Clinical Decision-Making When Treating High Bleeding Risk Patients: A Japanese Perspective

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Ischemic events after stenting have decreased considerably in recent years thanks to the introduction of newer-generation drug-eluting stents (DESs) and progressive refinement of pharmaco-interventional techniques. However, due to more potent and prolonged platelet inhibition, the incidence of bleeding complications has increased, especially in patients with high bleeding risk (HBR).

To reduce bleeding complications after percutaneous coronary intervention (PCI) in HBR patients, optimal discrimination of HBR patients is needed before taking practical measures, namely pharmacological and interventional approaches. Pharmacological approaches include a shorter duration of dual antiplatelet therapy (DAPT), and de-escalation and dose adjustment of a P2Y12 inhibitor. Interventional approaches include simpler strategies and less thrombogenic devices, which may help reduce thrombotic events without requiring a longer DAPT duration. These practices may be used alone or in combination.

The European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend DAPT duration according to the clinical status and risks of bleeding and ischemia.[1,2] Several bleeding risk scores established from large-scale studies are used in clinical practice. The ESC guidelines use the PRECISE-DAPT score to discriminate HBR patients.[3] For HBR patients with a PRECISE-DAPT score ≥ 25, a suitable DAPT duration depends on the coronary status: 3 months for those with stable coronary artery disease and 6 months for those with acute coronary syndrome (ACS). The ACC/AHA guidelines reference the DAPT score to quantify risk for ischemia and bleeding; a score ≥ 2 correlates with a favorable risk/benefit ratio for prolonged DAPT, whereas a score < 2 has an unfavorable risk/benefit profile for prolonged DAPT.[4] The 2016 ACC/AHA guidelines gave a class I, level A recommendation for a minimum mandatory DAPT duration of 6 months for patients with stable ischemic heart disease being treated with a newer-generation DES, a reduction from the former ACC/AHA recommendation of 12 months. Additionally, they gave a class IIb, level C-LD recommendation for discontinuation of P2Y12 inhibitor after 3 months for those who develop a high risk of bleeding or are at high risk for severe bleeding complications. For patients with ACS being treated with BMS or DES, the recommendation for at least 12 months of DAPT remained.[2] Other well-known scores include the PARIS score[5] and CREDO-Kyoto risk score.[6] The contributing factors of these scores are quite different from one another (Table 1). Using them

TABLE 1. CRITERIA USED IN BLEEDING RISK SCORES

Score Name	PARIS[5]	PRECISE-DAPT[3]	Credo-Kyoto[6]	DAPT[4]
Age	Yes	Yes	-	Yes
BMI	Yes	-	-	-
Current smoking	Yes	-	-	Yes
Anemia	Yes	Yes	-	-
CKD	Yes	Yes	Yes	-
TAPT on discharge	Yes	-	-	-
White blood cell count	-	Yes	-	-
Previous bleeding	-	Yes	-	-
Platelet count	-	-	Yes	-
PVD	-	-	Yes	-
Heart failure	-	-	Yes	Yes
Malignancy	-	-	Yes	-
Atrial fibrillation	-	-	Yes	-

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; PVD, peripheral vascular disease; TAPT, triple antithrombotic therapy.

to discriminate HBR patients in real-world settings needs careful attention to the differences in patient populations, as will be described in this article.

DOSING CONSIDERATIONS FOR THE JAPANESE POPULATION

De-escalation of P2Y12 inhibitor treatment (eg, switching from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy,[7] especially for patients with ACS who are deemed unsuitable for 12-month potent platelet inhibition in the ESC/ESCTA guidelines. A widely used dose of prasugrel in Japan, however, is different from the global standard. The efficacy of this strategy cannot be easily applied to practice in Japan because of the difference in physique. The ACC/AHA guidelines do not recommend the use of platelet function testing, as no randomized controlled trial has demonstrated an improvement in outcomes when used to guide P2Y12 inhibitor treatment; similarly, no randomized data are available on the long-term safety of efficacy of switching patients to a different P2Y12 inhibitor.[2]

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) showed that in ACS patients with scheduled PCI, prasugrel therapy with a loading dose of 60 mg and a maintenance dose of 10 mg was associated with reduced ischemic events, but was also associated with increased bleeding events, in comparison with clopidogrel therapy.[8] On the basis of the report that East Asians have a higher bleeding risk and a lower ischemic event risk than Westerners (known as "East Asian Paradox"),[9] the PRASFIT-ACS (Prasugrel Compared with Clopidogrel for Japanese Patients with ACS Undergoing PCI) determined an appropriate dose of prasugrel (loading dose of 20 mg and maintenance dose of 3.75 mg) and confirmed its safety and efficacy in Japanese ACS patients; therefore, an adjusted dose of prasugrel is more commonly used in Japan instead of clopidogrel for both ACS and stable coronary artery disease patients.[10] Furthermore, efficacy of a maintenance dose of prasugrel 2.5 mg was demonstrated as an option for HBR-ACS patients with low body weight (≤ 50 kg), advanced age (≥ 75 years), or renal insufficiency (estimated glomerular filtration rate ≤ 30 mL/min/1.73 m^2).[11] Further dose adjustment of prasugrel may be an option for HBR patients in Japan.

COMBINATION THERAPY

Combination therapy of oral anticoagulant and antiplatelet therapy, although less known, is an additional risk factor for HBR patients. The ACC/AHA recommendations on DAPT duration are generally not considered applicable to patients treated with oral anticoagulants, as patients on oral anticoagulants were excluded from almost all studies of DAPT duration.[2] In the ESC/EACTS guidelines, the use of direct oral anticoagulant (DOAC) is recommended on the basis of some randomized studies demonstrating a comparison of warfarin with DOAC for atrial fibrillation patients with PCI.[12] Also, the use of a newer P2Y12 inhibitor, ticagrelor or prasugrel, as a part of a triple therapy regimen is discouraged; however, no comments are made on a dual therapy combining ticagrelor or prasugrel with a DOAC as a possible alternative for a triple therapy with aspirin, clopidogrel, and a DOAC. Using one of these newer P2Y12 inhibitors with a (D)OAC under certain circumstances (eg, perceived high thrombotic risk, ACS, complex PCI, and prior stent thrombosis) may be considered. When using a newer P2Y12 inhibitor in HBR patients with these risk factors, bleeding complications may be prevented with a shorter duration, switching between newer P2Y12 inhibitors, or dose adjustment.

COMPLEX PCI

For HBR patients with complex PCI, balancing the risks of bleeding and ischemia is very important and difficult. A recent study demonstrated that patients who had undergone complex PCI had a higher risk of ischemic events, but had no benefit from long-term DAPT.[13] For these patients, choosing a simpler PCI strategy may be recommended. Generally, newer-generation DESs are less thrombogenic than first-generation DESs. Newer-generation DESs are coated with permanent polymer or biodegradative polymer, which may lead to less thrombogenicity. Animal studies have suggested that there are differences in antithrombogenicity between newer-generation DESs.[14] Choosing a less thrombogenic DES for complex PCI may be considered in the treatment of HBR patients.

CONCLUSION

In summary, clinical decision-making when treating HBR patients requires balancing the risks of bleeding and ischemia, which should be adjusted to each patient on the basis of guidelines, randomized studies, and clinical experience; patients' physiological differences in geographic regions (eg, Japanese versus Western) should also be kept in mind when analyzing guidelines. ■

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