CHAPTER 224

Erythropoietin Therapy in Critically Ill and Acute Kidney Injury Patients

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OBJECTIVES

This chapter will:

1. Describe the issues with and treatment options for critical care patients with anemia.
2. Discuss the risks and benefits of transfusions versus erythropoiesis-stimulating agents (ESAs) treatment.
3. Present results of clinical trials of critical care patients treated with ESAs.
4. Evaluate hypotheses associated with organ protection by ESAs.

ANEMIA AND TRANSFUSION IN THE INTENSIVE CARE UNIT

U.S. studies report that almost all patients are anemic by day 3 after admission to an intensive care unit (ICU).[1] Despite controversies regarding the benefits,[2] approximately 50% of patients in the United States are transfused, usually early in the course of the admission.[3,4] Similarly, a multicenter European study showed that 63% of ICU patients had a hemoglobin less than 12 g/dL, and 29% less than 10 g/dL, at the time of admission and 37% were transfused during their ICU stay.[5] However, transfusions have been associated with longer hospital lengths of stay and an increase in mortality.[3]

Factors contributing to anemia in ICU subjects include direct causes such as hemorrhage or hemolysis associated with the initiating events such as trauma, infarction, and stroke. Additional factors include coagulopathies, occult blood loss, and the large amount (perhaps 40 to 60 mL daily) of blood removed during repeated diagnostic phlebotomy in the ICU.[4] Indirect factors blunt the erythropoietic response to anemia. These include activation of proinflammatory cytokines that directly inhibit erythropoiesis (by blunting the response to erythropoietin) including IL-1, TNF-α, and IL-6. The latter upregulates the acute phase protein hepcidin. By mediating degradation and internalization of the iron transport protein, ferroportin-1, hepcidin-1 limits availability of iron absorption in the gut and release from stores. IL-6 thus indirectly limits erythropoiesis by impairing heme synthesis.[6,7] Additional factors include shortened red cell survival from pathogen and immune-mediated hemolysis. The resultant anemia in critically ill subjects is usually normocytic and normochromic as in subjects with chronic kidney disease.

Publication in 1999 of the Transfusion Requirements in Critical Care study (TRICC),[8] when there was a liberal approach to transfusion in the ICU, resulted in a reassessment in use of transfusions in critical care patients. The TRICC trial demonstrated that a restrictive approach to transfusion (Hb threshold for transfusion <70 g/L) had similar or even superior mortality outcomes to a more liberal approach (Hb <90 g/L), with better outcomes in younger, less critically ill subjects) but with the possible exception of patients with acute myocardial infarction and unstable angina. Similar results were obtained in a large randomized controlled trial of liberal (Hb <100 g/L) versus restrictive (Hb <80 g/L) transfusion in 2016 patients undergoing surgery for hip fracture.[9] A liberal transfusion strategy (a hemoglobin threshold of 100 g/L), as compared with a restrictive strategy (symptoms of anemia or at physician discretion for a hemoglobin level of <80 g/L), did not reduce rates of death or inability to walk independently (across a room) on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk.

Further studies of transfusion in subjects with myocardial ischemia suggest that the benefits of transfusion outweigh the risks when Hb is below 70 g/L.[7,10,11] The results of transfusion are even more controversial in anemia associated with sepsis. Although some studies show no benefit of transfusion on tissue oxygenation,[7,12] others suggest that because the microcirculation is improved by blood transfusion but not by crystalloids or colloids, that transfusion remains a useful option, perhaps particularly in sepsis.[13,14]

Erythropoietin-Stimulating Agent Administration in the Critical Care Setting; Comparison to Transfusions

Erythropoietin (EPO) is the primary regulator of red blood cell formation. Because EPO is produced mainly by the kidney, patients with kidney disease can have severe anemia because of decreased EPO production. The preferred treatment option for patients with end-stage kidney disease (ESKD) is renal transplantation, which not only restores renal function but also alleviates the symptoms of anemia. The next most frequent treatment option, for renal patients and also other ICU patients, is to administer transfusions with the associated problems noted earlier. In long-term treatment settings, such as with ESKD patients, transfusions also could result in iron overload and produce allosensitization, which will reduce the number of suitable donor kidneys for a given individual with ESKD, or increase the risk of rejection of the transplanted kidney. With the approval of the first erythropoiesis-stimulating agent (ESA, epoetin alfa) there was a potentially practical alternative to transfusion, which offered pharmacologic treatment of anemia in multiple patient populations.

It is tempting to assume that the process of raising Hb with an ESA would be physiologically similar to that of transfusion. However, ESA treatment provides a slow rather than instantaneous (transfusion) rate of rise in Hb, and it may be desirable to have a fast or slow increase depending on conditions. For example, immediate correction is warranted with severe blood loss. For less severe conditions, a slower rise in Hb may be desirable because of the ability of the body to adapt. With ESA administration, iron is mobilized to support Hb synthesis. In the absence of administered iron, there can be depletion of iron stores, which has been hypothesized to promote a prothrombotic state.[15]

The major rationale for use of ESAs was that administration would not only treat symptoms of anemia but also reduce the number of transfusions and thereby avoid their negative impacts.[16] Thus a number of clinical trials were initiated to determine if ESA treatment would reduce transfusion rates and improve outcomes.

Erythropoietin-Stimulating Agents and Anemia Correction

In clinical trials with patients having heart and kidney disease, ESAs were shown to increase Hb levels in a dose-dependent manner and reduce blood transfusion rates (Tables 224.1 and 224.2). There also was evidence that anemia symptoms could be improved, especially in cardiac patients (dyspnea, exercise tolerance) (Fig. 224.1) but with little or no improvement in quality of life. Some studies showed an improvement in outcomes (e.g., mortality or rehospitalization rates), such as in patients after trauma (Fig. 224.2). However, in larger trials and in meta-analysis of the combined results of the small trials, the benefits

TABLE 224.1

Outcomes in Randomized Controlled Trials to Prevent or Correct Anemia

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Ghali 2008[40]	Cardiac failure and anemia	DA (0.75 ug/kg/SC/2 wks) with dose adjusted to target an Hb of 130–150 g/L	N = 319: ESA (162), placebo (157)	Increased Hb. No improvement in exercise duration, NYHA class, or quality of life score
Abraham 2010[41]	Cardiac failure and anemia	Pooled analysis of 2 studies. DA (0.75 ug/kg/SC/2 wks or 50 ug/kg/SC/2 wks) with adjustments to target an Hb of 130–150 g/L	N = 475: ESA (266), placebo (209)	No difference in composite of all-cause mortality and rate of first hospitalization for cardiac failure. Improvement in composite for the ESA subgroup that had a Hb increase > 10 g/L
Swedberg 2013[42]	Cardiac failure and anemia	DA (0.75 ug/kg/SC/2 wks) with dose adjusted to target an Hb of 130 g/dL	N = 2278: ESA (1136), placebo (1142)	Increased Hb, reduced blood transfusion rate. No effect on all-cause mortality or first hospitalization for worsening cardiac failure. Increased rate of ischemic stroke, embolic, and thrombotic events
Roger 2004[43]	CKD and anemia	Epoetin α administered weekly (SC) with dose adjusted to target an Hb of 105–115 or 130–150 g/L	N = 152: high Hb (75), low Hb (78)	Increased Hb. No difference in LVMI or eGFR or creatinine at 2 yr
Levin 2005[44]	CKD and anemia	Epoetin α with dose adjusted to target an Hb of 90–105 or 120–140 g/L. Starting dose 2000 U/wk/SC then titrated	N = 152: high Hb (78), low Hb (74)	Increased Hb. No difference in LVMI, NYHA level, or rate of change in creatinine clearance
Drueke 2006[45]	CKD and anemia	Epoetin β with dose adjusted to target a Hb of 110–125 or 130–150 g/L. Median weekly dose 5000 U in high Hb and 2000 U in low Hb median dose/wk	N = 603: high Hb (301), low Hb (302)	Increased Hb. No difference in deaths or cardiovascular event (sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris, prolongation of hospitalization, amputation, necrosis, or cardiac arrhythmia). No difference in cardiac (LVMI, time to increased NYHA class) or renal function (eGFR)

TABLE 224.1

Outcomes in Randomized Controlled Trials to Prevent or Correct Anemia—cont'd

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Singh 2006[46], Inrig 2012[47]	CKD and anemia	Epoetin α with dose adjusted to target an Hb of 105–110 g/dL or 130–135 g/dL. Average dose 11,215 U/wk/SC (high Hb) and 6,276 U/wk/SC (low Hb)	N = 1432: high Hb (715), low Hb (717)	Increased Hb. More rapid progression of composite end point (death, myocardial infarction, hospitalization for CHF) and kidney disease (composite of doubling of serum creatinine, RRT, or death). No difference in myocardial infarction or stroke
Ritz 2007[48]	CKD, diabetes, and anemia	Epoetin β (2,000 U/SC - initial dose) with adjustments to target high (130–150 g/L) or low Hb (105–115 g/L)	N = 160: high Hb (85), low Hb (75)	Increased Hb. No effect on cardiac function (LVMI, FS, or LVEF) or renal function (rate of creatinine clearance or eGFR decrease)
Pfeffer 2009[49]	CKD, diabetes, and anemia	DA monthly (average 176 ug/SC) targeted to Hb of 130 g/L	N = 4038: high Hb (2012), control (2026)	Increased Hb, reduced transfusion rate. No effect on time to first fatal or nonfatal cardiac failure or myocardial infarction, hospitalization for myocardial ischemia, or progression to ESKD. Increased risk of stroke
Still 1995[50]	Critical illness: Burns	Epoetin α (300 U/kg/IV) within 72 hr then daily × 7, then 150 U/kg alternate daily to 30 d	N = 40: ESA (19), control (21)	No differences in Hb, transfusion rate, or mortality
Corwin 1999[51]	Critical illness	Epoetin α (300 U/kg/SC) on d3, daily × 5 then alternate daily until Hct > 38%	N = 160: ESA (80), placebo (80)	Increased Hb, reduced blood transfusion rate. No differences in mortality, DVT, adverse events
Corwin 2002[52]	Critical illness	Epoetin α (40,000 U/SC) on d3 and continued weekly (×3). Added dose on ICU day 21	N = 1302: ESA (650), placebo (652)	Increased Hb, reduced blood transfusion rate. No differences in 29-day mortality, morbidity, or hospital length of stay. Reduced mortality in trauma patients
Georgopoulos 2005[53]	Critical illness	rHuEpo (not specified) 40,000 U/SC 1×/wk or 3×/wk for 1–3 wks targeted to Hb of 120 g/L	N = 148: ESA (100), control (48)	Dose-dependent increase in Hb, reduced blood transfusion rate. No differences in ICU length of stay, hospital length of stay, incidence of adverse events, or mortality
Silver 2006[54]	Critical illness: Long-term care	Epoetin α (40,000 U/SC) before d7 then weekly up to 12 doses	N = 86: ESA (42) placebo (44)	Increased Hb, decreased transfusion rate. No differences in mortality or serious adverse clinical event
Corwin 2007[55]	Critical illness	Epoetin α (40,000 U/SC) on day 1, then weekly (×3)	N =1460: ESA (733) placebo (727)	Increased Hb, no difference in transfusion rate. No difference in mortality, ICU, or hospital length of stay. Reduced mortality in trauma patient subgroup. Increased thrombotic events
Lundy 2010[56]	Critical illness: Burns	rHuEPO (not specified) (40,000 U) within 72 hrs post admission then weekly for 1–35 wks (mean 10 wks)	N = 105: ESA (25), no ESA (27), historical control (53)	No reduction in transfusion rate. No differences in Hb, mortality, thrombotic events
Luchette 2012[57]	Critical illness: Blunt trauma and anemia	Epoetin α (10,000–40,000 U/SC) weekly for up to 12 wks after discharge or until Hb ≥120 g/dL (mean 3.1 wks)	N = 192: ESA (97), placebo (95)	Increased Hb. No difference in transfusion rate, patient health (SF-36, APACHE II, SOFA) or neurologic function (COG)
Weber 2005[58]	Surgery: Orthopedic moderate/no anemia	Epoetin α (40,000 U/SC) for 3 wks before (×3), at surgery then weekly (×3)	N = 733: ESA (487), control (237)	Increased Hb and reduced transfusion rate. No effect on time to ambulation or time to discharge. In both groups transfused patients had a longer time to discharge.
Cladellas 2012[59]	Surgery: Cardiac valve replacement and anemia	Epoetin β (500 U/kg/d/IV) and iron sucrose (IV) weekly, fifth dose 48 hrs preoperatively	N = 134: ESA (75), control (59)	Increased Hb and reduced transfusion rate. Decreased hospitalization, morbidity, in-hospital mortality, acute kidney injury, and cardiac failure
Talving 2010[60]	Traumatic brain injury and anemia	Epoetin α (100 U/kg/SC weekly) or DA (0.45 mcg/kg/SC weekly) for 30 d	N = 286: ESA (89), no ESA (178)	Increased Hb, no difference in transfusion rate. Decreased in-hospital mortality. No difference in morbidity but increased length of stay in hospital
Talving 2012[61]	Traumatic brain injury and anemia	DA (0.40 μg/kg/SC weekly) for 30 days	N = 150: ESA (75), no ESA (75)	Increased Hb, no difference in transfusion rate. Decreased in-hospital mortality but longer stay in the ICU and hospital. No difference in complications or neurologic outcome (GCS)

APACHE II, Acute physiology and chronic health evaluation II; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *COG,* cognitive function test; *d,* day; *DA,* darbepoetin alfa; *DVT,* deep vein thrombosis; *eGFR,* estimated glomerular filtration rate; *ESA,* erythropoiesis stimulating agent; *ESKD,* end-stage kidney disease; *FS,* fractional shortening; *GCS,* Glasgow Coma Scale; *hr,* hour; *LVEF,* left ventricular ejection fraction; *LVMI,* left ventricular mass index; *min,* minute; *mo,* month; *NYHA,* New York Heart Association; *RRT,* renal replacement therapy; *SF-36 PF, 36*-item short form health survey; *SOFA,* sepsis-related organ failure assessment; *wk,* week.

TABLE 224.2

Outcomes in Randomized Controlled Trials to Prevent or Correct Anemia (Meta-Analysis)

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Alghamadi 2006[62]	Surgery: cardiac	ESA (40–800 U/SC/IV) and iron (IV/oral) administered at least 1 wk before surgery and 1–3×/wk for 1–4 wks	11 trials, N = 7 08: ESA (471), control (237)	Reduced risk of transfusion
Alsaleh 2013[63]	Surgery: knee and hip arthroplasty	ESA (40,000–120,000 U total) 0–28 days before surgery	26 trials, N = 3450: ESA or ESA + ABD (2059), ABD, placebo or iron (1391)	Increased Hb and reduced transfusions. No difference in thromboembolism
Desai 2010[64]	Chronic heart failure and anemia	ESA 1–3×/wk for 2–72 mos to raise Hb to target	9 trials, N = 2039: ESA (1023) control (1016) (TREAT[49] HF subset)	Neutral for mortality and nonfatal heart failure events
Kotecha 2011[39]	Chronic heart failure and anemia	ESA to raise Hb to higher target (epoetin α or β - 1–3× wk/4000–15,000/weekly total, DA - q2wk-qMonthly/1.5–2.0 ug/kg monthly total)	11 trials, N = 794: ESA (430), control (placebo or no ESA, 352) (does not include RED-HF[42])	Increased Hb, improved exercise tolerance (exercise duration, peak O_2 consumption), cardiac function (NYHA class, ejection fraction, B-type natriuretic peptide), and quality-of-life. Reduced CHF-related hospitalization and reduction in all-cause mortality. No difference in stroke or thrombotic events
Kang 2016[65]	Chronic heart failure and anemia	ESA (epoetin - 1–3× wk/4000–15,000/weekly total, DA - 1/0r 2×/mo/1.5–5.0 ug/kg monthly total) to raise Hb to higher target	13 trials, N = 3172: ESA (1609), control (1523) (includes RED-HF[42])	Increase in Hb. No effect on all-cause mortality or rehospitalization. Improved dyspnea, NYHA grade, and quality-of-life measured by subjective questionnaires. Increased risk for thromboembolic events
Zarychanski 2007[66]	Critical illness: Mixed medical, surgical	Medium-term ESA (rHuEpo - daily-weekly/40,000–140,000/weekly total) for 3–12 wks	9 trials, N = 3314: ESA (1695), control (placebo or no ESA (1619)	Reduced risk of transfusion. No effect on overall mortality or length of stay in hospital or intensive care unit.
French 2016[32]	Critical illness: traumatic brain injury, mixed medical, surgical	Epoetin α or β within 6 hr to 6 d of injury, 1–10 doses with total/mo of 20,000–160,000 U	9 trials, N = 2607: ESA (1221), control (placebo or no ESA, 1184)	No difference in transfusions. No difference in functional neurologic outcome. Reduced mortality overall but no difference in patients with traumatic brain injury. No difference in thrombotic events
Parfrey 2009[11]	CKD, ESKD, and anemia	ESA to increase Hb to target (ESA, dose and schedule not disclosed)	15 trials: N = 1731: high (>120 g/L) vs. low (<120 g/L) Hb target	Reductions in LVMI when starting at low (<100 g/L) but not moderate (>100 g/L) Hb
Palmer 2010[10]	CKD and anemia	Epoetin α, epoetin β, or DA to target low (95–120 g/L) vs. high (120–150 g/L) Hb (dose and schedule not disclosed)	27 trials, N = 10,452: high (>120 g/L) vs. low (<120 g/L) Hb target. (includes TREAT[49])	No differences in mortality, serious cardiovascular events, or progression to ESKD with higher Hb target. Increased risks for hypertension, stroke, and vascular access thrombosis
Koulouridis 2013[67]	CKD, ESKD, and anemia	Epoetin α, epoetin β, or DA to raise Hb to higher target (epoetin α or β - starting dose 5,500–44,000 U)	31 trials: N = 12,956 (includes TREAT[68]): high Hb (100–150 g/L) vs. low (range 8.2–11.5)	Reduced transfusion risk. No association between ESA dose and annual eGFR change, progression to ESKD, or cardiovascular events. Increase in all-cause mortality, stroke, and thrombotic events but decreased serious adverse events with increased dose
Elliott 2017[17]	CKD and anemia	Epoetin α, epoetin β, or DA (epoetin - 1×–3× wk/20,000–80,000 total/wk, DA - 1×–4×/mo, 120–200 ug total/mo) to correct anemia	18 trials, N = 8020: targeted to high (3964) or low Hb (4056)	No difference in progression to RRT

ABD, Autologous blood donation; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *ESKD,* chronic kidney disease; *DA,* darbepoetin alfa; *eGFR,* estimated glomerular filtration rate; *ESA,* erythropoiesis stimulating agent; *ESKD,* end-stage kidney disease; *LVMI,* left ventricular mass index; *NYHA,* New York Heart Association; *RRT,* renal replacement therapy.

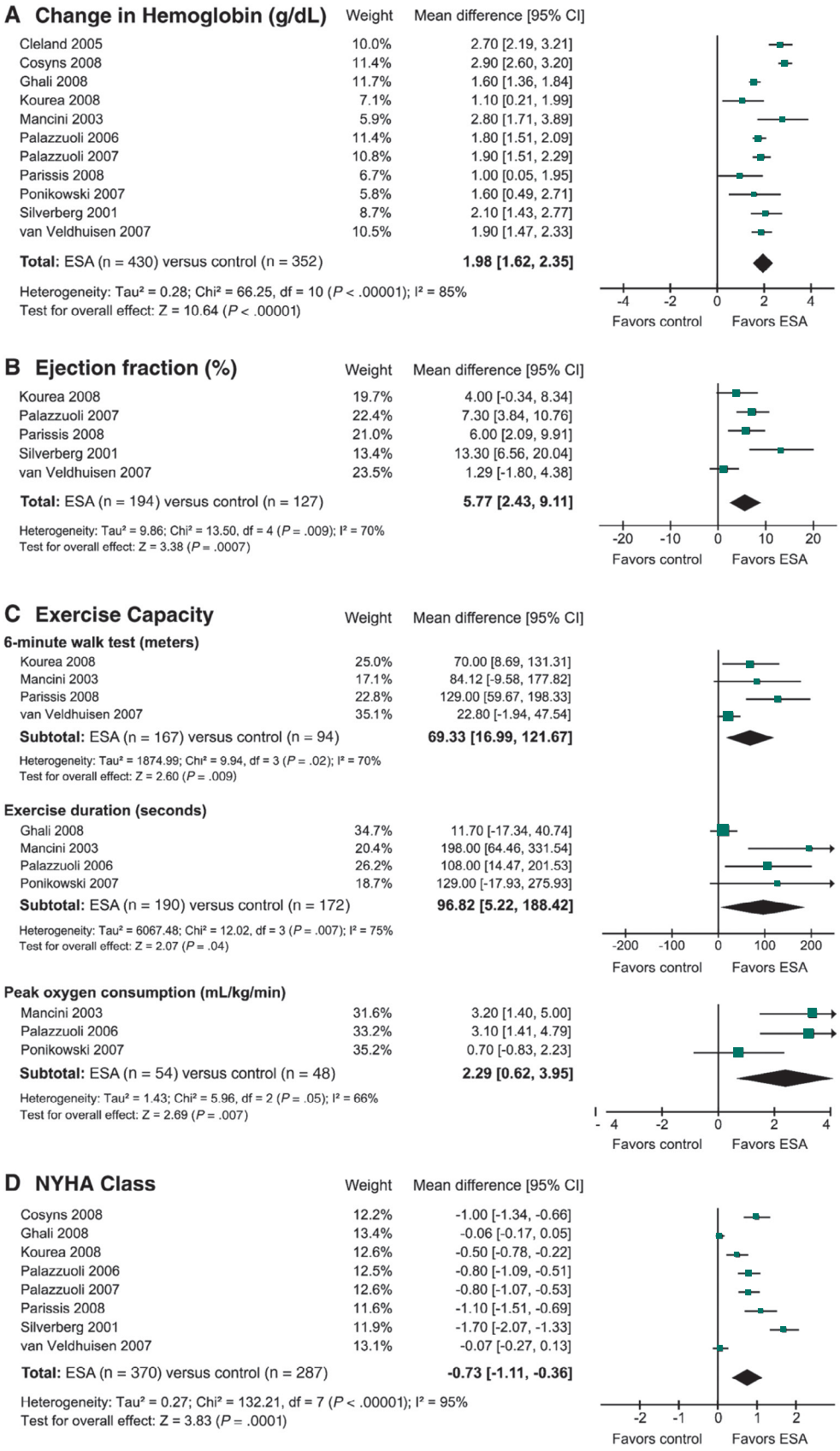

FIGURE 224.1 Mortality in critical care trauma patients: meta-analysis of randomized clinical trials. (From French CJ, et al. Erythropoiesis-stimulating agents in critically ill trauma patients: a systematic review and meta-analysis. *Ann Surg.* 2016.)

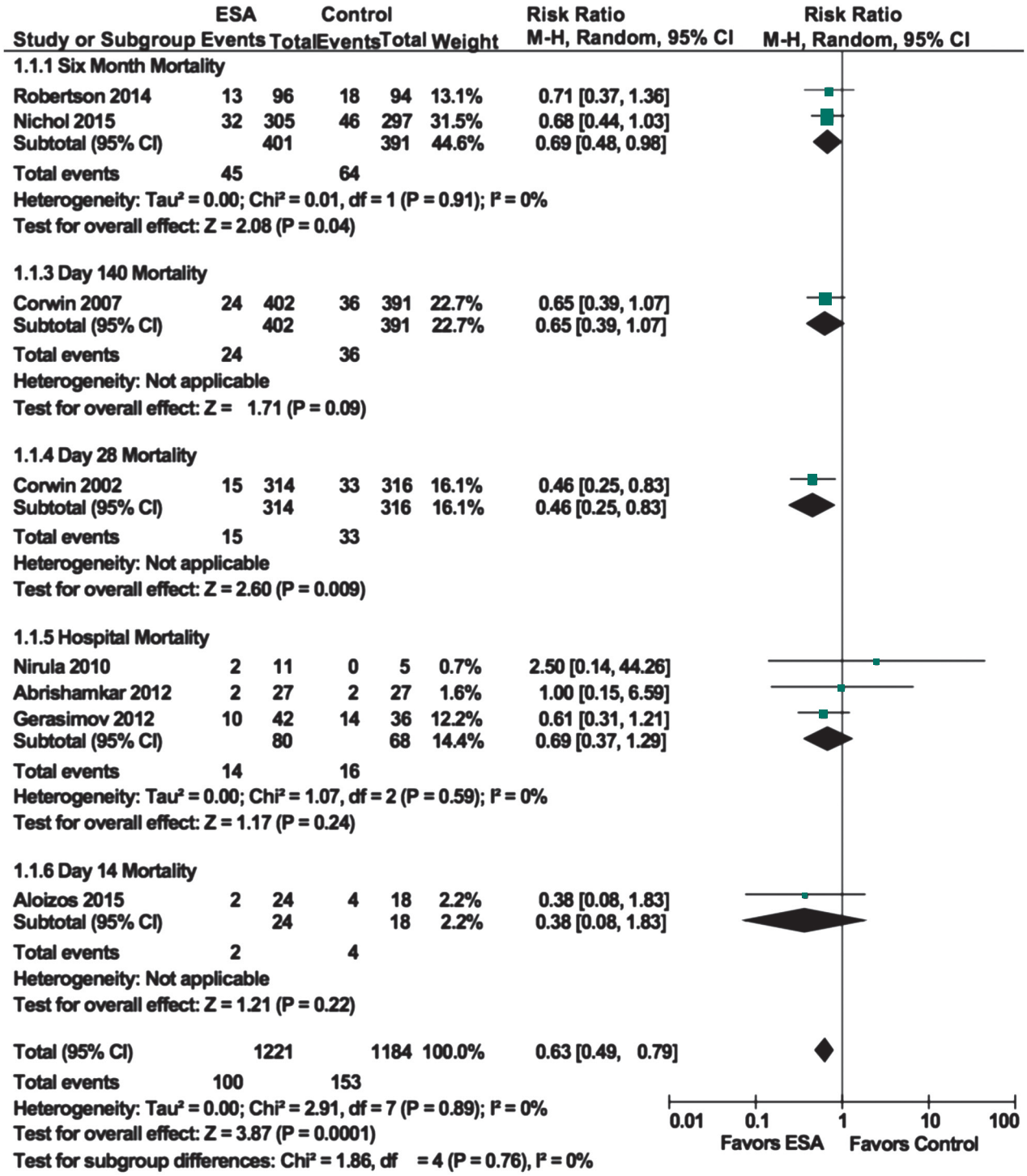

FIGURE 224.2 Effect of ESAs on exercise capacity and heart function in heart failure patients. (From Kotecha D, et al. Erythropoietin as a treatment of anemia in heart failure: systematic review of randomized trials. [Review]. *Am Heart J.* 2011:61:822–831.)

disappeared. In addition, there was evidence of increased risk of thrombotic events and ischemic stroke in some settings, but without an increase in mortality.

Clinical trials to test the possibility that ESA treatment may improve cardiac function or reduce progression of renal disease produced mixed results (Tables 224.1 through 224.4), with meta-analysis showing no benefit in slowing the rate of progression of chronic kidney disease,[17] but there was evidence of improvement in cardiac function. For example, there were reports that anemia correction may reduce left ventricular mass index and improve cardiac failure (NYHA class). The benefit of anemia correction in improving heart function was greater in patients at a lower starting Hb level.[11]

TABLE 224.3

Tissue Protection with Short-Term ESA Treatment

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Binbrek 2009[69]	Cardioprotection: STEMI	Epoetin β (30,000 U/IV) before thrombolysis	N = 236: ESA (115), no ESA (121)	No difference in Hb. No difference in cardiac function (enzymatically estimated infarct size, ECHO, mitral flow, EF, LV end systolic volume or LV wall motion score index)
Liem 2009[70]	Cardioprotection: Non-STE-ACS	Epoetin α (40,000 U/IV) within 8 hr of diagnosis	N = 51: ESA (26) placebo (25)	No effect on troponin or infarct size (CK-MB release)
Ott 2010[71]	Cardioprotection: STEMI	Epoetin β (3× 33,300 U) immediately after PCI, 24, and 48 hr	N = 138: ESA (68), Placebo (70)	No difference at 3 mos of LVEF or infarct size. No difference at 6 mos of death, recurrent myocardial infarction, stroke, vessel revascularization, LVEF measured by MRI, or infarct size
Ludman 2011[72]	Cardioprotection: STEMI	Epoetin β (50,000 U/IV) before PCI and 24 hr later	N = 51: ESA (26), placebo (25)	No difference in length of hospital stay, LVEF, troponin T or infarct size (CMR). Increased LVEDV, LVESV, and LV mass
Najjar 2011[73]	Cardioprotection: STEMI	Epoetin α (15,000, 30,000 or 60,000 U/IV) within 4 hrs of reperfusion	N = 222: ESA (125) placebo (97)	No difference in Hb. infarct size (CMR), LV mass, LVEF, death, stroke, or thrombosis. Increase in adverse events and composite outcome (death, MI, stroke, or stent thrombosis)
Suh 2011[74]	Cardioprotection: STEMI	Epokine (50 U/kg/IV) immediately before PCI	N = 57: ESA (29), control (27)	No difference in infarct size (CK, CK-MK, MRI), or LVEF
Prunier 2012[75]	Cardioprotection: STEMI	Epoetin β (1,000 U/kg/IV) immediately after PCI	N = 107: ESA (53), placebo (44)	At d5 no difference in peak CK release but decreased incidence of MVO, reduced LV volume, mass, and function impairment. At 3 mos no difference in infarct size, LV mass, volume, or function
Roubille 2013	Cardioprotection: STEMI	DA (150 ug/intracoronary) after PCI	N = 51: ESA (27), control (24)	No difference in creatinine kinase or infarct size (by CMR)
Fokkema 2013[76]	Cardioprotection: STEMI	Epoetin α (60,000 U/IV) within 3 hr after PCI	N = 529: ESA (263), control (266)	No difference in composite end point (all-cause mortality, re-infarction, target vessel revascularization, stroke, or heart failure) or thrombotic events
Yoo 2011[77]	Cardioprotection: valvular heart surgery with anemia	ESA (epocain, 500 U/kg/IV) 16–24 hrs before surgery	N = 74: ESA (37) control (37)	Reduced transfusion risk and risk of AKI. No difference in mortality
Dardashti 2014[78]	Cardioprotection, renoprotection, neuroprotection: Surgery (CABG), patients with impaired renal function	ESA (Retacrit 400 U/kg/IV) preoperatively	N = 70: ESA (35) placebo (35)	No difference in Hb, transfusions. No difference in markers of renal function (cystatin C, NGAL, creatinine, eGFR), incidence of AKI, heart function (BNP, CK-MB), brain damage (S100B), or adverse events
Joyeux-Faure 2012[79]	Cardioprotection, neuroprotection: Surgery (CABG)	Epoetin β (800 U/kg/IV) 1–3 hrs before CPB	N = 50: ESA (25), placebo (25)	No difference in cardiac function ejection fraction and markers (troponin T, NT-proBNP, creatine kinase MB), cerebral (S100B) markers, inflammation markers (TNF-α, IL-6, IL-10. No difference in mortality
Springborg 2007[80]	Neuroprotection: Stroke (subarachnoid hemorrhage)	Epoetin α (500 U/kg IV) immediately after randomization and at 24 and 48 hr	N = 53: ESA (24) placebo (30)	No difference in Glasgow outcome score, markers of brain damage (S-100B and NSE), surrogate markers of secondary ischemia (glutamate, lactate/pyruvate), blood–brain barrier integrity (CSF:serum ratio of albumin) or brain injury (mean maximum flow velocities in the middle or anterior cerebral arteries)

Continued

TABLE 224.3

Tissue Protection with Short-Term ESA Treatment—cont'd

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Ehrenreich 2009[27]	Neuroprotection: Stroke (ischemic)	Epoetin α (40,000 U/IV) within 6 hr of symptom onset, and at 24 and 48 hr	N = 522: ESA (238), placebo (253)	No difference in MRI imaging (d7), Barthel Index, or NIHSS on d30 or d90. Increased mortality and intracerebral hemorrhage. Increased deaths
Tseng 2009[81]	Neuroprotection: Stroke (subarachnoid hemorrhage)	Epoetin β (30,000 U/IV) on day of recruitment and every 48 hr (90,000 U total)	N = 80: ESA (40) placebo (40)	No difference in vasospasm or ischemia (THRT). Reduced severe vasospasm. No difference in overall mRS or GOS score at discharge or 6 mos. No difference in thromobembolisms
Yip 2011[82]	Neuroprotection: Stroke (ischemic)	Epoetin β (5000 U/SC) at 48 and 72 hr after stroke	N = 167: ESA (83) placebo (84)	No change in Hb. Improvement in 90 d clinical outcome (MANE). No difference in NIHSS, mRS. or Barthel index
Pang 2013[83]	Neuroprotection: CO_2 poisoning	rHuEPO (10,000 U/SC) within 12 hr of poisoning, then daily for 1 wk	N = 103: ESA(54), placebo (49)	Improved NIHSS score and Barthel index (30 d) and S-100β levels decreased
Cramer 2014[84]	Neuroprotection: Stroke (ischemic)	Epoetin α (escalating dose 4000–20,000 U/IV, d7, 8, 9) and β-hCG (10,000 U/IV) on d1,3,5) initiated 24–48 hr after stroke onset	N = 96: ESA (72), placebo (24)	No difference in neurologic recovery (NIHS baseline to d90, Barthel index or mRankin), adverse events or death
Robertson 2014[30]	Neuroprotection: TBI	Epoetin α (500 U/kg/IV) within 6 hr of injury, daily for 2 d, then weekly for 2 wks (74 patients) or 1 dose within 6 hr of injury (126 patients)	N = 200: ESA (102), placebo (98)	No difference in transfusions. No difference in mortality or neurologic outcome (GOS) at 6 mos. Higher Hb transfusion threshold (70 vs. 100 g/L), had increased thrombotic events
Nichol 2015[31]	Neuroprotection: TBI	Epoetin α (40,000 U/SC) 1×/wk, up to 3× starting within 24 hr of injury	N = 606: ESA (308), placebo (298)	No difference in proportion of patients with a GOS (extended) level of 1–4, 6-month mortality, lesion mass, or occurrence of lower limb DVT
Cariou 2016[85]	Neuroprotection: Cardiac arrest	Epoetin α (40,000 U/IV) ×5 every 12 hr immediately postresuscitation	N = 476: ESA (234), No ESA (242)	No difference in CPC, irreversible brain damage, or mortality. Increased SAEs and thrombotic events in ESA group
Endre 2010[35]	Renoprotection: AKI	Epoetin β (500 U/kg/IV to a maximum of 50,000 U) within 6 hr and a second dose 24 hr later	N = 163: ESA (84) placebo (78)	No difference in incidence of AKI, dialysis, length of hospital stay, or deaths
de Seigneux 2012[86]	Renoprotection: Cardiac surgery	Epoetin α (20,000 U or 40,000 U/IV) 1 to 4 hr after surgery	N = 80: ESA (40) placebo (40)	No difference (0–48 hr) in Hb, incidence of AKI, creatinine, cystatin C and urinary NGAL levels, mortality, or hospital stays
Tasanarong 2013[87]	Renoprotection: Cardiac surgery	Epoetin β (200 U/kg/IV) 3 d before CABG and 100 U/kg at surgery	N = 100: ESA (50) or saline (50)	No difference in Hb. At 1–3 d, there was reduced incidence of AKI. Improvement in eGFR and urine NGAL
Oh 2012[88]	Renoprotection: Coronary artery bypass grafting	Epoetin β (300 U/kg/IV) before CABG	N = 71: ESA (36), saline (35)	Reduced incidence of AKI
Olweny 2012[89]	Renoprotection: Partial nephrectomy	Epoetin α (500 IU/kg/IV) 30 min before hilar occlusion	N = 106: ESA (52), control (54)	No difference in adverse events or eGFR at 3 wks or 12 mos
Kim 2013[90]	Renoprotection: Valvular heart surgery	Epocain (300 U/kg/IV) after anesthetic induction	N = 98: ESA (49) control (49)	No difference in Hb, incidence of AKI, SCr levels, eGFR, creatinine clearance, or biomarkers of renal injury (cystatin C and NGAL)
Kim 2016[91]	Renoprotection: Thoracic aorta surgery	Epocain (500 U/kg/IV) before surgery	N = 63: ESA (31) Saline (32)	No difference in incidence or severity of AKI, NGAL (0–48 hr), creatinine (0–7 d), time in ICU or hospital, or mortality

ACS, Acute coronary syndrome; *AKI,* acute kidney injury; *CABG,* coronary artery bypass graft; *CMR,* cardiac magnetic resonance; *CPB,* cardiopulmonary bypass; *CPC,* cerebral performance category; *d,* day; *DVT,* deep vein thrombosis; *eGFR,* estimated glomerular filtration rate; *GOS,* Glasgow outcome score; *hr,* hour; *LVEF,* left ventricular ejection fraction; *LVEDV,* left ventricular end diastolic volume; *LVESV,* left ventricular end systolic volume; *MANE,* major adverse neurologic event; *min,* minute; *mo,* month; *mRS,* modified Rankin score; *NGAL,* neutrophil gelatinase-associated lipocalin; *PCI,* percutaneous coronary intervention; *SCr,* serum creatinine; *TBI,* traumatic brain injury; *THRT,* transient hyperemic response test; *wk,* week.

TABLE 224.4

Tissue Protection with Short-Term ESA Treatment (Meta-Analyses)

REFERENCE	GROUP	ESA TREATMENT	SUBJECTS	OUTCOMES IN ESA/HIGH Hb ARMS
Gao 2012[92]	Cardioprotection: STEMI	ESA (1–3×, 4,000–100,000 U total), 1 d before or up to 2 d after event	13 RCTs N = 1564	No difference in LVEF, infarct size, creatinine kinase, risk of heart failure, risk of stent thrombosis
Ali-Hassan 2015[93]	Cardioprotection: STEMI or AMI	1–3 ESA doses (epoetin 14,000–60,000 U, or DA 300 ug) before or within 3 hrs of PCI, with additional doses 24–48 hrs post PCI	5–14 trials depending on end point: N = 525–2044	No difference in cardiac function (LVEF, LVESV, LVEDV, incidence of heart failure, infarct size, creatinine kinase), all-cause mortality, or incidence of stroke or thrombosis
Tie 2015[94]	Renoprotection; Cardiac surgery	Single dose of epoetin (20,000–40,000 U/IV) before or immediately post surgery	5 trials: N= 423	No difference in incidence of AKI or hospital mortality
Zhao 2015[95]	Renoprotection: Trauma and surgical	1–4 doses (14,000–40,000 U) before surgery or up to 3d after admission to the ICU with additional doses for up to 3 wks	10 trials, N = 2759: ESA (1391), placebo or no treatment (1368)	No difference in incidence of AKI, requirement for dialysis or mortality
Elliott and Endre 2016[17]	Renoprotection: AKI - trauma and surgical or kidney transplant	AKI trials: 14,000 U–40,000 U preoperatively or within 6 hrs of event, or 7000 U within 14 d of AKI (1 trial). Transplant trials: 7,000–100,000 U at time of surgery with additional doses up to 14 days postsurgery. In 2 trials lower-doses 10,000–17,000 U were given within 1 wk and continued for 1–3 mos	7 AKI trials, N = 1020: ESA (490), placebo or no ESA (530). 7 transplant trials, N = 450: ESA (223), placebo or no ESA (227)	No difference in incidence of AKI in patients at risk for AKI or delayed graft function/renal recovery in kidney transplant patients

AKI, Acute kidney injury; *AMI,* acute myocardial infarction; *d,* day; *ECHO,* echocardiogram; *ESA,* erythropoiesis stimulating agent; *hr,* hour; *LVEF,* left ventricular ejection fraction; *LVESV,* left ventricular end systolic volume; *LVEDV,* left ventricular end diastolic volume; *mo,* month; *STEMI,* ST segment elevated myocardial infarction; *wk,* week.

Erythropoietin-Stimulating Agents and Tissue Protection

In preclinical studies, animals subject to ischemic damage to the brain and heart had reduced damage and better recovery of function. This work was followed by numerous other studies suggesting that ESAs may protect other organs such as kidney, liver, and other adverse conditions.[18] Indeed, the "powerful and beneficial pleotropic effects" of ESAs promoted considerable excitement, particularly as some of the evidence suggested that these benefits extended beyond prevention to protection after administration after tissue injury.[19] A possible mechanism was proposed: EPO receptors (EpoR) may be present on cell surfaces at high levels, and the receptors were functional in the tissues of interest. ESAs were thought to activate such receptors resulting in the anti-apoptotic effects observed in various tissues (e.g., in the kidney[20] and the brain[21]).

The hypothesis was controversial, however. Many preclinical studies showed no benefit of ESAs in tissue protection experiments.[18,22,23] Supportive studies were based on detection of EpoR transcripts and protein, primarily via RT-PCR and western blots or immunohistochemistry experiments with anti-EpoR antibodies. In the absence of direct detection of EpoR, in vitro experiments were performed in which cell lines or cell cultures were treated with ESAs and functional responses were reported, indirectly supporting the presence of EpoR. However, the antibodies employed were shown to give false-positive results because of nonspecificity. RT-PCR can detect vanishingly low levels of transcripts of questionable significance.[24] The in vitro experiments showed only modest effects and lacked critical controls to detect false-positive results. Importantly many such studies demonstrated low/no EpoR and no effects in vitro.[18,23]

In contrast to in vitro studies, most of which are predicated on EPO working through EpoR, studies in experimental animals tended to show positive results in tissue protection after cardiac, renal, and cerebral ischemia. Alternative hypotheses to receptor-mediated protection also were developed to explain tissue protection, such as indirect cytoprotection or neovascularization through the EPO-mediated mobilization of endothelial progenitor cells.[25]

Despite the serious concerns, numerous clinical studies have been performed to assess mortality in the critical care setting and to determine whether ESAs reduce ischemic damage to the heart, brain, kidney, and other organs because of blood loss or trauma. The results of such clinical trials are summarized in Tables 224.3 and 224.4, whereas the affects and subject groups are discussed below.

Effect of Erythropoietin-Stimulating Agents on Anemia

ESAs had little effect on Hb levels in tissue-protection studies mostly because of the short time period that patients were in the ICU and the limited number of ESA administrations. There was therefore little effect on transfusion rates. In addition, it was thought that single high doses of ESAs would show immediate benefit through direct effects on ischemic tissues, limiting the need of excessive drug exposure. Overall, although some positive effects were reported, there was little benefit on organ function in most trials.

Effect of Erythropoietin-Stimulating Agents on Stroke

In an early ESA stroke study, there was a nonsignificant trend toward reduced infarct size and improved cognitive function when ESAs were administered within a few hours of stroke symptoms.[26] These promising results were not replicated in a larger stroke trial of high-dose epoetin α in 522 subjects, where mortality actually increased in the ESA study arm.[27]

Effect of Erythropoietin-Stimulating Agents on Traumatic Brain Injury

Trauma is a major global cause of disability, and traumatic brain injury is particularly devastating.[28] Early studies in experimental TBI suggested that ESA administration offered useful neuroprotection.[29] These encouraged clinical studies of neuroprotection, the results of which have been less inspiring. In one study of 200 patients with closed head injury, neither the administration of erythropoietin nor maintaining a hemoglobin concentration of greater than 100 g/L resulted in improved neurologic outcome at 6 months.[30] Furthermore, the transfusion threshold of 100 g/L was associated with a higher incidence of adverse events. In a recent, larger (606-patient) multicenter, multinational trial of high-dose epoetin α in patients with traumatic brain injury (EPO-TBI), in which ESA was started within 6 hours of injury, there was no benefit from ESA on the extended global outcome score (GOS-E).[31] At 6 months there was no difference in mortality, and unlike in some other studies (Table 224.3), there was no increase in thrombotic events.

A recent meta-analysis of nine studies, comprising 2607 critically ill trauma patients randomly assigned to ESA or placebo, showed that ESA therapy was associated with a substantial reduction in mortality (RR 0.63 CI: 0.49–0.79) compared with placebo.[32] This benefit persisted across relevant subgroups and did not appear to be influenced by the dose, route, or timing of ESA administration. Given the doubt surrounding true tissue protection by EPO (see later in this chapter), an alternative explanation offered by the meta-analysis authors for the survival benefit seen was that ESAs may reduce the risk of hemorrhagic death. ESA therapy did not increase the risk of lower limb venous thrombosis. However, after TBI, the number of survivors with moderate disability or good recovery were not increased with ESAs. Given the broad societal implications of a poor functional outcome of survivors of trauma, the burden for patients and caregivers, and the health economic consequences, the results emphasize that any future trials rigorously evaluate functional outcome and quality of life. Indeed, the meta-analysis authors concluded that, despite the overall improvement in survival, "routine use of ESAs is not advised, particularly in TBI, where the effect on long-term functional neurologic outcome and quality of life remains uncertain."[32]

Effect of Erythropoietin-Stimulating Agents on Myocardial Infarction and Cardiac Failure

Outcomes with ESAs in cardiac patients were similar to those with brain injury. Cardiac patients such as those presenting in the ICU with myocardial infarction or undergoing surgical procedures showed only modest or no improvement in ischemic damage to the heart, or to heart function, over time. Most of those trials were small, making conclusions difficult. However, in a recent large trial in 529 patients presenting with myocardial infarct given a high-dose ESA within 3 hours of PCI, there was no mortality or cardiovascular benefit compared with controls.[33] A meta-analysis of 10 similar trials with a total of 1242 patients also showed no difference in outcomes.[34]

Effect of Erythropoietin-Stimulating Agents on Acute Kidney Injury

Patients with, or at risk of, acute kidney injury (AKI) also were examined in ESA clinical trials with mixed results, possibly because all trials were small in size (see Table 224.3). The largest trial randomized 162 patients and was double-blind and placebo controlled.[35] In that trial, there was no difference in renal outcomes, nor was there benefit in meta-analyses of that and other similar trials (see Table 224.4).

ESA-treated kidney transplant recipients may be a considered a good human model to test the preclinical tissue-protection hypothesis. In such studies, patients present to the clinic under controlled conditions and are given kidneys subjected to prior ischemic damage (due to removal from the donor). Importantly, ESAs can be given at scheduled, although perhaps not optimal, times. Meta-analysis of trials in such subjects also showed no improvement in renal outcomes with ESAs.[17] It may be argued that most of these studies were confounded by relatively long and variable ischemia times before organ retrieval, because ESA was administered to the kidney recipient rather than given directly to the donor kidney before retrieval by administration to the deceased donor. Furthermore, it must also be acknowledged that most, if not all, of these studies were underpowered and major heterogeneity of methodologic differences between the studies limits interpretation of the outcomes.

Failure to Translate Preclinical Success Into Clinical Utility

Except for improved survival after trauma, most studies do not support the use of low- or high-dose ESA for tissue protection, especially where short-term treatment offers little possibility of reductions in symptoms of anemia or reductions in transfusion rates. Explanations for this is a broad topic, too extensive to discuss in detail here. Briefly, the inability to translate results of preclinical studies to the clinic could be explained by the heterogeneity in patient context, including comorbidity, preclinical or clinical study design, or by the difficulty in replicating such conditions in the laboratory. Alternatively, the hypothesis and interpretation of earlier results may have to be reconsidered. Indeed, a consortium of investigators recently attempted to test the neuroprotection hypothesis by performing multiple controlled rat studies in three established models in which the animals were subjected to traumatic brain injury and given two doses of ESA. Overall there was no difference in terms of behavioral, histopathologic, and biomarker outcomes in ESA-treated animals compared with controls.[36]

Such newer studies raise questions about the methodologic rigor in the design of experimental studies in early

studies of tissue protection with ESAs. In general, they echo concerns regarding the similar failure to translate studies of tissue protection and treatment of experimental AKI by any agent into clinical success.[37] Recommendations to improve preclinical study design have been made. For example, animal experiments involving a test compound should be blinded, power calculations should be performed with predefined primary outcomes, and all outcomes, including unanticipated experimental mortality, should be reported.[37] It remains to be seen whether implementation of such reasonable but expensive strategies to foreshadow and underpin translational studies will be funded outside industry-supported consortia.

CONCLUSION

Short-term ESA administration in the ICU has had little benefit on hard end points (mortality, Hb increase, or organ function). Longer-term treatment that produces a corresponding increase in Hb can reduce blood transfusions. There may be improvement in some anemia symptoms with longer-term ESA treatment (e.g., dyspnea and LVMI in CHF patients with anemia correction, especially when patients are initiated with ESA at a low starting Hb). Clearly this is of little benefit in the ICU. Although there is some evidence for increased survival in trauma patients, there is also evidence for an increased rate of thrombotic adverse events, including stroke, in some settings.

Overall, the risk-benefit ratio from these studies does not support a role for the off-label use of ESAs in the critically ill. The temptation to switch to transfusions to treat anemia also should be considered cautiously. Transfusions also have risks that may exceed those of ESAs in some end points, and the negative effects seem to be increased when the Hb transfusion trigger is high.[38] Clearly patients with severe anemia should be treated; the question becomes one of balancing risks and benefits and assessing the degree of anemia where this balance favors ESA treatment.

There may still be a place for ESAs in subjects in whom blood transfusions are needed but cannot be administered for religious or other reasons (e.g., Jehovah's witnesses), or where the benefits clearly outweigh risks (e.g., CKD patients with severe anemia). However, ESA administration beyond the treatment of anemia is not warranted without clear clinical trial support or a better understanding of mechanisms associated with harm.

Key Points

1. Anemia is a frequent occurrence with serious consequences in critical care patients.
2. Anemia can be corrected in critical care patients with transfusions and ESAs, but if the time in the hospital or the number of administrations ESAs is inadequate, the effect on Hb levels is limited.
3. Transfusions and ESAs can have different risks and benefits.
4. There is little effect on organ function but some benefits on mortality with anemia correction, particularly in patients with very low hemoglobin levels.
5. Beneficial direct organ protecting effects of ESAs observed in vitro and in animals have not translated into benefit in the clinic.

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