Cordis
a Johnson & Johnson company

Response to LRiG Addendum Report: Additional Evidence and Analyses Requested by Appraisal Committee (for Review of Guidance No. 71).

Executive Summary

- Long lesions and small vessels have been accepted as commonly occurring risk factors for repeat revascularisation in the Addendum (p35).

- The Addendum does not report several important studies that identify diabetes as an independent risk factor for repeat revascularisation, instead relying on risk factors identified from one uncorroborated study at CTC Liverpool. These unreported studies are presented on page 5 of our response.

- The Addendum does not accurately represent absolute repeat revascularisation rates in BMS, instead continuing to depend upon the CTC dataset that the Appraisal Committee have already judged as not representative. In answer to the Appraisal Committee's specific question, the repeat revascularisation rate was **13%** for the general population in the Scottish registry for the year 2000/2001 (page 10 of our response). The 12m BMS target vessel revascularisation rate from the BASKET trial is consistent with the Scottish registry at 13.6%.

- LRiG have used poorly defined and unnecessarily complicated correction factors to apply treatment effects defined in terms of target lesion revascularisations to baseline total revascularisation rate. This introduces considerable errors and uncertainty into LRiG's cost effectiveness estimates.

- LRiG have understated the reduction in repeat revascularisation conferred by Cypher. LRiG use a 41% risk reduction rather than a proven 68% indicated from randomised trials without protocol-mandated angiographic follow up (page 14 of our response).

- The use of 'market prices' in this review introduces confounding factors unique to devices that the Committee needs to recognise. The use of list prices, as agreed at the scoping meeting, is more informative.

- The market price of BMS has been influenced by the existing NICE guidance resulting in appropriate DES use in over 50% of patients. The list price of DES at launch was equivalent to the list price of bare metal stents at their launch. Using market prices makes decisions on the QALY time-dependent and liable to 'flip-flop' back and forth.

- As shown in our initial submission, when the correct assumptions are entered into the model, the 2-year ICERs for Cypher stents in patients without risk factors listed above is £ 29,259 per QALY gained, £10,178 for those with vessels <3mm in diameter, £16,460 for those with lesions >15mm length and £9,702 for those with diabetes.

- **With long lesions and small vessels confirmed as placing patients at increased risk of repeat revascularisation and trial evidence showing that the treatment effect of Cypher has not diminished since Guidance 71 was issued, it follows that there is no reason to change the existing Guidance with respect to these risk factors.**

- **In fact, as diabetes has been established as an independent predictor of repeat revascularisation, this Review should also recommend the use of DES for all diabetic patients undergoing PCI.**

Introduction

- The deliberations from the first Appraisal Committee meeting identified a number of potential issues for the addendum to consider. Consistent with Committee's comments, we suggest that the key issues driving cost effectiveness and thus requiring consideration are:

  A. The independent risk factors for repeat revascularisation – consistently shown in the literature to be small vessels, longer lesions and diabetes.
  B. The absolute risk of revascularisation with bare metal stents (BMS) – values of 12% to 14% are demonstrated when all data sources are considered for an unselected population, and higher in patients with the above mentioned risk factors.
  C. The risk reduction gained from DES – Cypher confers a 68% reduction in TVR.
  D. The price differential between BMS and DES.

Our response below considers these issues in turn.

- We believe that a number of other questions the Committee asked LRiG to consider will not be drivers of cost effectiveness and thus require no further comment. These issues are:

Risk of AMI for BMS and DES -	We do not claim any difference.
Mortality risks with PCI & CABG -	We do not claim any difference.
Disutility -	We are willing to accept the manner in which utility has been applied up until now. We are also willing to accept the utility values from our initial submission, or the LRiG original report.
Wastage -	We accept the inclusion of this factor, but we do not consider it to be a pivotal decision point

A. Risk Factors for Repeat Revascularisation

- Overall, LRiG's representation and interpretation of the extensive published literature pertaining to previous risk factor studies appears to us to be highly selective. Much of the literature is dismissed by LRiG as being based on 'beliefs' and 'perceptions'. There is an unfortunate implication here that only LRiG has undertaken any serious study of this question (page 31):

  "The success of the LRiG formulations to outperform other possibilities is not surprising since they were developed to provide 'best fit' to these data. However, it is notable that none of the additional variables ***widely believed*** *to be most influential by the clinical community (and therefore factored into trial designs) showed any indication of independent effect, or acted to modify the LRiG factors to any serious extent. This suggests that* ***common perceptions*** *about the genesis of restenosis may be misconceived".*

- Had all the available evidence been presented in the Addendum, then the conclusion that long lesions, small vessels and diabetes frequently show signficant independent effects, would be the only one that could be drawn. The omission of such evidence could lead to the Appraisal Committee being mis-informed.

- It appears to us that a substantial body of evidence has been readily dismissed when it does not appear to fit with LRiG's own published findings, yet deference is paid to the 'weight of prior evidence' when it does fit their message. For example, in reviewing the evidence for AMI and mortality (*for which we make no claim*), the report concludes on page 23: *"The* ***weight of prior***

evidence is sufficiently strong *that a very compelling body of new information would be necessary to alter the current consensus that PCIs provide symptomatic relief but do not alter life expectancy…".*

- With respect to other studies that considered the question of predictors of repeat revascularisation, we would draw the Committee's attention to the recent paper by Gotschall *et al* (2006) in which the authors state: *"Indeed, prediction of restenosis after PCI is one of the most studied topics in interventional cardiology".* There is a wealth of data to draw upon beyond LRiG's analysis.

- The reason for presenting separate analyses for elective and non-elective patients, both in the Assessment report and the Addendum is not explained and it is an unneccessary, complicating factor in the analysis. In the absence of any stated scientific rationale, this is presumably to maintain consistency with the Bagust paper from Liverpool (Bagust *et al*, 2005). This paper itself does not provide any argument for the separation of elective and non-elective patients either.

- LRiG have presented in Table A6.2 (p37), a more wide-ranging, (but still incomplete) review of the literature pertaining to risk factors for repeat revascularisation than in either the AR or the Bagust paper. As a result, they now acknowledge that long lesions and small vessels are commonly occurring risk factors in the literature. Thus, a necessary condition for the original guidance recommending DES for use in lesions >15mm length and vessels <3mm diameter is supported.

- The Committee should note that Table A6.2 *"Summary of risk model factors in reviewed papers"* does not present the results of a further 7 risk models identified by Cordis. Curiously, 5 out of these 7 identify diabetes as an independent risk factor for repeat revascularisation, 5/7 identify small vessels as predictive and 3/7 identify longer lesions as predictive. Table 1 below reproduces LRiG's Table A6.2 to include these other data sources, all of which have been highlighted in earlier industry submissions.

- We note that LRiG judge their own risk model as robust with relative risks as low as 1.51, but in commenting on the published risk models they reviewed in Table A6.2 of the Addendum, they state on page 35 that *"very few individual factors achieved a level of significance generally considered as unequivocal evidence of a clear effect (RR of 2 or greater).* It is unclear why LRiG place so much weight on their own risk model when 3 out of 6 of their risk factors also have a RR <2. LRiG's criteria for selecting risk factors seem variable.

	Sources cited by LRiG							Sources not cited by LRiG						
Risk Factor	SCRR (Pell *et al* 2001)	Toulouse (Elbaz *et al* 2002)	Netherlands (Agema *et al* 2004)	Cleveland (Ellis *et al* 2004)	Washington (Wu *et al* 2004)	LRiG elective	LRiG non-elective	Kastrati et al 1997^	Singh *et al* 2005$	Iakovou *et al* 2003^	Kornowski *et al* 1999^	Nikolsky *et al* 2005	Jilaihawi et al 2005^	Gotschall *et al* 2006^
3 vessel disease	√			√	√	√								
Previous MI			√		√					√				
Ostial location				√					√					
Unstable angina				√			(√)		√		√			
Restenotic				√		√√								
Saphenous graft				√										
LAD				√					√					
Stable angina (vs. none)					√									
Creatinine					√									
Lesion length			√	√	√				√			√		√
Small vessel		√√	√√	√			√√	√√		√	√	√		√
Diabetes			√~		√#			√	√	√	√		√*	
Previous CABG							√√		√					
Calcification						√√								
Angulation						√								
Multiple stents								√√						
Age									√					
Smoker									√					
Hypertension									√					
Number of lesions									√					
Use of rotablator									√					
Previous PCI										√√	√			
Body mass index												√√		
Acute coronary syndromes														√√

Table 1: Clinical and procedural factors independently predictive of repeat revascularisation after coronary stenting with BMS.

√ = p < 0.05 & RR, hazard ratio or odds ratio < 1.6. √√ = RR, hazard ratio or odds ratio >= 1.9.

√~ Netherlands: Diabetes was independently predictive of TVR in the publication (RR 1.52, 0.99-2.32). Excluded by LRiG because univariate predictors with p < 0.10 were entered into the multivariate regression model. ***LRiG appear to have made an error in excluding this study because p < 0.10 is the standard criterion for entry into a backwards stepwise regression model.***

√# Washington: Diabetes excluded by LRiG because it was predictive of repeat revascularisation by CABG only (HR 1.52, 1.03-2.23). Revascularisation by CABG is still revascularisation!

√* UK data (Dr H Jilaihawi, personal communication). RR = 1.8, p = 0.05.

^ 5 out of 7 Risk models not cited by LRiG were developed from clinical databases without mandated angiographic follow up.

$ PRESTO study – ischaemia-driven TVR required presence of ischaemic signs & symptoms.

- Small vessels, long lesions and diabetes are the most commonly occurring factors when all risk models are considered.

- Two studies in Table 1 specifically inform the 'vessels <3mm' element of current guidance. The relative risk for TLR with an MLD <3mm was 2.09 (95% CI 1.42-3.07, P = 0.0002) in the Toulouse study (Elbaz *et al* 2002). The odds ratio for TLR with an MLD <3mm was 2.05 (95% CI 1.77-2.34) in the Kastrati study (Kastrati *et al* 1997). These two studies showing MLD <3mm as predictive of repeat revascularisation are highly relevant and clearly demonstrate that this strongly predictive factor should be retained in the new guidance.

- LRiG dismiss the '<3mm factor', stating on page 33 that *"since this factor cannot be known when the choice of stent is made it is of no immediate value in assessing sub-groups with the highest risk of subsequent revascularisation"*. However, this assertion is wrong. The reference vessel diameter is known prior to stenting and is a key factor determining stent selection. Trials consistently show that MLD after stenting is smaller than the reference vessel diameter. Thus, if DES are implanted in vessels <3mm diameter, the post-procedural MLD will invariably be <3mm.

- LRiG undertake further work in Figure A3 (page 30) to show that diabetes is not a risk factor for repeat revascularisation. They do this using a risk model developed from the CTC database. The CTC data have already been judged by the Appraisal Committee as unrepresentative and come from a single centre that may not reflect patients managed in the wider NHS.

- Gotschall *et al* (2006) did not find that diabetes reached formal statistical significance as an independent predictor of 1-year TVR (OR 1.62, 0.85-3.06, p = 0.14), but in testing three different risk models, they concluded:
    - *"The results demonstrate that the model that most appropriately fit the data included the reference vessel diameter, lesion length and diabetes mellitus (Hosmer-Lemeshow goodness-of-fit statistic = 2.339; p = 0.969)."*
    - *"Indeed, the variables included in this (risk) score (reference vessel diameter, lesion length and diabetes mellitus) have also been consistently associated with outcomes in several clinical and experimental studies."*
    - *"The clinical implications of this study relate to the prediction of a new TVR after coronary stenting based on pre-procedural characteristics, which can aid to the decision to implant a drug-eluting or a bare metal stent."*

- Table 2 summarises the risk for repeat revascularisation posed by diabetes based on the studies in Table 1.

Study	Diabetes Risk Statistic (95% CI)
Agema et al 2004 (TVR)	RR = 1.52 (0.99-2.32)
Wu et al 2004 (first repeat revasc)	HR = 1.52 (1.03-2.23)
Kastrati et al 1997 (TLR)	OR = 1.45 (1.11-1.80)
Singh et al 2005 (TVR)	OR = 1.42 (1.08-1.87)
Iakovou et al 2003 (TLR)	OR = 1.00 (1.00-1.01)
Kornowski et al 1999 (TLR)	OR = 1.48 (1.12-1.82)
Jilaihawi et al 2005 (TLR)	RR = 1.8

Table 2. Risk of repeat revascularisation posed by diabetes as an independent risk factor. *Risk statistics are raw data as reported in each study, RR = relative risk, HR =hazard ratio, OR = odds ratio.*

- LRiG's comparison of their risk factors versus the 'conventional' risk factors is not valid because they have compared both sets of risk factors against the CTC dataset. LRiG's risk factors will always perform well against the dataset they were produced to fit – it's a self-fulfilling prophecy which LRiG themselves acknowledge in the comments:

  "The success of the LRiG formulations to outperform other possibilities is not surprising since they were developed to provide 'best fit' to these data."

- Good practice would suggest using an independent dataset to obtain an unbiased comparison of the discriminatory power of the different sets of risk factors.

- In addition to the published studies, Cordis have commissioned a risk model based on the combined datasets of the the SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL studies aimed at identifying predictors of 720-day TVR for BMS. These studies also formed the basis of our economic submission to this review.

- Table 3 shows the characteristics that were candidate variables entered into the Cordis risk model. Also included is the prevalence of these risk factors in the LRiG risk model (Bagust *et al* 2005), dispelling LRiG's assertion that RCT-based risk models do not consider a wide range of variables. These differences reinforce the need to consider, and report, the results of all available risk models to assess the frequency with which predictive risk factors occur – this has not been done in the Bagust paper, the Assessment Report or the Addendum.

	Cordis Risk Model Dataset	LRiG Elective Risk Model Dataset	LRiG Non-elective Risk Model Dataset
Patient Characteristic			
Patient age (mean, 95% CI)	61.9 (32 – 89) years	60.3 (54 – 67) years	61.2 (53 – 69) years
Male gender (%)	71.5	72.1	77.5
Prior MI (%)	35.7	Not included	Not included
Prior CABG (%)	7.4	7.4	5.6
Diabetes Mellitus (%)	26.8	13.2	12.9
Hypertension (%)	63.3	49.5	42.4
Smoking History (%)	29.8	68.1	70.2
CCS* III or IV angina (%)	41.4	Not included	Not included
Vessel Location - LAD (%)	46.7	Not included	Not included
Lesion Characteristic			
Bend >= 45° (%)	11.9	27.5	19.3
Pre-procedure thrombus (%)	1.2	4.3	33.2
Calcification (%)	17.5	13.0	7.3
AHA C-type lesion (%)	18.5	43.3	39.0
Lesion Length-mm (mean, SD)	13.9 ± 5.9	Reported as 10-20mm or >20mm	
Pre-procedure RVD-mm (mean, SD)	2.72 ± 0.48	Reported as <2mm or >4mm	
Pre-procedure in-lesion MLD-mm (mean, SD)	0.94 ± 0.37	Not included	Not included
Post-procedure in-stent diameter stenosis % (mean, SD)	7.2 ± 8.6	Not included	Not included
Number of stents implanted-mm (mean, SD)	1.39 ± 0.61	Not included	Not included
Total stented length-mm (mean, SD)	22.5 ± 8.1	Not included	Not included

Table 3. Comparison of clinical populations included in different risk models. *LAD = left anterior descending coronary artery, RVD = reference vessels diameter, MLD = minimum lumen diameter.*

- When the characteristics in Table 3 were input into a multiple logistic regression model using the combined dataset of the SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL trials to determine predictors of TVR at 720 days, four factors emerged (Table 3):

Predictor of 720-day TVR (BMS)	Odds Ratio (95% CI)	P value
Total stent length implanted (per mm)	1.05 (1.03 to 1.07)	< 0.0001
Prior CABG	2.54 (1.42 to 4.54)	0.002
History of diabetes	1.53 (1.07 to 2.20)	0.021
Vessel location --LAD	1.34 (0.95 to 1.88)	0.091

Table 4. Multivariate predictors of 720-day TVR in BMS from the combined dataset of the SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL trials.

- A multivariate model including just lesion length, vessel diameter and diabetes was also run on the same dataset (Table 5).

Predictor of 720-day TVR (BMS)	Odds Ratio (95% CI)	P value
Lesion length (per 10mm increase)	1.62 (1.25 to 2.09)	0.0002
History of diabetes	1.46 (1.03 to 2.07)	0.031
Pre-procedure vessel diameter (per 1mm increase)	0.72 (0.51 to 1.02)	0.065

Table 5. Odds ratios for lesion length, diabetes and vessel diameter as multivariate predictors of 720-day TVR in BMS from the combined dataset of the SIRIUS, E-SIRIUS, C-SIRIUS and RAVEL trials. *Longer lesions, diabetes and smaller vessels are predictive.*

- The wealth of published literature and Cordis' additional modelling above show that longer lesions, small vessels and diabetes are frequently occurring predictors of repeat revascularisation in many studies. This is in contrast to LRiG's single-centre uncorroborated analysis.

- It is important to realise that formal statistical significance may not be achieved for each risk factor in every model due to sample size/power issues. The question for this Review is whether the risk factors that form the basis of the current guidance are predictive and discriminating of patients at increased risk of repeat revascularisation. The wider literature consistently shows that they are.

Summary of Risk Factors for Repeat Revascularisation

- Long lesions, small vessels and diabetes are the most commonly occurring independent predictors of repeat revascularisation in BMS across many studies.
- LRiG have failed to present several important studies detailing predictors of repeat revascularisation both in the AR and the Addendum.
- The studies omitted by LRiG commonly find diabetes to be in independent predictor of repeat revascularisation.

B. Absolute Risk of Repeat Revascularisation in BMS

It is useful to recap the origin of the debate around the absolute risk of repeat revascularisation in BMS.

- LRiG asserted in the Bagust paper that protocol-mandated follow up angiograms in the randomised trials inflate repeat revascularisation rates beyond those that would have been observed in routine practice without mandated angiographic follow up.
- LRiG also asserted that corrections for this effect by reporting clinically-driven rates were still over-estimates because this definition still included revascularisations based on *"an in-lesion diameter stenosis >70% in the absence of ischaemic signs and symptoms.."*
- LRiG favoured data that reported lower rates from other sources including the CTC, BCIS and Leicester databases.
- The Committee concluded that the CTC and Leicester registries were not reliable sources of repeat revascularisation rates and felt that the Scottish registry and the BASKET trial (Switzerland) may be more representative.

- LRiG new analysis looked at these and other data, attempting to make adjustments to estimate "total revascularisation rates", 100% BMS usage and 12m rates.

We have a number of concerns with the new analysis undertaken by LRiG. These are first listed, then explained below:

- Failure of LRiG to clearly address the Committee's question of the absolute risk of revascularisation of BMS taken from the Scottish registry data
- Continued use of "Total Revascularisations"
- Conversion rate used for baseline data – converting to 100% BMS usage
- Conversion of data to 12 month outcomes

Absolute Risk of Repeat Revascularisation from the Scottish Registry

- LRiG dismiss the Scottish 2003/04 report as being *"out of line with the published paper from the same source"* (page 26). The basis of this comment is unclear as the Scottish publication (Pell *et al* 2001) gives a revascularisation rate of 17.1% and the Scottish 2003/04 report gives a rate of 14.7%. These two figures are not out of line with each other.

- Scottish registry data for the specific year 2000/01, in which the BMS stent usage was >80% (Pell and Slack 2004), show the repeat revascularisation rate to be approximately **13%** (Figure 1 below). It is unclear why these data were not included in the Addendum report. This rate, requested by the Committee, probably represents the most reliable estimation of repeat revascularisation rates in a general population from UK registry data. This is an average rate across different types of patients and specific sub-population risk groups of small vessels, longer lesions and diabetics will have higher rates of repeat revascularisation.

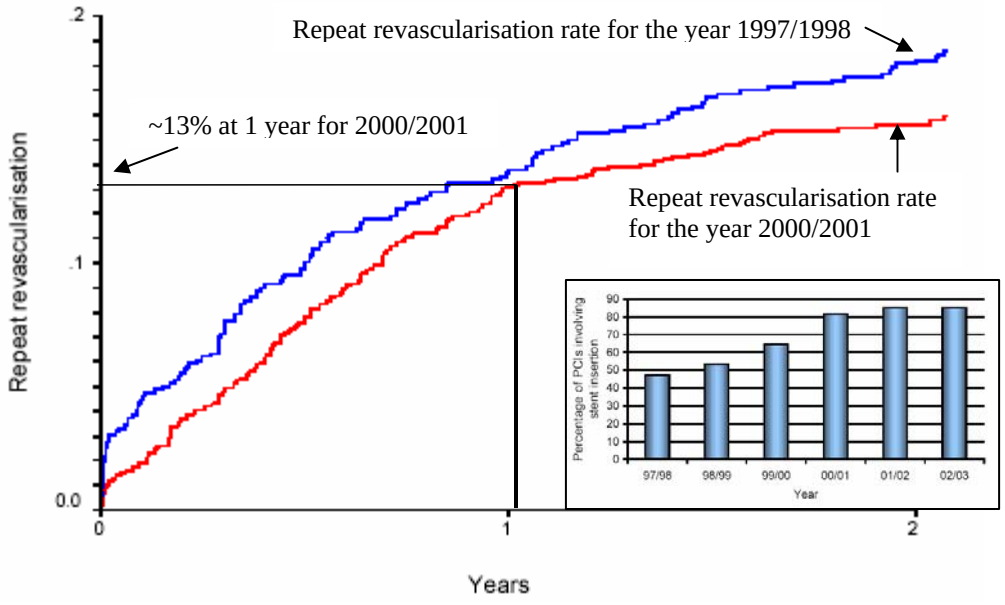


Figure 1. Repeat revascularisation rates and stent usage from Scottish Revascularisation Register (Pell and Slack 2004). *The 12m rate in 2000/2001 (prior to the introduction of DES) was ~13%. Inset shows use of stents over time, ~ 47% in 1997/1998 and ~84% in 2000/2001. Repeat revascularisation rates are approximately the same for both years despite increased BMS usage, probably reflecting more complex case mix in the later year.*

- We would further submit that ever more complex patients are being treated by percutanoeus interventions, as evidenced, for example, by the change in patient demographics from the ARTS I to the ARTS II trials (Serruys *et al* 2005). It is thus likely the the real world repeat revascularisation rates in 2006 would be higher, not lower, than the Scottish numbers shown above.

Continued use of Total Revascularisations (Total Rev)

- The dependence of LRiG on this end-point is most likely driven by the fact that the CTC data are unable to differentiate between TLR, TVR and Total Rev in some cases (Original Assessment Report, 8.2.3), hence they cannot reliably model cost effectiveness based on TVR or TLR, the standard measures used.

- LRiG attempt to convert TLR and TVR data from 6 other sources (Table 5.1 p 28) to Total Rev to maintain consistency with the CTC data. This estimation uses conversion factors derived from the CTC data. As the CTC data have already been judged unreliable, these conversions are also unreliable and introduce further errors into LRiG's results.

- TVR (used in the published UK model by Hawkins, Sculpher and Rothman [2005]) captures all of the additional costs and disutility of repeat revascularisation relevant to DES. The added complication of manipulating data to Total Rev is without precedent, clinically unnecessary, introduces additional statistical uncertainty and relies on unclear estimations of the risk reduction DES confer on Total Rev.

- The risk reductions DES confer on BMS TLR and TVR rates are known, widely reported, transparent and subject to far less uncertainty than the multitude of corrections and estimates LRiG rely on in their continued use of Total Rev.

- In attempting to convert the BCIS and Leicester data to Total Rev, LRiG have, for reasons that are not clear, neglected to account for repeat revascularisation by CABG. BCIS data only account for PCI for restenosis (Ludman 2004) and the Leicester (Glenfield) data only include TLR by PCI and not CABG.

Conversion to 100% BMS usage

- The BCIS data used to convert 'unstented' patients to 'stented' in Table 5.1 of the Addendum is recognised by the Committee as unreliable. Adjustments based on these data will also be unreliable and introduce yet more error and uncertainty into LRiG's results.

- Even accepting the BCIS data, the calculation methods for this conversion are unclear. Converting the Scottish data (Table 5.1, Row 1, Pell-SCRR), an adjustment of 0.49 has been applied to adjust the data to account for 49% of patients receiving POBA (no stent). This reduces the TOTAL revascularisation rate in that population by half. What that means is the relative risk of revascularisation in **POBA is three times higher than with a BMS**[1]. This magnitude of benefit was not observed during the original review of bare metal stents compared with POBA, TA no 4, May 2000.

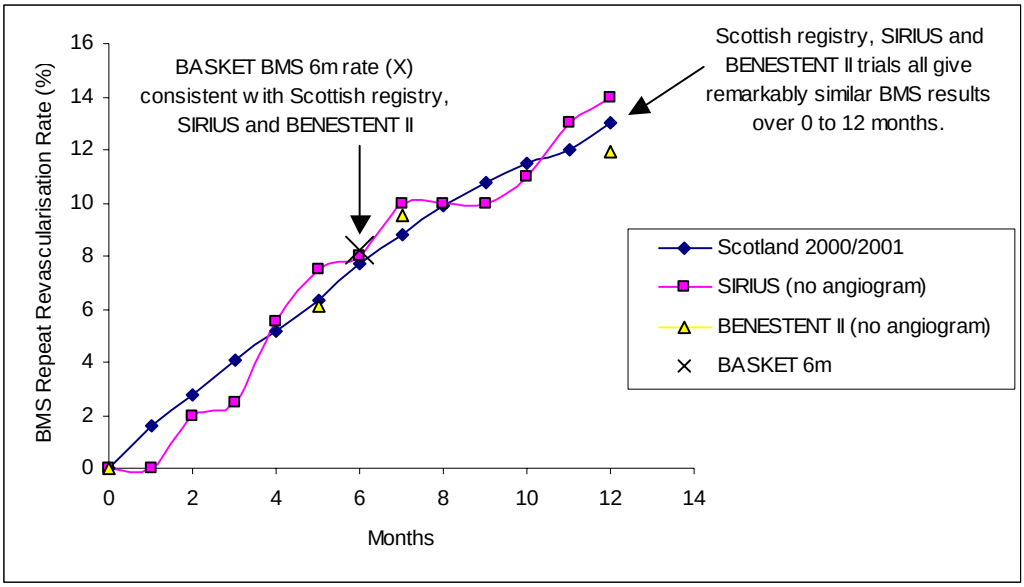
[1] For the adjusted risk of 8.4% to be correct, the contribution to the orginal rate of 17.1% from BMS patients must be 8.4%/2=4.2% (~50% population receiving BMS). Therefore, rate in original population due to POBA = 17.1%-4.2% = 12.9%. Relative difference 3 fold!

Conversion of Data to 12-month Outcomes

- LRiG do not state what objective criteria they use to define the results of their data adjustments as acceptable or not. LRiG appear happy to accept the results of their adjustments when the answers are low, yet dismiss the adjustment when the results are above an arbitrary threshold – P 26, pt 6:

  "For converting from 9 to 12 months follow-up we have applied a multiplier derived from the CTC revascularisation time profile. However, we found that adopting a similar approach to move from 6 to 12 months suggested unrealistically large adjusted rates."

- Realistic estimates of increases in revascularisation rates from 6 to 12 months can be obtained from a number of sources; the Scottish 2000/2001 registry (Pell and Slack 2004), the SIRIUS trial BMS arm (patients without angiographic follow up, Holmes *et al* 2004) and the BENESTENT II trial BMS arm (patients without angiographic follow up, van Hout *et al* 2005) These data are shown in Figure 2 below.



	6m rate (%)	12m rate (%)	6m-12m multipying factor
Scotland 2000/2001	7.7%	13.0%	1.69
SIRIUS BMS (no angio)	8.0%	14.0%	1.75
BENESTENT II BMS (no angio)	7.8%	11.9%	1.53
Mean 6m to 12m multiplying factor			1.65

Figure 2. Estimates of factors for converting 6m repeat revascularisation rates to 12m rates. *Scotland 2000/2001 = Scottish registry, SIRIUS = BMS rates from patients in the SIRIUS trial who did not have a protocol-mandated follow up angiogram, BENESTENT II = BMS rates from patients in the BENESTENT II trial who did not have a protocol-mandated follow up angiogram BASKET = actual 6m BMS result from BASKET study.*

- Figure 2 shows that LRiG's 6m to 12m conversion factor of 1.3 (Table 5.1) is unrealistically small and not consistent with the available evidence. This is not surprising as they describe their factor to be *"without specific evidence to support it"* (page 26).

- The true 6m to 12m conversion factor is **1.655**. Applying this to the BASKET trial 6m outcomes results in an estimate of **13.6% for 12m TVR** for an unselected 'base case' population.

- The rates LRiG dismiss as *"unrealistically large adjusted rates"* are actually in line with the Scottish registry, BASKET and many other published rates previously brought to the Committee's attention in our submission and response to the original Assessment Report. LRiG's systematic exclusion of these rates is perverse and not scientifically robust.

- It should be noted from Figure 2 that the 12m rates from the randomised trials without the effect of the follow up angiogram are remarkably consistent with the Scottish registry data. Indeed, the 12m TVR rate for the base case BMS group in Cordis' response to the AR was 13.6% - the same as the estimated 12m rate from BASKET and very similar to the actual 12m rate (13%) from the Scottish registry. It follows that Cordis' cost-effectiveness estimations for Cypher, which exclude all repeat revascularisations based on the angiogram alone, are reliable.

Summary of Absolute Risk of Repeat Revascularisation

- The Appraisal Committee, in specifying the additional analyses required in the Addendum, requested 12m repeat revascularisation rate from the Scottish registry. This rate' for an unselected population prior to the introduction of DES (2000/2001), was **13%**.
- The estimated 12m overall TVR rate for the BASKET trial is **13.6%**.
- Cordis' previous submissions estimated a rate of **12%** for an unselected population from a range of sources that did not included a protocol-mandated angiogram.
- **The 12m BMS repeat revascularisation rate in an unselected population is therefore 12% to 14% when all data sources are considered and realistic adjustments from 6m to 12m are made.**
- UK and non-UK sources yield very similar results**.**
- The BMS repeat revascularisation rates used in Cordis' economic model are entirely consistent with these rates, supporting the validity of our cost effectiveness results.

C. The Risk Reduction Gained with Cypher

- In Table A6.3 (page 38) of the Addendum, LRiG present further cost effectiveness estimates for small vessels, diabetes and long lesions. LRiG have used a 41% risk reduction, which appears to be the **6m relative risk reduction** for combined Cypher and Taxus outcomes from the BASKET trial. This will under-estimate the true 12m risk reduction conferred by Cypher and inflate the ICER. The Appraisal Committee specified further modelling based on 12m outcomes.

- It is clear based on all available major randomised controlled trial data that the difference in revascularisation rates for Cypher and BMS continues to widen until at least 12 months post-procedure.

- In addition, LRiG's own meta-analysis in the Assessment Report and the recent meta-analysis published by Kastrati *et al* (2005) show a significant difference in treatment effect between Cypher and Taxus in favour of Cypher (odds ratio **0.64**, 95% CI 0.49 to 0.84). This was also reflected as a clear trend in BASKET, but BASKET was under-powered to register formal statistical significance. It is unclear why LRiG's cost effectiveness analyses use a risk reduction that appears to be an average of Cypher and Taxus versus BMS, when the UK-specific cost

effectiveness analysis by Hawkins and Sculpher (2005) that employed device-specific risk reductions, showed a clear cost effectiveness advantage of Cypher over both BMS and Taxus in patients with lesions >15mm length, vessels <3mm diameter and diabetics.

- Figure 3 below shows that Cypher conferred a 67.9% reduction in repeat revascularisation in the SIRIUS trial cohort that did not have a protocol-mandated angiogram. SIRIUS has already been shown to be consistent with BASKET and the Scottish registry in Figure 2 above.

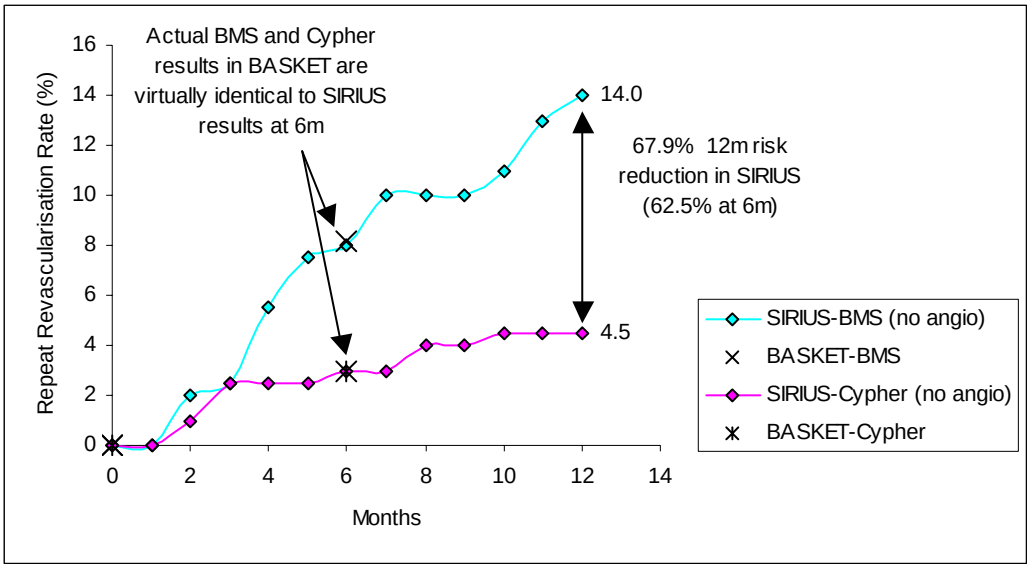


Figure 3. Estimation of the 12m risk reduction conferred by Cypher based on the BASKET and SIRIUS trial patients that did not receive angiographic follow up. *BASKET and SIRIUS are virtually identical at 6m, supporting the reliability of the SIRIUS 12m risk reduction.*

- Figure 3 shows that the Cypher arms of the SIRIUS 'no angiogram' group and BASKET are identical at 6m, thus SIRIUS is a good model to extrapolate the BASKET-Cypher 6m data to 12m. This yields a TVR rate of 4.5% in the Cypher arm of BASKET at 12m.

- Thus, with estimated 12m TVR rates of 13.6% for BMS (Figure 2 above) and 4.5% for Cypher (Figure 3), the absolute 12m risk reduction for the Cypher stent in BASKET is 9.1%. Cypher confers a 66.9% reduction in 12m TVR using BASKET and a 67.9% reduction using SIRIUS. Both of these statistics are based on datasets that did not include protocol-mandated angiographic follow up. These risk reductions are virtually identical to those used in Cordis' own economic modelling for both the original submission and response to the AR. LRiG's use of 41% is completely unjustified with respect to Cypher.

<u>Summary of Risk Reduction Gained with Cypher</u>

- Cypher confers a reduction in 12-month TVR of 67 – 68% based on the BASKET and SIRIUS trial patients who did not have protocol-mandated angiographic follow up.
- This risk reduction is virtually identical to that used in Cordis' original economic submission, supporting the validity of our cost effectiveness results.
- LRiG's use of 41% risk reduction is totally unjustified with respect to Cypher and will result in over-inflated ICERs and incorrect conclusions concerning cost effectiveness.

D. Price Differential between Bare Metal Stents and Drug-eluting Stents

- We stress again that the pricing of medical devices raises a number of issues unique to devices that the Institute does not face with pharmaceuticals. We take as read our response to the original Assessment Report. With that in mind, the key points we wish the Committee to consider at this time are:

- The availability of DES has continued to drive down effective DES prices although this may not always be evident in the headline price, depending on the nature of the agreement between supplier and purchaser.

- The average sellling price of DES is now lower than at launch in 2002 and there is no reason to assume that market forces will not continue to produce decreases in DES prices.

- The use of 'market prices' in this Review introduces confounding factors unique to devices that the Committee needs to recognise. The use of list prices, as agreed at the scoping meeting, is more informative.

- The current low market price of BMS has been influenced by the availability of DES, and the existing NICE guidance (that has resulted in appropriate DES use in over 50% of patients) has continued the price pressure on BMS. If DES were not available, the BMS price would not now be so low. Since DES became available, the demand for BMS has fallen. The principles of supply and demand dictate that if demand falls but supply remains, the price will fall.

- There is a price paradox within device appraisals. The appraisal process needs to take account of the current and future price dynamics for both the new technology (in this case DES) and the less effective comparator (in this case BMS) and how it affects the use of the QALY as a factor to determine cost effectiveness. As the market for BMS significantly decreased after the publication of the existing stent guidance (TA no. 71), the price dropped as there were many suppliers chasing a much smaller cohort of patients. Furthermore, reports suggest some manufacturers may have reduced the price of their BMS to 'free-up' funding for DES. Therefore, if the original analysis had been re-run just 6 months after the initial guidance was published using revised average selling prices, the Committee's decision could have been reversed on cost effectiveness grounds, despite the fact that the reduction in BMS prices was actully making it easier for hospitals to implement the guidance. Using market prices for devices, where prices can change rapidly compared with drugs, makes decisions on the QALY time-dependent and liable to 'flip-flop' back and forth.

- If the declining price of a less effective technology is pursued to its logical conclusion, there would potentially be regression to the least expensive therapy even if it had already been rendered obsolete on effectiveness grounds. This perverse logic, if applied in this manner, has wide ranging negative implications for the introduction of all new medical device technology that seems to be neither justified nor in the best interest of patient care.

- It should be remembered that the list price of DES at launch was the same as the list price for BMS at their initial launch. We struggle to identify a 'next generation' pharmaceutical product whose list price was the same as the original list price for the '1st generation' product.

- The Committee may find the change in actual reported costs for PCI over time from all NHS Trusts more informative. Using NHS Reference Costs from 1998 to the most recently

published 2005 data, it can be seen that there has been limited change in the average cost to the NHS of treating patients with PCI (Figure 4). This spans the time from 1998, when 69% of patients received a BMS, through 2000 when TA no. 4 recommended all patients should receive a BMS, to publication of the current guidance TA. 71 recommending use of DES, to 2005 where it was anticipated 60% received a DES. This suggests that the costs of stents fall significantly over time and almost completely offsets the cost of increased utilisation to the NHS. This compares with the average reported cost of treating via CABG, where the average reported cost has increased by almost 40%.

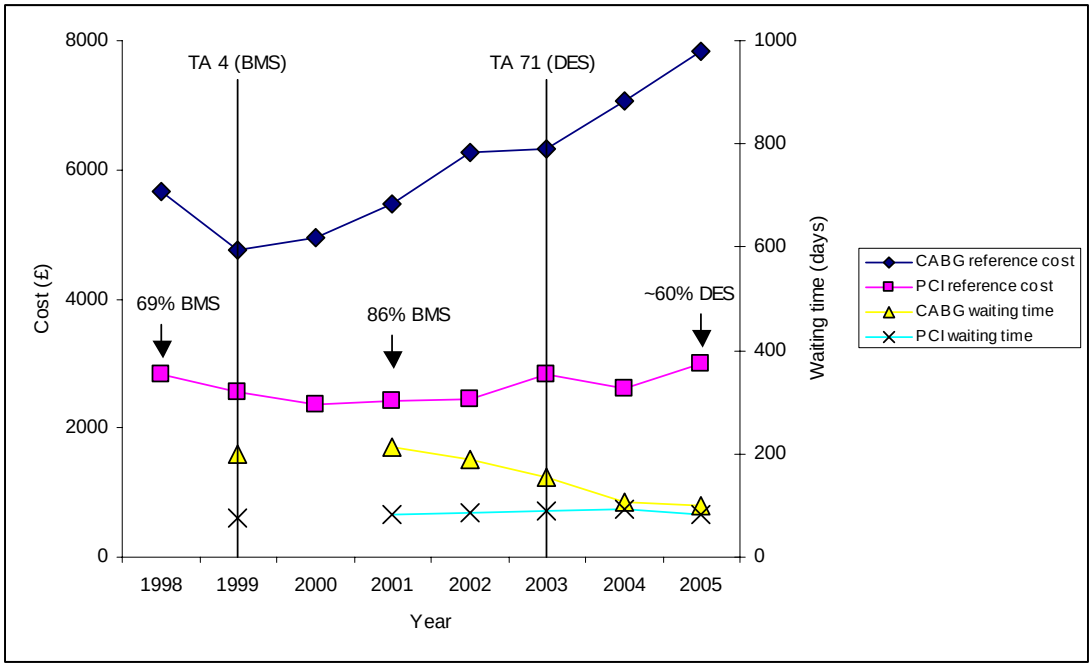


Figure 4. **Changes in reference costs, waiting times and stents usage in the UK since 1998.** *Despite the increase in BMS and then DES usage PCI reference costs have barely changed since 1998. This suggests that the costs of stents fall significantly over time and almost completely offsets the cost of increased utilisation to the NHS.*

- Hospital Episode Statistics data spanning the same period indicate the annual number of PCIs has increased considerably (2-3 fold). This will in part explain the cost stability over time, as economies of scale have been introduced. Furthermore, as reported above, the BMS price was significantly higher at launch, so the impact of time needs to be considered in the mix.

- Whilst the number of PCI procedures has grown significantly over time, the average waiting time has not increased (Figure 4), and the proportion of patients on the waiting list compared to those treated annually is still significantly lower than those managed by CABG. The annual through-put for patients receiving CABG has remained constant over the same period.

Summary of Price Differential between Bare Metal Stents and Drug-eluting Stents

- The availability of DES has influenced the reduction in BMS prices as DES have been used in accordance with the guidance in TA no. 71.
- The list price of DES at launch was equivalent to the list price of bare metal stents at their launch.
- NHS reference costs for PCI have barely changed since 1998, indicating that the fall in the cost of stents over time has almost completely offset the cost of increased utilisation of both BMS and DES.

Overall Conclusions

- Long lesions and small vessels have been confirmed as placing patients at increased risk of repeat revascularisation.

- Diabetes is also an independent predictor of repeat revascularisation.

- The absolute risk of repeat revascularisation in BMS is **13%** for a general population in the Scottish registry and is higher for the risk groups of long lesions, small vessels and diabetic patients.

- Cypher confers a 68% reduction in 12m TVR versus BMS.

- DES cost effectiveness results presented in the Addendum are unreliable because:

    - The unreliable CTC dataset still forms the basis of the additional analyses.
    - Key sources of data pertaining to diabetes as a risk factor for repeat revascularisation have been omitted.
    - The absolute risks of repeat revascularisation with BMS have been under-estimated.
    - The risk reduction conferred by the Cypher sirolimus-eluting stent has been under-estimated.

- The current guidance correctly identifies patients with vessels <3mm diameter or lesions >15mm length as being at increased risk of repeat revascularisation. With trial evidence showing that the treatment effect of Cypher has not diminished since the Guidance 71 was issued, it follows that there is no reason to change the existing Guidance with respect to these risk factors.

- Cordis' original submission showed that 2-year ICERs for Cypher stents are £10,178 for patients with vessels <3mm in diameter and £16,460 for those with lesions >15mm length.

- As diabetes has been established as an independent predictor of repeat revascularisation, this Review should also recommend the use of DES for all diabetic patients undergoing PCI. The 2-year ICER for diabetic patients treated with Cypher stents is £9,702.

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