Off-Label Use of Drug-Eluting Stents
Putting it in Perspective*

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Since Food and Drug Administration (FDA) approval of the first drug-eluting stent (DES) in April 2003, their use increased to 90% of all coronary stent procedures in the U.S. by 2006 (1). With restenosis virtually eliminated, DES were applied to increasingly more complex coronary lesions. However, over the past few years, reports of late stent thrombosis began to emerge. Additional reports of late stent thrombosis and increased mortality compared with bare-metal stents (BMS) emerged from the European Society of Cardiology meeting in the fall of 2006 (2). These reports were eventually thought to be not entirely accurate owing to incomplete data and the methods of analysis. However, media attention, litigation concerns, and physician confusion resulted in a remarkable 42% decrease in the sales of DES over the next 6 months (3). Was the cardiology community overreacting, or was this drop in utilization of DES justified?

The FDA Process
To address these concerns, the FDA convened the Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to fully characterize the risk of DES thrombosis (4). They concluded that, compared with BMS, both types of FDA-approved DES (Cypher [Cordis, Miami Lakes, Florida] and Taxus [Boston Scientific, Natick, Massachusetts]) are associated with a small increase in stent thrombosis that emerges 1 year after stent implantation. However, this was not associated with an increased risk of death and MI (possibly owing to insufficient numbers or being offset by a reduction in events from prevention of restenosis and additional revascularization procedures). They concluded that concerns about thrombosis do not outweigh the benefits of DES when implanted for approved indication.

The FDA panel also observed that at least 60% of current DES use is off-label, and off-label use is associated with increased events. However, they acknowledge that “with more complex patients there is an expected increased risk in adverse events” and noted that the FDA does “not regulate how [DES] are used by individual clinicians in the practice of medicine” (4).

Although some have accused our regulatory agency of being too lenient, the FDA approval process is thought to be more arduous, expensive, and delayed than in most other countries (5). Even after initial FDA approval, expanding the approved indications is costly and requires 4 or more years of work (6). Some have estimated that excessive delays in FDA approval may have resulted in death in hundreds of thousands of patients and morbidity in millions of Americans (5).

Although the current controversy surrounds off-label use of DES, even balloons and BMS have very limited indications (7). Moreover, aspirin, unfractionated heparin, and clopidogrel are not FDA approved for routine elective percutaneous coronary intervention (PCI). Clearly, an interventional cardiologist would not omit these important antithrombotic agents even though they are not FDA approved for PCI. Likewise, physicians must use their clinical judgment in deciding the best device to use in the coronary artery. In fact, FDA guidelines acknowledge that “good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment (6–8)” and does not confine the use to FDA-approved indications.

DES: Outcomes With Off-Label Compared With FDA-Approved Indications
In several clinical series, off-label use occurred in nearly 60% of patients undergoing DES. These patients are a high-risk population with numerous comorbidities, unfavorable lesion morphology and unstable clinical presentations. Similar to BMS use for off-label indications, the results obtained with DES were generally less favorable than in patients treated for “on-label” indications.

Beohar et al. (9) reported a multicenter registry in which 5,541 patients received DES, of which 47% were for off-label or untested indications. The 30-day risk of death, myocardial infarction (MI), or stent thrombosis and 1-year rate of target vessel revascularization (TVR) was significantly higher when DES were used off-label compared with approved indications; however, absolute event rates were quite low. Win et al. (10) reported a multicenter registry of 3,323 patients treated with DES, of whom 55% had at least 1 off-label indication. They noted similar mortality but a higher risk of MI, stent thrombosis, and TVR in off-label compared with FDA-approved DES indications.

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Rao et al. (11) reported the largest series: 408,033 procedures using DES in the National Cardiovascular Data Registry. When DES were used for off-label indications (acute MI, in-stent restenosis, bypass grafts, chronic total occlusions), the rates of in-hospital events were actually lower than expected from a validated model. These data suggest that case selection and physician decision making regarding use of DES for off-label indications appears to be safe and appropriate.

**DES Compared With BMS for Off-Label Indications**

In this issue of the *Journal*, Applegate et al (12) report their single-center observational study of 1,164 consecutive patients treated with BMS (before availability of DES) and 1,285 consecutive patients treated with DES. Stents were used for off-label indications in 75% of BMS and 80% of DES, attesting to the complexity of some cardiology practices. As expected, off-label use of either stent type was associated with worse outcomes at 2 years than on-label applications. However, for high-risk off-label indications, DES was superior to BMS at reducing death (hazard ratio [HR] 0.72) and the combined end point of death or nonfatal MI (HR 0.78). Limitations of this study include the lack of randomization, the fact that the BMS group was historical, changes in pharmacotherapy over time, and that the study was underpowered to determine stent thrombosis. However, better clinical outcomes with DES and no increase in stent thrombosis at 2 years should be reassuring to the interventional cardiology community.

Although randomized trials of off-label DES versus BMS have not yet been reported, numerous registries and randomized trials suggest that DES are safe and effective in subsets of patients and lesions that were not tested in the pivotal trials (13,14). Over the past year, several prospective randomized trials demonstrated improved angiographic and clinical outcomes comparing DES with BMS in complex lesion subsets (15), long lesions requiring overlapping stents (16), in-stent restenosis (17–19), saphenous vein grafts (20), chronic total occlusions (21), and 8 different primary PCI trials (22).

Because off-label use of both BMS and DES is widespread, one may look to large population registries to determine safety. Although the original SCAAR (Swedish Coronary Angiography and Angioplasty Registry) publication suggested an increase in late events in DES-treated patients (23), a larger more updated report showed a 50% reduction in restenosis and similar long-term mortality. Furthermore, there was a significant reduction in MI/death within the first 6 months after DES, which was no longer significant at 4 years (24). Similarly, registries from Canada and Denmark have demonstrated that DES were associated with reduced TVR with either superior or similar rates of death and MI compared with BMS (25,26).

Finally, Settler et al. (27) conducted a meta-analysis of all 38 trials (18,023 patients) that prospectively randomized patients to DES, including trials of primary PCI and off-label indications. At 4 years of follow-up, mortality and the risk of stent thrombosis were similar between DES and BMS. Interestingly, sirolimus-eluting stents were associated with a significant reduction in the risk of MI (HR 0.81, 95% confidence interval [CI] 0.66 to 0.97; p = 0.03) compared with BMS, and there was a significant reduction in target lesion revascularization (HR 0.70, 95% CI 0.56 to 0.84; p = 0.0021). The authors concluded that sirolimus-eluting stents seemed to be clinically better than either BMS or paclitaxel-eluting stents.

In summary, although additional trials are warranted, it appears that DES are safe and effective both for FDA-approved indications as well as for many off-label indications. Physicians seem to be using their best judgment to use off-label DES for lesions at high risk of restenosis, namely, small vessels, long lesions, in-stent restenosis, chronic occlusions, or vein grafts. These applications seem very reasonable. However, the use of DES for primary PCI remains controversial, with less restenosis benefit, more patient noncompliance with clopidogrel, and higher risk of stent malapposition due to size mismatch. Therefore, in my practice I avoid DES for primary PCI but use them liberally in most other patients. Of course, the DES field is always changing, and with the wide adoption of prolonged dual antiplatelet therapy (28), high pressure inflations for stent deployment, and increased use of imaging techniques to assure stent apposition, we hope that late stent thrombosis will no longer be a concern.

**References**


