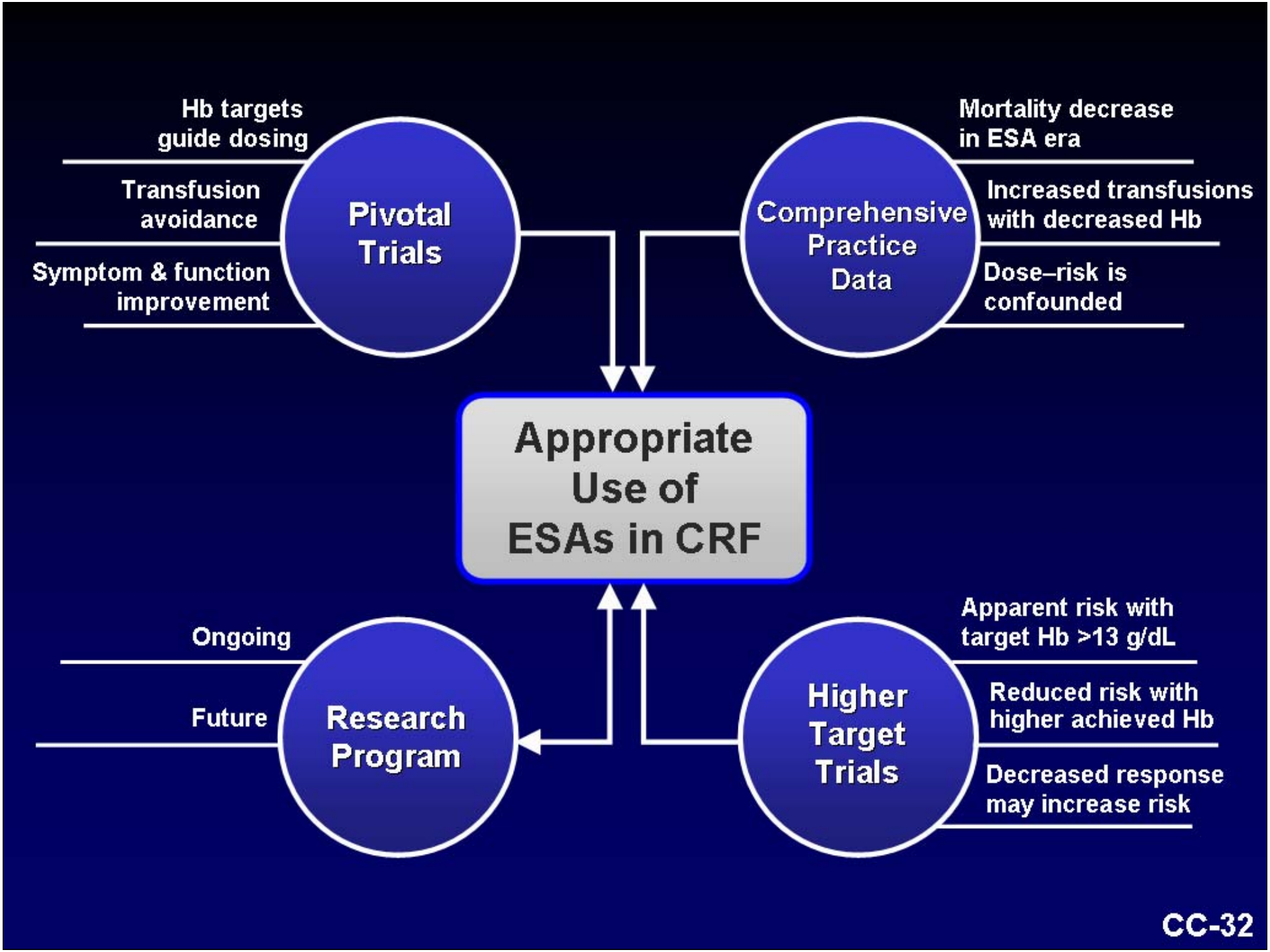
Presentation Outline

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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Ongoing
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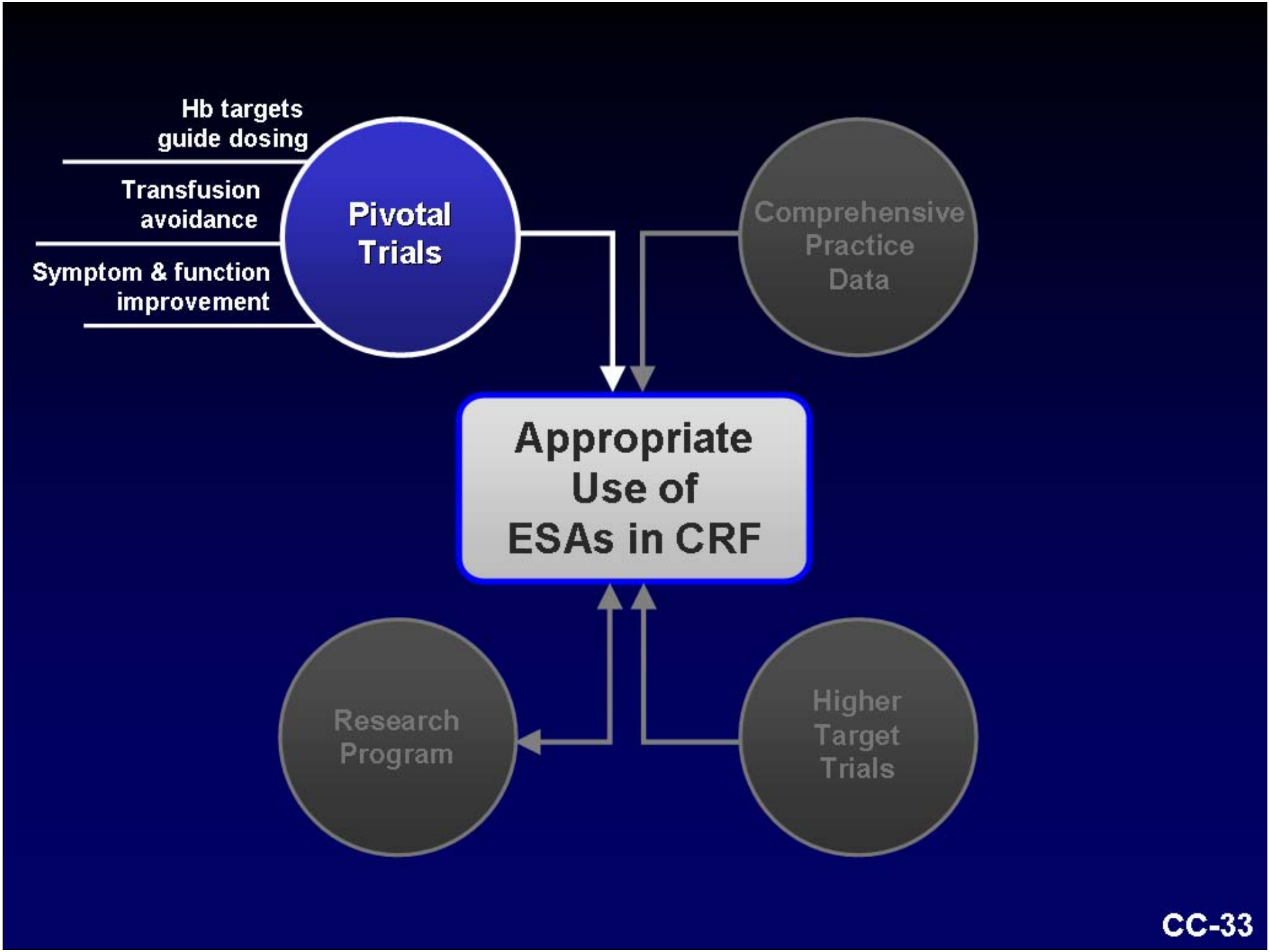
Reduced risk with higher achieved Hb
Decreased response may increase risk
Higher Target Trials
CC-32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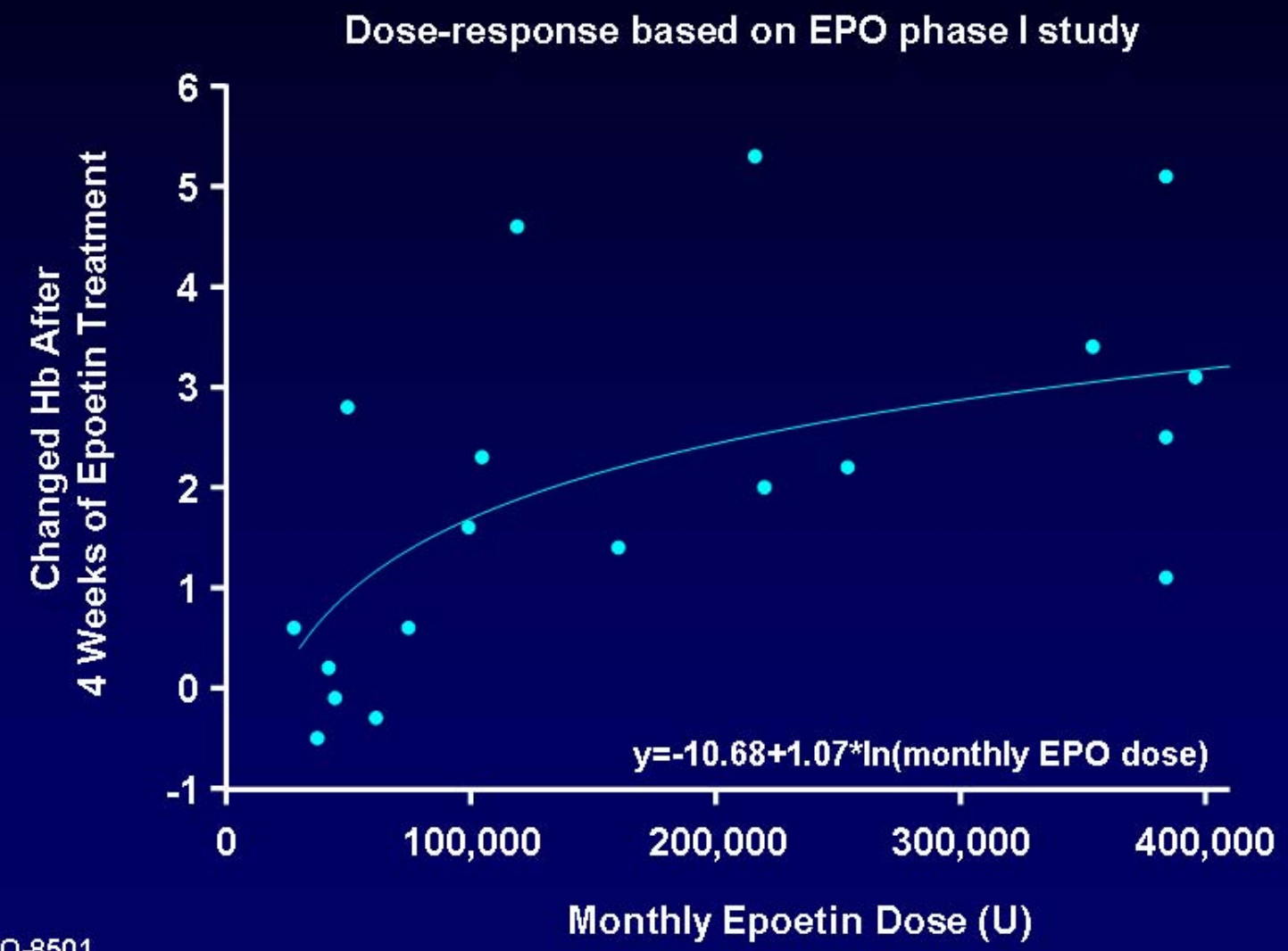
Hb Targets Important for Anemia Management

- **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**

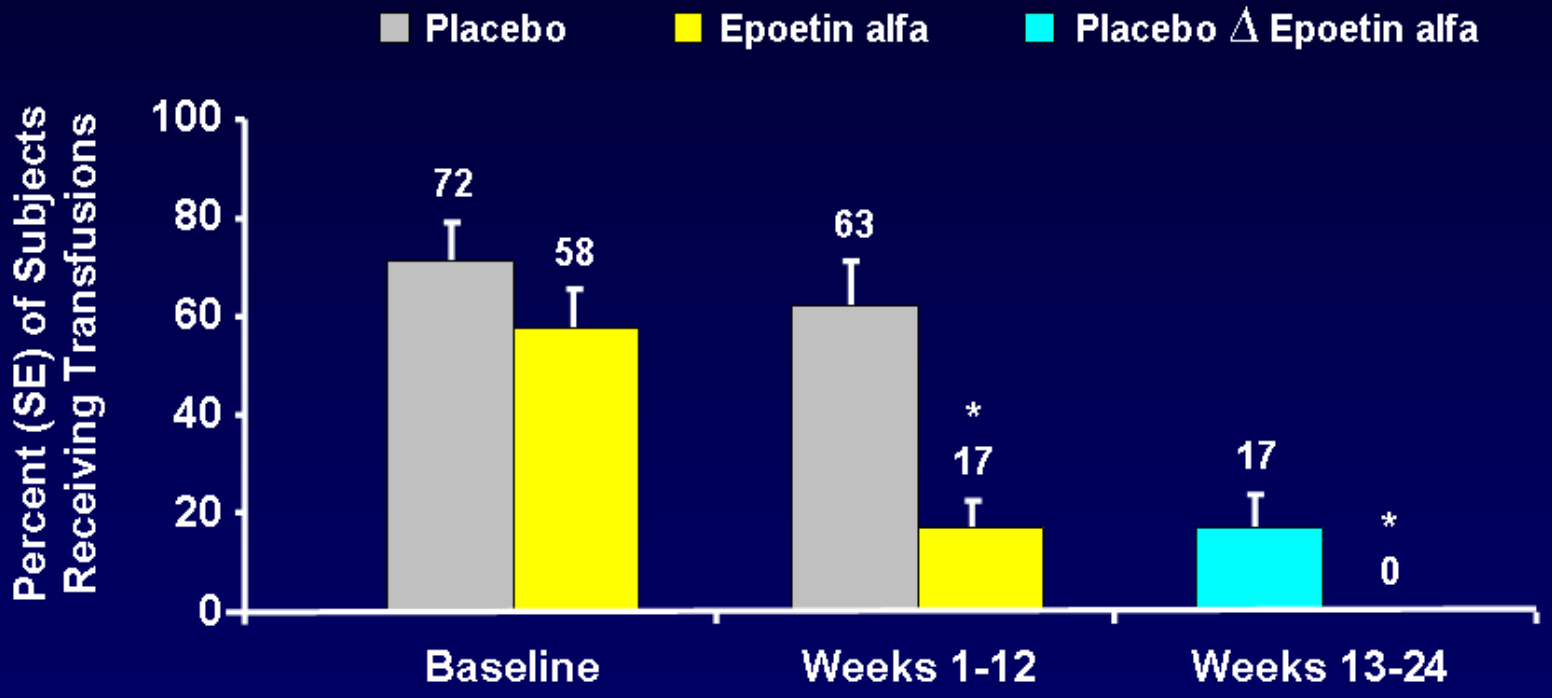
Epoetin alfa Phase I/II Study: Dose-response



Study EPO-8501

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 Δ 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

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

[1]Loss to follow-up=19%
[2]Loss to follow-up=24%
[3]Kidney Disease Questionnaire
[4]Loss to follow-up=16%

CESG Demonstrated Improvements in Physical Function

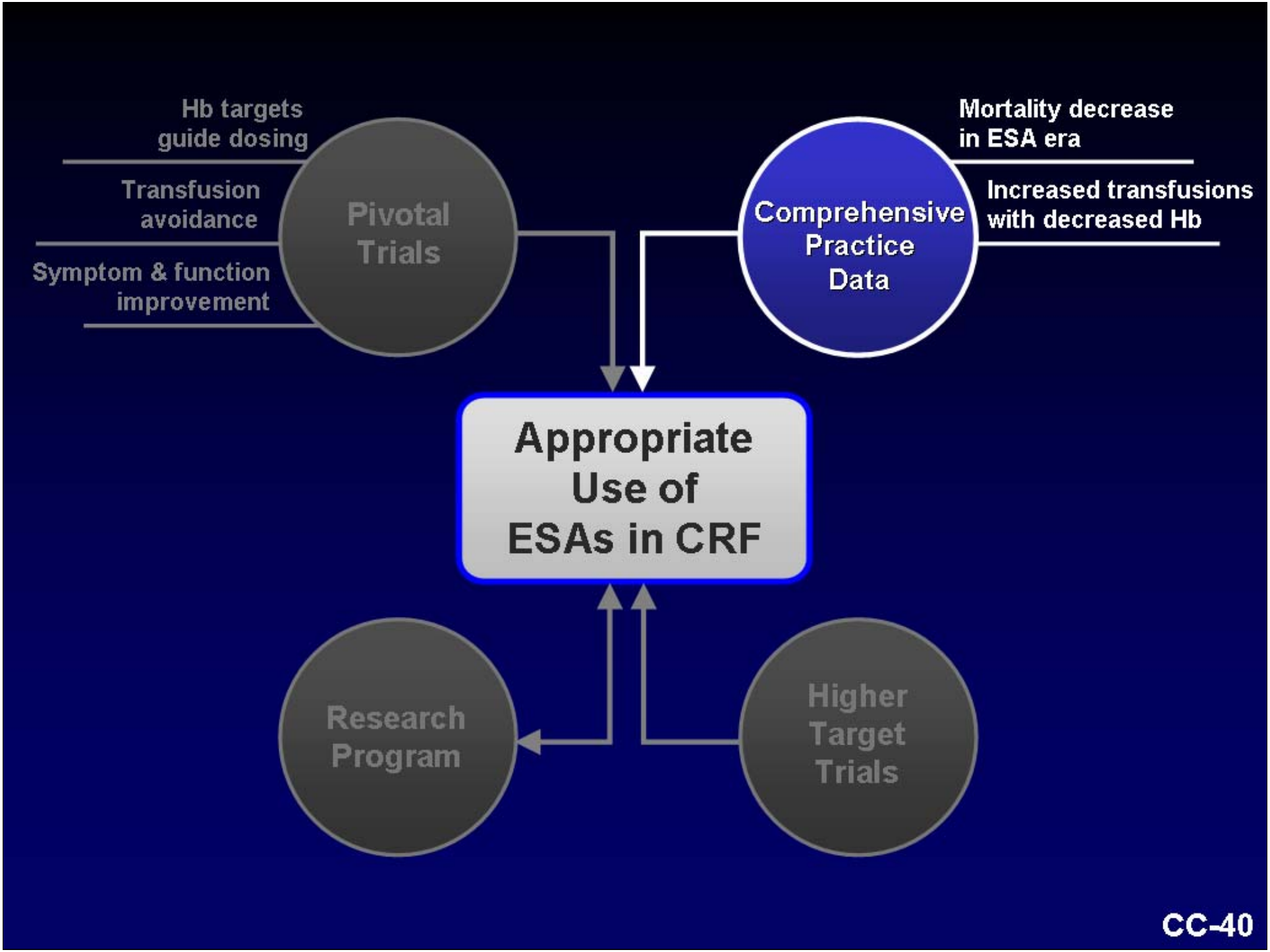
Measure	Placebo (Δ BL to 6 mo)	Group A (Δ BL to 6 mo)	Group B (Δ BL to 6 mo)	p-value†
Hb (g/dL)	+0.2	+3.1	+4.6	<0.0001
Exercise stress (modified Naughton)				
Minutes walked	+1.3	+3.1	+4.8	<0.001
6-Minute walk				
Meters walked	-5.5	+24.6	+54.6	<0.05

- **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
†ITT repeated measures mixed model, placebo vs treatment over time

ESAs Provide Meaningful Clinical Benefit

- 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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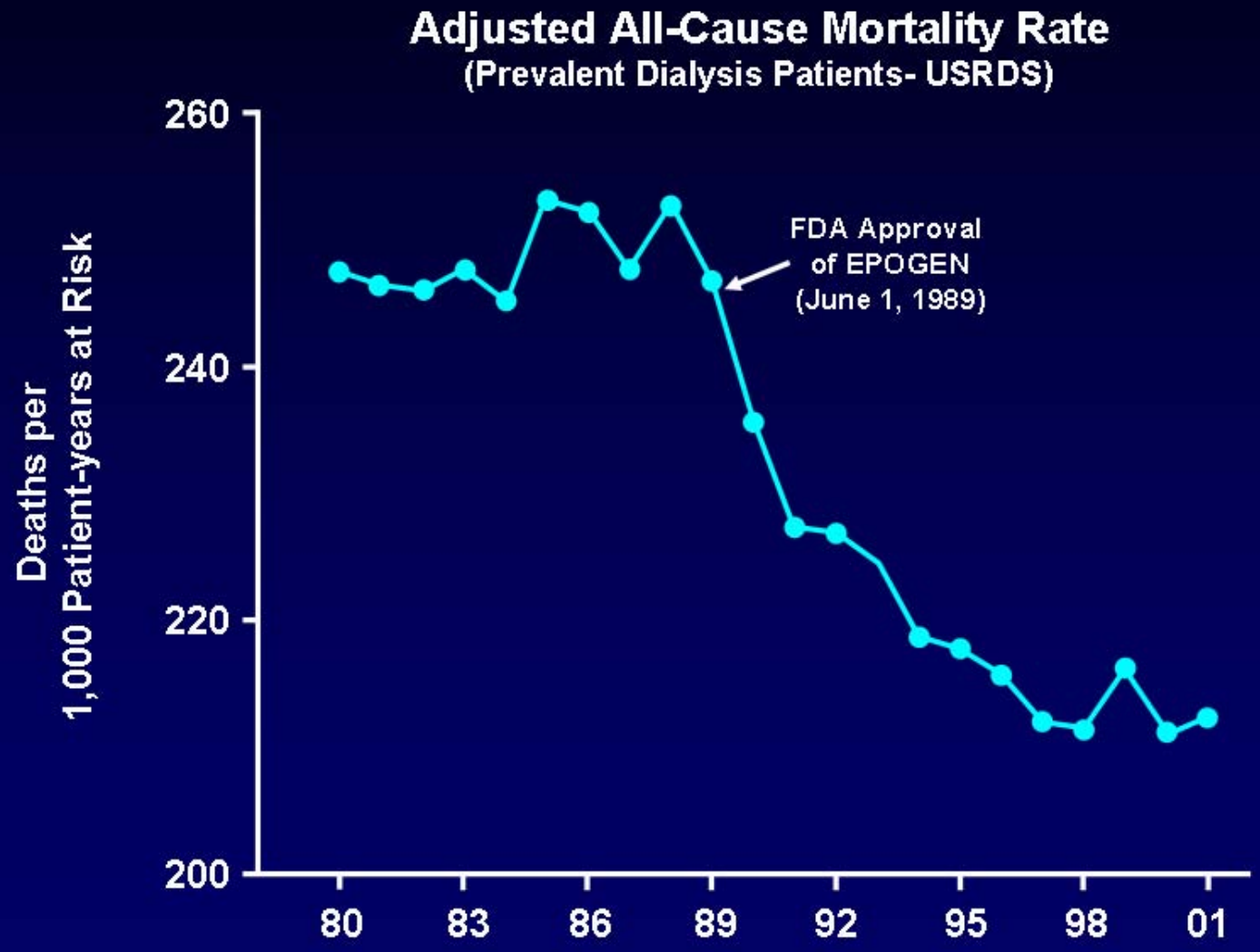
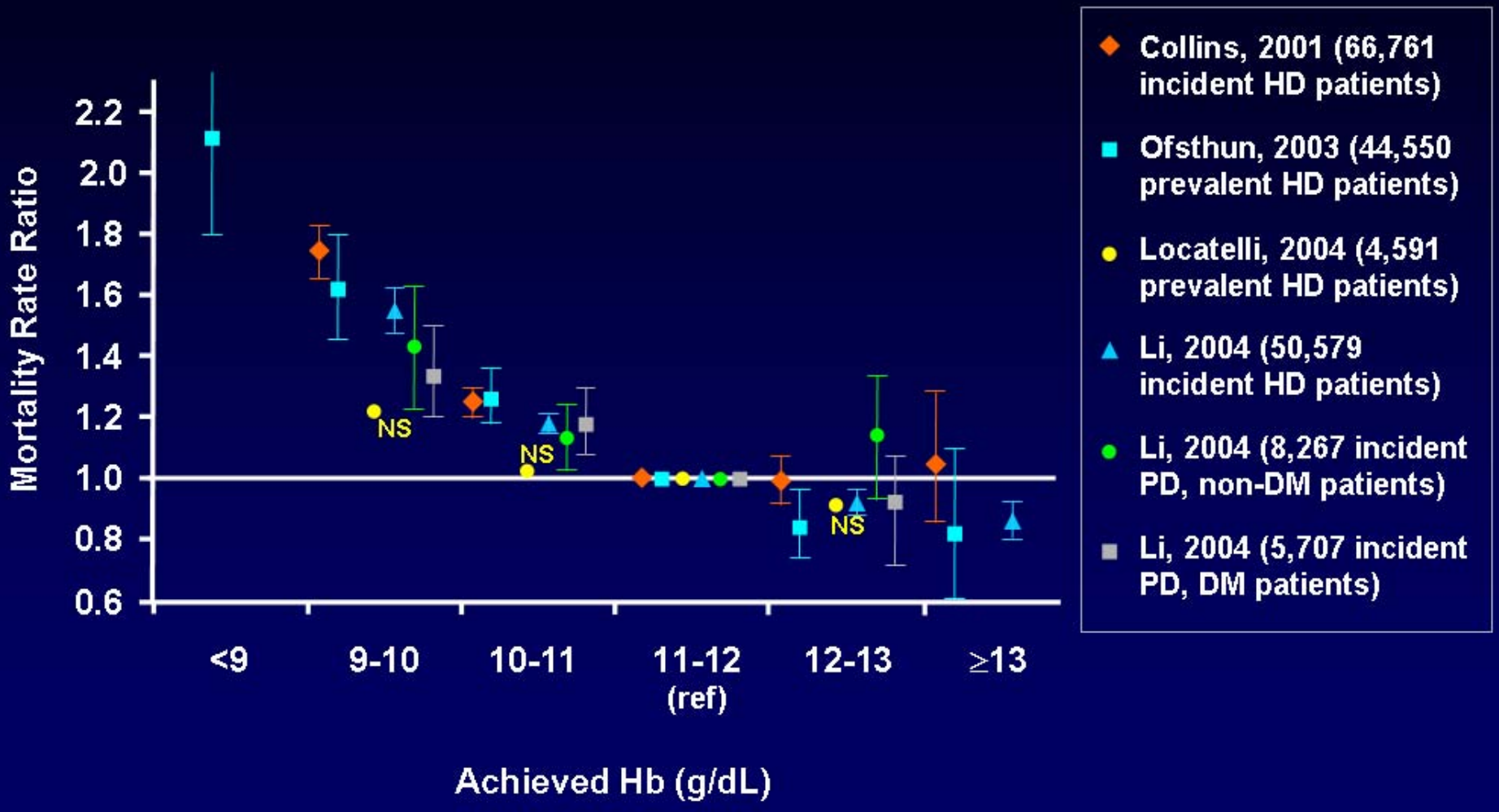
Mortality in Dialysis Has Declined in ESA Era



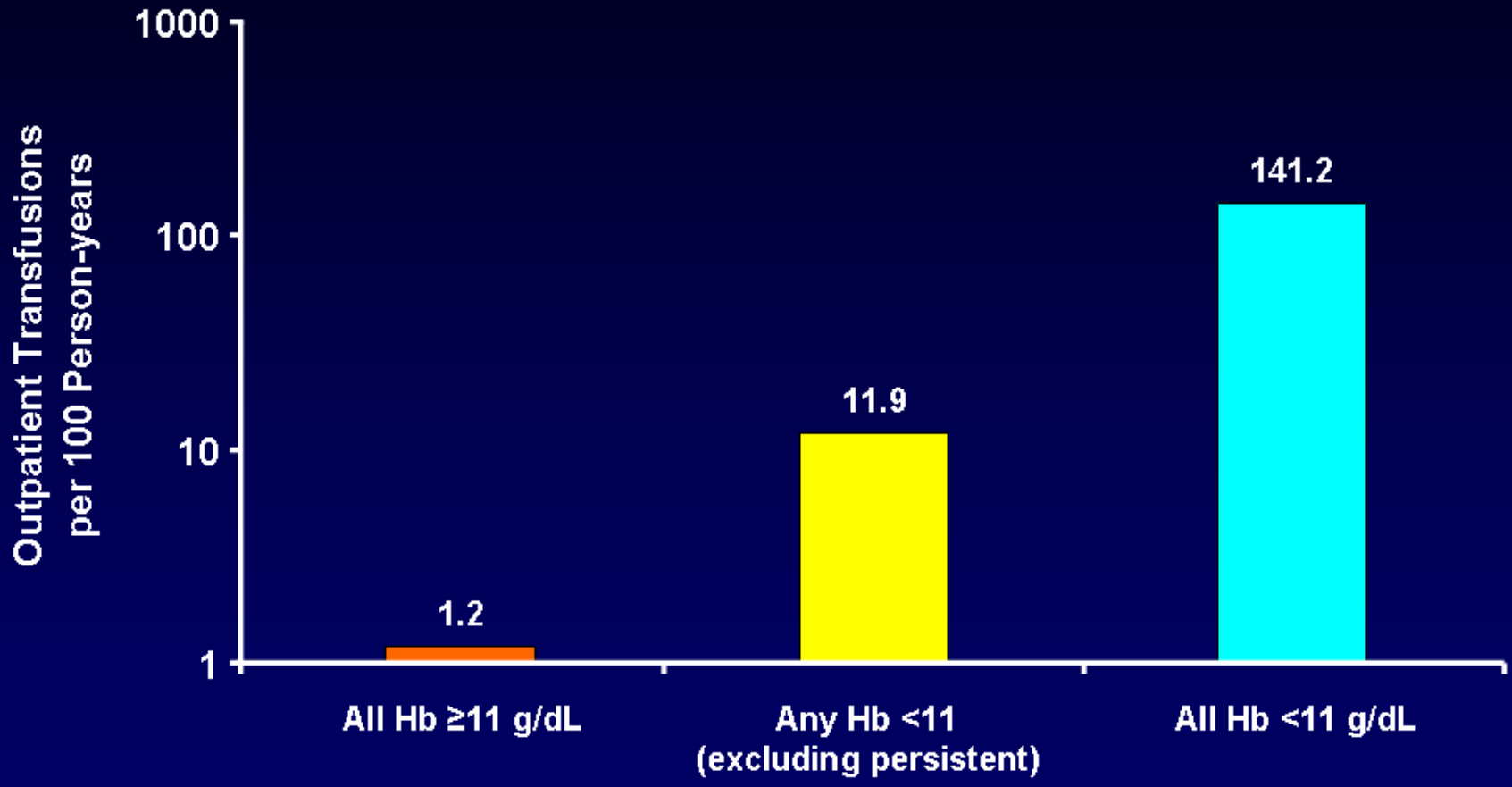
USRDS 2003 ADR

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

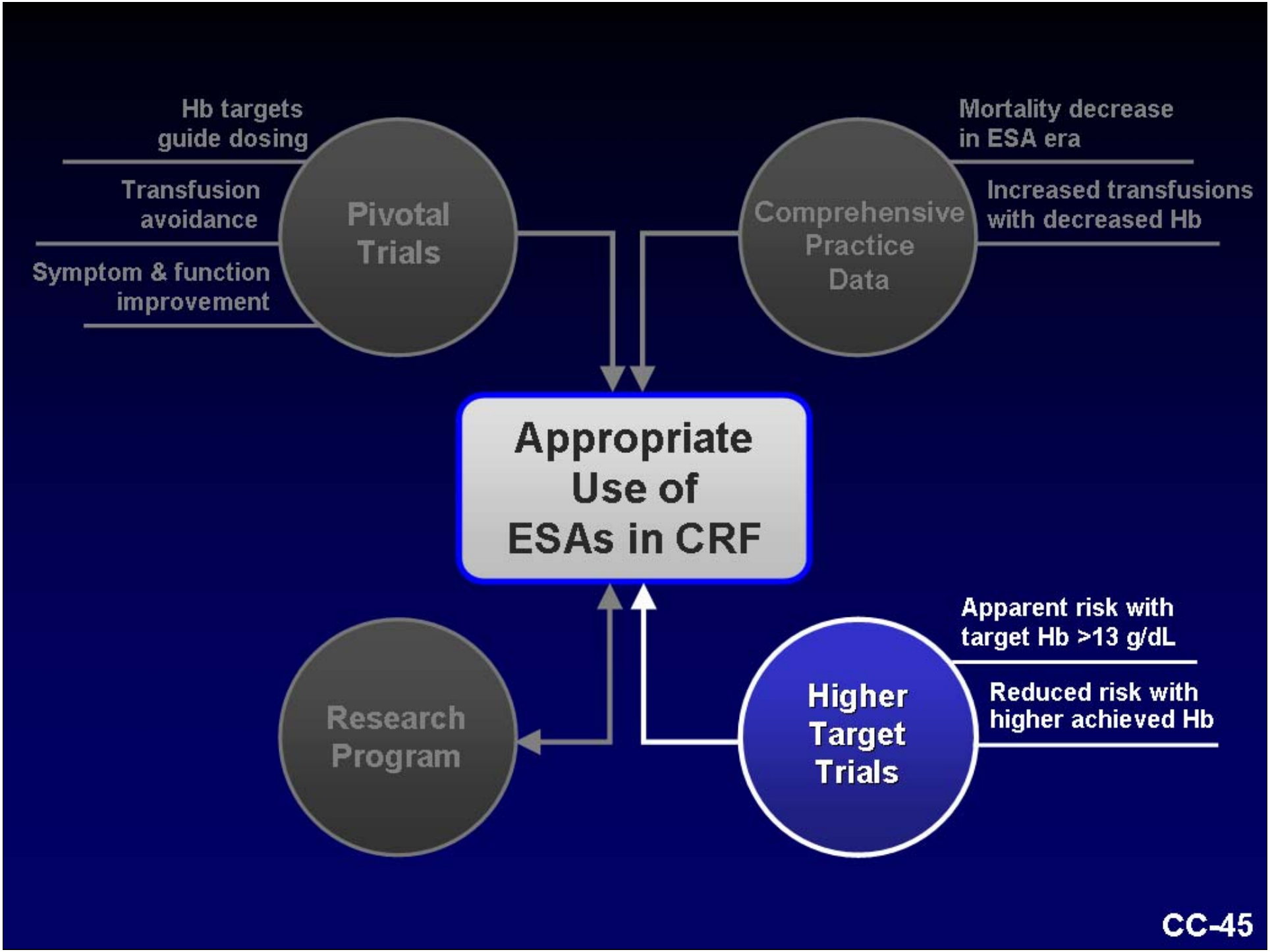


Percent of patients	40.0	58.6	1.4

N=161,597
Medicare ESRD database.

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

- **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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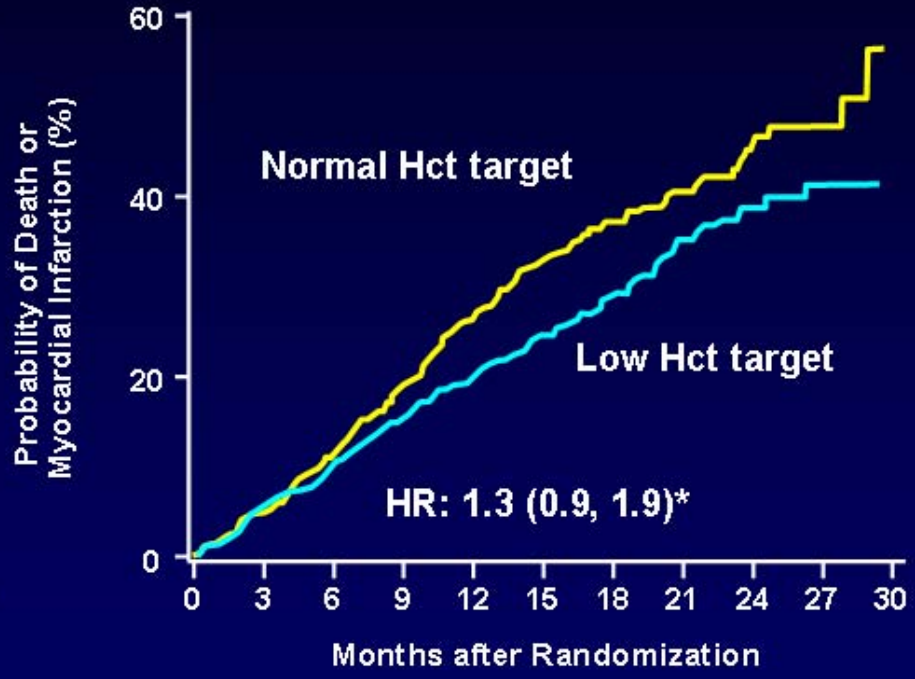
CC-45

Complete vs Partial Correction of Anemia

- **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

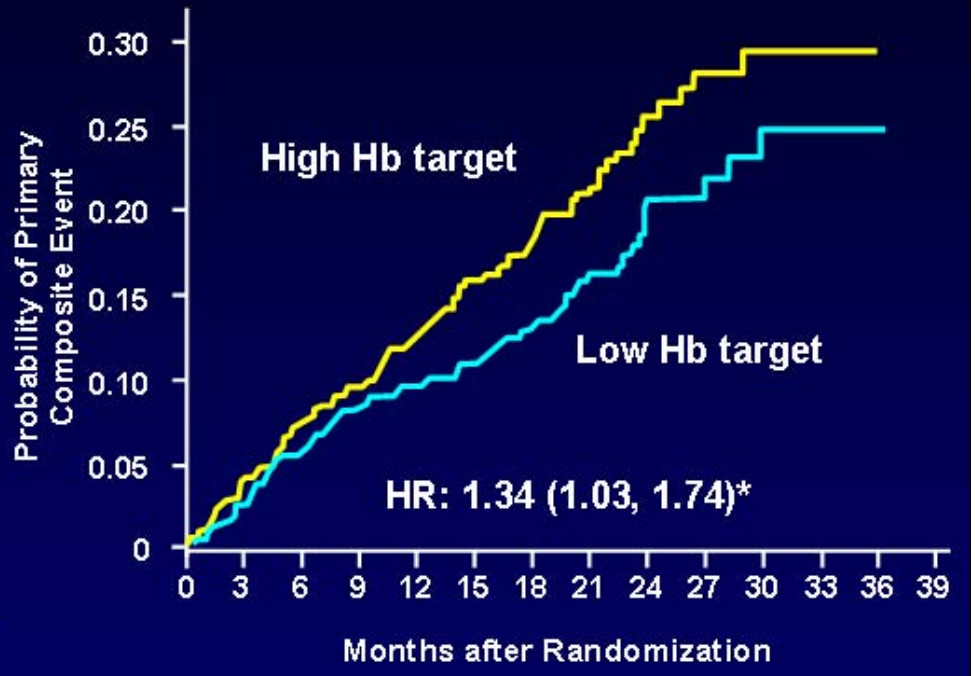


*95% CI

Besarab. *N Engl J Med* 1998.

Clinical Trial to Investigate Hb Normalization Identified Unexpected Risks: CHOIR

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

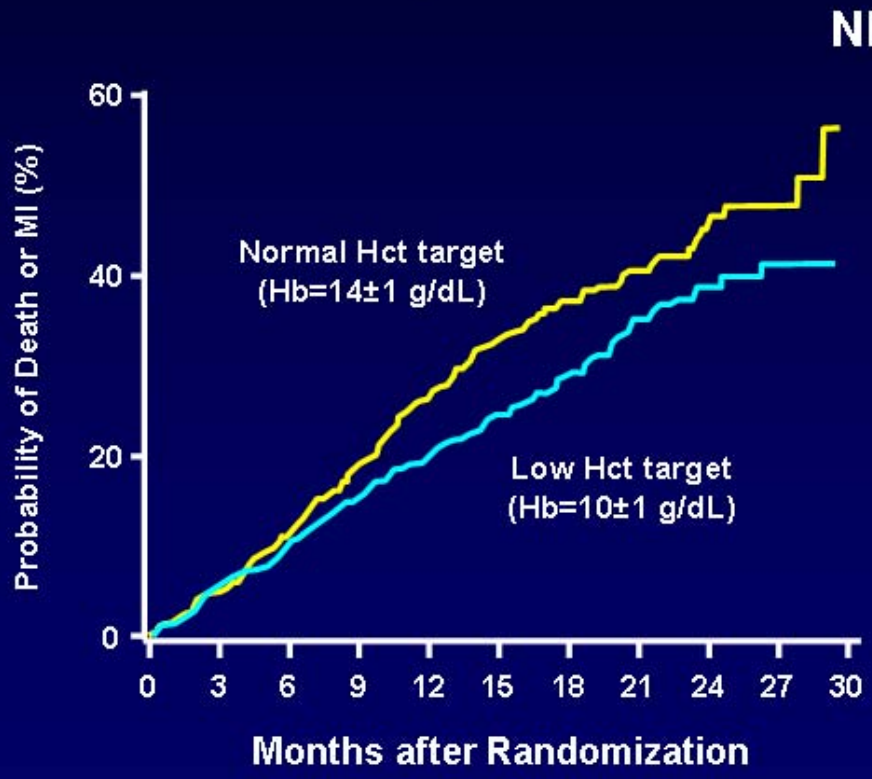


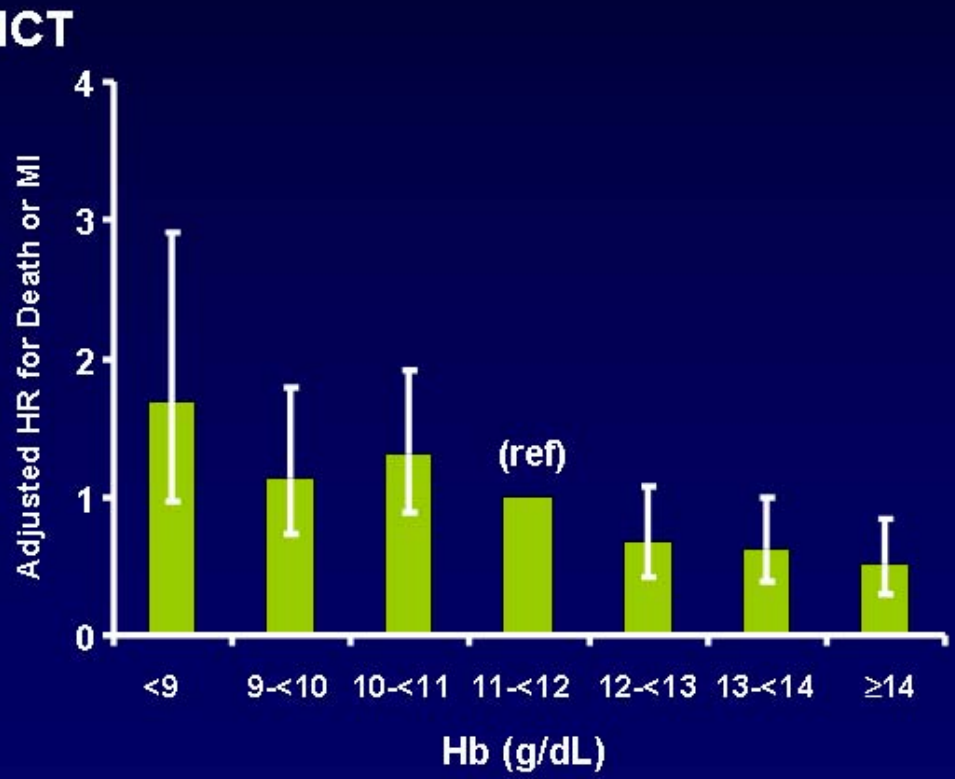
*95% CI

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.

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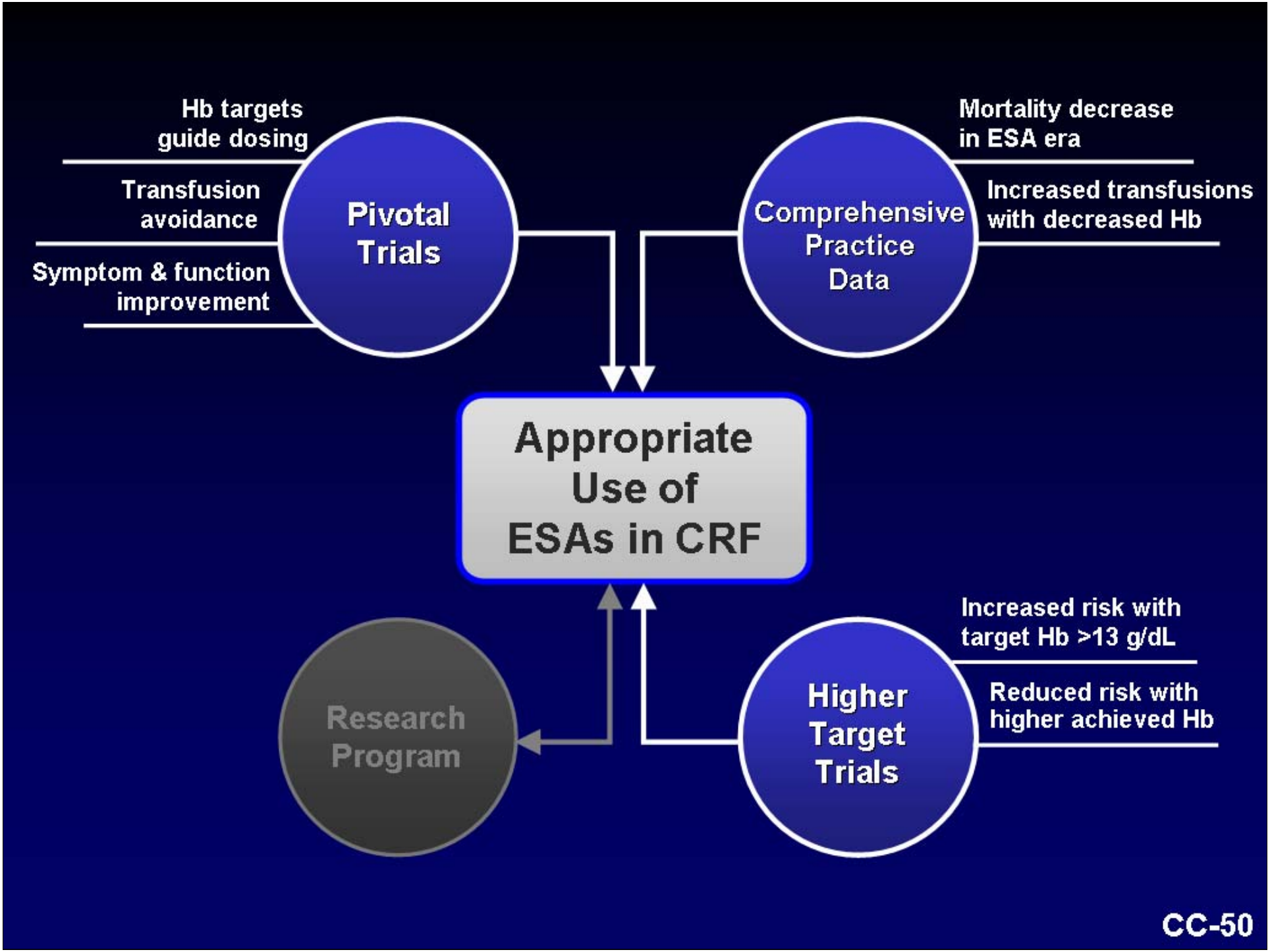
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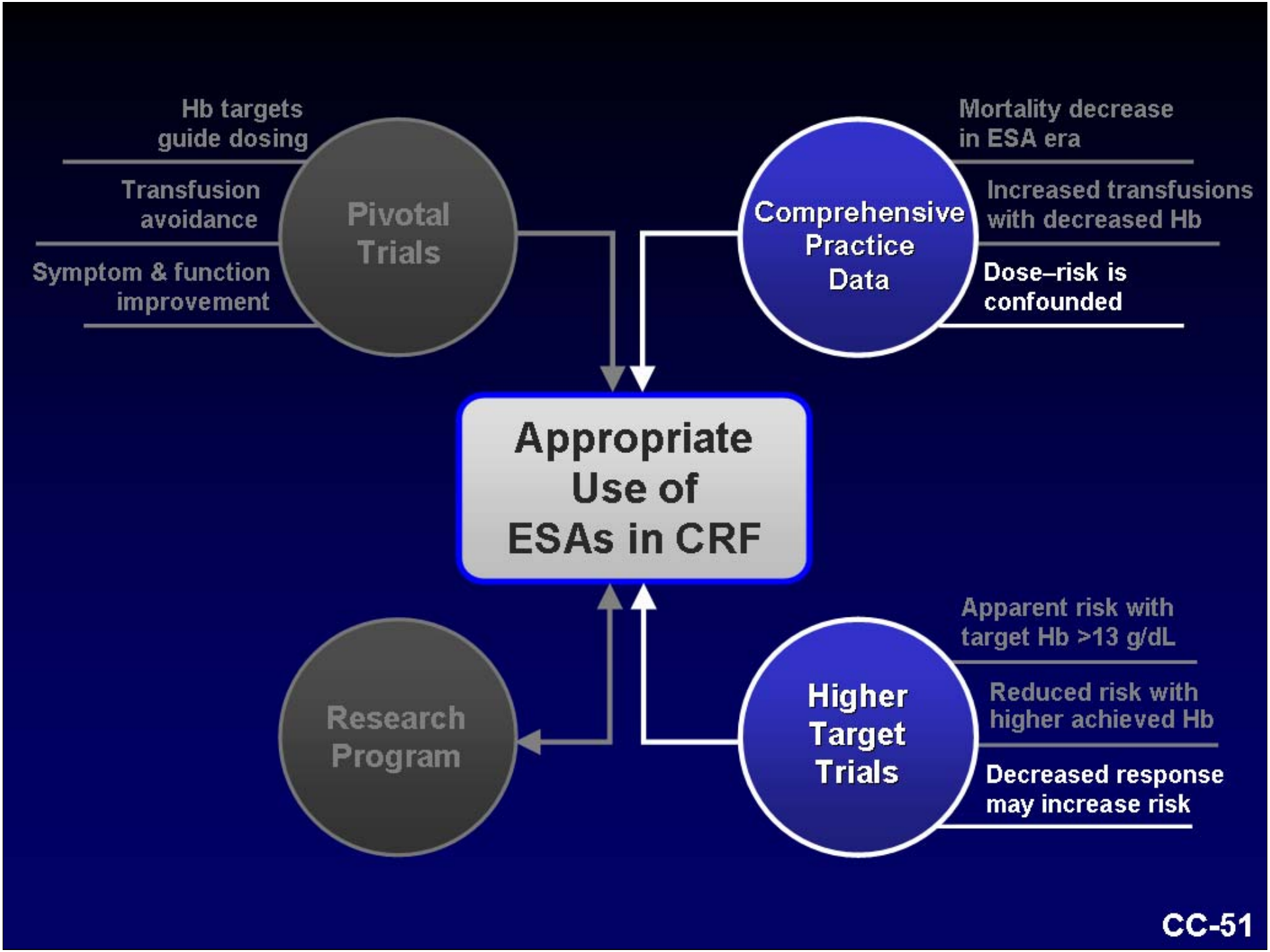
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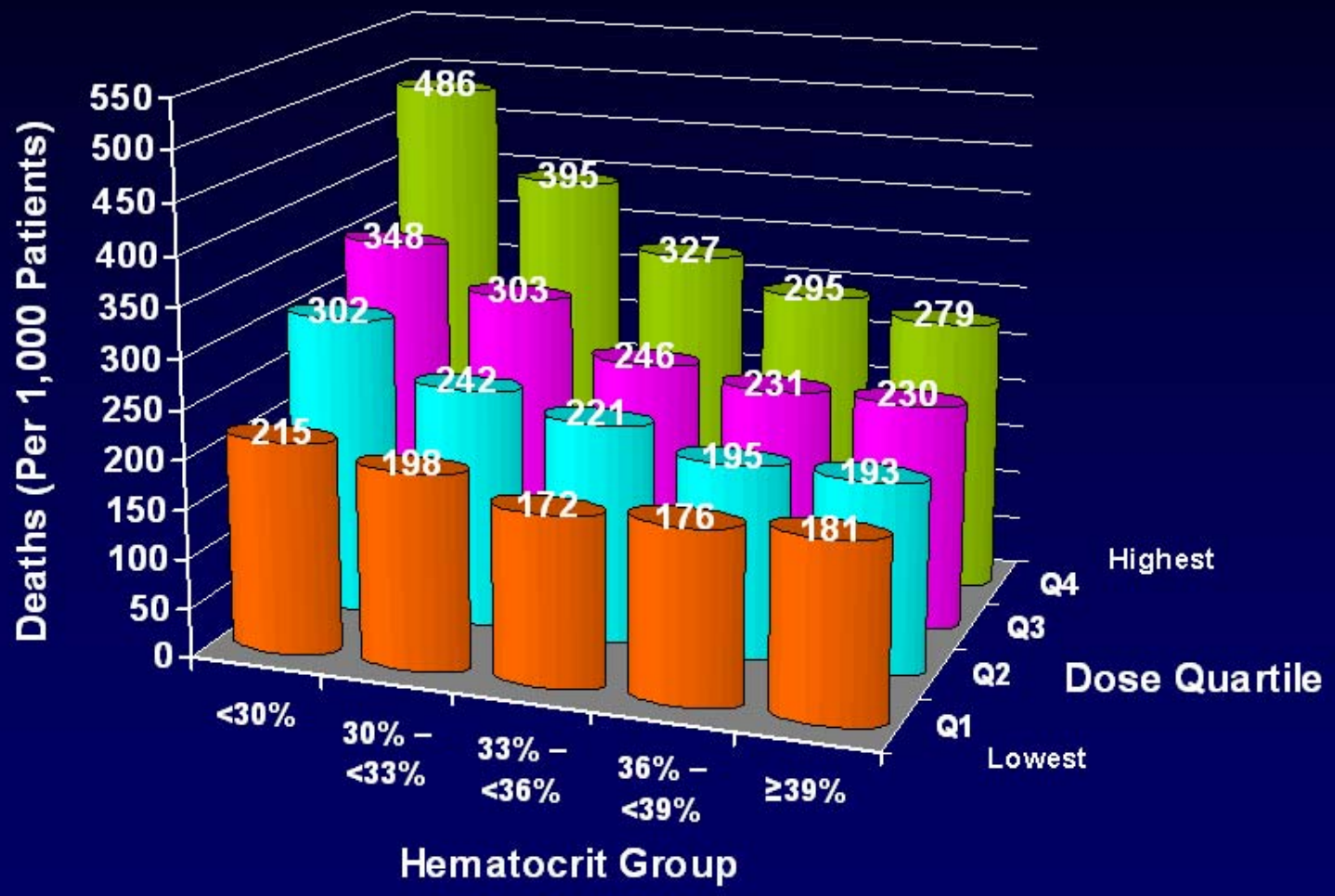
Potential Effect of Dose is Confounded by Health Status and Responsiveness

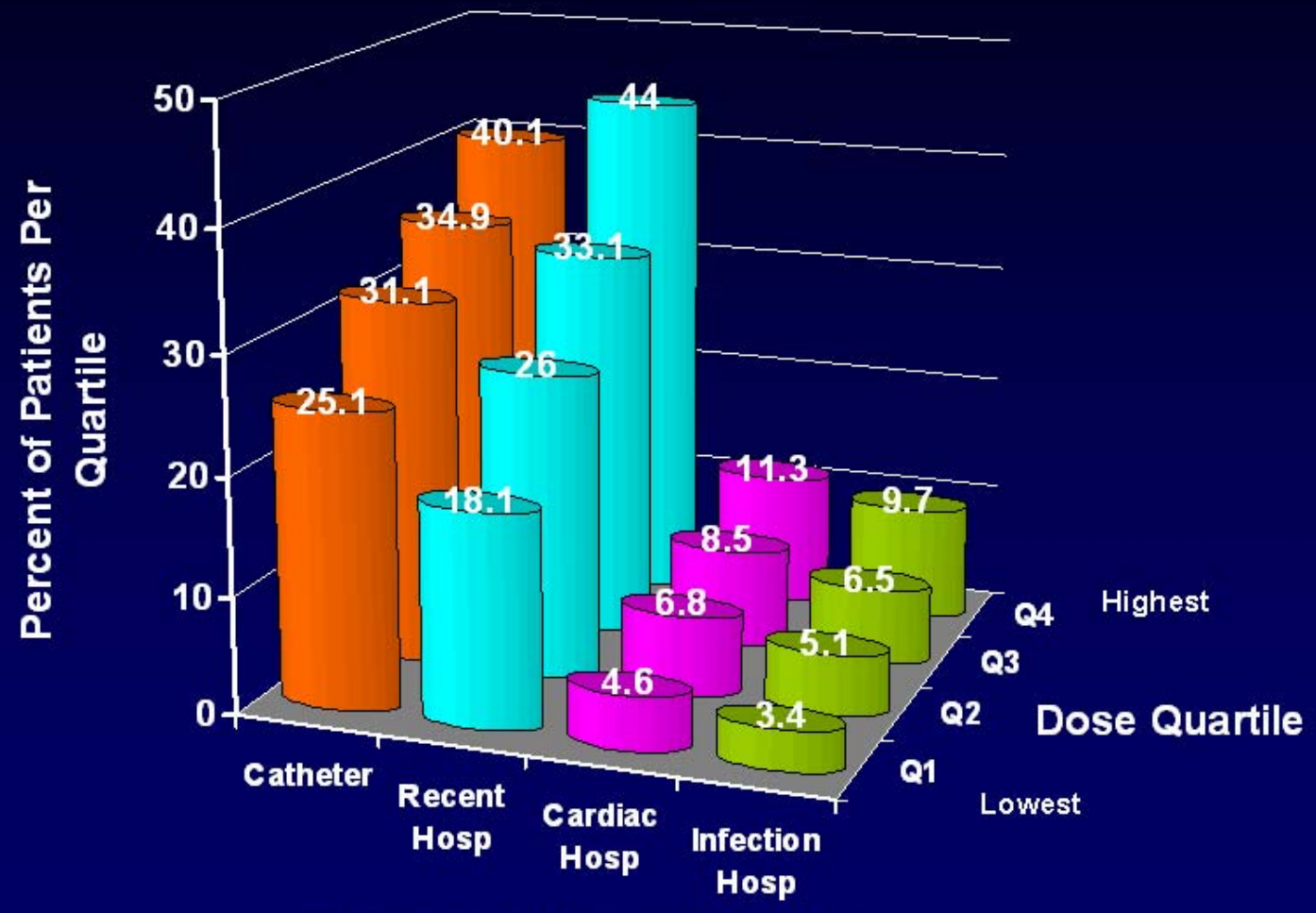
- **May not be possible to directly determine effect due to inseparable link among Hb, dose, and health status**
- **Patients with the worst health status have highest dose requirements and highest mortality**
- **Without control for confounding, effects of health status on outcomes may be mistakenly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

Greater ESA Dose is Associated with Mortality in an Unadjusted Analysis



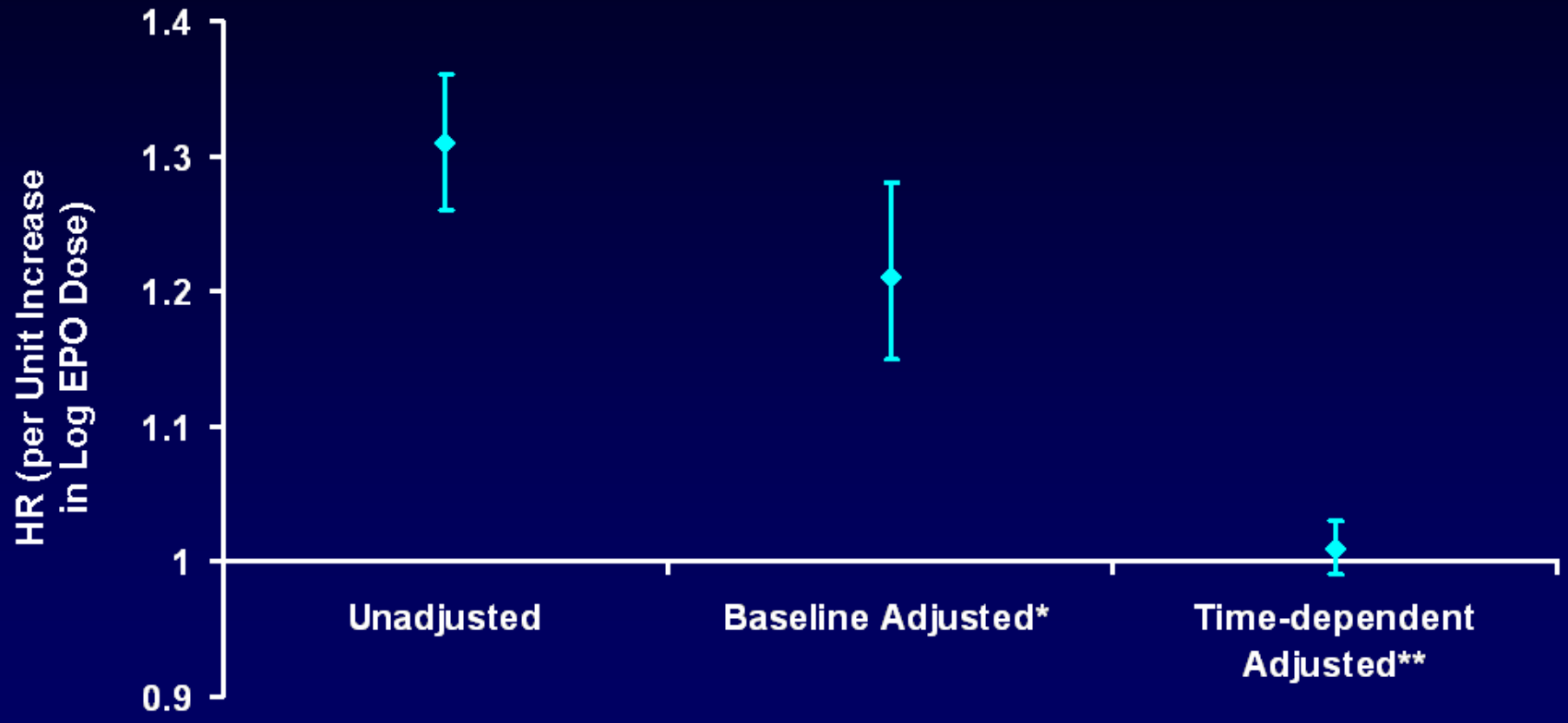
Zhang, *Am J Kidney Dis*, 2004.
Dose quartiles: Q1, 1388 to 7905 U/week; Q2, >7905 to 13,377 U/week; Q3, >13,377 to 22,068 U/week; Q4, >22,068 U/week

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



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

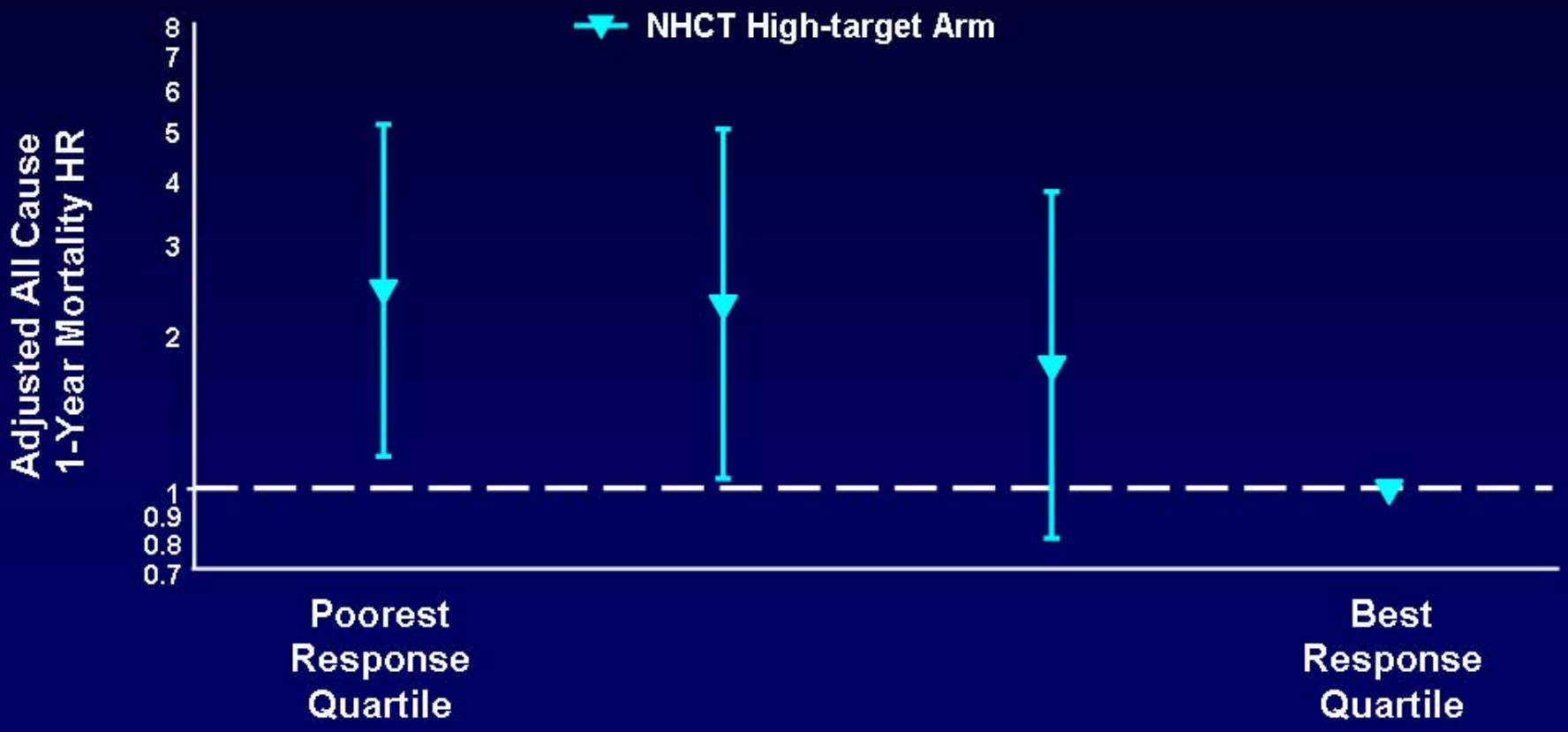
Association Between ESA Dose and Mortality Attenuated with Adjustment for Confounding



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

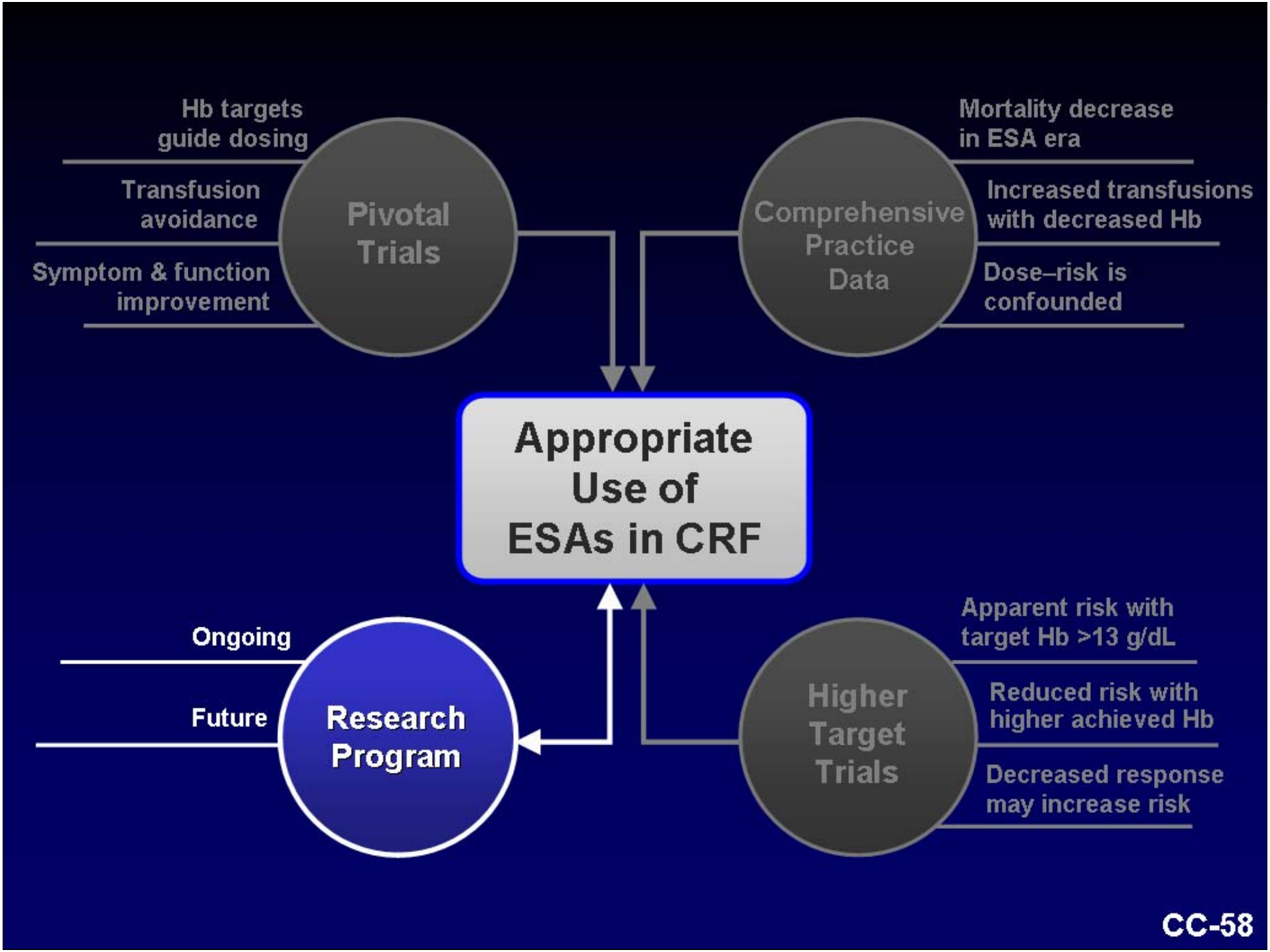
- **Dose challenge: 50% increase from baseline in high target arm**
- **Hb response: change in Hb over first three weeks**



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

- **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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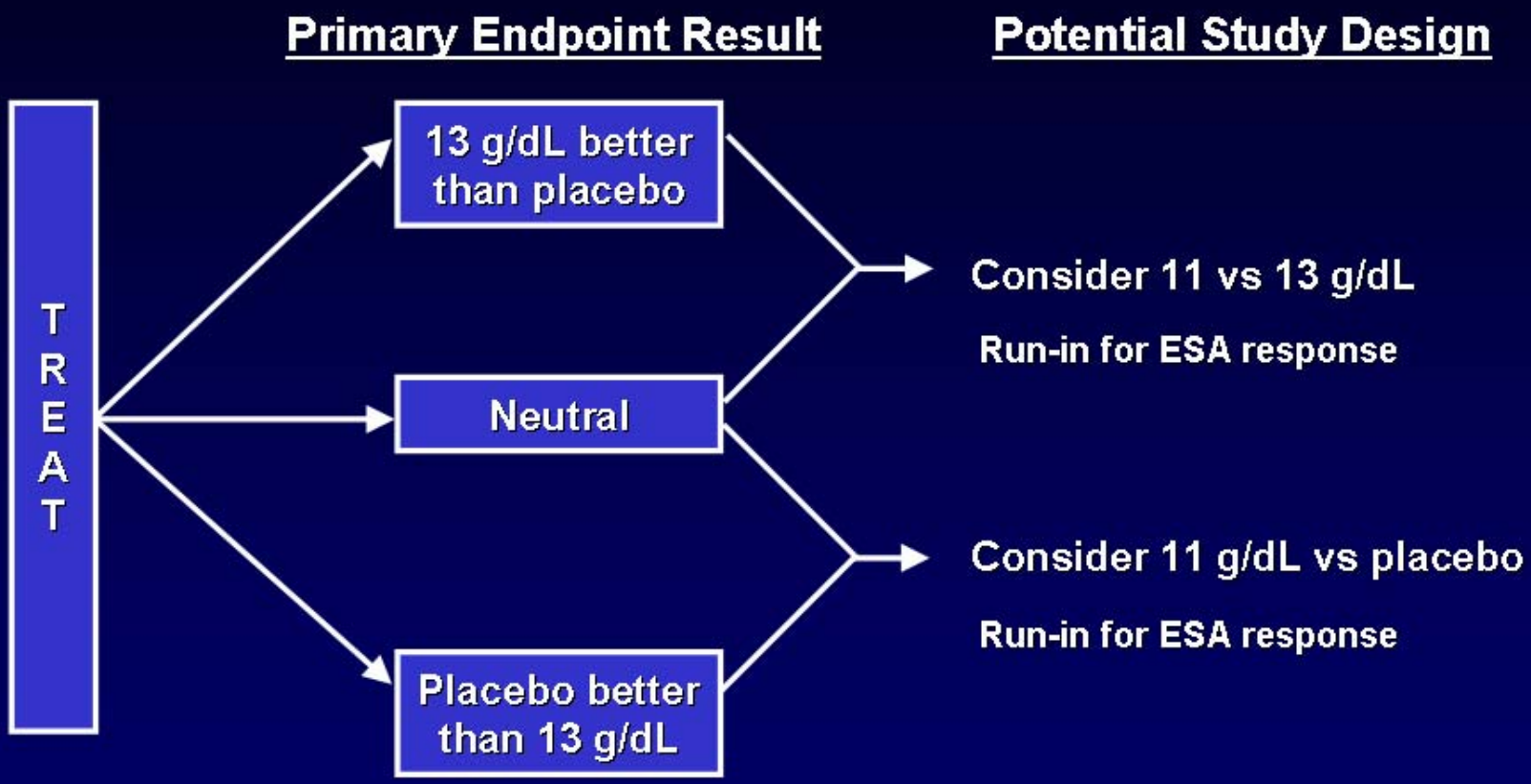
Sponsors Are Committed to Additional Research to Address Key Issues

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

TREAT Will Inform Future Research



Considerations of Appropriate CRF Population

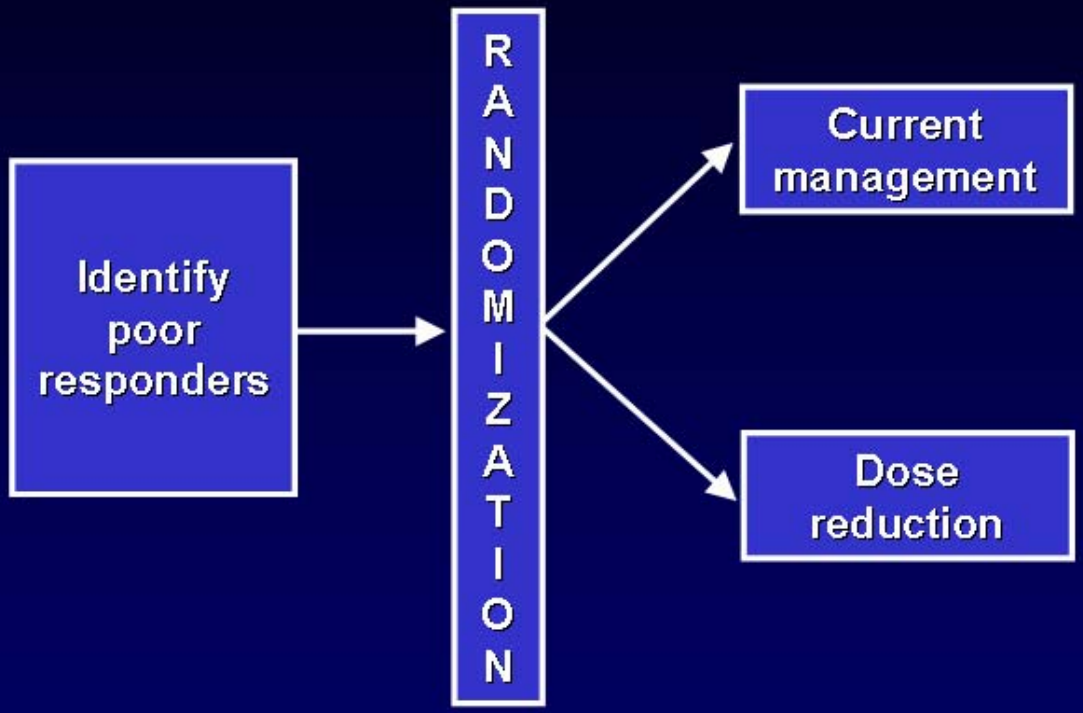
ESA responsiveness

- 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 ≤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



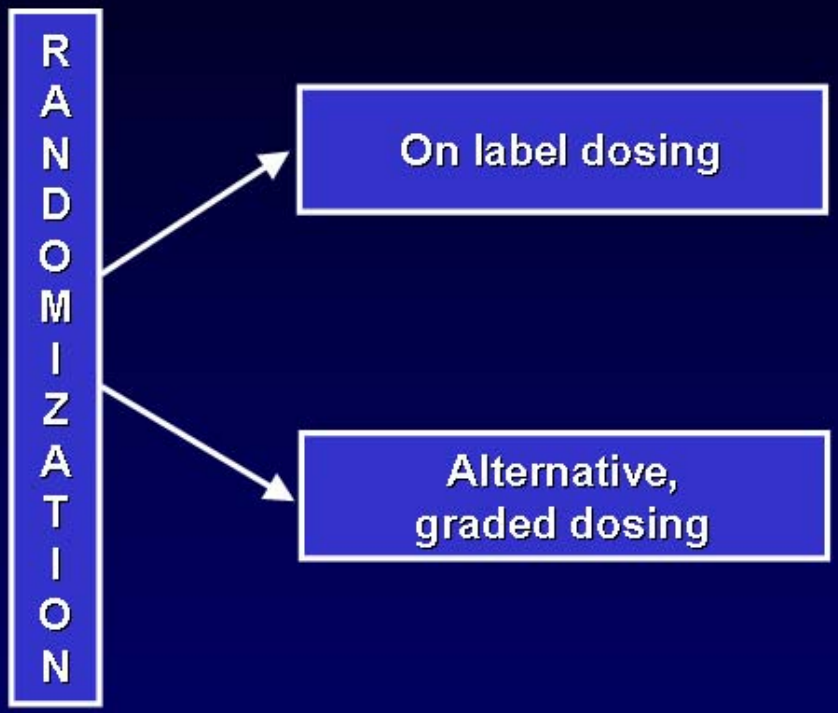
Primary endpoint

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

Secondary endpoints

- Transfusion
- PRO
- Exercise capacity

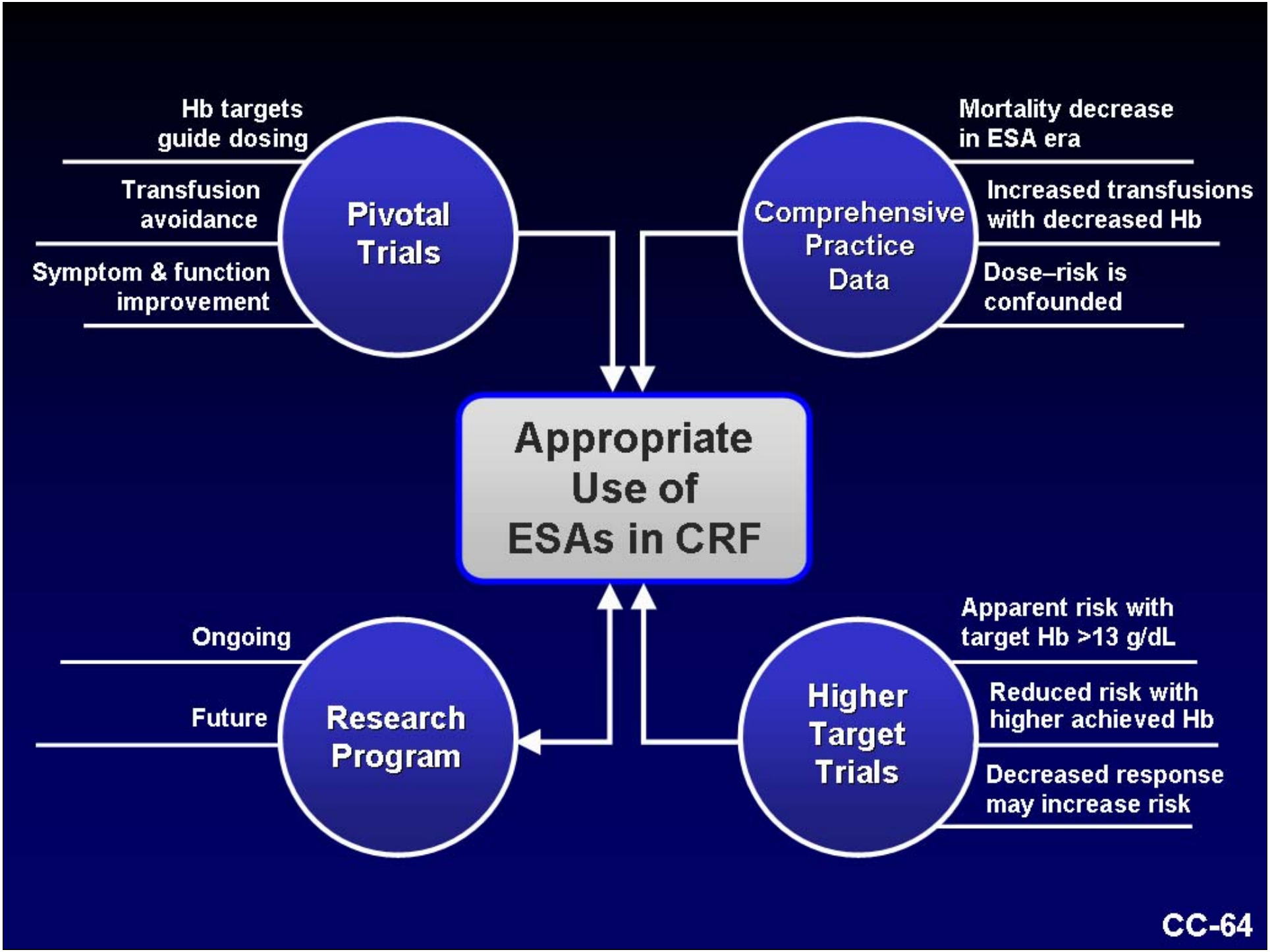
Potential Study to Minimize Hb Cycling



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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Comprehensive Evidence Supports Appropriate Use of ESAs in CRF

- **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**