

Cardio *UPDATE*

A news magazine from Cordis

N°6 AUGUST 2003



New SIRIUS

e-CYPHER

CYPHER Stent news update

Case reports

Targeting the Platelet

Cordis

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Setting the standards in 'high-risk' patients

Welcome to the latest edition of Cardio Update, Cordis Corporation's news magazine for interventional cardiologists and those healthcare professionals associated with interventional cardiology.

With Cardio Update we want to keep you informed about what's going on in the cardiology arena - whether it's the latest clinical trial evidence, developments in clinical practice, updates on current issues or a look into the future with new product developments.

In this issue we cover a variety of topics. Our special report on pages 2-4 examines the findings from New SIRIUS (the combined data from C- and E-SIRIUS). As was always planned, the core laboratory and the investigators from both C- and E-SIRIUS have been studying the data for sometime and their findings in this challenging patient group make interesting reading and better define the standards by which drug-eluting stents should be measured.

The limited availability of CYPHER™ Sirolimus-eluting coronary Stents has been of concern in recent months. This is a matter that we take very seriously as meeting supply with demand is of major importance to all concerned. I regret any inconvenience this may have caused you and your patients and I am pleased to report that we have addressed the problem and are now in the process of fulfilling outstanding orders for CYPHER Stents.

Also of interest is the latest news from the CYPHER Sirolimus-eluting coronary Stent clinical trial program including E-SIRIUS and e-CYPHER which, with more than 8,000 patient records entered, is the single, largest post marketing surveillance registry of any drug-eluting stent. Professor Joachim Schofer will present the results of direct stenting versus pre-dilatation with CYPHER Stent from E-SIRIUS during an ESC Hot Line on Monday, 1st September. Professor Patrick Serruys will also present the latest results from the RESEARCH registry during a second Hot Line on 1st September.

Additional editorial includes some very challenging case reports featuring CYPHER Stent and AQUA T3™ PTCA balloon, an article on important aspects of technique when using CYPHER, a short feature on patient selection for drug-eluting stents and a comprehensive review on the evolving role of glycoprotein IIb/IIIa inhibitors in the age of new percutaneous technologies.

I look forward to meeting many of you at the Cordis booth at ESC 2003 and wish you an enjoyable and successful congress.

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

New SIRIUS: evolving new standards in coronary artery disease



*William Wijns M.D.
Co-Director
Cardiovascular
Center, Aalst,
Belgium*

Background

Unlike the case with balloon angioplasty, atherectomy and other ablative techniques, intracoronary stent implantation has become established as the predominant method of percutaneous coronary artery revascularisation. This is because of its ease of use and because of the predictability and quality of its initial angiographic and clinical results. Continuous improvements in stent technology and operator skills combined with better use of adjunctive anti-platelet therapy have contributed to the improvement in short-term outcomes of patients treated by Percutaneous Coronary Interventions (PCI).

Because coronary artery disease (CAD) remains one of the major causes of mortality and morbidity among adults, intracoronary stenting is generally considered the most important development in the field of mechanical revascularisation since the introduction of balloon angioplasty in 1977. However, while bare metal stents have targeted the underlying issues of elastic recoil and arterial remodeling, angiographic restenosis continues to be the 'Achilles Heel' of interventional cardiology with an estimated 17%-32% of patients requiring repeat treatment.

The introduction of drug-eluting stents (DES) is helping to transform the practice of intracoronary stenting and to offer hope to those patients considered to be 'high risk' such as diabetics, patients previously treated with balloon angioplasty or those for whom surgery was previously the only option.

The difference in outcome as measured by Major Adverse Coronary Events (MACE) between DES implantation and coronary artery bypass graft surgery (CABG) has decreased to almost single digits. This has led experts to predict that, with the advent of DES there will be little or no difference between PCI and CABG in terms of outcome at one year.

This article discusses the recent advances and lessons learned about the use of the CYPHER™ Sirolimus-eluting coronary stent (SES) in the management of CAD based on the latest clinical evidence from New SIRIUS (the combined results from C- and E-SIRIUS, two of the four major clinical trials from the SES international clinical trial program).

Introduction

Since the preview of the preliminary results of the early research of the SES at Euro-PCR 2000, the level of anticipation for DES has grown beyond expectation. Now in its fifth year, the SES clinical trial program is the largest DES database of its kind. Designed and powered to provide healthcare professionals with clear safety and efficacy data, the program evolves through 5 distinct phases. First was the feasibility study (FIM) involving small numbers of patients (up to 45 patients). Pivotal studies then followed - mainly for regulatory approval such as CE mark and FDA approval. The RAVEL randomized trial provided the efficacy results from angiographic primary endpoints. RAVEL was followed by large scale, prospective, randomized, multi-center, double blind controlled trials that involved a large numbers of patients (SIRIUS, C- and E-SIRIUS) evaluating both safety and efficacy in terms of clinical primary endpoints. In addition, these trials were designed to provide health economic data to support reimbursement. Further studies designed to evaluate the technology in expanding indications are in varying stages of implementation - initially as feasibility studies and then, dependent upon the outcome of the feasibility studies, larger studies are being undertaken (TROPICAL for in-stent restenosis, FREEDOM and DECODE for diabetes, and bifurcation). More recently the interest has been fuelled by the disclosure of the latest 9 months results from E- and C- SIRIUS.

E-SIRIUS

E-SIRIUS is a double blind clinical trial that involved 352 patients at 35 European centres. It is also the first DES trial to evaluate direct stenting.

Data show a significant improvement in minimal lumen diameter (MLD) with DES compared to bare stent at 8 months angiographic follow up. Comparisons between the two techniques, direct stenting vs. the more conventional technique involving pre-dilatation, revealed no difference. This maintenance of the MLD and concomitant suppression of neo-intimal hyperplasia translates into an event-free survival rate from MACE of 92% at 270 days in patients treated with a

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SES, which is significantly superior ($P < 0.001$) to the 77% event-free survival rate for patients treated with a conventional, bare-metal, Bx Velocity stent in the control arm of the study. Clinical results at 9-months served to reinforce the efficacy and safety of SES with an 81% reduction in the need for target lesion revascularisation (TLR), meaning that repeat intervention was avoided in 170 patients out of 1000 patients and a stent thrombosis rate of 1.1%.

The most important observations from the study were that in contrast to SIRIUS, the US regulatory trial, patients enrolled into E-SIRIUS had a higher clinical risk profile, had longer lesions in smaller vessels, received more often multiple stents, were treated less often with glycoprotein IIb/IIIa inhibitors, and received combined anti-platelet therapy for a shorter period of time (2 months vs. 3 months). Moreover, the maintenance of therapeutic efficacy at the proximal stent margin evident in E-SIRIUS indicates that the incomplete suppression of neointimal hyperplasia observed in this region in SIRIUS is related to procedural technique rather than device failure.

C-SIRIUS

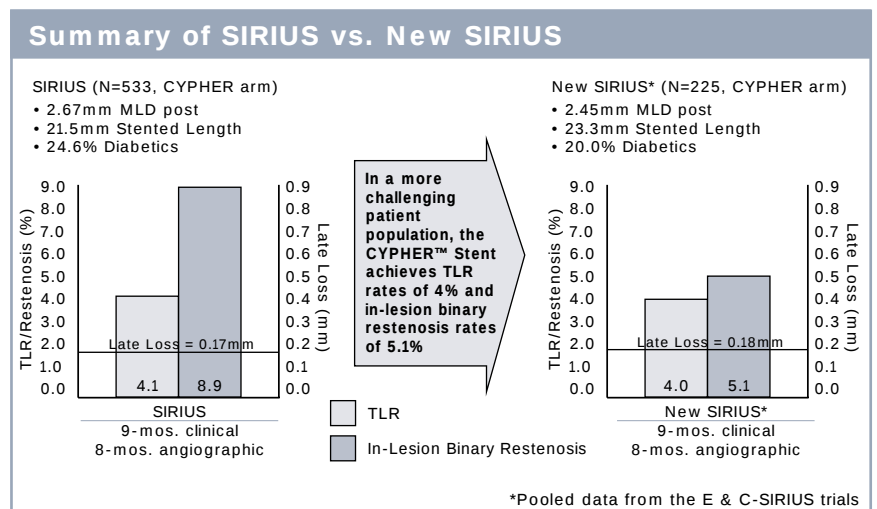
As with E-SIRIUS, the Canadian Multi-Center, Randomized, Double-Blind Trial of the SES in patients with *de novo* Coronary Artery lesions: C-SIRIUS involved more complex patient and lesion types than SIRIUS. Particularly challenging outcome predictors included 24.0% diabetics, post-MLD of 2.53mm, and a stented length of 26.1mm.

The angiographic results revealed a highly significant difference in 8-month in-stent MLD (primary endpoint) thanks to a marked reduction in in-stent late loss of 91% (0.09mm for the SES). There was also a significant reduction in late loss at the proximal margin. The investigators highlighted the 'particularly noteworthy' 100% reduction in in-stent restenosis rate (0% vs. 41.9% for control). In-lesion results revealed only one patient (2.3%) presenting with binary restenosis in DES arm, compared to 23 (53.5%) in the control group.

In summary, as was the case with two earlier landmark clinical trials, RAVEL and SIRIUS, these results confirm the efficacy of the SES in a broad range of lesions types and patient subsets. However, unlike the SIRIUS trial there was no evidence of the phenomenon of peri-stent restenosis in either C- or E-SIRIUS.

New SIRIUS: 'A new benchmark for comparison'

In the 17 months since the SES first became available we have come to recognise the valuable lessons learned from 'real world' experience. We became aware of the importance of TLR rates and Late Loss as predictors of long term outcome with DES. The results from New SIRIUS clearly show the benefits to be gained from careful operator technique if we are to avoid peri-stent restenosis.



As the SES clinical trial program has evolved perhaps the most important observation we can make are the remarkable results from New SIRIUS. The inclusion of a more challenging patient population (Table 1) make the results of these combined trials much more relevant to 'real-life' situations.

A detailed analysis of the results from New SIRIUS and SIRIUS showed that the difference in in-lesion binary restenosis rate is primarily due to the difference in the restenosis at the proximal edge. The results are as follows:

Binary Restenosis	NEW SIRIUS	SIRIUS
Proximal	2.1%	5.5%
In-Stent	3.1%	3.2%
Distal	1.5%	2.0%

TABLE 1	NEW SIRIUS	SIRIUS
# DES pts	225	533
Mean age	61.6	62.1
Number of men %	70.2	72.6
Stent length (mm)	23.3	21.5
Diabetics (%)	20.0	24.6
RVD (mm)	2.61	2.80
Stent(ed) length (mm)	23.3	21.5
Lesion length (mm)	14.8	14.4
Stent: lesion length ratio	1.7	1.5
Overlapping stents (%)	34.3	28.5
Direct stenting (%)	27.0	0.0
In stent MLD (mm)		
Pre-procedure	0.87	0.98
Post procedure	2.45	2.67
Follow-up (8-month)	2.27	2.50
In-stent Late Loss (mm) @ 8 months	0.18	0.17
In-lesion binary restenosis (%) @ 8 months	5.1	8.9
In-stent binary restenosis (%) @ 8 months	3.1	3.2
TLR (%)	4.0	4.1

These compelling findings can be attributed to the different technique employed in New SIRIUS, primarily the use of shorter post-dilatation balloons and direct stenting of 27% of the patients. Overall, New SIRIUS adds further support to the belief that the impressive results of both RAVEL and SIRIUS may now be extended to more complex patients with longer lesions and smaller vessel size. In fact New SIRIUS showed greater reductions in late loss, binary restenosis, TLR and MACE than SIRIUS, despite the more challenging patient population. This was particularly noticeable with the in-lesion angiographic results that suggest a beneficial effect of increasing the SES/lesion length ratio (from 1.5 in SIRIUS to 1.7 in New SIRIUS) where greater coverage of areas that may be exposed to balloon trauma would naturally reduce neointimal hyperplasia in the segment.

New SIRIUS has clearly established the new standard in randomised clinical trials against which all other DES will be measured. At a time when many interventional cardiologists

continue to use angiographic binary restenosis, as well as Late Loss and TLR, as key comparators between individual DES trials, every percentage point of restenosis is likely to influence the long-term outcome of our patients.

In summary, DES technology has come a long way since Sousa and Serruys presented the preliminary findings from the First-in-Man feasibility study and Morice presented the unprecedented results from RAVEL. In the interim period, the SES has confirmed safety and efficacy in four randomised, controlled clinical trials as well as in large post-marketing surveillance registries - either multicentric and international such as e-CYPHER (8,000 patients and growing) or monocentric such as RESEARCH (over 1,000 patients in Rotterdam). The small but significant incremental improvement in results that was achieved in New SIRIUS suggests a growing understanding of how to maximise clinical outcomes with the SES and implies that a binary restenosis rate of less than 6% will be the yardstick by which other DES will be measured.

e-CYPHER

results from EuroPCR



*Dr. Philip Urban,
Hospital De La Tour, Meyrin-Geneva, Switzerland,
Member of the e-CYPHER European Advisory Board.*

The e-CYPHER registry is the largest single registry of a drug-eluting stent in routine clinical practice worldwide. It is an internet-based post-marketing surveillance registry designed to assess the safety and effectiveness of the CYPHER™ Sirolimus-eluting Coronary Stent (CYPHER Stent) in the routine clinical setting, and with some 8,000 patient records entered into the database is providing valuable answers to questions asked by interventional cardiologists and referring physicians with little or no experience of drug-eluting stents.

e-CYPHER was developed in association with an independent advisory board comprising of a worldwide executive board and three regional advisory boards. Ongoing involvement includes global and regional safety monitoring, epidemiological studies and review of procedural practices. A critical event committee has also been formed to review and adjudicate all deaths and selected serious events.

Patients receiving one or more CYPHER Stents, for both on- and off-label usage are eligible for enrolment. The registry aims to recruit 15,000 patients, with clinical follow-up carried out at

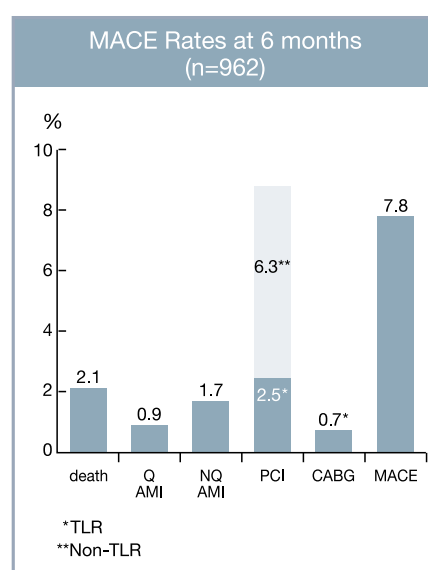
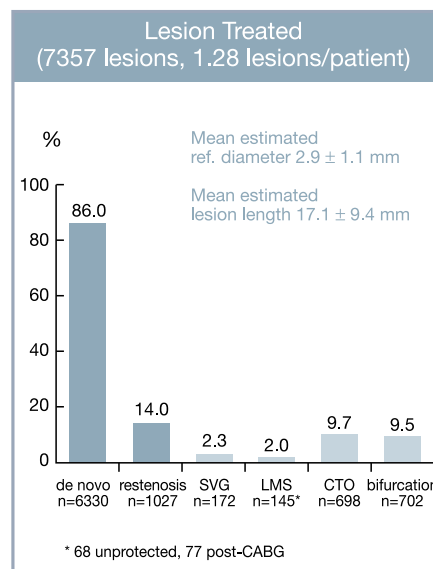
one, six and twelve months. There is no mandatory angiographic follow-up required. Data input is achieved on-site via the Internet, and audits and data quality checks are in place to ensure accuracy. As at EuroPCR in May 2003, the e-CYPHER registry has analysed data from 6,700 patients from 317 sites in 35 countries across Europe, Latin America, the Middle East, and Asia Pacific.

Most patients involved so far have been treated for stable and unstable angina, although treatment of silent ischemia and acute myocardial infarction has accounted for 15% and 7% of cases respectively. While the majority of lesions treated have been *de novo* lesions (n=6,330), significant numbers of restenotic lesions (14%) have also been treated. Other off-label uses have included bifurcations, chronic total occlusions, Saphenous Vein Graft (SVG) and Left Main Stem (LMS). Baseline angiography of the current total of 7,357 lesions treated has revealed a mean estimated reference vessel diameter of 2.9mm and a mean estimated lesion length of 17.1mm.

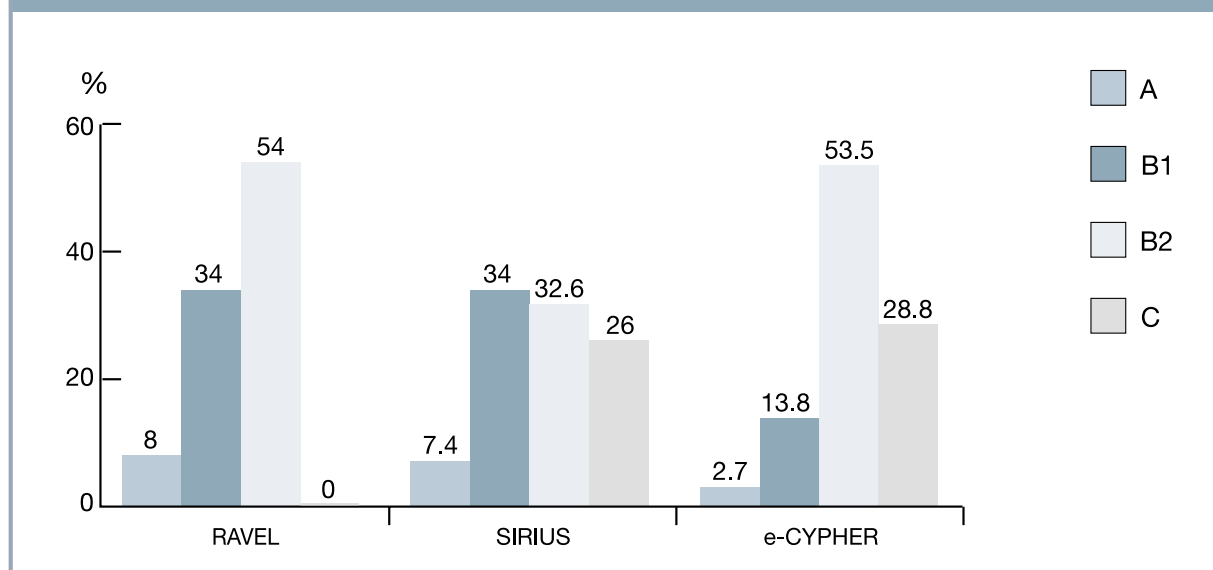
Patient Demographics	%
Mean Age (years)	62
Male Gender	77
Prior PCI	32
Prior CABG	12
PVD	9
Prior CVA	3
Diabetics	29
Multivessel Disease	54

The types of lesions treated in e-CYPHER have been generally more complex than in previous randomised controlled trials. Multiple CYPHER Stents were required for almost one in ten patients, and 83% of multiple stenting involved overlapping CYPHER Stents. The average stent: lesion length ratio of 1.16 was somewhat lower than currently completed randomized controlled clinical trials (RAVEL 1.9, SIRIUS 1.5, E-SIRIUS 1.7, C-SIRIUS 1.8). Slightly more than one quarter of the procedures involved direct stenting, while post-dilatation was used in 17.1% of cases. Anti-platelet therapy prescribed at discharge nearly always involved indefinite use of aspirin (96%), while clopidogrel/ticlopidine therapy varied from 1 month to permanent use, although in the majority it was given for 2-3 months.

Follow-up clinical results just presented at EuroPCR involved available 6-month data from 962 out of 3,601 eligible patients. At 6 months, Target Lesion Revascularisation (TLR) was as low as 3.2% and the Major Adverse Cardiac Event (MACE) rate was 7.8%. This compares very favourably with event-free survival rates in the aforementioned clinical trials, despite more challenging outcome predictors i.e. more complex lesions, longer lesions, a higher incidence of diabetics, restenotic lesions, Chronic Total Occlusions (CTO), and bifurcations. Although this follow-up data is not yet complete, these interim results are very encouraging. While off-label use was quite prevalent (in-stent restenosis, CTO, bifurcations), in-hospital data showed excellent feasibility and safety for a wide range of indications and anatomical subsets. If these findings remain robust with greater numbers of patients over an extended period of follow-up, they will have a significant impact on routine clinical practice.



Lesions Treated (%): e-CYPHER vs. previous randomised controlled trials



NOTE: Additional results from e-CYPHER will be presented at TCT in Washington (15 - 19 September 2003)

Broad therapeutic window of sirolimus encourages the use of multiple or overlapping CYPHER Stents:

a sub-analysis of the SIRIUS trial



*Carlo Di Mario, MD Interventional Cardiologist
Royal Brompton Hospital, London, England
and Professor of Cardiology, Imperial College, London*

The CYPHER Stent is the only drug-eluting stent with which the practice of overlapping stents has been studied as an approved implantation technique rather than a rare bail out indication.

This has been possible in part because of the excellent safety results from pre-clinical animal trials. In these trials, sirolimus-eluting stents demonstrated a broad therapeutic window. Biological activity was exhibited with doses ranging from 18-1200 $\mu\text{g}/\text{stent}$ without displaying toxicity to the vessel wall. Furthermore, observed re-endothelialisation was similar for all doses, with the first evidence visible at 3 days, and complete within 14 days. The highest dose tested was over 6 times that of the CYPHER Stent. In the clinical setting, this broad therapeutic profile suggests that long, overlapping or adjoining stents can be deployed without the risk of toxicity. It may also minimise the need for extended anti-platelet therapy, and encourage 'creative' approaches to lesion treatment such as the use of the 'crush' or culotte techniques for bifurcations, all characterised by the creation of a triple or double layer of stent against the vessel wall.

In the SIRIUS trial, 176 patients received overlapping CYPHER Stents (n=168 for control). Average lesion length was 18.2mm, average stent length 28.3mm, and average stent overlap 4.6mm. At 8 months, minimal in-stent late loss of 0.23mm (vs. 1.14mm for control, $p<0.001$) resulted in an in-stent restenosis rate of only 7.1% (vs. 42.7% for control, $p<0.001$). At 9 months, this translated into very low TLR and MACE rates of 4.5% and 8.5% respectively (vs. 17.9% and 22.6% for control, $p<0.001$).

Importantly, with a combined treatment with aspirin and clopidogrel limited to 3 months SAT was very low and identical to control (0.6%), and there were no incidences of late thrombosis up to 9 months. In the series of restenoses observed in a consecutive series of patients treated in Milan the patterns observed and just published did not suggest a higher risk in segments of stent overlapping.

The possibility of using overlapping CYPHER Stents, and the excellent results seen in long lesion subsets, suggests that unlike with bare metal stents implantation of an additional CYPHER Stent at the edge of the initially deployed stent should be always be performed whenever a residual narrowing or dissection is present. The only remaining issue with overlapping CYPHER Stents is the lack of reimbursement in most European countries.



Practical advice for selecting patients for drug-eluting stents

Niall Mulvihill, M.D. Interventional Cardiologist,
St. James's Hospital and Trinity College, Dublin, Ireland.

The introduction of drug eluting stents into clinical practice is undoubtedly transforming the practice of interventional cardiology. This technology is allowing us to overcome the Achilles' heel of coronary stenting, namely in-stent restenosis. Just one year following the introduction of this technology in Europe in excess of 100,000 drug-eluting stents have to date been implanted.

In order to prospectively assess the introduction of this novel technology into clinical practice outside of the setting of clinical trials, Professor Patrick Serruys and his colleagues in the Erasmus Thoraxcenter in Rotterdam made a decision to use sirolimus-eluting

stents in all patients undergoing percutaneous coronary intervention for a 9 month period. The information on all these patients has been collected in the RESEARCH registry.

In RESEARCH, 1,083 patients had Sirolimus-eluting stents implanted between April 2002 and January 2003, truly reflecting 'real world practice' including all patient and lesion subsets such as *de novo* and restenotic lesions, saphenous vein graft lesions and patients with acute myocardial infarction and multi-vessel disease. Complex lesion subsets such as unprotected left main, chronic total occlusions and bifurcations were also included.

In comparison to the 1,270 patients who have had drug-eluting stents implanted in 8 randomized controlled trials only 31% of patients in the RESEARCH registry would have been eligible for enrolment in one of those trials (Figure 1). The fact that 69% of patients had either clinical or lesion characteristics, which would have prevented their participation in the drug-eluting stent trials

performed to date, dramatically demonstrate the difference between randomized controlled clinical trials and real world practice. Until the additional feasibility studies and controlled trials investigating DES in the more challenging lesion types report we must rely on our own clinical experience and the observations from registries such as RESEARCH and e-CYPHER (see page 6).

In order to use this technology in the safest and most clinically and economically effective manner we need to select the patients with the highest risk of restenosis and apply the lessons learned in the clinical trials to date.

Patients and lesions treated so far in these trials (trial limitations)

8 Randomized Trials (n=1270pts with DES)

- No main stem
- No chronic occlusion
- No very long lesions
- No very small vessels
- No acute MI
- No SVG
- No MVD stenting
- No in-stent restenosis
- No renal failure
- No very old patients
- Bifurcation

Thoraxcenter Practice (n=1083pts with DES from Apr/02-Jan/03)

- 4%
- 11%
- 20% (stented length >36mm)
- 16% (stent diameter = 2.25mm)
- 17%
- 4%
- 31%
- 9%
- 5% (serum creat > 150 mmol/L)
- 5% (age > 80 years)
- 18%

In total, 69% of our patients could not be included

Figure 1. Comparative experience of using drug-eluting stents in the setting of clinical trials versus the real world experience of the RESEARCH registry.

Evidence from clinical trials

The First-in-Man (FIM) pilot studies of the sirolimus-eluting stent (CYPHER, Cordis Corp.) demonstrated a remarkable abolition of restenosis, now with durability of the results for up to 3 years. The first double-blind multicenter randomized trial (RAVEL) in 238 patients corroborated these early observations with a reduction in angiographic binary restenosis at 6-months follow-up from 26% in the bare metal stent control to 0% in the sirolimus-eluting stent group. Although the RAVEL patient cohort represented a relatively simple lesion subset (focal *de novo* lesions in vessels 2.5 to 3.5mm in diameter, covered by a single 18mm-long stent), the latest evidence shows a sustained effect out to 2 years.

More recently, the 9-month results of a large US multicenter double-blind study (SIRIUS) have been reported. The patients and lesions were more complex in SIRIUS, including more cardiac risk factors (especially diabetes), longer lesions (15 to 30mm), and frequent overlapping stents (28% of patients). Angiographic restenosis at 8 months was reduced by 75% in the sirolimus treatment group ($P<0.001$), and the primary end point, target vessel failure at 9 months, was similarly reduced by 59% ($P<0.001$). Superior results in a more challenging patient population and lesion types have been reported in the C-SIRIUS and E-SIRIUS trials (Canadian and European trials very similar in design and inclusion criteria to SIRIUS).

Experience with bare metal stents has taught us that there are both patient and lesion characteristics that can increase the risk of restenosis: diabetes mellitus, long lesions and small vessel diameters. In the SIRIUS trial the sirolimus-eluting stent significantly reduced restenosis both for patients with a lower and a higher predicted risk of restenosis. Non-diabetics with short lesions ($<12\text{mm}$) and large vessels ($\geq 3\text{mm}$) had an 81.7% risk reduction of in-segment restenosis whereas patients at a higher risk of restenosis; diabetics with longer lesions

($\geq 15\text{mm}$) in small vessels ($<2.5\text{mm}$) had a 64.5% reduction in the risk of restenosis. The RAVEL trial also demonstrated similar reductions in the risk of restenosis for patients in the tercile of vessel size $<2.36\text{mm}$ as for patients in the tercile of vessel size $>2.84\text{mm}$.

The RESEARCH registry has demonstrated that implantation of sirolimus-eluting stents was safe in patients with acute coronary syndromes with no difference in 30 day major adverse cardiac event rates to a control group treated with bare metal stents. The preliminary analysis of the first 280 patients treated in this registry reveals a 6-month repeat revascularisation rate of 2.9% and major adverse cardiac event rate of 6.7%. These results appear very encouraging especially considering the inclusion of patients with multivessel stenting, bifurcations and in-stent restenosis, however before we can routinely advocate the use of drug-eluting stents in these more challenging lesion and patient subsets we require these results to be validated in larger clinical studies.

Despite the limited scientific data it is undoubtedly the lack of reimbursement that has limited more widespread use of drug-eluting stents. While we await data from clinical trials of drug-eluting stents in more challenging patient and lesion cohorts it makes practical clinical and economic sense for cardiologists to select patients with the highest risk of restenosis using clinical and lesion characteristics. Therefore, utilising the results of the clinical trials to date, the use of drug-eluting stents can be recommended in the following situations:

- *De novo* lesions 50%-99% stenosed in native vessels, $>15\text{mm}$ in length and in vessels $<3.0\text{mm}$ in diameter.
- *De novo* lesions 50%-99% stenosed in native vessels, up to 30mm in length in vessels 2.5-3.5mm in diabetic patients.
- Bifurcation lesions with drug-eluting stent implantation in the parent vessel and balloon angioplasty of the side branch.

Independent clinical research

The Cordis CYPHER™ Sirolimus-eluting coronary stent now involves 40 completed or ongoing clinical trials ranging from studies for regulatory bodies and research into additional indications such as diabetes, small vessels, bifurcation lesions and in-stent restenosis. Not surprisingly many centres are conducting their own independent research into this exciting new technology, perhaps the most well-known of which is RESEARCH (Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital). In this edition of Cardio Update we report on two such studies.



Independent clinical research: The Scandstent study

*Dr. Henning Kelbæk, Cardiac Catheterisation Laboratory,
The Heart Centre, Rigshospitalet, Denmark*

Stenting is efficient in simple and in slightly complex coronary lesions, but our knowledge of stenting bifurcational, angulated, ostial lesions in addition to long total occlusions is limited.

Whereas the RAVEL and SIRIUS studies have documented convincing results on reduced restenosis rates after CYPHER stenting of simple and slightly complex coronary lesions, the Scandstent study will focus upon the effects of balloon angioplasty vs. bare metal stents and bare metal stents vs. drug-eluting stents (DES) in more complex coronary lesions.

The Scandstent study, a Scandinavian initiative, is designed to evaluate the clinical and angiographic outcome of balloon angioplasty (POBA) vs. bare metal stenting and stenting with bare metal vs. drug-eluting stents in patients with complex coronary artery lesions like bifurcational, angulated, ostial and long total occlusions.

Patients are included if they exhibit one of the characteristics listed in Figure 1.

Involving several Scandinavian centres, the study will include at least 300 patients. To date 100 patients have been enrolled at two Danish centres, Skejby Hospital and Rigshospitalet, and a centre in Odense, Denmark, will be actively recruiting patients from August 2003. In addition, an ethics committee is at present considering approval of the study in Tromsø, Norway.

Balloon angioplasty is performed with slightly undersized balloons compared with the reference diameter of the vessel in an attempt to limit the severity of dissections. An optimal result is acquired when the residual stenosis measures $\leq 30\%$ by QCA with $\leq$ type C dissection and no signs of ischaemia.

If an optimal result is achieved with balloon dilatation (POBA) alone, the patient can be randomised 1:1 to either no further treatment or stenting with a bare stent. If an optimal POBA result cannot be achieved, patients are randomised 1:1 to stenting with a BX SONIC™ or a CYPHER™ stent (Figure 2). Treatment of more than one lesion is allowed, but only one lesion is randomised in the study.

The follow up flow chart and end points are shown in Figures 3 and 4.

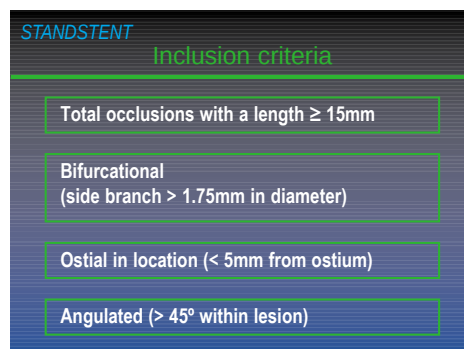


Figure 1

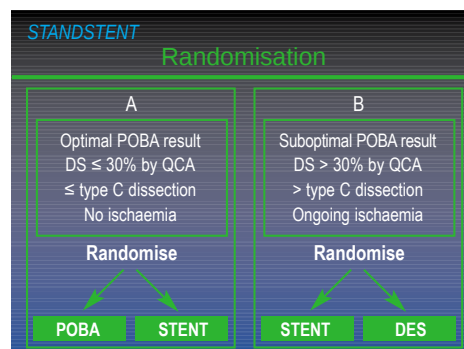


Figure 2

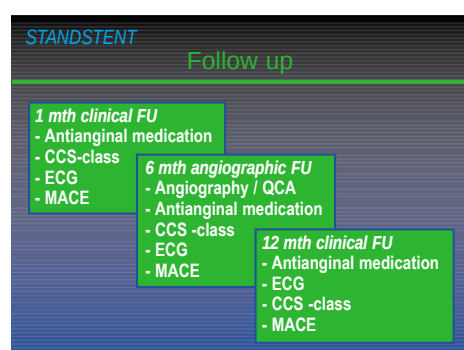


Figure 3

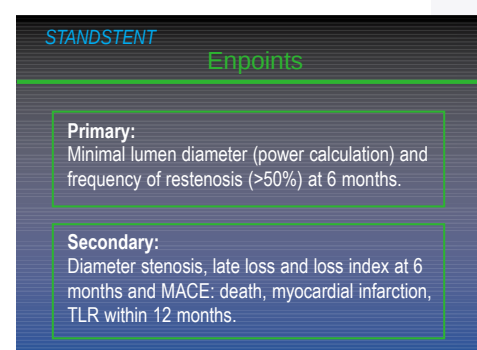


Figure 4

CYPHER™ sirolimus-eluting coronary stents for the treatment of 'non-SIRIUS' patients and lesions: The paradox of case selection (LACYR).



Fábio Sândoli de Brito Jr., MD, PhD
Interventional Cardiology
Albert Einstein Hospital, São Paulo, Brazil

CYPHER Sirolimus-eluting coronary stent (SES) has been shown to dramatically reduce neointimal hyperplasia and, therefore, to prevent in-stent restenosis^(1,2).

Undoubtedly, this technology has initiated a new era, broadening the spectrum of patients that can be efficaciously treated by percutaneous coronary interventions. However, the lack of reimbursement in most countries still hampers the widespread use of SES, and therefore, the need for a careful selection of patients and lesions to receive this new stent is a reality in most centres, especially in Latin America and third world countries. Because of the need for case selection, interventional cardiologists are facing a real paradox in daily clinical practice.

To date, based on results of randomized clinical trials, we only have strong data to support the use of this technology in elective patients with relatively simple lesions, where bare stents can achieve inferior but acceptable results. For more complex situations, data is still missing. So far, the studies including patients and lesions with the highest risk profile were SIRIUS (US, Canadian and European), but even in these investigations, more complex subsets were excluded, as ostial lesions, lesions with thrombus, long lesions (>30-32 mm), diffuse disease, unprotected left main, chronic total occlusions, vein graft lesions, very small vessels (<2,5 mm) and in-stent restenosis, as well as clinical situations like impaired renal function, LV ejection fraction <25%, multi-vessel stenting and acute MI⁽³⁾. Paradoxically, these 'non-SIRIUS' cases are exactly those that instantaneously bring to the mind of an interventional cardiologist

the desire of using a drug-eluting stent. Although it cannot be considered an evidence-based practice of medicine, it is very important to consider the judgment of an experienced physician choosing the therapy with the best chance of lasting benefit for his high-risk patient. We have all seen a similar situation before with bare stents and even after a much longer period of experience, still today many of the lesions being treated have never been evaluated by randomized clinical trials. It is natural and inevitable that this happens with new developments in interventional cardiology. Actually, we do have some data on SES for high-risk cases, obtained from

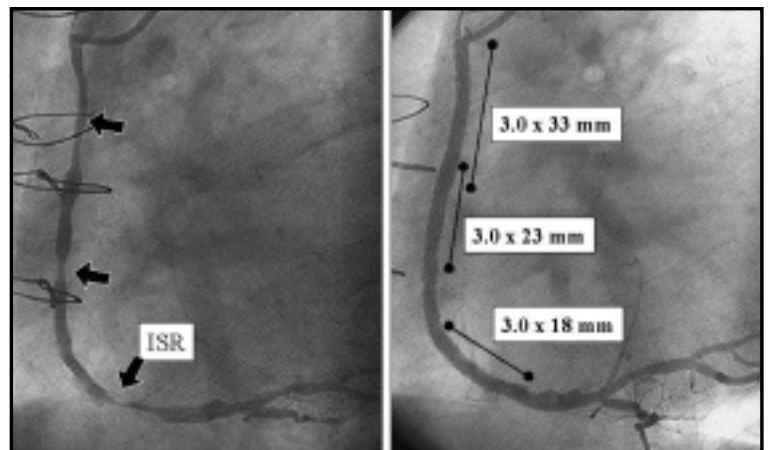


Fig 1. Saphenous vein graft to the right coronary artery with a long lesion in the proximal segment, a focal lesion in the middle and an in-stent restenosis (ISR) lesion in the distal segment (arrows). Three SES were implanted (minimal overlap of the proximal stents) and postdilated with a 3.5 x 15 balloon. After 8 months of clinical follow-up, the patient remains asymptomatic.

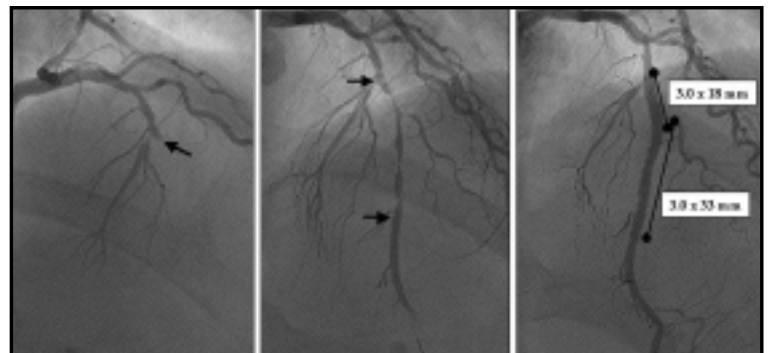


Fig 2. Acute myocardial infarction with an occluded left anterior descending artery treated by primary angioplasty. After crossing the lesion with the 0.014" wire, flow was re-established and a long lesion was detected (arrows). Two SES were implanted, with a minimal overlap. A good angiographic result with TIMI 3 flow was obtained. After 6 months of clinical follow-up, the patient remains asymptomatic.

sub-analyses of RAVEL and SIRIUS, although not 'a priori' designed for this kind of evaluation.

These data indicate that the most complex cases have the greatest absolute benefit in terms of reduction of restenosis, although associated with a lower relative benefit when compared to the low-risk population.

As examples, in SIRIUS, diabetics with small vessels ($\leq 2.5\text{mm}$) and longer lesions ($\geq 15\text{mm}$) presented an unprecedented 43.1% (66.8% vs. 23.7%) absolute reduction of restenosis rates, representing a 64.5% relative reduction. On the other hand, patients at lower-risk, like non-diabetics, with large vessels ($\geq 3\text{mm}$ in diameter) and short lesions ($\leq 12\text{mm}$ in length) presented only a 15.2% (18.6% vs. 3.4%) absolute reduction of restenosis, which represented a high relative reduction of 81.7%.

Recently, after completing our first year experiencing the so called 'indication paradox' in a daily basis, the feeling was that, even in the 'real world' scenario, results were exceptional. To confirm this impression, an analysis of the results of SES CYPHER for the treatment of patients and lesions classified as 'non-SIRIUS' was performed. All the cases had been previously included in the LACYR registry (Latin American Cypher Registry) and were performed between May 2002 and May 2003 at Albert Einstein Hospital (São Paulo, Brazil). During this period, a total of 187 patients were treated with SES. Interestingly, the 'non-SIRIUS' cases were the majority, representing 64.7% (121 patients) of the SES population (Figures 1 and 2). The reasons for classification as 'non-SIRIUS' were diverse and are depicted in Table 1. Diabetes was present in 28.1% of these patients, one third on insulin. Procedural success was 97.5% and the number of SES used per patient was 1.4.

The recommendation to this high-risk group was to maintain aspirin indefinitely and clopidogrel for at least 3 months after the index procedure.

One single sub-acute stent thrombosis causing a non-Q-wave MI was diagnosed 3 weeks after the procedure and was directly associated with discontinuation of aspirin and clopidogrel because of a life-threatening gastrointestinal bleeding. So far, 79 (65.3%) patients have completed at least 6 months of clinical follow-up and 3 patients in this high-risk group needed a percutaneous clinically driven re-intervention due to restenosis (2 in-lesion and 1 in-segment). One additional patient, with a perfect, non-restenotic SES in the LAD, needed CABG because of disease progression in the left main.

What lessons did I learn from this small and initial experience? I definitely learned that the dream of 0% restenosis is still just a dream in the 'real-world' scenario. Interestingly, I only awoke to this reality when the first SES patient came back with restenosis. However, after the first, it took quite a long time for the second and third to appear and, so far, this is all for this complex, 'non-SIRIUS' population. The 'disappointment' of the first restenosis is now clearly overcome by the satisfaction of seeing, with my own eyes, patients with, for example, multi-vessel disease and recurrent in-stent restenosis, being brought back from the operating room to the cath lab simply because of the excellent perspective offered by this new and effective technology. It was really an evolution and that was the major lesson learned from my modest experience treating these high-risk patients with SES. The excessive initial enthusiasm is now replaced by a realistic enthusiasm.

Table 1. Characteristics for classification as 'non-SIRIUS'

Patient characteristics*	121 patients (158 lesions)
Multivessel disease / stenting, n(%)	33 (27.3%)
Acute myocardial infarction, n(%)	22 (18.2%)
Lesion / vessel characteristics *	
Ostial lesion, n(%)	21 (13.3%)
In-stent restenosis, n(%)	24 (15.2%)
Chronic total occlusion, n(%)	6 (3.8%)
Bifurcation, n(%)	31 (19.6%)
Lesion > 30 mm in length, n(%)	17 (10.8%)
Vein graft lesion, n(%)	9 (5.7%)
Presence of thrombus, n(%)	16 (10.1%)
Vessel < 2.5 mm in diameter, n(%)	37 (23.4%)

* Patients / lesions / vessels may present more than 1 'non-SIRIUS' characteristic.

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Case Report:

Complex In-stent Restenosis in a Saphenous Vein Graft treated with a CYPHER Stent

*Niall Mulvihill, M.D. Interventional Cardiologist,
St. James's Hospital and Trinity College, Dublin, Ireland.*

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 September 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 3.0 x 18mm 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/left circumflex.

This case report reflects the clinical judgement of the authors in selecting CYPHER™ Stent for these challenging cases. Prior to use, please refer to the Instructions for Use supplied with the device for indications, contraindications, side effects, recommended procedures, warnings and precautions.

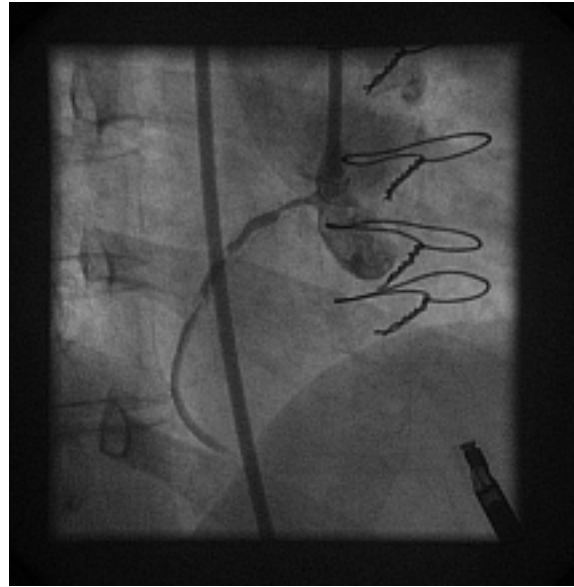


Figure 1 A&B. Diffuse proliferative in-stent restenosis in a saphenous vein graft to the right coronary artery with poor distal run off.

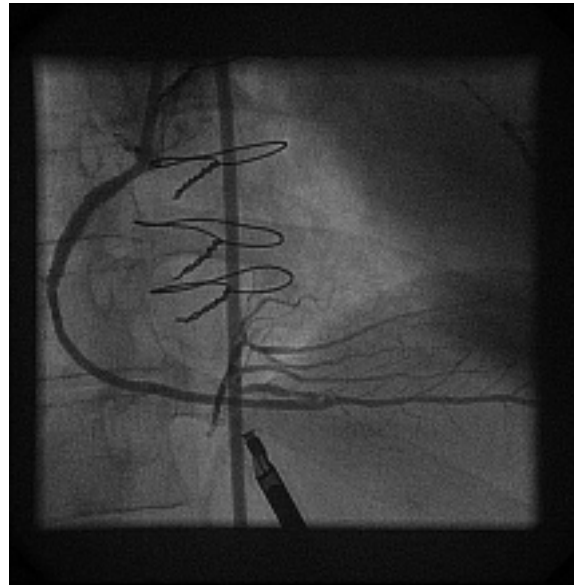
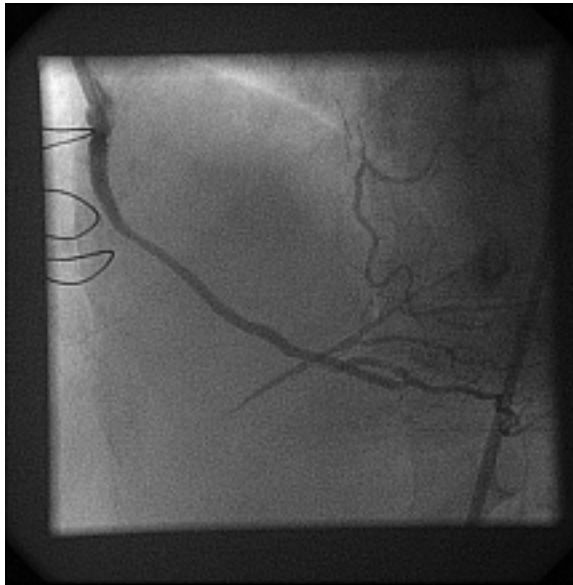


Figure 2 A&B. Final images following implantation of a 3.0 x 33mm CYPHER Stent to cover the in-stent restenosis. Good distal flow with opacification of the distal right coronary artery

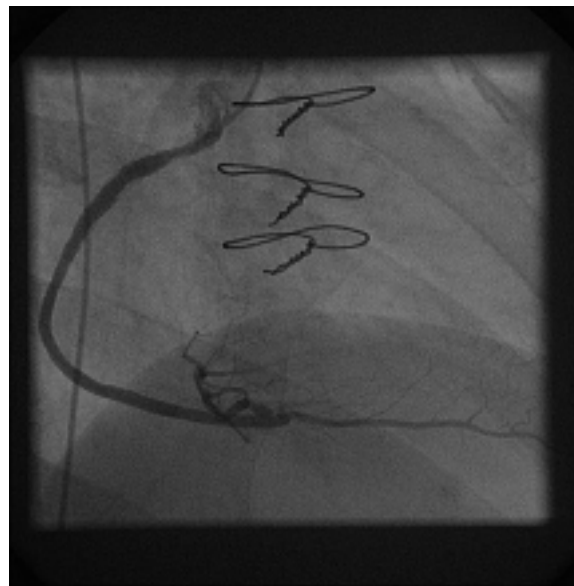
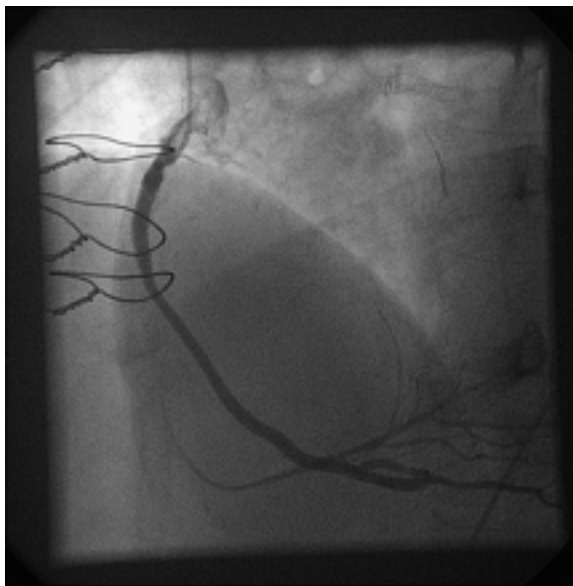
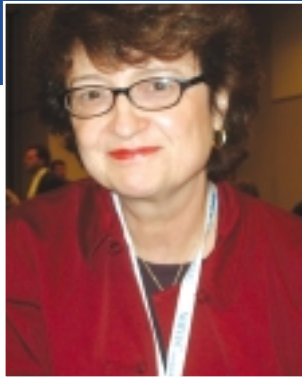


Figure 3 A&B. Follow up angiogram after 6 months demonstrating a widely patent CYPHER Stent in the saphenous vein graft with no angiographic evidence of restenosis.

Optimising outcomes with the CYPHER Stent



Marie-Claude Morice M.D. Consultant Cardiologist
Institut Cardiovasculaire, Paris-Sud

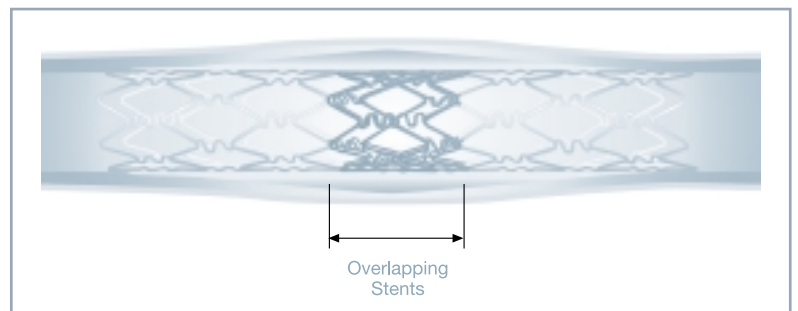
In the 17 months since the CYPHER Sirolimus-eluting coronary Stent (SES) first became available we have all come to recognise the valuable lessons learned from ongoing controlled clinical trials and 'real world' experience.

We are all now more aware of the importance of target lesion revascularisation (TLR) rates and Late Loss as predictors of long term outcome with a drug-eluting stent (DES) and the results from C- and E-SIRIUS (described as New SIRIUS) clearly show the benefits to be gained from careful operator technique if we are to avoid peri-stent restenosis and attain restenosis rates of 5% or less (as revealed in New SIRIUS). In this short article I have tried to summarise the key lessons we have learned when implanting a SES.

All efforts should be taken to make sure that the stent is not under-dilated - the internal stent diameter should match the size of the reference vessel diameter. In the RAVEL and SIRIUS trials, the average deployment pressure used was approximately 14 atm.

If full contact with the vessel wall is not achieved, a larger post-dilatation balloon may be used to expand the stent further. Post-dilatation occurred in 54% of cases to achieve true stent apposition in the SIRIUS trial. Post-dilatation balloons should be shorter than the stent length, and again centred within the stented area to prevent injury outside of the stent edges. The use of a balloon without a hydrophilic coating may minimize balloon movement during inflation, minimising injury outside the stented area. It is important not to exceed the expansion limits of the CYPHER Stent e.g. 3.75mm for a 6-cell CYPHER Stent (2.5 & 3.0mm).

When overlapping two CYPHER Stents, it is obviously crucial not to leave a gap.



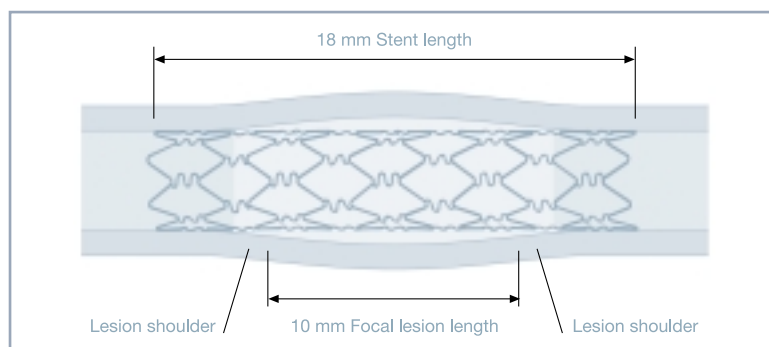
Experience from clinical trials has reinforced the need for careful operator technique to maximize the potential benefit of CYPHER Stent implantation. Stent and balloon selection, deployment technique and adjunctive drug regimens may all be critical to success.

To cover adequately reference segment disease it is recommended that clinicians first choose the stent length based on the diseased area to be treated. Use of a marker-wire may optimise stent length selection. It is important to stent disease-free to disease-free normal reference vessel areas, by choosing a 'safe landing zone' outside the shoulders of the lesion. This will reduce exposed areas that may be prone to

disease progression. If after measuring a lesion the stent length is still in question, it is preferable to choose a longer stent.

Pre-dilatation balloons should be shorter than the intended stent length, and centred within the intended stent area. Care should be taken to note exactly where pre-dilatation occurs in order to cover any injured areas with the stent. Foreshortening of the CYPHER Stent varies from 0.3-1.0mm depending on stent length and diameter. Based on clinical experience, several physicians have recommended a 3-4mm overlap to avoid geographic miss.

therapy is obligatory, although the length of treatment may vary. In RAVEL 2 months APT was used whereas in the 'real-world' patient cohort of SIRIUS, clopidogrel/ticlopidine was prescribed for 3 months, and in New SIRIUS (C- & E-SIRIUS) for 2 months.



To ensure there is no gap following deployment of a second stent, the distal balloon marker of the second stent should be inside the first deployed stent.

Concerning adjunctive drug regimens, it is recommended that current GP IIb/IIIa practice is maintained, with consideration for the lesion and patient type to be treated. Anti-platelet

Elsewhere in this edition of Cardio Update there are interesting reports of personal experience with the CYPHER Stent. IF we can harness this wealth of experience and if a consistency of technique along the lines described here can be achieved, the best possible patient outcomes will undoubtedly follow.



Parameters for evaluating drug-eluting stents

Marco A. Costa, MD, PhD, Assistant Professor of Medicine, Director of Research and Cardiovascular Image Core Laboratories, Division of Cardiology, University of Florida, Shands-Jacksonville

Only 3 years have passed since the first successful attempt to eliminate restenosis using sirolimus-eluting stents was reported, and the drug-eluting stent (DES) frenzy has already reached physicians, patients, hospital administrators, healthcare providers and device companies around the globe.

Much has been learned in this short period of time. Some of the initially very promising devices have already disappeared, while others are continuously being added to the list of DES under evaluation. After some early disappointing results and significant adjustments in dosing and coating technology, taxol-eluting stents are starting to show clinical efficacy. From its first clinical experience, sirolimus-eluting stents (SES) have demonstrated excellent efficacy, which has since been reproduced in clinical trials worldwide. The somewhat superior results of the combined E- & C-SIRIUS trials may have demonstrated the maturation of this technology. Operators used shorter post-dilatation balloons and direct stented 27% of the

patients, achieving a 4.0% TLR rate and a 5.1% in-lesion binary restenosis. This would support the concept that refinement in deployment techniques may further improve clinical outcomes.

In this rapidly evolving field, careful examination of the performance of these novel technologies is essential. To date, one can only make judgments on the performance of each DES individually, as head-to-head comparisons among different DES have not yet been performed. Previous stent trials have established late loss, binary restenosis and repeat revascularization rates, as major effectiveness endpoints. The proper understanding of their relative significance is crucial. Classic binary restenosis is based on a percentage diameter stenosis and is highly dependent on the reference vessel size and the “normal” angiographic appearance of the reference vessel. Based on its “binary” definition, a patient with 51% stenosis responses and clinical outcomes. It is clear that this is not necessarily true. In addition, due to statistical problems in small, early clinical studies, the value of binary restenosis is limited and should be interpreted with caution. Furthermore, angiographic restenosis is not necessarily linked to clinical outcomes, as many “restenotic” patients do not require repeat revascularization. Because of the limitations mentioned above, binary restenosis should be placed lower in the hierarchy of objective parameters that are used to assess the biological effects of the DES. However, it may still provide useful information for studies with large patient populations.

Intravascular ultrasound (IVUS) measurement of neointimal hyperplasia represents the most accurate assessment of the biological effects of DES. However, IVUS data are not available in all clinical trials. Therefore, in-stent late loss has been used as the angiographic surrogate for neointimal proliferation. The significance of this parameter was not fully appreciated in the era of mechanical prevention of restenosis, because there were essentially no differences in neointimal proliferation between bare metal stents (average of 1.0mm late loss). Late loss represents an essential objective endpoint to determine the anti-proliferative effect of DES, which is the ultimate goal of these devices. Failure to produce a dramatic reduction in late loss compared to bare metal stents will likely eliminate DES chances of becoming a clinically successful device. However, the best figure for late loss has generated some controversy. The short answer would be “the lower, the better”, as interventional cardiologists are expected to treat more and more small vessels with DES, and minimal changes in lumen diameter are amplified in this situation. It is nevertheless important to realize the limitations of both angiography and IVUS. One should not use angiographic late loss

as a surrogate for re-endothelialization. The resolution required to detect the microscopic endothelial cell monolayer by far exceeds the resolution of a plain luminographic method such as angiography. Even intravascular ultrasound does not have sufficient axial resolution to determine re-endothelialization. A recent histological post mortem analysis (Guagliumi, Virmani, *et al. Circulation*. 2003;107:1340) demonstrated the presence of intimal hyperplasia and > 80% endothelium coverage 16 months after the implantation of sirolimus-eluting stent. One of the major lessons from this elegant pathological case report was that zero angiographic late loss or lack of neointimal hyperplasia by IVUS does not necessarily mean true absence of neointimal hyperplasia or endothelialization. In fact, the occurrence of late loss or the presence of intimal hyperplasia by IVUS cannot be extrapolated as stent endothelialization. Such speculation is not based on scientific grounds and our previous experience with radiation therapy proves this assumption to be erroneous. The IVUS echolucent appearance of “neointimal hyperplasia” in some patients treated with radiation therapy was completely different from neointimal hyperplasia of bare metal stents (Kay *et al. Eur Heart J*. 2001; 22:1311-7). These patients had late loss on angiography, but endothelial cells were not found as part of the cellular components of the so called “black hole” phenomenon, which were identified only after histological examination (Kay *et al. Eur Heart J*. 2001; 22:1311-7).

Unfortunately, there is no technology available to answer the important issue of re-endothelialization after DES in humans. Therefore, indirect clinical surrogates such as MI and late thrombosis rates should be used. For instance, in RAVEL trial there were 0 (zero) SATs and no late thrombosis with virtually no late loss. Beyond “biological effectiveness”, clinical outcomes, particularly target lesion revascularization (TLR) and target vessel revascularization (TVR) are regarded as the true measure of clinical success from the patient’s perspective. An objective evidence of ischemia is now required before a study patient undergoes repeat revascularization. Clinically driven TLR rates attempt to eliminate the unnecessary repeat interventions, often driven by the visual appearance of the coronary obstruction, namely oculo-stenotic reflex. Other clinical end-points such as mortality and myocardial infarction rates are essential to determine the ultimate outcome and should not be forgotten. However these parameters have limited value for the assessment of restenosis. Whether DES will achieve the supreme goal of reducing mortality remains subject of speculation.

At this point in time, we can, and should, only enjoy the virtual elimination of restenosis.

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Diabetes and Restenosis:



treating coronary artery disease in diabetics is particularly challenging

*Kevin Beatt, Consultant Cardiologist
Hammersmith Hospital, London, UK*

Diabetic patients are recognised at being at high risks for vascular complications in a variety of situations.

In recent years there has been increasing recognition of the diversity of mechanisms responsible for prevalence of adverse events although there are still many aspects that are poorly understood.

Current data suggests that diabetes will continue to consume an increasing proportion of medical resources including resources for the treatment of coronary artery disease. They more often have a pattern of multi-vessel disease, more often present with acute coronary syndromes and have a less favourable outcome when compared to non-diabetics. Therefore, it is particularly appropriate to focus on this group when considering multi-vessel revascularisation in both the acute and chronic situations (figure 1).

Type II diabetics or Non-Insulin Dependent Diabetes Mellitus (NIDDM) represent the vast majority of diabetics and have a particularly diverse and complex series of interactions involved in the disease process. These can be divided into 4 areas: endothelial dysfunction, platelet and clotting abnormalities, lipid abnormalities and the consequences of hyperglycaemia, including protein and collagen modifications, oxidative stress and Protein Kinase C (PKC) activation.

All interact with each other to produce a cycle of disease progression which affects every organ system in the body. In the context of revascularisation the main consequences are thrombotic events as a result of increased platelet activity and restenosis related to the underlying arterial disease and a complex series of multiple interactions stimulated by vessel wall injury.

Platelet inhibitors, in particular abciximab and clopidogrel have been shown to be effective at modifying the abnormal platelet activity in diabetics and have made a significant impact at reducing thrombotic events in Percutaneous Coronary Intervention (PCI) in general, and PCI in diabetics in particular. Several trials have shown that abciximab and other GPIIb/IIIa inhibitors improve acute outcome and that this benefit may be sustained in the long term. In particular the combination of stents and GPIIb/IIIa inhibitors appears to be most effective⁽¹⁾.

Major Trials: Revascularisation in all corners

Trials conducted in either pre- or post- stent era - all corners

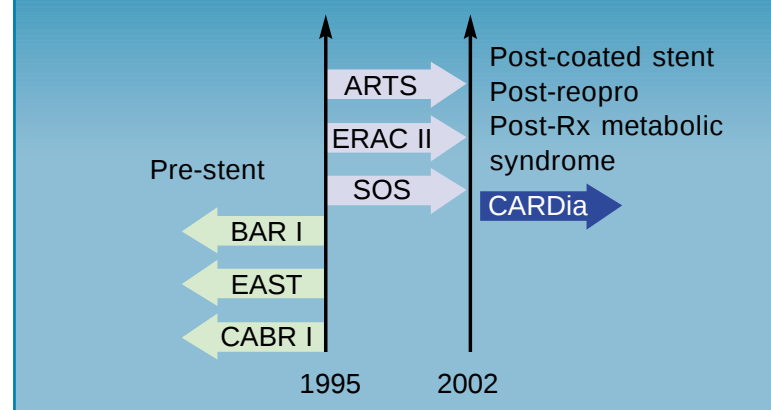


Figure 1

In the EPISTENT study, the composite of death, myocardial infarction, or target vessel revascularisation at 6 months was reduced from 25% to 13% (a 48% reduction, $p=0.005$) in diabetics treated with abciximab and stenting as opposed to stenting alone⁽²⁾. The combined benefit of stenting and abciximab in diabetics undergoing PCI persisted at 1-year follow-up. The death and MI rate was reduced from 16.3% to 6.8% at 1 year in diabetic patients treated with abciximab compared to placebo, with cardiac event rates reduced to the level seen in non-diabetic patients⁽³⁾.

Despite these improvements, the main limitation of PCI in diabetics continues to be the high rate of restenosis. In the stent era several studies demonstrated diabetes to be an independent risk factor for restenosis with restenosis rates following stent as high as 46% depending on lesion length and/or the diameter of the lumen immediately after the procedure. The STRESS (Stent Restenosis Study) and Benestent trials demonstrated that in selected patients, coronary stents reduce the risk of restenosis and subsequent clinical events^(4,5), a reduction most marked in diabetic patients⁽⁶⁾.

In a further study of 954 patients who underwent coronary artery stent implantation, insulin-requiring patients with diabetes had a two-fold increased risk of adverse cardiac events and repeat revascularisation vs. non-diabetic control ($p<0.01$).⁽⁷⁾

In April 2002 the Sirolimus-eluting coronary stent (CYPHER Stent, Cordis), obtained CE mark approval; the first drug-eluting stent specifically designed to overcome the problem of restenosis. Sirolimus actively inhibits neointimal proliferation via a dual mechanism of action that targets proliferating smooth muscle cells and reduces inflammatory activity. The latter effect may be particularly useful in diabetics who are subject to a chronic inflammatory state as exhibited by raised inflammatory indices and the presence of increased number of inflammatory cells in vascular lesions. The cytostatic action of sirolimus is unlike cytotoxic agents in that it does not kill cells, and allows natural re-endothelialisation of the vessel wall. 80% of the drug is steadily released from a polymer coating over 30 days, the crucial period for inhibiting neointimal hyperplasia.

From the First-in-Man feasibility studies, to the latest multi-centre, randomised, controlled clinical trials (RAVEL, SIRIUS, C-SIRIUS & E-SIRIUS), sirolimus-eluting stents have achieved unprecedented results. Both RAVEL⁽⁸⁾ and SIRIUS⁽⁹⁾ studies have reported specific data for the diabetic subset in each trial. In the RAVEL trial where there were relatively few diabetics recruited, ($n=44$) there was a dramatic difference in late loss at 6 months (0.08mm for the sirolimus group against 0.82mm for the bare metal stent group $p<0.0001$) now accepted as one of the most sensitive measurements for the prevention of neo-intimal proliferation. Data from the SIRIUS investigators supports the previous encouraging results from RAVEL. In a more complex patient population consisting of 26% diabetics ($n=279$), small vessels and complex lesions (Type B2 and C = 58.6%) the investigators reported consistent reductions in late loss and restenosis in the diabetic subgroup. On an absolute basis, the diabetic patient subset in SIRIUS showed an in-segment restenosis rate of 17.6% compared to 50.5% in the subset of patients treated with a conventional bare metal stent. This treatment effect was large compared to the non-diabetic group, where the absolute reduction was smaller - from 31.2% to 6.1% in the sirolimus treated group⁽⁹⁾ (figure 2).

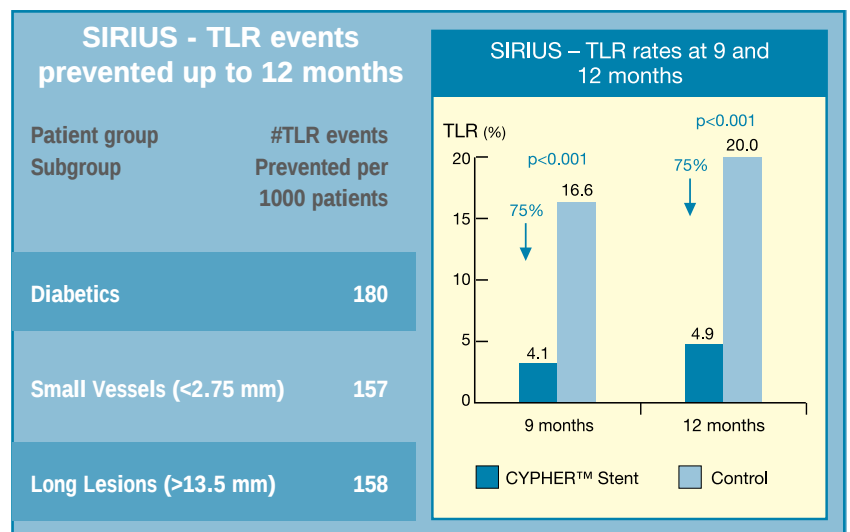


Figure 2

When reviewing efficacy by subgroup the data suggest that for every 100 diabetic patients treated with sirolimus-eluting coronary stents we may prevent 15.4 target lesion revascularisation events. These data will help to drive the economic argument in favour of drug-eluting stents. It is important to remember that in patients with diabetes, progression of the disease is common, and this applies whether patients are treated by angioplasty or surgery. It is imperative that the interventional cardiologist, even in the era of drug-eluting stents, are aware that the progression of the disease in diabetic patients is crucial, and requires vigorous long-term monitoring of the

diabetic status, with the use of lipid lowering therapy, optimal glycaemic and blood pressure control.

With recognised advances in the treatment of diabetics with angioplasty the question now arises: have these improvements reached the stage when PCI can challenge surgery as the optimal revascularisation strategy in multivessel diabetics?

To answer this question the CARDia (Coronary Artery Revascularisation in Diabetes) Trial (figure 3) has been set up in the United Kingdom and Ireland. It is an investigator initiated study and is the first prospective study designed specifically to address the hypothesis; optimal percutaneous coronary intervention (PCI) with stenting and abciximab is not inferior to up-to-date coronary artery bypass grafting (CABG) as a revascularisation strategy for diabetics with multi-vessel or complex single vessel coronary disease. The primary endpoint is the well established composite of death, non-fatal myocardial infarction (MI) and cerebrovascular accident (CVA) at one year. Twenty-one centres in the UK have begun to recruit 600 diabetic patients randomised to PCI or surgery and a further group randomised to a bare metal vs. sirolimus eluting (CYPHER) stents. (see figure 1). Recruitment is due to be completed in 2004.

In conclusion, the evidence base for coronary revascularisation in the diabetic patient continues to grow. Although the available clinical trial results and data from large scales post marketing surveillance registries such as e-CYPHER and RESEARCH are encouraging, it remains to be seen if drug-eluting stents, coupled with the use of adjunctive therapy such as glycoprotein IIb/IIIa inhibitors and optimal diabetic control will establish percutaneous coronary intervention as the treatment of choice for diabetics. As of now, the evidence suggests that treatment with sirolimus-eluting stents appears to convey added benefit to the diabetic patient and is the stent of choice in when undertaking PCI.

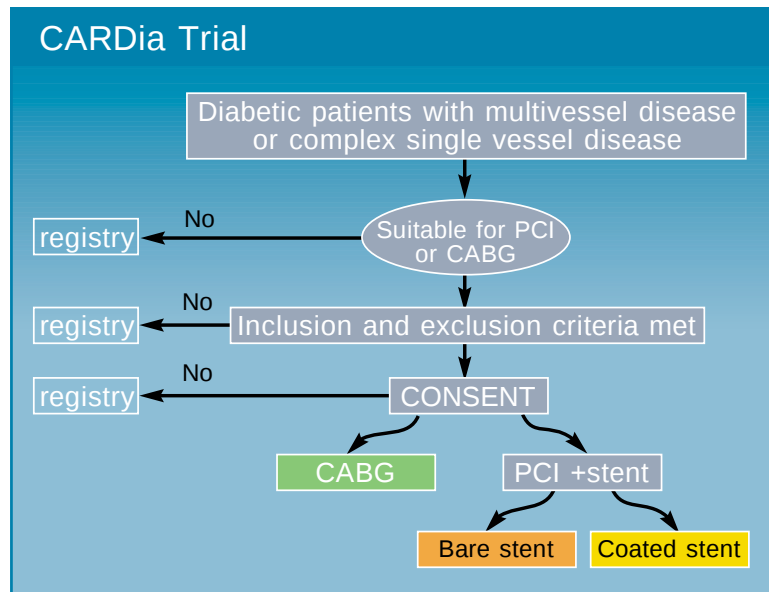


Figure 3

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AQUA T3 Kissing Balloon Technique in complex proximal LAD

Philippe Guyon, Centre Cardiologique du Nord, Saint Denis, France

Patient History

A 66 year old man, a previous smoker who had been treated for hypertension was admitted to hospital with a recent onset of limiting angina. After a short observation in a coronary care unit under medical treatment, a coronary angiogram was performed. This examination showed a single vessel disease, with a long, ostial, calcified and tied stenosis in the left anterior descending artery, including one bifurcation with the first diagonal branch (Figure A). Left ventriculography disclosed 76% ejection fraction without any regional wall motion abnormalities. A percutaneous transluminal revascularisation of the LAD was decided in first intention to treat.

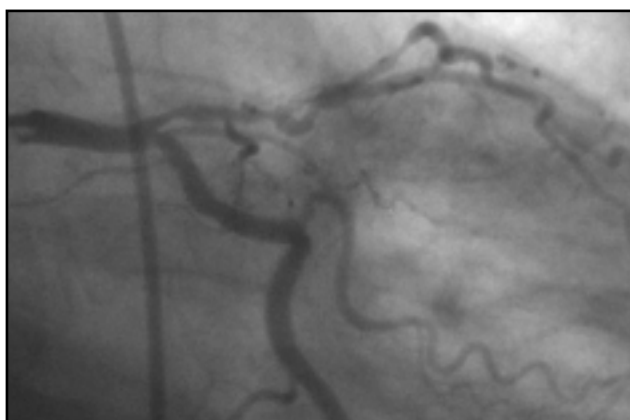


Figure A

PTCA procedure

Treatment with aspirin and clopidogrel was started and after 48 hours PTCA using the femoral approach was performed. To improve the guiding catheter support with a maximal lumen size, the new 6 French Cordis Vista Brite tip (XB curve) was chosen. Due to lesion calcifications, lesion length, and so as to avoid any damage at the diagonal ostium (bifurcated lesion) a rotational atherectomy was performed, following placement of the the rotaguide wire. In total 135 seconds and 10 runs with a 1.75 mm burr were necessary to open this LAD artery stenosis.



Figure B

However, the result was considered to be unsatisfactory (Figure B) and a second guidewire was placed in the second diagonal and the first Bx Hepacoat Stent (Cordis) was implanted in the distal segment of the LAD to cover the diagonal branch. So as to obtain good stent deployment, this stent was deployed at 12 atm for 40 seconds. The diagonal jailed guide wire was repositioned in the true lumen to cross the stent strut. A new AQUA T3 (Cordis) PTCA balloon (3.0 mm/20 mm length) was then positioned with no problems through the stent

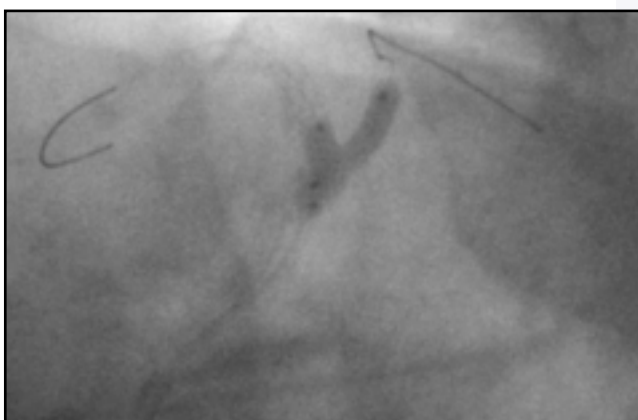


Figure C

AQUA T3

strut of the Bx Hepacoat Stent. In accordance with accepted bifurcation practice, a kissing balloon technique was performed using two AQUA T3 balloons (3.0 mm/20 mm length) across the 6 French Cordis guiding catheter lumen (Figure C). To improve the angiographic result and, due to an elastic recoil in the proximal LAD, a second Cordis Bx Hepacoat Stent was placed to cover the LAD ostium and over lap the first stent.

Although the angiographic results in the Circumflex branch was acceptable, a snow plough effect occurred (Figure D). Therefore, a guide wire was positioning in the Circumflex branch and a new kissing balloon was performed using two AquaT3 balloons (3.0 mm /20mm length)(Figure E). Low pressure (4 atm) was used in the two balloons. After a 20 seconds inflation time, a good angiographic result was achieved. Ten minutes later and after intracoronary nitrates injection, angiographic controls without any guide wires were performed to confirm the good angiographic result in all the coronary treated segments (Figure F).

In hospital follow-up

No complications occurred during the hospital phase, and sample blood showed CK 123 UI/l and troponin IC 1,2UI/l results 24 hours after the procedure (respectively the normal values in our institution

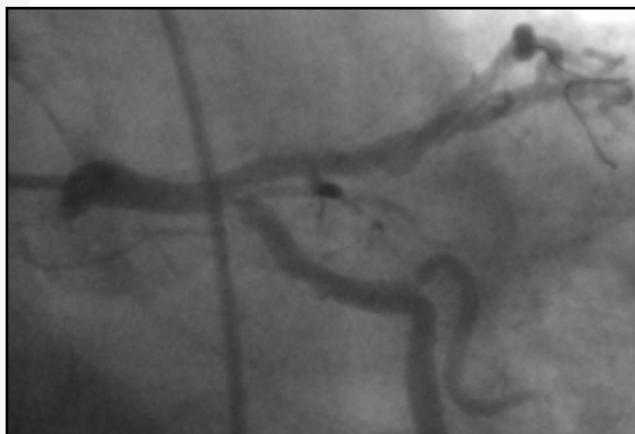


Figure D

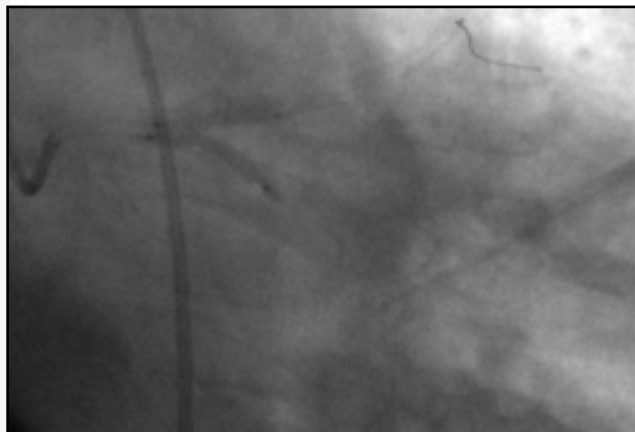


Figure E

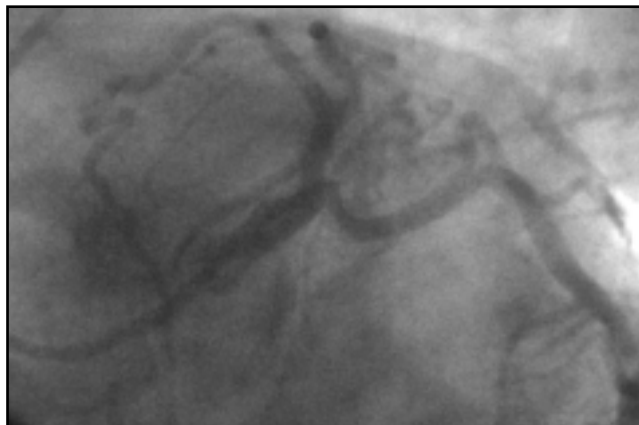


Figure F

were 232 UI/l and 0,1 UI/l for the CK and I C troponin). The patient was discharged from the hospital 2 days later on aspirin, clopidogrel, sopro and coversyl. At the 1-month outpatient visit, he was free of angina and symptoms.

Discussion:

The features and performance of PTCA balloons have considerably improved over the last 30 years. The inability to cross a coronary stenosis has become the exception.

One of the last remaining challenges for our good old balloons is the crossing of (non-open) struts of a stent implanted in a main vessel in order to reach the ostium of a collateral branch of a bifurcation lesion. This crossing through the struts of a stent requires the best available technologies: lowest profile and tapered tip (without being too fragile and hence prone to kinking), perfect crossability, absence of friction between the balloon and the stent struts, good pushability of the catheter shaft to transfer the force to the tip, and last but not least a robust design of the entire system in order to avoid any rupture or breaking loose of components which could have disastrous consequences.

In addition to the above essential criteria, interventional cardiologists always want more performance & flexibility in their practice, hence the requirement to realize the kissing balloon technique (in the treatment of bifurcation lesions) with the guiding catheter they mostly use, i.e. a 6 French.

This clinical case is a very good example of how the new AQUA T3 PTCA balloon from Cordis satisfies all of the above requirements. Based on new technological concepts, its design allows the operator to perform kissing balloon technique in 6F without any friction inside the guiding catheter nor loss of push efficiency. The crossability of the PTCA catheter is not compromised and enables the balloon to pass the most rigid and non-deformable object that can be found in a human coronary artery, i.e. the struts of a stent.

This case report reflects the clinical judgement of the authors in selecting AQUA T3 for these challenging cases. Prior to use, please refer to the Instructions for Use supplied with the device for indications, contraindications, side effects, recommended procedures, warnings and precautions.

New - Rapid Exchange System

Ease of Use...

- Rapid exchange sheaths
- Faster procedures
- Enhanced wire control

...Safety through Protection

- 8 nitinol struts providing optimal wall apposition
- Continuous perfusion with effective capture of microemboli
- Excellent visualisation and control of the procedure



Targeting the Platelet:

The evolving role of glycoprotein IIb/IIIa receptor antagonist therapy in the age of new percutaneous technologies



*Dr Elliot J Smith, Research Registrar,
London Chest Hospital UK*

*Prof Martin T Rothman, Professor of Interventional Cardiology,
Director of Cardiac Research & Development,
Barts & The London NHS Trust,
The London Chest Hospital UK*

Introduction

Interventional practice in Cardiology continues to evolve at breakneck pace, with new technologies emerging into the market place, competing to take their place in the percutaneous armoury. With novel stent materials, drugs for elution, and expansion in the fields of thrombectomy and distal protection, we feel empowered to take a mechanical approach to almost any pattern of disease that either stable or acute coronary syndromes can throw our way.

To allow this revolution in PCI to occur, an equally rapid advance in our understanding of the dynamic behaviour of coronary plaque and in particular endothelial responses to injury has needed to take place. We continue to redefine our major biological enemies, and search out new therapeutic targets against them. Public enemy number one however, remains the platelet, and the glycoprotein (GP) IIb/IIIa receptor complex on its surface is one of the most clinically important targets. GP IIb/IIIa receptor antagonists (GPRAs) have made an enormous impact upon interventional practice, with clear reductions in major adverse events following percutaneous intervention (PCI) across a spectrum of indications⁽¹⁻⁴⁾. With this our understanding of platelet behaviour has also evolved as we continually learn that the impact of these agents goes well beyond procedural anticoagulation.

Here we examine the current role of GPRA therapy in clinical practice, in the setting of elective and emergent PCI. We readdress where the therapy fits in alongside new PCI technologies, and question whether an improved understanding of platelet behaviour could allow us to become more selective in prescribing this therapy, or if it should be the first name on the team sheet at the outset of any coronary intervention.

The Target - the GPIIb/IIIa complex

The IIb/IIIa receptor complex is the most abundant platelet membrane glycoprotein and is further upregulated on platelet stimulation. The resting protein undergoes conformational change allowing binding of fibrinogen which in turn allows cross linking of platelets and formation of aggregates. This process is the final common pathway of platelet aggregation leading to thrombus formation, and as such GPRAs are potent anticoagulants when compared with other anti-platelet therapies such as aspirin and thienopyridines.

Current place for GpIIb/IIIa receptor antagonists - what is high risk?

There is no debate that GPRAs have a proven benefit in high-risk PCI. In the setting of PCI for non-ST-elevation acute coronary syndromes (NSTEMI/ACS), significantly reduced event rates have been demonstrated with upstream GPRA therapy using either abciximab or tirofiban, with the greatest benefit seen in patients with elevation of cardiac troponins^(5,6). While there is also some evidence to support the role of GPRA therapy as purely medical treatment for NSTEMI/ACS, the benefit is predominantly confined to those who then undergo a PCI⁽⁷⁾, and indeed GPRAs are probably detrimental in low risk NSTEMI/ACS patients not undergoing intervention⁽⁸⁾. In addition, there is strong data supporting the role of GPRA therapy in ST elevation Myocardial Infarction (STEMI), facilitating primary PCI^(9,10), again with the greatest benefit for

those treated as early as possible prior to intervention⁽¹¹⁾.

Within non-ACS PCI cases, high-risk subgroups deriving most benefit from GPRAs can also be defined. While the EPISTENT investigators concluded that abciximab has a role in all stenting procedures, major adverse cardiac event (MACE) reductions were most striking in the diabetic subgroup. Importantly diabetics had a 50% reduction in target vessel revascularization (TVR) at 6 months (16.6% stent only vs. 8% stent + abciximab, $p=0.021$) not seen in non-diabetics⁽¹²⁾. This led to speculation that abciximab directly influences the restenotic process. It is uncertain whether cross reactivity of abciximab with other integrins such as the $\alpha_V \beta_3$ (vitronectin) receptor and the MAC-1 (CD11b/CD18) leucocyte receptor may be mechanisms behind this effect. While experimental models have demonstrated that inhibition of $\alpha_V \beta_3$ can reduce intimal hyperplasia and vascular smooth muscle cell migration⁽¹³⁾, other clinical studies of abciximab in the reduction of restenosis have been less supportive. The ERASER study⁽¹⁴⁾ found no such reduction in in-stent restenosis in a predominantly non-diabetic population. Nevertheless the overall EPISTENT MACE reduction in diabetics is impressive, and has established this therapy with most operators for all diabetic PCI.

Complex lesions, vein grafts and distal protection

Angiographic lesion morphology can also assist selection of patients for GPRA therapy. Combined analysis of EPILOG and EPISTENT suggested that abciximab confers additive long-term benefit in terms of death, MI and TVR when stenting complex lesions (including long, calcified, restenotic, ostial or chronically occluded vessels, bifurcations, multivessel PCI, and vein grafts)⁽¹⁵⁾. The issue of saphenous vein graft (SVG) PCI taken in isolation remains more difficult. Degenerate graft intervention carries a high risk of distal embolisation resulting in myocardial damage (in-hospital non-Q-MI with CKMB elevation 16-18%) and adverse long term event rates (one-year mortality 6-11%, TLR 16-24%)⁽¹⁶⁾, and it would seem intuitive to employ GPRA therapy to address this. Indeed many operators advocate intracoronary GPRA use in SVGs with high thrombus burden, and case series have been supportive of intravenous GPRA infusion followed by delayed PCI in this setting⁽¹⁷⁾. However, pooled analysis of 30-day outcome from EPIC, EPILOG, EPISTENT, IMPACT II and PURSUIT⁽¹⁸⁾ demonstrated no improvement in outcome (6-month Death/MI/revascularisation 39.4% with abciximab vs. 32.7% placebo, $p=0.07$), evidence that an aggressive anti-platelet approach cannot deal with embolisation of friable plaque debris. While distal protection and thrombectomy devices are now revolutionising this field, the case for GPRAs is no clearer. The SAFER study⁽¹⁹⁾ demonstrated important reductions in MACE using the GuardWire Distal Balloon Protection System (Percuturge Corporation) for SVG PCI. Interestingly, the 61% of patients receiving GPRA therapy had a higher overall MACE (Table 1), possibly reflecting operator selection of GPRAs for higher risk cases.

However, while with GPRA therapy there was a significant MACE reduction using distal protection (10.7% vs. 19.4%, $p=0.008$), this was not the case in those who did not receive a GPRA (8% vs. 11.5%, $p=0.34$). While this may simply indicate that lower risk lesions do not require distal protection, it is also possible to argue that adjuvant GPRA therapy is necessary to derive benefit from the device. In order to truly unravel this issue a randomised trial comparing distal protection with and without GPRA therapy would be needed. With no such study forthcoming, at present the evidence suggests that combined GPRA and distal protection are at least compatible and probably complementary.

Do we need GPRAs in the drug-eluting stent era?

The anti-platelet decision making process has now been further complicated by the advent of drug-eluting stents (DES) in the prevention of in-stent restenosis. As we struggle to assimilate the expanding body of trial data to select those who benefit most from these already expensive technologies, we are simultaneously faced with a dilemma in choosing optimal anti-platelet therapy in these cases. The greatest concern has been the perceived risk of late stent thrombosis, necessitating the need for prolonged thienopyridine (clopidogrel) therapy. Thus far the data has been reassuring as studies to date have not demonstrated an excess of late thrombotic events despite clopidogrel durations as short as 3 months. In SIRIUS (Sirolimus-Eluting Stent in *De Novo* Coronary Lesions Trial) the rate of stent thrombosis out to 12 months was 0.4% DES vs. 0.8% bare stent ($p=NS$) (data presented at the American College of Cardiology Scientific Sessions 2003). However the role of GPRAs has been less clear. The rationale for DES is reduction in neointimal hyperplasia and in turn clinical restenosis (i.e. target vessel revascularisation). The role of GPRA therapy is in reduction of platelet aggregation, embolisation, peri-procedural thrombotic events, and in the case of abciximab reduction in periprocedural MI, and longer-term mortality. These mechanisms are not mutually exclusive. As progressive studies randomise patients with more complex lesions, experience of combined DES and GPRA therapy is also increasing. GPRA use in SIRIUS was approximately 60% in each arm, compared with 10% in RAVEL (**R**andomized study with the sirolimus-eluting **VE**LOCITY balloon-expandable stent in the treatment of patients with *de novo* native coronary artery **L**esions)⁽²⁰⁾ which randomised patients with shorter less complex lesions using a single stent (Table 1). In SIRIUS the 9-month rate of MI was similar in both the bare stent and sirolimus groups (3.4% vs. 3.0% $p=NS$) suggesting a similar GPRA effect irrespective of drug elution.

Less is known about the role of DES in the setting of acute coronary syndromes. Although the sirolimus studies have included a large proportion of unstable patients, subjects with angiographically evident thrombus or recent MI were excluded. It is recognised that anti-proliferative stent coatings may impair healing and endothelialisation following implantation⁽²¹⁾. It is therefore possible to speculate that DES implantation

in a culprit ruptured thrombotic lesion could be disadvantageous, as the usually maladaptive restenotic process may in part be necessary as a healing response to restore plaque stability. Furthermore, sirolimus has been demonstrated to increase platelet aggregation in renal transplant patients⁽²²⁾, perhaps suggesting an extended role for anti-platelet therapy. In fact data from the RESEARCH registry (Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital)⁽²³⁾ suggest that DES can be safely implanted during ACS, with no difference in 30-day MACE, compared with a cohort treated with bare stents (6.1% DES vs. 6.6% control). Interestingly GPRA use was significantly lower in the DES group than the control group (Table 1), (27% vs. 42%, $p < 0.01$) despite more primary angioplasties and bifurcation lesions in the DES group, and equal numbers of diabetic and unstable patients. This early non-randomised data suggests that there is no need for extra caution when DES meets ruptured plaque. However it is difficult to know whether event rates might be further reduced with increased GPRA use in both groups, as might have been expected in this high-risk population.

Low Risk - Can we get away without a GPRA?

More difficult still is the question of treating low-risk lesions and patients. Data is now emerging to tackle this issue by readdressing standard adjunctive PCI anti-thrombin (bolus unfractionated heparin) and anti-platelet (thienopyridine) therapies. Kastrati *et al* have recently demonstrated that increasing the dose of thienopyridine (clopidogrel) loading may obviate the need for GPRA therapy in the setting of low-risk PCI (data presented at the American College of Cardiology 2003 Scientific Sessions). Loading with 600mg of clopidogrel was followed by randomisation to abciximab or placebo. There was no significant difference in 30-day death, MI, or TVR between the two groups, but transfusion requirements were significantly elevated in the abciximab group.

An alternative approach has been to challenge the universal and relatively unopposed status of unfractionated heparin in PCI. The 'Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events' (REPLACE 2) study⁽²⁴⁾ randomised low-risk subjects patients (ACS patients were excluded) to the alternative thrombin inhibitor bivalirudin (Angiomax) with provisional GPRA therapy, or combined unfractionated heparin and elective GPRA therapy (either with abciximab or eptifibatide). Bivalirudin was non-inferior to combination heparin/GPRA, with a non-significant trend towards benefit in the bivalirudin arm (composite primary endpoint 10% heparin/ GPRA vs. 9.2% bivalirudin, $p = \text{NS}$). Importantly however, this trend was driven by a reduction in major bleeding in the bivalirudin group. Exclusion of

in-hospital major bleeding from the composite endpoint (leaving death/MI/ urgent revascularisation), reversed this trend towards greater efficacy with heparin/GPRA (7.1% vs. 7.6% respectively), as a result of a non-significant excess of post procedure non-Q-wave MI in the bivalirudin group. Thus a slight reduction of efficacy appeared to be balanced by an increase in safety. This encapsulates the current state of play for GPRA therapy in low-risk cases. The benefit is likely to be marginal, and must be weighed against the risk of bleeding in low-risk patients. What these recent studies do demonstrate is that improvements in other anti-platelet and anti-thrombotic therapies may provide the answer to choosing the optimal treatment for this group.

Future directions - improving selection and defining new therapeutic targets

There remains a problem however in that low-risk patients represent the minority of 'real world' clinical practice. The challenge therefore is to further improve patient selection for GPRA therapy, which remains expensive and not without risk. Current research in platelet biology may go some way towards assisting patient selection for GPRAs in the future. Genotyping might offer one potential future method of risk stratification in elective cases. For example heterozygosity of the GpIIb PLA (PLA1/PLA2) platelet polymorphism was associated with an increased responsiveness to abciximab in one in vitro study of platelets from healthy individuals⁽²⁵⁾ although subsequent studies produced conflicting results^(26,27). In addition, progress in our understanding of the link between platelet activation and inflammation has lead to encouraging results in improving selection of ACS patients for GPRA therapy. CD40 ligand (CD40L) is a pro-inflammatory cytokine that provides a measure of platelet activation.

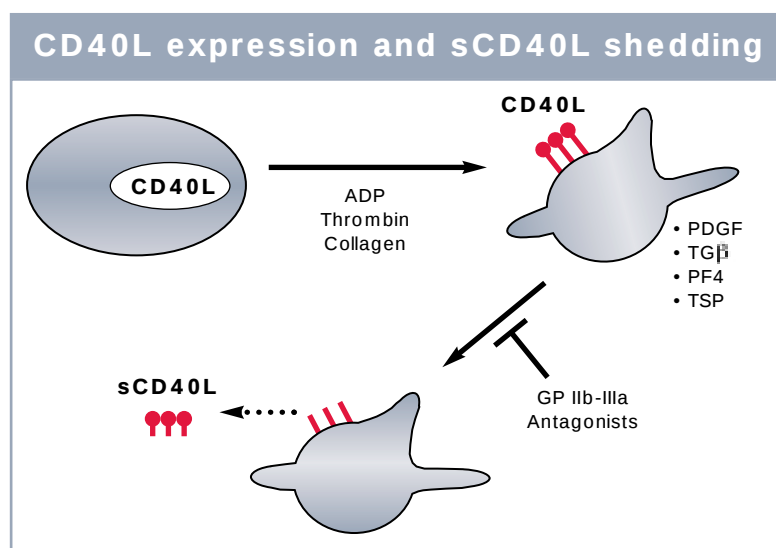


Figure 1 CD40L is translocated to the platelet surface when platelets are activated (e.g. by adenosine diphosphate (ADP), thrombin, or collagen). The surface-expressed CD40L is cleaved and shed from the platelet surface as sCD40L from platelets. Expression of CD40L coincides with release of platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ), platelet factor 4 (PF4) and thrombospondin (TSP) from alpha granules.

(From André P *et al* *Circulation* 2002 (28))

Originally identified on immune cells, up to 95% of circulating CD40L exists in platelets, and is translocated to the surface upon activation (Figure 1).

Furthermore its soluble cleavage product sCD40L, which is released into the circulation following surface expression, itself has pro-inflammatory and prothrombotic properties⁽²⁸⁾. Recent data from the CAPTURE investigators demonstrated that baseline elevation of sCD40L in NSTEMI-ACS patients undergoing PCI was associated with angiographic thrombus burden, was an independent predictor of outcome, and most importantly identified patients that derived benefit from abciximab independently of troponin release⁽²⁹⁾. Thus the deciding factor before administering a GPRA for ACS patients in future may become a rapid sCD40L assay. The next logical step may then be the development of novel therapeutic agents directed against this and other platelet targets. The inevitable problem we will face however is that in the presence of already established treatments (aspirin, clopidogrel, and GPRAs

themselves) it will become increasingly difficult to discern which combinations of platelet inhibition are necessary in which situations.

Conclusions

The rapid development of new mechanical technologies is radically altering the way we approach PCI such that we are able to treat an increasingly high-risk population. What is clear however is that these technologies simultaneously necessitate selection of appropriate anti-platelet strategies. For the foreseeable future, GPRA therapy is likely to remain a vital adjunct to event reduction in large proportion of PCI procedures irrespective of the technology employed. However, while the mechanical approach will always necessitate a simultaneous anti-platelet strategy, studies in platelet biology and genetics may enable improved patient selection in the short term. Ultimately novel anti-platelet targets may lead to the development of superior therapies, though it is unlikely that GPRAs will be rendered completely obsolete.

Table 1 - Use of Glycoprotein IIb/IIIa antagonists with new technologies

TRIAL	Patients	Device	GpIIb/IIIa use treatment arm (%)	GpIIb/IIIa use control arm (%)	P value	Comments
SAFER	Saphenous vein graft PCI	GuardWire distal protection	60%	62.5%	NS	Benefit of the device confined to patients receiving GPRA
RAVEL	De novo, low risk lesions	Sirolimus Eluting Cypher Stent	10.1%	9.5%	NS	
SIRIUS	De novo lesions, 2.5-3.5mm diameter, 15-30mm long	Sirolimus Eluting Cypher stent	60.4%	59.2%	NS	Increased GPRA use with higher risk population
RESEARCH	ACS patients (registry)	Sirolimus Eluting Cypher stent	27%	42%	P< 0.01	Equivalent 30 day MACE despite low usage in sirolimus group. Long term follow up needed

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Executive Editor: Ingvild Van Petegem, Cordis Cardiology Europe

Editorial and Production Management: David Barrow

Editorial Assistant: Rachel Dixon

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Correspondence: Comments, corrections, letters to the editor and suggestions for articles to be sent to the Executive Editor, Cardio Update, Cordis, A Johnson & Johnson company, Waterloo Office Park, Drève Richelle 161 H, 1410 Waterloo, Belgium via telephone (+32 2 352 1411) or fax (+ 32 2 352 1553).

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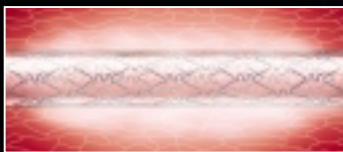
Date	Conference	Location	Website
10-13 October	14th Great Wall International Congress of Cardiology	Beijing, China	heart@gw-icc.org
10-11 October	Annual meeting of the Irish Cardiac Society	Dublin, Ireland	peterkearney@eircom.net
11-14 October	Turkish Congress of Cardiology	Antalya, Turkey	tkd@ixir.com
19-22 October	5th International Congress on Coronary Artery Disease	Florence, Italy	www.kenes.com/CAD5
15-18 October	Annual Congress of the Spanish National Society of Cardiology	Sevilla, Spain	sec@secardiologia.es
9-11 November	AHA - American Heart Association	Orlando, USA	sessions@heart.org
6-9 December	5th Frontiers in Interventional Cardiology	Tel Aviv, Israel	www.kenes.com

2004

12-14 January	13th Singapore Live	Singapore	www.singlivecourse.com
21-24 January	Annual Meeting of the French Society of Cardiology	Paris, France	contact@cardio-sfc.org
29-31 January	23rd Annual Scientific Meeting of the Belgian Society of Cardiology	Brussels, Belgium	Lisa.hobbs@bvc-sbc.be
12-14 February	Joint International Meeting (JIM)	Rome, Italy	www.jim-vascular.com
7-10 March	American College of Cardiology (ACC)	New Orleans, USA	www.acc.org
22-26 March	The 19th Annual International Cardiology 2004: The International Symposium	Snowmass Village, USA	education@promedica-intl.com
2-4 April	3rd European Conference on Management of Coronary Heart Disease	Nice, France	cardiology@markallengroup.com
15-17 April	Annual Meeting of the German Cardiac Society	Mannheim, Germany	info@dgkardio.de
5-7 May	Swedish Cardiovascular Spring Meeting	Göteborg, Sweden	atj@cardio.ks.se
14-15 May	Nordic Congress of Cardiology	Nyborg, Denmark	dcs@dadlnet.dk
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