**Supplementary Appendix:**

*Methods:*

We performed a systematic review and meta-analysis to determine the impact of a single preoperative or intraoperative dose of erythropoietin on perioperative red blood cell transfusion and latest available postoperative hemoglobin concentration, relative to control treatment, in adults undergoing cardiac surgery.

We searched the MEDLINE and Cochrane Collaboration Central Register of Controlled Trials databases from inception until March 15th 2021 using groups of keywords for erythropoietin and cardiac surgery. Additionally, the reference lists of relevant reviews and all included trials were searched for further studies.

To be included in the systematic review, the inclusion criteria were: 1) study design of a randomized controlled trial; 2) patient population of adults undergoing cardiac surgical procedures; 3) intervention of a single dose of preoperative or intraoperative erythropoietin relative to control during the patient’s admission for surgery; and 4) reporting at least the outcomes of perioperative red blood cell transfusion or postoperative hemoglobin concentration. We excluded studies where: 1) we were unable to distinguish patients of interest from a larger study population; 2) patients underwent acute noromovolemic hemodilution and/or participated in a pre-autologous blood donation program; 3) patients only received erythropoietin treatment in the postoperative period. In the case of a duplicate publication, we included the study with the most complete information.

The outcomes for this analysis were perioperative red blood cell transfusion (binary: Yes/No) and latest available postoperative hemoglobin concentration (continuous: reported as g/L). A reviewer independently screened citations to select studies, and abstracted data using a data extraction form for study methodology, patient characteristics, intervention/comparator information, and outcomes.

Binary data were combined to estimate the pooled risk ratio and its associated 95% confidence interval. Continuous data were combined to estimate the mean difference and its associated 95% confidence interval. Pooled effect estimates were estimated by the inverse variance approach using the random-effects model of DerSimonian and Laird for estimating variances. Heterogeneity was tested by an inverse variance weighted Chi Square test quantified by I2. All analyses were conducted using Review Manager 5.3 software (Cochrane Collaboration, UK).

*Study Characteristics:*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Size (N)** | **Population** | **Intervention and comparator** | **Details of Intervention** |
| Dardashti 20141 | 75 | Patients undergoing scheduled CABG surgery with pre-existing renal impairment | Erythropoietin  (400IU/Kg; Retacrit®)  Saline Placebo | Bolus infusion in central venous line after induction of anesthesia and before skin incision. |
| Foroughi 20202 | 132 | Patients without anemia (Hb > 11.5g/dL) undergoing CABG surgery on CPB | Erythropoietin  (300 IU/Kg; PDpoetin®)  Saline Placebo | Infusion in central venous line: 1) after induction of anesthesia until CPB initiation; or 2) at start of CPB until aortic declamping. |
| Kim 20133 | 98 | Patients with preoperative risk factors for acute kidney injury undergoing complex valvular surgery. | Erythropoietin  (300IU/Kg; Epocain®)  Saline Placebo | Intravenous bolus after induction of anesthesia |
| Song 20094 | 71 | Patients undergoing scheduled CABG | Erythropoietin  (300IU/Kg; Recormon®)  Saline Placebo | Intravenous bolus immediately after induction of anesthesia |
| Spahn 20195 | 484 | Patients with anemia (women: Hb <120 g/L; men: Hb <130 g/L) or iron deficiency (ferritin <100 mcg/L and no anemia) undergoing elective cardiac surgery | Bundle of: Erythropoietin (40000IU; Eprex®) Iron (20mg/Kg; Ferinject®) Vitamin B12 (1 mg; Vitarubin®) Folic Acid (5mg; acidum folicum)  Saline Placebo | Erythropoietin was administered as a subcutaneous injection. Treatment occurred on day of anesthetic evaluation (~1 day before surgery). |
| Weltert 20156 | 600 | Patients (with Hb <14.5g/dL) undergoing cardiac surgery | Erythropoietin  (80,000IU; Eprex®)  No Placebo  *All patients received oral iron supplementation* | Subcutaneous bolus on day of hospital admission (~2 days before surgery) |
| Yoo 20117 | 74 | Patients with anemia women: Hb <120 g/L; men: Hb <130 g/L) undergoing valvular heart surgery | Erythropoietin  (500IU/Kg; Epocain®)  Iron Sucrose  (200mg; Venoferrum®)  Saline Placebo | Intravenous bolus 16-24h before surgery |

CABG, Coronary artery bypass graft; CPB, cardiopulmonary bypass; Hb, hemoglobin

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