Efficacy and Safety of Triple Therapy and Dual Therapy With Direct Oral Anticoagulants Compared to Warfarin

Hideo Amano, MD, Daiga Saito, MD, Takayuki Yabe, MD, Ryo Okubo, MD, Mikihito Toda, MD, and Takanori Ikeda, MD

Summary

The efficacy and safety of direct oral anticoagulants (DOAC) with antiplatelet therapy compared to warfarin are unclear. The subjects were 280 patients who received antiplatelet therapy with oral anticoagulation (OAC) for the treatment of or protection from thromboembolism between January 2012 and September 2015. Among the 280 subjects, 79 (28.2%) received dual therapy (OAC plus aspirin or P2Y₁₂ inhibitor) with DOAC, 75 (26.8%) dual therapy with warfarin, 46 (16.4%) triple therapy (OAC plus aspirin and P2Y₁₂ inhibitor) with DOAC, and 80 (28.6%) triple therapy with warfarin.

Compared to triple therapy with warfarin, triple therapy with DOAC had slightly lower bleeding (3.5 versus 12.0/100 persons-years, HR: 0.24, 95%CI: 0.03 to 1.96, \( P = 0.183 \)), and similar benefit outcomes (cardiac death, acute myocardial infarction or stroke) and thromboembolism (7.0 versus 10.5, HR: 0.53, 95%CI: 0.10 to 2.75, \( P = 0.453 \); 7.0 versus 7.5, HR: 0.96, 95%CI: 0.18 to 5.22, \( P = 0.964 \), respectively). Compared to dual therapy with warfarin, dual therapy with DOAC had slightly lower bleeding (3.0 versus 8.4, HR: 0.38, 95%CI: 0.07 to 2.18, \( P = 0.279 \)), and similar benefit outcomes and thromboembolism (4.6 versus 4.2, HR: 1.66, 95%CI: 0.30 to 9.25, \( P = 0.565 \); 4.6 versus 1.4, HR: 3.11, 95%CI: 0.23 to 42.84, \( P = 0.397 \), respectively). Bleeding mainly occurred after 3 months (16/17, 94.1%).

Triple therapy and dual therapy with DOAC were not inferior to triple therapy and dual therapy with warfarin in terms of major bleeding, benefit outcomes, and thromboembolism. Bleeding mainly occurred in the late phase. (Int Heart J 2017; 58: 570-576)

Key words: Anticoagulation, Antiplatelet therapy, Atrial fibrillation, Percutaneous coronary intervention, Bleeding

Stroke prevention in cases of atrial fibrillation (AF), mechanical heart valves, and the treatment and prevention of thromboembolic events requires oral anticoagulation (OAC). Dual antiplatelet therapy (DAPT) is necessary following percutaneous coronary intervention (PCI) for angina and acute myocardial infarction or stroke) and thromboembolism (7.0 versus 10.5, HR: 0.53, 95%CI: 0.10 to 2.75, \( P = 0.453 \); 7.0 versus 7.5, HR: 0.96, 95%CI: 0.18 to 5.22, \( P = 0.964 \), respectively). Compared to dual therapy with warfarin, dual therapy with DOAC had slightly lower bleeding (3.0 versus 8.4, HR: 0.38, 95%CI: 0.07 to 2.18, \( P = 0.279 \)), and similar benefit outcomes and thromboembolism (4.6 versus 4.2, HR: 1.66, 95%CI: 0.30 to 9.25, \( P = 0.565 \); 4.6 versus 1.4, HR: 3.11, 95%CI: 0.23 to 42.84, \( P = 0.397 \), respectively). Bleeding mainly occurred after 3 months (16/17, 94.1%).

Triple therapy and dual therapy with DOAC were not inferior to triple therapy and dual therapy with warfarin in terms of major bleeding, benefit outcomes, and thromboembolism. Bleeding mainly occurred in the late phase. (Int Heart J 2017; 58: 570-576)

Key words: Anticoagulation, Antiplatelet therapy, Atrial fibrillation, Percutaneous coronary intervention, Bleeding

Stroke prevention in cases of atrial fibrillation (AF), mechanical heart valves, and the treatment and prevention of thromboembolic events requires oral anticoagulation (OAC). Dual antiplatelet therapy (DAPT) is necessary following percutaneous coronary intervention (PCI) for angina and acute myocardial infarction (AMI). Accordingly, triple therapy with OAC and DAPT is necessary for PCI in patients with thromboembolic disease. However, the most effective duration of treatment, dose, and combination of drugs are not clear. The WOEST trial reported that dual therapy (OAC with clopidogrel) was superior to triple therapy (OAC with aspirin and clopidogrel) in terms of both efficacy and safety. However, the WOEST trial has problems in that the number of patients was small and only vitamin K antagonists (VKA) were used. A joint European consensus document recommends triple therapy for one month after PCI for acute coronary syndrome (ACS) with AF. However, there are few studies supporting this evidence. In addition, while direct oral anticoagulants (DOAC) are now available, there are few reports on triple therapy using DOAC. Here we have investigated the efficacy and safety of triple therapy and dual therapy, the difference between DOAC and warfarin, and the timing of the onset of bleeding events.

METHODS

Patient population: This study was a retrospective, non-randomized, and observational study. The study was conducted in 280 consecutive patients who began concomitant use of antiplatelet therapy with oral anticoagulation for the treatment of or protection from thromboembolism at our institution between January 2012 and September 2015. The subjects had AF, pulmonary embolism, deep vein thrombosis, apical aneurysm, or post coronary artery bypass grafting. This study was performed in accordance with the Code of Federal Regulations and the Declaration of Helsinki. This protocol was approved by the Toho University Omori Medical Center Ethics Committee (institutional review board approval number: 26-171). Written informed consent was obtained from each patient before the study.

Antithrombotic treatment regimens: Patient observation be-
At the start of concomitant use of antiplatelet therapy with oral anticoagulation between January 2012 and September 2015. The subjects were divided into the following 4 treatment groups: (1) DOAC plus single antiplatelet drug (aspirin or P2Y12 inhibitor); Dual therapy with DOAC group; (2) DOAC plus aspirin and P2Y12 inhibitor; Triple therapy with DOAC group; (3) warfarin plus single antiplatelet drug (aspirin or P2Y12 inhibitor); Dual therapy with warfarin group; and (4) warfarin plus aspirin and P2Y12 inhibitor: Triple therapy with warfarin group. We excluded cases whose duration of the regimen was less than 1 month. The maximum follow-up period was 12 months. The primary endpoint of the study was a composite of death or major bleeding. The end of follow-up was March 31, 2016.

Definitions: Major bleeding was defined as Bleeding Academic Research Consortium (BARC) criteria types 3 and 5.  AMI was defined based on the confirmed diagnosis.  Stroke was defined as the sudden onset of a focal neurologic deficit caused by an ischemic or hemorrhagic event. Computed tomography or magnetic resonance imaging was used for all suspected strokes. Thromboembolism was defined based on a diagnosis including ischemic stroke, transient ischemic attack, and systemic thromboembolism. Benefit outcomes were defined as cardiac death, acute myocardial infarction, or stroke. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/minute/1.73 m².

Treatments: The doses of antiplatelet drugs were; aspirin (80-100 mg/day), clopidogrel (75 mg/day), ticlopidine (200 mg/day), and prasugrel (3.75 mg/day: approved daily dose in Japan). The doses of DOAC were; dabigatran (10 mg/day), apixaban (5 mg/day), and edoxaban (30 mg/day). We used warfarin as a VKA because warfarin was the only VKA available in Japan. The target prothrombin time-international normalized ratio (PT-INR) was set as 2.0 to 3.0 (< 70 years old) or 1.6 to 2.6 (≥ 70 years old) according to the Japanese guideline for AF treatment.  The time in therapeutic range (TTR) was calculated using the method of Rosendaal, et al  with exclusion of the PT-INRs from the first week and after discontinuation of the study drug.

Statistical analysis: Statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). Categorical and consecutive data are presented as the number (percentages) or mean and standard deviation. Continuous variables were compared using the unpaired Student’s t test. Categorical variables were compared with the chi-square test or Fisher exact test. The incidence rates were calculated using the person-year method (events per 100 person-years). Cox’s proportional hazards regression analysis was used to estimate benefit and safety outcomes. These models were adjusted by age, sex, and risk factors (congestive heart failure, hypertension, diabetes mellitus, and stroke/transient ischemic attack) for ischemic stroke and thromboembolism; and adjusted by age, sex, and risk factors (hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, and usage of nonsteroidal anti-inflammatory drug) for major bleeding; and adjusted by age, sex, and risk factors (hypertension and diabetes mellitus) for death and benefit outcomes. The Kaplan-Meier method was used for building event curves. A probability value < 0.05 was considered statistically significant.

Results

A total of 280 patients were included [age, 70 ± 11 years; males 218 (77.9%)]. Of these patients, 79 (28.2%) were receiving dual therapy with DOAC, 46 (16.4%) triple therapy

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual therapy with DOAC</td>
</tr>
<tr>
<td>(n = 79)</td>
</tr>
<tr>
<td>Follow-up period, months (median)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>Comorbidity</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>History of heart failure</td>
</tr>
<tr>
<td>History of stroke</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Indication for oral anticoagulation</td>
</tr>
<tr>
<td>Prevalent AF</td>
</tr>
<tr>
<td>Incident AF</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Indication for antiplatelet therapy</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as number (percentage). DOAC indicates direct oral anticoagulants; Dual therapy, an anticoagulant + aspirin or P2Y12 inhibitor; Triple therapy, an anticoagulant + aspirin and P2Y12 inhibitor; and AF, atrial fibrillation.
with DOAC, 75 (26.8%) dual therapy with warfarin, and 80 (28.6%) triple therapy with warfarin. The mean follow up period was 9.9 ± 3.1 months.

The characteristics of the study population according to antithrombotic regimen are shown in Tables I and II. With respect to the indications for antithrombotic therapy, prevalent AF was present in 73 patients (26.1%), incident AF in 80 patients (28.6%), and other indications (pulmonary embolism, deep vein thrombosis, apical aneurysm, and post coronary artery bypass grafting) in 127 patients (45.4%). The benefit and safety outcomes in multiple antithrombotic regimens are shown in Table III. The cumulative incidences of major bleeding in multiple antithrombotic regimens are shown in the Figure. Compared to triple therapy with warfarin, triple therapy with DOAC had slightly less major bleeding (3.5 versus 12.0/100 persons-years, HR: 0.24, 95%CI: 0.03 to 1.96, \( P = 0.183 \)), similar benefit outcomes, and thromboembolism (7.0 versus 10.5/100 persons-years, HR: 0.53, 95%CI: 0.10 to 2.75, \( P = 0.453 \); 7.0 versus 7.5/100 persons-years, HR: 0.96, 95%CI: 0.18 to 5.22, \( P = 0.964 \), respectively). Compared to dual therapy with warfarin, dual therapy with DOAC had slightly less major bleeding (3.0 versus 8.4/100 persons-years, HR: 0.38, Table II.

### Table II. Clinical Characteristics and Treatments at Baseline

<table>
<thead>
<tr>
<th>Regimen of DOAC</th>
<th>Dual therapy with DOAC (n = 79)</th>
<th>Dual therapy with Warfarin (n = 75)</th>
<th>P</th>
<th>Triple therapy with DOAC (n = 46)</th>
<th>Triple therapy with Warfarin (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 score</td>
<td>2.5 ± 1.3</td>
<td>2.2 ± 1.3</td>
<td>0.171</td>
<td>2.5 ± 1.3</td>
<td>2.2 ± 1.1</td>
<td>0.185</td>
</tr>
<tr>
<td>CHA2DS2 -VASc score</td>
<td>4.1 ± 1.7</td>
<td>3.6 ± 1.7</td>
<td>0.067</td>
<td>4.2 ± 1.6</td>
<td>3.6 ± 1.5</td>
<td>0.043</td>
</tr>
<tr>
<td>TTR (%)</td>
<td>53.3 ± 28.6</td>
<td>-</td>
<td>-</td>
<td>48 ± 31.6</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen of antiplatelet drug</th>
<th>Dual therapy with DOAC (n = 79)</th>
<th>Dual therapy with Warfarin (n = 75)</th>
<th>P</th>
<th>Triple therapy with DOAC (n = 46)</th>
<th>Triple therapy with Warfarin (n = 80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>59 (74.7)</td>
<td>63 (84.0)</td>
<td>0.467</td>
<td>46 (100)</td>
<td>80 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>18 (22.8)</td>
<td>11 (14.7)</td>
<td>0.382</td>
<td>38 (92.6)</td>
<td>72 (90.3)</td>
<td>0.097</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>2 (2.5)</td>
<td>1 (1.3)</td>
<td>0.650</td>
<td>3 (6.5)</td>
<td>6 (7.5)</td>
<td>-</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>5 (10.9)</td>
<td>2 (2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Loading of antiplatelet drug</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>2 (4.3)</td>
<td>1 (1.3)</td>
<td>0.555</td>
</tr>
<tr>
<td>Medications in use at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>46 (58.2)</td>
<td>43 (57.3)</td>
<td>&gt; 0.999</td>
<td>38 (82.6)</td>
<td>49 (61.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>44 (55.7)</td>
<td>58 (77.3)</td>
<td>0.006</td>
<td>40 (87.0)</td>
<td>61 (76.3)</td>
<td>0.223</td>
</tr>
<tr>
<td>Statin</td>
<td>34 (43.0)</td>
<td>35 (46.7)</td>
<td>0.750</td>
<td>33 (71.7)</td>
<td>45 (56.3)</td>
<td>0.091</td>
</tr>
<tr>
<td>Glucose-lowering drug</td>
<td>17 (21.5)</td>
<td>17 (22.7)</td>
<td>&gt; 0.999</td>
<td>11 (23.9)</td>
<td>20 (25.0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>NSAID</td>
<td>1 (1.3)</td>
<td>2 (2.7)</td>
<td>0.613</td>
<td>1 (2.2)</td>
<td>1 (1.3)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>PPI or H2 blocker</td>
<td>62 (78.5)</td>
<td>63 (84.0)</td>
<td>0.416</td>
<td>42 (91.3)</td>
<td>73 (91.3)</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>

TTR indicates time in therapeutic international normalized ratio range; ACE-inhibitor, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II-receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor; and H2 blocker, histamine H2-receptor antagonist.

### Table III. Outcomes in Multiple Antithrombotic Regimens

<table>
<thead>
<tr>
<th>Death</th>
<th>Dual therapy with DOAC (n = 79)</th>
<th>Dual therapy with Warfarin (n = 75)</th>
<th>P</th>
<th>Hazard ratio (95%CI)</th>
<th>P</th>
<th>Triple therapy with DOAC (n = 46)</th>
<th>Triple therapy with Warfarin (n = 80)</th>
<th>P</th>
<th>Hazard ratio (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>2 (3.0)</td>
<td>4 (5.6)</td>
<td>0.61 (0.10-3.59)</td>
<td>0.586</td>
<td>2 (7.0)</td>
<td>2 (3.0)</td>
<td>1.67 (0.21-13.50)</td>
<td>0.633</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
<td>1.85 (0.09-38.80)</td>
<td>0.694</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (3.5)</td>
<td>3 (4.5)</td>
<td>0.68 (0.07-6.62)</td>
<td>0.736</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3 (4.6)</td>
<td>3 (4.2)</td>
<td>1.52 (0.24-9.47)</td>
<td>0.657</td>
<td>1 (3.5)</td>
<td>4 (6.0)</td>
<td>0.37 (0.04-3.71)</td>
<td>0.399</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>3 (4.6)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (3.5)</td>
<td>2 (3.0)</td>
<td>1.85 (0.09-38.80)</td>
<td>0.694</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>0 (0)</td>
<td>3 (4.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0 (0)</td>
<td>2 (3.0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Disabling</td>
<td>2 (3.0)</td>
<td>2 (2.8)</td>
<td>1.46 (0.17-12.60)</td>
<td>0.729</td>
<td>1 (3.5)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>3 (4.6)</td>
<td>1 (1.4)</td>
<td>3.11 (0.23-42.84)</td>
<td>0.397</td>
<td>2 (7.0)</td>
<td>5 (7.5)</td>
<td>0.96 (0.18-5.22)</td>
<td>0.964</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit outcomes</td>
<td>3 (4.6)</td>
<td>3 (4.2)</td>
<td>1.66 (0.30-9.25)</td>
<td>0.565</td>
<td>2 (7.0)</td>
<td>7 (10.5)</td>
<td>0.53 (0.10-2.75)</td>
<td>0.453</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (3.0)</td>
<td>6 (8.4)</td>
<td>0.38 (0.07-2.18)</td>
<td>0.279</td>
<td>1 (3.5)</td>
<td>8 (12.0)</td>
<td>0.24 (0.03-1.96)</td>
<td>0.183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0 (0)</td>
<td>2 (2.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as number (incidence rates). Incidence rates are events per 100 person-years. Benefit outcomes, cardiac death, acute myocardial infarction, or stroke. CI indicates confidence interval. Adjusted by age, sex, and risk factors (congestive heart failure, hypertension, diabetes mellitus, and stroke/transient ischemic attack) for ischemic stroke and thromboembolism; and adjusted by age, sex, and risk factors (hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, and usage of nonsteroidal anti-inflammatory drug) for major bleeding; and adjusted by age, sex, and risk factors (hypertension and diabetes mellitus) for death and benefit outcomes.
and similar benefit outcomes and thromboembolism (4.6 versus 4.2/100 persons-years, HR: 1.66, 95% CI: 0.30 to 9.25; 4.6 versus 1.4/100 persons-years, HR: 3.11, 95% CI: 0.23 to 42.84, respectively). The backgrounds of the bleeding cases are shown in Table IV. Fatal bleeding was observed only in the dual therapy with warfarin group (2/2, 100%). All of the bleeding patients on DOAC had chronic kidney disease (3/3, 100%), and 9 out of 14 patients with bleeding on warfarin had chronic kidney disease (64.3%). Bleeding cases in the warfarin group showed marked increases in PT-INR at the time of bleeding (4.5 ± 3.3), but the increase was not observed at pre-bleeding clinic visits in the same patients (1.9 ± 0.7). The period from drug administration to bleeding was up to 3 months in 5.9% (1/17), up to 6 months in 52.9% (9/17), and 6 months or later in 41.2% (7/17), with the majority of patients experiencing bleeding after 3 or more months [94.1% (16/17)].

A sub-analysis of AF patients is presented in Table V. Triple therapy with DOAC (n = 25) had similar major bleeding, benefit outcomes, and thromboembolism (7.2 versus 14.4/100 persons-years, HR: 0.97, 95% CI: 0.07 to 12.87; P = 0.980; 14.4 versus 14.4/100 persons-years, HR: 1.08, 95% CI: 0.15 to 7.59, P = 0.940; 14.4 versus 9.6/100 persons-years, HR: 1.48, 95% CI: 0.18 to 12.12, P = 0.716, respectively) compared to triple therapy with warfarin (n = 27). Dual therapy with DOAC (n = 64) had similar major bleeding and benefit outcomes (3.8 versus 8.6/100 persons-years, HR: 0.72, 95% CI: 0.10 to 5.27, P = 0.742; 5.6 versus 5.7/100 persons-years, HR: 1.65, 95% CI: 0.24 to 11.56, P = 0.614, respectively) as dual therapy with warfarin (n = 37).
The WOEST trial reported that dual therapy (VKA with clopidogrel) was superior to triple therapy (VKA with aspirin and clopidogrel) in terms of both efficacy and safety. Dual therapy with dabigatran plus dual antiplatelet drugs is as effective as an anticoagulant in triple therapy in cases of short-term use, had a high use rate of low-dose DOAC, and no loading of antiplatelet drugs. In addition, there was no fatal bleeding or cerebral hemorrhage with dual therapy with DOAC. It is believed DOAC might be effective as an anticoagulant in dual therapy. All of the bleeding patients on DOAC had chronic kidney disease. DOAC should be used carefully and with caution in patients with chronic kidney disease.

**Discussion**

Efficacy and safety of triple therapy with DOAC and warfarin:

Compared to triple therapy with warfarin, there was no increase in major bleeding and similar thromboembolism and benefit outcomes with triple therapy with DOAC. For sub-analysis of AF patients, triple therapy with DOAC had similar major bleeding, thromboembolism, and benefit outcomes. The efficacy and safety of triple therapy with DOAC has been reported previously. Dabigatran plus dual antiplatelet drugs is associated with more bleeding events than dabigatran plus a single antiplatelet drug. The addition of apixaban to dual antiplatelet drugs increases major bleeding events without a significant reduction in recurrent ischemic events. The addition of very low dose rivaroxaban to dual antiplatelet drugs reduces the risk of cardiac death, myocardial infarction, or stroke, but results in more major bleeding and intracranial hemorrhage. A few studies have examined the relation between dual therapy with DOAC and warfarin. Apixaban with aspirin reduced stroke or systemic embolism and had less major bleeding than warfarin with aspirin. However, the only antiplatelet drug used was aspirin. In our study, dual therapy with DOAC did not increase major bleeding and thromboembolism and benefit outcomes were similar to those of dual therapy with warfarin. In sub-analysis of AF patients, dual therapy with DOAC had similar major bleeding and benefit outcomes. This may be because dual therapy with DOAC in our study was short-term use, had a high use rate of low-dose DOAC, and no loading of antiplatelet drugs. In addition, there was no fatal bleeding or cerebral hemorrhage with dual therapy with DOAC. It is believed DOAC might be effective as an anticoagulant in dual therapy. All of the bleeding patients on DOAC had chronic kidney disease. DOAC should be used carefully and with caution in patients with chronic kidney disease.

Timing of onset of bleeding:

In our study, bleeding mainly occurred after 3 months when used concomitantly with antiplatelet therapy with an oral anticoagulant drug. Bleeding in DOAC patients only occurred at 3 months or later. Previous reports have examined the timing of the onset of bleeding. Lambert, et al reported triple therapy had the highest incidence of bleeding within 3 months, and the risk of bleeding continued after 3 months. Rogacka, et al reported triple therapy had a high incidence of bleeding in the first month, followed by a subsequent reduction. The ISAR-TRIPLE trial reported that 6 weeks of triple therapy was not superior to 6 months with respect to clinical outcomes and major bleeding. Two reports found that triple therapy increased bleeding in long-term follow-up. In our study, TTR for triple therapy was low at about 50%, and so the effect of warfarin might be low in the early phase. In addition, the loading of antiplatelet drugs was low, and so the effect of antiplatelet drugs might be low in the early phase. Therefore, it is possible that there were few inci-

<table>
<thead>
<tr>
<th>Table V. Outcomes in Sub-Analysis of Atrial Fibrillation Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>All-cause</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Ischemic</td>
</tr>
<tr>
<td>Haemorrhagic</td>
</tr>
<tr>
<td>Disabling</td>
</tr>
<tr>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Benefit outcomes</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
<tr>
<td>Fatal bleeding</td>
</tr>
</tbody>
</table>

*Adjusted by age, sex, and risk factors (congestive heart failure, hypertension, diabetes mellitus, and stroke/transient ischemic attack) for ischemic stroke and thromboembolism; and adjusted by age, sex, and risk factors (hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, and usage of nonsteroidal anti-inflammatory drug) for major bleeding; and adjusted by age, sex, and risk factors (hypertension and diabetes mellitus) for death and benefit outcomes.
dences of early bleeding. After the therapeutic range for warfarin and antiplatelet drugs reached, bleeding might occur in the late phase. There are a few reports on bleeding onset in DOAC plus dual antiplatelet drugs. Apixaban plus dual antiplatelet drugs has a high incidence of major bleeding and is soon terminated. The plasma concentration of DOAC reached the therapeutic range immediately after administration, and DOAC has an immediate effect in early period. However, there were no bleeding events within 3 months in our study. The reason for this might be the short-term use, the high use rate of low-dose DOAC, the low degree of loading of antiplatelet drugs, and the high use rate of PPI or H2 blockers. A joint European consensus document recommends that the period of triple therapy after stent implantation in AF patients should be 1 month. In this study, triple therapy increased bleeding at 3 months. We believe that an early reduction of antiplatelet drugs is necessary. Short-term use, low-dose of oral anticoagulant drugs, low level of loading of antiplatelet drugs, and use of PPI or H2 blockers might be effective at preventing bleeding in the early phase.

**PT-INR as an index of safety in concomitant use of antiplatelet therapy with warfarin:** It has been reported that bleeding events increase when PT-INR is 2.6 or higher. In our study, PT-INR at pre-bleeding clinic visits was within the normal range (1.9 ± 0.7) for the concomitant use of antiplatelet therapy with warfarin. Abruptly, PT-INR was prolonged at the time of bleeding. It might be difficult to predict bleeding from PT-INR at clinic visits by outpatients in the case of concomitant use of antiplatelet therapy with warfarin.

**Limitations:** This study was a single center, retrospective, non-randomized, and observational study. The selections of anticoagulants and period of treatment were not randomized as the decisions were made by the physicians. The observation period differed according to the anticoagulant regimen. There were variations in the indication for oral anticoagulation or antiplatelet therapy. The number of patients was small and the follow-up period was short. Future large-scale randomized studies should be conducted.

**Conclusions:** Triple therapy and dual therapy with DOAC were not inferior to triple therapy and dual therapy with warfarin in terms of major bleeding, benefit outcomes, and thromboembolism. Bleeding mainly occurred in the late phase. It was difficult to predict bleeding from PT-INR at outpatient clinic visits for concomitant use of antiplatelet therapy with warfarin.

**DISCLOSURE**

T.I. has received research funding through his institution from Daiichi Sankyo, Bristol-Myers Squibb, Boehringer Ingelheim; and remuneration from Bayer Healthcare, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Tanabe-Mitsubishi, and Ono Pharmaceutical.

**REFERENCES**


