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

Article short title: Impact of anemia in PCI

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Abstract

Anemia is common amongst patients undergoing percutaneous coronary intervention (PCI) and current guidelines fail to offer recommendations for its management. This review aims to examine the relationship 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 non-anemic 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 26,514/170,914 (16%). There was an elevated risk of mortality and MACE with anemia compared to no anemia pooled RR 2.39 (2.02-2.83), p<0.001 and RR 1.51 (1.34-1.71), p<0.001, respectively. The risk of myocardial infarction and bleeding with anemia compared to no anemia was elevated, pooled RR 1.33 (1.07-1.65), p=0.01 and RR 1.97 (1.03-3.77), p<0.001, respectively. The risk of mortality per unit incremental decrease in hemoglobin(g/dl) was RR 1.19 (1.09-1.30), p<0.001 and the risk of mortality, MACE and re-infarction per 1 unit incremental decrease in hematocrit(%) was RR 1.07 (1.05-1.10), p=0.04, RR 1.09 (1.08-1.10) and RR 1.06 (1.03-1.10), respectively. The prevalence of anemia in contemporary cohorts of patients undergoing PCI is significant and is associated with significant increases in post procedural mortality, MACE, re-infarction and bleeding. The optimal strategy for the management of anemia in such patients remains uncertain.

Keywords: Percutaneous coronary intervention; anemia; mortality

Introduction

The prevalence of anemia amongst patients undergoing percutaneous coronary interventions (PCI) is reported between 10-23% in randomized controlled trials,[1-3] with rates >30% reported in observational registries.[4,5] Current clinical guidelines fail to offer recommendations for its concurrent management in patients undergoing PCI. Patients with anemia who undergo PCI are frequently older,[5-6] with multiple co-morbidities[1,7-12] and more extensive and complex coronary disease.[11-12] These clinical and procedural characteristics are well known to be associated with poorer outcomes post PCI. Many studies previously have reported that the presence of baseline anemia is independently associated with mortality[5,7,8,13] and major adverse cardiovascular events (MACE)[5,14] and major bleeding complications[15] and several PCI risk scores have used anemia as important predictors for both mortality[16] and bleeding outcomes.[17] In contrast, other studies suggest that whilst these relationships exists for unadjusted data, anemia is no longer associated with increased mortality following adjustment for potential confounders[14,18-19] To the best of our knowledge, there has not been a systematic review or meta-analysis of the prevalence and prognostic impact of anemia in the setting of PCI. We have therefore undertaken a meta-analysis to systematically study the impact of anemia in patients who have undergone PCI on mortality, MACE, major bleeding and re-infarction.

Methods

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. We also included studies that evaluated the risk of adverse outcomes for incremental increase or decrease in hemoglobin.

A search of MEDLINE and EMBASE was performed on OVID SP on April, 8 2014. The exact search strategy is shown in Supplementary Table 1 (online only). There was no restriction on the search based on language and both abstracts and unpublished literature were included.

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 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 and follow up. 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 analyses with >10 studies and no evidence of substantial heterogeneity.[20]

We used RevMan (version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark) 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 ratios because cardiovascular events were rare events.[21] We chose to pool adjusted results when available and crude results when adjusted results were not available. For datasets with the multiple time points we chose to pool the results of the longest time-point (up to 4.5 year interval) in the individual 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 both the incremental decrease in hemoglobin per unit and incremental decrease in hematocrit and the risk of adverse outcomes. For the main analysis of anemia and risk of mortality, we

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

Results

The process of study selection is shown in Figure 1. 44 studies[S1-S44] (Online Supplementary Data**)** were included with a total of 230,795 participants. The number of participants ranged from 100 to 73,067 and the overall prevalence of anemia was 26,514/170,914 (15.5% (15.3-15.7)) and for individual studies the prevalence ranged from 3% to 41%. The study design, study dates, country of origin and indications for PCI are shown in Table 1. There were 4 post hoc analyses of randomized 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 only NSTEMI patients and all patients included in the analysis underwent PCI.

Supplementary Table 2 (online only) shows the risk of bias table for the included studies. Almost all of the studies specified that blood measurements were taken prior to PCI except one study with unclear timing of blood sampling. A variety of methods were used to ascertain adverse outcomes after PCI and loss to follow up was reported in 18 studies. The majority of studies reported at least one adjusted analysis except for 5 studies.

The study definitions of anemia, lengths of follow up and results are shown in Table 2 and Supplementary Table 3 (online only). The most frequent definition of anemia was the WHO criteria and the mean follow up of the studies ranged from in-hospital events up to 4.5 years. The risk of mortality and MACE (as defined by each study in Supplementary Table 4 (online only)) with anemia compared to no anemia 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. There was a significant difference between the unadjusted and

adjusted results for anemia and mortality (p=0.02). The risk of re-infarction and bleeding with anemia compared to no anemia 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. A summary of key results are shown in Figure 6.

The analysis for incremental decrease in hemoglobin and hematocrit is shown in Figure 7. The risk of mortality for incremental decrease in every 1 unit of hemoglobin (g/dl) was RR 1.19 (1.09-1.30) (7 studies, 82,208 participants) and the risk of mortality, MACE and re-infarction 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.

Sensitivity analysis was performed considering the subgroup of studies that had used adjustments for baseline hemoglobin or renal impairment or severity of anemia (Figure 8). The pooled results of 3 studies that adjusted for baseline hemoglobin showed a significant increase in mortality (RR 1.81 (1.62-2.01)). Similarly, a significantly higher mortality was observed for studies that adjusted for renal impairment (RR 2.05 (1.69-2.49)). Kitai et al was the only study that considered severity of anemia and showed a dose response relationship; mild anemia (>10 g/dL) was associated with RR 1.86 (1.42-2.43) while moderate to severe anemia (<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 (online only) and Supplementary Table 5 (online only). There were significant increases in mortality, MACE and bleeding outcomes for patients with anemia in both the ACS and elective setting in adjusted analyses. However, there was only a significant increase in mortality with incremental decrease in hemoglobin in elective cases but not ACS.

Discussion

This meta-analysis of 44 studies including 230,795 patients has shown that the mean prevalence of anemia 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 associated with incremental decreases in hemoglobin levels. This increased risk appears to be independent of the common causes of anemia such as chronic renal disease or bleeding events sustained peri-procedurally, and is of similar magnitude in both the elective and ACS setting. The present analysis is the first to systematically study the prognostic impact of anemia in contemporary cohorts undergoing PCI.

Previous studies report conflicting data regarding the association between anemia and clinical outcomes in patients undergoing PCI, with studies reporting both an independent association with increased mortality, MACE and major bleeding complications[3,5,7-9,13-15] or no increase in risk following adjustment for differences in age, comorbidity burden and procedural demographics,[8,18] or only associated with poorer outcomes in patients with severe anemia but not mild or moderate anemia.[10] Other studies have suggested that post-procedural anemia is independently associated with MACE.[19]

There are a number of biological and clinical reasons why chronic anemia may lead to worse clinical outcomes in patients undergoing PCI. Our analysis suggests that anemia is independently associated with a two-fold increased risk of major bleeding complications, which themselves are independently associated with increased risk of mortality.[22] Anemia is also independently associated with a 2.5-fold increased risk of stent thrombosis,[8] which might further contribute to the adverse outcomes reported. Furthermore, patients with anemia are less likely to be prescribed dual antiplatelet therapy peri-procedurally[3,23] although Pilgrim et al. report that the presence of anemia did not influence the choice of peri-procedural antithrombotic or antiplatelet regime at the time of hospital discharge post PCI.[8] Contemporary 3rd generation stent platforms require shorter duration DAPT, with current

European Society of Cardiology Guidelines advocating only 6 months DAPT for PCI cases undertaken electively,[24] whilst the LEADERS FREE study that included high bleeding risk patients, including those with anemia demonstrated no excess risk in a DES platform with mandated DAPT for 1 month compared to bare-metal stents.[25] Furthermore, in the study of Pilgrim et al,[8] patients with hemoglobin <10 g/dl had an overall transfusion rate that was 6.5-fold higher compared with patients with hemoglobin >12 g/dl (64.2% vs 9.9%, p <0.0001). Our previous meta-analysis showed 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.[26] Finally anemia 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. 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.[27]

Whilst our meta-analysis highlights the independent association between the presence of anemia and adverse clinical outcomes in the PCI setting, there are no current recommended guidelines for the treatment of anemia in this setting and whether there is a threshold level of anemia at which treatment should be considered. Previous reports derived from the National Cardiovascular Data Registry dataset have reported significant variations in the prevalence of transfusion events in hospitals across the United States following PCI, with significant differences in hemoglobin threshold that prompts transfusion.[28] Furthermore, randomized trials have yielded conflicting data regarding optimal treatment of anemia in ACS and PCI settings, for example, in the CRIT (conservative versus liberal red cell transfusion in acute myocardial infarction) trial, 45 anemic patients with myocardial infarction were randomized to either a transfusion arm or a control arm, with worse outcomes reported in patients assigned to the transfusion arm (composite endpoint of in-hospital

mortality, re-infarction or HF (38% vs 13%; p = 0.046). In contrast, in the MINT pilot study of anemic patients undergoing angiography, patients randomized to a liberal blood transfusion strategy had lower MACE rates (10.9%) compared to 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).[29]

Our analysis has limitations. Although our meta-analysis suggests a dose dependent association between the presence of anemia and adverse clinical outcomes in PCI, it cannot infer causality. Whilst papers included in this analysis have adjusted for differences in baseline characteristics, 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 we report that anemia is independently associated with major bleeding complications, the studies included in this meta-analysis do not differentiate between access and non-access site bleeding complications, which have different prognostic impacts.[30] Another limitation was that several analyses had at least a moderate level of statistical heterogeneity so we performed sensitivity analysis. Finally, our analysis does not provide insight as to whether different etiologies of anemia have a differential relationship with clinical outcomes.

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Figure Legend

Figure 1: Flow diagram of study selection

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

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

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

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

Figure 6: A summary of main results

Figure 7: Risk of adverse outcomes by incremental decrease in hemoglobin (Hb) or hematocrit (Hct)

Figure 8: Subgroup analysis of risk of mortality with anemia compared to no anemia

Online Supplementary Table 1: Search strategy

Online Supplementary Table 2: Risk of bias table

Online Supplementary Table 3: Crude results

Online Supplementary Table 4: Definition of MACE

Online Supplementary Table 5: Sensitivity analysis by indication

Online Supplementary Figure 1: Effect of anemia and low hemoglobin on 30-day mortality by indication

Online Supplementary Figure 2: Effect of anemia and low hemoglobin on in-hospital MACE by indication

Online Supplementary Figure 3: Effect of anemia and low hemoglobin on in-hospital myocardial infarction by indication

Online Supplementary Figure 4: Effect of anemia and low hemoglobin on in-hospital bleeding by indication

Online Supplementary Data: References to additional studies

Table 1: Study design and participant characteristics

Study ID	Date/Year	Design	Country	No. of centers	Total no. of participants, no. anemic (% anemic)
Akgul 2013	Dec 2010 to May 2012.	Prospective observational study.	Turkey.	Single	520, 64 (12%) anemic.
Ali 2004	Jul 2002 to May 2010	Prospective observational study.	USA.	Unclear.	11,991, 4,815 (40%) anemic.
Ayhan 2011	Unclear.	Retrospective cohort study.	Turkey.	Single.	2,509, 616 (25%) anemic.
Bolinska 2011	May to Dec 2005.	Retrospective cohort study.	Poland.	Single.	551, 61 (11%) anemic.
Catakoglu 2007	Oct 2001 to June 2002.	Prospective cohort study.	Turkey.	Single.	100, 31 (31%) anemic.
Chi 2012	Unclear.	Cohort study.	China.	Unclear.	1014, 253 (25%) anemic.
Cho 2011a	Nov 2005 to Jun 2009.	Retrospective cohort study.	South Korea.	Single.	739, 152 (21%) anemic.
Cho 2011b	Mar 2006 to Dec 2009	Prospective cohort study.	South Korea.	Unclear.	2,849, 679 (24%) anemic.
Dada 2009	Unclear.	Cohort study.	USA.	Unclear.	6,538, 2,159 (33%) anemic.
Dunbar 2012	Jan 2006 to Apr 2008.	Retrospective cohort study.	Turkey.	Single center.	1,625, 395 (24%) anemic.
Feldman 2009	2004 to 2005.	Cohort study.	USA.	Single.	2,504, 709 (28%) anemic.
Greenberg 2010	Jan 2001 to Dec 2007.	Prospective cohort study.	Israel.	Single.	1,042, 208 (20%) anemic.
Gurm 2004	Unclear.	Post hoc analysis of RCT.	USA.	Multicenter.	6,322, 638 (10%) anemic.
Hanna 2013	Jan 2007 to Dec 2009.	Cohort study.	USA.	354 centers.	73,067, 2,417 (3%) anemic.
Hosseini 2014	Apr 2005 to Sept 2008	Cohort study.	Iran.	Single.	2,819, 493 (17%) anemic.
Husemann 2007	Jan 2001 to Dec 2001.	Retrospective cohort study.	Germany.	Single.	709, 128 (18%) anemic.
Jones 2010	Jan 2004 to Mar 2009.	Prospective cohort study.	UK.	Single.	1657, 331 (20%) anemic.
Kim 2012	Jan 2004 to Dec 2009.	Retrospective cohort study.	South Korea.	Single.	3,549, 1,321 (37%) anemic.
Kitai 2013	Jan 2005 to Dec 2007.	Retrospective cohort study.	Japan.	26 centers.	7,299, 2,209 (30%) anemic.
Kruk 2010	Feb 2001 to Dec 2004.	Prospective cohort study.	Poland.	Unclear.	1880, 385 (20%) anemic.
Kurek 2010	Sept 2004 to Dec 2007.	Prospective cohort study.	Poland.	Single center.	1,497, 248 (17%) anemic.
Liu 2008	Jul 2003 to Sept 2005.	Cohort study.	China.	Single.	3,809, 744 (20%) anemic.
Liu 2009	Unclear.	Cohort study.	Unclear.	Unclear.	3770.
Maluenda 2009	2003 to 2007	Retrospective cohort study.	USA.	Single.	6,025, 210 (3%) anemic.
Manzano-Fernandez 2008	Unclear.	Cohort study.	Spain.	2 centers.	278, 114 (41%) anemic.
McKechnie 2004	July 1997 to May 2003.	Prospective cohort study.	USA.	18 hospitals.	48,851.
Nikolsky 2004a	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	2,027, 260 (13%) anemic.
Nikolsky 2004b	1994 to 1999	Prospective cohort study.	USA.	Single.	6,929, 1,708 (25%) anemic.
Oduncu 2013	Unclear.	Cohort study.	Turkey.	Single.	2,411, 623 (26%) anemic.
Ozasa 2012	2005 to 2007	Retrospective cohort study.	Japan.	Unclear.	5,336, 1,788 (34%) anemic.
Park 2012	2004 to 2010.	Cohort study.	South Korea.	Unclear.	881, 349 (40%) anemic.
Poludasu 2009	Jan 2003 to Aug 2005.	Retrospective cohort study.	USA.	Unclear.	715.
Rathod 2014	Jan 2004 to Aug 2010.	Retrospective cohort study.	UK.	Single.	2,178, 419 (19%) anemic.
Reinecke 2003	1998 to 1999	Retrospective cohort study.	Germany.	Single.	689.
Rodriguez 2013	2007 to 2011.	Prospective cohort study.	Spain.	Single.	759, 226 (30%) anemic.
Schroder 2013	2004 to 2006.	Retrospective cohort study.	Germany.	Unclear.	2,056.
Sgura 2010	2002 to 2008.	Cohort study.	Italy.	Single.	673.

Shishehbor 2009	Mar 2003 to June 2007.	Prospective cohort study.	USA.	Single.	2,172.
Tsujita 2010	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	3,153, 331 (10%) anemic.
Uchida 2013	Unclear.	Cohort study.	Japan.	Unclear.	337, 59 (18%) anemic.
Varma 2010	Apr 2003 to Dec 2005.	Retrospective cohort study.	USA.	Unclear.	120.
Vis 2010	Jan 1997 to Mar 2005.	Prospective cohort study.	Netherlands.	Single.	292.
Voeltz 2007	Unclear.	Post hoc analysis of RCT.	International.	Multicenter.	6,010, 1,371 (23%) anemic.
Vrslovic 2012	Unclear.	Prospective cohort study.	Croatia.	Single.	543.

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

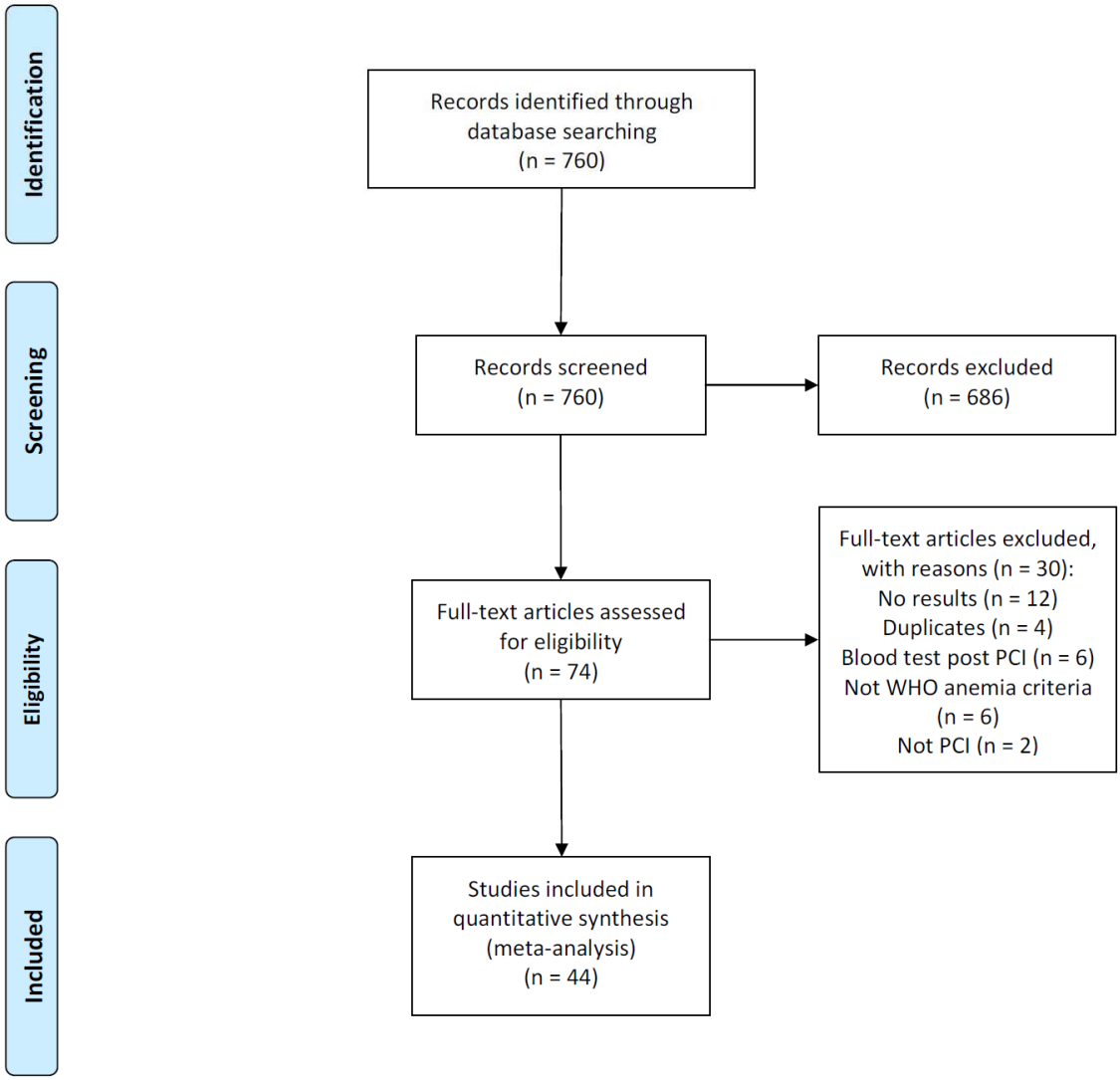
Table 2: Study results

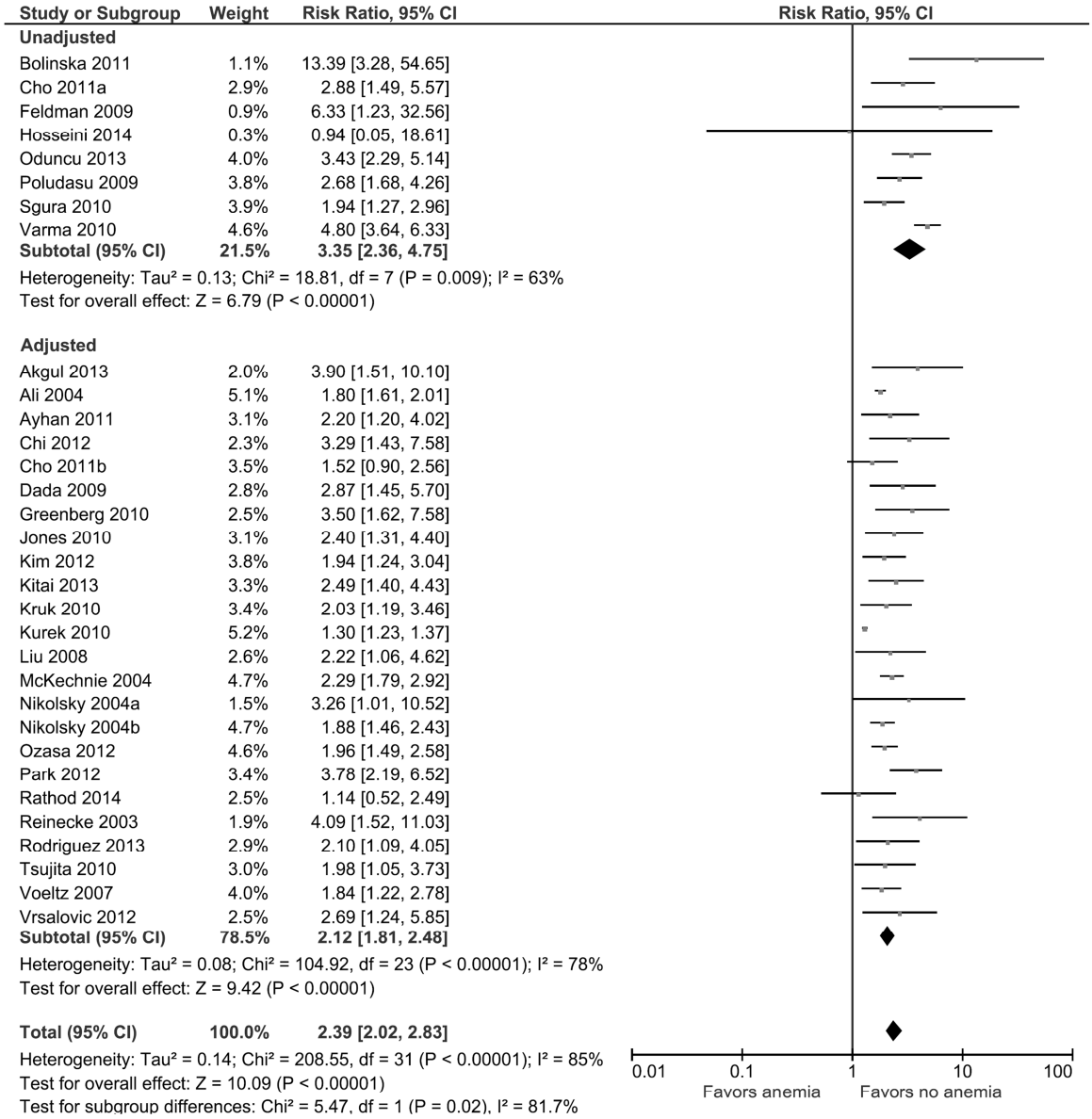
Study ID	Definition of anemia		Follow up	Results
	Hb (mg/dL)	Hct (%)	(mo)	
Akgul 2013	<13(M)<12(F)	-	6	Odds of cardiovascular mortality with anemia vs no anemia: aOR 3.9 (1.52-10.2).
Ali 2004	<13(M)<12(F)	-	31	Odds of long term mortality with anemia: aOR: 1.8 (1.6-2.0). In-hospital major bleeding: aOR: 3.3 (2.3-4.6).
Ayhan 2011	<13(M)<12(F)	-	In-hospital	Odds of long term cardiovascular mortality with anemia vs no anemia: aOR 2.2 (1.2-4.0).
Bolinska 2011	<13(M)<12(F)	-	In-hospital	Odds of death or cardiovascular complication with incremental Hb: aOR 0.89 (0.754-1.051).
Catakoglu 2007	-	<39%(M)<36%(F)	12	Odds of nonfatal coronary events with anemia vs no anemia: aOR 2.507 (1.379-4.555).
Chi 2012	<13(M)<12(F)	-	17	Risk of long term mortality with anemia vs no anemia: RR 3.293 (1.431-7.578).
Cho 2011a	<13(M)<12(F)	-	6	See crude results in Supplementary Material.
Cho 2011b	<13(M)<12(F)	-	24	Risk of mortality with anemia vs no anemia: aHR 1.52 (0.90-2.56). MACE: aHR 1.78 (1.14-2.78).
Dada 2009	<13(M)<12(F)	-	9	Odds of in-hospital mortality with anemia vs no anemia: OR 2.87(1.58-6.23). 9 month mortality OR 1.46(1.07-1.99).
Dunbar 2012	<13(M)<12(F)	-	In-hospital	Odds of in-hospital mortality per 1 g/dl decrease in Hb: aOR 1.28 (1.01-1.63).
Feldman 2009	≤12	-	25	See crude results in Supplementary Material.
Greenberg 2010	-	<39%(M)<36%(F)	12	Odds of 1 month mortality with anemia vs no anemia: OR 3.5 (1.6-7.5).
Gurm 2004	-	<35%, 35-40%	36	Risk of 3 year mortality per % of continuous hematocrit: aHR 0.953 (0.930-0.977).
Hanna 2013	<10, 10-12	-	In-hospital	Odds of death per 1 g/dl decrease in Hb <15 g/dl: aOR 1.07 (1.02-1.11).
Hosseini 2014	<13(M)<12(F)	-	12	MACE with anemia mild aHR 1.249(0.652-2.39) moderate aHR 1.462(0.584-3.66) severe aHR 4.623(1.642-13.021).
Husemann 2007	<13(M)<12(F)	-	"Long term"	Risk of long term mortality per unit increase in Hb: HR 0.711 (0.616-0.819).
Jones 2010	<13(M)<12(F)	-	36	Odds of 3 year mortality with anemia vs no anemia: aOR 2.4 (1.1-3.7).
Kim 2012	<13(M)<12(F)	-	25	Risk with anemia: MACE aHR 1.479(1.025-2.134), death aHR 1.943(1.241-3.043), MI aHR 1.182(0.476-2.936).
Kitai 2013	<13(M)<12(F)	-	36	See results in Supplementary Material for mild/moderate-severe anemia.
Kruk 2010	-	<39%(M)<36%(F)	In-hospital	Anemia: death HR 2.03(1.19-3.46) HF HR 1.09(0.79-1.51) death/HF HR 1.34(0.98-1.82) bleed HR 1.67(1.12-2.45)
Kurek 2010	<13(M)<12(F)	-	19	Risk of 1 year outcomes with anemia: death aHR1.31(1.14-1.48) MACE aHR1.14(1.03-1.25). See Supplementary Material.
Liu 2008	<13(M)<12(F)	-	Unclear	Risk of mortality with anemia: aRR 2.216 (1.019-4.428).
Liu 2009	-	-	Unclear	Risk of long term mortality and Hb: HR 0.952 (0.921-0.984).
Maluenda 2009	-	-	12	Risk with incremental hematocrit: death HR 0.92(0.91-0.93), MI HR 0.94(0.91-0.97), death/MI HR 0.92(0.91-0.93).
Manzano 2008	<13(M)<12(F)		19	Risk of major bleed with anemia: aHR 2.15 (1.08-4.30).
McKechnie 2004	<13(M)<12(F)		In-hospital	Anemia: death OR 2.29(1.79-2.92) MACE OR 1.2(1.05-1.34) ↓Hb: death (M) aOR 1.21(1.14-1.28), (F) aOR 1.05(0.97-1.14).
Nikolsky 2004a	-	<39%(M)<36%(F)	12	Risk of outcome with anemia: in-hospital mortality: aHR 3.26 (1.01-10.52), 1 year mortality aHR 2.38 (1.18-4.81).
Nikolsky 2004b	-	<39%(M)<36%(F)	12	Odds of 1 year mortality with anemia vs no anemia: aOR 1.88 (1.46-2.43).
Oduncu 2013	<13(M)<12(F)	-	48	Risk of MACE with anemia vs no anemia: aHR 3.12 (1.15-6.59).
Ozasa 2012	<13(M)<12(F)	-	Unclear	Risk of mortality with anemia vs no anemia aHR 1.96 (1.49-2.58) and cardiac mortality: aHR 1.36 (0.90-2.06).
Park 2012	<13(M)<12(F)	-	24	Odds of 2 year mortality with anemia vs no anemia: OR 3.78 (2.19-6.52).
Poludasu 2009	<13(M)<12(F)	-	38	See crude results in Supplementary Material.
Rathod 2014	<13(M)<12(F)	-	36	Risk of mortality with anemia vs no anemia: propensity score matched HR 1.14 (0.52-2.49).
Reinecke 2003	<13	-	23	Risk of death with incremental increase in Hb HR 0.68 (0.59-0.78) and anemia vs no anemia HR 4.09 (1.52-11.05).
Rodriguez 2013	<13(M)<12(F)		27	Risk of mortality with anemia vs no anemia: aHR 2.1 (1.1-4.1).
Schroder 2013	-	-	32	Risk of mortality with incremental increase in Hb: aHR 0.784 (0.62-0.991).
Sgura 2010	<13(M)<12(F)	-	30	See crude results in Supplementary Material.
Shishehbor 2009	-	<40%(M)<36%(F)	54	Risk of mortality with incremental increase in hematocrit aHR 0.93 (0.91-0.96).
Tsujita 2010	-	<39%(M)<36%(F)	12	Risk of with anemia vs no anemia: 1 year mortality aHR 1.98 (1.05-3.73), major bleeding: aHR 2.15 (1.43-3.24).
Uchida 2013	<13(M)<12(F)	-	Unclear	Risk of adverse events with anemia vs no anemia: aHR 2.58 (1.01-6.60).

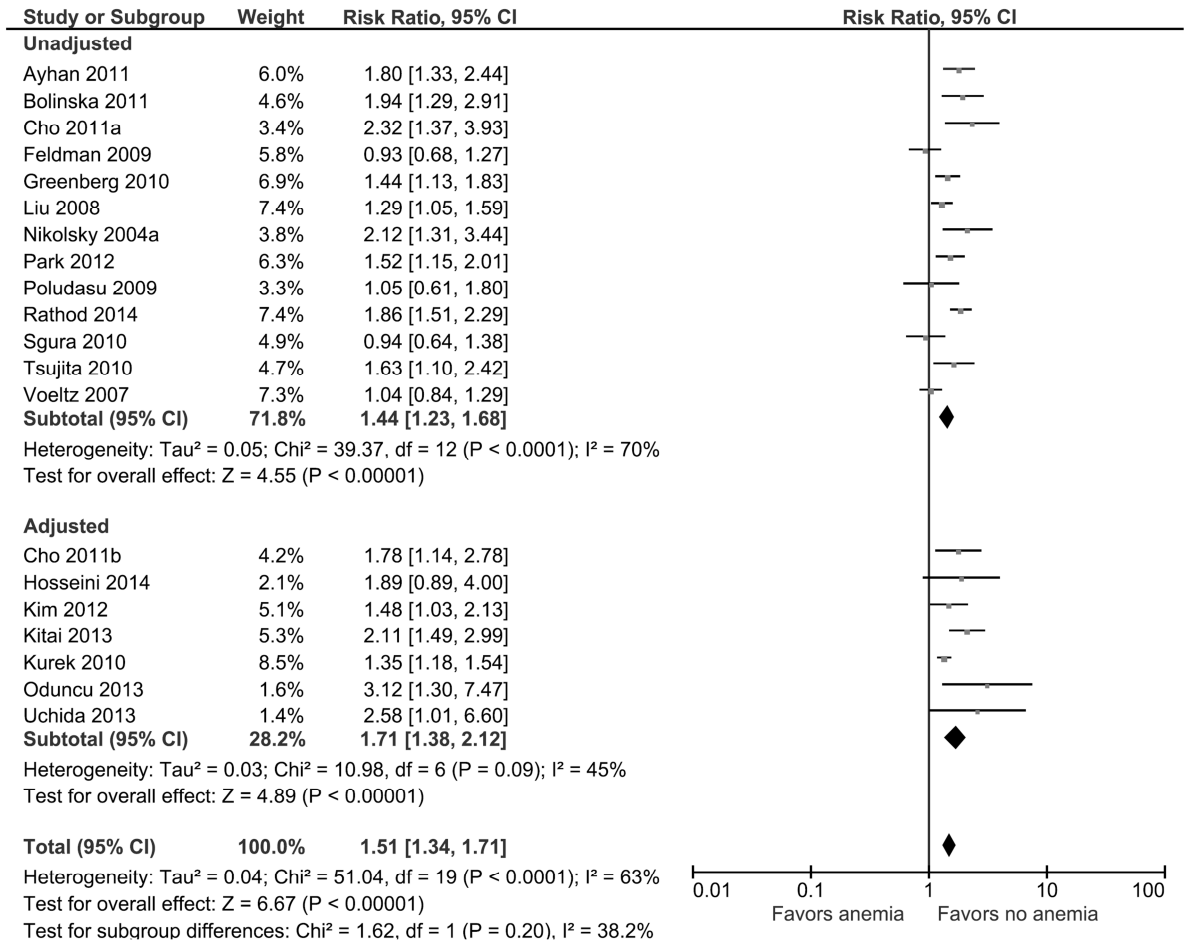
Varma 2010	<13(M)<12(F)	-	30	See crude results in Supplementary Material.
Vis 2010	<13(M)<12(F)	-	12	Odds of 1 year mortality with incremental Hb: aOR 0.992 (0.992-1.423).
Voeltz 2007	<13(M)<12(F)	-	12	Risk of 1 year mortality with anemia vs no anemia: aHR 1.84 (1.22-2.78).
Vrsalovic 2012	<13(M)<12(F)	-	1	Odds of 30 day mortality with anemia vs no anemia: aOR 2.69 (1.24-5.86).

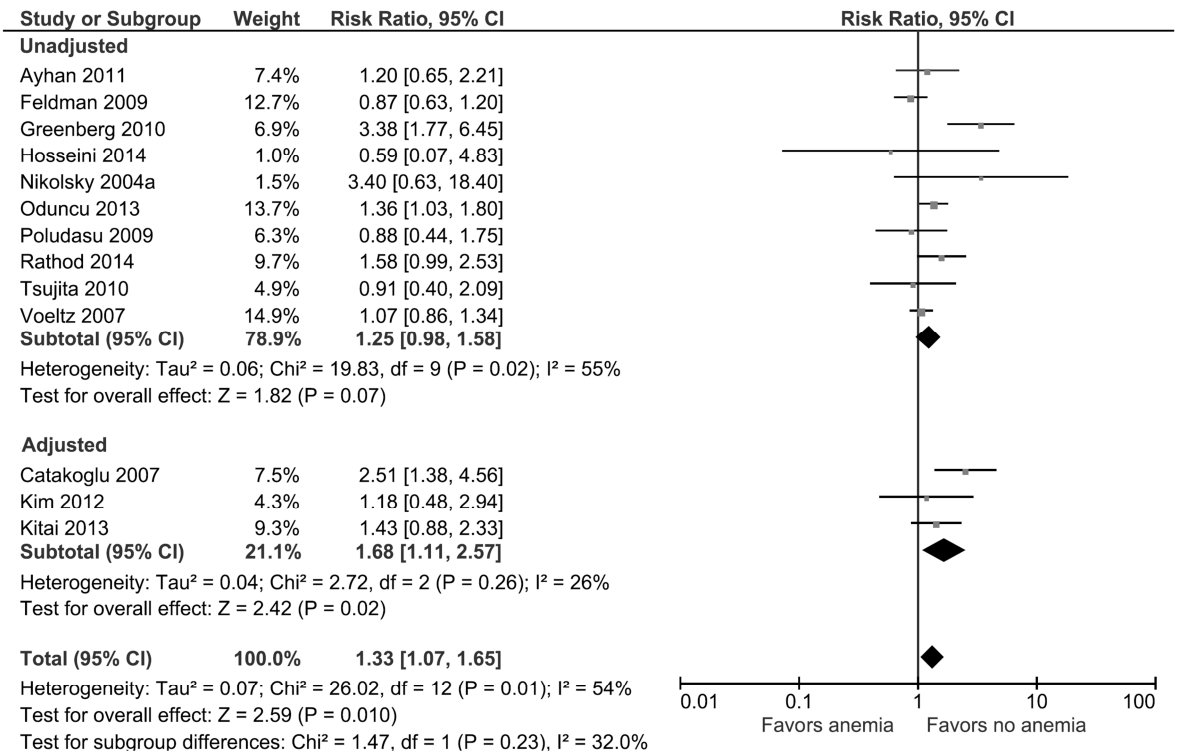
M=male, F=female, Hb=hemoglobin, HF=heart failure aHR=adjusted hazard ratio. aOR=adjusted odds ratio. aRR=adjusted relative risk.

PRISMA 2009 Flow Diagram









Study or Subgroup	Weight	Risk Ratio, 95% CI
Unadjusted		
Ayhan 2011	9.3%	7.40 [4.77, 11.48]
Feldman 2009	9.6%	0.46 [0.40, 0.54]
Oduncu 2013	9.3%	2.74 [1.82, 4.12]
Poludasu 2009	8.0%	1.44 [0.56, 3.70]
Rathod 2014	9.0%	2.66 [1.51, 4.68]
Rodriguez 2013	9.4%	2.26 [1.54, 3.31]
Tsujita 2010	9.0%	1.12 [0.64, 1.96]
Voeltz 2007	8.9%	1.64 [0.89, 3.03]
Subtotal (95% CI)	**72.5%**	**1.87 [0.81, 4.29]**
Heterogeneity: Tau² = 1.36; Chi² = 233.25, df = 7 (P < 0.00001); I² = 97%		
Test for overall effect: Z = 1.47 (P = 0.14)		
Adjusted		
Ali 2004	9.4%	3.30 [2.33, 4.67]
Kruk 2010	9.3%	1.67 [1.13, 2.47]
Manzano-Fernandez 2008	8.7%	2.15 [1.08, 4.29]
Subtotal (95% CI)	**27.5%**	**2.31 [1.44, 3.72]**
Heterogeneity: Tau² = 0.12; Chi² = 6.64, df = 2 (P = 0.04); I² = 70%		
Test for overall effect: Z = 3.46 (P = 0.0005)		
Total (95% CI)	**100.0%**	**1.97 [1.03, 3.77]**
Heterogeneity: Tau² = 1.13; Chi² = 289.29, df = 10 (P < 0.00001); I² = 97%		
Test for overall effect: Z = 2.05 (P = 0.04)		
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%