



Health Technology Clinical Committee
Date: May 8, 2009
Time: 8:00 am – 5:00 pm
Location: Marriott Hotel – 3201 South 176th Street, Seattle, WA 98188
Teleconference Bridge: 1-360-923-2997 Access Code: 360-946-1464
Adopted: March 20, 2009

HTCC MINUTES

Members Present: Brian Budenholzer; Michael Myint; Carson Odegard; Richard Phillips; Michelle Simon; C. Craig Blackmore; Michael Souter; Louise Kaplan; Megan Morris and Christopher Standaert.

HTCC FORMAL ACTION

1. **Call to Order:** Dr. Budenholzer, Chair, called the meeting to order at 8:00 a.m. Sufficient members were present to constitute a quorum.
2. **Cardiac Computed Tomographic Angiography (CCTA) Decision & Findings:** Dr. Budenholzer referred members to the draft findings and decision and called for further discussion or objection. The CCTA findings & decision was unanimously approved by the committee on March 20th, 2009 with a condition. Final approval was subject to a review by the Chair of any additional comments received through the close of the public comment period.
 - *Action: Eight committee members unanimously approved the Computed Tomographic Angiography findings and decision document. The two newly appointed committee members abstained from voting since they were not present at the previous clinical committee public meeting.*
3. **March 20th, 2009 Meeting Minutes:** Chair referred members to the draft minutes and called for a motion and discussion.
 - *Action: Six committee members unanimously approved the March 20th, 2009 meeting minutes. Four committee members abstained from voting due to not being present at the meeting.*
4. **Cardiac Stents – Comparison of Drug Eluting Stents (DES) and Bare Metal Stents (BMS):** The HTCC reviewed and considered the Drug Eluting Stent (DES) compared to Bare Metal Stent (BMS) for the treatment of coronary artery disease technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, agency medical directors, a clinical expert, and several public members. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.



HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Cardiac Stents	0	2	8

- Conditions for coverage: The committee decided to continue coverage for bare metal stents and conditionally cover drug eluting stents. Conditions for DES are patients with highest risk of revascularization: vessels of less than 3 mm, lesions longer than 15 mm, diabetics.
- *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on Cardiac Stents reflective of the majority vote for final approval at the next public meeting.



SUMMARY OF HTCC MEETING TOPICS, PRESENTATION, AND DISCUSSION

Agenda Item: Welcome & Introductions

- ✓ The Health Technology Clinical Committee (HTCC) met on May 8, 2009.

Agenda Item: Meeting Open and HTA Program Update

Dr. Brian Budenholzer, HTCC Chair opened the public meeting. Leah Hole-Curry, HTA Program Director, provided an overview of the agenda, meeting guide and purpose, room logistics, and introductions.

Leah Hole-Curry, HTA Program Director, provided an update on HTA program activities and outcomes.

- ✓ New Committee Member Appointments: Leah Hole-Curry introduced the new committee member appointments of Megan Morris and Dr. Christopher Standaert due to the resignation of two previous committee members.
- ✓ Evidence Reports Underway: Bone Growth Stimulators, Calcium Scoring, Vagus Nerve Stimulator and Hip Resurfacing are currently underway with the vendor and the HTA program. Evidence Reports not yet started are Glucose Monitoring and Sleep Apnea Diagnosis and Treatment.
- ✓ Program Operations: The Governor, Chris Gregoire, has featured the Health Technology Clinical Committee (HTCC) and Health Technology Assessment (HTA) program in several presentations, including at the White House Regional Health Reform. Current HTCC member has been included to participate in a new legislatively created committee workgroup for evidence based radiology guidelines. Lastly, bill for proposed program changes did not pass the legislative committee.
- ✓ Program presented HTCC members with a letter of thanks from Governor Chris Gregoire.

Agenda Item: Previous Meeting Business

- ✓ March 20th, 2009 Meeting Minutes: Chair referred members to the draft minutes and called for a motion and discussion.
 - *Action: Six committee members unanimously approved the March 20th, 2009 meeting minutes. Two committee members abstained from voting.*
- ✓ Cardiac Computed Tomographic Angiography (CCTA) Findings and Decision: Chair referred members to the draft findings and decision and called for further discussion or objection. The CCTA findings & decision was unanimously approved by the committee on March 20th, 2009 with a condition. Final approval was subject to a review by the Chair of any additional comments received through the close of the public comment period.
 - *Action: Eight committee members unanimously approved the Cardiac Computed Tomographic Angiography (CCTA) findings and decision document. The two newly appointed committee members abstained from voting since they were not present at the previous clinical committee public meeting.*

Agenda Item: Cardiac Stents Topic Review

Leah Hole-Curry, HTA Program Director, introduced the primary technology topic to up for discussion:

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- ✓ Drug Eluting Stents (DES) with Bare Metal Stents (BMS) for the treatment of coronary artery disease: review of the evidence of the safety, efficacy and cost-effectiveness of Cardiac Stents.

Cardiac Stents

- ✓ Heart disease is the leading cause of death and disability in US: with 700,000 deaths. The most common heart disease in the US is coronary artery disease (CAD), which can lead to heart attack. CAD is a narrowing of one or more coronary arteries that result in an insufficient supply of oxygen to the heart muscle and is a leading cause of death in the US and developed countries.
 - CAD may be asymptomatic or lead to chest pain (angina), heart attack, myocardial infarction (MI) or death.
- ✓ Treatments include:
 - Manage and reduce risk factors, such as: smoking, obesity, high blood pressure and cholesterol.
 - Medication therapy – beta blockers, nitrates, statins, antiplatelet agents and calcium channel blockers.
 - Surgical treatment by mechanically opening the artery with a catheter with or without stent (percutaneous coronary intervention – PCI) and bypass surgery.
- ✓ Use of PCI has steadily risen over past decade while bypass remains relatively unchanged. PCI accounts for over 60% of surgical treatment. Unanswered questions remain about best use of each option, when and for what patient.
- ✓ Cardiac Stents are small tubes placed in an artery to keep it open. Stents are either not coated (bare metal stents) or coated with a drug (drug eluting stents).
- ✓ Cardiac Stent Advantages: physically opening the artery and being less invasive than bypass surgery.
- ✓ Cardiac Stent Disadvantage: targeted solution to widespread disease, unclear protocols, clotting and re-operation.
- ✓ Important, unanswered questions remain about whether and when stent placement is appropriate versus other medical management or surgery.
- ✓ Current FDA approval for cardiac stents is for the placement of a single stent in a new lesion occurring in arteries of a specific size. In acute situations, stenting is also performed outside FDA indications.
- ✓ In general, for non-acute situations, clinical guidelines indicate stent placement is appropriate after a trial of optimal medical therapy and where documented evidence of ischemia exists, but do not limit use to single stent or certain disease severity or location. In practice, stenting is now routinely performed in patients with varying disease levels, locations and symptoms.
- ✓ Cardiac Stent Research Issues – Stent studies vary in population and disease level and do not specifically focus on efficacy of non-FDA approved uses, and may not categorize multiple stent placements separately or use same definitions.
- ✓ Medicare Coverage and Clinical Guidelines:
 - Centers for Medicare and Medicaid Services (2008) -- no national coverage decision (NCD). Overall PTA coverage memo: PTA (with and without a placement of a stent) is

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covered when used in accordance with FDA approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who exhibit the following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; and (3) lesions amenable to angioplasty. Coverage for all other indications is at local Medicare contractor discretion

- Guidelines -- No guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES. Most comprehensive joint ACC/AHA guidelines address broader perspective on setting and issues involved in the decisions leading to coronary stent placement.

Agenda Item: Public Comments

- ✓ Scheduled Public Comments: Four scheduled public comments–
 - Robert Bersin, MD, representing SCAI presented concerns with the technology assessment and recommends DES be used based on physician decision.
 - Mary Greg, MD, representing COAP; provided additional information on COAP (WA state) data, the ACC guidelines, and urged collaboration with data collection and quality organizations.
 - Wayne Powell, representing SCAI presented information on issues and concerns with cost information and analysis.
 - Will Calliccoat representing Providence Health & Services presented concerns with limits on DES and recommends DES maintained as covered.

- ✓ Open Public Comments: Four individuals provided comments during the open portion (limited to three minute comments):
 - Oren Sreebny, patient, provided a statement about his positive personal experience with DES.
 - John Capps, individual and potential consumer, provided a statement approving the use of DES based on quality of life years measured.
 - Dan Fishbein, University of Washington, provided a statement about using real world patients, particularly with the Douglas trial, regarding DES.
 - Richard Page, head of Cardiology at the University of Washington, provided a statement approving the use of DES.

Agenda Item: Cardiac Stent Topic – Agency Data

Dr. Jeff Thompson, Department of Social & Health Services (DSHS) Medical Director, presented to the committee the agency utilization and outcomes for Cardiac Stents.

- ✓ Key agency concerns for prioritization:
 - Efficacy concerns – High: efficacy of stenting to prevent death or major cardiac event and high stent diffusion with low or mixed evidence on appropriateness. Concerns about high use variation, especially 70% non-FDA approved uses in generally sicker or more



complicated patients; drug eluting stent use; use instead of optimized medical therapy in lower risk patients and instead of CABG in high risk patients.

- Safety concerns – High: long term risks, procedure risks, frequency, FDA panel findings on thrombosis for DES off label.
- Cost concerns – Medium: reflect mainly concern about over or mis-utilization, and wide cost differences between treatment choices.
- 70% of stent use is “off label” – increasingly common are stent use in multiple vessels, multiple stents in a single vessel, or in vessels outside FDA diameters and lengths.
- The majority of patients with PCI have no assessment of MI risk.

✓ State Agency Utilization Criteria for Cardiac Stents:

Procedure	UM/UR
PTCA (HCA, LNI, DSHS)	No PA or restrictions
Stents (HCA, LNI, DSHS)	No PA or restrictions
On Label vs. Off Label (DSHS)	Some risk for an audit

✓ Cardiac Stent Procedure Utilization: 2004 thru 2007 – Clinical Outcomes Assessment Program (COAP)*

	Year	2004	2005	2006	2007
Total PCI Procedures**		15,158	15,330	15,686	14,164
No Prior PCI		10,022	10,146	10,265	9,135
Repeat Procedures		5,136	5,184	5,421	5,029
% Repeat Procedures		34%	34%	35%	36%
PCI Procedures with Stents		13,348	14,104	14,542	13,032
% stented PCIs		88%	92%	93%	92%
Count of All Stents		18,860	19,931	21,048	19,688
Count of Bare Metal Stents		3,224	1,408	2,122	5,214
Count of Drug-Eluting Stents		15,636	18,523	18,926	14,474
% Bare Metal Stents		17%	7%	10%	26%

* A program of the Foundation for Healthcare Quality in WA State

** Inpatient and outpatient procedure

✓ Cardiac Stent Procedure Utilization: 2004 thru 2007

2004	2005	2006	2007
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Total Costs*	\$14,263,103	\$15,505,519	\$17,218,988	\$16,544,589
Total Procedures**	988	1,010	1,040	954
Bare Metal***	175	80	117	283
Drug-Eluting***	781	919	904	650

* Inpatient, outpatient, Medicaid and Uniform Medical Plan as primary and secondary payers
 ** Procedure codes 36.06, 36.07, 92980, 92981, G0290 and G0291 performed as primary or secondary procedures
 *** Excludes patients who received both types in same procedure

✓ Cardiac Stent Procedure Costs and BMS/DES Cost Differential

2009 Procedure Costs †	Costs	Differential
Medicaid		
<i>Inpatient</i>		
Bare Metal	\$13,024	
Drug-Eluting	\$16,670	\$3,646
<i>Outpatient</i>		
Bare Metal	\$4,863	
Drug-Eluting	\$6,615	\$1,752
Uniform Medical Plan		
<i>Inpatient</i>		
Bare Metal	\$22,360	
Drug-Eluting	\$26,497	\$4,137
<i>Outpatient</i>		
Bare Metal	\$13,038	
Drug-Eluting	\$17,345	\$4,307

† Inpatient costs based on APDRGs 852 and 854. Outpatient costs based on weighted facility fees for CPT code 92980 and HCPCS code G0290

- ✓ Other Health Technology Assessments
 - Aetna: Members with angina and >50% stenosis
 - Cigna: DES for symptomatic disease; however, DES for E&I including acute MI, unprotected LMCA and SVG – not covered.
 - VA: Covers PCI for one or more arteries for FDA and conditions may be considered for cost sharing.
 - Ontario HTA: Two of following (1) long lesions (>20mm), (2) narrow lesions (<2.75mm) and (3) diabetes, to target higher risk clients.

- ✓ Agency Recommendations: Non-emergent PCI should be subject to some form of prior authorization or quality controls to ensure effective “on label” and evidence based “off label” use. Coverage limitations for DES should be limited to high risk clients (e.g., diabetes). Quality controls should ensure the client has adequate informed consent of safety, revascularization, risks, benefits and options.

Agenda Item: Evidence Review Presentation

Spectrum Research, Inc. presented an overview of their evidence report.

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- ✓ Scope: Research comparing drug-eluting stents (DES) with bare metal stents (BMS) for the treatment of coronary artery disease.
- ✓ Stent placements in coronary artery disease were designed to address narrowing of coronary vessels caused by plaque. A catheter is inserted across the lesion. Balloon inflation expands the stent and compresses plaque. The stent remains to act as a scaffold to keep the lumen open allowing increased blood flow. New endothelial lining forms over the stent.
- ✓ Cardiac Stent Background: PTCA (balloon angioplasty) initially decreased lumen narrowing, injury to the vessel walls led to acute closures (6% - 8%) and restenosis (30% - 50%). Bare Metal Stents (BMS), approved by the FDA in 1993, was introduced as a way to overcome the limitations of PTCA. BMS created a more uniform vessel opening, leaving in place a metal scaffolding to prevent closure. Inflammatory reaction and exaggerated cell proliferation resulted in re-stenosis in 20% - 25% of patients within 6 months. Drug-eluting stents (DES) were designed to prevent neointimal hyperplasia and subsequent restenosis. A polymer coating applied to the metal stent releases anti-proliferative drugs into the local environment. Anti-platelet therapy is used with BMS and DES.
- ✓ FDA: Indications – treatment of symptomatic ischemic disease in patients with de novo lesions in native coronary arteries. Contraindications – hypersensitivity to stent components (including drugs used in DES, polymers and metals used); patients in whom anti-platelet or anti-coagulation therapy is contraindicated; and lesions that don't allow for complete balloon inflation. FDA approval granted for 9 BMS and 4 DES designs.
- ✓ Literature Search: 304 potentially relevant citations; 10 previous health technology assessments or similar reports; 12 meta-analyses or pooled analysis, one of which was of non-randomized studies; 13 reports of long-term follow-up or sub-analyses to previous RCTs or new RCTs found; 26 non-randomized or registry studies and 1 full economic study and one systematic review.
- ✓ Primary Date Source Overview:
 - HTA's or similar reports – 2 (Hill, ECRI) did own meta-analysis of RCTs; 1 (KCE) used results from previous meta-analyses; 1 (Ontario) did meta-analysis on registry studies; 4 (Hill, KCE, Ontario, FinOHTA) did full economic analyses
 - Meta-analyses published after HTA's - 1 meta-analysis in general populations included 38 RCTs, N = 18,023 (Stettler 2007). 1 meta-analysis with outcomes for diabetic patients separated and length of anti-platelet therapy evaluated from 35 RCTs, N = 14,799 (Stettler 2008).
- ✓ Revascularization: refers to repeat revascularization with PCI or CABG to address narrowing (restenosis) of the vessel from scar tissue growing beneath the new endothelial layer.
- ✓ Efficacy Summary: Neither DES or BMS are favored with respect to mortality, cardiac mortality or myocardial infarction based on conventional MA and follow-up to 4 years. DES are favored with regard to TLR.
- ✓ Efficacy Summary (non randomized): There are mixed results; it is unclear whether DES or BMS are favored with regard to mortality, cardiac mortality and myocardial infarction in studies with > 1 year follow-up. DES are favored with regard to TLR.
- ✓ Special Populations -- Diabetic Patients Summary:

- Efficacy – no difference in mortality, cardiac death or MI in those with ≥ 6 months DAT (0 to 4 years). 2-fold increase in mortality and cardiac death in those with < 6 months (0 to 4 years). Significant reduction in TLR with DES.
- Effectiveness – Mixed results for death/cardiac death, no difference in MI. TLR less frequent with DES.
- Safety – Although no differences between DES and BMS for stent thrombosis or late stent thrombosis were found, there may be insufficient power to detect a difference.
- ✓ Safety Summary: Most previous HTAs and meta-analysis indicate no statistically significant different between DES and BMS with regard to risk of stent thrombosis.
 - 1 review focused on safety concluded that the majority of evidence suggested an increased risk with DES. 2 reports concluded there was significantly higher risk after 1 year with DES. Stent thrombosis is a rare event; studies may have been underpowered to detect a difference.
 - FDA conclusions: DES for off-label indications was related to increased incidence of stent thrombosis, MI and death. Discontinuation of anti-platelet therapy was an independent risk factor. Risk of thrombosis does not outweigh advantage of DES over BMS in reducing repeated revascularization when used for approved indications.
- ✓ Economic Analysis Summary: HTA reviews of 43 economic studies + 5 additional analysis suggested DES is not cost effective across populations vs. BMV but may be in special populations. Broad range of outcomes and ICERs. Significant variability in modeling, quality and consistency of findings.
- ✓ Conclusions: Evidence review - interpretation for what is known
 - There is no statistically significant different between DES and BMS with regard to death, cardiac death or myocardial infarction up to 4 years.
 - DES are consistently associated with lower rates of TLR.
 - While no statistically significant differences in stent thrombosis or late stent thrombosis were seen, analyses may be underpowered; no comparative studies for bleeding.
 - Among diabetic patients, < 6 months of dual anti-platelet therapy was associated with a 2-fold increase in death and cardiac death with DES but there was no difference in MI regardless of therapy duration.
 - Nonrandomized studies show mixed results for death and MI.
 - Most extensive CEAs concluded DES were not cost-effective in general populations; ICERs driven by DES cost, #, TLR.
 - Professional guidelines do not address use of DES vs. BMS.
- ✓ Conclusions: What we don't know from the evidence
 - Are statistically significant findings also clinically significant? Are the risk differences of public health importance?
 - How should the relative importance of the various outcomes be weighed, over the short-term and over the long-term?

- Is TLR/TVR correlated with decreased rates of death, cardiac death and MI over the long term? Why or why not?
- How might newer DES designs or drugs compare with BMS for various outcomes in the short term and long term?
- What is the long term safety of prolonged anti-platelet use?
- What are the specific indications for DES vs. BMS in general and special populations? What are the indications for TLR?
- Will methodologically rigorous US-based CEAs draw different conclusions from HTA CEAs as ICERs are driven by DES cost, number of stents and TLR?
- How does comparison of DES vs. BMS fit within the bigger context of comparative effectiveness with medical therapy, CABG and other treatments?

Agenda Item: HTCC Cardiac Stents Discussion and Findings

Brian Budenholzer, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost effectiveness of Cardiac Stents beginning with identification of key factors and health outcomes, and then a discussion of what evidence existed on those factors.

1. Evidence availability and technology features

- 1.1 The evidence based technology assessment report indicates that Coronary Artery Disease (CAD), a narrowing of the arteries that supply the heart with oxygen, is very common and is an important public health concern. Patients with CAD range from no symptoms, to chest pain (angina), to myocardial infarction (MI), to death. Prediction of risk and symptoms is difficult: while the location and severity of obstructions are used, they do not always correlate with symptoms or outcome.
- 1.2 Treatment options for CAD to open the arteries include medical therapy and lifestyle management, percutaneous coronary intervention (PCI) a catheter with or without stenting, and coronary artery bypass grafting (CABG). Catheter based interventions that leave a stent to hold open the arteries can include bare metal stents (BMS) or drug eluting stents (DES). The main difference between the stents is that DES are treated with a drug coating intended to prevent restenosis that occurred with PCI using BMS.
- 1.3 The evidence based technology assessment report identified a large amount of literature, including previously done technology assessments. Due to the large amount of already produced material, this evidence report summarizes previous technology assessments and then updates the summary with information from subsequently published studies. Recently conducted technology assessments had a high degree of overlap in the included studies. The evidence base consisted of 304 potentially relevant citations. There were 10 previous health technology assessments or similar reports; 12 meta-analyses or pooled analysis, one of which was of non-randomized studies; 13 reports of long-term follow-up or sub-analyses to previous RCTs or new RCTs found; 26 non-randomized or registry studies and 1 full economic study and one systematic review. The evidence basis also included trials or separately reported sub-analysis amenable to evidence review on several subpopulations: diabetic patients, and patients with acute MI. Registry study on the elderly discussed in section 1.5.
- 1.4 Given the high overlap in studies, the evidence review focused on summarizing five recent health technology assessments, most conducted with their own meta-analysis, and one focusing on registry studies. The evidence review included one meta-analysis of 38 trials that

was published after the technology assessments, *Stettler 2007*. The Stettler study meta-analyzed 38 randomized trials with 18,023 patients; and a separate analysis of diabetics in 35 of the trials with 14,799 patients. Additionally, 26 recently published non-randomized studies were included to update the information. The evidence review presents study results related to key questions in each of the three categories (HTA, Meta-analysis, and Non-randomized studies) if the studies contained applicable information. The technology assessment also includes a color coded summary table of the overall evidence for each key question and important health outcome (see pg 159).

- 1.5 Additional evidence: some additional studies were published after the draft and final evidence report. The final evidence report includes a brief summary of the study published after the draft which linked Medicare data with ACC registry data, *Douglas, et. al*. An uncorrected proof of this registry study contained summary information on data of 260,000 over 65 year old Medicare patients for up to 30 months. Two additional study abstracts were published one day prior to the meeting. The studies were briefly reviewed by the evidence review vendor and made available to committee members. First, a registry follow-up study from Sweden (SCAAR 2) on 47,967 patients through 2006 that were followed from one to five years. A second randomized trial, *Stone, et al*, of 3006 patients comparing BMS and DES in patients with ST-segment elevation myocardial infarction. The technology assessment vendor urged caution in relying on these studies as none are critically appraised. The technology assessment vendor also noted that the study results, if valid, did not significantly alter conclusions already in the report related to mixed findings of non-randomized studies and results in myocardial infarction patients.
- 1.6 The committee commented on the large amount of randomized and observational studies available comparing DES and BMS on many of the important health outcomes they identified for stents. Committee discussed the nature of the evidence and the role of registries and observational studies in the face of robust randomized trial evidence. Some committee members advocated that the evidence hierarchy is well established and randomized trials provide the highest level of confidence in reported outcomes, so if relevant and well conducted RCT's, or as here, meta-analysis of multiple RCT's are available for important outcomes, observational studies should not be used to contradict findings. For these members, the appropriate role of observational studies is to shed light on rare complications and potential additional sub-population information. Other committee members advocated that these observational studies were on a significantly larger population, are better powered to detect rare events and are more valid or relevant because of the inclusion of "real world" patients. The committee discussed the inclusion of the recently published articles and whether an additional appraisal was necessary, but chose to move forward with the outcomes discussion bearing in mind that the newer studies had not yet been critically appraised and noting that if the majority of committee members felt further review was necessary because their final vote might change based on the un-appraised studies, additional specific information could be obtained from the evidence vendor and presented at a later meeting.

2. Evidence about the technology's safety

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- 1.1 Overall Mortality and Cardiac Mortality: this topic was discussed in the context of efficacy (see below).
- 1.2 Stent Thrombosis: The evidence based technology assessment report indicated that this is a rare, but serious complication (generally occurring in about 1.5% of cases) with potentially

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higher rates in DES. This topic prompted a review of evidence by an FDA panel in 2006 that concluded DES used for approved indications (single, new lesion of certain size) and with anti-platelet therapy is prescribed for at least 1 year (instead of 3 to 6 months) were safe. From the most recent meta-analysis with four year follow up, thrombosis rates are low and not statistically different: 1.4% SES; 1.7% PES and 1.2% BMS; though the evidence review indicates that even large studies may be underpowered to detect statistically significant differences.

- The evidence based technology assessment report summarized seven HTA's, including one HTA of registry data: most concluded no statistically significant difference, though several indicated may be underpowered, three reported there was a higher risk of stent thrombosis with DES.
- The evidence based technology assessment also included a summary from Stettler's more recent meta-analysis of randomized trials related to thrombosis (included 24 trials and 12,973 patients which showed an overall rate of thrombosis at 1.4% and no statistically significant difference between BMS and DES in up to four years, though some statistical differences were observed in subgroups comparing SES, PES and BMS and short versus longer time periods. Adherence and length of anti-platelet therapy are not well documented in trials, though a 2008 Stettler updated meta-analysis found no statistically significant difference in thrombosis rates, regardless of anti-platelet therapy regimen.
- The evidence based technology assessment also included information from ten recent nonrandomized studies, with most showing no difference, and 1 reporting significantly higher rate of very late stent thrombosis for DES.

- 1.3 Stent Thrombosis in diabetics: The evidence based technology assessment report included several analysis and studies reporting on this rare, but serious complication in the diabetic subpopulation. One HTA noted patients more likely to benefit from DES to be diabetic patients, small vessels, and chronic kidney disease, were at the same time at higher risk for developing late stent thrombosis. The later Stettler meta-analysis specific to diabetic patients indicate no statistically significant difference up to four years, but wide confidence intervals suggest variability perhaps related to sample size. This finding is consistent with two other, later published meta-analysis and several randomized trials. One HTA of registry data indicated higher in-stent thrombosis with DES (2.4 to 4.4%) versus BMS (0.8%).
- 1.4 Stent Thrombosis in patients with acute MI: The evidence based technology assessment report included several analysis and studies reporting on this rare, but serious complication in the subpopulation of patients treated with a stent after acute MI. One HTA, two meta-analyses, and three recent RCT's report no statistically significant difference in rates of stent thrombosis between DES and BMS groups.
- 1.5 Bleeding: the evidence based technology assessment report reviewed this safety issue, however no randomized studies or HTA's compared DES to BMS for this outcome. One non-randomized study compared different DES patients, with overall rates of bleeding at 3.1%, patients on dual antiplatelet use and over age 65 were significant risk factors for major bleeding in DES patients.
- 1.6 Stent Fracture: The evidence based technology assessment did not identify any HTA or randomized trials with evidence about comparison between DES and BMS of this complication. Small case series in DES patients indicated that fracture ranged from 1.9% to 7.7%.

3. Evidence about the technology's efficacy and effectiveness



The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- 1.1 Freedom from Overall and Cardiac Mortality: The evidence based technology report includes death, and specifically cardiac-related death, as a key health outcome in treatments for cardiac artery disease. It was noted both by the evidence review and committee members that the updated FDA recommendation to continue dual anti-platelet therapy for one year in DES patients may be a related factor that was not separately reported in many studies.
- The evidence review of previous HTA and the meta-analysis report no statistically significant difference in overall or cardiac mortality between DES and BMS up to four years.
 - Studies including registry data cite the SCAAR (Sweden) where authors found increased risk of death with DES at 6 months and 3 years (relative risk of 1.18%). In other registry studies, the findings were mixed, with six suggesting no difference; and three showing higher BMS risk.
 - Freedom from mortality in elderly subpopulation. The Douglas study (not critically appraised) of Medicare patients indicates a 3% higher risk of mortality from BMS than DES.
 - Overall committee discussion centered on agreement that majority of reliable evidence finds no difference between DES and BMS in mortality or cardiac mortality.
 - Freedom from mortality in acute MI subpopulation. The evidence based technology report summarized results from one recent HTA, a meta-analysis and three recent RCT's that concluded no statistically significant difference in DES and BMS groups with acute MI for mortality.
 - Freedom from mortality in diabetics subpopulation. The evidence based technology report indicates that diabetics tend to have multi-vessel disease, smaller coronary arteries, and longer lesions. Previous HTAs had only limited evaluation of diabetics, but recent meta-analysis reported a two fold increase in mortality for diabetic patients receiving less than 6 months of dual anti-platelet therapy. Three recent meta-analyses indicate that the overall mortality risk is similar between BMS and DES.
- 1.2 Freedom from MI: The evidence based technology report and committee agreed that subsequent myocardial infarction (MI or heart attack) is a key health outcome in treatments for cardiac artery disease, including stents.
- The evidence review of previous HTAs, the Stettler meta-analysis and two other meta-analyses report no statistically significant difference in MI between DES and BMS in trials with two to five years follow up. One meta-analysis with follow up at 6 to 12 months reported lower MI with DES (3.3%) than BMS (4.2%).
 - Mixed results in non-randomized studies reporting on MI – with 7 studies showing no significant difference in MI, while 3 studies showed a lower rate in DES patients.
 - Freedom from MI in diabetics subpopulation. The evidence based technology report focused on the recent meta-analysis with up to four years follow up indicating no difference in MI outcomes between BMS and DES diabetic patients.
 - Freedom from MI in acute MI subpopulation. The evidence based technology report focused on the recent meta-analysis with up to four years follow up indicating no difference in MI outcomes between BMS and DES in acute MI patients.
 - Freedom from MI in elderly subpopulation: The evidence report summarized the Douglas study (not critically appraised) finding a higher rate of MI (1.4% risk difference) in BMS patients.

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- 1.3 Freedom or reduction of Target vessel revascularization/target lesion revascularization (TVR): The evidence based technology report and committee agreed that TVR, or repeat procedures to open the same vessel, is a key health outcome in stent comparisons.
- The committee discussed the implication of dual anti-platelet therapy and whether that impacts revascularization rates.
 - The evidence review of previous HTAs, the Stettler meta-analysis and two other meta-analyses report a lower rate of TVR using DES compared to BMS. The Stettler meta-analysis reported a revascularization rate of DES at 6.9% to 9.0% and BMS at 19.0% with up to 4 year's follow up – this represents an 11.1% reduction.
 - The results of the reviewed non-randomized studies also suggested lower revascularization rates for DES (5.2% - 14.2%) and for BMS (8.1% to 24.4%).
 - Revascularization rates in studies of the Acute-MI subpopulation also reported decreased revascularization using DES (4.8% to 5.1%) versus BMS (12.0% to 13.1%).
 - Revascularization rates in HTA's and meta-analysis of the diabetic subpopulation also reported significant decreased revascularization using DES, regardless of use of dual anti platelet therapy, out to one year DES (6.3% to 11.3%) versus BMS (19.3% to 31.1%).
 - Revascularization rates in studies of the elderly subpopulation reported a no difference in revascularization rate between DES (23.5%) and BMS (23.4%) at 30 months.
- 1.4 Quality of Life: The evidence based technology report included quality of life as a key outcome, but studies did not report or define this measure. The committee commented that quality of life is important and future studies should include. Additionally, TVR is a part of a quality of life where less need for re-surgery would be positive but the metric is incomplete and it appears that short term results may favor DES but longer term results are similar.

4. Evidence about the technology's value and cost-effectiveness

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

- 1.1 Overall context from the evidence based technology report and discussed by the committee: there remains uncertainty regarding efficacy, effectiveness, and safety of DES versus BMS and differing assumptions contribute to variability in analysis. The incremental cost effectiveness ratios (ICER) were most influenced by the price premium of DES.
- 1.2 The evidence included 43 cost effectiveness, but focused on evidence from previous HTA's which concluded that DES might be cost effective in higher risk patients and not cost-effective with low risk patients; when more realistic assumptions and data values were used, DES may be cost effective only under very limited circumstances, and several studies were industry supported.
- 1.3 Price premium for DES in HTA's ranged from \$563 Euro to \$1,299. ICER for use of DES ranged from a low of \$27,540 to a high of \$1,099,858 QALY; with the four economic analyses performed as part of HTA's ranging from \$64,394 to over 1 million Euros. ICER's for repeat revascularizations ranged from \$1,650 to \$7,000.
- 1.4 Washington state use data: from the COAP database which gathers information on all WA procedures, from 2004 to 2007, BMS was used 15% and DES 85%.
- 1.5 State agency cost data: Utilization at the three agencies over the same time period is 15% BMS and 83% DES.



Medicare Decision and Expert guidelines

Committee reviewed and discussed the Medicare coverage decision and expert guidelines as identified and reported in the technology assessment report.

- Centers for Medicare and Medicaid Services (2008) – there is no national coverage decision (NCD) relating to drug eluting versus bare metal stents. There is coverage memo on percutaneous intervention overall (PTA) which covers treatment with conditions: PTA (with and without a placement of a stent) is covered when used in accordance with FDA approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who exhibit the following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; and (3) lesions amenable to angioplasty.
- Guidelines -- No guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES. The most comprehensive guideline, a joint ACC/AHA guideline addresses broader perspectives on setting and issues involved in the decisions leading to coronary stent placement as well as other treatments.
- Two other organizations, England's NHS and Ontario's OHTAC have recommendations for use of DES in narrow lesions (<3.0 or 2.75mm) long lesions (>15 or 20 mm). Patients with diabetes and a price differential cap of \$300 pounds are additional limits.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

1. Evidence availability and technology features

The committee concludes that the best available evidence on cardiac stents has been collected and summarized. The evidence is comprehensive and robust:

- 1.1. Where evidence from meta-analysis of multiple, well designed randomized or well designed controlled trials, with adequate participants, assessment of all patient centered health outcomes, and for sufficient duration exists for efficacy, that evidence should have highest weight. A large body of high quality evidence on over 30,000 patients studying use of BMS and DES stents exists.
- 1.2. Additionally, complications and adverse events, especially rare events, can be identified by case-review studies and other sources such as the FDA database.

2. Is it safe?

The committee concludes that the comprehensive evidence reviewed shows that the technology of DES has been proven equally safe to BMS. Key factors to the committee's conclusion included:

- 2.1. *Morbidity related to Stent Thrombosis:* The committee agreed with the evidence report conclusions that these are rare events, where even the larger RCT's and observational data may not be powered to detect. However, the best available meta analysis of RCT data shows difference relied heavily on the most recent meta-analysis with four year follow up: 1.4% SES; 1.7% PES and 1.2% BMS.
- 2.2. *Bleeding:* the committee concluded that bleeding is a very serious complication. Due to dual anti-platelet therapy proscribed with DES, this complication could be higher in DES; but not enough information and registry data, though lower quality, showed equivalence with 3.4% BMS vs 3.6% DES rate.

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- 2.3. *Stent Fracture*: The committee agreed that this issue was not applicable since evidence was not obtainable on this outcome and no other reason to believe rates between the two stent types would be different.

3. Is it effective?

The committee concludes that the comprehensive evidence reviewed shows that the DES technology has been proven equally effective to BMS, and more effective than BMS in one area:

- 3.1. The committee identified four key health outcomes that impacted effectiveness; with three have high quality evidence available.
- 3.2. *Freedom from Cardiac Mortality*: the committee concluded that data from multiple RCTs demonstrated that there is no overall or cardiac related benefit with DES compared to BMS.
- 3.3. *Freedom from Myocardial Infarction (MI)*: the committee concluded that the data from multiple RCTs demonstrated that there is no benefit from DES compared to BMS in reducing rates of MI.
- 3.4. *Freedom or reduction of revascularization (TVR)*: the committee concluded that data from multiple RCTs demonstrates a benefit of an 11% reduction in the rate of revascularization with use of DES compared to BMS.
- 3.5. *Quality of Life*: the committee believes that quality of life is an important health outcome to demonstrate overall effect of treatment, but concluded that there was not reliable data to conclude whether DES provided a benefit over BMS. The committee discussed the previous revascularization reduction as a component of quality of life.

4. Is it cost-effective?

The Committee concludes that the comprehensive evidence review shows that the DES technology is less cost-effective overall. However, the committee also addressed cost-effectiveness in a certain situation, for high risk patients, and was split with five finding that DES were more cost effective and five finding that DES was unproven or less cost-effective for this population.

- 4.1. The committee noted that the evidence review contained multiple cost effectiveness studies and agreed that the most important factors were the cost premium for DES, but also discussed the cost of medications, revascularization cost, issue of lack of ability to demonstrate higher overall efficacy, and the concept of measuring DES in terms of cost per revascularization versus cost per QALY (which takes revascularization and other factors into account).
- 4.2. The committee agreed that overall, DES is not cost-effective, especially considering the state's \$3,600 differential, where lower price premiums produced "staggering" cost he cost per QALYs.
- 4.3. For certain subpopulations of high risk patients, some HTAs reported, and five committee members agreed that DES is cost-effective.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, additional just published studies, input from a clinical expert, and agency and state utilization information. The committee concluded that the current evidence on Cardiac Stents demonstrates that there is sufficient evidence of a health benefit to cover the use of cardiac stents, but limit the use of Drug eluting stents to certain circumstances. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. The committee

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found that drug eluting stents were proven to be equivalent to bare metal stents in safety and efficacy overall. The committee found that drug eluting stents were proven to be more effective in one area: reducing revascularization, and were proven to cost more.

Based on these findings, the committee voted 8 to 2 to cover drug eluting stents, with conditions: limited to patients with highest risk of revascularization (less than 3 millimeter vessel, or lesion longer than 15 millimeters, or diabetics).

Cardiac Stent Vote

The clinical committee utilized their decision tool to first gauge committee judgment on the status of the evidence in the three primary areas of safety, efficacy, and cost.

Cardiac Stent Evidentiary Votes:

Is there sufficient evidence under some or all situations that the Drug Eluting Stents, as compared with Bare Metal Stents are:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	1	9	0	0
Effectiveness (Revascularization)	0	0	0	10
Safe	1	9	0	0
Cost-effective Overall	0	0	10	0
Cost-effective Some Situations	4	0	1	5

Cardiac Stent Coverage vote: Based on the evidence provided and the information and comments presented, the committee moved to a vote on coverage.

HTCC COMMITTEE COVERAGE DETERMINATION			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Cardiac Stent - DES	0	2	8

- Outcome: The committee chair directed HTA staff to prepare a Findings and Decision document on Cardiac Stents reflective of the majority vote for final approval at the next public meeting.
 - Bare metal stents continue to be covered. Drug Eluting stents are conditionally covered. Conditions for DES coverage are limited to patients with a vessel diameter of less than 3 millimeters; or a lesion longer than 15 millimeters; or diabetic patients.