

REVIEW TOPIC OF THE WEEK

Should We Still Have Bare-Metal Stents Available in Our Catheterization Laboratory?



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ABSTRACT

The introduction of bare-metal stents (BMS) has represented a major advancement over plain old balloon angioplasty in the management of coronary artery disease. However, the high rates of target lesion revascularization associated with use of BMS have led to the development of drug-eluting stents, which require prolonged dual antiplatelet therapy due to the increased risk of late and very late stent thrombosis. The improvements in newer-generation drug-eluting stents have translated into better safety and efficacy compared with earlier generation and BMS, thus allowing shorter dual antiplatelet therapy duration. Here, we aim to provide reasons as to why we still need BMS in our cardiac catheterization laboratory. (J Am Coll Cardiol 2017;70:607-19) © 2017 by the American College of Cardiology Foundation.

Drug-eluting stents (DES) were engineered specifically to address restenosis, thanks to their antiproliferative drug coatings (1-3). The initial enthusiasm for DES was tempered by an increased risk of stent thrombosis (ST), possibly due to the delayed endothelialization caused by the antirestenotic drugs or delayed hypersensitivity reactions to the polymer (4-10). The concern of ST with the first-generation of DES transiently reduced their use and led to development of new-generation DES with a better safety profile.

To overcome the issue of ST, new generations of DES have been developed with the following improvements: 1) cobalt (or platinum)-chromium platforms, allowing reduction of strut thickness from between 97 and 140 μm to between 81 and 91 μm , and improved deliverability and flexibility (11,12); 2) limus-family antiproliferative drugs, due to their demonstrated overall superiority over paclitaxel in terms of reduced late lumen loss and target lesion revascularization (TLR) (13); and 3) use of new polymers with more biocompatibility or biodegradable

polymers, or polymer-free stents that induce fewer inflammatory reactions and, therefore, provide better endothelial coverage (14,15). There are even laboratory data demonstrating that metal stents covered by a fluorinated polymer are less thrombogenic than metal stents (16). Nevertheless, we cannot dismiss the fact that DES have an antiproliferative drug on top of the polymer and that this combination will prolong the time for complete endothelialization.

Numerous randomized controlled trials (17-20), meta-analyses (21-25), and large-scale registries (26-30) have shown a marked improvement in clinical safety and efficacy with new-generation DES, compared with first-generation DES and bare-metal stent (BMS), in a wide spectrum of patients. Consequently, the use of new-generation DES has become the standard of care in revascularization, for efficacy and safety (31). Moreover, the reduction in late and very late ST with new DES, which allows the duration of dual antiplatelet therapy (DAPT) to be shortened, raises the question of the current need for BMS in clinical practice.



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Manuscript received April 11, 2017; revised manuscript received May 21, 2017, accepted May 26, 2017.

ABBREVIATIONS AND ACRONYMS

BA9 = biolimus A9

BMS = bare-metal stent(s)

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

MI = myocardial infarction

OAC = oral anticoagulant agent(s)

PCI = percutaneous coronary intervention

ST = stent thrombosis

TIMI = Thrombolysis In Myocardial Infarction

TLR = target lesion revascularization

TVR = target vessel revascularization

The key point of this review is that BMS may allow a short DAPT duration, whereas DAPT is currently recommended for at least 3 months with DES. In circumstances where DAPT becomes an issue, the biolimus A9 (BA9)-coated BioFreedom stent (Biosensors International, Singapore) is a reasonable alternative, but it is not universally available, its deliverability in complex anatomies is not optimal, and only 1 study (32) supports its effectiveness and safety compared with BMS in patients at high bleeding risk treated with a short (30 days') duration of DAPT.

ARE BMS LESS THROMBOGENIC THAN DES? AND WHAT IS THE REALITY WITH REGARD TO DAPT?

Among many interventionists, improvements in polymer and stent biocompatibility, and the associated lower rates of ST observed

in recent meta-analyses, have raised the notion that current-generation DES are less thrombogenic than BMS are (22-24,33). Moreover, although the issue of restenosis (the main weakness of BMS) is often thought of as nonmalignant, there is evidence that in ~10% of cases, patients with in-stent restenosis present with myocardial infarction (MI), as opposed to stable angina, further compromising BMS safety (34).

Can we hypothesize that BMS are less thrombogenic than last-generation DES? Although Kolandavelu *et al.* (16) showed, in a controlled model of early ST, that drug-eluting polymer-coated stents have significantly lower thrombosis and platelet deposition compared with their bare-metal counterparts, other experimental studies have demonstrated contradictory results (35,36), and a definitive answer is not available. However, outside of technical issues (such as suboptimal dilation and apposition and residual dissection outside the stent), the most important pathophysiological mechanism of ST is delayed or incomplete endothelialization, with experimental and autopsy data suggesting that delayed healing (leading to uncovered struts) occurs more frequently with DES (37,38). In addition, endothelialization provides a natural barrier against thrombosis; however, polymer and antiproliferative drug combinations used on DES have been implicated as contributing to poor endothelialization (38).

Regarding the consequences of restenosis, we agree that in-stent restenosis may occasionally present as an acute coronary syndrome, and in view of BMS use being most commonly associated with aggressive restenosis in long lesions and/or in small

vessels, the operator should be aware of these limitations. In addition, MI associated with restenosis are not rare, and the clinical impact of higher MI rates with BMS needs to be taken into account (39).

The risk of bleeding is another point to consider, together with the potential thrombosis and restenosis risk, in choosing the best type of stent in a specific patient with a specific clinical/angiographic presentation. In this regard, the introduction of current-generation DES, associated with reduced stent failure events, has raised a crucial question regarding the duration of DAPT, shifting the clinical need to decreasing DAPT-associated complications. A number of studies have been conducted that aim to shorten DAPT duration to 6 months, and even to 3 months (40-44), with the majority showing that a shorter DAPT duration resulted in similar rates of ischemic and bleeding events compared with standard DAPT duration. Moreover, several ongoing studies will give us further information on the safety of very short DAPT duration with new-generation DES (SENIOR [Efficacy and Safety of New Generation Drug Eluting Stents Associated With an Ultra Short Duration of Dual Antiplatelet Therapy: Design of the Short Duration of Dual Antiplatelet Therapy With Synergy II Stent in Patients Older Than 75 Years Undergoing Percutaneous Coronary Revascularization] trial [NCT02099617]; MASTER DAPT [Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen] trial [NCT03023020]; POEM [Bioresorbable Polymer-Coated EES in Patients at High Bleeding Risk Undergoing PCI Followed by 1-Month DAPT] registry [NCT03112707]).

However, assuming that 3 months of DAPT are sufficient to allow acceptable endothelial coverage of struts of current-generation DES to protect against ST, are we equally sure that this is still applicable when DAPT duration is shortened to <3 months or even <1 month? For example, the optimal strategy for management of the unstable patient with coronary artery disease who needs an urgent noncardiac surgical procedure, or for a patient presenting with ST-segment elevation MI and found to be severely anemic, has yet to be defined. There are no studies available to help select the most appropriate way to revascularize these patients. We have plenty of retrospective studies reporting that both types of patients have high rates of bleeding and ischemic complications, especially when DAPT needs to be interrupted. In the absence of data, our current rationale in these situations is to prefer BMS with intracoronary imaging guidance to optimize the final

result. Luckily, such circumstances are not frequent. However, it is important to optimally manage all clinical scenarios, providing the most effective therapy with the lowest possible risk of side effects, bearing in mind that the major side effect of stent implantation is ST.

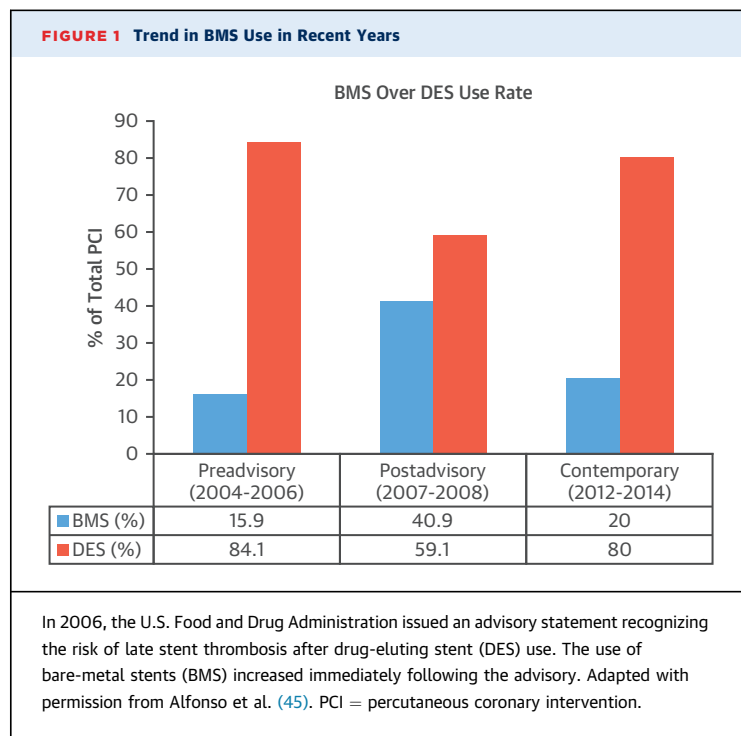
CONSIDERATIONS WITH BMS

BMS usage has progressively decreased following the publication of studies supporting the clinical benefit of current-generation DES over conventional BMS. Indeed, the prevalence of BMS use in developed countries approximates 20% of all percutaneous coronary intervention (PCI) procedures, an estimate that has continued to decrease annually over the past 5 years (**Figure 1**) (45-47). However, demonstration of the superiority of newer-generation DES should not automatically translate to declaring the end of BMS. BMS have continued to improve, with thinner struts, better radio-opacity, deliverability, and conformability. When considering implanting a BMS, selection should favor thin strut devices (**Figure 2**). Moreover, they have mainly potential advantages for very short duration DAPT in special-risk patients. Additionally, we should consider that no trials will identify the strengths of these devices in the current-generation DES era. We need to recognize that current studies comparing outcomes of patients treated with BMS or DES carry an important bias. The decision to treat a patient with BMS conveys a “risk factor,” regarding a coexisting condition that challenges DAPT adherence and/or highlights increased risks, such as excessive bleeding, advanced age, impending need for noncardiac surgery, or even noncompliance. For these reasons, patients treated with BMS may demonstrate characteristics for which they are routinely excluded from contemporary stent trials.

A recent observational study investigated the reasons for BMS implantation in 774 consecutive patients in 31 European centers over a 2-month period in 2012 (48). As displayed in **Figure 3**, the most frequent reason for BMS use related to concerns with regard to DAPT compliance, followed by the presence of a target vessel with a large reference diameter, treatment of patients with acute MI, concerns over reimbursement, and planned noncardiac surgery within 1 year from stent implantation.

A DECISION TREE FOR STENT SELECTION

Whenever PCI is considered the therapy of choice for our patients, the selection of the most appropriate stent type is based on the characteristics of both the



patient and the lesion. The main issue with respect to the patient’s characteristics is whether DAPT can be tolerated for a time period sufficient to guarantee the lowest possible risk of ST, with a minimal risk of bleeding. Generally, DAPT should be continued for 1 month (minimum 15 days) following BMS and for 6 to 12 months following DES implantation, with recent data supporting 3 months of DAPT following implantation of new-generation DES, especially those with resorbable polymers (40-44). Available bleeding risk scores should be used to identify patients with contraindications to DAPT or with a high risk of bleeding on DAPT therapy (49-52). Moreover, the choice to implant a BMS should also take into account vessel size and lesion length, known factors associated with stent restenosis.

The **Central Illustration** summarizes the decision tree for stent selection in our daily clinical practice in special-risk patients, according to their clinical and angiographic presentation.

1. The patient can tolerate DAPT for at least 3 months. As multiple studies showed a marked improvement in clinical safety and efficacy with new-generation DES compared with BMS across different clinical and angiographic settings, DES should be considered our routine choice in patients who can tolerate DAPT for at least 3 months (**Central Illustration**). A discussion of

FIGURE 2 Current BMS

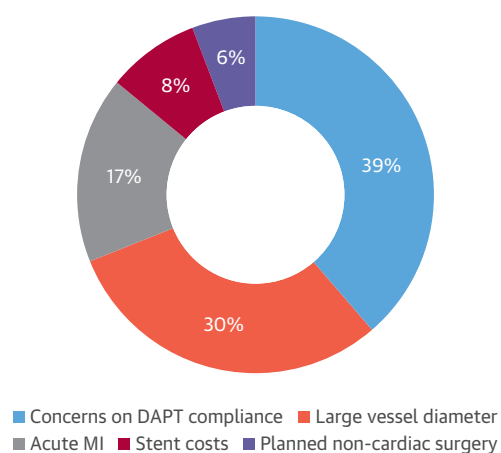
MANUFACTURER	COMMERCIAL NAME	ALLOY	STRUT THICKNESS (Inch / μ m)	DIAMETER (mm)	LENGTH (mm)
Boston Scientific	Rebel	PtCr	81 μ m (for 3 mm ϕ)	2.25-4.50	8-32
Boston Scientific	VeriFLEX	SS /316L	96 μ m (for 3 mm ϕ)	2.75-5.00	8-32
Abbott	Multilink8	CrCo /L-605	81 μ m (for 3 mm ϕ)	2.25-4.00	8-28
Abbott	Multilink Vision	CrCo /L-605	81 μ m (for 3 mm ϕ)	3.00-4.00	8-28
Medtronic	Integrity	CoNi /MP35N	91 μ m (for 3 mm ϕ)	2.25-4.00	8-30
Medtronic	Driver BMS	CrCo /F-562	91 μ m (for 3 mm ϕ)	3.00-4.00	9-30
Biotronik	Pro-Kinetic Energy	CrCo /L-605	60 μ m (for 3 mm ϕ)	2.00-5.00	9-40
B.Braun	Coroflex Blue Neo	CrCo /L-605	60 μ m (for 3 mm ϕ)	2.75-4.00	8-32
Terumo	Kaname	CrCo /L-605	81 μ m (for 3 mm ϕ)	2.50-4.00	9-28
Terumo	Tsunami	SS /316L	80 μ m (for 3 mm ϕ)	2.00-4.00	8-30
Biosensors	Gazelle	SS /316L	112 μ m (for 3 mm ϕ)	2.25-4.00	8-28

Main characteristics of current bare-metal stents (BMS). CoNi = cobalt nickel; CrCo = chromium cobalt; PtCr = platinum chromium; SS = stainless steel.

DAPT duration for less or more than 6 months is beyond the scope of this review.

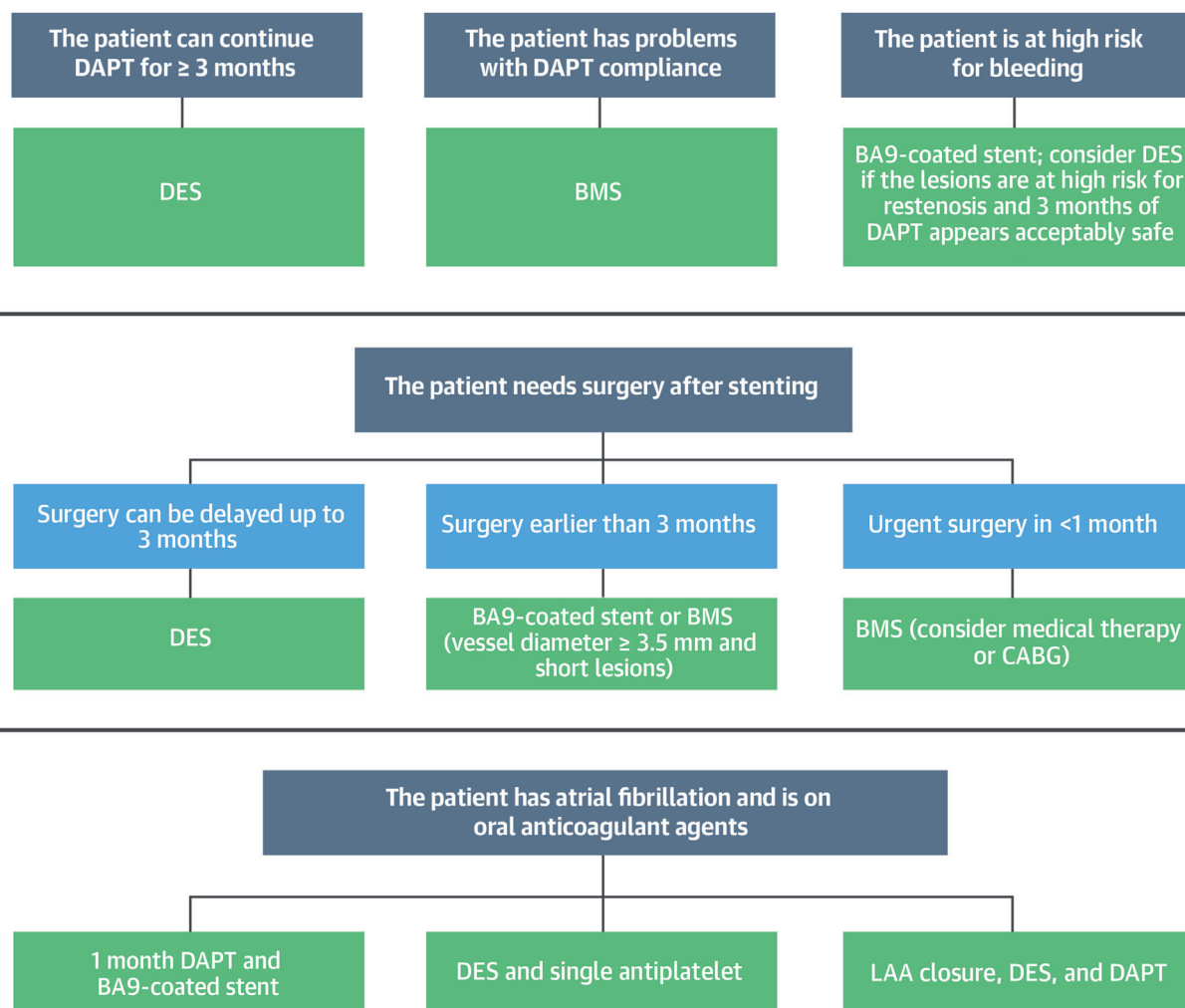
2. The patient is at high bleeding risk ([Table 1](#)). Patients at high bleeding risk requiring PCI are a challenging subset and need careful evaluation of both thrombotic and bleeding risks when selecting a stent and determining duration and intensity of antithrombotic management. Little evidence exists to aid such decisions, due to the exclusion of these patients from many clinical trials, with guidelines advocating conflicting DAPT durations and unclear bleeding risk definitions ([53,54](#)). Due to rapid fibro-intimal tissue proliferation, the risk of ST after implantation of a BMS is largely limited to the first month after implantation. The need for a very short course of DAPT (30 days followed by long-term aspirin) has led operators to often prefer BMS to DES for such patients ([54,55](#)). Presently, DES are assigned a Class III recommendation for patients who may not adhere to prolonged DAPT ([53](#)). In this context, in 2015, the LEADERS FREE (Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent Versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk) trial ([32](#)) showed a lower primary safety endpoint (a composite of cardiac death, MI, and ST: 9.4% vs. 12.9%; $p < 0.001$ for non-inferiority, $p = 0.005$ for superiority) and a better primary efficacy endpoint (clinically driven TLR: 5.1% vs. 9.8%; $p < 0.001$) with the use of the BA9-coated stent compared with a BMS (the Gazelle stent, Biosensors Interventional

Technologies) at the 390-day follow-up in 2,466 patients at high bleeding risk treated with a short duration (30 days) of DAPT. The study clearly addressed a high bleeding risk population, including patients ≥ 75 years of age and/or those with comorbidities, such as renal failure and/or on

FIGURE 3 Reasons for BMS Rather Than DES Use

Main reasons for BMS use, as investigated by a recent observational study in a cohort of 774 consecutive patients with coronary artery disease undergoing PCI at 31 European centers over a period of 2 months in 2012. Adapted with permission from Morice *et al.* ([48](#)). DAPT = dual antiplatelet therapy; MI = myocardial infarction; other abbreviations as in [Figure 1](#).

CENTRAL ILLUSTRATION Stent Selection in Special-Risk Patients: A Decision Tree



Colombo, A. et al. *J Am Coll Cardiol.* 2017;70(5):607-19.

Drug-eluting stents (DES) should be considered our routine choice in patients who tolerate dual-antiplatelet therapy (DAPT) for at least 3 months. In patients with a high bleeding risk, when DAPT is contraindicated, or in patients with a high risk of DAPT discontinuation within 30 days from stenting, bare-metal stents (BMS) should be the preferred type of stent. In patients with high risk of DAPT discontinuation between the first and the third month due to high bleeding risk, BMS should be preferred if the biolimus A9 (BA9)-coated stent is not available. If the BA9-coated stent is available, the choice should be made according to vessel size and lesion length, and mainly according to the risk of earlier or later DAPT discontinuation within the 3-month window. In patients who need surgery within 30 days from the stenting procedure, BMS should be preferred. When surgery is planned between the first and the third month after stenting, the choice between BMS and DES should be according to BA9-coated stent availability and the risk of restenosis as in patients at high bleeding risk. In patients with poor adherence to medical therapy, BMS should be preferred, especially when the coronary lesion appears to be at moderate-to-low risk for restenosis. In patients with atrial fibrillation on anticoagulant therapy, use of the BA9-coated stent and 1 month of DAPT should be considered. In patients at high bleeding risk, if the BA9-coated stent is not available, single antiplatelet therapy after DES is a reasonable alternative. BMS could be considered in coronary lesions at very low risk of restenosis (coronary vessel diameter ≥ 3.5 mm) in patients with a high bleeding risk profile. An additional pathway to be considered in the patient who has lesions at high risk for restenosis, and who really may benefit from a DES, is to perform transcatheter occlusion of the left atrial appendix and more safely continue DAPT. CABG = coronary artery bypass graft; LAA = left atrial appendage.

oral anticoagulant therapy, or with other known bleeding risk factors. A substudy of the same trial, involving 659 patients presenting with acute coronary syndrome, reported that the BA9-coated

stent was both safer in terms of cardiac mortality (3.4% vs. 6.9%; $p = 0.0490$) and MI (6.9% vs. 13.8%; $p = 0.005$) and more efficacious than BMS in terms of clinically driven TLR (3.9% vs. 9.0%;

TABLE 1 Main Trials Comparing BMS and DES in Patients With High Bleeding Risk

Study	Design (DAPT Duration)	Patients (n)	Primary Safety Endpoints (Follow-Up)	Primary Efficacy Endpoints (Follow-Up)	Primary Safety Endpoints Failure (Follow-Up)	Primary Efficacy Endpoints Failure (Follow-Up)	Ref. #
1 LEADERS FREE (prospective, randomized, double-blinded)	BioFreedom (umirolimus) vs. Gazele (BMS) (1 month DAPT)	2,466	1. Cardiac death 2. MI 3. ST (390 days follow-up)	Clinically driven TLR (390 days follow-up)	DES: n = 112 (9.4%) at 390 days BMS: n = 154 (12.9%) at 390 days	DES: n = 59 (5.1%) TVR at 390 days BMS: n = 113 (9.8%) TVR at 390 days	(54)
2 ZEUS (prospective, randomized, multinational, single-blinded)	Endeavor (ZES) vs. thin-strut ($\leq 100 \mu\text{m}$) BMS, in uncertain candidates for DES (1 month DAPT)	1,606	1. Cardiac death 2. MI 3. ST (1 yr follow-up)	Clinically driven TLR (1 yr follow-up)	DES: n = 140 (17.5%), of whom 2.9% had MI and 2.0% ST at 1 yr BMS: n = 178 (22.1%), of whom 8.1% had MI and 4.1% ST at 1 yr	DES: 5.9% TVR at 1 yr BMS: 10.7% TVR at 1 yr	(57)

BMS = bare-metal stent(s); DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); LEADERS FREE = Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent Versus the Gazele Bare-Metal Stent in Patients at High Bleeding Risk trial; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; ZES = zotarolimus-eluting stent; ZEUS = Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates.

$p = 0.009$) (56). Two-year outcomes of the LEADERS FREE trial showed the safety and efficacy of the BA9-coated stent over BMS was maintained over time (primary safety endpoint: 12.6% vs. 15.3%; $p = 0.039$ along with the primary efficacy endpoint: 6.8% vs. 12.0%; $p < 0.0001$) (57). Whether the observed favorable clinical results with the BA9-coated stent are transferrable to other polymer-free DES, DES with bioresorbable polymers, or DES with permanent polymers considered “less thrombogenic polymers” is still open to debate. Moreover, despite all the positive features of the BA9-coated stent, we should be aware that very complex anatomy may make delivery of this device difficult, and a new-generation BMS should be available as a bailout. The ZEUS (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates) trial (58) reported favorable results in patients with high bleeding, high thrombosis risk (such as cancer, or allergy to aspirin or P2Y₁₂ inhibitors), or low restenosis risk (such as no planned stent with a diameter < 3.0 mm) and receiving a zotarolimus-eluting stent (Endeavor Drug-Eluting Stent System, Medtronic Vascular, Minneapolis, Minnesota), compared with those receiving BMS. In this study, DAPT duration was on the basis of patient characteristics, rather than stent characteristics, and allowed for a personalized 1-month DAPT. However, the zotarolimus-eluting stent used in this study is no longer available. The more biocompatible polymer and the thinner stent struts of the new-generation Resolute family (Medtronic) may confer additional protection. From a practical

point of view, when DAPT is contraindicated or in patients with a high risk of DAPT discontinuation within 30 days of stenting, the indication and modality of coronary revascularization should be critically re-evaluated, and, when PCI is thought to be necessary, BMS should be preferred. Furthermore, in patients, who due to a high bleeding risk, have a high risk of discontinuing DAPT between the first and the third month, BMS should be the preferred choice if the BA9-coated stent is not available. If available, the choice between the BA9-coated stent and BMS should be made according to vessel size and lesion length (known risk factors for stent restenosis), and primarily considering the risk of earlier versus later DAPT discontinuation. Moreover, we strongly recommend the use of intracoronary imaging guidance to optimize stent implantation (and fast strut coverage) in all cases of high bleeding risk and probable early DAPT discontinuation, given the evidence of higher ST rates in high bleeding risk patients and the fact that optimal stent deployment is a protective factor against ST.

3. Planned noncardiac surgery. A common cause of DAPT discontinuation in patients following PCI is the need for noncardiac surgery within 6 weeks from BMS or 6 to 12 months from DES deployment (59), with the most critical period for adverse events, such as ST, MI, or death, when surgery needs to be undertaken within 6 weeks from stent implantation (60-62). In the absence of prospective randomized studies, the issue remains open. If the problem of possible urgent surgery following coronary revascularization is known before the

revascularization procedure, the operator should also consider plain balloon angioplasty or coronary artery bypass graft. When the patient requires PCI, we suggest BMS when surgery needs to be undertaken urgently (within 30 days or even <15 days from the stenting procedure). Indeed, although only 1 study has been conducted to demonstrate the safety of BMS with DAPT duration <15 days (63), there is a rationale for believing that endothelialization should be faster when no antiproliferative compound is present on the stent (64,65). In patients with surgery planned between the first and the third month, the choice between BMS and DES should be done according to BA9-coated stent availability and the risk of restenosis as discussed in high bleeding risk patients. For patients who need urgent neurosurgery, PCI should be performed only with balloons, using BMS for flow-limiting dissections, and elective coronary artery bypass graft should be considered. Moreover, the decision on stopping 1 or both antiplatelet agents before urgent surgery after stenting needs to be individualized taking into account: type of stent implanted; timing of surgery from stenting; risk profile of the patient for thrombotic events; and type of surgery and specific discussion with the surgeon.

4. The patient is known or suspected to have poor adherence to DAPT. Poor adherence to DAPT is important, but frequently overlooked. Psychological, social, and socioeconomic factors can decrease adherence to medical therapy and the interventionist needs to take these factors into account when choosing the stent to implant. Indeed, when dealing with suspected poor adherence to medical therapy, and when the patient does not have any insurance coverage, plain balloon angioplasty or coronary artery bypass graft should be considered. When PCI is required, the selection of a BMS, especially in case of lesions with moderate-to-low risk for restenosis, is an appropriate choice.
5. Atrial fibrillation. Approximately 10% to 15% of patients who undergo PCI have atrial fibrillation (66). It is well known that the risk of bleeding increases when aspirin, clopidogrel, or both are added to oral anticoagulant agents (OAC) (67). The goal is to shorten the duration of DAPT as much as possible, or to use a single antiplatelet agent. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) study (68) was the first randomized clinical trial to evaluate the

possibility of reducing the risk of bleeding in patients receiving OAC and undergoing PCI. A total of 573 patients receiving OAC (~70% due to atrial fibrillation) were randomly assigned to clopidogrel alone (experimental treatment) or clopidogrel and aspirin (control treatment) for a period of 1 month after BMS and 12 months after DES implantation. The primary endpoint, Thrombolysis In Myocardial Infarction (TIMI) flow grade bleeding, was significantly lower in the dual therapy group (even if there was no difference in terms of major bleeding), without an increase in MI, target vessel revascularization (TVR), stroke, or ST. Although the study supports the possible safety of single antiplatelet therapy on top of OAC when DES have been implanted, this was a single study with a relatively small number of patients, and a definite conclusion is still pending regarding the real safety of a single antiplatelet agent. Additional data comes from the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) trial (69). Patients with atrial fibrillation undergoing PCI with stent placement (both DES or BMS), were randomized to a low dose of rivaroxaban (15 mg/day) plus a single P2Y₁₂ inhibitor, or very low dose (2.5 mg twice a day) rivaroxaban plus DAPT, or vitamin K antagonists and DAPT (standard triple therapy). Rivaroxaban with single antiplatelet therapy or with DAPT was associated with a lower risk of clinically significant bleeding than standard triple therapy.

In selection of the type of stent for patients with atrial fibrillation, it is important to remember that the risk of ST is highest in the early phase after stent implantation and declines over time (70). In contrast, the risk of bleeding stays constant over the duration of therapy (71). The notion that ST may be higher following implantation with BMS versus DES is likely a consequence of selection bias, considering that older patients with more comorbidities and higher bleeding risk are usually treated with BMS, rather than with DES. Even carefully done propensity matching has limitations. In an analysis of the 929 patients in the prospective AFCAS (Atrial Fibrillation undergoing Coronary Artery Stenting) registry, the largest observational study of patients receiving triple therapy, 673 patients (72.4%) received BMS and 220 (23.7%) received at least 1 DES (72). At the

TABLE 2 Main Trials Comparing BMS and DES in Large Coronary Arteries

Study	Design (DAPT Duration)	Patients (n)	Primary Safety Endpoints (Follow-Up)	Primary Efficacy Endpoints (Follow-Up)	Primary Safety Endpoints Failure (Follow-Up)	Primary Efficacy Endpoints Failure (Follow-Up)	Ref. #
1 BASKET (prospective, randomized, double-blinded)	Cypher/Taxus vs. Vision (BMS): evaluation of cost-effectiveness. (6 months DAPT)	826	1. Cardiac death 2. MI 3. TVR (6 months follow-up)	Cost-effectiveness (6 months f-up)	DES: 39 of 544 patients (7.2%) at 6 months BMS: 34 of 280 patients (12.1%) at 6 months	DES: mean \$10,544 at 6 months follow-up BMS: mean \$9,639 at 6 months follow-up	(74)
2 BASKET-PROVE (prospective, randomized, multinational, double-blinded)	Cypher (sirolimus), Xience (everolimus), or Vision (BMS) ≥ 3 mm stents (12 months DAPT)	2,314	1. Cardiac death 2. MI (2 yrs follow-up)	TVR (2 yrs f-up)	Cypher: 2.6% of patients at 2 yrs Xience: 3.2% of patients at 2 yrs Vision: 4.8 of patients at 2 yrs	Cypher: 3.7% of patients at 2 yrs Xience: 3.1% of patients at 2 yrs Vision: 4.8% of patients at 2 yrs	(76)

BASKET = Basel Stent Kosten Effektivitäts trial; BASKET-PROVE = Evaluation of Late Clinical Events After Drug-Eluting Versus Bare-Metal Stents in Patients at Risk: Basel Stent Kosten Effektivitäts Trial—Prospective Validation Examination; other abbreviations as in Table 1.

12-month follow-up, the rates of major adverse cardiac and cerebrovascular events and total bleeding events were comparable between the 2 groups (22.0% with BMS vs. 19.5% with DES; $p = 0.51$, and 19.5% vs. 15.0%, respectively; $p = 0.16$). Definite/probable ST was more frequent in the BMS group (1.9% vs. 0%; $p = 0.046$). Selection bias and play of chance should be considered.

The availability of BA9-coated stents is a very useful alternative to consider in patients with atrial fibrillation. The possibility of continuing triple therapy for only 1 month after DES is a very reasonable alternative. Therefore, the role of BMS in these situations remains very limited, and probably almost absent. Our suggestion is to consider BMS in large vessels and short lesions when the patient is at high bleeding risk and is known to have atrial fibrillation requiring anticoagulant therapy, in addition to antiplatelet treatment, and when a polymer-free stent is not available. In patients with lesions at high risk for restenosis who may really benefit from a DES, an additional pathway to consider is performing transcatheter occlusion of the left atrial appendix and more safely continuing DAPT.

SITUATIONS WHERE A BMS WAS AN ACCEPTABLE ALTERNATIVE TO A DES: NOT ANYMORE!

1. Large coronary arteries (Table 2). With BMS, there should theoretically be an inverse relationship between vessel size and the incidence of adverse clinical outcomes after PCI (73), as given a similar degree of neointimal hyperplasia, a larger reference vessel size would be associated with a relatively lower rate of restenosis and events. A subgroup analysis of the BASKET (Basel Stent

Kosten Effektivitäts) trial (74) on patients with coronary arteries ≥ 3.0 mm in diameter revealed an increased rate of death or MI in those receiving first-generation DES, with no benefit in TVR reduction with DES compared with BMS. Moreover, ST occurred more frequently at 6 months after DES implantation, and death/MI beyond 6 months also increased in this group (9.1 vs. 3.8%; $p = 0.009$) (75). However, in the BASKET-PROVE (Basel Stent Kosten Effektivitäts Trial—Prospective Validation Examination), including patients requiring stents ≥ 3.0 mm in diameter, TVR was significantly reduced in the DES group during the 2-year follow-up period (sirolimus-eluting stents: 3.7% everolimus-eluting stents [EES]: 3.1%, BMS: 8.9%; $p < 0.001$), without significant differences in death, MI, or ST between the groups (76). Crucially, DAPT duration was 6 months in BASKET and 12 months in BASKET-PROVE, which might explain the different results.

2. ST-segment elevation MI (Table 3). Previous concerns related to the higher ST rate with first-generation DES use in ST-segment elevation MI have not been borne out in studies with new-generation DES (20,77). In the EXAMINATION (Everolimus-Eluting Stent vs. BMS in ST-Segment Elevation Myocardial Infarction) trial (77), EES treatment was associated with a lower 5-year rate of the composite primary endpoint of all-cause death, any MI, or any revascularization, as compared with BMS (21% vs. 26%; $p = 0.033$). COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) (20) showed that patients treated with biopolymer DES, compared with those receiving BMS, had a lower risk of the composite primary

TABLE 3 Main Trials Comparing BMS and DES in STEMI

Study	Design (DAPT Duration)	Patients (n)	Primary Safety Endpoints (Follow-Up)	Primary Efficacy Endpoints (Follow-Up)	Primary Safety Endpoints Failure (Follow-Up)	Primary Efficacy Endpoints Failure (Follow-Up)	Ref. #
1 EXAMINATION (prospective, randomized, multinational, single-blinded)	Xience-V vs. cobalt-chromium BMS in STEMI (1 yr DAPT)	1,498	1. All-cause death 2. MI 3. Any revascularization (5 yrs follow-up)	—	EES: n = 159 (21%) at 5 yrs BMS: n = 192 (26%) at 5 yrs		(77)
2 COMFORTABLE AMI (Prospective, randomized, multinational, single-blinded)	BioMatrix (biolimus) vs. Gazelle (BMS) in STEMI (1 yr DAPT)	1,161	1. Cardiac death 2. Target vessel MI (1 yr follow-up)	TLR (1-yr f-up)	DES: 1. CD: 2.9% 2. TVMI: 0.5% DES: total of 4.3% patients at 1 yr BMS: 1. CD: 3.5% 2. TVMI: 2.7% BMS: total of 8.7% patients at 1 yr	DES: TLR: 1.6% patients at 1 yr BMS: TLR 5.7% patients at 1 yr	(20)

CD = cardiac death; COMFORTABLE AMI = Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction trial; EES = everolimus-eluting stent; EXAMINATION = Everolimus-Eluting Stent vs. BMS in ST-Segment Elevation Myocardial Infarction trial; STEMI = ST-segment elevation myocardial infarction; TVMI = target vessel-related reinfarction; other abbreviations as in Table 1.

endpoint of cardiac death, target vessel MI, and TLR (4.3% vs. 8.7%; $p = 0.004$), and a lower risk of target vessel MI (0.5% vs. 2.7%; $p = 0.01$). A further pooled analysis demonstrated a lower risk of ST and reinfarction with DES than with BMS (78). We currently privilege DES for primary PCI, reserving BMS for patients at high risk of bleeding or poor adherence to DAPT. The role of polymer-free DES have not been evaluated in ST-segment elevation MI.

3. Saphenous vein grafts (Table 4). Percutaneous intervention of saphenous vein grafts is associated with higher early and late complications and worse outcomes compared with native coronary artery intervention (79). The superiority of DES over BMS in saphenous vein graft intervention has been challenged in some studies (80-82). A recent meta-analysis (83) from 5 randomized controlled trials comparing BMS with first-generation DES (84-88) showed significantly lower TVR and a trend toward reduction in major adverse cardiac event rate with DES. However, there were no significant differences in cardiovascular mortality, all-cause mortality, MI, or ST. Additionally, as newer DES are superior to older ones, in terms of efficacy and safety, there is no reason to justify the use of BMS in this setting.
4. Stent cost. A number of studies on cost-effectiveness suggested that beneficial effects and cost could be balanced by limiting use of first-generation DES to patients at increased risk of restenosis (89-92), with only a small impact on the risk of repeat revascularization procedures (89,90). However, the reduction in cost from the first, somewhat expensive DES to the last-generation

DES, combined with improvements in safety, long-term coronary effects, and medical care with antiplatelet treatments, have modified the risk-benefit ratio and cost-effectiveness (91,93). Therefore, stent cost does not justify the use of BMS over DES.

Additional settings where the use of BMS should be routinely limited include chronic total occlusions, bifurcations requiring more than 1 stent, and left main disease, unless the vessel diameter is ≥ 3.5 mm and the lesion is short in a patient at high bleeding risk.

INSIGHTS FROM NORSTENT

The lack of a head-to-head comparison between contemporary DES and BMS led the NORSTENT (Norwegian Coronary Stent Trial) investigators to design the largest randomized controlled trial to compare the latest-generation DES and BMS (Table 5) (94). Exclusion criteria were previous treatment with coronary stent, bifurcation lesion requiring treatment with a 2-stent technique, life expectancy <5 years, and contraindication to DAPT. Patients were randomized to receive contemporary DES (82.9% were EES and 13.1% zotarolimus-eluting stent) or contemporary BMS (primarily the Driver [Medtronic CardioVascular, Santa Rosa, California], Integrity [Medtronic, Minneapolis, Minnesota], Liberté [Boston Scientific, Natick, Massachusetts], or Multi-Link Vision [Abbott Vascular, Santa Clara, California]). All patients in both groups were treated with DAPT for 9 months after the procedure, regardless of the randomized assignment or the indication for PCI. After a median follow-up of 6 years, there were no

TABLE 4 Main Trials Comparing BMS and DES in SVG

Study	Design (DAPT Duration)	Patients (n)	Primary Safety Endpoints (Follow-Up)	Primary Efficacy Endpoints (Follow-Up)	Primary Safety Endpoints Failure (Follow-Up)	Primary Efficacy Endpoints Failure (Follow-Up)	Ref. #
1 BASKET-SAVAGE (prospective, RCT)	Taxus Liberté (paclitaxel) vs. Liberté (BMS) in SVG (1 yr DAPT)	173	1. Cardiac death 2. Nonfatal AMI 3. TVR (1 yr follow-up)	TVR	DES: 2.3% of patients at 1 yr follow-up BMS: 17.9% of patients at 1 yr follow-up	DES: 0% of patients at 1 yr follow-up BMS: 11.9% of patients at 1 yr follow-up	(84)
2 ISAR-CABG (prospective, randomized superiority trial)	Cypher (sirolimus), Taxus (paclitaxel), Yukon Choice PC (biodegradable, sirolimus) vs. BMS in SVG patients (1 yr DAPT)	610	1. Death (all causes) 2. MI 3. TLR (1 yr follow-up)		DES: n = 44 (15%) at 1 yr follow-up 1. 15 (5%) died 2. 12 (4%) had AMI 3. 19 (7%) had TLR BMS: 66 patients (22%) at 1 yr follow-up 1. 14 (5%) died 2. 18 (6%) had AMI 3. 37(13%) had TLR		(86)
3 DELAYED RRISC (prospective, randomized single-blinded)	Cypher (sirolimus) vs. BMS in SVG patients at long-term (32-36 months) follow-up (6 months DAPT)	75	1. All-cause mortality 2. MACE: • Cardiac death • MI • TVR (32-36 months follow-up)		DES: 1. 11 deaths (29%), 7 were cardiac deaths; 2. 1 nonfatal AMI at 32 months follow-up 3. 5 (13%) documented ST BMS: 1. 0 deaths (0%) at 32 months follow-up 2. No nonfatal AMI at 32 months follow-up 3. No documented ST		(87)
4 SOS (prospective, multicenter RCT)	Taxus (paclitaxel) vs. Express2 (BMS) in SVG (BMS: 1 month; DES: 6 months; 1 yr DAPT for both since 2006)	80	Binary angiographic ISR, assessed by quantitative coronary angiography (12 months follow-up)		DES: • 9% binary angiographic restenosis • 5% TLR and 15% TVR • 22% target vessel failure • 12% mortality BMS: • 51% binary angiographic restenosis • 28% TLR and 31% TVR • 46% target vessel failure • 5% mortality		(88)

AMI = acute myocardial infarction; BASKET-SAVAGE = Basel Kosten Effektivitäts Trial-Saphenous Venous Graft Angioplasty Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents; DELAYED RRISC = Death and Events at Long-Term Follow-Up Analysis: Extended Duration of the Reduction of Restenosis in Saphenous Vein Grafts With Cypher Stent; ISAR-CABG = Is Drug-Eluting-Stenting Associated With Improved Results in Coronary Artery Bypass Grafts?; ISR = in-stent restenosis; MACE = major adverse cardiac event; RCT = randomized controlled trial; SOS = Stenting of Saphenous Vein Grafts; SVG = saphenous venous graft; other abbreviations as in Table 1.

between-group differences in either the primary composite endpoint of death and nonfatal, spontaneous MI (16.6% in DES group vs. 17.1% in BMS group; $p = 0.66$) or in the individual primary endpoint components (7.5% vs. 7.4% for death; $p = 0.21$; 9.8% vs. 10.5% for nonfatal/spontaneous MI; $p = 0.10$). No differences were found in secondary outcomes, including subcategories of deaths of specific cause, stroke, hospitalization for unstable angina, major bleeding episodes, and health-related quality of life.

As expected, BMS recipients experienced a significantly higher rate of repeat revascularization compared with DES recipients (19.8% vs. 16.5%; $p < 0.001$), particularly with regard to TLR (10.3% to 5.3%; $p < 0.001$). Interestingly, the late ST rate was only marginally in favor of DES treatment (0.8% vs. 1.2%; $p = 0.0498$).

The finding that no difference between DES and BMS was observed in the primary composite endpoint of all cause death/spontaneous MI after a median

TABLE 5 Main Trial Comparing New-Generation BMS to New-Generation DES

Study	Design (DAPT Duration)	Patients (n)	Primary Safety Endpoints (Follow-Up)	Primary Efficacy Endpoints (Follow-Up)	Primary Safety Endpoints Failure (Follow-Up)	Primary Efficacy Endpoints Failure (Follow-Up)	Ref. #
1 NORSTENT (prospective, randomized, single-blinded)	Contemporary DES vs. contemporary BMS (9 months DAPT)	9,013	1. All-cause death 2. MI (6 yrs follow-up)	1. RR 2. ST (6 yrs follow-up)	DES: 16.6% patients at 6 yrs follow-up	DES: 1. 16.5% RR 2. 0.8% ST at 6 yrs follow-up	(94)

NORSTENT = Norwegian Coronary Stent Trial; RR = repeat revascularization; other abbreviations as in Table 1.

follow-up of 5 years, should not come as a surprise, given that stents have not been shown to affect survival. This confirms that second-generation DES do what they are designed for: they reduce the need for revascularization and are still safe in terms of ST events. Moreover, the fact that the rate of ST following BMS was 1.2% versus 0.8% following DES implantation in the NORSTENT trial, casts doubts on the increased thrombogenicity of DES. Nevertheless, we cannot assume that the same would happen following early discontinuation of DAPT, which is the main situation where BMS may be justified.

CONCLUSIONS

A large body of evidence has demonstrated a significant improvement in coronary stent safety and efficacy with device evolution. The outcomes observed with second-generation DES make them the preferred devices in the majority of clinical situations, taking into account recent recommendations on shorter DAPT duration. However, even in the second- and

third-generation DES era, BMS remains an option for PCI, especially in patients who cannot complete the recommended duration of DAPT because of noncompliance, the need for noncardiac surgery, or increased risk for bleeding, especially if the culprit lesion is present in large coronary vessels. The recent availability (outside of the United States) of polymer-free DES has narrowed the area where a BMS may be needed.

As we await further technological advancement and data to support routine DAPT for 30 days following DES implantation, BMS should still be available in the catheterization laboratory and play a role in facilitating the optimal management of every patient presenting to the interventional cardiologist.

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REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al., for the RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346:1773-80.
2. Moses JW, Leon MB, Popma JJ, et al., for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349: 1315-23.
3. Stone GW, Ellis SG, Cox DA, et al., for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
4. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.
5. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006;27: 2784-814.
6. Lagerqvist B, Carlsson J, Fröbert O, et al., for the Swedish Coronary Angiography and Angioplasty Registry Study Group. Stent thrombosis in Sweden: a report from the Swedish Coronary Angiography and Angioplasty Registry. *Circ Cardiovasc Interv* 2009;2:401-8.
7. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007;115:1440-55.
8. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. *Circulation* 2007;115: 2352-7.
9. Lüscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007;115:1051-8.
10. Byrne RA, Kastrati A. Duration of antiplatelet therapy following intracoronary stenting: are changes needed? *Eur Heart J Suppl* 2008;10: 125-9.
11. Kereiakes DJ, Cox DA, Hermiller JB, et al., for the Guidant Multi-Link Vision Stent Registry Investigators. Usefulness of a cobalt chromium coronary stent alloy. *Am J Cardiol* 2003;92:463-6.
12. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO-2) trial. *J Am Coll Cardiol* 2003;41: 1283-8.
13. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 2007;50:1373-80.
14. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol* 2008;52:333-42.
15. Kang SH, Chae IH, Park JJ, et al. Stent thrombosis with drug-eluting stents and bioresorbable scaffolds: evidence from a network meta-analysis of 147 trials. *J Am Coll Cardiol Interv* 2016;9:1203-12.
16. Kollandaivelu K, Swaminathan R, Gibson WJ. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;123:1400-9.
17. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real life practice (COMPARE): a randomised trial. *Lancet* 2010;375: 201-9.
18. Stone GW, Rizvi A, Newman W, et al., for the SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 2010;362:1663-74.
19. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer sirolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;378:1940-8.
20. Räber L, Kelbæk H, Ostojic M, et al., for the COMFORTABLE AMI Trial Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 2012;308:777-87.
21. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient years of follow-up from randomized trials. *Circulation* 2012;125:2873-91.
22. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and

- bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;379:1393-402.
23. Bangalore S, Toklu B, Amoroso N, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 2013;347:f6625.
 24. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J* 2012;33:1214-22.
 25. Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 2014;348:g3859.
 26. Räber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation* 2012;125:1110-21.
 27. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *J Am Coll Cardiol Interv* 2013;6:1267-74.
 28. Sarno G, Lagerqvist B, Fröbert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012;33:606-13.
 29. Briguori C, Sarais C, Pagnotta P, et al. In-stent restenosis in small coronary arteries: impact of strut thickness. *J Am Coll Cardiol* 2002;40:403-9.
 30. Sketch MH Jr., Ball M, Rutherford B, et al., for the Driver Investigators. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. *Am J Cardiol* 2005;95:8-12.
 31. Bangalore S, Gupta N, Guo Y, Feit F. Trend in the use of drug eluting stents in the United States: insight from over 8.1 million coronary interventions. *Int J Cardiol* 2014;175:108-19.
 32. Urban P, Meredith IT, Abizaid A, et al., for the LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med* 2015;373:2038-47.
 33. Rudolph A, Teske M, Illner S, et al. Surface modification of biodegradable polymers towards better biocompatibility and lower thrombogenicity. *PLoS One* 2014;10:e0142075.
 34. Magalhaes MA, Minha S, Chen F, et al. Clinical presentation and outcomes of coronary in-stent restenosis across 3-stent generations. *Circ Cardiovasc Interv* 2014;7:768-76.
 35. Koppa T, Cheng Q, Yahagi K, et al. Thrombogenicity and early vascular healing response in metallic biodegradable polymer-based and fully bioabsorbable drug-eluting stents. *Circ Cardiovasc Interv* 2015;8:e002427.
 36. Eppihimer MJ, Sushkova N, Grimsby JL, et al. Impact of stent surface on thrombogenicity and vascular healing: a comparative analysis of metallic and polymeric surface. *Circ Cardiovasc Interv* 2013;6:370-7.
 37. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006;48:193-202.
 38. Vorpahl M, Yazdani SK, Nakano M, et al. Pathobiology of stent thrombosis after drug-eluting stent implantation. *Curr Pharm Des* 2010;16:4064-71.
 39. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006;151:1260-4.
 40. Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125:505-13.
 41. Colombo A, Chieffo A, Frasieri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;64:2086-97.
 42. Schulz-Schüpke S, Byrne RA, Ten Berg JM, et al., for the ISAR-SAFE Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 2015;36:1252-63.
 43. Kim BK, Hong MK, Shin DH, et al., for the RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60:1340-8.
 44. Feres F, Costa RA, Abizaid A, et al., for the OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;310:2510-22.
 45. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014;63:2659-73.
 46. Rymer JA, Harrison RW, Dai D, et al. Trends in bare-metal stent use in the United States in patients aged ≥ 65 years (from the CathPCI Registry). *Am J Cardiol* 2016;118:959-66.
 47. Go AS, Mozaffarian D, Roger VL, et al., for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6-245 [Published correction appears in *Circulation* 2013;127:e841.].
 48. Morice MC, Urban P, Greene S, Schuler G, Chevalier B. Why are we still using coronary bare-metal stents? *J Am Coll Cardiol* 2013;61:1122-3.
 49. Costa F, van Klaveren D, James S, et al., for the PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025-34.
 50. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;67:2224-34.
 51. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 2009;119:1873-82.
 52. Yeh RW, Secemsky EA, Kereiakes DJ, et al., for the DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735-49 [Published correction appears in *JAMA* 2016;316:350].
 53. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122.
 54. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2014;35:2541-619.
 55. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082-115.
 56. Naber CK, Urban P, Ong PJ, et al., for the LEADERS FREE Investigators. Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a Leaders Free ACS sub-study. *Eur Heart J* 2017;38:961-9.
 57. Garot P, Morice MC, Tresukosol D, et al., for the LEADERS FREE Investigators. 2-year outcomes of high bleeding risk patients after polymer-free drug-coated stents. *J Am Coll Cardiol* 2017;69:162-71.
 58. Valgimigli M, Patialiakas A, Thury A, et al., for the ZEUS Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol* 2015;65:805-15.
 59. Hawn MT, Graham LA, Richman JR, et al. The incidence and timing of noncardiac surgery after cardiac stent implantation. *J Am Coll Surg* 2012;214:658-66; discussion 666-7.
 60. Benerjee S, Angiolillo DJ, Boden WE, et al. Use of antiplatelet therapy/DAPT for post-PCI patients undergoing noncardiac surgery. *J Am Coll Cardiol* 2017;69:1861-70.

61. Cruden NL, Harding SA, Flapan AD, et al., for the Scottish Coronary Revascularisation Register Steering Committee. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ Cardiovasc Interv* 2010;3:236-42.
62. To AC, Armstrong G, Zeng I, Webster MW. Noncardiac surgery and bleeding after percutaneous coronary intervention. *Circ Cardiovasc Interv* 2009;2:213-21.
63. Berger PB, Bell MR, Hasdai D, Grill DE, Melby S, Holmes DR Jr. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999;99:248-53.
64. Xie Y, Takano M, Murakami D, et al. Comparison of neointimal coverage by optical coherence tomography of a sirolimus-eluting stent versus a bare-metal stent three months after implantation. *Am J Cardiol* 2008;102:27-31.
65. Chen BX, Ma FY, Luo W, et al. Neointimal coverage of bare-metal and sirolimus-eluting stents evaluated with optical coherence tomography. *Heart* 2008;94:566-70.
66. Sutton NR, Seth M, Ruwende C, Gurm HS. Outcomes of patients with atrial fibrillation undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2016;68:895-904.
67. Capodanno D, Lip GY, Windecker S, et al. Triple antithrombotic therapy in atrial fibrillation patients with acute coronary syndromes or undergoing percutaneous coronary intervention or transcatheter aortic valve replacement. *Euro-Intervention* 2015;10:1015-21.
68. Dewilde WJ, Oirbans T, Verheugt FW, et al., for the WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial. *Lancet* 2013;381:1107-15.
69. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-34.
70. Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J* 2009;30:2714-21.
71. Lamberts M, Olesen JB, Ruwald MH, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2012;126:1185-93.
72. Kiviniemi T, Puurunen M, Schlitt A, et al. Bare-metal vs. drug-eluting stents in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Circ J* 2014;78:2674-81.
73. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspective from multicenter clinical trials. *J Am Coll Cardiol* 2002;40:2082-9.
74. Kaiser C, Brunner-La Rocca HP, Buser PT, et al., for the BASKET Investigators. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitäts Trial (BASKET). *Lancet* 2005;366:921-9.
75. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, et al., for the BASKET Investigators. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice: does stent diameter matter? Three-year follow-up of BASKET. *Eur Heart J* 2009;30:16-24.
76. Kaiser C, Galatus S, Erne P, et al., for the BASKET-PROVE Study Group. Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med* 2010;363:2310-9.
77. Sabaté M, Brugaletta S, Quequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet* 2016;387:357-66.
78. Sabaté M, Räber L, Heg D, et al. Comparison of newer generation drug-eluting with bare-metal stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of the EXAMINATION (Clinical Evaluation of the Xience-V stent in Acute Myocardial Infarction) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials. *J Am Coll Cardiol Interv* 2014;7:55-63.
79. Brilakis ES, Rao SV, Banerjee S, et al. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients: a report from the National Cardiovascular Data Registry. *J Am Coll Cardiol Interv* 2011;4:844-50.
80. Wiisanen ME, Abdel-Latif A, Mukherjee D, Ziada KM. Drug-eluting stents versus bare-metal stents in saphenous vein graft interventions: a systematic review and meta-analysis. *J Am Coll Cardiol Interv* 2010;3:1262-73.
81. Paradis JM, Bélsisle P, Joseph L, et al. Drug-eluting or bare metal stents for the treatment of saphenous vein graft disease: a Bayesian meta-analysis. *Circ Cardiovasc Interv* 2010;3:565-76.
82. Hakeem A, Helmy T, Munsif S, et al. Safety and efficacy of drug eluting stents compared with bare metal stents for saphenous vein graft interventions: a comprehensive meta-analysis of randomized trials and observational studies comprising 7,994 patients. *Catheter Cardiovasc Interv* 2011;77:343-55.
83. Bavishi C, Chatterjee S, Stone GW. Does current evidence favor drug-eluting stents over bare-metal stents for saphenous venous grafts interventions? Insights from an updated meta-analysis of randomized controlled trials. *J Am Coll Cardiol Interv* 2016;9:2456-8.
84. Jeger RV, Farah A, Engström T, et al., for the BASKET-SAVAGE Investigators. Drug-eluting vs. bare metal stents in saphenous vein grafts: the prospective randomized BASKET-SAVAGE trial. Available at: https://www.escardio.org/static_file/Escardio/Press-media/Press%20releases/2016/ESC%20Congress/Hot%20Line%20-%20Coronary%20Artery%20Disease%20and%20Stenting/basket-savage.pdf. Accessed May 30, 2017.
85. Jeger RV, Schneider S, Kaiser C, et al., for the BASKET Investigators. Drug-eluting stents compared with bare metal stents improve late outcome after saphenous vein graft but not after large native vessel interventions. *Cardiology* 2009;112:49-55.
86. Mehilli J, Pache J, Abdel-Wahab M, et al., for the ISAR-CABG Investigators. Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. *Lancet* 2011;378:1071-8.
87. Vermeersch P, Agostoni P, Verheye S, et al., for the DELAYED RRISC Investigators. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC trial. *J Am Coll Cardiol* 2007;50:261-7.
88. Brilakis ES, Lichtenwalter C, de Lemos JA, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol* 2009;53:919-28.
89. Amin AP, Spertus JA, Cohen DJ, et al. Use of drug-eluting stents as a function of predicted benefit: clinical and economic implications of current practice. *Arch Intern Med* 2012;172:1145-52.
90. Venkitachalam L, Lei Y, Stolker JM, et al., for the EVENT Registry Investigators. Clinical and economic outcomes of liberal versus selective drug-eluting stent use: insights from temporal analysis of the multicenter Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry. *Circulation* 2011;124:1028-37.
91. Schafer PE, Sacrinty MT, Cohen DJ, et al. Cost-effectiveness of drug-eluting stents versus bare metal stents in clinical practice. *Circ Cardiovasc Qual Outcomes* 2011;4:408-15.
92. Amin AP, Reynolds MR, Lei Y, et al. Cost-effectiveness of everolimus- versus paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization (from the SPIRIT-IV Trial). *Am J Cardiol* 2012;110:765-70.
93. Baschet L, Bourguignon S, Marque S, et al. Cost-effectiveness of drug-eluting stents versus bare-metal stents in patients undergoing percutaneous coronary intervention. *Open Heart* 2016;3:e000445.
94. Bønaa KH, Mannsverk J, Wiseth R, et al., for the NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;375:1242-52.

KEY WORDS drug-eluting stent, dual antiplatelet therapy, high bleeding risk patients, in-stent restenosis, stent thrombogenicity, stent thrombosis