

## **Biodegradable stents as a platform to drug loading.**

Tsuji T, Tamai H, Igaki K, Kyo E, Kosuga K, Hata T, Nakamura T, Fujita S, Takeda S, Motohara S, Uehata H.

Despite technical and mechanical improvement in coronary stents the incidence of restenosis caused by in-stent neointimal hyperplasia remains high. Oral administration of numerous pharmacological agents has failed to reduce restenosis after coronary stenting in humans, possibly owing to insufficient local drug concentration. Therefore, drug-eluting stents were developed as a vehicle for local drug administration. The authors developed a new drug-eluting polymer stent that is made of poly-l-lactic acid polymer mixed with tranilast, an anti-allergic drug that inhibits the migration and proliferation of vascular smooth muscle cells induced by platelet-derived growth factor and transforming growth factor- $\beta$ 1. Polymer stents might be superior to polymer-coated metallic stents as local drug delivery stents in terms of biodegradation and the amount of loaded drug. Drug-mixed polymer stents can be loaded with a larger amount of drug than can drug-coated metallic stents because the polymer stent struts can contain the drug. Clinical application is required to assess the safety and efficacy of drug-eluting polymer stents against stent restenosis.

## Local drug delivery via a coronary stent with programmable release pharmacokinetics.

Finkelstein A, McClean D, Kar S, Takizawa K, Varghese K, Baek N, Park K, Fishbein MC, Makkar R, Litvack F, Eigler NL.

**B**ACKGROUND: Fixed drug release kinetics and vessel wall partitioning may limit the effectiveness of drug-eluting stents. We report preliminary experience using a new coronary stent with programmable pharmacokinetics. **METHODS AND RESULTS:** A newly designed metallic stent contains honeycombed strut elements with inlaid stacked layers of drug and polymer. In vitro studies evaluated recipes for loading paclitaxel to establish the parameters for controlling drug release. Manipulation of the layers of biodegradable polymer and drug allowed varying of the initial 24-hour burst release of paclitaxel from 69% to 8.6% ( $P < 0.0001$ ). Late release of drug could be adjusted dependently or independently of early burst release. A biphasic release profile was created by the addition of blank layers of polymer within the stack. In the 30-day porcine coronary model ( $n=17$  pigs), there was a 70% reduction in late loss ( $0.3 \pm 0.5$  versus  $1.0 \pm 0.5$  mm,  $P=0.04$ ), a 28% increase in luminal volume ( $132 \pm 12$  versus  $103 \pm 21$  mm<sup>3</sup>,  $P=0.02$ ), and a 50% decrease in histological neointimal area ( $2.0 \pm 0.5$  versus  $4.0 \pm 1.6$  mm<sup>2</sup>;  $P < 0.001$ ) compared with bare metal controls. Temporal and regional variations in vascular healing were seen histologically. **CONCLUSIONS:** Layered polymer/drug inlay stent technology permits flexible and controllable pharmacokinetic profiles. Programmable, complex chemotherapy using this approach may be feasible for the treatment of cardiovascular disease.

## **Numerical simulation of local pharmacokinetics of a drug after intravascular delivery with an eluting stent.**

**Sakharov DV, Kalachev LV, Rijken DC.**

**W**e use mathematical modelling to delineate the influence of two important factors on local pharmacokinetics of a drug delivered via an eluting stent, namely: (1) diffusional resistance of a stent coating, and (2) reversible binding of a drug to the vascular tissue. A system of differential equations that describes diffusion of the drug out of the polymeric coating of the stent into the vascular tissue and into the bloodstream, as well as reversible binding of the drug within the vascular tissue, was solved numerically and the spatial profiles of the concentration of the drug at various points of time were produced and analysed. Also, kinetic curves of the spatial average concentration of the drug within the wall were constructed, and the areas under those curves (AUC) were calculated. The simulations showed that AUC might be enhanced, if the stent is coated with a continuous layer of a drug-releasing medium with a high diffusional resistance. Both the residence time and the average concentration of the drug within the vascular wall increase in this case mainly because the coating imposes a diffusional barrier between the vascular tissue and the bloodstream, thereby reducing the wash-out. If the drug reversibly binds to the tissue, the residence time increases greatly, but the AUC for the free (unbound) drug remains unchanged, implying that the presence of the drug in the vessel is prolonged at the expense of a proportional reduction in concentration of a free drug within the tissue. These findings justify the design of eluting stents with continuous coatings with enhanced diffusional resistance and the engineering of drugs with enhanced affinity to the vascular matrix. Reversible binding to tissue may be beneficial for prolonging the presence of the drug in the target tissue, and for avoiding potential toxic peak effects of high concentrations of the free (unbound) drug.

**Paclitaxel coating reduces in-stent intimal hyperplasia in human coronary arteries: a serial volumetric intravascular ultrasound analysis from the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT).**

Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH, Song JK, Kim JJ, Weissman NJ, Fearnot NE, Park SW, Park SJ; ASian Paclitaxel-Eluting Stent Clinical Trial.

**B**ACKGROUND: The aim of this study was to use serial volumetric intravascular ultrasound (IVUS) to evaluate the effect of a paclitaxel coating on in-stent intimal hyperplasia (IH). METHODS AND RESULTS: Patients were randomized to placebo (bare metal stents) or 1 of 2 doses of paclitaxel (low dose: 1.28 microg/mm<sup>2</sup>; high dose: 3.10 microg/mm<sup>2</sup>). Complete post-stent implantation and follow-up IVUS were available in 81 patients, including 25 control patients and in 28 receiving a low-dose and 28 receiving a high dose. Volumetric analysis of the stented segment and of both reference segments was performed. Baseline stent measurements and both reference measurements were similar among the groups. With increasing doses, there was a stepwise reduction in IH accumulation within the stented segment (31+/-22 mm<sup>3</sup> in control, 18+/-15 mm<sup>3</sup> in low dose, and 13+/-14 mm<sup>3</sup> in high dose, P<0.001). Post hoc analysis showed less IH accumulation when low- and high-dose patients were compared with control (P=0.009 and P<0.001, respectively), but not when low-dose patients were compared with high-dose patients (P=0.2). Focal late malapposition was seen in 1 high-dose patient. With increasing doses, there was no significant change in the reference segments. CONCLUSIONS: Paclitaxel-coated stents are effective in reducing in-stent neointimal tissue proliferation in humans. They are not associated with edge restenosis or significant late malapposition.

## **Drug-eluting stents in vascular intervention.**

**Fattori R, Piva T.**

**C**ONTEXT: Restenosis is the most important long-term limitation of stent implantation for coronary artery disease, occurring in 15-60% of patients. In-stent restenosis, a refractory coronary lesion resulting from neointimal hyperplasia, challenges both vascular biologist and interventional cardiologist. Various drugs and devices have been used tried to overcome restenosis but are not particularly successful. Over 1500000 percutaneous coronary interventions are done annually. Restenosis is not only important clinically but also for its impact on health-care costs. **S**TARTING **P**POINT: Growth and migration of vascular smooth-muscle cells result in neointimal proliferation after vascular injury and are the key mechanism of in-stent restenosis. The rationale of the most recent approaches to restenosis (eg, brachytherapy and immunosuppressive agents) arises from the similarity between tumour-cell growth and the benign tissue proliferation which characterises intimal hyperplasia. Several immunosuppressants have been tested for their potential to inhibit restenosis, with the novel strategy of administering the drug via a coated stent platform. Local drug delivery achieves higher tissue concentrations of drug without systemic effects, at a precise site and time. The first multicentre trial with stents coated with sirolimus was by Marie-Claude Morice and colleagues (*N Engl J Med* 2002; 346: 1773-80). In a trial of 238 patients, restenosis of 50% or more at 6 months was 0% and 27% with sirolimus or normal stents ( $p < 0.001$ ), respectively, after percutaneous revascularisation. Muzaffer Degertekin and colleagues (*Circulation* 2002; 106: 1610-13) present data on 2-year follow-up of 15 patients who had been implanted with the sirolimus stent in another study, and confirm persistent inhibition of restenosis and an absence of unexpected adverse events. **W**HERE **N**EXT; Local application of antiproliferative agents is a promising technique and research is developing. Other agents with potential benefits (eg, statins, local gene-therapy, adenovirus-mediated arterial gene-transfer, L-arginine, abciximab, angiopeptin, recombinant pegylated hirudin, and iloprost) as well as improvements in polymer technology (biodegradable smart polymers, coatings for multiple-drug release) are under evaluation. The clinical impact of the elimination of restenosis may influence the approach to coronary artery disease, the future of cardiac surgery, and health-care economics in cardiology.

## **Wire or coated balloon? Searching for an optimal source for intravascular brachytherapy with beta emitters using $(^{32}\text{P})$ as an example.**

**Lehmann J, King CR.**

This study identifies basic dosimetric differences between two designs for intravascular brachytherapy (IVBT) in current clinical practice and ongoing trials and their clinical implications within beta emitting systems using  $\text{P-32}$  as an example. The two designs are (i) the wire-type source, where the radioactive source material is confined to a wirelike structure within the vessel lumen, and (ii) the balloon-surface source, where the radioactive source material is distributed over a surface area (balloon-wall) which is brought in close proximity with the vessel wall. Using Monte Carlo simulations with the EGS4 code, the target coverage, the influence of centering errors, and the perturbation of the dose distribution caused by metallic stents have been compared. The radial dose fall-off in the target region was found to be steeper for balloon surface systems compared with wire systems. The inner lumen wall dose for a balloon surface source was 25% higher than that for a wirelike source (2.5 mm vessel diameter). However, the comparably shallower fall-off from wire-type systems is very sensitive to centering uncertainties. A 0.5 mm displacement, for example, will cause the dose to change by a factor of 2 at the inner vessel wall and by a factor of 1.8 at the prescription point. It is shown that the interference from metallic stents is more significant for wire-type systems than it is for balloon-surface-type systems, where double the dose variation beyond the stent at the radial prescription distance may occur. Centering uncertainties dominate the dose perturbation effects for wire-type systems. Balloon-surface-type designs show a more predictable dose distribution that features, however, a higher inner vessel surface dose. Since a direct clinical comparison of systems of both types is not likely, these findings should be considered when interpreting clinical results from treatments with either type of source and, possibly, for future source design.

## **Initial experience with paclitaxel-coated stents.**

**Grube E, Bullesfeld L.**

Local delivery of immunosuppressive or antiproliferative agents using a drug-eluting stent is a new technology that is supposed to inhibit in-stent restenosis, thus providing a biological and mechanical solution. This technique is a very promising. To date, several agents have been used, including paclitaxel, QP-2, rapamycin, actinomycin D, dexamethason, tacrolimus, and everolimus. Several studies, published recently or still ongoing, have evaluated these drugs as to their release kinetics, effective dosage, safety in clinical practice, and benefit. These studies include: SCORE (paclitaxel derivative), TAXUS I-VI, ELUTES, ASPECT, DELIVER (paclitaxel), RAVEL, SIRIUS (sirolimus), ACTION (actinomycin), EVIDENT, PRESENT (tacrolimus), EMPEROR (dexamethason), and FUTURE (everolimus). Paclitaxel was one of the first stent-based antiproliferative agents under clinical investigation that provided profound inhibition of neointimal thickening depending on delivery duration and drug dosage. The randomized, multicenter SCORE trail (Quanam stent, paclitaxel-coated) enrolled 266 patients at 17 sites. At 6-month's follow-up, a drop of 83% in stent restenosis using the drug-eluting stent could be achieved (6.4% drug-eluting stent vs 36.9% control group), which was attributable to a remarkable decrease in intimal proliferation. Unfortunately, due to frequent stent thrombosis and side-branch occlusions, the reported 30-day MACE rate was 10.2%. The randomized TAXUS-I safety trial (BSC, NIRx, paclitaxel-coated) also demonstrated beneficial reduction of restenotic lesions at 6-month's follow-up (0% vs 10%) but was associated with the absence of thrombotic events presumably due to less drug dosage. The ongoing TAXUS II-VI trials are addressing additional insight regarding the efficacy of the TAXUS paclitaxel-eluting stent. ASPECT and ELUTES evaluated paclitaxel-coated stents (i.e., Cook and Supra G), including subgroups with different drug dosages. With respect to stent restenosis and neointimal proliferation, both studies demonstrated a clear dose response. The RAVEL and the SIRIUS trials evaluated sirolimus-coated stents (i.e., Cordis, Johnson & Johnson, and Bx VELOCITY stents). Results confirmed the beneficial findings regarding reduction of renarrowing using a drug-eluting stent without any major adverse effects. Although parameters such as drug toxicity, optimal drug dosage, or delayed endothelial healing still need to be evaluated, today's clinical experience indicates that drug-coated stents are extremely beneficial in the interventional treatment of coronary lesions.

## **Drug-eluting stents: clinical experiences and perspectives.**

**Grube E, Gerckens U, Buellesfeld L.**

**D**rug-eluting stents (DES) have entered the arena and are about to change the landscape of Interventional Cardiology. Today, the number of agents under preclinical and clinical investigation has increased considerably, including drugs such as Paclitaxel, Sirolimus, Tacrolimus, Everolimus, Dexamethasone, etc. Several studies have recently been published or are still ongoing evaluating different stent designs with respect to their safety and efficacy in treatment of coronary lesions. The SCORE trial (Paclitaxel) revealed a significant reduction in restenosis at follow-up (FU) in the drug-eluting stent group (6.4% vs 36.9% control group), attributable to decreased intimal proliferation. However, stent thromboses and myocardial infarctions, due to both stent design and high drug dosages, were observed causing a MACE rate of 10.2% in the DES group. Confirming the beneficial reduction of stent re-narrowing using a local drug-eluting device, the rate of restenosis in the TAXUS-I trial (Paclitaxel) was 0% at follow-up in patients with DES vs 10% in patients with bare stents. Differences in MACE were not observed, which underlined the potential impact of an optimal stent design. First clinical experiences with a Sirolimus-coated stent (FIM trial) demonstrated again a profound inhibition of neointimal ingrowth at 4-month follow-up. The RAVEL trial, the first multicenter trial evaluating the Sirolimus stent and the largest DES study published so far, confirmed the FIM findings with a rate of restenosis in the DES group of 0% at 6 month FU. At 12 month FU, the beneficial impact on neointimal growth inhibition was persistent. The pivotal study SIRIUS is addressed to evaluate this stent design more extensively. However, given all the results being available today, local application of anti-proliferative agents delivered by coronary stents is one of the most promising techniques in treatment of coronary lesions. Nevertheless, we need more trials and an agreement of definitions in order to evaluate this treatment concept and eliminate unwanted side-effects.

## **Drug-eluting stent: the emerging technique for the prevention of restenosis.**

**Sheiban I, Carrieri L, Catuzzo B, Destefanis P, Oliaro E, Moretti C, Trevi GP.**

**P**ercutaneous coronary interventions (PCI) have surpassed coronary artery bypass grafting as the most common means for treating coronary artery disease, because of materials improvement, the use of stent and pharmacotherapy. However, despite the variety of mechanical techniques such as dilatation, debulking or conventional stent implantation, the incidence of restenosis on short and mid-term follow-up is still representing an important limitation to PCI. Restenosis is mainly due to elastic recoil, negative vessel remodelling and neointimal proliferation, as a response to vessel injury induced by angioplasty devices. The use of conventional stents has provided an efficient method to avoid elastic recoil and negative vessel remodelling, thus partially reducing restenosis as compared to conventional balloon dilatation. However, neointimal proliferation (biological vessel response to injury caused by stent implantation) is not affected by stenting technique. Thus, the extensive use of coronary stent, even in complex lesions, have produced again a "new" disease: the in-stent restenosis especially in some patients' subset (diabetics) or in some lesion subset (bifurcations, long lesions, small vessels, total occlusions, diffuse disease). Therefore, the main target of today's interventional cardiologists is to resolve this problem. The combination between mechanical control of elastic recoil and negative remodelling (stent) and the control of neointimal proliferation - biological response to vessel injury - (antiproliferative drugs) is the emerging approach against restenosis. This emerging approach consists in using the stent as drug carrier to the target site. Local delivery of antiproliferative or immunosuppressive agents using a drug-coated stent is supposed to inhibit in stent restenosis. The first antiproliferative agents being used successfully in clinical trials are sirolimus and paclitaxel and, so far, the data available of these trials demonstrated a marked reduction of restenosis using sirolimus- and paclitaxel-coated stents as compared to conventional stents. However, many questions are still to be answered and several other clinical trials with drug-eluting stents are ongoing, evaluating safety and efficacy of sirolimus and paclitaxel in a larger number of patients and in different subset of coronary lesions type and morphology. Based on the very impressive results available at the present time, we can expect, in the very near future, remarkable changes in our clinical practice and the beginning of a new "era" of interventional cardiology.

## Drug-eluting stents.

Chieffo A, Colombo A.

Drug-eluting stents represent the third revolution in the field of Interventional Cardiology following balloon angioplasty (PTCA) and the implantation of metal stents. The main limitation of percutaneous coronary intervention (PCI) is restenosis. The introduction of drug eluting stents able to release antiproliferative compounds led to the evaluation of several antiproliferative drugs in order to reduce restenosis. Rapamycin (Sirolimus) has been demonstrated to inhibit smooth muscle cell (SMC) proliferation and migration in vitro and to reduce in vivo neointima formation with blockage of the cell cycle progression at the G1-S transition. In a pilot study, recently confirmed by a randomized trial, rapamycin drug-eluting stents have been reported to eliminate restenosis after stent implantation. Promising data also come from the use of paclitaxel drug-eluting stents. Paclitaxel (Taxol) is a microtubule-stabilizing agent with potent antiproliferative activity. Even if drug-eluting stents represent one of the most promising fields in Interventional Cardiology today before being sure of their real potential it is necessary to wait for results from several ongoing clinical studies, their usage in real-world lesions and extended follow-up to 5 years.

## **Stent coating: a new approach in interventional cardiology.**

**Wieneke H, Sawitowski T, Wnendt S, Fischer A, Dirsch O, Karoussos IA, Erbel R.**

**B**ACKGROUND: Since its introduction in clinical cardiology, several studies have shown the superiority of coronary stent implantation as compared to conventional angioplasty. However, restenosis still remains a major drawback of this new technique. Basic research in animal models could identify stent-related factors like stent-material and stent-design as major determinants of intima proliferation. Since materials with good biocompatibility often have unsuitable mechanical properties and vice versa, the concept of stent coating has been developed to allow the combination of favorable characteristics from different materials. **PASSIVE COATING:** In general, passive coatings, which only serve as a barrier between the stainless steel and the tissue, and active coatings, which directly interfere with the process of intima proliferation have been identified. Currently there are several passive coatings commercially available with good results in animal models and preliminary reports from clinical studies. **ACTIVE COATING:** As any surface induces some kind of tissue reaction promoting restenosis, an active stent coating with antiproliferative drugs has been proposed. However, while animal studies revealed convincing results, preliminary clinical studies not only showed active stent coating effective in preventing restenosis, but also demonstrated the potential risks of this new approach. Although this technique may harbor some specific risks, with the introduction of stent coating a new chapter of interventional cardiology has been flipped open.

**Estrogen-eluting, phosphorylcholine-coated stent implantation is associated with reduced neointimal formation but no delay in vascular repair in a porcine coronary model.**

New G, Moses JW, Roubin GS, Leon MB, Colombo A, Iyer SS, Tio FO, Mehran R, Kipshidze N.

**E**strogen can inhibit intimal proliferation and accelerate endothelial regeneration after angioplasty. This suggests that estrogen may prevent in-stent restenosis. Unlike other therapies to prevent restenosis, estrogen may also not delay endothelial regrowth, thereby avoiding the risk of late stent thrombosis. The purpose of this work was to determine the effect of a 17beta-estradiol-eluting stent on neointimal formation in a porcine model. Each artery of six pigs was randomized to either a control, low-dose, or high-dose 17beta-estradiol-eluting stent. All animals were sacrificed at 30 days for histopathological analysis. There was a 40% reduction in intimal area in the high-dose stents compared with control stents (2.54 +/- 1.0 vs. 4.13 +/- 1.1 mm<sup>2</sup>), for high dose vs. control, respectively; P < 0.05). There was complete endothelial regeneration at 30 days and similar inflammatory response to stenting on histopathology in all the stent groups. This is the first study to show that 17beta-estradiol-eluting stents are associated with reduced neointimal formation without affecting endothelial regeneration in the pig model of in-stent restenosis. Estrogen-coated stents may have a potential benefit in the prevention and treatment of in-stent restenosis. Copyright 2002 Wiley-Liss, Inc.

**Human internal mammary artery organ culture model of coronary stenting: a novel investigation of smooth muscle cell response to drug-eluting stents.**

Swanson N, Javed Q, Hogrefe K, Gershlick A.

**L**ocal drug delivery by coronary stents is of current research interest. Organ culture of human vascular tissue is a model of intimal hyperplasia. We report an ex vivo organ culture model of stented vessels. This allows stent-artery interactions to be studied in living tissue. The recognized anti-restenosis agent paclitaxel was chosen to test the organ culture model. Mammary artery specimens were cultured 'closed' (i.e. without opening them flat) for 72 h. Phosphocholine-coated stents, half of them loaded with the anti-restenosis drug paclitaxel, were implanted. The absorption and elution characteristics of paclitaxel were established. Artery tissue remained viable at 72 h when cultured closed, despite stent implantation. Specimens developed smooth muscle cell proliferation. The stents absorbed up to  $127 \pm 29$  microg of paclitaxel, with a biphasic elution curve. A mean of 13% of the absorbed paclitaxel remained after a 24 h perfusion. In mammary artery, these paclitaxel stents reduced or abolished smooth muscle cell proliferation compared with controls. This model allows the effects of stenting on human arterial tissue to be studied for at least 72 h, long enough to demonstrate effects on smooth muscle cell proliferation. Phosphocholine-coated stents absorb adequate doses of paclitaxel, which is eluted gradually, inhibiting muscle cell proliferation. Such an organ culture model of stented mammary artery will provide useful data in addition to that from animal or cell culture models of drug-eluting stents.

## **Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results.**

Duda SH, Pusich B, Richter G, Landwehr P, Oliva VL, Tielbeek A, Wiesinger B, Hak JB, Tielemans H, Ziemer G, Cristea E, Lansky A, Beregi JP.

**B**ACKGROUND: Stent implantation for obstructive femoropopliteal artery disease has been associated with poor long-term outcomes. This study evaluated the effectiveness of shape memory alloy recoverable technology (SMART) nitinol self-expanding stents coated with a polymer impregnated with sirolimus (rapamycin) versus uncoated SMART stents in superficial femoral artery obstructions. **METHODS AND RESULTS:** Thirty-six patients were recruited for this double-blind, randomized, prospective trial. All patients had chronic limb ischemia and femoral artery occlusions (57%) or stenoses (average lesion length, 85+/-57 mm). Patients were eligible for randomization after successful guidewire passage across the lesion. Eighteen patients received sirolimus-eluting SMART stents and 18 patients received uncoated SMART stents. The primary end point of the study was the in-stent mean percent diameter stenosis, as measured by quantitative angiography at 6 months. The in-stent mean percent diameter stenosis was 22.6% in the sirolimus-eluting stent group versus 30.9% in the uncoated stent group (P=0.294). The in-stent mean lumen diameter was significantly larger in the sirolimus-eluting stent group (4.95 mm versus 4.31 mm in the uncoated stent group; P=0.047). No serious adverse events (death or prolonged hospitalization) were reported. **CONCLUSIONS:** The use of sirolimus-eluting SMART stents for superficial femoral artery occlusion is feasible, with a trend toward reducing late loss compared with uncoated stents. The coated stent also proved to be safe and was not associated with any serious adverse events.

## **Optimization of local methylprednisolone delivery to inhibit inflammatory reaction and neointimal hyperplasia of coated coronary stents.**

Huang Y, Wang L, Verweire I, Qiang B, Liu X, Verbeken E, Schacht E, De Scheerder I.

Polymer coating can optimize the surface characteristics of metallic coronary stents and serve as a vehicle for local drug delivery. Major problems, however, include the lack of biocompatibility of the polymers used and the limited amount of drug that can be loaded onto the stent. Stainless-steel stents were spray-coated or spray-coated combined with a barrier coating using a fluorinated polymethacrylate PFM-P75 impregnated with different methylprednisolone concentrations. When spray-coated with highly concentrated methylprednisolone (33%) fluorinated polymethacrylate PFM-P75, the surface became progressively more rough. Adding a barrier coating, however, could decrease these surface irregularities of methylprednisolone-loaded PFM-P75 spray-coated stents. In vitro, most of the methylprednisolone was released in the first 48 hours. A barrier coating could dramatically slow down the drug release from 80% to 13% during the first 48 hours. Histomorphometric analysis showed that the inflammatory response and neointimal hyperplasia of methylprednisolone-loaded stents were lower than in control stents. Neointimal hyperplasia of methylprednisolone-loaded PFM-P75 stents spray-coated with a barrier coating was decreased compared to the non-barrier-coated methylprednisolone-loaded stents. In conclusion, spray coating enables the use of high methylprednisolone concentrations. A barrier coating could significantly slow down the methylprednisolone release. Methylprednisolone-loaded PFM-P75-coated stents could significantly inhibit the inflammatory response and neointimal hyperplasia. The response to methylprednisolone was related to the dose used and the release time of the drug.

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## **No delayed restenosis at 18 months after implantation of sirolimus-eluting stent.**

Tanabe K, Degertekin M, Regar E, Ligthart JM, van der Giessen WJ, Serruys PW.

**S**irolimus-eluting stent is emerging as a potential solution for the prevention of restenosis. Recently, a sustained suppression of neointimal proliferation 12 months after implantation of this stent was reported. This is the first report of angiographic and IVUS images 18 months after the implantation of a sirolimus-eluting stent. Copyright 2002 Wiley-Liss, Inc.

## **In-vivo biocompatibility evaluation of stents coated with a new biodegradable elastomeric and functional polymer.**

Lee SH, Szinai I, Carpenter K, Katsarava R, Jokhadze G, Chu CC, Huang Y, Verbeken E, Bramwell O, De Scheerder I, Hong MK.

**B**ACKGROUND: In-stent restenosis may be prevented by impregnating an antiproliferative agent in a polymer from a stent platform. This approach requires both an antiproliferative agent effective in small doses and a biocompatible polymer. **METHODS:** A series of new biodegradable elastomeric poly(ester-amide)(co-PEA) polymers having functional carboxyl groups for drug conjugation were synthesized from non-toxic building blocks. The in-vivo biocompatibility was tested in porcine coronary arteries, by comparing the polymer-coated stents with bare metal stents in 10 pigs. **RESULTS:** All animals survived until sacrifice 28 days later and follow-up angiography prior to sacrifice revealed identical diameter stenosis ( $21 \pm 23\%$ ) in both groups. Histology confirmed similar injury scores ( $0.34 \pm 0.34$  compared with  $0.34 \pm 0.32$ ), inflammatory reaction ( $1.18 \pm 0.38$  compared with  $1.11 \pm 0.32$ ) and area stenosis ( $26 \pm 17\%$  compared with  $28 \pm 22\%$ ). **CONCLUSIONS:** This study suggests that the newly developed copoly(ester-amide) elastomers may be suitable for stent-based local drug delivery.

## Twenty-eight-day efficacy and pharmacokinetics of the sirolimus-eluting stent.

Klugherz BD, Llanos G, Lieuallen W, Kopia GA, Papandreou G, Narayan P, Sasseen B, Adelman SJ, Falotico R, Wilensky RL.

**B**ACKGROUND: In-stent restenosis is caused by neointimal hyperplasia. Sirolimus (rapamycin; Wyeth Research, Radnor, Pennsylvania, USA) inhibits vascular smooth muscle cell proliferation and we evaluated the efficacy of sirolimus in reducing neointimal formation in a rabbit iliac model and in-vivo pharmacokinetics in the porcine coronary model. DESIGN: Randomized, blinded, prospective animal study. METHODS: Bilateral rabbit iliac artery stent implantation was performed using crossflex stents (Cordis Corporation, Warren, New Jersey, USA) coated with sirolimus incorporated in a nonerodable polymer. Arteries were randomized to one of four stent groups: uncoated stents (n = 8); polymer control stents (n = 10); low-dose sirolimus-eluting stents (n = 9); and high-dose sirolimus-eluting stents (n = 10). Histomorphometry was performed at 28 days. Arterial tissue and stents were retrieved at 8, 14 and 28 days and blood samples were obtained daily during the first week. RESULTS: Treatment with low-dose sirolimus was associated with a 23% (P = NS) reduction in neointimal area and treatment with high-dose sirolimus with a 45% (P < 0.05) reduction. Sustained drug release from the stent and prolonged intramural arterial deposition were confirmed for up to 28 days. No detectable sirolimus was found in the blood after 2 days. CONCLUSION: Controlled-release local delivery of a cell-cycle inhibitor from a nonerodable polymer-coated stent reduced neointimal formation in rabbit iliac arteries in a dose-dependent manner and represents a promising strategy for preventing restenosis.

## **Coronary artery stents: evaluating new designs for contemporary percutaneous intervention.**

**Kandzari DE, Tcheng JE, Zidar JP.**

**I**ntracoronary stents have markedly improved the short- and long-term safety and efficacy of percutaneous coronary intervention by improving acute gains in luminal dimensions, decreasing abrupt vessel occlusion, and reducing restenosis. At present, nearly 90% of all coronary interventions involve stenting. A variety of advances in stent technology and design have expanded the clinical application of stenting to include complex coronary lesions, multivessel disease, and small-diameter vessels. In addition, the development of stents as drug delivery systems for antithrombotic or antiproliferative agents has the potential to expand the role of coronary stenting, and early clinical experience appears promising. The purpose of this review is to describe recent developments in stent design, examine the results of clinical trials of contemporary stents, and present future directions for investigation of new stent technologies. Copyright 2002 Wiley-Liss, Inc.

## **Angiopeptin-eluting stents: observations in human vessels and pig coronary arteries.**

**Armstrong J, Gunn J, Arnold N, Malik N, Chan KH, Vick T, Stratford P, Cumberland DC, Holt CM.**

**L**ocal drug delivery from polymer-coated coronary stents may reduce the incidence of in-stent restenosis. Angiopeptin, an inhibitor of smooth muscle cell proliferation, may reduce the clinical impact of restenosis. The objectives of this study were to characterize the release kinetics and distribution of angiopeptin-loaded phosphorylcholine (PC)-coated drug delivery (DD) BiodivYsio stents and assess their safety and efficacy at reducing neointima formation. I125-angiopeptin-loaded DD-PC-coated stents were implanted into human saphenous vein segments *ex vivo*, and I125 angiopeptin was detected in the medial layer at 1 hour. When implanted in pig coronary arteries, I125 angiopeptin was found adjacent to the stent at intervals up to 28 days. No significant amounts were found elsewhere. To assess efficacy, twelve angiopeptin-loaded DD-PC-coated stents, twelve non-loaded DD-PC stents, ten standard PC-coated stents and 8 uncoated stents were implanted into normal porcine coronary arteries. Stents were harvested at 28 days and neointima formation was assessed by computerized morphometry. No adverse tissue reactions were seen with any of the PC-coated stents. No significant differences were seen in neointimal or luminal cross-sectional areas between study groups. Local delivery of I125 angiopeptin into the vascular wall can be achieved using a PC-coated stent. Delivery of angiopeptin from drug delivery PC-coated stents is safe, but does not lead to a significant reduction in neointimal growth at 28 days within the parameters of this study.

## **Analysis of a phosphorylcholine-based polymer coating on a coronary stent pre- and post-implantation.**

Lewis AL, Tolhurst LA, Stratford PW.

There has been a move towards surface treatments for metallic coronary stents in an effort to improve their compatibility within the body and to provide a vehicle for the delivery of therapeutics. The Biodiv Ysio range of stents is characterised by a biocompatible coating comprised of a crosslinked phosphorylcholine (PC)-based polymer. In addition to a review of some of the data collected to support safety and efficacy of this device, this paper also describes a number of techniques that have been employed to both visualise and quantify the coating on the stent. Explantation of both coated and uncoated stents from porcine coronary arteries revealed that both coated and uncoated stents were >90% endothelialised after 5 days. Typical histological analysis of stented vessel sections after 4 and 12 weeks implantation showed the presence of cell types characteristic of the inflammatory response associated with the trauma caused by stent placement, with no evidence for any additional coating-related adverse inflammatory sequelae. Finally, it was demonstrated by AFM and SEM that both the thickness and force required to remove the coating were essentially unchanged after 6 months implantation. Thus, both the long-term stability and relative biological inertness of the coating has been confirmed in vivo, supporting its use as a vehicle for local drug delivery.

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21. Analysis of a phosphorylcholine-based polymer coating on a coronary stent pre- and post-implantation.

Lewis AL, Tolhurst LA, Stratford PW..

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**J Am Coll Cardiol ,2001;37(5):1335-43**

**Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience.**

Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR.

**OBJECTIVES:** The objective of this study was to test the hypothesis that the intracoronary administration of a direct donor of nitric oxide is a safe and effective method to treat impaired blood flow (no-reflow phenomenon) that occurs during percutaneous transluminal coronary interventions (PTCI). **BACKGROUND:** The absence of blood flow or decreased blood flow in a coronary artery following PTCI despite the presence of a patent epicardial vessel or graft is designated "no-reflow" or "impaired flow." This alteration in blood flow is a serious complication of percutaneous revascularization strategies that results in an increased incidence of morbidity, myocardial infarction and mortality. **METHODS:** Nineteen consecutive patients undergoing standard percutaneous revascularization procedures complicated by either no-reflow or impaired flow that received intracoronary nitroprusside treatment were studied. One patient had two procedures performed on two separate grafts on two successive days. Interventions were performed on either saphenous vein grafts or native vessels and utilized angioplasty, stent deployment or rotational atherectomy strategies. Following interventions that were associated with impaired flow, varying total doses (of nitroprusside 50 to 1,000 microg) were administered into the coronary artery or saphenous vein graft. The angiographic archives before and after intracoronary administration of nitroprusside were analyzed for TIMI grade flow and a frame count method was used to quantitate blood flow velocity. **RESULTS:** Following a PTCI that resulted in either no-reflow or impaired flow, nitroprusside (median dose 200 microg) was found to lead to a highly significant and rapid

improvement in both angiographic flow ( $p < 0.01$  compared with pretreatment angiogram) and blood flow velocity ( $p < 0.01$  compared with pretreatment angiogram). No significant hypotension or other adverse clinical events were associated with nitroprusside administration. CONCLUSIONS: The direct nitric oxide donor nitroprusside is an effective, safe treatment of impaired blood flow and no-reflow associated with PTCL. The use of nitroprusside to treat syndromes secondary to microvascular dysfunction may provide a novel therapeutic strategy for treating no-reflow or impaired blood flow following percutaneous interventions.

Circulation ,2001;104(5):600-5

Physiological transport forces govern drug distribution for stent-based delivery.

Hwang CW, Wu D, Edelman ER.

BACKGROUND: The first compounds considered for stent-based delivery, such as heparin, were chosen on the basis of promising tissue culture and animal experiments, and yet they have failed to stop restenosis clinically. More recent compounds, such as paclitaxel, are of a different sort, being hydrophobic in nature, and their effects after local release seem far more profound. This dichotomy raises the question of whether drugs that have an effect when released from a stent do so because of differences in biology or differences in physicochemical properties and targeting. METHODS AND RESULTS: We applied continuum pharmacokinetics to examine the effects of transport forces and device geometry on the distribution of stent-delivered hydrophilic and hydrophobic drugs. We found that stent-based delivery invariably leads to large concentration gradients, with drug concentrations ranging from nil to several times the mean tissue concentration over a few micrometers. Concentration variations were a function of the Peclet number (Pe), the ratio of convective to diffusive forces. Although hydrophobic drugs exhibited greater variability than hydrophilic drugs, they achieved higher mean concentrations and remained closer to the intima. Inhomogeneous strut placement influenced hydrophilic drugs more negatively than hydrophobic drugs, dramatically affecting local concentrations without changing mean concentrations. CONCLUSIONS: Because local concentrations and gradients are inextricably linked to biological effect, our results provide a potential explanation for the variable success of stent-based delivery. We conclude that mere proximity of delivery devices to tissues does not ensure adequate targeting, because physiological transport forces cause local concentrations to deviate significantly from mean concentrations.

Circulation ,2001;104(4):380-3

Novel drug-delivery stent: intravascular ultrasound observations from the first human experience with the QP2-eluting polymer stent system.

Honda Y, Grube E, de La Fuente LM, Yock PG, Stertz SH, Fitzgerald PJ.

**BACKGROUND:** The aim of this study was to use serial intravascular ultrasound (IVUS) to evaluate the long-term effect of stent-based 7-hexanoyltaxol (QP2, a taxane analogue) delivery on neointimal tissue growth within the stent and on vessel dimensions at the adjacent reference segments. **METHODS AND RESULTS:** Serial IVUS analyses (immediately after intervention and at follow-up at 8.3 months) were performed in 15 native coronary lesions treated with the QuaDS-QP2 stent. IVUS measurements were performed at 8 cross-sections in each target segment (4 cross-sections within the stent and 2 cross-sections in each reference segment). At baseline, no significant plaque protrusion or thrombus was detected in the target segment. Mild incomplete stent apposition and edge dissection were observed in one and two cases, respectively. Percent expansion of the stent (minimum stent area/average reference lumen area) was 96.0+/-21.7%. At follow-up, mean neointimal area within the stent was 1.2+/-1.3 mm<sup>2</sup>, and mean cross-sectional narrowing (neointimal area/stent area) was 13.6+/-14.9%. At the vessel segments immediately adjacent to the stent, a significant increase in plaque area (1.9+/-2.6 mm<sup>2</sup>, P=0.001) was observed, but vessel area remained unchanged. However, no patients showed clinically significant in-stent or edge restenosis (diameter stenosis >=50%) during the follow-up period. **CONCLUSIONS:** The first human experience with the new drug-delivery stent showed a minimal amount of neointimal proliferation in the stented segment. Late lumen loss at the reference sites adjacent to the stent was acceptable and predominantly due to plaque proliferation.

Circulation ,2001;104(4):473-9

Pathological analysis of local delivery of paclitaxel via a polymer-coated stent.

Farb A, Heller PF, Shroff S, Cheng L, Kolodgie FD, Carter AJ, Scott DS, Froehlich J, Virmani R.

**BACKGROUND:** Paclitaxel can inhibit vascular smooth muscle proliferation in vitro, and early studies suggest that paclitaxel may be useful in preventing restenosis. Early and late intimal growth and local vascular pathological changes associated with paclitaxel delivered via stents have not been fully explored. **METHODS AND RESULTS:** Localized drug delivery was accomplished with balloon-expandable stainless steel stents coated with a cross-linked biodegradable polymer, chondroitin sulfate and gelatin (CSG), containing various doses of paclitaxel. CSG-coated stents with paclitaxel (42.0, 20.2, 8.6, or 1.5 microgram of paclitaxel per stent), CSG-coated stents without paclitaxel, and uncoated stents (without paclitaxel or CSG) were deployed in the iliac arteries of New Zealand White rabbits, which were killed 28 days after implant. Mean neointimal thickness at stent strut sites was reduced 49% ( $P<0.0003$ ) and 36% ( $P<0.007$ ) with stents containing 42.0 and 20.2 microgram of paclitaxel per stent, respectively, versus CSG-coated stents without paclitaxel. However, histological findings suggested incomplete healing in the higher-dose (42.0 and 20.2 microgram) paclitaxel-containing stents consisting of persistent intimal fibrin deposition, inraintimal hemorrhage, and increased intimal and adventitial inflammation. Stents coated with CSG alone (without paclitaxel) had similar neointimal growth as uncoated stents. In a separate group of rabbits killed at 90 days, neointimal growth was no longer suppressed by CSG-coated stents containing 42.0 or 21.0 microgram of paclitaxel. **CONCLUSIONS:** CSG coating appears to be a promising medium for localized drug delivery. Paclitaxel polymer-coated stents reduce neointima formation but are associated with evidence of incomplete healing at 28 days. However, neointimal suppression was not maintained at 90 days.

Circulation ,2001;104(8):928-33

Stent coating with titanium-nitride-oxide for reduction of neointimal hyperplasia.

Windecker S, Mayer I, De Pasquale G, Maier W, Dirsch O, De Groot P, Wu YP, Noll G, Leskosek B, Meier B, Hess OM; Working Group on Novel Surface Coating of Biomedical Devices (SCOL).

**BACKGROUND:** Coronary stents prevent constrictive arterial remodeling but stimulate neointimal hyperplasia. Stainless steel induces a metallic foreign body reaction, which is absent for titanium. The hypothesis of the present study was that titanium renders the stent surface biologically inert, with reduced platelet and fibrinogen binding. **METHODS AND RESULTS:** Twelve pigs were instrumented with a stainless steel and 2 titanium-nitride-oxide-coated stents (TiNOX 1, ceramic; TiNOX 2, metallic). Animals were restudied after 6 weeks. Histological specimens of stented segments were analyzed by digital morphometry. Platelet

adhesion and fibrinogen binding studies were performed in the perfusion chamber. Under in vitro conditions, TiNOX 1 showed reduced platelet adhesion (65+/-3%) compared with TiNOX 2 (72+/-5%; P<0.05) and stainless steel (71+/-4%; P<0.05). Platelet adhesion 48 hours after incubation with human plasma, however, was not different between TiNOX 1 (17+/-3%) and 2 (15+/-3%) but was significantly higher with stainless steel (23+/-2%; P<0.05). Fibrinogen binding was significantly reduced with TiNOX 2 (54+/-3%) compared with TiNOX 1 (82+/-4%, P<0.05) or stainless steel (100%, P<0.05). Histomorphometry revealed a significantly larger neointimal area in stainless steel (2.61+/-1.12 mm<sup>2</sup>) than in TiNOX 1-coated (1.47+/-0.84 mm<sup>2</sup>, P<0.02) or TiNOX 2-coated (1.39+/-0.93 mm<sup>2</sup>, P<0.02) stents. The reductions were 44% and 47%, respectively. CONCLUSIONS: TiNOX coating significantly reduces neointimal hyperplasia in stainless steel stents. The antiproliferative effect was similar for both TiNOX coatings, suggesting that the electrochemical properties are more important for attenuation of neointimal proliferation than the observed differences in platelet adhesion and fibrinogen binding.

Circulation ,2001;104(17):2007-11

Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up.

Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW.

BACKGROUND: We have previously reported a virtual absence of neointimal hyperplasia 4 months after implantation of sirolimus-eluting stents. The aim of the present investigation was to determine whether these results are sustained over a period of 1 year. METHODS AND RESULTS: Forty-five patients with de novo coronary disease were successfully treated with the implantation of a single sirolimus-eluting Bx VELOCITY stent in Sao Paulo, Brazil (n=30, 15 fast release [group I, GI] and 15 slow release [GII]) and Rotterdam, The Netherlands (15 slow release, GIII). Angiographic and volumetric intravascular ultrasound (IVUS) follow-up was obtained at 4 and 12 months (GI and GII) and 6 months (GIII). In-stent minimal lumen diameter and percent diameter stenosis remained essentially unchanged in all groups (at 12 months, GI and GII; at 6 months, GIII). Follow-up in-lesion minimal lumen diameter was 2.28 mm (GIII), 2.32 mm (GI), and 2.48 mm (GII). No patient approached the >=50% diameter stenosis at 1 year by angiography or IVUS assessment, and no edge restenosis was observed. Neointimal hyperplasia, as detected by IVUS, was virtually absent at 6 months (2+/-

5% obstruction volume, GIII) and at 12 months (GI=2+/-5% and GII=2+/-3%). CONCLUSIONS: This study demonstrates a sustained suppression of neointimal proliferation by sirolimus-eluting Bx VELOCITY stents 1 year after implantation.

Am J Cardiol 2002;89(4):363-7

Effect of local delivery of L-arginine on in-stent restenosis in humans.

Suzuki T, Hayase M, Hibi K, Hosokawa H, Yokoya K, Fitzgerald PJ, Yock PG, Cooke JP, Suzuki T, Yeung AC.

To determine whether intramural administration of L-arginine reduces intimal thickening after optimal Palmaz-Schatz stent deployment in humans, 50 patients with native coronary artery disease who received a single Palmaz-Schatz stent were enrolled in this pilot study. Patients were randomized into 2 treatment groups: an L-arginine group (n = 25) and a saline group (n = 25). After stent deployment, L-arginine (600 mg/6 ml) or saline (6 ml) was locally delivered via the Dispatch catheter (Scimed) over 15 minutes. Serial angiography and intravascular ultrasound examinations (motorized pull-back at 0.5 mm/s) were performed before and after the procedure, and at 6-month follow-up. Measurements of stent area, lumen area, and neointimal area were computed within the stents at 1-mm intervals, by technicians who were blinded to the treatment assignment. Using Simpson's rule, stent, plaque, and lumen volumes, neointimal volume within the stent, and percent neointimal volume were measured before and after the procedure, and at 6-month follow-up. The 6-month volume data in quantitative coronary ultrasound showed that neointimal volume in the L-arginine group was significantly less than in the saline group (25 vs 39 mm<sup>3</sup>; p = 0.049). Similarly, percent neointimal volume was significantly less in the L-arginine group at 6-month follow-up (17 +/- 13% vs 27 +/- 21%; p = 0.048). Thus, these results showed that local delivery of L-arginine reduces in-stent neointimal hyperplasia in humans, indicating that this approach may be a novel strategy to prevent in-stent restenosis.

Circulation,2002;105(9):1104-9

Vascular gene transfer of phosphomimetic endothelial nitric oxide synthase (S1177D) using ultrasound-enhanced destruction of plasmid-loaded microbubbles improves vasoreactivity.

Teupe C, Richter S, Fisslthaler B, Randriamboavonjy V, Ihling C, Fleming I, Busse R, Zeiher AM, Dimmeler S.

**BACKGROUND:** Local gene therapy has enormous potential for the treatment of vascular disease. We determined whether diagnostic ultrasound-mediated destruction of plasmid-loaded albumin microbubbles is a feasible and efficient technique for local vascular gene delivery. For gene transfer, we used a phosphomimetic, active endothelial nitric oxide synthase (eNOS) construct in which Ser1177 was replaced by aspartic acid (S1177D) and exhibits a 2-fold higher basal activity than the wild-type enzyme. **METHODS AND RESULTS:** Gas-filled microbubbles (3.0 +/- 1.2 microm) were created by sonication of 5% human albumin in the presence of plasmid DNA encoding for LacZ or eNOS S1177D. Porcine coronary arteries were perfused with DNA-loaded albumin microbubbles *in vitro*, exposed to diagnostic ultrasound (5 seconds), and incubated for a further 24 hours. Detection of the beta-galactosidase in LacZ-transfected vessels revealed a predominant staining of endothelial cells without any functional impairment of vasoreactivity. Western blotting demonstrated the expression of the eNOS S1177D construct in extracts from the transfected segments. Vascular responsiveness was tested with prostaglandin F(2alpha) and the NOS inhibitor N(omega)nitro-L-arginine. Compared with segments treated with the expression plasmid alone, the contractile response to prostaglandin F(2alpha) was impaired in segments transfected with eNOS S1177D, whereas the contractile response to the administration of N(omega)nitro-L-arginine was markedly enhanced. **CONCLUSIONS:** Ultrasound-mediated destruction of eNOS S1177D DNA-loaded albumin microbubbles is a feasible and efficient method for vascular gene transfection. Transfection resulted in significant protein expression and enhanced NO-mediated relaxation of bradykinin-stimulated porcine coronary arteries.

Circulation ,1994;90:944-951

Transcatheter delivery of c-myc antisense oligomers reduces neointimal formation in a porcine model of coronary artery balloon injury

Y Shi, A Fard, A Galeo, HG Hutchinson, P Vermani, GR Dodge, DJ Hall, F Shaheen and A Zalewski

**BACKGROUND:** Smooth muscle cell proliferation and extracellular matrix accumulation are the principal

mechanisms leading to vascular restenosis. We have previously demonstrated the growth-inhibitory effect of antisense oligomers targeting the c-myc proto-oncogene in human smooth muscle cells. The goal of this study was to investigate whether c-myc antisense oligomers reduce neointimal formation in balloon-denuded porcine coronary arteries. METHODS AND RESULTS: First, type I collagen synthesis, which reflects synthetic function, was markedly reduced following c-myc antisense oligomers in porcine vascular smooth muscle cells independent of the growth inhibition. These effects in vitro provided the rationale for assessing c-myc antisense oligomers in the prevention of neointima in vivo. Second, the efficiency of single transcatheter delivery of oligomers into denuded porcine coronary arteries was determined. Despite rapid plasma clearance following local delivery, oligomers persisted at the site of injection for at least 3 days, exceeding by severalfold their concentration in peripheral organs. Third, morphometric analyses were carried out in balloon-denuded coronary arteries at 1 month after transcatheter c-myc antisense oligomer administration. Maximal neointimal area was reduced from 0.80 +/- 0.17 mm<sup>2</sup> in the control group (n = 12) to 0.24 +/- 0.06 mm<sup>2</sup> in the antisense-treated group (n = 13, P < .01). Likewise, a significant reduction in maximal neointimal thickness was observed in the antisense-treated group (P < .01). These changes in vascular remodeling following denuding injury resulted in an increase in residual lumen from 64 +/- 6% in the control group to 81 +/- 5% in the antisense-treated group (P < .05). CONCLUSIONS: (1) Single transcatheter administration allowed for endoluminal delivery of oligomers to the site of coronary arterial injury. (2) C-myc antisense oligomers reduced the formation of neointima in denuded coronary arteries, implying a therapeutic potential of this approach for the prevention of coronary restenosis. (3) It is postulated that the c-myc proto-oncogene is involved in the process of vascular remodeling, regulating smooth muscle cell proliferation and extracellular matrix synthesis.

#### Summary

1. Type I collagen synthesis - markedly reduced following c-myc antisense oligomers in porcine vascular smooth muscle cells
2. Oligomers persisted at the site of injection for at least 3 days, exceeding by severalfold their concentration in peripheral organs.
3. Maximal neointimal area was reduced from 0.80 ( 0.17 mm<sup>2</sup> in the control group to 0.24 ( 0.06 mm<sup>2</sup> in the antisense-treated group (P < .01).
4. A significant reduction in maximal neointimal thickness was observed in the antisense-treated group (P < .01).

Circulation,1995;91:2793-2801

Local Delivery of Vascular Endothelial Growth Factor Accelerates Reendothelialization and Attenuates Intimal Hyperplasia in Balloon-Injured Rat Carotid Artery

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**Background.** Most strategies designed to reduce restenosis by the use of pharmacological or biological reagents involve direct inhibition of vascular smooth muscle cell (SMC) proliferation. Alternatively, SMC proliferation might be indirectly inhibited if reendothelialization could be specifically facilitated at sites of balloon-induced arterial injury. Accordingly, we investigated the hypothesis that application of an endothelial cell (EC)-specific mitogen to a freshly denuded intimal surface could accelerate reendothelialization and thereby attenuate intimal hyperplasia.

**Methods and Results.** The left carotid artery of 31 Sprague-Dawley rats was subjected to balloon injury, after which 16 rats were treated with a 30-minute incubation with 100  $\mu$ g of vascular endothelial growth factor (VEGF), an EC-specific mitogen. Control animals (n=15) received a 30-minute incubation with 0.9% saline. At 2 weeks after balloon injury, carotid artery reendothelialization was markedly superior in the VEGF-treated group compared with the control group ( $14.59 \pm 1.12$  versus  $7.96 \pm 0.51$  mm<sup>2</sup>,  $P < .0005$ ). The extent of reendothelialization measured at 4 weeks after balloon injury remained superior for arteries treated with VEGF ( $18.04 \pm 0.90$  mm<sup>2</sup>) versus saline ( $13.42 \pm 0.84$  mm<sup>2</sup>,  $P < .005$ ). Neointimal thickening was correspondingly attenuated to a statistically significant degree in arteries treated with VEGF versus the control group at both the 2-week and 4-week time points. Immunostaining for proliferating cell nuclear antigen (PCNA) disclosed a threefold increase in PCNA-positive cells in the neointima of control arteries versus VEGF-treated arteries at 2 weeks after injury.

**Conclusions.** Application of VEGF, an EC-specific growth regulatory molecule, may be effectively used in vivo to promote reendothelialization and thereby indirectly attenuate neointimal thickening due to SMC proliferation.

## Summary

Carotid artery reendothelialization(mm<sup>2</sup>)

Circulation, 1997;96:636-645

Paclitaxel Inhibits Arterial Smooth Muscle Cell Proliferation and Migration In Vitro and In Vivo Using Local Drug Delivery

Dorothea I. Axel, PhD; Wolfgang Kunert, MD; Christoph Goggelmann; Martin Oberhoff, MD; Christian Herdeg, MD; Axel Kuttner; Doris H. Wild; Bernhard R. Brehm, MD; Reimer Riessen, MD; Gerhard Koveker, MD; Karl R. Karsch, MD

**Background.** The antineoplastic compound paclitaxel (Taxol) causes an increased assembly of extraordinarily stable microtubules. The present study was designed to characterize the effects of paclitaxel on proliferation and migration of human arterial smooth muscle cells (haSMCs) *in vitro* and on neointima formation in an *in vivo* experimental rabbit model.

**Methods and Results.** Both monocultures of haSMCs and cocultures with human arterial endothelial cells (haECs) were used. Cell growth after 4, 8, and 14 days was determined in the absence or presence of platelet-derived growth factor-AB (PDGF-AB), basic fibroblast growth factor (bFGF), or thrombin. Nonstop paclitaxel exposure, as well as single-dose applications of paclitaxel for 24 hours or even 20 minutes (0.1 to 10.0  $\mu\text{mol/L}$ ), caused a complete and prolonged inhibition of haSMC growth up to day 14, with an IC<sub>50</sub> of 2.0 nmol/L.

Mitogens or cocultures with stimulating haECs did not significantly attenuate paclitaxel-induced effects. Immunohistochemistry showed characteristic cytoskeletal changes predominantly in the microtubule network. Additionally, in 20 male New Zealand White rabbits, intimal plaques were produced by electrical stimulation. In 10 animals, paclitaxel was locally applied by use of microporous balloons. Histologically, the intima wall area, wall thickness, and degree of stenosis were reduced significantly in paclitaxel-treated animals compared with controls.

**Conclusions.** Our data show that paclitaxel inhibits haSMC proliferation and migration in a dose-dependent manner in monocultures and cocultures even in the presence of mitogens. Furthermore, paclitaxel prevents neointima formation in rabbits after balloon angioplasty. The long-lasting effect after just several minutes' exposure time makes this lipophilic substance a promising candidate for local antiproliferative therapy of restenosis.

### Summary

1. Paclitaxel(nonstop exposure and single-dose application) - a complete and prolonged inhibition of haSMC growth up to day 14, with an IC<sub>50</sub> of 2.0 nmol/L.
2. Mitogens or cocultures with stimulating haECs - no significant effect on paclitaxel-induced effects.
3. Immunohistochemistry: cytoskeletal changes predominantly in the microtubule network.
4. In rabbits: intima wall area, wall thickness, and degree of stenosis - reduced significantly in paclitaxel-treated animals compared with controls

Circulation ,1999 ;99: 354-360.

## Vascular Effects of Estrogen and Cholesterol-Lowering Therapies in Hypercholesterolemic Postmenopausal Women

Kwang Kon Koh, Carmine Cardillo, Minh N. Bui, Londa Hathaway, Gyorgy Csako, Myron A. Waclawiw, Julio A. Panza, and Richard O. Cannon, III

**Background-**Lipoproteins affect endothelium-dependent vasomotor responsiveness. Because lipoprotein effects of estrogen and cholesterol-lowering therapies differ, we studied the vascular responses to these therapies in hypercholesterolemic postmenopausal women.

**Methods and Results-**We randomly assigned 28 women to conjugated equine estrogen (CE) 0.625 mg, simvastatin 10 mg, and their combination daily for 6 weeks. Compared with respective baseline values, simvastatin alone and combined with CE reduced LDL cholesterol to a greater extent than CE alone (both  $P < 0.05$ ). CE alone and combined with simvastatin raised HDL cholesterol and lowered lipoprotein(a) to a greater extent than simvastatin alone (all  $P < 0.05$ ). Flow-mediated dilation of the brachial artery (by ultrasonography) improved (all  $P < 0.001$  versus baseline values) on CE ( $4.0 \pm 2.6\%$  to  $10.2 \pm 3.9\%$ ), simvastatin ( $4.3 \pm 2.4\%$  to  $10.0 \pm 3.9\%$ ), and CE combined with simvastatin ( $4.6 \pm 2.0\%$  to  $9.8 \pm 2.6\%$ ), but similarly among therapies ( $P = 0.507$  by ANOVA). None of the therapies improved the dilator response to nitroglycerin (all  $P \geq 0.184$ ). Only therapies including CE lowered levels of plasminogen activator inhibitor type 1 and the cell adhesion molecule E-selectin (all  $P < 0.05$  versus simvastatin).

**Conclusions-**Although estrogen and statin therapies have differing effects on lipoprotein levels, specific improvement in endothelium-dependent vasodilator responsiveness is similar. However, only therapies including estrogen improved markers of fibrinolysis and vascular inflammation. Thus, estrogen therapy appears to have unique properties that may benefit the vasculature of hypercholesterolemic postmenopausal women, even if they are already on cholesterol-lowering therapy.

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Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final

report of the ROXIS study

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Aims Mounting evidence suggests infection, specifically *Chlamydia pneumoniae*, plays a role in atherosclerosis. We tested whether antibiotic treatment with the macrolide roxithromycin improves clinical outcome in patients with acute non-Q-wave coronary syndromes. Preliminary reports revealed a reduction in events in the roxithromycin group at 30 days. We now report the long-term follow-up results.

Methods and Results Sixty-four per cent of the initial 202 patients with unstable angina who were randomly assigned to receive either roxithromycin or placebo for 30 days completed the active treatment period. At day 30, the primary triple and double end-point rates were 9% and 4% in the placebo group compared to 2% and 0% in the roxithromycin group (unadjusted  $P=0.032$  and  $0.058$ , respectively). The secondary triple and double end-point rates were again higher in the placebo group at day 90 (12.5% and 6.25% vs 4.37% and 0%, unadjusted  $P=0.065$  and  $0.029$ , respectively), and at day 180 (14.6% and 7.29% vs 8.69% and 2.17%, unadjusted  $P=0.259$  and  $0.17$ , respectively). Anti-*C. pneumoniae* IgG titres were unchanged in both groups while C-reactive protein levels decreased in both strategies, with a more significant decrease in the roxithromycin arm ( $P=0.03$ ). Elevated C-reactive protein levels predicted the need for revascularization.

Conclusions

In this pilot trial, roxithromycin appears to extend the clinical benefit of preventing death and re-infarction for at least 6 months after initial treatment.

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Angiographically Documented Late Reocclusion After Successful Coronary Angioplasty of an Infarct-Related Lesion Is a Powerful Predictor of Long-Term Mortality

Christophe Bauters, Maxence Delomez, Eric Van Belle, Eugene McFadden, Jean-Marc Lablanche, and Michel E. Bertrand

Background-Late reocclusion of an infarct-related artery (IRA) that was patent in the early days after acute myocardial infarction (MI) is a frequent event; the reocclusion rate may be as high as 30%. Few studies have been designed to analyze the impact of late reocclusion of the IRA on late survival.

**Methods and Results**-We studied 528 patients who all had a patent IRA after a successful PTCA procedure 10±6 days after MI and who underwent systematic 6-month angiographic follow-up to assess late patency of the IRA. We compared long-term survival of patients with and without late reocclusion. Based on the results of 6-month follow-up angiography, 2 groups of patients were defined: (1) 90 patients (17%) with reocclusion (Thrombolysis In Myocardial Infarction [TIMI] flow 0 or 1) and (2) 438 patients (83%) without reocclusion. Long-term clinical follow-up was obtained for all 528 patients at a median of 5.7 years after follow-up angiography (6.4 years after PTCA). The overall actuarial 8-year total mortality rate was 13%. At the end of follow-up, there were 35 deaths (8%) among the 438 patients without reocclusion and 18 deaths (20%) among the 90 patients with reocclusion (P=0.002). The actuarial 8-year total mortality rate was 10% in patients without reocclusion and 28% in patients with reocclusion (P=0.0003). The actuarial cardiovascular mortality rate was 7% in patients without reocclusion and 25% in patients with reocclusion (P<0.0001). The impact of reocclusion on long-term mortality was greater in patients with anterior MI.

**Conclusions**-Late IRA patency is strongly associated with long-term survival after MI. These observations should encourage prospective studies to evaluate the impact of strategies designed to prevent late reocclusion in postinfarction patients.

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#### Dose-Response Effects of <sup>32</sup>P Radioactive Stents in an Atherosclerotic Porcine Coronary Model

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**Background**-Experimental studies have demonstrated that <sup>32</sup>P radioactive stents reduce neointimal formation at 28 days in porcine iliac and coronary arteries. Our objective was to determine the long-term dose-response effects of 1.0- to 12.0- $\mu$ Ci <sup>32</sup>P radioactive stents in a porcine atherosclerotic coronary model.

**Methods and Results**-Control (n=19) and 1.0- to 12.0- $\mu$ Ci <sup>32</sup>P radioactive (n=43) stents (total, n=62) were implanted in the coronary arteries of 31 miniature swine at 28 days after creation of a fibrocellular plaque by overstretch balloon injury and cholesterol feeding. Angiography and histomorphometry were performed at 6 months. Stent thrombosis occurred in 3 radioactive (7.7%) and no control stents (P=0.54). On histology, the mean neointimal area and the percent in-stent stenosis correlated positively with increasing stent activity (r=0.64, P<0.001). The mean neointimal area (mm<sup>2</sup>) for the stents with  $\geq 3.0 \mu$ Ci <sup>32</sup>P (3.57±1.21) was significantly greater than that for the nonradioactive stents (1.78±0.68, P<0.0001). The neointima of the stents

with  $\geq 3.0$   $\mu\text{Ci}$   $^{32}\text{P}$  was composed of smooth muscle cells, matrix proteoglycans, calcification, foam cells, and cholesterol clefts.

**Conclusions**-Continuous low-dose-rate irradiation delivered by high-activity  $^{32}\text{P}$  radioactive stents promotes the formation of an “atheromatous” neointima after 6 months in this experimental model. These data may be useful for predicting late tissue responses to radioactive stents in human coronary arteries.

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Vascular remodeling and the local delivery of cytochalasin B after coronary angioplasty in humans

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**OBJECTIVES** This study sought to determine the safety, feasibility and outcome of local delivery of cytochalasin B at the site of coronary angioplasty.

**BACKGROUND** Previous failures in the pharmacologic prevention of restenosis may have been related to inadequate dosing at the angioplasty site as a result of systemic drug administration. Alternatively, although previous experimental protocols have typically targeted control of excess tissue growth (intimal hyperplasia), it now appears that overall arterial constriction (vascular remodeling) is the major contributor to late lumen loss. Cytochalasin B inhibits the polymerization of actin and has proved to be a potent inhibitor of vascular remodeling in animal models.

**METHODS** In this phase I, multicenter, randomized, controlled trial, cytochalasin B (or matching placebo) was administered to the site of a successful balloon angioplasty using a microporous local delivery infusion balloon.

**RESULTS** The rate of drug delivery at a constant infusion pressure varied significantly from patient to patient (range 1.7 to 20.2 ml/min), perhaps related to a variable constricting effect of the atherosclerotic plaque on the infusion balloon. The minimal stenosis diameter after the procedure was slightly better in the active drug group ( $1.86 \pm 0.44$  vs.  $1.49 \pm 0.63$  mm,  $p < 0.03$ ), but this difference was not seen at four to six weeks. Although the study was not powered for clinical outcomes ( $n = 43$ ), the combined end point (death, nonfatal infarction or repeat revascularization) was encountered in 20% of the patients receiving cytochalasin B and in 38% of the patients receiving placebo. Clinical restenosis occurred in 18% of the treatment group and 22% of the placebo group. There were no significant differences between groups in biochemical or electrocardiographic variables.

**CONCLUSIONS** Cytochalasin B can be safely administered by local delivery after successful coronary

angioplasty and warrants further study of its efficacy in reducing restenosis.

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Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart disease: results of a Phase I open-label dose escalation study

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**OBJECTIVES** Evaluate the safety, tolerability and preliminary efficacy of intracoronary (IC) basic fibroblast growth factor (bFGF, FGF-2).

**BACKGROUND** FGF-2 is a heparin-binding growth factor capable of inducing functionally significant angiogenesis in animal models of myocardial ischemia.

**METHODS** Phase I, open-label dose-escalation study of FGF-2 administered as a single 20-min infusion in patients with ischemic heart disease not amenable to treatment with CABG or PTCA.

**RESULTS** Fifty-two patients enrolled in this study received IC FGF-2 (0.33 to 48 g/kg). Hypotension was dose-dependent and dose-limiting, with 36 g/kg being the maximally tolerated dose. Four patients died and four patients had non-Q-wave myocardial infarctions. Laboratory parameters and retinal examinations showed mild and mainly transient changes during the 6-month follow-up. There was an improvement in quality of life as assessed by Seattle Angina Questionnaire and improvement in exercise tolerance as assessed by treadmill exercise testing (510 ± 24 s at baseline, 561 ± 26 s at day 29 [p = 0.023], 609 ± 26 s at day 57 (p < 0.001), and 633 ± 24 s at day 180 (p < 0.001), overall p < 0.001). Magnetic resonance (MR) imaging showed increased regional wall thickening (baseline: 34 ± 1.7%, day 29: 38.7 ± 1.9% [p = 0.006], day 57: 41.4 ± 1.9% [p < 0.001], and day 180: 42.0 ± 2.3% [p < 0.001], overall P = 0.001) and a reduction in the extent of the ischemic area at all time points compared with baseline.

**CONCLUSIONS** Intracoronary administration of rFGF-2 appears safe and is well tolerated over a 100-fold dose range (0.33 to 0.36 k/kg). Preliminary evidence of efficacy is tempered by the open-label uncontrolled design of the study.

Local paclitaxel delivery for the prevention of restenosis: biological effects and efficacy in vivo

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**OBJECTIVE** The aim of this study was to evaluate the potential of paclitaxel to prevent restenosis in vivo.

**BACKGROUND** Paclitaxel (Taxol) is a microtubule-stabilizing compound with potent antitumor activity. It influences the cytoskeleton equilibrium by increasing the assembly of altered microtubules, thereby inducing cellular modifications that result in reduced proliferation, migration and signal transduction.

**METHODS** Before the in vivo study, delivery efficiency was determined with radiolabeled paclitaxel in porcine hearts. After induction of a defined plaque in the right carotid arteries of 76 New Zealand rabbits by electrical stimulation, 27 animals underwent balloon dilation and subsequent local paclitaxel delivery (10 ml, 10 mol/liter) with a double-balloon catheter. Twenty-nine animals served as control with angioplasty only, 10 animals underwent local delivery of vehicle only (0.9% NaCl solution) and 10 animals were solely electrostimulated. Vessels were excised one, four, and eight weeks after intervention.

**RESULTS** The extent of stenosis in paclitaxel-treated animals was significantly reduced compared with balloon-dilated control animals ( $p = 0.0012$ , one, four and eight weeks after intervention: 14.6%, 24.6% and 20.5%, vs. 24.9%, 33.8% and 43.1%, respectively). Marked vessel enlargement compared with balloon-dilated control animals could be observed ( $p = 0.0001$ , total vessel area after one, four and eight weeks: paclitaxel group: 1.983, 1.700 and 1.602 mm<sup>2</sup>, control: 1.071, 1.338 and 1.206 mm<sup>2</sup>, respectively). Tubulin staining and electron microscopy revealed changes in microtubule assembly, which were limited to the intimal area. Vasocontractile function after paclitaxel treatment showed major impairment.

**CONCLUSIONS** Local delivery of paclitaxel resulted in reduced neointimal stenosis and enlargement in vessel size. Both these effects contribute to a preservation of vessel shape and are likely to be caused by a structural alteration of the cytoskeleton.

#### Local delivery

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