THE APROPRIATE USE OF ESA AGENTS IN THE TREATMENT AND PREVENTION OF CHRONIC KIDNEY DISEASE

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Raising hemoglobin levels to normal range 13-16gm/dl using accepted medicare exceptions 2000-2007.

Exceptions– coronary heart disease, cerebral vascular disease, peripheral vascular disease, congestive heart failure, and chronic obstructive pulmonary disease.

Pre-dialysis patients with stage 3 and stage 4 chronic kidney disease, and hemodialysis patients stage 5 chronic kidney disease.

When hemoglobin levels were raised to normal the results were dramatic. These patients walked much better, they walked with a spring in their step and moved more quickly. They were mentally much more alert. The non communicative, uninterested patients who slept most of the dialysis woke up, and carried on quite intelligent conversations. There exercise tolerance was more normal.

The contrast was equally dramatic in 6 different dialysis units where a total of 138 dialysis showed a dramatic improvement in quality of life compared to an equal number of patients from other nephrology practices maintained in the 10-12gm/dl hemoglobin range.

TABLE 1. Patient Characteristics

figure	age	initials	sex	BP+	BMI	SleepApne	COPD	CAD	CHF	Anemia	diab	Gout	DegJointD	ACE/ARB	B Block	Statin	Uprot	GFR
1	47	MC	F	yes	48	yes		yes		yes	yes				yes	yes	5820	46
2	48	AC	M	yes	26					yes	yes			ACE	yes		965	29
3	52	MR	F		34			CVA		yes							125	31
4	53	CR	F	yes	24					yes	yes	allopurinol		ACE/ARB	yes	yes	302	23
5	62	CM	F	yes	45					yes	yes	allopurinol		ARB	yes			24
6	62	JT	M	yes	32			yes	yes	yes	yes	allopurinol		ACE	yes	yes	86	21
7	64	RD	M	yes	35	yes	yes	yes		yes		allopurinol		ACE			548	30
8	64	HF	F	yes	36	yes	yes	yes		yes			nonsteroid	ACE	yes	yes	353	46
9	64	PS	M	yes	34	yes	yes	yes	NY3	yes		allopurinol	yes	ARB	yes	yes	0	18
10	65	AA	M	yes	27			yes	yes	yes	yes	allopurinol		ACE	yes	yes		36
11	66	HC	F	yes	24					yes				ACE	yes	yes	960	26
12	70	AP	F	yes	27			yes		yes		allopurinol			yes		461	35
13	70	AR	M	yes	29					yes		allopurinol	nonsteroid	ACE/ARB		yes	1958	57
14	70	BO	M	yes	28					yes		allopurinol		ACE/ARB	yes	yes	3479	51
15	70	CC	M	yes	21			yes		yes		allopurinol		ARB	yes	yes	4615	31
16	72	HD	M	yes	28			yes	yes	yes		allopurinol		ACE/ARB	yes	gemf		30
17	74	OT	M	yes	39	yes		yes		yes	yes		yes	ARB		yes	168	37
18	75	CC	F	yes	21			yes	yes	yes	yes	allopurinol	nonsteroid	ARB	yes		80	28
19	75	JN	M	yes	23					yes		allopurinol	yes	ACE		yes	1140	17
20	75	HT	M	yes	30					yes			RA				75	51
21	77	RW	M	yes	27					yes		allopurinol		ARB	yes	gemf	343	37
22	78	JF	F	yes	16		yes			yes			crest/SLE	ACE	yes		187	18
23	78	HW	F	yes	21					yes				ARB	yes		6	51
24	83	CG	M	yes	21			yes	yes	yes	yes	allopurinol		ARB	yes		24	24
25	88	MW	F	yes	23		yes	yes		yes			chrohns					37
26	89	WP	M	yes	26			yes	yes	yes					yes	yes		27

TABLE 2. Erythropoietin duration, dose every 2 weeks, and end points

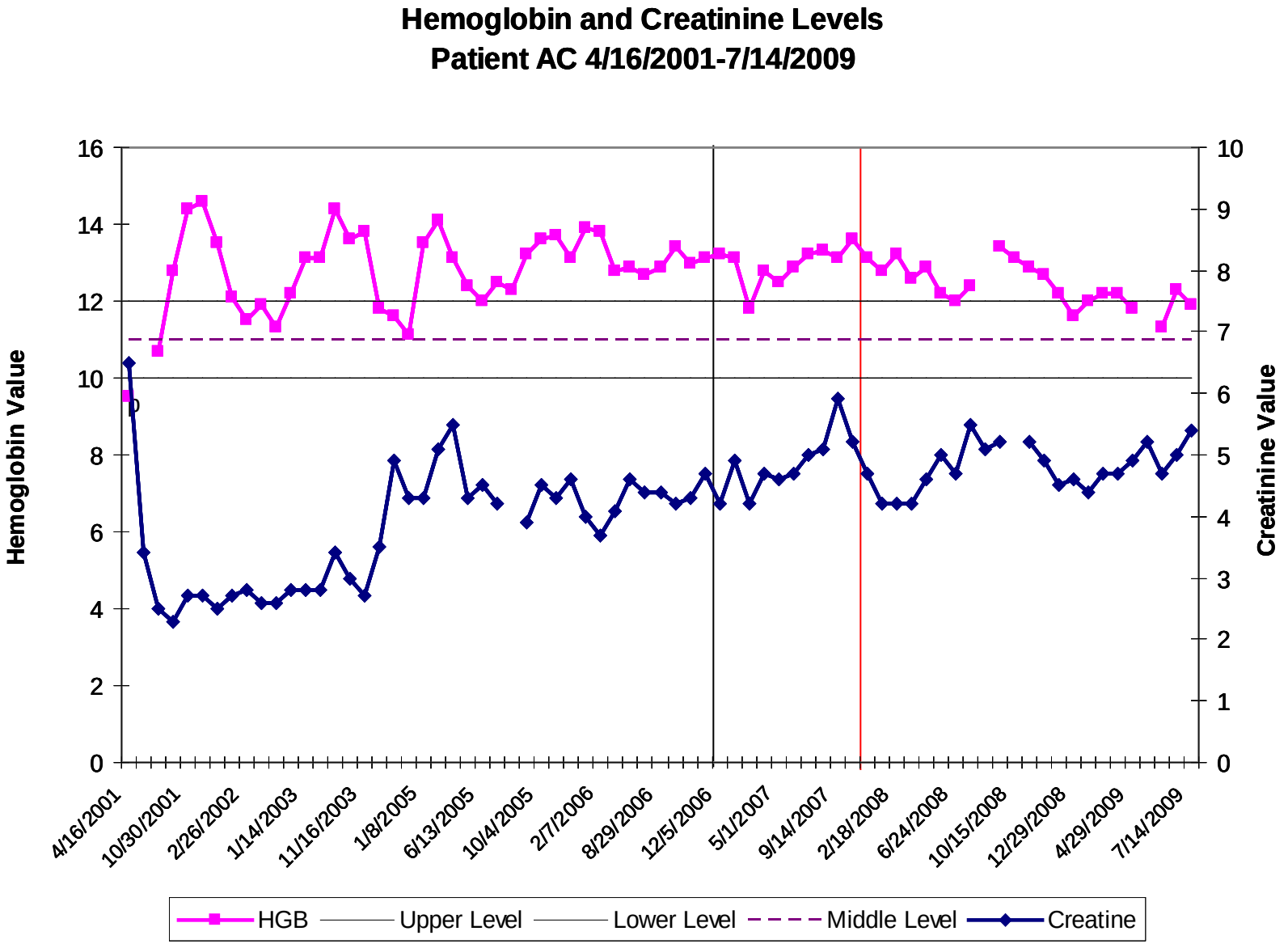
figure	age	initials	Disease	EPOstart	EPOend	event	06 Hb<13	07 Hb<12	Epo-years	Epo-dose	CauseE.P	average
1	47	MC	Diabetes	10/3/2001	9/29/2008	hemodialy	yes	yes	7	8-10,000	Hb<12	to endpoint
2	48	AC	Diabetes	4/18/2001				yes	8 5/12	8-10,000		
3	52	MR	CKD unknown	10/7/2002	5/17/2008	transplant		yes	5.5	10,000	Hb<12	age <60
4	53	CR	Diabetes	10/2/2002	4/17/2007	hemodialy	yes		4.5	6-8,000	diabetes	6.25 years
5	62	CM	Diabetes	7/3/2003	10/10/2007	hemodialy			4.25	40,000	Hb<12	
6	62	JT	Diabetes	6/13/2002	4/4/2007	chemo/Dialysis			4 5/6	40,000	chemo	
7	64	RD	Hypertension	8/12/2001	8/26/2009	death	yes	yes	8	14,000	Hb<12	
8	64	HF	Hypertension	8/27/2003					6	5,000		
9	64	PS	Hypertension	11/10/2003				yes	5.75	24,000		age 61-65
10	65	AA	Diabetes	5/19/2004	6/19/2009	hemodialy		yes	5	20,000	Hb<12	5.66 years
11	66	HC	Diabetes	1/21/2002			yes	yes	7.5	20,000		
12	70	AP	Hypertension	4/24/2001	7/15/2008	hemodialy	yes	yes	7.25	7,000	Hb<12	
13	70	AR	Hypertension	2/23/2001	9/21/2007	hemodialy	yes		6.5	20,000	Hb<12	
14	70	BO	FSGS	2/14/2002	9/1/2009	death		yes	7.5	20,000	debility	age 66-70
15	70	CC	Hypertension	7/3/2003	3/11/2008	death	yes		4 2/3	14,000	CABG	6.65 years
16	72	HD	Cardiomyopathy	5/16/2003	10/23/2008	death	yes	yes	5 5/12	10,000		
17	74	OT	Hypertension	11/11/2003			yes	yes	5.75	40,000		
18	75	CC	Diabetes	11/25/2003	5/4/2008	death			4.5	20,000	CADdebility	
19	75	JN	Wegeners	7/10/1996	1/20/2006	death			9.5	5,000	KneeSurg	age71-76
20	75	HT	Membranous	2/3/2004					5 7/12	10,000		6.10 years
21	77	RW	Nephrect Carc	6/18/2002			yes	yes	7.25	10,000		
22	78	JF	Nephrect Carc	8/20/2002					7	5,000		age 76-80
23	78	HW	Hypertension	8/27/2003				yes	6	10,000		6.75 years
24	83	CG	Diabetes	4/20/2000	11/16/2007	death			7 7/12	40,000	age	
25	88	MW	Hypertension	3/11/2003	1/19/2008	death			4 5/6	8-10,000	age	age 81-90
26	89	WP	Cardiomyopathy	12/14/2002	11/5/2007	death			4 11/12	20,000	age	5.83 years

As of September 2009

26 patients with stage 3 and 4 chronic kidney disease were treated to full correction of anemia with erythropoietin combined with aggressive treatment of other risk factors for periods of 4.5 to 9.5 years. With hemoglobin levels maintained in the normal range 12-16 gm these patients felt normal, functioned normally and renal function ceased to progress for periods of 4.5 to 9.5 yrs.

When hemoglobin levels fell into the 10-12 gm range renal function deteriorated with a rise in serum creatinine, reversible if Hgb levels were restored quickly to the normal range, but permanent if there was a substantial delay. When Hgb levels remained in the 10-12gm range for longer periods of time renal function declined progressively over 2 years to initiation of dialysis, or death from unresponsive cardiac failure.

Figure 2


Hemoglobin and Creatinine Levels
Patient AC 4/16/2001-7/14/2009
Hemoglobin Value
Creatinine Value
16
14
12
10
8
6
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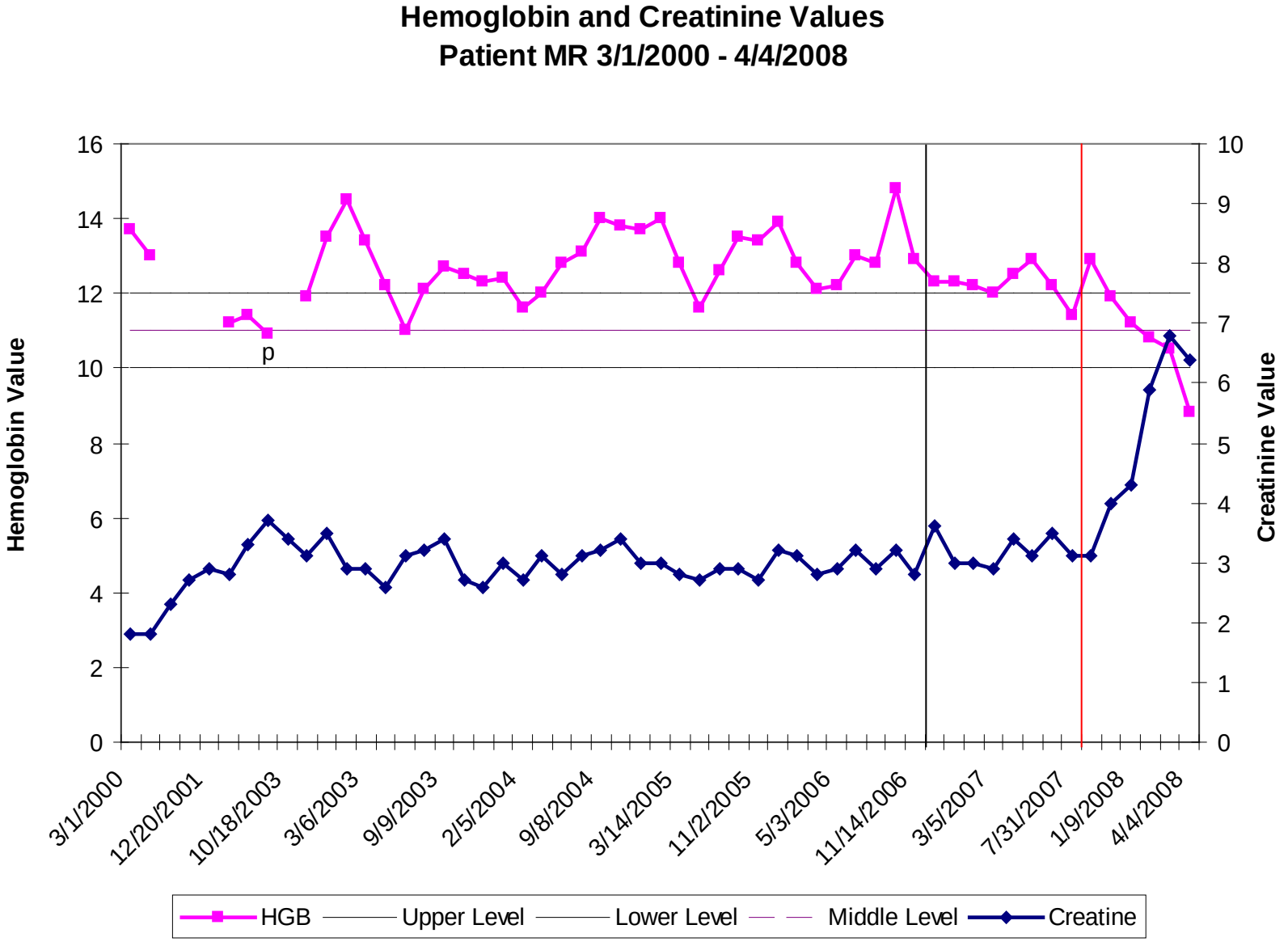
4/16/2001
10/30/2001
2/26/2002
1/14/2003
11/16/2003
1/8/2005
6/13/2005
10/4/2005
2/7/2006
8/29/2006
12/5/2006
5/1/2007
9/14/2007
2/18/2008
6/24/2008
10/15/2008
12/29/2008
4/29/2009
7/14/2009
HGB
Upper Level
Lower Level
Middle Level
Creatine

Figure 3


Hemoglobin and Creatinine Values
Patient MR 3/1/2000 - 4/4/2008
Hemoglobin Value
Creatinine Value
16
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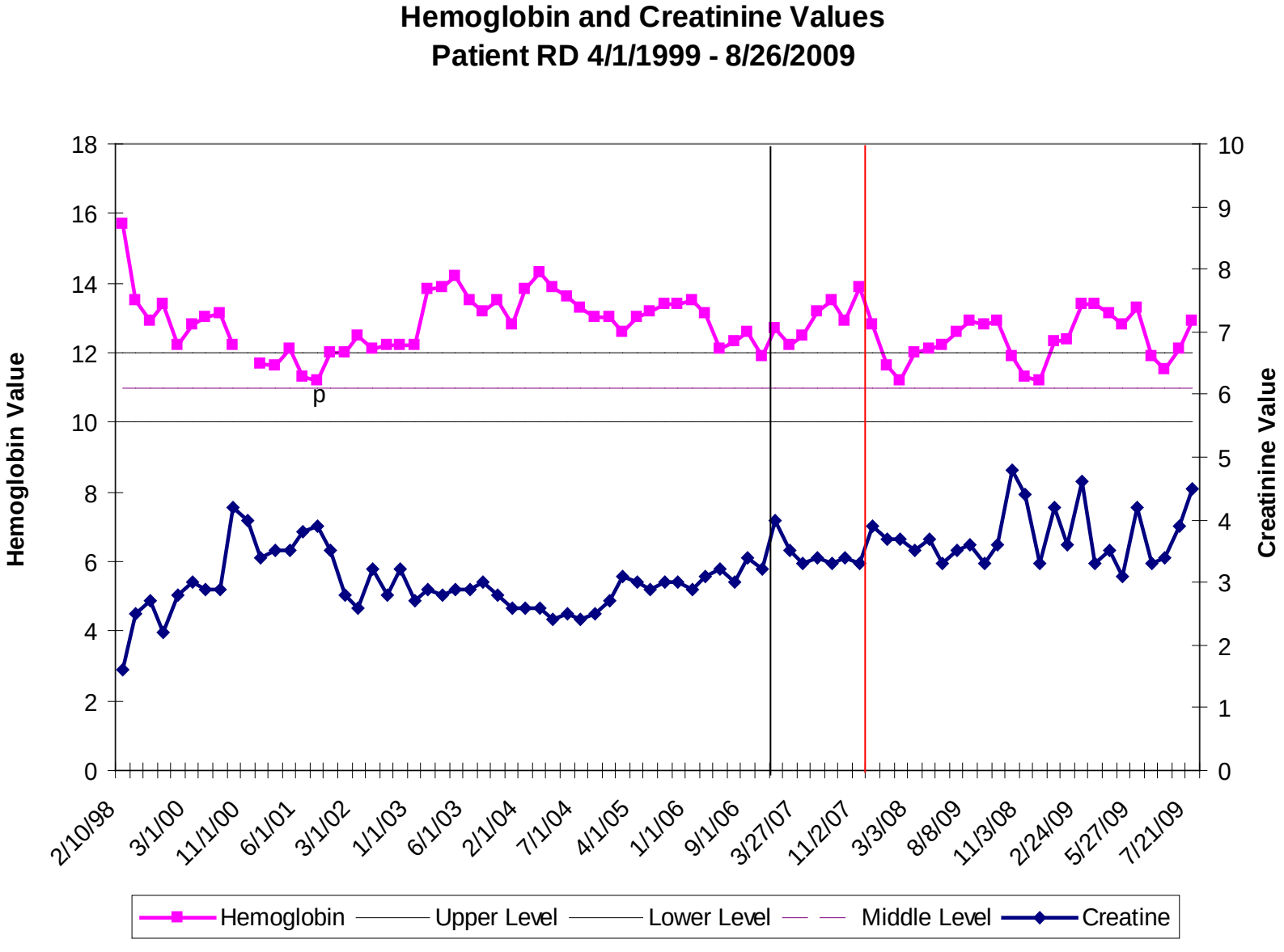
12/20/2001
10/18/2003
3/6/2003
9/9/2003
2/5/2004
9/8/2004
3/14/2005
11/2/2005
5/3/2006
11/14/2006
3/5/2007
7/31/2007
1/9/2008
4/4/2008
HGB
Upper Level
Lower Level
Middle Level
Creatine

Figure 7


Hemoglobin and Creatinine Values
Patient RD 4/1/1999 - 8/26/2009
Hemoglobin Value
Creatinine Value
18
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12
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8
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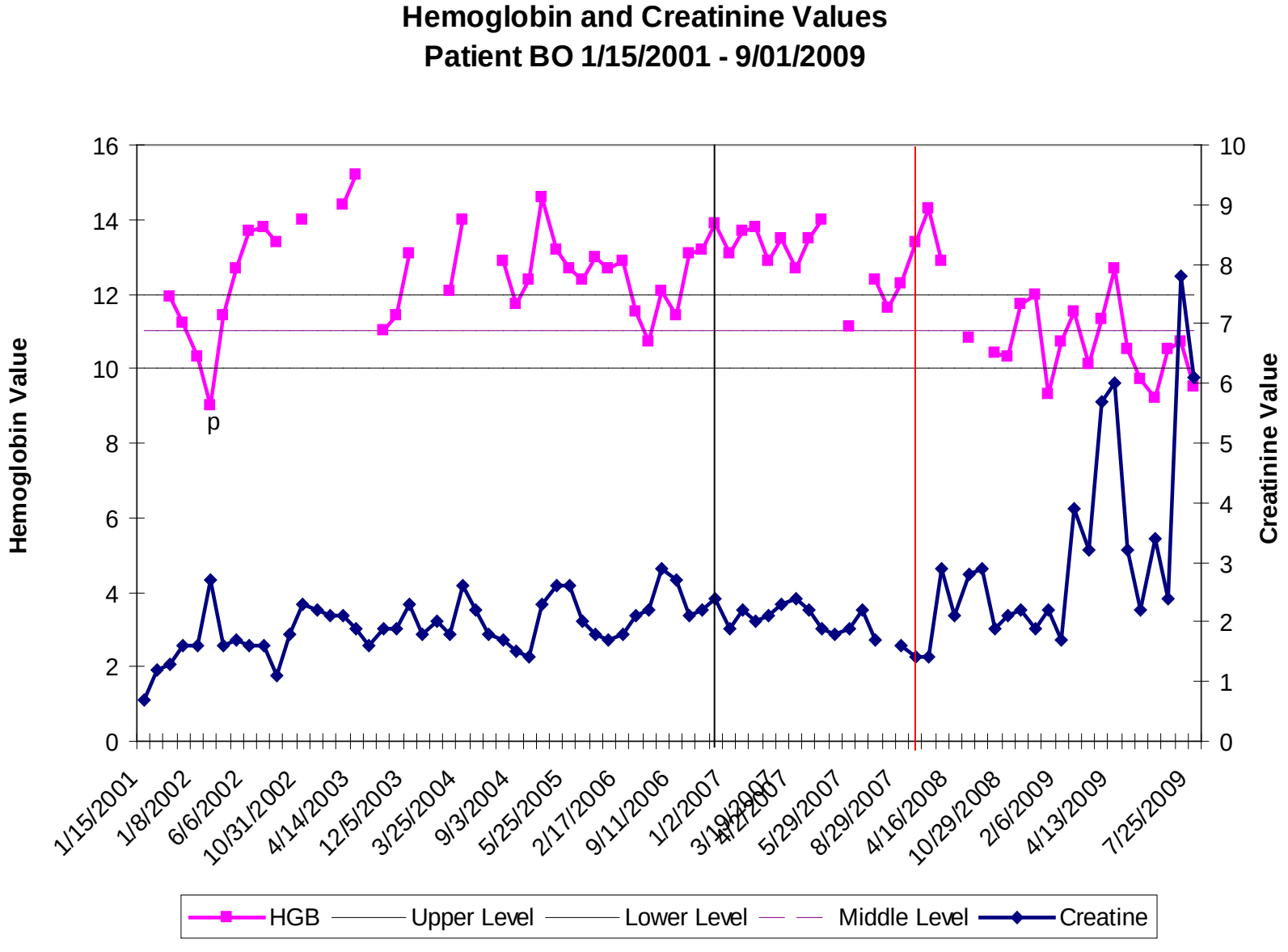
3/1/00
11/1/00
6/1/01
3/1/02
1/1/03
6/1/03
2/1/04
7/1/04
4/1/05
1/1/06
9/1/06
3/27/07
11/2/07
3/3/08
8/8/09
11/3/08
2/24/09
5/27/09
7/21/09
Hemoglobin
Upper Level
Lower Level
Middle Level
Creatine

Figure 14


Hemoglobin and Creatinine Values
Patient BO 1/15/2001 - 9/01/2009
Hemoglobin Value
Creatinine Value
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9
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7
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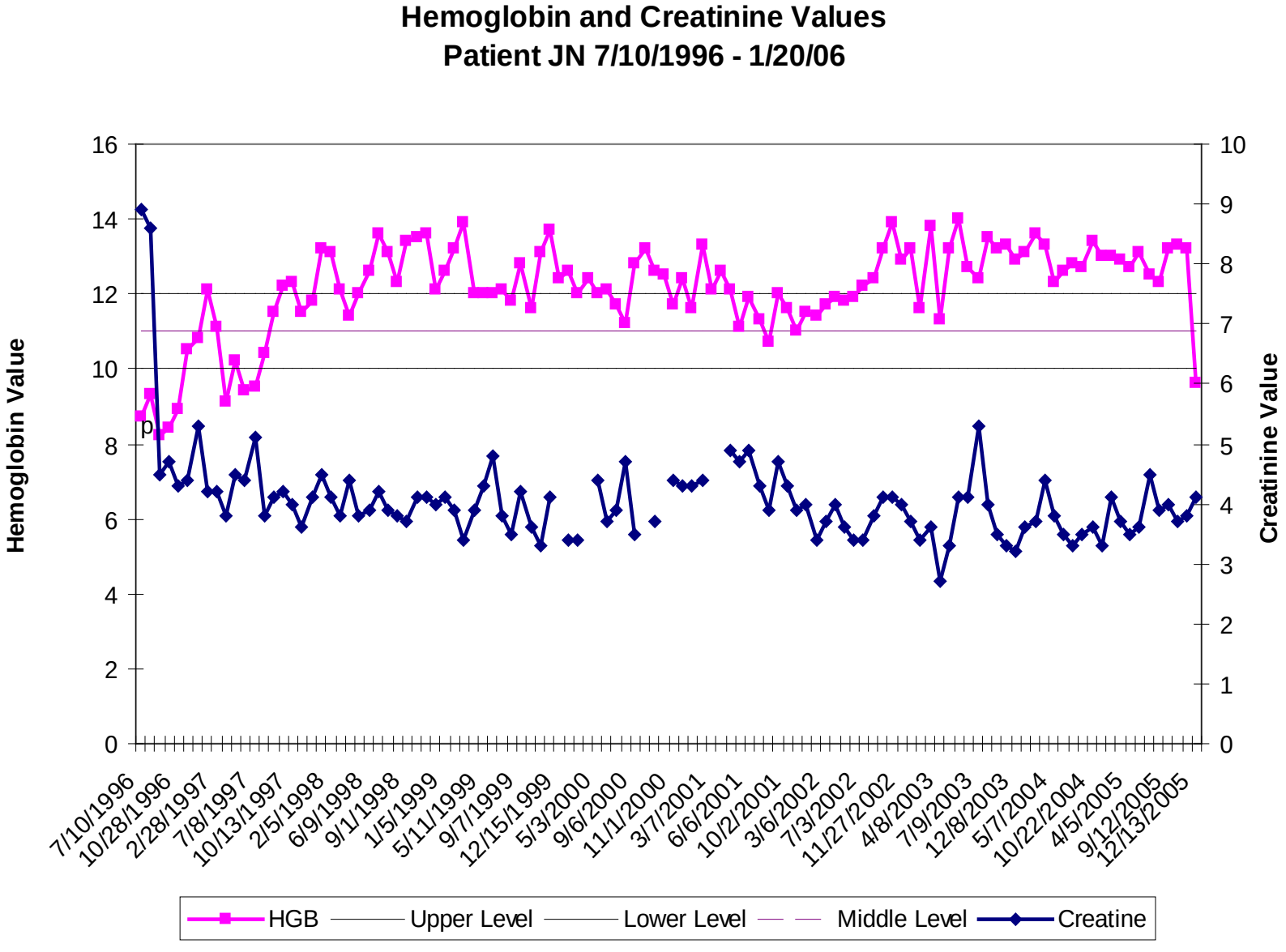
1/15/2001
1/8/2002
6/6/2002
10/31/2002
4/14/2003
12/5/2003
3/25/2004
9/3/2004
5/25/2005
2/17/2006
9/11/2006
1/2/2007
3/19/2007
4/2/2007
5/29/2007
8/29/2007
4/16/2008
10/29/2008
2/6/2009
4/13/2009
7/25/2009
HGB
Upper Level
Lower Level
Middle Level
Creatine

Figure 19


Hemoglobin and Creatinine Values
Patient JN 7/10/1996 - 1/20/06
Hemoglobin Value
Creatinine Value
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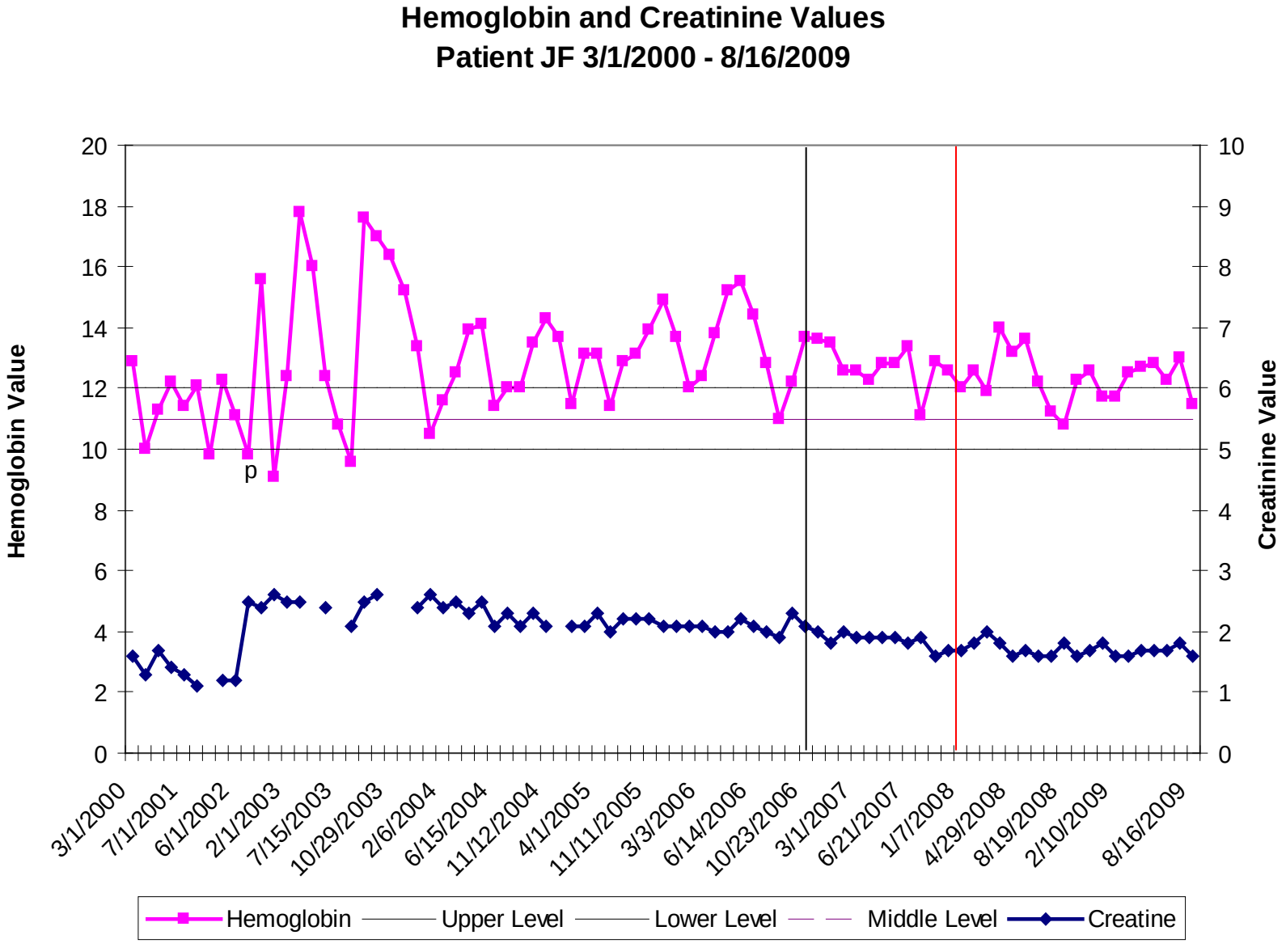
10/13/1997
2/5/1998
6/9/1998
9/1/1998
1/5/1999
5/11/1999
9/7/1999
12/15/1999
5/3/2000
9/6/2000
11/1/2000
3/7/2001
6/6/2001
10/2/2001
3/6/2002
7/3/2002
11/27/2002
4/8/2003
7/9/2003
12/8/2003
5/7/2004
10/22/2004
4/5/2005
9/12/2005
12/13/2005
HGB
Upper Level
Lower Level
Middle Level
Creatine

Figure 22


Hemoglobin and Creatinine Values
Patient JF 3/1/2000 - 8/16/2009
Hemoglobin Value
Creatinine Value
20
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10/23/2006
3/1/2007
6/21/2007
1/7/2008
4/29/2008
8/19/2008
2/10/2009
8/16/2009
Hemoglobin
Upper Level
Lower Level
Middle Level
Creatine

Table 8

Comparison of Baseline Hemoglobin and Erythropoietin Levels:
Delaying Correction of Anemia creates More Hypoxia, More Tissue Damage, and Greater Erythropoietin Resistance

Trials	Starting Hemoglobin	Erythropoietin Dose to achieve Hgb13.5gm	Q.O.L
ACORD all diabetic	11.9	3500units/week	improved
CREATE 31% diabetic	11.6	5000units/week	improved
CHOIR 47% diabetic	10.1	10,700units/week only 12.6gm	not improved

Prevention of chronic kidney disease is better than Cure and far more cost effective.

Treat with small doses of erythropoietin when Hemoglobin drops below 13.0 -13.5 gm/dl for postmenopausal women and 14.0-14.5 gm/dl for men before hypoxic tissue damage occurs.

Cost less than $1,500 X 30-40 years = $45,000-$60,000

Too little, too late. waiting for Hgb to reach 10.0 gm/dl then treating in range of 10-12.gm/dl after hypoxic cardiac and renal damage has occured

Cost of dialysis 5-6 years at $80,000 /year = $400,000-$480,000

Progression of chronic kidney disease.

Anemia, Smoking, Obesity, Hypertension and Cardiac Disease are all conditions that cause progression of chronic kidney disease.

They all individually and collectively in any combination have a profound effect on the delivery of oxygen to the tissues.

With increasing numbers of risk factors the risk for myocardial infarction and chronic kidney disease rise exponentially.

Yusuf S, Hawken S,et al'The INTERHEART study. Lancet 2004:364:937-952.

Foley RN, Murray AM, et al Chronic Kidney Disease and the risk for cardiovascular disease ...1998 to 1999. J Am Soc Nephrol 2005;16:489-495

Table 3

Classification of Hypoxia

Hypoxic Hypoxia po2 reduced	COPD, Obesity
Anemic Hypoxia reduced hgb.	Smoking, Anemia
Stagnant Hypoxia decreased delivery	Hypertension, Cardiac Disease non-steroidal anti inflammatory agents
Histotoxic Hypoxia unable to utilize or toxic	Diabetes Mellitus carnitine deficiency IV contrast agents

Hypoxia/anaerobic respiration/ increased cell death/more phagocytosis

Anemia
Smoking
Stress
Hypertension
Obesity/Sleep Apnea
Cardiac Disease
Diabetes Mellitus

all collectively
increase hypoxia,
all collectively
increase TNFa
IL-6 and CRP.

Table 4

Hypoxia	Oxidative Stress
Anemia Smoking Stress Hypertension Obesity/ Sleep Apnea Cardiac Disease Diabetes Mellitus	All associated with increased TNFa, IL-6, and CRP. = phagocytic response to increased cell death from anaerobic respiration on top of usual daily replacement of old cells

Table 5a

Erythropoietin resistance 1

Total Hypoxia = combined effect of all risk factors

= anaerobic respiration,

= more cells dying increasing phagocytosis

= increasing TNFa, IL-6 and CRP levels.

= level of erythropoietin resistence

= dose of erythropoietin to

raise hemoglobin to 13.5gm

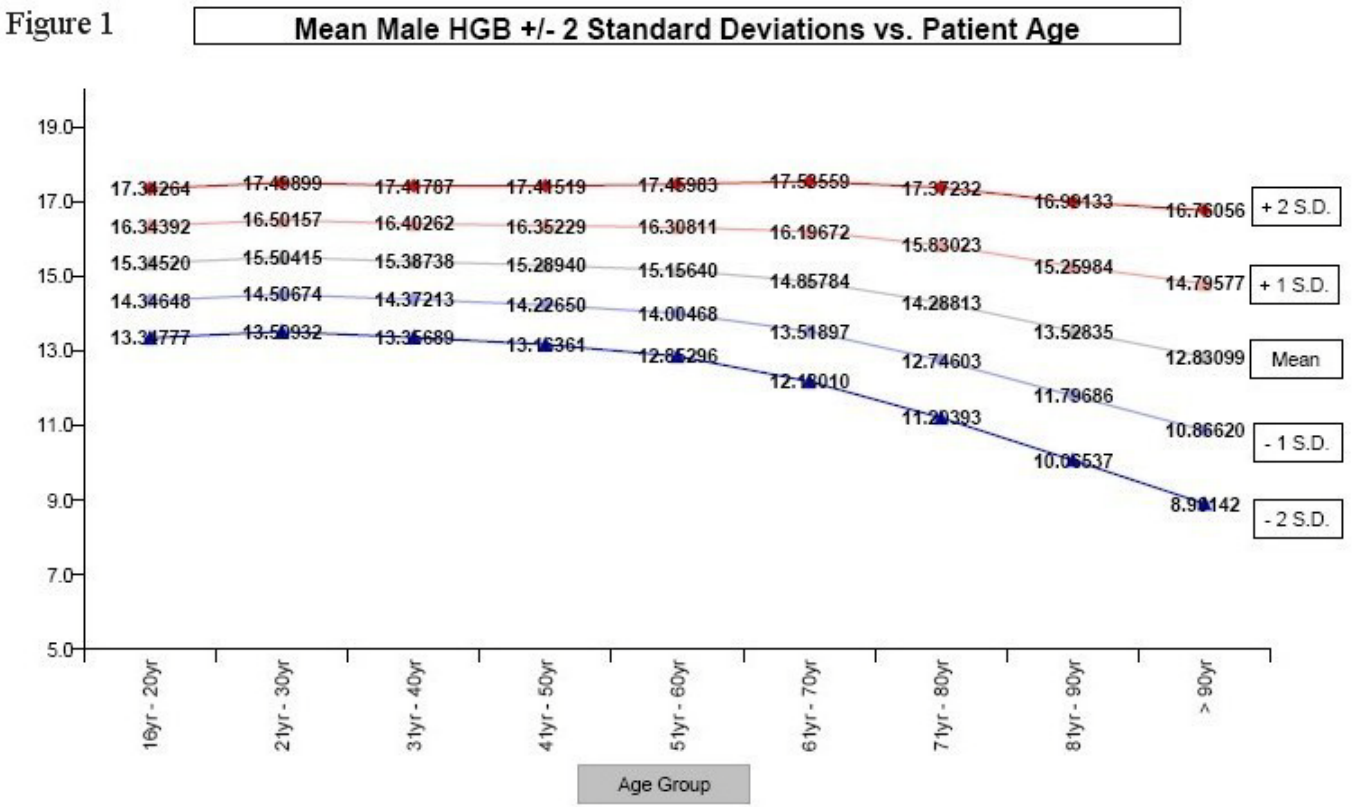
Table 5b

Erythropoietin resistance 2

The greater the degree of hypoxia
the greater the rate of anaerobic respiration.
the greater the level of tissue destruction.
the higher the levels of TNFa, IL-6, and CRP.
the sicker the patient.
the closer the patient is to death
the higher the erythropoietin dose needed
for improved and prolonged survival

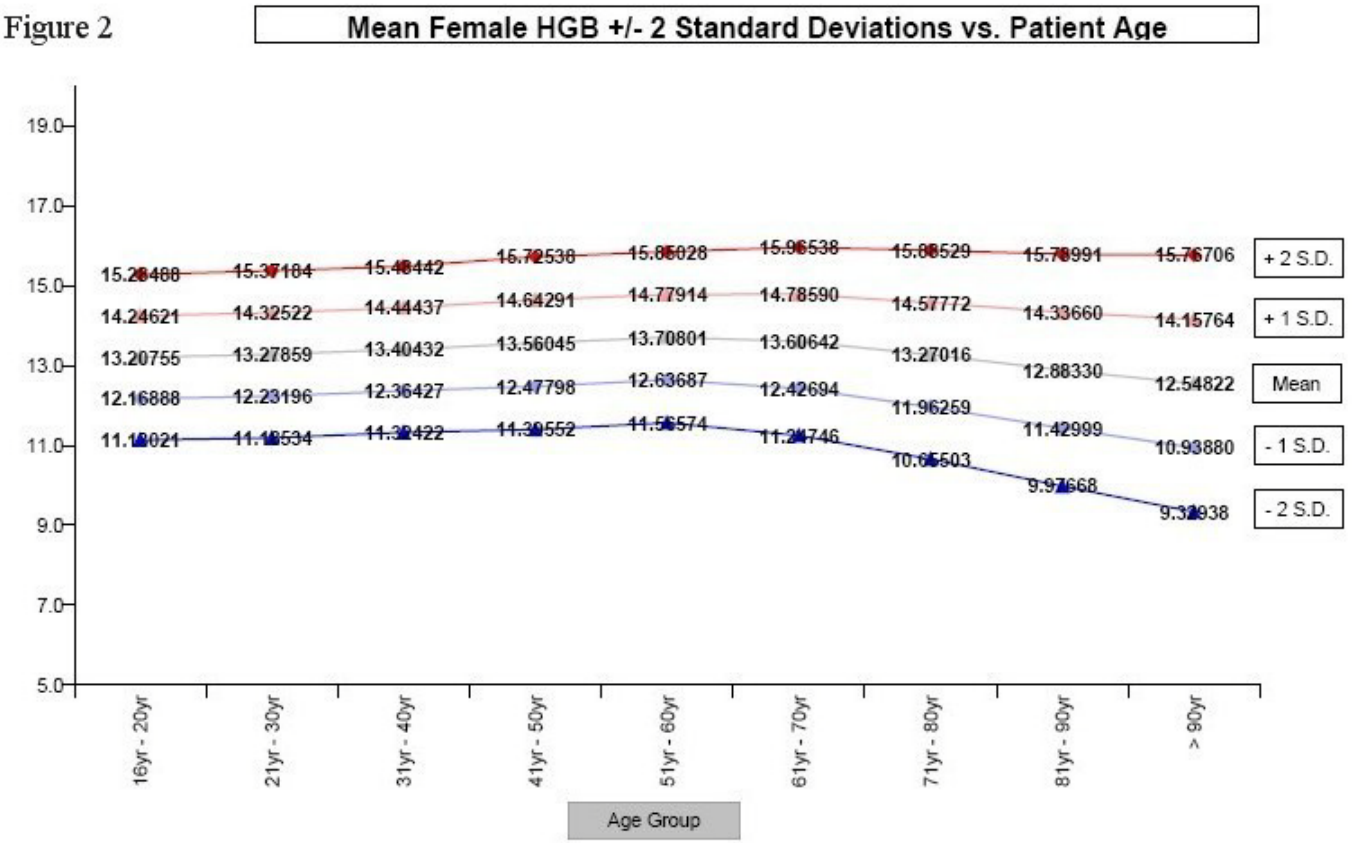
Hemoglobin Results, 112,756 Male Patients > 16yrs. 01/01/1998 to 02/23/2009

Figure 1



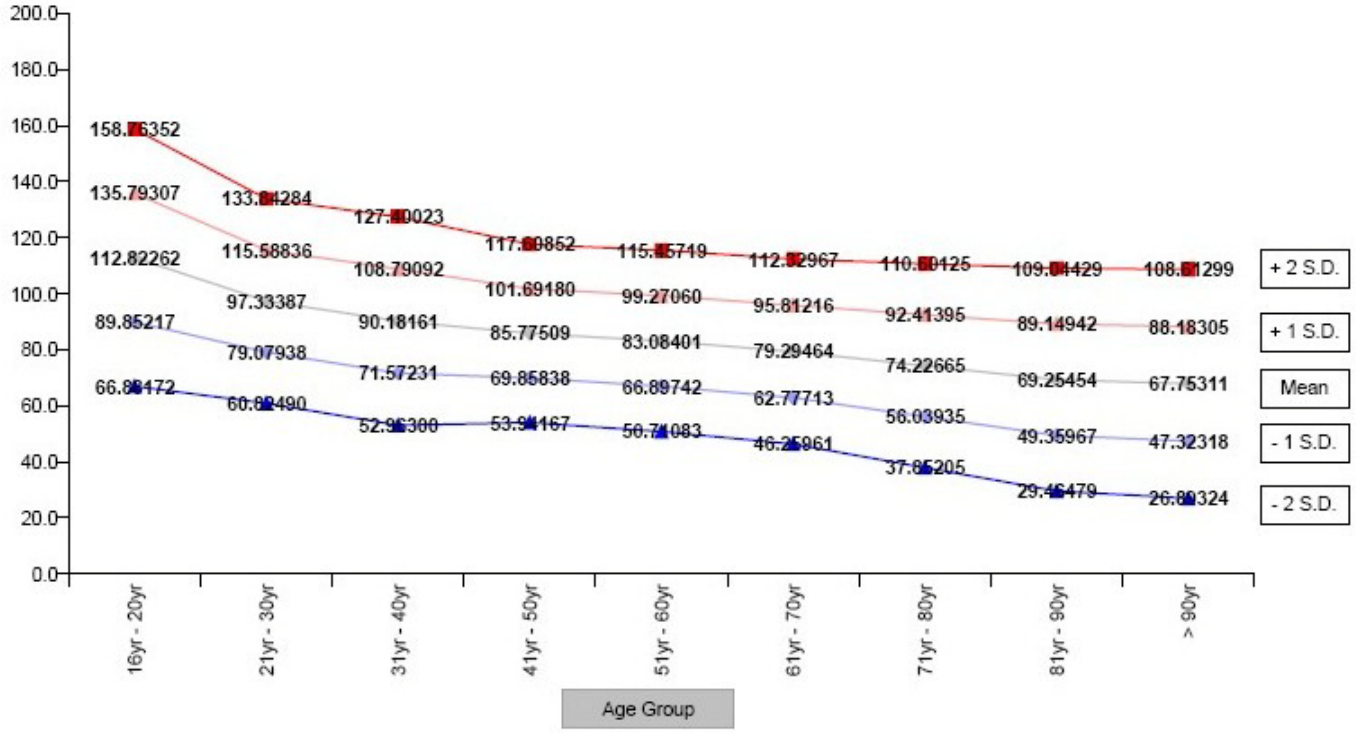
Hemoglobin Results, 174,438 Female Patients >16yrs
01/01/1998 to 02/23/2009

Figure 2



Gomerular Filtration Rates, 75,963 Male Patients > 16yrs 01/01/1998 to 02/23/2009

Figure 3 **Mean Male Non African American GFR +/- 2 Standard Deviations vs. Patient Age**



Glomerular Filtration Rates, 114,864 Female Patients >16 yrs. 01/01/1998 to 02/23/2009,

Figure 4

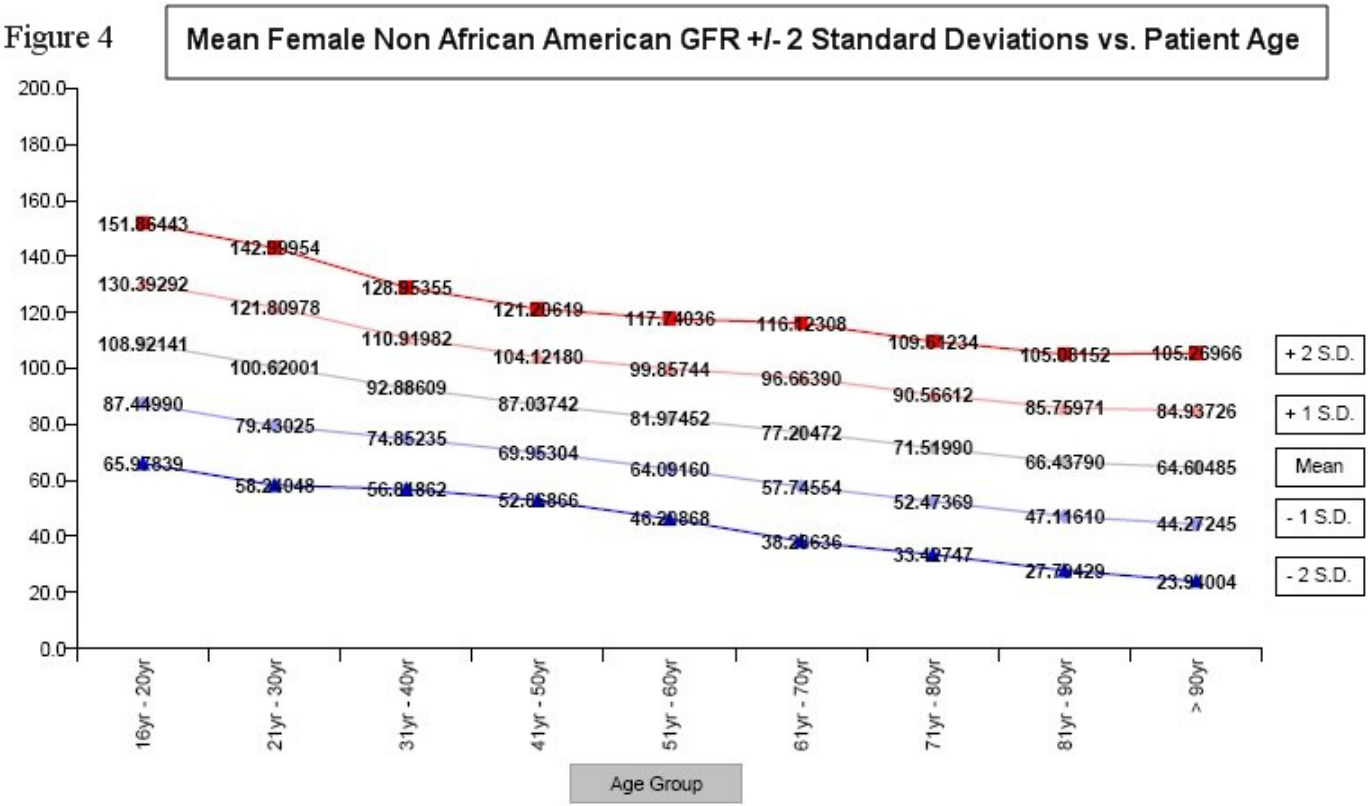


Table 6

Average Hemoglobin levels and erythropoietin doses in 138 hemodialysis patients in early 2004 using accepted medical justifications for payment.

Hemoglobin levels	Number of patients	Erythropoietin dose Average dose	Erythropoietin range = EPO resistance
15.1-16.0gm	9	101 units/kg	13 – 314 units/kg
14.1-15.0gm	29	97 units/kg	16 – 373 units/kg
13.1-14.0gm	50	101 units/kg	7 – 458 units/kg
12.1-13.0gm	32	104 units/kg	33 – 353 units/kg
11.1-12.0gm	18	172 units/kg	15 – 462 units/kg

Common Medical Events Seen in Patients with Chronic Kidney Disease

Anemia less than 13gm/dl causes

Angina in men, and intractable CHF.

Anemia less than 12gm/dl causes

Angina, and CHF in women

Myocardial infarction in men

Ischemic limbs, gangrene and amputations, particularly in diabetics.

Transient Ischemic Attacks and Strokes

Anemia less than 11gm/dl causes

all of the above, generally ending in death.

US Erythropoietin Stimulating Agent Trials
"Too Little, Too Late."

NHCT Trial	Hgb 10.0 gm
CHOIR Trial	Hgb 10.0 gm
TREAT Trial	Hgb 10.4 gm

"Insanity is doing the same thing over and over again and expecting different results." Albert Einstein

Figure 5

FDA -- Mortality v Average Hemoglobin Levels NHCT and CHOIR Trials.

Unger EF, www.fda/ohrms/dockets/ac/cder07.htm#CardiovascularRenal scroll to Sept 11th 2007, click on FDA briefing material (pdf); 24-54

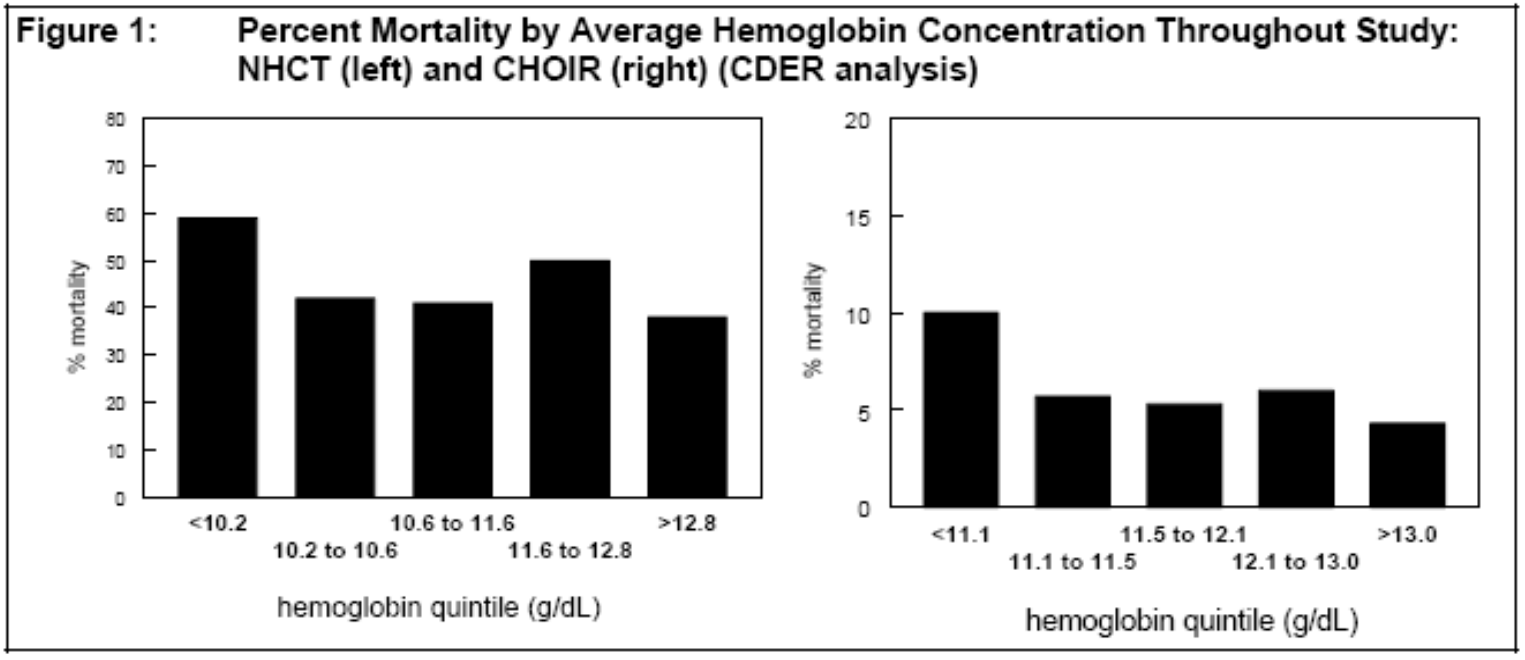


Figure 6a

FDA – NHCT Study: Serious Adverse Events v Dynamic Hemoglobin Levels

Unger EF, www.fda/dockets/ac/cder07.htm#CardiovascularRenal scroll to Sept 11th 2007 , click on FDA briefing material (pdf); 24-54

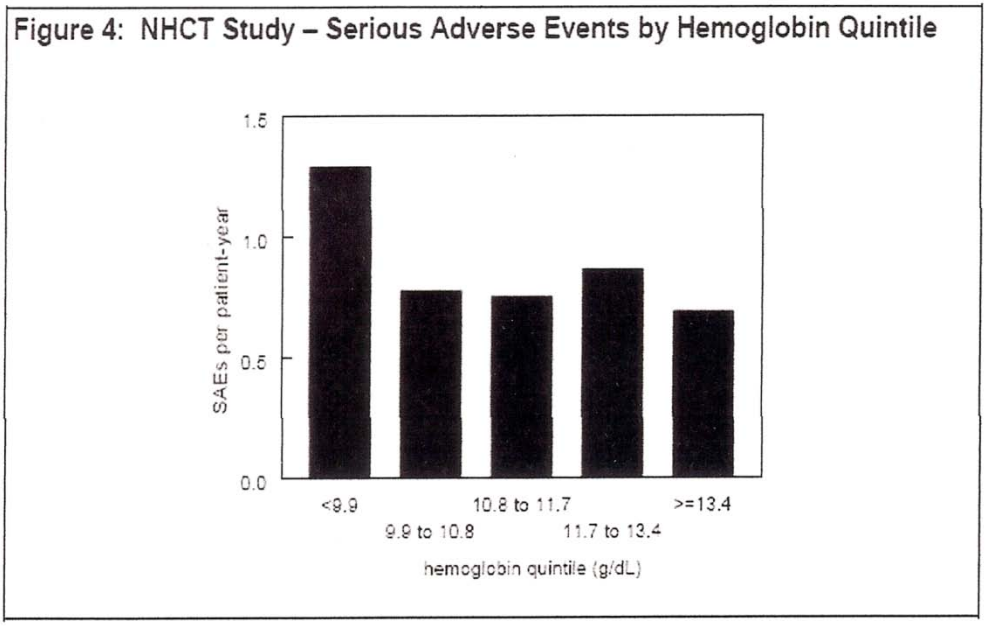


Figure 6b

FDA – CHOIR Study: Serious Adverse Events v Dynamic Hemoglobin Levels

Unger EF, www.fda/ohrms/dockets/ac/cder07.htm#CardiovascularRenal scroll to Sept 11th 2007, click on FDA briefing material (pdf); 24-54

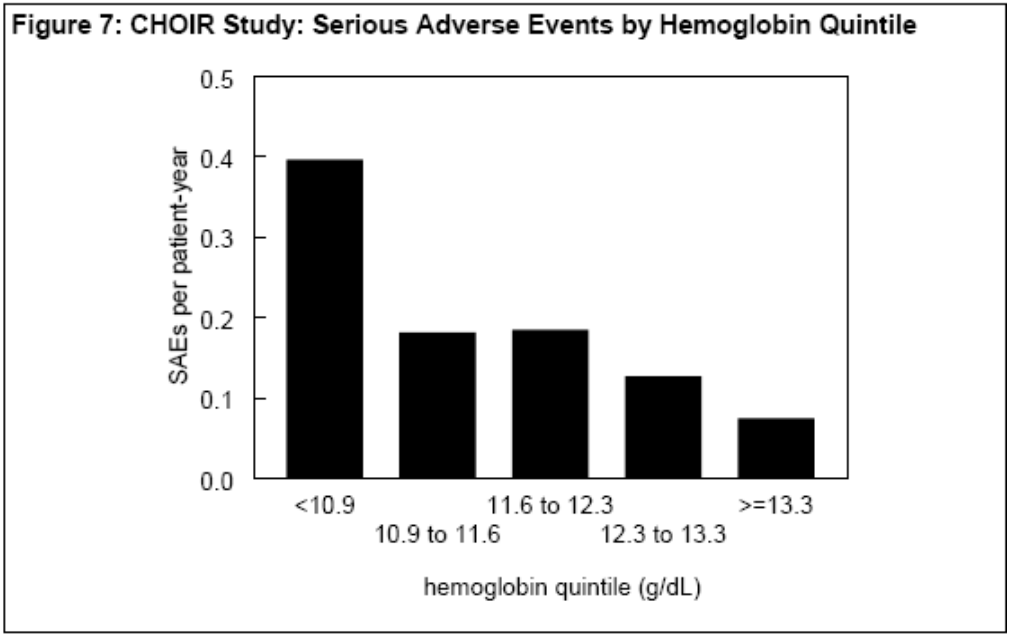
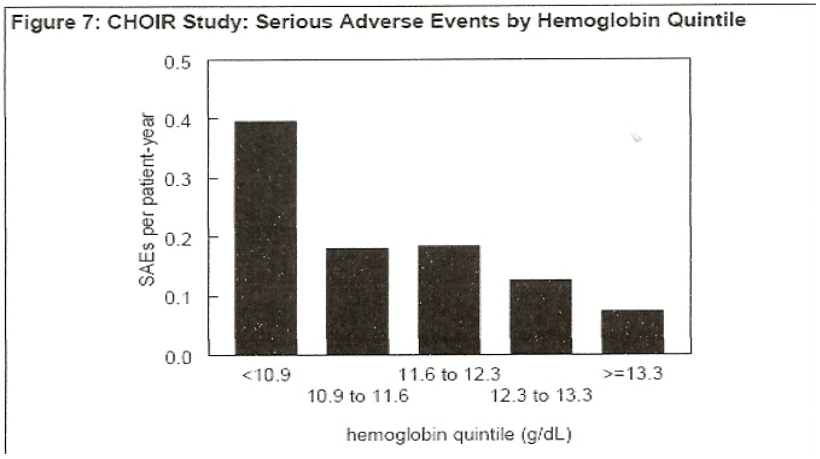


Figure 7

CHOIR Trial: Serious adverse events and death rates by hemoglobin quintiles.

Unger EF, www.fda/ohrms/dockets/ac/cder07.htm#CardiovascularRenal scroll to Sept 11th 2007, click on FDA briefing material (pdf); 24-54



Lowest event rate in 281 people in Quintile with Hgb >13.3gm

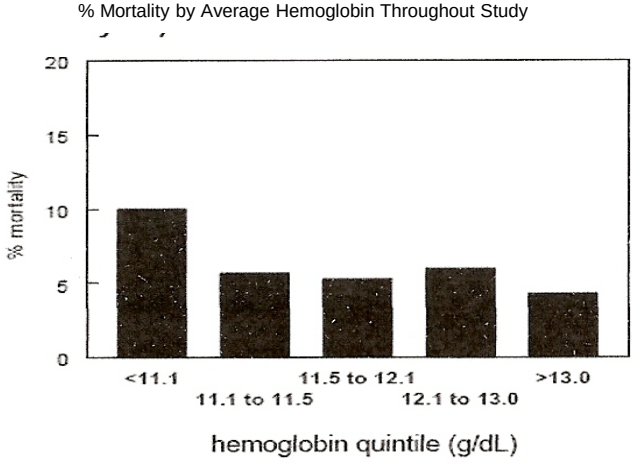
Quintile 12.3-13.3gm 2x events

Quintile 11.6-12.3gm 3x events

Quintile <10.9 gm 6x events

Lowest death rate in 281 people in quintile with Hgb >13.0 gm.

Lowest Quintile Hgb <11.1gm has Death rate 2.5 times higher.



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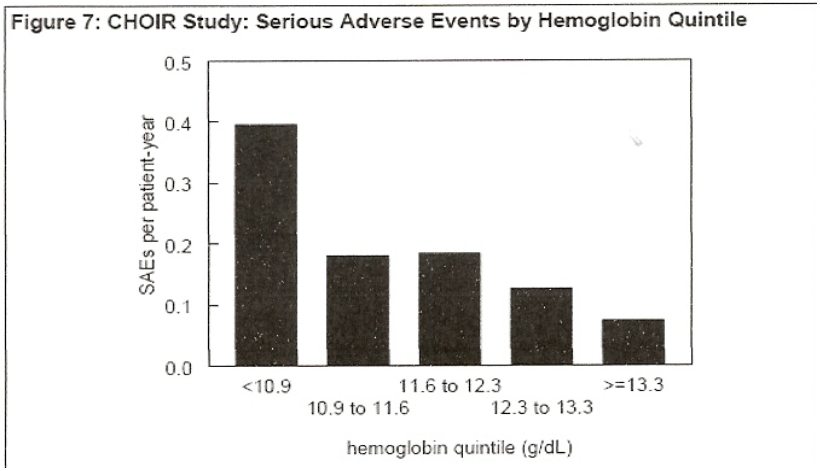
all of the above, generally ending in death.

Figure 8

CHOIR Trial: The truth, a controlled trial advocating normal hemoglobin levels.



Lowest event rate in 281 people in Quintile with Hgb >13.3gm

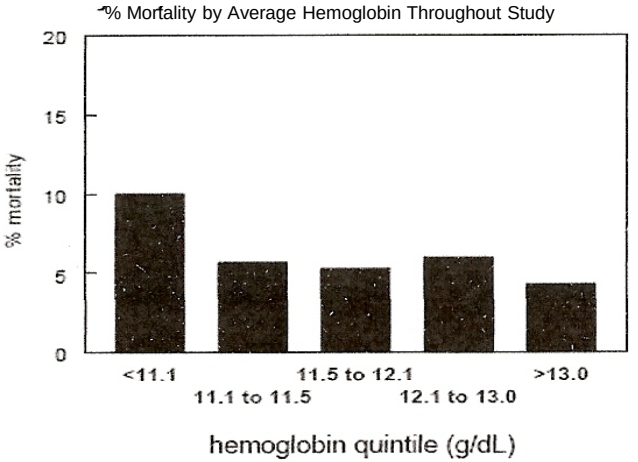
Quintile 12.3-13.3gm 2x events

Quintile 11.6-12.3gm 3x events

Quintile <10.9 gm 6x events

Lowest death rate in 281 people in quintile with Hgb >13.0 gm.

Lowest Quintile Hgb <11.1gm has Death rate 2.5 times higher.



Do not need to wait for more trials

Halting the Progression of Chronic Kidney Disease.

- Stopping smoking
- Treating blood pressure to less than 130/70, 120/70 if Proteinuria.
- Treating diabetes to HbA1c < 7.0, preferably <6.5
- Treating obesity with weight reduction, diet and exercise and aggressively looking for sleep apnea a very frequent association.
- Treating sleep apnea with Continuous Positive Airway Pressure, CPAP and/or Oxygen.
- Avoid medications with nephrotoxic tendencies – non-steroidal anti-inflammatory medications and IV contrast agents
- Treating with an ACE inhibitor and/or Angiotensin Receptor Blocker, or both to inhibit the Renin Angiotensin Aldosterone Axis.
- Restoring Hemoglobin levels to Normal 13.5-16 gm/dl with ESA’s.