Achieving higher HB & outcomes, ESA vs. Iron

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Disclosure of Financial Relationships

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I have no conflict of interest to declare

Objectives

The purpose of my presentation is to argue that:

- While ESAs and IV iron preparations are highly valuable for the care of CKD/ESRD patients, their indiscriminate use in pursuit of arbitrary HB targets can be harmful.
- Our task as physicians is to treat the individual patients as opposed to the numbers on the lab report
- The range of HG values which could be safely reached varies among different patients and within the same patient under different conditions
- The response to therapeutic interventions is frequently limited by patient's biological capacity & concurrent co-morbidities
- Aggressive interventions to drive the system beyond its capacity can cause harm and should be avoided

Trends in the treatment of anemia of CKD in the US prior to 2007

- During the decade preceding 2007 the use of ESAs & IV iron preparations and mean HGB level in the ESRD population steadily increased in the US
- Similarly use of ESAs for management of anemia in cancer patients sky rocketed during this period with astronomical doses being used in this population

The main impetus behind these trends included:

I- The highly publicized observational studies

II- NKF (KDOQI) guidelines

III- Favorable Medicare reimbursement policies

Evolving concept of optimal anemia management

The common perception and official guidelines on the optimal range of HB for anemia management in patients with CKD/ESRD shifted in opposite direction in 2007

These changes were driven by the results of the randomized clinical trials which contradicted the conclusions drawn from the earlier observational studies

Since biological reality is constant, the contradictory conclusions drawn from the results of the observational and randomized clinical trials must be due to misinterpretation of the corresponding data

Observational Studies of the Effect of Anemia on Morbidity and Mortality

- Observational studies have consistently shown strong correlation between severity of anemia and cardiovascular & overall morbidity and mortality in CKD/ESRD populations
- These observations have been taken to imply that the adverse outcomes must be, in part, caused by anemia
- If true, therapeutic interventions aimed at amelioration and/or correction of anemia should lower the risk of CV and overall morbidity and mortality
- This assumption formed the basis of the clinical practice guidelines and a number of prospective clinical trials.

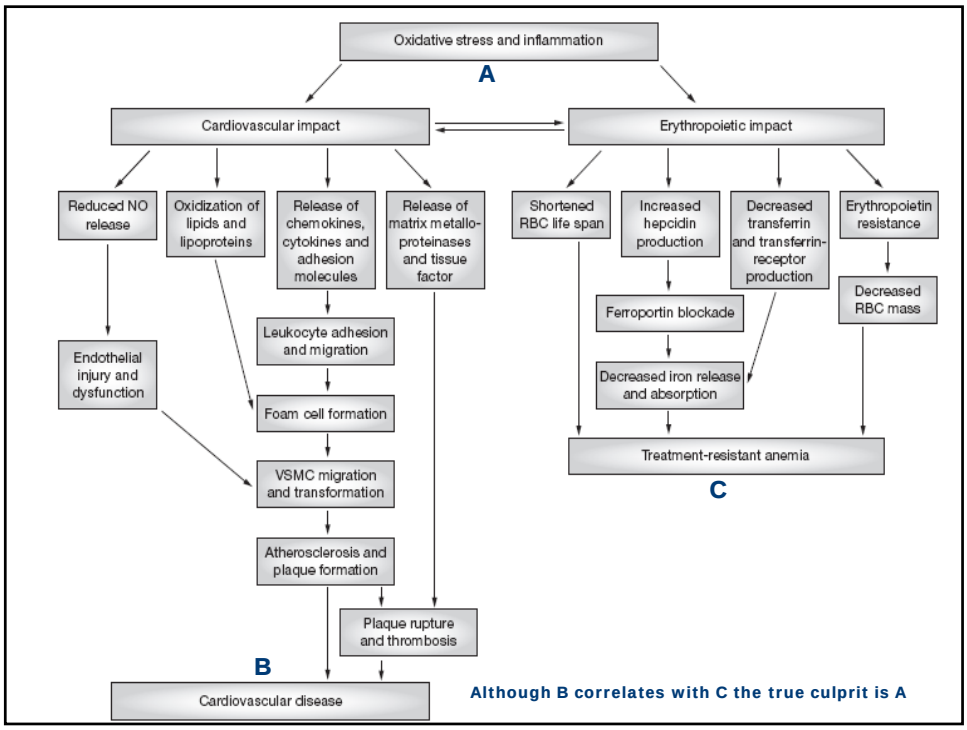
Randomized Trials of the effect of anemia correction

- Contrary to the expectations, large randomized clinical trials exploring the effect of normalization of HG revealed increased morbidity and mortality in patients randomized to normal HGB group.
- These results were taken to imply that HG values exceeding 12 g/dl are potentially hazardous in ESRD/CKD patients
- It is of note that despite massive doses of ESAs and iron preparations, target HG could not be reached in a significant minority of patients who also experienced disproportionate share of adverse outcomes. None the less these patients were classified as if they had reached high HB target!!!

Reasons for Apparent Disparity in Results of Observational and Interventional Studies

Potential Flaws in Interpretation of Observational Studies

- The assumption of causality between low HB and high M/M has been primarily based on statistical correlations. (Adjustments, if any, for co-morbid conditions are inherently incomplete and imprecise)
- The assumption of causality ignores the possibility that severity of anemia and heightened M/M may be unrelated to one another and both caused by the underlying systemic disorders
- Likely candidates include: **inflammation, oxidative stress, the constellation of clinical & biochemical disorders commonly mislabeled as malnutrition, systemic decline in biological capacity**, etc.
- Conversely, lower M/M in patients who easily achieve high HG is likely due to the **absence or lesser severity of the above disorders** and a better biological condition



Non-erythropoietic actions of ESAs & Iron may contribute to the adverse outcomes

- In addition to their hematopoietic actions, EPO and iron have numerous other functions which are essential at physiological levels and harmful at high levels
- Consequently the unintended effects of these agents can lead to adverse outcomes when high doses are used to achieve target HB
- Therefore high doses of ESAs and IV iron used to reach target HB in subgroup of patients with R_x-resistant anemia must have contributed to higher morbidity/mortality in patients assigned to high HB targets than those assigned to the low HB target in RCTs.

Examples of Non-Erythropoietic Side Effects of ESAs

EPO causes Hypertension

EPO-induced HTN is due to increased SVR as opposed to increased hematocrit (Kaupke, Kim, Vaziri, 1994; Vaziri 1995) & is mediated by:

a - Elevation of VSMC $[Ca^{2+}]_i$ & sarcoplasmic Ca stores leading to elevated vascular tone & NO resistance (Vaziri et al, 1996; Wang & Vaziri, 1998)

c – Reduction of NO production (increased ADMA) (Scalera et al, 2005)

d – Increased NO inactivation by superoxide (Rancourt et al, 2010)

e -- Up-regulation of tissue Renin-Angiotensin System (Eggena et al 1991, Lebel et al, 1998)

f – Increased endothelin production (Carlini et al '93, Takahashi 1993, Lebel et al, 2006)

g – Increased thromboxane and reduced prostacyclin production (Bode-Borger,1996, Rodrigue, 2003, 2005)

EPO causes vascular cell proliferation

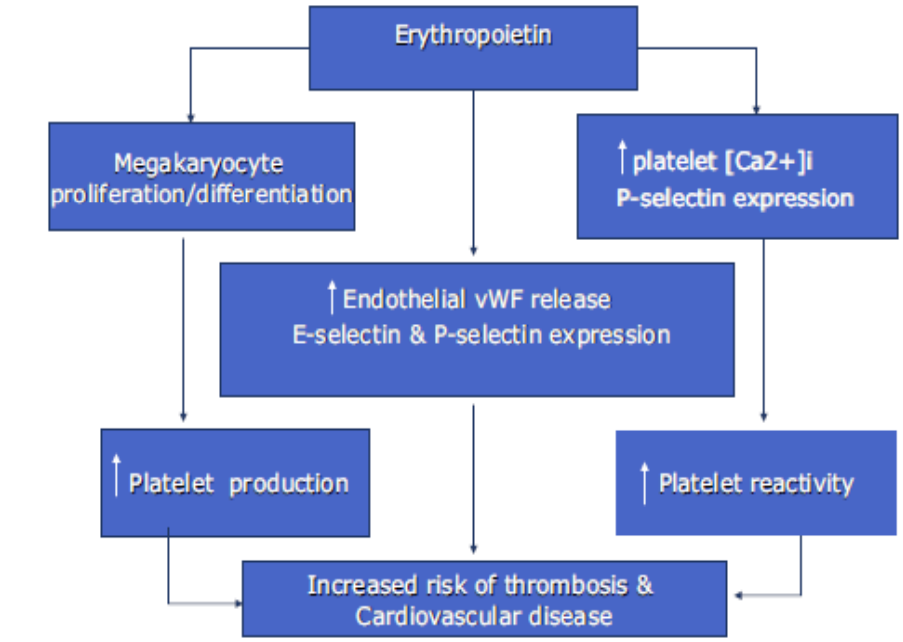
EPO stimulates endothelial and VSMC proliferation in vitro (Gogusev et al 1994, Ammarguellat, Gogusev and, Drueke 1996, Wang and Vaziri 1999)

EPO augments angiogenic activity in cultured rat aorta rings (Carlini et al 1995)

The EPO-induced VSMC proliferation may contribute to vascular remodeling and blood access stenosis in ESRD population and its angiogenic activity may contribute to tumor growth in cancer patients and proliferative retinopathy in diabetics

EPO can promote Blood Coagulation

- EPO administration raises platelet production
  (Kaupke, Butler, Vaziri JASN 1993)
- EPO Rx increases platelet activity & shortens bleeding time by augmenting Ca^{2+} signaling independent of HCT **(Zhou, Vaziri NDT 2002)**
- EPO increases vWF concentration, P selectin, E selectin & PAI-1 expression, and circulating hyperactive reticulated platelets



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Potential role of ESAs in proliferative retinopathy

- EPO level is elevated & EPO receptor is heavily expressed in the epi-retinal membrane in patients with proliferative diabetic retinopathy (Kase et al Br J Ophthalmology 2007)
- Polymorphism of the EPO gene promoter that causes increased EPO production has been shown to be strongly linked to development of severe diabetic proliferative retinopathy and nephropathy (Tong et al, *PNAS* 2008)
- These data suggest that high doses of EPO may accelerate proliferative diabetic retinopathy progression of CKD

The positive and negative attributes of iron

- **Fe is essential for biosynthesis and activity of hemoglobin, myoglobin, numerous enzymes & other important molecules.**
- **The versatile properties of Fe are due to the ease with which it can donate & accept electrons and exist in either trivalent (Fe^{3+}) or divalent (Fe^{2+}) state.**
- **This property of Fe is indispensable for mitochondrial oxidative phosphorylation & countless other biochemical / biological functions.**
- **However, by promoting oxidative stress, catalytically-active Fe causes tissue damage and dysfunction.**
- **For this reason, iron absorption, transport, storage & retrieval from the storage sites, Fe uptake by Fe-consuming cells and disposal of Fe-containing molecules are tightly regulated.**
- **On each occasion, Fe is embedded in binding proteins e.g. transferrin or ferritin to prevent direct exposure to the redox-active Fe.**

Use of intravenous iron preparations

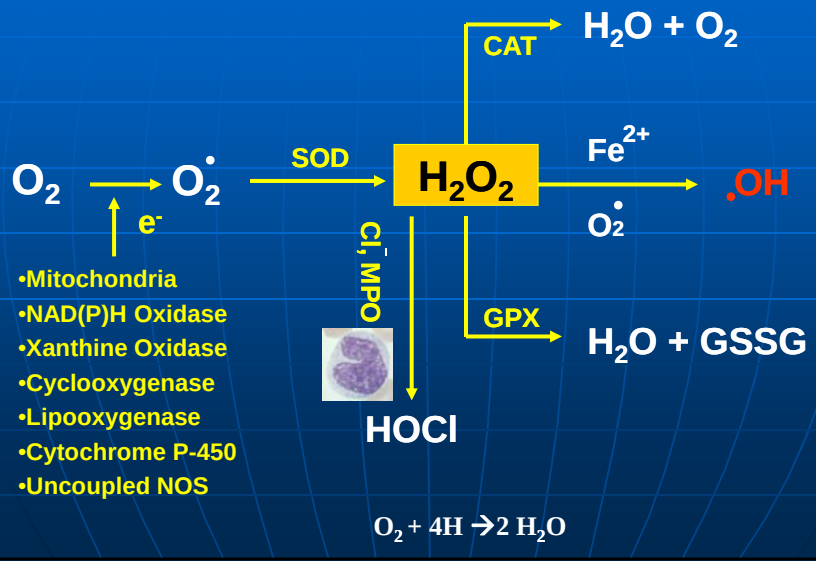
- IV iron preparations are widely used in the treatment of anemia of CKD. Use of these agents has greatly facilitated Fe repletion which is often impossible to achieve with oral supplements in hemodialysis patients.
- However, in many instances IV iron preparations are used routinely with insufficient attention to the total body iron stores or the state of inflammation.
- Particularly disturbing is when these products are used in highly inflamed patients with elevated plasma ferritin & EPO resistant anemia, a condition commonly mislabeled as functional iron deficiency.

Potential risk of excess IV iron in inflamed patients

- Systemic inflammation results in increased production of hepcidin & ferritin and consequent inhibition of Fe absorption and mobilization, reduction of serum Fe and transferrin. These events represent a coordinated biological response designed to limit intensification of oxidative stress and tissue injury by Fe
- By bypassing these natural safeguards, indiscriminate use of IV iron can pose a problem in patients with systemic inflammation
- It is of note that adverse effects of Fe are chronic in nature. Unfortunately nearly all safety data on IV iron products are derived from short-term trials. For this reason IV iron preparations should be used with caution to minimize adverse long-term consequences particularly in inflamed patients

Potential adverse effects of iron overload

Role of iron in Production of Reactive Oxygen Species (ROS) & Oxidative Stress



Iron overload & Immune system

- ESRD is associated with immune deficiency as evidenced by increased risk of microbial infections & impaired response to vaccination
- This is associated with and, in part, due to marked reduction of CD4+ T cells, B cells, dendritic cells & defective monocytes/neutrophils phagocytic capacity
- Since lymphocytes are poorly equipped to sequester iron in ferritin, excess iron delivered by hydrophilic chelates can be toxic for these cells
- In fact iron overload in patients with transfusion-dependents thalassemia leads to CD4+ T cell depletion
- Therapeutic concentrations of IV iron products raise intracellular ROS and shortens survival of CD4+ lymphocyte in vitro
- High doses of IV iron preparations impair phagocytic activity and microbial killing capability of neutrophils
- Thus excessive use of IV iron can compound uremia-induced immune deficiency

Iron overload & microbial infections

- Infection is the second most common cause of mortality among ESRD patients
- There is mounting evidence that iron overload increases susceptibility to infections in both ESRD and general populations.
- This is because:

a-Fe is essential for bacterial multiplication & iron availability is closely associated with bacterial virulence

b-Iron overload impairs immune function, thereby heightens susceptibility to and increases severity of infection

Role of Iron in the Pathogenesis of Diabetes

- Overt Fe overload results in increased risk of type 2 diabetes, marked by insulin deficiency & resistance
- Iron overload causes apoptosis of beta cells which are exquisitely susceptible to oxidative stress due to their limited antioxidant capacity and high affinity for Fe uptake
- Even subtle increases in dietary iron content (red meat) and modest elevation of body iron pool are associated with insulin resistance, metabolic syndrome, and gestational diabetes
- In contrast reduction of body iron pool with bloodletting or blood donation ameliorates insulin resistance and improves glycemic control in type 2 diabetics
- Iron chelation therapy and blood donation reduce the risk of diabetes in normal subjects
- Iron deficiency improves insulin sensitivity and lowers the risk of diabetes

Role of Iron in the complications of Diabetes

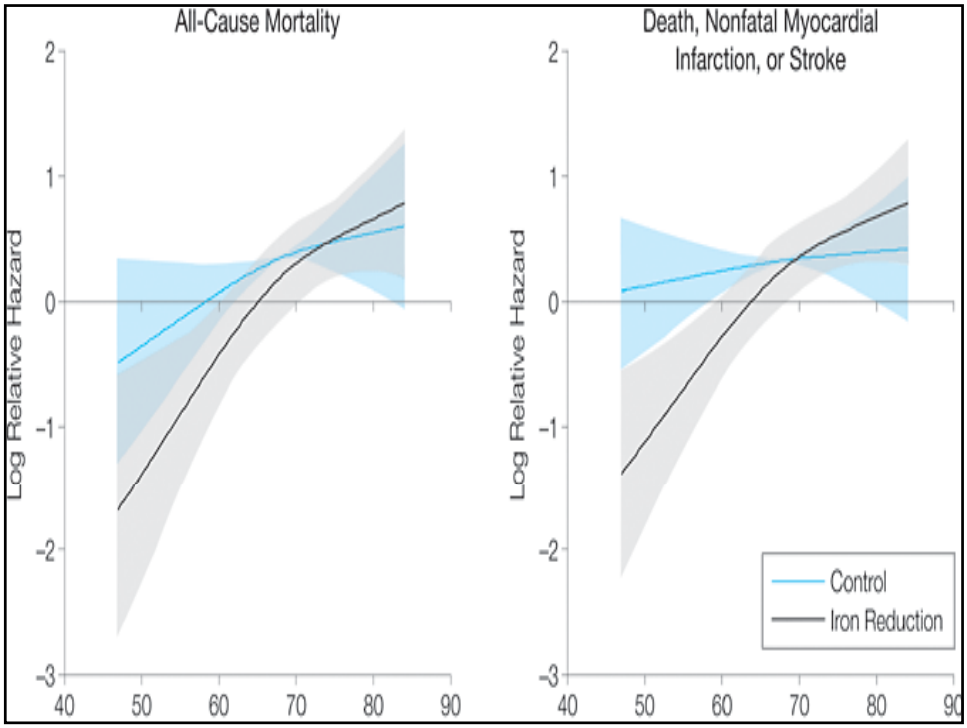
- Iron and other transition metals facilitate protein glycation which is critical in renal & vascular complications of diabetes. In fact iron chelation therapy lowers glycated hemoglobin levels in diabetic animals and humans
- Glycated proteins avidly bind transition metals forming complexes in which transition metals retain catalytic activities . Thus transition metals facilitate formation of glycated proteins and glycated proteins sustain their catalytic activities, events that contribute to oxidative stress, inflammation & renal and cardiovascular complications of diabetes
- In this context renal tissue iron content is significantly elevated in diabetic animals and urine iron level is markedly increased in diabetic patients.
- Plasma non-transferrin-bound iron is commonly elevated in diabetic patients and contributes to the pathogenesis of the associated vascular complications
- Preliminary studies have revealed significant reduction in proteinuria with iron chelation therapy in patients with diabetic nephropathy

Role of iron in cardiovascular disease (animal &in vitro data)

- Iron accumulates in and contributes to formation of atherosclerosis plaques in experimental animals, iron supplementation accelerates and iron chelation therapy retards plaque formation in these models
- Administration of iron chelator, deferoxamine, significantly inhibits intimal thickening and VSMC proliferation in the carotid balloon injury model in hypercholesterolemic rabbits pointing to the role of iron in arterial remodeling
- In vitro addition of iron compounds results in upregulation of adhesion molecules and monocyte adhesion in cultured human endothelial cells, these events can be reversed or prevented by iron chelators

Role of iron in cardiovascular disease (human data)

- Carotid artery lesions in humans contain large amounts of iron which strongly correlates with the plaque's cholesterol and oxidized protein contents.
- In patients with carotid atherosclerosis serum ferritin level correlates with the level of low molecular weight iron compounds and lipid peroxidation products in the carotid endarterectomy specimens. This observation illustrates the link between redox-active iron within atherosclerotic lesions and the extent of body iron stores and/or systemic inflammation
- In addition to contributing to plaque formation, interaction of iron and lipoproteins in the plaque promotes plaque instability by inducing foam cell apoptosis
- The randomized trial of mild iron reduction therapy (phlebotomy Q 6 months) in elderly patients with peripheral vascular disease (the"FeAST" trial) showed that Fe reduction strategy is safe and that it can reduce CV and overall M & M if initiated early but not late in the course of the disease. (Reduction of Iron Stores and Cardiovascular Outcomes in Patients With Peripheral Arterial Disease, A Randomized Controlled Trial, *JAMA. 2007*)



Role of iron in progression of renal disease

Catalytically active iron accumulates in the renal tissue in various models of acute kidney injury and iron chelation therapy attenuates renal injury and dysfunction in these models

Proteinuria results in accumulation of iron in the proximal tubular epithelial cells (most likely through uptake of filtered iron-binding proteins) causing cell damage

Iron chelation therapy or iron deficient diet ameliorate proteinuria and improve renal function and structure in animal models of anti-GBM glomerulonephritis, puromycin-induced minimal change disease, membranous nephropathy (passive Haymann nephritis) and immune complex glomerulonephritis induced

Taken together these observations provide strong evidence for the role of iron in AKI, progression of CKD and potential loss of residual renal function in CKD and ESRD patients treated with excessive amounts of IV iron.

Thus Non-Erythropoietic Side Effects of ESAs & Iron Overdose can account for the Adverse Outcomes observed in Clinical Trials of anemia correction and perhaps many unrecognized cases in clinical practice

What is the Optimal HG Target for CKD/ESRD Patients?

- The range of HG values which could be safely reached varies among different patients and within the same patient under different conditions.
- The response to therapeutic interventions is frequently limited by concurrent pathobiological conditions.
- Aggressive interventions to drive the system beyond its capacity can cause injury, dysfunction & death.

Draw backs of arbitrary HG Targets

Use of An Arbitrary HG Targets imply that:

- It is justified to push ESA and Fe doses as much as it takes to reach the given limit (risk of drug toxicity)
- Rx should be abruptly stopped when HG rises above target (creating an unhealthy fluctuation of HG)
- By extension it may imply usefulness of phlebotomy to reduce HG to 12 or less in occasional patient who maintains normal HG without EPO !!

Conclusions

- Designation of a fixed range of HB values as the optimal target for all patients is unrealistic and potentially harmful.
- The optimum HB level is patient- and time-specific. It is a HB level which could be achieved safely to avoid drug dosage toxicity.

Thank You