Supplement to

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Cardiac Interventions TODAY

May/June 2019

MANAGING THE HIGH BLEEDING RISK PCI PATIENT

The latest thinking on DAPT guidelines and patient care.

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The latest thinking on DAPT guidelines and patient care.

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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.

BY THOMAS CUISSET, MD

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,

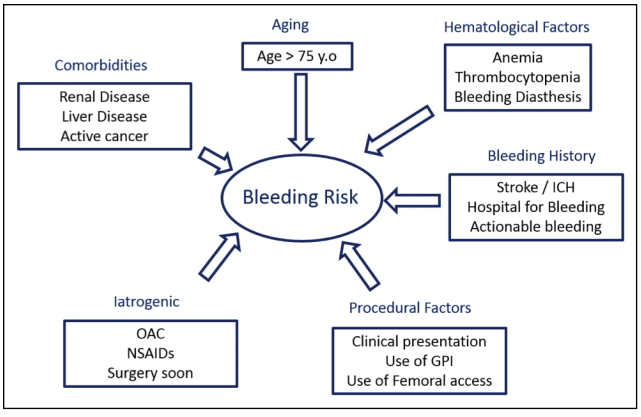

Figure 1. Frequently included criteria used to define HBR patients.

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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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.

BY MICHEL ZEITOUNI, MD, AND GILLES MONTALESCOT, MD, PHD

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

See Important Safety Information referenced within.

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

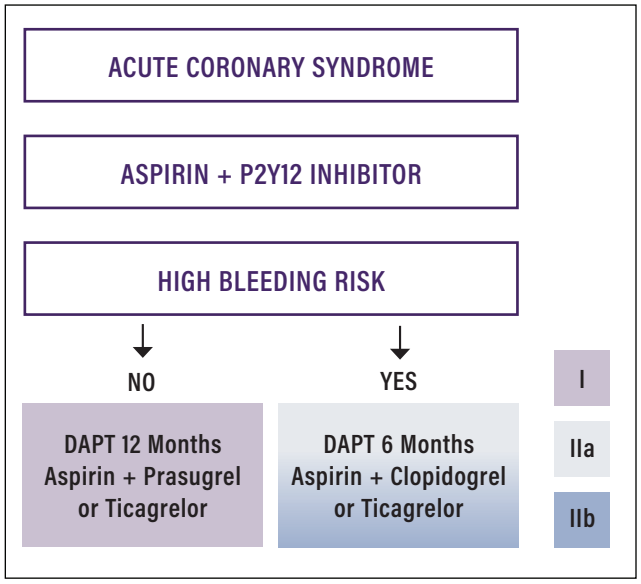

Figure 1. Algorithm for DAPT duration in HBR patients admitted for ACS based on the 2017 ESC guidelines for DAPT management. Adapted from Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the 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.

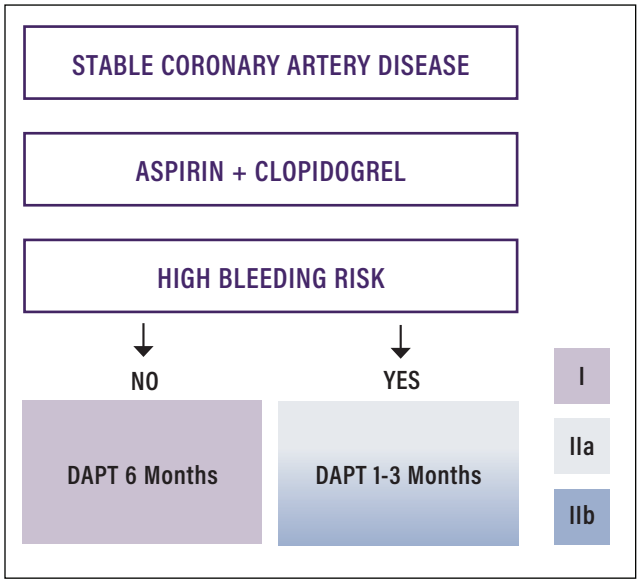

Figure 2. Algorithm for DAPT duration in HBR patients admitted for stable coronary artery disease based on the 2017 ESC guidelines for DAPT management. Adapted from Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration 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,

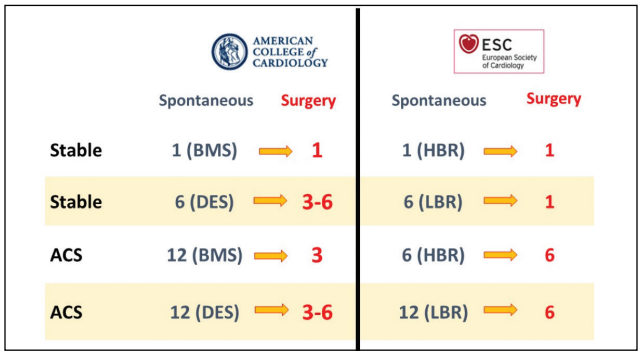

Figure 3. AHA/ACC and ESC guidelines for months of DAPT duration after PCI, spontaneously (no surgery scheduled) or when elective surgery is scheduled. LBR, low bleeding risk.

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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Clinical Decision-Making When Treating High Bleeding Risk Patients: A Japanese Perspective

BY KAZUSHIGE KADOTA, MD, PHD

Ischemic events after stenting have decreased considerably in recent years thanks to the introduction of newer-generation drug-eluting stents (DESs) and progressive refinement of pharmaco-interventional techniques. However, due to more potent and prolonged platelet inhibition, the incidence of bleeding complications has increased, especially in patients with high bleeding risk (HBR).

To reduce bleeding complications after percutaneous coronary intervention (PCI) in HBR patients, optimal discrimination of HBR patients is needed before taking practical measures, namely pharmacological and interventional approaches. Pharmacological approaches include a shorter duration of dual antiplatelet therapy (DAPT), and de-escalation and dose adjustment of a P2Y12 inhibitor. Interventional approaches include simpler strategies and less thrombogenic devices, which may help reduce thrombotic events without requiring a longer DAPT duration. These practices may be used alone or in combination.

The European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend DAPT duration according to the clinical status and risks of bleeding and ischemia.[1,2] Several bleeding risk scores established from large-scale studies are used in clinical practice. The ESC guidelines use the PRECISE-DAPT score to discriminate HBR patients.[3] For HBR patients with a PRECISE-DAPT score ≥ 25, a suitable DAPT duration depends on the coronary status: 3 months for those with stable coronary artery disease and 6 months for those with acute coronary syndrome (ACS). The ACC/AHA guidelines reference the DAPT score to quantify risk for ischemia and bleeding; a score ≥ 2 correlates with a favorable risk/benefit ratio for prolonged DAPT, whereas a score < 2 has an unfavorable risk/benefit profile for prolonged DAPT.[4] The 2016 ACC/AHA guidelines gave a class I, level A recommendation for a minimum mandatory DAPT duration of 6 months for patients with stable ischemic heart disease being treated with a newer-generation DES, a reduction from the former ACC/AHA recommendation of 12 months. Additionally, they gave a class IIb, level C-LD recommendation for discontinuation of P2Y12 inhibitor after 3 months for those who develop a high risk of bleeding or are at high risk for severe bleeding complications. For patients with ACS being treated with BMS or DES, the recommendation for at least 12 months of DAPT remained.[2] Other well-known scores include the PARIS score[5] and CREDO-Kyoto risk score.[6] The contributing factors of these scores are quite different from one another (Table 1). Using them

TABLE 1. CRITERIA USED IN BLEEDING RISK SCORES

Score Name	PARIS[5]	PRECISE-DAPT[3]	Credo-Kyoto[6]	DAPT[4]
Age	Yes	Yes	-	Yes
BMI	Yes	-	-	-
Current smoking	Yes	-	-	Yes
Anemia	Yes	Yes	-	-
CKD	Yes	Yes	Yes	-
TAPT on discharge	Yes	-	-	-
White blood cell count	-	Yes	-	-
Previous bleeding	-	Yes	-	-
Platelet count	-	-	Yes	-
PVD	-	-	Yes	-
Heart failure	-	-	Yes	Yes
Malignancy	-	-	Yes	-
Atrial fibrillation	-	-	Yes	-

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; PVD, peripheral vascular disease; TAPT, triple antithrombotic therapy.

See Important Safety Information referenced within.

to discriminate HBR patients in real-world settings needs careful attention to the differences in patient populations, as will be described in this article.

DOSING CONSIDERATIONS FOR THE JAPANESE POPULATION

De-escalation of P2Y12 inhibitor treatment (eg, switching from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy,[7] especially for patients with ACS who are deemed unsuitable for 12-month potent platelet inhibition in the ESC/ESCTA guidelines. A widely used dose of prasugrel in Japan, however, is different from the global standard. The efficacy of this strategy cannot be easily applied to practice in Japan because of the difference in physique. The ACC/AHA guidelines do not recommend the use of platelet function testing, as no randomized controlled trial has demonstrated an improvement in outcomes when used to guide P2Y12 inhibitor treatment; similarly, no randomized data are available on the long-term safety of efficacy of switching patients to a different P2Y12 inhibitor.[2]

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) showed that in ACS patients with scheduled PCI, prasugrel therapy with a loading dose of 60 mg and a maintenance dose of 10 mg was associated with reduced ischemic events, but was also associated with increased bleeding events, in comparison with clopidogrel therapy.[8] On the basis of the report that East Asians have a higher bleeding risk and a lower ischemic event risk than Westerners (known as "East Asian Paradox"),[9] the PRASFIT-ACS (Prasugrel Compared with Clopidogrel for Japanese Patients with ACS Undergoing PCI) determined an appropriate dose of prasugrel (loading dose of 20 mg and maintenance dose of 3.75 mg) and confirmed its safety and efficacy in Japanese ACS patients; therefore, an adjusted dose of prasugrel is more commonly used in Japan instead of clopidogrel for both ACS and stable coronary artery disease patients.[10] Furthermore, efficacy of a maintenance dose of prasugrel 2.5 mg was demonstrated as an option for HBR-ACS patients with low body weight (≤ 50 kg), advanced age (≥ 75 years), or renal insufficiency (estimated glomerular filtration rate ≤ 30 mL/min/1.73 m^2).[11] Further dose adjustment of prasugrel may be an option for HBR patients in Japan.

COMBINATION THERAPY

Combination therapy of oral anticoagulant and antiplatelet therapy, although less known, is an additional risk factor for HBR patients. The ACC/AHA recommendations on DAPT duration are generally not considered applicable to patients treated with oral anticoagulants, as patients on oral anticoagulants were excluded from almost all studies of DAPT duration.[2] In the ESC/EACTS guidelines, the use of direct oral anticoagulant (DOAC) is recommended on the basis of some randomized studies demonstrating a comparison of warfarin with DOAC for atrial fibrillation patients with PCI.[12] Also, the use of a newer P2Y12 inhibitor, ticagrelor or prasugrel, as a part of a triple therapy regimen is discouraged; however, no comments are made on a dual therapy combining ticagrelor or prasugrel with a DOAC as a possible alternative for a triple therapy with aspirin, clopidogrel, and a DOAC. Using one of these newer P2Y12 inhibitors with a (D)OAC under certain circumstances (eg, perceived high thrombotic risk, ACS, complex PCI, and prior stent thrombosis) may be considered. When using a newer P2Y12 inhibitor in HBR patients with these risk factors, bleeding complications may be prevented with a shorter duration, switching between newer P2Y12 inhibitors, or dose adjustment.

COMPLEX PCI

For HBR patients with complex PCI, balancing the risks of bleeding and ischemia is very important and difficult. A recent study demonstrated that patients who had undergone complex PCI had a higher risk of ischemic events, but had no benefit from long-term DAPT.[13] For these patients, choosing a simpler PCI strategy may be recommended. Generally, newer-generation DESs are less thrombogenic than first-generation DESs. Newer-generation DESs are coated with permanent polymer or biodegradative polymer, which may lead to less thrombogenicity. Animal studies have suggested that there are differences in antithrombogenicity between newer-generation DESs.[14] Choosing a less thrombogenic DES for complex PCI may be considered in the treatment of HBR patients.

CONCLUSION

In summary, clinical decision-making when treating HBR patients requires balancing the risks of bleeding and ischemia, which should be adjusted to each patient on the basis of guidelines, randomized studies, and clinical experience; patients' physiological differences in geographic regions (eg, Japanese versus Western) should also be kept in mind when analyzing guidelines. ■

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Sponsored by Abbott

The Role of Stent Biomaterials In Reducing DAPT Duration

Expert commentary on the roles of technology and pharmacology.

BY HIROYUKI JINNOUCHI, MD; RENU VIRMANI, MD; AND ALOKE V. FINN, MD

Despite developments in drug-eluting stent (DES) technology, stent thrombosis (ST) continues to be one of the most feared complications, with high morbidity and mortality after percutaneous coronary interventions (PCI).[1] In addition to procedural and patient-specific factors, the propensity for ST can be influenced by stent design, including features such as strut thickness, polymer coating, and type of antiproliferative drug used.[2] Without question, antithrombogenicity is one of the most important and preferred characteristics for coronary stents. Oral pharmacologic therapy with dual antiplatelet therapy (DAPT; ie, aspirin in combination with a thienopyridine, such as clopidogrel) is the standard strategy after PCI[3] to reduce the risk of ST while healing takes place after stent placement. According to the 2016 American College of Cardiology/American Heart Association guidelines, this standard strategy requires DAPT usage for at least 1 month after bare-metal stent (BMS) use and at least 6 months after DES use in patients with stable ischemic heart disease, whereas patients with acute coronary syndrome require at least 12 months of DAPT.[3]

With decades of research into biomaterial-blood interactions, our understanding of the potential of antithrombotic stent coating technologies continues to evolve. Such an approach offers the possibility of greatly reducing the need for prolonged DAPT,[4] which is associated with an increased risk of bleeding and overall higher mortality after PCI in some analyses.[5]

In this article, we discuss in detail how different coating technologies (eg, durable polymer versus biodegradable polymer) used in DESs can play an important role in shaping the future of antiplatelet therapy after PCI. We examine preclinical and clinical data regarding the antithrombotic effect of stent coatings and summarize how differences in DES polymer coating design may modify DAPT duration.

DEVELOPMENT IN STENT POLYMERS

The first commercially available DESs employed durable polymers such as -SIBS (poly[styrene-b-isobutylene-b-styrene]) in paclitaxel-eluting stents (Taxus‡, Boston Scientific Corporation) and polyethylene-co-vinyl acetate and poly(n-butyl methacrylate) (PBMA) in sirolimus-eluting stents (SESs) (Cypher‡, Cordis).[6] In porcine coronary arteries, Cypher‡ implantation was associated with granulomatous and eosinophilic reaction, which is reported to have peaked at 3 months and remained high even at 6 months.[6] Similar rare but overwhelming localized inflammatory reactions leading to ST have also been reported in humans who have received SES implants.[7,8] The timeline of this phenomenon suggests a lack of biocompatibility because these findings tended to occur after the end of the elution of the immunosuppressive drug. Furthermore, along with ST, such inflammation at the stented site has been associated with greater neointimal growth and development of neoatherosclerosis over time.[9,10]

With continued evolution of DESs, different durable polymers were applied and side-chain modifications were made to the sirolimus molecule, resulting in analogues such as zotarolimus, with greater lipophilicity, and everolimus. Second-generation DESs, such as the cobalt-chromium everolimus-eluting stent (CoCr-EES) (XIENCE EES, Abbott) is covered by a base layer of PBMA encapsulated by a poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP), whereas the polymer on Resolute Integrity‡ zotarolimus-eluting stents (Medtronic) consists of a mixture of C10, C19, and polyvinylpyrrolidone polymers (BioLinx). The use of different polymers (in addition to changes in stent platforms) contributed to a reduction in late ST rates relative to earlier-generation DESs.[11,12] Despite these improvements, the association of durable polymers with potentially harmful effects lingered, and the assumption that BMS had a greater biocompatibility than durable-polymer DESs persisted. Biodegradable-polymer (eg, Synergy‡, Boston Scientific Corporation) and polymer-free (eg, Biofreedom‡, Biosensors International Group, Ltd.) DESs were developed under the assumption that a DES eventually becomes a BMS through polymer degradation and therefore should be more biocompatible

than a durable-polymer DES. Most biodegradable polymers are synthetic polyesters from the poly (α-hydroxy acid) family, including polylactic acid, polyglycolic acid, and their copolymer polylactic-co-glycolic acid. The most important question with regard to DAPT duration for these different devices is the relative thromboresistance of these different polymers and whether any would allow shortening of DAPT because of its behavior in the setting of flowing blood.

BLOOD-MATERIAL INTERACTIONS RELEVANT TO DES

Stent surfaces are directly in contact with the blood after implantation until neointimal tissue fully covers the stent struts. The behavior and interactions of the stent surface with blood elements is important in understanding the performance of different stents with regard to thrombosis risk. Blood-biomaterial interactions for each stent are different, and these interactions influence whether the surface repels or attracts platelets and prothrombotic blood elements, such as fibrinogen and inflammatory cells. Inflammatory cell adhesion and activation can further promote thrombosis.[13-16]

Of the polymers in medical applications, fluoropolymers have been well known to be capable of reducing platelet adhesion and activation and thrombosis as compared to nonfluorinated controls.[17-20] Dependent on degree of fluorine substitution, suppression of platelet adhesion and activation increases accordingly.[20] In the PVDF-HPF coating on CoCr-EESs, more than 50% of the carbon backbone is substituted with fluorine to form a hydrophobic surface. In addition to its role in PCI, fluorinated polymers have been used in vascular grafts to lower thrombogenicity and inflammatory reaction and to promote faster endothelialization, which are ideal properties for stent coatings and vascular devices.[21]

There is considered to be a protective "cloaking" mechanism; when fluoropolymers contact blood, the surface becomes covered by a high concentration of albumin. This albumin binding to fluorinated surfaces prevents more reactive proteins, such as fibrinogen, from adsorbing.[22] The main role of fibrinogen is to stimulate platelet adhesion and activation via their glycoprotein IIb/IIIa receptor at three different sites, resulting in the binding of platelets to fibrinogen.[23-27] Thus, through this mechanism of preventative binding, albumin-coated surfaces are thought to have antithrombotic effects. In this regard, Szott et al compared several different types of coating, including PVDF-HFP, PBMA, and polystyrene-b-polyisobutylene-b-polystyrene (SIBS1—102T 15% styrene 85% isobutylene, molecular weight [MW] 100,000; SIBS2—103T 30% styrene 70% isobutylene, MW 100,000), and 316L stainless steel (SS).[28] Albumin adsorption from a pure protein solution was higher in order

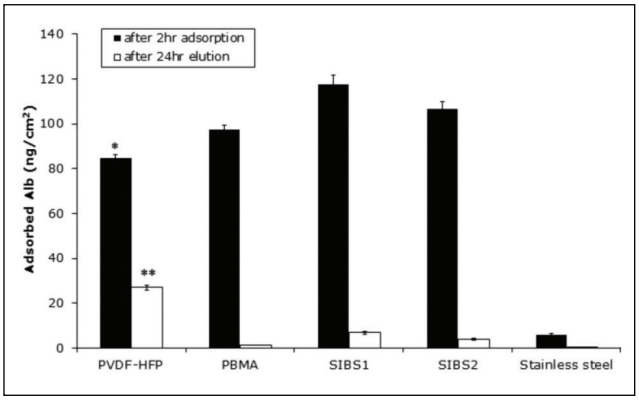

Figure 1. Albumin adsorption and retention. Two-hour albumin adsorption from a pure Alb solution (0.3 mg/mL) in CPBSzI (black) and the retained Alb on the surfaces after a 24-hour elution with 2% SDS (white). Data are expressed as mean ± standard error of the mean (n = 4). Single asterisks denote statistically significant differences in the amount of adsorbed Alb on to PVDF-HFP as compared to all other materials (α = 0.05). Double asterisks denote a significantly higher amount of retained Alb on PVDF-HFP as compared to all other materials studied (α = 0.05). Reprinted with permission from Szott LM, Irvin CA, Trollsas M, et al. Blood compatibility assessment of polymers used in drug eluting stent coatings. Biointerphases. 2016;11:029806. Copyright 2016, American Vacuum Society.[28]

of SIBS1, SIBS2, PBMA, PVDF-HFP, and SS. However, in the situation of flowing blood and removal by blood elements, albumin retention may be more important than its initial binding. When using a detergent (eg, sodium dodecyl sulfate [SDS]) in vitro to evaluate protein retention, the amount of albumin was greatest on PVDF-HFP among all test samples (Figure 1). Higher albumin:fibrinogen ratios are thought to correlate with lower thrombogenicity. In this regard, PVDF-HFP showed favorable results because the albumin:fibrinogen ratio was highest in PVDF-HFP, whereas SIBS2 showed a slightly higher amount of fibrinogen than albumin. When samples were preadsorbed using 1% plasma, adherent platelets were lower in order of PVDF-HFP, SIBS2, PBMA, and SIBS1, albeit without significant differences between them. Also, monocyte adhesion, as a marker of inflammation, is lowest in order of PVDF-HFP, PBMA, SIBS1, SIBS2, and SS, with no significant difference except between PVDF-HPF and SS and between PBMA and SS.

In addition, another type of fluorinated polymer showed similar data to that reported on PVDF-HPF. Poly(bis[trifluoroethoxy]phosphazene) was compared with polymethylmethacrylate, silicone, and other materials (hydroxylated glass, aldehyde-, alkyl-, or amino-terminated surfaces). Poly(bis[trifluoroethoxy]phosphazene) showed the highest human serum albumin on the surface and the

lowest amount of fibrinogen.[29] Collectively, these data have contributed to a better understanding of the potential mechanisms behind the pro/antithrombotic mechanisms of different polymers. However, preclinical studies may provide greater insight into the behavior of different polymers because thrombus formation in vivo is a more complex process than just protein adsorption.

PRECLINICAL DATA SUPPORTING THE IMPORTANCE OF FLUOROPOLYMERS IN BLOOD-MATERIAL INTERACTIONS

Acute thrombogenicity of various stent designs and polymer coatings can be evaluated using models that better replicate the complexity of human conditions. An ex vivo porcine arteriovenous shunt model has been developed at CVPath institute.[30] In this model, three DESs are consecutively deployed in Sylgard mock vascular phantoms, and blood flows through the shunt under low-dose heparin conditions for 90 to 120 minutes. In these models, the activated clotting time was targeted to be between 150 and 190 seconds. Stents are assessed for platelet and leukocyte adhesion through immunostaining and evaluation by confocal microscopy. The stents are also evaluated by scanning electron microscopy (SEM) for thrombus evaluation.

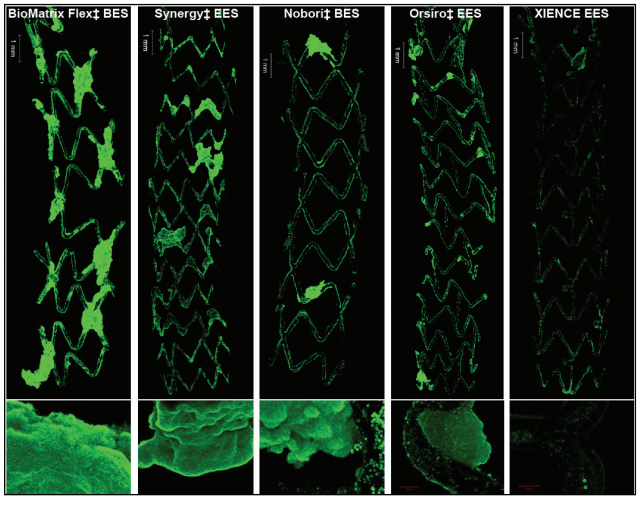

Figure 2. Representative confocal microscopic images of BioMatrix Flex‡ BES, Synergy‡ EES, Nobori‡ BES, Orsiro‡ EES, and XIENCE Xpedition™ EES (XIENCE EES) with immunofluorescent staining against dual platelet markers (CD61/CD42b) in a swine shunt model. Low and high power confocal microscopic images showing least thrombus-occupied area in XIENCE Xpedition™ (XIENCE EES) as compared with the other four CE Mark-approved biodegradable polymer-coated DES. Note: the stent struts of XIENCE EES are barely identified. Reprinted from JACC: Cardiovascular interventions, Vol 9, Otsuka F, et al, pgs 1248-1260, Copyright 2015, with permission from Elsevier.[30]

Using this model, we examined the acute thrombogenicity of CoCr-EES coated by PVDF-HFP fluoropolymer relative to four different CE Mark-approved biodegradable-polymer DESs: (1) BioMatrix Flex‡ biolimus-eluting stent (BES) (Biosensors International Group, Ltd.); (2) Nobori‡ BES (Terumo Interventional Systems); (3) platinum-chromium EES (Synergy‡); and (4) Orsiro‡ SES (Biotronik, Inc.). Stents were bisected and stained against specific platelet markers: CD61 as a marker of platelet aggregation (Immunotech, IM0540, dilution 1:100; Beckman Coulter) and CD42b as a marker of platelet adhesion (sc-7070, dilution 1:40; Santa Cruz Biotechnology) to capture both originating and propagated platelet thrombus. Positive staining was visualized using a secondary antibody conjugated to an Alexa Fluor 488 fluorophore (Life Technologies). Fluorescence area indicating platelet aggregation and propagation was least in the CoCr-EES relative to all four biodegradable-polymer DESs (Figure 2). Also, the number of platelet aggregate clots (> 0.1 mm^2) was the least in the CoCr-EES. Inflammatory cells that attach to strut surfaces may also affect clot formation via platelet-leukocyte interactions. The number of cell nuclei on strut surfaces, as assessed through 4′,6-diamindino-2-phenylindole staining and likely indicative of immune cell deposition, was the least in the CoCr-EES. BMSs, which lack a surface coating, were identified as the most thrombogenic stent. Regardless of whether the polymer coatings and/or drug has some protective effect relative to a metal surface, the effects were most pronounced for the CoCr-EES.

In another study, the polymer-free DES (BioFreedom‡) showed higher platelet adherence relative to CoCr-EES (Figure 3).[31] The abluminal surface of the polymer-free DES may be a contributing factor in the higher acute thrombogenicity that was observed. Higher strut thickness and lack of drug in a luminal side can contribute to higher thrombogenicity in polymer-free DESs. Biolimus A9 is coated only on the abluminal surface of polymer-free DES. When using inflammatory markers for neutrophils (PM-1) and monocytes (CD-14), the inflammatory effect of polymer-free DES was significantly greater than that of CoCr-EES and similar to that of BMS (Figure 4). Aggregated thrombus can provoke inflammatory cell adherence because platelet aggregation on the surfaces is recognized as a trigger to recruit circulating leukocytes (eg, neutrophils and monocytes).[32] In the same study, fluoropolymer-only stents without drugs showed significantly less platelet aggregation as compared to BMS. Interestingly, anti-inflammatory effects in fluoropolymer-only stents without drugs were comparable to BMS, although CoCr-EES with drugs showed significantly lower inflammation relative to BMS. Thromboresistance due to fluoropolymer coating and anti-inflammatory effect due

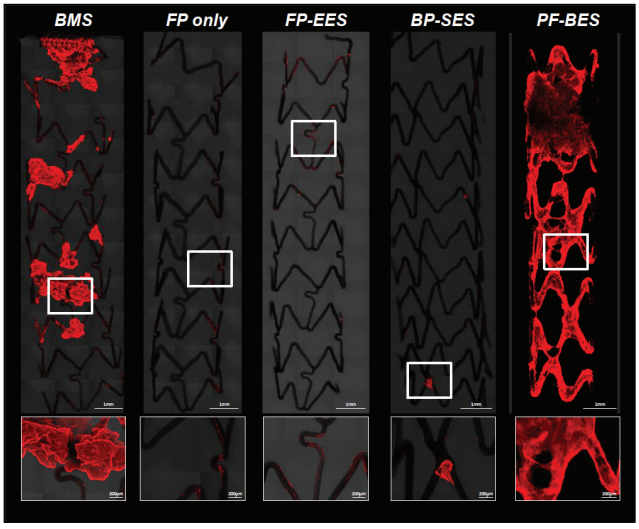

Figure 3. Representative confocal microscopic images of BMS, FP-only, FP-EES, and PF-BCS with immunofluorescent staining against dual platelet markers (CD61/CD42b) in a swine shunt-model. Low and high power confocal microscopic images showing the least thrombus-occupied area in stents with fluoropolymer (FP-only and FP-EES) as compared with the other stents. Note: minimal thrombus are only observed in link portion of FP-only and FP-EES, whereas large thrombus have covered almost all the struts in PF-BES. Reprinted from EuroIntervention Vol 16/No 14, Torii S, Cheng Q, Mori H, et al, Acute thrombogenicity of fluoropolymer-coated versus biodegradable and polymer-free stents, pgs 1685-1693, Copyright 2018, with permission from Europa Digital & Publishing.[31]

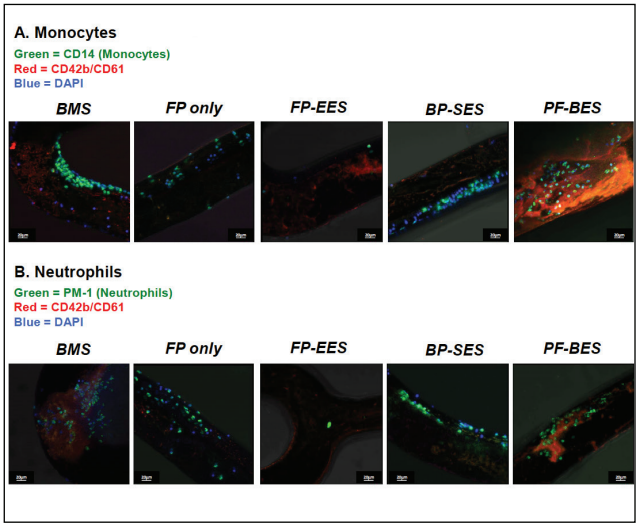

Figure 4. Representative confocal images of each stent with inflammatory cells in a swine shunt-model. CD14 stained nuclei represent adherent monocytes, whereas PM-1 stained nuclei represent adherent neutrophils. DAPI is a fluorescent stain for DNA. Reprinted from EuroIntervention Vol 16/No 14, Torii S, Cheng Q, Mori H, et al, Acute thrombogenicity of fluoropolymer-coated versus biodegradable and polymer-free stents, pgs 1685-1693, Copyright 2018, with permission from Europa Digital & Publishing.[31]

to the drug can thus each play an important role in blood-material interactions.

CLINICAL IMPLICATIONS OF BLOOD-MATERIAL INTERACTIONS ON STENT THROMBOGENICITY IN HUMANS

The results of the collective experimental findings described thus far indicate that the fluoropolymer coating serves as a protective barrier against acute thrombus formation, and this protective effect of the fluoropolymer is further illustrated through clinical outcomes. Clinical trials and a network meta-analysis reported by Palmerini et al have shown a lower prevalence of ST with CoCr-EES as compared to BMS and early DES use.[11,33,34] When analyzing data from 13 randomized clinical trials, CoCr-EES showed significantly lower ST, target lesion revascularization, and myocardial infarction as compared to other stents.[35] In a network meta-analyses conducted by Palmerini et al, the use of biodegradable polymer BES had higher rates of definite ST compared with CoCr-EES at 1 year.[33] The increased risk for definite ST with biodegradable-polymer BES compared with CoCr-EES was apparent both before 30 days as well as between 30 days and 1 year. In another network meta-analysis, Bangalore et al confirmed these findings, demonstrating lower rates of definite ST with CoCr-EES compared to several biodegradable-polymer DESs.[36] Although conformal polymer coatings may have lower thromboresistance than BMS, biodegradable polymer coatings may also have disadvantages in terms of platelet aggregation because of the eventual loss of polymer.[37]

However, when directly comparing the durable fluoropolymer CoCr-EES with biodegradable polymer DES, significant differences in terms of safety have not yet been demonstrated. In the BIOFLOW-II trial (n = 452) comparing CoCr-EES and an ultra-thin strut (61 µm) biodegradable-polymer SES (O-SES, Orsiro‡),[38] definite/probable ST was not significantly different (0% vs 0%; O-SES vs CoCr-EES). In unselected populations enrolling 7,640 patients, CoCr-EES was compared with O-SES with propensity score matching and the final study population consisted of 2,902 matched patients. The rate of definite ST did not differ significantly between them (CoCr-EES, 0.8% vs O-SES, 0.8%; P = 1.00).[39] Recent meta-analysis enrolling 19,886 patients from 16 randomized controlled trials showed that there were no significant differences of ST between the two DESs.[40] Also, biodegradable-polymer DESs and durable-polymer

DESs showed similar clinical outcomes regardless of the DAPT duration (≥ 6 months vs ≥ 12 months).[40] These trials, however, were all conducted using relatively long periods of DAPT (6–12 months).

DAPT DURATION

It remains uncertain whether fluoropolymer coating might provide an advantage relative to biodegradable-polymer DES in curtailing DAPT because of their superior thromboresistance profile, as seen in the preclinical studies referenced previously. In the field of current commercially available DES, the optimal duration for very short (< 3 months) DAPT remains unknown.[41-43] A comprehensive meta-analysis from 10 clinical trials enrolling a total 32,287 patients evaluated the benefits of < 12 months of DAPT relative to extended (>12 months) DAPT.[43] The most frequently used stent was CoCr-EES. Short-duration DAPT (3 or 6 months) was associated with lower rates of major bleeding relative to long-duration DAPT (> 12 months) (odds ratio, 0.58; 95% confidence interval, 0.36-0.92; *P* = .02). Also, ischemic or thrombotic outcomes were statistically comparable. Thus, the specific properties of CoCr-EES discussed previously may mean that when implanted in noncomplex lesions, it is feasible to safely shorten the DAPT duration to 3 to 6 months.

However, the conversation regarding DAPT has moved to even shorter durations (< 3 months). Within this period of time, stent struts may not be fully covered by endothelium. In animal models, endothelialization of BMSs occurs quicker than with DESs.[44] Therefore, within this early period (< 3 months after PCI) the feature of thromboresistance imparted by polymer coatings may be even more important in helping to curtail the need for DAPT. Because of its superior thromboresistant profile, CoCr-EES equipped with fluoropolymer coating may be the most favorable for a short duration of DAPT as compared to other types of DESs.

The first conducted randomized study to assess 1-month DAPT after implanting DES was the landmark LEADERS FREE trial.[45] This study, which included 2,466 patients at high risk of bleeding treated with polymer-free DES or BMS, showed a significantly favorable primary safety endpoint (defined as a composite of cardiac death, myocardial infarction, or stent thrombosis) for polymer-free DES relative to BMS at 1 year (9.4% vs 12.9%, respectively; *P* = .005), although there was no significant difference of definite or probable ST between them. Additionally, the 2-year results in the same study still showed a favorable primary safety endpoint for polymer-free DES (12.6% vs 15.3%, respectively; *P* = .039).[46] However, it must be acknowledged that polymer-free DES showed a relatively high rate of definite or probable ST (2%) at 1 year; while comparable to BMS (2.2%), this rate is higher than what is reported for other DESs that use polymers for drug elution. Whether this was due to thick struts or other patient-specific characteristics remains uncertain. One would hope that we could improve on this rate of ST with DES use (such as CoCr-EES) because, as mentioned previously, polymer-free DESs showed greater thrombogenicity than CoCr-EES in the ex vivo pig arteriovenous shunt model.

To date, CoCr-EES has shown promising results for short-term DAPT. The STOP-DAPT study was a prospective, multicenter, single-arm study evaluating 3-month DAPT duration after CoCr-EES implantation. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, definite ST, and TIMI major/minor bleeding at 1 year; 1,525 patients were enrolled from 58 Japanese centers, with complete 1-year follow-up in 1,519 patients (99.6%). Thienopyridine was discontinued within 4 months in 94.7% of patients. The event rates beyond 3 months were very low (cardiovascular death, 0.5%; MI, 0.1%; ST, 0%; stroke, 0.7%; and TIMI major/minor bleeding, 0.8%).[47] These data suggest very promising results for reducing DAPT duration after CoCr-EES implantation.

Additional studies are being conducted to further refine the optimal duration of DAPT. In this regard, the XIENCE 28 Global Study is a prospective, single-arm, multicenter, open-label, nonrandomized trial to further evaluate the safety of 1-month DAPT in subjects at high risk of bleeding who are undergoing PCI with XIENCE EESs. The XIENCE 90 study is a prospective, single-arm, multicenter, open-label trial to evaluate the safety of 3-month DAPT in subjects at high bleeding risk who are undergoing PCI with XIENCE EESs within the United States. Overall, these data will help us to understand whether short duration of DAPT is truly safe in combination with a stent that has consistently demonstrated a favorable thromboresistant profile.

CONCLUSION

Despite advances in DES technology, ST is still not infrequent and is associated with high morbidity and mortality. Such data continue to influence physicians to use DAPT for long periods of time, which is associated with an increased risk for bleeding. It is increasingly being recognized that stent related factors, especially coating technologies, have the potential to reduce the risk for ST through favorable blood-material interactions and thus perhaps allow for a shortened duration of DAPT. Fluorinated polymers have shown significant promise in modifying this risk through their interaction with specific plasma proteins, which prevents the adhesion and aggregation of platelets to the stent surface, thus minimizing thrombus formation. Clinical data supporting a role for fluorinated polymers in reducing ST are especially convincing. Thus, it seems likely that CoCr-EES coated by a fluoropolymer may be the most suitable DES for a short-duration DAPT strategy. ■

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Disclosures: Honoraria from Abbott Vascular, Biosensors, Boston Scientific Corporation, Celonova, Cordis, Medtronic, OrbusNeich Medical, Sinomed, Terumo Interventional Systems; consultant for Abbott Vascular, Boston Scientific Corporation, Celonova, Cordis, Medtronic, OrbusNeich Medical, Sinomed, and Terumo Interventional Systems.

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CASE REPORT

Antiplatelet Therapy After Complex PCI in the Anticoagulated Patient

BY MICHAEL P. SAVAGE, MD, FACC, FSCAI, FACP; DAVID L. FISCHMAN, MD, FACC, FACP; AND MARGUERITE DAVIS, BS, RT(R), RCIS

The optimal strategy for antiplatelet therapy in patients treated with coronary drug-eluting stents (DESs) who require anticoagulation has been an issue fraught with uncertainty and controversy. This conundrum is not uncommon, as approximately 6% to 8% of patients undergoing PCI require concomitant anticoagulation. Compared to DAPT alone, the addition of anticoagulation to DAPT is associated with a two-to-threefold increase in bleeding complications.[1-3] In the case described in this article, we performed multivessel percutaneous coronary intervention (PCI) of chronic total occlusions (CTOs) using DESs in a patient with severe ischemic cardiomyopathy who was on anticoagulation for prior mechanical mitral and aortic valve replacement. Discussion of the case at our instutition's heart team conference yielded divergent recommendations with respect to dual antiplatelet therapy (DAPT) duration before ultimately deciding on the patient's course.

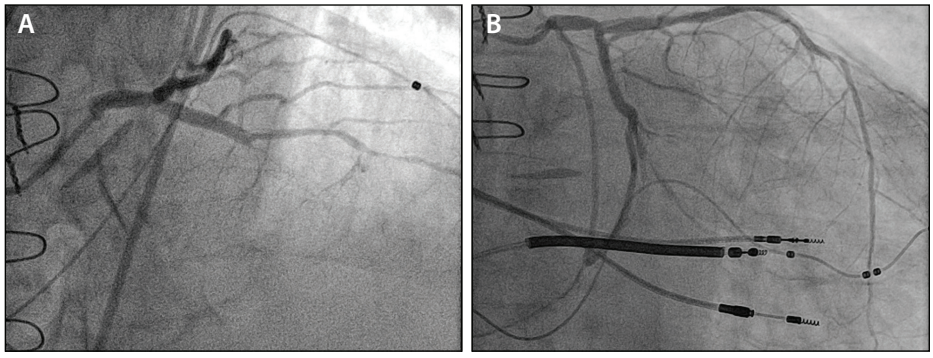

Figure 1. Coronary angiograms showing in-stent restenosis with CTOs in both the LAD (A) and LCx-OM (B).

CASE REPORT

A 69-year-old man was hospitalized for progressively worsening exertional dyspnea and automatic internal cardiac defibrillator shocks. He had prior cardiac surgery with St. Jude mitral and aortic valve replacements, for which he was on chronic warfarin therapy. He had a history of an ischemic cardiomyopathy (ejection fraction 10% to 15%) due to prior asymptomatic myocardial infarctions. Cardiac risk factors included type 2 diabetes, hypertension, hyperlipidemia, and prior smoking.

PRESENTATION AND TREATMENT OPTIONS

One year prior to this admission, the patient had undergone PCI at an outside hospital with placement of bare-metal stents in the left anterior descending (LAD) and left circumflex obtuse marginal (LCx-OM) coronary arteries. Repeat cardiac catheterizations demonstrated restenosis with CTO of both stented vessels (Figure 1). A cardiac MRI demonstrated viability in the anterior wall. Cardiac surgery consultation deemed the patient too high

STRATEGIES TO REDUCE BLEEDING RISK IN PATIENTS ON TRIPLE THERAPY[2,3]

- Use of low dose aspirin (≤ 100 mg daily)
- Clopidogrel is the preferred P2Y12 inhibitor
- Non-vitamin K oral anticoagulants favored over warfarin for nonvalvular atrial fibrillation
- If warfarin is used, target international normalized ratio of 2 to 2.5
- Keep triple therapy as short as possible; consider dual therapy with clopidogrel and anticoagulation in patients at lower thrombotic risk
- Prophylactic use of proton pump inhibitor with triple therapy

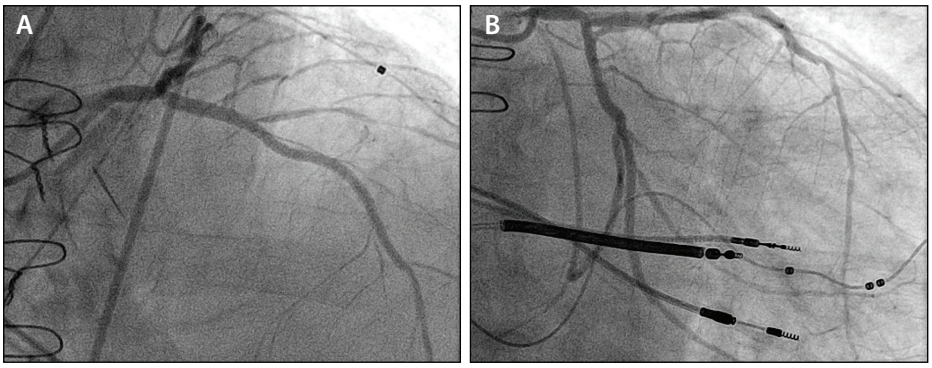

Figure 2. Coronary angiograms after successful PCI of in-stent CTOs of the LAD (A) and LCx-OM (B). Three everolimus-eluting stents were placed (28-mm and 23-mm stents in the LAD and a 33-mm stent in the LCx-OM; cumulative stent length, 84 mm).

risk for bypass surgery, and the patient was referred to our institution for complex PCI.

PROCEDURE

Repeat PCI was performed successfully with placement of two everolimus DESs (28 mm and 23 mm) in the LAD and a long 33-mm everolimus DES in the LCx-OM; total stent length was 84 mm (Figure 2).

POST-PROCEDURAL ANTIPLATELET THERAPY

The risk and benefit trade-offs for DAPT duration in this complex case were debated within our institution. The patient had several high-risk features for stent thrombosis and recurrent ischemic events including multivessel stenting, treatment of CTO, use of at least three stents, stent length > 60 mm, chronic renal disease, diabetes, and severe cardiomyopathy.[3] Because our patient was at high thrombotic risk and tolerated chronic warfarin plus aspirin therapy without bleeding, a 3-month course of DAPT was recommended.

DISCUSSION

Duration of DAPT after PCI in patients on anticoagulation remains a perplexing challenge. The uncertainty regarding DAPT duration is also reflected in disparities among current cardiovascular society guidelines. Current algorithms and consensus documents fail to do justice to the variable interplay of thrombotic and bleeding risks in individual patients. As a consequence, opinions and practices on DAPT duration vary widely (see sidebar, *Use of Social Media for Contemporaneous Insights*). A variety of strategies can be utilized to lower the bleeding risk of patients treated with triple antithrombotic therapy (see sidebar, *Strategies to Reduce Bleeding Risk in Patients on Triple Therapy*). Ongoing trials focused on the safety of shortening DAPT duration with newer-generation DESs should hopefully enlighten and bring consensus to the clinical management of these complex patients. ■

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USE OF SOCIAL MEDIA FOR CONTEMPORANEOUS INSIGHTS

Inspired by the internal debate at our institution surrounding optimal DAPT duration, we decided to seek opinions from a wider international medical community using Twitter as a polling vehicle. Today, an increasing number of interventional cardiologists are on Twitter, regularly engaging with the #CardioTwitter hashtag to discuss topics like DAPT. The poll feature on Twitter allows a user to post a question to their account for up to a week, and any registered user can vote for one of up to four different answers. Twitter tallies all votes in real time and displays a final result once the poll time has concluded. It should be noted that there are limitations to using social media as a polling mechanism and should not be mistaken for a peer-reviewed publication or guideline. From an analytics standpoint, voters' identities are anonymous, so it is not possible to verify the demographic makeup of those who participated (eg, whether the voters are physicians, industry, or unrelated; the geographic region of each voter; etc). Polls on social media are simply a vehicle to gauge opinions, and as such, the results should not be considered as a guidance toward treatment strategy.

Being mindful of these limitations, we wanted to use this emerging platform to gain some additional opinions on DAPT duration using the case study described in this article. A poll was posted to Dr. Savage's Twitter account on June 2, 2017 and ran for 5 days. Four options for DAPT duration were given: (1) DAPT for 1 month, then clopidogrel only; (2) DAPT for 3 to 6 months; (3) DAPT for at least 1 year; (4) clopidogrel only, no aspirin. The pre- and post-PCI coronary angiograms (shown in Case Report) were tagged to the poll tweet. The poll received 10,346 impressions (views), 859 engagements (any time someone clicked on the Tweet, including replies, follows, likes, retweets, etc), and 306 votes (Figure 1). Although Twitter poll voters are kept anonymous, respondents who interacted with the tweet by other means (eg, replying, retweeting, or liking) are identified. Assessing those respondents, 75% were men, 25% were women, and 38% were from outside the United States. More than 93% of the identified respondents were described on their Twitter page as health care professionals, and nearly all worked in cardiovascular disease.

The results highlight the lack of consensus on the management of DAPT in patients on anticoagulation: three different DAPT options were chosen by approximately 30% of the respondents (1 month, 3 to 6 months, and at least 12 months). Less than 10% voted for the option of clopidogrel without aspirin.

Since the initial poll, randomized trials have accrued to suggest that bleeding in patients on anticoagulation who undergo PCI can be significantly reduced by eliminating postprocedure aspirin while continuing a P2Y12 inhibitor with anticoagulation.[1-3] Conjecturing that clinical practice patterns may have changed in response to these trials, the poll was reposted to Dr. Savage's Twitter on January 19, 2019 (more than a year and a half after the initial poll was conducted). Similar to the original post, the poll ran for 5 days.

The follow-up poll had more than twice as many impressions (21,963) as the original with 511 votes (Figure 2). Similar to the first poll, there remained no consensus of opinion on DAPT duration. In the current poll, slightly more than half favored shortening DAPT to 1 month or less, while slightly less than half favored longer DAPT durations.

The results of the two polls are compared in Figure 3. As anticipated, there has been a shift towards shorter DAPT duration. While omitting aspirin after discharge remained the least frequent choice, this option nearly doubled from 9% in 2017 to 17% in 2019. Prescribing DAPT for 1 month (after which only clopidogrel is continued) was the most commonly selected option in both polls. There was a significant increase in the recommendation for shortening postprocedural DAPT to 0 to 1 month from 43% in 2017 to 56% in 2019 ($P < .001$).

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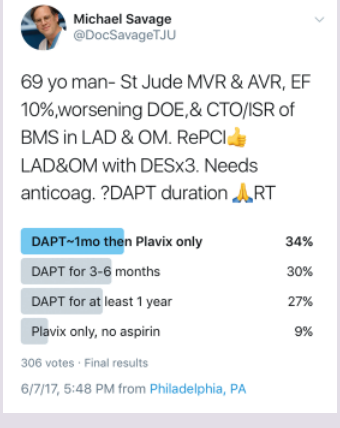

Figure 1. Final voting results of Twitter poll posted in June 2017.

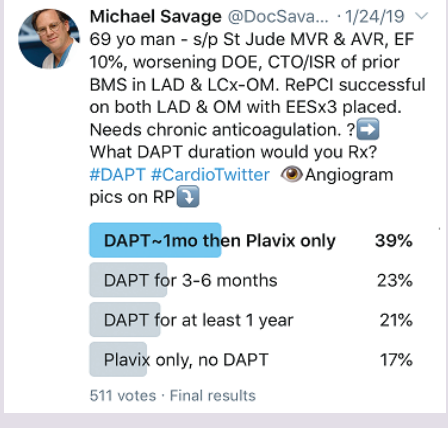

Figure 2. Final results of the Twitter poll reposted in January 2019.

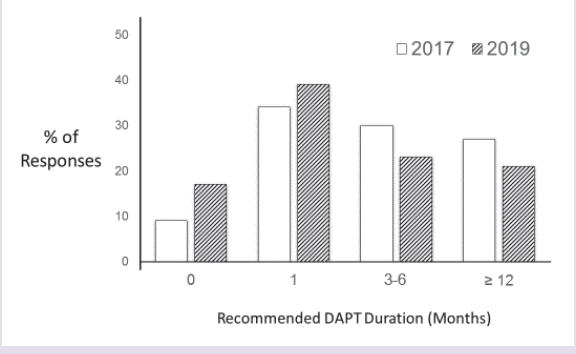

Figure 3. Comparison of the 2017 and 2019 poll results.

IMPORTANT SAFETY INFORMATION

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The XIENCE V®, XIENCE nano®, XIENCE PRIME®, XIENCE PRIME® LL, XIENCE Xpedition®, XIENCE Xpedition® SV and XIENCE Xpedition® LL, XIENCE Alpine® (XIENCE Family) of Everolimus Eluting Coronary Stents on the MULTI-LINK VISION® or MULTI-LINK MINI VISION® Delivery Systems

INDICATIONS
The XIENCE Family of Everolimus Eluting Coronary Stent Systems are indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease due to de novo native coronary artery lesions for XIENCE V (length ≤ 28 mm), XIENCE PRIME, XIENCE Xpedition and XIENCE Alpine (lengths ≤ 32 mm) with reference vessel diameters of ≥2.25 mm to ≤ 4.25 mm. Additionally, the entire XIENCE Family is indicated for treating de novo chronic total coronary occlusions.

CONTRAINDICATIONS
The XIENCE Family of stents is contraindicated for use in patients:
- Who cannot receive antiplatelet and/or anti-coagulant therapy
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and/or fluoropolymers.

WARNINGS
- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because the use of this device carries the associated risk of stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

PRECAUTIONS
- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent are presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglycerides levels.
- A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. See Instructions for Use for current data on multiple stent implantation.
- Safety and effectiveness of the XIENCE Family of stents have not been established for subject populations with the following clinical settings:
  - Patients with prior target lesion or in-stent restenosis related brachytherapy, patients in whom mechanical atherectomy devices or laser angioplasty catheters are used in conjunction with XIENCE Family stents, women who are pregnant or lactating, men intending to father children, pediatric patients, unresolved vessel thrombus at the lesion site, coronary artery reference vessel diameters < 2.25 mm or > 4.25 mm or lesion length > 32 mm, lesions located in saphenous vein grafts, unprotected left main coronary artery, ostial lesions, lesions located at a bifurcation or previously stented lesions, diffuse disease or poor flow (TIMI < 1) distal to the identified lesions, excessive tortuosity proximal to or within the lesion, recent acute myocardial infarction (AMI) or evidence of thrombus in target vessel multivessel disease, and in-stent restenosis
- Everolimus has been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE Family of stents because of limited systemic exposure to everolimus eluted from the stent.
- Everolimus is an immunosuppressive agent. Consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

- Oral everolimus use in renal transplant patients and advanced renal cell carcinoma patients was associated with increased serum cholesterol and triglycerides, which in some cases required treatment.
- Nonclinical testing has demonstrated that the XIENCE Family of stents, in single and in overlapped configurations are MR conditional up to 68 mm in length for XIENCE V and XIENCE nano only and up to 71 mm in length for all other XIENCE Family stents. It can be scanned safely under the conditions in the Instructions for Use.
- The XIENCE Family of stents should be handled, placed, implanted, and removed according to the Instructions for Use.

POTENTIAL ADVERSE EVENTS

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedure including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure, Access site pain, hematoma, or hemorrhage, Acute myocardial infarction, Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent, Aneurysm, Arterial perforation and injury to the coronary artery, Arterial rupture, Arteriovenous fistula, Arrhythmias, atrial and ventricular, Bleeding complications, which may require transfusion, Cardiac tamponade, Coronary artery spasm, Coronary or stent embolism, Coronary or stent thrombosis, Death, Dissection of the coronary artery, Distal emboli (air, tissue or thrombotic), Emergent or non-emergent coronary surgery, Fever, Hypotension and / or hypertension, Infection and pain at insertion site, Injury to the coronary artery, Ischemia (myocardial), Myocardial infarction (MI), Nausea and vomiting, Palpitations, Peripheral ischemia (due to vascular injury), Pseudoaneurysm, Renal Failure, Restenosis of the stented segment of the artery, Shock/pulmonary edema, Stroke / cerebrovascular accident (CVA), Total occlusion of coronary artery, Unstable or stable angina pectoris, Vascular complications including at the entry site which may require vessel repair, Vessel dissection

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain (including upper abdominal pain); Anemia; Angioedema; Anorexia; Asthenia; Constipation; Cough; Delayed wound healing/fluid accumulation; Diarrhea; Dyslipidemia (including hyperlipidemia and hypercholesterolemia); Dyspnea; Dysgeusia; Dyspepsia; Dysuria; Dry skin; Edema (peripheral); Epistaxis; Fatigue; Headache; Hematuria; Hyperglycemia (may include new onset of diabetes); Hyperlipidemia; Hyperkalemia; Hypertension; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Increased serum creatinine; Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections); Insomnia; Interaction with strong inhibitors and inducers of CY3PA4 or PgP; Leukopenia; Lymphoma and other malignancies (including skin cancer); Male infertility (azospermia and/or oligospermia); Mucosal inflammation (including oral ulceration and oral mucositis); Nausea; Neutropenia; Non-infectious pneumonitis; Pain: extremity, incision site and procedural, back, chest, and musculoskeletal; Proteinuria; Pruritus; Pyrexia; Rash; Stomatitis; Thrombocytopenia; Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/ Hemolytic uremic syndrome (HUS); Tremor; Urinary tract infection; Upper respiratory tract infection; Vomiting
- Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

CAUTION: This product is intended for use by or under the direction of a physician. Prior to use, reference the Instructions for Use, inside the product carton (when available) or at eifu.abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

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