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

Comments from the British Cardiac Society; British Cardiovascular Intervention Society; and Royal College of Physicians. January 2006

This response to your request for initial comments on the Liverpool Reviews and Implementation Group (LRiG) report on Drug Eluting Stents (review of guidance 71) is endorsed by the British Cardiac Society (BCS), the British Cardiovascular Intervention Society (BCIS) and the Royal College of Physicians (RCP).

The BCS, BCIS and RCP believe that the conclusions in the report do not fairly reflect the randomised trial data. They confirm that it was inappropriate for the Liverpool Reviews and Implementation Group (LRiG) to produce the assessment for NICE. The report is a reiteration of a single, extreme and previously expressed opinion rather than the presentation of a considered review of the published data.

Incorporation of the report into new guidance by the Appraisal Committee will be a major retrograde step for cardiology – and cardiac patients - in the UK. Given the enormous advances of British Cardiology in recent years (the UK, rather remarkably, is now regarded by the rest of Europe as a paradigm of the benefits of medical investment) this would be unfortunate, both clinically and politically.

Executive Summary

The British Cardiac Society; the British Cardiovascular Intervention Society (BCIS), an affiliated group of the BCS representing clinicians performing coronary angioplasty within the UK; and the Royal College of Physicians strongly disagrees with the Assessment Report produced by the LRiG. We have major reservations over the methodology and impartiality of the report and are particularly unhappy about recurrent statements that impugn the integrity of clinical investigators performing trials with industry funding.

The use of non-randomised data from a single, unrepresentative and almost certainly incomplete local database to form national policy is inappropriate and unacceptable.

We do not accept that the benefits of drug eluting stents (DES) should be downgraded within any economic model because of protocol or angiographically driven or non target vessel revascularisation. We present arguments to highlight the inappropriateness of these assertions.

We believe the original guidelines are robust and evidence based. However, in addition, diabetes should be added as a further indication for a DES. We also believe that the current literature strongly supports the use of drug-eluting stents in the treatment of restenosis lesions.

Specific comments

The BCS, BCIS and RCP could probably have written this response prior to receiving the LRiG review since its views were already well-known. Indeed many of our comments and opinions are contained within the editorial (1) written in response to the paper by Bagust et al (2) that the LRiG stated would be published at the scoping meeting. However, rather than merely reading this editorial, we ask the Committee to consider the following specific points.

We were amazed to discover that there were no clinicians in the review team. This is, clearly, ludicrous for a group that was commissioned to review clinical data. It is reflected by the Group's obvious lack of understanding of the disease process, conduct of clinical trials and the role of clinical cardiologists performing these trials that is evident in various sections of the report.

We acknowledge that there were clinicians on the advisory panel, but do not find this reassuring. For example, Dr Martyn Thomas, BCIS President, was on the advisory panel for the previous review. He was so concerned by the Review Group's refusal to pay attention to his advice (including the section, which was removed only from the final draft, suggesting that angioplasty caused cancer) that he asked for his name to be removed from the final document. Despite his request, this did not happen.

We therefore suggest that the Appraisal Committee asks for the specific comments of the clinicians involved on the advisory panel. It could then be assured that the final document reflects the clinicians' views. Without this, there is truly no clinical input to this document. The extra-ordinary statement "a variety of guide-wires and devices to assist insertion of the stents exist and although some stents are provided on set insertion systems, interventionists do have some choice" (page 31 of the report) suggests a complete lack of clinical input and understanding of interventional cardiology.

The arguments with regard to the benefit of drug eluting stents (DES) were exhausted during the last appraisal. No-one has ever suggested that there is a mortality benefit from stenting, let alone from DES. Revisiting this argument is not useful. We do believe, however, that the dismissal of recurrent angina by the LRiG as a serious clinical event reflects the lack of clinical input that is apparent throughout the document. Those of us with regular interaction with patients know the incapacitating effect of angina but this does not seem to be appreciated (once again) by the authors of the report. The impact of work time lost through angina has never been adequately addressed by this group.

The conclusion of this report appears to be that, on economic grounds, DES should be used in only 1.4% of patients. The original appraisal of DES (3) supported their use in small vessels (<3mm) and longer lesions (>15mm). It was anticipated this would result in a 30% use per lesion. This was based on a thorough review of the published data. It attempted to identify a high risk lesion subset of patients who would gain particular benefit from a DES.

The interventional community as a whole believes that these were entirely sensible guidelines. No new information has become available to suggest they should be adjusted downwards. The LRiG repeatedly references the Basket trial (4) as an example of a "more pragmatic effectiveness study". It correctly describes the result of the study as showing that DES were "cost ineffective except in high risk patients" (a statement with which we would all agree). However, the LRiG does not go on to explain that the high risk lesions identified in this study were small vessels and long lesions! Thus the trial that the LRiG identifies as an example of a recent well performed study supports the original NICE guidance. Moreover the stent used in the Basket trial was not bare metal; it was a more expensive cobalt chromium device.

We firmly believe that the original guidelines were reasonable. In addition, however, we contend (as argued in the BCIS submission to the committee) that compelling evidence now exists that diabetes is an independent risk factor for restenosis (above and beyond vessel size and lesion length). It should, therefore, be added (as a patient rather than lesion characteristic) to the "indications" for a DES. The failure by the LRiG to identify diabetes as a risk factor reflects the systematic bias of the local audit and the inadequacies of the data collection.

The report gives little or no information on the quality control of the CTC database. Enormous effort is required to collect complete and validated data. No clinical registry can ever achieve the level of accuracy required by a trial. Does the CTC database document the number of patients who developed recurrent angina but elected to remain on medical therapy? This level of detail is not provided. The extensive data that highlight the benefit of DES in diabetic patients have been published since the previous NICE review.

The sole basis of the "change of heart" of the LRiG appears to be a 12 month audit from a single centre in the United Kingdom, the Cardiothoracic Centre-Liverpool (CTC). LRiG argue that these non randomised data, from a single centre, indicate that the previous NICE guidelines were incorrect.

The remarkable feature of the report is the weight given to a single, internally generated, retrospective, local audit and the inappropriate dismissal of multiple well conducted multi-centre multinational randomised (bare metal stent) studies. These properly performed peer reviewed studies, with independent Data and Safety Monitoring Boards, which were published in internationally respected journals have consistently identified the presence of diabetes, small vessels and longer lesions (the basis of the previous NICE guidelines) as multivariate predictors of target lesion revascularisation (TLR) or target vessel revascularisation (TVR) (5-8). These factors have also proved positively predictive in DES trials using both sirolimus and paclitaxel (9-12).

The interventional community accepted the previous NICE guidelines for the use of both bare metal and drug-eluting stents as being reasonable and appropriate because they are based on properly performed randomised controlled clinical trials. If the NICE method of assessment of technologies has changed, the stakeholders – the clinicians and patients - should have been informed.

The LRiG states:

“At the time the previous Technology Assessment Report was prepared it was evident that there was little independent evidence available to address some important issues confronting the Appraisal Committee. Virtually all of the clinical trial results were obtained from industry-sponsored trials where the selected patient populations were not representative of the mix of conditions presenting in normal UK practice. Moreover, the measures of efficacy generally reported were often not directly translatable into terms relevant to treatment decisions in the consulting room. The previous guidance attempted to reflect an understanding of the limited body of evidence then to hand, but key questions remained unresolved which could potentially alter the balance of costs and benefits in either direction. In this current assessment we have attempted to supply some of this want of evidence from several sources, and undertaken a revised economic evaluation taking the new information into account.”

We believe this statement leads to two conclusions:

1. That optimal assessments should be based on randomised clinical trials. We agree. Despite this, the subsequent LRiG document is essentially based on a local retrospective audit.
2. That the probity and integrity of the investigators and clinicians who carried out the industry-sponsored trials is open to question. This theme is repeated throughout the document including the statement on page 145 of “no check on the discretion of clinicians”. We consider this anti-clinician theme deeply offensive and inappropriate for inclusion in a report of this nature.

One of the most extra-ordinary parts of the report appears on page 71. The LRiG conducts what they call a “critical appraisal of economic evaluations”. It claims critically (but not independently) to assess 10 studies, including its own.

Under the checklist item “the choice of model used and the key parameters on which it is based are justified”, it scores 5 of the 10 studies poorly. This is purely subjective. We wonder what the scores would be if assessed by one of the authors of the competitive papers. We find this totally unacceptable in such an important evaluation document. We are not surprised that the LRiG scores its own article the highest. This piece of self-congratulation, in our opinion, virtually invalidates the entire “objective” element of the document. This view is reinforced by page 61 of the document where the LRiG quotes its own publication, over and above others, to support its view that diabetes is not a risk factor for restenosis in the real world. This is, surely, utter nonsense.

The conclusions of the document are invalid for the following reasons:

(a) A retrospective, single centre, local audit has inherent systematic bias which does not make it appropriate for the formation of national policy. The systematic bias is highlighted by the low level of diabetic patients in the local audit compared to the internationally-recognised Sirius (13) trial (13% v 25%).

(b) Dismissal of other data which do not support the LRiG's view by a "critical appraisal" supporting its own study is unacceptable and invalid.

(c) The report states that stent trials fail to report 'all revascularisation', instead reporting "angiographic restenosis (not all clinically significant), and event rates specific to the lesion or vessel initially revascularised." This is described as "selective reporting" and it is argued that it "exaggerates the apparent benefit attributable to DES". In the SIRIUS trial (13), the Cypher stent was associated with a 75.6% reduction in TLR at 12months, and a 68.3% reduction in TVR. The use of TLR certainly does not qualify as "selective reporting" of the trials and is the most sensitive measure of the effectiveness of the device.

The arguments in section 8.2.3 on "Effectiveness estimates from observational data" should be seriously challenged as they markedly affect the cost-effective data. They argue that in a third of cases on the CTC database the vessel treated is not that treated with the original DES and, therefore, the benefit of the device in the economic model should be downgraded. This is inappropriate for the following reasons:

1. These are data from a single centre, and the clinicians from this centre may choose to work in a particular manner; eg for cost and tariff reasons the CTC may choose to perform "culprit vessel" angioplasty only. Once again this may well reflect the systematic bias of retrospective registry data.
2. In randomised trials, the non-target PCI rate will equally affect both groups yet the treatment effect remains 75%.

Certainly, DES cannot prevent new disease. The idea of "downgrading" the effect of DES in the LRiG model to reflect this is nonsense. The "fog" that this argument produces and the downgrading of the "benefits" of DES (from 75% to 35-50%) in the LRiG economic model are totally unjustified and not applicable to clinical practice. The LRiG readily admits that the data from the CTC database do not allow it to identify the true reason for a repeat procedure in 49% of cases.

(d) The document argues that protocol-driven follow-up angiography overestimates both the risk of recurrence and the benefit of using DES by promoting angiographically rather than symptom driven repeat revascularisation. We believe the LRiG have, once again, misinterpreted the data, probably as a consequence of the lack of clinical input.

The timing of clinical and angiographic restenosis relates to the well known and extensively published biological phenomenon of the restenotic process. All restenosis that is going to happen has done so by 6-9 months.

In the 12 month SIRIUS data (13) the difference in clinically-driven TLR event rates between the sirolimus-eluting stent and bare metal stent groups in all patients (i.e. including those who had protocol-mandated angiographic follow-up) was 15.1% at one year. The equivalent measure (14.0%) was also reported for the patients who did not have angiographic follow-up, indicating that the treatment effect in the absence of the angiogram is virtually the same.

Furthermore the proportion of patients whose TLR was based solely on angina symptoms, without consideration of other modalities, such as exercise testing, was 96.2% for sirolimus-eluting and 81.0% for control stent patients. If the 12 month clinically-driven TLR rates of 4.9% for sirolimus-eluting and 20.0% for control stent patients are further adjusted for these respective percentages, this gives 12 month angina-driven TLR rates of 4.7% for sirolimus-eluting and 16.2% for control stent patients, an absolute difference of 11.5% and a 71.0% "treatment" effect.

In addition the LRiG quote the new FDA definition for “clinical revascularisation” including the statement:

> “The procedure was considered clinically driven if the patient had "a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms and an in-lesion diameter stenosis greater than 50 percent. Revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70 percent in the absence of the above mentioned ischaemic signs or symptoms were also considered clinically driven".

A major US regulatory body, therefore, considers that the angiographic appearance is relevant in the decision making process with regard to revascularisation. The LRiG view on this is less clear.

(e) Finally, are there other “cost effective” data available in the literature? The LRiG reviewed 10 such studies. Eight of the 10 studies identified diabetes as a risk factor for restenosis but this is then dismissed. The majority of studies concluded that DES were more cost-effective for high risk patients (consistent with the previous guidelines and with which BCIS would agree). Three studies showed even more favourable results for DES. However, these are outrageously dismissed as “these studies had received industry funding”. This is yet another example of the unacceptable agenda that appears to have been brought to this project by the LRiG.

In section 8.7.3 LRiG states that the studies are “unanimous in affirming that DES cannot be considered generally cost-effective except for a limited number of high-risk patients. The word “limited” is subjective and is inserted by the LRiG; and the high risk groups identified in these studies are diabetes, long lesions and small vessels. The fact that these were not identified within the CTC database reflects a problem with this local database rather than an error in the other 9 papers.

Two of the papers clearly demonstrated the cost-effectiveness of DES. A Canadian study, estimated the cost-effectiveness of the Cypher stent over a patient’s lifetime by applying the relative risk of repeat revascularisation derived from a meta-analysis of four Cypher trials to absolute risk data from the Alberta province (14). This study showed that the Cypher stent was associated with an overall cost-effectiveness ratio of £25,100. It was also noted that DES were more cost-effective in patients at higher risk of restenosis and, interestingly, showed an incremental cost per QALY gained of £18,850 in diabetic patients.

A different approach was taken by van Hout et al (15) who conducted a cost-effectiveness analysis based on actual resource use in the RAVEL trial using Dutch cost data. The authors acknowledged the potential impact of the follow-up angiogram and adjusted the analysis to allow for only clinically-driven events. At one year, total costs were £113 higher in the Cypher arm, which the authors described as an “attractive balance between costs and effects for sirolimus-eluting stents”.

A further paper has appeared in print in recent days (16). This study assessed the cost-effectiveness of the Cypher stent from a UK perspective based on 3 trials representing patients with small vessels (RAVEL trial), longer lesions (SIRIUS trial) and a combination of both (E-SIRIUS trial). Using UK cost data and a probabilistic decision model, this paper reported incremental cost-effectiveness ratios of £15,198 (RAVEL trial), £7,461 (SIRIUS trial) and £3,181 (E-SIRIUS trial). At a DES price premium of £500 over bare metal stents, the probability that Cypher was cost effective at a threshold of £30,000 per Qualy gained was 87%, 100%, and 99% respectively for these three trials. This paper clearly demonstrates the cost-effectiveness of sirolimus-eluting stents from an NHS perspective and, unlike the Assessment Report, adopted the modelling methodology now preferred by the Institute (17).

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