Outcomes in culprit only *versus* multivessel percutaneous coronary intervention in ST elevation myocardial infarction during index procedure

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Abstract

Aims: Multivessel disease seen in 40 - 65% of STEMI patients is associated with higher mortality. ACC/AHA guidelines do not give clear indications regarding revascularization of non-infarct related arteries in the absence of cardiogenic shock while ESC/EACTS guidelines provide a class 2b recommendation for multivessel PCI in the primary intervention in select patients. This meta-analysis aims to evaluate the role of multivessel versus culprit only percutaneous intervention (PCI) in STEMI with multivessel disease.

Methods and results: Data from 12 studies enrolling 32,548 patients was examined. Multivessel PCI was defined as PCI of culprit and non-culprit lesions during the index procedure while culprit only PCI was defined as PCI of the infarct related vessel. In-hospital all-cause mortality (OR 0.59, CI 0.36 - 0.97) and 30 day MACE (OR 0.43, CI 0.19-0.99) favored culprit vessel only PCI compared to multivessel PCI, but this did not remain significantly lower at longer follow-up. The culprit only group experienced a lower rate of stent thrombosis (OR 0.41, CI 0.21 -0.78). At later follow-up, multivessel PCI was associated with lower cardiac death at 12-30 months (OR 2.58, CI 1.22 - 5.42) and lower rates of repeat revascularization at 2 – 2.5 years (OR 3.77, CI 2.26, 6.27).

Conclusion: In conclusion, this meta-analysis demonstrated lower in-hospital all-cause mortality and 30-day MACE events and higher repeat revascularization with culprit only PCI. However, multi-vessel PCI during the index procedure was associated with a lower risk of cardiac death at 12-30 months. Either approach is however safe as evidenced by comparable rates of all cause death, MI, stroke, MACE events, major bleeding or vascular complications at 12 months follow-up. A significant reduction in repeat revascularization and cardiac at later follow-up was seen in patients who underwent multivessel revascularization.

Introduction

Primary percutaneous coronary intervention (p-PCI) of the culprit (infarct related) artery has become the standard of care for patients presenting with ST-elevation myocardial infarction (STEMI). Multivessel disease is seen in 40 to 65% of these patients during index angiography, and is associated with poor outcomes including higher mortality [1]. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines on management of patients with STEMI are clear regarding percutaneous coronary intervention (PCI) of the culprit artery in STEMI patients with multivessel disease; however, the guidelines do not give clear indications in support of or against revascularization of non-infarct related arteries with significant stenosis at the time of p-PCI in the absence of cardiogenic shock. They acknowledge the paucity of data on the subject which makes it hard to draw robust conclusions [1]. Meanwhile, the European Society of Cardiology/ European Association for Cardio-Thoracic Surgery (ESC/ EACTS) guidelines give a class 2b recommendation for multivessel PCI in the p-PCI in select patients [2,3]. Since the both guidelines were published, results from Randomized Trial of Preventive Angioplasty in Myocardial Infarction (PRAMI) and Randomized Trial of Complete *Versus* Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease (CvLPRIT) trials have become available [3,4]. This meta-analysis seeks to evaluate the role of multivessel *versus* culprit only PCI

in STEMI with multivessel disease during the index procedure.

Methods

Search strategy

A systematic search was performed to identify relevant studies in MEDLINE (PubMed), Cochrane Library, and Scopus from January 1, 2002 to March 31, 2015. Year 2002 was chosen as the initial year to focus on studies where drug eluting stents (DES) were commercially available for use. Medical Subject Heading (MeSH) keywords included were "myocardial infarction, culprit, multivessel, and PCI." Studies were limited to adult humans and excluded studies in languages other than English when translations were not available. The initial search yielded 159 citations (Scopus 75, MEDLINE 72, and Cochrane 12).

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After reviewing titles and abstracts, 8 studies met inclusion criteria. A manual review of their references was conducted which resulted in the inclusion of 5 additional papers. However, one study was excluded because it did not provide outcomes of interest [5]. Figure 1 outlines the search methodology.

Study selection

Two reviewers (D.W. and M.A.) independently reviewed the 12 studies. The included studies reported comparative outcomes for multivessel PCI *versus* culprit vessel only PCI in STEMI. Studies that focused on cardiogenic shock were excluded. All included studies either excluded cardiogenic shock or reported separate outcomes. The Newcastle Ottawa Scale was used to measure the quality of non-randomized studies. Multivessel PCI was defined as PCI of culprit and non-culprit lesions during the index procedure. Culprit only PCI was defined as PCI of the infarct related vessel during the index procedure.

We extracted baseline patient characteristics, treatment strategy, and outcome data from each included study. Primary clinical outcomes included all-cause mortality and MACE, defined as the composite end-point of death, non-fatal myocardial infarction (MI), or repeat revascularization. Secondary outcomes included cardiac death, non-fatal MI, stroke, repeat revascularization, stent thrombosis or symptomatic graft occlusion.

Endpoints such as contrast induced nephropathy and refractory angina were not evaluated due to paucity of data among the pooled studies or low number of events. Outcomes were reported at 30 days, and at 12, 24, 30 and 42 months when available. The studies' defined end-points were used for the analyses.

Statistical analyses

Percentages and means ± SD were calculated to describe the distributions of categorical and continuous variables, respectively. Odds Ratios (OR) and their 95% Confidence Intervals (CIs) were utilized to summarize the effect size for each clinical outcome at the corresponding time point using the random-effects model. Continuous variables were compared using the two-tailed independent samples Student's t test. Categorical variables were compared using the Chi-square test with Yates' correction or Fisher's exact test, when appropriate. Measures of heterogeneity calculated include Cochran's Q-statistic, the I^2 index, and the tau-squared tests. I^2 greater than or equal to 25% was considered as significant heterogeneity.

Publication bias was assessed using the Funnel Plot analysis for all-cause mortality and MACE. A p value ≤ 0.05 was considered statistically significant. Baseline data was analyzed using the Statistical Package for Social Scientists (SPSS Inc., 19.0 for Windows). The meta-analyses were performed using Review Manager (version 5.0, Cochrane Collaboration).

Results

This analysis included a total of 12 studies (5 RCTs, 5 retrospective cohort studies, 1 prospective observational study, and 1 case control study) enrolling 32,548 patients. Of those 32,548 patients, 27,785 underwent culprit only and 4,763 patients underwent multivessel PCI in the index procedure for STEMI. Table 1 outlines basic characteristics and follow-up of the 12 studies. The Newcastle Ottawa Scale is provided in the supplement. All studies scored at least 7/9. Weighted pooled analysis of baseline characteristics are summarized in Table 2. Baseline characteristics of patient populations included in each individual study are available in the supplement.

The incidence of diabetes mellitus, previous cerebrovascular accident (CVA), triple vessel CAD, and Left Anterior Descending (LAD) artery as culprit lesion (Table 3) did not vary significantly between the two groups. Patients in the culprit only PCI group were more likely to have HTN, prior MI, prior angioplasty, and prior CABG. Patients in the multivessel PCI group were more likely to be male and have history of hyperlipidemia (HLD), tobacco use, and prior CVA.

Results of our meta-analysis show that in-hospital all-cause mortality was significantly lower in patients undergoing culprit vessel only PCI compared to patients who underwent multivessel PCI (OR 0.59, CI 0.36 - 0.97), but did not remain significantly lower at longer follow-up (30 days, 12 months, and 24 months) (Table 3, Figures 2a,2b). Short term (defined as in-hospital or at 30 days) MACE was significantly lower for the culprit only group (OR 0.43, CI 0.19-0.99), but had comparable rates at 1 year (OR 1.00, CI 0.57 - 1.74) (Figures 3a,3b). Culprit only group experienced a lower rate of stent thrombosis (OR 0.41, CI 0.21 -0.78), but this outcome was only reported by 2 of the 12 studies (Figure 4). Multivessel PCI was associated with lower cardiac death at 12-30 months (OR 2.58, CI 1.22 - 5.42) (Figure 5). Multivessel PCI was also associated with lower rates of repeat revascularization at 2 – 2.5 years (OR 3.77, CI 2.26, 6.27) (Figures 6a, 6b).
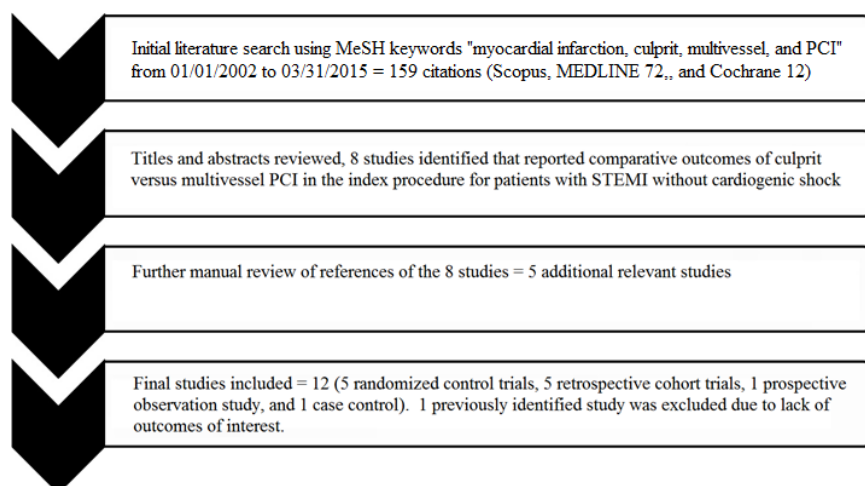

Figure 1. Literature search methodology.

Table 1. Summary of studies included in meta-analysis.

	First Author	Year	Design	Culprit only (n)	Multivessel PCI (n)	Region	Mean follow-up (months)
1	Abe D	2014	Retrospective cohort study	22	54	Japan	12*
2	Cavender MA	2009	Retrospective cohort study	25809	3134	USA	0**
3	Corpus RA	2004	Retrospective cohort study	354	26	USA	12
4	Di Mario C.	2004	Randomized controlled trial (HELP AMI)	17	52	Europe	12
5	Gerschlick AH	2015	Randomized controlled trial (CVLPRIT)	146	150	Europe	12
6	HannanEL	2010	Case control study	503	503	USA	22*
7	Khattab AA	2008	Prospective observational study	45	28	Europe	12
8	Kornowski R	2011	Randomized control trial (Horizons-AMI)***	393	275	Asia, Europe, S. America, USA	12
9	Politi L	2010	Randomized control trial	84	65	Europe	30
10	Qarawani D	2008	Retrospective cohort study	25	95	Israel	12
11	Varani E	2008	Retrospective cohort study	156	147	Europe	20
12	Wald DS	2013	Randomized control trial (PRAMI)	231	234	Europe	23
* median follow-up							
** in-hospital data only							
*** post-hoc analysis							

Table 2. Summary of baseline characteristics.

	Culprit Only	Multivessel	p
Mean Age	66.1	65.3	0.48
Male	20031/27622 (72.5%)	3534/4737 (74.6%)	0.003
DM	6310/26963 (23.4%)	926/4036 (22.9%)	0.5334
HTN	16929/26963 (62.8%)	2334/4087 (57.1%)	0.0001
HLD	12483/26648 (46.8%)	2026/3788 (53.5%)	0.0001
Tobacco Use	13286/26879 (49.4%)	2452/4022 (61%)	0.0001
Prior MI	5066/26817 (18.9%)	625/3942 (15.9%)	0.0001
Prior CABG	2571/26457 (9.7%)	193/3610 (5.3%)	0.0001
Prior CVA	2032/26756 (7.6%)	294/3925 (7.5%)	0.8432
Prior angioplasty	4529/26366 (17.2%)	528/3654 (14.4%)	0.0001
3v Dz	430/1427 (30.1%)	409/1328 (30.8%)	0.7357
LAD culprit	13910/26834 (51.8%)	1958/3844 (50.9%)	0.304

Table 3. Clinical outcomes in patients undergoing culprit only or multivessel PCI for STEMI.

Outcome	Follow-up	Studies	Patients	Event Rate Culprit Only N / total	%	Event Rate Multivessel N / total	%	Odds Ratio (Random)	Q [‡]	P[#]	I²[§]	τ²[‖]
All-Cause Death	In-hospital	8	31237	642/27161	2.36	136/4076	3.34	0.59 (0.36 - 0 0.97)	14.52	0.04	52	0.21
	30 - days	2	453	25/399	6.27	19876	11.11	0.41 (0.15 - 1.10)	1.19	0.28	16	
	12 - months	8	2886	118/1703	6.93	99/1183	8.37	0.60 (033-1.07)	17.79	0.01	61	0.37
	24 - months	2	1471	92/737	12.48	72/737	9.77	1.35 (0.43 -4.25)	11.45	0.0007	91	0.63
	24–42 - months	3	1620	126/818	15.40	94/802	11.72	1.53 (0.74 - 3.20)	9.82	0.007	80	0.32
MACE [*]	Short term (30-day or in-Hospital)	3	67	56/416	13.46	11/97	11.34	0.43 (0.19 - 0.99)	1.02	0.6	0	0
	12 – months	5	1486	200/955	20.94	91/531	17.14	1.20 (0.66 - 2.18)	11.7	0.02	66	0.28
Myocardial infarction	In-hospital	3	569	14/396	3.54	4/173	2.31	2.32 (0.30 - 17.73)	2.44	0.12	59	1.29
	12 - months	6	1760	47/1175	4.00	28/585	4.79	0.82 (0.50-1.36)	3.41	0.64	0	0
Non-fatal Stroke	Short term (30-day or in-Hospital)	3	29389	110/26201	0.42	13/3188	0.41	1.02 (0.58 - 1.81)	0.34	0.84	0	0
	12 - months	3	1238	10/759	1.32	4/479	0.84	1.34 (0.39 -4.59)	0.23	0.89	0	0
Target Vessel Revascularization	30 - days	2	453	30/399	7.52	19784	5.56	1.12 (0.27 - 4.76)	0.77	0.38	0	0
	12-month	5	1691	141/1158	12.18	47/533	8.82	1.18 (0.81 - 1.71)	2.68	0.61	0	0
Repeat Revascularization	In-hospital	3	262	20/87	22.99	14/175	8.00	2.48 (0.76 -8.14)	3.75	0.15	47	0.5
	2 - 2.5 years	2	614	74/315	23.49	22/299	7.36	3.77 (2.26 - 6.27)	0.42	0.52	0	0
Cardiac Death	12-30 - months	3	910	27/461	5.86	10/449	2.23	2.58 (1.22 - 5.42)	0.34	0.84	0	0
Stent thrombosis	12 - months	2	942	21/613	3.43	22/329	6.69	0.41 (0.21 -0.78)	0.08	0.77	0	0
Major Bleeding	12 - months	3	1344	60/893	6.72	31/451	6.87	0.98 (0.50 - 1.93)	2.54	0.28	21	0.1
CABG	12-30 - months	2	529	44/438	10.05	33329	4.40	1.40 (0.44 - 4.40)	0.06	0.8	0	0
Vascular Complications	24 - months	3	29619	1076/26312	4.09	156/3307	4.72	1.04 (0.54 - 2.02)	2.66	0.25	25	0.14

[*]Composite endpoint of death, non-fatal myocardial infarction, and repeat revascularization. [‡]Cochran's Q-score for heterogeneity; [§]I² index for degree of heterogeneity; [‖] tau-squared measure of heterogeneity; # P-value for Cochran's Q-score for heterogeneity

a)

Study or Subgroup	Culprit Only PCI Events	Total	Multi-Vessel PCI Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Di Mario et al. 2004	0	17	1	52	2.2%	0.98 [0.04, 25.20]	2004
Corpus et al. 2004	20	354	5	26	12.6%	0.25 [0.09, 0.74]	2004
Varani et al. 2008	6	156	8	147	12.4%	0.69 [0.24, 2.05]	2008
Qarwani et al. 2008	1	25	4	95	4.3%	0.95 [0.10, 8.88]	2008
Cavender et al. 2009	586	25802	88	3134	28.5%	0.80 [0.64, 1.01]	2009
Hannan et al. 2010	10	503	17	503	17.2%	0.58 [0.26, 1.28]	2010
Politi et al. 2010	7	84	2	65	7.3%	2.86 [0.57, 14.27]	2010
Abe et al. 2013	12	220	11	54	15.5%	0.23 [0.09, 0.54]	2013
Total (95% CI)		**27161**		**4076**	**100.0%**	**0.59 [0.36, 0.97]**	
Total events	642		136				

Heterogeneity: Tau² = 0.21; Chi² = 14.52, df = 7 (P = 0.04); I² = 52%
Test for overall effect: Z = 2.09 (P = 0.04)

b)

Study or Subgroup	Culprit Only PCI Events	Total	Multi-Vessel PCI Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Di Mario et al. 2004	0	17	1	52	2.9%	0.98 [0.04, 25.20]	2004
Corpus et al. 2004	42	354	5	26	13.9%	0.57 [0.20, 1.58]	2004
Qarwani et al. 2008	2	25	9	95	8.7%	0.83 [0.17, 4.11]	2008
Khattab et al. 2008	3	45	2	28	7.1%	0.93 [0.15, 5.93]	2008
Hannan et al. 2010	28	503	36	503	20.5%	0.76 [0.46, 1.27]	2010
Kornowoski et al. 2011	9	393	25	275	17.0%	0.23 [0.11, 0.51]	2011
Abe et al. 2013	24	220	17	54	17.8%	0.27 [0.13, 0.54]	2013
Gerschlik et al. 2015	10	146	4	150	12.2%	2.68 [0.82, 8.76]	2015
Total (95% CI)		**1703**		**1183**	**100.0%**	**0.60 [0.33, 1.07]**	
Total events	118		99				

Heterogeneity: Tau² = 0.37; Chi² = 17.79, df = 7 (P = 0.01); I² = 61%
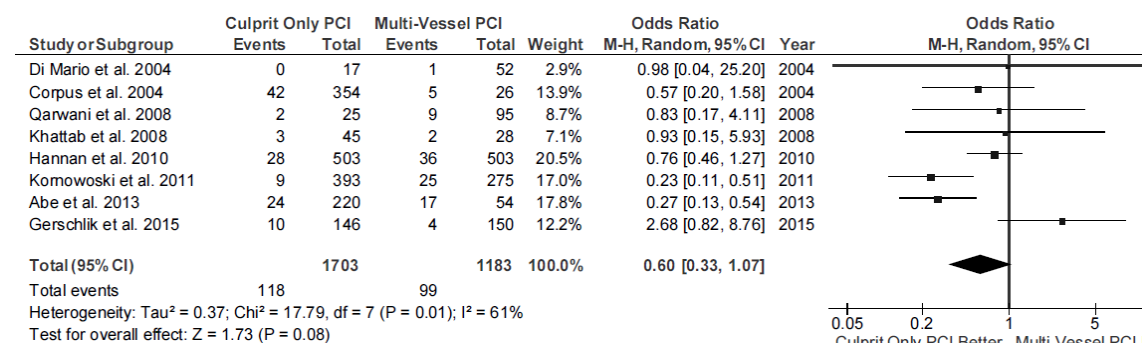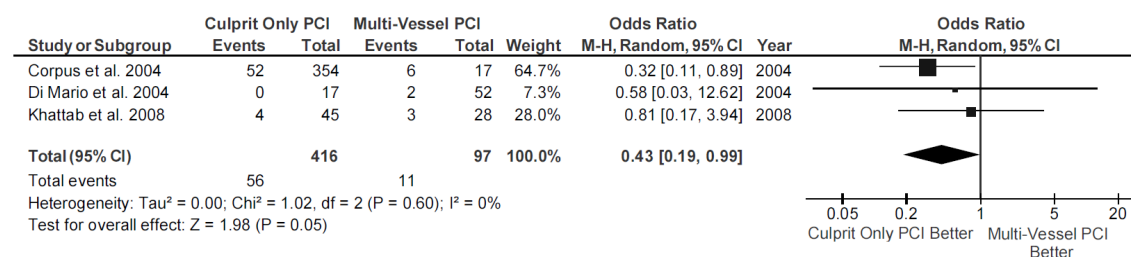Test for overall effect: Z = 1.73 (P = 0.08)

Figure 2. All-Cause Mortality (a) All-Cause Mortality (In-Hospital). Culprit only is associated with lower all cause in-hospital mortality compared to multivessel PCI for STEMI. (b) All-Cause Mortality (12 Months). Culprit only and multivessel PCI were associated with similar all-cause mortality at 12 months.

a)

Study or Subgroup	Culprit Only PCI Events	Total	Multi-Vessel PCI Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Corpus et al. 2004	52	354	6	17	64.7%	0.32 [0.11, 0.89]	2004
Di Mario et al. 2004	0	17	2	52	7.3%	0.58 [0.03, 12.62]	2004
Khattab et al. 2008	4	45	3	28	28.0%	0.81 [0.17, 3.94]	2008
Total (95% CI)		**416**		**97**	**100.0%**	**0.43 [0.19, 0.99]**	
Total events	56		11				

Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)

b)

Study or Subgroup	Culprit Only PCI Events	Total	Multi-Vessel PCI Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Corpus et al. 2004	98	354	9	26	19.7%	0.72 [0.31, 1.68]
Di Mario et al. 2004	6	17	11	52	14.0%	2.03 [0.61, 6.73]
Gerschlik et al. 2015	31	146	15	150	23.1%	2.43 [1.25, 4.72]
Khattab et al. 2008	12	45	6	28	15.1%	1.33 [0.44, 4.08]
Kornowoski et al. 2011	53	393	50	275	28.0%	0.70 [0.46, 1.07]
Total (95% CI)		**955**		**531**	**100.0%**	**1.20 [0.66, 2.18]**
Total events	200		91			

Heterogeneity: Tau² = 0.28; Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
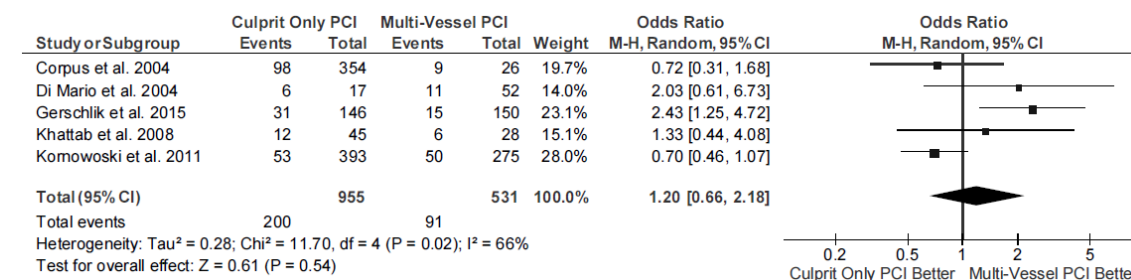Test for overall effect: Z = 0.61 (P = 0.54)

Figure 3. MACE 3(a) MACE (Short Term, 30-Day or In-Hospital). Culprit only was associated with lower short term (30 day or in-hospital) MACE compared to multivessel. (b) MACE (12 Months). Culprit only and multi-vessel were associated with similar rate of MACE at 12 months.
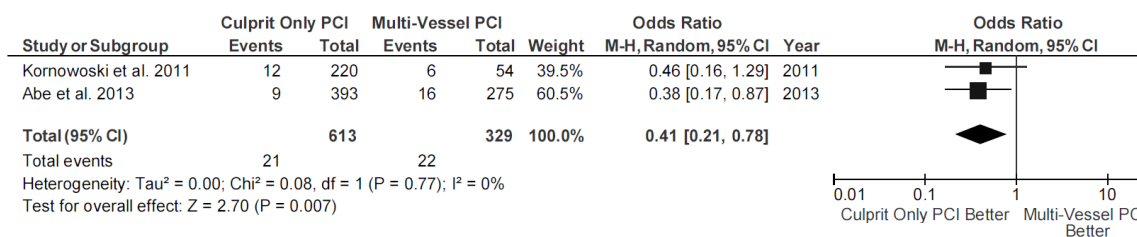
Figure 4. Stent Thrombosis (12 Months). Culprit only was associated with lower stent thrombosis at 12 months compared to multivessel PCI for STEMI.
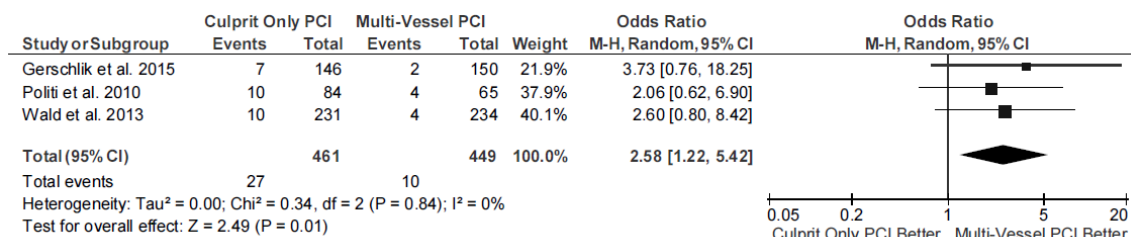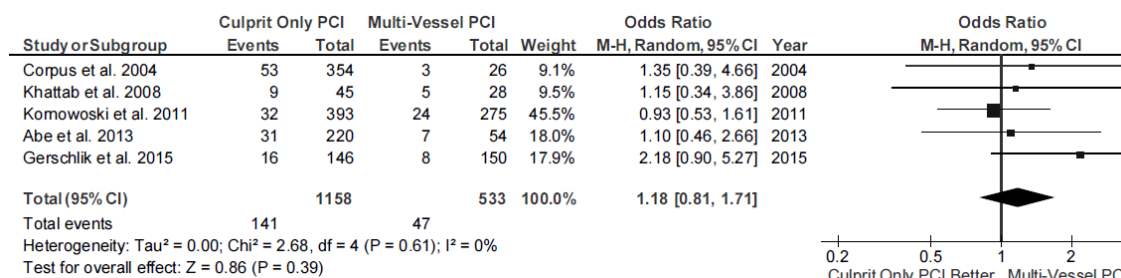

Figure 5. Cardiac Death (12 -30 months). Multivessel PCI was associated with a lower rate of cardiac death at 23-36 months compared to culprit only PCI.
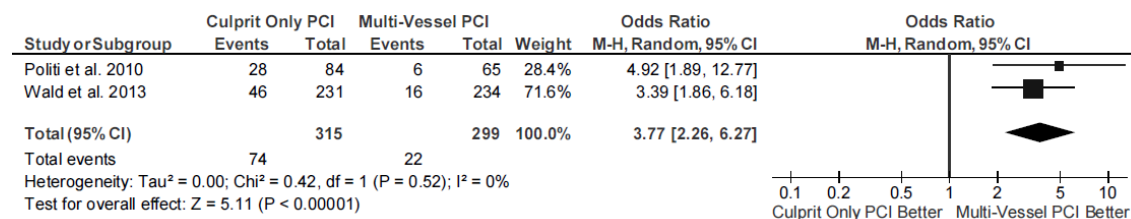
a)

b)

Figure 6. Revascularization (a) Target Vessel Revascularization (12 months). Culprit only and multivessel PCI were associated with similar target vessel revascularization at 12 months. (b). Total Repeat Revascularization (2 - 2.5 years). Multivessel PCI was associated a lower rate of repeat revascularization at longer term follow-up (23-36 months) than culprit only PCI.

The two groups had comparable rates of non-fatal MI, non-fatal stroke, target vessel revascularization, and major bleeding at 12 months follow-up (Table 3). Similarly, rates of CABG and vascular complications at 12-30 months follow-up were not significantly different between groups (Figures 7a, 7b).

Discussion

In our meta-analysis of 12 studies and 32,548 patients we found that culprit only PCI compared to multivessel PCI in the setting of STEMI was associated with a significantly lower incidence of in-hospital all-cause mortality and 30-day MACE events. However, overall mortality and MACE did not differ significantly at 12 months and beyond. The mitigation of the positive outcomes at 30 days was largely driven by

a higher incidence of repeat revascularization in the culprit only PCI group at 2 – 2.5 years. Interestingly, multivessel PCI was associated with a lower isolated risk of cardiac death at 12- 30 months and a higher rate of stent thrombosis at 12 months. The longer procedural time and greater number of stents deployed may worsen short-term outcomes with multivessel PCI, but improvement in outcomes at later follow-up intervals may be due to more complete revascularization. Complete revascularization when compared to incomplete revascularization in the setting of both CABG and PCI, is associated with improved mortality, decreased revascularization, and a lower rate of reinfarction [6].

Significant coronary stenosis in multiple arteries is seen in 40–65% of patients undergoing primary PCI for STEMI and leads to significantly worse outcomes [7]. The 2013 ACCF/AHA guidelines for
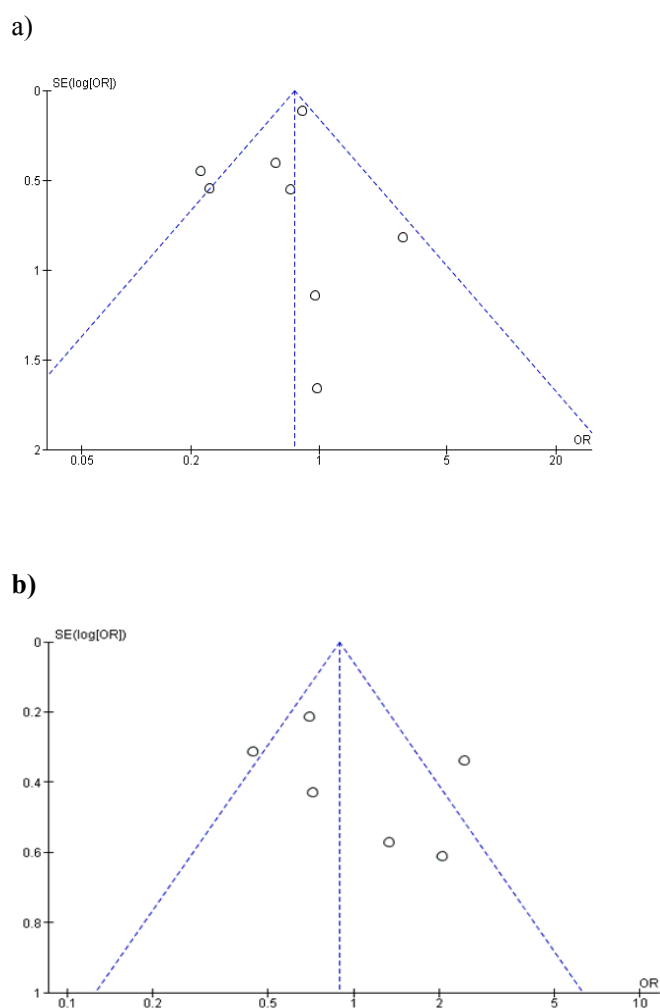
a)

b)

Figure 7. Funnel Plots (a) All Cause Mortality (Inhospital). (b) MACE (12 Months). a-b. We are comparing the odds ratio (x axis) of individual studies to standard error of odds ratio (y-axis) on logarithmic scale. Visual inspection shows the studies are evenly distributed around no effect line, thus favoring lack of selection bias.

management of patients with STEMI acknowledged the variability in the evaluation and management of non-culprit coronary artery disease in hemodynamically stable patients with STEMI [1]. However, the 2012 appropriate use criteria for coronary revascularization deemed revascularization of a non-culprit artery during index hospitalization as inappropriate [7]. Both ACCF/AHA and ESC/EACTS guidelines have reiterated the need for additional evidence to clarify the indications for and timing of non-infarct artery revascularization [1,2]. Indeed, the results of two randomized controlled trials have since become available on the subject.

Existing studies have shown mixed results with some favoring culprit only and other favoring multivessel PCI. The studies have been limited either by observational design and the consequent selection bias [5,8-13] or a small sample size [14-17] with inadequate power to demonstrate a significant difference in hard end points like mortality or recurrent myocardial infarction. Both, culprit only and multivessel revascularization have their set of advantages and pitfalls. With a complete multivessel revascularization approach, an improvement in blood flow to the peri-infarct myocardium and stabilization of unstable, non-culprit plaques, seen in greater than 1/3rd of patients

with STEMI, can be achieved. Moreover, there is data from smaller studies indicating a significant improvement in ejection fraction with an initial multivessel PCI approach [18]. However, multivessel PCI has longer procedural time, higher risk for contrast induced nephropathy, and possibility of failed revascularization of non-culprit arteries. Furthermore, our meta-analysis found a higher rate of stent thrombosis in the multivessel group, likely related to the higher number of deployed stents. However, this was based on two 2 studies with limited events and therefore this finding may lack statistical power. Our meta-analysis helps put the findings of these important trials in perspective by addressing the limitations in these important outcomes.

This meta-analysis has a few limitations. First, as in all meta-analysis, publication bias associated with individual studies is inevitably inherent. Second, the included studies differed in inclusion/exclusion criteria or in the duration of follow-up. To minimize heterogeneity we only included studies where drug eluting stents were used and applied a random-effects model to account for inherent heterogeneity in the data. In addition, various outcomes were only pooled when available at pre-defined follow-up periods. Third, although a significant reduction in cardiovascular mortality is seen in our results, a limited number of studies (4 with a total of 979 patients) provided this outcome. Lastly, there was limited data on secondary outcomes such as stent thrombosis, major bleeding, contrast volume and vascular complications. Therefore the reduction in cardiovascular mortality and stent thrombosis as seen in our study is best considered hypothesis generating at this point. Enrollment in the Complete *Versus* Culprit-Only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) trial is underway, which is expected to enroll 3,900 patients and is expected to be powered for outcomes such as long term myocardial infarction and cardiovascular mortality [18].

In conclusion, this meta-analysis demonstrated lower in-hospital all-cause mortality and 30-day MACE events and higher repeat revascularization with culprit only PCI. However, multi-vessel PCI during the index procedure was associated with a lower risk of cardiac death at 12-30 months. Either approach is however safe as evidenced by comparable rates of all cause death, MI, stroke, MACE events, major bleeding or vascular complications at 12 months follow-up. A significant reduction in repeat revascularization and cardiac at later follow-up was seen in patients who underwent multivessel revascularization.

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