Drug-Eluting Stents for Off-Label Indications

A review of studies comparing DES to BMS for on- and off-label uses.

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The past decade has brought about monumental improvements in interventional cardiology, helping millions of patients with coronary artery disease. Although angioplasty and bare-metal stenting were the building blocks of interventional cardiology, restenosis rates between 10% and 30% remained the weakness of bare-metal stents (BMS). The notion that repeat procedures for in-stent restenosis may be eliminated created a great deal of anticipation for drug-eluting stents (DES). After US Food and Drug Administration (FDA) approval, DES allowed for high rates of procedural success and significantly decreased the need for target lesion revascularization (TLR).

DES APPROVAL

Two DES were studied head-to-head with BMS, leading to FDA approval in 2003 in the United States, which was a year later than in Europe. These initial trials for both stents enrolled low-risk, stable patients with de novo coronary lesions, and overall, these patients were young, with low rates of diabetes and freedom from complex coronary disease. The trials concluded that DES were equally as safe as BMS, with significantly lower rates of TLR during the following 9 to 12 months.[1-9] The sirolimus-eluting stent was approved for lesions 2.5 to 3.5 mm in diameter and up to 30 mm in length, and shortly after, the paclitaxel-eluting stent was approved for lesions 2.5 to 3.75 mm in diameter and up to 28 mm in length.

The FDA's approval of DES was for the limited indications previously listed. The apparent advantages of reduced restenosis and repeat procedures led to a great deal of excitement within the cardiology community, and within 6 months of approval, more than 80% of stents being placed were DES.[10] The first hint of a problem with DES surfaced in late 2003, when approximately 300 cases of subacute stent thrombosis (including 60 deaths) were reported via the Medical Devise Reporting system. This voluntary method of reporting contains limited clinical information, making the determination of causality impossible. In response, the FDA published a notification reminding physicians of the approved DES indications and the risks of using them in alternative manners.[11]

LONG-TERM SAFETY CONCERNS FOR DES

Within the first 2 years of approval, DES usage continued to increase and accounted for 80% to 90% of all stents used. By 2006, there were more than 6 million DES placed worldwide; however, only 40% were placed for the indications studied in the original trials.[4,12] In September 2006, the long-term safety of DES began to be questioned. The first prospective trials following patients to look at the safety of real-world DES use were the BASKET and BASKET LATE trials. In these trials, patients were randomized 2:1 to receive either DES or BMS and clopidogrel for 6 months after stent placement. They were followed for 12 months, and the investigators found that DES were associated with higher rates of cardiac death and myocardial infarction (MI), which was frequently related to stent thrombosis (ST). There was significant debate regarding these results, but in general,

many were skeptical that DES could truly be harmful. It should be noted that in the following year with longer follow-up to 18 months, it now became apparent that there was actually no difference in death or MI in the two groups' studied.[13]

In the wake of these results, two separate meta-analyses were presented in abstract form at the 2006 World Congress of Cardiology in Barcelona and suggested that all-cause death and MI were higher in patients with DES compared to BMS (6.26% vs 3.91%; $P = .03$). DES were also associated with higher rates of ST, on the order of 2% to 3.4% per year, and results appeared especially worse in patients receiving DES for indications not included in the original studies. At this point, the data had not been published or peer reviewed, and opinions on the legitimacy of these results divided the cardiology community. Some believed that these studies confirmed that DES were harmful and their use should be limited, while others were more skeptical of the results and awaited further studies.[14,15] During the same time, there was also a prevailing trend that outcomes were worse when DES were used for more complex indications.

The news of these results triggered widespread panic among patients, the press, and cardiologists regarding what should be done for patients in whom DES had already been placed and how to prospectively treat patients. This prompted the FDA to plan an emergency meeting with its Circulatory System Devices Panel in December 2006. In anticipation of this meeting, the Academic Research Consortium (ARC) was created to standardize the definitions of ST. With various trials using their own definition of ST, a comparison between key trials was not possible. In an effort to better understand the risk of ST, the FDA asked for results from key trials to be recalculated using the ARC definitions. The ARC definitions would include definite ST, probable ST, and possible ST, as well as early (1–30 days), late (31–360 days), and very late (> 360 days) ST.[16] It wasn't surprising that DES usage quickly plummeted from nearly 90% to about 60%.

FDA MEETING WITH CIRCULATORY SYSTEM DEVICES PANEL

This 2-day meeting was meant to tackle several key issues: first, to discuss safety for on-label and off-label indications for DES, and second, to consider the optimal duration of dual-antiplatelet inhibition.

In March 2007, the FDA published their position, which stated that when DES were used for approved indications, the benefits of lower rates of repeat revascularization outweighed the risks compared to BMS. However, the FDA stressed it was prudent that further studies should be conducted in complex conditions and patient populations such as bifurcation stenting, acute MI, diabetes, and multivessel coronary disease. It was at this time that the distinction between on-label and off-label stent usage became so prominent. The FDA also commented that despite the lack of evidence, a short duration of clopidogrel was associated with ST, and they felt that dual-antiplatelet inhibition should be continued for at least 12 months in patients who were not at high risk for bleeding.[12] However, the optimal duration of dual-antiplatelet inhibition remained unclear.

The term *off-label* is now used when stents are placed for indications other than those originally approved by the FDA. The off-label indications can be seen in the *Characteristics of Off-Label Indications* sidebar and include angiographic (in-stent restenosis, left main stenosis, bypass graft, bifurcation, ostial lesions, total occlusion, vessels < 2.5 mm or > 3.75 mm, and lesions > 30 mm in length) and clinical (acute MI, diabetes, and left ventricular ejection fraction of < 30%) uses of stents.

SAFETY OF DES FOR ON-LABEL VERSUS OFF-LABEL USE

The DESCOVER and EVENT registries were the first to examine the outcomes of the off-label use of DES. The DESCOVER prospective registry included 140 medical centers in the United States and a total of 7,752 patients who underwent stent placement between January and June of 2005 and were subsequently followed for 1 year. Once enrollment was completed, patients were divided into three categories for comparison: those receiving DES for on-label indications, off-label indications (restenosis, bypass graft lesions, long lesions, or for vessels outside the information for recommended use), or untested indications (left main stenosis, ostial lesion, bifurcation lesion, or total occlusion). Ninety percent of these patients received DES, with 53% used for on-label indications, 25% for off-label indications, and 22% for untested indications. The primary outcome analyzed occurrences of death, MI, ST, or target vessel revascularization (TVR) at 1 year between the three indication groups. The authors concluded that the off-label use of stents was associated with higher death (4.3% vs 2.6%; $P < .01$), higher TVR (7.6% vs 4.4%; $P < .0001$), and a composite of death, MI, or ST (6.9% vs 4.3%; $P = .001$) compared to on-label use. There was no difference in death, MI, or ST between on-label use and untested indications.[17]

The Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry was another multicenter trial involving 42 hospitals in the United States, which enrolled 3,323 patients who received DES for a reason other than acute MI from July 2004 to September 2005.

The main outcome was a composite of death, MI, and TVR. Of the 3,323 patients, 55% received DES for off-label indications. The composite endpoint occurred in 10.9% of patients in the off-label group compared to 5% in the on-label group ($P < .001$) during index hospitalization, with the difference in groups being driven primarily by an increase in MI. At 1 year, the composite endpoint again occurred more often in the off-label group (17.5% vs 8.9%; $P < .001$) and was driven by an increase in MI and TLR rates, with no difference in death. ST was also more frequent in the off-label group both during index hospitalization (0.4% vs 0%) and at 1 year (1.6% vs 0.9%).[18]

These registries, in agreement with several others, concluded that off-label use of DES was associated with higher rates of adverse events compared to on-label use during the first year.[19,20] Given the lack of a control arm, in which an alternative strategy could have been used, there was no answer as to whether the adverse outcomes seen in these patients were related to DES use or due to the complexity of disease. To resolve this, further studies comparing DES to BMS for off-label indications would be necessary.

DES COMPARED TO BMS FOR OFF-LABEL INDICATIONS

To help answer this question, the National Heart, Lung, and Blood Institute dynamic registry was the first to study the safety and effectiveness of DES compared to BMS for both on-label and off-label use.[21] This registry involves 17 medical centers and recruited consecutive patients undergoing percutaneous coronary intervention at prespecified time periods between 1997 and 2006. Five recruitment waves each enrolled approximately 2,000 patients. Waves 1 through 3 occurred from 1997 until 2003, before DES approval, so all patients received BMS. Waves 4 and 5 occurred in 2004 and 2005 and include 4,286 patients, of which 63% received at least one DES, 15.1% received BMS, and 2.6% received both. Patients receiving DES from waves 4 and 5 were compared to patients receiving BMS in waves 1 through 3. Patients receiving BMS or both BMS and DES in waves 4 and 5 were excluded because of a significant selection bias (ie, more patients with cardiogenic shock received BMS in waves 4 and 5).

Therefore, a total of 6,551 patients were included in the study and were followed for the occurrence of cardiovascular events or death. Although patients will ultimately be followed for 5 years, the original publication reported 1-year outcomes. Patients were divided into four groups based on whether the patients received BMS or DES for either on-label or off-label use. Off-label use occurred in 2,110 of the 3,858 patients who received BMS and in 1,312 of 2,693 patients who received DES. The off-label DES group had a higher likelihood of comorbidities including diabetes, hypertension, renal disease, previous revascularization, previous MI, and rates of triple-vessel disease.

At 1 year, the on-label group had lower rates of death (2.7% vs 5.3%) or MI (3.8% vs 5.3%) compared to the off-label group. Within the off-label group, DES had lower rates of death (3.7% vs 6.4%) and MI (4.4% vs 5.9%) compared with BMS. After adjusting for differences between the off-label DES and BMS groups, DES was associated with a lower incidence of MI and repeat revascularization at 1 year but showed no significant difference in death or the combined endpoint of death or MI. The authors concluded that the use of DES was not associated with a higher risk of death or MI compared to BMS but was associated with lower rates of repeat revascularization and therefore supported the use of DES for off-label indications.

After this study, several other authors reported results from registries with similar results as the National Heart, Lung, and Blood Institute.[22,23] These studies further supported that DES was safe and may even be associated with lower rates of death or MI compared to BMS in the short term. However, late stent thrombosis occurred only in the DES group, and therefore, long-term safety remained a concern.

CHARACTERISTICS OF OFF-LABEL INDICATIONS

Off-Label Angiographic Characteristics

- In-stent restenosis
- Bypass graft
- Bifurcation
- Ostial lesions
- Left main stenosis
- Total occlusion
- Vessels < 2.5 mm or > 3.75 mm in diameter
- Long lesions > 30 mm in length

Off-Label Patient Characteristics

- Acute myocardial infarction
- Reduced left ventricular ejection fraction
- Diabetes mellitus

STUDIES WITH LONG-TERM FOLLOW-UP

The previously mentioned studies reported the safety and efficacy of DES compared to BMS for off-label indications in the short term of 1 to 2 years. However, it was still unknown whether the safety of DES would continue beyond the first year. There has been a fear that DES would be associated with late adverse clinical events due to ST, a concern termed as catch up. If this was proven to be true, the deleterious event of ST may negate the short-term benefits seen in the previous studies.[13,24,25]

Applegate et al initially published their 2-year data,[22] and more recently, their 3-year comparison data on 1,246 patients receiving DES versus 1,147 patients receiving BMS.[26] In this cohort, 75% of BMS and 80% of DES were placed for off-label indications, and clopidogrel use was higher in the DES group up to 1 year, after which rates were similar. Reduction in all-cause death, nonfatal MI, or death and TVR with DES occurred entirely within the first year, with similar rates between DES and BMS at 2 and 3 years. Late ST by ARC criteria was more frequent in the DES group during the second and third year of follow-up; however, cumulative 3-year rates were identical between BMS and DES.

Although this study and others including the NHLBI[27,28,29] appear to support the safety and efficacy of DES over a longer period of time, continued reporting of clinical outcomes in these patients over time is critical in assessing the long-term safety of these devices because they are used in routine clinical practice.

META-ANALYSIS

Individual randomized trials or observational studies were limited in sample size, making it difficult to detect subtle differences. Combining studies into meta-analyses allows for a means to study relatively infrequent complications. Most recently, in 2009, a comprehensive meta-analysis combing 22 randomized clinical trials (RCTs) with 9,470 patients and 34 observational studies for a total of 182,901 patients shed more light on this issue.

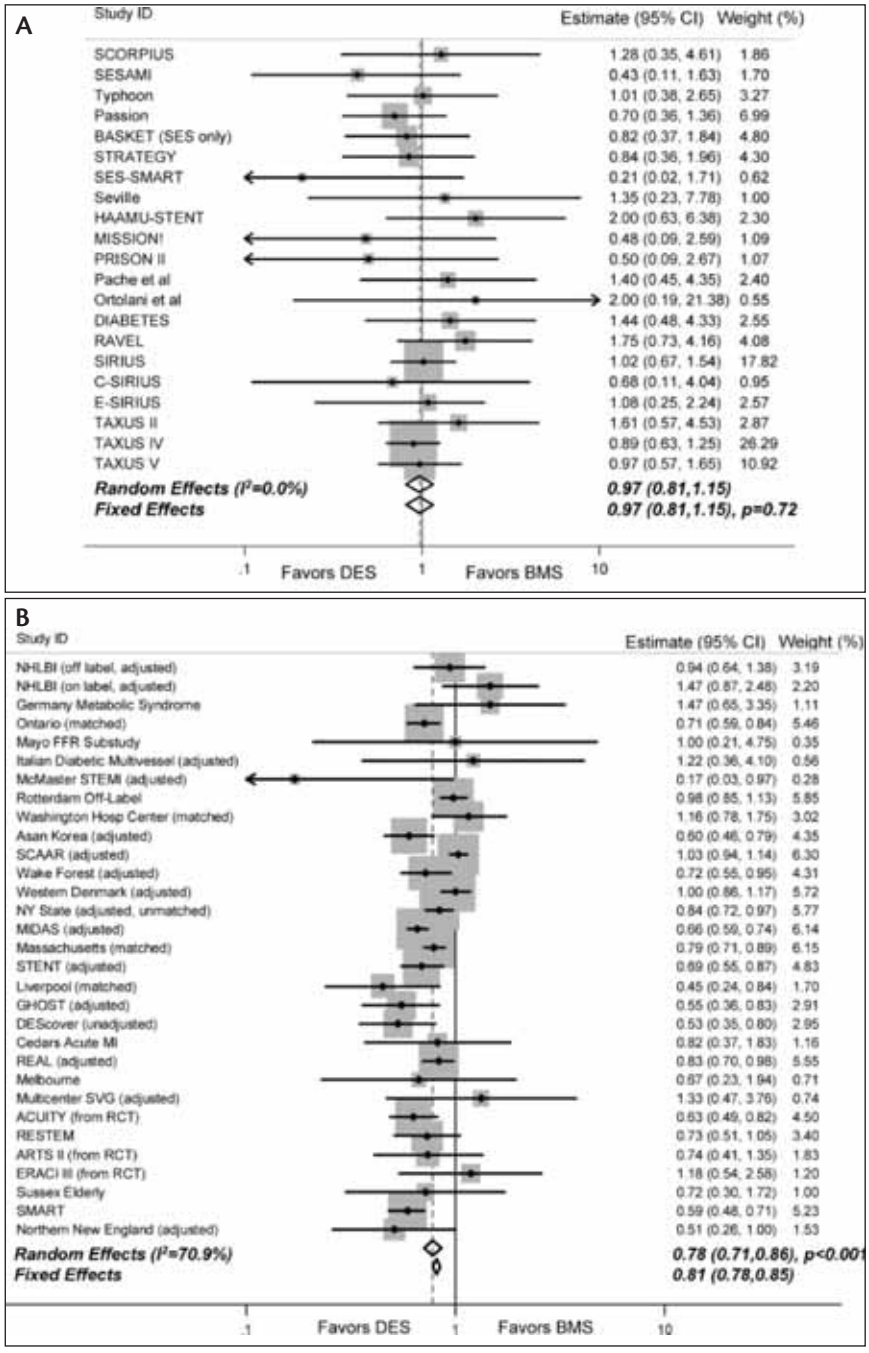

Figure 1. Meta-analysis results for all-cause mortality between BMS and DES in RCTs (A) and observational studies (B). Abbreviation: CI, confidence interval. Reprinted with permission from Kirtane AJ et al. Circulation. 2009;119:3198-3206.[30]

Meta-analysis of the RCTs found that there was no significant difference between DES and BMS in mortality (Figure 1A) or MI during 4 years of follow-up. In these RCTs, it was found that TVR was reduced 55% with DES, extending to 4 years (Figure 2A). When the patients in the observational studies were pooled together, there appeared to be a 22% reduction in mortality (Figure 1B) and a 13% reduction in MI among the patients receiving a DES compared to BMS. TVR was also reduced by 46% in DES patients (Figure 2B).

Although there is a difference in safety between the results of the RCTs and the observational studies, the important finding is that DES are not associated with an increased risk of death or MI and significantly lowers the need for TVR. There are several explanations as to why mortality rates were lower in the observational studies compared to the RCTs, including the fact that observational studies have a larger number of patients and therefore allow for the detection of small differences. However, confounders and selection bias limit observational studies because choice of stent type is not randomized and cannot always be accounted for in multivariate analysis. Although this meta-analysis provides further insight into the issue of safety of DES in off-label indications, only eight of the 56 studies had follow-up to 4 years, and the number of patients with long-term follow-up is limited.[30]

SPECIFIC OFF-LABEL INDICATIONS INCLUDING ACS

In addition to the previously mentioned studies comparing the safety and efficacy of DES versus BMS, many studies have looked at outcomes in specific off-label indications. Of the off-label indications, acute coronary syndrome (ACS) remains one of the most frequent off-label uses of DES and studies.[21,24] Initial small registries[31,32] suggested harm with DES use in the setting of ACS, but early small RCTs[33,34,35] found no difference in death or MI, with significantly lower rates of reintervention. These trials were small and underpowered to truly determine the safety of DES in this setting. With great anticipation in 2009, the HORIZONS-AMI study published their 1-year data on PES versus BMS in the setting of ST-elevation MI. This remains the largest RCT to date, and proved that DES was associated with lower rates of ischemia-driven

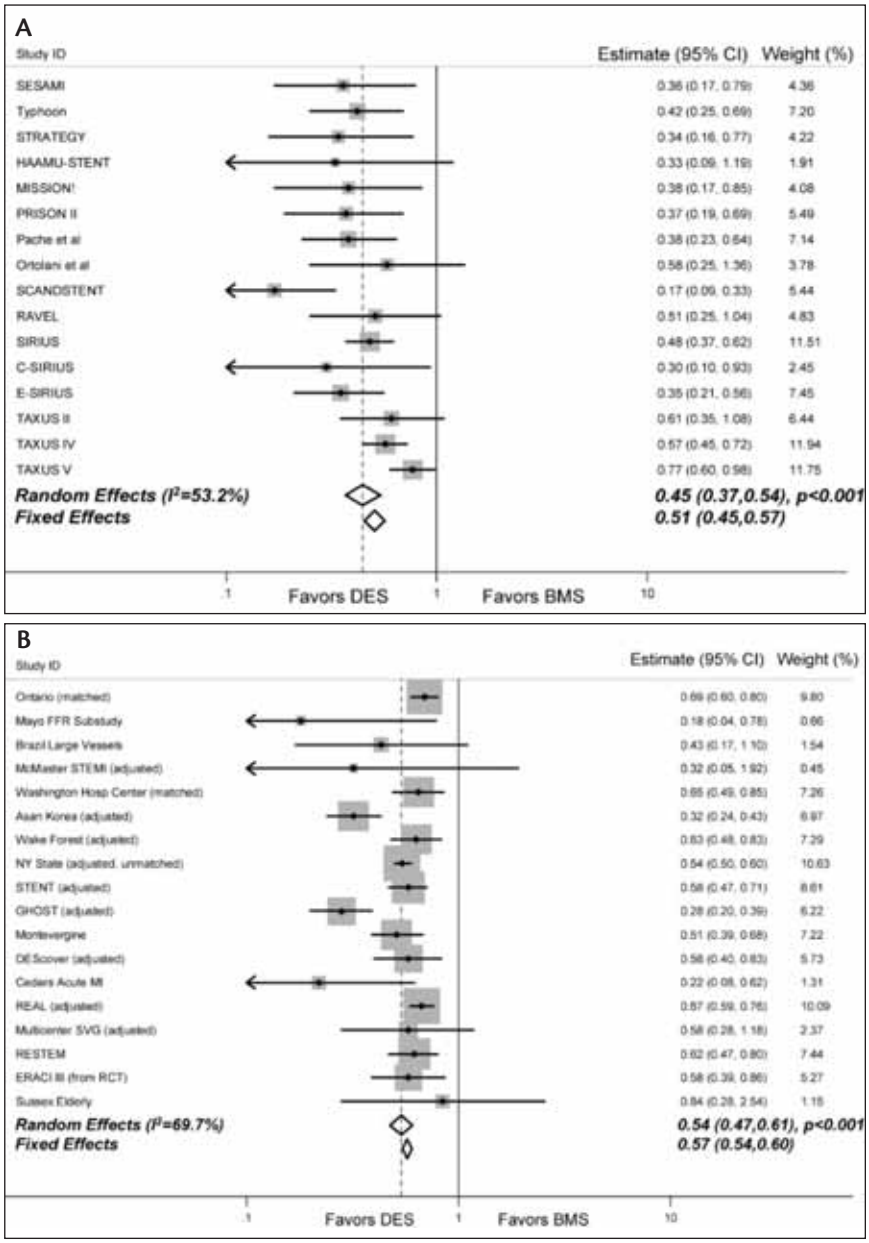

Figure 2. Meta-analysis results for TVR between BMS and DES in RCTs (A) and observational studies (B). Reprinted with permission from Kirtane AJ et al. Circulation. 2009;119:3198-3206.[30]

revascularization with noninferior rates of safety endpoints including death, MI, or restenosis.[36] Combining these trials into a meta-analysis also supports the safety of DES with greater efficacy at reducing repeat interventions.[37]

An overview of the other off-label indications and specific trials supporting DES use can be seen in Table 1. This table includes RCTs for each indication and when available a meta-analysis otherwise key observational studies.

NEW-GENERATION DES

The second-generation DES (everolimus and zotarolimus) and the new Taxus platform Liberté have been developed to improve deliverability, efficacy, and safety. Their use continues to grow; however, their safety and efficacy for off-label indications remains unclear. Recently, the COMPARE study was published and was designed to compare second-generation everolimus-eluting stents with paclitaxel-eluting stents in real-world use. The 1,800 patients in the study were randomly assigned to the stent they received, and the majority of stents were used for off-label indications, with 60% being used for acute coronary syndromes. Primary endpoints of death, MI, and TVR within 12 months occurred less frequently in the everolimus-eluting arm. However, similar to the early trials of first-generation DES, longer-term follow is crucial and is still needed.[75]

In addition, a newer generation of SES and PES stents have been developed and FDA approved. In 2008, the Taxus-Atlas program studied the new thinner-strut PES and found that in small vessels (diameter 2.25 mm) and long lesions (length 38 mm) that this new stent platform reduced angiographic restenosis, TLR, and MI compared to the older Taxus Express stent.[59] In 2009, the 2-year results of the SES-SMART also showed that 2.25-mm SES compared to BMS had lower rates of TLR and MI in small vessels.[60] This led to the FDA approval of these new DES for de novo small or long coronary lesions.

CONCLUSION

In the relatively short period of time that DES have been approved, their usage has experienced a rollercoaster ride. From the initial excitement and near-universal application to now roughly 70% of stents implanted being DES, it is clear that the medical community has

TABLE 1. TRIALS SUPPORTING DES IN SPECIFIC OFF-LABEL INDICATIONS

Off-Label Characteristics	Randomized Clinical Trials (Title or Author)	Meta-Analyses/Observational Trials (Title or Author)
In-stent restenosis	ISAR-DESIRE 1&2[38,39] SISR[40]	
Bypass graft	RRISC,[41] SOS[42]	Joyal[43]
Bifurcation	ARTS II,[44] CACTUS,[45] Colombo,[46] Pan[47]	Athappan[48]
Ostial lesions		Iakovou,[49] Seung,[50] SCANDSTENT[51]
Left main stenosis	Erglis,[52] ISAR-LEFT-MAIN[53]	Park,[54] RESEARCH,[55] MAIN-COMPARE[56]
Total occlusion	PRISON II[57]	DeFelica[58]
Vessels < 2.5 mm or > 3.75 mm in diameter	Turco,[59] SES-SMART,[60] ISAR SMART 3[61]	SIRTAX,[62] Rodriguez-Granillo[63]
Long lesions > 30 mm in length	Turco[59]	Kereiakes,[64] Kim,[65] Shishehbor[66]
Acute myocardial infarction	HORIZONS-AMI[36]	Dibra[37]
Reduced left ventricular ejection fraction		Nusca,[67] Gioia[68]
Diabetes mellitus	DIABETES[69]	TAXUS IV,[70] SIRIUS,[71] Akin,[72] NHLBI[73,74]

learned a lot from this process. The controversy surrounding DES has taught us the importance of studying new technologies in various patient populations and that one size does not fit all. The questions of optimal dual-antiplatelet inhibition, the role of DES in specific off-label indications, and the safety of next-generation DES for off-label use still need to be answered. Based on the current data with relatively short follow-up, it appears that DES use in off-label indications is as safe as and more efficacious than BMS; we feel, however, that continued follow-up, especially focusing on the safety of DES in these higher-risk groups, is warranted in order to fully understand the long-term safety of these devices. ■

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