

# Impact of anemia on long-term ischemic events and bleeding events in patients undergoing percutaneous coronary intervention: a system review and meta-analysis

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**Background:** Data focused on the ischemic events and bleeding events are still limited. We systematically reviewed the current available literature to investigate whether anemia increase incidence of long-term ischemic events and long-term bleeding events in patients undergoing PCI.

**Methods:** PubMed and Embase were searched for case-control studies regarding the impact of anemia on long-term outcomes in patients undergoing percutaneous coronary intervention (PCI). The primary outcome was long-term ischemic events and long-term bleeding events. Mantel-Haenszel method with random effects model or fixed effects model was used to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs).

**Results:** Seventeen studies involving 68,528 patients (17,123 anemic patients and 51,405 non-anemic patients) were included. Pooled analysis suggested that anemic patients were at higher risk for long-term composite ischemic events (OR: 1.95, 95% CI, 1.21-3.14,  $P < 0.01$ ,  $I^2 = 84\%$ ), long-term reinfarction (OR: 1.63, 95% CI, 1.16-2.28,  $P < 0.01$ ,  $I^2 = 82\%$ ) and long-term bleeding events (OR: 2.89, 95% CI, 1.68-4.98,  $P < 0.001$ ,  $I^2 = 89\%$ ). Anemia was also associated with long-term mortality (OR: 3.20, 95% CI, 2.72-3.75,  $P < 0.01$ ,  $I^2 = 65\%$ ) and major adverse cardiac events (MACE) (OR: 2.06, 95% CI, 1.48-2.86,  $P < 0.01$ ,  $I^2 = 91\%$ ).

**Conclusions:** Anemic patients undergoing PCI are at higher risk for both long-term ischemic events and bleeding events, and also at higher risk for long-term mortality and MACE. There's a need for further clarification and consistency regarding dosage, timing and duration of antithrombotic therapy for the prevention of ischemic events and bleeding events in anemic patients.

**Keywords:** Anemia; ischemia; hemorrhage; percutaneous coronary intervention (PCI); meta-analysis

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## Introduction

The presence of anemia is associated with worse clinical outcomes in patients with (1-5) or without (6-8) cardiovascular disease. The Atherosclerosis Risk in Communities (ARIC) study (9) and the Women's Ischemia Syndrome Evaluation (WISE) study (10) have

identified anemia as an independent predictor for adverse cardiovascular outcomes. Similar results have been described in patients undergoing percutaneous coronary intervention (PCI) (11-13). Previous studies have shown that anemia was a risk factor for mortality (14,15) and major adverse cardiac events (MACE) (16) in patients undergoing

**Table 1** Search strategy and terms

PubMed	Embase
1. "Anemia" [Mesh]	1. 'Anemia'/exp/mj
2. "Percutaneous Coronary Intervention" [Mesh]	2. 'Percutaneous Coronary Intervention'/exp/mj
3. Not "Review"	3. Not 'Review'
4. 1 AND 2 AND 3	4. 1 AND 2 AND 3

PCI. Anemia has also been reported to be associated with ischemic events (17) and major bleeding events (11,18) in patients undergoing PCI. Improved anemia is associated with favorable outcomes in patients undergoing PCI (19) or with cardiovascular diseases (20). In addition, the non-recovery of anemia is a biomarker of poor outcome (21).

However, data focused on the ischemic events and bleeding events are still limited. Furthermore, considering that many studies (13,16,17,22) were retrospective analysis without pre-specified design, these studies should be considered hypothesis generating, and thus not adequately powered to reach the conclusion that anemia increase the risk of ischemic or bleeding events.

In order to provide the latest and most convincing evidence, we systematically reviewed the current available literature to investigate whether anemia increase incidence of long-term ischemic events and long-term bleeding events in patients undergoing PCI. The secondary objective was to evaluate the effect of anemia on long-term mortality and MACE.

## Materials and methods

The systematic review and meta-analysis was conducted and reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### Literature search and selection criteria

PubMed and Embase were searched for records reporting the impact of anemia on long-term outcomes in patients undergoing PCI. The search strategy is shown in *Table 1*. An English language restriction was imposed. The last search was run on October 29, 2015. Two independent investigators carried out the initial search, deleted duplicate records, screened the titles and abstracts for relevance, and identified as excluded or requiring further assessment. Then

we reviewed the full-text articles for inclusion. We also manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies.

Studies meeting the following inclusion criteria were included: (I) population: patients undergoing PCI; (II) intervention: anemic patients; (III) comparison: non-anemic patients; (IV) outcome: long-term ischemic events and bleeding events; (V) design: case-control studies.

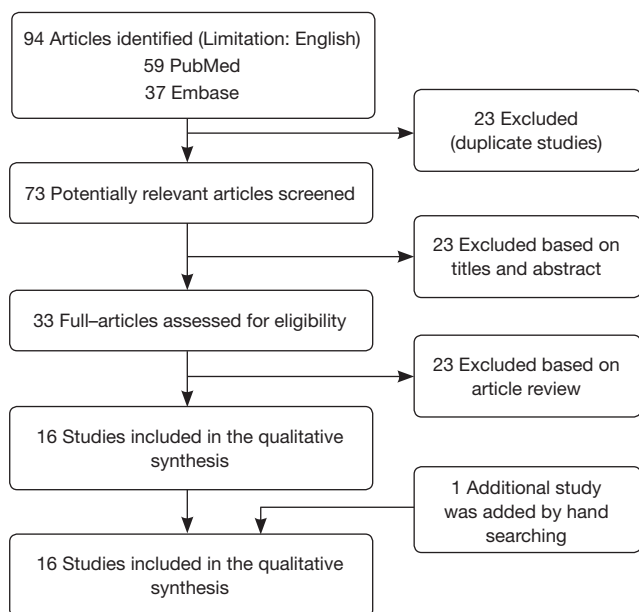
### Data extraction and quality assessment

Data extraction was performed by Xiaoyan Wang and confirmed independently by Miaohan Qiu. The following information was extracted from each study: first author, year of publication, patient characteristics, No. of patients, study design, outcomes, definition of anemia. Extracted data were entered into a standardized Excel file. Discrepancies were resolved by discussion between the two investigators. The primary outcome was long-term ischemic events (including composite ischemic events, reinfarction, TVR. Secondary outcomes included long-term bleeding events, long-term mortality and long-term MACE. The methodologic quality of each study was evaluated using Newcastle-Ottawa Scale.

### Statistical analysis

Differences were expressed as odds ratio (OR) with 95% confidence intervals (CIs). Heterogeneity across studies was tested by using the  $I^2$  statistic, which was a quantitative measure of inconsistency across studies. Studies with an  $I^2$  statistic of 25-50% were considered to have low heterogeneity, those with an  $I^2$  statistic of 50-75% were considered to have moderate heterogeneity and those with an  $I^2$  statistic of >75% were considered to have a high degree of heterogeneity. An  $I^2$  value greater than 50% indicates significant heterogeneity (23). The Mantel-Haenszel method with random effects model was used to calculate pooled ORs and 95% CIs. Post hoc analysis of RCTs was considered as equivalent to observational studies.

The presence of publication bias was evaluated by using the Begg *et al.* (24) and Egger *et al.* (25) tests. A P value <0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA) and RevMan 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark).



**Figure 1** Selection process for studies included in this meta-analysis.

## Results

### Study identification and selection

A total of 96 records were identified by the initial database search. Twenty three records were excluded for duplicates, and 40 records were excluded based on the titles and abstracts. The remaining 33 full-text articles were assessed for eligibility, and 17 (19,26-41) of them were excluded, among which five studies (19,28,31,34,36) didn't divide the cohort into anemia and no anemia, seven studies (26,30,32,35,38,40,41) didn't provide data of incidence of adverse events in anemic or non-anemic patients, four studies (27,29,33,39) didn't provide data of adverse events after 1-year or more, one study (37) defined anemia as post-PCI anemia which is inconsistent with our definition. In addition, one study (42) was added by handle searching. Finally, 17 studies were included in the meta-analysis. The selection process is shown in *Figure 1*.

### Study characteristics

The main characteristics of included studies are described in *Table 2*. These studies were published between 2004 and 2015. The sample size ranged from 312 to 13,032 (a total of 68,528 patients: 17,123 anemic patients and 51,405 non-

anemic patients). The follow-up times range from 12 to 46.7 months. Among the 17 studies, five (11,14,18,46,48) were conducted in North America, six (16,22,42,43,45,50) in Asia, three (12,44,47) in Europe. Three (13,17,50) studies were multicenter studies. All studies were published in English.

Considering ischemic events, two studies reported data regarding composite outcome of ischemic events. Eight studies provided data for target vessel revascularization (TVR) and reinfarction, which were major elements in ischemic events. Among the eight studies (13,16,17,22,43,44,47,49), five studies (13,22,43,44,49) reported the incidence of TVR after PCI, eight studies (13,16,17,22,43,44,47,49) reported incidence of reinfarction after PCI. For bleeding events, four studies (11,18,47,49) reported the incidence of bleeding events. Fifteen studies (12-14,16-18,22,42-49) reported incidence of mortality and nine studies (12,16,22,42-44,47,49,50) reported incidence of MACE. Among the 17 studies, eight studies (11,16,22,43-45,47,50) provided both the number and the incidence of adverse events, four studies (12,13,46,49) provided the incidence of adverse events. Voeltz *et al.* (18) provided the incidence of mortality and the number of bleeding events. Kunadian *et al.* (17) provided RR for adverse events (ischemic events, revascularization, reinfarction, mortality), Lee *et al.* (14), Poludasu *et al.* (48) and Wang *et al.* (42) provided HR for mortality.

### Quality assessment

Risk-of-bias assessment of the included studies is presented in *Table 3*. All studies included have a total score of more than five, among which three study (14,17,48) was eight, five studies (12,16,42,43,45) was seven, five studies (13,18,22,44,49) was six, four studies (11,46,47,50) was five.

### Primary outcome: long-term ischemic events

#### Long-term composite ischemic events

Wang *et al.* (42) and Kunadian *et al.* (17) provided data for ischemic events. Considering the substantial heterogeneity among these studies, a random effect model was used to combine the results. The pooled analysis of the two studies using a random effect model show that anemic patients are at higher risk for ischemic events (OR: 1.95, 95% CI, 1.21-3.14,  $P < 0.01$ ) (*Figure 2A*). There's a high degree of heterogeneity between the two studies ( $I^2 = 84\%$ ,  $P = 0.01$ ) (*Figure 2A*).

Table 2 Characteristics of included studies

Study	Publication year	Setting	Population	No. of patients (anemia/non-anemia)	Follow-up time	Outcomes	Definition of anemia
Ayhan et al. (43)	2011	Turkey	Patients with STEMI undergoing primary PCI	N=2,509; 616 (24.6%)/1,893 (75.4%)	21 months	Cardiovascular mortality, TVR, MACE	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Ali et al. (11)	2014	America	Patients who underwent PCI with bivalirudin as the primary antithrombotic agent were included	N=11,991; 4,815 (40.2%)/7,176 (59.8%)	31.2 months (range, 16.8–42) months	Major bleeding	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Greenberg et al. (22)	2009	Israel	Patients with STEMI undergoing primary PCI	N=926; 208 (22.5%)/718 (77.5%)	12 months	Mortality reinfarction TVR, MACE	Anemia, hematocrit <36% for women and <39% for men; normal, hematocrit 36–46% for women and 39–47% for men
Hosseini et al. (44)	2014	Iran	Patients undergoing PCI	N=2,819; 493 (17.5%)/2,326 (82.5%)	12 months	Total MACE, TVR, nonfatal MI, cardiac death	Preprocedural Hb levels ≤12.0 g/dL in women and ≤13.0 g/dL in men
Kitai et al. (16)	2013	Japan	Patients undergoing elective PCI	N=7,299; 2,206 (30.2%)/5,093 (69.8%)	36 months	MACE, All cause death, MI	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Kunadian et al. (17)	2014	Multiple center	Patients who underwent an early invasive strategy for moderate- or high-risk none ST-segment elevation MI or unstable angina	N=13,032; 2,199 (16.9%)/10,833 (83.1%)	12 months	Composite ischemic event, mortality, MI, unplanned revascularization	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Kurek et al. (12)	2010	Poland	Patients with AMI undergoing PCI	N=1,497; 248 (16.6%)/1,249 (83.4%)	18.5 months (range, 6–48) months	MACE mortality	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Lee et al. (14)	2004	America	Patients undergoing PCI	N=6,116; 1,404 (23.0%)/4,712 (76.0%)	12 months	Mortality	Anemia was defined as hemoglobin level <12 g/dL
Matsue et al. (45)	2013	Japan	Patients with AMI undergoing PCI	N=312; 91 (29.2%)/221 (70.8%)	46.7±21.7 months	Mortality	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Nikolsky et al. (13)	2004	Multiple center	Patients with AMI undergoing PCI	N=2,027; 260 (12.8%)/1,767 (87.2%)	12 months	Mortality, reinfarction, TVR, composite adverse events	Hematocrit <36% for women and <39% for men

Table 2 (continued)

Table 2 (continued)

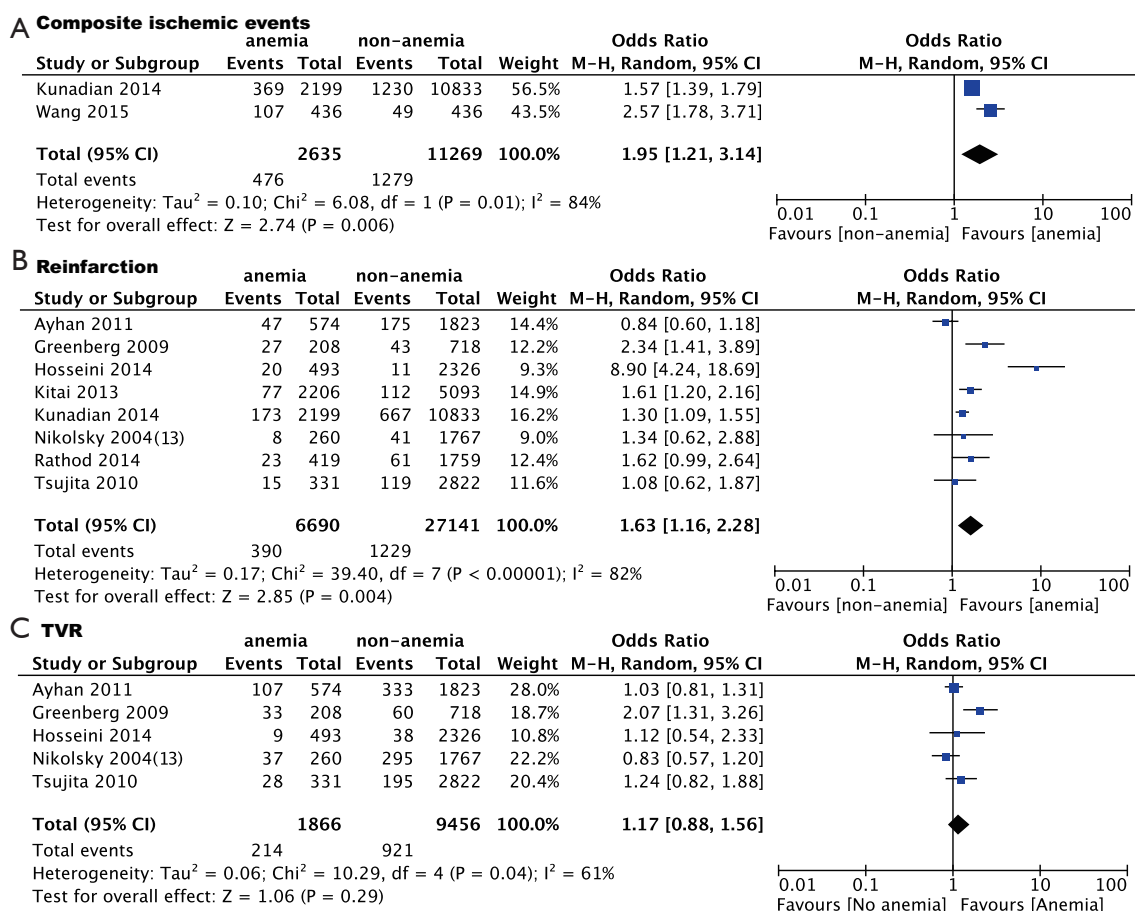
Study	Publication year	Setting	Population	No. of patients (anemia/non-anemia)	Follow-up time	Outcomes	Definition of anemia
Nikolsky <i>et al.</i> (46)	2004	America	Patients undergoing PCI	N=6,929; 1,708 (24.6%)/5,221(75.4%)	12 months	Mortality	Hematocrit <36% for women and <39% for men.
Rathod <i>et al.</i> (47)	2014	England	Patients undergoing PPCI for STEMI	N=2,178; 419 (19.0%)/1,759 (81.0%)	14.4–43.2 months	Bleeding, MI, mortality, reintervention PCI	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Poludasu <i>et al.</i> (48)	2008	America	Patients who underwent PCI with glycoprotein IIb/IIIa bolus-only regimen	N=713; 313 (43.8%)/402 (56.2%)	38.4 months (range, 28.8–45.6) months	Mortality	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Tsujita <i>et al.</i> (49)	2010	Multiple center	Patients with STEMI undergoing PCI	N=3,153; 331(10.5%)/2,822 (89.5%)	12 months	Mortality, reinfarction, TVR, bleeding, MACE	Hematocrit <36% for women and <39% for men
Uchida <i>et al.</i> (50)	2015	Japan	Patients with STEMI undergoing PCI	N=337; 59 (17.4%)/278 (82.5%)	54.8 months	MACE	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Voeltz <i>et al.</i> (18)	2007	America	Patients undergoing PCI	N=5,816; 1,317 (22.6%)/4,499(77.4%)	12 months	Mortality, major bleeding, ischemic events	Anemia was defined as hemoglobin level <13 g/dL for men and <12 g/dL for women
Wang <i>et al.</i> (42)	2015	China	Patients undergoing PCI	N=872; 436 (50%)/436 (50%)	36 months	ischemic events, mortality, MACE	Anemia was defined as a 63 Hb level <11.0 g/dL for women or <12.0 g/dL for men

PCI, percutaneous coronary intervention; TVR, target vessel revascularization; MACE, major adverse cardiac events.

Table 3 Risk-of-bias assessment of the case-control studies

Studies	Selection				Exposure			Total score	
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of Controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls		Non-Response Rate
Ayhan et al. (43)	*	*	*	*	-	*	*	*	7
Ali et al. (11)	*	*	*	-	-	*	*	-	5
Greenberg et al. (22)	*	*	*	*	-	*	*	-	6
Hosseini et al. (44)	*	*	*	*	-	*	*	-	6
Kitai et al. (16)	*	*	*	-	**	*	*	-	7
Kunadian et al. (17)	*	*	*	*	**	*	*	-	8
Kurek et al. (12)	*	*	*	-	**	*	*	-	7
Lee et al. (14)	*	*	*	*	**	*	*	-	8
Matsue et al. (45)	*	*	*	-	**	*	*	-	7
Nikolsky et al. (13)	*	*	*	*	-	*	*	-	6
Nikolsky et al. (46)	*	*	*	-	-	*	*	-	5
Rathod et al. (47)	*	*	*	-	-	*	*	-	5
Poludasu et al. (44)	*	*	*	*	**	*	*	-	8
Tsujita et al. (49)	*	*	*	*	-	*	*	-	6
Uchida et al. (50)	*	*	*	-	-	*	*	-	5
Voeltz et al. (18)	*	*	*	*	-	*	*	-	6
Wang et al. (42)	*	*	*	-	**	*	*	-	7

\*, score of 1; \*\*, score of 2.



**Figure 2** Meta-analysis of impact of anemia on ischemic events. (A) Composite ischemic events; (B) reinfarction; (C) TVR. TVR: target vessel revascularization.

### Long-term reinfarction

Eight studies provided data for reinfarction. The pooled analysis using a random effect model show that anemic patients are at significantly higher risk for long-term reinfarction (OR: 1.63, 95% CI, 1.16-2.28,  $P < 0.01$ ) (Figure 2B), with a high degree of heterogeneity for the included studies ( $I^2 = 82\%$ ,  $P < 0.01$ ) (Figure 2B).

### Long-term TVR

Five studies provided data for TVR. The pooled analysis using a random effect model shows that there is a trend that anemic patients are at higher risk for long-term revascularization (OR: 1.77, 95% CI, 0.88-1.56), but the difference was not statistically significant ( $P = 0.29$ ) (Figure 2C). There is significant heterogeneity among those included studies ( $I^2 = 61\%$ ,  $P = 0.04$ ) (Figure 2C).

### Long-term bleeding events

Four studies reported the incidence of long-term bleeding events. The pooled analysis using a random effect model shows that anemic patients are at a significantly higher incidence of bleeding events (OR: 2.89, 95% CI, 1.68-4.98,  $P < 0.001$ ) (Figure 3). There is a high degree of heterogeneity among the included studies ( $I^2 = 89\%$ ,  $P < 0.01$ ) (Figure 3).

### Secondary outcomes: long-term mortality and long-term MACE

#### Long-term mortality

Fifteen studies provided data for long-term mortality. The pooled analysis using a random effect model shows that anemic patients are at high risk for long-term mortality (OR: 3.20, 95% CI, 2.72-3.75,  $P < 0.01$ ) (Figure 4). There is a moderate heterogeneity among those included studies ( $I^2 = 65\%$ ,  $P < 0.01$ ) (Figure 4).

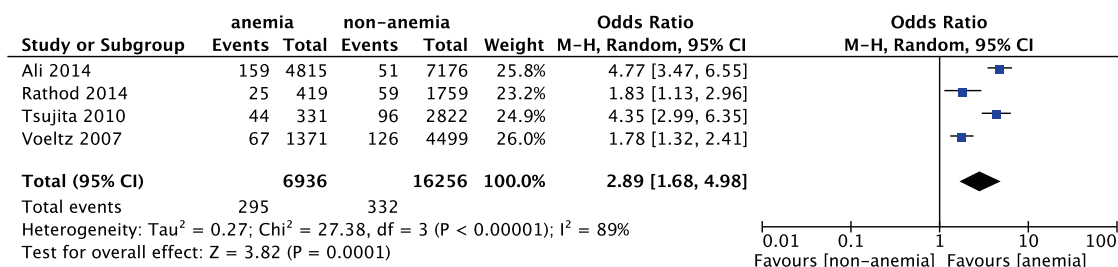


Figure 3 Meta-analysis of impact of anemia on bleeding events.

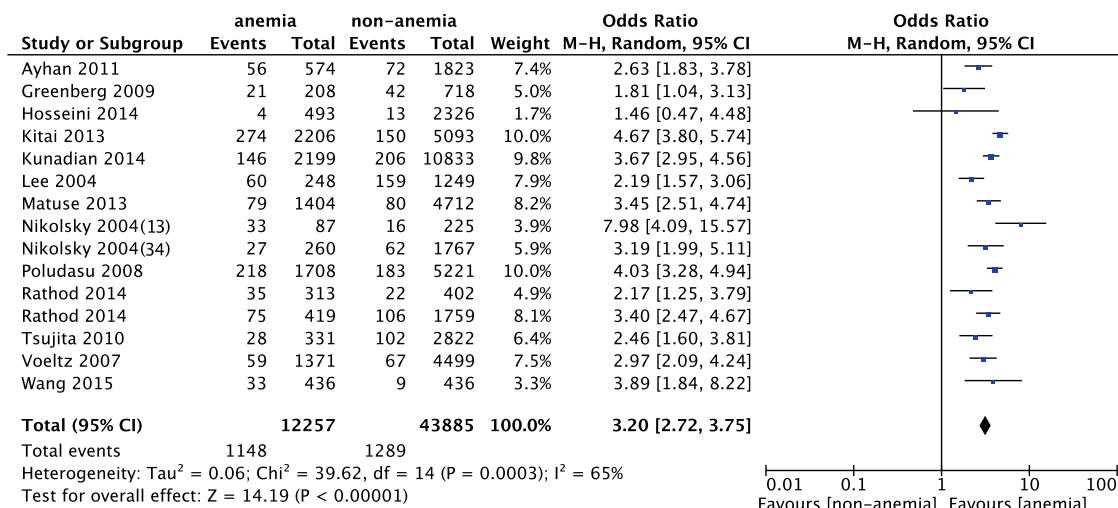


Figure 4 Meta-analysis of impact of anemia on mortality.

### Long-term MACE

Nine studies provided data for long-term MACE. The pooled analysis using a random effect model shows that compared with non-anemic patients, anemic patients are at high risk for long-term MACE (OR: 2.06, 95% CI, 1.48-2.86, P<0.01) (Figure 5). There is a high degree of heterogeneity among the included studies (I<sup>2</sup>=91%, P<0.01) (Figure 5).

### Publication bias

We cannot evaluate publication bias of the only 2 studies reporting the data of ischemic events, so we evaluate publication bias of the impact of anemia on reinfarction instead. There was no evidence of significant publication bias by formal statistical tests (Egger's test, P=0.91; Begg's test P=1.00)

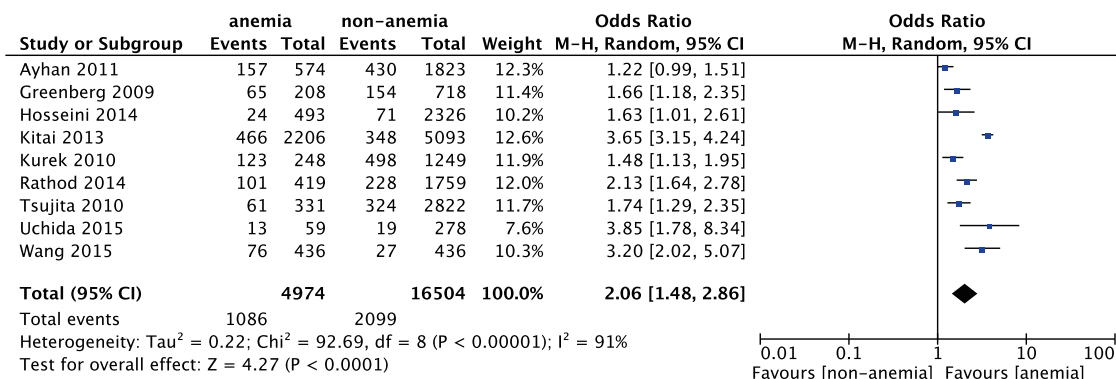
### Discussion

This meta-analysis identified 17 case-control studies

investigating the impact of anemia on long-term ischemic events in patients undergoing PCI. To our known, this is the first meta-analysis evaluated the impact of anemia on the long-term adverse events in patients undergoing PCI. Our analysis showed that anemia patients were at higher risk for long-term ischemic events and bleeding events. In addition, anemia patients are at higher risk for long-term mortality and MACE.

Previous studies have shown the association between anemia and ischemic events (3,10) in patients in different settings, but studies reporting the association between anemia and composite ischemic events in patients undergoing PCI are still limited. Although there're only two studies in our meta-analysis provided the data for composite ischemic events, the two studies deduced a same conclusion that anemic patients are at risk for ischemic events. What's more, the pooled analysis of the impacts of anemia on reinfarction also relate anemia to ischemic events. For long-term TVR, our analysis showed that anemic patients are also





**Figure 5** Meta-analysis of impact of anemia on MACE, MACE: major adverse cardiac even.

at higher risk for TVR than non-anemic patients (OR: 1.77), but the difference was not statistically significant ( $P=0.29$ ). This result may be explained by the fact that some patients with ischemic events choose drug therapy instead of revascularization, which can weaken the association between anemia and revascularization. In addition, due to some included studies didn't provide the incidence of total revascularization (they only provided the incidence of TVR, TLR or CABG, but the incidence of total revascularization can't be simply summarized by the above incidence of single events), we only use the incidence of TVR in these studies. Thus, whether anemia is associated with the incidence of total revascularization need more studies to identify. Overall, Our results agree with previous studies relating anemia to ischemic events, and further identified this association of anemia and long-term ischemic events in patients undergoing PCI.

It has also been shown that anemia is associated with bleeding events (11,51). In our study, four studies provided data for long-term bleeding events, but Tsujita *et al.* (49) and Voeltz *et al.* (18) only provided data for TIMI major bleeding or minor bleeding events not the total bleeding events. Considering the incidence of total bleeding events can't be simply summarized by major and minor bleeding events, we use the data of TIMI major bleeding events in the two studies. Our results agree with previous studies relating anemia to bleeding events. Previous studies show that anemia is associated with in-hospital or long-term mortality, MACE in patients undergoing PCI, our analysis further confirms it.

We have discussed the reason for ischemic events in our previous study (42). In brief, the presence of anemia can decrease oxygen delivery to the myocardium and induce myocardial ischemia through mismatches in oxygen

supply and demand, especially in patients with coronary artery stenosis. This effect may induce an increased heart rate and blood volume that is mainly mediated through the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (52,53). The latter can sharpen the mismatch between supply and demand of oxygen through ventricular remodeling and cardiac dysfunction, and thus increase the incidence of ischemic events.

The potential mechanisms of higher bleeding events are list as follows. First, anemia may be associated with the reduction of thrombogenesis, the abnormal function of platelet, higher degrees of inflammation, which can increase the risk of bleeding. Second, anemic patients are more often elder patients and with chronic kidney disease. Advanced age has been found to be associated with an increased risk of vascular complications following PCI (54). The presence of local vascular changes, or of more advanced vascular disease, has been postulated as a potential explanation for the increased incidence of bleeding complications in elderly patients. Similarly to advanced age, renal dysfunction has been identified as an important correlate of adverse outcomes following percutaneous cardiac procedures (55,56). Platelet dysfunction (57), elevated levels of anti-Xa (58), impaired clearance of low-molecular-weight heparin (59), and additional abnormalities in the coagulation cascade are all plausible explanations for the increased bleeding risk observed in renally impaired patients.

There are some limitations in our study. First, there are only two studies provided data of composite ischemic events; we cannot get enough data to make the results powerful enough. Second, as we discussed earlier, due to some included studies didn't provide the incidence of total revascularization or total bleeding events, so we analyzed

the impact of anemia on TVR and TIMI major bleeding events instead. This may have some influence on our results. Third, the time for adverse events in our study ranged from 12-46.6 months, we haven't analyzed the association of anemia and adverse events in different years after PCI. Whether the association between anemia and adverse events in the first year after PCI is the same with the 5 years remains unknown.

Further studies should focus on the further points. First, there's a need for further clarification and consistency regarding dosage, timing and duration of antithrombotic therapy for the prevention of ischemic events and bleeding events. Second, anemic patients were more likely to be female, elder patients, and often have more comorbidities, which can increase the risk for adverse events. Further studies need to explore whether there're differences among those different subgroups. Finally, whether the impact of anemia on the outcomes differs at different stage after PCI need more studies to confirm.

## Conclusions

Anemic patients undergoing PCI are at higher risk for both long-term ischemic events and bleeding events, and also at higher risk for long-term mortality and MACE. There's a need for further clarification and consistency regarding dosage, timing and duration of antithrombotic therapy for the prevention of ischemic events and bleeding events in anemic patients.

## Acknowledgements

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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