Washington State Health Care Authority

Health Technology Assessment

Cardiac Stents – Re-Review

Final Evidence Report: Appendices

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Provided by:

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Final Report
APPENDICES

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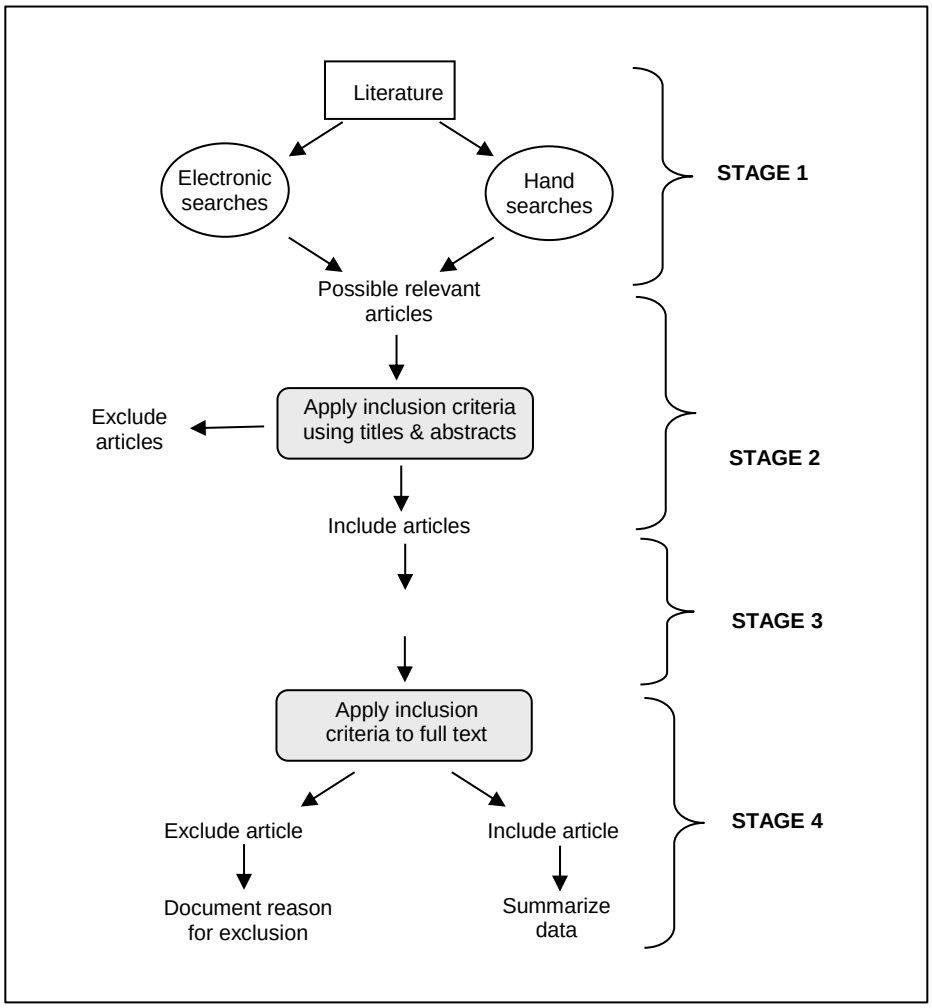
Abbreviations

ACE: Angiotensin converting enzyme
ACS: Acute coronary syndrome
ARB: Angiotensin receptor blocker
BARI 2D: Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes
BASKET-PROVE: Basel Stent Kosten Effektivitats Trial—Prospective Validation Examination
BMI: body mass index
BMS: bare metal stent
BP: Blood pressure
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CHF: congestive heart failure
CoE: Class of Evidence
COURAGE: Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation
CVA: cerebrovascular accident
DAPT: dual antiplatelet therapy
DASI: Duke Activity Status Index
DES: drug eluting stent
ECG: electrocardiography
EES: Everolimus eluting stent
EF: Ejection fraction
ENDEAVOR II: The Medtronic Endeavor Drug Eluting Coronary Stent System in Coronary Artery Lesions
EXAMINATION: Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients with ST-Segment Elevation Myocardial Infarction
f/u: follow-up
FDA: United States Food and Drug Administration
GDMT: Guideline directed medical therapy
HF: Heart failure
HR: hazard ratio
HTA: health technology assessment
IQR: interquartile range
IVUS: intravascular ultrasound
KAMIR: Korea Acute Myocardial Infarction Registry
KQ: key question
LAD: left anterior descending artery
LMWH: low molecular weight heparin
LVEF: Left ventricular ejection fraction
MACE: major adverse cardiovascular events
MASS II: Medicine, Angioplasty, or Surgery Study
MCID: minimal clinically important difference

MI: myocardial infarction
MT: medical therapy
NC: non calculable
NR: not reported
NSTEMI: non ST-segment elevation MI
OMT: optimal medical therapy
OR: Odds ratio
PCI: percutaneous coronary intervention
PCI: Percutaneous coronary intervention
PRODIGY: Prolonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study
PTCA: percutaneous transluminal coronary angioplasty
QHES: Quality of Health Economic Studies
RCA: right circumflex artery
RCT: randomized controlled trial
RD: risk difference
RR: relative risk/risk ratio
SAQ: Seattle Angina Questionnaire
SCAAR: Swedish Coronary Angiography and Angioplasty Registry
SD: standard deviation
SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey
SIHD: Stable ischemic heart disease
SOE: Strength of Evidence
SR: Systematic review
STEMI: ST-segment elevation MI
TLR: target lesion revascularization
TVR: target vessel revascularization
UA: Unstable angina
XIMA: Xience or Vision Stents for the Management of Angina in the Elderly
X-MAN: Xience vs. Multi-Link Stent in Acute Myocardial Infarction Trial
ZES: zotarolimus eluting stent
ZEUS: Zotarolimus-eluting Endeavor Spring Stent in Uncertain DES Candidates Study
ACE: Angiotensin converting enzyme
ACS: Acute coronary syndrome
ARB: Angiotensin receptor blocker

APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below are the search strategies for PubMed and EMBASE. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (Medline)
Search date: July 09, 2015
Meta-analyses, Randomized Controlled Trials—Key Questions 1, 2, 3

	Search Code	Number Of Articles In 2009 Search	Number Of Articles In 2015 Search
1	"Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh]	151,129	44,821
2	“Stents”[Mesh] OR “Drug-eluting Stents”[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	52,828	40,710
3	#1 AND #2	11,132	8,063
4	#1 AND #2 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	2,559	5,557
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	1,118
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	1,011
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	903
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	246

Search strategy (Medline)
Search date: July 09, 2015
Adverse events search—Key Question 2

	Search Code	Number Of Articles In 2009 Search	Number Of Articles In 2015 Search
1	"Myocardial Ischemia/therapy"[Mesh] OR "Myocardial Revascularization"[Mesh]	151,129	44,821
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	292
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	160
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	1,059	2,249
5	"Coronary Vessels"[Mesh] Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	2,509	5,360
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	14,377	28,377
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	913
8	#4 AND #5 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	77	178
9	Search #4 AND #6 Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, English	501	869
10	Search Limits: Publication Date from 2005/06/01 to 2009/01/15, only items with abstracts, Humans, Comparative Study, English	117,555	209,013
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	35
12	“bleeding stent coronary”	181	1,435
13	#12 NOT review	15	1,072

Search strategy (Medline)
Search date: July 09, 2015
Registry search—Key Questions 1, 2, 3

Search code		Number of articles in 2009 search	Number of articles in 2015 search
1	"Myocardial Ischemia/therapy"[MEesh] OR "Myocardial Revascularization"[Mesh]	151,301	20,887
2	"Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	52,939	40,710
3	#1 & #2	11,171	5,312
4	"Registries[Mesh]"	34,293	26,433
5	#3 & #4	350	487
Limits	Publication Date from 2006/07/01 to 2009/01/15, only items with abstracts, Humans, English	131	458

Search strategy (Medline)
Search date: July 09, 2015
Econ literature search—Key Questions 1, 2, 3

Search code		Number of articles in 2009 search	Number of articles in 2015 search
1	"Myocardial Ischemia/therapy"[MEesh] OR "Myocardial Revascularization"[Mesh]	151,712	20,887
2	"Stents"[Mesh] OR "Drug-eluting Stents"[Mesh] OR "paclitaxel" OR "sirolimus" OR "zotarolimus" OR "everolimus"	52,234	40,710
3	#1 & #2	11,319	5,312
4	"Costs"	53,234	70,019
5	#3 & #4 and Limits: Publication Date from 2006/07/01 to 2009/02/20, only items with abstracts, Humans, English	69	57

Search strategy (EMBASE)
Search date: July 09, 2015
Safety and Efficacy Meta-analyses search
Filters: Publication date 2009-2015

	Search Code	Number Of Articles In 2015 Search
1	('stents'/exp OR 'stents') AND [2009-2015]/py	71,762
2	coronary AND [2009-2015]/py	212,919
3	coronary* AND [2009-2015]/py	212,971
4	#1 AND #3	27,942
5	eluting AND [2009-2015]/py	20,990
6	#4 AND #5	14,699
7	#5 AND [meta analysis]/lim AND [2009-2015]/py	621
8	#6 AND [meta analysis]/lim AND [2009-2015]/py	436

Search strategy (EMBASE)
Search date: July 09, 2015
Safety and Efficacy RCT
Filters: Publication date 2009-2015

	Search Code	Number Of Articles In 2015 Search
1	('stents'/exp OR 'stents') AND [2009-2015]/py	71,762
2	coronary AND [2009-2015]/py	212,919
3	coronary* AND [2009-2015]/py	212,971
4	#1 AND #3	27,942
5	eluting AND [2009-2015]/py	20,990
6	#4 AND #5	14,699
7	#6 AND [randomized controlled trial]/lim AND [2009-2015]/py	957
8	#5 AND [randomized controlled trial]/lim AND [2009-2015]/py	811

Search strategy (EMBASE)
Search date: July 09, 2015
Registries search
Filters: Publication date 2009-2015

	Search Code	Number Of Articles In 2015 Search
8	#6 AND #7 AND [2008-2015]/py	210
7	'registries'/exp AND [2008-2015]/py	57,623
6	#4 AND #5	3,197
5	eluting AND [2007-2009]/py	5,933
4	#1 AND #3	30,202
3	coronary* AND [2008-2015]/py	230,572
2	coronary AND [2008-2015]/py	230,520
1	'stents'/exp OR 'stents' AND [2008-2015]/py	76,944

Search strategy (EMBASE)
Search date: July 09, 2015
Economic Studies
Filters: Publication date 2009-2015

	Search Code	Number Of Articles In 2015 Search
31	#30 AND [english]/lim	435
30	#28 AND #29	452
29	'heart disease'/exp	1,522,466
28	#27 AND [humans]/lim	713
27	#25 AND #26 AND [2008-2015]/py	826
26	'drug eluting stent'/exp	20,871
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	1,311,094
24	#19 AND #21	161,966
23	#19 AND #20	27,550
22	#19 AND #18	64,173
21	unit*:de,cl,ab,ti	2,175,566
20	variable*:de,cl,ab,ti	758,128
19	cost*:de,cl,ab,ti	734,937
18	estimate*:de,cl,ab,ti	806,857

	Search Code	Number Of Articles In 2015 Search
17	'cost minimization analysis'/exp	2,674
16	#12 OR #13 OR #14 OR #15	204,621
15	financial	170,276
14	fiscal	7,672
13	'funding'/exp	23,501
12	'finance'/exp	10,211
11	'hospital cost'/exp	28,092
10	'health economics'/exp	656,966
9	'health care financing'/exp	11,787
8	'health care cost'/exp	219,883
7	'financial management'/exp	329,010
6	'economic aspect'/exp	1,220,638
5	'cost control'/exp	52,453
4	'cost of illness'/exp	15,000
3	'cost effectiveness analysis'/exp	107,633
2	'cost benefit analysis'/exp	67,677
1	'socioeconomics'/exp	191,335

APPENDIX C. Excluded Articles

Articles excluded as primary studies after full text review, with reason for exclusion.

Key Question 1.

	Citation	Reason For Exclusion After Full-Text Review
	Studies considered and excluded from KQ1 (a-c)	
1.	Beohar, N., et al. (2013). "Race/ethnic disparities in risk factor control and survival in the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial." Am J Cardiol **112**(9): 1298-1305.	Data not stratified for the PCI vs. medical therapy treatment groups
2.	Bradley, S. M., et al. (2015). "Validation of the appropriate use criteria for percutaneous coronary intervention in patients with stable coronary artery disease (from the COURAGE trial)." Am J Cardiol 116(2): 167-173.	Beyond scope.
3.	Chung, S. C., et al. (2011). "Body mass index and health status in the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D)." Am Heart J 162(1): 184-192 e183.	Data not stratified for the PCI vs. medical therapy treatment groups
4.	Dagenais, G. R., et al. (2013). "Prognostic impact of the presence and absence of angina on mortality and cardiovascular outcomes in patients with type 2 diabetes and stable coronary artery disease: results from the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial." J Am Coll Cardiol 61(7): 702-711.	Data not stratified for the PCI vs. medical therapy treatment groups
5.	Gosselin, G., et al. (2012). "Effectiveness of percutaneous coronary intervention in patients with silent myocardial ischemia (post hoc analysis of the COURAGE trial)." Am J Cardiol 109(7): 954-959.	Single subgroup (does not evaluate differential efficacy or safety across subgroups).
6.	Kendziorra, K., et al. (2005). "Changes in myocardial perfusion due to physical exercise in patients with stable coronary artery disease." Eur J Nucl Med Mol Imaging 32(7): 813-819.	Wrong outcomes
7.	Kim, L. J., et al. (2009). "Factors related to the selection of surgical versus percutaneous revascularization in diabetic patients with multivessel coronary artery disease in the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial." JACC Cardiovasc Interv 2(5): 384-392.	Does not address KQs; wrong comparisons.
8.	Mancini, G. B., et al. (2014). "Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia." JACC Cardiovasc Interv 7(2): 195-201.	Does not address KQs; wrong comparisons.
9.	Maron, D. J., et al. (2009). "Impact of an initial strategy of medical therapy without percutaneous coronary intervention in high-risk patients from the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial." Am J Cardiol 104(8): 1055-1062.	Single subgroup (does not evaluate differential efficacy or safety across subgroups).
10.	Pereira, A. C., et al. (2006). "Clinical judgment and treatment options in stable multivessel coronary artery disease: results from the one-year follow-up of the MASS II (Medicine, Angioplasty, or Surgery Study II)." J Am Coll Cardiol **48**(5): 948-953.	Wrong outcomes

	Citation	Reason For Exclusion After Full-Text Review
11.	Shaw, L. J., et al. (2008). "Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy." Circulation 117(10): 1283-1291.	Wrong outcomes
12.	Tamis-Holland, J. E., et al. (2013). "Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes)." J Am Coll Cardiol 61(17): 1767-1776.	Data not stratified for the PCI vs. medical therapy treatment groups
13.	Thomas, S. B., et al. (2010). "Racial differences in the association between self-rated health status and objective clinical measures among participants in the BARI 2D trial." Am J Public Health 100 Suppl 1: S269-276.	Does not address KQs; wrong comparisons.
	Studies considered and excluded from KQ1 (d)	
1.	Caruba, T., et al. (2014). "Treatment for stable coronary artery disease: a network meta-analysis of cost-effectiveness studies." PLoS One 9(6): e98371.	Network meta-analysis of economic studies.
2.	Eisenstein, E. L., et al. (2009). "Assessing the economic attractiveness of coronary artery revascularization in chronic kidney disease patients." J Med Syst 33(4): 287-297.	Unclear whether patients had stable or unstable CAD (particularly because all patients started by undergoing catheterization); unclear what percentage of patients received stents.
3.	Wijeysundera, H. C., et al. (2013). "Medical therapy v. PCI in stable coronary artery disease: a cost-effectiveness analysis." Med Decis Making **33**(7): 891-905.	Wrong population: 49% of patients had CCS class IV angina

Key Question 2

	Citation	Reason for exclusion after full-text review
	Studies considered and excluded from KQ2 (a-c)	
1.	Ahmed, K., et al. (2012). "Coronary stents in patients with ST-elevation myocardial infarction and chronic kidney disease undergoing primary percutaneous coronary intervention." Korean circulation journal **42**(12): 830-838.	Nonrandomized study that does not adjust for confounding
2.	Atary, J. Z., et al. (2010). "Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (from the MISSION! Intervention Study)." The American journal of cardiology **106**(1): 4-12.	Wrong intervention (1st generation DES)
3.	Beijk, M. A., et al. (2007). "Two-year results of a durable polymer everolimus-eluting stent in de novo coronary artery stenosis (The SPIRIT FIRST Trial)." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology	Too few patients (<70 per arm)

	Citation	Reason for exclusion after full-text review
	of the European Society of Cardiology **3**(2): 206-212.	
4.	Berta B., et al. (2011). "Study of Xience v Everolimus-eluting and Vision cobalt-chromium coronary stent." EuroIntervention **7**:M29.	Abstract; no full length publication
5.	Boden, H., et al. (2012). "Five-year clinical follow-up from the MISSION! Intervention Study: sirolimus-eluting stent versus bare metal stent implantation in patients with ST-segment elevation myocardial infarction, a randomised controlled trial." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology **7**(9): 1021-1029.	Wrong intervention (1st generation DES)
6.	Brugaletta, S., et al. (2013). "Predictors and clinical implications of stent thrombosis in patients with ST-segment elevation myocardial infarction: insights from the EXAMINATION trial." International journal of cardiology **168**(3): 2632-2636.	Prognostic study, factors associated with thrombosis
7.	Chacko, R., et al. (2009). "Impact of target lesion and nontarget lesion cardiac events on 5-year clinical outcomes after sirolimus-eluting or bare-metal stenting." JACC: Cardiovascular Interventions **2**(6): 498-503.	Wrong intervention (1st generation DES)
8.	Chakravarty, T., et al. (2010). "Meta-analysis of incidence, clinical characteristics and implications of stent fracture." The American journal of cardiology **106**(8): 1075-1080.	Wrong intervention (1st generation DES)
9.	Choi, J., et al. (2013). "Comparison of long term clinical outcomes between bare metal stent versus different types of drug eluting stents for treatment of acute myocardial infarction." European heart journal **34**(suppl 1): 2593.	Abstract; no full length publication
10.	Chung, W. S., et al. (2008). "The incidence and clinical impact of stent strut fractures developed after drug-eluting stent implantation." International journal of cardiology **125**(3): 325-331.	Wrong intervention (1st generation DES)
11.	Costa, R. A., et al. (2005). "Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial)." The American journal of cardiology **95**(1): 113-116.	Date is prior to cutoff of 2008
12.	Di Lorenzo, E., et al. (2009). "Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial." American heart journal **158**(4): e43-e50.	Wrong intervention (1st generation DES)
13.	Di Lorenzo, E., et al. (2009). "The PASEO (paclitaxel or sirolimus-eluting stent versus bare metal stent in primary angioplasty) randomized trial." JACC: Cardiovascular Interventions **2**(6): 515-523.	Wrong intervention (1st generation DES)
14.	Dudek, D., et al. (2013). "Impact of advanced age on the safety and effectiveness of paclitaxel-eluting stent implantation in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty." Catheterization and Cardiovascular	Wrong intervention (1st generation DES)

	Citation	Reason for exclusion after full-text review
	Interventions **82**(6): 869-877.	
15.	Ellis, S. G., et al. (2009). "Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent)." JACC: Cardiovascular Interventions **2**(12): 1248-1259.	Wrong intervention (1st generation DES)
16.	Ferenc, M., et al. (2012). "One-year outcome after percutaneous treatment for de-novo coronary bifurcation lesions with bare metal stents, first and second generation drug eluting stents." European heart journal, Oxford Univ Press Great Clarendon St, Oxford OX2 6DP, England.	Abstract; no full length publication
17.	Ferrante, G., et al. (2012). "Sex-specific benefits of sirolimus-eluting stent on long-term outcomes in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: insights from the Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study trial." American heart journal **163**(1): 104-111.	Wrong intervention (1st generation DES)
18.	Freixa, X., et al. (2012). "Long-term outcomes after a strategy of percutaneous coronary intervention of the infarct-related artery with drug-eluting stents or bare metal stents vs medical therapy alone in the Occluded Artery Trial (OAT)." American heart journal **163**(6): 1011-1018.	Wrong intervention (1st generation DES)
19.	Giglioli, C., et al. (2014). "Comparison between drug-eluting and bare metal stent on ST-elevation myocardial infarction outcome: Should second-generation drug-eluting stent be preferred?" Journal of cardiology **63**(4): 296-301.	Nonrandomized study that does provide data on safety
20.	Goto, K., et al. (2015). "Mechanisms and Patterns of Intravascular Ultrasound In-Stent Restenosis Among Bare Metal Stents and First- and Second-Generation Drug-Eluting Stents." The American journal of cardiology.	Do not provide total patients so we can't calculate overall incidence; only describe subset with in-stent restenosis
21.	Guagliumi, G., et al. (2010). "Strut Coverage and Vessel Wall Response to a New-Generation Paclitaxel-Eluting Stent With an Ultrathin Biodegradable Abluminal Polymer Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI)." Circulation: Cardiovascular Interventions **3**(4): 367-375.	Too few patients (<70 per arm)
22.	Guo, N., et al. (2010). "Incidence, Mechanisms, Predictors, and Clinical Impact of Acute and Late Stent Malapposition After Primary Intervention in Patients With Acute Myocardial Infarction An Intravascular Ultrasound Substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial." Circulation **122**(11): 1077-1084.	Wrong intervention (1st generation DES)
23.	Hansen, K., et al. (2013). "Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: Importance of vessel size."	Data not stratified for PCI vs. medical therapy, first and second gen stents combined into DES group.

	Citation	Reason for exclusion after full-text review
	International journal of cardiology **169**(1): 29-34.	
24.	Herdeg, C., et al. (2009). "Catheter-based delivery of fluid paclitaxel for prevention of restenosis in native coronary artery lesions after stent implantation." Circulation: Cardiovascular Interventions **2**(4): 294-301.	Wrong intervention (1st generation DES)
25.	Holmvang, L., et al. (2013). "Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction)." JACC: Cardiovascular Interventions **6**(6): 548-553.	Wrong intervention (only 13% of population received newer generation DES (zotarolimus) and results not stratified)
26.	Huang, W., et al. (2013). "Clinical Outcomes of Long-length (> 28 Mm) Drug-eluting Stents Versus Long-length (> 28mm) Bare Metal Stents in Primary Percutaneous Coronary Intervention for ST Elevation Myocardial Infarction." The American journal of cardiology **111**(7): 10B.	Abstract; no full length publication
27.	Jaguszewski, M., et al. (2013). "Drug-eluting stents compared to bare-metal stents improve short-term survival in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a nationwide prospective analysis of the AMIS Plus registry." Kardiologia polska **72**(4): 315-323.	Population unclear; likely a mix of 1st and 2nd generation DES
28.	Jimenez-Quevedo, P., et al. (2009). "Four years follow-up of DIABETES trial." Journal of the American College of Cardiology, ELSEVIER SCIENCE INC 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.	Wrong intervention (1st generation DES)
29.	Jiménez-Quevedo, P., et al. (2013). "Sirolimus-eluting stent versus bare metal stent in diabetic patients: the final five-year follow-up of the DIABETES trial." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology **9**(3): 328-335.	Wrong intervention (1st generation DES)
30.	Kaltoft, A., et al. (2010). "Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 3-year follow-up of the randomized DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) Trial." Journal of the American College of Cardiology **56**(8): 641-645.	Wrong intervention (only 13% of population received newer generation DES (zotarolimus) and results not stratified)
31.	Kandzari, D. E., et al. (2013). "Final 5-year outcomes from the endeavor zotarolimus-eluting stent clinical trial program: comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents." JACC: Cardiovascular Interventions **6**(5): 504-512.	Nonrandomized study using indirect comparisons; only head-to-head comparison is already included
32.	Kim, S. S., et al. (2010). "Two-year clinical outcome after abciximab-coated stent implantation in patients with coronary artery disease." Circulation Journal **74**(3): 442-448.	Non-FDA approved Stent

	Citation	Reason for exclusion after full-text review
33.	Koo, B.-K., et al. (2010). "Incidence of diffuse and focal chronic stent recoil after implantation of current generation bare-metal and drug-eluting stents." International journal of cardiology **144**(1): 132-134.	Intermediate outcome
34.	Kosonen, P., et al. (2013). "Intravascular ultrasound assessed incomplete stent apposition and stent fracture in stent thrombosis after bare metal versus drug-eluting stent treatment the Nordic Intravascular Ultrasound Study (NIVUS)." International journal of cardiology **168**(2): 1010-1016.	Wrong intervention (focus is on 1st generation DES)
35.	Larsen, A. I., et al. (2013). "Long-term prognosis of patients presenting with ST-segment elevation myocardial infarction with no significant coronary artery disease (from the HORIZONS-AMI trial)." The American journal of cardiology **111**(5): 643-648.	Wrong intervention (1st generation DES)
36.	Leibundgut, G., et al. (2009). "Stent thrombosis up to 3 years after stenting for ST-segment elevation myocardial infarction versus for stable angina—comparison of the effects of drug-eluting versus bare-metal stents." American heart journal **158**(2): 271-276.	Wrong intervention (1st generation DES)
37.	Lim, S., et al. (2013). "Second-generation drug-eluting stents versus bare-metal stents in patients with acute myocardial infarction." Journal of the American College of Cardiology **61**(10_S).	Abstract; no full length publication
38.	Menozzi, A., et al. (2009). "Twenty-four months clinical outcomes of sirolimus-eluting stents for the treatment of small coronary arteries: the long-term SES-SMART clinical study." European heart journal **30**(17): 2095-2101.	Wrong intervention (1st generation DES)
39.	Musto, C., et al. (2013). "Long-term outcome of sirolimus-eluting vs bare-metal stent in the setting of acute myocardial infarction: 5-year results of the SESAMI trial." International journal of cardiology **166**(2): 399-403.	Wrong intervention (1st generation DES)
40.	Omar, A., et al. (2014). "Long-term safety and efficacy of second-generation everolimus-eluting stents compared to other limus-eluting stents and bare metal stents in patients with acute coronary syndrome." Catheterization and Cardiovascular Interventions **84**(7): 1053-1060.	Wrong population (>20% of patients had prior PCI and no mention of de novo lesions as target lesion)
41.	Onuma, Y., et al. (2009). "The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry." Journal of the American College of Cardiology **54**(3): 269-276.	Nonrandomized study with historical controls that does not control for confounding
42.	Philip, F., Kapadia, S. (2015). "Long term outcomes after primary percutaneous coronary intervention using second generation drug eluting stents: A comprehensive network meta-analysis of trials in ST segment myocardial infarction." Catheter Cardiovasc Interv 85:S17.	Abstract; no full length publication
43.	Rahel, B. M., et al. (2009). "Three-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomized comparison of bare-metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (Primary Stenting of Totally Occluded Native	Wrong intervention (1st generation DES)

	Citation	Reason for exclusion after full-text review
	Coronary Arteries [PRISON] II study)." American heart journal **157**(1): 149-155.	
44.	Ribichini, F., et al. (2013). "Long-term clinical follow-up of the multicentre, randomized study to test immunosuppressive therapy with oral prednisone for the prevention of restenosis after percutaneous coronary interventions: Cortisone plus BMS or DES veRsus BMS alone to EliminAte Restenosis (CEREA-DES)." European heart journal: eht079.	Wrong intervention (1st generation DES)
45.	Rubartelli, P., et al. (2010). "Comparison of sirolimus-eluting and bare metal stent for treatment of patients with total coronary occlusions: results of the GISSOC II-GISE multicentre randomized trial." European heart journal **31**(16): 2014-2020.	Wrong intervention (1st generation DES)
46.	Sarno, G., et al. (2011). "Considerably lower risk of stent thrombosis and restenosis in" new generation" drug-eluting stents: a report from the nation wide complete Swedish Coronary Angiography and Angioplasty Registry (SCAAR)." European heart journal, Oxford Univ Press Great Clarendon St, Oxford, OX2 6DP, England.	Abstract; no full length publication
47.	Serruys, P. W., et al. (2005). "A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology **1**(1): 58-65.	Too few patients (<70 per arm)
48.	Sinning, J.-M., et al. (2012). "Five-year results of the Multicenter Randomized Controlled Open-Label Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients with De Novo Native Coronary Artery Lesions (SCORPIUS) study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients." American heart journal **163**(3): 446-453. e441.	Wrong intervention (1st generation DES)
49.	Spaulding, C., et al. (2011). "Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty)." JACC: Cardiovascular Interventions **4**(1): 14-23.	Wrong intervention (1st generation DES)
50.	Stoicescu, C., et al. (2013). "Outcome and Predictors of Stent Thrombosis in the First Romanian Registry of Drug Eluting Stent (RODESINO EXTENSION)." Maedica **8**(2): 153.	Wrong intervention (>50% with 1st generation DES, results not stratified)
51.	Stone, G. W., et al. (2009). "Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction." New England Journal of Medicine **360**(19): 1946-1959.	Wrong intervention (1st generation DES)
52.	Stone, G. W., et al. (2010). "Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial." Journal of the American College of Cardiology **56**(19): 1597-1604.	Wrong intervention (1st generation DES)

	Citation	Reason for exclusion after full-text review
53.	Stone, G. W., et al. (2011). "Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial." The Lancet **377**(9784): 2193-2204.	Wrong intervention (1st generation DES)
54.	Tada, T., et al. (2013). "Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients." JACC: Cardiovascular Interventions **6**(12): 1267-1274.	Wrong intervention (>80% received DES that are not FDA approved)
55.	Tebaldi, M., et al. (2009). "The 5-year clinical outcomes after a randomized comparison of sirolimus-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction." Journal of the American College of Cardiology **54**(20): 1900-1901.	Wrong intervention (1st generation DES)
56.	Tsuchida, K., et al. (2005). "One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial)." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology **1**(3): 266-272.	Too few patients (<70 per arm)
57.	Tsuchiya, Y., et al. (2006). "Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials)." The American journal of cardiology **98**(4): 464-469.	Date is prior to cutoff of 2008
58.	Valgimigli, M., et al. (2013). "Three-year follow-up of the MULTIcentre evaluation of single high-dose bolus TiRofiban versus abciximab with sirolimus-eluting STEnt or bare-metal stent in acute myocardial infarction StudY (MULTISTRATEGY)." International journal of cardiology **165**(1): 134-141.	Wrong intervention (1st generation DES)
59.	Van den Branden, B., et al. (2012). "Five-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomised comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (PRISON II study)." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology **7**(10): 1189-1196.	Wrong intervention (1st generation DES)
60.	Vink, M. A., et al. (2011). "5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial." JACC: Cardiovascular Interventions **4**(1): 24-29.	Wrong intervention (1st generation DES)
61.	Violini, R., et al. (2010). "Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction: 3-year results of the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial." Journal of the American College of Cardiology **55**(8): 810-814.	Wrong intervention (1st generation DES)

	Citation	Reason for exclusion after full-text review
62.	Wanitschek, M., et al. (2013). "Long-term benefits and risks of drug-eluting compared to bare-metal stents in patients with versus without chronic kidney disease." International journal of cardiology **168**(3): 2381-2388.	Data not stratified for PCI vs. medical therapy, first and second gen stents combined into DES group.
63.	Weisz, G., et al. (2009). "Five-year follow-up after sirolimus-eluting stent implantation: results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial." Journal of the American College of Cardiology **53**(17): 1488-1497.	Wrong intervention (1st generation DES)
64.	Wiemer, M., et al. (2010). "Five-year long-term clinical follow-up of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: The SPIRIT FIRST trial." Catheterization and Cardiovascular Interventions **75**(7): 997-1003.	Too few patients (<70 per arm)
65.	Wijnbergen, I., et al. (2014). "Long-term comparison of sirolimus-eluting and bare-metal stents in ST-segment elevation myocardial infarction." Coronary artery disease **25**(5): 378-383.	Wrong intervention (1st generation DES)
66.	Witzenbichler, B., et al. (2011). "Paclitaxel-Eluting Stents Compared With Bare Metal Stents in Diabetic Patients With Acute Myocardial Infarction The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial." Circulation: Cardiovascular Interventions **4**(2): 130-138.	Wrong intervention (1st generation DES)
	Studies considered and excluded from KQ2 (d)	
1.	Applegate, R., et al. (2012). "TCT-606 Cost Effectiveness of Everolimus-Eluting Stents Compared to Propensity Score Matched Bare Metal Stents in Contemporary Clinical Practice." Journal of the American College of Cardiology **60**(17_S).	Poster abstract; no full publication
2.	Ariyaratne, T., et al. (2014). "PW241 The Cost-Effectiveness of Guideline-Driven Use of Drug-Eluting Stents in Victorian Public Hospitals." Global Heart **9**(1): e307.	Abstract; no full length publication
3.	Barone-Rochette, G., et al. (2010). “A cost-effectiveness assessment of the Sirolimus-Eluting Stent in diabetic and non-diabetic patients versus Bare Metal Stents (BMS): Analysis of the French cohort EVASTENT.” European heart journal, Oxford Univ Press Great Clarendon St, Oxford, OX2 6DP, England.	Wrong intervention (DES = sirolimus)
4.	Canoui-Poitrine, F., et al. (2009). "Cost effectiveness of sirolimus-eluting stents compared with bare metal stents in acute myocardial infarction." Applied health economics and health policy **7**(1): 19-29.	Wrong intervention (DES = sirolimus)
5.	Carrillo Gomez D.C., et al. (2012). “Cost-effectiveness of drug eluting stents versus bare metal stents in coronary heart disease. A systematic literature review.” Revista Argentina de Cardiologia.**80**(5):366-376.	14/16 included studies used sirolimus or paclitaxel DES; the 2 remaining studies used zotarolimus and are already included
6.	Caruba, T., et al. (2014). "Treatment for stable coronary artery disease: a network meta-analysis of cost-effectiveness studies." PLoS ONE. **9**(6).	3/4 studies evaluating DES vs. BMS used sirolimus (SIRIUS, RAVEL) and paclitaxel (TAXUS IV): 4th study is included – (ENDEAVOR II)

	Citation	Reason for exclusion after full-text review
7.	ElSisi, G., et al. (2013). "Cost-Effectiveness of Drug-Eluting Stents Versus Bare Metal Stents in Egyptian Diabetic Patients." Value in Health **7**(16): A530.	Abstract; no full length publication
8.	Fang, N., et al. (2015). "PMD41-The cost-effectiveness of Drug-Eluting stents versus bare Metal stents in Taiwan." Value in Health **18**(3): A45.	Abstract; no full length publication
9.	Fearon, W. F., et al. (2013). "Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve." Circulation **128**(12): 1335-1340.	Wrong comparison; FAME 2 trial = DES vs. medical; wrong intervention = CT FFR
10.	Ferreira, E., et al. (2010). "Analysis of the cost-effectiveness of drug-eluting and bare-metal stents in coronary disease." Arquivos brasileiros de cardiologia **94**(3): 306-312.	Wrong intervention--Taxus DES (paclitaxel)
11.	Greenhalgh, J., et al. (2010). "Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes." The Cochrane Library.	SR not econ study
12.	Lee, V., et al. (2013). "Clinical management of acute coronary syndrome in Hong Kong." International journal of cardiology **2**(164): S2.	Abstract; no full length publication
13.	Lee, S., et al. (2014). "Cost-Effectiveness of Drug-Eluting vs. Bare-Metal Stents in Patients with Coronary Artery Disease from the Korean National Health Insurance Database." Yonsei medical journal **55**(6): 1533-1541.	Wrong intervention (DES = sirolimus and paclitaxel)
14.	Milic, N., et al. (2010). Efficacy, safety and cost-effectiveness of drug-eluting stents over a 4 year time horizon. European heart journal, Oxford Univ Press Great Clarendon St, Oxford, OX2 6DP, England.	Abstract; no full length publication
15.	Milic, N., et al. (2013). "Safety and cost-effectiveness of DES vs. BMS: evidence from accomplished 5 years' follow up RCTs." European heart journal **34**(suppl 1): P3348.	Abstract; no full length publication
16.	Mohan, S. and A. Dhall (2010). "A comparative study of restenosis rates in bare metal and drug-eluting stents." The International journal of angiology: official publication of the International College of Angiology, Inc **19**(2): e66.	Not a formal econ study; wrong intervention (DES = unknown)
17.	Molinari, V., et al. (2012). "Cost effectiveness of titanium nitride-coated bioactive coronary stents compared to BMS and DES." European Journal of Hospital Pharmacy: Science and Practice **19**(2): 206-207.	Abstract; no full length publication
18.	Neyt, M., et al. (2009). "Cost Effectiveness of Drug-Eluting Stents In Belgian Practice." Pharmacoeconomics **27**(4): 313-327.	Wrong intervention (DES = sirolimus and paclitaxel)
19.	Neyt, M., et al. (2009). "Cost-effectiveness analyses of drug eluting stents versus bare metal stents: a systematic review of the literature." Health Policy **91**(2): 107-120.	Wrong intervention (majority of DES = sirolimus and paclitaxel)

	Citation	Reason for exclusion after full-text review
20.	Schafer, P. E., et al. (2011). "Cost-effectiveness of drug-eluting stents versus bare metal stents in clinical practice." Circulation: Cardiovascular Quality and Outcomes **4**(4): 408-415.	Wrong intervention (DES = sirolimus and paclitaxel)
21.	Suh, H., et al. (2010). "PCV81 drug-eluting stents versus bare-metal stents for acute myocardial infarction: an economic analysis approach." Value in Health **13**(3): A165.	Abstract; no full length publication
22.	Tamburino, C., et al. (2009). "Cost-effectiveness of the real-world use of drug-eluting stents at 9-month follow-up: results from the Sicilian DES Registry." Journal of Cardiovascular Medicine **10**(4): 322-329.	Wrong intervention (DES = sirolimus and paclitaxel)
23.	Willich, S., et al. (2010). Health economics baseline evaluation of the German drug-eluting stent registry (DES. DE). European heart journal, Oxford Univ Press Great Clarendon St, Oxford, OX2 6DP, England.	Abstract; no full length publication
24.	Wisloff, T. (2011). "Drug-eluting stents cost effective vs bare metal stents in Norway." PharmacoEconomics & Outcomes News **635**: 20.	Wrong intervention (DES = sirolimus and paclitaxel)
25.	Yan, B., et al. (2012). "PMD28 Cost Effectiveness of Drug-Eluting Stent for Patients Undergoing Percutaneous Coronary Revascularization in Hong Kong." Value in Health **15**(4): A67.	Abstract; no full length publication
26.	Yan, B., et al. (2012). "PMD32 Cost-Effectiveness of Drug-Eluting Stents Versus Bare-Metal Stents for Single-and Multi-Vessel Percutaneous Coronary Intervention." Value in Health **15**(4): A67-A68.	Abstract; no full length publication
27.	Yan, B., et al. (2011). "Cost-Effectiveness of Drug-Eluting Stents in Large (≥ 3.5 mm) Coronary Arteries." Heart, Lung and Circulation **20**: S29-S30.	Abstract; no full length publication
28.	Zhao, F.-h., et al. (2010). "Clinical outcomes and cost-utility after sirolimus-eluting versus bare metal stent implantation." Chinese medical journal **123**(20): 2797-2802.	Wrong intervention (DES = sirolimus)

APPENDIX D. Class of Evidence, Strength of Evidence, and QHES Determination

Each study is rated against pre-set criteria that resulted in an evidence rating (Class of Evidence I, II, III, or IV) and presented in a table. The criteria are listed in the Tables below.

Definition of the class of evidence and risk of bias for studies on therapy*

Class	Bias Risk	Studies of Therapy*	
		Study design	Criteria*
I	**Low risk:** Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Allocation concealment • Intent-to-treat analysis • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size
II	**Moderately low risk:** Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	• Violation of one or more of the criteria for good quality RCT (but not violation of both random sequence generation and allocation and one or more other criteria)
		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 80%+ • Adequate sample size • Controlling for possible confounding‡
III	**Moderately High risk:** Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of both random sequence generation and allocation concealment criteria, and • Violation of one other criteria for a good quality RCT
		Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
		Case-control	• Any case-control design
IV	**High risk:** Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	• Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt{Oxman, 1992 #1355}:

- Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
- Is the subgroup difference suggested by comparisons within rather than between studies?

- Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?
- Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a smaller number tested?
- Is the subgroup difference consistent across studies and across important outcomes?
- Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.

‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

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 primary outcomes was determined. The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher and independently reviewed by a second researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ). The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., heterogeneity of treatment effect, HTE) based on recommendations from Oxman and Guyatt. Primary criteria considered include the following: sub group analyses/hypotheses should be developed a priori, including hypothesized direction of effect differences, subgroup differences should be evaluated within studies, statistical analysis evaluating the role of chance as an explanation for subgroup differences, number of hypotheses tested, consideration of subgroup difference consistency across studies for important outcomes and consideration of biological or sociological plausibility for the hypothesized subgroup difference as described above under risk of bias assessement.

The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Questions related to economic studies was not assessed.

Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. HIGH = RCTs, LOW = observational studies.

DOWNGRADE: Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** RCTs	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Observational	**NO** consistent, direct, and precise estimates	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** Observational	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation.
Additional domains: dose-response, strength of association, publication bias.

**Single study = "consistency unknown"

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[3]. QHES embodies the primary components relevant for critical appraisal of economic studies[2,3]. 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 (e.g., 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 (e.g., 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 (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., 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.

Appendix E. Study quality: CoE and QHES evaluation

CoE Evaluation:

KQ1 comparative studies

Appendix Table E1. Risk of bias and class of evidence for RCTs evaluating PCI vs Medical

Methodological Principle	Hambrecht (2004)	BARI 2D (2009)	MASS-II (2004)	COURAGE (2007)
Study design				
Randomized controlled trial	■	■	■	■
Prospective cohort study				
Retrospective cohort study				
Case-control				
Case-series				
Random sequence generation*	no‡	unclear**	unclear††	yes
Concealed allocation*	no‡	unclear**	unclear††	unclear‡‡
Intention to treat*	yes	yes	yes	yes
Independent or blind assessment	yes	varies**	unclear††	varies‡‡
Co-interventions applied equally	yes	yes	yes	yes
Complete follow-up of ≥80% and <10% difference in follow-up between groups	varies‡	varies**/ unclear**	yes	varies‡‡
Controlling for possible confounding†	yes	yes	varies††	yes
Evidence class	III	III	III	II
Risk of bias	**Moderately high**	**Moderately high**	**Moderately high**	**Moderately low**

‡Hambrecht (2004):

- random sequence generation or concealed allocation: randomization was achieved by drawing envelope containing group assignment and no other information was provided

- complete f/u of ≥80% and <10% difference in f/u between treatment groups: credit given for hard clinical outcomes (100% f/u in both groups) but not clinical symptoms and exercise capacity (74% (PCI) vs. 84% (exercise) f/u)

**BARI 2D

- random sequence generation or concealed allocation: randomization was stratified by clinical site, however, no additional information was provided regarding how randomization was achieved or how treatment allocation was concealed
- independent or blind assessment of outcomes: credit given for death, MI, stroke (all three were classified by the core laboratory or were adjudicated by an independent committee), and revascularization; but not for angina, which was patient-reported (as patients could not be blinded to treatment received)
- complete f/u of ≥80% and <10% difference in f/u between treatment groups: credit for complete f/u of ≥80% for death, MI, stroke, angina, and revascularization were reported for a mean follow-up with a range and last data were carried forward but no credit for health status outcomes as the % f/u was unclear; no credit for <10% difference in f/u b/w treatment groups, as % follow-up was not reported by treatment group

††MASS-II

- random sequence generation or concealed allocation: no information was provided regarding how randomization was achieved or how treatment allocation was concealed
- independent or blind assessment of outcomes: no information provided
- controlling for confounding: there were baseline differences between PCI and control groups in history of MI (52% versus 39%, p=0.0072), diabetes (23% versus 36%, p=0.0039), and positive treadmill test (47% versus 33%, p=0.0061); multivariate analysis was done to control for baseline differences in some but not all analyses. Credit given only when adjusted risk estimates are reported.

‡‡COURAGE

- concealed allocation: no information was provided
- complete f/u of ≥80% and <10% difference in f/u between treatment groups: credit for clinical outcomes; no credit for patient reported outcomes at any follow-up as data were available for <80% of randomized patients (see Weintraub 2008)

independent or blind assessment of outcomes: credit given for clinical outcomes (which were adjudicated by an independent committee), and revascularization; but not for patient-reported outcomes (as patients could not be blinded to treatment received)

KQ2 comparative studies

Appendix Table E2. Risk of bias and class of evidence for RCTs evaluating DES vs. BMS

Methodological Principle	BASKET PROVE Kaiser 2010, Pedersen 2014	ENDEAVOR II Fajadet 2010, Eisenstein 2009	EXAMINATION Sabate 2012, Sabate 2014,	PRODIGY Valgimigli 2014	XIMA de Belder 2014	X-MAN Dharma 2014	ZEUS Valgimigli 2015
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■	■	■	■
Random sequence generation*	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Statement of concealed allocation*	Unclear†	Yes	Yes	Unclear†	Unclear	Unclear	Unclear
Intention to treat*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent or blind assessment	No‡	Yes	Yes	Yes	Yes	Yes	Yes
Co-interventions applied equally	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete follow-up of ≥80% and <10% difference in follow-up between groups	Yes (2 yrs. 93%; DES 94%; BMS 93%)	Yes (1, 4, 5 yrs. 97%-99%; DES 97%-99%; BMS 97%-99%)	Yes (1, 2 yrs. 98%; DES 98%-99%; BMS 97%-98%)	Yes (2 yrs. 99%; ZES 99%; EES 99%; BMS 99%)	Unclear	Yes§	Yes (1 yr. 99%; DES 99%; BMS 99%)
Controlling for possible confounding**	Yes	Yes	Yes	Yes	No††	Yes	Yes
Evidence class	II	I	I	II	II	II	II
Risk of Bias	Moderately Low	Low	Low	Moderately Low	Moderately Low	Moderately Low	Moderately Low

*Applies to randomized controlled trials only.

†Authors state that allocation occurred via sealed envelopes; however, they did not specify that the envelopes were opaque so the study did not receive credit for this criteria.

‡An independent critical events committee adjudicated all clinical end points. This assessment was conducted in a blinded fashion for the initial two thirds of events. However, as a result of illness of one of the study monitors, there was a delay in adjudicating the final one third of events. Because of time constraints for the completion of the analysis, these files were adjudicated without blinding.
§Small pilot study. Death is reported but not clear if there was other loss to follow-up; however, given the short follow-up period (30-days) credit was given under the assumption that >20% of patients would not be lost to follow-up in that short time frame.
**Patient characteristics must be similar between groups at baseline or any differences controlled for via multivariate regression analysis or stratification.
††History of previous MI and stent lengths were different between groups at baseline and not adjusted for.

Appendix Table E3. Class of Evidence for studies analyzing data from registries that were included in the AHRQ report

Methodological principle	Garg 2014	Piao 2014 KAMIR registry	Sarno 2012/2014 SCAAR registry
Designed specifically for conditions evaluated	Yes	Unclear	Yes
Includes prospective data only	Yes	No	Yes
Validation of completeness and quality of data	Yes	Unclear	Yes
Patients followed long enough for outcomes to occur	Yes	Yes	Yes
Independent outcome assessment*	Varies†	Varies†	Varies†
Complete follow-up of ≥ 85%	Varies‡	Unclear	Unclear
Controlling for possible confounding§	Yes	Yes	Yes
Accounting for time at risk**	Yes	Yes	Yes††
Evidence class	**III**	**IV**	**III**
Risk of Bias	**Moderately high**	**High**	**Moderately high**

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.
†Garg 2014: unclear for stent thrombosis and reinfarction and yes for death; SCAAR registry: unclear for stent thrombosis and restenosis and yes for death <30 days; KAMIR: unclear for stent thrombosis and yes for in hospital death and bleeding.
‡Authors state that clinical follow-up was complete up to 12 months in 96.6% of patients; however, no information provided on 24 month follow-up.
§ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
** Equal follow-up times or for unequal follow-up times, accounting for time at risk.
†† Mean follow-up time for new generation DES was 359±194 days and for BMS 607±190 days; cox proportional hazard method was used to calculate the adjusted cumulative risk of stent thrombosis and restenosis up to 24 months in Sarno 2012 and stent thrombosis up to 36 months in Sarno 2014.

Appendix Table E4. Quality of Health Economic Studies (QHES) score of included RCTs comparing PCI and Medical therapy (KQ 1d)

QHES Question (pts possible)		Hambrecht (2004)	Hlatky (2009) (BARI 2D)	Weintraub (2008), Zhang (2011) (COURAGE)	Favarato (2003), Vieira (2012) (MASS-II)
1.	Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	0	7	7	7
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	0	0	0	0
3.	Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	8	8	8	8
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1 (n/a)	1 (n/a)	1	1 (n/a)
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	0	9	9	0
6.	Was incremental analysis performed between alternatives for resources and costs? (6 pts)	0	0	6	0
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	0	0	5	0
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 pts)	0	7	7	0
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	8	8	8	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 pts)	0	0	6	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 pts)	7	7	7	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 pts)	0	0	8	0
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	0	7	7	0
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	0	0	0	0
15.	Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	8	8	9	8
16.	Was there a statement disclosing the source of funding for the study? (3 pts)	3	3	3	3

Appendix Table E5. Quality of Health Economic Studies (QHES) score of included formal economic analyses comparing new generation DES with BMS (KQ 2d)

QHES Question (pts possible)		Eisenstein (2009) [ENDEAVOR II]
1.	Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	7
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	0*
3.	Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	8
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1 (n/a)
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	0
6.	Was incremental analysis performed between alternatives for resources and costs? (6 pts)	6
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	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 pts)	7
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	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 pts)	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 pts)	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 pts)	8
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	7
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	0
15.	Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	8
16.	Was there a statement disclosing the source of funding for the study? (3 pts)	3
	Total score (out of possible 100):	81

*Not specifically state in the article but assumed to be healthcare based on costs included.

APPENDIX F. Study characteristics

Key Question 1

Appendix Table F1. PCI plus stenting versus medical therapy for stable angina: Study and Patient Characteristics

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
BARI-2D Chaitman 2009 Brooks 2010, BARI 2D Study Group 2008/2009 Multicenter (49 sites) United States (73.7%), Canada (13.6%), Brazil (7.9%), Mexico (2.1%), Czech Republic/ Austria (2.7%)†	N = 1605‡	Inclusion: Age ≥25 years; diagnosis of type 2 diabetes (based on need for treatment with insulin or oral hypoglycemic drugs or confirmed elevated blood glucose level); documented ischemia; angiographically documented CAD with at least 1 significant lesion of a major epicardial artery (≥50% stenosis associated with a positive stress test or classic angina with ≥70% stenosis) Exclusion: In need of immediate coronary revascularization or had undergone revascularization within 12 months before study entry; NYHA functional class III or IV congestive heart failure; need for concurrent major vascular surgery; stenosis ≥50% of	PCI (n=798); with (n=669; 424 BMS, 245 DES) or without stenting (n=129) PCI to be done within 4 weeks of randomization; all patients treated according to current guidelines: • intensive medical therapy with common use of statins, aspirin, beta-blockers, and either angiotensin converting-enzyme inhibitors or angiotensin-receptor blockers (%NR) • target levels for: glycated	Medical therapy (n=807) Could receive PCI during study period if indicated by progression of angina or development of an ACS or severe ischemia All patients treated according to current guidelines: • intensive medical therapy with common use of statins, aspirin, beta-blockers, and either angiotensin converting-enzyme inhibitors or	Age: 62.1 ± 9.0 vs 62.0 ± 9.3 years Male: 68.6% vs 67.0% Angina status at entry: Classic Angina: 60.6% vs 59.4% Angina equivalents: 22.7% vs 21.8% No angina nor equivalents: 16.7% vs 18.7% Cigarette Smoking status: Never smoked: 34.0% vs 31.4% Former smoker: 52.2% vs 56.0% Current smoker: 13.7% vs 12.6% History of hypertension: 81.7% vs 82.4% Duration of diabetes: 10.3 ± 8.7 vs 10.5 ± 8.9 BMI: 32.3 ± 6.5 vs 32.4 ± 6.1	Overall follow-up: mean 5.3 years (range, 3.4 to 7.8 years) 3 years (86.7%; 2053/2368) 5 years (47.3%; 1121/2368) Cross-over (medical to any revascularization): • 2.6% (31/1192) by 1 month; • 12.9% (154/1192) by 6 months; • 42.1% (502/1192) by 5 years	National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases; several pharmaceutical companies provided supplemental funding and/or donated medicati

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		the left main coronary artery; hemoglobin A_{1c} (HbA_{1c}) >13%; serum creatinine >2.0 mg/dL; and hepatic disease	hemoglobin <7.0%; LDL < 100 mg per deciliter; blood pressure ≤ 130/80 mm Hg. • counseling regarding smoking cessation, weight loss, and regular exercise.	angiotensin-receptor blockers (%NR) • target levels for: glycated hemoglobin <7.0%; LDL < 100 mg per deciliter; blood pressure ≤ 130/80 mm Hg. • counseling regarding smoking cessation, weight loss, and regular exercise.	History of MI: 30.8% vs 29.5% History of Stroke: 9.7 vs 11.3 Number of diseased vessels: 1: 45.2% vs 43.8% 2: 34.5% vs 35.7% 3: 20.2% vs 20.5% Previous PCI: 23.7% vs 22.5% Previous CABG: 8.0% vs 9.9%	(43.3% [349/807] in the PCI stratum)	on or supplies
COURAGE Boden 2007, Weintraub 2008, Boden 2009, Teo 2009, Chaitman 2010, Maron 2010, Mancini 2011,	N = 2287	Inclusion: CCS class I-III patients with CHD, including patients with one of the following: - Prior PCI or CABG with evidence of ischemia - Chronic stable angina - Post-MI patients without class IV angina, severe LV dysfunction, or arrhythmia - Asymptomatic ischemia detected by exercise or perfusion scintigraphy or 24-hour ambulatory ECG recording	A: Percutaneous Coronary Intervention (PCI) + Optimal Medical Therapy (OMT) (n=1149) Revascularization of the culprit stenosis or stenosis is undertaken; a complete myocardial revascularization is performed as	B: Optimal Medical Therapy (OMT) only (n=1138) Medical therapy conforms to updated AHA Treatment Guidelines. All patients receive antithrombotic therapy with aspirin 91 to 325 mg/d. In aspirin therapy,	A: PCI + OMT vs. B: OMT only Age: 61.2 ± 10.1 vs. 61.8 ± 9.7 Female: 15% (169/1149) vs. 15% (169/1138) Race: - White: 86% (988/1149) vs. 86% (975/1138) - Black: 5% (57/1149) vs. 5% (57/1138) - Hispanic: 6%	Length f/u: 2.5 to 7.0 years (median: 4.6) Complete f/u: 91% (2083/2287) Cross-over: NR Did not cross over within the first 3 months: NR vs. 78% (895/1135)	Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development, in collabora

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
Maron 2011, Zhang 2011, Shaw 2012 Multicenter (50 sites) United States and Canada		- Patients with a ≥80% lesion in ≥1 vessels subtending a large area of myocardium even in the absence of objective ischemia - Patients who meet one of the existing AHA/ACC Joint Task force Class I or II indications for PCI. These indications are Patients with single-vessel CAD who are asymptomatic to severely symptomatic and who have a large area of ischemic myocardium subtending a significant (>50% diameter reduction) coronary stenosis (AHA/ACC Class I indication) or a moderate area of ischemia (AHA/ACC Class II indication). Patients with multivessel CAD who are asymptomatic or mildly symptomatic who have a large ischemic area or moderate ischemic area (AHA/ACC Class II indication) for asymptomatic or minimally symptomatic patients.	possible, but is considered unnecessary if incomplete revascularization is thought to be adequate in relieving ischemia. Use if glycoprotein IIb/IIIa inhibitors is at operator discretion. Unfractionated heparin is dose-adjusted and a 12-lead ECG is obtained before and within 24 hours after PCI. In patients receiving stents, 300 mg clopidogrel at the time of PCI is used, follow by 75 mg everyday for at least 6 to 9 months.	clopidrogel 75 mg/d is prescribed. For patients undergoing PCI, tirofiban and aspirin plus clopidrogel is used as an accepted practice. Medical anti-ischemic therapy for stable angina includes long-acting metroprolol, amlodipine, or isosorbide 5-mononitrate, alone or in combination. Post-MI patients receive standard secondary prevention with beta-blockers (unless contraindicated) and an ACE inhibitor (lisinopril) for LVEF of <40% or anterior MI location. Patients	(68/1149) vs. 5% (58/1138) - Other: 3% (35/1149) vs. 4% (47/1138) CCS class 0: 12% (135/1149) vs. 13% (148/1138) CCS class 1: 30% (340/1149) vs. 30% (341/1138) CCS class 2: 36% (409/1149) vs. 37% (425/1138) CCS class 3: 23% (261/1149) vs. 19% (221/1138) CCS class 4: NR (excluded) Missing CCS class data: <1% (3/1149) vs. <1% (2/1138) Duration of angina (median): 5 (IQR*, 1 to 15) vs. 5 (IQR*, 1 to 15) months Anginal episodes/week with exertion or at rest within last month (median): 3 (IQR*, 1 to 6) vs. 3 (IQR*, 1 to 6) months		tion with the Canadian Institutes of Pharmaceuticals; Bristol-Myers Squibb Medical Imaging; Fujisawa; Kos Pharmaceuticals; Data Scope; Astra Zeneca Pharmaceuticals; Astra Zeneca-Canada; Schering-Plough Corporation, Ltd.; Sanofi-Aventis, Inc.; First

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		- Has at least 1 vessel for angioplasty meeting one of the follow criteria: right coronary artery: proximal to the posterior descending artery in a right dominant vessel; Left circumflex coronary artery: proximal to 1 or 2 OM branches or proximal to the posterior descending artery + posterolateral branches in a left dominant vessel; LAD: proximal or mid-vessel; SVG or LIMA: graft must supply the same regions as outlined previously, or, in the opinion of the interventionalist, the coronary stenosis subtends a major mass of myocardium. - Has objective evidence of myocardial ischemia including one of the following: spontaneous new ST-T changes on resting ECG defined as either ≥1.0 mm ST-segment deviation from the baseline (80 mm from J point) or ≥2.0 mm T-wave inversion		with unstable angina are treated aggressively, including unfractionated heparin and tirofiban, as needed. All patients with BP > 130/85 mm Hg received antihypertensive therapy, with an ACE inhibitor being first-line, although dihydropyridine calcium antagonist, an angiotensin II receptor blocker, or a diuretic may be used. All patients also receive aggressive low-density lipoprotein lowering using up to 80 mg of	Diabetes: 32% (367/1149) vs. 35% (399/1138) Hyperlipidemia: NR Hypertension: 66% (757/1149) vs. 67% (764/1138) Prior MI: 38% (437/1149) vs. 39% (439/1138) Prior PCI: 15% (174/1149) vs. 16% (185/1138) Prior CABG: 11% (124/1149) vs. 11% (124/1138) Current smoker: 23% (260/1149) vs. 23% (259/1138) Number of diseased vessels: - 1 vessel: 31% (361/1149) vs. 30% (343/1138) - 2 vessels: 39% (446/1149) vs. 39% (439/1138) - 3 vessels: 30% (341/1149) vs. 31% (355/1138) Lesion length: NR Cerebrovascular		Horizon; and GE Healthcare.

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		(or pseudonormalization, if T waves were previous inverted) in a minimum of 2 contiguous leads within 1 of 3 ECG lead groups (anterior V1-V2; inferior II, III, aVF; lateral I, aVl, V6-V6) - Objective evidence of stress-induced myocardial ischemia as detected by standard 12-lead exercise stress test, exercise or pharmacologic stress (adenosine or dipyridamole) coupled with perfusion scintigraphy, exercise or pharmacologic stress (dobutamine) coupled with 2D echocardiography, or exercise radionuclide ventriculography, based on one of the following: >1.0 mm ST-segment deviation from baseline on standard treadmill exercise using 12-lead ECG; ≥1 scintigraphic perfusion defects during exercise technetium Tc 99m sestamibi or thallium-based isotope imaging; >1 perfusion defects (reversible or partial		simvastin daily alone or in combination with ezetimibe. Patients also undergo individualized life-style interventions (diet, weight loss, smoking cessation/relapse prevention, and regular aerobic exercise).	<u>disease:</u> 9% (100/1149) vs. 9% (102/1138) <u>Congestive heart failure:</u> 5% (57/1149) vs. 4% (51/1138) P > 0.05 unless otherwise noted		

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		reversible) with pharmacologic stress (dipyridamole, adenosine) during technetium Tc-00m sestamibi or thallium imaging; ≥1 wall motion abnormalities during exercise radionuclide ventriculography; 2D echocardiography (exercise or dobutamine). Exclusion: - Unstable angina and symptoms refractory to maximal oral and intravenous medical therapy (persistent CCS class IV) - Post-MI course complicated by persistent rest angina, shock, and persistent CHF for which the need or likelihood of urgen myocardial revascularization is high, - Coronary angiographic exclusions: patients with no prior CABG and left main coronary disease ≥50%; coronary arteries technically unsuitable or					

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		hazardous for PCI; patients with nonsignificant CAD in whom PCI would not be considered appropriate or indicated - EF <30%, except <35% if patient has 3-vessel disease including >70% LAD proximal stenosis - Cardiogenic shock - Pulmonary edema or CHF unresponsive to standard medical therapy - CABG or PCI within the last 6 months - Concomitant valvular heart disease likely to require surgery or affect prognosis during follow-up - Congenital or primary cardiac muscle disease likely to affect prognosis during follow-up - Resuscitated out-of-hospital sudden death or symptomatic sustained or nonsustained ventricular tachycardia - Significant systemic hypertension (BP>200/100 mm Hg) unresponsive to medical therapy					

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
Hambrecht 2004 Kendziorra 2005, Walther 2008 Single center Germany	N = 101	Inclusion: Males; age ≤70 years; stable CAD and 1 native coronary artery stenosis of ≤75% by visual assessment amenable to PCI; CCS class I to III angina pectoris with documented myocardial ischemia during stress ECG or ^{99m}Tc scintigraphy Exclusion: ACS or recent MI (<2 months); left main stenosis >25% or high-grade proximal LAD stenosis; LVEF <40%; significant valvular heart disease; insulin-dependent diabetes mellitus; smoking; occupational, orthopedic, or other condition that precluded regular exercise; previous PCI or CABG within last 12 months. Patients living within a 25-km radius of the institution were recruited.	PCI with stenting and medical therapy (n=50); 98% (49/50) received allocated treatment (2% [1/50] had new target vessel occlusion) Mean interval b/w randomization and PCI = 14.8 ± 3.3 days Procedure: All patients given acetylsalicylic acid 100 mg/d and clopidogrel 300 mg/d on the day before the procedure and a bolus of 10,000 IU of heparin of the day of Lesion treated with a 6F guiding catheter Acetylsalicylic acid 100 mg/d was continued	Exercise training plus medical therapy (n=51); 100% received allocated treatment Mean interval b/w randomization and initiation of training therapy = 21.3 ± 2.6 days Exercise program: For first 2 weeks, exercise in the hospital 6x/day for 10 minutes on a bicycle ergometer at 70% of the symptom-limited maximal heart rate Upon discharge, patients were asked to exercise on their bicycle ergometer close to the target heart rate for 20 mins./day and to participate in one	*PCI vs. exercise* Subgroup: Males Age: 60 ± 1 vs. 62 ± 1 years Sex (%male): 100% Race: NR CCS I angina: 30% (15/50) vs. 41% (21/51) CCS II angina: 66% (33/50) vs. 53% (27/51) CCS III angina: 4% (2/50) vs. 6% (3/51) Diabetes: 22% (11/50) vs. 23% (12/51) Hyperlipidemia (LDL > 3.5 mmol/L): 86% (43/50) vs. 77% (39/51) Hypertension (systolic RR >140 mm Hg or diastolic RR >90 mm Hg): 70% (35/50) vs. 82% (42/51) Prior MI: 39% (20/50) vs. 52% (26/51) Prior PCI or CABG: NR Current smoker: 16%	12 months Hard clinical outcomes: 100% (101/101) Clinical symptoms/ exercise capacity follow-up: 75.2% (76/101) Cross-over: NR	Aventis Germany (unconditional scientific grant)

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
			throughout the study period, and clopidogrel 75 mg/d was continued for 4 weeks. Medical therapy was adjusted according to current clinical guidelines and continued by patients' private physicians.	60-min. group training session of aerobic exercise per week. Medical therapy was adjusted according to current clinical guidelines and continued by patients' private physicians.	(8/50) vs. 18% (9/51) Single vessel disease: 60% (30/50) vs. 57% (29/51) Double vessel disease: 28% (14/50) vs. 26% (13/51) Triple vessel disease: 12% (6/50) vs. 18% (9/51) Target lesion: *LAD*, 18% (9/50) vs. 22% (11/51); *left circumflex*, 50% (25/50) vs. 43% (22/51); *RCA*, 32% (16/50) vs. 35% (18/51) Lesion type: type A, 20% (10/50) vs. 22% (11/51); type B, 68% (34/50) vs. 67% (34/51); type C, 12% (6/50) vs. 14% (6/51) Lesion length: 10.3 ± 3.3 vs. 9.5 ± 3.4 mm Concurrent medications: *ACE inhibitors/ AT1-receptor antagonists*, 88% (44/50) vs. 74% (38/51); *beta-HMG-*		

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
					CoA reductace inhibitors, 80% (40/50) vs. 72% (36/51); *beta-receptor antagonists*, 86% (43/50) vs. 88% (45/51); *Acetylsalicylic acid*, 98% (49/50) vs. 98% (50/51) *Statins (simvastatin, atorvastatin, fluvastatin):* baseline, 80% (40/50) vs. 72% (37/51); 2 years, 84% (42/50) vs. 76% (39/51); all medication types similarly distributed in both groups		
MASS-II Hueb 2004 Lima 2013, Rezende 2013, Vieira 2012; Hueb 2010, Lopes 2008, Hueb 2007, Soares 2006	N = 408§	Include: angiographically documented proximal multivessel coronary stenosis >70% by visual assessment and documented ischemia (either stress testing or CCS typical stable angina assessment, class II or III); lesion amenable to revascularization by either PCI or CABG	PCI (n=205) with stents, lasers, directional atherectomy, or balloon angioplasty; available within 3 weeks of randomization 95% (194/205) received PCI (3% [6/205] had CABG; 1.0% [2/203] died prior to tx; 1.5%	Aggressive medical therapy (n=203); 100% received assigned treatment All patients received optimal medical regiment consisting of: stepped-care approach using nitrates, aspirin, beta-blockers,	*PCI vs. medical* Subgroup: none Age: 60 ± 9 vs. 60 ± 9 years Sex (%male): 67% (137/205) vs. 69% (140/203) Race: NR Class II or III angina: 78% (160/205) vs. 78% (158/203) Diabetes: 23% (47/205) vs. 36% (73/203)	1 year 5 years** 10 years (100%, 408/408) Cross-over (medical to PCI): 2.0% (4/203) at 1	Zerbini Foundation (research grant)

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
		Exclusion: Unstable angina or acute MI requiring emergency revascularization; ventricular aneurysm requiring surgical repair; LVEF <40%; a history of PCI or CABG; single-vessel disease; history of congenital heart disease, valvular heart disease, or cardiomyopathy; unable to understand or cooperate with the protocol requirements or to return for follow-up; left main coronary artery stenosis ≥50%; or suspected or known pregnancy or another coexisting condition that was a contraindication to CABG or PCI	[3/205] received medical therapy) No Glycoprotein IIb/IIa agents were used All patients received optimal medical regiment consisting of: stepped-care approach using nitrates, aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs, unless contraindicated Hydroxymethyl-glutaryl-coenzyme A reductase inhibitors, along with a low fat diet on an individual basis	calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs, unless contraindicated Hydroxymethyl-glutaryl-coenzyme A reductase inhibitors, along with a low fat diet on an individual basis	Diabetes: 23% (47/205) vs. 36% (73/203) Total cholesterol (mmol/L): 5.7 ± 1.1 vs. 5.7 ± 1.0 LDL (mmol/L): 3.8 ± 0.9 vs. 3.8 ± 0.9 HDL (mmol/L): 1.0 ± 0.3 vs. 1.0 ± 0.3 Triglycerides (mmol/L): 2.0 ± 0.8 vs. 2.0 ± 0.9 Hypertension: 61% (125/205) vs. 55% (112/203) Prior MI: 52% (107/205) vs. 39% (79/203) Prior PCI or CABG: 0% Smoking: 27% (55/205) vs. 33% (67/203) Double vessel disease: 42% (86/205) vs. 41% (83/203) Triple vessel disease: 58% (119/205) vs. 59% (120/203) LAD disease: 93% (191/205) vs. 89% (181/203)	year; 8.9% (18/203) at 5 years; 14.3% (29/203) at 10 years Cross-over (PCI to medical): 1.5% (3/205) received medical instead of PCI after randomization	

Trial	N*	Inclusion & Exclusion Criteria	PCI plus stenting and medical therapy	Medical therapy	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (% (n/N))	Funding
					Mean EF: 67% ± 8% vs. 68% ± 7%		

*N: number randomized, IQR = Interquartile range
† Percentage of patients included in the PCI intended stratum in each geographic region
‡ A total of 2368 patients were randomized, 763 CABG patients are excluded from our analysis.
§ A total of 611 patients were randomized, 203 CABG patients are excluded from our analysis.
** At 1 and 5 years, Hueb 2004 and Hueb 2007 clearly state that no patients were lost to follow-up in the medical [and CABG] group but no statement at all is made for the PCI group.

Key Question 2

Appendix Table F2. Drug-eluting versus bare metal stenting for stable or unstable angina: Study and Patient Characteristics

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
Zotarolimus Trials			**DES vs BMS**	**DES vs BMS**	**DES vs BMS**		
ENDEAVOR II Eisenstein 2009, Fajadet 2006, Fajadet 2010 Multicenter (72 sites) Europe, Asia Pacific, Israel,	N=1197†	Inclusion: clinical evidence of ischemia or a positive functional study who were undergoing stenting of a single, de novo lesion in a native coronary vessel with a reference vessel diameter of	DES: Zotarolimus-eluting (Endeavor, Medtronic) (n=598) BMS: Cobalt-alloy (Driver, Medtronic)	Identical for both DES and BMS groups Procedure • ECG and cardiac enzymes obtained pre- and post-procedure • Pre-dialation (balloon) mandatory • Additional stents (≤48 mm length) permitted at operator discretion in	Subgroup: None Age: 61.6 ± 10.5 vs. 61.9 ± 10.5 years Sex (%male): 77.2% (461/597) vs. 75.3% (449/596) Race (minority): 6.0% (36/597) vs. 6.3% (38/596) Prior MI: 39.7% (236/594) vs. 41.5% (247/595)	1 year (98.6%; 1180/1197) 4 years (97.5%; 1167/1197) 5 years (96.8%; 1159/1197)	Medtronic CardioVascular

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
New Zealand, and Australia		2.25 to 3.5 mm and a lesion length between 14 mm and 27 mm. Exclusion: left ventricular ejection fraction <30%; >50% stenosis proximal or distal to the target lesion; MI within the previous 72 hours; contraindications or allergy to aspirin, heparin, clopidogrel, cobalt, nickel, or chromium; hypersensitivity to contrast media; serum creatinine >2.0 mg/dL (177 µmol/L); leukocyte count <3000 cells/mm3; platelet count <100,000 or >700,000 cells/mm3;	(n=599)	event of an edge dissection or incomplete coverage • Post-dialation allowed as required to optimize stent expansion Medications *Pre/peri-procedure*: • Aspirin ≥75 mg and clopidogrel 300 mg bolus • Unfractionated heparin to maintain clotting >250 sec. or between 200-250 if a glycoprotein IIb/IIIa inhibitor *Post-procedure:* • Aspirin ≥75 mg daily indefinitely • Clopidogrel 75 mg daily for 12 weeks • Dual-antiplatelet therapy similar between DES and BMS groups at all time points over 5-yrs of follow-up	Prior PCI: 21.7% (129/595) vs. 18.0% (107/594) Prior CABG: 4.5% (28/597) vs. 4.9% (29/596) Diabetes: 18.2% (108/595) vs. 22.2% (132/595) Hyperlipidemia: 80.5% (476/591) vs. 76.9% (455/592) Hypertension: NR Current smoker: 35.3% (207/587) vs. 35.2% (207/588) Number of diseased vessels treated: one Number of stents implanted: none, 1.0% (6/597) vs. 0.8% (5/596); one, 87.8% (525/597) vs. 88.5% (530/596); two, 11.0% (66/597) vs. 10.2% (61/596) % stenosis: 69.7% ± 10.8% vs. 69.5% ± 11.0% Target lesion: LAD, 43.2% (255/590)	Crossover: NR	

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		interventional coronary procedure within 30 days before or planned after implantation of the study stent; left main or ostial target lesion; severe calcification by angiography; bifurcation lesion; or location of target lesion at a >45° bend.			vs. 47.5% (281/591); Left Circumflex, 22.4% (132/590) vs. 21.2% (125/591); RCA, 34.4% (203/590) vs. 31.3% (185/591) Reference vessel diameter (mm): 2.7 ± 0.5 vs. 2.8 ± 0.5 Lesion length (mm): 14.1 ± 5.6 vs. 14.4 ± 5.7		
ZEUS Valgimigli 2013, Valgimigli 2015 Multisite (20 sites) Italy, Switzerland, Portugal, Hungary	N=1606	Inclusion: Patients were eligible for recruitment if they were considered to be uncertain DES candidates based on 3 major inclusion criteria: 1) high bleeding risk and/or the presence of relative or absolute contraindications to long-term dual	DES: Zotarolimus-eluting (Endeavor, Medtronic Vascular, Minneapolis, MN) (n=802) BMS: Various (Tsunami, Terumo, Leuven, Belgium; Skylor, Medtronic;	Procedure Details NR Medication: *Pre/peri-procedural:* • Aspirin (160-325 mg orally or 500 mg intravenously as a loading dose and then 80-160 mg orally) or prasugrel (60 mg loading dose) • Those not eligible for DAPT were treated with either aspirin or clopidogrel (or	Age: 71.8 ± 11 (IQR 63.8 to 81.0) vs 71.8 ± 12 (IQR 64.0 to 81.0) Male: 70.0% (561/802) vs 71.1% (572/804) BMI (median): 26.7 (IQR = 24.2 to 29.4) vs 26.5 (IQR 24.2 to 29.3) Diabetes: 26.8% (215/802) vs 35.5% (205/804) Hypertension: 76.3% (612/802) vs 75.2% (605/804) Hyperlipidemia: 47.5% (381/802) vs 49.6%	30 days, 6 months, 12 months 12 month F/u: 99.9% (803/804) vs 99.9% (801/802); overall 99.9% (1604/1602) Crossover: BMS to study DES =	Medtronic unrestricted grant to Consozrio Ferrara Ricerche

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		anti-platelet treatment and/or 2) high thrombosis risk due to systemic disorders or planned non-cardiac surgery and/or 3) low restenosis risk based on angiographic findings. Exclusion: Pregnancy: Women of childbearing potential must have had a negative pregnancy test (urine or serum HCG), preferably <24 hours, but at a minimum within 7 days prior to randomisation. Subjects who were unable to give informed consent and/or were	Integrity, Medtronic; Vision, Abbott, Santa Clara, CA; Avant-Garde, CID Vascular, Saluggia, Italy) (n=802)	prasugrel) monotherapy *Post Procedural* • Clopidogrel 75 mg/d or prasugrel 10 or 5 mg/d • When DAPT was discontinued, patients were left free to continue either the 2 antiplatelet agents (aspirin or clipidogrel/prasugrel) at the discretion of the physician	(399/804) Smoker: 20.8% (167/802) vs 21.0 (169/804) On dialysis: 2.6% (21/802) vs 1.5% (12/804) Previous MI: 24.2% (194/802) vs 23.6% (190/804) Previous PCI: 19.3% (155/802) vs 18.5% (149/804) Previous CABG: 6.7% (54/802) vs 7.3% (59/804) Previous stroke or transient ischemic attack: 6.4% (51/802) vs 6.6% (53/804) Chronic obstructive pulmonary disease: 6.9% (55/802) vs 8.1% (65/804) Peripheral artery disease: 14.6% (117/802) vs 17.5% (141/804) Left ventricular ejection fraction (median): 50.0 (IQR 40-	0.6% (5/804) BMS to any DES = 1.7% (14/804) DES to BMS = 1.0% (8/802)	

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		unwilling to undergo planned follow-up through 12 months.			56) vs 50.0 (IQR 40-55) Stable angina: 36.8% (295/802) vs 36.7% (295/804) Acute Coronary Syndrome: 63.2% (507/802) vs 63.3% (509/804) Unstable Angina: 17.3% (139/802) vs 16.3% (131/804) N-STEMI: 26.8% (215/802) vs 28.1% (226/804) STEMI: 19.1% (153/802) vs 18.9% (152/804) Diseased vessels: 1 vessel: 41.4% (332/802) vs 38.9% (313/804) 2 vessels: 33.2% (266/802) vs 35.4% (285/804) 3 vessels: 25.4% (204/802) vs 25.6% (206/804) High bleeding risk: 52.9% (424/802) vs 50.2% (404/804) High thrombosis risk:		

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					17.5% (140/802) vs 18.0% (145/804) Stable CAD: 21.2% (170/802) vs 20.8% (167/804) Unstable CAD: 37.8% (303/802) vs 37.4% (301/804)		
Everolimus Trials							
BASKET-PROVE Pfisterer 2008, Kaiser 2010, Pedersen 2014 Multicenter (11 sites) Switzerland (7), Denmark (1), Austria (1), Italy (1)	N=2314	Inclusion: Aged >18 years treated with PCI + stenting independent of its indication, in need for stents ≥3.0 mm only. Exclusion: Patients with vessels >4.0 mm, cardiogenic shock, in-stent restenosis or stent thrombosis,	DES Everolimus-eluting (Xience, Abbott Vascular, Abbott Laboratories, IL) (n=775) BMS Cobalt-chromium (Vision, Abbott Vascular, Abbott Laboratories, IL)	Procedure and co-intervention details identical for DES and BMS groups Procedure: • Performed according to standard techniques at discretion of operators in each center. • Size of vessel was assessed visually after intracoronary injection of nitroglycerin. • Stents were expanded as	*DES vs BMS* Age (mean ± SD): 66 ± 11 vs 67 ± 11 Male: 76% (587/774) vs 77% (586/765) Diabetes mellitus: 15% (119/774) vs 14% (108/765) Systemic arterial hypertension: 61% (469/774) vs 63% (485/765) Hyperlipidemia: 64% (498/774) vs 65% (495/765) Smoker: 34%	12 months, 24 months, 2 years, 3 years, 5 years *DES vs BMS* 2 years f/u: 98.4% (762/774) vs 98.9% (756/765) Received wrong stent (total	Swiss National Foundation for Research, Berne; Basel Foundation of Cardiovascular Research, Basel, Switzerland; unrestricted research grant in Denmark (further details NR)

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		unprotected left main or bypass-graft disease to be stented, planned surgery within the following 12 months, need for anticoagulants or increased bleeding risk for other reasons, known intolerance of aspirin and/or clopidogrel, no compliance expected, no follow-up possible, significant stenosis impossible to be treated, or no consent.	(n=765)	much as possible and feasible. • Stent size must be at least 3.0 mm for all lesions. • If necessary, multiple vessels were treated within 3 months. Medication: • Patients given aspirin 75 or 100 mg daily for long-term after an appropriate loading dose, if not already on aspirin. • Clopidrogel was prescribed at a dose of 75 mg/d for 12 months after a loading dose of 300 or 600 mg. • Life-long statin therapy was strongly recommended in all patients. Other medications could be given at the discretion of physician in charge as clinically indicated	(267/774) vs 34% (261/765) Previous MI: 11% (82/774) vs 13% (103/765) Previous PCI: 12% (93/774) vs 12% (88/765) Previous CABG: 3% (20/774) vs 3% (20/765) Stable angina: 35% (271/774) vs 37% (285/765) Unstable angina: 34% (264/774) vs 32% (246/765) STEMI: 31% (239/774) vs 31% (234/765) Arteries treated: *Left main with bypass graft:* 1% (7/774) vs 1% (9/765) *Left Anterior Descending:* 53% (412/774) vs 52% (400/765) *Left Circumflex:* 26% (202/774) vs 27% (203/765) *Right coronary:* 40%	population): 0.8% (18/2314) Crossover: NR	

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					(310/774) vs 42% (325/765) CAD Complexity: *Multivessel disease:* 41% (319/774) vs 43% (327/765) *Bifurcation lesion*: 7% (58/774) vs 9% (68/765) *Chronic total occlusion:* 4% (34/774) vs 5% (39/765) Procedural characteristics: Number treated segments per pt (mean ± SD): 1.4 ± 0.8 vs 1.5 ± 0.8 Number stents per pt (mean ± SD): 1.7 ± 1.1 vs 1.7 ± 1.1 Total no. of stents: 1302 vs 1324 Stent length per pt (mean ± SD) (mm): 31.1 ± 23.3 vs 31.1 ± 22.5 Stent length per lesion (mean ± SD) (mm): 22 ± 11 vs 21 ± 11		

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
EXAMINATION Sabate 2011, Sabate 2012, Gomez-Lara 2013, Sabate 2014, Ielasi 2015 Multicenter (12 sites) Spain (8), Italy (2) Netherlands (2)	N=1498	Inclusion: STEMI up to 48 hours after the onset of symptoms requiring emergent PCI, vessel sizes 2.25 to 4.0 mm Additionally, patients with multivessel disease needing staged PCI Exclusion: < 18 years; pregnancy; known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus, or contrast; chronic treatment with anti-vitamin K agents; STEMI secondary to stent thrombosis, vessel size >4.0 mm or < 2.25 mm.	DES: Everolimus-eluting stent (Xience V, Abbott Vascular) (n=751) BMS: Bare-metal stent (Multilink Vision, Abbott Vascular) (n=747)	Procedure: PCI is performed according to standard techniques in thrombotic scenarios. Full lesion coverage must be insured by implantation of one or multiple stents, with no mixture of stent types. There was no limit to the number of vessels and lesions that could be treated. In patients who needed staged PCI due to multivessel disease, operators can consider the stent type that is considered best for the pt's condition. Medication: *Pre/peri-procedural* • Pre-procedural aspirin (loading dose 250-500 mg), clopidogrel (loading dose 300 mg) administered for those not on chronic antiplatelet treatment. • Unfractionated	*DES vs BMS* Age (mean ± SD): 60.8 ± 12 vs 61.6 ± 13 Male: 84% (634/751) vs 82% (610/747) BMI (mean ± SD): 27.2 ± NR vs 27.4 ± NR Previous or current smoker: 72% (544/751) vs 72% (538/747) Diabetes mellitus: 18% (137/751) vs 16% (121/747) Arterial hypertension: 46% (347/751) vs 51% (378/747) Hyperlipidemia: 47% (354/751) vs 40% (301/747) Previous MI: 4% (33/751) vs 6% (47/747) Previous PCI: 4% (29/751) vs 4% (32/747) Previous CABG: <1% (3/751) vs 1% (7/747) Previous Stroke: 2% (12/751) vs 3% (19/747) Primary PCI (<12 h):	30 days, 6 months, 1, 2, 3, 4, 5 years *DES vs BMS* 1 year f/u: 97.7% (734/751) vs 97.1% (726/747) 2 year f/u: 98.7% (741/751) vs 98.1% (733/747) 3-5 years f/u: NR No crossover occurred from DES to BMS or vice versa at the index procedure.	Spanish Heart Foundation

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
				heparin or bivalirudin administered for procedural anticoagulation *Post-procedural* • Continue with clopidogrel for at least 1 year (75 mg/day) and with aspirin (100 mg) indefinitely	84% (630/751) vs 85% (638/747) Rescue PCI: 7% (50/751) vs 6% (48/747) Infarct-related artery: Left anterior descending: 42% (317/751) vs 39% (291/747) Left circumflex: 14% (105/751) vs 15% (112/747) Right coronary: 42% (318/751) vs 45% (334/747) Left main: <1% (6/751) vs <1% (4/747) Saphenous vein graft: <1% (4/751) vs <1% (6/747) Single vessel disease: 86% (645/751) vs 88% (656/747) Multivessel disease: 13% (100/751) vs 12% (88/747) Ejection fraction (%, mean ± SD): 51.1 ± 11 vs 51.0 ± 10		

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
XIMA De Belder 2014 Multisite (22 sites) United Kingdom and Spain	N=800	Inclusion: Patients ≥80 years; Coronary disease warranting use of DES (≥15 mm long or <3 mm wide); Patients presenting with other subsets of disease that have a high risk of restenosis (chronic total occlusions, bifurcations, left main stem disease) Patients with non-ST-segment elevation myocardial infarction, unstable angina, and stable angina Exclusion: Patients with acute ST-segment elevation MI, cardiogenic shock, thrombocytopenia (<50 x 10^9/mm^3),	DES Everolimus-eluting (Xience, Abbott Vascular, Santa Clara, CA) (n=399) BMS (Vision, Abbott Vascular) (n=401)	Procedure: • Techniques for stent deployment were left to discretion of operator • Lesion preparation before stent deployment was encouraged • Creatinine kinase and troponin level were measured 16 to 22 hours after PCI Medication: *Pre/Peri-procedural*: • Aspirin loading dose of 300 mg, Clopidogrel 600 mg loading dose; unless pts were established on these drugs • Use of glycoprotein IIb/IIIa inhibitors at the discretion of the operator *Post Procedural* • Pts. receiving BMS had mandatory DAPT for 1 month • Pts receiving DES had	DES vs. BMS Subgroup: All patients are ≥80 years Male: 61.1% (244/399) vs 59.1% (237/401), p = 0.64 Age (mean ± SD): 83.6±3.2 vs. 83.4±3.1, p=0.35 Diabetes: 25.6% (102/399) vs 24.2% (97/401) Hypertension: 75.1% (300/399) vs 77.6% (311/401) Hypercholesterolemia: 57.6% (230/399) vs 52.9% (212/401) Smoker: 5.0% (20/399) vs 4% (16/401) Previous CVA/TIA: 7.8% (31/399) vs 10.7% (43/401) Peripheral vascular disease: 10.3% (41/399) vs 12.5% (50/401) Previous MI: 12.8% (51/399) vs 10.2% (41/401) Previous CABG: 7.0%	6 months, 1 year Complete f/u: NR Crossover: NR	Unrestricted educational grant from Abbott Vascular

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		poor life expectancy, gastrointestinal hemorrhage ≤3 months, or previous intracerebral bleeding		1 year DAPT	(30/399) vs. 4.2% (17/401) Correct stent deployed: 93.9% (375/399) vs. 95.0% (381/401), p=0.73		
X-MAN Dharma 2014 Single-center Indonesia	N=150	Inclusion: Presence of acute myocardial infarction with ≤12 hours of symptom onset (chest pain of more than 20 minutes, not relieved by sublingual nitrates), ST-segment elevation in two or more contiguous leads (≥2 mm in precordial leads, ≥1 mm in limb leads), and planned for primary PCI with stent implantation. Exclusion:	DES: Everolimus-eluting (XIENCE V or XIENCE Prime, Abbott Vascular) (n=75) BMS: Cobalt-chromium (Multi-link or Vision, Abbott Vascular) (n=75)	Procedure: • Primary PCI was performed according to standard techniques. Stenting was performed only in the infarct-related coronary artery. Technical considerations (e.g. direct stenting or balloon pre-dilation) were left to the operator's discretion. Manual thrombus aspiration was recommended, thrombus aspiration was routinely performed in a totally occluded culprit vessel. If a large thrombus burden was visualized,	Age (mean ± SD): 56 ± 9.6 (n=75) vs 54 ± 9.5 (n=75), p = 0.16 Male: 89% (67/75) vs 81% (61/75), p = 0.17 BMI (kg/m^2, median (IQR): 24 (23-27) (n=75) vs 25 (23-27) (n=75), p = 0.9 Hypertension: 49% (37/75) vs 51% (37/75), p = 1.0 Diabetes: 29% (22/75) vs 23% (17/75), p = 0.35 Dyslipidemia: 48% (36/75) vs 49% (37/75), p = 0.87 Smoker: 61% (46/75) vs 64% (48/75), p = 0.86 Family history of CAD: 27% (20/75) vs 27%	1 month Complete f/u: NR Crossover: NR	Funding NR

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		Patients with left main disease, previous PCI, history of fibrinolytic treatment, past CABG, cardiogenic shock, renal failure, recent major bleeding, known hemorrhagic diathesis, and end-stage chronic diseases.		manual thrombectomy was performed. Direct stenting was advised if a lesion with a small thrombus burden was present. <u>Medication:</u> *Pre/Peri-procedural* • Intravenous eptifibatide using weight adjusted dose of single bolus of 180ug/kg followed by continuous infusion of 2 ug/kg/min up to 12-18 hours, additional doses were given at operator discretion • Pretreated with 160 to 320 mg acetylcalicylic acid and 600 mg clopidogrel orally • Intravenous bolus of unfractionated heparin (50-60 IU/kg) *Post procedural* • 75 mg clopidogrel/day for 1 year • 80-100 mg/day acetylsalicylic acid	(20/75), p = 1.0 <u>Infarction in anterior wall</u>: 49% (37/75) vs 52% (39/75), p = 0.74 <u>Onset of infarction</u> ≤2 hours: 8% (6/75) vs 4% (3/75), p = 0.49 2-6 hours: 59% (44/75) vs 68% (51/75), p = 0.24 >6 hours: 33% (25/75) vs 28% (21/75), p = 0.48		

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
				indefinitely			
Everolimus AND Zotarolimus trials							
PRODIGY Valgimigli 2014	N = 1508 One arm of study excluded (n = 505); for arms of interest: N = 1003	Inclusion: ≥18 years of age, chronic stable coronary artery disease or acute coronary syndromes, including non-STEMI and STEMI. At least 1 lesion with a diameter ≥50% that was suitable for coronary stent implantation in a vessel with a reference vessel diameter of at least 2.25 mm. No limit was set for the number of treated lesions, vessels, or lesion length. Exclusion: known allergy to acetylsalicylic acid or clopidogrel, planned surgery	DES: Everolimus-eluting stent (EES) (brand NR), (n = 501) OR Zotarolimus-eluting stent (ZES) (Medtronic Cardiovascular) (n = 502) BMS: Bare-Metal stent (brand NR)	Procedure: All interventions were performed according to current standard guidelines and the final intervention strategy was left entirely to the discretion of the operator, except for the stent use. Medication: *Pre/Peri-procedural* • Aspirin (160 to 325 mg orally or 500 mg intravenously) as a loading dose • Clopidogrel (300 or 600 mg as a loading dose) • Anticoagulation was accomplished with unfractionated heparin or bevalirudin • Glycoprotein IIb/IIIa antagonists, pre or post dilation were left to the discretion of the operator *Post procedural* • Aspirin 80 to 160 mg	*EES vs ZES vs BMS* Age (mean ± SD): 68 ± 11 (n = 501) vs 68 ± 11 (n = 500) vs 69 ± 11 (n = 502) Male: 76% (383/501) vs 78% (391/500) vs 74% (369/502) BMI (mean ± SD): 27± 4 (n = 501) vs 27 ± 4 (n = 500) vs 27 ± 4 (n = 502) Diabetes: 24% (120/501) vs 24% (118/500) vs 24% (118/502) Hypertension: 71% (355/501) vs 69% (342/500) vs 75% (376/502) Hyperlipidemia: 59% (296/501) vs 53% (263/500) vs 51% (254/502) Smoker: 22% (112/501) vs 26% (128/500) vs 25% (126/502) Previous MI: 29%	30 days, 6 months, 12 months, 18 months, 2 years *EES vs ZES vs BMS* 2 year f/u: 99.8% (500/501) vs 99.6% (500/502) vs 98.6% (498/505) Overall 2 year f/u: 99.3% (1498/1508) Crossover: NR	Grants from Merck, Iroko, Eli Lilly, and Medtronic

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		within 24 months of PCI unless DAPT could be maintained, history of bleeding diathesis, major surgery within 15 days, active bleeding or previous stroke in the last 6 months, concomitant or foreseeable need for oral anticoagulation therapy, pregnancy, life expectancy <24 months; participation in another trial and inability to provide informed consent.		orally indefinitely • Clopidogrel 75 mg/day for the treatment duration as follows: 6 months in the 6-month treatment arm (a shorter (>30 day) duration was allowed); or 24 months for those in the 24 month treatment arm	(143/501) vs 24% (121/500) vs 23% (114/502) Previous CABG: 12% (61/501) vs 11% (57/500) vs 9% (45/502) Left ventricular ejection fraction (%, mean ± SD): 51 ± 10 (n = 501) vs 51 ± 11 (n = 500) vs 50 ± 11 (n = 502) Stable angina pectoris: 25% (125/501) vs 27% (137/500) vs 24% (122/502) Acute Coronary Syndrome (ACS): 75% (376/501) vs 73% (363/500) vs 76% (380/502) NSTEMI ACS: 43% (214/501) vs 38% (191/500) vs 42% (209/502) Unstable Angina: 20% (99/501) vs 18% (92/500) vs 19% (93/502) NSTEMI: 23%		

Trial	N*	Inclusion & Exclusion Criteria	Treatment groups	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					(115/501) vs 20% (99/500) vs 23% (116/502) STEMI: 32% (162/501) vs 34% (172/500) vs 34% (171/502) Single vessel disease: 29% (144/501) vs 28% (139/500) vs 34% (170/502) Multivessel disease: 71% (357/501) vs 72% (361/500) vs 66% (332/502)		

ACS: Acute Coronary Syndrome; BMI: Body Mass Index; BMS: bare metal stent; CABG: coronary artery bypass grafting; DAPT: Dual Antiplatelet Therapy; DES: drug-eluting stent; ECG: electrocardiogram; EES: Everolimus-Eluting Stent; f/u: follow-up; LAD: left anterior descending; MI: myocardial infarction; NSTEMI: Non-ST-Elevation Myocardial Infarction; NR: Not Reported; PCI: Percutaneous Coronary Intervention; RCA: right coronary artery; STEMI: ST-Elevation Myocardial Infarction; ZES: Zotarolimus-Eluting Stent

*N: number randomized

†Four (1 ZES and 3 BMS) participants were randomized but did not undergo a procedure; therefore, the intent-to-treat population included 1,193 participants (597 ZES, 596 BMS)

Appendix Table F3. Drug-eluting versus bare metal stenting for stable or unstable angina: Study and patient characteristics for nonrandomized comparative studies and case series designed specifically to evaluate safety outcomes.

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
Nonrandomized comparative studies							
Garg 2014 Multicenter prospective registry (2 sites) United States	N=1939	Inclusion: Consecutive patients with STEMI treated with emergency PCI from 2003 through 2011. Exclusions: NR	DES (n=752): Stent choice was determined by operator, included zotarolimus-eluting stents (Endeavor, Medtronic) (n=73) and everolimus-eluting stents (model NR) (n=679) BMS (n=1187): Details NR	**Procedural details**: Patients treated with contemporary standard of care for primary PCI, including aspiring, unfractionated heparin, and glycoprotein IIb/IIIa platelet inhibitors, and more recently, aspirin and bivalirudin without glycoprotein IIb/IIIa plateley inhibitors. Clopidogrel was given before or at the time of PCI **Cointerventions:** DAPT (drugs and dose NR) was recommended for at least one year after primary PCI.	Subgroup: STEMI Age: 61 (IQR, 62, 71) vs. 61 (IQR, 51, 74) Sex (% male): 73.9% vs. 71.5% Race (minority): NR Prior MI: 11.3% (n=85) vs. 15.9% (n=189) Prior PCI: NR Prior CABG: 4.9% (n=37) vs. 5.7% (n=68) Diabetes: 18.4% (n=138) vs. 15.8% (n=188) Hyperlipidemia: NR Hypertension: 56.1% (n=422) vs. 56.4% (n=669) Current smoker: 35.7% (n=266) vs. 46.2% (n=544) Number of diseased vessels treated: NR Type of diseased vessel treated/infarct	Mean 2 years (%NR) 1 year (96.6%) Crossover NR	Le Bauer Charitable Research Foundation, the Minneapolis Heart Institute Foundation; National Institutes of Health Intramural Project (grant Z01ES45005)

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					vessel: Left main: 0.7% (n=5) vs. 0.5% (n=6) Left anterior descending: 37.9% (n=285) vs. 33.4% (n=397) Circumflex: 14.6% (n=110) vs. 13.8% (n=164) Right coronary artery: 44.9% (n=338) vs. 49.5% (n=588) Graft: 1.3% (n=10) vs. 2.6% (n=31) % stenosis (mean ± SD): NR Target lesion: NR Reference vessel diameter (mean ± SD, mm): NR Lesion length (mean ± SD, mm): NR		
Piao 2014 KAMIR Retrospective registry (no. sites NR)	N=509	Inclusion: Octogenarians with STEMI who were successfully treated with PCI with stenting, with 12 month follow-up	DES (n=323): Either Everolimus-eluting (n=132) or Zotarolimus-eluting (n=191) stents were implanted.	Clopidrogel treatment was recommended for DES patients for at least 12 months, and for at least 1 month for BMS patients.	Subgroup: Octogenarians with STEMI Age: 84.6 ± 3.8 vs. 85.2 ± 4.2 Sex (% male): 43.3% vs. 47.8% Race (minority): NR	12 months Complete f/u NR Cross-over NR	Korean Health Technology R&D project (HI13C1527) sponsored by the Ministry for Health and Welfare,

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
Korea		Exclusion: NR	BMS (n=186): NR		Prior acute MI: 4.3% (n=14) vs. 3.8% (n=7) Prior PCI: 2.8% (n=9) vs. 1.6% (n=3) Prior CABG: NR Prior stroke: 8.4% (n=27) vs. 8.1% (n=15) Diabetes: 24.5% (n=79) vs. 18.7% (n=34) Hyperlipidemia: 6.5% (n=21) vs. 7.7% (n=14) Hypertension: 61.3% (n=198) vs. 51.6% (n=94), p=0.03 Current smoker: 13.5% (n=43) vs. 27.1% (n=49), p<0.001 Killip Class >II: 25.6% (n=79) vs. 34.7% (n=60), p=0.03 Number of diseased vessels: One: 35.3% (n=114) vs. 52.7% (n=98), p<0.001		Republic of Korea

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					Two: 32.8% (n=106) vs. 19.4% (n=36), p=0.001 Three: 27.6% (n=89) vs. 24.2% (n=45), p NS Culprit vessel: Left main: 1.9% (n=6) vs. 1.6% (n=3), p NS LAD: 53.6% (n=173) vs. 42.5% (n=79), p=0.01 LCX: 7.4% (n=24) vs. 5.9% (n=11), p NS RCA: 37.2% (n=120) vs. 50% (n-93), p=0.005 Number stents implanted per patient (mean ± SD): 1.5 ± 0.8 vs. 1.4 ± 0.7, p=0.03 % stenosis (mean ± SD): NR Target lesion: NR Reference vessel diameter (mean ± SD, mm): NR Lesion length (mean ± SD, mm): NR		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					p>0.05 unless otherwise noted		
SCAAR Sarno 2012 Multicenter prospective registry (29 sites) Sweden	N=75,182	Inclusion: All consecutive patients undergoing coronary angiography or PCI in Sweden from November 2006 to October 2010. Exclusion: NR	DES (n=10,551): Details NR BMS (n=64,631): Details NR	NR	DES vs. BMS Subgroup: NR Age: 65.8 ± 10.5 vs. 67 ± 11.2 Sex (% male): 74% vs. 72% Race (minority): NR Prior MI: 36.3% (n=2334) vs. 22.7% (n=9698) Prior PCI: NR Prior CABG: 13.8% (n=885) vs. 8.2% (n=3522) Diabetes: 25.3% (n=1623) vs. 15.8% (n=6756) Hyperlipidemia: 62% (n=3983) vs. 45.6% (n=19,505) Hypertension: 62.3% (n=4002) vs. 51.4% (n=21,972) Current smoker: 17.1% (n=1101) vs. 21.5% (n=9181) Former smoker: 39.2% (n=2517) vs. 33.4% (n=14,279) Number of diseased	2 years f/u NR Cross-over NR	Swedish Health Authorities, Swedish Heart and Lung Foundation

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					vessels treated: NR Number of diseased vessels: One: 39.6% (n=2546) vs. 48.5% (n=20,760) Two: 24.8% (n=1591) vs. 28.7% (n=12,274) Three: 15.8% (n=1017) vs. 16.9% (n=7239) Type of diseased vessels treated: RCA: 22.2% (n=1427) vs. 35.5% (n=15,188) Left main: 3.4% (n=216) vs. 1.6% (n=671) LAD: 41.5% (n=2669) vs. 41.2% (n=17,641) LCX: 16.7% (n=1076) vs. 18.7% (n=7996) CABG: 3.6% (n=231) vs. 2.9% (n=1277) Number of stents implanted per procedure (mean ± SD): 1.63 ± 0.93 vs.		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					1.45 ± 0.77 % stenosis: NR Chronic total occlusions (%): 6.3% (n=406) vs. 1.3% (n=577) Lesion classification: Type A: 5.8% (n=372) vs. 12.6% (n=5396) Type B1: 27.8% (n=1790) vs. 39.4% (n=16,854) Type B2: 31.8% (n-2044) vs. 33.2% (n=14,199) Type C: 22% (n-1413) vs. 14.8% (n=6324) Target lesion: NR Reference vessel diameter (mm): NR Lesion length (mm): NR		
SCAAR Sarno 2014 Multicenter prospective registry (29 sties)	N=29,876	Inclusion: Consecutive patients in Sweden with STEMI undergoing primary PCI from January 2007 to January 2013.	DES (n=4811): Stents included Endeavor Resolute (Medtronic In., Minneapolis, MN); Xience V and Xience Prime	DES vs. BMS Medications used during PCI: - ASA: 10.7% (n=514) vs. 12.9 (n=3233) - Clopidrogel: 23.2% (n=1115) vs.	DES vs. BMS Subgroup: STEMI Age: 67.8 ± 11.3 vs. 66 ± 11.6 Sex (%male): 73.8% vs. 75% Race (minority): NR Prior MI: 19.9%	3 years f/u NR cross-over NR	Funding NR

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
Sweden		Exclusion: NR	(Abbott Vascular, Santa Clara, CA); Promus and Promus Element (Boston Scientific); and Endeavor (Medtronic). BMS (n=25,065): Stents included were the Multilink Vision, Multilink MiniVision, Multilink 8, and Mulitlink Flexmaster (Abbott Vascular); Driver, Micro Driver coronary, and Integrity (Medtronic); Liberte (Boston Scientific); Braun Coroflex Blue (B. Braun, Melsungen, Germany); and the Chrono stent (CUD, Saluggia, Italy).	22.8% (n=5727) - Ticagrelor: 13.8% (n=363) vs. 11.7% (n=513) - Bivalrudin: 65.8% (n=3168) vs. 45.1% (n=11,296) - GP IIb/IIIa: 24.3% (n=1170) vs. 43.4% (n=10,878) - Heparin: 54% (n=2599) vs. 58.3% (n=14,616) - LMWH: 3.9% (n=188) vs. 5% (n=1265)	(n=1411) vs. 28.1% (n=2085) ST segment elevation MI: 18.3% (n=1297) vs. 28.6% (n=2118) Prior PCI: NR Prior CABG: 10.4% (n=741) vs. 12.2% (n=902) Diabetes: 26.7% (n=1892) vs. 24.9% (n=1844) Hyperlipidemia: 67.7% (n=4802) vs. 52.7% (n=3905) Hypertension: 65.6% (n=4650) vs. 58.9% (n=4365) Current smoker: 19.3% (n=1367) vs. 24.1% (n=1786) Number of diseased vessels treated: NR Type of diseased vessel treated: Left anterior descending coronary artery: 44.8% (n=5447) vs. 41% (n=4394) Left circumflex		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					coronary artery: 23% (n=2802) vs. 21.2% (n=2265) Right coronary artery: 27% (n=3286) vs. 30.7% (n=3290) Left main trunk: 4.3% (n=523) vs. 2.6% (n=282) Saphenous vein graft: 0.8% (n=96) vs. 4.5% (n=477) Number of stents implanted per procedure (mean ± SD): 1.96 ± 1.10 vs. 1.78 ± 0.99 % stenosis (mean ± SD): Before procedure: 68.5% ± 16.1% vs. 70.6% ± 19.8% Post procedure: 2.61% ± 0.53% vs. 2.8% ± 0.56% Target lesion: NR Reference vessel diameter (mean ± SD, mm): 2.88 ± 0.55 vs. 2.9 ± 0.57 Lesion length (mean		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					± SD, mm): 17.1 ± 10 vs. 14.1 ± 8.2		
Single-arm studies							
Inaba 2014 Retrospective case series (single center) United States	N=136	Inclusion: Consecutive patients who underwent IVUS follow-up who had either symptoms of or evidence of ischemia by noninvasive imaging from October 2010 to February 2012. Exclusion: NR	DES (N=177) Everolimus-eluting, details NR.	NR	Age: 65 ± 8 Sex (% male): 76.5% (n=13) Race (minority): NR Prior MI: NR Prior PCI: NR Prior CABG: NR Diabetes: 58.5% (n=10) Hyperlipidemia: 94.1% (n=16) Hypertension: 88.2% (n=15) Current smoker: NR Number of diseased vessels treated: NR Type of diseased vessel treated: Left anterior descending: 11.8% (n=2); Left circumflex: 0%; Right: 70.6% (n=12); Saphenous vein graft: 17.6% (n=3) % stenosis (mean ± SD): Baseline: 64.1% ± 23.3%;	Follow-up: 441 ± 317 days	

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					After procedure: 10% ± 5.5%; At follow-up: 51.8% ± 19%; Target lesion: NR Reference vessel diameter (mean ± SD, mm): Baseline: 2.96 ± 1.99; After procedure: 3.31 ± 0.59; At follow-up: 3.18 ± 1.38 (n=14) Lesion length (mean ± SD, mm): NR		
Kuramitsu 2012 Retrospective case series Japan	N=1035*	Inclusion: Patients who underwent successful implantation with EES at one of two treatment centers; and who underwent follow-up angiography 6 to 9 months after the initial procedure, irrespective of clinical symptoms, or before 6	DES (N=1208) Everolimus-eluting (Xience V, Promus)	**Procedural details**: • All interventions performed using standard technique • Predilation, postdilation, and use of intravascular ultrasound (IVUS) were left to the operator's discretion **Cointerventions**: • Either ticlopidine	Age: 69.7± 9.6 Sex (% male): 75.6% (n=782) Race (minority): NR Prior MI: 31.5% (n=325) Prior PCI: 63.5% (n=657) Prior CABG: 7.1% (n=74) Prior CI: 10.7% (n=111) Diabetes: 44.2% (n=496) Hyperlipidemia: 75.9% (n=786)	6-9 months 85.7% (1035/1208)*	NR

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		months for recurrent symptoms; and written informed consent Exclusion: NR		(200 mg/daily) or clopidogrel (75 mg/daily) were prescribed for at least one year after stent implantation • A continued aspirin regimen (81-162 mg/daily) was recommended for all patients unless contraindicated	Hypertension: 82.3% (n=852) Current smoker: 19.6% (n=203) Multivessel disease: 27.5% (285) Number of diseased vessels treated: One: 72.1% (n=746); Two: 23.8% (n=246); Three 4.1% (n=43); % stenosis (mean ± SD): Baseline: 73.1% ± 13.1%; After procedure: 16.4% ± 7.2%; Chronic total occlusions (%): 10.3% (138) Lesion classification: Type A: 8.3% (n=111); Type B1: 23.4% (n=314); Type B2: 21.1% (n=282); Type C: 47.2% (n=632) Target lesion:		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					Right coronary artery: 31.4% (n=421); Left anterior descending: 40.0% (n=535); Left circumflex: 22.0% (n=295); Left main trunk: 6.0% (n=81); Saphenous vein graft: 0.4% (n=5); Left internal thoracic artery: 0.2% (n=2) Reference vessel diameter (mean ± SD, mm): Baseline: 2.59 ± 0.93 Lesion length (mean ± SD, mm): 23.0 ± 11.8		
Kuramitsu 2015 Retrospective case series Japan	N=700*	Inclusion: Consecutive patients who underwent successful stent implantation and were treated only with PtCr-EES (PROMUS	DES (N=816) Everolimus-eluting (PtCr-EES)	**Procedural details**: • All interventions performed using standard technique • Predilation, postdilation, and use of intravascular	Age: 69.7± 9.7 Sex (% male): 73.0% (n=511) Race (minority): NR Prior MI: 19.9% (n=140) Prior PCI: 44.7% (n=314) Prior CABG: 5.1%	6-9 months 85.7% (700/816)*	NR

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
		Element); and who underwent follow-up angiography 6 to 9 months after the initial procedure, irrespective of clinical symptoms, or before 6 months for recurrent symptoms Exclusion: implantation of another stent type		ultrasound and optical coherence tomography were left to the operator's discretion **Cointerventions**: • Either ticlopidine (200 mg/daily) or clopidogrel (75 mg/daily) were prescribed for at least one year after stent implantation • A continued aspirin regimen (81-162 mg/daily) was recommended for all patients unless contraindicated	(n=36) Prior CI: 7.6% (n=53) Diabetes: 45.5% (n=320) Hypertension: 80.0% (n=562) Current smoker: 17.1% (n=120) Multivessel disease: 28.9% (202) Number of diseased vessels treated: - One: 71.1% (n=499) - Two: 25.0% (n=175) - Three 3.7% (n=26) % stenosis (mean ± SD): - Baseline: 71.8% ± 15.0% - After procedure: 15.8% ± 6.7% Chronic total occlusions (%): 8.0% (72) Lesion classification: - Type A: 5.3% (n=44) - Type B1: 29.9% (n=247)		

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
					- Type B2: 22.6% (n=187) - Type C: 41.9% (n=346) Target lesion: - Right coronary artery: 36.1% (n=326) - Left anterior descending: 40.9% (n=370) - Left circumflex: 21.5% (n=195) - Left main trunk: 0.7% (n=7) - Saphenous vein graft: 0.3% (n=3) - Left internal thoracic artery: 0.1% (n=1) Reference vessel diameter (mean ± SD, mm): - Baseline: 2.58 ± 0.4 Lesion length (mean ± SD, mm): 26.0 ± 12.9		
Pitney 2011 Prospective case series	N=1,000	Inclusion: Consecutive Endeavor stents (7 crown	DES: Zotarolimus-eluting stent (Endeavor)	**Procedural details**: • typically performed from the femoral	NR	NR (data collected over a 3 year period); 6	NR

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
using database information from a single site Australia		Endeavor/ Micro Drivers) <u>Exclusion</u>: Bifurcations treated with two stents or kissing inflations		approach using 6 or 7 Fr sheaths using standard technique • The stent was chosen to match the size of the artery or the vessel at the distal edge if it tapered • post-dilation was left to the discretion of the operator; balloon length would always be shorter than stent length and nominal size typically 0.5 mm larger **Cointerventions:** NR		months for clinical follow-up	
Williams 2012	N=4,455	<u>Inclusion:</u> Patients who underwent stent implantation between September 2007 and September 2011	<u>DES:</u> 82.4% of stents (n=9,310 stents; mean 2.1 stents/procedure) <u>BMS:</u> 17.6% of stents (n=9,310 stents;	NR	NR	NR (data collected over a 4 year period)	NR

Trial	N	Inclusion & Exclusion Criteria	Treatment groups (DES vs. BMS)	Procedural and cointervention details	Patient characteristics	Length f/u Complete f/u (% (n/N)) Cross-over % (n/N)	Funding
			mean 2.1 stents/procedure)				

BMS: Bare metal stent; CABG: Coronary artery bypass grafting; DAPT: Dual antiplatelet therapy ; DES: Drug eluting stent; F/U: Follow-up; IVUS: Intravascular ultrasound; KAMIRL: Korea Acute Myocardial Infarction Registry; LAD: Left anterior descending artery; LCX: Left circumflex; LMWH: Low molecular weight heparin; MI: Myocardial infarction; NR: Not reported; PCI: Percutaneous coronary intervention; Pt-Cr-EES: Platinum-chromium everolimus-eluting stent (PtCr-EES); RCA: Right coronary artery; SCAAR: Swedish Coronary Angiography and Angioplasty Registry; SD: Standard deviation; STEMI: ST-elevation myocardial infarction.
*N represents the number of patients who had angiographic follow-up out of the total population.

APPENDIX G. Results Tables for Key Question 1 (Efficacy, Safety, HTE, Meta-analysis)

Appendix Table G1. Clinically significant improvement* in Seattle Angina Questionnaire (SAQ) score from baseline

Percentage of patients with clinically significant improvement*						
Time point	RCT	PCI	MT	Risk difference (95% CI)	Effect Size (95% CI)	p-value
Angina Stability						
1 mo.	COURAGE	57% (495/866)	50% (437/873)	7.1% (2.4% to 11.8%)	RR = 1.14 (1.05 to 1.25)	0.0030
3 mos.	COURAGE	56% (482/860)	51% (439/860)	5.0% (0.3% to 9.7%)	RR = 1.10 (1.01 to 1.20)	0.0377
6 mos.	COURAGE	56% (495/883)	52% (430/827)	4.1% (–0.7% to 8.8%)	RR = 1.08 (0.99 to 1.18)	0.0920
12 mos.	COURAGE	51% (430/843)	50% (405/810)	1.0% (–3.8% to 5.8%)	RR = 1.02 (0.93 to 1.12)	0.6820
24 mos.	COURAGE	53% (395/746)	48% (352/733)	4.9% (–0.2% to 10.0%)	RR = 1.10 (1.00 to 1.22)	0.0582
36 mos.	COURAGE	51% (294/576)	46% (267/580)	5.0% (–0.8% to 10.8%)	RR = 1.11 (0.98 to 1.25)	0.0887
Angina Frequency						
1 mo.	COURAGE	39% (341/875)	30% (266/885)	8.9% (4.5% to 13.3%)	RR = 1.2966 (1.14 to 1.48)	0.0001
3 mos.	COURAGE	47% (409/871)	40% (349/873)	7.0% (2.3% to 11.6%)	RR = 1.17 (1.05 to 1.31)	0.0033
6 mos.	COURAGE	50% (449/898)	44% (370/840)	6.0% (1.3% to 10.6%)	RR = 1.14 (1.03 to 1.26)	0.0130
12 mos.	COURAGE	52% (449/863)	46% (381/829)	6.1% (1.3% to 10.8%)	RR = 1.13 (1.03 to 1.25)	0.0126
24 mos.	COURAGE	54% (413/764)	47% (351/746)	7.0% (2.0% to 12.0%)	RR = 1.15 (1.04 to 1.27)	0.0065
36 mos.	COURAGE	57% (332/583)	50% (295/589)	6.9% (1.2% to 12.6%)	RR = 1.14 (1.02 to 1.27)	0.0186
Treatment Satisfaction						
1 mo.	COURAGE	27% (236/873)	26% (229/882)	1.1% (–3.1% to 5.2%)	RR = 1.04 (0.89 to 1.22)	0.6118
3 mos.	COURAGE	28% (243/869)	29% (253/873)	–1.0% (–5.3% to 3.2%)	RR = 0.96 (0.83 to 1.12)	0.6381
6 mos.	COURAGE	30% (268/894)	31% (260/839)	–1.0% (–5.4% to 3.3%)	RR = 0.97 (0.84 to 1.12)	0.6476
12 mos.	COURAGE	39% (336/861)	33% (274/829)	6.0% (1.4% to 10.5%)	RR = 1.18 (1.04 to 1.34)	0.0106
24 mos.	COURAGE	32%	38%	–5.9% (–10.7% to	RR = 0.84 (0.74 to	0.0164

Percentage of patients with clinically significant improvement*						
Time point	RCT	PCI	MT	Risk difference (95% CI)	Effect Size (95% CI)	p-value
		(244/761)	(281/740)	–1.1%)	0.97)	
36 mos.	COURAGE	31% (182/586)	34% (202/593)	–3.0% (–8.4% to 2.3%)	RR = 0.91 (0.77 to 1.07)	0.2710
Quality of Life						
1 mo.	COURAGE	52% (454/873)	43% (379/882)	9.0% (4.4% to 13.7%)	RR = 1.21 (1.10 to 1.34)	0.0002
3 mos.	COURAGE	60% (521/869)	54% (471/872)	5.9% (1.3% to 10.6%)	RR = 1.11 (1.02 to 1.20)	0.0123
6 mos.	COURAGE	64% (574/897)	56% (469/838)	8.0% (3.4% to 12.6%)	RR = 1.14 (1.06 to 1.24)	0.0006
12 mos.	COURAGE	65% (560/862)	61% (504/827)	4.0% (–0.6% to 8.6%)	RR = 1.07 (0.99 to 1.15)	0.0871
24 mos.	COURAGE	65% (496/763)	67% (495/739)	–2.0% (–6.8% to 2.8%)	RR = 0.97 (0.90 to 1.04)	0.4192
36 mos.	COURAGE	69% (404/586)	69% (408/591)	–0.1% (–5.4% to 5.2%)	RR = 1.00 (0.93 to 1.08)	0.9723
Physical Limitation						
1 mo.	COURAGE	45% (383/850)	38% (323/850)	7.1% (2.4% to 11.7%)	RR = 1.19 (1.06 to 1.33)	0.007
3 mos.	COURAGE	49% (417/852)	43% (366/855)	6.1% (1.4% to 10.9%)	RR = 1.14 (1.03 to 1.27)	0.0110
6 mos.	COURAGE	51% (448/878)	42% (344/820)	9.1% (4.4% to 13.8%)	RR = 1.21 (1.10 to 1.35)	0.0002
12 mos.	COURAGE	48% (405/844)	44% (357/812)	4.0% (–0.8% to 8.8%)	RR = 1.09 (0.98 to 1.21)	0.1009
24 mos.	COURAGE	49% (365/745)	44% (323/735)	5.1% (–0.03% to 101%)	RR = 1.11 (1.00 to 1.24)	0.0517
36 mos.	COURAGE	45% (258/573)	47% (274/583)	–2.0% (–7.7% to 3.8%)	RR = 0.96 (0.85 to 1.09)	0.5014

CI: Confidence Interval; MT: Medical Therapy; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

* Defined clinical significance as a difference of 8 points or more on the physical-limitation scale, 25 or more on the angina-stability scale, 20 or more on the angina-frequency scale, 12 or more on the treatment-satisfaction scale, and 16 or more on the quality-of-life scale.

Appendix Table G2. Seattle Angina Questionnaire (SAQ) subscale scores

SAQ (mean ± SD)					
Time point	**RCT**	**PCI**	**MT**	**Mean difference (95% CI)**	**p-value**
Angina Stability					
Baseline	COURAGE	54 ± 33 (n=953)	53 ± 32 (n=947)	1.00 (–1.93 to 3.93)	0.503
1 mo.	COURAGE	81 ± 26 (n=866)	73 ± 28 (n=873)	8.00 (5.45 to 10.55)	0.0001
3 mos.	COURAGE	77 ± 28 (n=860)	73 ± 27 (n=860)	4.00 (1.39 to 6.61)	0.0026
6 mos.	COURAGE	76 ± 28 (n=883)	73 ± 28 (n=827)	3.00 (0.34 to 5.66)	0.027
12 mos.	COURAGE	74 ± 27 (n=843)	70 ± 28 (n=810)	4.00 (1.34 to 6.66)	0.0032
24 mos.	COURAGE	73 ± 27 (n=746)	69 ± 27 (n=733)	4.00 (1.24 to 6.76)	0.0045
36 mos.	COURAGE	72 ± 28 (n=576)	70 ± 28 (n=580)	2.00 (–1.24 to 5.24)	0.2249
Angina Frequency					
Baseline	COURAGE	68 ± 26 (n=969)	69 ± 26 (n=969)	–1.00 (–3.32 to 1.32)	0.3973
1 mo.	COURAGE	82 ± 23 (n=875)	76 ± 24 (n=885)	6.00 (3.80 to 8.20)	0.0001
3 mos.	COURAGE	85 ± 22 (n=871)	80 ± 23 (n=873)	5.00 (2.88 to 7.12)	0.0001
6 mos.	COURAGE	87 ± 20 (n=898)	83 ± 22 (n=840)	4.00 (2.02 to 5.98)	0.0001
12 mos.	COURAGE	87 ± 19 (n=863)	84 ± 21 (n=829)	3.00 (1.09 to 4.91)	0.0021
24 mos.	COURAGE	89 ± 18 (n=764)	86 ± 19 (n=746)	3.00 (1.13 to 4.87)	0.0017
36 mos.	COURAGE	89 ± 18 (n=583)	88 ± 18 (n=589)	1.00 (–1.07 to 3.07)	0.3418
Treatment Satisfaction					
Baseline	COURAGE	88 ± 15 (n=971)	86 ± 16 (n=956)	2.00 (0.61 to 3.39)	0.0047
1 mo.	COURAGE	92 ± 12 (n = 873)	88 ± 15 (n=882)	4.00 (2.73 to 5.27)	0.0001
3 mos.	COURAGE	92 ± 12 (n=869)	90 ± 14 (n=873)	2.00 (0.77 to 3.23)	0.0014
6 mos.	COURAGE	92 ± 13 (n=894)	90 ± 14 (n=839)	2.00 (0.73 to 3.27)	0.0021
12 mos.	COURAGE	92 ± 12 (n=861)	90 ± 14 (n=829)	2.00 (0.76 to 3.24)	0.0016
24 mos.	COURAGE	92 ± 13 (n=761)	92 ± 13 (n=740)	0.00 (–1.32 to 1.32)	1.00
36 mos.	COURAGE	92 ± 12 (n=586)	92 ± 11 (n=593)	0.00 (–1.32 to 1.32)	1.00
60 mos.	COURAGE	92 (SD NR) (n NR)	94 (SD NR) (n NR)	Not calculable	NR
Quality of Life					

Baseline	COURAGE	51 ± 25 (n=969)	51 ± 25 (n=958)	0.00 (–2.24 to 2.24)	1.00
1 mo.	COURAGE	68 ± 24 (n=873)	62 ± 24 (n=882)	6.00 (3.75 to 8.25)	0.0001
3 mos.	COURAGE	73 ± 22 (n=869)	68 ± 23 (n=872)	5.00 (2.88 to 7.12)	0.0001
6 mos.	COURAGE	75 ± 22 (n=897)	70 ± 23 (n=838)	5.00 (2.88 to 7.12)	0.0001
12 mos.	COURAGE	76 ± 21 (n=862)	73 ± 22 (n=827)	3.00 (0.94 to 5.06)	0.0042
24 mos.	COURAGE	77 ± 22 (n=763)	76 ± 22 (n=739)	1.00 (–1.23 to 3.23)	0.3786
36 mos.	COURAGE	79 ± 20 (n=586)	77 ± 20 (n=591)	2.00 (–0.29 to 4.29)	0.0865
Physical Limitation					
Baseline	COURAGE	66 ± 25 (n=939)	66 ± 35 (n=939)	0.00 (—2.76 to 2.76)	1.00
1 mo.	COURAGE	73 ± 24 (n=850)	70 ± 24 (n=850)	3.00 (0.71 t0 5.29)	0.0101
3 mos.	COURAGE	76 ± 24 (n=852)	72 ± 23 (n=855)	4.00 (1.76 to 6.24)	0.0005
6 mos.	COURAGE	77 ± 23 (n=878)	72 ± 24 (n=820)	5.00 (2.76 to 7.24)	0.0001
12 mos.	COURAGE	75 ± 24 (n=844)	73 ± 24 (n=812)	2.00 (–0.32 to 4.32)	0.0902
24 mos.	COURAGE	74 ± 24 (n=745)	72 ± 24 (n=735)	2.00 (—0.45 to 4.45)	0.1092
36 mos.	COURAGE	74 ± 24 (n=573)	74 ± 24 (n=583)	0.00 (—2.77 to 2.77)	1.00

CI: Confidence Interval; MT: Medical Therapy: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

Appendix Table G3. Clinically significant* RAND-36 score increase from baseline

		RAND-36 (mean ± SD)				
Time point	**RCT**	**PCI**	**MT**	**Mean difference (95% CI)**	**Effect Size (95% CI)**	**p-value**
Physical Functioning						
1 mo.	COURAGE	41% (367/896)	33% (295/894)	7.9% (3.5% to 12.0%)	1.24 (1.09 to 1.40)	0.0005
3 mos.	COURAGE	48% (413/861)	40% (347/867)	7.9% (3.2% to 12.0%)	1.19 (1.07 to 1.33)	0.0009
6 mos.	COURAGE	50% (450/899)	43% (363/844)	7.0% (2.3% to 11.7%)	1.16 (1.05 to 1.28)	0.003
12 mos.	COURAGE	47% (403/857)	43% (364/847)	4.9% (0.2% to 9.7%)	1.11 (1.01 to 1.23)	0.09
24 mos.	COURAGE	42% (322/766)	42% (319/759)	0% (–4.9% to 4.9%)	1.00 (0.88 to 1.12)	0.99
36 mos.	COURAGE	42%	39%	2.9% (–2.6% to	1.07 (0.93 to 1.23)	0.29

		RAND-36 (mean ± SD)				
Time point	RCT	PCI	MT	Mean difference (95% CI)	Effect Size (95% CI)	p-value
		(250/596)	(232/595)	8.5%)		
Role Limitation- Physical						
1 mo.	COURAGE	34% (303/892)	34% (304/893)	0% (–4.4% to 4.3%)	0.99 (0.87 to 1.13)	0.97
3 mos.	COURAGE	45% (388/862)	40% (346/866)	5.0% (0.4% to 9.7%)	1.12 (1.00 to 1.25)	0.03
6 mos.	COURAGE	48% (431/897)	43% (363/844)	5.0% (0.3% to 9.7%)	1.11 (1.00 to 1.23)	0.03
12 mos.	COURAGE	47% (402/856)	47% (397/845)	0% (–4.7% to 4.7%)	0.99 (0.90 to 1.10)	0.99
24 mos.	COURAGE	45% (344/765)	45% (342/759)	0% (–5.0 to 4.9%)	0.99 (0.89 to 1.11)	0.97
36 mos.	COURAGE	44% (262/595)	46% (273/595)	–1.8% (–7.5% to 3.8%)	0.95 (0.84 to 1.08)	0.52
Role Limitation- Emotional						
1 mo.	COURAGE	28% (250/892)	27% (240/888)	1.0% (–3.1% to 5.1%)	1.03 (0.89 to 1.20)	0.63
3 mos.	COURAGE	33% (283/857)	32% (276/863)	1.0% (–3.3% to 5.4%)	1.03 (0.90 to 1.18)	0.64
6 mos.	COURAGE	37% (331/894)	33% (278/843)	4.0% (–0.4% to 8.5%)	1.12 (0.98 to 1.27)	0.07
12 mos.	COURAGE	34% (291/857)	34% (287/845)	0% (–4.5% to 4.4%)	0.99 (0.87 to 1.14)	0.99
24 mo.	COURAGE	33% (251/761)	33% (250/758)	0% (–4.7% to 4.7%)	1.00 (0.86 to 1.15)	0.99
36 mos.	COURAGE	33% (195/592)	32% (189/590)	0.9% (–4.4% to 6.2%)	1.02 (0.87 to 1.21)	0.73
Energy/Fatigue						
1 mo.	COURAGE	41% (367/894)	33% (295/893)	8.0% (3.5 to 12.4%)	1.24 (1.09 to 1.40)	0.0005
3 mos.	COURAGE	49% (422/861)	40% (346/866)	9.0% (4.3% to 13.7%)	1.22 (1.10 to 1.36)	0.0002
6 mos.	COURAGE	47% (422/898)	45% (380/844)	1.9% (–2.7% to 6.6%)	1.04 (0.94 to 1.15)	0.40
12 mos.	COURAGE	47% (403/858)	45% (380/846)	2.0% (–2.6%to 6.7%)	0.98 (0.91 to 1.06)	0.79
24 mo.	COURAGE	46% (352/766)	33% (249/756)	13.0% (8.1% to 17.8%)	1.39 (1.22 to 1.58)	<0.0001
36 mos.	COURAGE	44% (262/596)	42% (249/594)	2.0% (–3.5% to 7.6%)	1.04 (0.91 to 1.19)	0.47
Emotional Well-being						
1 mo.	COURAGE	29%	23%	6.0% (1.9% to	1.26 (1.07 to 1.47)	0.003

		RAND-36 (mean ± SD)				
Time point	RCT	PCI	MT	Mean difference (95% CI)	Effect Size (95% CI)	p-value
		(259/894)	(205/893)	10.0%)		
3 mos.	COURAGE	32% (275/861)	27% (234/866)	4.9% (0.6% to 9.2%)	1.18 (1.02 to 1.36)	0.02
6 mos.	COURAGE	32% (287/898)	28% (236/844)	4.0% (–0.3% to 8.3%)	1.14 (0.98 to 1.32)	0.06
12 mos.	COURAGE	29% (249/858)	29% (245/846)	0% (–4.2% to 4.3%)	0.99 (0.86 to 1.15)	0.99
24 mos.	COURAGE	32% (245/766)	30% (226/756)	2.0% (–2.5% to 6.7%)	1.06 (0.92 to 1.2	0.37
36 mos.	COURAGE	31% (185/596)	27% (160/594)	4.1% (–1.0% to 9.2%)	1.15 (0.96 to 1.37)	0.11
Social Functioning						
1 mo.	COURAGE	40% (358/894)	41% (366/893)	–0.9% (–5.4% to 3.6%)	0.97 (0.87 to 1.09)	0.68
3 mos.	COURAGE	46% (396/861)	44% (381/866)	2.0% (–2.6% to 6.6%)	1.04 (0.94 to 1.16)	0.40
6 mos.	COURAGE	48% (431/898)	45% (380/845)	3.0% (–1.6% to 7.7%)	1.06 (0.96 to 1.18)	0.20
12 mos.	COURAGE	45% (386/857)	47% (398/846)	–2.0% (–6.7% to 2.7%)	0.95 (0.86 to 1.06)	0.40
24 mos.	COURAGE	46% (352/766)	46% (349/758)	0% (–5.0% to 4.9%)	0.99 (0.89 to 1.11)	0.67
36 mos.	COURAGE	41% (244/596)	43% (255/594)	–1.9% (–7.6% to 3.6%)	0.95 (0.83 to 1.09)	0.48
Pain						
1 mo.	COURAGE	48% (429/893)	43% (384/893)	5.0% (0.4% to 9.6%)	1.11 (1.00 to 1.23)	0.03
3 mos.	COURAGE	52% (448/861)	50% (433/866)	2.0% (–2.6% to 6.7%)	1.04 (0.94 to 1.14)	0.39
6 mos.	COURAGE	52% (466/897)	49% (414/844)	2.9% (–1.8% to 7.6%)	1.05 (0.96 to 1.16)	0.22
12 mos.	COURAGE	51% (437/857)	49% (414/845)	2.0% (–2.7% to 6.7%)	1.04 (0.94 to 1.14)	0.41
24 mos.	COURAGE	48% (367/765)	46% (349/758)	1.9% (–3.0% to 6.9%)	1.04 (0.93 to 1.15)	0.45
36 mos.	COURAGE	44% (262/596)	47% (279/594)	–3.0% (–8.6% to 2.6%)	0.93 (0.82 to 1.06)	0.29
General Health						
1 mo.	COURAGE	37% (332/896)	25% (224/894)	12.0% (7.7% to 16.2%)	1.47 (1.28 to 1.70)	<0.0001
3 mos.	COURAGE	39% (336/862)	30% (260/867)	8.9% (4.5% to 13.4%)	1.29 (1.13 to 1.48)	0.0001

		RAND-36 (mean ± SD)				
Time point	RCT	PCI	MT	Mean difference (95% CI)	Effect Size (95% CI)	p-value
6 mos.	COURAGE	39% (350/898)	35% (296/845)	3.9% (–0.5% to 8.4%)	1.11 (0.98 to 1.25)	0.08
12 mos.	COURAGE	37% (317/858)	36% (305/847)	0.9% (–3.6% to 5.5%)	1.02 (0.90 to 1.16)	0.68
24 mos.	COURAGE	34% (260/766)	35% (266/759)	–1.1% (–5.8% to 3.6%)	0.96 (0.84 to 1.11)	0.65
36 mos.	COURAGE	37% (221/596)	34% (202/595)	3.1% (–2.3% to 8.5%)	1.09 (0.93 to 1.27)	0.25

CI: Confidence Interval; MT: Medical Therapy; NR: Not Reported; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

*A clinically significant change was defined as a difference of ≥10 points in a given domain.

Appendix Table G4. RAND (COURAGE) and SF-36 (MASS II) subscale scores*

		RAND/SF-36 (mean ± SD)			
Time point	RCT	PCI	MT	Mean difference (95% CI)	p-value
Physical Functioning (RAND and SF-36)					
Baseline	COURAGE	58 ± 27 (n=987)	59 ± 27 (n=973)	–1.0 (–3.4 to 1.4)	0.41
	MASS II†	~58	~54	NR	NR
1 mo.	COURAGE	65 ± 27 (n=896)	61 ± 27 (n=894)	4.0 (1.49 to 6.51)	0.001
3 mos.	COURAGE	69 ± 27 (n=861)	65 ± 26 (n=867)	4.0 (1.49 to 6.51)	0.001
6 mos.	COURAGE	68 ± 27 (n=899)	66 ± 26 (n=844)	2.0 (–0.50 to 4.50)	0.1158
	MASS II†	~71	~63	NR	NR
12 mos.	COURAGE	69 ± 27 (n=857)	66 ± 28 (n=847)	3.0 (0.38 to 5.62)	0.02
	MASS II†	~73	~66	NR	NR
24 mos.	COURAGE	66 ± 28 (n=766)	65 ± 27 (n=759)	1.0 (–1.77 to 3.77)	0.47
36 mos.	COURAGE	66 ± 29 (n=596)	64 ± 28 (n=595)	2.0 (–1.25 to 5.25)	0.22
Role Limitation- Physical (RAND and SF-36)					
Baseline	COURAGE	38 ± 41 (n=987)	37 ± 42 (n=971)	1.0 (–2.69 to 4.69)	0.59
	MASS II†	~34	~38	NR	NR
1 mo.	COURAGE	47 ± 42 (n=892)	46 ± 43 (n=893)	1.0 (–2.95 to 4.95)	0.61
3 mos.	COURAGE	61 ± 42 (n=862)	52 ± 43 (n=866)	9.0 (4.98 to 13.02)	<0.0001
6 mos.	COURAGE	62 ± 42 (n=897)	57 ± 43 (n=844)	5.0 (1.00 to 9.00)	0.01
	MASS II†	~47	~40	NR	NR

		RAND/SF-36 (mean ± SD)			
Time point	RCT	PCI	MT	Mean difference (95% CI)	p-value
12 mos.	COURAGE	64 ± 42 (n=856)	61 ± 42 (n=845)	3.0 (–1.00 to 7.00)	0.14
	MASS II†	~54	~46	NR	NR
24 mos.	COURAGE	62 ± 42 (n=765)	61 ± 42 (n=759)	1.0 (–3.23 to 5.23)	0.64
36 mos.	COURAGE	66 ± 42 (n=595)	60 ± 42 (n=595)	6.0 (1.22 to 10.78)	0.01
Role Limitation- Emotional (RAND and SF-36)					
Baseline	COURAGE	56 ± 43 (n=987)	57 ± 43 (n=968)	–1.0 (–4.82 to 2.82)	0.60
	MASS II†	~65	~63	NR	NR
1 mo.	COURAGE	62 ± 42 (n=892)	62 ± 42 (n=888)	0.0 (–3.91 to 3.91)	1.0
3 mos.	COURAGE	69 ± 41 (n=857)	65 ± 42 (n=863)	4.0 (0.07 to 7.93)	0.04
6 mos.	COURAGE	70 ± 41 (n=894)	68 ± 41 (n=843)	2.0 (–1.87 to 5.87)	0.30
	MASS II†	~64	~62	NR	NR
12 mos.	COURAGE	73 ± 38 (n=857)	70 ± 40 (n=845)	3.0 (–0.72 to 6.72)	0.11
	MASS II†	~66	~68	NR	NR
24 mo.	COURAGE	69 ± 41 (n=761)	70 ± 40 (n=758)	–1.0 (–5.08 to 3.08)	0.63
36 mos.	COURAGE	71 ± 40 (n=592)	68 ± 42 (n=590)	3.0 (–1.69 to 7.69)	0.20
Energy/Fatigue (RAND) or Vitality (SF-36)					
Baseline	COURAGE	47 ± 24 (n=986)	47 ± 23 (n=974)	0.0 (–2.09 to 2.09)	1.0
	MASS II†	~64	~59	NR	NR
1 mo.	COURAGE	53 ± 23 (n=894)	48 ± 24 (n=893)	5.0 (2.82 to 7.18)	<0.0001
3 mos.	COURAGE	56 ± 23 (n=861)	52 ± 23 (n=866)	4.0 (1.83 to 6.17)	0.0003
6 mos.	COURAGE	56 ± 23 (n=898)	53 ± 23 (n=844)	3.0 (0.83 to 5.17)	0.006
	MASS II†	~72	~63	NR	NR
12 mos.	COURAGE	56 ± 23 (n=858)	54 ± 24 (n=846)	2.0 (–0.24 to 4.24)	0.07
	MASS II†	~72	~63	NR	NR
24 mo.	COURAGE	55 ± 24 (n=766)	52 ± 24 (n=756)	3.0 (0.58 to 5.42)	0.01
36 mos.	COURAGE	56 ± 23 (n=596)	52 ± 24 (n=594)	4.0 (1.32 to 6.68)	0.003
Emotional Well-Being (RAND) or Mental Health (SF-36)					
Baseline	COURAGE	71 ± 20 (n=986)	71 ± 20 (n=974)	0.0 (–1.78 to 1.78)	0.0

		RAND/SF-36 (mean ± SD)			
Time point	RCT	PCI	MT	Mean difference (95% CI)	p-value
	MASS II†	~53	~53	NR	NR
1 mo.	COURAGE	74 ± 19 (n=894)	73 ± 19 (n=893)	1.0 (–0.77 to 2.77)	0.26
3 mos.	COURAGE	76 ± 19 (n=861)	74 ± 19 (n=866)	2.0 (0.20 to 3.80)	0.02
6 mos.	COURAGE	75 ± 19 (n=898)	75 ± 19 (n=844)	0.0 (–1.79 to 1.79)	0.56
	MASS II†	~72	~68	NR	NR
12 mos.	COURAGE	75 ± 19 (n=858)	75 ± 20 (n=846)	0.0 (–1.86 to 1.86)	1.0
	MASS II†	~75	~70	NR	NR
24 mos.	COURAGE	75 ± 20 (n=766)	76 ± 19 (n=756)	–1.0 (–2.97 to 0.97)	0.31
36 mos.	COURAGE	75 ± 19 (n=596)	74 ± 20 (n=594)	1.0 (–1.22 to 3.22)	0.37
Social Functioning (RAND and SF-36)					
Baseline	COURAGE	71 ± 27 (n=988)	70 ± 27 (n=974)	1.0 (–1.40 to 3.40)	0.41
	MASS II†	~71	~73	NR	NR
1 mo.	COURAGE	75 ± 25 (n=894)	75 ± 26 (n=893)	0.0 (–2.37 to 2.37)	1.0
3 mos.	COURAGE	81 ± 24 (n=861)	79 ± 25 (n=866)	2.0 (–0.32 to 4.32)	0.09
6 mos.	COURAGE	81 ± 24 (n=898)	79 ± 26 (n=845)	2.0 (–0.35 to 4.35)	0.09
	MASS II†	~83	~77	NR	NR
12 mos.	COURAGE	81 ± 25 (n=857)	80 ± 25 (n=846)	1.0 (–1.38 to 3.38)	0.40
	MASS II†	~84	~79	NR	NR
24 mos.	COURAGE	79 ± 26 (n=766)	81 ± 24 (n=758)	–2.0 (–4.52 to 0.52)	0.11
36 mos.	COURAGE	80 ± 26 (n=596)	79 ± 26 (n=594)	1.0 (–1.96 to 3.96)	0.50
Pain (RAND and SF-36)					
Baseline	COURAGE	61 ± 26 (n=986)	62 ± 26 (n=974)	–1.0 (–3.31 to 1.31)	0.39
	MASS II†	~62	~61	NR	NR
1 mo.	COURAGE	68 ± 26 (n=893)	66 ± 25 (n=893)	2.0 (–0.37 to 4.37)	0.09
3 mos.	COURAGE	72 ± 25 (n=861)	68 ± 26 (n=866)	4.0 (1.59 to 6.41)	0.001
6 mos.	COURAGE	71 ± 26 (n=897)	70 ± 26 (n=844)	1.0 (–1.45 to 3.45)	0.42
	MASS II†	~75	~67	NR	NR
12 mos.	COURAGE	72 ± 25 (n=857)	70 ± 27 (n=845)	2.0 (–0.48 to 4.48)	0.11

		RAND/SF-36 (mean ± SD)			
Time point	**RCT**	**PCI**	**MT**	**Mean difference (95% CI)**	**p-value**
	MASS II†	~73	~68	NR	NR
24 mos.	COURAGE	70 ± 26 (n=765)	69 ± 26 (n=758)	1.0 (–1.62 to 3.62)	0.45
36 mos.	COURAGE	70 ± 27 (n=596)	68 ± 27 (n=594)	2.0 (–1.08 to 5.08)	0.20
General Health (RAND and SF-36)					
Baseline	COURAGE	57 ± 20 (n=987)	55 ± 20 (n=974)	2.0 (0.23 to 3.77)	0.02
	MASS II†	~68	~65	NR	NR
1 mo.	COURAGE	61 ± 20 (n=896)	55 ± 20 (n=894)	6.0 (4.14 to 7.86)	<0.0001
3 mos.	COURAGE	62 ± 21 (n=862)	57 ± 21 (n=867)	5.0 (3.02 to 6.98)	<0.0001
6 mos.	COURAGE	61 ± 21 (n=898)	58 ± 21 (n=845)	3.0 (1.02 to 4.98)	0.002
	MASS II†	~73	~69	NR	NR
12 mos.	COURAGE	61 ± 21 (n=858)	58 ± 21 (n=847)	3.0 (1.00 to 5.00)	0.003
	MASS II†	~74	~69	NR	NR
24 mos.	COURAGE	60 ± 22 (n=766)	58 ± 22 (n=759)	2.0 (–0.21 to 4.21)	0.07
36 mos.	COURAGE	60 ± 22 (n=596)	57 ± 22 (n=595)	3.0 (0.50 to 5.50)	0.01

CI: Confidence Interval; MT: Medical Therapy; NR: Not Reported; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

* RAND and SF-36 nearly identical outcome measurement tools; however, RAND lacks the additional SF-36 question for assessment of change in health over past year (not reported here).
† MASS II scores are estimated from charts.

Appendix Table G5. Duke Activity Status Index (DASI) score

		DASI (mean scores estimated from graphs)			
Time point	**RCT**	**PCI**	**MT**	**Mean difference (95% CI)**	**p-value**
Baseline	BARI-2D*	~20.0 (n NR)	~19.0 (n NR)	NR	NR
12 mos.	BARI-2D*	~22.0 (n NR)	~20.5 (n NR)	NR	NR
24 mos.	BARI-2D*	~21.5 (n NR)	~20.0 (n NR)	NR	NR
36 mos.	BARI-2D*	~19.0 (n NR)	~20.5 (n NR)	NR	NR
48 mos.	BARI-2D*	~19.5 (n NR)	~19.0 (n NR)	NR	NR

CI: Confidence Interval; MT: Medical Therapy; NR: Not Reported; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

*These trials are in special populations: Hambrecht = males; BARI 2D = type 2 diabetes

Appendix Table G6. Modified RAND* scores

		DASI (mean scores estimated from graphs)			
Time point	**RCT**	**PCI**	**MT**	**Mean difference (95% CI)**	**p-value**
Energy/Fatigue					
Baseline	BARI-2D†‡	~54 (n NR)	~54.5 (n NR)	NR	NR
12 mos.	BARI-2D†‡	~55 (n NR)	~53 (n NR)	NR	NR
24 mo.	BARI-2D†‡	~55 (n NR)	~54 (n NR)	NR	NR
36 mos.	BARI-2D†‡	~54 (n NR)	~53.5 (n NR)	NR	NR
48 mos.	BARI-2D†‡	~53.5 (n NR)	~54 (n NR)	NR	NR
Self-Rated Health					
Baseline	BARI-2D†‡	~39.5 (n NR)	~37.5 (n NR)	NR	NR
12 mos.	BARI-2D†‡	~46.0 (n NR)	~43.5 (n NR)	NR	NR
24 mos.	BARI-2D†‡	~46.0 (n NR)	~44.0 (n NR)	NR	NR
36 mos.	BARI-2D†‡	~47.0 (n NR)	~43.5 (n NR)	NR	NR
48 mos.	BARI-2D†‡	~45.5 (n NR)	~43.5 (n NR)	NR	NR
Health Distress					
Baseline	BARI-2D†‡	~42.0 (n NR)	~43.0 (n NR)	NR	NR
12 mos.	BARI-2D†‡	~33.4 (n NR)	~34.5 (n NR)	NR	NR
24 mos.	BARI-2D†‡	~33.0 (n NR)	~34.0 (n NR)	NR	NR
36 mos.	BARI-2D†‡	~47.0 (n NR)	~43.5 (n NR)	NR	NR
48 mos.	BARI-2D†‡	~45.5 (n NR)	~43.5 (n NR)	NR	NR

CI: Confidence Interval; MT: Medical Therapy; NR: Not Reported; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; RCT: Randomized Controlled Trial; SD: Standard Deviation

* Modified RAND subscales are derived from RAND Medical Outcomes Study.

† Study is a special population: BARI 2D = type 2 diabetes

‡ Values are estimated from charts.

Results reported as follows:

Does the subgroup modify treatment effect for PCI + medical therapy versus medical therapy alone?
Interaction p-value
Follow-up
Trial
A priori or post-hoc

Appendix Table G7. Differential efficacy and safety in subpopulations

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
Sex (male, female)								YES (p=0.03) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*		SAQ angina stability domain YES (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori* SAQ domains (all except angina stability) NO (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.08)	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
										Through 36 months COURAGE (Weintraub 2008) *a priori*	
Age (≥65, <65)	NO (p=0.21) (55.2 mos.‡) COURAGE (Teo) *a priori* NO (p=NR) (120 mos.) MASS-II (Lima 2013) *a priori*	NO (p=NR) (120 mos.) MASS-II (Lima 2013) *a priori*	NO (p=0.95) (55.2 mos.‡) COURAGE (Teo) *a priori* NO (p=NR) (120 mos.) MASS-II (Lima 2013) *a priori*		NO (p=0.58) (55.2 mos.‡) COURAGE (Teo) *a priori*			NO (p=0.66) (55.2 mos.‡) COURAGE (Teo) *a priori*	NO (p=0.77) (55.2 mos.‡) COURAGE (Teo) *a priori*	SAQ domains (all) NO (p≥0.11) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori*	
Age (>65, ≤65)								NO (p=0.62) (55.2 mos.‡) COURAGE (Boden			

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
								2007) *a priori*			
Age (<60, 60-69, ≥70)											(PCI or CABG) NO (p=0.36) (60 mos.) BARI 2D (Chung 2011) *a priori*
Race (white, nonwhite)								NO (p=0.43) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*			
Race (stratification NR)										SAQ domains (all) NO (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.35) Through 36 months COURAGE	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
										(Weintraub 2008) *a priori*	
Baseline angina (CCS class 0-1, CCS class II-III)								NO (p=0.73) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*			
Baseline angina (CCS class, stratification NR)										SAQ domains (all) NO (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.13) Through 36 months COURAGE (Weintraub 2008) *a priori*	
Baseline	NO (p=NR)		NO			NO (p=NR)			NO		

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
angiographic risk (lower two tertiles, higher tertile)	(63.6 mos.*) BARI 2D (Brooks 2012) *unclear*		(p=NR) (post-periprocedural to 55.2 mos.*) BARI 2D (Brooks 2012) *unclear* NO (p=NR) (peri-procedural) BARI 2D (Brooks 2012) *unclear*			(post-periprocedural to 55.2 mos.*) BARI 2D (Brooks 2012) *unclear* NO (p=NR) (peri-procedural) BARI 2D(Brooks 2012) *unclear*			(p=0.16) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Baseline Framingham risk (lower two tertiles, higher tertile)									NO (p=0.87) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Baseline angiographic risk/ Baseline Framingham risk§ (lower two	NO (p=NR) (60 mos. †) BARI 2D (Brooks 2012) *unclear*		NO (p=NR) (60 mos.†) BARI 2D (Brooks			NO (p=NR) (60 mos.†) BARI 2D (Brooks 2012) *unclear*			NO (p=0.58) (60 mos.†) BARI 2D (Brooks		

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
tertiles, higher tertile)			2012) *unclear*						2012) *unclear*		
Baseline angina severity: physical limitation domain (SAQ) (lower tertile, middle tertile, highest tertile)	NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*			NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	SAQ physical limitation (significant improvement (≥8 points) from baseline & mean scores) YES (p<0.0001 for both) Through 36 months COURAGE (Weintraub 2008) *A priori*	
Baseline angina severity: angina frequency domain (SAQ) (lower tertile, middle tertile, highest tertile)	NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*			NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		MAYBE (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	MAYBE (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	SAQ angina frequency (significant improvement (≥20 points) from baseline & mean scores) YES	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
										(p<0.001 & p=0.008, respectively) Through 36 months COURAGE (Weintraub 2008) *A priori*	
Baseline angina severity: quality of life domain (SAQ) (lower tertile, middle tertile, highest tertile)	NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		NO (p= NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*			NO (p= NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*		MAYBE (p= NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	NO (p=NR) (55.2 mos.‡) COURAGE (Zhang 2011) *unclear*	SAQ quality of life (significant improvement (≥16 points) from baseline & mean scores) YES (p<0.0001 for both) Through 36 months COURAGE (Weintraub 2008) *A priori*	
Baseline ischemia (none/mild, moderate/severe)	NO (p=NR) (55.2 mos.‡) COURAGE (Shaw		NO (p=NR) (55.2 mos.‡) COURAGE					NO (p=NR) (55.2 mos.‡) COURAGE			

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
	2012) *Post hoc*		(Shaw 2012) *Post hoc*					(Shaw 2012) *Post hoc*			
Number diseased vessels (1, 2, 3)								(excludes peri-procedural MI) NO (p=0.96) COURAGE (Mancini 2009) *Post hoc*	NO (p=0.83) (60 mos.†) BARI 2D (Brooks 2012) *a priori*		(PCI or CABG) NO (p=NR) (60 mos.†) BARI 2D
Number diseased vessels (1, ≥2)								NO (p=0.65) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*			
Subgroup of patients who required symptom-driven second angiogram during f/u with index lesion stenosis (≥50%, <50%)				MAYBE (p=NR) (15.6 mos.*) COURAGE (Mancini 2011) *NR*						(Symptom progression) MAYBE (p=NR) (15.6 mos.*) COURAGE (Mancini 2011) *NR*	(PCI only) MAYBE (p=NR) (15.6 mos.*) COURAGE (Mancini 2011) *NR*
Myocardial									NO		NO (p=NR)

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
Index Jeopardy score (<55, ≥55)									(p=0.40) (60 mos.†) BARI 2D (Brooks 2012) *a priori*		(60 mos.†) BARI 2D (Dagenais 2011) *a priori*
Modified Duke Jeopardy score with ≥50% stenosis threshold (0-1, 2-3, 4-6)								(excludes peri-procedural MI) NO (p=0.06) (55.2 mos.‡) COURAGE (Mancini 2009) *Post hoc*			
Modified Duke Jeopardy score with ≥70% stenosis threshold (0-1, 2-3, 4-6)								(excludes peri-procedural MI) NO (p=0.98) (55.2 mos.‡) COURAGE (Mancini 2009) *Post hoc*			
Number of									NO		

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
lesions (<6, ≥6)									(p=0.63) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Total occlusion (yes, no)									NO (p=0.99) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Proximal LAD (yes, no)									NO (p=0.53) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Prior revascularization (yes, no)									NO (p=0.70) (60 mos.†) BARI 2D (Brooks 2012) *a priori*		(PCI or CABG) NO (p=NR) (60 mos.†) BARI 2D (Dagenais 2011) *a priori*
Prior CABG (yes, no)								NO (p=0.81)		SAQ angina frequency &	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
								(55.2 mos.‡) COURAGE (Boden 2007) *a priori*		quality of life domains YES (p=0.0113 & p=0.0270, respectively) Through 36 months COURAGE (Weintraub 2008) *a priori* SAQ domains (all except angina frequency and quality of life) NO (p≥0.25) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.08) Through 36 months COURAGE	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
										(Weintraub 2008) *a priori*	
LVEF (normal, abnormal)									NO (p=0.17) (60 mos.†) BARI 2D (Brooks 2012) *unclear*		
Ejection fraction (>50%, ≤50%)								NO (p=0.72) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*			
Baseline angina (none, angina equivalents only, angina)											(PCI or CABG) NO (p=NR) (60 mos.†) BARI 2D (Dagenais 2011) *unclear*
History of MI (yes, no)								NO (p=0.15) (55.2 mos.‡) COURAGE (Boden 2007)		SAQ domains (all) NO (p≥0.13) Through 36 months COURAGE	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
								a priori		(Weintraub 2008) *a priori* RAND-36 domains (all) NO (p≥0.12) Through 36 months COURAGE (Weintraub 2008) *a priori*	
Current smoking (yes, no)								NO (p=0.71) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*			
Diabetes (yes, no)	NO (p=NR) (12. 60, 120 mos.) MASS-II (Soares 2006, Lima 2013) *a priori*	NO (p=NR) (120 mos.) MASS-II (Lima 2013) *a priori*						NO (p=0.33) (55.2 mos.‡) COURAGE (Boden 2007) *a priori*		SAQ domains (all) NO (p≥0.12) Through 36 months COURAGE (Weintraub 2008) *a priori* RAND-36 domains	

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
										(all) NO (p≥0.05) Through 36 months COURAGE (Weintraub 2008) *a priori*	
Metabolic syndrome/ diabetes status (-MetS/-DM, +MetS/-DM, -MetS/+DM, +MetS/+DM)								NO (p=NR) (55.2 mos.‡) COURAGE (Maron 2011) *post hoc*			
CKD (yes, no)	NO (p=0.78) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*	NO (p=0.39) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*	NO (p=0.42) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*		(cardiac hospitalization) NO (p=0.51) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*	NO (p=0.75) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*	(hospital-ization for new CHF) NO (p=0.84) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*			(Clinically significant improvement in any SAQ domain) NO (p>0.08) (longitudinal analysis from 0-36 mos.) COURAGE (Sedlis 2013) *Post hoc*	(PCI or CABG) NO (p=0.68) (55.2 mos.‡) COURAGE (Sedlis 2009) *Post hoc*
Healthcare system	NO (p=0.55)				NO (p=0.96) (55.2 mos.‡)		NO (p=0.80)	NO (p=0.17)	NO (p=0.17)	(SAQ angina frequency	(PCI or CABG) YES (p<0.001)

Subpopulation (subgroups)	All-cause mortality	Cardiac death	MI	MI/ACS and PCI	ACS hospitalization	Stroke	CHF	Death/MI	Death/MI / stroke	Symptoms	Revascularization
(Canada, US non-VA, US-VA)	(55.2 mos.‡) COURAGE (Chaitman 2010) *A priori*				COURAGE (Chaitman 2010) *A priori*		(55.2 mos.‡) COURAGE (Chaitman 2010) *A priori*	(55.2 mos.‡) COURAGE (Boden 2007) *a priori*	(55.2 mos.‡) COURAGE (Chaitman 2010) *A priori*	domain scores) NO (p=0.NR) (55.2 mos.‡) COURAGE (Chaitman 2010) *A priori*	(55.2 mos.‡) COURAGE (Chaitman 2010) *A priori*

CHF: congestive heart failure; CKD: chronic kidney disease
*mean f/u
†Kaplan-Meier 60-month estimates
‡median f/u
§4 subgroups created for angiographic risk/Framingham risk: low/low vs. low/high vs. high/low vs. high/high

Appendix Table G8. PCI plus stenting versus medical therapy for stable angina: Efficacy and Safety Outcomes

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
BARI 2D Chaitman 2009, BARI 2D Study Group, Brooks 2010	*PCI vs Med* **All cause death** Mean 5.3 years 12.8% (102/798) vs 11.9% (96/807), p = 0.48; RR= 1.07 (95% CI 0.83 to 1.39), p = 0.59 5 year Kaplan Meier Estimate: 10.8% vs 10.2% **Cardiac death** Mean 5.3 years 5.5% (44/798) vs 4.1% (33/807), p = 0.16; RR = 1.35 (95% CI 0.89 to 2.10), p = 0.18 5 year Kaplan Meier Estimate: 5.0% vs 4.2%	*PCI vs Med* **Non-procedural Q wave MI** Mean 5.3 years 2.1% (17/798) vs 2.2% (18/807); RR = 0.96 (95% CI 0.50 to 1.84), p = 0.89 5 year Kaplan Meier Estimate: 2.3% vs 2.6%, p = 0.93 **Non-procedural, non-Q wave MI** Mean 5.3 years 6.6% (51/798) vs 6.7% (54/807), p = 0.87; RR = 0.96 (0.67 to 1.38), p = 0.80 5 year Kaplan Meier	*PCI vs Med* **Non-periprocedural stroke** Median 4.6 (2.5-7) years 2.6% (21/797) vs 2.6% (21/805); RR= 1.01 (95% CI 0.56 to 1.83), p = 0.97 *DES vs BMS vs Med* **Event rate** (event rate; DES vs Med HR; BMS vs Med HR) 4 years Stroke: 1.4% vs 2.6% vs 2.7%; Unadjusted HR = 0.48 (0.14 to 1.60), Adjusted HR = 0.52 (0.15	*DES vs BMS vs Med* **Self-reported angina*** (defined as patients who experienced angina symptoms during each year f/u) Baseline† ~60% (147/245) vs ~61% (259/424) vs 59% (476/807), p = 0.92; 1 year† ~32% (78/245) vs ~38% (161/424) vs 47% (379/807), p < 0.01 2 years 29% (71/245) vs 37% (157/424) vs 39% (315/807), p = 0.04 3 years† ~27% (66/245) vs ~32% (136/424) vs 33% (266/807), p = 0.27 4 years 21% (51/245) vs 24% (102/424) vs 28% (226/807), p = 0.18 *Revasc (CABG or PCI) vs Med* **Duke Activity Status Index†§** (higher score, better health; 0-58.2) Baseline: 20.0 vs 19.0 1 year: 22.0 vs 20.5 2 years: 21.5 vs 20.0 3 years: 19.0 vs 20.5	*DES vs BMS vs Med* **Subsequent revascularization** 4 years 20.8% (51/245) vs 28.9% (123/424) vs 39.9% (317/807) **Subsequent PCI** 4 years 18.1% (44/245) vs 23.9% (101/424) vs 32.4% (261/807) *Randomized to PCI* **Underwent clinically indicated revascularization** 5 years 452/1192 (37.9%) **Cumulative rate of first revascularizations** (f/u NR) Baseline: 0% vs 0% 1 year: 12% vs 19%	*PCI vs Med* **Death or MI** Mean 5.3 years 21.7% (173/798) vs 19.5% (157/807), p = 0.19); RR = 1.11 (95% CI 0.92 to 1.35), p = 0.27 5 year Kaplan Meier Estimate: 21.1% vs 19.6% **Cardiac death or MI** Mean 5.3 years 15.8% (126/798) vs 12.5% (101/807), p = 0.045; RR = 1.26 (95% CI 0.99 to 1.61) p = 0.06 5 year Kaplan Meier Estimate: 16.0% vs 14.2% **Cardiac death of nonprocedural MI** Mean 5.3 years 13.2% (105/798) vs 11.5% (93/807), p = 0.29; RR= 1.14	*PCI vs Med* **MI*** (procedure-related) 2.9% (23/798) vs 1.2% (10/807); RR= 2.33 (95% CI 1.11 to 4.86), p = 0.02 *PCI Stratum* **All cause death** 30 days 0.5% (4/798) **Death, MI, or Stroke** 30 days 3.5% (28/798)

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
	Sudden cardiac death Mean 5.3 years 4.3% (34/798) vs 3.2% (26/807), p = 0.25; RR‡ = 1.32 (95% CI 0.80 to 2.18) p = 0.27 5 year Kaplan Meier Estimate: 3.8% vs 3.4% **Cardiac deaths** (by post-randomization non-procedural MI status) 5 year MI: % (11/798) vs % (19/807), HR = 0.54 (95% CI 0.26 to 1.15) No MI: % (33/798) vs % (14/807); HR = 2.41 (1.28 to	Estimate : 6.6% vs 8.0%, p = 0.87 **Non-procedural MI (all)** Mean 5.3 years 9.0% (72/798) vs 9.8% (79/807); RR= 0.92 (95% CI 0.6801 to 1.2491), p = 0.5989 5 year Kaplan Meier Estimate: 9.4% vs 11.4% *DES vs BMS vs Med* **Event rate** (event rate; DES vs Med HR; BMS vs Med HR) 4 years MI: 9.1% vs 12.0% vs 10.9%; Unadjusted HR	to 1.85); Unadjusted HR = 0.94 (0.47 to 1.89), Adjusted HR = 0.92 (0.45 to 1.89)	4 years: 19.5 vs 19.0 Treatment effect (at least one f/u) = 0.53, p = 0.28 Treatment effect (imputed**) = 0.57, p = 0.22 OR = 1.07, p = 0.40 **Modified RAND instrument: Energy†‡‡** (f/u NR, 0-100, higher score better health) Baseline: 54 vs 54.5 1 year: 55 vs 53 2 years: 55 vs 54 3 years 54 vs 53.5 4 years: 53.5 vs 54 Treatment effect (at least one f/u); OR = 0.96, p = 0.18 Treatment effect (imputed**) = 0.93, p = 0.22 OR = 1.12, p = 0.17 **Modified RAND instrument: Health Distress†‡‡‡** (f/u NR, 0-100, higher score, better health) Baseline: 42.0 vs 43.0	2 years: 19% vs 28% 3 years: 24% vs 34% 4 years: 27% vs 39% 5 years: 30% vs 43%, Log-rank P-value < 0.001 **Patients with revascularization**5 years 26.8% (213/796) vs 39.1% (315/806) Reasons for revascularization: Acute coronary syndrome: 26% vs 22% Severe angina symptoms: 33% vs 45% Worsened ischemia: 18% vs 20% Unsatisfactory results of recent intervention: 3% vs 0% Objective evidence of CAD	(95% CI 0.88 to 1.48), p = 0.32 5 year Kaplan Meier Estimate: 13.3% vs 13.2% **Death, MI, or stroke***** 5 years 23.1% (184/798) vs 21.1% (170/807), RR= 0.93 (95% CI 0.46 to 1.12), p = 0.85	

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
	4.50) *DES vs BMS vs Med* **Event rate** (event rate; DES vs Med HR; BMS vs Med HR) <u>4 years</u> Death: 7.8% vs 8.8% vs 7.0%; Unadjusted HR = 0.99 (95% CI 0.62 to 1.61), Adjusted HR = 1.12 (95% (0.66 to 1.89); Unadjusted HR = 0.97 (0.70 to 1.36); Adjusted HR 0.94 (0.67 to 1.32)	= 0.90 (0.56 to 1.46), Adjusted HR = 0.86 (0.52 to 1.42); Unadjusted HR = 1.16 (0.83 to 1.62), Adjusted HR = 1.20 (0.85 to 1.69)		<u>1 year</u>: 33.0 vs 34.5 <u>2 years</u>: 33.0 vs 34.0 <u>3 years</u>: 47.0 vs 43.5 <u>4 years</u>: 45.5 vs 43.5 Treatment effect (at least one f/u) t = 0.19, p = 0.82 Treatment effect (imputed**) = 0.34, p = 0.67 OR = 0.97, p = 0.69 **Modified RAND instrument: Self-Rated Health†§§§** (f/u NR, 0-100, higher score, better health) <u>Baseline</u>: 39.5 vs 37.5 <u>1 year</u>: 46.0 vs 43.5 <u>2 years</u>: 46.0 vs 44.0 <u>3 years</u>: 47.0 vs 43.5 <u>4 years:</u> 45.5 vs 43.5 Treatment effect (at least one f/u) = 1.38, p = 0.079 Treatment effect (imputed**) = 1.51, p = 0.1 OR = 0.92, p = 0.36	progression: 13% vs 8% Other reasons: 8% vs 6% *DES vs BMS vs Med* **Event rate** (event rate; DES vs Med HR; BMS vs Med HR) <u>4 years</u> Subsequent Revascularization: 20.8% vs 28.9% 39.3%; Unadjusted HR = 0.47 (0.35 to 0.64), Adjusted HR = 0.46 (0.33 to 0.63); Unadjusted HR 0.68 (0.55 to 0.83), Adjusted HR 0.69 (0.56 to 0.85) Subsequent PCI: 18.1% vs 23.9% vs 32.4%; Unadjusted HR = 0.51 (0.37 to 0.71, Adjusted HR = 0.49 (0.35 to 0.69); Unadjusted HR 0.68 (0.54 to		

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				PCI vs Med **Worsening Angina†§§** (changing pattern of angina worsening in severity) 1 year: ~17.5% (131/742) vs ~25.0% (186/760), p = 0.001; RR = 0.72 (95% CI 0.59 to 0.88), p = 0.001 2 years: ~14.0% vs ~14.0%, p = 0.935 3 years: ~11.0% vs ~15.0%, p = 0.019 4 years: ~10.0% vs ~11.5%, p = 0.539 5 years: ~9.5% vs ~9.5%, p = 0.952 **Freedom from Angina†** (Subset of patients who had classic angina at entry; percent of patients who absence of angina) 1 year: ~41% vs ~24%, p < 0.001 2 years: ~54% vs ~48%, p = 0.107 3 years: ~60% vs ~55%, p = 0.112 4 years: ~60% vs ~57%, p = 0.361 5 years: ~62% vs ~59%, p = 0.69 **New Angina†** (Subset of patients that did not show angina at entry, and developed classic angina) Baseline**: ~**0% vs ~0% 1 year: ~24% vs ~27% 2 years: ~36% vs ~44%	0.85), Adjusted HR 0.70 (0.55 to 0.88) Subsequent CABG: 4.6% vs 8.1% vs 9.9%; Unadjusted HR = 0.56 (0.23 to 0.87), Adjusted HR = (0.51 (2.54 to 1.01); Unadjusted HR = 0.86 (0.58 to 1.26), Adjusted HR = 0.82 (0.55 to 1.21)		

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				3 years: ~41% vs ~50% 4 years: ~46% vs ~56% 5 years: ~50% vs ~58%, Log-rank P = 0.053			
COURAGE Boden 2007, Weintraub 2008, Boden 2009, Teo 2009, Chaitman 2010, Maron 2010, Mancini 2011, Maron 2011, Zhang 2011, Shaw 2012	**All cause death††** Median 4.6 (2.5-7) years 7.4% (85/1149) vs. 8.3% (95/1138); HR = 0.87 (0.65 to 1.16) p = 0.38 **All cause death****** Median 4.6 (2.5-7) years 5.9% (68/1149) vs 6.5% (74/1138); RR = 0.91 (95% CI, 0.67 to 1.25), p = 0.56 **Cardiac Death** Median 4.6 (2.5-7) years†††† 2.0% (23/1149) vs. 2.2% (25/1138); RR	**Nonfatal MI** Median 4.6 (2.5-7) years 9.4% (108/1149) vs. 10.5% (119/1138); RR= 0.90 (95% CI 0.70 to 1.15), p = 0.40 **Spontaneous MI** (presence of an acute eschemic syndrome with new ECG Q waves or abnormal biomarker activity) Median 4.6 (2.5-7) years 10.4% (109/1149) vs. 9.5% (113/1138); HR, 0.91 (95% CI, 0.70 to 1.18), p = 0.46	**Stroke** Median 4.6 (2.5-7) years 1.9% (22/1149) vs. 1.2% (14/1138); HR, 1.56 (0.80 to 3.04), p = 0.19	**Freedom from angina (CCS classification)** Baseline 12% (135/1148) vs. 13% (148/1137); RR = 0.90 (95% CI, 0.72 to 1.12), p = 0.36 1 year 66% (680/1031) vs. 58% (595/1010), p < 0.001; RR = 1.11 (95% CI, 1.04 to 1.19), p = 0.001 3 years 72% (602/820) vs. 67% (558/824), p = 0.02; RR = 1.08 (95% CI, 1.01 to 1.15), p = 0.01 5 years 74% (316/423) vs. 72% (196/406); RR = 1.02 (95% CI 0.94 to 1.11), p = 0.55 **Freedom from angina** (as a score of 100 on the SAQ angina frequency domain) Baseline: 21% (203/969) vs. 23% (223/969), p = 0.35; RR= 0.91 (95% CI 0.77 to 1.08), p = 0.27 1 month: 42% (368/875) vs. 33% (292/885), p <0.001; RR= 1.27 (95% CI 1.13 to 1.44), p < 0.01	**Revascularization (PCI or CABG)** Median 4.6 (2.5-7) years 19.8% (228/1149) vs. 30.6% (348/1138); HR, 0.60 (0.51 to 0.71), p < 0.001 **Subsequent CABG** Median 4.6 (2.5-7) years 6.7% (77/1149) vs. 7.1% (81/1138); RR = 0.94 (95% CI, 0.69 to 1.27), p=0.69 **Subsequent PCI ‡‡‡‡** Median 4.6 (2.5-7 years) 13.1% (151/1149) vs 23.5% (267/1138), RR= 0.56 (95% CI 0.47 to 0.67), p < 0.01	**Death and nonfatal MI** Median 4.6 (2.5-7) years 18.4% (211/1149) vs. 17.8% (202/1138); HR, 1.05 (0.87 to 1.27), p = 0.62 **Cardiac death and MI** Median 4.6 (2.5-7) years 15% (172/1149) vs. 14.2% (162/1138); HR, 1.07 (95% CI, 0.86 to 1.33), p = 0.62 **Death, nonfatal MI, and stroke** Median 4.6 (2.5-7) years 19.3% (222/1149) vs. 18.8% (213/1138); HR, 1.05 (0.87 to 1.27), p = 0.62	**MI** Periprocedural 3.0% (35/1149) vs. 0.8% (9/1138); RR = 3.85 (95% CI, 1.86 to 7.97), p < 0.01 **PCI revascularization MI** Periprocedural 3.4% (37/1149) vs. 1.0% (11/1138); HR, 3.57 (95% CI, 1.83 to 6.96), p<0.001 **CABG revascularization MI** Periprocedural 0.08% (1/1149) vs. 0.1% (2/1138); RR = 0.49 (95% CI, 0.04 to 5.45), p = 0.55

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
	= 0.91 (95% CI, 0.52 to 1.59), p = 0.74 Median 4.6 (2.5-7 years)§§§§ 3.4% (39/1149) vs. 3.9% (44/1138); HR, 0.87 (95% CI, 0.56 to 1.33), p = 0.51	**Total MI** (spontaneous, Peri-PCI, and MI after CABG) Median 4.6 (2.5-7) years 12.8% (147/1149) vs. 11.1% (126/1138); HR, 1.14 (95% CI, 0.90 to 1.44), p = 0.48		3 months: 53% (462/871) vs. 42% (367/873), p <0.001; RR= 1.26 (95% CI 1.14 to 1.39), p < 0.01 6 months: 56% (503/898) vs. 47% (395/840), p <0.0003; RR= 1.19 (95% CI 1.09 to 1.31), p < 0.01 12 months: 57% (492/863) vs. 50% (415/829), p <0.0048; RR= 1.14 (95% CI 1.04 to 1.25), p < 0.01 24 months: 59% (451/764) vs. 53% (395/746), p <0.0097; RR= 1.11 (95% CI 1.02 to 1.22), p = 0.02 36 months: 59% (344/583) vs. 56% (330/589), p = 0.30; RR= 1.05 (95% CI 0.95 to 1.16), p = 0.30 **SAQ clinically significant improvement from baseline** *Physical limitation****** 1 month: 45% (383/850) vs. 38% (323/850), p = 0.007; RR= 1.19 (95% CI 1.06 to 1.33) p < 0.01 3 months: 49% (417/852) vs. 43% (366/855), p = 0.008; RR= 1.14 (95% CI 1.03 to 1.27), p = 0.01 6 months: 51% (448/878) vs. 42% (344/820), p <0.001; RR= 1.21 (95% CI 1.10 to 1.35), p < 0.01 12 months: 48% (405/844) vs. 44% (357/812), p = 0.095; RR= 1.09 (95% CI 0.98 to 1.21), p = 0.10 24 months: 49% (365/745) vs. 44% (323/735), p = 0.08; RR = 1.11 (95%		**Cardiac death/ MI/stroke** Median 4.6 (2.5-7) years 16.4% (188/1149) vs. 15.2% (173/1138); HR, 1.10 (95% CI, 0.89 to 1.35), p = 0.45	**Unable to cross lesion** 2.0% (27/1149) vs. NR

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				CI 1.00 to 1.24), p = 0.05 36 months: 45% (258/573) vs. 47% (274/583), p = 0.50; RR = 0.96 (95% CI 0.85 to 1.09), p = 0.50 *Angina Stability****** 1 month: 57% (495/866) vs. 50% (437/873), p = 0.008; RR= 1.14 (95% CI 1.05 to 1.25), p < 0.01 3 months: 56% (482/860) vs. 51% (439/860), p = 0.06; RR= 1.10 (95% CI 1.01 to 1.20), p = 0.04 6 months: 56% (495/883) vs. 52% (430/827), p = 0.14; RR= 1.08 (95% CI 0.99 to 1.18), p = 0.09 12 months: 51% (430/843) vs. 50% (405/810), p = 0.46; RR= 1.02 (95% CI 0.93 to 1.12), p = 0.68 24 months: 53% (395/746) vs. 48% (352/733), p = 0.096; RR= 1.10 (95% CI 1.00 to 1.22), p = 0.06 36 months: 51% (294/576) vs. 46% (267/580), p = 0.14; RR= 1.11 (95% CI 0.98 to 1.25), p = 0.09 *Angina frequency****** 1 month: 39% (341/875) vs. 30% (266/885), p < 0.001; RR= 1.30(95% CI 1.14 to 1.48), p < 0.01 3 months: 47% (409/871) vs. 40% (349/873), p = 0.004; RR= 1.17 (95% CI 1.05 to 1.31), p < 0.01 6 months: 50% (449/898) vs. 44% (370/840) p = 0.010; RR= 1.14 (95% CI 1.03 to 1.26), p = 0.01			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				12 months: 52% (449/863) vs. 46% (381/829), p = 0.016; RR= 1.13 (95% CI 1.03 to 1.25), p = 0.01 24 months: 54% (413/764) vs. 47% (351/746), p = 0.012; RR= 1.15 (95% CI 1.04 to 1.27), p < 0.01 36 months: 57% (332/583) vs. 50% (295/589), p = 0.045; RR= 1.14 (95% CI 1.02 to 1.27), p = 0.02 *Treatment satisfaction****** 1 month: 27% (236/873) vs. 26% (229/882), p = 0.054; RR= 1.04 (95% CI 0.89 to 1.22), p = 0.61 3 months: 28% (243/869) vs. 29% (253/873), p = 0.77; RR= 0.96 (95% CI 0.83 to 1.12), p = 0.64 6 months: 30% (268/894) vs. 31% (260/839), p = 0.75; RR= 0.97 (95% CI 0.84 to 1.12), p = 0.65 12 months: 39% (336/861) vs. 33% (274/829), p = 0.23; RR= 1.18 (95% CI 1.04 to 1.34), p = 0.0106 24 months: 32% (244/761) vs. 38% (281/740), p = 0.05; RR= 0.84 (95% CI 0.74to 0.97), p = 0.02 36 months: 31% (182/586) vs. 34% (202/593), p = 0.28; RR= 0.91 (95% CI 0.77 to 1.07), p = 0.27 *Quality of life****** 1 month: 52% (454/873) vs. 43% (379/882), p = 0.001; RR= 1.21 (95% CI 1.10 to 1.34), p < 0.01 3 months: 60% (521/869) vs. 54%			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				(471/872), p = 0.02; RR= 1.11 (95% CI 1.02 to 1.20), p = 0.01 6 months: 64% (574/897) vs. 56% (469/838), p = 0.001; RR= 1.14 (95% CI 1.06 to 1.24), p < 0.01 12 months: 65% (560/862) vs. 61% (504/827), p = 0.17; RR= 1.07 (95% CI 0.99 to 1.15), p = 0.09 24 months: 65% (496/763) vs. 67% (495/739), p = 0.65; RR= 0.97 (95% CI 0.90 to 1.04), p = 0.42 36 months: 69% (404/586) vs. 69% (408/591), p = 0.93; RR= 1.00 (95% CI 0.93 to 1.08), p = 0.97 **Seattle Angina Questionnaire scores (mean score ±SD, n)** *Physical limitation****** Baseline: 66 ± 25 (n = 939) vs. 66 ± 35 (n = 939), p = 0.58 1 month: 73 ± 24 (n = 850) vs. 70 ± 24 (n = 850), p = 0.003 3 months: 76 ± 24 (n = 852) vs. 72 ± 23 (n = 855), p = 0.004 6 months: 77 ± 23 (n = 878) vs. 72 ± 24 (n = 820), p < 0.001 12 months: 75 ± 24 (n = 844) vs. 73 ± 24 (n = 812), p = 0.21 24 months: 74 ± 24 (n = 745) vs. 72 ± 24 (n = 735), p = 0.16 36 months: 74 ± 24 (n = 573) vs. 74 ± 24 (n = 583), p= 0.68 *Angina Stability*			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				Baseline: 54 ± 33 (n = 953) vs. 53 ± 32 (n = 947), p = 0.56 1 month: 81 ± 26 (n = 866) vs. 73 ± 28 (n = 873), p < 0.001 3 months: 77 ± 28 (n = 860) vs. 73 ± 27 (n = 860), p = 0.002 6 months: 76 ± 28 (n = 883) vs. 73 ± 28 (n = 827), p = 0.02 12 months: 74 ± 27 (n = 843) vs. 70 ± 28 (n = 810), p = 0.02 24 months: 73 ± 27 (n = 746) vs. 69 ± 27 (n = 733), p = 0.003 36 months: 72 ± 28 (n = 576) vs. 70 ± 28 (n = 580), p = 0.39 *Angina frequency******* Baseline: 68 ± 26 (n = 969) vs. 69 ± 26 (n = 969), p = 0.20 1 month: 82 ± 23 (n = 875) vs. 76 ± 24 (n = 885), p < 0.001 3 months: 85 ± 22 (n = 871) vs. 80 ± 23 (n = 873), p < 0.001 6 months: 87 ± 20 (n = 898) vs. 83 ± 22 (n = 840), p < 0.001 12 months: 87 ± 19 (n = 863) vs. 84 ± 21 (n = 829), p = 0.003 24 months: 89 ± 18 (n = 764) vs. 86 ± 19 (n = 746), p = 0.002 36 months: 89 ± 18 (n = 583) vs. 88 ± 18 (n = 589), p = 0.37 *Treatment satisfaction******* Baseline 88 ± 15 (n = 971) vs. 86 ± 16 (n = 956), p = 0.008			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				1 month: 92 ± 12 (n = 873) vs. 88 ± 15 (n = 882), p < 0.001 3 months: 92 ± 12 (869) vs. 90 ± 14 (n = 873), p = 0.001 6 months: 92 ± 13 (n = 894) vs. 90 ± 14 (n = 839), p = 0.007 12 months: 92 ± 12 (n = 861) vs. 90 ± 14 (n = 829), p = 0.002 24 months: 92 ± 13 (n = 761) vs. 92 ± 13 (n = 740), p = 0.35 36 months: 92 ± 12 (n = 586) vs. 92 ± 11 (n = 593), p = 0.78 60 months: 92 (p = 0.08 compared to baseline) vs. 94 (p = 0.001 compared to baseline), p=0.91 *Quality of Life****** Baseline: 51 ± 25 (n = 969) vs. 51 ± 25 (n = 958), p = 0.80 1 month: 68 ± 24 (n = 873) vs. 62 ± 24 (n = 882), p < 0.001 3 months: 73 ± 22 (n = 869) vs. 68 ± 23 (n = 872), p < 0.001 6 months: 75 ± 22 (n = 897) vs. 70 ± 23 (n = 838), p < 0.001 12 months: 76 ± 21 (n = 862) vs. 73 ± 22 (n = 827), p = 0.008 24 months: 77 ± 22 (n = 763) vs. 76 ± 22 (n = 739), p = 0.10 36 months: 79 ± 20 (n = 586) vs. 77 ± 20 (n = 591), p = 0.32 **RAND-36 clinically significant**			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				improvement from baseline *Physical functioning (≥10 pt improvement from baseline)* 1 month: 41% (367/896) vs. 33% (295/894), p = 0.001; RR = 1.24 (95% CI, 1.09 to 1.40), p < 0.01 3 months: 48% (413/861) vs. 40% (347/867), p = 0.002; RR = 1.19 (95% CI, 1.07 to 1.33), p < 0.01 6 months: 50% (450/899) vs. 43% (363/844), p = 0.011; RR = 1.16 (95% CI, 1.05 to 1.28), p < 0.01 12 months: 47% (411/857) vs. 43% (364/847), p = 0.20; RR = 1.11 (95% CI, 1.00 to 1.23), p = 0.03 24 months: 42% (322/766) vs. 42% (319/759), p = 0.89; RR = 1.00 (95% CI, 0.88 to 1.12), p = 0.99 36 months: 42% (250/596) vs. 39% (232/595), p = 0.27; RR = 1.07 (95% CI, 0.93 to 1.23), p = 0.29 *Role Limitation- Physical (≥10 pt improvement from baseline)* 1 month: 34% (303/892) vs. 34% (304/893), p = 0.91; RR = 0.99 (95% CI, 0.87 to 1.13), p = 0.97 3 months: 45% (388/862) vs. 40% (346/866), p = 0.04; RR = 1.12 (95% CI, 1.00 to 1.25), p = 0.03 6 months: 48% (431/897) vs. 43% (363/844), p = 0.04; RR = 1.11 (95% CI, 1.00 to 1.23), p = 0.03 12 months: 47% (402/856) vs. 47%			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				(397/845), p = 0.95; RR = 0.99 (95% CI, 0.90 to 1.10), p = 0.99 24 months: 45% (344/765) vs. 45% (342/759), p = 0.95; RR = 0.99 (95% CI, 0.89 to 1.11), p = 0.97 36 months: 44% (262/595) vs. 46% (273/595), p = 0.58; RR = 0.95 (95% CI, 0.84 to 1.08), p = 0.52 *Role Limitation- Emotional (≥10 pt improvement from baseline)* 1 month: 28% (250/892) vs. 27% (240/888), p = 0.51; RR = 1.03 (95% CI, 0.89 to 1.20), p = 0.63 3 months: 33% (283/857) vs. 32% (276/863), p = 0.72; RR = 1.03 (95% CI, 0.90 to 1.18), p = 0.64 6 months: 37% (331/894) vs. 33% (278/843), p = 0.09; RR = 1.12 (95% CI, 0.98 to 1.27), p = 0.07 12 months: 34% (291/857) vs. 34% (287/845), p = 0.90; RR = 0.99 (95% CI, 0.87 to 1.14), p = 0.99 24 months: 33% (251/761) vs. 33% (250/758), p = 0.88; RR = 1.00 (95% CI, 0.86 to 1.15), p = 0.99 36 months: 33% (195/592) vs. 32% (189/590), p = 0.92; RR = 1.02 (95% CI, 0.87 to 1.21), p = 0.73 *Energy/Fatigue (≥10 pt improvement from baseline)* 1 month: 41% (367/894) vs. 33% (295/893), p = 0.0004; RR = 1.24 (95% CI, 1.09 to 1.40), p < 0.01			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				3 months: 49% (422/861) vs. 40% (346/866), p = 0.0005; RR = 1.22 (95% CI, 1.10 to 1.36), p < 0.01 6 months: 47% (422/898) vs. 45% (380/844), p = 0.51; RR = 1.04 (95% CI, 0.94 to 1.15), p = 0.40 12 months: 47% (403/858) vs. 45% (380/846), p = 0.27; RR = 0.98 (95% CI, 0.91 to 1.06), p = 0.79 24 months: 46% (352/766) vs. 33% (249/756), p < 0.0001; RR = 1.39 (95% CI, 1.22 to 1.58), p < 0.01 36 months: 44% (262/596) vs. 42% (249/594), p = 0.36; RR = 1.04 (95% CI, 0.91 to 1.19), p = 0.47 *Well-being (≥10 pt improvement from baseline)* 1 month: 29% (259/894) vs. 23% (205/893), p = 0.005; RR = 1.26 (95% CI, 1.07 to 1.47), p < 0.01 3 months: 32% (275/861) vs. 27% (234/866), p = 0.04; RR = 1.18 (95% CI, 1.02 to 1.36), p = 0.02 6 months: 32% (287/898) vs. 28% (236/844), p = 0.08; RR = 1.14 (95% CI, 0.98 to 1.32), p = 0.06 12 months: 29% (249/858) vs. 29% (245/846), p = 0.96; RR = 0.99 (95% CI, 0.86 to 1.15), p = 0.99 24 months: 32% (245/766) vs. 30% (226/756), p = 0.51; RR = 1.06 (95% CI, 0.92 to 1.24), p = 0.37 36 months: 31% (185/596) vs. 27%			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				(160/594), p = 0.08; RR = 1.15 (95% CI, 0.96 to 1.37), p = 0.11 *Social functioning (≥10 pt improvement from baseline)* 1 month: 40% (358/894) vs. 41% (366/893), p = 0.76; RR = 0.97 (95% CI, 0.87 to 1.09), p = 0.68 3 months: 46% (396/861) vs. 44% (381/866), p = 0.44; RR = 1.04 (95% CI, 0.94 to 1.16), p = 0.40 6 months: 48% (431/898) vs. 45% (380/845), p = 0.24; RR = 1.06 (95% CI, 0.96 to 1.18), p = 0.20 12 months: 45% (386/857) vs. 47% (398/846), p = 0.50; RR = 0.95 (95% CI, 0.86 to 1.06), p = 0.40 24 months: 46% (352/766) vs. 46% (349/758), p = 0.98; RR = 0.99 (95% CI, 0.89 to 1.11), p = 0.67 36 months: 41% (244/596) vs. 43% (255/594), p = 0.47; RR = 0.95 (95% CI, 0.83 to 1.09), p = 0.48 *Pain (≥10 pt improvement from baseline)* 1 month: 48% (429/893) vs. 43% (384/893), p = 0.02; RR = 1.11 (95% CI, 1.00 to 1.23), p = 0.03 3 months: 52% (448/861) vs. 50% (433/866), p = 0.33; RR = 1.04 (95% CI, 0.94 to 1.14), p = 0.39 6 months: 52% (466/897) vs. 49% (414/844), p = 0.17; RR = 1.05 (95% CI, 0.96 to 1.16), p = 0.22			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				12 months: 51% (437/857) vs. 49% (414/845), p = 0.55; RR = 1.04 (95% CI, 0.94 to 1.14), p = 0.41 24 months: 48% (367/765) vs. 46% (349/758), p = 0.59; RR = 1.04 (95% CI, 0.93 to 1.15), p = 0.45 36 months: 44% (262/596) vs. 47% (279/594), p = 0.28; RR = 0.93 (95% CI, 0.82 to 1.06), p = 0.29 *General health (≥10 pt improvement from baseline)* 1 month: 37% (332/896) vs. 25% (224/894), p < 0.0001; RR = 1.47 (95% CI, 1.28 to 1.70), p < 0.01 3 months: 39% (336/862) vs. 30% (260/867), p = 0.0004; RR = 1.29 (95% CI, 1.13 to 1.48), p < 0.01 6 months: 39% (350/898) vs. 35% (296/845), p = 0.12; RR = 1.11 (95% CI, 0.98 to 1.25), p = 0.08 12 months: 37% (317/858) vs. 36% (305/847), p = 0.69; RR = 1.02 (95% CI, 0.90 to 1.16), p = 0.68 24 months: 34% (283/766) vs. 35% (266/759), p = 0.88; RR = 1.05 (95% CI, 0.92 to 1.2), p = 0.44 36 months: 37% (221/596) vs. 34% (202/595), p = 0.37; RR = 1.09 (95% CI, 0.93 to 1.27), p = 0.25 **RAND-36 scores (mean score ±SD, n)** *Physical Functioning*			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				Baseline: 58 ± 27 (n = 987) vs 59 ± 27 (n = 973), p = 0.39 1 month: 65 ± 27 (n = 896) vs 61 ± 27 (n = 894), p = 0.0003 3 months: 69 ± 27 (n = 861) vs 65 ± 26 (n = 867), p = 0.001 6 months: 68 ± 27 (n = 899) vs 66 ± 26 (n = 844), p = 0.035 12 months: 69 ± 27 (n = 857) vs 66 ± 28 (n = 847), p = 0.018 24 months: 66 ± 28 (n = 766) vs 65 ± 27 (n = 759), p = 0.61 36 months: 66 ± 29 (n = 596) vs 64 ± 28 (n = 595), p = 0.22 *Role Limitation-Physical* Baseline: 38 ± 41 (n = 987) vs 37 ± 42 (n = 971), p = 0.51 1 month: 47 ± 42 (n = 892) vs 46 ± 43 (n = 893), p = 0.72 3 months: 61 ± 42 (n = 862) vs 52 ± 43 (n = 866), p = 0.0001 6 months: 62 ± 42 (n = 897) vs 57 ± 43 (n = 844), p = 0.024 12 months: 64 ± 42 (n = 856) vs 61 ± 42 (n = 845), p = 0.11 24 months: 62 ± 42 (n = 765) vs 61 ± 42 (n = 759), p = 0.66 36 months: 66 ± 42 (n = 595) vs 60 ± 42 (n = 595), p = 0.03 *Role Limitation-Emotional* Baseline: 56 ± 43 (n = 987) vs 57 ± 43 (n = 968), p = 0.76 1 month: 47 ± 42 (n = 892) vs 62 ±			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				42 (n = 888), p = 0.87 3 months: 69 ± 41 (n = 857) vs 65 ± 42 (n = 863), p = 0.045 6 months: 70 ± 41 (n = 894) vs 68 ± 41 (n = 843) p = 0.46 12 months: 73 ± 38 (n = 857) vs 70 ± 40 (n = 845) p = 0.10 24 months: 69 ± 41 (n = 761) vs 70 ± 40 (n = 758) p = 0.73 36 months: 71 ± 40 (n = 592) vs 68 ± 42 (n = 590) p = 0.21 *Energy/Fatigue* 1 month: 47 ± 24 (n = 986) vs 47 ± 23 (n = 974), p = 0.91 2 months: 53 ± 23 (n = 894) vs 48 ± 24 (n = 893), p = 0.0001 3 months: 56 ± 23 (n = 861) vs 52 ± 23 (n = 866), p < 0.0001 6 months: 56 ± 23 (n = 898) vs 53 ± 23 (n = 844), p = 0.008 12 months: 56 ± 23 (n = 858) vs 54 ± 24 (n = 846), p = 0.028 24 months: 55 ± 24 (n = 766) vs 52 ± 24 (n = 756), p = 0.026 36 months: 56 ± 23 (n = 596) vs 52 ± 24 (n = 594), p = 0.014 *Emotional Well-being* Baseline: 71 ± 20 (n = 986) vs 71 ± 20 (n = 974), p = 0.82 1 month: 74 ± 19 (n = 894) vs 73 ± 19 (n = 893), p = 0.23 3 months: 76 ± 19 (n = 861) vs 74 ± 19 (n = 866), p = 0.039			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				6 months: 75 ± 19 (n = 898) vs 75 ± 19 (n = 844), p = 0.56 12 months: 75 ± 19 (n = 858) vs 75 ± 20 (n = 846), p = 0.63 24 months: 75 ± 20 (n = 766) vs 76 ± 19 (n = 756), p = 0.21 36 months: 75 ± 19 (n = 596) vs 74 ± 20 (n = 594), p = 0.17 *Social Functioning* Baseline: 71 ± 27 (n = 988) vs 70 ± 27 (n = 974), p = 0.95 1 month: 75 ± 25 (n = 894) vs 75 ± 26 (n = 893), p = 0.95 3 months: 81 ± 24 (n = 861) vs 79 ± 25 (n = 866), p = 0.022 6 months: 81 ± 24 (n = 898) vs 79 ± 26 (n = 845), p = 0.03 12 months: 81 ± 25 (n = 857) vs 80 ± 25 (n = 846), p = 0.69 24 months: 79 ± 26 (n = 766) vs 81 ± 24 (n = 758), p = 0.31 36 months: 80 ± 26 (n = 596) vs 79 ± 26 (n = 594), p = 0.59 *Pain* Baseline: 61 ± 26 (n = 986) vs 62 ± 26 (n = 974), p= 0.73 1 month: 68 ± 26 (n = 893) vs 66 ± 25 (n = 893), p= 0.052 3 months: 72 ± 25 (n = 861) vs 68 ± 26 (n = 866), p= 0.006 6 months: 71 ± 26 (n = 897) vs 70 ± 26 (n = 844), p= 0.29 12 months: 72 ± 25 (n = 857) vs 70			

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				± 27 (n = 845), p= 0.10 24 months: 70 ± 26 (n = 765) vs 69 ± 26 (n = 758), p= 0.55 36 months: 70 ± 27 (n = 596) vs 68 ± 27 (n = 594), p= 0.36 *General Health* Baseline: 57 ± 20 (n = 987) vs 55 ± 20 (n = 974), p = 0.044 1 month: 61 ± 20 (n = 896) vs 55 ± 20 (n = 894), p < 0.0001 3 months: 62 ± 21 (n = 862) vs 57 ± 21 (n = 967), p < 0.0001 6 months: 61 ± 21 (n = 898) vs 58 ± 21 (n = 845), p = 0.0009 12 months: 61 ± 21 (n = 858) vs 58 ± 21 (n = 847), p = 0.010 24 months: 60 ± 22 (n = 766) vs 58 ± 22 (n = 759), p = 0.044 36 months: 60 ± 22 (n = 596) vs 57 ± 22 (n = 595), p = 0.033			
Hambrecht Hambrecht 2004, Walther 2008	**Cardiac death** 1 year 0.0% (0/50) vs 0.0% (0/51), RR = NC **Non-Cardiac Death** 2 years* 4% (2/50) vs 2% (1/51), RR= 2.04 (95% CI 0.19 to 21.79),	**Acute MI** (nonfatal) 2 years* 2% (1/50) vs 2% (1/51), RR= 1.02 (0.07 to 15.86), p = 0.99	**Cerebrovascular event** 1 year 6.0% (3/50) vs 3.9% (2/51), RR= 1.53 (95% CI 0.27 to 8.77), p = 0.63	*Other outcomes:* **CCS Class Score** Baseline 1.7 ± 0.1 (n = 50) vs 1.5 ± 0.1 (n = 51) 1 year 0.6 ± 0.1 (n = 37) vs 0.4 ± 0.1 (n = 43)	**CABG** 1 year 2.0% (1/50) vs 0.0% (0/51), RR = NC **PTCA of target lesion** 1 year 4.0% (2/50) vs 3.9% (2/51), RR= 1.02 (95% CI 0.15 to 6.96), p = 0.98	**Major ischemic events** (CVA, CABG, PTCA for unstable angina pectoris) 1 year 28% (14/50) vs 9.8% (5/51), RR= 2.86 (95% CI 1.11 to 7.34), p = 0.02 **Any ischemic event†††††**	No adverse events were observed in the med group during training sessions.

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
	p = 0.58				2 year 10% (5/50) vs 13.7% (7/51), RR= 0.73 (95% CI 0.25 to 2.14), p = 0.56 **PTCA of other coronary segments** 1 year 14.0% (7/50) vs 2.0% (1/51), RR= 7.14 (95% CI 0.91 to 55.95), p = 0.02	1 year 42% (21/50) vs 11.8% (6/51), RR= 3.57 (95% CI 1.57 to 8.10), p < 0.01 2 years 38.0% (19/50) vs 19.6% (10/51); RR = 1.94 (95% CI 1.00 to 3.75), p = 0.04 **Hard Clinical events** (stroke, TVR, PCI of de-novo lesion, CABG) 12 months 30 % (15/50) vs 11.8% (6/51)	
MASS II Hueb 2004, Favarato 2007, Lima 2013, Rezende 2013, Hueb 2010, Hueb 2007, Soares 2006,	**Death** (definition unspecified) 1 year 4.4% (9/205) vs 1.5% (3/203), RD = 2.9% (95% CI -.04% to 6.2%); RR= 3.0 (95% CI 0.8 to 10.8), p = 0.0821	**Q-wave MI** 1 year 8.3% (16/205) vs 5.0% (10/203), RR= 1.58 (95% CI 0.74 to 3.40), p = 0.23 **Acute MI** 5 years 11.2% (23/205) vs 15.3%	**Cerebrovascular event** 1 year 1.0% (2/205) vs 1.5% (3/203), RR = 0.66 (95% CI 0.11 to 3.91), p = 0.65 **CVA** 5 years	**Angina Free** (definition unspecified) 1 year 52% (107/205) vs 36% (74/203), RR= 1.43 (95% CI 1.1 to 1.79), p < 0.01 5 years 77.3% (119/205) vs 54.8% (92/203) p < 0.001, RR= 1.28 (95% CI 1.06 to 1.55), p = 0.01 10 years 59% (120/205) vs 43% (88/203), p < 0.001, RR= 1.35 (95% CI 1.11 to	**CABG** 1 year 3.5% (7/205) vs 6.0% (12/203), RR= 0.58 (95% CI 0.23 to 1.44), p = 0.23 5 year 9.3% (19/205) vs 15.3% (31/203), RR= 0.61 (95% CI 0.36 to 1.04), p =	**Mortality, MI, refractory angina req. revascularization** 1 year 24% (50/205) vs 14.2% (29/203), RR= 1.71 (95% CI 1.13 to 2.58), p < 0.01 5 years 55.12% (113/205)	**Major in-hospital events‡‡‡‡‡** In-hospital Death: 2.4% (5/205) Q-wave MI: 1.0% (2/205) Emergency CABG: 1.0% (2/205) Emergency PCI (definition NR): 1.0% (2/205)

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
Vieira 2012, Lopes 2008	**Overall mortality** 5 years 11.7% (24/205) vs 12.3% (25/203), RR= 0.95 (95% CI 0.56 to 1.61), p = 0.85 10 years* 24.1% (49/205) vs 31.0% (63/203), RR = 0.77 (95% CI 0.56 to 1.06) p= 0.11 **Cardiac death** 1 year 4.4% (9/205) vs 1.5% (3/203), RR= 2.98 (95% CI 0.82 to 10.82), p = 0.08 5 years 11.6% (24/205) vs 12.3% (25/203), RR= 0.95 (95% CI 0.56 to 1.61),	(31/203), Adjusted RR ††† = 1.22 (95% CI 0.66 to 2.25), p = 0.51 10 years 13.3% (27/205) vs 20.7% (42/203), RR= 0.637 (95% CI 0.41 to 0.99), p = 0.04 **Nonfatal MI** 1 year 8.3% (16/205) vs 5% (10/203), RR= 1.58 (95% CI 0.74 to 3.41), p = 0.23 5 year 11.2% (23/205) vs 15.3% (31/203), RR= 0.74 (95% CI 0.44 to 1.22), p = 0.23 10 years 13.2% (27/205) vs 20.7% (42/203), RR=	3.4% (7/205) vs 3.5% (7/203), RR= 0.99 (95% CI 0.354 to 2.77), p = 0.9851 10 years 5.4% (11/205) vs 6.9% (14/203), RR= 0.78 (95% CI 0.36 to 1.67), p = 0.52	1.64), p < 0.01 **SF-36 Questionnaire mean scores†** (36 items from which summary score is obtained by simple unweighted summation of item scores, 0-100) *Physical Functioning (10 item summary)* Baseline ~58 vs ~54, p = NR 6 months ~71 vs ~63, p = NR 1 year ~73 vs ~66, p = NR *Vitality (4 item summary)* Baseline ~64 vs ~59, p = NR 6 months ~72 vs ~63, p = NR 1 year ~72 vs ~63, p = NR *General Health (five item summary)* Baseline ~68 vs ~65, p = NR 6 months ~73 vs ~69, p = NR 1 year ~74 vs ~69, p = NR *Role functioning, physical (four item summary)* Baseline	0.06 10 years 13.2% (27/205) vs 25.1% (51/203), RR= 0.52 (95% CI 0.34 to 0.80), p < 0.01 **PCI** 1 year 8.78% (18/205) vs 1.97% (4/203), RR= 4.46 (95% CI 1.54 to 12.94), p < 0.01 5 year 22.9% (47/205) vs 8.9% (18/203), RR= 2.59 (95% CI 1.56 to 4.30), p < 0.01 10 year 28.3% (58/205) vs 14.3% (29/203), RR= 0.35 (95% CI 0.13 to 0.96), p = 0.03 **All Additional (non-index procedure) Revascularizations** 1 year	vs 43.41% (89/203), Adjusted RR ††† = 0.93 (95% CI 0.67 to 1.30) **Event-free survival** (no incidence of overall mortality, MI, or refractory angina req. revasc.) 5 years 55.12% (113/205) vs 43.41% (89/203), HR = 0.93 (95% CI 0.67 to 1.30) 10 years NR vs NR, HR = 0.79 (95% CI 0.62 to 1.01)	Stroke: 1.0% (2/205) **Major events** 30 days Death: 2.4% (5/205) vs NR AMI: 3.0% (6/203) vs 8.3% (17/205)

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
	p = 0.85 10 years 14.3% (29/205) vs 20.7% (42/203), RR= 0.68 (95% CI 0.44 to 1.05), p = 0.08	0.64 (95% CI 0.41 to 0.99), p = 0.04 **Fatal MI** 1 year 4.5% (9/205) vs vs 1.5% (3/203), RR= 2.97 (95% CI 0.82 to 10.82), p = 0.08 5 year 11.6% (24/205) vs 12.3% (25/203), RR= 0.95 (95% CI 0.56 to 1.61), p = 0.85 10 year 14.1% (29/205) vs 20.7% (42/203), RR= 0.68 (95% CI 0.44 to 1.05), p = 0.08		~34 vs ~28, p = NR 6 months ~47 vs ~40, p = NR 1 year ~54 vs ~46, p = NR *Role functioning, emotional (three item summary)* Baseline ~53 vs ~53, p = NR 6 months ~64 vs ~62, p = NR 1 year ~66 vs ~68, p = NR *Mental health (five item summary)* Baseline ~65 vs ~63, p = NR 6 months ~72 vs ~68, p = NR 1 year ~75 vs ~70, p = NR *Pain (two item summary)* Baseline ~62 vs ~61, p = NR 6 months ~75 vs ~67, p = NR 1 year ~73 vs ~68, p = NR *Social functioning (two item summary)* Baseline ~71 vs ~73, p = NR	12.2% (25/205) vs 7.9% (16/203), RR= 1.55 (95% CI 0.85 to 2.81), p = 0.15 5 years 32.2% (66/205) vs 24.1% (49/203), RR= 1.33 (95% CI 0.97 to 1.83), p = 0.07 10 years 41.5% (85/205) vs 39.4% (80/203), RR= 1.05 (95% CI 0.83 to 1.33), p = 0.67		

Trial	Mortality (All –cause, cardiac) >30 days	Myocardial infarction >30 days	Stroke >30 days	Patient-reported outcomes and other outcomes	Revascularization	Composite outcomes *(define, provide data)*	Safety
				6 months ~83 vs ~77, p = NR 1 year ~84 vs ~79, p = NR Other Outcomes: **CCS Class II or III angina** 1 year 45.3% (87/205) vs 63.6% (126/203)			

* n or N back-calculated from % and N or n
† estimated from figure
‡ Calculated from Kaplan-Meier Estimates
§ Duke Activity Status Index is a 12 item index from 0 to 58.2 that assesses the activities that one can do without difficulty such as walking a block or two on level ground or doing housework.
** Imputed by the mean value in the designated intended revascularization stratum. Missing outcomes were not imputed for the primary analyses. To control for potential "missing not at random" data, pattern mixture model methods (as per Hedeker and Gibbons) were used by incorporating a categorical variable indicating 3 missing data patterns: completers, noncompliance, and dropouts. In sensitivity analyses, multiple imputation was used to impute nonexistent outcome values for every randomized BARI2D patient.
†† Includes those that had a nonfatal MI before subsequent death
‡‡ Modified RAND-Energy is a 5-item scale 0-100 (worst-best) that measures the degree that a person has energy and full of pep or alternatively feels tired and worn out.
§§ Defined as: a changing pattern of angina that distinctly worsened in severity and/or frequency, from no classic angina at entry to CCS grade III or IV angina, or from any status at entry to unstable angina
*** N's back calculated based on number randomized to IS and IP groups, then IS and IP n's were combined to get to get PCI vs Med n's
††† Adjusted for age, gender, smoking status, hypertension, MI, total cholesterol, high-density lipoprotein cholesterol, triglycerides, ejection fraction, DM, angina status, number of diseased vessels, positive treadmill test, and treatment allocation.
‡‡‡ Modified RAND-Health distress: a 4-item scale that assesses the amount of time one feels discouraged, frustrated, or worried by his or her health status
§§§ Modified RAND-Self-rated health: a single-item Likert scale, as follows: "in general, would you say your health is excellent, very good, good, fair, poor?"
**** Excludes those who had a nonfatal MI before subsequent death
†††† Includes only deaths entirely attributable to cardiac causes, as other subcategories of death (other and unknown) are also provided.
‡‡‡‡ Calculated from Revascularizations minus subsequent CABG.

§§§§ Any cardiac death, does not specify if other deaths are attributed to cardiac death, but this is likely the case.
***** For the SAQ, a clinically significant difference was defined as follows; **physical limitation:** 8 points**, angina stability:** 25 points**, angina frequency:** 20 points**, treatment satisfaction:** 12 points**, quality of life:** 16 points
†††† Defined as death from cardiac causes, resuscitation after cardiac arrest, nonfatal myocardial infarction, cerebrovascular accident, coronary artery bypass grafting, angioplasty, and worsening angina with objective evidence resulting in hospitalization
‡‡‡‡ No in-hospital events were reported for the Med group. It is unclear if these reported in-hospital events are from the index procedure or if they include follow-up procedures.

ppendix Table G9. PCI plus stenting versus medical therapy for stable angina: Differential Efficacy and Safety in Subgroups

Trial	Differential efficacy	Differential safety
BARI 2D Chaitman 2009, BARI 2D Study Group, Brooks 2010	PCI versus medical therapy: **Subgroup: Baseline angiographic risk*** No formal test for interaction was reported and it does not appear that baseline angiographic risk modifies treatment effect: *Outcome: Non-periprocedural MI (through a mean f/u of 4.6 years)*: • Low angiographic risk: 7.6% (45/594) vs 7.4% (45/610); RR= 1.027 (95% CI 0.69 to 1.53), p = 0.90 • High angiographic risk: 11.3% (23/203) vs 16.4% (32/195); RR= 0.69 (95% CI 0.42 to 1.14), p = 0.14 *Outcome: Non-periprocedural stroke (through a mean f/u of 4.6 years)*: • Low angiographic risk: 3.0% (18/594) vs 2.1% (13/610); RR= 1.42 (95% CI 0.70 to 2.88), p = 0.32 • High angiographic risk: 1.5% (3/203) vs 4.1% (8/195); RR= 0.36 (95% CI 0.10 to 1.34), p = 0.11 Low versus high baseline angiographic risk did not modify treatment effect with respect to the composite outcome of death/MI/stroke through 5 years (based on Kaplan-Meier estimates) (interaction p-value, p=0.87). **Subgroup: Baseline Framingham risk†** Low versus high baseline Framingham risk did not modify treatment effect with respect to the composite outcome of death/MI/stroke through 5 years (based on Kaplan-Meier estimates) (interaction p-value, p=0.16). **Subgroup: Baseline Framingham risk/Angiographic risk†** Baseline Framingham/Angiographic risk (low/low, low/high, high/low, high/high) did not modify treatment effect with respect to the composite outcome of death/MI/stroke through 5 years (based on Kaplan-Meier estimates) (interaction p-value, p=0.58). Baseline Framingham/Angiographic risk (low/low, low/high, high/low, high/high) did not appear to modify treatment effect (i.e., there were no significant differences in treatment effect for any risk	PCI versus medical therapy: **Subgroup: Baseline angiographic risk*** No formal test for interaction was reported and it is not apparent that baseline angiographic risk modifies treatment effect: *Outcome: Periprocedural MI* • Low angiographic risk: 2.9% (17/594) vs 1.5% (9/610); RR= 1.94 (95% CI 0.87 to 4.32), p = 0.10 • High angiographic risk: 4.9% (10/203) vs 1.0% (2/195); RR= 4.80 (95% CI 1.07 to 21.64), p = 0.02 *Outcome: Periprocedural Stroke* • Low angiographic risk: 0.3% (2/594) 0.2% (1/610); RR= 2.05 (95% CI 0.19 to 22.59), p = 0.55 • High angiographic risk: 0.5% (1/203) vs 0.5% (1/195); RR= 0.96 (95% CI 0.06 to 15.25), p = 0.98

Trial	Differential efficacy	Differential safety
	subgroup) of death or MI (evaluated individually and calculated using 5-year Kaplan-Meier estimates), although interaction p-values were not reported. No formal test for interaction was reported and it does not appear that baseline Framingham risk/angiographic risk modifies treatment effect: *Outcome: Stroke (through 5 years based on Kaplan-Meier estimates):* • Low Framingham Risk/Low Angiographic risk: 3.5% vs. 2.4%, p = 0.32 • Low Framingham Risk/High Angiographic risk: 2.8% vs. 4.0%, p = 0.79 • High Framingham Risk/Low Angiographic risk: 4.1% vs. 2.0%, p = 0.57 • High Framingham Risk/High Angiographic risk: 0.0% vs. 9.5%, p = 0.0255 **Other cardiovascular risk factors**. None of the following baseline risk factors (assessed individually) modified the treatment effect on the composite outcome of death/MI/stroke through five years (estimates based on Kaplan-Meier analysis): • number of diseased vessels (1 vs. 2 vs. 3) (interaction p=0.83) • myocardial jeopardy index score (<55 vs. ≥55) (interaction p=0.40) • number of lesions (<6 vs. ≥6) (interaction p=0.63) • any total occlusion (yes vs. no) (interaction p=0.53) • any proximal LAD (left anterior descending artery) (yes vs. no) (interaction p=0.70) • prior revascularization (yes vs. no) (interaction p=0.70) • abnormal LVEF (left ventricular ejection fraction (yes vs. no) (p=0.17) No formal test for interaction was reported and it is not clear that prior revascularization modifies treatment effect with respect to: *Outcome: worsening angina (data estimated from graph)* • No prior revascularization: estimated OR 0.4 (95% CI 0.5 to 0.9), p<0.05, favors PCI group • Prior revascularization: estimated OR 1.2 (95% CI 0.8 to 1.7, p=NS *Outcome: freedom from angina in subgroup of patients with classic angina at baseline (data estimated from graph)* • No prior revascularization: estimated OR 1.6 (95% CI 1.2 to 2.2), p<0.05, favors PCI group • Prior revascularization: estimated OR 1.1 (95% CI 0.7 to 1.7), p=NS *Outcome: new angina in subgroup of patients without classic angina at baseline (data estimated from graph)* • No prior revascularization: estimated OR 0.7 (0.4 to 0.9), p<0.05, favors PCI group • Prior revascularization: estimated OR 1.5 (0.8 to 2.7), p=NS *Outcome: subsequent revascularization (data estimated from graph)* • No prior revascularization: estimated OR 0.5 (0.4 to 0.7), p<0.05, favors PCI • Prior revascularization: estimated OR 0.9 (0.6 to 1.3), p=NS **Subgroup: Age (<60 versus 60-69 versus ≥70 years)** Age does not modify treatment effect with respect to revascularization through 5 years follow-up (p =	

Trial	Differential efficacy	Differential safety
	0.36 in test for interaction).	
COURAGE Boden 2007, Weintraub 2008, Boden 2009, Teo 2009, Chaitman 2010, Maron 2010, Mancini 2011, Maron 2011, Zhang 2011, Shaw 2012	**Sex (male vs. female) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Male: 19% (186/979) vs. 18% (174/968), HR = 1.15 (95% CI, 0.93 to 1.42) Female: 18% (30/169) vs. 26% (44/169), HR = 0.65 (95% CI, 0.40 to 1.06) P for interaction = 0.03 **Myocardial infarction (yes MI vs. no MI) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Yes: 23% vs. 25%, HR = 0.91 (95% CI, 0.69 to 1.21) No: 17% vs. 14%, HR = 1.22 (95% CI, 0.93 to 1.60) P for interaction = 0.15 **Extent of CAD (multivessel vs. single vessel) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Multivessel: 21% vs. 21%, HR = 1.04 (95% CI, 0.84 to 1.30) Single vessel: 15% vs. 12%, HR = 1.17 (95% CI, 0.76 to 1.80) P for interaction = 0.65 **Smoking (current vs. not current) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Current: 20% vs. 21%, HR = 1.00 (95% CI, 0.71 to 1.41) Not current: 19% vs. 18%, HR = 1.08 (95% CI, 0.86 to 1.36) P for interaction = 0.71 **Diabetes (yes diabetes vs. no diabetes) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Yes: 25% vs. 24%, HR = 0.99 (95% CI, 0.73 to 1.32) No: 17% vs. 15%, HR = 1.20 (95% CI, 0.92 to 1.56) P for interaction = 0.33 **CCS Angina Class (classes 0 or I vs. classes II or III) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT)	NR

Trial	Differential efficacy	Differential safety
	0 or I: 17% vs. 20%, HR = 1.01 (95% CI, 0.75 to 1.38) II or III: 20% vs. 15%, HR = 1.20 (95% CI, 0.92 to 1.56) P for interaction = 0.73 **Ejection Fraction (>50% vs. ≤50%) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) ≤50%: 28% vs. 26%, HR = 1.14 (95% CI, 0.77 to 1.70) >50%: 17% vs. 16%, HR = 1.05 (95% CI, 0.84 to 1.32) P for interaction = 0.72 **Age (>65 years vs. ≤65 years) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) >65 years: 24% vs. 22%, HR = 1.10 (95% CI, 0.83 to 1.46) ≤65 years: 16% vs. 16%, HR = 1.00 (95% CI, 0.7 to 1.32) P for interaction = 0.62 **Previous CABG (yes vs. no previous CABG) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) No: 17% vs. 17%, HR = 1.04 (95% CI, 0.87 to 1.34) Yes: 34% vs. 29%, HR = 0.98 (95% CI, 0.52 to 1.82) P for interaction = 0.81 **Race (white vs. nonwhite) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) White: 19% vs. 18%, HR = 1.08 (95% CI, 0.87 to 1.34) Nonwhite: 19% vs. 24%, HR = 0.87 (95% CI, 0.54 to 1.42) P for interaction = 0.43 **Health care system (Canada vs. US vs. US-VA) (Boden 2007)** Outcome: Death/MI at median 4.6 years (PCI vs. OMT) Canada: 17% vs. 14%, HR = 1.27 (95% CI, 0.90 to 1.78) US Non-VA: 15% vs. 21%, HR = 0.71 (95% CI, 0.44 to 1.14) US VA: 22% vs. 22%, HR = 1.06 (95% CI, 0.80 to 1.38) P for interaction = 0.17	

Trial	Differential efficacy	Differential safety
	Patient age (≥65 years vs. <65 years of age) (Teo 2009) A priori analysis indicated that age (≥65 vs. <65) did not modify treatment effect over a median 4.6 year follow-up with respect to the individual outcomes of death (interaction p= 0.21), MI (interaction p=0.95), hospitalization acute coronary syndrome (p for interaction = 0.58); or the composite outcomes of death/MI/stroke (p for interaction = 0.77) or death/MI (p interaction = 0.66). The analysis was conducted a-priori. **Health care system: US non-VA vs. US VA vs. Canada (Chaitman 2010)** Post hoc analysis indicated that health care system (US non-VA vs. US VA vs. Canada) did not modify treatment effect over a median 4.6 year follow-up with respect to the individual outcomes of death (interaction p = 0.52), hospitalization for acute coronary syndromes (interaction p = 0.96), congestive heart failure (p for interaction = 0.80); or the composite outcomes of death/MI (p for interaction = 0.20), death/MI without peri-procedural MI (p for interaction = 0.26), or death/MI/stroke (p for interaction = 0.17). Additionally, health care system did not appear to modify treatment effect over a median 4.6 year follow-up with respect to the Seattle Angina Questionnaire angina frequency domain scores, although interaction p-values were not reported. However, health care system did appear to modify treatment effect over a median 4.6 year follow-up with regards to revascularization (PCI or CABG). <u>Outcome: Revascularization (PCI vs. OMT)</u> VA: 28.1% (124/441) vs. 32.6% (146/448) US: 23.4% (43/184) vs. 34.8% (62/178) Canada: 12.9% (61/473) vs. 32.5% (141/434) P for interaction <0.001 **Patients undergoing a second angiogram: Index lesion ≥50% vs. <50% (Mancini 2011)** In the subgroup of patients undergoing a symptom-driven second angiogram during follow-up, it appears that index lesion diameter stenosis at baseline (lesion ≥50% vs. <50%) *may* modify treatment effect for the composite outcome of MI/ACS and PCI or the single outcome of revascularization (PCI) at an average of 1.3 years follow-up (median, 0.7 years; IQR, 0.3 to 2.0 years; range, 5.8 years) such that patients with ≥50% stenosis were significantly more likely to have these outcomes when treated with OMT alone, although interaction p-values were not reported and sample sizes were likely too small for results to be	

Trial	Differential efficacy	Differential safety
	conclusive. Although no formal test for interaction was reported, index lesion diameter stenosis at baseline did appear to have an effect on the outcome of symptom progression at an average 1.3 years follow-up. It is not stated if these subgroup analyses were conducted post hoc or a priori: <u>Outcome: MI/ACS and PCI (PCI vs. OMT)</u> Lesions originally <50% stenosis: 28% (13/47) vs. 33% (27/83); RR = 0.85 (95% CI, 0.48 to 1.48), p = 0.56 Lesions originally ≥50% stenosis: 21% (10/47) vs. 67% (56/83); RR = 0.31 (95% CI, 0.17 to 0.55), p < 0.01 P for interaction NR <u>Outcome: Revascularization (PCI) (PCI vs. OMT)</u> Lesions originally <50% stenosis: 16% (11/70) vs. 32% (48/152); RR = 0.49 (95% CI, 0.27 to 0.89), p = 0.01 Lesions originally ≥50% stenosis: 16% (11/70) vs. 68% (104/152); RR = 0.23 (95% CI, 0.13 to 0.39), p < 0.01 P for interaction NR <u>Outcome: Symptom progression‡ only (PCI vs. OMT)</u> Lesions originally <50% stenosis: 37% (33/88) vs. 35% (17/49); RR = 1.08 (95% CI, 0.67 to 1.72), p = 0.74 Lesions originally ≥50% stenosis: 24% (21/88) vs. 65% (32/49); RR = 0.36 (95% CI, 0.23 to 0.55), p < 0.01 P for interaction NR **Patients presenting with a metabolic syndrome or diabetes mellitus (Maron 2011) (Table 4)** Post-hoc analysis of presentation of metabolic syndromes (MetS) or diabetes mellitus (DM) at baseline did not appear to modify treatment effect of death or MI at a median 4.6 years follow-up, although interaction p-values were not reported. <u>Outcome: Rate of death or MI over median 4.6 year follow-up (PCI vs. OMT)</u> -MetS/-DM: 15% (60/391) vs. 13% (49/374), RR = 1.17 (95% CI, 0.83 to 1.66), p = 0.38 +MetS/-DM: 18% (65/368) vs. 15% (52/349), RR = 1.19 (95% CI, 0.85 to 1.66), p = 0.32 -MetS/+DM: 16% (10/62) vs. 17% (10/59), RR = 0.95 (95% CI, 0.43 to 2.12), p = 0.90 +MetS/+DM: 25% (75/305) vs. 25% (86/340), RR = 0.97 (95% CI, 0.74 to 1.27), p = 0.84 **Anginal severity§ (1st vs. 2nd vs. 3rd tertile) (Zhang 2011)** Baseline anginal severity (comprised of the individual domains physical limitation, angina frequency, or	

Trial	Differential efficacy	Differential safety
	quality of life domains as measured by the Seattle Angina Questionnaire) did not appear to modify the treatment effect of composite outcome of death or MI at a median 4.6 years follow-up, although interaction p-values were not reported. It is not indicated if this subgroup analysis was conducted post hoc or a priori. **Anginal severity domain: Physical limitation (1st vs. 2nd vs. 3rd tertile) (Zhang 2011) (Table 1)** Baseline physical limitation appears to modify treatment effect of the single outcomes of event rate of death (p for interaction < 0.0001), MI (p for interaction = 0.0007), stroke (p for interaction < 0.0001), and the composite outcome of event rate of death + MI (p for interaction < 0.0001) at median 4.6 years follow-up. It is not stated if this subgroup analysis was conducted post hoc or a priori. <u>Outcome: Event rate of death at median 4.6 years (PCI vs. OMT)</u> 1st tertile: 11.3% (36/319) vs. 11.9% (38/320) 2nd tertile: 5.3% (17/322) vs. 7.2% (21/291) 3rd tertile: 2.3% (8/298) vs. 4.9% (16/328) P for interaction < 0.0001 <u>Outcome: Event rate of MI at median 4.6 years (PCI vs. OMT)</u> 1st tertile: 16.0% (51/319) vs. 16.6% (53/320) 2nd tertile: 12.4% (40/322) vs. 9.6% (28/291) 3rd tertile: 9.4% (28/298) vs. 9.8% (32/328) P for interaction = 0.0007 <u>Outcome: Event rate of death and nonfatal MI at median 4.6 years (PCI vs. OMT)</u> 1st tertile: 25.7% (82/319) vs. 26.6% (85/320) 2nd tertile: 17.1% (55/322) vs. 15.8% (46/291) 3rd tertile: 11.4% (34/298) vs. 13.1% (43/328) P for interaction < 0.0001 <u>Outcome: Event rate of stroke at median 4.6 years (PCI vs. OMT)</u> 1st tertile: 5.0% (16/319) vs. 2.2% (7/320) 2nd tertile: 0.6% (2/322) vs. 1% (3/291) 3rd tertile: 0.3% (1/298) vs. 1.2% (4/328) P for interaction < 0.0001	

Trial	Differential efficacy	Differential safety
	Outcome: Event rate of death/MI/stroke at median 4.6 years (PCI vs. OMT) 1st tertile: 28.2% (90/319) vs. 28.4% (91/320) 2nd tertile: 17.4% (56/322) vs. 16.5% (48/291) 3rd tertile: 11.7% (35/298) vs. 14.0% (46/328) P for interaction < 0.0001 **Anginal severity domain: Anginal frequency (1st vs. 2nd vs. 3rd tertile) (Zhang 2011) (Suppl Table 1)** Baseline angina frequency appears to modify treatment effect of the single outcome of MI event rate (p for interaction = 0.003); the composite outcomes of death/MI/stroke event rate (p for interaction < 0.0001) and death/MI event rate (p for interaction = 0.0004). It does not appear to modify the treatment effect for the single outcomes of death event rate (p for interaction = 0.08) or stroke event rate (p for interaction = 0.07). Follow-up for all these outcomes was at median 4.6 years. It is not stated if this subgroup analysis was conducted post hoc or a priori. Outcome: Event rate of MI at median 4.6 years (PCI vs. OMT) 1st tertile: 19.1% (58/304) vs. 11.3% (30/265) 2nd tertile: 9.9% (36/362) vs. 15.1% (58/385) 3rd tertile: 9.2% (28/303) vs. 8.8% (28/319) P for interaction = 0.003 Outcome: Death and nonfatal MI at median 4.6 years (PCI vs. OMT) 1st tertile: 28% (85/304) vs. 11.3% (30/265) 2nd tertile: 14.6% (53/362) vs. 15.1% (58/385) 3rd tertile: 13.9% (42/303) vs. 8.8% (28/319) P for interaction = 0.0004 Outcome: Death/MI/Stroke at median 4.6 years (PCI vs. OMT) 1st tertile: 29.9% (91/304) vs. 19.6% (52/265) 2nd tertile: 15.2% (55/362) vs. 23.1% (89/385) 3rd tertile: 14.5% (44/303) vs. 16.3% (52/319) P for interaction < 0.0001 **Anginal severity domain: Quality of Life (1st vs. 2nd vs. 3rd tertile) (Zhang 2011) (Suppl Table 2)** Baseline quality of life appears to modify treatment effects of the single outcomes MI event rate (p for interaction = 0.003) and stroke event rate (p for interaction = 0.0007), and the composite outcomes	

Trial	Differential efficacy	Differential safety
	death/MI (p for interaction = 0.0008) and death/MI/stroke (p for interaction < 0.0001), but not the treatment effect of single outcome death event rate (p for interaction = 0.26). Follow-up for all these outcomes was at median 4.6 years. It is not stated if this subgroup analysis was conducted post hoc or a priori. Outcome: MI at median 4.6 years (PCI vs. OMT) First tertile: 15.9% (51/321) vs. 14.7% (46/314) Second tertile: 12.5% (42/335) vs. 12.2% (39/319) Third tertile: 8.9% (27/313) vs. 9.2% (30/325) P for interaction = 0.003 Outcome: Stroke at median 4.6 years (PCI vs. OMT) First tertile: 4.4% (14/321) vs. 2.2% (7/314) Second tertile: 1.5% (5/335) vs. 0.6% (2/319) Third tertile: 0% (0/313) vs. 1.5% (5/325) P for interaction = 0.0007 Outcome: Death/MI at median 4.6 years (PCI vs. OMT) First tertile: 22.7% (73/321) vs. 23.6% (74/314) Second tertile: 18.5% (62/335) vs. 16.9% (54/319) Third tertile: 16.3% (53/313) vs. 0.36% (n NR) P for interaction = 0.0008 Outcome: Death/MI/stroke at median 4.6 years (PCI vs. OMT) First tertile: 25.2% (81/321) vs. 25.2% (79/314) Second tertile: 9.1% (64/335) vs. 17.6% (56/319) Third tertile: 13.7% (43/313) vs. 17.5% (57/325) P for interaction < 0.0001 **Anginal severity domain: Quality of Life (1st vs. 2nd vs. 3rd tertile) (Zhang 2011) (Suppl Table 1)** Baseline SAQ QoL score ***may*** modify treatment in terms of the composite outcome of death and nonfatal MI through median of 4.6 years, however interaction p-values were not reported. It is not stated if this subgroup analysis was conducted post hoc or a priori. Outcome: Death/MI at median 4.6 years (PCI vs. OMT)	

Trial	Differential efficacy	Differential safety
	1st tertile: 22.7% (73/321) vs. 23.6% (74/314); RD –0.8% (–7.4% to 5.7%); RR 0.97 (0.73 to 1.28) (p=0.805) 2nd tertile: 18.5% (62/335) vs. 16.9% (54/319); RD 1.6% (–4.3% to 7.4%); RR 1.09 (0.79 to 1.52) (p=0.597) 3rd tertile: 16.3% (53/313) vs. 0.36% (10/325); RD 13.9% (9.3% to 18.4%); RR 5.50 (2.85 to 10.62) (p<0.001) P for interaction NR **Ischemia severity§ (no to mild ischemia vs. moderate to severe ischemia) (Shaw 2012)** Post hoc analysis of baseline ischemia severity (no to mild ischemia vs. moderate to severe ischemia) does not appear to modify treatment effect for the composite outcome of death/MI (p for interaction = 0.65) at a median follow-up of 4.6 years. Post hoc analysis of baseline ischemia severity does not appear to modify treatment effect for the single outcomes of death or MI at a median 4.6 years follow-up, although interaction p-values were not reported. <u>Outcome: death at median 4.6 years (PCI vs. OMT)</u> None/mild ischemia: 7.2% (33/459) vs. 9.5% (43/454); HR 0.70 (95% CI 1.13 to 9.43), p=0.14 Moderate/severe ischemia: 7.2% (16/223) vs. 9.0% (22/245); HR 0.62 (95% CI 0.30 to 1.28), p=0.20 P for interaction NR <u>Outcome: MI at median 4.6 years (PCI vs. OMT)</u> None/mild ischemia: 12.4% (57/459) vs. 9.9% (45/454); HR 1.21 (95% CI 0.80 to 1.83), p=0.36 Moderate/severe ischemia: 16.6% (37/223) vs. 11.8% (29/245); HR 1.37 (95% CI 0.82 to 2.26), p=0.23 P for interaction NR <u>Outcome: Death/MI at median 4.6 years (PCI vs. OMT)</u> None/mild ischemia: 17.9% (82/459) vs. 17.6% (80/454); HR 0.99 (95% CI 0.72 to 1.38), p=0.97 Moderate/severe ischemia: 21.5% (48/223) vs. 19.2% (47/245); HR 1.08 (95% CI 0.71 to 1.65), p=0.72 P for interaction NR **Chronic kidney disease status (+CKD vs. –CKD)** (Sedlis 2013)** Post hoc longitudinal analysis indicated that chronic kidney disease status was not related to change in percentage of clinically significant improvement over follow-up time for patients treated with either PCI plus OMT or OMT alone for any of the SAQ domains (p>0.08 for all interactions treatment status X CKD status) over a median follow-up of 4.6 years. Mean SAQ scores were also evaluated and are reported in	

Trial	Differential efficacy	Differential safety
	Table 2. **Chronic kidney disease status (+CKD vs. –CKD)** (Sedlis 2009)** Post hoc analysis indicated that chronic kidney disease status did not modify treatment effect over median 4.6 years follow-up with respect to the individual outcomes of death (p for interaction = 0.78), cardiac mortality (p for interaction = 0.39), MI (p for interaction = 0.42), stroke (p for interaction = 0.75), revascularization (p for interaction = 0.68), hospitalization for new chronic heart failure (p for interaction = 0.84), repeat catheterization (p for interaction = 0.80), or cardiac hospitalization (p for interaction = 0.51); nor the composite outcome of death/MI/hospitalization for acute coronary syndromes (p for interaction = 0.68). **Modified Duke Jeopardy score, ≥50% diameter stenosis threshold (Score 0, 1 vs. Score 2, 3 vs. Score 4, 5, 6)†† (Mancini 2009)** Post hoc analysis indicated that baseline Modified Duke Jeopardy score at a ≥50% diameter stenosis threshold did not appear to modify treatment effect (p for interaction = 0.06‡§§) of the composite outcome of death/nonfatal MI (excluding periprocedural MI) rate over a median 4.6 years follow-up. <u>Outcome: Death/Nonfatal MI (excluding periprocedural MI) rate at median 4.6 years (PCI vs. OMT)</u> Score 0, 1: 12.3% vs. 12.6%; HR = 0.99 (95% CI, 0.62 to 1.58) Score 2, 3: 12.5% vs. 17.8%; HR = 0.66 (95% CI, 0.48 to 0.92) Score 4, 5, 6: 21.7% vs. 21.0%; HR = 1.27 (95% CI, 0.80 to 1.82) P for interaction 0.06 **Duke Jeopardy score, ≥70% diameter stenosis threshold (Score 0, 1 vs. Score 2, 3 vs. Score 4, 5, 6)†† (Mancini 2009)** Post hoc analysis indicated that baseline Modified Duke Jeopardy score at a ≥70% diameter stenosis threshold did not appear to modify treatment effect (p for interaction = 0.98‡§§) of the composite outcome of death/nonfatal MI (excluding periprocedural MI) rate over a median 4.6 years follow-up. **Vessel Disease (VD) (0, 1 VD vs. 2 VD vs. 3 VD) (Mancini 2009)** Post hoc analysis indicated that baseline number of diseased vessels did not appear to modify treatment effect (p for interaction = 0.96‡§§) of the composite outcome of death/nonfatal MI (excluding periprocedural MI) rate over a median 4.6 years follow-up. **Subgroup of Patients Undergoing Exercise Stress Testing (Myocardial Perfusion Single Photon Emission**	

Trial	Differential efficacy	Differential safety
	Computerized Tomography) (Shaw 2008) Outcome: Exertional chest pain, pretreatment (PCI vs. OMT)§‡‡: 30% vs. 43%, p = 0.26 Outcome: Exertional chest pain, at 6 to 18 months follow-up (mean=374 ± 50 days) (PCI vs. OMT)§‡‡: 11% vs. 28%, p = 0.06 PCI paired within-treatment p = 0.007 OMT paired within-treatment p = 0.15 Outcome: No residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT)§‡‡: 15.2% (24/159) vs. 8.8% (14/155) Outcome: Minimal residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT)§‡‡: 40% (64/159) vs. 39.8% (62/155) Outcome: Mild residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT)§‡‡: 29% (46/159) vs. 24.4% (38/155) Outcome: Moderate to severe residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT)§‡‡: 15.8% (25/159) vs. 27% (42/155) P for PCI vs. OMT = 0.047 P for no ischemia vs. with ischemia = 0.06 P for moderate to severe vs. no to mild ischemia = 0.02 Outcome: ≥5% Reduction to no ischemia in patients with residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT): 31.4% (17/53) vs. 17.8% (5/29) Outcome: ≥5% Reduction to minimal ischemia in patients with residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT): 26.6% (14/53) vs. 28.5% (8/29) Outcome: ≥5% Reduction to mild ischemia in patients with residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT): 26.5% (14/53) vs. 43% (12/29) Outcome: ≥5% Reduction to moderate to severe ischemia in patients with residual ischemia at 6 to 18 months (mean=374 ± 50 days) (PCI vs. OMT): 5.5% (3/53) vs. 10.7% (3/29) P for PCI vs. OMT = 0.04 P for no ischemia vs. with ischemia = 0.006	

Trial	Differential efficacy	Differential safety
	P for moderate to severe vs. no to mild ischemia = 0.32 **Clinically Significant Increase (change >20 points from baseline) in Anginal Severity: Angina Frequency Domain, Baseline Tertile‡ (1st vs. 2nd vs. 3rd) (Weintraub 2008) (Table 3)** Post hoc analysis indicated that baseline Anginal Severity tertile modifies the treatment effect of clinically significant increases in anginal frequency scores at 36 months follow-up (p for interaction < 0.001). No N's were reported for these outcomes. Outcome: Clinically significant increase from baseline in Anginal Frequency Domain (PCI vs. OMT) *6 months follow-up* 1st tertile: 85% vs. 81%, p = 0.26 2nd tertile: 64% vs. 56%, p = 0.04 3rd tertile: 0% vs. 0%, p NC *12 months follow-up* 1st tertile: 86% vs. 84%, p = 0.56 2nd tertile: 67% vs. 58%, p = 0.04 3rd tertile: 0% vs. 0%, p NC *36 months follow-up* 1st tertile: 92% vs. 88%, p = 0.14 2nd tertile: 71% vs. 64%, p = 0.11 3rd tertile: 0% vs. 0%, p NC Among all tertiles, p for interaction for clinically significant improvement for time x baseline tertile x treatment group < 0.001 **Anginal Severity: Angina Frequency Scores, Baseline Tertile Scores‡ (1st vs. 2nd vs. 3rd) (Weintraub 2008) (Table 3/Table 7S)** Post hoc analysis indicated that baseline anginal severity modifies the treatment effect of angina frequency scores at 36 months follow-up (mean p for interaction = 0.008). No N's were reported for these raw scores. **Anginal Severity: Physical Limitation Tertile Scores, Baseline Tertile‡ (1st vs. 2nd vs. 3rd) (Weintraub 2008) (Table 8S)** Post hoc analysis indicated that baseline anginal severity modifies the treatment effect of physical limitation scores at 36 months follow-up (mean p for interaction <0.0001). No N's were reported for	

Trial	Differential efficacy	Differential safety
	these raw scores. **Anginal Severity: Quality of Life Tertile Scores, Baseline Tertile‡ (1st vs. 2nd vs. 3rd) (Weintraub 2008) (Table 9S)** Post hoc analysis indicated that baseline anginal severity modifies the treatment effect of quality of life scores at 36 months follow-up (mean p for interaction <0.0001). No N's were reported for these raw scores. **Clinically Significant Increase (change ≥8 points from baseline) in Anginal Severity: Physical Limitation Domain, Baseline Tertile‡ (1st vs. 2nd vs. 3rd) (Weintraub 2008) (Table 10S)** Post hoc analysis indicated that baseline anginal severity tertile modifies the treatment effect of clinically significant increases in physical limitation scores at 36 months follow-up (p for interaction <0.0001). No N's were reported for these outcomes. Outcome: Clinically significant increase from baseline in Physical Limitation Domain (PCI vs. OMT) *6 months follow-up* 1st tertile: 74% vs. 62%, p = 0.006 2nd tertile: 61% vs. 52%, p = 0.054 3rd tertile: 19% vs. 17%, p = 0.56 *12 months follow-up* 1st tertile: 71% vs. 69%, p = 0.65 2nd tertile: 56% vs. 52%, p = 0.42 3rd tertile: 17% vs. 14%, p = 0.28 *36 months follow-up* 1st tertile: 72% vs. 74%, p = 0.65 2nd tertile: 52% vs. 56%, p = 0.46 3rd tertile: 13% vs. 16%, p = 0.50 Among all tertiles, p for interaction < 0.0001 **Clinically Significant Increase (change >16 points from baseline) in Anginal Severity: Quality of Life Domain, Baseline Tertile‡ (Weintraub 2008) (Table 11S)** Post hoc analysis indicated that baseline anginal severity tertile modifies the treatment effect of clinically significant increases in quality of life scores at 36 months follow-up (p for interaction <0.0001). No N's were reported for these outcomes. Outcome: Clinically significant increase from baseline in Quality of Life Domain (PCI vs. OMT) *6 months follow-up*	

Trial	Differential efficacy	Differential safety
	1st tertile: 88% vs. 78%, p = 0.0029 2nd tertile: 73% vs. 64%, p = 0.11 3rd tertile: 30% vs. 30%, p = 0.96 *12 months follow-up* 1st tertile: 89% vs. 88%, p = 0.80 2nd tertile: 72% vs. 71%, p = 0.79 3rd tertile: 34% vs. 30%, p = 0.32 *36 months follow-up* 1st tertile: 93% vs. 90%, p = 0.31 2nd tertile: 78% vs. 81%, p = 0.51 3rd tertile: 36% vs. 33%, p = 0.55 Among all tertiles, p for interaction <0.0001 **Anginal Severity (SAQ) Domains, baseline covariates (Weintraub 2008) (Table 12S)** Post hoc analysis indicated that the baseline covariates of age, gender, race, diabetes, prior MI, prior CABG, and CCS angina class did not appear to modify the treatment effects of SAQ scores in the domains of physical limitation, treatment satisfaction, and quality of life (p for interaction >0.05 for all) at 36 months follow-up. Post hoc analysis indicated that the baseline covariate of gender modified the treatment effect of SAQ scores in the angina stability domain (p for interaction = 0.0041), and that the baseline covariate of prior CABG modified the treatment effect of SAQ scores in the angina frequency domain (p for interaction = 0.0113) at a median of 4.6 years follow-up. The baseline covariates of age, race, diabetes, prior MI, prior CABG, and CCS angina class did not appear to modify the treatment effects of SAQ scores in the angina stability domain (p for interaction > 0.05 for all). The baseline covariates of age, gender, race, diabetes, prior MI, and CCS angina class did not appear to modify the treatment effects of SAQ scores in the angina frequency domain (p for interaction > 0.05 for all). **RAND-36 Domains, baseline covariates (Weintraub 2008) (Table 15S)** Post-hoc analysis indicated that the baseline covariates of age, gender, race, diabetes, prior MI, prior CABG, or CCS angina class did not modify the treatment effect for RAND-36 scores in any domain at a 36 months follow-up. RAND-36 domains include physical functioning, role limitation- physical, role limitation- emotional, energy/fatigue, emotional well-being, social functioning, pain, and general health.	
Hambrecht	NR	NR

Trial	Differential efficacy	Differential safety
Hambrecht 2004, Walther 2008		
MASS II Hueb 2004, Favarato 2007, Lima 2013, Rezende 2013, Hueb 2010, Hueb 2007, Soares 2006, Vieira 2012, Lopes 20082013	**Subgroup: Sex (specified a priori)** No formal test for interaction was reported and it does not appear that sex modifies treatment effect with respect to the composite outcome of Mortality/MI/refractory angina requiring revascularization(through 10 years) (Hueb 2010) (interaction p-value NR) *Outcome: Mortality, MI, refractory angina req. revasc.(through 10 years) (Hueb 2010)* • Male: HR = 1.13 (95% CI 0.84 to 1.53), p = 0.410 • Female: HR = 1.57 (95% CI 1.01 to 2.46), p = 0.047 **Subgroup: Age (specified a priori)** No formal test for interaction was reported and it does not appear that baseline age modifies treatment effect: *Outcome: Survival (through 10 years)* • ≥65 years: 52% (35/68) vs 57% (39/68), RR = 0.90 (95% CI 0.66 to 1.22), p = 0.49 • <65 years: 81% (111/137) vs 67% (90/135), RR = 1.22 (95% CI 1.05 to 1.40) p < 0.01 *Outcome: New revascularizations (through 10 years)* • ≥65 years: 58% (39/68) vs 59% (40/68), RR = 0.98 (95% CI 0.73 to 1.30), p = 0.86 • <65 years: 62% (85/137) vs 60% (81/135), RR = 1.06 (95% CI 0.79 to 1.41), p =0.69 *Outcome: Free from MI (through 10 years)* • ≥65 years: 77% (52/68) vs 82% (56/68), RR = 0.93 (95% CI 0.78 to 1.10), p = 0.40 • < 65 years: 92% (126/137) vs 79% (107/135), RR = 1.16 to (1.05 to 1.28), p = 0.40 *Outcome: Mortality, MI, refractory angina req. revasc.(through 10 years) (Hueb 2010)* • ≤65 years: HR = 1.47 (95% CI 1.08 to 2.01), p = 0.020 • >65 years: HR = 0.97 (95% CI 0.65 to 1.47), p = 0.90 **Subgroup: Diabetes (specified a priori)**	NR

Trial	Differential efficacy	Differential safety
	No formal test for interaction was reported, and it does not appear that baseline diabetic status modified treatment effect: *Outcome: Mortality (through 1 year) (Soares 2006)* • Diabetics: 5.4% (3/56) vs 2.7% (2/75), RR = 2.01 (95% CI 0.35 to 11.62), p = 0.43 • Non Diabetics: 5.4% (8/149) vs 1.6% (2/128), RR = 3.44 (95% CI 0.74 to 15.90), p = 0.09 *Outcome: Mortality (through 5 year) (Soares 2006)* • Diabetics: 16% (9/56) vs 25% (19/75), RR = 0.63 (95% CI 0.31 to 1.30), p = 0.20 • Non Diabetics: 13% (19/149) vs 13% (16/128), RR = 1.02 (95% CI 0.55 to 1.90), p = 0.95 *Outcome: Mortality (through 10 years) (Lima 2013)* • Diabetics: 31.3% (20/64) vs 37.5% (33/88), RR = 0.83 (95% CI 0.53 to 1.31), p = 0.43 • Non Diabetics: 20.6% (29/141) vs 26.1% (30/115), RR = 0.79 (95% CI 0.50 to 1.23), p = 0.30 *Outcome: Cardiac Mortality (through 10 years) (Lima 2013)* • Diabetics: 18.8% (12/64) vs 26.1% (23/88), RR = 0.72 (95% CI 0.39 to 1.33), p = 0.29 • Non Diabetics: 12.1% (17/141) vs 16.5% (19/115), RR = 0.73 (95% CI 0.40 to 1.34), p = 0.31 **Subgroup: Metabolic Syndrome** In the subgroup of patients for whom baseline metabolic syndrome status was known, it appeared that metabolic syndrome did not modify treatment effect with respect to 2-year mortality, although no formal test for interaction was performed. The patient numbers could not be calculated as the study did not report the number of patients in each subgroup. *Outcome: Mortality (through 2 years)* • Metabolic syndrome: 11.2% vs 10.6% • No Metabolic syndrome: 3% vs 5.2% **Subgroup: Hypertension (Hueb 2010) (specified a priori)** No formal test for interaction was reported and it does not appear that hypertension modifies treatment effect with respect to the composite outcome of Mortality/MI/refractory angina requiring	

Trial	Differential efficacy	Differential safety
	revascularization(through 10 years) (Hueb 2010) (interaction p-value NR) *Outcome: Mortality, MI, refractory angina req. revasc (through 10 years):* • No hypertension: HR = 0.99 (95% CI 0.67 to 1.47), p = 0.970 • Hypertension: HR = 1.53 (95% CI 1.11 to 2.10), p = 0.010 **Subgroups: Smoking status, previous MI, diabetes (Hueb 2010) (specified a priori)** No formal test for interaction was reported and it does not appear that smoking status (no smoking, smoking), previous MI (no, yes), or diabetes (yes, no) modifies treatment effect with respect to the composite outcome of Mortality/MI/refractory angina requiring revascularization(through 10 years) (Hueb 2010) (interaction p-value NR)	

* The BARI-2D angiographic risk score was based on the predicted probability of experiencing a death, MI, or stroke by 3 years based on the following candidate variables: myocardial jeopardy index, number of diseased vessesl ≥50% stenosis, location of diseased vessels, proximal LAD disease ≥50%, presence of 1 or more proximal lesions ≥50%, total number of lesions ≥20%, history of prior coronary revasc, LVEF <50%, presence ofd total occlusions, and presence of class C lesions. The top tertile of patients were considered high risk.

† Framingham risk score includes sex, age, history of diabetes mellitus, total cholesterol/high-density lipoprotein, and the additional variables of systolic blood pressure and current smoking in women. Patients in the top tertile were considered high risk.

‡ Anginal severity was determined from 3 domains of the Seattle Angina Questionnaire—physical limitation, anginal frequency, and QoL. The cut points for each tertile for the physical limitation domain were <53, 58 to 81, >81; for anginal frequency, <50, 50 to 80, >80; and for quality of life, <42, 42 to 59, >59. Higher tertile indicates better health status

§ *No to mild ischemia* was defined as 0 to 2 ischemic segments and ≥3 ischemic segments defined *moderate to severe ischemia.*

** This is event rate for only the primary outcome of death + MI.

†† Seattle Angina Questionnaire. Scores reported as intention to treat excluding patients lost to follow up or those who had died. An assessment was done of only those patients who did not cross over in the first 3 months, which was the time of greatest improvement. The results of this assessment showed that from baseline to 3 months, physical limitation scores improved from 67 ± 25 to 73 ± 23, angina-frequency scores from 70 ± 26 to 80 ± 23, and quality-of-life scores from 52 ± 25 to 68 ± 23. According to the authors, these results were similar to those of the entire medical therapy group (including data for those who crossed over).

‡‡ P values represent the interaction between the treatment effects and subgroup variables.

§§ RAND-36 Score significant improvement from baseline, defined as 10 point increases for all domains. Excludes patients no longer being followed, and those who died.

*** For the SAQ, a clinically significant difference was defined as follows; **physical limitation:** 8 points**, angina stability:** 25 points**, angina frequency:** 20 points**, treatment satisfaction:** 12 points**, quality of life:** 16 points

Appendix Table G10. Summary of FAME 2 Trial (provided for context; study did not meet inclusion criteria)

Trial year (N) Funding	Inclusion and Exclusion Criteria	Length f/u Complete f/u % (n/N) Crossover % (n/N)	Patient Characteristics	Results for primary outcomes relevant to this HTA
FAME 2 N = 888* DeBruyne 2012, 2014 Multicenter (28 sites, North America and Europe) A: Fractional Flow Reserve (FFR)-Guided PCI + Optimal Medical Therapy (OMT) (n=447) B: OMT (n=441) Funding: St. Jude Medical	**Inclusion:** 1) Patients with a. stable angina pectoris (Canadian Cardiovascular Class [CCS] 1, 2, 3) b. or, angina pectoris CCS class 4 subsequently stabilized medically (minimum 7 days) or, c. atypical chest pain or no chest pain but with documented silent ischemia on non-invasive testing 2) In whom at least one stenosis is present of at least 50% in one major native epicardial coronary artery with a diameter of at least 2.5 mm and supplying viable myocardium 3) Eligible for PCI 4) Signed written informed consent obtained 5) Patients with restenosis in native	Length f/u: 2 years Complete f/u, PCI vs. OMT: 95.5% (427/447) vs. 96.8% (427/441) Crossover, 2 years; PCI to OMT: 8.1% (31/447) vs. OMT to PCI 40.6% (179/441); HR 0.16 (95% CI, 0.11 to 0.22), p<0.001	PCI vs. OMT Subgroup: None Age: 63.52 ± 9.35 vs. 63.86 ± 9.62 years Sex (% male): 79.6% (n=356) vs. 76.6% (n=338) BMI (mean ± SD): 28.29 ± 4.27 vs. 28.44 ± 4.55 Race: NR Asymptomatic angina: 11.9% (53/447) vs. 10.5% (46/440) CCS I angina: 18.3% (82/447) vs. 22.3% (98/440) CCS II angina: 45.6% (204/447) vs. 44.8% (197/440) CCS III angina: 17.9% (80/447) vs. 14.8% (65/440) CCS class IV, stabilized: 6.3% (28/447) vs. 7.7% (34/440) Silent ischemia: 16.3% (73/447) vs. 7.7% (34/440) Diabetes: 27.5% (123/557) vs. 26.5% (117/441) Hyperlipidemia: 73.8% (330/447) vs. 78.9% (348/441) Hypertension: 77.6% (347/447) vs. 77.8% (343/441) Prior MI: 37.1% (164/442) vs. 37.8% (165/436) Prior PCI in target vessel: 17.9% (80/447) vs. 17.2% (76/441)	**PRIMARY** • Death (all cause) ○ To 12 months HR 0.33 (95% CI, 0.03 to 3.17) ○ To 24 months HR 0.74 (0.26 to 2.14) • Cardiac death ○ To 12 months HR 0.96 (0.06 to 15.17) ○ To 24 months HR 0.99 (0.20 to 4.90) • Myocardial infarction (any after periprocedural) ○ To 12 months HR 1.05 (0.51 to 2.19) ○ To 24 months HR 0.85 (0.50 to 1.45) • Stroke ○ To 12 months HR 0.49 (0.04 to 5.50) ○ To 24 months HR 1.74 (0.51 to 5.94) **INTERMEDIATE/SECONDARY** Revascularization • Any ○ To 12 months HR 0.14 (95% CI, 0.08 to 0.26) ○ To 24 months HR 0.16 (0.11 to 0.22) • Urgent ○ To 12 months HR 0.13 (0.06 to 0.30) ○ To 24 months HR 0.23 (0.14 to 0 .38) • Non-urgent ○ To 12 months HR 0.17 (0.08 to 0.39) ○ To 24 months HR 0.13(0.08 to 0.22) **SAFETY** ○ Definite stent thrombosis: NOT REPORTED ○ Definite OR probable stent thrombosis: ▪ To 12 months HR 4.98 (0.59 to 42.25);

Trial year (N) Funding	Inclusion and Exclusion Criteria	Length f/u Complete f/u % (n/N) Crossover % (n/N)	Patient Characteristics	Results for primary outcomes relevant to this HTA
	coronary arteries; patients with previous stents and restenosis; and patients sustaining a STEMI or a NSTEMI more than one week ago may be included. 6) Total occlusion - included if this vessel supplies viable myocardium, and if recanalization is deemed likely and useful by the operator and if it is not the only lesion with a significant FFR. **Exclusion:** 1) Patients in whom the preferred treatment is CABG 2) Patients with left main CAD requiring revascularization 3) Patients with a recent (<1 week) STEMI or NSTEMI 4) Prior CABG 5) Contraindication to dual antiplatelet therapy		Current smoker: 19.9% (89/447) vs. 20.4% (90/441) At least one lesion in proximal or middle LAD: 62.4% (279/447) vs. 59.6% (263/441) Family history of CAD: 28.3% (216/447) vs. 46.9% (207/441) Renal insufficiency: 1.8% (8/447) vs. 2.7% (12/441) Peripheral vascular disease: 9.6% (43/447) vs. 10.7% (47/441) History of stroke or transient ischemic attack: 7.4% (33/447) vs. 6.3% (28/441) LVEF >50%: 19.6% (83/423) vs. 13.7% (56/410) Concurrent medications, baseline: *ACE inhibitors/ AT1-receptor antagonists*: 69% (308/447) vs. 70% (309/441), *beta-HMG-CoA reductase inhibitors beta-receptor antagonists*: 76% (338/447) vs. 78% (344/441), *Acetylsalicylic acid:* 87% (390/447) vs. 90% (396/441), *Statins (simvastatin, atorvastatin, fluvastatin):* 83% (370/447) vs. 82% (361/441)	more events in PCI group ▪ To 24 months HR 3.48 (0.72 to 16.8); more events in PCI group ○ Peri-procedural (≤ 30 days) complications (e.g. death, MI) (From 2014 publication) ▪ Death WITHIN 7 days only: 0% (0/447) vs. 0% (0/441) ▪ MI WITHIN 7 days only: To 24 months: 2.0% (9/447) vs. 0.2% (1/441) ▪ Urgent Revascularization WITHIN 7 days only: 0.4% (2/447) vs. 0.9% (4/441) ○ Stroke: NR ○ Cerebrovascular event (not further specified): 0.7% (3/447) vs. 0.5% (2/441) ○ Major bleeding: NR ○ Bleeding (not further specified): 4.5% (20/447) vs. 2.5% (11/441) ○ Any serious adverse event: 26.8% (120/447) vs. 25.4% (112/441) ○ Non-cardiovascular serious adverse events†: 16.1% (72/447) vs. 16.1% (71/441) ○ Serious cardiovascular events: 17.0% (120/447) vs. 25.4% (112/441) ▪ Atrial fibrillation: 1.6% (7/447) vs. 1.4% (6/441) ▪ Heart failure: 2.0% (9/447) vs. 0.7% (3/441) ▪ Syncope: 0.9% (4/447) vs. 0.7% (3/441) ▪ Chest pain: 4.7% (21/447) vs. 6.1% (27/441) ▪ Pacemaker implantation: 0.9% (4/447) vs. 0.2% (1/441) ▪ Diagnostic angiography: 5.4% (24/447) vs. 5.0% (22/441)

Trial year (N) Funding	Inclusion and Exclusion Criteria	Length f/u Complete f/u % (n/N) Crossover % (n/N)	Patient Characteristics	Results for primary outcomes relevant to this HTA
	6) LVEF <30% 7) Severe LV hypertrophy (defined as a septal wall thickness at echocardiography of more than 13 mm) 8) Planned need for concomitant cardiac surgery (e.g., valve surgery or resection of aortic or left ventricular aneurysm, etc.) 9) Extremely tortuous or calcified coronary arteries precluding FFR measurements 10) Life expectancy <2 years 11) Age <21 12) Pregnancy or intention to become pregnant during course of the trial 13) Refusal or inability to sign informed consent. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the			▪ Other (not specified): 3.4% (15/447) vs. 2.9% (13/441) **TIME FRAME "Landmark" ANALYSIS** • Death ○ To 12 months: ≤ 7d (none in either); 8 days to 24 months: RR 0.33 (95% CI, 0.03 to 3.17); no test for interaction ○ To 24 months: ≤7 days (none in either); NS different between groups in 8d to 2 years, HR 0.74 (0.26 to 2.14); no test for interaction • MI ○ To 12 months: ≤7 days: RR 7.99 (95% CI, 0.99 to 64.57) (more events in PCI, favors OMT); 8 days to 24 months: NS different, RR 0.52 (95% CI, 0.21 to 1.32); results in opposite directions, test for interaction significant (p=0.007) ○ To 24 months: ≤7 days, HR 9.01 (95% CI, 1.13 to 72.0) (more events in PCI, favors OMT); 8d to 24 months: NS different, HR 0.58 (95% CI, 0.32 to 1.05); results in opposite directions, test for interaction significant (p=0.002) • Urgent revascularization ○ To 12 months: ≤7 days, RR 0.49 (95% CI, 0.09 to 2.70); 8 days to 24 months: RR 0.10 (95% CI, 0.04 to 0.26) (more events in OMT, favors PCI); test for interaction not significant ○ To 24 months: ≤7 days NS different between groups, HR 0.49 (95% CI, 0.09 to 2.70); 8d to 24 months: HR 0.21 (95% CI, 0.12 to 0.37) (more events in OMT, favors PCI); test for interaction not significant

Trial year (N) Funding	Inclusion and Exclusion Criteria	Length f/u Complete f/u % (n/N) Crossover % (n/N)	Patient Characteristics	Results for primary outcomes relevant to this HTA
	nature, scope, and possible consequences of the trial or mental retardation or language barrier such that the patient is unable to give informed consent 14) Potential for noncompliance towards the requirements in the trial protocol (especially the medical treatment) or follow-up visits 15) Participation or planned participation in another cardiovascular clinical trial before two year follow-up is completed			**Subgroup analysis (2014 report, Supplemental Figure S3)** At 2 years follow-up, none of the following factors modified the treatment effect for the primary study endpoint: Age (>60 vs. ≤60 years, p for interaction = 0.64), gender, (male vs. female, p for interaction = 0.06), diabetes (present vs. absent, p for interaction = 0.50), history of stroke/TIA (yes vs. no, p for interaction = 0.97), history of MI (yes vs. no, p for interaction = 0.55), history of PCI (yes vs. no, p for interaction = 0.45), LVEF (≤50% vs. >50%, p for interaction = 0.57), FFR (<0.65 vs. ≥0.65, p for interaction = 0.07), diameter stenosis (≥70% vs. <70%, p for interaction = 0.96), and multivessel disease (yes vs. no, p for interaction = 0.26)

CABG: Coronary Artery Bypass Graft; FFR: Fractional Flow Reserve; HR: Hazard Ratio; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; NR: Not Reported; NS: Not Statistically Significant; OMT: Optimal Medical Therapy; PCI: Percutaneous Coronary Intervention; RR: Relative Risk; TIA: Transient Ischemic Attack

* Study also included a registry cohort (n=166) that received only OMT; populations is not included in this table.

† Defined as cerebrovascular events, peripheral vascular events, bleeding, gastrointestinal, genitourinary, infection, injury, musculoskeletal, neoplasm, renal, respiratory, and other (not further specified)

APPENDIX H. Results Tables for Key Question 2 (Safety, Efficacy, HTE)

Appendix Table H1. Subgroup analysis from the EXAMINATION trial: primary and secondary Outcomes up to 1 year of follow-up in patients age <75 and ≥75 years and with and without proximal LAD

Outcome	Subgroup	DES % (n/N)	BMS % (n/N)	Risk difference (95% CI)	Risk Ratio (95% CI)	Within-group p-value*	Between-group p-value†
Primary outcomes							
Mortality (all-cause)	Age <75 years	1.3% (8/638)	1.6% (10/615)	–0.4% (–1.7% to 1.0%)	0.8 (0.3 to 1.9)	0.58	<0.001
	Age ≥75 years	15.9% (18/113)	12.1% (16/132)	3.8% (–4.9% to 12.6%)	1.3 (0.7 to 2.5)	0.39	
	Proximal LAD	4.4% (7/158)	6.8% (9/132)	–2.4% (–7.8% to 3.0%)	0.6 (0.2 to 1.7)	0.38	0.03
	Non-Proximal LAD	3.0% (18/593)	2.8% (17/615)	0.3% (–1.6% to 2.2%)	1.1 (0.6 to 2.1)	0.78	
Mortality (cardiac)	Age <75 years	1.3% (8/638)	1.0% (6/615)	0.3% (–0.9% to 1.4%)	1.3 (0.4 to 3.7)	0.64	<0.001
	Age ≥75 years	14.2% (16/113)	11.4% (15/132)	2.8% (–5.6% to 11.2%)	1.2 (0.6 to 2.4)	0.51	
	Proximal LAD	3.8% (6/158)	4.5% (6/132)	–0.8% (–5.4% to 3.9%)	0.8 (0.3 to 2.5)	0.75	0.12
	Non-Proximal LAD	2.9% (17/593)	2.4% (15/615)	0.4% (–1.4% to 2.2%)	1.2 (0.6 to 2.3)	0.64	
Any MI	Age <75 years	0.6% (4/638)	1.3% (8/615)	–0.7% (–1.8% to 0.4%)	0.5 (0.1 to 1.6)	0.22	0.35
	Age ≥75 years	1.8% (2/113)	1.5% (2/132)	0.3% (–3.0% to 3.5%)	1.2 (0.2 to 8.2)	0.88	
	Proximal LAD	0.6% (1/158)	0.8% (1/132)‡	–0.1% (–2.1% to 1.8%)	0.8 (1.0 to 13.2)	0.90	1.0
	Non-Proximal LAD	0.8% (5/593)	1.3% (8/615)	–0.5% (–1.6% to 0.7%)	0.6 (0.2 to 2.0)	0.44	
Target vessel MI	Age <75 years	0.5% (3/638)	1.1% (7/615)	–0.7% (–1.7% to 0.3%)	0.4 (0.1 to 1.6)	0.18	0.51
	Age ≥75 years	0.9% (1/113)	1.5% (2/132)	–0.6% (–3.3% to 2.1%)	0.6 (0.1 to 6.4)	0.66	
Secondary outcomes							
TLR	Age <75 years	2.0% (13/638)	5.4% (33/615)	–3.3% (–5.4% to –1.2%)	0.4 (0.2 to 0.7)	0.002	0.53
	Age ≥75 years	2.7% (3/113)	3.0% (4/132)	–0.3% (–4.5% to 3.9%)	0.9 (0.2 to 3.8)	0.86	
	Proximal LAD	1.3% (2/158)	6.8% (9/132)	–5.6% (–10.2% to –0.9%)	0.2 (0.04 to 0.8)	0.01	0.80
	Non-Proximal LAD	2.4% (14/593)	4.6% (28/615)	–2.2% (–4.2% to –0.1%)	0.5 (0.3 to 0.9)	0.04	
TVR	Age <75 years	3.3% (21/638)	7.3% (45/615)	–4.0% (–6.5% to –1.6%)	0.5 (0.3 to 0.8)	0.001	0.98

Outcome	Subgroup	DES % (n/N)	BMS % (n/N)	Risk difference (95% CI)	Risk Ratio (95% CI)	Within-group p-value*	Between-group p-value†
	Age ≥75 years	6.2% (7/113)	4.5% (6/132)	1.7% (–4.0% to 7.3%)	1.4 (0.5 to 3.9)	0.57	
	Proximal LAD	1.3% (2/158)	7.6% (10/132)	–6.3% (–11.2% to –1.5%)	0.2 (0.03 to 0.7)	0.007	0.33
	Non-Proximal LAD	4.4% (26/593)	6.7% (41/615)	–2.3% (–4.9% to 0.3%)	0.7 (0.4 to 1.1)	0.08	

BMS = bare metal stent; CI = confidence interval; DES = drug-eluting stent; MI = myocardial infarction; RCT = randomized controlled trial; TLR = target lesion revascularization; TVR = target vessel revascularization.

*P-value for comparison of DES vs. BMS within those aged <75 years and those ≥75 years; and within those with proximal LAD and with non-proximal LAD

†P-value for comparison of age <75 years vs. ≥75 years and of proximal LAD vs. non-proximal LAD, irrespective of stent type.

‡Typo in results table of article; percent calculated incorrectly as 1.5%.

Appendix Table H2. Adverse events up to 1 year of follow-up in patients age <75 and ≥75 years and with and without proximal LAD from the EXAMINATION trial

Adverse event	Subgroup	DES % (n/N)	BMS % (n/N)	Risk difference (95% CI)	Risk Ratio (95% CI)	Within-group p-value*	Between-group p-value†
Stent thrombosis (definite)	Proximal LAD	0% (0/158)	0.8% (1/132)	–0.8% (NC)	NC	0.27	0.14
	Non-Proximal LAD	0.7% (4/593)	2.1% (13/615)	–1.4% (–2.8% to –0.1%)	0.3 (0.1 to 0.9)	0.03	
Stent thrombosis (definite/ probable)	Age <75 years	0.8% (5/638)	2.4% (15/615)	NR	0.3 (0.1 to 0.9)	0.02	0.35
	Age ≥75 years	1.8% (2/113)	3.0% (4/132)	NR	0.6 (0.1 to 3.1)	0.52	
	Proximal LAD	0.6% (1/158)	2.3% (3/132)	–1.6% (–4.5% to 1.2%)	0.3 (0.02 to 2.6)	0.23	0.60
	Non-Proximal LAD	1.0% (6/593)	2.6% (16/615)	–1.6% (–3.1% to –0.1%)	0.4 (0.2 to 0.9)	0.04	
Bleeding (major)	Age <75 years	0.9% (6/638)	1.3% (8/615)	NR	0.7 (0.3 to 2.1)	0.54	0.09
	Age ≥75 years	2.7% (2/113)	2.3% (3/132)	NR	0.8 (0.1 to 4.6)	0.78	
	Proximal LAD	1.9% (3/158)	0.8% (1/132)	1.1% (–1.5% to 3.7%)	2.5 (0.3 to 23.8)	0.41	0.94
	Non-Proximal LAD	1.0% (6/593)	1.6% (10/615)	–0.6% (–1.9% to 0.7%)	0.6 (0.2 to 1.7)	0.35	
Bleeding (minor)	Age <75 years	2.4% (15/638)	3.7% (23/615)	NR	0.6 (0.3 to 1.2)	0.15	0.07
	Age ≥75 years	5.3% (6/113)	5.3% (7/132)	NR	1.0 (0.3 to 3.0)	0.99	
	Proximal LAD	0.7% (2/158)	1.4% (4/132)	–1.8% (–5.2% to 1.6%)	0.4 (0.1 to 2.2)	0.29	0.16
	Non-Proximal LAD	3.2% (19/593)	4.2% (26/615)	–1.0% (–3.2% to 1.1%)	0.8 (0.4 to 1.4)	0.35	

BMS = bare metal stent; CI = confidence interval; DES = drug-eluting stent; MI = myocardial infarction; RCT = randomized controlled trial; TLR = target lesion revascularization; TVR = target vessel revascularization.

*P-value for comparison of DES vs. BMS within those aged <75 years and those ≥75 years; and within those with proximal LAD and with non-proximal LAD

†P-value for comparison of age <75 years vs. ≥75 years and of proximal LAD vs. non-proximal LAD, irrespective of stent type

Appendix Table H3. Drug-eluting versus bare metal stenting for stable or unstable angina: Efficacy and Safety Outcomes

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
Zotarolimus Trials							
ENDEAVOR II Eisenstein 2009, Fajadet 2006, Fajadet 2010	**All-cause death** 1 year 1.4% (8/590) vs. 0.7% (4/590), p=0.39, RR = 2.00 (95% CI 0.61 to 6.61), p = 0.25 4 years * 5.0% (29/583) vs. 5.2% (30/584), p=0.90; RR = 0.97 (95% CI 0.59 to 1.59), p = 0.8991 5 years 6.2% (36/577) vs. 7.6% (44/582), p=0.42; RR = 0.83 (95% CI 0.54 to 1.26), p = 0.38 **Cardiac death** 1 year 1.0% (6/590) vs. 0.7% (4/590), p= 0.75; RR = 1.50 (95% CI 0.43 to 5.29), p = 0.53 5 years 3.1% (18/577) vs. 3.6% (21/582), p= 0.75; RR = 0.86	**Nonfatal MI** 4 years * 3.2% (19/583) vs. 4.4% (26/584), p=0.29; RR = 0.73 (95% CI 0.41 to 1.31), p = 0.29 **Any MI (Q- or non-Q wave)†** (all target vessel MIs) 1 year 2.7% (16/590) vs. 3.9% (23/590), p=0.33; RR = 0.70 (95% CI 0.37 to 1.30), p = 0.2545 5 years 3.8% (22/577) vs. 4.8% (28/582), p=0.47; RR = 0.79 (95% CI 0.46 to 1.37), p = 0.40 **Q-wave MI†** (all		**TVR** 1 year 7.5% (44/590) vs. 14.1% (83/590), p<0.001; RR= 0.53 (95% CI 0.37 to 0.75), p < 0.01 4 years *‡ *Total*: 10.4% (61/583) vs. 21.5% (126/584), RD= 11.1 (95% CI -16.0 to -6.1), RR= 0.49 (95% CI 0.37 to 0.64); p<0.001 *PCI*: 9.8% (57/583) vs. 19.8% (116/584), RD= 10.0 (95% CI -14.7 to -5.3), RR= 0.49 (95% CI 0.37 to 0.66); p<0.001 *CABG*: 0.7% (4/583) vs. 1.7% (10/584); RD = 1.1 (95% CI -2.3 to 0.2), RR = 0.40 (95% CI 0.13 to 1.27); p=0.10 5 years 10.7% (62/577) vs.	**Death or MI** 4 years * 7.9% (46/583) vs. 9.0% (53/584), p=0.47; RR= 0.87, (95% CI 0.60 to 1.27), p = 0.47 **Death or MI or TVR** 4 years * 15.3% (89/583) vs. 24.4% (142/584), p<0.001; RR= 0.63 (95% CI 0.49 to 0.80), p < 0.01 **Death, MI, emergent CABG, or TLR** 1 year 8.8% (52/590) vs. 15.6% (92/590), p<0.001; RR= 0.57 (95% CI 0.41 to 0.78), p < 0.01 5 years 15.4% (89/577) vs. 24.6% (143/582), p<0.001; RR= 0.63 (95% CI 0.49 to 0.80), p < 0.01 **Target vessel failure-TVR, recurrent Q- or non–Q-wave MI, or cardiac death that**	**Stroke (not further defined)** 4 years * 1.7% (10/583) vs. 1.5% (9/584), p=0.81; RR = 1.11 (95% CI 0.46 to 2.72), p = 0.81	**Stent Thrombosis** *(protocol-defined)§* Early (0-30 days): 0.5% (3/577) vs. 1.2% (7/582), p=0.34; RR = 0.43 (95% CI 0.11 to 1.66), p = 0.21 Late (31-12 mos.): 0% (0/577) vs. 0% (0/582), RR = NC Very late (>12 mos.): 0% (0/577) vs. 0.2% (1/582), p=1.0; RR = NC Any: 0.5% (3/577) vs. 1.4% (8/582), p=0.34; RR = 0.38 (95% CI 0.10 to 1.42), p = 0.13

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
	(95% CI 0.47 to 1.61), p = 0.65	target vessel MIs) <u>1 year</u> 0.3% (2/590) vs. 0.8% (5/590), p=0.45; RR = 1.00 (95% CI 0.14 to 7.08), p = 1.00 <u>5 years</u> 0.3% (2/577) vs. 1.2% (7/582), p=0.18; RR = 0.29 (95% CI 0.06 to 1.38), p = 0.10 **Non-Q-wave MI†** (all target vessel MIs) <u>1 year</u> 2.4% (14/590) vs. 3.1% (18/590), p=0.59; RR = 0.78 (95% CI 0.39 to 1.55), p = 0.47 <u>5 years</u> 3.5% (20/577) vs. 3.6% (21/582), p=1.0; RR = 0.96 (95% CI 0.53 to 1.75),		20.1% (117/582), p<0.001; RR= 0.53 (95% CI 0.40 to 0.71), p < 0.01 **TLR** <u>1 year</u> 5.9% (35/590) vs. 13.1% (77/590), p<0.001; RR= 0.45, (95% CI 0.31 to 0.67), p < 0.01 <u>5 years</u> 7.5% (43/577) vs. 16.3% (95/582), p<0.001; RR= 0.46 (95% CI 0.32 to 0.64), p < 0.01 **Any revascularization** at 4 years was significantly lower in the DES vs. BMS group (27.4% vs. 35.7%; p=0.03) driven by PCI (26.2 vs. 33.3, p=0.05). No differences were seen between groups for **non-TVR** at 4 years and **non-target lesion TVR** at 1 and 5 years.	**cannot be clearly attributed to a vessel other than the target vessel** <u>1 year</u> 10.0% (59/590) vs. 16.6% (98/590), p=0.001; RR= 0.60 (95% CI 0.45 to 0.81), p < 0.001 <u>5 years</u> 15.4% (89/577) vs. 24.4% (142/582), p<0.001; RR= 0.63 (95% CI 0.50 to 0.80), p < 0.001		

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
		p = 0.90					
ZEUS Valgimigli 2013, Valgimigli 2015	**All-cause mortality** 1 year 11.1% (89/802) vs. 11.4% (92/804); HR = 0.97 (95% CI. 0.72 to 1.29), p=0.83 **Cardiovascular mortality** 1 year 7.6% (61/802) vs. 8.3% 67/804); HR = 0.91 (95% CI, 0.64 to 1.29), p=0.65	**MI** 1 year 2.9% (23/802) vs. 8.1% (65/804); HR = 0.35 (95% CI, 0.22 to 0.56), p<0.001	NR	**TVR** 1 year 5.9% (47/802) vs. 10.7% (86/804); HR = 0.53 (95% CI, 0.37 to 0.75), p=0.001 **TLR** 1 year 5.2% (42/802) vs. 10.4% (84/804); HR = 0.48 (95% CI, 0.33 to 0.70), p<0.001	**MACE** *(death, MI, TVR)* 1 year 17.5% (140/802) vs. 22.1% (178/804); HR = 0.76 (95% CI, 0.61 to 0.95), p=0.011 **Any death or nonfatal MI** 1 year 13.1% vs. 17.4%; HR = 0.73 (95% CI, 0.57 to 0.94), p=0.018 **Cardiovascular death or nonfatal MI** 1 year 9.7% vs. 14.6%; HR = 0.65 (95% CI, 0.49 to 0.87), p=0.004	**Ischemic stroke** 1 year 1.1% (9/802) vs. 1.5% (12/804); HR = 0.75 (95% CI, 1.32 to 1.77), p=0.71	**Definite stent thrombosis at 1 year** *(ARC definition)* 1.0% vs. 2.2%; HR = 0.44 (95% CI, 0.19 to 1.02), p=0.054 **Major bleeding at 1 year** 0.9% (7/802) vs. 1.6% (13/804), p=0.26; RR = 0.54 (95% CI 0.22 to 1.35), p = 0.18 **Minor bleeding at 1 year** 0.9% (7/802) vs. 0.5% (4/804), p=0.39; RR = 1.75 (95% CI 0.52 to 5.97), p = 0.36 **Bleeding requiring medical attention at 1 year** 3.5% (28/802) vs. 4.4% (35/804), p=0.44; RR = 0.80 (95% CI 0.49 to 1.31), p = 0.374 **TIMI classification at 1 year** 1.7% (14/802) vs. 2.1% (17/804); HR NR, p=0.72; RR = 0.83 (95% CI 0.41 to 1.66), p = 0.59
Everolimus Trials							
BASKET-PROVE Pfisterer 2008, Kaiser 2010,	**All-cause death** 2 years 3.2% (25/774) vs. 4.4% (34/765); HR = 0.73 (95% CI 0.43 to 1.22),	**Nonfatal MI** 2 years 1.7% (13/774) vs 2.6% (20/765); HR = 0.67 (95% CI 0.33 to 1.36),	NA	**TVR** 2 years 3.7% (29/774) vs 10.3% (79/765); HR = 0.41 (95% CI 0.27 to 0.65), p=0.002**	**Death from cardiac causes or nonfatal MI** 0-6 mo. 1.3% (10/774) vs 2.7% (21/765); HR = 0.47 (95% CI 0.22 to 1.01),	NA	**Stent thrombosis, definite** *(ARC definition)* 2 years 0.3% (2/774) vs 0.8% (6/765); HR = 0.33 (95% CI 0.07 to 1.62), p=0.42

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
Pedersen 2014	p=0.46 **Cardiac death** 2 years 1.7% (13/774) vs 2.9% (22/765); HR = 0.58 (95% CI 0.29 to 1.14), p=0.37	p=0.51		2 years non-MI related 3.1% (24/774) vs 8.9% (68/765); HR = 0.39 (95% CI 0.24 to 0.63), p=0.002** MI related 0.6% (5/774) vs 1.4% (11/765); HR = 0.49 (95% CI 0.17 to 1.44), p=0.43	p=0.22 7-24 mo. 1.9% (15/774) vs 2.1% (16/765); HR = 0.90 (95% CI 0.44 to 1.82), p=0.90 2 years 3.2% (25/774) vs 4.8% (37/765); HR = 0.66 (95% CI 0.40 to 1.10), p=0.37 **Death, MI, TVR** 2 years 7.6% (59/774) vs 12.9% (99/765); HR = 0.56 (95% CI 0.41 to 0.78), p=0.005		There were no significant between-group differences in either early or late rates of stent thrombosis.
EXAMIN-ATION Sabate 2011, Sabate 2012, Gomez-Lara 2013, Sabate 2014, Ielasi 2015	**All cause death** 1 year: 3.5% (26/751) vs 3.5% (26/747); RD = -0.02 (95% CI -1.87 to 1.84), p=1.00 2 years: 4.3% (32/751) vs 5.0% (37/747); RD = -0.7(95% CI -2.8 to 1.4), p=0.52 **Cardiac death** 1 year:	**MI** *(WHO definition)*† 1 year: 1.3% (10/751) vs 2.0% (15/747); RD = -0.68 (95% CI -1.97 to 0.62), p=0.32 2 years 1.9% (14/751) vs 2.4% (18/747); RD = -0.3 (95% CI -1.5 to 0.9), p=0.45 **Target vessel**		**TVR** 1 year 3.7% (28/751) vs 6.8% (51/747); RD = -3.10 (95% CI -5.36 to -0.84), p=0.0077 2 years 4.8% (36/751) vs 7.9% (59/747); RD = -3.1 (95% CI -5.6 to -0.6), p=0.009 **TLR** 1 year 2.1% (16/751) vs 5.0% (37/747); RD =	**All-cause death, any MI or Revascularization** 1 year 11.9% (89/751) vs 14.2% (106/747); RD = –2.34 (95% CI -5.75 to 1.07), p=0.19 2 year 14.4% (108/751) vs 17.3% (129/747); RD = –2.9 (95% CI, –6.6 to 0.8), p=0.11 **Cardiac death, TVMI, TLR**		**Stent thrombosis, definite** *(ARC definition)* <30 days 0.4% (3/751) vs 1.6% (12/747); RD = -1.21 (95% CI -2.22 to -0.20), p=0.0204 1 year 0.5% (4/751) vs 1.9% (14/747); RD = -1.34 (95% CI -2.44 to -0.24), p=0.0183 2 year 0.8% (6/751) vs 2.1% (16/747); RD = -1.3 (95% CI -2.6 to -0.1), p=0.03 **Death**

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
	3.2% (24/751) vs 2.83% (21/747); RD = 0.38 (95% CI = -1.34 to 2.11), p=0.76 2 years 3.7% (28/751) vs 3.7% (28/747); RD = 0.0 (95% CI -1.9 to 1.9), p=1.0 **Vascular death** 1 year: 0.1% (1/751) vs 0.4% (3/747); RD = -0.27 (95% CI -0.79 to 0.25), p=0.37 2 years 0.4% (3/751) vs 0.4% (3/747); RD = 0.0 (95% CI -0.6 to 0.6), p=0.99	**related MI** 1 year 1.1% (8/751) vs 2.0% (15/747); RD = -0.68 (95% CI -1.97 to 0.62), p = 0.32 **Non-target vessel related MI** 1 year 0.3% (2/751) vs 0% (0/747); RD = 0.27 (95% CI -0.10 to 0.63), p = 0.49		-2.82 (95% CI -4.69 to -0.96), p=0.0032 2 years 2.9% (22/751) vs 5.6% (42/747); RD = -2.7 (95% CI -4.7 to -0.6), p=0.01 **Non-TVR** 1 year 5.3% (40/751) vs 5.5% (41/747); RD = -0.16 (95% CI -2.45 to 2.13), p=0.90 2 years 6.1% (46/751) vs 7.0% (52/747); RD = -0.8 (95% CI -3.3 to 1.7), p=0.51 **Any Revascularization** 1 year 8.0% (60/751) vs 10.6% (79/747); RD = -2.59 (95% CI -5.52 to 0.35), p=0.09 2 years 9.7% (73/751) vs 12.5% (95/747); RD = -3.0 (95% CI -6.2 to 0.0), p=0.05	1 year 5.9% (44/751) vs 8.4% (63/747); RD = -2.57 (95% CI -5.18 to 0.03), p=0.03		< 30 days 1.5% (11/751) vs 1.9% (14/747); RD = -0.41 (95% CI -1.71 to 0.89), p=0.55 **Cardiac death** <30 days 1.5% (11/751) vs 1.9% (15/747); RD = -0.41 (95% CI -1.71 to 0.89), p=0.55 **Vascular death** < 30 days 0% (0/751) vs 0% (0/747); N/A **MI** < 30 days 0.7% (5/751) vs 1.2% (9/747); RD = -0.54 (95% CI -1.51 to 0.44), p=0.29 **Target vessel related MI** <30 days 0.7% (5/751) vs 1.2% (9/747); RD = -0.54 (95% CI -1.51 to 0.44), p = 0.29 **Non-target vessel related** <30 days 0% (0/751) vs 0% (0/747); RD = NC, p = NC **TVR** < 30 days 1.2% (9/751) vs 3.4% (25/747); RD = -2.15 (95% CI -3.65 to -0.64), p=0.0053 **TLR**

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
							<u>< 30 days</u> 0.5% (4/751) vs 2.0% (15/747); RD = -1.48 (95% CI -2.61 to -0.34); p=0.0111 **Non TVR** <u>< 30 days</u> 1.1% (8/751) vs 1.7% (13/747), RD = -0.68 (95% CI -1.87 to 0.52), p=0.28 **Any revascularization** <u>< 30 days</u> 2.3% (17/751) vs 4.2% (31/747); RD = –1.89 (95% CI –3.67 to -0.10), p=0.0406 **Bleeding, all** <u>1 year</u> 4% (29/751) vs 5% (39/747); RD = -1.4 (95% CI -3.47 to 0.75), p=0.19 **Bleeding, major** <u>1 year</u> 1% (9/751) vs 2% (12/747); RD = -1.4 (95% CI -1.60 to 0.78), p=0.19 **Bleeding, minor** <u>1 year</u> 3% (21/751) vs 4% (30/747); RD=-1.2 (95% CI -3.06 to 0.62), p=0.21
XIMA De Belder	**All-cause death:** <u>0-12 months</u>: 8.5% (34/399)vs.	**MI:** <u>0-12 months</u>: 4.3% (17/399)	NR	**TVR:** <u>0-12 months</u>: 2.0% (8/399) vs. 7.0%	**Death, MI, CVA, TVR, Major hemorrhage:** <u>0-12 months</u>: 14.3%	**CVA, any:** <u><30 days</u> 0.0% (0/399)	**Stent thrombosis, definite *** *(ARC definition)*: <u>5 year</u>

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
2014	7.2% (29/401), p=0.51; RR= 1.18 (95% CI 0.73 to 1.90), p = 0.4987 1-6 months: 3.3% (13/399) vs. 2.7% (11/401), p=0.68; RR = 1.19 (95% CI 0.54 to 2.62), p = 0.67 6-12 months: 3.8% (15/399) vs. 3.2% (13/401), p=0.71; RR= 1.16 (95% CI 0.56 to 2.41), p = 0.69 **Cardiac death:** 0-12 months: 3.3% (13/399) vs. 4.7% (19/401), p=0.37; RR= 0.69 (95% CI 0.34 to 1.37), p = 0.29 1-6 months:1.8% (7/399) vs. 2.5% (10/401), p=0.63; 0.70 (95% CI 0.27 to 1.83), p = 0.47 6-12 months: 1.0% (4/399) vs. 1.5% (6/401), p=0.75; 0.67 (95% CI 0.19 to 2.36), p	vs. 8.7% (35/401), p=0.014; RR= 1.18 (95% CI 0.73 to 1.90), p = 0.50 1-6 months: 1.0% (4/399) vs. 4.2% (17/401), p=0.006; RR= 0.24 (95% CI 0.08 to 0.70) p = 0.004 6-12 months: 0.8% (3/399) vs. 1.0% (4/401), p=1.00; RR= 0.75 (95% CI 0.17 to 3.34), p = 0.71		(28/401), p=0.0009; RR= 0.29 (95% CI – 0.13 to 0.62), p < 0.001 1-6 months: 1.0% (4/399) vs. 4.2% (17/401), p=0.007; RR= 0.24 (95% CI 0.08 to 0.70), p = 0.004 6-12 months: 0.5% (2/399) vs. 2.2% (9/401), p=0.064; RR = 0.12 (0.03 to 0.51) p < 0.001	(57/399) vs. 18.7% (75/401), p=0.09; RR= 0.76 (95% CI 0.56 to 1.05), p = 0.09 1-6 months: 5.35% (21/399) vs. 7.5% (30/401), p=0.25; RR= 0.70 (95% CI 0.41 to 1.21), p = 0.20 6-12 months: 4.5% (18/399) vs. 5.7% (23/401), p=0.52; RR= 0.79 (95% CI 0.43 to 1.43), p = 0.43	vs. 0.7% (3/401), p=0.25; RR= NC 0-12 months: 1.5% (6/399) vs. 1.2% (5/401), p=0.77; RR= 1.21 (95% CI 0.37 to 3.92), p = 0.76 1-6 months: 1.0% (4/399) vs. 0.0% (0/401), p=0.061; RR= NC 6-12 months: 0.5% (2/399) vs. 0.5% (2/401), p=1.00; RR= 1.01 (95% CI 0.14 to 7.10), p = 0.99 **CVA, hemorrhagic:** <30 days 0.0% vs. 0.0%, p=1.0; RR= NC 0-12 months: 0.8% (3/399)	0.5% (2/399) vs. 0.5% (2/401); RR= 1.01 (95% CI 0.14 to 7.10), p = 1.00 **TIMI minor hemorrhage** 5 year 3.5% (14 */399) vs. 2.0% (8 */401), p=0.20; RR= 1.76 (95% CI 0.75 to 4.15), p = 0.19 **All cause death** <30 days 1.5% (6/399) vs. 1.2% (5/401), p=0.77; RR= 1.21 (95% CI 0.37 to 3.92), p = 0.76 **Cardiac death** <30 days 0.5% (2/399) vs. 0.7% (3/401), p=1.00; RR= 0.67 (0.11 to 3.99), p = 0.66 **Non-cardiac death** <30 days 1.0% (4/399) vs. 0.5% (2/401), p=0.45; RR= 2.01 (95% CI 0.49) to 8.31), p = 0.41 **Major hemorrhage** <30 days 0.5% (2/399) vs. 0.7% (3/401), p=1.0; RR= 0.67 (95% CI 0.11 to 3.99), p = 0.66 **MI** <30 days 2.5% (10/399) vs. 3.5% (14/401), p=0.53; RR= 0.72

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
	= 0.53 **Non-cardiac death:** 0-12 months: 5.3% (21/399) vs. 2.5% (10/401), p=0.045; RR= 2.11 (1.01 to 4.42), p = 0.04 1-6 months: 1.5% (6/399) vs. 0.2% (1/401), p=0.069; RR= 6.03 (95% CI 0.73 to 49.86), p = 0.06 6-12 months:2.8% (11/399) vs. 1.7% (7/401), p=0.48; RR= 2.77 (95% CI 0.89 to 8.61), p = 0.07					vs. 0.2% (1/401), p=0.37; RR= 3.01 (0.3149-28.8635), p = 9.3140 1-6 months: 0.3% (1/399) vs. 0.0%, p=0.50; RR= NC 6-12 months: 0.55% (2/399) vs. 0.2% (1/401), p=0.62; RR= 2.01 (0.18 to 22.18), p = 0.56 **CVA, Ischemic:** <30 days 0.0% vs. 0.7% (3/401), p=0.25; RR= NC 0-12 months: 0.8% (3/399) vs. 1.0% (4/401), p=1.00; RR= 0.75 (95% CI 0.17 to 3.35),	(0.32 to 1.60), p = 0.41 **TVR** <30 days 0.5% (2/399) vs. 0.5% (2/401), p=1.0; RR= 1.01 (95% CI 0.14 to 7.10), p = 1.00 **Death, MI, CVA, TVR, Major hemorrhage** <30 days 4.5% (18/399) vs. 5.5% (22/401), p=0.63; RR= 0.82 (95% CI 0.45 to 1.51), p = 0.53

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
						p = 0.71 <u>1-6 months</u>: 0.8% (3/399) vs. 0.0%, p=0.25; RR= NC <u>6-12 months</u>: 0.0% vs. 0.2% (1/401), p=1.00; RR= NC	
X-MAN Dharma 2014	NR	NR	NR	NR	NR	NR	**In-hospital bleeding** *(GUSTO criteria definition)* *Severe*: 0.0% (0/75) vs. 0.0% (0/75); RR = NC *Moderate*: 0.0% (0/75) vs 4.0% (3/75); RR = NC *Mild*: 5.0% (4/75) vs. 5.0% (4/75); RR = 1.00 (95% CI 0.26 to 3.85), p = 1.00 For all, p = 0.37 **MACE** *(death, re-MI, TVR)* <u>1 month</u> 1.3% (1/75) vs. 1.3% (1/75), p=1.0; HR = 0.9 (95% CI, 0.06 to 15.8) **Stent thrombosis, definite** *(ARC definition)* <u>1 month</u> 0% (0/75) vs 0% (0/75); RR = NC
Everolimus AND Zotarolimus trials							

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
PRODIGY Valgimigli 2014	NR	NR	NR	*EES vs ZES vs BMS* **TVR *** 1 year 4.8% (24/501) vs 10.4% (52/502) vs 15.1% (76/505) *EES vs BMS*: RR= 0.32 (95% CI 0.20 to 0.50), p < 0.001 *ZES vs BMS:* RR= 0.69 (95% CI 0.49 to 0.96), p = 0.03 2 year 6.2% (31/501) vs 12.2% (61/502) vs 18.3% (92/505) *EES vs BMS:* RR= 0.34 (95% CI 0.23 to 0.50), p < 0.00 *ZES vs BMS:* RR= 0.67 (95% CI 0.49 to 0.90), p < 0.01 **TLR *** 2 year 5.2% (26/501) vs 11.6% (58/502) vs 17.1% (86/505) *EES vs BMS:* RR= 0.30 (95% CI 0.20 to 0.46), p < 0.001 *ZES vs BMS:* RR= 0.68 (95% CI 0.50 to	*EES vs ZES vs BMS* **All-cause death, MI, TVR *** 1 year: 16.0% (80/501) vs 23.6% (118/502) vs 27.3% (138/505) *EES vs BMS*: RR= 0.58 (95% CI 0.46 to 0.75), p < 0.001 *ZES vs BMS:* RR= 0.86 (95% CI 0.70 to 1.06), p = 0.16 2 year 19.2% (96/501) vs 27.3% (137/502) vs 32.1% (162/505) *EES vs BMS: RR*= 0.60 (95% CI 0.48 to 0.74), p < 0.001 *ZES vs BMS:* RR= 0.85 (95% CI 0.70 to 1.03), p = 0.10 **Death or nonfatal MI *** 1 year 13.6% (68/501) vs 15.0% (75/502) vs 16.9% (85/505) *EES vs BMS:* RR= 0.81 (95% CI 0.60 to 1.08), p = 0.15	NR	NR

Trial	Mortality (All – cause, cardiac) >30 days DES vs BMS	Myocardial infarction >30 days DES vs BMS	Patient-reported outcomes	Revascularization DES vs BMS	Composite outcomes *(define, provide data)* DES vs BMS	Stroke >30 days DES vs BMS	Safety DES vs BMS
				0.92), p = 0.01	*ZES vs BMS:* RR= 0.89 (95% CI 0.67 to 1.18), p = 0.41 <u>2 year</u> 16.0% (80/501) vs 18.0% (90/502) vs 20.1% (102/505) *EES vs BMS:* RR= 0.79 (95% CI 0.61 to 1.03), p = 0.08 *ZES vs BMS*: RR= 0.89 (95% CI 0.72 to 1.10), p = 0.36		

ARC: Academic Research Consortium; CABG: coronary artery bypass graft; CI: confidence interval; HR: Hazard Ratio; MI: myocardial infarction; NC: Non-Calculable; PCI: percutaneous coronary intervention; TLR: target lesion revascularization; TIMI: Thrombosis In Myocardial Infarction; TVR: target vessel revascularization.

*N's or n's were backcalculated from percentages and n's or Ns, and rounded to nearest integer.

†MI was not indicated as fatal nor nonfatal by author

‡Outcome reported in terms of "events per 100 subjects"

§ Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of vessel occlusion or thrombus within or adjacent to a previously stented segment; in the absence of angiography, stent thrombosis could be confirmed by acute MI in the distribution of the treated vessel or death resulting from cardiac causes within 30 days.

**Significant after adjustment for multiple comparisons by means of the step-up procedure

Appendix Table H4. Drug-eluting versus bare metal stenting for stable or unstable angina: Differential Efficacy and Safety in Subgroups

Trial	Differential efficacy (DES vs BMS; EES vs ZES vs BMS)	Differential safety (DES vs BMS; EES vs ZES vs BMS)
Zotarolimus Trials		
ENDEAVOR II Eisenstein 2009, Fajadet 2006, Fajadet 2010	NR	NR
ZEUS Valgimigli 2013, Valgimigli 2015	None of the following characteristics modified treatment effect of DES versus BMS for the outcome of Death or MI at 12 months (HR = DES vs. BMS): **High bleeding risk (Yes vs. No); interaction p=0.96** • Yes (n=828): HR = 0.71 (95% CI, 0.53 to 0.96) • No (n=778): HR = 0.70 (95% CI, 0.43 to 1.15) **High thrombotic risk (Yes vs. No); interaction p=0.13** • Yes (n=285): HR = 1.03 (95% CI, 0.62 to 1.73) • No (n=1321): HR = 0.66 (95% CI, 0.49 to 0.88) **Low restenosis risk (Yes vs. No); interaction p=0.25** • Yes (n=941): HR = 0.62 (95% CI, 0.41 to 0.92) • No (n=665): HR = 0.83 (95% CI, 0.60 to 1.13)	None
Everolimus Trials		
BASKET-PROVE Pfisterer 2008, Kaiser 2010, Pedersen 2014	**Patients with NSTE-ACS** 2 year outcomes CV death: 1.1% (3/264) vs 2.0% (5/246); HR = 0.75 (95% CI, 0.37 to 1.53); p=0.43 Non-fatal MI: 1.1% (3/264) vs 3.7% (9/246); HR = 0.55 (95% CI, 0.29 to 1.06); p=0.08 *CV death or MI: 2.3% (6/264) vs 4.9% (12/246); HR = 0.74 (*95% CI, *0.44 to 1.24) p=0.25* *TVR: 3.0% (8/264) vs 9.3% (23/246); HR = 0.52 (*95% CI, *0.34 to 0.78), p=0.002* *Results in italics were adjusted—CV death was adjusted for gender, diabetes, and number of stents; TVR was adjusted for hypertension, heart failure, diseased LAD.*	None
EXAMINATION	**Age (≥75 vs <75)**	**Age**

Trial	Differential efficacy (DES vs BMS; EES vs ZES vs BMS)	Differential safety (DES vs BMS; EES vs ZES vs BMS)
Sabate 2011, Sabate 2012, Gomez-Lara 2013, Sabate 2014, Ielasi 2015	Age did not modify treatment effect (nor appear to modify in the cases where no p-value for interaction was reported. Interaction P-values between age and treatment effect are as follows: All-cause death: p = 0.092 Cardiac death: p = 0.277 *Patients <75 years* <u>1 year outcomes</u> All Cause Death: 1.3% (8/638) vs 1.6% (10/615), p=0.580; RR = 0.7712 (95% CI 0.3064 to 1.9410), p = 0.5802 Cardiac Death: 1.3% (8/638) vs 1.0% (6/615), p=0.639; RR = 1.2853 (95% CI 0.4485 to 3.6828), p = 0.6395 Any MI: 0.6% (4/638) vs 1.3% (8/615), p=0.221; RR = 0.4820 (95% CI 0.1459 to 1.5924), p = 0.2210 TVMI: 0.5% (3/638) vs 1.1% (7/615), p=0.184; RR = 0.4131 (95% CI 0.1073 to 1.5904), p = 0.1842 TLR: 2.0% (13/638) vs 5.4% (33/615), p=0.002; RR = 0.3797 (95% CI 0.2018 to 0.7124), p = 0.0017 TVR: 3.3% (21/638) vs 7.3% (45/615), p<0.001; RR = 0.4498 (95% CI 0.2712 to 0.7461), p = 0.0014 NonTVR: 5.5% (35/638) vs 5.2% (32/615), p = 0.824; RR = 1.0543 (0.6613 to 1.6809), p = 0.8241 *Patients ≥75 years* <u>1 year outcomes</u> All Cause Death: 15.9% (18/113) vs 12.1% (16/132), p=0.390; RR = 1.3142 (95% CI 0.7035 to 2.4548), p = 0.3911 Cardiac Death: 14.2% (16/113) vs 11.4% (15/132), p=0.512; RR = 1.2460 (95% CI 0.6452 to 2.4062), p = 0.5126 *Any MI*: 1.8% (2/113) vs 1.5% (2/132), p=0.875; RR = 1.1681 (95% CI 0.1672 to 8.1601), p = 0.8756 *TVMI*: 0.9% (1/113) vs 1.5% (2/132), p=0.655; RR = 0.5841 (95% CI 0.0537 to 6.3572), p = 0.6554 TLR: 2.7% (3/113) vs 3.0% (4/132), p=0.806; RR = 0.8761 (95% CI 0.2003 to 3.8324), p = 0.8607	Age did not modify treatment effect (nor appear to modify in the cases where no p-value for interaction was reported. Interaction P-values between age and treatment effect are as follows: Bleeding: p = 0.75 *Patients <75 years* <u>1 year outcomes</u> Bleeding: 3.3% (21/638) vs 4.7% (29/615), p=0.198; RR = 0.69 (95% CI 0.4025 to 1.2106), p = 0.1982 Bleeding, major: 0.9% (6/638) vs 1.3% (8/615), p=0.544; RR = 0.73 (95% CI 0.2523 to 2.0716), p = 0.5442 Bleeding, minor: 2.4% (15/638) vs 3.7% (23/615), p=0.152; RR = 0.6287 (0.3312 to 1.1934), p = 0.1520 *Patients ≥75 years* <u>1 year outcomes</u> Bleeding: 7.1% (8/113) vs 7.6% (10/132), p=0.892; RR = 0.9345 (95% CI 0.3818 to 2.2874), p = 0.8823 Bleeding, major: 2.7% (2/113) vs 2.3% (3/132), p=0.847; RR = 0.7788 (95% CI 0.1324 to 4.5789), p = 0.7818 Bleeding, minor: 5.3% (6/113) vs 5.3% (7/132), p=0.998; RR = 1.0013 (95% CI 0.3465 to 2.8932), p = 0.9981 **Proximal vs non-proximal LAD** Proximal and non-proximal LAD did not appear to modify treatment effect, though interaction

Trial	Differential efficacy (DES vs BMS; EES vs ZES vs BMS)	Differential safety (DES vs BMS; EES vs ZES vs BMS)
	TVR: 6.2% (7/113) vs 4.5% (6/132), p=0.566; RR = 1.3628 (95% CI 0.4716 to 3.9380), p = 0.5667 Non-TVR: 4.4% (5/113) vs 6.8% (9/132), p=0.421; RR = 0.6490 (95% CI 0.2239 to 1.8806), p = 0.4220 *All MI was WHO defined* **Proximal vs non-proximal LAD** Proximal and non-proximal LAD did not modify treatment effect (nor appear to modify in cases where no p-value for interaction was reported). Interaction P-values between LAD and treatment effect are as follows: Clinically driven TVR: p = 0.05 *Patients with non-proximal LAD* 1 year outcomes All cause death: 3.0% (18/593) vs 2.8% (17/615), p=0.775; RR = 1.0981 (95% CI 0.5714 to 2.1102); p = 0.7789 Cardiac death: 2.9% (17/593) vs 2.4% (15/615); RR = 1.1754 (95% CI 0.5924 to 2.3319), p = 0.6436 MI: 0.8% (5/593) vs 1.3% (8/615), p=0.443; RR = 0.6482 (95% CI 0.2133 to 1.9701), p = 0.4411 Revascularization: 8.8% (52/593) vs 10.1% (62/615), p=0.441; RR = 0.8698 (95% CI 0.6124 to 1.2354), p = 0.4356 TLR: 2.4% (14/593) vs 4.6% (28/615), p=0.038; RR = 0.5185 (95% CI 0.2757 to 0.9752), p = 0.0377 TVR: 4.4% (26/593) vs 6.7% (41/615), p=0.084; RR = 0.6577 (95% CI 0.4077 to 1.0610), p = 0.0833 NTVR: 5.7% (34/593) vs 4.9% (30/615), p=0.502; RR = 1.1754 (95% CI 0.7289 to 1.8954), p = 0.5071 *Patients with proximal LAD* 1 year outcomes All cause death: 4.4% (7/158), 6.8% (9/132), p=0.375; RR = 0.6498 (0.2487 to 1.6976), p = 0.3759 Cardiac death: 3.8% (6/158) vs 4.5% (6/132), p=0.750; RR = 0.8354 (95% CI 0.2759 to 2.5293), p = 0.7505	p-values were NR. *Patients with non-proximal LAD* 1 year outcomes Stent thrombosis, definite: 0.7% (4/593) vs 2.1% (13/615), p=0.034; RR = 0.3191 (95% CI 0.1046 to 0.9731), p = 0.0338 Bleeding: 4.2% (25/593) vs 5.6% (36/615), p=0.231; RR = 0.7202 (95% CI 0.4379 to 1.1846), p = 0.1939 Bleeding, major: 1.0% (6/593) vs 1.6% (10/615), p=0.352; RR = 0.6223 (95% CI 0.2276 to 1.7014), p = 0.3508 Bleeding, minor: 3.2% (19/593) vs 4.2% (26/615), p=0.351; RR = 0.7579 (95% CI 0.4240 to 1.3546), p = 0.3479 *Patients with proximal LAD* 1 year outcomes Stent thrombosis, definite: 0% (0/158) vs 0.8% (1/132), p=0.273; RR = NC Bleeding: 3.2% (5/158) vs 3.4% (5/132), p=0.772; RR = 0.8354 (95% Ci 0.2472 to 2.8238), p = 0.7724 Bleeding, major: 1.9% (3/158) vs 0.8% (1/132), p=0.407; RR = 2.5063 (95% CI 0.2638 to 23.8123), p = 0.4075 Bleeding, minor: 0.7% (2/158) vs 1.4% (4/132), p=0.293; RR = 0.4177 (95% CI 0.0777 to 2.2449), p = 0.2940

Trial	Differential efficacy (DES vs BMS; EES vs ZES vs BMS)	Differential safety (DES vs BMS; EES vs ZES vs BMS)
	MI: 0.6% (1/158) vs 1.5% (2/132), p=0.460; RR = 0.4177 (0.0383 to 4.5558), p = 0.4604 Revascularization: 5.1% (8/158) vs 12.9% (17/132), p=0.018; RR = 0.3931 (95% Ci 0.1753 to 0.8819), p = 0.0184 TLR: 1.3% (2/158) vs 6.8% (9/132), p=0.014; RR = 0.1857 (95% Ci 0.0408 to 0.8443), p = 0.0139 TVR: 1.3% (2/158) vs 7.6% (10/132), p=0.007; RR = 0.1671 (95% CI 0.0373 to 0.7492), p = 0.0073 NTVR: 3.8% (6/158) vs 8.3% (11/132), p=0.102; RR = 0.4557 (95% CI 0.1732 to 1.1991), p = 0.1021	
XIMA De Belder 2014	No statistically significant subgroup findings were noted for the following categories, and interaction p-values were not reported: <u>Primary end point of death/MI/TVR/CVA/major hemorrhage at 12 months</u> • Age (80-85 vs. 85-90 vs. >90 years) • Sex (Females vs. Males) • Diabetes (Yes vs. No) • Kidney disease (creatinine >200 vs. <200) • Catheter approach (Radial vs. Femoral) • Number of diseased vessels (1 vs. 2 vs. >2) • Rotational atherectomy (Yes vs. No) • Left main disease (Yes vs. No) • Presentation (Stable vs. Unstable) This subgroup analysis was conducted post-hoc. **No interaction p-value was reported** but all confidence intervals overlaps significantly	None
X-MAN Dharma 2014	NR	NR
Everolimus AND Zotarolimus trials		
PRODIGY Valgimigli 2014	NR	NR

ARC: Academic Research Consortium; BMS: Bare Metal Stent; CABG: coronary artery bypass graft; CI: confidence interval; DES: Drug Eluting Stent; EES: Everolimus Eluting Stent; HR: Hazard Ratio; MI: myocardial infarction; NC: Non-Calculable; PCI: percutaneous coronary intervention; TLR: target lesion revascularization; TIMI: Thrombosis In Myocardial Infarction; TVR: target vessel revascularization; ZES: Zotarolimus Eluting Stent

Appendix Table H5. Drug-eluting versus bare metal stenting for stable or unstable angina: Safety and harms outcomes from nonrandomized comparative studies and case series (single-arm studies).

Trial	Safety
Comparative studies	
Garg 2014 STEMI Retrospective database/case series (2 sites) United States	DES vs. BMS • **Stent thrombosis (ARC definition) at mean follow-ups, 2.7 and 1.4 years:** 1.6% (12/752) vs. 4.0% (47/1187), p=NR *Kaplan-Meier estimates* • **Stent thrombosis at 24 months:** 1.4% (10/752) vs. 3.8% (39/1187), p=0.031; adjusted HR* (BMS vs. DES): 1.92, 95% CI 1.00 to 3.69, p=0.049 • **Stent thrombosis at 30 days:** 1% (7/752) vs. 1.7% (19/1187), p=0.20 • **Cardiac mortality at 30 days:** 2.3% (17/752) vs. 7.9% (93/1187), p<0.001 • **Reinfarction at 30 days:** 1.4% (10/752) vs. 2.1% (24/1187), p=0.23
Piao 2014 Octogenarians, STEMI Retrospective database/case series (KAMIR) Korea	DES vs. BMS • **Stent thrombosis (ARC definition) at 12 months:** 0.9% (3/323) vs. 3.8% (7/186); adjusted HR† = 0.19 (95% CI, 0.04 to 0.93), p=0.04 • **In-hospital cardiac death:** 13.3% (43/323) vs. 13.4% (25/186); p=0.967 • **In-hospital major bleeding:** 1.2% (4/323) vs. 2.7 (5/186); p=0.298

Sarno 2012
 	
SCAAR
 	
Multicetner retrospective
	DES vs. BMS
	• **Rate of definite ST (ARC definition):**
	  ○ 12 months: 0.5% (n at risk=4188) vs. 1.2% (n at risk=47,968)
	  ○ 24 months: 0.6% (n at risk=847) vs 1.4% (n at risk=32,698)
	  ○ Cumulative risk up to 24 months: adjusted HR‡ 0.38 (95% CI, 0.28 to 0.52)

Trial	Safety
registry (29 sites) Sweden	• **Rate of restenosis** ○ 12 months: 2.8% (n at risk=4188) vs. 6.3% (n at risk=47,968) ○ 24 months: 3.9% (n at risk=847) vs. 7.4% (n at risk=32,698) ○ Cumulative risk up to 24 months: adjusted HR‡ 0.29 (95% CI, 0.25 to 0.33)
Sarno 2014 SCAAR STEMI Multicenter retrospective registry/case series Sweden	<u>DES vs. BMS</u> The assumption of proportionality of the hazards for ST during the 3-year follow-up period was not met (p=0.07) • **Definite stent thrombosis (ARC definition)** *Cumulative rates:* ○ 30 days: 0.5% (n at risk=4649) vs. 0.9% (n at risk=24,851) ○ 12 months: 0.9% (n at risk=4497) vs. 1.5% (nat risk=21,962) ○ 24 months: 1.2% (n at risk=2751) vs. 1.8% (n at risk=19,336) ○ 36 months: 1.3% (n at risk=1235) 2.0% (n at risk=15,882) *Early/late thrombosis (up to 12 months):* adjusted HR§ 0.65 (95% CI, 0.43 to 0.99), p=0.04 *Very late f/u (>12 months, up to 36 months):* adjusted HR§ 1.52 (95% CI, 0.78 to 2.98), p=0.21 • **Cumulative rate of all-cause mortality at 30 days post-PCI:** 3.7% (n at risk=4667) vs. 4.8% (n at risk=23,893)
Single arm studies	
Inaba 2014 Retrospective case series (single center) United States	<u>DES (everolimus)</u> • **Incidence of mechanical complication:** 12.5% (17/136) of patients; 9.6% (17/177) lesions at 14.7 ± 10.6 months ○ Stent fracture: complete with separation (1/17); partial with separation (3/17) ○ Longitudinal deformation (11.8%; 2/17) or stent strut fracture (64.7%; 11/17) with overlapping of the proximal and distal stent fragments. ○ *On angiography (Popma classification):* ▪ Type I: n=0 ▪ Type II: n=4 ▪ Type III: n=2 ▪ Type IV: n=3 • **In-stent restenosis:** focal (94.1%; n=16/17) and diffuse (5.9%, n= 1/17) • Repeat revascularization: 88.2% (15/17) • >50% neointimal hyperplasia in the setting of overlapping either fracture or deformation: 92.3% (12/13)
Kuramitsu 2012 Retrospective case series (two centers) Japan	<u>DES (Xience V; everolimus-eluting)</u> <u>N=1035 (1339 lesions) ; median f/u 7.8 (IQR, 6.2 to 8.2) months</u> (N is number with angiographic follow-up at 6-9 months or before 6 months for recurrent symptoms; total 1208 pts with 1562 lesions) • **Stent fracture:** 3.8% (39/1035) of patients; 2.9% (39/1339) of lesions *On angiography (Popma classification)***:** ○ Type 1 (minor): 0% ○ Type 2 (V-form): 53.8% (21/39) ○ Type 3 (complete separation without displacement): 25.6% (10/39) ○ Type 4 (complete separation with displacement): 2.6% (1/39)

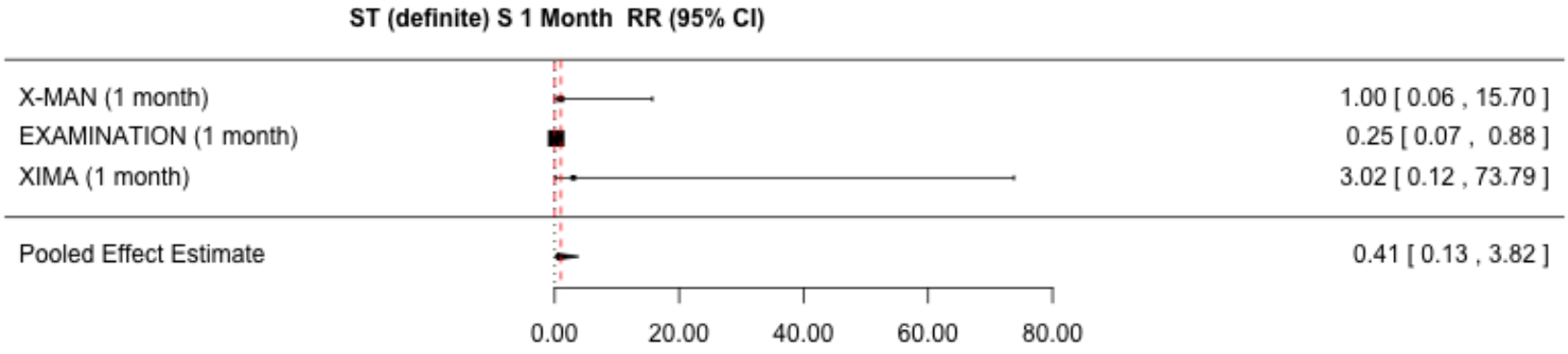
Trial	Safety
	○ Not angiographically visible/angiographically unclassified: 17.9% (7/39) *On IVUS (performed only in patients undergoing TLR, n=21)* ○ Complete fracture: 57.1% (12/21) ○ Partial fracture: 42.9% (9/21) • **In-stent restenosis** ○ Patients with stent fracture: 71.8% (28/39); mostly focal (56.4%; 22/39) ○ Overall: 8.9% (92/1035) patients; 6.9% (92/1339) lesions; mostly focal (7.1% (73/1035) and 5.5% (73/1339), respectively) • **In-segment restenosis** ○ In stent fracture group: 74.3% (29/39) ○ Overall: 11.3% (117/1035) patients; 8.7% (117/1339) lesions • **Definite Stent Thrombosis (ARC criteria)** ○ Early (0-30 days): 0.3% (3/1035) ○ Late (>30 days to 1 year): 0.3% (3/1035) ○ In patients with stent fracture: 0% (0/16) early; 5.1% (2/39) late
Kuramitsu 2015	DES (PROMUS Element; everolimus-eluting) N=700 (898 lesions); median f/u 6.3 (IQR, 6.1 to 7.8) months (N is number with angiographic follow-up at 6-9 months or before 6 months for recurrent symptoms; total 816 pts/1094 lesions) • **Stent fracture:** 2.6% (18/700) of patients; 2.0% (18/898) of lesions (total of 18 fractures in 16 lesions; in two patients fractures occurred at 2 or more points per lesion) *On angiography (Menown classification)* ○ Type 1 (partial separation): 0% ○ Type 2 (complete separation without displacement): 44.4% (8/18) ○ Type 3a and 3b (complete separation with displacement): 27.8% (5/18) and 27.8% (5/18), respectively *On IVUS or OCT (n=5)* ○ Complete fracture: 100% (5/5) • **In-stent restenosis** ○ Patients with stent fracture: 56.2% (9/16); mostly focal (43.7%; 7/16) ○ Overall: 13.7% (96/700) patients; 10.7% (96/898) lesions (mostly focal: 11.7% [82/700] and 9.1% [82/898], respectively) • **In-segment restenosis** ○ Patients with stent fracture: 56.2% (9/16) ○ Overall: 14.9% (104/700) patients; 11.6% (104/898) lesions • **Definite Stent Thrombosis** ○ Early (0-30 days): 0.1% (1/700) (at day 5) ○ Late (>30 days to 1 year): 0.1% (1/700) (at day 32) ○ Patients with stent fracture: 0% (0/16) • **Coronary aneurysm:** 0% (0/16) (only reported in those with stent fracture)
Pitney 2011	DES (Endeavor, zotarolimus-eluting) N=1000; 6 months *On angiography* • **Stent separation and pseudo-fracture:** 1.4% (14/1000) ○ Of those where post-dilation was attempted: 1.8% (14/775)

Trial	Safety
	• **Distal dissection:** 7% (1/14) • **In-stent restenosis:** 29% (4/14) (14% (2/14) early and 14% (2/14) late) • **Stent thrombosis:** 0% (0/14) • **Re-stent required:** 64% (9/14) • **Total 30 day MACE:** 21% (3/14)

Williams 2012	DES (n=4585) and BMS (n=1265)
	• **Longitudinal stent deformation:**
	  ○ All DES: 0.2% (7/4585 stents)
	  ▪ XIENCE V/Promus (everolimus): 0% (0/2691 stents)
	  ▪ Endeavor (zotarolimus): 0.1% (1/995 stent)
	  ▪ Promus Element (everolimus): 0.9% (6/696 stent)
	  ▪ Resolute Integriy (zotarolimus): 0% (0/203)
	  ○ BMS: 0% (0/1265)

ARC: Academic Research Consortium; BMS: Bare metal stent; CABG: Coronary artery bypass grafting; DES: Drug eluting stent; F/U: Follow-up; HR: Hazard ratio; IVUS: Intravascular ultrasound; KAMIR: Korea Acute Myocardial Infarction Registry; MACE: Major adverse cardiac events
MI: Myocardial infarction; OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; SCAAR: Swedish Coronary Angiography and Angioplasty Registry; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction
*Propensity adjusted outcome; scores based on backward selection for age, sex, diabetes, hypertension, prior CABG, prior MI, anterior MI, cardiogenic shock, current smoker, and TIMI 2-3 flow on angiography pre-PCI.
†Authors do not report what variables were included in the adjusted model.
‡Adjusted for age, sex diabetes, hypertension, dyslipidaemia, smoking status, clinical indication of the procedure, use of acetyl salicylic acid, GPIIb–IIIa and/or P2Y12 receptor inhibitors at the index procedure, treated vessel, previous myocardial infarction (MI), previous coronary artery bypass grafting (CABG), previous PCI, year of the index procedure, enrolling centre, lesion type, bifurcation lesions, restenotic lesions, chronic total occlusions (CTO), stent type, stent diameter, stent length, three-vessel/left main disease, the use of additional stents, and maximal inflation pressure.
§Adjusted for age, sex, diabetes, hypertension, dyslipidemia, smoking status, use of acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, and/or P2Y12 receptor inhibitors at the index procedure, treated vessel, previous myocardial infarction, previous coronary artery bypass grafting, previous PCI, year of the index procedure, enrolling center, lesion type, bifurcation lesions, and 3-vessel/left main disease.

Appendix Figure H1. Comparison of newer-generation DES with BMS for definite stent thrombosis from RCTs: Profile likelihood method at ≤ 30 days



APPENDIX I. Clinical Experts

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