Treating Anemia in Non-dialysis and Dialysis Kidney Disease

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Current Status of Anemia Management

- **4 RCTs >7000 patient experience demonstrate no benefit or increased risk with targeting high Hb**
- **FDA review planned**
  - **REMS strategy "APPRISE" for cancer-induced anemia**
- **New Guidelines (KDIGO) planned**
- **Bundling Jan 2011 and its effect on anemia management**

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Targeting higher Hgb with ESA associated with increased risk.

- Point estimate of risk (in the direction of harm)
  - Normal Hematocrit 30% (95% confidence intervals of 0.9,1.9)
  - CREATE 22% (95% CI, 0.53 and 1.14)
  - CHOIR 34% (95% CI, 1.03 and 1.74)
  - TREAT 5% (95% CI 0.94 to 1.17)

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Benefits

- Reducing blood transfusion rate
  - Normal Hematocrit study by ≈10% (31% in low arm)
  - CHOIR by ≈0.8% (7.7% in low arm)
  - CREATE by ≈2.3% (10.9% in low arm)
  - TREAT by ≈9.7% (24.5% in placebo rescue)

  _____

  - No protocol or algorithm for transfusion in trials
  - No validated Hb threshold for transfusion
  - Quality of data collection on who received transfusion limited

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Benefits: HRQOL/Patient Reported Outcome

- Inconsistent improvement in QOL in NHCT, CREATE, CHOIR and TREAT
- Limitations of data
  - No consistent benefit across instruments
  - Mostly data from open label studies
  - Changes observed in 1st year not sustained through 2nd year
  - Early vs. late treatment of anemia
  - Selective reporting of domains
  - Instruments not validated by FDA

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Trials of Anemia Targets in CKD

- **Normal Hematocrit**
  - **1233 subjects, High risk symptomatic pts w/ CVD on chronic HD**
  - **Epoetin-alfa**
  - **Hb 9-10 g/dL vs. 13-14 g/dL.**
  - **Study stopped by Data and Safety and Monitoring Board**

- **CREATE study**
  - **603 subjects, 100 centers. Non dialysis CKD, 22 countries**
  - **Epoetin-beta**
  - **Hb 13.49g/dL vs. 11.6g/dL. Early treatment vs. Late Treatment**

- **CHOIR study**
  - **1432 subjects non dialysis CKD patients, US**
  - **Epoetin-alfa**
  - **Hb 13.5 g/dL vs 11.3 g/dL**
  - **Study stopped by Data and Safety and Monitoring Board**

- **TREAT study**
  - **4,038 subjects, CKD and type 2 diabetes, 623 centers, 24 countries**
  - **Darbepoietin**
  - **Placebo-controlled with rescue arm: Hb 9.0 g/dL vs 13.0 g/d**

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The Normal Hematocrit Study

- Tested hypothesis that patients with normal Hb 13-14 g/dL will have better outcomes than patients with Hb 9-10 g/dL

- 1233 HD patients with CAD or CHF

- Primary end-point: Death or MI

- Study terminated early due increased risk

- Higher rate of vascular access thrombosis in normal Hct group: (243 patients, or 39 percent, vs. 176 patients, or 29 percent; $P=0.001$).

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Normal Hematocrit Study

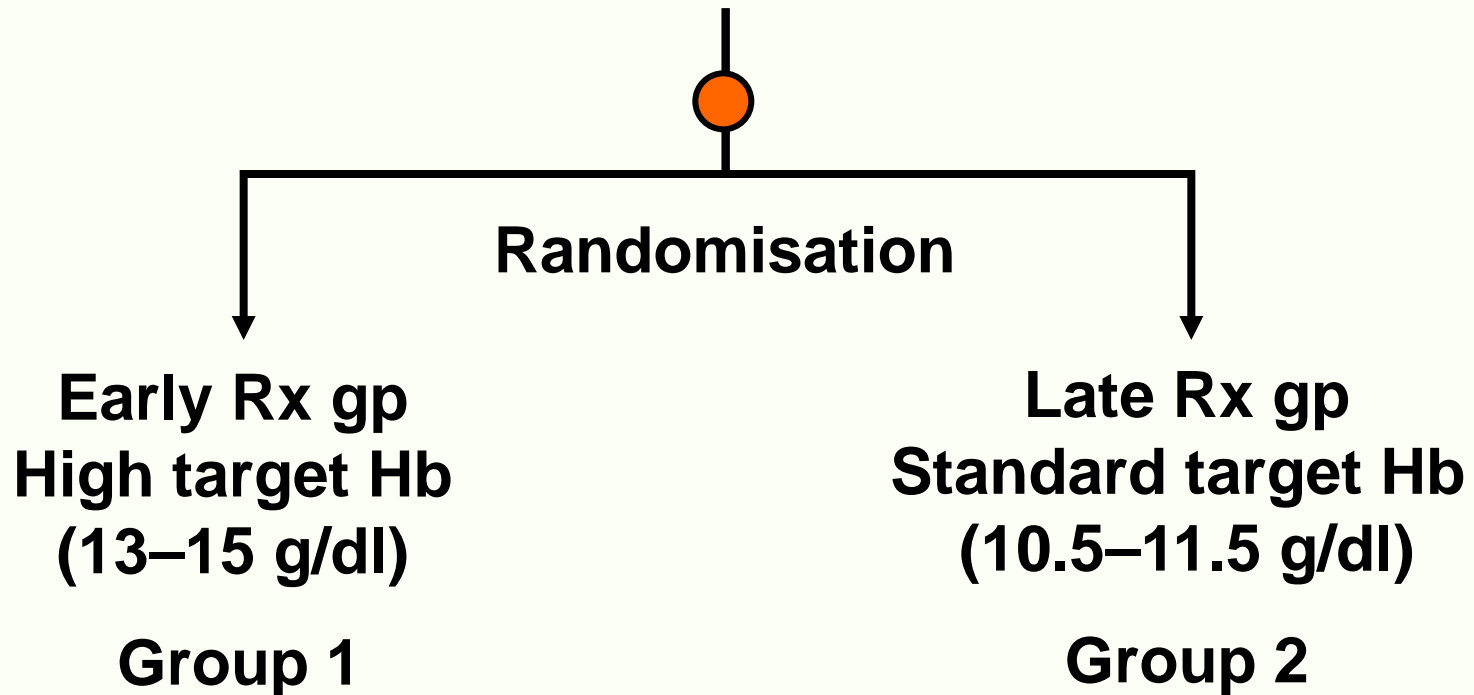|	Low Hct	Normal Hct
n	618	615
Hct	30	42 (achieved 39%)
Epoetin dose	160	460
Total deaths	150	183
Non-fatal MI	14	19
RR		1.3 (0.9-1.9)

The incidences of non-fatal MI were 3.1% and 2.3% in the normal and low hematocrit groups, respectively. The incidences of CVA (39% versus 29%) and all other thrombotic events (22% versus 18%) were also higher in the normal hematocrit group. There was a trend to decreasing mortality with increasing hematocrit values within both groups.

"Study was halted when differences in mortality between the groups were recognized as sufficient to make it very unlikely that continuation of the study would reveal a benefit for the normal-hematocrit group and the results were nearing the statistical boundary of a higher mortality rate in the normal hematocrit group"
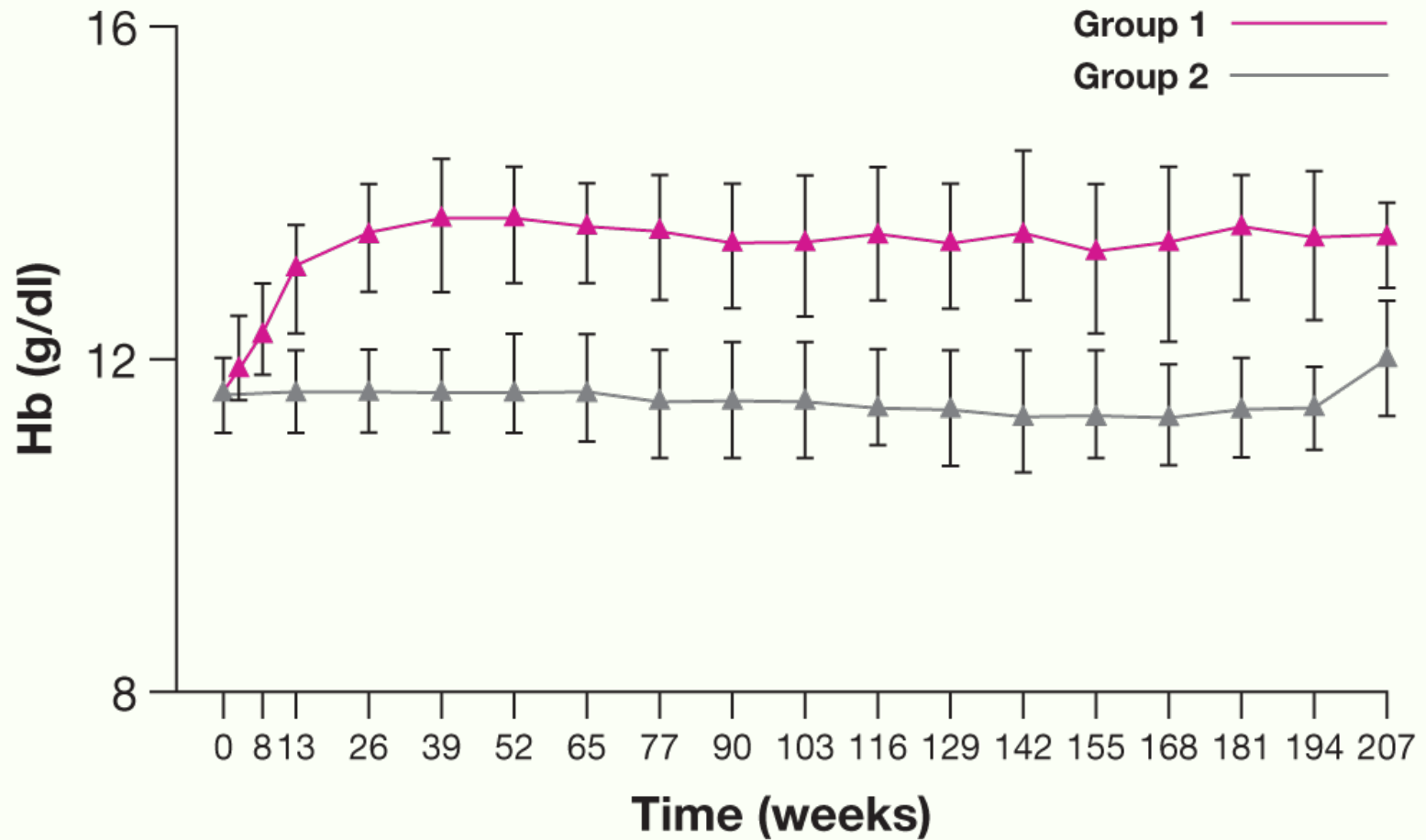
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Besarab et al. N Engl J Med 339:584-590, 1998

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Cardiovascular risk Reduction by Early Anaemia Treatment with Epoeitin-β (CREATE)

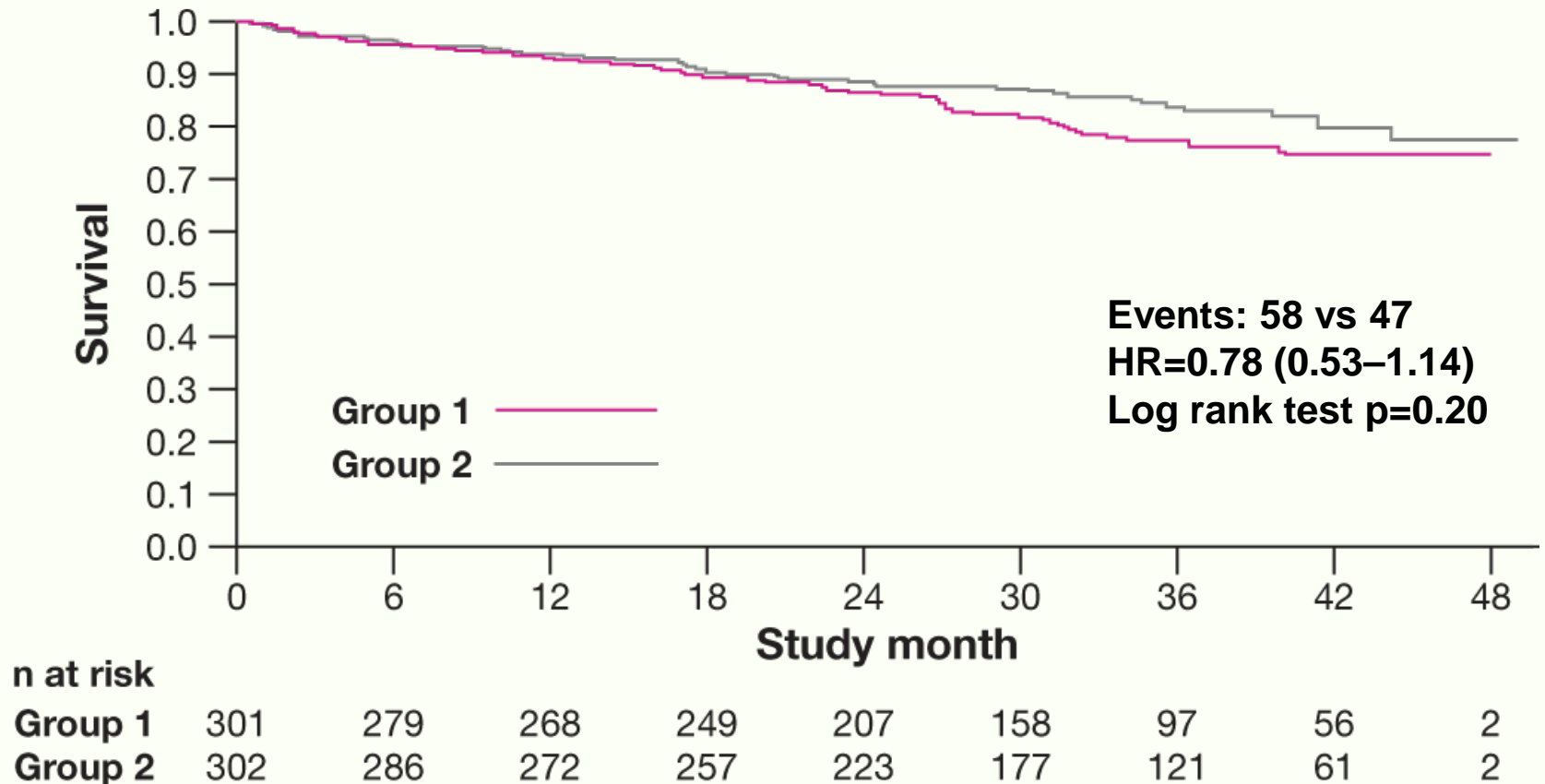**600 patients, 100 centers, from 22 countries**
Epoeitin-β

Randomisation

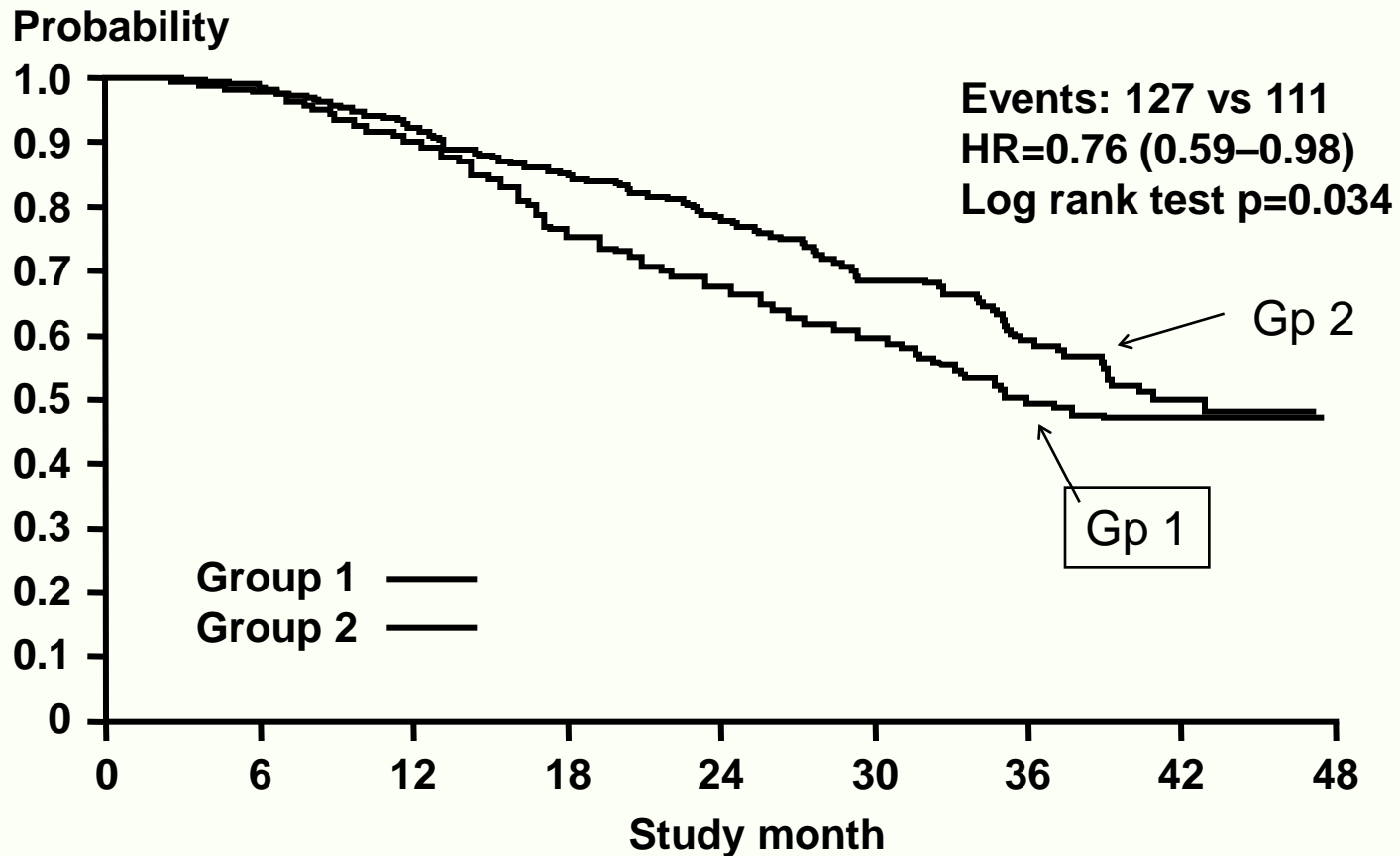**Early Rx gp**
High target Hb
(13–15 g/dl)

Group 1

Late Rx gp
Standard target Hb
(10.5–11.5 g/dl)

Group 2

Drueke TB, et al N Engl J Med. 355:2071-84, 2006

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Hemoglobin over time

Primary endpoint
Time to first CV events (105 events)

Events: 58 vs 47
HR=0.78 (0.53–1.14)
Log rank test p=0.20

Drueke TB, et al N Engl J Med. 355:2071-84, 2006

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Secondary endpoints
Time to dialysis

Probability

Events: 127 vs 111
HR=0.76 (0.59–0.98)
Log rank test p=0.034

Gp 2

Gp 1

Group 1 ——
Group 2 ——

Study month

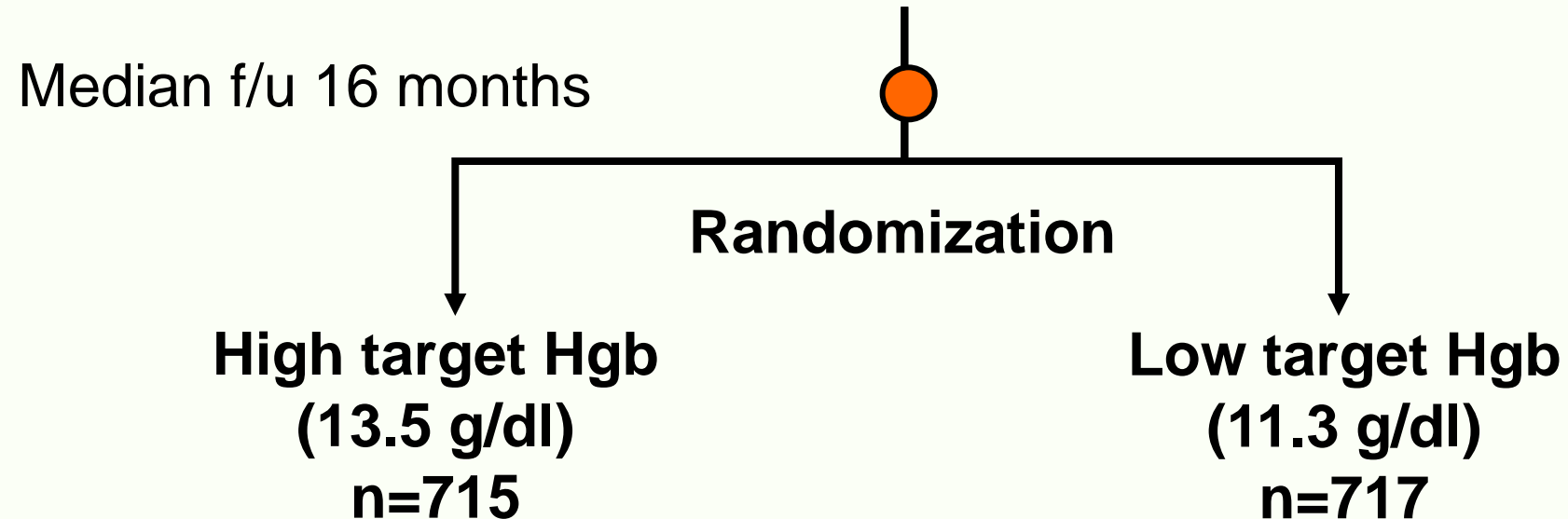| n at risk									
Group 1	301	281	255	211	162	115	62	35	0
Group 2	302	293	269	243	199	138	82	33	0

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CREATE Results: QOL
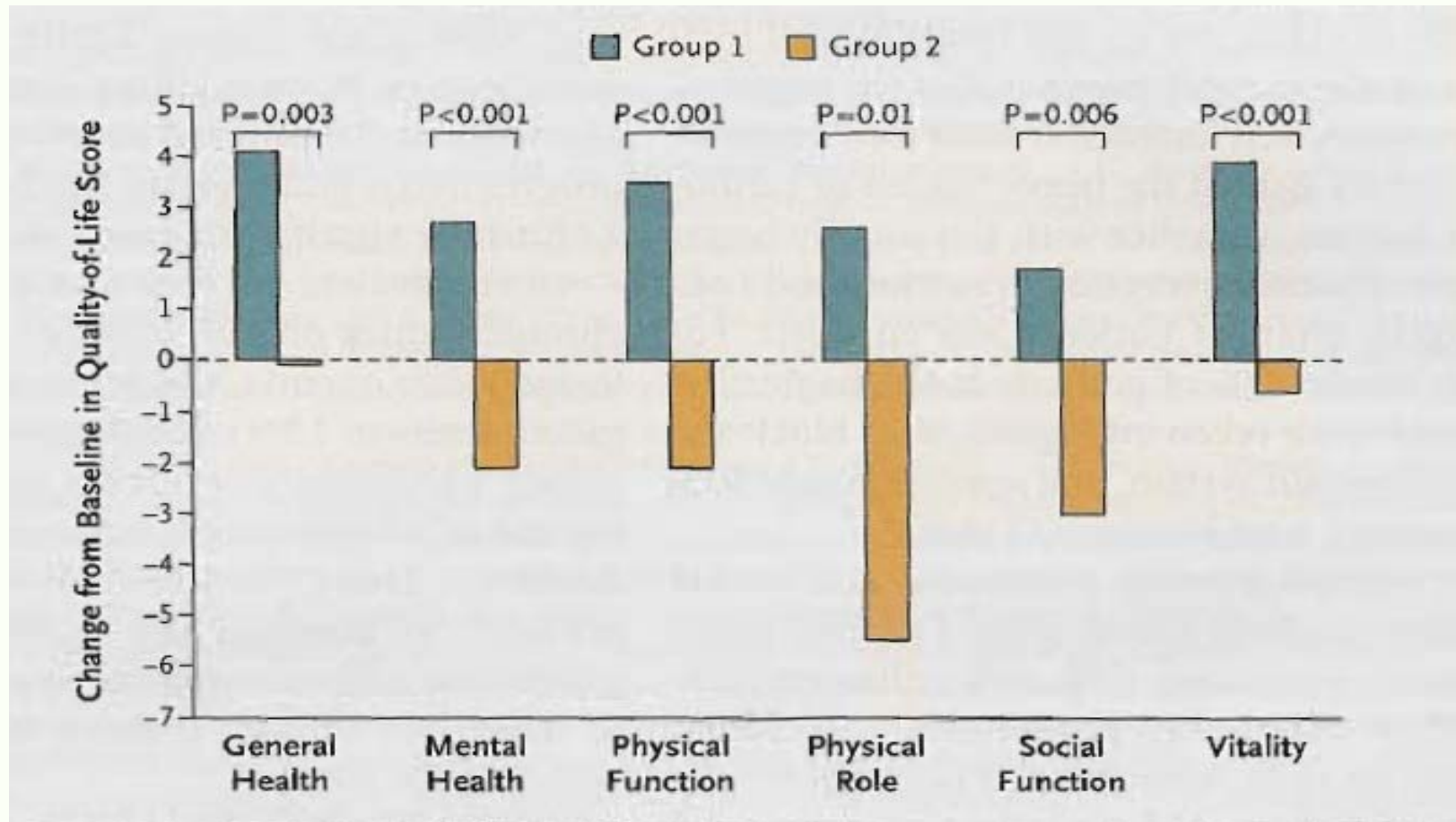
- Patients knew which arm they were randomized to
- 1st yr: 98% of patients in high arm received injections ;only 32% in the low arm.
- Low Hb arm pts had to develop worsening anemia prior to epoetin therapy

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CHOIR: Patient Flow

1432 patients, 130 centers, US only
Epoetin-alfa

Median f/u 16 months

Randomization

High target Hgb
(13.5 g/dl)
n=715

Low target Hgb
(11.3 g/dl)
n=717

Singh et al,New Engl J Med 2006; 355:2085-98

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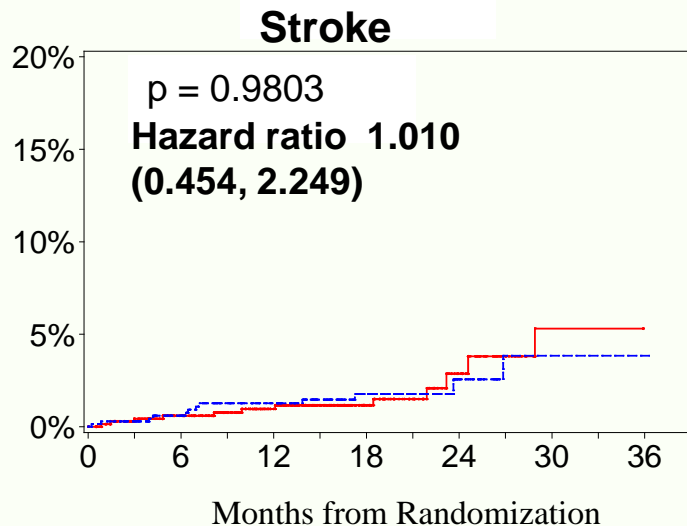
Mean Weekly Doses of Epoetin alfa and Hgb

Singh et al,New Engl J Med 2006; 355:2085-98

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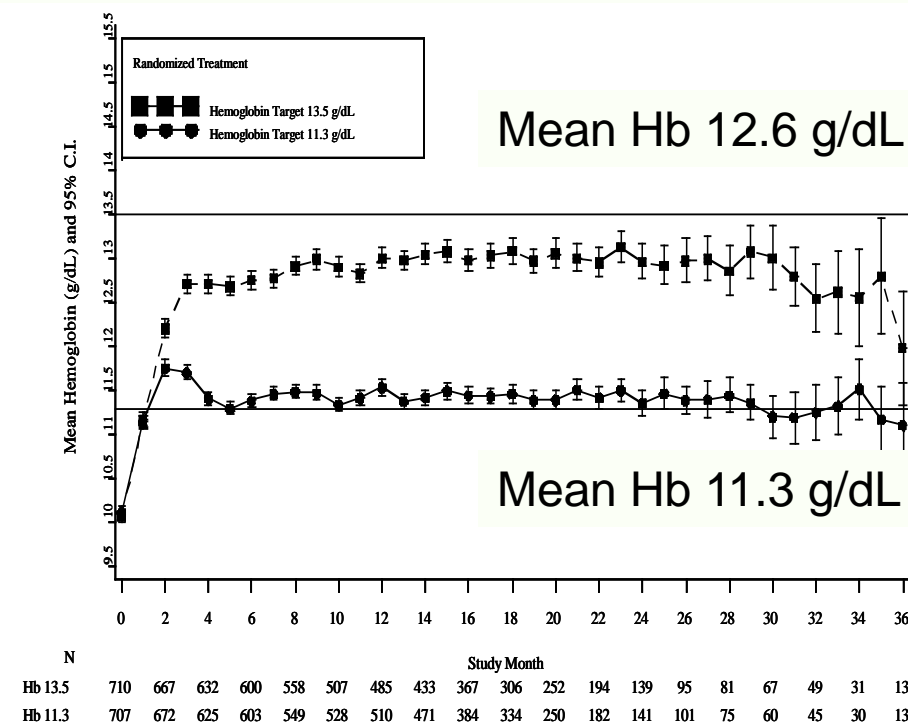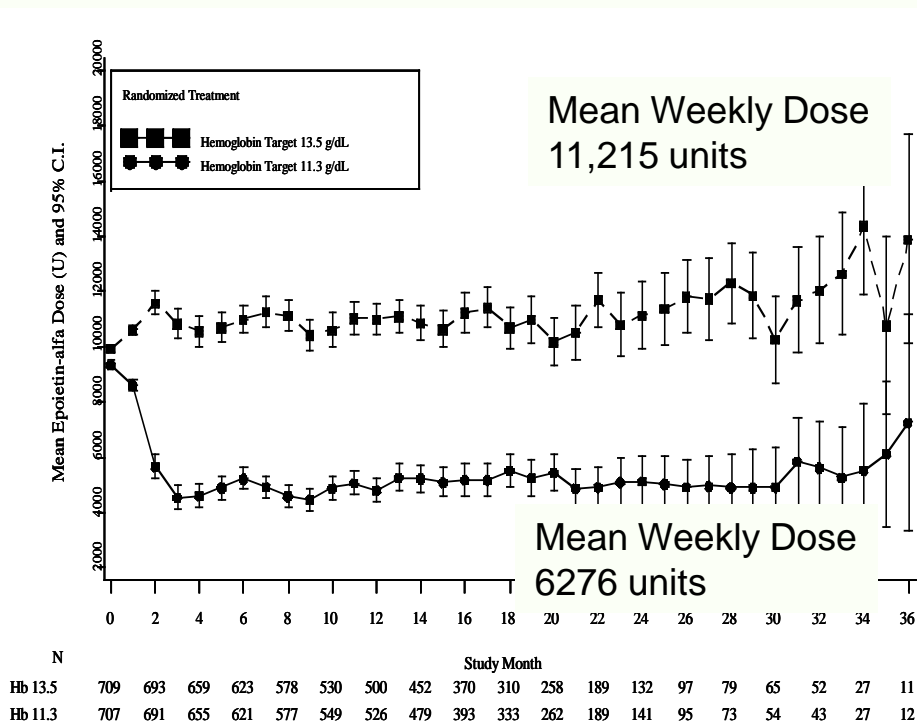
Kaplan-Meier Plot of the Time to the Primary Composite Event between Randomization and Termination: ITT Population

Primary Composite Endpoint:
Death, MI, CHF hosp (no RRT) and/or stroke

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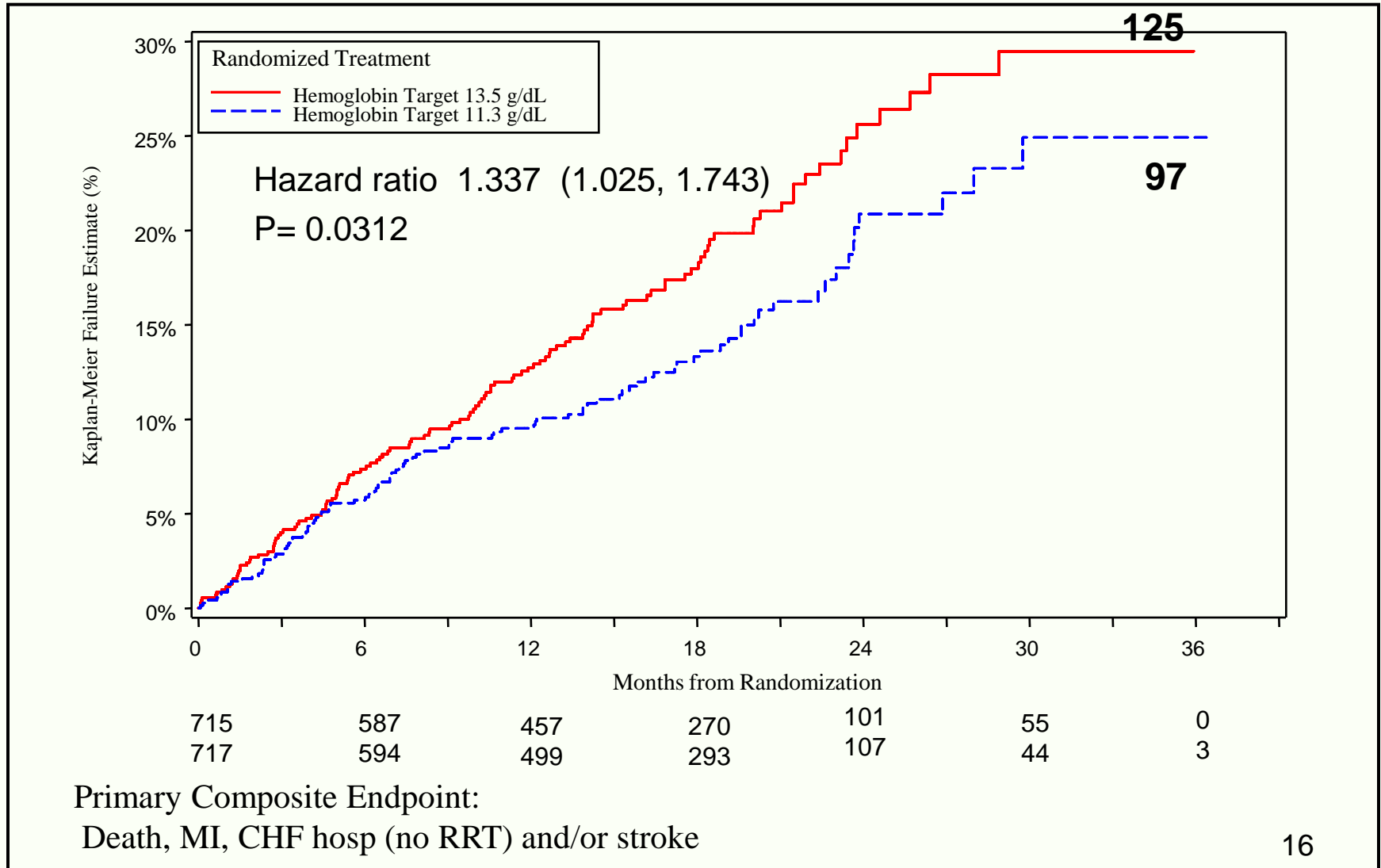
Components of the Primary Endpoint

Death   65 deaths

p = 0.0674
**Hazard ratio 1.483
(0.969, 2.268)**

CHF Hospitalization (where RRT did not occur)

p = 0.0727
**Hazard ratio 1.409
(0.967, 2.054)**

Stroke

p = 0.9803
**Hazard ratio 1.010
(0.454, 2.249)**

Myocardial Infarction

p = 0.7836
**Hazard ratio 0.915
(0.484, 1.729)**

Months from Randomization

Months from Randomization
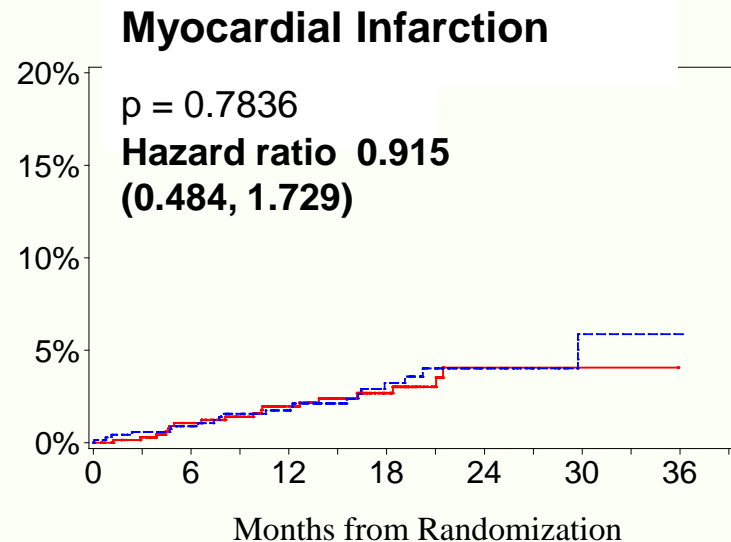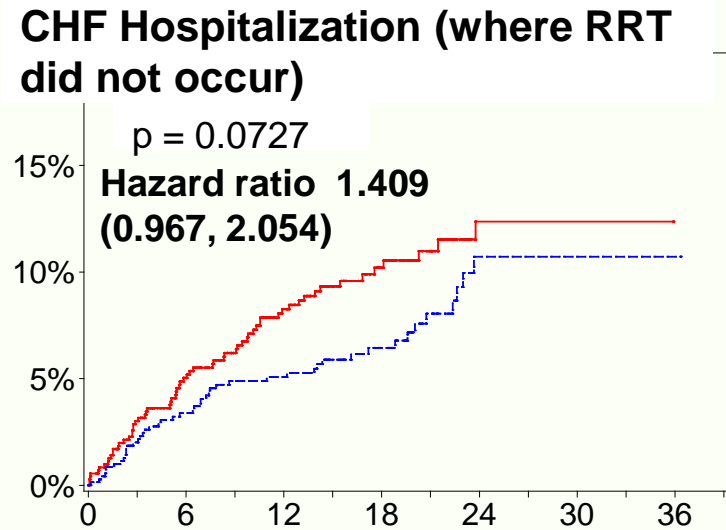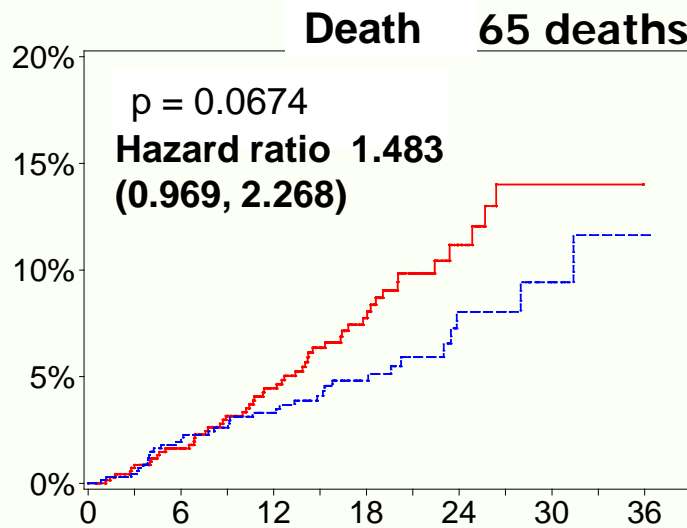
Randomized Treatment   —— Hemoglobin Target 13.5 g/dL   - - - Hemoglobin Target 11.3 g/dL

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CHOIR: QOL

- 3 instruments
  - LASA
  - KDQ
  - SF-36

QOL Increased in both groups

No difference between groups

Singh et al, New Engl J Med 2006; 355:2085-98

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CHOIR KDQ: Fatigue

Week	High Hb 13.5 g/dL	Low Hb 12.3 g/dL	Difference betw'n gp	P value
0				
24	0.9	0.8	0.1	
48	0.9	0.8	0.1	
72	0.7	0.7	0.0	
96	0.7	0.5	0.2	
120	0.6	0.5	0.1	
144	-0.7	0.2	-.0.9	
Final	0.6	0.6	0.0	0.664

Longitudinal Analysis

	High Gp	Low Gp	Difference	P value
Estimate	0.0275	0.0248	0.0027	0.527
SD	0.0031	0.003		

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CHOIR QOL: Vitality

Week	High Hb !3.5 g/dL	Low Hb 12.3 g/dL	Difference betw'n gp	P value
0				
24	14.9	12.1	2.8	
48	13.9	10.9	3.0	
72	7.8	10.6	-2.8	
96	11.4	8.5	2.9	
120	4.1	5.0	0.9	
144	-13.3	13.1	26.4	
Final	10.0	8.2		0.577

Longitudinal Analysis

	High Gp	Low Gp	Difference	P value
Estimate	0.3778	0.3527	0.0251	0.701
SD	0.0468	0.0455		

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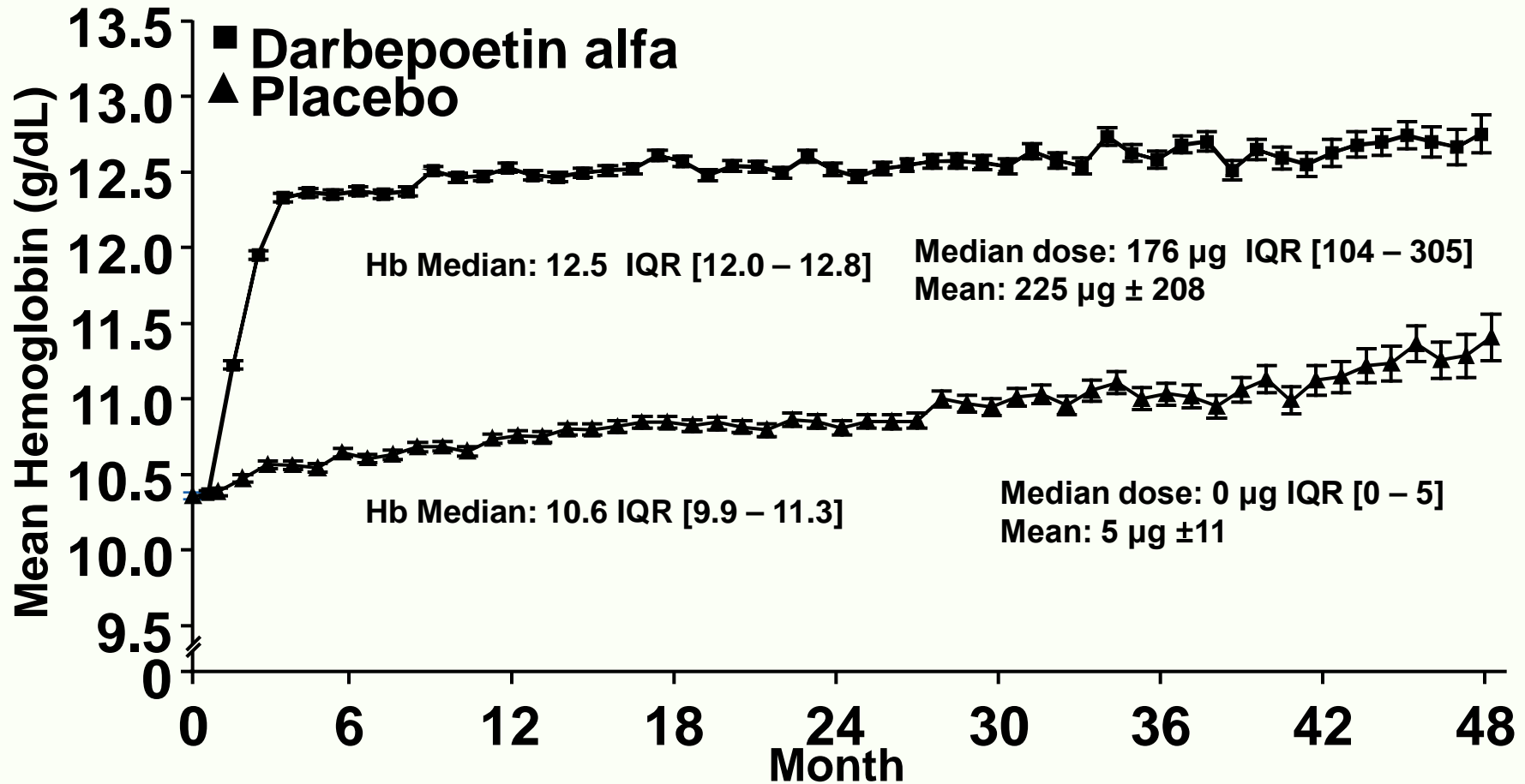# Trial to Reduce Cardiovascular Events with Aranesp Therapy

Hypothesis

In patients with type 2 diabetes, chronic kidney disease not requiring dialysis, and concomitant anemia, raising hemoglobin with darbepoetin alfa would lower the rates of death and cardiovascular morbidity and/or death and end-stage renal disease

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Design

- International (24) multi-center (623), double-blind, placebo-controlled randomized trial
- Randomization in a 1:1
  - Active: darbepoetin alfa to attempt to achieve and maintain a hemoglobin (Hb) of 13 g/dL
  - Control: placebo: with "rescue therapy" if Hb <9.0 g/dL with resumption of placebo once Hb≥9.0 g/dL
- Blinding maintained during computer directed adjustments assigning pre-filled syringes
- 2 composite primary endpoints*
  - Cardiovascular composite: death, MI, myocardial ischemia, CHF, stroke. *alpha 0.048*
  - Renal composite: death or ESRD. *alpha 0.002*

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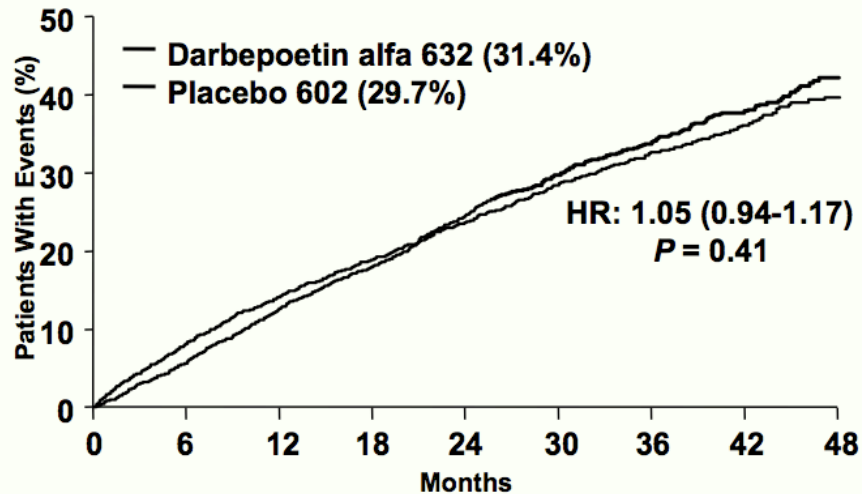
Hemoglobin Levels

Mean Hemoglobin (g/dL) vs Month

- ■ Darbepoetin alfa
- ▲ Placebo

Hb Median: 12.5 IQR [12.0 – 12.8]

Median dose: 176 µg IQR [104 – 305]
Mean: 225 µg ± 208

Hb Median: 10.6 IQR [9.9 – 11.3]

Median dose: 0 µg IQR [0 – 5]
Mean: 5 µg ±11

No. of Patients

	0	6	12	18	24	30	36	42	48
Darbepoetin alfa	2004	1768	1503	1300	946	635	404	253	97
Placebo	2019	1742	1460	1221	887	620	356	216	79

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TREAT Composite endpoints

Cardiovascular Composite: Death, MI, Myocardial Ischemia, HF, Stroke

— Darbepoetin alfa 632 (31.4%)
— Placebo 602 (29.7%)

HR: 1.05 (0.94-1.17)
P = 0.41

Renal Composite: Death or ESRD

— Darbepoetin alfa 652 (32.4%)
— Placebo 618 (30.5%)

HR: 1.06 (0.95-1.19)
P = 0.29

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All Cause Mortality

Patients With Events (%)

— **Darbepoetin alfa 412 (20.5%)**
— **Placebo 395 (19.5%)**

HR: 1.05 (0.92-1.21)
P = 0.48

Months

50
40
30
20
10
0

0   6   12   18   24   30   36   42   48

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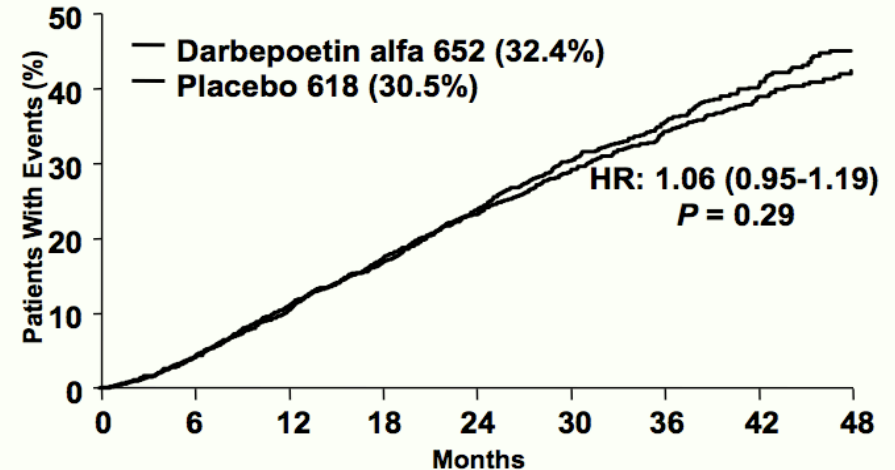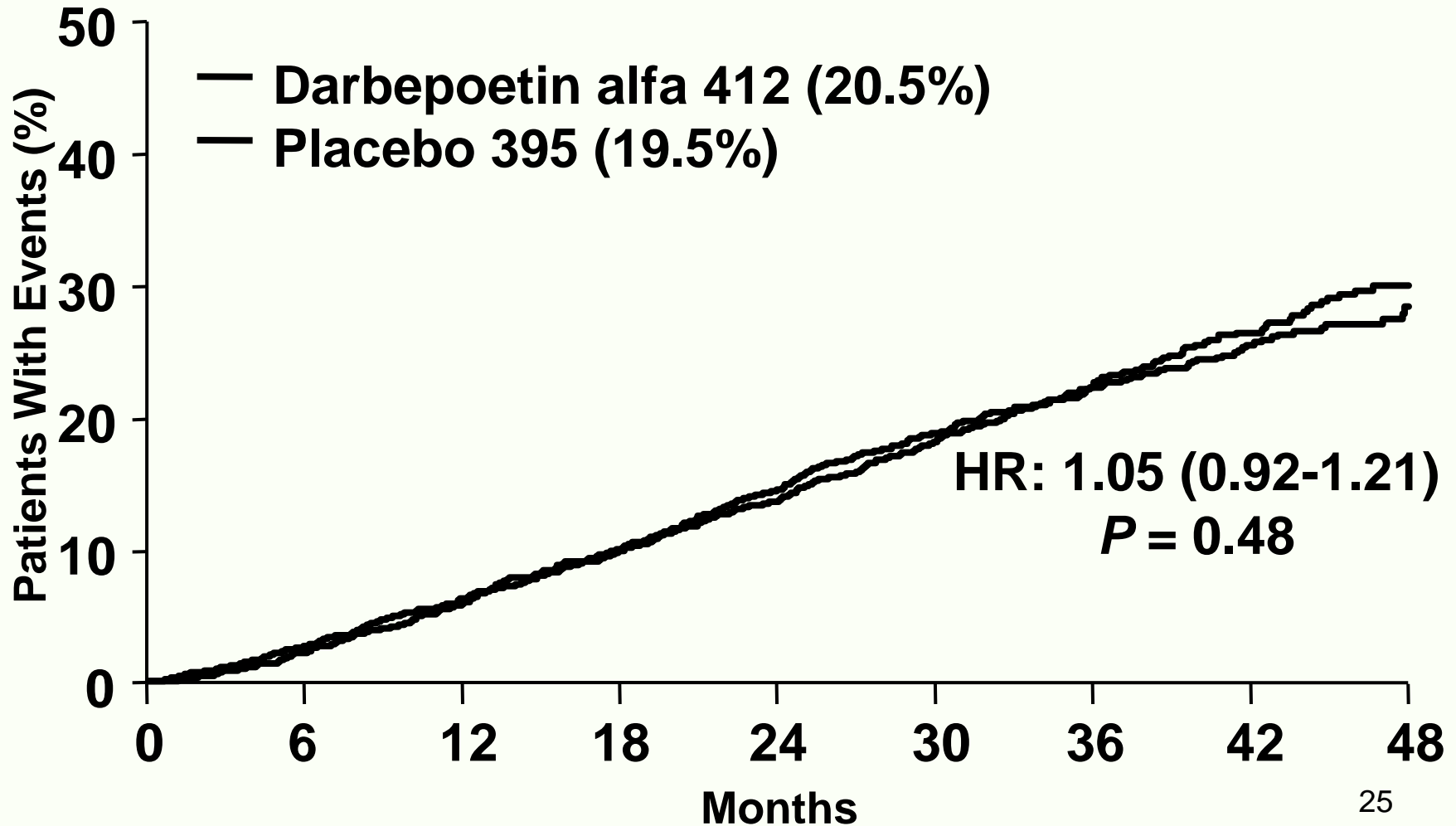
Fatal and Nonfatal Stroke

Patients With Events (%) (y-axis, 0 to 50)

— **Darbepoetin alfa 101 (5.0%)**
— **Placebo 53 (2.6%)**

HR: 1.92 (1.38 – 2.68)
P < 0.001

Months (x-axis, 0 to 48)

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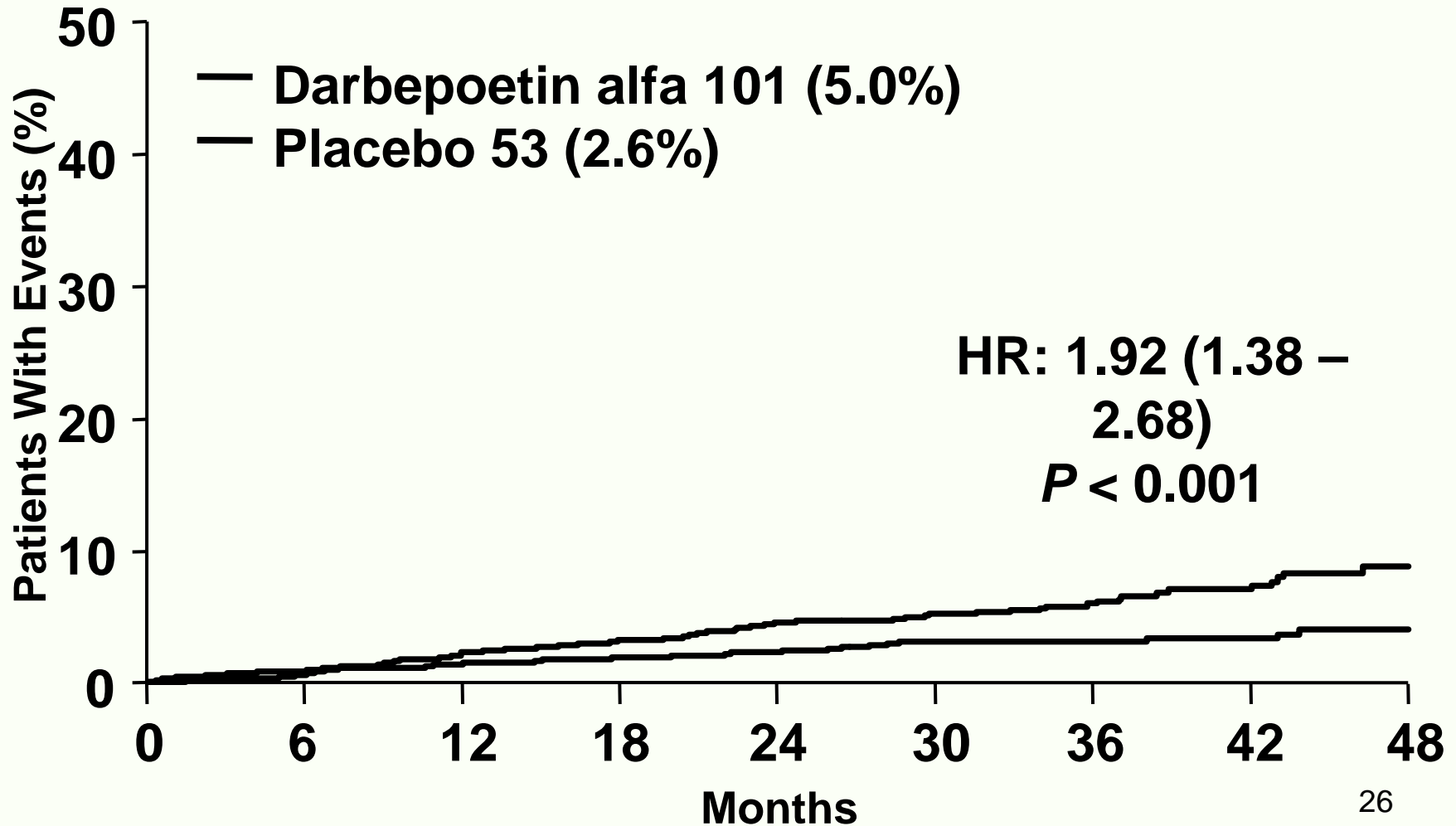
Malignancy in TREAT

	Darbepoetin alfa	Placebo	P-value
Overall			
Cancer-related AE	**139/2012 6.9%**	**130/2026 6.4%**	**0.53**
Deaths attributed to cancer	**39/2012 1.9%**	**25/2026 1.2%**	**0.08**
Subgroup: Baseline ☑ History of malignancy (n = 348)			
All cause mortality	**60/188 31.9%**	**37/160 23.1%**	**0.13**
Deaths attributed to cancer	**14/188 7.4%**	**1/160 0.6%**	**0.002**

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Patient Reported Outcomes
FACT-Fatigue Score at 25 Weeks
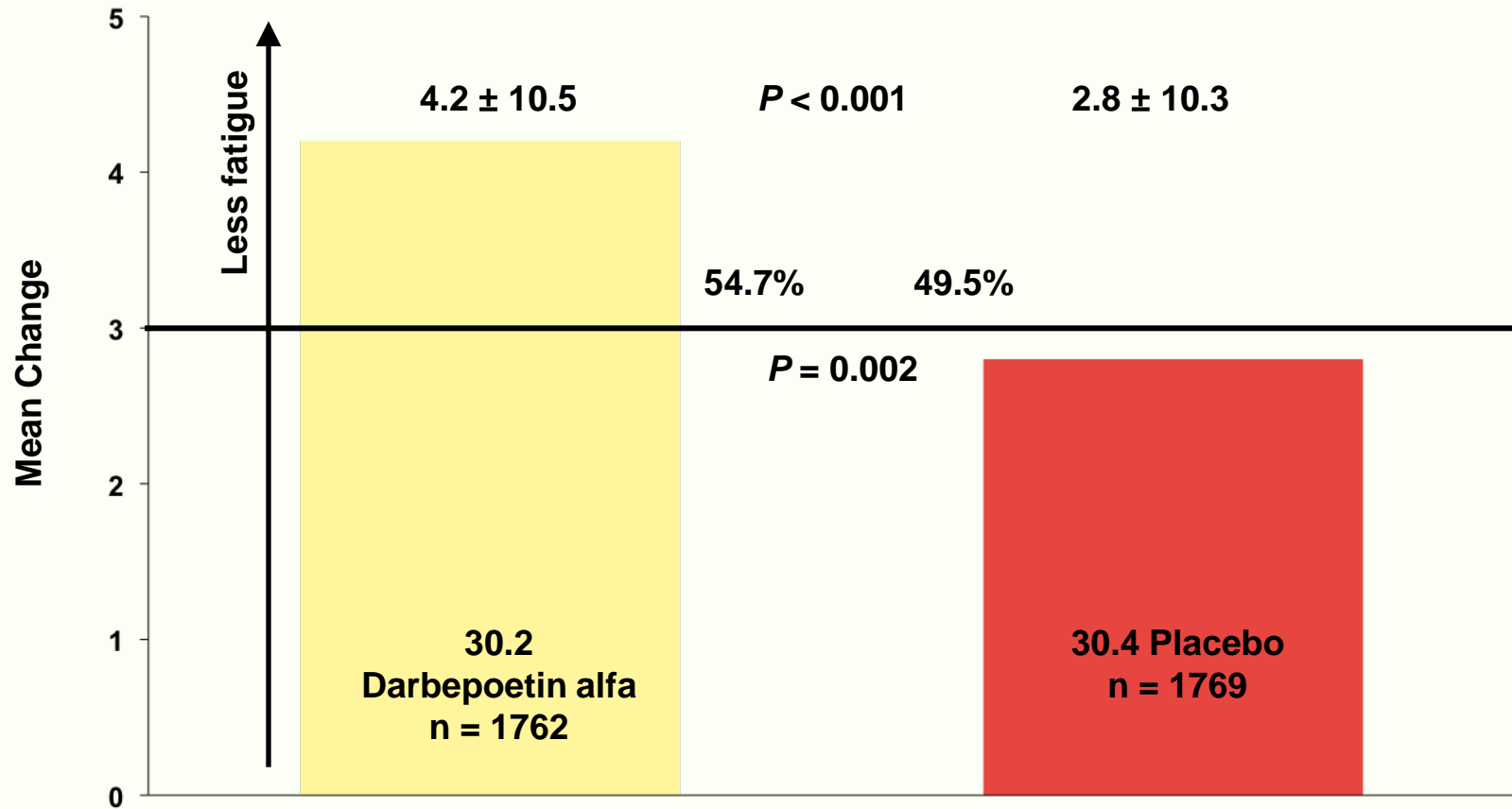
FACT-Fatigue range: 0: most fatigued, to 52: least fatigued

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Patient Reported Outcomes Supportive Analysis

Short-Form 36 Mean Change at 25 Weeks in 2 Domains

| Domains	Darbepoetin alfa n = 1138	Placebo n = 1157	P-value
Energy	2.6 ± 9.9	2.1 ± 9.7	0.20
Physical Function	1.3 ± 9.2	1.1 ± 8.8	0.51

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What explains heterogeneity of adverse outcomes?

- Class effect
  - Epoetin-alfa
  - Darbepoetin-alfa
  - Epoetin-beta
- Exposure to higher and different doses of ESA
  - CHOIR higher hemoglobin arm received median of 10,952 units per week.
  - TREAT median dose of 8800 units per week in the darbepoetin treated arm
  - CREATE, median dose of 5000 units of epoetin-beta per week was used in the higher hemoglobin arm.
- Enrollment of different populations?
  - TREAT, all diabetics
  - CHOIR ≈50% diabetics
  - CREATE ≈25% diabetes mellitus

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Molecular Comparison of
Aranesp™ (darbepoetin alfa) and rHuEPO
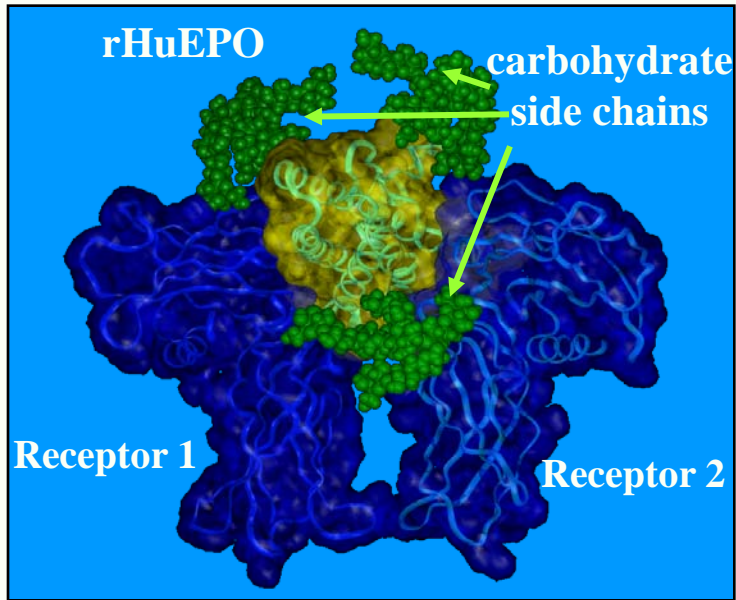
- 3 N-linked (CHO) chains

- Maximum 14 sialic acids

- MW ~ 30,400 daltons

- 40% carbohydrate
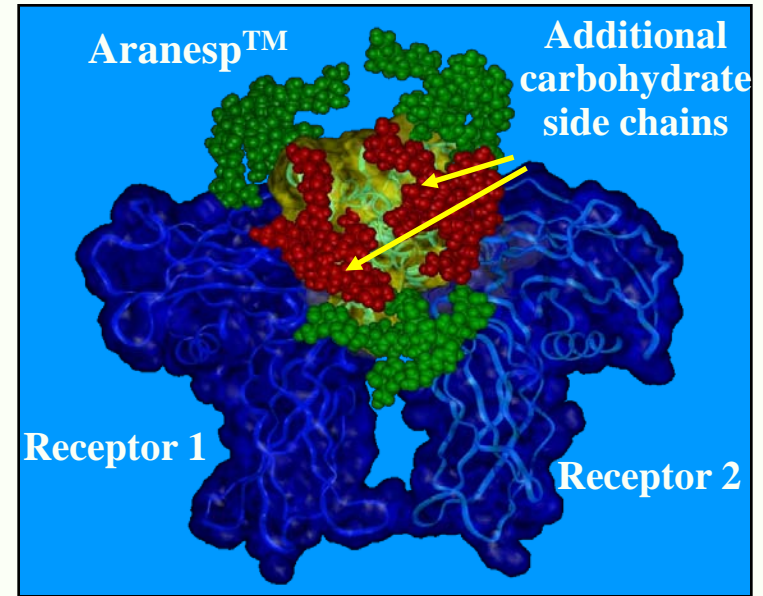
- 5 N-linked (CHO) chains

- Maximum 22 sialic acids

- MW ~ 37,100 daltons

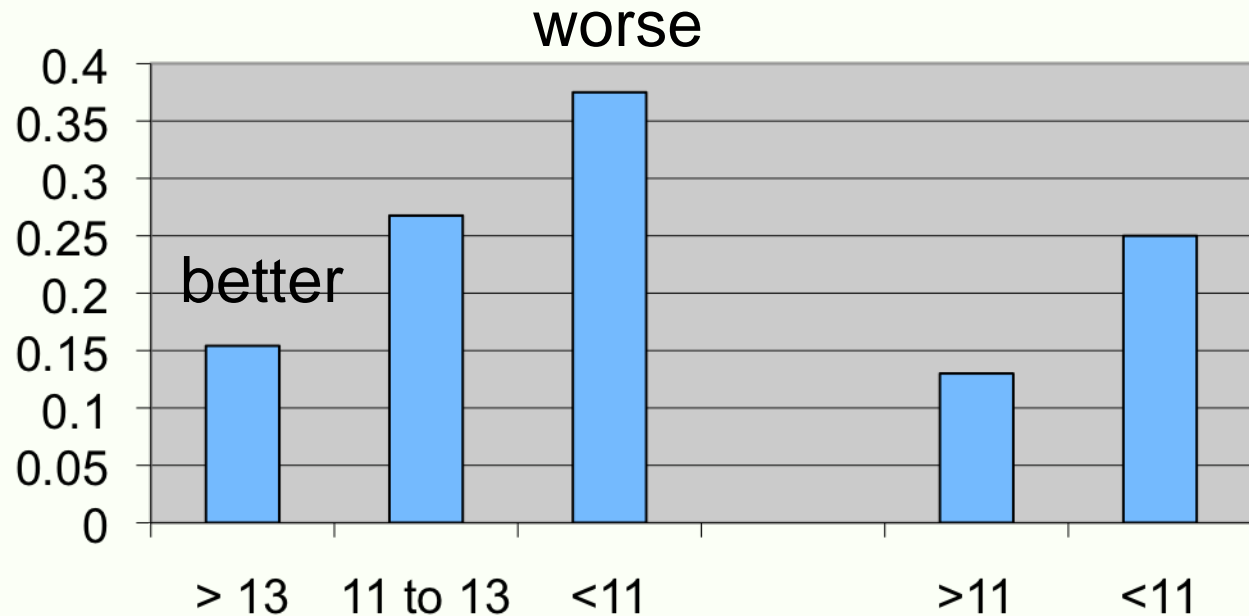- 51% carbohydrate

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What explains the higher rate of adverse outcomes in the RCTs

- Iron exposure
- Rapid rise in Hgb
- Blood pressure
- ESA versus Hgb versus both
  - Non-physiologic doses of ESA
  - Activation of EpoR in non-hematopoietic tissue beds
  - High hematocrit activating endothelial cells and platelets

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CHOIR: Primary Endpoint by Achieved Hgb

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Association between dose and primary outcome in Group A (9 month Landmark)

CHOIR (9-Month Landmark Analysis)
Time to the Primary Endpoint between Randomization and Termination
Target Hb 13.5 g/dL (Group A) [N=519, Events=62]

Dashed lines = 95% confidence bounds
*If a patient experienced a primary event, only doses prior to the event were used to determine average weekly dose.

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Szczech LA, et al: Kidney Int 74: 791–798, 2008

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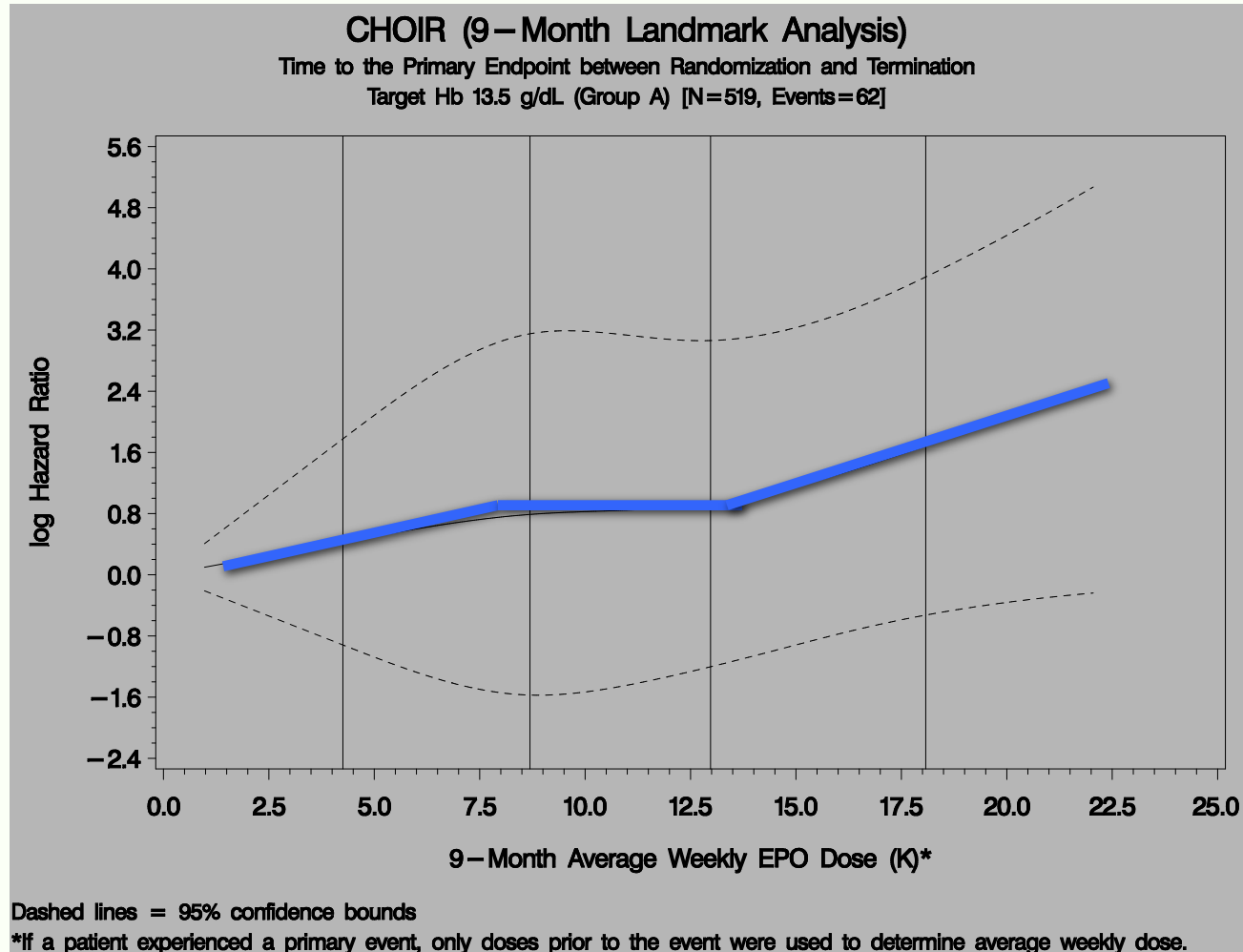
Epoetin requirements predict mortality in hemodialysis patients.

Zhang et al. AJKD 2004.

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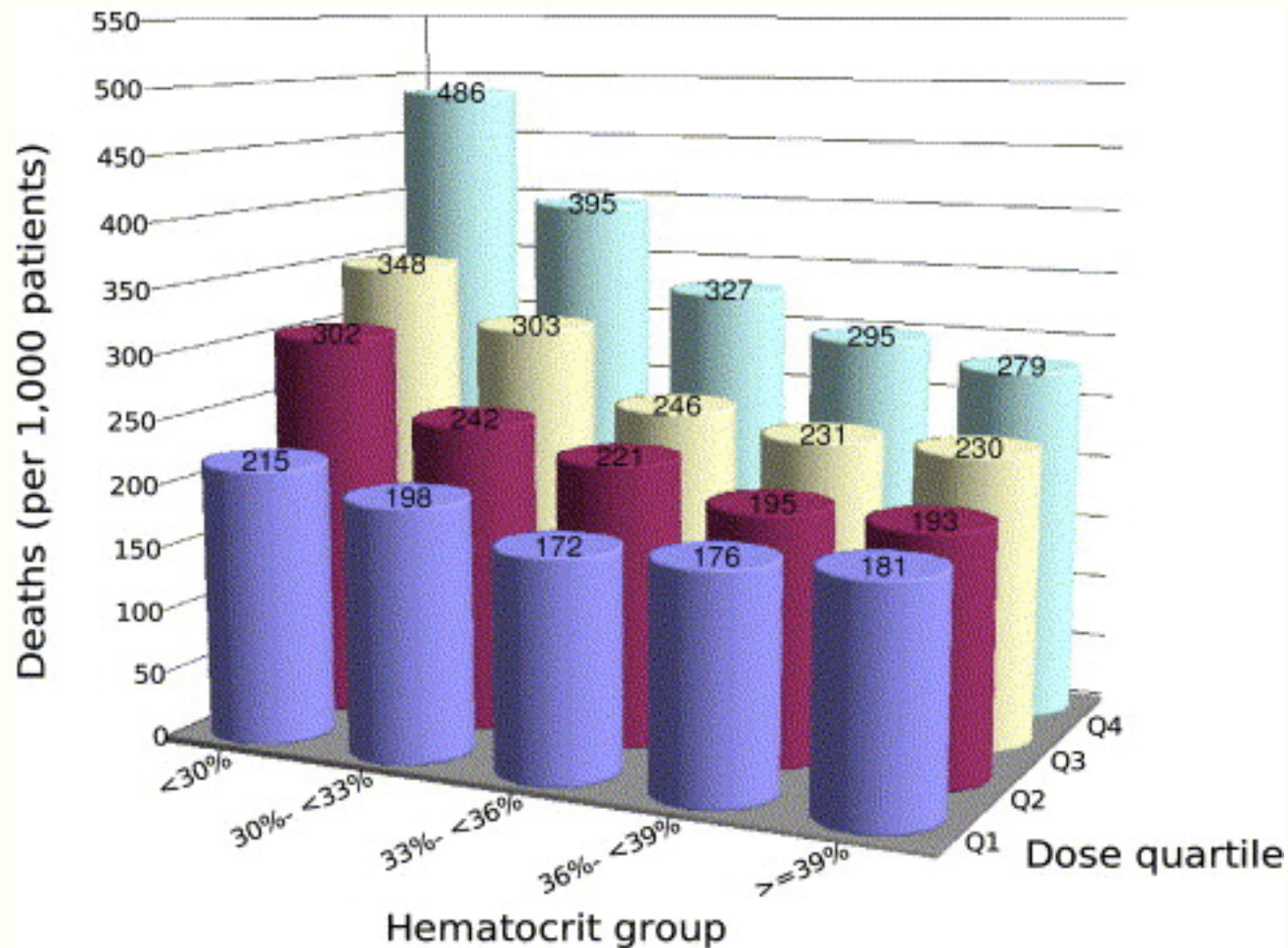
Epo and Iron and mortality: Center level analysis

Table 2. Dialysis Center Anemia Management Practice and 1-Year Mortality Risk Among Incident Patients[a]

Hematocrit Range, %	Dialysis Center ESA Dosing Profile		Dialysis Center Intravenous Iron Use Profile	
	Predicted Center-Level ESA Dose (for Hematocrit Range), Units/d	Hazard Ratio (95% CI)	Center-Level Probability of Iron Use per Month (for Hematocrit Range), %	Hazard Ratio (95% CI)
<30	Q1 (<3744)	1 [Reference]	Q1 (<50.1)	1 [Reference]
	Q2 (3745-4381)	0.97 (0.95-1.00)		
	Q3 (4382-5039)	0.97 (0.94-1.00)		
	Q4 (5040-5696)	0.98 (0.95-1.02)		
	Q5 (>5696)	0.94 (0.90-0.97)		
30-32.9	Q1 (<2780)	1 [Reference]		
	Q2 (2781-3224)	1.01 (0.98-1.03)		
	Q3 (3225-3689)	0.99 (0.96-1.02)	Q3 (55.5-63.3)	0.99 (0.96-1.02)
	Q4 (3690-4343)	1.00 (0.96-1.03)	Q4 (63.4-71.1)	0.97 (0.94-1.00)
	Q5 (>4343)	0.99 (0.95-1.04)	Q5 (>71.1)	0.95 (0.91-0.99)
33-35.9	Q1 (<1927)	1 [Reference]	Q1 (<40.2)	1 [Reference]
	Q2 (1927-2241)	1.01 (0.98-1.04)	Q2 (40.2-51.5)	1.01 (0.98-1.04)
	Q3 (2242-2562)	1.04 (1.01-1.07)	Q3 (51.6-61.5)	1.01 (0.98-1.05)
	Q4 (2563-3017)	1.04 (1.01-1.08)	Q4 (61.6-71.5)	0.99 (0.96-1.03)
	Q5 (>3017)	1.07 (1.03-1.12)	Q5 (>71.5)	1.00 (0.96-1.05)
≥36	Q1 (<1392)	1 [Reference]		
	Q2 (1392-1626)	1.04 (1.01-1.07)		
	Q3 (1629-1836)	1.05 (1.02-1.08)		
	Q4 (1837-2141)	1.08 (1.03-1.10)		
	Q5 (>2141)	1.11 (1.07-1.15)		

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent.
[a] Model is stratified on age (in 5-year groups) and calendar year. Multivariable ... in Table 1 in addition to geographic region indicator variables.

Higher ESA dose=better outcome

Higher ESA dose= worse outcome

n=269717

4500 dialysis units

33541 annual anemia management profiles

Brookhart, MA, JAMA, 303, 857-864, 2010

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Conclusions

- RCTs demonstrate increased risk with targeting a higher Hb

- Observational studies and secondary analyses of RCTs shows risk is not associated with high achieved Hb (i.e., lower Hb worse outcome, higher Hb better outcome).

- QOL data inconsistent

- Dosage of ESA associated with worse outcome

- Evidence for Hb threshold of >9 g/dL (Normal Hematocrit and TREAT) but not for target range

- Evidence for reducing ESA dose

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Conclusions-2

- **Hb should be >9 g/dL**
  - WHY?
  - Because Normal HCT study Hb>9 g/dL, TREAT>9 g/dL. Raising Hb from 9 g/dL to higher not associated with a clinically meaningfully improvement in QOL.
- **No upper Hb target**
  - WHY?
  - Because no higher Hb level or target range supported by data
  - Aiming for higher Hb associated with risk and use of high doses of ESA
- **Avoid ESA or Use low ESA doses**
  - WHY?
  - Because observational data and secondary analyses of RCTs suggests risk associated with high ESA dosage
  - ESAs are pleiotropic cytokines
  - Activate EpoR both high affinity (bone marrow) and low affinity (everywhere else)
  - Data from cancer, spine study, critically ill patients

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JASN editorial, January 2010

- Avoid ESA in most **non-dialysis CKD** patients
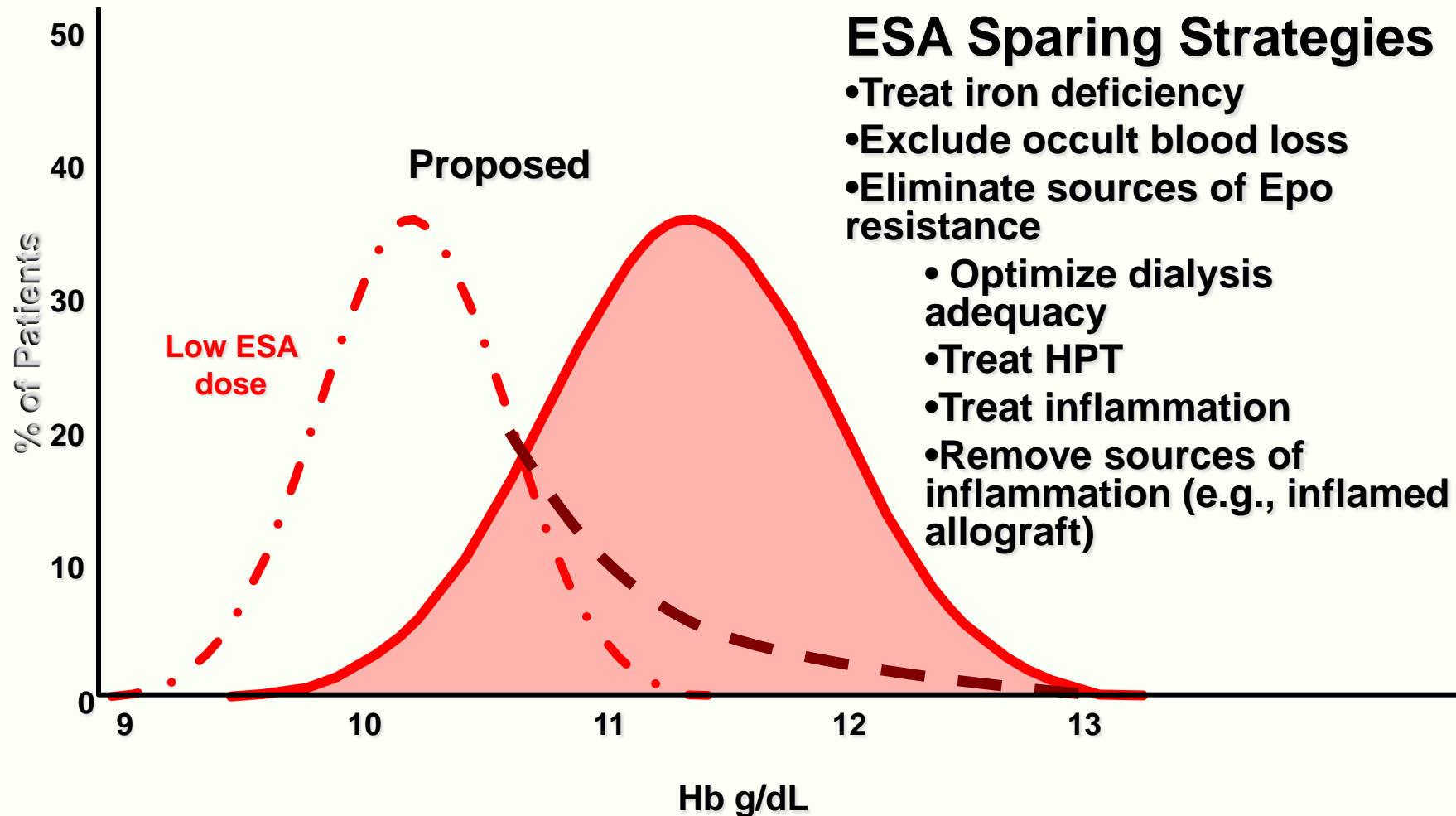 - Exceptions: very low Hgb < 9 g/dL
  - Transplant candidates

"Most cancer patients with CKD should be managed with blood transfusions and not ESAs. "

"avoiding use of ESAs in managing anemia in non-dialysis CKD patients is now the soundest approach given the remarkable observations from the TREAT study. Many anemic CKD patients will not need ESAs and can be managed using other strategies. "

JASN editorial, In press

- Reduce ESA dose **in dialysis CKD** patients
- Hb threshold of >9 g/dL
- Individualize therapy

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Distribution of Hb with different scenarios

ESA Sparing Strategies
- Treat iron deficiency
- Exclude occult blood loss
- Eliminate sources of Epo resistance
  - Optimize dialysis adequacy
  - Treat HPT
  - Treat inflammation
  - Remove sources of inflammation (e.g., inflamed allograft)

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Conclusions-3

- **Recommend:**
  - **1.) Change to a lower Hb threshold of >9 g/dL**
  - **2.) Eliminate target range, i.e, upper Hb level**
  - **3.) Emphasize low dosage of ESA and avoid ESA if possible**
  - **4.) For dialysis patients, key is to be able to individualize therapy**

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