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Blood Transfusion After Percutaneous Coronary Intervention and Risk of Subsequent Adverse Outcomes

A Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES This study sought to define the prevalence and prognostic impact of blood transfusions in contemporary percutaneous coronary intervention (PCI) practice.

BACKGROUND Although the presence of anemia is associated with adverse outcomes in patients undergoing PCI, the optimal use of blood products in patients undergoing PCI remains controversial.

METHODS A search of EMBASE and MEDLINE was conducted to identify PCI studies that evaluated blood transfusions and their association with major adverse cardiac events (MACE) and mortality. Two independent reviewers screened the studies for inclusion, and data were extracted from relevant studies. Random effects meta-analysis was used to estimate the risk of adverse outcomes with blood transfusions. Statistical heterogeneity was assessed by considering the I^2 statistic.

RESULTS Nineteen studies that included 2,258,711 patients with more than 54,000 transfusion events were identified (prevalence of blood transfusion 2.3%). Crude mortality rate was 6,435 of 50,979 (12.6%, 8 studies) in patients who received a blood transfusion and 27,061 of 2,266,111 (1.2%, 8 studies) in the remaining patients. Crude MACE rates were 17.4% (8,439 of 48,518) in patients who had a blood transfusion and 3.1% (68,062 of 2,212,730) in the remaining cohort. Meta-analysis demonstrated that blood transfusion was independently associated with an increase in mortality (odds ratio: 3.02, 95% confidence interval: 2.16 to 4.21, $I^2 = 91\%$) and MACE (odds ratio: 3.15, 95% confidence interval: 2.59 to 3.82, $I^2 = 81\%$). Similar observations were recorded in studies that adjusted for baseline hematocrit, anemia, and bleeding.

CONCLUSIONS Blood transfusion is independently associated with increased risk of mortality and MACE events. Clinicians should minimize the risk for periprocedural transfusion by using available bleeding-avoidance strategies and avoiding liberal transfusion practices. (J Am Coll Cardiol Intv 2015;8:436–46) © 2015 by the American College of Cardiology Foundation.

Advances in antiplatelet and antithrombotic therapy have improved outcomes in patients undergoing percutaneous coronary intervention (PCI) through a reduction in ischemic events, albeit at the expense of increased risk of bleeding complications. Major bleeding observed during PCI independently predicts mortality and major adverse cardiac events (MACE), and a recent meta-analysis demonstrated an independent 3-fold increase in both mortality and MACE events following a major bleed (1). Between 2.0% and 4.0% of all patients undergoing PCI receive a blood transfusion (2–5), often

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following major bleeding events, with previous studies reporting marked variation in the use of red blood cell transfusion among patients with acute coronary syndromes (6) and in patients undergoing PCI (5). Whereas the presence of anemia is independently associated with an increase in cardiac mortality and myocardial infarction in patients with acute coronary syndromes or undergoing PCI (7,8), the optimal use of blood products in such patients remains controversial. National transfusion practice guidelines offer no recommendation for or against a liberal or restrictive transfusion threshold for such patients (9). National PCI registries have demonstrated that patients with bleeding events receive blood transfusions across the spectrum of hemoglobin values with significant variation in practice (5), and a single-center study showed that a large proportion of patients undergoing PCI received transfusion for indications outside of published guidelines (10).

SEE PAGE 447

A previous meta-analysis of 10 studies including 203,665 patients reported that blood transfusion in the setting of acute myocardial infarction is associated with a 3-fold increase in all-cause mortality and a 2-fold increase in recurrent myocardial infarction (11), although it included studies mainly of patients with acute coronary syndromes who did not undergo PCI and were managed medically, hence the applicability of the findings to patients undergoing PCI remains unclear. Defining the role of transfusion in patients undergoing PCI can inform clinical practice. There has not been a systematic review or meta-analysis of the prevalence and prognostic impact of blood transfusion in the setting of PCI. We have therefore undertaken a meta-analysis to systematically study the impact of blood transfusion in patients who have undergone PCI on mortality and MACE outcomes. In this meta-analysis, we provide an overview of the cohorts, evaluating the rates of blood transfusion events and systematically studying the differences in the prognostic impact of blood transfusion in patients undergoing PCI.

METHODS

ELIGIBILITY CRITERIA. Studies were selected of patients who underwent PCI reporting mortality or cardiovascular events among patients with and without blood transfusion with no restriction based on study design or the indication for PCI. Studies that did not report on transfusion and those that did not report either mortality or MACE were excluded.

SEARCH STRATEGY. A search of EMBASE (1974 to March 4, 2014) and MEDLINE (1946 to March 4, 2014) was conducted on OVID SP. We used the following search terms: (transfusion AND (percutaneous coronary intervention OR PCI) AND mortality). Studies in all languages and both abstracts and unpublished studies were included. The bibliographies of the included studies and relevant review articles were checked for additional relevant articles. Authors were contacted in situations in which there was uncertainty regarding the data in the studies.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

MACE = major adverse cardiac events

OR = odds ratio

PCI = percutaneous coronary intervention

STUDY SELECTION AND DATA EXTRACTION. Two reviewers (C.S.K. and S.W. or S.N.) independently checked all titles and abstracts for studies potentially meeting the inclusion criteria. The full reports of these studies were retrieved, and data were independently extracted on study design, participant characteristics, interventions used, type of transfusions, outcome events, and follow-up. Any discrepancies between the 2 reviewers were resolved by consensus after consulting a third reviewer (M.A.M.).

QUALITY ASSESSMENT. Risk of bias was assessed by considering ascertainment of transfusion, ascertainment of outcomes, baseline differences between the transfused and not transfused group, loss to follow-up, and use of adjustment in data analysis. Publication bias was assessed using funnel plots when there were >10 studies available in the meta-analysis and there was no evidence of substantial statistical heterogeneity (12).

DATA ANALYSIS. The program RevMan (version 5.1.7, Nordic Cochrane Centre, Copenhagen, Denmark) was used to do random effects meta-analysis using the inverse variance method for pooled odds ratios. Similarity was assumed between the odds ratio and other relative measures such as relative risk, rate ratios, or hazard ratios (HRs) because cardiovascular events and death were rare events (13). Adjusted or propensity-matched risk estimates were used where available. For datasets reporting multiple time-points, the earliest time point was included in the primary analysis. The I^2 statistic was used to assess statistical heterogeneity.

Several analyses were undertaken. The primary analysis was the risk of mortality and MACE with and without transfusion. In addition, further analysis considering adverse outcomes at a longer follow-up duration were undertaken. Additional analyses were performed to evaluate the risk of death considering anemia, the influence of number of units

transfused, the transfusion volume, the red blood cell storage age, use of platelet transfusion, and use of plasma/cryoprecipitate. There was no strict definition of anemia.

RESULTS

STUDY SELECTION. Study selection is shown in **Figure 1**. We retrieved 19 relevant studies of patients who underwent PCI (2,5,14-30) (total number of subjects 2,381,623 in 16 studies (2,5,14,16-26,29,30), 3 studies examined different types of transfusions in the same cohort (15,27,28), 54,380 transfused, 2,327,243 not transfused), which evaluated the risk of adverse events with and without blood transfusion. The number of participants in each study ranged from 1973 (26) to 2,258,711 (5), and the prevalence of blood transfusion varied from 1.6% (25) to 22% (20).

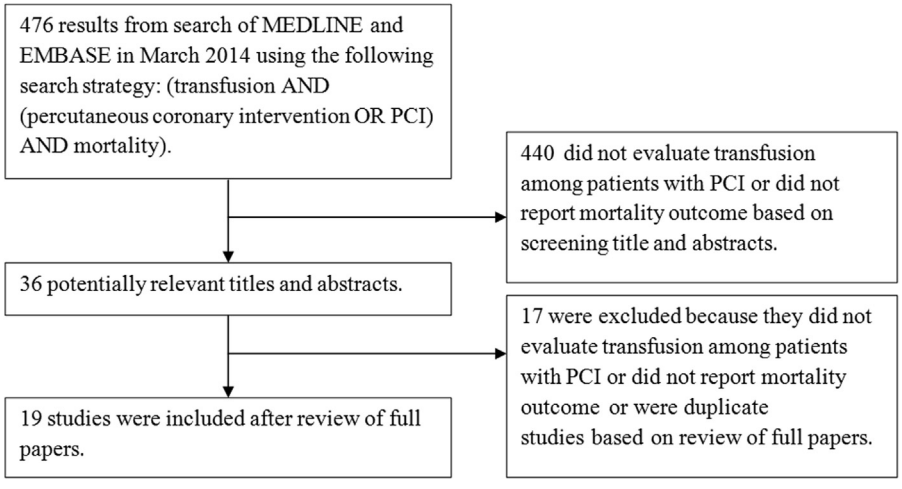
DESCRIPTION OF STUDIES INCLUDED. The study designs, date of study, country of origin, and indication for PCI are shown in **Table 1**. There were 3 that were post-hoc analyses of randomized controlled trials, 6 prospective cohort studies, 4 retrospective cohort studies, 5 cohort studies, and 1 case-control study. There were more multicenter studies than single-center studies (n = 10 and n = 6). The age, sex, comorbidities, and treatments are shown in Online Table 1.

Table 2 provides an overview of the PCI cohort, type of transfusion, and outcomes for each study included in the meta-analysis. All studies evaluated red blood cell transfusion, and 1 study also evaluated platelet transfusion and use of plasma or cryoprecipitate. Fifteen studies assessed transfusion and risk of death, and 5 studies assessed transfusion and risk of MACE. In addition, 1 study considered anemic and non-anemic (pre-PCI anemia defined as hemoglobin <13 g/dl in male and <12 g/dl in female) subgroups (17), and 2 studies evaluated the number of units of blood transfused (18,28). Follow-up of patients varied from in-hospital outcomes up to 5 years.

QUALITY ASSESSMENT. Online Table 2 shows the quality assessment for included studies. Ascertainment of transfusion and outcomes varied from medical record reviews to prospective evaluation in trials with adjudicated bleeding and outcome events. There were baseline differences in the transfusion and non-transfused group in 14 studies (74%), and 8 studies (42%) reported some degree of loss to follow-up. All studies included in this meta-analysis used adjustment or propensity matching.

TRANSFUSION AND RISK OF MORTALITY AT ANY TIME POINT. The impact of transfusion on mortality outcomes was considered in 19 studies, reporting outcomes in 2,419,969 patients (2,5,14-30). As summarized in **Table 2**, 54,380 participants with transfusions were reported. Mortality rate was 6,435 of 50,979 (13%, 8 studies (2,5,19-21,26,29,30), as not all studies report crude rate of events) in patients who received a blood transfusion and 27,061 of 2,266,111

FIGURE 1 Flow Diagram of Study Selection



From 476 studies identified from the initial search, a total of 19 studies were included after screening titles and reviewing the full manuscripts of potentially relevant studies. PCI = percutaneous coronary intervention.

TABLE 1 Study Design, Location, and Participant Inclusion Criteria

	Year	Design	Date of Study	Centers, n	Country	Participant Inclusion Criteria
Brugts et al. (14)	2009	Post-hoc analysis of randomized control trial (EXCITE trial)	June 1997 to April 1998	412	International	Participants had angiographic evidence of clinically significant coronary artery disease necessitating percutaneous transluminal coronary revascularization.
Byrne et al. (15)	2009	Prospective cohort study (British Columbia Cardiac Registry)	January 1999 to December 2005	4	Canada	Participants had PCI.
Chase et al. (2) (Same cohort as Byrne et al.)	2008	Prospective cohort study (British Columbia Cardiac Registry)	January 1999 to December 2005	4	Canada	Participants had PCI.
Cosgrove et al. (16)	2009	Retrospective cohort study (MIDAS)	2003 to 2004	Multiple	USA	Participants had PCI and STEMI.
Dada et al. (17)	2009	Cohort study	Unclear	Unclear	USA	Participants had PCI.
Doyle et al. (18)	2008	Cohort study (Mayo Clinic)	1994 to June 2005	1	USA	Participants had transfemoral PCI.
Ergelen et al. (19)	2012	Retrospective cohort study	October 2003 to March 2008	1	Turkey	Participants had PCI and STEMI.
Jani et al. (20)	2007	Prospective cohort study (BMC_2)	June 1997 to January 2004	Multiple	USA	Participants had PCI.
Jolicoeur et al. (21)	2009	Post-hoc analysis of randomized control trial (APEX-AMI trial)	2004 to 2006	296	International	Participants had PCI and STEMI.
Kim et al. (22)	2007	Cohort and case-control study	January 2000 to April 2002	1	USA	Participants had PCI.
Kinnaird et al. (23)	2003	Retrospective cohort study	1991 to 2000	1	USA	Participants had PCI.
Leung et al. (24)	2010	Prospective cohort study (Dartmouth Dynamic Registry)	July 1998 to July 2006	1	USA	Participants had cardiac catheterization.
Maluenda et al. (25)	2009	Cohort study	Unclear	Unclear	USA	Participants had PCI.
Nikolsky et al. (26)	2009	Post-hoc analysis of randomized control trial (CADILLAC trial)	November 1997 to December 1999	Multiple	International	Participants had acute myocardial infarction and primary PCI.
Robinson et al. (27) (Same cohort as Byrne et al.)	2010	Prospective cohort study (British Columbia Cardiac Registry)	January 1999 to December 2005	4	Canada	Participants had PCI.
Robinson et al. (28) (Same cohort as Byrne et al.)	2012	Prospective cohort study (British Columbia Cardiac Registry)	January 1999 to December 2005	4	Canada	Participants had PCI.
Sherwood et al. (5)	2014	Retrospective cohort study (CathPCI Registry)	July 2009 to March 2013	1,400	USA	Participants had cardiac catheterization or PCI.
Tajstra et al. (29)	2013	Cohort study	January 1999 to December 2004	1	Poland	Participants with STEMI who underwent immediate coronary intervention.
Valenti et al. (30)	2010	Cohort study	1995 to 2007	Unclear	Italy	Participants had primary PCI for acute myocardial infarction.

APEX-AMI = Assessment of Pexelizumab in Acute Myocardial Infarction; BMC_2 = Blue Cross Blue Shield of Michigan Cardiovascular Consortium; CADILLAC = Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; EXCITE = Evaluation of Oral Xemilofiban in Controlling Thrombotic Events; MIDAS = Myocardial Infarction Data Acquisition System; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Participants, Types of Transfusions, and Outcomes

	Year	Cohort	Type of Transfusion	Outcomes and Follow-Up	No. of Events/Total Participants Transfused	No. of Events/Total Participants Not Transfused	Results
Brugts et al. (14)	2009	PCI	RBC	Death and death/MI/stroke at 7 months	Total: 189	Total: 6,506	Death: aHR 4.54 (2.48–8.33) Composite: aHR 2.61 (1.96–3.60)
Byrne et al. (15)	2009	PCI	RBC	Adverse outcome at unclear follow-up	Total: 38,346	NA	Adverse outcome: aHR 2.86 (2.52–3.25)
Chase et al. (2) (Same cohort as Byrne et al.)	2008	PCI	RBC	Death at 30 days and 1 yr	Death at 30 days: 122/967 Death at 1 yr: 221/967	Death at 30 days: 476/37,905 Death at 1 yr: 1,216/37,905	Death at 30 days: aOR 4.01 (3.08–5.22), propensity matched RR 3.9 (1.89–8.0) Death at 1 yr: aOR 3.58 (2.94–4.36), propensity matched RR 3.38 (2.22–5.14)
Cosgrove et al. (16)	2009	STEMI and PCI	RBC	Death at 3 yrs	Total: 207	Total: 5,381	Death at 3 yrs: aHR 1.36 (1.03–1.83)
Dada et al. (17)	2009	PCI	RBC	Death in-hospital and 9 months	Total: 291	Total: 6,247	Death in-hospital: anemic: OR 2.74 (1.10–6.82), non-anemic: OR 0.48 (0.01–23.02). Death at 9 months: anemic: OR 3.01 (1.71–5.32), non-anemic: OR 0.06 (0.003–1.35)
Doyle et al. (18)	2008	PCI	RBC	Death at 30 days	Total: 1,205	Total: 16,696	Death at 30 days: 3+ U: aHR 18.1 (13.7–24.0), 1–2 U: aHR 8.9 (6.3–12.6)
Ergelen et al. (19)	2012	STEMI with PCI	RBC	Death and MACE (CV death, reinfarction, TVR) in-hospital and at 21 months	Death in-hospital: 9/88 MACE in-hospital: 21/88	Death in-hospital 67/2,449 MACE in-hospital 155/2,449	CV death in-hospital: OR 8.1 (1.8–35.7) MACE in-hospital: 21/88 vs. 155/2,449 Death at 21 months: 11/88 vs. 119/2,449 MACE at 21 months: 31/88 vs. 571/2,449
Jani et al. (20)	2007	Any (STEMI and NSTEMI with PCI)	RBC	Death in-hospital	150/1,033	108/3,590	Death in-hospital: aOR 2.02 (1.47–2.79)
Jolicoeur et al. (21)	2009	STEMI with PCI	RBC	Death at 3 months	53/204	203/4,984	Death at 3 months: aHR 2.16 (1.20–3.88)
Kim et al. (22)	2007	PCI	RBC	Death in-hospital and at 1 yr	Total: 146	Total: 292	Death in-hospital: OR 2.03 (1.00–3.83) Death at 1 yr: OR 2.42 (1.32–4.46)
Kinnaird et al. (23)	2003	PCI	RBC	Death in-hospital and at 1 yr	Total: 593	Total: 10,381	Death in-hospital: OR 2.0 (1.1–3.2) Death at 1 yr: OR 1.9 (1.4–2.5)
Leung et al. (24)	2010	PCI (cardiac catheterization)	RBC	Death at 30 days and long term	Total: 709	Total: 11,952	Death at 30 days: aOR 2.22 (1.57–3.14) Long-term mortality: aOR 1.41 (1.19–1.67)
Maluenda et al. (25)	2009	PCI	RBC	Death/MI at 1 yr	Total: 61	Total: 3,677	Composite at 1 yr: aHR 1.93 (0.81–4.17)
Nikolsky et al. (26)	2009	Any (STEMI and NSTEMI with PCI)	RBC	Death at 1 and 12 months	11/82	87/1,891	Death at 30 days: HR 4.71 (1.97–11.26) Death at 1 yr: HR 3.16 (1.66–6.03)
Robinson et al. (27) (Same cohort as Byrne et al.)	2010	PCI	RBC	Death at 1 month	Total: 909	Total: 31,671	Death at 30 days: RBC transfusion volume: HR 1.28 (1.19–1.38), mean RBC storage age: HR 1.03 (1.02–1.05)
Robinson et al. (28) (Same cohort as Byrne et al.)	2012	PCI	RBC, platelet, and plasma/cryoprecipitate	Death at 1 month	Total: 32,580	NA	Death at 30 days: RBC transfusion 1–2 U: HR 4.49 (3.21–6.28), >2 U: HR 6.33 (4.37–9.18), platelet transfusion: HR 3.92 (2.52–6.11), plasma/cryoprecipitate transfusion: HR 3.92 (2.52–6.11)

Continued on the next page

TABLE 2 Continued

	Year	Cohort	Type of Transfusion	Outcomes and Follow-Up	No. of Events/Total Participants Transfused	No. of Events/Total Participants Not Transfused	Results
Sherwood et al. (5)	2014	PCI	RBC	Death in-hospital and MACE	Death in-hospital: 6,052/48,430 MACE: 8,418/48,430	Death in-hospital: 25,833/2,210,281 MACE: 67,907/2,210,281	Overall in-hospital mortality: OR 4.63 (4.57–4.69) Overall MACE: OR 3.62 (3.59–3.66) With bleed in-hospital mortality: OR 1.07 (1.01–1.13) With bleed MACE: OR 1.16 (1.11–1.22) Without bleed in-hospital mortality: OR 4.96 (4.89–5.03) Without bleed MACE: OR 3.66 (3.63–3.69)
Tajstra et al. (29)	2013	STEMI with PCI	RBC	Death at 5 yrs	13/82	98/2,333	Death in-hospital rate: 15.8% vs. 4.2% Death at 30 days: HR 3.1 (1.41–6.8) Death at 1 yr: HR 2.33 (1.30–4.17) Death at 5 yr: rate 42.7% vs. 19%, HR 1.45 (1.0–2.1)
Valenti et al. (30)	2010	PCI	RBC	Death at 6 months	25/93	189/2,678	Cardiac death: HR 2.33 (1.49–3.64)

ORs and HRs are followed by (95% CI).

aHR = adjusted hazard ratio; aOR = adjusted odds ratio; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; NA = not available; NSTEMI = non-ST-segment elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RBC = red blood cells; RR = risk ratio; STEMI = ST-segment elevation myocardial infarction; TVR = target vessel revascularization; U = units.

(1%, 8 studies (2,5,19-21,26,29,30) in the remaining patients.

Meta-analysis of these data demonstrated that the overall risk of mortality was significantly greater among patients who had a blood transfusion (odds ratio [OR]: 3.02, 95% confidence interval [CI]: 2.16 to 4.21, I^2 = 91%, 15 studies) (2,5,14,16-24,26,29,30) (**Figure 2A**).

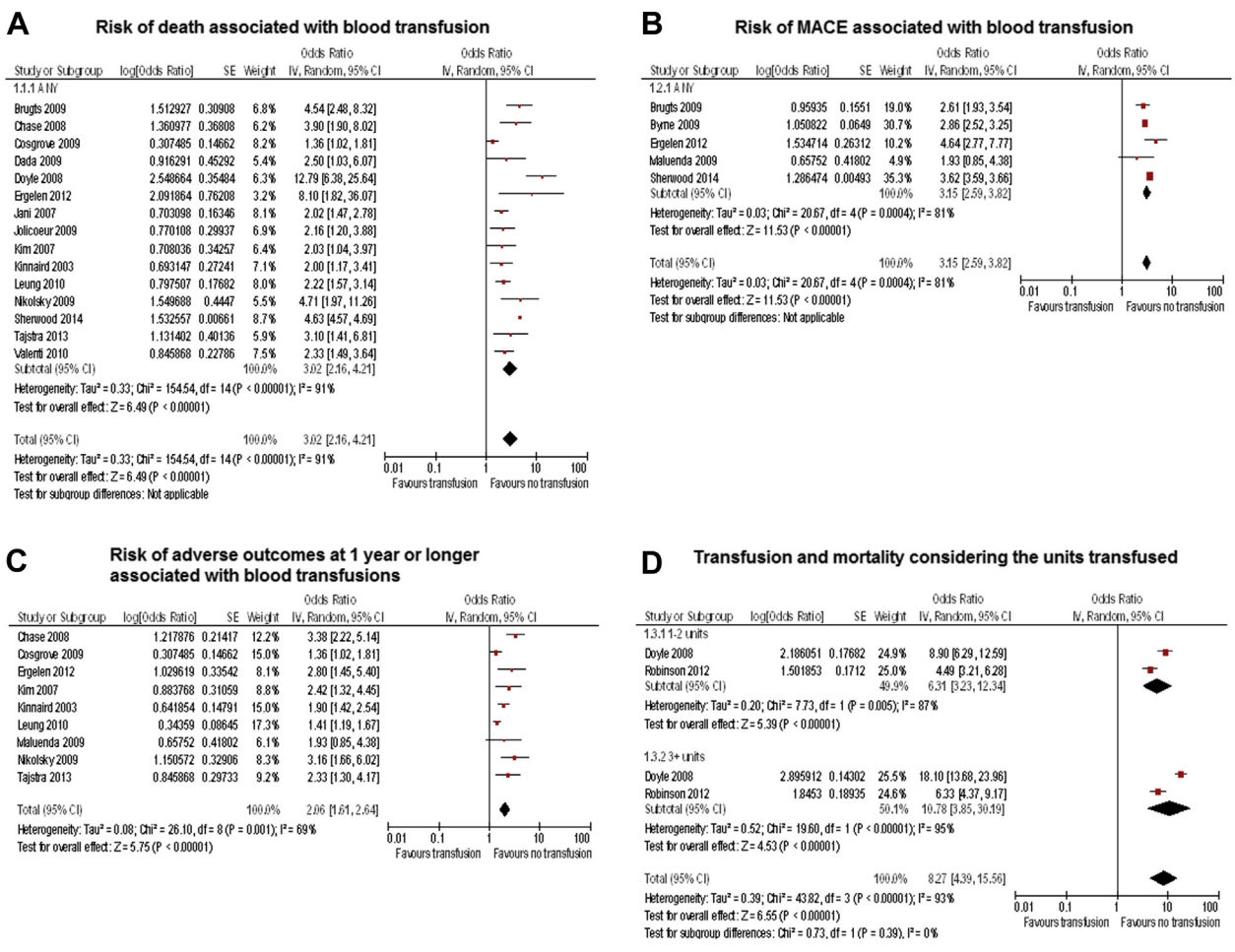
TRANSFUSION AND RISK OF MACE. The impact of transfusion on MACE was assessed in 5 studies (5,14,15,19,25) with 2,310,047 patients. Crude rates or risk estimates for MACE in individual studies are shown in **Table 2**; 48,768 patients who received a transfusion (2%) were included. MACE rates were 17% (8,439 of 48,518) in patients who had a blood transfusion and 3% (68,062 of 2,212,730) in patients who did not have blood transfusion. The risk of MACE was significantly higher among patients with blood transfusion (OR: 3.15, 95% CI: 2.59 to 3.82, I^2 = 81%) (**Figure 2B**). Transfusion and the risk of adverse outcomes at >1-year follow-up is shown in **Figure 2C**. The risk of adverse outcomes in patients with >1-year follow-up remained increased (OR: 2.06, 95% CI: 1.61 to 2.64, 9 studies) (2,16,19,22-26,29).

ADJUSTMENT FOR BASELINE ANEMIA, HEMATOCRIT, AND BLEEDING. Meta-analysis of studies that adjusted for baseline anemia, hematocrit, or major bleeding are presented in **Table 3**. Even after adjustment for baseline anemia, hematocrit, or bleeding events at baseline, receipt of a blood transfusion was consistently associated with a significant 2-fold increase in both mortality and MACE complications.

ANEMIA AND TRANSFUSION UNITS, TRANSFUSION, AND DEATH. One study evaluated the influence of anemia in patients who received a blood transfusion and demonstrated that risk of mortality was significantly higher in the anemic group (anemic OR: 2.74, 95% CI: 1.10 to 6.82) compared with the non-anemic cohort (OR: 0.48, 95% CI: 0.01 to 23.03) (**Table 4**) (17). The effect of number of units transfused is considered in **Table 4**. Mortality risk increases with the number of units transfused (1 to 2 units [OR: 6.31, 95% CI: 3.23 to 12.34, I^2 = 87%] and 3 or more units [OR: 10.78, 95% CI: 3.85 to 30.19, I^2 = 95%]) (**Figure 2D**) (18,28).

SENSITIVITY ANALYSIS. The results of the sensitivity analysis are displayed in **Table 4**. Significant differences were found for risk of death with higher transfusion volume (HR: 1.28, 95% CI: 1.19 to 1.38), red blood cell storage age (HR: 1.03, 95% CI: 1.02 to 1.05), platelet transfusion (HR: 3.92, 95% CI: 2.52 to 6.11), plasma/cryoprecipitate transfusion (HR: 3.92,

FIGURE 2 Risk of Adverse Outcomes With Blood Transfusion



Meta-analysis of the risk of mortality, major adverse cardiac events (MACE), and the risk of adverse outcomes at 1 year or more associated with blood transfusions and the risk of mortality with the number of units of blood transfused. CI = confidence interval; IV = intravenous.

95% CI: 2.52 to 6.11), and death among patient with bleeds and no bleeds (27).

PUBLICATION BIAS. Publication bias was not assessed because there was only 1 analysis with more than 10 studies, and there was evidence of substantial statistical heterogeneity.

DISCUSSION

The optimal use of blood products in patients undergoing PCI remains controversial. To the best of our knowledge, the present analysis is the first to systematically review blood transfusion and its use in contemporary PCI practice and to study its prognostic impact. Our meta-analysis of 19 studies including more than 2 million patients with more than 54,000 transfusion events has shown that the mean prevalence of blood transfusions in contemporary PCI is 2.3% and is independently associated with a 3-fold increased risk of mortality and MACE events. Furthermore, our data suggest a dose-dependent adverse influence on mortality.

Both our current analysis and previous reports of transfusion practice nationally (5) have reported a wide variation in the prevalence of blood transfusions in patients undergoing PCI. Whereas part of this variation may be explained by differences in patient characteristics and clinical settings, a recent analysis of the National Cardiovascular Data Registry dataset has reported significant variations in the prevalence of transfusion events in hospitals across the United States, with significant differences in hemoglobin

TABLE 3 Adjustments for Baseline Hematocrit, Anemia, and Bleeding

	Studies Included	Outcome Evaluated	Pooled Risk Estimate
Studies that adjusted for baseline/nadir anemia	(16,19,20,26,29)	Risk of death	2.47 (1.53–3.97), $I^2 = 72\%$, $p < 0.001$
Studies that adjusted for baseline/nadir hematocrit	(22,24)	Risk of death	2.18 (1.60–2.96), $I^2 = 0\%$, $p < 0.001$
Studies that adjusted for bleeding	(22,24,29)	Risk of death	2.28 (1.71–3.04), $I^2 = 0\%$, $p < 0.001$
Propensity matched studies	(17)	Risk of death	2.50 (1.03–6.07)
Studies that adjusted for baseline/nadir anemia	(19)	Risk of MACE	4.64 (2.77–7.77)
Studies that adjusted for baseline/nadir anemia	(16,19,26,29)	Risk of MACE at 1 yr or more	2.16 (1.37–3.40), $I^2 = 67\%$, $p < 0.001$
Studies that adjusted for baseline/nadir hematocrit	(22,24)	Risk of MACE at 1 yr or more	1.70 (1.03–2.82), $I^2 = 64\%$, $p = 0.04$
Studies that adjusted for bleeding	(22,24,29)	Risk of MACE at 1 yr or more	1.83 (1.22–2.75), $I^2 = 60\%$, $p = 0.004$

Values are OR (95% CI).
Abbreviations as in Table 2.

threshold that prompts transfusion (5). Furthermore, previous studies have documented that a significant proportion of patients receive blood transfusions in the absence of bleeding events (5,21,26). Previous studies in the critical care setting have reported significant institutional variation in critical care transfusion practice that was independent of baseline clinical characteristics and baseline hemoglobin concentration (31), reflecting the lack of clarity in contemporary guidelines recommendations (9). A recent review of blood transfusion practices reported that variability in practices may be the result of insufficient understanding of published guidelines and different recommendations of medical societies (32). The prevalence of anemia in patients undergoing PCI is significant, with anemia documented in 23% of patients undergoing elective or urgent PCI in the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial (33) and between 20% and 30% in other registries (7,34,35), with optimal hemoglobin threshold for transfusion not clearly defined.

Patients who receive blood transfusions are generally older, more likely to be female, have more comorbidities (5,20,21,26,27,29) and hemodynamic compromise (21,23), and hence are more likely to have a higher mortality. Nevertheless, even after accounting for these confounders, the studies included in this meta-analysis demonstrated that blood transfusion was an independent predictor of mortality.

The provision of blood transfusions in PCI may relate to an acute bleeding event or occur in the context of chronic anemia. It is therefore possible that the relationship observed between blood transfusion and adverse outcomes may be a surrogate marker for periprocedural bleeding complications, which we have shown in a previous meta-analysis (1) to independently predict mortality (OR: 3.31, 95% CI: 2.86 to 3.82) and MACE (OR: 3.89, 95% CI 3.26 to 4.64). In the study of Kinnaird et al. (23) the provision of a blood transfusion was associated with increased in-hospital mortality in patients undergoing PCI with both major bleeding events (10.6% if transfused vs. 5.1% if not transfused) and in those without major bleeding (10.3% vs. 0.4%) (23). Similarly, in the study of Sherwood (5), patients who were transfused and did not experience a bleed had a greater increased risk of mortality (OR: 4.96, 95% CI: 4.89 to 5.03) than did those patients who were transfused in the context of a bleeding complication (OR: 1.07, 95% CI: 1.01 to 1.13). The prognostic impact of blood transfusion is influenced by pre-procedural anemia, and in the study by Sherwood (5), the influence of blood transfusion on myocardial infarction, stroke, or in-hospital death was less in patients with a pre-procedure hemoglobin level of <10 g/dl (OR: 1.56, 95% CI: 1.51 to 1.62) than in those whose hemoglobin was >15 g/dl (OR: 8.12, 95% CI: 7.96 to 8.29). We have attempted to separate the prognostic

TABLE 4 Summary of All Results

	Number of Studies (Studies Included)	Risk of Adverse Outcomes
Transfusion and death	15 (2,5,14–30)	OR 3.02 (2.16–4.21), $I^2 = 91\%$
Transfusion and MACE	5 (5,14,15,19,25)	OR 3.15 (2.59–3.82), $I^2 = 81\%$
Transfusion and adverse outcome with 1-yr or longer follow-up	9 (2,16,19,22–26,29)	OR 2.06 (1.61–2.64), $I^2 = 69\%$
Anemia and transfusion and death	1 (17)	Anemic: OR 2.74 (1.10–6.82) Non-anemic: OR 0.48 (0.01–23.03)
Transfusion units and adverse outcomes	2 (18,28)	1 to 2 U: OR 6.31 (3.23–12.34), $I^2 = 87\%$ 3+ U: OR 10.78 (3.85–30.19), $I^2 = 95\%$
Transfusion volume and death	1 (27)	HR 1.28 (1.19–1.38)
RBC storage age and death	1 (27)	HR 1.03 (1.02–1.05)
Platelet transfusion and death	1 (28)	HR 3.92 (2.52–6.11)
Plasma/cryoprecipitate transfusion and death	1 (28)	HR 3.92 (2.52–6.11)
Transfusion and bleed and death	1 (5)	OR 1.07 (1.01–1.13)
Transfusion and no bleed and death	1 (5)	OR 4.96 (4.89–5.03)

ORs and HRs are followed by (95% CI).
Abbreviations as in Table 2.

impact of blood transfusion from bleeding and baseline anemia and hematocrit by undertaking additional analyses. A number of studies analyzed in this meta-analysis adjusted for baseline bleeding complications (22,24,29), and meta-analysis of these studies revealed that receipt of a blood transfusion was associated with a significant increased risk of mortality (OR: 2.28, 95% CI: 1.71 to 3.04, $I^2 = 0\%$, $p < 0.001$). Furthermore, adjustment for either baseline hematocrit or anemia did not alter the relationship between receipt of a blood transfusion and increased risk of mortality or MACE outcomes (**Table 3**). It appears that blood transfusion has an adverse prognostic impact irrespective of whether this has been given in the setting of a bleeding complication and is independent to the degree of baseline anemia or hematocrit nadir, although its greatest prognostic value appears to be in those patients without a bleeding event.

Differences in blood transfusion practice may have an impact on outcomes; in the CRIT (Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction) randomized pilot trial, 45 patients with myocardial infarction and a hematocrit level ≤30% were randomized to either a liberal transfusion arm or a conservative arm, and the composite endpoint of in-hospital death, recurrent myocardial infarction, or congestive heart failure was significantly higher among patients assigned to the liberal arm (38% vs. 13%; $p = 0.046$). In contrast, in the MINT (A Multicenter, Randomized Study of Argatroban Versus heparin as Adjunct to Tissue Plasminogen Activator [TPA] in Acute Myocardial Infarction: Myocardial Infarction With Novastan and TPA) pilot study undertaken in 110 patients presenting with an acute coronary syndromes or stable angina with anemia undergoing cardiac catheterization, patients randomized to a liberal blood transfusion strategy had one-half the primary outcome rate of death, myocardial infarction, and unscheduled revascularization (10.9%) as did those patients randomized to a restrictive transfusion strategy (25.5%), with lower 30-day mortality (1.8%) compared with restrictive transfusion patients (13.0%) ($p = 0.032$) (36). These pilot trials support the need for a larger National Heart, Lung, and Blood Institute–sponsored definitive trial.

The pathophysiological mechanisms linking transfusion and adverse outcomes are likely to be multifactorial (37). Patients receiving blood transfusions exhibit increased platelet reactivity (38), possibly through activation of the $P2Y_{12}$ platelet receptor or within the adenosine diphosphate pathway by agonist or mediators contained in red blood cell packs, placing patients at high risk of ischemic events. Blood transfusions also increase procoagulant proteins such as plasminogen activator inhibitor protein (39), an inhibitor of physiological processes that promote the degradation of thrombus. The oxygenating capability of transfused blood may also be impaired through a reduction in 2,3-diphosphoglyceric acid levels in stored red blood cells, which increases the affinity of hemoglobin for oxygen, thereby decreasing the release of oxygen to the tissues (40), but also through mechanisms of impaired small vessel vasodilation by a reduction in the nitric oxide transport by red transfused blood cells, impairing increases in the regional blood flow in zones of hypoxia (41). Finally, during storage, significant changes in the deformability of red blood cells, as well as changes in their shape, may predispose to “plugging” of transfused cells at the microvascular level, leading to tissue ischemia (37).

STUDY LIMITATIONS. Whereas our meta-analysis suggests an association between transfusion and mortality outcomes, it cannot confer a causal relationship. Also, the provision of blood transfusions in the setting of PCI may be related to an acute bleeding event or may be in the context of chronic anemia. Although we have attempted to account for the additional prognostic impact of bleeding, anemia, and baseline hematocrit through a separate analyses of studies that have adjusted for these covariates and have shown that receipt of a blood transfusion is consistently associated with an increased risk of mortality, it is likely that the patients who receive a blood transfusion are sicker and more hemodynamically compromised, hence unmeasured confounders may contribute to the adverse outcomes recorded. Whereas studies in this meta-analysis have attempted to adjust for confounders through adjustment of baseline covariates and procedural demographics, hematocrit, anemia, and bleeding events, they have not compared the outcomes of patients with indications for blood transfusions and have not been transfused to those who have received a blood transfusion, hence confounding by indication remains a significant limitation.

Finally, we found a high degree of statistical heterogeneity in several of our analyses, partly due to the heterogeneous nature of the cohorts analyzed, as well as the presence of large studies that have narrow confidence intervals, and their risk estimates do not overlap with other studies. Whereas statistical heterogeneity is a limitation in some of our analyses, the direction of the risk estimates of individual studies consistently suggests increased harm among patients

who receive blood transfusions, and the heterogeneity observed may partly reflect differences in the magnitude of the harm associated with transfusion.

CONCLUSIONS

Our meta-analysis of 19 studies including more than 2 million patients with more than 54,000 transfusion events has shown that the prevalence of blood transfusions in contemporary PCI is significant with a reported prevalence of 2.3% and is independently associated with an increased risk of mortality and MACE. Clinicians should minimize the risk of periprocedural bleeding complications during PCI through the use of bleeding-avoidance strategies such as the use of anticoagulants associated with reduced bleeding risk (42) and use of the transradial access site approach for PCI, particularly in patients at high risk of bleeding complications (43). Clinicians should avoid the use of judicious blood transfusions after PCI in the absence of significant or active bleeding complications. Our data support the need for a larger definitive trial to define optimal transfusion strategies in patients undergoing PCI given the significant variation in practices reported.

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APPENDIX For supplemental tables, please see the online version of this paper.