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Drug-Eluting Stents versus Bare Metal Stents in Unprotected Left Main Coronary Artery Stenosis: a Meta-Analysis

Sanjay B. Pandya, MD[§], Young-Hak Kim, MD[†], Sheridan N. Meyers, MD[§], Charles J. Davidson, MD[§], James D. Flaherty, MD[§], Duk-Woo Park, MD[†], Anuj Mediratta, MD[§], Karen Pieper, MS[¶], Eric Reyes, MS[¶], Robert O. Bonow, MD[§], Seung-Jung Park, MD[†], and Nirat Beohar, MD[§]

[§]Feinberg School of Medicine, Northwestern University, Chicago, Illinois

[†]University of Ulsan College of Medicine, Seoul, Korea

[¶]Duke Clinical Research Institute, Durham, North Carolina

Abstract

Objectives—We undertook a meta-analysis to assess outcomes for drug-eluting (DES) and bare metal stents (BMS) in percutaneous coronary intervention (PCI) for unprotected left main coronary stenosis (LMCA).

Background—Uncertainty exists regarding the relative performance of DES versus BMS in unprotected LMCA PCI.

Methods—Of a total of 838 studies, 44 met inclusion criteria (N=10,342). The co-primary endpoints were mortality, myocardial infarction (MI), target vessel/target lesion revascularization (TVR/TLR), and major adverse cardiac events (MACE: mortality, MI, TVR/TLR).

Results—Event rates for DES and BMS were calculated at 6–12 months, at 2 years and at 3 years. Crude event rates at 3 years were: mortality (8.8% and 12.7%), MI (4.0% and 3.4%), TVR/TLR (8.0% and 16.4%), and MACE (21.4% and 31.6%). Nine studies were included in a comparative analysis (N=5,081). At 6–12 months the adjusted odds ratio (OR) for DES vs. BMS were: mortality 0.94 (95% confidence interval [CI] 0.06–15.48; p=0.97), MI 0.64 (95% CI 0.19–2.17; p=0.47), TVR/TLR 0.10 (95% CI 0.01–0.84; p=0.01) and MACE 0.34 (95% CI 0.15–0.78; p=0.01). At 2 years the OR were: mortality 0.42 (95% CI 0.28–0.62; p<0.01), MI 0.16 (95% CI 0.01–3.53; p=0.13), and MACE 0.31 (95% CI 0.15–0.66; p<0.01). At 3 years the OR were: mortality 0.70 (95% CI 0.53–0.92; p=0.01), MI 0.49 (95% CI 0.26–0.92; p=0.03), TVR/TLR 0.46 (95% CI 0.30–0.69; p<0.01), and MACE 0.78 (95% CI 0.57–1.07; p=0.12).

Conclusion—Our meta-analysis suggests that DES is associated with favorable outcomes for mortality, MI, TVR/TLR, and MACE as compared to BMS in unprotected LMCA PCI.

Introduction

Unprotected left main coronary artery stenosis (LMCA) is associated with poor clinical outcomes. Studies have shown improved long-term outcomes in those who undergo surgical revascularization as compared to optimal medical therapy alone (1,2). This is the basis for the ACC/AHA class I recommendation for coronary artery bypass surgery (CABG) in patients with $\geq 50\%$ left main stenosis (3).

Early percutaneous attempts at revascularization with balloon-only angioplasty were associated with suboptimal clinical outcomes (4). This led to an ACC/AHA class III (contraindicated) guidelines recommendation for percutaneous coronary intervention (PCI) in CABG-eligible patients (5). The subsequent advent of coronary stents, which reduced peri-procedural risks and improved clinical outcomes, renewed interest in unprotected LMCA PCI. This interest was further fueled by the subsequent introduction of drug-eluting stents (DES), which led to substantially lower rates of restenosis in coronary lesions (6,7). On the basis of improved clinical outcomes, the most recent ACC/AHA guidelines have given unprotected LMCA PCI a class IIb recommendation (8).

However, there remains some clinical uncertainty over the ideal stent type for unprotected LMCA PCI. The use of DES in the left main position is considered an off-label application; prior studies have identified increased adverse events for such off-label applications (9). Additionally, although the reduction in restenosis seen with DES use is particularly attractive for unprotected LMCA PCI, the large caliber of most left main arteries could attenuate this benefit. Finally, concern exists over potentially increased rates of late stent thrombosis with DES, which has serious implications in unprotected LMCA PCI (10).

We performed a meta-analysis of the current literature to assess outcomes of PCI in unprotected LMCA and to compare the relative performance of DES and BMS in this application.

Methods

Search strategy

Pubmed, clinicaltrials.gov, and BioMedCentral databases were searched from January 2000 to September 2009; there were no language restrictions. Search terms included “left main”, “coronary”, “intervention”, and “stenting”. Citations were screened and evaluated using the established inclusion/exclusion criteria at the abstract level by two operators (SP and NB), and relevant studies were retrieved as full manuscripts. Inclusion criteria were: a) involving unprotected left main disease, b) involving bare metal or drug eluting stents, and c) involving at least 20 patients in the overall study cohort. Exclusion criteria were defined as: a) unpublished studies, b) abstract only, c) angioplasty without stenting d) ST elevation myocardial infarction, e) cardiogenic shock, f) experimental devices, g) non-English studies, h) studies not reporting relevant clinical outcomes. Data regarding patient demographics and clinical outcomes were then entered into a database.

Endpoints

The co-primary endpoints were mortality, myocardial infarction (MI), target vessel/target lesion revascularization (TVR/TLR), and major adverse cardiovascular events (MACE, defined as mortality, MI, and TVR/TLR). These endpoints were reported for the following time periods post-PCI: 6–12 months, 2 years, and 3 years. Data for all endpoints at each time period were not available for every study.

Statistical analysis

Crude event rates were reported for mortality, MI, and TVR/TLR for both DES and BMS. Since these estimates were based, in part, on studies for which a causal link between stent type and outcome was not established, direct comparison of rates is not appropriate, and rates can only be seen as descriptive in nature. Subsequent comparative analysis was performed evaluating studies that provided adjusted outcomes on relevant endpoints or were randomized according to stent types; odds ratios (OR) were reported for this analysis. When both hazard ratios (HR) and OR were reported as endpoints across trials they were

combined, assuming that the follow-up was fairly complete (and thus the HR would be similar to the expected OR). Similarly, Kaplan-Meier rates and percentages were combined when one of the two was not available for an endpoint. Several endpoints did not meet the assumption of homogeneity of rates across studies, and thus random effects modeling techniques were used to combine rates and calculate confidence intervals. Comprehensive Meta Analysis software version 2.2.048 was used for all analyses (Comprehensive Meta Analysis, www.Meta-Analysis.com)(11).

Results

Database searches retrieved an initial 838 studies, of which 76 were deemed relevant; 32 of these studies were eventually excluded. A final 44 studies meeting inclusion/exclusion criteria were included in the analysis, consisting of 10,342 patients (see Figure 1). Studies fell into general categories involving a) use of only BMS, b) use of only DES, c) comparative studies of BMS versus DES, or d) comparison studies of PCI versus CABG (see Table 1).

Patient demographics in the group undergoing BMS placement were generally similar to those undergoing DES placement (see Table 2). There was incomplete reporting of baseline demographics across studies. Medication profiles – including duration of antiplatelet drug therapy – were inconsistently reported.

Estimates of rates for mortality, MI, and TVR/TLR at each of the three recorded time points are displayed in Table 3. The rates of events are numerically higher for patients treated with BMS for most endpoints, at most timepoints. However, without adjustment, the significance and/or relevance of the differences noted cannot be fully determined. As expected, the overall rates of events are higher in patients undergoing unprotected LMCA PCI than in conventional PCI patients.

Subsequent analysis was performed on those studies comparing DES and BMS and providing either adjusted event rates, or randomization according to stent type. Of the 12 comparative studies, 9 studies reported relevant endpoints, consisting of 5,081 patients (see Table 4). Most utilized propensity scoring for adjustment. Comparative event estimates for DES versus BMS were calculated (see Table 5). At 6–12 months, the OR for mortality was 0.94 (95%CI 0.06 – 15.48, $p=0.97$) and for MI was (0.64, 95%CI 0.19 – 2.17, $p=0.47$). The OR clearly favored DES for TVR/TLR (0.10, 95%CI 0.01 – 0.84, $p=0.01$) and MACE (0.34, 95%CI 0.15 – 0.78, $p=0.01$) at 6–12 months. At 2 years the OR favored DES for mortality (0.42, 95%CI 0.28 – 0.62, $p<0.01$) and MACE (0.31, 95%CI 0.15 – 0.66, $p<0.01$); the OR for MI did not reach statistical significance (0.16, 95%CI 0.01 – 3.53, $p=0.13$). The OR for TVR/TLR at 2 years could not be estimated due to a lack of reported data. Findings at 3 years favored DES for mortality (0.70, 95%CI 0.53 – 0.92, $p=0.01$), MI (0.49, 95%CI 0.26 – 0.92, $p=0.03$), and TVR/TLR (0.46, 95%CI 0.30 – 0.69, $p<0.01$); the OR for MACE did not reach statistical significance (0.78, 95%CI 0.57 – 1.07, $p=0.12$).

Discussion

PCI is increasingly being performed for lesions previously considered contraindicated, such as unprotected LMCA. Given the lower rates of restenosis reported with DES in PCI of standard coronary lesions, there has been a trend towards their use in unprotected LMCA PCI. However, the superiority of DES over BMS for unprotected LMCA has not been clearly established.

We reviewed the literature on unprotected LMCA PCI to compare outcomes between DES vs. BMS. We identified 44 studies involving PCI for unprotected LMCA as a source for

crude event rates. Crude event rates were lower for DES than BMS for mortality, TVR/TLR and MACE at 6–12 months, 2 years, and 3 years, but appeared equivalent for MI at these same timepoints. However, these rates are unadjusted, rendering them prone to selection bias and confounding.

To address this, we performed a subsequent analysis involving studies that provided adjusted event rates or randomized patients according to stent type (DES vs. BMS). Although event rates at 6–12 months favored DES, the sample size was small, involving predominantly one study (12). At 2 and 3 years post-PCI, the sample size was larger and improved outcomes with DES over BMS were observed for mortality, MI, TVR/TLR, and MACE. Statistically significance differences were observed in most cases.

Although the finding of lower TVR/TLR rates is consistent with the known performance of DES, no study to date has shown a consistent mortality benefit with DES over BMS in unprotected LMCA PCI. The reason for the lower mortality rate in the DES group seen in our meta-analysis is unclear. It may be that DES, with known lower rates of restenosis, provides a true advantage over BMS. In the critical left main position a small or moderate degree of restenosis could theoretically precipitate critical ischemia. Alternatively, this finding could be due to methodological issues. Selection bias may have favored DES: patients with fewer medical comorbidities may have preferentially undergone DES placement. A review of overall patient demographics in our analysis does not support this, as similar rates of cardiac risk factors were found between both groups (see Table 2). An alternative explanation may relate to a procedural learning curve, as operators may have become more technically proficient at unprotected LMCA PCI by the time DES were favored. Finally, as medication profiles at baseline and follow-up were not consistently reported, it is possible that the benefit seen with DES could be due, in part, to a longer duration of dual antiplatelet drug therapy as compared to BMS. Similarly, patients deemed to be poor candidates for long-term dual or triple antiplatelet therapy may have been denied treatment with DES.

A recent meta-analysis of patients undergoing DES for unprotected LMCA by Biondi-Zoccai et al noted similar findings, reporting an adjusted OR of 0.34 for both MACE and TVR, favoring DES over BMS (13). This meta-analysis was performed through 2006 and included far fewer patients than our analysis (206 DES patients, 190 BMS patients). Since our analysis was performed, Buszman et al have reported on the long-term follow-up of a group of 252 patients from the LE-MANS registry (14). Their results mirror ours. Unmatched analysis showed a significantly lower rate of major adverse cardiovascular or cerebral events (MACCE) with DES as compared to BMS at four-year follow-up (14.9% vs. 25.9%, $p=0.039$); subsequent propensity matched analysis showed similar results. They noted that mortality rates favored DES, although this did not reach statistical significance (9.6% vs. 13.3%, $p=NS$). In a subgroup of patients with distal unprotected LMCA, however, DES was associated with a statistically significant lower mortality rate as compared to BMS ($p=0.03$). Results from the left main subset of the SYNTAX trial (15) were presented at TCT 2008. Reported 12 month DES event rates were similar to our cumulative crude estimates, with a rate of 4.2% for mortality, 4.3% for MI, and 15.8% for major cardiac or cerebrovascular adverse events (MACCE) (16). As these results have yet to be published they were not included in our analysis. SYNTAX did not include a BMS arm and thus would not impact our comparative analysis.

Currently there are no large, randomized controlled clinical trials comparing DES to BMS in unprotected LMCA. Two ongoing studies comparing PCI with DES to CABG for unprotected LMCA (PRE-COMBAT and REVASCULARIZE) do not include a comparison with BMS. Therefore our meta-analysis may offer evidence to guide clinical practice.

Study limitations

Our study has clear limitations. The limitations of the meta-analytical approach are well known and documented (17); the meta-analytical approach with observational data is even more fraught with limitations (18). The inclusion of only published studies makes our analysis prone to publication bias. Our results, particularly the crude event rates, are prone to confounding and selection bias and thus direct comparison of these overall rates was not performed. We did not have data for all studies at each time period; therefore this limits comparison of rates across time within a specific endpoint. Finally, we were unable to control for the specific type of DES or BMS used, as some studies suggest heterogeneous outcomes within the stent types.

Conclusions

The results of this meta-analysis suggest that DES is associated with favorable outcomes as compared to BMS in unprotected LMCA PCI. The improved outcomes observed with DES compared to BMS support a continued re-evaluation of the role of PCI for the treatment of unprotected LMCA.

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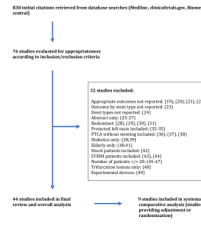


Figure 1. Methods

Table 1

Included studies

Study	Year	Design	Stent Type	N	DES (N)	BMS (N)	Location	Follow-up (months)
BMS only studies: 5								
Black (50)	2001	Retrospective Cohort study	BMS	92	0	92	Europe	7+/-5
Kelley (51)	2003	Retrospective cohort study	BMS	43	0	43	US/Europe	12
Lee BK (52)	2007	Propective cohort study	BMS	187	0	187	Asia	71+26
Silvestri (53)	2000	Prospective cohort study	BMS	140	0	140	Europe	12
Takagi (54)	2002	Prospective cohort study	BMS	64	0	64	Europe	31+/-23
DES only studies: 21								
Agostini (55)	2005	Retrospective cohort study	DES	58	58	0	Europe	15
Arampatzis (56)	2003	Retrospective cohort study	DES	31	31	0	Europe	5.1+/-1.8
Chieffo (57)	2007	Retrospective cohort study	DES	147	147	0	US/Asia/Europe	30+/-10
Chieffo (58)	2008	Retrospective cohort study	DES	731	731	0	US/Asia/Europe	29+/-13
Cherradi (59)	2008	Prospective cohort study	DES	101	101	0	Europe	12+/-3
de Lezo(60)	2004	Prospective cohort study	DES	52	52	0	Europe	12
Ge L (61)	2007	Retrospective cohort study	DES	70	70	0	Asia/Europe	12
Khattab (62)	2007	Prospective cohort study	DES	82	82	0	Europe	36
Kim (63)	2006	Retrospective cohort study	DES	116	116	0	Asia	18
Kim (64)	2008	Retrospective cohort study	DES	63	63	0	US	12+/-8
Lee, SH (65)	2005	Nonrandomized study (SES vs PES)	DES	54	54	0	Asia	6
Lozano (66)	2004	Prospective cohort study	DES	42	42	0	Europe	11
Mehilli (67)	2009	Randomized controlled trial (SES vs PES)	DES	607	607	0	Europe	24
Meliga (68)	2008	Retrospective cohort study	DES	358	358	0	US/Europe	36
Migliorini (69)	2006	Prospective cohort study	DES	101	101	0	Europe	10+/-6
Price (70)	2006	Prospective cohort study	DES	50	50	0	US	9
Sanmartin (71)	2007	Prospective cohort study	DES	100	100	0	Europe	12
Sheiban (72)	2007	Prospective cohort study	DES	85	85	0	Europe	20+/-7
Vaquero (73)	2009	Prospective cohort study	DES	291	291	0	Europe	24

Study	Year	Design	Stent Type	N	DES (N)	BMS (N)	Location	Follow-up (months)
Vecchio (74)	2007	Prospective cohort study	DES	114	114	0	Europe	17+/-9
Wood (75)	2008	Retrospective cohort study	DES	100	100	0	US	28
BMS and DES studies: 12								
Cheiffo (76)	2005	Nonrandomized study	DES vs BMS	149	85	64	Europe	6
Erglis (12)	2007	Randomized Controlled Trial	DES vs BMS	103	53	50	Australia	6
Gao (77)	2008	Nonrandomized study	DES vs BMS	424	220	224	Asia	15
Han (78)	2009	Nonrandomized study	DES vs BMS	287	178	109	Asia	35+/-14
Hertting (79)	2008	Nonrandomized study	DES vs BMS	54	16	38	Europe	24
Kim (80)	2009	Nonrandomized study	DES vs BMS	1217	864	353	Asia	36
Palmerini (81)	2008	Nonrandomized study	DES vs BMS	1453	1111	342	Europe	24
Park (63)	2005	Nonrandomized study	DES vs BMS	123	102	121	Asia	12
Schrale (82)	2008	Retrospective cohort study	DES and BMS	100	55	45	Europe	21+/-14
Tamburino (83)	2009	Nonrandomized study	DES vs BMS	849	611	238	Europe	36
Tamburino (84)	2009	Nonrandomized study	DES vs BMS	479	334	145	Europe	36
Wood (85)	2005	Nonrandomized study	DES vs BMS	161	61	100	US	12
PCI/CABG studies: 6								
Buszman (86)	2008	Randomized controlled trial	CABG vs PCI	52	18	34	Europe	28+/-10
Chieffo (87)	2006	Nonrandomized study	CABG vs DES	107	107	0	Europe	12
Makikallo (88)	2008	Nonrandomized study	CABG vs DES	49	49	0	Europe	12+/-6
Palmerini (89)	2006	Nonrandomized study	CABG vs PCI	157	94	63	Europe	14
Sanmartin (90)	2007	Nonrandomized study	CABG vs DES	96	96	0	Europe	13+/-8
Seung (91)	2008	Randomized Controlled Trial	CABG vs PCI	603	396	207	Asia	34

Table 2

Baseline Patient Demographics for Studies Included in the Overall Analysis

	DES		BMS	
	n		n	
Age (years)	4768	67.5 (65.8 – 69.3)	1621	67.8 (66.0 – 69.7)
		Percent (95% CI)		Percent (95% CI)
Male	6464	74 (73 – 75)	2091	61 (69 – 73)
Diabetes Mellitus (DM)	6691	28 (27 – 29)	2170	22 (20 – 23)
Insulin dependent DM	85	11.0 (4.2 – 17.8)	63	8.9 (1.9 – 15.9)
Hypertension	6297	65 (64 – 67)	2032	53 (51 – 55)
Hypercholesterolemia	6111	57 (57 – 59)	1892	39 (36 – 41)
History of Prior MI	3036	23 (21 – 24)	1165	12 (10 – 14)
History of PCI	1912	19 (18 – 21)	794	13 (10 – 15)
COPD	1962	9.4 (7.9 – 10.9)	996	1.6 (0.8 – 2.4)
Renal Insufficiency	3570	7.7 (6.8 – 8.5)	1241	4.5 (3.4 – 5.6)
Peripheral Arterial Disease	1168	6.8 (5.5 – 8.2)	560	0.9 (0.03– 1.9)

* n refers to the number of patients within the studies who contributed to the estimate of interest. Rates are the estimated percent of patients with the characteristic, and associated 95% confidence intervals.

Table 3

Estimated Cumulative Event Rates by Stent Type in the Overall Analysis

	Stent Type	6–12 Months	2 years	3 years
Mortality	DES	5.94% (4.73% – 7.44%) n = 2691	7.89% (6.07% – 10.20%) n = 4430	8.80% (6.20% – 12.34%) n = 2912
	BMS	7.24% (3.51% – 14.33%) n = 763	14.14% (8.96% – 21.62%) n = 1266	12.71% (6.94% – 22.15%) n = 959
MI	DES	6.26% (4.71% – 8.27%) n = 2356	3.90% (1.98% – 7.55%) n = 2182	4.04% (2.33% – 6.91%) n = 2516
	BMS	9.97% (6.09% – 15.90%) n = 157	3.06% (1.18% – 7.69%) n = 607	3.43% (1.87% – 6.21%) n = 752
TVR/TLR	DES	7.83% (5.95% – 10.24%) n = 2257	10.20% (8.55% – 12.13%) n = 4772	8.03% (5.62% – 11.37%) n = 2912
	BMS	16.95% (12.92% – 21.92%) n = 985	16.15% (13.93% – 18.66%) n = 1241	16.40% (12.23% – 21.64%) n = 959
MACE	DES	15.87% (12.93% -19.32%) n=2593	18.99% (14.92%-23.86%) n=2623	21.43% (14.85%-29.91%) n=1652
	BMS	39.31% (31.68%-47.50%) n=554	32.69% (17.72%-52.26%) n=441	31.60% (23.15%-41.47%) n=399

* n refers to the number of patients within the studies who contributed to the estimate of interest. Rates are the estimated percent of patients with the event and associated 95% confidence intervals.

Table 4

Comparative studies of DES versus BMS

	Design	Method of Adjustment	DES (n)	BMS (n)	F/u (months)	Adjusted Point Estimate Mortality at f/u	Adjusted Point Estimate MI at f/u	Adjusted Point Estimate TVR/TLR at f/u	Adjusted Point Estimate MACE at f/u
Chieffo 2005 (76)	Nonrandomized study	Propensity score matching	85	64	6	N/A	N/A	OR 0.28 (0.09-0.81) p=0.01	OR 0.27 (0.09-0.73) p=0.007
Erglis 2007 (12)	Randomized Controlled trial	Randomization	53	50	6	OR 0.94 (0.06-15.48) p=1.00	OR 0.64 (0.19-2.17) p= 0.47	OR 0.10 (0.01-0.84) p=0.01	OR 0.36 (0.13-0.96) p=0.04
Gao 2008 (77)	Prospective Cohort study (DES compared to historical BMS cohort)	Propensity score matching	220	224	15	N/A	N/A	N/A	OR 0.49 (0.26-0.94) p=0.032
Han 2009 (78)	Prospective Cohort study	Propensity score matching	178	109	35+/-14	OR 0.25 (0.08-0.81) p<0.01	OR 0.16 (0.01-3.53) p=0.13	OR 0.26 (0.08-0.83) p<0.001	OR 0.23 (0.09-0.56) p<0.001
Kim 2009 (80)	Prospective Cohort study	Weighting with propensity score	864	353	36	HR 0.86 (0.50-1.47) p=0.569	N/A	HR 0.32 (0.17-0.61) P<0.001	HR 0.81 (0.54-1.21) p=0.31
Palmerini 2007 (40)	Nonrandomized study	Propensity score as a covariate	1111	342	24	HR 0.48 (0.32-0.74) p=0.002	N/A	N/A	N/A
Schrale 2008	Retrospective Cohort study	Multivariate Cox regression	55	45	21+/14	HR 0.23 (0.06-0.91) p=0.034	N/A	N/A	N/A
Tamburino 2009 (83)	Nonrandomized study	Propensity score matching	611	238	36	HR 0.75 (0.52-1.12) p=0.17	HR 0.49 (0.26-0.92) p=0.03	HR 0.46 (0.29-0.74) p=0.001	N/A
Tamburino 2009 (84)	Nonrandomized study	Propensity score matching	334	145	36	HR 0.51 (0.30-0.86) p=0.01	N/A	HR 0.79 (0.33-1.90) p=0.39	HR 0.73 (0.44-1.21) p=0.22

* n refers to the number of patients within the studies who contributed to the estimate of interest. Odds ratios (OR) and Hazard ratios (HR) are reported with 95% confidence intervals.

Table 5

Cumulative Odds Ratios for Comparative Studies (DES versus BMS)

	Time	Contributing studies	DES (n)	BMS (n)	OR (95% CI)	P value
Mortality	6-12 months	Erglis 2007 (12)	53	50	0.94 (0.06-15.48)	p=0.97
	2 years	Han 2009 (78) Palmerini 2007 (40) Schrale 2008 (82)	1344	496	0.42 (0.28-0.62)	p<0.01
	3 years	Kim 2009 (80) Tamburino 2009 (83) Tamburino 2009 (84)	1809	736	0.70 (0.53-0.92)	p=0.01
MI	6-12 months	Erglis 2007 (12)	53	50	0.64 (0.19-2.17)	p= 0.47
	2 years	Han 2009 (78)	178	109	0.16 (0.01-3.53)	p=0.13
	3 years	Tamburino 2009 (83)	611	238	0.49 (0.26-0.92)	p=0.03
TVR/TLR	6-12 months	Erglis 2007 (12)	53	50	0.10 (0.01-0.84)	p=0.01
	2 years	No studies	--	--	--	--
	3 years	Kim 2009 (80) Tamburino 2009 (83) Tamburino 2009 (84)	1809	736	0.46 (0.30-0.69)	p<0.01
MACE	6-12 months	Chieffo 2005 (76) Erglis 2007 (12)	138	114	0.34 (0.15-0.78)	P=0.01
	2 years	Gao 2008 (77) Han 2009 (78)	398	333	0.31 (0.15-0.66)	P<0.01
	3 years	Kim 2009 (80) Tamburino 2009 (84)	1198	498	0.78 (0.57-1.07)	P=0.12

* n refers to the number of patients within the studies who contributed to the estimate of interest. OR are reported with 95% confidence intervals.