

Viability Tested with Dobutamine Stress Echocardiography and Prognosis Early after Acute Myocardial Infarction: A Meta-Analysis

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Abstract

In non-high risk patients treated without primary PCI for acute myocardial infarction (AMI), the updated American Heart Association/American College of Cardiology guidelines recommend a selective pharmacoinvasive strategy (IIb, level C). Early risk assessment is essential to select patients with an increased risk for ischemic events or cardiac death. A potential prognostic value has been ascribed to viability in the infarct region. Viability-testing with Low Dose Dobutamine echocardiography (LDDE) can safely be performed in the early phase after AMI. Since the prognostic value of viability after acute myocardial infarction remains unclear and is still debated, we performed a meta-analysis of post-infarction studies to elucidate the importance and prognostic value of viability early after AMI. The literature was scanned by formal searches of electronic databases from 1966 to June 2010. We used the following selection criteria for inclusion in this meta-analysis: a) viability testing with LDDE within 14 days after Acute Myocardial Infarction (AMI), b) preserved left ventricular function (ejection fraction(EF) $\geq 40\%$ or wall motion score index (WMSI) ≤ 1.9), c) prognosis scored by clinical endpoints (death, AMI or unstable angina (UA)). Eight observational studies were included in the meta-analysis (2301 patients). Results: The presence of viability was strongly associated with an increase in ischemic cardiac events [OR 5.0 (1.53 - 16.36), $p=0.008$]. No predictive value was found for mortality [OR 0.91 (0.38 - 2.18), $p=0.84$]. In conclusion, patients with preserved left ventricular function and proven viability early after AMI are at risk for ischemic cardiac events, without any difference in mortality (Meta-analysis, acute myocardial infarction, viability, echocardiography).

Background

The last two decades, management of acute myocardial infarction has evolved considerably. Widespread use of thrombolysis, aspirin, clopidogrel, statins, beta-blocking agents, and ACE-inhibitors has reduced mortality. The advent of Percutaneous Coronary Intervention (PCI) has further improved outcome. Primary PCI is increasingly being used, because it offers the best possible results, when performed in an optimal setting [1-4]. Nevertheless, because of the low availability of primary PCI, even in developed countries, many patients are still being treated with intravenous thrombolysis. Furthermore, a substantial number of patients do not receive active reperfusion therapy at all, in many cases because of late presentation [4,5].

Without PCI, the issue of recurrent ischemic events remains to be addressed. As known, after successful thrombolysis, more than 50% of patients have a significant residual stenosis and about 30% of patients have spontaneous or inducible ischemia, despite optimal medical therapy [6-8]. Reocclusion of the infarct-related artery is a potential threat in this group of patients, since it is associated with recurrent ischemia or recurrent infarction [9,10]. The American Heart Association/American College of Cardiology guidelines recommend a selective pharmacoinvasive strategy in non-high risk patients [3].

Early risk assessment is essential to select patients with an increased risk for ischemic events or cardiac death. Non-invasive risk stratification has particularly focused on exercise/stress testing. Important limitations for the detection of ischemia with exercise testing remain the inability to exercise, the low diagnostic accuracy, resting ECG abnormalities, and safety concerns in the very early phase after acute myocardial infarction [11,12]. These limitations have stimulated the search for other suitable non-invasive tests to perform risk stratification after acute myocardial infarction.

Several post-infarction observational studies investigated the potential of viability as prognosticator, since ischemic events are expected to occur in viable tissue only. The prognostic value of viability

in patients with CAD and chronic left ventricular (LV) dysfunction has been clearly elucidated in the last decades [13]. However, the prognostic value of viability after AMI still remains a matter of discussion even after being studied over the last several years. In many studies viability in the infarct zone is thought to be a potential substrate for future cardiac events like recurrent ischemia, recurrent infarction, left ventricular failure and death, particularly when this viable myocardium is jeopardized by an unstable residual stenosis in the infarct-related coronary artery [14-23]. In other post-infarction studies a protective effect is ascribed to viable tissue and therefore associated with an improved prognosis [24-27]. In a meta-analysis of non-randomized data by Iskander [13], the impact of revascularization on clinical outcome in patients with viability after AMI and left ventricular dysfunction was studied. In revascularized patients with viability in the infarct area, a significant decrease in future cardiac events was observed, when compared to medically treated patients with demonstrated viability (annual event rate: 6% vs. 27%). In contrast, the outcome in patients without viability in the infarct area did not change by an invasive strategy (annual event rate: 7% vs. 5%).

Picano et al. even postulated that the impact of viability on prognosis in patients evaluated early after an AMI is a paradox. In

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patients with good ventricles, viability was associated with a higher ischemic instability, but in patients with depressed left ventricular function, the presence of viability recognized by low dose dobutamine echocardiography was associated with a better survival [25]. The reason for this “paradox” is not quite understood and warrants further investigation.

To elucidate the importance and prognostic value of viability detected early after AMI in patients with a relatively preserved left ventricular function, we analyzed and reviewed all available post-infarction studies evaluating viability with low dose dobutamine echocardiography (LDDE).

Methods

Search strategy and selection criteria.

A Medline, Embase and Cochrane Library database search for literature published in English since 1966 until 18 June 2010 was performed. The search algorithm used the following keywords: “Myocardial infarction, Stress echocardiography, Viability, Prognosis.” To prevent heterogeneity caused by the diagnostic tool for viability, only studies using LDDE for viability-testing were included.

We found 88 citations in Medline, 87 citations in Embase and none in the Cochrane Library. After screening of titles and abstracts the majority of these citations represented studies investigating the prognosis of viability in patients with advanced coronary artery disease and depressed left ventricular function but without a recent AMI. No randomized clinical trials were available on this topic. Therefore, we only included observational studies.

The time-course of viability after AMI was investigated by Knudsen et al. Using LDDE early after AMI, one third of the viable kinetic segments lost their ability to respond to dobutamine during 90 days follow up [28]. Therefore, it was recommended to perform viability testing early after acute myocardial infarction to achieve maximal yield. Only LDDE studies that tested their patients within 14 days, resulting in a better comparable study population, were reviewed in this meta-analysis. Reviewing literature about viability testing with LDDE reveals different thresholds for the definition of preserved viability. The number of improving segments during LDDE to define viability varies from 1 to 3 segments in a 16 segments model. Changes from hypokinesia to normokinesia and from dyskinesia or akinesia to hypo- or normokinesia are considered an improvement in wall motion abnormality. Dyskinesia changing to akinesia is not considered as an improvement. In this meta-analysis the included studies used a viability threshold of ≥ 2 segments.

Eventually, we used the following selection criteria for inclusion in this meta-analysis: a) viability testing with LDDE within 14 days after AMI, b) preserved left ventricular function (ejection fraction (EF) $\geq 40\%$ or wall motion score index (WMSI) ≤ 1.9) [29], c) prognosis scored by clinical endpoints (death, AMI or unstable angina (UA), with or without revascularization).

To evaluate the influence of revascularization on prognosis in patients with viability, all information (if available) about revascularization procedures were collected with the intention to calculate an interaction odd of revascularization and clinical endpoints.

Eight articles were included after fulfilling the inclusion criteria in title and abstract. After the database search, we screened the reference lists of the included articles. No new articles fulfilling our inclusion criteria were found.

Corresponding authors were contacted for additional data in case absolute values were not provided in the manuscript.

Statistical analysis

From each study, baseline characteristics, hard endpoints, and number of cardiac events at follow up were extracted and pooled in two groups: patients with or without demonstrated viability. Pooled odds ratio's (ORs) and 95% confidence intervals (CIs) were calculated. Studies were tested for statistical heterogeneity by using the Q statistic. Because of the low number of studies OR's were pooled using random effects models (DerSimonian & Laird method), independent from the results of the heterogeneity analysis. Presence of publication bias and small study effects was explored using funnel plots of effect size against standard error and was formally tested using Egger's test [30]. Because Egger's test is prone to give biased results (i.e. inappropriate type I error rates) we also used an alternative method proposed by Peters et al. (Peters's test) to evaluate publication bias and small studies effects [31]. In case of zero cells a value of 0.5 was added to each cell of that specific study. STATA software (version 11.0, Stata Corporation, College Station, Texas) was used for the analyses.

Results

All studies used dobutamine echocardiography with low (LDDE) or high dose protocol including atropine augmentation (DASE) in 1987 patients with a mean follow up of 13.8 months [15,19,21-24,26].

The studies analyzed

An overview of the studies discussed in this article is given in Table 1. Baseline characteristics (if available) of the investigated population in the different studies were comparable (Table 2). Five studies demonstrated an adverse prognosis with higher event rates in patients with viability. Three studies reported a better prognosis with less cardiac events in patients with preserved viability after AMI (Table 3). All studies included patients with AMI documented by typical chest pain lasting >30 minutes, elevated creatine kinase and MB fraction, and electrocardiographic changes (ST elevation or depression), representing a mixed bag of patients with ST-elevation myocardial infarction (STEMI) or non ST-elevation myocardial infarction (NSTEMI). Eventually, 58% of all patients were treated with thrombolysis.

Viability and adverse prognosis (5 studies)

Sicari et al. used dobutamine stress echocardiography (DSE) in a multicenter, prospective and non-randomized study [23]. A total of 778 patients were evaluated 12 ± 5 days after uncomplicated first myocardial infarction. Myocardial viability appeared to be the most important predictor of spontaneous events (death, reinfarction and unstable angina). An event rate of 18.8% was seen in patients with viability in the infarct region, compared to 10.0% in patients without viability during a mean follow up of 9 months. No significant difference in survival was found. Of all patients with a positive DSE, 28% were revascularized during follow up, compared with 15% in patients with negative DSE. The percentages viable and nonviable patients were unknown.

Previtali et al. used dobutamine stress echocardiography (DSE) in a multicenter, prospective, non-randomized study [21]. A total of 152 patients were evaluated 9 ± 5 days after uncomplicated first acute myocardial infarction treated within 6 hours with thrombolysis. After a mean of 15 months follow up, viability and ischemia or viability alone

Author	Design	Prospective	Test	Year of publ.	Timing	pts	FU (mos)	Events
Carlos	Observational	Yes	DSE	1997	2-7 d	214	12	D, re-MI, VT/VF
Sicari	Observational	Yes	DSE	1997	7-17 d	778	9	D, re-MI, UA
Previtali	Observational	Yes	DSE	1998	6-15 d	152	15	D, re-MI, UA
Picano	Observational	No	DSE	1998	6-18 d	314	9	D
Salustri	Observational	Yes	DSE	1999	6-14 d	245	17	D, re-MI, UA
Samad	Observational	Yes	LDDE	1999	2-6 d	49	18	D, re-MI
Bigi	Observational	Yes	DSE	2001	5-11 d	411	11	D, re-MI, UA
Nijland	Observational	Yes	LDDE	2001	2-5 d	138	19	D, re-MI, UA

DSE = Dobutamine Stress Echocardiography; LDDE = Low Dose Dobutamine Echocardiography; D = Death
re-MI = Reinfarction; UA = Unstable Angina; VT = Ventricular Tachycardia ; VF = Ventricular Fibrillation; FU = Follow UP
NA = Not Available; d = days; mos = months

Table 1: An overview of the study.

Author	Age (mean)	Men (%)	pts (n)	Hypertension (%)	Diabetes (%)	Q-wave (%)	Creatine kinase U/L (mean)	Thrombolysis (%)	WMSI
Carlos	58	76	214	NA	NA	57	2133	57	1.67
Sicari	58	87	778	NA	NA	74	NA	58	1.5
Previtali	54	93	152	26	NA	74	2140	100	1.54
Picano	58	86	314	NA	NA	89	NA	58	1.89
Salustri	60	86	245	28	11	89	NA	48	1.41
Samad	63	70	49	NA	NA	82	NA	100	1.65
Bigi	57	87	411	24	13	86	1993	54	1.48
Nijland	60	80	138	36	10	71	1705	69	1.55

EF = Ejection Fraction; WMSI = Wall Motion Score Index; NA = Not Available; n=number

Table 2: Baseline characteristics of the investigated population.

Author	FU Events (%)		Revascularization (%)		
	Viable	Nonviable	Viable		Nonviable
Carlos	9 ¹	20 ¹		38	
Sicari	18.2	10	NA		NA
Previtali	46 ²	20 ²	19		2
Picano	1.9	5.5		28	
Salustri	23 ²	11 ²	NA		NA
Samad	3.6	28.6	43		10
Bigi	45	6.9	33		16
Nijland	44	22	55		29

Med = medical treatment; Rev = revascularization; NA = Not Available

¹Indirectly taken from figure

²Positive DES (improving, worsening, or biphasic response)

Table 3: Study report for better prognosis with less cardiac events in patients.

detected early after treatment was associated with an event rate of 46%, whereas patients showing no viability in the infarct zone had a better prognosis with an event rate of 20% (death, reinfarction and unstable angina). Revascularization procedures were equally distributed in both groups.

In a single-center, prospective, non-randomized study by Salustri et al. [22], similar results were found in 245 patients after a mean of 17 months follow up. Patients showing viability (with or without ischemia) 6 to 14 days after their first uncomplicated acute myocardial infarction determined by DSE experienced an event rate of 23% compared to 11% in patients without viability in the infarct area (death, reinfarction and unstable angina). No information about revascularization was given.

Bigi et al. prospectively assessed the long-term effect of viability, ischemia, or their combination on survival after an uncomplicated acute myocardial infarction by dobutamine stress echocardiography before discharge (5-11 days after AMI) in a group of 411 patients [15]. Patients with viability (with or without ischemia) in the infarct

region had an event rate at 11 months follow up of 45%. However, patients without viability/ischemia had a low event rate of 6.9% (death, reinfarction and unstable angina). Sixteen percent (16%) of these patients were revascularized, compared with 33% of the patients with viability and/or ischemia.

In a double-center, prospective, non-randomized study, Nijland et al. investigated the in-hospital and long-term prognostic value of viable myocardium detected by LDDE early after acute myocardial infarction in 138 consecutive patients [19]. Viability testing was performed 3 ± 1 days after an uncomplicated acute myocardial infarction. In-hospital event rate was 20% in patients with viability versus 7% in patients without viability (death, reinfarction and unstable angina). Viability was the only independent predictor for cardiac events. No significant difference in mortality or sustained ventricular tachycardia was seen in patients with viable myocardium compared to patients without viable myocardium. After a mean of 19 months follow up, viability remained the single independent predictor of cardiac events with an event rate

of 44% in the viable group. The non-viable group had an event rate of 22%. The viable group was revascularized more often (55% vs. 29%).

Viability and good prognosis (3 studies)

In a prospective, observational study Carlos et al. performed dobutamine stress echocardiography to investigate the prognostic value of viability or ischemia early after myocardial infarction [24]. DSE was performed in 214 patients within the first 7 days after acute myocardial infarction. At 12 months follow up, an event rate (death, re-MI, VT/VF) of 9% was seen in the patient group with viability in the infarct zone. However, non-viability of the infarct zone indicated an increased risk of cardiac events (20.0%). In 38% of the total study group, a revascularization procedure was performed. Further information about the distribution between both groups, was not given by the authors.

A retrospective, non-randomized study was conducted by Picano et al. to investigate the prognostic value of myocardial viability early after acute myocardial infarction in 314 patients [25]. Viability was determined by low-dose dobutamine echocardiography 12 ± 6 days after uncomplicated myocardial infarction with moderate to severe left ventricular dysfunction. After a mean of 9 months follow up, a non-significant trend for better survival was found. The mortality rate in the group patients with viable myocardium in the infarct area was 1.9%, compared to 5.5% in the non-viable group (p=0.14). The revascularization rate of studied population is 28%, but not specified by the investigators.

Samad et al. evaluated the ability of low-dose dobutamine echocardiography (LDDE) to predict late functional recovery after thrombolized acute myocardial infarction in 49 patients [26]. Viability was tested 4 ± 2 days after acute myocardial infarction. All patients were re-evaluated clinically at 3, 6, and 12 months. Patients with proven viability showed an event rate of 3.6% after 18 months follow-up. Patients without viability experienced an event rate of 28.6% (death, recurrent AMI). The viable patient group was revascularized in 43% versus only 10% of the nonviable patient group.

Results of the meta-analysis on viability and clinical outcome

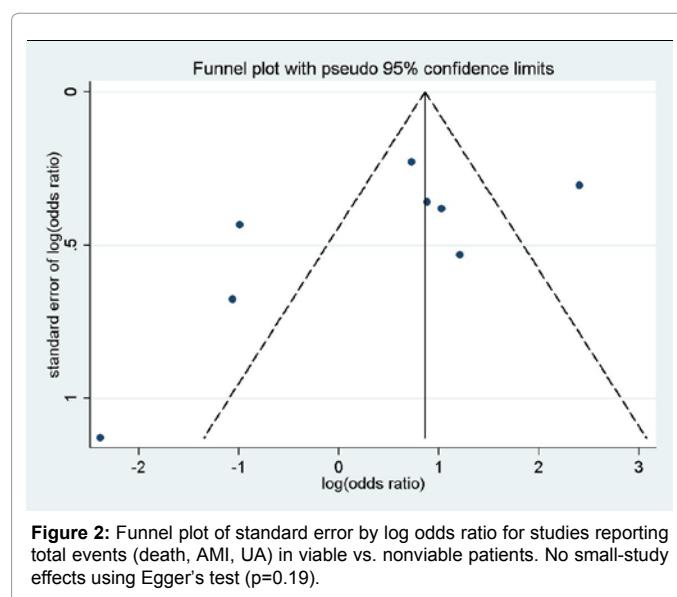
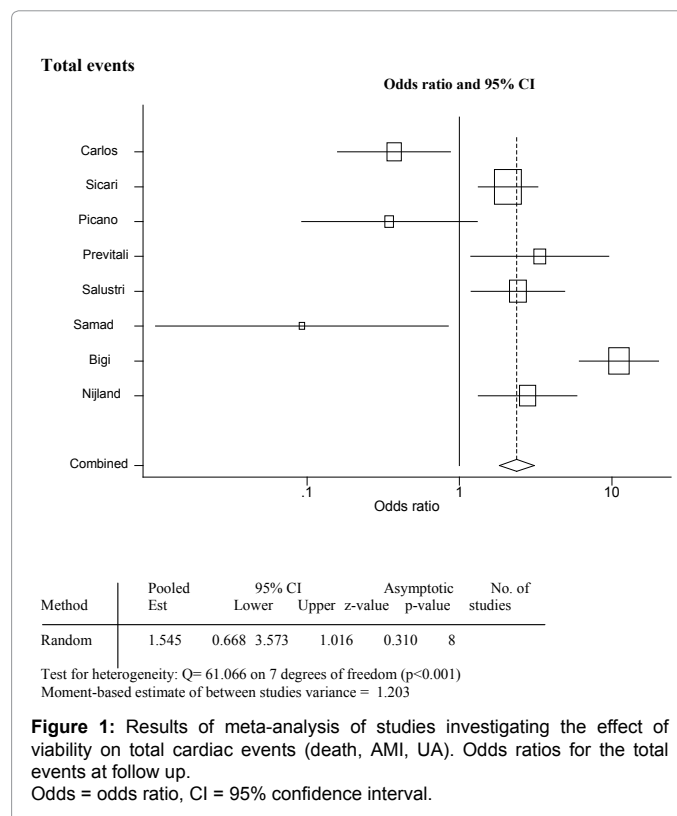
All cardiac events: Only 2 studies showed a statistically significant favorable effect of viability on outcome. Figure 1 shows an overview of total event rates of 8 studies. After pooling all studies, viability is not associated with more events [Odds Ratio (OR) 1.55 (0.67 – 3.57, p=0.31)]. The Q value of 61.1 % indicates heterogeneity (p<0.001). The funnel plot and related Egger’s test did not reveal publication bias or small-study effects (Figure 2, p=0.19), which was confirmed by the alternative test proposed by Peters et al. (p=0.33).

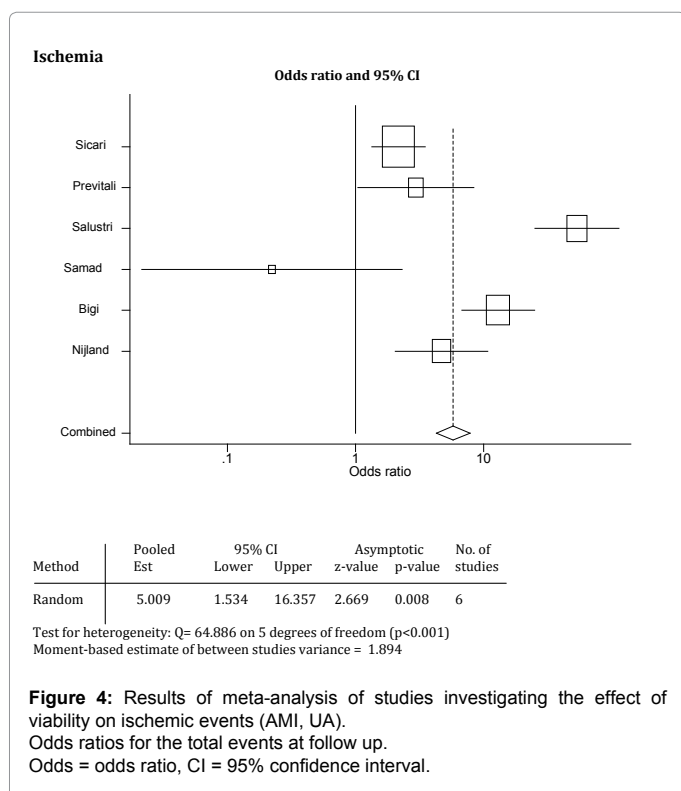
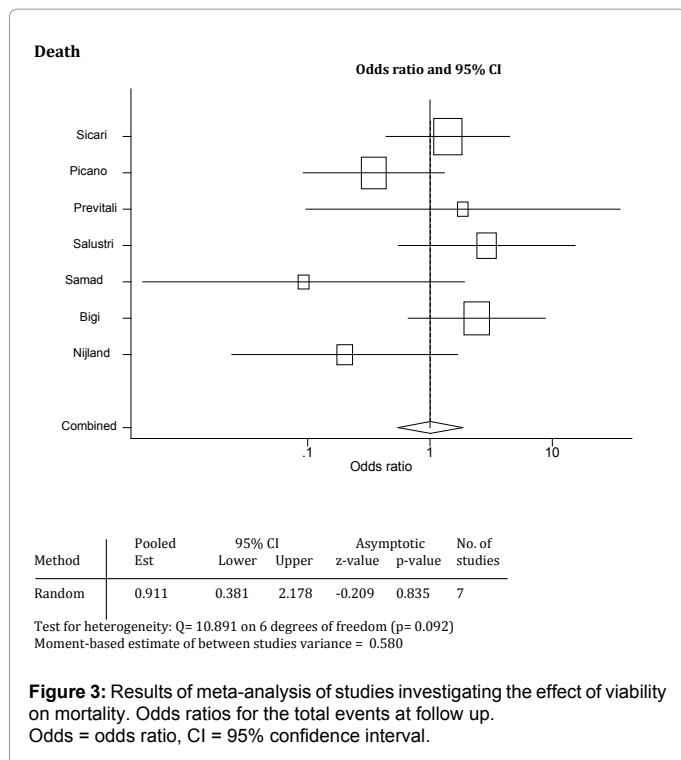
Mortality: No significant difference is seen after pooling the mortality data [OR 0.91 (0.38 - 2.18), p=0.84] (Figure 3). The Q value of 10.9 % indicates low heterogeneity (p=0.09). Information about mortality is not provided in the study performed by Carlos et al. Therefore, this study is not incorporated in the pooled analysis on mortality. No indication for publication bias or small-study effects was seen in Egger’s test (p=0.40). Also, the Peters’s test revealed no asymmetry of the funnel plot for indicating publication bias or small-study effects (p=0.13).

Ischemia: All studies, except the one by Samad, showed a significant increase of ischemic events in patients with viability in the infarct area. Despite the high heterogeneity that is observed (Q: 64.9%, p<0.001), our meta-analysis showed a significant increase in ischemic

events if viability is present [OR 5.0 (1.53 - 16.36), p=0.008]. This is shown in Figure 4, without a significant indication for publication bias or small-study effects in Egger’s test (Figure 5, p=0.94) and Peters’s test (p=0.73).

Revascularization: Only 4 studies are reporting about revascularization procedures in the viable vs. the non-viable patients groups. The group with viability receives more than twice as many revascularization procedures compared with the group without viability in the infarct region present [OR 2.3 (1.21 – 4.21), p=0.01]. No





indication for heterogeneity is demonstrated ($Q: 5.5, p=0.14$) (Figure 6). The Egger's test showed no publication bias or small study effects ($p=0.24$). In contrary, the Peter's test showed significant asymmetry of the funnel plot, indicating publication bias or small study effects ($p=0.04$).

Discussion

To the best of our knowledge, this is the first meta-analysis describing the prognostic value of viability early after AMI in patients with preserved LV function. Many studies and some meta-analyses evaluated the prognostic value of viable myocardium in patients with ischemic cardiomyopathy and moderate to severe left ventricular dysfunction [13,32,33]. No randomized clinical trial until now has addressed this topic.

Several issues have to be discussed that could have influenced our results. The first issue is the high level of heterogeneity in the outcome of ischemic events. To account for this, we used random effects models for pooling the results of the studies. Presence of publication bias and small study effects was explored using funnel plots of effect size against standard error and was formally tested using Egger's test. We also used an alternative procedure (Peters's test) to explore publication bias and small study effects because the Eggers's test is prone to erroneous results and unstable p-values.

Also, the post-myocardial infarction treatment strategies could differ significantly, especially with respect to the number of revascularization procedures, their timing and distribution in the viable and non-viable groups. This could play a role because the possible influence of revascularization on clinical outcome is well illustrated in a meta-analysis from Iskander and Iskandrian of patients with coronary artery disease and left ventricular dysfunction [13]. In another meta-analysis from Bourque et al. an interaction odds ratio of 2.76 was observed in viable patients receiving revascularization therapy. The chance of dying was 2.76 times lower if a revascularization procedure was performed in the viable patient group [33]. In our review an interaction odd could not be calculated, since revascularization procedures were not reported in all studies. Analyzing only the reporting studies, viable patients were 2.3 times more often revascularized [OR 2.3 (1.21 – 4.21), $p=0.01$], probably due to the increased ischemic event-rate in the viable patients. However, these results may be influenced by publication bias as indicated by the Peters's test ($p=0.04$) and must be interpreted with caution. Therefore, the influence of revascularization on prognosis could not be determined in this meta-analysis.

An important part of the heterogeneity in the outcome ischemic events seems to be caused by the small study of Samad et al., without indicating a small-study effect by the Egger's test (Figures 4 and 5) and Peters's test. Patients with proven viability experienced an event rate of only 3.6%, versus 28.6% in the non-viable group. However, these viable patients were 4.3 times more often revascularized compared to non-viable patients (43% vs. 10%) (Table 3, Figure 6). Although we were not informed about the timing of these revascularization procedures, this difference in revascularization procedures could in part explain this heterogeneity.

Severe LV dysfunction is an important and frequently used explanation for the paradoxical outcome in viability studies after acute myocardial infarction with respect to mortality. In patients with good ventricles, viability was associated with a higher ischemic instability, but in patients with depressed left ventricular function, the presence of viability was associated with a better survival [25]. It can be argued that patients with viability have a potential of recovery of LV function (spontaneous or by revascularization), thereby improving their survival. The reason for this "paradox" is not quite understood and warrants further investigation. In our meta-analysis, only studies with moderately impaired LV function ($EF \geq 40\%$, $WMSI < 1.9$) were reviewed. Therefore, we could only in part confirm this seeming paradox.

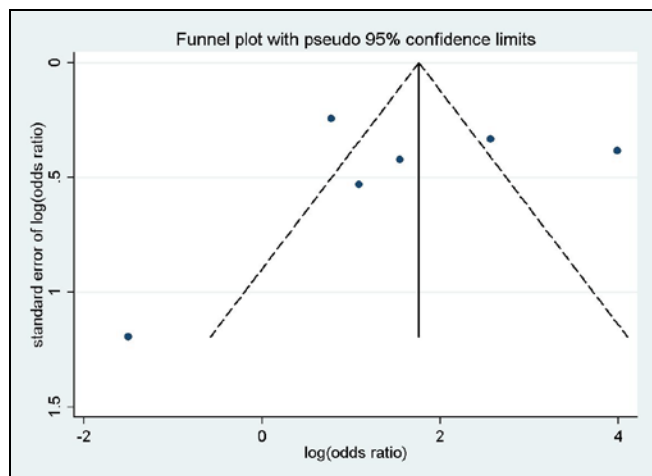
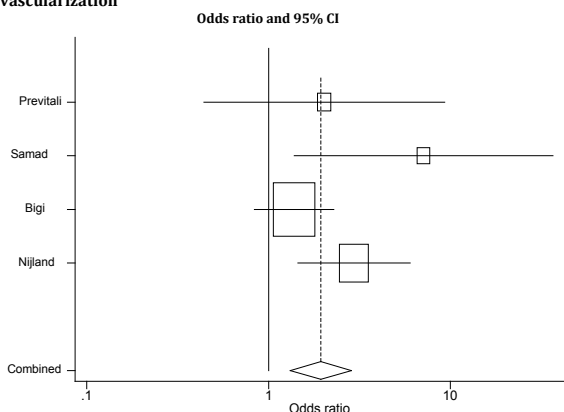


Figure 5: Funnel plot of standard error by log odds ratio for studies reporting ischemic events (AMI, UA) in viable vs. nonviable patients. No small-study effects using Egger's test ($p=0.94$).

Revascularization



Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z-value	p-value	No. of studies
Random	2.257	1.211	4.207	2.563	0.01	4

Test for heterogeneity: $Q= 5.505$ on 3 degrees of freedom ($p=0.138$)
Moment-based estimate of between studies variance = 0.173

Figure 6: Results of meta-analysis of studies investigating the effect of viability on revascularizations. Odds ratios for the total events at follow up. Odds = odds ratio, CI = 95% confidence interval.

Not all the available data about the prognostic value of viability after acute myocardial infarction are discussed in this review. In the DREAM study 212 stable patients underwent dobutamine stress echocardiography (DSE) a mean of 4.8 days after AMI [34]. Myocardial viability was an independent predictor for better long term survival. A revascularization procedure was performed in 48% of the study population. Since the exact data about patient numbers and preserved viability were lacking, even after contacting the authors, we couldn't implement this study in our meta-analysis. Implementing the results of the DREAM study could have been of influence in the meta-analysis with respect to mortality.

Limitations

All analyzed studies were observational studies. As a consequence, all studies were liable to multiple biases and confounders resulting in a more or less selected population. Therefore, the results of this meta-analysis must be interpreted with some caution. Furthermore, the included studies are all published more than 10 years ago. The management of AMI has evolved and changed considerably during this time. Not only because of better availability of PCI facilities, but also because of better concomitant medication (Thienopyridines, GPIIb/IIIa receptor blockers, etc.). Translation of the results of this meta-analysis to the present era of infarct management is somewhat limited.

Clinical implications

As it appears that viability detects a potential substrate for ischemic events, an invasive approach in viable patients might be beneficial by addressing the Infarct related artery (IRA) in order to reduce future ischemic events.

Randomized studies are needed to investigate the prognostic value of viability after AMI in patients not treated with primary PCI, comparing optimal medical treatment with a revascularization strategy.

Recently, the Viability-guided Angioplasty after acute Myocardial Infarction (VIAMI) trial showed a beneficial effect of revascularization (IRA PCI with stenting) on prognosis early after AMI in patients with proven viability, compared to a conservative (ischemia guided) treatment. An invasive approach in patients with viability resulted in a clear reduction in ischemic events and a long-term uneventful clinical course [35,36].

Conclusion

The main finding of this meta-analysis is that significantly more ischemic events (AMI and UA) occur in patients with proven viability and preserved left ventricular function early after AMI (not treated with primary PCI), without differences in mortality. This increase in ischemic events parallels a more than twofold increase in revascularization procedures in viable patients.

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