Health Technology Assessment

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

Date: Friday, April 10, 2009

Health Technology Assessment Program
676 Woodland Square Loop SE
P.O. Box 42712
Olympia, WA 98504-2712
http://www.hta.hca.wa.gov

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

Provided by:

Spectrum Research, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Ann M. Derleth, PhD, MSPH
Erika D. Ecker, BS
Robin E. Hashimoto, PhD
Carin M. Olson, MD, MS
Joseph R. Dettori, PhD, MPH

With assistance from:
Ellen Van Alstyne, MS
Catherine O. Johnson, PhC
Jennifer A. Mayfield, MD, MPH

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

TABLE OF CONTENTS--Appendices

Appendix A_Search Strategies

Medline Searches:
Meta-analyses, Randomized Controlled Trials- Key Questions 1, 2 and 3

#	Search terms	# citations
1	"Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh]	151129
2	"Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	52828
3	#1 AND #2	11132
4	#1 AND #2 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	2559
5	#1 AND #2 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English	387
6	Search #5 NOT (imaging OR fibrinolytic OR pharmacokinetic) Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English	343
7	Search #5 NOT (imaging OR fibrinolytic OR pharmacokinetic OR ultrasound) Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English	294
8	Search ("Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus") AND ("Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh]) AND systematic[sb] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, English	72

From this search 72 of the 294 were potentially relevant and selected for abstract review based on title

Adverse events search Key Question 2

#	Search terms	# citations
1	"Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh]	151129
2	"Stents/adverse effects"[Mesh] OR "Drug-Eluting Stents/adverse effects"[Mesh] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English	92
3	#1 AND #2 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English	54
4	"Stents/adverse effects"[Mesh] OR "Drug-Eluting Stents/adverse effects"[Mesh] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	1059

5	"Coronary Vessels"[Mesh] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	2509
6	"Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	14377
7	#4 AND (#5 OR #6) Limits: **P**ublication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	518
8	#4 AND #5 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	77
9	Search #4 AND #6 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	501
10	Search Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Comparative Study, English	117,555
11	Search #8 AND #10 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Comparative Study, English	89
12	"bleeding stent coronary"	181
13	#12 NOT review	15

From this set of search strategies 22 articles were selected for abstract review based on title only.

Medline: Registry search: **Key Questions 1, 2, 3** Last search: January 24, 2009

#	**Search terms**	**# citations**
1	"Myocardial Ischemia/therapy"[MEesh] OR "Myocardial Revascularization"[Mesh]	151,301
2	"Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	52,939
3	#1 & #2	11,171
4	"Registries[Mesh]	34,293
5	#3 & #4	350
Limits:	Publication Date from 2006/07/01 to 2009/01/15, only items with abstracts, Humans, English	131

The title and abstracts of the 131 articles were reviewed.
Exclusions:

Already in HTA registry reviews	13
Not the topic of interest	34
Not comparative or not comparison of interest	71

Remaining (16) papers pulled – 3 related to special populations

Econ lit search: Key Questions 1, 2, 3 Last search: February 20, 2009

#	Search terms	# citations
1	"Myocardial Ischemia/therapy"[MEesh] OR "Myocardial Revascularization"[Mesh]	151,712
2	"Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	53,234
3	#1 & #2	11,319

4	"Costs"	53,234
5	#3 & #4 and	
Limits:	Publication Date from 2006/07/01 to 2009/02/20, only items with abstracts, Humans, English	69

Title review reduced it to 23 articles.
Already reviewed in HTA 2
Not cost effectiveness/formal econ analysis- 14
Not comparator of interest 4
Studies selected for full review– 5
Used in previous HTA or CE systematic lit review, therefore excluded- 3 (Groeneveld, Ligthart, Kuukasjarvi (FinOHTA))
Used in this HTA = 1 (LaRocca)
Excluded on paper review – not full cost effectiveness study (Mahieu)
Other papers in econ section – HTA reports – were already available from prior searches

INAHTA- Database search: Key Questions 1, 2 and 3 - January 8, 2009

RESTRICT YR 2006 2009

1. MeSH Stents: 472 documents found
2. coat* OR elut* OR "Sirolimus" OR "Paclitaxel" OR taxus OR cypher OR medicat*: 3569 documents found
3. #1 AND #2: 37 documents found
4. english:la: 36557 documents found
5. # 3 AND #4: 36 documents found
   - DARE n = 17
   - NHS EED n = 16
   - HTA n = 3 [all 3 previously identified – NICE/NHS, Ontario, ECRI)

EBMASE SEACHES-
Dates to search: June 2007- February 1, 2009

Search for Safety and Efficacy Meta-analyses

search #	terms
1	('stents'/exp OR 'stents') AND [2007-2009]/py
2	coronary AND [2007-2009]/py
3	coronary* AND [2007-2009]/py
4	#1 AND #3
5	*eluting AND [2007-2009]/py
6	#4 AND #5
7	#5 AND[meta analysis]/lim AND [2007-2009]/py
8	#6 AND[meta analysis]/lim AND [2007-2009]/py

Repeated same strategy replacing meta-analysis with RCT

Search for Registries in EMBASE

search #	terms
1	('stents'/exp OR 'stents') AND [2007-2009]/py
2	coronary AND [2007-2009]/py
3	coronary* AND [2007-2009]/py
4	#1 AND #3
5	*eluting AND [2007-2009]/py
6	#4 AND #5
7	'registries'/exp AND [2007-2009]/py
8	#6 AND #7 AND [2007-2009]/py

EBMASE For Economic studies:

search #	terms
1	'socioeconomics'/exp
2	'cost benefit analysis'/exp
3	'cost effectiveness analysis'/exp
4	'cost of illness'/exp
5	'cost control'/exp
6	'economic aspect'/exp
7	'financial management'/exp
8	'health care cost'/exp
9	'health care financing'/exp
10	'health economics'/exp
11	'hospital cost'/exp
12	'finance'/exp
13	'funding'/exp
14	fiscal
15	financial
16	#12 OR #13 OR #14 OR #15
17	'cost minimization analysis'/exp
18	estimate*:ti,ab,de,cl
19	cost*:ti,ab,de,cl
20	variable*:ti,ab,de,cl
21	unit*:ti,ab,de,cl
22	'#19 * 4 #18' OR '#18 *4 #19'
23	'#19 *4 #20' OR '#20 *4 #19'
24	'#19 *4 #21' OR '#21 *4 #19'
25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 OR #22 OR #23 OR #24
26	'drug eluting stent'/exp
27	#25 AND #26 AND [2007-2009]/py
28	#27 AND [humans]lim
29	'heart disease'/exp
30	#28 AND #29
31	#30 AND [english]/lim

From the 218 citations yielded from the EMBASE searches, 10 unique references were found after the following deletions:

1. 43 duplicates already included in our Master EN library from previous searches were deleted, 175 references remaining
2. studies not in English- n = 13, with 162 references remaining
3. 4 deleted - in list of Econ studies, registry studies or RCTs included in HTAs or other meta-analyses

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ- Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

INAHTA membership sites searched for cardiac stent HTAs or economic analyses outside of the UK or Canada. Searches of the UK and Canada member sites were conducted

Search as of January 20, 2009-

Australia
MSAC www.msac.gov.au
AHTA www.adelaide.edu.au/ahta
Australia and New Zealand Horizon Scanning Network (ANZHSN) www.horizonscanning.gov.au
ASERNIP-S www.surgeons.org/asernip-s

New Zealand
HSAC www.healthsac.net

France
HAS http://www.has-sante.fr
CEDIT http://cedit.aphp.fr

Belgium
KCE www.kenniscentrum.fgov.be

Switzerland
MTU-SFOPH www.snhta.ch

The Netherlands
ZonMw www.zonmw.nl
GR www.gr.nl
CVZ www.cvz.nl

Denmark
DSI www.dsi.dk
DACEHTA www.dacehta.dk

Sweden
SBU www.sbu.se

Austria
LBI of HTA http://hta.lbg.ac.at

Germany
IQWiG www.iqwig.de
DAHTA www.egms.de

USA
AHRQ www.ahrq.gov

Canada
IHE www.ihe.ca
Mexico
CENETEC www.cenetec.goc.mx

HTA database www.crd.york.ac.uk/crdweb/

Appendix B. Level of Evidence Determination

Methods for critical appraisal and level of evidence assessment

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine, [Phillips] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group [Atkins, 2004] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ) [West]. Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Procedures for determining adherence to level of evidence (LoE) criteria

Each study was rated against pre-set criteria that resulted in an evidence rating (Level of Evidence I, II, III, or IV) and presented in a table. For therapeutic articles, the criteria are listed in the Table below and an example is given. All criteria met are marked. A blank for the criterion indicates that the criterion was not met, could not be determined or was not reported by the author.

Table B.1. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size
II	Moderate or Poor quality RCT	• Violation of any of the criteria for good quality RCT
	Good quality Cohort	• Blind or independent assessment in a prospective study or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 85%+ • Adequate sample size • Controlling for possible confounding†
III	Moderate or Poor quality Cohort	• Violation of any of the criteria for good quality cohort
	Case Control	
IV	Case Series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Table B.2. Example of methods evaluation for articles on therapy

Methodological Principle	Author 1	Author 2	Author 3	Author 4
Study design Randomized controlled trial Cohort Study Case-series	■	■	■	■
Statement of concealed allocation*	■	■		
Intention to treat*	■	■		
Independent or blind assessment	■		■	
Co-interventions applied equally	■	■	■	
Complete follow-up of ≥85%	■			■
Adequate sample size	■	■	■	
Controlling for possible confounding	■	■	■	
Evidence Level	**I**	**II**	**III**	**IV**

* Applies to randomized controlled trials only.

Table B.3. Assessment check list for HTAs, systematic reviews and meta-analyses

	Example
Methodological Principle*	
Purpose, aim, study question, and/or hypothesis stated	■
Literature search described	■
Unpublished sources sought	■
Inclusion/exclusion criteria stated	■
Characteristics of included studies provided	
Quality of included studies formally assessed and method described	■
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II
Quantitative analysis	
• Studies appraised critically	
• Magnitude and direction of effect sizes evaluated	■
• Consistency of effect sizes evaluated	■
• Stability of effect sizes (e.g. confidence intervals) evaluated	■
• Scientific quality of studies considered in conclusions	
• Methods to enhance objectivity incorporated	■
Quantitative analysis	
• Heterogeneity evaluated	■
• Heterogeneity explored, if present	NA
• Missing data handled appropriately	
• Effect sizes pooled appropriately	■
• Sensitivity analysis conducted	
• Publication bias explored	
Potential conflict of interest stated	

Report type:

The type and purpose of the report influence the extent to which some of the factors listed above are applicable. For instance, for some purposes, quantitative analysis and statistical pooling may not be possible, necessary or appropriate.

Health Technology Assessments (HTAs) and similar reports are those which systematically evaluate the effectiveness, safety, cost implications and other properties of technology use (frequently therapeutic or diagnostic technologies) in health care, generally with respect to competing alternatives. HTA methods generally include formal systematic search for and critical appraisal of medical literatures and may include meta-analytic techniques for combining data across studies. HTAs and similar reports are frequently done by governmental agencies and/or commissioned by such agencies from private vendors. The primary purpose is to advise or inform technology-related decision and policy-making in a variety of settings, including individual (e.g. patient and/or provider) and institutional (provider organizations, health plans, government agencies) on local, regional, national or international levels.

Systematic review is a general term used to describe focused summaries of medical literature to address specific clinical questions using explicit strategies for literature search, inclusions and exclusions of studies and documentation of processes used to find and summarize data from the medical literature. Systematic reviews may or may not include formal meta-analysis and pooling of data.

Meta-analysis is a term used for systematic reviews which use quantitative, statistical methods to pool data to summarize results across studies. A systematic review generally forms the basis of meta-analysis in that a formally systematic approach to finding and selecting relevant studies for summarization is done. Pooling of data across studies may enhance statistical power to detect differences between groups. The quality of the studies to be pooled and potential for bias based on methodological flaws in individual studies needs to be considered. Methods for pooling studies (or individual patient data from a number of studies) should be stated and appropriate for the types of data and studies from which they come. Heterogeneity across studies can compromise the credibility of the pooled estimate. Heterogeneity can be related to clinical, patient or study characteristics which may or may not manifest in statistical heterogeneity. Formal evaluation and exploration of statistical heterogeneity should be done using accepted methods and modeling done accordingly (e.g. use of random effects model instead of fixed model). In evidence-based medicine, meta-analyses of the highest quality studies (usually RCTs) is considered to the highest level of evidence, however, limitations of meta-analysis should also be considered.

Pooled analyses frequently combine outcomes from individual patients enrolled in primary studies; the patient is the unit of analysis. These analyses may not be part of a complete systematic review of the literature. As with meta-analyses, tests for homogeneity should be done and the basis of pooling should be well described.

Criteria:

1. **Purpose, aim,** study (or key) questions and/or hypothesis for the report or analysis should be stated clearly.

2. **The literature search** should be described including timing of the search, data sources searched and search strategies used.

3. **Inclusion and exclusion criteria** for include studies should be stated and relevant to the purpose and questions to be addressed in the report and consistent with accepted methods for conduct of the type of report.

4. **Characteristics of included studies** should be given with regard to study design, populations studied and technologies applied as relevant to the report's purpose and aims.

5. **Quality of included studies** should be formally assessed using a specified system for evaluation that takes into account study design, potential sources of bias, methodological limitations, statistically power and use of appropriate analyses (e.g. controlling for confounding), usually leading to an overall score, classification or grade of evidence.

6. **The Level of Evidence (LoE)** of individual studies included should be the highest possible based on the primary focus of the report. Spectrum Research's LoE criteria are described below. If all included studies are RCTs (randomized controlled trials), the LoE using Spectrum Research's approach is either I or II. For trials of surgery or other interventions where clinician and/or patients are not blinded, the LoE is often II, since there is the opportunity for bias in assessment by the clinician and/or bias in patient response. Whether this criterion is met depends on the primary outcome and whether it could have been assessed in a blinded fashion. Subanalyses of RCTS are considered LoE II/III since randomization is generally not preserved. Registry studies are primarily retrospective cohort studies and subject to bias from a variety of sources and are classified as LoE III.

7. **Qualitative analysis:** Some reports may primarily provide qualitative assessment of included studies. Systematic reviews and meta-analyses should incorporate most of these components. The extent to which the following criteria are met provides some indication of the overall quality of the assessment

    - **Critical appraisal of included studies** – The report should describe a formal method of evaluating individual quality with regard to study design, methodological issues and potential for bias, such as the LoE system described below. A "grade" or other classification of study quality should be described and applied across studies.
    - **Evaluation of estimate magnitude and direction:** The report should accurately interpret and describe these, including statistical significance and any statistical adjustments to effect size estimates.
    - **Estimate consistency**: Reports should describe the general patterns of effect size estimates across studies and how consistent they are. Reports should describe if estimates from different studies have the same general direction and magnitude across studies or not.
    - **Estimate stability**: Reports should comment on the general stability of estimates, based in consideration of things like confidence intervals, effects of missing data,

study sample size, confounding and other factors which may influence estimate stability
- Consideration of the **overall scientific quality** of the evidence for a specific question: Do the report's conclusions consider the overall strength of evidence based on the scientific quality of the studies, the consistency, direction and magnitude of the estimates used to formulate the conclusions?

8. **Quantitative analysis: T**his involves the statistical combining and evaluation of data from multiple studies and applies to situations where meta analysis is done.
   - **Pooling** of data may or may not be appropriate depending on the types of studies and data available. Various methods for pooling data are possible. The report should adequately describe how pooling was done and methods used to create summary estimates should be appropriate to the data, included studies and consideration of factors such as clinical and statistical heterogeneity. Methods for study weighting and modeling of pooled estimates should be described.
     - Formal meta-analysis is a structured process with specific types of methodologies for combining data, weighting studies, modeling and assessing heterogeneity across studies in order to arrive at pooled estimates of effect size.
     - Not all reports that pool data across studies are true meta-analyses from a methodological perspective.
   - **Evaluation of heterogeneity**. Description of how heterogeneity was evaluated should be consistent with the type of analysis and modeling done to pool the data and specific criteria for determining heterogeneity should be described and applied. The results of heterogeneity evaluations should be stated.
   - **Exploration of heterogeneity if present**: If there is significant heterogeneity present, a description of possible sources and methods used to explore it should be described and the results reported.
   - **Missing data:** Does the report describe missing data, how it was handled and the extent to which it may influence estimate stability, which may in part be done with sensitivity analysis
   - **Sensitivity analysis:** The report should explore the stability of estimates using appropriate sensitivity analyses, including around missing data or areas of heterogeneity. Exploration of publication bias should be described as appropriate.

9. **Potential conflicts of interest:** Is the source of funding for the report stated and/or is there information on potential conflicts of interest for authors presented?

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence for the relevant question or topic is determined. Methods for determining the overall strength of evidence for diagnostic studies are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (LoE), quantity of studies and consistency of results across studies as described by AHRQ [West].

The following definitions are used by SRI to determine whether or not the body of evidence meets the criteria for each domain:

Domain	Definition/Criterion
Quality	• At least 80% of the studies are LoE I or II
Quantity	• There are at least three studies which are adequately powered to answer the study question
Consistency	• Study results would lead to a similar conclusion (similar values, in the same direction) in at least 70% of the studies

Based on the criteria described above, the possible scenarios that would be encountered are described below. Each scenario is ranked according to the impact that future research is likely to have on both the overall estimates of an effect and the confidence in the estimate. This ranking describes the overall "Strength of Evidence" (SoE) for the body of literature on a specific topic. The method and descriptions of overall strength are adapted for diagnostic studies from system described by the GRADE Working Group [Atkins] for the development of clinical guidelines.

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	**High**	Very unlikely to change confidence in effect estimate	+	+	+
2	**Moderate**	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	**Low**	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	**Very Low**	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al [Ofman] QHES embodies the primary components relevant for critical appraisal of economic studies [Chiou]. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention

comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (eg, complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:
- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more).
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument **Study** _____

Questions	Points	Yes	No
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**		
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**		
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**		
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**		
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**		
6. Was incremental analysis performed between alternatives for resources and costs?	**6**		
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**		
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**		
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**		
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**		
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**		
16. Was there a statement disclosing the source of funding for the study?	**3**		
TOTAL POINTS	**100**		

Appendix C. RCTs included in meta-analyses or HTAs

Table C1. RCTs included in HTA or similar reports

	HTA or similar report								
	EUnetHTA* 2008	ECRI 2008	CTAF† 2007	Hill§ NHS HTA 2007	Hayes† Report 2007	FinOHTA § ‡ 2007	CCOHTA § ‡ 2005	AETMIS ‡ 2004	MSAC 2004
No. patients	**Total NR**	**7321**	**Total NR**	**Total NR**	**Total NR**	**Total NR**	**5090**	**Total NR**	**3659**
No. RCTs	**17**	**14**	**22**	**17**	**16**	**12**	**11**	**15**	**7**
RCTs									
RAVEL	x	x	x	x	x	x	x	x	x
SIRIUS	x	x	x	x	x	x	x	x	x
C-SIRIUS	x	x	x	x	x	x	x	x	x
E-SIRIUS	x	x	x	x	x	x	x	x	x
TAXUS I	x	x	x	x		x	x	x	x
TAXUS II	x	x	x	x		x	x	x	x
TAXUS IV	x	x	x	x		x	x	x	x
TAXUS V de novo	x	x	x	x					
TAXUS VI	x	x	x						
ASPECT			x			x	x	x	
ELUTES	x		x		x	x	x	x	
DELIVER I	x		x			x	x	x	
FUTURE I			x					x	
FUTURE II			x					x	
SES-SMART	x	x	x	x	x				
ENDEAVOR II			x	x					
PATENCY			x			x	x	x	
SCORE			x					x	
BASKET	x	x	x	x	x	x			
DIABETES	x	x	x	x	x				
SCANDSTENT		x	x	x	x				
PRISON II					x				
TYPHOON					x				
DECODE					x				
Pache et al		x	x	x	x				
SCORPIUS					x				
SESAMI					x				
STRATEGY				x	x				
JUPITER									
JUPITER II									
SPIRIT I				x					
STEALTH									
Li				x					
PASSION									
HAAMU-STENT									
RRISC									
MISSON									
SELECTION									
ACTION			x					x	
Di Lorenzo									
Pasceri									
Erglis et al									
Park	x								
Stone 2004	x								
Weisz	x								
Ortolani et al									

*Not a complete HTA with partially outdated content.

† These reports do not perform their own meta-analyses. They describe outcomes from published meta-analyes, RCTs and other studies.

§ Hill uses published and unpublished sources including confidential data for ENDEAVOR. The total N used in analyses is not provided.

‡ Primarily an economic evaluation

Table C2. RCTs included in KCE* or HTA/similar reports

	Published meta-analyses in KCE or HTA/similar reports

	Moreno† 2007	Kastrati 2007	Stone 2007	Camenzind 2007	Mauri 2007	Ellis 2007	Spaulding 2007
No. patients	**9791**	**4958**	**5261**	**5112**	**4545**	**3445**	**1748**
No. RCTs	**23**	**14**	**9**	**9**	**8**	**4**	**4**
RCTs							
RAVEL	x	x	x	x	x		x
SIRIUS	x	x	x	x	x		x
C-SIRIUS	x	x	x	x	x		x
E-SIRIUS	x	x	x	x	x		x
TAXUS I	x		x	x	x		
TAXUS II	x		x	x	x	x	
TAXUS IV	x		x	x	x	x	
TAXUS V de novo	x		x	x	x	x	
TAXUS VI	x		x	x		x	
ASPECT							
ELUTES							
DELIVER I							
FUTURE I	x						
FUTURE II	x						
SES-SMART	x						
ENDEAVOR II	x						
PATENCY							
SCORE							
BASKET	x	x					
DIABETES	x	x					
SCANDSTENT	x	x					
PRISON II	x	x					
TYPHOON		x					
DECODE		x					
Pache et al	x	x					
SCORPIUS		x					
SESAMI		x					
STRATEGY	x	x					
JUPITER	x						
JUPITER II	x						
SPIRIT I	x						
STEALTH	x						
Li							
PASSION							
HAAMU-STENT							
RRISC							
MISSON							
SELECTION							
ACTION							
Di Lorenzo							
Pasceri							
Erglis et al							
Park							
Stone 2004							
Weisz							
Ortolani et al							

*The KCE-Belgian HTA uses select meta-analyses to describe efficacy, effectiveness and safety but focuses primarily on economic evaluation based on Belgian registry data.

†TAXUS SR and TAXUS MR trials counted together as TAXUS II in other meta-analyses so are counted as 1 trial here for Moreno 2007 a and b making the total 20 versus 21 trials included; in addition, BASKET-Cy and BASKET-Tx were also combined in other meta-analyses and are counted as 1 trial for Moreno (b) making the total studies 23 versus the 25 reported in the abstracts.

Table C3. Special population subgroup analyses included in KCE or similar reports

	Published meta-analyses of special populations subgroup analyses					
	Boyden 2007 (diabetes)	**Stettler 2006 (diabetes)**	**Lord 2005 (diabetes, lesion, vessel types)**	**Solinas 2007 (gender)**	**Kereiakes 2006 (stent overlap)**	**Moreno 2005 (stent length)**
No. patients	**1520**	**4513**	**3390**	**1748**	**1510**	**5030**
No. RCTs	**10**	**10**	**7**	**4**	**3**	**10**
RCTs						
RAVEL	x	x	x	x		x
SIRIUS	x	x	x	x	x	x
C-SIRIUS	x	x	x	x	x	x
E-SIRIUS	x	x	x	x	x	x
TAXUS I		x	x			x
TAXUS II	x	x	x			x
TAXUS IV	x	x	x			x
TAXUS V de novo	x					
TAXUS VI	x	x				
ASPECT						x
ELUTES						x
DELIVER I						x
FUTURE I						
FUTURE II						
SES-SMART	x	x				
ENDEAVOR II						
PATENCY						
SCORE						
BASKET						
DIABETES	x	x				
SCANDSTENT						
PRISON II						
TYPHOON						
DECODE						
Pache et al						
SCORPIUS						
SESAMI						
STRATEGY						
JUPITER						
JUPITER II						
SPIRIT I						
STEALTH						
Li						
PASSION						
HAAMU-STENT						
RRISC						
MISSON						
SELECTION						
ACTION						
Di Lorenzo						
Pasceri						
Erglis et al						
Park						
Stone 2004						
Weisz						
Ortolani et al						

Table C4. RCTs not included in KCE* or HTA or similar reports

	Published meta-analyses not in KCE or HTA/similar reports				
	Fuchs 2008	**Stettler 2007**	**Moreno§ 2007**	**Lemos 2007**	**Stone 2007b**
No. patients	**5373**	**18,023**	**8641**	**4982**	**3445**
No. RCTs	**15**	**38†**	**20**	**10**	**4**
RCTs					
RAVEL	x	x	x	x	
SIRIUS	x	x	x	x	
C-SIRIUS	x	x	x	x	
E-SIRIUS	x	x	x	x	
TAXUS I	x	x	x	x	
TAXUS II		x	x	x	x
TAXUS IV		x	x	x	x
TAXUS V de novo		x	x		x
TAXUS VI		x	x		x
ASPECT	x			x	
ELUTES	x			x	
DELIVER I				x	
FUTURE I	x		x		
FUTURE II			x		
SES-SMART	x	x	x		
ENDEAVOR II	x		x		
PATENCY					
SCORE					
BASKET					
DIABETES	x	x	x		
SCANDSTENT	x	x	x		
PRISON II	x	x	x		
TYPHOON	x	x			
DECODE		x			
Pache et al	x	x	x		
SCORPIUS		x			
SESAMI		x			
STRATEGY			x		
JUPITER					
JUPITER II			x		
SPIRIT I			x		
STEALTH					
Li					
PASSION		x			
HAAMU-STENT		x			
RRISC		x			
MISSON		x			
SELECTION					
ACTION					
Di Lorenzo					
Pasceri					
Erglis et al					
Park					
Stone 2004					
Weisz					
Ortolani et al		x			

*The KCE-Belgian HTA uses select meta-analyses to describe efficacy, effectiveness and safety but focuses primarily on economic evaluation based on Belgian registry data

†This network meta-analysis included 38 trials total, 23 of which were direct comparisons of either SES or PES with BMS and listed in this table.

§ TAXUS SR and TAXUS MR trials counted together as TAXUS II in other meta-analyses so are counted as 1 trial here for Moreno 2007 a and b making the total 20 versus 21 trials included; in addition, BASKET-Cy and BASKET-Tx were also combined in other meta-analyses and are counted as 1 trial for Moreno (b) making the total studies 23 versus the 25 reported in the abstracts.

Table C5. Special population subgroup analyses not included in KCE or similar reports

	Published meta-analyses of special populations subgroup analyses						
	Stettler 2008 (diabetes)	**Kumbhani 2008 (diabetes)**	**Patti 2008 (diabetes)**	**Kirtane 2008 (diabetes) pooled analysis**	**Kastrati 2007 (acute MI)**	**Pasceri 2007 (Acute MI)**	**Moses 2006 (intermediate target lesions)**
No. patients	**10,947 non DM, 3852 DM**	**9799 (1879 diabetic)**	**1141 diabetic patients**	**3513**	**2786**	**2357**	**167**
No. RCTs	**35***	**12**	**9**	**5**	**8**	**7**	**4**
RCTs							
RAVEL	x	x	x				
SIRIUS	x	x	x				x
C-SIRIUS	x		x				
E-SIRIUS	x	x	x				
TAXUS I	x			x			
TAXUS II	x	x	x	x			
TAXUS IV	x	x	x	x			x
TAXUS V de novo	x	x		x			
TAXUS VI	x	x	x	x			
ASPECT							
ELUTES							
DELIVER I							
FUTURE I							x
FUTURE II							x
SES-SMART	x	x	x				
ENDEAVOR II							
PATENCY							
SCORE							
BASKET	x				x		
DIABETES	x	x	x				
SCANDSTENT	x						
PRISON II	x						
TYPHOON	x				x	x	
DECODE	x	x					
Pache et al	x	x					
SCORPIUS	x	x					
SESAMI	x				x	x	
STRATEGY					x	x	
JUPITER							
JUPITER II							
SPIRIT I							
STEALTH							
Li							
PASSION	x				x	x	
HAAMU-STENT	x				x	x	
RRISC	x						
MISSON	x				x	x	
SELECTION	x						
ACTION							
Di Lorenzo					x		
Pasceri						x	
Erglis et al	x						
Park							
Stone 2004							
Weisz							
Ortolani et al	x						

*This network meta-analysis included 35 trials total, 26 of which were direct comparisons of either SES or PES with BMS and listed in this table.

Appendix D. Registries, Nonrandomized Trials and Economic Studies Included in Previous HTA or meta-analyses

Table D1. Registries included in previous HTA

	HTA or similar reports				
	Ontario 2007	**KCE 2007**	**Hill 2007**	**Hayes 2007**	**CTAF 2007**
No. registries	14	7	4	3	1
Registries*					
ARTS, ARTS II (n = 271)	x				
Belgian Registry (BWGIC) (n = 15237)		x			
BRIDGE (n = 1000)			x		
CCN CARDIACCESS (n = 20321)	x				
de Araujo Goncalves et al (n = 203)		x			
DEScover (n = 5541)				x	
DEScover (n = 6906)	x	x			
DEScover (n = 7500 goal?)			x		
Eisenstein Duke Heart Center (n = 2555)	x				
Eisenstein Duke Heart Center (n = 4666)					x
KOMATE (n = 92)	x				
Latib (n = 3650)	x				
LONG DES (n = 527)	x				
NHLB Dynamic Registry (n = 3223)		x			
NHLB Dynamic Registry (n = 2690)			x		
NHLB Dynamic Registry (n = 74)	x				
ONASSIS (n = 928)	x			x	
RESEARCH (n = 1171)			x		
RESEARCH (n = 958)	x				
SCAAR (n = 19771)	x	x		x	
STENT Registry (n = 4029)	x				
SVELTE Registry (n = 424)	x				
T-SEARCH/RESEARCH (n = 505)		x			
T-SEARCH/RESEARCH (n = 181)		x			
Titan PORI Registry (n = 405)	x				

*Some registries are listed multiple time because different studies were cited in the various HTAs. See the registry bibliography for a complete list.

Table D2. Registry References

Registries	Reference
ARTS, ARTS II (n = 271)	Duilesse B. Cost-effectiveness of PCI with or without drug-eluting stents versus bypass surgery for treatment of multivessel coronary disease among patients with diabetes mellitus: 1-year results from the ARTS trial and ARTS II registry [abstract]. J Am Coll Cardiol 2006;47(4 Suppl 2):29B.
Belgian Registry (BWGIC) (n = 15237)	KCE Chapter 5
BRIDGE (n = 1000)	Cordis Johnson and Johnson. Ongoing Cypher Trials: Cordis industry submission to NICE 2003. London: NICE
CCN CARDIACCESS (n = 20321)	Bowen et al, Ontario, Rept HTA002-0705-02
de Araujo Goncalves et al (n = 203)	de Araujo Goncalves P, Seabra-Gomes R. Teles R, Almeida M, Aguiar C, Raposo L, et al. Complementary effect of sirolimus-eluting stents and glycoprotein Iib/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: One-year follow up of single centre registry. Heart. 2006;92(8):1155-6.
DEScover (n = 5541)	Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA. 2007;297(18):1992-2000.
DEScover (n = 6906)	Williams DO, Abbott JD, Jip KE, DEScover Investigators. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: report of the DEScover Registry. Circulation 2006; 114:2154-62.
DEScover (n = 7500 goal)	Williams DO, Kereiakes DJ. Safety and efficacy of drug-eluting stents. Rev Cardiovasc Med 2005;6(Suppl. 1):S22-30. Simonton CA, Brodie BR, Wilson BH. Drug-eluting stents for emerging treatment strategies in complex lesions. Rev Cardiovascular Med 2005;6(Suppl. 1):S38-47.
Eisenstein Duke Heart Center (n = 2555)	Eisenstein El, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159-68
Eisenstein Duke Heart Center (n = 4666)	Eisenstein El, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. Dec 5 2006
KOMATE (n = 92)	Kim BK, Oh S, Jeon DW, Choi D, Jang Y, Kwon HM, et al. Clinical outcomes following sirolimus-eluting stent implantation in patients with end-stage renal disease: Korean Multicenter Angioplasty Team (KOMATE) Registry [in Korean, not in file]. Sunhwangi 2006;36(6):424-30.
Latib (n = 3650)	Latib A, Corbett S, Cosgrave J, Tavano D, Godino C, Palloshi A, et al. A real-world comparison of outcomes after bare metal and drug-eluting stent implantation [abstract no 428]. In: TCT 2006; 2006
LONG DES (n = 527)	Kim YH, Park SW, Lee CW, Hong MK, Gwon HC, Jang Y, et al. Comparison of sirolimus-eluting stent, placlitaxel-sluting stent, and bare metal stent in the treatment of long coronary lesions. Catheter Cardiovasc Interv 2006;67(2):181-7.
NHLB Dynamic Registry (n = 3223)	Abbott JD, Vlachos HA, Selzer F, et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). American Journal of Cardiology. 2007;99(5):626-31
NHLB Dynamic Registry (n = 2690)	Williams DO, Kereiakes DJ. Safety and efficacy of drug-eluting stents. Rev Cardiovasc Med 2005;6(Suppl. 1):S22-30. Laskey W, Williams D, Vlachos H, Cohen H, Holmes D, King S, et al. Changes in the practice of percutaneous coronary intervention: a comparison of enrollment waves in the National Heart, Lung and Blood Institute (NHLBI) Dynamic Registry. Am J Cardiol 2001; 87:964–9.
NHLB Dynamic Registry (n = 74)	Halkin A, Selzer F, Marroquin O, Laskey W, Detre K, Cohen H. Clinical outcomes following percutaneous coronary intervention with drug-eluting vs, bare-metal stents in dialysis patients. J Invasive Cardiol 2006;18(12):577-83.
ONASSIS (n = 928)	Voudris V, Alexopoulos E, Karyofillis P, Malakos J, Manginas A, Spargias C, et al. Prospective native coronary artery stenosis treated with sirolimus-eluting stend

	(ONASSIS) registry--acute results and mid-terms outcomes: a single-center experience. J Invasive Cardiol 2005;17(8):401-5.
RESEARCH (n = 1171)	Lemos PA, Serruys PW, Van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the 'real-world': the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry. Circulation 2004;109:190–5.155-157, 91 Arampatzis CA, Hoye A, Lemos PA, Saia F, Tanabe K, Degertekin M, et al. Elective sirolimuseluting stent implantation for multivessel disease involving significant LAD stenosis: one-year clinical outcomes of 99 consecutive patients – The Rotterdam experience. Catheter Cardiovasc Interv 2004;63:57–60. Degertekin M, Arampatzis CA, Lemos PA, Saia F, Hoye A, Daemen J, et al. Very long sirolimuseluting stent implantation for de novo coronarylesions. Am J Cardiol 2004;93:826–9. Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL. Risk of thrombosis with the use of Sirolimuseluting stents for percutaneous coronary intervention (from registry and clinical trial data). Am J Cardiol 2005;95:1469–72.
RESEARCH (n = 958)	Daemen J, Ong ATL, Stefanini GG, Tsuchida K, Spindler H, Sianos G, et al. Three-year clinical follow-up of the unrestricted use of sirolimus-eluting stents as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry. Am J Cardiol 2006;98(7):895-901.
SCAAR (n = 19771)	Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with durg-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356(10):1009-19.
STENT Registry (n = 4029)	Brodie B, Stuckey T, Pulsipher M, Downey W, Humphrey A, Bradshaw B, et al. Stent thrombosis and target vessel revascularization following primary percutaneous coronary intervention with drug-eluting stents versus bare metal stents for ST elevation myocardial infarction: results from the STEN Registry [abstract]. J Am Coll Cardiol;47(4 Suppl 2):41B.
SVELTE Registry (n = 424)	Meier B, Sousa E, Guagliumi G, Van den BF, Grenadier E, Windecker S, et al. Sirolimus-eluting coronary stents in small vessels. Am Heart J 2006; 151(5):1019.e1-1019.e7.
T-SEARCH/RESEARCH (n = 505)	Daemen J, Tanimoto S, Garcia-Garcia HM, Kukreja N, van de Sande M, Sianos G, et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents veruses bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH) Registries). American Journal of Cardiology. 2007;99(8):1027-32.
T-SEARCH/RESEARCH (n = 181)	Valgimigli M, Van Mieghem CAG, Ong ATL, Aoki J, Rodriguez Granillo GA, McFadden EP, et al. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: Insights from the Rapamycin-Eluting and Taxus Stent Evaluated at Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH). Circulation. 2005;111(11):1383-9.
Titan PORI Registry (n = 405)	Karjalainen PP, Ylitalo A, Airaksinen JK. Titanium and nitride oxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population. J Invasive Cardiol 2006;18(10):462-8.

Table D3. Economic studies included in previously published HTA

	Study/Author (year)	Previously Published HTA										
		EUnetHTA* (2008)	Ligthart† (2007)	Hill/NHS (2007)	KCE (2007)	Ontario (2007)	Hayes (2007)	FinOHTA (2007)	ECRI (2006)	CCOHTA (2005)	AETMIS§ (2004)	MSAC (2004)
HTA economic analyses	NICE (2003)								x			
	AETMIS (2004)			x								
	MSAC (2004)	x			x			x				
	Hill (2004)	x	x		x			x				
	CCOHTA (2005)								x			
	Brophy (2005)	x	x		x	x	x	x				
	Greenberg (2002)		x									x
	Morneault (2002)									x		
	Morton (2002)									x		
	Galanaud (2003)		x							x		
	Ruffy (2003)		x									
	Polanczyk (2003)									x		
	Greenberg (2004)		x	x	x		x				x	
	Cohen (2004)	x	x	x	x		x	x	x	x		x
	Oliva (2004)	x						x				
	Tarricone (2004)		x	x	x							
	Brophy (2004)				x							
	NOKC (2004)	x						x				
	Kong (2004)	x					x	x				
	Ward (2005)		x									
	Lord (2005)		x		x		x					
	Van Hout (2005)	x	x	x	x		x	x	x			
	Shrive (2005)	x	x	x	x	x	x	x		x		
	Kaiser (2005)	x	x	x	x		x	x	x			
	Mittmann (2005)	x	x	x	x	x	x	x				
	Bowen (2005)	x	x		x	x	x	x				
	Brophy (2005)	x			x	x	x	x				
	Bagust (2006)	x	x	x	x	x	x	x	x			
	Bakhai (2006)		x		x		x		x			
	Ekman (2006)		x		x		x					
	Ikeda (2006)		x		x		x					
	Ong (2006)				x		x					
	Rinfret (2006)				x							
	Russell (2006)				x							
	Kuukasjarvi (2007)	x										
	Polanczyk (2007)				x							

*Not a full health technology assessment.
†Systematic review of economic studies.
§The Greenberg 2003 article was cited in this study but contains the same data and analysis as the more recent Greenberg 2004 article.

Appendix E. Overview of Previous HTAs

Table E1. Overview of HTA reporting on general patient populations

Report (year)	Search dates	Inclusion	Exclusion	Efficacy	Effectiveness	Safety	Special Pop	Econ Eval	Formal critical appraisal	Focus and Comments
EUnetHTA (2008)	CRD search 2001 to 11/2006; PubMed 2003 to 11/2006	CAD; compared DES sirolimus or paclitaxel with BMS; reporated data on mortality and morbidity; followed for min. 1 year; RCT design	compared DES with BMS in non-native coronary arteries; used other eluting drugs; direct comparisions of DES with each other	NR	meta-analysis of 17 RCTs; primary outcome was mortality at 1, 2, and 3 years; secondary outcomes included morbidity, function/QOL, and patient satisfaction	NR	NR	13 economic evaluations assessed	Yes	Not a complete HTA for decision making - pilot of EUnetHTA core model
Hill- NHS (2007)	2002-August 2005	Clinical - RCT, non-RCTs (ie, prospective registries), non-controlled studies, adults with CAD undergoing tx of native and intervention naïve vessels by PCI with stent, DES which were expected to be avialable for use by the NHS close to time of the assessment, compared DES vs BMS or DES vs DES, reported	Clinical - single case reports; RCTs that provided only unplanned, interim findings, provided data on only a subgroup of the enrolled pts, that were continuing to recruit pts, where pts #'s treated with specific intervention (ie, type of stent) could not be determined; studies of tx of in-stent restenosis or	meta-analysis of 17 RCTs BMS vs DES for mortality, acute MI, TVR/TLR, binary restenosis, MACE	Review of RCTs; prospective registries; non-controlled stuides (except case report of single patient experience)???	meta-analysis of 12 studies; Late loss, thrombosis discussion of FDA findings	subgroup analyses from selected MA to describe	extensive-primary focus-model	Yes- formal critical appraisal of studies in MA; Yes - critique of previously done economic studies	Primary focus on Econ eval; update to Hill 2004 report; data includes abstracts, manufacturer data, gray lit

on combined event rate (MACE, TVF or event-free survival), mortality, AMI, TLR, TVR, repeat revasc, adverse effects, restenosis, late loss, health related QoL; Cost - full economic evals comparing 2 or more options and considered both costs and consequences including cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis; adults with CAD undergoing treatment of native and intervention naive vessels by PCI with stent; DES stents expected to be available for use by NHS close to time of assessment; DES vs BMS	saphenous vein grafts; comparison of DES with other PCI interventions, DES with surgery, variations of drug-loading among single DES types Cost - main source of clinical efficacy data was not explicitly stated; no attempt to synthesise cost and benefits; source was a letter, editorial, review, commentary or methodological paper

		or DES vs DES; QALYs; disease-specific measures such as MACE, repeat revasc avoided, MACE-free survival, TLR and TVR								
Hayes (2007)	MEDLINE 2003-October 2006; and targeted searches of major journals 2003-August 2007	noncomplex CAD; single de novo lesion of native coronary arteries; silent ischemia or stable or unstable angina	acute MI; complex lesions	NR	Description, critique of 55 studies; Outcomes described: TLR, TVR, TVF, repeat PCI or CABG, MACE, AMI, stent thrombosis, intra- and postprocedural complications, early and late mortality, cumulative event-free survival, MACE-free survival	Description, critique of 55 studies comparing DES with BMS; Outcomes described: death, MI, stent thrombosis	data not provided	present 18 studies-QALY is primary outcome	Yes	Primary focus is effectiveness and safety; look at off-label use
KCE-Belgium (2007)	2004-2007	Clinical - meta-analyses comparing DES with BMS in patients with coronary heart disease, without a-priori language restriction, and with clinical followup of of	Clinical NR; Economic: anything that contradicts the inclusion criteria	Meta-analysis list n = 29 MAs - selected MAs of individual patient data described;	overview of registry studies- no analysis	Meta-analysis list (n = 29); selected MAs described + FDA report summaries; overview of on vs. off-label use	Meta-analysis list-data from selected MAs to describe	extensive-primary focus; models using Belgian registry data	No formal critical appraisal of studies in MAs cited; Yes for critique of previously done economic studies	Primary focus is econ eval Does not include own data analysis for efficacy; Analysis of registry data done for ecomomic modeling

		[3] 6 months Economic - full economic evaluation, compare 2 or more alternatives, consider both cost and consequences including cost-effectiveness, cost-utility and cost-benefit analysis; patients eligible for PCI whether or not at high risk of restenosis, DES vs BMS or DES vs DES; outcomes expressed as costs per life-years gained (LYG), costs per quality-adjusted life years (QALYs) gained, or other appropriate disease-specific health outcome								
ECRI (2008)	through January 2006	Full articles in English, peer-reviewed literature; control group of patients treated with	NR	NR	Meta analysis of 14 RCTS; reviewed data from 1 new RCT and a meta-analysis; outcomes	15 RCTs reviewed for rates of adverse events including stent thrombosis, MI, death, and	NR	7 studies reviewed addressing cost-effectiveness	No	Update to ECRI's May 2006 Windows on Medical Technology report (one

		BMS; 10 or more patients in each treatment group; CAD treated electively; reported patient-oriented outcomes; included a DES that is currently marketed in the United States or Europe			analyzed were angina recurrence, TLR (symptom driven and overall)	hypersensitivity				additions report identified); comparative effectiveness systematic review
CTAF (2007)	NR	NR	NR	Description, critique of selected MAs ; Outcomes described: MACE, restenosis, MI, mortality, stent thrombosis	NR	Description, critique of selected MAs ; Outcomes described: MACE, restenosis, MI, mortality, stent thrombosis	data not provided	NR	not described	Primary focus is safety
Ontario (2007)	1990-	random assignment to tx with DES vs BMS; active drug either sirolimus or paclitaxel; primary report of the clinical trial data to include subanalyses; report on acute MI, stroke, death, MACE, TLR, TVR; have at least	reporting on outcomes other than those listed for inclusion	data not provided	meta analysis of registry data	meta analysis of registries	?? Patients stratified into 4 primary cohorts based on recent history of MI and diabetes	models using Ontario data; ICER DES vs BMS, QALY and expected # revascularizations at 2 yrs post initial PCI	No formal critical appraisal	Primary focus - Econ eval; Does not include own data analysis for efficacy, safety; Analysis of registry data done for ecomomic modeling

12 months of f/u data; tx for stable /unstable angina or silent ischemia or within 7 days of an acute MI

The *European Network for Health Technology Assessment* (EUnet-HTA) (2008) evaluated many aspects of DES: general design, health problem and current use, description and technical characteristics, clinical effectiveness, costs and economic evaluation, ethical analysis, organizational aspects, social aspects, and legal aspects. Each aspect was addressed by a different team. Each team took a different approach to addressing its topic. For example, the team addressing costs and economic evaluation conducted a formal cost-effectiveness analysis. The team addressing clinical effectiveness conducted a meta-analysis. Our appraisal checklist refers only to that aspect of the HTA. The EUnetHTA (page 47, top) says "The work is based on the review by Nordmannet al. Mortality in randomized controlled trials comparing drug-eluting vs BMS in coronary artery disease: a meta-analysis. Eur Heart J 2006:27(23):2784-2814, including additional analyses of unpublished data." And EUnetHTA (page 46, bottom) says "...while A. Nordmann and M Briel provided and discussed the data and ran further analyses beyond the analyses done in their original paper." The meta-analysis included 17 randomized controlled trials (RCTs) with 8200 patients with 1 year of follow-up. Although the methods say they abstracted patient characteristics, features of the intervention, and the outcomes, those results are not reported. Similarly, the methods say they assessed quality of RCTs, those results are not reported. They were not able to conduct subgroup analyses, since they did not have individual patient data. Results are reported for 1, 2, and 3 year intervals. They commented on new data about long-term outcomes that became available after their meta-analysis had been completed. The re-organized the primary trials differently to come up with 17 described. Nordmann includes Scand-Stent and Taxus VI, but EUnet has neither. EUnet reports results as RRs, while Nordmann reports ORs. EUnet looks for many secondary outcomes, but NOT thrombus, while the only secondary outcome Nordmann reports is thrombus.

Hill et al (2007) evaluated efficacy, safety, and costs between DES and BMS and between difference types of DES for the National Institute for Health and Clinical Excellence/National Health Service (NICE/NHS). To evaluate safety and efficacy of DES vs BMS, they conducted their own meta-analysis of 17 RCTs. They combined results from RCTs comparing SES to BMS with RCTs comparing PES to BMS. They also examined evidence from non-randomized studies about new stents; examined evidence from registries about real-world experience; reviewed prior cost-effectiveness evaluations; and conducted their own cost-effectiveness analysis. The meta-analysis comparing DES with BMS is the only aspect addressed in our appraisal checklist and is the only source for the results displayed in our efficacy table.

Hayes et al (2007) conducted a systematic, narrative review that included 25 RCTs with 4 secondary analyses, 17 meta-analyses, and 24 observational studies to assess the efficacy of DES vs BMS. They also reported the positions of government and professional organizations and reviewed prior cost-effectiveness evaluations. Although they commented on the quality of the studies they reviewed, they did not describe quality characteristics evaluated or consider quality in their conclusions. They described RCTs and their outcomes individually, but did not synthesize their results. When possible, they discussed SES and PES separately. For most outcomes, we summarized the results of the

individual studies in our summary table. For the outcome of late stent thrombosis, we reported the results of meta-analyses and pooled analyses of individual patient data with long follow-up times in our summary table, since such analyses have more power than individual studies to detect differences in such rare outcomes.

The *Belgian Health Care Knowledge Centre (KCE)* (2007) assessed the efficacy, effectiveness, and cost-effectiveness of DES compared with BMS. For the efficacy analysis, they saw that only the more recent meta-analyses reported long-term follow-up, so they systematically examined several large, recent meta-analyses and some additional RCTs. They described those meta-analyses and RCTs and their outcomes individually, but did not synthesize their results. The efficacy analysis is the only one described in our appraisal checklist, although many of the items do not apply. For the effectiveness and cost-effectiveness analyses, they reviewed registry data and conducted their own study using registry data from patients in Belgium.

The *Emergency Care Research Institute* (ECRI) (2006) updated an earlier report on DES, reviewing 17 RCTs and 1 meta-analysis. While they stated that the quality of evidence is high, they did not describe their method of assessing quality or consider quality in their conclusions. They summarized results by the "vote count" method, in which the number of studies with positive results is compared to the number of studies with negative results. In our appraisal checklist, this was considered evaluating consistency of effect sizes. They presented results for different time intervals after stent placement, with some pooled data. They also performed their own meta-analysis, but reported none of its numerical results.

The *California Technology Assessment Forum* (2007) reviewed previous observational studies and meta-analyses, abstracts, and conference proceedings that discussed late stent thrombosis and the relevance of anti-platelet therapy. Theirs was a narrative review, with no description of a literature search, evaluation of evidence, or quantitative synthesis of evidence. Although it lacks many of items on our appraisal checklist suggesting objectivity, it is one of the most readable HTAs.

The *Ontario Ministry of Health and Long-term Care* (2007) conducted a systematic review of registry data and analyzed the experience using DES (either SES or PES) and BMS in Ontario. Registry data showed DES were more likely to be used in women, patients with diabetes or multi-vessel disease, and those who had a previous percutaneous intervention In Ontario, DES were more likely to be used in patients with narrower, longer lesions, or with diabetes. This selection of patients for DES—in fact, selecting those patients with the highest disease risk—illustrates why registry data are not valid for comparing outcomes with DES vs BMS.

Description of Efficacy Outcomes

Overall and cardiac mortality
Mortality was examined in 5 previous HTAs using data from RCTs and meta-analyses. Different RCTs reported mortality as death from any cause, cardiac death, or non-cardiac death in. Previous HTAs found consistent results between studies. They found no significant difference in death, cardiac death, or noncardiac death with SES or PES at any time or among any patient subgroup. One meta-analysis (the EUnetHTA, 2008) noticed a nonsignificant trend for increasing non-cardiac mortality with SES over 3 years.

Acute myocardial infarction
Acute myocardial infarction (MI) was examined in 5 previous HTAs using data from RCTs and meta-analyses. Different RCTs reported any MI, Q-wave MI, or non−Q-wave MI. The previous HTAs concluded that there was no significant difference in MI of any sort at any time or among any patient subgroup. The HTA by KCE-Belgium reported the only meta- analysis (Stettler 2007) to find a significant difference overall: fewer MIs with SES compared with BMS. That meta-analysis was unusually large, including 38 RCTs and 18, 023 patients. The ECRI reported 2 RCTs that found significantly fewer MIs with DES compared with BMS from 0 to 12 months after stent placement. Some RCTs reported by Hayes et al's HTA found significantly fewer MIs with SES or PES among patient subgroups. Results from subgroup analyses should be interpreted with caution because of possible random variation and inadequate power to detect differences.

Revascularization
Revascularization was examined in 6 previous HTAs using data from RCTs and meta-analyses. Revascularization is required when there is new stenosis at the site of the lesion that had been stented before or in the same vessel that had been stented before. Different RCTs reported revascularization, target lesion restenosis (TLR), target vessel restenosis, or target vessel failure. Many RCTs required assessment of the stent site to determine success of the stent, and so identified restenosis that was not clinically apparent. Thus, the need for revascularization was higher among patients in RCTs than in patients who did not have their stents assessed unless it was clinically indicated. Such patients are described in registries.

All previous HTAs concluded that DES significant lower revascularization rates from 6 months to 3 years after stent placement. Hill et al noted that there were no further reductions in TLR rates beyond 1 year after stent placement. The HTA by Hayes et al reported that no RCT comparing PES to BMS found a significant difference in revascularization rates at 30 days; the number of cases was small. The HTA by Hill et al found nonsignificant improvements with PES at 3 years, although confidence intervals were wide. The EUnetHTA, Hill et al, and KCE-Belgium reported lower revascularization rates with SES vs BMS than with PES vs BMS.

Combined events or major adverse cardiac events
Combined events or major adverse cardiac events were examined in 4 previous HTAs using data from RCTs and meta-analyses. These events were defined differently by

individual RCTs, but were typically death, myocardial infarction, or the need for target lesion revascularization; their numbers were combined. HTAs found significantly fewer major adverse cardiac events with DES (either SES or PES) or with SES from 1 month to 3 years after stent placemen, except where there was heterogeneity between studies. Studies comparing PES with BMS found no significant difference in major adverse cardiac events 30 days after stent placement, but most found significantly fewer from 6 months to 1 year after stent placement. When the combination of death of myocardial infarction was analyzed separately for those studies comparing SES with BMS, there was no significant difference. This shows that the improvement in major adverse cardiac events is primarily due to an improvement in the need for revascularization.

Description of Safety Outcomes

Stent thrombosis
Stent thrombosis was examined in 5 previous HTAs using data from RCTs and meta-analyses. Whereas restenosis develops gradually and typically presents with recurrent, stable symptoms, thrombosis often presents suddenly with acute myocardial infarction or death. Individual RCTs used their own definitions for "thrombosis," which made comparisons between studies difficult. Therefore, definitions were standardized by the Academic Research Consortium. Some meta-analysts examined outcomes using both definitions. Stent thrombosis occurring in the first month after stent placement is called "subacute." Its frequency has been decreased by using DES rather than BMS. Stent thrombosis occurring at least 1 month after stent placement is "late," and thrombosis occurring at least 1 year after stent placement is "very late." (CTAF)

Most RCTs and meta-analyses with up to 1 year of follow up found no significant difference in stent thrombosis. Some meta-analyses with follow-up more than 1 year after stent placement found an increased number of stent thrombosis with DES than BMS. Those numbers were not always significantly different.

Late stent thrombosis
Late stent thrombosis (ie, occurring more than 1 year after stent placement) was examined in 6 previous HTAs using data from RCTs and meta-analyses. Late stent thrombosis is a rare event, so large numbers of patients are needed to detect a difference in outcomes with DES vs BMS. Therefore, only results from meta-analyses that are reported in HTAs are presented in our table. Most meta-analyses found more late stent thromboses with DES than with BMS. These differences were not always significant. HTAs generally concluded that there is a small increased risk of last stent thrombosis with DES compared with BMS.

Appendix F. Included Meta-analyses and Pooled Analyses: Characteristics and Outcomes

Table F1. Characteristics of meta-analyses and pooled analyses

Source	Patient n	Trial n	Focus	Most recent source/ search	Length of F/U	Length of anti-platelet therapy	Sub-groups	Funding	Comments
					Meta-Analyses				
Stettler 2007	18,023	38	Safety	3/2007	4 y	NR	Yes: DM	Swiss Nat'l Science Foundation	Network meta-analysis
Fuchs 2008	10,251	21	Throm-bosis	2007	1 y	NR	No	German Research Foundation and private foundation	
de Lemos 2007	4892	10	CABG	2004	NR	NR	NR	None	
					Pooled analyses				
Stone 2007 *NEJM*	5261	9	Safety	2005	2-5 y	6 m	NR	Cardio-vascular Research Foundation	
Kastrati 2007	4958	14	Death	9/2006	> 1 y	2-12 m	Yes: DM	Deutsches Herzzentrum [Heart Center]	
Stone 2007 *Circ*	3445	4	Death or AMI	2005	3.2 y	6 m	NR	Boston Scientific	
Spaulding 2007	1748	4	Death	2004	4 y	2-3 m	Yes	NR	

AMI is acute myocardial infarction; Circ is *Circulation*; DM is diabetes mellitus; m is months; F/U is follow-up; *NEJM* is the *New England Journal of Medicine*; NR is not reported; PES is paclitaxel eluting stent; SES is sirolimus eluting stent; y is years; * See text about characteristics

Characteristics of meta-analyses and pooled analyses

General comments about systematic reviews, meta-analyses and pooled analyses of individual patient data

Individual randomized controlled trials (RCTs) may not have enough participants to show differences between treatment groups in rare outcomes—they lack power. Combining results from individual RCTs increases the number of participants and increases the power to detect differences between treatment groups. Systematic reviews aim to avoid bias by incorporating all relevant RCTs and being objective. Meta-analyses and pooled analyses are types of systematic reviews that combine results from individual primary studies, such as RCTs. Meta-analysis combines outcomes from primary studies, weighting them for study size and variance; the primary study is the unit of analysis. Pooled analysis combines outcomes from individual patients enrolled in primary studies; the patient is the unit of analysis. The best meta-analyses and pooled analyses are characterized by searching widely for primary studies; objectively selecting studies for inclusion and abstracting data; assessing primary studies for quality; assessing heterogeneity of primary studies, to see whether combining results is appropriate; performing a sensitivity analysis, to see whether results depend on assumptions; addressing publication bias; and analyzing subgroups. These characteristics are recorded in our tables. Some systematic reviews may have performed the actions indicating quality, but not reported doing so.

Some meta-analyses and pooled analyses combined data from primary studies that were of similar design and patient populations, and so were inherently similar. Such reviews typically did not conduct a literature search or look for unpublished sources, assess studies for quality, assess homogeneity, or assess publication bias. Instead, they would comment on the general quality of the studies. Since quality characteristics of individual studies were not displayed, the level of evidence could not be determined.

Heterogeneity is usually measured using procedures that generate a p-value. A low p-value (typically < 0.05) indicates heterogeneity. However, a p-value > 0.05 does not prove homogeneity. Stettler et al 2007 assessed heterogeneity between studies with between-trial variance (τ^2). When τ^2 is low, between-trial heterogeneity is low.

A review's funding is important to consider whether manufacturers' interests may have influenced the review. Some reviews did not report funding. Some foundations may be supported by manufacturers. For example, "the Cardiovascular Research Foundation receives research or educational fudging from Boston Scientific, Cordis, Sanofi-Aventis, and Bristol-Myers Squibb" (Stettler 2007). In addition to a review's funding, some authors may have received support from manufacturers in the form of grants, lecture fees, honoraria, stock, consulting fees, etc.

Comments about outcomes of stent trials

In some trials, once patients required revascularization, they were no longer considered for other outcomes such as thrombosis. Using this definition ensures that outcomes are

related to the stent that was initially placed. However, it may underestimate the incidence of all thromboses occurring after the initial stent placement. The Academic Research Consortium (ARC) standardized definitions of thrombosis to include thromboses occurring after revascularization. They also standardized definitions of thrombosis with respect to the interval after stent placement. Some reviews used only the ARC definition, some only the trial's definition ("per-protocol" definition), and some used both. Most trials were designed and powered to detect differences in primary end points such as revascularization, lumen loss or composite endpoints.

Comments about individual meta-analyses or pooled analyses

Stettler et al 2007 searched widely for RCTs comparing sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) with bare metal stents (BMS). Two investigators independently reviewed RCTs for inclusion, and found 38 trials with 18,023 patients with up to 4 years of follow-up to include in their meta-analysis. Two investigators also independently extracted data. Stettler et al assessed heterogeneity between studies with between-trial variance (τ^2). They report "all estimates of statistical heterogeneity between trials were low, except for comparisons... of target lesion revascularization," meaning there was little heterogeneity between trials. Stettler et al report outcomes as hazards ratios with 95% "credibility intervals." A 95% credibility interval may be interpreted as meaning there is a 95% chance that the true value lies within the interval. (This is how confidence intervals are intuitively interpreted.) Stettler et al conducted one sensitivity analysis, limiting it to high-quality studies, finding no effect on results. They conducted another sensitivity analysis adjusting for type of stent, finding differences in stent thromboses became greater for PES. They analyzed whether a patient's having diabetes affected results. They present outcomes over the entire 4-year follow-up period and at various intervals after stent placement; they also present outcomes for SES vs BMS and for PES vs BMS separately. They analyzed thrombosis using both ARC and per-protocol definitions. This meta-analysis is the largest, and has all the characteristics of a high-quality study.

Stone et al 2007 (*New England Journal of Medicine*) conducted a pooled analysis of individual patient data, using data from those double-blind RCTs on which approval in the US and Europe was based. Thus, they did not search for studies or assess them for quality; they felt the studies included were all of high quality. They report outcomes from stent placement to 4 years after placement; and for intervals within that time. In our tables, the results for 0-4 years are reported for death, cardiac death, myocardial infarction (MI), death or MI, or target lesion revascularization. In addition, they report noncardiac death, Q-wave MI, non−Q-wave MI, death or Q-wave MI, cardiac death or MI, and target vessel revascularization.

Kastrati et al 2007 pooled individual patient data from 14 RCTs identified through a wide search. They assessed long term outcomes with SES vs BMS, and so included only those RCTs with at least 1 year of follow-up. They assessed RCTs for quality. They assessed RCTs for heterogeneity, and found none for the outcome of death or the combined outcomes of death or MI. However, they found heterogeneity between studies for the

combined outcome of death, MI, or reintervention. Heterogeneity for thrombosis was not reported. Kastrati et al conducted sensitivity analyses by removing each trial from the analysis to see whether outcomes were affected, and by adjusting for whether the trial was double blinded, the length of follow-up, the duration of antiplatelet therapy, and whether the patient had an acute MI. They used per-protocol definitions for thrombosis.

Fuchs et al 2008 assessed subacute stent thrombosis (1-30 days after procedure) and late stent thrombosis (31 days – 1 year after procedure) using data from trials comparing a DES with BMS or BMS to balloon angioplasty. Using a wide search, they identified 28 trials for inclusion, although only 21 compared DES with BMS. Although it is not clearly stated, outcomes for patients with BMS seem to have been combined from trials comparing DES with BMS or comparing BMS with angioplasty. Data in our table reflect the number of trials and patients contributing to the comparison of DES with BMS. Based on their definition of late stent thrombosis, outcomes seem to reflect only 1 year of follow-up. Fuchs et al assessed heterogeneity and publication bias, finding no evidence for either. Outcomes other than subacute and late stent thrombosis were not reported. Fuchs et al used ARC definitions of thrombosis.

de Lemos et al 2007 conducted a meta-analysis to investigate whether DES prevent the need for coronary artery bypass grafting (CABG). The meta-analysis was conducted through the Brazilian Cochrane Center, and was the only one to use the "Literatura Latino-Americana e do Caribe em Ciências da Saúde" as a search engine.Two reviewers independently selected RCTs for inclusion; the RCTs were assessed for quality. Although the participants are described as those "with restenosis post-stent implantation," the numbers of participants shown in the figure are the total number of participants in the RCTs, i.e., this is not an analysis of a subgroup with restenosis. They report heterogeneity for the outcome of CABG, and found studies of polymer-based PEPS to be heterogeneous. de Lemos et al report separate results for "need for CABG," percutaneous revascularization, and restenosis. For the outcome of CABG, de Lemos et al report outcomes of polymer-based and polymer-free PES separately. For other outcomes, they group all DES. Only results for all DES are reported in our summary table. They do not report which definition for thrombosis they used, nor do they report the length of follow-up. However, many of the studies included have > 1 year of follow-up. Results are reported under "0-4 y" in our tables.

Stone et al 2007 (*Circulation*) examine the balance of death or non-fatal MI related to restenosis against those same outcomes related to thrombosis, among patients treated with PES or BMS. They conducted a pooled analysis of 4 RCTs of PES vs BMS with a median follow-up of 3.2 years. They used data from 4 of the TAXUS trials, which had similar designs and entry criteria. They did not explain how they chose these studies for inclusion or whether they searched for others; hence, many quality characteristics do not apply. End points were judged by an independent committee blinded to stent type, which shows objectivity in the analysis. They did not test for heterogeneity between studies, but commented on their similarity and quality. Thrombosis was defined as per protocol. In a sensitivity analysis, Stone et al defined thrombosis using ARC definitions, but their conclusions did not change. They defined death or MI occurring within 7 days before or

after target lesion revascularization or stent thrombosis as being directly related to the revascularization or thrombosis. They excluded revascularizations performed within 30 days of stent placement solely based on angiographic follow-up without clinical indications. Because Stone et al count only death and non-fatal MI related to restenosis or thrombosis, their outcomes are not comparable to those in other reviews and so are not reported in our results table; those results are reported in the results text.

Spaulding et al 2007 conducted a pooled analysis of individual patient data using 4 trials comparing SES with BMS with similar designs and patient populations. They did not conduct a literature search, define inclusion criteria, assess study quality, or look for publication bias. While they did not describe the studies in detail, they described the pooled patient populations in detail. Three investigators determined the cause of death, enhancing objectivity. They assessed thrombosis using both per-protocol and ARC definitions. They found heterogeneity for treatment effects among patients with diabetes. To explore why, they examined the cause of death among diabetics, finding increased risk of very late stent thromboses. The details of this exploration are reported in on-line appendices.

Pasceri et al 2007 conducted a meta-analysis of trials involving patients with acute MI, after an observational study suggested such patients may have increase risk of MI, revascularization, or death. Using a wide search strategy, they identified 7 trials, including 4 that were unpublished. (This is the only meta-analysis that included unpublished trials.) They found no heterogeneity between studies and no evidence of publication bias. Six trials had 1 year of follow-up, the other trial had 8 months of follow-up. In a sensitivity analysis, they comment that results using on the 6 trials with a full year of follow-up do not change. Pasceri et al combined outcomes for trials using SES with those using PES.

Moses et al 2006 conducted a pooled analysis of individual patients who had stenting for intermediate coronary lesions, ie, < 50% diameter stenosis. Although trials' inclusion criteria required patient to have a coronary lesion with > 50% stenosis, 6.7% of the patient included actually had less stenosis and are the subject of this analysis. Moses et al combined outcomes for trials using SES with those using PES. They found no heterogeneity between studies. They conducted a sensitivity analysis by stratifying by stent type and administration of glycoprotein IIb/IIIa inhibitors. They report incidence rates with p-values for significance of differences. While in-hospital, at 30 days, and at 1 year after stent placement, they report outcomes for cardiac death, MI, target vessel revascularization, and a composite (cardiac death, MI, or target vessel revascularization): only the 1 year outcomes are reported in our table. They do not report all-cause mortality. At 1 year, they also report Q-wave and non-Q-wave MI, target vessel revascularization, and stent thrombosis.

*Comments about meta-analyses or pooled analyses that were **excluded** from this section:*

Biondi-Zoccai et al 2008. Biondi-Zoccai et al compared DES with BMS and DES with CABG for patients with disease in an unprotected left main coronary artery.

Traditionally, this has been an indication for CABG, rather than percutaneous intervention. Biondi-Zoccai et al found no randomized trials including such patients: apparently, they had excluded. Their analysis is based on registry data and nonrandomized comparisons. INCLUDED UNDER REGISTRY STUDIES

Hoffman et al 2007. Hoffman et al conducted a pooled analysis of 325 patients from 3 RCTs comparing SES with BMS. These patients were a subset who had intravascular ultrasound for follow-up 6-8 months after stent placement. Hoffman et al were concerned with incomplete stent apposition, "defined as one or more stent struts separated from the vessel wall," as it may cause late stent thrombosis. Comparisons were between patients who had incomplete stent apposition and those who did not have incomplete stent apposition. The only comparison of SES with BMS was through multivariate analyses. One multivariate analysis showed having an SES was an independent predictor of higher risk for incomplete stent apposition: OR, 4.47 (95% CI, 2.069 – 9.56). Another showed having an SES was an independent predictor for lower risk for major adverse cardiac events (death, MI, or target-lesion revascularization): OR 0.27 (95% CI, 0.14 – 0.54).

Holmes et al 2006 conducted a pooled analysis of 4 double-blind RCTs comparing SES with BMS. They did not explain how they chose these studies for inclusion or whether they searched for others. They did not test for heterogeneity between studies, but commented on their similarity. They explored associations between survival time and patient clinical characteristics, angiographic findings, and procedural characteristics, which might be considered similar to conducting a sensitivity analysis or subgroup analysis. The only outcomes they report are death, cardiac death, non-cardiac death, and thrombosis. Any death from an unknown cause was classified as cardiac, assuming a worst-case scenario; these deaths may have included death due to thrombus. Thrombus was defined as per protocol.

Kimura et al 2008. Kimura et al report data derived from intravascular ultrasound imaging, which was conducted during follow-up angiography 9 months after stent placement among a convenience sample of patients enrolled in 3 RCTs comparing PES with BMS. Outcomes reported include vessel diameter, vessel stenosis, acute gain, and late loss. Since these outcomes are different from the clinical outcomes reported in other reviews, they are not included in this report. Kimura et al compared angiographic and ultrasonic outcomes among patients with and without diabetes who had a PES. Kimura et al also compared angiographic and ultrasonic outcomes for PES vs BMS among patients with diabetes. Finally, Kimura et al compared ultrasonic outcomes for PES vs BMS among patients with insulin-dependent diabetes. Essentially, they found worse outcomes among patients with diabetes than those without diabetes; but better outcomes among patients with diabetes and among patients with insulin-dependent diabetes who were treated with a PES compared with those who were treated with a BMS.

Table F2. Outcomes from meta-analyses and pooled analyses

	Outcomes									
	Death 0-4+ y		Cardiac death 0-4+ y		MI 0-4+ y		Revasc 0-4+ y		Death or MI 0-4+ y	
Source	SES vs BMS	PES vs BMS	SES vs BMS	PES vs BMS	SES vs BMS	PES vs BMS	SES vs BMS	PES vs BMS	SES vs BMS	PES vs BMS
Stettler 2007 HR (95% CrI)	1.00 (0.82 – 1.25)	1.03 (0.84 – 1.22)	1.02 (0.80 – 1.31)	1.05 (0.80 – 1.36)	0.81 (0.66 – 0.97)	1.00 (0.81 – 1.23)	0.30 (0.24 – 0.37)	0.42 (0.33 – 0.53)	0.92 (0.77 – 1.08)	1.00 (0.84 – 1.23)
Stone 2007 *NEJM* HR (95% CI)	1.27 (0.86 – 1.88)	0.94 (0.70 – 1.26)	1.26 (0.73 – 2.18)	0.86 (0.55 – 1.35)	1.03 (0.71 – 1.51)	1.06 (0.81 – 1.39)	0.29 (0.22 – 0.39)	0.46 (0.38 – 0.55)	1.12 (0.84 – 1.49)	1.03 (9 84 – 1.26)
Kastrati 2007 OR (95% CI)	1.03 (0.80 – 1.30)						0.43 (0.34 – 0.54)		0.97 (0.80 – 1.16)	
	Death 0-2.6 y		Cardiac death 0-2.6 y							
Holmes 2006 rate (%) (p)	4.1 SES, 3.2 BMS 0.37		1.3 SES, 1.4 BSM 0.55							

Outcomes (continued)

Source	Death 0-1 y DES vs BMS	Cardiac death 0-1 y DES vs BMS	MI 0-1 y DES vs BMS	Revasc 0-1 y DES vs BMS	Death, or MI 0-1 y DES vs BMS
Pasceri 2007 RR (95% CI) F/U 8-12 m	0.90 (0.53 – 1.51)			0.40 (0.30 – 0.54)	0.84 (0.62 – 1.15)
de Lemos 2007 RR (95% CI) F/U unstated	1.23 (0.70 – 2.17)		0.84 (0.61 – 1.17)		
	Death 0-8 m DES vs BMS	Cardiac death 0-8 m DES vs BMS	MI 0-8 m DES vs BMS	Revasc 0-8 m DES vs BMS	Death, or MI 0-8 m DES vs BMS
Moses 2006 rate (%) (p) F/U 6-8 m		0 DES, 2.7 BMS p = 0.11	3.4 DES, 5.4 BMS p = 0.49	1.2 DES, 20.3 BMS p<0.0001	

Fuchs 2008 did not report any of these outcomes. de Lemos et al did not state the length of follow up. However, some of the studies included in their meta-analysis had > 1 year of follow-up. Pasceri has only 8-12 months of follow-up. Passceri did not report on MI as an independent outcome.

Appendix G. Evidence Table: New RCTs Comparing DES versus BMS

Table G1. Evidence table of new RCTs comparing DES with BMS

Study	LoE, Design	Demographics comorbidities	Clinical presentation and adjunct treatment	Stent Types	Outcomes- Effect sizes (Adjusted estimates unless otherwise noted)	Comments:
• Additional, recently published follow-up or substudies to previously reported RCTs						
Pfisterer (2009) BASKET (Basel Stent Kosten-Effektiviäts Trial) subanalysis of large versus small stents Switzerland single site	I/II RCT sub-analysis: II/III F/U: 3 years F/U: 97.7%	N = 826 DES, n = 545 BMS, n = 281 large stents, n = 558 small stents, n = 268 % male: 79% DES: 79% BMS: 79% large stents: 78% small stents: 80% age: 64 ± 11 years DES: 64 ± 11 years BMS: 64 ± 11 years large stents: 63 ± 11 years small stents: 66 ± 11 years • diabetes: 19% (n = 154) DES: 17% (n = 93) BMS: 22% (n = 61) large stents: 17% (n = 97) small stents: 22% (n = 57) • HTN: 67% (n = 550) DES: 66% (n = 358) BMS: 68% (n = 192) large stents: 63% (n = 354) small stents: 73% (n = 196) • hyperlipidemia: 76% (n = 628) DES: 76% (n = 414) BMS: 76% (n = 214) large stents: 75% (n = 420) small stents: 77% (n = 206)	• STEMI: 21% (n = 176) DES: 21% (n = 115) BMS: 22% (n = 61) large stents: 25% (n = 142) small stents: 13% (n = 34) • unstable: 36% (n = 301) DES: 37% (n = 200) BMS: 36% (n = 101) large stents: 36% (n = 201) small stents: 37% (n = 100) • stable: 42% (n = 349) DES: 42% (n = 230) BMS: 42% (n = 119) large stents: 39% (n = 215) small stents: 50% (n = 134) • multivessel disease: 69% (n = 566) DES: 68% (n = 371) BMS: 69% (n = 195) large stents: 62% (n = 347) small stents: 82% (n = 219) • GPIIb/IIIa: 26% (n = 212) DES: 26% (n = 141) BMS: 25% (n = 71) large stents: 28% (n = 156) small stents: 21% (n = 56) • dual antiplatelet therapy for 6 months; clopidogrel stopped at 6 months	**BMS:** third generation cobalt-chromium **DES:** Cypher (sirolimus-eluting, n = 264) Taxus (n = 281)	• Total death after 3 years *overall* DES: 8.3% BMS: 6.8% *P* = .49 *large stents* DES: 7.3% BMS: 5.5% *P* = .49 *small stents* DES: 10.2% BMS: 9.9% *P* = 1.0 • Cardiac death *overall* DES: 4.8% BMS: 3.2% *P* = .36 *large stents* DES: 4.2% BMS: 2.0% *P* = .23 *small stents* DES: 5.9% BMS: 6.2% *P* = 1.0 • Cardiac death/MI *overall*	• ADJUSTING: Cox regression models • THROMBUS definition: ARC • Stent size/vessel size may be an important consideration • Since 66% is "off label" use and really overall NS difference in MI free survival? • TVR not that different btwn DES and BMS really??

- current smoker: 29% (n = 238)
  DES: 28% (n = 151)
  BMS: 31% (n = 87)
  large stents: 33% (n = 184)
  small stents: 20% (n = 54)

- previous MI: 27% (n = 226)
  DES: 28% (n = 151)
  BMS; 27% (n = 75)
  large stents: 23% (n = 126)
  small stents: 37% (n = 100)

- previous PCI: 16% (n = 133)
  DES: 17% (n = 91)
  BMS: 15% (n = 42)
  large stents: 14% (n = 78)
  small stents: 21% (n = 55)

- previous CABG: 13% (n = 105)
  DES: 13% (n = 70)
  BMS: 12% (n = 35)
  large stents: 6% (n = 33)
  small stents: 27% (n = 72)

- bifurcations: 5% (n = 44)
  DES: 5% (n = 27)
  BMS: 6% (n = 17)
  large stents: 4% (n = 20)
  small stents: 9% (n = 24)

- CTO: 28% (n = 3)
  DES: 3% (n = 14)
  BMS: 3% (n = 14)
  large stents: 2% (n = 11)
  small stents: 6% (n = 17)

stented segments: 1.5 ± 0.7
DES:

DES: 12.7%
BMS: 10.0%
P = .31

No significant effects of DES found (HR = 1.24, 95% CI,).79-1.943, *P* = .35)

large stents
DES: 13.4%
BMS: 6.5%
P = .02

DES a risk factor (HR = 2.08, 95% CI, 1.11-3.89)

small stents
DES: 11.2%
BMS: 18.5%
P = .12

No significant effects of DES found (HR = 0.69, 95% CI, 0.33-1.46, P = .33)

- Non-MI TVR

overall
DES: 9.9%
BMS: 13.9%
P = .10

large stents
DES: 9.5%
BMS: 11.5%
P = .47

small stents
DES: 10.7%
BMS: 19.8%
P = .05

- Any TVR

overall
DES: 14.7%
BMS: 17.5%

P = .29

large stents
DES: 14.0%
BMS: 14.1%
P = .98

small stents
DES: 16.0%
BMS: 25.9%
P = .06

- MACE

overall
DES: 21.1%
BMS: 22.8%
P = .59

large stents
DES: 20.9%
BMS: 17.0%
P = .27

small stents
DES: 21.4%
BMS: 37.0%
P = .01

- Thrombosis

over entire 3 years

overall
DES: 9.0%
BMS: 7.5%
P = .51

small stents
DES: 10.2%
BMS: 16.0%
P = .17

large stents
DES: 8.4%
BMS: 4.0%
P = .05

from 0-6 months

overall
DES: 2.9%
BMS: 3.9%
P = .45

small stents
DES: 2.7%
BMS: 8.6%
P = .03%

large stents
DES: 3.1%
BMS: 2.0%
P = .45

from 7-36 months
overall
DES: 6.5%
BMS: 3.6%
P = .08

small stents
DES: 8.1%
BMS: 7.4%
P = .86

large stents
DES: 5.7%
BMS: 2.0%
P = .04

- Early and late events for cardiac death/MI

there was an early non-significant benefit of DES

beyond 6 months, there was a significantly higher rate of cardiac death/MI (mainly due to increase in such events in patients with large stents
DES: 9.1%
BMS: 3.8%

					P = .009 *large* DES: 9.7% BMS: 3.1% *P* = .006 *small* DES: 7.9% BMS: 5.8% *P* = .57 yearly rates after 6 months *overall* DES: 3.6% (95% CI, 2.6-4.6) BMS: 1.5% (95% CI, 0.6-2.5) *large* DES: 3.9% (95% CI, 2.6-5.2) BMS: 1.3% (95% CI, 0.3-2.3) *small stents* DES: 3.1% (95% CI, 1.5-4.7) BMS: 2.3% (95% CI, 0.1-4.6)		
Kelbaek (2008) SCANDSTENT Danish multi-site	I/II RCT F/U: 3 years %F/U: NR	N = 322 SES: n = 163 BMS: n = 159 % male SES: 74% BMS: 79% age SES: 62.9 ± 9.2 years BMS: 62.5 ± 9.4 years • diabetes SES: 18% BMS: 18% • HTN SES: 46% BMS: 38% • hyperlipidemia	• patients had complex coronary artery lesions: occluded, bifurcated, ostial, angulated • unstable angina SES: 25% BMS: 26% • multivessel disease SES: 43% BMS: 45% • coronary artery LAD SES: 45% BMS: 53% CX SES: 25% BMS: 23% RCA SES: 30%	BMS VELOCITY balloon-expandable stent DES Cypher (sirolimus-eluting)	• Death SES: 5.6% (n = 9) BMS: 1.9% (n = 3) *P* = .14 • Cardiac death SES: 2.5% (n = 4) BMS: 1.3% (n = 2) *P* = .69 • MI SES: 3.7% (n = 6) BMS: 9.6% (n = 15) *P* = .04 • TLR SES: 4.9% (n = 8) BMS: 33.8% (n = 53) *P* < .001 • TVR	• ADJUSTING: NR • THROMBUS definition: ARC • These 2 (Thuesen) reports most likely have overlap of patients • More SES pts died (any cause) than BMS – underpowered to detect difference • was repeat angio part of protocol OR clinically driven? • patients were informed of stent type • manufacturer not involved in any part of study

SES: 81%
BMS: 84%

- previous MI
SES: 54%
BMS: 50%

BMS: 24%

- lesion length
SES: 18.8 mm
BMS: 17.2 mm

- antiplatelet therapy
all patients treated with clopidogrel for ≥ 12 months and aspirin indefinitely

- GP inhibitors were used at the discretion of the operator

SES: 8.0%
BMS: 34.4%
P < .001

- MACE
SES: 12.3%
BMS: 37.6%
P < .001

- MACE in different types of lesions
occlusions (n = 115)
SES: 6.8% (n = 4)
BMS: 41.1% (n = 23)
P < .001

bifurcations (n = 107)
SES: 19.3% (n = 11)
BMS: 36.5% (n = 19)
P = .054

ostial lesions (n = 72)
SES: 11.4% (n = 4)
BMS: 36.8% (n = 14)
P = .014

angulation (n = 25)
SES: 8.3% (n = 1)
BMS: 23.1% (n = 3)
P = .59

total
SES: 12.3% (n = 20)
BMS: 37.1% (n = 59)
P < .001

- Thrombosis
early
definite
SES: n = 0
BMS: n = 1.9% (n = 3)
probable
SES: 0.6% (n = 1)
BMS: n = 0
possible
SES: n = 0

BMS: n = 0

late
definite
SES: n = 0
BMS: 1.9% (n = 3)
probable
SES: n = 0
BMS: n = 0
possible
SES: n = 0
BMS: n = 0

very late
definite
SES: 0.6% (n = 1)
BMS: n = 0
probable
SES: n = 0
BMS: 0.6% (n = 1)
possible
SES: 1.9% (n = 3)
BMS: n = 0

total
definite
SES: 0.6% (n = 1)
BMS: 3.8% (n = 6)
probable
SES: 0.6% (n = 1)
BMS: 0.6% (n = 1)
possible
SES: 1.9% (n = 3)
BMS: n = 0

Brunner-LaRocca (2007) BASKET (Basel Stent Kosten-Effektiviäts Trial) Switzerland single site There is probably overlap in patient population with	I/II RCT F/U: 18 months	N = 826 BMS, n = 281 DES, n = 545 Cypher, n = 264 Taxus, n = 281 % male: 79% Cypher: 79% Taxus: 78% BMS: 79%	• STEMI: 21% (n = 176) Cypher: 24% (n = 64) Taxus: 18% (n = 51) BMS: 22% (n = 61) • unstable: 36% (n = 301) Cypher: 36% (n = 96) Taxus: 37% (n = 104) BMS: 36% (n = 101)	**BMS** third generation cobalt-chromium **DES** Cypher Taxus	at 18 months • *cardiac death/MI* DES: 8.4% BMS: 7.5% *P* = .70 (HR = 1.11, 95% CI, 0.66-1.86) • *non-MI-related TVR* DES: 7.5% BMS: 11.6%	• ADJUSTING: Cox regression models • THROMBUS definition: ARC • Proportional hazards were time dependent (survival curves for DES and BMS crossed for most curves)

the Pfisterer 2009 population	age: 64 ± 11 years Cypher: 64 ± 12 years Taxus: 64 ± 11 years BMS: 64 ± 11 years • diabetes: 19% (n = 154) Cypher: 16% (n = 41) Taxus: 19% (n = 52) BMS: 22% (n = 61) • HTN: 67% (n = 550) Cypher: 65% (n = 172) Taxus: 66% (n = 186) BMS: 68% (n = 192) • hyperlipidemia: 76% (n = 628) Cypher: 75% (n = 198) Taxus: 76% (n = 216) BMS: 76% (n = 214) • current smoker: 29% (n = 238) Cypher: 29% (n = 77) Taxus: 26% (n = 74) BMS: 31% (n = 87) • previous MI: 27% (n = 226) Cypher: 28% (n = 73) Taxus: 28% (n = 78) BMS: 27% (n = 75) • previous PCI: 16% (n = 133) Cypher: 17% (n = 44) Taxus: 17% (n = 47) BMS: 15% (n = 42) • previous CABG: 13% (n = 105) Cypher: 14% (n = 37) Taxus: 12% (n = 33) BMS: 12% (n = 35)	• stable: 42% (n = 349) Cypher: 39% (n = 104) Taxus: 44% (n = 126) BMS: 42% (n = 119) • GPIIb/IIIa: 26% (n = 212) Cypher: 28% (n = 74) Taxus: 24% (n = 67) BMS: 25% (n = 71) • multivessel disease: 69% (n = 566) Cypher: 65% (n = 172) Taxus: 71% (n = 199) BMS: 69% (n = 195) • CTO: 3% (n = 28) Cypher: 2% (n = 5) Taxus: 3% (n = 9) BMS: 5% (n = 14) • bifurcations: 5% (n = 44) Cypher: 3% (n = 9) Taxus: 6% (n = 18) BMS: 6% (n = 17) • stented segments: 1.5 ± 0.7 Cypher: 1.5 ± 0.7 Taxus: 1.5 ± 0.7 BMS: 1.7 ± 0.7		*P* = .05 (HR = 0.62, 95% CI, 0.39-0.99) • *MACE* DES: 15.5% BMS: 18.9% *P* = .22 (HR = 0.81, 95% CI, 0.57-1.14) no significant differences were seen in any of these events between the two DES used • small versus large stents: smaller size (< 3.0 mm) benefits from DES in cumulative rates of survival free of MI, non-MI-related TVR, MACE free survival (P = .03, .02, .001) but not larger stents (P = .05, .38, .43)

Grube (2007) TAXUS VI Germany multi-site high-risk subgroup analysis for TLR	I/II RCT sub-anaylsis II/III F/U: 2 years F/U% SES: 98.6% BMS: 95.6%	N = 446 DES: n = 219 BMS: n = 227 % male DES: 76.3% BMS: 76.2% age DES: 61.8 ± 9.7 years BMS: 63.4 ± 9.9 years • diabetes DES: 17.8% (n = 39) BMS: 22.0% (n = 50) • insulin requiring diabetes DES: 6.8% (n = 15) BMS: 8.8% (n = 20) • non-insulin requiring diabetes DES: 11.0% (n = 24) BMS: 13.2% (n = 30) • hyperlipidemia DES: 70.3% (n = 149) BMS: 73.4% (n = 163) • HTN DES: 57.5% (n = 126) BMS: 58.1% (n = 132) • current smoker DES: 22.5% (n = 47) BMS: 23.9% (n = 52) • previous PCI DES: 17.9% (n = 39) BMS: 20.7% (n = 47)	• unstable angina DES: 24.7% (n = 54) BMS: 22.9% (n = 52) • GP IIb/IIIa used at discretion of the physician† • aspirin ≥ 75 mg/day and clopidogrel 75 mg mg/day were continued for a minimum of 6 months after the procedure, and aspirin alone after that	BMS uncoated Express stent DES Taxus MR	*2 years* • MACE DES: 21.3% (n = 46) BMS: 25.1% (n = 55) *P* = .37 • cardiac death DES: 0.5% (n = 1) BMS: 1.4% (n = 3) *P* = .62 • Q-wave MI DES: 1.4% (n = 3) BMS: 1.4% (n = 3) *P* = 1.0 • non-Q-wave-MI DES: 7.4% (n = 16) BMS: 5.5% (n = 12) *P* = .44 • TVR DES: 13.9% (n = 30) BMS: 21.9% (n = 48) *P* = .033 • thrombosis *0-30 days* DES: 0.5% (n = 1) BMs: 0.9% (n = 2) *P* = 1.0 *31-180 days* DES: 0% BMS: 0% *181-365 days* DES: 0% BMS: 0% *366-730 days* DES: 0.5% (n = 1) BMS: 0% *P* = 1.0	• ADJUSTING: NR • THROMBUS definition: per protocol as the clinical presentation of an acute coronary syndrome with angiographic evidence of stent thrombosis, acute MI in the distribution of the treated vessel, or death within 30 days without other obvious cause (Clinical Events Committee) • single de novo lesions + treatment of "non-study" target vessel prior to randomization?? • Trial sponsored by Boston Scientific; some authors employees/stock holders probably underpowered

					• cumulative survival rates free from TLR 1 year DES: 91.7% BMS: 80.0% 2 years DES: 90.3% BMS: 79.0% *P* < .001 high risk subgroup analysis showed a TLR reduction at 2 years from 72% to 84% by using the DES • subgroup analysis of TLR at 2 years *overall* BMS: 21.0% (46/219) DES: 9.7% (21/216) *P* = .001 (RR = 0.46, 95% CI, 0.29-0.75) *RVD < 2.5 mm* BMS: 29.5% (18/61) DES: 8.3% (5/60) *P* = .005 (RR = 0.28, 95% CI, 0.11-0.71) *lesion length > 26 mm* BMS: 27.8% (10/36) DES: 4.4 % (2/45) *P* = .004 (RR = 0.16, 95% CI, 0.04-0.68) *overlapping stents* BMS: 25.0% (n = 15/60) DES: 4.8% (3/63) *P* = .002 (RR = 0.19, 95% CI, 0.06-0.62) *medically treated diabetes* BMS: 23.9% (11/46) DES: 10.3% (4/39) *P* = .153 (HR = 0.43, 95% CI, 0.15-1.24)		
Morice (2007)* RAVEL (A Randomized Comparison of a	I/II RCT	N = 238 SES, n = 120 BMS, n = 118	• unstable angina: 50% SES: 48% BMS: 52%	**BMS** VELOCITY balloon-expandable BMS	Nonhierarchical ranking of cumulative incidence of MACE at 5 years (table 1) • death	• ADJUSTING: NR • THROMBUS definition: ARC and per-protocol

Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) multisite	F/U: 5 years F/U% SES: 92.5% (98/106) NMS: 89.1% (98/110)	% male: 76% SES: 70% BMS: 81% age: 60.7 ± 10.4 years SES: 61.8 ± 10.7 years BMS: 59.7 ± 10.1 years • previous MI: 36% SES: 38% BMS: 34% • diabetes: 19% SES: 16% BMS: 21% • hyperlipidemia: 40% SES: 38% BMS: 43% • HTN: 61% SES: 62% BMS: 61% • current smoker: 30% SES: 27% BMS: 33%	• stable angina: 30% SES: 41% BMS: 37% • silent ischemia: 11% SES: 11% BMS: 11% • target coronary artery LAD: 50% SES: 49% BMS: 51% RCA: 27% SES: 27% BMS: 27% LCX: 23% SES: 24% BMS: 22% • GP IIB/IIIa SES: 10.1% BMS: 9.5% • post-procedural dual antiplatelet therapy 325 mg aspirin daily, indefinitely, and with clopidogrel 75 mg daily or ticlopidine 250 mg 2x daily for 8 weeks	**DES** Cypher (sirolimus-eluting)	SES: 12.1% (n = 14) BMS: 7.1% (n = 8) *P* = .20 • MI SES: 8.9% (n = 10) BMS: 6.9% (n = 8) *P* = .65 • TLR SES: 10.3% (n = 11) BMS: 26.0% (n = 30) *P* < .001 *surgical* SES: 3.6% (n = 4) BMS: 1.8% (n = 2) *P* = .41 *percutaneous* SES: 7.5% (n = 8) BMS: 24.2% (n = 28) *P* < .001 • TVR SES: 2.7% (n = 3) BMS: 2.6% (n = 3) *P* = .98 • Survival rates free from TLR *1 year* SES: 99.2% BMS: 75.9% *2 years* SES: 93.8% BMS: 75.0% *3 years* SES: 89.7% BMS: 74.0% *P* < .001 • Thrombosis *per-protocol* late stent thrombosis defined posthoc by the clinical events committee as all target-vessel-related MI with angiographic evidence of vessel occlusion occurring past 30 days after the index procedure, in absence of interim TLR	• Unstable angina was defined according to the Braunwald classification; stable angina according to the CCS • single de novo lesions • underpowered to detect rare events • more DES all cause mortality • Funding source not stated, several industry authors

SES: only 1 late incident occurred
BMS: no incidences occurred

ARC definitions
all ARC
SES: 3.3% (n = 4)
BMS: 6.8% (n = 8)

no acute, subacute, or late events occurred in the SES group

no acute or subacute events occurred in the BMS group

late
definite
SES: n = 0
BMS: n = 0
probable
SES: n = 0
BMS: 1.7% (n = 2)
possible
SES: n = 0
BMS: 0.8% (n = 1)
definite + probable
SES: n = 0
BMS: 1.7% (n = 2)
any
SES: n = 0
BMS: 2.5% (n = 3)

very late
definite
SES: 0.8% (n = 1)
BMS: 0.8% (n = 1)
probable
SES: 0.8% (n = 1)
BMS: 0
possible
SES: 1.7% (n = 2)
BMS: 3.4% (n = 4)
definite + probable
SES: 1.7% (n = 2)
BMS: 0.8% (n = 1)
any
SES: 3.3% (n = 4)

Valgimigli (2007) STRATEGY Italy multi-site	I/II RCT F/U: 720 days F/U%: 100	N = 175 BMS, n = 88 SES, n = 87 % male SES: 77% BMS: 69% age (median) SES: 62 years BMS; 63 years • diabetes SES: 17% (n = 15) BMS: 12% (n = 11) • HTN SES: 55% (n = 48) BMS: 50% (n = 44) • current smoker SES: 39% (n = 34) BMS: 41% (n = 36) • prior CABG SES: 2% (n = 2) BMS: 2% (n = 2) • prior PCI SES: 5% (n = 4) BMS: 2% (n = 2) • prior MI SES: 13% (n = 11) BMS: 9% (n = 8) • prior CVA SES: 6% (n = 5) BMS: 5% (n = 4)	• artery involved LAD SES: 49% (n = 43) BMS: 41% (n = 36) right coronary SES: 33% (n = 29) BMS: 38% (n = 33) circumflex SES: 17% (n = 15) BMS: 21% (n = 19) • 1-vessel disease SES: 53% (n = 46) BMS: 65% (n = 57) • 2-vessel disease SES: 32% (n = 28) BMS: 23% (n = 20) • 3-vessel disease SES: 15% (n = 13) BMS: 12% (n = 11) • dual antiplatelet therapy (either clopidogrel or ticlopidine and aspirin) SES: 182 ± 92 days BMS: 155 ± 105 days only the use of thienopyridines was shown to be protective with respect to MACE (HR = 0.74, 95% CI, 0.36-1.53, *P* = .42) cumulative incidence of death or nonfatal MI similar between 2 groups when compared starting from the time of thienopyridine discontinuation SES: 7.7% BMS: 7% (HR = 1.07, 95% CI, 0.33-3.57, *P* = .90)	BMS abciximab plus BMS DES tirofiban infusion followed by SES	BMS: 4.2% (n = 5) *30 days* • Death BMS: 3% (n = 3) SES: 2% (n = 2) *P* > .99 • Re-AMI BMS: 3% (n = 3) SES: 1% (n = 1) *P* = .62 • Urgent TVR BMS: 3% (n = 3) SES: 1% (n = 1) *P* = .62 • CVA BMS: n = 0 SES: n = 0 *P* > .99 • Thrombosis BMS: 2% (n = 2) SES: n = 0 *P* = .24 • Death/re-MI BMS: 7% (n = 6) SES 3% (n = 3) *P* = .49 • Death/re-MI/urgent TVR BMS: 8% (n = 7) SES: 3% (n = 3) *P* = .33 *12 months* • Death BMS: 9% (n = 8) SES: 8% (n = 7) *P* = .59 (HR = 0.77, 95% CI, 0.29-2.1)	• ADJUSTING: NR • THROMBUS definition: ARC • probably underpowered • appears to be follow- up to • Valgimigli M. JAMA 2005;293:2109 and Valgimigli M, Cardiovasc Drugs Ther 2004;18:225–30.

- re-AMI

BMS: 9% (n = 8)
SES: 7% (n = 6)
P = .60
(HR = 0.75, 95% CI, 0.26-2.22)

- TVR

BMS: 20% (n = 18)
SES: 7% (n = 6)
P = .01
(HR = 0.30, 95% CI, 0.12-0.77)

- Thrombosis

definite
BMS: 2% (n = 2)
SES: n = 0
P = .24
probable
BMS: 2% (n = 2)
SES: 1% (n = 1)
P > .99
possible
BMS: 1% (n = 1)
SES: 25 (n = 2)
P > .99
any
BMS: 6% (n = 5)
SES: 3% (n = 3)
P = .50
(HR = 0.63, 95% CI, 0.15-2.5)

- Death/re-AMI

BMS: 17% (n = 15)
SES: 13% (n = 11)
P = .39
(HR = 0.71, 95% CI, 0.34-1.5)

- Death/re-AMI/TVR

BMS: 32% (n = 28)
SES: 18% (n = 16)
P = .04
(HR = 0.53, 95% CI, 0.28-0.92)

24 months

- Death

BMS: 14% (n = 12)
SES: 11% (n = 10)
P = .66
(HR = 0.84, 95% CI, 0.36-1.96)

- re-MI

BMS: 9% (n = 9)
SES: 8% (n = 7)
P = .77
(HR = 0.82, 95% CI, 0.31-2.4)

- TVR

BMS: 24% (n = 21)
SES: 9% (n = 8)
P = .01
(HR = 0.34, 95% CI, 0.16-0.77)

- Stroke

BMS: n = 0
SES: n = 0
P > .99

- Thrombosis

definite
BMS: 2% (n = 2)
SES: n = 0
P = .49
probable
BMS: 2% (n = 2)
SES: n = 0
P > .99
possible
BMS: 2% (n = 2)
SES: 2% (n = 2)
P > .99
any
BMS: 7% (n = 6)
SES: 3% (n = 3)
P = .34
(HR = 0.51, 95% CI, 0.13-2.1)

- Death/re-AMI

BMS: 20% (n = 18)
SES: 16% (n = 14)
P = .56
(HR = 0.77, 95% CI, 0.38-1.55)

Kelbaek (2006) SCANDSTENT substudy: Total coronary occlusions Danish multi-site	II/III RCT substudy F/U: 7 months %F/U: NR	N = 127 SES: n = 64 BMS: n = 63 All patients had total coronary occlusions (interrupted contrast filling, TIMI flow 0 or 1) % male SES: 77% BMS: 81% age SES: 63.6 ± 10.4 years BMS: 61.2 ± 8.9 years	• unstable angina SES: 28% BMS: 19% • multivessel disease SES: 39% BMS: 38% • coronary artery LAD SES: 31% BMS: 38% LCX SES: 22% BMS: 22% RCA	BMS VELOCITY balloon-expandable stent DES Cypher (sirolimus-eluting)	• Death/re-AMI/TVR BMS: 39% (n = 34) SES: 24% (n = 21) *P* = .038 (HR = 0.56, 95% CI, 0.33-0.98) • Death/re-AMI/CVA/restenosis BMS: 46% (n = 41) SES: 24% (n = 21) *P* = .002 • Cumulative incidences *MACE* SES: 24.2% BMS: 38.6% *P* = .038 (HR = 0.56, 95% CI, 0.33-0.98) *death/MI* SES: 16.1% BMS: 20.5% *P* = .43 HR = 0.77 , 95% CI, 0.38-1.55) *TVR* SES: 9.8% BMS: 25.5% *P* = .01 (HR = 0.34, 95% CI, 0.16-0.77) • Death SES: 0.0% BMS: 0.0% *P* = NS • Cardiac death NR • MI SES: 0.0% BMS: 1.6% *P* = 0.50 • TLR SES: 0.0% BMS: 33.3%	• ADJUSTING: NR • THROMBUS definition: the occurrence of angiographical signs of a contrast filling defect in the target lesion in connection with ACS. • All patients reported in Kelbaek 2008, some patients possibly overlap with Thuesen 2006 • Revascularization should be clinically driven (performed in the presence of documented

		• diabetes SES: 19% BMS: 21% • HTN SES: 48% BMS: 33% • hyperlipidemia SES: 84% BMS: 95% • previous MI SES: 64% BMS: 55%	SES: 47% BMS: 40% • lesion length SES: 27.5 mm BMS: 22.8 mm (*P* = 0.04) • stented length SES: 35.3 mm BMS: 28.1 mm (*P* = 0.01) • number of stents SES: 1.6 BMS: 1.4 (*P* = 0.03) • antiplatelet therapy all patients treated with clopidogrel for ≥ 12 months and aspirin indefinitely • GP inhibitors were used at the discretion of the operator	*P* < .001 • TVR SES: 4.7% BMS: 33.3% *P* < 0.001 • Thrombosis SES: 0.0% BMS: 1.6% *P* = 0.5 • MACE-free survival at 7 months SES: 95.3% BMS: 65.1% Log rank < 0.001	ischemia and a significant stenosis of the lesion). • patients were informed of stent type • manufacturer not involved in any part of study
New RCTS			•			•
Kelbaek (2008) DEDICATION Denmark multi-site	I/II RCT F/U: 8 months F/U%: 100	N = 626 DES, n = 313 BMS, n = 313 % male DES: 72.8% BMS: 73.5% age DES: 61.8 years BMS: 62.6 years • diabetes DES: 9.3% BMS: 11.5% • HTN DES: 32.3% BMS: 33.9% • hyperlipidemia DES: 18.5%	• diseased vessels one DES: 65% BMS: 60% two DES: 25% BMS: 29% three DES: 10% BMS: 11% • infarct-related artery RCA DES: 47% BMS: 45% LAD DES: 40% BMS: 43% left circumflex DES: 13% BMS: 12%	**BMS Stents** cobalt alloy (38%) stainless steel from Boston Scientific (39%) miscellaneous stainless steel (23%) **DES Stents** sirolimus-eluting (47%) paclitaxel-eluting (40%) zotarolimus-eluting (13%)	*MACE at 8 months* • death DES: 5.1% (n = 16) BMS: 2.6% (n = 8) *P* = .14 • cardiac death DES: 4.2% (n = 13) BMS: 1.6% (n = 5) *P* = .09 • MI DES: 1.6% BMS: 2.6% *P* = .42 • re-infarction DES: 1.0% BMS: 1.9% *P* = .51	• ADJUSTING: Cox proportional hazard models • THROMBUS definition: ARC • 8 month f/u - sufficient?? • Industry funding • Majority SVD or 2 VD~40% LAD inovlvment 45% RCA • 4.4 %DES/5.4 % previous PCI /CABG • 65 DES 70% BMS had TIMIT flow = 0-1 • probably underpowered to detect rare events

BMS: 21.4%

- current smoker
  DES: 52.7%
  BMS: 54.7%

- prior MI
  DES: 6.1%
  BMS: 7.0%

- prior PCI/CABG
  DES: 4.4%
  BMS: 5.4%

- GPIIb/IIIa
  BMS: 97% (n = 304)
  DES: 96% (n = 299)

- stents per lesion
  BMS: 1.3 ± 0.62
  DES: 1.3 ± 0.62

- patients discharged on a daily dose of clopidogrel for 12 months and aspirin indefinitely

- TLR
  DES: 5.1%
  BMS: 13.1%
  P < .001

- MACE
  DES: 8.9% (n = 28)
  BMS: 14.4% (n = 45)
  P < .05

- TVR
  DES: 6.4%
  BMS: 16.0%
  P < .001

- stroke
  DES: 1.6%
  BMS: 1.0%
  P = .73

- thrombosis
  DES: 2.0% (n = 7)
  BMS: 2.6% (n = 8)
  P = .72

quantitative coronary angiography, mean (SD)

- in-lesion zone

number at f/u
DES (n = 258)
BMS (n = 267)

reference vessel diameter, mm
after procedure
DES: 3.11 (0.56)
BMS: 3.13 (0.56)
P = .62
at 8 month f/u
DES: 3.31 (0.61)
BMS: 3.00 (0.61)
P < .001

minimal lumen diameter, mm
after procedure
DES: 2.40 (0.56)

BMS: 2.38 (0.59)
P = .62
at 8 month f/u
DES: 2.36 (0.77)
BMS: 1.91 (0.77)
P < .001
diameter stenosis
after procedure
DES: 23.3 (11.0)
BMS: 24.3 (12.3)
P = .22
at 8 month f/u
DES: 29.4 (17.5)
BMS: 36.8 (21.0)
P < .001
late lumen loss, mm
DES: 0.06 (0.66)
BMS: 0.47 (0.69)
P < .001
binary restenosis
DES: 6.7% (n = 21)
BMS: 17.9% (n = 56)
P < .001

- in-stent zone

number at f/u
DES (n = 257)
BMS (n = 264)

reference vessel diameter, mm
after procedure
DES: 3.18 (0.51)
BMS: 3.16 (0.53)
P = .62
at 8 month f/u
DES: 3.32 (0.59)
BMS: 3.01 (0.60)
P < .001
minimal lumen diameter, mm
after procedure
DES: 2.69 (0.50)
BMS: 2.70 (0.53)
P = .92
at 8 month f/u
DES: 2.61 (0.78)
BMS: 2.00 (0.80)

P < .001
diameter stenosis
after procedure
DES: 15.3 (9.5)
BMS: 14.7 (9.0)
P = .42
at 8 month f/u
DES: 21.7 (18.4)
BMS: 34.0 (21.9)
P < .001
late lumen loss, mm
DES: 0.09 (0.69)
BMS: 0.69 (0.66)
P < .001
binary restenosis
DES: 4.8% (n = 15)
BMS: 16.6% (n = 52)
P < .001

Valgimigli (2007) MULTISTRATEGY Italy, Argentina, Spain multi-site	I/II RCT F/U: 8 months F/U: 99.8%	N = 745 BMS: n = 372 SES: n = 372 % male BMS: 76.3% SES: 75.6% age BMS: 65 years SES: 63 years • diabetes BMS: 14.8% (n = 55) SES: 14.3% (n = 53) • HTN BMS: 59.1% (n = 220) SES: 55.3% (n = 206) • hyperlipidemia BMS: 54.9% (n = 204) SES: 51.6% (n = 192) • current smoker BMS: 37.6% (n = 140)	• number of diseased vessels one BMS: 42.8% (n = 159) SES: 47.1% (n = 175) two BMS: 34.7% (n = 129) SES: 33.6% (n = 125) three BMS: 21.0% (n = 78) SES: 18.0% (n = 67) • stents implanted (median) BMS: 1 (1-1) SES: 1 (1-1) • 1 or more SES implanted: 94.0% • patients received aspirin 160-325 mg orally or 250 intravenously followed by 80-125 mg/day orally indefinitely, and clopidogrel 300 mg orally and then 75 mg/day for at least 3	**BMS** abciximab plus uncoated stent (n = 186) tirofiban plus uncoated stent (n = 186) **DES** abciximab plus sirolmus-eluting stent (n = 186) tirofiban plus sirolmus-eluting stent (n = 186)	*30 days* • death BMS: 2.2% (n = 8) SES: 1.3% (n = 5) *P* = .40 • reinfarction BMS: 2.7% (n = 10) SES: 1.3% (n = 5) *P* = .19 • death or reinfarction BMS: 4.8% (n = 18) SES: 2.7% (n = 10) *P* = .12 • TVR BMS: 2.2% (n = 8) SES: 1.6% (n = 6) *P* = .59 • composite of death, reinfarction, or TVR BMS: 5.1% (n = 19) SES: 3.2% (n = 12)	• ADJUSTING: Cox proportional hazard model • THROMBUS definition: ARC • demographics/clinical presentation pooled to create BMS and SES groups • open label • 10 – 17% had previous MI • 5-12 % had previous PCI or CABG • ~60% had MVD • 8 months –

SES: 36.8% (n = 137)

- prior MI
  BMS: 8.1% (n = 30)
  SES: 7.5% (n = 27)

prior PCI
  BMS: 4.6% (n = 20)
  SES: 6.2% (n = 23)

- prior CABG
  BMS: 1.3% (n = 5)
  SES: 0.75% (n = 3)

- prior stroke or transient ischemic attack
  BMS: 6.5% (n = 24)
  SES: 3.0% (n = 11)

months

P = .20

- thrombosis
  definite
  BMS: 1.9% (n = 7)
  SES: 1.3% (n = 5)
  P = .56
  probable
  BMS: 1.1% (n = 4)
  SES: 0.3% (n = 1)
  P = .18
  definite or probable
  BMS: 3.0% (n = 11)
  SES: 1.6% (n = 6)
  P = .22

- safety analysis
  major bleeding
  BMS: 2.3% (n = 8)
  SES: 1.9% (n = 7)
  P = .79
  minor bleeding
  BMS: 7.0% (n =26)
  SES: 4.0% (n = 15)
  P = .09
  red blood cell transfusion ≥ 1 units
  BMS: 3.5% (n = 13)
  SES: 2.4% (n = 9)
  P = .39
  red blood cell transfusion ≥ 2 units
  BMS: 2.7% (n = 10)
  SES: 1.9% (n = 7)
  P = .46
  severe thrombocytopenia (< 50,000 cells/mm^3)
  BMS: 2.2% (n = 8)
  SES: 0.8% (n = 3)
  P = .23
  moderate thrombocytopenia (< 100,000 cells/mm^3)
  BMS: 0.8% (n = 3)
  SES: 1.1% (n = 4)
  P = .70

8 months

- composite of death, reinfarction, or TVR

					BMS: 14.5% (n = 54) SES: 7.8% (n = 29) *P* = .004 • death BMS: 4.0% (n = 15) SES: 3.0% (n = 11) *P* = .42 • reinfarction BMS: 4.6% (n = 17) SES: 3.2% (n = 12) *P* = .34 • death or reinfarction BMS: 7.5% (n = 28) SES: 5.9% (n = 22) *P* = .37 • TVR BMS: 10.2% (n = 32) SES: 3.2 (n = 12) *P* < .001 • thrombosis *definite* BMS: 3.0% (n = 11) SES: 2.4% (n = 9) *P* = .65 *possible* BMS: 1.1% (n = 4) SES: 0.8% (n = 3) *P* = .71 *definite or probable* BMS: 4.0% (n = 15) SES: 2.7% (n = 10) *P* = .31 *definite or probable or possible* BMS: 4.6% (n = 17) SES: 3.5% (n = 13) *P* = .45	
Diaz de la Llera (2007) Spain	I/II RCT	N = 120 BMS, n = 54 SES, n = 60	• number of diseased vessels one BMS: 51.7% (n = 31)	BMS uncoated stents	*30 days* • death BMS: 3.6% (n = 2)	• ADJUSTING: multivariate logistic regression • THROMBUS definition:

single-site

F/U: 1 year

F/U%: 100%

% male
BMS: 78.3%
SES: 80/0%

age
BMS: 65 ± 13 years
SES: 64 ± 12 years

- diabetes
BMS: 28.3% (n = 17)
SES: 26.7% (n = 16)

- current smoker
BMS: 68.3% (n = 41)
SES: 68.3% (n = 41)

- prior MI
BMS: 10.0% (n = 6)
SES: 5.0% (n = 3)

- prior PCI
BMS: 6.7% (n = 4)
SES: 5.0% (n = 3)

- prior CABG
BMS: 1.7% (n = 1)
SES: 0%

SES: 55.0% (n = 33)
two
BMS: 31.7% (n = 19)
SES: 31.7% (n = 19)
three
BMS: 16.7% (n = 10)
SES: 13.3% (n = 8)

- infarct-related artery
right coronary
BMS: 53.3% (n = 32)
SES: 35.0% (n = 21)
LAD
BMS: 30.0% (n = 18)
SES: 53.3% (n = 32)
left circumflex
BMS: 15.0% (n = 9)
SES: 11.7% (n = 7)
left main
BMS: 1.7% (n = 1)
SES: 0%

- GP IIb/IIIa was used in all patients

- all patients received aspirin 300-500 mg orally as the loading dose and then 100 mg/day indefinitely, and clopidogrel 300 or 600 mg as loading dose and then 75 mg/day for at least 1 or 9 months depending on the type of stent used (BMS vs SES)

DES
sirolimus-eluting stent

SES: 3.3% (n = 2)
P = .914

- death/nonfatal reinfarction
BMS: 5.4% (n = 3)
SES: 5.0% (n = 3)
P = .894

- urgent TVR
BMS: 1.8% (n = 1)
SES: 1.7% (n = 1)
P = .940

- acute or subacute stent thrombosis
BMS: 1.8% (n = 1)
SES: 1.7% (n = 1)
P = .940

- death, reinfarction, urgent TVR
BMS: 5.4% (n = 3)
SES: 5.0% (n = 3)
P = .894

1 year

- death
BMS: 3.6% (n = 2)
SES: 5.0% (n = 3)
P = .736

- death or nonfatal reinfarction
BMS: 5.4% (n = 3)
SES: 6.7% (n = 4)
P = .260

- TVR
BMS: 5.7% (n = 3)
SES: 0%
P = .064

- late stent thrombosis
BMS: 0%
SES: 1.7% (n = 1)
P = .341

an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either MI in the distribution of the treated vessel or death not clearly attributable to other causes

- all deaths were considered cardiac unless otherwise documents

- probably underpowered

					• total death, reinfarction, TVR BMS: 11.1% (n = 6) SES: 6.7% (n = 4) *P* = .402 RR = 1.75, 95% CI, 0.47-6.57	
RCT specific to special populations						
Maresta (2008) DESSERT Italy multi-site	I/II RCT F/U: 12 months F/U% BMS: 93% SES: 91%	N = 150 BMS, n = 75 SES, n= 75 % male SES: 63% BMS: 495 age SES:71 ± 9 years BMS: 69 ± 9 years • prior MI SES: 36% (n = 27) BMS: 25% (n = 19) • prior PCI SES: 15% (n = 11) BMS: 11% (n = 8) • prior CABG SES: 7% (n = 5) BMS: 4% (n = 3) • prior CVA SES: 5% (n = 4) BMS: 5% (n = 4) • HTN SES: 77% (n = 58) BMS: 75% (n = 56) • hyperlipidemia SES: 47% (n = 35) BMS: 52% (n = 39) • smoking history SES: 43% (n = 32) BMS: 39% (n = 29)	• stable angina SES: 29% (n = 22) BMS: 28% (n = 21) • unstable angina SES: 47% (n = 35) BMS: 48% (n = 36) • recent MI SES: 16% (n = 12) BMS: 12% (n = 9) • silent ischemia SES: 8% (n = 6) BMS: 12% (n = 9) • number of diseased vessels one SES: 28% (n = 21) BMS: 35% (n = 26) two SES: 38% (n = 29) BMS: 34% (n = 26) three SES: 34% (n = 25) BMS: 31% (n = 23) • artery involved LAD SES: 60% (n = 45) BMS: 57% (n = 43) left circumflex SES: 36% (n = 27) BMS: 31% (n = 23) right coronary SES: 33% (n = 25) BMS: 39% (n = 29)	BMS Sonic DES Cypher	*inhospital* • MACE 9.3% of patients with no difference between the 2 groups • Q-wave-MI BMS: n = 1 SES: NR • non-Q-wave MI BMS: 9.3% (n = 7) SES: 8.0% (n = 6) • cerebrovascular attack BMS: n = 1 SES: NR • major bleeding SES: n = 1 (treated with transfusion) BMS: NR *30 days* • MACE SES: 12% BMS: 13.9% P = .733 (OR = 1.18, 95% CI, 0.41-3.43) • non-Q-wave MI BMS: n = 1 SES: n = 2 • TVR BMS: n = 2 SES: n = 2 • TVF	• ADJUSTING: linear and logistic regressions • THROMBUS definition: ARC • ~80% had MVD • ~ 25 % had 2 or more vessels treated and 7-12% hae more than 1 stent per lesion • Some wide confidence intervals for ORs – • Check thrombus definition Industry sponsored

- type I diabetes
  SES: 7% (n = 5)
  BMS: 11% (n = 8)

- insulin treatment in last 3 months
  SES: 24% (n = 18)
  BMS: 27% (n = 20)

- oral hypoglycemics in last 3 months
  SES: 89% (n = 67)
  BMS: 75% (n = 56)

- stent/lesion (% based on lesions, n = 109)
  one
  SES: 88% (n = 96)
  BMS: 93% (n = 101)
  two
  SES: 12% (n = 12)
  BMS: 7% (n = 8)

- all patients were treated with oral aspirin 100mg/day and clopidogrel (loading dose 300 mg and then 75 mg/day)

- all DES patients received 6 months of clopidogrel therapy

- 70-IU/kg IV heparin bolus given to all patients

- GP IIb/IIIa given to all patients

only baseline C-reactive protein was independent predictor of 30-day TVF (OR = 1.14, 95% CI, 1.01-1.28, P = .031)

- subacute thrombosis
  SES: n = 1
  BMS: NR

12 months

- MACE
  BMS: 40% (n = 28)
  SES: 22.1% (n = 15)
  P = .023
  (OR = 2.36, 95% CI, 1.05-5.33)

only stent type was an independent predictor of 12-month MACE (OR = 2.35, 95 CI, 1.12-4.98, *P* = .024)

- TVF
  BMS: 34.3% (n = 24)
  SES: 14.7% (n = 10)
  P = .008
  (OR = 3.03, 95% CI, 1.23-7.59)

multivariate analysis showed that hemoglobin A1c (OR = 1.40, 95% CI, 105-1.87, *P* = 0.24) and stent type (OR = 2.97, 95% CI, 1.29-6.84, *P* = .010) were independent predictors of TVF.

- death
  BMS: 2.9% (n = 2)
  SES: 4.4% (n = 3)
  P = .678
  (OR = 0.64, 95% CI, 0.07-4.89)

- MI (any)
  BMS: 20% (n = 14)
  SES: 16.2% (n = 11)
  P = .559
  (OR = 1.30, 95% CI, 0.50-3.38)

- Q-wave-MI
  BMS: 4.3% (n = 3)

SES: 1.5% (n = 1)
P = .620
(OR = 3.00, 95% CI, 0.27-76.03)

- non-Q-wav-MI

BMS: 15.7% (n = 11)
SES: 14.7% (n = 10)
P = .869
(OR = 1.08, 95% CI, 0.39-3.01)

- TLR

BMS: 30% (n = 21)
SES: 5.9% (n = 4)
P < .001
(OR = 6.86, 95% CI, 2.04-25.37)

- TVR

BMS: 30% (n = 21)
SES: 7.4% (n = 5)
P < .001
(OR = 5.4, 95% CI, 1.76-17.72)

- thrombosis (all)

BMS: 1.4% (n = 1)
SES: 1.5% (n = 1)
P = 1.0
(OR = 0.97, 95% CI, 0.03-36.37)

acute (0-1 day)
BMS: 0%
SES: 0%

subacute (2-30 days)
BMS: 0%
SES: 1.5% (n = 1)
P = .493
(OR = 0.01, 95% CI, 0.00-17.00)

late (31days-1 year)
BMS: 1.4% (n = 1)
SES: 0%
P = 1.0

8 month angiographic results (SES, n = 84; BMS, n = 80)

					• in-stent binary restenosis SES: 3.6% BMS: 38.8% *P* < .001 • proximal edge binary restenosis SES: 2.4% BMS: 3.8% *P* = .676 • distal edge binary restenosis SES: 0% BMS: 5.1% *P* = .053	
Subanalyses of previous RCTs						
Thuesen (2006) SCANDSTENT substudy: Bifurcated lesions Danish multi-site	II/III RCT substudy F/U: 7 months %F/U: NR	N = 126 SES: n = 68 BMS: n = 58 All patients had bifurcated lesions % male SES: 78% BMS: 79% age SES: 61 ± 8 years BMS: 63 ± 10 years • diabetes SES: 16% BMS: 14% • HTN SES: 43% BMS: 31% • hyperlipidemia SES: 82% BMS: 83% • previous MI SES: 51%	• unstable angina SES: 25% BMS: 38% • multivessel disease SES: 40% BMS: 45% • coronary artery LAD SES: 77% BMS: 65% LCX SES: 21% BMS: 22% PDA SES: 2% BMS: 13% • lesion length NR • stented length SES: 29.8 mm BMS: 24.6 mm (*P* = 0.006) • number of stents SES: 1.8 BMS: 1.6	BMS VELOCITY balloon-expandable stent DES Cypher (sirolimus-eluting)	• Death SES: 0.0% BMS: 1.8% *P* = NS • Cardiac death NR • MI SES: 3.0% BMS: 5.2% *P* = 0.NS • TVR SES: 6.0% BMS: 21.1% *P* = 0.016 • MACE SES: 9.0% BMS: 28.1% *P* = 0.009 • Thrombosis SES: 0.0% BMS: 8.8% *P* = 0.019	• ADJUSTING: NR • THROMBUS definition: the occurrence of angiographical signs of a contrast filling defect in the target lesion in connection with ACS. • All patients reported in Kelbaek 2008, some patients possibly overlap with Thuesen 2006 • Revascularization should be clinically driven (performed in the presence of documented ischemia and a significant stenosis of the lesion). • patients were informed of stent type • manufacturer not involved in any part of study

		BMS: 53% • antiplatelet therapy all patients treated with clopidogrel for ≥ 12 months and aspirin indefinitely • GP inhibitors were used at the discretion of the operator	• Event-free survival at 7 months SES: 91.2% BMS: 71.9% Log rank = 0.006			
Halkin (2005) Subanalysis from TAXUS-IV trial - renal insufficiency USA multi-site	II/III RCT F/U: 1 year F/U%: 100	N = 1300 normal RF, n = 658 mildly impaired RF, n = 419 RI, n = 223 % male normal: 80.7% mild: 71.4% RI: 47.1% age normal: 56.2 ± 8.8 years mild: 66.2 ± 8.5 years RI: 74.0 ± 8.1 years • current smoker normal: 30.0% mild: 16.7% RI: 10.2% • HTN normal: 67.0% mild: 71.8% RI: 76.0% • hyperlipidemia normal: 68.2% mild: 63.8% RI: 65.2% • diabetes normal: 26.0% mild: 22.2% RI: 22.4% • diabetes-insulin normal: 28.7%	• unstable angina normal: 34.5% mild: 32.5% RI: 35.4% • stable angina normal: 50.8% mild: 54.7% RI: 49.3% • silent ischemia normal: 14.7% mild: 12.9% RI: 15.2% • target vessel right coronary artery normal: 30.5% mild: 29.6% RI: 37.7% LAD normal: 42.1% mild: 42.7% RI: 32.3% left circumflex artery normal: 27.4% mild: 27.7% RI: 30.0% • GPIIb/IIIa normal: 59.0% mild: 56.3% RI: 53.4% • one stent implanted normal: 93.2% mild: 90.0%	BMS EXPRESS stent DES TAXUS stent	*1 year clinical events* *normal* *DES: n = 312* *BMS: n = 346* *mild* *DES: n = 219* *BMS: n = 200* *RI* *DES: n = 123* *BMS: n = 100* • death *normal* DES: 1.9% BMS: 1.5% *P* = .64 *mild* DES: 1.4% BMS: 1.6% *P* = .91 *RI* DES: 4.3% BMS: 3.0% *P* = .66 • cardiac death *normal* DES: 1.3% BMS: 1.2% *P* = .88 *mild* DES: 0.9% BMS: 0.6% *P* = .62 *RI* DES: 1.6% BMS: 3.0%	• ADJUSTING: Cox proportional hazards regression model, logistic regression • THROMBUS definition: NR • Definitions *normal RF*: CrCl ≥ 90 mL/min *mildly impaired RF*: CrCl 60-89 mL.min *RI*: CrCl < 60 mL/min • Patterns of in-stent restenosis characterized by the Mehran classification

mild: 32.3%
RI: 48.0%

- diabetes-oral medication
  normal: 71.3%
  mild: 67.7%
  RI: 52.0%

- peripheral arterial disease
  normal: 6.5%
  mild: 11.5%
  RI: 16.7%

- prior CVA
  normal: 3.1%
  mild: 4.6%
  RI: 6.4%

- previous PCI
  normal: 29.1%
  mild: 31.7%
  RI: 32.4%

- previous CABG
  normal: 7.0%
  mild: 10.7%
  RI: 16.6%

- previous MI
  normal: 30.2%
  mild: 28.4%
  RI: 33.6%

RI: 92.8%

P = .49

- MI
  normal
  DES: 3.5%
  BMS: 4.7%
  P = .49
  mild
  DES: 1.8%
  BMS: 4.5%
  P = .12
  RI
  DES: 5.7%
  BMS: 5.2%
  P = .78

- TLR
  normal
  DES: 4.6%
  BMS: 17.2%
  P < .0001
  RR = .025 (95% CI, 0.14-0.45)
  mild
  DES: 5.0%
  BMS: 13.5%
  P = .002
  RR = 0.33 (95% CI, 0.16-0.69)
  RI
  DES: 3.3%
  BMS: 12.2%
  P = .01
  RR = 0.26 (95% CI, 0.08-0.81)

- TVR
  normal
  DES: 6.9%
  BMS: 19.0%
  P < .0001
  mild
  DES: 8.0%
  BMS: 15.5%
  P = .009
  RI
  DES: 6.6%
  BMS: 15.2%
  P = .04

- MACE
  normal
    DES: 9.7%
    BMS: 22.3%
    P < .0001
  mild
    DES: 10.7%
    BMS: 17.1%
    P = .03
  RI
    DES: 13.1%
    BMS: 19.1%
    P = .28

- thrombosis
  normal
    DES: 0.6%
    BMS: 0.6%
    P = .92
  mild
    DES: 0.5%
    BMS: 0.5%
    P = .95
  RI
    DES: 0%
    BMS: 2.0%
    P = .12

9-month angiographic data
  normal
    DES: n = 139
    BMS: n = 152
  mild
    DES: n = 102
    BMS: n = 75
  RI
    DES: n = 48
    BMS: n = 39

- MLD, analysis segment (mm)
  normal
    DES: 2.03 ± 0.53
    BMS: 1.62 ± 0.64
    P < .0001
  mild

DES: 2.01 ± 0.61
BMS: 1.75 ± 0.52
P = .003
RI
DES: 2.06 ± 0.49
BMS: 1.75 ± 0.62
P = .001

- MLD, in-stent (mm)
normal
DES: 2.26 ± 0.56
BMS: 1.70 ± 0.69
P < .0001
mild
DES: 2.27 ± 0.63
BMS: 1.80 ± 0.54
P < .0001
RI
DES: 2.23 ± 0.55
BMS: 1.82 ± 0.65
P = .002

- diameter stenosis, analysis segment (%)
normal
DES: 25.87 ± 15.11
BMS: 42.36 ± 19.44
P < .0001
mild
DES: 28.29 ± 17.36
BMS: 37.07 ± 14.82
P = .0006
RI
DES: 23.21 ± 11.66
BMS: 35.72 ± 19.36
P = .0008

- diameter stenosis, in-stent (%)
normal
DES: 17.19 ± 16.71
BMS: 39.36 ± 21.22
P < .0001
mild
DES: 18.40 ± 19.97
BMS: 35.21 ± 15.37

P < .0001
RI
DES: 16.42 ± 16.06
BMS: 33.48 ± 20.67
P = .0008

- late loss, analysis segment (mm)
normal
DES: 0.22 ± 0.44
BMS: 0.69 ± 0.60
P < .0001
mild
DES: 0.28 ± 0.47
BMS: 0.53 ± 0.49
P = .0007
RI
DES: 0.18 ± 0.35
BMS: 0.49 ± 0.56
P = .004
- late loss, in-stent (mm)
normal
DES: 0.37 ± 0.49
BMS: 0.96 ± 0.60
P < .0001
mild
DES: 0.42 ± 0.53
BMS: 0.86 ± 0.50
P < .0001
RI
DES: 0.41 ± 0.45
BMS: 0.90 ± 0.62
P = .0001

- binary restenosis, analysis segment
normal
DES: 7.2%
BMS: 32.9%
P < .0001
mild
DES: 11.8%
BMS: 17.3%
P = .38
RI

DES: 2.1%
BMS: 20.5%
P < .009

- binary restenosis, in-stent

normal
DES: 5.8%
BMS: 30.3%
P < .0001
mild
DES: 6.9%
BMS: 16.0%
P = .08
RI
DES: 2.1%
BMS: 18.4%
P = .02

- restenosis pattern

focal
normal
DES: 2.9%
BMS: 9.9%
P = .02
mild
DES: 4.9%
BMS: 5.3%
P = .99
RI
DES: 2.1%
BMS: 2.6%
P = .99
diffuse
normal
DES: 1.4%
BMS: 17.1%
P < .001
mild
DES: 1.0%
BMS: 9.3%
P = .01
RI
DES: 0%
BMS: 13.2%
P = .01
proliferative
normal

DES: 0.7%
BMS: 2.0%
P = .62
mild
DES: 0%
BMS: 1.3%
P = .42
RI
DES: 0%
BMS: 2.6%
P = .44
total occlusion
normal
DES: 0%
BMS: 0%
P = NA
mild
DES: 1.0%
BMS: 0%
P = .99
RI
DES: 0%
BMS: 0%
P = NA

- restenosis length (mm)

normal
DES: 9.90 ± 4.91
BMS: 15.11 ± 9.06
P = .01
mild
DES: 8.92 ± 4.43
BMS: 13.29 ± 6.11
P = .05
RI
DES: NA
BMS: NA
P = NA

In BMS, renal function was by multivariate analysis independently associated with risk of 9-month binary restenosis (OR = 1.14, 95% CI, 1.03-1.25, *P* = .009)

In DES, renal function was not associated

											with restenosis (OR = 1.04, 95% CI, 0.84-1.20, *P* = .58) Among patients with baseline RI, DES was predictor of freedom from restenosis (OR = 0.002, 95% CI, 0.00-0.29, *P* = .01) and TLR (HR = .021, 95% CI, 0.06-0.75, *P* = .02) Among patients without baseline RI DES was also predictor of freedom from restenosis (OR = 0.26, 95% CI, 0.15-0.46, *P* < .0001) and TLR (HR = 0.30, 95% CI, 0.19-0.47, *P* < .0001)

ARC = Academic Research Consortium, BMS = bare metal stent, CABG = coronary artery bypass grafting, CCS = Canadian Cardiovascular Society, CI = confidence interval, CrCl = creatinine clearance, CTO = chronic total occlusion, DES = drug eluting stent, GP = glycoprotein, HR = hazard ratio, HTN = hypertension, LAD = left anterior descending artery, LCX: left circumflex artery, MACE = major adverse cardiac events, MI = myocardial infarction, NA = not applicable, NR = not reported, NS = not significant, OR = odds ratio, PCI = percutaneous coronary intervention, PDA = posterior descending artery. RCA: right coronary artery, RF = renal function, RI = renal insufficiency, RR = relative risk, SES = sirolimus-eluting stent, TLR = target lesion revascularization, TVR = target vessel revascularization, TVF = target vessel failure.
*Demographic data are as abstracted in the original trial.
†GP IIB/IIIa use as reported in the original trial.

Appendix H. Evidence Table: Registry Studies or Nonrandomized Trials Comparing DES versus BMS

Table H1. Characteristics of registry or nonrandomized trials in general and special populations comparing DES versus BMS

Study	LoE, Design	Demographics comorbidities	Clinical presentation and adjunct treatment	Stents	Outcomes- Effect sizes (Adjusted estimates unless otherwise noted)	Comments:
Ajani et al (2008) Melbourne Interventional Group (MIG), Australia, multicenter	III Retrospective registry cohort F/U: 30-day and 12 months F/U %: 30 days: 94.7% (n = 6787/7167); 12 months: 59.3% (n = 4253/7167) In table 4; 2 years; April 2004 to August 2007 enrollment;	N = 6364 patients with 7167 procedures BMS = 3294 procedures DES = 3482 procedures Male: All 74% DES 73.9% BMS 74.0% Age: All 64.7 years (SD 12.0) DES 65.0 years (SD 11.9) BMS 64.3 years (SD 12.0) Diabetes all n = 1708 (23.8%) DES n = 1054 (30.3%) BMS n = 557 (n = 16.9%) Hypertension: All n = 4550 (63.6%) DES n = 2269 (65.3%) BMS n = 2023 (61.5%) Hypercholesterolaemia: all n = 5076 (71.3%) DES n = 2516 (72.6%) BMS n = 2272 (69.6%) Previous MI: All n = 2153 (30.1%) DES n = 1151 (33.1%) BMS n = 841 (25.6%) Previous CABG:	**stable angina:** all 32.3% (n = 2290) DES 34.2% (n = 1187) BMS 29.0% (n = 945) **ACS, unstable angina:** All 14.9% (n = 1058) DES 16.8% (n = 586) BMS 12.8% (n = 422) **ACS, NSTEMI:** all 23.2% (n = 1651) DES 23.1% (n = 803) BMS 23.6% (n = 778) **ACS, STEMI:** all 23.1% (n = 1640) DES 17.4% (n = 607) BMS 28.8% (n = 948) **Multi-vessel disease:** All 58.1% (n = 2678) DES 62.7% (n = 1346) BMS 52.3% (n = 1170) **Glycoprotein IIa-IIIb use**: All 27.0% (n = 1934) DES 25.1% (n = 874) BMS 29.4% (n = 970) **≥ 12 month dual antiplatelet tx**: pharmacotherapy is in table 5: Aspirin: All n = 3300 (87.6%) DES n = 1714 (87.2%)	BMS only At least one DES Brands of stents not described	**Peri-procedural and in-hospital events** **PCI complications:** Major bleeding: 1.8% Coronary perforation: 0.2% Cardiac tamponade: 0.2% **In-hospital events:** Mortality: 1.5% MI: 1.5% Emergency PCI: 0.8% Emergency CABG: 0.8% **Death** 30 days: DES 41/3307 (1.2%) BMS 68/3108 (2.2%) OR = 0.56 (0.38-0.83) aOR = 0.83 (0.50-1.37) 12 months: DES 86/2157 (4.0%) BMS 110/1840 (6.0%) OR = 0.65 (0.49-0.87) aOR = 0.82 (0.56-1.20) **Myocardial infarction** 30 days: DES 84 (2.5%) BMS 65 (2.1%) OR = 1.22 (0.86-1.71) aOR = 1.02 (0.66-1.57) 12 months: DES 130 (6.0%) BMS 105 (5.7%) OR = 1.10 (0.84-1.46) aOR = 0.80 (0.57-1.13) **TLR:**	Late thrombosis (31-365 days after stent implantation) defined as "definite" if it satisfied the ARC definition Propensity score adjusted OR for all outcomes listed in table 4 Ajani – propensity score adjusted – 3482 DES out of 7167 PCI's, 6364 consecutive pts

			BMS n = 1416 (88.4%) Clopidogrel: All n = 2131 (56.9%) DES n = 1303 (66.4%) BMS n = 746 (47.0%) Statins, β-blockers, and ACE inhibitors also listed oral antiplatelet therapy followed current internationally accepted guidelines: combination of aspirin and clopidogrel for min 4 weeks for BMS and 6-12 months for DES patients		30 days: DES 53 (1.6%) BMS 45 (1.4%) OR = 1.19 (0.79-1.79) aOR = 1.30 (0.81-2.08) 12 months: DES 91 (4.2%) BMS 110 (6.0%) OR = 0.69 (0.52-0.92) aOR = 0.57 (0.39-0.82) **TVR:** 30 days: DES 60 (1.8%) BMS 51 (1.6%) OR = 1.18 (0.80-1.73) aOR = 1.41 (0.86-2.33) 12 months: DES 138 (6.4%) BMS 136 (7.4%) OR = 0.84 (0.66-1.08) aOR = 0.66 (0.48-0.90) **MACE:** 30 days: DES 159 (4.8%) BMS 154 (5.0%) OR = 0.96 (0.77-1.21) aOR = 1.11 (0.83-1.51) 12 months: DES 296 (13.7%) BMS 290 (15.8%) OR = 0.85 (0.71-1.01) aOR = 0.75 (0.60-0.94) **Late thrombosis:** 12 months: DES 16 (0.8%) BMS 18 (1.1%) OR = 0.74 (0.38-1.46) aOR = 0.55 (0.23-1.29)	
Alidoosti et al. (2008) Single center	Retrospective analysis of registry data. N=1796 consecutive patients, 1568 BMS, 228 DES				**In-hospital events:** Non-Q-wave MI: DES: 2.7% BMS: 0.9% (*P* = 0.03)	Excluded those with MI within 48 hours preceding the PCI. Physicians chose

						whether to use DES or BMS- influenced by patient's financial situation.
Anstrom et al (2008) Duke Databank for Cardiovascular Disease	III Registry cohort Initial revascularization from January 1, 2000, through July 31, 2005 F/U: overall 97% at 1 year	N = 4666 DES = 1501 BMS = 3165 Male: DES: 63.2% BMS: 62.9% Age: DES: 61 years BMS: 60 years Diabetes DES: 27.7% BMS: 25.0% Previous MI DES: 42.2% BMS: 48.3% Smoking DES: 45.0% BMS: 50.4%	**# vessels treated** one vessel DES: 56.9% BMS: 63.9% two vessels DES: 31.4% BMS: 28.4% three vessels DES: 11.7% BMS: 7.8% **Antiplatelet tx:** NR	DES = sirolimus or paclitaxel eluting stents BMS	**All cause mortality- unadjusted** 6 months DES: 4.2% BMS: 3.9% (HR = 0.3, 95% CI, -0.9-1.5, P = .66) P = .66 12 months DES: 6.1% BMS: 5.6% (HR = 0.5, 95% CI, -1.0-1.9, P = .51) 24 months DES: 8.5% BMS: 8.6% (HR = -0.1, 95% CI, -2.0-1.8, P = .90) **MI – unadjusted** 6 months DES: 1.5% BMS: 3.1% (HR = -1.7, 95% CI, -2.5 to -0.8, P < .001) 12 months DES: 2.6% BMS: 3.6% (HR = -1.0, 95% CI, -2.1 to -0.0, P = 0.5) 24 months DES: 3.3% BMS: 4.6% (HR = -1.3, 95% CI, -2.6 to -0.0, P = .04) **TVR - unadjusted** 6 months DES: 3.0% BMS: 8.9% (HR = -5.8, 95% CI, -7.1 to -4.5, P < .001)	No significant differences in rates of death or MI for subset of 1206 patients with diabetes (24 mo: DES 15.4%, BMS 16.2%, difference CI -6.1 to 4.5) Article conclusion: Similar overall long term rates of death or MI, but substantially lower rates of TVR

					12 months DES: 4.9% BMS: 12.3% (HR = -7.5, 95% CI, -9.1 to -5.9, P < .001) 24 months DES: 7.4% BMS: 15.3% (HR = -7.9, 95% CI, -10.0 to -5.0, P < .001) **Propensity Score Adjusted** **All cause mortality** 6 months DES: 4.4% BMS: 3.8% (HR = 0.6, 95% CI, -0.7 – 2.0, P = .37) 12 months DES: 6.4% BMS: 5.4% (HR = 1.0, 95% CI, -0.6-2.6, P = .23) 24 months DES: 8.6% BMS: 8.6% (HR = 0.1, 95% CI, -2.0-2.1, P = .94) **MI** 6 months DES: 1.5% BMS: 3.3% (HR = -1.8, 95% CI, -2.7 to -0.9, P < .001) 12 months DES: 2.8% BMS: 3.8% (HR = -1.0, 95% CI, -2.2 to 0.2, P = .11) 24 months DES: 3.3% BMS: 4.8% (HR = -1.5, 95% CI, -2.8 to -0.2, P = .02)	

					TVR 6 months DES: 2.6% BMS: 9.6% (HR = -6.9, 95% CI, -8.3 to -5.6, P < .001) 12 months DES: 4.4% BMS: 13.2% (HR = -8.7, 95% CI, -10.4 to -7.1, P < .001) 24 months DES: 6.6% BMS: 16.3% (HR = -9.7, 95% CI, -11.7 to -2.2, P < .001)	
Austin et al (2008) Propensity score matched outcome study	III Registry cohort F/U: median 16 months (9-24) PCI between January 2003 and September 2005	N = 1642 DES = 821 BMS = 821 Male: DES: 69.3% (n = 569) BMS: 67.8% (n = 557) Age DES: 60.8 years (SD 10.9) BMS: 60.6 years (SD 10.8) Diabetes DES: 18.1% (n = 149) BMS: 18.9% (n = 155) Prior MI DES: 32.4% (n = 266) BMS: 32.6% (n = 268) Prior CABG DES: 10.6% (n = 87)	**Stable angina** DES: 49.5% (n = 406) BMS: 48.8% (n = 401) **Unstable angina** DES: 17.2% (n = 141) BMS: 16.8% (n = 138) **NSTEMI** DES: 22.9% (n = 188) BMS: 24.8% (n = 204) **STEMI** DES: 7.8% (n = 64) BMS: 7.3% (n = 60) **# vessels treated** 1-vessel DES: 49.9% (n = 410) BMS: 45.7% (n = 375) 2-vessel DES: 15.2% (n = 125) BMS: 17.5% (n = 144) 2-vessel (with proximal	DES = paclitaxel-eluting or sirolimus-eluting stents BMS = thin strut or cobalt-chromium stents	**All-cause death** 1 month DES: 1.8% BMS: 2.4% 6 months DES: 2.9% BMS: 4.1% 12 months DES: 3.5% BMS: 5.3% 24 months DES: 6.6% BMS: 7.7% (HR = 0.63, 95% CI, 0.40 – 0.99, P = .04) **MI** 1 month DES: 2.4% BMS: 2.8% 6 months DES: 3.7% BMS: 4.8% 12 months	Demographics and outcomes after propensity score matching Off label DES use

		BMS: 10.2% (n = 84)	LAD) DES: 12.3% (n = 101) BMS: 13.3% (n = 109) 3-vessel or left main coronary artery disease DES: 22.6% (n = 185) BMS: 23.5% (n = 193)		DES: 5.0% BMS: 5.7% 24 months DES: 7.5% BMS: 7.3% (HR = 1.02, 95% CI, 0.69-1.54, P = .92) **TVR** 1 month DES: 1.1% BMS: 1.3% 6 months DES: 4.8% BMS: 7.1% (HR = 0.66, 95% CI, 0.44-0.99, P = .04) 12 months DES: 7.7% BMS: 11.4% 24 months DES: 10.7% BMS: 13.9% (HR = 0.67, 95% CI, 0.49-0.93, P = .02)	
Brodie et al (2008) the Strategic Transcatheter Evaluation of New Therapies (STENT) group STEMI patients	III Registry cohort	N = 1840 DES: 1292 BMS: 548 Male DES: 72.5% (n = 936) BMS: 72.6% (n = 398) Age DES: 58.9 years (SD 12.1) BMS: 61.8 years (SD 12.5) Diabetes DES: 19.8% (n = 256) BMS: 18.3% (n = 100) HTN	**Multi-vessel PCI** DES: 3.6% (n = 47) BMS: 1.6% (n = 9) **Multi-lesion PCI** DES: 17.5% (n = 226) BMS: 14.4% (n = 79)	DES = sirolimus-eluting and paclitaxel-eluting stents	**9 months** **(DES, n = 1292; BMS, n = 548)** **Death** DES: 6.3% (n = 81) BMS: 8.4% (n = 46) (HR = 0.92, 95% CI, 0.60-1.40) Unadjusted P = .100 Adjusted P = .68 **MI** DES: 1.6% (n = 33) BMS: 5.5% (n = 30) (HR = 0.81, 95% CI, 0.46-1.42) Unadjusted P = .002 Adjusted P = .45	supported by unrestricted grants from industry Adjusted HRs reported

		DES: 59.7% (n = 771) BMS: 57.5% (n = 315) Hyperlipidemia DES: 50.8% (n = 656) BMS: 41.4% (n = 227 Smoker DES: 67.7% (n = 874) BMS: 66.6% (n = 365) Prior MI DES: 10.5% (n = 135) BMS: 14.4% (n = 79) Prior CABG DES: 4.1% (n = 53) BMS: 6.8% (n = 37) Prior PCI DES: 12.5% (n = 161) BMS: 14.1% (n = 77)			**TVR** DES: 4.0% (n = 51) BMS: 7.5% (n = 41) (HR = 0.55, 95% CI, 0.34-0.89) Unadjusted P = .002 Adjusted P = .014 **Thrombosis** DES: 1.0% (n = 13) BMS: 2.7% (n = 15) (HR = 0.40, 95% CI, 0.17-0.95) Unadjusted P = .006 Adjusted P = .039 **24 months** **(DES, n = 663; BMS, n = 335)** **Death** DES: 8.0% (n = 53) BMS: 13.7% (n = 46) (HR = 0.80, 95% CI, 0.51-1.26) Unadjusted P = .004 Adjusted P = .332 **MI** DES: 5.0% (n = 33) BMS: 6.9% (n = 23) (HR = 1.01, 95% CI, 0.55-1.86) Unadjusted P = .220 Adjusted P = .967 **TVR** DES: 8.0% (n = 53) BMS: 11.3% (n = 38) (HR = 0.57, 95% CI, 0.35-0.92) Unadjusted P = .080 Adjusted P = .020	

					Thrombosis DES: 1.8% (n = 12) BMS: 3.9% (n = 13) (HR = 0.47, 95% CI, 0.19-1.17) Unadjusted P = .048 Adjusted P = .105	
Campolo et al (2007) RESTEM Registry (REgistro delle PCI in era di STEnt Medicati); Italy; Multicenter (7 sites)	III Registry cohort F/U: overall was 96.7% at 30 days, 96% at 1 year, 91.2% at 2 years; of 5524 enrolled, 5439 followed, excluding 7 intraprocedural deaths and 78 unsuccessful procedures PCI between October 2002 and June 2004; elective or urgent PCI enrolled; N = 5524 patients enrolled; 5439 were followed; includes other groups not only SES or BMS	N = 4781 SES = 807 BMS = 3974 (also POBA or DBK n = 454, BMS + SES n = 209) Male: All 79% SES 77.9% BMS 79.1% Age: All 64.7 years (SD 10) SES 63.0 (10.4) BMS 65.1 (10.1) Diabetes: All n = 994 (20.8%) SES n = 195 (24.2%) BMS n = 799 (20.1%) Previous AMI: All n = 1382 (28.9%) SES n = 236 (29.2%) BMS n = 1146 (28.8%) Previous PCI: all n = 704 (14.7%) SES n = 178 (22.1%) BMS n = 526 (13.2%) Previous CABG: All n = 492 (10.2%) SES n = 108 (13.4%) BMS n = 384 (9.7%)	**ACS, unstable angina** SES n = 149 (18.5%) BMS n = 1153 (29.0%) **Multi-vessel disease**: SES n = 368 (45.6%) BMS n = 1690 (42.5%) **# vessels treated:** **Multilesion PCI:** SES n = 111 (13.8%) BMS n = 1010 (25.4%) **≥ 12 month dual antiplatelet tx**: lifelong aspirin and ticlopidine (250mg/d) or clopidogrel (75 mg/d) for at least 1 month for BMS, and at least 3 months for SES patients	SES = sirolimus eluting stents Technique classified with utilized device	Cumulative n/N (%); N is same for all entries of SES or BMS, respectively; from table 2 and table 3 *MACCE = major adverse cardiovascular and cerebrovascular event **Overall MACCE:** 30 day: SES 28/782 (3.6%) BMS 183/3841 (4.8%) 12 months: SES 144/775 (18.6%) BMS 970/3812 (25.4%) 24 months: SES 191 (26.0%) BMS 1195 (33.0%) **Deaths:** 30 day: SES 7 (0.9%) BMS 40 (1.0%) 12 months: SES 21 (2.7%) BMS 143 (3.8%) 24 months: SES 33 (4.5%) BMS 221 (6.1%) **Q wave AMI:** 30 day: SES 4 (0.5%) BMS 28 (0.7%) 12 months: SES 16 (2.1%) BMS 103 (2.7%) 24 months:	Stent thrombosis was considered "defined" thrombosis only when patients experienced AMI, followed by angiographic evidence of an occluded vessel previously treated with SES or BMS. Campolo "multivariate analysis" 5524 consecutive pts, 72% BMS, 15% SES, 4% combined

					SES 23 (3.2%) BMS 142 (3.9%) **Non Q wave AMI or UA** 30 day: SES 7 (0.9%) BMS 46 (1.2%) 12 months: SES 49 (6.4%) BMS 216 (5.7%) 24 months: SES 69 (9.5%) BMS 276 (7.6%) **Stroke:** 30 day: SES none tabulated BMS 2 (0.1%) 12 months: SES 1 (0.1%) BMS 22 (0.6%) 24 months: SES 1 (0.1%) BMS 30 (0.8%) **Revascularizations (PCI or CABG):** 30 day: SES 16 (2.0%) BMS 107 (2.8%) 12 months: SES 103 (13.4%) BMS 756 (19.8%) 24 months: SES 129 (17.6%) BMS 884 (24.5%) **TVR:** 30 day: SES 5 (0.6%) BMS 46 (1.2%) 12 months: SES 41 (5.3%) BMS 386 (10.1%) 24 months: SES 58 (8.0%)	

					BMS 464 (12.8%) **Subacute thrombosis:** 30 day: SES 3 (0.4%) BMS 28 (0.7%) **Late thrombosis:** 12 months: SES 4 (0.5%) BMS 42 (1.1%) 24 months: SES 6 (0.8%) BMS 51 (1.4%) **TLR:** 30 day: SES 3 (0.4%) BMS 22 (0.6%) 12 months: SES 27 (3.5%) BMS 240 (6.3%) 24 months: SES 38 (5.2%) BMS 293 (8.1%) Unadjusted and adjusted OR SES vs BMS (BMS is adj OR of 1) (IC) for 12 and 24 months **Death + stroke + AMI + UA:** 12 months: OR = 0.86 (0.66-1.10) aOR = 0.95 (0.69-1.31) 24 months: OR = 0.9 (0.72-1.12) aOR = 0.96 (0.72-1.26) **Revascularizations (PCI or CABG):** 12 months: OR = 0.61 (0.49-0.77) aOR = 0.74 (0.57-0.95) 24 months:	

					OR = 0.65 (0.53-0.80) aOR = 0.76 (0.60-0.96) **TVR:** 12 months: OR = 0.49 (0.35-0.69) aOR = 0.52 (0.35-0.75) 24 months: OR = 0.57 (0.43-0.76) aOR = 0.66 (0.48-0.91) **Primary endpoint (composite of death, AMI, new hospitalization for unstable angina, revascularizations):** 12 months: OR = 0.68 (0.56-0.83) aOR = 0.78 (0.62-0.98) 24 months: OR = 0.73 (0.61-0.87) aOR = 0.84 (0.68-1.08) *the following from table 5are cumulative results *minus* the first month's results: first year and second year tallies n/N (%): ***overall MACCE:** 1 year: SES 116/775 (15.0%) BMS 787/3812 (20.6%) 2 year: SES 47/736 (6.4%) BMS 225/3622 (6.2%) ***Deaths:** 1 year: SES 14 (1.8%) BMS 103 (2.7%) 2 year: SES 12 (1.6%) BMS 78 (2.2%) ***Q wave AMI:**	

					1 year: SES 12 (1.5%) BMS 75 (2.0%) 2 year: SES 7 (1.0%) BMS 39 (1.1%) ***Unstable angina:** 1 year: SES 42 (5.4%) BMS 170 (4.5%) 2 year: SES 20 (2.7%) BMS 60 (1.7%) ***Stroke:** 1 year: SES 1 (0.1%) BMS 20 (0.5%) 2 year: SES 0 (0%) BMS 12 (0.3%) ***Revascularization (PCI or CABG)** 1 year: SES 87 (11.2%) BMS 649 (17.0%) 2 year: SES 26 (3.5%) BMS 128 (3.5%) ***TVR:** 1 year: SES 36 (4.6%) BMS 340 (8.9%) 2 year: SES 17 (2.3%) BMS 78 (2.2%) ***Late thrombosis:** 1 year: SES 1 (0.1%) BMS 14 (0.4%) 2 year: SES 2 (0.3%)	

					BMS 9 (0.2%) ***TLR:** 1 year: SES 24 (3.1%) BMS 218 (5.7%) 2 year: SES 11 (1.5%) BMS 53 (1.5%)	
Godino et al (2008) TRUE registry (TAXUS in Real life Usage Evaluation); European; multicenter (7 sites)	III Retrospective registry cohort	N = 675 PES BMS Male: 77% Age: 65 years (SD 11) Diabetes: n = 206 (30.5%) Insulin dependent DM: n = 82 (12.1%) Hypertension: n = 460 (68.1%) Hyperlipidemia: n = 468 (69.3%) Acute MI: n = 19 (2.8%) Previous MI: n = 285 (41.7%) Previous CABG: n = 112 (16.5%)	stable angina n % ACS, unstable angina n % ACS, NSTEMI ACS, STEMI Silent ischemia n % Post MI n % Multi-vessel disease: # vessels treated: Glycoprotein IIa-IIIb: ≥ 12 month dual antiplatelet tx:		Table 6 lists total and small vessel n/N (%); the total column is listed here. Cardiac death:	Only PES; compares small and very small vessel lesions Godina – historical BMS controls, 675 pts
Harjai et al (2008) GHOST study (Guthrie Health System Off-Label StenT Study from Guthrie PCI registry); USA; single site	III Registry cohort N = 3044 PCI between July 2001 to December 2005; 409 without stents excluded; 443 with previous PCI excluded; 69 with DES + BMS	N = 1354 DES n = 483 BMS n = 871 Male: All 69% DES 65% BMS 70% Age: All 64 years (SD 12)	**stable angina** n % **ACS includes unstable angina, NSTEMI, or STEMI** All 1145 (85%) DES 377 (78%) BMS n = 768 (88%) **ACS, NSTEMI** All n = 462 (34%) DES n = 175 (36%)	DES only or BMS only; DES group does not included DES + BMS patients	Non-adjusted numbers n/N (%): **Death:** DES 25/483 (5.2%) BMS 100/871 (11.5%) **MI:** DES 33 (6.8%) BMS 54 (6.2%) **Death/MI**	Stent thrombosis was deemed to occur if ARC criteria for definite or probably stent thrombosis were met. Adjustment for baseline clinical characteristics, then also for lesion characteristics, then

	excluded; of remaining 2123 patients, N = 1354 included with PCI for complex lesions F/U DES: 494 days BMS: 838 days	DES 64 years (SD 12) BMS 66 (SD 12) Diabetes mellitus: All n = 361 (27%) DES n = 156 (32%) BMS n = 205 (24%) Prior CABG: All n = 279 (21%) DES n = 87 (18%) BMS n = 192 (22%)	BMS n = 287 (33%) **ACS, STEMI** All n = 468 (35%) DES n = 126 (26%) BMS n = 342 (39%) **Multi-vessel disease**: All n = 237 (n = 18) DES n = 105 (22%) BMS n = 132 (15%) **# vessels treated**: All n = 709/1103 (64%) DES n = 294/397 (74%) BMS n = 415/706 (59%) **≥ 12 month dual antiplatelet tx**: All n = 555/1103 (50%) DES n = 217/397 (55%) BMS n = 338/706 (48%)		DES 54 (11%) BMS 145 (17%) **Stent thrombosis** DES 14 (2.9%) BMS 23 (2.6%) **TVR:** DES 32 (6.6%) BMS 161 (19%) **MACE:** DES 72 (15%) BMS 259 (30%) After adjustment for baseline clinical characteristics in all patients, DES compared to BMS associated with (fig 3A) **Less TVR** (DES 6.6%, BMS 18.5%, HR = 0.38, CI 0.26-0.56) **Less MACE** (DES 14.9%, BMS 29.7%, HR 0.56, CI 0.42-0.74) **No sig impact on death** (DES 5.2%, BMS 11.5%, HR = 0.72, CI 0.45-1.14) **No sig impact on death/MI** (DES 11.2%, BMS 16.7%, HR = 0.91, CI 0.65-1.28) **No sig impact of stent thrombosis** (DES 2.9%, BMS 2.6%, HR = 1.17, CI 0.58-2.38) After adjustment for lesion characteristics also in all patients, DES compared to BMS associated with: **Less TVR** (HR = 0.35, CIC 0.23-0.51) **Less MACE** (HR = 0.52, CI 0.39-0.69) **No sig impact on death** (HR = 0.63, CI 0.39-1.03)	also for those treated year 2003 and later. Two groups "not contemporaneous"

					No sig impact on death/MI (HR = 0.83, CI 0.58-1.18) **No sig impact on stent thrombosis** (HR = 1.13. CI 0.55-2.30) After adjustment for baseline clinical characteristics in 2003 and later patients, DES compared to BMS associated with (fig 3B): **Less TVR** (DES 6.6%, BMS 18.4%, HR = 0.37, CI 0.24-0.55) **Less MACE** (DES 14.9%, BMS 30.7%, HR = 0.52, CI 0.38-0.72) **No sig impact on death** (DES 5.2%, BMS 12.0%, HR = 0.83, CI 0.50-1.40) **No sig impact on death/MI** (DES 11.2%, BMS 17.8%, MR = 0.95, CI 0.70-1.40) **No sig impact on stent thrombosis** (DES 2.9%, BMS 2.4%, HR = 1.20, CI 0.50-2.90)	
Kornowski et al (2008) Rabin Medical Center registry; Israel; single center	III Retrospective registry cohort Patients enrolled from January 2004 to December 2006 includes n = 122 receiving SES, PES or ZES; and 506 receiving BMS during same time or within 24 months prior F/U 100% at one and six months evals; F/U 97% at 12 months for	Matched analysis N = 628 DES n = 122 BMS n = 506 Male: All 85% DES 87% BMS 84% Age: All 59 years (SD 12) DES 59 years (SD 12) BMS 59 years (SD 12) Diabetes mellitus:	Chest pain to PCCI time (h): DES 3.2 hours (SD 1.4) BMS 3.4 hours (SD 1.2) ACS, unstable angina n % Multi-vessel disease: DES 62% BMS 55% Glycoprotein IIa-IIIb: DES 84% BMS 81% prescribed lifelong aspirin and clopidogrel	Cypher-SES; Taxus-PES; Endeavor-ZES DES composed of 66% patients receiving SES, 26% PES and 8% ZES	**Death**: One month: DES 0% BMS 3.8% P = 0.03 Six months: DES 0.8% BMS 6.0% P = 0.03 12 months: DES 3.3% BMS 7.1% P = 0.1 **Re-MI** One month: DES 0% BMS 3.4%	Stent thrombosis defined by ARC definitions as "definite" in the context of acute coronary syndrome and/or re-infarction in the culprit coronary territory with angiographically proven thormbosis of the previously implanted stent

	BMS and 98% for DES	All 29% DES 28% BMS 29% Prior MI: All 4.6% DES 3.2% BMS 4.9%	for 12 months after DES		P = 0.04 Six months: DES 0% BMS 5.7% P = 0.02 12 months: DES 0% BMS 6.1% P = 0.02 **AST** One month: DES 0% BMS 2.2% P = 0.09 Six months: DES 0.8% BMS 2.2% P = 0.19 12 months: DES 0.8% BMS 3.6% P = 0.07 **MACE**: One month: DES 3.3% BMS 7.7% P = 0.08 Six months: DES 7.4% BMS 16.7% P = 0.02 12 months: DES 11.5% BMS 21.3% P = 0.01 **TLR**: Six months: DES 1.9% BMS 10.8% P = 0.002 12 months: DES 2.5% BMS 14.0%	

					P = 0.004 **TVR**: Six months: DES 3.8% BMS 11.8% P = 0.002 12 months: DES 5.7% BMS 15.2% P = 0.006	
Mack et al (2008) Society of Thoracic Surgeons (STS) National Cardiac Database and American College of Cardiology (ACC) database; USA; Multicenter (8 sites)	III Registry cohort Patients undergoing PCI from February 1, 2004 to July 31, 2004 F/U at 6, 12, 18 months	Demographics includes DES, BMS, and no stent patients in the PCI cohort: N = 3089 Age: 63.5 years (SD 12.5) Male: 69% DES n = 2249 BMS n = 476 No stent n = 352 (DES includes those treated with both DES and BMS) Diabetes n = 1013 (32.8%) Hypercholesterolemia n = 2076 (67.3%) Previous CABG: n = 618 (20.0%) MI: 815 (26.4%)	Clinical presentation data not provided in the paper in most categories Clopidogrel use at 18 months: DES 61.3% BMS 60.8% P = 0.88	DES group includes those with both DES and BMS	Clinical results at 18 months, Table 5: **Mortality overall** DES n = 165/2121 (7.8%) BMS n = 47/451 (10.4%) P = 0.064 **Mortality peri-op** DES n = 33 (1.6%) BMS n = 9 (2.0%) P = 0.5 **Mortality late** DES n = 132 (6.2%) BMS n = 38 (8.4%) P = 0.087 **MI** DES n = 34 (1.7%) BMS n = 8 (2.0%) P = 0.61 **Revascularization overall** DES n = 259 (12.1%) BMS n = 69 (14.9%) P = 0.096 **Revasc by CABG** DES n = 43 (2.0%) BMS n = 14 (3.1%) P = 0.16 **Revasc by PCI** DES n = 216 (10.1%)	DES vs BMS comparisons are part of a larger study of CABG vs PCI ARC definitions of definite or probable stent thrombosis; stent thrombosis is reported as a composite of ARC definite and probable.

					BMS n = 55 (12.0%) P = 0.23 **MACE** DES n = 460 (21.2%) BMS n = 125 (26.5%) P = 0.012 **Thrombosis:** DES n = 65 (2.9%) BMS n = 19 (4.2%) P = 0.12 **18 month event free survival:** DES 87.7% (SD 0.7%) BMS 80.6% (SD 1.8%)	
Marroquin et al (2008) National Heart, Lung, and Blood Institute Dynamic Registry observational study off-label comparison	III Registry cohort F/U: 1 year F/U%: NR	N = 6551 DES n = 2693 standard use n = 1381 off-label n = 1312 BMS n = 3858 standard use n = 1748 off-label n = 2110 % male DES standard use: 66.9 off-label: 68.8 BMS standard use: 62.7 off-label: 66.7 age DES standard use: 63.7 years off-label: 63.4 years BMS standard use: 62.6 years off-label: 63.4 years Diabetes DES standard use: 32.8% off-label: 35.4% BMS	**AMI** DES standard use: 25.3% off-label: 30.2% BMS standard use: 25.4% off-label: 31.5% **Unstable angina** DES standard use: 36.2% off-label: 31.7% BMS standard use: 42.8% off-label: 40.8% **Stable angina** DES standard use: 20.1% off-label: 21.3% BMS standard use: 22.1% off-label: 18.5% **Ischemia** DES standard use: 12.8% off-label: 12.7% BMS	DES (sirolimus or paclitaxel) BMS	*Inhospital outcomes* **Death** off-label: 1.3% standard: 0.4% *P* < .001 patients in off-label group treated with DES had lower mortality rate: 0.5% vs. 1.9%, *P* < .001 **MI** off-label: 2.5% standard: 1.3% *P* < .001 No significant difference in rate of MI between DES and BMS in off-label group *Cumulative 1 year event rates* **Death** DES standard use: 2.8% off-label: 3.7% BMS standard use: 2.7%	Mulitvariable Cox proportional hazards regression used Off-label use; defined as use in restenotic lesions, lesion in a bypass graft, left main coronary artery disease, or ostial, bifurcated, or totally occluded lesions, as well as use in patients with a reference-vessel diameter of < 2.5 mm or greater than 3.75 mm or a lesion length or more than 30 mm Possible selection bias

		standard use: 26.0% off-label: 27.1% HTN DES standard use: 78.1 off-label: 78.1 BMS standard use: 64.4% off-label: 64.6% Prior PCI DES standard use: 27.3% off-label: 39.0% BMS standard use: 18.2% off-label: 27.7% Prior CABG DES standard use: 11.7% off-label: 24.6% BMS standard use: 7.5% off-label: 22.5% Prior MI DES standard use: 20.9% off-label: 27.1% BMS standard use: 28.8% off-label: 33.1%	standard use: 5.6% off-label: 5.5% **Diseased vessels one** DES standard use: 41.3% off-label: 31.9% BMS standard use: 48.0% off-label: 38.1% **two** DES standard use: 32.4% off-label: 30.9% BMS standard use: 33.8% off-label: 31.1% **three** DES standard use: 26.1% off-label: 36.7% BMS standard use: 18.1% off-label: 30.2% **Glycoprotein IIb/IIIa inhibitors use** DES standard use: 31.9% off-label: 41.8% BMS standard use: 35.8% off-label: 42.3% **antiplatelet therapy at 1 year** DES: 71.7% BMS: 5.9%		off-label: 6.4% *P* = 0.88 standard *P* < .001 off-label **MI** DES standard use: 3.3% off-label: 4.4% BMS standard use:4.1% off-label: 5.9% *P* = .24 standard *P* = .06 off label **Death/MI** DES standard use: 5.8% off-label: 7.5% BMS standard use: 6.4% off-label: 11.6% *P* = .42 standard *P* < .001 off label **repeat PCI** DES standard use: 6.5% off-label: 11.4% BMS standard use:10.5% off-label: 13.6% *P* < .001 standard *P* = .07 off-label **CABG** DES standard use: 1.4% off-label: 1.5% BMS standard use:4.3% off-label: 5.1% *P* < .001 standard *P* < .001 off-label	

					Revascularization DES standard use: 7.7% off-label: 12.7% BMS standard use:13.4% off-label: 17.5% *P* < .001 standard *P* < .001 off-label **Adjusted HRs at 1 year for off-label use of DES vs BMS** **MI** HR = 0.71, 95% CI, 0.50-1.00 Death HR = 0.94, 95% CI, 0.64-1.38 Death/MI HR = 0.78, 95% CI, 0.60-1.02 repeat PCI HR = 0.75, 95% CI, 0.61-0.93 repeat revascularization HR = 0.63, 95% CI, 0.52-0.77	
Marzocchi et al (2007) REAL registry (Registro regionale AngiopLastiche dell'Emilia-Romagna); Italy; multisite (13 public and private centers); WWW-based registry	III On-going registry cohort F/U: 703 days (range 182-1279) July 2002 to June 2005; PCI in 15027 patients; n = 1229 excluded because treated with both SES	N = 10629 DES n = 3064 BMS n = 7565 (Excludes those treated with both DES and BMS) Age: All 67 years (SD 11) DES 65 years (SD 11) BMS 68 years (SD 11	**stable angina pectoris:** DES 47.6% BMS 48.2% **ACS, unstable angina pectoris:** DES 52.4% BMS 51.8% **Multi-vessel disease:** DES 21.6% BMS 20.7%	SES n = 1939 PES n = 1032 Both SES and PES n = 93	Two-year unadjusted incidence: **All MACE:** DES 17.8% BMS 21.0% P = 0.003 **Death:** DES 5.7% BMS 8.0% P = 0.0002 **Cardiac death:** DES 3.5%	Propensity score analysis of the data performed by use of a logistic regression model for treatment of DES vs BMS; including clinical, angiographic, procedural variables P values by Cox proportional hazards model for propensity

	and BMS; and n = 3169 excluded because STEMI diagnosis at admission, leaving N = 10629	Male: All 75% DES 74.7% BMS 75.4% Diabetes (DM): All 25% DES 30.7% BMS 22.4% Hypertension: All 72% DES 70.5% BMS 72.5% Hypercholesterolemia: all 55% DES 58.7% BMS 54.0% Prior MI: All 28% DES 26.9% BMS 27.9% Prior CABG: All 9.7% DES 9.8% BMS 9.6%	**# vessels treated:** **Glycoprotein IIa-IIIb**: DES 25.9% BMS 23.0% **≥ 12 month dual antiplatelet tx**: prescribed according to current standards, including lifelong aspirin for all patients; 1 month of ticlopidine (250 mg BID) or clopidogrel (75 mg/d) for BMS and same for at least 2 months for DES patients		BMS 4.6% P = 0.05 **Noncardiac death:** DES 2.1% BMS 3.3% P = 0.001 **Unknown death:** DES 0.1% BMS 0.1% P "…" **Acute MI** DES 5.5% BMS 5.4% P = 0.64 **TVR** DES 11.2% BMS 12.0% P = 0.60 **TVR-PCI** DES 9.6% BMS 10.3% P = 0.60 **TVR-CABG** DES 1.7% BMS 1.6% P = 0.9 **TLR** DES 7.3% BMS 9.2% P = 0.009 **Angiographic stent thrombosis** DES 1.0 BMS 0.6 P = 0.09 **Thrombosis – Acute <24 h:** DES 0.1% BMS 0.1% P = 0.4 **Thrombosis – subacute (24h-30d):** DES 0.3% BMS 0.3% P = 0.8 **Thrombosis – late (30d to 6mo):**	score-adjusted incidence. Probable stent thrombosis defined as unexplained deaths within 30 days after the procedure or acute MI that involved the target-vessel territory without angiographic confirmation, and possible stent thrombosis, defined as unexplained deaths that occurred at least 30 days after the procedure.

					DES 0.2% BMS 0.1% P = 0.7 **Thrombosis – very late (>6mo):** DES 0.4% BMS 0.1% P = 0.01 Two-year propensity score-adjusted cumulative incidence of MACE in patients treated with BMS or DES: **All MACE:** DES 16.5% (n = 3064) BMS 21.8 % (n = 7565) P < 0.0001 aHR = 0.74 (0.65-0.85) **Death, total:** DES 6.8% BMS 7.4% P = 0.35 aHR = 0.90 (0.72-1.13) **Death, cardiac:** DES 4.4% BMS 4.3% P = 0.9 **Death, noncardiac:** DES 2.4% BMS 3.0% P = 0.2 **Acute MI:** DES 5.3% BMS 5.8% P = 0.46 aHR = 0.91 (0.72-1.16) **TVR total:** DES 9.1% BMS 12.9% P < 0.0001	

					aHR = 0.68 (0.57-0.80) **TVR, PCI:** DES 7.8% BMS 11.2% P < 0.0001 **TVR, CABG:** DES 1.4% BMS 1.7% P = 0.2 **Target-lesion revascularization:** DES 5.8% BMS 9.9% P < 0.0001 **Death and MI:** DES 10.9% BMS 12.3% aHR = 0.87 (0.73-1.04) Figure 3 shows cumulative incidence of overall stent thrombosis, angiographic stent thrombosis, probable stent thrombosis, and possible stent thrombosis in the propensity score-matched population of patients treated with DES (n = 1677) and BMS (n = 1677): **Overall stent thrombosis at 24 months:** DES 3.0% BMS 2.7% **Angiographic stent thrombosis at 24 months:** DES 1.6% BMS 1.5% **Probable stent thrombosis at 24 months:** DES 0.2% BMS 0.6% **Possible stent thrombosis at**	

					24 months: DES 1.2% BMS 0.6%	
Mauri et al (2008) acute care, non-US government hospitals in Massachusetts	III Registry cohort PCI with stenting between April 1, 2003, and September 30, 2004	N = 17,793 DES, n = 11,556 BMS, n = 6237 Male: DES: 68% (n = 7854) BMS: 67.8% (n = 4228) Age DES: 64.4 (± 12.3) years BMS: 65.3 (± 13.0) years DM DES: 28.9% (n = 3341) BMS: 27.4% (n = 1710) Hyperlipidemia DES: 77.2% (n = 8926) BMS: 72.0% (n = 4490) HTN DES: 76.4% (n = 8824) BMS: 72.6% (n = 4528) Prior MI DES: 27.1% (n = 3126) BMS: 28.7% (n = 1790) Prior CABG DES: 13.1% (n = 1513) BMS: 16.1% (n = 1002) Prior PCI DES: 22.9% (n = 2640) BMS: 20.9% (n = 1305)	**Stable angina** DES: 21.9% (n = 2533) BMS: 14.5% (n = 902) **Unstable angina** DES: 29.4% (n = 3399) BMS: 23.6% (n = 1471) **Non-STEMI** DES: 20.8% (n = 2398) BMS: 21.6% (n = 1349) **STEMI** DES: 13.3% (n = 1533) BMS: 28.9% (n = 1805) **# diseased vessels** DES: 1.75 ± 0.80 BMS: 1.82 ± 0.82 **# stents** DES: 1.51 ± 0.90 BMS: 1.45 ± 0.83 **Aspirin pre-treatment** DES: 97.9% (n = 11.313) BMS: 96.3% (n = 6005) **GP IIb/IIIa inhibitor pre-treatment** DES: 16.1% (n = 1858) BMS: 23.3% (n = 1456) **Clopidogrel pre-treatment** DES: 35.2% (n = 4069) BMS: 33.9% (n = 2115)	DES = sirolimus or pacilataxel eluting stents BMS	**All-cause mortality – unadjusted** 30 days DES: 1.1% BMS: 3.3% 1 year DES: 4.1% BMS: 8.6% 2 years DES: 7.0% BMS: 12.6% **MI - unadjusted** 30 days DES: 2.3% BMS: 3.5% 1 year DES: 5.2% BMS: 8.2% 2 years DES: 7.6% BMS: 10.5% **TVR - unadjusted** 30 days DES:1.9% BMS: 3.2% 1 year DES: 7.8% BMS: 13.7% 2 years DES: 11.5% BMS: 16.8% All unadjusted rates are P < .0001 **Propensity Score Matched (n = 5549 for both groups)** **All-cause mortality** 30 days DES: 1.9%	

					BMS: 2.9% (HR = -1.0, 95% CI, -1.5 to -0.4, P = .0008) 1 year DES: 6.0% BMS: 8.0% (HR = -2/0, 95% CI, -3.0 to -1.1, P < .0001) 2 years DES: 9.8% BMS: 12.0% (HR = -2.1, 95% CI, -3.3 to -1.0, P = .0002) **MI** 30 days DES: 2.2% BMS: 3.2% (HR = -1.0, 95% CI, -1.6 to -0.4, P = .0013) 1 year DES: 3.5% BMS: 8.0% (HR = -2.5, 95% CI, -3.4 to -1.5, P < .0001) 2 years DES: 8.3% BMS: 10.3% (HR = -1.9, 95% CI, -3.0 to -0.8, P = .0005) **TVR** 30 days DES: 2.2% BMS: 3.1% (HR = -0.9, 95% CI, -1.5 to -0.3, P = .0039 1 year DES: 7.5% BMS: 13.7% (HR = -6.2, 95% CI, -7.6 to -5.1, P < .0001) 2 years DES: 11.0% BMS: 16.8% (HR = -5.8, 95% CI, -7.1 to -4.5, P < .001)	

					Propensity score differences are all significant P < or = .004	
Ortolani et al (2008) REAL registry (Registro Regionale Angioplastiche dell'Emilia-Romagna; Web based retistry; Italy; 13 centers, multicenter	III Registry cohort; diabetic patients PCI between July 2002 and December 2004; F/U at 30 days, 12 months, 24 months Total registry patients N = 12155; includes 2238 diabetics with de-novo lesion PCI; excluded n = 383 with STEMI; leaving 1855 diabetics without STEMI; excluded n = 207 with both BMS and DES, or more than one type of DES; leaving n = 1648 diabetics (apparently not all diabetics are insulin-dependent; and subacute STEMI is included)	N = 1648 diabetics DES n = 559 BMS n = 1099 Male: All 70% DES 71.2% BMS 69.3% Age: All 68 years (SD 10 years) DES 66.3 years (SD 9.9) BMS 69.3 years (SD 9.6) Insulin-dependent diabetes mellitus: All 27% DES 30.9% BMS 25.4% Hypertension: All 67% DES 66.1% BMS 67.9% Hypercholesterolemia: all 41% DES 43.4% BMS 39.5% Prior MI: All 26.7% DES 26.5% BMS 26.7% Prior CABG: All 11.5% DES 11.2% BMS 11.6%	**stable angina pectoris including silent ischemia:** DES 33.5% BMS 29.8% **ACS, NSTEMI, or unstable angina pectoris:** DES 54.7% BMS 52.2% **Subacute STEMI** DES 11.8% BMS 18.0% **Multi-vessel disease:** DES 83.4% BMS 83.1% **# vessels treated per patient**: DES 1.4 (SD 0.7) BMS 1.5 (SD 0.8) **Multivessel interventions:** DES 21.1% BMS 22.6% **Glycoprotein IIa-IIIb:** DES 29.1% BMS 25.4% **antiplatelet tx:** Lifelong aspirin prescribed to all patients. One month ticlopidine (250 mg twice a day) or clopidogrel (75 mg/d) recommended to all patients treated with BMS. Taking one of the	SES or PES	Unadjusted cumulative frequencies for BMS vs DES: **All cause mortality:** 30 days: DES 1.6% BMS 1.7% P = 0.955 1 year: DES 7.2% BMS 8% P = 0.550 2 year: DES 10.2% BMS 12.3% P = 0.218 **Nonfatal AMI:** 30 days: DES 0.9% BMS 0.7% P = 0.568 1 year: DES 6.6% BMS 7% P = 0.799 2 years: DES 9.1% BMS 8.9% P = 0.894 **Death or AMI:** 30 days: DES 2.1% BMS 2.3% P = 0.855 1 year: DES 11.6% BMS 14% P = 0.190 2 years: DES 16.3% BMS 19.3%	Stent thrombosis is angiographically documented as complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) of a previously successfully treated artery. To adjust for potential confounders, a propensity score analysis was per formed by use of a logistic regression model, testing the propensity to receive a DES rather than a BMS. Ortolani – "propensity score adjustment" BMS 1089, DES 559

			other of the medications for at least 2 months recommended for SES patients and for at least 6 months for PES patients		P = 0.144 **TVR**: 30 days: DES 2.0% BMS 1.5% P = 0.452 1 year: DES 9.9% BMS 12.4% P = 0.128 2 years: DES 12.8% BMS 14.4% P = 0.314 **MACE:** 30 days: DES 3.2% BMS 3.4% P = 0.855 1 year: DES 17.4% BMS 22.2% P = 0.019 2 years: DES 22.5% BMS 28.1% P = 0.014 **Angiographically proven stent thrombosis:** 30 days: DES 0.5% BMS 0.3% P = 0.62 1 year: DES 1.1% BMS 0.7% P = 0.482 2 years: DES 1.5% BMS 0.7% P = 0.176 Two-year propensity score	

					adjusted cumulative incidence: **All-cause mortality:** DES 11.1 BMS 11.8 HR = 0.94; 95% CI, 0.69-1.28; P = 0.73 **All-cause mortality or nonfatal myocardial infarction:** DES 16.9% BMS 19.4% HR = 0.96; 95% CI, 0.68-1.35; P = 0.82 **TVR:** DES 11.6% BMS 15.0% HR = 0.66; 95% CI, 0.46-0.96 P = 0.041 **Any of these major adverse events:** DES 23.0% BMS 28.8% HR = 0.77; 95% CI, 0.59-1.01 P = 0.09 Estimated 2 year incidence from figure 3: **Angiographically proven stent thrombosis:** DES 1.5% BMS 0.7% P = 0.18	
Palmerini et al (2008) Gruppo Italiano	III retrospective registry	N = 1453 DES n = 1111 BMS n = 342	**ACS, unstable angina** All 496 (34%) DES n = 359 (66.7%) BMS n = 137 (57.6%)		**Two year survival:** DES 90.1% BMS 75.9% P = 0.00001	

Studi Emodinamici Survey on ULMCA Stenosis; Italy; multicenter; 19 centers	ULMCA stenosis treated using PCI from January 2002 to December 2006; inclusion >50% stenosis of the left main; not protected by a cornary bypass graft; excluded acute STEMI F/U: 2 years	Male: All 72% DES 74.1% BMS 66.1% Age: All 72 years (20-97) DES 77 years (20-95) BMS 71 years (29-97) Diabetes mellitus: All n = 398 (29%) DES n = 321 (30.7%) BMS n = 77 (24.4%) Systemic hypertension: all n = 961 (69%) DES n = 735 (68.8%) BMS n = 226 (71.6%) Hypercholesterolemia: all n = 836 (61%) DES n = 669 (62.9%) BMS n = 167 (53.0%) Acute coronary syndrome: All 59% DES n = 621 (55.5%) BMS n = 238 (70.0%)	**ACS, NSTEMI** DES n = 179 (33.3%) BMS n = 101 (42.4%) **Multi-vessel disease:** DES n = 598 (57.1%) BMS n = 180 (57.1%) **multivessel treatment:** DES n = 282 (32.2%) BMS n = 82 (30.0%) **Glycoprotein IIa-IIIb:** DES n = 325 (29.2%) BMS n = 123 (36.1%) **≥ 12 month dual antiplatelet tx:** DES n = 322 (49.5%) BMS n = 63 (26.0%)		**Survival free from cardiac death:** DES 93.1% BMS 82.4% P = 0.00001 **Propensity adjusted cardiac mortality for DES vs BMS:** To 30 days: aHR = 0.139; CI, 0.45-0.436; P = 0.001 31 to 180 days: aHR = 0.388; CI 0.181-0.833; P = 0.015 181-360 days: aHR = 1.249; CI 0.316-4.932; P = 0.751 361-720 days: aHR = 0.761; CI 0.263-2.202; P = 0.614 **Propensity-adjusted Cox multivariable analysis of survival free from cardiac death in the period 30 days to 2 years for DES vs BMS:** HR = 0.563; CI 0.323-0.981; P = 0.043	
Philpott et al (2009) Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry; Alberta, Canada; multisite	III Prospective cohort PCI between April 1, 2003 to March 31, 2006; N = 6471 of which n = 31 excluded due to undeployed stents F/U: at least 1 year	N = 6440 DES n = 1120 BMS n = 5320 Male: All 75% DES 71.3% BMS 75.6% Age: All 62 years (SD 12 years) DES 62.3 years (SD 11.6) BMS 62.5 years (SD 11.9) Diabetes mellitus:	**ACS** DES n = 726 (64.8%) BMS n = 4460 (83.8%) **Non-acute coronary syndrome** DES n = 387 (34.6%) BMS n = 848 (15.9%) **Multi-vessel disease:** High risk anatomy includes 2- or 3-vessel disease DES n = 431 (38.5%) BMS n = 1617 (30.4%) Low risk anatomy		n/N (%) and crude and adjusted odds ratio (95% CI) for all patients (breakdowns for patients with acute coronary symdromes and with non-acute coronary syndromes are also listed in table 2) **death:** 30 day: DES 8/1120 (0.7%) BMS 96/5320 (1.8%) OR = 0.50 (0.33-0.76) adjOR = 0.40 (0.25-0.64) 6 month:	Propensity scores to compare outcomes of patients in 2 stent groups. Likelihood to receive drug-eluting stents was modelled, then outcomes compared for the 2 groups across tertiles of likelihood to receive drug-eluting stents; Then propensity analysis extended to conduct a 1-to-1 match of each patient

		All n = 1473 (23%) DES n = 367 (32.8%) BMS n = 1106 (20.8%) Hyperlipidemia: All n = 5281 (82%) DES n = 983 (87.8%) BMS n = 4298 (80.8%) Hypertension: All n = 4323 (67%) DES n = 791 (70.6%) BMS n = 3532 (66.4%) Prior MI: All n = 3569 (55%) DES n = 510 (45.5%) BMS n = 3059 (57.5%) Prior CABG: All n = 435 (6.8%) DES n = 132 (11.8%) BMS n = 303 (5.7%)	includes 2- or 1- vessel disease DES n = 604 (53.9%) BMS n = 3400 (63.9%) **# vessels treated:** 1 stent used: DES n = 750 (67.0%) BMS n = 2793 (52.5%) 2 stents used: DES n = 263 (23.5%) BMS n = 1612 (30.3%) 3 stents used: DES n = 80 (7.1%) BMS n = 557 (10.5%) 4 stents used: DES n = 19 (1.7%) BMS n = 248 (4.7%) 5 or more stents used: DES n = 8 (0.7%) BMS n = 110 (2.1%) **Glycoprotein IIa-IIIb:** DES n = 627 (56.0%) BMS n = 2777 (52.2%)		DES 21 (1.9%) BMS 151 (2.8%) OR = 0.62 (0.45-0.85) AdjOR = 0.53 (0.37-0.75) 1 year: DES 33 (3.0%) BMS 195 (3.7%) OR = 0.74 (0.57-0.96) adjOR = 0.62 (0.46-0.83) **composite outcomes (death or repeated revascularization – percutaneous coronary intervention or CABG surgery):** 30 days: DES 46 (4.1%) BMS 335 (6.3%) OR = 0.44 (0.33-0.58) adjOR = 0.42 (0.31-0.57) 6 months: DES 100 (8.9%) BMS 665 (12.5%) OR = 0.44 (0.36-0.53) adjOR = 0.38 (0.30-0.48) 1 year: DES 143 (12.0%) BMS 841 (15.8%) OR = 0.47 (0.40-0.56) adjOR = 0.40 (0.33-0.49)	with drug-eluting stents to a single patient with bare-metal stents. Adjusted for age, sex, comorbidities, indication, use of glycoprotein Iib/IIIA inhibitors, mean length and diameter of stent, ejection fraction, coronary anatomy, and Duke Myocardial Jeopardy score Propensity analysis is in Appendix 1 Philpot – adjusted odds ratios, survival curves 1120 – DES, 5320 BMS
Rodriguez et al (2007) ERACI III registry study; Buenos Aires, Argentina; multicenter	III Prospective cohort; from RCT (BMS) and from registry (DES) F/U 30 day, 1 year; 3 year safety and efficacy ERACI II BMS patients: from 1996 to 1998; n = 225; ERACI III DES patients: from 2002 to 2004; of 446	N = 450 for BMS and DES arms BMS: n = 225 (from RCT ERACI II (PCI vs CABG) DES: n = 225 (from registry) Male: All 80% DES 84% BMS 78% Age: All 63 years (SD 10)	**ACS, unstable angina**: DES n = 167 (74.2%) BMS n = 208 (92.4%) **Multi-vessel disease**: 2-vessel CAD: DES n = 139 (61.8%) BMS n = 102 (45.3%) 3-vessel CAD: DES n = 86 (38.2%) BMS n = 123 (54.7%) **# of stents:** DES: mean 1.79 (SD 0.71)	SES (Cypher) or PES (Taxus)	Incidence of clinical endpoints; n/N (%); RR (95% CI) **Procedural and in-hospital complications** Death- DES 2 (0.9%) BMS 2 (0.9%) (*P* = 1.4) Non-fatal Q wave MI DES 2 (0.9%) BMS 2 (0.9%) (*P* = 1.4) Stroke	Stent thrombosis defined as: suspected stent thrombosis, when patient suffered unexpected cardiac or sudden death or had an ST-segment elevation MI which correlated with the area of DES placement. Non-STEMI related to the treated vessel was not considered to represent stent

	treated with DES, n = 225 form the study population for this report: excluded those with prior CABG, PCI in the preceding year, in-stent restenosis, acute MI < 48 hours, ejection fraction < 35%, two or more chronic total occlusions, severe valvular or myocardial heart disease, limited life expectancy, cerebrovascular accident history, neutropenia or thrombocytopenia, aspirin or thienopyridine intolerance, need vascular or general surgery, unsuitable to long-term anti-PLT therapy, or not amenable to treatment with DES	DES 65.5 years (SD 10.6) BMS 60.6 years (SD 10.1) Prior AMI: All n = 135 (30%) DES n = 71 (32%) BMS n = 64 (28%) Diabetes: All n = 85 (19%) DES n = 46 (20%) BMS n = 39 (17%) Hyperlipidemia: All n = 319 (71%) DES n = 178 (79.1%) BMS n = 39 (17.3%)	BMS: mean 1.39 (SD 0.56) **Glycoprotein IIa-IIIb:** Strongly recommended in patients with unstable angina class III or C or diabetics Antiplatelet Tx: recommended 75 mg of clopidogrel daily for 3 months minimum for SES and 6 months minimum for PES; aspirin therapy continued indefinitely		DES 3 (1.3%) BMS 0 (0%) (*P* = 0.5) **Death:** 1 year: DES 7/225 (3.1%) BMS 7/225 (3.1%) RR = 1 (0.356-2.804) 3 years: DES 13 (5.7%) BMS 11 (4.8%) RR = 1.18 (0.54-2.58) **AMI, fatal and nonfatal:** 1 year: DES 6 (2.7%) BMS 5 (2%) RR = 1.2 (0.371-3.875) 3 years: DES 14 (6.2%) BMS 6 (2.7%) RR = 2.3 (0.913-5.963) **CVA:** 1 year: DES 5 (2%) BMS 4 (1.8%) RR = 1.23 (0.337-4.553) 3 years: DES 7 (3.1%) BMS 4 (1.8%) RR = 1.75 (0.519-5.895) **TVR:** 1 year: DES 20 (8.9%) BMS 38 (16.9%) RR = 0.52 (0.316-0.87) 3 years: DES 32 (14.2%) BMS 55 (24.4%) RR = 0.58 (0.392-0.863) **MACCE:** 1 years: DES 27 (12%)	thrombosis. Patients whose electrocardiogram from the time of the acute event could not be reviewed were not included. Confirmed stent thrombosis, when patient had angiographically documented stent thrombosis with TIMI flow 0 or 1 or the presence of flow-limiting thrombus (TIMI flow 1 or 2. Both suspected and confirmed stent thrombosis were counted as overall stent thrombosis. Thrombosis was readjudicated then using ARC definition, including events which occurred after repeated TVR; acute, subacute, late, very late. Rodriguez – not clear any adjustment – experience with pts with complex lesion in ERACI III compared to ERACI II pts with BMS, DES, CABG – 225 pts each arm - ?matched Abstract mentions

					BMS 50 (22.2%) RR = 0.54 (0.351-0.830) 3 years: DES 51 (22.7%) BMS 67 (29.8%) RR = 0.68 (0.501-0.921) **Stent thrombosis by ARC definition at 3 years:** BMS: n = 3 acute DES n = 1 acute; n = 3 subacute, n = 4 late; n = 2 very late: of these, n = 6 definite; n = 2 probable; n = 2 possible **Freedom from death at 3 years:** DES 94.2% BMS 95.1% P = 0.082 **Freedom from non-fatal MI at 3 years:** DES 95.6% BMS 97.3% P = 0.179 **Freedom from TVR at 3 years:** DES 85.8% BMS 75.6% P = 0.0001 **Freedom from MACCE at 3 years:** DES 77.3% BMS 70.2% P = 0.1651	EuroSCORE as tho it is a severity index of some sort, but doesn't say adjusted.
Roy et al (2008)	III Registry cohort F/U: 12 months PCI between April	Demographics from table 1; after propensity-score matching: N = 1092 DES n = 546	**From table 1** **Stable angina** DES: 17.2% (n = 94) BMS: 21.6% (n = 118) **Unstable angina**	DES = sirolimus-eluting or paclitaxel-eluting stents	12 months **Cardiac death** no significant difference between groups, % not reported (would need to be estimated from figure 4)	Patients receiving ≥ DES for ≥ off-label indication(s) were considered Off-label use included total stented

	2003 to June 2006	BMS n = 546 Male DES: 69.7% (n = 380) BMS: 70.7% (n = 386) Age DES: 64.5 years (SD 11.9) BMS: 64.4 years (SD 12.3) Diabetes DES: 31.5% (n = 172) BMS: 34.1% (n = 186) HTN DES: 76.6% (n = 418) BMS: 72.3% (n = 395) Dyslipidemia DES: 82.2% (n = 449) BMS: 81.1% (n = 443) Prior MI DES: 47.1% (n = 257) BMS 46.9% (n = 256) Prior CABG DES: 27.3% (n = 149) BMS: 28.9% (n = 158) Prior PCI DES: 33.3% (n = 182) BMS: 36.3% (n = 198)	DES: 58.1% (n = 317) BMS: 57.3% (n = 313) **Acute MI** DES: 16.7% (n = 91) BMS: 17.4% (n = 95) **From table 2, procedural characteristics, based on number of lesions treated** DES: n = 1041 BMS: n = 985 **# lesions treated** DES: 1.9 ± 1.0 BMS: 1.8 ± 1.0 **Glycoprotein IIb/IIIa inhibitor use** DES: 17.9% (n = 98) BMS: 16.7% (n = 91) All patients given 325 mg aspirin prior to PCI and 300-600 mg clopidogrel. Dual antiplatelet therapy recommended for DES group for a minimum of 6 months.		**Q-wave MI** DES: 3.4% BMS: 6.7% P = .02 **TVR** DES: 20.2% BMS: 13.1% P = .003	length per lesion > 33 mm, in-stent restenotic lesions, saphenous vein graft lesions, use of > 2 stents per patient, acute MI, unprotected left main coronary artery, and ostial lesions
Shishehbor et al (2008)	III Registry cohort F/U: 4.5 years PCI between March 1, 2003 and June 30, 2007	**Overall population** N = 8036 DES, n = 6053 BMS, n = 1983 Male DES: 68% (n = 4130)	**Overall population only** **Acute MI** DES: 9% (n = 537) BMS: 18% (n = 348) **Unstable angina** DES: 36% (n = 2176) BMS: 35% (n = 687)	BMS = 53% stainless steel and 47% cobalt/chromium	All-cause mortality during 4.5 years follow-up **Overall nonpropensity-matched** DES: 8% (n = 499) BMS: 17% (n = 333) (HR = 0.62, 95% CI, 0.53-0.73, P < .001)	

		BMS: 68% (n = 1356) Age DES: 65 years (SD 11) BMS: 66 years (SD 12) Diabetes DES: 34% (n = 2067) BMS: 32% (n = 635) Family history of CAD DES: 28% (n = 1690) BMS: 25% (n = 501) Smoking DES: 17% (n = 1053) BMS: 20% (n = 397) Prior MI DES: 38% (n = 2314) BMS: 42% (n = 827) Prior CABG DES: 30% (n = 1830) BMS: 31% (n = 607) **Propensity matched population** N = 3602 DES, n = 1801 BMS, n = 1801 Male DES: 68% (n = 1229) BMS: 67% (n = 1200) Age DES: 66 years (SD 12) BMS: 66 years (SD 12) Diabetes DES: 34% (n = 608) BMS: 32% (n = 593)	**# of diseased vessels** 1-vessel DES: 65% (n = 3905) BMS: 71% (n = 1398) 2-vessel DES: 26% (n = 1547) BMS: 19% (n = 383) 3-vessel DES: 10% (n = 601) BMS: 10% (n = 202) **Medications on admission** aspirin DES: 93% (n = 5656) BMS: 93% (n = 1841) clopidogrel DES: 96% (n = 5808) BMS: 95% (n = 1892) angiotensin-converting enzyme DES: 40% (n = 2396) BMS: 39% (n = 769) beta-blockers DES: 32% (n = 1955) BMS: 34% (n = 670) statins DES: 69% (n = 4173) BMS: 60% (n = 1197) heparin DES: 35% (n = 2126) BMS: 50% (n = 982) glycoprotein IIb/IIIa inhibitors DES: 37% (n = 2249) BMS: 53% (n = 1051)		**Propensity-matched** DES: 10% (n = 189) BMS: 16% (n = 283) (HR = 0.54, 95% CI, 0.45-0.66, P < .001)	

		Family history of CAD DES: 26% (n = 468) BMS: 25% (n = 460) Current smoking DES: 21% (n = 377) BMS: 19% (n = 346) Prior MI DES: 41% (n = 746) BMS: 41% (n = 746) Prior CABG DES: 29% (n = 524) BMS: 30% (n = 535)				
Tu et al (2007) Cardiac Care Network of Ontario registry; Canada; multicenter	III Retrospective registry cohort PCI between December 1, 2003 to March 31, 2005 Index cohort of 18314 patients with PCI by BMS or DES or multiple stents, all the same type; excluded n = 4961 who had invalid Ontario health card number, or otherwise missing information needed to propensity score matching; or who had PCI in past year, or PCI for left main coronary artery disease	Demographics from table 2; after propensity-score matching: N = 7502 DES n = 3751 BMS n = 3751 Male: All 71% DES 71.2% BMS 70.7% Age: All 62 years (SD 12 years) DES 62.3 years (SD 11.5 years) BMS 62.3 years (SD 11.7) Hypertension: All 36.6% DES 36.7% BMS 36.6% MI; same day as index PCI: All 9.2% DES 9.2%	**CCS angina classification:** Class 0: DES 6.6% BMS 7.3% Class I: DES 5.4% BMS 5.5% Class II: DES 15.0% BMS 15.1% Class III: DES 23.7% BMS 23.3% Class IVA: DES 26.6% BMS 27.0% Class IVB: DES 11.2% BMS 11.1% Class IVC: DES 10.6% BMS 9.7% Class IVD: DES 0.9% BMS 1.0% **Mean # vessels stented**: DES 1.1 (SD 0.4)	In matched cohort, 82.9% of DES were PES and 17.1% were SES	Outcome rates after index PCI: **TVR:** At 6 months: DES 3.2% BMS 6.0% At 1 year: DES 5.2% BMS 8.6% At 2 years: DES 7.4% BMS 10.7% **MI:** At 6 months: DES 2.6% BMS 3.3% At 1 year: DES 3.8% BMS 3.9% At 2 years: DES 5.7% BMS 5.2% **Death:** At 6 months: DES 2.1% BMS 2.7%	Propensity score matching of pairs of patients Tu – propensity matched cohorts – 3751 pairs

		BMS 9.1% MI, 1-7 days before index PCI: All 19.6% DES 19.8% BMS 19.5% MI, 8-365 days before index PCI: All 12.3% DES 11.9% BMS 12.7% Prior CABG: All 8.8% DES 8.5% BMS 9.0% Diabetes: All 32.6% DES 32.6% BMS 32.6%	BMS 1.1 (SD 0.4) **Mean # stents per patients:** DES 1.5 (SD 0.8) BMS 1.5 (SD 0.8)		At 1 year: DES 2.7% BMS 4.0% At 2 years: DES 4.3% BMS 6.1% At 3 years: DES 5.5% BMS 7.8% **MI or death:** At 6 months: DES 4.8% BMS 5.7% At 1 year: DES 6.1% BMS 7.5% At 2 years: DES 9.3% BMS 10.5%	
Vlaar et al (2008) Mayo clinic PCI registry, Rochester, MN; single site; DES placement for STEMI patients compared to BMS placement for STEMI patients	III Retrospective registry cohort DES for STEMI from May 2003 to October 2005; BMS for STEMI from January 1999 to march 2003 Patients excluded if they refused permission for their records to be used for research	N = 1129 DES n = 552 BMS n = 577 Male: All 68% DES n = 367 (66%) BMS n = 397 (69% Age: All 64 years (SD 14) DES 63 years (SD 14) BMS 65 years (SD 14) Diabetes mellitus: All n = 201 (18%) DES n = 92 (17%) BMS n = 109 (19%) Hypertension: All n = 649 (57%) DES n = 324 (66%)	**STEMI:** DES 100% BMS 100% **Multi-vessel disease:** DES 359 (67%) BMS 374 (66%) **Mean # stents placed:** DES 1.3 (SD 0.7) BMS 1.5 (SD 0.7) **Glycoprotein IIa-IIIb:** Administered at operator discretion DES n = 448 (81%) BMS n = 501 (87%) Aspirin 325 mg administered prior to procedure and continued indefinitely; clopidogrel given with a loading dose	Cypher SES or Taxus PES	Kaplan-Meier estimates of adverse events at f/u: **In-hospital complications** Death- DES- 16 (2.9%) BMS- 20 (3.5%) (*P* = 0.059) MI -occurrence was similar between groups (data NR) CABG -occurrence was similar between groups (data NR) **All cause mortality: (P = 0.93)** 30 days DES 0.6% (n = 536) BMS 0.7% (n = 557) 6 months:	Vlaar – STEMI pts – retrospective cohort – 552 DES, 557 BMS (historical match?) no mention of adj – would have to see paper to decide, but these are MI pts

		BMS n = 325 (60%) Cholesterol >240 mg/dL: All n = 664 (59%) DES n = 319 (69%) BMS n = 345 (72%) Prior CABG: All n = 63 (5.6%) DES n = 29 (5%) BMS n = 34 (6%) Prior MI > 7 days: All n = 156 (14%) DES n = 29 (5%) BMS n = 34 (6%)	of 300-600 mg at beginning of the procedure and continued at 75mg dose for at least 6 months		DES 1.9% BMS 2.7% 12 months: DES 3.7% BMS 4.2$ 24 months: DES 6.4% BMS 6.4% **Any re-MI: (P = 0.31)** 30 days DES 1.0% BMS 1.1% 6 months: DES 2.1% BMS 2.6% 12 months DES 2.7% BMS 4.3% 24 months DES 7.2% BMS 5.6% **TVR: (P = 0.002)** 30 days DES 1.1% BMS 2.4% 6 months DES 3.1% BMS 7.9% 12 months DES 6.2% BMS 10.4% 24 months DES 7.7% BMS 11.5% **TLR: (P < 0.001)** 30 days DES 0.8% BMS 2.4% 6 months DES 2.1% BMS 7.9% 12 months DES 2.9%	

					BMS 10.4% 24 months DES 4.7% BMS 11.1% **MACE: (P = 0.18)** 30 days DES 2.3% BMS 3.1% 6 months DES 6.5% BMS 10.5% 12 months DES 9.1% BMS 15.3% 24 months DES 16.3% BMS 18.8% HR long-term f/u (95% CI) from table III; table III footnotes indicate for which factors the HR is adjusted for each outcome : **Death**: HR = 1.02 (0.65-1.62) aHR = 0.92 (0.57-1.49) **Death/re-MI:** HR = 1.01 (0.72-1.42) aHR = 0.93 (0.65-1.32) **MACE:** HR = 0.82 (0.62-1.09) aHR = 0.75 (0.65-1.01)	
Yan et al (2008) Melbourne Interventional Group registry; Australia; multicenter; 7 sites	III Registry cohort F/U: up to 12 months PCI from April 1, 2004 to October 10, 2006;	N = 2919 DES n = 1630 BMS n = 1289 Male: All 73.1% DES 73.0% BMS 73.2% Age: All 65 years (SD 12) DES 65.4 years (SD 11.9)	**All ACS:** All 61.4% DES 59.9% BMS 63.2% **ACS, unstable angina pectoris:** All 19.3% DES 20.9% BMS 17.2% **ACS, NSTEMI:** All 22.5%	In DES cohort, both DESs and BMSs implanted in 8.7% of patients (n = 142) and 1.2% of lesions (n = 42)	% incidence, P value, unadjusted OR (95% CI) **Death:** 30 days: DES 2.0% BMS 3.3% P = 0.03 OR = 0.60 (0.38-0.95) 12 months: DES 3.9% BMS 5.3% P = 0.08	Stent thrombosis by ARC definitions of definite, probable, possible; early (0-30 days) or late (31-365 days); definite ST required presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion

		BMS 64.4 years (SD 12.0) Diabetes mellitus: All 22.7% DES 29.6% BMS 14.0% Hypertension: All 61.2% DES 61.0% BMS 61.5% Hypercholesterolemia: all 69.4% DES 68.9% BMS 70.0% Prior MI: All 29.1% DES 31.0% BMS 26.2%	DES 22.8% BMS 22.0% **ACS, STEMI:** All 19.6% DES 16.2% BMS 24.0% **Glycoprotein IIa-IIIb:** All 26.4% DES 25.3% BMS 27.9% **Planned clopidogrel duration ≥ 12 months:** All 45.4% DES 61.0% BMS 25.5% **Absence of clopidogrel at 12 months**: All 52.7% DES 38.7% BMS 58.3%		OR = 0.73 (0.52-1.04) **MI:** 30 days: DES 2.5% BMS 2.0% P = 0.43 OR = 1.22 (0.74-2.01) 12 months: DES 4.7% BMS 4.2% P = 0.49 OR = 1.13 (0.79-1.62) **TLR:** 30 days: DES 1.7% BMS 1.7% P = 0.98 OR = 1.00 (0.57-1.77) 12 months: DES 3.7% BMS 5.6% P = 0.01 OR = 0.65 (0.46-0.92) **TVR:** 30 days: DES 2.0% BMS 1.9% P = 0.84 OR = 1.06 (0.62-1.80) 12 months: DES 5.8% BMS 6.6% P = 0.36 OR = 0.87 (0.64-1.17) **MACEs:** 30 days: DES 5.8% BMS 6.4% P = 0.50 OR = 0.90 (0.66-1.22) 12 months: DES 12.3%	Yan – "predictors of ST" for BMS vs DES – in pop where DES used for higher risk – 2919 pts, abstract doesn't id #DES vs BMS

					BMS 13.6% P = 0.32 OR = 0.90 (0.71-1.11) **Stent thrombosis:** **Early:** DES n = 11 (0.7%) BMS n = 4 (0.3%) P = 0.17 OR = 2.18 (0.69-6.87) Early definite: DES n = 6 BMS n = 2 P = 0.27 Early probable: DES n = 5 BMS n = 2 P = 0.47 **Late thrombosis:** DES n = 15 (0.9%) BMS n = 14 (1.1%) P = 0.65 OR = 0.85 (0.41-1.76) Late definite: DES n = 5 BMS n = 5 P = 0.51 Late probable: DES n = 2 BMS n = 1 P = 0.78 Late possible: DES n = 8 BMS n = 8 P = 0.35 **Total thrombosis:** DES n = 26 (1.6%) BMS n = 18 (1.4%) P = 0.66 OR = 1.15 (0.63-2.10)	
Le Feuvre et al (2008)	III	N = 3579 DES n = 2318 patients	**Multivessel PCI:** All n = 956 (27%)		**Stent thrombosis:** DES n = 16 (1.3%) BMS n = 36 (1.6%)	Stent thrombosis defined as in-stent thrombosis

Institut de cardiologie, Département de cardiologie médicale, Groupe hospitalier Pitié-Salpêtrière, Paris, France; single site	PCI between January 2003 and April 2007; N = 3579 DES selected in accordance with guidelines taking into account proximal left anterior descending artery, diabetes, vessel diameter < 3 mm, lesions length > 15 mm, and in-stent restenosis	with 2815 lesions BMS n = 1261 patients with 1536 lesions Demographics not given for DES or BMS as a group. Demographics are given for those with stent thrombosis or without stent thrombosis Demographics are given for those with DES thrombosis (n = 16); or with BMS thrombosis (n = 36) Male: All 80.5% Age: All 63 years Diabetes mellitus: All n = 1125 (31%) Hypertension: All n = 1827 (51%) Prior CABG: All n = 280 (7.8%) Prior MI: All n = 806 (22.5%)	**IV anti-PLT therapy during initial PCI:** All n = 1102 (31%) Treatment with aspirin continued indefinitely. Clopidogrel treatment stopped after 1 month for BMS, and 6 to 12 months for DES			confirmed angiographically, with or without vessel occlusion, and associated with clinical or electrocardiographic signs of acute ischaemia or elevation of CK levels to twice normal within 48 hours of angiography; ie "definite" stent thrombosis by ARC definitions. Partial thrombosis referred to an intrastent filling defect with TIMI flow of 1-3 in the coronary artery, and total stent occlusion referred to intrastent thrombosis with TIMI flow of 0. "probable" or "possible" stent thrombosis by ARC definition.
Ong et al (2005) Thoraxcenter, Erasmus Medical Center, Rotterdam; Netherlands	III Retro cohort n = 506 BMS patients before April 2002, n = 1017 SES patients April 2002 to February 2003, n =	N = 2512 SES n = 1017 PES n = 989 BMS n = 506 Male: SES 70% PES 74%	**stable angina** SES 43% PES 41% BMS 42% **ACS, unstable angina** SES 46% PES 30% BMS 35%	Cypher SES; Taxus PES	**Angiographic stent thrombosis:** 30 days: SES n = 10 (1.0%) PES n = 10 (1.0%) BMS n = 6 (1.2%) **Possible ST:** 30 days:	Stent thrombosis definite when confirmed angiographically by TIMI flow grade 0-1 or TIMI flow grade 1-2 in acute or subacute time period after stent

	989 PES patients February 2003 to December 2003	BMS 73% Age: SES 61.9 years (SD 11.3) PES 61.7 years (SD 11.4) BMS 61.0 years (SD 11.4) Diabetes: SES 18% PES 17% BMS 16% Hypercholesterolemia: SES 55% PES 60% BMS 52% Hypertension: SES 41% PES 41% BMS 40% Previous MI: SES 32% PES 35% BMS 43% Previous PCI: SES 25% PES 26% BMS 22% Previous CABG: SES 9% PES 8% BMS 11%	**Acute MI:** SES 19% PES 26% BMS 20% **Silent ischemia** SES 2% PES 3% BMS 3% **Multi-vessel disease:** SES 57% PES 56% BMS 54% **# vessels treated:** SES n = 1399, mean 1.4 SD 0.6 PES n = 1347, mean 1.4 SD 1.6 BMS n = 668, mean 1.4 SD 0.6 **Glycoprotein IIa-IIIb:** SES 21% PES 28% BMS 37% Lifelong aspirin prescribed; Clopidogrel for at least one month in the BMS group, for at least three months in the SES group, for at least six months in the PES group		SES n = 5 (0.5%) PES n = 6 (0.3%) BMS n = 1 (0.0%) **6 month mortality due to thrombosis:** SES n = 0 PES n = 3 BMS n = 0	implantation. "Possible" when sudden death within first 30 days, or fatal out-of-hospital cardiac arrest, or MI no clearly attributable to another coronary lesion and no repeat angiography
Percoco et al (2006) Registry Regionale Angioplastiche (REAL); Italy; multisite	III Prospective registry cohort Registry started July 1, 2002 and ongoing at time of publication	N = 1617 SES n = 205 BMS n = 1412 Male: All n = 1187 (73%) SES n = 156 (76%)	**Multi-vessel disease**: All n = 811 (50%) SES n = 105 (50%) BMS n = 706 (50%) **Glycoprotein IIa-IIIb**: All n = 1365 (84%) SES n = 193 (94%)	SES vs BMS	Unadjusted cumulative incidence at median 396 days **MACE:** SES 14% BMS 20.3% P = 0.03	Thrombotic stent occlusion angiographically documented as complete occlusion or a flow limiting thrombus of the previously stent IRA

	9 March 2006 Median F/U: All 396 days SES 390 days BMS 400 days Maximum F/U: SES 821 days BMS 868 days At 6 months F/U complete in all patients included in the analysis	BMS n = 1031 (73%) Age: All 64 years (SD 13) SES 60 years (SD 12) BMS 65 years (SD 13) Diabetes mellitus: All n = 303 (19%) SES n = 49 (24%) BMS n = 254 (18%) Hypertension: All n = 920 (57%) SES n = 115 (56%) BMS n = 805 (57%) Hypercholesterolemia: All n = 695 (43%) SES n = 74 (36%) BMS n = 621 (44%) Prior CABG: All n = 32 (2%) SES n = 4 (2%) BMS n = 28 (2%) Prior MI: All n = 177 (11%) SES n = 22 (11%) BMS n = 155 (11%)	BMS n = 1172 (83%) Aspirin given indefinitely; ticlopidine or clopidogrel for one month for BMS and 3 months for SES		**Mortality:** SES 6.2% BMS 12.8% P = 0.02 **Reinfarction**: SES 4.8% BMS 3.1% P = 0.3 **TVR:** SES 3.4% BMS 5.1% P = 0.2 **Stent thrombosis**: SES 1% BMS 1.5% P = 0.8 Including within 24 hours: SES n = 0 BMS n = 3 Between 1-30 days: SES n = 1 BMS n = 12 Between 31-370 days: SES n = 1 BMS n = 6 Effectiveness of SES implantation adjusted for propensity score (HR, 95% CI): **Death:** aHR = 0.66 (0.36-1.23) **MI:** aHR = 1.11 (0.5-2.46) **Death and MI:** aHR = 0.75 (0.45-12.6) **TVR:** aHR = 0.41 (0.2-0.85)	(infarct-related artery) Propensity score analysis by logistic regression with treatment (SES) as the dependent variable and patient clinical characteristics as covariates.

					MACE: aHR = 0.62 (0.4-0.95)	
Yanagi et al (2007)			stable angina n %	SES or PES		SES vs PES comparison
Maeng et al (2008) Western Denmark Heart Registry, Denmark; multicenter (3 centers)	III Registry study January 1, 2002 to June 30, 2005 N = 19,867 lesions; excluded undefined stent type (n = 5), combo of BMS and DES (n = 462), included index procedure (n = 2248 subsequent interventions excluded), only known diabetes mellitus at time of PCI: n = 1423 patients, n = 2094 lesions	N = 1423 DES n = 552 BMS n = 871 Male: 67% DES 70% BMS 66% Age: 64 years DES 62 years BMS 65 years Insulin treated diabetes: All 31% DES 36% BMS 29% Hypertension: All 59% DES 63% BMS 56% Prior CABG: All 9.8% DES 10.5% BMS 9.4% Prior MI: All 34% DES 34% BMS 35%	**stable angina pectoris:** all n = 660 (46%) DES n = 298 (54%) BMS n = 362 (42%) **unstable angina pectoris or NSTEMI:** All n = 444 (31%) DES n = 161 (29%) BMS n = 283 (33%) **ACS, STEMI** All n = 266 (19%) DES n = 72 (13%) BMS n = 194 (22%) **Multi-vessel disease: more than one treated coronary stenoses**: All n = 510 (36%) DES n = 237 (43%) BMS n = 273 (31%) **# vessels treated**: All n = 2094 DES n = 914 BMS n = 1180 after PCI, lifelong aspirin prescribed; before November 2002, clopidogrel for 3-12 months; thereafter standardized to 12 months		Cumulative incidence up to 15 months: **Mortality:** ≤ 12 months: DES n = 34 (6.2%) BMS n = 83 (9.5%) aRR = 0.69 (0.45-1.05) > 12 months: DES n = 3 (0.5%) BMS n = 11 (1.3%) aRR = 0.49 (0.14-1.75) Cardiac: DES n = 20 (3.6%) BMS n = 62 (7.2%) aRR = 0.53 (0.31-0.90) **MI** 28 days to 12 months: DES n = 26 (4.8%) BMS n = 39 (4.7%) aRR = 0.77 (0.44-1.35) 12 months and later: DES n = 5 (0.9%) BMS n = 2 (0.2%) aRR = 5.93 (0.66-53.3) **Stent thrombosis:** Definite: DES n = 3 (0.3%) BMS n = 4 (0.3%) aRR = 0.59 (0.10-3.26) Probable: DES n = 1 (0.2%) BMS n = 12 (1.4%) aRR = 0.17 (0.0-1.32) Possible: DES n = 9 (1.6%) BMS n = 13 (1.5%) 1.05 (0.41-2.69)	Defined by ARC definition with a modification by probable stent thrombosis

					Combined: Acute (24 hours): DES 0% BMS n = 3 (0.3%) 1-30 days: DES n = 3 (0.5%) BMS n = 11 (1.3%) aRR = 0.47 (0.13-1.70) 30 days to 12 months: DES n = 10 (1.8%) BMS n = 9 (1.0%) aRR = 1.68 (0.66-4.27) 12 months and later: DES 0% BMS n = 5 (0.6%) The aRR's listed above were adjusted for age, gender, clinical indication, procedure time **TLR** Within 15 months DES 5.1% BMS 8.4% RR = 0.58 (0.41-0.83) aRR = 0.48 (0.33-0.71) P < 0.0001 TLR aRR was adjusted for age, gender, clinical presentation, stent length, reference vessel size	
Groeneveld et al (2008) Medicare beneficiaries age 66 and older; USA	III Registry cohort Patients treated between April 24, 2003 and December 2003 for DES; between July 1, 2002 and December 31, 2003 for BMS	N = 71,965 DES + 71,965 BMS = 143960 total matched to BMS controls (both contemporary and historical controls) Demographics listed for DES vs matched contemporary BMS controls		SES vs BMS	Unadjusted clinical outcomes for matched contemporary BMS controls: **Mortality:** 90 days: DES 3.0% BMS 4.4% P < 0.001 1 year: DES 6.5% BMS 8.9%	

	Exluded prior PCI or CPBG within 6 months; included age 66 and older only Of N = 76525; 71965 could be matched to controls; 94% of overall DES patients identified in database	Male: All 57% DES 57% BMS 57% Age: All 75 years DES 75 years BMS 75 years Hypertension: All 61% DES 61% BMS 60% Prior Acute MI: All 28% DES 27% BMS 29% Diabetes: All 26% DES 27% BMS 26%			P < 0.001 2 years: DES 10.7% BMS 13.5% P < 0.001 Overall mortality: HR = 0.84 (0.82-0.87) aHR = 0.83 (0.81-0.86) **Hospitalization for subsequent AMI:** 1 year: DES 7.2% BMS 9.3% P < 0.001 HR = 0.76 (0.73-0.79) aHR = 0.76 (0.73-0.79) 2 years: DES 9.2% BMS 11.2% P < 0.001 HR = 0.80 (0.77-0.83) aHR = 0.80 (0.78-0.83) **Coronary revascularization:** 1 year: DES 12.6% BMS 14.6% P < 0.001 HR = 0.84 (0.83-0.87) aHR = 0.84 (0.81-0.86) 2 years: DES 17.2% BMS 19.1% P < 0.001 HR = 0.88 (0.86-0.91) aHR = 0.87 (0.85-0.90)	

Appendix I. Evidence Tables: Safety Outcomes Comparing DES versus BMS in General and Special Populations Included in Recent Meta-Analyses

General Population

Table I1. Stent thrombosis results from Stettler et al. (2008) network meta-analysis: non-diabetic patients

	All trials		Trials with ≥ 6 months dual antiplatelet therapy	
	Hazard ratio (95% CI)	IC	Relative risk (95% CI)	IC
Overall (0 to 4 years)				
ARC-defined "definite" stent thrombosis				
SES vs BMS	1.35 (0.76–2.73)		1.24 (0.58–3.08)	
PES vs BMS	1.54 (0.83–3.13)	32%*	1.48 (0.69–3.40)	20%*
Protocol-defined stent thrombosis				
SES vs BMS	1.43 (0.78–3.00)		1.48 (0.74–3.41)	
PES vs BMS	1.73 (0.88–3.61)	8%*	1.80 (0.89–3.67)	10%*
Early (0 to 30 days)				
ARC-defined "definite" stent thrombosis				
SES vs BMS	NR		1.19 (0.43–3.09)	
PES vs BMS	NR	NR	1.11 (0.38–2.97)	NR
Protocol-defined stent thrombosis				
SES vs BMS	NR		1.11 (0.47–2.81)	
PES vs BMS	NR	NR	0.99 (0.44–2.33)	NR
Late (> 30 days to 4 years)				
ARC-defined "definite" stent thrombosis				
SES vs BMS	NR		1.19 (0.43–4.13)	
PES vs BMS	NR	NR	1.83 (0.67–5.85)	NR
Protocol-defined stent thrombosis				
SES vs BMS	NR		2.29 (0.83–7.77)	
PES vs BMS	NR	NR	4.12 (1.55–13.1)	NR

IC = Inconsistency of network, given as the percentage difference between hazard ratios between direct randomized comparisons within trials and indirect comparisons between trials. If all comparisons in network are consistent, the value will be close to 0, and the hazard ratio estimates comparing stents will be fully coherent. As values deviate more away from 0, the more inconsistent the network becomes. The range of possible IC values goes from 0 to infinity. An IC value of 25% indicates low inconsistency, 50% moderate, and 100% high consistency.

ARC: Academic Research Consortium, BMS = bare-metal stent, CI = confidence interval, NR = not reported, PES = paclitaxel-eluting stent, SES = sirolimus-eluting stent

*IC percentages may apply to three comparators (SES vs BMS; PES vs BMS; SES vs PES), one of which is not relevant here.

Table I2. Stent thrombosis event rates from Stettler et al. (2008) trials with ≥ 6 months of dual antiplatelet therapy: non-diabetic patients

	Events (%)			
Variable	**BMS**	**PES**	**SES**	**Total**
ARC-defined "definite" stent thrombosis				

# patients at risk	2439	1490	984	4913
Overall (0 to 4 years)	34 (1.39%)	26 (1.74%)	26 (2.64%)	86 (1.75%)
Early (0 to 30 days)	19 (0.78%)	10 (0.67%)	15 (1.52%)	44 (0.90%)
Late (> 30 days to 4 years)	15 (0.62%)	16 (1.07%)	11 (1.12%)	42 (0.85%)
Protocol-defined stent thrombosis				
# patients at risk	2577	1742	962	5281
Overall (0 to 4 years)	29 (1.12%)	28 (1.61%)	25 (2.60%)	82 (1.55%)
Early (0 to 30 days)	22 (0.85%)	12 (0.69%)	15 (1.56%)	49 (0.93%)
Late (> 30 days to 4 years)	7 (0.27%)	16 (0.92%)	10 (1.04%)	33 (0.62%)

ARC: Academic Research Consortium, BMS = bare-metal stent, PES = paclitaxel-eluting stent, SES = sirolimus-eluting stent

Table I3. Stent thrombosis outcomes reported in meta-analyses for general populations

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Stettler et al. (2008)	Meta-analysis of 22 RCTs (N = 4913) (SES vs BMS; PES vs BMS): non-diabetic patients	ARC definite stent thrombosis (in patients with ≤ 6 months dual antiplatelet therapy) RR (95% CI): • Overall (0–4 years) SES vs BMS: 1.24 (0.58–3.08) PES vs BMS: 1.48 (0.69–3.40) • Early (0–30 days): SES vs BMS: 1.19 (0.43–3.09) PES vs BMS: 1.11 (0.38–2.97) • Late (31 days –1 year): SES vs BMS: 1.19 (0.43–4.13) PES vs BMS: 1.83 (0.67–5.85) Protocol-defined stent thrombosis (in patients with ≤ 6 months dual antiplatelet therapy) RR (95% CI): • Overall (0–4 years) SES vs BMS: 1.48 (0.74–3.41) PES vs BMS: 1.80 (0.89–3.67) • Early (0–30 days): SES vs BMS: 1.11 (0.47–2.81) PES vs BMS: 0.99 (0.44–2.33) • Late (31 days –1 year): SES vs BMS: 2.29 (0.83–7.77) PES vs BMS: 4.12 (1.55–13.1)	• For non-diabetic patients, there was NS difference in overall (0-4 years), early (<30 days), or late (>30 days to 4 years) stent thrombosis in PES vs BMS or SES vs BMS whether the ARC or protocol-definition of stent thrombosis was used.	• Hierarchial random effects (RE) model used. • ARC and protocol definitions of stents were applied and compared. • NS heterogeneity. • May have been underpowered.
Stettler et al. (2007)	Represented in text of current HTA			
Fuchs et al. (2008)	Pooled analysis of 21 RCTs (N = 10,252*) (DES vs BMS)	• Stent thrombosis developed in the following number of patients: • Overall (6–60 months, mean 16 months): 107 (1.05%) DES: 56 (1.01%) BMS: 51 (1.10%) OR (95% CI): 0.87 (0.58–1.3) (P < 0.48) • Subacute (1–30 days): 42 DES: 21 (0.43%) BMS: 21 (0.53%) 0.86 (0.50–1.5) (P < 0.6) • Late (31 days –1 year): 27 DES: 27	• NS at any time	• Used ARC definitions of stent thrombosis. • Fixed-effect (FE) model used. • No publication bias was detected (used Egger's funnel plot). • NS heterogeneity (used Cochran's Q statistic). • Individual patient data was not used. • Follow-up ranged from 6 to 60 months (mean 16 months). • May have been

		BMS: 20 0.92 (0.50–1.68) ($P < 0.78$)		underpowered. • The rate of stent thrombosis did not vary between patients receiving differently coated DES.
Lemos et al. (2007)	Pooled analysis of 10 RCTs (N = 4892) (DES vs BMS)	Stent thrombosis, f/u NR: RR (95% CI): • 1.1 (0.48–2.12) (NS) (f/u NR)	• NS difference. • NS difference in any of the individual studies.	• Follow-up NR. • Random effects (RE) model used. • Results also inspected for differences if FE model used. • Quantitative heterogeneity not assessed.

Ellis et al. (2007)	Pooled analysis of 4 RCTs: TAXUS II, IV, V, VI (N = 3445) (PES vs BMS)
	1–3 year f/u (only 26.8% (N = 922) patients followed beyond 2 years)
		• 3-year cumulative stent thrombosis:
		  • PES: 1.28% ± 0.31%
		  • BMS: 0.76% ± 0.23%
		  • Hazard ratio (95% CI): 1.51 (0.73–3.14) ($P = 0.26$)
		• Thrombosis-free survival at 3 years
		  • PES: 98.7%
		  • BMS: 99.2%
		  • Log-rank test:
		  $P = 0.26$ (≤ 3 years)
		  $P = 0.021$ (6 months – 3 years)
		• Incidence (# patients):
		  • ≥ 3 years: 30 (PES: 18; BMS: 12)
		  • Early (≤ 30 days): 17
		  • Late (31 days to 6 months): 4
		  • Very late (> 6 months): 9
		  • ≥ 2 years: 0
		• Correlates of stent thrombosis:
		  • Clopidogrel or ticlopidine usage at 1 month: ($P = 0.04$)
		  • patients with stent thrombosis: 23/26 (88.5%)
		  • patients without stent thrombosis: 3343/3384 (98.8%)
		  • Multivariate correlates of all stent thrombosis (N = 30)
		  Hazard ratio (95% CI):
		  • Clopidogrel or ticlopidine usage at discharge: 0.07 (0.01–0.50) ($P = 0.009$)
		  • Current smoking: 2.26 (1.06–4.81) ($P = 0.035$)
		  • Male: 10.18 (1.38–75.03) (P 0.023)
		  • Multivariate correlates of early stent thrombosis (N = 17)
		  Hazard ratio (95% CI):
		  • Clopidogrel or ticlopidine usage at discharge: 0.04 (0.01–0.38) ($P = 0.004$)
		  • Current smoking: 3.32 (1.20–8.65) ($P = 0.021$)
		  • Multiple non-overlapping stents: 3.79 (1.17–12.27) ($P = 0.026$)
		  • Multivariate correlates of late stent thrombosis (N = 13)
		  Hazard ratio (95% CI):
			• NS difference in cumulative 3-year rates of stent thrombosis.
			• NS difference in 3-year thrombosis-free survival.
			• Significantly lower 6 month – 3 year thrombosis-free survival in PES-treated patients ($P = 0.021$)
			• Based on multivariate analysis, significant independent risk factors for stent thrombosis included nonuse of clopidogrel at 1 month, male gender, smoking, and the use of multiple non-overlapping stents.
				• Individual patient data used.
				• Protocol definition of stent thrombosis used.
				• Precise number of patients available for each time point was not clear since authors indicate that only 922/3445 patients were followed to 3 years.
				• Quantitative heterogeneity was not evaluated.
				• Each subject group included all patients who were alive at the beginning of each time interval.
				• Patients with previous stent thrombosis were not censored from later time periods.
				• Stent thrombosis was only counted once for each time period.
				• Time periods used: early stent thrombosis: ≤ 30 days; late stent thrombosis: 30–180 days; very late stent thrombosis: > 180 days.
				• May have been underpowered
				• Clopidogrel therapy: 6–9 months
				• Aspirin therapy recommended indefinitely

		• MACE within 30 days of stenting: 5.34 (1.16–24.49) (*P* = 0.031) • Multivariate correlates of very late stent thrombosis (N = 9) Hazard ratio (95% CI): • SES use: 8.09 (1.01–64.67) (*P* = 0.021)		

ARC: Academic Research Consortium definition of stent thrombosis used, BMS = bare-metal stent, CI = confidence interval, DES = drug-eluting stent, FE = fixed effects meta-analysis model, f/u = follow-up, NR = not reported, NS = not statistically significant , OR = odds ratio, PES = paclitaxel-eluting stent, RCT = randomized controlled trial, RE = random effects meta-analysis model , SES = sirolimus-eluting stent
* The number of patients used in DES vs BMS trials was not given. The N given here was calculated using information from the text, and may not be accurate.

Stent thrombosis in the general population

Stettler et al. (2008) published a network meta-analysis that compared outcomes in patients with and without diabetes who received DES or BMS. The authors considered the report to be an expanded and updated version of their 2007 meta-analysis. Compared to the earlier study, the 2008 meta-analysis stratified according to diabetic status and included five additional trials as well as outcomes for cardiac death, MI, stent thrombosis and TLR. The primary safety outcome of interest was overall mortality, while TLR was the primary outcome for effectiveness. Secondary safety outcomes included death (cardiac death, procedure- or concomitant treatment related death, and deaths of unknown cause), MI (fatal and non-fatal non-Q wave or Q wave), a composite of death and MI, and stent thrombosis within the stented region (reported two ways: as defined by ARC or protocol criteria). The duration of dual antiplatelet therapy was included to minimize this potential source of network inconsistency.

Outcomes for patients with and without diabetes were compared for PES, SES, and BMS. Extensive systematic searches of a variety of sources were performed in order to identify relevant studies. A total of 35 RCTs (N = 14,799) that stratified data by diabetic status and had follow-ups of at least 6 months were included although at least some of these compared SES and PES. 22 of these trials reported data on SES or PES versus BMS in non-diabetic patients (N = 4913). Stettler et al. considered 24 of the 35 trials to be of high quality. Investigators or stent manufacturers provided additional data for 32 of these trials. Appropriate methods for allocation concealment were described in 29 trials; blind adjudication for clinical outcomes was reported in 28 trials; the intention-to-treat principle was applied in 30 trials.

A hierarchial random effects model for mixed treatment comparisons was used with piecewise constant hazards and random effects at the levels of the trials, adjacent time periods, and comparisons levels. Time periods with zero events in both groups were excluded. Heterogeneity was assessed and was defined as "variability of results across trials within comparisons over and above chance." "The duration of dual antiplatelet

therapy specified in trial protocols was the only variable with a treatment by trial characteristic interaction at $P < 0.05$. Therefore [the authors] restricted the dataset to trials with a duration of dual antiplatelet therapy of six months or longer and repeated all analyses."

Relative risks for stent thrombosis were derived using a random effects Poisson regression model because the number of event rates was too for this outcome to accurately estimate random effects at the level of time periods. The authors reported protocol-defined as well as "definite" ARC-defined stent thrombosis, the latter to ensure inclusion of "secondary" stent thrombosis following TVR. In order to minimize variation, thrombosis rates in trials whose patients received dual antiplatelet therapy for at least six months were reported separately. Five trials specified 2 months of dual antiplatelet therapy, three specified 3 months, eighteen specified 6 months, one specified 9 months, and eight specified 12 months. All trials with less than 6 months of dual antiplatelet therapy compared SES with BMS. Relative risks for overall (0 days to 4 years), early (0 to 30 days), and late (31 days to 4 years) rates of stent thrombosis in non-diabetic patients suggest that there is no significant increase in risk with DES compared to BMS when either definition of stent thrombosis was used, with one exception. When all trials were pooled there was an increased risk in the PES group of developing protocol-defined late stent thrombosis when compared to the BMS group, although this effect was not seen when only trials with dual antiplatelet therapy of at least 6 months were pooled. .However, use of the ARC defnition of stent thrombosis increases comparability between trials and limits bias, and may provide more accurate results. Restricting the network to trials with dual antiplatelet therapy for at least 6 months resulted in a decrease in the network inconsistency for SES vs BMS but not PES vs BMS. In addition, the hazard ratios were similar. No significant heterogeneity between trials was detected for any comparator set. The model fit was also evaluated and was considered to be an adequate representation of the data for each comparator set used. However, stent thrombosis was a rare event, affecting less than 2.7% of patients and the meta-analysis may have been underpowered to detect the true rate of events. (Number needed to treat, number needed to harm not given for stent thrombosis).

Fuchs et al. (2007) assessed the incidence of stent thrombosis using data from 21 clinical trials that evaluated DES versus BMS (N = 10,252). Trials were identified by a formal literature search for RCTS that evaluated DES, BMS, and balloon angioplasty. Stent thrombosis was considered the primary endpoint. Stent thrombosis was redefined with the ARC definition and reported as subacute (SAT), occurring between 1 and 30 days after the index procedure, or late (LST), occurring 31 days to 1 year after stenting. However, because follow-up data was available up to a range of 6 to 60 months (mean of 16 months), the number of patients available for each time point was not clear. Furthermore, the authors also reported on trials that compared BMS to balloon angioplasty, and the number of patients in the DES vs BMS trials had to be calculated using information in the text, and may be inaccurate. Baseline patient characteristics were only provided for 15 of the 21 trials. Men accounted for 62% to 94% of patients, and approximately one out of three patients had a history of previous MI. Odds ratios

were calculated using the fixed effects model by weighting each study for its estimated inverse variance; individual patient data was not used.

No significant difference in the overall risk of stent thrombosis between DES and BMS groups was identified ($P < 0.48$). Similarly, there was no difference in the rates of sub-acute (SAT) and late stent thrombosis (LST) between groups ($P < 0.6$ and $P < 0.78$, respectively). There was a nonsignificant trend towards increase LST rates with DES (27 LST cases versus 20 SAT cases). The overall rate of stent thrombosis was 1.05% (107 cases), and rates ranged from 0% to 3.6% among studies. Forest plots were depicted for overall and sub-acute stent thrombosis, though not for late stent thrombosis, and showed that although some studies favored DES and others BMS, none of the individual studies appeared to have statistically significant differences in the rates of overall or sub-acute thrombosis between groups. The overall study results were homogenous by Cochran's *Q* statistic for heterogeneity, although the outcomes were not given quantitatively. Funnel plots showed no evidence of publication bias. Although over 13,000 patients were included in this meta-analysis, it may have been underpowered to detect the true rate of thrombotic events since thrombosis was a rare event. Another limitation of the study is that individual patient data was not used.

Ellis et al. (2007) analyzed individual patient data from the four main TAXUS trials using follow-up data available up to 1–3 years (N = 2445). Stent thrombosis was the primary outcome of interest and was protocol-defined as any of the following: (1) an ACS with angiographically documented thrombosis at the site of the stent; (2) an AMI caused by the treated vessel; or (3) sudden cardiac death within 30 days of stenting in the absence of an alternative obvious cause. Patients with previous stent thrombosis were not censored from later time periods; each subject group included patients who were alive at the beginning of the time period. The time periods used were: early stent thrombosis: ≤ 30 days; late stent thrombosis: 30–180 days; very late stent thrombosis: > 180 days. Men accounted for the majority of patients (72%); approximately 31% of patients had unstable angina, 32% had a history of previous MI, 23% had treated DM, 41% had stent implantation in the LAD, and 18% had the implantation of multiple stents.

Stent thrombosis was relatively rare, occurring in only 0.87% of patients (N = 30); thus the meta-analysis may have been underpowered to detect statistically significant differences between the two groups and the results should be considered appropriately. The authors did not describe possible sources of clinical heterogeneity or possible statistical heterogeneity.

No significant difference in the cumulative incidence of stent thrombosis between the PES and BMS groups was found at 3 years post-procedure. Survival analysis similarly showed no significant difference in thrombosis-free survival between patients treated with SES and BMS at 3 years ($P = 0.26$), although there was a statistically significant decrease in thrombosis-free survival after 6 months in patients treated with SES ($P = 0.021$). However, only 26.8% (N = 922) of patients were followed to 3 years, and the number of patients for each time point is not clear. Furthermore, there were no incidences of stent thrombosis after 2 years.

Based on multivariate analysis adjusted for baseline characteristics, significant independent risk factors for 3-year risks of stent thrombosis (N = 30) included nonuse of clopidogrel or ticlopidine at discharge ($P = 0.009$), male gender ($P = 0.023$), current smoking ($P = 0.035$), and possibly the use of multiple non-overlapping stents ($P = 0.062$). Non-adherence with recommended clopidogrel or ticlopidine therapy at one month was additionally associated with an increased risk of stent thrombosis ($P = 0.004$). Early stent thrombosis (N = 17) was associated with nonuse of clopidogrel or ticlopidine at discharge ($P = 0.004$), current smoking ($P = 0.021$), and the use of multiple non-overlapping stents ($P = 0.021$). For late stent thrombosis (N = 13), a MACE (major adverse cardiac event) within 30 days of implantation was the only independent correlate ($P = 0.031$). Finally, the only significant independent predictor of very late stent thrombosis (N = 9) was Taxus stent use ($P = 0.021$). It is important to note that patients who were lost to follow-up and those who died before 6 months (N = 33 and 36, respectively) were removed from the data set, while those with treated stent thrombosis before 6 months were retained. As a consequence the hazard ratio for very late stent thrombosis is not based on the full group as randomized, and there is the possibility of survival bias in the estimates. Furthermore, the confidence intervals for late and very late stent thrombosis hazard ratios were both quite wide due to the very low incidences of these events. The small number of events and large number of variables may create instability in the estimates; therefore these results should be interpreted with caution.

Severe clinical consequences are associated with stent thrombosis. Early stent thrombosis occurred in 17 patients, and led to 30-day death rates of 29.4%, MI of 76.5%, and TVR of 70.6%; overall mortality was 41.2%. Late stent thrombosis occurred in 4 patients, with 30-day death rates of 50.0%, MI of 75.0%, and TVR of 25.0%. One patient had been undergoing a TVR procedure for thrombosis when he died; dual antiplatelet therapy had been discontinued in preparation for this surgery four days earlier. Another patient had discontinued clopidogrel 7 days prior to the thrombotic event. Very late stent thrombosis was associated with 30-day rates of death in 0.0% of patients, MI in 88.9%, and TVR in 77.8%; overall mortality was 11.1%. Of the 9 patients with very late stent thrombosis, one had discontinued aspirin use for surgery, and another took aspirin only intermittently; none were taking clopidogrel, most likely because they had completed the recommended course of therapy.

Lemos et al. (2007) published a brief systematic review of ten clinical trials to analyze the need for repeat revascularization with CABG in patients who received DES versus those who received BMS. Pooled analysis of thrombosis rates for 4892 patients was performed. No statistically significant difference in thrombosis rates was identified in either the pooled studies or in any of the individual studies. The follow-up period was not specified so it is not clear whether early or late stent thrombosis was analyzed or whether follow-up times were similar between all the studies. Quantitative heterogeneity was not analyzed. Very little information was given regarding the studies used and the conclusions drawn about thrombosis, and the results should be interpreted accordingly.

Table I4. Restenosis in general populations: summary of finding from meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Lemos et al. (2007)	Pooled analysis of 10 RCTs (N = 4892) (DES vs BMS)	RR (95% CI): • 0.30 (0.21–0.43) favoring DES	• There was significantly less restenosis in patients treated with DES versus BMS. • 7 RCTs favored DES, 3 found NS difference between DES and BMS,	• Follow-up NR. • Random effects (RE) model used. • Results also inspected for differences if FE model used. • Quantitative heterogeneity* not assessed.

BMS = bare-metal stent, CI = confidence interval, DES = drug-eluting stent, FE = fixed effects meta-analysis model, NR = not reported, NS = not statistically significant, OR = odds ratio, PES = paclitaxel-eluting stent, RCT = randomized controlled trial, RE = random effects meta-analysis model, SES = sirolimus-eluting stent.
* Quantitative heterogeneity considered statistically significant: χ^2 test ($P \leq 0.10$) or I^2 statistic (≥40%).

Lemos et al. (2007) published a brief systematic review of ten clinical trials. The authors performed pooled estimates of restenosis rates for 4892 patients treated with either DES or BMS and found that restenosis rates were significantly lower in the DES group. The follow-up period was not specified. Quantitative heterogeneity was not analyzed, but seven of the ten studies favored DES while three had no statistically significant difference for either group. Very little information was given regarding the studies used and the conclusions drawn about restenosis, as the focus of the review was future need for CABG.

Safety in Special Populations

Diabetes

Table I5. Thrombosis in patients with diabetes: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kirtane (2008)	Patient-level pooled analysis of 5 RCTs comparing DES (paclitaxel-eluting) vs. BMS. No studies specifically enrolled diabetic patients. Total N=827	Stent Thrombosis (4 yr. follow-up) *Per Protocol* • DES: 1.4% (4); BMS: 1.2% (5) • HR (95% CI): 0.83 (0.22, 3.09) *ARC Definition (all)* • DES: 4.8% (15); BMS: 3.1% (11) • HR (95% CI): 1.38 (0.63, 3.00) *ARC Definition (definite/probable)* • DES: 2.2% (6); BMS: 1.4% (4) • HR (95% CI): 1.22 (0.37, 4.01)	Stent Thrombosis • NS differences at 4 years of follow-up.	• Cox PH Regression used • Analyses were truncated at 4 years of follow-up • No information was supplied regarding the use of antiplatelet therapies by study participants. • 827 patients enrolled in the 5 trials had diabetes; 408 received DES, 419 received BMS. • Results from analyses using ARC definitions of thrombosis were restricted to a subset of trials.
Kumbhani (2008)	Meta-analysis performed on 16 RCTs comparing DES (either	Stent Thrombosis (8-12 mo. follow-up) • DES: 0.4%; BMS: 1.4% • RR (95% CI): 0.41 (0.13, 1.27)	Stent Thrombosis • NS differences at 8-12 months of follow-up.	• Results from random-effects (RE) models reported • Heterogeneity across studies was assessed using the Cochrane Q

	paclitaxel-eluting or sirolimus-eluting) vs. BMS. 5 studies enrolled diabetic subjects exclusively. Total N=2,951			test • Publication bias was assessed using Begg's funnel plot • Clinical follow-up data were reported at 8-12 months; angiographic follow-up data were reported at 6-12 months • Antiplatelet therapy • In 13 studies, loading doses of 325 mg of aspirin and 300 to 600 mg of clopidogrel were administered prior to the procedure. • In 3 studies, loading doses of 325 mg of aspirin and either 300 to 600 mg of clopidogrel or 500 mg of ticlopidine were administered prior to the procedure. • In all studies, patients received indefinite maintenance therapy of 100 to 325 mg of aspirin daily and either 75 mg of clopidogrel daily or 250 mg ticlopidine once to twice daily. • Studies were excluded if paclitaxel or sirolimus were given orally, if non-polymeric stents were used or if newer generation drug-eluting stents were used.

Patti (2008)	Meta-analysis of 9 RCTs comparing DES vs. BMS.
	1 trial specifically enrolled diabetic patients; 8 trails reported post hoc outcome analyses on subsets of diabetic patients.
	Not all studies were used for all outcomes.
	Total N: 1,141
		<u>Stent Thrombosis (12 mo. follow-up)</u>
		• DES: 1.1%; BMS: 1.2%
		• OR (95% CI): 0.98 (0.31, 3.13)
			<u>Stent Thrombosis</u>
			• NS differences at 12 months of follow-up.
				• Fixed-effects (FE) estimates reported
				• Random effects (RE) estimates calculated; did not differ signficantly from FE results
				• Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes
				• Mean duration of follow up was 12 months (range: 8 to 24)
				• Anti-platelet therapies
				  • Aspirin (≥ 75mg/day) given prior to procedure and continued indefinitely in all studies
				  • Loading dose of clopidogrel (300 mg) was administered prior to procecdure in all studies
				  • Clopidogrel (75 mg/day) was recommended for 2 months in 4 studies, for 3 months in one study; for 6 months in 3 studies, and for 1 year in 1 study
				  • No data on compliance available

Stettler (2008)	Meta-analysis performed on 35 RCTs comparing DES (either paclitaxel-eluting or sirolimus-eluting) vs. BMS
	Four trials specifically enrolled subjects with diabetes.
	Not all trials were used for all analyses.
		<u>Stent Thrombosis</u>
		<u>Overall – 0-4 yr follow-up</u>
		Per Protocol
		• PES: 2.0% (18); SES: 0.8% (7); BMS: 2.2% (16)
		• RR (95% CI):
		  o PES vs. BMS: 0.73 (0.19, 2.80)
		• RR (95% CI):
		  o SES vs. BMS: 0.20 (0.05, 0.68)
		Per ARC Definition
		• PES: 1.9% (17); SES: 1.1% (9); BMS: 2.3% (13)
		• RR (95% CI):
			<u>Stent Thrombosis</u>
			• Overall results – NS differences over 4 years of follow-up, except for the comparison between per protocol events for SES and BMS – the point estimate indicates an 80% reduction in the risk of thrombosis, this difference was statistically significant.
				• Hierarchial random effects (RE) model used.
				• ARC and protocol definitions of thrombotic events were applied and compared.
				• Heterogeneity between trials and goodness of fit of the model to the data were both evaluated
				• Inconsistency of the network was defined as the variablilty of results across different comparisons of the network. This was assessed by calculating inconsistency factors: the estimated difference between the log hazard ratios from direct comparisons within randomized trials and the log

	Total N=3,852	o PES vs. BMS: 0.82 (0.23, 3.09) • RR (95% CI): o SES vs. BMS: 0.33 (0.09, 1.09) <u>Early – 0-30 days follow-up</u> *Per Protocol* • PES: 1.1% (10); SES: 0.6% (5); BMS: 1.5% (11) • RR (95% CI): o PES vs. BMS: 0.55 (0.09, 3.05) • RR (95% CI): o SES vs. BMS: 0.23 (0.03, 1.08) *Per ARC Definition* • PES: 1.0% (9); SES: 0.8% (6); BMS: 2.0% (11) • RR (95% CI): o PES vs. BMS: 0.39 (0.05, 2.36) • RR (95% CI): o SES vs. BMS: 0.25 (0.04, 1.11) <u>Late – 31 days – 4 yrs follow-up</u> *Per Protocol* • PES: 0.9% (8); SES: 0.2% (2); BMS: 0.7% (5) • RR (95% CI): o PES vs. BMS: 0.87 (0.06, 10.3) • RR (95% CI): o SES vs. BMS: 0.10 (0.01, 0.93) *Per ARC Definition* • PES: 0.9% (8); SES: 0.4% (3); BMS: 0.4% (2) • RR (95% CI): o PES vs. BMS: 3.54 (0.23, 78.6) • RR (95% CI): o SES vs. BMS: 0.72 (0.04, 10.8)	• Early events – NS for both definitions of events and for both types of DES. • Late events – NS differences, except for the comparison of per protocol events for SES and BMS – the point estimate indicates an 89% reduction in the risk of thrombosis, this difference was statistically significant.	hazard rations from indirect comparisons between randomized trials with one intervention in common. • The variable for duration of anti-platelet therapy specified in the trial protocols had a treatment by trial characteristic interaction term with a p-value less than 0.05, thus the authors restricted their analyses to trials with a duration of six months or longer and compared the results.

- Kirtane et al. (2008) analyzed patient-level pooled data from 5 RCTs that compared DES (paclitaxel-eluting) with BMS. Their dataset was comprised of 827 subjects with diabetes who were recruited as part of one of five TAXUS trials (I, II, IV, V, and VI). The TAXUS trials were also included in the network meta-analysis performed by Stettler et al. Subjects were followed for up to four years in all studies. The incidence of stent thrombosis in DES patients was 1.3%, in BMS patients it was 0.8% (p-value=0.16). Analyses were also done comparing outcomes between non insulin-dependent and insulin-dependent diabetic subjects; no significant differences in the rates of stent thromboses for patients receiving DES vs. those receiving BMS were seen between these two types of diabetic patients. These results should be interpreted with caution, however, as they are based on very few events. Tests for quantitative heterogeneity were not statistically significant. This meta-analysis is methodologically sound, but is limited by a relatively small number of subjects who could be included from the TAXUS trials.

- Kumbhani et al. (2008) conducted a meta-analysis comparing DES to BMS in diabetic patients (N=2,951). Sixteen studies were included; clinical follow-up data were reported at 9 to 12 months and angiographic follow-up data were reported at 6 to 12 months. All of the studies included in this meta-analysis were also analyzed by Stettler et al. in their 2007 network meta-analysis. Studies were judged to be of high quality according to the criteria suggested by Jadad et al. Heterogeneity across studies was assessed using the Cochrane *Q* test and measured inconsistency across trials; no heterogeneity was found for the outcome of stent thrombosis. Begg's funnel plot was used to assess potential publication bias. The incidence of stent thrombosis was 0.4% for subjects who received DES and 1.4% for subjects who received BMS (RR (95%CI) 0.41 (0.13, 1.27)); this difference was not statistically significant. Forest plots were depicted and suggest that none of the individual studies found a significant difference in the risk of stent thrombosis between the DES and BMS groups, although the point estimates for all studies favored DES. The authors did not present separate results for early vs. late thrombotic events, so no conclusions can be inferred regarding the impact of the type of stent on the rates of early and late thrombotic events. In addition, because thrombosis was a relatively rare event, this meta-analysis may be underpowered to detect a true difference between rates of thrombosis in the two groups.

- Patti et al. (2008) conducted a meta-analysis of 9 trials which included 1,141 subjects with diabetes. All of the trials included in their analyses were also part of the network meta-analyses conducted by Stettler et al. Studies were evaluated for quality on the basis of adequacy of allocation concealment, adherence to the intent-to-treat principle, and degree of blinding for assessment of outcomes. Heterogeneity was assessed using Q statistics and measured inconsistency across trials. Both fixed-effects and random-effects methods were used to estimate pooled odds ratios; fixed-effects results are reported. Funnel plot analysis were used to assess publication bias; the funnel plots are displayed in the paper. The incidence of stent thrombosis was 1.1% for subjects who received DES vs. 1.2% for subjects who received BMS (OR (95%CI): 0.98 (0.31, 3.13)); this difference was not statistically significant. Forest plots were depicted and suggest that one of the studies found a significant difference in the risk of stent thrombosis between the DES and BMS groups. In addition, the direction of the association was not consistent across studies. The authors did not present separate results for early vs. late thrombotic events, so no conclusions can be inferred regarding the impact of stent type on the rates of these different events. In addition, because thrombosis was a relatively rare event, this meta-analysis may be underpowered to detect a true difference between rates of thrombosis in the two groups.

- Stettler et al. (2008) published a network meta-analysis that served as an expanded and updated version of their 2007 meta-analysis. Outcomes for patients with and without diabetes were compared for PES, SES, and BMS. A total of 35 RCTs (N = 14,799) with follow-ups of at least 6 months were included. The trials used in the network meta-analysis were: BASKET, C-SIRIUS, CORPAL, DECODE, DIABETES, E-SIRIUS, ISAR-DESIRE, ISAR-DIABETES, ISAR-SMART3, LONG-DES, MISSION, PASSION, PRISON II, RAVEL, REALITY, RRISC, SCANDSTENT,

SCORPIUS, SELECTION, SESAMI, SES-SMART, SIRIUS, SIRTAX, TAXi, TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI, TYPHOON, and the studies conducted by Cervinka et al., Erglis et al., Pache et al., and Petronio et al. This network meta-analysis represents the most comprehensive list of RCTs comparing DES with BMS available. Stent thrombosis was evaluated in detail, though the primary safety outcome was overall mortality. The authors reported protocol-defined as well as "definite" ARC-defined stent thrombosis, the latter to ensure inclusion of "secondary" stent thrombosis following TVR. In order to minimize variation, thrombosis rates in trials whose patients received dual antiplatelet therapy for at least six months were reported separately. Five trials specified 2 months of dual antiplatelet therapy, three specified 3 months, eighteen specified 6 months, one specified 9 months, and eight specified 12 months. All trials with less than 6 months of dual antiplatelet therapy compared SES with BMS. Detailed results of this trial are included in Appendix F. Hazard ratios for overall (0 days to 4 years), early (0 to 30 days), and late (31 days to 4 years) rates of stent thrombosis in diabetic patients suggest that there is no significant increase in risk with DES compared to BMS.

Table I6. Restenosis in patients with diabetes: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kimura et al. (2008)	Meta-analysis of 3 RCTs: TAXUS IV, V, VI (N = 956) (PES vs BMS) Diabetes present in 28.6% (N = 273) of patients	Mean (25% to 75% percentile): • Angiographic in-stent; in-segment diameter stenosis (%): PES/diabetics: 22.5 (7.9–32.2); 32.3 (18.7–38.9) BMS/diabetics: 43.6 (26.9– 62.3); 46.9 (31.6– 63.6) ($P < 0.0001$ for both above comparators) • IVUS IH volumes (mm3), %IH at 9 months: PES/diabetics: 29.7 (3.4–42.5); 13.7 (3.0–22.7) BMS/diabetics: 78.9 (37.6–106.4); 34.9 (23.9–46.4) ($P < 0.0001$ for both above comparators)	• There was significantly less restenosis in diabetic patients who were treated with PES versus BMS.	• All patients underwent serial volumetric IVUS analysis immediately after stenting and again at 9 months' follow-up. • Individual patient data used. • Small sample size. • Heterogeneity was assessed using the Breslow-Day test, which tests for differences in treatment effects across studies • Short-term follow-up for IVUS. • Follow-up period not specified for angiography.
Kumbhani (2008)	Meta-analysis performed on 16 RCTs comparing DES (either paclitaxel-eluting or sirolimus-eluting) vs. BMS. 5 studies enrolled diabetic subjects exclusively. Total N=2,951	<u>In-segement Restenosis</u> • RR (95% CI): 0.31 (0.25, 0.40) • RD (95% CI): 28.4% (24.1, 32.7)	<u>In-segment Restenosis</u> • Diabetic subjects receiving DES were approximately two-thirds less likely to experience restenosis as compared with those receiving BMS; this difference was statistically significant	• Results from random-effects (RE) models reported • Heterogeneity across studies was assessed using the Cochrane Q test • Publication bias was assessed using Begg's funnel plot • Clinical follow-up data were reported at 8-12 months; angiographic follow-up data were reported at 6-12 months • Antiplatelet therapy • In 13 studies, loading doses of 325 mg of aspirin and 300 to 600 mg of clopidogrel were administered prior to the procedure. • In 3 studies, loading

				doses of 325 mg of aspirin and either 300 to 600 mg of clopidogrel or 500 mg of ticlopidine were administered prior to the procedure. • In all studies, patients received indefinite maintenance therapy of 100 to 325 mg of aspirin daily and either 75 mg of clopidogrel daily or 250 mg ticlopidine once to twice daily. • Studies were excluded if paclitaxel or sirolimus were given orally, if non-polymeric stents were used or if newer generation drug-eluting stents were used.

Patti (2008)	Meta-analysis of 9 RCTs comparing DES vs. BMS.
	1 trial specifically enrolled diabetic patients; 8 trails reported post hoc outcome analyses on subsets of diabetic patients.
	Not all studies were used for all outcomes.
	Total N: 1,141
		<u>In-segment Restenosis (12 mo. follow-up)</u>
		• RR (95% CI): 0.13 (0.09, 0.20)
			<u>In Segment Restenosis</u>
			• The risk of restenosis for diabetic subjects who received DES is approximately one-eighth that of diabetic subjects who received BMS; this difference is highly statistically significant.
				• Fixed-effects (FE) estimates reported
				• Random effects (RE) estimates calculated; did not differ signficantly from FE results
				• Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes
				• Mean duration of follow up was 12 months (range: 8 to 24)
				• Anti-platelet therapies
				  • Aspirin (≥ 75mg/day) given prior to procedure and continued indefinitely in all studies
				  • Loading dose of clopidogrel (300 mg) was administered prior to procecdure in all studies
				  • Clopidogrel (75 mg/day) was recommended for 2 months in 4 studies, for 3 months in one study; for 6 months in 3 studies, and for 1 year in 1 study
				  • No data on compliance available

* Quantitative heterogeneity considered statistically significant: χ^2 test ($P \leq 0.10$) or I^2 statistic (≥40%).

- Kimura et al. (2008) conducted a meta-analysis using individual patient data from a subgroup of 956 patients who had undergone mandatory serial volumetric intravascular ultrasound (IVUS) in three of the Taxus trials (IV, V, VI). Angiographic results suggested that diabetic patients had significantly lower rates of restenosis when they had been treated with PES rather than BMS ($P < 0.0001$ for both); in contrast, diabetic patients who received BMS had higher restenosis rates

than their non-diabetic counterparts ($P \leq 0.0026$). No statistically significant difference was found between diabetic and non-diabetic patients treated with PES, or between any of the four patient groups at pre- and post-procedure angiography. IVUS was used to acquire intravascular measurements indicative of restenosis. At 9 months follow-up, diabetic patients treated with BMS had greater intimal hyperplasia (IH) volumes and percentage IH (IH divided by stent) than did non-diabetics ($P = 0.0095$ and $P = 0.0186$, respectively). However, both diabetic and non-diabetic patients who received PES had similar IH volumes and percentage IH's ($P = 0.35$ and $P = 0.27$, respectively). Similarly, diabetic patients treated with PES instead of BMS had significantly lower IH volumes and less percentage IH, which led to greater minimal luminal areas and volumes as well as longer neo-intimal-free stented regions in PES-treated diabetic patients ($P < 0.0001$ for all outcomes except $P < 0.0038$ for minimum luminal areas and $P < 0.0318$ for luminal volumes). These results suggest that when treated with BMS, diabetic patients have higher rates of restenosis than non-diabetics, but that the use of PES "neturalized the adverse impact of diabetes on producing excess neointimal proliferation." Limitations to this study include relatively small sample sizes and short follow-up.

- Kumbhan*i* et al. (2008) conducted a meta-analysis comparing DES to BMS in diabetic patients (N=2,951). Sixteen studies were included; clinical follow-up data were reported at 9 to 12 months and angiographic follow-up data were reported at 6 to 12 months. The authors included results from the TAXUS II, IV, V, and VI trials which were also included in the analysis by Kirtane et al, but this study added additional data from other trials thus expanding their subject population. Studies were judged to be of high quality according to the criteria suggested by Jadad et al. Heterogeneity across studies was assessed using the Cochrane *Q* test and measured inconsistency across trials; no heterogeneity was found for the outcome of stent thrombosis. Begg's funnel plot was used to assess potential publication bias. The incidence of in-segment restenosis was 11.5% for subjects who received DES and 38.7% for subjects who received BMS (RR (95%CI) 0.31 (0.25, 0.39)); this difference was highly statistically significant. Forest plots were depicted and suggest that all of the individual studies found a significant difference in the risk of in-segment restenosis between the DES and BMS groups

- Patti et al. (2008) conducted a meta-analysis of 9 trials which included 1,141 subjects with diabetes. Eight out of nine studies (DIABETES, RAVEL, SES-SMART, SIRIUS, E-SIRIUS and TAXUS II, IV, VI) were included in the meta-analysis performed by Kumbhani et al; Patti et al. also included data from C-SIRIUS in their analyses. Studies were evaluated for quality on the basis of adequacy of allocation concealment, adherence to the intent-to-treat principle, and degree of blinding for assessment of outcomes. Heterogeneity was assessed using Q statistics and measured inconsistency across trials. Both fixed-effects and random-effects methods were used to estimate pooled odds ratios; fixed-effects results are reported. Funnel plot analysis were used to assess publication bias; the funnel plots are displayed in the paper. The incidence of in-segement restenosis was 8% for subjects who received DES vs. 41% for subjects who received BMS (OR (95%CI): 0.13 (0.09,

0.20)); this difference was highly statistically significant. Forest plots were depicted and suggest that all but one of the studies (TAXUSII) found a significant difference in the risk of in-segment restenosis between the DES and BMS groups.

Intermediate Lesions (< 50% diameter stenosis as defined by QCA)

Table I10. Thrombosis in patients with intermediate lesions: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Moses (2006)	Meta-analysis of patient-level data from four RCTs comparing DES vs. BMS among patients with intermediate lesions. (N=167)	Stent Thrombosis DES: 0% (0); BMS: 0% (0); p-value=NA	Stent Thrombosis No patients suffered a thrombotic event during the 1 year of follow-up for this study.	Cox PH Regression was used Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Three trials recommended clopidogrel therapy for 6 months post-procedure, the fourth recommended 3 months. 6.7% of patients from the four specified trials were able to be included. Assessment of outcomes varied across trials Clinical outcomes were assessed in-hospital, at 30 days post-procedure, and at 1 year post-procedure; angiographic outcomes were assessed at 6-9 months post-procedure

Moses et al. (2006) collected patient-level from four trials on subjects who were classified as having intermediate lesions (<50% diameter stenosis as defined by QCA). All four trials (SIRIUS, TAXUS-IV, and FUTURE-I and –II) required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. At 1 year, no subjects had suffered a thrombotic event. While this study provides useful information regarding the safety and effectiveness of DES vs. BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution. In particular, given that thrombosis is generally a relatively rare event, it is likely that this study is underpowered to detect a difference in risk between the two types of stents studied.

Table I11. Restensosis in patients with intermediate lesions: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Moses (2006)	Meta-analysis of patient-level data from four RCTs comparing DES vs. BMS among patients with intermediate lesions. (N=167)	Binary Restenosis – Analysis Segment DES: 1.8%; BMS: 34.0%; p-value<0.0001 Binary Restenosis – In-stent DES: 1.8%; BMS: 32.1%; p-value<0.0001	Stent Thrombosis Subjects in the DES group were much less likely to experience restenosis than those in the BMS group; this difference was highly statistically significant.	Cox PH Regression was used Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Three trials recommended clopidogrel therapy for 6 months post-procedure, the fourth recommended 3 months. 6.7% of patients from the four specified trials were able to be included. Assessment of outcomes varied across trials Clinical outcomes were assessed in-hospital, at 30 days post-procedure, and at 1 year post-procedure; angiographic outcomes were assessed at 6-9 months post-procedure

Moses et al. (2006) collected patient-level from four trials on subjects who were classified as having intermediate lesions (< 50% diameter stenosis as defined by QCA). All four trials (SIRIUS, TAXUS-IV, and FUTURE-I and –II) required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Restenosis in the analysis segment occurred in 1.8% of the DES group vs. 34.0% of the BMS group. In-stent restenosis occurred in 1.8% of the DES group vs. 32.1% of the BMS group. Both of these differences were highly statistically significant. While this study provides useful information regarding the safety and effectiveness of DES vs. BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution.

Table I12. Late luminal loss in patients with intermediate lesions: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Moses (2006)	Meta-analysis of patient-level data from four RCTs comparing DES vs. BMS among patients with intermediate lesions. (N=167)	Late luminal loss – Analysis Segment DES: 0.15 ± 0.34 (mm) BMS: 0.68 ± 0.71 (mm) p-value<0.0001 Late luminal loss – In-stent DES: 0.15 ± 0.38 (mm) BMS: 0.86 ± 0.71 (mm) p-value<0.0001	Stent Thrombosis Subjects in the DES group had less late luminal loss at follow-up as compared with the BMS group; this difference was highly statistically significant.	Cox PH Regression was used Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Three trials recommended clopidogrel therapy for 6 months post-procedure, the fourth recommended 3 months. 6.7% of patients from the four

				specified trials were able to be included. Assessment of outcomes varied across trials Clinical outcomes were assessed in-hospital, at 30 days post-procedure, and at 1 year post-procedure; angiographic outcomes were assessed at 6-9 months post-procedure.

Moses et al. (2006) collected patient-level from four trials on subjects who were classified as having intermediate lesions (<50% diameter stenosis as defined by QCA). All four trials (SIRIUS, TAXUS-IV, and FUTURE-I and –II) required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Mean difference in lumen diameter for the analysis segment was 0.15 ± 0.34 mm in the DES group as compared with 0.68 ± 0.71 mm in the BMS group. The in-stent mean difference in lumen diameter was 0.15 ± 0.38 mm in the DES group as compared with 0.86 ± 0.71 mm in the BMS group. Both of these differences were highly statistically significant. While this study provides useful information regarding the safety and effectiveness of DES vs. BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution.

Acute Myocardial Infarction (AMI)

Table I13. Thrombosis in patients with AMI: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kastrati (2007)	Meta-analysis of 8 RCTs comparing DES vs. BMS among patients with acute ST-segment elevation myocardial infarction. Patient-level data was available for 7 trials. N=2786	Stent Thrombosis DES: 1.7% (25); BMS: 29% (29) HR (95% CI): 0.80 (0.46, 1.39)	Stent Thrombosis NS differences at 12 months of follow-up.	Mantel-Cox method was used to perform survival analyses. Cochrane's test was used to assess heterogeneity across trials. I^2 statistic was also calculated to measure the consistency of among trials. Hazard ratios from individual trials were pooled using random effects methods. Sensitivity analyses wer conducted by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 3 trials.
Paceri (2007)	Meta-analysis of 7 RCTs on use of DES vs. BMS in patients with AMI, N = 2357 patients; (DES:	Stent Thrombosis DES: 2.3% (27); BMS: 2.6% (31) RR (95% CI): 0.87 (0.53, 1.45) *P* = 0.60	Stent Thrombosis NS difference at 8-12 months. Forest plots were depicted: 5/7 studies favored DES; results were not	Mantel-Haenszel fixed-effects model was used to estimate pooled RRs. There was no significant heterogeneity: heterogeneity across trials was evaluated with Q statistics; the extent of

	1177, BMS: 1180) F/U 8-12 months RCTS: 1 published only as an abstract, 3 presented at interentional conferences and were available electronically. Pasceri STRATEGY PASSION TYPHOON SESAMI HAAMU-STENT MISSION		statistically significant any of the trials.	inconsistency across trials was evaluated with I^2 statistics (significant heterogeneity if $P < 0.10$ and/or $I^2 = 50\%$). Sensitivity analysis not performed. Results were not adjusted. Funnel plot analysis demonstrated no publication bias. Two trials used PES, 5 used SES; type of BMS was operator-choice. Routine angiographic follow-up performed in 5 trials and in a subgroup of 1 trial. Definition of stent thrombosis used was not specified. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 2 trials. 3 studies published in peer-reviewed journals, 1 published only as an abstract, 3 presented at interentional conferences and were available electronically.

Kastrati et al. (2007) conducted a meta-analysis of randomized trials which compared DES (either paclitaxle-eluting or sirolimus-eluting) with BMS among patients with acute ST-elevation myocardial infarctions. The authors identified 8 trials with follow-up of at least 12 months; patient-level data was available for 7 of these trials. The trials included BASKET-AMI, HAAMU-STENT, MISSION, PASSION, SESAMI, STRATEGY, and the trial conducted by Di Lorenzo et al; 2,786 subjects were included. The authors used Cox proportional hazards regression, stratified by trial, to analyze their results for the trials with patient-level data. Hazard ratios calculated from data from indiviudal trials were pooled using the random effects method of DerSimonian and Laird. Heterogeneity of the treatment effect was evaluated by the Cochrane test; the I^2 statistic was also calculated to assess consistency among trials. At 1 year, the incidence of stent thrombosis was 1.7% in the DES group and 2.2% in the BMS group; this difference was not statistically significant (HR (95% CI) 0.76 (053, 1.10)). A forest plot was depicted, showing the results from the individual trials included. Two trials (BASKET-AMI and SESAMI), found that the risk of stent thrombosis was elevated in the DES group as compared to the BMS group, while the rest of the studies found either a reduced risk or no association between stent thrombosis and stent type. However, none of the associations were statistically significant. Overall, the authors conclude that the use of DES in persons with acute myocardial infarction is safe and appropriate.

Pasceri et al. (2007) analyzed the outcomes of acute ST elevation myocardial infarction (STEMI) patients treated with DES or BMS from seven RCTs (N = 2357). One major drawback to this analysis is that the source of data for three of the studies was online records of presentations at international meetings rather than the peer-reviewed literature

(SESAMI, HAAMU-STENT, and MISSION trials, available at www.cardiosource.com); furthermore, one included study had only preliminary results available and had been published in abstract only (Pasceri et al., 2003). Most of the patients were male (72% to 82%). The incidence of stent thrombosis in DES patients was 2.3% and in BMS patients it was 2.6%. No significant difference was detected at 8 to 12 months follow-up in AMI patients treated with DES compared to BMS ($P = 0.60$). A Forest plot was depicted and indicated that DES was favored in five studies, BMS in one study, and neither was favored in one study; none of these results appeared to be statistically significant, however. Tests for quantitative heterogeneity were not statistically significant, and no publication bias was detected. Finally, this meta-analysis may have been underpowered, and results should be interpreted with caution.

Appendix J. Evidence Tables: Efficacy and Effectiveness of DES verus BMS in Special Populations Included in HTA and Meta-analyses
(For safety outcomes in special populations see APPENDIX I)

Results from HTA

Diabetic patients and those with long or otherwise complex lesions are considered special populations in stent research. While they are generally considered to be a higher risk for restenosis and other complications, data on these patients are lacking since they are often not enrolled in large numbers in effectiveness and safety studies on different types of stents [Iakovou, 2005, Seabra-Gomes, 2006]. In a 2006 report, the FDA found that these patients were at higher risk of stent thrombosis, although this increase was small [Farb, 2007]. These risks were deemed highest in patients who did not continue with antiplatelet therapy post-procedure [Farb, 2007]. Results from other analyses and literature reviews suggest that patients in these subgroups are more likely to benefit from a reduced rate of restenosis due to DES placement, but that they are higher risk of death and MI when DES are used as compared with BMS (CTAF 2007, Hayes 2007, KCE-Belgium 2007). However, other reports have not found these elevated risks, or have found mixed results when examining the available data (CCOHTA 2005, ECRI 2006, Hill 2007, MSAC 2004, Ontario 2007).

The following outcomes are reported:

1. Mortality
2. Major adverse cardiac events (MACE)
3. Target Vessel Revascularization (TVR)
4. Target Lesion Revascularization (TLR)
5. Late Loss

Outcome 1, defined as either all-cause mortality or cardiac mortality, was examined in 3 HTAs included in this report

Outcome 2, defined as cardiac mortality or myocardial infarction, was examined in 1 HTA included in this report.

Outcome 3, defined as percutaneous revascularization or bypass of the target lesion or any segment of the epicardial coronary artery containing the target lesion, was examined in 1 HTA included in this report.

Outcome 4, defined as percutaneous revascularization or bypass of the target lesion, was examined in 1 HTA included in this report.

Outcome 5, defined as in-stent thrombosis occurring at least 3 months post-procedure, was examined in 2 HTAs included in this report.

Previous HTAs: A summary of findings from other HTAs is found in the table below.

Table J1. Summary of results reported in previous HTAs related to special populations

Author (Year)	Evidence Base and Approach	Effect size	Conclusions	Comments
CCOHTA (2005)	Decision analytic model based on clinical trial data and commonly accepted treatment alogorithims for acute coronary syndrome developed to assess the cost-effectiveness of DES vs. BMS	None reported	None	• The authors state that patients with diabetes are at higher risk of restenosis after treatment. • They conclude that DES are more cost-effective in patients at higher risk of restenosis.
CTAF (2007)	Literature review and critique of available RCTs, meta-analyses, and registries	None reported	None	• The authors conclude that the risk of death and myocardial infarction is elevated in patients with complex lesions and those with comorbidities such as diabetes. • The authors did not find any evidence that patients aged 65 years and over differed with regard to safety and efficacy as compared with younger patients.
ECRI (2006)	Literature review and critique of available RCTs, meta-analyses, and registries	None reported	None	• The authors draw no conclusions about the effectiveness, efficacy or safety of DES in special populations as compared with BMS
Hayes (2007)	Literature review and critique of available RCTs, meta-analyses, and registries. Two studies enrolled only diabetic subjects; one (DIABETES) compared DES vs. BMS, while the other compared two different types of DES. Results for subgroup analyses from meta-analyses also presented.	Diabetes Mortality [Kastrati, 2007] OR (95% CI) • 1.27 (NS) Major Adverse Cardiac Events (MACE) [Jimenez-Quevedo, 2007] • 9 months: 10% in DES group vs. 36.3 in BMS (p-value <0.001) Target Lesion Revascularization (TLR) [Jimenez-Quevedo, 2007] • 9 months: 6.3% in DES group vs. 31.3% in BMS group (p-value <0.001)	Diabetes Mortality NS differences reported from meta-analysis. MACE • Significant differences at 9 months between DES and BMS groups; results favor DES in this population TLR • Significant differences at 9 months between DES and BMS groups; results favor DES in this population	• The authors describe several subgroup analyses in the text of the file indicating that DES performed better in diabetic patients than BMS, however statistical evidence regarding the strength of these associations was not included. • The authors conclude that DES are more effective in special populations, including patients with diabetes and long lesions, but that results on safety endpoints are mixed and inconclusive.

Author (Year)	Evidence Base and Approach	Effect size	Conclusions	Comments

Hill (NICE/ NHS) (2007){Hill, 2007 #140}	Meta-analysis performed on 17 RCTs comparing DES vs. BMS as part of HTA. Two studies enrolled only diabetic subjects; one (DIABETES) compared DES vs. BMS; the other compared two different types of DES.	Diabetes Late Loss [Jimenez-Quevedo, 2007] WMD (95%CI) • At 9 months: o -0.58 (-0.73, -0.43)	Diabetes Late Loss • Results presented for DIABETES study favor DES; difference is statistically significant	• Separate meta-analysis on special populations not conducted • Effect size and conclusions are based on data presented for one study (DIABETES) • ISAR-DIABETES also enrolled exclusively diabetic subjecs, but studied two types of DES
KCE-Belgian (2007)	Previously published meta-analyses – four of which are highlighted for safety	**Diabetes** Mortality [Kastrati, 2007] HR (95%CI) • 2.90 (1.38,6.10) [Stettler, 2007] • 1.24 (0.74,1.87) SES vs. BMS • 1.16 (0.78,1.84) PES vs. BMS Late Loss [Sabate, 2005] • 0.06 ± 0.4 vs. 0.47 ± 0.5mm (DES vs. BMS; p-value <0.001)	**Diabetes** Mortality • Diabetic patients receiving DES were more likely to die; this difference is statistically significant • Diabetic patients receiving DES were more likely to die; this difference is not statistically significant • Late loss (measured at 9 months) was reduced in diabetic patients receiving DES as compared to those receiving BMS; this difference is statistically significant.	• Results from a registry were also reported o Two-year cumulative incidence of mortality was not statistically different between diabetic patients receiving DES and those receiving BMS. o In-stent thrombosis was higher in the DES group; however it is not stated whether this difference is statistically significant.
MSAC (2004)	Literature review and critique of RCTs and available studies	None reported	None	• The authors state that there is insufficient evidence to draw conclusions about effectiveness and efficacy in special populations. • The authors state that the available data from RCTs does indicate a statistically significant reduction in revascularization procedures and MACE in diabetic patients and those with long lesions at up to 12 months of follow-up.

Author (Year)	Evidence Base and Approach	Effect size	Conclusions	Comments
Ontario (2007)	Literature review, data analysis of an observational study, and cost-effictiveness analysis	Mortality RD (95% CI) Without prior MI • 6 months: -1.05% (-2.04%, -0.06%) • 7-24 months: -0.82% (-1.79%, 0.15%) With prior MI • 6 months: -4.21% (-7.98%, -0.44%) • 7-24 months: -1.58% (-2.86%, -0.30%) Target Vessel Revascularization (TVR) Log-rank p-value <0.01, favoring DES over BMS in patients without prior MI	Mortality • At 6 months, patients in the DES group with diabetes, but without prior MI were less likely to die than those in the BMS group; this difference was statistically significant • At 7-24 months, patients in the DES group with diabetes, but without prior MI were less likely to die than those in the BMS group; this difference was not statistically significant • At 6 months, patients in the DES group with diabetes and prior MI were less likely to die than those in the BMS group; this difference was statistically significant	• While the authors found a reduced risk of mortality in the DES group, they urge caution as they were not able to identifiy the cause of death. In addition there are possible confounders that are unaccounted for, including unbalanced allocation of patients to DES and BMS group.

		Log-rank p-value=0.09, NS difference in patients with prior MI	• At 7-24 months, patients in the DES group with diabetes and prior MI were less likely to die than those in the BMS group; this difference was statistically significant <u>Target Vessel Restenosis (TVR)</u> • In patients without prior MI, DES was associated with lower rates of TVR; this difference was significant. • In patients with prior MI, DES was associated with lower rates of TVR; this difference, however, was not significant.	

CCOHTA: The authors did not provide any estimates of effect size in subgroup populations. They state that diabetic patients are at higher risk of restenosis after treatment, and their cost-effectiveness analyses indicate that DES are more cost-effective in higher-risk patients such as diabetics.

CTAF: The authors did not provide any estimates of effect size in subgroup populations. They conclude, based on the literature, that the risk of death and myocardial infarction is elevated in patients with complex lesions and those with such comorbidities as diabetes.

ECRI: The authors did not provide any estimates of effect size in subgroup populations. They draw no conclusions about effectiveness, efficacy, or safety of DES in special populations as compared with BMS.

Hayes: The authors did not provide estimates of effect size in subgroup populations as part of their analyses; data on the DIABETES study, which enrolled exclusively diabetic patients, was available in the text. This study found a reduction in MACE and TLR in patients receiving DES vs. those receiving BMS; these differences were statistically significant. Hayes et al. did provide an estimate of mortality data from a meta-analysis paper - Kastrati et al. found that there was no statistically significant difference in rates of all-cause mortality between patients receiving DES vs. those receiving BMS [Kastrati, 2007]. The authors describe several subgroup analyses in the text of the document that indicate that DES performed better in diabetic patients than BMS, however no statistical evidence regarding the effect size or strength of these associations was included in the report. The authors conclude that DES are more effective in special populations, but that results on safety endpoints are inconclusive.

Hill: The authors did not perform separate meta-analyses on special population subgroups. However, data from the DIABETES trial, which enrolled only diabetic patients, was included in the report. These data indicate that DES were associated with a lower rate of late loss in diabetic patients.

KCE-Belgium: The authors do present some limited subgroup analyses in their report. They find mixed results with regards to mortality in diabetic patients. One meta-analysis found an elevated risk; another found no statistically significant differences between mortality rates for DES vs. BMS recipients. The authors also included data on the late

loss outcome from the DIABETES trial; these data indicate that DES were associated with a lower rate of late loss in diabetic patients as compared with BMS.

MSAC: The authors provide no estimates of effect size in special populations, and state that there is insufficient evidence to draw conclusions about effectiveness of DES in these populations.

Ontario: The authors show results from an observational study, which indicate that there may be a reduction in mortality risk among diabetic patients who receive DES as compared to BMS; not all estimates presented are statistically significant. They also found in a reduced rate of TVR among DES recipients in this study.

As the DIABETES trial is the only available RCT to compare DES with BMS in this population, most of the results described above come from this population. Clearly, this presents a problem, as over-reliance on one study may bias the information presented inappropriately. None of the HTAs described above conducted independent meta-analyses of subgroup populations, and none are able to draw definitive conclusions based on the available data.

META-ANALYSES

Table J2. Characteristics of meta-analyses and pooled analyses addressing patients with diabetes mellitus

Source	Patient n	Trial n	Focus	Most recent source/ search	Length of F/U	Length of anti-platelet therapy	Sub-groups	Funding	Comments
Meta-Analyses									
Stettler 2009	14,799	35	Death	10/2007	1-4 y	2-12 m		Swiss National Science Foundation	Network meta-analysis
Kumbhani 2008	1,879	12	TLR	2007	8-12 m	2-6 m	Type I DM	NR	Included unpublished RCTs
Patti 2008	1,141	9		2005	8-24 m	2-12 m	Type I DM	NR	
Pooled analyses									
Kirtane 2008	3,513	5	Death, restenosis	2005	2-4 y	NR	Type I DM	Cardiovascular Research Foundation	

Table J3. Characteristics of meta-analyses and pooled analyses addressing patients with special characteristics

Source	Patient n	Patient Characteristic	Trial n	Outcome	Most recent source/ search	Length of F/U	Length of anti-platelet therapy	Sub-groups	Funding	Comments
Meta-Analyses										
Pasceri 2007	2357	AMI	7	MACE	2007	8-12 m	3-12 m	Best quality studies	NR	Included unpublished RCTs
Pooled analyses										
Moses 2006	167	< 50% stenosis	4	Death or AMI	2005	6-8 m	3-6 m		NR	

AMI is acute myocardial infarction; Circ is *Circulation*; DM is diabetes mellitus; m is months; F/U is follow-up; MACE is major acute coronary events 9death, myocardial infarction, revascularization); *NEJM* is the *New England Journal of Medicine*; NR is not reported; PES is paclitaxel eluting stent; RCT is randomized controlled trial; SES is sirolimus eluting stent; y is years; TLR is target lesion revascularization .

Characteristics of meta-analyses and pooled analyses addressing patients with diabetes or other special characteristics

Stettler et al (2008) conducted a network meta-analysis comparing outcomes with SES vs BMS or PES vs BMS among patients with diabetes and among patients without diabetes; and comparing outcomes for patients with diabetes vs patients without diabetes. They identified 35 trials with 14,799 patients. Two investigators extracted data independently, enhancing objectivity. They analyzed thrombosis using both per-protocol and Academic Research Consortium definitions. They examined potential reasons for variability between trials: the period when the trial was conducted, the duration of follow-up, the duration of antiplatelet therapy, and the trial's quality. The duration of antiplatelet therapy was the only factor that influenced the effect of treatment. When they restricted the analyses to trials in which antiplatelet therapy lasted at least 6 months, heterogeneity decreased. For example, using all trials, SES showed increased risk for death compared with BMS (RR 2.37 (95% confidence interval [CI], 1.18 – 5.12). However, when the analysis was restricted to trials with at least 6 months of antiplatelet therapy, there was no increased risk for death (RR 0.89; 95% CI, 0.58 – 1.40). Many facets of the meta-analysis are reported in online tables and appendices and were included in our appraisal checklist. This meta-analysis is among the largest, and has all the characteristics of a high-quality study.

Kumbhani et al (2008) conducted a meta-analysis comparing outcomes with DES vs BMS and comparing SES vs PES among patients with diabetes. They retrieved 16 studies with 2951 patients, but only 12 of these studies with 1879 patients compared DES with BMS. Six of the 16 studies had not yet been published but had had been presented at conferences or as abstracts. Three reviewers abstracted data from studies, enhancing objectivity. Kumbhani et al looked for heterogeneity between studies, and found low to moderate heterogeneity only for the outcome of major adverse cardiac events (mortality, MI, or stent thrombosis). They looked for publication bias, but found none. They examined studies for quality, and found their quality to be high.

Patti et al (2008) conducted a meta-analysis that incorporated 9 RCTs with 1,141 patients. Two reviewers independently abstracted data, enhancing objectivity. In a sub-group analysis, they compared outcomes among insulin-dependent and non−insulin-dependent diabetics. They looked for heterogeneity and publication bias, but found no evidence for either. They evaluated study's quality, but did not report those results or consider them in their conclusions.

Kirtane et al (2008) conducted a pooled analysis of 3,513 patients from 5 trials that compared PES with BMS. They selected these trials because they were the basis for approval in the US and Europe. They did not search the literature, seek unpublished trial results, state inclusion criteria, or assess the trials' quality. They found no heterogeneity between trials. While the trials they included had 2 to 5 years of follow-up, Kirtane et al truncated follow-up at 4 years. They compared outcomes for PES vs BMS among patients with diabetes and among patients without diabetes; and compared outcomes for patients with diabetes vs patients without diabetes. They analyzed results using both the per-protocol and ARC definitions for stent thrombosis. They analyzed subgroups: the

trials using slow-release PES, patients with insulin-dependent diabetes, and patients with non−insulin dependent diabetes.

Pasceri et al 2007 conducted a meta-analysis of trials involving patients with AMI (acute MI), after an observational study suggested such patients may have increased risk of MI, revascularization, or death. Using a wide search strategy, they identified 7 trials, including 4 that were unpublished. They found no heterogeneity between studies and no evidence of publication bias. Six trials had 1 year of follow-up, the other trial had 8 months of follow-up. In a sensitivity analysis, they commented that results using only the 6 trials with a full year of follow-up did not change. Pasceri et al combined outcomes for trials using SES with those using PES. They found no evidence that DES increase the risk of MI, revascularization, or death among patients with AMI.

Moses et al 2006 conducted a pooled analysis of individual patients who had stenting for intermediate coronary lesions, ie, < 50% diameter stenosis. Such lesions may not be clinically important, so the risk/benefit ratio of intervention may be altered. Although trials' inclusion criteria typically required patients to have a coronary lesion with > 50% stenosis, 6.7% of the patient included actually had less stenosis and were the subject of this analysis. Moses et al included 4 trials with similar entry criteria, without describing a literature search, inclusion criteria, or quality assessment. They combined outcomes for trials using SES with those using PES. They found no heterogeneity between studies. Moses et al pooled data from individual RCTs using a Cox proportional hazards model. They conducted a sensitivity analysis by stratifying by stent type and administration of glycoprotein IIb/IIIa inhibitors. They reported incidence rates with p-values for significance of differences. They reported outcomes for cardiac death, MI, target vessel revascularization, and a composite (cardiac death, MI, or target vessel revascularization) while patients were in-hospital, at 30 days, and at 1 year after stent placement: only the 1 year outcomes are reported in our table. They also report Q-wave and non-Q-wave MI, target vessel revascularization, and stent thrombosis at 1 year. Moses et al did not report all-cause mortality.

*Comments about meta-analyses or pooled analyses that were **excluded** from this section:*

Kimura et al 2008. Kimura et al report data derived from intravascular ultrasound imaging, which was conducted during follow-up angiography 9 months after stent placement among a convenience sample of patients enrolled in 3 RCTs comparing PES with BMS. Outcomes reported included vessel diameter, vessel stenosis, acute gain, and late loss. Since these outcomes are different from the clinical outcomes reported in other reviews, they are not included in this report. Kimura et al compared angiographic and ultrasonic outcomes among patients with and without diabetes who had a PES. Kimura et al also compared angiographic and ultrasonic outcomes for PES vs BMS among patients with diabetes. Finally, Kimura et al compared ultrasonic outcomes for PES vs BMS among patients with insulin-dependent diabetes. Essentially, they found worse outcomes among patients with diabetes than those without diabetes; but better outcomes among patients with diabetes and among patients with insulin-dependent diabetes who were treated with a PES compared with those who were treated with a BMS.

OUTCOMES IN SPECIAL POPULATIONS

Diabetes

Table J4. All-cause mortality and cardiac mortality in patients with diabetes: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Effect size	Conclusions	Comments
Kirtane (2008)	Patient-level pooled analysis of 5 RCTs comparing DES (paclitaxel-eluting) vs. BMS No studies specifically enrolled diabetic patients	All-Cause Mortality • HR (95% CI): 0.88 (0.53, 1.45) Cardiac Mortality • HR (95% CI): 1.10 (0.53, 2.28)	Mortality • NS differences for all-cause and cardiac mortality	• Cox PH Regression used • Analyses were truncated at 4 years of follow-up • No information supplied regarding use of antiplatelet therapies by study participants.
Kumbhani (2008)	Meta-analysis performed on 16 RCTs 5 studies specifically enrolled diabetic patients; the remaining studies reported results for the diabetic population separately. Not all studies were used for all outcomes.	Mortality • RR (95%): 0.64 (0.32, 1.28)	Mortality • NS differences between groups	• Random-effects (RE) reported • Heterogeneity across studies was assessed using the Cochrane Q test • Publication bias was assessed using Begg's funnel plot • Clinical follow-up data were reported at 9-12 months; angiographic follow-up data were reported at 6-12 months • Antiplatelet therapy • In 13 studies, loading doses of 325 mg of aspirin and 300 to 600 mg of clopidogrel were administered prior to the procedure. • In 3 studies, loading doses of 325 mg of aspirin and either 300 to 600 mg of clopidogrel or 500 mg of ticlopidine were administered prior to the procedure. • In all studies, patients received indefinite maintenance therapy of 100 to 325 mg of aspirin daily and either 75 mg of clopidogrel daily or 250 mg ticlopidine once to twice daily. • Studies were excluded if paclitaxel or sirolimus were given orally, if non-polymeric stents were used or if newer generation drug-eluting stents were used.
Patti (2008)	Meta-analsis performed on 9 RCTs comparing DES vs. BMS 1 trial specifically enrolled diabetic patients; 8 trials reported post hoc outcome analyses on subsets of diabetic patients	Mortality • OR (95% CI): 1.05 (0.46, 2.35)	Mortality • NS differences • Distinction between cardiac and non-cardiac death made only in one study	• Fixed-effects (FE) estimates reported • Random effects (RE) estimates calculated; did not differ signficantly from FE results • Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes • Mean duration of follow

	Not all studies were used for all outcomes			up was 12 months (range: 8 to 24) • Anti-platelet therapies • Aspirin (≥ 75mg/day) given prior to procedure and continued indefinitely in all studies • Loading dose of clopidogrel (300 mg) was administered prior to procecdure in all studies • Clopidogrel (75 mg/day) was recommended for 2 months in 4 studies, for 3 months in one study; for 6 months in 3 studies, and for 1 year in 1 study • No data on compliance available
Stettler (2008)	Collaborative network meta-analysis of 35 randomized trials Data presented separately for sirolimus-eluting stents (SES) and paclita	HR (95% CI) SES vs. BMS All- Cause Mortality • All trials: 1.14 (0.74, 1.60) • Restricted[1]: 0.88 (0.55, 1.30) Cardiac Death • All trials: 1.09 (0.63, 1.93) • Restricted[1]: 0.80 (0.42, 1.57) PES vs. BMS All-Cause Mortality • All trials: 1.09 (0.71, 1.66) • Restricted[1]: 0.91 (0.60, 1.38) Cardiac Mortality • All trials: 1.08 (0.62, 2.28) • Restricted[1]: 0.94 (0.52, 1.87) •	SES vs. BMS Mortality • NS differences for both analyses • Restriction reduced point estimate, but associations still NS Cardiac Death • NS differences for both analyses • Restriction reduced point estimate, but associations still NS PES vs. BMS Mortality • NS differences for both analyses • Restriction reduced point estimate, but associations still NS Cardiac Death • NS differences for both analyses • Restriction reduced point estimate, but associations still NS	• Hierarchical random effects model used • Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes • Average of four years of follow-up • Data were analyzed separately for trials where subjects were on dual antiplatelet therapy for at least 6 months • Patient-level data on compliance with antiplatelet therapy for was incomplete for all studies; the authors evaluated the available data to decide on the "likely percentage" of persons using antiplatelet therapy for 6 or more months in each trial.

All-Cause Mortality and Cardiac Mortality

- Kirtane et al. (2008) analyzed patient-level pooled data from 5 RCTs that compared DES (paclitaxel-eluting) with BMS. Their dataset was comprised of 827 subjects with diabetes who were recruited as part of one of five TAXUS trials (I, II, IV, V, and VI). The TAXUS trials were also included in the network meta-analysis performed by Stettler et al. Subjects were followed for up to four years in all studies. The incidence of all-cause mortality in DES patients was 5.4%, in BMS patients it was 5.5% (p-value=0.92). Analyses were also done comparing outcomes between non insulin-dependent and insulin-dependent diabetic subjects; no significant differences in the rates of all-cause mortality for patients receiving DES vs. those receiving BMS were seen between these two types of diabetic patients. These results should be interpreted with caution, however, as they are based on very few events. Tests for quantitative heterogeneity were not statistically significant. This meta-analysis is methodologically sound, but is limited by a relatively small number of subjects who could be included from the TAXUS trials.

- Kumbhani et al. (2008) conducted a meta-analysis comparing DES to BMS in diabetic patients (N=2,951). Sixteen studies were included; clinical follow-up data were reported at 9 to 12 months and angiographic follow-up data were reported at 6 to 12 months. All of the trials included in this analysis were also part of the 2007 network meta-analysis conducted by Stettler and colleagues. Studies were judged to be of high quality according to the criteria suggested by Jadad et al. Heterogeneity across studies was assessed using the Cochrane *Q* test and measured inconsistency across trials; no heterogeneity was found for the outcome of stent thrombosis. Begg's funnel plot was used to assess potential publication bias. The incidence of all-cause mortality was 1.6% for subjects who received DES and 2.6% for subjects who received BMS (RR (95%CI) 0.64 (0.32, 1.28)); this difference was not statistically significant. Forest plots were depicted and suggest that none of the individual studies found a significant difference in the risk of all-cause mortality between the DES and BMS groups. In addition, the direction of the association differed between the various studies.

- Patti et al. (2008) conducted a meta-analysis of 9 trials which included 1,141 subjects with diabetes. The trials included in these analyses were also used by Stettler et al in their network meta-analysis. Studies were evaluated for quality on the basis of adequacy of allocation concealment, adherence to the intent-to-treat principle, and degree of blinding for assessment of outcomes. Heterogeneity was assessed using Q statistics and measured inconsistency across trials. Both fixed-effects and random-effects methods were used to estimate pooled odds ratios; fixed-effects results are reported. Funnel plot analysis were used to assess publication bias; the funnel plots are displayed in the paper. The incidence of all-cause mortality was 2.4% for subjects who received DES vs. 2.3% for subjects who received BMS (OR (95%CI): 1.05 (0.46, 2.35)); this difference was not statistically significant. Forest plots were depicted and suggest that none of the studies found a significant difference in the risk of all-cause mortality between the DES and BMS groups. In addition, the direction of the association was not consistent across studies.

- Stettler et al. (2008) published a network meta-analysis that served as an expanded and updated version of their 2007 meta-analysis. Outcomes for patients with and without diabetes were compared for PES, SES, and BMS. A total of 35 RCTs (N = 14,799) with follow-ups of at least 6 months were included. The trials used in the network meta-analysis were: BASKET, C-SIRIUS, CORPAL, DECODE, DIABETES, E-SIRIUS, ISAR-DESIRE, ISAR-DIABETES, ISAR-SMART3, LONG-DES, MISSION, PASSION, PRISON II, RAVEL, REALITY, RRISC, SCANDSTENT, SCORPIUS, SELECTION, SESAMI, SES-SMART, SIRIUS, SIRTAX, TAXi, TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI, TYPHOON, and the studies conducted by Cervinka et al., Erglis et al., Pache et al., and Petronio et al. This network meta-analysis represents the most comprehensive list of RCTs comparing DES with BMS available. The primary safety outcome was overall mortality; cardiac death was also evaluated. Five trials specified 2 months of dual antiplatelet therapy, three specified 3 months, eighteen specified 6 months, one specified 9 months, and eight specified 12 months. All trials with less than 6 months of dual antiplatelet therapy compared SES with BMS. The incidence of all-cause mortality over the 4 years of

follow-up was 7.7% for the PES group, 7.3% for the SES group, and 7.6% for the BMS group (PES vs. BMS - HR (95% CI): 0.91 (0.60, 1.38); SES vs. BMS – HR (95% CI): 0.88 (0.55, 1.30)). The incidence of cardiac mortality over the 4 years of follow-up was 4.8% for the PES group, 4.7% for the SES group, and 4.2% for the BMS group (PES vs. BMS – HR (95% CI): 0.94 (0.52, 1.87); SES vs. BMS (0.80 (0.42, 1.57)). Neither all-cause or cardiac mortality was significantly associated with stent type in this meta-analysis.

Table J5. Myocardial infarction in patients with diabetes: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kirtane (2008)	Patient-level pooled analysis of 5 RCTs comparing DES (paclitaxel-eluting) vs. BMS No studies specifically enrolled diabetic patients	Myocardial Infarction PES: 6.9% (24), BMS: 8.9% (35) HR (95% CI): 0.70 (0.41, 1.17)	Myocardial Infarction NS difference at 4 years of follow up	• Cox PH Regression used • Analyses were truncated at 4 years of follow-up • No information supplied regarding use of antiplatelet therapies by study participants.
Kumbhani (2008)	Meta-analysis performed on 16 RCTs 5 studies specifically enrolled diabetic patients; the remaining studies reported results for the diabetic population separately. Not all studies were used for all outcomes.	Non-Q-Wave Myocardial Infarction DES: 3.1% , BMS:5.9% RR (95% CI): 0.57 (0.32, 0.99) RD (95% CI): 2.6% (0.24%, 5.0%) Q-Wave Myocardial Infarction DES: 0.7%, BMS:1.0% RR (95% CI☺0.25, 2.07	Non-Q-Wave Myocardial Infarction Subjects with diabetes mellitus who received DES were approximately half as likely to have a non-Q-wave myocardial infarction; this difference was statistically significant Q-Wave Myocardial Infarction NS differences	• Random-effects (RE) reported • Heterogeneity across studies was assessed using the Cochrane Q test • Publication bias was assessed using Begg's funnel plot • Clinical follow-up data were reported at 9-12 months; angiographic follow-up data were reported at 6-12 months • Antiplatelet therapy • In 13 studies, loading doses of 325 mg of aspirin and 300 to 600 mg of clopidogrel were administered prior to the procedure. • In 3 studies, loading doses of 325 mg of aspirin and either 300 to 600 mg of clopidogrel or 500 mg of ticlopidine were administered prior to the procedure. • In all studies, patients received indefinite maintenance therapy of 100 to 325 mg of aspirin daily and either 75 mg of clopidogrel daily or 250 mg ticlopidine once to twice daily. • Studies were excluded if paclitaxel or sirolimus were given orally, if non-polymeric stents

				were used or if newer generation drug-eluting stents were used.

Patti (2008)	Meta-analsis performed on 9 RCTs comparing DES vs. BMS
	1 trial specifically enrolled diabetic patients; 8 trials reported post hoc outcome analyses on subsets of diabetic patients
	Not all studies were used for all outcomes
		Myocardial Infarction
		DES: 3.5%, BMS: 7.2%
		OR (95% CI): 0.48 (0.26, 0.87)
			Myocardial Infarction
			Subjects who received DES were 52% less likely to have a myocardial infarction; this difference was highly statistically significant.
				• Fixed-effects (FE) estimates reported
				• Random effects (RE) estimates calculated; did not differ signficantly from FE results
				• Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes
				• Mean duration of follow up was 12 months (range: 8 to 24)
				• Anti-platelet therapies
				  • Aspirin (≥ 75mg/day) given prior to procedure and continued indefinitely in all studies
				  • Loading dose of clopidogrel (300 mg) was administered prior to procecdure in all studies
				  • Clopidogrel (75 mg/day) was recommended for 2 months in 4 studies, for 3 months in one study; for 6 months in 3 studies, and for 1 year in 1 study
				  • No data on compliance available

Stettler (2008)	Collaborative network meta-analysis of 35 randomized trials Data presented separately for sirolimus-eluting stents (SES) and paclita	Myocardial Infarction PES vs. BMS HR (95% CI): 0.84 (0.55, 1.31) SES vs. BMS HR (95% CI): 0.68 (0.44, 1.05)	Myocardial Infarction NS difference for either comparison	• Hierarchical random effects model used • Studies were evaluated for adequacy of allocation concealment, performance of analysis according to the intention-to-treat principle, and blind assessment of outcomes • Average of four years of follow-up • Data were analyzed separately for trials where subjects were on dual antiplatelet therapy for at least 6 months • Patient-level data on compliance with antiplatelet therapy for was incomplete for all studies; the authors evaluated the available data to decide on the "likely percentage" of persons using antiplatelet therapy for 6 or more months in each trial.

Myocardial Infarction

- Kirtane et al. (2008) analyzed patient-level pooled data from 5 RCTs that compared DES (paclitaxel-eluting) with BMS. Their dataset was comprised of 827 subjects with diabetes who were recruited as part of one of five TAXUS trials (I, II, IV, V, and VI). The TAXUS trials were also included in the network meta-analysis performed by Stettler et al. Subjects were followed for up to four years in all studies. The incidence of myocardial infarction in DES patients was 6.9%, in BMS patients it was 8.9% (p-value=0.17). Analyses were also done comparing outcomes between non insulin-dependent and insulin-dependent diabetic subjects; no significant differences in the rates of myocardial infarction for patients receiving DES vs. those receiving BMS were seen between these two types of diabetic patients. These results should be interpreted with caution, however, as they are based on very few events. Tests for quantitative heterogeneity were not statistically significant. This meta-analysis is methodologically sound, but is limited by a relatively small number of subjects who could be included from the TAXUS trials.

- Kumbhani et al. (2008) conducted a meta-analysis comparing DES to BMS in diabetic patients (N=2,951). Sixteen studies were included; clinical follow-up data were reported at 9 to 12 months and angiographic follow-up data were reported at 6 to 12 months. All of the trials included in this analysis were also part of the 2007 network meta-analysis conducted by Stettler and colleagues. Studies were judged to be of high quality according to the criteria suggested by Jadad et al. Heterogeneity across studies was assessed using the Cochrane *Q* test and measured inconsistency across trials; no heterogeneity was found for the outcome of stent thrombosis. Begg's funnel plot was used to assess potential publication bias. The incidence of non-Q-wave myocardial infarction was 3.1% for subjects who received DES and 5.9% for subjects who received BMS (RR (95%CI): 0.57 (0.32, 0.99)); this difference was statistically significant. The risk difference was 2.6% (95% CI: 0.24%, 5.0%). Forest plots were depicted and suggest that the point estimates for each of the individual studies favored DES, however none of the study-specific results were statistically significant. The incidence of Q-wave myocardial infarction was 0.7% for DES and 1.0% for BMS (RR (95% CI): 0.72 (0.25, 2.07); this difference was not statistically significant. No further information was provided for Q-wave myocardial infarction in this study.

- Patti et al. (2008) conducted a meta-analysis of 9 trials which included 1,141 subjects with diabetes. The trials included in these analyses were also used by Stettler et al in their network meta-analysis. Studies were evaluated for quality on the basis of adequacy of allocation concealment, adherence to the intent-to-treat principle, and degree of blinding for assessment of outcomes. Heterogeneity was assessed using Q statistics and measured inconsistency across trials. Both fixed-effects and random-effects methods were used to estimate pooled odds ratios; fixed-effects results are reported. Funnel plot analysis were used to assess publication bias; the funnel plots are displayed in the paper. The incidence of myocardial infarction was 3.5% for subjects who received DES vs. 7.2% for subjects who received BMS (OR (95%CI): 0.48 (0.26, 0.87)); this difference was statistically significant. Forest plots were depicted and suggest that while all of the point estimates for the individual studies favored DES, non

of the study-specific results were significant. The results from this meta-analysis indicate that DES are associated with a reduced risk of myocardial infarction.

- Stettler et al. (2008) published a network meta-analysis that served as an expanded and updated version of their 2007 meta-analysis. Outcomes for patients with and without diabetes were compared for PES, SES, and BMS. A total of 35 RCTs (N = 14,799) with follow-ups of at least 6 months were included. The trials used in the network meta-analysis were: BASKET, C-SIRIUS, CORPAL, DECODE, DIABETES, E-SIRIUS, ISAR-DESIRE, ISAR-DIABETES, ISAR-SMART3, LONG-DES, MISSION, PASSION, PRISON II, RAVEL, REALITY, RRISC, SCANDSTENT, SCORPIUS, SELECTION, SESAMI, SES-SMART, SIRIUS, SIRTAX, TAXi, TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI, TYPHOON, and the studies conducted by Cervinka et al., Erglis et al., Pache et al., and Petronio et al. This network meta-analysis represents the most comprehensive list of RCTs comparing DES with BMS available. Five trials specified 2 months of dual antiplatelet therapy, three specified 3 months, eighteen specified 6 months, one specified 9 months, and eight specified 12 months. All trials with less than 6 months of dual antiplatelet therapy compared SES with BMS. The incidence of myocardial infarction over the 4 years of follow-up was 6.4% for the PES group, 5.1% for the SES group, and 7.4% for the BMS group (PES vs. BMS - HR (95% CI): 0.84 (0.55, 1.31); SES vs. BMS – HR (95% CI): 0.68 (0.44, 1.05)). Myocardial infarction was not significantly associated with stent type in this meta-analysis.

Table J6. TLR/TVR in patients with diabetes: results from recent meta-analyses

Author (Year)	Number of Trials (N diabetic patients)	Relative Risk Estimate
Patti (2008)	9 RCTs, N = 1,141 diabetic patients	Overall TLR OR (95% CI): 0.23 (0.16-0.33) (*P* < 0.00001)
Kumbahni (2008)	12 RCTs (or less), N = 1,879 (or less)	Overall TLR RR (95% CI): 0.35 (0.27-0.46) (*P* < 0.0001)
Kirtane (2008)	5 trials, N = 832 diabetic patients	HR (95% CI) TLR Overall: 0.42 (0.30-0.60) (*P* < 0.0001) PTCA: 0.52 (0.35-0.75) (*P* = 0.0004) CABG: 0.09 (0.02-0.39) (*P* < 0.0001) Overall TVR Overall: 0.67 (0.50-0.89) (*P* = 0.005) PTCA: 0.70 (0.51-0.96) (*P* = 0.025) CABG: 0.59 (0.33-1.08) (*P* = 0.083)

TLR/TVR

Patti et al. (2008) conducted a meta-analysis of 9 trials of 1,141 subjects with diabetes. All trials had at least 6 months follow-up. The trials included here were also evaluated in Stettler's (2008) network meta-analysis. Studies were evaluated for quality on the basis of adequacy of allocation concealment, adherence to the intent-to-treat principle, and degree of blinding for assessment of outcomes. Heterogeneity was assessed using Q statistics and measured inconsistency across trials. Both fixed-effects and random-effects methods were used to estimate pooled odds ratios; fixed-effects results are reported. Funnel plot analysis was used and demonstrated no evidence of publication bias. TLR rates were significantly lower in patients who received DES compared to those who received BMS (8% DES versus 27% BMS) ((OR (95% CI): 0.23 (0.16-0.33) (*P* < 0.00001)). Forest plots were depicted and showed that each RCT favored DES, although results were not statistically significant for 2 RCTs (SES-SMART, TAXUS II). In addition, the direction of the association was not consistent across studies. Patient-level data was not used.

Kumbhani et al. (2008) conducted a meta-analysis comparing DES to BMS in 1879 diabetic patients from 12 RCTs. Four additional studies were evaluated that compared SES and PES. Of the 16 total studies included, 6 were abstracts from confererences, and

5 enrolled only diabetic patients. It was not clear which studies were included for pooled estimates of TLR rates, thus the total N may be less than 1879. Angiographic follow-up data were reported at a mean of 9.4 months (range of 8-12 months). TLR rates were significantly lower in patients treated with DES compared to those who received BMS (7.3% for DES versus 22.2% for BMS) ((RR (95% CI) 0.35 (0.27-0.46) ($P < 0.0001$)). Forest plots were depicted for 6 studies (SIRIUS, SES-SMART, DIABETES, DECODE, SCORPIUS, TAXUS) and suggest that all of the studies favored none of the individual studies found a significant difference in the risk of all-cause mortality between the DES and BMS groups.

Kirtane et al. (2008) analyzed patient-level pooled data from 5 RCTs that compared DES (paclitaxel-eluting) with BMS. Their dataset was comprised of 832 subjects with diabetes who were recruited as part of one of five TAXUS trials (I, II, IV, V, and VI). The TAXUS trials were also included in the network meta-analysis performed by Stettler et al. At 4 years follow-up, diabetic patients treated with PES had significantly lower TLR rates (12.4% PES versus 24.7% BMS) (HR (95% CI) 0.42 (0.30-0.60) ($P < 0.0001$). When stratified according to TLR by PTCA or CABG, similar results were found (PTCA (11.9% PES versus 19.5% BMS); CABG (0.5% PES versus 6.3% BMS) see table HR details). TVR rates at 4 years was similarly significantly lower for patients treated with PES compared to BMS (24.4% PES versus 30.2% BMS) (HR (95% CI) 0.67 (0.50-0.96) ($P = 0.005$). When stratified according to TVR by PTCA, results were similar (18.7% PES versus 23.7% BMS), but when stratified according to TVR by CABG, results were only marginally significant (6.55 PES versus 8.8% BMS) ($P = 0.083$) (see table for HR details). Revascularization rates were reported for up to four years in all studies. Tests for quantitative heterogeneity were not statistically significant for either outcome. This meta-analysis is methodologically sound, but is limited by a relatively small number of subjects who could be included from the TAXUS trials.

Intermediate Target Lesions (< 50% diameter stenosis as defined by QCA)

Table J10. All-cause mortality and cardiac mortality in patients with intermediate target lesions: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Moses (2006)	Meta-analysis of patient-level data from four RCTs comparing DES vs. BMS among patients with intermediate lesions. (N=167)	Cardiac Mortality In-hospital DES: 0% (0); BMS 0% (0); p-value=NA 30-day (cumulative) DES: 0% (0); BMS 0% (0); p-value=NA 1 year (cumulative) DES: 0% (0); BMS: 2.7% (2); p-value=0.11	Cardiac Mortality NS differences at all time points.	Cox PH Regression was used Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Three trials recommended clopidogrel therapy for 6 months post-procedure, the fourth recommended 3 months. 6.7% of patients from the four specified trials were able to

				be included. Assessment of outcomes varied across trials Clinical outcomes were assessed in-hospital, at 30 days post-procedure, and at 1 year post-procedure; angiographic outcomes were assessed at 6-9 months post-procedure

All-Cause Mortality and Cardiac Mortality
Moses et al. (2006) collected patient-level from four trials on subjects who were classified as having intermediate lesions (<50% diameter stenosis as defined by QCA). All four trials (SIRIUS, TAXUS-IV, and FUTURE-I and –II) required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. No deaths occurred within 30 days of the procedure. At 1 year, the incidence of cardiac mortality was 0% in the DES group and 2.7% in the BMS group; this difference was not statistically significant. While this study provides useful information regarding the safety and effectiveness of DES vs. BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution.

Table J11. Myocardial infarction in patients with intermediate target lesions: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Moses (2006)	Meta-analysis of patient-level data from four RCTs comparing DES vs. BMS among patients with intermediate lesions. (N=167)	Myocardial Infarction In-hospital DES: 1.1% (1); BMS 2.7% (2); p-value=0.58 30-day (cumulative) DES: 1.1% (1); BMS 4.0% (3); p-value=0.22 1 year (cumulative) DES: 3.4% (3); BMS: 5.4% (4); p-value=0.0.49	Myocardial Infarction NS differences at all time points.	Cox PH Regression was used Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. Three trials recommended clopidogrel therapy for 6 months post-procedure, the fourth recommended 3 months. 6.7% of patients from the four specified trials were able to be included. Assessment of outcomes varied across trials Clinical outcomes were assessed in-hospital, at 30 days post-procedure, and at 1 year post-procedure; angiographic outcomes were assessed at 6-9 months post-procedure

Myocardial Infarction
Moses et al. (2006) collected patient-level from four trials on subjects who were classified as having intermediate lesions (<50% diameter stenosis as defined by QCA). All four trials (SIRIUS, TAXUS-IV, and FUTURE-I and –II) required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion

diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. No deaths occurred within 30 days of the procedure. At 1 year, the incidence of myocardial infarction was 3.4% in the DES group and 5.4% in the BMS group; this difference was not statistically significant. While this study provides useful information regarding the safety and effectiveness of DES vs. BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution.

Table J12. TLR/TVR in patients with intermediate target lesions: results from recent meta-analyses

Author (Year)	Number of Trials (N patients with intermediate lesions)	Results
Moses (2006)	4 RCTs, N = 167 patients with intermediate lesions	TVR at 30 days DES: 0 BMS: 0 (TLR, TVR) at 1 year DES: (1.2%, 3.4%) BMS: (20.3%, 20.3%) (P = 0.0004, P < 0.0001, respectively)

TLR/TVR
Results suggest that DES are more effective than BMS at reducing revascularization rates in patients with intermediate lesions the first year after stenting, although only 167 patients were analyzed.

Moses (2005) performed a meta-analysis of four RCTs in which 167 lesions (of 2478 total lesions) were of intermediate severity according to QCA analysis. In patients with intermediate lesions, rates of TLR, defined as repeat PCI of the target lesion or CABG of the target vessel due to recurrent angina, ischemia, or QCA diameter stenosis ≥ 70%, were significantly lower in the DES compared to the BMS group at 1 year (P = 0.0004). Similarly, rates of TVR, defined by clinically-driven repeat PCI or CABG of the target vessel, were significantly lower in patients treated with DES versus BMS at one year (P < 0.0001). There were no cases of TVR in either group at 30 days. There was no significant statistical heterogeneity between trials. These results suggest that DES are effective at reducing revascularization rates during the first year following stenting in patients with intermediate target lesions. However, only a small number of patients were evaluated. Furthermore, assessing outcomes in patients with intermediate target lesions was not prespecified by the RCTs.

Acute Myocardial Infarction (AMI)

Two RCTs were identified that reported outcomes in patients with AMI. Kastrati et al 2007 reported on all outcomes of interest for the purposes of this HTA. Paceri et al 2007 reported MACE and Death or MI, which were not evaluated in this assessment but included here for informational purposes; outcomes for TLR and thrombosis were also reported.

Table J13. MACE and composite death or MI in patients with AMI: results from Paceri et al 2007

Paceri (2007)	Meta-analysis of 7 RCTs on use of DES vs. BMS in patients with AMI, N = 2357 patients; (DES: 1177, BMS: 1180) F/U 8-12 months RCTS: 1 published only as an abstract, 3 presented at interentional conferences and were available electronically. Pasceri STRATEGY PASSION TYPHOON SESAMI HAAMU-STENT MISSION	MACE (death + MI, + revascularization): (primary outcome): DES: 9.3% (110); BMS: 17.6% (208) RR (95% CI): 0.53 (0.43, 0.66) $P < 0.00001$ Death or MI DES: 5.8% (68); BMS: 6.9% (81) RR (95% CI): 0.84 (0.62, 1.15) $P = 0.28$	MACE There was a significantly lower risk of MACE with DES vs. BMS at 8-12 months. Forest plots were depicted: all studies favored DES; results were statistically significant for three trials. Death + MI NS difference at 8-12 months. Forest plots were depicted: 4/7 studies favored DES; results were not statistically significant any of the trials.	Mantel-Haenszel fixed-effects model was used to estimate pooled RRs. There was no significant heterogeneity: heterogeneity across trials was evaluated with Q statistics; the extent of inconsistency across trials was evaluated with I^2 statistics (significant heterogeneity if $P < 0.10$ and/or $I^2 = 50\%$). Sensitivity analysis not performed. Results were not adjusted. Funnel plot analysis demonstrated no publication bias. Two trials used PES, 5 used SES; type of BMS was operator-choice. Routine angiographic follow-up performed in 5 trials and in a subgroup of 1 trial. Definition of stent thrombosis used was not specified. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 2 trials. 3 studies published in peer-reviewed journals, 1 published only as an abstract, 3 presented at interentional conferences and were available electronically.

Table J14. All-cause mortality and cardiac mortality in patients with AMI: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kastrati (2007)	Meta-analysis of 8 RCTs comparing DES vs. BMS among patients with acute ST-segment elevation myocardial infarction. Patient-level data was available for 7 trials. N=2786	All-cause mortality DES: 4.1% (60); BMS: 5.1% (67) HR (95% CI): 0.76 (0.53, 1.10)	All-cause mortality NS differences at 12 months post-randomization	Mantel-Cox method was used to perform survival analyses. Cochrane's test was used to assess heterogeneity across trials. I^2 statistic was also calculated to measure the consistency of among trials. Hazard ratios from individual trials were pooled using random effects methods. Sensitivity analyses wer conducted by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 3 trials.

All-Cause Mortality and Cardiac Mortality

Kastrati et al. (2007) conducted a meta-analysis of randomized trials which compared DES (either paclitaxle-eluting or sirolimus-eluting) with BMS among patients with acute ST-elevation myocardial infarctions. The authors identified 8 trials with follow-up of at least 12 months; patient-level data was available for 7 of these trials. The trials included BASKET-AMI, HAAMU-STENT, MISSION, PASSION, SESAMI, STRATEGY, and the trial conducted by Di Lorenzo et al; 2,786 subjects were included. The authors used Cox proportional hazards regression, stratified by trial, to analyze their results for the trials with patient-level data. Hazard ratios calculated from data from indiviudal trials were pooled using the random effects method of DerSimonian and Laird. Heterogeneity of the treatment effect was evaluated by the Cochrane test; the I^2 statistic was also calculated to assess consistency among trials. At 1 year, the incidence of cardiac mortality was 4.1% in the DES group and 5.1% in the BMS group; this difference was not statistically significant (HR (95% CI) 0.76 (0.53, 1.10)). A forest plot was depicted, showing the results from the individual trials included. All but one trial (HAAMU-STENT) found that the risk of death was reduced in the DES group, but none of the associations were statistically significant. Overall, the authors conclude that the use of DES in persons with acute myocardial infarction is safe and appropriate.

Table J15. Myocardial infarction in patients with AMI: results from recent meta-analyses

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Kastrati (2007)	Meta-analysis of 8 RCTs comparing DES vs. BMS among patients with acute ST-segment elevation myocardial infarction. Patient-level data was available for 7 trials. N=2786	Myocardial Infarction DES: 3.1% (46); BMS: 4.0% (52) HR (95% CI): 0.72 (0.48, 1.08)	Myocardial Infarction NS differences at 12 months post-randomization	Mantel-Cox method was used to perform survival analyses. Cochrane's test was used to assess heterogeneity across trials. I^2 statistic was also calculated to measure the consistency of among trials. Hazard ratios from individual trials were pooled using random effects methods. Sensitivity analyses wer conducted by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 3 trials.

Myocardial infarction

Kastrati et al. (2007) conducted a meta-analysis of randomized trials which compared DES (either paclitaxle-eluting or sirolimus-eluting) with BMS among patients with acute ST-elevation myocardial infarctions. The authors identified 8 trials with follow-up of at least 12 months; patient-level data was available for 7 of these trials. The trials included BASKET-AMI, HAAMU-STENT, MISSION, PASSION, SESAMI, STRATEGY, and the trial conducted by Di Lorenzo et al; 2,786 subjects were included. The authors used Cox proportional hazards regression, stratified by trial, to analyze their results for the trials with patient-level data. Hazard ratios calculated from data from indiviudal trials were pooled using the random effects method of DerSimonian and Laird. Heterogeneity of the treatment effect was evaluated by the Cochrane test; the I^2 statistic was also calculated to assess consistency among trials. At 1 year, the incidence of myocardial infarction was 3.1% in the DES group and 4.0% in the BMS group; this difference was not statistically significant (HR (95% CI) 0.72 (0.48, 1.08)). A forest plot was depicted, showing the results from the individual trials included. All but one trial (BASKET-AMI) found that the risk of myocardial infarction was reduced in the DES group, but none of the associations were statistically significant. Overall, the authors conclude that the use of DES in persons with acute myocardial infarction is safe and appropriate.

Table J16. TLR/TVR in patients with AMI: results from recent meta-analyses

Author (Year)	Number of Trials (N)	Relative Risk Estimate
Kastrati (2007) (Euro Heart J)	8 RCTs, N = 2786	Overall TLR HR (95% CI): 0.38 (0.29-0.50) (*P* < 0.001)
Paceri (2007)	7 RCTs, N = 2357	Overall TLR RR (95% CI): 0.40 (0.30, 0.54) *P* < 0.00001

TLR/TVR

Kastrati et al. (2007) performed a meta-analysis of 8 randomized trials evaluating DES versus BMS in 2786 acute STEMI patients. Patient-level data was available from 7 of the 8 trials. At 1 year, the incidence of target lesion revascularization was significantly lower in patients treated with DES compared to BMS (HR (95% CI): 0.38 (0.29-0.50)) (*P* < 0.001). Similar results were found after excluding the trial in which individual patient data was not available (MISSION trial). A forest plot was depicted, showing the results from the individual trials included. All trials favored DES, although results were not statistically significant for 3 of the trials (BASKET-AMI, HAAMU-STENT, PASSION trials). There was no significant statistical heterogeneity between trials. Kaplan-Meier curves of the pooled population show that the probability of reintervention at 1 year was 5.0% for patients treated with DES and 13.3% for those greated with BMS. Overall, the authors conclude that the use of DES in persons with acute myocardial infarction is safe and appropriate.

Appendix K : COAP information and data

Spectrum Research note:
The following pages provide additional information about the Clinical Outcomes Assessment Program (COAP) as well as additional data regarding PCI utilization in Washington State.

The COAP database is potentially a very rich source of information about PCI and CABG procedures in Washington State. Beginning in 2008, all Washington State hospitals contribute data to COAP, with the addition of Madigan in 2008. There are 31 sites that do PCI, 19 of which have cardiac surgery backup.

To put the data into context, several features of this registry/database need to be considered.

- Data are cross sectional by year and are not longitudinal in that currently there is no unique patient identifier that allows for patient follow-up across multiple years.
- The numbers of procedures is represented, not the number of unique patients.
- There is no unique patient identifier so patients may be represented more than once in a given year and may be represented in more than one year.
- It should be noted that the number of repeat procedures includes any type of PCI, i.e. with or without stenting and may include other PCI interventions. Additionally patients may be represented more than once.
- Data definitions may have changed slightly over the years
- In some patients, such as diabetic patients, if they received both a BMS and DES, they are represented in both counts. This may also be the case for other co-morbidities and risk factors reported, since categories are not mutually exclusive.
- Denominators for ejection fraction are lower, because it is missing for many procedures.

The Clinical Outcomes Assessment Program (COAP) is a Washington State initiative designed to produce clinical information needed to improve quality of care and meet the growing demand for accountability in the health care industry. COAP's physician-led Management Committee, in partnership with State officials and key stakeholders, has created this program as a model of collaboration in which Washington State's cardiac community can work together toward a common goal — improving patient care and health outcomes.

COAP's timely reporting mechanism provides hospitals with clinical feedback on a quarterly basis. Through the protection of Washington State law and private contract, COAP offers special protection for the confidentiality of quality improvement information. COAP is operated under the auspices of the Foundation for Health Care Quality a non-profit 501(c)3 corporation. All hospitals in Washington State that perform percutaneous coronary interventions (PCI) participate in COAP, and report data on 100% of PCI procedures.

COAP has been collecting data on PCI and cardiac surgeries since 1999. In 2004, we began to collect information on what type of stent was used during a percutaneous coronary intervention. Raw numbers for the type of stent used as well as associated clinical outcomes are available and we are pleased to work with you in analyzing this data.

Table 1: Stent cases by year: All cases (COAP 2003-2007)

Year	# stent procedures	# stents	# bare metal	# drug eluting	# CABG
2003	12,533	14,416	----	----	4228
2004	13,348	18,860	3224	15,636	3864
2005	14,104	19,931	1408	18,523	3595
2006	14,542	21,048	2122	18,926	3329
2007	13,032	19,688	5214	14,474	3098

Table 2: Stent cases by year: Prior revascularization (COAP 2003-2007)

Year	# repeat procedures**	# stents	# bare metal	# drug eluting	# repeat CABG
2003	3965	4507	----	----	239
2004	4377	6252	941	5311	196
2005	4618	6789	425	6364	168
2006	4905	7179	571	6608	115
2007	4490	6776	1486	5290	138

** We can not identify repeat stent cases, only those undergoing repeat angioplasty, although most of these are stents.

Table 1a: PCI and CABG cases by year: All cases (COAP 1999-2007)

Year	# PCI	# with stents	BMS	DES	# CABG
1999	8437	6493 (77%)	6493	----	5067
2000	10,867	8852 (81%)	8852	----	5362
2001	12,411	9963 (80%)	9963	----	5066
2002	13,308	10,814 (81%)	10,814	----	4770
2003	14,579	12,533 (86%)	12,533	----	4228
2004	15,158	13,348 (88%)	2655	11,271	3864
2005	15,330	14,104 (92%)	1226	13,108	3595
2006	15,686	14,542 (93%)	1776	13,262	3329
2007	14,164	13,032 (92%)	4333	9630	3098

Table 1b: PCI volumes by year (COAP 1999-2007)

Year	# PCI	# first	# repeats
1999	8437	5892 (70%)	2545 (30%)
2000	10,867	7611 (70%)	3256 (30%)
2001	12,411	8607 (69%)	3804 (31%)
2002	13,308	8808 (64%)	4500 (36%)
2003	14,579	9336 (64%)	5243 (36%)
2004	15,158	10,022 (66%)	5136 (34%)
2005	15,330	10,146 (66%)	5184 (34%)
2006	15,686	10,265 (65%)	5421 (35%)
2007	14,164	9135 (64%)	5029 (36%)

Table 1c: Chest pain characteristics by stent type (COAP 2004-2007)

Year	Chest pain characteristic	Bare metal stent	Drug eluting stent
2004		**(n=2653)**	**(n=11,255)**
	No angina	296 (11%)	1355 (12%)
	Stable angina	403 (15%)	2966 (26%)
	ACS-unstable angina	750 (28%)	3522 (31%)
	ACS-NSTEMI	481 (18%)	1679 (15%)
	ACS-STEMI	723 (27%)	1733 (15%)
2005		**(n=1223)**	**(n=13,090)**
	No angina	128 (10%)	1328 (10%)
	Stable angina	194 (16%)	3336 (25%)
	ACS-unstable angina	336 (27%)	4178 (32%)
	ACS-NSTEMI	254 (21%)	2166 (16%)
	ACS-STEMI	311 (25%)	2082 (16%)
2006		**(n=1775)**	**(n=13,260)**
	No angina	168 (10%)	1209 (9%)
	Stable angina	365 (21%)	3500 (26%)
	ACS-unstable angina	525 (30%)	4506 (34%)
	ACS-NSTEMI	362 (20%)	2031 (15%)
	ACS-STEMI	355 (20%)	2014 (15%)
2007		**(n=4330)**	**(n=9620)**
	No angina	347 (8%)	844 (9%)
	Stable angina	776 (18%)	2527 (26%)
	ACS-unstable angina	1141 (26%)	3171 (33%)
	ACS-NSTEMI	997 (23%)	1615 (17%)
	ACS-STEMI	1069 (25%)	1463 (15%)

Table 1d: Procedural characteristics by stent type (COAP 2004-2007)

Year	Procedural characteristic	Bare metal stent	Drug eluting stent
2004			
	Primary PCI	880/2655 (33%)	2312/11,271 (20%)
	Elective PCI	1218/2653 (46%)	6381/11,268 (57%)
	Treated for acute MI	935/2653 (35%)	2413/11,259 (21%)
	Diabetic patient	715/2655 (27%)	3086/11,271 (27%)
	High risk lesion	986/2655 (37%)	3300/11,271 (29%)
2005			
	Primary PCI	387/1226 (32%)	2958/13,108 (23%)
	Elective PCI	591/1226 (48%)	7489/13,105 (57%)
	Treated for acute MI	434/1226 (35%)	3130/13,106 (24%)
	Diabetic patient	336/1226 (27%)	3760/13108 (29%)
	High risk lesion	432/1226 (35%)	4433/13,108 (34%)
2006			
	Primary PCI	767/1776 (43%)	4326/13,262 (33%)
	Elective PCI	831/1775 (47%)	7353/13,257 (56%)
	Treated for acute MI	537/1776 (30%)	2925/13,262 (22%)
	Diabetic patient	495/1776 (28%)	3839/13,262 (29%)
	High risk lesion	686/1776 (39%)	4646/13,262 (35%)
2007			
	Primary PCI	2150/4333 (50%)	3250/9630 (34%)
	Elective PCI	1660/4331 (38%)	4889/9621 (51%)
	Treated for acute MI	1459/4333 (34%)	2175/9623 (23%)
	Diabetic patient	1279/4333 (30%)	2947/9630 (31%)
	High risk lesion	1906/4333 (44%)	4087/9630 (42%)

Table 2bi: Total number of PCIs and stents COAP (COAP 2004-2007), no prior revascularization

Year	# PCIs	# with BMS	# with DES	#BMS/procedure	#DES/procedure
2004	8689	1576	6545	1.4±0.8	1.2±0.5
2005	8826	721	7631	1.4±0.8	1.1±0.4
2006	8876	1062	7556	1.4±0.8	1.2±0.5
2007	8010	2716	5367	1.5±0.9	1.2±0.5

Table 2bii: Risk factors by stent type (COAP 2004-2007), no prior revascularization

Year	Risk factor	Bare metal stent	Drug eluting stent
2004			
	LVEF < 50%	379/1204 (32%)	1021/4965 (21%)
	Hx diabetes	365/1576 (23%)	1549/6545 (24%)
	Hx hypertension	986/1576 (63%)	4373/6542 (67%)
	Hx peripheral vascular disease	127/1576 (8%)	519/6545 (8%)
2005			
	LVEF < 50%	169/551 (31%)	1334/5802 (23%)
	Hx diabetes	173/721 (24%)	1888/7631 (25%)
	Hx hypertension	472/721 (66%)	5226/7631 (68%)
	Hx peripheral vascular disease	61/721 (8%)	620/7631 (8%)
2006			
	LVEF < 50%	237/819 (29%)	1451/6078 (24%)
	Hx diabetes	251/1062 (24%)	1907/7556 (25%)
	Hx hypertension	709/1062 (67%)	4991/7555 (66%)
	Hx peripheral vascular disease	104/1062 (10%)	556/7556 (7%)
2007			
	LVEF < 50%	578/2154 (27%)	948/4208 (22%)
	Hx diabetes	1684/2716 (25%)	1395/5367 (26%)
	Hx hypertension	1785/2713 (66%)	3658/5366 (68%)
	Hx peripheral vascular disease	209/2716 (8%)	360/5367 (7%)

Table 2biii: Outcomes by stent type (COAP 2004-2007), no prior revascularization

Year	Outcome	Bare metal stent	Drug eluting stent
2004			
	Hospital mortality	37/1576 (2.3%)	71/6540 (1.1%)
	Post procedure stroke	1/1576 (0.1%)	21/6539 (0.3%)
	Post procedure vascular complication	4/1576 (0.3%)	18/6545 (0.3%)
	Unplanned CABG	11/1576 (0.7%)	11/6544 (0.2%)
2005			
	Hospital mortality	34/721 (4.7%)	105/7631 (1.4%)
	Post procedure stroke	1/721 (0.1%)	22/7631 (0.3%)
	Post procedure vascular complication	2/721 (0.3%)	18/7631 (0.2%)
	Unplanned CABG	5/721 (0.7%)	18/7631 (0.2%)
2006			
	Hospital mortality	25/1062 (2.4%)	97/7554 (1.3%)
	Post procedure stroke	1/1062 (0.1%)	24/7555 (0.3%)
	Post procedure vascular or bleeding complication	17/1062 (1.6%)	110/7555 (1.5%)
	Return to OR for non elective CABG or transferred for CABG	10/1062 (0.9%)	32/7556 (0.4%)
2007			
	Hospital mortality	82/2716 (3.0%)	971/5366 (1.3%)
	Post procedure stroke	12/2716 (0.4%)	22/5366 (0.4%)
	Post procedure vascular or bleeding complication	58/2716 (2.1%)	90/5365 (1.7%)
	Return to OR for non elective CABG or transferred for CABG	25/2716 (0.9%)	28/5367 (0.5%)

Table 2biv: Outcomes by stent type (COAP 2004-2007), no prior revascularization history of diabetes

Year	Outcome	Bare metal stent	Drug eluting stent
2004			
	Hospital mortality	15/365 (3.8%)	24/1547 (1.6%)
	Post procedure stroke	0/365 (0%)	5/1548 (0.3%)
	Post procedure vascular complication	0/365 (0%)	3/1549 (0.2%)
	Unplanned CABG	2/365 (0.5%)	5/1549 (0.3%)
2005			
	Hospital mortality	5/173 (2.9%)	37/1888 (2.0%)
	Post procedure stroke	0/173 (0%)	9/1888 (0.5%)
	Post procedure vascular complication	0/173 (0%)	5/1888 (0.3%)
	Unplanned CABG	3/173 (1.7%)	2/1888 (0.1%)
2006			
	Hospital mortality	8/251 (3.2%)	27/1907 (1.4%)
	Post procedure stroke	1/251 (0.4%)	5/1907 (0.3%)
	Post procedure vascular or bleeding complication	5/251 (2.0%)	32/1907 (1.7%)
	Return to OR for non elective CABG or transferred for CABG	2/251 (0.8%)	10/1907 (0.5%)
2007			
	Hospital mortality	18/684 (2.6%)	28/1395 (2.0%)
	Post procedure stroke	6/684 (0.9%)	4/1395 (0.3%)
	Post procedure vascular or bleeding complication	10/684 (1.5%)	20/1395 (1.4%)
	Return to OR for non elective CABG or transferred for CABG	6/684 (0.9%)	4/1395 (0.3%)

Appendix L. Excluded Studies for Comparison of DES versus BMS

Studies and meta-analyses that were included in previously published HTA or meta-analyses were excluded.

Articles excluded at the level of full article review are listed below.

No direct comparison between DES and BMS

Denvir, M. A., A. J. Lee, et al. (2007). "Effects of changing clinical practice on costs and outcomes of percutaneous coronary intervention between 1998 and 2002." Heart 93(2): 195-9.

Godino, C., S. Furuichi, et al. (2008). "Clinical and angiographic follow-up of small vessel lesions treated with paclitaxel-eluting stents (from the TRUE Registry)." Am J Cardiol **102**(8): 1002-8.

Valgimigli, M., N. Mittmann, et al. (2008). "A strategy to offset the extra cost of sirolimus-eluting stent in patients undergoing intervention for acute myocardial infarction." Int J Cardiol **128**(1): 53-61.

Shrive, F. M., W. A. Ghali, et al. (2007). "Use of the U.S. and U.K. scoring algorithm for the EuroQol-5D in an economic evaluation of cardiac care." Med Care **45**(3): 269-73.

Varani, E., M. Balducelli, et al. (2007). "Comparison of multiple drug-eluting stent percutaneous coronary intervention and surgical revascularization in patients with multivessel coronary artery disease: one-year clinical results and total treatment costs." J Invasive Cardiol **19**(11): 469-75.

Lasala, J. M., D. A. Cox, et al. (2008). "Usage patterns and 2-year outcomes with the TAXUS express stent: results of the US ARRIVE 1 registry." Catheter Cardiovasc Interv **72**(4): 433-45.

Fewer than 50 patients per study arm

Strozzi, M. and D. Anic (2007). "Comparison of stent graft, sirolimus stent, and bare metal stent implanted in patients with acute coronary syndrome: clinical and angiographic follow-up." Croat Med J **48**(3): 348-52.

Li, J. J., X. W. Qin, et al. (2008). "Randomized comparison of early inflammatory response after sirolimus-eluting stent vs bare metal stent implantation in native coronary lesions." Clin Chim Acta **396**(1-2): 38-42.

Ma, H. Y., Y. J. Zhou, et al. (2008). "Long-term outcome of patients of over 85 years old with acute coronary syndrome undergoing percutaneous coronary stenting: a comparison of bare metal stent and drug eluting stent." Chin Med J (Engl) **121**(10): 887-91.

Primary focus on angiographic outcomes, IVUS or different protocols for stenting

Chechi, T., G. Vittori, et al. (2007). "Single-center randomized evaluation of paclitaxel-eluting versus conventional stent in acute myocardial infarction (SELECTION)." J Interv Cardiol **20**(4): 282-91.

Kimura, M., G. S. Mintz, et al. (2008). "Meta-analysis of the effects of paclitaxel-eluting stents versus bare metal stents on volumetric intravascular ultrasound in patients with versus without diabetes mellitus." Am J Cardiol **101**(9): 1263-8.

Erglis, A., I. Narbute, et al. (2007). "A randomized comparison of paclitaxel-eluting stents versus bare-metal stents for treatment of unprotected left main coronary artery stenosis." J Am Coll Cardiol **50**(6): 491-7.

Hoffmann, R., M. C. Morice, et al. (2008). "Impact of late incomplete stent apposition after sirolimus-eluting stent implantation on 4-year clinical events: intravascular ultrasound analysis from the multicentre, randomised, RAVEL, E-SIRIUS and SIRIUS trials." Heart **94**(3): 322-8.

Not an FDA approved device

Konig, A., M. Leibig, et al. (2007). "Randomized comparison of dexamethasone-eluting stents with bare metal stent implantation in patients with acute coronary syndrome: serial angiographic and sonographic analysis." Am Heart J **153**(6): 979 e1-8.

Not full economic study

Mahieu, J., A. De Ridder, et al. (2007). "Economic analysis of the use of drug-eluting stents from the perspective of Belgian health care." Acta Cardiol 62(4): 355-65.

Prognostic study, not in scope

Holmes, D. R., Jr., J. W. Moses, et al. (2006). "Cause of death with bare metal and sirolimus-eluting stents." Eur Heart J **27**(23): 2815-22.

Le Feuvre, C., G. Helft, et al. (2008). "Characteristics and prognosis of patients with angiographic stent thrombosis: comparison between drug-eluting and bare-metal stents." Arch Cardiovasc Dis **101**(4): 220-5.

Appendix M. Peer Reviewers

The individuals listed below provided peer review on the initial public draft when it became available to the public.

The role of peer reviewer should not be construed to mean that the individuals were authors or contributors to the formulation of the draft, nor does it imply endorsement, approval, or disapproval of the process or report.

Individual	Expertise/Experience
Rita F. Redberg, MD, MSc UCSF Division of Cardiology, Professor of Clinical Medicine	▪ MD, University of Pennsylvania; ▪ ABIM-Internal medicine and Cardiovascular specialty ▪ MSc, London School of Economics ▪ Over 20 years of research-related and clinical experience. ▪ Research areas include cardiovascular disease in women, cardiovascular imaging, health policy and technology assessment, evidence based-practice ▪ Reviewer/consultation for AHRQ, USPSTF, MCAC, CDRH
Keith A. Comess, MD Chief Medical Officer Corazon X	▪ MD, University of Arizona ▪ ABIM-internal medicine and cardiovascular disease ▪ ASE and National Board Echocardiography certifications ▪ Nuclear cardiology ▪ Level II- CT-angiography ▪ Over 20 years clinical experience and research in cardiology, focused on non-invasive imaging ▪ Research interests include stroke prevention, hypertension/blood pressure; non-invasive imaging and evaluation of coronary artery disease
Steven L. Goldberg, MD Director, Cardiac Catheterization Laboratory, University of Washington Medical Center Chief clinical officer- Cardiac Dimensions	▪ MD, University of Kansas ▪ ABIM –internal medicine and cardiovascular disease and interventional cardiology ▪ Proctor –Palmaz-Schatz and Wikto Stents ▪ Over 15 years invasive cardiology experience ▪ Clinical experience in several “third-world” settings ▪ Research interests include intravascular ultrasound imaging, percutaneous interventions including intracoronary stenting techniques and restenosis

Appendix N. Additional Information: CAD diagnosis, treatment, product information and clinical guidelines

1. Background

1.1 The Condition: Coronary artery disease

Coronary artery disease (CAD) is a condition characterized by slow deposition of plaques on the arterial walls and sudden plaque disruption leading to thrombosis below the plaquea.[1] These features cause narrowing (stenosis) of the coronary arteries, impairing the blood supply (ischemia) critical to the wellbeing of heart muscle (myocardium). CAD is the fundamental condition of ischemic heart disease (IHD), characterized by an imbalance between the blood supply to the myocardium and the requirements of the myocardium for oxygenated blood. IHD syndromes include chest pain (angina, stable and unstable), myocardial infarct (MI), heart failure (HF), arrythmias and sudden death. Coronary artery stents have been developed specifically to address the narrowing caused by plaque formation in CAD.

1.2 Epidemiology of CAD

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD), is the single leading cause of death for both men and women in the U.S. and is the most common form of cardiovascular disease. According to the American Heart Association, more than 13 million people have CAD, and approximately 650,000 deaths were due to CAD in the U.S. in 2003, with 221,000 of those resulting from myocardial infarctions (MI). Furthermore, approximately 900,000 Americans are estimated to have a heart attack each year, and approximately 400,000 Americans have stable angina. Men have a 1 in 2 lifetime risk of developing CAD after the age of 40 and women have a 1 in 3 risk; CAD incidence in women lags behind men by 10 years. Although some genetic factors play a role, the major risk factors for CAD development include tobacco use, hypertension, elevated blood cholesterol, and diabetes mellitus. The total of direct and indirect costs of CAD in 2006 was $142.5 billion, with $11.6 billion paid to Medicare beneficiaries ($11,308 per hospital discharge for coronary atherosclerosis).[2] Reduction in the prevalence, morbidity and mortality related to CAD is an important public health goal given the significant disease burden and contribution to total health care costs.

1.3 Pathogenesis of CAD

An understanding of the basic pathophysiology of IHD and CAD may facilitate appreciation of the strengths and limitations of various treatment options.

CAD begins with the slow deposition of cholesterol, other lipids, calcium, and fibrous tissue including collagen onto the arterial wall. Plaque development can begin in childhood and eventually causes narrowing of the lumen of the coronary vessels, thus restricting blood flow to the myocardium. Coronary artery plaques are responsible for over 90% of IHD.[1] CAD may be asymptomatic for many years and the onset of

symptoms depends on the location and severity of these obstructions; however, the severity of the lesions is poorly correlated with symptoms.

The partial stenosis due to plaque can quickly be transformed into a critical obstruction. The process starts with a small fissure or superficial erosion at the edge of a stable plaque. This opening exposes the thrombogenic subendothelial basement membrane to blood and sets off the clotting cascade. The opening also exposes the highly thrombogenic plaque constituents. Hemorrhage and platelet-fibrin thrombosis quickly form behind the plaque, expanding the volume of the plaque, and within seconds can completely obstruct the narrowed lumen. This obstruction, depending on the location and duration, may lead to death of myocardium that depended upon the involved segment of coronary artery. The triggers for this deadly cascade of events are not well known, but may include adrenergic stimulation from stress. Disrupted lesions characteristically have a marked eccentric configuration, a large soft core of necrotic debris and lipids, a high density of macrophages, and a thin fibrous cap. They are more likely to be moderately stenotic (50-75% obstructed) and thus less likely to have caused stable angina. Coronary atherosclerotic plaque disruption and associated intralulminal platelet-fibrin thrombus formation are responsible for the acute coronary syndromes of acute MI, unstable angina, and probably for sudden death. Table 1 compares the relative impact of stenosis, thrombosis, and plaque disruption to several IHD syndromes.[1]

Table 1. Comparison of stenosis, thrombosis, and plaque disruption in IHD syndromes[1]

Syndrome	Stenoses	Plaque Disruption	Plaque-Associated Thrombus
Stable angina	> 75%	No	No
Unstable angina	Variable	Frequent	Nonocclusive, often with thromboemboli
Transmural myocardial infarction	Variable	Frequent	Occlusive
Subendocardial myocardial infarction	Variable	Variable	Widely variable, may be absent, partial/complete or lysed
Sudden death	Usually severe	Frequent	Often small platelet aggregates or thrombi and/or thromboemboli

Other physiologic processes may mitigate the impact of atherosclerosis and plaque disruption. Arterial blood flow can be maintained by compensatory arterial vasodilation, but this mechanism fails when more than 75% of the cross-sectional area is obstructed. Collateral vessels often develop slowly along with the slow forming plaques and may provide sufficient blood supply to protect the myocardium when the primary artery is occluded. Recent research suggests that plaque disruption and the ensuing platelet aggregation and intraluminal stenosis are common, repetitive, and often clinically silent. If the thrombosis breaks up quickly and blood supply is re-established, the myocardium may sustain only a subendocardial infarct rather than a full thickness infarct. Medications that slow the development of plaque or stabilize the plaque (e.g. statins) and medications

that impair the formation of thrombosis (e.g. aspirin) have come to play an increasingly important role in controlling CAD.

Angina

The clinical impact of IHD depends on the number, distribution and degree of narrowing by the atheromatous plaques, but the symptoms are not strongly predicted by these features. The most common symptom is chest pain (angina). Classic angina is characterized by retrosternal chest discomfort, often described as a crushing pressure. The discomfort may radiate to the jaw, neck, back, shoulder or arm. It can be accompanied with dyspnea, diaphoresis, nausea and syncope. If the discomfort presents (1) in a predictable pattern, (2) is brought on by physical or mental stress, and (3) subsides with rest or angina medication such as nitroglycerin, it is called **stable angina**.[3] The development of angina suggests that at least one artery has a 75% or greater stenosis. Up to 50% of patients with coronary artery disease present first with angina. Other common symptoms associated with coronary ischemia include dyspnea or early fatigue with exertion, indigestion, palpitations, tightness in the throat, or neck pain. These symptoms, when documented to be associated with CAD, are called "anginal equivalents." These symptoms are also seen in many common noncardiac conditions including gastroesophageal reflux, esophageal spasm and cervical disc disease. However, many patients have no symptoms at all.

Women and persons with diabetes are less likely to experience classic angina, making early diagnosis of CAD difficult.[4] Because of the poor correlation between symptoms and CAD, clinicians must rely on a careful history and other modalities to detect and confirm a suspicion of CAD. The Canadian Cardiovascular Society has developed a classification system for angina that facilitates quantifying angina for clinical assessment and treatment, Table 2.[5]

Unstable angina (U/A), NonSTwave elevation myocardial infarction (NSTEMI)

Unstable angina is now classified as part of acute coronary syndrome (ACS). A change in the anginal pattern may signal a significant decrease in coronary perfusion. Angina that occurs with less exertion, causes greater discomfort, or takes longer than 20 minutes to subside may be an ominous warning of critical ischemia and is called unstable angina. Electrocardiographic (ECG) changes of ST depression noted during angina suggest ischemia. The location of the ST depression indicates which arteries are involved. Unstable angina is defined by the clinical syndrome described above plus ST-T wave depression, T wave inversion, and increase in troponin. Another syndrome with similar clinical presentation to UA, but results in death of the myocardium (myocardial infarction (MI)), is called non-ST wave elevation myocardial infarction (NSTEMI). The symptoms, ECG, and labs on presentation are similar for UA and NSTEMI, so they are often grouped together for clinical assessment and management.

Table 2. Grading of Angina pectoris by the Canadian Cardiovascular Society Classification System[5]

Angina Class	Effect of angina on activity level	Causes of angina
Class I	Ordinary physical activity, such as walking or climbing stairs, does not	• Strenuous, rapid, or prolonged exertion

	cause angina.	
Class II	Some limitations of regular activity	• Walking; • Climbing stairs; • Rapidly walking uphill; or • Walking or climbing stairs: • after meals • in cold • in wind • only within the first few hours after awakening • Walking more than 2 blocks (level); and • Climbing more than one flight of stairs at a normal pace and in normal condition
Class III	Significant limitations of normal physical activity	• Walking 1-2 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

Myocardial infarction (MI)

MI is defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Criteria for an MI include any of the following:

- detection of risk and or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile with symptoms of ischemia, ECG changes, development of Q-waves or imaging evidence of a new loss of viable myocardium or new regional wall motion defect.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, ST elevation, new left bundle branch block (LBBB), or fresh thrombus on angiography or autopsy.
- PCI with normal baseline troponin PLUS post-procedural elevation of the troponin level three times greater than the 99th percentile suggesting peri-procedural myocardial necrosis.
- CABG with normal baseline troponin PLUS post-procedural elevation of the troponin level five times greater than the 99th percentile, new pathological Q-waves or new LBBB, new graft or coronary artery occlusion, or imaging evidence of new loss of viable myocardium. All these would be suggestive of a peri-procedural myocardial necrosis.
- Pathologic findings of an acute myocardial infarction.

A prior MI can be detected by the development of new Q-waves, imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, or pathological findings of a healed or healing myocardial infarction.[6]

An acute MI is suggested by ST elevation, and thus is called ST elevated MI (STEMI). The EKG changes can begin within minutes of the onset of the severe, acute ischemia and evolve over several days as the myocytes die (see diagnostic tests). Within a few minutes, the dying cells will leak cardiac biomarkers (troponin) into the serum, which generally increase over the next 24 hours, then resolve back to normal over 3-5 days. Immediate coronary angiography may show the stenosis or blockage. Immediate echocardiography may show decreased (hypokinesis) or absent muscle function of the affected area, and may even show the development of a ventricular wall aneurysm. Radionucleotide imaging will show a new perfusion defect in the damaged area. MI may

be the first presentation of CAD and IHD. Up to a third of persons with MI report no prior diagnosis of CAD or angina.

Acute Coronary Syndrome (ACS)
UA, NSTEMI and STEMI all signal a severe threat to the myocardium and are often grouped together as acute coronary syndrome (ACS) for clinical assessment and management.

Arrythmias and sudden death
Other symptoms associated with coronary artery disease include palpitations, syncope and sudden death. Palpitations and syncope are non-specific signs and are not always associated with CAD.

Heart failure
Fluid retention in the ankles (pedal edema) and lungs (pulmonary edema) may signal that CAD has damaged the heart muscle, causing heart failure.

1.4 Diagnostic testing for CAD and IHD

The symptoms of CAD have poor specificity and sensitivity for CAD, so other modalities must be used to confirm or refute a clinical suspicion of CAD. Most of the diagnostic testing for IHD evaluates the impact of ischemia on the myocardium. Only angiography and coronary artery ultrasound provide direct information on the condition of the coronary arteries. Findings from these studies assist in risk assessment and decision making regarding treatment.

Electrocardiography (ECG)
The patterns of electrical activity transmission across the myocardium can signal ischemia changes to the myocardium. Mild ischemia generally causes ST-T wave depression, while impending death of the myocardium is signaled by ST-T wave elevation and T wave enlargement or inversion in the area affected. ECG changes start soon after the onset of a MI and evolve over several hours to days. Eventually, a Q-wave forms in the affected area, serving as a permanent marker that some myocardium has been lost.

ECGs obtained at rest and with exertion (exercise stress test) provide significant information about the adequacy of blood supply to the myocardium when its needs are increased with activity. Stress ECGs are less accurate in women or in persons with diabetes.

Cardiac biomarkers
Dead myocardial cells release several enzymes and other biomarkers that can be measured that indicate recent myocardial death. The earliest and most specific of the biomarkers is troponin I or T. These compounds can also be released in small amounts from cells that are profoundly ischemic or stressed, but have not yet completely died. Rapid testing techniques are now available that provide results within a few minutes in

the bedside environment. The appearance of these compounds in sufficient amounts indicates that death of the cells has already occurred.

Echocardiography
This study is conducted using sound waves across the chest and can be performed at the bedside by an experienced cardiac sonographer. The results can immediately be read by a trained cardiologist and can provide information on myocardial wall function. Areas of ischemia or partial damage may exhibit decreased movement (hypokinesis), poorly coordinated movement (dyskinesis) or a total absence of movement (akinesis) indicating the myocardium is dead. On occasion the echocardiogram may show paradoxical bulging movement suggesting an aneurysm of the ventricular wall that has previously been severely damaged by infarct. The condition of the heart valves and thickness of the myocardium (which may suggest years of uncontrolled hypertension) can be assessed. The efficiency of the pump action of the heart (ejection fraction) can be estimated. Stress tests can be performed with echocardiography, but it is technically difficult to quickly obtain an adequate scan in the exercising patient on a treadmill and requires a skilled cardiologist to assess the nuances of heart wall movement that may indicate ischemia. Pharmalogical agents can also be used to induce stress while doing the echocardiogram. Some data suggests that stress echocardiograms are more accurate in women.[7]

Radionucleotide imaging
Several radionucleotides are available to assess myocardial perfusion. The patient is given an infusion of a radiotracer and the heart is then imaged with a nuclear scan. The heart is generally evaluated at rest and then with some form of stress. The stress can be provided by exercise on a treadmill or pharmacologic stress that increases the heart rate and pumping activity. A decrease in radiotracer activity in areas of myocardium during the stress portion suggests areas of ischemia. This test has fair sensitivity and specificity, but false negatives and positives can occur.

Angiography
In the 1970's a method was developed to slide a small catheter into the coronary arteries from a percutaneous approach. The most commonly used site is the femoral artery in the groin. Dye is injected and observed by cine or direct fluoroscopy. The size, position and possible stenotic areas in vessels can be visualized. Many lesions are eccentric, so stenosis can vary depending on the angle of visualization. Reproducibility on measurement of stenosis is considered only moderate.

CT Angiography
Using a multi-slice CT, coronary vessel anatomy can be evaluated.

1.5 Risk Conditions associated with CAD

The risk of developing CAD is increased with age, male sex, tobacco use, high blood pressure, high serum total cholesterol and low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, and family history of premature CAD, especially if it occurs in men under the age of 55 years or in women under the age of 65 years. Diabetes mellitus, metabolic syndrome, physical inactivity and obesity are also

associated with an increased risk of CAD. Other risk factors include non-white ethnicity and stress. [5, 8-10] A number of risk stratification systems have been developed to help patients and clinicians in the complex decision making associated with IHD.

Framingham Risk Scoring System – This cardiovascular event risk scoring system was developed from a prospective, longitudinal, observational study of a community in the Boston area conducted by the National Institutes of Health.[11] The risk of developing a "hard" cardiovascular event of MI or cardiovascular death in the next 10 years can be calculated based on age, sex, tobacco use, blood pressure, total cholesterol, HDL cholesterol, prior MI and the presence of diabetes.[12] However, the study population consisted of white patients and may not predict accurate risk for non-white populations. Risk assessments can guide both primary and secondary prevention efforts for hypertension and lipid management, but are not accurate enough to provide specific guidance on which patients should be evaluated further for CAD. This risk assessment scoring system is available on the web.[9] Framingham: http://hp2010.nhlbihin.nte/atpiii/calculator.sap?usertype=prof

Other risk systems have been developed to assist management of a patient on presentation with ACS. These tools can provide guidance on surveillance and treatment measures. All three may be used at hospital admission.

TIMI Risk Score – The Thrombolysis in Myocardial Infarction (TIMI) Risk Scoring system was developed during a clinical trial of patients with UA/NSTEMI (non-ST elevation MI) to predict the 14-day risk of all cause mortality, MI and the need for urgent revascularization. The system uses data that is readily available at the time of presentation to an emergency room and requires a simple addition of dichotomous variables. The scoring system is highly predictive of a range of outcomes and has been used to assign treatment.[3, 13, 14]

GRACE Risk Model – The Global Registry of Acute Coronary Events (GRACE) Risk Model was developed on the basis of patients in GRACE and predicts in-hospital mortality, composite of in-hospital mortality or MI, and 6 month risk of all-cause mortality in patients presenting with NSTEMI-ACS, STEMI or, UA. It is used to provide a basis for guiding treatment type and intensity.[13, 15, 16]

PURSUIT Risk Model – The Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Risk Model is based on patients enrolled in the PURSUIT trial presenting with NSTEMI-ACS. The model is used to provide a basis for therapeutic decision making and evaluates critical factors associated with an increased 30-day risk of death and the composite of death or (re)MI. [3, 13, 17]

Table 3. Risk stratification tools for ACS at presentation to hospital

Risk stratification tool	When used	Patient presentation	Factors considered in risk assessment	Predicts
TIMI Risk Score[3, 13, 14]	At hospital admission, used to provide basis in therapeutic decision making	NSTE-ACS	1 point given for each of the following variables at admission: • Age ≥65 years • ≥3 risk factors for CAD • Prior coronary stenosis of ≥50%	14-day risk of composite outcomes: • All-cause mortality • New or recurrent MI • Severe recurrent ischemia requiring urgent

			• ST-segment deviation on ECG presentation • ≥2 anginal events in prior 24 hours • Use of aspirin in prior 7 days • Elevated serum cardiac biomarkers	revascularization
PURSUIT trial Risk Model[3, 13, 17]	At hospital admission, used to provide basis in therapeutic decision making	NSTE-ACS	Associated with increased risk (in order of strength): • Age • Heart rate • Systolic blood pressure • ST-segment depression • Signs of heart failure • Elevated cardiac enzymes	30-day risk of: • Death • The composite risk of death or (re)MI
GRACE study Risk Model [13, 15, 16]	At hospital admission, used to provide basis in guiding treatment type and intensity	NSTE-ACS, STEMI	• Older age • Killip class • Systolic blood pressure • ST-segment deviation • Cardiac arrest during presentation • Serum creatine level • Positive initial cardiac markers • Heart rate	• In-hospital mortality • Composite risk of In-hospital mortality or MI • 6-month risk of all-cause mortality

GRACE: Global Registry of Acute Coronary Events, NSTE: Non-ST-segment elevation acute coronary syndrome (includes UA/NSTEMI), TIMI: Thrombolysis in Myocardial Infarction, PURSUIT: Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy.

1.6 Treatment of CAD

Primary Prevention of CAD:

The American Heart Association recommends that everyone over the age of 40 be assessed for absolute risk of developing CAD at least every 5 years.[10] The Framingham risk scoring system provides a useful framework to discuss the risk and identify modifiable risk factors.[18] High quality evidence supports recommendations for smoking cessation, blood pressure, and lipid control to reduce the risk of developing CAD. Persons over age 50 can reduce their risk of sudden death due to CAD by taking an aspirin 81 mg-325 mg every day.

Secondary Prevention of CAD/IHD:

Once a person is diagnosed with CAD, should obtain baseline evaluation including an ECG, blood pressure determination, fasting lipid and glucose levels, and a risk factor assessment. Modifiable risk factors should be addressed.[19]

Evaluation with echocardiogram may identify patients with long-standing hypertensive heart disease or heart failure. A stress test (exercise or pharmacologic) will identify the degree and location of ischemia. A negative stress test may suggest that the symptoms are due to some other cause. Further evaluation will depend on the patient's symptoms, risk factors, and findings on stress testing and will be discussed below.

In general, persons with angina already have CAD lesions with at least 75% obstruction and are at increased risk of MI, heart failure and sudden death due to plaque destabilization and thrombosis. Evidence-based recommendations for medical management are now advised for all persons with CAD.[20] Medical management includes:

- Aspirin - to provide antithrombotic effect

- Beta blocker - to decrease the sympathetic system that may set off a plaque disturbance
- Statin to reduce further buildup of plaque and provide stabilization of the endothelium
- ACE-inhibitors should be considered for those with metabolic syndrome, diabetes, or heart failure. This medication has been shown to slow kidney decline and improve heart failure management.
- Blood pressure control – should start with beta blockers as noted above. ACE inhibitors and calcium channel blockers can be added as needed.

The ACC/AHA suggests the goals for treatment of stable angina are to (1) prevent MI and death and (2) reduce the occurrence of ischemia and (3) eliminate (or nearly eliminate) the symptoms of angina so that the patient can resume normal activities. The latter goal is often the patient's greatest concern.[5] Patients should be given nitrates and clear instructions on how to use them. Patients should be encouraged to maintain an active life style. Issues around exertion, and sexually activity should be discussed and patient concerns addressed.

Tertiary prevention

The management of patients with advanced CAD and IHD has been addressed in a number of guidelines by professional organizations. Both the disease and intervention guidelines involve the stent technology that is the focus of this assessment. The remainder of this technical review addresses other modalities for the management of CAD, including thrombolytic therapy, angiography, percutaneous coronary interventions (PCI), and coronary artery bypass grafting (CABG).

The evolution of percutaneous coronary intervention (PCI) from balloon angioplasty to stenting

PCI relieves coronary narrowing by utilizing a mechanical device (usually a balloon) at the end of a catheter to dilate an area of stenosis within the coronary artery. Access to the heart and coronary arteries is typically obtained through the femoral artery. The catheter is advanced into the ascending aorta and then threaded into the coronary artery. Angiography is then performed by injecting radiopaque dyes through the catheter tip to delineate the coronary artery anatomy and identify possible areas of stenosis. If a significant stenotic area is identified, the catheter tip can be advanced to that area and the balloon inflated to dilate the arterial lumen and compress the plaque. The balloon is then deflated and the catheter removed. This process, called a balloon angioplasty, was initially termed "percutaneous transluminal coronary angioplasty" (PTCA), but has now been shortened to "percutaneous coronary intervention (PCI)."

PTCA was first introduced in 1977 as the first non-surgical means of dilating the coronary artery.[21] Initially, the success rate was only 64%, with emergency CABG required in 14%, but over time, with increasing experience, the success rate grew to around 90%.[22] However, balloon dilation injures the vascular wall, resulting in a variety

of morphological changes, including (1) endothelial denudation and rapid accumulation of platelets and fibrin; (2) plaque disruption, causing intimal dissection, medial tearing, and aneurismal dilation of the media and adventia; (3) elastic recoil; and (4) post-injury arterial narrowing (constrictive negative remodeling). These changes or "controlled injuries" are responsible for acute vessel closure and restenosis, two of the major disadvantages of PTCA. Acute vessel closure typically occurs in 6-8% of cases within 24 hours following PTCA. Restenosis, defined as greater than 50% reduction in post-procedural luminal diameter, often manifests within the first 6 months after PTCA with rates ranging from 30% to 50%.[23]

The high rates of acute vessel closure and restenosis following PCI were the predominant factors that led to the development of bare-metal stents (BMS), as well as to widen the lumen and ensure a uniform shaped opening of the artery at the site of the plaque. A stent is a stainless mesh tube that can be collapsed and attached to the end of a balloon catheter. When the catheter tip is floated to an area of stenosis, the balloon is inflated to expand the stent. The balloon is then deflated and detached from the stent. The stent remains in the artery permanently to act as a physical scaffold to help keep the artery open. BMS were first introduced in 1986[24] and approved by the U.S. Food and Drug Administration (FDA) in 1993.[23]

As reported by Newsome et al 2008, a 10% decrease in restenosis rates, 22% to 32%, was observed in patients receiving BMS (versus PCI alone) in premarket clinical trials that led to FDA-approval of these devices. Although many efforts were made to further decrease the incidence of restenosis, rates within six months of BMS implantation remain high at 20-25%. These rates are even higher in patients with complex lesions or other serious disorders (diabetes, renal insufficiency) and the incidence has been reported to approach 80% in such populations. Furthermore, approximately 60-80% of restenotic lesions require repeat revascularization.[25] As stated previously, restenosis is caused primarily by elastic recoil and neoinitimal hyperplasia. Because stents were designed to prevent elastic recoil and negative remodeling, restenosis following a BMS is primarily caused by neointimal proliferation, an inflammatory response that results in vessel lumen encroachment.[19] Another complication of BMS is subacute stent thrombosis (blood clot formation) which initially occurred in 4-24% of BMS patients.[26-31] However, addition of dual-antiplatelet therapy (clopidogrel and aspirin) as well as refinement of the stent placement procedure reduced the occurrence of BMS thrombosis to the current rate of 1.2%.[32-34]

The continued difficulties with early restenosis and thrombosis with BMS led investigators to explore ways to modify the stent to minimize these adverse outcomes, leading to the conception of drug-eluting stents (DES). DES are essentially BMS that have been coated with a polymer containing an antiproliferative drug. These drugs inhibit vascular smooth cell proliferation and migration and are released from a non-resorbable polymer into the local environment to achieve high local drug concentrations. The drug is intended to prevent the neo-intimal hyperplasia that appeared to cause the restenosis observed with BMS implantation. According to Newsome et al, when compared with BMS, DES have been shown to reduce neointimal hyperplasia, restenosis, and

reintervention at 6 to 12 months, with a continued 74% reduction in restenosis at 4 years.[23]

However, despite the reduction in restenosis rates, reports of high rates of subacute in-stent thrombosis (clot formation) after DES placement became cause for concern soon after FDA approval of these devices.[35, 36] Thrombosis is a serious complication that often results in acute MI or death. The FDA convened an advisory panel meeting in 2006 to review the data on DES and concluded that DES did not increase the risk of in-stent thrombosis if used for their approved indications (on-label use): lesions that were newly diagnosed, less than 28-30mm long, and in clinically stable patients without other serious medical problems. The risk for in-stent thrombosis is approximately 1% when DES are implanted for the approved indications, a rate similar to that which occurs with BMS. However, it is estimated that at least 60% of DES use is off-label, meaning that stents are implanted in patients who do not meet the criteria of the premarket clinical trials. These patients have an approximately 5% chance of developing in-stent thrombosis following DES implantation. The FDA concluded that off-label use of DES, such as implantation in complex lesions (e.g., bifurcation lesions, lesions requiring overlapping stents, or lesions from acute MI) or in patients with conditions such as renal dysfunction or diabetes, is what led to increased rates of stent thrombosis.[26, 29, 37, 38] Thrombotic occlusion of stents has been and remains a concern since the early days of stenting.

In 2002, all stents were BMS. Within a year after the FDA approval of the first DES stent, 75% of all PCI utilized a DES stent,[39] and by 2005 nearly 90% of all PCI utilized a DES.[40] DES were used in approximately 80% of PCI procedures in the U.S. [37] By 2003, an estimated 84% of PCI patients received a stent,[2] and today, virtually all PCI procedures involve placement of a stent.[38]

To date, the FDA has approved four DES to treat symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries, Table 4. The first DES to be approved by the FDA were sirolimus- and paclitaxel-eluting stents (Cypher©, Cordis Corporation and Taxus©, Boston Scientific) in 2003 and 2004. Sirolimus is a macrolide immunosuppressant that also inhibits mammalian target of rapamycin (mTOR) thereby blocking cell division by interfering at the transition from G1 to S phase.[41] Paclitaxel is a derivative of the yew plant that inhibits the cell cycle by stabilizing microtubules and has been used as an anti-proliferative drug in the treat of breast, lung and ovarian cancer.[42] In 2008, two other DES were approved: zotarolimus- and everolimus-eluting stents (Endeavor©, Medtronic Vascular and Xience©, Abbott Vascular). Zotarolimus is a tetrazole-containing immunosuppressant. Its mechanism of action has not been established conclusively but *in vitro* research suggests that zotarolimus binds to FKBP-12, leading to the formation of a trimeric complex with the protein kinase mTOR inhibiting its activity thus halting cell division, much like sirolimus.[43] Everolimus is a novel semi-synthetic macrolide immunosuppressant synthesized by chemical modification of rapamycin (sirolimus). At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, it binds to and interferes with FKBP-12, leading to the inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 phase.[44]

Indications, contraindications for FDA-approved DES and BMS

To date, the FDA indications of four DES to treat symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries with indications listed in Table 4.

Table 4. FDA indications of four DES to treat symptomatic ischemic disease in patients with de novo lesions in native coronary arteries

DES (manufacturer)	Date of FDA approval	Drug	Lesion length	Lesion diameter	Number of lesions (stents)	Specific contraindications
CYPHER (Cordis Corporation)	4/24/2003	Sirolimus	≤30mm	2.5-3.5mm	1 (≤2 overlapping)	hypersentivity to sirolimus or its derivatives known hypersensitivity to polymethacrylates or polyolefin copolymers
TAXUS Express (Boston Scientific Corporation)	3/4/2004	Paclitaxel	≤28mm	2.5-3.75mm	1 (1)	known hypersensitivity to paclitaxel or structurally-related compounds known hypersensitivity to the polymer or its individual components
Endeavor (Medtronic Vascular)	2/1/2008	Zotarolimus	≤27mm	2.5-3.5mm	1 (1)	known hypersensitivity to zotarolimus or structurally-related compounds known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum) known hypersensitivity to the Phosphorylcholine polymer or its individual components
XIENCE (Abbott Vascular) will also be distributed as Promus	7/2/2008	Everolimus	≤28mm	2.5-4.25mm	1 (1)	known hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers

Contraindications for FDA-approved DES include:[43-46]

- Patients with a hypersensitivity to stent components, including the drugs and their derivatives, polymers used to coat the stent, and the metals the stent is composed of
- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon

To date, the FDA has approved nine BMS, to include two coated stents, to treat symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries with indications listed in Table 5.

Table 5. FDA indications of nine BMS to treat symptomatic ischemic disease in patients with de novo lesions in native coronary arteries

BMS (manufacturer)	Date of FDA approval	Metal	Lesion length	Lesion diameter	Number of lesions (stents)	Specific contraindications
BeStent2 with Discrete Technology OTW and Rapid Exchange Coronary Stent Delievery Systems (Medtronic)	10/16/2000	316L (grade 2) stainless steel with a gold markers at both ends of the stent	≤30mm	3.0-4.0 mm	NR	antiplatelet and/or anticoagulation therapy in contraindicated a lesion that prevents complete inflation of an angioplasty balloon
Liberte Monorail and OTW Coronary Stent Systems (Boston Scientific)	04/12/2005	316L grade stainless steel	≤28mm	2.75-5.0 mm	NR	contraindication to antiplatelet and/or anticoagulant therapy a lesion that prevents complete inflation of an angioplasty balloon known allergies to stainless steel
MULTI_LINK VISION RX and OTW Coronary Stent System (Guidant)	07/16/2003	L-605 Cobalt Chromium (CoCr) alloy	≤25mm	3.0-4.0 mm	NR	antiplatelet and/or anticoagulation therapy in contraindicated a lesion that prevents complete inflation of an angioplasty balloon
NIRflex Premounted Coronary Stent System (Medinol Ltd.)	10/24/2003	316L grade stainless steel	≤25mm	2.5-4.0 mm	NR	contraindication to antiplatelet and/or anticoagulant therapy a lesion that prevents complete inflation of an angioplasty balloon known allergies to stainless steel
Driver Over-The-Wire, Rapid	10/01/2003	Co-Ni-Cr-Mo alloy	≤30mm	3.0-4.0 mm	NR	contraindication to antiplatelet and/or

BMS (manufacturer)	Date of FDA approval	Metal	Lesion length	Lesion diameter	Number of lesions (stents)	Specific contraindications
Exchange, and Multi Exchange Coronary Stent Systems (Medtronic Vascular)						anticoagulant therapy a lesion that prevents complete inflation of an angioplasty balloon
Express/Express 2 Monorail and Over-The-Wire Coronary Stent Systems	09/11/2002		≤18mm treatment of abrupt or threatened abrupt closure in patients with failed interventiona l therapy: ≤30mm	3.0-5.0 mm treatment of abrupt or threatened abrupt closure in patients with failed interventional therapy: 2.25-5.0mm	NR	antiplatelet and/or anticoagulant therapy is contraindicated judged to have a lesion that prevents complete inflation of an angioplasty balloon known allergies to stainless steel.
Ave Micro Stent II Over-The_Wire Coronary Stent System and Ave GFX Over-The – Wire Coronary Stent System (Medtronic Ireland)	10/23/1997	NR	<30mm	3.0-4.0mm	NR	NR
ACS Multi-Link TM Coronary Stent System (Abbot Vascular Inc.)	10/02/1997	NR	device with acs multi-link(tm) css, acs rx multi-link hp(tm) css and acs otw multi-link hp(tm) css delivery platforms: <20mm device with acs rx multi-link(tm) css delivery platform: <22mm	device with acs multi-link(tm) css, acs rx multi-link hp(tm) css and acs otw multi-link hp(tm) css delivery platforms: 3.0mm-3.75mm device with acs rx multi-link(tm) css delivery platform: 3.0-3.5mm	NR	NR
Gianturco-Roubin Coronary Fles-Stent (Cook, Inc.)	07/22/1993	NR	NR	NR	NR	NR

Table 6. Coated stents approved by the FDA

BMS (manufacturer)	Date of FDA approval	Metal and coating	Lesion length	Lesion diameter	Number of lesions (stents)	Specific contraindications
Bio*divYsio* (Biocompatibles Cardiovascular, Inc.)	9/20/2000	316-L grade stainless steel cross-linked phosphorylcholine (PC) polymer	≤25mm	3.0-4.0 mm		intolerance or contraindication to antiplatelet or anticoagulant therapy a lesion that prevents complete inflation of an angioplasty balloon
Rithron-XR Coronary Stent System (Biotronik GmbH)	04/29/2005	316-L grade stainless steel with a gold markers at both ends of the stent amorphic silicon carbide	≤20mm	3.0-4.0 mm		antithrombogenic and atnicoagulent therapy in contraindicated stenoses that inhibit the complete inflation of an angioplasty balloon allergies to stainless steel, gold, or silicon carbide, or exhibit incompatibility with the coating material

Devices approved for use outside of the US market:

- Abbott Laboratories Inc. (Abbott Park, IL, USA): everolimus-eluting XIENCE V stent; February 2006
- Biosensors International Inc. (Singapore, China): paclitaxel-eluting Axxion stent; July 2005
- Boston Scientific Inc. (Natick, MA, USA): paclitaxel-eluting TAXUS Liberté stent; January 2003
- Boston Scientific Inc. (Natick, MA, USA): paclitaxel-eluting TAXUS Express stent; February 2005
- Boston Scientific Inc. (Natick, MA, USA): everolimus-eluting Promus stent; October 2006
- Conor Medsystems Inc. (Menlo Park, CA, USA): paclitaxel-eluting CoStar stent; February 2006

- Cook Group Inc. (Bloomington, IL, USA): paclitaxel-eluting Achieve stent; September 2002. This stent has not been commercially available since November 2002.
- Cook Group Inc. (Bloomington, IL, USA): paclitaxel-eluting V-Flex Plus PTX stent; September 2002. This stent has not been commercially available since November 2002.
- Cordis Corporation (Miami, FL, USA): sirolimus-eluting Cypher stent; April 2002
- Cordis Corporation (Miami, FL, USA): sirolimus-eluting Cypher Select stent; April 2004
- Cordis Corporation (Miami, FL, USA): sirolimus-eluting Cypher Select Plus stent; June 2006
- Eurocor Inc. (Bonn, Germany): drug-eluting Taxcor stent; July 2006
- Medtronic Inc. (Minneapolis, MN, USA): zotarolimus-eluting Endeavor stent; August 2005
- Sahajanand Medical Technologies Inc. (Surat, Gujarat, India): paclitaxel-eluting Infinnium stent; December 2005
- Sorin Biomedica Cardio Inc. (Milan, Italy): tacrolimus-eluting Janus Flex stent; February 2006
- Translumina Inc. (Hechingen, Germany): drug-eluting Yukon stent; 2006
- Beijing Lepu Medical Devices Inc. (Beijing, China): sirolimus-eluting Tong Xin Partner stent; 2005
- MicroPort Medical Inc. (Shanghai, China): rapamycin-eluting Firebird stent; 2003

Complications

Major complications associated with PCI with stent placement (both BMS and DES) include death, acute MI, and stroke; other complications include aneurysm, arrythmias, coronary perforation or dissection, distal emboli, intracoronary thrombosis, heart failure, infection, pericardial effusion, prolonged angina, renal failure, respiratory failure, tamponade, and vessel trauma requiring surgical repair.[19] In addition, abrupt stent closure, stent compression, stent migration, incomplete stent apposition, failure to deliver the stent to the intended site, and allergic or drug reactions may occur.

Multiple Stents

In practice, stent placement has become increasingly common in situations outside FDA approved indications. Characteristics of patients encountered commonly in clinical practice may differ from those of patients enrolled in the FDA trials. One or more vessels may be involved and/or narrowing may not be confined to a small or isolated region of a

vessel in a large percentage of patients seen in a cardiology practice. Use of stents in multiple vessels; use of multiple stents in the same vessel; left main disease; placement at a branch; emergent clinical presentation; or in vessels with diameters or lesion lengths not currently included in the FDA approved indications have become increasingly common. Such uses account for as much as 70% of all stent placements even though such uses are not part of the currently approved indications and the related research on safety and efficacy. The placement of multiple stents is estimated to account for as much as 30% of non-approved usage. A specific patient population for multiple stent was not identified, though patients in whom multiple stents are placed typically have a more complex condition and a CAD disease state that is more widely diffused. Thus, there are uncertainties regarding the evidence for use of cardiac stents (bare-metal or drug-eluting) for more complex indications outside of the uses studied and approved by the FDA.

Comparators

Coronary Artery Bypass Surgery (CABG)

Description
CABG is the surgical comparator for PCI-stent. CABG is a surgical procedure in which conduits are placed to reroute blood flow around blockages in the coronary arteries. The conduits are made from segments of the patient's arteries or veins that have been excised from other areas. The saphenous vein from the leg is commonly used; the left internal mammary artery has also been used, as it tends to remain open longer than the saphenous vein and its use as a graft is associated with a reduction in perioperative mortality. CABG is typically performed with the heart stopped, requiring the use of cardiopulmonary bypass. More recently, some CABG procedures are being performed through limited incisions and without the use of cardiopulmonary bypass, which may reduce morbidity and/or mortality associated with CABG. Antiplatelet therapy in the form of aspirin is continued indefinitely after CABG.[47]

Advantages
CABG is the preferred procedure over PCI for left main coronary artery stenosis or three-vessel disease by the ACC/AHA[20] because a more complete revascularization independent of lesion complexity or number of diseased lesions is possible. Another major advantage of CABG over PCI is greater durability. A recent study of 2000 patients who underwent CABG in western Sweden found that 5 and 10 years following CABG, only 56% and 54% (respectively) of patients remained free of chest pain.[48]

Disadvantages
CABG is a major surgery requiring several hours on the cardiopulmonary machine. It requires a large team of surgeons and highly-trained technicians to perform and thus is more expensive compared with PCI. The most common problem following surgery is the return of angina.[47] Although research shows that 98% of patients remain angina-free for the first year following CABG, only about half remain free of angina at 10 to 12 years post-surgery.[49] Risks associated with bypass surgery may include risks associated with

anesthesia, death, heart attack, stroke, excessive bleeding, infection, and subtle problems in long-term memory, comprehension, and concentration.

Optimal Medical Therapy (OMT)

Management of CAD with various medications, rather than surgical procedures, has been gaining increasing recognition and respect for its effectiveness. Although CAD is characterized by arterial stenosis, it is the unstable plaque creating thrombosis that is responsible for most MI and cardiovascular death.

Goals for treatment of CAD are prevention of MI and death as well as a decrease in symptoms. Medical management may achieve these goals in part by controlling blood pressure and cholesterol levels. Treatment includes lifestyle changes, including exercise, changes in diet, and cessation of tobacco use in addition to pharmacological therapy. The ACC/AHA recommends aspirin and beta-blockers as initial therapy, and calcium antagonists and/or long-acting nitrates, nitroglycerin, and lipid-lowering therapy as needed for high cholesterol. Daily use of aspirin in patients with stable angina has been correlated with a 33% decrease in risk of adverse cardiovascular events. In patients with unstable angina, aspirin was associated with a reduction in short- and long-term risk of MI. In patients with chronic stable angina, beta-blockers decrease heart rate and blood pressure during physical exertion, thus decreasing the likelihood of angina. Calcium antagonists reduce coronary vascular resistance and increase coronary blood flow.[5, 8, 20]

Data from the RITA-II (Randomized Intervention Treatment of Angina) trial, the VA cooperative study, suggested that medical management was as effective as PCI in reducing the risk of MI in patients with chronic stable angina. However, PCI relieved symptoms more effectively than medical management alone. In addition, revascularization procedures improved quality of life more than medical therapy alone. Results from the COURAGE study suggest that for stable CAD, medical therapy was as effective as PCI for long term outcomes.

1.7 Clinical Guidelines

Overview

A number of clinical guidelines for treating patients with CAD are available on the National Guideline Clearinghouse (NGC), the primary repository for evidence-based clinical guidelines [http://www.guideline.gov]. These guidelines include those on stable CAD, UA/NSTEMI and STEMI, and use of PCI. Another guideline on the appropriateness for PCI was published in January of 2009 and is not yet available on the NGC, but is available on Pubmed.[50] Unfortunately, no guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES, the central focus of this technology assessment. However, the guidelines on CAD management provide an important perspective on the setting and issues involved in the decisions leading to coronary stent placement. The guidelines also address some of the broader questions raised by the Washington State Health Technology Assessment Program as outlined in the background of this document. Thus, we have included a brief overview of these guidelines.

National Guideline Clearinghouse (NGC)

The NGC includes 36 potentially relevant guidelines for CAD management, including clinical management of various symptoms, clinical conditions and interventions. The most extensive and detailed guidelines were formulated by combined efforts of the American College of Cardiology (ACC) and American Heart Association (AHA) in conjunction with other US-based professional societies. These appear to be the most salient for patient care in Washington State. The most recent ACC/AHA guidelines with focused updates are listed in Table 7 below.

Table 7. ACC/AHA guidelines

Guideline Topic	Reference
Chronic Stable Angina	Initial guideline, 1999[5]
	Update 2002[8]
	Update 2007 on medical therapy[20]
UA/NSTEMI	Initial guideline, 2000[51]
	Update 2002[52]
	Update 2007[13]
STEMI	Initial guideline, 2004[53]
	Update 2007[14]
PCI	Initial guidelines 2001[54]
	Update 2005[55]

	Focused update, 2007[3]
Special Populations	NSTEMI in the elderly, Part I [56]
	STEMI in the elderly, Part II[57]
	Women

Selected recommendations from ACC/AHA clinical guidelines relevant to stenting are briefly summarized below, then are compared to guidelines from other professional organizations. *The reader is advised to consult the published guideline to review other recommendations in the guideline.*

Ratings of recommendations

Almost all of the recommendations from the ACC/AHA include an assessment of quality of evidence underlying the recommendation and the benefit versus risk using the following system[3]:

Evidence Level

- Level A: Multiple randomized clinical trials or meta-analysis
- Level B: Single randomized clinical trial or observational data (case control, longitudinal data)
- Level C: Case reports, expert opinion, or current clinical practice

Benefit versus risk

- Class I: Benefit >>> risk; procedure or treatment SHOULD be performed (i.e. is recommended, indicated, useful/effective/beneficial)
- Class IIa: Benefit >> risk; procedure or treatment IS REASONABLE to perform
- Class IIb: Benefit < risk, procedure or treatment MAY BE CONSIDERED
- Class III: Risk outweighs the benefit; procedure SHOULD NOT be performed

A recent review was undertaken to assess the scientific evidence underlying the 53 ACC/AHA Clinical Practice Guidelines published between 1984 to 2008.[58] These guidelines included 7196 recommendations on 22 topics. Over time, the total numbers of recommendations increased 48%, and were primarily in Class II recommendations. Of the current recommendations, only 11% of the recommendations were supported with Level A evidence, while 48% had level C evidence. Although most of the Level A evidence was concentrated in Class I recommendations, only 19% of the Class I recommendations had Level I evidence. The investigators noted a high proportion of guidelines were developed from lower levels of evidence or expert opinion and that better quality evidence to support recommendations did not appear to be increasing over time.

Table 8. Distribution of Levels of Evidence Across Classes of Recommendation Adapted from table 3 [58]

Guidelines	Year	I-A	I-B	I-C	II-A	II-B	II-C	III-A	III-B	III-C
Disease										
Stable angina	2002	12(5.1)	34(14.5)	32(13.6)	1(0.4)	39(16.6)	58(24.7)	2(0.9)	19(8.1)	38(16.2)
Unstable angina	2007	57(19.1)	82(27.5)	47(15.8)	5(1.)	52(17.4)	25(8.4)	8(2.7)	5(1.7)	16(5.4)
STEMI	2004	45(10.7)	95(22.5)	108(25.6)	5(1.2)	50(11.8)	68(16.1)	7(1.7)	21(5.0)	23(5.5)
Interventional										
PCI (n=136)	2005	14(10.3)	18(13.2)	7(5.1)	1(0.7)	34(25.0)	34(25.0)	0	4(2.9)	24(17.6)
CABG (N=84)	2004	12(14.3)	25(29.8)	2(2.4)	4(4.8)	19(22.7)	11(13.1)	0	7(8.3)	4(4.8)
Diagnostic										
Exercise testing (n=71)*	2002	0	2(2.8)	1(1.4)	0	1(1.4)	2(2.8)	0	0	3(4.2)
Radionuclide Imaging (n=84)	2003	4(4.8)	28(33.3)	4(4.8)	0	29(34.5)	14(16.7)	0	1(1.2)	4(4.8)

* 62 of the 71 recommendations had no evidence rating

Optimum Medical Therapy (OMT)

Optimum medical therapy provides fundamental and effective therapy for CAD.[20] OMT was initially described as appropriate for management of chronic stable angina, its value has become increasing appreciated for secondary prevention and management of other IHD syndromes, including unstable angina, MI, and heart failure. Most guidelines view OMT as an adjuvant to other modalities, but a few recent studies suggest it as an appropriate alternative for certain populations and disease conditions. All of the CAD-related guidelines emphasize the fundamental importance OMT. In addition to the recommendations below, many also add nitrates as needed for intermittent anginal pain or long-acting form for frequent angina.

Table 9. Selected recommendations for Optimum Medical Therapy[20]

Rating	Recommendation
I-B	Smoking Cessation
I-A	Blood Pressure Control less than 140/90, 130/80 for those diabetes or chronic kidney disease
I-C	Preferred use of beta blocker for blood pressure control
I-B	Dietary changes – low fat diet, low sodium, weight loss if obese
I-B	Daily physical activity
I-A	Lipid management – LDL < 100 mg/dl using lipid-lowering agents
II-B	LDL goal < 70 mg/dl is reasonable in person with high-risk CAD
I-A	Aspirin 81-325 mg per day
I-A	Beta blocking agents for those with MI, ACS, or heart failure

I-A	ACE inhibitors for those with ejection fraction < 40%, diabetes or renal disease

Chronic stable angina guidelines (ACC/AHA)
OMT is emphasized for all patients[20]

Table 10. Chronic stable angina guidelines (ACC/AHA)[3]

Rating	Guideline
I-A	CABG for left main coronary disease, 3 vessel disease, 2 vessel disease involving significant left anterior descending CAD or abn LV function
IIa-B	PCI for asymptomatic ischemia or CCS class I or II angina and with 1 or more significant lesions in 1 or 2 coronary arteries suitable for PCI with a high likelihood of success and a low risk of morbidity and mortality. The vessels to be dilated must subtend a moderate to large area of viable myocardium or be associated with a moderate to severe degree of ischemia on noninvasive testing.
IIa-C	PCI for asymptomatic ischemia or CCS class I or II angina, and recurrent stenosis after PCI with a large area of viable myocardium or high-risk criteria on noninvasive testing.
IIa-B	PCI for asymptomatic ischemia or CCS class I or II angina with significant left main coronary artery disease (CAD) (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for coronary artery bypass grafting (CABG).
IIb-B	The effectiveness of PCI for patients with asymptomatic ischemia or CCS class I or II angina who have 2- or 3-vessel disease with significant proximal left anterior descending (LAD) artery CAD who are otherwise eligible for CABG with 1 arterial conduit and who have treated diabetes or abnormal LV function is not well established.
IIb-C	PCI might be considered for patients with asymptomatic ischemia or CCS class I or II angina with nonproximal LAD CAD that subtends a moderate area of viable myocardium and demonstrates ischemia on noninvasive testing.

Rating	Guideline
III –C	PCI is not recommended in patients with asymptomatic ischemia or CCS class I or II angina who do not meet the criteria as listed above or who have 1 or more of the following: a. Only a small area of viable myocardium at risk b. No objective evidence of ischemia c. Lesions that have a low likelihood of successful dilatation d. Mild symptoms that are unlikely to be due to myocardial ischemia e. Factors associated with increased risk of morbidity or mortality f. Left main disease and eligibility for CABG g. Insignificant disease (less than 50% coronary stenosis)

Unstable angina/NSTEMI (Non-ST-Segment Elevation MI) – Acute Coronary Syndrome (ACS) Guidelines (ACC/AHA)

Definition: Angina of increasing severity, duration, or onset, accompanied by ST depression or T wave inversion on EKG and troponin elevation.[13]

Table 11. Unstable angina/NSTEMI (Non-ST-Segment Elevation MI) – Acute Coronary Syndrome (ACS) Guidelines (ACC/AHA)[3]

Rating*	Recommendation
I-A	Early invasive PCI if no serious comorbidity, lesion amenable to PCI + characteristics for invasive therapy
I-B	PCI (or CABG) – 1 or 2 vessel disease ± significant proximal LAD CAD but with large areas of viable myocardium + high risk criteria on noninvasive testing
I-A	PCI (or CABG)- patients w/multivessel disease + suitable anatomy + normal LV function, without diabetes
I-A	IV platelet GPIIb/IIIa inhibitor useful with PCI
I-B	Diagnostic angio with intent to perform revasculalrization in patients with refractory angina or hemodynamic or electrical instability (w/o serious comorbidities or contraindications

IIa-C	PCI for focal saphenous vein graft lesions or multiple stenosis + poor candidates for reoperative surgery
IIa-B	PCI (or CABG) for 1-2 vessel CAD +/- significant prox LAD but with mod area of viable myocardium showing ischemia
IIa-B	PCI (or CABG) for 1 vessel disease with significant proximal LAD CAD
IIa-B	PCI with significant left main CAD (>50% stenosis) if lesion amenable to PCI and not a surgical candidate or hemodynamically unstable
IIb-B	PCI for single-vessel or multivessel CAD who have 1 or more lesions with reduced likelihood of success
IIb-B	PCI for 2-3 vessel disease, significant proximal LAD CAD and treated diabetes or abnormal left ventricular function
IIb-B	In initially stabilized patients, selectively invasive strategy may be considered for pt with elevated risk for clinical events, including those with elevated troponin
IIb-C	Invasive strategy may be reasonable for those with renal insufficiency

* Class of recommendation and basis of evidence

Class III

1. Percutaneous coronary intervention (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. (*Level of Evidence: C*) (New recommendation*)

2. In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:

    a. Only a small area of myocardium at risk (*Level of Evidence: C*)

    b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success (*Level of Evidence: C*)

    c. A high risk of procedure-related morbidity or mortality (*Level of Evidence: C*)

    d. Insignificant disease (less than 50% coronary stenosis) (*Level of Evidence: C*)

    e. Significant left main CAD and candidacy for CABG (*Level of Evidence:*)

Whether PCI or CABG is chosen is influenced by the patient's coronary anatomy, anticipated life expectancy, severity of disease (ventricular function, functional capacity, severity of symptoms, and the amount of viable myocardium at risk), and comorbidity.[3]

Based on the recommendations, a patient that presents with ACS should be managed in the following fashion:

Early risk stratification[13]
Upon presentation with chest pain or other symptoms suggestive of ACS, the following steps should be taken:

- Rapid assessment for:
  - risk of obstructive CAD
  - risk of cardiovascular events (e.g., death or (re)MI)
- ECG conducted:
  - within 10 minutes of arrival in the hospital,
  - every 15-30 minutes thereafter if the ECG is not diagnostic but chest pain persists.
  - continuous ECG monitoring may be performed in patients if the ECG is not diagnostic but chest pain persists
- Patient should be given oxygen by nasal cannula or mask and 325 mg of Aspirin (not enteric coated). Patient with chest pain should be given nitroglycerin 0.4 mg sl or morphine IV to control pain.
- Cardiac biomarkers, preferably a cardiac-specific (TnT or TnI), measured:
  - as soon as possible
  - repeat after 8-12 hours until levels begin to decline in order to provide information regarding infarct size and the dynamics of necrosis
  - repeat after 8-12 hours in patients with unelevated cardiac biomarkers
- Risk-stratification models may be used to assist in the decision-making process regarding treatment:
  - TIMI (Thrombolysis in Myocardial Infarction)
  - GRACE (Global Registry of Acute Coronary Events)
  - PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy)
  - Ideally, a combination of these should be used, as appropriate

Immediate management[3]
(from ACC/AHA UA/NSTEMI guideline revision 2007)

- Patient history, physical examination, 12-lead ECG, and cardiac biomarker measurements should be considered to make a diagnosis of:
  - definite ACS
  - possible ACS
  - chronic stable angina
  - noncardiac diagnosis

- Angina grade defined in accordance with the Canadian Cardiovascular Society Classification System.[5]
- If ACS is suspected but ECG and cardiac biomarker measurements are normal:
  - an exercise or pharmacological stress test or a noninvasive imaging test (e.g., CCTA) should be conducted within 72 hours
  - ECG repeated as described above.
  - cardiac biomarkers retested as described above
  - precautionary pharmacological treatment may be given.
- If ACS is definite and the patient has continual ischemia as well as positive cardiac biomarkers, new ST-segment deviations, new deep T-wave inversions, hemodynamic abnormalities, or a positive stress test, the patient should be admitted.
- If ST-segment is elevated in leads V_7 to V_9 as a result of left circumflex occlusion, immediate reperfusion therapy should be considered.

Early hospital care[13]

- Patients with UA/NSTEMI, ongoing symptoms that suggest ACS, positive cardiac biomarkers, or ECG ST-segment deviations should be admitted for continuous monitoring and either invasive or conservative treatment, as outlined in Table D. In addition, LV function should be assessed.

Revascularization[13]

- The SCAI lesion classification may be helpful in assessing the risk of complications with PCI[19], Table 12.
- Variables associated with risk of death as a result of PCI include:
  - advanced age
  - female gender
  - diabetes
  - prior MI
  - multivessel disease
  - left main or equivalent coronary disease
  - a large area of myocardium at risk,
  - pre-existing impairment of LV or renal function
  - post-PCI worsening of renal function
  - collateral vessels supplying significant areas to myocardium that originate distal to the segment to be dilated
  - periprocedural stroke
  - PCI in the setting of STEMI (versus elective PCI)
- In general, an early invasive PCI strategy is considered appropriate for patients with:
  - lesions amenable to PCI
  - no high-risk features or serious comorbidity, including:
    - 3-vessel CAD
    - left main stenosis

  - left ventricular dysfunction
  - treated diabetes mellitus

- CABG is considered appropriate for patients with any of these conditions
- Medical therapy may be an appropriate alternative to PCI or CABG in patients with 1- or 2- vessel disease in the absence of the above comorbidities

Table 12. SCAI Lesion Classification System[19]

Lesion classification	Lesion morphology
Type I	• Does not meet any criteria for type C lesion • Patent
Type II	• Meets any of the criteria for type C lesion (except total occlusions >3 months old and/or bridging collaterals) • Occluded
Type III	• Does not meet any criteria for type C lesion • Occluded
Type IV	• Meets any of the criteria for type C • Occluded
Type C (high-risk) lesion	• Diffuse (length >2 cm) • Excessive tortuosity of proximal segment • Extremely angulated segments, >90° • Total occlusions >3 months old and/or bridging collaterals (high risk for technical failure and restenosis, not for acute complications) • Inability to protect major side branches • Degenerated vein grafts with friable lesions (high risk for technical failure and restenosis, not for acute complications)

SCAI: Society for Cardiovascular Angiography and Interventions

Appropriateness criteria for Interventions for CAD

The focus of revascularization should be the improvement in health outcomes (e.g. mortality, freedom from MI, quality of life). However, based on published evidence, identification of the most appropriate indications for PCI with stenting or of specific patient groups which may benefit most from these interventions is not always clear.[59]

Appropriateness Criteria for Coronary Revascularization (ACCR) were published in January 2009 as a joint report of the American College of Cardiology Foundation (ACCF) Appropriateness Criteria Task Force, the Society for Cardiovascular Angiography and Interventions (SCAI), Society of Thoracic Surgeons (STS), American Association for Thoracic Surgery (AATS), American Heart Association (AHA) and the American Society of Nuclear Cardiology (ASNC) as a supplement to available ACC/AHA clinical guidelines.[50]

In addition to providing a framework for clinical decision making and discussions between providers and patients regarding treatment options, these criteria may facilitate assessment of utilization patterns and overall patterns of patient care. While they are not intended to replace clinical judgment, they provide guidance regarding the suitability of coronary revascularization in a diverse set of common clinical scenarios. In general, the criteria consider both PCI and CABG as viable revascularization procedures but provide some specific suggestions for when each of these may be more appropriate. The criteria and their basis are briefly described below. Interested readers are encouraged to review the entire report.[50]

Development of the criteria reportedly combined evidence-base medicine precepts with clinical guidelines and practical clinical experience by use of a modified Delphi process with a technical panel of providers. The panel was comprised of physicians with varying perspectives and not comprised solely of experts (e.g. interventional cardiologists or cardiovascular surgeons). External review was also done as part of the process. The authors of the report indicate that no indications or scenarios rated as "appropriate" correlated with the ACC/AHA Class III recommendations and similarly, none of the "inappropriate" indications correlated with Class I guideline recommendations. (See below for summary of Class definitions). For each indication, recommendations from ACC/AHA clinical guidelines and the level of evidence and class for the guideline recommendations are given if available. The extent to which the appropriateness ranking for each indication is supported by high quality evidence from research is not, however, explicitly stated. Some indications have no current relevant guideline recommendation and now description of supporting evidence. Descriptions of FDA indications for stent use are not explicitly described as part of the indications or appropriateness criteria.

A number of variables and their permutations go into the decision making process, however, the most common variables for most situations are:

1. Patient clinical presentation (e.g. stable angina, ACS, etc.)
2. Angina severity (e.g. asymptomatic, CCS class)
3. Extent of ischemia or myocardium at risk based on non-invasive testing and the presence/absence of prognostic factors such as decreased left ventricular function, diabetes, congestive heart failure (CHF).
4. Extent of medical therapy
5. Extent of anatomic disease based on angiography (e.g. number of vessels, which vessels)

In the report, risk stratification for traditional exercise testing is as follows:

- **Low risk** stress test findings are associated with a cardiac morality of < 1% per year
- **Intermediate-risk** findings are associated with a 1%-3% per year cardiac mortality
- **High-risk** findings are associated with > 3% per year cardiac mortality.

Implicit in the above stratification is determination of the extent of myocardial ischemia or myocardium at risk. In clinical practice, the role of the first four factors is critical in decision making before evaluation of the coronary anatomy. In general keeping with ACC/AHA clinical guidelines, with the exception of presentation with acute myocardial infarction, these four aspects should be thoroughly evaluated prior to consideration for revascularization.

The report describes appropriateness for 73 different clinical scenarios (indications) considered by the group to represent the most common ones leading to possible revascularization. Each indication was assessed by the panel based using the following definition:

> Coronary revascularization is appropriate when the expected benefits in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure.

A nine-point scale was used to evaluate each indication for appropriateness. Scores were divided into the following somewhat arbitrary categories (emphasis is as written in the report):

> Appropriate: Score 7-9: Appropriate for the indication provided, meaning that coronary revascularization **is** generally acceptable and **is** a reasonable approach for the indication and is **likely** to improve the patients' health outcomes or survival.
>
> Uncertain: Score 4-6: Uncertain for the indication provided, meaning coronary revascularization **may** be acceptable and **may** be a reasonable approach for the indication but with uncertainty implying that more research and/or patient information is needed to further classify the indication. (Note: This category includes consideration of diversity of clinical opinion and/or where available research is limited or conflicting.)
>
> Inappropriate: Score 1-3: Inappropriate for the indication provided, meaning that coronary revascularization is **not** generally acceptable and is **not** a reasonable approach for the indication and is **unlikely** to improve the patients' health outcomes or survival.

The authors suggest that ranking of an indication as "uncertain" should not be viewed as excluding the use of revascularization and that patient and condition-specific information are important in the decision making.

Overall, in patients with ACS and combinations of significant symptoms and ischemia, revascularization was considered favorably. In asymptomatic patients or those with low-risk findings on noninvasive testing and minimal medical therapy, revascularization was viewed less favorably.

Of the 73 potential indications for revascularization, 11 apply to patients with acute coronary syndromes (ACS), 36 apply to patient who have not had previous bypass, 12 apply to patients with prior CABG but without ACS and 14 apply to patients with advanced CAD. Categorization refers to appropriateness for revascularization by either PCI or CABG in all but the last 14 indications for which PCI and CABG are rated separately. Detail of all indications' ratings is beyond the scope of this report and interested readers are referred to the report.[50]

In patient with more advanced CAD, appropriateness ratings were provided for CABG and PCI as separate treatment options. The report does not discuss appropriateness in light of currently approved FDA indications for stent use. Four anatomic situations (two vessel disease with proximal LAD stenosis, three vessel disease, isolated left main stenosis and left main stenosis and additional CAD) and three clinical scenarios (no

diabetes and normal LV ejection fraction (LVEF), presence of diabetes or depressed LVEF) were used. CABG was considered appropriate for all combinations of these factors. PCI was considered to be:

- **appropriate** in patients with two vessel disease including those without diabetes and normal LVEF, those with diabetes and those with depressed LVEF
- **inappropriate** in patients with isolated left main stenosis or left main stenosis with additional CAD, regardless of LVEF or diabetes status
- **of uncertain appropriateness** in patients with three vessel disease, regardless of LVEF or diabetes status.

No distinction in types of PCI or stents is made as part of these criteria that might be relevant to this technology assessment report.

REFERENCES

1. Schoen F. Chapter 13, The Heart. In: Cotran RS KV, Collins T, ed. *Robbins Pathophysiologic Basis of Disease*. sixth ed. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W. B. Saunders Company; 1999:543-599.

2. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* Feb 14 2006;113(6):e85-151.

3. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol.* Jan 15 2008;51(2):172-209.

4. Bairey Merz N, Bonow RO, Sopko G, et al. Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: executive summary. *Circulation.* Feb 17 2004;109(6):805-807.

5. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *Circulation.* Jun 1 1999;99(21):2829-2848.

6. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation.* Nov 27 2007;116(22):2634-2653.

7. Chen G, Redberg RF. Noninvasive diagnostic testing of coronary artery disease in women. *Cardiol Rev.* Nov-Dec 2000;8(6):354-360.

8. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation.* Jan 7 2003;107(1):149-158.

9. Grundy SM, Pasternak R, Greenland P, Smith S, Jr., Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation.* Sep 28 1999;100(13):1481-1492.

10. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation.* Jul 16 2002;106(3):388-391.

11. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol.* Jul 1976;38(1):46-51.
12. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* May 12 1998;97(18):1837-1847.
13. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol.* Aug 14 2007;50(7):e1-e157.
14. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2008;117(2):296-329.
15. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* Jun 9 2004;291(22):2727-2733.
16. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* Oct 27 2003;163(19):2345-2353.
17. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation.* Jun 6 2000;101(22):2557-2567.
18. Greenland P, Smith SC, Jr., Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation.* Oct 9 2001;104(15):1863-1867.
19. Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation.* Feb 21 2006;113(7):e166-286.
20. Fraker TD, Jr., Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol.* Dec 4 2007;50(23):2264-2274.
21. Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. *Am Heart J.* Jan 1995;129(1):146-172.
22. Bentivoglio LG. Immediate and long-term results of percutaneous transluminal coronary angioplasty. Comparison of the National Heart, Lung and Blood Institute Registry experience with current experience. *Herz.* Oct 1985;10(5):275-280.
23. Newsome LT, Kutcher MA, Royster RL. Coronary artery stents: Part I. Evolution of percutaneous coronary intervention. *Anesth Analg.* Aug 2008;107(2):552-569.
24. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med.* Mar 19 1987;316(12):701-706.
25. Hoffmann R, Mintz G. Coronary in-stent restenosis - predictors, treatment and prevention. *Eur Heart J.* 2000;21:1739-1749.
26. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med.* Aug 25 1994;331(8):496-501.
27. King SB, 3rd. The development of interventional cardiology. *J Am Coll Cardiol.* Mar 15 1998;31(4 Suppl B):64B-88B.

28. Ruygrok PN, Serruys PW. Intracoronary stenting. From concept to custom. *Circulation.* Sep 1 1996;94(5):882-890.
29. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med.* Aug 25 1994;331(8):489-495.
30. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. *N Engl J Med.* Jan 3 1991;324(1):13-17.
31. Coolong A, Kuntz RE. Understanding the drug-eluting stent trials. *Am J Cardiol.* Sep 3 2007;100(5A):17K-24K.
32. Kereiakes DJ, Choo JK, Young JJ, Broderick TM. Thrombosis and drug-eluting stents: a critical appraisal. *Rev Cardiovasc Med.* Winter 2004;5(1):9-15.
33. Topol EJ, Serruys PW. Frontiers in interventional cardiology. *Circulation.* Oct 27 1998;98(17):1802-1820.
34. Wenaweser P, Rey C, Eberli FR, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. *Eur Heart J.* Jun 2005;26(12):1180-1187.
35. Rodriguez AE, Mieres J, Fernandez-Pereira C, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol.* Jan 3 2006;47(1):205-207.
36. Tsimikas S. Drug-eluting stents and late adverse clinical outcomes lessons learned, lessons awaited. *J Am Coll Cardiol.* May 16 2006;47(10):2112-2115.
37. Farb A, Boam AB. Stent thrombosis redux--the FDA perspective. *N Engl J Med.* Mar 8 2007;356(10):984-987.
38. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA.* May 9 2007;297(18):2001-2009.
39. Huang HW, Brent BN, Shaw RE. Trends in percutaneous versus surgical revascularization of unprotected left main coronary stenosis in the drug-eluting stent era: a report from the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Catheter Cardiovasc Interv.* Dec 2006;68(6):867-872.
40. Leon MB, Stone GW, CIT 2006. Crossfire: trials, tribulations, current trend and future directions. Avaliable from: http://www.tctmd.com/csportal/appmanager/tctmd/main?_nfpb=true&_pageLabel=TCTMDSearchResults.
41. Gingras AC, Raught B, Sonenberg N. mTOR signaling to translation. *Curr Top Microbiol Immunol.* 2004;279:169-197.
42. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *Bmj.* 2008;337:a1331.
43. U.S. Food and Drug Administration. Endeavor® Zotarolimus-Eluting Coronary Stent on the Over-the-Wire (OTW), Rapid Exchange (RX), or Multi Exchange II (MX2) Stent Delivery Systems - P060033. http://www.fda.gov/cdrh/pdf6/p060033.html. Accessed Aug 20, 2008.
44. U.S. Food and Drug Administration. XIENCE™ V Everolimus Eluting Coronary Stent System and PROMUS™ Everolimus Eluting Coronary Stent System - P070015. http://www.fda.gov/cdrh/pdf7/p070015.html. Accessed Aug 20, 2008.
45. U.S. Food and Drug Administration. CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR® Over-the-Wire Delivery System or RAPTORRAIL® Rapid Exchange Delivery System - P020026. http://www.fda.gov/cdrh/pdf2/P020026.html. Accessed Aug 20, 2008.
46. U.S. Food and Drug Administration. TAXUS™ Express 2™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire) - P030025. http://www.fda.gov/cdrh/pdf3/P030025.html Accessed Aug 20, 2008.
47. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation.* Oct 5 2004;110(14):e340-437.

48. Herlitz J, Brandrup-Wognsen G, Caidahl K, et al. Symptoms of chest pain and dyspnea and factors associated with chest pain and dyspnea 10 years after coronary artery bypass grafting. *Am Heart J.* Sep 2008;156(3):580-587.

49. Gillinov MA, Loop FD. *Coronary artery bypass surgery in Textbook of Cardiovascular Medicine.* 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2002.

50. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization. A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. *Circulation.* Jan 8 2009.

51. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). *Circulation.* Sep 5 2000;102(10):1193-1209.

52. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation.* Oct 1 2002;106(14):1893-1900.

53. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol.* Aug 4 2004;44(3):671-719.

54. Smith SC, Jr., Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation.* Jun 19 2001;103(24):3019-3041.

55. Smith CT, Williamson PR, Marson AG. An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-analysis of time-to-event outcomes. *J Eval Clin Pract.* Oct 2005;11(5):468-478.

56. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* May 15 2007;115(19):2549-2569.

57. Alexander KP, Newby LK, Armstrong PW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. *Circulation.* May 15 2007;115(19):2570-2589.

58. Pierluigi Tricoci, Allen J.M., Kramer J.M., Califf R.M., Smith Jr S.C. Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines. *JAMA.* 2009;301(8):831-841.

59. Hayes. Hayes Directory: Drug-eluting stents for treatment of coronary artery disease. Sept 12 2007.