

# Erythropoiesis-Stimulating Agent (ESA) Therapy in Chronic Renal Failure (CRF)

Joint Meeting Between the  
Cardiovascular and Renal Drugs &  
Drug Safety and Risk Management  
Advisory Committees

11 September 2007

# Presentation Outline

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## **TREAT**

**Marc Pfeffer, MD, PhD**

Dzau Professor of Medicine, Harvard Medical School,  
Cardiovascular Division, Brigham and Women's Hospital

## **Introduction**

**Paul Eisenberg, MD, MPH, FACC**

Global Regulatory Affairs & Safety, Amgen Inc

## **Clinical Perspective**

**Allen R. Nissenson, MD, FACP, FASN**

Professor of Medicine, Associate Dean, Director,  
Dialysis Program, David Geffen School of Medicine, UCLA

## **Benefit/Risk**

**Preston Klassen, MD, MHS**

Global Development, Amgen Inc

## **Risk Management**

**Paul Eisenberg, MD, MPH, FACC**

Global Regulatory Affairs & Safety, Amgen Inc

# Amgen and J&JPRD Guests

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<b>Fredric Finkelstein, MD</b>	<b>Chief of Nephrology, Hospital of St. Raphael Clinical Professor of Medicine, Yale University School of Medicine</b>
<b>Patrick Marquis, MD, MBA</b>	<b>Global Director, Mapi Values</b>
<b>Kenneth J. Rothman, DrPH</b>	<b>Vice President of Epidemiology Research, RTI Health Solutions</b>
<b>Donald B. Rubin, PhD</b>	<b>John L. Loeb Professor of Statistics, Harvard University</b>
<b>Robert J. Rubin, MD</b>	<b>Clinical Professor of Medicine, Georgetown University</b>
<b>Theodore Steinman, MD</b>	<b>Professor of Medicine, Harvard Medical School, Nephrologist, Beth Israel Deaconess Medical Center</b>
<b>John E. Ware, Jr., PhD</b>	<b>Research Professor, Tufts School of Medicine, Senior Scientist and CEO, QualityMetric Incorporated</b>
<b>James B. Young, MD</b>	<b>Professor and Chairman, Division of Medicine, Cleveland Clinic Foundation</b>

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# Randomized Trials of ESAs in CRF

Marc A. Pfeffer MD, PhD

Dzau Professor of Medicine

Harvard Medical School, Cardiovascular  
Division, Brigham and Women's Hospital

Chair, TREAT Executive Committee

# TREAT: Executive Committee and DSMC

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## Executive Committee

- E Burdmann
- M Cooper
- KU Eckhardt
- AS Levey
- J McGill
- J McMurray
- P Parfrey
- HH Parving
- M Pfeffer (Chair)
- G Remuzzi
- A Singh
- S Solomon
- R Toto
- D de Zeeuw

## DSMC

- G Chertow
- D DeMets (Chair, SDAC)
- E Frohlich
- C Hennekens (Chair)
- P O'Brien
- J Rouleau

# ESA RCTs in CRF

		<b>CREATE</b>	<b>CHOIR</b>	<b>TREAT</b>
<b>Design</b>		Randomized, open-label	Randomized, open-label	Randomized, double-blind, placebo-controlled
<b>Agent</b>		NeoRecormon® (epoetin beta)	PROCRIT® (Epoetin alfa)	Aranesp® (darbepoetin alfa)
<b>Hb Target(s), g/dL</b>	<b>Arm 1</b>	13.0-15.0	13.5	13.0
	<b>Arm 2</b>	10.5-11.5*	11.3	Placebo; rescue for Hb <9.0
<b>N</b>		603	1432	(planned ~4000)
<b>Primary Composite Endpoint</b>		All-cause mortality or CV morbidity: MI, HF, stroke, TIA, angina, arrhythmia or PVD complications	All-cause mortality or CV morbidity: MI, Stroke, HF hospitalization (without RRT)	All-cause mortality or CV morbidity: MI, Stroke, HF requiring medical attention, Myocardial Ischemia
<b>No. of Endpoints</b>		105	222	Projected: 1203
<b>Censor at RRT</b>		No	Yes	No

\*Treatment starts when Hb <10.5 g/dL

# TREAT: Trial to Reduce Cardiovascular Events with Aranesp<sup>®</sup> (Darbepoetin alfa) Therapy

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## Hypothesis:

Treatment of anemia with Aranesp<sup>®</sup> reduces the risk of mortality and nonfatal cardiovascular events (stroke, HF requiring medical attention, MI, or myocardial ischemia) in patients with CKD and type 2 diabetes

### Study Population

- Hb  $\leq$  11 g/dL
- eGFR 20-60 mL/min/1.73m<sup>2</sup>
- Type 2 DM

N = 2000      Aranesp<sup>®</sup> Group (Target Hemoglobin 13 g/dL)

Design – randomized (1:1), double-blind, controlled

N = 2000      Placebo (rescue if Hb < 9 g/dL)

Event-driven: 1203 patients with events

# CHOIR Results

	Number of Events		HR	P-value
	High Hb N=715	Low Hb N=717		
Primary Endpoint	125	97	1.34 (1.03, 1.74)	0.03
KM—3 yr event rate	29.5%	24.9%		
Death	52	36	1.48 (0.97, 2.27)	0.07
CHF hospitalization (without RRT)	64	47	1.41 (0.97, 2.05)	0.07
Stroke	12	12	1.01 (0.45, 2.25)	0.98
MI	18	20	0.92 (0.48, 1.73)	0.78

# TREAT Response to CHOIR

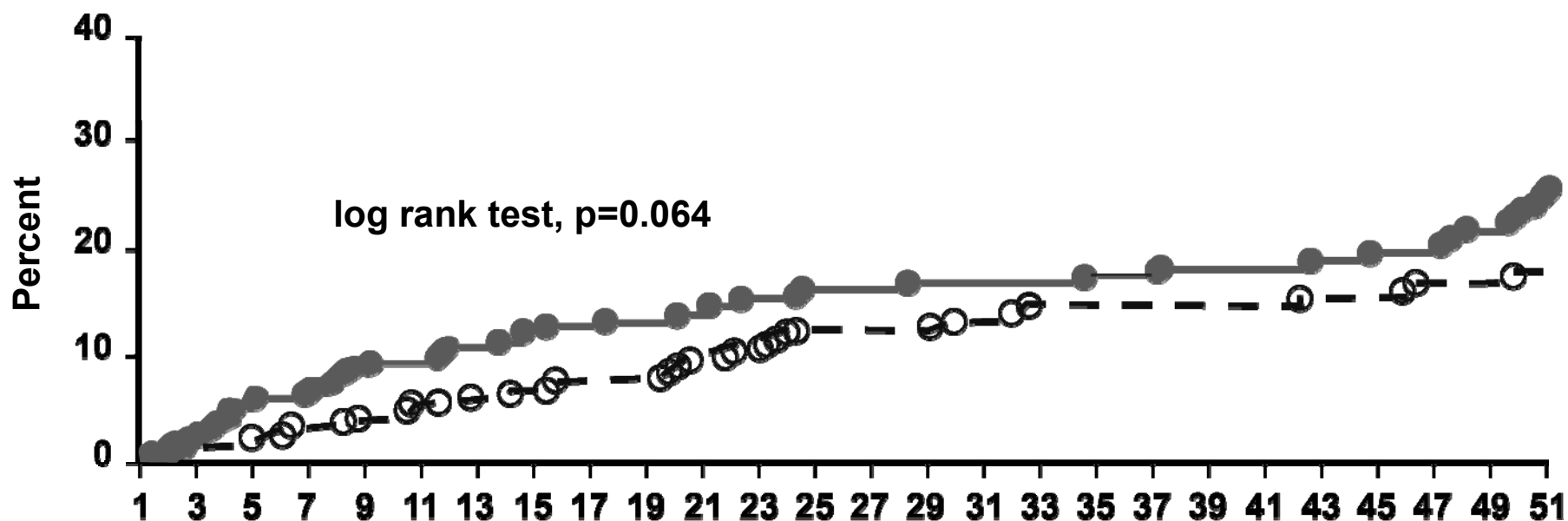
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- **Preliminary CHOIR data released April 2006**
  - **DSMC and sites updated May 2006**
  - **Informed Consent updated June 2006**
- **CHOIR data published in NEJM November 2006**
  - **DSMC and sites updated November 2006**
- **US Aranesp<sup>®</sup> label changed March 9th, 2007**
  - **Executive Committee briefed sites and DSMC on US label changes**
  - **Informed Consent updated**
- **In May 2007, Executive Committee requested that the DSMC adopt a very conservative stopping rule for harm (one sided  $p < 0.05$  at any time)**
- **On July 18th, 2007 the DSMC met and found no cogent reasons to recommend alteration or termination of TREAT**
- **It can be inferred that the HR for harm did not exceed 1.16**

# Phase 2 HF Results Suggest Improved Outcome with Darbepoetin alfa Treatment Targeted to Normalize Hb

Kaplan-Meier Plot of All-cause Mortality or First HF Hospitalization (as Adjudicated)

○ Darbepoetin alfa (N=266) ● Placebo (N=209)

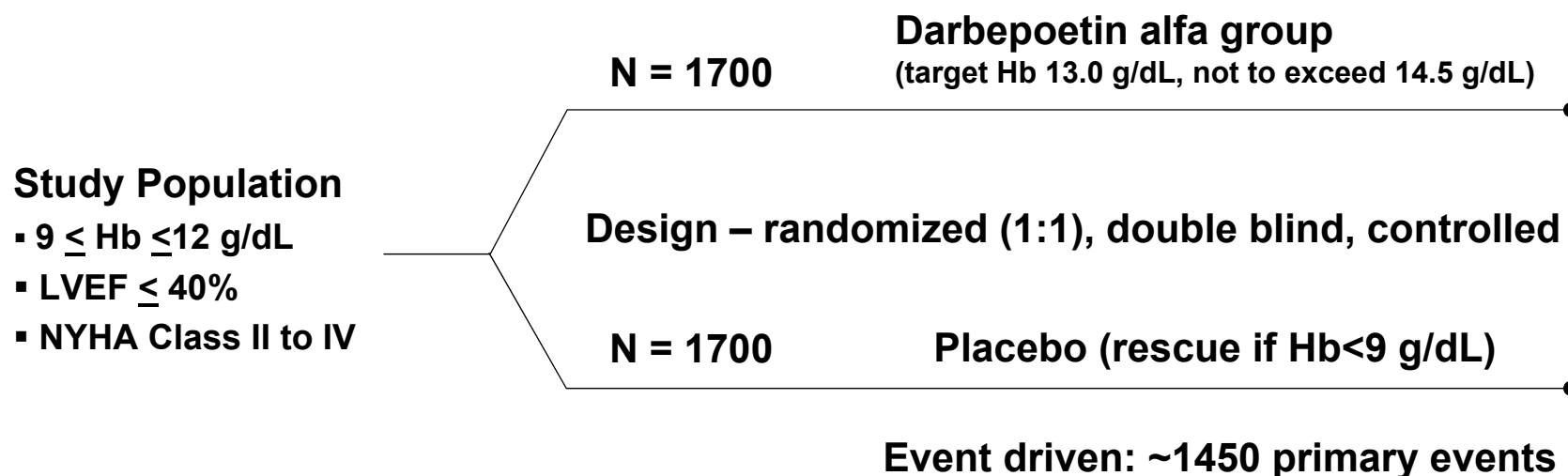


Outcomes Measures	Hazard Ratio (95% CI)
Composite morbidity & mortality	0.67 (0.44, 1.03)
All-cause mortality	0.76 (0.39, 1.48)
HF hospitalization	0.66 (0.40, 1.07)

# RED-HF Trial Study Design

## Hypothesis:

Treatment with darbepoetin alfa in subjects with symptomatic left ventricular systolic dysfunction and anemia decreases the risk of all-cause mortality or hospital admission for worsening HF



## Primary Endpoint\*

- Time to death from any cause or first hospital admission for worsening HF, whichever is first

\*Endpoint events are adjudicated by an independent clinical endpoint committee

# Total Subject Exposure and Endpoints in TREAT Exceed CHOIR

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<b>Study</b>	<b>N</b>	<b>Total (Patient years)</b>	<b>Events</b>
<b>CREATE</b>	<b>603</b>	<b>1763</b>	<b>105</b>
<b>CHOIR</b>	<b>1432</b>	<b>1943</b>	<b>222</b>
<b>TREAT</b>	<b>3789*</b>	<b>4920*</b>	<b>514*</b> <b>(1203 projected)</b>

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\*As of 1 Sep 07

# Importance of TREAT

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- **TREAT addresses the proper question**
  - Hypothesis even more important than when we started
- **Appropriate (well-treated) patient population**
- **Enrollment nearly complete (largest sample size)**
- **High compliance**
- **High follow-up**
- **Event rates are on track (largest number of adjudicated CV endpoints)**

**Uncertainty can only be addressed by robust RCT data**

# Summary

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- **TREAT and RED-HF will provide a sufficient totality of evidence on which to base the most rational judgments for individual patients and the health of the general public**
- **In the meanwhile the sponsors are proposing reasonable and useful guidelines for risk management of patients receiving ESA therapy**

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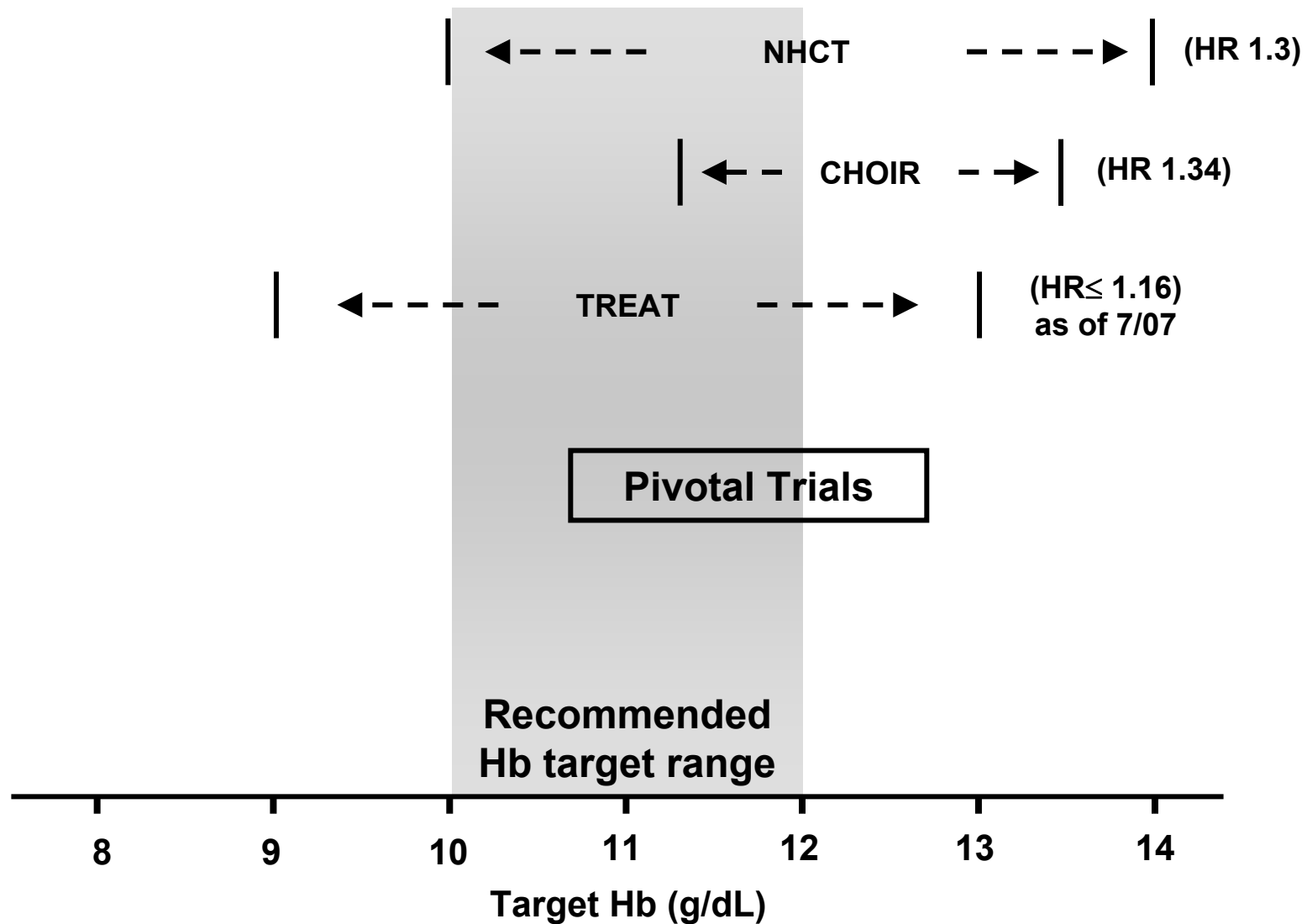
# Key Points

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- **ESAs provide clear clinical benefits in CRF patients**
  - Transfusion avoidance
  - Improvements in anemia symptoms, physical function, and exercise capacity
- **Different risks are associated with targeting vs achieving specific Hb levels**
  - Targeting higher Hb (>13 g/dL) appears to confer risk
  - Patients who achieve Hb level >11 g/dL have less risk, however, this observation is complicated by factors such as underlying health status
  - Relationship of dose to risk is confounded
- **Rapid rise or decline in Hb (cycling) should be minimized**
- **Target Hb range of 10-12 g/dL is recommended as a prudent approach to risk management**
  - Managing risk through an achieved Hb ceiling of 12 g/dL is not consistent with results of RCTs

# Summary Benefit and Risk of ESAs in Nephrology as Defined in RCTs

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# Sponsors Are Committed to Additional Risk Management on Key Issues

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- **Hb target**
- **ESA responsiveness**
- **Hb cycling**

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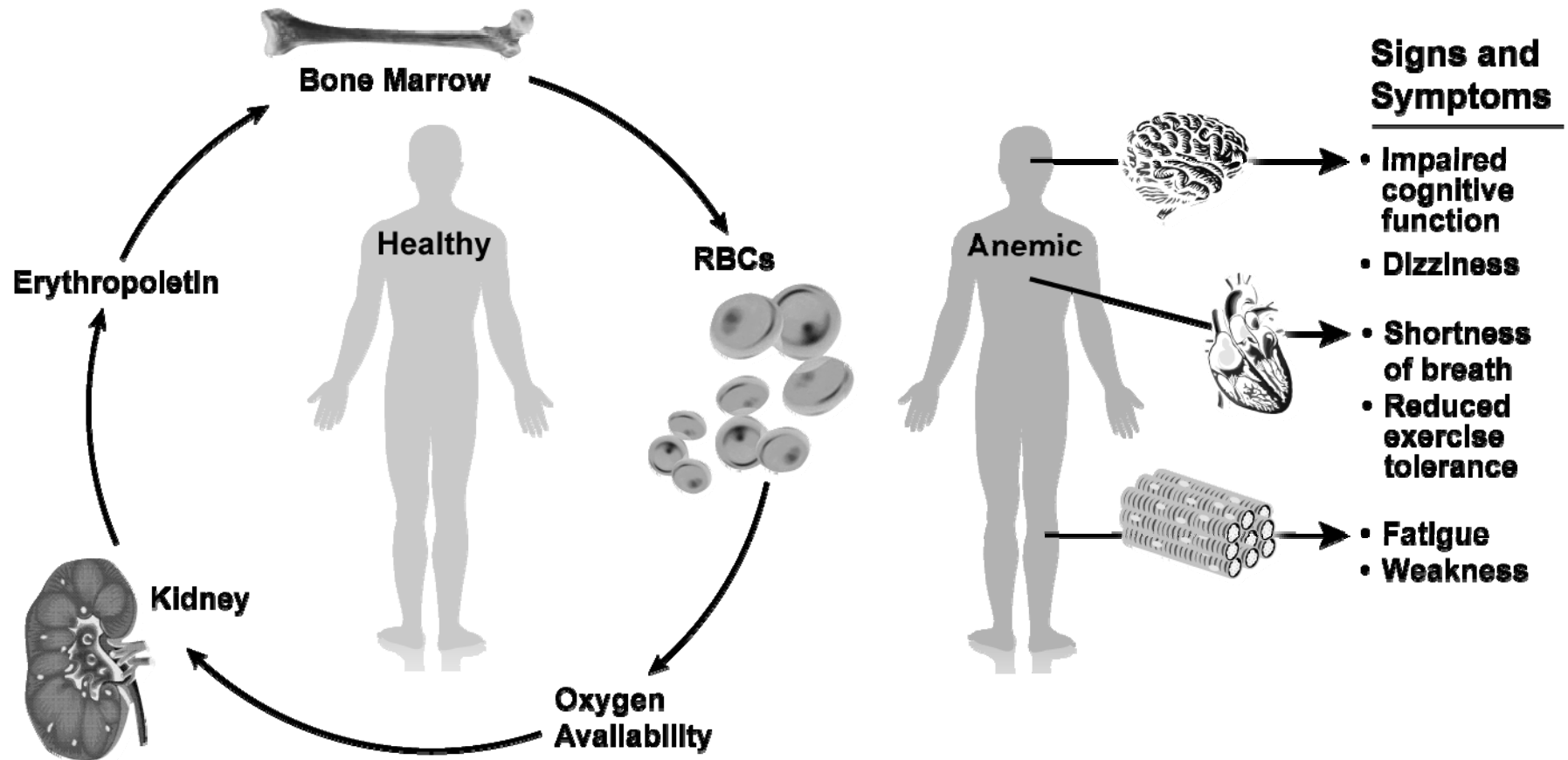
Global Development, Amgen Inc

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# Anemia in CRF



# Anemia Treatment was a Rescue Therapy in Pre-ESA Era

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- **Anemia of CRF was major source of functional impairment**
- **Treatment of anemia was important unmet medical need**
  - **Available options were inadequate**
    - **Blood transfusions (average 6-8 units per patient/yr)**
    - **Parenteral iron therapy**
    - **Androgen therapy**

Eschbach, *Kidney Int*, 1989.

Eschbach, *Ann Intern Med*, 1989.

Churchill, *Am J Kidney Dis*, 1992.

Winearls, *Nephrol Dial Transplant*, 1998.

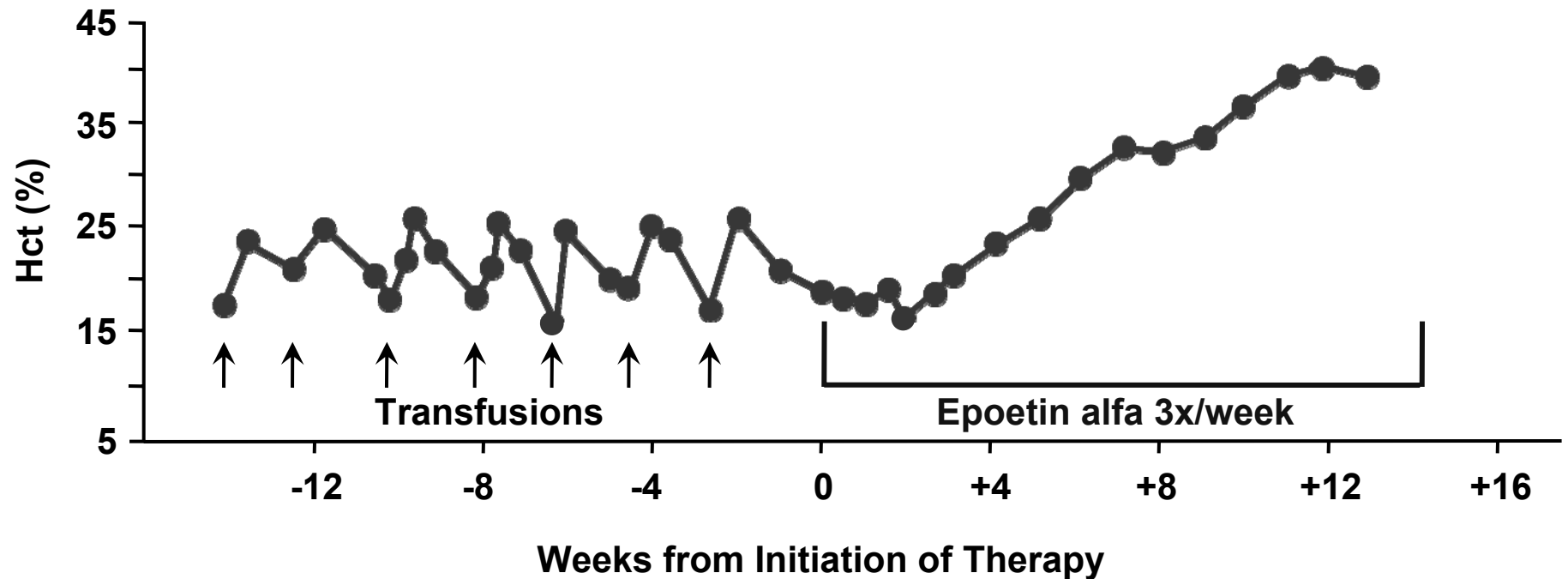
# Complications of Blood Transfusions in Patients with CRF

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- **Volume overload and pulmonary edema is common and requires concomitant dialysis therapy**
- **Allo-immunization increases with transfusion and reduces opportunity for kidney transplantation**
- **Iron overload**
- **Hyperkalemia**
- **Infection**

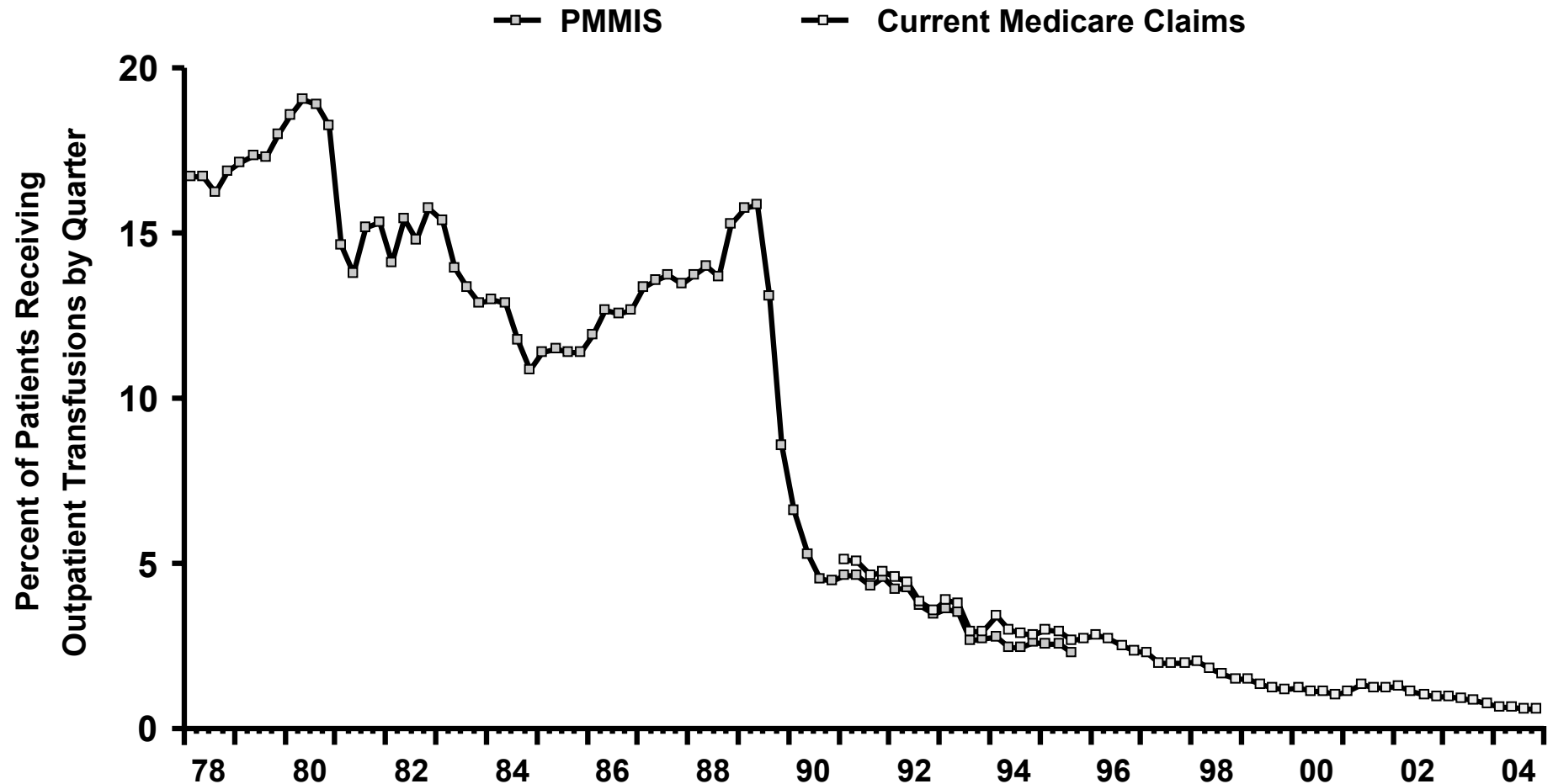
# Epoetin alfa Introduced Paradigm Change: Partial Hb Restoration Instead of Transfusion Rescue

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Adapted from: Eschbach, *N Engl J Med.* 1987

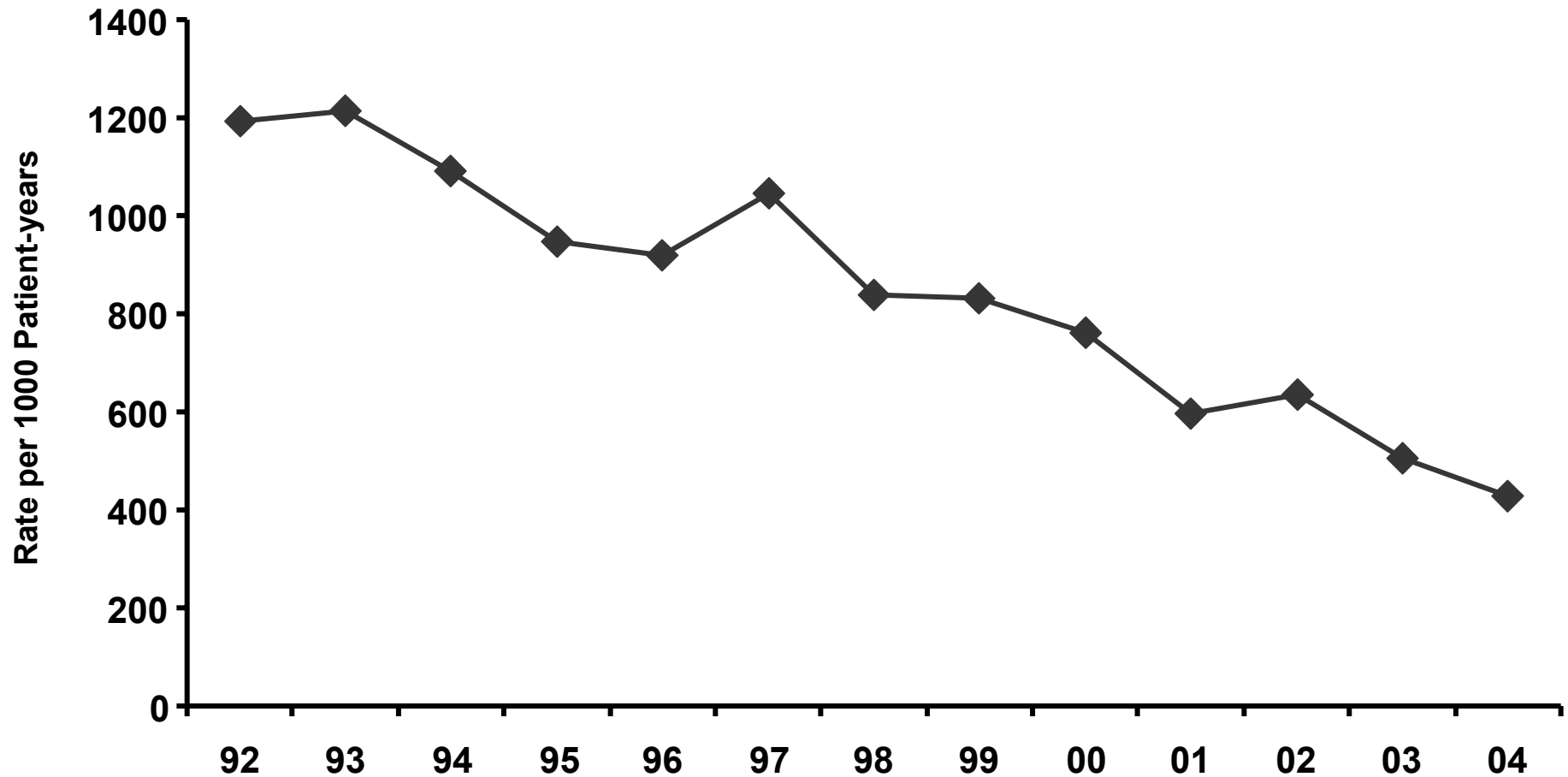
# Transfusions Dramatically Reduced in Dialysis Patients Since Introduction of ESAs



PMMIS= Healthcare Financing Administration Program Medical Management and Information Systems

# Transfusions Reduced in Non-dialysis CKD Patients Since Introduction of ESAs

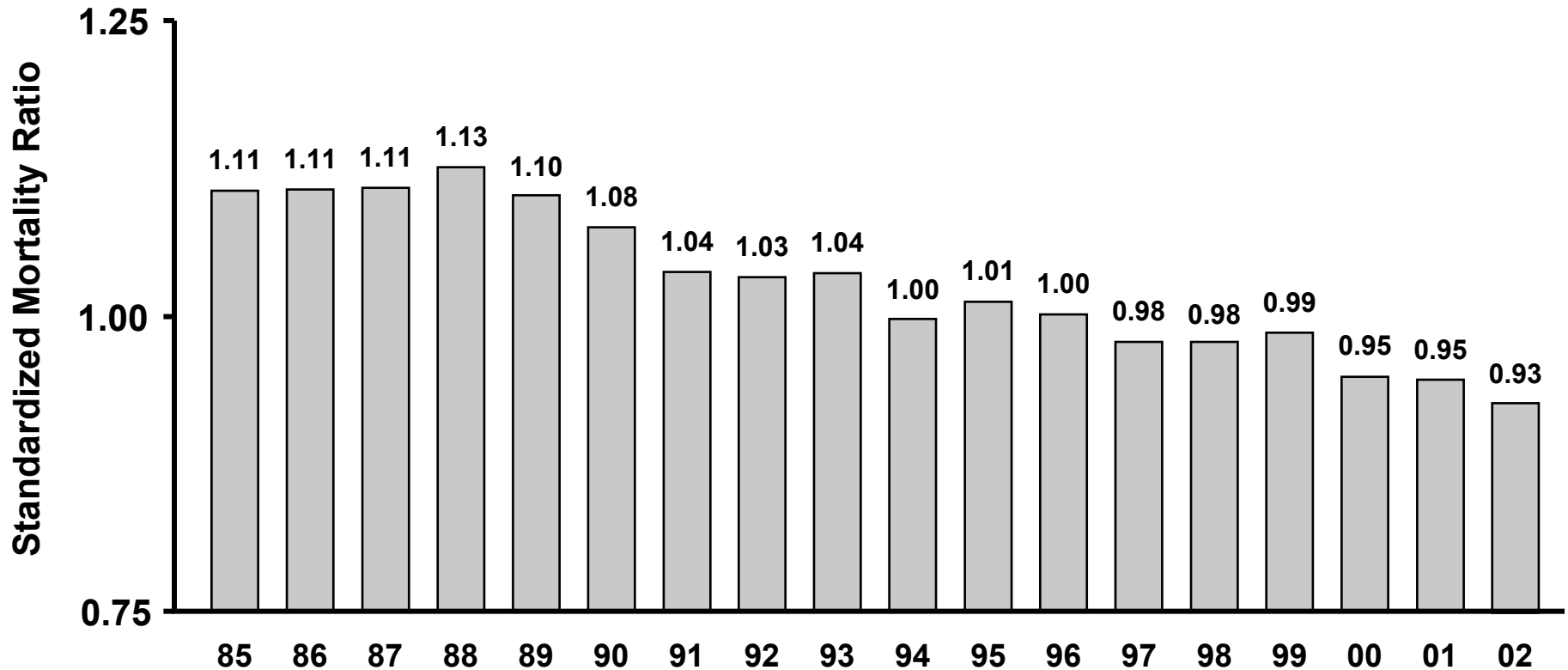
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5% General Medicare Denominator File.

# Standardized Mortality Ratio Has Decreased 17% Since Introduction of EPO

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# Patient Well-Being: The Clinician's Journey

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- **Initial patient reports of dramatic improvements**
- **Patient requests to come off transplant lists and not to pursue home dialysis**
- **Patient reported outcomes studies**
- **Functional capacity studies**

# Nephrology Community Has Over 18 Years of Experience with ESAs

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- **ESAs fundamentally changed practice of nephrology**
- **ESAs enhance patient well-being**
- **Returning to a pre-ESA approach to anemia would set back the care of CRF patients nearly 2 decades**
- **A legitimate scientific debate continues over the appropriate target Hb for populations of patients**

# Nephrology Community Has Over 18 Years of Experience with ESAs

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- **Recent revisions to evidence-based clinical practice guidelines for anemia have incorporated important safety information regarding higher Hb targets**
- **For an individual patient, benefits must be weighed against the risks**
  - Nephrologists and patients are in the best position to work together to optimize anemia management
- **Clinical trial in dialysis targeting Hb  $\leq 10$  g/dL would lack equipoise**
- **Extensive clinical experience of nephrologists and patients *matters***

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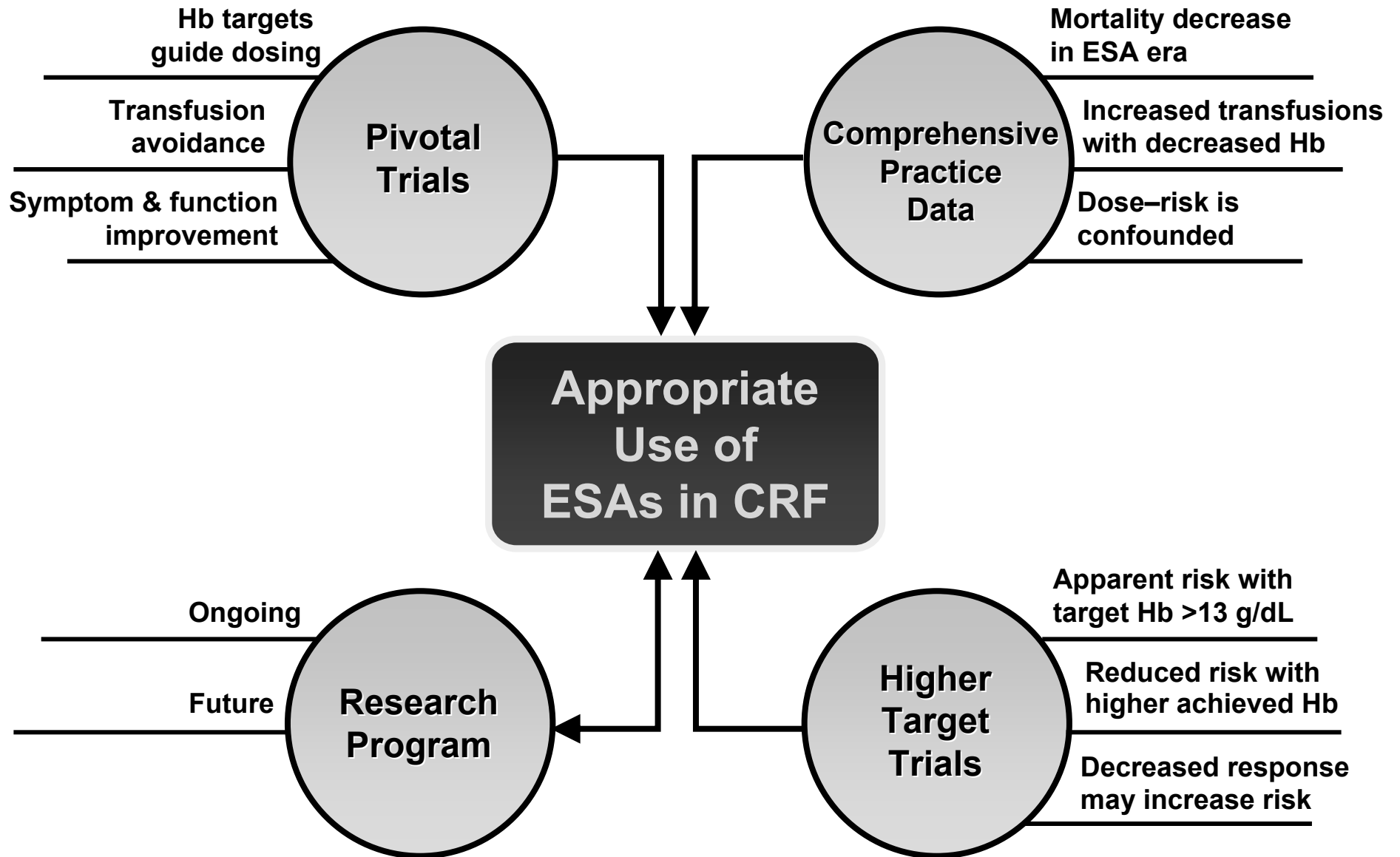
**Preston Klassen, MD, MHS**

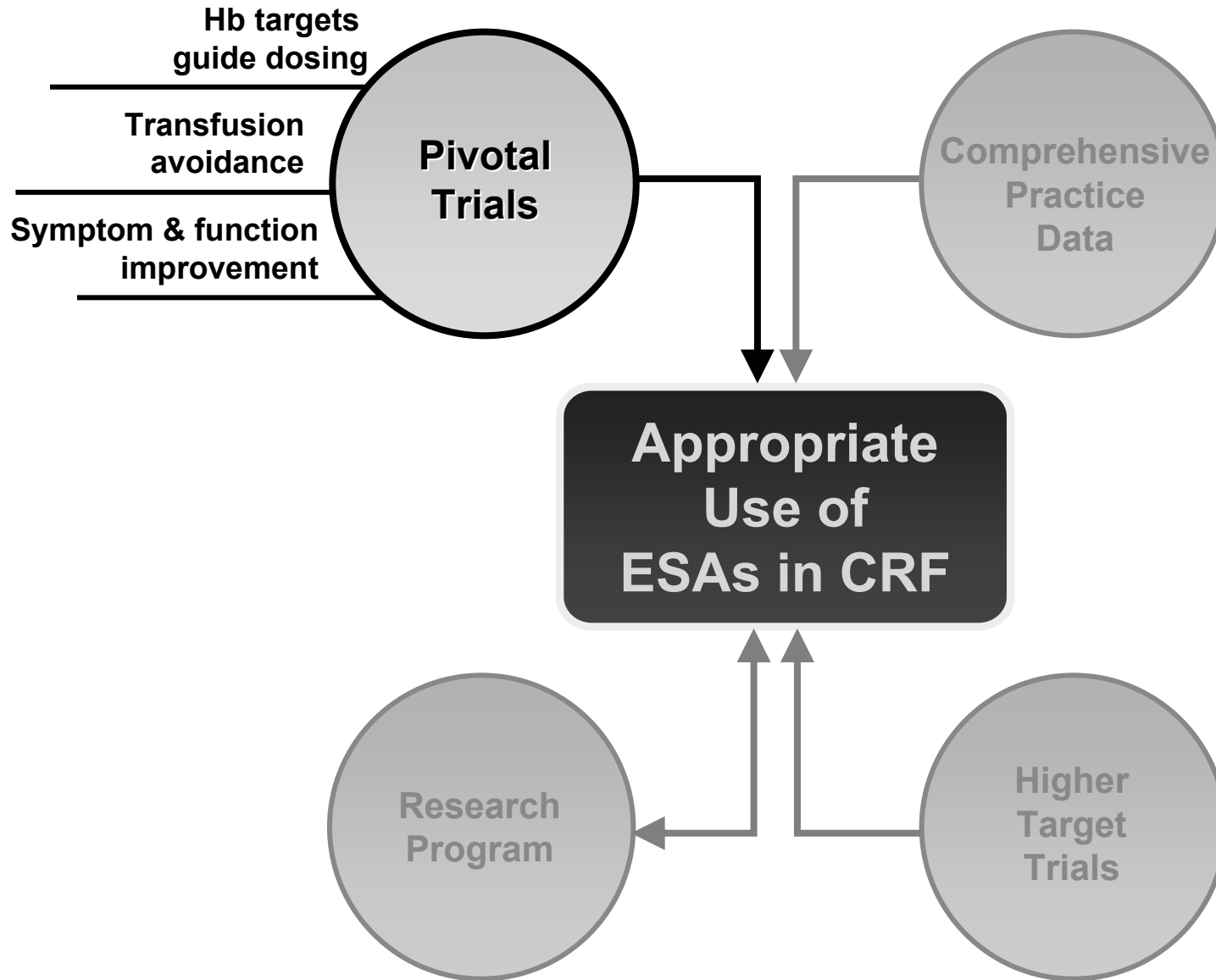
Global Development, Amgen Inc

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Global Regulatory Affairs & Safety, Amgen Inc



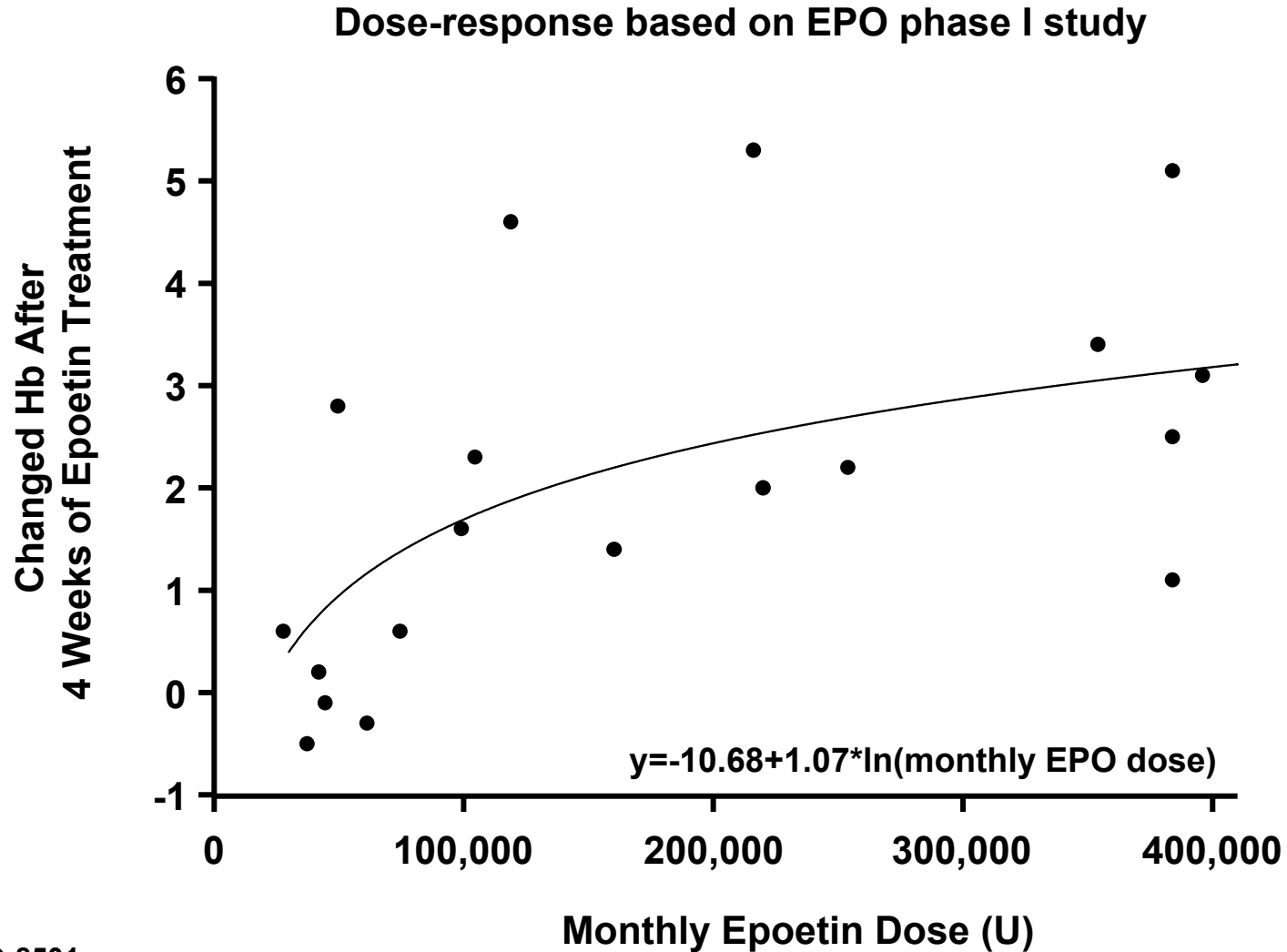


# Hb Targets Important for Anemia Management

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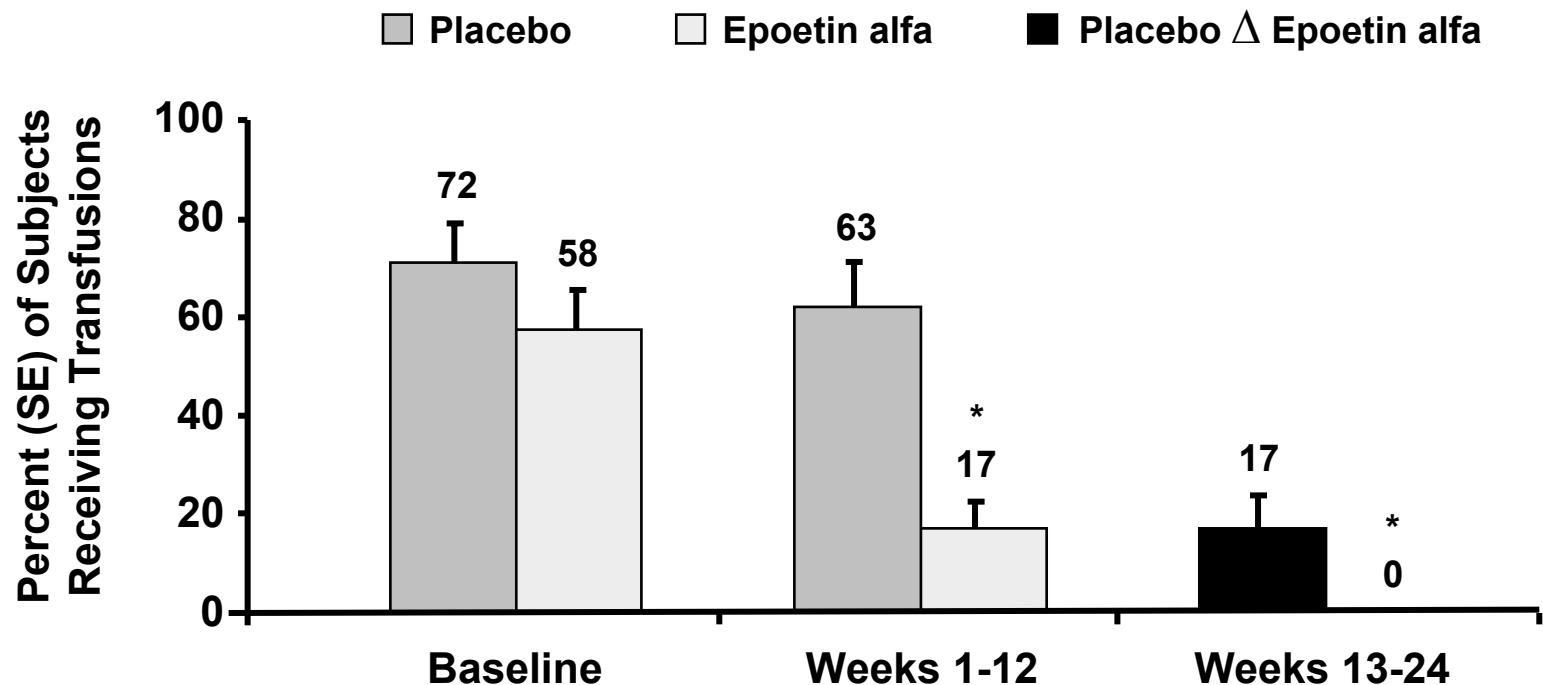
- **Therapeutic targets accepted to guide dose adjustment**
- **Clinical trials established benefits using Hb target range (10.7-12.7 g/dL)**
- **Hb target in ESA labels prior to recent revisions**
  - Epoetin alfa: 10-12 g/dL
  - Darbepoetin alfa: not to exceed 12 g/dL

# Epoetin alfa Phase I/II Study: Dose-response



# Placebo-controlled Trials Demonstrated Transfusion Avoidance with Epoetin alfa

- Baseline Hct 22% (Hb 7.3 g/dL)
- Target Hct 35 +/- 3% (Hb 10.7-12.7 g/dL)



N=32 (placebo); N=36 (Epoetin alfa); \*p<0.05 placebo vs Epoetin alfa

Baseline rates are based on the 6 months before the start of the study.

Placebo  $\Delta$  Epoetin alfa group: Transfusion requirements for subjects originally randomized to receive placebo in Study 8701 who began to receive Epoetin alfa after week 12.

# CESG (EP86-004) Evaluated Anemia Symptoms and Physical Function in Dialysis

<b>Study design</b>	Randomized, double-blind, placebo-controlled trial
<b>Inclusion Hb (g/dL)</b>	<9
<b>Hb target (g/dL)</b>	
<b>Placebo (n=40)</b>	–
<b>Group A (n=38)</b>	9.5-11.0
<b>Group B (n=40)</b>	11.5-13.0
<b>Exercise endpoints</b>	6-minute walk test <sup>1</sup> , modified Naughton stress test <sup>2</sup>
<b>PRO endpoints</b>	KDQ <sup>3,4</sup> , SIP <sup>4</sup>
<b>PRO and exercise assessment time points</b>	Baseline, 2, 4, and 6 months
<b>Analysis</b>	ITT Repeated measures mixed model Repeated measures LOCF Bonferroni multiplicity correction

<sup>1</sup>Loss to follow-up=19%

<sup>2</sup>Loss to follow-up=24%

<sup>3</sup>Kidney Disease Questionnaire

<sup>4</sup>Loss to follow-up=16%

# CESG Demonstrated Improvements in Physical Function

Measure	Placebo ( $\Delta$ BL to 6 mo)	Group A ( $\Delta$ BL to 6 mo)	Group B ( $\Delta$ BL to 6 mo)	p-value <sup>†</sup>
Hb (g/dL)	+0.2	+3.1	+4.6	<0.0001
<b>Exercise stress (modified Naughton)</b>				
Minutes walked	+1.3	+3.1	+4.8	<0.001
<b>6-Minute walk</b>				
Meters walked	-5.5	+24.6	+54.6	<0.05

- **Significant improvements in patient reported measures of physical function, energy and weakness**

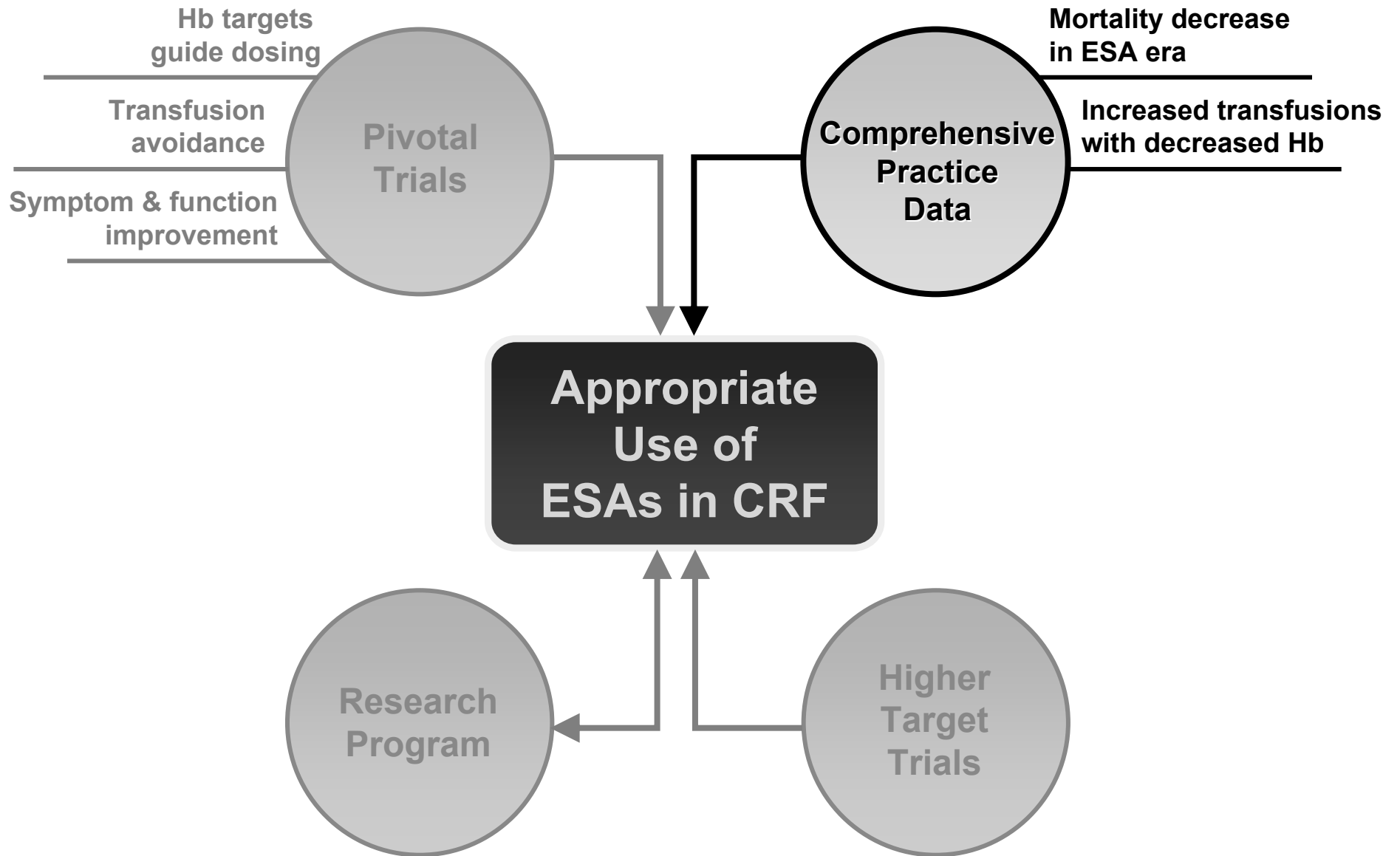
Target Hb Group A=9.5-11.0 g/dL, Group B=11.5-13.0 g/dL

<sup>†</sup>ITT repeated measures mixed model, placebo vs treatment over time

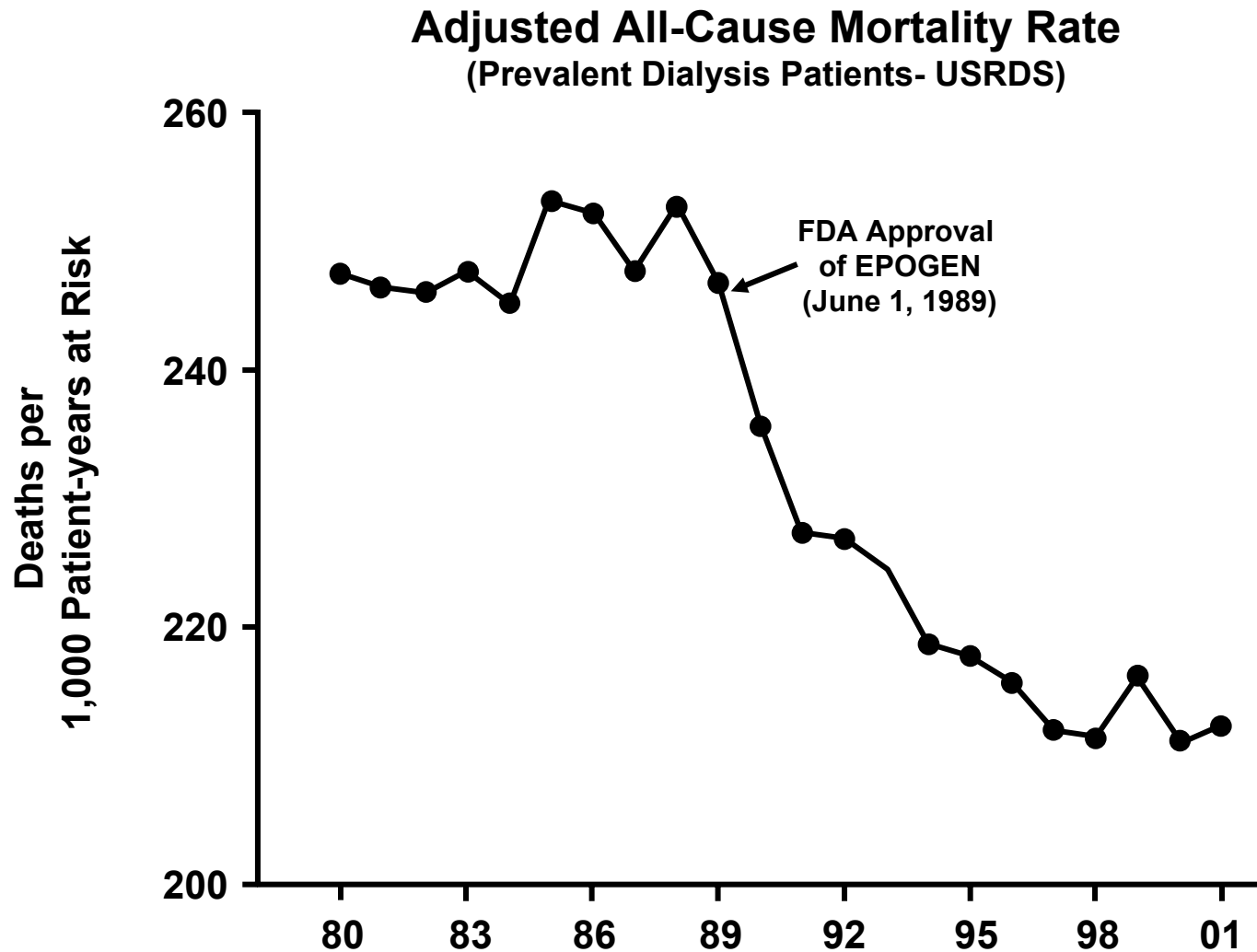
# ESAs Provide Meaningful Clinical Benefit

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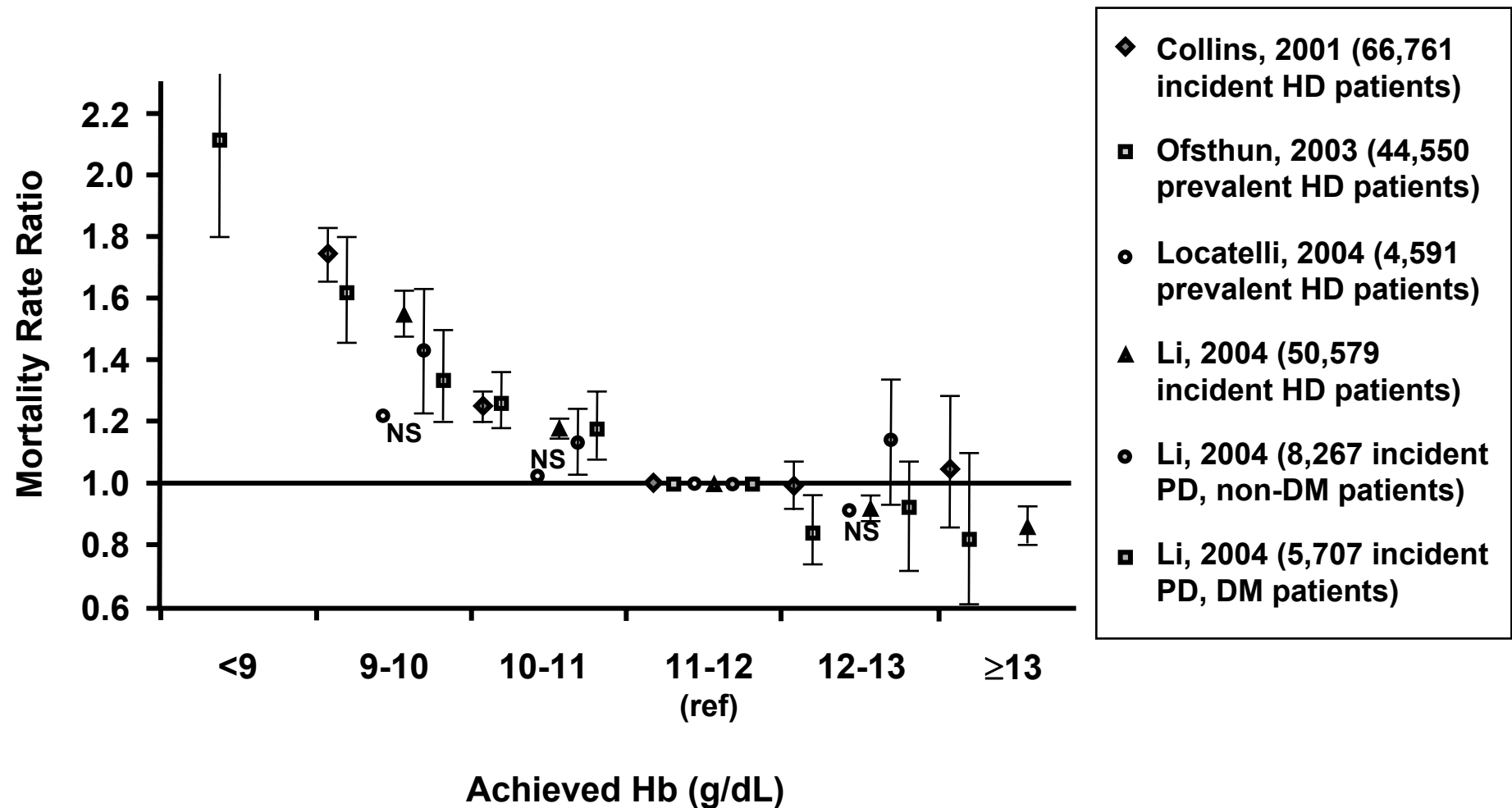
- **Clear reduction in burden and risks of transfusions**
- **Double-blind, placebo-controlled data demonstrate**
  - Improved exercise capacity
  - Improved patient reported symptoms and physical function
- **Anemia symptom and function improvement corroborated by published literature**
  - 11 studies of exercise capacity
  - 15 studies of physical functioning
  - 7 studies of energy
- **Hb target is clinically important**



# Mortality in Dialysis Has Declined in ESA Era

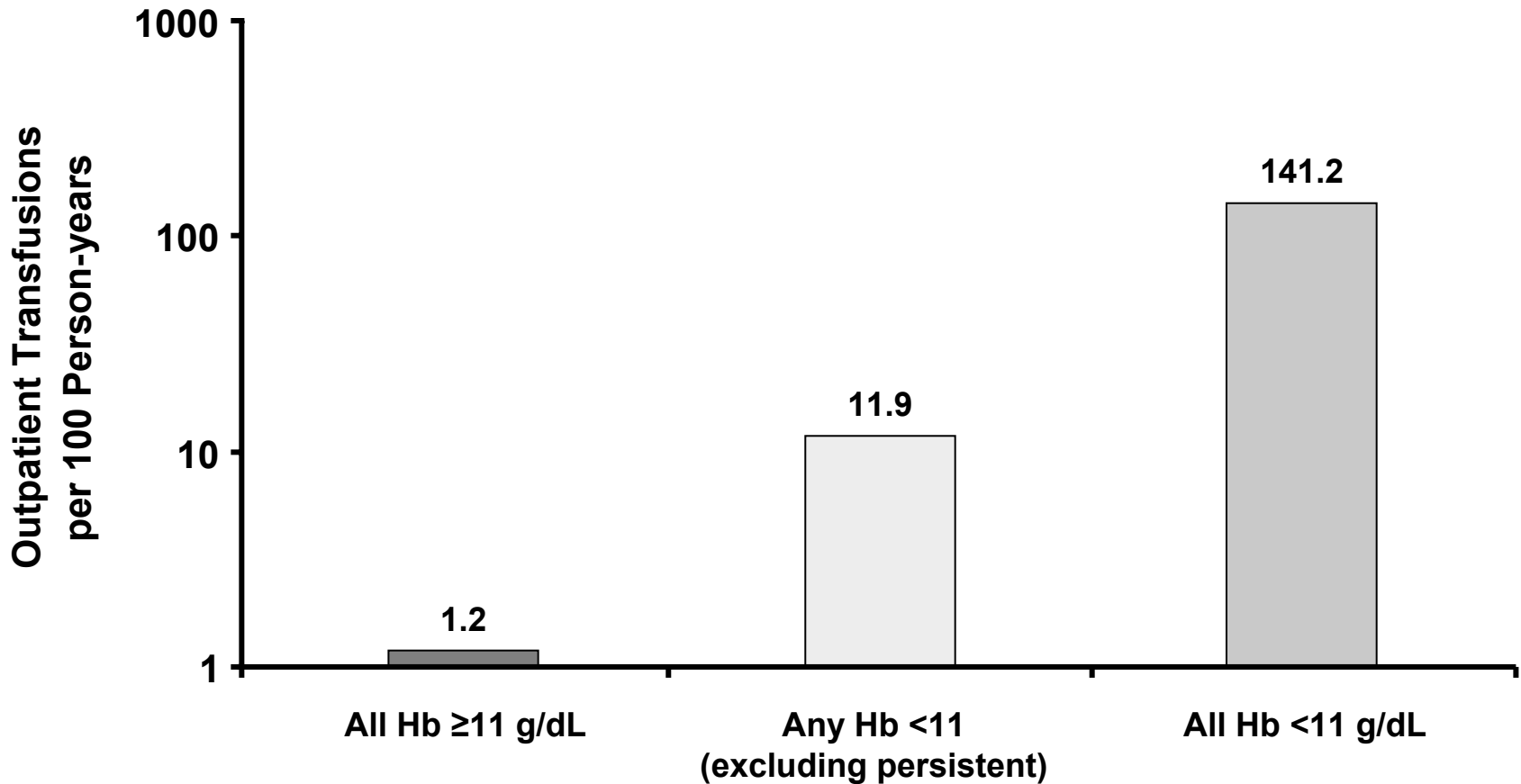


# Achieved Hb and Outcomes in Comprehensive Clinical Practice Data



95% CI; NS=not significant  
Adapted from: Volkova & Arab, *AJKD* 2006.

# Dialysis Patients with Persistent Hb <11 g/dL Have Increased Risk of Transfusion



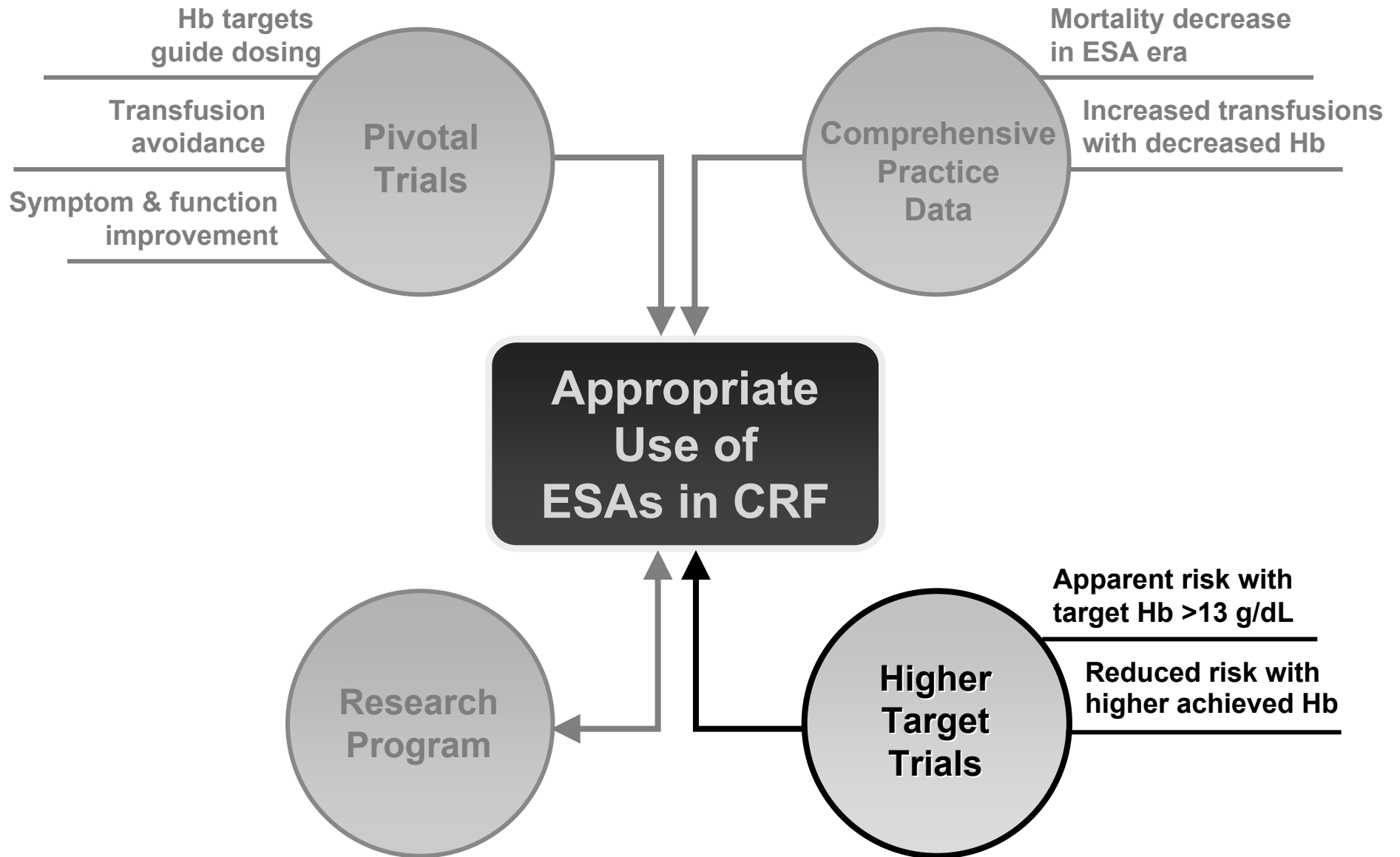
Percent of patients	40.0	58.6	1.4
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N=161,597  
Medicare ESRD database.

# Rationale for Proposed Hb Target 10-12 g/dL in CRF Patients

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- **Clinical trials established appropriate use of ESAs based on Hb target range (10.7-12.7 g/dL)**
  - Transfusion avoidance
  - Improvement in symptoms and function
- **Clinical benefits supported by comprehensive practice data**
- **Minimum target Hb 10 g/dL necessary in CRF patients to achieve demonstrated clinical benefit**
- **Upper end of target range 12 g/dL**
  - Well below target Hb associated with risk in CHOIR and NHCT



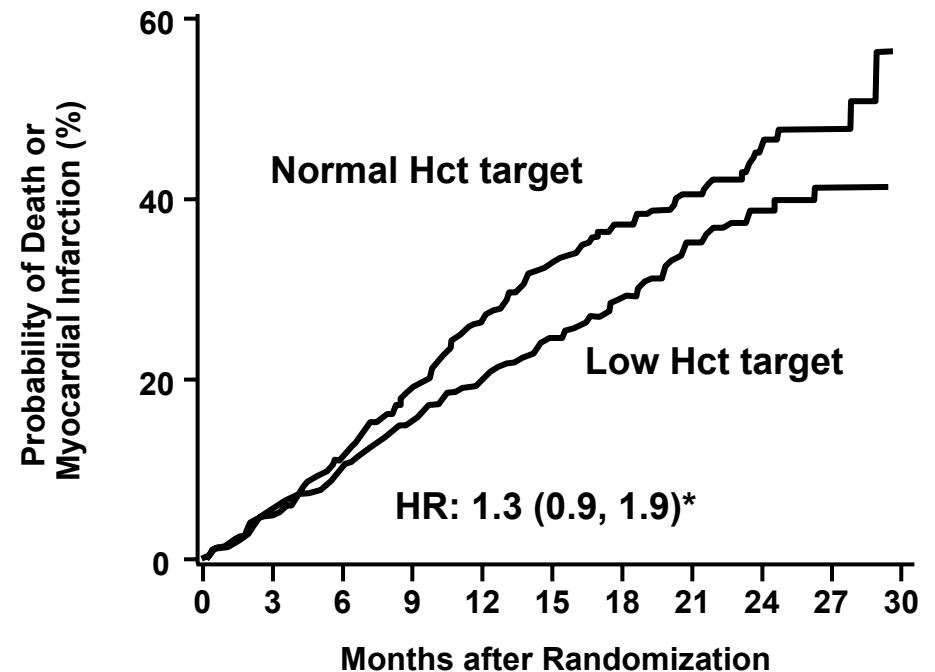
# Complete vs Partial Correction of Anemia

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- **Partial correction demonstrated clinical benefits**
- **Principal question in the nephrology community following the adoption of ESAs was whether greater clinical benefit would result from complete correction**

# Clinical Trial to Investigate Hb Normalization Identified Unexpected Risks: NHCT

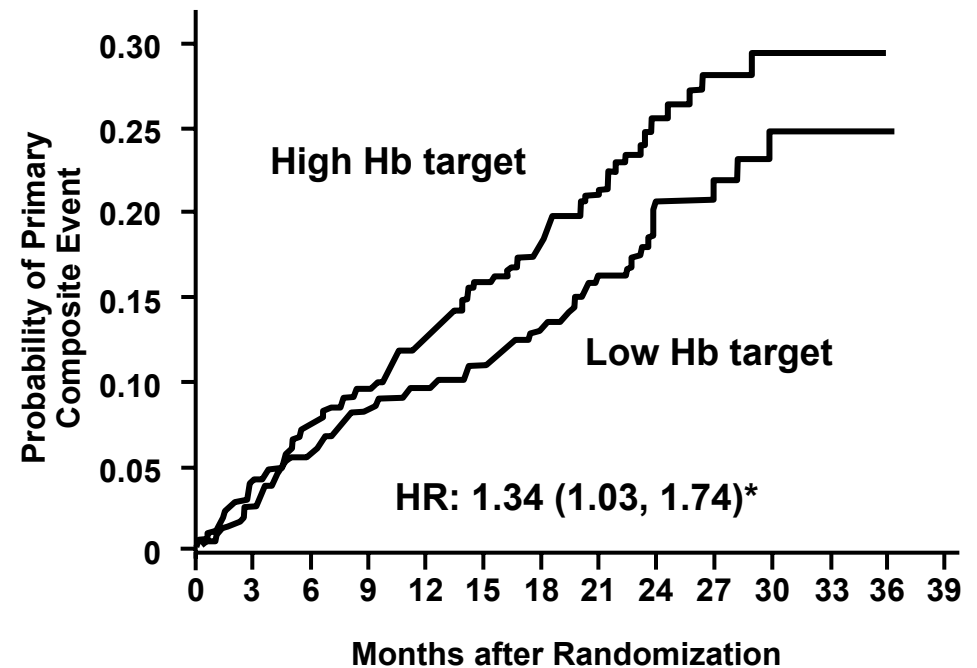
Design	Randomized, prospective, open-label	
Inclusion	Hemodialysis CV disease Hct: 27% - 33% stable Epoetin alfa	
Target Hct % (Hb g/dL)	Normal n=618	42±3% (14±1 g/dL)
	Low n=615	30±3% (10±1 g/dL)
Primary endpoint	Time to death or first non-fatal MI	



\*95% CI  
 Besarab. *N Engl J Med* 1998.

# Clinical Trial to Investigate Hb Normalization Identified Unexpected Risks: CHOIR

<b>Design</b>	Randomized, prospective, open-label	
<b>Inclusion</b>	Non-dialysis CRF, eGFR: 15-50 ml/min/1.73m <sup>2</sup> Hb <11 g/dL	
<b>Hb Target(s) (g/dL)</b>	High n=715	13.5
	Low n=717	11.3
<b>Primary endpoint</b>	Time to death or first non-fatal MI, CHF hospitalization (without RRT), stroke	

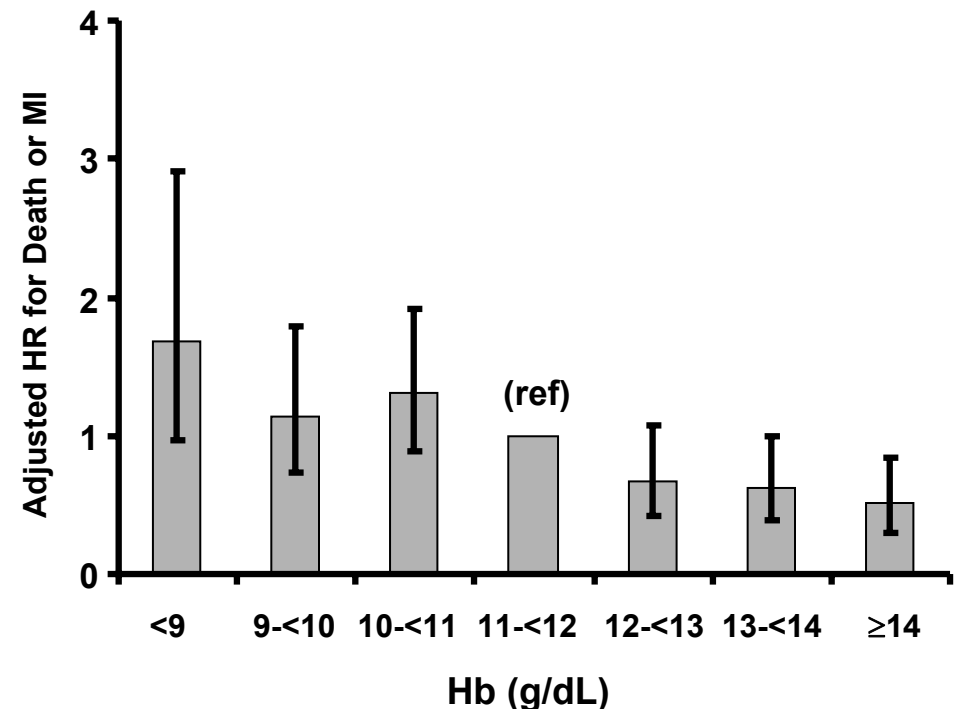
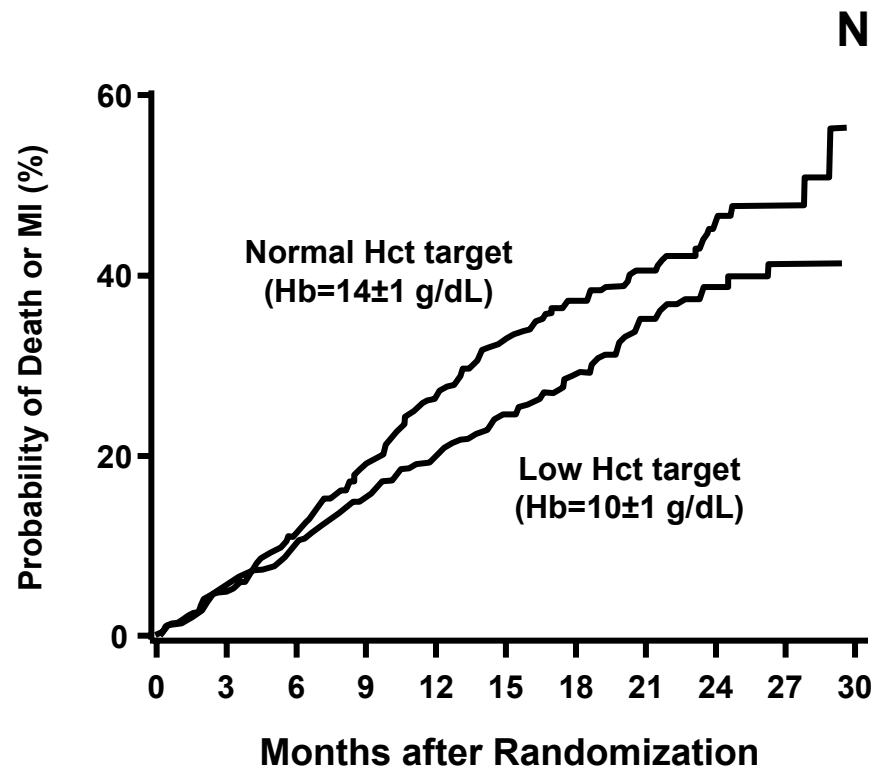


\*95% CI  
Singh AK. *N Engl J Med*, 2006.

# Apparent Paradox of Targeted vs Achieved Hb

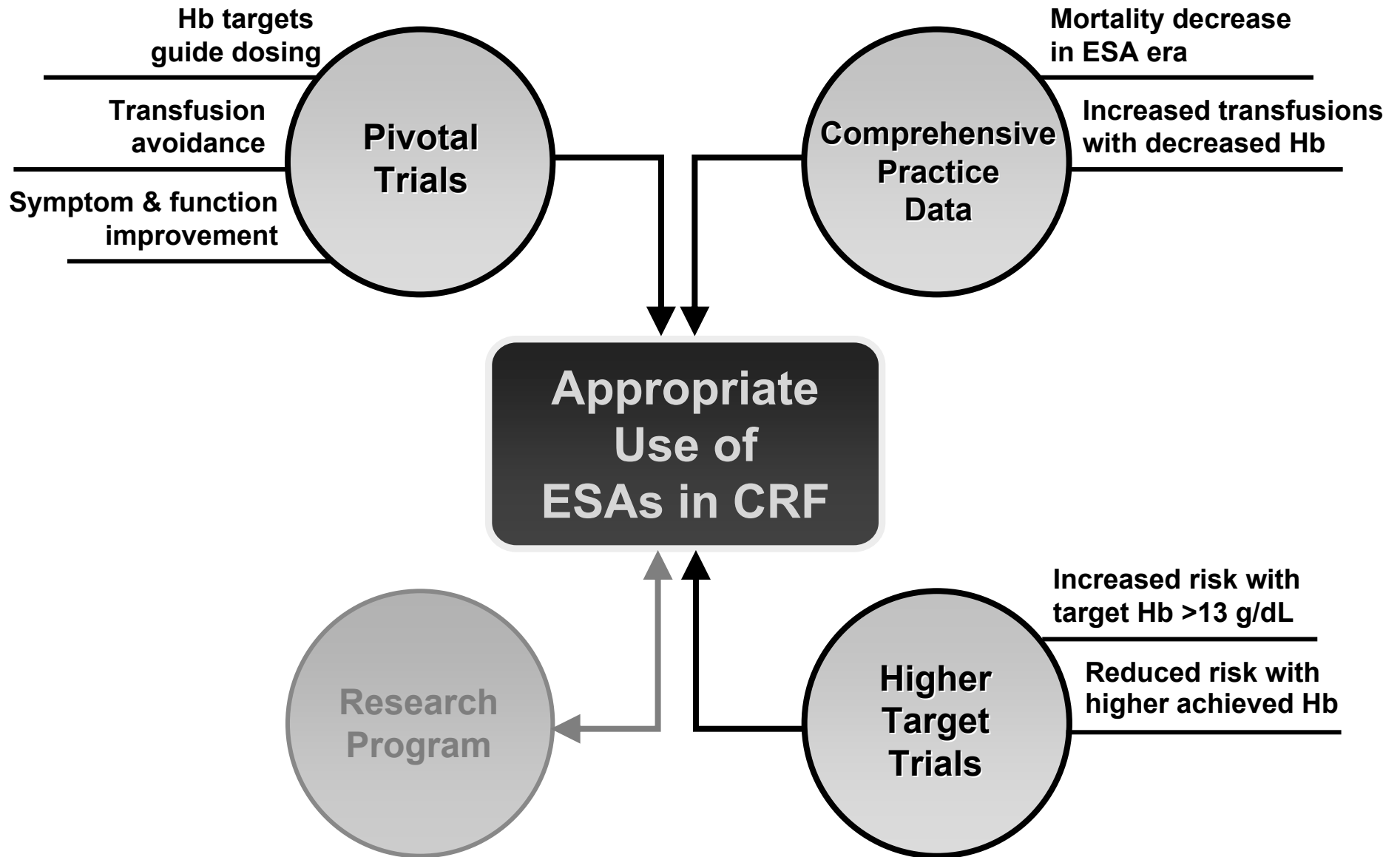
- Evidence suggests targeting high Hb results in greater risk

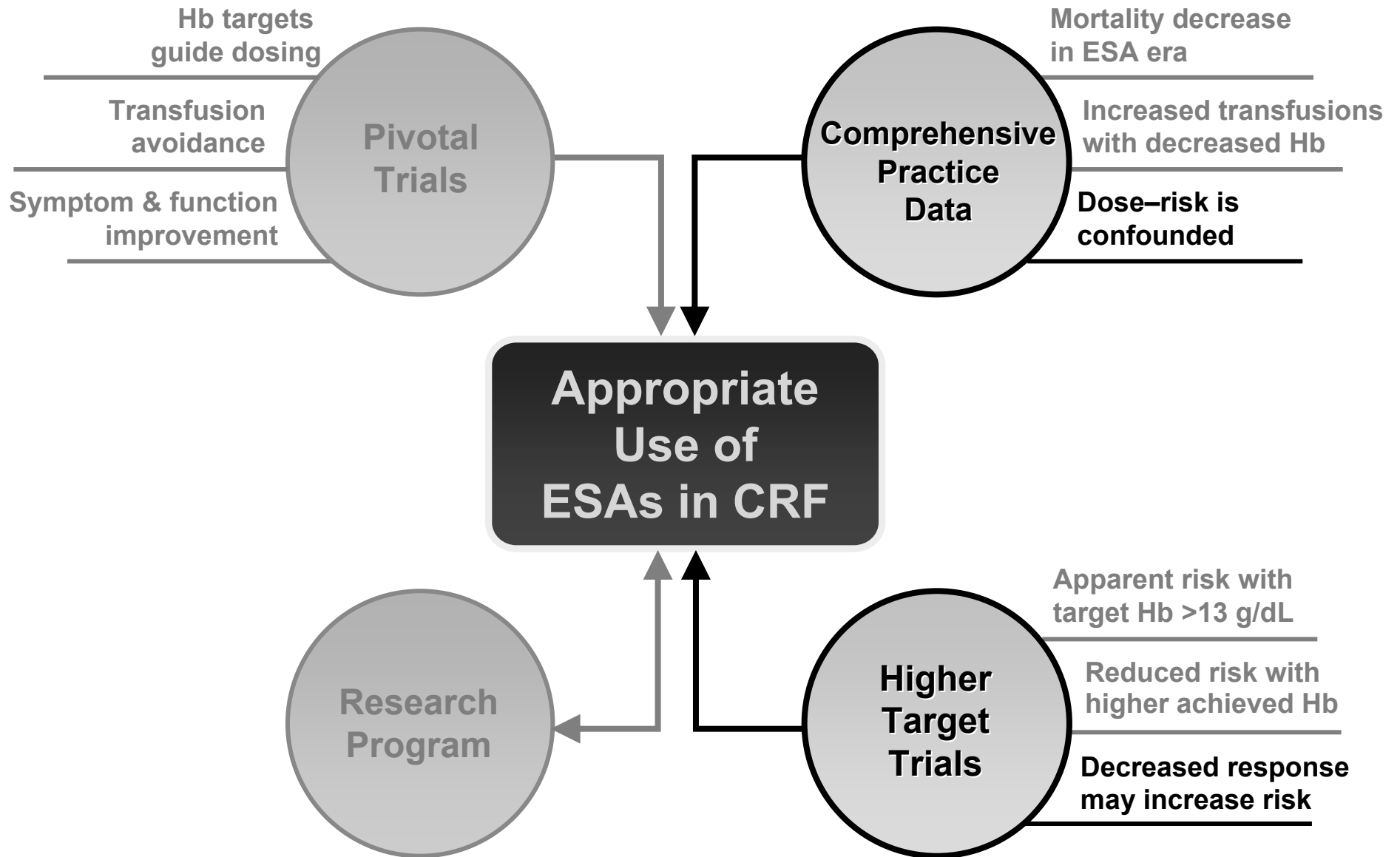
- Patients achieving a higher Hb exhibit better clinical outcomes



Besarab. *N Engl J Med* 1998.

95% CI.



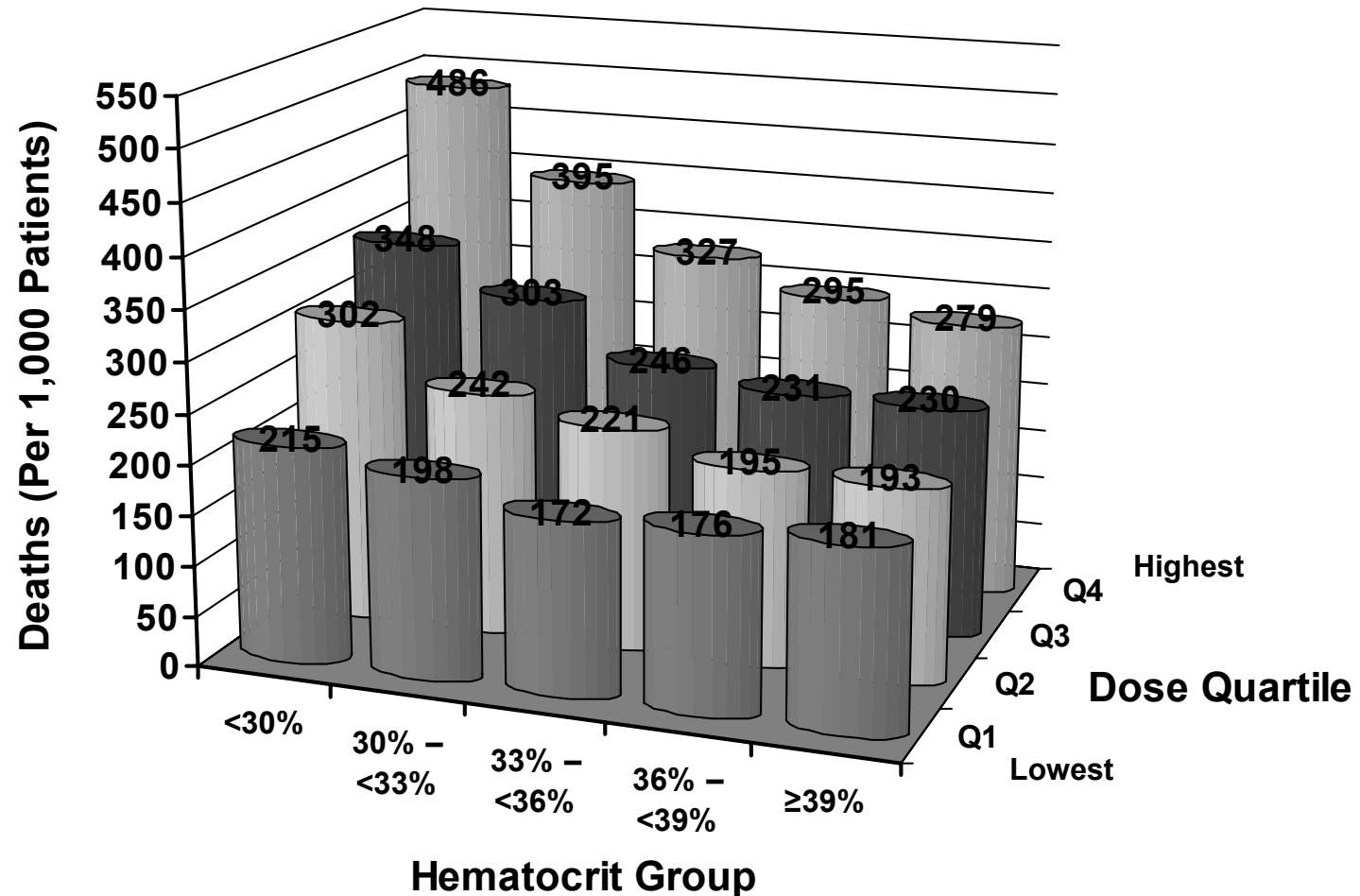


# Potential Effect of Dose is Confounded by Health Status and Responsiveness

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- **May not be possible to directly determine effect due to inseparable link among Hb, dose, and health status**
- **Patients with the worst health status have highest dose requirements and highest mortality**
- **Without control for confounding, effects of health status on outcomes may be mistakenly attributed to dose**

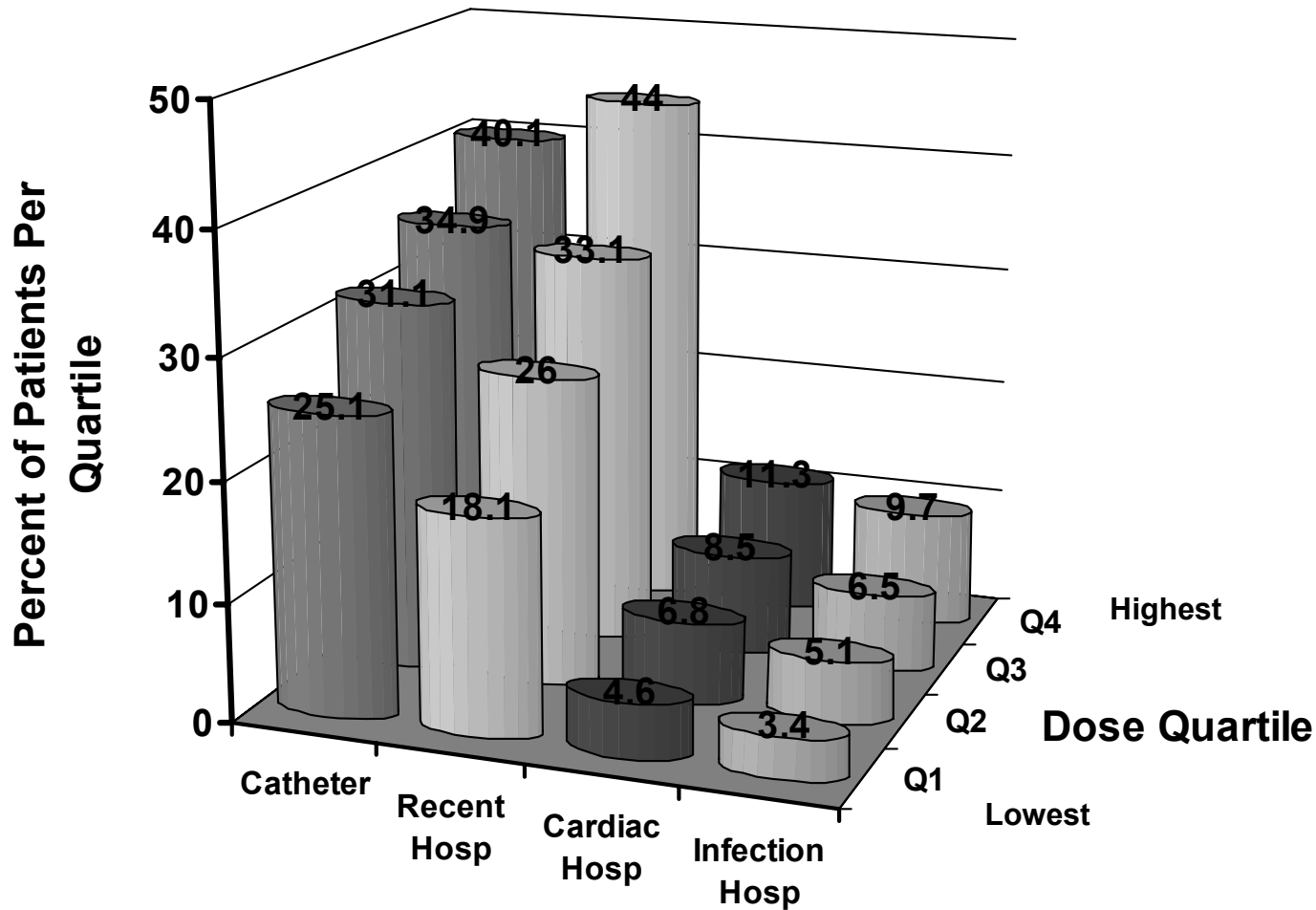
# Greater ESA Dose is Associated with Mortality in an Unadjusted Analysis



Zhang, *Am J Kidney Dis*, 2004.

Dose quartiles: Q1, 1388 to 7905 U/week; Q2, >7905 to 13,377 U/week; Q3, >13,377 to 22,068 U/week; Q4, >22,068 U/week.

# Greater Dose Requirements Correlate with Measures of Poor Health Status at Baseline

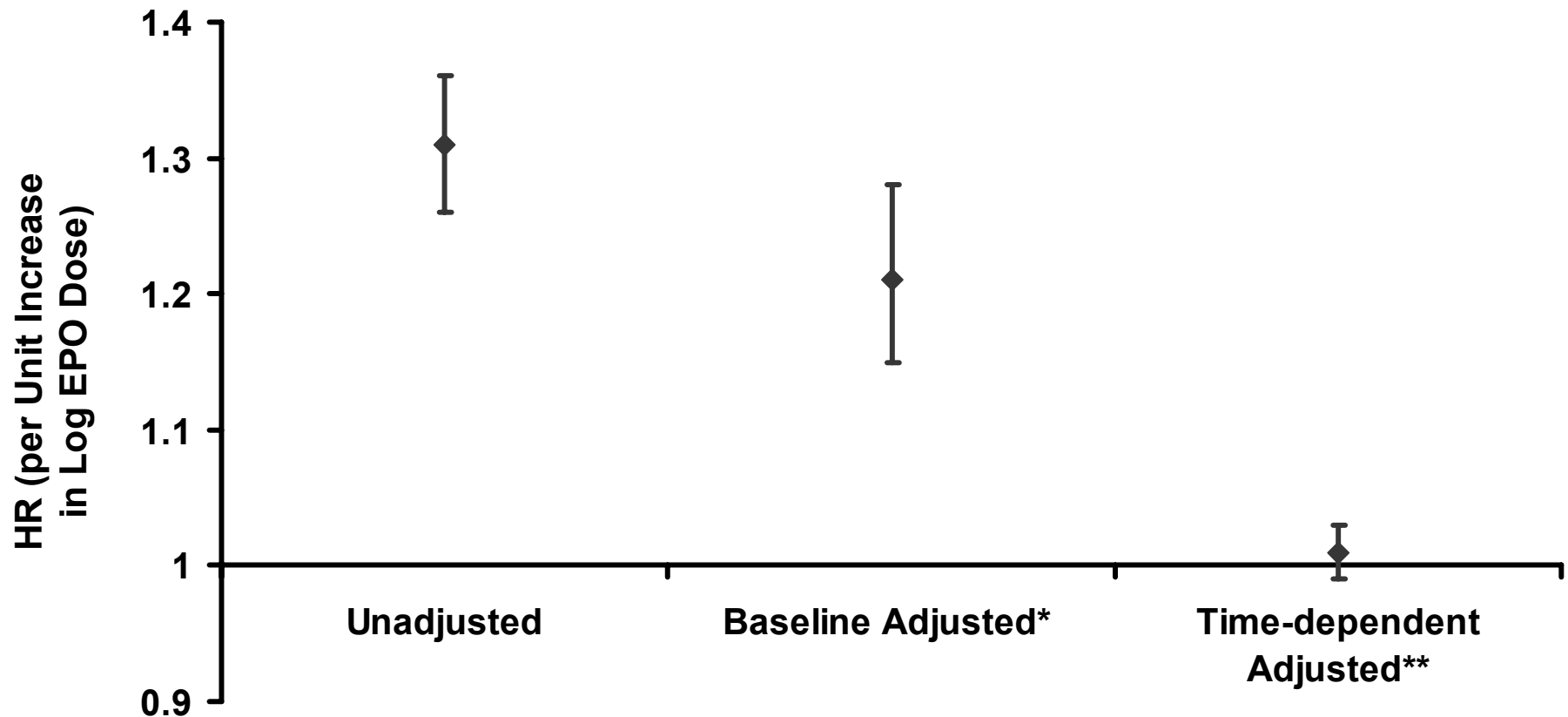


FMC-NA  
N=12,001; Achieved Hb 10-12 g/dL

Measures of BL Health Status

# Association Between ESA Dose and Mortality Attenuated with Adjustment for Confounding

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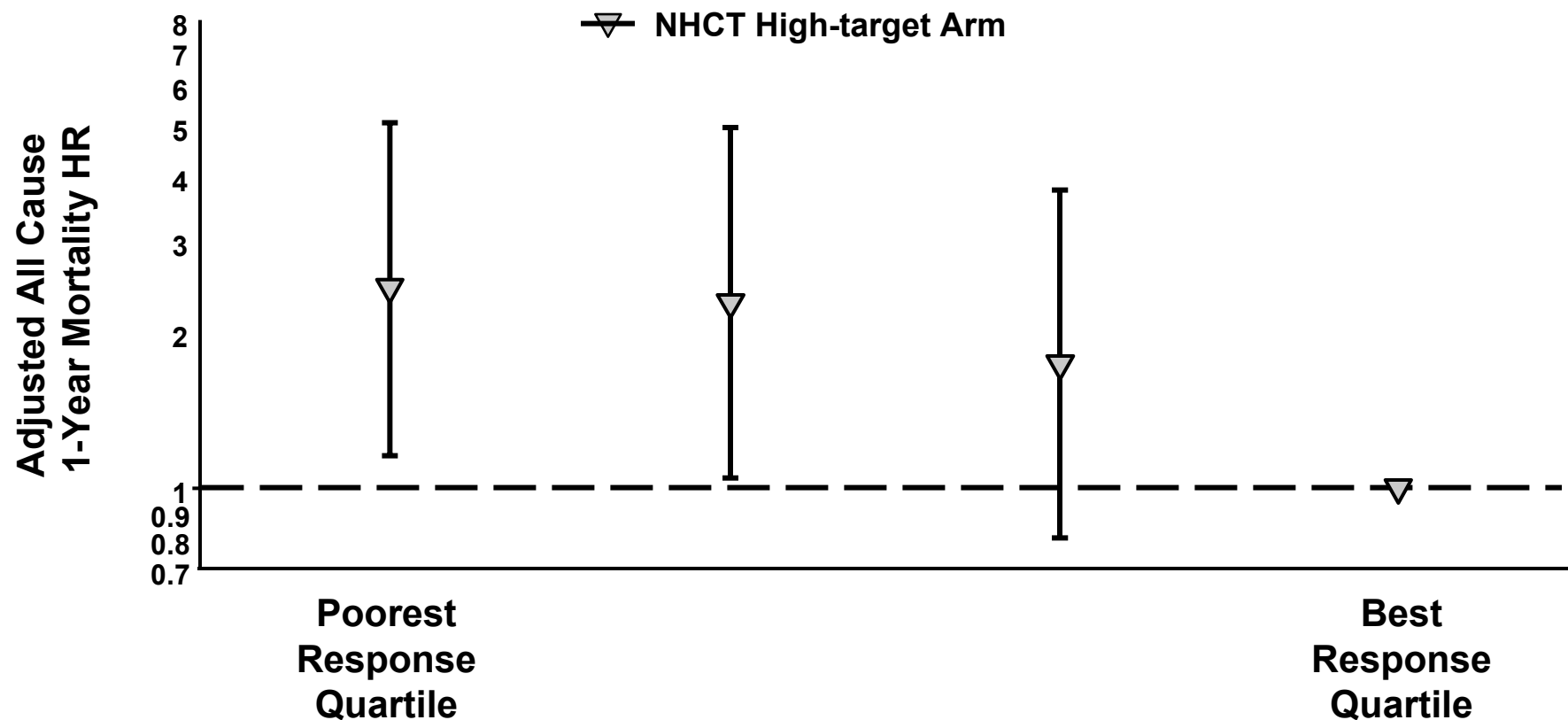
FMC-NA (N=22,955, 95% CI), In Press (*Am J Kidney Disease*)

\*Dose at baseline adjusted for baseline Hb and health status.

\*\*Time dependent dose adjusted for baseline health status and time-dependent Hb.

# Patients with Lowest ESA Response Had Greatest Mortality Risk in NHCT

- Dose challenge: 50% increase from baseline in high target arm
- Hb response: change in Hb over first three weeks

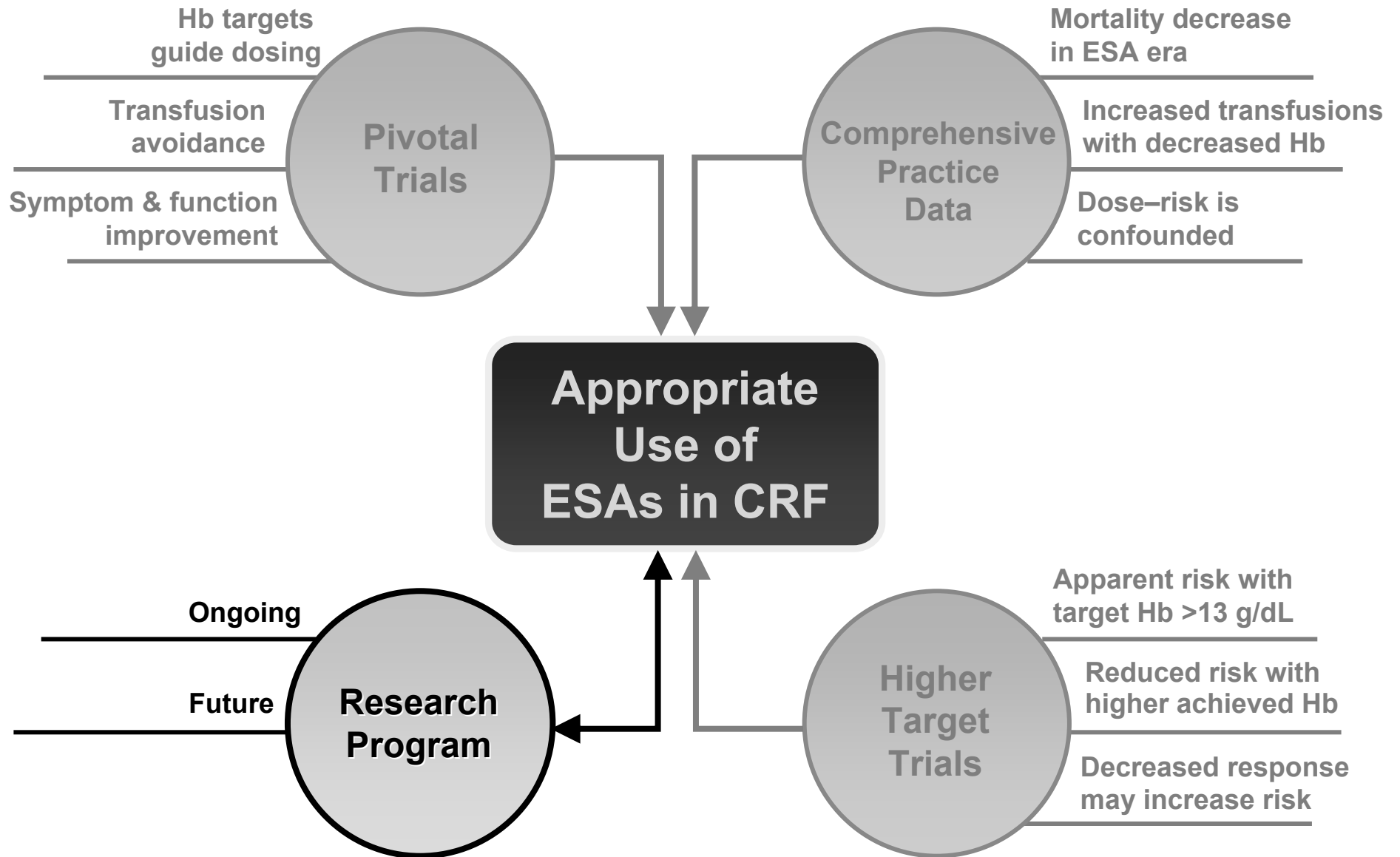


95% CI; Adjusted for age, gender, race, diabetes, dialysis vintage, vascular access type, baseline EPO dose, lymphocytes, albumin, transferrin saturation, ferritin, BMI, Kt/v and NYHA class.

# Conclusions Regarding Dose and ESA Responsiveness

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- **Unadjusted associations between ESA dose and clinical outcomes confounded by**
  - Underlying health status
  - Other unmeasured confounding variables
- **Poor ESA responsiveness is a risk factor**
  - Should be recognized and evaluated
  - Working definitions of hyporesponsiveness have been developed
  - Precise quantitative definitions can be explored in future research



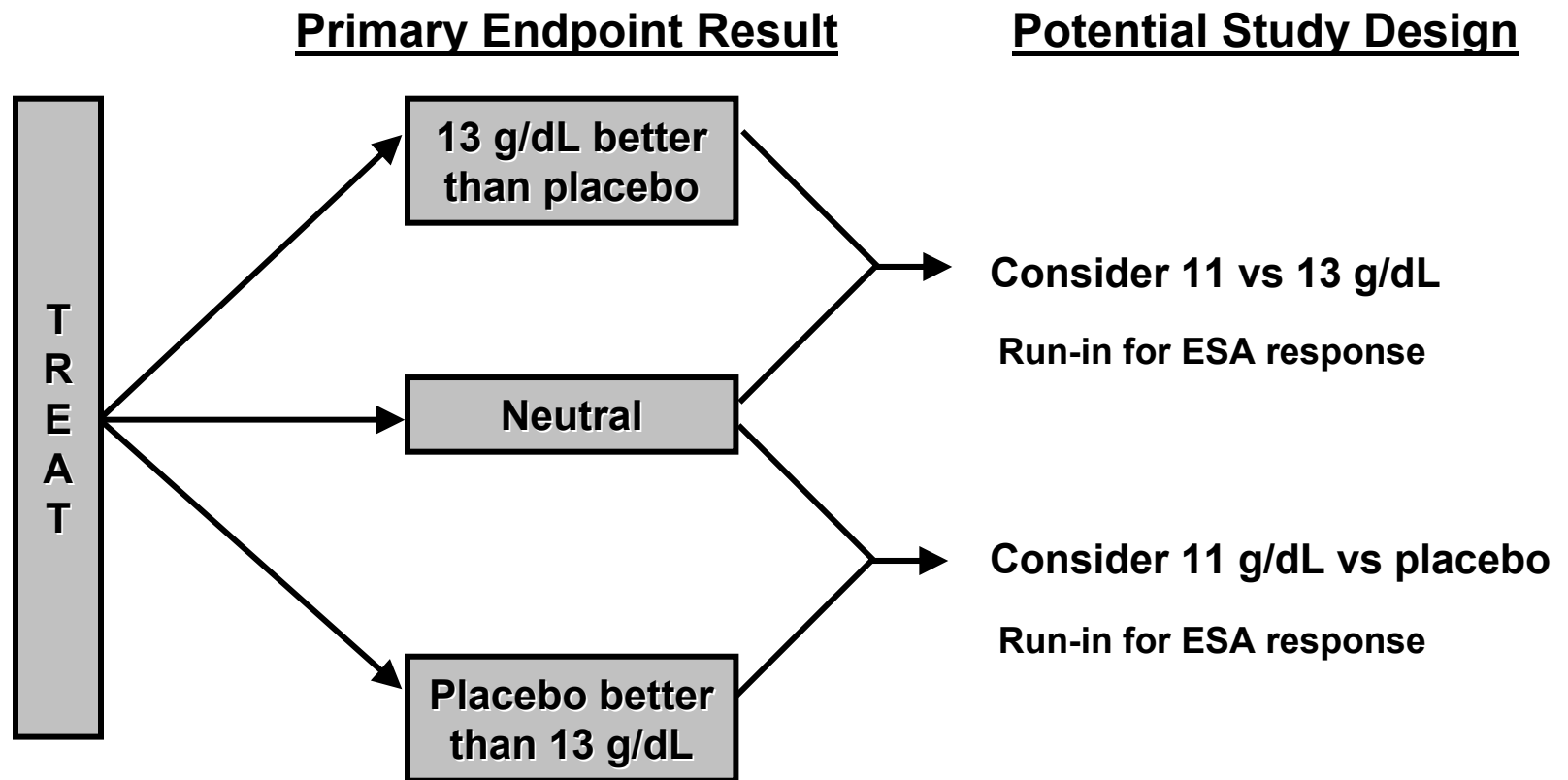
# Sponsors Are Committed to Additional Research to Address Key Issues

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- **Hb target**
- **ESA responsiveness**
- **Hb cycling**

# TREAT Will Inform Future Research

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# Considerations of Appropriate CRF Population

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## **ESA responsiveness**

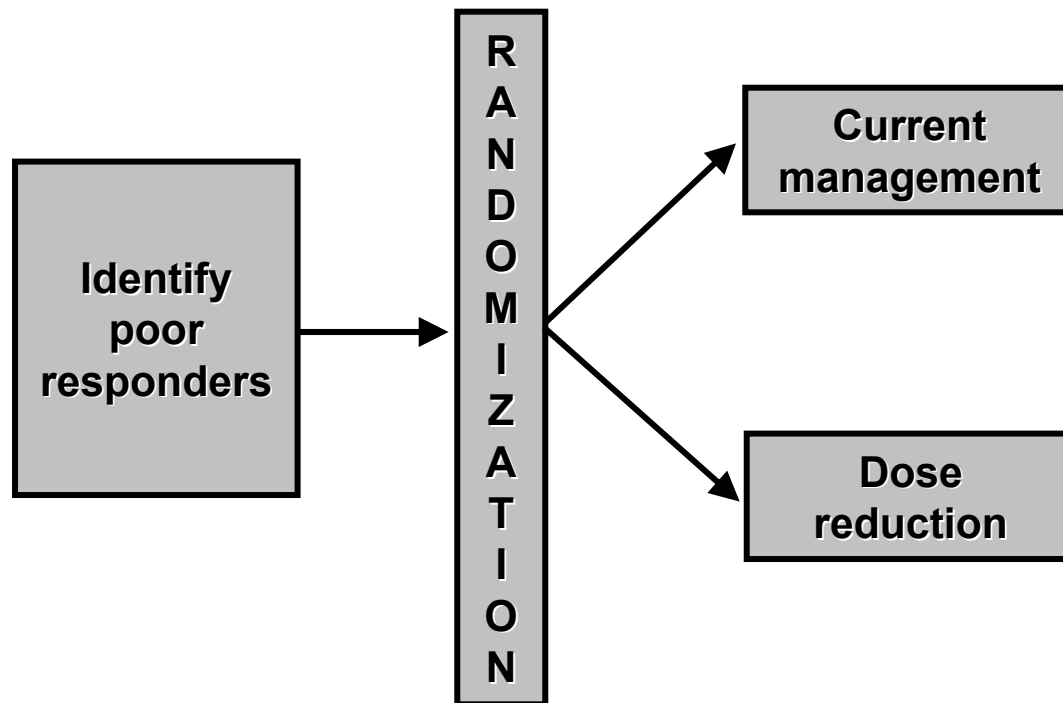
- **Run-in period with dose challenge to assess ESA responsiveness is feasible in non-dialysis CRF**

## **Hb target**

- **Feedback from nephrology community strongly suggests any dialysis study with Hb target  $\leq 10$  g/dL would be difficult to enroll with appropriate patients due to lack of clinical equipoise**

# Management of Poor ESA Responders Can Be Investigated in CRF

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## Primary endpoint

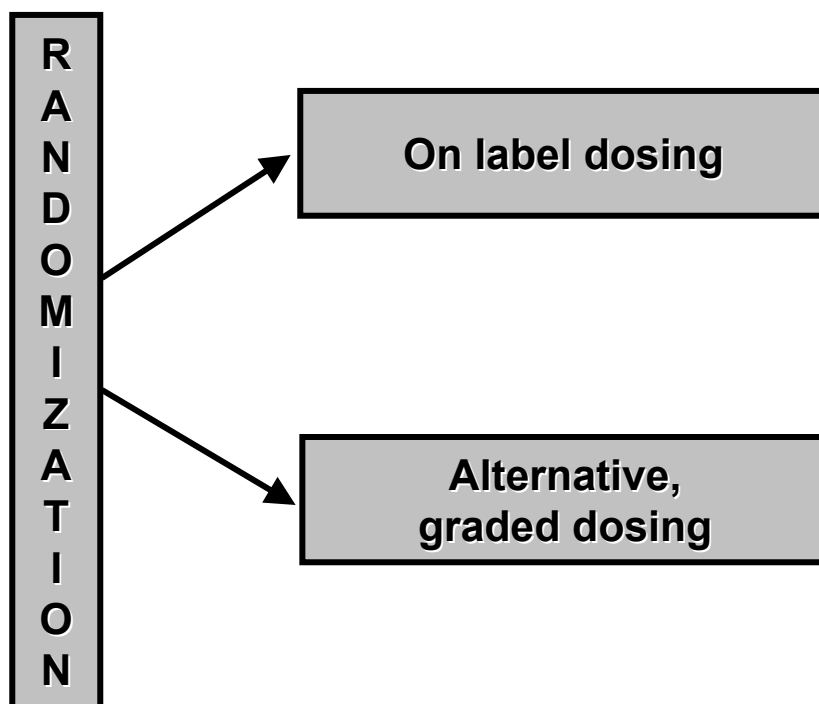
- Time to all cause death or first non-fatal CV event

## Secondary endpoints

- Transfusion
- PRO
- Exercise capacity

# Potential Study to Minimize Hb Cycling

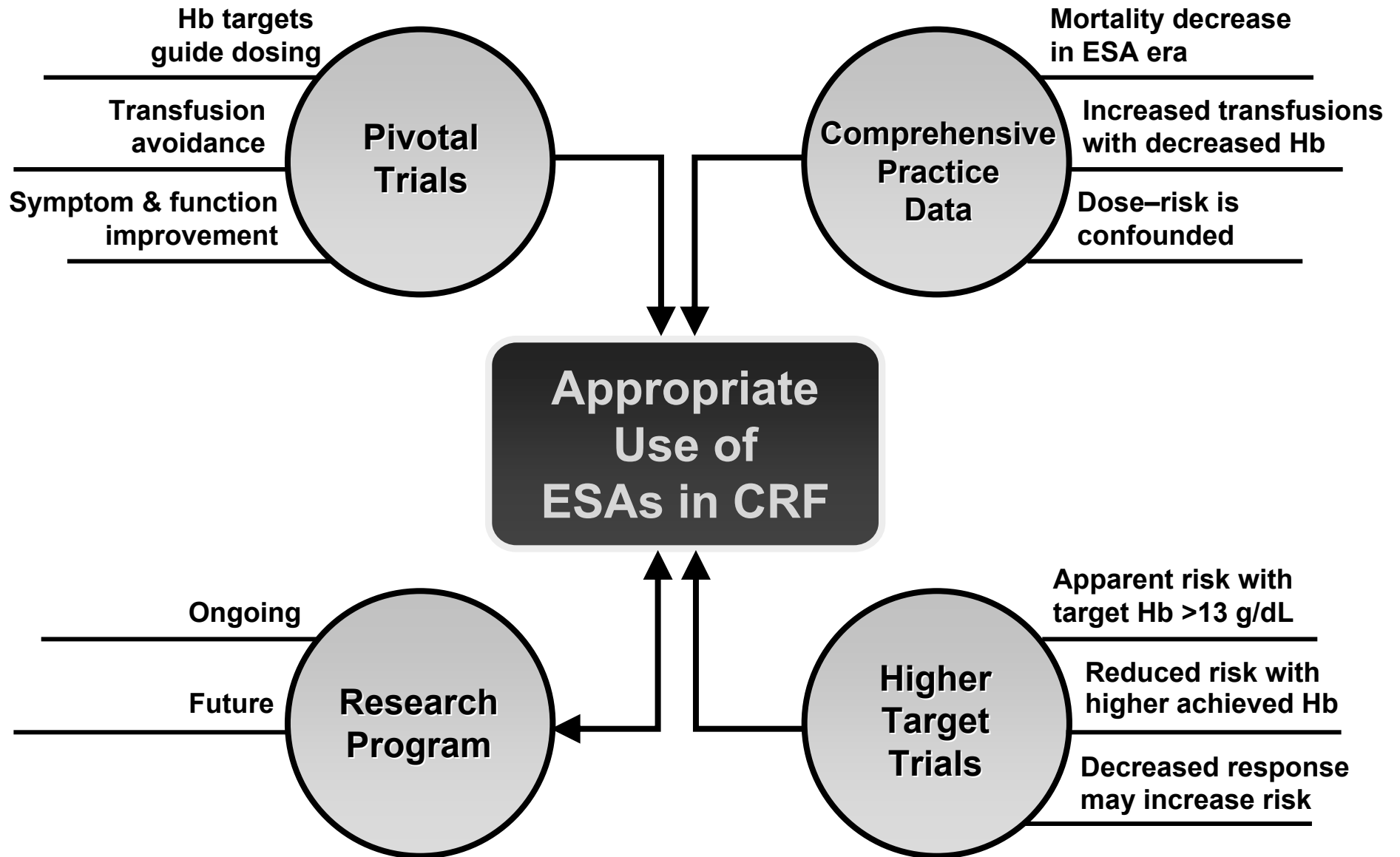
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## Endpoints

- Hb
- Hb standard deviation
- Time with Hb in target range
- Time to return Hb from out of target to within target

Hb (g/dL) from Target	On Label Dosing	Graded Dosing
0.5-1.0	25% dose adjustment	10% dose adjustment
1.0-2.0	25% dose adjustment	25% dose adjustment
>2.0	25% dose adjustment	50% dose adjustment



# Comprehensive Evidence Supports Appropriate Use of ESAs in CRF

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- **Hb target is clinically important (label recommendation 10-12 g/dL)**
- **Relationship between dose and outcomes is highly confounded**
- **Additional investigation of hyporesponsiveness and outcome required**

# Presentation Outline

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## **TREAT**

**Marc Pfeffer, MD, PhD**

Dzau Professor of Medicine, Harvard Medical School,  
Cardiovascular Division, Brigham and Women's Hospital

## **Introduction**

**Paul Eisenberg, MD, MPH, FACC**

Global Regulatory Affairs & Safety, Amgen Inc

## **Clinical Perspective**

**Allen R. Nissenson, MD, FACP, FASN**

Professor of Medicine, Associate Dean, Director,  
Dialysis Program, David Geffen School of Medicine, UCLA

## **Benefit/Risk**

**Preston Klassen, MD, MHS**

Global Development, Amgen Inc

## **Risk Management**

**Paul Eisenberg, MD, MPH, FACC**

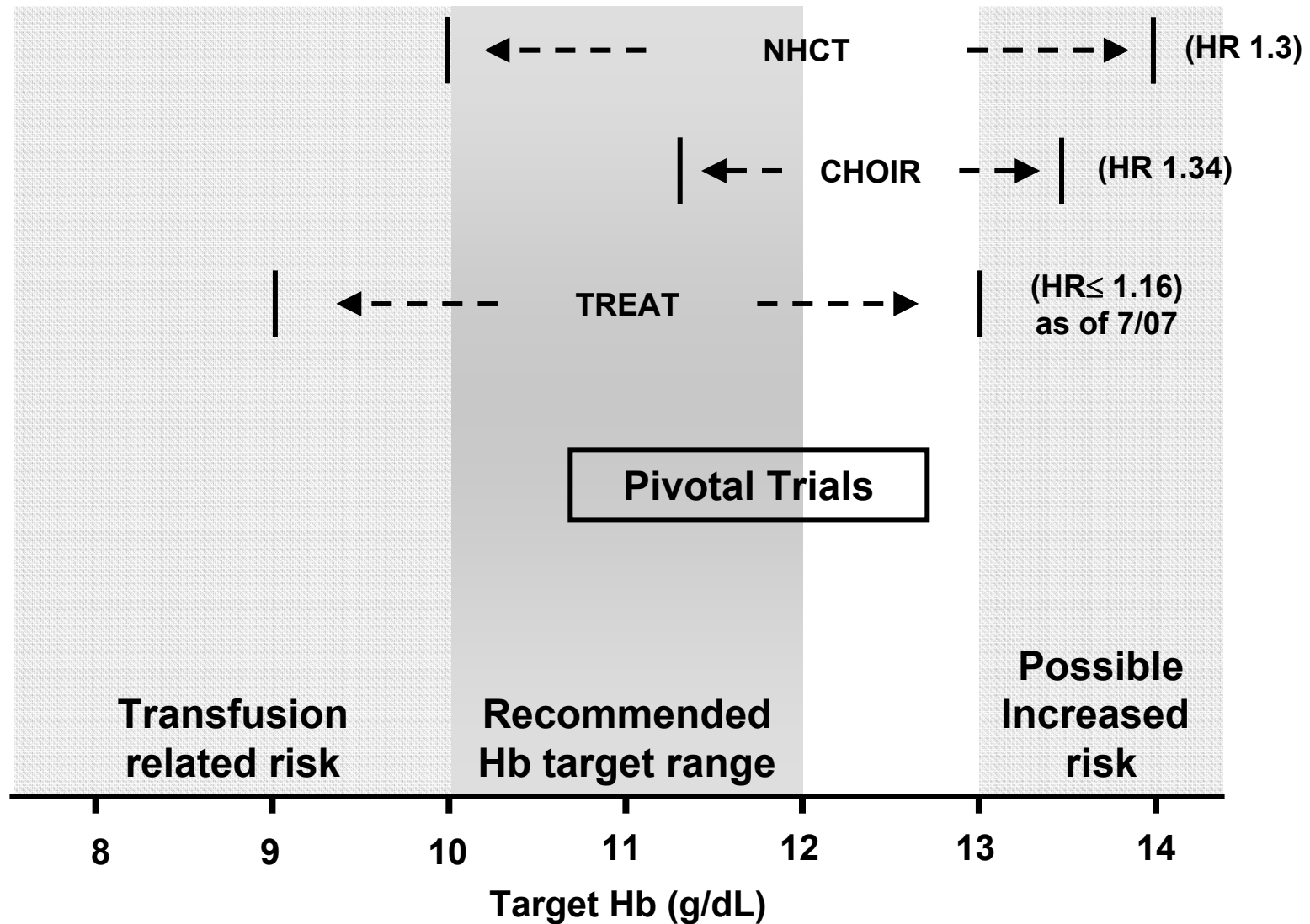
Global Regulatory Affairs & Safety, Amgen Inc

# Sponsors Are Committed to Additional Risk Management on Key Issues

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- **Hb target**
- **ESA responsiveness**
- **Hb cycling**

# Hb Target



# Risk Management Summary

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**Hb target**

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**ESA responsiveness**

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**Hb cycling**

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# Risk Management Summary

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	<b>Risk Management</b>	<b>Additional Risk Assessment</b>
	<b>Label – target 10-12 g/dL</b>	
<b>Hb target</b>	<b>Dose according to current label Physician and patient education (eg medication guide)</b>	<b>TREAT study RCT to evaluate Hb target based on TREAT outcome</b>

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# Risk Management Summary

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	<b>Risk Management</b>	<b>Additional Risk Assessment</b>
<b>Hb target</b>	<b>Label – target 10-12 g/dL</b> <b>Dose according to current label</b> <b>Physician and patient education (eg medication guide)</b>	<b>TREAT study</b> <b>RCT to evaluate Hb target based on TREAT outcome</b>
<b>ESA responsiveness</b>	<b>Label advising recognition and management</b> <b>Description of increased risk</b> <b>Dose limitations should be individualized</b>	<b>RCT to evaluate appropriate management</b>

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# ESA Responsiveness

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- **Proposed definition of hyporesponsiveness in product labeling**
  - **Unable to achieve desired Hb target within range of 10-12 g/dL despite use of appropriate dose titrations per label over a 12 week period**
  
- **Patient management**
  - **Evaluate for reversible causes**
  - **Use lowest dose to maintain stable Hb**
  - **Periodically reassess responsiveness**
  
- **Additional RCTs to refine risk management**

# Risk Management Summary

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	<b>Risk Management</b>	<b>Additional Risk Assessment</b>
<b>Hb target</b>	<b>Label – target 10-12 g/dL</b> <b>Dose according to current label</b> <b>Physician and patient education (eg medication guide)</b>	<b>TREAT study</b> <b>RCT to evaluate Hb target based on TREAT outcome</b>
<b>ESA responsiveness</b>	<b>Label advising recognition and management</b> <b>Description of increased risk</b> <b>Dose limitations should be individualized</b>	<b>RCT to evaluate appropriate management</b>
<b>Hb cycling</b>	<b>Advise to maintain stable Hb within target of 10-12 g/dL</b>	<b>Clinical studies</b>

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# Risk Management Summary

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	<b>Risk Management</b>	<b>Additional Risk Assessment</b>
<b>Hb target</b>	<b>Label – target 10-12 g/dL</b> <b>Dose according to current label</b> <b>Physician and patient education (eg medication guide)</b>	<b>TREAT study</b> <b>RCT to evaluate Hb target based on TREAT outcome</b>
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# Erythropoiesis-Stimulating Agent (ESA) Therapy in Chronic Renal Failure (CRF)

Joint Meeting Between the  
Cardiovascular and Renal Drugs &  
Drug Safety and Risk Management  
Advisory Committees

11 September 2007