Stent Thrombosis After Percutaneous Coronary Intervention

From Bare-Metal to the Last Generation of Drug-Eluting Stents

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KEYWORDS

• BMS • DES • BRS • Thrombosis • Stent

KEY POINTS

- Although rare, thrombosis still remains a major complication after coronary stent implantation.
- Although the causes of stent thrombosis are multifactorial, the device-related mechanism is a key factor.
- Knowing the different characteristics of the stents is of paramount importance for choosing the most suitable stent for the specific patient in clinical practice.

INTRODUCTION

The introduction in clinical practice of coronary stents has set a milestone in the history of interventional cardiology. Developed to overcome the limitation of plain old balloon angioplasty (POBA), this technology over the years has become a standard of care in the treatment of coronary artery disease. The continuous technical evolution has brought several types of stents to cope with the increasing complexity of the lesions that currently are accessible to the percutaneous approach. Accordingly, being familiar with the technical features of each platform and its related safety and efficacy profile is becoming of paramount importance. Stent thrombosis (ST) is an uncommon but harmful complication of percutaneous coronary implantation (PCI), causing myocardial infarction in approximately 60% to 70% of the cases, and leading to an increased risk of mortality (20%–25%).[1] The type of stent implanted is a major factor in determining the risk of coronary ST.[2] Therefore, this review article describes evidence from clinical trials or observational studies on the coronary stent types used most often (**Fig. 1**) and their related risk of ST in the modern era of interventional cardiology.

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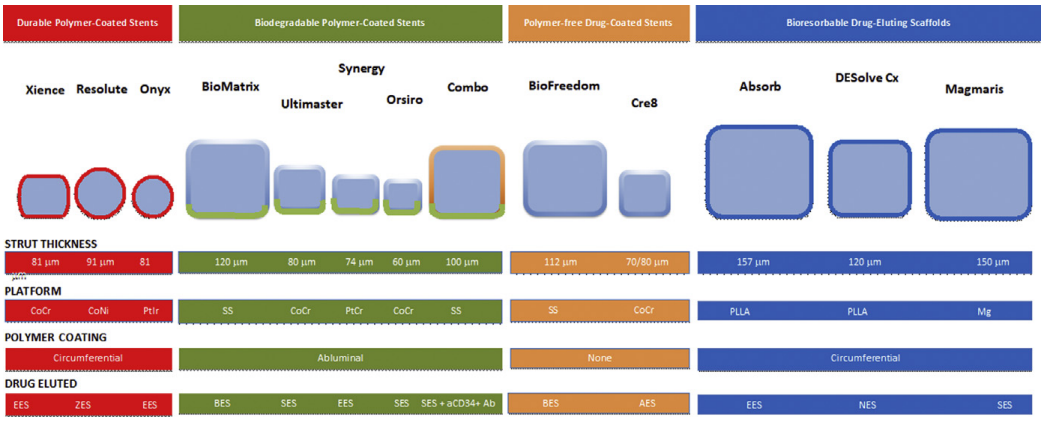

Fig. 1. Comparison of the main characteristics of different categories of coronary stent.

BARE-METAL STENT

Bare-metal stents (BMSs) have been developed to avoid elastic recoil and late vascular remodeling after POBA. Since their introduction in clinical practice in 1986 with the Wallstent (Schneider AG) and in 1987 with the first Food and Drug Administration–approved Palmaz-Schatz stent (Johnson & Johnson), BMSs progressively replaced POBA and became standard of care for PCI in the late 1990s. Despite the continuous improvement in stent technology, however, long-term follow-up revealed 20% to 30% incidence of in-stent restenosis (ISR).[3] The high rate of ISR observed with these platforms is caused by the proliferation and migration of vascular smooth muscle cells within stent struts, a phenomenon widely studied using in vitro and in vivo models.[4–7] The introduction in clinical practice of drug-eluting stents (DESs) to overcome this limitation led to progressive decline in the use of BMSs, with a significant reduction of ISR. Several studies and registries have shown that the rates of early ST between BMSs and first-generation DESs were quite similar[8]; the risk of very late ST (VLST) was surprisingly higher with DESs, thus becoming a concern for fast and generalized use of medicated platforms.[9] Characteristics and potential mechanisms underlying VLST differ significantly between BMS and DES platforms. In 61 patients with VLST, reported by Nakamura and colleagues,[10] using the optical coherence technique, the malapposed or uncovered strut and stent underexpansion were observed more frequently in DESs, whereas thin-cap fibroatheroma, neoatherosclerosis, and lipid neointima were observed more frequently in BMSs than in DESs.

Despite the improvement of implantation techniques and the introduction in clinical practice of the less thrombogenic second-generation DESs that ensure reasonable discontinuation of the dual antiplatelet therapy (DAPT),[11] the BMS has continued to be used for a long time, for those patients in whom a prolonged antithrombotic therapy did not ensure a reasonable risk-benefit tradeoff. The recently published Italian Multicenter Registry of Bare Metal Stent Use in Modern Percutaneous Coronary Intervention Era (AMARCORD) registry, including 58,879 patients undergoing PCI and stent implantation in 18 Italian sites, reported a progressive decrease in BMS use, from 10.1% in 2013% to 0.3%, in 2017. The main reasons for BMS implantation were ST-elevation myocardial infarction (STEMI) (23.1%), advanced age (24.4%), and physician perception of high bleeding risk (HBR) (34.0%). At a mean follow-up of 2.2 years ± 1.5 years, the rates of definitive ST were 2.3% (1.2% at 30 days and 1.9% at 1 year).[12] Several clinical trials and prospective studies have shown superiority of second-generation DESs compared with BMSs.

DURABLE POLYMER DRUG-ELUTING STENT

Evidence from post mortem pathology and intracoronary imaging supports the concept that the increased thrombosis observed in patients receiving first-generation DESs essentially was due to the fact that the cytotoxic drugs eluted by the stents inhibit not only the proliferation and migration of the vascular smooth muscle cells that are responsible for restenosis but also the growth and mobility of endothelial cells, fundamental for the healing of the vessel after the stent implantation.[13,14] Furthermore, first-generation DESs were coated with permanent polymers like methacrylate compounds that facilitate drug release but remain on the stent after drug elution, causing vascular inflammation, hypereosinophilia, and thrombogenic reactions.[15,16] The increased stent strut thickness that was necessary to warrant sufficient radial strength to first-generation DESs also has a major impact in thrombosis. Several studies demonstrated that thick-strutted stents

are more thrombogenic than comparable thin-strutted devices.[17]

The second-generation DESs were designed to overcome these safety issues, employing new and more biocompatible polymer coatings, less toxic antiproliferative drugs and thin-strut metal alloys. The introduction of cobalt chromium (CoCr), a more biocompatible material, increasingly is used in new-generation coronary stents. In comparison with stainless steel, CoCr has a higher radiopacity and radial strength. This allows for the production of thinner struts with a similar radiological visibility and radial strength. For all these reasons, the zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES) have demonstrated a decreased risk of late ST and very-late ST in comparison with old-generation DESs.

In the COMPARE trial, the rates of definite and probable ST were reduced significantly among EES compared with paclitaxel-eluting stent-treated patients (0.7% vs 2.6%, respectively; $P = .002$) at 12 months.[18] In recent work published by Tada and colleagues,[19] in unselected patients in a large German cohort, the cumulative incidence of definite ST at 3 years was 1.5% with the BMS, 2.2% with the first-generation DESs, and 1.0% with the second-generation DESs. The consistent superiority of newer-generation DESs also is demonstrated in meta-analyses, showing odds ratios between 0.31 and 0.56 for ST in different DES types compared with BMSs.[20] Furthermore, much evidence also supports second-generation DESs for those patients who historically have been treated with BMSs, because of low risk of ISR or high risk of early coronary thrombotic events (such as STEMI patients) or because of not tolerating a prolonged DAPT (such as HBR patients). In regard to STEMI patients, several clinical trials and observational registries have shown superiority of DESs over BMSs.[21,22] In a large pooled analysis, including 2665 patients enrolled in the Clinical Evaluation of the Xience-V stent in Acute Myocardial Infarction) (EXAMINATION) and Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE-AMI) trials, newer-generation DESs were associated with a significant reduction of 1-year definite ST (relative risk 0.35; 95% CI, 0.16–0.75; $P = .006$) compared with BMSs.[22]

For patients with large vessel diameter, BMSs seemed a reasonable option, because of the theoretically lower risk of developing a clinical overt ISR. Despite a similar risk of ST compared with DESs, BMSs have shown higher rates of stent failure. In a recently published post hoc analysis from the EXAMINATION trial, including 1498 patients with ST-segment elevated myocardial infarction undergoing primary PCI, despite no differences in terms of ST between groups, DES implantation was associated with a trend toward a reduction of the target lesion (hazard ratio [HR] 0.53; 95% CI, 0.27–1.02; $P = .05$) and target vessel revascularization (HR 0.60; 95% CI, 0.34–1.03; $P = .066$) in patients with larger vessel diameter.[23]

Finally, the perception of HBR has become the most frequent reason supporting BMS implantation in these last years. The rationale underlying this choice is the possibility of avoiding the prolonged antithrombotic therapy required to prevent the mild and long-term risk of ST observed with DESs.[24–27] Improvement in stent technology and implantation technique, however, significantly decreased such risk, thus supporting early DAPT discontinuation after DES implantation even for this subgroup of patients.[25] Several trials and prospective registries have shown the superiority of the second-generation DESs over BMSs under a mandated short DAPT period.[28,29]

Recently, the ZEUS study[30] showed that a treatment strategy consisting of ZES implantation followed by a personalized course of DAPT, resulted in a lower risk of major adverse cardiac events (MACEs) and definite or probable ST compared with BMSs (ST, 2.0% vs 4.1%, respectively; $P = .019$) in patients at HBR or thrombosis or at low risk of restenosis (no planned stent <3.0 mm diameter was intended to be implanted) at 1-year follow-up. Several studies recently have been published, or are ongoing, aiming at generalizing this concept to an even more larger types of DESs in HBR population, including the Xience Short DAPT programs (NCT03218787), the EVOLVE Short DAPT[31] (NCT02605447), the ONYX ONE[32] (NCT03344653), the POEM (NCT03112707), and MASTER DAPT[33] (NCT03023020) studies. The ONYX trial, randomizing either Resolute Onyx (Medtronic, CA, USA) DES (durable polymer [DP] DES) (n = 1003) or BioFreedom polymer-free [PF]-drug-coated stent (DCS) (n = 993) with 1-month DAPT, documented noninferiority of the DP-ZES compared with the BioFreedom DCS in the primary endpoint, including death from cardiac causes, myocardial infarction, or ST, with no differences in the rate of ST between groups (1.3% for the Onyx DES and 2.1% for the BMS).

Looking at the long-term performances of second-generation DESs in this high-risk population, in a pooled analysis from 4 all-comer postapproval registries that included 10,502 HBR patients who underwent PCI with CoCr-EES implantation, the 4-year rate of probable or definite ST was 1.5%.[34] Rates were similar to the ones

observed in other all-comers registries testing the long-term effectiveness of CoCr-EES. For example, the Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention (RESOLUTE) trial, randomizing patients to Resolute ZES (R-ZES) (n = 1140) or CoCr-EES (n = 1152), showed 1.6% and 2.3% of ST at 4 years of follow-up, respectively, in the EES and R-ZES groups.

BIORESORBABLE POLYMER DRUG-ELUTING STENT

Another direction to improve drug-carrier systems was the development of erodible polymers. Biodegradable polymers (BPs) remain temporary on the DES surface and have the potential to enhance biocompatibility and improve the delayed healing in the vessel. These stents use BPs that remain only temporarily on the DES surface and have the potential of less chronic vessel wall inflammation, similar to a BMS, as reported by Yin and colleagues.[35]

Long-term data, however, after implantation of newer generations of thin-strut BP-based DESs still are lacking. A meta-analysis by Cassese and colleagues[36] showed for the first time that the ultra–thin-strut BP–sirolimus-eluting stent (SES) displays a performance comparable to the DP-EES, the benchmark of contemporary DESs, also for ST (1.3% vs 1.9%; $P = .45$) at 1-year follow-up, and, more interestingly, there was no time-dependent risk of ST associated with BP-SES versus DP-EES.

Long-term data are available only for early-generation BP–biolimus eluting-stents (BESs). Lu and colleagues[37] showed that BP-BESs were associated with lower rates of MACEs, target lesion revascularization, and ST (2.6% vs 3.8%, respectively; $P = .003$) to the DP-DES of first and second generations at 5 years of follow-up. When BP-BES was compared with CoCr-EES, however, no differences in ST (BP-BES 0.4% vs CoCr-EES 0.7%) were observed at 2-year follow-up[38] and also at longer-term follow-up (5 years).[39] With the intention of improving the characteristics of the BP-DES, in terms of strut thickness, polymer biodegradation coating, and drug release kinetics, new devices were developed. The Synergy (Boston Scientific, Marlborough, USA) BP-DES, a novel thin-strut platinum/chromium alloy stent that elutes everolimus from a rapid BP matrix, was one of the most intensively studied. In the EVOLVE II trial, it was noninferior to the PROMUS (Boston Scientific, Marlborough, USA) Element Plus EES with respect to definite/probable ST (0.4% vs 0.6%, respectively; $P = .50$) at 1-year follow-up.[40]

The Orsiro coronary stent (Biotronik AG, Bülach, Switzerland) consists of an ultra–thin-strut CoCr design with a bioresorbable, poly-L lactic acid polymer coating that elutes the antiproliferative drug sirolimus. This bioresorbable polymer SES was evaluated in the BIOFLOW V trial. At 1-year follow-up, the number of patients with late ST was significantly lower in the bioresorbable polymer SES group than in the DP-EES group, despite similar rates of definite or probable ST between groups (<1% vs 1%, respectively; $P = .694$).[41]

POLYMER-FREE DRUG-ELUTING STENT

To overcome the limitations related to DPs and BPs, PF-DES platforms were introduced. Elimination of the polymer might lower the rates of late ST, as suggested by previous studies in comparison with first-generation DESs.[42] The attainment of optimal drug-release kinetics, however, is the real challenge of PF-DES technology. First-generation devices had the limit of a too rapid drug elution (90% within 2 days) and failed to achieve the desirable inhibition of neointima formation.[43] After that, several randomized controlled trials were performed to evaluate the clinical performance of different PF-DES platforms. Recently, the MiStent, a DES with a fully absorbable polymer coating containing and embedding a microcrystalline form of sirolimus into the vessel wall, was evaluated in the DESSOLVE III trial[44] At 1-year follow-up, the rate of definite/probable ST was similar in comparison with DP-EES (0.7% vs 0.9%, respectively; $P = .76$).

Despite their improvements, PF platforms showed clinical outcomes and rates of ST comparable with modern permanent or BP-based DES up to 5 years' follow-up[45] Recently, Torii and colleagues[46] tested the hypothesis that the fluoropolymer on EES (FP-EES) is the most important component of its design with respect to thromboresistance by comparing stents of similar design with and without coating in a swine ex vivo shunt model. They demonstrated that FP-EES has the lowest platelet adherence compared with BP-DES, PF-DES, and BMS, with the lowest inflammatory cell density. These results reflect the phenomenon of fluoropassivation, representing one proposed mechanism for clinically observed low ST rates in FP-EES.[46] Because of their supposed lower risk of VLST, PF-DESs have been tested in high-risk profile populations, such as patients at HBR or with diabetes. The LEADERS FREE trial randomized 2466 HBR patients to either the BioFreedom DCS (Biosensors

Europe, Morges, Switzerland) or a similar BMS undergoing PCI under a 1-month mandated DAPT therapy. DESs were noted to be superior to BMSs for the primary composite endpoint, including cardiac death, MI, or ST at 2 years of follow-up, with a similar 2-year rate of definite/probable ST between the groups (2.1% for the DCS and 2.3% for the BMS). The Cre8 stent (CID SpA, member of Alvimedica, Saluggia, Italy) is an 80-μm–strut thickness CoCr PF-DES, releasing sirolimus from reservoirs placed on the abluminal stent surface. In a recently published propensity match analysis pooling 2 recent multicenter, observational independent studies conducted at 22 Italian centers, such as the Amphilimus Italian Multicentre Registry (ASTUTE) and the Polymer Free Biolimus-Eluting Stent Implantation in All-Comers Population (RUDI-FREE), aimed at comparing the safety and efficacy profile of Cre8 stent and BioFreedom biolimus-eluting stent (BES) PF-DESs in real-world patients undergoing PCI. In a total population of 2320 patients, both BES and Cre8 stents had similar rates of 1-year target lesion failure (4.2% vs 4.0%, respectively; HR 0.98; 95% CI; 0.57–1.70) as well as low 1-year rate of definite or probable ST (0.9% and 0.8%, respectively; HR 1.17; 95% CI, 0.36–3.81). The subgroup analysis showed a potential benefit of Cre8 in patients with diabetes mellitus, while of BioFreedom BES in patients without diabetes mellitus (*P* for interaction = 0.002).[47] Randomized trials comparing PF-DES to the DP-DES, however, are warranted to establish the safety and efficacy profile of these platforms in dedicated subgroups of patients.

BIORESORBABLE VASCULAR SCAFFOLD

In order to overcome the limits of DESs, fully bioresorbable scaffolds (BRSs) were introduced in 2012. The most studied BRS was the Absorb BVS.[48] Despite promising results at short-term follow-up, the Absorb BVS showed an increase of in-scaffold thrombosis in comparison with EES at long-term follow-up.[49–53]

The negative results of ABSORB II and AIDA at 3 years' follow-up[54,55] confirmed by several meta-analyses (ST, BRS 2.4% vs EES 0.7%),[52,56–59] resulted in the end of Absorb BVS use and withdrawal from the market in September 2017.

The experience with Absorb BVS, however, provided some precious lessons, in particular about the paramount role of implantation techniques. Several studies[60–65] in different clinical settings showed that an optimal deployment technique—pre-dilation, proper sizing, and post-dilation[66,67]—significantly reduced the rates of scaffold thrombosis (ScT), the Achilles heel of Absorb BVS.[68] These results were contrasted across the studies and some doubt remained whether the risk of ScT is due to the Absorb BVS platform or the implantation technique.[69]

The initial assumption of BRSs was to provide temporary mechanical support to the vessel without compromising the restoration of vascular physiology with the potential of preventing late adverse events after the complete resorption.[70] The 5-year outcome data of ABSORB Japan[71] showed that there were no significant differences in the composite or individual endpoint outcomes between the Absorb BVS and Xience arms through 5 years or between 3 years and 5 years. Similar results were reported in a single-center study, where the incidence of very late adverse events in patients with a BRS implantation decreased over years (ScT was 3.6% in the first year, 2.2% in the second-third year, and 0.6% in the fourth to fifth years after implantation). Recently, a summary-level meta-analysis by Stone and colleagues[72] of 4 trials, reporting 5-year follow-up data, showed a ScT in 0.1% of BVS-treated patients versus 0.3% of EES-treated patients between 3 years and 5 years (HR 0.44; 95% CI, 0.07–2.70) (*P* for interaction = .03), suggesting that the period of ScT risk for the Absorb BVS ends at 3 years.

OTHER BIORESORBABLE PLATFORMS

In such a scenario, the Biotronik magnesium-based Magmaris, Fantom (Reva Medical, San Diego, California), poly-L lactide-based polymer scaffold (Elixir Medical Corporation, Sunnyvale, California), ART (Terumo, Tokyo, Japan), and several other ones, including materials, such as tyrosine polycarbonate, salicylic acid polymer, and iron, were introduced. Although promising, the use of these devices in clinical practice is currently limited for the lack of randomized clinical studies and the current guidelines that limit their use.[73]

Recently, despite initial success of first studies, the Reva Medical company filed for bankruptcy protection in early 2020, although the next-generation DREAMS 3G, the evolution of Magmaris, with thinner struts and prolonged scaffolding time while keeping a 12-month resorption time, is being tested in the First in Men Study (BIOMAG-I; NCT04157153) and will be available for clinical trials in the near future.

Finally, it is unclear if the material technology will allow in future to overcome the limitations of current BRSs.

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