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EDITORIAL COMMENT

ARC-HBR Criteria Can Identify HBR in East Asian Patients

What Comes Next to Reduce Bleeding?*

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For patients who undergo percutaneous coronary intervention (PCI), the assessment of high bleeding risk (HBR) is used to determine the duration of subsequent dual antiplatelet therapy (DAPT). The American College of Cardiology/American Heart Association guidelines recommend that patients with HBR (Class IIb) discontinue $P2Y_{12}$ inhibitors after PCI at 3 months for stable ischemic heart disease and at 6 months for acute coronary syndrome (ACS).[1] However, how best to determine the HBR is still ill-defined, and early DAPT discontinuation after PCI is not recommended. This is a particularly important consideration for East Asian patients because of the so-called "East Asian paradox" (low thromboembolic risk and HBR).[2]

The Academic Research Consortium for High Bleeding Risk (ARC-HBR), which consists of 31 members from the United States, Asia, and Europe, proposed the ARC-HBR criteria in 2018.[3] The criteria provide a consensus definition of patients at a high risk for PCI-related bleeding. To date, several large-scale studies have validated the use of the ARC-HBR criteria in PCI registry populations from European countries. Single- or multicenter studies validating the ARC-HBR criteria have also been reported from East Asian countries, mostly consisting of patients with chronic coronary syndrome (CCS) or a mixture of CCS and ACS in whom the usefulness of the ARC-HBR criteria has been demonstrated.

It is generally considered that the incidence of major bleeding is high in patients with ACS because of the need for rapid loading of antithrombotic therapy during the acute phase. Therefore, for patients with ACS, the management of bleeding risk requires special consideration, particularly in East Asian patients.[2] To date, the data on cohorts consisting solely of patients with ACS from East Asian countries validating the ARC-HBR criteria are scarce.[4,5]

In this issue of *JACC: Asia*, Lee et al[6] validated the use of the ARC-HBR criteria in a randomized clinical trial cohort (TICAKOREA [Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management] trial) in which the incidence of Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding at 1 year for HBR and non-HBR patients based on the ARC-HBR criteria was 10.0% and 3.7%, respectively.[6] The incidence of major adverse cardiovascular events at 1 year in the respective groups was 14.3% and 6.1%. These results are in line with previous studies on patients with ACS from Korea.[4,5] In a multicenter registry of patients with acute myocardial infarction, the incidence of 1-year BARC 3 or 5 bleeding was 9.8% and 2.9%, respectively.[4] In a randomized clinical trial cohort (TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome] trial), the major bleeding incidence at 1 year (defined by the Thrombolysis In Myocardial Infarction [TIMI] criteria) was 2.7% and 0.6%, respectively.[5]

However, based on the results of Lee et al from the TICAKOREA trial,[6] the following question arises: Is the incidence of BARC 3 or 5 bleeding in non-HBR patients (3.7% at 1 year) clinically acceptable to be regarded as "low risk," which is near the threshold (4%) of the HBR definition. Three studies validating

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TABLE 1 Studies Validating the ARC-HBR Criteria in Patients Who Underwent PCI in East Asian Clinical Trials

	Lee et al[6]	Lee et al[5]	Watanabe et al[7]
Patient population, country	TICAKOREA trial (Korea)	TICO trial (Korea)	STOPDAPT-2 (Japan)
Patients, n	800	2,980	3,009
Age, y	HBR: 72.9 Non-HBR: 60.5	HBR: 70.6 Non-HBR: 59.1	
Male	HBR: 75 (58.1) Non-HBR: 517 (77.9)	HBR: 290 (64.0) Non-HBR: 2,090 (82.7)	
Body mass index, kg/m^2	HBR: 23.6 Non-HBR: 24.9	HBR: 24.2 Non-HBR: 25.1	
Date of PCI procedures	July 2014-June 2017	August 2015-October 2018	December 2015-December 2017
Clinical presentation	ACS only	ACS only	CCS/ACS
ACS	800 (100)	2,980 (100)	HBR: 310 (29.4) Non-HBR: 838 (42.9)
CCS	0 (0)	0 (0)	HBR: 744 (70.6) Non-HBR: 1,117 (57.1)
Transfemoral approach	–	HBR: 222 (49.0) Non-HBR: 1,093 (43.3)	HBR: 179 (17.0) Non-HBR: 203 (10.4)
DES	–	2,980 (100)	
Use of proton pump inhibitors	20 (2.5)	–	HBR: 818 (77.6) Non-HBR: 1,565 (80.1)
DAPT duration	–	–	
1-month DAPT	–	–	HBR: 496 (47.1) Non-HBR: 1,004 (51.4)
3-month DAPT	–	HBR: 212 (46.8) Non-HBR: 1,277 (50.5)	–
12-month DAPT	800 (100)	HBR: 241 (53.2) Non-HBR: 1,250 (49.5)	HBR: 558 (52.9) Non-HBR: 951 (48.6)
ARC-HBR patients	129 (16.3)	453 (15.2)	1,054 (35.0)
Major criteria assessed	11	4	7
Minor criteria assessed	6	5	5
Prevalence of common individual ARC-HBR criteria among the HBR subgroup			
Age ≥75 y	68 (52.7)	–	947 (89.8)
OAC	–	–	13 (1.2)
Moderate CKD	49 (38.0)	–	883 (83.8)
Severe or end-stage CKD	14 (10.9)	–	166 (15.7)
Mild anemia	46 (35.7)	–	651 (61.8)
Moderate/severe anemia	41 (31.8)	–	263 (25.0)
Clinical events at 1 year (HBR vs non-HBR patients)			
Major bleeding definition	BARC 3 or 5	TIMI	BARC 3 or 5
Major bleeding, %	Total: 10.7 vs 3.8 Ticagrelor: 11.0 vs 5.3 Clopidogrel: 10.1 vs 2.4	Total: 2.7 vs 0.6 3-month DAPT: 0.5 vs 0.2 12-month DAPT: 4.7 vs 1.0	1-month DAPT: 3.48 vs 0.50 12-month DAPT: 5.98 vs 0.96
ICH, %			
Ischemic endpoint definition	MACE[a]	NACE[b]	NACE[c]
Ischemic endpoint, %	Total: 14.3 vs 6.1 Ticagrelor: 19.5 vs 6.6 Clopidogrel: 8.4 vs 5.4	Total: 5.4 vs 1.9 3-month DAPT: 2.4 vs 1.3 12-month DAPT: 8.0 vs 2.6	1-month DAPT: 1.81 vs 0.61 12-month DAPT: 3.26 vs 2.36
All-cause death (%)	Total: 12.6 vs 1.4 Ticagrelor: 15.0 vs 1.6 Clopidogrel: 10.0 vs 1.2	Total: 2.3 vs 0.2 3-month DAPT: 2.0 vs 0.2 12-month DAPT: 2.5 vs 0.2	1-month DAPT: 2.67 vs 0.81 12-month DAPT: 2.16 vs 0.64

Values are n (%) unless otherwise indicated. [a]Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [b]Composite of major bleeding and major adverse cardiac and cerebrovascular events from 3 to 12 months after index PCI. Major adverse cardiac and cerebrovascular events included all-cause death, myocardial infarction, stent thrombosis, stroke, and target vessel revascularization. [c]Composite of cardiovascular death, myocardial infarction, definite stent thrombosis, stroke, or TIMI major or minor bleeding.

ACS = acute coronary syndrome; ARC-HBR = Academic Research Consortium High Bleeding Risk; BARC = Bleeding Academic Research Consortium; CCS = chronic coronary syndrome; CKD = chronic kidney disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); HBR = high bleeding risk; ICH = intracranial hemorrhage; MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event; OAC = oral anticoagulation therapy; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

the ARC-HBR criteria from East Asian countries using clinical trial cohorts are listed in Table 1, 2 of which consisted solely of patients with ACS[5,6] and the other one consisted of a mixture of CCS and ACS patients.[7] Among the trials, the major bleeding incidence (defined by BARC 3 or 5 criteria for 2 trials and TIMI criteria for 1 trial) was higher in the TICAKOREA trial than in the other 2 trials. I would like to discuss

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several points on how to reduce major bleeding by comparing the 3 trials.

First, Lee et al[6] raised the point that ticagrelor increased the bleeding risk compared with clopidogrel.[6] The incidence of BARC 3 or 5 bleeding with ticagrelor vs clopidogrel was 11.0% vs 10.1% ($P = 0.78$) in HBR patients and 5.3% vs 2.4% ($P = 0.07$) in non-HBR patients, respectively.[6] When using other definitions for bleeding, the incidence of PLATO (Platelet Inhibition and Patient Outcomes) major bleeding for ticagrelor vs clopidogrel was 16.5% vs 10.0% ($P = 0.24$) in HBR patients and 5.7% vs 3.0% ($P = 0.09$) in non-HBR patients, respectively. Thus, the incidence of major bleeding was numerically (but nonsignificantly) higher with ticagrelor than with clopidogrel. However, given that the incidence of TIMI major bleeding was much lower in the TICO trial (HBR: 5.4% vs non-HBR: 1.9%) in which all patients received ticagrelor, reasons other than ticagrelor use should be considered to explain the high bleeding incidence in the TICAKOREA trial.

Second, a shorter DAPT duration is associated with a lower major bleeding incidence than a longer DAPT duration. In the TICAKOREA trial, all patients underwent DAPT for 12 months irrespective of the type of $P2Y_{12}$ inhibitor used. In the TICO trial, the incidence of TIMI major bleeding for HBR vs non-HBR patients was 4.7% vs 1.0% for patients undergoing 12-month DAPT, which decreased to 0.5% vs 0.2% for patients undergoing 3-month DAPT.[5] In the STOPDAPT-2 trial from Japan in which CCS and ACS roughly accounted for 60% and 40%, respectively, the incidence of BARC 3 or 5 bleeding for HBR vs non-HBR was 5.98% vs 0.96% for patients with 12-month DAPT, which decreased to 3.48% vs 0.50% for patients undergoing 1-month DAPT.[7] Both studies showed a numerically lower incidence of the ischemic endpoint with the shorter DAPT duration than with 12-month DAPT. Thus, the shorter DAPT duration is supported irrespective of the type of HBR in East Asian patients with ACS. Moreover, the merit of the shorter DAPT duration is more remarkable in HBR patients than in non-HBR patients.

Third, in the main paper of the TICAKOREA trial,[8] there was a remarkable difference in the incidence of gastrointestinal bleeding between the ticagrelor and the clopidogrel arms (number: 6/400 vs 1/400; difference = 5), which accounted for nearly half of the difference in PLATO major bleeding between the 2 arms (number: 29/400 vs 16/400; difference = 13). This result clearly indicates the importance of preventing gastrointestinal bleeding in patients with ACS, which sheds light on the significance of proton pump inhibitor use. In the TICAKOREA trial, the prescription rate of proton pump inhibitors as discharge medications was only 2.5%.[8] However, in the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent trial 2) trial,[7] the prescription rate of proton pump inhibitors was dramatically high (77.6% for HBR and 80.1% for non-HBR). Considering both the mental and physical stress in the acute phase of ACS and the rapid loading of antithrombotic medications, the routine use of proton pump inhibitors may be helpful to reduce gastrointestinal bleeding in patients with ACS.

Fourth, the PCI access site may also be important. Periprocedural bleeding is more frequent with the transfemoral approach than with the radial approach. In the TICO trial, the proportion of HBR patients who underwent the transfemoral approach was 49.0%, and 43.4% of non-HBR patients underwent the transfemoral approach. In STOPDAPT-2, the proportion of patients who underwent the transfemoral approach was extremely low (17.0% and 10.4% in patients with HBR and non-HBR, respectively).[7] The data were lacking in the TICAKOREA trial; thus, we cannot discuss whether the access site affected the major bleeding incidence. However, for thin patients, who are relatively common in East Asia, the radial approach should be considered wherever possible.

Validation of the ARC-HRB criteria from the TICAKOREA trial reported by Lee et al[6] empowered the usefulness of this consensus definition of PCI-related bleeding in East Asian patients with ACS. However, even if patients with ACS can be stratified into HBR and non-HBR, several points should be considered to further reduce the risk of bleeding. From the clinical perspective, whether or not the non-HBR truly reflects a low bleeding risk is important.

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