

The Current Role of Bare-Metal Stents

An evaluation of the importance of BMS in contemporary practice.

BY ITSIK BEN-DOR, MD; RON WAKSMAN, MD; AUGUSTO D. PICHARD, MD;
JOSEPH LINDSAY, MD; AND LOWELL F. SATLER, MD

Drug-eluting stents (DES) prevent restenosis through the controlled release of drugs that inhibit intimal proliferation. Compared to bare-metal stents (BMS), DES have similar rates of death and myocardial infarction (MI) but lower rates of restenosis. Because of this advantage, DES were rapidly adopted into clinical practice after their introduction in 2003. However, early enthusiasm has been tempered in recent years. Ironically, the foremost concern has been stent thrombosis, a consequence of the ability of DES to reduce restenosis by retarding re-endothelialization. Other potential causes of stent thrombosis include hypersensitivity reactions to polymers and incomplete stent apposition.

Importantly, in contrast to BMS, in which complete re-endothelialization is believed to occur 3 to 4 months after placement, only a small percentage of DES exhibit complete intimal coverage at 6 months.^{1,2} As a consequence, although dual-antiplatelet therapy is recommended for 1 month after BMS implantation, a minimum of 1 year is regarded as standard of care for DES placement. However, there are important clinical situations in which such extended antiplatelet therapy is a significant problem. Primary among these conditions is the need for noncardiac surgery before the year has elapsed. In addition to the requirement for prolonged antiplatelet treatment, there are patients with specific clinical scenarios or lesion characteristics for which DES do not appear to offer an advantage over BMS. This article focuses on common clinical applications in which BMS may be more desirable.

SAFETY AND EFFICACY

DES clearly offer an advantage over BMS with regard to restenosis. Randomized trials and registries have consistently shown the superiority of DES over BMS regarding clinical and angiographic restenosis. BMS are associated with a 1-year angiographic in-stent restenosis rate of

approximately 30%³ as compared to that of DES (approximately 10%).⁴ Despite this clear advantage, uncertainty over the long-term safety of DES has persisted. Initially, a meta-analysis of 14 randomized controlled trials reported a fivefold greater risk of very late stent thrombosis with DES compared to BMS.⁵ Subsequently, a series of publications raised the concern that DES might have a higher long-term rate of death or MI driven by late (up to 1 year) and very late (> 1 year) stent thrombosis.^{6,7}

These observations led the US Food and Drug Administration to conclude that off-label use of DES is associated with increased risk of both early and late stent thrombosis, as well as death and MI.⁸ After that review, the use of DES declined. A pooled analysis of trends in DES use in four countries (178,000 lesions) showed a post-2006 decline and identified marked variation in DES use both among countries and within countries (Figure 1A).⁹ A similar decline in DES use occurred at our institution as well. Shortly after the introduction of DES, these stents were used in 90% of lesions, but the rate declined rapidly to approximately 70% (Figure 1B). This decline was also confirmed by the National Cardiovascular Data Registry. A decline from more than 90% DES use to 64% was identified in this nationwide registry. This report also noted a slight rebound to 76% in 2009 (Figure 1C).¹⁰

This recent increase appears to have been stimulated by reports of long-term follow-up data in which the safety of DES deployment was comparable to that of BMS with regard to rates of death and MI. Specifically, 5-year follow-up data from major randomized controlled trials were recently published and revealed no difference in death, MI, or stent thrombosis.^{11,12} In addition, 3-year follow-up data from recent meta-analyses showed no difference in death or MI.^{13,14} A systematic review of off-label use of DES versus BMS reports similar rates of mortality, MI, and stent thrombosis, whereas target lesion revascularization (TLR) rates were lower with DES.¹⁵

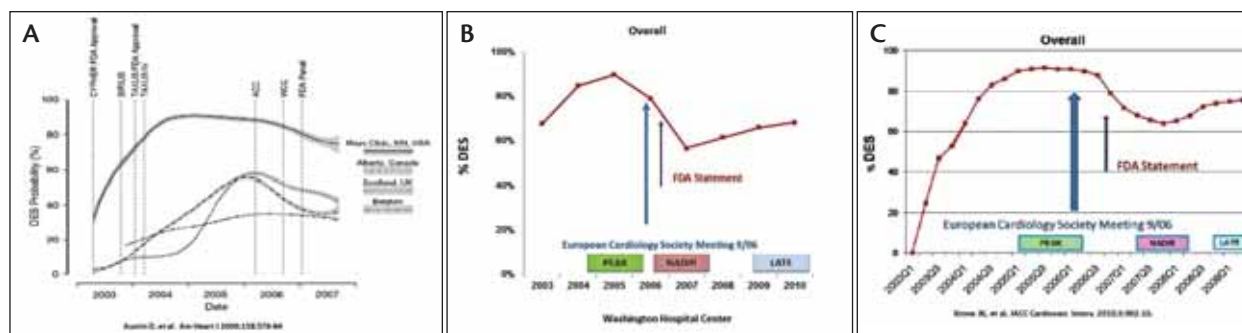


Figure 1. DES use in Canada, Belgium, the United States (Mayo Clinic), and Scotland (Reprinted from the *American Heart Journal*, 158(4), Austin D et al. Drug-eluting stents: a study of international practice, 576–584. Copyright (2009), with permission from Elsevier⁹) (A); DES use in Washington Hospital Center (B); DES use in the United States (Reprinted from the *Journal of the American College of Cardiology*, 3(9), Krone RJ et al. Acceptance, panic, and partial recovery the pattern of usage of drug-eluting stents after introduction in the U.S. (a report from the American College of Cardiology/National Cardiovascular Data Registry), 902–910, Copyright (2010), with permission from Elsevier¹⁰) (C). WCC, World Congress of Cardiology; ACC, American College of Cardiology.

An additional impetus to increased DES use has come from newer data suggesting that the original, very restrictive indications accompanying the release of DES could be broadened without loss of safety. A comprehensive meta-analysis of randomized trials and observational studies, including up to approximately 200,000 patients, found no significant difference between BMS and DES in the long-term rates of death and MI when used for either off-label or on-label indications. In fact, recent real-world nonrandomized observational studies showed that DES use was associated with reduced death and MI.¹⁶

However, concern persists despite these reassuring results. For example, data from the Western Denmark Heart registry found a greater incidence of very late definite stent thrombosis and MI in patients receiving DES compared to BMS.¹⁷ Such observations have revived concern for DES safety.

In addition, these observations have stimulated interest in examining mechanisms for this catastrophic event. Autopsy studies of thrombosed DES have shown extensive eosinophilic infiltration characteristic of a hypersensitivity reaction.¹⁸ Similarly, histological examination of thrombus aspirated at the time of primary percutaneous coronary intervention (PCI) has been reported to show eosinophile counts that are tenfold higher in specimens from very late DES stent thrombosis as compared to those from patients with spontaneous MI or BMS stent thrombosis.¹⁹ It can be speculated that hypersensitivity to the polymer binding the antiproliferative agent to the DES is responsible.

Stent malapposition, perhaps acquired from local drug effects, may play a role in very late stent thrombosis. A recent meta-analysis reported that late stent malapposi-

tion is higher after DES compared with BMS implantation and is associated with late stent thrombosis.²⁰ Support for this hypothesis comes from optical coherence tomography. Significantly, more incomplete stent apposition 5 months after implantation was found with DES compared to BMS.²¹ In view of these persistent safety issues, BMS may be more appealing in selected settings.

LESION CHARACTERISTICS FOR WHICH BMS ARE A GOOD ALTERNATIVE TO DES Large Coronary Arteries

There is an inverse relationship between vessel size and the incidence of adverse clinical outcomes after PCI with the use of BMS.²² Comparable data with DES are not convincing. Reports from our group and three other registries indicate good clinical outcomes after PCI in large coronary arteries (≥ 3.5 mm) and no advantage of DES over BMS (Table 1).^{23–26} Furthermore, our group reported similar 1-year outcomes in patients with either BMS or DES with nonostial proximal left anterior descending artery lesions with regard to efficacy (TLR) and safety (death or MI).²⁷ A recent publication reported that PCI with a 4-mm stent in a large single coronary artery carries a very low risk of major adverse cardiovascular events and target vessel revascularization (TVR) up to 2 years. The clinical outcomes were not affected by the type of stent used.²⁸

The efficacy of DES and BMS in large coronary arteries was recently evaluated in a large, prospective, randomized multicenter trial. BASKET-PROVE (Basel Stent Kosten Effektivitäts Trial Prospective Validation Examination)²⁹ randomized 2,314 patients requiring a coronary stent (≥ 3 mm) to receive a BMS (cobalt chromium), a first-

TABLE 1. DES VERSUS BMS IN LARGE CORONARY ARTERIES

Author/Study	Number of Patients	Follow-Up	Vessel Size	Death	MI	TVR	Stent Thrombosis (Definite/Probable)
Steinberg et al ²³	233	1 year	≥ 3.5 mm	DES, 4%; BMS, 3.5% (<i>P</i> = NS)	DES, 1.7%; BMS, 0.7 (<i>P</i> = NS)	DES, 3.4%; BMS, 3.5% (<i>P</i> = NS)	DES, 0%; BMS, 0%
Quizhpe et al ²⁴	500	1 year	≥ 3 mm	DES, 1.2%; BMS, 2.4% (<i>P</i> = NS)	DES, 1.2%; BMS, 0.8% (<i>P</i> = NS)	DES, 1.6%; BMS, 4.8% (<i>P</i> = NS)	NA
Yan et al ²⁵	672	1 year	≥ 3.5 mm	DES, 0.5%; BMS, 2.9% (<i>P</i> = NS)	DES, 6.3%; BMS, 3.4% (<i>P</i> = NS)	DES, 3.6%; BMS, 4.8% (<i>P</i> = NS)	DES, 0.9%; BMS, 1% (<i>P</i> = NS)
Na et al ²⁶	240	6 months	≥ 3.5 mm	DES, 1.02%; BMS, 0% (<i>P</i> = NS)	DES, 0.5%; BMS, 0% (<i>P</i> = NS)	DES, 4.6%; BMS, 5.3% (<i>P</i> = NS)	NA
Bonello et al ²⁷	487	1 year	Proximal LAD	DES, 4.9%; BMS, 5.9% (<i>P</i> = NS)	DES, 1.2%; BMS, 1.5% (<i>P</i> = NS)	DES, 8.6%; BMS, 9% (<i>P</i> = NS)	NA
Kim et al ²⁸	304	2 years	≥ 4 mm	DES, 3.4%; BMS, 1.8% (<i>P</i> = NS)	DES, 0.7%; BMS, 1.2% (<i>P</i> = NS)	DES, 4.8%; BMS, 5.7% (<i>P</i> = NS)	DES, 1.4%; BMS, 0.6% (<i>P</i> = NS)
Kaiser et al ²⁹	2,314 (SES, 775; EES, 774; BMS, 765)	2 years	≥ 3 mm	SES, 3.6%; EES, 3.2%; BMS, 4.4% (<i>P</i> = NS)	SES, 2.6%; EES, 3.2%; BMS, 4.8% (<i>P</i> = NS)	SES, 4.3%; EES, 3.7%; BMS, 10.3% (<i>P</i> = .005)	SES, 0.8%; EES, 0.6%; BMS, 1.2% (<i>P</i> = NS)

Abbreviations: EES, everolimus-eluting stent; LAD, left anterior descending; NA, not available; NS, nonsignificant; SES, sirolimus-eluting stent.

generation DES (sirolimus-eluting), or a second-generation DES (everolimus-eluting). The primary endpoint was a composite of death from cardiac causes or nonfatal MI at 2 years. The main secondary endpoints were late events (7–24 months) and TVR. The rates of the primary endpoint were statistically similar for all three groups: 2.6% for the sirolimus-eluting stent group, 3.2% for the everolimus-eluting stent group, and 4.8% for the BMS group. There were no significant differences in the rates of late events or the rates of death, MI, or stent thrombosis. However, the non-MI-related TVR rates were 3.7% for the sirolimus-eluting stent group, 3.1% for the everolimus-eluting stent group, and 8.9% for the BMS group. The difference in TVR between the DES patients and BMS patients was statistically significant (*P* = .007).

Thus, results of the BASKET-PROVE trial imply that in patients with stenting of large coronary arteries (≥ 3 mm), DES and BMS had equivalent rates of death and MI but experienced a significantly higher rate of TVR after BMS implantation. These results are different from some of the previous registry data regarding TVR in large vessels. The major difference is that the registries evaluated larger coronary arteries (≥ 3.5 mm) as compared to the ≥ 3-mm arteries in this trial. In our center, for large coronary arteries (≥ 3.5 mm), we predominately deploy BMS, with the exception of long lesions or in diabetic patients.

Saphenous Vein Grafts

Observational comparisons of the outcomes of BMS and DES after saphenous vein graft (SVG) intervention

TABLE 2. META-ANALYSIS COMPARING BMS AND DES IN SVG INTERVENTIONS

Author/Study	Number of Trials	Number of Patients	Death	MI	TVR	Stent Thrombosis
Lee et al ³³	2 RCTs, 17 registries	3,420	OR, 0.78; 95% CI, 0.59–1.02	OR, 0.69; 95% CI, 0.49–0.99	OR, 0.59; 95% CI, 0.49–0.72	OR, 0.41; 95% CI, 0.15–1.11
Meier et al ³⁴	3 RCTs, 26 registries	202/ 7,549	OR, 2.2; 95% CI, 0.17–29.5 (<i>P</i> = NS)/ OR, 0.69; 95% CI, 0.55–0.85 (<i>P</i> < .001)	OR, 1.25; 95% CI, 0.22–6.9 (<i>P</i> = NS)/ OR, 0.68; 95% CI, 0.49–0.95 (<i>P</i> = .02)	OR, 0.5; 95% CI, 0.24–1 (<i>P</i> = NS)/ OR, 0.49; 95% CI, 0.49–0.79 (<i>P</i> < .001)	OR, 0.78; 95% CI, 0.03–21.7 (<i>P</i> = NS)/ OR, 0.58; 95% CI, 0.38–0.84 (<i>P</i> < .001)
Sanchez-Recalde et al ³⁷	3 RCTs, 19 registries	5,543	OR, 0.69; 95% CI, 0.49–0.98 (<i>P</i> = .04)	OR, 0.89; 95% CI, 0.6–1.32 (<i>P</i> = NS)	OR, 0.56; 95% CI, 0.41–0.76 (<i>P</i> < .001)	OR, 0.82; 95% CI, 0.43–1.59 (<i>P</i> = NS)
Hakeem et al ³⁹	2 RCTs, 26 registries	7,994	RR, 0.82; 95% CI, 0.7–0.97 (<i>P</i> = .02)	RR, 0.72; 95% CI, 0.57–0.91 (<i>P</i> = .007)	RR, 0.71; 95% CI, 0.59–0.85 (<i>P</i> < .001)	RR, 0.61; 95% CI, 0.35–1.06 (<i>P</i> = .08)
Paradis et al ³⁶	25 registries	5,755	OR, 0.85; 95% CI, 0.62–1.2	OR, 0.83; 95% CI, 0.53–1.3	OR, 0.55; 95% CI, 0.39–0.76	OR, 0.54; 95% CI, 0.13–1.39
Testa et al ³⁵	3 RCTs, 15 registries	3,294	OR, 0.75; 95% CI, 0.57–1 (<i>P</i> = NS)	OR, 0.86; 95% CI, 0.52–1.44 (<i>P</i> = NS)	OR, 0.53; 95% CI, 0.38–0.75 (<i>P</i> < .001)	OR, 0.53; 95% CI, 0.15–1.9 (<i>P</i> = NS)
Joyal et al ³⁸	2 RCTs, 18 registries	3,902	OR, 0.69; 95% CI, 0.53–0.91	OR, 0.85; 95% CI, 0.48–1.5	OR, 0.54; 95% CI, 0.37–0.79	NA

Abbreviations: CI, confidence interval; NA, not available; NS, not significant; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

offer contradictory information. Many studies show equivalent repeat revascularization rates; one report identified an excess of clinical events as being associated with DES use.

There are three very small randomized trials that also had conflicting results. Brilakis et al³⁰ reported no difference in mortality or MI in 80 patients who were randomized to BMS or DES but noted a lower TLR rate with BMS compared to DES. Vermeersch et al³¹ described a randomized comparison of 75 patients in which they observed higher mortality rates in patients who were

randomized to DES compared to BMS at 3 years but found similar rates of MI and TVR. Similarly, Jeger et al³² randomized 47 patients and found a similar rate of mortality and MI but a lower rate of TVR with DES.

In 2010 alone, seven meta-analyses comparing BMS and DES for SVG intervention have been reported (Table 2). Most of these included far more registry reports than randomized trials. However, taken together, they indicate that placing a DES provides superior clinical outcomes, including a lower TVR rate,^{33–36} lower risk of mortality,^{37–38} and a lower risk of MI.³⁹

Shishehbor et al⁴⁰ compared the safety and efficacy of DES and BMS in a large cohort of consecutive, unselected patients who underwent PCI of SVG. Importantly, their study spanned the introduction of DES. Their results showed that when compared to BMS procedures performed during the years in which DES were available, DES use showed a trend toward a lower incidence of their primary endpoint of death, MI, or TLR. This reduction was mainly driven by lower mortality. However, DES were not associated with a lower rate of death, MI, or TLR when compared with a cohort of patients who received BMS before 2003. This highlights the possibility that unrecognized biases in observational registries could account for the reported benefit of DES over BMS for treating SVG. A recently identified late “catch-up” phenomenon regarding TVR points out that the follow-up interval is another source of variability in observational data in SVG outcomes. Despite a clear benefit for DES in the first year, later restenosis may result in similar long-term results.⁴¹

It appears at this time that there are insufficient data to develop a clear recommendation with regard to stent choice in SVG. A large, multicenter, randomized controlled trial is required to resolve this dilemma. In the absence of definitive data, we believe that the use of BMS as an alternative to DES is reasonable.

STEMI

Data from many randomized controlled trials and meta-analyses indicate that DES do not provide an advantage over BMS with regard to death or recurrent MI. However, they do support a conclusion that the need for repeat revascularization is reduced by DES use in this patient subset. Moreover, these conclusions are reinforced by the results of meta-analyses of patients with acute ST-elevation MI (STEMI).⁴²⁻⁴⁴ However, it should be recognized that most of these studies enrolled a small-to-moderate number of patients, and in many, the protocol required performance of routine angiographic follow-up. As is typical of protocol-driven follow-up, TLR procedures were undertaken that would not have occurred with symptom-driven follow-up. This phenomenon results in an overestimation of the benefit of DES.

In HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), the largest prospective randomized trial of STEMI, the 12-month benefit of DES compared with BMS was confined to a modest reduction in ischemia-driven TLR (4.5% vs 7.5% for DES vs BMS, respectively).⁴⁵ Among patients with low risk of restenosis (excluding those with a reference vessel diameter ≤ 3 mm, a lesion length ≥ 30 mm, or insulin-treated diabetes mellitus), no difference in TLR at 12 months was present between DES

TABLE 3. CLINICAL SCENARIOS FAVORING BMS OVER DES

- Nonelective surgery required
- Expected poor compliance with dual-antiplatelet therapy
- Intolerance/allergy to aspirin or clopidogrel/prasugrel/ticagrelor
- Bleeding risk
- Indication for long-term anticoagulation

and BMS.⁴⁶ To add to the confusion, a recent study comparing BMS and DES in patients with acute MI reported similar death and reinfarction rates. Use of DES resulted in a reduction of TVR at 1 year, but this benefit was no longer apparent at the subsequent 2-year follow-up.⁴⁷

The long-term safety of DES in STEMI must be considered. Importantly, vessel healing at the treated lesion in acute MI cases treated with DES is substantially delayed compared with that in cases receiving DES for stable angina.⁴⁸ In cases of unstable plaque, optical coherence tomography shows a disturbingly high frequency of inadequately apposed struts that are uncovered by neointima.⁴⁹ In addition, Kaltoft et al reported a higher cardiac mortality rate using DES versus BMS in patients with STEMI at 3 years.⁵⁰

Overall, there appears to be a small reduction in the absolute risk of TLR when choosing DES for this patient subset. This benefit must be balanced against uncertainties regarding compliance with dual-antiplatelet therapy and residual concern of safety after DES implantation in acute MI. Thus, a general recommendation regarding the choice of stent in this patient subset is not possible. We currently reserve DES for primary PCI in patients who are deemed to be at high risk of restenosis.

SETTINGS IN WHICH BMS ARE SUPERIOR

There are several clinical settings in which dual-antiplatelet therapy for 1 year presents a challenge. Most common is the patient who is not expected to be closely compliant with the antiplatelet regimen. In other situations, the patient may have an increased risk of bleeding or may need noncardiac surgery within the year. In these clinical settings, the small anticipated benefit to be gained from reduced restenosis may be crushed by the need to withhold the antiplatelet regimen (Table 3).

SETTINGS IN WHICH DES ARE BETTER

There are specific lesions that are at high risk for restenosis in which DES have better clinical outcomes than BMS: long lesions, small vessels, chronic total

occlusions, diabetes mellitus, in-stent restenosis, and unprotected left main artery disease.⁵¹⁻⁵³ A detailed discussion of these restenosis-prone lesions is beyond the scope of this article. In the United Kingdom, the National Institute for Health and Clinical Excellence recommended DES in non-MI patients with lesions > 15 mm in length and in vessels < 3 mm in diameter.⁵⁴ Canadian guidelines recommend DES in diabetic patients, in lesions > 18 mm, and in vessels ≤ 2.75 mm in size.⁵⁵

SUMMARY

DES rather consistently reduce restenosis rates compared to BMS and should be the treatment of choice for patients who are at high risk of restenosis. This assumes that the patient will tolerate and adhere to the prescribed dual-antiplatelet regimen. In cases with clinical contraindication to prolonged dual-antiplatelet therapy, BMS should be used. BMS remain a valuable alternative to DES in large vessels, in patients with STEMI, and in SVG stenoses. ■

Itzik Ben-Dor, MD, is with the Washington Hospital Center in Washington, DC. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Ron Waksman, MD, is with the Washington Hospital Center in Washington, DC. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Augusto D. Pichard, MD, is with the Washington Hospital Center in Washington, DC. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Joseph Lindsay, MD, is with the Washington Hospital Center in Washington, DC. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein.

Lowell F. Satler, MD, is with the Washington Hospital Center in Washington, DC. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Satler may be reached at (202) 877-5975; satlerlowell@gmail.com.

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COVER STORY

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