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ORIGINAL ARTICLE
Cardiovascular Intervention

Temporal Trends in Antithrombotic Therapy for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention From 2014 to 2022 in Japan

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Background: Recent revisions of clinical guidelines by the Japanese Circulation Society, American Heart Association/American College of Cardiology, and European Society of Cardiology updated the management of antithrombotic strategies for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). However, the extent to which these guidelines have been implemented in real-world daily clinical practice is unclear.

Methods and Results: We conducted surveys on the status of antithrombotic therapy for patients with AF undergoing PCI every 2 years from 2014 to 2022 in 14 cardiovascular centers in Japan. The primary use of drug-eluting stents increased from 10% in 2014 to 95–100% in 2018, and the use of direct oral anticoagulants increased from 15% in 2014 to 100% in 2018, in accordance with the revised practice guidelines. In patients with acute coronary syndrome, the duration of triple therapy within 1 month was approximately 10% until 2018, and increased to >70% from 2020. In patients with chronic coronary syndrome, the duration of triple therapy within 1 month was approximately 10% until 2016, and >75% from 2018. Since 2020, the most common timing of discontinuation of dual antiplatelet therapy to transition to anticoagulation monotherapy during the chronic phase of PCI has been 1 year after PCI.

Conclusions: Japanese interventional cardiologists have updated their treatment strategies for patients with AF undergoing PCI according to revisions of clinical practice guidelines.

Key Words: Antithrombotic therapy; Atrial fibrillation; Percutaneous coronary intervention; Survey

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting over 33 million people worldwide.[1] The prevalence of AF and deaths due to AF are increasing globally.[2] An association between AF and stroke has been reported in rigorous studies, indicating a true association rather than a spurious finding;[3] therefore, therapeutic prevention with oral anticoagulation (OAC) is required.[4,5]

In Japanese registries, it is reported that approximately 10% of patients undergoing percutaneous coronary intervention (PCI) have an indication for long-term OAC due to AF.[6,7] The management of patients with AF undergoing

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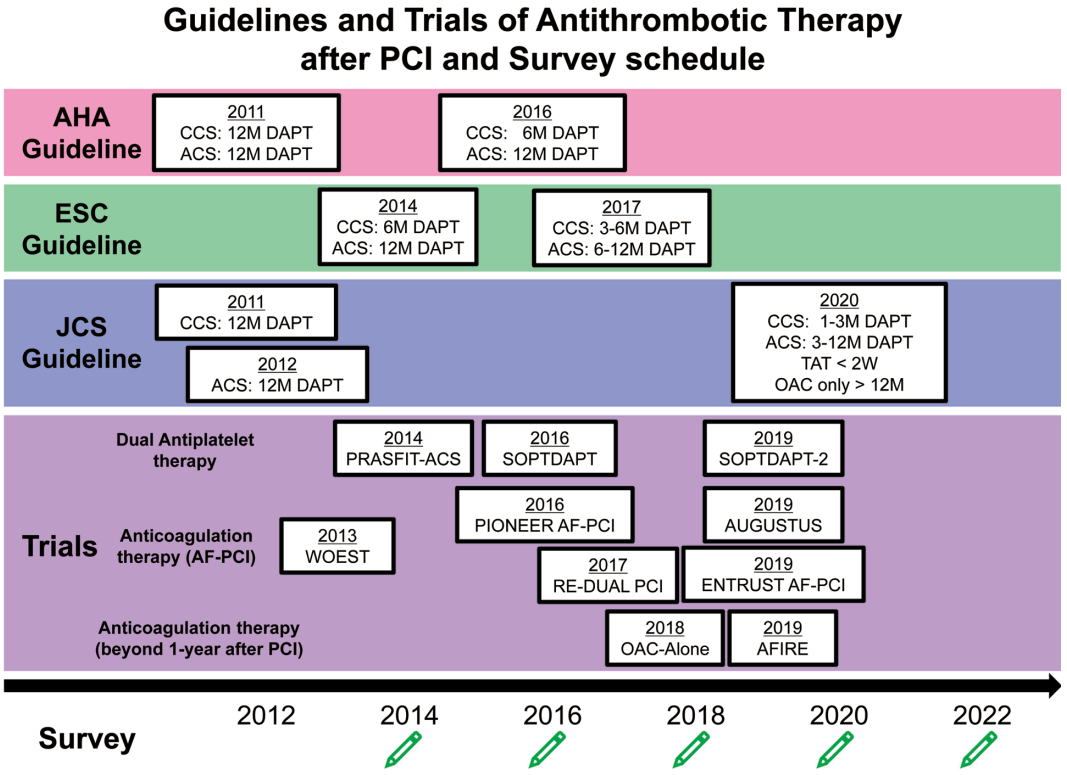

Figure 1. Guidelines and trials of antithrombotic therapy after percutaneous coronary intervention (PCI) and survey schedule. ACS, acute coronary syndrome; AF, atrial fibrillation; AHA, American Heart Association; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; JCS, Japanese Circulation Society; M, months; OAC, oral anticoagulant; TAT, triple antithrombotic therapy; W, weeks. Trials: AFIRE, Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; AUGUSTUS, An Open-Label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST AF-PCI, Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation; PIONEER AF-PCI, Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; PRASFIT-ACS, PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome undergoing Percutaneous Coronary Intervention; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention OAC-Alone, Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; STOPDAPT, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2; WOEST, What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

PCI presents challenges given that there are several potential antithrombotic therapy strategies. A multitude of clinical evidence on antithrombotic therapy after PCI or patients with AF complications has accumulated and been promulgated[8–10] (**Figure 1**). The duration of dual antiplatelet therapy (DAPT) after implantation of a drug-eluting stent (DES) has gradually been shortened according to the Japan Circulation Society (JCS) guidelines,[11] American Heart Association (AHA)/American College of Cardiology (ACC) guidelines, and European Society of Cardiology (ESC) guidelines.[12,13] Patients with AF undergoing PCI have a high bleeding risk because of the mandatory triple antithrombotic therapy (TAT): DAPT plus OAC. However, dual therapy with a $P2Y_{12}$ inhibitor plus warfarin was shown to result a significantly lower incidence of both bleeding and ischemic events compared with triple therapy in the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial.[14] In the direct oral anticoagulant (DOAC) era, 4 AF-PCI trials using DOACs have been published comparing DOAC plus $P2Y_{12}$ inhibitor to triple therapy in the acute phase after PCI.[15–18] In the

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Table. Survey Questionnaire
Q1. In your practice as a cardiologist, what is your estimate of the percentage of patients who have atrial fibrillation/flutter that necessitates anticoagulation and who undergo stent implantation?
Q2. How often will you select a BMS to implant in a patient with atrial fibrillation/flutter on an oral anticoagulant?
Q3. Which anticoagulant in the setting of triple antithrombotic treatment is your preferred choice?
Q4. How long will you continue treatment with triple antithrombotic treatment in the following setting? (A) CCS+DES; (B) ACS+DES
Q5. Which antiplatelet agent will you prefer to drop first?
Q6. When will you stop the second antiplatelet agent (i.e., treat with OA only)?
Q7. For a patient with atrial fibrillation undergoing DES implantation, which is your preferred strategy?
(a) WOEST-like strategy: anticoagulation and clopidogrel for at least 1 month (BMS) or 12 months (DES or ACS)
(b) Triple antithrombotic treatment for 1 month followed by anticoagulation+aspirin
(c) Triple antithrombotic treatment for 1 month followed by anticoagulation+clopidogrel
(d) Triple antithrombotic treatment for 1 year

ACS, acute coronary syndrome; BMS, bare-metal stent; CCS, chronic coronary syndrome; DES, drug-eluting stent; OA, oral anticoagulant; WOEST, What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

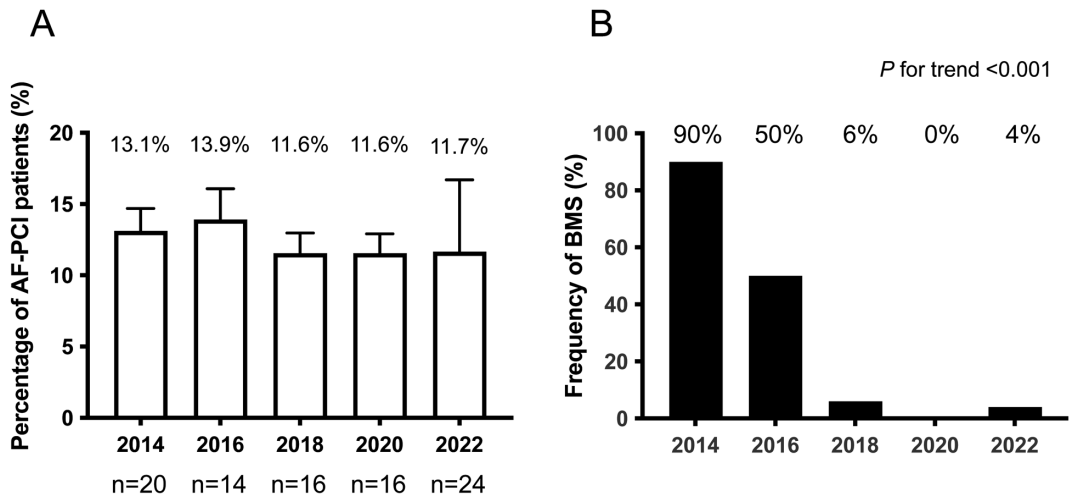

Figure 2. (**A**) Estimated percentage of patients with atrial fibrillation (AF) or atrial flutter who undergo stent implantation (Question 1). (**B**) Frequency of bare-metal stent (BMS) implantation (Question 2). PCI, percutaneous coronary intervention.

chronic phase of coronary artery disease (CAD), OAC monotherapy is encouraged based on 2 Japanese randomized studies.[19,20] Accordingly, the guidelines of the Japanese Circulation Society have been revised periodically, and have presented a comprehensive and evidence-based set of consensus statements on antithrombotic therapy for patients with AF undergoing PCI.[10]

One of the important aims of clinical guidelines is to standardize clinical practice, thereby improving procedure-related and clinical outcomes. However, healthcare providers have not consistently adhered to these clinical consensus guidelines.[21] It is very important to know how prescribing has changed in actual clinical practice as the guidelines have changed. However, it is unclear to what extent these guidelines have been implemented in actual clinical practice. There have been few reports showing real clinical data, with only one report from the US in 2014.[22]

In this study we conducted biennial surveys on the actual status of antithrombotic therapy for patients with AF undergoing PCI in 2014, 2016, 2018, 2020, and 2022, and investigated the temporal trends of antithrombotic therapy after PCI for patients with AF in Japan.

Methods

A questionnaire was sent electronically to interventional cardiologists practicing in affiliated facilities (14 cardiovascular centers in Japan) of the Department of Cardiovascular Medicine, Kyushu University (Fukuoka, Japan), which hosts the Kyushu Cardiovascular Intervention Conference (QcVIC), and performs approximately 4,000 PCI procedures per year. The annual number of PCI cases at the time of the survey at each facility is listed in the **Supplementary Table**. Participating physicians were asked to complete a questionnaire using Google Forms. The survey questions were prepared based on a previous report,[22] and are listed in the **Table**. We conducted biennial surveys on the actual status of antithrombotic therapy for patients with AF undergoing PCI in 2014, 2016, 2018, 2020, and 2022. The answer to Question (Q) 4 provided options of 0, 1, 3, 6, and

12 months; the 0-month option was introduced in 2018.

The data obtained included estimates of the prevalence of the condition, as well as physicians' preferences with regard to stent class, anticoagulation type, and antiplatelet treatment (type and duration). Data were collected at Kyushu University Hospital. Descriptive results are presented.

Statistical Analysis

Data are presented as percentages for each study period. Secular trends during the study period were tested using Cochran-Armitage tests.

Results

In all surveys, approximately 70% of respondents estimated that 5–10% of patients undergoing PCI in their clinical practice had AF or atrial flutter that required anticoagulation. Approximately 20% of respondents estimated that 11–20% of patients undergoing PCI in their clinical practice had AF or atrial flutter that required anticoagulation. The average percentage of patients with AF that required anticoagulation among patients undergoing stent implantation was approximately 10%; this trend remained unchanged across the 5 surveys (**Figure 2A**).

In 2014, 90% of respondents reported that they preferred bare-metal stents (BMSs) over DESs for patients with AF (Q2). In 2016, approximately half the respondents preferred BMSs over DESs, and from 2018 most respondents reported that they preferred DESs over BMSs (**Figure 2B**).

Regarding the selection of anticoagulants in this population, most respondents (85% [17/20]) preferred warfarin over other treatment options in the 2014 survey, even when DOACs were available in Japan. Although only 15% (3/20) preferred DOACs as the routine first-line treatment in this clinical scenario, the rate of DOAC usage increased to over 78.6% (11/14) in 2016, and thereafter all respondents preferred DOACs (**Figure 3**). We also investigated the preferred DOACs in this population. As shown in the **Supplementary Figure**, apixaban was the preferred DOAC from 2016. Rivaroxaban has been preferred since the 2020 survey.

Figure 4 shows preferences regarding the duration of TAT in different clinical scenarios (acute coronary syndrome [ACS] with DES implantation or chronic coronary syndrome [CCS] with DES implantation). In both scenarios, the duration of TAT shortened each year (**Figure 4**). However, the shortening trend in the CCS with DES implantation group appeared earlier compared with the ACS group (**Figure 4A**). The 2022 survey was the first time that a substantial number of respondents (75% [18/21] in the case of CCS; 41.7% [10/21] in the case of ACS) indicated that they preferred a TAT of 0 months.

Over half the respondents preferred to discontinue aspirin after the initial TAT phase (**Figure 5A**). The proportion of respondents who preferred this treatment strategy decreased over 2016 and 2018, when DOACs were more frequently used as a part of TAT. In contrast, this treatment strategy was preferred by over 90% of respondents after 2020 (93.8% [15/16] in 2020; 91.6% [22/24] in 2022).

Although the indefinite continuation of antiplatelet therapy was preferred by most respondents until 2018,

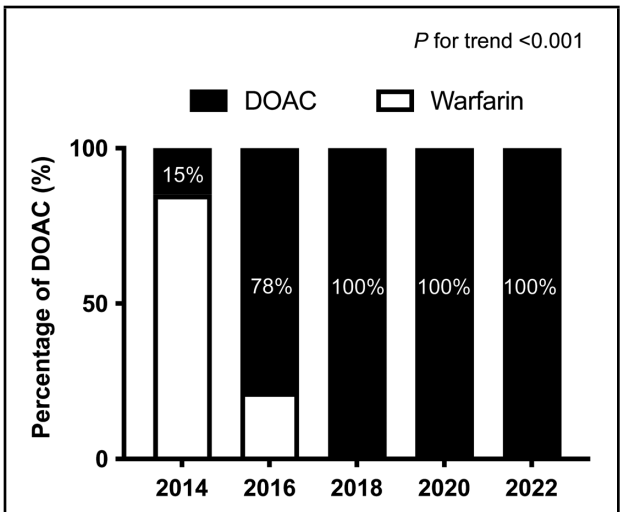

Figure 3. Choice of direct oral anticoagulant (DOAC) vs. warfarin for anticoagulant (Question 3).

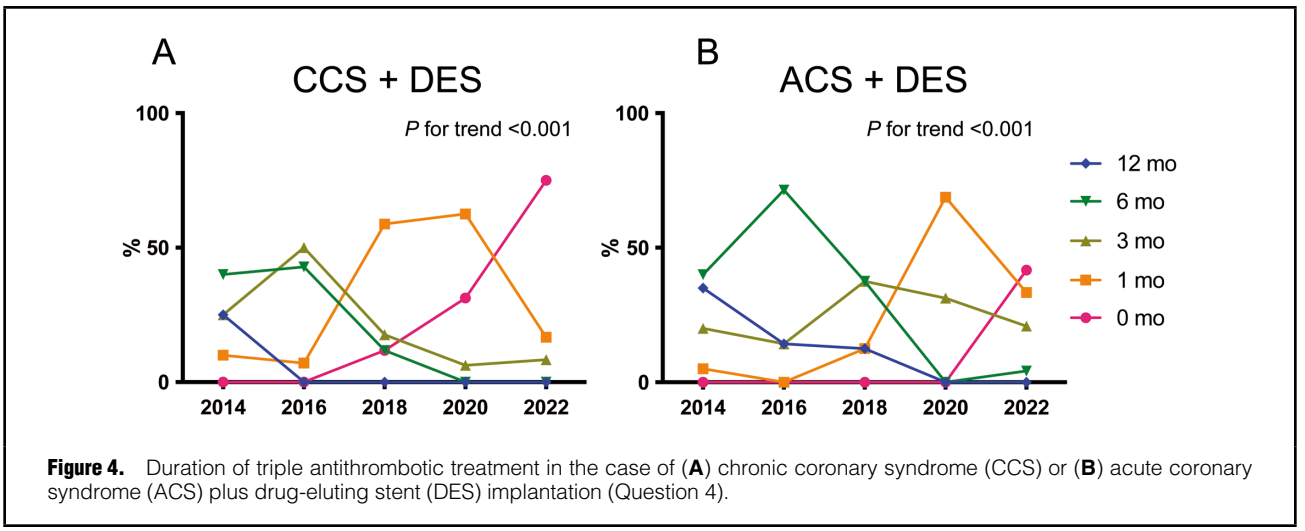

Figure 4. Duration of triple antithrombotic treatment in the case of (**A**) chronic coronary syndrome (CCS) or (**B**) acute coronary syndrome (ACS) plus drug-eluting stent (DES) implantation (Question 4).

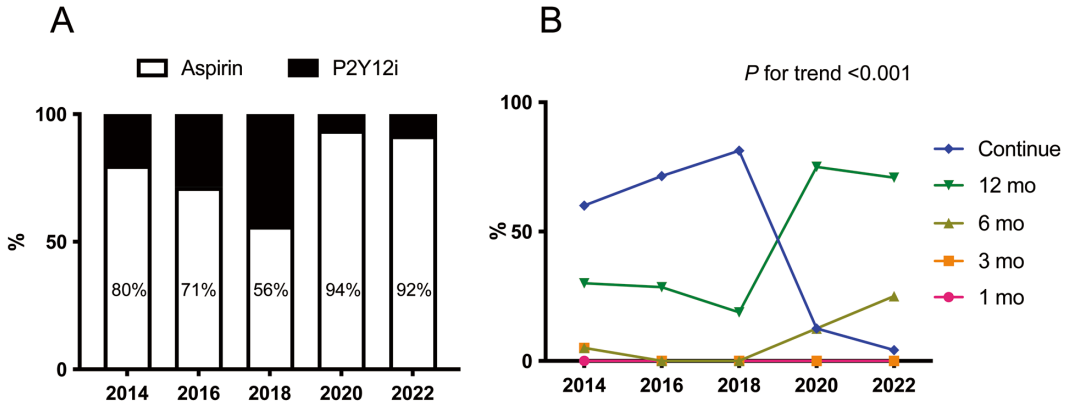

Figure 5. (**A**) Antiplatelet agent stopped first and (**B**) its timing (Questions 5 and 6). mo, months; P2Y$_{12}$i, P2Y$_{12}$ inhibitor.

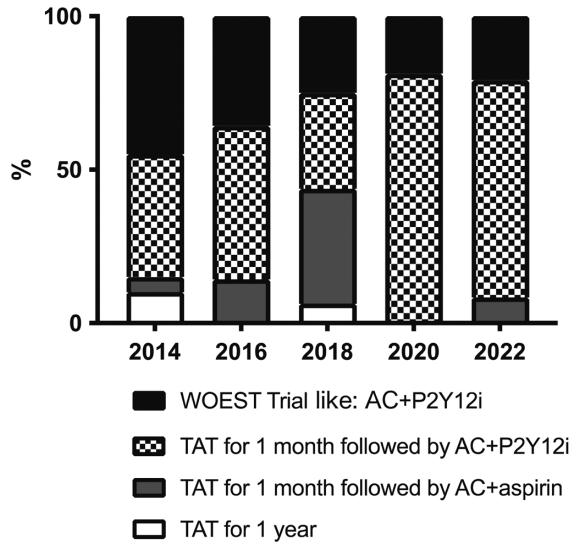

Figure 6. Preferred antithrombotic treatment strategy (Question 7). AC, anticoagulant; P2Y$_{12}$i, P2Y$_{12}$ inhibitor; TAT, triple antithrombotic therapy.

since 2020 most patients with AF undergoing PCI were treated with an antiplatelet-free strategy in the 12 months after the intervention (Q6; **Figure 5B**).

We asked respondents about their preferred treatment strategy for patients with AF undergoing DES implantation. As shown in **Figure 6**, there has been great interest in dropping 1 of 2 antiplatelet agents, either immediately or after 1 month. After 2020, no respondents preferred the treatment strategy of TAT for 1 year (**Figure 6**).

Discussion

We conducted surveys on the actual status of antithrombotic therapy for patients with AF undergoing PCI every 2 years from 2014 to 2022 in 14 Japanese cardiovascular centers that perform approximately 4,000 PCI procedures per year.

In our survey, the average percentage of patients with AF undergoing PCI that required anticoagulation was approximately 10%, which is in line with previous reports;[6,7] this trend remained unchanged across the 5 surveys (**Figure 2A**).

In this setting, most interventional cardiologists preferred BMS implantation over DES implantation for the majority of their patients at the beginning of the survey (**Figure 2B**). Indeed, the North American and European recommendations suggested that DESs should be totally avoided (and BMSs should be used) due to concerns over the safety of enhanced and prolonged antithrombotic therapy in patients with a high risk of bleeding.[23,24] However, a subanalysis of the WOEST trial showed no advantage for patients who received a BMS as compared with a DES.[25] Moreover, the rates of target vessel revascularization and stent thrombosis are markedly lower after DES implantation, and the difference in the rate of stent thrombosis after DES compared with BMS seems to have disappeared with the newer-generation DES.[25] After 2018, possibly influenced by such evidence (**Figure 2B**), the interventional cardiologists in this survey shortened the duration of DAPT after DES implantation and discontinued the selection of BMSs when performing PCI for patients with CAD and AF.

Warfarin is a well-established intervention for patients with AF or atrial flutter; however, it is associated with a moderate risk of embolic events, increases the risk of hemorrhage, and is difficult to use.[26,27] DOACs, approved in 2010 in Japan, have been proven to be effective for stroke prevention in patients with AF and are increasingly preferred over warfarin due to a reduced need for frequent therapeutic monitoring, improved patient convenience, greater predictability, faster onset of anticoagulation effect, and lower potential for food and drug interactions.[26,28–30] Furthermore, several studies have published evidence on antithrombotic therapy in PCI for patients with AF.[14–17] In our survey, all respondents preferred DOACs over warfarin from 2018 (**Figure 3**). Although DOAC is widely prescribed over warfarin, warfarin should be the treatment of choice in cases of severe renal dysfunction, mitral stenosis, and so on. Among the DOACs, apixaban was the most commonly used, and that trend has not changed since 2016 (**Supplementary Figure**). One possible explanation for this is a study that reported that for patients with AF undergo-

ing PCI, apixaban plus P2Y12 inhibitors (among regimes that included other DOACs plus P2Y12 inhibitors) was associated with the lowest rate of bleeding, with no increase in ischemic outcomes.[31]

Because DAPT failed to reduce thrombotic events compared with OAC in patients with AF, triple therapy (DAPT and an OAC) should be considered for patients undergoing coronary stent deployment.[32] However, subsequent research showed that TAT was not associated with a reduction in the risk of recurrent coronary events or thromboembolism, whereas the risk of bleeding was significantly increased.[33] In addition, dual therapy with clopidogrel plus warfarin was associated with significantly lower rates of both bleeding and ischemic events compared with triple therapy in the WOEST trial.[13] This regimen (i.e., an OAC plus a P2Y12 inhibitor without aspirin), called the "WOEST-like regimen", has had a large impact on antithrombotic therapy. In the DOAC era, 4 AF-PCI trials using DOACs have been published comparing the WOEST-like regimen to triple therapy.[14–17] Furthermore, from the 2020 update of the JCS guidelines, the guideline on antithrombotic therapy for patients with CAD was revised and the duration of TAT was shortened each year. As shown in **Figure 4**, the trend towards shorter TAT appeared earlier in patients with CCS who underwent DES implantation than in patients with ACS who underwent DES implantation. The 2022 survey was the first time that a substantial number of respondents indicated that they preferred a TAT duration of 0 months; this was likely due to the influence of the JCS 2020 guidelines.

Figure 5A showed that P2Y12 inhibitor monotherapy was conducted in 2014, because warfarin was the main anticoagulant for AF in this era and the combination of warfarin and aspirin was less effective for the prevention of in-stent thrombosis in the STARS (Stent Angicoagualtion Restenosis Study) trial published in 1998.[34] Hence, most respondents may prefer the combination of warfarin and a P2Y12 inhibitor for patients with AF undergoing PCI. The previous JCS guideline on revascularization of stable CAD (2018 edition[35]) states that when OAC is required in addition to DAPT, the discontinuation of aspirin at the time of discharge or for no longer than 1 month is recommended to decrease bleeding complications; this recommendation is based on the results of the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial and the REDUAL-PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trials.[14,15] A recent network meta-analysis demonstrated that the use of a DOAC plus a P2Y12 inhibitor without aspirin may be the most favorable treatment option and the preferred antithrombotic regimen for most patients with AF undergoing PCI.[10] In our survey, most respondents preferred a treatment strategy of aspirin discontinuation, especially from 2020 (**Figure 5A**).

During the chronic phase of CAD, OAC monotherapy is encouraged based on 2 Japanese randomized studies: the OAC-Alone (Oral Anticoagulation Alone) trial,[19] which demonstrated the non-inferiority of OAC alone relative to combination therapy with an antiplatelet agent for a composite of cardiovascular and bleeding events; and the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial, which demonstrated the superiority of rivaroxaban monotherapy over combination therapy with rivaroxaban and an antiplatelet agent for both bleeding events and cardiovascular events in patients with stable CAD and AF, from 1 year after PCI.[18,36] The percentage of rivaroxaban use also increased after 2020, presumably due to the results of the AFIRE trial. **Figure 5B** shows that most patients with AF atrial or flutter undergoing PCI have been treated with an antiplatelet-free strategy 12 months after the intervention since 2020.

The present study does have some limitations. This survey is based on the principle of prescription by each cardiologist or in each cardiologist and does not reflect the real prescription rate in each patient. Therefore, this survey may not show the actual status of antithrombotic therapy for patients with AF undergoing PCI.

Conclusions

The present study demonstrated that Japanese interventional cardiologists updated their antithrombotic treatment strategies for patients with AF undergoing PCI according to the current clinical practice guidelines.

Authors Contribution

Y.N. and T.M. (Department of Cardiovascular Medicine, Kyushu University) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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IRB Information

This study presents a summary of the findings from a questionnaire that does not contain any patient information and, as such, ethics approval was not deemed necessary by the Kyushu University Institutional Review Board for Clinical Research.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Files

Please find supplementary file(s);
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