Review

# Red blood cell transfusion and mortality among patients hospitalized for acute coronary syndromes: A systematic review

Michael Garfinkle [a], Patrick R. Lawler [b,c], Kristian B. Filion [d], Mark J. Eisenberg [a,b,e,*,1]

[a] McGill University Faculty of Medicine, Montreal, Quebec, Canada
[b] Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, Montreal, Quebec, Canada
[c] Department of Medicine, McGill University Health Center, Montreal, Quebec, Canada
[d] Division of Clinical Epidemiology, Jewish General Hospital/McGill University, Montreal, Quebec, Canada
[e] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

## ARTICLE INFO

## ABSTRACT

*Background:* Observational studies have suggested a relationship between anemia and adverse outcomes among patients presenting with acute coronary syndromes (ACS). However, the hemoglobin level at which packed red blood cell (PRBC) transfusion is beneficial remains unclear as available data are conflicting. We therefore performed a systematic review of all relevant observational studies, with a particular focus on examining optimum hemoglobin thresholds for transfusion among patients hospitalized for ACS.
*Methods:* We systematically searched MEDLINE, as well as relevant bibliographies, to identify all observational studies examining the effects of PRBC transfusion among post-ACS patients. Inclusion was restricted to English language studies that reported data for the risk of mortality, congestive heart failure (CHF), or recurrent myocardial infarction (MI).
*Results:* We identified 11 studies that met our inclusion criteria, involving a total of 290,847 patients. When reported, the main indication for transfusion appeared to be major bleeding. Overall, patients who received transfusions were at greater unadjusted risk of mortality (range of odds ratio [OR]: 1.9 to 11.2). When hemoglobin-stratified analyses were examined, a graded association between PRBC transfusion and mortality was seen, wherein transfusion had beneficial or neutral effects on mortality below 8.0 g/dL, and harmful or neutral effects above 11.0 g/dL.
*Conclusions:* PRBC transfusion in patients post-ACS undertaken at hemoglobin levels below 8.0 g/dL was found to be beneficial or, at worst, neutral. Conversely, there was suggestion of harm when transfusion was undertaken at hemoglobin levels above 11.0 g/dL, supporting a more conservative transfusion strategy.

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## 1. Introduction

Numerous observational studies have suggested that anemia is an independent predictor of mortality among patients hospitalized with an acute coronary syndrome (ACS) [1–3]. However, the extent to which anemia contributes causally to this associated increased risk of mortality is unclear, and the current American Heart Association/American College of Cardiology guidelines do not make firm recommendations regarding correction of anemia with packed red blood cell (PRBC) transfusion in patients with ACS [4,5]. Furthermore, studies in other intensive care settings [6] and a small pilot study that randomized 45 post-ACS patients [7] suggested a benefit to more conservative transfusion practices, but clinical equipoise remains regarding optimal transfusion thresholds. We therefore conducted a systematic review of observational studies investigating the effect of transfusion in the setting of hospital admission for ACS. Our specific objectives were: [1] to examine the effect of PRBC on the risk of all-cause mortality, reinfarction, and congestive heart failure (CHF); and [2] to identify the optimum transfusion threshold in these patients.

## 2. Methods

### 2.1. Search strategy

A systematic literature search was performed in MEDLINE to identify studies examining the effect of transfusion in patients hospitalized with an ACS. This search was conducted on April 19th, 2011 and is described in detail in Online Appendix 1. Briefly, the search strategy involved the use of terms related to the intervention ("transfusion", "blood transfusion"), the population of interest ("acute coronary syndrome", "myocardial infarction"), and outcomes of interest ("mortality", "heart failure", "reinfarction"). Bibliographies of relevant articles were also reviewed manually for additional relevant articles not obtained from the electronic search.

* Corresponding author at: Divisions of Cardiology and Clinical Epidemiology, Jewish General Hospital/McGill University, 3755 Côte Ste-Catherine Road, Suite H-421, Montreal, Quebec, Canada H3T 1E2. Tel.: +1 514 340 8222x3564; fax: +1 514 340 7564.
E-mail address: mark.eisenberg@mcgill.ca (M.J. Eisenberg).
[1] National Researcher of the Quebec Foundation for Health Research.

*2.2. Inclusion criteria*

We included cohort studies and retrospective analyses of randomized controlled trials (RCTs) that examined the effect of in-hospital PRBC transfusion in patients admitted with an ACS on cardiovascular outcomes. Inclusion was restricted to those studies that reported data for the risk of mortality, CHF, or recurrent myocardial infarction (MI) and to those published in English language, peer-reviewed journals.

*2.3. Data extraction*

Two investigators independently extracted data using a predefined form. Disagreements were resolved by consensus or by a third reviewer. Data extraction included study characteristics (e.g., sample size, duration of follow-up), baseline patient characteristics, and baseline hemoglobin/hematocrit levels. In-hospital data such as the proportion of patients transfused, proportion of patients revascularized, nadir hemoglobin, and in-hospital bleeding risk were also extracted. Outcome data extracted included mortality, CHF and reinfarction count data, and the results of multivariable regression analyses (including level of statistical adjustment). When studies adjusted for hemoglobin/hematocrit levels, the type of adjustment was recorded. If stratification was used, data were extracted separately for each hemoglobin/hematocrit level. Patient characteristic and outcome data were only extracted if they were reported separately for the transfused and non-transfused patient groups. When the results of multiple regression models were presented, results of the model with the most rigorous adjustment for potential confounders were extracted. Variables included in multivariable regression analyses were also recorded. To maximize the comparability of data, hemoglobin values were favored over hematocrit values. For studies that only reported hematocrit levels, values were converted into hemoglobin by multiplying the hematocrit by the average erythrocyte hemoglobin concentration (33.25 g/dL) [8]. Data were not meta-analyzed, because variability in the reporting of study-specific hemoglobin strata precluded pooling data across studies.

# 3. Results

*3.1. Search results*

Our literature search identified 569 potentially relevant articles (Fig. 1). A total of 548 articles were excluded based on title review and 9 were excluded following abstract review. One additional article was identified in the manual review of bibliographies. Two articles were excluded following full-text review, and the remaining 11 articles [1,2,9–17] were included in the systematic review.

*3.2. Study characteristics*

Type of included ACS varied among the studies (Table 1). Sample sizes ranged from 370 to 85,111 patients, with five studies including more than 10,000 patients each. Follow-up ranged from in-hospital to one year post-ACS. Three studies [12,13,16] included only patients that went on to received PCI in-hospital. Two studies had some overlap in their cohort populations: Shishehbor et al. [14] performed a retrospective secondary analysis using data from the GUSTO trial, while Rao et al. [11] included the GUSTO study population (15% of total three-study cohort), along with two other RCT cohorts in their analysis. The single-cohort study was not discarded due to duplication since it reported outcome data at a maximum of one year, while the three-cohort study reported a maximum follow-up of only one month. In addition, Alexander et al. [10] and Yang et al. [9] were both sampled from the CRUSADE database, but their study populations were selected from different years.

*3.3. Patient characteristics*

The proportion of patients transfused varied greatly among the studies, ranging from 4 to 30% (Table 1). Included patients were predominately male; there was a higher proportion of women among transfused patients than non-transfused patients (Table 2). Transfused patients also tended to be older and presented with higher proportions of important co-morbidities, including diabetes mellitus and hypertension. No consistent trend was seen among studies between the prevalence of prior MI and the likelihood of transfusion. Differences in the use of PCI or CABG among transfused versus non-transfused patients were difficult to determine because these data were inconsistently reported.

The main indication for transfusion appeared to be major bleeding. Overall, patients who received PRBC transfusion presented with mildly lower baseline hemoglobin values, but subsequently experienced a significant drop in their hemoglobin value during admission (Table 2). Information on the risk of major bleeding is summarized in Table 3. Four studies reported the risk of bleeding in transfused
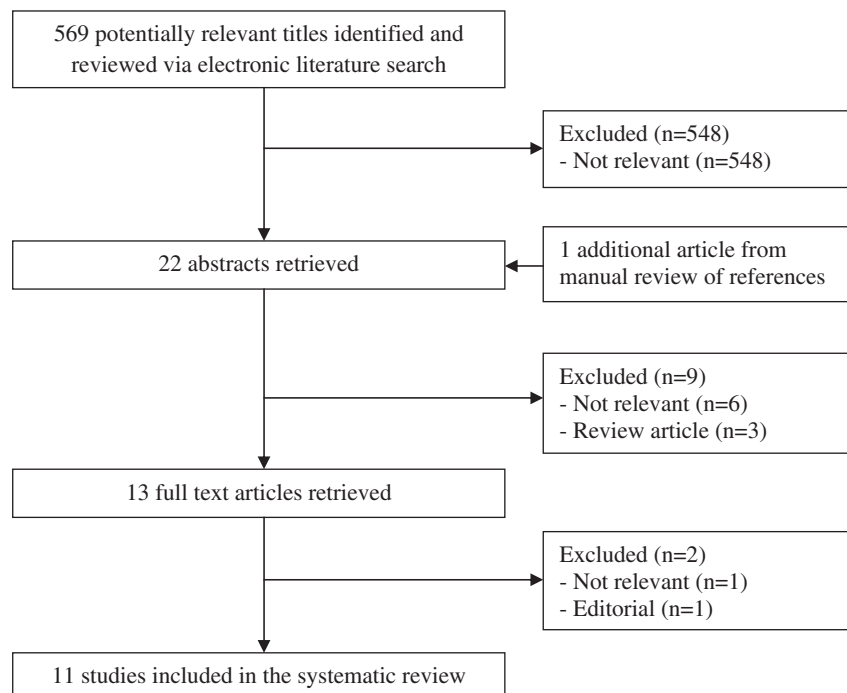


**Fig. 1.** Flow diagram of systematic literature search of observational studies examining the effect of transfusion in patients following admission for acute coronary syndromes.