

# Cardiovascular Indications and Complications of Recombinant Human Erythropoietin

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## ABSTRACT

Exogenous recombinant human erythropoietin (rHuEPO) is a beneficial therapeutic agent for correction of anemia in chronic kidney disease (CKD), end-stage renal disease, chemotherapy, and has been used as prophylaxis to prevent anemia after surgery. The erythropoietin receptor is widely distributed in the cardiovascular system, including endothelial cells, smooth muscle cells and cardiomyocytes. rHuEPO has potentially beneficial effects on the endothelium including cytoprotective, mitogenic and angiogenic activities. Early studies in heart failure patients with anemia suggest that rHuEpo therapy is safe and effective in reducing left ventricular hypertrophy, enhancing exercise performance and increasing ejection fraction. The use of rHuEPO, however, may also be associated with distinct side effects. Although not clearly demonstrated, a relationship between an increased red blood cell count and thrombus formation. Some reports suggest that rHuEpo may have prothrombotic or alters platelet aggregatory responses. Most notable is hypertension (HTN), partial correction of anemia with intravenous rHuEPO causes HTN. CREATE study found a trend toward increased mortality risk with a higher Hb target of 13-15 g/dl. Therefore aiming for a higher hematocrit level is still a controversial issue in the management of anemia in renal failure. Despite some potential adverse effects further studies are needed to define the role of rHuEPO in chronic cardiovascular settings.

## Introduction

Anemia is the frequent complication of patient with chronic kidney disease (CKD) and is mainly characterized by reduced ability of the damaged kidney to produce endogenous erythropoietin. Erythropoiesis, a complex physiological process maintaining homeostasis of oxygen (O<sub>2</sub>) levels in the body, is primarily regulated by erythropoietin (EPO), a 30-kDa, 165 d amino acid hematopoietic growth factor produced by the kidneys.<sup>[1]</sup> Correction of renal anemia

by the use of recombinant human erythropoietin (rHuEPO) has been proven to be an effective treatment with several beneficial effects on exercise capacity due to reduction of hypoxia and improvement of cardiac function.<sup>[2]</sup> At present, rHuEPO is approved also for treatment of anemia caused by other conditions, including anemia-associated with renal failure, chemotherapy and HIV antiviral treatment or to reduce the need for transfusion in preoperative surgical patients. However, beside these beneficial effects, potential risk factors of a rHuEPO treatment have been reported. Treatment with rHuEPO has been linked to an increased risk of thrombotic events, and EPO seems to affect various cardiovascular and hemostatic parameters unrelated to increase in hematocrit.<sup>[3]</sup> Thus, as the potential uses of EPO therapy increases, it is important to reconsider its cardiovascular effects.

## Biology of erythropoietin

EPO is synthesized by peritubular cells in the cortex-medullary border of the kidney<sup>[4]</sup> and in the liver during fetal and neonatal development.<sup>[5]</sup> A variety of other tissues have been reported to express EPO including bone marrow macrophages,<sup>[6]</sup> trophoblasts,<sup>[7]</sup> breast glands,<sup>[8]</sup> and astrocytes<sup>[9]</sup>.

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## Endogenous erythropoietin receptor signaling pathway

In bone marrow, EPO acts on a specific receptor (EPO-R), with subsequent activation of various signalling pathways (STAT5, MAPK, PI3/Akt). Interestingly, rather than stimulating proliferation, activation of these pathways leads to resulting in the proliferation and terminal differentiation of erythroid precursor cells i.e., inhibition of programmed cell death (apoptosis). EPO thus acts primarily as a survival factors for erythroid progenitor cells, and in this manner increases the number of mature red blood cells in the circulation.

Binding of EPO to EPO-R induces 1) Phosphorylation of the STAT5 transcription factor that will then homodimerize and translocate into the nucleus and activate target genes encoding anti-apoptotic molecules, such as Bcl-XL, 2) Phosphorylation of phosphatidylinositol 3-kinase (PI-3 kinase) that, in turn, phosphorylates protein kinase B (PKB)/Akt, which then phosphorylates (a) Proapoptotic molecules, such as Bad, caspase 9 or glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), leading to their inactivation, (b) FOXO transcription factors (FOXO TF), inducing their retention into the cytoplasm and thus preventing activation of target genes, such as Fas ligand or Bim, and (c) I-kB, leading to the activation of the transcription factor NF-kB; (3) Phosphorylation of I-kB, which allows the release of the transcription factor NF-kB, its translocation into the nucleus and activation of target genes encoding anti-apoptotic molecules, such as XIAP and c-IAP2; and (4) activation of Hsp70, which binds to and inactivates proapoptotic molecules, such as apoptosis protease-activating factor-1 (Apaf-1) and apoptosis-inducing factor (AIF) [Figure 1].<sup>[10]</sup>

## Treatment with recombinant human erythropoietin

RHuEPO should be started if patients Hb remains below 11gm% despite correcting the nutritional and iron deficiencies. The intravenous route is recommended in patients on hemodialysis while in others it can be used subcutaneously two to three times a week. EPO should be started in a dose of 120-180 U/kg/week in two to three divided doses. Hb should be monitored once in two weeks till target Hb is achieved.

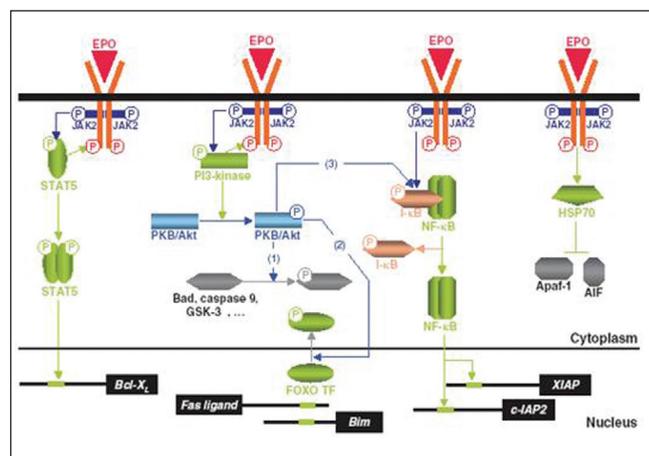


Figure 1: Schematic representation of the pathways by which the binding of erythropoietin (EPO) to its receptor can inhibit apoptosis

Once target Hb is achieved, Hb should be monitored every month. At the end of 2 weeks with EPO therapy the Hb should rise by 1 gm%. If the rise is less than 1 gm%, the dose of EPO should be increased by 50%, till the target Hb is achieved. If the rise in Hb% is more than 2 gm% at the end of two weeks then the dose of EPO can be reduced by 25%. Once the target Hb is reached or exceeded, then reduce the dose of EPO by 25%. The blood pressure should be checked with each dose and brought under control. EPO resistance should be suspected when the dose requirement exceeds 450 U/ kg/week

## Cardiovascular indication and complications of EPO Therapy

### Correction of hemoglobin outcomes in renal insufficiency (CHOIR) study

CHOIR was an open-label, randomized trial that studied 1432 patients with CKD. Seven hundred and fifteen patients were randomized to receive epoetin- $\alpha$  targeted to achieve an Hb of 13.5 g/dl, and 717 were randomized to receive epoetin- $\alpha$  targeted to achieve an Hb of 11.3 g/dl.

One hundred and thirty centers in the United States participated in the study. The mean and median study duration was 16 months. Key eligibility criteria included age >18 years, estimated GFR of 15–50 ml/min/1.73m<sup>2</sup>, and the exclusion of patients with refractory anemia, active malignancy and active cardiovascular disease.

The primary endpoint was a composite of death, myocardial infarction, congestive heart failure (CHF) hospitalization (excluding hospitalization during which renal replacement therapy occurred) and stroke. Secondary endpoints included the components of the primary endpoint, as well as cardiovascular and total hospitalizations, quality of life (QOL) and the time-to-dialysis.

Two hundred and twenty-two composite events occurred: 125 events among the high Hb group and 97 events among the low Hb group  $P=0.03$ , hazard ratio (HR) of 1.34; with 95% confidence interval of 1.03 and 1.74. There was a statistically significantly higher rate of serious adverse events in the higher vs. lower Hb group.<sup>[11]</sup>

## Erythropoietin and thrombosis

One of the potential side effects of EPO therapy is an increase in thrombotic events. In a prospective trial, 618 dialysis patients were randomized to achieve a target hematocrit of 42% versus a target hematocrit of greater than 30% in 615 control patients.<sup>[12]</sup> After 29 months, the relative risk of death in the high hematocrit group was 1.3 (95% confidence interval 0.9–1.9), and the trial was stopped. Factors such as exposure to intravenous iron and decreased dialysis adequacy may have been contributory, but the increased doses of EPO could also explain this result. An increase in cardiovascular events, including vascular access thrombosis, stroke and myocardial infarction, has been associated with a rapid rate of rise in hemoglobin.<sup>[13]</sup>

Darbepoetin- $\alpha$  results in an increased rate of thrombotic events, including pulmonary embolism when administered to patients receiving chemotherapy. The concerns regarding thrombosis have been evaluated in an animal model. RHuEPO administration resulted in a nearly 3-fold increase in the content of platelets in the thrombi in an A–V shunt model, which reverted to normal after cessation of EPO administration.<sup>[14]</sup>

A variety of mechanisms have been cited for increased thrombosis with EPO therapy, possibly because of increased blood viscosity<sup>[15]</sup> or an enhancement of platelet attachment to the sub-endothelium.<sup>[16]</sup> rHuEPO therapy has been reported to shorten the bleeding time even before the correction of anemia indicating that the elevation of hematocrit cannot explain this effect.

Enhanced thrombin generation has also been reported after rHuEPO therapy, manifest as an increase in the TAT complex in rHuEPO-treated dialysis patients, which peaked at 2 months of therapy. The increment in TAT was comparable to that observed with myocardial infarction and was higher than that reported in DVT or DIC.<sup>[17]</sup>

Lower levels of protein C and S have been reported after rHuEPO therapy, which could contribute to elevated pro-thrombotic markers. It has been reported, a reduction in total and free protein S, as well as protein C after initiation of rHuEPO.<sup>[18]</sup>

## Effects of erythropoietin on platelets

*In vitro* stimulation of whole blood with high concentration of rHuEPO did not alter any agonist induced aggregation. Therefore it seems feasible that rHuEPO does not exert direct effects on circulating platelets, but rather modulates platelet during synthesis and maturation in the bone marrow. EPO interacted with EPO-R on the cell surface, triggering activation of the JAK-signal transducers and activators of transcription, PI-3 kinase and mitogen-activated protein kinase pathways (Elliott *et al.* 2008).

The changes in platelet reactivity reported is the result of EPO-induced synthesis of new platelets exhibiting altered agonist responses, possibly due to alterations in expression of receptors and intracellular signalling proteins. It has also been reported to stimulate tyrosine kinase-dependent signal transduction pathways and increase in basal and stimulated cytosolic calcium levels in platelets (Haiden, 2005 and Peng, 1994).

Several studies have documented a decrease in the bleeding time of dialysis patients after initiation of rHuEPO therapy. Although this response could be due to changes in the vessel wall or circulating proteins, several lines of evidence suggest that at least part of the response is from direct action on platelets. Hemodialysis patients undergoing rHuEPO therapy have increased spontaneous platelet aggregation in whole blood, which reverses by withdrawing EPO and can be inhibited by aspirin administration.<sup>[19]</sup> rHuEPO therapy was associated with increased Ca uptake and increased Ca stores in the platelets.<sup>[20]</sup>

EPO therapy of uremic patients improves the intra platelet signaling induced by thrombin through tyrosine phosphorylation of proteins associated with the cytoskeleton.<sup>[21]</sup> Enhanced transient platelet reactivity has been observed in dialysis patients treated with rHuEPO.<sup>[22]</sup> The use of rHuEPO in dialysis patients was associated with a significantly higher PMP count compared to untreated patients.<sup>[23]</sup> The infusion of rHuEPO at 100 U or 500 U/kg in normal healthy male volunteers resulted in increased percentages of P-selectin and CD63-positive platelets after stimulation by TRAP.

Furthermore, circulating levels of soluble P-selectin were also elevated consistent with increased *in vivo* platelet activation.<sup>[24]</sup> EPO binds to megakaryocytes, where it may contribute to megakaryocytic maturation. In patients treated with rHuEPO, the platelet count may increase by 10–20%. Recent data from a porcine model suggest that even modest rises in platelet count can increase the propensity for arterial thrombosis. rHuEPO therapy has been reported to increase the mean platelet volume<sup>[25]</sup> with larger platelets being more active

than smaller platelets.<sup>[26]</sup>

Platelets from animals pretreated with rHuEPO alters all four agonist i.e., ADP, arachidonic acid, thrombin and collagen-induced *ex vivo* platelet aggregation at significant level. The mechanisms of such early improvement of platelet function with rHuEPO are unknown but identifying receptors available on the platelet surface more prone for aggregation in presence of agonists and targeting with specific antagonist would be beneficial.

Klinkhardt *et al.*, 2003, reported that rHuEPO-treated rats show increased plasma levels of soluble P-selectin, further indicators of platelet hyper-reactivity. It has been reported that clopidogrel but not aspirin reduces P-selectin expression and formation of platelet-leukocyte aggregates in patients with atherosclerotic vascular disease.

## Erythropoietin effects on the vascular endothelium

EPO stimulates the production of endothelin, an effect that is additive with Ang II or thrombin.<sup>[27]</sup> Six proteins have been identified that are tyrosine phosphorylated following stimulation of cultured HUVEC with rHuEPO, one has been identified as STAT5.<sup>[28]</sup>

There is evidence for the activation of the endothelium *in vivo* following intravenous rHuEPO administration. In healthy male volunteers given rHuEPO 100 or 500 U/kg three times weekly, there was a dose-dependent increase in soluble E-selectin, with an increase of more than 100% in the 500 U/kg dose group and a significant, though smaller increase in the low dose group. rHuEPO infusion also increased soluble VCAM-1 but not soluble ICAM-1.<sup>[29]</sup>

Although the clinical consequences of this endothelial activation are unknown, it is possible that enhanced thrombogenicity could occur in patients with atherosclerosis or a history of thrombotic disorders.

To evaluate the effect of EPO on endothelial function in an animal model, rabbits were given EPO for 1 week.<sup>[30]</sup> Blood pressure and vascular resistance were significantly less responsive to endothelium-dependent vasodilators after rHuEPO therapy. Responses to endothelium-independent vasodilators did not change with rHuEPO therapy.

These observations suggest that rHuEPO may selectively suppress endothelial NO synthase activity. This finding is in agreement with studies of cultured human endothelial cells in which incubation with rHuEPO decreased basal and Ach-stimulated NO production and depressed NO synthetase expression.<sup>[31]</sup>

Although the direct effect of EPO on the vascular endothelium may suppress NO synthetase, there appears to be a compensatory increase in NO production when EPO-induced erythrocytosis occurs.

Transgenic mice that over-express human EPO have higher plasma nitrate levels than control mice a factor that helps prevent thrombosis despite a high hematocrit.<sup>[32]</sup> Similarly, rats with erythrocytosis induced by exogenous EPO administration have enhanced NO production, which helps maintain a normotensive state in these animals.<sup>[33]</sup>

## Hypertension

Hypertension (HTN) is a common complication of recombinant EPO therapy, but the mechanism of the EPO-associated HTN is uncertain. EPO and the vehicle alone on rat caudal artery contractile

response and basal and thrombin-stimulates platelet cytosolic Ca<sup>2+</sup> concentration. At high concentrations (200 U/ml) EPO caused a small but consistent contraction in the caudal artery rings without affecting the response to either angiotensin II (ANG II) or the  $\alpha$ 1-agonist methoxamine. Incubation with EPO significantly increased basal platelet calcium and augmented the thrombin-induced rise of long-term EPO administration led to a significant elevation of BP within 2 weeks regardless of whether the hematocrit was allowed to rise or was kept constant by dietary iron deficiency. In contrast, single intravenous administration of high-dose EPO (400 and 5,000 U/kg), estimated to yield plasma concentrations comparable with those employed *in vitro*, failed to either alter BP or modify the BP response to ANG II during a 60-min observation period. This was associated with a significant rise in plasma guanosine 3',5'-cyclic monophosphate but no discernible change in plasma atrial natriuretic peptide, suggesting enhanced nitric oxide (NO) release. Thus, at high concentrations, EPO appears to possess a fast-acting pressor effect *in vitro* but not *in vivo*. The observed discrepancy may be due to enhanced NO release with EPO administration *in vivo*. However, HTN does occur with repeated EPO administration in a time-dependent and hematocrit-independent manner.<sup>[34]</sup> In human coronary artery endothelial cell culture, EPO exposure resulted in adose-dependent inhibition of basal and acetylcholinestimulated NO production and eNOS protein expression<sup>[35]</sup> In humans, a single injection of rHuEPO (9000 U in hemodialysis patients and 6000 U in CKD patients) increased blood pressure and positively correlated with ET-1 release in hemodialysis patients, but did not in predialysis CKD patients<sup>[36]</sup> further demonstrated that the same pathway with phosphorylation of both STAT5 and ERK (MAP kinase) underlies angiogenesis in diabetic retinopathy.<sup>[37]</sup>

## Effects of erythropoietin on the heart

RHuEPO produces a dose-dependent increase in neonatal rat cardiomyocyte proliferation. The effects of rHuEPO on the myocyte cells appear to be related to the capacity of EPO to stimulate Na, K-ATPase activity, likely secondary to the activation of tyrosine kinase and protein kinase C.

In the myocardium from uremic rats, there is a decrease in high affinity binding sites for ouabain, which is restored by EPO treatment. This finding suggests a mechanism for improved myocardial contractility in renal failure patients after rHuEPO administration.<sup>[38]</sup>

Patients with cyanotic congenital heart disease have elevated EPO levels, which can induce erythrocytosis, with subsequent hyper viscosity, exacerbation of heart failure, as well as seizures and thromboembolic events.

Mice over expressing the human EPO gene develop severe erythrocytosis (HCT 50.80), resulting in decreased survival, increased heart weights and biventricular dilatation.<sup>[39]</sup>

In dialysis patients, lower hemoglobin levels are associated with increased frequency of LVH, possibly through renin-angiotensin system activation. There is a 30% increased risk of developing LV mass for each 0.5 g/dl drop in hemoglobin.<sup>[40]</sup>

Chronic anemia increases the work load on the heart and increased LV mass is observed in anemic patients with both end-stage renal disease (ESRD) and normal renal function. Partial correction of the anemia of renal failure by rHuEPO ameliorates LVH. In ESRD patients, the effect of rHuEPO on LVH may be dependent upon the degree of anemia prior to initiation of rHuEPO therapy.<sup>[41]</sup>

In anemic patients with renal insufficiency, rHuEPO therapy enhances cardiac output, reduces sympathetic tone, increases peripheral vascular resistance, improves coronary circulation and exercise tolerance, induces regression of LVH and increases LVEF in patients with LV dysfunction. More than 79% of patients with class IV CHF have an Hb 12 g/dl, even if the degree of renal impairment is only mild. Hemodilution accounts for nearly half of all cases of apparent anemia.<sup>[42]</sup>

Several studies have demonstrated that the presence of anemia is associated with increased mortality in patients with CHF with an excess of approximately 13% for each 1 g/dl decrease in the hemoglobin. Importantly, the decreased survival was noted at relatively mild anemia (11.6 g/dl in women and 12.6 g/dl in men). In an open label study, rHuEPO administration along with intravenous iron to patients with CHF improved NYHA functional class, EF, the number of hospitalized days, the dose of diuretics and slowed the rate of progression of renal failure.

## Conclusions

The use of EPO has resulted in profound improvements in the health and quality of life of dialysis patients and has been a landmark achievement in the care of ESRD patients. Although classically described as a hormone that stimulates erythroid precursors, EPO is now known to have effects on many cells and tissues. EPO stimulates endothelial cells with potential benefits. EPO can activate platelets, an effect that could enhance thrombosis risks when this therapy is used in patients with cardiovascular diseases. Additional studies are needed to confirm these findings and to examine the effect of recombinant human EPO.

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