British Cardiovascular Society

Promoting Cardiovascular Health

BCIS

Dear Sir/Madam

Please find enclosed the British Cardiac Society/British Cardiovascular Intervention Society response to the Ischaemic Heart Disease-stents review document from the Liverpool group: Assessment Report Supplement 3'' and 4'.

You will see that we continue to have major problems with the LiG analysis which we fundamentally disagree with, as we have done from the onset.

We have included our own analysis of the cost effective data using published trial base data. We realise this may a relatively unusual submission from a Professional Body but we felt this was necessary as the LiG continued to not respond to the requests that were made of them by the NICE committee. In addition we have attached our original response which we believe demonstrates the consistency of our response to this appraisal.

The BCS and BCIS would be delighted to provide expert witnesses for the committee meeting of July 4th if you think this will be useful.

Dr Nick Brooks: President of the BCS

Dr Nick Boon: President-elect of the BCS

Dr Mark de Belder: BCS

Dr Tony Gershlick: Scientific Information Officer of BCIS

Dr MartynThomas: President of BCIS

The joint British Cardiovascular Society (BCS) and British Cardiovascular Interventional Society (BCIS) response to "Assessment Report Supplement 3 and 4"

Appointed clinical representative experts from The British Cardiovascular Society and the British Cardiovascular Intervention Society have reviewed Supplements 3 and 4 which outline the further work requested by NICE from the Liverpool Implementation Group on Drug Eluting Stents. The following response is the result of a careful review by the clinical experts of the data produced on efficacy and cost efficacy of drug eluting stents. The fundamental issue of using inappropriate source data by LiG remains, as well as the apparently immutable inaccuracies that result when unsubstantiated figures are factored by this group into the proposed model. The professional groups also recognise the concerns around the issue of potential late stent thrombosis when drug eluting stents are used and that safety concerns need to be considered in addition to the proven efficacy of drug eluting stents. We have therefore summarised the current understanding regarding late stent thrombosis towards the end of this review

Assessment Report Supplement 3'' and 4'.

General Comments

The professional bodies remain deeply concerned that there exists the potential for National Guidelines and patient care to be driven by data from an unvalidated and thereby flawed local audit of questionable quality. The differences in outcomes, between this dataset and the published data, questions its suitability for an exercise of this importance. We are surprised that very few of the questions we have asked, both in written and expert testimony, have been addressed. We continue to be surprised by this reliance on an un-adjudicated database that takes little account of pro-active complete patient follow up and that contains indicators of local differences in practice from the national "norm", such as excess staged procedures. We are especially concerned about three areas of inaccuracy that result from the use of the Liverpool database and the LiG interpretation of this and published data:

(a) the under-estimate of bare metal stent restenosis;
(b) the under estimate of reduction in need for repeat procedure with DES; and
(c) the underestimate of risk magnitude in the high risk groups. With this regard we have attached our original response to addendum 3'

All comments on Addenda 3'' and 4' have to be interpreted within this context as we fundamentally do not agree with the local audit on which they are based.

BCS and BCIS continue to believe that National Guidelines should be based on internationally recognised published randomised trials rather than the local audit data used in this assessment. If the core data used are wrong then all other interpretations of the data and the modelling will also be inaccurate.

Revisiting Cost-effectiveness

There are a number of issues that continue to compromise the Liverpool cost-effectiveness model presented in Addenda 3'' and 4'. These are:

- Continued reliance on the CTC database to establish baseline risks for repeat revascularisation. This is inconsistent with the Appraisal Committee's request that the Liverpool group update the economic model with absolute risk of repeat revascularisation taken from the Scottish registry (Addendum 3' page 48) and other larger substantiated published databases.
- Continued reliance by LiG on the CTC database to derive the absolute quantitative relative risk excess for the independent risk factors of small vessels, long lesions and diabetes. This is inconsistent with the Appraisal Committee's request that the Liverpool group update the economic model with the relative risks taken from the published trials (Addendum 3' page 48).
- Continued use of a 41% risk reduction consequent on the use of DES by LiG (as indicated in Addendum 3' page 38). It is quite clear that without even addressing the inappropriate use of TVF versus TLR, the continued use of 41% TVR is based on BASKET trial results at 6 months and under-estimates the risk reduction expected at 12 months. Again this was a NICE discussion point at the last assessment meeting.
- The assumption that 100% of DES patients receive only 3 months Clopidogrel when those with acute coronary syndromes (44% of patients treated on a national scale according to the BCIS 2005 audit) already receive 12 months Clopidogrel.

Given these issues, particularly noting that the first two points were supposed to have been implemented in the first Addendum (3'), we have recalculated the cost-effectiveness of DES using the correct clinical data inputs. This is perhaps unusual for a professional society at this stage of an Appraisal, but is necessary because the Liverpool group have persistently failed to use these data. Failure to do so makes a mockery of the purpose of the exercise in finding the true benefit and cost efficacy of the device.

The economic model used in this professional body response has been constructed using the equations shown on page 104 of the original Assessment Report and employs cost data, resource use data and quality of life data shown on page 113 of the Assessment Report and pages 3 to 5 of Addendum 4'. We have not separated elective and non-elective patients, but used elective costs and resource use. This is because elective repeat revascularisation costs are lower and stents per procedure higher, thus making the model less favourable to the cost-effectiveness of DES. We have adopted a simple approach to repeat PCI by using the NHS reference cost for PCI as this inherently allows for the case mix of PCI involving no stents, BMS or DES.

Model Structure

The model calculates the additional procedural cost of using a DES and offsets against that, the costs saved by avoidance of investigation of recurrent symptoms, repeat revascularisation, post-revascularisation follow up and non-fatal MI. Allowance has been made for 1% stent wastage, as suggested by LiG. The model is fundamentally that used in the current Assessment reports but with the correct (trial based) figures factored in. Additional Clopidogrel can be added according to the proportion of patients who would not already receive it under current practice, i.e. non-ACS patients (see previous NICE guidance

on ACS). The gain in QALYs is calculated by multiplying the QALY loss awaiting repeat revascularisation and the QALY loss due to the procedure by the absolute risk reduction gained from DES, taking into account the proportion of patients who have repeat revascularisation by either PCI or CABG. We have also included the QALY gain by avoidance of non-fatal MI.

The major changes in data input, compared to the Liverpool model, are:

- A more representative absolute risk of repeat revascularisation with bare metal stents .
- A more realistic mean relative risk increase for each of the risk factors, i.e. long lesions, small vessels and diabetes (again taken as a mean from multiple data sources).
- A more realistic "benefit" of DES (taken from LiG and NICE accepted published sources at 12 rather than 6 months).

12-month cost-effectiveness has been calculated for the base-case, small vessels, long lesions and diabetic patients. The base-case scenario employs the absolute risk of repeat revascularisation from the Scottish registry prior to DES (13% for the year 2000-2001, Pell and Slack 2004). This is supported by multiple other registries previously presented in slide form to NICE by the medical experts. All point, especially when Pell and the 12 month Basket data (11.6% rather than 7.8%) is added in, to a figure for repeat intervention of 13%.

Absolute risk of repeat revascularisation for BMS (no protocol mandated angiogram): published evidence

Source	Population (N)	No. of revascs (n)	% Revascs	Follow-up	Weight
Bagust et al, 2005	2,884	255	8.8%	12m TVR, CTC clinical database	5.3%
Shrive et al, 2005	7,334	601	8.2%	12m any revasc, clinical database	13.4%
Singh et al, 2005	11,484	1,609	14.0%	PRESTO trial. 9m TVR, is chaemia-related revasc	21.0%
Jilaihawi et al, 2005	1,003	51	5.1%	12m TLR, clinical database	1.8%
Serruys et al, 1998	206	16	7.8%	BENESTENT II trial.12m TLR no angio group	0.4%
Gershlick et al, 2004	38	6	15.8%	ELUTES trial control group.12m TLR symptom driven revasc	0.1%
Stone et al, 2004	385	49	12.7%	TAXUS IV trial control group.12m TLR no angio cohort	0.7%
Homes et al, 2004	525	85	16.2%	SIRIUS trial control group.12m TLR angina driven revasc	1.0%
Lemos et al, 2004	380	41	10.8%	12m TVR angina driven, clinical database	0.7%
Serruys et al, 2001	600	102	17.0%	ARTS trial stent arm.12m all revascs, no follow-up angio	1.1%
Wu et al, 2004	3,571	577	16.2%	12m revasc, prospective registry of routine practice	6.5%
Agema et al, 2004	3,177	304	9.6%	9m TVR in routine clinical practice	5.8%
Gotschall et al, 2006	848	63	7.4%	12m TVR, clinical database	1.6%
Ellis et al, 2004	5,239	702	13.4%	9m all revascularisations, clinical database	9.6%
Brophy et al, 2005	16,746	2143	12.8%	9m re-intervention, clinical database	30.6%
Kaiser et al, 2005	281	22	7.8%	6m TVR, BASKET trial, no angiogram	0.5%
Overall	**54,701**	**6,626**	**12.1%**		**100.0%**

- Studies in red were cited in the Assessment report. The 2 largest studies (Singh et al and Brophy et al) were not cited.
- Liverpool database constitutes 5% of the patients in the literature.

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We have then applied to this, the mean relative risk for each of the risk factors derived from published trials and clinical databases. Clinical databases have been included to increase the sample size, reduce error and achieve a mix of randomised trial and 'real world' risks.

We have also identified, again from published randomised trials and clinical databases, relative risk reductions due to DES for each risk factor in order to estimate the absolute risk reduction that is required for the economic model. Where published results were presented as odds ratios, we have converted them to relative risks. In some cases, estimates have been made where patient counts do not appear in the publication, but in using the mean of all the relative risks we have identified for each sub-group, selection bias or the impact of calculation uncertainties is minimised. We have also included the relative risks for the risk factors from the CTC database and presented in the Assessment Report. Table 1 shows the relative risks associated with each risk factor and Table 2 shows the relative risk reduction due to DES for each risk factor.

Sub-group	Relative Risk	Comment	Source
Small vessels			
	1.55	12m non-MI related TVR, stents <3mm diameter	BASKET trial, Kaiser et al 2006
	1.17	12m TLR, vessels <2.75mm vs vessels >2.75mm	SIRIUS trial, Holmes et al 2004
	2.09	24m TLR, minimum lumen diameter <3mm	Stent design trial, Elbaz et al 2002
	1.79	9m revascularisation, vessels <2.75mm vs >2.75mm in lesions <20mm length (estimate)	Clinical database, Ellis et al 2004
	1.52	12m reintervention, vessels <2mm, elective patients	Assessment Report Addendum 3"
	2.62	12m reintervention, vessels <2mm, non-elective patients	Assessment Report Addendum 3"
	1.78	12m TVR, vessels <3mm vs vessels >3mm (estimate)	Clinical database, Gotschall et al 2006
	1.33	12m TLR (estimate)	Clinical database, Kornowski et al 1999
	1.71	6m TLR, mimimum lumen diameter <3mm	Clinical database, Kastrati et al1997
	1.84	9m TLR, <3mm vs vessels >3mm (estimate)	ENDEAVOR II trial, Fajadet et al 2006
	1.85	12m TLR, longer stent length	TAXUS IV trial, Stone et al 2004
Mean	***1.75***		
Long lesions			
	1.10	12m TLR (estimate) per 5mm lesion length increase, no angiographic follow up	Trial meta analysis, Cutlip et al 2002
	1.18	12m TLR, lesions >13.5mm vs lesions < 13.5mm	SIRIUS trial, Holmes et al 2004
	1.02	12m TVR, per unit (undefined) increase	Clinical database, Agema et al 2003
	2.11	9m revascularisation, lesions >20mm vs <20mm in vessels >3.25mm diameter (estimate)	Clinical database, Ellis et al 2004
	1.01	12m revascularisation, per 1mm increase in stent length	Clinical database, Wu et al 2004
	1.20	12m reintervention, lesions >20mm, elective patients	Assessment Report Addendum 3"
	1.19	12m reintervention, lesions >20mm, non-elective patients	Assessment Report Addendum 3"
	2.15	12m TVR, lesions >20mm vs lesions <20mm (estimate)	Clinical database, Gotschall et al 2006
	1.42	12m TVR, lesions >20mm vs lesions <20mm (estimate)	PRESTO trial, Singh et al 2005
	1.41	9m TLR, lesions >16mm vs lesions <16mm (estimate)	ENDEAVOR II trial, Fajadet et al 2006
	1.04	12m TLR, longer stent length	TAXUS IV trial, Stone et al 2004
Mean	***1.35***		
Diabetes			
	1.81	12m TVR	RESEARCH registry, Lemos et al 2004
	1.51	12m TLR	SIRIUS trial, Holmes et al 2004
	1.80	12m TVR	TAXUS IV trial, Pinto et al 2006
	1.42	12m TLR (estimate), no angiographic follow up	Meta analysis, Cutlip et al 2002
	1.57	12m TVR	Clinical database, Agema et al 2003
	1.52	12m revascularisation by CABG	Clinical database, Wu et al 2004
	1.38	12m reintervention, elective patients	Assessment Report Addendum 3"
	1.36	12m TVR (estimate)	Clinical database, Gotschall et al 2006
	1.35	12m TLR (estimate)	Clinical database, Kornowski et al 1999
	1.34	6m TLR (estimate)	Clinical database, Kastrati et al1997
	1.73	12m TLR (estimate)	Clinical database, Jilaihawi et al 2005
	1.39	9m TLR	ENDEAVOR II trial, Fajadet et al 2006
Mean	***1.52***		

Table 1. Relative risk for repeat revascularisation for the independent risk factors of small vessels, long lesions and diabetes.

This table justifies the values used in the **re**-modelling for the relative risk of repeat revascularisation for the 3 risk factors.

Small Vessels: relative risk 1.75
Long Lesions: relative risk 1.35
Diabetes: relative risk 1.52

Sub-group	DES Risk Reduction	Comment	Source
Base case			
	0.67	12m TVR	RESEARCH registry, Lemos et al 2004
	0.75	12m TLR	SIRIUS trial, Holmes et al 2004
	0.65	12m TVR, no angiographic follow up	TAXUS IV trial, Pinto et al 2006
	0.53	9m TVR	TAXUS VI trial, Dawkins et al 2005
	0.56	9m TLR, no angiogram subset	ENDEAVOR II trial, Fajadet et al 2006
Mean	***0.63***		
Small vessels			
	0.67	12m TVR, vessels </= 2.5mm	RESEARCH registry, Lemos et al 2004
	0.76	12m TLR, vessels 2.5-3.0mm in non-diabetics	SIRIUS trial, Holmes et al 2004
	0.83	9m TLR, vessels <2.5mm	TAXUS VI trial, Dawkins et al 2005
	0.61	12m non-MI related TVR, stents <3mm	BASKET trial, Kaiser et al 2006
	0.57	9m TLR, vessels <2.5mm	ENDEAVOR II trial, Fajadet et al 2006
	0.71	12m TLR, vessels <3mm (estimate)	TAXIS IV trial, Stone et al 2004
Mean	***0.69***		
Long lesions			
	0.59	12m TVR, lesion >/= 33mm	RESEARCH registry, Lemos et al 2004
	0.78	12m TLR, lesions >15mm in non-diabetics with vessels >3mm	SIRIUS trial, Holmes et al 2004
	0.83	9m TLR, lesions >26mm	TAXUS VI trial, Dawkins et al 2005
	0.57	9m TLR, lesions >16mm	ENDEAVOR II trial, Fajadet et al 2006
	0.75	12m TLR, lesions > 20mm	TAXIS IV trial, Stone et al 2004
Mean	***0.70***		
Diabetes			
	0.28	12m TVR	RESEARCH registry, Lemos et al 2004
	0.77	12m TLR, in vessels >3mm, lesions 12-15mm in length	SIRIUS trial, Holmes et al 2004
	0.88	9m TLR	TAXUS VI trial, Dawkins et al 2005
	0.51	9m TLR	ENDEAVOR II trial, Fajadet et al 2006
	0.63	12m TLR	TAXIS IV trial, Stone et al 2004
Mean	***0.61***		

Table 2. Relative risk gained from DES for the independent risk factors of small vessels, long lesions and diabetes.

This table justifies the values used in the **re**-modelling for the absolute benefit of DES in the base case and for the 3 risk factors.

Base Case: Benefit of DES 63%
Small Vessels: Benefit of DES 69%
Long Lesions: Benefit of DES 70%
Diabetes: Benefit of DES 61%

Results

Table 3 shows the results of the model using a £300 price premium for DES, the CTC base-case elective repeat revascularisation rates (7.43%), the 6m BASKET risk reduction (41%) and 9 months additional Clopidogrel for all DES patients. The base-case scenario itself closely reproduces the result for this price premium shown in Table B on page 7 of Addendum 4' (ICER of £274,401 in the BCIS model and £277,100 in the Liverpool model). This has been undertaken merely to demonstrate to the committee the validity of the subsequent process.

This then provides us the validated opportunity to demonstrate to the Appraisal Committee:

- the impact of implementing their request for use of the Scottish registry revascularisation rate in the base-case; 13% rather than 7.43%
- the impact of implementing their request for use of the relative risks for the risk factors derived from the trials (albeit including information from other clinical databases as well); as demonstrated in table 1.
- the impact of using realistic risk reductions gained from DES; as demonstrated in table 2.
- the impact of applying the additional cost of Clopidogrel to a realistic proportion of patients; using UK BCIS data.

These effects are shown sequentially for the base-case in Figure 1. When **appropriate data** are imputed into the model (that we have shown is capable of reproducing Liverpool's results), the ICER is reduced by a staggering 80%. Clearly the base-case shows that DES are not cost-effective in all patients, but BCIS have never argued this to be so. We have consistently argued this point and that the initial NICE guidelines were appropriate. Diabetes is the only additional factor we feel necessary to add to the guidance.

Index stenting		
Cost per BMS	£278	
DES premium	£300	
Mean stents per procedure	1.615	
Additional procedure cost of using DES	£489	
Repeat revascularisation risk		***Base case***
Risk factor relative risk		1.00
BMS risk within 12 months		7.43%
Relative risk reduction		0.41
Absolute RR		3.05%
Investigation of recurrent symptoms		
Cardiology OP visits	2.10	
Cardiac surgery OP visits	0.19	
Angiography	1.00	
Cost of cardiology OP visit	£134	
Cost of cardiac surgery OP visit	£208	
Cost of angiography	£724	
Cost of referal and re-investigation (rePCI)	£1,005	
Cost of referal and re-investigation (reCABG)	£764	
Repeat revascularisation		
Proportion as CABG	0.09	
Proportion as PCI	0.91	
Cost of CABG	£7,066	
Cost of PCI	£2,609	
Average cost of revascularisation	£3,010	
Follow-up post revascularisation		
Cardiology OP follow-up visits	2.18	
Cardiac surgery OP follow-up visits	0.81	
Cost of cardiology OP follow-up visits	£94	
Cardiac surgery OP follow-up visits	£156	
Cost of follow up (rePCI)	£205	
Cost of follow up (reCABG)	£126	
Non-fatal MI saving	£13	
Impact of additional Clopidogrel		
Clopidogrel for 28 days	£35.31	
Clopidogrel for 9 months	£345.45	
Proportion non-ACS	100.0%	
Additonal Clopidogrel cost	£345.45	
Incremental cost of using DES		£694
Health-related utility		
QALY loss from PCI	0.00304	
QALY loss from CABG	0.03808	
QALY loss awaiting PCI	0.06070	
QALY loss awaiting CABG	0.03946	
Non-fatal MI saving	0.00055	
Avoided QALY loss using DES		0.002530
Incremental cost effectiveness ratio		**£274,401**

Table 3. Structure and results of the economic model using base-case 1% stent wastage, absolute risk, DES risk reduction and additional Clopidogrel costs from Addendum 4' (LiG values).

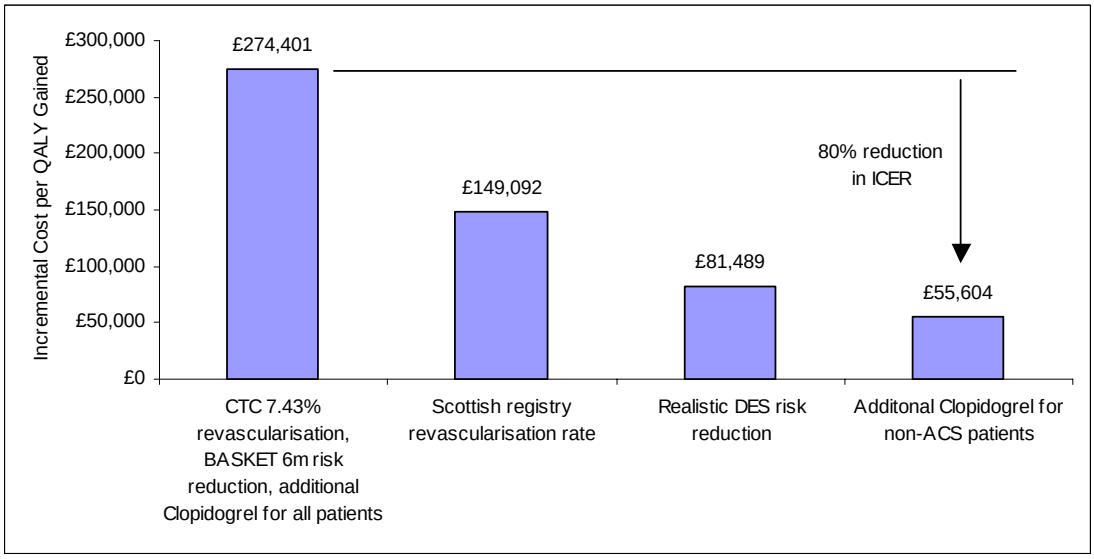

Figure 1. Impact of sequentially introducing Scottish registry baseline repeat revascularisation rates, 12m DES risk reduction and 9 months additional Clopidogrel for non-ACS patients only. The ICER falls by 80% from the value almost equivalent to that shown in Assessment Report Addendum 4'. This is the results when appropriate data input is used to generate ICREs for ALL patients

The BCIS model can now be extended to generate ICERs for each of the sub-groups by applying the risk factor relative risk increase and the risk reduction due to DES in Tables 1 and 2. The results, shown in Table 4, indicate that DES are cost-effective in all three risk factors groups up to a price premium of £354. Repetition of some elements shown in Table 3 is avoided. This price premium is reasonable given that the Appraisal Committee have received evidence that procurement processes have taken the premium down as low as £255 (Addendum 3' page 48).

Index stenting					
Cost per BMS	£278				
DES premium	£354				
Mean stents per procedure	1.615				
Additional procedure cost of using DES	£577				
Repeat revascularisation risk		***Base case***	***Small vessels***	***Long lesions***	***Diabetes***
Risk factor relative risk		1.00	1.75	1.35	1.52
BMS risk within 12 months		13.0%	22.8%	17.5%	19.7%
Relative risk reduction		0.63	0.69	0.70	0.61
Absolute RR		8.22%	15.7%	12.3%	12.1%
Non-fatal MI saving	£13				
Impact of additional Clopidogrel					
Clopidogrel for 28 days	£35.31				
Clopidogrel for 9 months	£345.45				
Proportion non-ACS	56.0%				
Additonal Clopidogrel cost	£193.45				
Incremental cost of using DES		£413	£98	£241	£251
Health-related utility					
QALY loss from PCI	0.00304				
QALY loss from CABG	0.03808				
QALY loss awaiting PCI	0.06070				
QALY loss awaiting CABG	0.03946				
Non-fatal MI saving	0.00055				
Avoided QALY loss using DES		0.005889	0.010776	0.008556	0.008400
Incremental cost effectiveness ratio		**£70,216**	**£9,118**	**£28,216**	**£29,939**

Table4. Outputs of the BCIS model for DES price premium of £354 (1% stent wastage).

The final question remaining is at what price premium are DES effective for each indication using the accurate input data? These results are shown in Table 5:

Indication	ICER by Price Premium				Threshold Premium (£30,000 per QALY gained)
	£100	£200	£255	£300	
All patients	DES dominant	£27,561	£42,795	£55,259	£208
Small vessels	DES dominant	DES dominant	DES dominant	£944	£491
Long lesions	DES dominant	DES dominant	£9,344	£17,922	£363
Diabetics	DES dominant	£36	£10,715	£19,453	£354

Table 5. Cost-effectiveness of DES by different price premiums and threshold price to achieve an incremental cost < £30,000 per QALY gained.

Limitations of the BCIS Model

There are potential limitations to our model. First, we have applied the relative risks for each risk factor to the absolute risk for BMS from the Scottish registry which is an unselected population rather than a population without the risk factors of interest. This may slightly increase the absolute risk for each subgroup and thus favour DES. However, even if we test this effect by reducing the base-case value by 10% (absolute 1.3%) to 11.7%, DES still fall below the £30,000 threshold value in all three sub-groups at a price premium of £308. It should be noted however that we could also be underestimating the absolute risk associated with bare metal stent use.

Second, the relative risks for each of the risk factors relate to slightly varying definitions of long lesions and small vessels as they appear in the literature. Where possible, we have identified sub-groups that are close to the existing NICE guidance criteria for the use of DES and sub-groups that are independent of other risk factors. The relative risk for long lesions may be underestimated because some of the data relate to 'relative risk per unit increase in length', where the unit may be undefined or as low as 1mm.

Third, we have not assumed any benefit from reduced mortality associated with avoiding repeat interventions. There are now 2 DES registries (Rotterdam and Danish Registry) which suggest there may well be a mortality benefit associated with DES.

Fourth, we may have underestimated the benefit due to avoided MI in patients with small vessels because the BASKET trials shows and absolute 7.5% reduction in MI at 18 months in this population (Kaiser et al 2006).

Summary

1. The BCIS model can reproduce the results of the Liverpool model within 1% when the same DES premium, wastage rate, CTC absolute revascularisation risk, 6-month DES risk reduction and proportion of patients receiving 9-months additional Clopidogrel are used as inputs.

2. Substituting repeat revascularisation rates from the Scottish registry, risk factor relative risks from the trials and wider literature, 12-month DES risk reduction from the randomised trials and wider literature reduces the base-case ICER by 80%.

3. All three high-risk sub-groups are cost effective up to a DES price premium of £354.

4. Threshold premiums to achieve an ICER of < £30,000 per QALY gained range from £354 to £491, dependent upon the sub-group.

5. BCIS recommend that the existing guidance for the use of DES be retained, with the addition of diabetics as an additional sub-group.

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Stent thrombosis and drug eluting stents

There has been a good deal of debate lately regarding the potential excess risk of stent thrombosis associated with the use of drug eluting stents (DES), especially late stent thrombosis (> one year) in higher risk patients.

The following facts have been established by peer review publication:

- Stent thrombosis occurs with bare metal stents (BMS) and in some studies has been shown to have an incidence of *late* stent thrombosis (1).
- The drug eluting from DES may result in delayed re-endothelialisation and thus leave stent struts exposed to platelet induced thrombus. Prolongation of the administration of dual anti-platelet therapy (aspirin and clopidogrel) to 3 months for the CYPHER (Sirolimus) stent and 6 months for the TAXUS (Paclitaxel) stent in the IFUs was a logical response to this, since animal data suggested that re-endothelialisation was complete by these times with these stents.
- Multiple meta-analyses comparing trial data (BMS versus DES or one DES versus another) showed that there was no difference in stent thrombosis or clinical event rates between BMS and DES or the two DES that were available at that time (2-5).
- These meta-analyses were based on trial patients, which had end points by the nature of the studies measured within one year.
- Dr.E.Camazind presented an un-peer reviewed abstract in the "hot-line" session at the European Society of Cardiology in September 2006 which suggested that there was a 40% excess relative risk associated with DES use. This was based on data that his team were able to obtain from the publications and was up to the time of "latest follow up" in the papers reviewed.
- Review by others subsequently failed to demonstrate any clinical excess risk beyond one year associated with the use of DES when patient level data was analysed. These data, encompassing all patients and thus different from the publication data, showed that while there is indeed a small but significant number of stent thromboses beyond one year (5 CYPHER versus 0 BMS controls out of 1780 trial patients and 9 TAXUS versus 2 BMS controls out of 3506 trial patients) this did not translate into any differences in clinical events (death or AMI). This may be because the event rate in stent thrombosis is approximately 50% rather than 100%. In addition, restenosis associated with BMS may be associated with acute coronary syndromes (6) and subsequent myocardial infarction and death.
- Variation in definitions between these trials led, in the autumn 2006, to the establishment of standard definitions of stent thrombosis (the so-called ARC definitions). All trial data were re-adjudicated by blinded and independent groups working with Dr D.Cutlip's group in Boston USA.
- The results using patient level data from the trial patients with standard definitions followed out to 4 years showed the following stent thrombosis rates

CYPHER	1.2% :	CONTROL BMS 0.6%	NS
TAXUS	1.3% :	CONTROL BMS 0.9 %	NS
ENDEAVOR	0.5%	CONTROL BMS 1.5%	NS

- These data were published in the New England Journal of Medicine 2007 356 998-1008
- A concerning has been raised regarding so-called off-label use of DES. Various registries have assessed the potential excess risk of stent thrombosis in patients either not included in the current labelling or as yet un-trialled. In this context the current labelling for the two main DES is as follows

CYPHER On label : up to 30 mm: 2.25 mm to 4.0mm : In-stent restenosis : diabetes

Off label : un-protected left main stem : chronic total occlusion : saphenous vein graft

Dossier submitted : AMI
Unspecified : direct stenting: bifurcations : multi-vessel disease

TAXUS On label : up to 32 mm : 2.25 mm to 5 mm : Diabetes (in Europe)- AMI : in-stent restenosis : chronic total occlusions

Off label : un-protected left main stem : saphenous vein grafts : bifurcation

There have been a number of "real life" registries that have looked at the stent thrombosis rates in the so-called off-label patients. Many of these were presented to the FDA hearing on drug eluting stents in late 2006. All suggest that for the "higher risk" patient there is a small excess of stent thrombosis beyond one year. This averages out at approximately 0.3%-0.6% per annum. Some have shown that although there is an excess risk this again appears not to be associated with excess clinical risk compared to BMS (the Duke data for example indicates that the difference in adjusted cumulative risk of mortality for those with DES off clopidogrel after one year is 7.2% versus 6.2% for BMS off clopidogrel (p=0.44). Further this database suggested that those still on clopidogrel beyond one year with DES had a lower incidence of death (3.1%) than those off clopidogrel ($p< 0.02$). There was no evidence of value in clopidogrel in BMS beyond one year. Such data are interesting but are open to a number of confounders including patient selection.

In late 2006 the FDA pronounced on stent thrombosis and dual anti-platelet therapy. The conclusions were:

On-Label DES Use

• **"Both approved DES are associated with a small increase in stent thrombosis compared to bare metal stents that emerges 1 year post implantation.**
• **<u>Increased risk of stent thrombosis was not associated with an increased risk of death or MI vs. BMS.</u>**
• **The concerns about thrombosis do not outweigh the benefits of DES compared to BMS when DES are implanted within the limits of their approved indications for use."**

Off--Label DES Use

• With more complex patients, there is an expected increased risk in adverse events for both DES and BMS.
• Off-label use of DES is associated with an increased risk of stent thrombosis, death or AMI compared to on-label use.
• Data on off-label use are limited, and additional studies are needed to determine optimal treatments for more complex patients.

Conclusions Regarding Antiplatelet Therapy

• A longer duration of antiplatelet therapy than is currently included in the CYPHER and TAXUS labelling may be beneficial. The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy
• The labelling for both approved DES should include reference to the ACC/AHA/SCAI PCI Guidelines.
– Aspirin should be continued indefinitely plus a minimum of 3 months (for Cypher) or 6 months (for TAXUS) of clopidogrel. Therapy should be extended to 12 months in patients at low risk of bleeding.

The debate regarding length of prescription time for clopidogrel is far from clear not least since there are other registry data from Colombo's group which suggest that most (n=42) stent thrombosis (total n= 58/3021 patients) occurs within the first 6 months and most of these (HR 11.1 ci 3.47-39.24) are due to discontinuation of clopidogrel within this time frame. 3 of the 6 late stent thromboses (> 1 year) had been off their clopidogrel for some time suggesting the mechanisms in these few patients are unclear and are unaffected by length of clopidogrel use. Early discontinuation of clopidogrel continues to be the factor most likely to cause stent thrombosis

Summary: Stent thrombosis appears not to exceed the incidence seen in BMS within the first year in trial patients. Dual anti-platelet therapy during this time is mandatory, especially in the first 6 months. Data supporting the extension of DAPT to one year are not conclusive. The decision of BCIS to recommend extension to 1 year was based on a consensus across the country amongst cardiologists. The safety of our patients is critically important to us and we felt this was a reasonable stance to take while further data are gathered and debate takes place. It is possible that in the future this recommendation will change and the duration could be reduced.
Certainly there may be an excess of stent thrombosis in DES especially in the more complex patient subsets (so called off label use) beyond one year. However, this does not appear, in both trial patients and in those registries that have studied clinical end points, to translate into excess clinical events in DES patients. Further studies in the higher risk off-label use extending out to 3-5 years are required. There are 3 such on-going trials. It is important to note that all patients receiving any stent (DES or BMS) in the context of an acute coronary syndrome should receive dual anti-platelet therapy for 12 months according to NICE guidance. At least 50% of patients treated in the UK are treated in the setting of acute coronary syndromes.

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We have read Addendum 3' of the Liverpool Reviews and Implementation Group (LRiG) in the continued process of the re-assessment of drug eluting stents (DES) for the National Institute for Health and Clinical Excellence.

The Appraisals Committee is in the unenviable position of having to deal with a fundamental difference of opinion between the clinical experts and the health economic analysts (LRiG) they have asked to advise on this subject. We continue to believe that the LRiG work remains deeply flawed and we do not believe they have either acknowledged or understood the criticisms of the original report that were put to them by the clinical experts at the NICE Appraisal Meeting on 1st Feb 2006.

These criticisms were:

- The use of a local audit to develop a model which dictates national policy is inappropriate.
- The absolute risk of repeat intervention had been systematically downgraded in the original assessment report and then "justified" by a highly selective review of the literature.
- The absolute benefit of drug eluting stents had been downgraded for spurious reasons which probably reflect peculiar local practices in Liverpool.
- The cost of both drug eluting stents and bare metal stents were not calculated using the list price as described in the NICE recommended methodology.

We do not believe any of these concerns have been adequately addressed. We have no desire to repeat all of the arguments used in our original response but given the extraordinary position that the LRiG continue to hold we feel we have no option.

It is worth stating at the onset that there are certain aspects of the LRiG report that we do agree with. These are that DES reduce the need for repeat revascularisation by approximately 75% and that the results of the randomised trials appear robust over time. They also seem to accept that "Results from RCTs are the accepted standard for establishing clinical efficacy of a given treatment". While it is also true that registry data may add information often it has incomplete monitoring and is subject to selection bias.

We will summarise our critique of the first report and discuss whether any of our concerns put forward at the first appraisal meeting have been addressed. Following this we will comment on the specific comments on the addendum.

(a) Fundamental problems with the original Appraisal Report.

(1) The CTC database.

The principal problem with the LRiG report is their reliance on the flawed CTC model. This was clearly explained both in our documentation and by the experts on the day of the meeting. National policy cannot be made on the basis of a local audit. The potential for systematic bias is huge in an audit but again this is not acknowledged.

Decisions on which method of revascularisation is used for an individual patient are made and influenced by knowledge of the published literature. The potential for the selection of a "low risk" population to undergo PCI is therefore obvious. This is best illustrated by the low incidence of diabetes in the Liverpool database. The 13% incidence of diabetes reported is very low compared to the 25% in the Sirius trial (ref). In the Kings College Hospital database the incidence is also considerably higher than the 13% reported by Liverpool. From April 2005 to March 2006 1326 patients were treated. Of these 20.2% were diabetic; 2.2% diet controlled, 10.8% NIDDM, 6.5% IDDM and 0.7% newly diagnosed (personal communication Dr Martyn Thomas). This clearly reflects a higher risk group in one population compared to another and we believe points to a "low risk" population undergoing PCI in the Liverpool audit. These concerns have not been addressed by the addendum. . If the prevalence of a variable is low in a relatively small population at low risk of future events, statistical analysis may well fail to reveal the significance of this variable as a predictor of restenosis, whereas the variable actually is an independent predictor of events in a more generalised and higher-risk population (in which the prevalence of the variable might be higher).

Furthermore, we remain concerned about the quality of the follow-up of the Liverpool audit data. We feel confident the in-hospital and short term data is acceptable, but this type of database is not designed to address follow-up events. Many such databases exist throughout the country but no unit would claim its database is suitable to allow the analysis carried out by the LRiG. This is why the DOH is investing so much time and money in the National Audit project (UKCCAD) which will allow linkage of the BCIS, MINAP, Cardiothoracic Surgery and ONS registries. This will be the only reliable way of truly tracking the patient journey. How reliable is the longer term follow up data from the Liverpool audit? We are aware that there is no systematic follow up of these patients. They will appear on the database and within the LRiG model only if they fortuitously happen to re-present to the base hospital within the 1 year time period. We are aware that because of long waiting lists in this unit many patients have repeat revascularisation greater than 1 year after the index procedure. We are told by LRiG that the number not included is 17 patients but our information suggests the number is 52 patients! (personal communication Rod Stables). These issues were raised during the committee meeting but have not been addressed in the current addendum and represent a fundamental flaw in the methodology.

Finally it is assumed within the model that all patients who have not represented are well with no angina and therefore no disutility. Is this correct? How many patients have had a follow up angiogram because of angina but a clinical decision made to treat the patient medically? We are not aware whether such information is known and certainly this has not been factored into the model. Again this was raised at the first meeting by the experts but has not been addressed in the addendum.

Therefore, we believe this methodology is fundamentally flawed. We believe any model should be based on the randomised trials and the systematic bias away from high risk patients and lack of careful longer follow up data in this local audit should exclude this model from being used to formulate national policy.

The absolute risk of repeat intervention.

Because of the limitations of the CTC database we believe the absolute risk of repeat revascularisation (7.8% in the elective population and 11% in the non-elective population) is falsely low and is an outlier in the published literature. During the committee meeting we presented evidence for the absolute risk of repeat revascularisation for bare metal stents (in the published literature where there is no protocol mandated angiogram appendix [table 1]). This table demonstrates that the Liverpool database constitutes only 5% of the patients in the literature and the repeat revascularisation rate of 8.8% is much lower than the largest 2 series (Singh et al [11,484 patients] and Brophy et al [16,746 patients]) which recorded 14% and 12.8% respectively. In addition this data remains unquoted in the assessment report and the addendum. The reason for this is unclear to us and we would continue to argue that the correct incidence for repeat revascularisation should be 12.1% as demonstrated in table 1.

The data from randomised trials is shown in table 2. Within these trials it can be seen that the target lesion revascularisation rates (TLR) are 4.2%-5.4% in the DES arms and 13.8%-20% in the DES arms. More importantly it is clearly shown that smaller vessels, longer lesions and diabetics are associated with a higher TLR within the scientific rigor of a randomised trial. Once more the absolute difference in rate of TLR between patients treated with DES and BMS in the LRiG model is at variance with the published randomised trials and it may even be above the 12.1% we have suggested.

(2) The absolute benefit of drug eluting stents.

In the randomised trials the "treatment effect" of DES is consistently 60-75%. We strongly argued that the downgrading of the treatment effect of DES in the Liverpool model (to 35-50%) was wholly inappropriate. It appears to be principally based upon the fact that repeat interventions in the Liverpool database were to a non-culprit artery at follow up in a significant number of cases. We repeat that this is nonsense. Again this may reflect unusual practice by the Liverpool clinicians and we were unclear how the effect of a DES could be downgraded if it did not influence a non treated artery. The logic of this argument is unclear and once more this has not been addressed in the addendum. Why has there not been further information requested from around the UK as to whether this is a "common" feature? This downgrading effect is so important in the model it is surprising (especially given the other idiosyncrasies of the Liverpool database) that this has not been verified with other units. Once more this is not addressed in the addendum.

(3) The cost of drug eluting stents.

Our understanding of the "NICE process" is that "list price" costing should be used in cost effective analyses. This was not used in the original assessment report and was pointed out in the first committee meeting. We remain unclear why these "new rules" have been allowed by the committee for the LRiG to use. This point still needs clarification.

(b) Specific comments on addendum 3'

(i) Data sources

We believe that the 12 papers quoted in the data sources demonstrate the fundamental problem with the LRiG approach to this assessment. 11 are registries and 1 is a randomised trial from a single centre. Most if not all of the world community believe that the "gold standard" for the assessment of a new device or drug is a multi-centre randomised clinical trial. The LRiG do not appear to agree with this which we believe is remarkable. We believe these papers are not reliable, including the BCIS database. The BCIS database was designed to give in hospital outcomes. BCIS has never reported the incidence of restenosis, nor the recurrence of angina, nor the need for repeat revascularisation, as its previous method of data collection was not designed to address these issues. It could only report on the proportion of interventions that were performed for a restenosis lesion. There has been no possibility of identifying those who undergo CABG for restenosis or those who choose to continue with their angina rather than undergo CABG or repeat PCI. If the LRiG is to quote registries it should, at the very least, understand what the registries were designed for and what their limitations are. The ability to track outcomes more accurately is one of the reasons why BCIS has enthusiastically supported the DOH audit initiative.

(ii) Wastage rates

The stent wastage rate is really a tiny part of the deep flaws in the LRiG analysis and we are amazed at the amount of effort which has gone into this unnecessary analysis compared to the more fundamental problems with the model. The time spent on what is a clinical irrelevance would appear to highlight how detached the LRiG is from the clinical world.

(iii) Procedural disutility

Once more we are surprised at the amount of effort put into the relative disutility of PCI versus CABG. Much more important would be to spend some time and effort actually finding out what happened to the patients. How many had a follow up angiogram but where then treated medically? How many have ongoing angina? We understand that this would require further work demanding clinical skills that the LRiG group do not have. The evaluation of efficacy of a treatment demands a very careful follow-up of all patients, and this is only ever achieved by the organisation around a randomised trial. Economic analyses should evaluate the results of a carefully collected and comprehensive database in which two treatments are compared and should not require a theoretical modelling exercise, especially when the assumptions made in the model are so obviously flawed.

Within this piece of work the difference in the mode of any follow up revascularisation between elective and non-elective patients is remarkable. Once more rather than checking if this was genuine or a "quirk" of the Liverpool unit the LRiG have assumed this was "true" and applied it to their model. This is clearly inappropriate.

Once more we would stress that the time and effort put into this "number crunching" rather than addressing the true clinical issues represents a major problem with the process, the expertise, the model and the LRiG.

(iv) AMI and mortality

We have never proposed there was a mortality benefit of DES compared to BMS and believe this element of the addendum was unnecessary. We do believe that trials have demonstrated that the mortality of stenting and CABG are similar in revascularisation and therefore any benefit of CABG over medical therapy in particular anatomical subgroups would equally apply to PCI (even though these trials have not been performed).

(v) Realistic repeat revascularisation rates.

We find this chapter most disturbing. This refers back to the "data sources". At the committee meeting the data from both tables 1 and 2 was presented. The reason that these data are now excluded in favour of such obscure registry references at the complete exclusion of the published data we have referred to is difficult to understand. Unfortunately, the result of their presentation is to make the reader believe that the LRiG continues to use a very selective approach to the published data to support what appears to be a very extreme view, rather than a systematic and objective view of the literature which should be demanded by the NICE committee. We believe realistic repeat revascularisation rates are shown in tables 1 and 2.

(vi) Risk factor models and subgroups

This chapter merely repeats all of the misconceptions introduced by the use of the CTC database to produce the model. We have already strongly argued that this is fundamentally flawed and any developed model should be based on risk factors for restenosis which are established from the properly controlled randomised trials.

Summary.

We continue to utterly reject this assessment report. We have repeatedly argued that the assessment is fundamentally flawed because of the use of non validated data from a local database with inadequate follow-up data collection and the selection of a low risk population for angioplasty. To change national policy on the basis of such data would be a major mistake.

We have strongly argued, in our original submission, in our subsequent comments on the Assessment report and with the views of the experts at the Committee Meeting that the original NICE evaluation on DES was correct and that small vessels and long lesions remain major indications for the use of DES. In addition we have used data from the published properly performed randomised trials to demonstrate that diabetes is an additional indication for a DES which should be added to the guidance. . More recently, there are very clear results from

randomised trials showing the very obvious advantages of using DES rather than BMS for the treatment of in-stent restenosis and chronic total occlusions.

We have sought the views of the interventional community. There is a universal view that if we are heavily constrained in our use of DES as proposed by the LRiG then we will have no option but to start a major re-referral process of many of our patients back to the surgeons for bypass grafting. We believe this would be an honest evidence-based approach to revascularisation in a world with very limited DES use and would be the best service to our patients. As explained by the experts to the committee this would be a clinical and political disaster. Patients can and should be treated by DES and should avoid surgery when possible. Because of government investment over the last few years the progress of the UK in cardiology has been huge because of investment and we are now used as an example of what can be achieved throughout Europe. Waiting lists have virtually disappeared and the NSF has essentially been delivered by coronary angioplasty. A return to surgery would be a retrograde step and would certainly mean that any chance of delivering an 18 week target from referral to treatment of coronary artery disease would be lost.

We hope the NICE committee will review the randomised trial data and agree with us that the current guidance for a DES should be a vessel <3mm in diameter, a lesion >15mm in length or the presence of diabetes.

Table 1.
Absolute risk of repeat revascularisation for BMS (no protocol mandated angiogram): published evidence

Source	Population (N)	No. of revascs (n)	% Revascs	Follow-up	Weight
Bagust et al, 2005	2,884	255	8.8%	12m TVR, CTC clinical database	5.3%
Shrive et al, 2005	7,334	601	8.2%	12m any revasc, clinical database	13.4%
Singh et al, 2005	11,484	1,609	14.0%	PRESTO trial. 9m TVR, ischaemia-related revasc	21.0%
Jilaihawi et al, 2005	1,003	51	5.1%	12m TLR, clinical database	1.8%
Serruys et al, 1998	206	16	7.8%	BENESTENT II trial.12m TLR no angio group	0.4%
Gershlick et al, 2004	38	6	15.8%	ELUTES trial control group.12m TLR symptom driven revasc	0.1%
Stone et al, 2004	385	49	12.7%	TAXUS IV trial control group.12m TLR no angio cohort	0.7%
Homes et al, 2004	525	85	16.2%	SIRIUS trial control group.12m TLR angina driven revasc	1.0%
Lemos et al, 2004	380	41	10.8%	12m TVR angina driven, clinical database	0.7%
Serruys et al, 2001	600	102	17.0%	ARTS trial stent arm.12m all revascs, no follow-up angio	1.1%
Wu et al, 2004	3,571	577	16.2%	12m revasc, prospective registry of routine practice	6.5%
Agema et al, 2004	3,177	304	9.6%	9m TVR in routine clinical practice	5.8%
Gotschall et al, 2006	848	63	7.4%	12m TVR, clinical database	1.6%
Ellis et al, 2004	5,239	702	13.4%	9m all revascularisations, clinical database	9.6%
Brophy et al, 2005	16,746	2143	12.8%	9m re-intervention, clinical database	30.6%
Kaiser et al, 2005	281	22	7.8%	6m TVR, BASKET trial, no angiogram	0.5%
Overall	**54,701**	**6,626**	**12.1%**		**100.0%**

- Studies in red were cited in the Assessment report. The 2 largest studies (Singh et al and Brophy et al) were not cited.
- Liverpool database constitutes 5% of the patients in the literature.

Table 2
Absolute Risk (%): Trial Data – similar f/u

Study name	Outcome	F/u	Cypher (%)	BMS (%)	Lesion Length (mm)	Vessel Diameter (mm)	Diabetes (%)
C-SIRIUS	TLR	9m	4.0%	18.0%	14.5	2.6	24.0
DIABETES	TLR	9m	7.5%	31.3%	15.0	***2.3***	***100.0***
E-SIRIUS	TLR	9m	4.0%	20.9%	15.0	2.6	23.0
PRISON II	TLR	9m	4.0%	19.0%	16.0	3.4	10.0
RAVEL	TLR	9m	0.8%	13.6%	9.6	2.6	19.0
SCANDSTENT	TLR	6m	2.5%	29.6%	*18.8*	2.9	18.0
SES-SMART	TLR	8m	7.0%	21.1%	13.0	***2.2***	***24.9***
SIRIUS	TLR	9m	4.1%	16.6%	14.4	2.8	***26.0***
STRATEGY	TLR	8m	5.7%	20.5%	13.0	***2.3***	17.0
Overall			**4.2%** (60/1437)	**20.0%** (285/1425)			

Study name	Outcome	F/u	Taxus (%)	BMS (%)	Lesion Length (mm)	Vessel Diameter (mm)	Diabetes (%)
TAXUS I	TLR	6m	0.0%	6.7%	10.7	3.0	23.0
TAXUS II	TLR	6m	3.8%	13.0%	10.5	2.8	11.0
TAXUS IV	TLR	9m	3.0%	11.0%	13.4	2.8	23.4
TAXUS V	TLR	9m	8.7%	15.7%	*17.3*	2.7	***31.7***
TAXUS VI	TLR	9m	6.9%	19.1%	*20.6*	2.8	20.0
Overall			**5.4%** (95/1753)	**13.8%** (242/1751)			

Smaller vessels, longer lesions, more diabetics = higher TLR.