Journal of Arrhythmia ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Journal of Arrhythmia

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

Original Article

Major determinants for the selecting antithrombotic therapies in patients with nonvalvular atrial fibrillation in Japan (JAPAF study)

Koichi Kusakawa [a,*], Kouji H. Harada [a], Tatsuo Kagimura [b], Akio Koizumi [a]

[a] Department of Health and Environmental Sciences, Kyoto University Graduate School of Medicine, Konoe-cho, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
[b] Department of Statistical Analysis, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, 1-5-4 Minatojima-minamimachi, Chuou-ku, Kobe 650-0047, Japan

ARTICLE INFO

Article history:
Received 12 February 2016
Received in revised form
24 May 2016
Accepted 24 June 2016

Keywords:
Antiplatelet
Cross-sectional study
Nonvalvular atrial fibrillation
Oral anticoagulant

ABSTRACT

Background: Oral anticoagulants (OACs) can help prevent stroke in patients with nonvalvular atrial fibrillation (NVAF). The aim of this study was to characterize the use of OACs other than direct thrombin inhibitors (DTIs) for NVAF.

Methods: Patients with NVAF taking antithrombotics other than DTIs were enrolled in this cross-sectional study. Patient demographics and medication history were collected, and the patients were classified as taking antiplatelet monotherapy (AP), anticoagulant monotherapy (AC), or combination therapy (AP+AC). OAC users were also stratified as naïve (N; initiated within 6 months), switcher (S; switched within 6 months), or prevalent user (P; continued for >6 months).

Results: A total of 3053 patients (AP, 216; AC, 2381; AP+AC, 456) from 268 sites were enrolled from 2012 to 2013. Significant differences were observed in $CHADS_2$ scores (AP/AC/AP+AC: 2.0/2.1/2.7, $P<0.0001$), angina complications (20.1/8.6/32.1, $P<0.0001$), myocardial infarction (5.1/2.8/18.1, $P<0.0001$), prothrombin time–international normalized ratio (PT–INR) ($-$/2.00/1.94, $P=0.0350$), and others. There were 2831 OAC users (N, 328; S, 213; P, 2290). Significant differences were observed in history of bleeding (N/S/P: 2.4/9.4/4.5, $P<0.001$), PT–INR (1.83/2.01/2.00, $P<0.0001$), and others.

Conclusions: Patients taking AP+AC had higher $CHADS_2$ scores than those taking an AP or AC alone. Additionally, the combination therapy (AP+AC) was preferred in patients with cardiovascular comorbidity. Changes in AC regimens were not influenced by $CHADS_2$ scores or complications but influenced by history of bleeding. These characteristics were thus identified as major factors affecting the selection of antithrombotic regimens other than DTIs in patients with NVAF.

1. Introduction

The prevalence of atrial fibrillation (AF) increases with aging in Japan [1]. An epidemiological survey conducted by the Japanese Circulation Society indicated that the prevalence of AF was gradually increasing, and estimated a prevalence rate of 0.79% by 2020 [2]. The results of cohort-based [3] and community-based [4] surveys showed that the prevalence of AF in Japan is already $>1\%$.

AF is an important risk factor for stroke. The incidence of stroke in patients with nonvalvular AF (NVAF) was reported to be about 5% per year, and 2- to 7-fold higher than in the population without AF [5,6]. The result of a Japanese study indicated that, among 15,831 patients hospitalized with acute cerebral infarction, AF was observed in 3335 patients, 78.4% of whom were found to have cardiogenic embolism [7]. Medical treatment in patients with AF should thus also be targeted at preventing cerebral thrombosis/embolism, as well as other types of embolisms.

Antithrombotic treatment is important for preventing stroke in patients with NVAF, and warfarin and anticoagulants have been the recommended treatments; additionally, aspirin and antiplatelet preparations have been acceptable. The Japanese Guidelines for Treatment of Stroke 2009 [8] recommended warfarin for managing NVAF patients with more than two risk factors (congestive heart failure, hypertension, age >75 years, or diabetes mellitus), whereas antiplatelet preparations are acceptable in patients with contraindications to warfarin. Additionally, the latest Japanese Guidelines for Pharmacotherapy of Atrial Fibrillation [9] addressed the importance of many risk factors when selecting suitable antithrombotic drug therapies such as warfarin, in accordance with the severity of the risk.

In March 2011, the new oral direct thrombin inhibitor (DTI) dabigatran, with a novel mechanism of action, was introduced on the market [10], and a new drug application for the factor Xa inhibitor rivaroxaban was filed in 2011. These drugs are superior,

* Corresponding author. Fax: +81 75 753 4458.
E-mail address: kusakawa.kouichi.26c@st.kyoto-u.ac.jp (K. Kusakawa).

http://dx.doi.org/10.1016/j.joa.2016.06.006

or at least not inferior, to warfarin in terms of efficacy and safety [11,12], and are therefore likely to change the standard of antithrombotic therapy in the near future.

The aim of this cross-sectional study was to investigate the relationships between patient characteristics and antithrombotic therapy prescribed for the prevention of ischemic stroke and systemic embolism in patients with NVAF in clinical practice. Additionally, because the data were to be used to compare with the characteristic data of postmarketing surveillance (PMS) for dabigatran by Nippon Boehringer Ingelheim [13], which was performed in parallel to this study, patients prescribed with dabigatran were excluded from this study.

2. Material and methods

This was a cross-sectional study carried out to investigate the characteristics, treatments, and pathological backgrounds of patients with NVAF treated for the prevention of ischemic stroke. Surveillance was performed from October 2011 to March 2014 (entry of patients: April 2012 to December 2013) at 268 medical sites that participated in the PMS for dabigatran throughout Japan. Patients with NVAF who received antithrombotic treatments to prevent ischemic stroke were registered. Site investigators collected the patient data from medical records at the first visit after registration.

2.1. Subjects

Adult patients with AF, regardless of sex, complications, hospitalization, or medical history, who received antithrombotic treatment to prevent a cerebrovascular ischemic attack, were enrolled in this study. The exclusion criteria were (i) patients who received artificial valve replacement, (ii) those with valvular disease, (iii) those with DTI preparation (dabigatran) use, and (iv) those without antithrombotic treatment.

2.2. Surveillance method

Patient characteristics, AF history and characteristics, comorbidity, and history of antithrombotic treatment were obtained from medical records and transcribed into an electrical case report by the site investigators. The collected characteristics included sex, date of birth, body weight, height, smoking history, and alcohol consumption. The AF history and characteristics included onset date, symptomatic or asymptomatic status, type of AF, and treatment including surgical intervention. Comorbidity included congestive heart failure, hypertension, diabetes mellitus, stroke, transient ischemic attack (TIA), systemic embolism, pulmonary embolism, peripheral artery diseases (arteriosclerosis obliterans, chronic arterial occlusion), dyslipidemia (hyperlipidemia), angina pectoris, myocardial infarction (MI), valvular disease, renal dysfunction including impaired creatinine clearance calculated by using the Cockcroft–Gault method [14], hepatic diseases, dementia, and bleeding events. Information was collected on current antithrombotic treatments and withdrawn treatments before this study. The start and end dates of administration, dosage of anticoagulant (warfarin, dabigatran, rivaroxaban, heparin, other non-oral anticoagulant [non-OACs]), and antiplatelet preparations (aspirin, ticlopidine, cilostazol, clopidogrel, eicosapentaenoic acid ethylate, beraprost sodium, sarpogrelate hydrochloride, and others) were included. Details on concomitant use of angiotensin II receptor blockers (ARB), angiotensin-converting enzyme inhibitors, beta-blockers, antihypertensives, insulin, oral hypoglycemics, and statins were also collected. The prothrombin time–international normalized ratio (PT–INR) within 3 months before visit was recorded for patients treated with warfarin, if available. The study protocol and provision of information to participants were carried out in line with the ethical guidelines for epidemiological research (established by the Ministry of Health, Labour, and Welfare in Japan) and approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (September 28, 2011; no. E1220). No medical intervention and no biological specimens from human subjects were specified in this study; therefore, verbal and/or anonymized information and consent were acceptable, as well as written informed consent. This study was registered to UMIN Clinical Trial Registry (no. 000009644).

2.3. Statistical analysis

For primary analysis, we classified the patients according to their antithrombotic regimen: antiplatelet monotherapy (AP), anticoagulant monotherapy (AC), and concomitant use of antiplatelet and anticoagulant (AP+AC). Patient characteristics, AF history and characteristics, comorbidity, and history of antithrombotic treatment were tabulated for each group and compared among the three groups. The measured values and order values are shown as means and standard deviations (SDs) in the tables, and P values were calculated by using ANOVA adjusted by sex and age, in 10-year steps. Nominal scale values are shown as frequencies and proportions, and P values were calculated by using the Cochran–Mantel–Haenszel method adjusted by sex and age. The pair-wise test for the factor with a statistical difference among the three groups was performed under a closed testing procedure as adjusted for multiplicity. Multivariate analysis was performed through multiple multinomial logit analysis with the above items as independent variables, and variable selection in the model by using a stepwise method.

Additionally, we further classified patients taking OACs (AC and AP+AC) into the following three groups: naïve (N) patients with an OAC regimen initiated within 6 months before the observation date and not changed; switchers (S), in whom OACs were changed within 6 months before the observation date; and prevalent users (P), who continued the use of the same OAC for >6 months before the observation date. We also classified patients taking OACs into warfarin users and rivaroxaban users, for reference. The patient distribution in the treatment history of OACs was also compared by using the analysis methods. A two-sided P value of ≤ 0.05 was considered significant. The statistical analysis was performed by using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Primary analysis

A total of 3138 patients from 274 medical sites were initially registered to this study. Eighty-five patients were ineligible because of not meeting the inclusion or exclusion criteria: patients with no antithrombotic treatment ($n=17$), with dabigatran treatment ($n=4$), with mitral valve stenosis ($n=21$) and those who underwent mitral valve replacement ($n=46$; 10 patients with mitral valve stenosis), with no detailed information on OACs ($n=1$), with input error ($n=5$), and with duplicated case registration ($n=1$). The remaining 3053 patients included 216 (7.1%) in the AP group, 2381 (78.0%) in the AC group, and 456 (14.9%) in the AP+AC group. The main antithrombotic regimens were warfarin ($n=2523$; mean $\pm$ SD daily dose: 2.70 ± 1.10 mg), aspirin ($n=479$, 99.5 ± 13.9 mg), rivaroxaban ($n=311$, 12.2 ± 2.5 mg), clopidogrel ($n=122$, 71.9 ± 8.2 mg), and cilostazol ($n=59$, 152.6 ± 56.8 mg).

ARBs ($n=1391$), beta-blockers ($n=1145$), statins ($n=873$), or antiarrhythmic drugs ($n=794$) were administered concomitantly

Please cite this article as: Kusakawa K, et al. Major determinants for the selecting antithrombotic therapies in patients with nonvalvular atrial fibrillation in Japan (JAPAF study). J Arrhythmia (2016), http://dx.doi.org/10.1016/j.joa.2016.06.006