Percutaneous Coronary Intervention : Current status

University Hospitals of Leicester UK
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My viewpoint

- **Balloon angioplasty is of historic interest only, due to the need for excess repeat procedures compared to CABG**
- **Bare metal stents made percutaneous intervention safer but patients still require re-intervention more frequently, the difference between BMS and surgery being 12-15% as a result of in-stent intimal hyperplasia**
- **PCI is now the dominant therapy for coronary artery disease (2004 : 63 000 PCIs versus 25 000 CABGs)**
- **Increased operator skill, newer equipment and the development of new techniques has radically changed the profile of patients undergoing PCI, with those normally receiving surgery (eg left main stem disease) now candidates for the percutaneous approach**
- **Older patients with more extensive and complex disease are now routinely treated with PCI**
- **Drug eluting stents have been proven to be beneficial in randomised controlled trials versus bare metal stents**
- **Drug Eluting Stents have allowed the good results of coronary intervention to be maintained with recurrence rates now < 5% for straightforward cases and <10% in high restenosis risk patients**
- **New stent programmes with new drugs and new platforms are being developed**
- **The acute, medium and longer term results of PCI with DES are now robust enough to challenge those of CABG**

The PCI rate grows at >10% pa, is the dominant therapy for treating patients with coronary artery disease and with the advent of Drug Eluting Stents may result in CABG becoming a niche therapy

Personal view :

As someone who has been involved in interventional cardiology from its inception, it is clear to me that the safety and longer term outcomes in patients treated with percutaneously coronary intervention has changed dramatically over the years. Balloon angioplasty was a start but was a very limited procedure. It taught how not to secure safe and robust longer term outcomes. Injury to the vessel wall led to clinical events that were dramatic when occurring in the immediate post-PCI period, with emergency surgery required on a regular basis and it was frequently depressing when the injury as part of the "response-to injury paradigm" of PCI led to recurrence rates of around 30% due the triple whammy of vessel recoil, late vessel remodelling and intimal cell hyperplastic scar formation.

Bare metal stents had an immediate impact reducing dramatically the need for urgent surgery through mechanical support of the disrupted inner vessel wall and by dealing with the first two factors that cause recurrence (recoil and vessel remodelling)

As a result recurrence rates fell to around 15% (with higher rates up to 40% for diabetics, those with small reference diameters and those with longer lesions). Recurrence after bare metal stenting is extremely difficult to treat. The tissue is non-

compressible, and use of cutting balloons, vascular-brachytherapy and debulking techniques did not lead to subsequent improved outcomes.
Drug–Eluting stents have moved the ability to provide improved outcomes for patients on a further quantum forward. The evidence based data for the angiographic and clinical outcomes following DES is robust, repeatable, affects all patient types and appears without significant downsides. Why would one ever not want to treat a patient with a DES when the risk of recurrence is now ~5%, thus producing good outcome without the need for a major surgical procedure, with its attendant complications? It is true that not all the progress in PCI is down to DES : operator skills, adjunctive pharmacotherapy, improved stents have all contributed to the acute success of the procedure. What DES do is provide a better guarantee that the achieved acute result is maintained so reducing the need for a repeat procedure. It is certainly true that stent geometry has improved and that restenosis rates with bare metal stents have fallen also, as the improvements in stent design role out to clinical practice . However bare metal stents have I believe reached their optimum: cobalt chromium, thin struts, easily deliverable are all factors believed buy the cognoscenti to be the best that you can achieve. The ENDEAVOR II trial compared (some would say a slightly less efficacy) DES system with a bare metal stent (The DRIVER) which as all these optimal characteristics and is consequently the BMS market leader. Target lesion revascularisation rates were highly significantly reduced in the DES (4.6% versus 11.8% $p<0.001$).

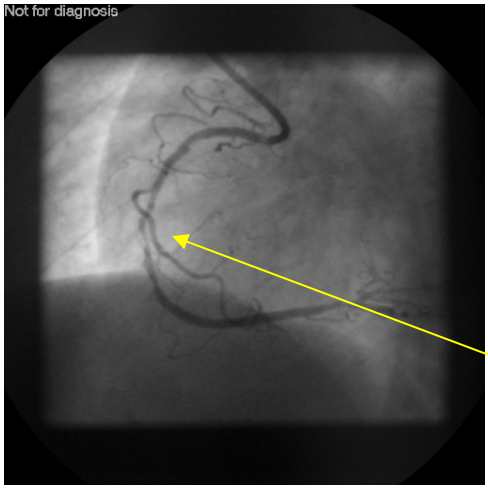
The previous recommendations N.I.C.E were apt and appropriate although limited since restenosis is reduced with DES in all patients groups. Diabetics were not included as a separate group although there is now abundant data to suggest that DES should be mandatory in diabetics. Good examples of the waste of money, patient pain and inconvenience are shown in the following examples.

Case 1 Female Long lesion in the RCA 2 :
1a) Stents placed as indicated and in accordance with previous N.I.C.E guidelines.
Stent 1- 2.75 x28 mm TAXUS DES. STENT 2- 3.0 x 8 mm DRIVER BMS.

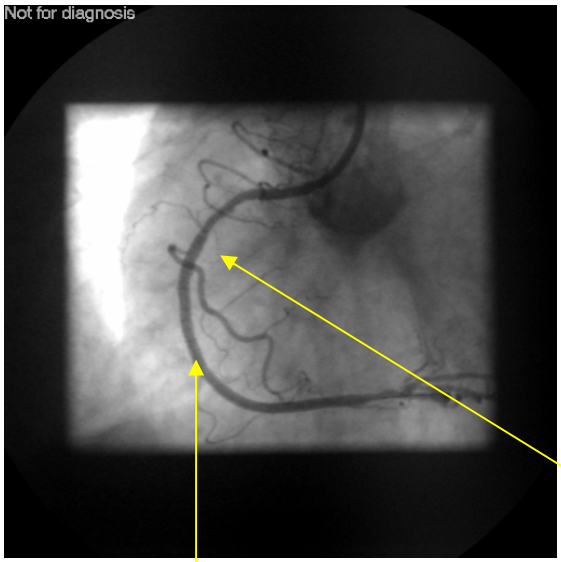
1b) Follow up angiogram following recurrence of symptoms at 5 months shows restenosis in the “large, non-N.I.C.E lesion BMS but no restenosis in the long higher risk (small, long lesion TAXUS). Following N.I.C.E guidelines did not prevent the need for a repat procedure in this patient
Case 2 Male High risk LMS disease
2a) DES stent in main vessel but BMS (3.0mm x 15 mm in the LAD (arrow 1) August 2005. Readmitted as emergency December 18 th 2005 with new ECG changes and evidence of a small heart attack
2b) Angiogram shows severe restenosis in BMS, but none in DES

If these cases are too anecdotal I have included a recent review of the evidence base written by myself for a chapter in a to-be-published textbook. This reviews all the trials and includes all the data there is even for the subgroups. For me DES have revolutionised the treatment of PCI and I would recommend that N.I.C.E encourage evidence based medicine by expanding the use of DES, and importantly somehow ensure that the PCT implement their guidelines.

The statements made at the beginning of this piece are based on the subsequently outlined review of the evidence base. To not expand the use of DES is denying patients proven therapy.

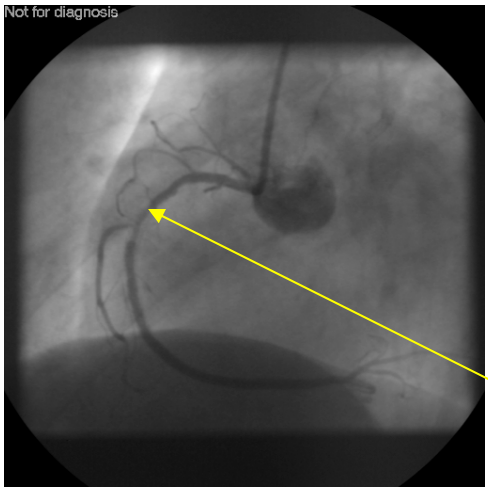


Initial Angiogram showing severe stenosis in Right Coronary Artery



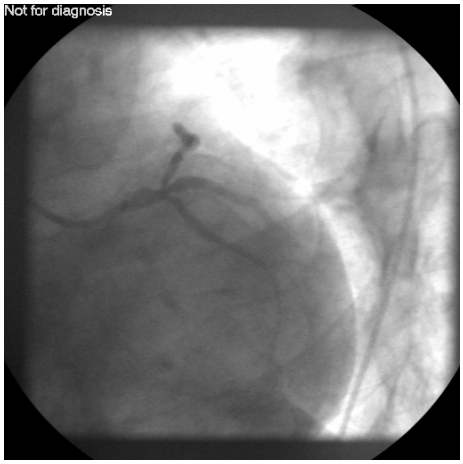
3x 8 mm BMS

2.75 x 28 mm TAXUS stent (DES)

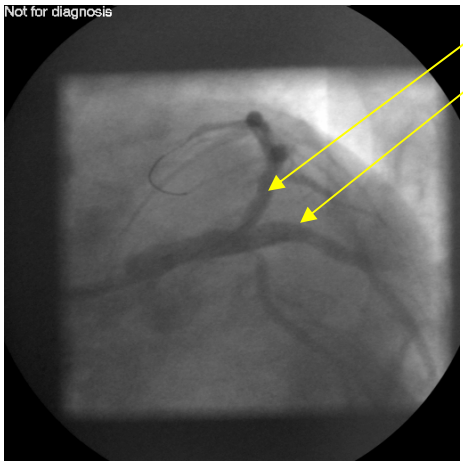


Severe In stent restenosis in short large BMS No restenosis in longer smaller TAXUS

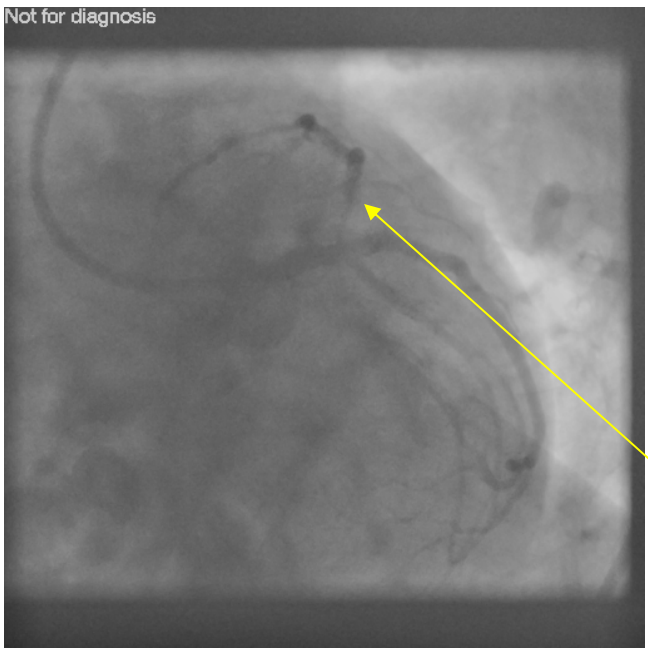
CASE 1 Restenosis in BMS



Initial Angiogram



2 a) Post PCI



2b) Severe In stent restenosis in BMS

Case 2 Restenosis in BMS Urgent admission

Trials that have changed PCI practice
University Hospitals of Leicester
September 2005

Background

Percutaneous coronary intervention (PCI) has become the dominant therapy for treating patients with ischaemia due to obstructive coronary artery disease. In 2004 63,000 UK patients were treated with PCI and 26,000 with surgery. In other European countries the ratio rises to 8 PCIs-1 CABG patient. Such a major change in patient care involving a shift from one therapeutic modality to another over a relatively short time (5-10 years) could only have occurred as a result of a number of reasons. Firstly there needed to be the drive to perform PCI by enthusiastic operators. Simultaneously techniques and equipment evolved to make the procedure safer and clinically effective and an understanding of the potential and the limitations of the procedure evolved. Finally all of this had to be underpinned by an evidence base consisting of randomised controlled trials (RCT) and registry data. While RCTs remain the corner-stone of evidence based treatment they have the limitations of (over) patient selection and applicability of results to the real world, which often includes patients excluded form the RCTs. This review will highlight the key evidence that has led to the opening statement in this article.

PCI (balloons and bare metal stents) versus CABG

Coronary angioplasty has evolved rapidly. During the early 1990s it was seen as a treatment for predominantly single vessel disease, with coronary surgery for all else. Although studies comparing balloon angioplasty with surgery indicated no difference in myocardial infarction or death, the need for re-vascularisation was about 5% pa with surgery but 30% for balloon angioplasty (1), due to a number of factors including vessel recoil, late remodelling (where the vessel gets smaller after vessel wall injury) and injury-induced scar tissue formation.
Stents arose from the need to reduce acute balloon angioplasty induced adverse outcomes (due to intimal dissection). As a bonus stents also reduced recoil and late negative re-modelling with a halving of the need for a repeat procedure to about 15%-20%, but with higher rates in certain sub-groups (diabetics and those with small reference diameters or longer lesions (2,3)) Figure 1. The benefit of safer acute outcomes and overall reduction in need for repeat procedures made stenting the standard of care, with >90% PCI patients now receiving stents.

Despite advantages over balloon angioplasty, stenting still resulted in a excess need for repeat intervention compared to multi-vessel stenting with coronary surgery: ARTS 1, SOS and ERACI studies (4-6) indicated a difference in re-intervention between 12%-15% at 6 months in the stent arm. A meta-analysis comparing PCI and surgery in multi-vessel disease (Mercado et al J Thoracic Cardiovasc. Surg.) suggests no difference in death, AMI, CVA (PCI-8.7% Surgery-9.1 HR=0.95 (95% ci 0.74-1.2). These studies were not trials of simple, single vessel disease-in ARTS-1 for example there was a mean 2.9 stents/patient and 2.7 grafts/patient-(93% with at least one internal mammary artery). Residual in-stent scar tissue formation remained a clinical limitation of stenting compared to surgery. The concept of delivering drugs from stents at local high concentrations to prevent within tissue in-growth evolved from local balloon drug delivery. Failure to retain drug at the site and inadequate local dose concentration limited the applicability of such balloons. Delivering drugs locally on stents became the goal. A number of drugs to limit the restenotic process have been delivered either by altering the surface of the stent or by utilising a polymer to load the drug.

Drug eluting stents versus bare metal stents

I. SIROLIMUS-Eluting-STENTS (SES)

Sirolimus (Rapamycin) is the metabolic substrate of the fungus streptomyces hygroscopicus. Loaded onto stents at a dose of 180 µg it inhibits cell proliferation after vessel wall injury by binding to a receptor protein (FKBP12)-the rapamycin/FKB12 complex then binds to mTOR (Mammalian Target Of Rapamycin), preventing its interaction with target proteins, such as regulatory tumour suppressor genes including P27, which are important in signalling pathways leading to cell proliferation.

The first Rapamycin trial (**RAVEL** (7)), while demonstrating efficacy was criticised for the simple nature of the lesions tested, although inclusion of such patients was appropriate for a "proof of principle" trial. There were also concerns about "excess effectiveness" with late loss ("angiographic difference in minimal lumen diameter from immediate post stenting to follow-up in mm") approaching 0 mm suggesting complete inhibition of tissue growth with no stent coverage. The US–based **SIRIUS** trial (8) included more complex lesions and late loss and binary restenosis rate were greater. SIRIUS trial patients with small reference vessel diameters (mean 2.3mm) had higher target lesion revascularisation (TLR) -7.3% compared to 1.8% in 3.0mm vessels, and a higher need for revascularisation in diabetics (TLR 7.2%). The TLR rate of 13.9% in insulin-dependant diabetics was particularly worrying although the numbers were small. The **NEW-SIRIUS** data addressed some of these issues. NEW-SIRIUS represents the pooled results of 2 trials **C-SIRIUS** (9) (the Canadian study of 100 patients) and **E-SIRIUS** (10) (the European study of 352 patients). The trials design was identical. Primary end-point was 8-month angiographic outcome with 9-month clinical follow-up. The late-loss was 0.18 mm in-stent and 0.17 mm outside the stent indicating the so-called "edge effect" in the SIRIUS trial had been overcome (presumably by a change in technique). The option of direct stenting in NEW-SIRIUS, (30% incidence) also reduced balloon injury. TLR for NEW-SIRIUS was 4% versus control 20.3%. The small-reference vessel subgroups results are better than in SIRIUS with in-stent restenosis rates of 3.8% for vessels with mean size 2.2 mm. TLR rates in diabetics was still around 7% however. A list of the "CYPHER Trials" and their outcomes are shown in Table 1.

Concerns have been raised that polymer and/or drug could be removed during direct stenting (which accounts for about 30% of all percutaneous coronary interventional procedures) potentially affecting DES efficacy. In NEW-SIRIUS this was found not to be the case with in-lesion restenosis in the pre-dilatation Sirolimus stenting group 7% versus 2.4% in the direct Sirolimus stent group. Other recently presented data includes longer term follow-up, with the RAVEL results maintained to 3 years and the First-in-Man (n=45) patients having little loss in any of the measures of initial success out to 4 years.

Concerning diabetics, Sabaté recently presented the "**DIABETES**" study. Angiographic restenosis in the Sirolimus arm was 7.7%, with target lesion revascularisation 7.5% and overall MACE 11.3%-all highly significantly improved (p=0.0001) over the control bare metal stented patients (11).

II. PACLITAXEL-ELUTING-STENT (PES)

While it was recognised in the 1960s that the extract of yew-bark killed artificially-preserved leukemia cells and was effective against ovarian tumors, it was only in 1978 that it was shown that it killed cancer cells in a novel way by microtubular stabilization. These properties make it a valuable agent for stent-delivery in the treatment of restenosis.

The agent has been delivered either with or without a polymer carrier. The **ELUTES** (12) and **ASPECT** (13) clinical trials tested paclitaxel applied directly to the stent. Both showed significant reduction in restenosis at dose density of 3ug/mm^2 of stent. These results led investigators to undertake the pivotal US **DELIVER 1** trial, in which paclitaxel was loaded without polymer onto a different stent to that used in either of the other two previous trials. The results were disappointing with no significant benefit in the treated group. The reasons for the differences from ELUTES/ASPECT will probably never be fully understood, but likely

due to inability to load the stent with the effective (ELUTES) dose. No further development of a non-polymer stent is likely, which is disappointing now there are concerns about the longer term effect of residual polymer once the any drug has eluted.

The difference in success between the non—polymer and polymer–coated paclitaxel (**TAXUS**) programmes cannot have been more acute. The success of **TAXUS II** (14) has been extended to more complex lesions in **TAXUS IV** (15). The outcomes for the increasingly complex TAXUS trials are shown in Table 2 The end-point of TAXUS IV was clinical with TLR rates of 3% versus 11% in controls ($p<0.0001$). TLR rates for smaller vessels are similar to the Sirolimus trials (3.4% for TAXUS IV <2.5 mm and 3.6% for mean 2.5mm in NEW-SIRIUS) but while in the non-direct comparisons outcomes of TAXUS diabetic patients appeared better than Sirolimus (TLR of 4.8% and insulin-dependant diabetics 5.9%), a recently presented direct comparison **ISAR-DIABETES** (16) gives Sirolimus the edge in these difficult patients. In 250 randomised diabetics showed no difference in death/MI at 9 months. However, late lumen loss in the Sirolimus group was 0.43mm compared 0.67mm ($p=0.002$) with TAXUS. The angiographic binary restenosis rates were 6.9% Cypher and 16.5% TAXUS ($p=0.03$), but the difference in clinical restenosis was not statistically significant (TLR 6.4% versus 12.0%). Figure 2

Robust efficacy is highlighted in **TAXUS VI** (17) which included longer lesions (20.6 mm) and multiple stenting. Total stent length of 33.4 mm, and AHA/ACC type C lesions of 55.6%. TLR was 19.4% in the control group and 9.1% in the TAXUS–(53% decrease in TVR, $p=0.0027$). The difference was independent of classic restenosis risk factors.

Are all DES equal?

The impact of the two current on clinical outcome DES versus BMS is shown in Figure 3. The recently presented **REALITY** trial (n=1386) (18) compared SES and TAXUS using 8 months angiographic restenosis as primary end point. It show significantly less late loss with SES (0.09 versus 0.31 $p<0.001$). TLR was no different however (5.0% versus 5.4% respectively). Why there was no difference in clinical end point despite a difference in late loss is unclear especially as from the **SIRTAX** trial (19) less of a difference in LL favouring SES translated into a clinical difference between devices (4.8% TLR Sirolimus versus 8.3% TAXUS $p=0.025$).

III. Real World Registries

Real world registry data exists for both currently available DES. Such studies, although subject to critism of selection bias, are important since many of the exclusion criteria in the RCTs include lesions treated in everyday practice (CTO, in-stent restenosis, bifurcation disease etc). The **e-Cypher registry** (20) reached its recruitment target of 15 000 patients in 2004 with 11 159 (87%) evaluated at 6 months. There are 1.3 stents per lesion and 30% direct stenting. 48.7% of patients were treated “off-label” (CTOs, SVG etc). Overall MACE was 3.2% with 6.4% in SVG, 6.6% left main stem, non-diabetic 2.6%, diabetic 4.6% and in bifurcation 4.8% (Figure 4) TLR rates are low in all subsets compared to historical data. In a further registry of Cypher stents, clinically driven TLR is 3.7% (n=508) (**RESEARCH** (21)).

In the **WISDOM TAXUS Registry** MACE rates of 4.5% and TLR of 1.8% have been reported in 604 patients. The **MILESTONE II** registry is designed to assess outcome by lesion subsets in 3000 patients. Data collection is ongoing.

IV. Higher risk patient populations

While DES are effective overall (Figure 3) there is no doubt that certain patients are at greater risk of restenosis (see Figure 1). These include those with small vessel disease, long lesions, and those with diabetes and ACS. Additionally we need to know the outcomes for those who have CTOs, left main stem and bifurcations. Much of the data is registry or post

hoc analyses, but provides some insight into potential outcomes of DES used in such clinical scenarios.

Small vessel disease: Problems occur in patients with small vessel reference diameter because the same tissue response has a greater impact within the confines of a smaller vessel. Even with DES, smaller vessel size is associated with an increased risk of restenosis or repeat revascularisation but the events rates are much reduced compared to BMS (mean late loss value falling from 0.8 to 0.04). Figure 5 presents combined data from randomised trials comparing the SES and bare metal stents Overall binary restenosis is reduced from 42.5% to 9.9% ($p < 0.0001$), with a 73% reduction in target lesion revascularisation from 17.7% to 4.8% ($p < 0.0001$). Similar findings emerge from the randomised TAXUS studies (Figure 6).

Long lesions**:** Why those with longer lesions should be more prone to restenosis is less clear. However the independent effects of stented lesion length, non-stented lesion length, and excess stent length, on coronary restenosis have been evaluated in 1,181 patients from 6 bare metal stent trials of de novo lesions in native coronary arteries (22). Stent length exceeded lesion length in 87% of lesions (mean difference 7.6±7.9 mm). At 6-9 month follow-up, mean percent diameter stenosis was 39±20%. In a multivariate model of percent diameter stenosis, each 10 mm of stented lesion length was associated with an absolute increase in percent diameter stenosis of 7.7% ($p < 0.0001$), whereas each 10 mm of excess stent length independently increased percent diameter stenosis by 4.0% ($p < 0.0001$) with increased TLR at 9 months (odds ratio 1.12, 95% confidence interval 1.02 to 1.24).

A multiple regression model was used to predict 8-month percent diameter in the angiographic follow-up of the SIRIUS trial (n=699) (23). Stented lesion length and excess stent length were associated with absolute increases in percent diameter stenosis per 10 mm of 9.1% ($p<0.0001$) and 3.6% ($p=0.053$) in the bare metal arm but 3.5% ($p<0.05$) and 2.1% ($p<0.05$) in the Sirolimus-eluting stent arm. Figure 7

Diabetes**:** This patient group remain a problem. The formation of advanced glycation end products (AGEs), in various tissues has been known to enhance immunoinflammatory reactions and local oxidant stresses in long standing diabetes, leading to excessive tissue response (24) However in diabetic sub-groups randomised to SES or PES versus bare metal stents an important biologically consistent reduction in restenosis (both angiographic and clinical) has been demonstrated with DES (Table 3). Data is available that directly compare BMS versus DES in diabetics only (the **DIABETES** (11) trial see above). At 9 months angiographic follow up, the late luminal loss was 0.44mm in the BMS group and 0.08mm in the Sirolimus arm ($p<0.001$).

To test the independent predictor of diabetes for restenosis Dawkins et al (25) have under taken a multivariate logistic regression analysis for TLR with predictors of lesion length (byQCA), RVD (by QCA), treatment (drug-eluting stents/bare metal stents), and diabetic status from the pooled database of three randomized TAXUS trials. The diabetic group consisted of 214 patients randomized to the TAXUS stent and 240 patients randomized to BMS control: the non-diabetic group consisted of 919 patients randomized to the TAXUS stent and 903 patients randomized to the BMS. Comparisons of baseline mean lesion length and RVD, as well as the outcome for TLR were made between treatments, and between the diabetic and non-diabetic patient subgroups.
Multivariate logistic regression for patients in the BMS arm indicated no diabetic benefit when controlling for RVD and lesion length. In non-diabetic patients, the 12-month TLR rate was reduced by 69% from 14.0% in Control to 4.3% in TAXUS ($p<0.0001$). This benefit was maintained in diabetics with a reduction by 63% from 20.2% in Control to 5.6% in TAXUS ($p<0.0001$). Multivariate logistic regression for patients in the TAXUS arm indicated a diabetic benefit when correcting for RVD and lesion length. Multivariate logistic regression for all patients in both arms indicated that the adjusted odds ratio for TLR for diabetic patients is 1.38 with a 95% confidence interval of [1.004, 1.905].

These reults are important since they support the concept that diabetes is an independent rsik factor for restenosis that is reduced by DES (in this instanceTAXUS) irrespective of other factors that normally influence restenosis.

PCI in AMI: The European Society of Cardiology has recently recommended that primary PCI be the preferred treatment for patients suffering acute myocardial infarction (26). It is thus critical that optimal short, medium and longer term outcomes be achieved in such patients.

BMS implantation has been shown be better than balloon alone in acute MI (27,28). However in-stent restenosis and vessel occlusion remained clinical problems. Conversely patients with acute coronary syndromes have increased thrombotic complications after PCI (29,30) and there have been concerns that these will be excessive with DES, with potential vessel re-endothelialisation being delayed by drug elution. The results of various registries of Sirolimus-and Paclitaxel eluting stents in AMI is shown in table 4 (31-33)

Because of the presence of a thrombotic (infarct-precipitating environment) stent thrombosis has received particular attention in this group of patients, however registry data does not support this concern.

DES in AMI appears appropriate.

Dug eluting stents in acute coronary syndromes (NSTEMI): For ACS patients requiring revascularisation the most common form of revascularisation is PCI and this is usually performed with intra coronary stents (NICE stent submission 2002).

In the RESEARCH registry (34) early outcomes of patients with ACS treated with SES were compared to those treated with BMS. 30 day MACE was similar (SES 6.1% vs BMS 6.1% p=0.8), Stent thrombosis was not significantly different between the groups, with even a trend favouring DES (SES 0.5% vs BMS 1.7% p=0.4).

Paclitaxel-eluting Stents have been compared to BMS (n=213) in acute coronary syndromes (35) (n=237). MACE at 30 days were 3.4% PES vs 2.3% BMS p=0.52. One year revascularisation rates were 6.5% PES vs 17.7 % BMS p=0.0003 and MACE 11.1 PES vs 21.7 BMS p=0.003, a reduction in composite MACE of 51%. Stent thrombosis was the same (0.8% PES vs 0.9% BMS). Comparison of unstable vs stable patients all treated with PES had a trend towards a higher rate of stent thrombosis at 30 days in the ACS group (0.8% unstable vs 0% stable p=0.06), but not at 1 year (0.8% unstable vs 0.5% stable p=0.55).

Both DES have been evaluated in registry (36) containing a high proportion of AMI and unstable angina (55% in each group). There were no differences in death or MI, TVR or MACE at 30 days, 6 months or 1 year between the two stent types.

Lesion specific Registry data
The registry/RCT outcome data for particular sub-groups is shown in (refs 35-52) (table 5)

Can DES challenge CABG ?

Drug eluting stents have been a major advance for interventional cardiology. Target TLR rates have fallen to ~5% (a >70% reduction compared to BMS) Even in complex cases the need for revascularisation is between 5% and 10% (17). Recently presented data indicated event-free survival between 9 months and two years of 92.2% for those in the original TAXUS trials, good considering vein graft attrition rates are between 2.5% and 5% pa, reaching 50% occlusion rate at 10 years. The standard of care for PCI is DES even in complex lesions. Recent studies have compared DES in multi-vessel disease to surgery.

The **ARTS-2** trial (52) compared SES with the previous ARTS 1 BMS and surgical arms. Freedom from major adverse cardiac and cardiovascular event (MACCE) rate was 89.5% with SES in ARTS 2 (re-vascularisation 7.4% (5.4% re-PCI, 2% CABG), compared to 88.5% MACCE free for ARTS-1 surgery (3% PCI). It would seem that in complex patient subsets DES appear to produce better outcomes than surgery.

IV. Ongoing DES programmes

New programmes in DES are important for a number of reasons.

- Firstly as we treat more complex lesions, more efficacious agents may be required. Stent delivered agents that are more lipophylic, have greater tissue penetration or greater residency time may have true advantages. We may want agents that are more stable or have different release kinetics or even agents that work in completely different ways. Clinical trials of such new DES will be required by the Regulatory authorities to be tested against currently available DES, not bare metal stents.
- Secondly we may wish for improved stent platforms. Treating complex lesions and making in-roads into previous surgical cases will be dependant on technology and operator skills, not merely effective DES.
- Thirdly new DES will result in competition and lower prices for this expensive technology.

Sirolimus-derivatives

Sirolimus has three important chemical regions: the FK binding protein region, the non-protein binding region that influences physical properties and the mTOR binding domain. C-43 sits in the first of these and substitution of the "HO" produces new agents (Figure 8). The **ABT578** 53 (substitution at C-43 with 5=N ring formation) has been loaded onto the Medtronic DRIVER stent using a bio-neutral (phosphorylcholine) polymer. The **ENDEAVOR** programme is based on laboratory and pre-clinical data suggesting ABT578 (10 ug/mm stent) has potent effects on smooth muscle cell growth, inhibiting intimal hyperplasia.

The pivotal **ENDEAVOR II** trial (54) randomised 1200 patients to ABT578/Biocompatible polymer/Driver stent or BMS. The primary endpoint of Target vessel failure (cardiac death, MI, TVR) at 9 months occurred in 8.1% ENDEAVOR compared to control 15.4%. TLR rates were 4.7% - competitive with the CYPHER and TAXUS programmes. An interesting aspect of this trial was the "high" late loss relative to the two other devices : 0.62 mm versus SIRUS-0.17mm and TAXUS IV–0.39mm). The relationship between late loss and clinical events is as yet not fully understood, but TLR may only become important only at >0.6mm (55). **ENDEAVOR III** has recently reported. It was a USA-based 30 centre study of 436 patients randomised 3:1 to ENDEAVOR stent or Cypher. Again primary end point will was angiographic "in-segment late loss" at 8 months because of likely small clinical differences. The Target lesion revascularisation rate at 9 months was 6.3% for the ENDEAVOR and 3.5% for CYPHER (NS). Stent thrombosis was 0% at this time. Again the late loss was 0.630 in stent but 3.4 mm in-segment, supporting the 0.6mm resulting in clinical event cut-off hypothesis. Of course in-segment restenosis will always be the more important than in-stent restenosis. **ENDEAVOR IV** is a comparison with the TAXUS stent in 1000 patients.

The **Abbott** programme also uses ABT-578 (now named Zotarolimus) but in a triple layered (stainless steel-tantalum-stainless steel) stent. They load the drug in a phosphorylcholine (bioneutral) polymer which covers the stent and which has been previously used on wires and stents implanted in many thousands of patients. ZoMaxx I the pivotal trial finished enrolling patients in July 2005. The final end point to the study is at 9 months and therefore that will be April 2006. It will then take a couple of months to

sort the data out. It is hoped to present the data Q3/Q4 2006 (ESC time). ZoMaxx II is primarily a USA study governed by the FDA. Initially it has 10 centres, and subject to acceptable initial results from 250 patients, with enrolment soon to be complete. Once FDA approval has been received the company will then go on to enrol up to an agreed 1670 patients. Other centres will join up to a maximum of 25 sites, realistically the data from this study will not be available until late 2007.

Everolimus is also a Sirolimus derivative, with reportedly better pharmacokinetics, tissue residency and stability than its parent compound (56) but unlike ABT578 is currently available, being used in organ transplantation. The Guidant Everolimus programme consists of loading drug onto the Biosensors Champion stent/bio-absorbable polymer (polylactic acid, which breaks down to lactic acid and has a high drug carrying potential) and which is already used in bio-prostheses. Safety and pilot efficacy data with this combination (**Future I & II** studies (n=42 & 64)) reported MACE rates of 7.7% and 4.8% resp. and low late loss of 0.15 mm. **Future III** will compare 6 month late loss in 800 patients randomised 3:1 to this drug/polymer/ stent combination or to bare metal Zeta stent and **FUTURE IV** will compare this combination with an FDA approved DES control (n=935 randomised 2:1). The future of this drug on the Vision stent will depend on the outcome of merger negotiations between J&J and Guidant.

BiolimusA9 is yet another Sirolimus derivative, claimed to be even more lipophylic with > 85% eluting into tissue within 8 hours, on a Biosensors stent and is being tested **STEALTH** trials. It is currently being tested on a conical ("bifurcation") DEVAXX stent.

The **CONNOR** stent has a unique stent design (Figure 9) with polymer-filled laser cut wells and configurered to release drug toward the vessel wall, toward the lumen or both. Stent deliverability appears good. The **PISCES** pilot study (57) tested different doses, released over different periods -10 or 30 ug Paclitaxel for between 10 and 30 days. Results suggest an overall 30 day MACE of 4.2%, with the best formulations (10 ug/30 day and 30 ug/30 day) being tested on a cobalt chromium Connor stent platform (**EuroSTAR** trial).

The Yukon Stent

The Yukon stent programme is different from the others in that it encompasses a system that delivers drug without the use of polymer- the abluminal surface is laser pitted and the drug is loaded in the cath lab, by injection onto the surface of the stent in ethanol and air dried off. To date the drug tested has been Sirolimus (concentration -2%). The results have been impressive with equivalence restenosis rates to those seen in the randomised trials of Sirolimus

Potential problem areas

1. Making PCI safe

a.Adjunctive therapy

i.Clopidogrel

Since the mid-1990s anti-platelet therapy has been the corner-stone of safe stenting. Recently published data suggests that pre-loading > 6 hours with clopidogrel improves outcome (**CREDO** (58) (Figure 10). Some data support the use of 600 mg of clopidogrel **ISAR-REACT** (59). Clopidogrel resistance, its frequency and significance are as yet unresolved (60,61).

It is clear that with the advent of DES and the potential risk of stent thrombosis (Figure 11) due to the presence of polymer or reduction in rate of re-endothelialisation, dual anti-platelet therapy should be continued, especially in complex cases, for a minimum 6 months and maybe even for a year with aspirin being continued forever, although there is no data to support any of these strategies.

ii.GP IIbIIIa

The use of GpIIbIIIa during PCI has been well established with Abciximab having been shown to benefit ACS patients, and diabetics undergoing intervention (62-65) Figure 12. Use of Abciximab in patients requiring intervention following an acute event (AMI) has been strengthened by the **ADMIRAL** (65) trial -those receiving ReoPro had a cumulative 6 month end-point of 7.4% compared to 15.9% in controls (p=0.02). However this difference was driven by those patients receiving treatment in a mobile intensive care rather than in the emergency room or pre-procedure.

Abciximab use increased to > 50% as PCI-cases became more complex, but its use has fallen back as stents and operators improve and aim for better acute results. Data suggest it may be cost effective to new anti-thrombins in more routine cases.

Anti-thrombins

Anti-thrombins are sophisticated heparins (consistency of inhibition, lack of need for intermediate anti-thombin and actions independent of platelet activity) but are more expensive. In **REPLACE-2** trial 6000 patients were randomised to Bivalirudin or heparin plus Abciximab. The results suggest no difference in 30 days outcome (composite end point reached in about 10% in both groups) and no difference in the longer term although bleeding was less in the Bivalirudin group (major bleed 2.4% versus 4.1% p<0.001) (66). The value of early ambulation, and of cost saving with bivalirudin have also been raised. Concerns have been raised as to whether the patients included are the “high risk” who would normally have received Abciximab. While 42% included in REPLACE-2 were ACS patients we will need to await the **ACUITY** study of pure ACS and **HORIZONS** (STEMI) to have such questions answered. In the mean time bivalirudin has made some inroads into less than straightforward (but not AMI) patients undergoing PCI. They will not be cost effective for straightforward (“heparin-alone”) cases.

Stent thrombosis

Stent thrombosis requires special mention although there is little randomised trial data. Late stent thrombosis due to polymer or reduced re-endothelialisation remains the concern with DES, with implications for duration of anti-platelet therapy.

Such concerns were raised through the National reporting service in 2003/4. Review of the NEW SRIUS data, the e-CYPHER registry, world-wide implant data (n=250000) showed Cypher stent thrombosis rate to be about 0.6% (similar to BMS) and to that seen in the TAXUS IV data.

A number of recent publications have again drawn attention to stent thrombosis.

McFadden reported four cases of stent thrombosis (two Cypher, two TAXUS) all occurring between 300 and 450 days after stent implantation and all soon after both aspirin and clopidogrel therapy were stopped (67).

The database consists of observational and meta-analyses.

Incidence with BMS

- A review 6058 patients with bare metal stents indicates that stent thrombosis was 1.6%. Importantly in the context of worries about DES delayed re-endothelialisation and its impact on late stent thrombosis, 8/24 patients suffered stent thrombosis beyond 6 months. Overall outcome was poor; 6 month major adverse clinical events comprised death (11%), re-infarction (16%), and recurrent stent thrombosis (12%) (68)

BMS v DES

- In a meta-analysis of 10 randomised studies, stent thrombosis rate for DES was 0.58% versus 0.54% for bare metal (69). Stented length was a predictor of thrombosis.
- In a review of 3 cohorts of patients: BMS (n=507) stent thrombosis rate=1.2%, SES (n=1017)=1.0% and PES (989)=1.0%. Mortality was 15% and AMI 60% in those who suffering stent thrombosis (70).
- A meta-analysis of six CYPHER trials (Sirius, E-Sirius, C-Sirius, Direct, SmVelte, Ravel n=2,074) has been presented (71) stent thrombosis was recorded, as SES 0.6%, control 0.6%.
- Similarly, data from TAXUS II, IV, V, and VI studies (n=3445) (72) showed stent thrombosis from implant to 6 months was 0.6% for control, 0.7% for TAXUS (p = 0.68). Stent thrombosis to 2 years was 0.7% for control, 1.2% for TAXUS (p = 0.44). However, stent thrombosis between 6 and 24 months was 0.7% control and 1.2% TAXUS which was statistically significant (p = 0.014). The data, therefore, do suggest a small increase in late stent thrombosis with TAXUS.

DES v DES

- The REALITY trial (18) which randomised patients to Sirolimus or Paclitaxel eluting stents suggested a non-significant increase in stent thrombosis in the PES group (0.6% versus 1.6% p=0.07)

Higher risk lesions

- Even in the thrombus rich AMI patient the stent thrombosis was not seen in any of the 186 Sirolimus patients compared to 1.6% in those in the bare metal arm (**RESEARCH AMI** registry) (73).

Precipitating factors

- Certain factors predict stent thrombosis, including stent under-expansion and residual reference diameter (74), supporting the concept that DES-use is not an excuse for

inadequate technique. Most importantly discontinuation of anti-platelet therapy is the most powerful predictor of stent thrombosis (FIGURE 13).

How long dual anti-platelet therapy should be continued for is unresolved. Further, what to do about the need to stop, versus the risk of stopping, such drugs for non-cardiac procedures and operations is unclear.

In summary we are unsure whether there is an additional problem of stent thrombosis with DES greater than that seen in the BMS era. We are unsure of the incidence of late stent thrombosis and we do not know therefore how long to recommend dual anti-platelet therapy for and what to recommend when patients need a non-cardiac surgical procedure. This will require ongoing monitoring. I am in the process of setting up a National Web based database to collect all stent thromboses.

Future trials

Trials of diabetes include

- **CARDia** (Coronary Revascularisation in Diabetes) is a UK multi-centre trial which will randomise 600 diabetic patients with multi-vessel or complex single-vessel disease to BMS-PCI, DES-PCI or CABG in a 1:1:2 ratio. The primary endpoint is death, MI or CVA at 1 year
- **FREEDOM** (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease) is a NHLBI multi-centre trial that will randomise 2300 patients to DES-PCI or CABG. The primary endpoint is 5 year mortality

Others

- **SYNTAX** trial. This is an important trial of LMS or 3 vessel disease randomised to PCI or surgery (n=1800) with separate surgical and PCI registries for patients only considered treatable with one of the procedures. This trial has 4 Uk centres who have contributed the most patients collectively.

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Table 1 Outcomes for CYPHER stents

Randomized Cypher vs. BMS Trials
Total: 2827 Patients (1420 Cypher, 1407 BMS)

Study	Pts (n)	Diabetic Pts (%)	RD (mm)	Lesion length (mm)	% Stenosis	B2/C lesions (%)	100% Occls. (%)	TLR % (@ X months)	MACE
RAVEL	238	19.0	2.62	9.6	63.8	57.0(B2)	0	**2.5** (36 mo)	**5.8** (36 mo)
SIRIUS	1058	26.0	2.80	14.4	65.3	56	0	**6.8** (36 mo)	**12.6** (36 mo)
E-SIRIUS	252	23.0	2.55	15.0	65.4	-	0	**4.6** (24 mo)	**10.3** (24 mo)
C-SIRIUS	100	24.0	2.64	13.5	69.7	59	0	**4.0** (9 mo)	**4.0** (9 mo)
DIABETES	160	100	2.34	15.0	-	80.1	13.1	**7.5** (12 mo)	**11.3** (12 mo)
SES-SMART	257	24.9	2.20	11.8	66.8	28.8	0	**7.0** (8 mo)	**9.3** (8 mo)
SCANDSTENT	322	18.0	2.86	18.0	76.6	-	35.7	**2.4** (6 mo)	**3.1** (6 mo)

Table 2. Outcome of the TAXUS trials

Randomized Taxus vs. BMS trials
Total: 3471 Patients (1732 Taxus, 1739 BMS)

Study	Pts (n)	Diabetic Pts (%)	RD (mm)	Lesion length (mm)	% Stenosis	B2/C lesions (%)	100% Occlus. (%)	TLR % (@ X months)	MACE
TAXUS I	61	18.0	2.97	11.3	56.5	36.0(B)	0	**3.0** (24 mo)	**3.0** (24 mo)
TAXUS II	536	14.0	2.75	10.4	64.4	-	0	**4.7** (12 mo) **5.5** (24 mo)	**10.9** (12 mo) **14.2** (24 mo)
TAXUS IV	1314	24.2	2.75	13.4	66.5	-	0	**5.6** (24 mo)	**14.7** (24 mo)
TAXUS V	1156	30.8	2.69	7.2	68.3	55.6 (C)	-	**8.6** (9 m0)	**15** (9 mo)
TAXUS VI	446	19.9	2.79	20.6	65.4	83.4	-	**9.7** (9 mo)	**21.3** (24 mo)

Table 3. Outcomes in diabetics in the various trials

TRIAL (% diabetics)	**Relative Reduction in Binary Restenosis (%) in diabetics**	**TLR rate in diabetics Treated with DES (%)**
RAVEL (18.5%)	100%	0
SIRIUS (26%)	65%	6.9
NEW-SIRIUS	81%	7
TAXUS II (15%)	100%	3.1
TAXUS IV (24%)	82%	5.9
TAXUS VI (19%)	80%	2.6

Table 4. Outcomes of AMI patients

REGISTRY (n=) Follow-up time (mo)	Mortality %		TLR %		MACE		Stent Thrombosis %	
	BMS	DES	BMS	DES	BMS	DES	BMS	DES
Saia [31] (n=96) (7.2 mo)		**7.3**		**1.1**		**8.4**		**0**
Lemos [32] (n=186) (10 mo)	**8.2**	**8.3**	**8.2**	**1.1**	**17**	**9.4** p=0.02	**1.6**	**0**
Gershlick [33] (n=803) (6 mo)	**NA**	**3.5**	**NA**	**1.7**	**NA**	**5.3**	**NA**	**1.5**

Table 5. Outcome registry & RCT data for lesions generally excluded from randomised trials of DES

Study with data where available		Target lesion revascularisation		MACE			Late loss mm / restenosis %		
Trial type	follow-up mo	*DES*	*p*	*BMS*	DES	p	BMS	DES	p BMS
Saphenous vein grafts									
Vermeersch [37] (RCT)	(12)				11%	*(NS)*	44%	LL 0.49	*0.005* 1.48
Hoye [38] (Reg)	(12)	5%		NA	26%		NA		
Ge [39] (Reg ~ historical controls)	(6)	3.3%	*0.003*	19.8%	11.5%	*0.02*	28.1%		
Bifurcations									
Colombo[40] (RCT~ double versus provisional)	(6)	Overall 8% (TVF =15 %)						Rest 28%	18.7%
Louvard [41]									
Chronic Total Occlusions									
Simes [42] (RCT bare metal stent trial "SICCO")	(12)	NA		22%					
Hoye [43] (Reg ~ historical controls)	(12)				3.6%	*<0.05*	17.2%	LL 0.13	
Werner [44] (Reg ~ matched BMS)	(12)				12.5%	*<0.001*	47.9%	Rest 8.3%	*<0.05* 51%
Left main stem disease									
Silvestri [45] (Reg~ bare metal stent)	(6)	NA		17.4%					
Tan [46] (Reg~bare metal stentl)	(19)				NA		39.4%		
Gershlick[47] (Reg ~ CYPHER stents)	(6)				6.6%				
Valgimigli [48](Reg~ DES versus historical controls)	(12)	6%	<0.0004	23%	10%	*<0.0006*	35%		
Park [49] (Reg ~ DES versus historical controls)	(12)				2%	*<0.0003*	18.6	LL 0.05	*<0.001* 1.27
Chieffo [50] (Reg ~ DES versus historical controls)	(6)				20%	*<0.04*	35.9%		
In-stent restenosis									
Gershlick [51] (Reg ~ CYPHER stents)	(6)				3.9%				
Kastrati [52] (RCT ~ SES v PES v balloon)	(6)	8% (SES)	*p<0.02*					Rest 14.3% (SES)	NA
		19% (PES)						21.7% (PES)	NA