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Peri-procedural Elevated Myocardial Biomarkers Predict Adverse Clinical Outcomes Following Elective Percutaneous Coronary Intervention: A Comprehensive Dose-Response Meta-Analysis of 24 Prospective Studies with 44972 patients

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Short title: Dose-response relationship between peri-procedural elevated myocardial biomarkers and mortality

The authors have no conflicts of interest to declare.

Abstract:

Aims: The optimal cut-off value of isolated cardiac biomarker elevation for defining prognostically important percutaneous coronary intervention (PCI)-related myocardial injury is not known. We performed a meta-analysis to evaluate the dose-response relationship between isolated cardiac biomarker elevations and risk of all-cause mortality following elective PCI.

Methods and Results: 24 prospective studies (44972 patients) were included. Patients with an isolated elevation of cardiac biomarkers, had increased risk of all-cause mortality when compared to those with no elevations (cardiac troponin I: odds ratio (OR) 1.42, 95% confidence interval (CI) 1.19-1.69; creatine kinase-MB isoenzyme (CK-MB) OR 1.43, 95% CI 1.19-1.70). For the dose-response analysis, elevations of cardiac troponin I >3x or CK-MB>1x99th percentile upper reference limit (URL) were associated with increased mortality (cardiac troponin I: OR 1.51 95% CI 1.05-2.17; CK-MB: OR 1.25, 95% CI 1.05-1.48). The pooled OR of mortality for each 3xURL increment of cardiac troponin I or CK-MB were 1.33 (95% CI 1.15-1.53) and 1.38 (95% CI 1.30 -1.47).

Conclusions: We found a positive dose-response relationship between isolated cardiac troponin I and CK-MB with all-cause mortality and elevated cardiac troponin I > 3x or CK-MB > 1x the 99th percentile URL was associated with the increased risk of mortality.

Classifications: Stable angina; Death; Myocardial infarction

Abbreviations:

CAD:coronary artery disease

CI: confidence intervals

DM: diabetes mellitus

CK-MB: creatine kinase MB isoenzyme

MACE: major adverse cardiovascular events

MOOSE : Meta-analysis of Observational Studies in Epidemiology

OR: odds ratio

PCI: percutaneous coronary intervention

RR: relative risk

UDMI: Universal Definition of Myocardial Infarction;

URL: upper reference limitor

Condensed abstract:

This comprehensive dose-response meta-analysis of 24 prospective studies (44972 patients) found that elevated levels of cardiac troponin I and CK-MB post-PCI were all associated with risk of all-cause mortality in patients undergoing elective PCI. More importantly, >3x the 99th percentile for cardiac troponin I or >1x 99th percentile URL for CK-MB was associated with increased risk of mortality. Crucially, mortality increased by 33% or 27% for each increment of 3x 99th percentile URL for cardiac troponin I or CK-MB levels post-PCI, respectively.

1. Introduction

Elective percutaneous coronary intervention (PCI) is an established treatment for stable coronary artery disease (CAD), accounting for more than 3 million PCI procedures annually worldwide[1-3]. One of the most common complications following PCI is peri-procedural myocardial injury and infarction (also known as Type 4a myocardial infarction). Together these occur in about 35% of elective PCI procedures, and their presence are associated with worse clinical outcomes[4, 5]. According to the latest fourth Universal Definition of Myocardial Infarction (UDMI) in 2018, Type 4a myocardial infarction has been defined by an elevation of cardiac troponin values >5x 99th percentile upper reference limit (URL) in patients with normal baseline values together with ECG, angiographic or imaging evidence of new myocardial ischaemia. Procedure-related myocardial injury has been defined as an elevation of cardiac troponin values >1x 99th percentile URL in patients with normal baseline values together with ECG[6].

In both these definitions, the thresholds for cardiac biomarker elevation have been "arbitrarily chosen" [6, 7]. The difficulty has been selecting the optimal threshold levels of elevated cardiac biomarkers for defining peri-procedural myocardial injury and infarction, which is challenging given the lack of evidence and mixed results from available studies investigating the association between elevated cardiac biomarkers and subsequent long term adverse clinical outcomes following elective PCI[8-30]. Therefore, we performed a comprehensive dose-response meta-analysis of all related prospective

studies to quantitatively assess the association between elevated post-PCI elevations in cardiac biomarkers [cardiac troponin I, cardiac troponin T, creatine kinase MB isoenzyme (CK-MB)] and adverse clinical outcomes [all-cause mortality, major adverse cardiovascular events (MACE)].

2. Methods

2.1 Search Strategy

We reported this meta-analysis following the guidance of MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement[31]. We searched Pubmed (Medline) and Embase from 1979 to August 2018. We also manually searched reference lists of the retrieved articles. The key words used in search were (creatine kinase or troponin) paired with (angioplasty or stent or PCI or MI).

2.2 Study Outcomes and Selection

The primary endpoint was all-cause mortality. The secondary outcome was MACE, The definitions of MACE used by each study included all cause death, cardiac death, revascularization or myocardial infarction, and have been listed for each study in Supplemental Table 1.

Inclusion criteria for the retrieved studies were as follows: (1) prospective design; (2) inclusion of outcomes of all-cause mortality and/or MACE; (3) inclusion of multivariable-adjusted or unadjusted relative risk (RR) or odds ratio (OR) and their corresponding 95% confidence intervals (CI); or provided the number of events and total population in each group; (4) inclusion of different levels of elevated cardiac

biomarkers and their related prognosis. To conduct a dose-response meta-analysis, studies with three or more categories of URL were included; and (5) normal cardiac biomarkers at baseline in CAD patients which was defined by individual studies. If the studies provided data for both elevated vs non-elevated cardiac biomarkers at baseline, only the non-elevated subgroup was selected.

2.3 Data Extraction

Data were extracted by two independent authors (Yuehua Li and Hanjun Pei). Discrepancies were resolved by group discussion. The extracted data included source of study (author, publication year, country), population characteristics (mean age, male proportion, percentage of positive cardiac biomarkers, number of subjects and case, percentage of smoking, diabetes mellitus (DM), hypertension, hyperlipidemia, previous myocardial infarction, stent implantation and multi-vessel disease), follow-up period, the different thresholds for cardiac biomarkers, the clinical endpoints, ORs or RRs and their corresponding 95% CI.

2.4 Statistical Analysis

We considered the RR as ORs in the prospective studies. We pooled the ORs from the elevated vs non-elevated categories of cardiac biomarkers in each study. If the study did not provided OR or RR, we calculated the OR by the number of events and total population in the non-elevated and elevated group. If different reference categories were reported, we chose the non-elevated category as reference. We pooled the OR by combining all the category of elevated biomarkers for comparing elevated and non-

elevated biomarkers category by DerSimonian and Laird random-effects model. The random-effects model was also used in the pooled analysis for the potential clinical heterogeneity[32]. If one study reported multiple categories (>=3 categories)， we would calculate OR using data on the number of cases and noncases in all of the elevated categories and referent groups. The heterogeneity was assessed by Q statistic, I-squared and P value ($P < 0.05$ was considered to be statistically significant). Univariate meta-regression analyses (including follow-up term, gender, area, age, percentage of smoking, DM, hypertension, hyperlipidemia, previous myocardial infarction, stent implantation, multi-vessel disease, side branch occlusion) were conducted to explore the potential sources of heterogeneity[33]. To provide different degrees of elevation of cardiac troponin I and CK-MB in relation to mortality, the degrees of elevated cardiac troponin I were categorized into 3 standardized intervals: "1 to < 3x URL", "≥3 to < 5x URL", "≥ 5x URL" as well as elevated CK-MB into 4 standardized intervals: "1 to < 3x URL", ""≥ 3 to < 5x URL", "" ≥5 to <8x URL", "≥ 8x URL". If the study provided the elevated level of cardiac biomarkers by numerical value, we converted it into the corresponding URL according to the upper reference value in each individual study. We separately pooled the ORs of Q-wave MI. We assigned the ORs from each study into standardized intervals according to the range or median of the degrees of elevated cardiac biomarkers in each category. The average URL of elevated biomarkers in each category was estimated by mean of lower and upper level. If the highest category had an open upper levels, mean URL was estimated to be 1.2 level of the lower levels [34]. The weighted

linear regression model was used to explore the dose-response relationship between elevated cardiac troponin I and CK-MB and the risk of mortality .

All data analyses were performed by STATA software (10.0 version, StataCorporation, TX, USA) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom).

3. Results

3.1 Search Results

24 prospective studies involving 43 582 subjects were included in our meta-analysis (selection process see Figure 1). The data of studies published by Novack et al [16] and Lindsey et al [35] were derived from the same EVENT registry. The former has provided the data on cardiac troponin I and CK-MB and the latter about detailed data on CK-MB[35]. To avoid duplication, we only extracted data related to cardiac troponin I in the study by Novack et al [16] and CK-MB by Lindsey et al [35].

3.2 Study Characteristics

Supplemental Table 1 showed the main characteristics of the data extracted from the included studies. The follow-up time ranged between 3 months to 5.6 years with a median value of 12 months.

3.3 Cardiac troponin I and all-cause mortality

Compared with the group with non-elevated cardiac troponin I levels post-PCI, the group with elevated one was associated with increased risk of all-cause mortality (11 studies, 13 932 subjects, OR 1.42, 95% CI 1.19 to 1.69, P = 0.000, I^2 = 12.1%, P for

heterogeneity 0.33) (Figure 2).In univariable meta-regression, none of the variables was related to risk of death (Supplemental Table 2).

Furthermore, an elevated cardiac troponin I > 3-5x99th percentile URL was associated with an increased risk of all-cause mortality (OR 1.51, 95% CI 1.05 to 2.17, P = 0.025) (Table 1). The dose-response analysis showed that for every 3x99th percentile URL increment in cardiac troponin I elevation, the pooled OR was 1.33 (95% CI 1.15 to 1.53, P = 0.000) for the risk of all-cause mortality in patients undergoing elective PCI.

3.4 CK-MB and all-cause mortality

Compared with the group with non-elevated CK-MB post-PCI, patients with elevated one were associated with increased risk of all-cause mortality (7 studies, 27 486 subjects, OR 1.43, 95% CI 1.19 to1.70, P = 0.000, I^2 = 54.6%, P for heterogeneity 0.04) (Figure 3). In univariable meta-regression, none of the variables was related to risk of death (Supplemental Table 3)

Furthermore, for different categories of elevation in CK-MB, a rise of 1-3x 99^{th} percentile URL or more was associated with all-cause mortality (OR 1.25, 95% CI 1.05 to 1.48 for the category of 1-3x URL, P = 0.014) (Table 1). The dose-response analysis showed that for every 3x99^{th} percentile URL increment in CK-MB elevation, the pooled OR was 1.38 (95% CI 1.30 to 1.47, P = 0.000) for the risk of mortality in patients undergoing elective PCI (Figure 4B).

3.5 Elevated cardiac biomarkers and MACE

Compared with the non-elevated group, patients with elevated cardiac troponin I, cardiac troponin T and CK-MB levels were associated with increased risk of MACE (Supplemental Figure1, 2 ,3)

4. Discussion

In this comprehensive dose-response meta-analysis of prospective studies, we found that elevated levels of cardiac troponin I and CK-MB post-PCI were all associated with risk of all-cause mortality in patients undergoing elective PCI. More importantly, >3x the 99th percentile for cardiac troponin I or >1x 99th percentile URL for CK-MB was associated with increased risk of mortality. Crucially, mortality increased by 33% or 27% for each increment of 3x 99th percentile URL for cardiac troponin I or CK-MB levels post-PCI, respectively.

Previous studies have provided conflicting results with regards to the relationship between elevated cardiac troponin levels post-PCI and long-term prognosis[10, 11, 16, 20, 30]. Previous meta-analyses including both retrospective and prospective studies have found a positive association between cardiac troponin and adverse events[4]. To avoid selection and recall bias, we only pooled all prospective studies and found a positive association between elevated cardiac troponin I and all-cause mortality or MACE, as well as elevated cardiac troponin T and MACE. Moreover, our meta-analysis has provided new insights. Furthermore, our meta-analysis has shown that cardiac troponin I >3x 99th percentile URL post-PCI was associated with increased risk of death whereas an elevation of 1-3x URL was not associated with mortality. Peri-procedural myocardial

injury/infarction, as an important procedural safety endpoint, has been highlighted for its high incidence and predictive value. Current AHA/AHC guidelines for PCI have indicated a class II-b recommendation for routine measurement of cardiac biomarkers[36]. Results from our meta-analysis showed that for each 3x 99th percentile URL increment of cardiac troponin I, the risk of mortality was increased by 33%. Therefore, it would be helpful to risk-stratify patients post-PCI by routine screening for cardiac troponin I within 24 hours. Our meta-analysis has indicated that a post-procedural rise in cardiac troponin T was related to the risk of MACE. Nevertheless, large-scale prospective trials are needed to confirm the relationship between post-procedural elevation in cardiac troponin T and prognosis, especially for the hard endpoints such as all-cause mortality.

Previous studies on the association between elevated CK-MB levels and adverse prognosis have also reported with mixed findings. Consistent with previous meta-analyses, we combined all the prospective trials finding a positive association between any elevation in CK-MB and all-cause mortality or MACE [37, 38]. Given that cardiac troponin is more sensitive and specific than CK-MB in detecting cardiac injury and infarction, the latter has not been included in the latest guidelines to define Type 4a MI[6]. Our meta-analysis has provided evidence that any elevation of CK-MB post-PCI could predict increased risk of death. Moreover, there was a linear dose-response relationship between CK-MB elevation and all-cause mortality. Each increment of 3x 99th percentile URL in CK-MB levels increased mortality by 27%. Results of our meta-analysis have provided evidence that CK-MB may still play a role for risk-stratification in patients

undergoing PCI where cardiac troponin are not available.

Patients undergoing complex PCI (such as chronic total occlusions (CTOs)[39] or multi-vessel PCI[40]) are at increased risk of sustaining peri-procedural myocardial injury/infarction, than simple PCI. As such, whether these patients should be treated with optimal medical therapy instead of revascularization by PCI is not clear. The results from the recently reported ISCHEMIA trial failed to show that routine invasive therapy with PCI was associated with a reduction in major adverse ischemic events, when compared with optimal medical therapy, among stable patients with moderate ischemia[41]. These findings suggests that, at least, in this patient group, optimal medical therapy should be considered first before proceeding to PCI. Whether this approach should also be applied to higher-risk PCI patients with CTO or multi-vessel disease is not clear and needs to be determined.

Limitations

We excluded some studies that did not separately report the data of cardiac troponin I, cardiac troponin T and CK-MB, so the unpooled data might affect the results. Not all of the included trials have provided the multivariable adjusted OR and the residual confounders were unnegligible. Stand-alone or isolated elevations in cardiac biomarkers points to the diagnosis of PCI-related myocardial injury but is insufficient for the diagnosis of type 4a myocardial infarction, which additional evidence of myocardial ischemia and angiographic complications as defined in the 4th UDMI. We could not perform the multiple meta-regression which covered all population

characteristics, because only 3 included trials have provided all of the variables for cardiac troponin I as well as 3 trial for CK-MB. We can not rule out the potential publication bias for our analyses. However, the test of publication bias was not performed for the problematic issue when heterogeneity is substantial. A number of studies have reported elevations in baseline (pre-PCI) in cardiac troponin to be strong predictors of clinical outcomes[42-44]. We undertook a subgroup analysis of the 4 studies which only included patients with baseline cardiac troponin I < 99th percentile URL (Supplemental Figure 4). Interestingly, we found that post-PCI elevations in cardiac troponin I did not predict mortality. Only 1 study used troponin T with actual 99th percentile URL. Although this subgroup analysis was likely to be underpowered due to the limited number of studies and patients, and a larger patient-level meta-analysis would be more meaningful. Finally, our meta-analysis used pooled data rather than individual data, which restricted detailed analysis for the potential confounding factors such as angiographic, procedural (e.g. use of calcium-modifying adjuncts), patient characteristics, and follow-up period. So future studies with prospective design, large sample size and hard endpoints are needed for further investigation for cardiac troponin and CK-MB.

5. Conclusion

Our comprehensive dose-response meta-analysis of 24 prospective studies comprising 44 972 patients has demonstrated that elevated levels of cardiac troponin I or CK-MB predict all-cause mortality following elective PCI. We provide evidence that

an optimal cut-off elevation of cardiac troponin I >3x or CK-MB >1x 99th percentile URL in relation to increased risk of mortality. Each increment of 3x99th percentile URL in cardiac troponin I and CK-MB was associated with an increased mortality by 33% and 27%, respectively. Future research aimed at preventing or reducing the development of PCI-related myocardial injury/infarction warrants further investigation.

Impact on daily practice:

1.The patients with an elevated levels of cardiac troponin I (a cut-off value of >3x cardiac troponin I 99th percentile URL) or CK-MB (a cut-off value of >1x CK-MB >3x 99th percentile URL) may have a mortality risk following elective PCI. In addition, each increment of 3x99th percentile URL in cardiac troponin I and CK-MB was associated with an increased mortality by 33% and 27%, respectively. 2.Using this cut-off value, patients at higher risk of MACE and death can be identified and may benefit from prolonged hospital stay, closer monitoring, more intensified treatment, or more intensive outpatient follow-up to improve outcomes. Therefore, our findings suggest that cardiac biomarkers should be routinely measured post-PCI,

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Figure Legends:

Figure 1. Flow Chart of the Trial Selection Process**.** CK-MB: creatine kinase MB isoenzyme; OR: odds ratio; RR: relative risk;

Figure 2. Elevated versus non-elevated cardiac troponin I levels and risk of all-cause mortality

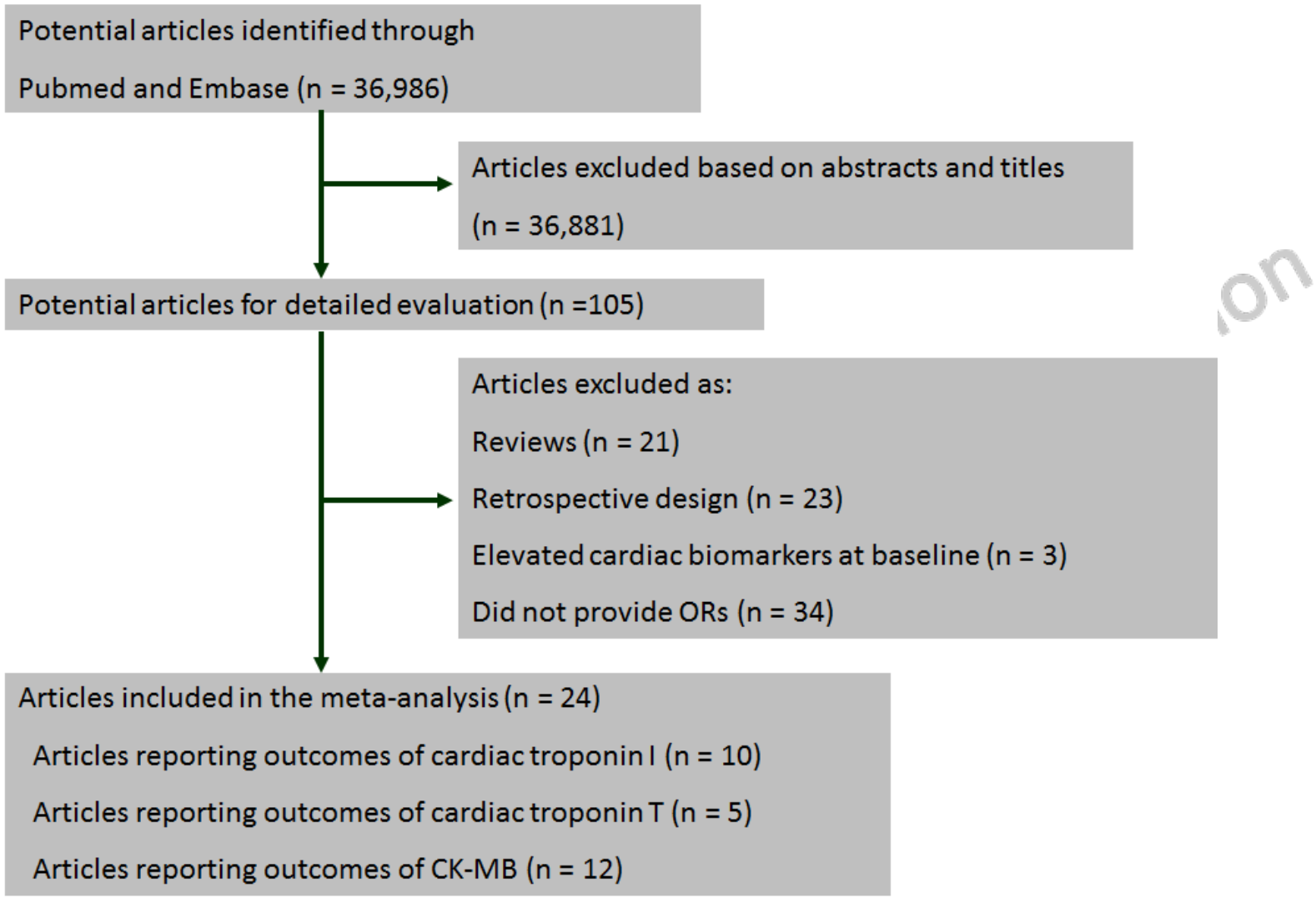
Figure 3. Elevated versus non-elevated CK-MB levels and risk of all-cause mortality

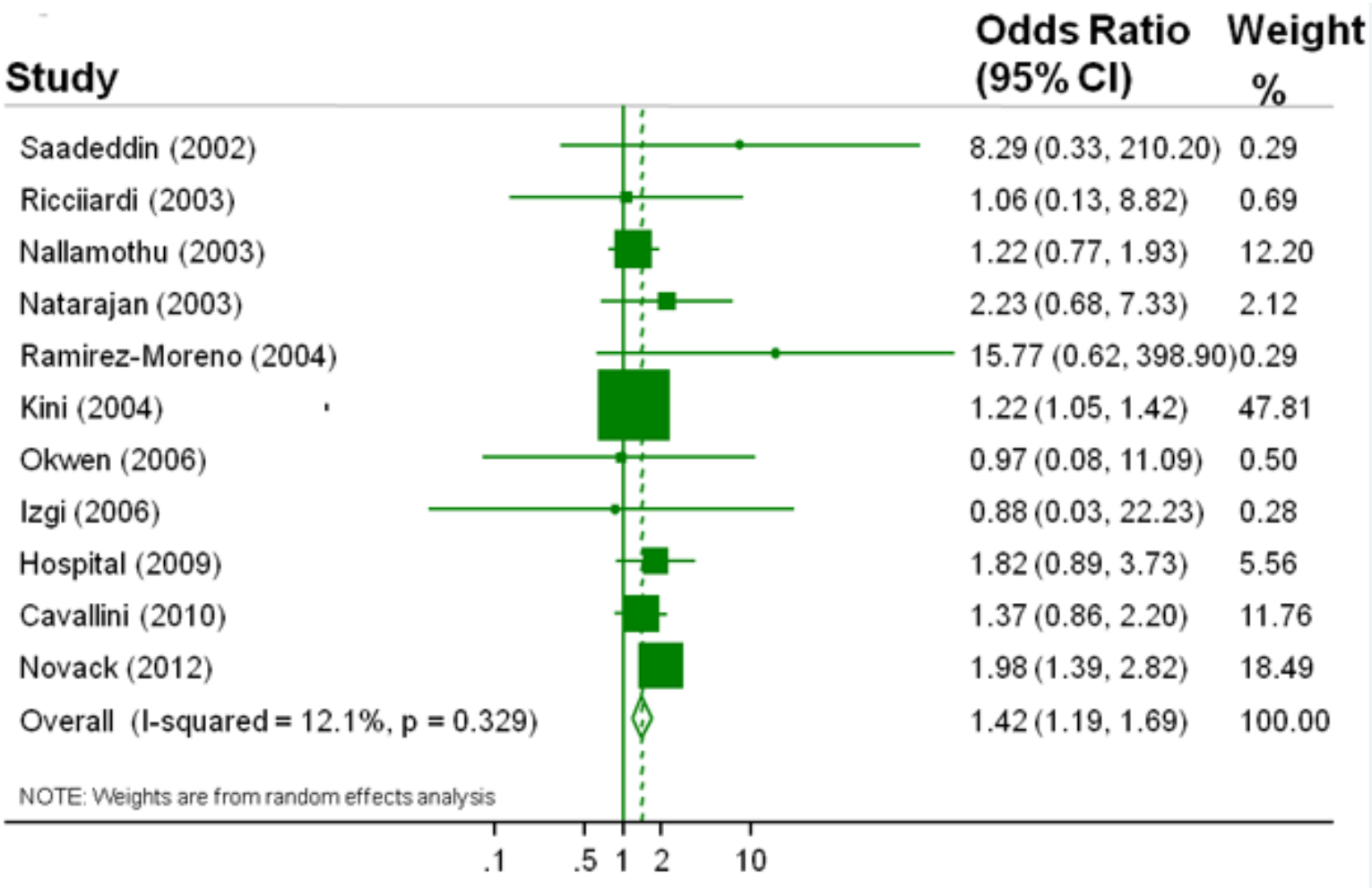
Figure 4. Dose-response relationship for cardiac troponin I (A) or CK-MB (B) and risk of all-cause mortality. Each black small circle indicates logOR for each category of cardiac troponin I levels which is proportional to its statistical weight; solid line represents weighted logOR, and its two accompanying dashed lines represent its lower and upper CIs. Horizonal solid line indicates the null hypoothesis (logOR = 0). CI: confidence interval; OR: odds ratio; CK-MB: creatine kinase MB isoenzyme;

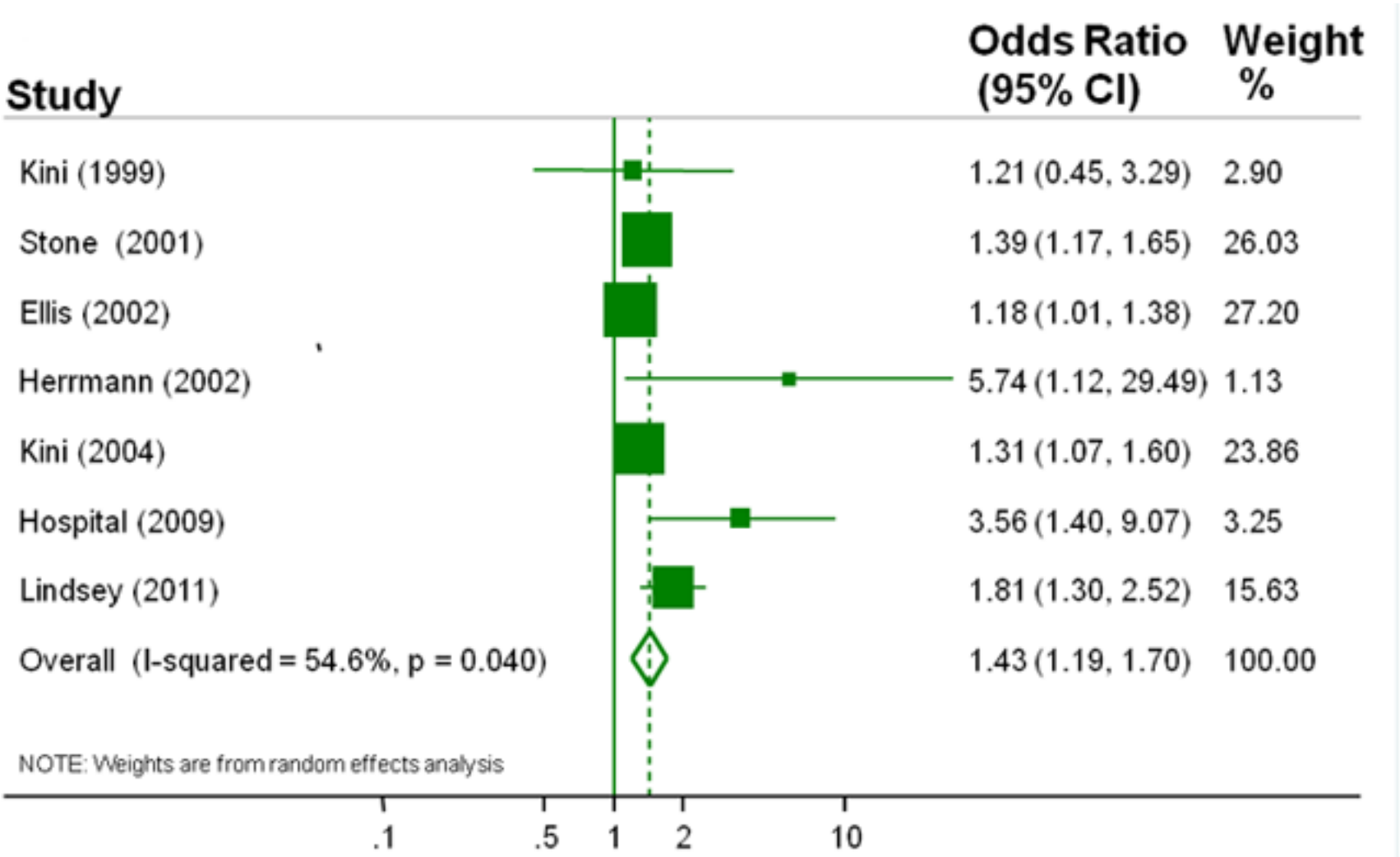
Table 1 Long-term mortality by categories of cardiac troponin I and CK-MB

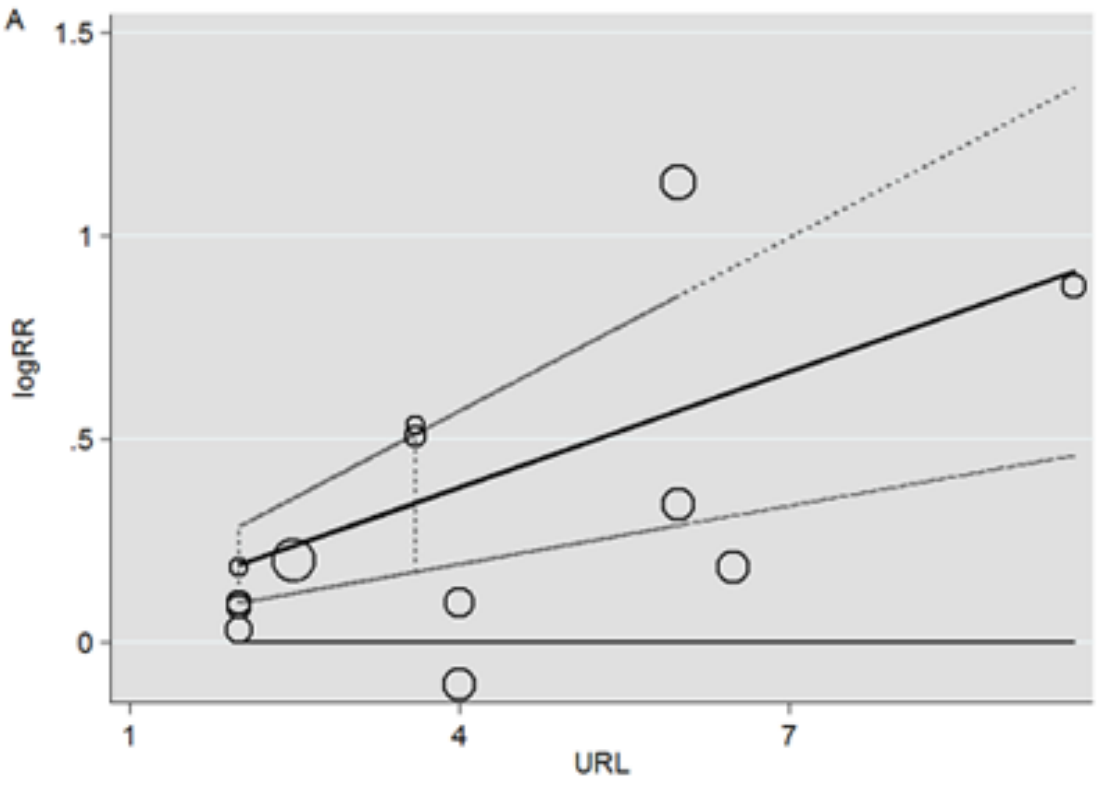
Cardiac troponi I ratio category URL	No. of studies	OR of mortality 95% CI	CK-MB ratio category URL	No. of studies	OR of mortality 95% CI
1 to < 3x	5	1.13 (0.84 to 1.53)	1 to < 3x	5	1.25 (1.05 to 1.48)
≥3 to < 5x	3	1.51 (1.05 to 2.17)	≥3 to < 5x	5	1.29 (0.99 to 1.68)
≥ 5x	3	2.23 (1.28 to 3.88)	≥5 to < 8x	6	3.48 (1.29 to 9.38)
Q-wave MI	2	9.83 (6.04 to 16.01)	≥ 8x	3	2.93 (1.76 to 4.90)

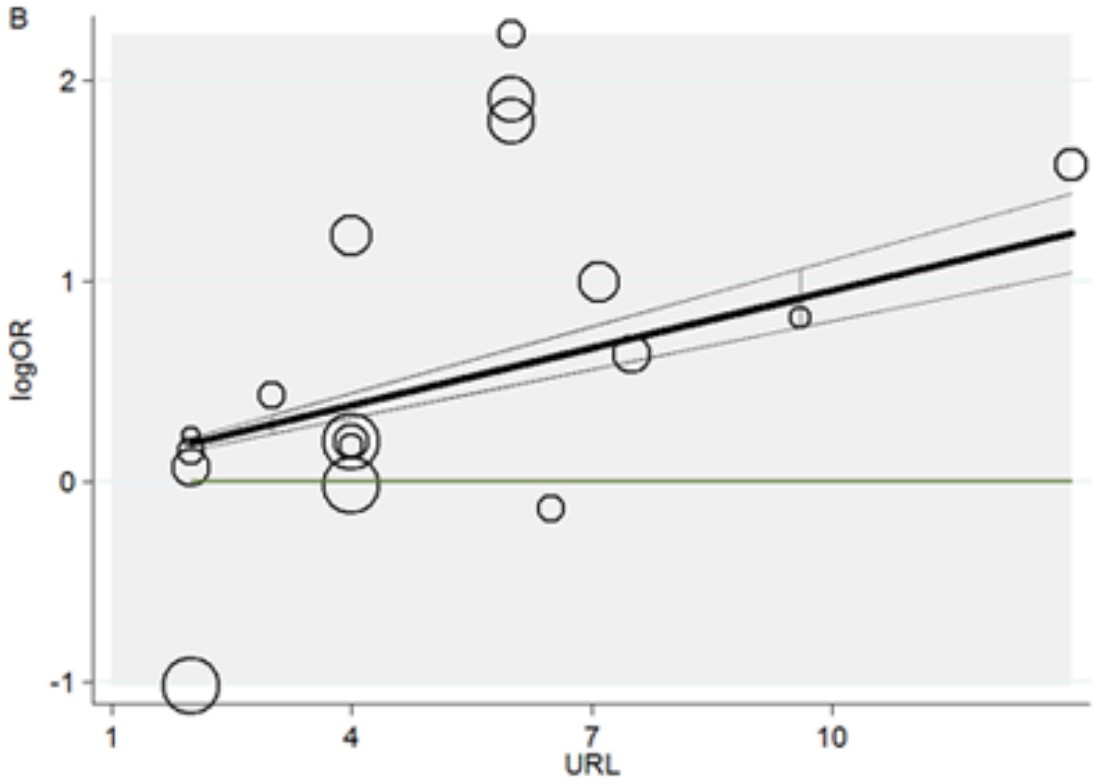
CI: confidence interval; CK-MB: creatine kinase-MB isoenzyme; OR:odds ratio; URL: upper reference limit;











Supplemental Table 1 Characteristics of included studies (cardiac troponin I)

Study	Year	Country	N Number	cTnI+ %	Mean age	Male %	DM %	Hyperlipidemia %	Hypertension %	Smoker %	Previous MI %	LVEF (%)	Ste %
Bertinchant et al	1999	France	105	22.0	61.0	75.2	22.9	57.1	45.7	48.6	38.1	64.2	N
Cantor et al	2002	Canada	481	48.0	57.5	75.5	17.7	54.6	52	37.6	20.7		82
Saadeddin et al	2002	Saudi Arabia	96	27.0	55.0	76	57.3	84.4	52.1	39.6	NA		71
Ricciiardi et al	2003	USA	286	13.6	62.2	69	25	67	63	51.0	32		7
Nallamothu et al	2003	USA	1157	29.0	63.6	65.2	26	NA	67.3	20.6	31.1		77
Natarajan et al	2003	Canada	1128	16.8	60.7	67	20	76	54	42.0	51		8
Ramirez-Moreno et al	2004	Spain	143	16.3	62.5	54.4	29.9	30.6	54.4	45.6	NA	63.3	46
Kini et al	2004	USA	2873	39.0	66.6	69.9	41	84	90	15.0	30.1	53.1	86
Okwen et al	2006	Turkey	100	34.0	55.7	83	11	30	37	51.0	34	53.7	5

Izgi et al	2006	Turkey	100	27.0	54.4	11	15	62	38	65.0	10.4	52.7	10
Gomez-Hospital et al	2009	Spain	757	22.9	63.0	74.9	32.1	68.4	55.6	59.6	29.2	60.0	91
Cavallini et al	2010	Italy	2362	39.4	62.5	79.7	18.2	61	NA	NA	49.8	57.7	76
Novack et al	2012	USA	4930	24.3	64.3	68.6	36.1	NA	NA	NA	NA		N

Supplemental Table 1 characteristics of included studies (cardiac troponin I) (continued)

Study	Year	Atrial fibrillation(%)	Chronic kidney disease(%)	Family history of CAD(%)	Peripheral artery disease(%)	Beta blocker (%)	Calcium channel blockers(%)	Aspirin (%)	Glycoprotein IIb/IIIa inhibitor(%)	Statins (%)	Angio suc (
Bertinchant et al	1999	NA	NA	21.9	NA	45.7	35.2	86.7	0.0	NA	N
Cantor et al[11]	2002	NA	0.2	60.5	NA	NA	NA	NA	21.4	NA	8
Saadeddin et al	2002	NA	NA	NA	NA	66.7	49.0	NA	NA	74.0	N
Ricciiardi et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Nallamothu et al	2003	NA	7.1	NA	NA	NA	NA	NA	75.0	NA	N
Natarajan et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	10
Ramirez-Moreno et al	2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	N
Kini et al	2004	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4	9
Okwen et al	2006	NA	NA	22.0	NA	NA	NA	NA	40.0	NA	N
Izgi et al	2006	NA	NA	42.0	NA	76.0	NA	NA	NA	74.0	N
Gomez-Hospital et al	2009	NA	4.8	NA	10.6	NA	NA	NA	4.8	NA	9
Cavallini et al	2010	4.7	3.9	NA	9.9	NA	NA	NA	NA	76.7	N
Novack et al[18]	2012	NA	24.4	NA	NA	NA	NA	NA	NA	NA	N

Supplemental Table 1 Characteristics of included studies (cardiac troponin T)

Study	Year	Country	N Number	cTnT +%	Mean age	Male %	DM %	Hyperlipidemia %	Hypertension %	Smoker %	Previous MI %	LVE (%)
Herrmann et al	2002	Germany	278	17.3	61.5	79.5	19.4	82	59.7	28.1	41.0	
Kizer et al	2003	USA	128	18.4	60	72	30	73	77	30	38.0	57.0
Miller et al	2006	USA	1619	57.3	66.6	71	25	86	74	NA	36.0	54.1
Nienhuis et al	2007	Netherlands	713	21	64	79	18	55.8	43.6	32.3	44.7	
Zeitouni	2018	France	1390	28.7	66.9	79.2	35.7	63.6	62.3	24.1	NA	55.7

Supplemental Table 1 characteristics of included studies (cardiac troponin T) (continued)

Study	Year	BMI	Atrial fibrillation(%)	Chronic kidney disease(%)	Family history of CAD(%)	Peripheral artery disease(%)	Beta blocker (%)	Calcium channel blockers(%)	Aspirin (%)	Glycoprotein IIb/IIIa inhibitor(%)	Statins (%)
Herrmann et al	2002	NA	NA	NA	17.6	NA	NA	NA	NA	NA	NA
Kizer et al	2003	NA	NA	NA	NA	NA	56.0	43.0	98.0	NA	NA
Miller et al	2006	NA	NA	NA	NA	NA	NA	NA	NA	64.9	NA
Nienhuis et al	2007	NA	NA	NA	35.0	NA	NA	NA	NA	NA	NA
Zeitouni	2018	26. 7	NA	48.6	NA	NA	NA	NA	44.3	NA	NA

Supplemental Table 1 Characteristics of included studies (CK-MB) (continued)

Study	Year	Country	N Number	CK-MB +%	Mean Age	Male %	DM %	Hyperlipidemia %	Hypertension %	Smoker %	Previous MI %	LVEF (%)	St
Herrmann et al	2002	Germany	278	14.7	61.5	79.5	19.4	82	59.7	28.1	41		3
Ricciiard et al	2003	USA	286	12.9	62.2	69	25	67	63	51	32		7
Nallamothu et al	2003	USA	1157	NA	63.6	65.2	26	NA	67.3	20.6	31.1		7
Ramirez-Moreno et al	2004	Spain	143	15.6	62.5	54.4	29.9	30.6	54.4	45.6	NA	63.3	4
Kini et al	2004	USA	2873	16.1	66.6	69.9	41	84	90	15	30.1	53.1	8
Nienhuis et al	2007	Netherlands	713	9.3	64	79	18	55.8	43.6	32.3	44.7		7
Lindsey et al	2011	USA	6347	25.6	64.5	68.8	36.3	76.9	79.9	23.2	32.9		N
Zhang et al	2014	China	1008	10.5	63	73.2	25.2	7	68	42.8	7.7	63.9	4
Kini et al	1999	USA	1675	18.7	65	68.4	24.9	47.3	70.1	17.3	34.7	49.6	6
Stone et al	2001	USA	7147	37.3	63.9	70.4	28.3	64	58.8	20.6	48.4		5
Ellis et al	2002	USA	8409	17.2	65	72	29.7	49.7	69.2	NA	0	52.6	6
Gomez-Hospital et al	2009	Spain	757	6.1	63	74.9	32.1	68.4	55.6	59.6	24.8	60.0	9

Supplemental Table 1 characteristics of included studies (CK-MB) (conti

Study	Year	Atrial fibrillation(%)	Chronic kidney disease(%)	Family history of CAD(%)	Peripheral artery disease(%)	Beta blocker (%)	Calcium channel blockers(%)	Aspirin (%)	Glycoprotein IIb/IIIa inhibitor(%)	Statins (%)
Herrmann et al	2002	NA	NA	17.6	NA	NA	NA	NA	NA	NA
Ricciiard et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nallamothu et al	2003	NA	7.1	NA	NA	NA	NA	NA	75.0	NA
Ramirez-Moreno et al	2004	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kini et al	2004	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4
Nienhuis et al	2007	NA	NA	35.0	NA	NA	NA	NA	NA	NA
Lindsey et al	2011	NA	21.9	NA NA	11.6	NA	NA	NA	NA	NA
Zhang et al	2014	NA	NA	NA	NA	74.9	NA	99.7	1.1	98.1
Kini et al	1999	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4
Stone et al	2001	NA	4.6	NA	NA	NA	NA	NA	NA	NA
Ellis et al	2002	NA	4.5	NA	NA	NA	NA	NA	53.4	NA
Gomez-Hospital et al	2009	NA	4.8	NA	10.6	NA	NA	NA	4.8	NA

Note: CAD: coronary artery disease; CK-MB: creatine kinase MB isoenzyme ;DM diabetes mellitus; F:female; M:male; MACE： major adverse cardiovascular events ;raft; TVR, target vessel revascularization; NA: not available

Supplemental Table 2 Univariate meta-regression of baseline characteristics for cardiac troponin I and risk of all-cause mortality

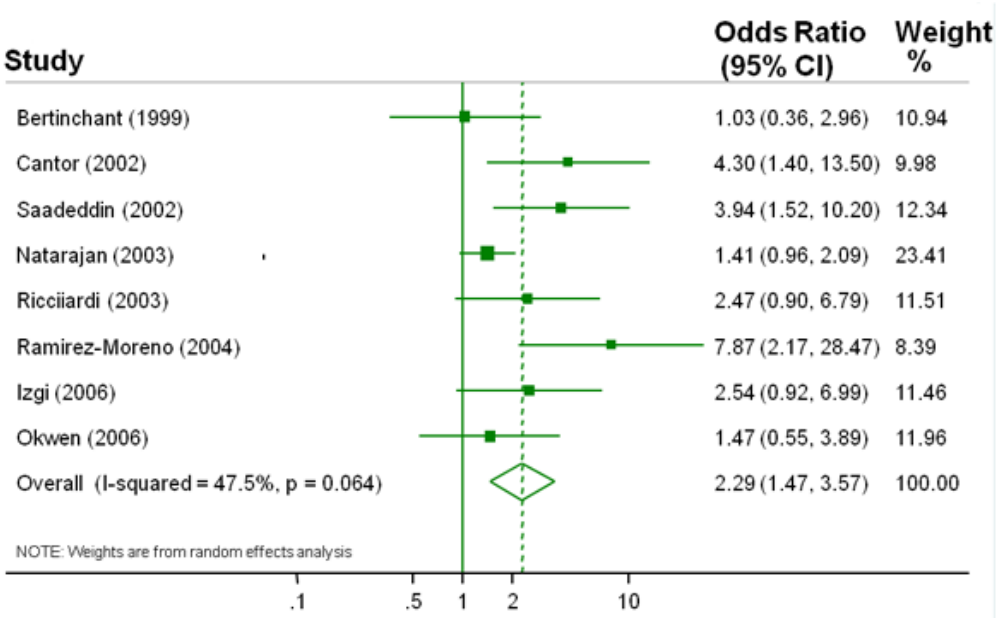
Baseline characteristics	Number of trials	Risk of all-cause mortality (cardiac troponin I)			
		Coefficient	95% CI	I^2 (%)	P
Age	11	-0.043	(-0.16 to 0.076)	0.00	0.43
Male proportion	11	-0.001	(-0.043 to 0.041)	20.86	0.97
DM proportion	11	0.003	(-0.029 to 0.035)	17.34	0.83
Follow-up term	11	0.063	(-0.021 to 0.034)	13.51	0.62
Hyperlipidemia proportion	9	-0.009	(-0.031 to 0.012)	0	0.32
Hypertension proportion	9	-0.008	(-0.024 to 0.008)	0	0.27
Smoking proportion	9	0.01	(-0.007 to 0.027)	0	0.21
Previous MI proportion	8	0.008	(-0.02 to 0.037)	0	0.50
Stent proportion	10	-0.01	(-0.045 to 0.025)	0	0.53
Multi-vessel diseases proportion	8	0.004	(-0.011 to0.019)	0	0.56
Side-branch occlusion	7	-0.016	(-0.129 to 0.0977)	14.19	0.73

DM, diabetes mellitus; MI, myocardial infarction;

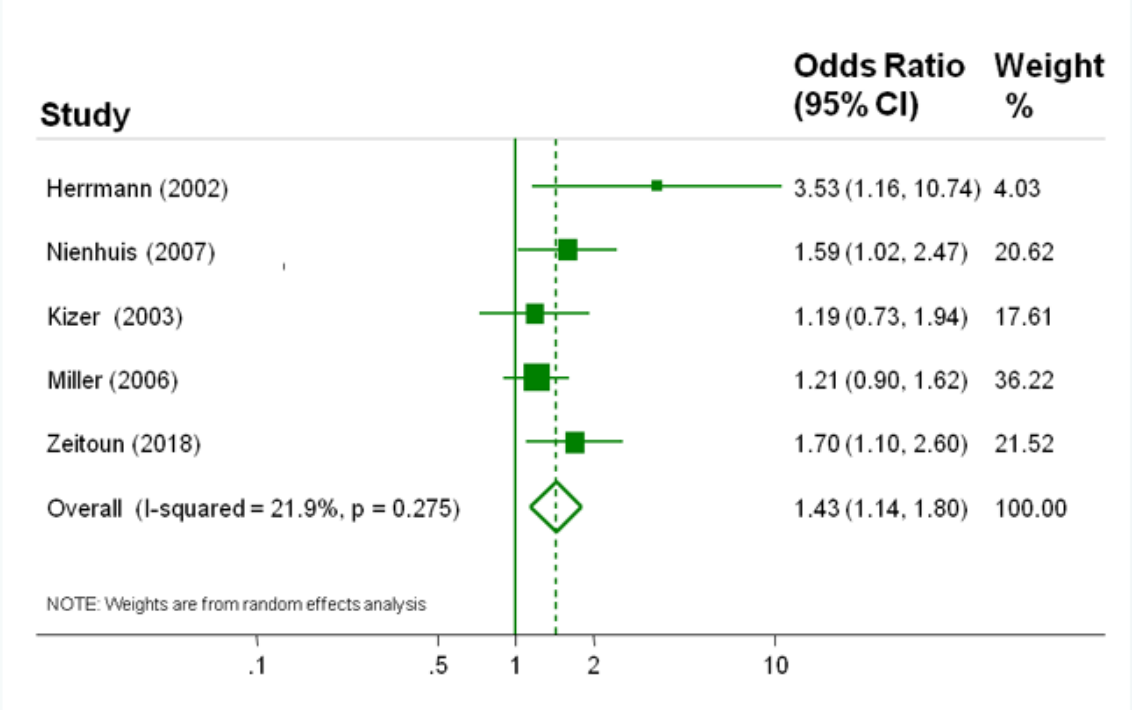
Supplemental Table 3 Univariate meta-regression of baseline characteristics for CK-MB and risk of all-cause mortality

Baseline characteristics	Number of trials	Risk of all-cause mortality (CK-MB)			
		Coefficient	95% CI	I^2 (%)	P
Age	7	-0.17	(-0.42 to 0.09)	55.38	0.16
Male proportion	7	0.094	(-0.07 to 0.258)	61.89	0.20
DM proportion	7	0.005	(-0.069 to 0.059)	61.94	0.85
Follow-up term	7	0.018	(-0.006 to 0.042)	33.35	0.12
Hyperlipidemia proportion	7	0.007	(-0.014 to 0.029)	53.25	0.42
Hypertension proportion	7	-0.007	(-0.038 to 0.023)	62.02	0.58
Smoking proportion	6	0.025	(-0.003 to 0.053)	0	0.07
Previous MI proportion	6	-0.008	(-0.071 to 0.055)	56.62	0.74
Stent proportion	7	0.004	(-0.013 to 0.02)	59.96	0.57
Multi-vessel diseases proportion	4	0.015	(-0.048 to 0.078)	63.20	0.42
Side-branch Oclussion	4	-0.822	(-5.16 to 3.52)	68.18	0.50

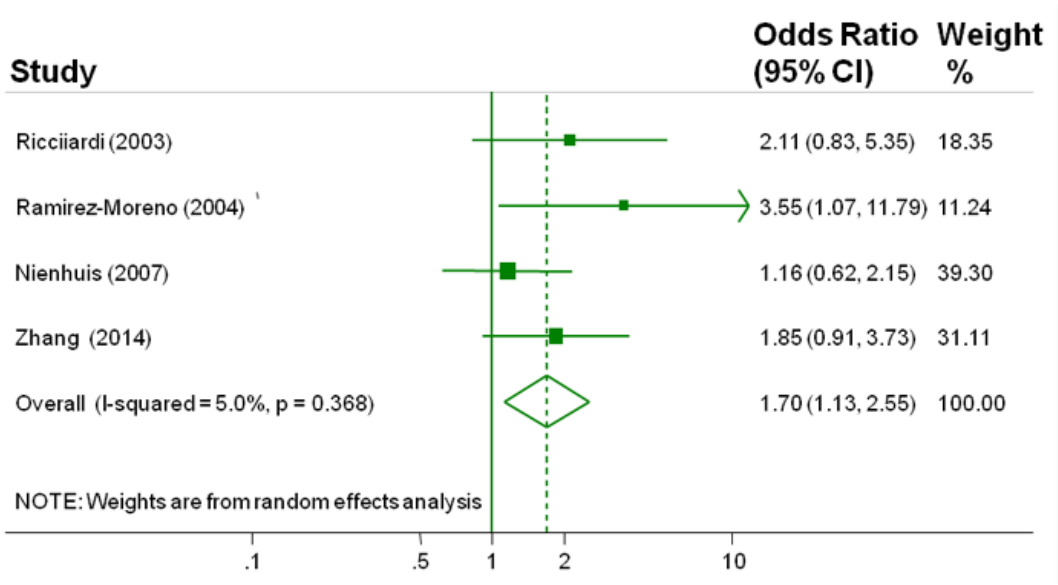
CK-MB: creatine kinase MB isoenzyme; DM, diabetes mellitus; MI, myocardial infarction;



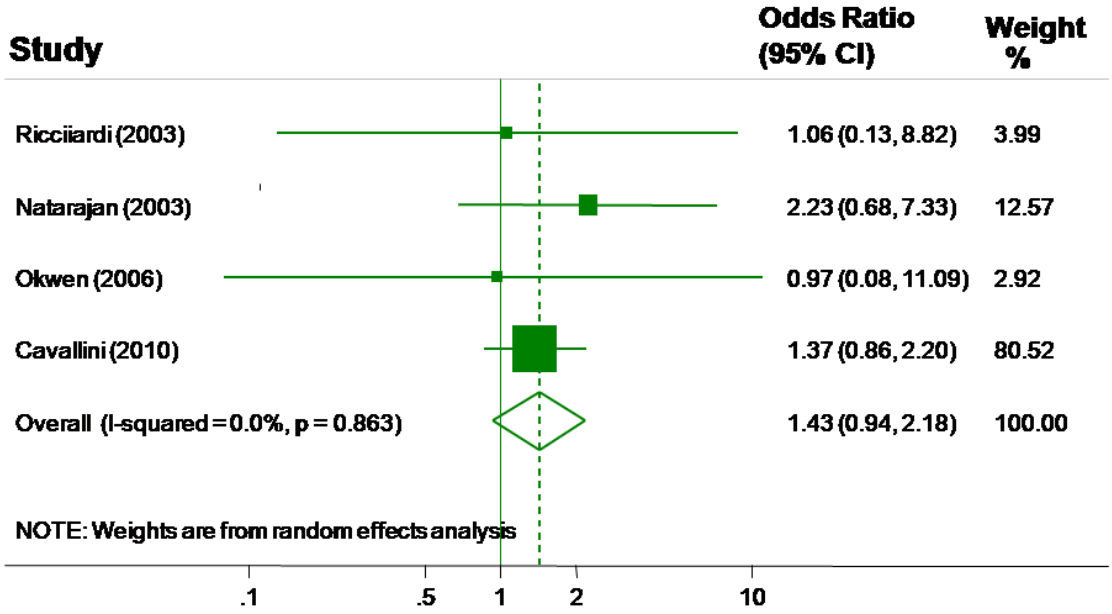
Supplemental Figure 1. Elevated versus non-elevated cardiac troponin I levels and risk of MACE



Supplemental Figure 2. Elevated versus non-elevated cardiac troponin T levels and risk of MACE



Supplementary Figure 3. Elevated versus non-elevated CK-MB levels and risk of MACEs.



Supplemental Figure 4. Subgroup analysis of the 4 studies who reported the actual 99% URL of cardiac troponin I.