Meta-analysis Comparing Multivessel Versus Culprit Coronary Arterial Revascularization for Patients With Non-ST-Segment Elevation Acute Coronary Syndromes

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We present a systematic review and meta-analysis comparing efficacy and safety outcomes between single procedure multivessel revascularization (MVR) and culprit vessel only revascularization in patients presenting with non-ST-segment-elevation acute coronary syndrome (NSTE-ACS). NSTE-ACS is the most common form of acute coronary syndrome (ACS), and multivessel disease is common. There is no consensus on the most efficacious single procedure revascularization strategy for patients undergoing percutaneous coronary intervention not meeting coronary artery bypass grafting criteria. Studies in PubMed and EMBASE databases were systematically reviewed, and 15 studies met criteria for inclusion in the meta-analysis. Baseline characteristics between the groups were similar. A random effects model was used to calculate odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity of studies was assessed using Cochrane's Q and Higgins I^2 tests. For short-term outcomes, patients who underwent MVR had higher rates of major adverse cardiac events (OR 1.14; 95% CI 1.01 to 1.29; p = 0.03); and stroke (OR 1.94; 95% CI 1.01 to 3.72; p = 0.05), but lower rates of urgent or emergent coronary artery bypass grafting (OR 0.35; 95% CI 0.29 to 0.43; p <0.00001). In the long-term, MVR patients had less frequent major adverse cardiac events (OR 0.76; 95% CI 0.61-0.93; p = 0.009), all-cause death (OR 0.83; 95% CI 0.71 to 0.97; p = 0.03), and repeat revascularization, (OR 0.62; 95% CI 0.42 to 0.90; p = 0.01). MVR following NSTE-ACS was associated with higher short-term risk, but long-term benefit. In conclusion, these results support the use of single procedure multivessel revascularization for NSTE-ACS patients who are suitable candidates at the time of percutaneous coronary intervention. **(Am J Cardiol 2019;124:1501−1511)**

Non-ST-segment-elevation acute coronary syndrome (NSTE-ACS) is the most common form of acute coronary syndrome (ACS), occurring in approximately 70% of patients presenting with ACS.[1] Unstable angina pectoris (UAP) accounts for 4% of hospitalizations with a primary diagnosis of ACS.[2] Up to 40% of patients who present with NSTE-ACS and undergo coronary angiography will have angiographic multivessel disease.[3] Despite the seeming consensus in guidelines on an early invasive strategy for high-risk patients with NSTE-ACS, the ideal strategy for multivessel revascularization (MVR) versus culprit vessel revascularization (CVR) through percutaneous coronary intervention (PCI) in patients with multivessel disease is unclear.[3] There is lack of consensus in guidelines on revascularization strategy in patients with NSTE-ACS who are not candidates for coronary artery bypass grafting (CABG).[3,4] This meta-analysis incorporates the latest studies involving patients with NSTE-ACS undergoing single procedure MVR or CVR.

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See page 1510 for disclosure information.

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Methods

We systematically reviewed relevant studies within the PubMed and EMBASE databases using searches with the following keywords: "NSTEMI," "non-ST-segment elevation," "non-ST-elevation," "acute coronary syndrome," or "unstable angina" with one or more of the following: "staged," "complete," "culprit," "multivessel," "percutaneous coronary intervention," "PCI," and/or "revascularization." We also reviewed references of relevant studies to expand our search.

Eligible studies were included based on the following characteristics: (1) Compared culprit versus multivessel revascularization using PCI; (2) included patients with NSTE-ACS and/or UAP within the study population; (3) directly compared outcomes of culprit versus multivessel revascularization at the time of index revascularization. Studies were excluded if there was no distinction made between STE-ACS and NSTE-ACS/UAP patients; or if there was a "staged" procedure where revascularization of multiple vessels was performed at different times in separate procedures. We identified 15 appropriate studies meeting this criteria using the search strategy outlined above that are included in the present meta-analysis (Figure 1).

Two reviewers (VS and HN) independently reviewed the literature, extracted, and entered data. Two reviewers (SB and XJ) resolved any discrepancies. Data extracted included authors; type of study; publication year; number

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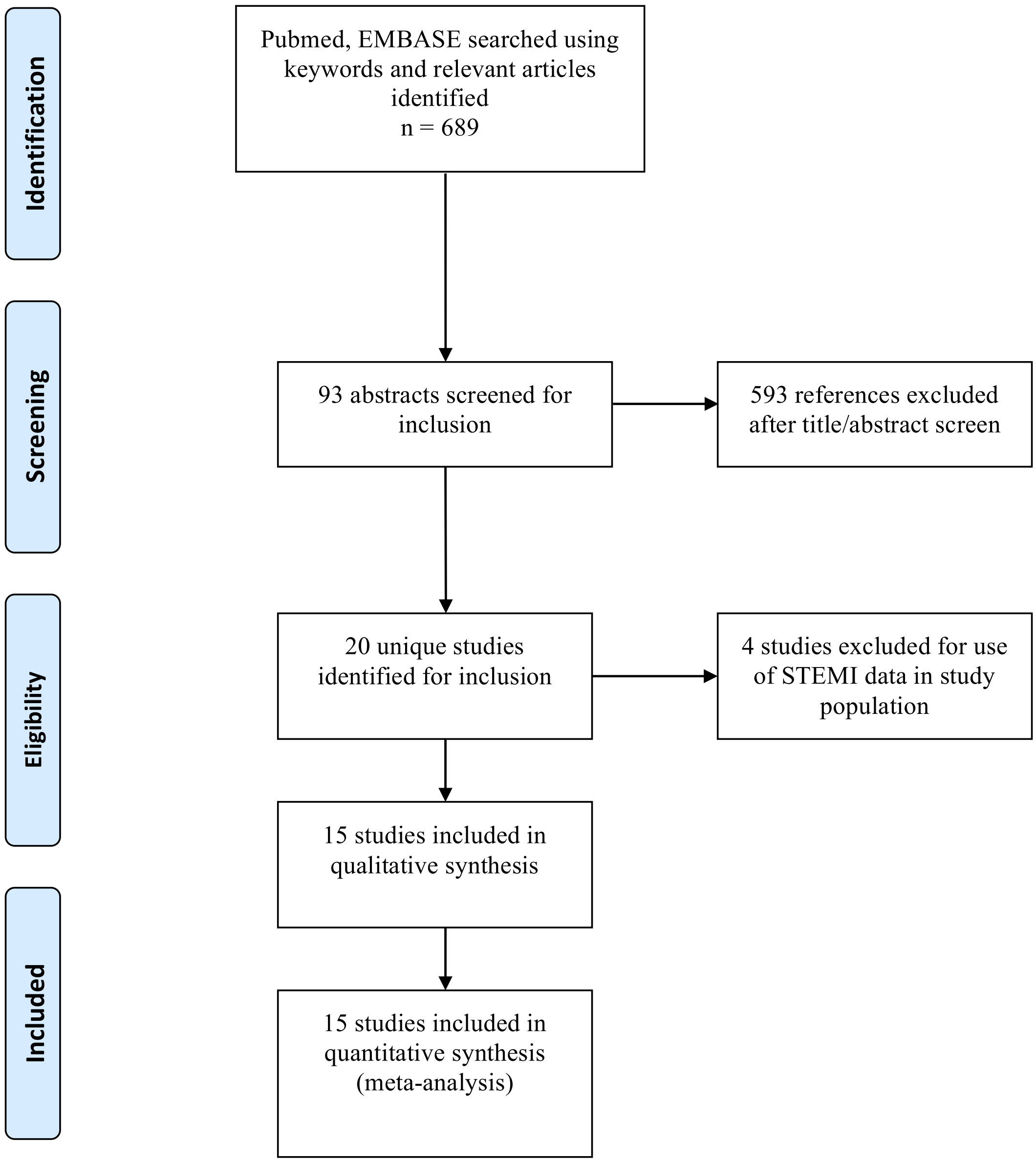


Figure 1. PRISMA diagram.

of patients studied; baseline demographic data (Table 1). Other data extracted include characteristics of the catheterization: timing of catheterization; access site (radial or femoral artery); number of diseased vessels and vessels treated; culprit vessel; mechanical support used; type of stent; use of intravascular ultrasound; contrast used; and procedural success rates. The following outcome data were extracted: major adverse cardiovascular events (MACE); nonfatal myocardial infarctions (MI); nonfatal cerebrovascular accidents (CVA); all-cause death and revascularization by either PCI or CABG. Outcome measures were further categorized as short-term (including in-hospital and 30 day data as reported) as well as long-term outcomes (from 6 to 51.4 months). In sub-analyses, the long-term outcomes data were further split into 2 groups: outcomes from 6 months to 1 year, and outcomes for ≥2 years. For outcomes on MACE, we used the studies' defined endpoint (Supplemental Table 2). These were mostly consistent across studies and included a combination of the following clinical end points: all-cause death, cardiovascular death, myocardial infarction, revascularization, CVA, heart failure, or rehospitalization for angina. The quality of the studies included was assessed using the Newcastle-Ottawa Scale, with all studies receiving a score of 6 or above (Table 2).

Continuous variables are reported as mean with standard deviation and categorical variables are expressed as incidence rate (n/N). Using the Mantel-Haenzel random effects model, we compared outcomes data between multivessel and culprit vessel PCI groups, computing odds ratios with 95% confidence intervals. We tested for overall effect, with $p < 0.05$ considered statistically significant. Heterogeneity was assessed using the Cochrane's Q and Higgins' I^2 statistic, with an $I^2 > 50\%$ considered significant heterogeneity.

Table 1
Baseline characteristics

First Author (Year)	Cohort	Total (N)	N		Age (years)		Male		Smoker		HTN		DM		Previous MI		Previous PCI	
			Multi	Culprit	Multi	Culprit	Multi	Culprit	Multi	Culprit	Multi	Culprit	Multi	Culprit	Multi	Culprit	Multi	Culprit
Mariani 2001	Prospective	207	23.7%	76.3%	63.7	63.9	73.5%	82.9%	–	–	–	–	26.5%	14.6%	36.7%	46.8%	–	–
Brener 2002	Retrospective	290	22.7%	77.2%	62	62	71.2%	67.0%	31.8%	25.9%	63.6%	70.1%	30.3%	27.2%	43.9%	42.9%	–	–
Palmer 2004	Prospective	128	55.5%	44.5%	62	63	69.0%	66.7%	71.8%	68.4%	33.8%	38.6%	21.1%	21.1%	28.2%	26.3%	16.9%	19.3%
Shishehbor 2007	Retrospective	1240	38.6%	61.4%	66	65	63.7%	64.5%	19%	26.3%	–	–	32.6%	30.7%	46.3%	46.9%	–	–
Brener 2008	Retrospective	105866	31.9%	68.1%	65	66	64.4%	64.7%	25.2%	27.3%	73.3%	74%	31.5%	31.9%	25.2%	29.3%	28.7%	32.2%
Zapata 2009	Retrospective	609	33.5%	66.5%	60.8	62.3	82.4%	83.2%	30.4%	31.1%	65.7%	64.7%	20.1%	22.2%	11.9%	26.9%	11.3%	17%
Kim 2011	Prospective	1919	52.7%	47.3%	65.2	65.5	65.2%	69.2%	51%	54.4%	56.4%	59.7%	33.7%	34.9%	–	–	–	–
Lee 2011	Retrospective	366	48.9%	51.5%	64.5	65.3	71.5%	62.6%	25.1%	18.7%	58.1%	62.6%	33.5%	40.6%	8.9%	8%	7.8%	15.5%
Bauer 2013	Prospective	1920	38.2%	61.8%	65.4	67.1	69.3%	73.4%	–	–	70.4%	75.6%	28.6%	30%	33.8%	34.1%	20.2%	23.1%
Onuma 2013	Retrospective	990	61.7%	38.3%	64.6	64.1	30.9%	30.3%	22.9%	25.3%	43.5%	42%	20.1%	18.5%	45.2%	52%	15.1%	32.5%
Hassanin 2015	Retrospective	2864	21.3%	78.7%	62	62	70.6%	72.3%	30.5%	30.7%	69.3%	71.8%	35%	32.3%	34%	37.1%	46.3%	51.3%
Wang 2016	Retrospective	31361	25.6%	74.4%	75	75	53.6%	54.7%	–	–	–	–	34.1%	32.8%	22.5%	23.8%	25%	26%
Quadri 2017	Retrospective	1459	42.4%	57.6%	68.7	68.1	73.2%	78.3%	–	–	71.6%	69.9%	35.7%	39.6%	19.8%	23.7%	–	–
Correia 2018	Retrospective	202	35.1%	64.9%	64.1	66	78.9%	76.3%	19.7%	25.2%	74.6%	69.5%	36.6%	33.6%	11.3%	19.1%	11.3%	13%
Rathod 2018	Prospective	21857	53.7%	46.3%	68.83	67.63	72.6%	75.8%	51.5%	52.9%	57%	58.5%	37.3%	31.3%	58.7%	43.6%	25.2%	17.7%

Table 2
Quality of each nonrandomized study rated using the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome
Mariani 2001	***	**	***
Brener 2002	***	**	**
Palmer 2004	***	**	***
Shishehbor 2007	***	**	***
Brener 2008	***	**	*
Zapata 2009	***	**	***
Kim 2011	***	**	***
Lee 2011	***	**	**
Bauer 2013	***	**	*
Onuma 2013	***	**	***
Hassanin 2015	***	**	**
Wang 2016	***	**	***
Quardri 2017	***	**	***
Correia 2018	***	**	**
Rathod 2018	***	**	***

Small study effect was appraised by graphical inspection of funnel plots (Figures 2 and 3). Meta-analysis was performed using Review Manager 5.3 software (Cochrane Collaboration) (Figure 4).

Results

The systematic review search yielded 689 potential peer-reviewed published articles of which 15 studies were used for the meta-analysis (Figure 1). A total of 171,279 patients were included with 58,275 who underwent MVR and 113,004 who underwent CVR. Baseline characteristics of the included studies are shown in Table 1. Age, gender, and clinical risk factors were similar between MVR and CVR groups. Of the studies included, 2 were post-hoc analyses of randomized controlled trials[5,6] that included 3,154 patients, and 13 were retrospective analyses of observational cohort studies that included 168,125 patients.[7–19]

With respect to short-term outcomes (in-hospital to 30 days) (Figure 5), MVR was significantly associated with higher rates of the composite end point of MACE and compared with CVR. Patients with MVR were significantly less likely to undergo CABG in the short term. There was no significant difference in short-term all-cause death, MI or in repeat PCI between the different revascularization strategies. The difference in MACE could possibly be due to excess of CVA in the MVR group, however, because the studies defined MACE differently, with some studies including CVA within MACE, it is difficult to definitively attribute the difference in MACE to excess CVA.

At long-term follow-up (defined as >6 months postindex procedure) (Figure 3), the MVR group was less likely to experience a MACE event, all-cause death or undergo repeat revascularization (PCI and/or CABG). Rates of MI did not differ between the 2 groups. When the long-term data were divided into subgroups of 6 months to 1 year and ≥2 years; the only significant difference was in all-cause death from 6 months to 1 year; which favored MVR.

Publication bias was evaluated using visual inspection of funnel plots (Supplemental Figure 1). Overall, funnel plots appeared symmetrical though the presence of publication

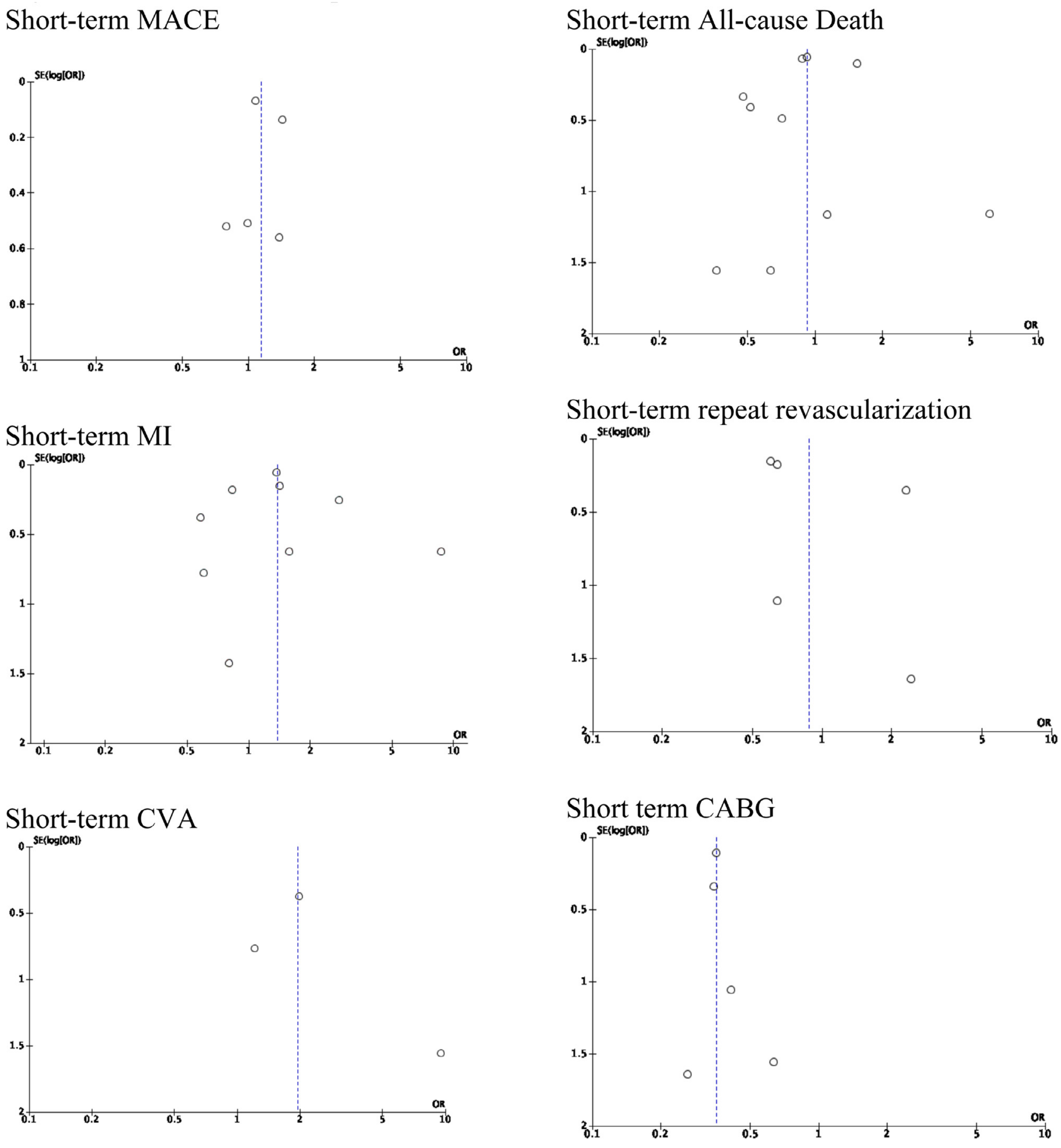


Figure 2. Short-term funnel plots.

bias cannot be ruled out due to the limited number of included studies.

Discussion

Our meta-analysis examined the effect of revascularization strategy: multivessel versus culprit-vessel only, at index PCI for NSTE-ACS or UAP on short-term and long-term clinical outcomes of MACE, MI, repeat PCI, CABG, CVA, and all-cause death. Overall, we found that multivessel revascularization showed greater efficacy in the long term at the expense of higher short-term risks. Our results are similar to those of previous meta-analyses on this topic, which both showed decreased rates of MACE and repeat revascularization in the MVR groups.[20,21] Our results add to the body of literature by incorporating the latest studies on the topic.

The finding of an increase in short-term risk is not unexpected, as there are factors complicating complete revascularization strategies including increased volumes of

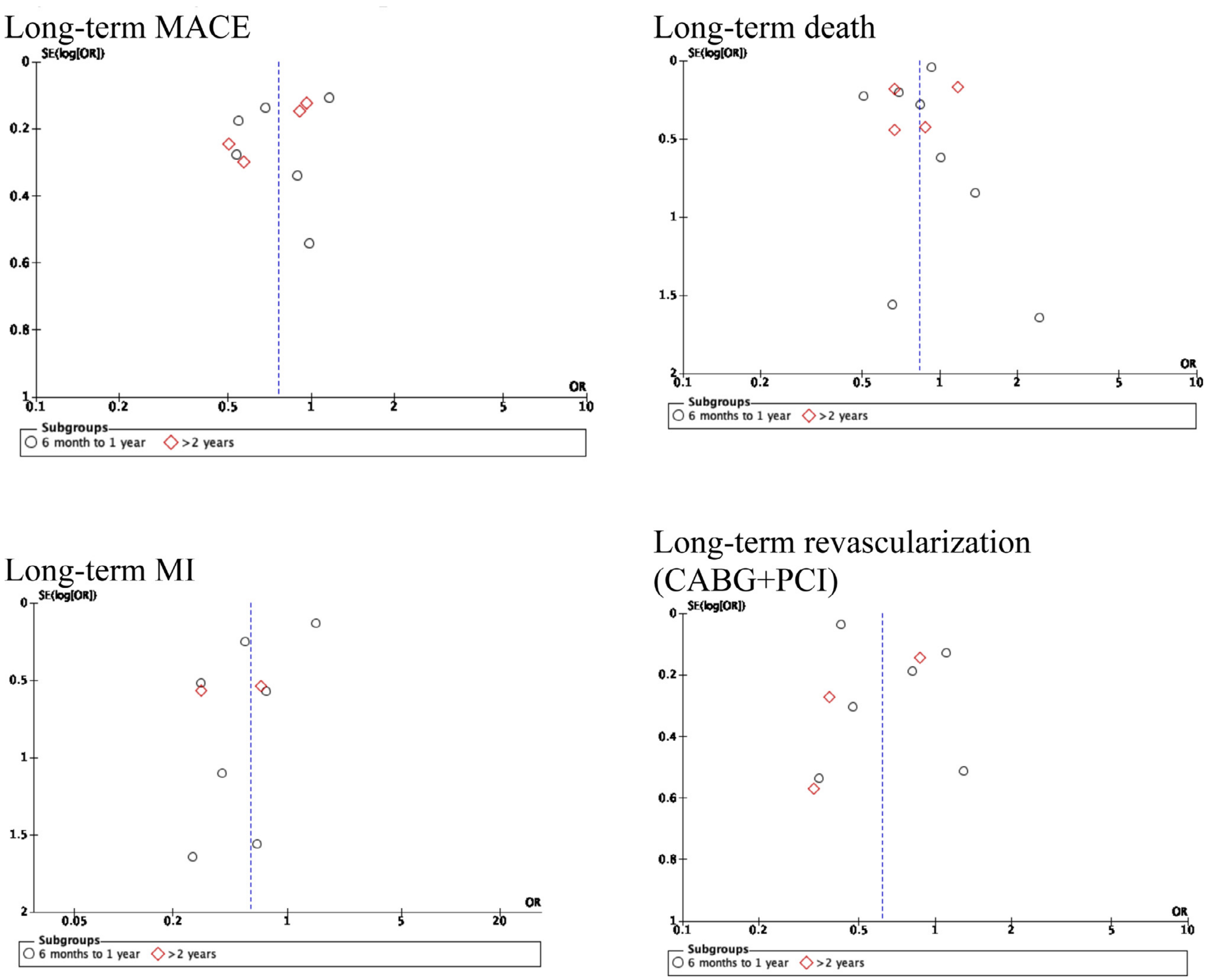


Figure 3. Long-term funnel plots.

intravenous contrast use predisposing to contrast-induced nephropathy,[14,19,22] periprocedural MI,[23] and procedural complications.[24]

Our findings of the long-term benefits of multivessel revascularization are similar to those observed in STE-ACS. The evidence for complete revascularization in patients with STE-ACS undergoing primary PCI without cardiogenic shock is mounting with the results of 2 recent meta-analyses.[25,26] Our results on NSTE-ACS and UAP patients undergoing MVR are consistent with this literature. The 2014 American College of Cardiology/American Heart Association guidelines give a Class IIB recommendation, stating it "may be reasonable" to perform multivessel PCI patients undergoing PCI in NSTE-ACS,[3] whereas the European guidelines recommend tailoring the revascularization strategy based on individual patient characteristics and preferences.[4] Importantly, multivessel PCI may decrease the patient-centered outcomes of residual angina, need for repeat PCI, and antianginal medical therapy.[14,15]

Careful patient selection is particularly emphasized in the European guidelines, so as to capitalize on the benefits of revascularization and minimize risks. Strategies like heart teams and the SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score have become popular as ways to risk-stratify and optimize revascularization strategies when comparing PCI to CABG. The "residual SYNTAX" score (rSS) was developed to prognosticate patients after incomplete revascularization based on the degree and complexity of residual stenosis after PCI in ACS patients.[27]

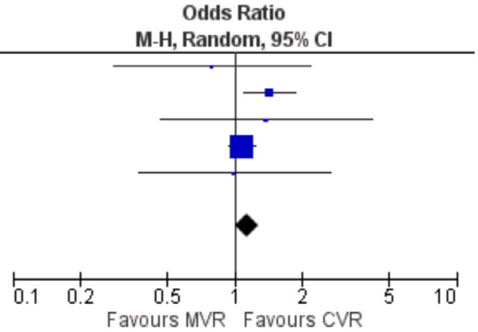
Vessel selection, as well as patient selection, is imperative for maximizing benefits of PCI. In contrast to STE-ACS, the culprit lesion cannot be identified in up to 51% of patients with NSTE-ACS.[28] A novel approach to identifying culprit vessels has been using delayed-enhancement cardiac magnetic resonance (DE-CMR) before catheterization in NSTE-ACS patients. In a recent study, the use of DE-CMR led to the reclassification of the culprit artery in 31% of patients.[28] There is little data or scoring systems available to appropriately identify patients with NSTE-ACS or UAP that would benefit from multivessel revascularization,[29] but it is possible that using a periprocedural rSS-based strategy or a novel strategy like DE-CMR could help determine suitability of multivessel revascularization and maximize benefits of PCI.

There are several limitations to be addressed. First, there were no randomized controlled trials, and there is risk of

MACE

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Brener 2002	5	66	21	224	1.4%	0.79 [0.29, 2.19]
Hassanin 2015	84	609	227	2255	20.1%	1.43 [1.09, 1.87]
Mariani 2001	5	49	12	158	1.2%	1.38 [0.46, 4.14]
Rathod 2018	481	11737	385	10120	75.8%	1.08 [0.94, 1.24]
Zapata 2009	6	204	12	405	1.5%	0.99 [0.37, 2.68]
Total (95% CI)		**12665**		**13162**	**100.0%**	**1.14 [1.01, 1.29]**
Total events	581		657			

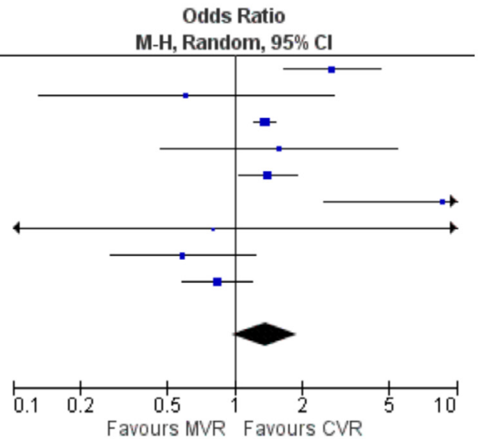
Heterogeneity: Tau² = 0.00; Chi² = 4.01, df = 4 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)



MI

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Bauer 2013	41	734	25	1186	14.8%	2.75 [1.66, 4.56]
Brener 2002	2	66	11	224	3.9%	0.61 [0.13, 2.80]
Brener 2008	507	33818	793	72048	21.9%	1.37 [1.22, 1.53]
Correia 2018	5	71	6	131	5.6%	1.58 [0.46, 5.37]
Hassanin 2015	61	609	165	2255	18.8%	1.41 [1.04, 1.92]
Mariani 2001	9	49	4	158	5.5%	8.66 [2.54, 29.58]
Palmer 2004	1	71	1	57	1.3%	0.80 [0.05, 13.08]
Quardri 2017	10	619	23	840	10.5%	0.58 [0.28, 1.23]
Rathod 2018	59	11737	61	10120	17.8%	0.83 [0.58, 1.19]
Total (95% CI)		**47774**		**87019**	**100.0%**	**1.37 [0.98, 1.91]**
Total events	695		1089			

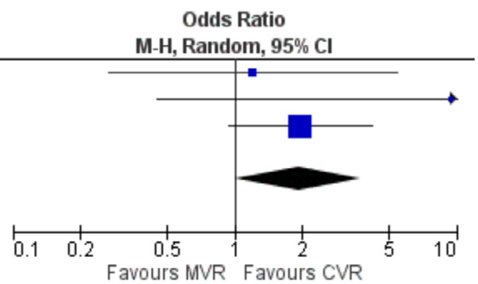
Heterogeneity: Tau² = 0.13; Chi² = 29.51, df = 8 (P = 0.0003); I² = 73%
Test for overall effect: Z = 1.86 (P = 0.06)



CVA

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Bauer 2013	3	734	4	1186	18.8%	1.21 [0.27, 5.43]
Correia 2018	2	71	0	131	4.5%	9.46 [0.45, 199.81]
Rathod 2018	23	11737	10	10120	76.6%	1.99 [0.94, 4.17]
Total (95% CI)		**12542**		**11437**	**100.0%**	**1.94 [1.01, 3.72]**
Total events	28		14			

Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)



All-cause death

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Bauer 2013	8	734	25	1186	7.4%	0.51 [0.23, 1.14]
Brener 2002	1	66	3	224	1.2%	1.13 [0.12, 11.08]
Brener 2008	406	33818	937	72048	25.4%	0.92 [0.82, 1.04]
Correia 2018	0	71	2	131	0.7%	0.36 [0.02, 7.65]
Hassanin 2015	5	609	26	2255	5.6%	0.71 [0.27, 1.86]
Kim 2011	14	1011	26	908	9.7%	0.48 [0.25, 0.92]
Mariani 2001	0	49	2	158	0.7%	0.63 [0.03, 13.39]
Palmer 2004	0	71	0	57		Not estimable
Rathod 2018	270	11737	152	10120	23.0%	1.54 [1.26, 1.89]
Wang 2016	289	8017	957	23344	25.0%	0.87 [0.77, 1.00]
Zapata 2009	3	204	1	405	1.2%	6.03 [0.62, 58.34]
Total (95% CI)		**56387**		**110836**	**100.0%**	**0.92 [0.71, 1.19]**
Total events	996		2131			

Heterogeneity: Tau² = 0.06; Chi² = 33.98, df = 9 (P < 0.0001); I² = 74%
Test for overall effect: Z = 0.62 (P = 0.53)

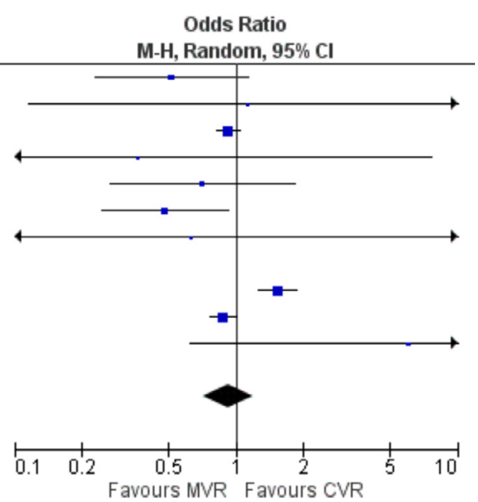
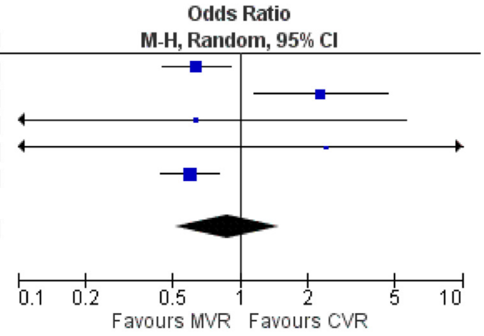


Figure 4. Short-term outcomes.

Repeat PCI

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Brener 2008	41	33818	137	72048	33.6%	0.64 [0.45, 0.90]
Hassanin 2015	13	609	21	2255	23.7%	2.32 [1.16, 4.66]
Mariani 2001	1	49	5	158	5.3%	0.64 [0.07, 5.59]
Palmer 2004	1	71	0	57	2.6%	2.45 [0.10, 61.21]
Rathod 2018	70	11737	101	10120	34.8%	0.60 [0.44, 0.81]
Total (95% CI)		**46284**		**84638**	**100.0%**	**0.88 [0.51, 1.50]**
Total events	126		264			

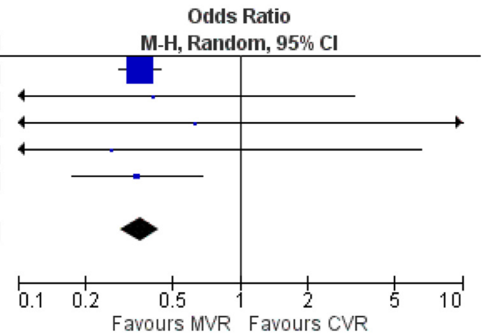
Heterogeneity: Tau² = 0.19; Chi² = 13.30, df = 4 (P = 0.010); I² = 70%
Test for overall effect: Z = 0.48 (P = 0.63)



CABG

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Brener 2008	95	33818	569	72048	88.8%	0.35 [0.28, 0.44]
Hassanin 2015	1	609	9	2255	1.0%	0.41 [0.05, 3.25]
Mariani 2001	0	49	2	158	0.5%	0.63 [0.03, 13.39]
Palmer 2004	0	71	1	57	0.4%	0.26 [0.01, 6.59]
Rathod 2018	12	11737	30	10120	9.4%	0.34 [0.18, 0.67]
Total (95% CI)		**46284**		**84638**	**100.0%**	**0.35 [0.29, 0.43]**
Total events	108		611			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 9.93 (P < 0.00001)



Overall

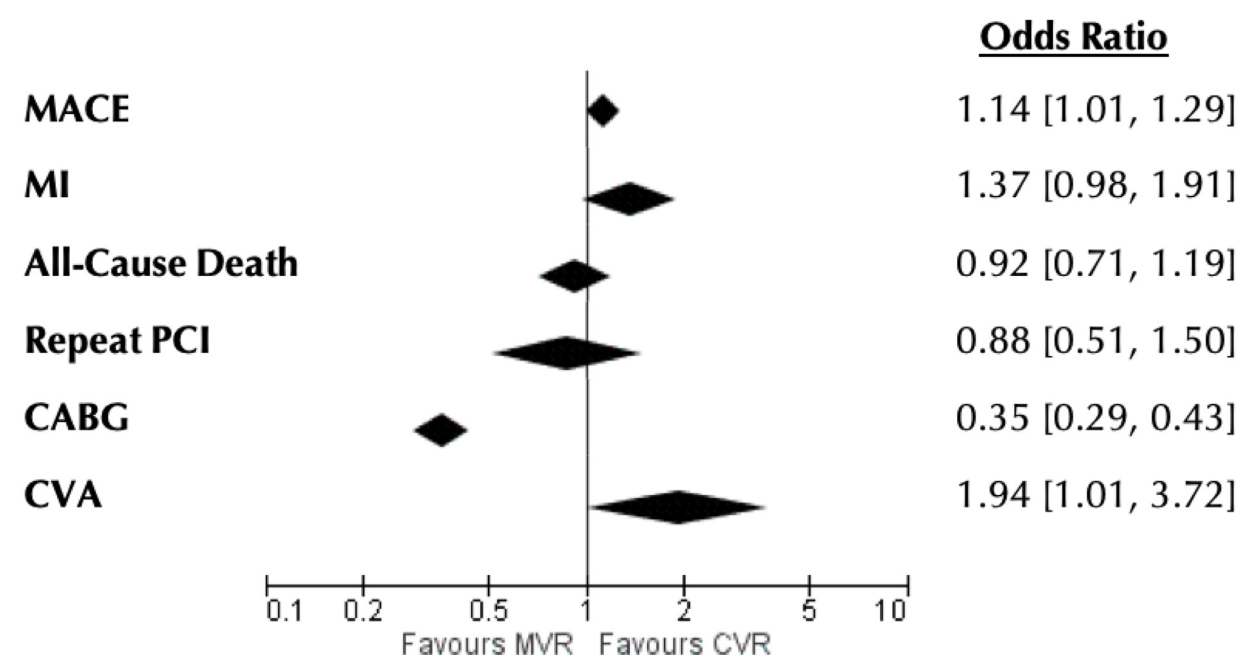
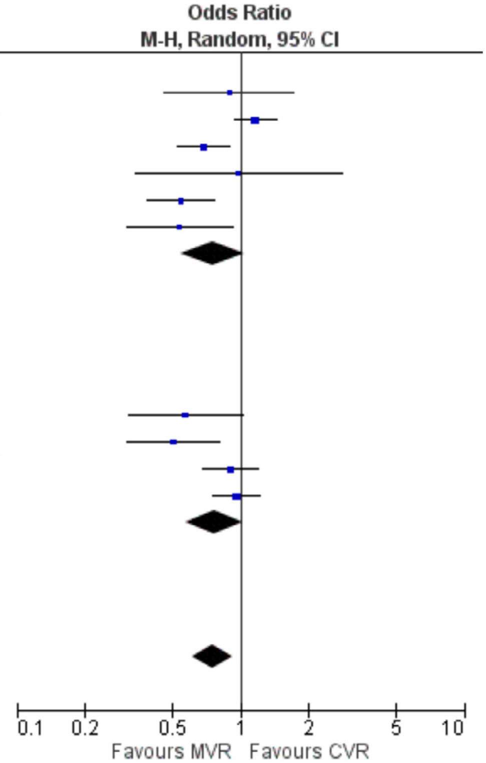


Figure 4. Continued

MACE

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 6 month to 1 year						
Brener 2002	14	66	52	224	6.2%	0.89 [0.46, 1.73]
Hassanin 2015	143	609	470	2255	14.5%	1.17 [0.94, 1.44]
Kim 2011	107	1011	134	908	13.3%	0.68 [0.52, 0.90]
Mariani 2001	5	44	17	147	3.2%	0.98 [0.34, 2.83]
Quardri 2017	50	619	117	840	11.6%	0.54 [0.38, 0.77]
Zapata 2009	19	201	66	404	8.0%	0.53 [0.31, 0.92]
Subtotal (95% CI)		**2550**		**4778**	**56.8%**	**0.75 [0.54, 1.05]**
Total events	338		856			
Heterogeneity: Tau² = 0.11; Chi² = 20.08, df = 5 (P = 0.001); I² = 75%						
Test for overall effect: Z = 1.66 (P = 0.10)						
2.1.2 >2 years						
Correia 2018	28	71	70	131	7.3%	0.57 [0.32, 1.02]
Lee 2011	35	179	61	187	9.0%	0.50 [0.31, 0.81]
Onuma 2013	159	611	106	379	12.9%	0.91 [0.68, 1.21]
Shishehbor 2007	168	479	274	761	14.0%	0.96 [0.76, 1.22]
Subtotal (95% CI)		**1340**		**1458**	**43.2%**	**0.76 [0.57, 1.02]**
Total events	390		511			
Heterogeneity: Tau² = 0.05; Chi² = 7.61, df = 3 (P = 0.05); I² = 61%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Total (95% CI)		**3890**		**6236**	**100.0%**	**0.76 [0.61, 0.93]**
Total events	728		1367			
Heterogeneity: Tau² = 0.07; Chi² = 27.68, df = 9 (P = 0.001); I² = 67%						
Test for overall effect: Z = 2.61 (P = 0.009)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						



MI

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
2.2.1 6 months to 1 year						
Brener 2002	4	66	18	224	11.9%	0.74 [0.24, 2.26]
Hassanin 2015	89	609	233	2255	20.7%	1.49 [1.14, 1.93]
Kim 2011	5	1011	15	908	12.9%	0.30 [0.11, 0.82]
Mariani 2001	0	44	2	147	3.1%	0.65 [0.03, 13.88]
Palmer 2004	0	71	1	57	2.8%	0.26 [0.01, 6.59]
Quardri 2017	23	619	55	840	18.6%	0.55 [0.33, 0.91]
Zapata 2009	1	201	5	404	5.4%	0.40 [0.05, 3.44]
Subtotal (95% CI)		**2621**		**4835**	**75.4%**	**0.65 [0.33, 1.27]**
Total events	122		329			
Heterogeneity: Tau² = 0.41; Chi² = 21.20, df = 6 (P = 0.002); I² = 72%						
Test for overall effect: Z = 1.26 (P = 0.21)						
2.2.2 >2 years						
Correia 2018	4	71	22	131	12.0%	0.30 [0.10, 0.90]
Lee 2011	6	179	9	187	12.6%	0.69 [0.24, 1.97]
Subtotal (95% CI)		**250**		**318**	**24.6%**	**0.46 [0.20, 1.05]**
Total events	10		31			
Heterogeneity: Tau² = 0.05; Chi² = 1.18, df = 1 (P = 0.28); I² = 15%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Total (95% CI)		**2871**		**5153**	**100.0%**	**0.60 [0.33, 1.06]**
Total events	132		360			
Heterogeneity: Tau² = 0.40; Chi² = 26.88, df = 8 (P = 0.0007); I² = 70%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						

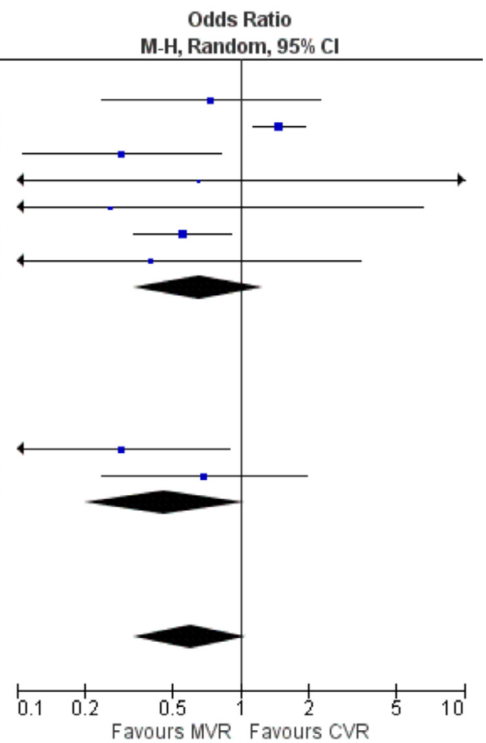
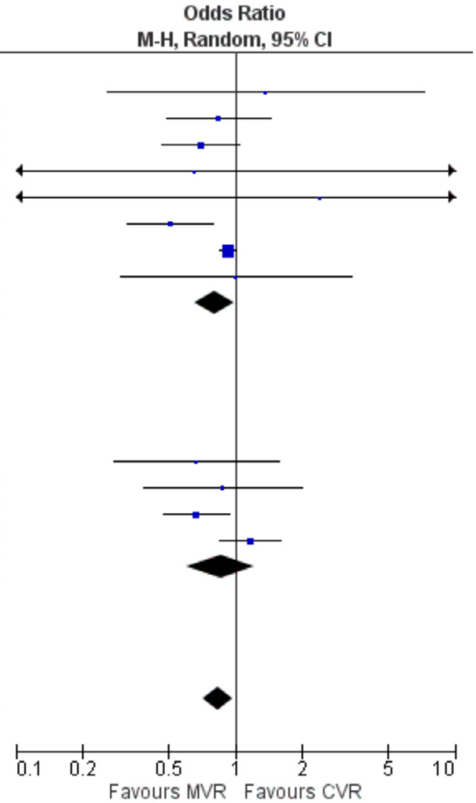


Figure 5. Long-term outcomes.

Death

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
2.3.1 6 months to 1 year						
Brener 2002	2	66	5	224	0.9%	1.37 [0.26, 7.22]
Hassanin 2015	16	609	70	2255	6.7%	0.84 [0.49, 1.46]
Kim 2011	45	1011	57	908	11.0%	0.70 [0.47, 1.04]
Mariani 2001	0	44	2	147	0.3%	0.65 [0.03, 13.88]
Palmer 2004	1	71	0	57	0.2%	2.45 [0.10, 61.21]
Quardri 2017	28	619	72	840	9.3%	0.51 [0.32, 0.79]
Wang 2016	810	8017	2521	23344	35.9%	0.93 [0.85, 1.01]
Zapata 2009	4	201	8	404	1.6%	1.01 [0.30, 3.38]
Subtotal (95% CI)		**10638**		**28179**	**65.9%**	**0.80 [0.66, 0.99]**
Total events	906		2735			
Heterogeneity: Tau² = 0.02; Chi² = 9.19, df = 7 (P = 0.24); I² = 24%						
Test for overall effect: Z = 2.09 (P = 0.04)						
2.3.2 >2 years						
Correia 2018	8	71	21	131	3.0%	0.67 [0.28, 1.59]
Lee 2011	11	179	13	187	3.3%	0.88 [0.38, 2.01]
Onuma 2013	79	611	69	379	13.2%	0.67 [0.47, 0.95]
Shishehbor 2007	72	479	100	761	14.6%	1.17 [0.84, 1.62]
Subtotal (95% CI)		**1340**		**1458**	**34.1%**	**0.86 [0.60, 1.21]**
Total events	170		203			
Heterogeneity: Tau² = 0.06; Chi² = 5.67, df = 3 (P = 0.13); I² = 47%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Total (95% CI)		**11978**		**29637**	**100.0%**	**0.83 [0.71, 0.97]**
Total events	1076		2938			
Heterogeneity: Tau² = 0.02; Chi² = 14.89, df = 11 (P = 0.19); I² = 26%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



Revascularization (PCI And CABG)

Study or Subgroup	MVR Events	MVR Total	CVR Events	CVR Total	Weight	Odds Ratio M-H, Random, 95% CI
2.4.1 6 months to 1 year						
Hassanin 2015	91	609	310	2255	14.2%	1.10 [0.86, 1.42]
Kim 2011	57	1011	62	908	13.2%	0.82 [0.56, 1.18]
Mariani 2001	6	44	16	147	7.3%	1.29 [0.47, 3.53]
Palmer 2004	6	71	12	57	7.0%	0.35 [0.12, 0.99]
Wang 2016	1034	8017	6023	23344	15.1%	0.43 [0.40, 0.46]
Zapata 2009	15	201	59	404	11.0%	0.47 [0.26, 0.85]
Subtotal (95% CI)		**9953**		**27115**	**67.8%**	**0.66 [0.40, 1.09]**
Total events	1209		6482			
Heterogeneity: Tau² = 0.30; Chi² = 63.66, df = 5 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 1.62 (P = 0.11)						
2.4.2 >2 years						
Correia 2018	4	71	20	131	6.5%	0.33 [0.11, 1.01]
Lee 2011	24	179	54	187	11.6%	0.38 [0.22, 0.65]
Shishehbor 2007	96	479	171	761	14.0%	0.86 [0.65, 1.15]
Subtotal (95% CI)		**729**		**1079**	**32.2%**	**0.53 [0.27, 1.05]**
Total events	124		245			
Heterogeneity: Tau² = 0.26; Chi² = 8.89, df = 2 (P = 0.01); I² = 77%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Total (95% CI)		**10682**		**28194**	**100.0%**	**0.62 [0.42, 0.90]**
Total events	1333		6727			
Heterogeneity: Tau² = 0.25; Chi² = 82.31, df = 8 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						

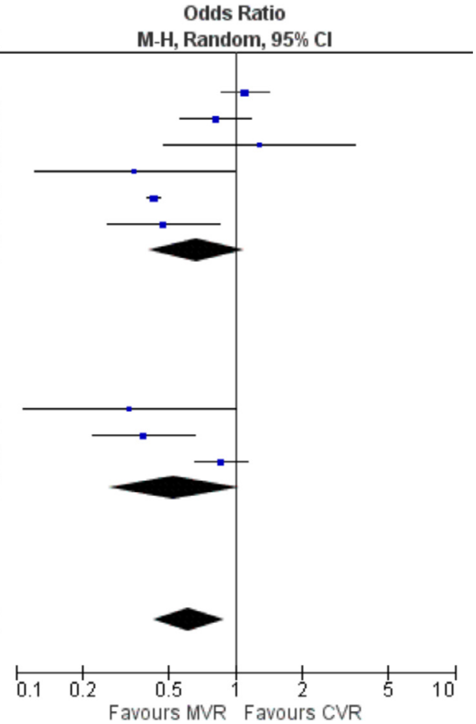


Figure 5. Continued

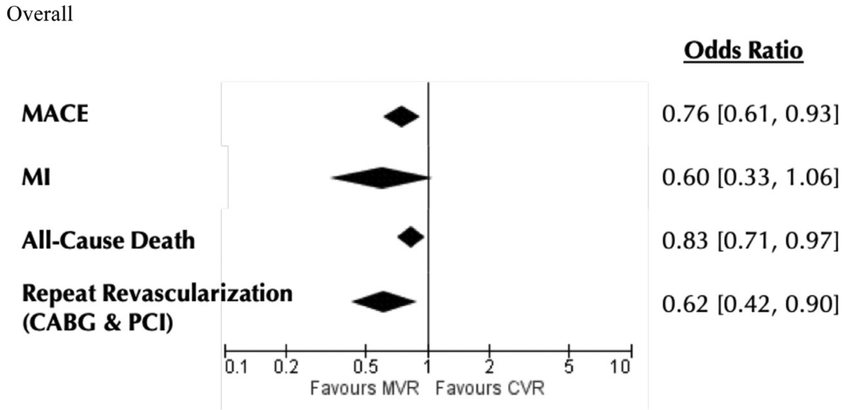


Figure 5. Continued

selection bias and significant confounding with registry data sets and retrospective studies. Further, there is no standardization for the selection of culprit vessels in patients with NSTE-ACS, which could lead to PCI of an erroneous nonculprit vessel or to indiscriminate multivessel revascularization if a culprit vessel was not easily identified.[12] Operator preference could lead to culprit-vessel only revascularization in cases of hemodynamic instability or complicated procedures. There was significant heterogeneity noted in the meta-analyses of several of the outcome measures including short-term MI, short-term death, short-term repeat PCI, as well as the following long-term outcome measures: MACE, MI, repeat revascularization (Figures 2 and 3).

In conclusion, the results of this meta-analysis show that multivessel PCI in patients presenting with NSTE-ACS leads to better long-term outcomes, including MACE, all-cause death, and repeat revascularization, at the expense of an increase in short-term risk due to higher rates of MACE and CVA, and no difference in short-term mortality. There is a high prevalence of multivessel disease in patients who present with NSTE-ACS, and with burgeoning technologies and risk stratification tools, randomized controlled trials are needed.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.071.

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics−2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6–e245.
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway Clifton W, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation* 2019;139:e56–e528.
3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC guideline for the management of patients with non−ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2014;64:e139–e228.
4. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267–315.
5. Brener SJ, Murphy SA, Gibson CM, DiBattiste PM, Demopoulos LA, Cannon CP. Efficacy and safety of multivessel percutaneous revascularization and tirofiban therapy in patients with acute coronary syndromes. *Am J Cardiol* 2002;90:631–633.
6. Hassanin A, Brener SJ, Lansky AJ, Xu K, Stone GW. Prognostic impact of multivessel versus culprit vessel only percutaneous intervention for patients with multivessel coronary artery disease presenting with acute coronary syndrome. *EuroIntervention* 2015;11:293–300.
7. Brener SJ, Milford-Beland S, Roe MT, Bhatt DL, Weintraub WS, Brindis RG. Culprit-only or multivessel revascularization in patients with acute coronary syndromes. *Am Heart J* 2008;155:140–146.
8. Bauer T, Zeymer U, Hochadel M, Möllmann H, Weidinger F, Zahn R, Nef HM, Hamm CW, Marco J, Gitt AK. Prima-vista multi-vessel percutaneous coronary intervention in haemodynamically stable patients with acute coronary syndromes: analysis of over 4.400 patients in the EHS-PCI registry. *Int J Cardiol* 2013;166:596–600.
9. Shishehbor MH, Lauer MS, Singh IM, Chew DP, Karha J, Brener SJ, Moliterno DJ, Ellis SG, Topol EJ, Bhatt DL. In unstable angina or non−ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? *J Am Coll Cardiol* 2007;49:849–854.
10. Mariani G, De Servi S, Dellavalle A, Repetto S, Chierchia S, D'Urbano M, Repetto A, Klersy C, ROSAI Study Group. Complete or incomplete percutaneous coronary revascularization in patients with unstable angina in stent era: Are early and one-year results different? *Catheter Cardiovasc Interv* 2001;54:448–453.

11. Zapata GO, Lasave LI, Kozak F, Damonte A, Meiriño A, Rossi M, Carbó S, Pollice A, Paolasso E, Picabea E. Culprit-only or multivessel percutaneous coronary stenting in patients with non-ST-segment elevation acute coronary syndromes: one-year follow-up. *J Interv Cardiol* 2009;22:329–335.
12. Kim MC, Jeong MH, Ahn Y, Kim JH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi DH, Cho MC, Kim CJ, Seung KB, Chung WS, Jang YS, Cho SY, Rha SW, Bae JH, Cho JG, Park SJ. What is optimal revascularization strategy in patients with multivessel coronary artery disease in non-ST-elevation myocardial infarction? Multivessel or culprit-only revascularization. *Int J Cardiol* 2011;153:148–153.
13. Lee HJ, Song YB, Hahn J-Y, Kim SM, Yang JH, Choi JH, Choi S-H, Choi J-H, Lee SH, Gwon H-C. Multivessel vs single-vessel revascularization in patients with non−ST-segment elevation acute coronary syndrome and multivessel disease in the drug-eluting stent Era. *Clin Cardiol* 2011;34:160–165.
14. Onuma Y, Muramatsu T, Girasis C, Kukreja N, Garcia-Garcia H, Daemen J, Gonzalo N, Piazza N, Einthoven J, Domburg R van, Serruys PW. Single-vessel or multivessel PCI in patients with multivessel disease presenting with non-ST-elevation acute coronary syndromes. *EuroIntervention* 2013;9:916–922.
15. Palmer ND, Causer JP, Ramsdale DR, Perry RA. Effect of completeness of revascularization on clinical outcome in patients with multivessel disease presenting with unstable angina who undergo percutaneous coronary intervention. *J Invasive Cardiol* 2004;16:185–188.
16. Correia C, Galvão Braga C, Martins J, Arantes C, Abreu G, Quina C, Salgado A, Álvares Pereira M, Costa J, Marques J. Multivessel vs. culprit-only revascularization in patients with non-ST-elevation acute coronary syndromes and multivessel coronary disease. *Revista Portuguesa de Cardiologia* 2018;37:143–154.
17. Quadri G, D'Ascenzo F, Moretti C, D'Amico M, Raposeiras-Roubin S, Abu-Assi E, Henriques JPS, Saucedo J, Gonzalez-Juanatey JR, Wilton SB, Kikkert WJ, Nunez-Gil I, Ariza-Sole A, Song X, Alexopolous D, Liebetrau C, Kawaji T, Huczek Z, Nie S-P, Fujii T, Correia L, Kawashiri M, Garcia-Acuna JM, Southern D, Alfonso E, Terol B, Garay A, Zhang D, Chen Y, Xanthopoulou I, Osman O, Helge M, Hiroki S, Pierluigi O, Antonio M, Francesca G, Silvia S, Michal K, Krzysztof F, Xiao W, Yan Y, Jing-Yao F, Yuji I, Takuya N, Kenji S, Masakazu Y, Oliver K, Sasko K, Ferdinando V, Fiorenzo G. Complete or incomplete coronary revascularisation in patients with myocardial infarction and multivessel disease: a propensity score analysis from the "real-life" BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registry. *EuroIntervention* 2017;13:407–414.
18. Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, Kalra SS, Dalby MC, O'Mahony C, Malik IS, Knight CJ, Mathur A, Redwood S, Sirker A, MacCarthy PA, Smith EJ, Wragg A, Jones DA. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. *J Am Coll Cardiol* 2018;72:1989–1999.
19. Wang TY, McCoy LA, Bhatt DL, Rao SV, Roe MT, Resnic FS, Cavender MA, Messenger JC, Peterson ED. Multivessel vs culprit-only percutaneous coronary intervention among patients 65 years or older with acute myocardial infarction. *Am Heart J* 2016;172:9–18.
20. Jang J-S, Jin H-Y, Seo J-S, Yang T-H, Kim D-K, Kim D-S, Cho K-I, Kim B-H, Park YH, Je H-G. Meta-analysis of multivessel versus culprit-only percutaneous coronary intervention in patients with non −ST-segment elevation acute coronary syndrome and multivessel coronary disease. *Am J Cardiol* 2015;115:1027–1032.
21. Qiao Y, Li W, Mohamed S, Nie S, Du X, Zhang Y, Jia C, Wang X, Liu X, Ma C. A comparison of multivessel and culprit vessel percutaneous coronary intervention in non-ST-segment elevation acute coronary syndrome patients with multivessel disease: a meta-analysis. *EuroIntervention* 2015;11:525–532.
22. Mehran R. Contrast-induced nephropathy remains a serious complication of PCI. *J Interv Cardiol* 2007;20:236–240.
23. De Innocentiis C, Zimarino M, De Caterina R. Is complete revascularisation mandated for all patients with multivessel coronary artery disease? *Interv Cardiol* 2018;13:45–50.
24. Gaffar R, Habib B, Filion KB, Reynier P, Eisenberg MJ. Optimal timing of complete revascularization in acute coronary syndrome: a systematic review and meta−analysis. *J Am Heart Assoc* 2017;6.
25. El-Hayek GE, Gershlick AH, Hong MK, Casso Dominguez A, Banning A, Afshar AE, Herzog E, Tamis-Holland JE. Meta-analysis of randomized controlled trials comparing multivessel versus culprit-only revascularization for patients with ST-segment elevation myocardial infarction and multivessel disease undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2015;115: 1481–1486.
26. Bangalore S, Toklu B, Stone GW. Meta-analysis of culprit-only versus multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction and multivessel coronary disease. *Am J Cardiol* 2018;121:529–536.
27. Généreux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) Score. *J Am Coll Cardiol* 2012; 59:2165–2174.
28. Heitner John F, Senthilkumar Annamalai, Kevin Harrison J, Klem Igor, Sketch Michael H, Ivanov Alexandr, Hamo Carine, Van Assche Lowie, White James, Washam Jeffrey, Patel Manesh R, Bekkers Sebastiaan CAM, Smulders Martijn W, Sacchi Terrence J, Kim Raymond J. Identifying the infarct-related artery in patients with non−ST-segment−elevation myocardial infarction. *Circ Cardiovasc Interv* 2019;12:e007305.
29. Windecker S, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann F-J, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541–2619.