Journal of Cardiology 65 (2015) 197–202

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Major bleeding complications related to combined antithrombotic therapy in atrial fibrillation patients 12 months after coronary artery stenting

Hideki Kawai (MD, PhD)[a,*], Eiichi Watanabe (MD, PhD)[a], Mayumi Yamamoto (MD)[a], Hiroto Harigaya (MD, PhD)[b], Kan Sano (MD, PhD)[c], Hidemaro Takatsu (MD)[d], Takashi Muramatsu (MD, PhD)[a], Hiroyuki Naruse (MD, PhD)[a], Yoshihiro Sobue (MD, PhD)[a], Sadako Motoyama (MD, PhD)[a], Masayoshi Sarai (MD, PhD)[a], Hiroshi Takahashi (BSc)[e], Tomoharu Arakawa (MD, PhD)[d], Shino Kan (MD)[b], Atsushi Sugiura (MD, PhD)[c], Toyoaki Murohara (MD, PhD)[f], Yukio Ozaki (MD, PhD, FJCC)[a]

[a] Department of Cardiology, Fujita Health University, Toyoake, Japan
[b] Department of Cardiology, Nagoya Memorial Hospital, Nagoya, Japan
[c] Department of Cardiology, Hekinan Municipal Hospital, Hekinan, Japan
[d] Department of Cardiology, Daido Hospital, Nagoya, Japan
[e] Department of Medical Statistics, Fujita Health University, Toyoake, Japan
[f] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

ARTICLE INFO

Article history:
Received 21 April 2014
Received in revised form 21 August 2014
Accepted 30 August 2014
Available online 26 September 2014

Keywords:
Antithrombotic therapy
Atrial fibrillation
Coronary artery stent

ABSTRACT

Background and purpose: Many patients with atrial fibrillation (AF) and coronary artery stent deployment are given both antiplatelet drug and warfarin. Little information is available as to the relationship between the antithrombotic therapies in the late phase after stenting and the clinical outcomes of these patients. We examined the clinical outcomes of AF patients 12 months after coronary artery stenting.
Methods: We retrospectively examined 146 patients and classified them into three groups according to the antithrombotic therapies [dual antiplatelet therapy (DAPT), single antiplatelet therapy (SAPT) plus warfarin, and DAPT plus warfarin] 12 months after stenting. We defined the primary endpoint as Thrombolysis in Myocardial Infarction major bleeding and the secondary endpoint as a composite of adverse events (CAE: all-cause death, nonfatal myocardial infarction, intracranial bleeding, and cerebral infarction).
Results: During a median follow-up of 37 months, major bleeding and CAE were observed in 14 (9.6%) and 46 (31.5%) patients, respectively. DAPT plus warfarin was an independent risk factor for major bleeding in a multivariate Cox hazard regression model after adjustment for age, gender, and the type of AF (hazard ratio: 4.20; 95% confidence interval: 1.13–17.27; $p = 0.033$). No significant clinical variables were found for CAE.
Conclusions: Prolonged use of DAPT with warfarin significantly increases the risk of major bleeding in AF patients after coronary artery stenting. Individualized antithrombotic treatment is required in these patients to prevent major bleeding.

Introduction

Atrial fibrillation (AF), the most common arrhythmia, is a leading cause of stroke, and is associated with increased mortality [1]. Long-term treatment with oral anticoagulants was shown to be effective to prevent thromboembolic episodes in AF patients [2]. Patients with AF often have coronary artery disease (CAD), and thus, an indication for platelet inhibitor therapy. The number of patients requiring prolonged dual antiplatelet therapy (DAPT) to

* Corresponding author at: 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. Tel.: +81 562 93 9298; fax: +81 562 93 2315.
E-mail addresses: hkawai@fujita-hu.ac.jp, hidekikawai@xc4.so-net.ne.jp (H. Kawai).

http://dx.doi.org/10.1016/j.jjcc.2014.08.013
0914-5087/

prevent stent thrombosis has been increasing since the introduction of drug-eluting stents (DES) [3].

Several sets of guidelines are available regarding the antithrombotic regimen in AF patients after coronary artery stenting [4,5], but there is no sufficient evidence about it in the late period. Furthermore, the prognosis of AF patients complicated with CAD has not been fully clarified, especially in Japan, where the prevalence of CAD and the incidence of late stent thrombosis after coronary artery stenting are lower, and the incidences of cerebral infarction and major bleeding due to antithrombotic agents are higher than in western countries [6–9]. We examined the current practice of concomitant antithrombotic therapy and its association with clinical outcomes among AF patients after deployment of coronary artery stent.

Methods

Patients

We retrospectively studied AF patients who were discharged alive after coronary artery stenting from October 2004 to May 2012 in Fujita Health University, Nagoya Memorial Hospital, Daido Hospital, and Hekinan Municipal Hospital. We excluded patients who died within 12 months of percutaneous coronary intervention (PCI) or were lost to follow-up. We examined the antithrombotic agents at 12 months after PCI, and divided patients into four groups: single antiplatelet therapy (SAPT); SAPT plus warfarin; DAPT; and DAPT plus warfarin. We analyzed patients within three groups after excluding SAPT group, since many patients in SAPT group have their own reasons for refraining from combined antithrombotic therapy, such as known severe bleeding disorders or other critical diseases with poor prognosis.

AF was defined as described in the European Society of Cardiology guidelines for management of AF. Paroxysmal AF was defined as self-terminating, usually within 48 h. Persistent AF was present when an AF episode either lasted longer than 7 days or required termination by cardioversion. Long-standing persistent AF has lasted for $\geq$1 year when it is decided to adopt a rhythm control strategy. Permanent AF was defined as existing when the presence of the arrhythmia was accepted by the patient and physician [4].

Hypertension was defined as current systolic/diastolic blood pressure >140/90 mmHg or use of antihypertensive agents. Dyslipidemia was defined as low-density lipoprotein cholesterol >140 mg/dl or triglycerides >200 mg/dl or use of cholesterol-lowering agents. Diabetes mellitus (DM) was considered present if the patient was taking insulin or oral hypoglycemic agents or had previously been diagnosed as having DM. We calculated the estimated glomerular filtration rate (eGFR) using an equation modified by the Japanese Society of Nephrology [10] and chronic kidney disease (CKD) was defined as eGFR <60 ml/min. A history of deployment of DES, prior myocardial infarction, and prior cerebral infarction was based on the medical records. We used the $CHADS_2$ score [11] (an acronym for Congestive heart failure, Hypertension, Age $\geq$75, Diabetes, Stroke or transient ischemic attack) as a measure of the stroke risk, and the HAS-BLED score [12] [an acronym for Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly (age >65 years), and Drug consumption/alcohol abuse] as that of the bleeding risk of the studied patients. Labile INR in the patients who had not been initiated warfarin was calculated as 0 point [13].

Follow-up and endpoints

Research coordinators and physicians recorded baseline data for all patients at the time of discharge from hospital. During the follow-up period, patients or their families were periodically sent a questionnaire and interviewed by telephone. Members of the events verification committee who were blinded to the antithrombotic therapy reviewed medical records. Patients were censored when antithrombotic agents were changed or discontinued; however we continued follow-up when the antithrombotic regimen was temporarily discontinued because of surgery or invasive examination. The study protocol was approved by the institutional review board and patients gave written informed consent at discharge from hospital.

We defined the primary endpoint as a major bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria [14,15], and the secondary endpoint as a composite of adverse events (CAE; i.e. all-cause death, nonfatal myocardial infarction, intracranial bleeding, and cerebral infarction). Cardiovascular causes of death include myocardial ischemia/infarction, heart failure, or lethal arrhythmia. Nonfatal myocardial infarction was defined as myocardial ischemia resulting in abnormal cardiac biomarkers (>99th percentile of the upper normal limits), together with evidence of myocardial ischemia with at least one of the following: clinical symptoms, electrocardiographic changes (new ST–T changes or new left-bundle-branch block), development of pathological Q waves, or new loss of viable myocardium or new regional wall-motion abnormality on imaging [16,17]. Stroke was defined as focal loss of neurological function caused by an ischemic or hemorrhagic event and diagnosed by a neurologist.

Statistical analysis

All data were presented as the mean $\pm$ SD for continuous variables and frequency (percentage) for categorical variables. Differences among three groups were evaluated by one-way analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables and by chi-square test for categorical variables. The incidence of events was assessed in univariate and multivariate models. Risk adjusted analyses were performed with Cox proportional hazard models to determine the independent prognostic value of major bleeding. Cumulative event rates were estimated with the Kaplan–Meier method and were compared with the log-rank test. All analyses were performed with JMP Version 10 (SAS Institute Inc., Cary, NC, USA) and a p-value of <0.05 was considered as statistically significant.

Results

Patients

We examined 177 patients (mean age 72.0 $\pm$ 8.1 years, 72.9% male, 58.8% using DES, 51.4% paroxysmal AF) 12 months after PCI, after excluding 9 patients who had died within 12 months of PCI, and 7 lost to follow-up. The nine dead patients included two patients with cardiac death, four with stroke death, one with peripheral artery thrombosis, and two with noncardiovascular death. On the basis of the antithrombotic agents at discharge, all patients were classified into the three groups, although no patients were in the SAPT group. At 12 months after PCI, 146 patients were classified into the three groups after 31 patients in SAPT were excluded as described in methods. The number of patients continuing DAPT decreased at 12 months after PCI, although that of those taking SAPT and warfarin increased (Fig. 1). Among the three groups, there were significant differences in the type of AF ($p = 0.0006$), deployment of DES ($p < 0.0001$), cerebral infarction ($p = 0.015$), and HAS-BLED score $\geq$3 ($p = 0.010$) (Table 1).

Outcomes

The follow-up durations, and frequencies of major bleeding and CAE according to the antithrombotic treatment, are listed in