Medicare Evidence Development & Coverage Advisory Committee Meeting
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Chronic Renal Disease & Anemia Management with Erythropoietic Stimulating Agents

Elizabeth Koller, M.D. (Medical Officer)

Historical Background:
End Stage Renal Disease Program in Medicare

- Established with Public Law 92-603 Section 2991 on 10/30/1972.
- Included *all ages* with *Stage 5* disease (requiring dialysis) & qualified by work history
- Coverage typically started during 4th month of dialysis
  - →Dialysis services **(out-patient, in-patient)**
  - →Dialysis supplies
  - →Blood transfusions
  - →Drugs associated with dialysis, e.g., heparin & ESAs *(Medicare Part B)*
  - →Transplantation & some transplantation-related costs
- ESA penetration rapid

  Within 1 yr of FDA approval of erythropoietin, it was used by
  - →60% of in-center dialysis patients in Medicare
  - →52% of all dialysis patients in Medicare

Powe 1992

Historical Background:
Erythropoietin Stimulating Agents & Medicare

- *National Coverage Determination*
  - →Current NCD for oncologic-related ESA use (2007)
  - →No current NCD for ESA use in pre-dialysis beneficiaries
  - →No current NCD for ESA use in dialysis beneficiaries
  - →Local coverage decisions and/or monitoring policies may be in effect

Historical Background:
Erythropoietin Stimulating Agents & Medicare

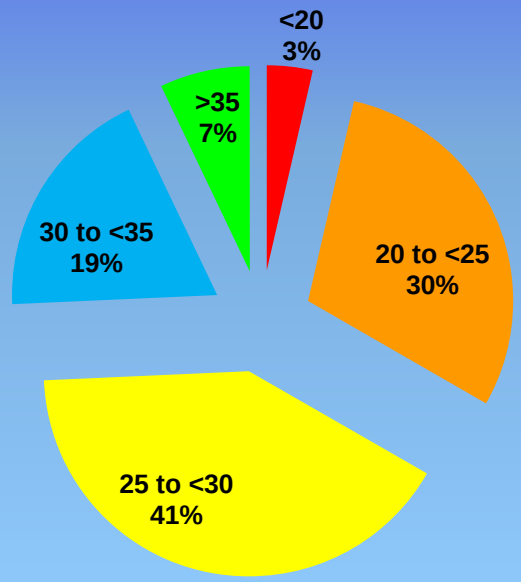
- *Erythropoietin Stimulating Agent (ESA) Monitoring Policy*
  - →Claims processing mechanism. Not a coverage policy.
  - →Latest update: 2008.
  - →Applied to ESAs provided as an ESRD benefit under 1881(b) of Social Security Act.
    ESAs furnished incident to physician service not included.
  - →Limited payment on billing claims if Hct >39% or Hb >13%
  - →Established new *medically unbelievable edits (MUE)*
    - Claims returned for presumed errors.
    - Erythropoietin (>400,000 U) & Darbepoetin (>1200 ug).

Anemia Prevalence: Historical Perspective

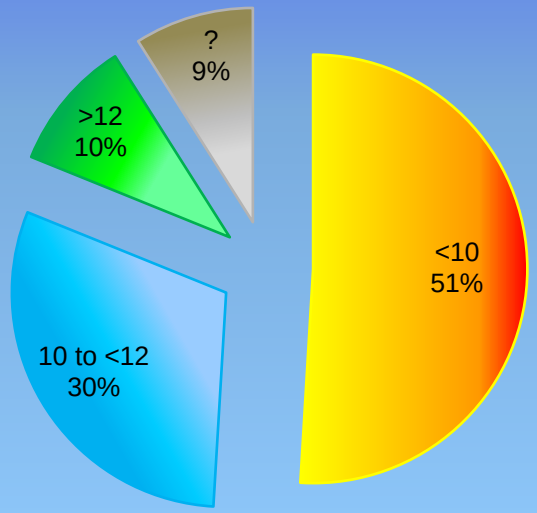
- Anemia long a recognized phenomenon
- Change in severity over time; temporal ↑ in Hb in ESA-naïve patients
- (Change in patient population & advances in patient management)

Eggers 2000

1990 Congress-OTA-H-451 (Hct [vol %])



2008 USRDS (Hb [g/dl])



(5.7% ESA use; no nephrologist)

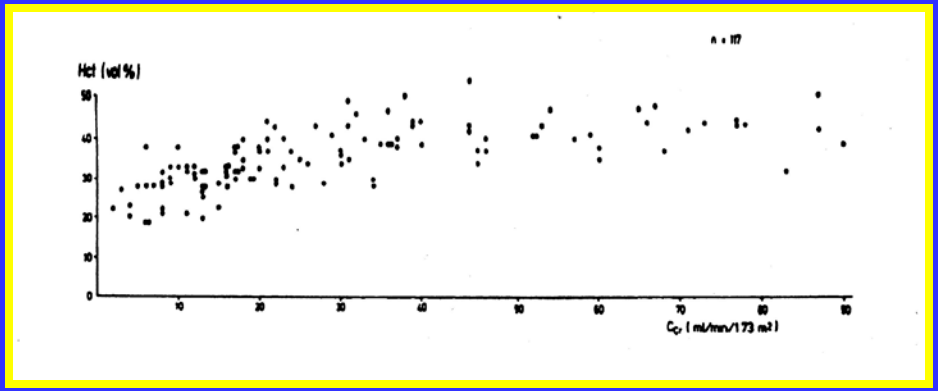
Etiology of Anemia in Renal Disease

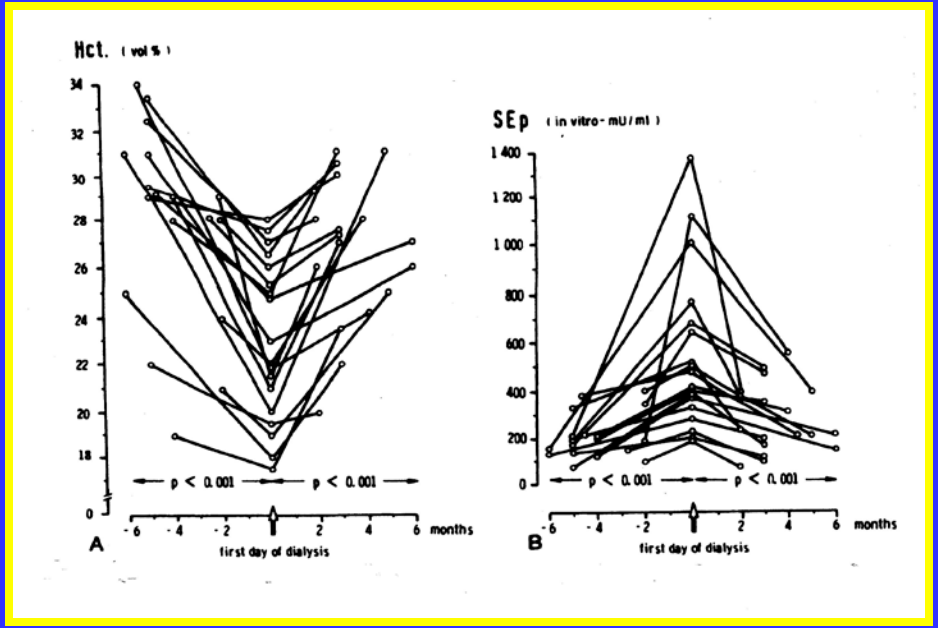
- Uremia → ↓RBC survival
  Marrow suppression
- Hemodialysis procedure & filters → Frank blood loss
  ↓ RBC survival
- Nutrient deficiency, e.g., Fe
- Al toxicity → Direct effects on hematopoiesis
  ↓ Fe metabolism
- Epo Deficiency (related to renal sufficiency level & disease type)
- Epo Resistance (e.g., inflammation)

- Co-morbid Condition: Anemia of Chronic Disease → Cytokines that :
  ↓ Nutrient utilization
  ↓ Epo production
  ↓ Epo effect

Anemia: Longitudinal Data

- Hct & CrCl related if CrCl <30 or 40 ml/min/173 m^2 (r=0.69)
- Hct levels ↓ in the 6 mo prior to dialysis & ↑ with dialysis (no ESA)
- Endogenous* Epo levels ↑ in the 6 mo prior to dialysis & ↓ with dialysis & the related improvement in anemia
- Endogenous Epo more preserved in polycystic kidney disease





Radtke 1979

*Endogenous=made by the body vs Exogenous=produced outside the body

Anemia: Tx

- Transfusions **(~19% 1 transfusion, 8% 2 transfusions, 7% ≥3 transfusions/1 yr p dialysis start ;1992)**
- Androgens
- Nutrients especially Fe (IV, po)
- ESAs: Erythropoietin α (recombinant hormone molecule)

  1989 FDA approval to manage anemia & ↓ transfusions in renal patients (if pre-dialysis, Hb <10)

  Darbepoetin α (2 carbohydrate chains → ↑ $t_{1/2}$)

  2002 FDA approval to ↑ Hb

  (Other brands & forms of epo; other countries)

  PEGylated Epo (not yet marketed in US)

  Epo Receptor Stimulators (under development)

- Fundamental Questions: Why should we treat?

  When should we treat?

Historical Rationale for Anemia Targets

Mortality Rates Deaths/1000 tx-yrs	**Hematocrit (Vol %)**			
Groups & Causes of Death	<27	27 to <30	30 to <33	33 to <36
Non-diabetic--All-cause	214.66	192.00	170.61	161.37
Cardiac	80.10	77.84	71.78	68.97
Diabetic-- All-cause	342.70	298.23	258.34	234.59
Cardiac	147.90	135.91	119.67	112.71

"After adjusting for these confounding pt characteristics, our results showed that pts with hct levels <30% have significantly higher risk of all-cause & cause-specific death, compared to pts with hct levels of 30% to <33%. …After adjusting for severity of disease, the impact of hct levels in the 33% to <36% range becomes vulnerable to the number of pts included but still demonstrates a further 4% reduced risk of death. Overall, our findings suggest that sustained increases in hct levels are associated with improved pt survival." Ma, Ebben, Xia, Collins 1999 *(Also similar work by Madore 1999)*

Historical Rationale for Anemia Targets

Limitations:

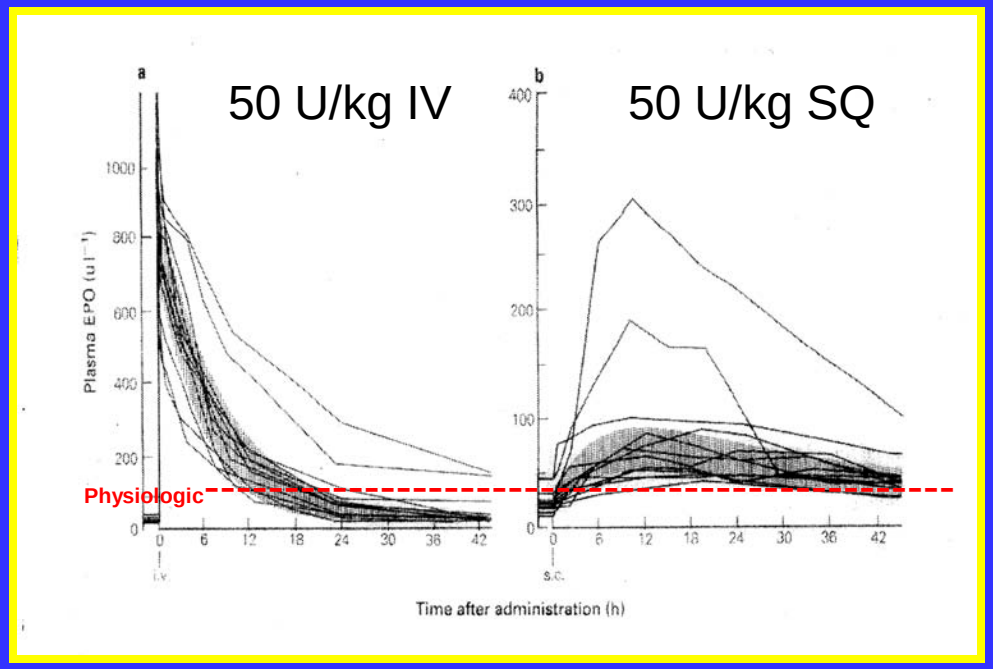
- Not natural history data
  - USRDS data (hct data supplied with ESA billing claims & often not available if ESA not used)
  - Exclusion of those with spontaneously higher hct
- Observational data
  - Anemia interventions not used as variables

Erythropoietin (Hormone)

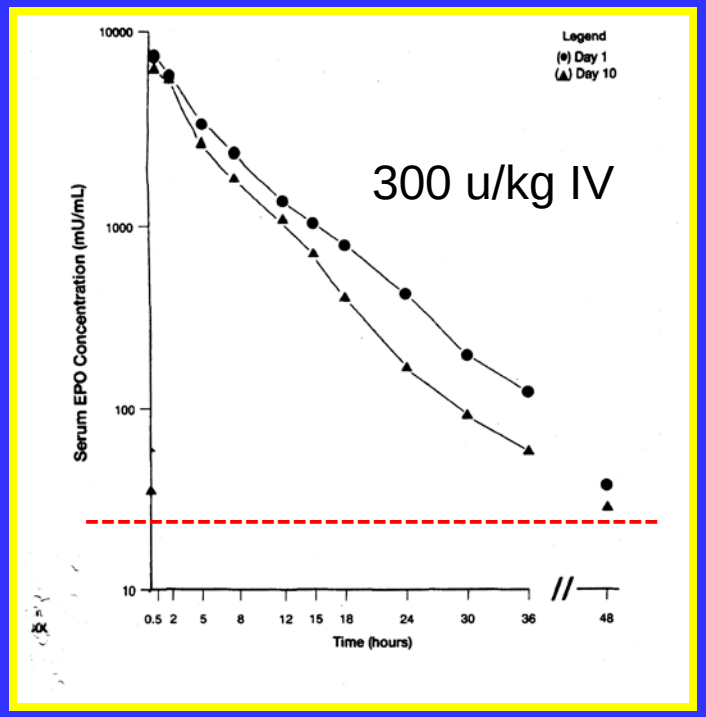
- Erythropoietin (epo): glycoprotein hormone from kidney (& liver)
  (normal levels ~6-32 U/L)
- Anemia or Hypoxia→ ↓O_2 tension in tissue
  → ?H_2O_2 signaling +/- Hypoxia inducible factors
  → epo transcription
  → levels may transiently ↑ by 1000x
- Epo→ ↑ proliferation & differentiation of RBC precursors
  ↓ RBC apoptosis
  may (in)directly ↑ angiogenesis
  may have other (proliferative) effects in other tissues
- Epo → classic receptor (& non-classic receptor[s])

Serum Levels: Physiologic & Pharmacologic

- Serum levels of epo are supraphysiologic for many hours to days (SQ < IV).
- Supraphysiologic exposure is present even at low dosing.
- Supraphysiologic exposure is even greater at higher dosing.



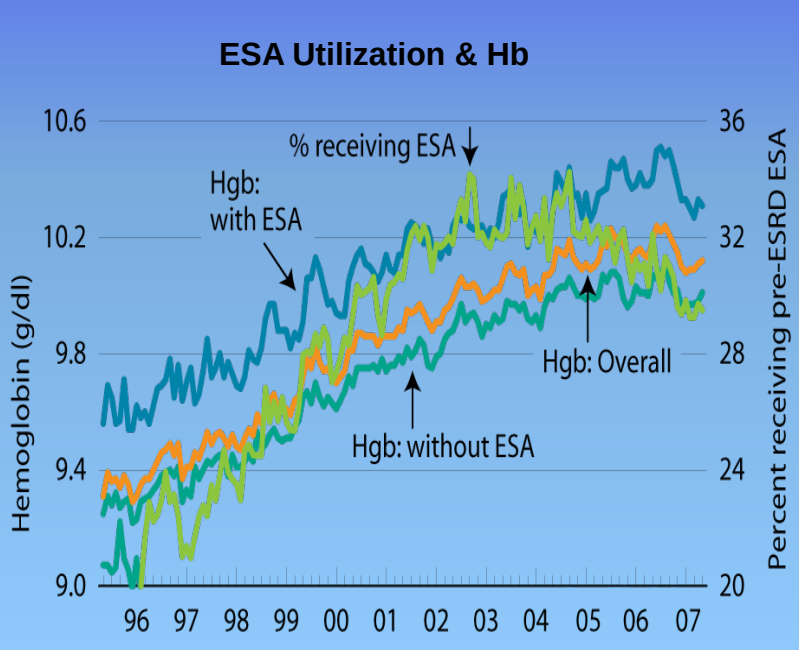
Brockmoller 1992

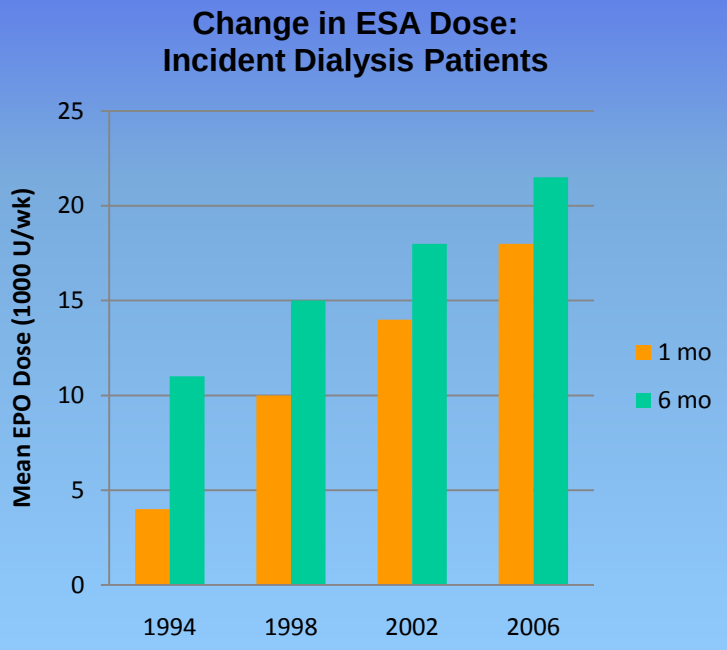


McMahon 1989

Anemia & ESA Use: X-sectional Data (USRDS)

- Temporal ↑ in ESA use in dialysis patients
- Temporal ↑ in ESA use prior to 1st dialysis
- Temporal ↑ in ESA use in less severe anemia
- Temporal ↑ in ESA dose





Subsequent Studies

Majority:

- Comparative effects of different ESA agents (switch studies; non-inferiority studies)
- Effects of route of administration
- Effects of changing dosing intervals
- Effects on bio-markers

Subsequent Studies

Majority:

- Not randomized, controlled, blinded studies
- Small size or underpowered for endpoint
- Short duration (≤6 months)
- No algorithm for transfusions
- Higher Hb entry permitted
- No exclusion of other causes of anemia
- No stratification by entry Hb
- No fixed dose regimen

Subsequent Studies: Darbepoetin Pivotal

	Study 117 ***(Nissenson 2002)***	**Study 200** ***(Varenterghem 2002)***
Design	Active control, randomized, double-blind (IND)	Active control, randomized, no blind (Non-IND)
Endpoint	Hb change t=0 to t=wk 21 to 28	Hb change t=0 to wk 25-32
Duration	28 weeks	32 weeks + 20 week maintenance
Size	504 (Darbe:Epo;1:2 [no error])	522 (Darbe:Epo; 2:1)
Route	IV	IV or SQ
Pt Type	Hemodialysis	Hemo- or Peritoneal dialysis
Inclusion	Hb 9.5-12.5 g/dl Stable ESA dose Fe sufficiency	Hb 9.5-12.5 g/dl Stable ESA dose Fe sufficiency
Exclusion	Recent transfusion CHF, Seizures, Uncontrolled HTN Evidence of infection, inflammation	Recent transfusion CHF, Seizures, Uncontrolled HTN Evidence of infection, inflammation

- Selection bias introduced by using non-naïve population reduced likelihood for detecting negative outcomes
- Cannot detect positive or negative outcomes dependent on duration of ESA exposure

Other Endpoint: Cardiac (Intermediate)

Study	Size	Duration	Blind	Hb(Hct)	Dose	Results
Conlon 2000 (part of NHCT)	31 w CHF or ischemia, hemodialysis	28 wks	Open	42 vs 30	Variable	Silent ischemia (Holter) not different
Cianciaruso 2008	95 pre-dialysis	24 mos (Δ 12 mos)	Open	12-14 vs No EPO unless <9	Variable	LV mass index not different
Levin 2005	172 (152) pre-dialysis	24 mos	Open	12-14 vs No EPO unless <9	Variable	LV mass index not different
Palazzuoli 2007	51 w CHF pre-dialysis	4 mos	Double	12-12.5 vs No EPO	6000 U 2x/wk	LV function & geometry better
Pappas 2007	31 pre-dialysis	1 yr	Not stated	>13 vs No EPO	Variable	LV function & geometry better
Parfrey 2005 Foley 2008,9	596 hemodialysis	96 wks	Double	13-14.5 vs 9.5-11.5	Variable	LV cavity volume not different
Roger 2004	155 pre-dialysis	2 yrs or dialysis	Open	12-13 vs 9-10	Variable	LV mass index not different
Sikole 1993	40 (38) hemodialysis	12 mo for controlled segment	Not stated	30-35 vs No EPO	Variable	LV mass & morphology better LV function not different

Studies by Abdulhadi 1990, Ayus 2005, Chen 2008, Frank 2004, Grutzmacher 1988, MacDougall 1990, Pascual 1991, 1992, Schwartz 1991, Silberberg 1990, Tagawa 1991 were not randomized

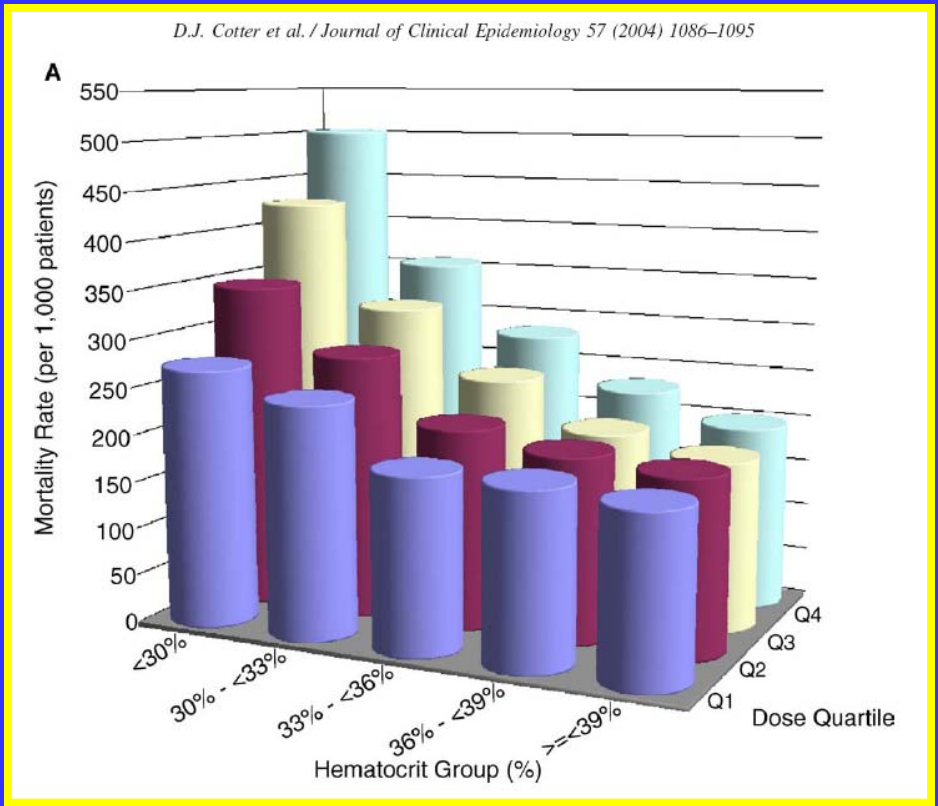
Other Endpoint: Exercise

Study	Size	Duration	Blind	Hb (Hct)	Dose	Results
Canadian Group 1990 Laupacis 1991	118 hemodialysis	6 mos	Double	11.5-13 vs 9.5 to 11 vs No EPO	Variable	Exercise stress test better Exercise tolerance (distance walked) not different
Clyne 1992	12 tx; 8 control pre-dialysis	3 mos	Open	30 vs No EPO	Variable	T=0 imbalance favored tx arm Δ in maximal exercise capacity (bike) better
Furland 2003	416 pre-dialysis hemo- & peri-toneal dialysis	48 to 76 wks	Open	13.5 -15 F & 14.5 -16 M vs 9-12	Variable	Powered for exercise tests. Not completed bc many patients could perform test.
McMahon 1999	14 completers (X-over) hemodialysis	4-8 mos titration; 4 wks maintenance	Double	14 vs 10	Variable	Peak work rate & peak VO_2 better (bike)
Painter 2002	65 hemodialysis	5 mos	Double	40-42 vs 30-33 $\pm$ exercise training	Variable	Peak VO_2 minimally better (& not normal) with exercise training, but not $\uparrow$ Hct
Palazzuoli 2006	40 w CHF pre-dialysis	3 mos	Double	11.5-12 vs No EPO	6000 U 2x/wk	Exercise tolerance (distance & time) walked better. Peak VO2 better. Correlation Δ peak VO_2 & Δ Hb: r=0.36.

Studies by Guthrie 1993, Lewis 1993, Lim 1989, Lundin 1991, MacDougall 1990, Mayer 1988, Robertson 1990 were not randomized.
Study by Stray-Gunderson 1997 found only as an abstract.

- *A randomized study by DePaul 2002 used resistive & aerobic training vs range-of-motion exercises → improved (although not normal) exercise tolerance w/o improved QOL*

Observational Data: Emerging Signals



- U.S. Renal Data System (USRDS) data (dialysis)
- Use of t=0 data for Hct & EPO dose; Use of t=12 mo mortality data
- Mortality highest in those with the most severe anemia & highest EPO doses
- Although confounding present: questions of dose response arose

Observational Data: Emerging Signals

Mortality Hazard Ratio (based on quarterly data)						
	Mean Hematocrit (Vol %)					
Epo Dose (u/wk)	<30	30-32.9	33-35.9	36-38.9	39-41.9	>42
0	2.84	1.68	1.12	1.32	1.67	1.96
1 to 5999	2.52	1.56	0.92	0.87	1.23	1.70
6000 to 11,999	2.82	1.63	1.00 reference	0.91	1.12	1.55
12000 to 17999	3.32	1.85	1.24	1.13	1.32	1.77
≥18,000	3.83	2.41	1.79	1.71	1.92	2.52

- ↑ Mortality at high & low hct levels: J-Shape
- For given Hct, <Epo dose → < mortality
- Co-morbidities an important variable

Messana 2009

Long-term Studies in Renal Disease

Study	Blind	N	Duration	Dose	Tx Target	1º Endpoint
NHCT **epo α** **1998**	No	1253 **51 sites** **USA only**	3+ yrs **(planned)**	-------- **IV or SQ** **3x pre-study dose**	Hct 39-45 vs 27-33	**T to death or 1st non-fatal MI**
CREATE **epo β** **2006**	No	603 **94 sites** **22 nations**	>2 yrs **Max 4.25 yrs** **Mean 3 yrs**	2000 U/wk **≤50% ↑ q 4 wks** **3-8000 vs 1-3000**	Hb 13-15 vs 10.5-11.5 **(ESA if <10.5)**	**T to death & CV composite**
CHOIR **epo α** **2006**	No	1432 **130 sites** **USA only**	Max 3 yrs	10,000 U/wk **20,000 IU/wk max SQ** **(in appendix)**	Hb 13-13.5 vs 10.5-11 (13.5 vs 11.3)	**(T to) mortality & CV composite**
TREAT **darbe α** **2009**	Yes	4038 **623 sites** **24 nations**	-------- **Max 4 yrs** **Mean 29 mo**	0.75 ug/kg **Max 6000 ug/mo** **104-305 ug/mo**	Hb ~13 **(ESA if <9)**	**T to death or CV composite &** **T to death or RF**

*** Furuland 2003 (n=416 [pre-dialysis, peritoneal dialysis, hemodialysis], 48-76 wks, open-label) not included because powered for exercise, not mortality. QOL performed only in 253, all on dialysis, at 48 wks.**

Study	Entry Criteria			Exclusion Criteria
	Anemia	*GFR*	*Other*	
NHCT **epo α** **1998**	Hct 27-33 **on ESA**	Hemodialysis	CHF Ischemic HD	**Recent cardiac events** **Diastolic HTN** **↓ life expectancy** **Fe insufficiency** **Androgen use**
CREATE **epo β** **2006**	Hb 11-12.5	Pre-dialysis **Calculated** **(CG) 15-35**	--------	**Non-renal anemia** **Transplant need** **Serious CVD** **Inflammation** **Prior ESA use**
CHOIR **epo α** **2006**	Hb <11	Pre-dialysis **Calculated** **(MDRD) 15-50**	--------	**GI bleed** **Frequent transfusion** **Angina** **Uncontrolled HTN** **CA** **Prior ESA**
TREAT **darb α** **2009**	Hb ≤11 **Transferrin >15%**	Pre-dialysis **Calculated** **(MDRD) 15-60**	Type 2 DM **Stratified by CVD & spot urine protein**	**Bleeding, Hematologic disease** **HIV, CA, or CA tx** **Transplant need** **Recent CV event** **Recent seizure** **Antibiotics** **Uncontrolled HTN** **Fe insufficiency** **Recent ESA**

Study	Results
NHCT **epo α** **1998**	Study stopped at 29 mo Withdrawal rates not indicated 183 deaths + 19 non-fatal MIs vs 150 deaths + 14 non-fatal MIs ↑ mortality with ↓ hematocrit ↑ venous access thrombosis Post hoc (2008): ↑ mortality with ↓ ESA responsiveness
CREATE **epo β** **2006**	Study stopped because ability to show efficacy unlikely Withdrawal: 25% experimental group; 17% control group 1st CV event 58 vs 47 (including CVA + TIA 13 vs 7) Mortality 31 vs 21 LV mass: no difference. QOL (SF-36): Δs in 1st yr not sustained.
CHOIR **epo α** **2006**	Study stopped because ability to show efficacy unlikely Withdrawal 38% with imbalance in those not →transplant Composite events: 125 vs 97. **(Death 52 vs 36, CHF 64 vs 47, MI 18 vs 20, CVA 12 vs 12)** Progression to renal replacement: 155 vs 134 Hospitalization: 369 vs 334 QOL (LASA, KDQ, SF-36): No difference
TREAT **darb α** **2009**	Imbalance at baseline for placebo CHF Withdrawal: Tx DCed, but followed 20% + DCed w/o f/u except +/- death status 13% Mortality and/or CV endpoint (includes CVA) 632 vs 602. CVA 101 vs 53 CA death 39 vs 25 QOL (FACT-fatigue): 1.4 (of 50) Δ. QOL (SF-36): No difference

Ancillary Slides

Initial Studies

Study	Population	Blind	Size	Duration	Entry Criteria	Exclusion Criteria
Eschbach 1989 x2, 1991 Adamson 1989 FDA 1989 *USA 9 sites*	Hemo Adults	No control Open	412 or 333 or 309	Not stated 12+ mos	Hct <30% Adequate Fe	Dx impairing EPO result Uncontrolled HTN
FDA 1989 *USA 3 sites*	Hemo Adults	Double to Open-label	101 or 62	12 wk control to 12 wk extension	---	---
Canadian Group 1990 Keown 1991 Laupacis 1991 FDA 1989 *Canada 13 sites*	Hemo Adults	Double	118	26 wks	Hb <9	Non-epo deficiency anemia Unable to do walk test
FDA 1989 *Canada 1 site*	Hemo	Double	18	9 wks	---	---
US-Teehan 1991 Abels 1990 G88-011 Lim 1989 ?Stone 1988 FDA 1989 *USA 15 sites*	Pre-dialysis Adults	Double to Open-label	117	8 wks to 6 mos extension	Hct ≤38 ≤32 Serum Cr used No GFR stated Good nutrition	Recent infection Major clinical dx Uncontrolled HTN Recent androgen use Recent transfusions
FDA 1989 Kleinman 1989 ? Watson 1990 *USA ? sites*	Pre-dialysis	Double to ?Open & > dose	93	12 wks ?12 wk extension	Anemia undefined Serum Cr 3 to11 mg/dl	Dx impairing EPO result Recent infection Major clinical dx, seizure Uncontrolled HTN Fe or vitamin deficiency GI/urinary blood loss Recent androgen use Obesity
FDA 1989 *Europe ? sites*	Pre-dialysis	Open-label	24	8 wks	---	---

Initial Studies

Study	Dose	Target Hb(Hct)	Transfusion Criteria	Stratification by		
				Hb (Hct)	Dose	Dialysis Adequacy or Renal Clearance
Eschbach 1989 x2 , 1991 Adamson 1989 FDA 1989	IV 300 to 150 to 75 U/kg	32 to 38%	None	No	No	No
FDA 1989	? Route 0 or 150 U/kg	35%	---	---	---	---
Canadian Group 1990 Keown 1991 Laupacis 1991 FDA 1989	IV 100 U/kg to variable	9.5 to 11 vs 11.5 to 13 vs No EPO	None	Not entry QOL by target	No	No
FDA 1989	IV 0, 50, 100, or 200 U/kg	---	---	---	---	---
USA-Teehan 1991 Abels 1990 G88-011 Lim 1989 ?Stone 1988 FDA 1989	IV 0, 50, 100, or 150 U/kg To IV or SQ & variable dose	Hct $\geq$40 $\geq$35-7 Δ 6 vol%	None	No	No	No
FDA 1989 Kleinman 1989 ?Watson 1990	SQ 0 or 100 U/kg (?150 U/kg extension)	Hct $\geq$40 $\geq$35	No	---	---	---
FDA 1989	IV 50, 100, or 150 U/kg	Hct $\geq$40 $\geq$35	---	---	---	---

Initial Studies

Study	Results
Eschbach 1989 x2, 1991 Adamson 1989 FDA 1989	T=0 hct data available for 304. Mean t=0 hct 22%. T=6 mos & 10 mos hct data available for n= 33 & 104. QOL testing limited to n=130 assessed at variable times . Reportedly transfusion need ↓, but no accounting for drop-out. Some kinds of transfusions, e.g., for dialysis blood loss not included in analysis. Non-responsive patients identified. Bone marrow bx not in protocol. HTN ↑ & perhaps associated with seizures. Vascular access clotting reported.
FDA 1989	62/101 evaluable for efficacy Patients also evaluated after X-over in extension study
Canadian Group 1990 Laupacis 1991 Keown 1991 FDA 1989	Mean t=0 hb 7 g/dl. Hb increased; mean dosing higher for higher targets. 41.5% had >6U PRBCs in prior yr. ↓ transfusions in Epo groups. QOL reportedly better with Epo for Sickness Impact Profile, but > rigorous Time Trade-off ,score. Also not better with higher vs lower Hb Epo tx levels. Exercise stress test better, walking tolerance not better Diastolic HTN & vascular access clotting ↑. Bone marrow bx not in protocol.
FDA 1989	Hct increased per dose response
USA-Teehan 1991 Abels 1990 G88-011 Lim 1989 ?Stone 1988 FDA 1989	Mean t=0 hct 28.8%. Hct increased per dose response. Doses 75-150 U/kg TIW corrected hct. 106/117 completed 8 wks; 11 DC for AEs No transfusion data in FDA summary. No information on QOL instrument in methods. HTN adverse event data limited by lack of definition. Bone marrow bx done in 6 of Stone subset n=12 @8 wks. Concerns about doses ≥100 U/kg. (Stone) PK data from 8 (Lim) Exercise data from 8 (1 placebo) (Lim)
FDA 1989 Kleinman 1989 ?Watson 1990	Hct corrected in 58% of Epo treated vs 4% of placebo No transfusion data in FDA summary. Bone marrow bx not in protocol. No complete publication. Kleinman subset n=14. ?Watson subset n=11.
FDA 1989	Hct increased per dose response No transfusion data in FDA summary. Bone marrow bx not in protocol.

Scandinavian Study

Cause of Death	Total		Pre-dialysis		Hemodialysis		Peritoneal Dialysis	
	N-Hb	*S-Hb*	*N-Hb*	*S-Hb*	*N-Hb*	*S-Hb*	*N-Hb*	*S-Hb*
	N=216	*N=200*	*N=36*	*N=36*	*N=157*	*N=136*	*N=23*	*N=28*
All cause	29	27	4	1	21	20	3	6
Cardiovascular	24	16	3	1	18	10	3	5
Non-cardiovascular	5	11	1	0	3	10	0	1

Furuland 2003

- n=416, 48-76 wks, open-label
- Entry: Hb 9-12 g/dl w/o ESA
- Excluded: Uncontrolled HTN & diabetes, renal management problems, infection/inflammation/cancer
- Tx: Epo dose for target: Subnormal-Hb 9-12 g/dl, Normal-Hb 13.5-15 g/dl♀, 14.5-16 g/dl♂
- Powered for exercise, not mortality

ESA Resistance: Putative/Established Etiology

Defects in the hormone

Defects in/suppression of hormone production

Cytokines, e.g., IL-1, TNF, interferons, & TGF (Means 1992)

Inhibitors to hormone binding

Antibodies to receptor (Casadevall 1996)

Antibodies to hormone receptor

Receptor mutations or defects in post receptor pathways

C-terminus domain exerts negative erythropoiesis control; Up-regulation mutation known (de la Chapelle 1993)

Alterations in target tissue environment/structure

Marrow fibrosis due to ESAs (Animal data, FDA 1989; Kennedy 2006)

Osteitis Fibrosa Cystica (Bhadada 2009, Rao 1993)

Other Myelofibrosis

Alterations in target tissue function

Diseases with Physiologic Inhibitors- Cytokines, e.g., IL-1, TNF, interferons & TGF (Means 1992)

Infection (Occult, Overt) (Elliot 2009, Nassar 2002)

Anemia of chronic disease

Malnutrition-inflammation complex syndrome (Kalantar-Zadeh 2003)

Inflammatory Disease , e.g., IBD (Schreiber 1996), ***?Type 2 DM***

Diseases with Toxins

Uremia & dialysis adequacy (Ifudu 1996, Markson 1956, Radtke 1981, Wallner 1981, Zappacosta 1982)

Diseases with progenitor dysfunction or accelerated apoptosis, e.g., Myelodysplastic Syndromes

Frank deficiency in required or supportive hematologic factors

Nutrients, e.g., Fe, folate (van Wyck 1989)

Impairment of hematologic co-factors

Fe by Vitamin C deficiency (Altallah 2006) **& ? Vitamin D deficiency** (Amato 2005, Goicoechea 1998)

Fe by Al toxicity (Bia 1989, Caramelo 1995)