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Mortality after bleeding versus myocardial infarction in coronary artery disease: a systematic review and meta-analysis

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KEYWORDS

- bleeding
- death
- myocardial infarction

Abstract

Background: Bleeding is the principal safety concern of antithrombotic therapy and occurs frequently among patients with coronary artery disease (CAD).

Aims: We aimed to evaluate the prognostic impact of bleeding on mortality compared with that of myocardial infarction (MI) in patients with CAD.

Methods: We searched Medline and Embase for studies that included patients with CAD and that reported both the association between the occurrence of bleeding and mortality, and between the occurrence of MI and mortality within the same population. Adjusted hazard ratios (HRs) for mortality associated with bleeding and MI were extracted and ratios of hazard ratios (rHRs) were pooled by using inverse variance weighted random effects meta-analyses. Early events included periprocedural or within 30-day events after revascularisation or acute coronary syndrome (ACS). Late events included spontaneous or beyond 30-day events after revascularisation or ACS.

Results: A total of 141,059 patients were included across 16 studies; 128,660 (91%) underwent percutaneous coronary intervention. Major bleeding increased the risk of mortality to the same extent as MI ($rHRs_{bleedingvsMI}$ 1.10, 95% CI: 0.71-1.71, p=0.668). Early bleeding was associated with a higher risk of mortality than early MI ($rHRs_{bleedingvsMI}$ 1.46, 95% CI: 1.13-1.89, p=0.004), although this finding was not present when only randomised trials were included. Late bleeding was prognostically comparable to late MI ($rHRs_{bleedingvsMI}$ 1.14, 95% CI: 0.87-1.49, p=0.358).

Conclusions: Compared with MI, major and late bleeding is associated with a similar increase in mortality, whereas early bleeding might have a stronger association with mortality.

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Abbreviations

ACS acute coronary syndrome
CAD coronary artery disease
HR hazard ratio
MI myocardial infarction
PCI percutaneous coronary intervention

Introduction

Bleeding is the principal safety concern in patients with coronary artery disease (CAD) receiving long-term antithrombotic therapy and the most common non-cardiac adverse event among those undergoing percutaneous coronary intervention (PCI). Single or dual antiplatelet therapy in patients with chronic atherosclerotic vascular disease carries a risk of major bleeding of 1-2% annually[1,2]. Moreover, in the setting of PCI, major bleeding occurs in 1-2% of patients periprocedurally and up to 4% at one year in the absence of high bleeding risk features[3,4].

There is a growing body of evidence showing that bleeding has a negative prognostic impact with a heightened risk of mortality[5]. Several randomised trials, performed in the chronic setting, showed a decreased risk of ischaemic complications by means of more potent antiplatelet therapies without a concomitant reduction in the risk of mortality. Arguably, the excess of clinically relevant bleeding with more effective antithrombotic regimens could erode their ischaemic benefit, resulting in a shift of the risk for all-cause mortality towards the null effect. However, although the trade-off between ischaemia and bleeding is increasingly recognised[6], it remains unclear whether the excess of mortality risk conferred by bleeding is of comparable magnitude to that ensuing after myocardial infarction (MI). Furthermore, whether differences between late and early events exist has not yet been determined. Therefore, we undertook a systematic review and meta-analysis to summarise the available evidence on the relative prognostic association of bleeding and MI with mortality in patients with CAD treated medically or with PCI.

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Methods

SEARCH STRATEGY AND SELECTION CRITERIA

Studies had to include participants with CAD irrespective of their management (either medically or with PCI) and had to determine both the association between the occurrence of bleeding and mortality, and that between the occurrence of MI and mortality within the same population. Studies providing only the association between bleeding and mortality or, alternatively, only the association between MI and mortality were excluded. All studies had to adjust at least for age.

Studies were identified by a systematic search in Medline and Embase from each database inception to January 2021. The detailed search algorithm is provided in **Supplementary Appendix 1**. Reasons for exclusion were discussed and discrepancies were resolved by consensus.

The study protocol was registered in PROSPERO (CRD42020154931).

DATA ANALYSIS

Data were independently extracted by two different reviewers (A. Oliva, M. Avvedimento). We extracted adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) for the risk of mortality associated with different types of bleeding and MI, extracting HRs with 95% CI by bleeding severity (i.e., major vs minor) and setting of bleeding and MI (i.e., early vs late). Early events were defined as periprocedural events or, alternatively, as events occurring within 30 days after revascularisation or acute coronary syndrome (ACS). Late events were defined as spontaneous events or, alternatively, as events occurring beyond 30 days after revascularisation or ACS. In view of the anticipated variation among studies in the bleeding definitions used, the Bleeding Academic Research Consortium (BARC) classification took precedence over Thrombolysis In Myocardial Infarction (TIMI), followed by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO), and the primary classification specified in the study's protocol in case neither BARC, TIMI nor GUSTO classifications were used. BARC type 3 bleeding was used as a reference to define major bleeding, and other definitions were mapped accordingly. For example, TIMI minor and major bleedings were both considered major bleedings, whereas TIMI minimal bleedings were considered minor **(Supplementary Table 1-Supplementary Table 3)**. In addition to the covariate of age, information was extracted on additional variables, if any, considered for deriving the adjusted HRs **(Supplementary Table 4)**. Two reviewers independently assessed the risk of bias of studies using a modified version of the Newcastle-Ottawa scale score[7], based on three selection criteria and three outcome criteria. We considered studies that met four or more of these Newcastle-Ottawa scale criteria to be of higher quality.

STATISTICAL ANALYSIS

The ratio of hazard ratios (rHRs) was used as a measure of the strength of the association between bleeding and MI in terms of mortality risk **(Supplementary Appendix 2)**. An $rHRs_{bleedingvsMI}$ >1 indicates a stronger association of bleeding with mortality as compared with MI (i.e., higher risk of death with bleeding), whereas an $rHRs_{bleedingvsMI}$ <1 indicates a stronger association of MI with mortality, as compared with bleeding (i.e., higher risk of death with MI)[8]. HRs with 95% CI as well as their ratios were pooled with inverse variance weighted random effects meta-analysis. HRs for the associations of bleeding and MI with mortality were derived from the same participants and correlated. We therefore calculated the median design factor, defined as standard error derived after accounting for correlation within participants divided by crude standard error, in the only study that appropriately derived ratios of HRs and allowed the calculation of the corresponding crude standard error[9]. This median design factor of 1.041 was used to inflate the crude standard errors of rHRs of the remaining studies. We accounted for different types of bleedings and MIs, separately analysing the HRs for early and late events, and for the composite of early or late events. We also accounted for bleeding

severity, analysing HRs for major bleeding or, if not available, for the composite of major or minor bleeding separately from HRs for minor bleeding events only. Sensitivity analyses were then performed by excluding outlying studies (outside the boundaries of Galbraith plots), between studies published before versus after 2015, as well as between randomised and non-randomised studies. We determined heterogeneity between trials using the I^2 statistic, with estimates near 25% indicating a small, near 50% a moderate, and near 75% a large extent of heterogeneity. Studies contributing to significant heterogeneity were identified by Galbraith plots in which the estimated effect of each study was plotted against its precision[10]. Sensitivity analyses were then performed by excluding outlying studies (outside the boundaries of Galbraith plots). All p-values are two-sided. Analyses were performed in Stata Release 14 (StataCorp, College Station, TX, USA).

Results

We screened 5,571 unique citations and deemed 17 reports related to 16 studies eligible after full-text review, including 141,059 participants[9,11-25]. **Table 1** shows the main features of the studies selected for analysis. The definitions of bleeding and MI used in each study are reported in **Supplementary Table 1** and **Supplementary Table 5**.

Studies were published between 2008 and 2020 and had a median follow-up of 22.5 months (interquartile range [IQR] 13.5-30). Median age was 63.7 (IQR 62.3-64.7) years and 27.7% of participants were female. The proportion of participants undergoing PCI or with ACS was 91% (N=128,660) and 63% (N=88,867), respectively. Procedural characteriscs of studies are reported in **Supplementary Table 6**. A total of 8,367 deaths occurred in 141,059 participants, with a median risk of 3.9% across 16 studies (IQR 2.9%-7%). Bleeding and MI event rates reported across the studies are displayed in **Supplementary Table 7**.

MAJOR BLEEDING (± MINOR BLEEDING) vs MI

RISK OF ALL-CAUSE MORTALITY AFTER EARLY OR LATE EVENTS

HRs for the composite of early or late events after PCI were available for eight studies (n=51,780 participants). The median risk of bleeding was 6.2% (IQR 1.9%-8.5%; 2,024 events/49,778 participants; 7 studies) and the median risk of death among participants with bleeding was 17.8% (IQR 14.6%-19%; 258 deaths/1,630 participants; 5 studies). The median risk of MI was 6.5% (IQR 3.1%-7.4%; 1,804 events/40,307 participants; 7 studies) and the median risk of death among participants with MI was 13.4%

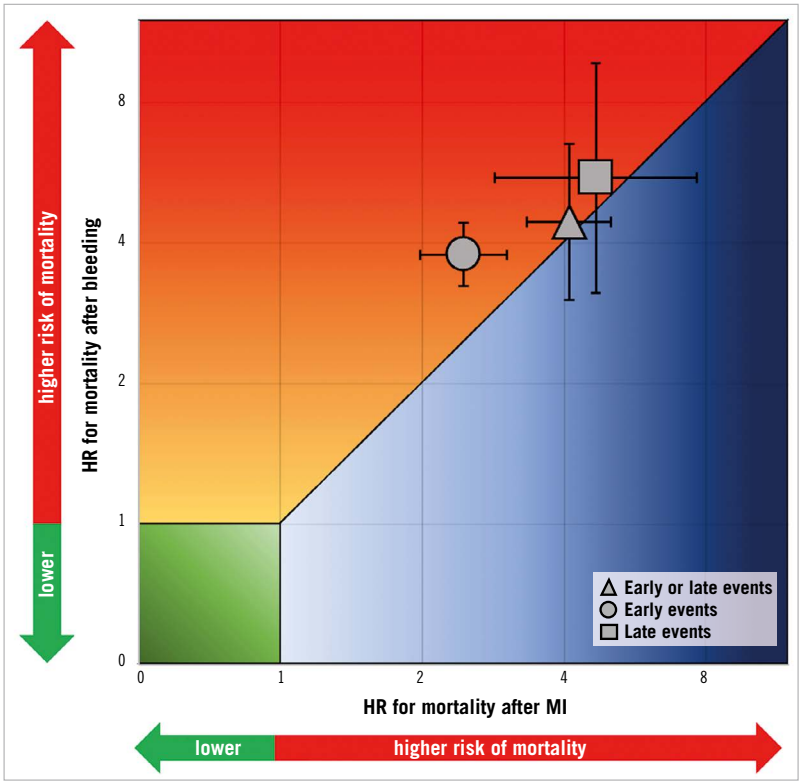
Table 1. Main features of the included studies.

Study, year	Acronym	Patient population	Type of study	Mean follow-up (months)	Patients (N)	Deaths (N)	Mean age (years)	Female (%)	Diabetes (%)	ACS (%)	PCI (%)
Ndrepepa et al, 2008		NSTE-ACS and elective patients undergoing PCI	RCT	12	5,384	197	66.6	25	34	38	100
Mehran et al, 2009	ACUITY	ACS patients	RCT	12	13,819	524	62.6	30	28	100	56.4
Montalescot et al, 2009	STEEPLE	Patients undergoing PCI	RCT	12	2,636	75	63.7	26	29	0	100
Lindsey et al, 2009	EVENT	Patients undergoing PCI	registry	12	5,961	167	64.7	33	35	34	100
Kim et al, 2011		Patients undergoing PCI	registry	36	3,148	134	60.5	29	27	14	100
Kikkert et al, 2013		STEMI patients undergoing PCI	registry	48	2,002	366	62.0	30	14	100	100
Stone et al, 2014	HORIZONS-AMI	STEMI patients undergoing PCI	RCT	36	3,202	197	59.9	23	16	100	100
Kazi et al, 2015		Patients undergoing PCI	registry	53	32,906	4,048	64.0	30	27	68	100
Généreux et al, 2015 and Stone et al, 2013	ADAPT-DES	Patients undergoing PCI	registry	24	8,577	311	63.6	26	32	52	100
Baber et al, 2016	PARIS	Patients undergoing PCI	registry	24	5,018	227	63.7	25	33	41	100
Garot et al, 2017	LEADERS FREE	High bleeding-risk patients undergoing PCI	RCT	24	2,386	320	75.7	30	56	72	100
Valgimigli et al, 2017	TRACER	NSTE-ACS patients	RCT	16	12,702	500	64.0	28	31	100	57.8
Palmerini et al, 2017		Patients undergoing PCI	pooled RCTs	18	11,473	267	63.1	30	31	42	100
Secemsky et al, 2017	DAPT	Patients undergoing PCI without ischaemic or bleeding events after 12 months of DAPT	RCT	21	11,648	222	61.3	25	29	46	100
Caneiro-Queija et al, 2018		ACS patients	registry	15	4,229	335	67.0	25	32	100	73.5
Hara et al, 2020	GLOBAL LEADERS	Patients undergoing PCI	RCT	24	15,968	477	64.5	23	19	47	100

(IQR 10.4%-29.2%; 267 deaths/1,600 participants; 6 studies). The risk of all-cause mortality was significantly increased among participants with early or late bleeding (HR 4.44, 95% CI: 3.02-6.52) and MI (HR 4.10, 95% CI: 3.34-5.03). The rHRs for bleeding versus MI were not significant ($rHRs_{bleedingvsMI}$ 1.10, 95% CI: 0.71-1.71, p=0.668) **(Central illustration, Figure 1, Figure 2)**. Heterogeneity was high for relative risks (I^2=89% and I^2=58%, for bleeding and MI, respectively) and their ratio (I^2=81%). However, after the exclusion of outlying studies, the ratio of HRs remained not significant ($rHRs_{bleedingvsMI}$ 1.03, 95% CI: 0.80-1.32, I^2=19%) **(Table 2)**.

RISK OF ALL-CAUSE MORTALITY AFTER EARLY EVENTS

HRs for early events were available for seven studies in 51,934 participants undergoing cardiac catheterisation and/or PCI. The median risk of early bleeding was 3.5% (IQR 1.5%-4.3%;



Central illustration. *Association between bleeding and myocardial infarction with mortality for early events, late events and early or late events.*

Types of events	No. of studies	No. of patients	Ratio of HRs	*p*-value	I^2
Early or late events					
Major bleeding vs MI	5	26,706	1.23 (0.62 to 2.47)	0.555	88.9%
Major or minor bleeding vs MI	3	25,074	0.91 (0.65 to 1.27)	0.579	0%
Combined	8	51,780	1.10 (0.71 to 1.71)	0.668	81.3%
Early events					
Major bleeding vs MI	4	27,800	1.28 (0.97 to 1.68)	0.076	0%
Major or minor bleeding vs MI	3	24,134	2.06 (1.27 to 3.35)	0.003	0%
Combined	7	51,934	1.46 (1.13 to 1.89)	0.004	7.2%
Late events					
Major bleeding vs MI	3	29,368	1.28 (0.93 to 1.76)	0.125	12.3%
Major or minor bleeding vs MI	5	64,828	1.04 (0.70 to 1.54)	0.852	60.6%
Combined	8	94,196	1.14 (0.87 to 1.49)	0.358	52.5%

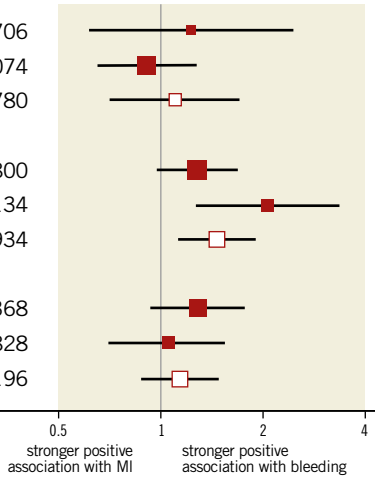


Figure 1. *Association of bleeding and myocardial infarction with mortality in patients with coronary artery disease treated with medical therapy or percutaneous coronary intervention.*

Table 2. Pooled hazard ratios (HRs) with and without outlying studies.

	HR (95% CI)	I^2	No. of studies
Bleeding			
Early or late			
Major	4.60 (2.51-8.43)	94%	5
Major, excluding outliers	3.43 (2.68-4.40)	0%	2
Major or minor	4.25 (3.40-5.32)	0%	3
Combined	4.44 (3.02-6.52)	89%	8
Combined, excluding outliers	3.86 (3.27-4.56)	0%	5
Minor	2.73 (2.07-3.61)	0%	2
Early			
Major	3.42 (2.48-4.12)	0%	4
Major or minor	4.65 (3.54-6.11)	0%	3
Combined	3.77 (3.23-4.41)	1%	7
Late			
Major	7.92 (3.80-16.51)	91%	3
Major, excluding outliers	5.62 (4.37-7.22)	0%	2
Major or minor	4.43 (2.28-8.63)	94%	5
Major or minor, excluding outliers	5.62 (4.59-6.87)	0%	4
Combined	5.51 (3.13-9.68)	95%	8
Combined, excluding outliers	5.62 (4.80-6.57)	0%	6
Minor	2.11 (1.53-2.90)	43%	4
Myocardial infarction			
Early or late	4.11 (3.34-5.03)	58%	8
Early or late, excluding outliers	4.13 (3.54-4.82)	8%	6
Early	2.45 (1.98-3.02)	25%	7
Late	4.67 (2.85-7.63)	94%	8
Late, excluding outliers	6.19 (4.86-7.89)	53%	6
Bleeding vs myocardial infarction			
Early or late			
Major	1.23 (0.62-2.47)	89%	5
Major, excluding outliers	1.13 (0.72-1.78)	57%	3
Major or minor	0.91 (0.65-1.27)	0%	3
Combined	1.10 (0.71-1.71)	81%	8
Combined, excluding outliers	1.03 (0.80-1.32)	19%	6
Minor	0.62 (0.42-0.92)	0%	2
Early			
Major	1.28 (0.97-1.68)	0%	4
Major or minor	2.06 (1.27-3.35)	0%	3
Combined	1.46 (1.13-1.89)	7%	7
Late			
Major	1.28 (0.93-1.76)	12%	3
Major or minor	1.04 (0.70-1.54)	61%	5
Major or minor, excluding outliers	0.86 (0.69-1.07)	0%	4
Combined	1.14 (0.87-1.49)	53%	8
Combined, excluding outliers	1.10 (0.82-1.24)	16%	7
Minor	0.35 (0.25-0.49)	19%	4

Outliers were identified by visual inspection of Galbraith plots, which are reported in Supplementary Figure 2-Supplementary Figure 24.
CI: confidence interval; HR: hazard ratio

1,439 events/49,928 participants; 6 studies with available data) and the median risk of death was 15.3% (IQR 14.4%-15.6%; 216 deaths/49,928 participants; 6 studies). The median risk of early MI was 5.2% (IQR 1.7%-5.8%; 1,836 events/49,928 participants; 6 studies) and the median risk of death was 8.6% among participants with early MI (IQR 8.1%-10.9%; 153 deaths/1,671 participants; 5 studies). The risk of all-cause mortality was increased to a greater extent after early bleeding (HR 3.77, 95% CI: 3.23- 4.41; I^2=1%) than early MI (HR 2.45, 95% CI: 1.98-3.02; I^2=25%), resulting in a significant rHRs ($rHRs_{bleedingvsMI}$ 1.46, 95% CI: 1.13-1.89, p=0.004; I^2=7%) **(Central illustration, Figure 2, Figure 3)**.

RISK OF ALL-CAUSE MORTALITY AFTER LATE EVENTS

HRs for late events were available for eight studies in 94,196 participants. The median risk of late bleeding was 3.1% (IQR 2.2%-5.8%; 3,261 events/94,196 participants; 8 studies) and the median risk of death among participants with late bleeding was 17.6% (IQR 13.4%-22.1%; 557 deaths/3,261 participants; 8 studies). The median risk of late MI was 2.9% (IQR 2.5%-4.7%; 3,150 events/94,196 participants; 8 studies) and the median risk of death among participants with late MI was 17.2% (IQR 10.9%-21.3%; 571 deaths/2,724 participants; 6 studies). As shown in **Figure 4**, the relative risk of all-cause mortality was significantly increased after late bleeding (HR 5.51, 95% CI: 3.13-9.68; I^2=95%) and late MI (HR 4.67, 95% CI: 2.85-7.63; I^2=94%). The rHRs was not significant ($rHRs_{bleedingvsMI}$ 1.14, 95% CI: 0.87-1.49, p=0.358; I^2=53%) **(Central illustration, Figure 2, Figure 4)**, suggesting a similar impact of the two events on mortality. The rHRs remained similar after the exclusion of the studies that were identified as outliers at visual inspection of Galbraith plots ($rHRs_{bleedingvsMI}$ 1.10, 95% CI: 0.82-1.24; I^2=16%) **(Table 2)**.

MINOR BLEEDING vs MI

The median rate of minor late bleeding was 4.7% (IQR 3%-7.1%; 1,523 events/33,597 participants; 4 studies) and the median risk of death among participants with minor late bleeding was 6.3% (IQR 4.6%-8.4%; 73 deaths/1,164 participants; 3 studies). As displayed in **Figure 5**, the risk of mortality for participants with late minor bleeding (HR 2.11, 95% CI: 1.53-2.90; I^2=43%) was lower than for those experiencing late MI (HR 5.78, 95% CI: 4.18-7.99; I^2=65%), resulting in a significant rHRs ($rHRs_{bleedingvsMI}$ 0.35, 95% CI: 0.25-0.49, p<0.001; I^2=19%). For the only two studies providing data on the composite of late or early minor bleeding, the rHRs was 0.62 (95% CI: 0.42-0.92).

SENSITIVITY ANALYSES, QUALITY OF STUDIES AND RISK OF BIAS

As shown in **Table 2**, rHRs for all-cause mortality associated with bleeding versus MI were largely consistent after the exclusion of outlying studies, identified by visual inspection of Galbraith plots **(Supplementary Figure 1-Supplementary Figure 24)**. Results were also consistent between studies published before versus after 2015, the median publication year **(Supplementary Table 8)**. Randomised and non-randomised studies yielded consistent findings, although

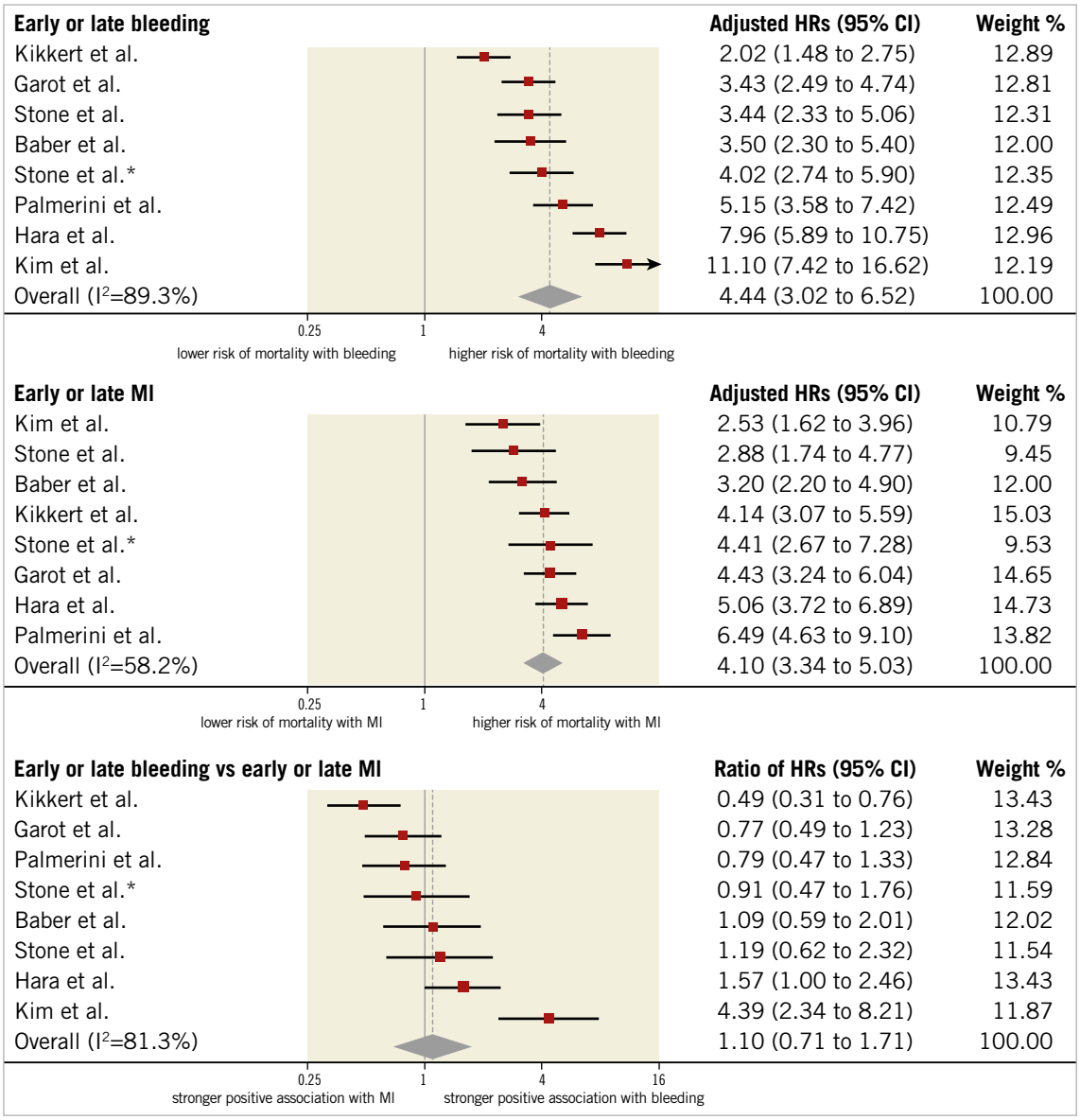


Figure 2. *Adjusted hazard ratios for all-cause mortality for patients with early or late events. HRs for bleeding are for major bleeding. *Refers to Stone et al 2013.*

there was a significant interaction for early events due to a lesser impact of early MI on mortality in non-randomised studies **(Supplementary Table 9)**. All included studies were of high quality according to the Newcastle-Ottawa scale **(Supplementary Table 10)**.

Discussion

In the present systematic review and meta-analysis of 16 studies, including 141,059 patients with CAD, we found strong evidence for a heightened risk of mortality associated with bleeding and MI events. However, there was a differential effect in the relative association between bleeding and MI according to the timing and severity of events: 1) early bleeding had a greater impact on mortality than early MI; 2) the risk of mortality after late bleeding was comparable to the risk of mortality after late MI; 3) the risk of mortality associated with bleeding and MI was comparable for major bleeding, whereas minor bleeding was prognostically less relevant than MI.

Bleeding after PCI is increasingly considered as important as MI. The trend in recent trials investigating antithrombotic therapies after PCI/ACS is to power for superiority with respect to bleeding reduction and only non-inferiority with respect to ischaemic/thrombotic endpoints. However, bleeding continues to represent the most common non-cardiac adverse event after PCI and is associated with increased morbidity and mortality, prolonged hospitalisation, and incremental costs[26]. Among bleeding avoidance strategies, the choice of vascular access plays a critical role. Indeed, in randomised and large observational studies, radial compared with femoral access showed a strong reduction in the risk of vascular and bleeding complications, affording a parallel

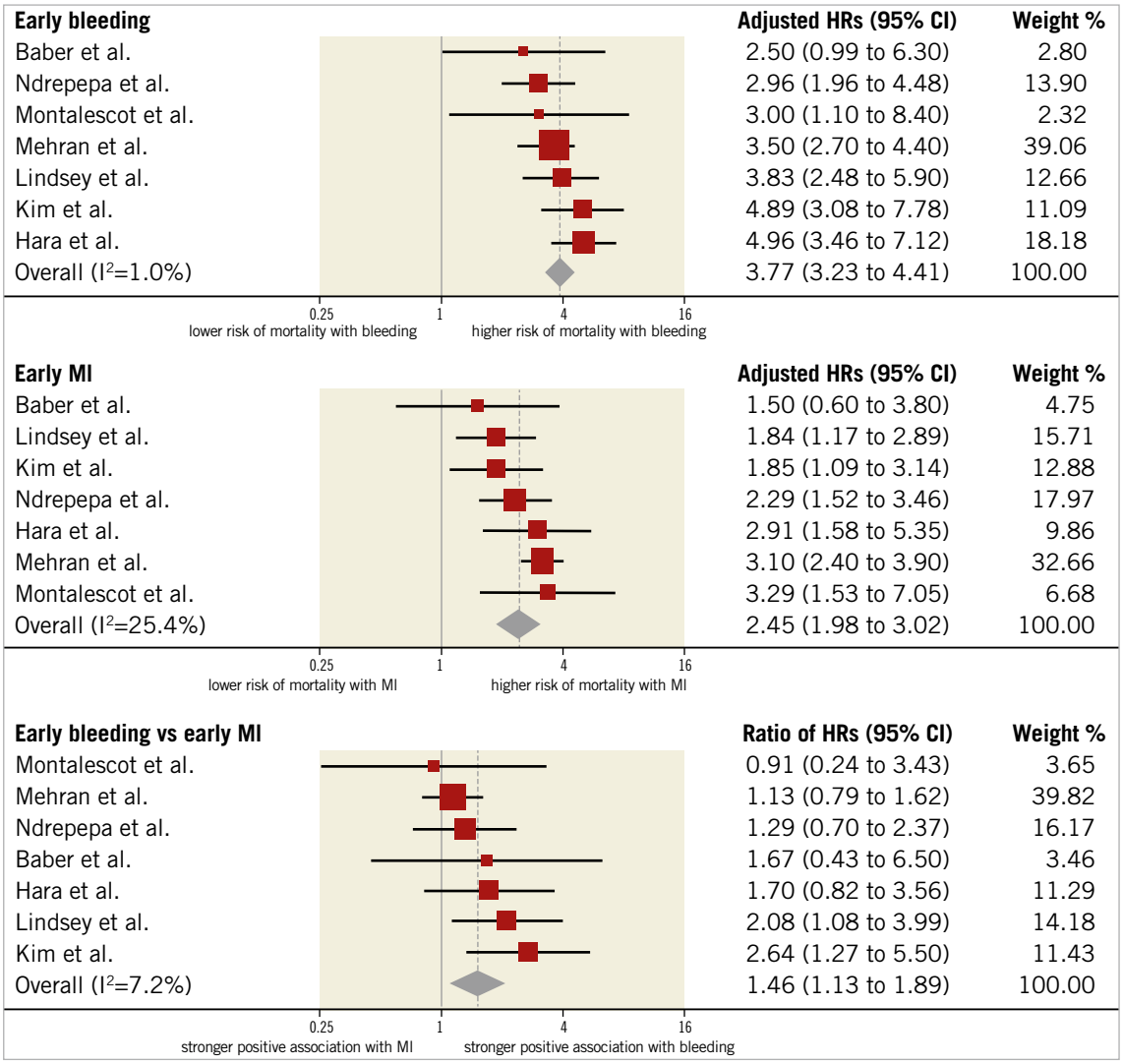


Figure 3. *Adjusted hazard ratios for all-cause mortality for patients with early events. HRs for bleeding are for major bleeding.*

decrease by 20-30% in the relative risk of all-cause mortality[27,28]. In a nested case-control analysis of the MATRIX trial comparing patients who died from causes other than bleeding with 1,370 matched control patients, actionable bleeding was associated with a threefold increase in the risk of mortality, therefore suggesting a link between bleeding prevention and mortality benefit related to radial access[29]. Similarly, in a trial of patients with chronic CAD and atrial fibrillation, a less intense antithrombotic regimen with rivaroxaban instead of rivaroxaban plus a single antiplatelet agent was associated with a 60% and 55% relative decrease in the risk of major bleeding and death, respectively[30]. A variety of mechanisms may help to explain the trade-off between bleeding and ischaemia. Discontinuation of antithrombotic therapy or the use of less effective drugs in patients with bleeding complications may result in an increased risk of ischaemic complications. Anaemia can directly affect oxygen delivery to the myocardium and induce a prothrombotic status by triggering erythropoietin release. Transfusions that are frequently required to correct anaemia in the setting of bleeding have been associated with poorer outcomes[31]. Also, major bleeding may increase the risk of mortality in patients suffering from trauma or malignancies.

Conversely, interventions proven effective in preventing ischaemic complications at the expense of increased major bleeding have not necessarily translated into a mortality benefit. In a patient-level meta-analysis of 48,817 patients, extended clopidogrel therapy on a background of aspirin significantly reduced the risk of ischaemic events and increased the risk of major bleeding, including fatal events, with no effect on mortality[32]. Along the same lines, in a meta-analysis of 10 trials, prolongation (≥12 months) of dual antiplatelet therapy after PCI yielded increased risks of major bleeding and all-cause mortality despite reduced risks of MI and stent thrombosis[6]. This observation, however, was largely influenced by a single randomised trial with a higher risk of non-cardiovascular fatalities among patients randomised to prolonged thienopyridine treatment, principally due to cancer-related deaths in the absence of clinically evident bleeding liability[33]. Collectively, these results might be reconciled in view of the comparable prognostic impact of late bleeding and MI on mortality as supported by the present study.

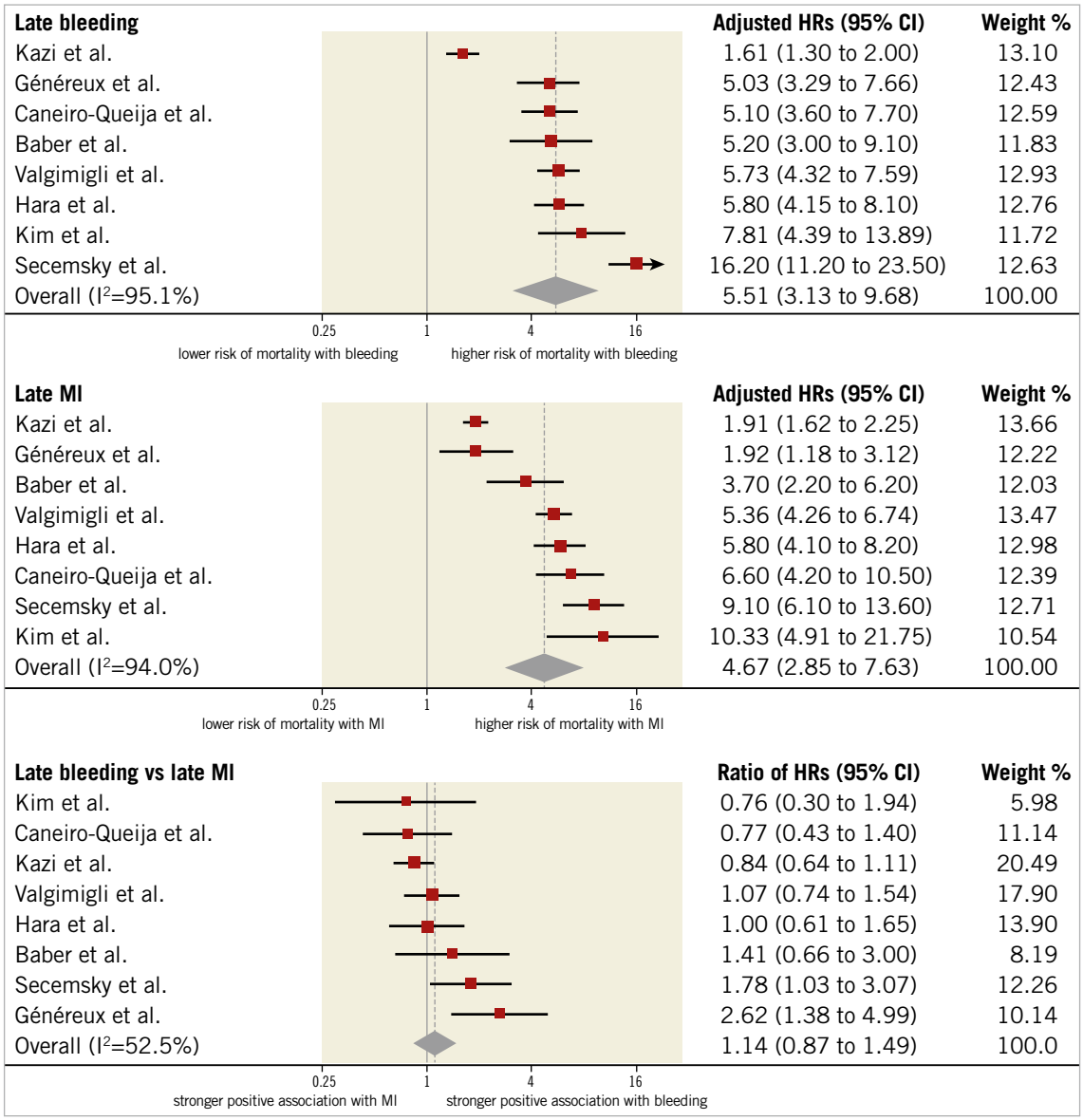


Figure 4. *Adjusted hazard ratios for all-cause mortality for patients with late events. HRs for bleeding are for major bleeding.*

Another principal finding of our meta-analysis is that early bleeding showed a greater impact on mortality than early MI. Again, this may explain the mortality benefit observed with radial access that is attributable to the prevention of access-site bleeding and also the decrease in major cardiovascular events reported by trials using safer anticoagulant strategies among patients undergoing PCI[34]. At the same time, it is noteworthy that early MI presented a weaker association with mortality with a pooled risk estimate similar to minor bleeding (HR 2.45 vs 2.11, respectively).

The present study may also have implications for the design of future randomised clinical trials. Given the equipoise between MI and major bleeding in terms of mortality, a net clinical outcome (or net clinical benefit) might be used as the primary endpoint in order to assess the risk-benefit ratio of a given intervention thoroughly and also increase the total number of endpoint events, resulting in more statistical precision and more accurate trials. Finally, by providing a quantitative description of the mortality risk associated with MI and different types of bleeding, the findings of this study may serve as the basis for the estimation of weighting factors in weighted composite endpoint methodologies, in which non-fatal events are accounted for differently based on their relative severity[35].

Study limitations

The results of this study should be interpreted in view of several limitations. First, bleeding and MI definitions were different across studies and this represented a source of heterogeneity, which unfortunately was present for most of the outcomes. Moreover, early events included both periprocedural and within 30-day post-PCI events. Similarly, late events included both spontaneous and after 30-day post-PCI events. However, associations remained

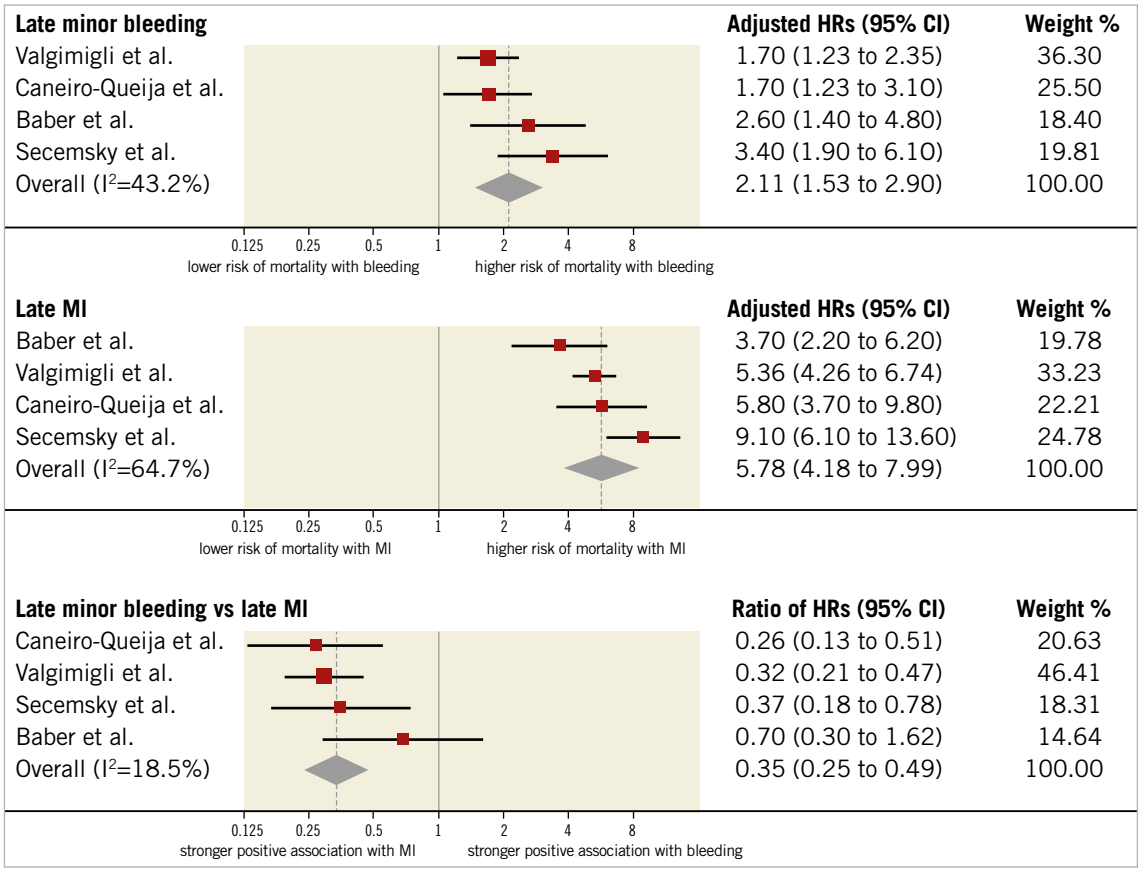


Figure 5. *Adjusted hazard ratios for all-cause mortality for patients with late minor bleeding. HRs for bleeding are for minor bleeding.*

largely unchanged after the exclusion of outlying studies. Second, although the meta-analysis showed an equipoise between major bleeding and MI in terms of subsequent risk of mortality, our findings do not prove causation of this association. Third, follow-up duration and periprocedural management, including antithrombotic therapy and vascular access, were not uniform across studies. Fourth, the included studies were published over a long period (from 2008 to 2020). However, the results remained largely consistent between newer versus older studies. Fifth, not all the included studies contributed to the analyses which might have affected the precision of pooled risk estimates. Sixth, although all studies had to provide HRs adjusted at least for age, there was substantial variation in the covariates used. Seventh, we used Galbraith plots to identify outlying studies visually, although they have limited value when the number of studies is low.

Conclusions

Our analysis showed that major and late bleedings were associated with a similar increase in the risk of all-cause mortality compared with MI. In the setting of PCI, early bleeding might have a stronger association with mortality than MI, emphasising the importance of bleeding avoidance strategies in perioperative management of patients undergoing percutaneous myocardial revascularisation.

Impact on daily practice

Major and late bleedings should be considered prognostically equivalent to MI, given the similar association with mortality. Early bleeding has an even stronger association with mortality than early MI, emphasising the importance of bleeding avoidance strategies among patients undergoing PCI.

Conflict of interest statement

R. Piccolo reports personal fees from Abbott Vascular. S. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed. M. Valgimigli reports grants and personal fees from Terumo, personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi Sankyo, Opsens, Bayer, CoreFlow, Idorsia Pharmaceuticals Ltd, Universität Basel Dept. Klinische Forschung, Vifor, Bristol Myers Squibb SA, iVascular, and Medscape. P. Jüni serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company, has received research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company,

and honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer, and he has no other relationships or activities that could appear to have influenced the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Search strategy.

Supplementary Appendix 2. Methods.

Supplementary Figure 1. Flow chart for the systematic review and meta-analysis.

Supplementary Figure 2. Galbraith plot for studies reporting HRs for the composite of late or early major bleeding.

Supplementary Figure 3. Galbraith plot for studies reporting HRs for the composite of late or early major or minor bleeding.

Supplementary Figure 4. Galbraith plot for studies reporting HRs for the composite of late or early major bleeding and for the composite of late or early major or minor bleeding.

Supplementary Figure 5. Galbraith plot for studies reporting HRs for early major bleeding.

Supplementary Figure 6. Galbraith plot for studies reporting HRs for early major or minor bleeding.

Supplementary Figure 7. Galbraith plot for studies reporting HRs of early major bleeding and for early major or minor bleeding.

Supplementary Figure 8. Galbraith plot for studies reporting HRs for late minor bleeding.

Supplementary Figure 9. Galbraith plot for studies reporting HRs for late major bleeding.

Supplementary Figure 10. Galbraith plot for studies reporting HRs for late major or minor bleeding.

Supplementary Figure 11. Galbraith plot for studies reporting HRs for late major bleeding and for late major or minor bleeding.

Supplementary Figure 12. Galbraith plot for studies reporting HRs for early myocardial infarction and late myocardial infarction.

Supplementary Figure 13. Galbraith plot for studies reporting HRs for early myocardial infarction.

Supplementary Figure 14. Galbraith plot for studies reporting HRs for late myocardial infarction.

Supplementary Figure 15. Galbraith plot for studies in which ratio of HRs was derived for the composite of late or early major bleeding versus the composite of late or early MI.

Supplementary Figure 16. Galbraith plot for studies in which ratio of HRs was derived for the composite of late or early major or minor bleeding versus the composite of late or early MI.

Supplementary Figure 17. Galbraith plot for studies in which ratio of HRs was derived for the composite of late or early major and major or minor bleeding versus the composite of late or early MI.

Supplementary Figure 18. Galbraith plot for studies in which ratio of HRs was derived for early major bleeding versus early MI.

Supplementary Figure 19. Galbraith plot for studies in which ratio of HRs was derived for early major or minor bleeding versus early MI.

Supplementary Figure 20. Galbraith plot for studies in which ratio of HRs was derived for the composite of early major and major or minor bleeding versus early MI.

Supplementary Figure 21. Galbraith plot for studies in which ratio of HRs was derived for late major bleeding versus late MI.

Supplementary Figure 22. Galbraith plot for studies in which ratio of HRs was derived for late major or minor bleeding versus late MI.

Supplementary Figure 23. Galbraith plot for studies in which ratio of HRs was derived for the composite of late major and major or minor bleeding versus late MI.

Supplementary Figure 24. Galbraith plot for studies in which ratio of HRs was derived for late minor bleeding versus late MI.

Supplementary Table 1. Bleeding definitions across studies.

Supplementary Table 2. Contribution of each study to the analysis of bleeding according to the timing and severity of bleeding.

Supplementary Table 3. Comparison across major bleeding definitions.

Supplementary Table 4. Covariates used for adjusted hazard ratios.

Supplementary Table 5A. Definitions of myocardial infarction for the analysis of early events.

Supplementary Table 5B. Definitions of myocardial infarction for the analysis of late events.

Supplementary Table 5C. Definitions of myocardial infarction for the analysis of the composite of early or late events.

Supplementary Table 6. Procedural characteristics of the studies.

Supplementary Table 7. Bleeding and myocardial infarction events reported across studies.

Supplementary Table 8. Sensitivity analysis according to median publication year of the included studies (before vs after 2015).

Supplementary Table 9. Sensitivity analysis for randomised versus non-randomised studies.

Supplementary Table 10. Newcastle-Ottawa scale.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01197

Supplementary data

Supplementary Appendix 1. Search strategy.

Ovid Medline			Embase		
#	Searches	Results	#	Searches	Results
1	exp Hemorrhage/	315,779	1	bleed*:ab,ti AND [embase]/lim	279,475
2	haemor*.mp.	52,961	2	hemor*:ab,ti AND [embase]/lim	228,970
3	hemor*.mp.	346,266	3	haemor*:ab,ti AND [embase]/lim	62,917
4	bleed*.mp.	195,940	4	1 or 2 or 3	518,161
5	1 or 2 or 3 or 4	573,225	5	'myocardial infarction':ab,ti AND [embase]/lim	226,132
6	exp Myocardial Infarction/	168,577	6	infarc*:ab,ti AND [embase]/lim	338,842
7	AMI.mp.	17,961	7	ischem*:ab,ti AND [embase]/lim	409,183
8	infarct*.mp.	323,236	8	5 or 6 or 7	662,597
9	ischem*.mp.	360,754	9	‘percutaneous coronary intervention':ab,ti AND [embase]/lim	47,325
10	6 or 7 or 8 or 9	613,418	10	'coronary artery disease':ab,ti AND [embase]/lim	114,891
11	exp Percutaneous Coronary Intervention/	49,573	11	'angioplasty':ab,ti AND [embase]/lim	51,458
12	exp Angioplasty, Balloon, Coronary/	34,885	12	9 or 10 or 11	198,645
13	exp Coronary Artery Disease/	57,101	13	4 and 8 and 12	8,363
14	PCI.mp.	24,239			
15	11 or 12 or 13 or 14	107,732			
16	5 and 10 and 15	4,320			

Supplementary Appendix 2. Methods.

To compare the relative effects of bleeding and myocardial infarction (MI) on the risk of mortality, we used the ratio of hazard ratios as principal risk estimate:

$$Ratio\ of\ HR_{bleeding\ vs.\ MI} = ex[\ln(HR_{bleeding}) - \ln(HR_{MI})]$$

To derive the 95% CI of the ratio of the two HRs and its standard error (SE), we used the following formulas:

$$SE_{HR_{bleeding}} = \frac{Width\ of\ CI_{bleedi}}{2x1.96} = \frac{ln(Upper\ 95\%CI_{bleeding}) - ln(Lower 95\%CI_{bleeding})}{2x1.96}$$

$$SE_{HR_{MI}} = \frac{Width\ of\ CI_{MI}}{2x1.96} = \frac{(Upper\ 95\%CI_{MI}) - ln(Lower 95\%CI_{MI})}{2x1.96}$$

$$SE_{ratio\ of\ HR} = \sqrt[2]{SE^2_{HR_{bleeding}} + SE^2_{HR_{MI}}}$$

$$95\%CI_{Ratio\ of\ HR} = ex[\ln(HR_{bleeding}) - \ln(HR_{MI})] \pm (1.96 \times SE_{ratio\ of\ HR})$$

For the definition of major bleeding, we aligned definitions according to other scales to BARC type 3 bleeding. Therefore, we considered the following as major bleeding: BARC 3, minor or major TIMI, moderate or severe GUSTO, major bleeding according to the ACUITY criteria, and major bleeding according to the STEEPLE criteria.

Supplementary Figure legends

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Supplementary Figure 7. Galbraith plot for studies reporting HRs of early major bleeding and for early major or minor bleeding.

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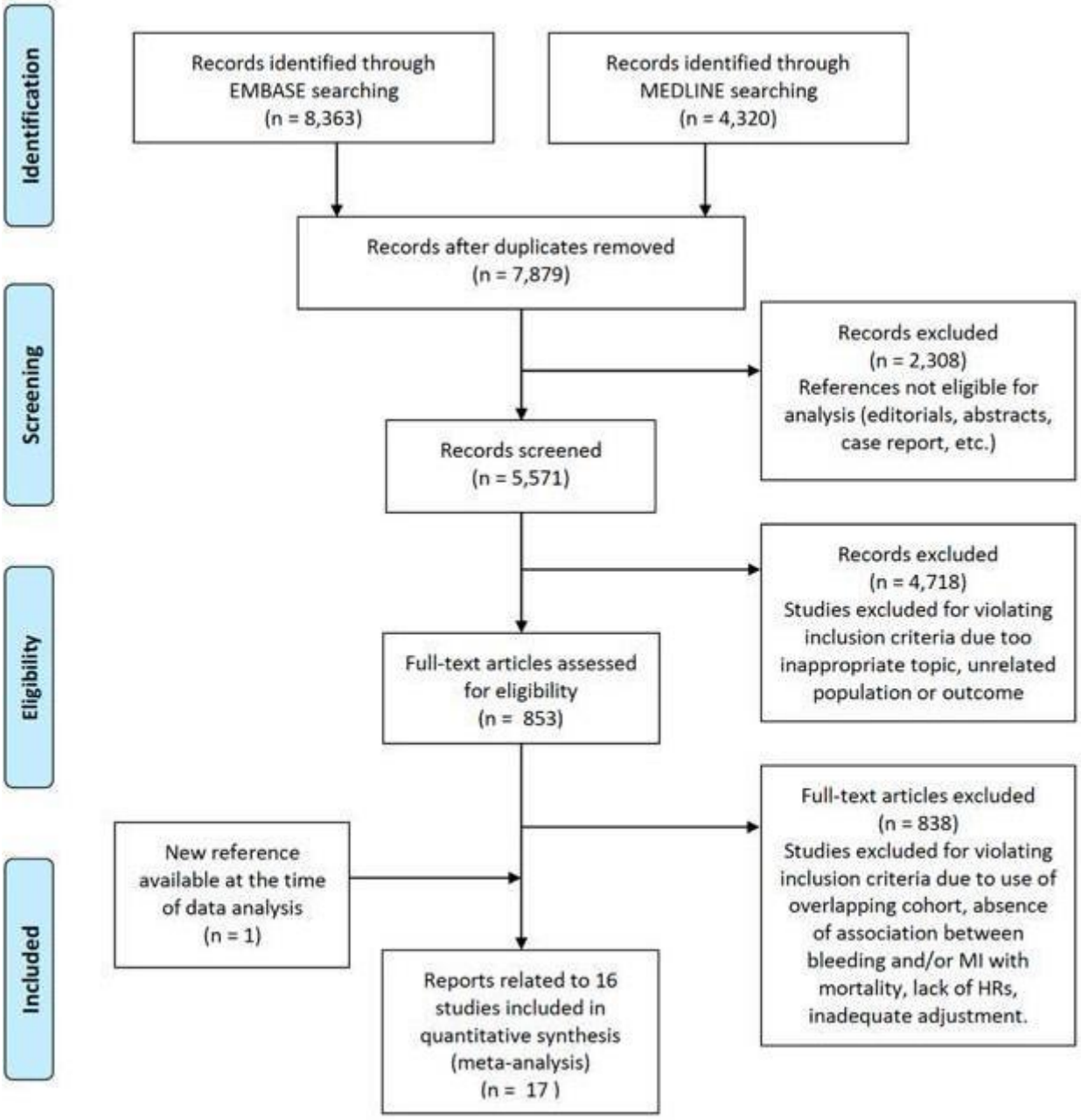
Supplementary Figure 24. Galbraith plot for studies in which ratio of HRs was derived for late minor bleeding versus late MI.

Supplementary Figure 1



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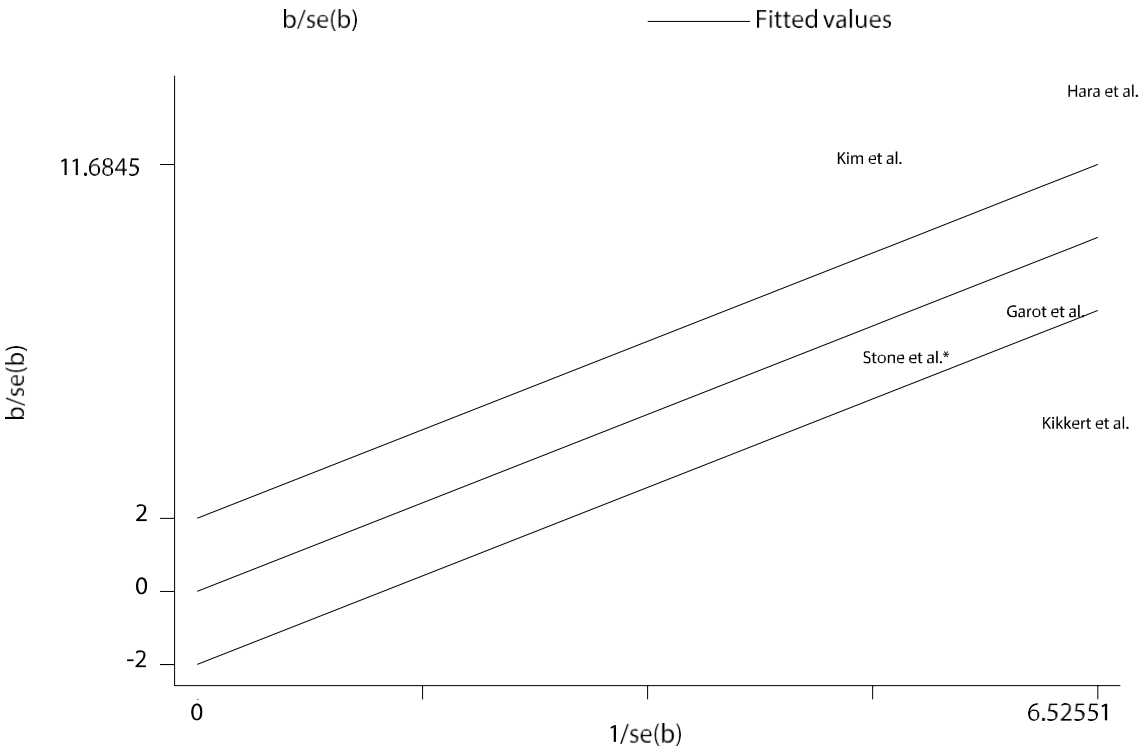
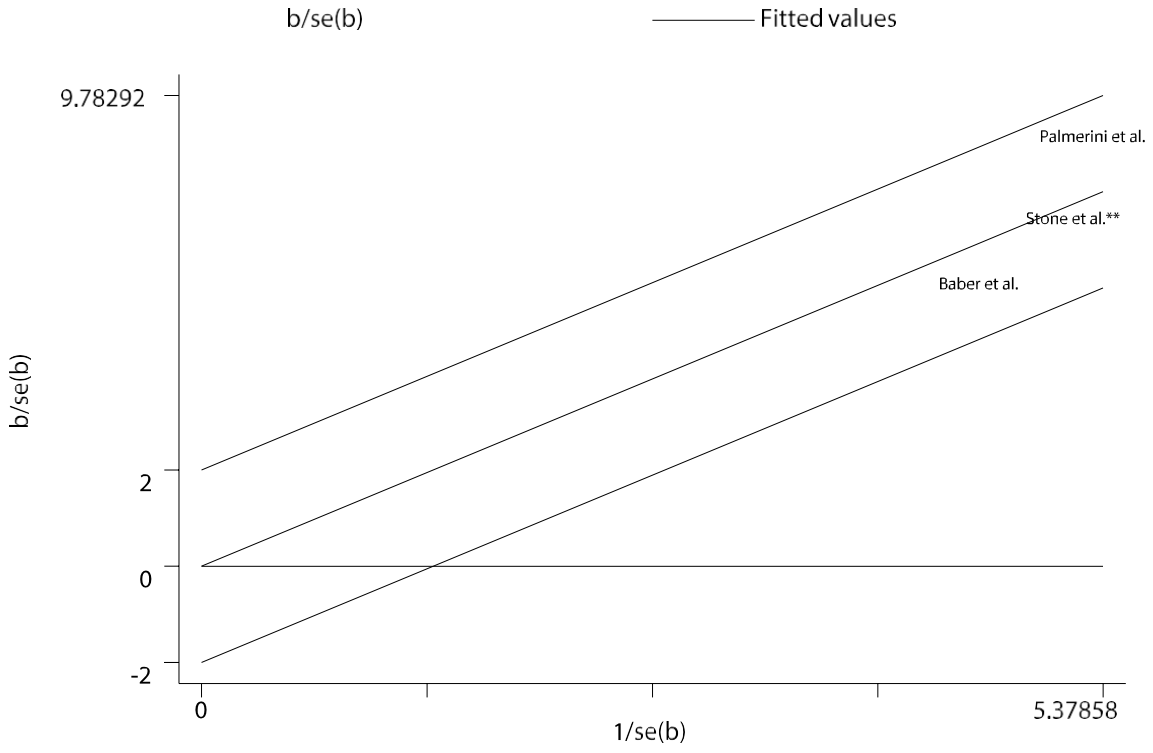
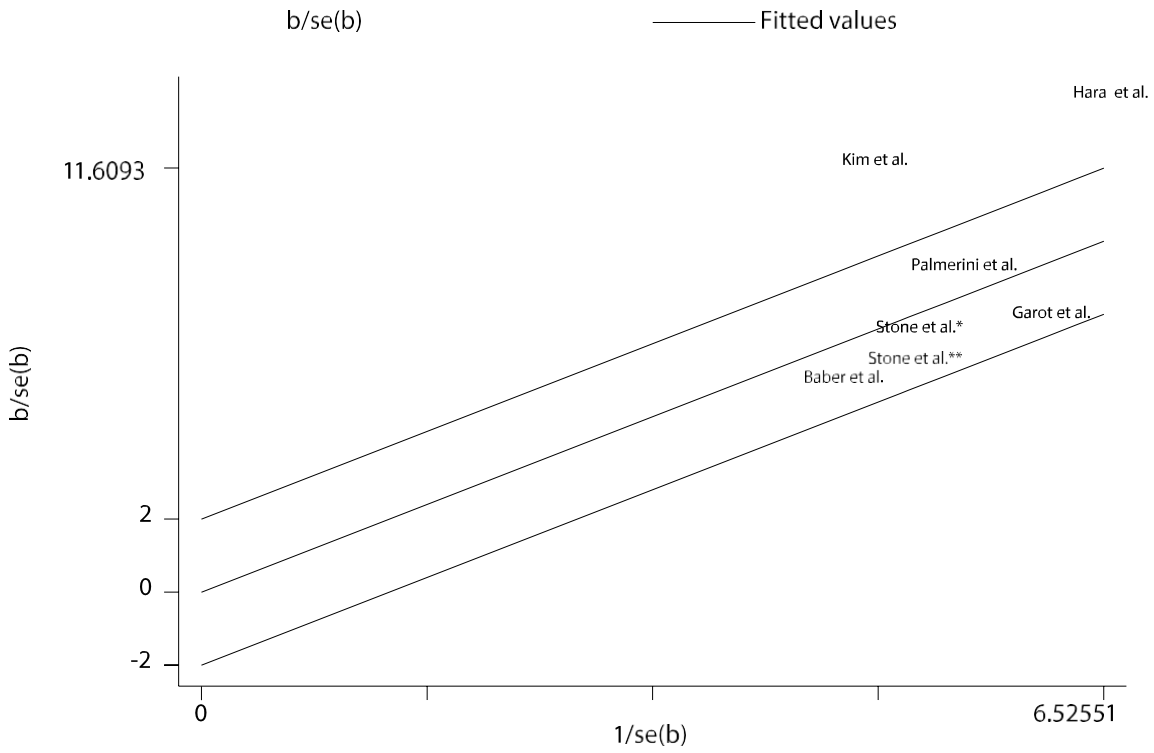
Supplementary Figure 2



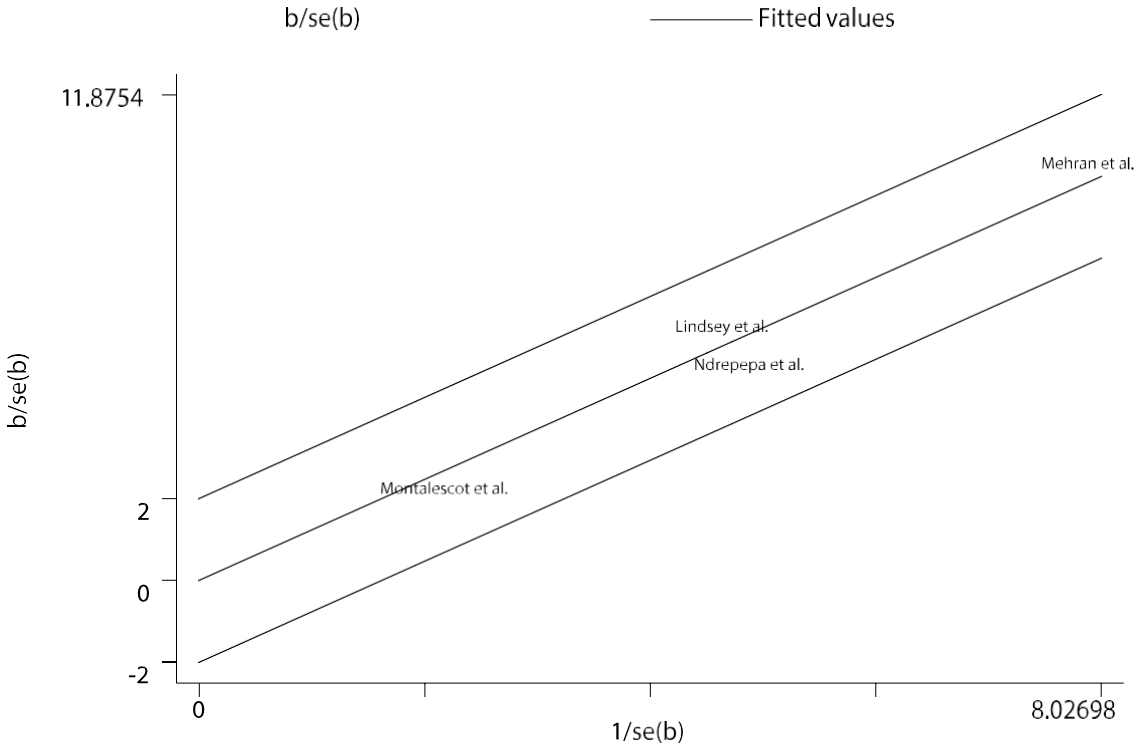
Supplementary Figure 3



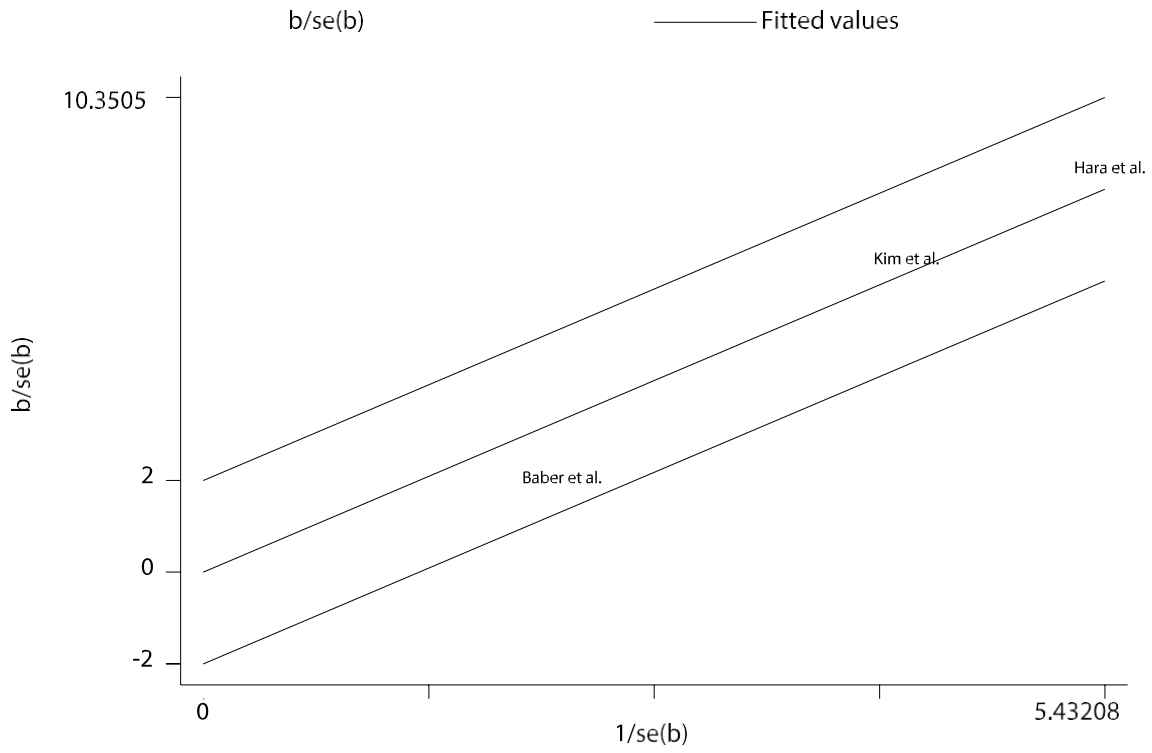
Supplementary Figure 4



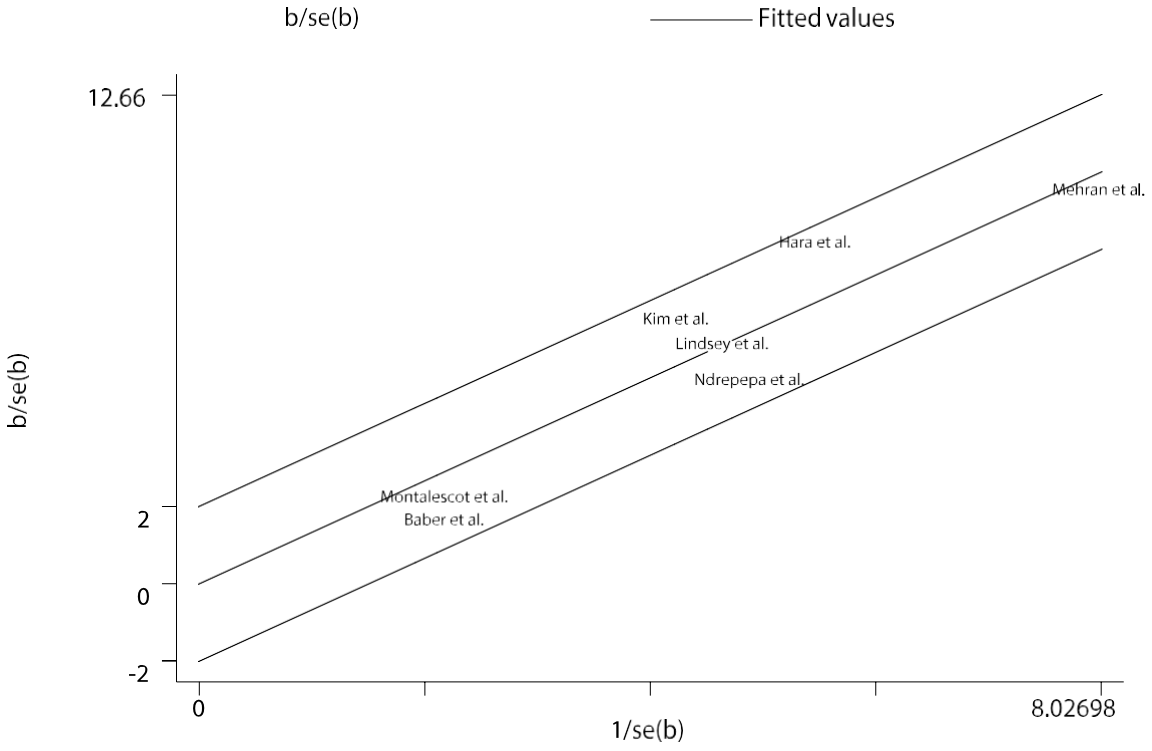
Supplementary Figure 5



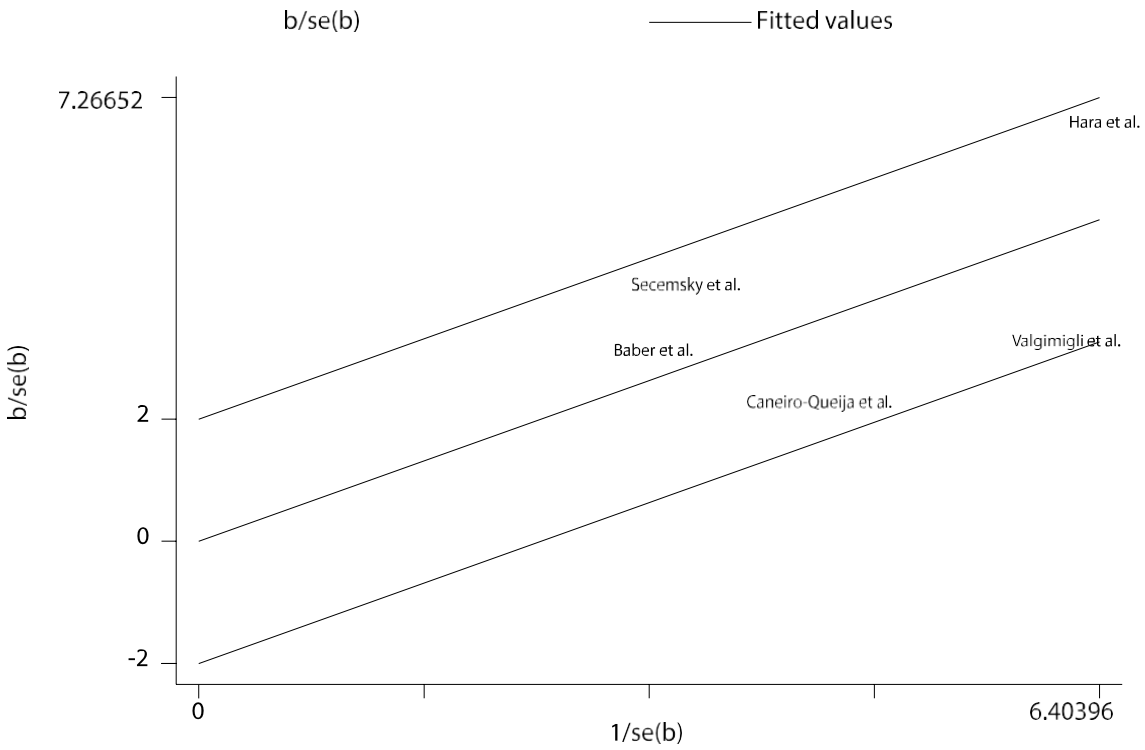
Supplementary Figure 6



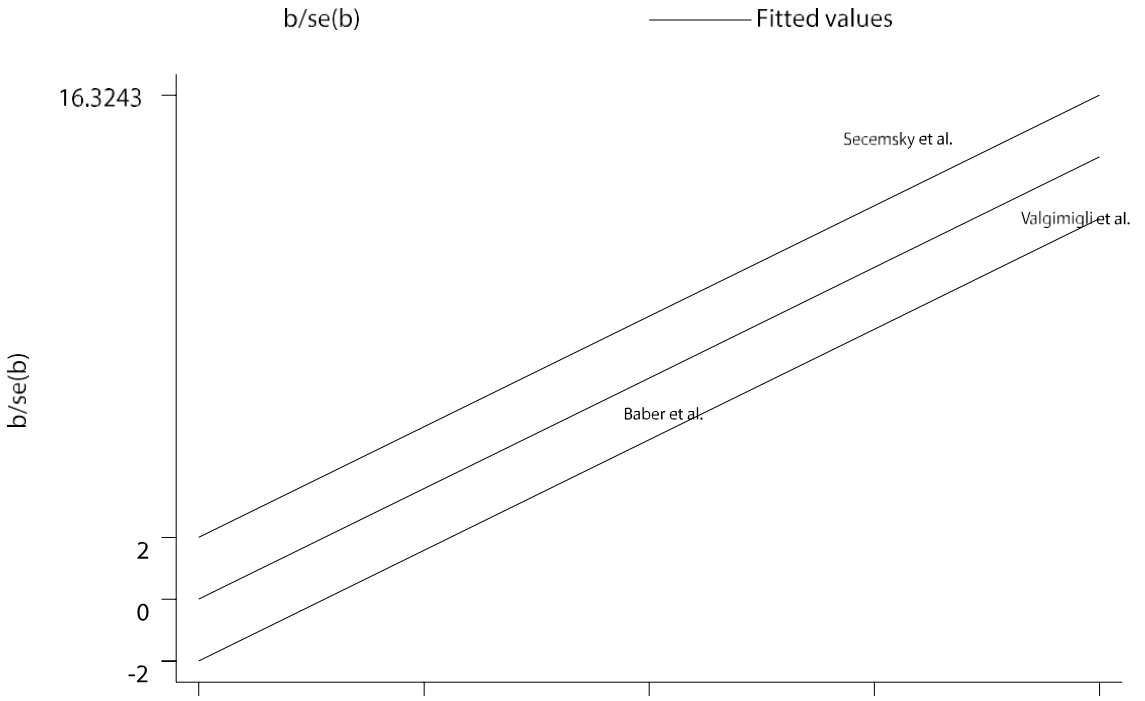
Supplementary Figure 7



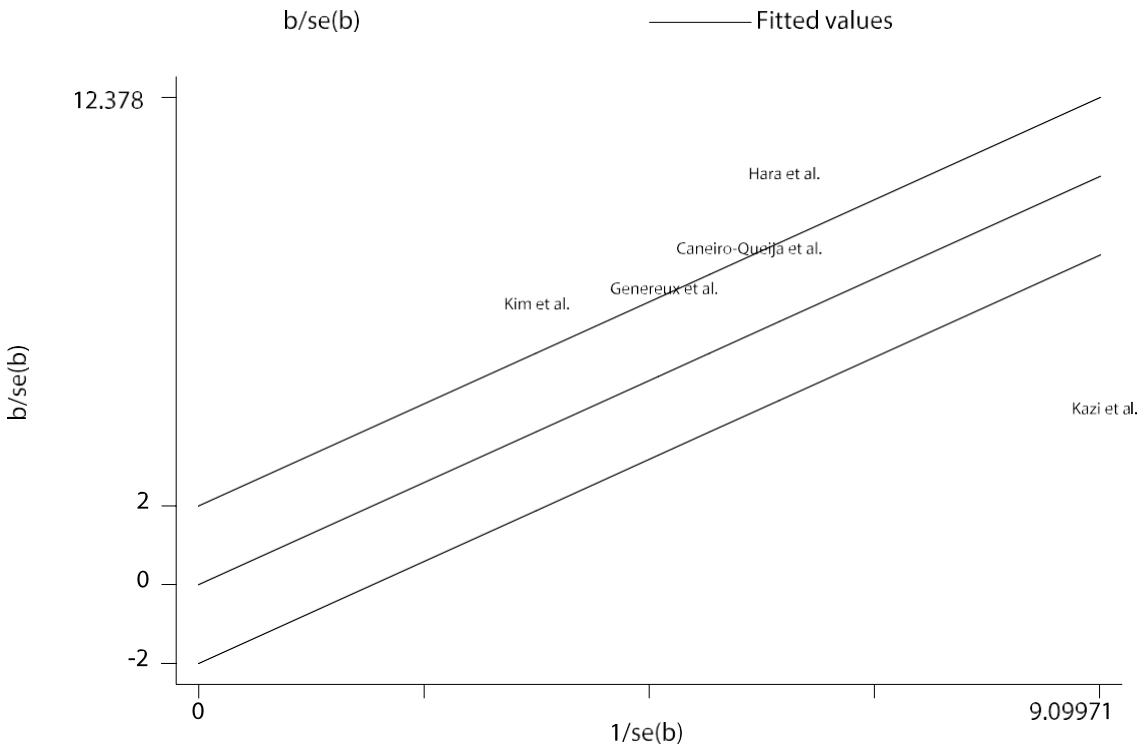
Supplementary Figure 8



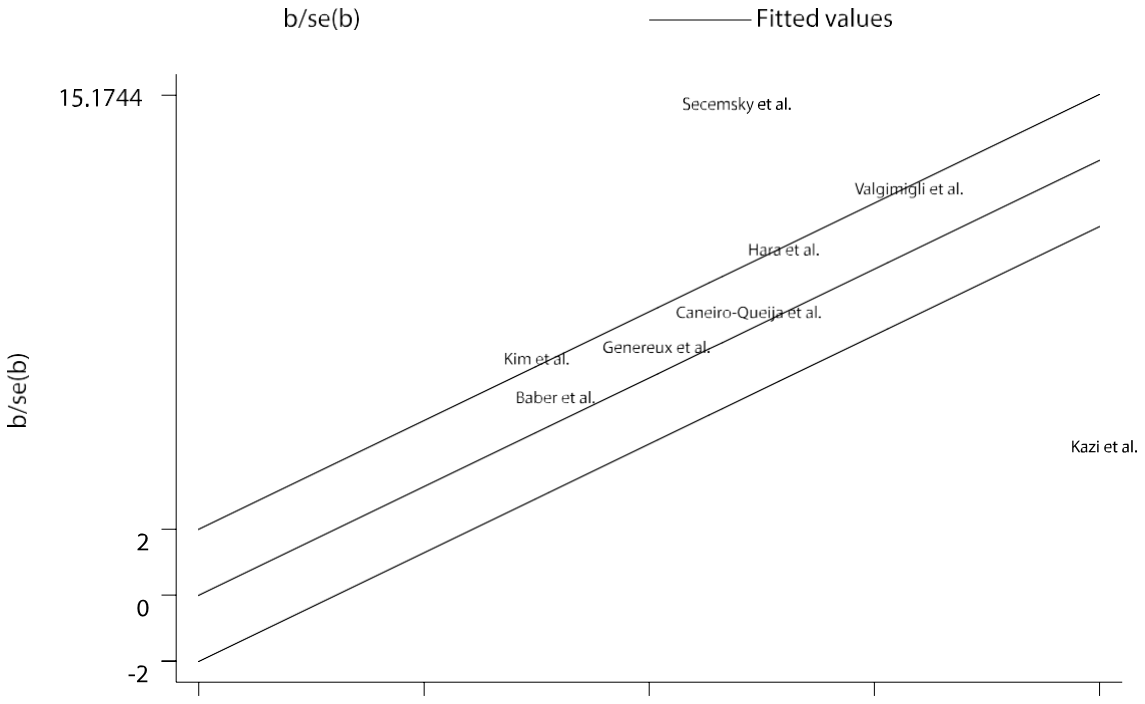
Supplementary Figure 9



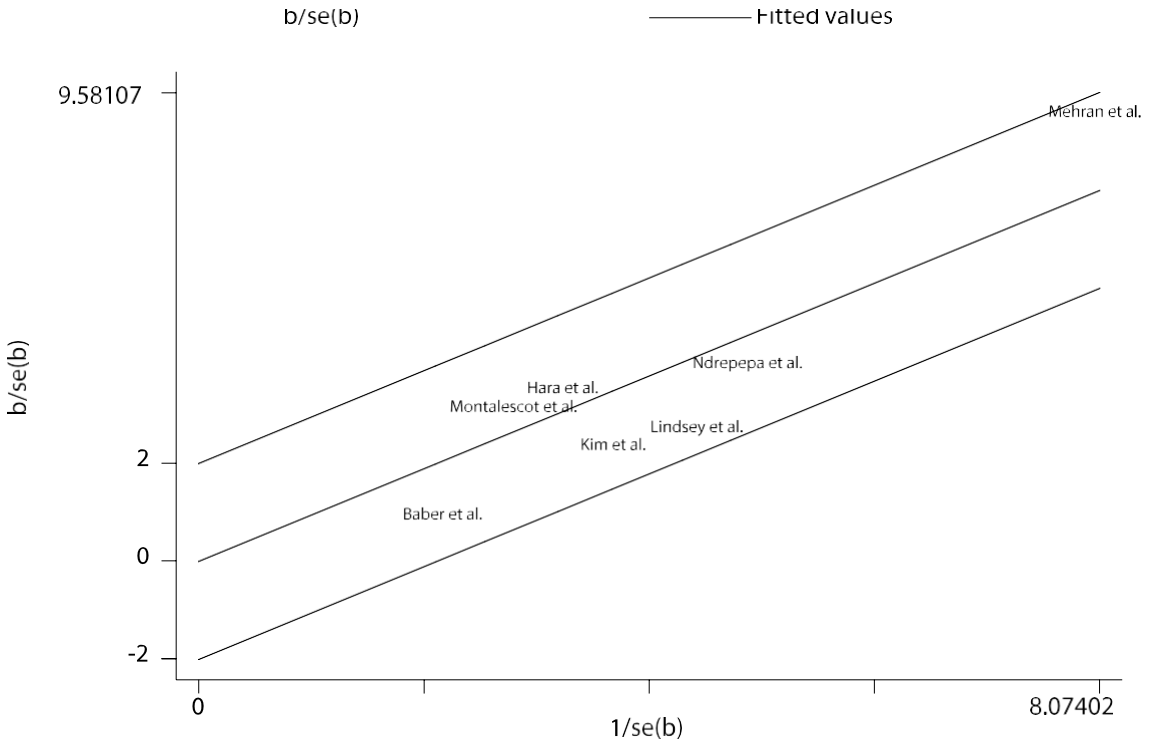
Supplementary Figure 10



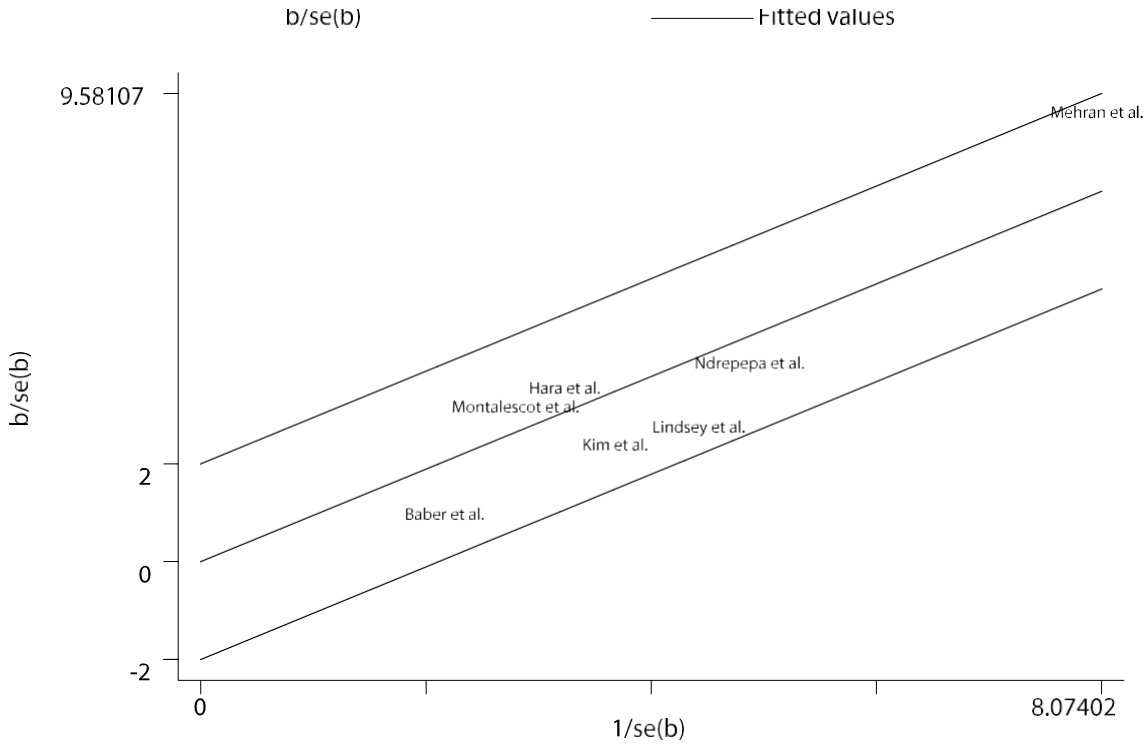
Supplementary Figure 11



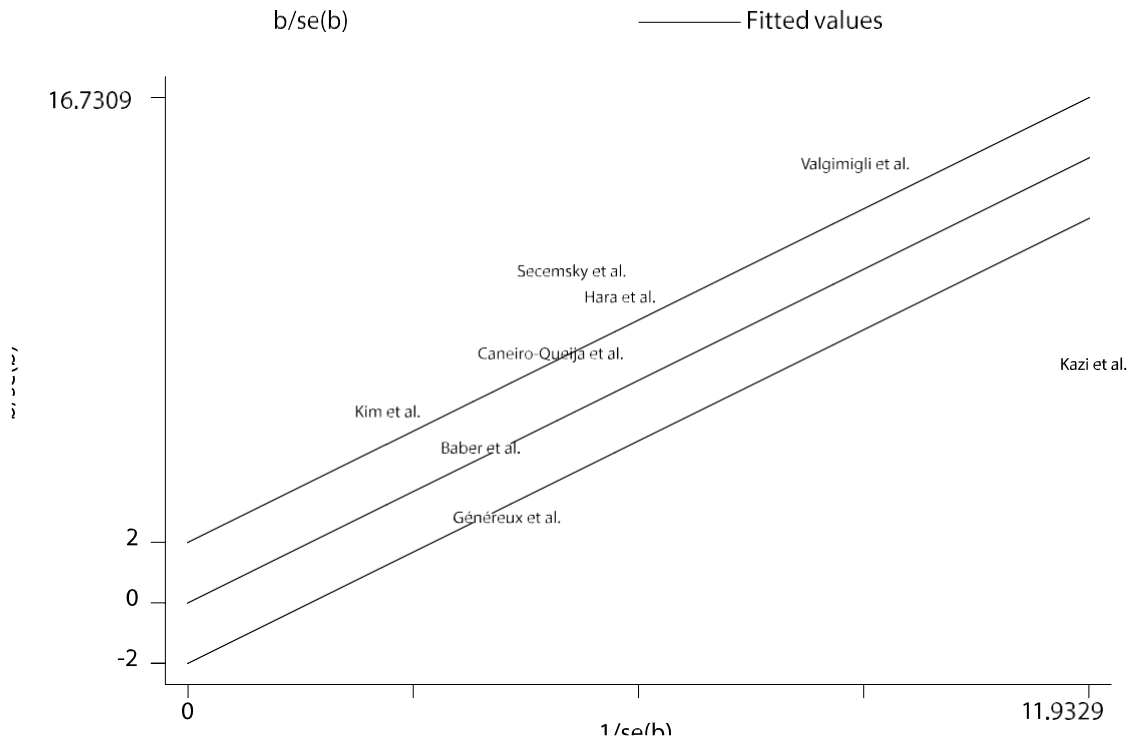
Supplementary Figure 12



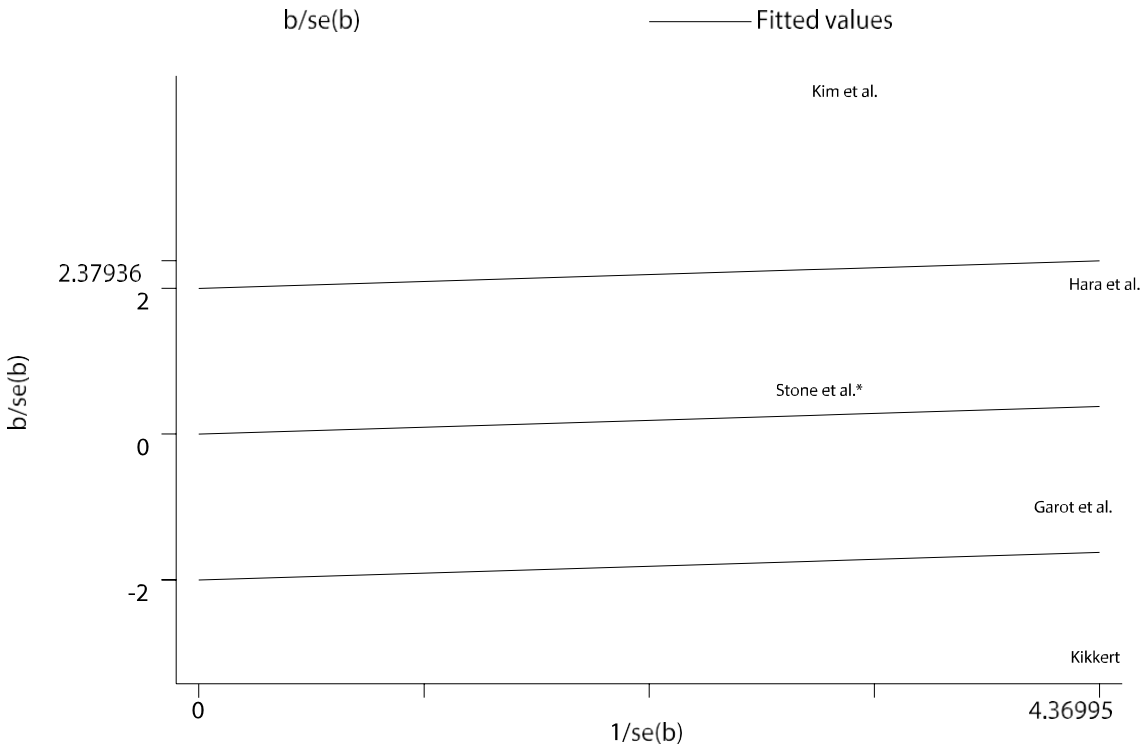
Supplementary Figure 13



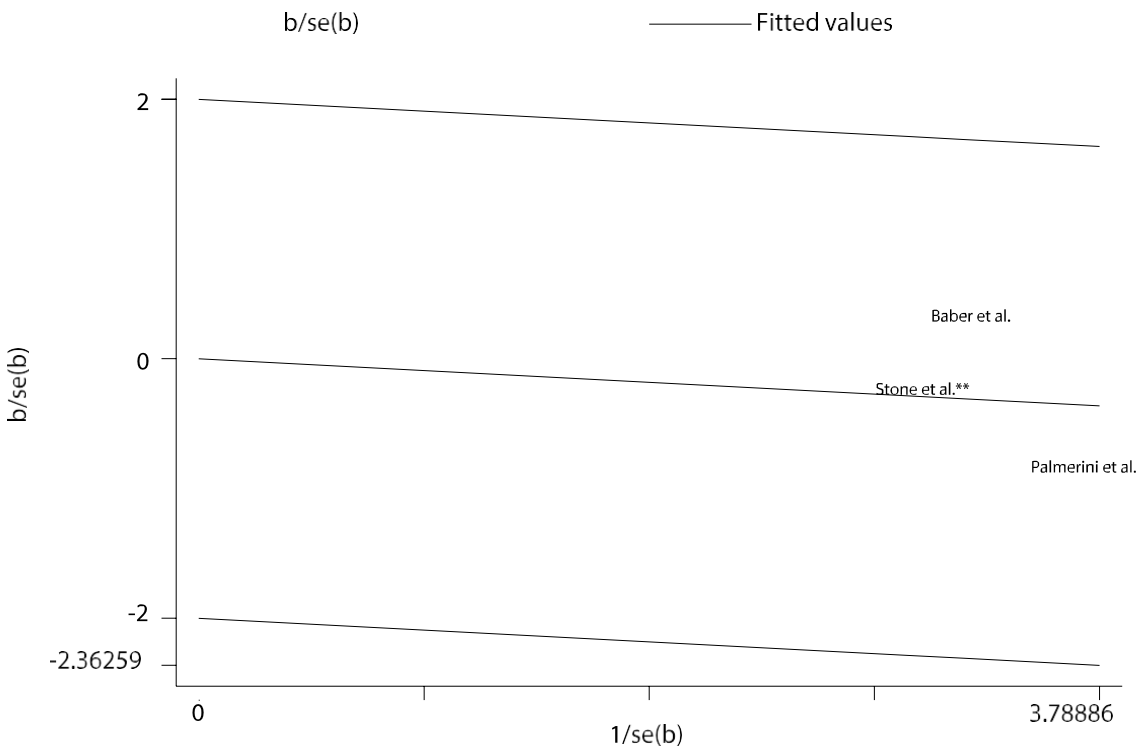
Supplementary Figure 14



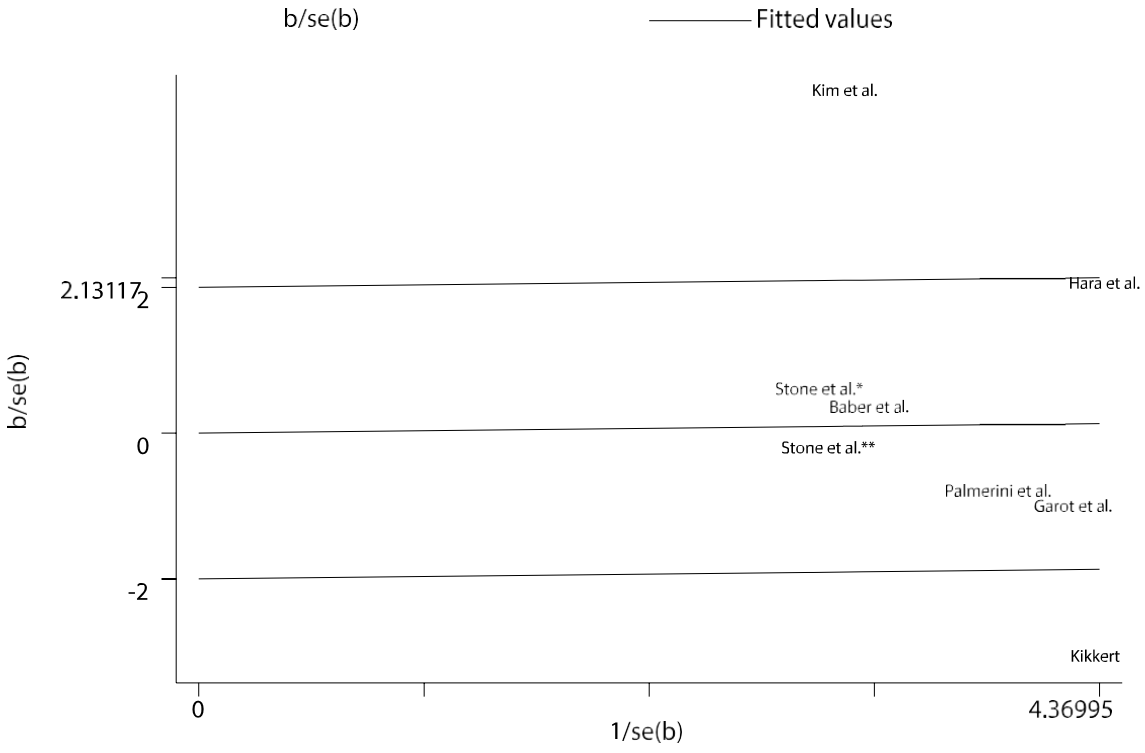
Supplementary Figure 15



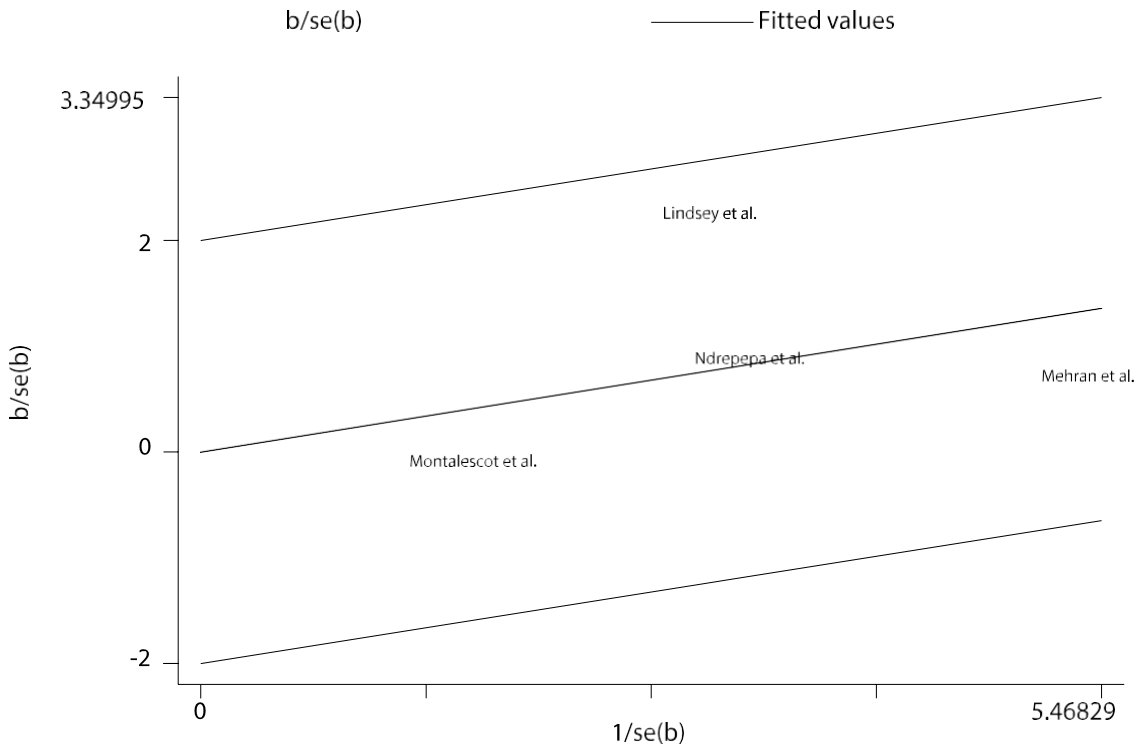
Supplementary Figure 16



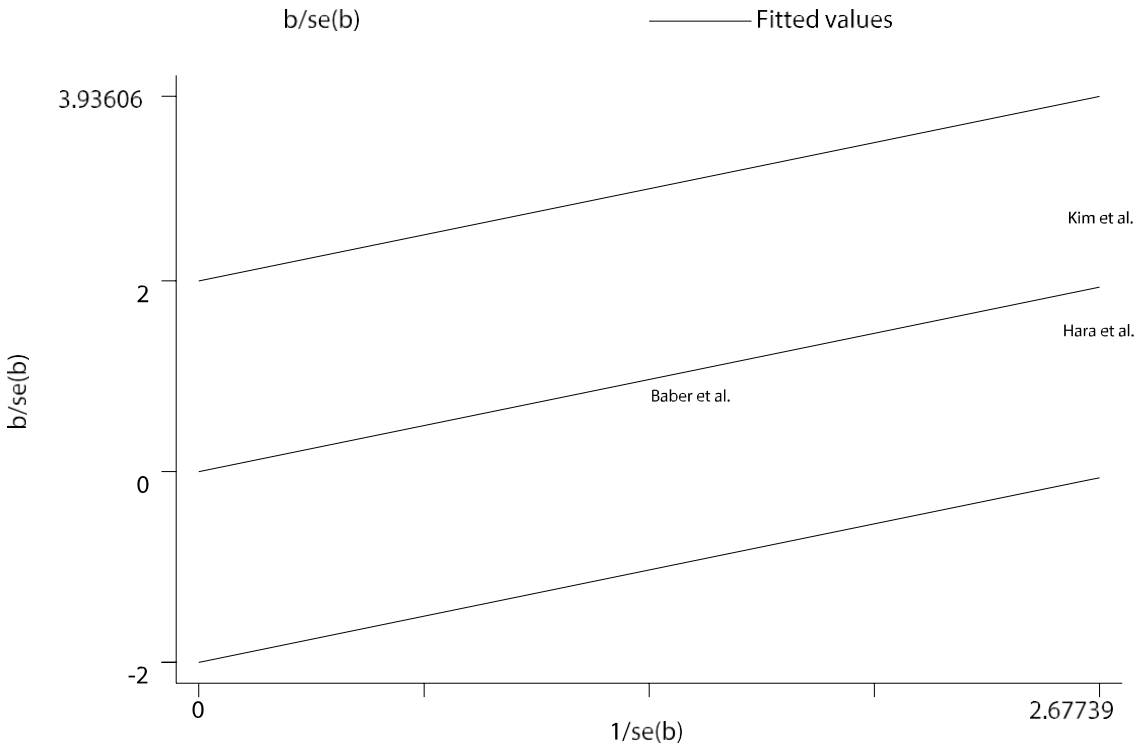
Supplementary Figure 17



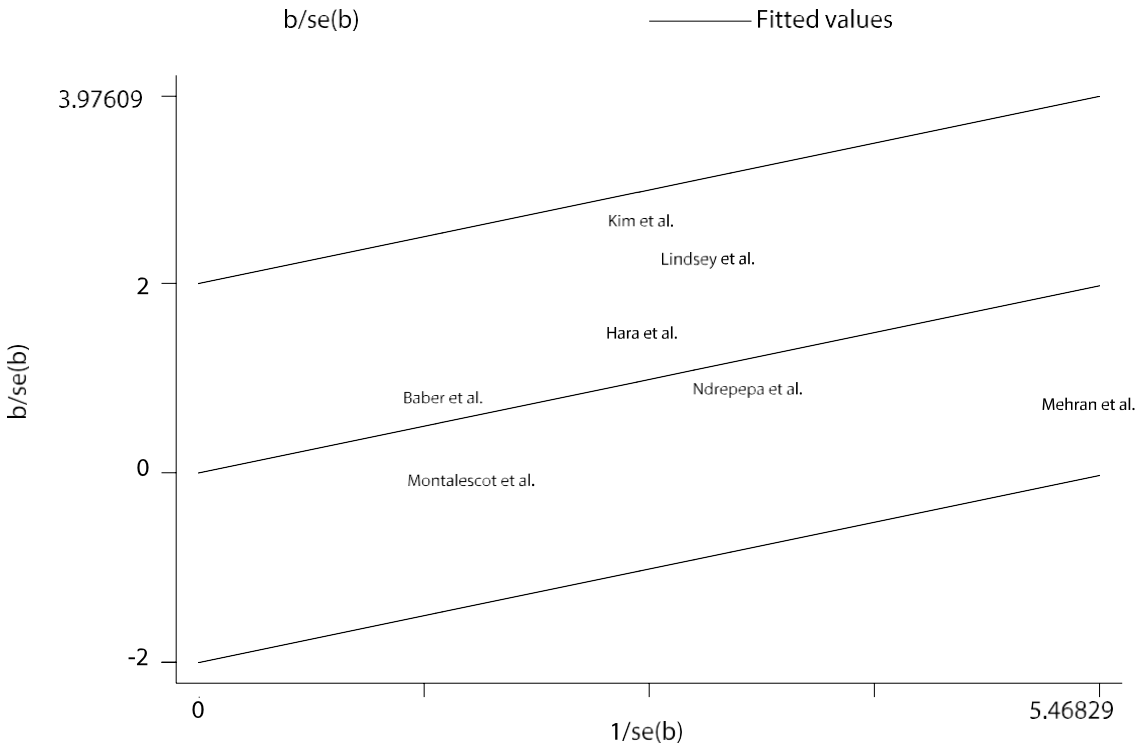
Supplementary Figure 18



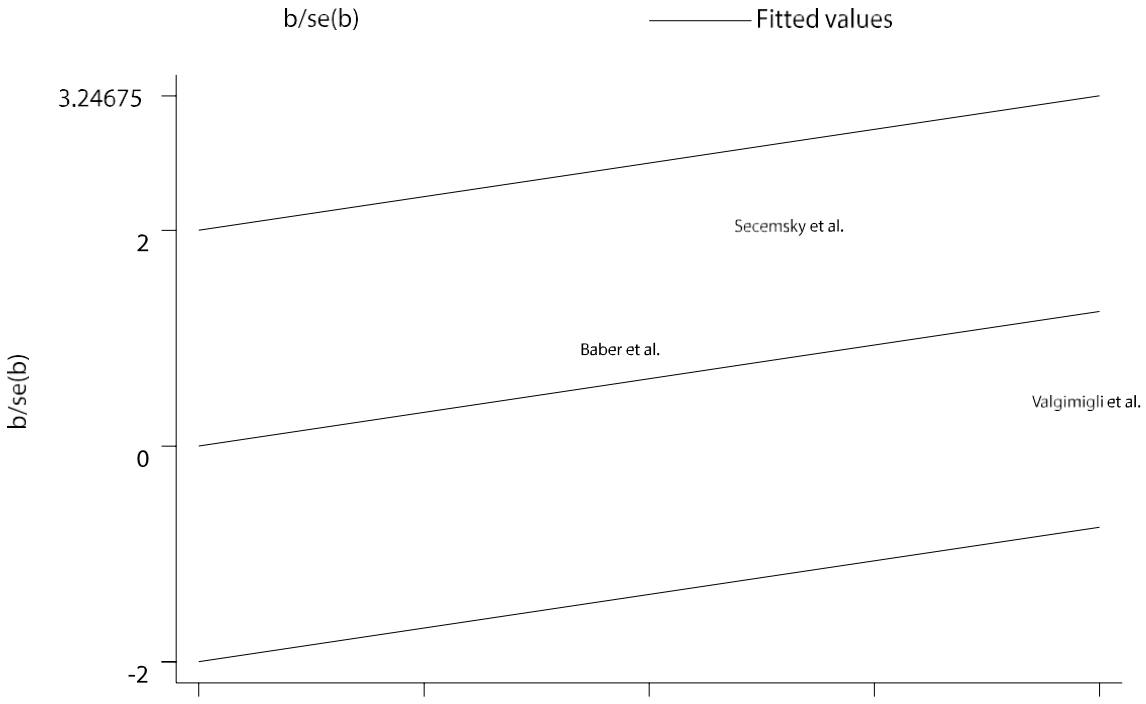
Supplementary Figure 19



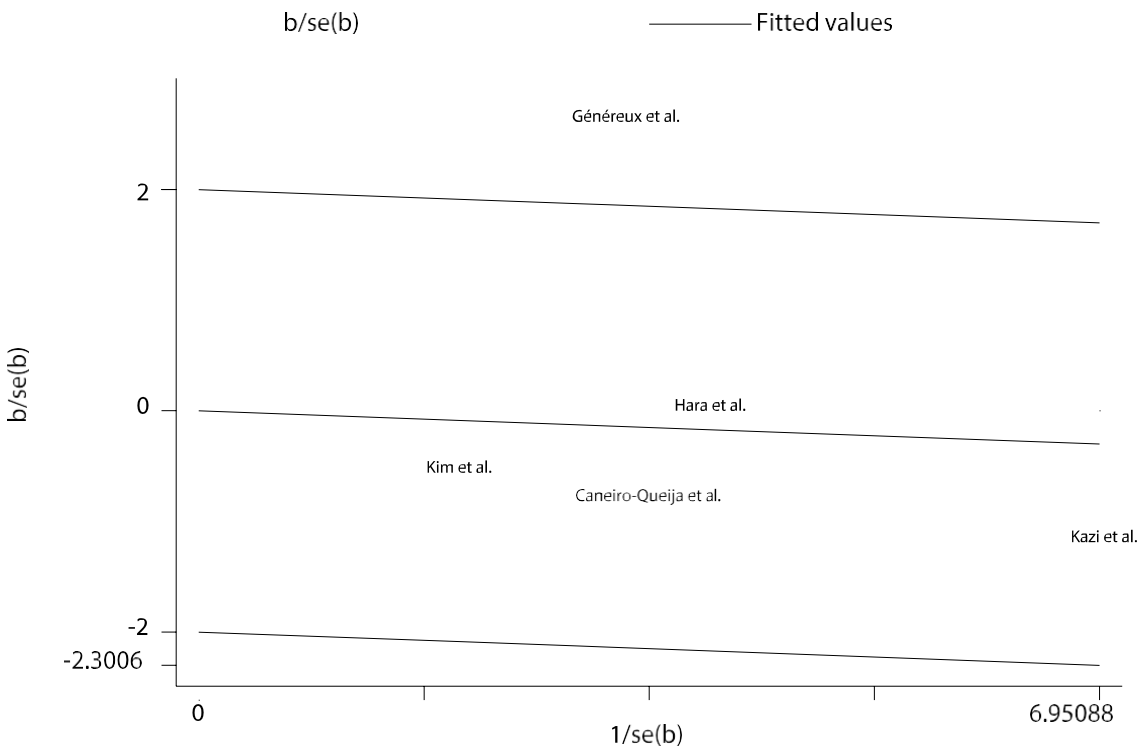
Supplementary Figure 20



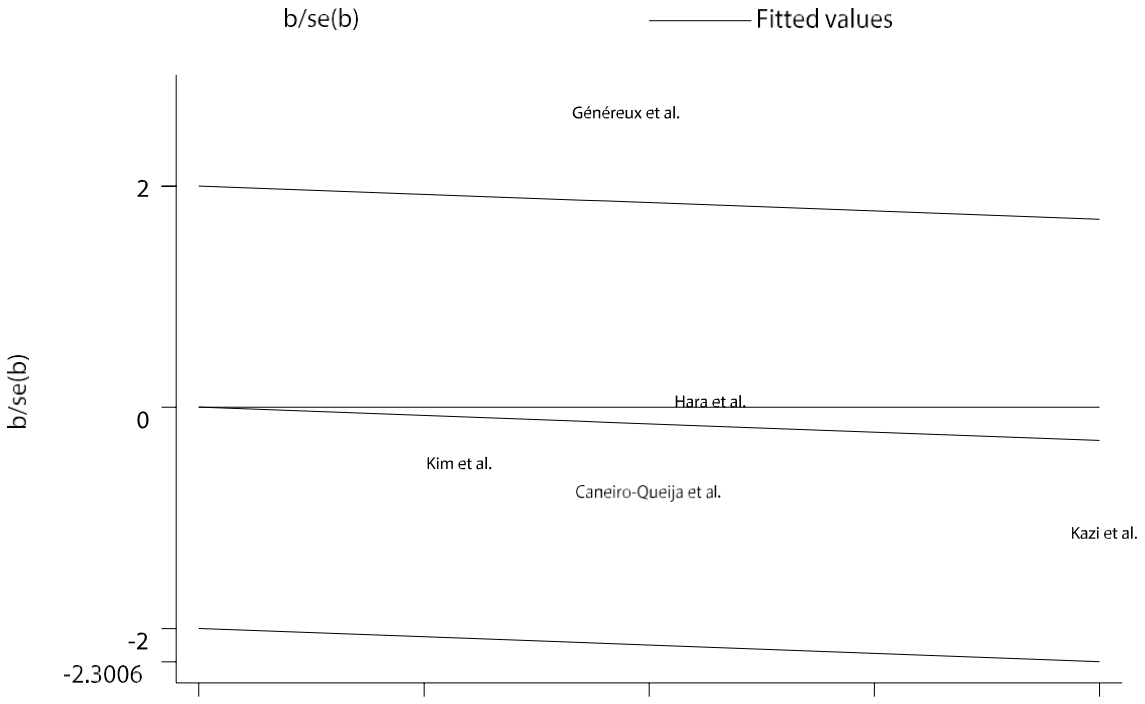
Supplementary Figure 21



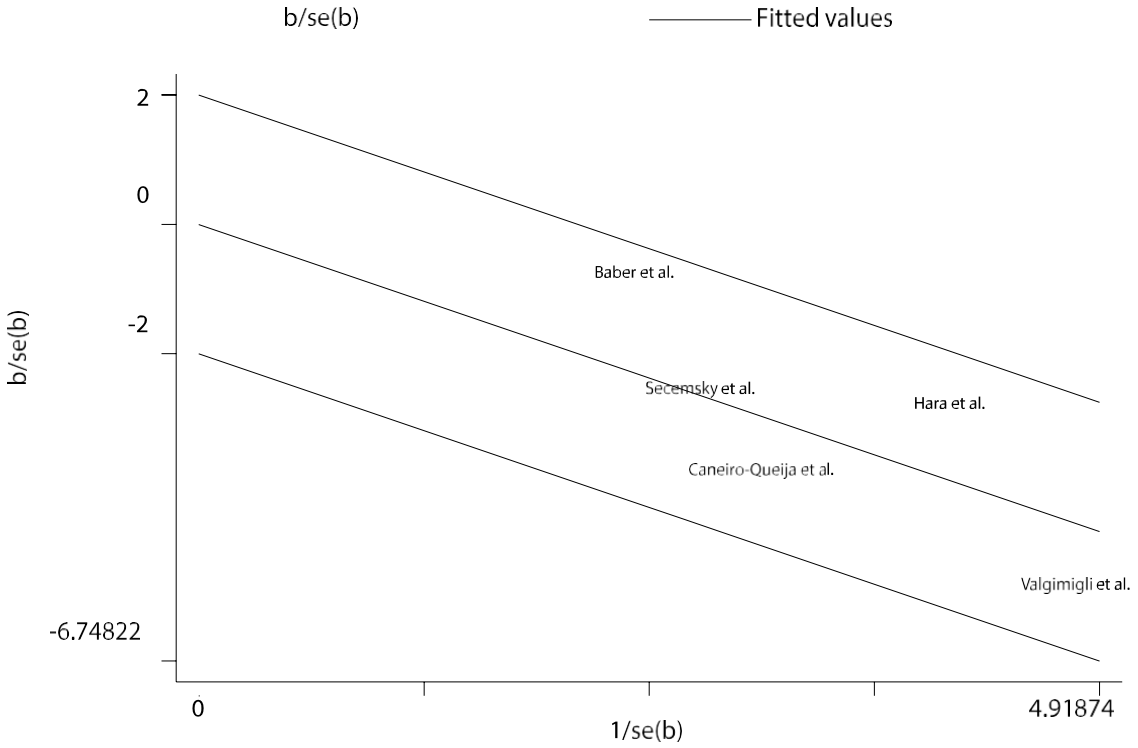
Supplementary Figure 22



Supplementary Figure 23



Supplementary Figure 24



Supplementary Table 1. Bleeding definitions across studies.

Study, year	Bleeding definitions
Ndrepepa et al. 2008	TIMI criteria
Mehran et al. 2009	ACUITY criteria
Montalescot et al. 2009	STEEPLE criteria
Lindsey et al. 2009	TIMI criteria
Kim et al. 2011	STEEPLE criteria
Kikkert et al. 2013	GUSTO criteria
Stone et al. 2014	ACUITY criteria
Kazi et al. 2015	International Classification of Diseases-Ninth Edition code
Genereux et al. 2015 and Stone et al. 2013	Bleeding included any bleeding according to TIMI, GUSTO, ACUITY criteria, and any post-discharge bleeding requiring medical attention
Baber et al. 2016	BARC criteria
Garot et al. 2017	BARC criteria
Valgimigli et al. 2017	BARC criteria
Palmerini et al. 2017	Mixed studies definitions
Secemsky et al. 2017	BARC criteria
Caneiro-Queija et al. 2018	BARC criteria
Hara et al. 2020	BARC criteria

BARC criteria

Type 0: No bleeding.

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalisation, or treatment by a healthcare professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a healthcare professional.

Type 2: Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria:

1. Requiring non-surgical, medical intervention by a healthcare professional.
2. Leading to hospitalisation of increased level of care.
3. Prompting evaluation.

Type 3a: Overt bleeding plus haemoglobin drop of 3 to <5** g/dL (provided haemoglobin drop is related to bleed). Any transfusion with overt bleeding.

Type 3b: Overt bleeding plus haemoglobin drop ≥5** g/dL (provided haemoglobin drop is related to bleed). Cardiac tamponade. Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / haemorrhoid). Bleeding requiring intravenous vasoactive agents.

Type 3c: Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal). Subcategories: confirmed by autopsy or imaging or LP. Intra-ocular bleed compromising vision.

Type 4: CABG-related bleeding.

1. Perioperative intracranial bleeding within 48 hours.
2. Reoperation following closure of sternotomy for the purpose of controlling bleeding.
3. Transfusion of ≥5 units of whole blood or packed red blood cells within 48-hour period.
4. Chest tube output ≥2 L within a 24-hour period.

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious.

Type 5b: Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation.

TIMI criteria

Major. Any intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI). Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL (or, when a haemoglobin value was not available, an absolute drop in the haematocrit of at least 15%). Fatal bleeding (bleeding that directly results in death within 7 days).

Minor. Clinically overt (including imaging), resulting in haemoglobin drop of 3 to <5 g/dL (or, when a haemoglobin value was not available, a fall in the haematocrit of 9 percentage points to <15 percentage points).

Other non-major or minor. Any overt bleeding event that does not meet the criteria above.

Bleeding in the setting of CABG. Fatal bleeding (bleeding that directly results in death). Perioperative intracranial bleeding. Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding. Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products. Chest tube output >2 L within a 24-h period.

GUSTO criteria

Severe or life-threatening. Intracerebral haemorrhage. Resulting in substantial haemodynamic compromise requiring treatment.
Moderate. Requiring blood transfusion but not resulting in haemodynamic compromise.
Mild. Bleeding that does not meet above criteria.

ACUITY criteria

Major. Intracranial or intraocular bleeding, access-site haemorrhage requiring intervention, ≥5 cm diameter haematoma, retroperitoneal bleeding, reduction in haemoglobin of ≥4 g/dL without an overt source of bleeding or ≥3 g/dL with an overt bleeding source, reoperation for bleeding or use of any blood product transfusion.

STEEPLE criteria

Major. Fatal bleeding. Retroperitoneal, intracranial, or intraocular bleeding. Bleeding that caused haemodynamic compromise requiring specific treatment. Bleeding that required intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event. Clinically overt bleeding. Requirement for any transfusion of ≥1 U packed red cells or whole blood. Clinically overt bleeding causing a decrease in haemoglobin of ≥3 g/dl (or if haemoglobin level not available, a ≥10% decrease in haematocrit).
Minor. Gross haematuria not associated with trauma. Epistaxis that was prolonged, repeated, or required plugging or intervention. Gastrointestinal haemorrhage. Haemoptysis. Subconjunctival haemorrhage. Haematoma >5 cm or leading to prolonged or new hospital stay. Clinically overt bleeding causing a decrease in haemoglobin of 2 to 3 g/dl. Uncontrolled bleeding requiring protamine sulfate administration.

Supplementary Table 2. Contribution of each study to the analysis of bleeding according to the timing and severity of bleeding.

	Early bleeding		Late bleeding			Early or late bleeding		
	Major	Major or minor	Major	Major or minor	Minor	Major	Major or minor	Minor
Ndrepepa et al. 2008	TIMI major or minor	-	-	-	-	-	-	-
Mehran et al. 2009	ACUITY major	-	-	-	-	-	-	-
Montalescot et al. 2009	STEEPLE major	-	-	-	-	-	-	-
Lindsey et al. 2009	TIMI major or minor	-	-	-	-	-	-	-
Kim et al. 2011	-	STEEPLE major or minor	-	STEEPLE major or minor	-	STEEPLE major	-	STEEPLE minor
Kikkert et al. 2013	-	-	-	-	-	TIMI major	-	-
Stone et al. 2014	-	-	-	-	-	ACUITY major	-	-
Kazi et al. 2015	-	-	-	Bleeding, ICD-9	-	-	-	-
Généreux et al. 2015 and Stone et al. 2013	-	-	-	Bleeding, other (major or minor)	-	-	Bleeding, other (major or minor)	-
Baber et al. 2016	-	BARC 2 or 3	BARC 3	-	BARC 2	BARC 3 or 5	-	-
Garot et al. 2017	-	-	-	-	-	BARC 3 or 5	-	-

Valgimigli et al. 2017	-	-	BARC 3	-	BARC 2	-	-	-
Palmerini et al. 2017	-	-	-	-	-	-	Bleeding, other (major or minor)	-
Secemsky et al. 2017	-	-	BARC 3 or 5	-	BARC 2	-	-	-
Caneiro-Queija et al. 2018	-	-	-	BARC 2 or 3	BARC 2	-	-	-
Hara et al. 2020	-	BARC 2, 3 or 5	-	BARC 2, 3 or 5	-	BARC 3	-	BARC 2

Supplementary Table 3. Comparison across major bleeding definitions.

		BARC 3	BARC 5	BARC 3 or 5	TIMI major	TIMI minor	GUSTO severe	GUSTO moderate	ACUITY major	STEEPLE major
BARC 3a	Overt bleeding and haemoglobin drop of 3 to 5 g/dL	✓	-	✓	-	✓	-	-	✓	✓
	Overt bleeding + transfusion	✓	-	✓	-	-	-	✓	✓	✓
BARC 3b	Overt bleeding and haemoglobin drop ≥5 g/dL	✓	-	✓	✓	-	-	-	✓	✓
	Cardiac tamponade	✓	-	✓	-	-	-	-	-	-
	Bleeding requiring surgical intervention	✓	-	✓	-	-	✓	-	✓	✓
	Bleeding requiring intravenous vasoactive agents	✓	-	✓	-	-	✓	-	-	✓
BARC 3c	Intracranial haemorrhage	✓	-	✓	✓	-	✓	-	✓	✓
BARC 5	Definite or probable fatal bleeding	-	✓	✓	✓	-	-	-	-	✓
OTHER	Other characteristics	-	-	-	-	-	-	-	Intraocular bleeding; access-site bleeding; ≥5 cm haematoma; retroperitoneal bleeding	Intraocular bleeding; retroperitoneal bleeding

Supplementary Table 4. Covariates used for adjusted hazard ratios.

Study, year	Covariates
Ndrepepa et al. 2008	Age, gender, diabetes, arterial hypertension, hypercholesterolaemia, smoking, prior MI, prior coronary artery bypass surgery, multivessel disease, duration of pre-treatment with clopidogrel, elevated troponin (elevated or not), lesion complexity, left ventricular ejection fraction, baseline creatinine, and abciximab therapy.
Mehran et al. 2009	Age, white blood cell count, diabetes, ST-deviation, left bundle branch block, gender, planned treatment (medical, PCI, CABG), cerebrovascular events, creatinine clearance, haemoglobin, elevated CKMB/troponins, current smoking, previous MI.
Montalescot et al. 2009	Age (≥75 years vs <75 years), sex, smoking status (current smoker vs former smoker or no history of smoking), presence or absence of obesity, diabetes, hypertension, hypercholesterolaemia, renal insufficiency (creatinine clearance, 60 ml or less per minute), peripheral arterial disease, family history of coronary artery disease, unstable angina or myocardial infarction within the previous 7 days, a haemoglobin level at entry of ≤10 g/dl for women or 11 g/dl for men, platelet count at entry of ≤80.000 per mm^3; number of diseased arteries (1 vs 2 or ≥3), use or non-use of enoxaparin, another low-molecular-weight heparin, unfractionated heparin, or a direct thrombin inhibitor within the previous 7 days, use or non-use of warfarin or other vitamin K antagonists within the previous 7 days, sheath size (<7 French vs ≥7 French), use or non-use of glycoprotein IIb/IIIa inhibitors during PCI,use or non-use of other antiplatelet drugs (aspirin or clopidogrel), country, time of randomisation (before November 22, 2004, vs after November 22, 2004) and treatment group.
Lindsey et al. 2009	Age, sex, body mass index, diabetes mellitus, hypertension, hypercholesterolaemia, congestive heart failure, peripheral arterial disease, estimated glomerular filtration rate, prior MI, prior coronary artery bypass grafting, acute coronary syndrome (ACS) at presentation, multivessel PCI, PCI of saphenous vein graft, PCI of proximal left anterior descending coronary artery.
Kim et al. 2011	Age, sex, hypertension, smoking history, diabetes mellitus, chronic renal failure, hypercholesterolaemia, prior history of PCI or coronary artery bypass graft, left ventricular ejection fraction, acute myocardial infarction, multivessel disease, multivessel PCI, multiple DES, use of glycoprotein IIb/IIIa inhibitor, use of warfarin or statin at discharge, baseline haemoglobin and platelet count.
Kikkert et al. 2013	Single vessel disease, multivessel disease without CTO, multivessel disease with CTO, post-procedural TIMI flow in

	IRA, amount of lesions treated, age, baseline thrombocyt count, white blood cell count >11.000/mm^3, anaemia, infarct-related artery, creatinine clearance <60, family history of CAD, history of malignant disease, haemodynamic shock at presentation, IABP, history of stroke or TIA, PCI access site.
Stone et al. 2014	Age, sex, diabetes mellitus, Killip classification, infarct artery, baseline haemoglobin, baseline creatinine clearance, baseline Thrombolysis In Myocardial Infarction flow, randomisation to bivalirudin and DES use.
Kazi et al. 2015	Age, sex, race, Hispanic ethnicity, history of MI or bleed prior to index date, MI or bleed during index hospitalisation or within 7 days after index discharge, time-varying history of smoking, hypertension, diabetes, dyslipidaemia, unstable angina, mitral or aortic valvular disease, stroke or transient ischaemic attack, atrial flutter or fibrillation, heart failure, peripheral arterial disease, dementia, chronic lung disease, hypothyroidism and systemic cancer, time-varying exposure to medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, anti-inflammatory agents, nitrates, digoxin, calcium channel blockers, statins, and diabetes medications), and time-varying estimated glomerular filtration rate.
Genereux et al. 2015 and Stone et al. 2013	Post-discharge bleeding, post-discharge MI, age, male, diabetes, current smoker, previous MI, baseline presentation with ST-segment elevation MI (STEMI) or non-STEMI (vs stable coronary artery disease), hyperlipidaemia, baseline haemoglobin, baseline white blood cells, baseline platelets, creatinine clearance, VerifyNow P2Y12 reactivity units >208, and intravascular ultrasound (IVUS) guidance.
Baber et al. 2016	Age, sex, acute coronary syndrome, stent type, region (United States vs Europe), diabetes mellitus, final TIMI (Thrombolysis In Myocardial Infarction) flow grade <3, current smoking, peripheral vascular disease, triple therapy at discharge, proton pump inhibitor use, body mass index, maximal stent diameter, prior PCI, prior MI, prior coronary artery bypass grafting, prior stroke, chronic kidney disease and haemoglobin.
Garot et al. 2017	Age, gender, BMI, hypertension, hypotension (<100 mmHg at baseline), measured systolic BP at baseline (continuous), active smoker, congestive heart failure, peripheral arterial disease, prior CABG or PCI, prior MI, prior stroke, planned use of OAC post-PCI, non-skin cancer <3 years, creatinine clearance <40 ml/min, plasma creatinine, haemoglobin <11 g/dl or recent TF or admission for bleeding <1 year, haemoglobin, surgery planned <1 year, diabetes, ACS presentation (NSTEMI or STEMI), multivessel disease.

Valgimigli et al. 2017	Age, body mass index, female sex, Killip class 2 at enrolment, history of peripheral arterial disease, prior stroke, prior MI, hypertension, hyperlipidaemia, diabetes mellitus, smoker at enrolment, and systolic blood pressure at enrolment.
Palmerini et al. 2017	Age, sex, diabetes, hypertension, hypercholesterolaemia, prior MI, and clinical presentation.
Secemsky et al. 2017	Age, sex, race, BMI, diabetes, hypertension, tobacco use, stroke or TIA, congestive heart failure, LVEF <30%, renal disease, peripheral arterial disease, prior PCI, prior CABG, prior MI, atrial fibrillation, history of cancer, PCI indication (STEMI, NSTEMI, stable angina, unstable angina, other), randomisation group (placebo, continued thienopyridine therapy), type of stent (non-paclitaxel drug-eluting, paclitaxel eluting, bare metal stent), >1 drug-eluting stent type , no. of stents, minimum stent diameter (<2.5, 2.5-3, >3), total stent length, treated vessel (left main, left anterior descending, right, circumflex, venous graft, arterial graft) and modified ACC/AHA lesion class B2 or C.
Caneiro-Queija et al. 2018	Age ≥65 years, female sex, body mass index (kg/m^2), current smoking, hypertension, dyslipidaemia, diabetes mellitus, prior coronary artery disease, history of congestive heart failure or left ventricular ejection fraction <40%, prior vascular disease, history of bleeding, malignant disease, chronic obstructive pulmonary disease, ACS type, baseline serum creatinine (mg/dL) and haemoglobin values (g/dL), multivessel coronary disease, in-hospital PCI, in-hospital coronary artery bypass graft, treatment at discharge and study centre.
Hara et al. 2020	Age >75, sex, body mass index, impaired renal function, geographic region, hypertension, hypercholesterolaemia, diabetes mellitus, previous MI, previous PCI, previous coronary artery bypass grafting, previous stroke, established peripheral vascular disease, chronic obstructive pulmonary disease, previous bleeding

Supplementary Table 5A. Definitions of myocardial infarction for the analysis of early events.

Study, year	Early MI	
	Timing of MI	MI definition
Ndrepepa et al. 2008	MI occurring within 30 days after PCI	Diagnosis of MI was based on development of new abnormal Q -waves in >2 contiguous precordial or >2 adjacent limb leads or an elevation of creatine kinase myocardial band (CK-MB) (or total CK if CK-MB was not available) >3 times the upper limit of normal. If the pre-PCI CK-MB (or total CK) was higher than the upper limit of normal, both an increase by at least 50% over the previous value and documentation that CK-MB (or total CK) had been decreasing before the suspected MI was necessary. If falling enzyme levels were not documented before the procedure, recurrent anginal symptoms or new electrocardiographic changes compatible with MI and a CK-MB elevation >50% above the peak level before randomisation for patients was required. In patients undergoing coronary bypass surgery, a CK-MB >10 times the upper limit of normal for patients was required to make a diagnosis of procedural MI.
Mehran et al. 2009	MI occurring within 30 days after PCI	**ACUITY criteria**. The definition of MI took into consideration the presence or absence of non-ST-elevation MI at baseline, its time of occurrence, and its association with PCI, CABG, or medical treatment. In patients with unstable angina (without non-ST-elevation MI) before angiography or in a medical treatment, MI was defined as any elevation of troponin or creatinine phosphokinase-MB (CPK-MB) (or CPK) greater than the upper limits of normal (ULN). In patients with non-ST-elevation MI before angiography or in a medical treatment, the diagnosis of MI required: (i) recurrent chest pain lasting ≥30 min or new electrocardiographic changes consistent with MI, and the next troponin or CPK-MB (or CPK) level measured 8–12 h after the event be elevated by at least 50% above the previous level if the peak troponin or CPK-MB (or CPK) had not yet been reached, (ii) a new elevation of troponin or CPK-MB (or CPK) >ULN if the troponin, CPK-MB or CPK level had returned to <ULN, (iii) a rise by >50% above the previous nadir level if the troponin or CPK-MB (or CPK) level had not returned to ULN. In patients treated with PCI, MI was defined as: (i) any CPK-MB (or CPK) ≥3 x ULN within 24 h after PCI that was also increased at least 50% over the most recent pre-PCI levels, or new, significant (³0.04 s) Q-waves in two or more contiguous electrocardiographic leads with CPK-MB (or CPK) .ULN if the elevated CPK-MB or CPK levels were falling or normal, (ii) recurrent chest pain ≥30 min or new electrocardiographic changes consistent with a second MI and the next CPK-MB (or CPK level) measured 8–12 h after the event is elevated by at least 50% above the previous level or new, significant (≥0.04 s) Q-waves in two or more contiguous electrocardiographic leads if the patients had non-ST-elevation MI at baseline but the peak CPK-MB (or CPK) had not yet been reached. In patients treated with CABG, MI was defined as any CPK-MB (or CPK) >10 x ULN within 24 h of CABG and increased at least 50% over the most recent pre-CABG levels, or any CPK-MB (or CPK) >5 x ULN within 24 h of CABG and increased at least 50% over the most recent pre-CABG levels and new, significant (> 0.04 s) Q-waves

		in two or more contiguous electrocardiographic leads

Montalescot et al. 2009	MI occurring within30 days after PCI	A new Q-wave in two or more leads or a total creatine kinase level or creatine kinase MB fraction that was ≥3 times the upper limit of the normal range during hospitalisation for the index PCI or that was ≥2 times the upper limit of the normal range after discharge.
Lindsey et al. 2009	Periprocedural MI	Periprocedural MI was defined as an elevation of CK-MB ≥3x the upper limit of normal (ULN). CK and CK-MB levels were assessed at baseline (within 1 h before the procedure) and every 8 h for a minimum of 2 samples after the procedure and assayed using each site's clinical laboratory and reference values. If a myocardial infarction was clinically suspected at a later point, additional biomarkers were obtained as indicated.
Kim et al. 2011	MI occurring within30 days after PCI	Presence of ischaemic symptoms or signs plus cardiac enzyme elevation: creatine kinase-MB elevation ≥3x ULN or creatine kinase elevation ≥2x ULN.
Baber et al. 2016	Periprocedural MI	**First universal definition of myocardial infarction.** Presence of clinical or electrocardiographic changes consistent with myocardial ischaemia in the setting of increased cardiac biomarkers above the upper limit of normal.
Hara et al. 2020	Periprocedural MI	**Third universal definition of myocardial infarction.** Percutaneous coronary intervention related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5 x 99th of the percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values >20% if the baseline values were elevated and are stable or falling. In addition, either: (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic electrocardiographic changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required.

Supplementary Table 5B. Definitions of myocardial infarction for the analysis of late events.

Study, year	Late MI	
	Timing of MI	**MI definition**
Kim et al. 2011	MI occurring beyond 30 days after PCI	Presence of ischaemic symptoms or signs plus cardiac enzyme elevation (CK-MB ≥3xURL or CK ≥2xURLI).
Kazi et al. 2015	MI occurring between 7-365 after discharge	International Classification of Diseases-Ninth Edition codes were used to identify subsequent hospitalisations for spontaneous MI (defined as a primary discharge diagnosis of an acute MI) between days 7 and 365 after discharge from the index hospitalisation for PCI.
Généreux et al. 2015	Post-discharge MI	**ACUITY criteria.** - MI diagnosis before angiography, or, in medically treated patients. Patients with unstable angina (without NSTEMI): any elevation of troponin or CPK-MB (or CPK) greater than the upper limits of normal (ULN). - MI diagnosis before angiography, or, in medically treated patients. Patients with NSTEMI: (1) If the peak troponin or CPK-MB (or CPK) has not yet been reached: Recurrent chest pain lasting ≥30 minutes, or new electrocardiographic changes consistent with MI and the next troponin or CPK-MB (or CPK) level measured approximately 8 to 12 hours after the event be elevated by at least 50% above the previous level. (2) If the elevated troponin or CPK-MB (or CPK) levels are falling or have returned to normal: A new elevation of troponin or CPK-MB (or CPK) >ULN if the troponin or CPK-MB (or CPK) level has returned to <ULN, or a rise by >50% above the previous nadir level if the troponin or CPK-MB (or CPK) level has not returned to <ULN.
Baber et al. 2016	Spontaneous MI	**First universal definition of myocardial infarction.** Presence of clinical or electrocardiographic changes consistent with myocardial ischaemia in the setting of increased cardiac biomarkers above the upper limit of normal.
Valgimigli et al. 2017	MI occurring beyond30 days after PCI	**Third universal definition of myocardial infarction.** Spontaneous myocardial infarction was defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (i) symptoms of ischaemia, (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), (iii) development of pathological Q-waves on the ECG, (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, (v) Identification of an intracoronary thrombus by angiography or autopsy.
Secemsky et al. 2017	Spontaneous MI occurring beyond 1 year after PCI	**Academic Research Consortium (ARC) criteria.** Troponin >URL or CKMB >URL and any of the following: (I) symptoms of ischaemia, (II) ECG changes indicative of new ischemia (new ST-T changes or new LBBB), (III) development of pathological Q-waves, or (IV) imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.

Caneiro-Queija et al. 2018	Spontaneous MI	**Third universal definition of myocardial infarction.** Spontaneous myocardial infarction was defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (i) symptoms of ischaemia, (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), (iii) development of pathological Q-waves on the ECG, (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, (v) Identification of an intracoronary thrombus by angiography or autopsy.
Hara et al. 2020	Spontaneous MI	**Third universal definition of myocardial infarction.** Spontaneous myocardial infarction was defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (i) symptoms of ischaemia, (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), (iii) development of pathological Q-waves on the ECG, (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, (v) Identification of an intracoronary thrombus by angiography or autopsy.

Supplementary Table 5C. Definitions of myocardial infarction for the analysis of the composite of early or late events.

Study, year	Early or late MI	
	Time of MI	**MI definition**
Kim et al. 2011	Any MI within or beyond 30 days after PCI	Presence of ischaemic symptoms or signs plus cardiac enzyme elevation (CK-MB ≥3xURL or CK ≥2xURL).
Kikkert et al. 2013	Any MI within or beyond 30 days after PCI	**Academic Research Consortium (ARC) criteria.** Troponin >URL or CKMB >URL and any of the following: (I) symptoms of ischaemia, (II) ECG changes indicative of new ischaemia (new ST-T changes or new LBBB), (III) development of pathological Q-waves, or (IV) imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.
Stone et al. 2014	Any MI within or beyond 30 days after PCI	MI defined according to Academic Research Consortium: Troponin >URL or CKMB >URL and any of the following: (I) symptoms of ischaemia, (II) ECG changes indicative of new ischaemia (new ST-T changes or new LBBB), (III) development of pathological Q-waves, or (IV) imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.
Baber et al. 2016	Periprocedural or spontaneous MI	**First universal definition of myocardial infarction.** Presence of clinical or electrocardiographic changes consistent with myocardial ischaemia in the setting of increased cardiac biomarkers above the upper limit of normal.
Garot et al. 2017	Any coronary thrombotic event (MI and/or ST) within or beyond 30 days after PCI	**Third universal definition of myocardial infarction.** - Spontaneous myocardial infarction: was defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (i) symptoms of ischaemia, (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), (iii) development of pathological Q-waves on the ECG, (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, (v) Identification of an intracoronary thrombus by angiography or autopsy. - Percutaneous coronary intervention related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5 x 99th of the percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values >20% if the baseline values were elevated and are stable or falling. In addition, either: (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic electrocardiographic changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required.
Palmerini et al. 2017	Periprocedural or spontaneous MI, within or beyond 30 days after PCI	Mixed study definitions.
Hara et al. 2020	Periprocedural or spontaneous MI	**Third universal definition of myocardial infarction.** - Spontaneous myocardial infarction: was defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th

		percentile upper reference limit (URL) and with at least one of the following: (i) symptoms of ischaemia, (ii) new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB) (iii) development of pathological Q-waves on the ECG (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (v) Identification of an intracoronary thrombus by angiography or autopsy. - Percutaneous coronary intervention related myocardial infarction was arbitrarily defined by elevation of cardiac troponin values (>5 x 99th of the percentile upper reference limit) in patients with normal baseline values (≤99th percentile of the upper reference limit) or a rise of cardiac troponin values >20% if the baseline values were elevated and are stable or falling. In addition, either: (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic electrocardiographic changes or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality was required.

Supplementary Table 6. Procedural characteristics of the studies.

Study	PCI (%)	CABG (%)	Medical therapy (%)	Femoral access (%)	GPI (%)	Bivalirudin (%)	UHF (%)
Ndrepepa et al.	100	0	0	.	50.1	.	100
Mehran et al.	56.4	11.1	32.5	93.8	66.6	66.7	33.3
Montalescot et al.	100	0	0	100	40	.	35.2
Lindsey et al.	100	0	0	.	33.6	34.9	52.3
Kim et al.	100	0	0	.	2.95	.	100
Kikkert et al.	100	0	0	95.5	.	.	100
Stone et al.	100	0	0	95.9	57.7	57.6	57.7
Kazi et al.	100	0	0	.	.	.	.
Généreux et al. and Stone et al.	100	0	0	95.4	1.6	57.6	42.4
Baber et al.	100	0	0	.	13.6	.	.
Garot et al.	100	0	0	35.8	1.7	1.5	90.1
Valgimigli et al.	57.8	10.1	.	.	20.9	6.2	54.1
Palmerini et al.	100	0	0	.	.	.	.
Secemsky et al.	100	0	0	.	.	.	.
Caneiro-Queija et al.	73.5	5.5	.	.	.	.	.
Hara et al.	99	1	0	26.1	.	87.3	12.7

Supplementary Table 7. Bleeding and myocardial infarction events reported across studies.

			Bleeding			Myocardial infarction	
	Patients (N)	Deaths (N)	Bleeding severity	Patients with bleeding / total patients (%)	Deaths among patients with bleeding (N)	Patients with MI / total patients (%)	Deaths among patients with MI (N)
Early or late events							
Kim et al.	3,148	134	Major	123/3,148 (3.9)	N/A	204/3,148 (6.5)	N/A
Kikkert et al.	2,002	366	Major	N/A	51	149/2,002 (7.4)	61
Stone et al.	8,583	161	Major or minor	531/8,583 (6.2)	45	224/8,583 (2.6)	21
Stone et al.	3,202	197	Major	271/3,202 (8.5)	N/A	221/3,202 (6.9)	28
Baber et al.	5,018	227	Major or minor	391/5,018 (7.8)	57	289/5,018 (5.8)	41
Garot et al.	2,386	320	Major	210/2,386 (8.8)	65	219/2,386 (9,2)	64
Palmerini et al.	11,473	267	Major or minor	189/11,473 (1.6)	36	N/A	45
Hara et al.	15,968	477	Major	309/15,968 (1.9)	55	498/15,968 (3.1)	52
Early events							
Ndrepepa et al.	5,384	197	Major	215/5,384 (4.0)	30	314/5,384 (5.8)	35
Mehran et al.	13,819	524	Major	645/13,819 (4.7)	93	705/13,819 (5.1)	77
Montalescot et al.	2,636	75	Major	N/A	N/A	N/A	N/A
Lindsey et al.	5,961	167	Major	180/5,961 (3.0)	28	426/5,961 (7.1)	22
Kim et al.	3,148	134	Major or minor	134/3,148 (4.3)	25	165/3,148 (5.2)	N/A
Baber et al.	5,018	227	Major or minor	32/5,018 (0.6)	5	87/5,018 (1.7)	7
Hara et al.	15,968	477	Major or minor	233/15,968 (1.5)	35	139/15,968 (0.9)	12
Late events							
Kim et al.	3,148	134	Major or minor	73/3,148 (2.3)	14	39/3,148 (1.2)	N/A
Kazi et al.	32,906	4,048	Major or minor	530/32,906 (1.6)	164	991/32,906 (3.0)	315
Généreux et al.	8,577	311	Major or minor	535/8,577 (6.2)	68	387/8,577 (4.5)	NA

Baber et al.	5,018	227	Major	169/5,018 (3.4)	36	139/5,018 (2.8)	25
Valgimigli et al.	12,702	500	Major	346/12,702 (2.7)	79	718/12,702 (5.7)	118
Secemsky et al.	11,648	222	Major	244/11,648 (2.1)	39	306/11,648 (2.6)	30
Caneiro-Queija et al.	4,229	335	Major or minor	500/4,229 (11.8)	70	204/4,229 (4.8)	43
Hara et al.	15,968	477	Major or minor	864/15,968 (5.4)	87	366/15,968 (2.3)	40

Supplementary Table 8. Sensitivity analysis according to median publication year of the included studies (before vs after 2015).

	Before 2015				After 2015				*p* for interaction
	No. of studies	HR (95% CI)	I^2	*p*-value	No. of studies	HR (95% CI)	I^2	*p*-value	
Bleeding									
Early or late	4	4.17 (2.07-8.40)	93%	<0.001	4	4.76 (3.13-7.22)	83%	<0.001	0.750
Early	5	3.60 (3.03-4.27)	0%	<0.001	2	4.04 (2.19-7.47)	45%	<0.001	0.723
Late	3	3.89 (1.41-10.7)	95%	0.009	5	6.81 (4.46-10.4)	85%	<0.001	0.318
Myocardial Infarction									
Early or late	4	3.48 (2.68-4.53)	35%	<0.001	4	4.71 (3.62-6.13)	59%	<0.001	0.111
Early	5	2.44 (1.90-3.12)	39%	<0.001	2	2.30 (1.23-4.28)	28%	0.009	0.863
Late	3	3.10 (1.42-6.76)	89%	0.004	5	5.92 (4.65-7.54)	53%	<0.001	0.121
Ratio of HRs									
Early or late	4	1.22 (0.47-3.18)	91%	0.682	4	1.02 (0.72-1.45)	49%	0.913	0.730
Early	5	1.49 (1.05-2.11)	35%	0.027	2	1.70 (0.89-3.24)	0%	0.110	0.727
Late	3	1.19 (0.55-2.60)	79%	0.660	5	1.13 (0.88-1.44)	11%	0.352	0.901

Supplementary Table 9. Sensitivity analysis for randomised versus non-randomised studies.

	Randomised studies				Non-randomised studies				*p* for interaction
	No. of studies	HR (95% CI)	I^2	*p*-value	No. of studies	HR (95% CI)	I^2	*p*-value	
Bleeding									
Early or late	5	4.58 (3.27-6.43)	79%	<0.001	3	4.26 (1.55-11.73)	95%	0.005	0.894
Early	4	3.68 (2.94-4.61)	25%	<0.001	3	4.06 (3.01-5.47)	0%	<0.001	0.606
Late	3	8.07 (4.29-15.18)	95%	<0.001	5	4.32 (2.20-8.51)	93%	<0.001	0.186
Myocardial Infarction									
Early or late	5	4.69 (3.73-5.03)	46%	<0.001	3	3.35 (2.52-4.45)	41%	<0.001	0.040
Early	4	2.90 (2.39-3.51)	0%	<0.001	3	1.80 (1.30-2.48)	0%	<0.001	0.013
Late	3	6.35 (2.85-8.53)	61%	<0.001	5	3.75 (2.01-7.00)	91%	<0.001	0.214
Ratio of HRs									
Early or late	5	1.02 (0.75-1.37)	35%	0.917	3	1.31 (0.37-4.67)	94%	0.677	0.707
Early	4	1.22 (0.92-1.61)	0%	0.16	3	2.23 (1.41-3.53)	0%	0.001	0.028
Late	3	1.19 (0.87-1.62)	26%	0.284	5	1.11 (0.70-1.75)	64%	0.657	0.805

Supplementary Table 10. Newcastle-Ottawa scale.

Study	Selection			Outcome			Total
	Patients with CAD managed medically or with PCI	Patients receiving more than a single antiplatelet agent	Bleeding and MI complications reported for the same cohort	HR adjusted for age and sex	Adequate follow-up duration (≥12 months)	Complete follow-up (≥90%)	
Ndrepepa et al.	★	★	★	★	★	★	6/6
Mehran et al	★	★	★	★	★	★	6/6
Montalescot et al	★	★	★	★	★		5/6
Lindsey et al.	★	★	★	★	★		5/6
Kim et al.	★	★	★	★	★	★	6/6
Kikkert et al.	★	★	★		★	★	5/6
Stone et al	★	★	★	★	★	★	6/6
Kazi et al	★	★	★	★	★	★	6/6
Généreux et al. and Stone et al.	★	★		★	★	★	5/6
Baber et al.	★	★	★	★	★	★	6/6
Garot et al.	★	★	★	★	★	★	6/6
Valgimigli et al	★	★	★	★	★	★	6/6
Palmerini et al.	★	★	★	★	★	★	6/6
Secemsky et al	★	★	★	★	★	★	6/6
Caneiro-Queija et al	★	★	★	★	★	★	6/6
Hara et al.	★	★	★	★	★	★	6/6

CAD: coronary artery disease; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention