Trial Design Principles for Patients at High Bleeding Risk Undergoing PCI

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Trial Design Principles for Patients at High Bleeding Risk Undergoing PCI

JACC Scientific Expert Panel

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ABSTRACT

Investigating the balance of risk for thrombotic and bleeding events after percutaneous coronary intervention (PCI) is especially relevant for patients at high bleeding risk (HBR). The Academic Research Consortium for HBR recently proposed a consensus definition in an effort to standardize the patient population included in HBR trials. The aim of this consensus-based document, the second initiative from the Academic Research Consortium for HBR, is to propose recommendations to guide the design of clinical trials of devices and drugs in HBR patients undergoing PCI. The authors discuss the designs of trials in HBR patients undergoing PCI and various aspects of trial design specific to HBR patients, including target populations, intervention and control groups, primary and secondary outcomes, and timing of endpoint reporting. (J Am Coll Cardiol 2020;76:1468–83) © 2020 by the American College of Cardiology Foundation.

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Patients at high bleeding risk (HBR) represent up to 40% of subjects undergoing percutaneous coronary intervention (PCI) in routine clinical practice (1–3). Historically, because of safety concerns, such patients were under-represented in PCI trials of device or drug therapies, resulting in a paucity of randomized clinical evidence to guide their optimal management. More recently, however, a number of completed and ongoing trials in patients undergoing PCI have focused on this clinical subgroup (4–11). Although this is a welcome development, there is significant heterogeneity among such trials with respect to many design elements.

Investigating the balance of risk for thrombotic and bleeding events after PCI is essential for optimal clinical decision making, such as choice of revascularization versus medical therapy, type and duration of dual antiplatelet therapy (DAPT), and timing of noncardiac surgery (12). Although understanding this balance is important in all patients, it is especially relevant for HBR patients. The Academic Research Consortium for HBR (ARC-HBR) recently proposed a consensus HBR definition in an effort to help standardize the patient population included in HBR trials (13,14). However, completed and ongoing trials of HBR patients undergoing PCI also differ with respect to a number of other aspects of their designs, including the types of investigational and control therapies, primary and secondary outcomes, and the timing of outcome assessment. Against this background, the aim of the present consensus-based document, the second initiative from the ARC-HBR, is to propose recommendations to guide the design of clinical device and drug trials in HBR patients undergoing PCI to promote consistency.

Two meetings of the ARC-HBR took place in Washington, District of Columbia, in April 2019 and Paris, France, in October 2019, organized by the Cardiovascular European Research Center (Massy, France) and attended by international experts from Europe, the United States, and Asia, as well as by representatives from the U.S. Food and Drug Administration, the

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ARC = Academic Research Consortium

ARC-HBR = Academic Research Consortium for High Bleeding Risk

BARC = Bleeding Academic Research Consortium

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HBR = high bleeding risk

MI = myocardial infarction

OAC = oral anticoagulation

PCI = percutaneous coronary intervention

PROM = patient-related outcome measure

TLR = target lesion revascularization

participants received fees or honoraria for their participation in the meetings or their contributions to this document. Dr. Capodanno has received consulting fees or honoraria from Abbott Vascular, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer. Dr. Morice is the chief executive officer of CERC, the contract research organization organizing the Academic Research Consortium for High Bleeding Risk initiative. Dr. Angiolillo has received consulting fees or honoraria from Abbott Vascular, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; has received payments for participation in review activities from CeloNova Biosciences and St. Jude Medical; and has received research grants to his institution from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry, Merck, Novartis, Osprey Medical, Renal Guard Solutions, and the Scott R. MacKenzie Foundation. Dr. Bhatt is an Advisory Board member for Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLX Pharma, and Regado Biosciences; is a member of the boards of directors of the Boston VA Research Institute, the Society of Cardiovascular Patient Care, and TobeSoft; is chair of the American Heart Association Quality Oversight Committee; is a member of data monitoring committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), the Cleveland Clinic (including for the ExCEED trial, funded by Edwards Lifesciences), the Duke Clinical Research Institute, the Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo), and the Population Health Research Institute; has received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News* and ACC.org; vice chair, ACC Accreditation Committee), the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), the Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), the *Journal of the American College of Cardiology* (Guest Editor, Associate Editor), Medtelligence/ReachMD (continuing medical education steering committees), the Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and U.S. national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), the Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (continuing medical education steering committees); is Deputy Editor of *Clinical Cardiology*; is Chair of the NCDR-ACTION Registry Steering Committee and the VA CART Research and Publications Committee; has received research funding from Abbott Vascular, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Eli Lilly, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); is a site co-investigator for Biotronik, Boston Scientific, Cardiovascular Systems, St. Jude Medical (now Abbott), and Svelte; is a trustee of the American College of Cardiology; and has conducted unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. Dr. Byrne has received research funding to the institution of previous employment from CeloNova Biosciences. Dr. Cutlip has received consulting fees from CeloNova Biosciences; and has received academic salary support from the Baim Institute for Clinical Research. Dr. Eikelboom has received consulting fees and grant support from AstraZeneca, Bayer, Boehringer Ingelheim,

Japanese Pharmaceuticals and Medical Devices Agency, a European notified body (DEKRA Certification, Arnhem, the Netherlands), and observers from the cardiovascular device and pharmaceutical industries (participants are listed in the Supplemental Appendix).

DESIGN OF COMPLETED AND ONGOING TRIALS IN PCI PATIENTS CONSIDERED TO BE AT HBR

To assess methodological differences, the consortium reviewed the designs of a number of completed trials investigating coronary devices in populations considered to be at HBR, including 4 randomized clinical trials, 1 subgroup analysis of a randomized

HIGHLIGHTS

- Investigating the balance of risk for thrombotic and bleeding events after PCI is especially relevant for HBR patients.
- The aim of this consensus-based document is to propose recommendations to guide the design of clinical trials of devices and drugs in HBR patients undergoing PCI.
- Consensus definitions promote consistency in trial design for the evaluation of novel technologies, iterations of existing devices, and antithrombotic strategies.

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Dr. Leon has received research grants from Abbott Vascular, Boston Scientific, Medtronic, Biosensors, and Sinomed; and has equity in Medinol. Dr. Mylotte has received speaker fees from Biosensors; and has received institutional research grants from Biosensors and Medtronic. Dr. Pocock has served on steering committees or data monitoring committees for trials sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Idorsia, Janssen, Medtronic, Novartis, Novo Nordisk, and Vifor; and has received grant funding from AstraZeneca and Merck. Dr. Valgimigli has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Opsens, Bayer, CoreFLOW, Idorsia Pharmaceuticals, Universität Basel, Dept. Klinische Forschung, Vifor, Bristol-Myers Squibb, iVascular, and Medscape; and has received grants and personal fees from Terumo. Dr. Varenne has received consulting and research grants from Boston Scientific, Abbott Vascular, AstraZeneca, and Servier. 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Dr. Mehran has received consulting fees to the institution from Abbott Laboratories and Spectranetics/Philips/Volcano; has received consulting fees from Boston Scientific, Cardiovascular Systems, Medscape, Siemens Medical Solutions, Regeneron Pharmaceuticals, Roivant Sciences, and Sanofi; is the spouse of a consultant for Abiomed and The Medicines Company; has received research funding to the institution from AstraZeneca, Bayer, Beth Israel Deaconess Hospital, Bristol-Myers Squibb, CSL Behring, Eli Lilly and Daiichi-Sankyo, Medtronic, Novartis Pharmaceuticals, and Orbus Neich; has received scientific Advisory Board fees from PLx Opco (dba PLx Pharma); has received scientific Advisory Board fees to the institution from Bristol-Myers Squibb; has received executive committee fees from Janssen Pharmaceuticals and Osprey Medical; has participated in speaking engagements for Abbott Laboratories; holds equity in Claret Medical and Elixir Medical; and has received data and safety monitoring board fees to the institution from Atermark Research Partners. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. This paper reflects the consensus views of the writing group and does not necessarily represent the practices, policies, requirements, or recommendations of the U.S. Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency. Further, any use of the words "required," "must," or "should" in the document is not intended to indicate an FDA requirement. Judith S. Hochman, MD, served as Guest Associate Editor for this paper. P.K. Shah, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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TABLE 1 Design of Completed and Ongoing High Bleeding Risk Trials

Trial (Ref. #)	Status	Design	N	Intervention(s)	Control	Background Therapy	Primary Outcome(s)	Timing
Randomized device trials								
LEADERS FREE (4)	Completed	RCT	2,466	PF-DCS	BMS	1-month DAPT	Cardiac death, MI, or ST (def/prob) CD-TLR	390 days
ZEUS-HBR (5)	Completed	RCT subgroup analysis	828	DP-DES	BMS	1-month DAPT	Death, MI, or TVR	12 months
SENIOR (6)	Completed	RCT	1,200	BP-DES	BMS	1-month DAPT*	Death, MI, stroke, or CD-TLR	12 months
ONYX ONE (7)	Completed	RCT	1,996	DP-DES	PF-DCS	1-month DAPT	Cardiac death, MI, or ST (def/prob)	12 months
DEBUT (8)	Completed	RCT	220	DCB	BMS	1-month DAPT	Cardiovascular death, MI, TLR	9 months
Randomized drug trials								
WOEST (19)	Completed	RCT	573	VKA-DAT	VKA-TAT	PCI	Any bleeding	12 months
ISAR-TRIPLE (20)	Completed	RCT	614	6-week TAT	6-month TAT	PCI	Death, MI, ST (def), stroke, or major bleeding	9 months
PIONEER-AF PCI (15)	Completed	RCT	2,124	DOAC-DAT, DOAC-TAT	VKA-TAT	PCI	Clinically significant bleeding	12 months
RE-DUAL PCI (16)	Completed	RCT	2,725	DOAC-DAT	VKA-TAT	PCI	Major or CRNM bleeding	14 months
AUGUSTUS (17)	Completed	RCT, 2x2	4,614	DOAC, DAT	VKA, TAT	±PCI	Major or CRNM bleeding	6 months
ENTRUST-AF PCI (18)	Completed	RCT	1,506	DOAC-DAT	VKA-TAT	PCI	Major or CRNM bleeding	12 months
MASTER DAPT (NCT03023020)	Ongoing	RCT	4,300	Abbreviated DAPT (1 month)	Prolonged DAPT (6–12 months)	DP-DES	Death, MI, stroke, or BARC 3 or 5 bleeding Death, MI, or stroke BARC 2-5 bleeding	11 months
TARGET SAFE (NCT03287167)	Ongoing	RCT	1,720	1-month DAPT	6-month DAPT	BP-DES	Death, MI, stroke, or major bleeding	18 months
Randomized strategy trials								
COBRA REDUCE (NCT02594501)	Ongoing	RCT	996	NC-BMS with 2-week DAPT	DP-DES with 3- or 6-month DAPT	–	BARC 2-5 bleeding Death, MI, stroke, ST (def/prob)	6 months
Single-arm studies								
LEADERS FREE II (9) (NCT02843633)	Completed	Registry	1,148	PF-DCS with 1-month DAPT	Historical control	–	Cardiac death, MI CD-TLR	12 months
EVOLVE Short DAPT (10) (NCT02605447)	Completed	Registry	2,009	BP-DES with 3-month DAPT	Historical control	–	Death or MI ST (def/prob)	15 months
ONYX ONE Clear (11) (NCT03647475)	Completed	Registry	1,506	DP-DES with 1-month DAPT	–	–	Cardiac death or MI	12 months
XIENCE 90 Short DAPT (NCT03218787)	Ongoing	Registry	2,047	DP-DES with 3-month DAPT	–	–	Death or MI	12 months
XIENCE 28 GLOBAL (NCT03355742)	Ongoing	Registry	960	DP-DES with 1-month DAPT	–	–	Death, MI, stroke, ST (def/prob), or BARC 2-5 bleeding	6 months
POEM (NCT03112707)	Ongoing	Registry	1,023	BP-DES with 1-month DAPT	–	–	Cardiac death, MI, or ST (def/prob)	12 months

*Except patients with acute coronary syndrome, in whom 6-month DAPT was recommended.

BARC = Bleeding Academic Research Consortium; BMS = bare-metal stent; BP-DES = biodegradable-polymer drug-eluting stent; CD-TLR = clinically driven target lesion revascularization; CRNM = clinically relevant nonmajor; DAPT = dual antiplatelet therapy; DAT = dual antithrombotic therapy; DCB = drug-coated balloon; def = definite; DOAC = direct oral anticoagulant; DP-DES = durable-polymer drug-eluting stent; MI = myocardial infarction; NC-BMS = nanocoated bare-metal stent; PF-DCS = polymer-free drug-coated stent; PCI = percutaneous coronary intervention; prob = probable; RCT = randomized clinical trial; ST = stent thrombosis; TAT = triple antithrombotic therapy; TVR = target vessel revascularization; VKA = vitamin K antagonist.

trial, and 3 single-arm trials with historical control or performance goals (4–11). The designs of 6 completed trials in PCI patients requiring oral anticoagulation (OAC) were also considered (15–20). Finally, the consortium considered the designs of 6 ongoing HBR trials of coronary devices, antithrombotic drug regimens, or a combination of device and drug regimens.

Heterogeneity with respect to the inclusion criteria used in these trials has been previously discussed and is summarized in Supplemental Figure 1 (13,14). An overview of the design characteristics of the aforementioned trials is shown in **Table 1**, and details of selected trials are further discussed in the Supplemental Appendix. It is notable that such trials

TABLE 2 Outcomes of Interest and ARC Sources for Clinical Trials of Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention

Endpoint	Classification	ARC Source (Ref. #)
Death*	Cardiovascular Noncardiovascular Undetermined All-cause	ARC-2 (22)
Myocardial infarction	Peri-procedural Spontaneous Any Target vessel	ARC-2 (22)
Revascularization	Target lesion Target vessel Clinically driven Any	ARC-2 (22)
Stroke	Ischemic Ischemic with hemorrhagic transformation Hemorrhagic Not otherwise specified	NeuroARC (30)
Stent thrombosis	Definite Probable	ARC-2 (22)
Bleeding	BARC types 3 and 5 BARC types 2, 3, and 5	BARC (27)
Device-oriented composite endpoint	Composite of cardiovascular death, target vessel myocardial infarction, or target lesion revascularization	ARC-2 (22)
Patient-oriented composite endpoint	Composite of all-cause death, any myocardial infarction, stroke, or any revascularization	ARC-2 (22)

*Undetermined death should be considered cardiovascular for reporting purposes. Death related to bleeding should be reported separately and labeled as cardiovascular (death from cardiovascular hemorrhage [including, e.g., subdural hematoma, aortic aneurysm, cardiac tamponade] and hemorrhagic stroke) and noncardiovascular.

ARC = Academic Research Consortium; BARC = Bleeding Academic Research Consortium; NeuroARC = Neurologic Academic Research Consortium.

often differed in terms of timing of randomization, proposed antiplatelet regimens, and primary hypotheses tested.

EXISTING ENDPOINT DEFINITIONS FROM PREVIOUS ACADEMIC RESEARCH CONSORTIUM INITIATIVES RELEVANT TO TRIALS IN HBR PATIENTS UNDERGOING PCI

Previous Academic Research Consortium (ARC) initiatives addressing the general PCI population have provided pragmatic endpoint definitions for thrombotic/ischemic and bleeding events that may be considered for use in clinical trials of HBR populations (**Table 2**). ARC-defined endpoints for assessment of adverse thrombotic/ischemic events related to the PCI procedure and disease progression established in 2007 have been incorporated widely into contemporary clinical trials (21–24) and have been recently updated (ARC-2) (22). ARC-HBR recommends using a modification of the definition proposed by ARC-2 for cardiovascular death (i.e., excluding death caused by cardiovascular hemorrhage, as discussed later in the text) and the definitions proposed by ARC-2 for cardiovascular or noncardiovascular death, myocardial infarction (MI; peri-procedural according to ARC-2 and spontaneous according to the latest available universal definition), stent thrombosis, and clinically driven repeat revascularization. ARC-HBR acknowledges that contemporary trials use an array of bleeding and cerebrovascular event definitions (15–18,25–29), the latter generally being protocol specific. Having assessed the relative merits of each classification, ARC-HBR recommends using the Bleeding Academic Research Consortium (BARC) (27) and the Neurologic Academic Research Consortium definitions (30). Additional background and classification details are provided in the Supplemental Appendix.

ARC-HBR DEFINITION AND IMPLICATIONS FOR TRIAL DESIGN

ASSESSMENT OF HBR. Criteria to prospectively identify HBR patients undergoing PCI have been proposed by the ARC-HBR on the basis of an estimated BARC 3 or 5 bleeding risk of ≥4% or a risk for intracranial hemorrhage of ≥1% at 1 year (13,14). Twenty demographic, clinical, and laboratory characteristics were identified as major or minor criteria for HBR (13,14). In 3 large external validation studies, the ARC-HBR criteria successfully identified patients at increased risk for bleeding (1–3). Although the ARC-HBR definition uses a binary approach for some continuous variables, favoring simplicity at the potential expense of accuracy, its reported discrimination ability (e.g., C-statistics ranging from 0.64 to 0.68) is consistent with other available bleeding risk models (2,3,31). In trials of HBR patients, the screening process may be facilitated using specific case report forms that allow the rapid identification of HBR patients and may be stored in patient files (**Figure 1**, Supplemental Figure 2). A web-based app (ARC-HBR) has also been developed for this purpose, which is available for download from the major app stores.

INCLUSION AND QUALIFYING CRITERIA. A standardized definition of an HBR trial may be useful for both medical device and drug regulatory agencies and physicians treating HBR patients. However, defining what constitutes an ARC-HBR trial is fraught with inherent challenges. Clinical research is a dynamic field, in which the actual bleeding risk of ARC-HBR patients might be mitigated by the intervention. The consortium proposes that a dedicated ARC-HBR trial include only patients considered to be at HBR according to ARC-HBR criteria (i.e., fulfilling ≥1 major criterion or ≥2 minor criteria). For trials of interventions in

FIGURE 1 **A Proposed Checklist to Facilitate the Screening Process and Rapid Identification of HBR Patients for Trial Inclusion**

ARC High Bleeding Risk Trial Checklist

HBR Study _____ Screening Date _____/_____/_____

Patient Details
Name _____
Date of Birth _____/_____/_____
MRN _____

Yes	No	HBR Criteria (■ Major Criterion, □ Minor Criterion)	Additional Information
□	□	Age ≥75 years	Age _____ years
■	■	Anticipated use of long-term oral anticoagulation	Drug: Details
■	■	Spontaneous bleeding requiring hospitalization or transfusion (≤6 months or recurrent)	Date ___/___/_____ Details
□	□	Spontaneous bleeding requiring hospitalization or transfusion (>6 and <12 months, non-recurrent)	Date ___/___/_____ Details
■	■	Chronic bleeding diathesis	Details
■	■	Active malignancy (<12 months)	Details
■	■	Liver cirrhosis with portal hypertension	Details
■	■	Intracranial hemorrhage (traumatic <12 months)	Details
■	■	Brain arteriovenous malformation	Details
■ □	■ □	Moderate or severe ischemic stroke ≤6 months Any ischemic stroke >6 months	Date ___/___/_____ Details
■	■	Major surgery or trauma <30 days	Date ___/___/_____ Details
■	■	Non-deferrable major surgery	Planned Surgery Date ___/___/_____ Details
■ □	■ □	eGFR <30 ml/min eGFR 30-59 ml/min	Test Date ___/___/_____ eGFR _____ ml/min
■ □	■ □	Hb <11 g/dl Hb 11-12.9 (♂□) or 11-11.9 (♀□) g/dl	Test Date ___/___/_____ Hb _____ g/dl
■	■	Platelet count <100x10^9/l	Test Date ___/___/_____ Platelet count _____ x 10^9/l
□	□	Chronic NSAID/steroid	Drug Details

Number of Major Criteria Met _____ Number of Minor Criteria Met _____

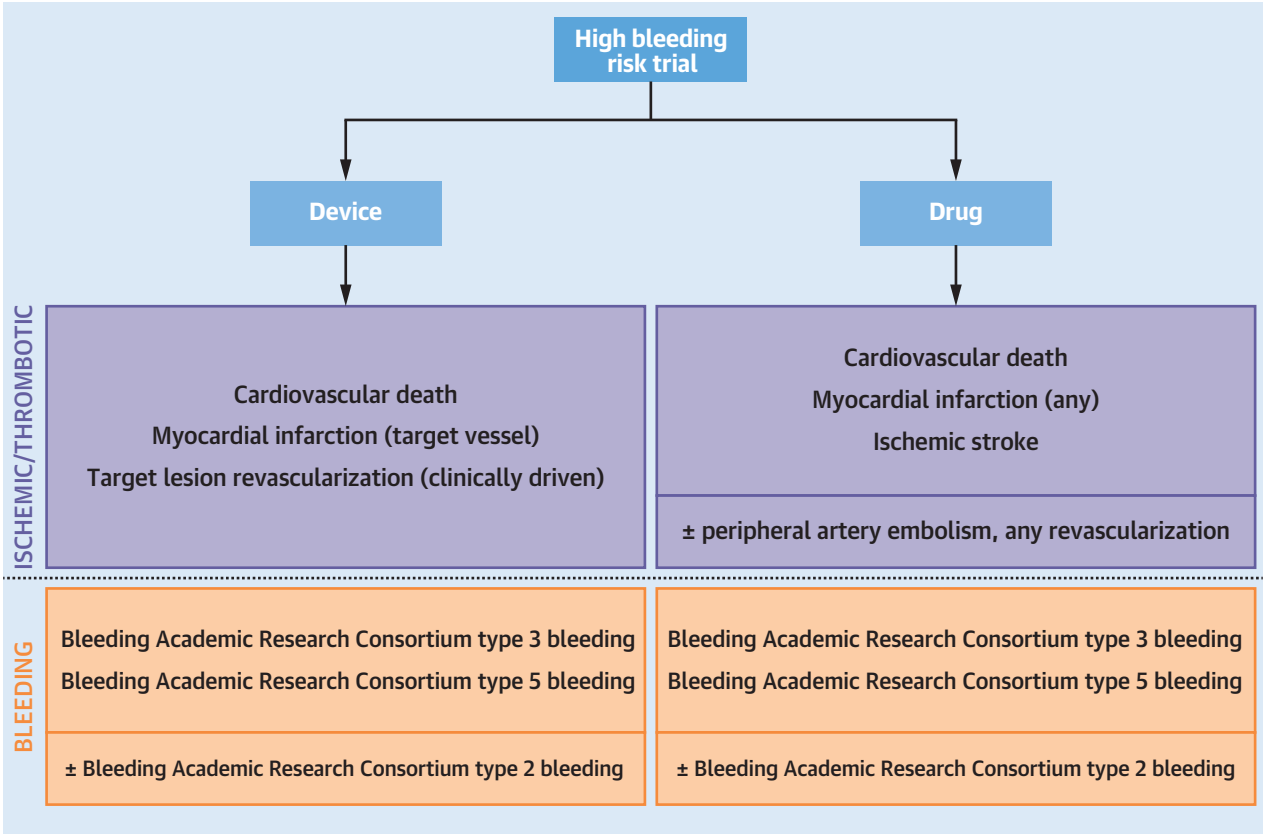
ARC HBR
≥ 1 Major criteria
≥ 2 Minor criteria

ARC HBR Criteria Satisfied?
Yes ☐ **No** ☐

Investigator Name _____
Investigator Signature _____ Date _____/_____/_____

Active malignancy is defined as a cancer diagnosis (excluding nonmelanoma skin cancer) within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy). ARC = Academic Research Consortium; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HBR = high bleeding risk; MRN = medical record number; NSAID = nonsteroidal anti-inflammatory drug.

CENTRAL ILLUSTRATION **Academic Research Consortium for High Bleeding Risk Thrombotic/Ischemic and Bleeding Primary Endpoints for Trials of Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention**



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Academic Research Consortium for High Bleeding Risk thrombotic/ischemic and bleeding primary endpoints are proposed for device and drug trials.

HBR patients using alternative inclusion criteria, reporting the proportion of enrolled patients according to ARC-HBR criteria is encouraged to facilitate consistency and comparability.

The proportion of enrolled patients with each HBR criterion in a given trial is also an important consideration. Previous trials aiming to include HBR populations enrolled patients with a high incidence of certain HBR criteria (most frequently older and use of OAC) but a low incidence of many other criteria (such as active cancer, cirrhosis with portal hypertension, and prior intracranial hemorrhage), most likely reflecting the different prevalence of these features in an unselected population. Although a trial focusing on only 1 subgroup of ARC-HBR patients (e.g., those meeting 1 specific major criterion, such as OAC use) qualifies as a dedicated ARC-HBR trial, it should be acknowledged that the trial's findings may not be generalizable to all HBR patients.

INTERVENTION AND CONTROL GROUP THERAPIES IN HBR TRIALS

TRIALS OF DEVICE THERAPIES. Current-generation drug-eluting stents (DES) are associated with generally favorable outcomes across the spectrum of patient and disease complexity (32,33). However, coronary devices with specific design features (e.g., polymer-free drug-coated stents, drug-coated balloons, novel bare-metal stents [BMS]) might offer incremental benefit in patient-oriented outcomes in particular timeframes, if their use permits a shorter duration or lower intensity of antiplatelet therapy than would otherwise be important with

conventional DES for reduction of device-related thrombotic events. Further clinical trials of coronary devices in HBR patients are needed to inform best treatment options for these patients.

In comparative assessment of different PCI devices in HBR patients, 2 approaches may be generally considered (Supplemental Figure 3). First is a comparison of device A versus device B, with the same duration and intensity of antithrombotic therapy in both groups. Because the focus of such a design is a comparison of devices, inferences about the safety and efficacy of the selected antithrombotic therapy are made with caution. For example, both ZEUS-HBR (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates HBR subgroup) and LEADERS FREE (A Randomized Clinical Evaluation of the BioFreedom Stent) randomized patients to DES or BMS followed by 1 month of DAPT (4,5). Although both studies showed superiority of DES over BMS with a short DAPT duration, conclusions regarding optimal DAPT duration in HBR patients cannot be drawn from either study.

Second is a comparison of device A plus antithrombotic therapy duration/intensity 1 (strategy X) versus device B plus antithrombotic therapy duration/intensity 2 (strategy Y). Such a trial may be informative from the standpoint of overall patient outcomes, allowing capture of both the potential advantage of the test device and the impact of the antiplatelet therapy associated with use of the test device. This study design assumes that the device-specific duration and/or intensity of antithrombotic therapy is well established. In most circumstances, a 2×2 factorial design may be preferable to allow ascription of benefit and harm to individual components of the test strategy.

Randomized clinical trials remain the ideal design for the investigation of coronary devices in HBR patients, and current-generation DES may be considered the preferred control device (see the Supplemental Appendix for additional background and details). Although the use of parallel groups is preferred, single-arm trials with performance goals or objective performance criteria may be informative in situations in which randomization is not feasible. Although single-arm studies have been advocated for and may be acceptable in certain circumstances in which the control group is no longer contemporary, caution is important in designing performance benchmarks because of the relative paucity of clinical trial data in HBR patients, which makes derivation of performance goals or objective performance criteria challenging.

TRIALS OF DRUG THERAPY AND PHARMACOLOGICAL STRATEGIES. Comparative assessment of antithrombotic strategies in HBR patients is somewhat more complex. Contemporary randomized trials focusing on reduction of bleeding events post-PCI have used 3 main approaches: 1) shortening DAPT duration (by discontinuing either aspirin or the $P2Y_{12}$ inhibitor at 1, 3, or 6 months) (20,34–50); 2) early aspirin omission (after a peri-procedural period of DAPT) (15–19); or 3) de-escalation of $P2Y_{12}$ inhibitor therapy (51–53) (Supplemental Figure 4).

The optimal duration of DAPT in HBR patients remains to be determined. Trial design considerations to address this question include evaluation of DAPT durations as short as 1 to 3 months and 3 to 6 months in patients with stable ischemic heart disease and acute coronary syndrome (ACS), respectively. Control groups for such trials may include guideline-recommended durations (i.e., currently 6 months for patients with stable ischemic heart disease and 12 months for patients with ACS) (54,55). It is important that the benefit of short DAPT duration be evaluated against the potential withdrawal of protection from stent- and non-stent-related events. Another consideration for HBR trial design is early discontinuation of aspirin with continuation of a $P2Y_{12}$ inhibitor alone, on the basis of promising findings from trials stopping aspirin at 1 or 3 months (34,43–45,56,57). Small studies conducted mostly in patients at low ischemic risk on a background of clopidogrel therapy have shown that dropping aspirin at 1 or 3 months post-PCI significantly reduced the risk for bleeding without a trade-off in thrombotic events compared with 12 months of DAPT (43,44). The largest study to date conducted in an all-comers PCI population, including patients at high ischemic risk, although not showing any superiority for ischemic events with a strategy of ticagrelor monotherapy (aspirin dropped after 1 month) versus the conventional DAPT strategy, did not raise safety concerns (34,56). Conversely, a strategy of dropping aspirin at 3 months after high-risk PCI proved safer than DAPT in another trial (45). Importantly, no such study has been done in an HBR population. Earlier (e.g., peri-procedural) discontinuation of aspirin has been tested in patients with indications for OAC after PCI or ACS, with reductions in bleeding events (15–19), at the price of a potential increase in stent thrombosis (58). Nonetheless, the optimal timing of aspirin cessation warrants further research. Finally, de-escalation (i.e., switching from prasugrel or ticagrelor to clopidogrel after the initial period post-procedure to reduce the risk for bleeding thereafter) is an emerging approach in ACS that has not been

TABLE 3 Academic Research Consortium for High Bleeding Risk Proposed Endpoint Definitions for Use in Clinical Trials of High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention

Endpoints	Definition
Cardiovascular death	
Cardiovascular death	Death resulting from cardiovascular causes. The following categories may be collected: 1. Death caused by acute MI 2. Death caused by sudden cardiac death, including unwitnessed death 3. Death resulting from heart failure 4. Death caused by stroke 5. Death caused by cardiovascular procedures 6. Death resulting from other cardiovascular causes
Undetermined death	Death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for endpoint determination.
Death from cardiovascular hemorrhage*	Death resulting from cardiovascular hemorrhage.*
MI	
Peri-procedural	ARC-2: Absolute rise in cardiac troponin (from baseline) ≥35 times upper reference limit plus 1 (or more) of the following criteria: new significant Q waves or equivalent, flow-limiting angiographic complications, and new "substantial" loss of myocardium on imaging.
Any MI (including nontarget vessel territory)	Per the 2018 universal definition: acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following: symptoms of myocardial ischemia, new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, and identification of a coronary thrombus by angiography or autopsy (only for infarctions of atherothrombotic nature).
Target vessel revascularization	Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.
Stent thrombosis	
Definite stent thrombosis	Angiographic or pathological confirmation of stent thrombosis.
Probable stent thrombosis	Regardless of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
Ischemic stroke	
Ischemic stroke	Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, 1) that persist for ≥24 h or until death, with pathology or neuro-imaging evidence that demonstrates either CNS infarction in the corresponding vascular territory (with or without hemorrhage) or absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected; 2) with symptoms lasting <24 h, with pathology or neuro-imaging confirmation of CNS infarction in the corresponding vascular territory.†
Ischemic stroke with hemorrhagic conversion	Ischemic stroke includes hemorrhagic conversion.
Stroke, undetermined	An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified (i.e., no neuro-imaging performed).
Hospitalization	
Hospitalization for arterial embolic reason	Any hospitalization for arterial embolic causes, including peripheral embolism (upper extremities, lower extremities, abdominal nonrenal, renal, other); stroke including retinal embolism; pulmonary embolism.
Hospitalization for ischemic reason	Any hospitalization for an ischemic event, including stent thrombosis, MI, and clinically driven coronary revascularization.
Hospitalization for bleeding reasons	Any hospitalization for a bleeding event.
BARC types 2, 3, and 5 bleeding	
Type 2	Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3 to 5 but does meet at least 1 of the following criteria: 1) requiring nonsurgical, medical intervention by a health care professional; 2) leading to hospitalization or increased level of care; or 3) prompting evaluation.
Type 3	BARC 3a: overt bleeding plus hemoglobin decrease of 3 to <5 g/dl (provided hemoglobin decrease is related to bleeding); transfusion with overt bleeding. BARC 3b: overt bleeding plus hemoglobin decrease <5 g/dl (provided hemoglobin decrease is related to bleeding), cardiac tamponade, bleeding requiring surgical intervention for control, bleeding requiring IV vasoactive agents. BARC 3c: intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision.
Type 5	BARC 5a: probable fatal bleeding. BARC 5b: definite fatal bleeding (overt or autopsy or imaging confirmation).

*For example, subdural hematoma, aortic aneurysm, cardiac tamponade, and hemorrhagic stroke. †When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (type 2a) and a transient ischemic attack (type 3a) but not as an ischemic stroke.

CNS = central nervous system; ECG = electrocardiographic; IV = intravenous; other abbreviations as in Tables 1 and 2.

tested in HBR patients to date (52,53,59). Additional background and details on antiplatelet strategies for HBR trials are provided in the Supplemental Appendix.

A key objective of trials of drug therapy and pharmacological strategies for HBR patients is to reduce bleeding, without a significant increase in thrombotic events, a goal that is more likely to be achieved using

established strategies for bleeding reduction (e.g., use of radial vs. femoral access and proton pump inhibitors). Rapid changes in clinical practice suggest the need for flexible standard-of-care definitions (and therefore of control therapies). Ultimately, the development of new antithrombotic agents (e.g., novel aspirin formulations) or antithrombotic strategies with less bleeding and no increase in thrombotic events remains an important goal (60–62).

PRIMARY ENDPOINTS FOR TRIALS OF HBR PATIENTS

As a general principle, the primary endpoint of any trial should depend on the hypothesis of the study. Because HBR trials of PCI investigate either device performance (device trials) or antithrombotic strategies (drug trials), or a combination of these, selection of the endpoint relies primarily on the study intervention. In relation to terminology, endpoints are sometimes referred to as safety- or efficacy-related events. To avoid confusion and facilitate the interpretability of HBR trials, the ARC-HBR suggests referring to thrombotic/ischemic and bleeding endpoints rather than efficacy or safety endpoints. When both thrombotic/ischemic and bleeding outcomes are captured in HBR trials, they may be considered separately as a primary thrombotic/ischemic endpoint and a primary bleeding endpoint. The thrombotic/ischemic and bleeding primary endpoints proposed by the ARC-HBR consensus are summarized in the **Central Illustration**. The definitions of the individual components of these primary endpoints are provided in **Table 3**.

PRIMARY THROMBOTIC/ISCHEMIC ENDPOINTS. Trials of HBR patients undergoing PCI are expected to include primary thrombotic/ischemic endpoints, usually with sufficient power to test for either noninferiority or superiority.

As the treatment efficacy in device trials in HBR patients is usually tested on the same background antithrombotic therapy in both the experimental and control arms, it is reasonable to consider primary thrombotic/ischemic endpoints that measure the failure of the specific study intervention. As such, the ARC-HBR endorses the ARC-2 device-oriented composite endpoint definition, including cardiovascular death (modified), MI not clearly attributable to a nontarget vessel, or clinically driven target lesion revascularization (TLR) (22). In trials of drugs in HBR patients, the ARC-HBR endorses the primary thrombotic/ischemic composite endpoint of cardiovascular death (modified), any MI, and ischemic stroke to capture major adverse events possibly related to the study intervention. Inclusion of additional thrombotic (e.g., peripheral artery embolism) or ischemic (e.g., any revascularization) events in the composite primary thrombotic/ischemic endpoint of drug trials may enable reduction in the sample size needed to achieve statistical power.

As the HBR population constitutes a subset of patients with higher risk for adverse events compared with non-HBR patients, the ARC-HBR advocates cardiovascular death as a more specific endpoint for inclusion as part of the thrombotic/ischemic endpoint. Although the ARC-2 definition of cardiovascular death includes cardiovascular death due to bleeding, the ARC-HBR recommends the exclusion of this subcategory from the thrombotic/ischemic endpoint, particularly in the presence of a bleeding coprimary endpoint. At a minimum, adjudication of cardiovascular death due to hemorrhage is recommended. The definition of spontaneous MI aligns with the 2018 fourth universal definition, which includes clinical criteria in addition to biomarker evidence of myocardial injury (63). The primary pathophysiological mechanism of neurological (i.e., brain, spinal cord, or retinal) events can be ischemic or hemorrhagic, and variations of antithrombotic therapy may contribute either to their prevention or occurrence. To account for the ischemia/bleeding trade-off of antithrombotic therapy, it is recommended that HBR drug trials report ischemic and hemorrhagic strokes separately.

PRIMARY BLEEDING ENDPOINT. The ARC-HBR recommends the use of the composite of BARC 3 and 5 bleeding as the primary bleeding endpoint of any HBR trial evaluating drugs or devices (27). Because of aspects of trial feasibility and potential recruitment, the consortium recognizes that in some trials, a primary bleeding endpoint may also incorporate BARC 2 bleeding (i.e., the composite of BARC 2, 3, and 5 bleeding) to allow a reduction in the sample size needed to achieve statistical power. A clinical justification is important if BARC 2 bleeding events are included in the primary bleeding endpoint.

SECONDARY OUTCOMES FOR TRIALS OF HBR PATIENTS

Ideally, secondary outcomes in HBR studies include the individual components of the composite primary endpoints used. For bleeding events, we recommend reporting the individual categories of BARC bleeding as secondary outcomes. Reporting of BARC 1 and BARC 2 bleeding rates may be relevant in certain situations, as such events may affect quality of life or lead to nonadherence to antithrombotic drugs (64).

Although phase 1 drug studies typically involve healthy volunteers and are therefore not relevant to HBR patients, in phase 2 studies of HBR patients, in which a signal of major bleeding alone may be undetected because of a lack of power, lower levels of bleeding tend to be important. Adjudication of BARC 2 and particularly BARC 1 bleeding events in phase 3 studies is challenging and may not always be practical. As such, for phase 3 studies of drugs and pivotal studies of devices, the writing group recommends reporting of BARC 3 and 5 bleeding as a minimal data point, with optional reporting of BARC 2 bleeding as deemed appropriate by the investigators.

With respect to thrombotic/ischemic outcomes, in trials comparing devices, these include cardiovascular death (modified), target vessel MI, clinically driven TLR, and definite or probable stent thrombosis. In trials comparing drugs or drug strategies, thrombotic/ischemic outcomes of interest include cardiovascular death (modified), any MI, ischemic stroke, and definite or probable stent thrombosis. The choice of thrombotic/ischemic secondary outcomes may differ in HBR trials investigating drugs or devices, with device trial endpoints often including events associated with the anatomic treatment target and the device's mechanism of action. Additional thrombotic/ischemic outcomes may include target vessel revascularization and any revascularization, both of which are less device specific than TLR.

Hospitalization may be a valuable secondary outcome in the HBR population, as it may influence drug adherence and quality of life. Hospitalization may be regarded as valid outcome, especially in the context of double-blind trials in which the lack of a priori knowledge of treatment arm allocation cannot bias clinical decision making. At present, a standardized definition for hospitalization is lacking, and it is important to consider the potential impact of regional differences in the thresholds for hospitalization worldwide. It is important to define the causes of hospitalization that are pertinent to the tested strategies. The consortium recommends, at a minimum, reporting of hospitalization for arterial thromboembolic or ischemic reasons and for bleeding (**Table 3**).

All-cause death is an important secondary outcome for HBR studies, as it assesses the overall treatment effect of a tested strategy. Although cardiovascular death often reflects thrombotic event-related events, all-cause mortality also includes mortality related to bleeding, which is crucial in HBR patients and will therefore provide a better estimation of the lifesaving benefits and risks, if any, associated with the tested strategy. For example, if an antithrombotic strategy reduces thrombotic/ischemic events to an extent that is similar to the increase in bleeding events, all-cause death will provide a meaningful appraisal of the net benefit of the investigated intervention. It is recommended that both cardiovascular death (excluding death due to bleeding) and death due to bleeding (BARC type 5) be reported as secondary outcomes in HBR trials. In keeping with ARC-2, the ARC-HBR recommends that death of undetermined cause be considered a cardiovascular death.

Patient-related outcome measures (PROMs) may be important in HBR patients, as some patients may favor quality of life over life expectancy, but their collection is challenging. PROMs assess health status by evaluating symptoms, function, and quality of life from the patient's perspective to assess the treatment benefit of a new device or a new antithrombotic strategy. Recommendations regarding the use of PROMs as secondary outcomes in coronary intervention trials are discussed in the ARC-2 consensus document (22). Angina relief can be assessed using the short Seattle questionnaire (65), but the most appropriate means of assessing PROMs for the HBR population remains undefined.

NET CLINICAL BENEFIT. Combining thrombotic/ischemic and bleeding outcomes into a single composite net benefit outcome is feasible but poses several challenges in the interpretation of trial results (66). Bleeding and thrombotic/ischemic risks usually trend in opposite directions depending on treatment exposure, especially in drug trials. Another limitation relates to the unequal prognostic relevance of the individual components of the composite. For example, if only event rates are considered, an increase in minor bleeding may overshadow a clinically more important reduction in ischemic stroke. Composite outcomes measuring overall effectiveness can be useful in trials in which thrombotic/ischemic and bleeding events are expected to be concordant, that is, trend in the same direction, irrespective of treatment exposure. For example, in some studies of coronary stents, interventions may be expected to reduce MI and stent thrombosis as well as allow shorter DAPT duration. Moreover, it is recommended that net clinical benefit outcomes include only events with significant adverse prognostic consequences, such as thrombotic/ischemic and bleeding events that are fatal or result in irreversible organ damage. Of note, for patients with ACS more than 30 days after PCI, BARC 2 and 3a bleeding were less prognostic for death compared with MI, while the risk for death was very similar for BARC 3b bleeding and MI and higher with BARC 3c bleeding (67). In light of these considerations, the ARC-HBR proposes a net clinical benefit

composite outcome of cardiovascular death, MI, ischemic stroke, or BARC 3b, 3c, and 5 bleeding to be used as secondary outcome to provide insight into the risk-benefit trade-off.

ADHERENCE. The collection and consideration of antithrombotic therapy adherence data is particularly important in HBR patients, as they represent a population with lower expected rates of adherence compared with non-HBR populations, because of higher rates of baseline characteristics (e.g., age, comorbidities, cognitive disorders) and bleeding events likely to affect drug compliance. In placebo-controlled trials, comparing adherence can be helpful to understand how much of the non-adherence is related to factors other than the experimental drug itself. However, as described for the PROMs, monitoring of adherence may be highly challenging in the HBR population (68). Although many tools have been proposed to assess adherence, such as questionnaires, e-blisters, and pill counts, none of these methods is ideal, and all would likely be more difficult to conduct in HBR patients. The ARC-HBR recommends the use of Non-Adherence Academic Research Consortium recommendations as a strategy for reporting, collecting, and analyzing adherence in HBR trials (64). It is useful to classify adherence according to type (e.g., dose change, under- or overexposure, temporary or permanent discontinuation), the decision maker responsible (e.g., medically driven by the investigator or another medical professional vs. patient driven), and the reason (e.g., a bleeding or an ischemic event or a drug-specific side effect) (64). In the case of nonadherence resulting from a clinical event, reporting the temporal relationship to the event is encouraged (e.g., an ischemic event occurring after antithrombotic drug discontinuation after a prior bleeding event).

TIMING OF EVENT REPORTING. Timing of event reporting in selected completed or ongoing HBR trials is summarized in Supplemental Table 1. In most of these trials, primary endpoint reporting is at 1 year with a time window of ±1 month. In most trials, primary endpoint evaluation is done by means of a patient visit to the study site. Timing of secondary outcomes reporting varies significantly among trials, ranging from 30 days (with a time window of ±1 week) to 2 years (with a time window of ±1 month). These time points are also used to perform landmark analyses. Secondary outcomes evaluation at time points other than that of primary endpoint evaluation is generally performed either by visit or phone contact.

On the basis of the individual trial objectives, the timing of primary endpoint evaluation is recommended at 12 months, while reporting of secondary outcomes is recommended at a minimum of 12 months or at the time of any significant treatment changes in the experimental and/or comparator arm. In drug trials, additional follow-up times may be advisable to capture a potential rebound in events after discontinuation of study drugs caused by loss of their protective effects. In contrast to trials comparing drugs, trials comparing 2 different device types may consider long-term follow-up, particularly in studies of investigational devices, because of the potential for device-dependent differences in clinical outcomes that may only emerge late (69,70). However, the challenge of long-term follow-up retention in HBR patients should be acknowledged.

ADDITIONAL DESIGN CONSIDERATIONS

General trial design principles involving HBR patients are similar to those of trials conducted in populations with standard bleeding risk, but some unique features should be acknowledged. HBR patients are relatively common in clinical practice (1), which may facilitate their enrollment in clinical trials. Thrombotic/ischemic and bleeding event rates are expected to be higher compared with non-HBR subjects, making it potentially easier to adequately power studies to identify true differences between therapies. Despite the broad nature of inclusion criteria in trials of HBR patients, some degree of selective patient enrollment can still occur, and careful scrutiny and reporting of screening logs is encouraged to appraise the external validity and generalizability of trial results.

Most trials in HBR patients are expected to be designated as exploratory or feasibility (e.g., studies of new drugs or antidotes, small-scale studies of device performance or intended use), pivotal (e.g., larger studies powered for thrombotic/ischemic and bleeding outcomes), or post-marketing investigations (e.g., studies intended to capture real-world data or to expand indications of devices and drugs that are already approved). In trials of both investigational and approved drugs, blinding adds complexity but has advantages in the ascertainment of certain endpoints and is therefore encouraged. In device trials in which the control arm does not involve an intervention, a sham control may be considered but is probably unnecessary in view of the inclusion of objective primary endpoint events (71). Conversely, assessor blinding (i.e., research staff performing follow-up assessments and event adjudication committee

members) is usually feasible for thrombotic/ischemic and bleeding endpoints and is endorsed by the ARC-HBR to enhance the validity of both drug and device trials, particularly if physician and/or patient blinding is not feasible. Stratification of randomization for selected variables is sometimes suggested for trials with modest sample size. Important stratification variables for HBR trials are clinical presentation (i.e., ACS or no ACS) and use of OAC. When evaluating new devices with anticipated antithrombotic properties, separate outcomes reporting in patients undergoing PCI for stable ischemic heart disease versus ACS is suggested to unravel potential interactions between baseline presentation and treatment effect on progressive atherosclerosis and recurrent non-device-related events.

Because HBR patients are frequently complex with multiple comorbidities, the design of HBR trials should balance efficiency and simplicity. Pragmatic trials such as registry-based randomized trials may be well suited for HBR patients. However, capturing bleeding events may be more challenging in the setting of passive follow-up using administrative datasets, resulting in potential ascertainment bias and event rate underestimation. Blanking periods (e.g., time intervals during which events that are more related to the procedure than to the tested intervention are not taken into account for the assessment of the endpoint) may be considered in some situations, but it is important to report and adjudicate events occurring during such periods. Finally, in addition to a clinical events committee, a data and safety monitoring committee is recommended for trials involving HBR patients to monitor the trial in real time to enhance study subject protection.

STATISTICAL CONSIDERATIONS

Statistical principles applicable to HBR trials do not differ from device or drug trials in general PCI cohorts, and recommendations can be obtained in published regulatory research as well as in the Consolidated Standards of Reporting Trials recommendations for randomized clinical trials. Superiority designs are preferred in drug trials in HBR patients using primary bleeding endpoints, and noninferiority designs are an acceptable approach in device trials as well as in coprimary thrombotic/ischemic endpoints of drug trials. Ensuring adequate power for both bleeding and thrombotic/ischemic endpoints is encouraged. Expected treatment effects of an experimental drug strategy and noninferiority margins for experimental devices are best informed by existing research and experience with the experimental therapy, and justified clinically.

In recent years, there has been increasing interest in the relative weight (or clinical relevance) of one versus another individual component of a composite endpoint, where, for example, a revascularization will not have the same weight as a spontaneous MI. However, the actual relative weights of such components are difficult to quantify and may vary in the context of HBR patients, where revascularization may be more important than in non-HBR patients because of the risks of re-exposure to antithrombotic therapy. Classical analyses of randomized clinical trials typically censor patients after they have the first event, but analyses of recurrent events have recently gained attention in cardiovascular research. However, recurrent events are also challenging to interpret in an HBR population because bleeding can lead to therapy discontinuation, driven by the protocol, clinical practice, or both. As such, including subsequent events may not be fully representative of the drug effect. Various methods for assessing repeated clinical events included in a composite endpoint are under investigation, which may be useful in improving the efficiency and interpretation of future HBR trials in which multiple nonfatal bleeding events are common (72).

GAPS IN KNOWLEDGE

Although the past 5 years have seen an increase in the number of clinical trials investigating the optimal management of HBR patients undergoing PCI or requiring antithrombotic therapy to treat coronary artery disease, gaps in evidence remain substantial. A number of specific clinical questions have priority for further investigation. First, the optimal duration and intensity of DAPT in HBR patients remains to be defined. Although 1 month of DAPT has been used in a number of studies, this may not be the most suitable duration, and perhaps shorter or longer DAPT durations may result in an improved risk/benefit ratio in specific subgroups of HBR patients.

Second, single antiplatelet therapy and its effect compared with other secondary prevention strategies that do not increase the risk for bleeding warrant further study in this subgroup.

Third, over the longer term, whether secondary prevention of coronary artery disease with antithrombotic therapy results in net clinical benefit in HBR patients remains an open question.

Fourth, additional device-versus-device studies can investigate whether specific stent platforms

may provide important clinical benefits in combination with specific antiplatelet therapy regimens.

Fifth, in patients undergoing PCI, alternative approaches to stenting, such as therapy with drug-coated balloons, can be studied. In addition, further trials of revascularization versus medical therapy in HBR patients are likely justified.

Finally, a certain degree of heterogeneity in the HBR population should be acknowledged, which adds complexity to trial designs and the interpretation of study results.

CONCLUSIONS

The development of pragmatic consensus definitions for use in trials that provide benefit/risk evidence for clinical and regulatory decision making is central to the ARC mission. Use of pragmatic definitions means that high-quality data collection is feasible and enhances the efficient use of resources. It also encourages the generation of data that support key trial design elements consistent with available regulatory guidance to help ensure patient safety and produce results with maximum freedom from bias.

Equally central to the regulatory dimension of ARC programs is the recognition that consensus definitions do not prescribe how such definitions are applied. Consensus definitions promote consistency in trial design across a potential spectrum of applications, including evaluation of novel technologies and subsequent device iterations. This is particularly relevant for the ARC-HBR definitions, which address patients commonly underrepresented in device and drug studies, and for whom there is a need for further understanding of both device and drug benefit/risk. In this respect, it is important to acknowledge that in clinical trials investigating HBR patients, bleeding risk in combination with thrombotic/ischemic risk are key considerations in regulatory and clinical decision making.

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KEY WORDS high bleeding risk, percutaneous coronary intervention, trial design

APPENDIX For a list of ARC-HBR participants, assessment of methodological differences in selected HBR trials, recommendations for bleeding and cerebrovascular event definitions, considerations regarding selection of control devices in HBR trials, and a supplemental table, figures, and references, please see the online version of this paper.