ACC 2003

Sustained Clinical Evidence of CYPHER™ Stent

Significance of Late Loss TLR

From Vulnerable Plaque to Peripheral Markers of Vulnerability
Welcome!

Long-term data confirm sustained benefits of CYPHER™ Stent

Following a thorough review of the overwhelming evidence generated by the most comprehensive clinical trial program ever undertaken for a drug-eluting stent there can be no doubt that the FDA approval of the CYPHER Sirolimus-eluting stent represented another major milestone in the history of interventional cardiology.

Long-term findings from three important clinical trials document the continued, unprecedented performance of the CYPHER Sirolimus-eluting Coronary Stent in patients with de novo coronary artery blockages. The data, presented at the American College of Cardiology, show a significant and sustained benefit in reducing the need for reintervention in the incidence of restenosis in patients treated with the CYPHER Sirolimus-eluting stent versus conventional bare metal stents.

In this issue of Cardio Update there is a summary of the major findings presented at ACC together with case reports on ‘real world’ patients. Major research presentations on the CYPHER Stent at ACC included the following: 1-year follow-up for patients enrolled in SIRIUS, the large-scale pivotal U.S. clinical trial; 2-year follow-up for patients enrolled in RAVEL, the large-scale pivotal groundbreaking clinical trial in Europe and Latin America that was the basis for approval outside the U.S.; 3-year follow-up for patients enrolled in the first-in-man pilot (feasibility) study in Sao Paolo, Brazil; the first presentation of the 8 & 9 month follow-up results from C & E – SIRIUS and impressive cost effective findings from SIRIUS.

These findings, together with experience of treating over 7,000 patients in clinical trials with the CYPHER Stent, represent the world’s largest body of data on the performance of a drug-eluting stent in a wide range of patients, including those considered to be ‘high risk’ (e.g. diabetics) and in challenging lesions such as small vessels, long lesions and multi-vessel stenting.

In addition, it is important to remember that sustained evidence of minimal late lumen loss—which translates to no or minimal restenosis and significant reduction in the need for retreatment – has been documented across all patient subgroups.

The findings are remarkably consistent - despite the wide variation in extent and severity of disease from patient to patient and study to study and have been key factors as we work to secure reimbursement for the CYPHER Stent with the various health authorities and private insurance companies across Europe.

I look forward to meeting many of you at the Cordis booth at EuroPCR in May and at other major congresses throughout the year.

Jean Luc Lemercier
Vice President Cardiology, Europe
Cordis, a Johnson & Johnson company

ACC 2003 provides additional clinical evidence of sustained effect of CYPHER™ Stent

A number of important clinical trials were presented this year in the area of interventional cardiology. Although drug-eluting stents remained the focus of many abstract presentations, the burgeoning evidence coming out of the CYPHER Sirolimus-eluting stent clinical trial program continued to dominate proceedings at the 52nd Scientific Sessions of the American College of Cardiology in Chicago. The main findings are summarised below.

SIRIUS 12-month clinical follow-up

Following presentation of 9-month data at TCT 2002, the pivotal US trial SIRIUS has now reported 12-month clinical follow-up at this year’s ACC. This multi-centre, randomised, controlled, double-blind study involving 1058 ‘real world’ patients demonstrated exceptional efficacy and safety across all angiographic, IVUS and clinical endpoints at 8-9 months. The 12-month analysis seeks to verify the durability of these results in this challenging population.
The remarkable 75% reduction in TLR seen at 9 months was sustained at this level at 12 months. Only 4.9% of CYPHER™ Stent patients required TLR up to one year post-implantation (0.75% TLR in-stent). Compared to control, this would confer that 150 out of every 1000 patients may avoid repeat intervention. Even in high-risk patients (diabetics, small vessels <2.5mm, long lesions >15mm) similar reductions in TLR rates were observed.

Previously impressive reductions in MACE reported at 9 months were also maintained at 12 months, with a highly significant 62% reduction achieved at both time points. At one year, 91.7% of CYPHER Stent patients were MACE free, compared to 77.7% with the control group (p<0.001). Of note, there was an absence of any incidences of stent thrombosis between 9 and 12 months in the CYPHER Stent group; the one-year rate remaining very low and the same as that reported at 9 months.

To conclude, the CYPHER Sirolimus-eluting Stent remains robust at one-year follow-up, with outstanding efficacy and safety demonstrated in all the high-risk subgroups of this challenging population.
What’s new at ACC

E-SIRIUS 8-month QCA and 9-month clinical results

E-SIRIUS, the European, multi-centre, randomised, controlled, double-blind study of the CYPHER Stent in de novo coronary lesions, provides insights into the treatment of an even more challenging patient population than SIRIUS. Patients had a higher clinical risk profile, with significantly more prior MI (42.1% vs. 30.5%, p<0.001) and current smokers (33.2% vs. 20.8%, p<0.001). Furthermore, vessels were smaller (RVD 2.55mm vs. 2.80mm, p<0.001) and lesions were longer (15.0mm vs. 14.4mm, p<0.001). Patients also received multiple and/or overlapping stents more often (48.0% vs. 35.1%, p<0.001), GP IIb/IIIa inhibitors less often (16% vs. 60%), and combined anti-platelet therapy for a shorter period of time (2 months vs. 3 months).

In addition, this study is the first to include direct stenting of the CYPHER Stent - employed in 25.7% of patients. The 8-month QCA results demonstrated the exemplary efficacy of the CYPHER Stent in this complex patient group. The primary endpoint of in-stent MLD at 8 months revealed a dramatic 81% reduction in in-stent late loss compared to control, with a similar effect seen in lesion. The minimal in-stent late loss (0.20mm) translated into a remarkably low in-stent restenosis rate (3.9%) that represented a 91% reduction vs. control (42.3%). Again, similar results were seen in-lesion. Peri-stent analysis also showed a significant treatment effect in both the proximal and distal margins.

Exceptional 9-month clinical results were obtained to further reinforce the excellent efficacy and safety profile of the CYPHER Stent in this complex patient group. TLR was reduced by a remarkable 81%, being required in only 4% of CYPHER patients. This means 170 out of every 1000 patients like these may avoid repeat intervention.

Subsequently there was a considerable and significant 65% reduction in the rate of MACE. The thrombosis rate was also very low, being of the same order of magnitude to SIRIUS, despite higher risk patients and less use of GP IIb/IIIa inhibitors and anti-platelet treatments.

In summary, the CYPHER Sirolimus eluting Stent has confirmed its previously demonstrated striking efficacy and safety in even more complex patients and lesions in E-SIRIUS.
What’s new at ACC

C-SIRIUS 8-month QCA and 9-month clinical results

Results for C-SIRIUS, the Canadian multicentre, randomised, controlled, double-blind study of the CYPHER Stent in de novo coronary lesions, were also presented at this year’s ACC. As with E-SIRIUS, this study involved more complex patient and lesion types than SIRIUS. Particularly challenging outcome predictors included 24.0% diabetics, post-MLD of 2.53mm, and a stented length of 26.1mm.

The 8-month angiographic results were once again remarkable. A highly significant difference in 8-month in-stent MLD (primary endpoint) resulted in an exceptional reduction in in-stent late loss of 91% (0.09mm for the CYPHER Stent arm). There was also a significant reduction in late loss at the proximal margin. Particularly noteworthy was the 100% reduction in in-stent restenosis rate (0% vs. 41.9% for control), with in-lesion results revealing only one patient (2.3%) with binary restenosis in the CYPHER Stent group, compared to 23 (53.5%) in the control group.

At 9 months, clinical assessment demonstrated a very low clinically driven TLR rate (4.0%), representing a significant 78% reduction versus control (18%, p=0.027). This equates to 140 patients out of every 1000 avoiding the need for repeat intervention during this period. Likewise, MACE rates were also very low in the CYPHER Stent arm (4.0%), being significantly less than control (18%, p=0.029). The very low thrombosis rate (2%, n=1) was the same for both arms.

Overall, this study adds further support to the belief that the highly impressive results of both RAVEL and SIRIUS may now be extended to more complex patients with longer lesions and smaller vessel disease. In fact, E-SIRIUS and C-SIRIUS showed greater reductions in late loss, restenosis, TLR and MACE than SIRIUS, despite the more challenging patient populations. This was particularly noticeable with the in-lesion angiographic results. This suggests a correlation to the increase in stent: lesion length ratio (SIRIUS=1.5; E-SIRIUS=1.7; CSIRIUS = 1.8), where greater coverage of areas that may be exposed to balloon trauma would naturally reduce neointimal hyperplasia in the segment.

C-SIRIUS - Study Design

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RAVEL 24-month clinical follow-up
RAVEL was the first multicentre, randomised, controlled, double-blind study of the CYPHER Stent, conducted across 19 centres in Europe, and involving 238 patients with de novo coronary lesions.

FIM 36-month clinical follow-up
The First In Man (FIM) pilot study of the safety and feasibility of the CYPHER Stent, the first ever clinical study of a drug-eluting stent, has just reported 3-year clinical follow-up from one of the two centres involved (Sao Paulo, n=30). The results were basically unchanged from the 2-year follow-up data. TLR remained at 6.7% (n=2/30), while event-free survival was maintained at 90.1% (27/30). No sub-acute thromboses have been reported, and only one late thrombosis has occurred to date.

These impressive findings, along with the latest 2-year RAVEL data, point to a long lasting effect of the CYPHER Stent in maintaining vessel patency, with an absence of any catch-up phenomena or significant adverse events. The implications of this are highly significant, with the prospect of greatly reduced repeat procedures meaning less patient morbidity, and more patients receiving treatment per interventional cardiologist per year.
In the Interventional Cardiology Department of the Thoraxcentre, Rotterdam, headed by Professor Patrick Serruys, CYPHER Sirolimus-eluting stents have been routinely used since April 2002 as the device of choice for all percutaneous interventions without any clinical or angiographic exclusion criteria – representing the ‘real world’ of clinical practice.

These patients are included in the Rapamycin Eluting Stent Evaluated at Rotterdam Hospital (RESEARCH) Registry from which cardiologists from the Thoraxcentre revealed impressive results across an extensive range of clinical conditions and lesion morphologies in patients treated in daily clinical practice, ranging from sub-acute stent thromboses, acute myocardial infarction, bifurcation lesions and in-stent restenosis (American College of Cardiology 52nd Annual Scientific Session, Chicago, USA).

Sub-acute stent thrombosis
Dr Evelyn Regar reported striking results in respect of sub-acute stent thrombosis rates. Among the first 510 consecutive patients treated with sirolimus-eluting stents, only 2 (0.4%) presented thrombotic stent occlusion in the first 3 months after the procedure.

Acute Myocardial Infarction Cohort
Dr Chi-Hang Lee, reporting results on the safety and efficacy of sirolimus-eluting stents in patients with acute myocardial infarction, (AMI), said there was “zero” incidence of repeat revascularisation during the first 6 months.

Bifurcation Lesion
Dr Kengo Tanabe presented equally impressive results from the bifurcation patient cohort with respect to target lesion revascularisation (TLR) of 9.8% and Late Loss numbers of 0.31mm in the side branch and 0.06mm in the main branch. Noting that these results match the earlier results from the Bifurcation feasibility study of Dr Antonio Colombo, Professor Serruys said that he is very encouraged by the outcomes in this challenging lesion subset.

Overall, 801 patients were submitted to stenting since from April to October 2002 (6 months enrolment). From these, CYPHER stents were used in 631 patients, (79%), with an average of 2.2 CYPHER Stents implanted per patient. In the remaining 170 patients, bare stents were used due to unavailability of an appropriate size or length of sirolimus-eluting stents in most of the cases.

The objective of the RESEARCH Registry is to test the limits of the new CYPHER Stent in the real-world setting of daily clinical practice. Although it is too early to make any formal conclusions based on the results obtained in multi-vessel disease, we believe that ARTS II will fulfil our expectation of matching the clinical outcomes achieved by surgery. Our preliminary findings indicate that the CYPHER Stent delivers exceptional clinical outcomes even in the most difficult-to-treat patients, including those with in-stent restenosis and acute myocardial infarction.
This is the case of a 66 year old female who underwent elective CABG x 3 in 2001 for symptomatic three vessel coronary artery disease. She represented in Sept. 2002, only 8 months after her coronary surgery with recurrent angina.

Her diagnostic angiogram at that time revealed native 3 vessel disease with occlusion of the native LAD and RCA. There was a 50% stenosis in the distal left main coronary artery extending into the ostium of the left circumflex. The LIMA to the LAD was patent with good distal run off. The saphenous vein graft (SVG) to the obtuse marginal was occluded and there was a tight stenosis in the proximal body of the saphenous vein graft to the distal right coronary artery. The patient subsequently underwent coronary angioplasty with implantation of a 3.5x18mm Medtronic S7 stent to the lesion in the SVG. The patient remained well post procedure for only 2 months and returned complaining again of recurrent angina. We proceeded to perform angiography again.

**Angiographic Findings:**

The severity of the stenosis in the left main coronary artery had progressed now to > 70%. The native LAD and RCA were occluded. The LIMA to the LAD remained widely patent. There was diffuse proliferative in-stent restenosis in the SVG to the RCA with poor distal run off (Fig. 1A and 1B). Left ventricular function remained normal (LVEF = 62%).

**Procedure:**

It was decided to treat this patient in a staged fashion firstly treating the left main stenosis and then treating the SVG in-stent restenosis during a second procedure. The lesion in the native left main coronary artery was successfully pre-dilated and a 3.5x18 mm Medtronic S7 stent was deployed from the left main into the left circumflex. The portion of the stent in the left main was post dilated with a short 4.0x10mm balloon. Following an uneventful recovery after left main stenting, the patient consented to be randomised in a trial assessing a new distal protection device (DPD) in the treatment of SVG stenosis. The DPD crossed the in-stent restenosis without difficulty and the lesion was pre-dilated with a 3.0 x 20 mm Medtronic Stormer balloon after successful deployment of the DPD. We elected to use a CYPHER Stent because of (i) early restenosis (< 2 months) and (ii) the aggressive pattern of in-stent restenosis. A 3.0 x 33 mm Cordis CYPHER Stent was then deployed across the previous stent with approximately 7mm of the CYPHER Stent overlapping both proximally and distally to the original stent. The CYPHER Stent was post dilated with a 3.5 x 20mm balloon located fully within the margins of the CYPHER Stent. The final angiographic result showed a well deployed CYPHER Stent in the SVG with normal distal flow (Fig. 2A and 2B). The DPD was retrieved and there was no post procedural complications nor rise in cardiac enzymes.

**Outcome:**

The patient has remained well for six months after this procedure. A follow up angiogram revealed no evidence of angiographic restenosis in either the CYPHER Stent in the SVG to the RCA (Fig. 3A and 3B) or in the bare metal stent in the stent in the left main/lef circumflex.
Figure 1 A&B. Diffuse proliferative in-stent restenosis in a saphenous vein graft to the right coronary artery with poor distal run off.

Figure 2 A&B. Final images following implantation of a 3.0 x 33mm CYPHER Stent to cover the in-stent restenosis. Good distal flow with opacification of the distal right coronary artery.

Figure 3 A&B. Follow up angiogram after 6 months demonstrating a widely patent CYPHER Stent in the saphenous vein graft with no angiographic evidence of restenosis.
Significance of Late Loss and Target Lesion Revascularisation
In Interpreting Drug-Eluting Stent Clinical Trial Results

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The field of drug-eluting stents is rapidly evolving. The lack of a standard format to report study findings, however, limits comparisons across clinical trials. This article will review the concepts of angiographic late loss and target lesion revascularization and their value in evaluating the anti-restenotic effects of drug-eluting stents.

Angiographically detected lesions of 50% or greater diameter stenosis (DS) at follow-up have been historically considered as representing “restenosis”. The classical binary definition based on percentage diameter stenosis does not accurately depict the degree of deterioration of the vessel post angioplasty and does not convey a measure of the vessel response to injury. The use of the term percentage diameter stenosis itself, carries with it the assumption of normal-appearing reference segments, which is known from IVUS studies to be an erroneous assumption. Furthermore, the binary definition of restenosis assumes that a patient with 51%DS lesion and a patient with 49%DS have different intimal hyperplasia responses and clinical outcomes. A disparity between binary angiographic restenosis and clinical outcomes has been documented in a recent retrospective analysis of multiple stent trials. In this study, only 45% of the patients with binary angiographic restenosis required repeat revascularization. Nearly half of the patients that met binary criteria for angiographic restenosis had follow-up lesions with < 60%DS. Did these patients have more neointimal hyperplasia than those with 40-50%DS?

A possible way to answer this question would be to compare angiographic late loss between the 2 groups. The use of continuous angiographic criteria of lumen deterioration, namely late loss, more closely reflects the magnitude of the reactive intimal hyperplasia after stenting. Late loss is calculated as minimal lumen diameter post-procedure (MLD) minus MLD.
Late Loss

Late loss represents an angiographic surrogate for neointimal proliferation because stents eliminate the elastic recoil and remodelling components of restenosis.

In the era of mechanical prevention of restenosis, there were essentially no differences in angiographic late loss between devices (average of 1.0mm late loss). Angiographic outcomes were mainly determined by the immediate luminal gains, the “bigger is better” adage. This strategy has been proven ineffective to eliminate restenosis.

Recently, the anti-restenosis paradigm has undergone a tremendous shift. Anti-proliferative strategies targeting the cell cycle have finally been able to inhibit neointimal proliferation and consequently decrease angiographic late loss. The significance of the late loss parameter for drug-eluting stent trials is remarkable, as it represents the only angiographic criteria to determine whether the agent under investigation had restraining or inhibitory effect on neointimal proliferation. In other words, late loss is a major determinant of drug-eluting stent effectiveness. In the RAVEL trial, a zero late loss observed at 6-month angiographic follow-up was associated with the absence of repeat revascularization after implantation of sirolimus-eluting stents.

In clinical trials testing the effect of a given therapy on restenosis, objective angiographic criteria have been preferred. As per above discussion, late loss represents the best angiographic determinant of device effectiveness. That being said, clinical outcomes, particularly target lesion revascularization (TLR), must be regarded as the true measure of success for anti-restenosis therapies. The incidence of target lesion revascularization may closer resemble our clinical practice, in which repeat coronary angiography is not performed routinely. Target lesion revascularization (TLR) is defined as any repeat revascularization procedure (percutaneous or surgical) of the original target lesion site, which includes the stented plus edge (typically 5 mm proximal and distal to the stent) segments. Thus, TLR is perceived to be the best clinical surrogate for angiographic restenosis. TLR is typically driven by clinical evidence of ischemic symptoms or positive stress-induced ischemia test, because asymptomatic patients with non-functional angiographic stenosis experience a benign course without re-intervention. While other clinical end-points, such as incidence of mortality, myocardial infarction, or any type of repeat revascularization are essential to determine safety of a new treatment strategy and the ultimate outcome for the patient, they do not contribute much to the assessment of clinical restenosis.

Pitfalls:

Any careful interpretation of restenosis studies must consider the time point at which the data are reported. There is approximately a 70% increase in target lesion revascularization rates between 6- and 12-month follow-up. The delay between the biological process and symptomatic presentation of restenosis may explain these findings. Further, additional reductions in lumen dimensions are observed beyond the six-month follow-up window. In the SCRIPPS trial, additional 0.37mm of late loss was observed at 3-year follow-up compared to 6 months in the radiation arm. There was a 34% increase in TLR rates during the same period. So, comparison between clinical restenosis studies with different...
time points is inappropriate. Drug-eluting stent studies have reported angiographic and clinical data at different time points (4, 6, 8, 9 or 12 months)\textsuperscript{7}-\textsuperscript{11}, which greatly limits any valid comparisons across current trials.

The “oculo-stenotic reflex” is another important factor that should be considered when interpreting the results of drug-eluting stent studies\textsuperscript{8}. This term derives from the observation that routine angiographic follow-up leads to a higher rate of repeat revascularization, most likely because of unnecessary interventions triggered by the visual appearance of the coronary obstruction. As a result, trials with routine angiographic follow-up tend to have higher TLR rates and should not be compared with clinical follow-up studies\textsuperscript{3,15}.

Finally, quantitative coronary angiography (QCA) results are highly dependable on the site of the measurements\textsuperscript{16}. The QCA methodology of drug-eluting stents should always include the stented and edge segments, commonly defined as the stent plus at least 5 mm proximal and distal to the stent borders. Data should be reported for both in-stent and in-lesion (stent plus margins) segments. This recommendation derives from the observation of a deleterious effect of brachytherapy and some pharmacological agents on the segments adjacent to the stent borders, so called “edge effect”\textsuperscript{17}.

In conclusion, both late loss and TLR are key indicators of drug-eluting stent effectiveness to prevent restenosis. However, one should take into account the QCA methodology, whether routine angiographic follow-up was performed, and the time of follow-up.

References:
1. Roubin GS, King SB, 3rd, Douglas JS, Jr. Restenosis after percutaneous transluminal coronary angioplasty: the Emory University Hospital experience. Am J Cardiol. 1987;60:39B-45B.
Sirolimus-eluting stent Implanted in Human Coronary Artery for 16 Months: Pathological Findings

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Compared to balloon angioplasty, coronary stenting provides a favourable outcome with an angiographic restenosis rate of 10 to 20% in short lesions and large vessels. However, in-stent restenosis occurs in over 30-60% of patients with diabetes, diffuse lesions, or lesions that take place in small coronary vessels and remains a significant clinical problem.

In light of the expanded use of coronary stents in everyday practice, data on the pathology of stents deployed in human coronary arteries is lacking. When compared to animal data, the pathology of human coronary stenting may provide valuable insights into the stent-vessel wall interaction and guide approaches to therapies to help prevent or treat in-stent restenosis in humans. In our recent paper (Circulation 2003; 107:1340-1341) we discuss the pathological findings on autopsy of a patient that died from non-cardiac complications who received a sirolimus-eluting stent 16 months earlier.

In brief, a 71-year-old woman who was enrolled in the RAVEL trial received a single sirolimus-eluting stent to treat a proximal left anterior descending (LAD) coronary artery that was estimated to have 80% stenosis. Angiographic and intravascular ultrasound at 6 months demonstrated zero percent restenosis with no evidence of neointimal hyperplasia. Sixteen months later, the patient presented with new onset chest pain; subtotal occlusion of the left obtuse marginal was revealed upon angiography. Angiography of the previous stented LAD containing the sirolimus-eluting stent continued to demonstrate zero restenosis. The obtuse lesion was successfully stented with a bare-metal stent; however, the patient experienced an ischemic stroke 24 hours post procedure and expired few days later.

The post mortem pathology of the sirolimus-eluting stent implanted 16 month before uncovered the following data:

- The 16 month old LAD sirolimus-eluting stent was widely patent. Stent struts were well opposed to the vessel wall with a thin neointima consisting of smooth muscle cells and collagen-rich matrix.
- The stent surface appeared well-healed. Scanning electron microscopy of the one half of the LAD stent cut longitudinally showed >80% endothelialization (visual estimation). There were focal, small areas of loosely formed endothelial cell junctions and occasional rare platelet aggregate close to side branch ostium.
- The polymer on struts was recognized but was not associated with inflammation.
- Fibrin deposits were occasionally identified near stent struts, especially within the necrotic core, and were minimal within the neointima.

From this case, the autopsy revealed the thin neointimal healing of this sirolimus-eluting BX stent 16 month after placement, was nearly
complete, consisting of smooth muscle cells in a proteoglycan and type III collagen matrix. Stent polymer covering was not associated with inflammatory reaction. Only minimal inflammation and persistent fibrin deposition around occasional struts were observed despite lipid core penetration by the stent struts. SEM showed near complete endothelialization (> 80% covered by a paved shape endothelial lining).

The present case study is the first to report pathological findings from a sirolimus-eluting stent placed in a native human coronary artery from the RAVEL trial. Although this is a single-case, data from this patient demonstrates the histological success associated with the implantation of a sirolimus-eluting stent. When possible, further human pathological findings are warranted to preserve the results demonstrated in this.
Since inflammation is seen as a crucial step governing susceptibility to disruption\textsuperscript{5-8}, investigators have focused on whether plasma levels of inflammatory markers could be a useful tool to identify these patients\textsuperscript{9}. Several markers involved in inflammatory process have been considered: inflammatory cells, membrane surface proteins, cytokines, metalloproteinases and acute phase proteins. We briefly review some of the recently described peripheral markers.

**CRP**

C-reactive protein (CRP) is an acute phase protein mainly produced in the liver in response to interleukin-6 (IL-6). Several studies confirm CRP as an independent risk factor for coronary, cerebral and peripheral artery disease\textsuperscript{10,11} and CRP appears to be weakly associated with atherosclerotic burden, making it a more specific predictor of plaque vulnerability rather than the extent of atherosclerosis. CRP can activate complement, induce VCAM, ICAM and MCP-1 in endothelial cells, stimulate monocytes/macrophages to synthesize IL-6, IL-1\beta and TNF-\alpha, and mediate LDL uptake by macrophages\textsuperscript{12}.

**Soluble Adhesion Molecule**

Considering their central role in the recruitment of inflammatory cells to the site of atheroma development, cell adhesion molecules (CAMs) represented by the immunoglobuline superfamily, selectins, and integrins are promising candidates to reflect underlying vascular inflammation. Intercellular cell adhesion molecule-1 and 2 (ICAM-1 and -2) and vascular cell adhesion molecule-1 (VCAM-1) are expressed by endothelial cells, leucocytes, platelets and smooth muscle cells\textsuperscript{13}. Pro-inflammatory cytokines such as IL-1, IL-4, IL-8, INF-\gamma and TNF-\alpha induce VCAM-expression\textsuperscript{14,15}. Elevated serum levels of the soluble form of VCAM-1 receptor (sVCAM-1) have been associated with the extent of coronary atherosclerosis in peripheral vascular disease\textsuperscript{16}.
and elevated levels of soluble ICAM-1 (s-ICAM-1) have been found to be inversely proportional to HDL levels as well as associated with an increased risk of acute myocardial infarction in apparently healthy men\(^7\). P-Selectin is expressed on plaque surface in the setting of unstable angina compared to stable angina\(^8\). Soluble P-Selectin may predict cardiac risk in healthy women, as shown in the Women's Health Study\(^9\). CD40-ligand (CD40L), a transmembrane protein structurally related to TNF, was originally identified on activated CD4\(^+\) T-cells. Both membrane-bound and soluble forms of this ligand may interact with CD40, which is constitutively expressed on macrophages, endothelial cells, and vascular smooth muscle cells, resulting in various immune and inflammatory responses. CD40L has also been recently found on activated platelets, which induce endothelial cells to secrete chemokines and to express adhesion molecules, for the recruitment of inflammatory cells causing endothelial cell damage. Aukrust and associates\(^10\) showed that levels of CD40 and CD40L were enhanced in patients with unstable angina, suggesting that CD40L-CD40 interaction may play a pathogenic role in both the triggering and the propagation of acute coronary syndromes. In support of this hypothesis, both CD40 and CD40L are abundantly expressed in the vulnerable shoulder regions of atherosclerotic plaques and elevated levels of CD40L among apparently healthy women\(^11\) are associated with an increased risk of MI, stroke or cardiovascular death.

**Inflammatory Cytokines**

Inflammatory cytokines known to mediate the amplification of pro-inflammatory signals within the atherosclerotic plaque (IL-1, IL-6, TNF-\(\alpha\), MCP-1) have also been investigated as markers of cardiovascular risk. Interleukin-6 (IL-6) is prominent in the early stages of focal inflammation; it is one of the main responsible cytokines for systemic activation in inflammatory process and the principal initiator of hepatocytes CRP expression. In The Physicians’ Health Study\(^12\) high IL-6 levels were detected in healthy men destined for MI and MI was proportionally related to IL-6 plasma levels. Serum IL-6 levels amongst patients presenting with ACS are a strong independent predictor of increased mortality and appear to have utility in terms of directing subsequent care; specifically amongst those with elevated IL-6 levels, randomization to an early invasive strategy led to a dramatic 65% relative reduction in mortality at 1 year. In contrast, amongst those without elevated IL-6 levels, randomization to an early invasive strategy did not confer any benefit over a conservative strategy\(^13\).

TNF-\(\alpha\) is a proinflammatory cytokine; its serum level correlates with the burden of atherosclerosis\(^14\). TNF-\(\alpha\) upregulation appears to mediate and amplify a multitude of interactions resulting in progressive inflammation, plaque destabilization, and prothrombotic tendencies\(^15\). Finally, TNF-\(\alpha\) increases following MI and serum elevations after MI in the stable phase are linked to an increased risk of coronary events\(^16\).

Monocyte Chemoattractant Protein (MCP-)1 is a chemokine responsible for recruitment of monocytes to sites of inflammation. It is highly expressed in the macrophage-rich area of the atherosclerotic lesions in human and in animal models. Elevated levels of MCP-1 have been found in patients with myocardial infarction and heart failure, as well as myocardial reperfusion. Among patients with ACS, elevated baseline level of MCP-1 were associated with an increased risk of MI, independent of baseline variables\(^17\).

**Metalloproteinases**

Matrix metalloproteinases (MMPs) are a set of enzymes that digest extracellular matrix. Inflammatory mediators in atheroma augment MMP expression in mononuclear phagocytes, endothelial and smooth muscle cells. MMPs have a key role in vascular and plaque remodelling, by degrading matrix and inducing plaque instability by weakening the fibrous cap. MMP activity, especially in vulnerable plaque, may be greater in areas with high oxidant levels; and thin caps from human aorta and carotid plaques may have increased MMP-1 and MMP-2.

Pregnancy Associated Plasma Protein (PAPP-A) belongs to the MMP family, first identified in serum of pregnant women and recently detected in macrophages and smooth muscle cells of vulnerable coronary plaques, while little to no expression is found in stable plaques. Circulating PAPP-A levels are elevated in ACS, however no correlation is found with atherosclerotic burden\(^18\). Recently, PAPP-A expression was also found to be markedly elevated in unstable carotid atherosclerotic plaques\(^19\).

**Lymphocytes And Macrophages**

Vulnerable plaque detection using responsible inflammatory cells in peripheral blood may also be possible. Attention has been focused on T-lymphocytes with emerging data indicating a monoclonal activation of inflammatory T-cells in unstable angina. CD4\((+)-CD28(null)\)

T-lymphocyte clones are indeed detected both in unstable plaque and in peripheral blood, thus suggesting that unstable angina may be related to a distinct T-cell population, with enhanced interferon-\(\gamma\) production\(^20\).
Conclusions

Vulnerable plaque and the detection thereof is currently a major problem that deserves our greatest attention. Identifying people at increased risk of having a major adverse ischemic event could have a significant impact on the socioeconomic burden. In an attempt to identify the ‘at risk’ patient different non-invasive and invasive techniques are being developed and their potential combination hold promise for the future characterization of vulnerable plaques. However, these tests carry an inherent cost problem, as they are still very expensive. In addition, the prevalence of high-risk subjects in the general population is low, amplifying diagnostic problems for vulnerable plaque.

Finding a panel of biochemical markers with high sensitivity and specificity will allow the application of these techniques at a relatively low cost and at large scale with the potential to identify high-risk patients before the development of acute coronary or cerebrovascular events.

References

ATW Marker Wire™

Determination of lesion length: a basic need when using a drug-eluting stent

Joachim Schofer, Michael Schlüter, Thilo Tübler.
Centre for Cardiology and Vascular Intervention, Hamburg, Germany.

The general efficacy of the CYPHER™ sirolimus-eluting stent in the suppression of coronary in-stent restenosis has been convincingly demonstrated in randomized clinical trials such as RAVEL and SIRIUS. However, to get optimum clinical and angiographic outcomes in every patient, it appears mandatory that the entire native coronary artery lesion should be covered with such a stent, that is, from normal to normal vessel segment.

A basic requirement to ensure complete lesion coverage by the stent(s) would be to know the length of the lesion as precisely as possible. This is more readily said than done, considering the foreshortening errors inherent in coronary angiograms. The ATW Marker Wire with its 4 distal platinum markers placed at 10-mm intervals may aid in the exact determination of coronary artery lesion lengths.

Case report

A 64-year old male patient with hypertension and known 2-vessel coronary artery disease (PTCA of left anterior descending coronary artery in 1993 and stenting of the proximal left circumflex coronary artery in 2000) presented at our institution with stable angina (CCS II) and exercise-induced myocardial perfusion deficits in the inferolateral to lateral region of the left ventricle (Tc-99m SPECT imaging). Coronary
angiography revealed a diffuse 90% de-novo stenosis in the proximal-to-middle segment of the first marginal branch of the left circumflex coronary artery (Figure 1). Using the 6F guide catheter as a reference, the length of the lesion was estimated at 12 mm.

However, when advancing the ATW Marker Wire across the lesion, foreshortening of the targeted artery segment – as indicated by the different distances between the wire markers on the angiogram – became apparent (Figure 2). Using the 4 markers as a reference, the lesion is now determined to be 15 mm in length. This corresponds to a 25% underestimation of the true lesion length without the marker wire.

The lesion was subsequently covered with a 2.50/18-mm CYPHER™ stent, using the marker wire to facilitate stent positioning (Figure 3).

Discussion

In the recent presentation (by Dr. J. Moses at TCT 2002) of the angiographic and clinical end points of the SIRIUS trial, binary restenosis at 8 months was reported to be 3.2% within the stent margins, yet 5.8% in the proximal 5-mm peri-stent region. This unexpected phenomenon of increased restenosis at the proximal stent end was primarily responsible for the in-segment restenosis rate (which included the 5-mm vessel segments adjacent to the stent) in SIRIUS of 8.9%. Apparently, the antiproliferative effect of sirolimus on neointimal growth was not as spectacularly manifest at the proximal stent margin as within the stent. The most probable explanation is that the lesion or, rather, the vessel segment injured during predilatation was not always adequately covered with the stent(s). The reasons may have been underestimation of the native lesion length, use of a predilatation balloon longer than the stented segment length, or postdilatation outside of the implanted stent(s). With respect to the determination of the exact native length as well the length of vessel injury during balloon predilatation, the Cordis ATW Marker Wire may turn out to be highly useful and aid in the optimal implantation of drug-eluting coronary stents.

Based on the previously published Swiss Heart Study, which suggested that folate therapy could reduce the restenosis rate by as much as 50 percent, some interventionalists have already begun giving folate therapy to prevent restenosis. According to Dr Helmut Lange, Heart Centre, Bremen, Germany the folate, B6, B12 vitamin combination should be avoided following coronary stent implantation.

Elderly enjoy bonus from treatment with statins

Elderly patients receiving statin therapy to lower blood cholesterol levels may enjoy another benefit as well: better mental health. Presenting results from a study of more than 600 people with an average age of 67, researchers reported that those who were regularly taking statins were about one-third less likely to experience depression, anxiety, or hostility during an average of four years of follow-up when compared to elderly people who had never taken statins. The benefits did not appear to hinge on how effective the statins were in lowering blood cholesterol levels.
Currently the largest single registry of any drug-eluting stent in routine clinical practice worldwide, e-CYPHER involves 284 centres in 35 countries and has enrolled over 6700 patients up to date.

Designed to determine safety and application in routine clinical use and assess the potential to replicate the results obtained in randomised controlled trials (RAVEL, SIRIUS, C-SIRIUS and E-SIRIUS) this internet-based registry of the CYPHER™ Stent will also provide evidence to show how sirolimus-eluting stents are actually being used in daily clinical practice. In addition, the independent advisory board of e-CYPHER will also interrogate the electronic database for the potential to identify predictors of MACE and monitor how clinical practice evolves over time.

By collecting real world data, including a comprehensive clinical follow-up, the registry will help interventional cardiologists to better understand how, when and in which patient to use CYPHER Stents. It will provide valuable information, relying on very large numbers, concerning the use of the CYPHER Stent in many clinical and angiographic patient subsets, such as those with acute AMI, unstable angina, bifurcation lesions, chronic total occlusions, in-stent restenosis, saphenous vein grafts, etc.

Based on the first 4236 patient records to be entered into the electronic database of e-CYPHER it is quite clear that the CYPHER Stent is being used for both on and off label procedures. Reports generated by e-CYPHER reveal for instance that 29% (1,221) of patients were diabetics, and 4.3% (195) were stented during the early hours of an acute AMI. Over 80% of treated lesions were type B2 or C, 9.2% (519) were chronic total occlusions and 16.5% (918) of them were in-stent restenosis. The most frequently used stent length was 18mm, and 9.3% of patients received 2 or more sirolimus-eluting stents. The great majority of patients were discharged on the day following the procedure with a prescription for aspirin and clopidogrel for 2-6 months.

Patient recruitment is planned to continue for at least another 12 months, but preliminary results from e-CYPHER will be available for presentation at Euro-PCR in May 2003.
OPENING SYMPOSIUM
Tuesday May 20 - 14h30-16h00 - Room 1

Title: **Changing Paradigms in Cardiovascular Disease**
Chairman: J. Marco

- How is evidence based medicine affecting clinical practice.
  - M. Leon
- Are Drug Eluting Stents changing your daily practice?
  - P. Serruys
- Tissue Engineering: The ongoing challenge.
  - E. Edelman
- The non-invasive approach to high-risk plaques.
  - V. Fuster

TISSUE ENGINEERING SYMPOSIUM
Thursday May 22 - 18h00-19h30 - Room 3

Title: **Navigated trans-endocardial delivery: a continuing challenge?**
Chairman: R. Kornowski

- Introduction: Where do we stand today?
  - R. Kornowski
- From porcine model to clinical maturity.
  - J-L Dubois-Rande
- The Euroinject-One VEGF study and how it compares to other VEGF Trials.
  - J. Kastrup
- What does the future hold?
  - P. Smits
- Concluding remarks.

CYPHER™ SIROLIMUS-ELUTING STENT SYMPOSIUM
Thursday May 22 - 13h00-14h30 - Room 1

Title: **CYPHER™ Sirolimus eluting stent: evolving new standards in Coronary Artery Disease?**
Chairperson: M-C Morice

- Unmatched efficacy, safety and interventional convenience.
  - A. Carter
- The clinical evidence continues to grow.
  - J. Fajadet
- Sirolimus eluting stent in complex patients.
  - A. Colombo
- A real life perspective.
  - P. Urban
- Conclusion: Beyond the blue horizon.
  - M-C Morice

DISTAL PROTECTION SYMPOSIUM
Friday May 23 - 13h00-14h30 - Room 2

Title: **Co-sponsored symposium on distal protection devices**
Medtronic: Chairman: A. Bartorelli

- Overview of protection systems in different clinical indications.
  - J. Schofer
- Distal protection in Acute MI - The future is here.
  - S. Saito

Cordis: Chairman: T. Lefevre

- Impact of distal microembolisation in coronary arteries.
  - U. Gerckens (E. Grube)
- 6-month follow-up data on the DIPLOMAT study.
  - B. Reimers
### International Conference Planner: 2003

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<td>Vascular 2003</td>
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<td>15-22 June</td>
<td>Advanced Cardiovascular Interventions</td>
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<td>19-21 June</td>
<td>6th International Workshop on Catheter Interventions in CDHD</td>
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<td>30 June</td>
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### 2004

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<td>CRT 2003</td>
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**Cardio Update**

**Issue Number 5**  
**May 2003**

Cardio Update is published three times per year and distributed on a controlled circulation to European interventionists by Cordis, a Johnson & Johnson company, Waterloo Office Park, Drève Richelle 161 H, 1410 Waterloo, Belgium.

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**Design & typesetting:** DNA Limited

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