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. These studies have suggested that each of the DES components – the stent platform, the elution polymer, and the specific antiproliferative agent – may provide 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 mixture 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. 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. The ENDEAVOR™ stent (Medtronic, Minneapolis, MN) utilizes a cobalt chromium stent platform, a polyethylene-co-vinyl acetate (PEVA) and polyvinyl propionate (PVPA), and another G1 cell cycle inhibitor, zotarolimus, which elutes from the PC coating over several days.

Results from large (>1,000 patients) randomized trials show that these DES reduced clinical events by 50-70% compared with bare metal stents. The benefit appears similar in a variety of patient and lesion subsets, including those with diabetes, long lesions, and small vessels. 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, 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 and delayed restenosis. 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.

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 at 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, and the Conor PISCES stent using...
with conventional stents. This unusual statistical distribution of late loss follows a peculiar behavior, different from lesions treated in a larger comparative DES trial. Thus, while in-stent late lumen of patients is small in this series, similar discordance was found in patients treated with a bare metal stent. Although the number rate of 7.7%, not different from the clinical restenosis rate of a biological “all-or-none” response of restenosis after sirolimus-eluting stenting is also suggested in current study – the late lumen more studies in the area are needed.

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. In addition, it has been advocated as a suitable primary endpoint for evaluating drug-eluting stents in early, nonrandomized studies. 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 skewness of the late lumen loss histogram, which all affect the ultimate need for clinical revascularization. With sirolimus eluting stents, the pattern of late loss follows a peculiar behavior, different from lesions treated with conventional stents. 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. Thus, while in-stent late lumen loss seems to be a suitable surrogate for clinical events in DES versus bare metal stent studies, 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. In contrast, some DES systems have show very mild to moderate progression of intimal hyperplasia within the stent between 4-6 months and one to two years after stent placement. 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. 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. Yet while there is little evidence to suggest that drug-eluting stents increase the risk of 30-day or one-year stent thrombosis, premature (< 3-6 months) discontinuation of the antiplatelet therapy has been associated with a markedly increased risk of stent thrombosis in clinical practice, 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.

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. A second is that the polymer may cause sustained inflammation to the vessel wall. 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


