

ATHENS CARDIOLOGY UPDATE 2010

Do the New Data on Second-Generation Drug Eluting Stents Provide Reassurance on Safety, Efficacy, Even for Off-Label Use?

Ioannis Iakovou, MD, PhD

1st Cardiology Department, Onassis Cardiac Surgery Center, Athens, Greece

KEY WORDS: *bleeding complications; stent restenosis; everolimus; zotarolimus*

ABBREVIATIONS

DES= drug-eluting stents
DAH= delayed arterial healing
EES= everolimus eluting stents
MACE= major adverse cardiac events
PES= paclitaxel eluting stents
TLR= target lesion revascularization
TVR= target vessel revascularization
ZES= zotarolimus eluting stents

Correspondence to:
Ioannis Iakovou, MD
1st Cardiology Department
Onassis Cardiac Surgery Center
356 Syggrou Ave
17674, Athens, Greece
Fax: +2109493336
E-mail: iako@hol.gr

FIRST GENERATION DRUG-ELUTING STENTS

In in-stent restenosis, drug-eluting stents (DES) are superior compared with bare metal stents (BMS). However, there are concerns about safety because of the reports of increased risk of late and very late stent thrombosis. Stent thrombosis remains a major pitfall in contemporary percutaneous coronary intervention (PCI), leading to high rates of death and nonfatal myocardial infarction.^{1,2} After the US approval of the first two DES, the sirolimus-eluting stent (Cypher) in 2003 and paclitaxel-eluting stent (Taxus) in 2004, concern was raised about the safety of the devices due to the occurrence of late and very late stent thrombosis. Pooled analyses of available randomized trials at the time, however, showed similar rates of death and myocardial infarction in patients treated with one of these DES compared to the BMS counterpart in randomized clinical trials.³ Registry studies also supported the safety of DES in unselected patients and off-label type lesions and identified predictors of stent thrombosis (Fig. 1).^{4,5} Nonetheless, knowledge of delayed healing in DES and concern for stent thrombosis led to the recommendation to increase the duration of dual anti-platelet therapy with aspirin and clopidogrel in patients treated with a DES to 12 months.⁶ The sirolimus-eluting (SES) and paclitaxel-eluting (PES) DES are often referred to as the *first-generation DES*.

SECOND GENERATION DES & CLINICAL STUDIES

More recently, two additional DES were approved in the US, the everolimus-eluting stent (EES) (Xience V) in 2007 and the zotarolimus-eluting stent (ZES) (Endeavor) in 2008. These two newer DES have similar basic components with the initially approved DES, with a stent platform, polymer and anti-restenotic drug. Due to advances in stent platforms, delivery systems and polymer biocompatibility coupled with the later time of approval, they are referred to as *second-generation DES*. These DES are designed from a cobalt–chromium alloy and are thinner and more flexible than the first-generation DES.

The antirestenotic efficacy of DES technology is based on the local delivery and modulated release of cytotoxic drugs targeted at inhibition of neointimal hyperplasia. Control of drug-release kinetics is a critical component of device efficacy. To date this has been most effectively performed by stent coatings comprised of non-erodable

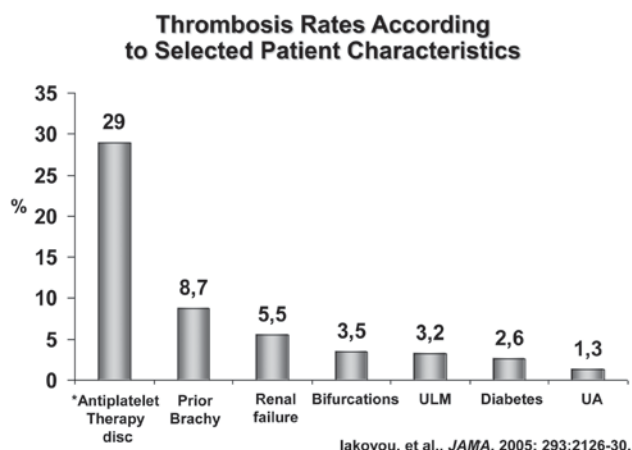


FIGURE 1. Incidence of stent thrombosis in patients with selected characteristics.⁵

(permanent) polymer which facilitate drug loading and delay elution of the active drug. In fact all 4 systems currently approved by the Food and Drug Administration (FDA) use a permanent polymer-based drug release system. Balancing the need for lipophilicity (to bind active drug) with hydrophilicity (which offers superior biocompatibility) is a key challenge in polymer technology. Delayed arterial healing (DAH) following DES implantation has been demonstrated in human autopsy studies and animal models and is implicated in late thrombotic occlusion and delayed loss of antirestenotic efficacy. It is characterized by 1) persistent fibrin deposition; 2) delayed endothelialization; 3) chronic inflammation; and 4) persistent platelet activation. Within segment heterogeneity in degree of healing is typical. Inflammatory response to polymer residue plays an important role and may be non-specific (monocyte-macrophage predominant) or hypersensitivity related.⁷ Failure of early preclinical models to sufficiently predict DAH in man was an important problem. Second-generation DES attempt to address the issue of DAH by using thinner stent struts, lower drug load and more biocompatible polymer. However, substantive comparative data among DES are lacking.

The SPIRIT program evaluated Xience V compared to Taxus in a series of studies. In patients with simple lesions and low-risk profiles, the Xience V resulted in reduced late loss at 6 to 8 months and non-inferior rates of 9-month target vessel failure compared to the Taxus (Fig. 2).⁸⁻¹¹ The findings of the COMPARE trial suggest an even greater benefit of Xience V compared to Taxus when used in unselected patients with potentially more complex lesion types than examined in the SPIRIT trials. However, longer follow-up is needed to determine if the initial benefits seen with Xience V will persist.

In terms of safety, the SPIRIT studies were not powered to detect differences in rare events such as stent thrombosis, but mortality was similar and myocardial infarction rates

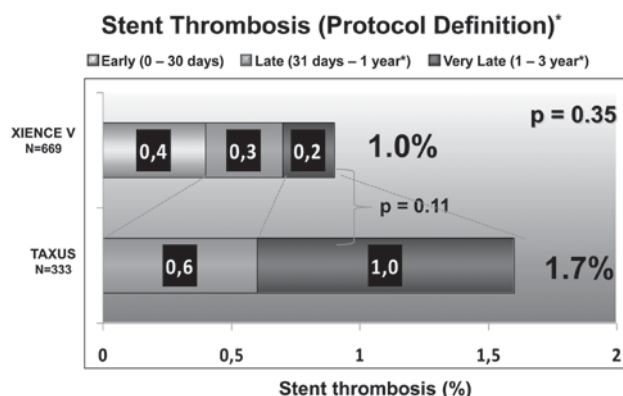


FIGURE 2. Incidence of stent thrombosis in SPIRIT III trial.¹¹

similar or lower in Xience compared to Taxus.⁸⁻¹⁰ Although the rates of stent thrombosis were numerically lower in the Xience V patients, the relative safety compared to Taxus in patients on or off dual anti-platelet therapy is not certain. The low rates of late and very late stent thrombosis with Xience are encouraging. Pre-clinical studies of stent healing suggest that endothelialization, a surrogate for stent thrombosis risk, is more rapid with Xience than the other 3 DES but that by 28 days strut coverage is similar.

The Xience V Stent Evaluated at Rotterdam Cardiac Hospital (X-SEARCH) registry is a single-center registry of 649 consecutive patients treated with EES. Patients treated with the Xience stent were compared with patients who were treated in the past with BMS, SES (RESEARCH registry) and PES (T-SEARCH registry). In this registry, patients treated with Xience were older; more often had myocardial infarction, and had more complicated lesions compared to the other groups. At 6 months, after adjustment, Xience was superior to BMS for target vessel revascularization and major adverse cardiac events (MACE), and had similar clinical outcomes to SES. Similar to the SPIRIT trials, PES had a higher risk of MACE compared to EES, extending the findings to a high risk, all-comers population.¹²

NEWER RANDOMIZED CLINICAL STUDIES

Very recently, the following studies with extended follow-up from randomized clinical trials for the first “second-generation” DES have been published for the first time and should be “reassuring” in terms of clinical benefit and safety of these devices:

- Four-year results from ENDEAVOR II, demonstrating the superiority of the Endeavor zotarolimus-eluting stent over the bare-metal Driver stent in reducing repeat target vessel revascularization (TVR), with no significant differences

in quality-adjusted survival or cost.¹³

- Three-year results from the SPIRIT II study of the Xience V everolimus-eluting stent vs the Taxus stent, demonstrating lower rates of cardiac death, myocardial infarction, target lesion revascularization (TLR), stent thrombosis, and major adverse cardiac events (MACE) in the Xience-treated patients.¹⁴
- Three-year results from the ENDEAVOR III trial, comparing the Endeavor DES with the Cypher sirolimus-eluting stent, suggesting that the newer stent is associated with a reduced rate of death or myocardial infarction, although also with higher use of bypass grafting (CABG). Costs are similar for the use of both stents.¹⁵
- Two-year results from the ENDEAVOR IV trial comparing the Endeavor with the Taxus. The results showed similar overall TVR, but fewer myocardial infarctions in the Endeavor group, with similar TLR and no differences in costs or cost-effectiveness.¹⁶

In addition, the “extended-use” of these stents (i.e., in those with more complex lesions/disease than the kinds of patients enrolled in the pivotal trials) does not seem to be accompanied with higher rates of complications. This has been shown by the very recent publication of an Italian registry which suggested that the devices were used predominantly for off-label use (almost 72% of stents) and associated with a relatively low rate of MACE (10.6%) and TLR (7.9%) and the E-Five registry of the Endeavor stent. In the latter study, researchers reported 12-month results, with relatively low rates of MACE, cardiac death, myocardial infarction, and TLR, despite the fact that 74.4% were «high-risk».^{17,18}

CONCLUSION AND FUTURE PERSPECTIVE

Each DES differs in stent platform, drug, and polymer, which may result in differences in stent performance in terms of efficacy in preventing intimal hyperplasia and safety from stent thrombosis due to delayed healing. In addition to advantages in deliverability, the second-generation DES may have superior long-term safety with similar or greater clinical efficacy compared to first-generation DES. More head-to-head randomized controlled trials are needed, however, before conclusions can be made. At present the focus of development of DES is towards biodegradable polymer coatings which offer the attractive prospect of controlled drug-release without the potential for late polymer-associated adverse effects. Whether their promise for greater safety holds true, it remains to be seen in the upcoming and ongoing studies.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents

- versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–1323.
2. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005;294:1215–1223.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus-and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998–1008.
4. Abbott JD, Voss MR, Nakamura M, et al. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice: findings from the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol* 2007;50:2029–2036.
5. Iakovou I, Schmidt T, Ge L, Sangiorgi GM, et al. Angiographic patterns of restenosis after paclitaxel-eluting stent implantation. *J Am Coll Cardiol* 2005;45:805–806.
6. Iakovou I, Mehran R, Dangas G. Thrombosis after implantation of drug-eluting stents. *Hellenic J Cardiol* 2006;47:31–38.
7. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol* 2008;52:333–342.
8. Serruys PW, Ong ATL, Piek JJ, et al. A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial. *Eurointervention* 2005;1:58–65.
9. Tsuchida K, Piek JJ, Neumann FJ, et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). *Eurointervention* 2005;1:266–272.
10. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *Eurointervention* 2006;2:286–294.
11. Onuma Y, Serruys PW, Kukreja N, Stone GW, Spirit II, Invest III. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: pooled analysis of two-year clinical follow-up from the SPIRIT II and III trials. *J Am Coll Cardiol* 2009;53:A9–A10.
12. Onuma Y, Kukreja N, Piazza N, et al. The everolimus-eluting stent in real-world patients 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) Registry. *J Am Coll Cardiol* 2009;54:269–276.
13. Eisenstein EL, Wijns W, Fajadet J, et al. Long-term clinical and economic analysis of the Endeavor drug-eluting stent versus the driver bare-metal stent: 4-year results from the ENDEAVOR II Trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578-Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2009;2:1178–1187.
14. Garg S, Serruys P, Onuma Y, et al. 3-year clinical follow-up of the XIENCE V Everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: The SPIRIT II trial (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2009; 2:1190–1198.

15. Eisenstein EL, Leon MB, Kandzari DE, et al. Long-term clinical and economic analysis of the endeavor zotarolimus-eluting stent versus the Cypher sirolimus-eluting stent: 3-year results from the ENDEAVOR III trial (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2009; 2:1199-1207.
16. Leon MB, Kandzari DE, Eisenstein EL, et al. Late safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with de novo coronary lesions: 2-year follow-up from the ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578]-Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2009; 2:1208-1218.
17. Latib A, Ferri L, Ielasi A, et al. Clinical outcomes after unrestricted implantation of everolimus-eluting stents. *JACC Cardiovasc Interv* 2009; 2:1219-1226.
18. Lotan C, Meredith IT, Mauri L, et al. Safety and effectiveness of the endeavor zotarolimus-eluting stent in real-world clinical practice: 12-month data from the E-Five Registry. *JACC Cardiovasc Interv* 2009; 2:1227-1235.