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Key Factors for Clinical Decisions When Treating Patients at High Bleeding Risk

Less is more when treating high bleeding risk patients with latest-generation DESs and short DAPT duration.

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Bleeding events are a recurrent downside of treating patients admitted for ST-segment elevation myocardial infarction (STEMI) or stable coronary artery disease. Regardless of the procedural success to restore coronary flow, major and minor bleeding events have a direct impact on the mortality of patients undergoing percutaneous coronary intervention (PCI).[1,2] In parallel, technical advances and procedural safety have expanded PCI indications to more vulnerable and complex patients who have a higher exposure to iatrogenic and bleeding events.[3,4] The subset of high bleeding risk (HBR) patients is the subject of ongoing studies and recent recommendations aimed at improving risk stratification and establishing tailored strategies.[5] These studies have provided key factors for clinical decisions in HBR patients, especially concerning (1) the identification of HBR patients; (2) selection of adequate antiplatelet therapy; and (3) creating a tailored approach to the duration of dual antiplatelet therapy (DAPT). This article reviews these key factors based on recent evidence and discusses perspectives for better assessment and treatment of HBR patients.

WHO ARE HIGH BLEEDING RISK PATIENTS?

In recent years, several strategies have emerged to improve ischemic and bleeding risk stratification of patients undergoing PCI. The objective was to identify HBR patients using simple clinical and biological characteristics, and then provide an estimation of the adequate DAPT duration to enable sufficient anti-ischemic protection without increasing bleeding events.

Risk Scores

Following the growing awareness of the burden of bleeding events on poor outcomes, several competing prediction models have emerged to stratify bleeding risks in patients undergoing PCI. Those scores were mostly modeled in registries or post hoc analyses of randomized trials addressing other questions (mostly antithrombotic and myocardial infarction [MI] care), with limited variables and only short-term evaluation of bleeding complications. In the list of scores, the most well-known are the CRUSADE score (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) derived from the CRUSADE registry, the ACTION score (Acute Coronary Treatment and Intervention Outcomes Network) derived from the National Get With the Guidelines Action registry, and the ACUITY/HORIZON-MI score derived from ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and HORIZON-MI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials.[6-8]

Gender, chronic kidney disease, baseline anemia, and type of presentation were recurrent significant risk features of these scores. Although these scores share many common variables and an overall moderate performance, they were applied to different populations, looking mostly at in-hospital bleeding (Table 1). The HAS-BLED score, although designed to evaluate the bleeding risk of patients with atrial fibrillation treated with anticoagulants, is also useful for patients admitted for acute coronary syndrome (ACS)[9]; it is easy to use and includes important variables such as alcohol use, liver dysfunction, and prior bleeding history.[10,11]

More recently, the PRECISE-DAPT investigators used individual data from eight randomized controlled trials to develop a bleeding risk score to guide DAPT duration.[12] Compared to previous scores, the PRECISE-DAPT score is the only score to provide a long-term risk stratification of bleeding events; furthermore, PRECISE-DAPT also takes into account the variable "prior bleeding," which weighs four times more than the other variables in the bleeding risk assessment. In this study, prolonged DAPT (> 6 months) in patients with HBR (PRECISE-DAPT score ≥ 25) was associated with an increase in bleeding

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TABLE 1. VARIABLES AND PERFORMANCE OF BLEEDING RISK SCORES

Scores	Population	Data Base	Number of Patients in the Derivated Cohort	Validation Cohort	Outcome	C-Statistic in the Validation Cohort
CRUSADE	NSTEMI and unstable angina	CRUSADE registry	71,277	Yes	In-hospital major bleeding	0.71
ACTION	STEMI and STEMI	ACTION registry-GWTG	72,313	Yes	In-hospital major bleeding	STEMI, 0.70; NSTEMI, 0.72
ACUITY	STEMI and STEMI	ACUITY trial/ HORIZON MI trial	17,421	None	Major bleeding within 30 days	0.74 in the derivated cohort
PRECISE-DAPT	All PCI	PRECISE-DAPT (patient-level data pooled from eight RCTs BIOSCIENCE, COMFORTABLE AMI, EXCELLENT, OPTIMIZE, PRODIGY, RESET, SECURITY, and ZEUS)	14,963	Yes	Out-of-hospital TIMI major or minor bleeding beyond 7 days	0.70

Abbreviations: NSTEMI, non–ST-segment myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; STEMI, ST-segment myocardial infarction; TIMI, thrombolysis in myocardial infarction.

events (number to treat to harm, 38), without decreasing the rate of ischemic events.[12]

The use of risk scores (specifically the PRECISE-DAPT and DAPT scores) for a tailored DAPT duration has recently entered the guidelines of the European Society of Cardiology (ESC), with a class IIb and level A of evidence.[5] Similarly, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest the use of the DAPT score for assessment of prolonged DAPT viability.[13,14] Despite the availability of multiple scoring systems and the abundant scientific literature regarding their validation, they remain poorly tested prospectively and poorly implemented in clinical practice.

Platelet Reactivity

Bedside monitoring of platelet reactivity has carried hope as a tool to provide an adequate and tailored antiplatelet therapy in the most vulnerable patients. Cohort studies have demonstrated an association between very low on-treatment platelet reactivity and major bleeding.[15] However, this did not translate into a net clinical benefit when test-guided antiplatelet strategies were evaluated in randomized trials, especially in the ANTARCTIC trial, which included high-risk patients aged ≥ 75 years admitted for ACSs.[16,17] Therefore, there is currently not enough evidence to support the use of this tool.

Better Identifying HBR Patients

Because of the moderate performance (C-Statistic shown in Table 1) of the clinical scores and their difficult implementation in clinical practice, identifying a HBR patient remains a major challenge. This can be explained by the fact that current large cardiology registries and pooled cohorts of randomized trials were not designed to capture the complex interactions between individual characteristics and the iatrogenic risk of antiplatelet therapy. This highlights the need for specific trials and studies with designs, inclusion criteria, and case report forms able to evaluate the relationship between HBR patients and treatments. Artificial intelligence will provide promising strategies to develop risk estimation models with the use of machine learning methods, pending the inclusion of sufficient variables regarding the overall patient, and not only the traditional ischemic risk factors.

ANTIPLATELET TREATMENTS IN HIGH BLEEDING RISK PATIENTS: WHICH ONES AND HOW LONG?

Which Antiplatelet Therapy?

Clopidogrel is the recommended antiplatelet for elective PCI in stable coronary artery disease, regardless of the bleeding risk.[5] The choice of the best antiplatelet therapy for HBR patients after an ACS is still to be

TABLE 2. INCLUSION CRITERIA OF HBR PATIENTS IN TRIALS EVALUATING SHORT-TERM DAPT WITH SECOND- AND THIRD-GENERATION STENTS

	Enrollment	Presentation	Age ≥ 75 Years	Concomit. Anticoag.	Chronic Kidney Disease	Recent Bleeding	Anemia	Liver Disease	Prior ICB	Prior Stroke	Hematol. Dis.	Concomit. NSAI	DAPT Duration
LEADERS FREE[22]	2,466	SCAD (57.7%) ACS (42.3%)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	1 month
ZEUS[21]	1,606	SCAD (36.7%) ACS (63.3%)	✓	✓	X	✓	✓	X	X	X	✓	✓	1 month
MASTER DAPT NCT03023020	4,300 (expected)	STEMI excluded	✓	✓	X	✓	✓	X	✓	✓	X	✓	1 month
EVOLVE SHORT DAPT NCT02605447	2,009 (expected)	STEMI and NSTEMI excluded	✓	X	✓	✓	X	X	X	✓	✓	X	3 months
XIENCE 90 Short DAPT NCT03218787	2,000 (expected)	STEMI excluded	✓	✓	✓	✓	✓	X	X	✓	✓	X	3 months
ONYX ONE NCT03647475	800 (expected)	SCAD and ACS	✓	X	✓	✓	X	✓	✓	X	✓	X	1 month
COBRA-REDUCE NCT02594501	996 (expected)	SCAD and ACS	X	✓	X	X	X	X	X	X	X	X	2 weeks

Abbreviations: ACS, acute coronary syndrome; concomit. anticoag., concomitant anticoagulation; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; hematol. dis, hematological disorders; ICB, intracerebral bleed; concomit. NSAI, concomitant nonsteroidal anti-inflammatory; SCAD, stable coronary artery disease.

determined. In the PLATO trial, ticagrelor was associated with a 20% increase of noncoronary artery bypass grafting–related major bleeding and a 30% increase of intracranial bleeding compared to clopidogrel.[18] In the TIMI TRITON-38 trial, prasugrel was associated with a 30% increase in major bleeding, especially in patients aged > 75 years, with a history of stroke, or who weighed < 60 kg (132 lb).[19] Therefore, ESC guidelines recommend prescribing a combination of aspirin with either clopidogrel or ticagrelor for a duration of 6 months (class IIa, level of evidence B) in HBR patients undergoing PCI for ACS.[5] The 2016 ACC/AHA guidelines give a class IIa, level of evidence B-R recommendation for the use of ticagrelor over clopidogrel for patients with ACS after PCI.[13]

DAPT Discontinuation: How Early After an ACS?

It is well described that the risk of recurrent thrombosis and cardiac events decrease over time after the index event while the bleeding risk increases with the duration of DAPT.[20] For a long time, bare-metal stents (BMSs) were the systematic choice for HBR patients, as they allowed a short 1-month DAPT duration without exposing patients to the risk of early stent thrombosis; nonetheless, this choice put patients at risk for restenosis and recurrent ischemic events. To overcome these difficulties, recent and ongoing randomized trials have been comparing BMSs to newer-generation drug-eluting stents (DESs) in the setting of a shorter (≤ 3 months) DAPT duration in HBR patients (Table 2).

The second-generation DESs have made short DAPT duration (≤ 3 months) possible, with better stent deployment and stronger efficacy regarding early and late thrombosis and restenosis. In the ZEUS randomized controlled trial (n = 1,606), HBR patients were assigned to a hydrophilic polymer-based, second-generation zotarolimus-eluting stent or BMS; both arms were treated with 1-month DAPT.[21] Of note, 63% of participants were included following an ACS. Patients receiving the second-generation DES benefited from a 25% reduction of ischemic outcomes at 1-year follow-up, with a major bleeding rate around 1.5% (BMS bleeding rate, 2.1%). The 12-month rate of major adverse cardiac events (all-cause mortality, MI, or target vessel revascularization was lower in the DES arm (17.5%) than the BMS arm (22.1%).

Polymer-free DESs—often referred to as third-generation DESs–are also opening the path for 1-month DAPT duration for HBR patients. LEADERS FREE

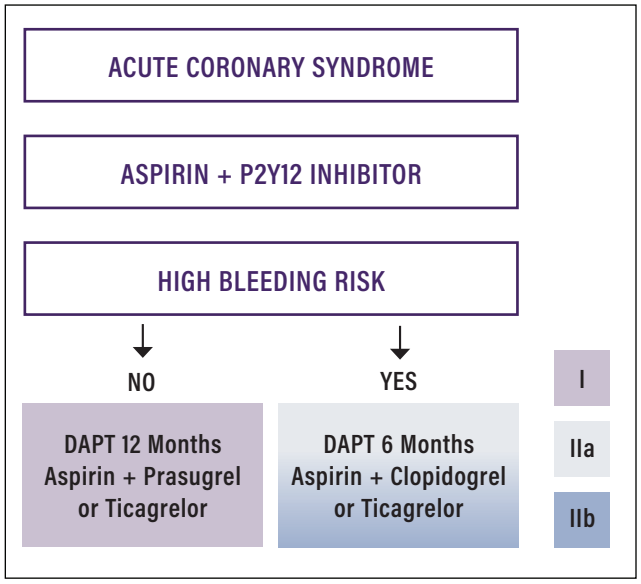

Figure 1. Algorithm for DAPT duration in HBR patients admitted for ACS based on the 2017 ESC guidelines for DAPT management. Adapted from Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213-254.

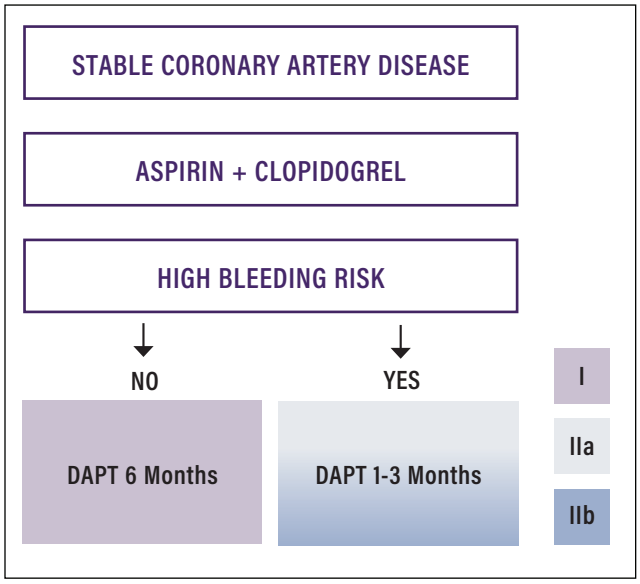

Figure 2. Algorithm for DAPT duration in HBR patients admitted for stable coronary artery disease based on the 2017 ESC guidelines for DAPT management. Adapted from Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213-254.

investigators used several important bleeding risk features as inclusion criteria for the 2,466 patients of the study population treated with 1-month DAPT (Table 2).[22] Of note, 64.5% of participants were aged > 75 years, 36.7% were treated with anticoagulants, and 17.9% had a creatinine clearance < 40 mL/min. At presentation, 58% of participants underwent PCI for stable coronary disease, 28% for MI, and 14% for unstable angina. Compared to BMS, the use of DES was associated with a 30% reduction in cardiac death, MI, or stent thrombosis at 390 days. The rate of Bleeding Academic Research Consortium (BARC) type 3 to 5 bleeding was high (7%) and similar in both groups.

These results have demonstrated the safety of a very short DAPT duration after PCI, regardless of the indication, in HBR patients treated with contemporary generation DESs. Based on these results, ESC guidelines on DAPT management have opened the path for a 1-month DAPT duration for HBR patients with stable coronary artery disease and 6 months after ACS (class IIb and IIc recommendation) (Figures 1 and 2).[5] Similarly, the 2016 ACC/AHA guidelines consider it reasonable to discontinue DAPT after 6 months for patients with ACS after PCI who have HBR or develop significant overt bleeding (class IIb, level of evidence C-LD recommendation).[13,23,24]

Reducing Bleeding Risk in Elective Noncardiac Surgery

Approximately 5% of patients will undergo elective noncardiac surgery within the first year after PCI and up to 30% in the subsequent 5 years.[25,26] They are at very high risk of perioperative major bleeding and ischemic events with a subsequent mortality risk.[27,28] On top of the early interruption of DAPT, the systemic stress and inflammation related to the perioperative setting are associated with a high risk of stent thrombosis and ischemic events; thus, the management of these patients should be cautiously planned with a preestablished strategy before performing PCI. The high risk of stent thrombosis associated with first-generation DESs led to previous guidelines favoring BMSs over DESs when elective surgery was planned. Of note, it was recommended to delay surgery up to 1 month after BMS implantation and 1 year after DES.[29,30]

As mentioned previously, contemporary generation DESs have allowed a shortened DAPT duration with a better efficacy against ischemic events than BMSs,

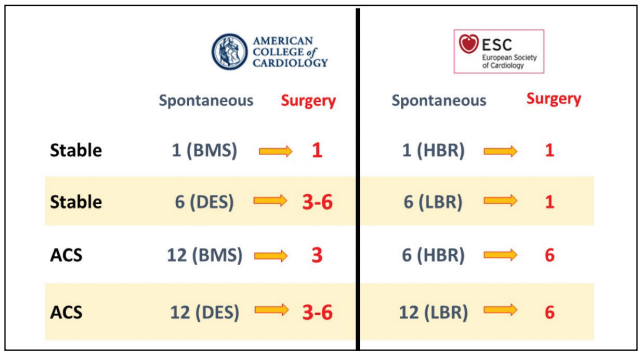

Figure 3. AHA/ACC and ESC guidelines for months of DAPT duration after PCI, spontaneously (no surgery scheduled) or when elective surgery is scheduled. LBR, low bleeding risk.

regardless of PCI indication. In 2016, a large cohort study (n = 39,362) assessed the interaction between stent types, time from PCI to surgery and MI, major bleeding, and mortality. Second-generation DESs were associated with fewer ischemic events compared to BMSs and first-generation DESs. Importantly, DAPT interruption appeared safe between 3 and 6 months when DESs were implanted without increased risk of stent thrombosis.[27]

The importance of timing was also evaluated by a large Danish cohort study that compared 4,303 patients treated with DESs who underwent a surgical procedure to 20,232 non-PCI patients undergoing similar surgical procedures. Surgery in PCI patients was associated with a significant increase in MI (1.6% vs 0.2%; odds ratio, 4.82; 95% confidence interval, 3.25–7.16) but not all-cause mortality. When stratified by time from PCI to surgery, the association with poor outcomes was significant within the first month but not beyond.[31] Because of this evidence, ESC guidelines strongly recommended DESs regardless of the indication and timing before surgery, allowing a DAPT interruption after 1 month in stable coronary artery disease and 3 to 6 months after an ACS (Figure 3).[5] Similarly, the 2016 ACC/AHA guidelines reduced their class I recommendation from at least 12 months to 6 months for length of delaying elective noncardiac surgery in patients previously treated with DES, and reduced the class IIB recommendation from 6 to 3 months.[13] In all cases, it is recommended to continue aspirin if the surgery allows and to resume the recommended antiplatelet therapy as soon as possible.

Despite the encouraging results of the newer DESs and shortened DAPT duration, surgery after PCI carries a high risk of adverse events and should be delayed as much as possible. The management of these situations should be multidisciplinary to provide a strategy that takes into account the patient's high-risk features, coronary artery disease history, and the surgical procedure.

WHEN HIGH BLEEDING RISK MEETS HIGH ISCHEMIC RISK

Age, admission for STEMI, history of cancer or stroke, and other characteristics are concomitant risk factors for both increased ischemic and bleeding events. Whether bleeding or ischemic prevention should be favored with a respective shorter or prolonged DAPT duration remains a challenging question, as this type of patient is increasingly seen in daily clinical practice.

The PRECISE-DAPT investigators recently studied the effects of DAPT duration in patients with concomitant complex PCI and high bleeding risk.[32] Prolonged DAPT (12 months) did not provide ischemic or mortality benefits in HBR patients (PRECISE-DAPT score ≥ 25), regardless of PCI complexity or acute presentation. Furthermore, prolonged DAPT was associated with increased bleeding events compared with a shorter DAPT duration (6 months), indicating that DAPT duration should be guided by the risk of bleeding more than prevention of ischemic events.

CONCLUSION

Bleeding events carry an important burden in mortality related to ischemic heart disease. More research is needed to better describe HBR patients and develop tailored antithrombotic strategies. Most of the evidence concerning HBR patients is derived from registries and randomized controlled trials that were not designed to provide information regarding this matter. The creation of risk scores has been an initial step toward a tailored approach, even if their implementation in daily clinical practice remains of unknown added value. When adequately identified, the bleeding risk should be the primary factor to guide DAPT duration, regardless of the PCI indication or its complexity. Recent trials, such as LEADERS FREE, ZEUS, MASTER DAPT, and others show promise that newer-generation DESs associated with a 1-month DAPT duration are providing effective ischemic protection to HBR patients, and further ongoing studies will provide definitive evidence. ■

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