EuroIntervention

Spirit First - Another hurdle is cleared

Jeffrey J. Popma*, MD, and Mark Tulli, MD

From the Department of Internal Medicine (Cardiovascular Division) of the Brigham and Women's Hospital, Boston, MA, USA

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Drug eluting stents (DES) are now the default therapy for patients undergoing percutaneous coronary intervention (PCI) for native vessel coronary artery disease. Three DES are currently available, having shown clinical and angiographic superiority over bare metal stents in large randomized clinical trials[1-3]. These studies have suggested that each of the DES components – the stent platform, the elution polymer, and the specific antiproliferative agent – may provided particular advantages in different clinical scenarios. The CYPHER™ (Cordis Corporation, Miami Lakes, FLA) stent is comprised of a stainless steel stent platform, a durable co-polymer mixuture of polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA), and the G1 cell cycle inhibitor sirolimus, which elutes completely from the polymer within 30 days[1]. The TAXUS™ (Boston Scientific, Natick, MA) stent employs a stainless steel stent platform, a polyolefin polymer derivative, and microtubular stabilizing agent paclitaxel, whose two-phase 30-day polymeric release kinetics that provides its antiproliferative effect[2]. The ENDEAVOR™ stent (Medtronic, Minneapolis, MN) utilizes a cobalt chromium stent platform, a durable, antithrombotic, phoshorylcholine (PC) encapsulated coating, and another G1 cell cycle inhibitor, zotarolimus, which elutes from the PC coating over several days[4].

Results from large (> 1,000 patients) randomized trials show that these DES reduced clinical events by 50-70% compared with bare metal stents[1-3]. The benefit appears similar in a variety of patient and lesion subsets[5-7], including those with diabetes[8], long lesions, and small vessels[7]. Deliverability becomes an important performance measure in patients as the lesion complexity increases, and newer DES may provide a particular advantage over prior stent designs, and may address the small (<5-10%) but lingering failure rate associated with conventional DES use.

Novel drug eluting stents

A number of important lessons have been learned as alternative DES systems have been evaluated. Some DES programs have had limited clinical efficacy[9], likely do to very rapid drug release or ineffective antiproliferative agents, and others have shown potential toxicity, such as paclitaxel eluting stent using a durable polymeric sleeve that was associated with high acute stent thrombosis rates[10] and delayed restenosis[11]. The elution of actinomycin-D in the ACTION trial found higher than expected restenosis rates and aneurysm formation in some patients treated with this DES[12].

The current study reports very favorable one year angiographic and ultrasound results associated with the use of the XIENCE™ stent. The components of the XIENCE™ stent provide potential improvements over prior generations of DES. The cobalt chromium rapid-exchange VISION™ stent (Guidant Corporation, Santa Clara, CA) may provide enhanced deliverability and radiopacity with thinner strut filaments. The durable polymer appears to provide sustained drug elution and vascular compatibility in these early studies. The antiproliferative agent, everolimus, has proven safety a much higher systemic doses in patients following renal transplantation. Compared to bare metal stents, the XIENCE™ DES system is associated with significantly less intimal hyperplasia at one year using a variety of angiographic and ultrasound parameters. This is an important hurdle to clear, and this system has the "green light" to proceed with larger, more definitive clinical trials.

Other novel systems that alter one of the three components of the DES are also undergoing evaluation. Bioabsorbable polymeric coatings may obviate the potential problems associated with durable polymer implantation. The Biosensors STEALTH stent, the FUTURE DES program using everolimus[13], and the Conor PISCES stent using

* *Corresponding author: Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA*

paclitaxel[14] are three examples of DES systems with an erodable polymer and favorable initial studies. Other agents, such as those that promote endothelial cell regeneration, are also under evaluation to promote more rapid healing of the arterial wall, potentially reducing intimal hyperplasia after stent placement[15].

What is considered "standard of care" for future first in man studies?

The current study used a bare metal stent as the comparator group, and may likely be one of last of its kind, considering the profound reductions in intimal hyperplasia associated with the use of DES. With our understanding of restenosis following bare metal stent implantation, one would wonder whether a control group is even required in these pilot evaluations. Accordingly, initial studies with other novel designs have either been performed as single arm registries (ENDEAVOR-1) or randomized comparisons with another drug eluting stent (ZOMAXX-I).

Is in-stent late lumen loss a suitable primary endpoint for initial DES studies?

In-stent late lumen loss is the most commonly used endpoint for the determination of the biologic effects of the new DES. In-stent late lumen loss can be measured in a continuous fashion over several timepoints, and is a suitable surrogate marker for binary angiographic restenosis in DES versus bare metal stent studies[16]. In addition, it has been advocated as a suitable primary endpoint for evaluating drug-eluting stents in early, nonrandomized studies[17]. As the objective of this study was to compare the effect of the XIENCE™ stent and a bare metal stent on the degree of intimal hyperplasia one year after PCI, the primary endpoint of a reduction in late lumen loss was easily achieved, suggesting a profound biologic effect associated with the use of the XIENCE™ stent.

In larger studies, the relationship between late lumen loss and clinical events is less well defined, and appears dependent on the mean late lumen loss, its variance, the rightward skewedness of the late lumen loss histogram, which all affect the ultimate need for clinical revascularization[18]. With sirolimus eluting stents, the pattern of late loss follows a peculiar behavior, different from lesions treated with conventional stents[19]. This unusual statistical distribution of a biological "all-or-none" response of restenosis after sirolimus-eluting stenting is also suggested in current study – the late lumen loss of 0.24 mm was associated with a target lesion revascularization rate of 7.7%, not different from the clinical restenosis rate in patients treated with a bare metal stent. Although the number of patients is small in this series, similar discordance was found in a larger comparative DES trial[20]. Thus, while in-stent late lumen loss seems to be a suitable surrogate for clinical events in DES versus bare metal stent studies[16], it may be too sensitive as a surrogate for "reasonable" equivalency in larger DES versus DES trials. Clearly more studies in the area are needed.

Is intimal hyperplasia permanently suppressed or just delayed with DES use?

Late angiographic angiographic evaluations have typically shown regression of intimal hyperplasia late (one to three years) after bare metal stent implantation[21,22]. In contrast, some DES systems have show very mild to moderate progession of intimal hyperplasia within the stent between 4-6 months and one to two years after stent placement[4,23]. Only one DES system had shown marked progression of intimal hyperplasia after six months, likely related to the inflammatory effects of the durable polymeric sleeve[11].

One intriguing aspect of this study is that there is a small (0.14 mm) amount of "catch-up" in late lumen loss from the 6-month to the one-year angiogram, both by angiographic and by intravascular ultrasound parameters. It is unlikely that this very small progression in intimal hyperplasia will have any significant clinical effect on outcomes, but it does generate a number of interesting questions. Do the processes that initiate intimal hyperplasia persist beyond 30 days? Does the durable polymer impart a risk for ongoing inflammation and intimal tissue growth? Does the suppression of vessel wall repair predispose to the development of atherosclerosis within the stent? Very late angiographic and ultrasound studies would be useful in sorting out these issues with this and other DES systems.

Can we be certain that drug eluting stents do not pose a late safety risk?

Extended (2-6 month) antiplatelet therapy with aspirin and a thienopyridine derivative has been recommended to all patients receiving a drug eluting stent. Aspirin is generally continued indefinitely for secondary prevents, and a thienopyridine derivative, most commonly clopidogrel, may be continued for variables periods up to one year after coronary intervention to lessen the frequency of new events at remote sites[24,25]. Yet while there is little evidence to suggest that drug-eluting stents increase the risk of 30-day or one-year stent thrombosis[26], premature (< 3-6 months) discontinuation of the antiplatelet therapy has been associated with a markedly increased risk of stent thrombosis in clinical practice[27], a common scenario when bleeding occurs or urgent non-cardiac surgery is required. Furthermore, as clinical follow-up of patients is extended before one year, a small (0.4-0.5%) risk of late angiographic stent thrombosis persists with both the CYPHER™ and TAXUS™ stents[28].

There may be several potential causes for these infrequent late thrombotic events. One is that incomplete stent apposition and delayed endothelial healing may pose a risk for late thrombosis[29]. A second is that the polymer may cause sustained inflammation to the vessel wall[11,29-31]. Although the XIENCE stent evaluated in this study showed a low occurrence of acquired incomplete stent apposition, the effects of the long-term durable polymer on the vessel wall response will require additional study. The low frequency of the event rate makes exact delineation of late thrombotic events of this and other DES systems difficult to determine. Nevertheless, careful monitoring up to 5 years is needed with all new DES systems.

Next steps

Based on the favorable results reported in this first-in-man study, further clinical study of the XIENCE™ V DES system is justified. SPIRIT II, a 300-patient prospective, single-blind, European, randomized non-inferiority trial compares the XIENCE V stent with the TAXUS paclitaxel eluting stent in patients with native coronary artery disease. The primary endpoint of SPIRIT II is 6-month in-stent late loss, with important secondary clinical endpoints, such as target

lesion revascularization. Recruitment for SPIRIT II was completed in November, 2005, and results are anticipated within the next year. Yet another hurdle has been cleared. SPIRIT III is a 1,380-patient global clinical trial evaluating the XIENCE V Stent System in the United States and Japan. The 1,002-patient randomized portion in the United States is a prospective, randomized trial that compares the clinical and angiographic non-inferiority of the XIENCE V and TAXUS paclitaxel eluting stents. To date (November, 2005), the randomized U.S. trial has enrolled approximately 400 patients. These two large randomized trials will provide important information about the relative benefit on clinical endpoints of the XIENCE V stent system, including target lesion revascularization, major adverse clinical events, and early and late stent thrombosis. The results of these additional clinical studies are anxiously awaited.

References

1. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349(14):1315-23.

2. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350(3):221-31.

3. Fajadet J, Wijns W, Laarman G, Kuck K, Ormiston J, Münzel T, *et al.* A Randomized, Double-blind, Multicenter Study of the Endeavor ABT-578-Eluting Phosphorylcholine-Encapsulated Stent for Treatment of Native Coronary Artery Lesions: Clinical and Angiographic Results of the Endeavor II Trial. Late Breaking Clinical Trials 2005; American College of Cardiology.

4. Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Bonan R, Popma JJ, Cutlip DE, Fitzgerald P, Prpic R, Kuntz RE. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I trial. *EuroInterv.* 2005;1:157-164.

5. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, Degertekin M, Hofma SH, Sianos G, McFadden E, van der Giessen WJ, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. *J Am Coll Cardiol* 2004;43(11):1954-8.

6. Lemos PA, Saia F, Hofma SH, Daemen J, Ong AT, Arampatzis CA, Hoye A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;43(4):704-8.

7. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME; TAXUS V Investigators. 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(10):1215-23.

8. Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, Russell ME, Ellis SG, Mehran R, Stone GW; TAXUS-IV Investigators. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45(8):1172-9.

9. Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA, O'Shaughnessy C, Applegate RA, Cannon LA, Mooney M, Farah A, Tannenbaum MA, Yakubov S, Kereiakes DJ, Wong SC, Kaplan B, Cristea E, Stone GW, Leon MB, Knopf WD, O'Neill WW; DELIVER Clinical Trial Investigators. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. *Circulation* 2004;109(16):1948-54.

10. Grube E, Lansky A, Hauptmann KE, Di Mario C, Di Sciascio G, Colombo A, Silber S, Stumpf J, Reifart N, Fajadet J, Marzocchi A, Schofer J, Dumas P, Hoffmann R, Guagliumi G, Pitney M, Russell ME; SCORE randomized trial. High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization: one-year results from the SCORE randomized trial. *J Am Coll Cardiol* 2004;44(7):1368-72.

11. Virmani R, Liistro F, Stankovic G, Di Mario C, Montorfano M, Farb A, Kolodgie FD, Colombo A. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. *Circulation* 2002;106(21):2649-51.

12. Serruys PW, Ormiston JA, Sianos G, Sousa JE, Grube E, den Heijer P, de Feyter P, Buszman P, Schomig A, Marco J, Polonski L, Thuesen L, Zeiher AM, Bett JH, Suttorp MJ, Glogar HD, Pitney M, Wilkins GT, Whitbourn R, Veldhof S, Miquel K, Johnson R, Coleman L, Virmani R; ACTION investigators. Actinomycin-eluting stent for coronary revascularization: a randomized feasibility and safety study: the ACTION trial. *J Am Coll Cardiol* 2004;44(7):1363-7.

13. Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C, Gerckens U, Lansky AJ, Fitzgerald PJ. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* 2004;109(18):2168-71.

14. Serruys PW, Sianos G, Abizaid A, Aoki J, den Heijer P, Bonnier H, Smits P, McClean D, Verheye S, Belardi J, Condado J, Pieper M, Gambone L, Bressers M, Symons J, Sousa E, Litvack F. The effect of variable dose and release kinetics on neointimal hyperplasia using a novel paclitaxel-eluting stent platform: the Paclitaxel In-Stent Controlled Elution Study (PISCES). *J Am Coll Cardiol* 2005;46(2):253-60.

15. Aoki J, Serruys PW, van Beusekom H, Ong AT, McFadden EP, Sianos G, van der Giessen WJ, Regar E, de Feyter PJ, Davis HR, Rowland S, Kutryk MJ. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. *J Am Coll Cardiol* 2005;45(10):1574-9.

16. Mauri L, Orav E, Kuntz R. Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison [In Process Citation]. *Circulation* 2005;111(25):3435-42.

17. Mauri L, Orav E, Candia S, Cutlip D, Kuntz R. Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials [In Process Citation]. *Circulation* 2005;112(18):2833-9.

18. Ellis SG, Popma JJ, Lasala JM, Koglin JJ, Cox DA, Hermiller J, O'shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Stone GW. Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45(8):1193-200.

19. Lemos P, Mercado N, van DR, Kuntz R, O'Neill W, Serruys P. Comparison of late luminal loss response pattern after sirolimus-eluting stent implantation or conventional stenting. *Circulation* 2004;110(20):3199-205.

20. Morice M. The REALITY Trial. Late Breaking Clinical Trials at the American College of Cardiology, Orlando, FLA March 2005.

21. Hermiller JB, Fry ET, Peters TF, Orr CM, Van Tassel J, Waller B, Pinkerton CA. Late coronary artery stenosis regression within the Gianturco-Roubin intracoronary stent. *Am J Cardiol* 1996;77:247-251.

22. Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Yokoi H, Hamasaki N, Nosaka H. Three-year follow-up after implantation of metallic coronary artery stents. *N Engl J Med* 1996;334:561-566.

23. Sousa JE, Costa MA, Sousa AG, Abizaid AC, Seixas AC, Abizaid AS, Feres F, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries [In Process Citation]. *Circulation* 2003;107(3):381-3.

24. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, Topol EJ; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288(19):2411-20.

25. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358(9281):527-33.

26. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol* 2005;45(6):947-53.

27. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293(17):2126-30.

28. Ong A, McFadden E, Regar E, de JP, van DR, Serruys P. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 2005;45(12):2088-92.

29. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;109(6):701-5.

30. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents [In Process Citation]. *Circulation* 2005;112(2):270-8.

31. Carter AJ, Aggarwal M, Kopia GA, Tio F, Tsao PS, Kolata R, Yeung AC, Llanos G, Dooley J, Falotico R. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc Res* 2004;63(4):617-24.