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Review Article

Antiplatelet therapy after PCI in patients with high risk of bleeding

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Abstract

The progress of percutaneous coronary interventions (PCI) over the last few decades facilitated treatment of increasingly complex patient populations. The introduction of drug-eluting stents (DESs) led to need of stronger and prolonged inhibition of platelets which in turn increased the incidence of bleeding complications. The identification and management of patients at high bleeding risk (HBR) during and after percutaneous coronary interventions (PCI) is still problematic in everyday clinical practice.

Keywords

percutaneous coronary interventions (PCI), dual antiplatelet therapy (DAPT), high bleeding risk (HBR), acetylsalicylic acid (ASA)

Introduction

Ischemic events after coronary stenting have declined significantly in recent years, thanks to the introduction of new drug-eluting stents (DESs) and the progressive improvement of technology. However, due to the stronger and prolonged inhibition of platelets, the incidence of bleeding complications is increased, especially in patients with high bleeding risk (HBR). In order to reduce these complications, optimal identification of patients with HBR is required before practical measures, namely pharmacological and interventional approaches, are taken. Dual antiplatelet therapy (DAPT) is a combination of two antiplatelet agents: one is acetylsalicylic acid (ASA) and the other is P2Y12 inhibitor. Pharmacological approaches include shorter duration of DAPT and de-escalation and dose adjustment of P2Y12 inhibitors. Interventional approaches include the selection of appropriate techniques and stents to reduce the risk of thrombosis without requiring longer DAPT. These practices can be used alone or in combination. The lack of sufficiently randomized data on percutaneous coronary interventions (PCIs) in patients with HBR creates serious challenges in modern interventional cardiology. In recent years, the development of technology has made it possible to treat extremely complex patients with significant complex lesions, including those with HBR. With the introduction of the first-generation DES in 2002, the duration of DAPT was recommended to be 3 to 6 months (Stone et al. 2004; Moses et al. 2003; Kandzari et al. 2006; Stone et al. 2008). Four years after DAPT was extended to 12 months due to doubts about late stent thrombosis. Anyway, HBR patients were considered unsuitable for long-term administration of DAPT and were therefore systematically excluded from randomized trials and were therefore treated with bare metal stents (BMS) or only medication. Recently, three randomized trials comparing DES and BMS with short-term administration of DAPT in HBR patients have shown an advantage in the safety and efficacy of DES. (Urban et al. 2015; Ariotti et al. 2016; Varenne et al. 2018) This offered an alternative for those patients who were not previously considered suitable candidates for DES. The challenges in determining their

optimal treatment really prove to be problematic, due to the lack of evidence-based facts and different definitions for patients with HBR.

Identifying patients with HBR

The definitions of HBR are different in intervention studies. Many criteria are used and the weight of each also varies. For example, age over 75 years is considered to be a major criterion for HBR in the SENIOR trial (Short Duration of Dual antiplatElet Therapy With SyNergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization) (Varenne et al. 2018), whereas in LEADERS FREE study (A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent Versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding),such a criterion is previous intracranial bleeding (Urban et al. 2015). It is clear that these two criteria have different attitudes towards bleeding risk. In recent years, several strategies have emerged to improve the assessment of ischemic and hemorrhagic risk in patients after PCI. The aim is to identify patients with HBR using simple clinical and biological characteristics and then to evaluate the adequate duration of DAPT. The main objective of this is to achieve a balance of sufficient anti-ischemic protection without increasing hemorrhagic incidents.

Bleeding risk assessment scores

Several risk stratification systems (scores) have emerged in HBR patients with increasing data and information on the adverse impact of hemorrhagic incidents on post-PCI outcomes. These scores are mostly modeled in registries or post-hoc analyzes of randomized trials, with other endpoints (eg antithrombotic risk, risk of myocardial infarction, etc.). They use a small number of variables and the follow-up time for bleeding complications is very short. The most famous are: the CRUSADE score (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC / AHA Guidelines) obtained from the CRUSADE registry; ACTION score (Acute Coronary Treatment and Intervention Outcomes Network) from the National Register Get With the Action Guidelines) ; ACUITY / HORIZON-MI score from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and HORIZON-MI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) studies. (Subherwal et al. 2009; Mehran et al. 2010; Mathews et al. 2011) The main recurrent significant risk characteristics in these scores are gender, chronic kidney disease (CKD), anemia, and clinical presentation. Although many common variables are included, that have been applied to a variety of patient populations, with major follow-up in-hospital bleeding. The HAS-BLED score is another system that, although it is intended to assess the risk of bleeding in patients with atrial fibrillation treated with anticoagulants, is particularly useful in patients with acute coronary syndrome (ACS) (Pisters et al. 2010) It is easy to administer and includes important variables such as alcohol use, liver dysfunction, and a previous history of bleeding. (Hsieh et al. 2015; Taha et al. 2015) The authors of the PRECISE-DAPT score use individualized data from eight randomized controlled trials to develop a hemorrhagic risk assessment system that determines the duration of DAPT in patients who have indications to receive such therapy. Compared to previous scores, the PRECISE-DAPT score is the only that offers long-term stratification of bleeding risk and also takes into account the variable "prior bleeding", which weighs four times more than other variables in the assessment. In this study, prolonged DAPT (> 6 months) in patients with HBR (PRECISE-DAPT score ≥ 25) was associated with an increase in bleeding incidents without reducing the incidence of ischemic events. (Costa et al. 2017) The use of risk scores (in particular PRECISE-DAPT and DAPT) to determine the duration of DAPT was included in the recommendations of the European Society of Cardiology (ESC), with class IIb and A level of evidence (Valgimigli et al. 2018). Similarly, the recommendations of the American Cardiac Academy and the American Heart Association (ACC/AHA) suggested the use of DAPT score for assessment of prolonged DAPT as a score ≥ 2 correlates with a favorable risk/benefit ratio for prolonged DAPT, while a score <2 has an adverse effect. (Levine et al. 2016; Yeh et al. 2016). In addition, the current ACC/AHA guideline recommends a mandatory DAPT duration of 6 months in patients with stable coronary artery disease (CAD) treated with newer DES compared to 12 months in the previous recommendations. However, for patients with ACS, regardless of whether they have been treated with BMS or DES, the recommendation is that the DAPT should be at least 12 months. Other well-known score systems are PARIS score (Baber et al. 2016) and CREDO-Kyoto score (Natsuaki et al. 2018) However, the determinants for different scores are quite different. (Table 1)

The use of all these systems to identify patients with HBR in real-world medical practice requires careful con-

Table 1. Criteria used in bleeding risk scores.

Criteria used in bleeding risk scores				
Score name	**Paris**	**Precise-dapt**	**Credo-kyoto**	**Dapt**
Age	Yes	Yes	–	Yes
BMI	Yes	–	–	–
Current smoking	Yes	–	–	Yes
Anemia	Yes	Yes	–	–
CKD	Yes	Yes	Yes	–
TAPT on discharge	Yes	–	–	–
WBC count	–	Yes	–	–
Previous bleeding	–	Yes	–	–
PLT count	–	–	Yes	–
PVD	–	–	Yes	–
Heart failure	–	–	Yes	Yes
Malignancy/cancer	–	–	Yes	–
Atrial fibrillation	–	–	Yes	–

Abbreviations: BMI – body mass index; CKD – chronic kidney disease; TAPT – triple antiplatelet therapy; WBC – white blood cells; PLT – platelets; PVD – peripheral vascular disease.

sideration of the differences in populations of these patients. Despite the accumulated scientific information, the application of different scores in daily practice is not systematic, so identifying them remains a challenge. This is an important issue as the overall percentage of high-risk patients increases.

Academic Research Consortium (ARC) for HBR patients

At the initiative of the Academic Research Consortium (ARC), a consensus definition of patients at high risk of bleeding was developed based on a review of available evidence. (Urban et al. 2019) The definition is intended to ensure consistency in the designation of these patients for clinical trials and decision making for clinical and regulatory reviews. The proposed High Bleeding Risk (ARC-HBR) Consensus Document represents the first pragmatic approach to consistently identify high bleeding risk in clinical trials evaluating the safety and efficacy of stents and drug regimens for patients with PCI. According to the consensus, twelve clinical criteria were identified, divided into major and minor (Table 2).

High-risk patients are those who meet at least 1 major or 2 minor criteria. Although it is recognized that the presence of additional risk factors for bleeding is associated with a gradual increase in the risk of bleeding from BARC (Bleeding Academic Research Consortium) 3 to 5 (Ariotti et al. 2016), there is currently insufficient data to create a point-based score to account for the relative severity of any criterion for HBR. However, the presence of a significant number of large or small criteria in each patient further increases the risk of bleeding, which may be considered in clinical decision making and clinical trial analysis. The proposed consensus-based definition takes into account the available evidence for patients with HBR undergoing PCI and is easy to apply in clinical trials, in line with current good clinical practice recommendations. The criteria determined the definition are age (≥ 75 years), concomitant diseases (CKD, liver disease, malignancy), laboratory abnormalities (anemia, thrombocytopenia), disorders of the central nervous system (CNS) (stroke, ICH, arteriovenous malformation), previous bleeding (diathesis, blood transfusion), iatrogenic (taking VKA, NSAIDs, major surgery or recent trauma against the background of DAPT) (see Table 2). Age ≥ 75 years is considered as a small criterion. Although elderly patients represent the fastest growing subset of patients who have undergone PCI, they tend to be underrepresented in randomized trials for DES and DAPT. The conclusions of both the SENIOR (Varenne et al. 2018) and LEADERS FREE (Urban et al. 2015) studies that the risk of bleeding increases with age is controversial and largely determined by the presence of comorbidities. Therefore, it must be recognized that biological age and chronological age may differ. Prolonged intake of oral anticoagulant (OAC) after PCI (whether Vitamin K antagonist (VKA) or new oral anticoagulant (NOAC)) is defined as a major criterion (Table 2). In these patients, the risk of AF thromboembolism, the risk of stent thrombosis and myocardial infarction after PCI, and the risk of bleeding with combination antithrombotic therapy should be balanced. The risk of bleeding is increased when triple antithrombotic therapy (OAC plus DAPT) is prescribed. The risk of bleeding may be different between VKAs and NOACs and also between individual NOACs and different doses, exposure time and changes in renal function. The determination of the severity of the relative risk of bleeding in the various OAC regimens is outside the scope of this definition. Severe or

Table 2. Clinical HBR criteria determined by the ARC-HBR consensus.

MAJOR	MINOR
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100 × 109/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time)	Any ischemic stroke at any time not meeting the major criterion
Previous traumatic ICH within the past 12 months	
Presence of a bAVM	
Moderate or severe ischemic stroke§ within the past 6 months	
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

Abbreviations: CKD-chronic kidney disease; eGFR-estimated glomerular filtration rate; NSAID-nonsteroidal anti-inflammatory drug; ICH-intracranial hemorrhage; bAVM- brain arteriovenous malformation; DAPT-dual antiplatelet therapy; PCI-percutaneous coronary intervention.

*This excludes vascular protection doses.

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.

terminal chronic kidney disease (CKD) with glomerular filtration (eGFR < 30 mL / min) is defined as the major consensus criterion, and moderate renal impairment with eGFR = 30–59 mL / min is defined as a small criterion. Patients with PCI and impaired renal function are few, but those with severe renal insufficiency are generally excluded from randomized trials. Even mild chronic renal failure (CKD) is an independent risk factor for bleeding after PCI and the risk increases gradually with its worsening (Baber et al. 2018). The consensus examines separately all other criteria and the supporting studies.

Platelet activity

Platelet activity testing is the only relatively objective indicator of providing adequate antiplatelet therapy in the most vulnerable patients. Cohort studies have shown a link between very low platelet reactivity in the background of treatment and high bleeding. (Cuisset et al. 2013) However, this has not led to great clinical benefit in randomized trials, especially in the ANTARCTIC trial (Assessment of a Normal Versus Tailored Dose of Prasugrel After Stenting in Patients Aged > 75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications), which includes high-risk patients aged ≥ 75 years admitted with ACS. Therefore, there is currently insufficient evidence to support the use of this indicator. (Collet et al. 2012; Cayla et al. 2016)

Antithrombotic regimens in patients with HBR

Clopidogrel is the recommended antiplatelet agent for elective PCI and stable coronary artery disease, regardless of the risk of bleeding. The best antiplatelet therapy in patients with ACS and HBR has not yet been determined. In the PLATO study (A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of Ticagrelor Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes (ACS) [PLATO- a Study of PLATelet Inhibition and Patient Outcomes]), Ticagrelor was associated with a 20% higher risk of non-cardiac surgery major bleeding and a 30% higher incidence of ICH compared with clopidogrel. (Wallentin et al. 2009) In TIMI TRITON-38 (Evaluation of Prasugrel Compared With Clopidogrel in Patients With Acute Coronary Syndromes: Design and Rationale for the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN With Prasugrel Thrombolysis In Myocardial Infarction 38), prasugrel is associated with a 30% higher incidence of major bleeding, especially in patients > 75 years age, with a history of stroke or weight < 60 kg (Wiviott et al. 2007) Therefore, the combination of aspirin with clopidogrel or ticagrelor for 6 months (class IIa, level of evidence B) is recommended in the European guidelines for patients with HBR and PCI in a setting of ACS. In 2016 ACC/AHA recommendations, the use of ticagrelor instead clopidogrel in this case is class IIa, level of evidence of B-R. (Levine et al. 2016)

Discontinuation of DAPT – how early after ACS?

The risk of recurrent thrombosis and cardiac events decreases over time after the index event, while the risk of bleeding increases with the duration of DAPT (Mehran et al. 2013) For a long time, BMSs have been the stents of choice for patients with HBR, as they allow a short DAPT duration of 1 month without exposing patients to the risk of early stent thrombosis but at the expense of a higher incidence of restenosis and recurrent ischemic events. With the introduction of the second-generation generation DESs, shortening of the DAPT (≤ 3 months) was made possible. In a randomized controlled trial of ZEUS (Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) Study) (n = 1.606), patients with HBR and implanted 2nd generation zotarolimus coated stents and BMS were compared, with both arms receiving DAPT for one month (Valgimigli et al. 2015) 63% of those enrolled have ACS. Patients with second generation DES found a 25% reduction in ischemic incidents at 1-year follow-up with an incidence of major bleeding of about 1.5% (with BMS bleeding rate of 2.1%). Likewise, major adverse cardiac events (overall mortality, myocardial infarction, or repeat revascularization) were lower in the DES arm (17.5%) than the BMS arm (22.1%). Polymer-free DES, often considered as third-generation DES also paves the way for a short, one-month DAPT duration in patients with HBR. Researchers in the LEADERS FREE study use several important risk factors for bleeding as criteria for enrolling 2466 patients in the study population treated with one-month DAPT administration. (Urban et al. 2015) It should be noted that 64.5% of participants are aged > 75 years, 36.7% were treated with anticoagulants, and 17.9% had creatinine clearance < 40 ml / min. In terms of clinical presentation, 58% of participants had PCI for stable coronary disease, 28% for MI and 14% for unstable angina. Compared with BMS, the use of DES was associated with 30% reduction in cardiac death, myocardial infarction, or stent thrombosis at 390 day follow-up. The risk of bleeding is similar for the two groups. These results demonstrate the safety of short DAPT after PCI in patients with HBR and advanced-generation DES, regardless of the indications. Based on these results, the European Antiplatelet Therapy Guide paved the way for one-month DAPT in patients with stable coronary artery disease and HBR and 6 months for ACS (class IIb and II c recommendation) (Figures 1, 2) (Valgimigli et al. 2018).

Similarly, the 2016 American College of Cardiology/ American Heart Association (ACC / AHA) Recommendations consider it reasonable to discontinue DAPT after 6 months for patients with ACS after PCI and HBR (Class

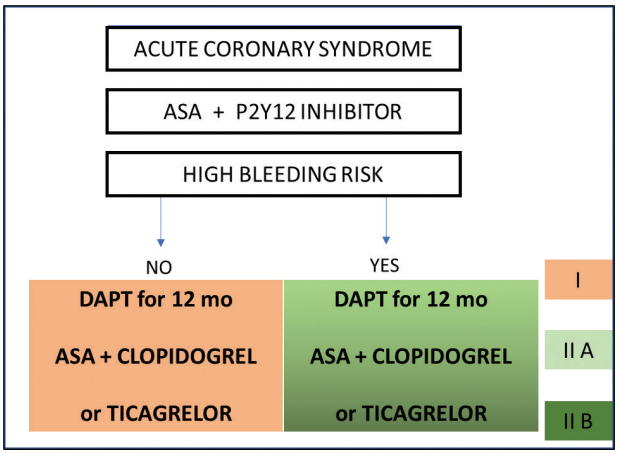

Figure 1. Algorithm for the duration of DAPT in patients with HBR and ACS according to the recommendations of the European Society of Cardiology (ESC) for DAPT from 2017. Abbreviations: ASA – acetylsalicylic acid; DAPT – dual antiplatelet therapy; mo – months.

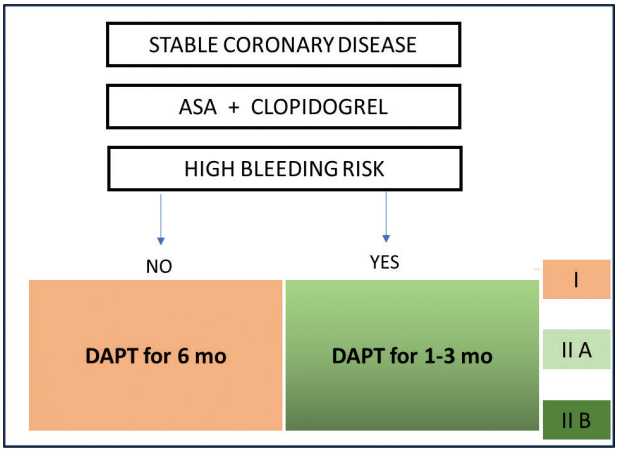

Figure 2. Algorithm for the duration of DAPT in patients with HBR and stable coronary disease according to the recommendations of the European Society of Cardiology (ESC) for DAPT from 2017. Abbreviations: ASA – acetylsalicylic acid; DAPT – dual antiplatelet therapy; mo – months.

IIb recommendation, C-LD level of evidence) (Mehta et al. 2001; Yusuf et al. 2001; Levine et al. 2016).

Reducing the risk of bleeding in elective cardiac surgery

Approximately 5% of patients undergo planned non-cardiac surgery within the first year after PCI and up to 30% over the next 5 years. (Berger et al. 2010; Cruden et al. 2010) They are at very high risk of perioperative major bleeding and ischemic events with a subsequent higher risk of death. (Kałuza et al. 2000; Egholm et al. 2016) In addition to the early discontinuation of DAPT, systemic stress and inflammation associated with the perioperative setting result in a higher risk of stent thrombosis and ischemic events, which requires that these patients be carefully planned with a pre-established strategy before the PCI is performed. The high risk of stent thrombosis associated with first-generation DES led to recommendations in previous guides to prefer BMS to DES in subsequent planned surgical intervention. In addition, it was recommended that the operation be postponed for 1 month after DES and at least 1 year after the IIA. (Fleisher et al. 2014; Windecker et al. 2014) As mentioned earlier, DESs of the newer generation allowed a shorter duration of DAPT with better efficacy against ischemic events by BMSs, regardless of the indication of PCI.

In 2016, a large cohort study (39 362 patients) evaluated the interaction between stent types, time from PCI to surgery, and complications: myocardial infarction, major bleeding, and mortality. Second-generation DESs were associated with fewer ischemic events compared to first-generation BMS and first-generation DESs. Importantly, the discontinuation of DAPT seemed safe between the 3rd and 6th months with adequate implantation of DES. (Egholm et al. 2016) The importance of stent implantation time was also evaluated by a large cohort study in Denmark comparing 4,303 patients treated with DES who had undergone a surgical procedure and 20,222 patients without PCI undergoing a similar surgical procedure. Surgery in patients with PCI was associated with a significant increase in myocardial infarction (1.6% versus 0.2%; OR, 4.82; 95% CI, 3.25–7.16), but not with an increase in overall mortality. When stratified according to the time from PCI to surgery, worse results are found within the first month, but not thereafter. (Saia et al. 2016) Therefore, the ESC recommends DES regardless of indication and time to surgery, which allows interruption of DAPT after 1 month in stable coronary disease and 3 to 6 months after ACS (Table 3). (Valgimigli et al. 2018) ACC / AHA responded similarly with its 2016 recommendations (Levine et al. 2016).

Table 3. AHA / ACC and ESC recommendations for the duration of DAPT months after PCI, standard (no surgery planned) or when surgery is planned.

	ACC/AHA		ESC	
	Standard	Surgery	Standard	Surgery
Stable CAD	1 (BMS)	1	1 (HBR)	1
Stable CAD	6 (DES)	3–6	6 (LBR)	1
ACS	12 (BMS)	3	6 (HBR)	6
ACS	12 (DES)	3–6	12 (LBR)	6

Abbreviations: ACC/AHA – American College of Cardiology /American Heart Association; ESC – European Society of Cardiology; CAD – coronary artery disease; ACS – acute coronary syndrome; HBR – high bleeding risk; LBR – low bleeding risk; BMS – bare metal stent; DES – drug-eluting stent.

In all cases, it is recommended that the aspirin should be continued if surgery allows and the recommended antiplatelet therapy be resumed as soon as possible. Despite the encouraging results of the newer DES and the shortened duration of the DAPT, post-PCI surgery carries a high risk of adverse events and should be delayed as much as possible. Solutions in these situations need to be multidisciplinary in order to provide a strategy that takes into account

both the characteristics of the high-risk patient and the severity of the coronary disease and surgical procedure.

When high bleeding risk meets high ischemic risk

Age, hospitalization for acute myocardial infarction, history of cancer or stroke, and other characteristics are accompanying risk factors for both ischemic and hemorrhagic risk. Whether the prevention of bleeding or ischemia is favored by the correspondingly shorter or longer DAPT remains a controversial question, but these types of patients are increasingly observed in daily clinical practice. Recently, PRECISE-DAPT researchers have examined the effects of DAPT duration in patients with complex PCI and high bleeding risk. (Costa et al. 2019) Long-term DAPT (12 months) did not show any benefit with respect to the risk of ischemic events or mortality in HBR patients (PRECISE-DAPT score ≥ 25), regardless of the complexity of the PCI or the presence of ACS. In addition, prolonged DAPT was associated with an increased incidence of hemorrhage compared to shorter DAPT (6 months), indicating that DAPT duration should be guided by the risk of bleeding rather than the goal of preventing ischemic events.

Conclusions and future directions

Hemorrhagic incidents have a significant impact on the mortality associated with ischemic heart disease. More studies are needed to identify patients with HBR and develop customized antithrombotic strategies. Most of the evidence was obtained from registries and randomized controlled trials that were not intended to provide information on the subject. Establishing rapid risk-assessment systems is an initial step towards an adapted approach, even if their use in everyday clinical practice remains limited. When adequately identified, the risk of bleeding should be the primary determinant of DAPT duration, regardless of the indication of PCI or its complexity. Studies such as LEADERS FREE, ZEUS and others show promising results that next-generation DESs associated with 1-month DAPT provide effective ischemic protection for patients with HBR, and further ongoing studies will provide definitive evidence.

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