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Limitations in Identifying and Managing HBR Patients Undergoing PCI

A deficit of randomized PCI data including the high bleeding risk population makes it challenging to define the optimal management of these patients.

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During the last decade, improvement of percutaneous coronary intervention (PCI) made treatment of more complex lesions and patients possible, including patients with high bleeding risk (HBR). With the first generation of drug-eluting stents (DESs), dual antiplatelet therapy (DAPT) duration was recommended as 3 to 6 months[1-4] and was even increased to 12 months after 2006 in the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography & Interventions (ACC/AHA/SCAI) recommendations due to concerns about late thrombotic events.[5] Therefore, HBR patients who were unsuitable for long-term DAPT were consistently excluded from DES studies and considered only as candidates for bare-metal stents (BMSs) or medical treatment.

Recently, three randomized trials comparing DES and BMS with short DAPT duration in HBR patients showed superior safety and efficacy with DES.[6-8] This represents an alternative treatment regimen for patients who were not previously considered candidates for DES. The challenges in defining the optimal management of HBR patients undergoing PCI was indeed an issue due to paucity of scientific data and varying definitions of an "HBR patient." The aim of this article is to provide an update on PCI treatment of HBR patients using available scientific evidence and current clinical practice recommendations.

CRITERIA USED TO DEFINE HBR

Definitions used in HBR PCI studies have been heterogeneous (main criteria used, Figure 1). Many criteria have been used to define HBR, and the weight of each criterion is clearly variable. For example, age over 75 years was used as a unique HBR criterion in the SENIOR study,[8] while prior history of intracranial bleeding has been used in other studies, such as LEADERS FREE[6]; clearly, these two criteria have different levels of impact on bleeding risk.[8] Several scores have been developed that predict long-term bleeding risk in patients taking antiplatelet therapy.[9-12] The 2017 European Society of Cardiology (ESC) focused update on DAPT in coronary artery disease recommended (class IIb recommendation, level of evidence A) that use of risk scores such as the PRECISE-DAPT and DAPT scores may be considered to guide antiplatelet therapy after PCI.[13] The 2016 ACC/AHA focused update highlights the use of the DAPT score to assess the benefit/risk ratio of prolonged DAPT.[14,15] Age is the only variable common to all scores, but thresholds to define "elderly" increased bleeding risk and their relative weights vary between risk scores. In addition, although baseline anemia was found to be one of the strongest independent predictors of bleeding assessed in PARIS, BleeMACS and PRECISE-DAPT, it was not assessed in development of the REACH or DAPT scores.[9-12]

The burning question for clinical practice is whether HBR should be defined by scores or clinical judgment based on a physician's experience. The PRECISE-DAPT score, for example, has been proposed to predict risk of post-PCI bleeding based on pooled analysis of PCI studies assessing different DAPT durations.[9] However,

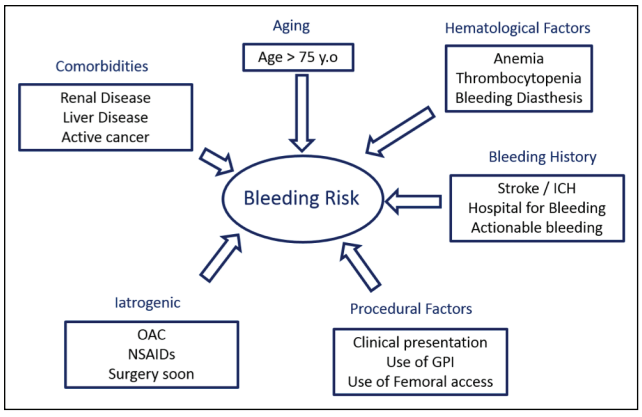

Figure 1. Frequently included criteria used to define HBR patients.

these trials have excluded HBR patients unsuitable for long-term DAPT and therefore, the PRECISE-DAPT score has been defined in a non-HBR population with low bleeding risk.[9] Defining HBR based on a score molded in a non-HBR population could have clear limitation. Additionally, although some risk factors are very rare in the PCI population (eg, severe liver disease), they were not identified in such statistical models, representing another limitation of such scores based on large PCI studies. For these reasons, few clinicians are using these scores in daily practice to define HBR and select a tailored strategy. An Academic Research Consortium HBR initiative aims to craft a consensual definition of HBR for patients undergoing PCI based on literature review and clinical consensus. This initiative is now ongoing and will soon provide a new proposal for consensual definition of HBR.

EVIDENCE AND ONGOING STUDIES FOR HBR PATIENTS UNDERGOING PCI

Three randomized trials investigating short DAPT durations have been completed that include PCI patients considered at increased bleeding risk,[6-8] and many trials are currently ongoing (Table 1). Inclusion criteria in these trials largely reflect exclusion criteria in prior DES studies of non-HBR patients randomized to different DAPT durations, but there is significant heterogeneity with respect to the patient populations studied. The LEADERS FREE trial (n = 2,466) had the most inclusive HBR criteria with an average of 1.7 bleeding risk criteria per patient.[6] The ZEUS trial (n = 1,606) enrolled uncertain DES candidates with a prespecified subgroup analysis of patients who met criteria for HBR (ZEUS-HBR; n = 828).[7] Finally, the SENIOR trial (n = 1,200) included elderly patients with no other specified inclusion criteria associated with increased bleeding risk.[8] The most common criteria for HBR in these three studies was advanced age (64% of enrolled patients in LEADERS FREE were considered advanced age, 51% in ZEUS-HBR, and 100% in SENIOR), although the lower age cut-off differed between trials (> 80 years in ZEUS-HBR vs ≥ 75 years in LEADERS FREE and SENIOR).[6-8] The second-most common criteria for HBR was indication for oral anticoagulant, which represented 36%, 38%, and

TABLE 1. REFERENCED HBR CRITERIA IN PUBLISHED AND ONGOING PCI STUDIES

	LEADERS FREE[6]	ZEUS-HBR[7]	SENIOR[8]	MASTER DAPT (NCT03023020)	ONYX ONE (NCT03344653)	COBRA REDUCE (NCT02594501)	EVOLVE SHORT DAPT (NCT02605447)	XIENCE 28/ XIENCE 90 (NCT03355742) (NCT03218787)
Trial type	RCT (published)	RCT (published)	RCT (published)	RCT (ongoing)	RCT (ongoing)	RCT (ongoing)	Single arm (ongoing)	Single arm (ongoing)
Age ≥ 75	✓	✓ (> 80)	✓	✓	✓		✓	✓
OAC	✓	✓		✓	✓	✓	✓	✓
Renal failure	✓				✓		✓	✓
Liver disease	✓			✓	✓			
Recent cancer	✓			✓	✓			
Anemia or transfusion	✓	✓		✓	✓			✓
Thrombocytopenia	✓	✓					✓	✓
Stroke or ICH	✓			✓	✓		✓	✓
Actionable bleed				✓			✓	✓
Hospitalization for bleeding	✓	✓		✓				
NSAID	✓	✓		✓	✓			
Early planned surgery	✓				✓			
PRECISE-DAPT score > 25				✓				

Abbreviations: ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory; OAC, oral anticoagulation; RCT, randomized controlled trial.

18% of patients in LEADERS FREE, ZEUS-HBR, and SENIOR, respectively.[6-8] The differences of inclusion criteria in completed trials are reflected in the differences in bleeding event rates. In LEADERS FREE and ZEUS-HBR, the 1-year rates of Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding in patients treated with 1 month of DAPT after PCI were 7.3% and 4.2%, respectively; in the SENIOR trial, the 1-year BARC 3 to 5 bleeding rate in patients treated with 1 to 6 months of DAPT after PCI was approximately 3.5%.[6-8] Such differences highlight the need for a standardized definition of HBR.

In these three studies focusing on HBR patients, DESs were compared to BMSs with a prespecified shorter DAPT duration.[6-8] Results of these studies showed greater efficacy of DES for prevention of restenosis and repeated revascularization and comparable safety compared to BMS with short DAPT for risk of stent thrombosis.[6-8] Based on this evidence, DES has become standard of care even in HBR patients, which represents a change of paradigm, and may further reduce the use of BMSs.[13] These published studies on HBR patients undergoing PCI and the ones ongoing are summarized in Table 1 with different inclusion criteria. Among ongoing projects, randomized controlled trials and single-arm studies will assess the safety of new-generation DESs with very short DAPT (eg, 1 month) in a larger population of HBR patients.

CONCLUSION

Identification of HBR patients remains a challenge; this represents an important issue, as the proportion of HBR patients is growing rapidly in our daily practice. Ongoing initiatives like the Academic Research Consortium HBR initiative will help the community reach a more consensual definition of an HBR patient. Beyond the definition, more evidence is still needed to confirm that this population can safely be treated with new DESs and very short DAPT duration without an increased risk of atherothrombotic events, including stent thrombosis. ■

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