The High Bleeding Risk Patient with Coronary Artery Disease

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KEYWORDS

• PCI • Coronary • Stent • DAPT • PRECISE-DAPT • Bleeding • Risk • Score

KEY POINTS

- Reducing bleeding complications has become a priority in modern cardiology.
- Bleeding carries a significant prognostic impact that could equate or surpass ischemic events.
- Specific tools and definitions to identify and treat high bleeding risk patients are now available and could support decisions for antiplatelet therapy duration selection.

INTRODUCTION

The role of antithrombotic therapy in the treatment of acute ischemic heart disease has been established for more than 40 years.[1] Discoveries linking myocardial infarction (MI) to coronary thrombosis have prompted research in the field of thrombocardiology, pushing boundaries for more effective and prolonged treatments to reduce recurrences of vascular thrombosis.[2] Dual antiplatelet therapy (DAPT), consisting of a combination of aspirin and a P2Y12 platelet receptor inhibitor, is mandatory after percutaneous coronary intervention (PCI) to reduce the risk of stent-related and non–stent-related coronary ischemic events.[3] Yet, the introduction of more potent or prolonged courses of treatment has invariably increased the rate of bleeding events.[4–6] Similar to coronary ischemic events, bleeding events could have a negative impact on prognosis, especially among individuals at high bleeding risk (HBR).[7] For this reason, identifying HBR patients is key to optimizing outcomes. Prognostic tools and standardized definitions recently have been proposed with this scope and have been endorsed by specialty guidelines.[8,9] This report provides a summary of the current available evidence regarding HBR-PCI and a description of the current tools to identify and individualize treatment in this subgroup.

PROGNOSTIC IMPACT OF BLEEDING EVENTS AFTER PERCUTANEOUS CORONARY INTERVENTION OR ACUTE CORONARY SYNDROME

In the past 2 decades, ischemic events after PCI halved, reduced from 18.4% to 9.1%, and out-of-hospital bleeding doubled, increasing from 2.5% in the period 1995 to 2000 to approximately 5% in the period 2013 to 2016.[10] Bleeding prevention has become a priority in modern cardiology.[11] Hemorrhagic events during antithrombotic treatment could occur at multiple organs (**Fig. 1**). In the ADAPT-DES study, 61.7% of out-of-hospital bleeding occurred in the gastrointestinal tract, 12.2% were peripheral, 8.6% were genitourinary, 7.4% were in the central nervous system, 7.0% were from the vascular access site, and 3.2%

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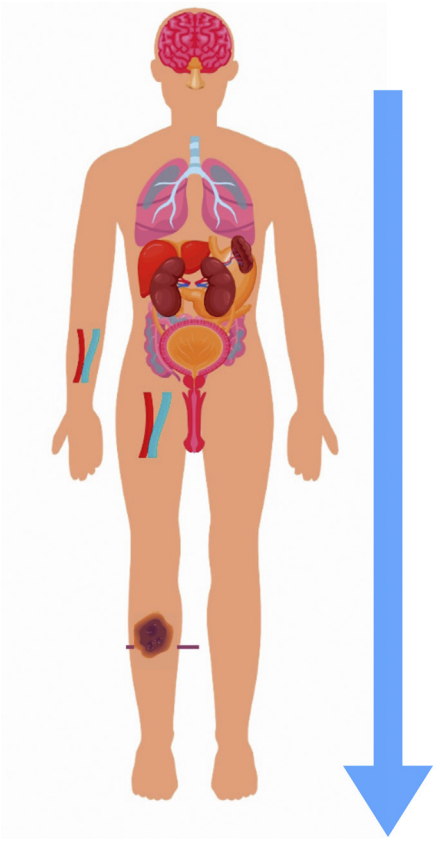

Site of bleeding	Incidence	Suggestion to prevent or to treat
Gastrointestinal	61,7%	- Use of proton-pump inhibitors - Avoid NSAIDs - Before elective PCI consider gastroscopy or colonoscopy if active bleeding is suspected
Peripheral	12,2%	- Local haemostatic measures - Cold water rinse - Tranexamic acid if mucosal bleed
Genitourinary	8,6%	- Urine cytology, imaging for diagnosis and treatment - Consider hormonal or local therapy for menometrorrhagia
Central Nervous System	7,4%	- Consider short DAPT in patients at risk of intracranial bleeding - Blood pressure management
Access site	7.0%	- Prefer radial access - Echo-guided puncture if femoral artery is needed
Retroperitoneal	3.2%	- Look for signs and symptoms - Make early diagnosis

When severe or life threatening bleeding consider:
- Surgical or endoscopic treatment of bleeding source if possible
- Fluid replacement
- Red blood cells transfusion
- Platelet transfusion

Fig. 1. Bleeding risk after PCI and bleeding avoidance strategies.

were retroperitoneal.[12] Depending on their location and severity, the prognostic impact of major bleeding could be similar or even worse compared with recurrent MI.[7] Even when not associated directly with worse outcomes, bleeding episodes are linked to poor drug adherence and deterioration in quality of life.[13–15]

HIGH BLEEDING RISK DEFINITION AND RISK STRATIFICATION

Proper identification of HBR patients is key to recognizing and then individualizing treatment.

In a survey published in 2015, advanced age, chronic renal failure, anemia, and a positive history of past bleeding events were considered the most important markers of HBR after PCI.[16]

Risk stratification tools previously have been proposed to improve in-hospital outcomes and quality metrics,[17] although most bleeding events related to DAPT after coronary stenting occur in the out-of-hospital setting. Only recently, multiple risk stratification tools have been proposed to measure this risk.

The PARIS score is a set of 2 prediction tools focused on ischemic and bleeding risk prediction after discharge.[18] These tools have been developed from a real-world cohort of 4190 patients undergoing drug-eluting stent (DES) implantation. The integer risk score developed for major bleeding at 2 years included 6 clinical features: age, body mass index, current smoking, anemia, renal impairment (ie, with a creatinine clearance <60 mL/min), and triple antithrombotic therapy at

discharge.[18] The predicted risk of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at 2 years was 1.80% among patients at low bleeding risk, 3.90% in the intermediate risk, and 10.0% in the HBR patients.[18]

The PRECISE-DAPT is a risk score focused on out-of-hospital bleeding events among patients treated with PCI and assigned to DAPT.[19] It has been developed from a collaborative data set of 8 randomized clinical trials, including 14,963 patients. The risk score developed for major bleeding at 1 year included 5 clinical and laboratory variables: age, a history of prior bleeding, hemoglobin, white blood cell count, and creatinine clearance. An alternative score excluding white blood cell count also was developed and validated.[19,20] A history of prior bleeding was the most important contributor to the model. The score has been validated in 2 different external cohorts from a large randomized controlled trial and from a large real-world registry.[4,21] High-risk patients carried a predicted risk of thrombosis in MI (TIMI) major or minor bleeding at 1 year greater than 1.85%.[19]

Score discrimination was decent in both the derivation cohort (C statistic = 0.73) and in the validation cohort from the PLATO trial (C statistic = 0.70); it was modest in the validation cohort from the Bern PCI registry (C statistic = 0.66).

Recently the HBR Academic Research Consortium (HBR-ARC) provided a consensus-based definition of HBR after PCI. HBR patients were defined as those with an estimated risk of major bleeding (ie, according to the standardized definition of the BARC 3 and 5) of at least 4% per year or a risk of intracranial bleeding of at least 1% year.[22] This threshold has been selected by consensus based on data from HBR-PCI trial literature, selecting a meaningful and clinical sound limit of events. The task force also listed a series of 20 clinical or laboratory criteria that could be used for identifying patients at HBR. These are divided in major or minor criteria of HBR, qualifying as HBR if at least 1 major criterion or 2 minor criteria are present in the single patient (**Fig. 2**). This definition has been independently validated in CREDO-Kyoto register.[23] In this population, HBR patients were associated with a significant increase of GUSTO moderate or severe bleeding at 1-year (10.4% vs 3.4%, respectively) and at 5-year follow-up (18.9% vs 6.6%, respectively; P <.0001). The presence of multiple risk criteria was associated with a linear increase in bleeding risk (no criteria: 6.6%; $\geq$2 minor criteria: 14.7%; 1 major criterion: 18.5%; 2 major criteria: 30.6%; and $\geq$3 major criteria: 49.9%, P<.0001).[23]

Another external validation of this definition recently has been provided from the Bern PCI registry.[24] In this population of all-comer patients treated with PCI in a single, large-volume tertiary center in Switzerland, a total of 39.4% of patients were deemed at HBR. As expected, HBR patients were associated to a significantly higher risk of BARC type 3 or 5 bleeding (6.4% vs 1.9%, respectively; P<.001). An increasing number of bleeding criteria was associated to a proportional higher risk of bleeding, which was greater than 10% at 12 months if greater than or equal to 3 major criteria were present.[24]

The criteria proposed by the HBR-ARC initiative have a robust literature confirming their link to a higher risk of bleeding. Oral anticoagulant (OAC) treatment is considered a major criterion in the HBR-ARC definition. The combination of OAC and antiplatelet therapy after PCI is associated with a 3-fold to 5-fold increase of bleeding risk.[25,26] Use of OAC is mandatory to reduce stroke and systemic thromboembolism in a series of conditions, including high-risk atrial fibrillation (AF). In PCI patients with need for long-term OAC for AF, implementation of direct OACs (DOACs), instead of vitamin K antagonists, and implementation of dual antithrombotic therapy, instead of triple antithrombotic therapy (ie, by excluding aspirin from the antithrombotic strategy), early after stenting is associated with a reduction of bleeding events[26]; yet, the rates of bleeding also with DOACs and single antiplatelet therapy with a P2Y12 inhibitor remain high, requiring a closer follow-up in this group of patients.[27]

Malignancy, defined as a diagnosis of active cancer in the previous 12 months before PCI or an ongoing illness on actual treatment, is considered a major criterion of HBR. Cancer poses patients at both higher risk of bleeding and thrombosis. It generally is associated with a hypercoagulable state with increased platelet activation and aggregation, despite a high prevalence of thrombocytopenia.[28,29] Hence, malignancy could be associated with major bleeding due to both blood dyscrasia or direct bleeding from the malignant tissue. In a prior report from the Bern PCI registry, a history of malignancy was a strong predictor of novel gastrointestinal bleeding, with a more than 2-fold higher risk.[21]

Moderate or severe thrombocytopenia (<100,000 elements per mm^3) is considered a major HBR-ARC criterion. Patients with chronic thrombocytopenia undergoing PCI have a more than doubled risk of postprocedural bleeding and greater postprocedural complications, with the risk of bleeding proportional to the degree of thrombocytopenia.[30,31] This also is associated with higher intrahospital mortality.[32] The association between thrombocytopenia and bleeding

MAJOR
Anticipated use of long-term oral anticoagulation
Severe or end-stage CKD (eGFR <30 mL/min)
Hemoglobin < 11 g / dL
Spontaneous bleeding requiring hospidalization or trasfusion in the past 6 mo or any time, if recurrent
Moderate or severe baseline thrombocytopenia (platelet < 100 x 10^9/L)
Chronic bleeding diathesis
Liver cirrhosis with portal hypertension
Active malignancy
Previous spontaneous ICH, previous traumatic ICH within the past 12 mo, Presence of bAVM, Moderate or severe ischemic stroke (National Institutes of Health Stroke Scale score ≥ 5) within the past 6 mo
Nondeferrable major surgery on DAPT
Recent major surgery or major trauma within 30 day before PCI
MINOR
Age ≥ 75 y
Moderate CKD (eGFR 30-59 mL/min)
Hemoglobin 11-12,9 g/dL for men, 11-11,9 g/dL for women
Spontaneous bleeding requiring hospidalization or trasfusion in the past 12 mo not meeting the major criterion
Long term use of oral NSAIDs or steroids
Any ischemic stroke at any time not meeting the major criterion

Fig. 2. Major and minor criteria for HBR after PCI according to HBR-ARC. Hb, hemoglobin; ICH, intracranial hemorrhage; PLT, platelet.

may be direct, owing to the limited platelet number or secondary to other comorbidities.

A history of spontaneous bleeding or blood transfusion is an important predictor of future bleeding events and is considered a major criterion, if occurring in the 6 months prior to PCI, or minor, if occurring 6 months to 12 months earlier. In addition, a prior history of recurrent bleeding any time before PCI, which have not been resolved, accounts as a major criterion of bleeding risk. Prior bleeding was the single variable associated most strongly with an increased risk of bleeding in several clinical studies.[19,33]

Brain arteriovenous malformations (bAVMs), a history of previous intracranial hemorrhage, and ischemic stroke in the 6 months prior to PCI (with National Institutes of Health Stroke Scale ≥5 scale at the clinical presentation) represent major HBR criterion. There is a paucity of evidence informing the best antithrombotic strategy in patients with bAVMs; hence, in the absence of robust evidence, a conservative treatment seems the most reasonable option in this group of patients.

Anemia is another pivotal marker of higher bleeding risk. Anemia is considered a major criterion, if the baseline hemoglobin value is less than 11 g/dL, or a minor criterion, if it is between 11 g/dL and 12.9 g/dL in men and 11 g/dL and 11.9 g/dL in women. Anemia frequently is found among patients with cardiovascular diseases and significantly affects the prognosis in patients with either heart failure or coronary artery disease undergoing PCI.[34] Anemia may represent a sign of a silent, nonclinically overt bleeding or more generally represent a marker of comorbidity and frailty, which indirectly influence the bleeding risk.

Renal function also is a major determinant of bleeding risk after PCI.[35,36] The HBR-ARC proposed severe or end-stage chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <30 mL/min) as a major criterion and moderate CKD (eGFR 30–59 mL/min) as a minor criterion. Multiple reasons place CKD patients at higher risk of bleeding, including the unpredictable pharmacokinetics of antithrombotic agents with the risk of accumulation and overdose.

Long-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (≥4 d/wk) is considered a minor HBR criterion. The use of these drugs is associated with a dose-dependent increase in gastrointestinal bleeding risk.

Finally, advanced age is one of the most recognized factors of HBR after PCI.[37] Advanced age has been the most common inclusion criteria among HBR-PCI stent trials.[38,39] It is, however, controversial whether advanced age qualifies per se as a marker of major bleeding risk, because many elderly patients without significant comorbidities do not necessarily qualify in this category.[24] Yet, on absolute terms, elderly patients are more likely to have comorbidities, which pose increased bleeding risk for them, reducing the benefit of prolonged or more potent antithrombotic treatments. In the TRITON trial, patients older than 75 years did not benefit from prasugrel, 10 mg, and showed a significant increase in bleeding events.[5] Similarly, in the PRODIGY study, elderly patients treated with DAPT for 24 months were associated with an excess of BARC 2, 3, and 5 bleeding events, compared with those undergoing DAPT for 6 months, with a higher absolute bleeding risk increase compared with younger patients.[40]

DUAL ANTIPLATELET THERAPY DURATION INDIVIDUALIZATION AMONG PATIENTS AT HIGH BLEEDING RISK

DAPT duration selection lies on the equilibrium between the risk of ischemia and bleeding and could be informed by various clinical and procedural elements (**Fig. 3**).[41–43] Prolonged DAPT has been shown to reduce the risk of stent thrombosis and coronary ischemic events after PCI, but it is associated with a higher risk of bleeding,[44–46] whereas a shorter-term DAPT is associated with a reduction in bleeding events.[47] The overall neutral impact on death makes the optimal risk/benefit balance unclear.[47,48]

Importantly, the risk/benefit balance can be very different in HBR patients, in which the higher baseline risk of bleeding and the higher severity of these events may outweigh the benefit of prolonged antithrombotic treatments.

Using algorithms to identify HBR patients and inform DAPT duration decision making recently has been proposed. The advantage of these tools lies in the objective estimate of the clinical risks.[49,50] A subjective evaluation tends to overestimate the ischemic and bleeding risk in low-risk patients and to underestimate it in high-risk patients.[51]

The first attempt to provide an objective stratification of the bleeding risk to guide DAPT decisions was proposed in a retrospective analysis of the PRODIGY trial, which randomized all-comer patients after PCI to 6 months versus 24 months of DAPT.[52] In this study, the population was stratified according to the CRUSADE score, which accounts for 8 clinical variables: female gender, signs of heart failure, diabetes and peripheral artery disease, hematocrit, creatinine clearance, heart rate, systolic pressure.[17] HBR patients (ie, with a CRUSADE score >40), which represented the 15.7% of the overall PRODIGY population, were associated with a more than 3-fold increased risk of BARC type 3 or 5 bleeding when treated with 24 months compared with 6 months' DAPT (9.7% vs 3.7%, respectively; $P = .04$). In contrast, patients at low bleeding risk (ie, with a CRUSADE ≤40) were not exposed to a significant increase of bleeding complications after a longer DAPT.[52] The risk of ischemic events, a composite of death, MI, or cerebrovascular accident, was similar for a 24-month compared with 6-month DAPT, irrespective of the baseline bleeding risk. Hence, patients at HBR were not deemed suitable for a longer treatment with DAPT given the exaggerated risk of bleeding. Yet, the CRUSADE score was developed to predict in-hospital bleeding, and for this reason its ability to be applied to long-term treatment decisions was suboptimal.

The DAPT score[53] was the first dedicated tool to inform decision making for DAPT duration after PCI. This algorithm developed within the DAPT study could be calculated after 12 months of uneventful DAPT to identify candidates who could benefit from prolonged treatment with DAPT beyond 12 months. The score includes age, smoking, diabetes mellitus, MI at presentation, previous MI or PCI, paclitaxel-eluting stent implantation, stent diameter less than 3 mm, heart failure or ejection fraction less than 30%, and stenting of a venous graft. The DAPT score was designed to evaluate the net benefit between ischemic and hemorrhagic endpoints for patients treated with a prolonged DAPT: those with a score less than 2 points are considered at higher bleeding than ischemic risk, whereas those with a score of 2

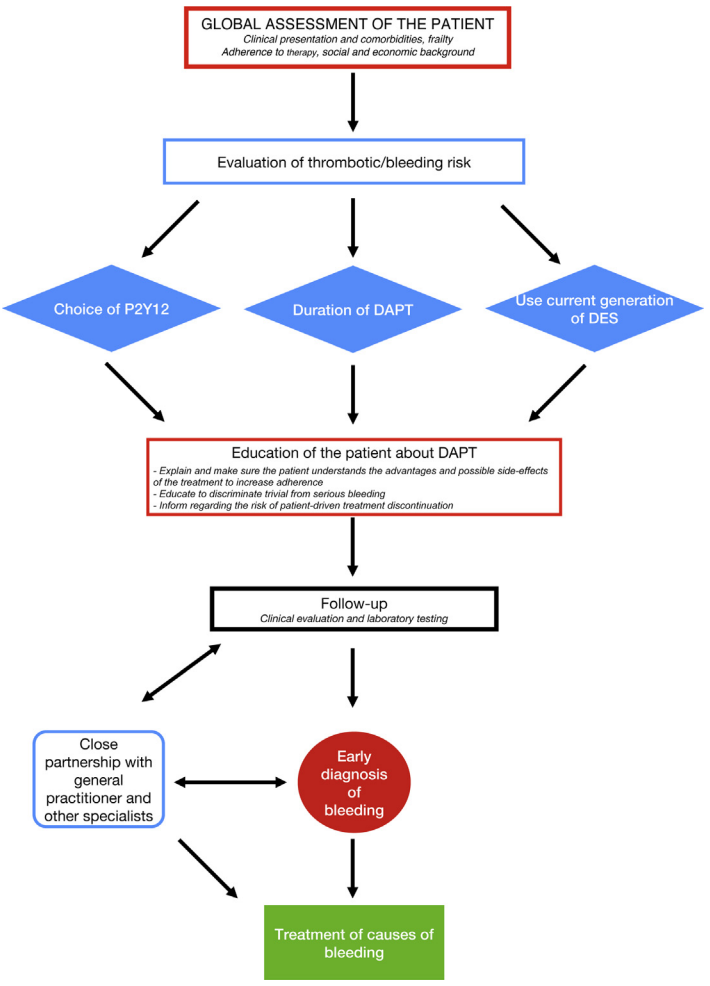

Fig. 3. Management of HBR patient after PCI. Patient-centered approach.

points are considered at higher ischemic than bleeding risk. Patients with scores less than 2 had a greater than 2-fold increase in bleeding events, with a prolonged DAPT beyond 12 months. Therefore, prolonged DAPT is not advantageous in this subset of patients. On the contrary, patients with a score of 2 points or more were associated with a reduction of ischemic events, without a significant increase in bleeding complications after prolonged DAPT.

At difference with the DAPT score, the PRECISE-DAPT score[19] provides a tool for decision making at the time of PCI. After PCI, patients were assigned to DAPT with aspirin and a P2Y12 inhibitor, whereas patients with OAC were excluded. In the subgroup of 10,081 patients assigned to a randomized duration of the DAPT (12–24 months' long or 3–6 months' short), the impact of the duration of DAPT was assessed within the risk categories defined by the score. Patients in the higher-risk quartile (PRECISE-DAPT $\geq$25 points) were considered HBR, whereas those with very low risk, low risk, or moderate risk were considered non-HBR. In this analysis, patients defined as HBR were associated with a significant increase in TIMI major or minor bleeding when assigned to a prolonged DAPT (absolute risk increase 2.59% [95% CI, +0.82 to +4.34]) whereas low-risk patients were not associated with a significant increase in bleeding events when treated with prolonged DAPT. Similarly, only not-HBR patients gained benefit in the composite endpoint of ischemia (MI, stent thrombosis, stroke, and target vessel revascularization) from prolonged DAPT (absolute risk reduction 1.53% [95% CI, –2.64 to −0.41]), but not those at HBR at baseline.

The early selection of a treatment duration of 3 months or 6 months in HBR patients (PRECISE-DAPT score $\geq$25) could avoid exposing patients

to a risk of excessive bleeding, whereas in non-HBR patients (PRECISE-DAPT score <25), standard (12-month) or prolonged (>12-month) treatment, if tolerated, could guarantee a further reduction of ischemic events without an excessive risk of bleeding complications. This algorithm has been further validated within the subgroup of HBR patients undergoing complex angioplasty,[54] which are associated with a high ischemic risk.[55,56]

Hence, international guidelines endorse the use of validated risk scores for DAPT decision making.[8,57,58] The PRECISE-DAPT score can be evaluated at the time of PCI, with clinical and laboratory values calculated in close proximity to the PCI. Instead, the DAPT score should be calculated among patients who already have been treated with DAPT without ischemic and bleeding events during the first 12 months to decide whether extend treatment up to 30 months or stop treatment.

The type of stent used (ie, DES vs bare-metal stent [BMS]) during the coronary interventional procedure traditionally has been linked to decisions regarding DAPT duration, but in modern practice should no more be a driver of treatment decisions.[59] BMSs, once considered safer than first-generation DESs during short DAPT strategy,[60–62] have been progressively limited in their use with the implementation of second-generation and third-generation DESs that proved safer and more biocompatible, even when a short DAPT strategy was necessary.[59] The first study assessing the impact of second-generation DES versus BMS in suboptimal candidates for DES was the ZEUS trial.[63] In the ZEUS, 1606 patients were randomized to DES with zotarolimus-eluting stent (Endeavor) or BMS. The primary outcome, including cardiovascular adverse events at 12 months (death from all causes, MI, or target vessel revascularization), was reduced in the DES group (17.5%) compared with the BMS group (22.1%); the bleeding risk in 2 arms was similar (TIMI major/minor bleeding: 1.7% vs 2.1%, respectively; $P = .72$). A large proportion of the patients included in the study were assigned to a very short DAPT (30 days) due to their HBR. In this subset of patients, the use of DES was associated with a reduction in the rate of major cardiovascular events of 25%, largely due to a significant reduction in MI and the need for revascularization of the treated vessel.[61]

These results were confirmed later in other 2 randomized trials in which BMSs were compared with bioresorbable polymer[38] or polymer-free[60] stents. More recent trials also have confirmed the role of novel-generation DES with a permanent polymer in patients managed with a short DAPT strategy.[39]

BMS is associated with an increased rate of restenosis and revascularization independently of the diameter of the treated vessel.[44] Therefore, multiple revascularizations in patients assigned to BMS potentially can lead to a paradoxically higher total exposure to DAPT than DES. For this reason, the use of BMSs in HBR patients no longer should be considered the gold standard for safety,[64] and the routine use of DES, regardless of DAPT duration and bleeding risk, is recommended.[9] In addition, the use of drug-eluting balloon is developing as a promising alternative to stent in patients with HBR[65] or with small diameter vessels.[66]

In conclusion, the identification of HBR patients should prompt the selection of treatment strategies aiming at reducing the bleeding risk and optimizing the secondary prevention of ischemic events with lipid-lowering drugs.[67] The most common bleeding events after PCI occur in the gastrointestinal tract,[12] and the use of drugs, such as proton pump inhibitors, that can reduce these complications should be liberal.[68,69]

SUMMARY

Patients at HBR represent a large proportion of the current population treated with PCI and undergoing DAPT. The clinical consequences and the prognostic impact of bleeding events is relevant. Focusing on HBR patients with correct risk stratification and individualized treatment is key to improving outcomes in modern practice.

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