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## *Rassegna della Letteratura*

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### **Treatment of Saphenous Vein Bypass Grafts With Ultrasound Thrombolysis: A Randomized Study (ATLAS)**

Mandeep Singh, Uri Rosenschein, Kalon K.L. Ho, Peter B. Berger, Richard Kuntz, and David R. Holmes, Jr. *Circulation* 2003; 107: 2331–2336

**Background** Percutaneous coronary interventions (PCIs) in saphenous vein grafts (SVGs) with thrombus have a high frequency of distal embolization. Acolysis (therapeutic ultrasound) can break up thrombus in vitro in animal models and humans. Whether this is beneficial during percutaneous SVG interventions is unknown.

**Methods and Results** We performed a trial of coronary ultrasound thrombolysis in which patients with an acute coronary syndrome undergoing PCI in SVGs were randomly assigned to receive acolysis or abciximab. The primary end point was a successful procedure, defined as final luminal diameter stenosis 30% or less with Thrombolysis In Myocardial Infarction grade 3 flow and freedom from major adverse cardiac events (composite of death, Q-wave, and non-Q-wave myocardial infarction [MI], emergency bypass procedure, disabling stroke, and target lesion revascularization). Of 181 enrolled, 92 received acolysis and 89 abciximab. Angiographic procedural success was achieved in 63% of acolysis patients and 82% of abciximab patients ( $P=0.008$ ). Incidence of major adverse cardiac events at 30 days was 25% with acolysis and 12% with abciximab ( $P=0.036$ ), attributable mainly to a greater frequency of non-Q-wave MI with acolysis (19.6% versus 7.9%,  $P=0.03$ ). The incidence of Q-wave MI was also higher with acolysis (5.4% versus 2.2%,  $P=\text{nonsignificant}$ ). The primary end point was achieved in 53.8% of acolysis patients and 73.1% of abciximab patients ( $P=0.014$ ).

**Conclusions** Use of therapeutic ultrasound in vein graft lesions in patients with acute coronary syndrome had poor angiographic outcome and increased the incidence of acute ischemic complications.

### **Sirolimus (Rapamycin) Monotherapy Prevents Graft Vascular Disease in Nonhuman Primate Recipients of Orthotopic Aortic Allografts**

Camille Dambin, Jochen Klupp, Tudor Birsan, Jorge Luna, Takeshi Suzuki, Tuan Lam, Peter Stähr, Bernard Hausen, Uwe Christians, Peter Fitzgerald, Gerald Berry, and Randall Morris. *Circulation* 2003; 107: 2369–2374

**Background** Delayed treatment with sirolimus (SRL) halts progression of graft vascular disease (GVD) in nonhuman primate (NHP) aortic allograft recipients. In this study, we investigated whether SRL monotherapy prevents the development of GVD.

**Methods and Results** Pairs of 3-cm infrarenal aortic segments were exchanged between mixed lymphocyte reaction–mismatched, blood group–compatible NHPs ( $n=12$ ). Six NHPs were untreated controls, and 6 were treated orally with SRL starting on the day of transplantation. Follow-up was 105 days. SRL doses were adjusted individually by assessing SRL blood concentrations, immune function, and clinical status. The severity of GVD was determined every 3 weeks by intravascular ultrasound, which quantified intimal area (IA) and intimal volume (IV) for the middle 1-cm graft segments. The mean $\pm$ SEM SRL plasma levels were 14.5 $\pm$ 9 ng/mL. In grafts from treated NHPs, IA and IV values on days 63, 84, and 105 were significantly lower than for controls ( $P<0.05$  to  $P<0.001$ ). On day 105, in the grafts from SRL-treated NHPs compared with grafts from controls, values (mean $\pm$ SEM) were IA, 2.9 $\pm$ 0.9 versus 5.5 $\pm$ 0.7 mm<sup>2</sup>,  $P<0.001$  and IV, 29.6 $\pm$ 4.6 versus 55.2 $\pm$ 2.8 mm<sup>3</sup>,  $P<0.001$ ; IA and IV values for grafts from SRL-treated NHPs did not increase significantly between days 21 and 105.

**Conclusions** We show that SRL monotherapy prevented GVD in NHP aortic allograft recipients, suggesting the value of SRL for controlling GVD in clinical transplantation.

### **Incomplete Resolution of ST-Segment Elevation Is a Marker of Transient Microcirculatory Dysfunction After Stenting for Acute Myocardial Infarction**

Laurent J. Feldman, Pierre Coste, Alain Furber, Patrick Dupouy, Michel S. Slama, Jean-Pierre Monassier, Christophe Tron, Antoine Lafont, Marc Faraggi, Dominique Le Guludec, Jean-Luc Dubois-Randé, and P. Gabriel Steg. *Circulation* 2003; 107: 2684 – 2689

**Background** Incomplete ST-segment resolution (STR) after successful primary angioplasty for acute myocardial infarction (AMI) is associated with a poor prognosis. We used intracoronary Doppler velocimetry to investigate whether incomplete STR after primary angioplasty is a marker of severe microcirculatory dysfunction.

**Methods and Results** Fifty patients with 12-h AMI underwent successful primary angioplasty and systematic stenting with a Doppler guidewire. Patients with incomplete (<50%) STR 60 minutes after TIMI 3 flow was restored had flow velocity features suggestive of severe microcirculatory dysfunction, including a higher incidence of early systolic retrograde flow (41% versus 9%,  $P=0.007$ ) and lower coronary flow velocity reserve (CVR, 1.3 versus 1.6,  $P<0.001$ ). CVR improved immediately after stenting in patients with 50% STR but not in patients with <50% STR. There was a significant correlation between STR and poststent CVR. At 3 months, CVR was similar in patients with <50% and 50% STR. However, left ventriculography indicated lower global (42% vs 55%,  $P=0.001$ ) and regional (16% vs 20%,  $P=0.03$ ) left ventricular ejection fractions and 201Tl rest-redistribution scintigraphy indicated a larger infarct size (34% versus 16% 201Tl defect,  $P=0.007$ ) in patients with <50% STR.

**Conclusions** After successful primary angioplasty with systematic stenting, <50% STR is a marker of severe albeit transient microcirculatory dysfunction in patients with AMI and is associated with more extensive myocardial damage.

### **Antibiotic Therapy After Acute Myocardial Infarction: A Prospective Randomized Study**

Ralf Zahn, Steffen Schneider, Birgit Frilling, Karlheinz Seidl, Ulrich Tebbe, Michael Weber, Martin Gottwik, Ernst Altmann, Friedrich Seidel, Jürgen Rox, Ulrich Höffler, Karl-Ludwig Neuhaus, Jochen Senges, and for the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte. *Circulation* 2003; 107: 1253-1259

**Background** Infection with *Chlamydia pneumoniae* is suspected to contribute to the pathogenesis of human atherosclerosis. We investigated whether treatment with the macrolide antibiotic roxithromycin would reduce mortality or morbidity in patients with an acute myocardial infarction.

**Methods and Results** Eight hundred seventy-two patients with an acute myocardial infarction (AMI) were randomly assigned to receive double-blind treatment with either 300 mg roxithromycin or placebo daily for 6 weeks. Primary end point was total mortality during 12-month follow-up. Four hundred thirty-three patients were treated with roxithromycin and 439 with placebo. With the exception of a higher proportion of patients suffering an anterior wall AMI (48.1% in the roxithromycin group versus 40.2% in the placebo group;  $P=0.027$ ) and a lower prevalence of chronic obstructive pulmonary disease in the roxithromycin group (3.5% versus 6.9%,  $P=0.028$ ), baseline characteristics, reperfusion therapy, and medical treatment were well balanced between the two groups. More patients in the roxithromycin group interrupted their study medication before completion of at least 4 weeks of treatment (78 of 433 [18%] versus 48 of 439 [11%];  $P=0.003$ ; odds ratio, 1.8; 95% CI, 1.2 to 2.6). Follow-up at 12 months was achieved in 868 of 872 (99.5%) patients. Total mortality at 12 months was 6.5% (28 of 431) in the roxithromycin group compared with 6.0% (26 of 437) in the placebo group (odds ratio, 1.1; 95% CI, 0.6 to 1.9;  $P=0.739$ ). There were also no differences in the secondary combined end points at 12 months.

**Conclusions** Treatment of AMI patients with roxithromycin did not reduce event rates during 12 months of follow-up. Therefore, our findings do not support the routine use of antibiotic treatment with a macrolide in patients with AMI.

**Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials**

Ellen C Keeley, Judith A Boura, Cindy L Grines *Lancet* 2003; 361: 13-20

**Background** Many trials have been done to compare primary percutaneous transluminal coronary angioplasty (PTCA) with thrombolytic therapy for acute ST-segment elevation myocardial infarction (AMI). Our aim was to look at the combined results of these trials and to ascertain which reperfusion therapy is most effective.

**Methods** We did a search of published work and identified 23 trials, which together randomly assigned 7739 thrombolytic-eligible patients with ST-segment elevation AMI to primary PTCA (n=3872) or thrombolytic therapy (n=3867). Streptokinase was used in eight trials (n=1837), and fibrin-specific agents in 15 (n=5902). Most patients who received thrombolytic therapy (76%, n=2939) received a fibrin-specific agent. Stents were used in 12 trials, and platelet glycoprotein IIb/IIIa inhibitors were used in eight. We identified short-term and long-term clinical outcomes of death, non-fatal reinfarction, and stroke, and did subgroup analyses to assess the effect of type of thrombolytic agent used and the strategy of emergent hospital transfer for primary PTCA. All analyses were done with and without inclusion of the SHOCK trial data.

**Findings** Primary PTCA was better than thrombolytic therapy at reducing overall short-term death (7% [n=270] vs 9% [360];  $p=0.0002$ ), death excluding the SHOCK trial data (5% [199] vs 7% [276];  $p=0.0003$ ), non-fatal reinfarction (3% [80] vs 7% [222];  $p<0.0001$ ), stroke (1% [30] vs 2% [64];  $p=0.0004$ ), and the combined endpoint of death, non-fatal reinfarction, and stroke (8% [253] vs 14% [442];  $p<0.0001$ ). The results seen with primary PTCA remained better than those seen with thrombolytic therapy during long-term follow-up, and were independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA.

**Interpretation** Primary PTCA is more effective than thrombolytic therapy for the treatment of ST-segment elevation AMI.

**Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial**

Bojan Cercek, Prediman K Shah, Marko Noc, Doron Zahger, Uwe Zeymer, Shlomi Matetzky, Gerald Maurer, Peter Mahrer, for AZACS Investigators *Lancet* 2003; 361: 809-13

**Background** There is serological and epidemiological evidence of an association between *Chlamydia pneumoniae* infection and coronary artery disease. Results of previous smaller studies have indicated a reduction of recurrent ischaemic events in patients with acute coronary syndrome when given macrolide antibiotics. We aimed to assess whether short-term treatment with the macrolide antibiotic azithromycin reduces recurrent ischaemic events in patients admitted for unstable angina or myocardial infarction.

**Methods** We assessed the effect of azithromycin in a multicentre, double-blind randomised trial in 1439 patients with unstable angina or acute myocardial infarction. Patients were randomly allocated to receive 500 mg azithromycin on the first day after randomisation, followed by 250 mg daily for 4 days or placebo. Patients were followed up for 6 months. The primary endpoints were death, recurrent myocardial infarction, or recurrent ischaemia necessitating revascularisation. Analysis was done by intention to treat.

**Findings** Treatment with azithromycin did not result in reduction of either individual endpoints or any of the primary endpoints. Of the 716 patients in the azithromycin group, 23 (3%) died, 17 (2%) developed myocardial infarction, 65 (9%) had recurrent ischaemia needing revascularisation, and 100 (14%) had one or more of these endpoints. In the placebo group (n=723) the corresponding numbers of patients were 24 (4%), 22 (3%), 59 (8%), and 106 (15%), respectively ( $p=0.664$ , 95% CI 0.72-1.24). 62 (9%) of patients in the azithromycin group and 59 (8%) in the placebo group reached the secondary endpoint of ischaemia or congestive heart failure necessitating admission (difference 0.5%, 95% CI 0.75-1.53;  $p=0.707$ ). We recorded few side-effects.

**Interpretation** Short-term treatment with azithromycin does not reduce development of recurrent events in patients with acute coronary syndrome.

**Coronary stenting versus coronary bypass surgery in patients with multiple vessel disease and significant proximal LAD stenosis: results from the ERACI II study**

A Rodriguez, M Rodríguez Alemparte, J Baldi, J Navia, A Delacasa, D Vogel, R Oliveri, C Fernández Pereira, V Bernardi, W O'Neill, and I F Palacios. *Heart* 2003 89: 184-188

**Purpose:** To compare percutaneous coronary intervention (PCI) using stent implantation versus coronary artery bypass graft (CABG) in patients with multiple vessel disease with involvement of the proximal left anterior descending coronary artery (LAD).

**Methods:** 230 patients with multiple vessel disease and severe stenosis of the proximal LAD (113 with PCI, 117 with CABG). They were a cohort of patients from the randomised ERACI (Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease) II study.

**Results:** Both groups had similar baseline characteristics. There were no significant differences in 30 day major adverse cardiac events (death, myocardial infarction, stroke, and repeat procedures) between the strategies (PCI 2.7% v CABG 7.6%,  $p = 0.18$ ). There were no significant differences in survival (PCI 96.4% v CABG 95%,  $p = 0.98$ ) and survival with freedom from myocardial infarction (PCI 92% v CABG 89%,  $p = 0.94$ ) at 41.5 (6) months' follow up. However, freedom from new revascularisation procedures (CABG 96.6% v PCI 73%,  $p = 0.0002$ ) and frequency of angina (CABG 9.4% v PCI 22%,  $p = 0.025$ ) were superior in the CABG group.

**Conclusion:** Patients with multivessel disease and significant disease of the proximal LAD randomly assigned in the ERACI II trial to PCI or CABG had similar survival and survival with freedom from myocardial infarction at long term follow up. Repeat revascularisation procedures were higher in the PCI group.

**Cost effectiveness of extended treatment with low molecular weight heparin (dalteparin) in unstable coronary artery disease: results from the FRISC II trial**

M Janzon, L-Å Levin, and E Swahn. *Heart* 2003 89: 287-292

**Background:** In unstable coronary artery disease short term treatment with low molecular weight heparin in addition to aspirin has been shown to be effective.

**Objective:** To assess the cost effectiveness of extended treatment with dalteparin in patients managed with a non-invasive treatment strategy.

**Design:** Prospective, randomised, multicentre study.

**Setting:** 58 centres in Sweden, Denmark, and Norway, of which 16 were interventional.

**Patients:** After at least five days' treatment with open label dalteparin, 2267 patients were randomised to continue double blind treatment with either subcutaneous dalteparin twice daily or placebo for three months. The patients' use of health service resources was recorded prospectively.

**Main outcome measure:** Death/myocardial infarction.

**Results:** After one month into the double blind period there was a 47% relative reduction in death or myocardial infarction in the dalteparin group compared with the placebo group ( $p = 0.002$ ). There was a non-significant mean cost difference, favouring the placebo group, of 849 Swedish crowns (SEK) per patient (equivalent to £58). The incremental cost effectiveness ratio for giving dalteparin treatment for one month was SEK 30 300 (range -78 000 to 139 000) (£2060, range -£5300 to £9400) per avoided death or myocardial infarct. At three months, the decrease in death or myocardial infarction was not significant, precluding cost effectiveness analyses.

**Conclusions:** There is a marginal and non-significant increase in costs for one month of extended dalteparin treatment compared with placebo. Extended dalteparin treatment lowers the risk of death or myocardial infarction in patients with unstable coronary artery disease. While in many countries the resources for early intervention are limited, extended dalteparin treatment up to one month is a cost effective bridge to invasive intervention.

**Drug eluting stents: are human and animal studies comparable?**

R Virmani, F D Kolodgie, A Farb, and A Lafont. *Heart* 2003 89: 133-138

Animal models of stenting probably predict human responses as the stages of healing are remarkably similar. What is characteristically different is the temporal response to healing, which is substantially prolonged in humans. The prevention of restenosis in recent clinical trials of drug eluting stents may represent a near absent or incomplete phase of intimal healing. Continued long term follow up of patients with drug eluting stents for major adverse cardiac events and angiographic restenosis is therefore imperative.

**Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients**

G Fischer, J Stieh, A Uebing, U Hoffmann, G Morf, and H H Kramer. *Heart* 2003 89: 199-204

**Aim:** To evaluate the safety and efficacy of transcatheter closure of secundum atrial septal defects (ASD) with the Amplatzer septal occluder.

**Methods:** 236 consecutive patients with a significant ASD (age 6 months to 46 years, median 5 years; body weight 6.5–79 kg, median 18 kg) were considered for transcatheter closure with the Amplatzer septal occluder; 18 patients with defects that were too large or with a deficient inferior margin were excluded from attempted transcatheter closure after initial transthoracic (4) or transoesophageal echocardiography (14).

**Results:** At cardiac catheterisation, devices were not implanted in 18 patients because the stretched diameter of the ASD was too large (4), the device was unstable (4), compromised the mitral valve (1), or obstructed the upper right pulmonary vein (1); eight patients with additional systemic or pulmonary vein anomalies (5) or a Qp:Qs less than 1.5 (3) were excluded after angiographic and haemodynamic assessment. Thus ASD closure was done successfully in 200 patients (procedure time 25–210 minutes, median 66 minutes; fluoroscopy time 2.5–60 minutes, median 12 minutes), among whom 22 had multiple ASDs (14) or a septal aneurysm (8). The diameter of the devices ranged between 6-34 mm. Severe procedure related complications (retroperitoneal bleeding, air embolism) occurred in two cases. At follow up (33 days to 4.3 years, median 2.3 years) complete closure was documented in 94%, with a trivial residual shunt in 12 patients.

**Conclusions:** The Amplatzer septal occluder is very efficient and offered interventional ASD closure in 84.7% of our group of consecutive patients, with excellent intermediate results.

### **Intravascular Ultrasound Analysis of Infarct-Related and Non-Infarct-Related Arteries in Patients Who Presented With an Acute Myocardial Infarction**

Jun-ichi Kotani, Gary S. Mintz, Marco T. Castagna, Ellen Pinnow, Chalak O. Berzingi, Anh B. Bui, Augusto D. Pichard, Lowell F. Satler, William O. Suddath, Ron Waksman, John R. Laird, Jr, Kenneth M. Kent, Neil J. Weissman. *Circulation* 2003 107: 2889 – 2893

**Background** Previous studies have reported diffuse destabilization of atherosclerotic plaques in acute myocardial infarction (AMI).

**Methods and Results** We used intravascular ultrasound (IVUS) to assess 78 coronary arteries (38 infarct-related arteries [IRAs] with culprit and nonculprit lesions and 40 non-IRAs) from 38 consecutive AMI patients. IVUS analysis included qualitative and quantitative measurements of reference and lesion external elastic membrane (EEM), lumen, and plaque plus media (P&M) area. Positive remodeling was defined as lesion/mean reference EEM >1.0. Culprit lesions were identified by a combination of ECG, wall motion abnormalities (ventriculogram or echocardiogram), scintigraphic perfusion defects, and coronary angiogram. Culprit lesions contained more thrombus (23.7% versus 3.4% in nonculprit IRA plaques and 3.1% in non-IRA plaques;  $P=0.0011$ ). Culprit lesions were predominantly hypoechoic (63.2% versus 37.9% of nonculprit IRA plaques and 28.1% of non-IRA plaques;  $P=0.0022$ ). Culprit lesions were longer ( $17.5\pm 10.1$ ,  $9.8\pm 4.0$ , and  $10.3\pm 5.7$  mm, respectively;  $P<0.0001$ ), had larger EEM area ( $15.0\pm 6.0$ ,  $11.5\pm 5.7$ , and  $12.6\pm 5.6$  mm<sup>2</sup>, respectively;  $P=0.0353$ ) and P&M area ( $13.0\pm 6.0$ ,  $7.5\pm 3.7$ ,  $9.3\pm 4.3$  mm<sup>2</sup>, respectively;  $P<0.0001$ ), smaller lumens ( $2.0\pm 0.9$ ,  $4.1\pm 3.1$ , and  $3.4\pm 2.5$  mm<sup>2</sup>, respectively;  $P=0.0009$ ), and more positive remodeling (79.4%, 59.0%, and 50.8%, respectively;  $P=0.0155$ ). The frequency of plaque rupture/dissection was greater in culprit, nonculprit IRA, and non-IRA plaques in AMI patients than in a control group of chronic stable angina patients with multivessel IVUS imaging.

**Conclusions** Culprit plaques have more markers of instability (thrombus, positive remodeling, and large plaque mass); however, these markers of instability are not typically found elsewhere. This suggests that the vascular event in AMI patients is determined by local pre-event lesion morphologies.

### **Clopidogrel for Coronary Stenting Response Variability, Drug Resistance, and the Effect of Pretreatment Platelet Reactivity**

Paul A. Gurbel, MD; Kevin P. Bliden, BS; Bonnie L. Hiatt, MD; Christopher M. O'Connor, MD. *Circulation* 2003 107: 2908 – 2913

**Background** Clopidogrel is administered to prevent stent thrombosis; however, the uniformity of platelet inhibition after treatment and the influence of pretreatment reactivity on drug response have not been described.

**Methods and Results** Platelet aggregation (5 and 20  $\mu\text{mol/L}$  ADP), the activation of glycoprotein IIb/IIIa (PAC-1 antibody), and the expression of P-selectin were measured in patients undergoing elective coronary stenting ( $n=96$ ) at baseline and at 2 hours, 24 hours, 5 days, and 30 days after stenting. All patients received aspirin (325 mg). Clopidogrel (300 mg) was administered in the catheterization laboratory and followed by 75 mg daily. There was marked interindividual variability in drug response as measured by all markers that showed a normal distribution. Resistance, defined as baseline aggregation (%) minus posttreatment aggregation (%)  $\geq 10\%$  by 5  $\mu\text{mol/L}$  ADP, was present in 31% and 15% of patients at 5 and 30 days, respectively. Patients with the highest pretreatment platelet reactivity remained the most reactive at 24 hours after treatment ( $P<0.0001$ ).

**Conclusions** Interindividual variability in the platelet inhibitory response from clopidogrel occurs in patients undergoing elective coronary stenting. Patients with high pretreatment reactivity are least protected. Alternative pharmacological strategies and the association of adverse ischemic events should be investigated in these patients.

### **Frame Count Reserve**

Martin G. Stoel, MD; Felix Zijlstra, MD, PhD; Cees A. Visser, MD, PhD. *Circulation* 2003 107: 3034 - 3039

**Background** The Doppler wire-derived (relative) coronary flow velocity reserve (CVR) that is used to evaluate functional significance of a coronary stenosis is a method performed only by interventional cardiologists. An angiographic method would be useful in the diagnostic catheterization laboratory. For this purpose, we investigated the relation between TIMI frame count reserve (FCR) and CVR.

**Methods and Results** In 38 patients, (relative) FCR of left anterior descending (LAD) and left circumflex coronary artery (LCx) was calculated by using manual, synchronized contrast agent injections and compared with (relative) CVR. In addition, vessel length was measured with an intracoronary guidewire and frame count flow velocity was calculated and compared with average peak velocity. There was a strong correlation between FCR and CVR ( $r=0.62$ ,  $P<0.001$ ) and between relative FCR and relative CVR ( $r=0.84$ ,  $P<0.001$ ). The LAD was significantly longer than the LCx (mean,  $14.3\pm 1.6$  cm versus  $11.4\pm 1.8$  cm,  $P<0.001$ ), and, therefore, TIMI frame count of LAD was significantly higher than of LCx (mean basal  $32.5\pm 15.1$  versus  $23.6\pm 9.1$  and hyperemic  $12.1\pm 6.6$  versus  $8.7\pm 3.2$ , both  $P<0.02$ ). However, all flow velocity measurements and estimations of volume flow were not different for LAD compared with LCx. There were also no differences between mean FCR and CVR of LAD or LCx, of both vessels compared with each other and between mean relative FCR and relative CVR.

**Conclusion** The (relative) frame count reserve can be used to estimate (relative) coronary flow velocity reserve.

### **Randomized Comparison of Distal Protection With a Filter-Based Catheter and a Balloon Occlusion and Aspiration System During Percutaneous Intervention of Diseased Saphenous Vein Aorto-Coronary Bypass Grafts**

Gregg W. Stone, Campbell Rogers, James Hermiller, Robert Feldman, Patrick Hall, Robert Haber, A. Masud, Patrick Cambier, Ron P. Caputo, Mark Turco, Richard Kovach, Bruce Brodie, Howard C. Herrmann, Richard E. Kuntz, Jeffrey J. Popma, Steve Ramee, and David A. Cox. *Circulation* 2003 108: 548 – 553

**Background** The high rate of periprocedural complications resulting from atherothrombotic embolization after percutaneous intervention in diseased saphenous vein grafts is reduced by distal microcirculatory protection using a balloon occlusion and aspiration system. Whether filter-based catheters, which offer the inherent advantages of maintained perfusion and ease of use, are as effective for this purpose has not been established.

**Methods and Results** A total of 651 patients undergoing percutaneous intervention of 682 saphenous vein graft lesions were prospectively randomized to distal protection with the filter-based FilterWire EX versus the GuardWire balloon occlusion and aspiration system. Device success was 95.5% and 97.2% with the FilterWire EX and GuardWire, respectively ( $P=0.25$ ). Postprocedural measures of epicardial flow and angiographic complications were similar between the 2 groups, although bailout IIb/IIIa inhibitors were required slightly less frequently in the FilterWire EX group (0% versus 1.5%,  $P=0.03$ ). The primary end point, the composite incidence of death, myocardial infarction, or target vessel revascularization at 30 days, occurred in 9.9% of FilterWire EX patients and 11.6% of GuardWire patients (difference [95% CI]=1.7% [-6.4%, 3.1%];  $P$  for superiority=0.53,  $P$  for noninferiority=0.0008).

**Conclusions** Distal protection with the FilterWire EX may be safely used as an adjunct to percutaneous intervention of diseased saphenous vein grafts and, compared with distal protection with the GuardWire balloon occlusion and aspiration system, results in similar rates of major adverse cardiac events at 30 days.

### **Repeat Intracoronary Radiation for Recurrent In-Stent Restenosis in Patients Who Failed Intracoronary Radiation**

Ron Waksman, Robert Lew, Andrew E. Ajani, Augusto D. Pichard, Lowell F. Satler, Kenneth M. Kent, Rosanna Chan, R. Larry White, William O. Suddath, Ellen Pinnow, Rebecca Torguson, Christian Dilcher, Roswitha Wolfram, and Joseph Lindsay. *Circulation* 2003 108: 654 – 656

**Background** Intracoronary radiation therapy (IRT) is the only proven treatment for in-stent restenosis (ISR). It is, however, associated with a significant failure rate. The present study evaluated the outcomes of patients who underwent repeat intracoronary radiation for recurrent ISR.

**Methods and Results** Fifty-one consecutive patients who failed a previous radiation treatment, presented with angina and angiographic evidence of ISR, and were treated with percutaneous coronary intervention (PCI) and repeat radiation to the same segment were studied. Twenty-five patients were treated with gamma radiation in a dose of 15 Gy, and 26 were treated with beta radiation doses of 18.3 to 23 Gy. The mean cumulative dose for this cohort was  $39.5 \pm 11.9$  Gy (range, 29 to 75.6 Gy). The outcomes of those patients were compared with outcomes of 299 patients who also failed initial radiation but were treated with repeat conventional PCI to a previously irradiated segment without repeat radiation. At 9 months after treatment, the repeat-IRT group had lower rates of target lesion revascularization (23.5% versus 54.6%;  $P < 0.001$ ) and major adverse cardiac events, including target vessel revascularization (29.4% versus 61.3%;  $P < 0.001$ ). At 9 months, patients with repeat IRT were free of angiographic and clinical events related to the radiation therapy.

**Conclusions** Repeat gamma or beta radiation to treat failed IRT for ISR after conventional PCI is safe and effective at 9 months and should be considered as a therapeutic option for this difficult patient subset.

### **Randomized Study to Assess the Effectiveness of Slow- and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for Coronary Artery Lesions**

Antonio Colombo, Janusz Drzewiecki, Adrian Banning, Eberhard Grube, Karl Hauptmann, Sigmund Silber, Dariusz Dudek, Stephen Fort, Francois Schiele, Krysztof Zmudka, Giulio Guagliumi, and Mary E. Russell *Circulation* 2003 108: 788 – 794

**Background** Early clinical studies demonstrated the feasibility of local paclitaxel delivery in reducing restenosis after treatment of de novo coronary lesions in small patient populations.

**Methods and Results** We conducted a randomized, double-blind trial of 536 patients at 38 medical centers evaluating slow-release (SR) and moderate-release (MR) formulations of a polymer-based paclitaxel-eluting stent (TAXUS) for revascularization of single, primary lesions in native coronary arteries. Cohort I compared TAXUS-SR with control stents, and Cohort II compared TAXUS-MR with a second control group. The primary end point was 6-month percent in-stent net volume obstruction measured by intravascular ultrasound. Secondary end points were 6-month angiographic restenosis and 6- and 12-month incidence of major adverse cardiac events, a composite of cardiac death, myocardial infarction, and repeat revascularization. At 6 months, percent net volume obstruction within the stent was significantly lower for TAXUS stents (7.9% SR and 7.8% MR) than for respective controls (23.2% and 20.5%;  $P < 0.0001$  for both). This corresponded with a reduction in angiographic restenosis from 17.9% to 2.3% in the SR cohort ( $P < 0.0001$ ) and from 20.2% to 4.7% in the MR cohort ( $P = 0.0002$ ). The incidence of major adverse cardiac events at 12 months was significantly lower ( $P = 0.0192$ ) in the TAXUS-SR (10.9%) and TAXUS-MR (9.9%) groups than in controls (22.0% and 21.4%, respectively), predominantly because of a significant reduction in repeat revascularization of the target lesion in TAXUS-treated patients.

**Conclusions** Compared with a bare metal stent, paclitaxel-eluting stents reduced in-stent neointimal formation and restenosis and improved 12-month clinical outcome of patients with single de novo coronary lesions.

**Lack of Adverse Clopidogrel–Atorvastatin Clinical Interaction From Secondary Analysis of a Randomized, Placebo-Controlled Clopidogrel Trial**

Jacqueline Saw, Steven R. Steinhubl, Peter B. Berger, Dean J. Kereiakes, Victor L. Serebruany, Danielle Brennan, and Eric J. Topol *Circulation* 2003 108: 921 – 924

**Background** Statins primarily metabolized by cytochrome P450 3A4 (CYP3A4) reportedly reduce clopidogrel's metabolism to active metabolite, thus attenuating its inhibition of platelet aggregation *ex vivo*. However, the clinical impact of this interaction has not been evaluated.

**Methods and Results** Clopidogrel for the Reduction of Events During Observation (CREDO) was a double-blind, placebo-controlled, randomized trial comparing pretreatment (300 mg) and 1-year (75 mg/d) clopidogrel therapy (clopidogrel) with no pretreatment and 1-month clopidogrel therapy (75 mg/d) (control) after a planned percutaneous coronary intervention. All patients received aspirin. The 1-year primary end point was a composite of death, myocardial infarction, and stroke. We performed a post hoc analysis to evaluate the clinical efficacy of concomitant clopidogrel and statin administration, categorizing baseline statin use to those predominantly CYP3A4-metabolized (atorvastatin, lovastatin, simvastatin, and cerivastatin) (CYP3A4-MET) or others (pravastatin and fluvastatin) (non-CYP3A4-MET). Of the 2116 patients enrolled, 1001 received a CYP3A4-MET and 158 a non-CYP3A4-MET statin. For the overall study population, the primary end point was significantly reduced in the clopidogrel group (8.5% versus 11.5%, RRR 26.9%;  $P=0.025$ ). This clopidogrel benefit was similar with statin use, irrespective of treatment with a CYP3A4-MET (7.6% clopidogrel, 11.8% control, RRR 36.4%, 95% CI 3.9 to 57.9;  $P=0.03$ ) or non-CYP3A4-MET statin (5.4% clopidogrel, 13.6% control, RRR 60.6%, 95% CI -23.9 to 87.4;  $P=0.11$ ). Patients given atorvastatin or pravastatin had similar 1-year event rates. Additionally, concomitant therapy with statins had no impact on major or minor bleeding rates.

**Conclusions** Although *ex vivo* testing has suggested a potential negative interaction when coadministering a CYP3A4-metabolized statin with clopidogrel, this was not clinically observed statistically in a post hoc analysis of a placebo-controlled study.

**Safety of an Aspirin-Alone Regimen After Intracoronary Stenting With a Heparin-Coated Stent: Final Results of the HOPE (HEPACOAT and an Antithrombotic Regimen of Aspirin Alone) Study**

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**Background** Stent thrombosis is an infrequent complication of intracoronary stenting that often has devastating clinical consequences. This study assesses the additional benefit of heparin coating with the BX VELOCITY Balloon-Expandable Stent with HEPACOAT, Carmeda end-point attached heparin (HEPACOAT) in patients with *de novo* or restenotic native coronary artery lesions treated with aspirin monotherapy after optimal stenting.

**Methods and Results** This was a multicenter, prospective, nonrandomized, pilot study. Two hundred patients (69% men; mean age,  $64.1 \pm 11.2$  years) meeting the eligibility criteria were treated with the HEPACOAT stent and aspirin alone after stenting. Any other antiplatelet or anticoagulation therapy was not permitted. Procedural success was achieved in all patients. There were 3 postprocedural non-Q-wave myocardial infarctions. The primary end point of stent thrombosis at 30 days occurred in 2 of 200 patients (1%): in one after blunt chest trauma and in the other in the setting of essential thrombocytosis. Major adverse cardiac events (death, myocardial infarction, target lesion revascularization, and coronary artery bypass grafting) were observed at 30 days in 5 of 200 (2.5%) patients.

**Conclusions** The BX VELOCITY stent with HEPACOAT and aspirin alone after the procedure was safe in select patients with *de novo* or restenotic lesions in native coronary arteries. Heparin coating provides additional protection against stent thrombosis.