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Review

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Optimal Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention: A Focused Review on High Bleeding Risk

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Dual antiplatelet therapy (DAPT) is a therapeutic cornerstone to prevent stent thrombosis following percutaneous coronary intervention (PCI) for coronary artery disease (CAD). However, the longer the DAPT duration, the higher the incidence of bleeding and mortality. Since the advent of second-generation drug-eluting stents (DES), the continuous evolution of DES has reduced the thrombotic risk and allowed for a shorter DAPT duration. On the other hand, concerns on the elevated risk of bleeding during antithrombotic therapy have been further raised due to the growing number of elderly CAD patients with multiple comorbidities. The consequent debate topic over post-PCI antithrombotic therapy has shifted from simply reducing thrombotic risk to safely minimizing bleeding risk. Due to the significant impact of bleeding on clinical outcomes, including prognosis, current guidelines on antithrombotic therapy for CAD prioritize stratification of patients at a high bleeding risk (HBR) as the top consideration in determining post-PCI antithrombotic therapy. Achieving optimal antithrombotic therapy for each patient undergoing PCI requires a better understanding of the clinical variables constituting the balance of bleeding and thrombotic risk. This review highlights relevant evidence required to optimize antithrombotic therapy for HBR patients undergoing PCI.

Key words: **High Bleeding Risk (HBR), Antithrombotic Therapy, Percutaneous coronary intervention (PCI)**

Introduction

Antithrombotic therapy effectively prevents recurrent thrombotic and ischemic events in patients with various clinical spectrums of coronary artery disease (CAD), which include acute coronary syndrome (ACS)[1, 2] and chronic coronary syndrome (CCS)[3, 4], and after revascularization procedures, such as coronary artery bypass grafting (CABG)[5] and percutaneous coronary intervention (PCI)[6]. On the other hand, antithrombotic therapy increases the risk of bleeding to a greater or lesser extent[7-9]. Nearly 40% of patients undergoing PCI and requiring subsequent dual antiplatelet therapy (DAPT) are reported to be at a high bleeding risk (HBR)[10], and the recent arrival of a super-aging society further accelerates the increased number of patients with HBR.

Maintaining antithrombotic efficacy without increasing bleeding events might be an ideal therapeutic goal; however, balancing between the risks of thrombosis and bleeding frequently includes dilemmas in practice[11] because the optimal tradeoff varies from patient to patient, and the "sweet spot" in the antithrombotic treatment can change over time from the acute to chronic phase even in the same patient[2]. Generally, the strategies to stratify patients at bleeding risk and modify the regimen and administration duration of antithrombotics according to bleeding risk-based strata can help avoid future bleeding events in treating thrombosis-related diseases[12]. Moreover, the importance of bleeding risk stratification strategies increases in clinical situations requiring intensified antithrombotics.

In the current treatment of CAD, the clinical use

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of DES with antithrombotic properties or the widespread optimal medical therapy, including intensified statin therapy, has contributed to the reduction of thrombotic and ischemic events after PCI. These therapeutic advances have significantly accelerated the shift of debate topic over antithrombotic therapy from the efficacy aspect of reducing the risk of thrombosis to the safety aspect of reducing the bleeding risk. As a result, shortening the duration of DAPT[13, 14] or de-escalating antithrombotic therapy[15] to reduce bleeding and related mortality can now be considered.

This article highlights recent evidence regarding antithrombotic therapy in HBR patients undergoing PCI. We hope that this review contributes to the achievement of optimal antithrombotic therapy for CAD patients with HBR.

What is HBR? Consensus definition by Academic Research Consortium (ARC) for HBR

First, a better understanding of the clinical background in which the consensus definition of HBR emerged would enrich the debate on antithrombotic therapy in HBR patients. Most clinical trials that tested the efficacy of previously emerging DES have included only patients who could tolerate continued 12 months or more extended periods of DAPT following PCI, the duration recommended by guidelines at that time, resulting in the exclusion of many HBR patients from these trials[16, 17]. Indeed, until recently, PCI with bare-metal stents (BMS) had the value of debate as one of the potent strategic options for HBR patients who could not use DAPT for at least 12 months as BMS requires only 1 month of DAPT[18]. The LEADERS FREE trial[19] and several other trials[18, 20, 21] were conducted to evaluate the efficacy of new DES, which are designed to be effective in HBR patients, given the clinical situations where a certain percentage of patients undergoing coronary stenting with DES have to discontinue DAPT due to bleeding complications, and this percentage shows an increasing trend with the increase in aging population with comorbidities. While each trial had shown favorable results, the lack of comparability between results due to wide variations in the definition of HBR patients and bleeding events across trials had been problematic. Moreover, the bleeding risk scores, such as PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score[22], DAPT score[23], PARIS (Patterns of Non-Adherence to Antiplatelet Regimen in Stented Patients) bleeding risk score[24], CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) Risk Score[25], and others, have demonstrated their usefulness in the prediction of bleeding events. However, the results from each bleeding risk prediction model also widely varied between studies due to differences in the definitions of bleeding and HBR patients, thus limiting clinical versatility of the above bleeding risk scores. Against these backgrounds, the ARC proposed a consensus definition of HBR, which was (1) a bleeding risk of ≥ 4% on Bleeding Academic Research Consortium bleeding criterion 3 or 5 or (2) a cerebral bleeding risk of ≥ 1% within 1 year after PCI. The ARC-HBR criteria consist of 20 major and minor clinical variables, of which patients with at least one major or two minor criteria were defined as HBR patients[16, 17]. Since then, multiple validation studies of the ARC-HBR criteria have been conducted worldwide and confirmed their validities[26, 27]. Natsuaki *et al.* demonstrated that the ARC-HBR criteria could identify patients with very HBR following PCI[28]. Nakamura *et al.* reported that the ARC-HBR criteria are appropriate for estimating bleeding risk in patients receiving second-generation (G2) DES implantation[29]. These studies proved that these criteria could be applied to an East Asian population at a lower risk of thrombosis and higher risk of bleeding than non-East Asians[30], supporting the usefulness of the ARC-HBR definition and criteria as a global standard for HBR patients beyond racial groups.

What Determines Antithrombotic Therapy Following PCI in Patients with HBR?

DAPT is the therapeutic cornerstone after PCI with DES. The balance between the risks of thrombosis and bleeding determines the duration and intensity of the DAPT and influences the post-DAPT antithrombotic regimen. Specific clinical variables that determine this balance in patients with HBR would include the type of DES, complex PCI, whether the clinical presentation is ACS or CCS, the choice of P2Y12 inhibitor, and the concomitant use of anticoagulants (OACs). The concise depiction of the decision scheme and decision-making factors for antithrombotics after PCI is presented in **Fig. 1**. We will outline and discuss the relevant evidence on each determinant of antithrombotic therapy in PCI patients with HBR.

1) Type of DES

First-generation (G1) DES historically emerged to solve the issues of stent restenosis in BMS. While

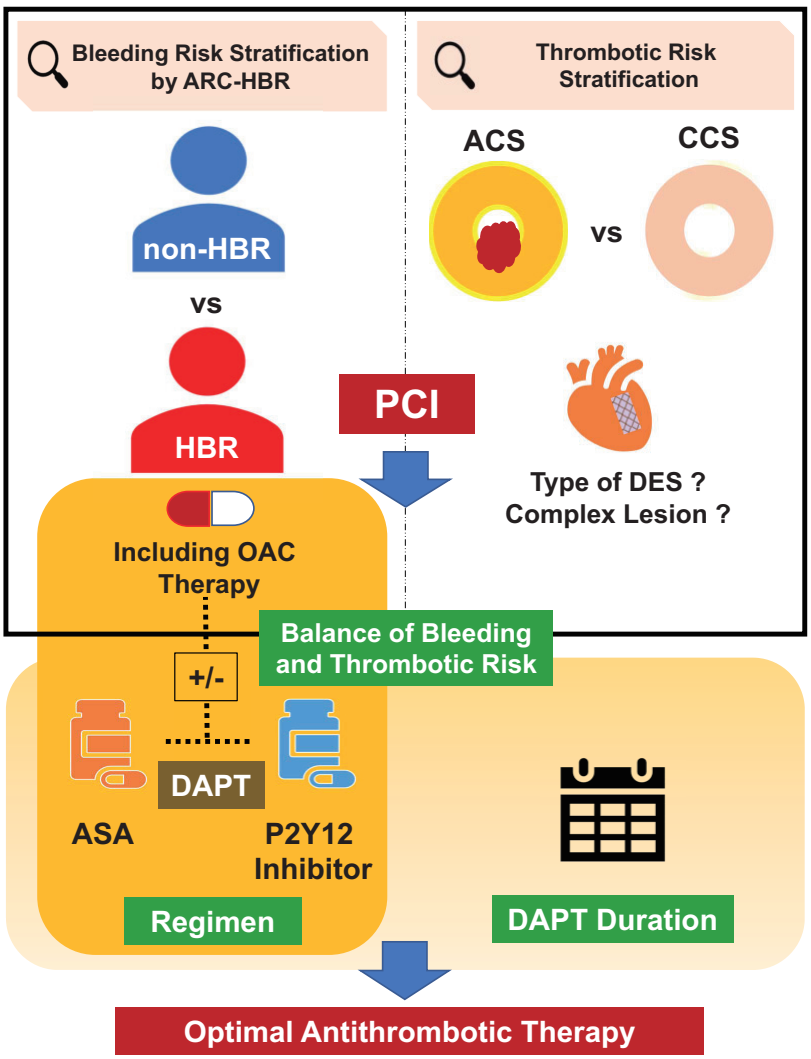

Fig. 1. Decision scheme and decision-making factors for antithrombotic therapy after PCI

ARC-HBR, Academic Research Consortium for High Bleeding Risk; OAC, oral anticoagulant; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DES, drug-eluting stent; PCI, percutaneous coronary intervention; DAPT, dual antiplatelet therapy; ASA, acetylsalicylic acid

exhibiting a powerful preventative effect for stent restenosis[31, 32], this generation of DES had concerns on late and very late stent thrombosis (LST/VLST) after DAPT discontinuation[33-37], partly due to excessive delay in re-endothelialization[38, 39], incomplete neointimal coverage[40, 41], and hypersensitivity to polymer[42, 43], requiring an extension of 1 year or more of DAPT duration. On the other hand, the longer the DAPT duration, the higher the incidence of bleeding events and mortality[44]. The G2 DES developed to resolve these issues has successfully preserved or improved efficacy for restenosis[45, 46] and significantly reduced the incidence of LST/VLST observed in the G1 DES[47, 48]. Dispelling concerns on LST/VLST through the recent advancement of DES provided the reason for the challenge to shorten the DAPT duration, which had been recommended for the continuation for 12 months or longer. Navarese *et al.* investigated the optimal duration of DAPT after PCI with DES, indicating that DAPT of less than 12 months after PCI, compared with the standard 12-month period, can reduce bleeding without increasing ischemic complications[49]. Recent meta-analyses have revealed that DAPT durations of 6 months or less and even shorter durations of 3 months or less compared with 12 months or more are associated with a lower risk of bleeding, comparable efficacy regardless of ACS or CCS, and a decreasing trend of overall mortality[50]. Currently, third-generation (G3) DES coated with bioabsorbable

polymer is clinically available and has shown at least comparable efficacy and safety results of G2 DES[51]. Furthermore, the safety and efficacy of 1-month DAPT have been proved in newer DES for HBR patients undergoing PCI for ACS and CCS[20, 52-54]. Due to the absolute decreased incidence of LST/VLST since the development of G2 DES, the impact of stent selection itself on thrombotic risks seems to be decreased relative to others and is no longer the highlight; however, its importance might be variable when considering further shortening of the DAPT duration and reduction of antithrombotic therapy.

2) Complex PCI

Complex PCI is usually defined as the composite of at least three stents implanted, at least three lesions treated, bifurcation with two stents implanted, total stent length >60 mm, and chronic total occlusion as a target lesion[55, 56]. Patients undergoing complex PCI have significantly higher thrombotic and ischemic risks than those undergoing non-complex PCI[57]. The magnitude of the antithrombotic effect of prolonged DAPT progressively increases as the degree of PCI complexity is more significant[56]. This trend is similar in patients undergoing complex PCI with newer-generation DES[58]. On the other hand, Costa *et al.* reported that patients who underwent complex PCI received beneficial effects from the prolonged duration of DAPT only in non-HBR patients, not in HBR patients[57]. This finding indicates that pursuing antithrombotic efficacy by a more prolonged duration of DAPT, even after complex PCI, is not reasonable for HBR patients. It remains unclear whether complex PCI is merely an indicator of CAD severity in the background or whether the complexity of the PCI procedure itself increases the risk of thrombosis. However, the modern PCI strategies, especially in HBR patients, appear to be moving toward fewer complex strategies, i.e., as few stents as possible in number and length and shorter DAPT duration, through the better use of intravascular imaging tools. This strategic trend also includes stentless PCI for *de novo* lesions using drug-coated balloons, which is currently limited to in-stent restenosis or small vessel lesions[59]. Bleeding risk may play a pivotal role in the decision not only on the duration of DAPT but also on the procedural strategy in PCI.

3) ACS vs. CCS

Thrombus formation with aggregated platelets and fibrin on ruptured or eroded coronary plaques is one of the pathological hallmarks of ACS[60]. Moreover, the culprit lesions in patients with ACS show an increased thrombogenicity compared with patients with CCS[61, 62]. Therefore, intensifying antithrombotic therapy in patients with ACS is reasonable to prevent subsequent recurrent thrombotic events. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial demonstrated the antithrombotic and anti-ischemic efficacy of adding P2Y12 inhibitor clopidogrel to aspirin in patients with ACS without ST-segment elevation. However, these efficacies were at the expense of an increased risk of bleeding[1]. Since major bleeding significantly increases mortality in patients with ACS[63, 64], a better prognosis after ACS requires bleeding and thrombotic event prevention. The latest focused update on DAPT duration in the AHA (American Heart Association), ESC (European Society of Cardiology), and JCS (Japanese Circulation Society) guidelines all recommend a longer duration of DAPT in ACS than in CCS in the absence of HBR. However, in HBR patients, whether the clinical presentation is ACS or CCS is limited in its role as a determinant of DAPT duration[55, 65, 66].

Recent evidence of DAPT after PCI with newer DES has shown that shortening the duration of DAPT to 1 month can reduce bleeding events without increasing thrombotic events. Investigation of this strategy extends to patients with high thrombotic risk, such as ACS. Valgimigli *et al.* demonstrated that patients with 1 month of DAPT had a similar rate of all-cause mortality or MI and significantly fewer bleeding events than those with 3 months of DAPT in the population in which approximately one-third of enrolled patients had ACS[67]. The result of the MASTER DAPT (Management of High-Bleeding-Risk Patients Post Bioresorbable Polymer-Coated Stent Implantation with an Abbreviated Versus Prolonged DAPT Regimen) trial in which 48.3% of enrolled patients were ACS indicated that the 1-month DAPT significantly reduced major or clinically relevant bleeding without increasing net adverse clinical events or major adverse cardiac or cerebral events compared with at least 3-month DAPT[53]. Conversely, the STOPDAPT-2 ACS (ShorT and OPtimal duration of Dual AntiPlatelet Therapy-2 study for patients with ACS) trial showed that 1 month of clopidogrel-based DAPT and subsequent clopidogrel monotherapy for 11 months failed to meet the criteria for noninferiority compared with the 12-month clopidogrel-based DAPT for the composite ischemic and bleeding endpoint in ACS patients undergoing PCI with everolimus-eluting stents[68]. The effect of 1-month DAPT after PCI on the efficacy and safety of patients with ACS is still unclear. HBR patients who developed ACS have coexisting risks of thrombosis and bleeding and require challenging management due to the antithrombotics' narrow

therapeutic "sweet spot" in efficacy and safety. Further relevant studies are required, which cover the drug choice of post-DAPT monotherapy or how to de-escalate antithrombotics for ACS.

4) Choice of P2Y12 Inhibitors in DAPT and Post-DAPT Monotherapies

The oral P2Y12 inhibitors that are currently used clinically include clopidogrel, prasugrel, and ticagrelor. The combination of clopidogrel and aspirin has been a standard regimen of DAPT following PCI, but clopidogrel has several limitations in clinical use, including variability in the antiplatelet response between patients and delayed onset of the drug effect. The attenuated antiplatelet effect in certain patients on clopidogrel can be explained partly by reduced hepatic biotransformation from a prodrug to an active form by the liver enzyme CYP2C19. Because the functional aberration of this enzyme is affected by the CYP2C19 genotype, selection of oral P2Y12 inhibitors considering the genotype seems reasonable for patients undergoing PCI[69]. Claassens *et al.* demonstrated that the CYP2C19 genotype-guided strategy for selecting oral P2Y12 inhibitors could reduce the bleeding risk without increasing thrombotic events in patients undergoing primary PCI[70]. In addition, given the differences in the antiplatelet potency among P2Y12 inhibitors, information on the CYP2C19 genotype may help in the selection of P2Y12 inhibitors for HBR patients. Contrarily, Pereira and colleagues reported that in patients with CYP2C19 loss-of-function alleles who developed ACS and CCS and underwent PCI, the genotype-guided oral P2Y12 inhibitor therapy failed to show statistically significant differences in the ischemic events and the related mortality at 12 months compared with the conventional clopidogrel treatment without point-of-care genotyping[71]. Furthermore, the results of genotype and functional testing by Hochholzer and colleagues indicated that the antiplatelet effect of clopidogrel is associated with the CYP2C19 genotype but that genotype alone or in combination with clinical factors does not fully explain the platelet reactivity to the clopidogrel[72]. The utility of the CYP2C19 genotype-guided strategy for selecting a P2Y12 inhibitor is still controversial, resulting in the updated guidelines of the AHA/ACC (American College of Cardiology), ESC, and JCS not recommending the routine use of genetic testing in clinical practice. However, there has been a drastic progress in the acquisition of genomic information and the ways to integrate genomics and clinical information. Further pharmacogenomic research is expected to determine optimal antithrombotic therapy following PCI.

Prasugrel and ticagrelor solve the drawbacks of clopidogrel as new P2Y12 inhibitors. The TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) 38 trial showed that prasugrel that has more potent antiplatelet effect, compared with clopidogrel, significantly reduced cardiovascular events, including stent thrombosis, but at the expense of increased bleeding events in patients with STEMI[73]. In the PRASFIT-ACS (PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI)[74] and PRASFIT-Elective (PRASugrel For Japanese PatIenTs with Coronary Artery Diseases Undergoing Elective PCI)[75] trials, the efficacy and safety of prasugrel were examined at a reduced dose setting (20-mg loading dose and 3.75-mg maintenance dose) equivalent to about one-third that was tested in the TRITON-TIMI38 study. The PRASFIT-ACS and PRASFIT-Elective trials demonstrated that adjustment of the dosing regimen of prasugrel for Japanese patients minimized the bleeding events and preserved efficacy equivalent to that of the TRITON-TIMI38 trial. Moreover, these two studies supported the concept that lowering the dose of new P2Y12 inhibitors might be one of the new ways to reduce the bleeding risk while preserving ischemic efficacy.

Wallentin and colleagues reported that ticagrelor, another new P2Y12 inhibitor, is more effective than clopidogrel, with no increase in major bleeding events observed in patients with ACS[76]. However, subsequent clinical trials of ticagrelor conducted at the same drug doses in Asia as in the USA and Europe reported increased bleeding events. Furthermore, the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial compared the efficacy and safety of prasugrel and ticagrelor in patients with ACS and reported fewer thrombotic events and similar bleeding events in the prasugrel group[77]. In patients with ACS, a potent new P2Y12 inhibitor, prasugrel, appears to be more effective than clopidogrel, but ticagrelor appears to have limited use in clinical practice.

A lifelong aspirin administration has been recommended as single antiplatelet monotherapy (SAPT) after DAPT. However, which drug is required as SAPT is still unclear because aspirin has concerns on the increased risk of gastrointestinal bleeding[78], especially in HBR patients. Chiarito *et al.* reported that a P2Y12 inhibitor is more effective than aspirin as SAPT for secondary prevention in patients with

established atherosclerosis[79]. Furthermore, a recent systematic review and meta-analysis demonstrated the safety and efficacy of the discontinuation of aspirin 1 to 3 months after PCI with continued use of P2Y12 inhibitors[80]. The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial demonstrated a significant reduction of bleeding events without worsening of the ischemic events over 1 year by a 3-month DAPT and subsequent ticagrelor monotherapy compared with 12-month combination therapy of aspirin and ticagrelor[81].

The consensus on the choice of P2Y12 inhibitors for DAPT and post-DAPT monotherapies in CAD patients with HBR will require further studies and careful discussions on the points, including the balance between thrombotic and bleeding risks, clopidogrel metabolism, and application of de-escalation strategies.

5) Concomitant Use of OACs

Atrial fibrillation (AF) is a common comorbidity in patients with CAD and requires long-term treatment with oral anticoagulant (OAC) to prevent stroke or systemic thromboembolism. Previous guidelines had recommended antithrombotic therapy with DAPT plus OAC as the standard care for AF-complicated CAD patients undergoing PCI. However, this triple antithrombotic therapy significantly increased the incidence of severe bleeding[82, 83]. The ARC-HBR criteria include the long-term use of anticoagulants as the major criteria of HBR[16, 17]. Given the severe concern on the triple therapy for bleeding outcomes, the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial was conducted, which showed that clopidogrel monotherapy significantly reduced bleeding events without increasing thrombotic events at 1 year compared with the clopidogrel and aspirin combination therapy in patients undergoing PCI while taking OAC[84]. After the emergence of direct oral anticoagulant (DOAC), several clinical trials have demonstrated that DOAC, in combination with a P2Y12 inhibitor, improves bleeding outcomes in patients undergoing PCI compared with triple therapy with warfarin[85-88]. In these trials, more than half of the patients had ACS. In both ACS and CCS, the combination of DOAC and clopidogrel had better outcomes than the triple therapy. A short-term triple therapy within 2 weeks perioperatively recommended by the 2020 JCS guideline, followed by at least 12 months of antithrombotic therapy with clopidogrel/prasugrel and DOAC, is suggested for patients with ACS/CCS and AF.

What is the appropriate regimen of antithrombotic therapy for AF patients beyond 1 year after coronary stenting? The OAC-ALONE (Optimizing Antithrombotic Care in patients with AtriaL fibrillatiON and coronary stEnt) trial challenged this question. This study investigated whether oral anticoagulation monotherapy is non-inferior to the combination of oral anticoagulation treatment and a single antiplatelet agent in AF patients at more than 1 year after stenting for CAD. This study was terminated early due to delayed enrollment and failure to answer the above question conclusively[89]. The AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial demonstrated that rivaroxaban monotherapy significantly improved bleeding and thrombotic outcomes as well as all-cause mortality compared with the combination of antiplatelet agents and OAC[90]. Based on this result, the 2020 JCS guideline recommends OAC monotherapy as standard therapy in the subsequent long-term management for stable CAD comorbid with AF.

Conclusions and Future Perspectives

Antithrombotic therapy for CAD has recently shifted from a thrombotic risk-first approach to a bleeding risk-first one. With the increasing number of elderly CAD patients suffering from multiple comorbidities, strategies for identifying HBR patients and optimizing the duration and regimen of antithrombotic therapy are being emphasized. However, because bleeding and thrombotic risks often coexist in the same patient, management of the tradeoff between these risks is challenging for the clinicians. Against these backgrounds, while clinical monitoring systems for assessing the efficacy and safety of antiplatelet and anticoagulation therapies are currently limited, there is a growing interest in tools for quantifying and visualizing the "sweet spot" of antithrombotic therapy. For example, the recently developed Total Thrombus-Formation Analysis System (T-TAS), a microchip-based system for assessing thrombus formation in whole blood, offers the potential for efficiently monitoring bleeding risk as an easy-to-use quantitative analysis system for thrombus formation[91].

The current post-PCI antithrombotic therapy applies a "treat without setting of target" strategy after stratifying bleeding risk and determining the treatment protocol for each stratum. In other words, until bleeding occurs after the initiation of antithrombotic therapy, it is unknown whether the

patient has crossed the bleeding-prone threshold. In the future, a strategy that visualizes the threshold of increased bleeding risk itself and applies the concept of "treat not beyond target" might be ideal for optimizing further antithrombotic therapy in HBR patients undergoing PCI. Further advances to precisely assess bleeding risk are warranted to realize this strategy.

Conflict of Interest (COI)

K.K. has received remuneration for lectures from Bayer Yakuhin, Daiichi-Sankyo, Novartis Pharma, and Otsuka Pharmaceutical; has received trust research/joint research funds from Bayer Yakuhin and Daiichi-Sankyo; and has received scholarship funds from Abbott Medical. The remaining authors have no conflicts of interest to declare.

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