

App-Based Approach

How to Assess Bleeding Risk in Patients Undergoing Percutaneous Coronary Interventions

Hans Rickli, Micha T. Maeder

Cardiology Department, Kantonsspital St. Gallen, Switzerland

Summary

A relevant proportion of patients undergoing percutaneous coronary intervention (PCI) have a high risk of bleeding. The associated individual risk of ischaemia can be differentiated by an app-based approach and helps to determine the duration of intensified antithrombotic therapy.

Keywords: PCI; high bleeding risk; antithrombotic therapy

Background and Aim

The choice of the optimal antithrombotic therapy and its duration after percutaneous coronary intervention (PCI) remains challenging [1]. From the perspective of ischemic risk, the type and duration of dual antithrombotic therapy (DAPT) depends on the clinical setting (e.g., acute coronary syndrome versus chronic coronary artery disease) and the complexity of the coronary anatomy and intervention (e.g., stent length and diameter, bifurcation treatment) [2, 3]. Prolongation of intensified antithrombotic therapy, i.e., DAPT, may reduce the risk of ischemia, but is associated with an

increased risk of bleeding and thus potentially increased mortality [1]. Current European and American guidelines recommend a DAPT duration of six months after PCI and implantation of drug-eluting stents for chronic coronary syndrome – an extension to twelve months for patients who remain free of bleeding complications and carry a high ischemic risk – and a reduction to 1–3 months for high bleeding risk [3, 4]. Both professional societies recommend a DAPT duration of twelve months for acute coronary syndrome with a possible extension for low bleeding risk and a reduction to six months for high bleeding risk

[3, 4]. In 2019, an initiative of an international expert panel named Bleeding Academic Research Consortium (BARC) on the Assessment of High Bleeding Risk (HBR) in PCI sought to define the available parameters for defining a high risk of bleeding after PCI based on the evidence to date [5]. In a subsequently published analysis, a first validation was performed and from this a two-stage scoring was modelled [6]. The aim of this brief overview is to present the importance of the standardized definition of high bleeding risk in the context of a subsequent validation that can be applied in daily clinical practice.

Underrepresentation of the High Bleeding Risk PCI Group in Previous Scores

Various scores derived from different populations to assess the individual risk of bleeding and ischemia have been published [7–14]. As stated by the BARC and presented in detail in table 1 [5], low to intermediate bleeding risk PCI populations were included. In many stud-

Table 1: Scores to assess bleeding risk in patients undergoing percutaneous coronary intervention (PCI) on dual anti-thrombotic therapy (adapted from [5])

	DAPT [10]*	PARIS [11]	PRECISE-DAPT [12]*	BleeMacS [14]
Publication year	2016	2016	2017	2018
Data set development	RCT	Registry	Pooled analysis of 8 RCT	Registry
Data set n	11648	4190	14963	15401
Patient population	Stable and event-free patients 1 year after PCI	Stable and unstable patients undergoing PCI	Stable and unstable patients undergoing PCI	Patients with ACS undergoing PCI
Bleeding outcome	Major bleeding between 12 and 30 months	Major bleeding at 2 years	Out-of-hospital bleeding at a median follow-up of 552 days	Serious spontaneous bleeding at 1 year
Bleeding definition applied	GUSTO moderate or severe	BARC 3-5	TIMI major or minor	Protocol defined
Proportion of patients at HBR	23.4%	8%	25%	25%
Rate of bleeding in the HBR group	2.7% between 13 and 30 months	10.7% at 2 years	1.8–4.2% at 1 year	8.03 at 1 year
Development discrimination	AUC 0.68	AUC 0.72	AUC 0.73	AUC 0.71
Validation data set	PROTECT	ADAPT DES	PLATO and Bern-PCI registry	SWEDHEART registry
Validation data set (n)	8136	8130	8598 AND 6179	66339
Validation discrimination	AUC 0.63	AUC 0.64 (bleeding)	AUC 0.70 and 0.66	AUC 0.65

ACS, Acute coronary syndrome; ADAPT-DES, Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents; AUC, Area under the curve; BARC, Bleeding Academic Research Consortium; BleeMacS, Bleeding Complications in a Multicenter Registry of Patients Discharged With Diagnosis of Acute Coronary Syndrome; DAPT, Dual Antiplatelet Therapy Trial; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries; HBR, High Bleeding Risk; PARIS, Patterns of non-adherence to anti-platelet regimens in stented patients; PLATO, Platelet Inhibition and Patient Outcomes; PRECISE-DAPT, Predicting Bleeding Complications In Patients Undergoing Stent Implantation and Subsequent Dual Anti Platelet Therapy; PROTECT, Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial; TIMI, Thrombolysis In Myocardial Infarction; RCT, Randomized controlled trial.

* The DAPT and the PRECISE-DAPT score are not purely bleeding risk scores; rather, scores to predict benefit versus harm of prolonged dual antiplatelet therapy (>1 year) in patients after PCI. Thus, integrating covariates independently associated with bleeding (but not ischemic) risk and vice versa.

ies evaluating the safety of a shortened period of DAPT, patients with a high risk of bleeding were excluded and bleeding was defined differently in different studies. In these studies, the annual bleeding rate was found to range between 0.3 and 2.8% [5]. Therefore, the applicability of bleeding risk scores remains limited and due to the different collectives on which the models are based, they are most applicable to a low or medium risk collective [15].

Standardization of Criteria for High Bleeding Risk (HBR) Based on HBR PCI Population

As stated above, in 2019, the BARC sought to standardize the criteria for HBR [5], based on three prospective randomized trials (completed at the time), that investigated a short duration of DAPT in a patient population undergoing PCI that was assumed to be at high risk of bleeding [16–18]. The rate of BARC 3–5 bleeding [19] within one year after PCI ranged from 3.5 to 7.2% in these studies. The threshold HBR was set at an annual BARC 3–5 bleeding rate of more than 4% (for details see Urban et al. [5]). The definition of BARC 3 bleeding is

an overt bleeding with a drop in hemoglobin (Hb) of at least 3 g/dl or an intracranial bleeding. BARC 4 bleeding is defined as a bleeding event within 48 hours after coronary bypass grafting and BARC 5 refers to fatal bleeding.

Twenty different clinical risk factors were defined by consensus as major and minor risk factors for bleeding based on the findings of the above-mentioned studies [16–18]. Patients are considered at HBR if at least one major or two minor risk factors are present (table 2) [5].

The Arc-HBR Trade Off Model [6]: A Two-Step Risk Stratification Approach to Individualize the Antithrombotic Management in PCI Patients with HBR

In the clinical context of percutaneous coronary interventions, the central question is how to find an adequate antithrombotic therapy in the individual patient situation to assess the risk of ischemic events in an individual HBR patient with an expected increased risk of bleeding. With the aim of improving the prognostic value for future ischemic or bleeding events, a group of researchers [6] undertook new modelling and compared the results with

the prognostic performance for bleeding and ischemia of previous well-established scores, including DAPT [10], PRECISE-DAPT [12] and PARIS [11]. Patients from six PCI studies conducted between 2009 and 2017 served as the basis for a new model for ischemic risk assessment and a model for bleeding risk assessment after PCI. A total of 6641 HBR patients were identified and their actual incidence of bleeding and stent thrombosis (ST) or myocardial infarction (MI) within one year was recorded. Among these 6641 patients, 350 (5.3%) had either a MI and/or ST and 381 patients (5.7%) suffered BARC 3 to 5 bleedings [6]. Eight independent baseline predictors of risk of MI- and/or ST-elevation, eight predictors for risk of major bleeding (BARC 3 to 5) and four predictors of both MI/ST and major bleeding were identified (table 3). The C-statistic of 0.74, expressing prognostic performance for bleeding, was better than for the PARIS score (C-statistic 0.63) and also better than for the PRECISE-DAPT score (C-statistic 0.64). Similar better prognostic performance was found for MI and/or ST [6]. This superior performance was probably primarily due to the

Table 2: Major and minor risk factors for high bleeding risk (HBR) at the time of percutaneous coronary intervention according to the ARC HBR criteria [5]

Major	Minor
Anticipated use of long-term therapeutic anticoagulation*	Age >75 years
Severe or end-stage CKD (eGFR 30 ml/min/1.73 m ²)	Moderate CKD (eGFR 30–59 ml/min/1.73 m ²)
Hemoglobin <11 g/dl	Hemoglobin 11–12.9 g/dl for men and 11–11.9 g/dl for women
Spontaneous bleeding requiring hospitalization or transfusion in the past six months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion in the past twelve months not meeting major criterion
Moderate or severe baseline thrombocytopenia† (<100×10 ⁹ /l)	Long-term use of oral NSAIDs or steroids
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
Active malignancy‡ within the past twelve months	
Previous spontaneous ICH (at any time), posttraumatic ICH within the past twelve months, presence of a bAVM, moderate or severe ischemic stroke§ within the previous six months	Any ischemic stroke at any time not meeting the major criterion
Non-deferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days before PCI	

ARC, Academic Research Consortium; bAVM, Brain arteriovenous malformation; CKD, Chronic kidney disease; DAPT, Dual antiplatelet therapy; eGFR, Estimated glomerular filtration rate; ICH, Intracranial hemorrhage; NSAID, Nonsteroidal anti-inflammatory drug; PCI, Percutaneous coronary intervention.

* This excludes vascular protection doses. † Baseline thrombocytopenia is defined as thrombocytopenia before PCI. ‡ Active malignancy is defined as diagnosis within twelve months and/or ongoing requirement for treatment (including surgery, chemotherapy or radiotherapy). § National Institutes of Health Stroke Scale score >5.

different cohorts on which the models are based. The results of this study also show that the HBR collective is not homogeneous: in 23.4% the risk of BARC 3–5 bleeding is higher than that of ischemia, in 32.4% the risk of BARC 3–5 bleeding and ischemia are similar and in 44.1% the risk of ischemia is higher than that of BARC 3–5 bleeding [6].

Based on this data, the study group developed an app-based staged assessment of HBR patients to determine the risk of BARC 3–5 bleeding on the one hand and the risk of ischemia on the other. For illustration purposes, three exemplary HBR patient cases were presented to illustrate [20].

Three major patient profiles can be distinguished: First, the risk of MI/ST exceeds the risk of major bleeding. Second, the risk of major bleeding exceeds the risk of MI/ST. Third, the risks of MI/ST and major bleeding are similar.

Figure 1 shows three of our own patient examples, which were calculated according to the ARC HBR app as follows:

Patient 1 is a 63-year-old man with an ischemic stroke one year ago, persistent atrial fibrillation, mild anemia (Hb 11.9 g/dl), chronic renal failure (estimated glomerular filtration rate [eGFR] 29 ml/min/1.73 m²), need for long-term oral anticoagulation (novel oral anticoagulant [NOAC] apixaban twice daily 2.5 mg), diabetes, non-ST segment elevation MI

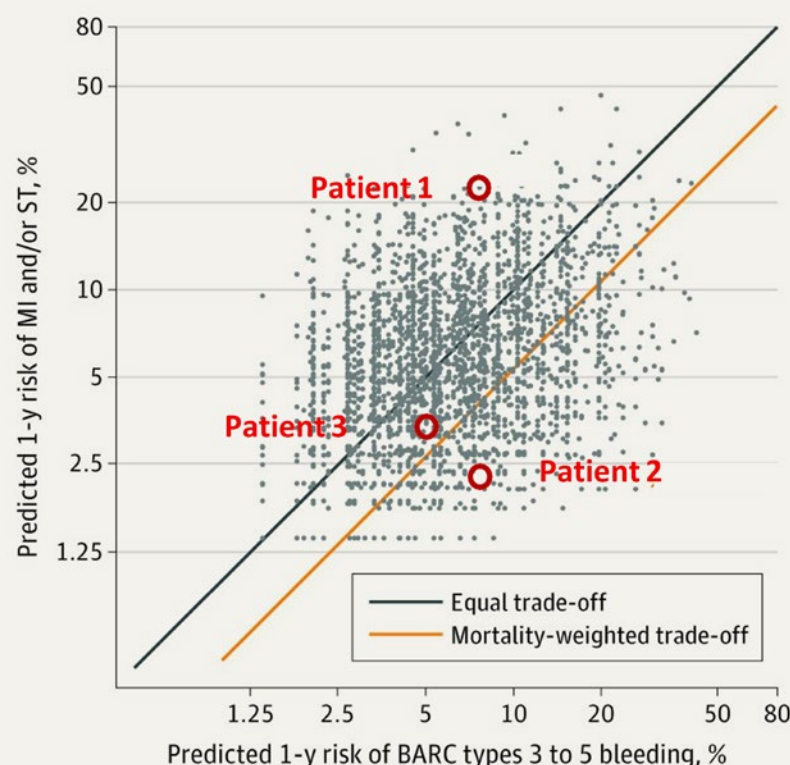


Figure 1: Predicted risks of Bleeding Academic Research Consortium (BARC) type 3–5 bleeding and myocardial infarction (MI) and/or stent thrombosis (ST) for patients at High Bleeding Risk (HBR) [6]. Predicted one-year risk of MI and/or ST and BARC type 3–5 bleeding (log scales) in patients at HBR according to the ARC. The equal trade-off line corresponds to the points where the risk of either BARC type 3–5 bleeding or MI and/or ST occurrence is the same. The mortality-weighted line takes the associated mortality of both events into account [6]. With the help of three patient examples the three categories are illustrated. For details see text.

Table 3: Multivariate predictors of BARC Type 3-5 bleeding and MI and/or ST at one year [6]

Predictor	BARC type 3-5 bleeding		MI and/or ST	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65	1.50 (1.08-2.08)	.01	NA	NA
Diabetes	NA	NA	1.56 (1.26-1.93)	<.001
Prior MI	NA	NA	1.89 (1.52-2.35)	<.001
Liver disease, cancer or surgery	1.63 (1.27-2.09)	.0001	NA	NA
COPD	1.39 (1.05-1.83)	.02	NA	NA
Current smoker	1.47 (1.08-1.99)	0.01	1.48 (1.09-2.01)	.009
NSTEMI or STEMI presentation	NA	NA	1.82 (1.46-2.25)	<.001
Haemoglobin, g/dl				
>13	1 (Reference)		1 (Reference)	
11-12.9	1.69 (1.30-2.20)	<.001	1.27 (.99-1.63)	.005
<11	3.99 (3.06-5.20)		1.50 (1.12-1.99)	
eGFR, ml/min/1.73 m ²				
>60	1 (Reference)		1 (Reference)	
30-59	0.99 (0.79-1.24)	.02	1.30 (1.03-1.66)	.001
<30	1.43 (1.04-1.96)		1.69 (1.20-2.37)	
Complex procedure ^b	1.32 (1.07-1.61)	.008	1.50 (1.21-1.85)	<.001
Bare metal stent ^c	NA	NA	1.53 (1.23-1.89)	<.001
OAC at discharge	2.00 (1.62-2.48)	<.001	NA	NA
C statistic	0.68	NA	0.69	NA

BARC, Bleeding Academic Research Consortium; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; eGFR, Estimated glomerular filtration rate; HR, Hazard ratio; MI, Myocardial infarction; NA, Not applicable; NSTEMI, Non-ST-segment elevation MI; OAC, Oral anticoagulants; ST, Definite or probable stent thrombosis; STEMI, ST-segment elevation MI; SI, conversion factor: to convert hemoglobin to grams per liter multiply by 10.0.

^a At least 1 of 3 modified ARC high bleeding risk criteria (cancer, severe liver disease, and planned major surgery); ^b As defined by Giustino et al [21]; ^c Compared with drug eluting stents or drug coated balloons.

presentation and very complex PCI. In addition to apixaban twice daily 2.5 mg, antithrombotic therapy was supplemented after PCI with clopidogrel 75 mg per day for one year and acetylsalicylic acid 100 mg daily for one week. The estimated BARC 3–5 bleeding risk after PCI (day 3–365) is 8.6% and the estimated risk of MI or ST (day 3–365) is 21.6% according to the ARC HBR app. The risk of MI/ST clearly exceeds the risk of bleeding, although the patient obviously has important bleeding risk factors. In principle, an extension of dual antithrombotic treatment beyond the twelve-month period should be considered, as the net benefit outweighs the increased risk of bleeding.

Patient 2 is a 77-year-old woman with stable angina pectoris CCS class II. An uncomplicated PCI with implantation of a drug-eluting

stent is performed. Comorbidities include mild anemia (Hb 10.7 g/dl), diabetes and mild chronic renal failure (eGFR 47 ml/min/1.73 m²). The estimated BARC 3–5 bleeding risk after PCI (day 3–365) is 8.6% and the estimated risk of MI or ST (day 3–365) is 2.1% according to the ARC HBR app. Therefore the risk of bleeding is greater than the risk of MI or ST. The risk of bleeding increased significantly and at the same time the risk of ischemia remains low. A shortening of the usual six-month dual antithrombotic therapy in stable coronary artery disease and stent implantation can be considered.

Patient 3 is a 51-year-old man with NSTEMI, straightforward single drug-eluting stent PCI of a first marginal branch, mild anemia (Hb 12.3 g/dl), liver cirrhosis and cur-

rently smoking. The estimated BARC 3–5 bleeding risk after PCI (day 3–365) is 5.5% and the estimated risk of MI or ST (day 3–365) is 3.4% according to the ARC HBR app. In this patient, the risks of bleeding and MI/ST can be considered equivalent, thus a normal twelve months of dual antithrombotic therapy should be given.

These examples demonstrate that the estimation of the absolute and relative risk of bleeding and MI and/or ST following PCI with the help of the ARC-HBR score can help to improve clinical decision-making for individual patients.

In summary, this defines three collectives (highlighted by the three patient examples) where a) a prolongation/intensification of antithrombotic therapy should be considered if there is a disproportionate risk of ischemia, b)

a shortening/simplification of antithrombotic therapy must be considered if there is a disproportionate risk of bleeding or c) the risk of ischemia and bleeding are more or less balanced. Accordingly, in this latter group DAPT can be given according to the guidelines, twelve months for acute coronary syndrome and 3–6 months after elective implantation of drug-eluting stents [6].

Keypoints

- Approximately 40% of an all-comers percutaneous coronary intervention population meet the criteria for high post-interventional bleeding risk (HBR) with dual antiplatelet therapy.
- The balance between bleeding and thrombotic risk varies from HBR patient to HBR patient.
- In contrast to previous scores, a currently available model with stepwise app-based scoring (ARC HBR App) for bleeding and ischemia is based on a HBR population.
- This scoring should be applied individually to patients at high risk of bleeding and can contribute to improved risk stratification.

Correspondence

Hans Rickli
Cardiology Department
Kantonsspital St. Gallen
Rorschacherstrasse 95
CH-9007 St. Gallen
hans.rickli[at]kssg.ch

Disclosure Statement

The authors have declared no potential conflicts of interest relevant to this article.

References

- 1 Khan SU, Singh M, Valavoor S, Khan MU, Lone AN, Khan MZ, et al. Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents: A Systematic Review and Network Meta-Analysis. *Circulation*. 2020 Oct;142(15):1425–36.
- 2 Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, et al. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. *J Am Coll Cardiol*. 2016 Oct;68(17):1851–64.
- 3 Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019 Jan;40(2):87–165.
- 4 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With
- Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016 Sep;134(10):e123–55.
- 5 Urban P, Mehran R, Collieran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. *Eur Heart J*. 2019 Aug;40(31):2632–53.
- 6 Urban P, Gregson J, Owen R, Mehran R, Windecker S, Valgimigli M, et al. Assessing the Risks of Bleeding vs Thrombotic Events in Patients at High Bleeding Risk After Coronary Stent Implantation: The ARC-High Bleeding Risk Trade-off Model. *JAMA Cardiol*. 2021 Apr;6(4):410–9.
- 7 Dangas GD, Claessen BE, Mehran R, Xu K, Fahy M, Parise H, et al. Development and validation of a stent thrombosis risk score in patients with acute coronary syndromes. *JACC Cardiovasc Interv*. 2012 Nov;5(11):1097–105.
- 8 Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009 Apr;119(14):1873–82.
- 9 Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010 Jun;55(23):2556–66.
- 10 Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al.; DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA*. 2016 Apr;315(16):1735–49.
- 11 Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol*. 2016 May;67(19):2224–34.
- 12 Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al.; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017 Mar;389(10073):1025–34.
- 13 Ducrocq G, Wallace JS, Baron G, Ravaud P, Alberts MJ, Wilson PW, et al.; REACH Investigators. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. *Eur Heart J*. 2010 May;31(10):1257–65.
- 14 Raposeiras-Roubin S, Faxén J, Iñiguez-Romo A, Henriques JP, D'Ascenzo F, Saucedo J, et al. Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the BleedMACS score. *Int J Cardiol*. 2018 Mar;254:10–5.
- 15 Pencina MJ, Goldstein BA, D'Agostino RB. Prediction Models – Development, Evaluation, and Clinical Application. *N Engl J Med*. 2020 Apr;382(17):1583–6.
- 16 Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, et al.; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med*. 2015 Nov;373(21):2038–47.
- 17 Ariotti S, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, et al.; ZEUS Investigators. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. *JACC Cardiovasc Interv*. 2016 Mar;9(5):426–36.

- 18 Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, et al.; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet*. 2018 Jan;391(10115):41–50.
- 19 Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011 Jun;123(23):2736–47.
- 20 ARC_HBR app
- 21 Giustino G, Baber U, Sartori S, Mehran R, Mastorisi I, Kini AS, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2015 Apr;65(13):1298–310.