardiac arrest at initial presentation were less common in the aspirin group (2.2% versus 5.6%, p = 0.012). Patients who had previously been treated with aspirin were more common in the aspirin group than in the non-aspirin group (22.4% versus 11.5%, p < 0.001). Statins, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were more commonly prescribed at discharge in the aspirin