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Periprocedural elevated myocardial biomarkers and clinical outcomes following elective percutaneous coronary intervention: a comprehensive dose-response meta-analysis of 44,972 patients from 24 prospective studies

Yuehua Li[1], MD, PhD; Hanjun Pei[2], MD, PhD; Heerajnarain Bulluck[3], MD, PhD; Chenghui Zhou[4]*, MD, PhD; Derek J. Hausenloy[5,6,7,8], MD, PhD

1. Department of Cardiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; 2. Department of Cardiology, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia, China; 3. Norfolk and Norwich University Hospital, Norwich, United Kingdom; 4. Department of Anesthesiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; 5. Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore, National Heart Research Institute Singapore, National Heart Centre, Singapore, and Yong Loo Lin School of Medicine, National University Singapore, Singapore; 6. The Hatter Cardiovascular Institute, University College London, London, United Kingdom; 7. Cardiovascular Research Center, College of Medical and Health Science, Asia University, Taichung, Taiwan; 8. Tecnologico de Monterrey, Centro de Biotecnologia-FEMSA, Nuevo Leon, Mexico

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KEYWORDS

- death
- myocardial infarction
- stable angina

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 the risk of all-cause mortality following elective PCI.

Methods and results: Twenty-four prospective studies (44,972 patients) were included. Patients with an isolated elevation of cardiac biomarkers had an 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 >1x the 99th 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 was 1.33 (95% CI: 1.15-1.53) and 1.38 (95% CI: 1.30-1.47).

Conclusions: We found that 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 an increased risk of mortality.

**Corresponding author: No. 167 Beilishi Road, Xicheng District, Beijing 100037, China.*
E-mail: chenghuizhou@yahoo.com

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Abbreviations

CAD coronary artery disease
CI confidence interval(s)
CK-MB creatine kinase MB isoenzyme
DM diabetes mellitus
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 limit

Introduction

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

In both these definitions, the thresholds for cardiac biomarker elevation have been "arbitrarily chosen"[6,7]. The difficulty has been in selecting the optimal threshold levels of elevated cardiac biomarkers for defining periprocedural myocardial injury and infarction. This 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[8-31]. Therefore, we performed a comprehensive dose-response meta-analysis of all related prospective studies to assess quantitatively 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]).

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Methods

SEARCH STRATEGY

We report this meta-analysis according to the guidance of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement[32]. We searched PubMed (Medline) and Embase from 1979 to August 2018. We also manually searched the reference lists of the retrieved articles. The keywords used in the search were (creatine kinase or troponin) paired with (angioplasty or stent or PCI or MI).

STUDY OUTCOMES AND SELECTION

The primary endpoint was all-cause mortality. The secondary outcome was MACE. The definition of MACE used by each study included all-cause death, cardiac death, revascularisation or myocardial infarction. These have been listed for each study in **Supplementary 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 which 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 elevated versus non-elevated cardiac biomarkers at baseline, only the non-elevated subgroup was selected.

DATA EXTRACTION

Data were extracted by two independent authors (Y. Li and H. 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 cases, percentage of smoking, diabetes mellitus [DM], hypertension, hyperlipidaemia, previous myocardial infarction, stent implantation and multivessel disease), follow-up period, the different thresholds for cardiac biomarkers, the clinical endpoints, ORs or RRs and their corresponding 95% CI.

STATISTICAL ANALYSIS

We considered the RRs as ORs in the prospective studies. We pooled the ORs from the elevated versus non-elevated categories of cardiac biomarker in each study. If the study did not provide ORs or RRs, we calculated the OR by the number of events and total population in the non-elevated and elevated groups. If different reference categories were reported, we chose the non-elevated category as reference. We pooled the ORs by combining all the categories of elevated biomarker for comparing elevated and non-elevated biomarker categories using the DerSimonian and Laird random-effects model. The random-effects model was also used in the pooled analysis for the potential clinical heterogeneity[33]. If one study reported multiple categories (≥3 categories), we would calculate the OR using data on the number of cases and non-cases in all of the elevated categories and referent groups. The heterogeneity was assessed by Q statistic, I-squared value 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, hyperlipidaemia, previous myocardial infarction, stent implantation, multivessel disease, side branch occlusion) were conducted to explore the potential sources of heterogeneity[34]. 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 categorised into three standardised intervals ("1 to <3x URL", "≥3 to <5x URL", "≥5x URL") as well as elevated CK-MB into four standardised 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 this 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 standardised 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 the mean of the lower and upper levels. If the highest category had an open upper level, the mean URL was estimated to be 1.2x the level of the lower levels[35]. 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 using Stata software, version 10.0 (StataCorp., College Station, TX, USA) and RevMan software, version 5.0 (Cochrane Collaboration, Oxford, United Kingdom).

Results

SEARCH RESULTS

Twenty-four prospective studies involving 43,582 subjects were included in our meta-analysis; the selection process is shown in **Figure 1**. The data of studies published by Novack et al[16] and Lindsey et al[36] were derived from the same EVENT registry. The former provided the data on cardiac troponin I and CK-MB and the latter detailed data on CK-MB[36]. To avoid duplication, we only extracted data related to cardiac troponin I in the study by Novack et al[16] and CK-MB in the study by Lindsey et al[36].

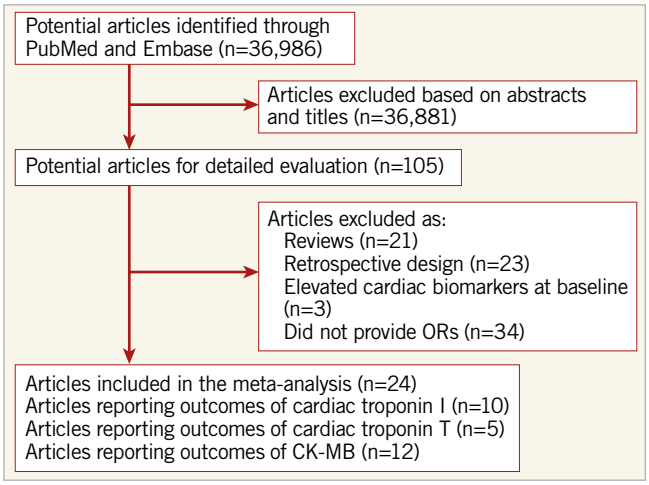

Figure 1. *Flow chart of the trial selection process. CK-MB: creatine kinase myocardial band isoenzyme; OR: odds ratio*

STUDY CHARACTERISTICS

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

CARDIAC TROPONIN I AND ALL-CAUSE MORTALITY

Compared with the group with non-elevated cardiac troponin I levels post PCI, the group with elevated ones was associated with an 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 **(Supplementary Table 2)**.

Furthermore, an elevated cardiac troponin I >3-5x the 99th 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 3x the 99th 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.

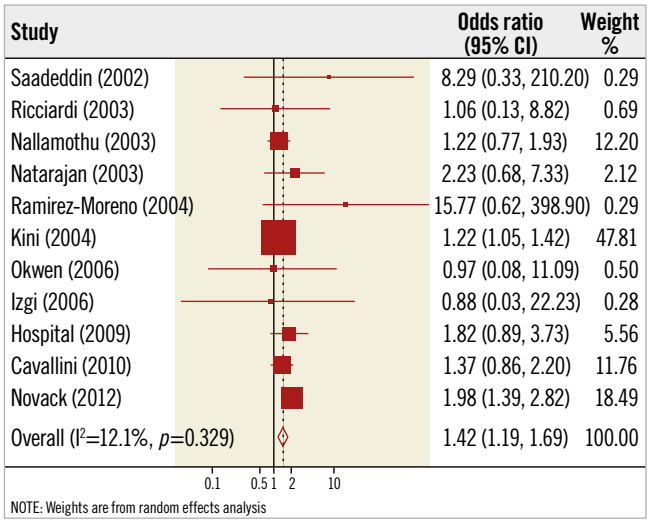

Figure 2. *Elevated versus non-elevated cardiac troponin I levels and risk of all-cause mortality.*

CK-MB AND ALL-CAUSE MORTALITY

Compared with the group with non-elevated CK-MB post PCI, patients with an elevated one were associated with an increased risk of all-cause mortality (7 studies, 27,486 subjects, OR 1.43, 95% CI: 1.19 to 1.70, 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 **(Supplementary Table 3)**.

Furthermore, for different categories of elevation in CK-MB, a rise of 1-3x the 99th percentile URL or more was associated with

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

Cardiac troponin 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 myocardial band isoenzyme; OR: odds ratio; URL: upper reference limit

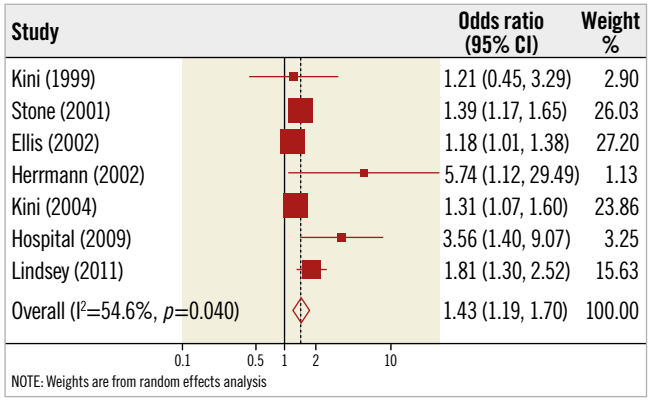

Figure 3. *Elevated versus non-elevated CK-MB levels and risk of all-cause mortality.*

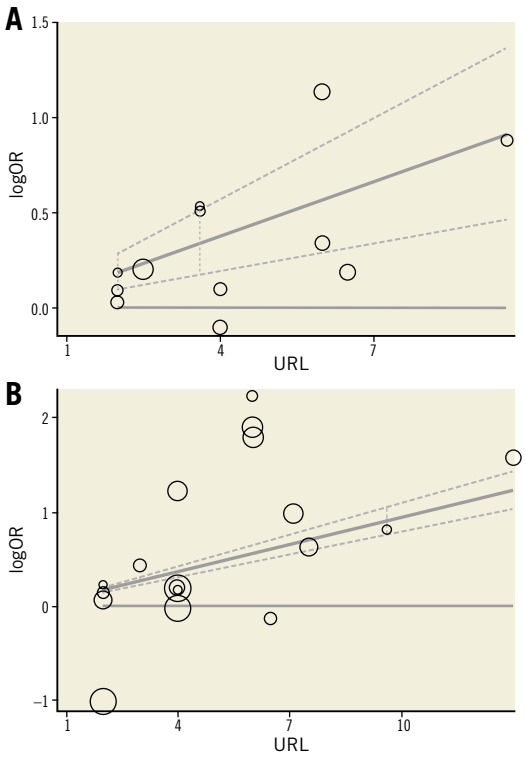

Figure 4. *Dose-response relationship for cardiac troponin I (A) or CK-MB (B) and risk of all-cause mortality. Each small black circle indicates logOR for each category of cardiac troponin I level which is proportional to its statistical weight; solid line represents weighted logOR, and its two accompanying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

all-cause mortality (OR 1.25, 95% CI: 1.05 to 1.48 for the category of 1-3x the URL, p=0.014) **(Table 1)**. The dose-response analysis showed that, for every 3x the 99th 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 4)**.

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 an increased risk of MACE **(Supplementary Figure 1-Supplementary Figure 3)**.

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 a risk of all-cause mortality in patients undergoing elective PCI. More importantly, >3x the 99th percentile for cardiac troponin I or >1x the 99th percentile URL for CK-MB was associated with an increased risk of mortality. Crucially, mortality increased by 33% or 27% for each increment of 3x the 99th percentile URL for cardiac troponin I or CK-MB levels post PCI, respectively.

Previous studies have provided conflicting results with regard 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 the 99th percentile URL post PCI was associated with an increased risk of death whereas an elevation of 1-3x the URL was not associated with mortality. Periprocedural myocardial injury/infarction, as an important procedural safety endpoint, has been highlighted for its high incidence

and predictive value. Current ACCF/AHA/SCAI guidelines for PCI have indicated a class II-b recommendation for routine measurement of cardiac biomarkers[37]. Results from our meta-analysis showed that, for each 3x the 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 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[38,39]. 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 universal definition criteria for MI to define type 4a[6]. Our meta-analysis has provided evidence that any elevation of CK-MB post PCI could predict an increased risk of death. Moreover, there was a linear dose-response relationship between CK-MB elevation and all-cause mortality. Each increment of 3x the 99th percentile URL in CK-MB levels increased mortality by 27%. The results of our meta-analysis have provided evidence that CK-MB may still play a role in risk stratification in patients undergoing PCI where cardiac troponin levels are not available.

Patients undergoing complex PCI (such as chronic total occlusions [CTOs][40] or multivessel PCI[41]) are at increased risk of sustaining periprocedural myocardial injury/infarction, compared to simple PCI. As such, whether these patients should be treated with optimal medical therapy instead of revascularisation 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 ischaemic events, when compared with optimal medical therapy, among stable patients with moderate ischaemia (Hochman JS, Spertus JA. International Study of Comparative Health Effectiveness With Medical and Invasive Approaches – ISCHEMIA. Presented at AHA 2019, Philadelphia, PA, USA, 16 November 2019). These findings suggest 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 multivessel 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; therefore, the unpooled data might have affected the results. Not all of the included trials provided the multivariable adjusted OR, and the residual confounders were not negligible. Stand-alone or isolated elevations in cardiac biomarkers point to a diagnosis of PCI-related myocardial injury but are insufficient for a diagnosis of type 4a myocardial infarction, for which additional evidence of myocardial ischaemia and angiographic complications as defined in the fourth UDMI is required. We could not perform a multiple meta-regression covering all population characteristics, because only three included trials provided all of the variables for cardiac troponin I along with three trials for CK-MB. We cannot rule out a potential publication bias for our analyses. However, a test of publication bias was not performed for the problematic issue of when heterogeneity is substantial. A number of studies have reported elevations in baseline (pre-PCI) cardiac troponin to be strong predictors of clinical outcomes[42-44]. We undertook a subgroup analysis of the four studies which only included patients with baseline cardiac troponin I <99th percentile URL **(Supplementary Figure 4)**. Interestingly, we found that post-PCI elevations in cardiac troponin I did not predict mortality. Only one study used troponin T with an actual 99th percentile URL. 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 potential confounding factors such as angiographic, procedural (e.g., use of calcium-modifying adjuncts), patient characteristics, and follow-up period. Therefore, future studies with a prospective design, large sample size and hard endpoints are needed for further investigation into cardiac troponin and CK-MB.

Conclusions

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 the 99th percentile URL relates to an increased risk of mortality. Each increment of 3x the 99th percentile URL in cardiac troponin I and CK-MB was associated with an increased mortality of 33% and 27%, respectively. Future research aimed at preventing or reducing the development of PCI-related myocardial injury/infarction is warranted.

Impact on daily practice

Patients with elevated levels of cardiac troponin I (a cut-off value of cardiac troponin I >3x the 99th percentile URL) or CK-MB (a cut-off value of CK-MB >1x the 99th percentile URL) may have a mortality risk following elective PCI. In addition, each increment of 3x the 99th percentile URL in cardiac troponin I and CK-MB was associated with an increased mortality of 33% and 27%, respectively. 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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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

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

Supplementary 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 MACE.

Supplementary Figure 4. Subgroup analysis of the four studies which reported the actual 99% URL of cardiac troponin I.

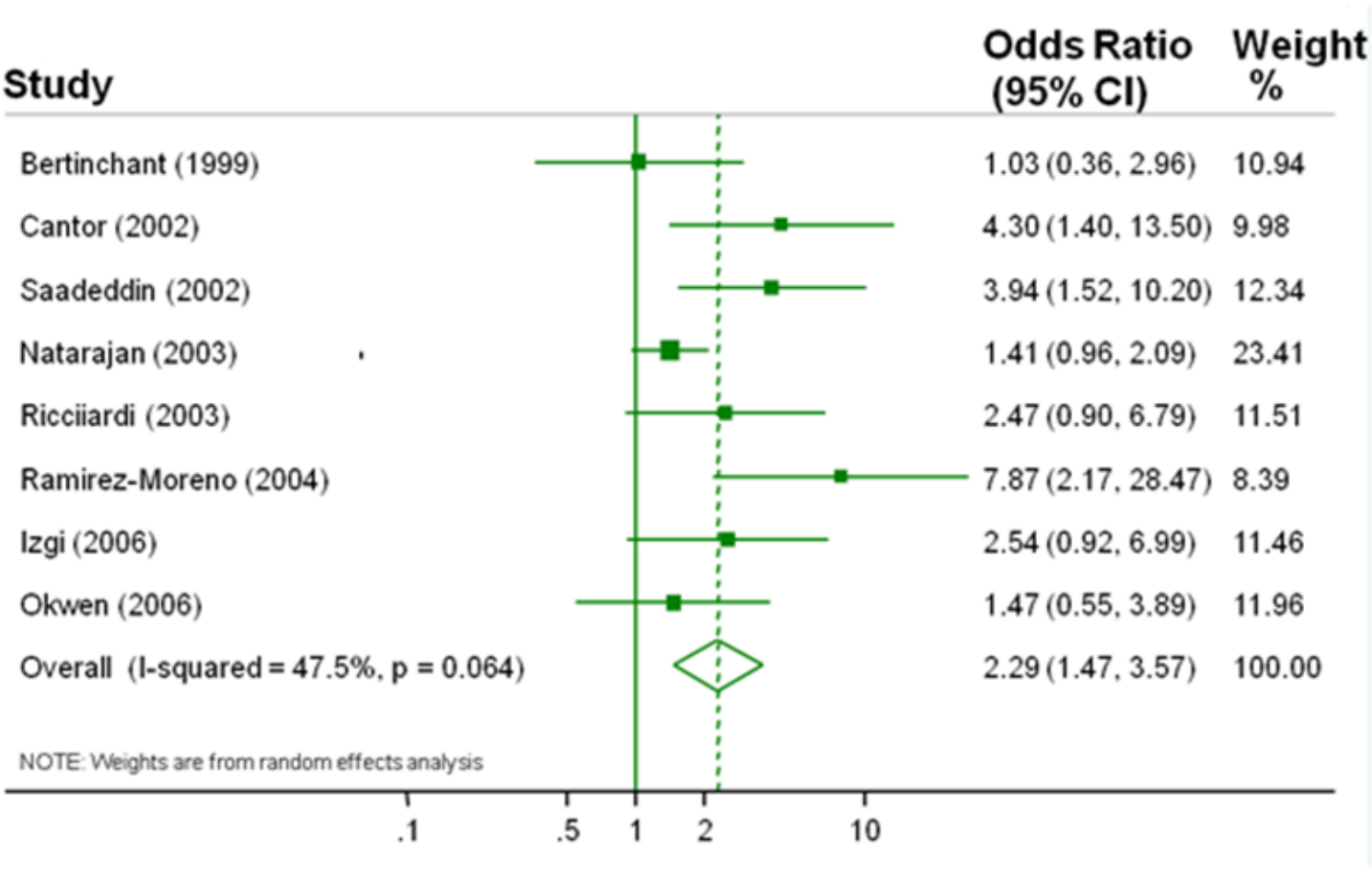
Supplementary Table 1. Characteristics of included studies (cardiac troponin I).

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

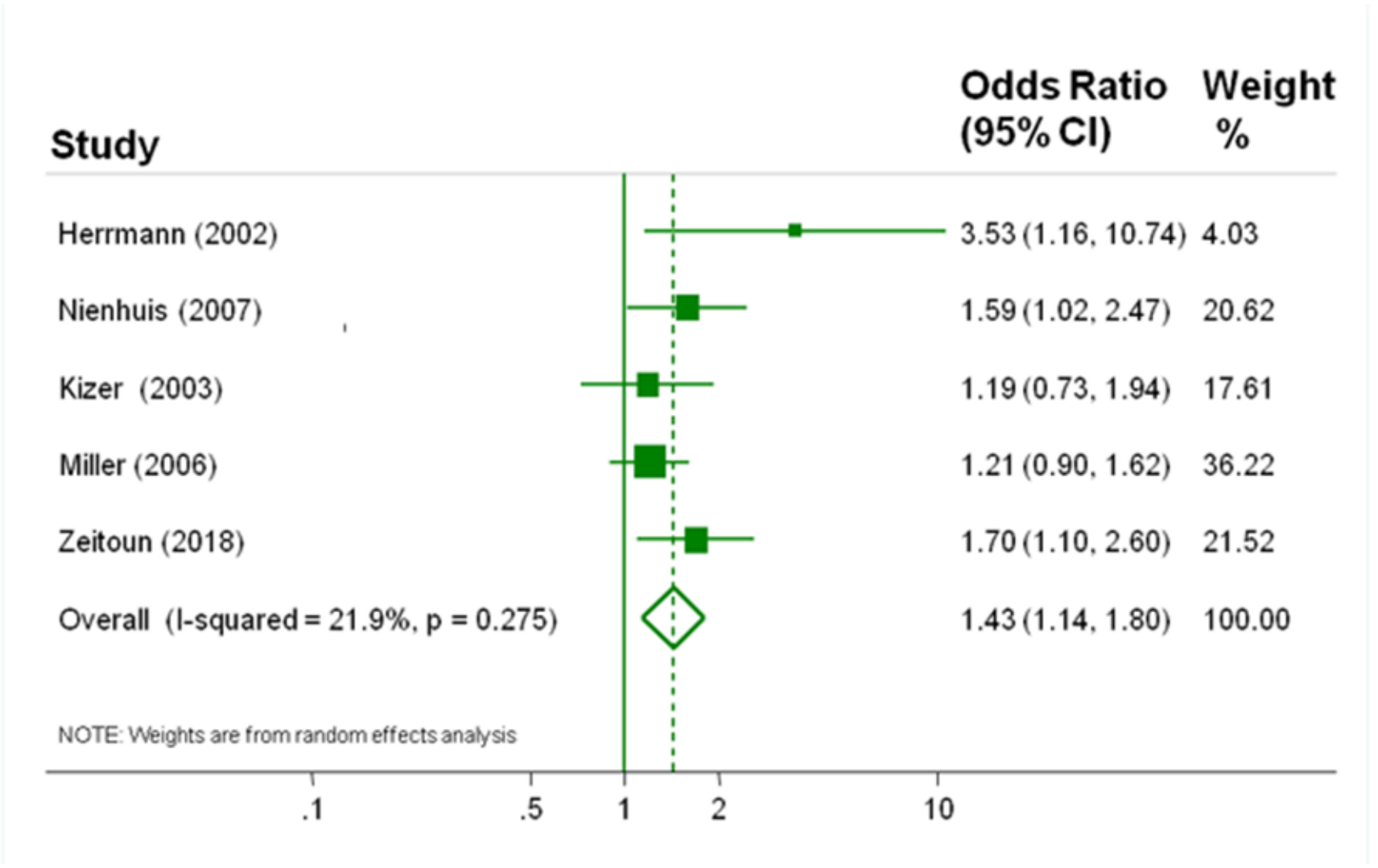
Supplementary Table 3. Univariate meta-regression of baseline characteristics for CK-MB and risk of all-cause mortality.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00737

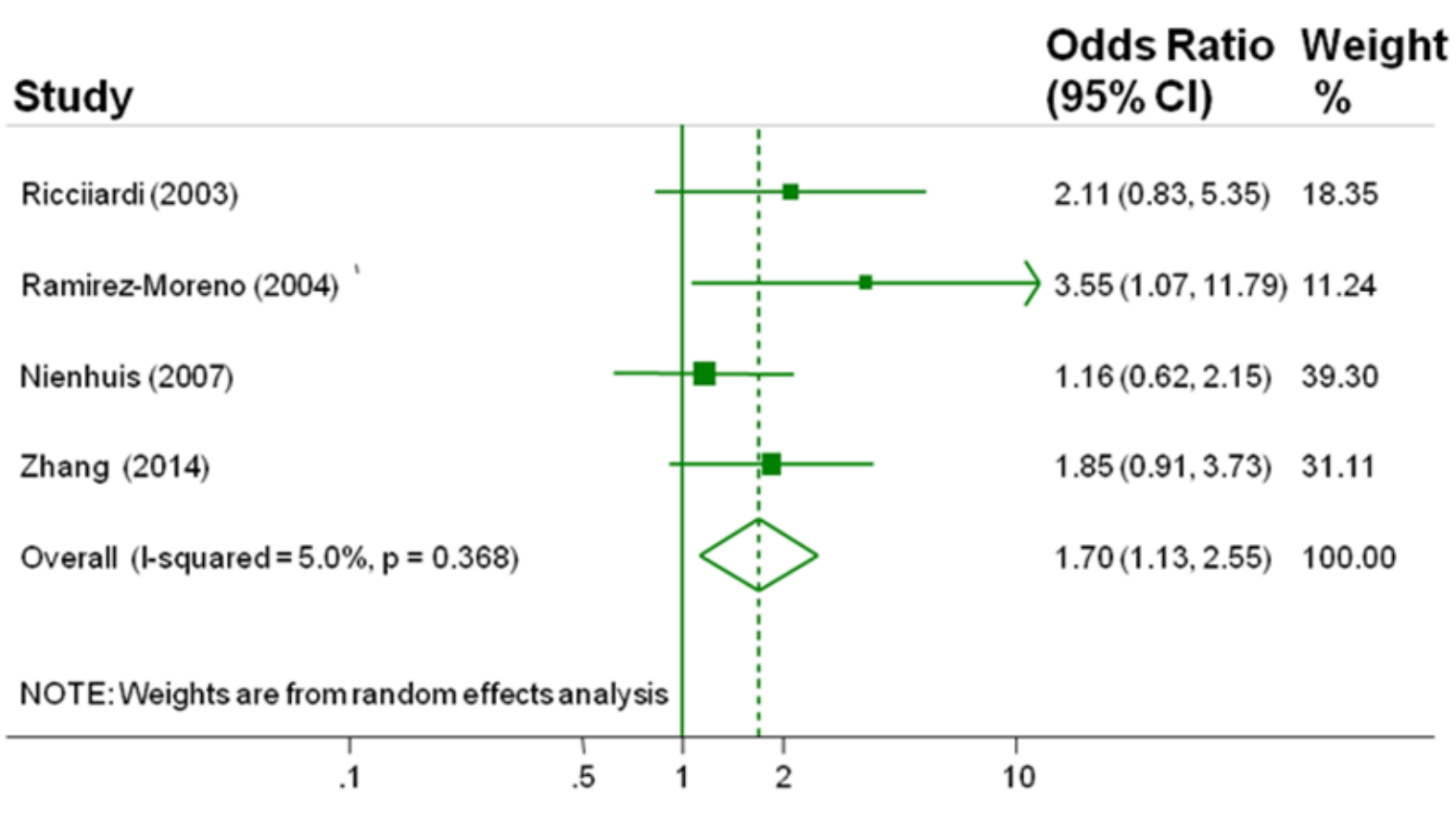
Supplementary data



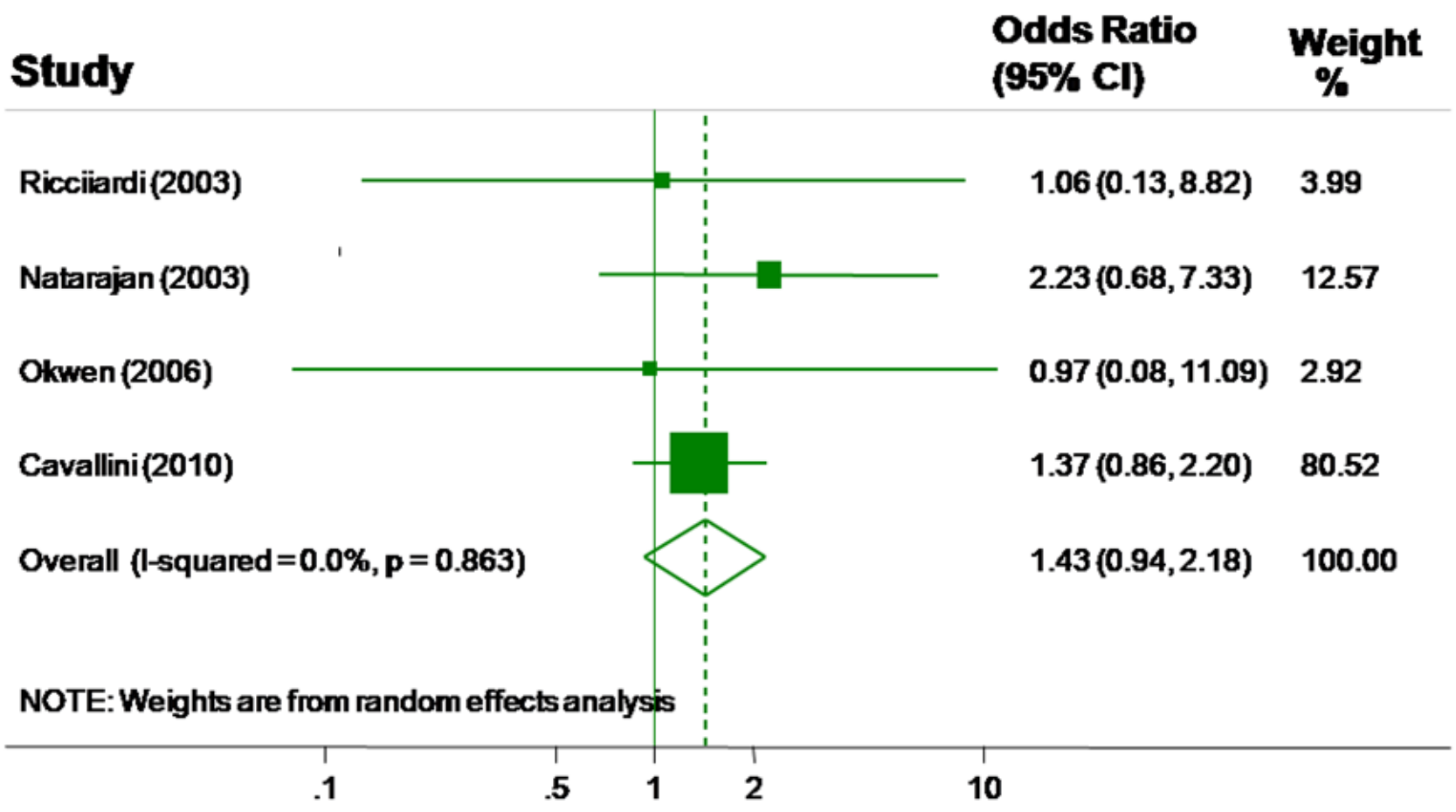
Supplementary Figure 1. Elevated versus non-elevated cardiac troponin I levels and risk of MACE.



Supplementary 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 MACE.



Supplementary Figure 4. Subgroup analysis of the four studies which reported the actual 99% URL of cardiac troponin I.

Supplementary Table 1. Characteristics of included studies (cardiac troponin I).

Study	Year	Country	N Number	cTnI+ %	Mean age	Male %	DM %	Hyperlipidaemia %	Hypertension %	Smoker %	Previous MI %	LVEF (%)	Stent %	Multivessel %	Follow-up time (months)	Cut-off value	Category	End point	MACE definition
Bertinchant et al	1999	France	105	22.0	61.0	75.2	22.9	57.1	45.7	48.6	38.1	64.2	NA	53.3	16	0.1 ug/L	2	MACE	Recurrent angina, MI, cardiac death, repeat PCI, CABG
Cantor et al	2002	Canada	481	48.0	57.5	75.5	17.7	54.6	52	37.6	20.7		82.3	48.5	3	1.5 ng/L	2	MACE	Death, MI, severe recurrent ischaemia
Saadeddin et al	2002	Saudi Arabia	96	27.0	55.0	76	57.3	84.4	52.1	39.6	NA		71.8	63.5	24	2.0 ug/L	2	Death, MACE	Recurrent angina, non-fatal MI, cardiac death, repeat PCI or CABG
Ricciardi et al	2003	USA	286	13.6	62.2	69	25	67	63	51.0	32		73	13	37	2.3 ng/mL	2	Death MACE	Death, MI, or need for PCI or CABG
Nallamothu et al	2003	USA	1,157	29.0	63.6	65.2	26	NA	67.3	20.6	31.1		77.8	59.5	12	2.0 ng/mL	5	Death	/
Natarajan et al	2003	Canada	1,128	16.8	60.7	67	20	76	54	42.0	51		83	31	12	NA	3	Death, MACE	Death, repeat PCI or CABG, TVR
Ramirez-Moreno et al	2004	Spain	143	16.3	62.5	54.4	29.9	30.6	54.4	45.6	NA	63.3	46.3	79.6	10.4	0.5 ug/L	2	MACE death	Recurrence of angina due to restenosis, underwent intra-stent angioplasty
Kini et al	2004	USA	2,873	39.0	66.6	69.9	41	84	90	15.0	30.1	53.1	86.7	23.4	12	2.0 ng/mL	4	Death	/
Okwen et al	2006	Turkey	100	34.0	55.7	83	11	30	37	51.0	34	53.7	54	NA	21	0.2 ng/mL	2	Death, MACE	Recurrent angina, acute MI, death, and revascularisation

Izgi et al	2006	Turkey	100	27.0	54.4	11	15	62	38	65.0	10.4	52.7	100	51	12	0.08 ng/mL		MACE	Cardiac death, acute MI and recurrent PCI or CABG
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	91.3	NA	45	0.6 ug/L	2	death	/
Cavallini et al	2010	Italy	2,362	39.4	62.5	79.7	18.2	61	NA	NA	49.8	57.7	76.7	37.9	24	0.15 ng/L	3	death	/
Novack et al	2012	USA	4,930	24.3	64.3	68.6	36.1	NA	NA	NA	NA		NA	NA	13	NA	5	death	/

Supplementary 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 (%)	Angiography success (%)	Side branch occlusion (%)	Bifurcation (%)	High-sensitivity troponin
Bertinchant et al	1999	NA	NA	21.9	NA	45.7	35.2	86.7	0.0	NA	NA	3.8	NA	no
Cantor et al	2002	NA	0.2	60.5	NA	NA	NA	NA	21.4	NA	88.6	NA	NA	no
Saadeddin et al	2002	NA	NA	NA	NA	66.7	49.0	NA	NA	74.0	NA	13.7	NA	no
Ricciardi et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15.0	NA	no
Nallamothu et al	2003	NA	7.1	NA	NA	NA	NA	NA	75.0	NA	NA	NA	NA	no
Natarajan et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	100.0	3.0	12.0	no
Ramirez-Moreno et al	2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.8	NA	no
Kini et al	2004	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4	98.2	6.0	NA	no
Okwen et al	2006	NA	NA	22.0	NA	NA	NA	NA	40.0	NA	NA	14.0	4.0	no
Izgi et al	2006	NA	NA	42.0	NA	76.0	NA	NA	NA	74.0	NA	3.0	NA	no
Gomez-Hospital et al	2009	NA	4.8	NA	10.6	NA	NA	NA	4.8	NA	95.4	6.2	NA	no
Cavallini et al	2010	4.7	3.9	NA	9.9	NA	NA	NA	NA	76.7	NA	NA	NA	no
Novack et al	2012	NA	24.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	no

Supplementary Table 1. Characteristics of included studies (cardiac troponin T) (continued)

Study	Year	Country	N Number	cTnT +%	Mean age	Male %	DM %	Hyperlipidaemia %	Hypertension %	Smoker %	Previous MI %	LVEF (%)	Stent %	Multivessel %	Follow-up (months)	Cut-off value	Category	End point	MACE definition
Herrmann et al	2002	Germany	278	17.3	61.5	79.5	19.4	82	59.7	28.1	41.0		NA	75.2	7.8	0.1 ng/L	2	MACE	Acute MI, bypass surgery, and cardiac death
Kizer et al	2003	USA	128	18.4	60	72	30	73	77	30	38.0	57.0	86.8	20.0	67.2	0.5 ng/L	4	MACE	Death, MI and revascularisation
Miller et al	2006	USA	1,619	57.3	66.6	71	25	86	74	NA	36.0	54.1	58.0	28.0	12	0.03 ug/L	2	MACE	Death, MI, CABG, redo PCI
Nienhuis et al	2007	Netherlands	713	21	64	79	18	55.8	43.6	32.3	44.7		70.3	48.0	10.9	0.05 ng/mL	2	MACE	Death, MI or coronary angiography, re-PCI, CABG, stroke, re-admission
Zeitouni	2018	France	1,390	28.7	66.9	79.2	35.7	63.6	62.3	24.1	NA	55.7	93.6	42.4	12	14 ng/L	2	Death MACE	Death, MI, ischaemic stroke, and refractory angina

Supplementary 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 (%)	Angiography success (%)	Side branch occlusion (%)	Bifurcation (%)	High-sensitivity troponin
Herrmann et al	2002	NA	NA	NA	17.6	NA	NA	NA	NA	NA	NA	NA	5.0	NA	no
Kizer et al	2003	NA	NA	NA	NA	NA	56.0	43.0	98.0	NA	NA	NA	NA	NA	no
Miller et al	2006	NA	NA	NA	NA	NA	NA	NA	NA	64.9	NA	NA	NA	NA	no
Nienhuis et al	2007	NA	NA	NA	35.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	no
Zeitouni	2018	26.7	NA	48.6	NA	NA	NA	NA	44.3	NA	NA	NA	NA	NA	yes

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

Study	Year	Country	N Number	CK-MB +%	Mean age	Male %	DM %	Hyperlipidaemia %	Hypertension %	Smoker %	Previous MI %	LVEF (%)	Stent %	Multivessel %	Follow-up time (months)	Cut-off value	Category	End point	MACE definition
Herrmann et al	2002	Germany	278	14.7	61.5	79.5	19.4	82	59.7	28.1	41		37.8	75.2	7.8	80 IU/L (M) 70 IU/L (F)	2	Death, MACE	Acute MI, CABG, and cardiac death
Ricciardi et al	2003	USA	286	12.9	62.2	69	25	67	63	51	32		73	13	37.2	9 ng/mL	2	MACE	Death, MI, or need for PCI or CABG
Nallamothu et al	2003	USA	1,157	NA	63.6	65.2	26	NA	67.3	20.6	31.1		77.8	59.5	12	NA	5	Death	/
Ramirez-Moreno et al	2004	Spain	143	15.6	62.5	54.4	29.9	30.6	54.4	45.6	NA	63.3	46.3	79.6	10.4	5 ug/L	2	MACE	Recurrence of angina due to restenosis, underwent intra-stent angioplasty.
Kini et al	2004	USA	2,873	16.1	66.6	69.9	41	84	90	15	30.1	53.1	86.7	23.4	12	10 ng/mL	4	Death	/
Nienhuis et al	2007	Netherlands	713	9.3	64	79	18	55.8	43.6	32.3	44.7		70.3	48	10.9	180 IU/L	2	MACE	Death, MI or coronary angiography, re-PCI, CABG, stroke, re-admission
Lindsey et al	2011	USA	6,347	25.6	64.5	68.8	36.3	76.9	79.9	23.2	32.9		NA	14.7	12	5 ng/mL	5	Death	/
Zhang et al	2014	China	1,008	10.5	63	73.2	25.2	7	68	42.8	7.7	63.9	43	10	26	25 umol/L	2	MACE	Death, hospitalisation due to non-fatal myocardial infarction, unplanned revascularisation or heart failure
Kini et al	1999	USA	1,675	18.7	65	68.4	24.9	47.3	70.1	17.3	34.7	49.6	60.4	32.9	13	16 U/L	4	Death	/
Stone et al	2001	USA	7,147	37.3	63.9	70.4	28.3	64	58.8	20.6	48.4		50.6	NA	16.8	4 ng/ml	5	Death	/
Ellis et al	2002	USA	8,409	17.2	65	72	29.7	49.7	69.2	NA	0	52.6	66.4	NA	4	8.8 unit	3	Death	/
Gomez-Hospital et al	2009	Spain	757	6.1	63	74.9	32.1	68.4	55.6	59.6	24.8	60.0	91.3	NA	45	1.26 ukat/L	2	Death	/

Supplementary Table 1. Characteristics of included studies (CK-MB) (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 (%)	Angiography success (%)	Side branch occlusion (%)	Bifurcation (%)
Herrmann et al	2002	NA	NA	17.6	NA	NA	NA	NA	NA	NA	NA	5.0	NA
Ricciardi et al	2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15.0	NA
Nallamothu et al	2003	NA	7.1	NA	NA	NA	NA	NA	75.0	NA	NA	NA	NA
Ramirez-Moreno et al	2004	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.8	NA
Kini et al	2004	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4	98.2	6	NA
Nienhuis et al	2007	NA	NA	35.0	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindsey et al	2011	NA	21.9	NA	11.6	NA	NA	NA	NA	NA	NA	NA	11.8
Zhang et al	2014	NA	NA	NA	NA	74.9	NA	99.7	1.1	98.1	NA	0.6	NA
Kini et al	1999	NA	NA	NA	NA	NA	NA	92.7	82.1	63.4	98.2	6.0	NA
Stone et al	2001	NA	4.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Ellis et al	2002	NA	4.5	NA	NA	NA	NA	NA	53.4	NA	NA	NA	NA
Gomez-Hospital et al	2009	NA	4.8	NA	10.6	NA	NA	NA	4.8	NA	95.4	6.2	NA

CABG: coronary artery bypass graft; CAD: coronary artery disease; CK-MB: creatine kinase myocardial band isoenzyme; DM: diabetes mellitus; F: female; M: male; MACE: major adverse cardiovascular events; MI: myocardial infarction; NA: not available; PCI: percutaneous coronary intervention; TVR: target vessel revascularisation

Supplementary 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*-value
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
Hyperlipidaemia 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
Multivessel diseases proportion	8	0.004	(-0.011 to 0.019)	0	0.56
Side branch occlusion	7	-0.016	(-0.129 to 0.0977)	14.19	0.73

DM: diabetes mellitus; MI: myocardial infarction

Supplementary 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*-value
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
Hyperlipidaemia 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
Multivessel diseases proportion	4	0.015	(-0.048 to 0.078)	63.20	0.42
Side branch occlusion	4	-0.822	(-5.16 to 3.52)	68.18	0.50

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