Washington State Health Care Authority

Health Technology Assessment

Cardiac Stents:
Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS)

Peer Review and Public Comments and Responses

April 13, 2009

SPECTRUM RESEARCH RESPONSE TO PEER REVIEW COMMENTS

Note 1: Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included. However, comments related to program decisions, process, or other matters not pertaining to the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness.

Note 2: Individuals who provided peer review on the published public draft (when it was published online) are listed in Appendix M. This role should not be construed to mean that the individuals were authors or contributors to the formulation of the draft, nor does it imply endorsement, approval, or disapproval of the process or report.

1. Rita F. Redberg, MD, MSc, UCSF Division of Cardiology, Professor of Clinical Medicine

   Dr. Redberg's comment on introduction, response
   The section has been reworded.

2. Keith A. Comess, MD, Chief Medical Officer, Corazon X

   Dr. Comess' comments-corrections to text, response
   We've corrected and reworded aspects of the text. Much of the detail from the background has been removed into an appendix.

3. Steven L. Goldberg, MD, Director, Cardiac Catheterization Laboratory, University of Washington Medical Center

   Dr. Goldberg's comments on study outcomes, response
   The final report notes that most randomized controlled trials were designed and powered to determine primary endpoints such as target lesion revascularization or composite endpoints. Target lesion revascularization results from meta-analyses, RCTS and non-randomized studies are reported in the efficacy and effectiveness sections. The most recent and complete meta-analyses available (and used in this HTA) chose to report survival and MI as primary outcomes, describing TLR as a secondary outcome. Evaluation of death and MI (as well as thrombosis) is in concert with the general themes described in the recent ACCF/SCAI/STS/AATS/AHA/ASNC document formulated by Patel, et. al (and various ACC/AHA guidelines) which indicate that the purpose of coronary revascularization should be the improvement of health outcomes (symptoms, functional status and/or quality of life) or survival.

   Dr. Goldberg's comments on revascularization rates, response
   Rates have been added to the summary for registry studies so that they can be compared. In registry studies is generally not clear to what extent TLR is based on clinical symptoms versus angiographic findings.

Dr. Goldberg's comments regarding off-label use, response
Studies that directly compared DES with BMS were included as described in the methods section. Some of the studies that met the inclusion criteria involved off-label use. Specific conclusions regarding these studies involving off-label use, or about off-label use in general are not made in the summary statements on effectiveness or safety since the focus of the report is on the comparison of DES versus BMS.

PEER REVIEW COMMENTS

1. Rita F. Redberg, MD, MSc, UCSF Division of Cardiology, Professor of Clinical Medicine

INTRODUCTION Comments

Page 28, bottom. Palpitations and syncope are non-specific sx, and are not always associated with CAD.

METHODS Comments

Yes, methods are clear, inclusion and exclusion are appropriate and LoE and data abstraction well done.

CONCLUSIONS Comments

Are the conclusions reached valid? YES

As the literature does not support any benefit for DES compared to BMS in terms of quality of life, nonfatal MI or mortality, it would be impossible for DES to be cost effective. In addition, revascularization avoided is a surrogate outcome without clinical validity, and again PCI would have to be compared to medical therapy for this endpoint before asking the next question of which type of stent.

OVERALL PRESENTATION and RELEVANCY Comments

Overall, I commend the Washington State HTA for a comprehensive, balanced, and authoritative review of the literature on the comparison of DES and BMS. They summarized all of the available data, taking all of the published literature, as well as other published HTA reports and synthesized this massive body of material in a usable and well organized way.

It is important to note that while this report addresses the comparison of DES to BMS, the question that must be asked and answered BEFORE that question is relevant is comparing PCI to medical management for treatment of stable CAD. As multiple meta-analysis show no benefit to PCI over medical rx, the question would be

why use any stenting over medical rx in these patients. As shown in the Katritisis (circ 2005) meta-analysis and others, and confirmed in COURAGE, PCI does not offer any benefit in terms of death, MI or need for subsequent revascularization compared with conservative medical treatment. The COURAGE study (NEJM 2007) found a small, short term difference in angina frequency that disappeared by the three year follow up. In addition, all studies comparing medical therapy versus revascularization have been unblended, and none have used sham control. It is well established that many patients will have short term symptom reduction with an invasive therapy unrelated to a therapeutic benefit of the invasive procedure. To establish that it is actually the stent that is associated with reduction of symptoms (short term), a sham control study must be done. Such a study has never been done.

2. Keith A. Comess, MD, Chief Medical Officer Corazon X

INTRODUCTION Comments

- Overview of topic is adequate? **Yes**
- Topic of assessment is important to address? **Yes**
- Public policy and clinical relevance are well defined? **Yes**

BACKGROUND Comments

- Content of literature review/background is sufficient? Yes

Page 12: difference efficacy/effectiveness? Aren't these synonyms?
Page 14, paragraph 2: SES should be defined, again
Page 14, paragraph 3: "DES were consistently associated with lower risk of target lesion revascularization." Does this mean lower restenosis rate?
Page 15: SES, PES, BMS should be redefined. So should ARC and RCT
Page 16: Not sure whether or not there is higher mortality with DES v BMS in patients with DM
Page 18: Don't grasp distinction between payer's perspective and societal perspective.
Page 21, paragraph 1: "non-endotheliazed stent [KCE]." Spelling. Definition of KCE. No comma after "thus". Somewhat is one word, not two.
Page 22: "risks" of revascularization would be better written as "chance of revascularization"
Page 23, last paragraph, section 1: Sentence 2 would be better written as "Revascularization is *performed* in...". Sentence 3 should be "or" non-fatal MI, not "of".
Page 24, sentence 1 "Background": Not all plaques rupture. Statement is too categorically asserted.
Page 26: I am not sure why the section on pathogenesis of CAD is necessary in this paper. Also, the statement on plaques which tend to rupture is inaccurate: most such are eccentric and far less than 50% obstructive.
Page 27: The section on "unstable angina" is generally incorrect. The term is also archaic and has been replaced by "ACS" (Acute Coronary Syndrome). ST-T wave changes have a very poor correlation with the location of the involved vessel
Page 28: "Risk" should be "Rise" in first indented paragraph in section 1. In paragraph 2, presence of Q-waves does *not* prove MI unless these meet certain criteria
Page 29, paragraph 2: "Modalities" should be "tests". Also, angiography is an indirect indicator: in fact, only intravascular ultrasound (IVUS) depicts the vessel architecture/lesion structure. Finally, nuclear and other functional studies appear to be better predictors of future events than does cath or IVUS
Page 29, paragraph 3: Q waves may/may not develop after an ST elevation MI. They may/may not be permanently present.
Page 29, echocardiography paragraph: "Sonar" is used incorrectly (**Sonar** is an acronym for **sound navigation and ranging**): this has nothing whatsoever to do with medical imaging. The adjective, "trained" before cardiologist should be dropped. "Akinesis" does not prove the myocardium is "dead", nor does "dyskinesis" show a prior infarct
Page 30, section on radionuclide imaging: Statement on sensitivity and specificity is out-of-context (Baysian considerations). It is highly sensitive and specific with appropriately selected study findings and patients.
Page 33: "sexually" should be "sexual"
Page 35: The discussion on the mechanism of action DES is far too technical and is irrelevant. The word "plant" after "yew" is misspelled as "plan"
Page 41: CABG disadvantages uses singular "surgeon"; it should be plural

Page 51: The SCAI table is used which repeatedly refers to a "Type C" lesion. This lesion was never defined in the text or in the table.

REPORT OBJECTIVES & KEY QUESTIONS Comments

- Aims/objectives clearly address relevant policy and clinical issue? Yes
- Key questions clearly defined and adequate for achieving aims? Yes

METHODS Comments

- Method for identifying relevant studies is adequate? Yes
- Criteria for the inclusion and exclusion of studies are appropriate? Yes
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes
- Data abstraction and analysis/review are adequate? Yes

RESULTS Comments

- Amount of detail presented in the results section appropriate? Yes
- Key questions are answered? Yes
- Figures, tables and appendices clear and easy to read? Yes
- Implications of the major findings clearly stated? Yes
- Have gaps in the literature been dealt with adequately? Yes
- Recommendations address limitations of literature? Yes

CONCLUSIONS Comments

- Are the conclusions reached valid? Yes

Everything that was written in the summary reflects an accurate synopsis of the issues with stents, as I understand them: lower restenosis with DES v BMS, no significant difference between the antimetabolites used with various DES, failure of stents to reduce morbidity and mortality in stable CAD, etc. Obviously, a vast amount of work went into the preparation of the statement; there was just some unevenness in the presentation, probably reflecting the combination of authors.

I know it's probably not part of your mandate to make a simple policy statement, but it seems to me that the data supports the position that: 1). All stents must be implanted within the accepted guidelines in order to be reimbursed (unless done as part of an approved research protocol), 2). Uncoated stents be used except in cases at high risk of restenosis. That would solve the financial matter.

OVERALL PRESENTATION and RELEVANCY Comments

- Is the review well structured and organized? Yes
- Are the main points clearly presented? Yes
- Is it relevant to clinical medicine? Yes
- Is it important for public policy or public health? Yes

QUALITY OF REPORT = Superior

3. Steven L. Goldberg, MD, Director, Cardiac Catheterization Laboratory, University of Washington Medical Center

The document and key questions lack focus and seems to exist primarily to cast a dismissive perspective on the current standard of practice of interventional cardiology. The presentation is unbalanced, from my perspective as an academic, active interventional cardiologist.

This dataset has been largely presented in the form of technology assessment reviews and meta-analyses. The document is unclear about a very important point. The meta-analyses that the document discuss looked primarily at death and myocardial infarction (MI), but virtually all of the trials reported on in the meta-analyases had primary endpoints of TLR, TVR, restenosis or some other lesion-specific characteristic. It is accepted that current data suggest mortality benefit for PCI only when done for an acute MI, and that the clinical benefit of PCI is in symptom relief. The document reads as if the studies being done were all negative, (in failing to show any reduction in death or MI, or their combination), when in reality virtually all of them successfully met their primary endpoints, with death and MI either secondary endpoints, or included as a combined primary endpoint. This point needs to be stated clearly early in the document, with sufficient discussion to make clear to any reader that the benefit of stenting is to relieve symptoms, with more objective surrogates such as angiographic restenosis, TLR and TVR being used in lieu of the more subjective descriptions of quality of life, etc. There should be a qualifying statement of any section addressing death and/or MI, that these studies were not designed to look at those as primary endpoints. For this reason, the initial discussion should focus upon TLR/TVR, not on death /MI.

The document repeatedly (I counted at least seven times) points out that the randomized trials required angiographic follow-up which can inflate rates of TLR/TVR. However, the relative rate reductions of TLR/TVR seen in the registry data was fairly close to the rates seen in the randomized trials, somewhat refuting the repeatedly made point. Yet this observation was not made – why not? Furthermore, the degree of rate reduction is quite robust, of ~60-70%, a point which was not elaborated upon (certainly not made seven or more times).

My initial impression was that the questions were to focus on off-label use of drug-eluting stents, but the entire discussion and key questions address comparisons of drug-eluting stents to bare metal stents, of which there is a very large dataset. I mention this because some of the discussion does in fact touch on off-label versus on-label use, with the implications strongly suggesting that off-label use of drug-eluting stents should be limited. This would not be an accurate reflection of the current data on this issue, but several relevant studies are not included. If the issue of off-label use of drug-eluting stents is to be raised, then the discussion should be balanced and comprehensive. There are other examples in the document of this type of almost off-handed dismissal of standard practice of care-givers, without providing a balanced perspective. (Another example would be the role for ad-hoc percutaneous coronary

intervention). This reflects as cynical view of the current approach to patient care and colors the document, creating an impression that care-givers are practicing in a manner which is less about patient care and more about economic gain. Although in any scenario there may be occasional abuses, there are significant clinical reasons why patients choose drug-eluting stents and ad-hoc angioplasty after pros-and-cons are discussed with them, and those are the predominant factors why these practices have become standard.

As mentioned above, there is a lack comprehensiveness regarding on-label versus off-label use of drug-eluting stents, so this document would not be acceptable to address those concerns. It should be specifically noted that studies addressing this were systematically excluded, with rare exception (Applegate et al, JACC 2008). The appendix does mention recent studies examining outcomes of drug-eluting stents versus bare metal stents for on-versus off-label use (Haraji et al, Marrroquin). This is relevant in so far the interventional cardiology community recognizes that there may be an enhanced role for drug-eluting stents in higher risk individuals and lesions – which is largely supported by the sections on special situations and on cost -effective analyses. However, FDA labeling was based upon controlled trials in more simple conditions – which are more uniform and therefore simpler to study. The vast majority of conditions physicians face are lacking in direct randomized trial data. This is reflected in the minority of approved guidelines being supported by higher levels of evidences. It is the nature of medicine for the practitioner to have to extrapolate from a rather limited data-set. In the field of coronary stenting we have the advantage of a large data set due to a highly prevalent disease state, yet it is not possible to study each eventuality. Although the recent article by Pierluigi has been held up as a criticism that the guidelines are inadequately supported by high quality evidence, it actually shows that the clinical practice of medicine is frequently based upon less information than any of us would desire. In these circumstances how should a physician make decisions? We rely on our ability to extrapolate based upon information which we have available to us and/or on the recommendations of those with acknowledged experience addressing these issues (guidelines). A report which attempts to limit the use of a widely-accepted therapy to only those situations in which the FDA has acknowledged the availability of superior quality information is impractical and nihilistic.

Virtually all studies were supported by industry, as no one else would be willing to fund these studies. There are rare exceptions at single center institutions, but the vast majority of data came from industry sponsored studies. Yet this terminology is only applied in certain circumstances, to suggest that some findings might not be valid for this reason. Although this might be a legitimate concern with regards to economic analyses, whereby there are very few people who understand how the assumptions being made and their validity, it would be equally valid to look at potential biases of the "outsiders" who may stand to gain notoriety, academic advancement or other secondary gain by offering a contrarian's perspective. My comment is not to criticize the specific authors, or to underline their conclusions – (I do not feel qualified to critically analyze the methods or conclusions of economic outlook analysts), but to

draw attention that the document suggested one area of potential bias, while failing to acknowledge other very common potential reasons for bias, creates an important bias in of itself. After these opening comments, I would respond to the key questions in this manner:

In Patients with CHD undergoing stenting of coronary vessels:

1) What is the evidence of efficacy and effectiveness of drug eluting (DES) versus bare metal stents (BMS**?): The evidence is overwhelmingly favorable in reducing the clinical endpoints of target lesion and/or target vessel revascularization, which is an important clinical endpoint that is meaningful to patients and is associated with decrease in hospitalizations, enhanced quality of life, and enhanced ability to work within their profession.**

    a. Including any effects on special populations, such as patients with and without diabetes, after myocardial infarction and not after myocardial infarction, and in different vessel and lesion characteristics. **As demonstrated in the document, the reduction in the primary endpoints of the studies presented there is improvement in the clinical outcomes of TLR/TVR in patients with and without diabetes, after myocardial infarction and not after myocardial infarction. Not discussed in the document there are reductions of these outcomes in small vessels, long lesions, bifurcation lesions, left main disease, chronic total occlusions and saphenous vein grafts, among different lesion characteristics.**

2) What is the evidence related to the safety profile of DES versus BMS? **The document clearly shows that there is no increase in death, myocardial infarction or stent thrombosis demonstrated by the trials. With regard to bleeding, since current guidelines recommend similar duration of dual antiplatelet therapy for all patients receiving stents, unless there is enhanced risk of bleeding, it is unlikely there will be an impact on bleeding. (The recommendations are based upon data suggesting that dual antiplatelet therapy is useful in treating non-stented areas of the coronary artery vasculature).**

3) What is the evidence of cost effectiveness and cost implications of DES versus BMS? **This is an area that remains murky, largely because there are so few who have a good grasp of the instruments used and the assumptions being made. As the document points out, the quality in this arena is less clear, and the potential for additional studies to re-draw conclusions is high. I would request that this document be evaluated by one or more individuals familiar with cost-effectiveness assessment before any attempt is made to make any**

implementations based upon the discussion in this document. It is of interest that the groups most likely to have a cost-effective benefit of drug-eluting stenting over bare metal stenting are the off-label (i.e., high-risk) indications.

SPECTRUM RESEARCH RESPONSE TO PUBLIC COMMENTS

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Response to industry comments

Abbott

Abbott comments regarding current evidence, SRI response: The studies provided do not directly compare DES with BMS and do not meet the inclusion criteria for this report.

Abbott comments regarding effectiveness, SRI response: Where studies compared DES and BMS directly and met other inclusion criteria, outcomes ranges were updated in the final report.

Abbott comments regarding cost-effectiveness, SRI response: Additional discussion has been added to the economics section.

Boston Scientific

Boston Comments regarding restenosis, SRI response:
Treatment of and prognostic factors for restenosis were not part of the included scope for this report, thus Stone, 2007 and Chen 2006 were excluded. Mauri 2008 is a non-randomized study. Data from this study are reflected in the ranges for outcomes reported in the effectiveness section in the final report.

Boston Comments regarding evidence continued to evolve, SRI response:
As with any study, there is a need to confine the time period for inclusion of new data or studies. The HTA process includes a schedule for re-review of reports so that new evidence can be considered, recognizing that evidence does continue to evolve.

Boston comments regarding cost-effectiveness, SRI response
Information from numerous economic studies which had been reviewed or included in prior HTAs, systematic reviews or meta-analyses is briefly summarized in this HTA, including the cited TAXUS IV report. New full economic studies published after these were included and critically appraised. The Groeneveld study cited was not a full economic analysis. Another Groeneveld review of economic studies is included. The Ryan report was not included because it is not a full economic analysis and does not compare DES and BMS head to head, but rather compares total costs in two time periods.

Cordis

Cordis comments on end points and power, SRI response

The final report notes that most trials may have been designed and powered to determine primary endpoints other than those in this HTA and may be underpowered to detect some outcomes. The pooling of data using meta-analytic methods enhances the statistical power to detect differences in such outcomes and, may or may not have sufficient power to detect rare outcomes, depending on the number of trials, number of patients and quality of outcome measurement in individual trials among other factors. It is agreed that more power facilitates the ability to detect a statistically significant difference. In addition, the power of a study should take into consideration what a clinically significant difference may be, which may vary by outcome. A statistically significant difference may or may not be clinically significant or translate into a significant public health impact. See response to Dr. Goldberg's comments.

Cordis comment-risk difference calculation, SRI response

The calculation of risk difference is taken from Table 3 of Stettler 2007 based on the reported NNT, where the RD = 1/NNT. The hazard ratio, confidence interval and p-values as well as NNT and RD are in the results section.

Cordis comment on Moreno analysis, SRI response

The Moreno 2007 meta-analysis of 25 trials was included in the results section. The outcomes are short term (6-12 months) and there were fewer patients than are represented in the Stettler 2007. There is significant overlap in the included trials for the Stettler and Moreno analyses. The risk differences in both analyses were similar: 1% (0.15-1.9%) for Stettler based on their NNT and 0.9% for Moreno.

Medtronic

Medtronic comment regarding outcomes

Target lesion revascularization results from meta-analyses, RCTS and non-randomized studies are reported in the efficacy and effectiveness sections. The final report notes that most trials were designed to evaluate this and other endpoints. See response to Dr. Goldberg's comments and to Cordis above.

Medtronic comment regarding cost effectiveness of DES versus BMS excluding CABG

The comment is correct that this review does not include studies that compared an alternative of CABG versus DES, since that was not a focus of this HTA.

Response to professional association comments

SCAI/ACC comments 1- 6 regarding executive summary and scope, SRI response

Some wording changes have been made. Meeting abstracts do not meet the inclusion criteria.

SCAI/ACC comment 7-16, SRI response

Additional references have been added and portions reworded.

SCAI/ACC comment 20 response: The paragraph relates to the FDA review of data in 2006. The Farb (2007) reference describes the 2006 FDA impressions from its review of registry studies available at the time. They report a range of < 1% to approximately 5% for rates of stent thrombosis in patients with complex lesions and those with renal dysfunction or diabetes and indicate that premature discontinuation of anti-platelet therapy is an independent risk factor. Rates from newer registry studies included in this HTA ranged from 0% to 2.9% for DES. Pooled rates of ARC–defined definite thrombosis from 0-4 years in the Stettler 2007 meta-analysis were 1.4% for SES and 1.7% for PES.

SCAI/ACC comments 21-23 response: Description of comparators is a common procedure in technology assessments as background material and the inclusion part of Spectrum's contract. Portions have been reworded. Detail regarding comparators and FDA product information has been moved to an appendix.

SCAI/ACC comment 25 response: Information in the report is consistent with the most recent policy (#0092, 12/15/08) available on the Cigna website.

SCAI/ACC comment 27 response
An updated table is included in the final report. Data are as provided by the State.

SCAI/ACC comment 28 response
Rates include any form of PCI and patients may have been represented multiple times, as described in the text below the table. The rates reflect number of procedures, not patients. It is not know whether the repeat represents intervention in the same or different vessel(s).

SCAI/ACC comment 29 response
Wording has been added regarding trial endpoints. See responses to Dr. Goldberg and Cordis comments above.

SCAI/ACC comment 30-36, response
The studies by Malenka and Hannan are not direct comparisons of DES with BMS and did not meet the inclusion criteria. The updated report from the SCAAR registry is a meeting abstract and therefore does not meet the inclusion criteria. The Ontario HTA met inclusion criteria. Information and data on outcomes and economic analyses from previous HTAs were provided as reported by authors of those HTAs. While many of the studies reviewed in the HTAs were from the RCTs, some were not, and in addition, the new full economic analyses, particularly those performed by the HTAs were full economic analyses of "real world" stent use based on registry data. Parameters used, including cost differentials of stents are reported in the accompanying Tables 61 and 62. Additional discussion has been added to the economics section.

SCAI/ACC comments regarding endpoints
Wording has been added regarding trial endpoints. See responses to Dr. Goldberg and Cordis comments above.

SCAI/ACC comment 37, response
The statement that cost and outcomes of stent thrombosis should be modeled is not intended to imply that it would drive additional cost in the DES group – CE results take into account both the cost and the QOL outcome associated with events modeled. One advantage of CE analysis is that different assumptions about rates of occurrence and cost and QOL outcomes can be modeled and compared. The text has been revised.

SCAI/ACC comment 38, response
The KCE review of economic studies reported that the range of stents per patient modeled in the studies was 1.1 to 1.9. In their own analysis (Table 62), the KCE study used an average of 1.3 stents per patient.

SCAI/ACC comment 40, response
The summary statement that DES may be cost effective in selected high risk groups refers to findings in the HTAs reviews of previous studies with their own analyses and most often was for subgroups of patients identified as having more than one of the stated high risk factors.

SCAI/ACC comment 41, response
These studies met the inclusion criteria and were not included in previous meta-analysis or HTAs.

Response to Washington State Health Technology Assessment Program
Spectrum research was provided with an updated table regarding costs and utilization in State agencies which is included in the final report.

PUBLIC COMMENTS

Abbot = 11 pages
Boston Scientific = 8 pages
Cordis = 5 pages
Medtronic = 2 pages
Professional Organization = 14 pages
Washington State Agency Comments = 1 page

Abbott Vascular
3200 Lakeside Drive
Santa Clara, CA 95054

tel: 408 845 3000
fax: 408 845 1231

March 27, 2009

Ms. Leah Hole-Curry, JD
Program Director
Health Technology Assessment Program
Health Care Authority
P.O. Box 42712
Olympia, WA 98504-2712

Dear Ms. Hole-Curry,

Abbott Vascular appreciates the opportunity to provide comments in response to the ***Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS) Draft Report*** posted on March 13, 2009. Abbott Vascular, a division of Abbott, is one of the world's leading vascular care businesses. The company is uniquely focused on transforming the treatment of vascular disease and improving patient care by combining the latest medical device innovations with world-class pharmaceuticals, investing in research and development and advancing medicine through training and education. As the market leader in bare metal stents (BMS) with the leading platform for drug eluting stents (DES), we share your commitment to optimizing health outcomes by making available advances in technology that improve the quality of life for residents in Washington State.

Summary of Comments and Recommendations

- **Efficacy of DES.** By excluding from the analysis head-to-head trials of new second generation stents such as the Abbott Vascular XIENCE V® drug eluting stent vs. first generation stents, the Draft Report underestimates the efficacy of DES vs. BMS. We recommend that the Final Report assess evidence on the efficacy of second generation DES stents in determining the efficacy of DES VS. BMS. We also recommend that the Final Report acknowledge that forthcoming evidence on the second generation of DES could change the conclusion of the assessment.

- **Effectiveness of DES.** The Draft Report does not consider the evidence from a number of recent real world DES registries that demonstrate that DES is more effective than BMS. We recommend that the Final Report consider this additional evidence and change the assessed level of evidence from low to moderate.

- **Cost-effectiveness.** The Draft Report draws heavily on cost-effectiveness studies performed in foreign countries. We urge that the Final Report address the difficulties associated with drawing conclusions for the cost-effectiveness of DES in WA State based largely on non-US studies.

Detailed comments

I. Efficacy of DES and second generation DES

As you may recall, Abbott Vascular submitted information in June 2008 and again in January 2009 regarding several on-going clinical trials involving the use of our recently FDA-approved drug eluting stent, XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V® EECSS or simply XIENCE V®) often referred to as a second-generation stent system. With specific trial activity looking at the efficacy in women, diabetics and other patient populations, we believe the results from these clinical trials will offer invaluable insight into the safety, utility and deliverability of the second generation of drug eluting stents.

The inclusion of XIENCE V® data in the HTA Final Report is important for your evaluation of coronary stenting because of its timeliness and clinical relevance. Failure to include evidence on newer, or second generation DES in the assessment results in an underestimate of the efficacy of DES vs. BMS. Since its introduction into the US marketplace in July 2008, Xience V has become the most widely used DES brand in the US (based on Q4 sales report, Data on file at Abbott Vascular) indicating a significant change in clinical practice and physician preference. The next few sections will elaborate on the evidence available that demonstrates that unique design features of the XIENCE V® stent lead to significantly better patient outcomes. We also include information on ongoing XIENCE V® clinical trials that will result in additional valuable evidence on the clinical benefits of DES vs. BMS.

Stent Design

In a landmark study conducted by Simon et al[i] endothelial coverage was shown to be highly dependent on the thickness of the stent implant; the thinner the strut the better the coverage. These results have been confirmed in clinical trials[ii,iii,iv] that demonstrated that thinner struts are associated with reduced arterial injury and restenosis. XIENCE V® was specifically designed to minimize strut thickness in comparison to the first generation drug eluting stents - CYPHER® and TAXUS Express[2].

In the placement of a stent in a lesion, the permanent addition of bulk to the arterial wall must be considered. Stainless steel stents such as CYPHER® and TAXUS® implant approximately 150µm to the arterial wall. In the event of overlap that figure would double to approximately 300 µm. In addition, the dose of drug eluted at the point of overlap would also double. With increased bulk and increased elution of drug, focal exposure may lead to lack of endothelialization. One can only speculate on the consequences of increased bulk and exposure. However, from a purely geometric argument, a flexible thin-strutted stent with a lower dose of an –olimus would provide the least bulk associated with the effective delivery of a drug.

INDICATIONS

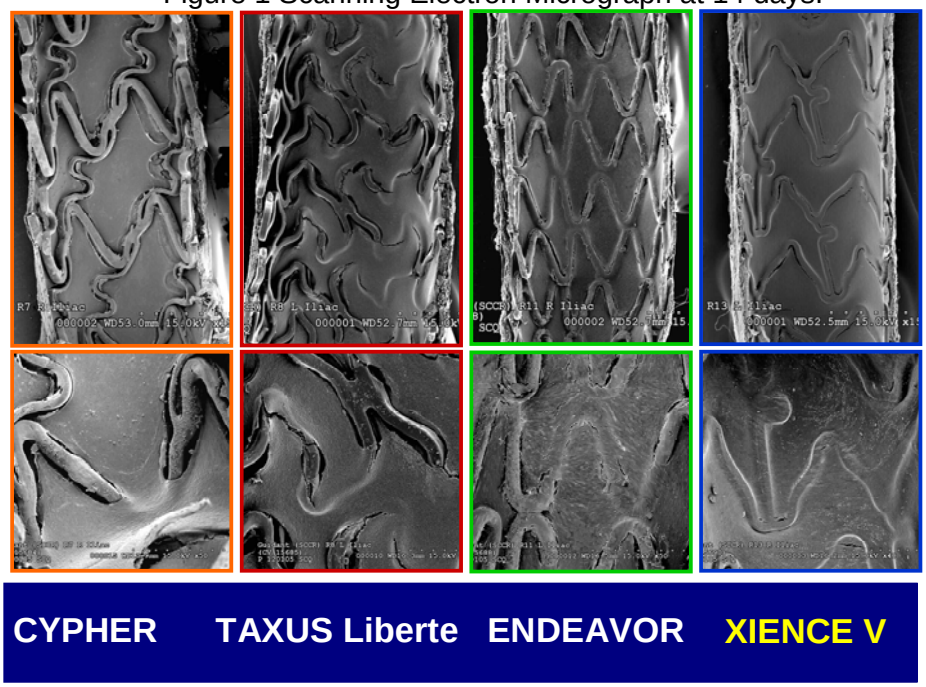
The XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V® stent) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

Pre-Clinical Studies

In publications of preclinical studies conducted by Finn et al[v] the authors emphasize that drug choice and release kinetics affect arterial healing. In preclinical models, XIENCE V® has greater endothelial coverage after implantation in comparison with TAXUS®. Finally, Joner et al[vi] suggest that trials powered for angiographic endpoints cannot predict the long-term safety of drug eluting stents and that delays in arterial healing may increase the risk of late stent thrombosis with CYPHER® and TAXUS®.

In a recent publication from Virmani's group[vii], endothelial cell recovery rates in drug eluting stents and bare metal stents were compared in a rabbit model. While pre-clinical studies have limitations, the selection of appropriate animal models may provide important and timely comparative information on endothelialization and healing associated with different drug eluting stents. The study was designed to assess the impact of stent implantation on endothelial recovery and compared a thin-strutted bare metal stent (strut thickness = 81mm) with a variety of drug eluting stents. The drug eluting stents were XIENCE V® (strut/polymer thickness = 89µm), ENDEAVOR (strut/polymer thickness = 96µm), TAXUS® Liberté™ (strut/polymer thickness = 113µm), and CYPHER® (strut/polymer thickness = 153µm). At 14 days, XIENCE V® had significantly more endothelial coverage on the struts than the other drug eluting stents evaluated. In addition, XIENCE V® had the fewest uncovered struts among the drug eluting stents. Figure 1 shows the scanning electron micrograph at 14 days.

Figure 1 Scanning Electron Micrograph at 14 days.



In addition to endothelial coverage, the function and integrity of the endothelial monolayer were assessed by Platelet/Endothelial Cell Adhesion Molecule 1 (PECAM-1) immunostaining. PECAM-1 immunostaining is localized in areas where cell to cell contact has been established. Cell to cell contact above the struts of XIENCE V® was significantly greater than the other drug eluting stents, suggesting a functional endothelial layer.

Another marker of delayed endothelial healing is Vascular Endothelial Growth Factor (VEGF). VEFG is actively expressed when the endothelium cell needs repair. In this study, VEGF expression was the lowest for XIENCE V® in comparison with the other drug eluting stents at 14 days, and similar to that observed with MULTI-LINK VISION®. Based on the results from these experiments the authors concluded that differences in endothelial recovery and arterial healing do exist and newer designs are favored over first generation drug eluting stents.

Clinical Evidence

Introduction to XIENCE V® and the SPIRIT Family of Trials

Drug eluting stents (DES) are the preferred treatment for the relief of obstructed coronary flow associated with the presence of atherosclerotic disease. The use of

DES has been found to greatly reduce both angiographic and clinical measures of restenosis relative to the use of bare-metal stents (BMS). The everolimus eluting XIENCE V® stent, a second generation DES, has been demonstrated to be both efficacious and safe in the treatment of a broad patient population with coronary artery disease (CAD).

The XIENCE V® EECSS is a balloon expandable stent, fabricated from a single piece of medical grade L-605 Cobalt Chromium alloy and is similar in strut design to the MULTI-LINK VISION® Stent (3.0 mm, 3.5 mm, 4.0 mm) and the MULTI-LINK MINI VISION® Stent (2.25 mm, 2.5 mm), Abbott Vascular's bare metal stents. The everolimus eluting stent has been designed to release its antiproliferative agent from a thin (7.8 *u*m), non-adhesive, durable, biocompatible fluoropolymer coated onto a low profile (0.0032" strut thickness), flexible cobalt chromium stent. Compared to the 316 L stainless steel used in TAXUS® and CYPHER®, the cobalt chromium in the XIENCE V® stent is more radiopaque, thinner, and elicits a less vigorous host response than stainless steel. Studies have shown that the use of a stent with thinner struts is associated with a significant reduction in angiographic and clinical restenosis after coronary artery stenting.

US approval of the XIENCE V® stent was based on the data from three randomized trials. All three of these clinical trials (SPIRIT FIRST, SPIRIT II and SPIRIT III) have met their primary and major secondary endpoints with no adverse safety signals to date. The SPIRIT FIRST trial was the first clinical evaluation of the XIENCE V® EECSS and demonstrated both the short-term and long-term clinical safety of XIENCE V® in the treatment of subjects with single, *de novo* target lesions.

In the SPIRIT II and SPIRIT III randomized clinical trials (RCT), XIENCE V® demonstrated not only non-inferiority, but superiority to the first-generation paclitaxel-eluting TAXUS® stent in terms of the primary endpoints in-stent and in-segment late loss, respectively. Both Taxus® Express^2™ (73% of lesions) and Taxus® Liberte® (27% of lesions) were used as controls in SPIRIT II. Taxus® Express^2™ was used as the control in SPIRIT III. Several attachments related to this data are included with this comment letter. Specifically, the SPIRIT III Pivotal Trial results published in *JAMA* 2008, the 2 Year SPIRIT III trial results published in *Circulation* in January 2009, and data from a meta-analysis of the SPIRIT II and III results presented at the Transcatheter Cardiovascular Therapeutics (TCT) Conference in 2008. As previously mentioned, the timeliness and clinically relevant results from these trials using XIENCE V® will be important data to consider in the HTA's Final Report expected in April 2009.

Overview of SPIRIT III Trial Design

The SPIRIT III randomized clinical trial (RCT) was designed as the pivotal trial to compare XIENCE V® EECSS to the widely used FDA-approved TAXUS® paclitaxel-eluting stent in patients with coronary artery disease (CAD) in the US. The objective of the prospective, randomized, single-blind, multi-center SPIRIT III clinical trial was to determine the safety and efficacy of the XIENCE V® for the treatment of subjects with a maximum to two *de novo* coronary artery lesions (each in a different epicardial vessel).

The US RCT study enrolled 1,002 patients (randomized 2:1 for XIENCE V® versus TAXUS®) at 65 centers and patients were grouped into three subgroups based on whether or not they would have angiographic and/or intravascular ultrasound (IVUS) follow-up at 240 days. Clinical follow-up was performed at 1, 6, 9, 12 months and 24 months. Further clinical evaluations will be performed yearly through 5 years.

Patients were considered eligible for enrollment if they were undergoing percutaneous coronary intervention (PCI) and were ≥18 years of age with stable or unstable angina or inducible ischemia. Eligibility was confirmed based on pre-procedure angiography. (Details regarding this trial including the inclusion criteria may be found in the 2008 *JAMA* publication included with this comment letter.)

The primary endpoint of the SPIRIT III RCT was in-segment late loss at 240 days. The major secondary endpoint was ischemia-driven target vessel failure (TVF) at 270 days, defined as a composite of cardiac death, myocardial infarction (QMI and NQMI), and ischemia-driven target vessel revascularization (TVR) by either PCI or CABG. The trial was powered for non-inferiority testing of both the primary and major secondary endpoints. Furthermore, the protocol included sequential non-inferiority and superiority testing of the primary endpoint as part of the statistical analysis if non-inferiority was met.

SPIRIT III Results

In the SPIRIT III RCT, the intent-to-treat (ITT) population included 1,002 subjects (669 subjects in the XIENCE V® arm and 333 subjects in the TAXUS® arm). Overall, the baseline demographics and angiographic characteristics were comparable between the subjects [1]. XIENCE V® demonstrated both non-inferiority and superiority to TAXUS®, in terms of the primary endpoint in-segment late loss at 8 months, for XIENCE V® and TAXUS®, respectively [0.14 mm (n=301 lesions) versus 0.28 mm (n=134 lesions), $P_{noninferiority} < 0.001$; $P_{superiority} = 0.004$]. A post hoc linear regression analysis was performed to ascertain whether this reduction was consistent across several key subgroups, including age, gender, diabetic status, vessel size, and dual vessel treatment. With the exception of age (where XIENCE V® treatment was

associated with a large reduction in late loss in elderly patients relative to TAXUS® treatment), there were no significant interactions between treatment assignment and in-segment late loss.

In terms of other key secondary angiographic endpoints, angiographic analysis at 240 days showed strong trends towards a reduction in both in-stent and in-segment binary restenosis, as well as a significant reduction in in-stent late loss for XIENCE V® relative to TAXUS®. Furthermore, the IVUS results strongly corroborated the angiographic endpoint results.

Additionally, SPIRIT III met its major secondary (co-primary) endpoint of TVF at 9 months. The safety and efficacy of the XIENCE V® EECSS was sustained through the one year follow-up. A 24% reduction in TVF rates was observed at one-year in the XIENCE V® arm compared to the TAXUS® arm.

Importantly, there were no significant differences between the two treatments in terms of cardiac death, myocardial infarction, or stent thrombosis at 1 year. The observed MACE rates, however, were significantly lower at one-year in the XIENCE V® arm relative to the TAXUS® arm [6.0% (39/653) versus 10.3% (33/320), P=0.02]. This reduction in MACE was consistent across all subgroups analyzed, with the exception of diabetic patients (this apparent difference is driven by an unusual finding in which MACE rates in patients treated with TAXUS® are higher in non-diabetics than in diabetics. A resolution of this unlikely finding must await analyses in a larger sample size).

Between 1 and 2 years of follow-up, the advantages of XIENCE V® in terms of long-term clinical safety and efficacy became more apparent [2]. The hazard curves for both MACE and TVF continued to diverge between 1 and 2 years such that at completion of the two-year follow-up, XIENCE V® compared with TAXUS® resulted in a significant reduction in both major adverse cardiac events (7.3% versus 12.8%; hazard ratio, 0.55; P = 0.004) and target vessel failure (10.7% versus 15.4%; hazard ratio, 0.68; P = 0.04) . Cardiac death rates remained similar between the two treatments at 2 years (0.3% versus 0.3%, P=1.0).

Summary of Current Evidence

The results of the SPIRIT III RCT at the two-year follow-up (see attached document from the January 26, 2009 edition of *Circulation*) demonstrate that the safety and efficacy of XIENCE V® that were observed at one year[8] were sustained through two years[viii] , as shown by the lower rates of TVF, MACE, and TLR in the XIENCE V® arm compared to the TAXUS® arm. Between 1 and 2 years, fewer MIs and very late stent thrombosis events were reported in XIENCE V® patients as compared to TAXUS®

patients. This encouraging trend was strongly observed in patients that discontinued Thienopyridine for the first time between 6 months and two years. In this particular subset of patients, TAXUS® usage was associated with a greater rate of subsequent stent thrombosis than XIENCE V® usage (2.6% versus 0.4%, P=0.10). Finally, results from the subgroup analysis were generally consistent with overall study results at 1 year.

We suggest that the evidence provided differentiates the XIENCE V® EECSS from first generation stents. In particular, the stent design and the thin strut technology of XIENCE V® - as well as the evidence from pre-clinical studies - demonstrates more complete endothelialization with XIENCE V® compared to first generation drug eluting stents. In summary, the clinical evidence demonstrates more favorable long-term outcomes with XIENCE V® in comparison with the first generation TAXUS® stent in the SPIRIT III pivotal trial.

Ongoing XIENCE V® Clinical Trials

In addition to the data from the SPIRIT III pivotal trial, there are other ongoing trials involving XIENCE V®. This data will be very useful in the assessment of DES outcomes.

For instance, SPIRIT IV, the largest (N=3600) XIENCE V® vs. TAXUS® randomized controlled clinical trial to date, will reach its primary endpoint in the second half of 2009 and we expect to present the results in Q4, 2009. In addition, follow-up on the clinical trials listed below will be presented in 2010:

- SPIRIT V, a 2,700 patient real world registry in Europe with a small randomized XIENCE V® vs. TAXUS® cohort in diabetics
- XIENCE V® SPIRIT Women, 2,000 patient real world International registry for women with a small randomized XIENCE V® vs. CYPHER® cohort
- XIENCE V® India, a 1,000 patient real world registry in India
- Resolute III, a 2,700 patient randomized XIENCE V® vs. RESOLUTE all comers clinical trial
- RENAL DES, 220 patient randomized comparison of XIENCE V® and Vision Coronary Stents in the same multi-vessel patient with chronic Kidney disease
- ISAR TEST-4: a 2600 patient randomized a biodegradable polymer Rapamycin-eluting stent vs. CYPHER® vs. XIENCE V®
- SEA-SIDE: a 150 patient randomized Sirolimus Versus Everolimus-Eluting Stent in Bifurcated Lesions
- BASE-ACS: 1,050 patient randomized comparison of Bio-Active-Stent to the Everolimus-Eluting Stent in Acute Coronary Syndrome

Abbott Vascular believes that this additional information will provide the robust evidence needed for the HTA to come to a definitive conclusion on the clinical benefits of DES vs. BMS. (More information from these trials may be obtained by sending an email to: medicalinformation@av.abbott.com).

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II. Effectiveness of DES

Efficacy, effectiveness, safety and cost-effectiveness were variables examined in the HTA Draft Report. While there were varying levels of evidence (as defined by Spectrum Research Inc.), it is rather disappointing that the effectiveness data was ranked as "low" given that more recent data is available to describe the "real world" experience of drug eluting stents. Listed below are several real world registries whose results have been published in peer reviewed journals that were not included in the Draft Report:

- S.T.E.N.T. registry: Catheterization and Cardiovascular Interventions 72:893–900 (2008)
- REWARDS registry: Am J Cardiol 2008;102:292–297
- EVENT registry: Catheter Cardiol Interv, Published Online: 9 Dec 2008
- ACC-NCDR CathPCI registry: AJC, February 2008;101: 286-292.
- ARRIVE I Catheter Cardiovasc Interv. 2008 Oct 1;72(4):433-45

These and other registries are representative of current practice patterns and provide important additional evidence on the effectiveness of drug eluting stents and would be worthwhile to include in the HTA. Overall we believe that the body of evidence on the effectiveness of DES vs. BMS, including the additional studies above, represents a moderate level of evidence. Accordingly we recommend that the assessed level of evidence be changed from low to moderate in the Final Report.

III. Cost-Effectiveness

Abbott Vascular agrees with the HTA that comparing results from one health technology assessment to another can be difficult since health status, medical practices, health systems (and therefore the cost of treatment) are different from one country to another. Additionally, not all reports or studies may be applicable to the US because of the tremendous variation from a healthcare system point of view (I.e., some countries have compulsory insurance, others have tiered payer systems and so on). Given the rapidly changing nature of stenting technology, it would be useful to have more up-to-date information on the cost-effectiveness of coronary stents., such as the cost-effectiveness analysis that will be performed for the SPIRIT IV clinical trial

When additional information is available, we suggest the following:

- Higher quality studies based on the QHES be considered
- since the evaluation of the quality of cost-effectiveness studies are somewhat subjective, more than one health economist should evaluate the studies
- Greater weight should be given to those studies conducted in the US

CONCLUSION

In conclusion, Abbott Vascular appreciates the opportunity to provide you and your colleagues with this information which we hope will be useful in the technology assessment of the safety, efficacy, effectiveness and health economic considerations of cardiac stents. We recommend that the Final Report:

- Assess evidence on the efficacy of second generation stents.
- Acknowledge that forthcoming evidence on the second generation of DES could change the conclusion of the assessment.
- Consider the evidence from a number of recent real world DES registries that demonstrate that DES is more effective than BMS and change the assessed level of evidence from low to moderate.
- Address the difficulties associated with drawing conclusions for the cost-effectiveness of DES in WA state based largely on non-US studies.
- Re-focus assessment on high quality cost-effectiveness studies particularly those conducted in the US

In addition to this letter, attached you will find the following:

- An article by Dr. Gregg W. Stone, Professor of Medicine at the Columbia University Medical Center and Chairman of the Cardiovascular Research Foundation (CRF) in New York. This article was published in JAMA (April 2008) with results from the SPIRIT III pivotal trial.
- An article by Dr. Gregg W. Stone, Professor of Medicine at the Columbia University Medical Center and Chairman of the Cardiovascular Research Foundation (CRF) in New York. This article was published in Circulation (January 2009) with 2 year results from the SPIRIT III pivotal trial.
- A PowerPoint presentation given by Dr. Stone last October at the Transcatheter Cardiovascular Therapeutics conference. This review highlights the two year results of a Pooled Meta-analysis from the SPIRIT II and III clinical trials.
- A brief overview of our SPIRIT family of trials using Xience V™.
- A copy of the IFU for XIENCE V®
- A copy of the MULTI-LINK VISION® IFU

Please do not hesitate to contact me if you have any comments or questions regarding this information.

Sincerely,

Roseann White

Roseann White
Director
Health Technology Assessment and Market Access
Abbott Vascular
3200 Lakeside Drive
Santa Clara, CA 95054
tel: 408-845-1498
fax: 408-845-1231

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Boston Scientific

March 27, 2009

Ms. Leah Hole-Curry
Director, Health Technology Assessment
Washington Health Care Authority
P.O. Box 42712
Olympia, WA 98504

RE: Cardiac Stents: Comparison of Drug-Eluting Stents (DES) with Bare Metal Stents (BMS) March 13, 2009 Draft Report by Spectrum Research, Inc.

Dear Ms. Hole-Curry:

Boston Scientific Corporation (Boston Scientific) appreciates the opportunity to submit comments in response to the Washington State Health Technology Assessment Program's (HTAP) Draft Report entitled, "Cardiac Stents: Comparison of Drug-Eluting Stents (DES) with Bare Metal Stents (BMS)" provided by Spectrum Research, Inc. This draft report looks at the evidence associated with efficacy and effectiveness, safety, special population considerations and cost effectiveness of DES versus BMS.

Boston Scientific's key points on this draft report are as follows:

- **Restenosis is not benign – it has implications for safety and efficacy.** The HTA draft report states that DES is consistently associated with lower risk of target lesion revascularization (TLR)**,** yet the draft report fails to acknowledge that restenosis has negative clinical and cost consequences. The positive impact of DES on the patient population, and thereby the overall tone of this report needs to incorporate this fact.
- **Evidence continues to evolve -** Recently published studies were not included in the analysis. Incorporating these studies would provide a more accurate assessment of the benefits and risks of DES.
- **Cost effectiveness data for DES exists –** The draft report's interpretation of the cost effectiveness studies seems to fly in the face of the significant amount of data demonstrating the cost effectiveness of DES over BMS. The primary driver of this cost-effectiveness is that patients who undergo DES face less restenosis and the costs of the clinical events that go with it. Your draft report should incorporate restenosis cost data when evaluating the cost-effectiveness of DES.

Given the above, we respectively request that Washington's HTAP consider these important issues as well as the recently-published data when developing your final report with an eye toward appropriately modifying its conclusions.

About BSC
As a worldwide developer, manufacturer and marketer of medical devices for over 25 years, Boston Scientific has advanced the practice of less-invasive medicine by providing a broad and deep portfolio of innovative products, technologies and services across a wide range of medical specialties. The company's products help physicians and other medical professionals improve their patients' quality of life by providing alternatives to surgery - alternatives that also significantly improve the productivity of health care delivery by reducing hospital stays, freeing surgical time and reducing patient wait times.

Background
Percutaneous coronary intervention (PCI) with or without stenting is a globally-recognized and exhaustively studied treatment option in the management of coronary artery disease. Worldwide, over 21 randomized controlled trials with more than 9,000 patients and more than 30 observational registries representing over 171,000 patients have resulted in hundreds of publications including meta-analysis of the available data. While no treatment is totally risk-free, the data, and treatments guidelines from organizations like the American Heart Association continue to support labeled and expanded use of DES and BMS utilization in the treatment of coronary artery disease (CAD).

Whether one considers bare metal stents which came on the scene in the late 1990s, or the advent of drug-eluting stents in 2003, it is clear that coronary stenting procedures have been found to be clinically appropriate to treat a wide variety of coronary artery stenosis. Their role as the standard of care is reflected by the fact that the American College of Cardiology (ACC), the American Heart Association (AHA) and the Society for Cardiovascular Angiography and Interventions (SCAI) have collectively established practice guidelines for the use of coronary stents.[1]

In summary, what follows are some key points from our responses to your Draft Report.

Restenosis is Not Benign
The HTA draft report acknowledges that DES are consistently associated with a lower risk of target lesion revascularization (TLR)**,** yet the draft report fails to acknowledge that restenosis has negative safety and clinical implications. Specifically, the draft report fails to take into consideration the following clinical outcomes associated with restenosis, as reported in four studies utilizing data from over 28,000 patients:

- DES treatment was associated with lower rates of mortality, myocardial infarction and target-vessels revascularization than BMS treatment in similar patients.[2]
- In patients with BMS in-stent restenosis, more than one third presented as myocardial infarction or unstable angina requiring hospitalization.[3]
- Marked reduction in restenosis with DES compared with BMS may counterbalance the potential excess risk from late stent thrombosis (ST) with DES.[4]
- There are risks associated with BMS in-stent restenosis (ISR), and the adverse outcomes associated with that risk have cost implications.

Studies Providing Data on the Safety and Efficacy Associated with Restenosis:

Offsetting Impact of Thrombosis and Restenosis on the Occurrence of Death and Myocardial Infarction After Paclitaxel-Eluting and Bare Metal Stent Implantation[5]

In one pooled patient level analysis of 3,445 patients, a comparison of DES with BMS examined the hypothesis that the prevention of restenosis-related adverse events by DES might offset some or all of

the risks associated with increased late stent thrombosis (ST). This study finds that patients who have a need for revascularization have a high incident rate of death and MI which outweighs the increased risk of ST with DES.

Long-Term Clinical Outcomes After Drug-eluting and Bare-Metal Stenting in Massachusetts[6]

In a matched population-based study of 11,556 patients with DES and 6,237 BMS patients, DES treatment was associated with lower rates of mortality, myocardial infarction and target-vessels revascularization than BMS treatment in similar patients. This contrasts with the draft report's assessment that there is no difference in BMS and DES outcomes along these measures. DES patients had an unadjusted mortality rate of 7.0% while BMS treated patients had a rate of 12.6% while the risk adjusted mortality rates were 9.8% and 12.0% respectively (P=0.0002). Myocardial infraction rates were 8.3% for DES and 10.3% for BMS The authors do suggest comprehensive follow-up beyond the two years reviewed to identify whether similar safety and efficacy remains in the state mandatory database population (P=0.0005).

Bare Metal Stent Restenosis Is Not a Benign Clinical Entity[7]

In 984 patients with BMS in-stent restenosis, more than one-third presented as myocardial infarction or unstable angina requiring hospitalization. The Cleveland Clinic Foundation reviewed their PCI database for BMS in-stent restenosis (ISR) between May 1999 and September 2003. ISR patients were classified into three categories 1) myocardial infraction, 2) unstable angina requiring hospitalization before angiography and 3) exertional angina. The authors concluded aggressive efforts, such as DES, to decrease the incidence of unstable angina due to BMS ISR are warranted.

Evidence Continues to Evolve

There has been and will continue to be a steady cadence of data related to coronary artery stenting. The WTA needs to consider data which has come out since this study was completed. The following table presents a sampling of recent articles published in 2009.

Title/Authors/Citation Conclusion/	**Journal**	**Publication Date**
Frequency of Coronary Artery Bypass Surgery Following Paclitaxel-Eluting and Bare-Metal Stent Implantation Martin J, Martin JL, Ellis SG, Colombo An, Grube E, Maloney T, Friedman MI, Baim DS, Dawkins K, Caputo R, Stone GW *Am J Cardiol*. 2009;103(1):11-16. **Conclusion:** Referral to CABG is significantly less common after stenting single coronary lesions with Taxus compared with bare-metal stents. The relative reductions in TLR CABG of 54% in patients without diabetes, 87% in patients with diabetes, 70% in left anterior descending artery lesions, and 54% in non–left anterior descending artery lesions with Taxus compared with bare-metal stents should be considered during stent selection..	*Am J Cardiol*	Published January 2009
An Integrated TAXUS IV, V, and VI Intravascular Ultrasound Analysis of the Predictors of Edge Restenosis After Bare Metal or Paclitaxel-Eluting Stents Liu J, Maehara A, Mintz GS, Weissman NJ, Yu A, Wang H, Mandinov L, Popma JJ, Ellis SG, Grube E, Dawkins KD, Stone GW *American Journal of Cardiology*. 2009;103(4):501-506 **Conclusion:** Integrated analysis of the TAXUS trials shows that the paclitaxel-eluting TAXUS Express stent effectively inhibits in-stent neointimal proliferation, even in high-risk and overlapping stent patients.	*Am J Cardiol*	Published Feb 2009

Title/Authors/Citation Conclusion/	Journal	Publication Date
TAXUS VI Final 5-Year Results: A multicenter, randomized trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. Grube E, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Joshi A, Mascioli S **Conclusion:** Treatment of complex coronary lesions with the TAXUS MR stent demonstrated similar MACE, similar TVR and reduced TLR rates compared with control through five years. Based on these positive results, the aetiology of increased non-TLR TVR rate in TAXUS remains unclear.	*Euro Intervention*	Published Online Jan 2009 [Epub]
One-Year Outcomes from the TAXUS Express Stent vs Cypher Stent - What's Your Real-World Experience? (**TC-WYRE**) Retrospective Registry Mayor M, Malik AZ, Minor RJ Jr, Deshpande MC, Strauss WE, Maloney TH, Baim DS, O'Neill W, Kandzari DE **Conclusion:** In this observational, retrospective analysis of DES-treated patients, PESs and SESs demonstrated similar overall safety and efficacy, but PESs were associated with a significant decrease in 1-year TVR rates in diabetic patients.	*Am J Cardiol*	Published Online Feb 2009 [Epub]
PCI vs. Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. (**SYNTAX**) Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass E, Van Dyck N, Leadley K, Dawkins KD, Mohr FW **Conclusion:** The results of our trial show that CABG, as compared with PCI, is associated with a lower rate of major adverse cardiac or cerebrovascular events at 1 year among patients with three-vessel or left main coronary artery disease (or both) and should therefore remain the standard of care for such patients.	*NEJM*	Published Online Feb 2009 [Epub]
3-Year Comparison of Drug-Eluting Versus Bare-Metal Stents Applegate, Robert J et al; **Conclusion:** The routine use of DES for "off-label" indications was associated with lower clinical end points (nonfatal MI and all-cause mortality) at 3 years than treatment with BMS in a comparable group of patients, with similar cumulative rates of stent thrombosis.	*JACC*	March 2009

As we have responded to earlier drafts of coronary stenting, we encourage you to keep in mind there are publications on mortality & MI risk reduction with DES. Additionally, further evidence will soon be published that show DES is associated with statistically significant reductions in mortality, MI and target vessel revascularization.[8]

Cost Effectiveness Data Exists

The draft report's interpretation of the cost effectiveness studies seems to fly in the face of the significant amount of data demonstrating the cost effectiveness of DES over BMS. The primary driver of this cost-effectiveness is that patients who undergo DES face less restenosis and the costs of the clinical events that go with it. The draft report should incorporate the following data:

TAXUS IV[9]

- DES are more cost-effective than BMS as they reduce the need for repeat vascularization.
- Cost-effectiveness data from TAXUS IV compares reasonably with that for other treatments that reduce coronary restenosis, including alternative drug-eluting stent platforms.

The Boston Scientific TAXUS IV trial cost-effectiveness analyses for its paclitaxel-eluting stent (PES) sought to compare aggregate medical care costs for patients undergoing percutaneous coronary intervention with PES and bare-metal stents (BMS). The review formally evaluated the incremental cost effectiveness of PES for patients undergoing single-vessel percutaneous coronary intervention and performed a prospective economic evaluation among 1,314 patients undergoing percutaneous coronary revascularization randomized to either PES (N = 662) or BMS (N = 652). Clinical outcomes, resource use, and costs (from a societal perspective) were assessed prospectively for all patients over a 1-year follow-up period. Cost-effectiveness was defined as the incremental cost per target vessel revascularization (TVR) event avoided and was analyzed separately among cohorts assigned to mandatory angiographic follow-up (n = 732) or clinical follow-up alone (n = 582).

Results showed the PES reduced TVR by 12.2 events per 100 patients treated, resulting in a 1-year cost difference of $572 per patient with incremental cost-effectiveness ratios of $4,678 per TVR avoided and $47,798/quality-adjusted life year (QALY) gained. Among patients assigned to clinical follow-up alone, the net one-year cost difference was $97 per patient with cost-effectiveness ratios of $760 per TVR event avoided and $5,105/QALY gained. In the TAXUS-IV trial, treatment with PES led to substantial reductions in the need for repeat revascularization while increasing one-year costs only modestly. The cost-effectiveness ratio for PES in the study population compares reasonably with that for other treatments that reduce coronary restenosis, including alternative SES drug-eluting stent platforms.

Medicare Standard Analytic File Analysis[10]

- Revascularizations increase costs
- This study is the first to demonstrate that in a true population-based analysis, the introduction of DES between 2001 and 2004 was temporally associated with both improved outcomes and lower per patient costs for older Americans undergoing coronary revascularization procedures.

This analysis acknowledges that DES have been shown to be cost-effective compared with bare-metal stents for select clinical trial patients. This study sought to determine whether these findings apply to the general population. Data from Medicare's 5% Standard Analytic Files were used to compare the practice and outcomes of coronary revascularization (by either percutaneous coronary intervention or coronary artery bypass grafting) in the United States between 2001 (pre– drug-eluting stent era, n=14,362) and 2004 (post– drug-eluting stent era, n=16,374).

Between 2001 and 2004, the rate of revascularization increased from 837 to 931 per 100,000, whereas the proportion of patients who underwent percutaneous coronary intervention as an initial revascularization procedure increased from 67.5% to 75.2% (P = 0.001). Over a median follow-up period of 25.5 months, no significant changes in mortality were found between 2001 and 2004 (13.8% versus 13.3%, P= 0.193).

However, significant decreases were seen, in the incidence of repeat revascularization (17.1% versus 16.0%, P_0.012) and myocardial infarction (10.6% versus 8.5%, P_0.001). Over this same time

period, total cardiovascular care costs per revascularized patient decreased by $1,680 (95% confidence interval $1164 to $2196, *P*_0.001) whereas total noncardiovascular costs increased by $2481 per patient (95% confidence interval $1844 to $3118, *P*_0.001). When the impact of overall procedural volumes was considered, aggregate cost to the Medicare program for cardiovascular services increased by $544 million over the 2-year follow-up period. Having said that,, after controlling for differences in demographic and clinical factors, significant reductions were found in both all-cause mortality (adjusted OR 0.90, 95% CI 0.83 to0.97, *P* 0.004) and MI (adjusted OR 0.75, 95% CI 0.69 to 0.81, *P*_0.001) between the 2001 and 2004 cohorts. Risk adjustment tended to accentuate the difference in cardiovascular costs that were noted in the crude analyses (adjusted cost reduction of $1998). The present study is thus the first to demonstrate that in a true population-based analysis, the introduction of DES between 2001 and 2004 was temporally associated with both improved outcomes and lower per patient costs for older Americans undergoing coronary revascularization procedures.

In conclusion, among the Medicare population undergoing coronary revascularization, the introduction of DES was associated with increased use of initial percutaneous coronary intervention and reduced bypass surgery along with improved clinical outcomes over two years of follow-up. Although total cardiovascular-related costs per revascularized patient decreased over this time period, total cost to the Medicare system still increased owing to greater overall use of revascularization procedures.

Groeneveld, P. W, et al Retrospective Medicare Claims Review Summary[11]***:***

- Despite higher initial drug-eluting stent costs (over bare metal), the lower follow-up costs during the first year resulted in relatively small cumulative drug-eluting and bare metal stent cost differences.

One recently published study looked at Medicare procedure data and analyzed at random a nationwide sample of over 4,000 beneficiaries who had received either drug-eluting stents or bare metal stents (one or multiple stents). Estimated costs for each patient were based on both physician and institutional claims beginning with the PCI hospitalization through the subsequent year. The results showed that while drug-eluting stent patients had higher 30-day costs compared to both historical controls (mean difference $2,131, 95% confidence interval (CI) $1,726 to $2,516) and contemporary controls ($1,882, 95% CI $1,480 to $2,322), at 1 year, the drug-eluting/bare metal stent mean cost differences had diminished substantially ($647, 95% CI $-385 to $1,664 compared to historical controls; $-84, 95% CI $-1,202 to $1,018 compared to contemporary controls) and were no longer statistically significant. The conclusion being, despite higher initial drug-eluting stent costs, the lower follow-up costs during the first year resulted in relatively small cumulative drug-eluting and bare metal stent cost differences.

Conclusion:

Coronary BMS and DES procedures rank among the most studied therapies available on the market today. This data has led to practice guidelines that reflect the fact that these procedures are the standard of care. Clearly, coronary stenting procedures have been found to be clinically appropriate for the treatment of a wide variety of coronary artery stenosis and DES is the treatment with decreased in-stent restenosis. We encourage HTAP to acknowledge the role of in-stent restenosis and the clinical and economic impacts associated with it. Incorporating in-stent restenosis as a primary clinical efficacy outcome instead of a secondary intermediate outcome in the final report will appropriately reflect the benefits of DES versus BMS.

- **Restenosis is not benign – it has implications for safety and efficacy.** The HTA draft report states that DES is consistently associated with lower risk of target lesion revascularization (TLR)**,** yet the draft report fails to acknowledge that restenosis has negative clinical and cost consequences. The positive impact of DES on the patient population, and thereby the overall tone of this report needs to incorporate this fact.

- **Evidence continues to evolve -** Recently published studies were not included in the analysis. Incorporating these studies would provide a more accurate assessment of the benefits and risks of DES.

- **Cost effectiveness data for DES exists –** The draft report's interpretation of the cost effectiveness studies seems to fly in the face of the significant amount of data demonstrating the cost effectiveness of DES over BMS. The primary driver of this cost-effectiveness is that patients who undergo DES face less restenosis and the costs of the clinical events that go with it. Your draft report should incorporate restenosis cost data when evaluating the cost-effectiveness of DES.

Boston Scientific appreciates the opportunity to comment on your draft report. We also appreciate your willingness to schedule a public hearing May 8, 2009.to gain further input from stakeholders.

Please call me at 763-494-2016 or email Tom.Meskan@bsci.com if your have any questions or would like additional information.

Sincerely,

Thomas L. Meskan
Director
Health Economics and Reimbursement, Cardiovascular

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Cordis Corporation
430 Route 22 East, Bridgewater, NJ08807
t (908) 541-4250 f (908) 541-4909

Mailing Address:
P.O. Box 6908, Bridgewater, NJ 08807-0908

March 27, 2009

Washington State Health Care Authority
Attention: Ms. Leah Hole-Curry, JD
Director Health Technology Assessment
P.O. Box 42682
Olympia, WA 98504-2682
Comments submitted via e-mail to: shtap@hca.wa.gov

RE: Cardiac Stent Health Technology Assessment – Comments to Draft Report Published on March 13, 2009

Dear Leah:

Cordis would like to thank the Washington State Health Care Authority for the opportunity to review and provide comment on the draft of the Health Technologies Assessment (HTA) of Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS).

While we feel that the overall review and critical appraisal is informative, we have identified some areas of concern.

In summary, our key concerns arise from the reported classification of mortality and myocardial infarction (MI) as primary outcomes, as well as the conclusions that are based on this. Clinical trials of DES and BMS were designed and powered to detect differences in restenosis. Although it makes clinical sense that MI and mortality would be reduced with DES, much larger sample sizes are required to observe this difference, and thus these events were not classified as primary outcomes in clinical trials. Regarding the HTA conclusions, it is recommended that this sample size limitation be considered. In addition, it is recommended that a few of the conclusions be reconsidered or reworded.

In the following pages, we provide our input regarding these concerns.

We hope that consideration of our comments will assist in the finalization of this evidence-based report.

1. Comments on Outcome Classification

The HTA report used “Death overall, cardiac death, and myocardial infarction (MI)” as the primary clinical outcomes of efficacy.” “Target Lesion Revascularization (TLR)” was considered a **secondary** outcome. The following rationale was used for the classification:

(*Page 21) “Since the primary focus of revascularization should be the improvement in clinical health outcomes (e.g., mortality and freedom from MI), and since such outcomes have been a primary focus in technology assessments, they are the primary outcomes reported in this assessment.”*

Cordis Response:

- The statement pertaining to "such outcomes have been a primary focus in technology assessments" could be seen as misleading. For example, the Hill et al., 2007 United Kingdom HTA did not explicitly classify mortality and MI as primary outcomes, although they referred to them as key outcomes. The Hill et al., report also noted that the primary end-point for most reviews has been either the composite endpoint of major adverse cardiac events (MACE), or the endpoint of repeat revascularization rates (page 7 of Hill 2007 report).

- The ability to use the primary outcome is not discussed in terms of the sample size and power required to detect a difference in death or MI.

The following rationale outlines the reasons as to why mortality and MI may not be appropriate primary outcomes, as well as the logic as to why differences may not be observed for these outcomes between BMS and DES in RCTs and meta-analyses.

- MI, cardiac death, and all-cause mortality were not used as primary endpoints in the DES clinical trials as DES were developed to reduce the risk of restenosis with BMS. As such, restenosis was often used as the primary endpoint, and trials were powered to detect differences in this endpoint.

- It makes clinical sense that use of DES would reduce MI since a portion of restenosis and/or thrombosis events would be expected to result in MIs. A larger sample size would be required to observe significant reductions in MIs, however, as they are less common then restenosis. While clinical trials to date have not generally been powered to detect differences in MIs, the largest meta-analysis completed of DES versus BMS does detect statistically significant improvements in MI for Sirolimus- eluting stents (SES) compared to BMS (i.e., Stettler et al., 2007). Over 15,000 patients were included in this meta-analysis, with approximately 5000 to 6000 per treatment arm.

- Similarly, an impact of DES on mortality makes clinical sense, as a portion of MIs would be fatal and would contribute to cardiac death and all-cause mortality. Again, a larger sample size would be required to see differences in cardiac or all-cause mortality, compared to the sample size for MI or restenosis as MI-related deaths are very rare. The reason that the largest meta-analysis of DES versus BMS does not show differences in cardiac death or all-cause mortality may be due to an inadequate sample size (i.e., Stettler et al., 2007).

The following figure graphically displays the relationship between initial sample size and different events in the Stettler et al., meta-analysis of DES and BMS. Specifically, the figure is added to illustrate the point that, if we are only starting to see significant differences in MI with the largest meta-analysis conducted to date then it is reasonable that we may not have sufficient sample size to detect differences in cardiac related mortality given that it is less common than MI.

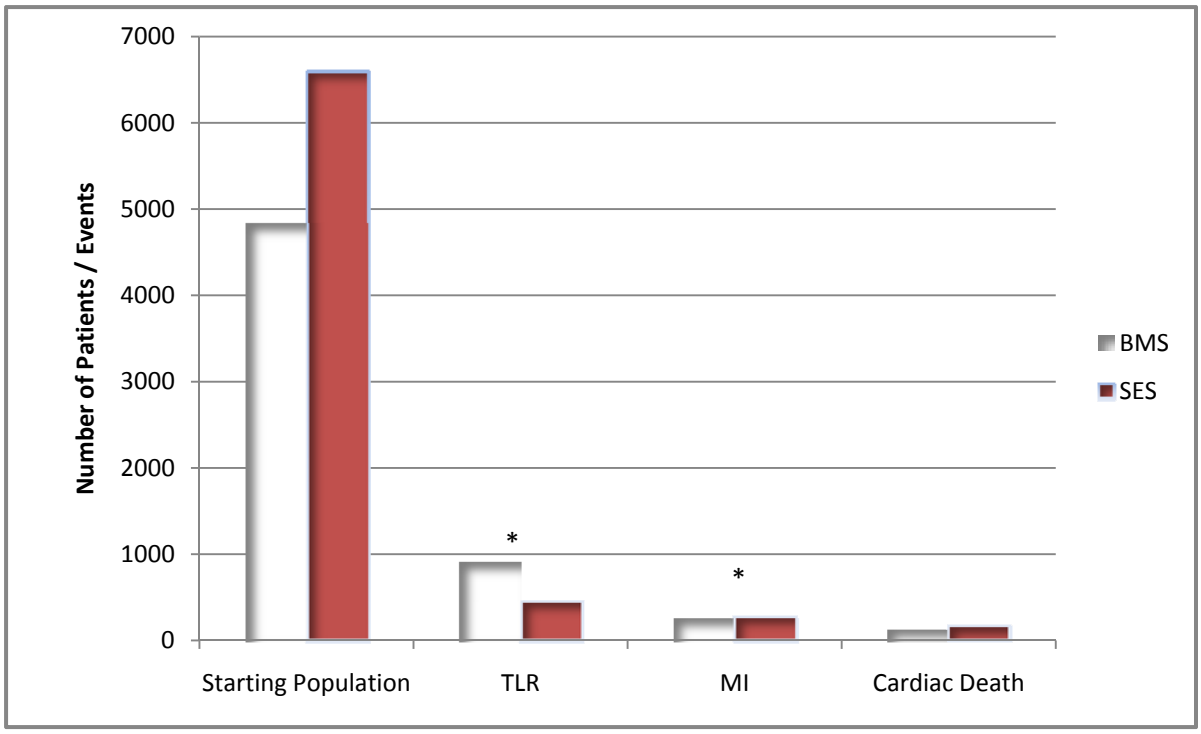


Figure 1: Number of patients and/or events over a 4 year period, reported in Stettler et al., 2007 meta-analysis of DES versus BMS. The (*) notes that SES shows significantly lower TLR and MI as compared with BMS. (This graph was re-created based on actual numbers provided in the Stettler meta-analysis, where the starting population represents the average number of patients for the treatment group).

2. Comments on HTA conclusions

2.1 Efficacy Conclusions

Within the "Efficacy" subheading of the Summary and Implications section of the HTA report, the following conclusion is made:

(Page 14) "Network meta-analysis of 38 RCTs indicates that DES are no better at preventing death or cardiac death than BMS. SES were associated with less risk of myocardial infarction compared with BMS in this network meta-analysis. The absolute differences in risk were however small, 1% (0.15% - 1.9%)."

Cordis Response:

- Clinical data suggests that the wording of the statement "DES are **no better** than BMS" requires additional clarification. The studies on which this meta-analysis was based did not seek to detect a difference in this outcome, and were thus not powered to detect a difference. Although the meta-analysis involves an increased sample size, it may have not been powered for this outcome (see argument above). The wording used by the authors in the original published Stettler et al., meta-analysis (i.e., "mortality was similar") would be more appropriate here.

- The statistical significance associated with the reduction in myocardial infarction was not included in the above HTA conclusion. In the original publication of the network meta-analysis, the authors conclude that "SES were associated with the lowest risk of myocardial infarction (p = 0.03 versus

BMS)." The HTA conclusions imply a trend, rather than the actual statistical significance observed.

- Calculations were included (i.e., difference in risk of 1% (0.15% - 1.9%) that were not cited in the original meta-analysis. Instead, the hazard ratio and confidence interval reported in the Stettler meta-analysis (i.e., HR 0.81, 95% CI 0.66-0.97, p=0.03), should be reported in the HTA conclusions.

Within the "Efficacy" subheading of the Summary and Implications section of the HTA report, the following conclusion is made:

(Page 14) "Technology assessments and conventional meta-analyses of between 14 and 24 head to head RCTs comparing DES with BMS indicate that DES are no better at preventing death, cardiac death or myocardial infarction than BMS."

Cordis Response:

- It is not understood why the Moreno et al., 2007 meta-analysis of 25 trials is not considered in these conclusions. Similar to the Stettler et al., 2007 meta-analysis, the Moreno study showed a significant reduction in MI in patients receiving DES (3.3%) compared with those receiving BMS (4.2%), p=0.03, when both Q-wave and non-Q-wave MI were pooled. As the overall HTA conclusions currently appear, only the Stettler meta-analysis found a difference in MI, when in fact, other meta-analyses have also.

2.2. Efficacy, Effectiveness and Safety Conclusions

The following efficacy, effectiveness, and safety conclusions are highlighted from the HTA report.

(Page 14, Efficacy) *"DES were consistently associated with lower risk of TLR…..rates of TLR may have been strongly influenced by protocol-driven angiographic follow-up and not based on clinical presentation and symptoms and may therefore be an over-estimate of rates in the general population."*

(Page 14, Efficacy) "*SES were associated with less risk of MI compared to BMS….the absolute differences in risk were however small."*

(Page 14, Effectiveness) "*Rates of revascularization are lower for DES patients…but there is substantial heterogeneity between the studies included."*

(Page 17, Diabetic Patients, Safety) "*No statistically significant differences in stent thrombosis were seen between treatments either early or late….however wide confidence intervals indicate lack of estimate stability and small numbers of events".*

Cordis Response:

- The four conclusions noted above are associated with improved efficacy, effectiveness and safety of DES as compared to BMS. As is noted, a limitation is highlighted for each of these conclusions. When considering all of the HTA conclusions, there appears to be an imbalance in the reporting of limitations. For example, there were some conclusions that involved no difference between DES and BMS, where limitations were not included, and it would have been appropriate to include them:

(Page 14, Efficacy) "*DES are no better at preventing death or cardiac death than BMS*".

- Regarding this conclusion, a discussion around limited sample size and lack of power to detect differences would be appropriate to include here.

(Page 14, Effectiveness) "*The evidence from past HTA reviews of registry data suggest that mortality and MI rates do not differ between DES and BMS*".

- As well, no limitations were identified with this conclusion. Given that there was inconsistency in the MI and mortality results across these studies, and a pooled analysis of registry studies showed heterogeneity between these studies, these limitations should be noted as well for this conclusion.

3. Additional Cordis Comments

- The HTA often cited the Stettler 2007 meta-analysis, and emphasized the high methodological quality and comprehensiveness of this meta-analysis. However, the key conclusions from the Stettler meta-analysis, (i.e., "Sirolimus-eluting stents seem to be **clinically better** than bare-metal and Paclitaxel-eluting stents") were not reported in the HTA conclusions.

- An error is noted in the WA HTA conclusions on page 22 of 186. They note that "no meta-analysis found a significant difference in death or MI with SES or PES compared with BMS at any time". This is incorrect given that the Stettler et al., 2007 meta-analysis reported a significant difference in MI for SES over BMS.

We respectfully request that your health technology assessment of cardiac stents critically review the conclusion that "DES are no better at preventing death or cardiac death than BMS." We believe that utilizing death overall, cardiac death and myocardial infarction as primary clinical outcomes of efficacy would only be appropriate if a clinical study were powered to report on these events. We also request that you include the Moreno et al. 2007 meta-analysis of 25 trials that appears to have been omitted from your research. We look forward to your response and in viewing the Final Report.

Sincerely,

Ryan H. Saadi, M.D., M.P.H.
Vice President, Health Economics, Reimbursement and
Strategic Pricing
Cordis Corporation

CC: Leah Hole-Curry, JD via e-mail: Leah.Hole-Curry@hca.wa.gov

Attachment: Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet Vol. 370 September 15, 2007. Stettler et. al.,

Medtronic Vascular
3576 Unocal Place
Santa Rosa, CA 95403 USA

March 27, 2009

Ms. Leah Hole-Curry, JD
Program Director
Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712
Sent electronically by email to shtap@hca.wa.gov

Dear Ms. Hole-Curry:

Thank you for the opportunity to comment on the HTA draft report, "Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS)," prepared by Spectrum Research Inc. for the Washington State Health Care Authority HTA Program. Medtronic is the world's leading medical technology company, specializing in implantable therapies that alleviate pain, restore health, and extend life. Medtronic is committed to the principles of evidence-based medicine and the appropriate use of scientifically-based health technology assessments to improve the overall health status of patients.

While the report clearly involved a great deal of work, it provides limited basis for a concrete recommendation on coverage. Instead, the report supports the status quo, where clinical decisions about whether or not a given patient should receive a DES versus a BMS (or, for that matter, versus CABG surgery or medical management) are left to the discretion of the physician and his or her patient after careful consideration of the clinical circumstances involved in each case.

The report addresses both efficacy and effectiveness but places an inappropriate focus on death overall, cardiac death, and myocardial infarction. Drug-eluting stents were designed to reduce restenosis, which will result in a reduced need for secondary interventions, either surgical or percutaneous revascularization. While the avoidance of these secondary procedures will also result in the avoidance of the risk associated with them, the intention is not the reduction of death or MI. In fact the FDA-approved labeling of these devices states that they are indicated for improving coronary luminal diameter and nowhere in the labeling does it state that they are designed to treat MI or stop death. In comparing efficacy and effectiveness of DES versus BMS, the only truly appropriate measure that should be evaluated is target lesion revascularlization or some surrogate that is clinically proven to be directly correlated to that true health outcome

With respect to the report's discussion of safety comparisons between DES and BMS, it is appropriately pointed out that there are no significant differences seen in existing studies. The report also points out that previous HTA reports have indicated that there may be a need for additional studies on this issue. These studies are ongoing and should be allowed to continue in order for the body of evidence to grow and thus enable greater analysis.

With respect to the cost-effectiveness of DES versus BMS, it should be noted that there is no absolute standard for evaluating cost-effectiveness in health care. While many models exist, each contains multiple assumptions and potential flaws. For instance, a model that evaluates cost per quality adjusted life year (QALY) gained with DES versus BMS will overlook the fact that many patients who are currently treated with DES would not have received a BMS in a pre-DES world, but instead would have received coronary artery bypass graft surgery. On the cost effectiveness issue the report rightly points out that:

• Nearly all the studies have taken the perspective of the health care payer. Few have addressed a societal perspective.

• Quality of life measures have received limited attention in the cost effectiveness studies, most using values from other studies, and the impact of more precise measurement is unknown.

While we agree that cost-effectiveness will vary depending on the individual patient characteristics, we do not believe there are adequate data contained within this report to determine specifically which patients and under what circumstances a DES will or will not be cost-effective. Additionally, until such time as there is broad agreement among the health care community regarding exactly how cost-effectiveness measures should be employed, we would argue that a coverage decision based solely on cost-effectiveness would be inappropriate and potentially harmful to patients, especially if it were discordant with broader coverage policies in place throughout the country and by CMS in particular and/or went against a physician's best medical judgment for an individual patient.

Finally, we wish to emphasize again that Medtronic believes the decisions about treatment modalities, and specifically the decision about the best approach for treating coronary artery disease, is one that should be made by the treating physician and his or her patient together, after careful consideration of the individual circumstances involved in the individual case. While Medtronic is committed to the principles of evidence-based medicine and health technology assessment, we believe that these tools are best employed to inform physician and patient decision-making rather than replace it.

Sincerely,

Mitchell Sugarman
Sr. Director
Health Economics, Policy and Payment
Medtronic Vascular
3576 Unocal Place
Santa Rosa, CA 95404
707-591-2180

Cc: Rob Clark
Sr. Director
State Government Affairs
Medtronic, Inc.
Phone: 763-505-2635
Mobile: 612-804-9474
rob.clark@medtronic.com

March 27, 2009

Submitted Electronically to: shtap@hca.wa.gov

Mr. Steve Hill
Administrator
Washington State Health Care Authority
P.O. Box 42682
Olympia, WA 98504-2682

Dear Mr. Hill:

The Society for Cardiovascular Angiography and Interventions, American College of Cardiology and the Washington State Chapter of the American College of Cardiology appreciate the opportunity to comment on the draft Health Technology Assessment on Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS). We applaud the effort to review and summarize the literature on one of the most heavily studied issues in modern medicine.

The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association representing over 4,000 invasive and interventional cardiologists. SCAI promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care.

The American College of Cardiology is a 36,000 member non-profit professional medical society and teaching institution whose mission is to advocate for quality cardiovascular care through education, research promotion, development and application of standards and guidelines, and to influence health care policy. The College represents more than 90 percent of the cardiologists practicing in the United States.

The Washington State Chapter of the ACC's Mission is to improve cardiovascular health for residents of Washington State through education, care, and advocacy.

We understand the important nature of comparing of the devices and within this letter will share our collective professional opinion on this matter.

This letter will discuss the following points:

I. The historical role of coronary stenting
II. The use of "FDA Approved Indications"
III. The primary benefit of DES and BMS
IV. The impact of DES on mortality and myocardial infarction
V. Comments on the draft HTA report

I. The historical role of coronary stenting:

In order to completely understand the widespread acceptance of coronary stenting and in particular the use of DES, one must appreciate some of the historical aspects of percutaneous intervention, previously called PTCA or balloon angioplasty. Coronary stents were originally developed to address several short-comings of balloon angioplasty most notably acute vessel closure and restenosis. The use of coronary stents in patients with acute or threatened closure

after balloon angioplasty led to a reduction in the need for emergency coronary bypass grafting for failed coronary balloon procedures from about 2.9% to approximately 0.3% today [1]. Obviously this represents an important and profound impact on this significant and previously common morbid outcome. The results from these studies led to FDA approval for this indication in 1994.

Early studies using bare metal stents to address restenosis following balloon angioplasty showed a profound impact on this morbid event as well, with rates decreasing from approximately 30% to 20% in early trials [2, 3]. These findings led to initial FDA approval for this indication in 1995. Subsequently DES were developed to further address restenosis and resulted in a reduction of restenosis rates to single digit levels when compared to BMS [4].

Considering the profound impact of coronary stenting on these important clinical endpoints we are perplexed by statements in the HTA suggesting that the rapid and broad acceptance of DES was somehow unexplained. To the contrary, we believe this acceptance was evidence based: garnered by decades of work and literally tens of thousands cases in peer reviewed publications. Physicians had nothing personally to gain from choosing DES over BMS and in reality, lost procedural volume due to reductions in the number of repeat procedures due to restenosis. The wide acceptance and growth in stenting, particularity DES, was driven by better outcomes; in particular target lesion revascularization (restenosis) which is the very thing they were designed to do.

II. The use of "FDA Approved Indications"

We believe it is important to address the confusion over FDA approved indications for devices and so called "off labeled" uses. The FDA serves the very important role of device approval via its ability to regulate the interstate sales of devices but is not authorized to regulate the practice of medicine. In order to obtain the statistically significant data needed for appropriate FDA device consideration, devices are most commonly studied in highly restricted and homogeneous populations that do not represent the universe of patients commonly treated. It does not have a role, nor should it, in determining clinical use of approved devices or for that matter approved drugs. Suggesting that "off label" means "inappropriate" or unstudied is not accurate [5]. Since "off label" typically equates to patients with higher risk of poorer outcome, frequently when these patients are more rigorously studied, the benefit is greater when compared to a lower risk "on label" population and in particular when compared to BMS [6,7] We agree that unfortunately the FDA process does not address the rapidly changing evidence base nor is their motivation on the part of companies to seek additional indications for their products based on a constantly changing body of evidence [5].

Additionally, we would like to highlight that the HTA concludes that off label use of DES carries a risk of stent thrombosis as well as DES may be cost effective in selected groups of higher risk patients, such as those with long lesions, narrow vessels, complex lesions, diabetics and post MI. However, some of these characteristics would be considered off label and possibly implicate higher risk of stent thrombosis, but it appears that DES happen to be most cost effective in the off label group.

Off label treatment of patients must be considered when physicians are faced with decisions regarding the unique individual patient. In addition, constantly increasing evidence makes the use of guidelines and appropriate use criteria helpful but problematic because they are frequently out of date by the time of publication. Also it is important to remember that medical evidence is strongest when it has been replicated by more than one group of investigators and followed by adequate peer review. Two recent examples in the medical literature of a rush to judgment were the premature presentation of inadequately vetted data during the European Society of Cardiology meeting in 2006 [8] which was found to be incorrect once patient level data was used in the analysis [9] and the publication of the SCAAR data in the New England Journal of Medicine in 2007 [10] that has subsequently been refuted with additional data analysis, see http://www.theheart.org/article/808471.do.

While meta-analysis can be used to shed light on inadequate evidence, it is not as rigorous as a randomized controlled trial and has led to several erroneous findings later refuted by randomized trials [11]. We do not suggest by these examples that we are not supportive of evidence based treatment, but wish to raise awareness of evidence limitations leaving the physician to do what he/she thinks is best based on their clinical experience and the strength of the evidence, for the individual patient. This makes a compelling argument that physicians should be allowed to use the best professional opinion and therapy for their individual patients including the type of stent to be implanted.

III. The primary benefit of DES and BMS

The HTA points out that the main benefit of DES vs. BMS has been a consistent and important reduction in restenosis or target lesion revascularization (TLR) in patients who have received DES. As previously noted, this was what DES was designed to do. Restenosis is a clinically important outcome as evidenced by a higher incidence of subsequent myocardial infarction in patients with restenosis who received BMS [12] this clinically important reduction should not be overlooked. Frequently, studies have been powered for the TLR endpoint because of its clinical importance. Mortality as an endpoint is usually a secondary endpoint or part of a composite endpoint since the trials are not powered to assess the question of mortality nor is that what is necessarily important to patients when there are no perceived differences in that parameter. Mortality is used in the pivotal trials to prove that the newer device does not cause greater harm, and as an important endpoint for FDA approval. Infrequently, trials are designed as a true comparison between therapies where adequate power within subgroups could yield important insights to patient care. This has not been done in trials comparing DES to BMS and cannot be fully evaluated by meta-analysis since meta-analysis frequently combines the inadequacy of individual trial design to produce at best inferences and not hard evidence.

IV. The impact of DES on mortality and myocardial infarction

One might also question the apparent equivalency of DES and BMS with respect to the impact of DES on mortality and myocardial infarction. Unfortunately the level of evidence in this area is inadequate. While this initially seems inconsistent with the evidence, the previous history of DES development should be considered. Following FDA approval and their broader use in thousands of patients, concern began to appear in the literature that stent thrombosis was more common in

patients receiving DES. This prompted reanalysis of the original trials which did not show an increase in stent thrombosis or more importantly, myocardial infarction or death [9]. Since that time, literally hundreds of publications of randomized trials and registries have looked at these important endpoints. There has not been a consistent adverse signal suggesting a problem. As pointed out in the HTA, unfortunately, the randomized trials have not been powered to look at either death or myocardial infarction. Because the trials are not adequately powered there is a possibility of alpha error. There are at least two ways to look at what we currently know: either there is not a problem or if trials are done with adequate power to look at these endpoints DES (or less likely BMS) would be found superior. Those trials may never be done because of the number of patients required and the expense. Therefore, we are left knowing that there does not seem to be an excess of death or myocardial infarction when DES is compared to BMS, a very important statement in light of the early concern of an excess of these events in patients receiving DES.

V. Comments on the draft HTA report:

Specific comments on the draft report follow:

1. On page 11, last paragraph: we suggest adding a statement that also points out that we do not know the outcomes in patients receiving BMS off label and that data suggest that the incidence of thrombosis is not higher with DES.

2. On page 11, 3rd paragraph: PCI refers to a percutaneous coronary intervention including balloon angioplasty, stenting and atherectomy.

3. On page 15 under “Summary of Safety”: The second bullet point has a misleading statement about aspirin. Aspirin is indicated lifelong after BMS as well as it is for any patient with coronary artery disease. The statement should be made clearer that DES does not drive that need.

4. Page 16, 2nd bullet point: In regard to bleeding, the Sacred Heart stent registry study detected no difference in subsequent hospitalization for bleeding events over a 2 year follow-up period in patients treated only with BMS compared to a strategy where DES was used in 85% of patients. See Ring ME, Daratha KB, Short RA, Dominik DA, Shuler L, Tuttle KR: Two-Year Safety and Revascularization Outcomes Following Coronary Artery Intervention with Bare Metal Stents Versus Strategies of Selective or Predominant Drug Eluting Stents in a Community Setting. Journal of the American College of Cardiology 51 (no. 10 suppl. B): B35, 2008 (Scientific Sessions of the American College of Cardiology, 2008).

5. Page 18, Summary with regard to economic studies, 2nd bullet point: Note that that the categories where DES may be cost effective (long vessels, small vessels, recent MI, complex lesions and diabetics) cumulatively constitute the majority of PCI patients.

6. At the bottom of page 19 beginning with point 1 and continuing on page 20 through point 6 as pointed out in the HTA are not within the scope of the document and we believe should be removed.

7. On page 22 in the second paragraph under "Interventions" we disagree that there is no clinical benefit to stenting and DES in particular. The interpretation depends on the definition of benefit. Symptom reduction vs. medical therapy is a benefit as is a reduction in TLR with DES. As pointed out, in stable patients there is no mortality benefit in selected patients but that is not the only benefit that a therapy should be held to prove. In addition, as we point out above, "off label" does not necessarily mean inappropriate use.

   We suggest including data regarding the use of stenting has declined after reaching a peak in 2004 in the US (CMS data with a similar slowing of utilization in Washington State) which predates the recent high profile publications reaffirming medical therapy's important impact on some outcomes in patients with stable symptoms. This information is available on the CDC website and in the Washington State COAP database.

8. On page 22: 3rd paragraph: Although it is stated that "most stents are used in stable CAD and in a growing number of asymptomatic patients who have no known benefit from this technology", the COAP 2007 data (page 136 of appendices) indicate that only approximately 1/3rd of Washington State PCI procedures were performed in patients with no or stable angina. Furthermore, the same COAP data on page 136 show a decline in PCI in asymptomatic patients from 2004 to 2007 from about 12% to 9%. In addition, relief of angina in stable CAD, especially in patients whose symptoms are not well controlled with medications, is considered a well accepted benefit and a Class IIa indication for PCI.

9. On page 22 the 3rd and 4th paragraphs are not supported by the evidence. The 3rd paragraph is by in large pure conjecture. We urge that the statements be removed or the individual points supported by citations. We are unaware of data to support the idea that ad hoc intervention (done at the same time as the diagnostic procedure) has increased the use of intervention. Additionally, we request that paragraph 4 be removed as it is outside the scope of this document

10. Statements on page 22 paragraph 5 and continuing on page 23 are also very vague and not supported by the evidence. We request clarification on the statement that there is no difference in thrombosis rates in the subsequent cited studies (all p values ns) but there is a discussion suggesting that there is a difference that should be weighed in the decision process vs. the obvious benefit of DES vs. BMS and TLR. This statement conflicts with the evidence cited and we request it be removed down to point 2.

11. On page 23, point 2 dealing with cost is a gross over simplification of the issues and the citation of one study for a non US healthcare system much different from ours seems inadequate. We suggest that the HTA state that this area of evidence is immature with respect to stenting. Data from evaluation of the Medicare database specifically refute this statement

12. On page 23 point 3 we agree with the HTA that patients need to be adequately educated in order to participate in decision making regarding their health. The SCAI and ACC are providing patient educational material regarding many aspects of coronary intervention available at: www.seconds-count.org and www.cardiosmart.org.

13. On page 24 in the first paragraph we would point out that the SCAI and many others in addition to the ACC/AHA have taken strong leadership roles in the development of guidelines.

14. On page 24 in the 2nd paragraph the conclusion that patients undergoing inappropriate procedures have poorer outcome assumes that patients not having assessment of ischemia is inappropriate. In some cases this is true but if the clinical story is consistent with coronary disease or the patient has acute coronary syndrome the use of additional testing is not beneficial and in some cases may be dangerous. We are concerned that using risk stratification and diagnosis of stress testing compound the problem by relating this to a certain utilization of testing in a group of diverse patients, some of whom do not benefit. The section should be expanded to include a statement that in some patients additional testing does not yield additional benefit and may be contraindicated.

15. On page 24 the last section below paragraph 2 is disappointing for such an important document. We are very concerned with the conclusions drawn from volume and outcome and how it relates to the way surgeons perceive their involvement in the process. We request the data supporting the contention that surgeons are left out of appropriate discussions about patient management as well as the data supporting the statement that stenting is done as a malpractice defense. If anything, with the initial hyperbole around stent thrombosis, there may have been an impact on decreased utilization of an important technology. We recommend the removal of this section from the document unless there is evidence provided to support the contentions.

16. On page 24 in section 5 what is the source of the statement that there are "some" who suggest that there be a separation of the diagnostic and interventional procedure? Not only is this a patient desire it is also less costly and potentially has less risk than separating the procedures in some situations. Which one of the key questions does this address? Please provide credible references or remove this section from the HTA

17. Page 25, Section 1.2: In the discussion regarding the epidemiology of CAD, there should be a discussion of the approximate 60% decline in age-adjusted mortality from CAD over the last three decades which has been partially attributed to the greater application of revascularization procedures including PCI.

18. Page 33, last sentence in 3rd paragraph: again PTCA refers to balloon angioplasty specifically while PCI includes other treatment modalities.

19. On page 35 we have addressed our concerns about the FDA and clinical indications in the sections above.
20. Page 35, 4th line: The rate of stent thrombosis in off-label DES use has not been reported to be 5% (except in cases of premature discontinuation of anti-platelet therapy). The accepted rate is 1.2 to 1.5%.

21. On page 41 we are concerned with the inclusion of comparators in the document. We do not believe they are in answer to the key questions or within the stated scope of the document. We restate our objections to the suggestion that certain forms of therapy, in this case surgery, may offer some advantages without offering supporting data especially with respect to coronary intervention. We believe this section should be removed since it is not within the scope of this document and does not address the key questions posed. If this section is not removed from the HTA we formally request to be allowed to respond in more specific detail to the factual bases of the statements made through the end of page 41

22. On page 42 we have the same concerns that alternatives are not within the scope of the HTA, including medical therapy. Additionally, we would like clarification of the following statement: "OMT is considered by most interventionist to be an adjuvant to interventional therapy with PCI, stents or CABG rather than an alternative treatment strategy." We are not aware of any data to support that statement. This is an unsupported and inflammatory statement and should be removed.

23. On page 53, in the last paragraph there is again some confusion and misstatements about the function of the FDA and appropriateness. Labeled indications are only one aspect of the delivery of clinical care as discussed above and that is the reason FDA labeling is not discussed in that document. We also point out that the data on CABG vs. PCI from the SYNTAX trial was recently published in the NEJM [13] and if this section is retained that data should be included in the HTA. We would like an opportunity to re-comment if it is included. We would also point out that this section again violates the scope and key questions posed and should be removed.

24. On page 54 there appears to be a typographical error, the "less than one" symbol for stent placements is unnecessary.

25. On page 55 we would point out that Cigna's coverage decision for the use of stents in acute MI and saphenous bypass grafts are out of date. DES stents are indicated for use in patients with acute MI. As an example see: http://www.abbottvascular.com/en_US/content/document/eIFU_XienceV.pdf. and BMS for vein grafts see: http://www.abbottvascular.com/en_US/content/document/eIFU_Ultra.pdf.

26. On page 58 the decision of the National Health Services in the UK to not cover "many cases" of chronic stable angina is again out of the scope of this document.

27. On page 59 we request citations for this data. It must be some subset of data since the number of cases is nowhere near the volume of PCI being performed in the State even in the groups referenced. In the second table how were these data determined? It is for 2009 but we are currently only partially through the 1st quarter? Is it annualized? For which patients? How is cost determined? Is it charges or was it determined by a cost to charge ratio? Please elaborate.

    If we assume the tables are correct, the State of Washington was the payer in 928 coronary stent patients in 2007 enrolled in either Medicaid or Uniform Medical Plan (UMP). According to the 2007 COAP data, this represents about 7% of the total State stent volume. Assuming that all DES patients were treated with BMS, the estimated immediate savings to the state would be approximately $2,500,000/year assuming an approximately $4,000 difference in payments between BMS and DES procedures. Has the state or the HTA authors calculated the projected final costs assuming an approximately 50% higher chance of repeat revascularization procedures with BMS relative to DES?

    What are the likely ramifications of a policy of no DES coverage in Medicaid or UMP patients when there are no similar restrictions in the remaining 93% of patients? A troubling possibility would be the perception of a two tier class of PCI care for Washington State patients. It should be also recognized that the nature of cardiology practice often precludes preauthorization for many, if not most procedures. Many PCI patients are admitted emergently and insurance status is typically not incorporated into treatment decisions. Presumably hospitals would absorb the cost of non-reimbursed DES implants which would add to already stressed finances. The ethical consequences of requiring the cardiologist to use a BMS when in their judgment; a DES would be a superior option should also be considered. Note that from a strictly financial viewpoint, cardiologists benefit greater in an only BMS strategy as professional reimbursement is the same for DES or BMS but BMS is associated with more “repeat business”. Hopefully it should be apparent from these comments that our interest in responding to the HTA is to advocate for the best medical care of our patients.

28. On page 60 table 15 we would like clarification for the repeat procedures row and accompanying percentages. Rates above 30% seem very much at odds with the literature and clinical experience during this same time period.

29. On page 66 we would like to point out that using TLR as a secondary endpoint is necessary because of study design. The use of death, cardiac death and MI were primary endpoints also because of study design. As we have stated, many of the comparative studies between BMS and DES were done in light of concerns over stent thrombosis or as part of the FDA pivotal trials where the concern was that DES should be as least as good as BMS in this aspect for approval to occur. As pointed out, these studies were not generally powered to answer the question and therefore could suffer for alpha error in favor of one stent or the other. While meta-analyses are used in an attempt to address this problem they have limitations as pointed out in the HTA and above. True comparative analysis has not been performed.

30. Page 68: 1st paragraph, last sentence: The HTA authors conclude that "registry studies …...were considered LoE III, based on their general methodological limitations." This is also discussed further on pg. 75 (last paragraph) and page 99 (last paragraph). Although registry studies were varied in terms of patient populations, comparison groups (if any), statistical analysis and follow-up, the relative dismissal of all registry studies irrespective of study design and size and the weight of evidence tilted to meta-analysis of RCT represents a major limitation of the HTA findings for the following reasons:
    - Although RCT are considered the "gold standard" for assessing treatment effects, it should be recognized that patients participating in RCTs are not completely representative of the general patient population in terms of clinical characteristics, compliance and socioeconomic status. In addition, patients in RCTs are followed much closer than non-study patients, a factor that may inadvertently affect the outcome of the study.
    - Most stent RCTs exclusively enrolled low risk patient and lesion subgroups. Approximately 60-70% of "real world" DES patients would be ineligible for participation in the majority of the RCTs.
    - An extremely important consideration is that registry studies based on "real world" patient populations typically have death and MI rates 3 to 4 times higher than observed in most stent RCTs. The high risk patients are most likely to experience the greatest benefit from DES, assuming it exists.
    - RCTs were designed to test BMS versus DES and most protocols did not allow for mixed stent use which occurs not infrequently in clinical practice.
    - Registry studies typically reflect contemporary clinical practice where the interventional cardiologist decides on the specific stent type and procedural strategy based on their clinical judgment and the specific nuances of the patient and lesion rather than a rigid study protocol as dictated by most RCTs.
    - Registry studies involving large numbers of patients which compare the outcomes of all patients treated during a time period when only BMS were used with a closely adjacent time period when both DES and BMS were available allows one to assess the effect of adding selective, if not predominant, DES use while retaining the option of BMS where appropriate. There are two recently published large studies which have taken the approach of comparing a BMS only era with a DES available era, neither of which were addressed or referenced in the HTA:
        a. Malenka et al., Outcomes Following Coronary Stenting in the Era of Bare-Metal vs. the Era of Drug-Eluting Stents, JAMA 2008;299:2868-2876. This study compared the outcome of 38,917 Medicare patients who underwent non-emergent stenting in the only BMS era (10/02 – 3/03) with 28,086 similar patients from the early DES era (9/03 – 12/03) where 61.5% of patients

received a DES. Two year follow-up revealed no change in death (8.4% both groups) and significant decline in STEMI in the DES vs. BMS eras (2.0 % vs. 2.4%, P<0.001). NSTEMI was not reported. Both repeat PCI and CABG were significantly reduced as well although TVR results were not reported.

b. Hannan et al., Comparison of Coronary Artery Stenting Outcomes in the Eras Before and After Introduction of Drug-Eluting Stents, Circulation; 2008; 117:2071-2078. This study examined the 2 year outcomes of 11,436 stent patients from the BMS only era (10/02 – 3/03) with 12,926 patients who underwent stenting after introduction of DES (10/03 – 3/04) in whom 73% received a DES. Compared to the BMS era group, patients in the DES group had significantly less adjusted MI rates (9.9% vs. 10.8%). The adjusted death rate for the DES group was non-significantly lower (5.9% vs. 6.3%) while TVR rates were clearly decreased in the DES era (11.2% vs. 17.9%, P<0.001).

Although the HTA authors have dismissed registry studies in general, the editors of JAMA and Circulation apparently felt these studies were of sufficient scientific merit to warrant publication in their journals. We believe more credence should be given to large well designed registries in the HTA.

31. On page 68 we agree that economic studies are lacking and favor efforts to do appropriate studies. Until that information is available any conclusions in this section are problematic.

32. On page 69 at the bottom of the page: why was the HTA using registry studies retained? This is especially critical considering that the tests for heterogeneity were significant. We believe this should be removed from the document and analysis.

33. One page 70 why was the Hayes Directory (2007) included? It apparently includes data from SCAAR which has subsequently come to the opposite conclusion (no difference between DES and BMS with respect to death) when an additional year of registry data was collected. See: http://www.theheart.org/article/808471.do. See also page 100 where the Hayes analysis is discussed with the incorrect updated data.

34. On page 84 under efficacy, 2nd paragraph, the contention that protocol driven angiography would potentially over-estimate true rates of TLR is true but the effect would be equal in both groups so the fact that TLR is consistently lower in DES is quite true. We are not sure what this statement adds to the section. See also page 98 regarding NNT where if your contention is correct but these are the only data that we have to make these assessments.

35. On pages 89 and 143 plus other areas in the HTA where the mortality impact of DES vs. BMS are discussed, we have made several comments about this endpoint.

We would like to once again state that the trials were in general not powered to answer the question, reveal conflicting results and despite meta-analyses may suffer individually from alpha error which could favor one over the other. However, we do agree that the studies point more to equivalency than to differences with respect to mortality. We also believe that the purpose of developing DES was to reduce TLR which they have done in a very impressive fashion, in every patient population, in multiple randomized studies.

36. On page 154 going forward to the end of that section we agree that the economic analyses are fraught with issues and we question their inclusion. This is especially true when one realizes that the cost of both BMS and DES have decreased and that calculations of cost in many of these analyses do not use actual cost but frequently use a cost to charge ratio which may have little bearing on true cost. We would also amplify on the issues of QALY and ICER since a key component of those analyses are the patient's perception of their quality of life given arbitrary clinical situations. This is highly subjective and could significantly taint the validity of the information derived. We do realize that these analyses are the current state of the art despite their significant potential limitations. . We would agree with retaining the information with the caveats contained in the section plus those outlined below since it is in answer to a key question.

    Important issues in economic analysis not adequately discussed in HTA:
    - Most economic analysis studies were performed as part of RCTs. As discussed above, the inclusion/exclusion criteria for most RCT defined a relatively low risk study group which would have excluded 60-70% of "real world" patients. This obviously limits applicability to patients with "off-label" stent indications who tend to be sicker and require more subsequent medical care. The cost of the support structure that improves patient compliance is also not included in these analyses which might also bias the results.
    - It is not clear what the cost assumptions for DES were. Since 2003, the acquisition costs of DES have declined from approximately $2,600 to $1,800 per stent.
    - How will the reduced cost of clopidogrel (Plavix), once it loses patent protection in 2010 or 2011, affect the cost analysis?
    - In clinical practice, it is not uncommon to place both DES and BMS in the same procedure depending on the specific lesion being treated. How is this handled in the economic analysis studies?
    - As indicated on page 158 (first bullet point), DES may be cost effective in recent MI, complex lesions, small vessels and long lesions, all of which were excluded in many RCT.
    - As indicated on page 161 (3rd paragraph), most DES economic analysis performed in the United States have suggested an advantage for DES. We recommend that US studies should be weighted higher than non-US studies.

37. On page 157 in the second paragraph we do not agree that thrombosis may drive additional cost in the DES group since there is no statistical difference in this

outcome between DES and BMS. That contention should be removed from the document.

38. Page 160: The average number of stents per case in the KCE report was 1.1 to 1.9. The COAP data indicates an average of 1.2 stents per DES case in 2007. The lower stent use in Washington State would favor the argument for DES in an economic calculation using a societal cost analysis.

39. Page 167: Summary and Implications – Efficacy, first bullet point: The present HTA is heavily reliant on previously performed HTAs, many if not most were done outside the United States. The health care policies and altitudes are clearly different in Europe and Canada and it is difficult to determine how this influenced their findings.

40. Page 171: Summary with regard to economic studies, 2nd bullet point: see comments above regarding pg. 18. DES may be cost effective in selected high risk groups which collectively make up the majority of DES patients. Per the COAP data for 2007, 32% of patients had recent STEMI or NSTEMI; 26% were diabetics. One cannot determine from the COAP data the frequency of small vessels, long lesions or "complex" lesions but cumulatively this is likely to exceed over a third of lesions.

41. General comments regarding selection of individual studies used in the figures: Only the data from TAXUS VI, BASKET and RAVEL were used in the figures. Each of these studies were relatively small in size (238 to 826 patients) and suggested higher MI and death risk (non-significant) with DES relative to BMS. What is the point of highlighting these particularly undistinguished RCTs relative to other studies which suggest either a neutral or beneficial effect of DES on MI and death? More valuable would be the citation of the recent report of 6 year outcomes using Cypher which demonstrated the durability of the results for DES without additional risk.

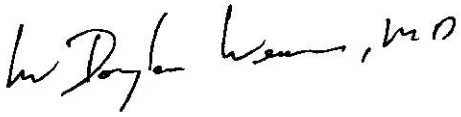
42. A major concern of the HTA is that the report approaches the comparison of DES with BMS as an "either or" proposition as opposed to providing DES as a choice by the interventional cardiologist to employ where appropriate using their experience and judgment. The issue at hand is not the choice between BMS and DES, but rather the choice of options to appropriately treat patients with coronary artery disease. As the COAP data demonstrates, cardiologists in Washington State do not exclusively utilize DES or BMS but select the best option based on their judgment.

Conclusion
Additional information will be presented at the American College of Cardiology Annual Scientific Session and Innovation in Intervention Summit (I2) this weekend. Several study results and outcome documents on the comparison of BMS and DES specifically mortality benefit are scheduled to be released during the meeting. Once they are published, we will forward this important information to you.

We very much appreciate the opportunity to respond to this draft HTA and look forward to working with the Department in strengthening the document. Please let us know if you have questions about our comments. We would like to express special thanks to Larry Dean, M.D., F.A.C.C., F.S.C.A.I. who is the primary author of this document as well as Charles Cannan, M.D., F.A.C.C., F.S.C.A.I and Michael Ring, M.D. F.A.C.C., F.S.C.A.I who assisted him in this process.

Sincerely,

Ziyad M. Hijazi, M.D., MPH, FSCAI
SCAI President



W. Douglas Weaver, M.D., F.A.C.C.

ACC President

/s/

Daniel P. Fishbein, M.D., F.A.C.C.
Washington State Chapter of the ACC President

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To: HTA Program
RE: Updated WA state Agency Utilization Information – Stents
DA: March 23, 2009

The initial data pull under-identified stent procedures because the query began with ICD-9 procedure codes, which were not always used or required for outpatient claims. Updated information includes claims initially missed that used CPT procedure codes.

Cardiac Stent Procedure Utilization: 2004-2007

State of WA

	2004	2005	2006	2007
Total Costs*	**$14,263,103**	**$15,505,519**	**$17,218,988**	**$16,544,589**
Total Procedures**	**988**	**1010**	**1040**	**954**
*Bare Metal****	*175*	*80*	*117*	*283*
*Drug-Eluting****	*781*	*919*	*904*	*650*

* Inpatient, outpatient, Medicaid and Uniform Medical Plan as primary and secondary payors

** Procedure codes 36.06, 36.07, 92980, 92981, G0290 and G0291 performed as primary or secondary procedure

*** Excludes patients who received both types in same procedure