BCIA

British Cardiovascular Industry Association
c/o BCOS Ltd., P O Box 20710, London E3 5UE
Email: BCIA@Bcos.demon.co.uk

Ms. C Fuller,
Technology Appraisals Manager,
National Institute for Clinical Excellence,
MidCity Place,
71 High Holborn,
London
WC1V 6NA.

12th January, 2006.

Dear Ms. Fuller,

Response to Assessment Report:
Coronary Artery Stents for the Treatment of Ischaemic Heart Disease
(Update to Guidance No. 71.

The British Cardiovascular Industry Association (BCIA) is a joint industry organisation made up of many of the companies who have an interest in the field of UK interventional cardiology. BCIA believes that the Assessment Report (AR) presents a very particular interpretation of the evidence pertaining to drug-eluting stents (DES), at one end of the spectrum of opinion about the value of this technology. Our concerns relate to three major issues that influence the overall conclusion of DES cost-effectiveness in the AR:

1. A conflict of interest within the Assessment Group.
2. The definition of DES effectiveness that underpins the economic evaluation.
3. The identification of patients who are at high risk of repeat revascularisation following stenting and the size of that high-risk population.

Conflict of Interest

Three months prior to the deadline for submission to this Review, a paper was published (Bagust A et al, 2005) that included amongst its authors, two key members of the Assessment Group responsible for the AR that NICE has now sent us. These people were Professor Bagust (who developed the economic model) and Professor Walley (responsible for interpreting the clinical and economic data).. This publication provides the foundation to the economic evaluation in the AR, yet there is no explicit declaration of an overlap in authorship and it is not mentioned in the "declaration of interests" at the beginning of the AR. Furthermore, this publication was subject to the same quality review as other publications, meaning that – perversely - the authors engaged in a critique of their own publication and (unsurprisingly), scored it highly.

To put the Bagust paper in perspective, it is an outlier in terms of other publications, in both its reported clinical and cost effectiveness results.

BCIA is concerned that this situation has introduced bias into the AR, in that some members of the Assessment Group entered the Review with a pre-formed, published opinion on the cost-effectiveness of DES. Herein lies the conflict – the authors have a vested interest in a piece of primary research in this area, which is at odds with previously published peer publications. This surely calls into question their ability to undertake an impartial assessment of all of the published and submitted evidence? At best they should be considered a stakeholder in the process, akin to commentator status. It is unclear why academic Appraisal Committee members who have an interest in a particular area have to declare the interest and be excused, yet those associated with

Assessment Groups (who produce the very base material on which the Appraisal Committee relies when making its decision) do not. Just because Assessment Groups may not be receiving funding for the research, or have shares in the technologies, such strongly held pre-formed opinions as those reported in the Bagust paper, must be viewed as a source of bias when the group comes to undertake what should be an independent AR. This conflict of interest was raised with the Institute & DoH in May, through the industry groups. In our view, academic conflicts of interest can only reasonably be treated in the same manner as commercial conflicts of interest.

The Definition of DES Effectiveness Used in the AR

The purpose of a DES is to reduce the rate of repeat revascularisation associated with restenosis of BMS. DES are not intended to reduce the need for other procedures in non-stented segments of the same artery or other arteries, that may become necessary at some future date due to disease progression. Thus, there is a need to differentiate between ***repeat*** revascularisation due to restenosis (which can be reduced by DES) and ***further*** revascularisation due to disease progression, which cannot be reduced by DES. There is a general acceptance amongst clinical experts that the most accurate way to measure the treatment effect of DES is to compare rates of target lesion revascularisation (TLR), i.e. the rates of repeat revascularisation due to restenosis within the stent (+ 5mm either side). By way of a hypothetical example, ***repeat*** TLR rates of 50/1000 (5%) for DES and 150/1000 (15%) for bare metal stents (BMS) equate to a reduction in TLR of 75% (100 out of 150 TLR events avoided). If further revascularisations due to disease progression (assumed to be 30 events in each arm) are now counted, the 'all revascularisation' rates (repeat + further) become 80/1000 (8%) for DES and 180/1000 (18%) for BMS. However, the reduction in 'all revascularisations' is only 56%, because DES have avoided the same 100 procedures, but out of a total of 180 procedures, not 150.

The AR argues that the TLR risk reduction seen in trials represents 'efficacy' and the smaller reduction in 'all revascularisation' should be used in the economic model because this, in the view of the Assessment Group, represents 'effectiveness'. This means that an artificially low treatment effect of DES was used in the AR economic model. However, this argument relies entirely on a flawed opinion of 'efficacy' versus 'effectiveness'. To reduce the treatment effect of DES by using 'all revascularisations' is at the extreme end of the spectrum of possible approaches to this review . Indeed the Assessment Group acknowledges that it may be unsafe, on page 135 of the AR. It is drastically over-conservative to dilute the treatment effect of DES by taking the 'all revascularisations' approach. To downgrade the DES treatment effect by counting further revascularisations of new lesions (which may not have even existed at the time of the initial procedure) is akin to downgrading the effectiveness of a right hip replacement because the left hip may need replacement at some future date! The purpose of a DES is to reduce the rate of repeat revascularisation that would have occurred due to restenosis *within a BMS*, had a BMS been implanted. DES should be assessed within that framework of intended action. TLR, or the more conservative TVR, are appropriate measures of effectiveness.

Identification of Patients at High Risk of Repeat Revascularisation and the Size of the High-Risk Population.

The original Technology Appraisal of DES identified patients with longer lesions (>15mm length) and small vessels (<3mm diameter) as being at increased risk of restenosis and the resulting Guidance recommended that patients meeting these 'anatomical' criteria should receive either a Cypher or Taxus DES. The AR creates a perception that longer lesions, small vessels and the presence of diabetes do not predispose patients to a high risk of restenosis, rather that these factors are "assumed" (page 13) or "presumed" (page 133) to define those at risk or represent a "belief" (page 61). The language implies that these risk factors are founded in folklore rather than clinical science. This representation is grossly misleading, is based largely on the findings presented in the Bagust paper (itself relying on data from a single hospital) and makes only brief reference to the wealth of other published data.

The original BCIA submission to this Review presented the results from 10 studies that sought to identify factors predictive of repeat revascularisation in patients who received BMS, 7 of them based on 'real world' clinical databases, not randomised trials. The purpose of this was to confirm that the original Guidance was still consistent with data that may have been published since it was issued. We adopted an approach of using all available evidence (including the Bagust paper). The result was that 6 studies identified smaller vessel diameter or a related measure of smaller in-stent area or smaller lumen diameter post procedure as being an independent predictor of restenosis or repeat revascularisation (all except one identified the clinical, not the angiographic outcome). Five studies identified longer stent/lesion length and 7 studies reported diabetes as an independent risk factor. Thus, the AR and the Bagust paper should be seen in context – they contribute to the dataset, but when *all* the evidence is considered, the Appraisal Committee was correct when it previously

identified patients with longer lesions and small vessel diameter as being at increased risk of restenosis and thus most likely to benefit from DES. As a result, BCIA believes that the current recommendations for DES in patients with lesions >15mm in length or vessels <3mm in diameter should be retained. In addition, diabetes is an independent risk factor; hence the guidance should be extended to include diabetic patients who fall outside these anatomical criteria.

The AR asserts that only when the risk of repeat revascularisation with BMS reaches 16-18% (page 120), do DES become cost-effective and these rates are only reached when 2 or more 'Liverpool' risk factors are present. However, the requirement for 2 or more risk factors relies on the assumption that the 'Liverpool' risk factors are correct. This assumption is unreliable as the wider literature shows that longer lesions, small vessels and diabetes are more widely validated risk factors. The AR also makes much of revascularisations driven by the follow up angiograms mandated by trial protocols. This was recognised as an issue in the BCIA submission, so an overview of all studies that DID NOT include trial protocol-driven revascularisations was presented. This analysis included the Bagust publication, recognising that it had something to contribute to the overall result. The BCIA analysis therefore does not select the single publication that best represents DES. The biggest single contributor to the review, the PRESTO trial, with 36% weighting, is not even referenced in the AR.

The results of the BCIA analysis, repeated below for convenience, demonstrate that the underlying risk in ALL PATIENTS is between 11-12%. Indeed, Table 7-4 (page 81) of the AR shows that the trial-based TLR/TVR rates used in the general populations in the Boston Scientific, Cordis and Medtronic economic models are in the range of 12.8-15.5%, within the range shown below. This demonstrates that the clinically-driven TLR/TVR rates seen in the DES randomised trials are not greatly different from the range of data seen in the literature where there is no protocol-mandated angiographic follow-up. Thus, any remaining effect of the angiogram in the clinically-driven trial repeat revascularisation rates is very small. Accepting that the rates in high-risk patients will, by definition, be greater than in the general population, it does not require a huge leap to accept that patients with longer lesions, small vessels and diabetes have a risk (excluding protocol-driven revascularisations) in the range of that which the AR suggests DES are clearly cost-effective.

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	9.1%
Shrive *et al*, 2005	7,334	601	8.2%	12m any revasc, clinical database	23.2%
Singh *et al*, 2005	11,484	1,609	14.0%	PRESTO trial. 9m TVR, ischaemia-related revasc	36.4%
Jilaihawi *et al*, 2005	1,003	51	5.1%	12m TLR, clinical database	3.2%
Serruys *et al*, 1998	206	16	7.8%	BENESTENT II trial. 12m TLR no angio group	0.7%
Kalzula *et al*, 2004	38	6	15.8%	ELUTES trial control group. 12m TLR symptom driven revasc	0.1%
Stone *et al*, 2004	385	49	12.8%	TAXUS IV trial control group. 12m TLR no angio cohort	1.2%
Holmes *et al*, 2004	525	85	16.2%	SIRIUS trial control group. 12m TLR angina driven revasc	1.7%
Lemos *et al*, 2004	380	41	10.9%	12m TVR angina driven, clinical database	1.2%
Serruys *et al*, 2001	600	102	21.0%	ARTS trial stent arm. 12m all revascs, no follow-up angio	1.9%
Wu *et al*, 2004	3,571	577	16.2%	12m revasc, prospective registry of routine practice	11.3%
Agema *et al*, 2004	3,177	304	9.6%	9m TVR in routine clinical practice	10.1%
Overall	**31,587**	**3,721**	**11.8%**		**100.0%**

Table 3 reproduced from BCIA submission. Summary of evidence for repeat revascularisation risk in a mixed population of patients <u>treated with bare metal stents</u>, excluding the effect of protocol-mandated angiographic follow-up. *'Weight' shows the percentage each study 'N' contributes to the overall 'N'. Clinical databases contribute 58.1% of the overall population. The 8.8% shown for Bagust et al represents the overall revascularisation rate in the complete CTC population.*

The cost-effectiveness results presented in the AR are crucially dependent upon the acceptance of the single-centre Liverpool data which, as we have noted above, is an outlier in terms of both the baseline risk of repeat revascularisation and the identification of high-risk groups. The AR points to another UK database (Jilaihawi *et al*, 2005) in support of its claim that BMS repeat revascularisation rates are very low in the general population. Curiously though, the AR fails to report that the same study found, in contradiction to the AR and the Bagust paper, that diabetes was a predictor of repeat revascularisation. We would argue that this must compromise the reliability of the AR given such selective use of data to support the pre-formed opinions expressed in the Bagust paper.

Minor Points

- The title of the AR suggests a poor understanding of the subject by the Assessment Group – "*Coronary Artery Stents for the Prevention of Ischaemic Heart Disease*". Stents do not prevent ischaemic heart disease; in current UK practice they are used predominantly in the treatment of angina.
- The AR recommends further comparison of DES to newer non-DES. The adoption of new alloy over stainless steel stents has been driven by improvements in deliverability not repeat revascularisation rates. The fact that all manufacturers are developing DES shows that DES, not new BMS, are the devices that confer reductions in repeat revascularisation.
- The AR suggests that DES have been over-implemented - more than the 30% suggested in the original Guidance (page 145) - and that clinicians will find any change to this "unpalatable". In response, we need to draw to the Committee's attention that, when consultation took place on the ACD and FAD during the original appraisal of DES, it was reported by many stakeholders that the figure of 30% under-represented the patients in the target groups, even though the 30% figure remained in the published Guidance. It is more the case, therefore, that the original Guidance under-estimated the true population size, rather than that DES have been over-used relative to that Guidance.

Summary

The AR presents a fringe view of the clinical and cost-effectiveness of DES. Overlap in the authorship of the AR and the Bagust paper means that the AR was never likely to reflect an impartial review of all the evidence. This is a serious conflict of interest that has resulted in an AR biased in its presentation of the type of patients at risk of restenosis, the magnitude of that risk and the consequent cost-effectiveness of DES.

In contrast, when all the available data are taken into account, the decision of the Committee to recommend DES for patients with lesions >15mm in length or vessels <3mm in diameter is shown to be robust and BCIA propose that it should be retained. In addition, diabetes is an independent risk factor for restenosis and BCIA suggest that this Review should extend the Guidance to include diabetic patients who fall outside these anatomical criteria.

Yours sincerely,

The British Cardiovascular Industry Association.

British Cardiovascular Industry Association

The British Cardiovascular Industry Association (BCIA) was founded in May 1997. Membership of the Association is available to the United Kingdom manufacturers and suppliers of cardiovascular equipment and pharmaceuticals to the National Health Service and private healthcare providers who are registered under the MDA and MCA.

The British Cardiovascular Intervention Society (BCIS) is the professional representative body for interventional cardiology in the UK,. The membership of BCIS consists primarily of cardiologists and senior allied professionals. As a reciprocal body, BCIA represents industry involved in promoting products to this specialist field.

A major objective of BCIA is to organise and support research, educational meetings and other events in the field of interventional cardiology such as the BCIS Advanced Angioplasty and regional Autumn Conferences. BCIA also acts as a unified voice of industry interfacing with bodies such as Department of Health, NHS Supplies, MHRA and the National Institute for Clinical Excellence (NICE).

Currently BCIA has a membership of over 25 companies both in the field of devices and pharmaceuticals.

List of BCIA Members

Company	Contact	Job Title
Abbott Vascular Devices		UK Sales Manager
Apex Medical Devices Ltd		Managing Director
Biotronik UK Ltd		Manager Vascular Intervention
Boston Scientific Corporation		UK Marketing Manager - Interventional Cardiology
Bristol-Myers Squibb Pharmaceuticals Ltd		Cardiovascular Medical Education Manager
Bristol-Myers Squibb Medical Imaging		Senior Product Manager, Europe
Cardinal InHealth Ltd.		Business Development Manager
Cardiologic Ltd		Sales Director
Cordis (A Johnson & Johnson Company),		Group Marketing Manager
Datascope Medical Co Ltd		UK Sales Manager
Eli Lilly		National Therapeutic Advisor
Ev3 Ltd		Managing Director
Glaxo Smith Kline		Healthcare Development Manager, UK
Guidant Ltd		UK Country Manager, Vascular Intervention
InterMedical		Managing Director
Kimal Scientific Products Ltd.		Marketing Manager
Kiwimed Ltd.		General Manager
Medcon UK		General Manager
Medtronic		Vascular Business Manager, UK & Ireland
Merck Sharp & Dohme		Sales & Marketing, Aggrastat
NMT Medical Inc		Sales & Marketing, UK
Nycomed UK Ltd		Marketing
Pyramed Marketing Ltd		Managing Director
RADI Medical Systems		UK Manager
Sanofi-Aventis		Senior Product Manager – Atherothrombosis
Sorin Biomedical Cardio Srl		UK Manager
St. Jude Medical		National Sales Manager
Terumo UK		UK Sales Manager
UK Medical		Managing Director
W L Gore & Associates (UK) Ltd		New Ventures s Manager

References

Agema WR, Monraats PS, Zwinderman AH, De Winter RJ, Tio RA, Doevendans PA, Waltenberger J, De Maat MP, Frants RR, Atsma DE, Van Der Laarse A, Van Der Wall EE, Jukema JW (2004). Current PTCA practice and clinical outcomes in The Netherlands: the real world in the pre-drug-eluting stent era. *Eur Heart J* **25**(13):1163-1170.

Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T (2005). Cost-effectiveness of drug-eluting coronary artery stenting in a UK setting: cost-utility study. *Heart* Apr 14; [Epub ahead of print] http://heart.bmjjournals.com/cgi/content/abstract/hrt.2004.053850v1.

Holmes DR, Leon MB, Moses, MD JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE (2004). Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 109:634-640.

Jilaihawi H, Khan S, Kovac J (2005). Low incidence of revascularisation of bare stents in the era of drug-eluting stents: a single tertiary centre experience. *Heart* 91 (Suppl 1):A5.

Kaluza GL, Gershlick AH, Park SJ, De Scheerder I, Chevalier B, Camenzind E, Goy JJ, Missault L, Reifart N, Vrints C, Urban P, Shim WH, Ho DS, Fearnot NE, Voorhees WD 3rd, Raizner AE (2004). Comparison of neointimal formation in polymer-free paclitaxel stents versus stainless stents (from the ASPECT and ELUTES randomized clinical trials). *Am J Cardiol* Jul 15;94(2):199-201.

Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ (2004). Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* Jan 20;109(2):190-195.

Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJRM, Schönberger JPAM, Buller N, Bonser R, van den Brand MJB, van Herwerden LA, Morel MAM, van Hout BA (2001). Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Eng J Med* 344(15):1117-1124.

Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA (1998). Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* Aug 29;352(9129):673-81

Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA (2005). Economic evaluation of sirolimus-eluting stents. *Canadian Medical Association Journal* 172(3):345-351.

Singh M, Gersh BJ, McClelland RL, Ho KK, Willerson JT, Penny WF, Holmes DR Jr (2005). Predictive factors for ischemic target vessel revascularisation in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. *J Am Coll Cardiol.* 45(2):198-203.

Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME (2004). One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 109:1942-1947.

Wu AH, Goss JR, Maynard C, Stewart DK, Zhao XQ (2004). Predictors of repeat revascularisation after nonemergent, first percutaneous coronary intervention in the community. *Am Heart J* 147(1):146-150.