Meta-Analysis of the Prognostic Impact of Anemia in Patients Undergoing Percutaneous Coronary Intervention

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Abstract

Anemia is common in patients undergoing percutaneous coronary intervention (PCI), and current guidelines fail to offer recommendations for its management. This review aims to examine the relation between baseline anemia and mortality, major adverse cardiovascular events (MACE), and major bleeding in patients undergoing PCI. We searched MEDLINE and EMBASE for studies that evaluated mortality and adverse outcomes in anemic and nonanemic patients who underwent PCI. Data were collected on study design, participant characteristics, definition of anemia, follow-up, and adverse outcomes. Random effects meta-analysis of risk ratios was performed using inverse variance method. A total of 44 studies were included in the review with 230,795 participants. The prevalence of baseline anemia was 26,514 of 170,914 (16%). There was an elevated risk of mortality and MACE with anemia compared with no anemia-pooled risk ratio (RR) 2.39 (2.02 to 2.83), p <0.001 and RR 1.51 (1.34 to 1.71), p <0.001, respectively. The risk of myocardial infarction and bleeding with anemia compared with no anemia was elevated, pooled RR 1.33 (1.07 to 1.65), p = 0.01 and RR 1.97 (1.03 to 3.77), p <0.001, respectively. The risk of mortality per unit incremental decrease in hemoglobin (g/dl) was RR 1.19 (1.09 to 1.30), p <0.001 and the risk of mortality, MACE, and reinfarction per 1 unit incremental decrease in hematocrit (%) was RR 1.07 (1.05 to 1.10), p = 0.04, RR 1.09 (1.08 to 1.10) and RR 1.06 (1.03 to 1.10), respectively. The prevalence of anemia in contemporary cohorts of patients undergoing PCI is significant and is associated with significant increases in postprocedural mortality, MACE, reinfarction, and bleeding. The optimal strategy for the management of anemia in such patients remains uncertain.

Introduction

Anaemia is common amongst patients undergoing percutaneous coronary interventions (PCI) with prevalent rates reported between 10-23% in randomised controlled trials (1-3)and rates greater than 30% reported in observational registries (4,5). Current clinical guidelines fail to offer recommendations for its concurrent management in patients undergoing PCI. Patients with anaemia who undergo PCI are frequently older (5-7), with multiple co-morbidities including higher rates of renal failure (1,8-11), diabetes (1,8), previous history of myocardial infarction (12,13) and more extensive and complex coronary disease (12-14). These clinical and procedural characteristics are well known to be associated with poorer outcomes post PCI. Previous studies have reported that the presence of baseline anaemia is independently associated with mortality (5,8,9,15) and major adverse cardiac events (MACE)(5,16) and major bleeding complications(17) and several PCI risk scores have used anaemia as important predictors for both mortality (18) and bleeding outcomes (19,20). In contrast, other studies suggest that whilst these relationships exists for unadjusted data, anaemia is no longer associated with increased mortality following adjustment for potential confounders such as age, comorbidity burden and procedural demographics, (16,21-23), MACE (11,23)or ischemic complications (2). Other studies have also suggested an independent association with mortality only in males but not females (1). Anaemia may occur following major bleeding events or in the presence of chronic renal disease, or relate to the presence of a diverse range of chronic diseases(24). Whilst both major bleeding (25,26) and chronic renal disease are known to independently predict adverse outcomes following PCI(27-29), several analyses that have focussed on the prognostic impact of anaemia have not adjusted for either renal function (6,30) or major bleeding events that may further confound relationships reported.

To the best of our knowledge, there has not been a systematic review or meta-analysis of the prevalence and prognostic impact of anaemia in the setting of PCI. We have therefore undertaken a meta-analysis to systematically study the impact of anaemia in patients who have undergone PCI on mortality, MACE, major bleeding and re-infarction and attempt to dissect out whether the associations reported between anaemia and adverse clinical outcomes are independent of clinical and procedural characteristics that are more prevalent in patients with anaemia and portend to worse outcomes. Finally, we study whether the reported relationships reported between anaemia and clinical outcomes are similar irrespective of whether the PCI is undertaken in the elective or ACS setting.

Methods

Eligibility criteria

We selected studies of participants who underwent PCI and reported any of the following adverse outcomes: mortality, MACE by any definition or combination of (adverse cardiovascular events and mortality), re-infarction and bleeding among patients who were anemic and non-anemic (no restriction on cutoffs of hemoglobin). We also included studies that evaluated the risk of adverse outcomes for incremental increase or decrease in hemoglobin. Studies that did not clearly report any of the adverse outcomes by anemia status or incremental changes in hemoglobin were excluded.

Search strategy

A search of MEDLINE and EMBASE was performed on OVID SP. The exact search strategy is shown in Supplementary Data 1. There was no restriction on the search based on language and both abstracts and unpublished literature were included. The bibliography of included studies and relevant reviews were evaluated for additional studies. Authors were contacted in situations where there was uncertainty regarding the data in the studies.

Study selection and data extraction

Three reviewers (C.S.K., A.P. and A.A.) independently screened all titles and abstracts for studies potentially meeting the inclusion criteria. The full reports of these studies were retrieved, and data from each study were extracted independently by two reviewers (C.S.K. and D. T.) Data extracted included study design, participant characteristics, participant inclusion criteria, definition of anemia or incremental hemoglobin change, adverse outcomes, follow up and results.

Quality assessment

Additional data was collected on quality of studies that included ascertainment of anemia, ascertainment of outcomes, loss to follow up and use of adjustments for confounding. Publication bias was assessed using funnel plots for an analysis with >10 studies and no evidence of substantial heterogeneity(31).

Data analysis

We used RevMan (version 5.3, Nordic Cochrane Centre, Copenhagen, Demark) to perform random effects meta-analysis using inverse variance methods for pooling risk ratios. We assumed similarity between odds ratio and other relative measures such as relative risk, rate ratios and hazard rations because cardiovascular events were rare events(32). We chose to pool adjusted results were available and crude results when adjusted results were not available. For datasets with the multiple time points were chose to pool the longest time-point in the primary analysis. The I^2 statistic was used to assess statistical heterogeneity.

We performed the primary analysis considering unadjusted and adjusted results for anemic and non-anemic patients for the outcomes mortality, MACE, re-infarction and bleeding. Secondary analysis was performed considering the incremental decrease in hemoglobin and the risk of adverse outcomes. For the main anemia and risk of mortality

analysis, we performed sensitivity analysis considering only studies that adjusted for baseline hemoglobin, renal impairment and severity of anemia and mortality. Further analysis was performed considering the effect of elective or ACS patients on outcomes.

Results

Study selection

The process of study selection is shown in Figure 1. A total of 44 studies were included in this meta-analysis with a total of with 230,795 participants. The number of participants ranged from 100 to 73,067 and the overall prevalence of anaemia was 26,514/170,914 (16%) and for individual studies the prevalence ranged from 3% to 41%.

Description of studies included

The study design, date of study, country of origin and indications for PCI are shown in Table 1. There were 4 post hoc analyses of randomised controlled trials, 14 prospective cohort studies, 14 retrospective cohort studies and 12 cohort studies of unclear design. There were 15 studies of patients with STEMI, 1 study of just STEMI patients and 28 studies of patients undergoing PCI.

Quality assessment

Table 2 shows the risk of bias table for the included studies. All of the studies aside for one specified that blood measurements were taken prior to PCI and the single study with unclear timing of blood sampling was presumed to be prior to PCI. A variety of methods were used to ascertain adverse outcomes after PCI. These included evaluating hospital records, interviewing patients, families, personal physicians, use of national death records and use of independent events adjudication committees. A total of 15 studies did not specify

how outcomes were ascertained. The loss to follow up was reported in 18 studies and was unclear in the remaining studies. All studies reported at least one adjusted analysis except for 5 studies.

Risk of adverse outcomes with anaemia compared to no anaemia

The study definitions of anaemia, follow up and results are shown in Table 3. The risk of mortality and major adverse cardiovascular events (MACE) with anaemia compared to no anaemia was RR 2.39 (2.02-2.83) (32 studies, 134,042 participants) (Figure 2) and RR 1.51 (1.34-1.71) (20 studies, 47,552 participants) (Figure 3), respectively. The risk of re-infarction and bleeding with anaemia compared to no anaemia was RR 1.33 (1.07-1.65) (13 studies, 36,316 participants) (Figure 4) and RR 1.97 (1.03-3.77) (11 studies, 34,388 participants) (Figure 5), respectively.

Incremental decrease in haemoglobin or haematocrit and adverse outcomes

The analysis for incremental decrease in haemoglobin and haematocrit is shown in Figure 6. The risk of mortality for incremental decrease in haemoglobin (g/dl) was RR 1.19 (1.09-1.30) (7 studies, 82,208 participants) and the risk of mortality, MACE and re-infarction for incremental decrease in haematocrit (%) was RR 1.07 (1.05-1.10) (3 studies, 14,519 participants), RR 1.09 (1.08-1.10) (1 study, 6,025 participants) and RR 1.06 (1.03-1.10) (1 study, 6,025 participants), respectively.

Subgroup analysis of anaemia compared to no anaemia

Sensitivity analysis was performed considering the subgroup of studies that had used adjustments for baseline haemoglobin and renal impairment and studies which evaluated severity of anaemia (Figure 7). The pooled results of 3 studies that adjusted for baseline

haemoglobin showed a significant increase in mortality (RR 1.81 (1.62-2.01)) and a significantly higher mortality were observed for studies that adjusted for renal impairment of renal function (RR 2.05 (1.69-2.49)). Kitai et al was the only study of mortality outcomes which considered severity of anaemia and they reported that mild anaemia (>10 g/dL) was associated with RR 1.86 (1.42-2.43) while moderate to severe anaemia (<10 g/dL) was associated with greater mortality (RR 3.35 (2.52-4.46)).

Further analyses considering elective cases only, ACS cases only and any PCI cases separately are shown in Supplementary Figures 1-4. After adjustments, there were significant increases in mortality for patients with anaemia in both the ACS and elective setting. However, there was only a significant increase in mortality with incremental decrease in haemoglobin in elective cases but not ACS. Similarly, anaemia was independently associated with worse MACE and bleeding outcomes in both the elective and ACS PCI setting.

Discussion

To the best of our knowledge, the present analysis is the first to systematically review the prevalence of anaemia in contemporary cohorts undergoing PCI to study its prognostic impact. Our meta-analysis of 44 studies including 230,795 patients has shown that the mean prevalence of anaemia in contemporary PCI is 16% and is independently associated with a 2-fold increased risk of mortality, MACE events and major bleeding with elevation in risk with incremental decreases in haemoglobin levels. This increased risk appears to be independent of the common causes of anaemia such as chronic renal disease of bleeding events sustained peri-procedurally, and the increased risk of adverse events associated with anaemia is of similar magnitude in both the elective and ACS setting.

Previous studies have reported conflicting data regarding the association between anaemia and clinical outcomes in patients undergoing PCI, with studies reporting both an

independent association with increased mortality, MACE and major bleeding complications (3,5,8-10,15-17) or no increase in risk following adjustment for differences in age, comorbidity burden and procedural demographics (9,21,22), or only associated with poorer outcomes in patients with severe anaemia but not mild or moderate anaemia (11). Other studies have suggested that post-procedural anaemia is independently associated with MACE (23).

There are a number of biological and clinical reasons why chronic anaemia may lead to worse clinical outcomes in patients undergoing PCI. Our analysis suggests that anaemia is independently associated with a two-fold increased risk of major bleeding complications, which themselves are independently associated with increased risks of peri-procedural and longer-term mortality (26). Other studies suggest that anaemia may also independently increase the risk of definite and definite or probable stent thrombosis by 250% (9), which might contribute to the increased mortality risk in this patient cohort. In support of this, an analysis of 73,067 patients from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry - Get With the Guidelines (ACTION-GWTG) (33) demonstrated that patients with anaemia were less likely to be prescribed dual antiplatelet therapy peri-procedurally, which might contribute to increased risks of future stent thrombosis. Furthermore, patients with haemoglobin <10 g/dl had an overall transfusion rate that was 6.5-fold higher compared with patients with haemoglobin >12 g/dl (64.2% vs 9.9%, p <0.0001). A previous meta-analysis has suggested that the receipt of a blood transfusion in the PCI setting is independently associated with a 3-fold increase in mortality and MACE, and this risk persists even in the absence of major bleeding events (34). Similarly, other studies have also reported that patients with anaemia do not receive optimal antiplatelet therapy post PCI (3) although Pilgrim et al. report that the presence of anaemia did not influence the choice of peri-procedural antithrombotic or antiplatelet regime at the

time of hospital discharge post PCI (9). Finally anaemia may merely be a marker of a greater co-morbid in frailer patients, and the statistical models may have been affected by incomplete adjustments for confounders such as co-morbid burden or frailty. Our previous work has shown that co-morbidity burden is significant in patients undergoing PCI and is independently associated with adverse shorter and longer-term clinical outcomes (35).

Whilst our meta-analysis highlights the independent association between the presence of anaemia and adverse clinical outcomes in the PCI setting, there are no current recommended guidelines for the treatment of anaemia, with no clarity as to whether there is a threshold level of anaemia at which treatment should be considered. Previous reports derived from the National Cardiovascular Data Registry dataset of transfusion practice nationally in the PCI setting have reported significant variations in the prevalence of transfusion events in hospitals across the United States, with significant differences in haemoglobin threshold that prompts transfusion(36). Furthermore, randomised trials have yielded conflicting data regarding optimal treatment of anaemia in ACS and PCI settings, for example, in the CRIT (conservative versus liberal red cell transfusion in acute myocardial infarction) randomized pilot trial, 45 patients with myocardial infarction and anaemia were randomized to either a liberal transfusion arm or a conservative arm, with worse outcomes reported in patients assigned to the liberal transfusion arm (composite endpoint of in-hospital mortality, re-infarction or heart failure (38% vs13%; $p = 0.046$). In contrast, in the MINT pilot study in patients presenting with anaemia undergoing cardiac catheterization, patients randomized to a liberal blood transfusion strategy had lower rates of death, myocardial infarction, and unscheduled revascularization (10.9%) compared to those patients randomized to a restrictive transfusion strategy (25.5%), with lower 30-day mortality (1.8%) compared with restrictive transfusion patients (13.0%) ($p = 0.032$)(37).

Our analysis has several limitations. Although our meta-analysis suggests a dose dependent association between the presence of anaemia and adverse clinical outcomes in PCI, it cannot confer a causal relationship. Whilst the papers included in this analysis have adjusted for differences in clinical and procedural characteristics, renal function and comorbidity, we cannot rule out unmeasured confounders such as frailty or chronic disease that are not fully captured by statistical models that may themselves contribute to the poorer outcomes observed. Whilst blood sampling in the majority of the studies included in this meta-analysis was undertaken prior to the PCI procedure, a small number of studies included in this analysis, the timing of blood sampling in a small number of studies included in the analysis was unclear, although exclusion of these studies did not significantly alter the relationships reported (mortality with anaemia RR 2.39 (2.00-2.85), MACE with anaemia RR 1.55 (1.38-1.75)). Finally, our analysis does not provide insight as to whether different aetiologies of anaemia have a differential relationship with clinical outcomes.

In conclusion, our meta-analysis of 44 studies including 230,795 patients has shown that the prevalence of anaemia in contemporary PCI is significant and reported at 16% and is independently associated with a 2-foldincreased risk of mortality, MACE events and major bleeding with incremental increases in risk with decreases in haemoglobin levels. This increased risk appears to be independent of the common causes of anaemia such as chronic renal disease or major bleeding events sustained peri-procedurally, and the increased risk of adverse events associated with anaemia is of similar magnitude irrespective of whether the PCI was undertaken in the elective or ACS setting. Our data support the need for a larger definitive trial to define the optimal treatment strategies for patients with anaemia undergoing PCI.

Table 1: Study design and participant characteristics

Study ID	Date/Year	Design	Country	No. of centers	Total no. of participants, no. anaemic (% anaemic)	Participants
Akgul 2013	Dec 2010 to May 2012.	Prospective observational study.	Turkey.	Single	520, 64 (12%) anemic.	Participants had PPCI for STEMI.
Ali 2004	Jul 2002 to May 2010	Prospective observational study.	USA.	Unclear.	11,991, 4,815 (40%) anemic.	Participants who underwent PCI with bivalirudin.
Ayhan 2011	Unclear.	Retrospective cohort study.	Turkey.	Single.	2,509, 616 (25%) anemic.	Participants had PPCI for STEMI.
Bolinska 2011	May to Dec 2005.	Retrospective cohort study.	Poland.	Single.	551, 61 (11%) anemic.	Participants had PPCI for STEMI.
Catakoglu 2007	Oct 2001 to June 2002.	Prospective cohort study.	Turkey.	Single.	100, 31 (31%) anemic.	Participants had non-urgent elective PCI.
Chi 2012	Unclear.	Cohort study.	China.	Unclear.	1014, 253 (25%) anemic.	Participants were ACS patients age ≥60 years who underwent PCI.
Cho 2011a	Nov 2005 to Jun 2009.	Retrospective cohort study.	South Korea.	Single.	739, 152 (21%) anemic.	Participants with STEMI who underwent PPCI.
Cho 2011b	Mar 2006 to Dec 2009	Prospective cohort study.	South Korea.	Unclear.	2,849, 679 (24%) anemic.	Participants were patients with drug eluting stents.

Dada 2009	Unclear.	Cohort study.	USA.	Unclear.	6,538, 2,159 (33%) anemic.	Participants with PCI.
Dunbar 2012	Jan 2006 to Apr 2008.	Retrospective cohort study.	Turkey.	Single center.	1,625, 395 (24%) anemic.	Participants with acute STEMI and PPCI.
Feldman 2009	2004 to 2005.	Cohort study.	USA.	Single.	2,504, 709 (28%) anemic.	Participants were in the 2004/2005 Cornell Angioplasty Registry who underwent urgent or elective PCI.
Greenberg 2010	Jan 2001 to Dec 2007.	Prospective cohort study.	Israel.	Single.	1,042, 208 (20%) anemic.	Participants had STEMI who underwent PPCI.
Gurm 2004	Unclear.	Post hoc analysis of RCT.	USA.	Multicenter.	6,322, 638 (10%) anemic.	Participants were randomized to EPIC, EPILOG and EPI stent trials who underwent PCI.
Hanna 2013	Jan 2007 to Dec 2009.	Cohort study.	USA.	354 centers.	73,067, 2,417 (3%) anemic.	Participants were in the ACTION-GWTG registry with NSTEMI.
Hosseini 2014	Apr 2005 to Sept 2008	Cohort study.	Iran.	Single.	2,819, 493 (17%) anemic.	Participants had elective PCI with preprocedural hemoglobin measured within 7 days prior to PCI.
Husemann 2007	Jan 2001 to Dec 2001.	Retrospective cohort study.	Germany.	Single.	709, 128 (18%) anemic.	Participants were treated with PCI.
Jones 2010	Jan 2004 to Mar 2009.	Prospective cohort study.	UK.	Single.	1657, 331 (20%) anemic.	Participants with STEMI who underwent PPCI at a London centre.
Kim 2012	Jan 2004 to Dec 2009.	Retrospective cohort study.	South Korea.	Single.	3,549, 1,321 (37%) anemic.	Participants received PCI with drug eluting stent in the CathOlic university of Korea percutAneous Coronary inTervention registry.

Kitai 2013	Jan 2005 to Dec 2007.	Retrospective cohort study.	Japan.	26 centers.	7,299, 2,209 (30%) anemic.	Participants were in the CREDO-Kyoto registry cohort-2 who underwent first elective PCI.
Kruk 2010	Feb 2001 to Dec 2004.	Prospective cohort study.	Poland.	Unclear.	1880, 385 (20%) anemic.	Participants had STEMI in a prospective registry.
Kurek 2010	Sept 2004 to Dec 2007.	Prospective cohort study.	Poland.	Single center.	1,497, 248 (17%) anemic.	Patients with AMI treated in the acute phase with PCI.
Liu 2008	Jul 2003 to Sept 2005.	Cohort study.	China.	Single.	3,809, 744 (20%) anemic.	Participants were in the DESIRE-2 revascularization registry.
Liu 2009	Unclear.	Cohort study.	Unclear.	Unclear.	3770.	Participants underwent PCI.
Maluenda 2009	2003 to 2007	Retrospective cohort study.	USA.	Single.	6,025, 210 (3%) anemic.	Participants who underwent PCI.
Manzano-Fernandez 2008	Unclear.	Cohort study.	Spain.	2 centers.	278, 114 (41%) anemic.	Participants with AF and indication for oral anticoagulation who underwent PCI.
McKechnie 2004	July 1997 to May 2003.	Prospective cohort study.	USA.	18 hospitals.	48,851.	Participants underwent PCI in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium.
Nikolsky 2004a	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	2,027, 260 (13%) anemic.	Participants had AMI who underwent PPCI in CADILLAC trial.
Nikolsky 2004b	1994 to 1999	Prospective cohort study.	USA.	Single.	6,929, 1,708 (25%) anemic.	Participants had elective PCI.
Oduncu 2013	Unclear.	Cohort study.	Turkey.	Single.	2,411, 623 (26%) anemic.	Participants with STEMI who underwent PPCI.

Ozasa 2012	2005 to 2007	Retrospective cohort study.	Japan.	Unclear.	5,336, 1,788 (34%) anemic.	Participants were in the CRED-Kyoto PCI/CABG Registry Cohort-2 who underwent PCI with drug eluting stent.
Park 2012	2004 to 2010.	Cohort study.	South Korea.	Unclear.	881, 349 (40%) anemic.	Participants had acute MI treated with PCI.
Poludasu 2009	Jan 2003 to Aug 2005.	Retrospective cohort study.	USA.	Unclear.	715.	Participants were African-Americans from a bolus-only glycoprotein IIb/IIIa database.
Rathod 2014	Jan 2004 to Aug 2010.	Retrospective cohort study.	UK.	Single.	2,178, 419 (19%) anemic.	Participants had STEMI who underwent PPCI.
Reinecke 2003	1998 to 1999	Retrospective cohort study.	Germany.	Single.	689.	Participants were male who underwent elective PCI.
Rodriguez 2013	2007 to 2011.	Prospective cohort study.	Spain.	Single.	759, 226 (30%) anemic.	Participants underwent PCI.
Schroder 2013	2004 to 2006.	Retrospective cohort study.	Germany.	Unclear.	2,056.	Participants were ≥75 years who underwent PCI with stent implantation.
Sgura 2010	2002 to 2008.	Cohort study.	Italy.	Single.	673.	Participants had STEMI who underwent PCI.
Shishehbor 2009	Mar 2003 to June 2007.	Prospective cohort study.	USA.	Single.	2,172.	Participants underwent PCI who received drug eluting or bare metal stent.
Tsujita 2010	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	3,153, 331 (10%) anemic.	Participants were in HORIZONS-AMI trial who underwent PCI and had STEMI.
Uchida 2013	Unclear.	Cohort study.	Japan.	Unclear.	337, 59 (18%)	Participants had STEMI who underwent PCI.

					anemic.	
Varma 2010	Apr 2003 to Dec 2005.	Retrospective cohort study.	USA.	Unclear.	120.	Participants with PCI.
Vis 2010	Jan 1997 to Mar 2005.	Prospective cohort study.	Netherlands.	Single.	292.	Participants had STEMI and underwent PPCI.
Voeltz 2007	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	6,010, 1,371 (23%) anemic.	Participants were in REPLACE-2 trial who underwent PCI.
Vrslovic 2012	Unclear.	Prospective cohort study.	Croatia.	Single.	543.	Participants had STEMI who underwent PPCI.

PPCI=primary percutaneous coronary intervention, PCI=percutaneous coronary intervention, STEMI=ST elevated myocardial infarction, RCT=randomized controlled trial.

Table 2: Risk of bias table

Study ID	Ascertainment of anaemia and timing of assessment	Ascertainment of outcome and frequency of follow up	Lost to follow up	Adjustments for confounding
Akgul 2013	Pre-PCI anaemia from blood sampling.	Hospital records or interviewing (directly of by telephone) patients, families or personal physicians.	25 patients were excluded, 5 for missing data.	Adjusted but for unclear variables, backward stepwise Cox regression analysis with variables with P<0.1.
Ali 2004	Blood sampling with measured before PCI and 6 and 12 hours after PCI.	In-hospital complications ascertained daily by trained research staff. All-cause mortality from National Social Security Death Index and New York State interventional database by matching patients social security numbers to death index records.	27 in-patient deaths were excluded.	Adjusted for age, gender, BMI, body surface area, race, indication, hypertension, diabetes, hyperlipidaemia, peripheral vascular disease, heart failure, coronary artery disease, chronic kidney disease, end stage renal disease, glycoprotein IIb/IIIa inhibitor use, discharge medications, LVEF, baseline Hb, target coronary artery, number of coronary vessels narrowed, stents and PCI successful.
Ayhan 2011	Blood sampling before PCI.	Hospital records or by interviewing (directly or by telephone) patients, their families, or their personal physicians.	Lost to follow up for 46 patients.	Adjusted but for unclear variables. Backward stepwise multivariate Cox regression analysis was used.
Bolinska 2011	Blood sampling on admission.	Retrospective review of medical records.	Unclear.	Adjusted for age, systolic blood pressure, Hb on admission and white blood count on admission.
Catakoglu 2007	Blood sampling was 1-3 days before procedure and retrieved from computer	Endpoints were adjudicated by an independent clinical-events committee.	Unclear.	Adjusted for age, sex, diabetes, hypertension, smoking, LDL cholesterol, GFR, previous PCI and previous CABG.

	database.			
Chi 2012	Pre-procedure blood sampling.	Unclear.	Unclear.	Adjusted but for unclear variables.
Cho 2011a	Blood sampling before PCI.	Data from Korean acute MI registry. Follow up to 6 months.	9 patients were lost to follow up.	Crude results only for anaemia and outcomes.
Cho 2011b	Pre-procedure blood sampling.	Unclear ascertainment of outcomes. Median follow up of 2.2 years.	Unclear.	Adjusted for baseline clinical and procedural characteristics but unclear variables.
Dada 2009	Blood sampling before PCI.	Unclear outcome ascertainment and follow up to 9 months.	Unclear.	Propensity score matched analysis likely with adjustments for age, diabetes, hypertension, hyperlipidaemia, renal insufficiency, prior history of PCI or previous CABG surgery.
Dunbar 2012	Baseline haemogram and biochemical tests were elicited from files and computer records in hospital. Unclear timing of sampling.	Unclear outcome ascertainment.	Unclear.	Adjusted for age, sex, diabetes, hypertension, dyslipidaemia, smoking, history of COPD, cardiogenic shock, history of ACEI/ARB use, GFR<60, history of dialysis, anterior infarct location, stent and tirofiban use, ST segment resolution<70%, LVEF, inotropic drug use and blood transfusion.
Feldman 2009	Blood sampling with unclear timing of sampling.	Mortality at mean follow up of 24.8 months. Unclear method of ascertainment.	Unclear.	Adjusted but for unclear variables.
Greenberg 2010	Blood sampling at baseline.	Hospital charts and standardized questionnaire completed by telephone	At 12 months 100% mortality data and 94%	Model included age, gender, diabetes, renal insufficiency, hypertension, smoking, previous stroke, white blood cell, peak creatinine kinase and

		or outpatient visit up to 12 months.	revascularization and re-infarction data.	multivessel disease.
Gurm 2004	Blood sampling before PCI.	Mortality and MI up to 3 years. Unclear method of ascertainment.	86 patients did not have preprocedural hematocrit.	Model with interactions between variables with significant interactions terms incorporated into the model p value <0.05 but unclear which variables.
Hanna 2013	Initial admission blood sampling.	Outcomes captured in the ACTION-GWTG database.	579 patients were missing hemoglobin values.	Adjusted for age, gender, race, weight, medical history of diabetes, previous peripheral arterial disease, hypertension, current or recent smoking, previous PCI, previous CABG, previous MI, previous heart failure, previous stroke, insurance status, home medications, systolic blood pressure, heart rate, heart failure or shock on admission, ECG findings, troponin and serum creatinine.
Hosseini 2014	Preprocedural blood sampling.	Patients were followed up by trained general practitioner or interventional cardiology fellow in clinic or through phone call by trained physician or research nurse.	90% of patients completed 12 months follow up.	Adjusted for age, smoking, hypertension, diabetes, creatinine clearance and renal failure.
Husemann 2007	Blood sampling before procedure.	Follow up with telephone calls with patients, relatives or referring physicians. If not possible then questionnaire sent by mail.	61 patients had missing baseline hemoglobin or creatinine levels. Follow up 100% complete for these	Adjusted for covariates which were found to have a p-value <0.1 in univariate analyses of mortality but unclear which variables.

			patients.	
Jones 2010	Baseline blood sampling.	Mortality was ascertained by information from the Office of National Statistics.	Unclear.	Adjusted for unclear variables.
Kim 2012	Initial and follow up blood sampling.	Patients were required to visit the outpatient clinic at 1st month and every 3 months after PCI for outcomes up to a median of 25.4 months.	129 patients were excluded who had MACE within 3 months for the change in anaemia analysis.	Propensity matched cohort with likely inclusion of age, sex, BMI, Hb, GFR<60, LVEF, diabetes, hypertension, hypercholesterolemia, current smoking, history of MI, PCI, CABG, cerebrovascular disease, family history of coronary artery disease, initial diagnosis, multivessel disease and ACC/AHA B2/C lesions.
Kitai 2013	Blood sampling at baseline.	Follow-up data from hospital charts or by contacting patients or referring physicians. Events adjudicated by clinical events committee.	96.9% patients had 1 year follow up.	Adjusted for age, male, BMI, hypertension, diabetes, current smoking, heart failure, multivessel disease, mitral regurgitation grade 3/4, LVEF, prior MI, prior stroke, peripheral vascular disease, eGFR, atrial fibrillation, platelet <100x10^9/L, COPD, liver cirrhosis, malignancy, number of target lesions, target proximal LAD, unprotected LMCA, CTO, bifurcation, total stents, stent length, minimum stent size, drug eluting stent, antiplatelet therapy and other medications.
Kruk 2010	Blood sampling on admission prior to coronary procedure.	Outcomes from hospital charts for death and heart failure.	Unclear.	Adjusted for sex, age, Killip class >1, prior coronary disease, smoking, TIMI flow, multivessel disease, systolic blood pressure, heart rate, white cell count, hyperglycaemia and serum creatinine.
Kurek 2010	Blood sampling just after admission before transfer	MACE and death from computerized database and long-term outcomes from	Unclear.	Adjusted for diabetes, incomplete revascularization, multivessel disease, impaired renal function, advance age and left ventricular

	to catheter laboratory.	a database of the National Fund of Health.		dysfunction.
Liu 2008	Pre-PCI blood sampling.	Unclear.	Unclear.	Adjusted for comorbidities but unclear variables.
Liu 2009	Pre-PCI blood sample.	Unclear.	Unclear.	Unclear.
Maluenda 2009	Blood sampling before and after PCI.	Independent research personnel conducted follow up via telephone or office visits. All clinical events adjudicated by independent physicians.	Unclear.	Unadjusted for haematocrit analysis.
Manzano-Fernandez 2008	Blood sampling at baseline.	Unclear.	Unclear.	Adjusted but for unclear variables.
McKechnie 2004	Preprocedural blood sampling.	Outcome data collected prospective from standardized form.	Missing or implausible hemoglobin for 3,686 cases.	Adjusted for unclear variables. Variables with $p<0.2$ in univariate analysis were included in stepwise regression for each outcome.
Nikolsky 2004a	Blood sampling at initial presentation.	Clinical follow up at 30 days, 6 months, 1 year and all events were adjudicated by independent clinical events committee.	Unclear.	Adjusted but for unclear variables.
Nikolsky 2004b	Blood samplings before PCI and after PCI.	Telephone interviews for out of hospital outcomes at 12 months.	1 year follow up available for 89% of patient with anaemia versus 90.2% who did	Adjusted for age, gender, BMI, angina class III or IV, diabetes mellitus, history of peripheral arterial disease, angiographic characteristics, creatinine clearance and anaemia.

			not have anaemia.	
Oduncu 2013	Blood sampling on admission.	Unclear method of ascertainment follow up up to 48 months.	Unclear.	Adjusted but for unclear variables.
Ozasa 2012	Unclear timing of blood sampling.	Unclear.	Unclear.	Adjusted for unclear variables.
Park 2012	Blood sampling at baseline.	Unclear followed up for up to 2 years.	Unclear.	Adjusted for unclear variables.
Poludasu 2009	Blood sampling at baseline.	Social Security Death Index for death.	131 patients did not have valid Social Security number.	Adjusted for unclear variables.
Rathod 2014	Blood sampling at baseline.	In-hospital events were recorded prospectively. Long term data from British Cardiovascular Intervention Society database.	240 patients excluded because of incomplete data sets.	Propensity score matched for age, sex, diabetes, hypertension, hypercholesterolaemia, previous CABG, previous PCI, previous MI, multivessel disease, eGFR, ejection fraction, glycoprotein IIb/IIIa inhibitor.
Reinecke 2003	Blood sampling 1 to 3 days before the procedure.	Follow up with questionnaire sent to all patients or telephone call with patients, relatives or referring physicians.	11 patients had no baseline hemoglobin and were excluded.	Adjusted for number of diseased vessels, smoking, creatinine, stent implantation, age, family history of cardiovascular disease, diabetes.
Rodriguez 2013	Blood sampling on admission.	Unclear outcome ascertainment with mean follow up of 26.5 months.	None.	Adjusted for unclear variables.

Schroder 2013	Blood sampling at time of hospital admission.	Follow-up questionnaire or telephone interview with patient or relative, contact patient's physician or registry office.	Unclear.	Adjusted for age, gender, Hb, serum CRP, serum LDL, and serum creatinine levels, and LVEF).
Sgura 2010	Blood sampling on admission.	Unclear but follow up was 30 months.	Unclear.	Crude results.
Shishehbor 2009	Blood sample pre-PCI.	Mortality from Social Security Death Index at a median of 1.8 year follow up.	Unclear.	Adjusted for age, gender, socioeconomic class, BMI, heart rate, LVEF, malignancy, depression, diabetes, family history, current smoking, blood markers, medical history, NYHA functional class, medications, type of anaemia, angiographic data, lesion location, procedural data.
Tsujita 2010	Blood sampling at initial presentation.	All events were adjudicated by an independent clinical events committee blinded to treatment assignment.	Unclear.	Adjusted for age, gender, race, hypertension, hyperlipidaemia, smoking, diabetes mellitus, peripheral vascular disease, congestive heart failure, angina, PCI, MI, CABG, Killip class, BMI, anaemia, platelet count, white blood count, creatinine clearance <60 ml/min, LAD coronary artery infarct vessel, reference vessel diameter, target lesion length, LVEF, index hospitalization, duration from symptom onset to first balloon inflation, antithrombotic randomization, clopidogrel loading dose, randomization to paclitaxel-eluting stent vs bare-metal stent, number of stents, use of heparin before randomization

				and final TIMI flow grade 3.
Uchida 2013	Baseline blood sampling.	Unclear outcome ascertainment and follow up.	Unclear.	Adjusted but for unclear variables.
Varma 2010	Blood was sampled 72 hours preintervention.	Mortality from Social Security database and hospital computer database with follow up of median 30 months.	Unclear.	Unadjusted.
Vis 2010	Admission blood sample.	Data from questionnaire, review of outpatient reports, general practitioners were contacted by phone or municipal death registry were consulted.	165 patients had missing data.	Adjusted for glucose, Hb and CrCl on admission, LVEF<40%, age, sex, TIMI flow less than 3, the presence of multivessel disease, ischemic and door-to-balloon times and the presence of diabetes on admission.
Voeltz 2007	Blood sampling at baseline.	End points determined by blinded clinical events committee.	Unclear.	Adjusted for unclear variables.
Vrsalovic 2012	Blood sampling on admission.	30 day outcomes based on medical documentation, telephone interviews with the patient, their family members or home physicians.	Unclear.	Adjust for PAMI risk score, gender, peak creatinine kinase value, admission troponin T, baseline serum creatinine, platelet count, time to treatment, initial and final TIMI flows, LVEF, in hospital medications, multivessel disease, CRP and mean platelet volume.

PCI= percutaneous coronary intervention, BMI=body mass index, Hb=haemoglobin, LDL=low density lipids, GFR=glomerular filtration rate, CABG=coronary artery bypass graft, MI=myocardial infarction, LVEF=left ventricular ejection fraction.

Table 3: Study results

Study ID	Definition of anaemia/hemoglobin/ hematocrit groups	Outcomes and timepoint of follow up	No. of events in anemic group	No. of events in non-anemic group	Results
Akgul 2013	Anaemia defined by Hb <13 mg/dl in men and <12 mg/dl in women.	6 month cardiovascular mortality.	Unclear. 64 anemic patients.	Unclear. 456 non-anemic patients.	6 month cardiovascular mortality: Multivariate OR: 3.9 (1.52-10.2).
Ali 2004	Anaemia defined as Hb <13 g/dl in men, <12 g/dl in women. Bloods before PCI, 6 and 12 hours post PCI.	Median follow up of 2.6 years for mortality.	Major bleed 159/4,815.	Major bleed 51/7,176.	Long term (median 2.6 years) mortality with anaemia: multivariate OR: 1.8 (1.6-2.0). In-hospital major bleeding and anaemia: multivariate OR: 3.3 (2.3-4.6).
Ayhan 2011	Anaemia defined by Hb <13 g/dl for men and <12 g/dl for women.	In-hospital: mortality, re-infarction, MACE (cardiac death, re-infarction, target vessel revascularization), major bleeding requiring transfusion. Long term cardiovascular	Crude events in-hospital: mortality 31/616, re-infarction 14/616, MACE 61/616, major bleeding requiring transfusion 65/616. Long term cardiac events: 56/574, re-infarction 47/574, MACE 157/574.	Crude events in-hospital: mortality 35/1893, re-infarction 36/1893, MACE 104/1893, major bleeding requiring transfusion 27/1893. Long term cardiac events: 72/1823, re-infarction 175/1823, MACE 430/1823.	Long term cardiovascular mortality with anaemia: multivariate OR 2.2 (1.2-4.0).

		mortality, re-infarction and MACE.			
Bolinska 2011	Anaemia defined by Hb, <12 g/dl for women and <13 g/dl for men.	In-hospital death and cardiovascular events.	In-hospital death: 5/61. CV complications 20/61 (33%).	In-hospital death: 3/490. CV complications: 83/490 (17%).	Risk factor for death or cardiovascular complication: multivariate Hb on admission OR 0.89 (0.754-1.051).
Catakoglu 2007	Anaemia defined by hematocrit <39% for men and <36% for women.	Nonfatal coronary events (MI, CABG or repeat PCI) during 1 year follow up.	Non-fatal coronary events: 23/31.	Non-fatal coronary events: 26/69.	Nonfatal coronary events with anaemia: multivariate OR 2.507 (1.379-4.555).
Chi 2012	Anaemia defined by Hb <130 g/l in men, <120 g/l in women.	Long term mortality at follow up of 528 days.	Unclear.	Unclear.	Long term mortality with anaemia: RR 3.293 (1.431-7.578).
Cho 2011a	Anaemia defined by Hb <13 mg/dl in men and <12 mg/dl in women.	Death or MACE at 1 month and 6 months.	1 month: MACE 22/182, death 16/182. 6 months: MACE 43/182, death 23/182.	1 month: MACE 29/557, death 17/557. 6 months: MACE 76/557, death 22/557.	See crude results.
Cho 2011b	Anaemia defined by Hb <12 g/dl for women, <13 g/dl for men.	Mortality and MACE at 2 years.	Mortality: 34/679. MACE 44/679.	Mortality: 39/2170. MACE: 52/2170.	Anaemia and risk of mortality: multivariate HR 1.52 (0.90-2.56). Anaemia and risk of MACE: multivariate HR 1.78 (1.14-2.78).
Dada 2009	Anaemia defined by Hb	In-hospital and 9 month	Unclear.	Unclear.	Anaemia and in-hospital mortality:

	<13 g/dl for men and <12 g/dl for women.	mortality.			propensity matched OR 2.87 (1.58-6.23). Anaemia and 9 month mortality: propensity matched OR 1.46 (1.07-1.99).
Dunbar 2012	Not WHO criteria.	In-hospital events: mortality, re-infarction, congestive heart failure, TIMI major bleeding.	Unclear.	Unclear.	Adjusted risk of in-hospital mortality per 1 g/dl decrease: OR 1.28 (1.01-1.63).
Feldman 2009	Anaemia defined by Hb ≤12 g/dl. Post-PCI bleed defined yb drop in Hb ≥2 g/dl.	In-hospital: death MI, MACE. 1 year death. Death followed up for mean of 24.8 months.	Anemic and bleed total 53. In-hospital death 3/53 (5.7%), MI 7/53 (13.2%), MACE 9/53 (17.0%). 1 year death 8/53 (15.1%). Long term death 13/53 (24.5%). Anemic and no bleed total 656. In-hospital death 2/656 (0.3%), MI 40/656 (6.1%), MACE 42/656 (6.4%). 1 year death 30/656 (4.6%). Long term death 53/656 (8.1%).	Not anemic and bleed total 290. In-hospital death 0/290 (0%), MI 38/290 (12.4%), MACE 38/290 (13.1%). 1 year death 13/290 (4.5%). Long term death: 16/290 (5.5%). Not anemic and no bleed total 1505. In-hospital death 2/1505 (0.1%), MI 99/1505 (6.6%), MACE 101/1505 (6.7%). 1 year death 26/1505 (1.7%). Long term death: 47/1505 (3.1%).	See crude results.

Greenberg 2010	3 groups: Anemic <36% women, <39% men, Normal 36-46 women, 39-47% men, Erythrocytosis >46% women, >47% men.	Mortality, re-infarction, MACE up to 12 months.	1 month: mortality 15/208, re-infarction 16/208. 6 month mortality 19/208, re-infarction 23/208. 12 month mortality 15/208, re-infarction 27/208, MACE: 65/208.	1 month: mortality 22/834, re-infarction 19/834. 6 month mortality 37/834, re-infarction 34/834. 12 month mortality 52/834, re-infarction 49/834, MACE: 181/834.	Anaemia and 1 month mortality: OR 3.5 (1.6-7.5).
Gurm 2004	Continuous hematocrit.	30 day and 6 month MI/mortality. 3 year mortality.	Unclear.	Unclear.	Continuous hematocrit and 3 year mortality: multivariate HR 0.953 (0.930-0.977).
Hanna 2013	Not WHO criteria.	In-hospital death.	Unclear.	Unclear.	Death per 1 g/dl decrease in hemoglobin <15 g/dl: multivariate OR 1.07 (1.02-1.11)
Hosseini 2014	Anaemia defined by Hb >12 g/dl for women, >13 g/dl for men.	In-hospital MACE, MI, death.	In-hospital: 2/493 MACE, 1/493 MI, 0/493 death. 12 month: 24/493 MACE, 11/493 MI, 4/493 death.	In-hospital: 11/2326 MACE, 8/2326 MI, 2/2326 death. 12 month: 71/2326 MACE, 20/2326 MI, 13/2326 death.	Adjusted risk of 12 month MACE: mild anaemia HR 1.249 (0.652-2.390), moderate anaemia HR 1.462 (0.584-3.660), severe anaemia HR 4.623 (1.642-13.021).
Husemann 2007	Continuous Hb.	In-hospital and long term mortality and MI.	Unclear.	Unclear.	Multivariate hazard ratio for mortality per unit increase in hemoglobin concentration: HR 0.711 (0.616-

					0.819).
Jones 2010	Anaemia defined by <12 g/dl for women and <13 g/dl for men.	Mortality at 3 years.	Mortality at 3 years: 64/331.	Mortality at 3 years: 166/1326.	Anaemia and mortality at 3 years: multivariate OR 2.4 (1.1-3.7).
Kim 2012	Anaemia defined by Hb <12 g/dl in women and <13 g/dl in men. Also grouped as sustained or improved anaemia at 3 months.	MACE, MI, death at median follow up of 25.4 months.	Unclear.	Unclear.	Anaemia and MACE (death, MI, stroke): multivariate HR 1.479 (1.025-2.134). Anaemia and death: multivariate HR 1.943 (1.241-3.043). Anaemia and MI: multivariate HR 1.182 (0.476-2.936).
Kitai 2013	Anaemia defined by Hb <12.0 g/dl for women, <13.0 g/dl for men.	3 years MACE, death, MI.	3 years: MACE 466/2206, death 274/2206, MI 77/2206.	3 years: MACE 348/5093, death 150/5093, MI 112/5093.	Mild anaemia and moderate to severe anaemia: MACE HR 1.77 (1.47-2.15), HR 2.53 (2.03-3.14), death HR 1.86 (1.42-2.42), HR 3.35 (2.52-4.47), MI HR 1.14 (0.74-1.75), HR 1.87 (1.13-3.09).
Kruk 2010	Anaemia defined by hematocrit <39% for men and <36% for women.	In-hospital death and heart failure.	Unclear.	Unclear.	Anaemia and death: HR 2.03 (1.19-3.46). Anaemia and heart failure: HR 1.09 (0.79-1.51). Anaemia and death and heart failure: HR 1.34 (0.98-1.82). Anaemia and bleeding: HR

					1.67 (1.12-2.45).
Kurek 2010	Anaemia defined by Hb <13 g/dl for men and <12 g/dl for women.	MACE and death mean follow up of 18.5 months.	Unclear.	Unclear.	Anaemia and in-hospital death: multivariate HR 1.30 (1.09-1.21). Anaemia and 30 day death: multivariate HR 1.19 (0.98-1.40). Anaemia and 1 year death: 1.31 (1.14-1.48). Anaemia and long term mortality: multivariate HR 1.45 (1.29-1.61). MACE 30 days: multivariate HR 1.35 (1.17-1.53). MACE 1 year: multivariate HR 1.14 (1.03-1.25).
Liu 2008	Anaemia defined by <120 g/l in women, <130 g/l in men.	Mortality and MACE (nonfatal MI, stroke and revascularization).	Mortality: 35/744 (4.7%). MACE: 104/744 (14.0%).	Mortality: 46/3065 (1.5%). MACE: 331/3065 (10.8%).	Anaemia and mortality: multivariate RR 2.216 (1.019-4.428)
Liu 2009	Continuous Hb.	Mortality with unclear follow up.	Unclear.	Unclear.	Hemoglobin and long term mortality: HR 0.952 (0.921-0.984).
Maluenda 2009	Continuous hematocrit.	1 year mortality or nonfatal MI.	Unclear.	Unclear.	Unadjusted baseline hematocrit and 1 year outcome: death HR 0.92 (0.91-0.93), MI HR 0.94 (0.91-0.97), death or MI HR 0.92 (0.91-0.93).
Manzano-	Anaemia defined by Hb	Major bleeding with	Major bleed: 23/114 (20%).	Major bleed: 18/164 (10.7%).	Anaemia and major bleed:

Fernandez 2008	<12.0 g/dl for women and <13/0 g/dl for men.	median follow up 19.2 months.			multivariate HR 2.15 (1.08-4.30).
McKechnie 2004	Anaemia defined by Hb <12.0 g/dl in women and <13.0 g/dl in men.	In-hospital MACE, mortality and MI.	Unclear.	Unclear.	Multivariate anaemia and in-hospital mortality: OR 2.29 (1.79-2.92). Multivariate anaemia and in-hospital MACE: OR 1.2 (1.05-1.34). Decreasing hemoglobin and in-hospital mortality: men adjusted OR 1.21 (1.14-1.28), women adjusted OR 1.05 (0.97-1.14).
Nikolsky 2004a	Anaemia defined by hematocrit <39% for men and <36% for women.	Follow up 30 days, 6 months and 1 year.	Mortality: in-hospital 12/260 (4.6%), 30 day 15/260 (5.8%), 1 year 27/260 (10.2%). Cardiac mortality: in-hospital 6/260 (2.4%), 30 day mortality 7/260 (2.8%), 1 year mortality 16/260 (6.1%). Re-infarction: in-hospital 2/260 (0.8%), 30 day 4/260 (1.6%), 1 year 8/260 (2.9%). MACE: in-hospital 20/260 (7.7%), 30	Mortality: in-hospital 19/1,767 (1.1%), 30 day 27/1,767 (1.5%), 1 year 62/1,767 (3.5%). Cardiac mortality: in-hospital 18/1,767 (1.0%), 30 day 25/1,767 (1.4%), 1 year 44/1,767 (2.5%). Re-infarction: in-hospital 4/1,767 (0.2%), 30 day 12/1,767 (0.7%), 1 year 41/1,767	Baseline anaemia and in-hospital mortality: multivariate HR 3.26 (1.01-10.52). Baseline anaemia and 1 year mortality: multivariate HR 2.38 (1.18-4.81).

			day 27/260 (10.4%), 1 year 53/260 (20.3%).	(2.3%). MACE: in-hospital 64/1,767 (3.6%), 30 day 92/1,767 (5.2%), 1 year 306/1,767 (17.3%).	
Nikolsky 2004b	Anaemia defined by hematocrit <39% for men and <36% for women.	In-hospital and 1 year mortality and MI.	In-hospital mortality 32/1,708 (1.9%), cardiac mortality 20/1,708 (1.2%), 1 year MI 132/1,708 (7.7%).	In-hospital mortality 21/5,221 (0.4%), cardiac mortality 16/5,221 (0.3%), 1 year MI 271/5,221 (5.2%).	Anaemia and 1 year mortality: multivariate OR 1.88 (1.46-2.43).
Oduncu 2013	Anaemia defined by Hb <13 mg/dl in men and <12 mg/dl in women.	Mortality, major bleeding and MACE up to 48 months.	In-hospital mortality 49/623 (7.9%), major bleeding 43/623 (6.9%). Long term mortality 165/623 (26.5%), heart failure 55/623 (8.9%), re-infarction 67/623 (10.8%).	In-hospital mortality 41/1,788 (2.3%), major bleeding 45/1,788 (2.5%). Long term mortality 191/1,788 (10.7%), heart failure 88/1,788 (4.9%), re-infarction 141/1,788 (7.9%).	Anaemia and MACE: multivariate HR 3.12 (1.15-6.59).
Ozasa 2012	Anaemia defined by Hb <13 g/dl for men and <12 g/dl for women.	All-cause and cardiac death unclear follow up.	All-cause mortality 293/1,788 (16.4%), cardiac mortality 127/1,788 (7.1%).	All-cause mortality 128/3,548 (3.6%), cardiac mortality 60/3,548 (1.7%).	Anaemia and all-cause mortality: multivariate HR 1.96 (1.49-2.58). Anaemia and cardiac mortality: multivariate HR 1.36 (0.90-2.06).
Park 2012	Anaemia defined by Hb <13 g/dl for men and <12	Mortality, cardiac death, MI and MACE	Mortality 46/349, cardiac death 36/349, MI 14/349,	Mortality 21/532, cardiac death 17/532, MI 10/532,	Anaemia and 2 year mortality: OR 3.78 (2.19-6.52).

	g/dl for women.	up to 2 years.	MACE 78/349.	MACE 78/532.	
Poludasu 2009	Anaemia defined by Hb <13 g/dl for men and <12 g/dl for women. Also grouped by Hb <11.1 and ≥11.1 to <12.6.	In-hospital MACE, death, MI and bleeding and mortality at 3.2 years.	In-hospital: MACE 22/313, death 0/313, MI 13/313, bleeding 9/313. Long term mortality 50/313.	In-hospital: MACE 27/402, death 0/402, MI 19/402, bleeding 8/402. Long term mortality 24/402.	Use crude results.
Rathod 2014	Anaemia defined by Hb <12 g/dl for women, <13 g/dl for men.	MACE, MI and death at 3 years.	In-hospital: major bleeding 19/419, mortality 35/419. 3 year: MACE 101/419, MI 23/419, death 75/419.	In-hospital: major bleeding 30/1,759, mortality 51/1,759. 3 year: MACE 228/1,759, MI 61/1,759, death 106/1,759.	Anaemia and mortality with propensity score match: HR 1.14 (0.52-2.49).
Reinecke 2003	Anaemia defined by Hb <13.0 g/dl (only male participants studied)	In-hospital mortality, at median 697 day follow up death, cardiac death, nonfatal MI.	In-hospital death: 1/144. Follow up death 30/144, cardiac death 19/144, nonfatal MI 4/144.	In-hospital death: 2/545. Follow up death 32/545, cardiac death 25/545, nonfatal MI 22/545.	Unadjusted hemoglobin and death at follow up: HR 0.68 (0.59-0.78). Anaemia and mortality: HR 4.09 (1.52-11.05).
Rodriguez 2013	Anaemia defined by <13 g/dl for men and <12 g/dl for women.	Bleeding, cardiac mortality, all-cause mortality at follow up of 26.5 months.	Bleeding 44/226 (19.5%), mortality 120/226 (5.3%). At follow up cardiac mortality 18/226 (8%), all-cause mortality 46/226 (20.4%).	Bleeding 46/533 (8.6%), mortality 8/533 (1.5%). At follow up cardiac mortality 15/533 (2.8%), all cause morality 26/533 (4.9%).	Anaemia and mortality: multivariate HR 2.1 (1.1-4.1)
Schroder 2013	Continuous Hb.	Mortality at mean follow up of 137 weeks.	Unclear.	Unclear.	Hemoglobin and mortality: multivariate HR 0.784 (0.62-0.991).

Sgura 2010	Anaemia defined by Hb <12 g/dl for women and <13 g/dl for men.	Mortality and MACE at mean of 30 months.	Mortality 26/128 (20.3%), MACCE 40/128 (31.2%).	Mortality 57/545 (10.5%), MACCE 118/545 (21.6%).	See crude results.
Shishehbor 2009	Continuous hematocrit.	Mortality and study took place over 4.5 year interval.	Unclear.	Unclear.	Continuous hematocrit and mortality: multivariate HR 0.93 (0.91-0.96).
Tsujita 2010	Anaemia defined by hematocrit <39% for men and <36% for women. Anaemia at presentation.	Death, cardiac death, re-infarction, TIMI major bleed, MACE up to 1 year.	30 day: death 16/331(4.8%), cardiac death 28/331 (8.5%), re-infarction 6/331 (1.9%), TIMI major bleeding 13/331 (4%), MACE 27/331 (8.2%). 1 year: death 28/331 (8.5%), cardiac mortality 19/331 (5.8%), re-infarction 15/331 (4.5%), TIMI major bleeding 15/331 (4.6%), MACE 61/331 (18.4%).	30 day: death 62/2,822 (2.2%), cardiac death 56/2,822 (2.0%), re-infarction 56/2,822 (2.0%), TIMI major bleeding 99/2,822 (3.5%), MACE 141/2,822 (5.0%). 1 year: death 102/2,822 (3.6%), cardiac death 73/2,822 (2.6%), re-infarction 119/2,822 (4.2%), TIMI major bleeding 104/2,822 (3.7%), MACE 325/2,822 (11.5%).	Multivariate anaemia and mortality at 1 year: HR 1.98 (1.05-3.73). Multivariate anaemia and major bleeding: HR 2.15 (1.43-3.24).
Uchida 2013	Anaemia defined by Hb <13 g/dl for men and <12	Cardiac death or hospitalization for	Unclear.	Unclear.	Anaemia and adverse events: multivariate HR 2.58 (1.01-6.60).

	g/dl for women.	congestive heart failure.			
Varma 2010	Anaemia defined by Hb <13.0 g/dl for men and Hb <12.0 g/dl for women.	Mortality at median of 30 months.	Death 8/30 (25%), cardiac death 2/30 (8%).	Death 5/90 (6%), cardiac death 1/90 (1%).	See crude results.
Vis 2010	Continuous Hb.	1 year mortality.	Unclear.	Unclear.	1 year mortality by hemoglobin: multivariate OR 0.992 (0.992-1.423).
Voeltz 2007	Anaemia defined by Hb <12.0 g/dl for women and <13.0 g/dl for men.	Major bleeding, MACE (death MI, revascularization), mortality and MI.	TIMI major bleeding 15/1,371 (1.1%), MACE 30 days 104/1371 (7.6%), MI 30 days 95/1371 (6.9%), death 30 days 12/1371 (0.9%). death 6 months 36/1371 (2.6%), death 1 year 59/1371 (4.3%).	TIMI major bleeding 30/4,499 (0.7%), MACE 30 days 328/4498 (7.3%), MI 30 days 292/4498 (6.5%), death 30 days 9/4498 (0.2%), death 6 months 31/4498 (0.7%), death 1 year 67/4498 (1.5%).	Multivariate anaemia and 1 year mortality adjusted for transfusions: HR 1.84 (1.22-2.78).
Vrsalovic 2012	Anaemia defined by Hb <13 g/dl for men and <12 g/dl for women.	Mortality at 30 days.	Unclear.	Unclear.	Multivariate 30 day mortality with anaemia: OR 2.69 (1.24-5.86).

Figure 1: Flow diagram of study selection

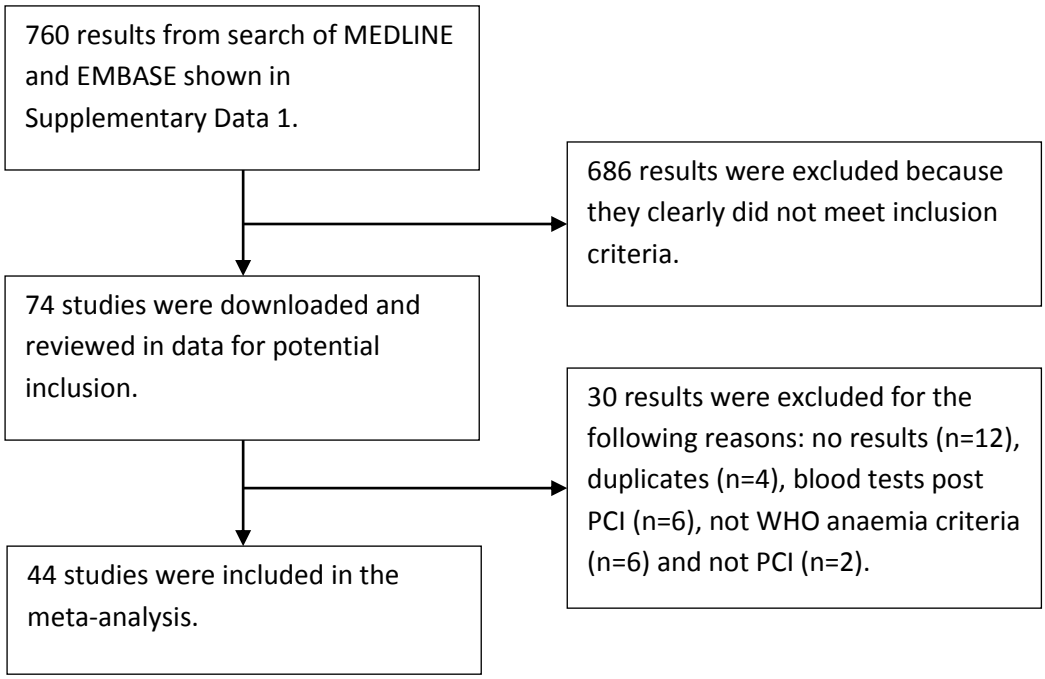


Figure 2: Risk of mortality with anaemia compared to no anaemia

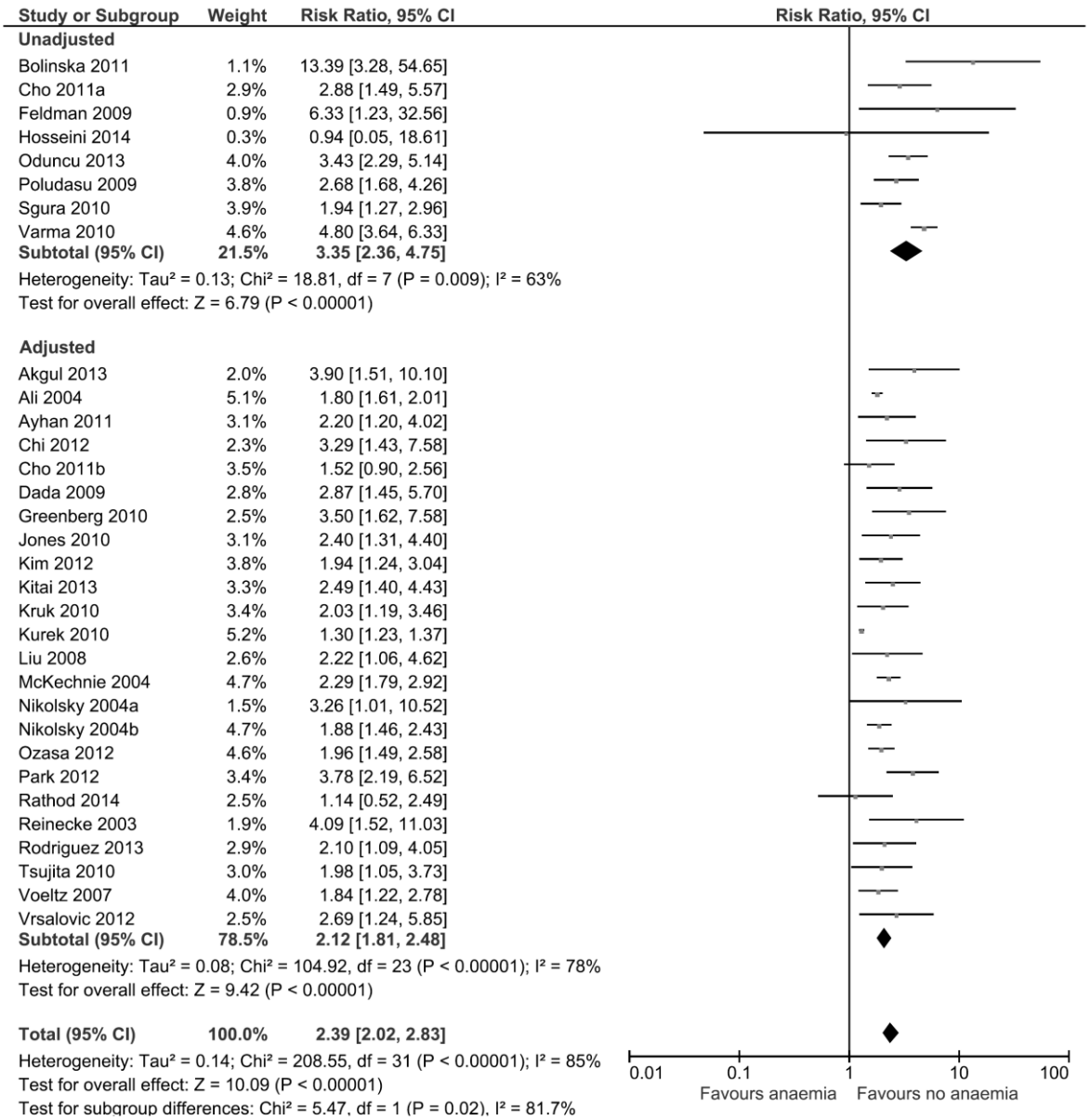


Figure 3: Risk of major adverse cardiovascular events with anaemia compared to no anaemia

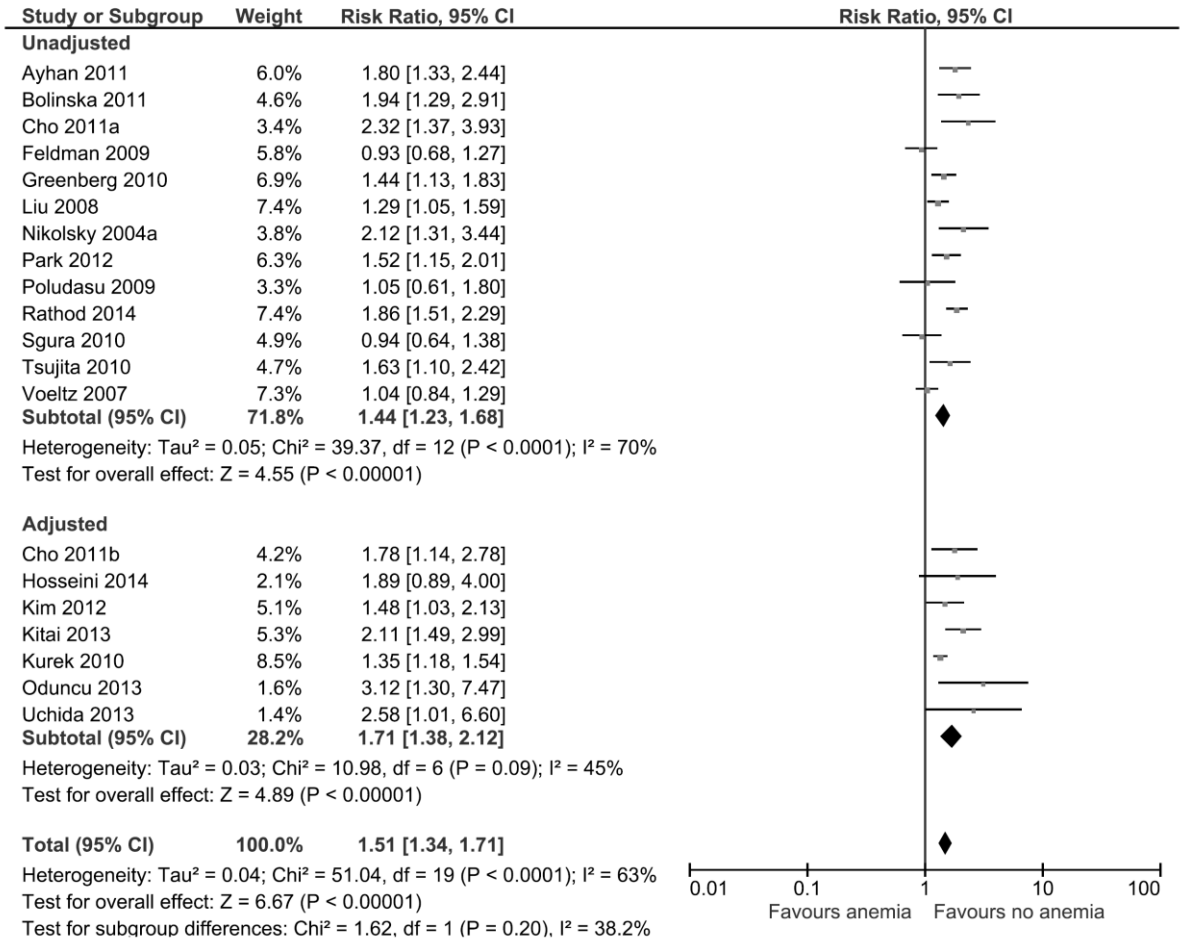


Figure 4: Risk of re-infarction with anaemia compared to no anaemia

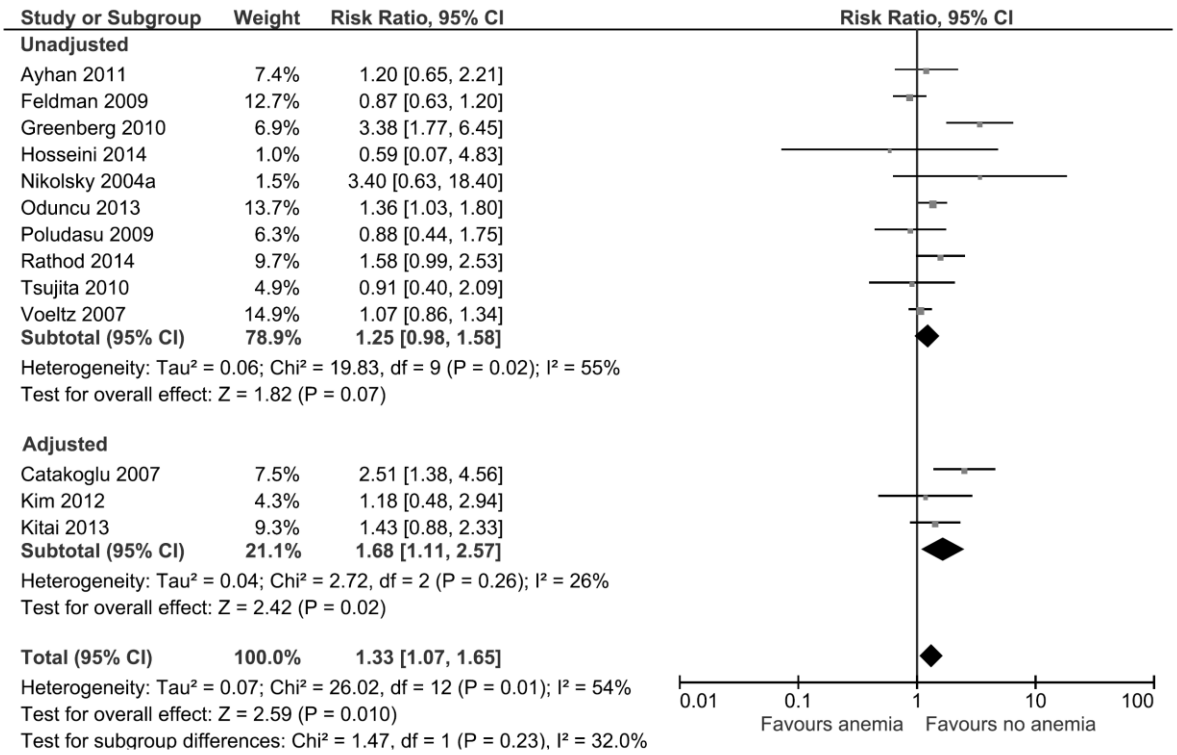


Figure 5: Risk of bleeding with anaemia compared to no anaemia

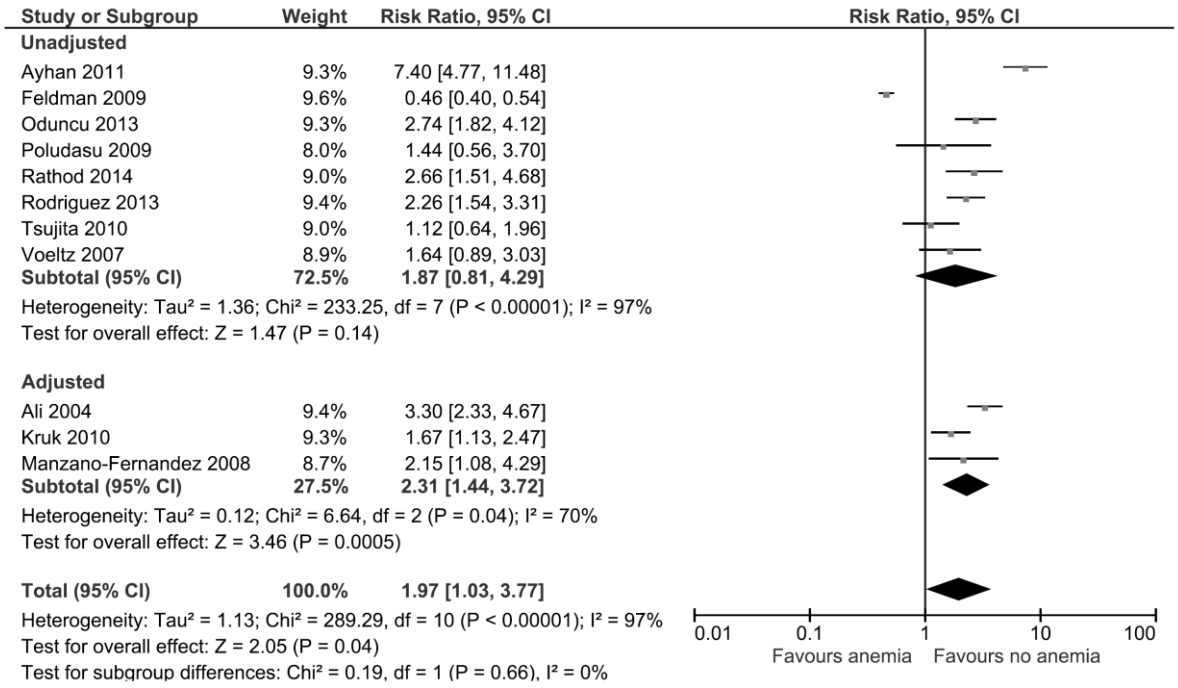


Figure 6: Risk of adverse outcomes by incremental decrease in haemoglobin (Hb) or haematocrit (Hct)

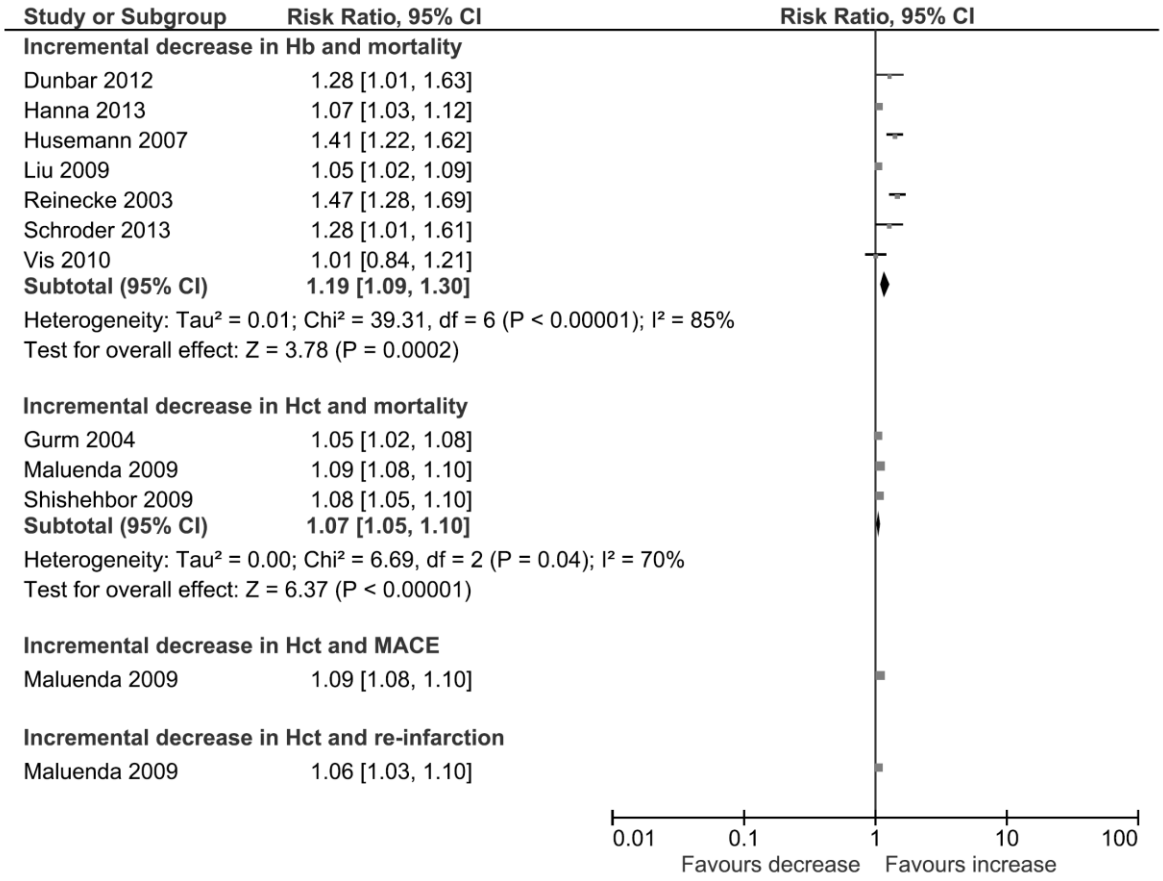
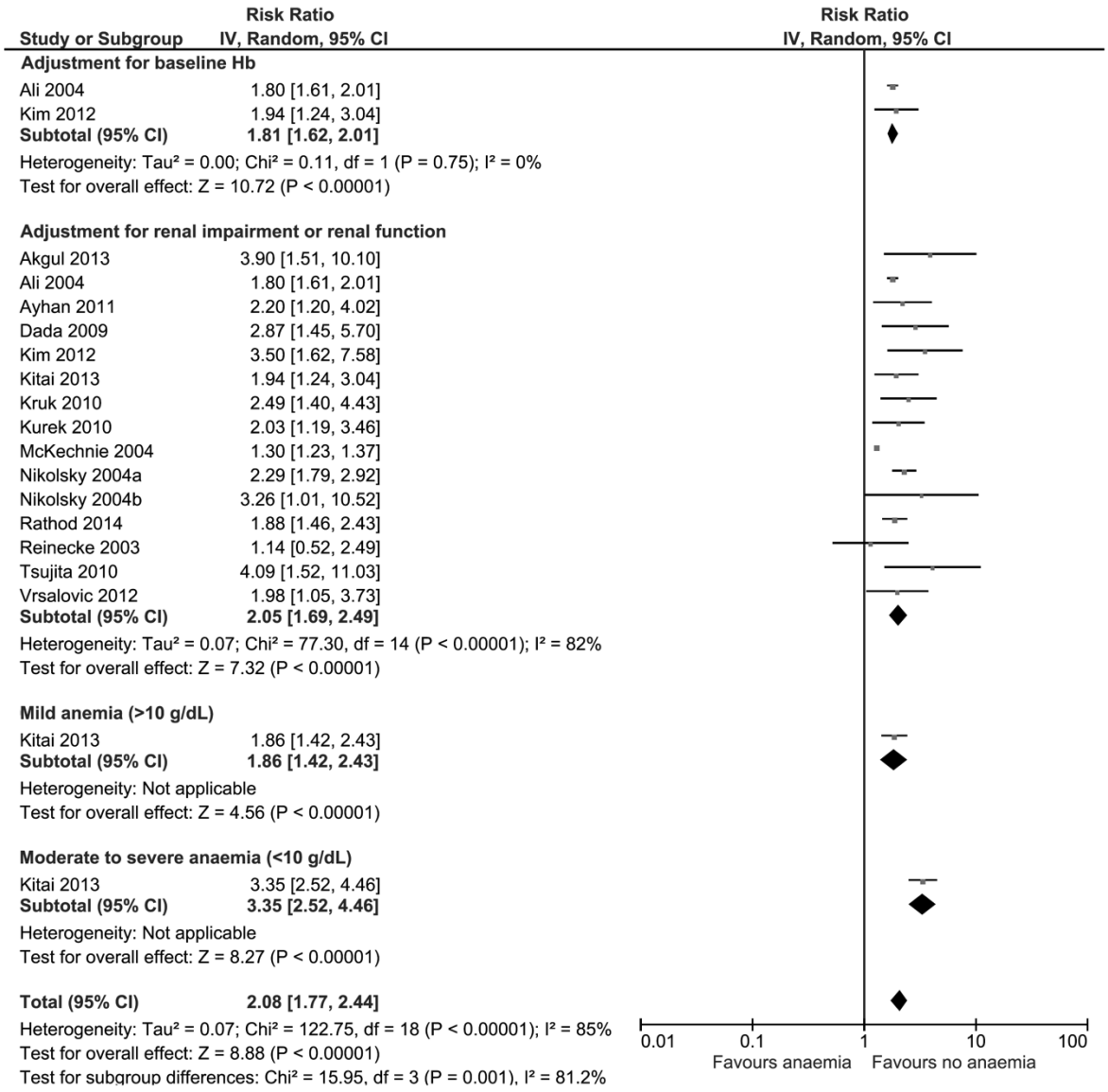


Figure 7: Subgroup analysis of risk of mortality with anaemia compared to no anaemia



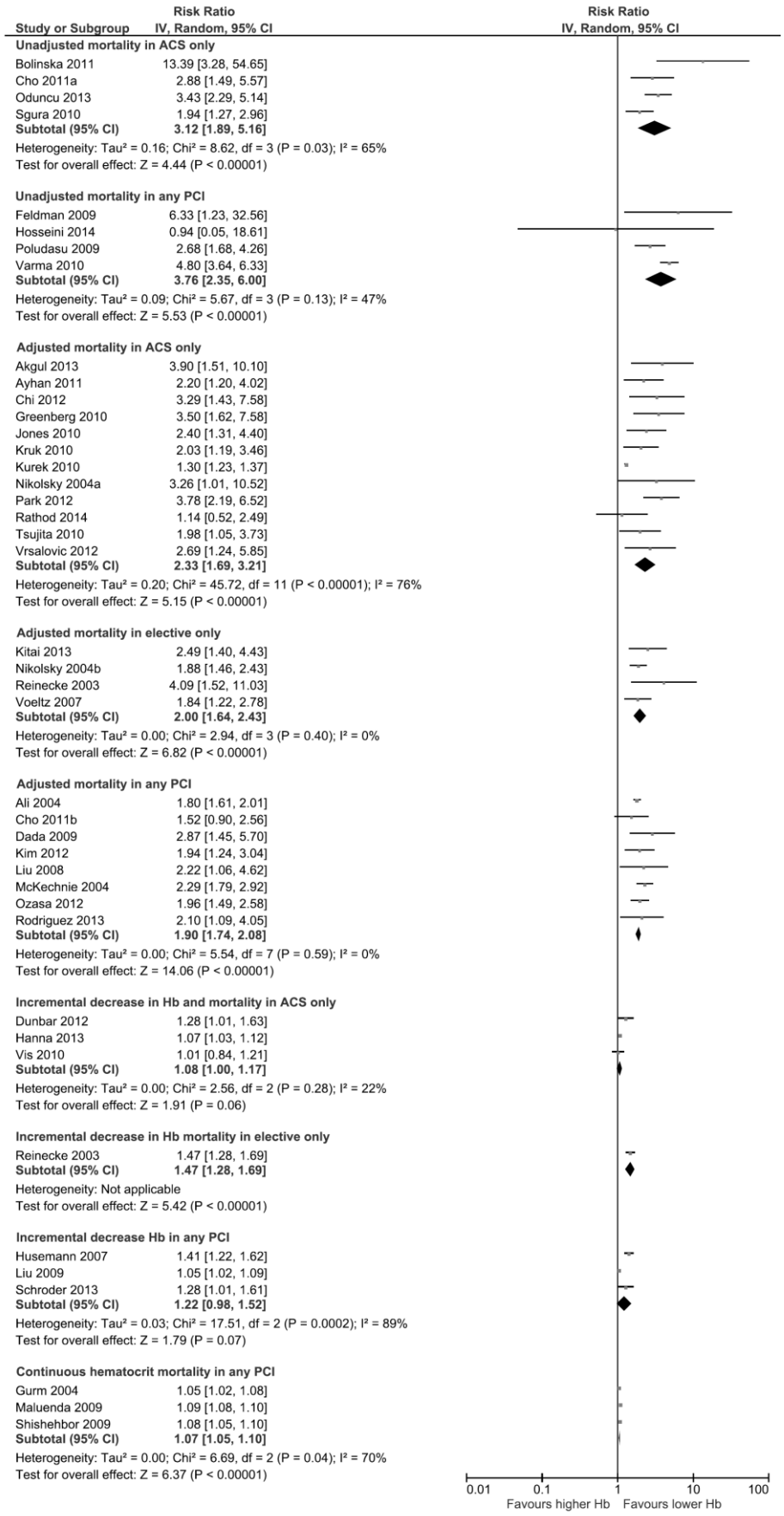
Supplementary Data 1: Search strategy

No.	Search terms	Results
1	PCI.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]	41063
2	coronary-intervention.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]	59810
3	coronary-angioplasty.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]	42063
4	1 or 2 or 3	110471
5	anaemia.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	57957
6	anaemia.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	377829
7	5 or 6	394945
8	4 and 7	896
9	Deduplication	760

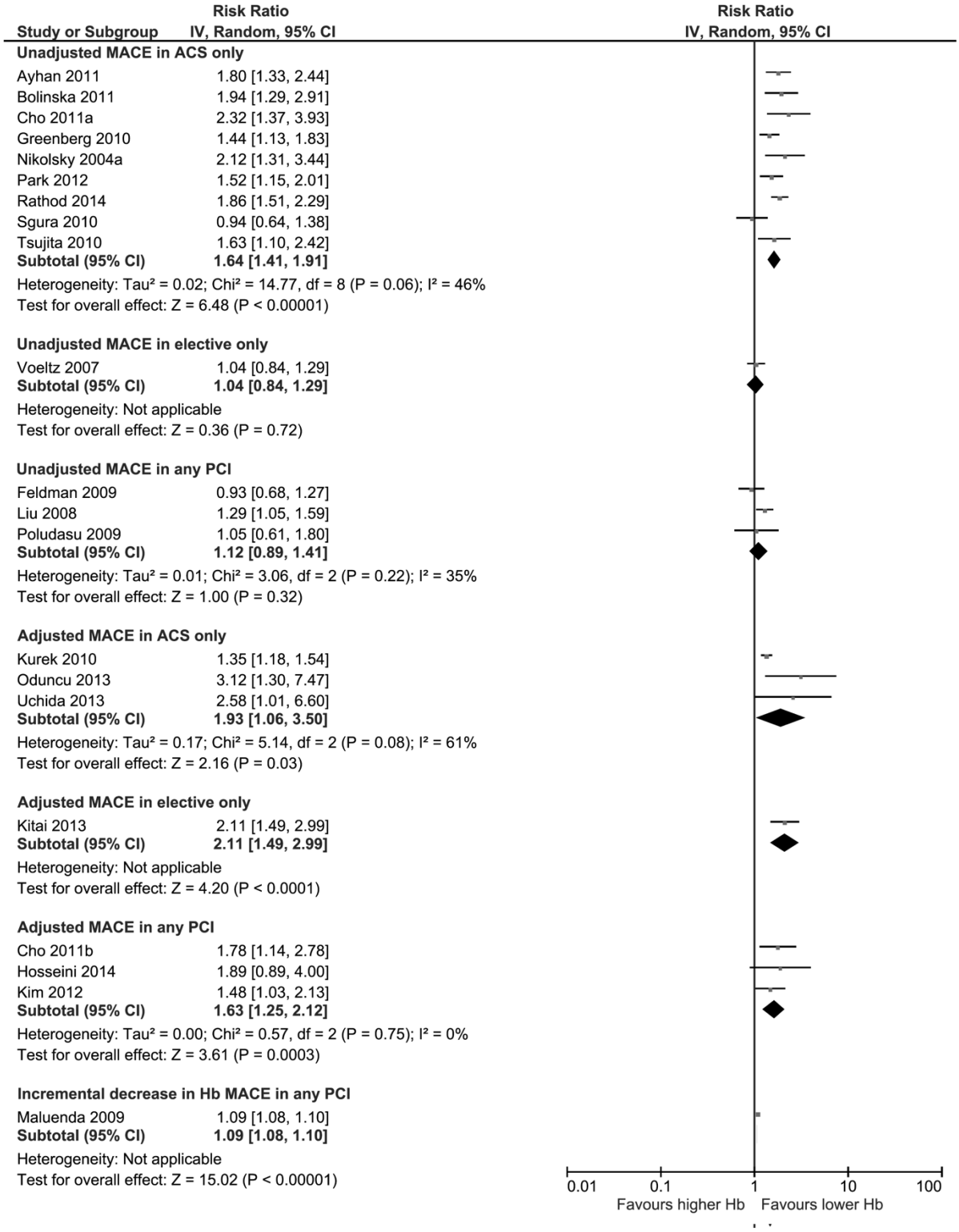
Supplementary Table 2: Sensitivity analysis by indication

Sensitivity analysis for mortality by indication	No. of studies	Risk ratio [95% CI]
Unadjusted mortality in ACS only	4	3.12 [1.89, 5.16]
Unadjusted mortality in any PCI	4	3.76 [2.35, 6.00]
Adjusted mortality in ACS only	12	2.33 [1.69, 3.21]
Adjusted mortality in elective only	4	2.00 [1.64, 2.43]
Adjusted mortality in any PCI	8	1.90 [1.74, 2.08]
Incremental decrease in Hb and mortality in ACS only	3	1.08 [1.00, 1.17]
Incremental decrease in Hb mortality in elective only	1	1.47 [1.28, 1.69]
Incremental decrease Hb in any PCI	3	1.22 [0.98, 1.52]
Continuous hematocrit mortality in any PCI	3	1.07 [1.05, 1.10]
Sensitivity analysis for MACE by indication	No. of studies	Risk ratio [95% CI]
Unadjusted MACE in ACS only	9	1.64 [1.41, 1.91]
Unadjusted MACE in elective only	1	1.04 [0.84, 1.29]
Unadjusted MACE in any PCI	3	1.12 [0.89, 1.41]
Adjusted MACE in ACS only	3	1.93 [1.06, 3.50]
Adjusted MACE in elective only	1	2.11 [1.49, 2.99]
Adjusted MACE in any PCI	3	1.63 [1.25, 2.12]
Incremental decrease in Hb MACE in any PCI	1	1.09 [1.08, 1.10]
Sensitivity analysis for reinfarction by indication	No. of studies	Risk ratio [95% CI]
Unadjusted reinfarction in ACS only	6	1.57 [1.13, 2.18]
Unadjusted reinfarction in elective only	1	1.07 [0.86, 1.34]
Unadjusted reinfarction in any PCI	3	0.87 [0.65, 1.16]
Adjusted reinfarction in elective only	2	1.84 [1.07, 3.18]
Adjusted reinfarction in any PCI	1	1.18 [0.48, 2.94]
Incremental decrease in Hb reinfarction in any PCI	1	1.06 [1.03, 1.10]
Sensitivity analysis for bleeding by indication	No. of studies	Risk ratio [95% CI]
Unadjusted bleeding in ACS only	4	2.82 [1.34, 5.96]
Unadjusted bleeding in elective only	1	1.64 [0.89, 3.03]
Unadjusted bleeding in any PCI	3	1.12 [0.32, 3.88]
Adjusted bleeding in ACS only	1	1.67 [1.13, 2.47]
Adjusted bleeding in any PCI	2	2.97 [2.07, 4.26]

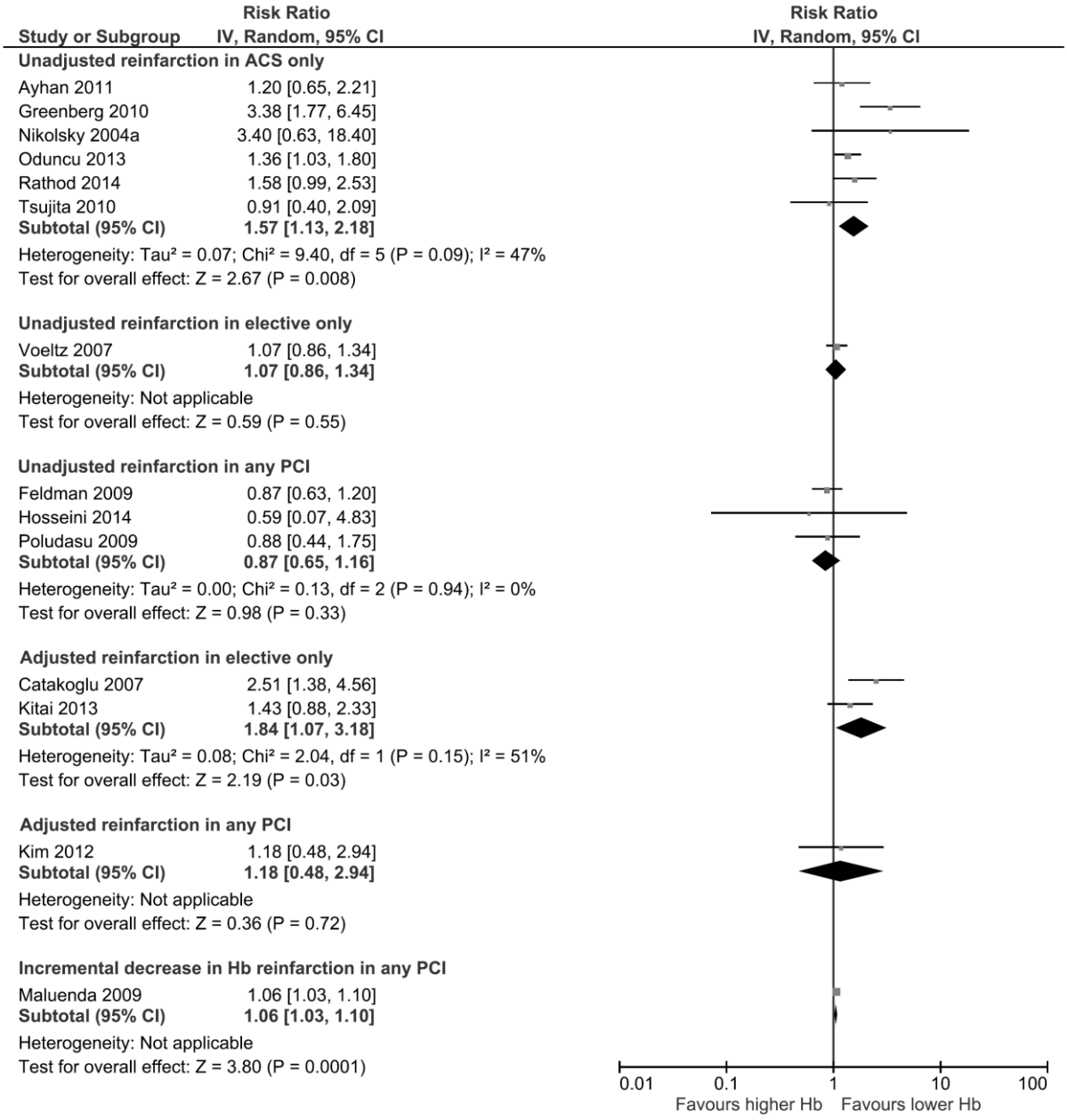
Supplementary Figure 1: Effect of anaemia and low haemoglobin on 30-day mortality by indication



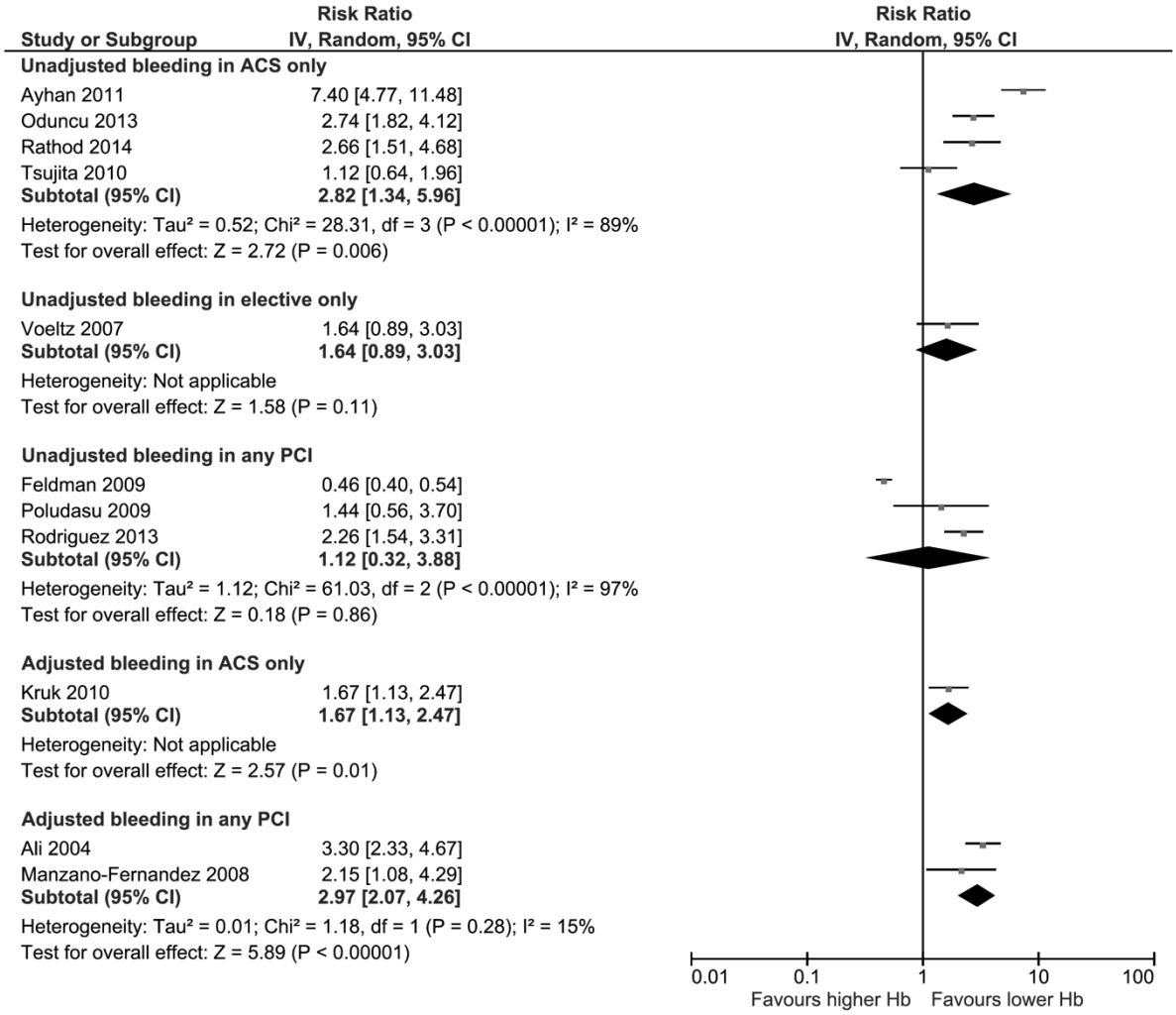
Supplementary Figure 2: Effect of anaemia and low haemoglobin on in-hospital MACE by indication



Supplementary Figure 3: Effect of anaemia and low haemoglobin on in-hospital reinfarction by indication



Supplementary Figure 4: Effect of anaemia and low haemoglobin on in-hospital bleeding by indication



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