Review of Coronary Artery Stents (Guidance No. 71)

Response to Assessment Report Addenda 3" and 4'.

1. **Introduction**

1.1. Thank you for the opportunity to comment on the two addendum reports. We recognise positive steps taken forward in some areas, and are able to comment on the general principles and issues discussed in the report. We are however unable to support the conclusions of the individual analyses because we consider, as we believe so does the Appraisal Committee given its original request for additional work (February 2006), that some of the key assumptions that underpin the analyses are still critically flawed.

1.2. **Absolute Risk of Repeat Revascularisation**: The Committee requested use of BASKET and Scottish registry data to inform the question of base case repeat revascularisation rates. Instead, LRiG have continued to use CTC database as their base-case in Addenda 3" and 4'.

Comment [AG1]: I would just nail this point by stating at the end what you would like them to do about it.

1.3. **Risk Factors**: We welcome the replacement of the risk factors derived from the CTC database with those of long lesions, small vessels and diabetes that have been shown to occur repeatedly in both trials and clinical databases reported in the literature. However, LRiG have continued to use relative risks for the independent risk factors derived from the CTC database rather than from the trials, as requested by the Appraisal Committee. A literature-based synthesis of relative risks would be more representative and could better inform the question of whether DES remain cost effective in patients treated under current NICE guidance (lesions >15mm length and vessels <3mm diameter).

1.4. **Relative Risk Reduction with DES**: It is also disappointing and concerning that the risk reduction associated with DES is still based on the 6-month BASKET data that underestimates the 12-month reduction. This consequently disadvantages DES in the economic model. 12-month risk reductions from BASKET and other sources are now available and should used by LRiG.

Comment [AG2]: I would just nail this point by stating at the end what you would like them to do about it.

1.5. **DES Price Premium**: We welcome the use of a range of DES price premiums and note that a recent PCI cost-effectiveness study used an incremental cost of DES of £200, reflecting the future cost reduction of DES technology (Rao et al, 2007). This is in line with market trends of falling DES prices and the Appraisal Committee's recognition of DES price premiums less than £300.

1.6. **Use of Clopidogrel**: Addendum 4' (impact of additional Clopidogrel) is seriously flawed. It does not take account of the fact that patients presenting with acute coronary syndromes (ACS), i.e. the non-elective group, receive at least 12 months of Clopidogrel, even if they are treated with a bare metal stent. This has not been factored into LRiG's calculations and thus again disadvantages DES.

Comment [AG3]: I would just nail this point by stating at the end what you would like them to do about it.

1.7. The Assessment Report and its addenda fail to reflect the conclusions of the considerable body of published clinical data and are still largely based on a single study published by LRiG in the journal Heart (Bagust et al 2005) prior to the start of this Review. No reasonable explanation for doing this, or for discounting any of the other published studies is given. Each issue above is explored more fully below.

2. **Absolute Risk of Repeat Revascularisation in BMS: Realistic Rates**

2.1. Following the Appraisal Committee meeting of February 2006, the specification of additional work that led to Addendum 3' included the comments:

"The Committee was persuaded that neither the Liverpool (CTC) and the Leicester registry data or the randomised controlled trial data were representative of repeat revascularisation rates in patients and as the BASKET trial and the Scottish Registry data had used methods that were likely to collect follow-up data from all patients, these data would therefore be more representative."

and

"The base-case scenario should be updated and if data allows should include: the absolute risk of revascularisation of BMS taken from the Scottish registry data"

2.2. LRIG have not implemented this request in any of the 3 Addenda, instead choosing to retain a base-case analysis derived from the CTC data that the Appraisal Committee determined was *"not representative of repeat revascularisation rates"*.

2.3. 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). This rate, requested by the Committee as the base-case scenario, has not been implemented by LRiG, yet it represents the most reliable estimate of repeat revascularisation rates in an unselected population from UK registry data. Specific sub-population risk groups of small vessels, longer lesions and diabetics will have higher rates of repeat revascularisation.

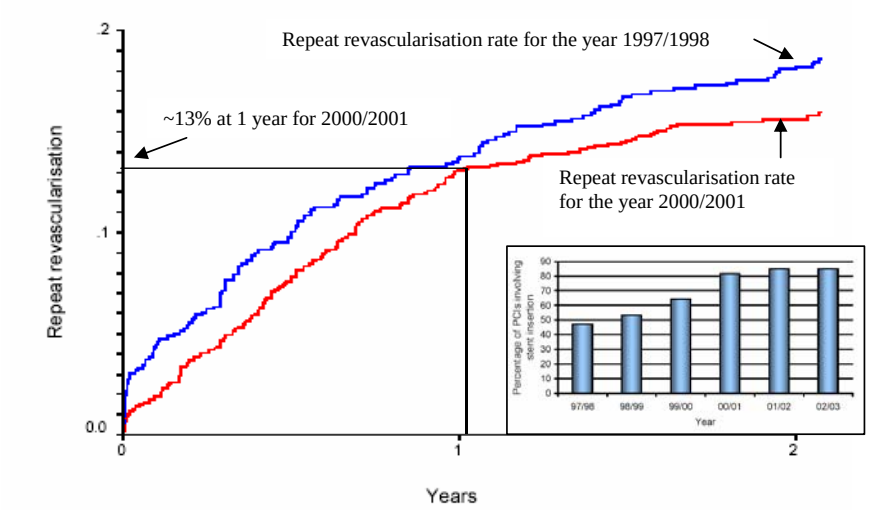

Figure 1. Repeat revascularisation rates and stent usage from Scottish Revascularisation Register (Pell and Slack 2004). *The 12m rate in 2000/2001 (prior to the introduction of DES) was ~13%. Inset shows use of stents over time, ~ 47% in 1997/1998 and ~84% in 2000/2001. Repeat revascularisation rates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

2.4. Further important information on the absolute risk of repeat revascularisation comes from the BASKET trial, a study that LRiG consider to be pragmatic and real-world.

18-month follow up of this trial was presented at the European Society of Cardiology in 2006 (Kaiser et al 2006). Figure 2 shows the cumulative risk of non-MI-related target vessel revascularisation (TVR) to 18 months in the total BASKET population. This of course is an under-estimate of total TVR. The bare metal stent (BMS) data show consistency with the Scottish data in Figure 1, once again demonstrating that rates of 7-9% derived from the CTC database are unrealistic under-estimates of the true rate.

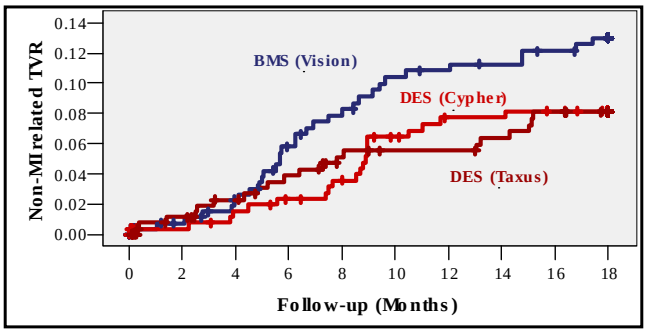

Figure 2. Target vessel revascularisation rates from the BASKET trial (Kaiser et al 2006). *The 12m rate is remarkably similar to the Scottish registry data in Figure 1 and substantially higher than estimates of 7-9% from the CTC database.*

2.5. Thus, as we have previously stated, the *realistic* base-case TVR rate in an unselected population lies in the range of 12-14% at 12 months.

3. Risk Factors for Repeat Revascularisation

3.1. Although Addenda 3" and 4' now present results for long lesions and small vessels, LRiG have defined long lesions as those >20mm in length and small vessels as <2mm in diameter. LRiG's criteria appear to be driven by those adopted in the Bagust paper. Furthermore, to use <2mm as a definition for small vessels treated by stenting is peculiar because in UK practice, with the smallest diameter commercially-available stents being generally 2.25mm, vessels of <2mm in diameter would rarely be stented. Given that this is a review of existing guidance, it would be more sensible to stay with the definitions used in Guidance 71, that is lesions >15mm length and <3mm diameter.

Comment [AG4]: Presumably supported by a greater volume of published data? In which case I would say so here.

3.2. LRiG's relative risk of 0.90 for diabetes in non-elective patients Table A of both Addenda 3" and 4' is both incorrect and perverse. Having implemented the Appraisal Committee's request to include diabetes because it increases the rate of repeat revascularisation, LRiG have used a relative risk that *reduces* the rate, due to their continued reliance on the CTC audit database. The wider literature (presented in our previous responses) suggests the correct relative risk to be in the order of 1.5 to 1.8.

3.3. The BASKET 18m results also inform the question of absolute risk in patients receiving stents <3mm in diameter – a good guide to the rates expected in patients with vessels <3mm diameter (current NICE guidance). Stents <3mm diameter and bypass graft PCI are shown to be predictive of major adverse cardiac events. Figure 3 shows BMS TVR rates for this combined group of patients to be approximately

18% at 12 months, rising to approximately 24% at 18 months. Although this is a mixed population of patients receiving stents <3mm diameter and bypass graft PCI, only 5% (14 patients) in the BMS arm of BASKET had bypass grafts, so these data largely reflect patients with vessels <3mm, covered by current NICE guidance.

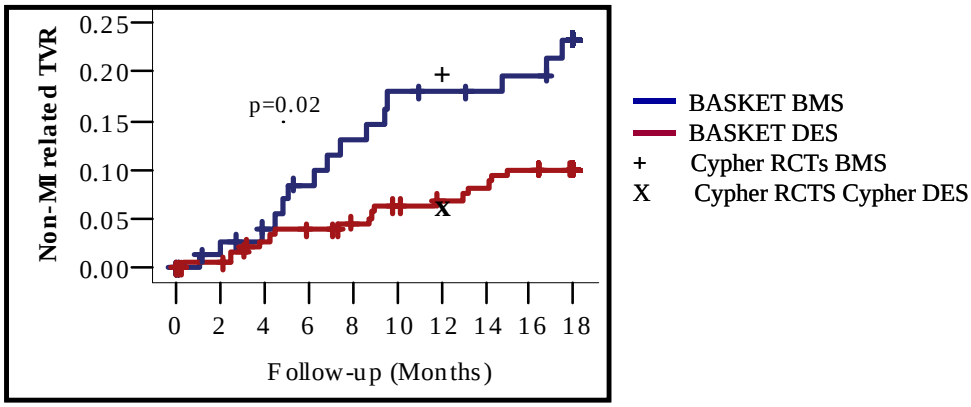

Figure 3. Target vessel revascularisation rates from the BASKET trial (Kaiser et al 2006) for patients receiving stents <3mm diameter and bypass graft PCI. *The 12m rate is approximately 18% and the 18m rate is approximately 24%. Superimposed on the BASKET curves are the 12-month point estimates for patients with vessels <3mm from the pooled Cypher randomised contolled trials (corrected to remove the impact of the follo wup angiogram).*

3.4. However, LRiG have not used this as a source of relative risk for the small vessel sub-group, despite the specification of additional work that led to Addendum 3' including the comments:

"The base-case scenario should be updated and if data allows should include: the relative risks of the independent risk factors (small vessel and long lesion) taken from the trials"

Comparing Figures 2 and 3 above shows BMS TVR rates of 11.6% at 12m for the unselected population and 18% for the sub-group with vessels <3mm in the BASKET trial. This suggests that the relative risk for the factor "vessels <3mm" is approximately 1.55 (1.82 at 18 months).

3.5. It should be noted that the combined RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS trials yield an absolute BMS risk of TVR of 19.4% at 12 months and 21.9% at 2 years for vessels <3mm diameter (after correction to remove the impact of the follow-up angiogram). When compared with the rates of 18% at 12m and 24% at 18m from BASKET in Figure 3, this shows the Cypher trials to be reflective of realistic TVR rates associated with BMS.

3.6. Data previously submitted by Cordis provide trial-based relative risks for the risk factors of interest to be:

Risk Factor	Relative Risk
Small vessels (<3mm diameter)	1.48
Long lesions (>15mm)	1.24
Diabetes	1.46

Table 1. Relative risks for the BMS risk factors for target vessel revascularisation from the pooled randomised Cypher trials.

It can again be seen how the Cypher randomised trial data is consistent with the BASKET data with respect to bare metal stents (BASKET relative risk for small vessels = 1.55 to 1.82)

3.7. Given the good agreement between the Cypher trials corrected for the impact of the follow up angiogram, and the BASKET results in section 3.6 to 3.8, the Cypher trials can also reliably inform the absolute risk of TVR for each of the sub-groups of interest (Table 2):

Risk Factor	BMS TVR Absolute Risk	Cypher TVR Absolute Risk	Relative Risk Reduction
Year 1			
No risk factors	13.1%	3.9%	0.70
Small vessels	19.4%	6.7%	0.65
Long lesions	16.2%	5.3%	0.68
Diabetes	19.1%	5.9%	0.69
Year 2			
No risk factors	1.7%	0.5%	0.70
Small vessels	2.6%	0.9%	0.66
Long lesions	2.1%	0.7%	0.68
Diabetes	2.5%	0.7%	0.71
Overall 2 years			
No risk factors	14.8%	4.4%	0.70
Small vessels	21.9%	7.6%	0.66
Long lesions	18.3%	5.9%	0.68
Diabetes	21.6%	6.6%	0.69

Table 2. Risk of target vessel revascularisation from the pooled RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS trials, corrected to remove the impact of angiographically-driven procedures. *These results are not simply protocol-defined clinically-driven TVR. Any procedures driven by the protocol definition '>70% stenosis in the absence of ischaemic signs and symptoms' have been removed. Thus, these data represent TVR performed only on the basis of ischaemic signs and symptoms.*

4. The Risk Reduction Associated with the Cypher Sirolimus-eluting Stent

4.1. LRiG appear to have continued to use a risk reduction of 41% to define the treatment effect associated with DES in Addenda 3" and 4', following the use of this factor in Addendum 3'. This was the risk reduction found for the combined DES group in the BASKET trial unselected population at 6-months. However, Figures 2 and 3 show that the risk reduction is greater at 12m compared with 6 months and greater in a high-risk population than the general population. It should also be noted that the definition of TVR was made more conservative for the BASKET 18m

Comment [AG5]: I would consider requesting an explanation as to why this is the case.

results presentation compared with BASKET 6m (by moving to a definition of non-MI-related TVR rather than any TVR), thus the 12-18m risk reductions are understated (Marco 2006).

4.2. BASKET shows that in higher-risk subgroups such as those with vessels <3mm diameter, the risk reduction at 12m is in the order of 61% for the combined Cypher and Taxus DES group. This is confirmed by the Cypher-specific RCTs as shown in Table 2. The higher rates of 66-71% risk reduction over 2 years reflect the findings of meta-analyses of the Cypher versus Taxus trials (original Assessment Report and Kastrati et al 2005) that show significantly lower repeat revascularisation rates with Cypher than with Taxus in randomised controlled trials.

4.3. These data show that the LRiG model should employ a 12m risk reduction of 61 to 71% if it is to reflect realistic repeat revascularisation rates.

5. Cypher Price Premium

5.1. The price premium of £433 used in our original submission now seems excessive in the light of the evidence presented to the Appraisal Committee's (Addendum 3' page 48) that procurement has taken the price premium of DES to less than £300 in some areas (Scotland £255 premium). We also note that in a recent UK publication (Rao et al 2007), the authors used a £200 premium to reflect the future cost of DES technology.

6. Impact of Additional Clopidogrel

6.1. The specification that led to Addendum 4' requested that the cost-effectiveness model be re-run to include an additional 9-months of Clopidogrel for DES. Unfortunately, LRiG have failed to account for the fact that patients treated for acute coronary syndromes (ACS) will receive 12m Clopidogrel, even if treated with a bare metal stent. Thus, additional Clopidogrel cost should only be applied to the proportion of patients who are non-ACS, i.e. elective patients. Even then some of elective patients treated with BMS may receive more than 3m Clopidogrel, depending on the nature of the case.

6.2. Table 3 below shows estimates of the percentage of patient in UK practice that are non-ACS and thus may warrant additional Clopidogrel (Ludman 2006, Pell and Slack 2007):

Source	% non-ACS Patients
BCIS audit 2005	56%
Scottish Coronary Revascularisation Register 2005	50.4%

Table 3. Estimates of the percentage of DES patients undergoing elective PCI and therefore requiring 9-months additional Clopidogrel.

6.3. It should also be recognised that the time-trend analysis of the Scottish Coronary Revascularisation Register between 1997 and 2003 (Pell and Slack 2004) noted:

"..the percentage of percutaneous interventions performed as urgent or emergency procedures has steadily increased from 38% to 52%. It is likely that the percentage of percutaneous coronary interventions performed as non-elective procedures will increase further in the future."

The Appraisal Committee should be mindful that the proportion of DES patients requiring additional Clopidogrel (compared with BMS) is likely to continue to fall as the proportion of non-elective cases increases. This means that the future cost-effectiveness of DES is likely to improve from current estimates.

6.4. Cordis's economic model did not originally include 9m additional Clopidogrel, therefore we show in Table 4 the impact of this additional cost when required in 56% of patients (BCIS 2005). We have also used the average number of stents per patient proposed by LRiG in the Assessment Report and shown the ICERs for various Cypher price premiums up to £300. Clearly, as the proportion of PCI for ACS increases in the future, so the cost-effectiveness of DES will improve further.

	Price Premium			
Risk Factor	**£100**	**£200**	**£255**	**£300**
No risk factors	£3,031	£21,007	£30,894	£38,983
Vessels <3mm diameter	DES dominant	£2,051	£8,775	£14,277
Lesions >15mm length	DES dominant	£10,256	£18,260	£24,808
Diabetes	DES dominant	£8,010	£15,688	£21,970

Table 4. ICERs for Cypher cost-effectiveness derived from the Cordis model modified to include 9 months additional Clopidogrel.

7. Long-term Safety and Efficacy of the Cypher Sirolimus-eluting Stent

7.1. A recent publication (Stone et al 2007) has shown that despite recent expression of concerns over the long-term safety of DES, rates of death or myocardial infarction do not differ significantly between Cypher and bare metal stents over 4 years. This is accompanied by maintenance of a significant difference in repeat revascularisation.

7.2. Below are data showing continued efficacy of Cypher to 4 years in sub-groups currently recommended to receive DES under the existing NICE guidance:

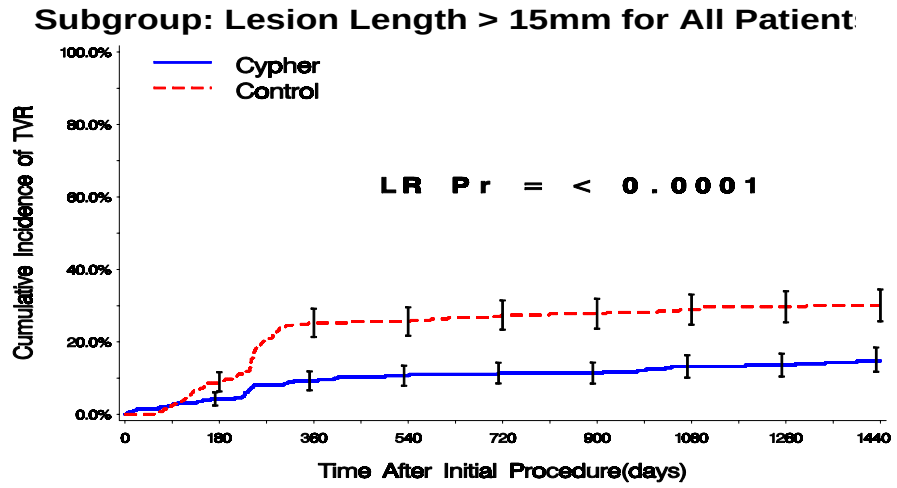

Figure 4. Cumulative incidence of target vessel revascularisation for patients with lesions >15mm length from the combined RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS trials at 4 years follow up.

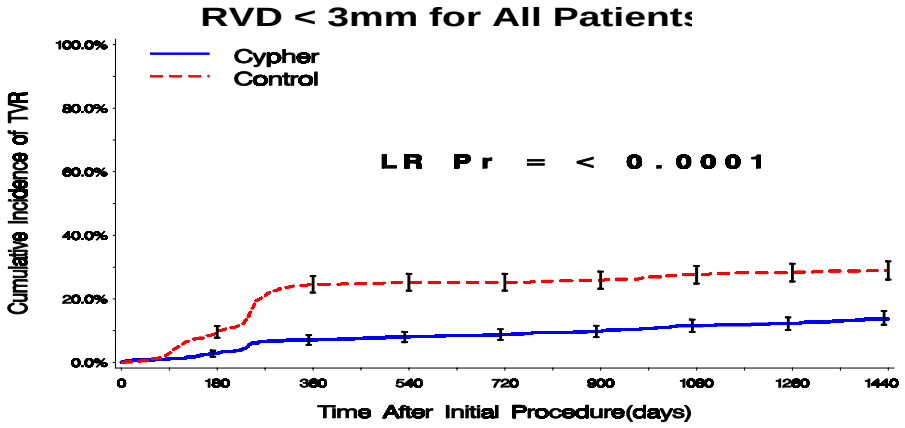

Figure 5. Cumulative incidence of target vessel revascularisation for patients with vessels <3mm diameter from the combined RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS trials at 4 years follow up.

Summary

- Addenda 3" and 4" are still compromised by LRiG's failure to implement the changes requested by the Appraisal Committee after the February 2006 meeting. Specifically:

- The continued use of unrealistically low base-case repeat revascularisation rates from the CTC audit database. The Scottish registry tells us that the 12-month rate in an unselected population is **13%**. We request that the model be re-run using this value as the base-case.

- As a consequence of using the CTC database, LRiG have presented unrealistically low absolute risks for the individual risk factors. BASKET and the Cypher trials show that the relative risks for the risk factors of small vessels, long lesions and diabetes are in the range of 1.24 to 1.55 at 12 months, conferring absolute risks of **16.2 to 19.4%**. We request that the model be re-run using literature-based relative risks applied to the base-case revascularisation rate from the Scottish registry.

- The continued use of an unrealistically low relative risk reduction associated with DES. The 41% risk reduction seen in the BASKET unselected population at 6 months is an underestimate compared with the **61-71%** seen **at 12 months** in the higher risk sub-groups of small vessels, long lesions and diabetes in the Cypher trials and BASKET. We request that the model be re-run using realistic relative risk reductions applied to the risk factor-based revascularisation rates derived as above.

- In modelling the impact of additional Clopidogrel on the cost effectiveness of DES, the model should be re-run with the additional cost applied only to the proportion of patients without acute coronary syndromes (50-56%).

References

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