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British Cardiac Society
Promoting Cardiovascular Health

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20 April 2006

Dear Ms Marschke

NICE addendum: Coronary artery stents for the prevention of ischaemic heart disease

I attach our response to the additional evidence that was submitted for the above appraisal. The paper has been prepared by the British Cardiac Society and the British Cardiovascular Intervention Society.

We still have major concerns about the assessment and continue to reject its conclusions which, we believe, are fundamentally flawed. We earnestly hope that the Appraisal Committee will accept the primacy of randomised trial over registry data and take into account the views of the wider interventional community.

Yours sincerely

President

Health Technology Appraisal
Ischaemic Heart Disease – Coronary Artery Stents

Comments on further evidence from the British Cardiac Society and British Cardiovascular Intervention Society

April 2006

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) whom 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 accept 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 outset 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 prevalence of diabetes in the Liverpool database. The 13% prevalence of diabetes reported is very low compared to the 25% in the Sirius trial (ref). In the Kings College Hospital database the prevalence 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, Consultant Cardiologist King's College Hospital, London). 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 are 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, Consultant Cardiologist, CTC Liverpool). 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, these data remain 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 risk for repeat revascularisation should be 12.1% as demonstrated in table 1.

The data from randomised trials are 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 diabetes 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 effectiveness 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, or the recurrence of angina, or 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 it 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 were 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 utterly to 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 and 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 with 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 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.

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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.

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