Washington State Health Care Authority

Agency Medical Director Comments

Cardiac Stents - Re-review

Charissa Fotinos, MD, MSc
Deputy Chief Medical Officer
Washington State Health Care Authority
January 15, 2016

Background

- This re-review examines whether/when stents are appropriate in the setting of stable asymptomatic CAD

AND

- Whether or not in the settings of stable, unstable or Acute Coronary Syndromes, if there are differences in outcomes based on the type of cardiac stent chosen, bare metal, BMS or drug-eluting, DES.

Cardiac Stents - Re-Review

Previous Cardiovascular HTCC Decisions

- **Cardiac Stenting: May 2009**
- Calcium Scoring: November 2009
- Coronary CT Angiography: May 2010
- Cardiac Nuclear Imaging: September 2013

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Previous Key Questions 2009

- What is the evidence of efficacy and effectiveness of drug-eluting (DES) vs. bare metal stents (BMS)?
  - Including any effects on special populations, before or after MI or by vessel or lesion type
- What is the evidence related to the safety profile of DES vs. BMS?
  - Including patients with and without continuation of anti-platelet medications
- What is the evidence of cost-effectiveness and cost implications of DES vs. BMS?
  - Including and effects of pharmacologic therapy and re-interventions

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Previous Determinations 2009

- **Covered with conditions**:
  - BMS: Covered w/o conditions
  - DES:
    - Stent diameter of 3 mm or less;
    - Length of stent(s) longer than 15 mm in a single vessel
    - Patients with diabetes
    - Stents placed to treat restenosis*
    - Treatment of left main coronary disease

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Current State Agency Policy

- **Medicaid** – Follows HTCC for DES, no PA for BMS
- **PEBB** – Follows HTCC Decision
- **Labor & Industries –** Follows HTCC Decision
- **Dept. of Corrections –** Requires PA

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Expansion of Scope & Re-review

Expanded Scope:

- In patients w/stable CAD:
  - PCI + medical therapy vs. medical therapy
    - Effectiveness, safety, subgroup benefit or harm, cost-effectiveness

Re-review:

- In patients w/CAD (stable or unstable) any updates from 2009 showing:
  - Newer generation DES more efficacious than BMS
    - Effectiveness, safety, subgroup benefit or harm, cost-effectiveness

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Outcomes of Interest

Effectiveness	Safety
▪ Mortality (all cause)	▪ Stent thrombosis
▪ Cardiac mortality	▪ Peri-procedural complications < 30 days
▪ MI	
▪ Reported quality of life	
▪ Target lesion revascularization (TLR)	
▪ Target vessel revascularization (TVR)	

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Additional Background Considerations

- Guidelines are published that recommend the use of PCI vs. CABG across a wide variety of patient and clinical variables
- A large registry based study looked at patient and clinical characteristics associated with the use of BMS vs DES.
- Studies also suggest the potential for savings if more BMS rather than DES were placed in patients at low risk of restenosis.

Guidelines Exist

- American College of Cardiology along with a number of other societies have developed Appropriate Use Criteria (AUC), for Stable Coronary Artery Disease
  - First in 2009, 2012, 2013
- Society for Cardiovascular Angiography and Interventions (SCAI), has also developed appropriateness criteria for the procedure
  - Both sites offer apps that can be downloaded to help inform the appropriateness of PCI given the patient's particular clinical presentation

Recommendations for Revascularization with Low Risk Findings on Non-Invasive Test or Asymptomatic

A: Acceptable **U**: Uncertain **I**: Inappropriate

Low-Risk Findings on Noninvasive Study						Asymptomatic					
Symptoms Med. Rx						**Stress Test Med. Rx**					
Class III or IV Max Rx	U	A	A	A	A	High Risk Max Rx	U	A	A	A	A
Class I or II Max Rx	U	U	A	A	A	High Risk No/min Rx	U	U	A	A	A
Asymptomatic Max Rx	I	I	U	U	U	Int. Risk Max Rx	U	U	U	U	A
Class III or IV No/min Rx	I	U	A	A	A	Int. Risk No/min Rx	I	I	U	U	A
Class I or II No/min Rx	I	I	U	U	U	Low Risk Max Rx	I	I	U	U	U
Asymptomatic No/min Rx	I	I	U	U	U	Low Risk No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1-vz.; no other disease	1-2-vz. disease; no prox. LAD	1-vz. disease of prox. LAD	2-vz. disease with prox. LAD	3-vz. disease; no left main	Coronary Anatomy	CTO of 1-vz.; no other disease	1-2-vz. disease; no prox. LAD	1-vz. disease of prox. LAD	2-vz. disease with prox. LAD	3-vz. disease; no left main

J Am Coll Cardiol. 2012;59(9):857-881. doi:10.1016/j.jacc.2011.12.001

Cardiac Stents - Re-Review

Background

- Choosing Wisely
  - Society for Cardiovascular Angiography & Intervention
  - Released March 2014

5 **Avoid PCI in asymptomatic patients with stable SIHD without the demonstration of ischemia on adequate stress testing or with normal fractional flow reserve (FFR) testing.**

For patients with stable ischemic heart disease, in the absence of symptoms, there is limited clinical benefit to PCI unless performed on a lesion with demonstrable hemodynamic significance (FFR <0.8) or causing a significant amount of ischemia as assessed by non-invasive stress testing. Rare exceptions would be a significant left main coronary artery lesion or a >90% proximal lesion in a major coronary artery.

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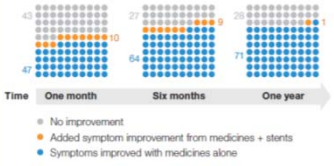
Mayo Clinic Decision Aid CCS I-II Angina

Benefits

Prevention of heart attack or death in stable coronary artery disease with medicines + stents compared to medicines alone:

NO DIFFERENCE in heart attack or death.

How symptoms improve in 100 people with medicines + stents compared to medicines alone:



Risks

During the stent procedure:
Bleeding, heart attack, stroke or death

In 100 people:

TWO will have bleeding or damage to a blood vessel; 98 will not.

ONE will have a complication such as heart attack, stroke or death; 99 will not.

During the first year after stent:
Bleeding and heart attack

In 100 people:

THREE will have a bleeding event from the additional blood thinner needed with a stent; 97 will not.

TWO will develop a clot that forms in the stent leading to a heart attack; 98 will not.

PCI Choice: Decision Aid Prototype for Class I/II Angina. Version 24; May 25, 2012

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DES Use & MD Variation

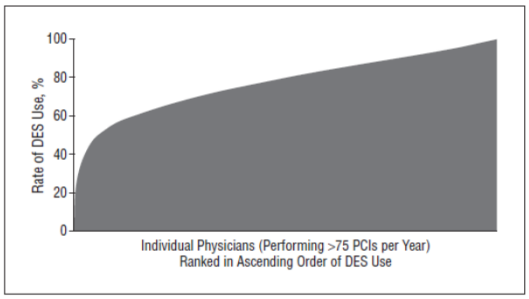

Figure 1. Physician level variation in the use of drug-eluting stents (DES). The physicians include the individual physicians (n = 2715) in the National Cardiovascular Data Registry (NCDR) CathPCI Registry, version 4 data, who performed more than 75 percutaneous coronary interventions (PCIs) annually. These physicians are ranked in ascending order of rate of DES use, such that those using the least DES are to the left and those using the highest DES are to the right.

Arch Intern Med. 2012;172(15)00

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Re-Stenosis Risk

Risks associated w/restenosis:

- Older age
- Male
- Diabetes
- Hypertension
- Lesion related risks
- Procedure related risks

Factors associated w/↑DES Use

- Female
- Private/HMO insurance
- Elective admission
- High hospital volume PCI

Factors associated w/↓DES Use

- AMI, shock
- Self-pay
- Higher co-morbidity score
- Weekends

Jukema, J.W. et. al. Nat. Rev. Cardiol. 9, 53-62

Panaich, et.al. Catheterization and Cardiovascular Interventions, May 29,2015.

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1-year Target Vessel Revascularization after PCI Risk Calculator

This tool calculates the predicted risk of target vessel revascularization in patients undergoing percutaneous coronary intervention. The expected risk can be calculated based on the use of either a drug-eluting or bare metal stent.

All risk factor values except Number of Lesions use 1=Yes and 0=No

Disclaimer: This risk calculator should be used for informational purposes only. If you have questions or concerns about the risk factor results, please consult with your health care doctor or cardiac care specialist. The computation is based on data from all Massachusetts hospitals, and is not specific to any one hospital.

Category	Risk Factors *(Reference Group in Blue)*
Age of Patient in Years (Choose one)	◉ 0 to 50 ○ *51 to 79* ○ 80 or older
History and Prior Risk Factors (Choose all that apply)	☐ Diabetes ☐ Peripheral Vascular Disease ☑ Hypertension
Previous PCI (Choose one)	◉ *None* ○ <= 1 Year ○ > 1 Year or Timing Unknown
Canadian Cardiovascular Society / New York Heart Association Class (Choose one)	○ *Class I* ◉ Class II ○ Class III ○ Class IV
PCI Indication (Choose one)	○ *No Chest Pain* ○ Atypical Chest Pain ◉ Stable Angina ○ Unstable Angina ○ Non-STEMI ○ STEMI
Disease Presentation Status (Choose one)	◉ *Elective* ○ Urgent ○ Emergent or Salvage
Vessel, Lesion, and Device Information (Choose all that apply)	☐ >= 2 Vessels with >= 70% Stenosis 2 Number of Lesions Treated (continuous) ☐ Drug Eluting Stent (Unchecked = Bare Metal) ☐ Device Diameter >= 3mm ☐ Device Length >= 30mm
Predicted Revascularization Risk:	**13.72%**
0% is the lowest risk, 100% is the highest risk	

Cardiac Stents - Re-Review

Clinical Factors

- <50 yrs
- Hypertension
- No prior PCI
- CCS Class II
- Stable Angina
- Elective
- See opposite

- Difference in restenosis risk w/DES

Vessel, Lesion, and Device Information

(Choose all that apply)

- ☐ >= 2 Vessels with >= 70% Stenosis
- 2 Number of Lesions Treated (continuous)
- ☑ Drug Eluting Stent (Unchecked = Bare Metal)
- ☐ Device Diameter >= 3mm
- ☐ Device Length >= 30mm

Predicted Revascularization Risk: 7.72%

0% is the lowest risk, 100% is the highest risk

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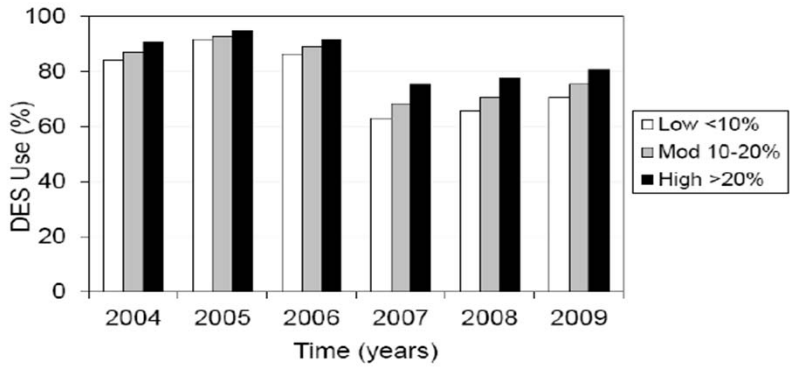
DES Use by Risk of Re-stenosis

eFigure 3. Rates of DES use by predicted TVR risk categories across years.



Arch Intern Med. 2012;172(15)

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PEBB/UMP
Stent Utilization: 2011-2014

Year	Type Stent	Unique Patients	Procedures	Submitted Amt	Allowed Amt	Paid Amt	Average Paid/Procedure
2011	BARE	22	23	$1,647,000	$827,000	$796,000	$35,992
	DRUG	108	110	$10,142,000	$3,979,000	$3,765,000	$36,181
2011 Total		130	133	$11,790,000	$4,807,000	$4,561,000	$36,148
2012	BARE	19	19	$1,504,000	$598,000	$591,000	$31,503
	DRUG	122	126	$9,600,000	$4,395,000	$4,279,000	$34,885
2012 Total		141	145	$11,104,000	$4,994,000	$4,871,000	$34,442
2013	BARE	10	10	$839,000	$312,000	$308,000	$31,242
	DRUG	106	109	$9,447,000	$3,555,000	$3,451,000	$32,621
2013 Total		116	119	$10,287,000	$3,868,000	$3,760,000	$32,505
2014	BARE	13	13	$1,055,000	$400,000	$396,000	$30,792
	DRUG	83	88	$8,271,000	$3,385,000	$3,338,000	$38,467
2014 Total		96	101	$9,326,000	$3,785,000	$3,735,000	$37,480

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PEBB Medicare
Stent Utilization: 2011-2014

Year	Type Stent	Unique Patients	Procedures	Submitted Amt	Allowed Amt	Paid Amt	Average Paid/ Procedure
2011	BARE	24	24	$2,123,000	$196,000	$27,000	$8,208
	DRUG	100	101	$9,366,000	$624,000	$152,000	$6,186
2011 Total		124	125	$11,489,000	$821,000	$180,000	$6,574
2012	BARE	24	25	$2,077,000	$402,000	$28,000	$16,089
	DRUG	112	114	$10,389,000	$1,804,000	$132,000	$15,829
2012 Total		136	139	$12,467,000	$2,206,000	$161,000	$15,876
2013	BARE	12	13	$1,095,000	$171,000	$15,000	$13,195
	DRUG	103	107	$9,727,000	$1,732,000	$126,000	$16,194
2013 Total		115	120	$10,822,000	$1,904,000	$142,000	$15,869
2014	BARE	17	17	$1,473,000	$270,000	$20,000	$15,935
	DRUG	91	91	$8,510,000	$1,445,000	$111,000	$15,887
2014 Total		108	108	$9,983,000	$1,716,000	$131,000	$15,894

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Medicaid FFS
Stent Utilization: 2011-2014

Year	Type Stent	Unique Patients	Procedures	Submitted Amt	Allowed Amt	Paid Amt	Average Paid/
2011	BARE	149	151	$857,000	$3,292,000	$2,833,000	$18,764
	DRUG	322	320	$2,151,000	$7,500,000	$6,973,000	$21,793
2011 Total			**471**	**$3,008,000**	**$10,792,000**	**$9,806,000**	
2012	BARE	138	143	$972,000	$3,713,000	$3,127,000	$21,873
	DRUG	279	288	$2,141,000	$6,571,000	$5,989,000	$20,797
2012 Total			**431**	**$3,113,000**	**$10,284,000**	**$9,116,000**	
2013	BARE	85	88	$683,000	$2,072,000	$1,839,000	$20,909
	DRUG	186	190	$1,390,000	$4,224,000	$3,714,000	$19,549
2013 Total			**278**	**$2,073,000**	**$6,296,000**	**$5,553,000**	
2014	BARE	100	100	$658,000	$2,610,000	$1,693,000	$16,934
	DRUG	256	257	$1,673,000	$5,892,000	$5,508,000	$21,435
2014 Total			**357**	**$2,331,000**	**$8,502,000**	**$7,201,000**	

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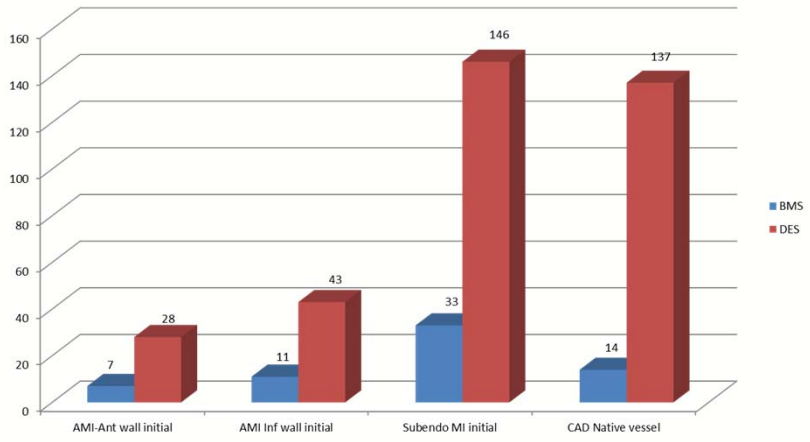
Medicare: Stent Type by Diagnosis



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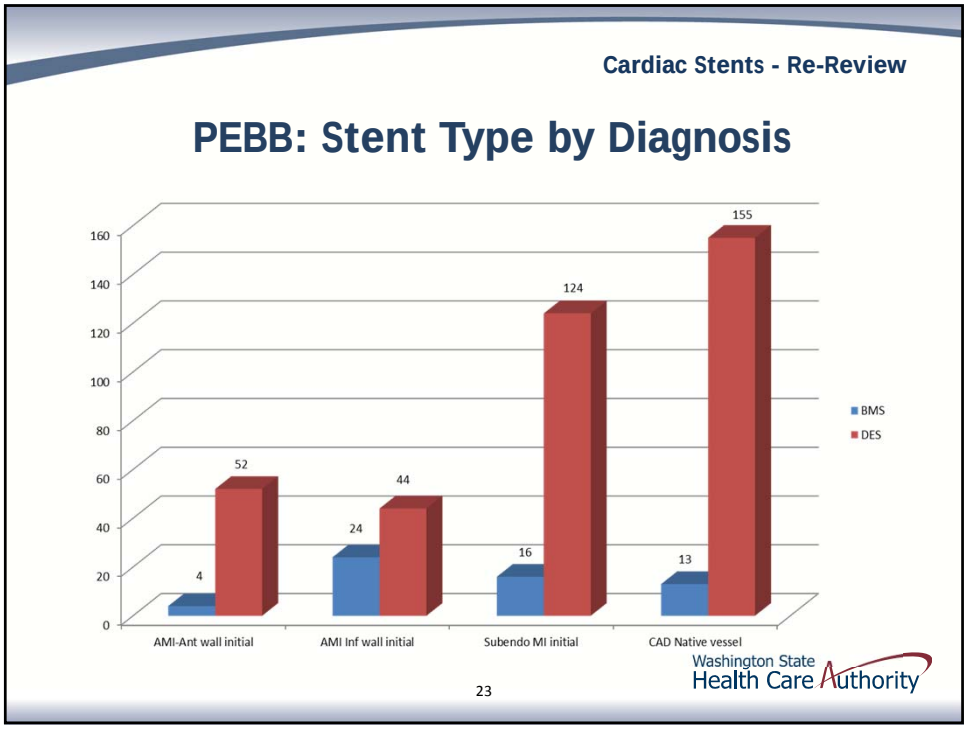
Cardiac Stents - Re-Review
PEBB: Stent Type by Diagnosis
160
140
120
100
80
60
40
20
0
4
52
24
44
16
124
13
155
AMI-Ant wall initial
AMI Inf wall initial
Subendo MI initial
CAD Native vessel
BMS
DES
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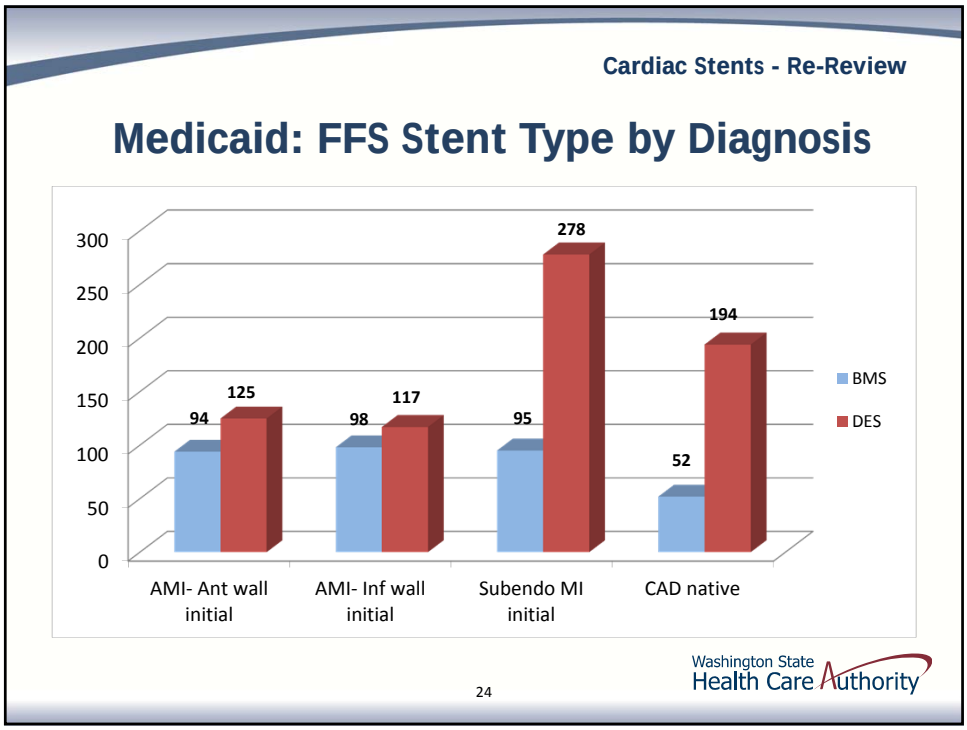
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Medicaid: FFS Stent Type by Diagnosis
300
250
200
150
100
50
0
94
125
98
117
95
278
52
194
AMI- Ant wall initial
AMI- Inf wall initial
Subendo MI initial
CAD native
BMS
DES
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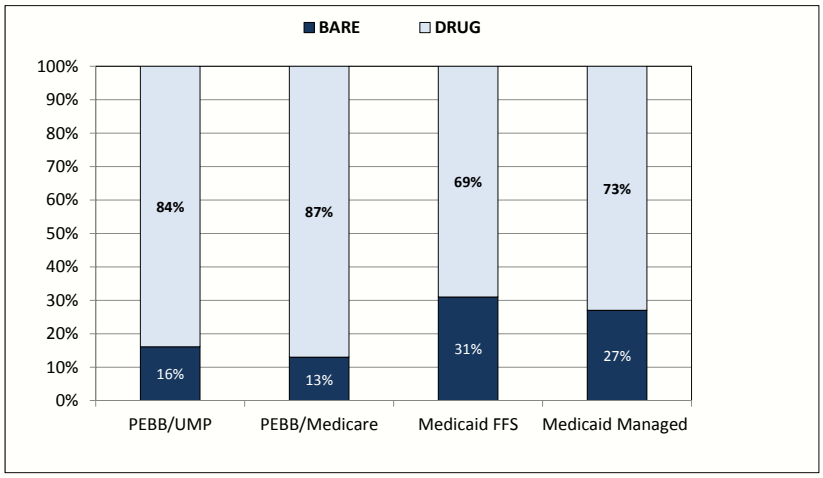
Average Distribution of Bare Metal vs. Drug-Eluting Stents for All Programs 2011-2014



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Agency Medical Director Summary

PCI + Medical Management vs. Medical Management Alone

- Mortality and cardiac mortality similar from 12-120 mo.
- Non-fatal MI- PCI may be better at 120 months
- Revascularization *favors* PCI + Med at 55 months, NNT ~ 10
- Revascularization for patients w/DM favors PCI at 60 months, high quality studies but high heterogeneity a caution
- Safety: Peri-procedural MI is higher in patients treated w/PCI (with and without DM), NNH=35-50
- Cost effective analysis: No cost advantage to PCI, cost of dual platelet therapy and bleeding risks should be considered
- *Professional guidelines for PCI performance should be followed in patients with stable angina CCS class I-III and in asymptomatic patients found to have lesions on angiography*

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Agency Medical Director Summary

New DES vs. BMS

- Mortality
  - No difference in overall, or cardiac mortality
  - Mixed results regarding risk of MI
- Total vessel and lesion revascularization (TVR) & (TLR)
  - Moderate evidence DES better at 12 mo., NNT=20
  - Lower level evidence equal outcome at 24 months
- Safety:
  - Lower rates of restenosis in patients with DM w/ DES
- Cost effectiveness analysis:
  - No difference at 4 years
- *Benefit of DES is with revascularization need: consider underlying risk*

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2009 Determinations (2009)

- **Covered with conditions:**
  - BMS: Covered w/o conditions
  - DES:
    - Stent diameter of 3 mm or less;
    - Length of stent(s) longer than 15 mm in a single vessel
    - Patients with diabetes
    - Stents placed to treat restenosis*
    - Treatment of left main coronary disease

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Agency Recommendations

PCI for patients with Stable CAD:

- **Covered with conditions**:
  - Patients with asymptomatic disease in whom non-invasive testing suggests they are at high risk, AND who are not on maximal medical therapy who have either: 1 or 2 vessel disease w/proximal LAD involvement or 3 vessel disease (no left main)
  - Patients with asymptomatic disease in whom non-invasive testing suggests they are at high risk AND who are on maximal medical therapy and have lesions other than due to chronic total occlusion
  - Patients with CCS Class I-II angina who continue to experience significant symptoms despite maximal medical therapy AND have either single vessel disease of the proximal LAD, 2 vessel disease with proximal LAD involvement or 3 vessel, (without L main), disease

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Agency Recommendations

DES use in patients with stable CAD:

- **Covered with conditions**:

  For patients w/Stable CAD in whom medical treatment fails, DES should only be used when risk of re-stenosis is high, > 20% or medium to high (>10%)

DES use in patients with unstable angina or ACS:

- **Covered**

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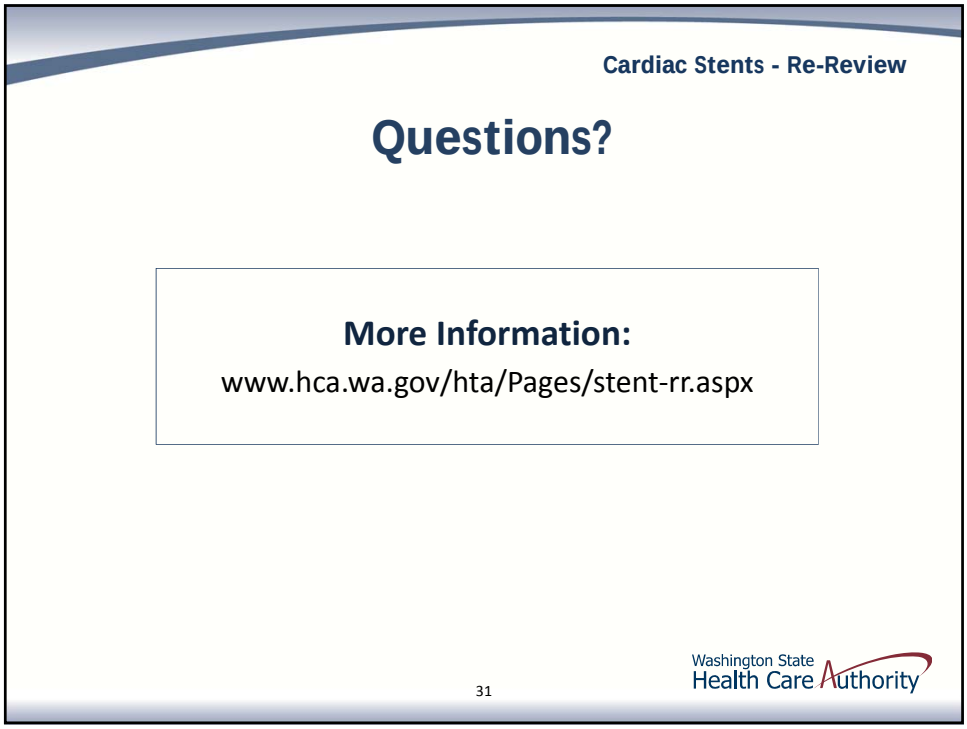
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Questions?
More Information:
www.hca.wa.gov/hta/Pages/stent-rr.aspx
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Health Technology Assessment

Public Comments:

Cardiac Stents – Re-review

	Name
1	Wayne Powell, Society of Cardiovascular Angiography and Interventions (SCAI)

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Health Technology Assessment

Cardiac Stents – Re-review

Clinical Expert

Michael R. Ring, MD, FACC, FSCAI

Interventional Cardiologist, Providence Spokane Cardiology

Quality Director
Providence Spokane Heart Institute

Co-Director Transcatheter Aortic Valve Replacement Program
Providence Sacred Heart Medical Center

Medical Executive Committee
Providence Sacred Heart Medical Center

Vice Chair, Management Committee
Clinical Outcomes Assessment Program (COAP.org)

American College of Cardiology NCDR Public Reporting Advisory Group

Immediate Past Governor
Washington State Chapter, American College of Cardiology

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	X	
2.	Equity interests such as stocks, stock options or other ownership interests.	X	
3.	Status or position as an officer, board member, trustee, owner.	X	
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

Medtronic: Proctor (paid) for CoreValve transcatheter aortic valve

Ab Initio Biotherapeutics (stock holder): Immuno-Oncology drug start-up co-founded by son

Management Committee (unpaid), Clinical Outcomes Assessment Program (COAP)

Immediate past-governor (unpaid), WA Chapter, American College of Cardiology

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		

If yes to #7, provide name and funding Sources: _____

_____

_____

_____

*If you believe that you do not have a conflict, but are concerned that it may appear that you do, you may **attach additional sheets** explaining why you believe that you should not be excluded.*

I certify that I have read and understand this Conflict of Interest form and that the information I have provided is true, complete, and correct as of this date.

X [redacted] 12/29/2015 Michael E. Ring, M.D.

Date *Print Name*

So we may contact you regarding this information, please provide the following:

Email Address: michael.ring@providence.org

Phone Number: cell: (509) 209-6895

CURRICULUM VITAE
Michael E. Ring, M.D., FACC, FSCAI

CONTACT AND PERSONAL INFORMATION:
Date and place of birth: October 11, 1956; Haifa, Israel
Work address: Providence Spokane Cardiology
122 W. 7th Ave., Suite 450
Spokane Washington, 99204
Work/fax/cell phone: (509) 455-8820; fax: (509) 838-4978; cell: (509) 209-6895
Email: michael.ring@providence.org
Home address: 12604 S. Flying Goose Lane, Spokane, WA 99224
Home phone: (509) 448-1919
Spouse's name: Beth A. Ring Children: Arielle, Aaron, Lauren

CURRENT POSITIONS:

- Interventional Cardiologist, Providence Spokane Cardiology; January 2012–present:
- Quality Director, Providence Spokane Heart Institute
- Co-Director Transcatheter Aortic Valve Replacement Program, Providence Sacred Heart Medical Center
- Medical Executive Committee, Providence Sacred Heart Medical Center
- Vice Chair, Management Committee, Clinical Outcomes Assessment Program (COAP.org)
- American College of Cardiology NCDR Public Reporting Advisory Group
- Immediate Past Governor, Washington State Chapter, American College of Cardiology

PREVIOUS EMPLOYMENT POSITIONS:

June 1990-Dec. 2011 (excluding 4/05-5/06): Cardiologist; Heart Clinics Northwest; Spokane, WA
April 2005-May 2006: Asst. Director, Cardiac Cath Lab, St Francis Medical Center, Hartford, CT
June 1999-March 2005: Director, Cardiac Catheterization Lab; Sacred Heart Med.Ctr; Spokane WA
May 2006-Dec. 2012: Medical Director, Cardiac Service Line and Cardiac Catheterization Lab; Providence Sacred Heart Medical Center, Spokane, WA

EDUCATION (DEGREE):

Sept. 1974 - June 1977	University of California, Los Angeles, CA (A.B. Psychobiology; Magna Cum Laude)
June 1977 - June 1978	U.C.L.A. Graduate School; Department of Pharmacology
August 1978 - May 1982	Vanderbilt Medical School, Nashville, TN (Medical Degree)

POSTGRADUATE TRAINING:

July 1982 - June 1985	Intern/Resident, Department of Internal Medicine University of Arizona School of Medicine
July 1985 - June 1988	Fellow, Section of Cardiology University of Arizona School of Medicine
Sept.1988 - June 1989	Interventional Fellow, Section of Cardiology Boston University School of Medicine

ACADEMIC POSITIONS:

Sept.1988 - June 1989	Clinical Instructor, Section of Cardiology Boston University School of Medicine
July 1989 - June 1990	Assistant Professor of Medicine, Division of Cardiology St. Louis University School of Medicine
Dec. 1990 - present	Clinical Assistant Professor of Medicine, Division of Cardiology University of Washington
April 2005 - May 2006	Clinical Assistant Professor of Medicine, Dept. of Cardiology University of Connecticut

AWARDS AND ACADEMIC HONORS:

California Regents Fellowship Recipient	1977
Vanderbilt-Karolinska Medical Exchange Program	1980
Research Fellow of the Massachusetts A.H.A.	1988
Spokane's "Best Doctor" for Cardiology	2003-2015

CERTIFICATIONS:

National Board of Medical Examiners	1983
American Board of Internal Medicine, Diplomate	1985 (lifetime certification)
Subspecialty of Cardiovascular Diseases, Diplomate	1989 (lifetime certification)
Subspecialty of Interventional Cardiology, Diplomate	2000, recertified 2010

ACTIVE LICENSURE:

Washington, Idaho

CLINICAL INTERESTS:

Interventional Cardiology including transcatheter aortic valve implantation, complex coronary interventions and peripheral vascular disease/interventions (excluding carotid), hyperlipidemia.

PROFESSIONAL ORGANIZATIONS:

American College of Cardiology, Fellow; Governor Washington ACC Chapter 2011 – 2014
Society for Cardiovascular Angiography and Interventions, Fellow
Spokane County Medical Association; President 1997
Washington State Medical Association
Spokane Society of Internal Medicine; President 2007

PROFESSIONAL SERVICE:

Spokane Co. Medical Society: President 1997; Board of Trustees/Executive Committee 1993-98
Spokane Physician Hospital Community Organization: Board of Directors 1995-1996
American Heart Association, Eastern Washington 1998: Board of Directors
Medical Executive Committee, Providence Sacred Heart Medical Center; 2006 - present
Spokane Society of Internal Medicine; President 2008
Clinical Outcomes Assessment Program; Management Committee 2008 – present
Washington State Health Care Authority Health Technology Assessment on Drug-Eluting Stents; Served as technical consultant and chairman of the ad hoc advisory committee; 2009
American College of Cardiology, Washington State Chapter; Governor-elect Nov. 2009-April 2011 Served as Governor April 2011 – April 2014.
Institute for Systems Medicine, Scientific Advisory Board, Chairman; 2010-2012
American College of Cardiology PINNACLE Steering Committee; 2010-2011.
American College of Cardiology PINNACLE Network Work Group; 2010-2012.
American College of Cardiology NCDR Public Reporting Advisory Group; 2013-2016.

PAPERS REVIEWED FOR:

American Heart Journal, Chest, Journal of the American College of Cardiology, Life Sciences

American College of Cardiology Official Reviewer:

1. Holmes, DR, Dehmer, GJ, Kaul, S, et. al. Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning". A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. J Am Coll Cardiol 56:321-341, 2010.

2. Harold JG, Bass TA, Bashore TM, et. al. ACCF/AHA/SCAI 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures: A Report of the American College of Cardiology Foundation/American Heart Association. J Am Coll Cardiol 2013.

RESEARCH SUPPORT:

1985-86: Effects of Diltiazem and Nifedipine on Platelet Function; American Heart Association, Arizona Affiliate; Principal Investigator

1986-88: Investigations of Platelet Ionized Cytoplasmic Calcium; American Heart Association, Arizona Affiliate; Principal Investigator

1987-88: Effect of the Calcium Antagonist Nimodipine on Platelet Activity and Fibrin Metabolism in Patients with Acute Stroke; Flinn Foundation; Co-Investigator

1987-88: The Measurement of Molecular Markers of Fibrin Metabolism in Patients with Acute Myocardial Infarction Treated with Tissue Type Plasminogen Activator; Burroughs Wellcome Co.; Principal Investigator

1988-89: Radiofrequency Angioplasty (Research Fellowship); American Heart Association, Massachusetts Affiliate; Sponsor: David Faxon, MD

2007-2010: Proposal to Study the Impact of Drug Eluting Stents on Intermediate Term Survival, Coronary Revascularization Rates and Economic Costs; Heart Institution (of Spokane) Foundation; Principal Investigator

MEDICAL SCHOOL COURSES:

University of Washington 2nd Year Medical School Spokane WAMI course lecturer "Ischemic Heart Disease", 2013 – present.

SELECTED INVITED LECTURES/CME EVENTS:

1. Providence St. Mary Medical Center Grand Rounds, Walla Walla, WA. May 2001. "*Acute Coronary Syndrome"*.
2. Heart Institution Cardiovascular Update Conference, Spokane, WA. October 2004. *"Update on Percutaneous Cardiac Interventions".*
3. Sacred Heart Medical Center Cardiac Grand Rounds, Spokane, WA. November 2006. *"Drug-Eluting Stents: A Big Mistake?"*
4. Sacred Heart Medical Center Cardiac Grand Rounds, Spokane, WA. September, 2007. *"Regional Variations In Cardiovascular Care – Results from the Dartmouth Atlas",*
5. St. Joseph Regional Medical Center, Lewiston, ID. January 2008. *"Cardiac Level-1 Program A Regionalized Approach to ST Elevation MI"*.
6. Sacred Heart Medical Center Cardiac Grand Rounds, Spokane, WA, March 2008. *"Current Status of Drug-Eluting Stents including a Report on 2 Year Safety & Revascularization Outcomes in >6000 Coronary Stent Patients at SHMC".*
7. 21st Annual Northwest Regional Rural Health Conference, Spokane, WA; March 2008. "*Rural Cardiac Program Offers Lifesaving Speed".*
8. North Puget Sound Region Level 1 Cardiac Program Kick-off Conference, Everett, WA; June 2008. *"Cardiac Level 1 - A Rural-Urban Partnership for Emergency Cardiac Care"*
9. Excellence in Emergency Cardiac Care (Regional STEMI Conference), Olympia, WA; June 2009. "*Cardiac Level 1 Protocol – Time is Muscle*".
10. Cardiovascular Update 2009, Spokane, WA; October 2009. *"Alcohol and the Cardiovascular System; The Good and the Bad".*
11. Washington State Chapter American College of Cardiology STEMI Forum, Seattle, WA; October 2009. *'Regional STEMI Systems of Care: Spokane Experience".*
12. Riding the Waves of Primary Care Conference, Maui, HI; November 2009. *"Alcohol and the Cardiovascular System, Acute Coronary Syndrome and Coronary Revascularization; When and How".*
13. COAP PCI Mortality Forum, Seattle, WA; March 2010. "*How to Reduce Your Hospital's Mortality: A Real Life Example".*
14. Transcatheter Cardiovascular Therapeutics Conference, Washington DC; September 2010; "*State-Based Decisions About DES Reimbursement; Where are the Minefields*"..
15. WSU Spokane Chancellor's Research Breakfast Series, Spokane, WA; April 2011, "*Health Outcomes after Coronary Artery Stenting".*
16. A Case for Cases: Updating Interventional Cardiology from the Cath Lab, Swedish Hospital,

Seattle, WA; October 2011. "*Transcatheter Treatment of an Extreme Risk Patient with Aortic Stenosis*".

17. Cardiovascular Update 2012, Providence Alaska Medical Center, Anchorage, AK; February 2012; "*Update on Percutaneous Aortic Valve Replacement*".
18. Current Trends in Cardiovascular Disease XIV: A Primary Care Approach. Spokane, WA, April, 2012. "*Transcatheter Aortic Valve Replacement"*.
19. Providence St. Mary Medical Center Grand Rounds, Walla Walla, WA. November 2013. "*Transcatheter Aortic Valve Replacement"*.

CME PROGRAM LEADERSHIP:

Heart Institute of Spokane Cardiovascular Update; Program Chair 1994, 2004
Spokane Society of Internal Medicine Annual Update; Program Chair 2008
Providence Sacred Heart Medical Center CME Committee 2006 – 2013
Transcatheter Cardiovascular Therapeutics 2010 Conference – Faculty
American College of Cardiology Scientific Sessions 2013 – Poster Session Moderator

PRESENT/PAST CONSULTANT/ADVISORY/PROCTORING APPOINTMENTS:

Boston Scientific Corporation, Medical Advisory Board
Abbott Vascular, Scientific Advisory Board
Phillips Interventional Cardiology Medical Advisory Board
Medtronic AVE, Inc., Proctor for CoreValve Transcatheter Aortic Valve Device

CLINICAL RESEARCH STUDIES:

1. CoreValve Study: CoreValve Continued Access Trial; Sponsored by Medtronic; Co-Principal Investigator, 2011.
2. SYMPLICITY HTN-3: Renal Denervation for Treatment of Resistive Hypertension; Sponsored by Medtronic; Co-Principal Investigator, 2011.
3. CoreValve Study: CoreValve United States Pivotal Trial; Sponsored by Medtronic; Co-Principal Investigator, 2010.
4. REWARDS-TLX: Registry Experience at the Washington Hospital Center, DES-Taxus-Liberte vs Xience V. Sponsored by Cardiovascular Research Center, Washington DC; Principal Investigator, 2010.
5. VERDICT: Vascular Evaluation for Revascularization: Defining the Indications for Coronary Therapy. A Prospective, Global, Multicenter Study to Determine the Correlation Between Fractional Flow Reserve (FFR) and Intravascular Ultrasound with Virtual Histology (VH-IVUS) in Patients with Intermediate Coronary Lesions; Sponsored by Volcano Corp., Principal Investigator, 2010.
6. SOLID-TIMI 52: A Clinical Outcomes Study of Darapladib versus Placebo in Subjects Following Acute Coronary Syndrome to Compare the Incidence of Major Adverse Cardiovascular Events (MACE); Sponsored by GlaxoSmithKline; Principal Investigator, 2010.
7. SPIRIT PRIME Clinical Trial: A Clinical Evaluation of the XIENCE PRIME ™ and XIENCE PRIME ™ Everolimus Eluting Coronary Stent System; Sponsored by Abbott Vascular Inc.; Principal Investigator, 2009.
8. RADAR: A Randomized, Partially-Blinded, Multi-Center, Active Controlled, Dose Ranging Study Assessing the Safety, Efficacy, and Pharmacodynamics of the REG1 Anticoagulation System Compared to Unfractionated Heparin or Low Molecular Heparin in Subjects with Acute Coronary Syndrome; Phase 2b study; Sponsored by Regado Biosciences, Principal Investigator, 2009.
9. PROMUS PLATINUM Clinical Trial: A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System (PROMUS Element™) for the Treatment of up to two De Novo Coronary Artery Lesions; Sponsored by Boston Scientific Corp.; Principal Investigator 2009.
10. ENGAGE - AF TIMI – 48: Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation; Sponsored by Diiachi Sankyo Inc.; Principal Investigator, 2009.

11. TRA 2P – TIMI 50 Study: A Multicenter, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard Care in Subjects with a History of Atherosclerotic Disease: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events; Sponsored by Schering-Plough, Principal Investigator 2008.
12. TAXUS PERSEUS: A prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System for the Treatment of De Novo Coronary Artery Lesions; Sponsored by Boston Scientific Corp.; Principal Investigator 2007.
13. TAXUS PERSEUS Small Vessel: A prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System for the Treatment of De Novo Coronary Artery Lesions in Small Vessels; Sponsored by Boston Scientific Corp.; Principal Investigator 2007.
14. CORAL Study: Cardiovascular Outcomes in Renal Atherosclerotic Lesions. Sponsored by National Institute of Health; Co-Investigator 2006.
15. TAXUS ATLAS Study: Elective Stenting of Coronary Arteries with the TAXUS Liberte System; Sponsored by Boston Scientific/Scimed, Inc.; Principal Investigator 2004.
16. ENDEAVOR III: A Randomized Controlled Trial of the Medtronic Endeavor Drug (ABT-578) Eluting Coronary Stent System versus the Cypher Sirolimus-Eluting Coronary Stent System in *De Novo* Native Coronary Artery Lesions. Sponsored by Medtronic AVE; Principal Investigator 2004.
17. Renaissance Study: A Prospective, Multi-Center, Single-Arm study Evaluating the Express Renal Premounted Stent System in the Treatment of Atherosclerotic Lesions in the Aortorenal Ostium; Sponsored by Boston Scientific/Scimed, Inc.; Sub-Investigator 2004.
18. AMEthyst Study: The Assessment of the Medtronic AVE Interceptor Saphenous Vein Graft Filter System; Sponsored by Medtronic AVE; Principal Investigator 2004.
19. Angiogenesis Protocol: A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Patients with Stable Angina; Sponsored by Berlix Laboratories; Principal Investigator 2003.
20. ELECT Trial: Elective Stenting of Coronary Arteries on Liberte System; Sponsored by Boston Scientific/Scimed, Inc.; Principal Investigator 2003.
21. The Clinical Evaluation of the Medtronic AVE Micro-Driver Coronary Stent System in the Treatment of Single *De Novo* Lesions in Small Diameter Coronary Arteries; sponsored by Medtronic AVE; Principal Investigator 2003.
22. CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; Sponsored by Sanofi-Synthelab and Bristol-Myers Squibb; Principal Investigator 2003.
23. SYMBIOT III: A Prospective Randomized Trial Evaluating the SYMBIOT III Covered Stent System In Saphenous Vein Grafts; Sponsored by Boston Scientific/Scimed, Inc.; Principal Investigator 2002.
24. The Clinical Evaluation of the Medtronic AVE S8 with Discrete Technology Coronary Stent System in *De Novo* and Restenotic Lesions; Sponsored by Medtronic AVE; Principal Investigator 2002
25. DELIVER Clinical Trial: Prospective, Randomized, Single-Blinded, Parallel-Group, Multi-Center, Clinical Evaluation of the RX Achieve Drug Coated Stent System in the Treatment of Patients with *De Novo* Native Coronary Artery Lesions; Sponsored by Guidant Corp.; Principal Investigator; 2002.
26. STEP-AMI: An Open Study with Blinded End-point Assessment to Assess the Safety, Tolerability and the Effect on Coronary Artery Patency of Intravenous AR-C69931MX as both Monotherapy and Adjunct to Activase in Patients with ST-elevation Myocardial Infarction; Sponsored by AstraZeneca LP; Principal Investigator; 2000.
27. TECBEST: A Multi-center, Randomized Study of the Treatment for Saphenous Vein Graft Lesions Using the TEC System for Extraction Athrectomy followed by Stenting with and without the Adjunctive use of GP IIb/IIIa Inhibitor; Sponsored by InterVentional Technologies; Principal Investigator 1999.
28. CAPRIE Study: The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events;

Sponsored by Sanofi and Bristol-Myers Squibb; Principal Investigator 1992.

ABSTRACTS:

1. Gerkins JF, Robertson D, Ring ME, Oates JA: Evidence that alpha-methylepinephrine is an antihypertensive metabolite of alpha-methyldopa. Proceedings of the World Conference on Clinical Pharmacology and Therapeutics, London, 3/80.
2. Potter WZ, Mellstrom B, Ring M, von Bahr C, Sj"qvist F: Metabolism of tricyclic antidepressants in human liver microsomes. Clinical Pharmacology and Therapeutics 29: 273, 1981.
3. Ring ME, Corrigan JJ, Fenster PE: Antiplatelet effects of oral diltiazem, propranolol and their combination. Clinical Research 35: 116A, 1987 (Western Section of the American Federation of Clinical Research, 2/87).
4. Ring ME, Butman SM, Bruck DC, Joyner S, Feinberg W, Corrigan JJ: Persistent fibrinolysis after cessation of tissue type plasminogen activator. Scientific Conference on Myocardial Ischemia and Reperfusion, American Heart Association, 3/87.
5. Ring ME, Huang SK, Gorman G, Graham AR: Determinants of impedance rise during catheter ablation of myocardium with radiofrequency energy. Circulation 76: IV-406, 1987 (60th Scientific Sessions of the American Heart Association, 11/87).
6. Ring ME, Huang SK, Graham AR, Gorman G, Bharati S, Lev M: Transseptal catheter ablation with radiofrequency energy. Circulation 76: IV-279, 1987 (60th Scientific Sessions of the American Heart Association, 11/87).
7. Ring ME, Butman SM, Bruck D, Joyner S, Feinberg WM, Corrigan JJ: Monitoring fibrin metabolism during tissue plasminogen activator therapy for myocardial infarction: Important clinical implications. Circulation 76: IV-100, 1987 (60th Scientific Sessions of the American Heart Association, 11/87).
8. Feinberg WM, Bruck DC, Ring ME, Corrigan JJ: Markers of thrombosis and fibrinolysis after acute stroke. Stroke 19: 133, 1988 (13th International Joint Conference on Stroke and Cerebral Circulation, 2/88).
9. Huang SKS, Lee MA, Graham AR, Ring ME, Gorman GD: Comparison of catheter ablation using radiofrequency versus direct-current energy -biophysical, electrophysiological and pathological observations. Circulation 78: II-307, 1988 (61st Scientific Sessions of the American Heart Association, 11/88).
10. Ring ME, Feinberg WM, Bruck DC, Smith RG, Copeland JG: Thrombus formation in recipients of the total artificial heart. Circulation 78: II-623, 1988, (61st Scientific Sessions of the American Heart Association, 11/88).
11. Ring ME, Ruocco NA, Holubkov R, Jacobs AK, Detre KM, Faxon DP and Participating Investigators: Favorable long term follow-up of patients having PTCA for chronic total occlusions: Report from the 1985-6 NHLBI PTCA Registry. Circulation 80: II-481, 1989, (62nd Scientific Sessions of the American Heart Association, 11/89).
12. Ring ME, Vecchione JJ, Fiore LD, Ruocco NA, Jacobs AK, Deykin D, Faxon DP: Assessment of intracoronary fibrin metabolism after coronary angioplasty in man. Journal of the American College of Cardiology 15 (suppl A): 154A, 1990, (39th Scientific Sessions of the American College of Cardiology, 3/89).
13. Kern MJ, Talley JD, Deligonul U, Serota H, Aguirre F, Gudipati C, Ring ME, Joseph A, Yussman ZA: Preliminary experience with 5F angiographic catheter as a guiding catheter for coronary angioplasty. Catheterization and Cardiovascular Diagnosis 19:295, 1990 (Scientific Sessions of the Society of Cardiac Angiography and Interventions).
14. Kern MJ, Deligonul U, Serota H, Aguirre F, Ring ME, Gudipati C: Equivalency of intravenous adenosine and papaverine for determination of coronary flow velocity reserve in patients. (XIIth Congress of the European Society of Cardiology, 1990).
15. Ring ME, Holubkov AL, Jacobs AK, Holubkov R, Ruocco NA, Detre KM, Ryan TJ, Faxon DP: The influence of coronary collaterals on the long term outcome of patients after unsuccessful PTCA a report from the 1985–1986, NHLBI PTCA registry. Journal of the American College of Cardiology; 17(2), 1991. (40th Scientific Sessions of the American College of Cardiology).
16. 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).

17. Ring ME, Daratha KB, Parrish PR, Dominik DA, Short RA, Tuttle KR: Comparison of Long Term Outcomes After Coronary Stenting in the Bare Metal Stent and Drug Eluting Stent Eras. Am J Cardiol 2009; 104:156-157D (Transcatheter Cardiovascular Therapeutics, 2009).
18. Kereiakes DJ, Cannon LA, Mooney M, Lee TC, Ring M, Underwood P, Dawkins KD, The PERSEUS Small Vessel Trial of the Novel Thin Strut Platinum-Chromium TAXUS Element Paclitaxel-Eluting Stent (submitted to 2010 ACC Scientific Sessions)
19. Ring ME, Jin R, Wu Y, Grunkemeier GL: Use of a Bare Metal Stent or Balloon Angioplasty Alone in Contemporary Percutaneous Coronary Interventional Practice is an Independent Predictor of In-Hospital Mortality. Journal of the American College of Cardiology 57 (no. 14 suppl. A): 127, 2011 (Scientific Sessions of the American College of Cardiology, 2011).
20. Waksman R, Ghali M, Goodroe R, Ryan T, Turco M, Ring M, McGarry T, Dobies D, Shammas N, Steinberg D, Swymelar S, Torguson R: REWARDS TLX: Registry Experience at Washington Heart Center: TAXUS Liberte vs. Xience V. Journal of the American College of Cardiology 57 (no. 14 suppl. A): 120, 2011 (Scientific Sessions of the American College of Cardiology, 2011).
21. Daratha KB, Ring ME, Himmelfarb J, Tuttle KR: Risk of Mortality and Re-Hospitalization among Patients with Acute Myocardial Infarction and Acute Kidney Injury. J Am Soc Nephrol 23: 119A, 2012 (American Society of Nephrology, Kidney Week; 2012).

PUBLICATIONS:

1. Ellison G, Ring M, Ross D, Axelrod B: Cumulative alterations in rat behavior during continuous administration of LSD or mescaline: absence of tolerance? Biological Psychiatry 15: 95-102, 1980.
2. Goldberg MR, Tung CS, Ring ME, Oates JA, Gerkins JF, Robertson D: Evidence that alpha-methylepinephrine is an antihypertensive metabolite of alpha-methyldopa. Clinical and Experimental Hypertension 4: 595-604, 1982.
3. Ring ME, Fenster PE: Exercise induced ST segment electrical alternans. American Heart Journal 111: 1009-1011, 1986.
4. Ring ME, Martin GV, Fenster PE: Clinically significant antiplatelet effects of calcium channel blockers. Journal of Clinical Pharmacology 26: 719-720, 1986.
5. Ring ME, Bressler R: Persistent chest pain in a 52 year old woman. Primary Cardiology 12(9): 80-88, 1986.
6. Ring ME, Corrigan JJ, Fenster PE: Effects of oral diltiazem on platelet function: alone and in combination with "low dose" aspirin. Thrombosis Research 44: 391-400, 1986.
7. Ring ME, Butman SM: Cocaine and acute myocardial infarction. Drug Therapy 16(9): 117-125, 1986.
8. Ring ME, Huang SK: Spontaneous termination from prolonged ventricular fibrillation. American Heart Journal 113: 1226-1228, 1987.
9. Ring ME, Corrigan JJ, Fenster PE: Antiplatelet effects of oral diltiazem, propranolol and their combination. British Journal of Clinical Pharmacology 24: 615-620, 1987.
10. Ring ME, Butman SM, Bruck DC, Feinberg WM, Corrigan JJ. Molecular markers of fibrin metabolism in acute myocardial infarction during reperfusion with tissue-type plasminogen activator and coronary angioplasty: Potential clinical implications. Thrombosis and Haemostasis 60: 428-433, 1988.
11. Ring ME, Feinberg WM, Bruck DC, Butman SM. Platelet activity during acute myocardial infarction treated with tissue plasminogen activator. Thrombosis Research 51: 331-334, 1988.
12. Ring ME, Huang SK, Gorman G, Graham AR. Determinants of impedance rise during catheter ablation of myocardium with radiofrequency energy. PACE 12: 1502-1513, 1989.
13. Ring ME, Feinberg WM, Levinson MM, Bruck DC, Smith RG, Icenogle T, Copeland JG. Platelet and fibrin metabolism in recipients of the Jarvik-7 total artificial heart. Journal of Heart Transplantation 8: 225-232, 1989.

14. Feinberg WM, Bruck DC, Ring ME, Corrigan JJ. Hemostatic markers in acute stroke. Stroke 20: 592-597, 1989.
15. Ring ME, Huang SK, Graham AR, Gorman G, Bharati S, Lev M. Catheter ablation of the ventricular septum with radiofrequency energy. American Heart Journal 117: 1233-1240, 1989.
16. Butman SM, Ring ME. Risk of acute myocardial infarction after donor plasmapheresis. Journal of Invasive Cardiology 1:181-185, 1989.
17. Ring ME, Kern MJ, Genovely H, Serota H, Vandormael H: Attenuation of pulsus alternans during coronary angiography. Catheterization and Cardiovascular Diagnosis 20: 193-195, 1990.
18. Ring ME, Vecchione JJ, Fiore LD, Ruocco NA, Jacobs AK, Deykin D, Ryan TJ, Faxon DP: Detection of intracoronary fibrin degradation following balloon angioplasty. American Journal of Cardiology 67: 1330-1334, 1991.
19. Huang SKS, Graham AR, Lee MA, Ring ME, Gorman GD, Schiffman R: Comparison of catheter ablation using radiofrequency versus direct current energy - Biophysical, electro-physiological and pathological observations. Journal of the American College of Cardiology 18: 1091-1097, 1991.
20. Kern MJ, Deligonul U, Serota H, Gudipati C, Ring ME, Aguirre F: Acute combined aortic and mitral insufficiency during balloon catheter valvuloplasty for a third recurrence of critical aortic stenosis. American Heart Journal 120: 1007-1011, 1990.
21. Kern MJ, Tatineni S, Gudipati C, Aguirre F, Ring ME, Serota H, Deligonul U: Regional coronary blood flow velocity and vasodilator reserve in patients with angiographically normal coronary arteries. Coronary Artery Disease. 1: 579-590, 1990.
22. Kern MJ, Talley JD, Deligonol U, Serota H, Aguirre F, Gudipati C, Ring M, Joseph A, Yussman ZA, Kulick D, et al. Preliminary experience with 5 and 6 French diagnostic catheters as guiding catheters for coronary angioplasty. Catheterization and Cardiovascular Disease 22: 60-63, 1991.
23. Ruocco NA, Ring ME, Holubkov R, Jacobs AK, Detre KM, Faxon DP: Acute and long-term outcome of coronary angioplasty for chronic total occlusions: The National Heart, Lung, and Blood Institute 1985-1986 Percutaneous Transluminal Coronary Angioplasty Registry. American Journal of Cardiology 69: 69-76, 1992.
24. Cannon LA, Kereiakes DJ, Mann T; Popma JJ, Mooney MR, Mishkel GJ, Lee TC, MD, Wilson BH, Stuckey TD, Orlow S, McGarry T, Ring ME, Kellett MA, Underwood P, Dawkins KD: TAXUS PERSEUS Small Vessel: A Prospective Evaluation in a non-Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System for the Treatment of *De Novo* Coronary Artery Lesions in Small Vessels. EuroIntervention 6: 920-927, 2011.
25. Daratha KD, Short RA, Corbett C, Ring ME, Alicic R, Choka R, Tuttle KR, Risks of Hospital Readmission and Death in Patients with Kidney Disease. Clinical Journal of the American Society of Nephrology 7: 409-416, 2012.
26. Povsic TJ, Vavalle JP, Aberle LG, Kasprzak JD, Cohen MG, Mehran R, Bode C, Buller CE, s Montalescot G, Cornel JH, Rynkiewicz A, Ring ME, Zeymer U, Natarajan M, Delarche N, Zelenkofske SL, Becker RC, Alexander JH on behalf of the RADAR Investigators: A Randomized, Partially Blinded, Multicenter, Active-Controlled, Phase 2b, Dose-Ranging Study Assessing the Safety, Efficacy, and Pharmacodynamics of the REG1 Anticoagulation System in Patients with Acute Coronary Syndromes: Results of the RADAR Phase 2b Trial. Eur Heart Journal; 2012 published on line August 2, 2012.
27. Waksman R, Ghali M, Goodroe R, Ryan T, Turco M, Ring M, McGarry T, Dobies D, Shammas N, Steinberg D, Swymelar S, Kaneshige K, Torguson R. Percutaneous Coronary Intervention With Second-Generation Paclitaxel-Eluting Stents Versus Everolimus-Eluting Stents in United States Contemporary Practice (REWARDS TLX Trial). Am J Cardiol 110: 1119-1124, 2012.
28. De Marchena E, Mesa J, Pomenti S, Marin y Kall C, Marinic X, Yahagi K, Ladich E, Kutz R, Aga Y, Ragosta M, Chawla A, Ring ME, Virmani R. Thrombus Formation Following Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv 8:728-739, 2015.

29. Dehmer GJ, Jennings J, Madden RA, Malenka D, Masoudi FA, MD, McKay C, Ness DL, Rao SV, Resnic FS, MD, Ring ME, Rumsfeld J, Shelton ME, Simanowith, M, Slattery L, Weintraub, W, Lovett, A, RN, Normand, S-L. The National Cardiovascular Data Registry Voluntary Public Reporting Program: An Interim Report from the National Cardiovascular Data Registry Public Reporting Advisory Group. J Am Coll Cardiol (in press).

BOOK CHAPTERS:

"Interventional Techniques", "High Risk Cardiac Catheterization", and "Special Techniques" in Cardiac Catheterization Handbook, Kern MJ ed., Mosby Press, 1991.

Coronary Artery Stenting: Re-Review

Presentation to

Washington State Health Care Authority

Health Technology Clinical Committee

Andrea C. Skelly, PhD, MPH

January 15, 2016

Report prepared by:
Andrea C. Skelly, PhD, MPH
Robin E. Hashimoto, PhD
Erika D. Brodt, BS

spectrumresearch

1

Update to 2009 HTA

2009 HTA

- Compared DES with BMS
- Majority of studies focused on first generation DES.

Since the publication of that report:

- Studies evaluating newer (2nd generation) DES had been published suggesting improved efficacy and safety with the use of newer DES.

An update was commissioned to evaluate:

- New evidence on FDA approved newer generation DES vs. BMS
- The efficacy, safety and cost-effectiveness of stenting plus medical therapy versus medical therapy alone in patients with stable CAD

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2

Background

Coronary artery disease (CAD); Ischemic Heart Disease (IHD)

- Single leading cause of death in U.S. (1 in 7 deaths in 2011)
- 2014, second most common cause of death in Washington
- ~635,000 Americans have new MI annually; ~300,000 have recurrent MI
- Estimated direct and indirect costs in 2010, $204.4 billion
- CAD/IHD: chronic, spans decades; typically cycles through clinically defined phases: asymptomatic, stable angina, accelerating angina and acute coronary syndrome; progression may not be linear (Fihn 2012 Guideline)
- Atherosclerosis: plaque builds on artery walls; may obstruct the vessel preventing cardiac muscle from receiving blood, oxygen; disruption of stable plaque may cause bleeding/thrombus formation, increase obstruction and result in unstable angina and MI.

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3

Background

Chest Pain: most common symptom of obstructive CAD:

Typical angina (definite)	**1) Substernal chest discomfort (can radiate) ; characteristic quality and duration (minutes) 2) provoked by exertion or emotional stress 3) relieved by rest or nitroglycerin**
Atypical (probable)	**Meets 2 of the above**
Noncardiac	**Meets 1 or none of the above**

- Patient history used to categorize: stable or unstable angina
- **Stable angina**
  - Chest discomfort 1) presenting in a predictable pattern, 2) brought on by physical or mental stress 3) subsides with rest or angina medications (King 2007 guideline)
  - Associated with stenosis, without plaque disruption or plaque-associated thrombosis

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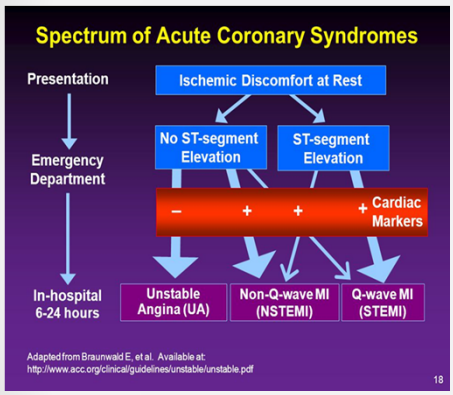
4

Canadian Cardiovascular Society (CCS) Classification of Angina

Class	Clinical Findings	Angina may be induced
Class I	No limitations of ordinary activity	• With strenuous, rapid, or prolonged exertion • Ordinary physical activity, such as walking or climbing stairs, does not cause angina.
Class II	Some limitations of ordinary activity	• Rapidly walking or climbing stairs; walking uphill; • Walking >2 blocks on level surface or > 1 flight of stairs at normal pace under normal conditions • Walking or climbing stairs after meals, in cold, in wind, within the first few hours after awakening
Class III	Significant (marked) limitations of normal physical activity	• Walking 1-2 level blocks; and • Climbing 1 flight of stairs under normal conditions and at normal pace
Class IV	Inability to carry on any normal physical activity without discomfort.	• Angina may occur while at rest

5

Acute Coronary Syndromes (ACS): Spectrum of conditions compatible with acute myocardial ischemia and/or infarction due to abrupt reduction in coronary flow



- **Unstable angina (UA)** = new onset (w/in 2 months) of ≥ CCS III, increasing (frequency, intensity, duration) or at rest, usually prolonged (>20 min)
  - UA subdivisions based on short-term risk of death, nonfatal MI
  - Low short-term risk: normal, unchanged ECG, normal cardiac markers, consider comparable to stable angina patients
  - Frequently associated with plaque disruption, nonocclusive plaque-associated thrombus, may have associated thromboemboli; cardiac biomarkers are negative
- **NSTEMI: Non-ST elevation MI**
- **STEMI: ST-elevation MI**

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6

Overview: Diagnosis and Treatment of CAD

Diagnosis

- Noninvasive testing (including stress /functional testing)
- Invasive coronary angiography (ICA)

Treatment

- Medical therapy (optimal MT, guideline directed MT)
  - Lifestyle, education, pharmacological
  - All CAD patients
- Revascularization (in addition to GDMT)
  - PCI (stenting)
  - CABG (not included in this review)

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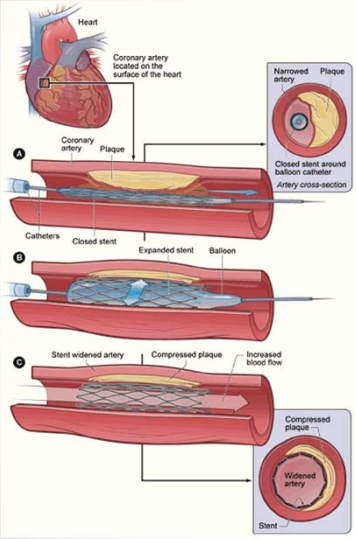
Stent placement in coronary artery disease



- Stents 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

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Coronary stents – Historical development

- PTCA (balloon angioplasty), first described in 1977. It initially decreased lumen narrowing, but injury to the vessel walls led to acute closure (6%-8%) and restenosis (30%-50%).
- Bare metal stents (BMS) were introduced in 1986 (FDA approved in 1993) 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.
  - Adding dual antiplatelet therapy (e.g. clopidogrel and aspirin) and placement refinement reduced thrombosis to ~1.2%.

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Coronary stents – Historical development

- Restenosis is a potentially serious problem
  - Morbidity and mortality
- 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
  - 2nd generation DES: thinner, new antiproliferative drugs, more biocompatible; studies comparing 1st vs. 2nd generation suggest lower stent thrombus risk with newer stents
- Dual anti-platelet therapy (DAPT) used with BMS and DES

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Newer generation FDA-approved DES

Name	Materials	Drug
Drug Eluting Stents in Use: de novo lesions in native coronary arteries		
Taxus Ion	Platinum Chromium	Paclitaxel
Xience	Cobalt Chromium	Everolimus
Promus Element	Platinum Chromium	Everolimus
Endeavor	Cobalt Chromium	Zotarolimus
Resolute	Cobalt Chromium	Zotarolimus
Drug Eluting Biodegradable Stents (FDA Approved October 2015)		
Synergy	Scaffold: Platinum Chromium Polymer: Poly (D,Llactide-co-glycolide) (PLGA)	Everolimus
(see Table 2 in full report for details)		

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Objectives and focus of report

Systematically review, critically appraise and analyze research evidence comparing the efficacy and safety of:

1) percutaneous coronary intervention with stenting (PCI) plus medical therapy versus medical therapy alone in patients with stable CAD

2) PCI with newer generation FDA-approved drug eluting stents (DES) with bare metal stent (BMS) as an update to the 2009 report.

The report focuses on the available evidence with least potential for bias (highest quality) based on formal systematic review of the literature

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Key Question 1

In patients with *stable* CAD

a. Is PCI with stenting and medical therapy more effective than medical therapy **in reducing death and MI and/or improving symptoms, functional status and health-related quality of life**? Does the effect vary by (a) BMS versus medical therapy (b) DES versus medical therapy

b. What is the comparative **safety** of PCI with stenting versus medical therapy (including evaluation of bleeding, renal insufficiency and serious adverse events such as nonfatal MI, death)?

c. If there is benefit to PCI compared with medical therapy alone, is there evidence of **differential benefit or harm** based on specific patient characteristics or subgroups (e.g. sex, diabetes, left main CAD, age)

d. What is the evidence of **cost-effectiveness** of PCI with stenting versus medical therapy?

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Key Question 2

In patients with CAD (stable or unstable presentation) is there updated evidence subsequent to the previous (May 2009) report that

a. Newer generation DES are more efficacious than BMS in **reducing MI and death and/or improving symptoms, functional status and patient quality of life?**

b. Newer generation DES are **safer** than BMS (including evaluation of thrombosis, serious adverse events)?

c. There is **differential efficacy or safety** of newer generation DES versus BMS based on specific patient characteristics or subgroups (e.g. sex, diabetes, left main CAD, age)

d. Newer generation DES are more **cost effective** than BMS

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PICO Scope (report Table 16): Inclusion Criteria

Population - Patients with

- KQ1: Stable CAD;
- KQ2: CAD (stable or unstable presentation) undergoing stenting of *de novo* coronary vessels

Intervention

- KQ1: FDA-approved BMS or DES; ≥70% receiving stenting
- KQ 2: FDA-approved 2nd or 3rd generation DES; DES that are no longer in routine use were excluded.

Comparator(s)

- KQ1: Medical therapy – studies must describe more contemporary components of medical therapy
- KQ2:FDA-approved BMS

Study design

- RCTs, observational studies (safety only), full economic studies; For KQ 2, studies published subsequent to 2009 report focused on newer DES

Publication

- Full-length studies published in English in peer-reviewed journals, FDA reports (no meeting abstracts, proceedings)

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Outcomes

- **Efficacy**
  - Primary:
    - All-cause mortality
    - Cardiac mortality
    - Myocardial infarction
    - Patient reported outcomes(HRQOL, symptom relief, function) using validated measures
  - Secondary/intermediate:
    - Revascularization (KQ1) ; Target lesion revascularization (KQ 2, repeat revascularization)
- **Safety**
  - ARC-defined definite stent thrombosis (any time)
  - Peri-procedural (≤ 30 days) complications (e.g. death, MI)
  - Stroke
  - Major bleeding
- **Economic:**
  - Cost-effectiveness outcomes (e.g. ICER)

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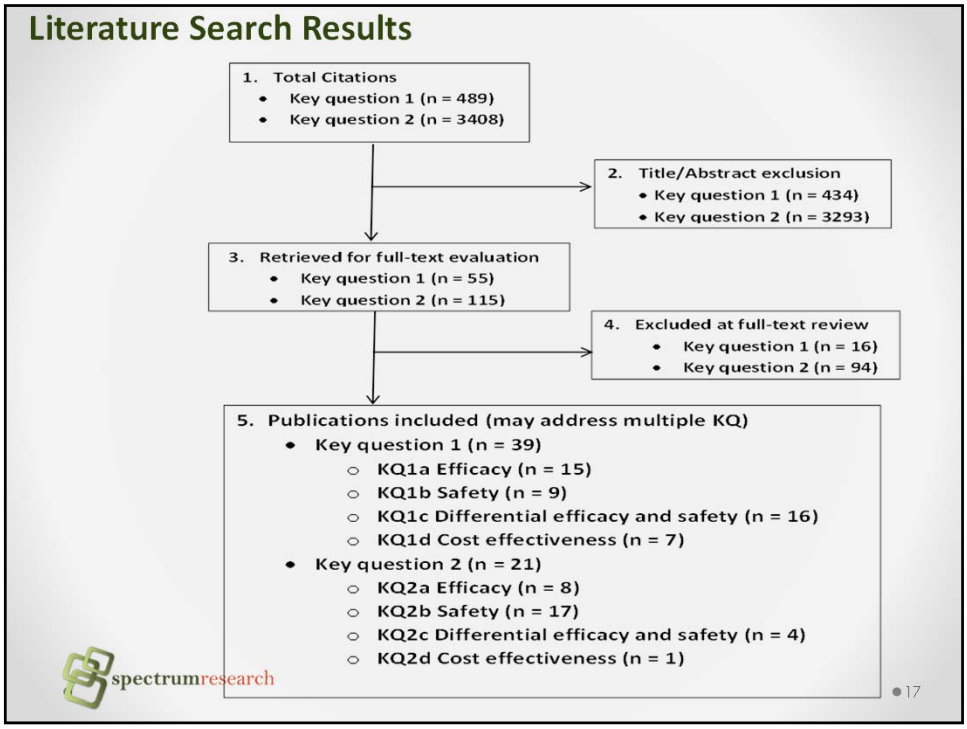
Literature Search Results



Overall strength of evidence (GRADE)

Quality rating	Interpretation
High	High confidence that the evidence reflects the true effect.
Moderate	Moderate confidence in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Insufficient	Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

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Key Question 1: PCI with medical therapy vs. medical therapy alone

Inclusion: Patients with Stable CAD

Exclusions: (Table 16)

- Patients with STEMI, NSTEMI patients with ST depression of >1mm in >1 lead + troponin elevation;
- Patients with persistent CCS class IV angina or post infarction angina
- Patients with refractory heart failure, ejection fraction <30%
- Post MI patients who are within 1 month post MI receiving stent
- Studies in which < 70% of patients received stenting
- Early vs. Late; routine vs. selective; FFR guided PCI

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KQ 1: Overview of Evidence Base

Total Citations: n = 39

Four primary RCTs (with related follow-up publications):

- 2 trials in general populations (COURAGE 2007/2009, MASS II 2004),
- 1 in diabetic persons (BARI 2D 2009)),
- 1 in males (Hambrecht 2004)

One RCT considered to be at moderately low risk of bias (COURAGE); three RCTs at moderately high risk of bias

Methodological concerns: Inadequate detail regarding random sequence generation and unclear allocation concealment. Trials were not blinded, thus, influence of placebo effect not clear for patient-reported outcomes

Cross-over from MT alone to PCI: 22% to 42% at 5 years; 14.3% at 10 years in 1 trial

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KQ 1a: Is PCI with stenting and MT more effective than MT alone in reducing death and MI and/or improving symptoms, functional status or HRQOL?

Results

General population: All-cause mortality

Outcome: All-cause mortality	Number of Studies (N)	Strength of Evidence	Absolute Risk Effect Size (95% CI)	Conclusions
through 12 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 4.4%, Med 1.5% RD 2.9% (-0.4% to 6.2%) RR 3.0 (0.8 to 10.8)	**No statistical differences between treatment groups at any time point**
through median of 55.2 months	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 7.4%, Med 8.4% RD -1.0% (-3.2% to 1.3%) RR 0.89 (0.67 to 1.17)	
through 60 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 11.7%, Med 12.3% RD -0.6% (-6.9% to 5.7%) Adjusted RR 0.92 (0.46 to 1.86)	
through 120 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 25.1%, Med 31.0% RD -7.1% (-15.7% to 1.5%) RR 0.8 (0.6 to 1.1)	

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KQ 1a: Is PCI with stenting and MT more effective than MT alone in reducing death and MI and/or improving symptoms, functional status or HRQOL?

KQ 1a: Results

Special Populations: All-cause mortality

Outcome: All-cause Mortality	Number of Studies (N)	Strength of Evidence	Absolute Risk Effect Size (95% CI)	Conclusions
through 24 months **Males**	1 RCT (Hambrecht) (N=101)	⊕⊕◯◯ LOW	PCI 4%, Exercise 2% RD 2% (-5% to 9%) RR 2.0 (0.2 to 21.8)	A difference was not detected due to low power.
through mean of 63.6 months **Type 2 DM**	1 RCT (BARI 2D) (N=1605)	⊕⊕⊕◯ MODERATE	PCI 12.8%, Med 11.9% RD 0.9% (-2.3% to 4.1%) RR 1.1 (0.8 to 1.4)	Mortality was similar between PCI and Med groups

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KQ 1a Results: Cardiac Death

Outcome Cardiac Death	Number of Studies (N)	Strength of Evidence	Absolute Risk Effect Size (95% CI)	Conclusions
General population: Cardiac Death				
through 12 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 4.4%, Med 1.5% RD 2.9% (-0.4% to 6.2%) RR 3.0 (0.8 to 10.8)	**No statistical differences between treatment groups at any time point**
through median of 55.2 months	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 2.0%, Med 2.2% RD -0.2% (-1.4% to 1.0%) unadjusted HR 0.87 (0.65 to 1.16)	
through 60 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 11.6%, Med 12.3% RD -0.6% (-6.9% to 5.7%) RR 1.0 (0.6 to 1.6)	
through 120 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 14.3%, Med 20.7% RD -6.5% (-13.9% to 0.8%) RR 0.7 (0.4 to 1.1)	
Special populations: Cardiac Death				
through 24 months **Males**	1 RCT (Hambrecht) (N=101)	⊕⊕◯◯ LOW	PCI 0%, Exercise 0%	**There were no cardiac deaths in either group; low power to detect**
through mean of 63.6 months **Type 2 DM**	1 RCT (BARI 2D) (N=1605) umresearch	⊕⊕⊕◯ MODERATE	PCI 5.5%, Med 4.1% RD 1.4% (-0.7% to 3.5%) RR 1.3 (0.9 to 2.1)	**Cardiac death was similar**

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KQ 1a Results: Myocardial Infarction

Outcome:	Number of Studies (N)	Strength of Evidence	Absolute Risk Effect Size (95% CI)	Conclusions
General population: nonfatal MI				
through 12 months **through 60 months**	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 8.3%, Med 5.0% RD 2.9% (-1.9% to 7.6%) RR 1.6 (0.7 to 2.4) 60 months: PCI 11.2%, Med 15.3% RD -4.1% (-10.6% to 2.5%) RR 0.7 (0.44 to 1.2)	**No statistical differences between groups**
post-peri-procedural through median of 55.2 months	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 9.4%, Med 10.5% RD -1.1% (-3.5% to 1.4%) RR 0.9 (0.9 to 1.2)	
through 120 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	**PCI 13.2%, Med 20.7%** **RD -7.5% (-17.8% to -0.3%)** **RR 0.64 (0.41 to 0.991)**	**Nonfatal MI was less common in the PCI versus Med group**
Special population: nonfatal MI				
through 12 months **through 24 month's** **Males**	1 RCT (Hambrecht) (N=101)	⊕⊕◯◯ LOW ⊕⊕◯◯ LOW	12 months: PCI 2%, Exercise 0%; RD 2% 24 months: PCI 2%, Exercise 2%,RD 0% (-6% to 6%) RR 1.0 (0.1 to 15.9)	**A difference was not detected due to low power.**
post-peri-procedural, fatal & nonfatal through mean of 55.2 months; Type 2 DM	1 RCT (BARI 2D) (N=1605) mresearch	⊕⊕⊕◯ MODERATE	PCI 8.5%, Med 9.6% RD -1.0% (-3.8% to 1.8%) RR 0.9 (0.7 to 1.2)	**MI similar between PCI and Med groups**

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KQ 1a Results: Angina

Outcome	Number of Studies (N)	Strength of Evidence	Conclusions
General Population: Freedom from angina (Not defined)			
12 and 36 months **60 months**	1 RCT (COURAGE) (N=1644-2041)	⊕⊕◯◯ LOW 60 months ⊕◯◯◯ INSUFFICIENT	Significantly more PCI than Med patients were angina-free at 12 and 36 months, but not at 60 months 12 months 66.0% vs. 58.9%,RR 1.11, 95% CI 1.04 to 1.19, p=0.001) 36 months (73.4% vs.67.7%), RR 1.08, 95% CI 1.01 to 1.15, p=0.01). 60 months **NS**): (74.7% vs. 72.9%)
12, 60, and 120 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	More PCI versus Med patients were angina-free at all times: 12 months 52.2% vs. 36.5%, RR 1.43, 95% CI 1.1 to 1.8, p=0.001 60 months 77.3% vs. 54.8%, RR 1.28, 95% CI 1.06 to 1.55, p=0.0102 120 months 58.5% vs. 43.3%, RR 1.35, 95% CI 1.11 to 1.64, p=0.0022
Special Population (worsening angina frequency, severity; change from none to any or UA)			
12 months **24-60 months**	1 RCT (BARI 2D) (N = 1502)	⊕⊕◯◯ LOW	Fewer PCI versus Med patients through 12 months (17.7% versus 24.5%; RR 0.7, 95% CI 0.6 to 0.9; p=0.0012). 24 months: ~14% each group 36 months: PCI ~11%, MT ~15%, p = 0.019 48 to 60 months: Similar between groups (~10% each group)

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KQ 1a Results: Other Patient Reported Outcomes

- **Seattle Angina Questionnaire: Clinically significant Improvement (1 trial COURAGE)**
- **Inconsistency across domains/times**
  - **Angina Frequency:** more PCI patients had clinically significant improvement at 6 (RR1.14, 95% CI 1.03 to 1.26) and 12 months (RR1.14, 95% CI (LOW) and 36 months (RR1.14 95% CI 1.02, 1.27) (INSUFFICIENT)
  - **Other domains**:
    - Angina Stability: No difference between groups at any time (LOW)
    - QOL and physical limitation: more PCI patients at 6 months (LOW) but not at 12 (LOW) or 36 months (INSUFFICIENT)
    - Satisfaction: More (39%) PCI vs. 33%, RR 1.18 (1.04 , 1.34) at 12 months (LOW); NS difference at other times

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KQ 1a Results: Other Patient Reported Outcomes

RAND-36: Clinically significant Improvement (COURAGE)

- Physical functioning, Role-Limitation-Physical at 6 months: More PCI patients had clinically meaningful improvement (LOW); NS difference at 12 months (LOW), 36 months (INSUFFICIENT)
- No differences between groups for any other domain at any other time (LOW for 6, 12 months, INSUFFICIENT at 36)

Modified RAND domains (BARI 2D)

- No differences between groups through 48 months (LOW)

SF-36: Mean scores (MASS II)

- Better mean scores with PCI for physical functioning, vitality at 12 months; NS differences in other domains (LOW)

Duke Activity Status Index: % improvement vs. baseline (BARI 2-D); No differences between groups over 48 months (LOW)

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KQ 1a Results: Revascularization (repeat revascularization for PCI group or primary revascularization in MT group)

Outcome	Number of Studies (N)	Strength of Evidence	Absolute Risk Effect Size (95% CI)	Conclusions
General Population: Any Revascularization				
through 12 months **60 months** **120 Months**	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	12 months: PCI 12.2%, Med 7.9% RR 1.55 (0.85 to 2.81) 60 months: PCI 32.2%, Med 24.1% RR 1.33 (0.97 to 1.83) 120 months: PCI 41.5%, Med 39.4% RR 1.05 (0.83 to 1.33)	**Revascularization was more common in PCI group, but statistical significance was not reached.**
through median of 55.2 months	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 19.8%, Med 30.6% RD -10.7% (-14.3% to -7.2%) RR 0.65 (0.56 to 0.75)	**Fewer in the PCI group had revascularization**
Special Populations: Any revascularization				
through 12 months Males	1 RCT (Hambrecht) (N=101)	⊕⊕◯◯ LOW	PCI 20%, Exercise 6% RD 14% (1% to 27%) RR 3.4 (1.0 to 11.6)	**More PCI patients had revascularization**
through 60 months Type 2 Diabetes	1 RCT (BARI 2D) (N=1605)	⊕⊕⊕◯ MODERATE	PCI 26.8%, Med 39.1% RD -12.3% (-16.9% to -7.8%) RR 0.68 (0.59 to 0.79)	**Fewer patients in the PCI group had revascularization**

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KQ 1c Results: Safety

Outcome	Number of Studies (N)	Strength of evidence	Absolute Risk Effect Size (95% CI)	Conclusions
In-hospital adverse events General Population	1 RCT (MASS-II) (N=205)	⊕⊕◯◯ LOW	Overall: PCI 1% to 2.4%, Med NA Death (2.4%), Q-wave MI (1.0%), emergency CABG (1.0%), emergency PCI (1.0%), stroke (1.0%).	**During the index PCI procedure, in-hospital events were relatively rare**
30-day mortality Type 2 DM	1 RCT (BARI 2D) (N=798)	⊕⊕◯◯ LOW	PCI 0.5%, Med NR	**30-day mortality occurred in 0.5% of PCI patients;.**
Peri-procedural MI General	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 3.0%, Med 0.8% RD 2.3% (1.1% to 3.4%) RR 3.85 (1.86 to 7.98)	**Significantly more common in PCI group**
Peri-procedural MI Type 2 DM	1 RCT (BARI 2D) (N=1602)	⊕⊕⊕◯ MODERATE	PCI 3.4%, Med 1.4% RD 2.0% (0.5% to 3.5%) RR 2.48 (1.24 to 4.96)	**Significantly more common in the PCI group**

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KQ 1a Results: Safety - Stroke

Outcome	Number Studies (N)	Strength of evidence	Absolute Risk Effect Size (95% CI)	Conclusions
Peri-procedural stroke Type 2 DM	1 RCT (BARI 2D) (N=1605)	⊕⊕◯◯ LOW	PCI 0.4%, Med 0.2% RD 0.1% (-0.4% to 0.7%) RR 1.52 (0.25 to 9.04)	**Periprocedural stroke was similar between PCI and Med groups**
General population: Cumulative Stroke				
median of 55.2 months	1 RCT (COURAGE) (N=2287)	⊕⊕⊕◯ MODERATE	PCI 1.9%, Med 1.2% RD 0.7% (–0.3% to 1.7%) RR 1.56 (0.80 to 3.03)	**Similar between groups.**
120 months	1 RCT (MASS-II) (N=408)	⊕⊕◯◯ LOW	PCI 5.4%, Med 6.9% RD –1.5% (–6.2% to 3.1%) RR 0.8 (0.4 to 1.7)	**Similar between groups at 120 months and when assessed through 12 and 60 months.**
Special population: Cumulative stroke				
12 months Males	1 RCT (Hambrecht) (N=101)	⊕⊕◯◯ LOW	PCI 6%, Exercise 4% RD 2% (–6% to 10%) RR 1.5 (0.3 to 8.8)	**A difference was not detected due to low power.**
mean of 55.2 months Type 2 DM	1 RCT (BARI 2D) (N=1605)	⊕⊕⊕◯ MODERATE	PCI 2.6%, Med 2.6% RD 0.03% (-1.5% to 1.6%) RR 1.0 (0.6 to 1.8)	**Similar between groups.**

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KQ 1c Results: Differential Efficacy or Safety (ES page 14)

- Baseline patient characteristics (age, sex, race, diabetes smoking), symptoms (e.g. angina), CAD characteristics (e.g. number diseased vessels, angiographic risk) do not appear to modified any of the primary clinical outcomes
- COURAGE: No clear conclusions possible from complex analysis of interaction of time, baseline tertiles of SAQ and patient characteristics
- Health care system (US-VA vs. US-non VA vs. Canada) may modify revascularization rates revascularization rates were different in different healthcare systems (Table 3 in ES)

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KQ 1d Results: Cost-effectiveness

General population

- COURAGE: PCI + medical therapy for stable CAD was not more cost effective than an initial treatment strategy of optimal medical therapy alone at any time horizon (QHES 90/100, Moderate)
- MASS II: PCI + optimal medical therapy for stable multivessel CAD was not more cost effective than an initial treatment strategy of optimal medical therapy alone for the time horizons of 1 and 5 years (QHES 48/100, Insufficient)

Special Populations :

- Males: Average cost to improve 1 CCS class greater with PCI (QHES 35/100, Insufficient)
- Type 2 Diabetes (BARI 2D): PCI + medical therapy for stable CAD was not more cost effective than an initial treatment strategy of medical therapy alone over 4 year horizon (QHES 79/100, Moderate)

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Key Question 2: Newer generation DES versus BMS

In patients with CAD (stable or unstable presentation) is there updated evidence subsequent to the previous (May 2009) report that

a. Newer generation DES are more efficacious than BMS in reducing MI and death and/or improving symptoms, functional status and patient quality of life?
b. Newer generation DES are safer than BMS (including evaluation of thrombosis, serious adverse events)?
c. There is differential efficacy or safety of newer generation DES versus BMS based on specific patient characteristics or subgroups (e.g. sex, diabetes, left main CAD, age)
d. Newer generation DES are more cost effective than BMS

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Key Question 2: Newer generation DES versus BMS

Inclusion: Patients with CAD (stable or unstable presentation)undergoing stenting of coronary vessels

Exclusions: (additional detail in report table 16)

- Patients presenting for treatment of restenosis, stent thrombosis or revascularization after initial PCI or CABG or rescue PCI
- Comparison of 1st vs. 2nd generation DES
- Studies of 1st generation DES or those that are no longer in routine use
- Studies comparing pharmacologic regimens, anti-platelet medications or fibrinolysis or adjunctive medical therapies or devices

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KQ 2: Overview of updated evidence base

Key KQ	Original 2009 Report	Update	Total
KQ 2a: Efficacy	52 publications, 9 HTA reports*	6 trials/2 follow-up studies* 0 observational	9 HTAs 75 publications (2009 Report = 54; 2015 Update = 21)
KQ 2b: Safety	52 publications, 9 HTA reports*	6 trials/2 follow-up studies* 9 observational	
KQ 2c: Differential effects	52 publications, 9 HTA reports*	3 trials/1 follow-up studies* 0 observational	
KQ 2d: Cost-effectiveness	2 full economic studies, 9 HTA reports*	1 full economic studies	

*The 2009 report included numerous, meta-analyses, systematic reviews, randomized controlled trials, and comparative observational studies, as well as prior Health Technology Assessments (HTAs) which contributed data to all Key Questions.

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KQ 2: Overview of Evidence Base

Total Citations: n = 21

7 primary RCTs (5 associated follow-up publications) for parts a, b, c:

- 4 trials: everolimus (EES) (BASKET-PROVE, EXAMINATION, X-MAN, XIMA
- 2 trials: zotarolimus (ZES) (ENDEAVOR II, ZEUS)
- 1 trial included both EES and ZES (PRODIGY)

Populations:

- General population of stable and unstable CAD (ENDEAVOR 2010, PRODIGY 2014)
- Octogenarians (XIMA 2014)
- STEMI (EXAMINATION 2012, XMAN 2014)
- Large vessels (BASKET-PROVE 2010)
- Uncertain bleeding risk (ZEUS 2015)

2 RCT considered low risk of bias, 5 RCTs moderately low risk of bias; 2 Registries and moderately high risk of bias, 1 at high risk of bias

3 Registry studies (4 citations) (moderately high risk of bias) ; 5 case series; 1 economic study

Methodological concerns: RCTs-unclear allocation concealment; Registries – lack of blinded assessment, unclear validation of data collected, loss to follow-up unclear.

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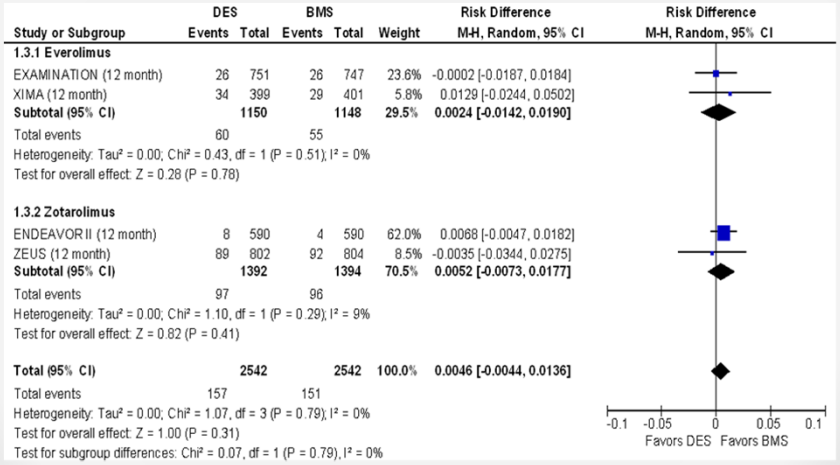
KQ 2a Results: All-cause mortality, 12 months

No difference between newer DES and BMS (SoE, HIGH)



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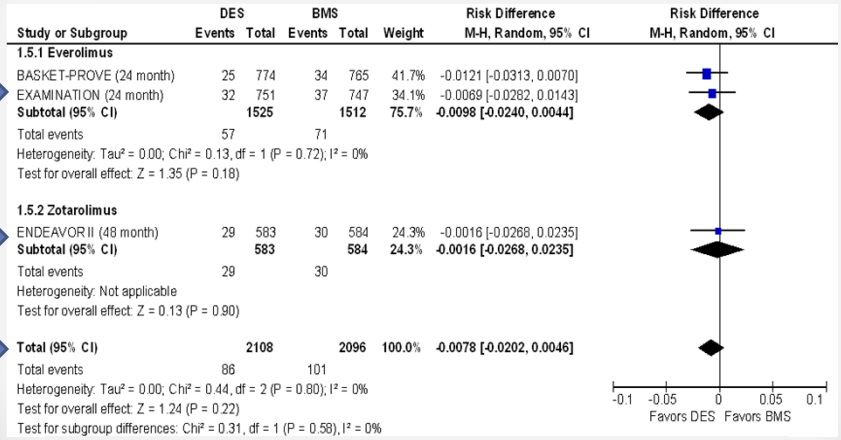
KQ 2a Results: All-cause mortality > 12 months

RCTS: No difference between newer DES and BMS >12 to 48 months (SoE, HIGH)



NS difference at 60 months in 1 RCT (MODERATE) or in IPD in women at 36 months (LOW)

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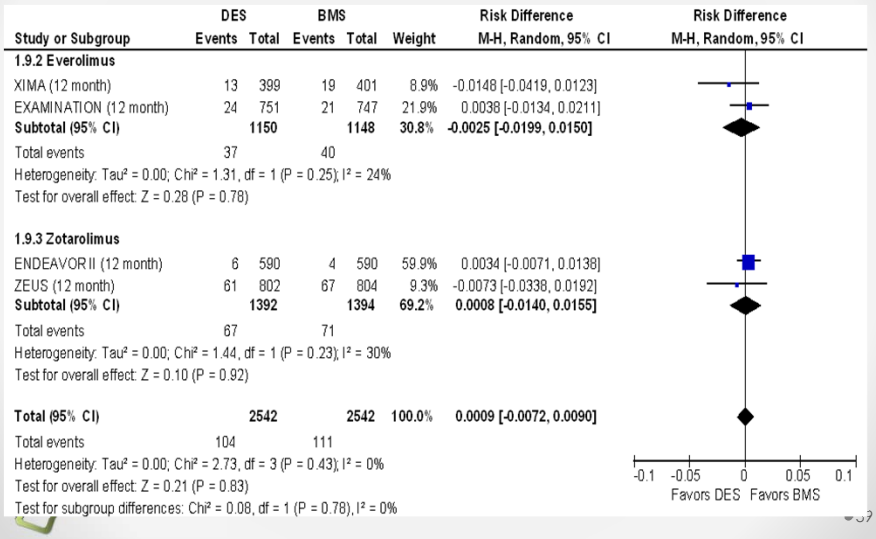
KQ 2a Results: Cardiac mortality 12 months

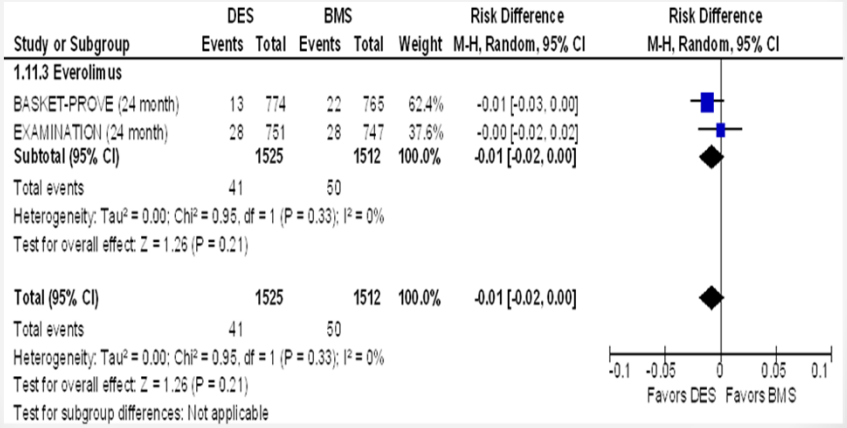
No difference between newer DES and BMS (SoE, HIGH)



Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Risk Difference M-H, Random, 95% CI
1.9.2 Everolimus						
XIMA (12 month)	13	399	19	401	8.9%	-0.0148 [-0.0419, 0.0123]
EXAMINATION (12 month)	24	751	21	747	21.9%	0.0038 [-0.0134, 0.0211]
Subtotal (95% CI)		**1150**		**1148**	**30.8%**	**-0.0025 [-0.0199, 0.0150]**
Total events	37		40			
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.9.3 Zotarolimus						
ENDEAVOR II (12 month)	6	590	4	590	59.9%	0.0034 [-0.0071, 0.0138]
ZEUS (12 month)	61	802	67	804	9.3%	-0.0073 [-0.0338, 0.0192]
Subtotal (95% CI)		**1392**		**1394**	**69.2%**	**0.0008 [-0.0140, 0.0155]**
Total events	67		71			
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**2542**		**2542**	**100.0%**	**0.0009 [-0.0072, 0.0090]**
Total events	104		111			
Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

KQ 2a Results: Cardiac mortality ≥ 24 months

RCTs: No difference between newer DES and BMS at 24 months (SoE, MODERATE)



Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Risk Difference M-H, Random, 95% CI
1.11.3 Everolimus						
BASKET-PROVE (24 month)	13	774	22	765	62.4%	-0.01 [-0.03, 0.00]
EXAMINATION (24 month)	28	751	28	747	37.6%	-0.00 [-0.02, 0.02]
Subtotal (95% CI)		**1525**		**1512**	**100.0%**	**-0.01 [-0.02, 0.00]**
Total events	41		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**1525**		**1512**	**100.0%**	**-0.01 [-0.02, 0.00]**
Total events	41		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Not applicable						

NS difference at 60 months in 1 RCT (MODERATE)

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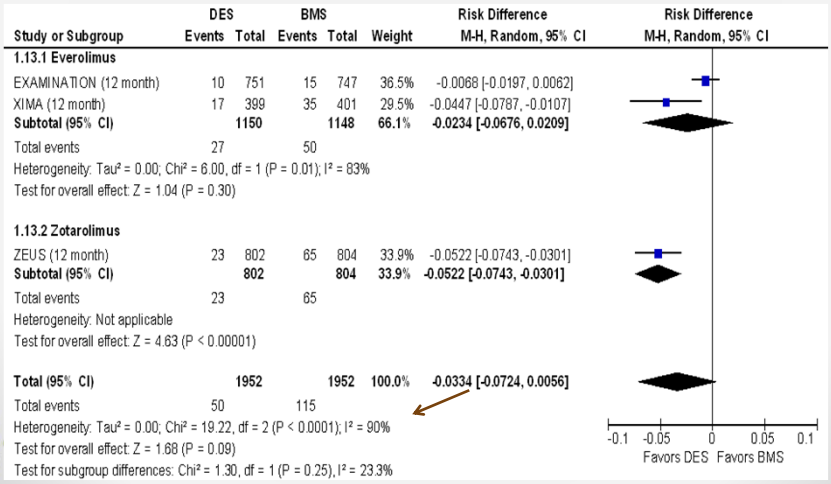
KQ 2a Results: Any MI cumulative to 12 months

Pooled estimate within the limits of chance (SoE, LOW); however, heterogeneity, lack of precision noted; 2 trials report fewer MI with DES; study populations differ



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KQ 2a Results: Other time frames and MI classifications

Any MI at 24 months (with/without periprocedural)I: Similar risk for DES and BMS;1 RCT (HIGH)

Target Vessel MI, 12 or 24 months: Similar risk, 2 RCTs (HIGH)

Q-wave MI and non-Q-wave, 12 or 60 months; Similar risk;1 RCT (HIGH)

Non-fatal MI (cumulative): Similar for DES and BMS at 24 months (1 RCT, LOW), and 48 months (1 RCT, HIGH)

Cumulative to 36 months: IPD meta-analysis in women, Unadjusted estimates DES 4.8% vs. BMS 7.7%, p = 0.03 (LOW)

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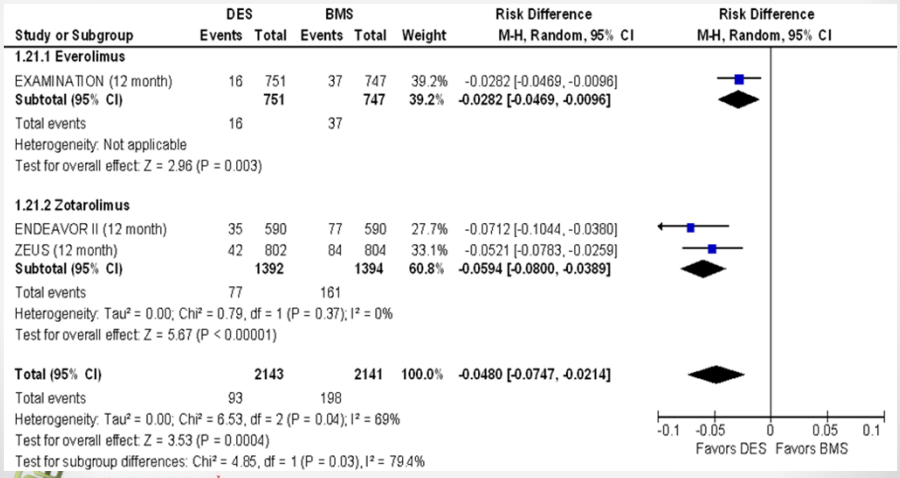
KQ 2a Results: Target lesion revascularization cumulative to 12 months

Significantly fewer TLR with newer DES and BMS for pooled estimate (SoE, MODERATE);



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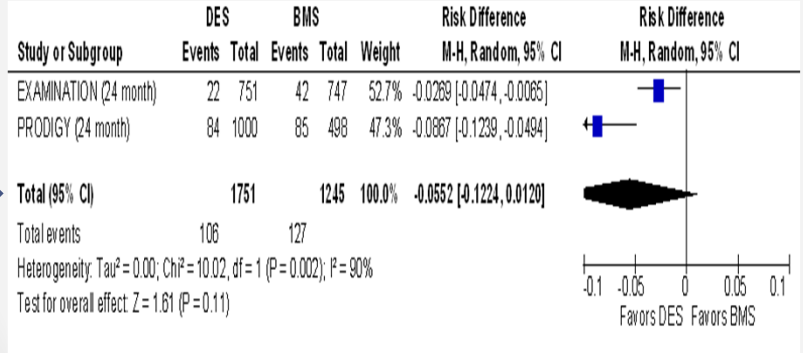
KQ 2a Results: Target lesion revascularization cumulative to 24 months, 36 months

TLR less common to 24 months with newer DES and BMS for pooled estimate but within the limits of chance (SoE, LOW); differences in populations may contribute



TLR less common with DES 36 months in IPD meta-analysis in women, HR 0.44, 95% CI 0.31 to 0.64 (LOW)

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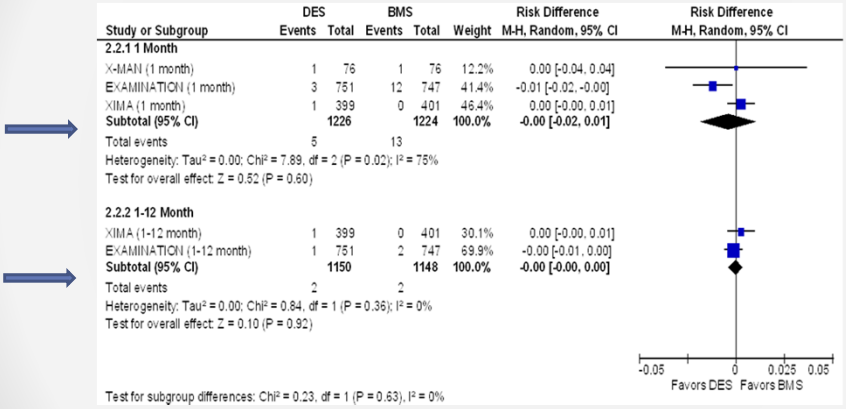
KQ 2b Results: Definite stent thrombosis ≤ 30 days and from 1 to 12 months

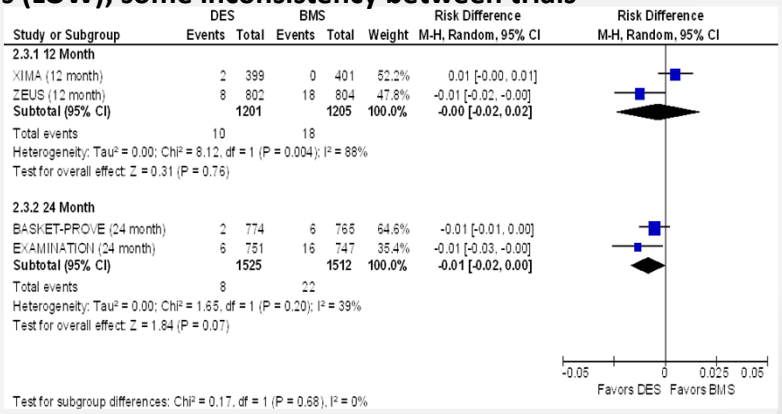
RCTs: No difference between newer DES and BMS ≤ 30 days and from 1-24 months (LOW);



2 Registry studies: similar risk in ST ≤ 30 days in STEMI; DES 0.5% to 1.0%, BMS 0.9% to 1.7% (INSUFFICIENT)

KQ 2b Results: Definite stent thrombosis Cumulative to 12 months, 24 months

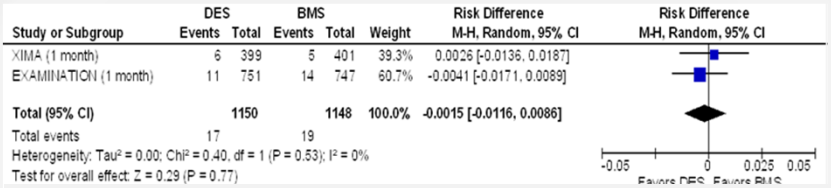
RCTs: Pooled estimates within the limits of chance between newer DES and BMS cumulative to 12 months (INSUFFICIENT) or to 24 months (LOW); some inconsistency between trials



ST to 12 months (0.5% vs. 0.6%) and from 12 to 36 months (0.07 vs. 0.3%) in IPD meta-analysis in women, unadjusted estimates (LOW)

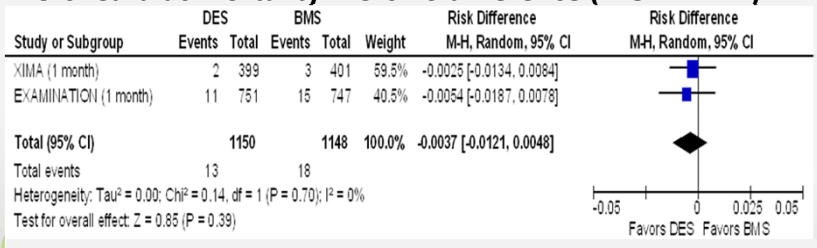
KQ 2b Results:
All-cause and cardiac mortality ≤ 30 days (periprocedural)

RCTs: All-cause mortality, no difference (MODERATE)



1 registry: mortality ~3.7% vs. ~4.8% in STEMI; (INSUFFICIENT)

RCTs: Cardiac mortality: RCTs no difference (MODERATE)



1 registry: cardiac mortality ~2.3% vs. ~7.9% in STEMI (p <0.001); (INSUFFICIENT)

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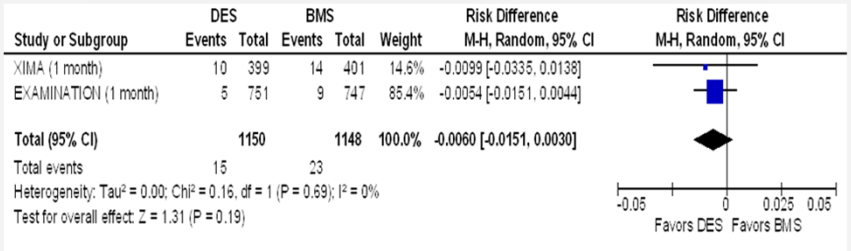
KQ 2b Results:
Myocardial infarction and re-infarction ≤ 30 days (periprocedural)

RCTs: Similar between newer DES and BMS (MODERATE)



1 Registry: Re-infarction in STEMI ~1.4% vs. ~2.1% (p <0.23); (INSUFFICIENT)

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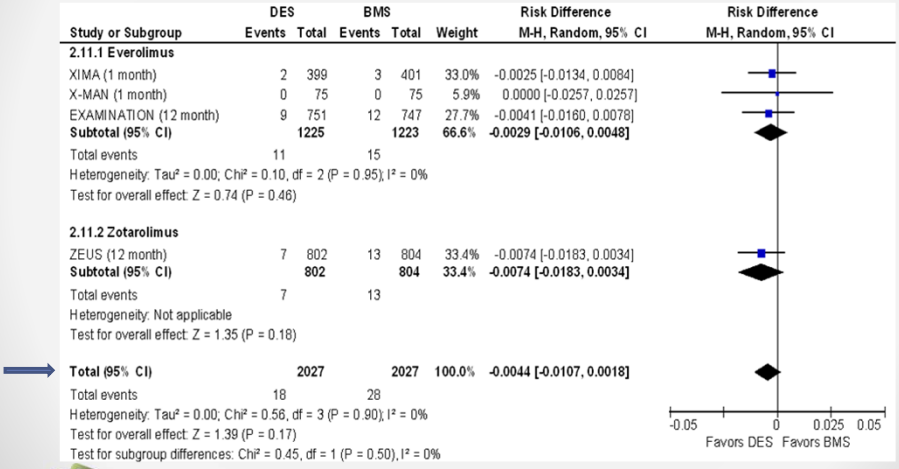
KQ 2b Results: Major bleeding (any time)

RCTs: Similar between newer DES and BMS (MODERATE)



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KQ 2b Results: Other complications

Stroke:

- 1 trial, octogenarians (LOW) :periprocedural, cumulative stroke at 6, 12 months similar between groups; excluding stroke ≤30 days, more DES patients experienced stroke (1% vs. 0%)at 6 months)
- Any stroke to 48 months: Similar between groups,1 RCT (MODERATE)
- Ischemic stroke similar between groups (LOW):1 RCT (6 months (excluding ≤30 days), 2 RCTs (12 months)

TLR ≤30 days: Less common with DES(0.5% vs. 2%), 1 RCT

DES fracture: complete or partial 2.6% to 3.8% (3 case series, 6 to 15 months) (INSUFFICIENT)

DES deformity: 0.2% to 1.5% (4 case series) (INSUFFICIENT)

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KQ 2c: Differential effectiveness/safety

One trial (STEMI patients) Age (≤ 75 years (n = 245) vs. >75 years) did not modify treatment through 12 months for (LOW)

- o All-cause mortality, p = 0.092 for interaction
- o Cardiac mortality, p = 0.277
- o Bleeding, P = 0.75

No other trials evaluated modification of treatment effect for primary outcomes

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KQ 2dResults: Cost-effectiveness of newer DES vs. BMS

One moderate quality study

- There were no significant differences in survival or quality-adjusted survival at 4 years, for newer DES (zotarolimus) vs. BMS –ICER not calculated

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Centers for Medicare and Medicaid Services (CMS)

Medicare (National Coverage Determination)

CMS will cover PCI (with and without the placement of a stent) 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) have angina refractory to OMT,
2) objective evidence of myocardial ischemia,
3) lesions amenable to angioplasty.

Coverage for all other is at the discretion of local CMS contractors.

Medicare (Regional Coverage Determination)

- No formal coverage determination for stent implantation. They last updated their billing guidance in 2013.

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Clinical Practice Guidelines

Primary evidence-based ACCF/AHA guidelines - (please consult page 58 in full report)

- Fihn 2012 and 2014 (Update) ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease
- Amsterdam 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes
- Levine 2011 and 2015 (Update) ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction

ACCF/SCAI/STS/AATS/AHA/ASHC/HFSA/SCCT Appropriate Use Criteria are also summarized (page 80)

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Summary

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Summary of Evidence: PCI with MT vs. MT alone

Outcome	Summary of findings
All-cause mortality	**General Population (2 RCTS)** • MODERATE: Mortality similar, median 55.2 months (COURAGE) • LOW: No statistical difference 12, 60,120 months (MASS II) **Special Populations:** • MODERATE: Mortality similar, 63.6 months (Diabetes 1 RCT)) • LOW: No difference (low power) 24 months (males 1 RCT)
Cardiac death	**General Population (2 RCTS)** • MODERATE: Similar through 55.2 months (COURAGE) • LOW: No statistical difference, 12, 60,120 months (MASS II) **Special Populations:** • MODERATE: Similar through 63.6 months (Diabetes 1 RCT)) • LOW: No deaths in either group (low power) through 24 months (males 1 RCT)
Myocardial infarction	**General Population (2 RCTS)** • MODERATE: Similar ,median of 55.2 months (COURAGE) • LOW: No statistical difference, 12, 60, months (MASS II) • LOW: Less common in the PCI, 120 months (MASS II) **Special Populations:** • MODERATE: Similar, 55.2 months (Diabetes 1 RCT) • LOW: No difference (low power) through 12, 24 months (males 1 RCT)

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Summary of Evidence: PCI with MT vs. MT alone

Outcome	Summary of findings
Symptom improvement	**General Population** • LOW: Significantly more PCI vs. Med patients angina-free at 12 months (COURAGE, MASS II); LOW that this persisted through 120 mos (MASS II); INSUFFICIENT at 60 months (COURAGE) **Special Populations (type 2 DM):** • LOW: Fewer PCI vs. Med patients through 12 months had worse angina or change to UA; Similar after 12 months up to 60 months
Patient-reported Outcome	Inconsistency across measures, domains, times; LOW evidence **General Population:** • LOW: SAQ (COURAGE) to 12 months; More PCI patients had clinically meaningful improvement in angina frequency at 6, 12 months, QOL and physical limitation at 6 moths and more were satisfied with treatment at 12 months with no differences at other times; No difference in angina stability any time; • LOW: RAND 36, SF 36; Better scores with PCI for physical function domains at 6 months (COURAGE) and 12 months (MASSII) and vitality (MASS II); NS differences in other domains **Special Populations (type 2 DM):** • LOW: Modified RAND, Duck Activity Status; NS difference to 48 months

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Summary of Evidence: PCI with MT vs. MT alone

Outcome	Summary of findings
Safety	**In-hospital adverse events (MASS II)** • LOW, events rare (death 2.4%, others 1%) **30day mortality (BARI 2D);** • LOW, 0.5% for PCI, NR for medical therapy **Periprocedural MI** • MODERATE, significantly more common with PCI in 2 RCTs (COURAGE, BARI 2D) **Stroke: General Population** • MODERATE: Similar between groups at 55.2 months (COURAGE); LOW that risk similar through 60 months (MASS II) **Stroke: Special Population** • MODERATE: Similar between groups at 55.2 months (BARI 2D) • LOW: difference not detected due to low power
Differential efficacy, safety	Patient and baseline factors do not appear to modify treatment effect for the primary outcomes of this HTA
Cost effectiveness	PCI with medical therapy is not more cost-effective than an initial strategy of medical therapy alone

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Summary of Evidence, newer DES vs. BMS

Outcome	Summary
All-cause mortality	Similar for newer DES and BMS at all time frames across RCTs • HIGH: 12months (4 RCTs), 24 months (2 RCTs), 48 mos (1RCT) • MODERATE: NS difference at 60 months (1 RCT) • LOW: IPD analysis in women at 36 months
Cardiac death	Similar for newer DES and BMS at all time frames across RCTs • HIGH: 12 months (4 RCTs) • MODERATE: 24 months (2 RCTs) and 60 months (1 RCT)
Myocardial infarction	Some inconsistency in findings across trials; varied definitions of MI • LOW: Any MI to 12 months; pooled estimate within chance (3 RCTs); 2 trials significantly fewer MI with DES; population differences noted • HIGH: Similar risk for: any MI (24 mos, 1 RCT), TV MI (12, 24 mos, 2 RCTs), Q-wave and non-Q-wave MI (12, 60 months 1 RCT), nonfatal MI (48 mos, 1RCT) • LOW: Similar risk nonfatal MI (24 months, 1 RCT); • LOW: IPD meta-analysis (women, 36 months); unadjusted estimates indicate fewer MI with newer DES
Symptoms and PROs	Not reported

Summary of Evidence, newer DES vs. BMS

Outcome	Summary of findings
TLR	• MODERATE: Significantly fewer TLR with DES to 12 months (3 RCTs) • LOW: TLR less common with newer DES at 24 months, 36 months
Safety	**Definite stent thrombosis; studies likely underpowered** • LOW: No difference ≤ 30 days (2 RCTs), 1-12 months (2 RCTs) • INSUFFICIENT to LOW: Differences within limits of chance cumulative to 12 months (2 RCTs) and 24 months (2 RCTs) • LOW: IPD analysis (women); lower ST with DES (unadjusted estimates) **All-cause mortality, cardiac death, MI (≤ 30 days); major bleeding** • MODERATE: risk similar for newer DES and BMS **Stroke (varied definitions, studies likely underpowered)** • LOW: Similar periprocedural, cumulative stroke at 6, 12 months (1 RCT); Similar risk of ischemic stroke 1-6 mos (1 RCT), 12 months (2 RCTs) • MODERATE: Any stroke, similar risk to 48 months (1 RCT)
Differential efficacy, safety	LOW: Age ≤75 vs. 75 years did not modify treatment for all-cause mortality, cardiac mortality or bleeding (1RCT, STEMI patients); studies underpowered
Cost effectiveness	(MODERATE) Newer DES not more cost-effective vs. BMS over 4 years;

Evidence Gaps and Remaining Questions

- Observations
  - Statistical power possibly low to hard clinical outcomes
  - Heterogeneity in patient populations
  - Variability in definitions, measures
  - PCI vs. medical therapy: Included RCTs do not reflect current GDMT or newer DES. The ISCHEMIA trial (estimated completion 2019) may provide some answers
  - Smaller evidence base for update for newer DES vs BMS
- PROs: Data are limited and studies were not blinded
- Thresholds for revascularization are not clearly delineated
- Unclear which patients may be the best candidates for PCI
- 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?

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Appendices

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Clinical guideline overview

Guideline-directed medical therapy (GDMT)

All CAD patients receive should receive guideline-directed medical therapy which is optimized to the individual and includes:

- Lifestyle modifications (physical activity, smoking cessation, weight management and dietary changes)
- Treatment of secondary conditions within current guidelines (diabetes and hypertension),
- Risk modification with antiplatelet drugs and management of lipid levels and treatment of angina symptoms if present.

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Clinical guideline overview: key recommendations - PCI for revascularization in STABLE CAD (see full report)

Fihn, 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS, 2014 Focused update and Levine, 2011 ACCF/AHA/SCAI	
Rating	**Recommendation**
I-C IIa-B	**For unprotected left main or complex CAD, a Heart Team approach is recommended** (1-C) and calculation of STS and SYNAX Scores is reasonable (IIa-B)
IIa-B,C	PCI to improve survival is reasonable in patients with: • Significant unprotected left main CAD with conditions associated with low risk of procedural complications and a high likelihood of good outcomes (IIa-B) • UA/NSTEMI when an unprotected left main coronary artery is the culprit lesion and patient not a candidate for CABG (IIa-B) • Acute STEMI when an unprotected left main coronary artery is the culprit lesion, distal coronary flow is less than TMI grade 3 and PCI can be performed more rapidly and safely than CABG (IIa-C)
I-A I-B I-C	CABG or PCI is beneficial: • In survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant stenosis in a major coronary artery (CABG I-B, PCI I-C) • To improve symptoms in patients with 1 or more significant coronary artery stenosis amenable to revascularization and unacceptable angina despite GDMT (I-A)
IIa-C	CABG or PCI to improve symptoms is reasonable in patients with 1 or more significant coronary artery stenosis and unacceptable angina for whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences

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Clinical guideline overview: key recommendations - PCI for revascularization in STABLE CAD CONTINUED (see full report)

Fihn, 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS, 2014 Focused update and Levine, 2011 ACCF/AHA/SCAI	
Rating	**Recommendation**
IIa-B	It is reasonable to choose CABG over PCI to improve survival or symptoms in patients with complex 3-vessel CAD with or without involvement of the proximal LAD artery who are good candidates for CABG
I-B	CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival, particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery
IIb-B	PCI may be reasonable as an alternative to CABG in selected stable patients with significant unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term; *and* 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes
III-B	PCI should not be performed: • in patients with significant unprotected left main CAD who have unfavorable anatomy for PCI and who are good candidates for CABG • with coronary stenting (BMS or DES) if the patient is not likely to be able to tolerate and comply with DAPT
III-B	CABG or PCI should not be performed with the primary or sole intent to improve survival in patients with SIHD with 1 or more coronary stenosis that are not anatomically or functionally significant, involve only the left circumflex or right coronary artery, or subtend only a small area of viable myocardium
III-C	CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomic or physiological criteria for revascularization

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Clinical guideline overview: key recommendations - PCI for revascularization in STEMI (see full report)

Fihn, 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS, 2014 Focused update and Levine, 2011 ACCF/AHA/SCAI	
Rating	**Recommendation**
IIa-B	It is reasonable to choose CABG over PCI to improve survival or symptoms in patients with complex 3-vessel CAD with or without involvement of the proximal LAD artery who are good candidates for CABG
I-B	CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival, particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery
IIb-B	PCI may be reasonable as an alternative to CABG in selected stable patients with significant unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term; *and* 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes
III-B	**PCI should not be performed:** • in patients with significant unprotected left main CAD who have unfavorable anatomy for PCI and who are good candidates for CABG • with coronary stenting (BMS or DES) if the patient is not likely to be able to tolerate and comply with DAPT
III-B	CABG or **PCI should not be performed** with the primary or sole intent to improve survival in patients with SIHD with 1 or more coronary stenosis that are not anatomically or functionally significant, involve only the left circumflex or right coronary artery, or subtend only a small area of viable myocardium
III-C	CABG or **PCI to improve symptoms should not be performed** in patients who do not meet anatomic or physiological criteria for revascularization

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Clinical guideline overview: key recommendations - PCI for revascularization in NSTEMI –ACS (see full report)

ACC/AHA Unstable angina/NSTEMI-ACS Guidelines [4]	
Rating	**Recommendation**
IIa-B	It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events
IIb-B	A strategy of multivessel PCI, in contrast to culprit lesion only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTE- ACS
IIb-B	Invasive physiological assessment (coronary flow reserve) may be considered with normal coronary arteries if endothelial dysfunction is suspected
IIb-B	A strategy of multivessel PCI, in contrast to culprit lesion only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTE- ACS
IIa-B	It is reasonable to choose CABG over PCI in older patients, particularly those with DM or multivessel disease, because of the potential for improved survival and reduced CVD events

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Appropriate Use Criteria
PCI for revascularization (see full report)

ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT: Task force Ratings		
	Appropriate Use Score* (1-9)	
Indication	**PCI**	**CABG**
Two-vessel CAD with proximal LAD stenosis	A (7)	A (8)
Three-vessel CAD with low CAD burden	A (7)	A (9)
Three vessel CAD with intermediate to high burden	U (4)	A (9)
Isolated left main stenosis	U (6)	A (9)
Left main stenosis and additional CAD with low CAD burden	U (5)	A (9)
Left main stenosis and additional CAD with intermediate to high CAD burden	I (3)	A (9)

Median Score 7 to 9 **:** Appropriate for indication (generally acceptable, **is** a reasonable approach for the indication)
Median Score 4 to 6: Uncertain for specific indication (**may** be generally acceptable, **may** be a reasonable approach for the indication). Uncertainty implies that more research and/or patient information is needed to classify the indication definitively.
Median Score 0 to 3*:* Inappropriate for that indication (**not** generally acceptable, **not** a reasonable approach for the indication).

Newer generation FDA approved stents: general indications/contraindications

- Indications (FDA)
  - 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
  - Lesions that don't allow for complete balloon inflation or proper stent placement

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Health Technology Clinical Committee Findings and Coverage Decision

Topic: Cardiac Stent
Meeting Date: May 8, 2009
Final Adoption: October 30, 2009

Number and Coverage Topic

20090508A – Cardiac Stent: Drug Eluting Stents (DES) and Bare Metal Stents (BMS) for the treatment of coronary artery disease.

HTCC Coverage Determination

Cardiac Stent is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination**.**

HTCC Reimbursement Determination

The committee reviewed the findings and decision, and amended the limitations of coverage to read as follows:

❖ Limitations of Coverage

1) Bare Metal Stents are covered without conditions.
2) Drug eluting stents are conditionally covered for:
    a. Stent diameter of 3 mm or less;
    b. Length of stent(s) of longer than 15 mm placed within a single vessel;
    c. Patients with diabetes mellitus;
    d. Stents placed to treat in stent restenosis; or
    e. Treatment of left main coronary disease.

❖ Non-Covered Indicators

Drug eluting stents are not covered for other indications.

❖ Agency Contact Information

Agency	Contact Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

Health Technology Background

The Cardiac Stent topic was selected and published in August 2007 to undergo an evidence review process. 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. Prediction of which patients with CAD will have serious versus no or a mild symptom remains difficult.

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 potential advantages: physically opening the artery and being less invasive than bypass surgery. Cardiac Stent potential disadvantages: targeted solution to widespread disease, unclear protocols, clotting and re-operation. Important, unanswered questions remain about whether, when, and what type of stent placement is appropriate versus other medical management or surgery.

In March 2009, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed, Cardiac Stent report is 175 pages, identified 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.

Upon circulation of the draft findings and decision, comments were received from a committee member and provider and professional groups expressing concerns or disagreement with the draft decision. At the August 28th HTCC public meeting, the clinical committee reviewed the draft findings and decision and public comments. Based on public input and committee discussion, the committee would like additional expert input prior to finalizing the conditional coverage criteria to ensure that additional high risk groups were not inadvertently left out.

Ad Hoc Advisory Group Scope and Role: Participate in a group of technical experts to identify groups at high risk of restenosis and the evidence supporting it that are not currently included in the draft criteria. Approve a report to the HTCC, in time for distribution prior to the October 30, 2009 scheduled meeting. Subject to discussion within the group, provide report or testimony to the HTCC. Two HTCC members; a hospital association and agency representative; the evidence vendor and four cardiologists formed the workgroup. The workgroup met publicly, twice - on October 5th and 16th and selected Dr. Mike Ring to serve as the clinical chair. The workgroup started with a review of the task and a discussion of the potential high risk categories that were included in public comment. The list was updated based on comments, and members submitted some articles and other information to a central repository; reviewed the information; and eventually provided a ranking from 0 to 10 of importance of certain risk categories. After second discussion, a report was produced summarizing the categories and rankings by the workgroup members.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other presented information shows it is safe, effective and has value. The committee met on May 8th, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at http://www.hta.hca.wa.gov in the committee section.

Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee finds the following key factors relevant to the coverage decision:

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. Prediction of risk of serious complication 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).

1.3 The committee found that there was a large amount of randomized and observational studies available comparing DES and BMS on many of the important health outcomes they identified for stents. The committee relied most heavily, as did the evidence based technology assessment report, on one recent meta analysis of 38 trials including 18,000 patients, and summarized information from five previous health technology assessments, most conducted with their own meta-analysis, and one focusing on registry studies

1.4 The committee also considered additional evidence 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.

2. Is the technology safe?

The committee found that stent thrombosis was the most significant safety outcome measure, and discussed briefly bleeding and stent fracture. The report identified the following evidence:

2.1. The evidence based technology assessment report indicated that stent thrombosis is a rare, but serious complication (generally occurring in about 1.5% of cases) with potentially 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.

2.1.1. 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 they may be underpowered, three reported there was a higher risk of stent thrombosis with DES.

2.1.2. 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.

2.2. Stent Thrombosis in special populations (diabetics and acute MI): Most HTA's and the Stettler meta-analysis in specific subpopulations generally reported no statistically significant difference between BMS and DES in stent thrombosis rates. 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. Although, one HTA of registry data indicated higher in-stent thrombosis with DES (2.4 to 4.4%) versus BMS (0.8%).

2.3. Bleeding and Stent Fracture: the evidence based technology assessment report reviewed these safety issues, 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.

3. Is the technology effective?

The committee found that there were four key health outcomes that were most significant in assessing the technology's effectiveness. The report identified the following evidence:

3.1. Freedom from Overall and Cardiac Mortality:

3.1.1. The evidence based technology report includes death, and specifically cardiac-related death, as a key health outcome in treatments for cardiac artery disease and core evidence indicates no difference between DES and BMS. 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.

3.1.2. 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.

3.1.3. Studies including registry data cite the SCAAR (Sweeden) 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.

3.1.4. 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.

3.1.5. 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.

3.1.6. 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.

3.2. Freedom from MI

3.2.1. 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 and core evidence indicates no difference between DES and BMS.

3.2.2. 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%).

3.2.3. 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.

3.2.4. 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.

3.2.5. 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.

3.3. Freedom or reduction of Target vessel revascularization/target lesion revascularization (TVR)

3.3.1. 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 and that DES results in 11% fewer TVR than BMS.

3.3.2. The committee discussed the implication of dual anti-platelet therapy and whether that impacts revascularization rates.

3.3.3. 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.

3.3.4. 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%).

3.3.5. 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%).

3.3.6. 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.

3.4. Quality of Life

3.4.1. 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 this outcome. 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. Is the technology cost-effective?

The committee found that there was key information about cost and value:

4.1. There remains uncertainty regarding efficacy, effectiveness, and safety of DES versus BMS and differing assumptions contribute to variability in cost analysis. The incremental cost effectiveness ratios (ICER) were most influenced by the price premium of DES.

4.2. The evidence included 43 cost effectiveness studies, 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.

4.3. 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.

4.4. 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%.

4.5. State agency cost data: Utilization at the three agencies over the same time period is 15% BMS and 83% DES.

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:

5. Evidence availability and technology features

The committee concludes that the best available evidence on cardiac stents has been collected and summarized, and the overall quality of this evidence is high and robust as follows:

5.1. There was a large amount of high quality, randomized and observational studies available comparing DES and BMS on many of the important health outcomes they identified for stents. The committee relied most heavily on a recent meta analysis of 38 trials including 18,000 patients, and summarized information from five previous health technology assessments.

5.2. Randomized or well designed controlled trials provide the highest level of confidence for proving efficacy, especially with adequate participants, assessment of all patient centered health outcomes, and for sufficient duration. The very recent registry studies may provide additional information (e.g. rare complications and additional subpopulation data) but should not be relied upon as the basis to overturn the RCT results. Recently published articles not included in critical appraisal were considered, but would not be relied upon for final determination without seeking additional review by evidence vendor.

5.3. Heart disease is a burdensome condition with potentially significant and life threatening outcomes. It is widespread condition with imprecise measures of those at risk for life threatening outcomes and thus is a significant health concern to ensure the right treatment for those at high risk as well as low risk.

5.4. Many treatments, including non-invasive treatments, are covered by agencies. The type of stent selected (issue for current review) does not have an effect on mortality or heart attack – the two potentially life threatening outcomes, but may impact need for revascularization need and cost.

6. Is it safe?

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

6.1. *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.

6.2. *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.

6.3. *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.

7. 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:

7.1. The committee identified four key health outcomes that impacted effectiveness; with three have high quality evidence available.

7.2. *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.

7.3. *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.

7.4. *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.

7.5. *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

8. 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.

8.1. 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).

8.2. 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 per QALYs.

8.3. For certain subpopulations of high risk patients, some HTAs reported, and five committee members agreed that DES is cost-effective.

9. Medicare Decision and Expert Treatment Guidelines

The committee deliberations included a discussion of National Medicare Decisions and expert treatment guidelines, and an understanding that the committee must find substantial evidence to support a decision that is contrary. RCW 70.14.110. Based on the following, the Committee concludes that a decision consistent with two expert treatment guidelines and contrary to the National Medicare Coverage Decision and one treatment guideline is justified:

9.1. 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.

9.2. 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.

9.3. 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 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 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 to continue coverage for bare metal stents and 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).

Health Technology Clinical Committee Authority

Washington State's legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC), determines how selected health technologies are covered by several state agencies. RCW 70.14.080-140. These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards[2]:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms[3]:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
-

The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.**Using evidence as the basis for a coverage decision**

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Health Technology Evidence Identification

Discussion Document:

What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Stent thrombosis	
Peri-procedural: death, MI	
Stroke	
Major bleeding	
Efficacy – Effectiveness Outcomes	**Efficacy / Effectiveness Evidence**
All cause mortality	
Cardiac mortality	
Myocardial infarction (MI)	
HRQOL- pt reported	
Symptom relief- pt reported	
Function- pt reported	
Revascularization- target vessel	
Repeat stent revascularization	
Special Population / Considerations Outcomes	**Special Populations/ Considerations Evidence**
Cost	
Cost-effectiveness	
Cost Outcomes	**Cost Evidence**
Costs	
Cost-effectiveness	

Medicare Coverage and Guidelines

[From page 73 of Final Evidence Report]

Medicare (National Coverage Determination)
The Centers for Medicare and Medicaid Services (CMS) will cover PCI both with and without the placement of a stent 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 have angina refractory to OMT, objective evidence of myocardial ischemia, lesions amenable to angioplasty. Coverage for all other is at the discretion of local CMS contractors.

[See pages 58-69 of Final Evidence Report for detailed information on clinical guidelines]

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
    - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
    - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
    - Refer to evidence identification document and discussion.
    - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
    - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

(2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
    - What are the known conditions/criteria and evidence state
    - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency

or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective				
Safe				
Cost-effective				

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered ____ Covered Unconditionally ____ Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.