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### **Five-Year Clinical Follow-Up After Intracoronary Radiation: Results of a Randomized Clinical Trial**

Circulation 2002 105: 2737 - 2740

**Background**— Several clinical trials indicate that intracoronary radiation is safe and effective for treatment of restenotic coronary arteries. We previously reported 6-month and 3-year clinical and angiographic follow-up demonstrating significant decreases in target lesion revascularization (TLR) and angiographic restenosis after radiation of restenotic lesions. The objective of this study was to document the clinical outcome 5 years after treatment of restenotic coronary arteries with catheter-based iridium-192 (192Ir).

**Methods and Results**— A double-blind, randomized trial compared 192Ir to placebo sources in patients with restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to 192Ir and 29 to placebo. At 5-year follow-up, TLR was significantly lower in the 192Ir group (23.1% versus 48.3%;  $P=0.05$ ). There were 2 TLRs between years 3 and 5 in patients in the 192Ir group and none in patients in the placebo group. The 5-year event-free survival rate (freedom from death, myocardial infarction, or TLR) was greater in 192Ir-treated patients (61.5% versus 34.5%;  $P=0.02$ ).

**Conclusions**— Despite apparent mitigation of efficacy over time, there remains a significant reduction in TLR at 5 years and an improvement in event-free survival in patients treated with intracoronary 192Ir. The early clinical benefits after intracoronary radiation with 192Ir seem durable at 5-year clinical follow-up.

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## ***Rassegna della Letteratura***

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Frank H. Gietzen, Christian J. Leuner, Ludger Obergassel, Claudia Strunk-Mueller, and Horst Kuhn

**Role of Transcatheter Ablation of Septal Hypertrophy in Patients With Hypertrophic Cardiomyopathy, New York Heart Association Functional Class III or IV, and Outflow Obstruction Only Under Provocable Conditions**

*Circulation*, Jul 2002; 106: 454 – 459

**Background**— Transcatheter ablation of septal hypertrophy (TASH) for hypertrophic cardiomyopathy seems to be an effective alternative to surgical myectomy. It remains a point of debate whether an outflow obstruction at rest is a necessary criterion for interventional therapy.

**Methods and Results**— TASH was compared in 45 consecutive patients with no resting gradient and a provocable gradient of  $\geq 30$  mm Hg (group I) and in 84 consecutive patients with a resting gradient of  $\geq 30$  mm Hg ( $80 \pm 33$  mm Hg) (group II). At baseline, all patients were in NYHA functional class (FC) III or IV, unresponsive to medical treatment. Patients in group I were older ( $63 \pm 12$  versus  $55 \pm 17$  years,  $P=0.005$ ) and had a lower postextrasystolic gradient ( $110 \pm 44$  versus  $171 \pm 40$  mm Hg,  $P<0.001$ ). The groups were similar with respect to NYHA FC ( $3.1 \pm 0.3$  versus  $3.1 \pm 0.3$ ), basal septal thickness ( $22 \pm 4$  versus  $23 \pm 3$  mm), maximal oxygen consumption ( $13.1 \pm 4.6$  versus  $14.5 \pm 5.0$  mL/kg per minute), and pulmonary artery mean pressure at workload ( $42 \pm 9$  versus  $42 \pm 10$  mm Hg) ( $P>0.05$ ). Median follow-up was 7 months after TASH. The 2 groups showed a significant and similar improvement in provocable obstruction (to  $24 \pm 24$  and  $56 \pm 51$  mm Hg, respectively), basal septal thickness (to  $12 \pm 3$  and  $12 \pm 4$  mm, respectively), NYHA FC (to  $1.7 \pm 0.6$  and  $1.5 \pm 0.6$ , respectively), maximal oxygen consumption (to  $16.0 \pm 5.3$  and  $16.6 \pm 6.0$  mL/kg per minute, respectively), and pulmonary artery mean pressure at workload (to  $36 \pm 9$  and  $34 \pm 9$  mm Hg, respectively) ( $P>0.05$ ).

**Conclusions**— TASH seems to have beneficial clinical and hemodynamic effects in patients with either provocable or resting outflow obstruction.

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## *Rassegna della Letteratura*

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Patrick W. Serruys, Muzaffer Degertekin, Kengo Tanabe, Alexandre Abizaid, J. Edouardo Sousa, Antonio Colombo, Giulio Guagliumi, William Wijns, Wietze K. Lindeboom, Jurgen Ligthart, Pim J. de Feyter, and Marie-Claude Morice

**Intravascular Ultrasound Findings in the Multicenter, Randomized, Double-Blind RAVEL (RAnimized study with the sirolimus-eluting VELOCITY balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) Trial**

*Circulation, Aug 2002; 106: 798 - 803.*

**Background**— The goal of this intravascular ultrasound investigation was to provide a more detailed morphological analysis of the local biological effects of the implantation of a sirolimus-eluting stent compared with an uncoated stent.

**Methods and Results**— In the RAVEL trial, 238 patients with single de novo lesions were randomized to receive either an 18-mm sirolimus-eluting stent (Bx VELOCITY stent, Cordis) or an uncoated stent (Bx VELOCITY stent). In a subset of 95 patients (sirolimus-eluting stent=48, uncoated stent=47), motorized intravascular ultrasound pullback (0.5 mm/s) was performed at a 6-month follow-up. Stent volumes, total vessel volumes, and plaque-behind-stent volumes were comparable. However, the difference in neointimal hyperplasia ( $2\pm 5$  versus  $37\pm 28$  mm<sup>3</sup>) and percent of volume obstruction ( $1\pm 3\%$  versus  $29\pm 20\%$ ) at 6 months between the 2 groups was highly significant ( $P<0.001$ ), emphasizing the nearly complete abolition of the proliferative process inside the drug-eluting stent. Analysis of the proximal and distal edge volumes showed no significant difference between the 2 groups in external elastic membrane or lumen and plaque volume at the proximal and distal edges. There was also no evidence of intrastent thrombosis or persisting dissection at the stent edges. Although there was a higher incidence of incomplete stent apposition in the sirolimus group compared with the uncoated stent group ( $P<0.05$ ), it was not associated with any adverse clinical events at 1 year.

**Conclusions**— Sirolimus-eluting stents are effective in preventing neointimal hyperplasia without creating edge effect and without affecting the plaque burden behind the struts.

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## ***Rassegna della Letteratura***

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Wayne B. Batchelor, Thaddeus R. Tolleson, Yao Huang, Rhonda L. Larsen, R. Michael Mantell, Patricia Dillard, Marie Davidian, Daowen Zhang, Warren J. Cantor, Michael H. Sketch, Jr, E. Magnus Ohman, James P. Zidar, Daniel Gretler, Peter M. DiBattiste, James E. Tchong, Robert M. Califf, and Robert A. Harrington

**Randomized COMparison of Platelet Inhibition With Abciximab, TiRofiban and Eptifibatide During Percutaneous Coronary Intervention in Acute Coronary Syndromes: The COMPARE Trial**

Circulation, Sep 2002; 106: 1470 – 1476

**Background**— The relative anti-aggregatory effects of currently prescribed platelet glycoprotein IIb/IIIa receptor antagonists during and after percutaneous coronary intervention for acute coronary syndromes have not been established.

**Methods and Results**— We randomized 70 acute coronary syndrome patients undergoing percutaneous coronary intervention to receive abciximab, eptifibatide, or tirofiban at doses used in the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT), Platelet glycoprotein IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT), and Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS)/Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trials, respectively. Platelet aggregation (PA) in response to 20  $\mu\text{mol/L}$  of adenosine diphosphate was measured with turbidimetric aggregometry in both D-phenylalanyl-L-prolyl-L-arginine chloromethylketone and citrate-anticoagulated blood early (15 and 30 minutes) and late (4, 12, and 18 to 24 hours) after drug initiation. At 15 and 30 minutes, PA was significantly less inhibited by the tirofiban-RESTORE regimen compared with abciximab ( $P=0.028$ ) and eptifibatide regimens ( $P=0.0001$ ). The abciximab regimen, however, showed increasingly varied anti-aggregatory effects during continued infusion for  $\geq 4$  hours. Citrate exaggerated ex vivo platelet inhibition after eptifibatide and tirofiban, but had the opposite effect on abciximab. Of all regimens evaluated, the eptifibatide regimen inhibited PA most consistently throughout both the early and late periods.

**Conclusions**— Currently recommended drug regimens to inhibit the platelet glycoprotein IIb/IIIa receptor have distinct pharmacodynamic profiles that might affect their relative efficacy in acute coronary syndromes and percutaneous coronary intervention.

E. Regar, P.W. Serruys, C. Bode, C. Holubarsch, J.L. Guermontprez, W. Wijns, A. Bartorelli, C. Constantini, M. Degertekin, K. Tanabe, C. Disco, E. Wuelfert, and M.C. Morice

**Angiographic Findings of the Multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): Sirolimus-Eluting Stents Inhibit Restenosis Irrespective of the Vessel Size**

*Circulation, Oct 2002; 106: 1949 - 1956.*

**Background**— Restenosis remains the major limitation of coronary catheter-based intervention. In small vessels, the amount of neointimal tissue is disproportionately greater than the vessel caliber, resulting in higher restenosis rates. In the Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) trial, 40% of the vessels were small (<2.5 mm). The present study evaluates the relationship between angiographic outcome and vessel diameter for sirolimus-eluting stents.

**Methods and Results**— Patients were randomized to receive either an 18-mm bare metal Bx VELOCITY (BS group, n=118), or a sirolimus-eluting Bx VELOCITY stent (SES group, n=120). Subgroups were stratified into terciles according to their reference diameter (RD; stratum I, RD <2.36 mm; stratum II, RD 2.36 mm to 2.84 mm; stratum III, RD >2.84 mm). At 6-month follow-up, the restenosis rate in the SES group was 0% in all strata (versus 35%, 26%, and 20%, respectively, in the BS group). In-stent late loss was  $0.01 \pm 0.25$  versus  $0.80 \pm 0.43$  mm in stratum I,  $0.01 \pm 0.38$  versus  $0.88 \pm 0.57$  mm in stratum II, and  $-0.06 \pm 0.35$  versus  $0.74 \pm 0.57$  mm in stratum III (SES versus BS). In SES, the minimal lumen diameter (MLD) remained unchanged ( $\Delta$  -0.72 to 0.72 mm) in 97% of the lesions and increased (=late gain,  $\Delta$ MLD <0.72 mm) in 3% of the lesions. Multivariate predictors for late loss were treatment allocation ( $P < 0.001$ ) and postprocedural MLD ( $P = 0.008$ ).

**Conclusions**— Sirolimus-eluting stents prevent neointimal proliferation and late lumen loss irrespective of the vessel diameter. The classic inverse relationship between vessel diameter and restenosis rate was seen in the bare stent group but not in the sirolimus-eluting stent group.

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## *Rassegna della Letteratura*

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Marie-Claude Morice, M.D., Patrick W. Serruys, M.D., Ph.D., J. Eduardo Sousa, M.D., Jean Fajadet, M.D., Ernesto Ban Hayashi, M.D., Marco Perin, M.D., Antonio Colombo, M.D., G. Schuler, M.D., Paul Barragan, M.D., Giulio Guagliumi, M.D., Ferenc Molnàr, M.D., Robert Falotico, Ph.D., for the RAVEL Study Group

### **A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization**

*NEJM* 2002;346:1776-80

**Background**— The need for repeated treatment of restenosis of a treated vessel remains the main limitation of percutaneous coronary revascularization. Because sirolimus (rapamycin) inhibits the proliferation of lymphocytes and smooth-muscle cells, we compared a sirolimus-eluting stent with a standard uncoated stent in patients with angina pectoris.

**Methods**— We performed a randomized, double-blind trial to compare the two types of stents for revascularization of single, primary lesions in native coronary arteries. The trial included 238 patients at 19 medical centers. The primary end point was in-stent late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months). Secondary end points included the percentage of in-stent stenosis of the luminal diameter and the rate of restenosis (luminal narrowing of 50 percent or more). We also analyzed a composite clinical end point consisting of death, myocardial infarction, and percutaneous or surgical revascularization at 1, 6, and 12 months.

**Results** — At six months, the degree of neointimal proliferation, manifested as the mean ( $\pm$ SD) late luminal loss, was significantly lower in the sirolimus-stent group ( $-0.01\pm 0.33$  mm) than in the standard-stent group ( $0.80\pm 0.53$  mm,  $P<0.001$ ). None of the patients in the sirolimus-stent group, as compared with 26.6 percent of those in the standard-stent group, had restenosis of 50 percent or more of the luminal diameter ( $P<0.001$ ). There were no episodes of stent thrombosis. During a follow-up period of up to one year, the overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group ( $P<0.001$ ). The difference was due entirely to a higher rate of revascularization of the target vessel in the standard-stent group.

**Conclusions**— As compared with a standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis, and associated clinical events.

Van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE.

**Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group.**

**Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial.**

*Lancet 2002 Jul 13;360(9327):109-13*

**Background:** Antiplatelet treatment with aspirin and oral anticoagulants reduces recurrence of ischaemic events after myocardial infarction. We aimed to investigate which of these drugs is more effective in the long term after acute coronary events, and whether the combination of aspirin and oral anticoagulants offers greater benefit than either of these agents alone, without excessive risk of bleeding.

**Methods:** In a randomised open-label trial in 53 sites, we randomly assigned 999 patients to low-dose aspirin, high-intensity oral anticoagulation, or combined low-dose aspirin and moderate intensity oral anticoagulation. Patients were followed up for a maximum of 26 months. The primary composite endpoint was first occurrence of myocardial infarction, stroke, or death.

**Findings:** The primary endpoint was reached in 31 (9%) of 336 patients on aspirin, in 17 (5%) of 325 on anticoagulants (hazard ratio 0.55 [95% CI 0.30-1.00],  $p=0.0479$ ), and in 16 (5%) of 332 on combination therapy (0.50 [0.27-0.92],  $p=0.03$ ). Major bleeding was recorded in three (1%) patients on aspirin, three (1%) on anticoagulants (1.03 [0.21-5.08],  $p=1.0$ ), and seven (2%) on combination therapy (2.35 [0.61-9.10],  $p=0.2$ ). Frequency of minor bleeding was 5%, 8% (1.68 [0.92-3.07],  $p=0.20$ ), and 15% (3.13 [1.82-5.37],  $p<0.0001$ ), in the three groups, respectively. 164 patients permanently discontinued the study drug. Analyses were done by intention to treat.

**Interpretation:** In patients recently admitted with acute coronary events, treatment with high-intensity oral anticoagulants or aspirin with medium-intensity oral anticoagulants was more effective than aspirin on its own in reduction of subsequent cardiovascular events and death.

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## ***Rassegna della Letteratura***

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Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, Wheatley DJ, Pocock SJ; Randomized Intervention Trial of unstable Angina Investigators.

**Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina.**

*Lancet* 2002 Sep 7;360(9335):743-51.

**Background:** Current guidelines suggest that, for patients at moderate risk of death from unstable coronary-artery disease, either an interventional strategy (angiography followed by revascularisation) or a conservative strategy (ischaemia-driven or symptom-driven angiography) is appropriate. We aimed to test the hypothesis that an interventional strategy is better than a conservative strategy in such patients.

**Methods:** We did a randomised multicentre trial of 1810 patients with non-ST-elevation acute coronary syndromes (mean age 62 years, 38% women). Patients were assigned an early intervention or conservative strategy. The antithrombin agent in both groups was enoxaparin. The co-primary endpoints were a combined rate of death, non-fatal myocardial infarction, or refractory angina at 4 months; and a combined rate of death or non-fatal myocardial infarction at 1 year. Analysis was by intention to treat.

**Findings:** At 4 months, 86 (9.6%) of 895 patients in the intervention group had died or had a myocardial infarction or refractory angina, compared with 133 (14.5%) of 915 patients in the conservative group (risk ratio 0.66, 95% CI 0.51-0.85,  $p=0.001$ ). This difference was mainly due to a halving of refractory angina in the intervention group. Death or myocardial infarction was similar in both treatment groups at 1 year (68 [7.6%] vs 76 [8.3%], respectively; risk ratio 0.91, 95% CI 0.67-1.25,  $p=0.58$ ). Symptoms of angina were improved and use of antianginal medications significantly reduced with the interventional strategy ( $p<0.0001$ ).

**Interpretation:** In patients presenting with unstable coronary-artery disease, an interventional strategy is preferable to a conservative strategy, mainly because of the halving of refractory or severe angina, and with no increased risk of death or myocardial infarction.

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## *Rassegna della Letteratura*

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Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P; Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction study group.

**Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study.**

Lancet 2002 Sep 14;360(9336):825-9

**Background:** Although both prehospital fibrinolysis and primary angioplasty provide a clinical benefit over in-hospital fibrinolysis in acute myocardial infarction, they have not been directly compared. Our aim was to find out whether primary angioplasty was better than prehospital fibrinolysis.

**Methods:** We did a randomised multicentre trial of 840 patients (of 1200 planned) who presented within 6 h of acute myocardial infarction with ST-segment elevation, initially managed by mobile emergency-care units. We assigned patients to prehospital fibrinolysis (n=419) with accelerated alteplase or primary angioplasty (n=421), and transferred all to a centre with access to emergency angioplasty. Our primary endpoint was a composite of death, non-fatal reinfarction, and non-fatal disabling stroke at 30 days. Analyses were by intention to treat.

**Findings:** The median delay between onset of symptoms and treatment was 130 min in the prehospital-fibrinolysis group and 190 min (time to first balloon inflation) in the primary-angioplasty group. Rescue angioplasty was done in 26% of the patients in the fibrinolysis group. The rate of the primary endpoint was 8.2% (34 patients) in the prehospital-fibrinolysis group and 6.2% (26 patients) in the primary-angioplasty group (risk difference 1.96, 95% CI -1.53 to 5.46). 16 (3.8%) patients assigned prehospital fibrinolysis and 20 (4.8%) assigned primary angioplasty died (p=0.61).

**Interpretation:** A strategy of primary angioplasty was not better than a strategy of prehospital fibrinolysis (with transfer to an interventional facility for possible rescue angioplasty) in patients presenting with early myocardial infarction.

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## *Rassegna della Letteratura*

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SOS trial group

**Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial.**

*Lancet 2002 Sep 28;360(9338):965-70.*

**Background:** Results of trials, comparing percutaneous transluminal coronary angioplasty (PTCA) with coronary artery bypass grafting (CABG), indicate that rates of death or myocardial infarction are similar with either treatment strategy. Management with PTCA is, however, associated with an increased requirement for subsequent, additional revascularisation. Coronary stents, used as an adjunct to PTCA, reduce restenosis and the need for repeat revascularisation. The aim of the Stent or Surgery (SoS) trial was to assess the effect of stent-assisted percutaneous coronary intervention (PCI) versus CABG in the management of patients with multivessel disease.

**Methods:** In 53 centres in Europe and Canada, symptomatic patients with multivessel coronary artery disease were randomised to CABG (n=500) or stent-assisted PCI (n=488). The primary outcome measure was a comparison of the rates of repeat revascularisation. Secondary outcomes included death or Q-wave myocardial infarction and all-cause mortality. Analysis was by intention to treat.

**FINDINGS:** All patients were followed-up for a minimum of 1 year and the results are expressed for the median follow-up of 2 years. 21% (n=101) of patients in the PCI group required additional revascularisation procedures compared with 6% (n=30) in the CABG group (hazard ratio 3.85, 95% CI 2.56-5.79,  $p<0.0001$ ). The incidence of death or Q-wave myocardial infarction was similar in both groups (PCI 9% [n=46], CABG 10% [n=49]; hazard ratio 0.95, 95% CI 0.63-1.42,  $p=0.80$ ). There were fewer deaths in the CABG group than in the PCI group (PCI 5% [n=22], CABG 2% [n=8]; hazard ratio 2.91, 95% CI 1.29-6.53,  $p=0.01$ ).

**Interpretation:** The use of coronary stents has reduced the need for repeat revascularisation when compared with previous studies that used balloon angioplasty, though the rate remains significantly higher than in patients managed with CABG. The apparent reduction in mortality with CABG requires further investigation.

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## *Rassegna della Letteratura*

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Voci P, Mariano E, Pizzuto F, Puddu PE, Romeo F.

**Coronary recanalization in anterior myocardial infarction: the open perforator hypothesis.**

*J Am Coll Cardiol.* 2002 Oct 2;40(7):1205-13.

**Objective:** Patent perforators, noninvasively imaged by transthoracic color-Doppler echocardiography, may reflect adequate reperfusion in anterior myocardial infarction (MI).

**Background:** The Thrombolysis In Myocardial Infarction (TIMI) classification may not fully reflect adequate myocardial reperfusion in MI.

**Methods:** We studied 61 patients with anterior MI undergoing thrombolysis (n = 28), primary stenting (n = 20), or neither one (n = 13). High-resolution color-Doppler ultrasound was used to image the left anterior descending coronary artery (LAD) and perforators in four segments of the anterior-apical wall and to build a new recanalization score (RS). The TIMI flow was assessed by angiography. Wall motion score index (WMSI), ejection fraction (EF), end-diastolic volume index, and end-systolic volume index (ESVI) were measured by echocardiography at baseline and at three-month follow-up. Linear regression equations, considering RS or TIMI flow as independent variables, were compared among these functional recovery parameters. A multivariate linear model, predicting percent changes of WMSI, EF, or ESVI, was used to investigate the contribution of several clinical covariates along with RS and TIMI flow.

**Results:** Sensitivity, specificity, and diagnostic accuracy of color-Doppler ultrasound in detecting LAD patency were 86%, 98%, and 97%, respectively. Mean and peak flow velocities discriminated ( $0.004 < p < 0.008$ ) TIMI flow but not RS. Regression equations showed that RS discriminated better than TIMI flow recovery of ventricular function ( $p < 0.012$ ). The RS was the best single multivariate predictor ( $p < 0.0001$ ) of percent changes in WMSI, EF, and ESVI.

**Conclusions:** Transthoracic color-Doppler ultrasound detects an open LAD after MI. Perforators reflect adequate myocardial reperfusion and are early noninvasive markers of myocardial viability.

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## ***Rassegna della Letteratura***

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Renu Virmani, Francesco Liistro, Goran Stankovic, Carlo Di Mario, Matteo Montorfano, Andrew Farb, Frank D. Kolodgie, and Antonio Colombo

### **Mechanism of Late In-Stent Restenosis After Implantation of a Paclitaxel Derivate-Eluting Polymer Stent System in Humans**

*Circulation* 2002 106: 2649–2651

**Background**— We recently reported delayed angiographic restenosis in 15 patients who received 7-hexanoyltaxol (QP2)-eluting polymer stents (QuaDS) for the treatment of in-stent restenosis. This study presents the histological findings of atherectomy specimens from a subset of these patients receiving implants.

**Methods and Results**— Between October and December 2001, 5 patients treated with QuaDS-QP2 stents underwent directional coronary atherectomy at  $11.2 \pm 1.0$  months for recurrent in-stent restenosis. Restenotic lesion composition was assessed with special stains, immunohistochemistry with quantitative image analysis, and, in one specimen, transmission electron microscopy. Atherectomy specimens contained fibrin interspersed in a smooth muscle cell-rich neointima with proteoglycan matrix. In 2 of 5 specimens, large aggregates of macrophages and T-lymphocytes were noted. These areas of active inflammation demonstrated a relatively high proliferation index by Ki-67 antibody staining, whereas the proliferation index in smoothmuscle cell-rich restenotic areas was low.

**Conclusion**— Restenotic lesions from QuaDS-QP2-eluting stents at 12 months show persistent fibrin deposition with varying degrees of inflammation. These pathological changes, representing delayed healing, are usually observed up to only 3 months in human coronary arteries with stainless steel balloon-expandable stents. The nonreabsorbable polymer alone may have induced chronic inflammation.

J. Eduardo Sousa, Marco A. Costa, Alexandre Abizaid, Amanda G.M.R. Sousa, Fausto Feres, Luiz A. Mattos, Marinella Centemero, Galo Maldonado, Andrea S. Abizaid, Ibraim Pinto, Robert Falotico, Judith Jaeger, Jeffrey J. Popma, and Patrick W. Serruys

**Sirolimus-Eluting Stent for the Treatment of In-Stent Restenosis: A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study**

Circulation 2003 107: 24 – 27

**Background**— We have previously reported the safety and effectiveness of sirolimus-eluting stents for the treatment of de novo coronary lesions. The present investigation explored the potential of this technology to treat in-stent restenosis.

**Methods and Results**— Twenty-five patients with in-stent restenosis were successfully treated with the implantation of 1 or 2 sirolimus-eluting Bx VELOCITY stents in São Paulo, Brazil. Nine patients received 2 stents (1.4 stents per lesion). Angiographic and volumetric intravascular ultrasound (IVUS) images were obtained after the procedure and at 4 and 12 months. All vessels were patent at the time of 12-month angiography. Angiographic late loss averaged  $0.07 \pm 0.2$  mm in-stent and  $-0.05 \pm 0.3$  mm in-lesion at 4 months, and  $0.36 \pm 0.46$  mm in-stent and  $0.16 \pm 0.42$  mm in-lesion after 12 months. No patient had in-stent or stent margin restenosis at 4 months, and only one patient developed in-stent restenosis at 1-year follow-up. Intimal hyperplasia by 3-dimensional IVUS was  $0.92 \pm 1.9$  mm<sup>3</sup> at 4 months and  $2.55 \pm 4.9$  mm<sup>3</sup> after 1 year. Percent volume obstruction was  $0.81 \pm 1.7\%$  and  $1.76 \pm 3.4\%$  at the 4 and 12-month follow-up, respectively. There was no evidence of stent malapposition either acutely or in the follow-up IVUS images, and there were no deaths, stent thromboses, or repeat revascularizations.

**Conclusion**— This study demonstrates the safety and the potential utility of sirolimus-eluting Bx VELOCITY stents for the treatment of in-stent restenosis.

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## *Rassegna della Letteratura*

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Wei C. Lau, Lucy A. Waskell, Paul B. Watkins, Charlene J. Neer, Kevin Horowitz, Amy S. Hopp, Alan R. Tait, David G.M. Carville, Kirk E. Guyer, and Eric R. Bates

### **Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation: A New Drug-Drug Interaction**

Circulation 2003 107: 32 – 37

**Background**— We observed that the prodrug clopidogrel was less effective in inhibiting platelet aggregation with coadministration of atorvastatin during point-of-care platelet function testing. Because atorvastatin is metabolized by cytochrome P450 (CYP) 3A4, we hypothesized that clopidogrel might be activated by CYP3A4.

**Methods and Results**— Platelet aggregation was measured in 44 patients undergoing coronary artery stent implantation treated with clopidogrel or clopidogrel plus pravastatin or atorvastatin, and in 27 volunteers treated with clopidogrel and either erythromycin or troleandomycin, CYP3A4 inhibitors, or rifampin, a CYP3A4 inducer. Atorvastatin, but not pravastatin, attenuated the antiplatelet activity of clopidogrel in a dose-dependent manner. Percent platelet aggregation was  $34\pm 23$ ,  $58\pm 15$  ( $P=0.027$ ),  $74\pm 10$  ( $P=0.002$ ), and  $89\pm 7$  ( $P=0.001$ ) in the presence of clopidogrel and 0, 10, 20, and 40 mg of atorvastatin, respectively. Erythromycin attenuated platelet aggregation inhibition ( $55\pm 12$  versus  $42\pm 12\%$  platelet aggregation;  $P=0.002$ ), as did troleandomycin ( $78\pm 18$  versus  $45\pm 18\%$  platelet aggregation;  $P<0.0003$ ), whereas rifampin enhanced platelet aggregation inhibition ( $33\pm 18$  versus  $56\pm 20\%$  platelet aggregation,  $P=0.001$ ).

**Conclusions**— CYP3A4 activates clopidogrel. Atorvastatin, another CYP3A4 substrate, competitively inhibits this activation. Use of a statin not metabolized by CYP3A4 and point-of-care platelet function testing may be warranted in patients treated with clopidogrel.

Eberhard Grube, Sigmund Silber, Karl Eugen Hauptmann, Ralf Mueller, Lutz Buellesfeld, Ulrich Gerckens, and Mary E. Russell

**TAXUS I: Six- and Twelve-Month Results From a Randomized, Double-Blind Trial on a Slow-Release Paclitaxel-Eluting Stent for De Novo Coronary Lesions**

Circulation 2003 107: 38 – 42

**Background**— The TAXUS NIRx stent (Boston Scientific Corp) provides local delivery of paclitaxel via a slow-release polymer coating. The TAXUS I trial was the first in-human experience evaluating safety and feasibility of the TAXUS NIRx stent system compared with bare NIR stents (control) (Boston Scientific Corp) for treatment of coronary lesions.

**Methods and Results**— The TAXUS I trial was a prospective, double-blind, three-center study randomizing 61 patients with de novo or restenotic lesions ( $\leq 12$  mm) to receive a TAXUS (n=31) versus control (n=30) stent (diameter 3.0 or 3.5 mm). Demographics, lesion characteristics, clinical outcomes were comparable between the groups. The 30-day major adverse cardiac event (MACE) rate was 0% in both groups (P=NS). No stent thromboses were reported at 1, 6, 9, or 12 months. At 12 months, the MACE rate was 3% (1 event) in the TAXUS group and 10% (4 events in 3 patients) in the control group (P=NS). Six-month angiographic restenosis rates were 0% for TAXUS versus 10% for control (P=NS) patients. There were significant improvements in minimal lumen diameter ( $2.60 \pm 0.49$  versus  $2.19 \pm 0.65$  mm), diameter stenosis ( $13.56 \pm 11.77$  versus  $27.23 \pm 16.69$ ), and late lumen loss ( $0.36 \pm 0.48$  versus  $0.71 \pm 0.48$  mm) in the TAXUS group (all  $P < 0.01$ ). No evidence of edge restenosis was seen in either group. Intravascular ultrasound analysis showed significant improvements in normalized neointimal hyperplasia in the TAXUS ( $14.8 \text{ mm}^3$ ) group compared with the control group ( $21.6 \text{ mm}^3$ ) ( $P < 0.05$ ).

**Conclusions**— In this feasibility trial, the TAXUS slow-release stent was well tolerated and showed promise for treatment of coronary lesions, with significant reductions in angiographic and intravascular ultrasound measures of restenosis.

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## ***Rassegna della Letteratura***

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Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ

**Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography.**

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**Background:** The use of iodinated contrast medium can result in nephropathy. Whether iso-osmolar contrast medium is less nephrotoxic than low-osmolar contrast medium in high-risk patients is uncertain.

**Methods:** We conducted a randomized, double-blind, prospective, multicenter study comparing the nephrotoxic effects of an iso-osmolar, dimeric, nonionic contrast medium, iodixanol, with those of a low-osmolar, nonionic, monomeric contrast medium, iohexol. The study involved 129 patients with diabetes with serum creatinine concentrations of 1.5 to 3.5 mg per deciliter who underwent coronary or aortofemoral angiography. The primary end point was the peak increase from base line in the creatinine concentration during the three days after angiography. Other end points were an increase in the creatinine concentration of 0.5 mg per deciliter or more, an increase of 1.0 mg per deciliter or more, and a change in the creatinine concentration from day 0 to day 7.

**Results:** The creatinine concentration increased significantly less in patients who received iodixanol. From day 0 to day 3, the mean peak increase in creatinine was 0.13 mg per deciliter in the iodixanol group and 0.55 mg per deciliter in the iohexol group ( $P=0.001$ ; the increase with iodixanol minus the increase with iohexol,  $-0.42$  mg per deciliter [95 percent confidence interval,  $-0.73$  to  $-0.22$ ]). Two of the 64 patients in the iodixanol group (3 percent) had an increase in the creatinine concentration of 0.5 mg per deciliter or more, as compared with 17 of the 65 patients in the iohexol group (26 percent) ( $P=0.002$ ; odds ratio for such an increase in the iodixanol group, 0.09 [95 percent confidence interval, 0.02 to 0.41]). No patient receiving iodixanol had an increase of 1.0 mg per deciliter or more, but 10 patients in the iohexol group (15 percent) did. The mean change in the creatinine concentration from day 0 to day 7 was 0.07 mg per deciliter in the iodixanol group and 0.24 mg per deciliter in the iohexol group ( $P=0.003$ ; value in the iodixanol group minus the value in the iohexol group,  $-0.17$  mg per deciliter [95 percent confidence interval,  $-0.34$  to  $-0.07$ ]).

**Conclusions:** Nephropathy induced by contrast medium may be less likely to develop in high-risk patients when iodixanol is used rather than a low-osmolar, nonionic contrast medium.