Review of Coronary Artery Stents (Guidance No. 71)

Comments on Economic Model.

Cordis, Johnson & Johnson

Executive Summary

- Whilst the structure of the economic model seems to include the major costs and effects for the first year after repeat revascularisation, it is somewhat simplistic and limited in its capacity to fully explore the long-term cost effectiveness of DES.

- Many of the data inputs are either out of date, based on incorrect assumptions or require clarification.

- The 1-year time horizon does not capture all the benefit of avoided repeat revascularisations (new events occur beyond year 1 with BMS) and avoided myocardial infarction (new events occur beyond year 1 with BMS and benefits of avoiding MIs persist into subsequent years).

- The model should be re-run incorporating:
    - A clear and transparent determination of the average DES price premium.
    - Data inputs revised based on a proportion of 48.5% non-elective patients.
    - 14.7% repeat revascularisation rate from the Scottish registry.
    - The trial-based absolute risk reductions for the Cypher stent published by Stettler et al (2007), ie 70% for TLR and 19% for MI.
    - The relative risks for the individual risk factors identified by BCIS.
    - The latest NHS reference costs (2005-06).
    - QALY loss based on the latest NHS waiting time data, with overall waiting times calculated according to the method of Hawkins et al (2005).
    - Clarification of the correct number of stents per procedure, especially for small vessels and small vessels + long lesions.
    - ACS as a separate risk factor group.
    - Separate TLR and MI risk reductions for Cypher and Taxus.

- Cordis urge the Institute to address all of the limitations of the economic model highlighted in this commentary. The outcome of the Review would be perverse if it were based on such out of date, unreliable and questionable inputs. Given that most of the key data inputs have now been found to require revision, we recommend that this Appraisal be referred to the Decision Support Unit to ensure proper scrutiny.

- The Institute should also be mindful of the impact on the wider UK health economy. In real terms, PCI reference costs fell by 1.6% between 2004-05 and 2005-06 despite the increase in DES usage. This is most likely to be a reflection of the falling DES acquisition costs that has benefited the NHS. It seems perverse for the current draft guidance to propose removing from the NHS, an undoubtedly effective treatment which is actually falling in cost.

1. **Introduction**

1.1. Whilst the structure of the economic model seems to include the major costs and effects in the first year after repeat revascularisation, we have major concerns over many of the data inputs, which are either out of date, based on incorrect assumptions, use single centre data where a wider literature exists, or are inconsistent with previous Assessment Report addenda.

2. **Modelling Methods**

2.1. Some of the inputs are hard coded rather than being transparently derived from raw data. This specifically applies to the QALY loss awaiting PCI/CABG, the AMI utility gain and the AMI costs saving.

2.2. The model does not attempt to handle parameter uncertainty using probabilistic sensitivity analysis and therefore LRiG have not followed NICE's Guide to the Methods of Technology Appraisal. This is a serious limitation. It is possible to estimate confidence limits around many of the data inputs, so we see no reason why LRiG should not have followed this practice.

2.3. The model does not explore cost effectiveness beyond the first year, probably due to LRiG's view that there are few data points after this time. This is certainly not the case now and given the potential impact of the draft guidance, it would be both diligent and fair to explore the longer-term. This is particularly important given that repeat revascularisations accrue beyond year 1 (thus so does the DES benefit) and the AMI utility gain is similarly so. Furthermore, AMI utility gains will also persist into each subsequent year and these effects are not accounted for within the 1-year time horizon.

3. **DES Price Premium**

3.1. The economic model investigates DES cost effectiveness at various levels of price premium. Interpretation of the results is critically dependent upon the price premium that the Appraisal Committee decides is representative of the UK. We request, for transparency and methodological reasons, clarification of how the correct DES price premium will be identified. If an average BMS price is used, as appears to be the case in the model, an average DES price should also be used to ensure equity. Averages would also be consistent with the use of NHS reference costs elsewhere in the model, as these are also averages.

3.2. It should be noted though, that the Institute's Guide to the Methods of Technology Appraisal states that "*Where the actual price paid for a resource may differ from the public list price (for example pharmaceuticals, medical devices), the public list price should be used*" (NICE 2004, section 5.6.1.1). We recognise the desire from the NICE to quote a price that all NHS hospitals can procure at, but NICE should also recognise that not all providers purchase BMS at the same price now. Furthermore, it would be inequitable to use list prices as a source of upper DES price certainty whilst at the same time using market prices for BMS.

4. **New UK Data on Proportion of Patients with Acute Coronary Syndromes (ACS)**

4.1. BCIS recently released data for 2006 showing that the proportion of patients presenting with ACS (i.e. incurring non-elective costs and resource use) has risen to 48.5% (Ludman 2007). This means that the proportions used in the model to combine LRiG's elective and non-elective datasets, and the proportion of DES patients who require 9-months additional clopidogrel, should be revised. The impact of this on individual data inputs is shown below.

5. **The Absolute Risk of Repeat Revascularisation with BMS**

5.1. It is not clear why the absolute risks of repeat revascularisation with BMS have been set at 10% for elective patients and 13% for non-elective patients. The submission to NICE by NHS QIS (dated 13th January 2006) states:

"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."

5.2. Combining these data in the correct proportions of ACS and non-ACS (48.5% ACS, Ludman 2007), the absolute risk of repeat revascularisation for the combined, unselected population is **14.7%**. The model should be re-run using these Scottish registry data.

6. **The Risk Reduction Associated with DES**

6.1. The model presents alternatives of 55% and 65% risk reduction associated with DES. This is not representative of the trial data pertaining to Cordis's Cypher Sirolimus-elutingStent.**********CiC removed.**********

6.2. CiC removed
********** This means that for the Cypher stent, the non-fatal MI QALY saving of 0.00055 used in the model is an under-estimate and should be revised to 0.0013502. (Calculation: absolute MI saving of 0.86% x (utility of CHD 0.84 (Hawkins et al 2005) - utility of MI year 1 0.683 (Jones et al 2004)).

7. **Relative Risks for the Independent Risk Factors**

7.1. The model employs an unusually low relative risk (RR) for diabetes of 1.19, which results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients. The non-elective RR appears to be spurious because a RR of <1 for a risk factor that has repeatedly been shown to increase the relative risk is perverse.

7.2. It would be more reasonable the use the relative risks for the individual risk factors previously submitted by BCIS as they are derived from the wider literature and are not solely reliant upon the CTC database.

8. NHS Reference Costs

8.1. The model uses reference costs from 2003-04, which are out of date, as the Department of Health has now published costs for 2005-06. Table 1 compares these two sets of costs. The 2003-04 data under-estimate the costs associated with repeat revascularisation and thus render the current model inaccurate. The model should be re-run using 2005-06 reference costs.

Item	2003-04 Reference Cost	2005-06 Reference Cost	Difference
Cardiology 1st out-patient attendance	£134	£148 (code 320F)	+£14
Cardiac surgery 1st out-patient attendance	£208	£274 (code 172F)	+£66
Cardiology out-patient follow up	£94	£104 (code 320F)	+£10
Cardiac surgery out-patient follow up	£156	£182 (code 172F)	+£26
Angiography	£724	£838 (day case E14)	+£114
PCI (elective)	£2609	£3093	+£484
Unstented PCI	£1453	£1937	+£484
CABG (elective)	£7066	£8172	+£1106

Table 1. Comparison of 2003-04 reference costs used in the LRiG model and the latest 2005-06 reference costs.

9. Calculation of QALY Loss Awaiting Repeat Revascularisation.

9.1. LRiG calculation of QALY loss awaiting repeat revascularisation is based on a 16 week wait for PCI, a 9 week wait for CABG and an assumed 4 week wait prior to joining the list. These are derived from NHS waiting time statistics for quarter 4 2004-05, and are again out of date, as the Department of Health has published waiting time statistics up to the 4th quarter 2006 and HES data for 2005-06 (see 8.3).

9.2. The waiting time for PCI and CABG procedures should be taken from HES data rather than the less specific NHS waiting times statistics. DES data give a specific mean waiting time for PCI and CAB procedures rather than, for example the entry for 'cardiothoracic surgery' in the NHS waiting time statistics. Cardiothoracic surgery includes other, non-revascularisation procedures and is therefore not specific.

9.3. LRiG's formula for estimating total waiting times is somewhat imprecise compared to the method published by Hawkins et al (2005). Hawkins et al considered the total wait to be made up of three elements: time waiting for first consultant appointment, time waiting for coronary angiography and time waiting for the revascularisation procedure. Latest data from the Dept. of Health suggests that these inputs should be: 6 weeks for 1st cardiology/cardiac surgery out-patient attendance (waiting time statistics, Q4 2006), 11.1 weeks waiting for angiography (HES 2005-06), 8.0 weeks waiting for PCI procedure and 9.3 weeks waiting for CABG procedure (HES 2005-06). The model should be re-run using the Hawkins formula and the data given above.

10. **Combination of Elective and Non-elective Datasets**

10.1. The combination of the incremental costs and utilities from the separate elective and non-elective models should be according to the national proportion of 48.5% non-elective, rather than the single centre, CTC proportion.

10.2. LRiG should also explain the discrepancy between the number of stents per procedure in their combined Table A of Addendum 6' and the number of stents shown in the separate elective and non-elective datasets in Table A of Addendum 5'. Combining the individual datasets in the proportion LRiG propose does not produce the results they report in Table A of Addendum 6'. It is our belief that Table A of Addendum 6' is incorrect, where the number of stents per procedure appears to be particularly inaccurate for small vessels and long lesions + small vessels. However, if Table A of Addendum 6' is correct (1.66 stents per procedure for small vessels and 2.24 for small vessels + long lesions) and the individual elective and non-elective number of stents per procedure are wrong, then the model overestimates the ICERs for small vessels and long lesions + small vessels in particular.

10.3. The Institute will note that Cordis raised this issue on 1st August, but the subsequent 'clarification' issued to consultees did not resolve the query. These key inputs should be checked and the correct data should be entered into the model.

11. **Acute Coronary Syndromes**

11.1. NICE's announcement of the development of a clinical guideline for the management of patients with ACS and the stated relevance of the guidance on the use of coronary stents to that guideline, suggests that ACS should be considered as an additional sub-group within this Review.

11.2. There are clinical and economic grounds for considering ACS in that the 16.6% repeat revascularisation rate for these patients shown in the Scottish registry gives cause to believe that there may be substantial benefit from DES in this population. Secondly, ACS patients receiving DES do not require 9m additional Clopidogrel for reasons previously stated and accepted by the Appraisal Committee. This removes a major cost item from the model and is likely to have a major impact on the ICER for ACS patients.

11.3. BCIA have previously shown that ACS and unstable angina do occur in the literature as independent risk factors for repeat revascularisation (BCIA response to Assessment Report Addendum), and that the risk increase for unstable angina is of a similar order to that for long lesions (odds ratio ~ 1.40). One study (Gotschall et al 2006) reported an odds ratio for target vessel revascularisation of 3.23 for ACS.

11.4. We propose that ACS be added as an additional sub-group for consideration, with modelling based on non-elective reference costs and resource use, as these patients present in the non-elective setting.

12. **Assumption of a DES Class Effect**

12.1. The model assumes that all DES confer an equal treatment effect for reductions in both repeat revascularisation and MI. This is not a valid assumption.

12.2. The Appraisal Committee will note that Stettler et al (2007) have shown a 30% reduction in TLR for Cypher versus Taxus (HR 0.70, 95%-CI 0.56-0.84, p=0.0021), a finding which has been confirmed by Schömig et al (2007) using patient-level data (HR 0.72, 95% CI 0.61 to 0.86, p < 0.001).

12.3. Stettler et al also recorded a significant difference in MI rates between the two DES in favour of Cypher (HR 0.83, 95%-CI 0.71-1.00, p=0.045), an effect that Schömig et al found strongly echoed in the patient-level data (HR 0.81, 95% CI 0.64 to 1.02, p = 0.07). This difference becomes even more pronounced after the first year (HR 0.45, 95% CI 0.25 to 0.80, p=0.006).

13. **Wider Impact on the National Health Economy**

13.1. Whilst the model is not intended to provide budget impact estimates, the Institute should be mindful of the impact that DES use has had on the NHS. Figure 1 shows the evolution of NHS reference costs for PCI and CABG, as well as the waiting times for each of these procedures. The reference costs have been inflated to 2007 values using the Health Service Cost Index.

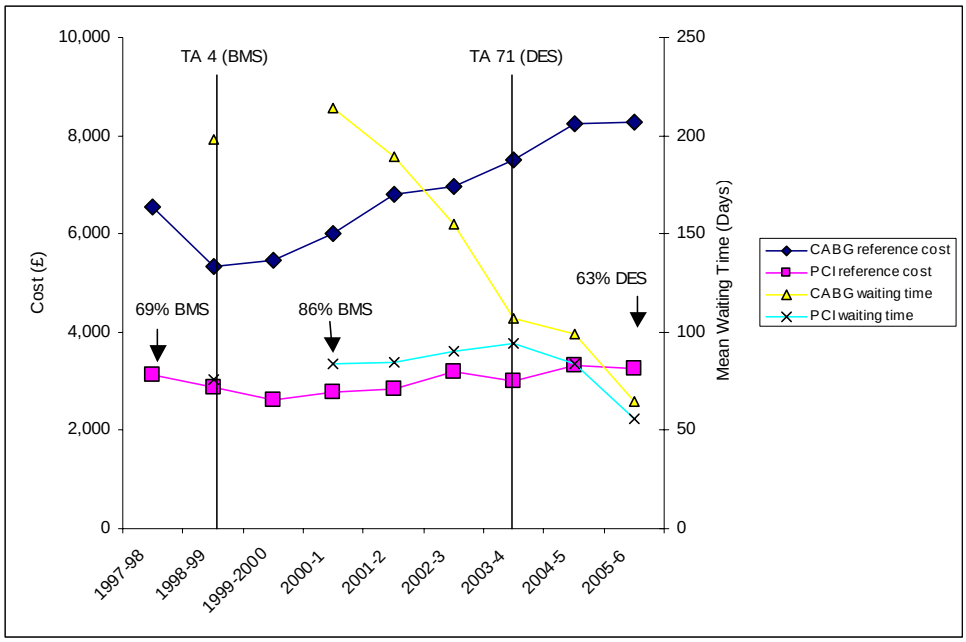

Figure 1. Evolution of NHS reference costs and waiting times for PCI and CABG over time. *Reference costs have been inflated to 2007 values. The reference cost for PCI fell by 1.6% between 2004-05 and 2005-06. TA = issue of NICE guidance on the use if stents resulting from technology appraisals.*

13.2. Figure 1 shows that the growth in the use of stents in general and the introduction of DES has had very little impact on the NHS procedural cost of PCI. Most notably, the PCI reference cost fell by 1.6% in real terms between 2004-05 and 2005-06, probably reflecting the fall in both BMS and DES market prices that we have outlined in previous submissions.

13.3. The Institute should consider carefully the impact of the current draft guidance in the light of these data. The potential swing from PCI (with a falling cost to the NHS) to CABG (with an increasing cost to the NHS) is likely to impose a net burden on the NHS of £55.2 million in 2008 alone.

14. Summary

14.1. The model should be re-run incorporating:

14.1.1. A clear and transparent determination of the average DES price premium.

14.1.2. Data inputs revised based on a proportion of 48.5% non-elective patients.

14.1.3. 14.7% repeat revascularisation rate from the Scottish registry.

14.1.4. The trial-based absolute risk reductions for the Cypher stent published by Stettler et al (2007).

14.1.5. The relative risks for the individual risk factors identified by BCIS.

14.1.6. The latest NHS reference costs (2005-06).

14.1.7. QALY loss based on the latest NHS waiting time data and waiting times calculated according to Hawkins et al (2005).

14.1.8. Clarification of the correct number of stents per procedure, especially for small vessels and small vessels + long lesions.

14.1.9. ACS as a separate risk factor group.

14.1.10. Separate TLR and MI risk reductions for Cypher and Taxus.

14.2. Cordis urge the Institute to address all of the limitations of the economic model highlighted in this commentary. The outcome of the Review would be perverse if it were based on such out of date, unreliable and questionable inputs.

References

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