# Everolimus for Stent-Based Intracoronary Applications

Eberhard Grube, MD, FACC, FECC, FACA, FSCAI, Lutz Buellesfeld, MD

Heart-Center Siegburg, Siegburg, Germany

*Everolimus, a novel proliferation signal inhibitor initially developed for the prevention of allograft rejection after organ transplantation, is a potent anti-proliferative and immunosuppressive agent. Compared to sirolimus, everolimus absorbs to local tissue more rapidly and possesses longer cellular residence time and activity. The stent-based intracoronary elution of everolimus was first investigated by BioSensors International using a bioabsorbable-PLA-polymer-coated S-Stent for drug delivery. Following preclinical animal studies that demonstrated excellent safety and efficacy of this device, the clinical FUTURE trial program was initiated. FUTURE I and II were designed to demonstrate safety and feasibility of the everolimus-eluting stent in a small patient population with focal* de novo *coronary lesions. At follow-up, an acceptable safety profile without evidence of stent thrombosis or late stent malapposition was observed. Moreover, these studies revealed a remarkable reduction of neointimal proliferation with everolimus-eluting stent implantation versus procedures utilizing bare-metal stents. Guidant Corporation licensed the exclusive rights to both the S-Stent and the bioabsorbable drug delivery platform. Guidant will conduct two pivotal trials (FUTURE III and IV) in order to demonstrate the efficacy of this stent design. FUTURE IV will make a non-inferiority comparison between everolimus and the already-approved drug eluting stent systems. Given the pooled results of FUTURE I and II, there is already some evidence suggesting that the everolimus-eluting stent is as potent a suppressor of reactive neointimal ingrowth as the sirolimus-eluting CYPHER™ stent. The everolimus-eluting coronary stent might shortly be established as a new and promising contender in the field of drug eluting stents for treatment of coronary heart disease.*

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**Key words:** Everolimus • Sirolimus • FUTURE Trial

Everolimus is a compound initially developed by Novartis Pharma AG. (Basel, Switzerland) for the prevention of allograft rejection in organ transplant patients. It is a novel proliferation signal inhibitor with potent antiproliferative and immunosupppressant properties, which has led to an intense interest in its use for the site-specific prevention of restenosis following coronary stent implantation.

## Pharmacodynamics of Everolimus

Everolimus is an orally active derivative of the immunosuppressant sirolimus (Rapamune®, Wyeth Laboratories, Philadelphia, PA), a macrolide synthesized by *Streptomyces hygroscopicus*. Everolimus, like sirolimus, blocks growth-factor derived cell proliferation, arresting the cell cycle in the late G1 phase.[1] It does not inhibit the synthesis of growth factors, but blocks growth factor-driven signal transduction in the cellular responses to alloantigens. In particular, IL-2- and IL-15-driven proliferation are inhibited, which is explained by block of p70S6 kinase.[2]

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The effect of everolimus is not restricted to T lymphocytes, but potentially affects other hematopoietic and non-hematopoietic cells, including smooth-muscle cells.[1] The IC50 for inhibition of smooth muscle cell proliferation with everolimus and sirolimus are similar.[3] Oral everolimus has been shown to reduce the development of post-cardiac transplant coronary vasculopathy.[4] Thus, this inhibitory action of everolimus on smooth-muscle cell proliferation, evidenced in animal models of vessel injury, has triggered interest in the use of everolimus as a stent coating for local inhibition of in-stent restenosis. Guidant Corporation (Indianapolis, IN) has acquired exclusive rights from Novartis to use everolimus for prevention and treatment of vascular disease via local delivery, including drug-eluting stents.

## The Everolimus-Eluting Stent

The advantage of more hydrophobic drugs like paclitaxel (as compared to hydrophilic agents) is slower transmural transport under the forces of diffusion and convection that allow for establishment of substantial partitioning and spatial gradients across the tissue. As paclitaxel is a known cytotoxin, and the endothelium is the binding site showing greatest attraction for lipophilic compounds, the establishment of such high localized and long-lasting concentrations in the endothelium could be expected to inhibit or at least reduce the rate of endothelial healing.[5] The observed rapid endothelial healing effects of everolimus-coated stents in pigs is possibly due to the less toxic nature of the compound for endothelial cells, and possibly a more uniform distribution of the drug in vitro due to its less hydrophobic affinities. Furthermore, everolimus is a derivative of sirolimus, rendered less hydrophobic by means of alkylation. Due to these specific pharmacokinetics, it can be hypothesized that feasibility and efficacy of an everolimus-eluting stent might be advantageous compared to sirolimus- and paclitaxel-eluting stent designs.

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For preclinical and clinical evaluation of safety and efficacy of an everolimus-eluting stent coating, a new stent was introduced based on the bare-metal S-Stent scaffold (BioSensors International, Singapore). With the abluminal side of the stent covered by a resorbable "composite" coating, the stent contains more than 50% of the immunosuppressive drug within a polyhydroxy acid, biodegradable polymer matrix. This ultrathin (< 10 µm) composite coating provides high adhesion to the metal substrate, controlled polymer resorption characteristics, high surface availability of the active agent, high mechanical flexibility, abrasion resistance, and strength. The drug release is based on a rapid resorption of an amorphous glassine solid without any topcoat. Both the polymer and the immunosuppressive drug are resorbed into the surrounding tissue.

Preclinical animal studies suggested the biocompatibility and efficacy of this everolimus-eluting stent compared to bare metal stents at 30 days, demonstrating a significant inhibition of smooth muscle cell proliferation with complete re-endothelialization and no evidence for delayed vessel wall healing (Figure 1).[6,7] These data formed the basis for first-in-man studies of the everolimus-eluting stent.

## Clinical Studies With the Everolimus-Eluting Stent

*FUTURE I Feasibility Study*

The FUTURE I trial was the first-in-man clinical trial with the Biosensor everolimus-eluting stent, which evaluated both safety and feasibility of this stent design in treatment of de novo coronary lesions. FUTURE I was a prospective, single-center, sin-

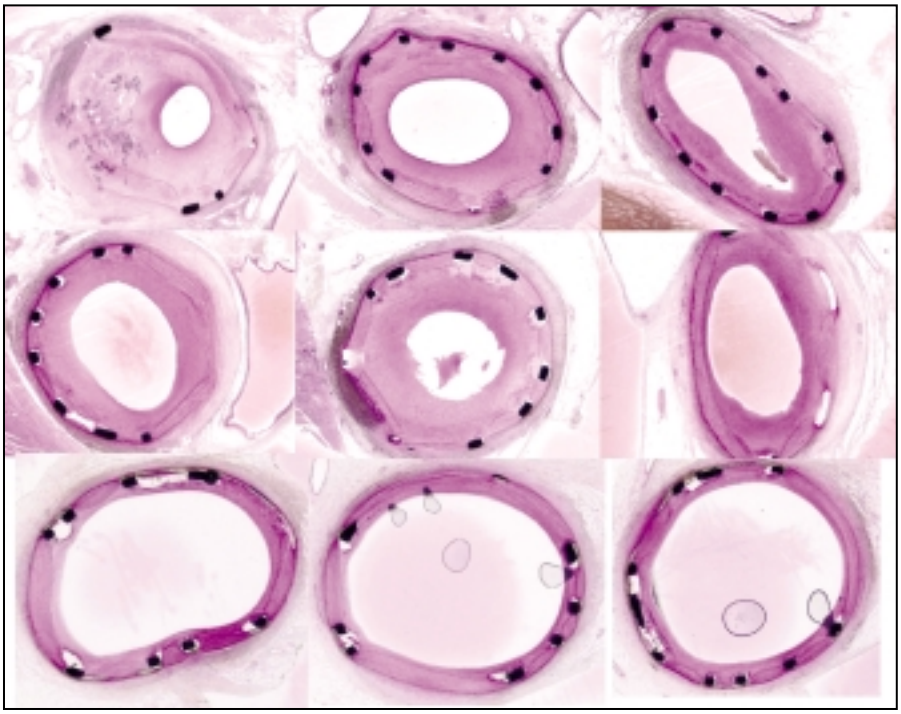

**Figure 1.** *Typical examples of stent cross-sections of porcine coronary arteries at 28 days in a balloon overstretch model (1:3 Balloon/artery ratio). Top: Bare stent. Middle: Polymer only coated stent. Bottom: High dose everolimus stent. Courtesy of Saibal Kar, MD, Cedars Sinai Medical Center, Los Angeles, CA.*

gle-blinded, randomized trial including 27 and 15 patients with native de novo coronary lesions allocated for drug and control groups respectively. Patients were included if angiography showed lesion length less than 18 mm, diameter stenosis between 50% and 99%, and vessel diameter between 2.75 and 4.0 mm. Patients were excluded if they had diabetes mellitus, an acute myocardial infarction within the 4 weeks prior to intervention, in-stent restenosis, or a left ventricular ejection fraction less than 30%.

The primary endpoint was 30-day survival, free from major adverse coronary events (MACE). MACE was defined as death from any cause, Q-wave myocardial infarction (MI), target vessel revascularization, or stent thrombosis. Secondary endpoints were device success, MACE, and restenosis rate at 6-month follow-up. Clinical evaluation was conducted at 1, 6, and 12 months after stent implantation. Coronary angiographic and intravascular ultrasound imaging was performed before and after stent implantation and at 6-month follow-up visit. Baseline demographics and lesion characteristics were similar between both study groups.

At 30 days after stent implantation, there was no incidence of MACE or stent thrombosis in either cohort, indicating a comparable safety profile for the everolimus-eluting stent relative to the uncoated control stent.[8] At 6 months, the MACE rate was 7.7% (2 events in 26 patients) for the everolimus group compared with 7.7% (1 event/13 patients) in the control group. The two MACE in the everolimus group were a pulmonary disease-related non-cardiac death and a target lesion revascularization due to in-segment restenosis at the distal margin of the study stent. There were no additional MACE events between 6 and 12 month follow-up in either group.

Follow-up angiography was performed in 25 everolimus patients (93%) and 11 control patients (73%) at 6 months. All quantitative angiographic indices (minimum lumen diameter, % diameter stenosis, lumen loss) were significantly ($P < .001$) improved in the everolimus stent group, compared with the control. The binary in-stent restenosis rate was 0.0% in the everolimus-eluting stent group versus 9.1% in the control. In-segment restenosis rates were 4.0% (1/25) versus 18.2% (2/11), respectively. In-stent late loss decreased from 0.85 mm (control) to 0.11 mm (everolimus stent).

Intravascular ultrasound examination at 6 months revealed a significant reduction of percent neointimal volume in the everolimus group (2.9 ± 1.9) compared with the control group (22.4 ± 9.4). In addition, there were no late acquired incomplete stent appositions in either group.[9]

With these results, an acceptable safety profile was established for the everolimus-eluting stent with a biodegradable coating system, with a very low MACE rate up to 6 months post-implantation. With all patients treated for 3 months with clopidogrel, no stent thromboses were reported in either group. The everolimus stent group demonstrated significant and concordant improvements in the sensitive intravenous ultrasound (IVUS) and quantitative computer-assisted angiography (QCA) parameters, with an 88% reduction of in-stent late loss in the everolimus-eluting stent group and an 87% reduction of % neointimal volume.

Moreover, the in-stent late loss of 0.11 mm suggests that the dosage as well as the release pattern of

everolimus disrupts the restenotic cascade, while allowing sufficient neointimal growth to promote healing and avoid late stent thrombosis. In order to extend these results, the multicenter FUTURE II study was conducted, which included patients with diabetes.

*FUTURE II Feasibility Study*

FUTURE II was a three-center study with a total of 64 patients randomized in a single-blind 1:2 fashion (21 patients in the everolimus group; 43 patients in the control group). The purpose of the "reverse" randomization was to equalize the total numbers of active and control arms included in both the FUTURE I and II studies. Baseline characteristics of both groups in FUTURE II were similar, with diabetics representing 23.8% (everolimus group) and 27.9% (control) of patients. At 30-day follow-up, there were no adverse cardiac events in the everolimus group versus one event in the control (2.3%; non-Q-wave MI).[10] At 6 months post-stent implantation, the MACE rate was 4.8% versus 17.5% in the everolimus and control groups respectively. Only 1 target lesion revascularization was observed in the everolimus stent group, due to a proximal edge (in-segment) restenosis. The 6-month binary restenosis rate was 0% (in-stent) and 4.8% (in-segment) for everolimus-eluting stents compared to 19.4% and 30.4% in the control. IVUS analysis revealed a significant reduction of the percent neointimal volume and no evidence of late stent malapposition in either treatment group.

Given these data, FUTURE II supported and extended the safety and feasibility results observed in FUTURE I by expanding treatment to a higher risk patient population, which included diabetics and patients with longer lesions. Finally, the pooled data analysis revealed an in-stent late lumen loss of 0.12 mm vs. 0.85 mm (Figure 2) as well as a binary restenosis rate of 0.0% vs. 17.0% (in-stent) and 4.3% vs. 27.7% (in-segment) in the combined everolimus and control groups respectively.

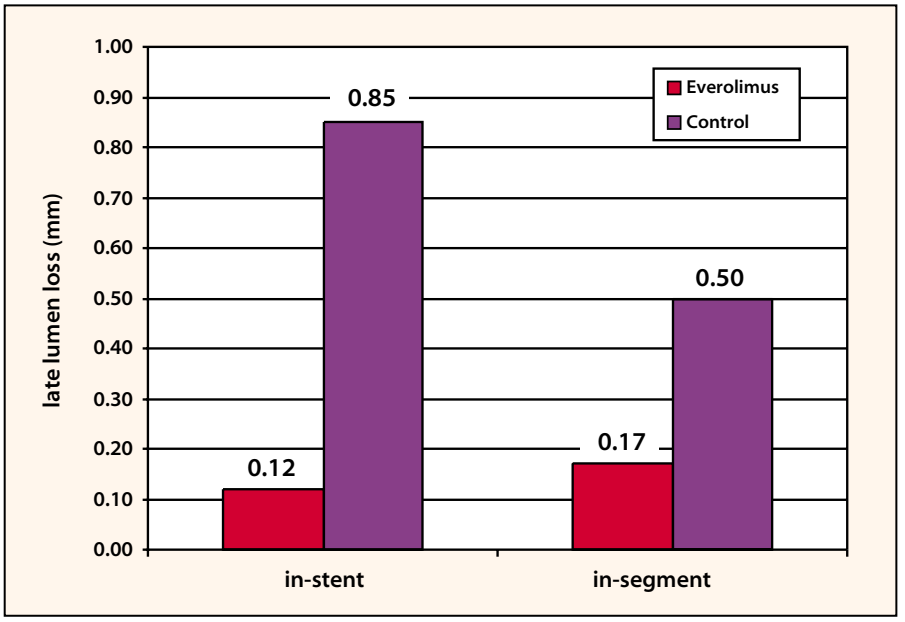


**Figure 2.** *FUTURE I and II pooled data analysis: Late lumen loss (mm).*

Based on these findings, Guidant Corporation entered into an exclusive agreement with BioSensors to enhance the everolimus-eluting S-Stent. Placing the S-Stent on the MULTI-LINK VISION® everolimus delivery system to improve performance, this device was re-named the "CHAMPION™" stent. In this stent design, the drug is loaded on the abluminal stent side and demonstrates an elution profile of 70% in approximately 30 days and 85% in 90 days. Porcine over-stretch models recently performed and reported have consistently shown safety and efficacy of this stent design with completeness of re-endothelialization of the CHAMPION™ stent similar to the control bare stent. Anticipating favorable results of these tests, two clinical studies have been planned, FUTURE III and FUTURE IV.

*FUTURE III–The Superiority Study*

FUTURE III is planned as a multicenter randomized study for evaluation of the efficacy of the everolimus-eluting CHAMPION™ Everolimus-Eluting Coronary Stent System compared to the bare metal MULTI–LINK ZETA® Coronary Stent System in a total of 840 patients. Up to 80 sites will be included in this international superiority study. Primary endpoint is defined as in-stent late loss at angiographic follow-up. FUTURE III will be conducted as a series of 3 sequential randomized trials with different intervals of follow-up for angiography and IVUS imaging. In the first series, 120 patients will be randomized (CHAMPION™ vs ZETA®) and will undergo follow-up at 4 months. The next 360 randomized patients will undergo angiography at 6-month follow-up and the final 360 patients will have angiography at 12 months post-implantation. Sub-studies will examine the impact of diabetes as well as inflammatory markers (hs-CRP). Long-term follow-up will be performed in all

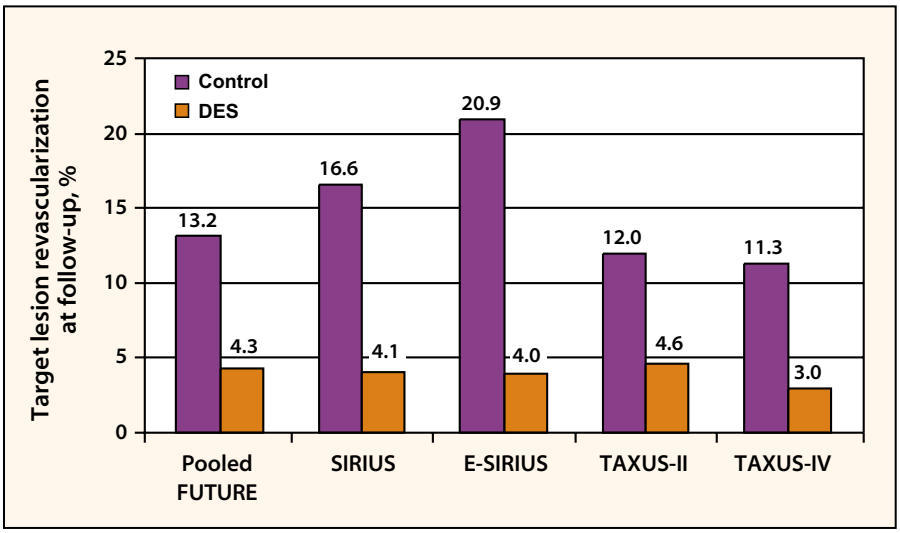


**Figure 3.** *FUTURE I and II in comparison. Overview of TLR rates in currently published drug-eluting stent trials.*

patients and the results pooled for analysis. FUTURE III enrollment started in April 2004.

*FUTURE IV – The US Pivotal Non-Inferiority Study*

In order to compare the everolimus-eluting stent system with already approved drug-eluting stents, FUTURE IV will be conducted as a randomized non-inferiority U.S. pivotal clinical trial. FUTURE IV is designed to secure U. S. FDA approval and will compare the CHAMPION™ Everolimus-Eluting Stent System to either the paclitaxel-eluting TAXUS™ (Boston Scientific, Natick, MA) or the sirolimus-eluting CYPHER™ (Cordis, Miami Lakes, FL) stent in a total of 975 patients at up to 80 study sites. Primary endpoint is angiographic in-segment late loss at 8 months. Secondary endpoint is clinically driven target vessel failure at 9 months. An angiographic and IVUS follow-up is scheduled at 8 months post stent implantation. Clinical follow-up will be performed at 1,6,8,9 and 12 months post-implantation, and then yearly for up to 5 years. Enrollment for this pivotal study is expected to begin in mid-2004.

## Conclusion and Perspective

Given the preclinical and clinical results observed so far, it can be anticipated that the everolimus-eluting CHAMPION™ stent is safe and highly effective in the prevention of restenosis in patients undergoing coronary interventions. Although similar in structure to sirolimus, everolimus is characterized by additional physicochemical properties that may be preferable for drug-eluting stent designs. Due to the current lack of head-to-head comparisons between everolimus and sirolimus/paclitaxel-eluting stents, it is difficult to compare the safety and efficacy data observed in FUTURE I and II with those observed with the already approved drug-eluting stent systems (CYPHER™, TAXUS™). However, safety results appear similar among the clinical studies of these three drug-eluting stent concepts. Moreover, in terms of efficacy assessment, the low 6-month late loss observed in the pooled FUTURE I and II analyses suggests striking potential for the

**Table 1**
**Overview of Angiographic and Clinical Parameters in Currently Published Drug-Eluting Stent Trials**

| | Pooled FUTURE I and II | | SIRIUS | | RAVEL | | E-SIRIUS | | TAXUS-II | | TAXUS-IV | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | DES | Control | DES | Control | DES | Control | DES | Control | DES | Control | DES |
| In-Stent RR (%) | 17.0 | 0.0 | 35.4 | 3.2 | 26.6 | 0.0 | 41.7 | 3.9 | 17.9 | 2.3 | 24.4 | 5.5 |
| In-Segment RR (%) | 27.7 | 4.3 | 36.3 | 8.9 | n/a | n/a | 42.3 | 5.9 | 20.1 | 5.5 | 26.6 | 7.9 |
| In-Stent LLL (mm) | 0.85 | 0.12 | 1.00 | 0.17 | 0.8 | -0.01 | 1.05 | 0.20 | 0.79 | 0.31 | 0.92 | 0.39 |
| In-Segment LLL (mm) | 0.50 | 0.17 | 0.81 | 0.24 | n/a | n/a | 0.80 | 0.19 | n/a | n/a | 0.61 | 0.23 |
| TLR (%) | 13.2 | 4.3 | 16.6 | 4.1 | 22.9 | 0.0 | 20.9 | 4.0 | 12.0 | 4.6 | 11.3 | 3.0 |
| MACE at 6 MFU (%) | 15.1 | 6.4 | n/a | n/a | n/a | n/a | n/a | n/a | 19.5 | 8.5 | n/a | n/a |
| MACE at 9 MFU (%) | n/a | n/a | 18.9 | 7.1 | n/a | n/a | 22.6 | 8.0 | n/a | n/a | 15.0 | 8.5 |

LLL, late lumen loss; MACE, major adverse coronary events; MFU, months follow-up; RR, restenosis rate; TLR, target lesion revascularization.

everolimus-eluting stent to reduce neointimal proliferation. This finding is closer to the late-loss values found with the sirolimus-eluting CYPHER™ stent rather than that of the TAXUS™ stent design (Figure 3, Table 1). However, the optimal amount of late loss reduction required to achieve the best clinical outcomes is not currently known. Still, with no evidence for the development of late stent malapposition, and a marked reduction of stent restenosis, the inhibition of neointimal proliferation using the everolimus-eluting stent in the current release form and drug dosage seems to be appropriate for achieving good clinical results. The up-coming FUTURE studies (FUTURE III and IV) will provide important additional insights into the efficacy of the everolimus-eluting CHAMPION™ stent as well as its performance in comparison to already approved drug-eluting stent systems, which will probably establish this stent concept as a new and promising contender in the field of drug-eluting stents in our daily clinical practice for treatment of coronary heart disease. ■

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## Main Points

- Everolimus is a novel proliferation signal inhibitor with potent antiproliferative and immunosupppressant properties, which have led to an intense interest in its use for the site-specific prevention of restenosis following coronary stent implantation.
- In the FUTURE I study comparing patients implanted with an everolimus-eluting stent versus a control group implanted with bare metal stents, the everolimus group demonstrated significant and concordant improvements, with an 88% reduction of in-stent late loss and an 87% reduction of % neointimal volume.
- In FUTURE I, the binary in-stent restenosis rate was 0.0% in the everolimus-eluting stent group versus 9.1% in the control.
- The FUTURE II trial supported and extended the safety and feasibility results observed in FUTURE I by expanding treatment to a higher risk patient population, which included diabetics and patients with longer lesions.
- After FUTURE I and II, everolimus-eluting technology was refined and coupled with Guidant Corporation's MULTI-LINK VISION™ delivery system to create the CHAMPION™ everolimus-eluting stent system.
- The CHAMPION system is currently being compared to a bare metal stent platform and to other drug-eluting platforms in ongoing FUTURE III and IV trials.
- Although similar in structure to sirolimus, everolimus is characterized by additional physicochemical properties that may be preferable for drug-eluting stent designs.