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Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Undergoing PCI: Adequate Time in Therapeutic INR Range

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Mini Review

Dual anti-platelet therapy (DAPT) is a standard procedure for patients undergoing percutaneous coronary intervention (PCI) using stents [1,2], whereas oral anticoagulation (OAC) is necessary, when $CHADS_2$-VASc scores are ≥ 2, to reduce stroke and embolic events in patients with atrial fibrillation (AF) [3,4]. Coronary artery disease (CAD) and AF often coexists in same patient, approximately 5-10% of patients who underwent PCI have AF [5,6]. Some studies have reported that DAPT with OAC (triple antithrombotic therapy [TT]) reduces major cardiovascular events and mortality compared with DAPT only in patients who underwent PCI with AF [7,8]. On the other hand, others have found that TT increases the bleeding and cardiovascular events [9,10]. Therefore, the optical combination antithrombotic therapy for the patients with AF undergoing PCI is uncertain.

The 2012 American College of Chest Physicians (ACCP) guidelines recommended TT (eg. OAC, aspirin and clopidogrel) for patients with AF ($CHADS_2$ score of 2 or greater) who undergoing PCI during the first month after placement of a bare-metal stent or first 3 to 6 months after placement of a drug-eluting stent. After this initial period of TT, OAC plus a single antiplatelet drug is recommended. At 12 months after PCI, OAC alone is suggested as for patients with AF and CAD (Grade 2C) [11]. The 2016 European Society of Cardiology (ESC) guidelines recommended TT during the first month after PCI (stable CAD and acute coronary syndrome with high bleeding risk) or first 6 months after PCI (acute coronary syndrome with low bleeding risk). After that, recommendation of antithrombotic therapy was same as the 2012 ACCP guidelines (class IIa, evidence level B or C) [12]. When a direct oral anticoagulant (DOAC) is used as for OAC, the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered.

Recently, DOAC is broadly used as for OAC instead of vitamin K antagonism (VKA) in patients with AF and venous thromboembolism. However, the patients of chronic kidney disease, high age and lean do not have the adaptation of DOAC. Among the patients with AF who undergoing PCI, the patients who do not have the adaptation of DOCA are not a little and these patients need to use VKA as for OAC. Therefore, one of critical issue of TT is still unclear regarding appropriate range of international normalized ratio of prothrombin time (PT-INR). In patients, who receive TT, the recommended range for the PT-INR varies between 2.0 and 2.5 in the ESC guidelines (class IIa, evidence level C) [13] and between 2.0 and 3.0 in the ACCP guidelines (grade 2C) [12]. However, a PT-INR value using TT has not been established. An open-label, multicenter, randomized, controlled trial (WOEST trial) [14] compared bleeding and thrombotic events between TT and double antithrombotic therapy (clopidogrel and warfarin) in patients undergoing PCI who required OAC. TT was associated with a significant increase in bleeding complications. In WOEST trial, target range of PT-INR was set between 2.0 and 3.0, and the control of PT-INR (time in the therapeutic range [TTR]) was unclear. From WOEST study, range of PT- INR (2.0-3.0) might inappropriate in therapeutic INR range in patients with TT. Therefore, we investigated whether warfarin control is associated with reduced cardiovascular events and major bleeding events in patients with TT [15]. We compared the outcomes between TT and DAPT in patients who underwent PCI using drug-eluting stents. Most of patients using DAPT did not have history of af. In our institute, the mean PT-INR was 1.8 ± 0.2 and the median TTR was 78.4% (inter-quartile range: 67.4-87.6) if the target level of PT-INR was set between 1.6 and 2.6 in TT group. The incidence of cardiovascular events and major bleeding events did not significantly differ between two groups (TT and DAPT group). This finding was consistent with J-RHYTHM Registry, which showed that a relatively low PT-INR range of 1.6-2.6 was safe and prevented thromboembolic or bleeding events in patients with AF [16]. In general, the target range of PT-INR is higher in the USA and Europe compared with Japan. However, the BAATAF and SPINAF studies performed outside Japan set the target range for PT-INR at 1.5-2.7, and at 1.4-2.8 in patients with AF [17,18], respectively. These studies found that a low PT-INR reduced the incidence of thromboembolic events in patients with AF. Furthermore, Rossini and colleague reported that PT-INR >2.6 was the only independent predictor of bleeding among patients who underwent PCI and required TT [19]. Therefore, it is possible that PT-INR 1.6-2.6 is acceptable and safe for patients who undergo PCI and require TT. Furthermore, it goes without saying, careful warfarin control is necessary.

This issue of TT is still controversy. Ongoing trials will inform about combination therapies in the future.

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