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Myocardial viability for decision-making concerning revascularization in patients with left ventricular dysfunction and coronary artery disease: A meta-analysis of non-randomized and randomized studies

Andrés Orlandini *[,1], Noelia Castellana [1], Andrea Pascual [1], Fernando Botto [1], M. Cecilia Bahit [1], Carolina Chacon [1], M. Luz Diaz [1], Rafael Diaz [1]

ECLA (Estudios Clínicos Latino América), Argentina

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ABSTRACT

Background: Myocardial viability tests have been proposed as a key factor in the decision-making process concerning coronary revascularization procedures in patients with left ventricular dysfunction and coronary artery disease (LVD–CAD).

Methods: We performed a systematic review and meta-analysis of studies that compared medical treatment with revascularization in patients with viable and non-viable myocardium and recorded mortality as outcome.

Results: Thirty-two non-randomized (4328 patients) and 4 randomized (1079 patients) studies were analyzed. In non-randomized studies, revascularization provided a significant mortality benefit compared with medical treatment ($p < 0.05$). Since the heterogeneity was significant ($p < 0.05$) a viability subgroup analysis was performed, showing that revascularization provided a significant mortality benefit compared with medical treatment in patients with viable myocardium ($p < 0.05$) but not in patients without ($p = 0.34$). There was a significant subgroup effect ($p < 0.05$) related to the intensity of the effect, but not to the direction. In randomized studies, revascularization did not provide a significant mortality benefit compared with medical treatment in either patients with viable myocardium or those without ($p = 0.21$). There was no significant subgroup effect ($p = 0.72$). Neither non-randomized nor randomized studies demonstrated any significant difference in outcomes between patients with and without viable myocardium.

Conclusions: The available data are inconclusive regarding the usefulness of myocardial viability tests for the decision-making process concerning revascularization in LVD–CAD patients.

Patients with viable myocardium appear to benefit from revascularization, but similar benefits were observed in patients without viable myocardium. Moreover, a neutral or adverse effect of revascularization cannot be excluded in either group of patients.

1. Introduction

Since 1982, when Rahimtoola [1] first described the recovery of ventricular function after revascularization in patients with left ventricular dysfunction and coronary artery disease (LVD–CAD), our interest in myocardial viability has progressed from determining its pathophysiology, to its diagnostic potential, and finally to its usefulness in the clinical setting.

After the concept of hibernating myocardium was introduced [2], numerous techniques were developed for evaluating its presence or absence in patients with LVD–CAD or previous myocardial infarction (MI).

Once myocardial viability could be diagnosed with acceptable accuracy [3], the next step was to establish whether its presence or absence could guide clinical practice. The prognosis of patients with LVD–CAD is strongly related to the ejection fraction (EF) [4]. Consequently, the hypothesis was that if patients have viable myocardium, revascularization can improve heart function and therefore survival; otherwise, patients will do better with medical therapy alone.

The cardiovascular community adopted this premise as true, and myocardial viability tests gained a key place in the decision-making process concerning myocardial revascularization in patients with LVD–CAD. However, the published literature on this matter remains unclear and controversial. Accordingly, we performed a systematic review and meta-analysis of studies that compared medical treatment with revascularization in patients with viable and non-viable myocardium.

* Corresponding author at: Madres de plaza de 25 mayo 3020, Floor 10, S2013SWJ Rosario, Argentina.
E-mail address: aorlandinimd@eclainternational.org (A. Orlandini).

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2. Materials and methods

2.1. Literature search

The MEDLINE database was searched using PubMed to retrieve publications from between January 1960 and July 2013. Studies were selected if they: (1) included patients with LVD–CAD and/or previous MI, (2) tested myocardial viability, (3) compared medical treatment and revascularization in patients with viable myocardium and/or in patients without viable myocardium, and (4) recorded cardiac death or all-cause mortality as outcomes. Previous meta-analyses and systematic reviews were also analyzed [5–8]. Appendix 1 shows the detailed search strategy and search terms.

For each study, data relating to patient characteristics, study designs, viability criteria, imaging techniques, and outcome events were systematically extracted.

2.2. Statistical methods

We calculated risk ratios (RR) and 95% confidence intervals (CIs) for the primary outcome (cardiac death or all-cause mortality) for each study/viability subgroup separately. Overall estimates of effect were calculated using random-effect models, in which the effect of every study/viability subgroup was weighted by the inverse of its variance.

Publication bias was tested by visual inspection of the funnel plot and, more formally, using the Begg–Mazumdar test. In the absence of publication bias, the test result is not significant, and in the funnel plot, studies are distributed symmetrically about the mean effect size. To assess heterogeneity, the chi-square Q statistic was used. The null hypothesis evaluated by this test is that all the study subgroups share a common effect size. The proportion of the observed variance that reflects real differences in effect size was evaluated through the I^2 statistic. The chi-square Q statistic was also evaluated to compare subgroup effects. The p-value threshold for statistical significance was set at 0.05. Calculations were performed using Comprehensive Meta-Analysis Software (version 2.0; Biostat Inc., USA).

3. Results

3.1. Studies and patients

The database search identified 389 potentially relevant citations; 30 additional articles were included from references (Fig. 1). On the basis of their title and abstract, 101 studies were retrieved as complete reports, of which 36 met the eligibility criteria.

We included 32 non-randomized studies [9–40] (4328 patients) and 4 randomized studies [41–44] (1079 patients) in the analyses (Table 1). The mean duration of follow-up was 28.4 months for non-randomized studies and 45.6 months for randomized studies. The mean age of the patients was similar in the non-randomized studies (60.7 years) and randomized studies (61.1 years). The mean left ventricular EF was 31.8% in non-randomized studies and 34.4% in randomized studies.

For this analysis, patients were divided into 4 groups based on the treatment strategy (medical or revascularization) and the presence or absence of viable myocardium.

Table 2 shows the primary outcome (cardiac death or all-cause mortality) according to the treatment strategy and viability status. In the non-randomized studies, 2050 patients underwent revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and 2278 patients were treated medically. In the randomized studies, 534 patients underwent revascularization by PCI or CABG, and 545 patients were treated medically.

3.2. Publication bias

Fig. 2 shows the funnel plot of standard error by log (risk ratio) and the results of the Begg–Mazumdar test for non-randomized studies (A) and randomized studies (B). Publication bias was observed in the non-randomized studies ($Z = 2.52$, $p = 0.012$); in the randomized studies, there was no significant publication bias ($Z = 0.24$, $p = 0.8$).

3.3. Meta-analysis

Figs. 3 and 4 show the forest plots for non-randomized and randomized studies, respectively. Fig. 5 presents a summary of the results.

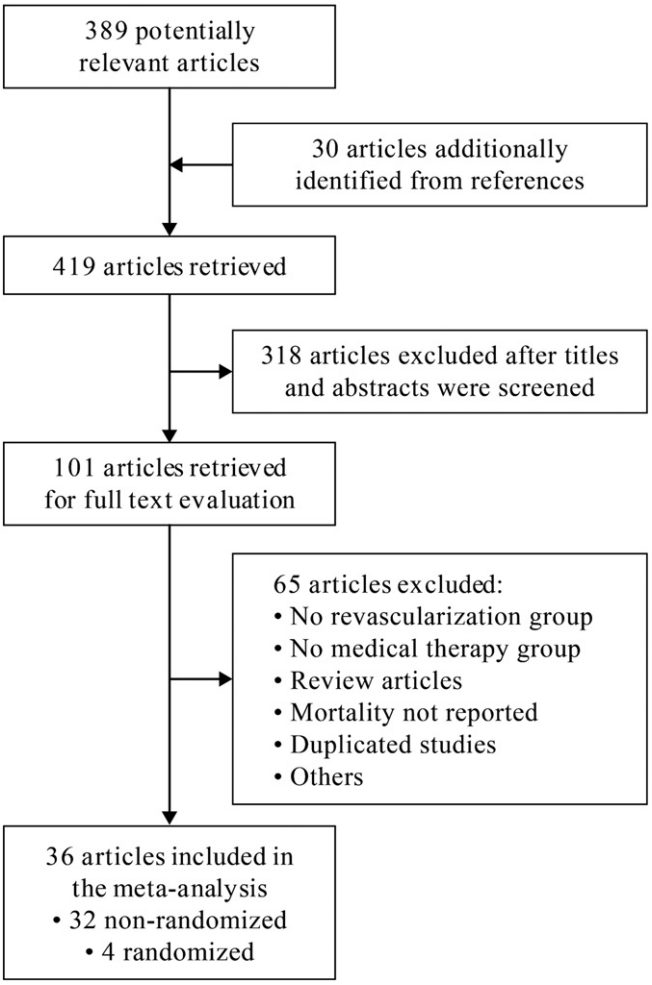

Fig. 1. Flow chart showing the process of study selection.

Overall estimates of the effect and estimations within each viability subgroup were calculated using random-effects models.

3.3.1. Non-randomized studies

Overall (Fig. 5), revascularization provided a significant mortality benefit compared with medical treatment (RR: 0.61, 95% CI: 0.53–0.69, $p < 0.05$). Since the heterogeneity was significant ($Q = 103.93$, $p < 0.05$, $I^2 = 46.12\%$), a viability subgroup analysis was performed. For patients with viable myocardium, revascularization also provided a significant mortality benefit compared with medical treatment (RR: 0.31, 95% CI: 0.25–0.39, $p < 0.05$); however, for patients without viable myocardium, this benefit was not statistically significant (RR: 0.92, 95% CI: 0.78–1.09, $p = 0.34$) (Fig. 3). There was a significant subgroup effect ($Q = 60.68$, $p < 0.05$) related to the intensity of the effect, but not to the direction (Fig. 5).

3.3.2. Randomized studies

Overall, revascularization did not provide a significant mortality benefit compared with medical treatment (RR: 0.89, 95% CI: 0.75–1.07, $p = 0.21$) (Fig. 5). Heterogeneity was not significant ($Q = 1.036$, $p = 0.90$). Revascularization did not provide a significant mortality benefit in either patients with viable myocardium or those without (Fig. 4). There was no significant subgroup effect ($Q = 0.13$, $p = 0.72$) (Fig. 5). Notably, the

Table 1
Characteristics of the included studies.

Author	Year	Diagnosis	Imaging technique	Viability criterion	n	Age	EF	Follow-up
Non-randomized								
Eitzman [9]	1992	CAD–LVD	FDG PET	Perfusion–metabolism mismatch of ≥1 segment viable	82	59	34	12
Yoshida [10]	1993	MI	FDG PET	Perfusion–metabolism mismatch	35	54	44	36
Lee [11]	1994	CAD–LVD	FDG PET	≥1 Viable segments	129	62	38	17
Gioia [12]	1995	CAD–LVD	Rest–redistribution TI	TI uptake score	85	65	30	31
Vom Dahl [13]	1997	CAD–LVD	FDG PET/MIBI	≥50% Mismatched myocardium	161	57	45	29
Afridi [14]	1998	CAD–LVD	DE	≥4 Viable segments	318	64	27	18
Anselmi [15]	1998	CAD–LVD	DE	≥1 Viable segments	202	59	33	16
Beanlands [16]	1998	CAD–LVD	FDG PET	Viability score	45	62	26	18
Cuoccolo [17]	1998	CAD–LVD	Rest–redistribution TI	TI uptake of ≥50% of peak activity	76	55	38	17
Di Carli [18]	1998	CAD–LVD	FDG PET	Perfusion–metabolism mismatch	93	68	25	45.6
Chaudhry [19]	1999	CAD–LVD	DE	≥5 Viable segments	80	64	27	26
Morse [20]	1999	CAD–LVD	Rest–redistribution TI	Viability index of >0.5	37	62	30	29
Pasquet [21]	1999	CAD–LVD	Rest–redistribution TI/DE	>50% Mismatched segments	137	62	35	33
Senior [22]	1999	CAD–LVD	DE	Inward motion of ≥5 in 12 segments	87	62	25	40
Smart [23]	1999	CAD–LVD	DE	Sustained improvement or biphasic response	168	61	30	18
Shapira [24]	2000	CAD–LVD	Rest–redistribution TI	Significant viability percentage of >55%	40	64	NA	34
Siagra [25]	2000	CAD–LVD	MIBI nitrate-augmented	≥10% Activity increase	99	61	34	27
Sicari [26]	2001	CAD–LVD	Dipyridamole ECHO	Improvement in WMSI of ≥0.20	307	60	28	36
Zhang [27]	2001	CAD–LVD	FDG PET MIBI	Perfusion–metabolism mismatch of >2 segments	123	56	35	26
Podio [28]	2002	CAD–LVD	Rest–redistribution TI	Improvement in TI uptake	153	59	46	45
Sawada [29]	2002	CAD–LVD	DE	Inward motion with dobutamine	139	59	32	23
Senior [30]	2002	CAD–LVD	TI/MIBI nitrate-augmented	>50% Mismatch of ≥5 segments	55	64	25	40
He [31]	2003	CAD–LVD	MIBI nitrate-augmented	>3 Nitrate-augmented reversible segments	78	55	38	23
Meluzin [32]	2003	CAD–LVD	DE	≥2 Dysfunctional but viable segments	113	58	26	27
Petrasinov [33]	2003	CAD–LVD	Rest–redistribution TI	201-TI uptake of >15% of peak activity	55	58	43	12
Sicari [34]	2003	CAD–LVD	DE	Improvement in WMSI of >0.40	425	61	28	37.2
Liao [35]	2004	CAD–LVD	DE	≥5 Segments viable	107	63	21	27
Acampa [36]	2005	CAD–LVD	MIBI at rest	MIBI uptake of ≥55% of peak activity	253	52	37	52
Desideri [37]	2005	CAD–LVD	FDG PET	Perfusion–metabolism mismatch	261	66	29	25.2
Penicka [38]	2007	CAD–LVD	TDI	(+) Pre-ejection velocity of ≥5 segments	117	67	30	11.8
Zhang [39]	2008	Aneurysm	FDG PET/Tc 99 MIBI	Perfusion–metabolism mismatch score	70	57	36	6
Romero Farina [40]	2009	CAD–LVD	MIBI rest–stress	≥3 Segments	198	64	30	27.6
Overall					4328	60.7*	31.8*	28.4*
Randomized								
HEART [41]	2010	CAD–LVD	DE	≥5 Segments viable	138	67	24	59
OAT-NUC [42]	2011	CAD–LVD	MIBI nitrate-augmented	MIBI uptake of ≥40% of peak activity	124	59	48	12
STICH [43]	2011	CAD–LVD	DE/SPECT	SPECT: ≥11 viable segments/Echo: ≥5 segments	601	61	27	61.2
VIAMI [44]	2012	MI	DE	Improvement of WMA in 2 or more segments	216	59	54	13.1
Overall					1079	61.1*	34.4*	45.6*

Age is expressed in years. CAD–LVD = coronary artery disease and left ventricular dysfunction; DE = dobutamine echocardiography; ECHO = echocardiography; EF = left ventricle ejection fraction expressed as percentage; FDE = F-18 fluorodeoxyglucose; Follow-up is expressed in months; MI = myocardial infarction; MIBI = Tc-99 sestamibi; NA = information not available; PET = positron emission tomography; SPECT = single photon emission computed tomography; TDI = tissue Doppler imaging; TI = thallium 201; WMA = wall motion abnormalities; WMSI = wall motion score index.
* Weighted averages.

subgroup without viable myocardium included only a small number of patients from one single study.

4. Discussion

In non-randomized studies, the revascularization procedures were associated with a significant reduction in mortality, regardless of the presence of viable myocardium. Although the heterogeneity test results between groups with and without viability were statistically significant, the difference was quantitative (different amount of benefit) and not qualitative (different direction of the effect). When only non-randomized studies were considered, it seemed as if all the patients could potentially benefit from revascularization.

The meta-analysis of non-randomized studies had several limitations: multiple small studies (32, ranging between 20 and 253 patients), some of them retrospective and others prospective; different myocardial viability tests, most of them considering viability as a dichotomous variable (yes/no, not grading the amount of viability); different follow-up durations; and wide temporal distribution (1992 to 2009). Most importantly, the results of the viability tests drove (at least in part) the decision for revascularization in most studies. Because of these relevant limitations, the results of the meta-analysis of non-randomized studies should only be considered as hypothesis generators.

The meta-analysis of randomized studies showed a non-significant trend towards a benefit from revascularization in the overall population. This means that we cannot exclude either a benefit or a deleterious effect from revascularization. Moreover, in this analysis, the heterogeneity test result between groups with or without viable myocardium was not statistically significant, reflecting a possibly similar effect in both groups.

The randomized studies also had limitations: different techniques used to diagnose viability; viability considered as a dichotomous variable; different follow-up periods; and only a few patients in one trial having no viable myocardium. Nevertheless, randomized trials have remarkable strengths compared with non-randomized studies. Furthermore, all of them were published in recent years, and reflect the current practice better; and importantly, the results of the tests did not drive the modality of treatment.

Despite these advantages, after the release of the STICH trial results numerous publications focused on pointing out its limitations [45–47], probably because this trial is the strongest evidence against

Table 2
Outcome according to the treatment strategy and presence or absence of viability.

	Viability (+)		Viability (−)	
	PCI/CABG	Medical Tx	PCI/CABG	Medical Tx
Author	n/N	n/N	n/N	n/N
Non-randomized				
Eitzman [9]	1/26	6/18	0/14	2/24
Yoshida [10]	2/20	0/5	2/4	3/6
Lee [11]	4/49	3/21	1/19	5/40
Gioia [12]	6/38	16/47	NI	NI
Vom Dahl [13]	2/57	2/14	2/27	7/63
Afridi [14]	5/85	24/119	5/30	17/84
Anselmi [15]	4/64	4/52	4/25	6/61
Beanlands [16]	1/31	4/14	NI	NI
Cuoccolo [17]	1/39	8/37	NI	NI
Di Carli [18]	7/26	11/17	5/17	14/33
Chaudhry [19]	2/24	10/34	4/4	10/18
Morse [20]	1/9	6/10	1/6	5/12
Pasquet [21]	5/58	4/16	9/36	7/27
Senior [22]	1/31	10/32	3/6	8/18
Smart [23]	7/78	44/90	NI	NI
Shapira [24]	0/11	7/9	3/9	6/11
Siagra [25]	9/75	6/24	NI	NI
Sicari [26]	1/41	7/38	16/83	30/145
Zhang [27]	0/42	8/30	5/25	1/26
Podio [28]	1/35	9/34	0/14	2/70
Sawada [29]	7/57	18/56	6/8	10/18
Senior [30]	2/23	10/32	NI	NI
He [31]	0/19	4/15	1/24	1/20
Meluzin [32]	4/39	10/29	6/23	7/22
Petrasinov [33]	0/25	1/11	2/10	4/9
Sicari [34]	4/52	13/36	37/136	72/201
Liao [35]	6/37	9/22	8/26	9/22
Acampa [36]	4/142	12/111	NI	NI
Desideri [37]	6/55	17/60	6/39	23/107
Penicka [38]	0/39	5/30	6/24	6/24
Zhang [39]	2/23	7/10	3/23	4/14
Romero Farina [40]	8/50	24/90	3/18	2/40
Overall	103/1400	319/1163	135/650	261/1115
Randomized				
HEART [41]	26/69	25/69	NI	NI
OAT-NUC [42]	4/61	3/63	NI	NI
STICH [43]	83/244	95/243	25/54	33/60
VIAMI [44]	2/106	3/110	NI	NI
Overall	115/480	126/485	25/54	33/60

Medical Tx = medical treatment; n = number of primary outcome events; N = number of total patients in the group; NI = no information; PCI/CABG = revascularization treatment.

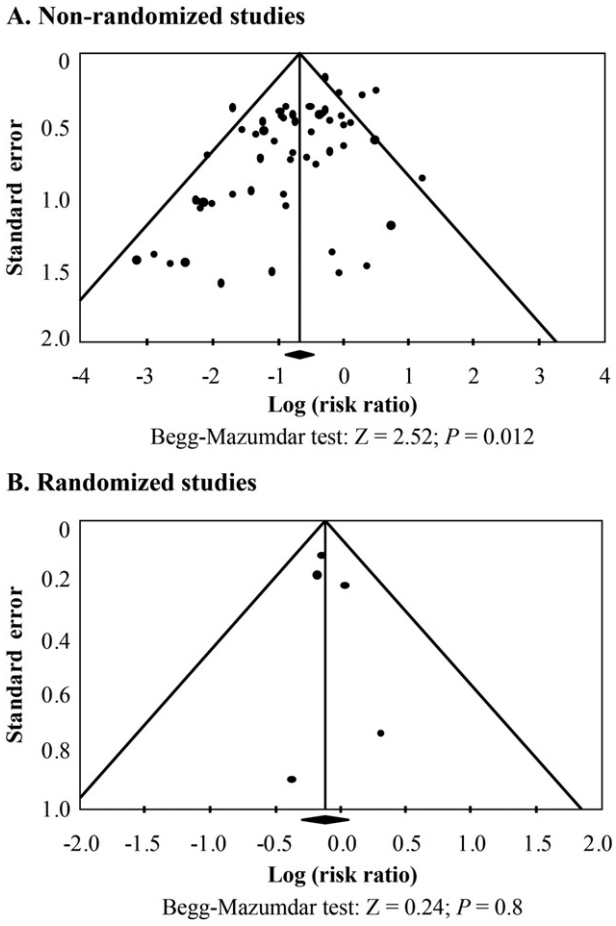

Fig. 2. Funnel plot of standard error by log (risk ratio) and the results of the Begg–Mazumdar test for non-randomized studies (A) and randomized studies (B) as a means of assessing publication bias.

the usefulness of myocardial viability tests in patients with LVD–CAD. Nevertheless, this was the largest trial in this field where the revascularization decision was independent of the results of the viability tests, but the number of patients included was insufficient to produce definitive conclusions.

Another important limitation of the studies included in both meta-analyses (randomized and non-randomized studies) is the fact that viability was not considered independently of ischemia. Viability and ischemia have different metabolic pathways and pathophysiology, and hence, probably different prognostic significance.

5. Conclusions

The available data are not conclusive regarding the usefulness of myocardial viability tests in the decision-making process concerning revascularization in patients with LVD–CAD. Patients with viable myocardium appear to benefit from revascularization, but the same benefits were observed in patients without viable myocardium. Moreover, a neutral or adverse effect of revascularization cannot be excluded in either group of patients.

A randomized clinical trial with an adequate number of patients, using recognized viability evaluation techniques, considering myocardial viability as a continuous variable independently of ischemia, with the selection of treatment not guided by the test results, is ultimately needed to reliably establish whether myocardial viability tests are useful in clinical practice.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.025.

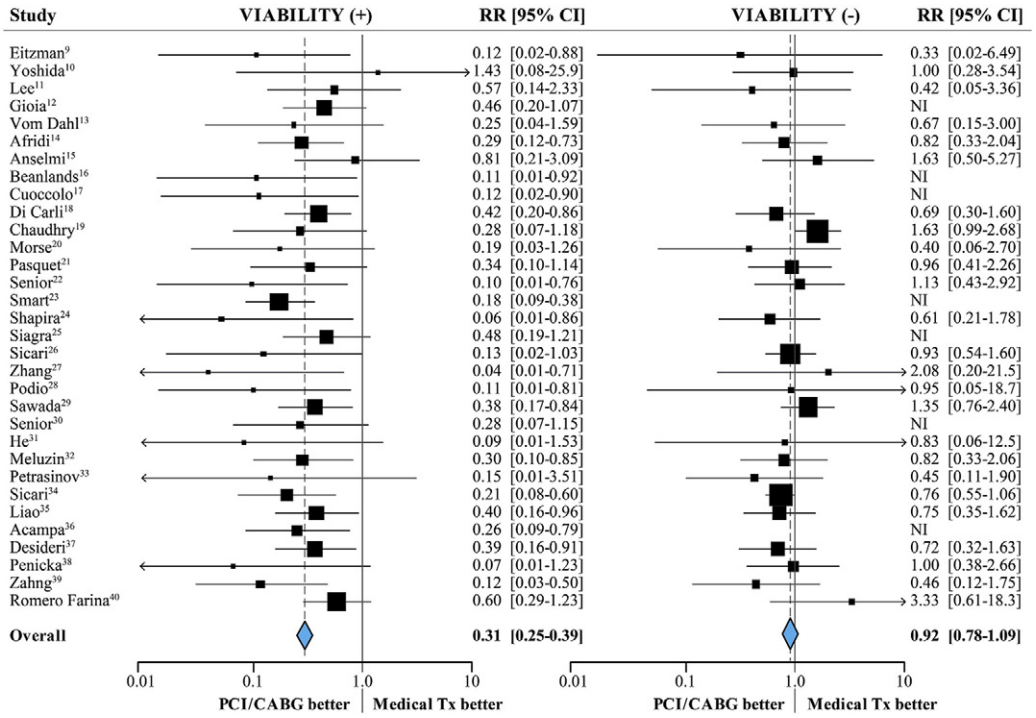

Fig. 3. Effect of revascularization versus medical treatment on all-cause and cardiac mortality in non-randomized studies. Results were stratified by viability subgroup. CI = confidence interval; medical Tx = medical treatment; PCI/CABG = revascularization treatment (percutaneous coronary intervention/coronary artery bypass grafting); RR = relative risk; viability (+) = patients with viable myocardium; viability (−) = patients without viable myocardium.

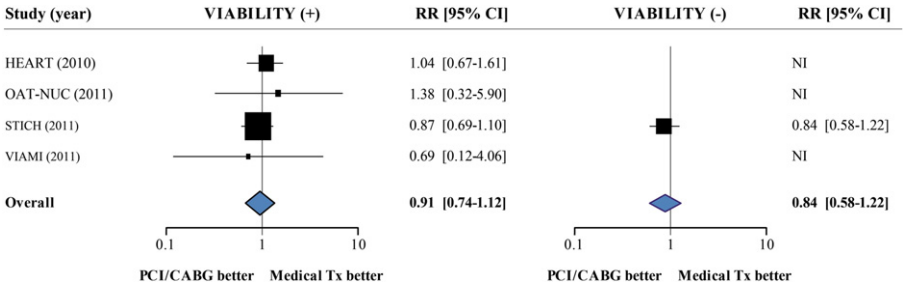

Fig. 4. Effect of revascularization versus medical treatment on all-cause and cardiac mortality in randomized studies. Results were stratified by viability subgroup. CI = confidence interval; medical Tx = medical treatment; PCI/CABG = revascularization treatment (percutaneous coronary intervention/coronary artery bypass grafting); RR = relative risk; viability (+) = patients with viable myocardium; viability (−) = patients without viable myocardium.

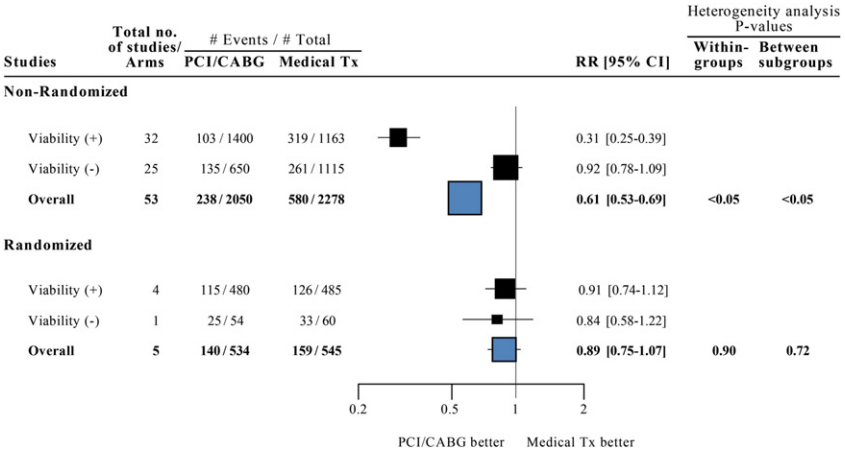

Fig. 5. Summary results of the effect of revascularization versus medical treatment on all-cause and cardiac mortality in each viability subgroup for non-randomized and randomized studies. CI = confidence interval; medical Tx = medical treatment; PCI/CABG = revascularization treatment (percutaneous coronary intervention/coronary artery bypass grafting); RR = relative risk; viability (+) = patients with viable myocardium; viability (−) = patients without viable myocardium.

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