Triple Antithrombotic Therapy
– Always One Too Many? –

Hidehira Fukaya, MD, PhD; Junya Ako, MD, PhD

Comorbidity of atrial fibrillation (AF) and ischemic heart disease (IHD) is not uncommon. Approximately 5–10% of IHD patients are reported to be complicated by AF.1–3 Anticoagulation is recommended for patients with AF to prevent stroke and systemic thromboembolic events.4–6 Dual antiplatelet therapy (DAPT: aspirin plus P2Y12 inhibitor) has been the cornerstone of prevention of stent thrombosis in patients undergoing percutaneous coronary intervention (PCI). Therefore, AF patients who undergo PCI are often treated with triple therapy (TT: DAPT plus anticoagulation); however, the optimal combination therapy for such patients has not been fully determined.

Previous studies3,7–10 have shown that TT increases bleeding complications while not clearly altering thrombotic event rates (Table). From those studies, it may be safe to conclude that the risk of bleeding often outweighs the benefit of TT. In fact, recent European Society of Cardiology guidelines discourage longer term TT.11 However, it is yet to be elucidated if such a regimen can be applied to all AF patients after PCI, considering the highly variable individual thrombotic and bleeding risks.

In this issue of the Journal, Sambola et al12 evaluated the efficacy and safety of TT in AF patients undergoing PCI compared with those of DAPT. They extracted data from a prospective multicenter registry that enrolled 585 AF patients undergoing PCI. The authors separately analyzed the results according to CHA2DS2-VASc score: CHA2DS2-VASc=1, 26.8% vs. CHA2DS2-VASc ≥2, 73.2%) In the 1-year follow-up of the patients, TT was not associated with less thromboembolic events, and the bleeding complication rate of TT was significantly higher compared with DAPT in the low thromboembolic risk group (CHA2DS2-VASc=1). In the higher thromboembolic risk group (CHA2DS2-VASc ≥2), TT was associated with a lower thromboembolic event rate compared with DAPT; however, the bleeding complication rate was higher. Multivariate analysis found that TT was an independent predictor for major bleeding complications; therefore, the authors concluded that TT involved a high risk for bleeding with no apparent benefit for AF patients with CHA2DS2-VASc=1 undergoing PCI.

The strength of this report lies in using the CHA2DS2-VASc score for risk stratification. Although previous studies1–3 have not investigated the individual risk of the patients, the comorbidity of atrial fibrillation (AF) and ischemic heart disease (IHD) is not uncommon. Approximately 5–10% of IHD patients are reported to be complicated by AF.1–3 Anticoagulation is recommended for patients with AF to prevent stroke and systemic thromboembolic events.4–6 Dual antiplatelet therapy (DAPT: aspirin plus P2Y12 inhibitor) has been the cornerstone of prevention of stent thrombosis in patients undergoing percutaneous coronary intervention (PCI). Therefore, AF patients who undergo PCI are often treated with triple therapy (TT: DAPT plus anticoagulation); however, the optimal combination therapy for such patients has not been fully determined.

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### Table. Studies of Multiple Antithrombotic Therapies for AF Patients Undergoing PCI: TT Compared With Other Therapies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year published</th>
<th>Comparison</th>
<th>Study design</th>
<th>n</th>
<th>Observation period (months)</th>
<th>Stroke in TT</th>
<th>Bleeding complications in TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sambola et al12</td>
<td>2016</td>
<td>TT vs. DAPT (ASA/Clop) in CHA2DS2-VASc ≥2</td>
<td>Prospective</td>
<td>585</td>
<td>12</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Dewilde et al7 (WOEST trial)</td>
<td>2013</td>
<td>TT vs. Clop/VKA</td>
<td>Prospective</td>
<td>573</td>
<td>12</td>
<td>NS</td>
<td>Increased</td>
</tr>
<tr>
<td>Sambola et al8 (MUSICA study)</td>
<td>2009</td>
<td>TT vs. VKA/APT vs. DAPT</td>
<td>Prospective</td>
<td>405</td>
<td>6</td>
<td>NS*</td>
<td>Increased*</td>
</tr>
<tr>
<td>Karjalainen et al9 (Danish Registry)</td>
<td>2007</td>
<td>TT vs. DAPT, ASA/VKA, Clop/VKA</td>
<td>Retrospective</td>
<td>239</td>
<td>12</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lambert et al10 (CREDO-Kyoto)</td>
<td>2013</td>
<td>TT vs. DAPT, ASA/VKA, Clop/VKA</td>
<td>Retrospective</td>
<td>12,165</td>
<td>12</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Goto et al9 (CREDO-Kyoto)</td>
<td>2014</td>
<td>TT vs. DAPT</td>
<td>Prospective</td>
<td>1,057</td>
<td>61</td>
<td>NS</td>
<td>Increased</td>
</tr>
</tbody>
</table>

*Multiple comparison. ASA, aspirin; Clop, clopidogrel; DAPT, dual antiplatelet therapy (ASA+Clop); TT, triple therapy; VKA, warfarin.
present study found that efficacy and safety of TT differed according to the patient’s thromboembolic risk. This study is noteworthy because the authors show that an individual risk-based therapeutic approach may help us further balance the efficacy and safety of antithrombotic therapy, especially when involving TT.

The importance of individualized risk assessment has been increasingly recognized in clinical trials of antithrombotic therapies. In the DAPT Study, a randomized control trial comparing 12-month DAPT vs. 30-month DAPT following drug-eluting stent implantation, the 30-month DAPT group was associated with a significantly lower rate of adverse cardiac events compared with 12-month DAPT, while there was an increase in the bleeding rate with 30-month DAPT. A subanalysis of the DAPT study constructed a “DAPT score”, which simultaneously evaluated thromboembolic and bleeding risks. In the DAPT study population, the DAPT score clearly stratified the patients who benefited from continued DAPT. It exemplifies the importance of individual patient risk assessment when using antithrombotic medicines. In that regard, the present study by Sambola et al. is an important first step in assessing risk in AF patients on anticoagulation therapy. This study has shown that patients with lower thromboembolic risk may not benefit from TT. However, at the same time, patients with much higher thromboembolic risk but relatively low bleeding risk may benefit from TT by lowering the incidence of stroke, although the number of such patients could be relatively limited.

Several limitations must be noted. Nonrandomized observational study always carries a risk for bias. A regimen of oral anti-agulant and a single P2Y12 inhibitor is often prescribed in clinical practice since the WOEST trial; however, that combination was not included in this study. In addition, direct oral anticoagulants (DOAC) have been increasingly used in AF patients, drastically changing clinical practice. Because there was no DOAC used as an anticoagulant in this study, the results may not be readily applicable to TT with DOACs because the efficacy and safety of DOAC combined with antiplatelet drugs could be different.

Nevertheless, these data from carefully followed patients are of clinical relevance. This study clearly showed the importance of an individualized risk-based strategy for AF patients undergoing PCI. Further studies are definitely needed to seek the optimal antithrombotic regimen for patients receiving antiplatelet therapy and anticoagulation therapy.

Disclosures

References