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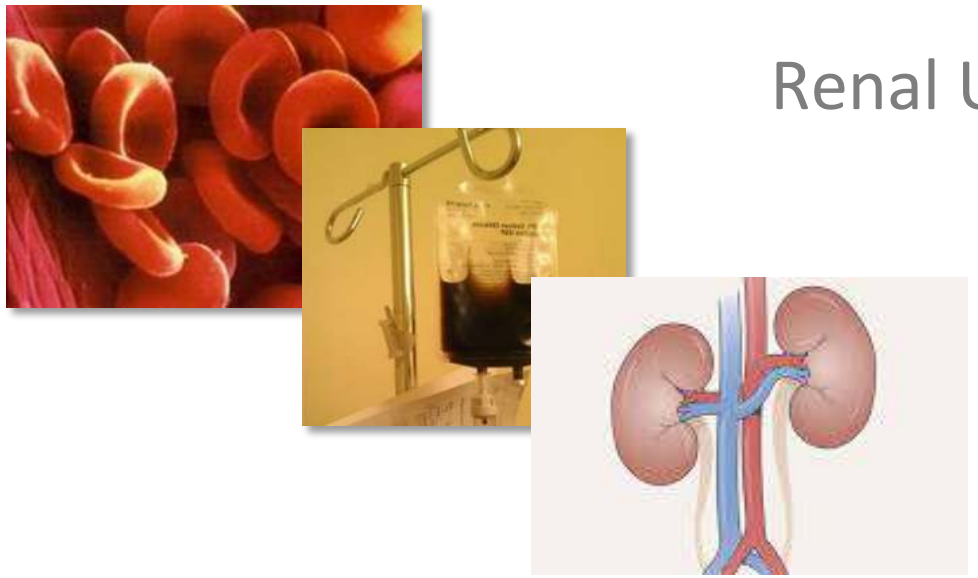
The PIVOTAL Trial – Role of IV iron in Renal Anemia

Iain C. Macdougall

Consultant Nephrologist & Professor of Clinical Nephrology

Renal Unit, King's College Hospital, London, UK

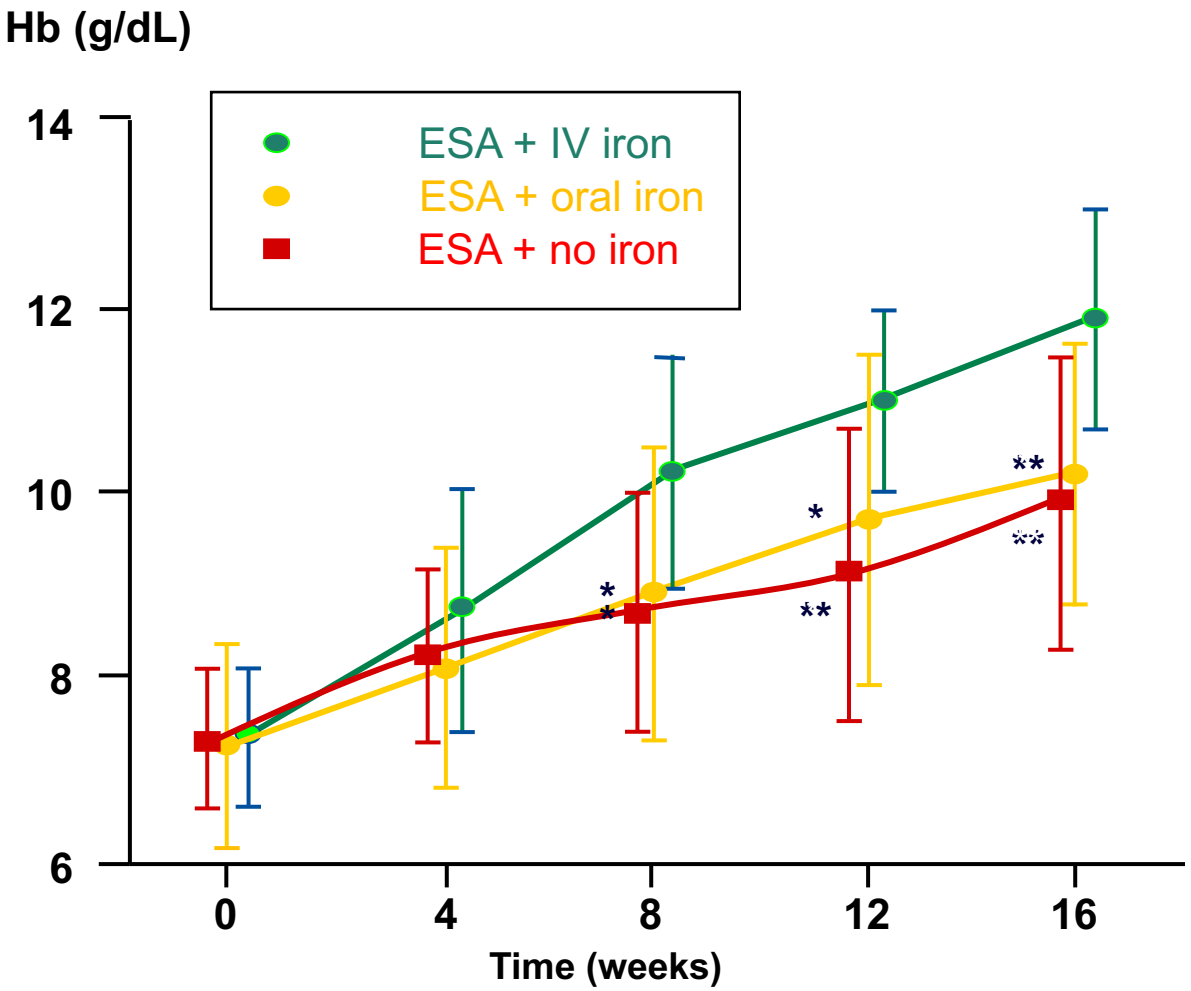


Management of anaemia in CKD

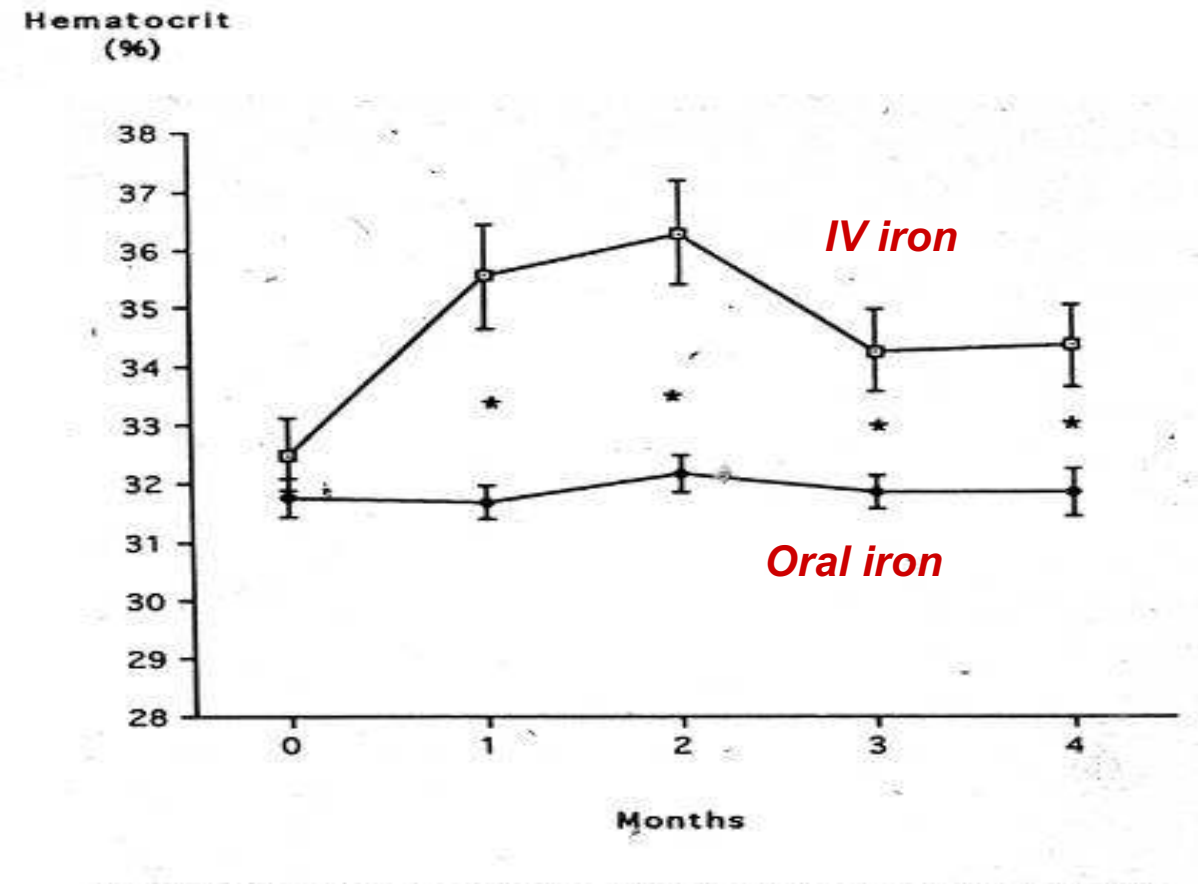
ESA therapy

IV iron

IV iron improves haemoglobin



Macdougall et al, *Kidney Int* (1996)



Fishbane et al, *Am J Kidney Dis* (1995)

IV iron reduces EPO doses

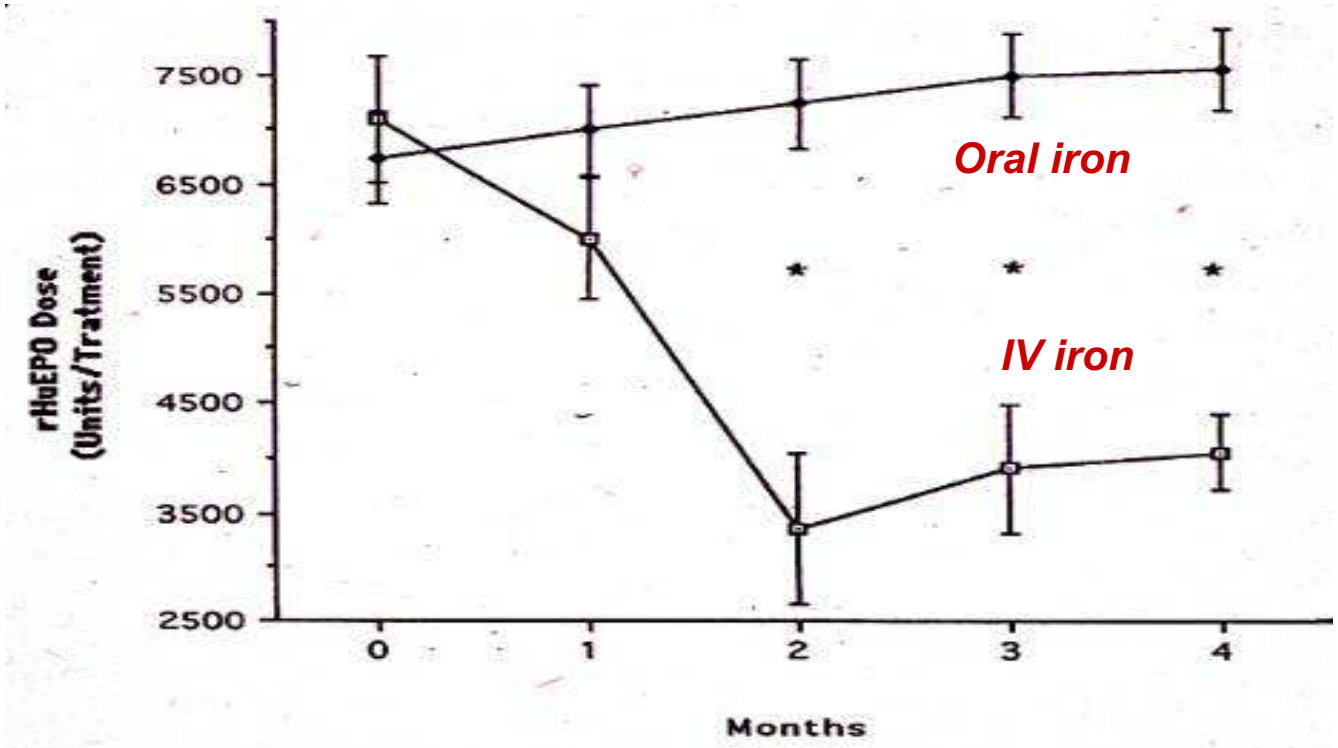
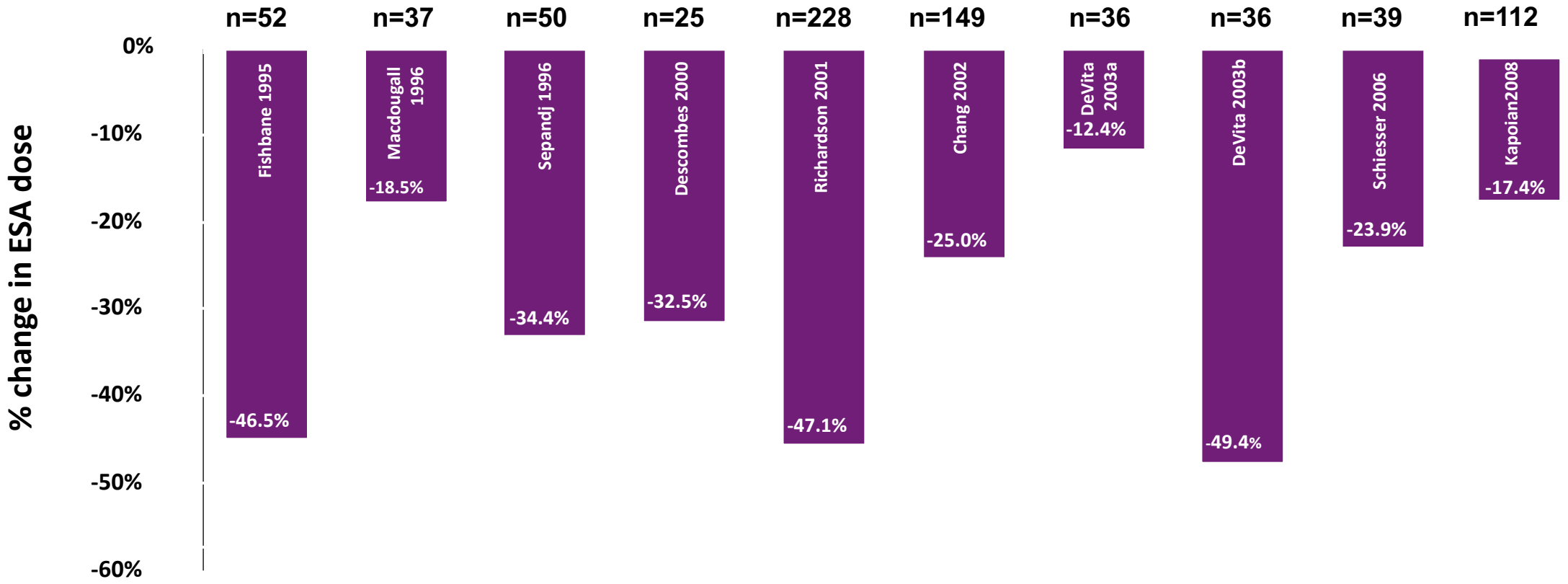


Fig 2. Mean rHuEPO dose at every month of follow-up in the two study groups. Squares indicate the intravenous group; diamonds indicate the oral group. *$P < 0.05$.

Fishbane et al, *Am J Kidney Dis* (1995)

IV iron reduces ESA doses



Fishbane S et al. *Am J Kidney Dis* 1995;26:41–46; Macdougall I et al. *Kidney Int* 1996;50: 1694–1699; Sepandj F et al. *Nephrol Dial Transplant* 1996;11:319–322; Descombes E & Fellay G. *Nephron* 2000;84:196–197; Richardson D et al. *Am J Kidney Dis* 2001;38:109–117; Chang CH et al. *Clin Nephrol* 2002;57:136–141; De Vita MV et al. *Clin Nephrol* 2003;60:335–340; Schiesser D et al. *Nephrol Dial Transplant* 2006;21:2841–2845; Kapoian T et al. *JASN* 2008;19:372–379

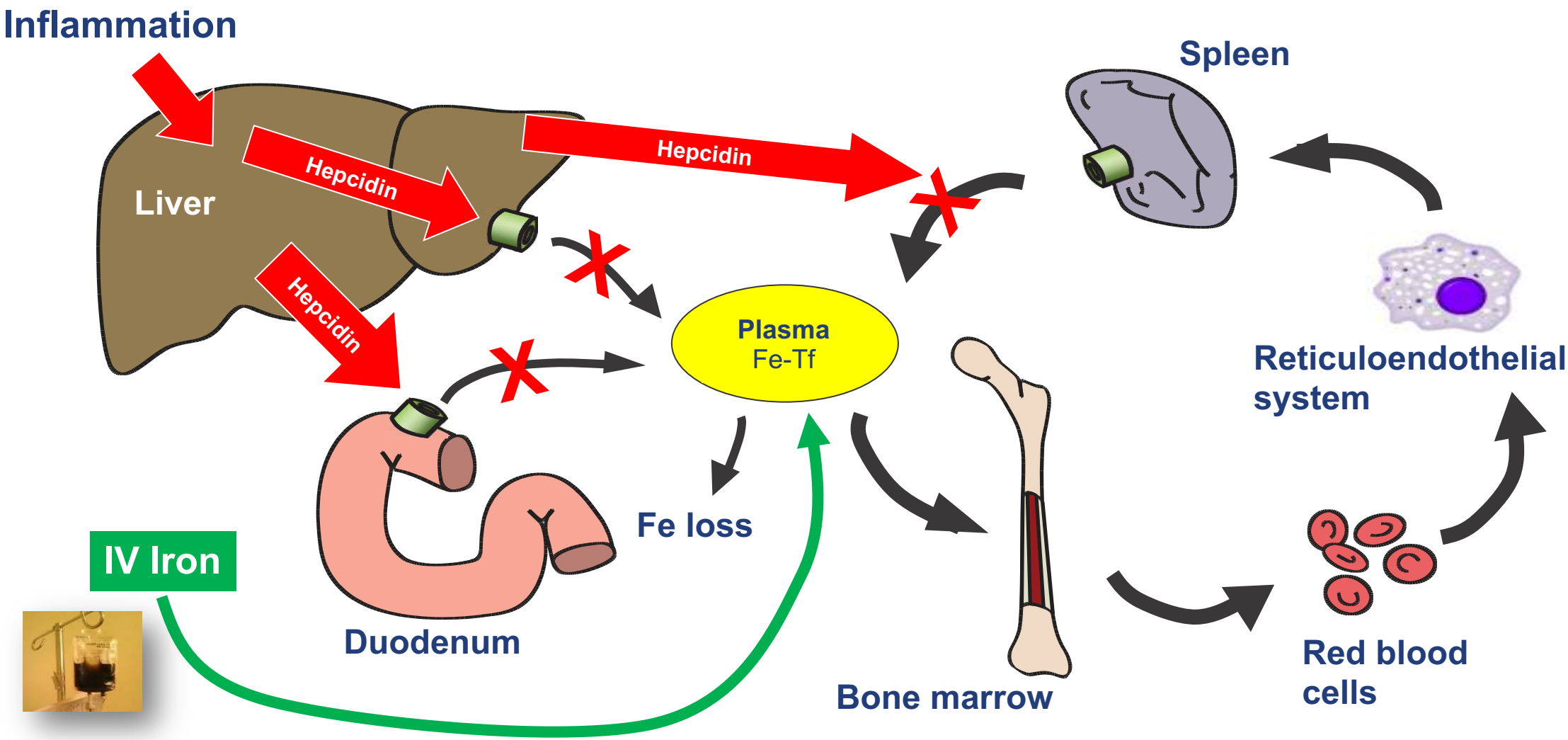
Haemoglobin, ESA, and IV iron use in US dialysis patients *(1992–2005)*

Table 2. Hemoglobin, Erythropoiesis-Stimulating Agent, and Iron Use Trends, 1992 to 2004 (even years shown)

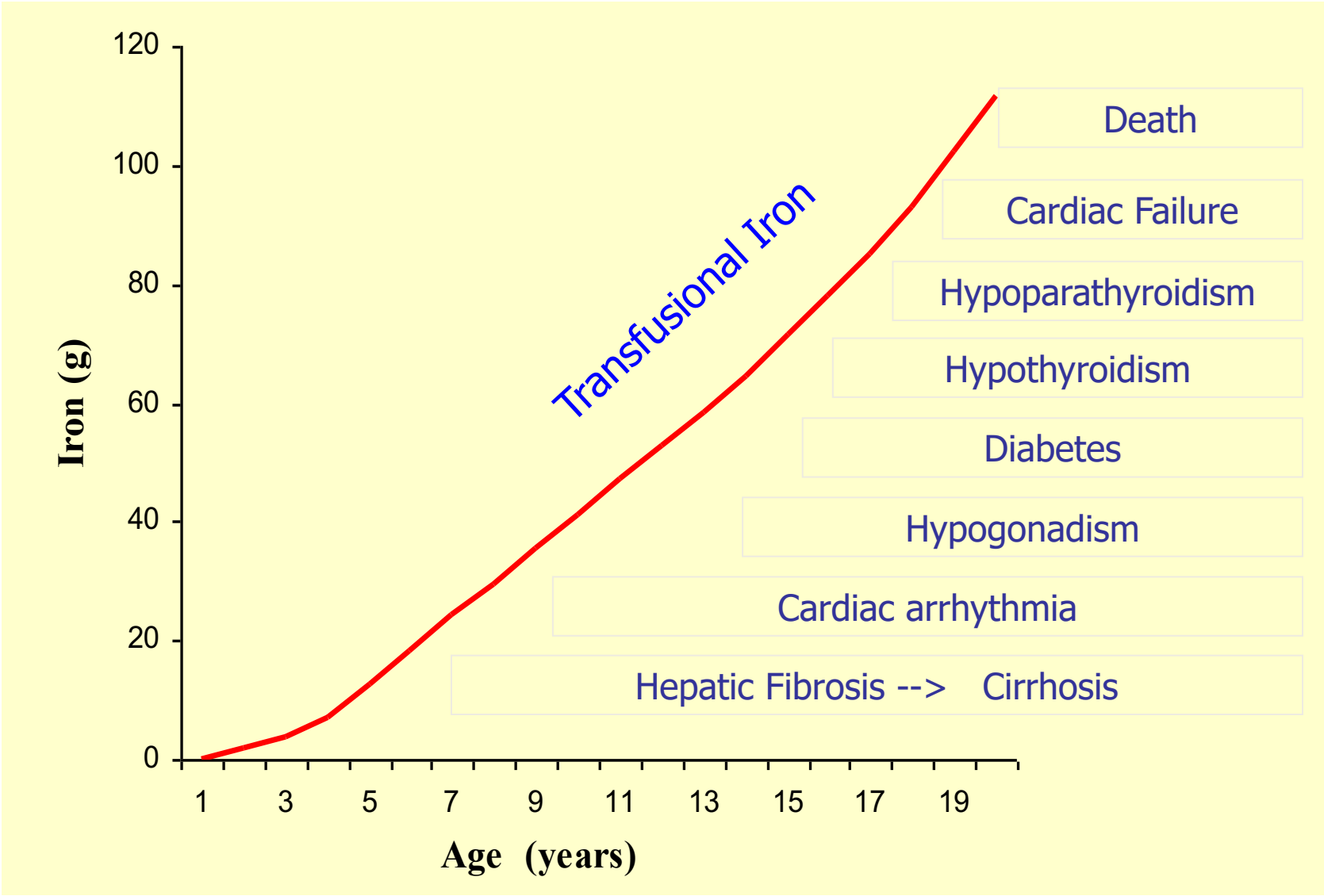
	Cohort Year						
	1992	1994	1996	1998	2000	2002	2004
	(n = 77,347)	(n = 89,815)	(n = 100,540)	(n = 109,685)	(n = 121,133)	(n = 140,227)	(n = 157,960)
Hemoglobin (g/dL)	9.7 ± 1.0	10.1 ± 1.0	10.5 ± 1.0	10.9 ± 0.8	11.5 ± 1.0	11.7 ± 1.0	11.8 ± 0.9
0-<11	49,471 (64.0)	58,160 (64.8)	54,345 (54.1)	48,704 (44.4)	27,398 (22.6)	23,507 (16.8)	18,775 (11.9)
≤11-≥12	4,453 (5.8)	10,411 (11.6)	23,452 (23.3)	40,642 (37.1)	49,005 (40.5)	60,484 (43.1)	65,070 (41.2)
>12	404 (0.5)	1,071 (1.2)	3,194 (3.2)	4,599 (4.2)	30,482 (25.2)	42,073 (30.0)	60,336 (38.2)
Missing/unknown	23,019 (29.8)	20,173 (22.5)	19,549 (19.4)	15,740 (14.4)	14,248 (11.8)	14,163 (10.1)	13,779 (8.7)
Total ESA use/mo							
None	23,125 (29.9)	19,988 (22.3)	18,973 (18.9)	15,506 (14.1)	14,244 (11.8)	14,085 (10.0)	13,631 (8.6)
0-≤28,000 units	31,676 (41.0)	31,786 (35.4)	29,336 (29.2)	32,791 (29.9)	28,866 (23.8)	33,586 (24.0)	36,514 (23.1)
28,000-≤58,000 units	18,884 (24.4)	27,234 (30.3)	31,298 (31.1)	35,219 (32.1)	36,086 (29.8)	41,957 (29.9)	46,233 (29.3)
>58,000 units	3,662 (4.7)	10,807 (12.0)	20,933 (20.8)	26,169 (23.9)	41,937 (34.6)	50,599 (36.1)	61,582 (39.0)
Iron use (yes)	258 (0.3)	22,601 (25.2)	36,781 (36.6)	63,678 (58.1)	75,385 (62.2)	83,718 (59.7)	113,03 (71.6)

Note: Values expressed as mean ± SE or number (percent). Hemoglobin in g/dL may be converted to g/L by multiplying by 10.

IV iron bypasses hepcidin blockade



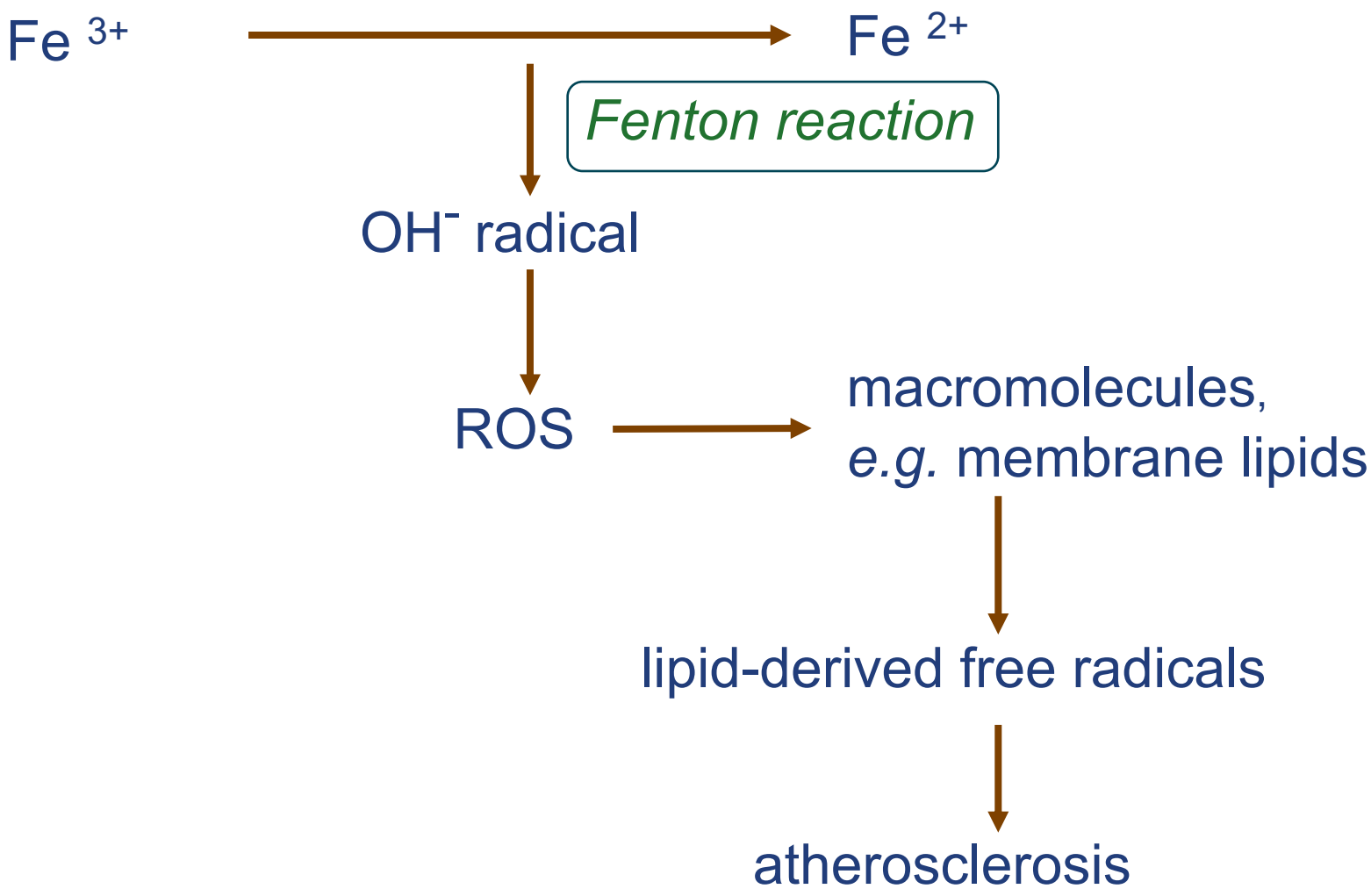
Transfusional iron overload in thalassaemia



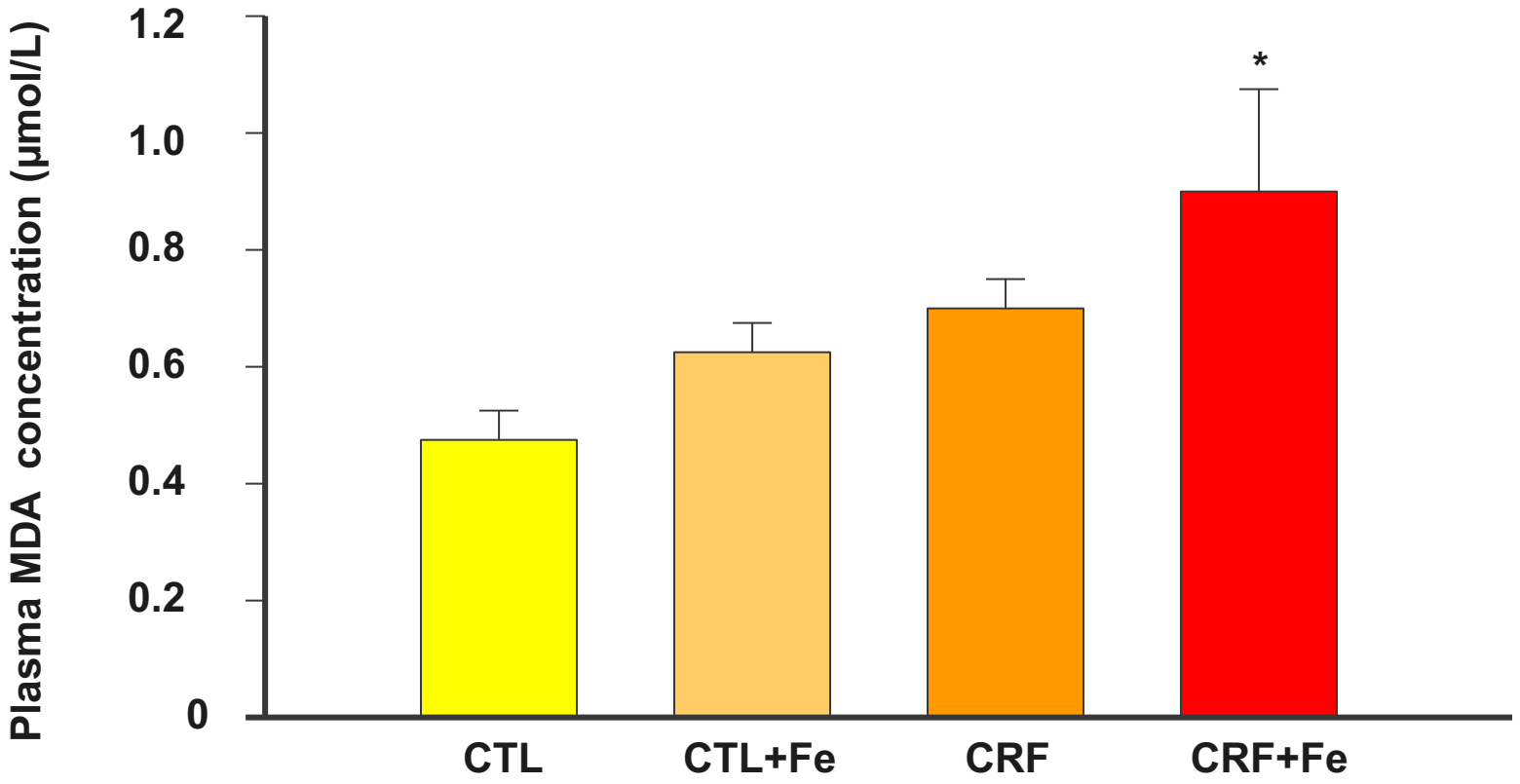
Concerns about IV iron

- Increased oxidative stress
- Increased atherogenesis
- CV toxicity
- Inflammation
- Immune dysfunction
- Cellular toxicity
- Increased infections

Iron and oxidative stress



Iron increases oxidative stress



Plasma malondialdehyde (MDA) levels in control rats (CTL), Fe-injected control rats (CTL+Fe), chronic renal failure rats (CRF), and Fe-injected CRF rats (CRF+ Fe). (*N = 6 in each group) ⁎P < 0.05 vs. CTL group.*

Lim C *et al. Kidney Int* 2004;65:1802–9.

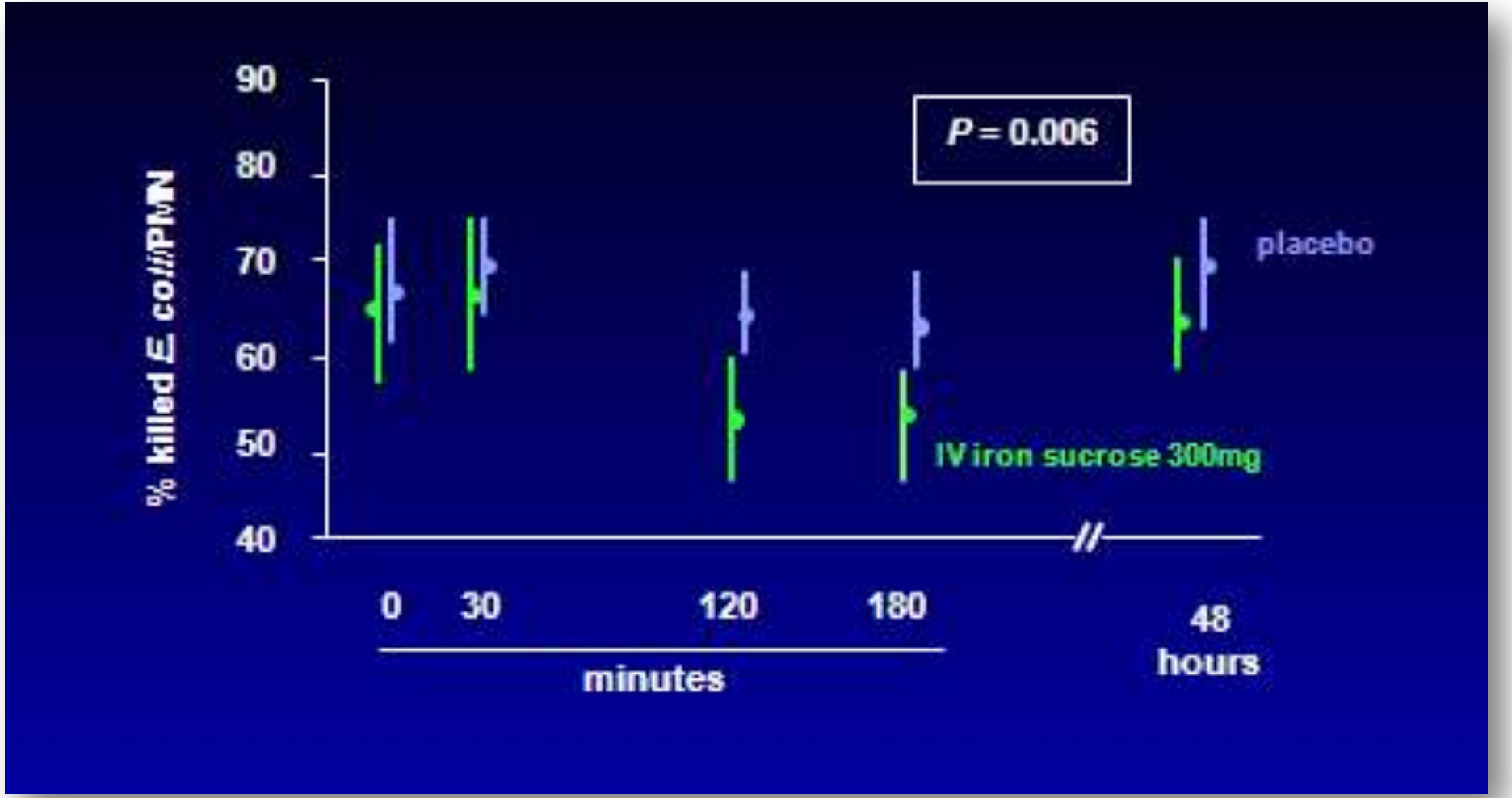
Iron and infection

Iron overload: ↑ bacterial growth / virulence

↓ PMN phagocytosis / bacterial killing

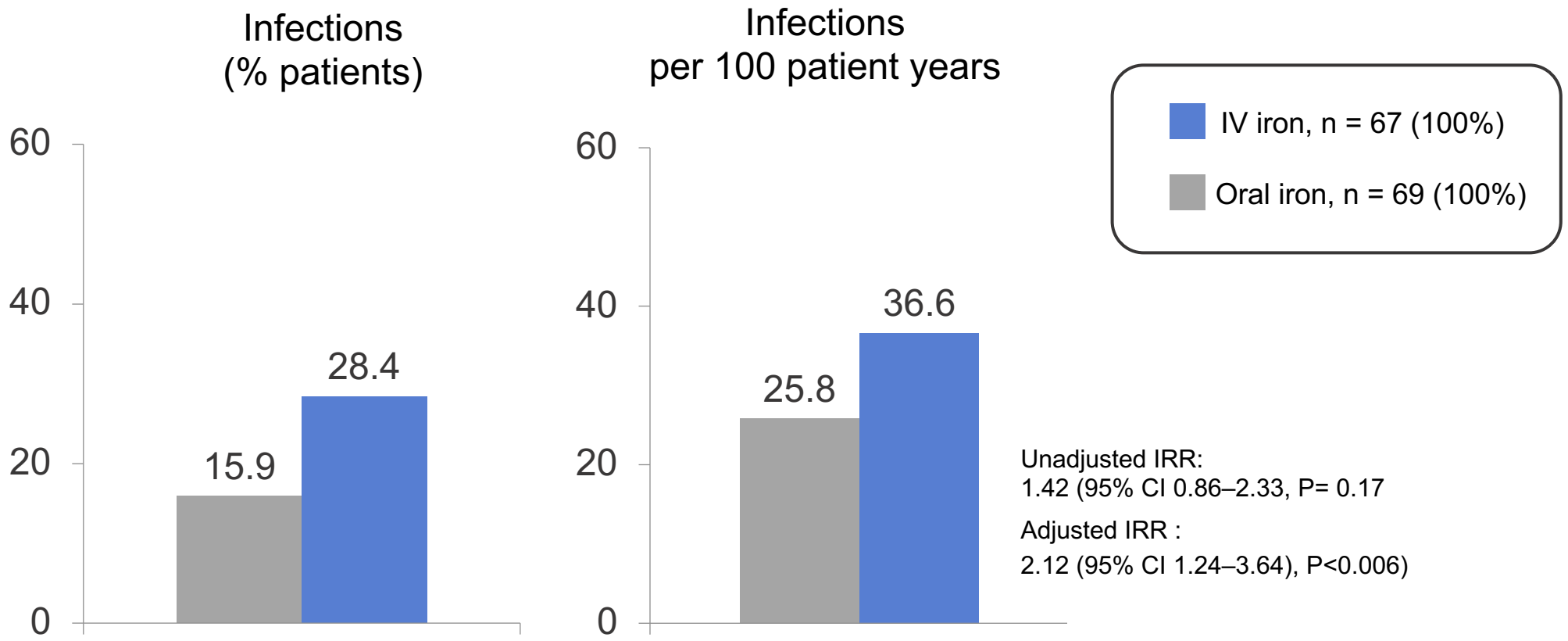
Animals: parenteral iron administered to rats or mice with active infection → harmful

IV iron decreases neutrophil killing capacity



Deicher R *et al*. *Kidney Int* 2003; 64: 728–36.

REVOKE study: *Infection-related SAEs*



- The incidence of lung and skin infections were increased 3–4 fold in the IV iron group

Agarwal et al. Kidney Int. 2015 Oct;88(4):905-14.

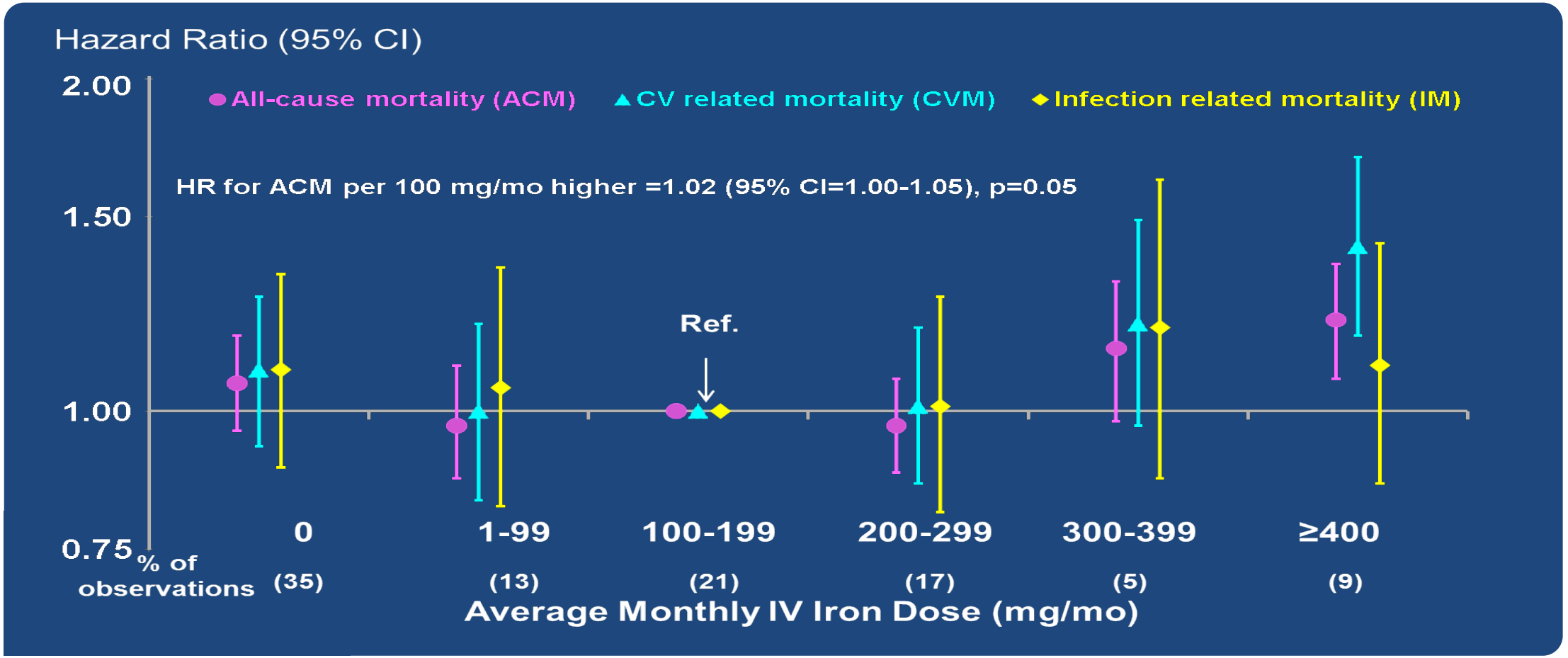
Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality

George R. Bailie[1], Maria Larkina[2], David A. Goodkin[2], Yun Li[2,3], Ronald L. Pisoni[2], Brian Bieber[2], Nancy Mason[4], Lin Tong[2], Francesco Locatelli[5], Mark R. Marshall[6], Masaaki Inaba[7] and Bruce M. Robinson[2,3]

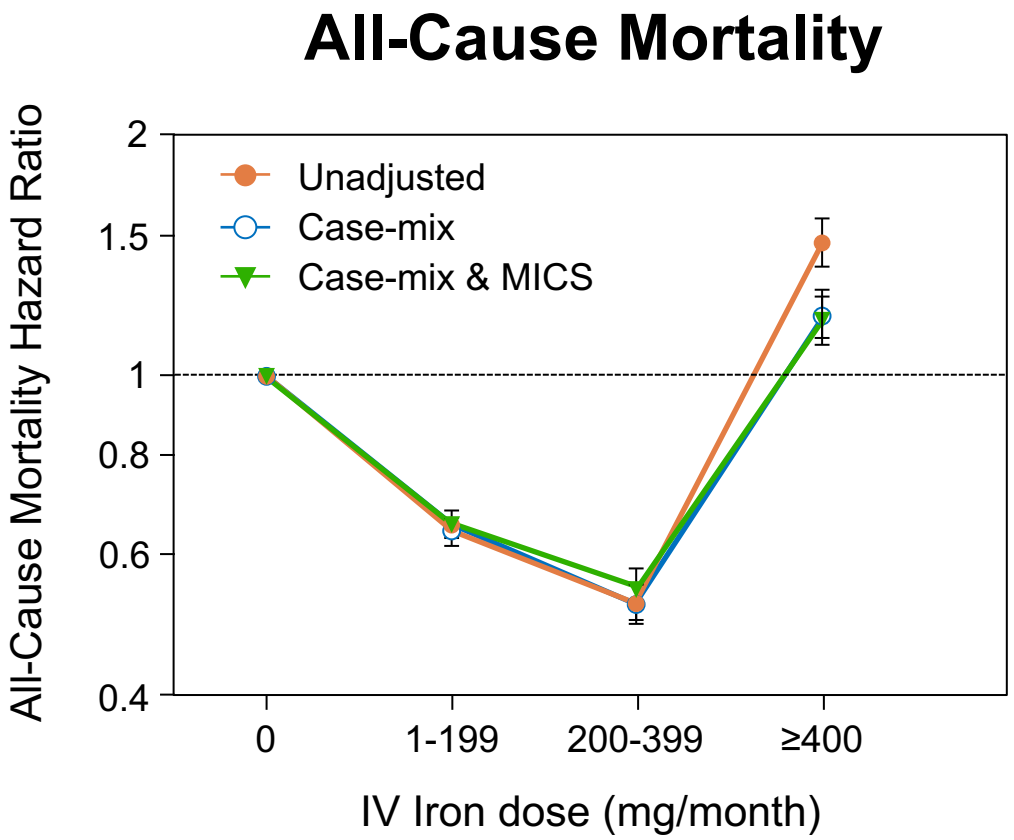
[1]Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, New York, USA; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA; [4]College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA; [5]Department of Nephrology and Dialysis and Renal Transplant, Alessandro Manzoni Hospital, Lecco, Italy; [6]Department of Renal Medicine, Middlemore Hospital, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand and [7]Department of Metabolism, Endrocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

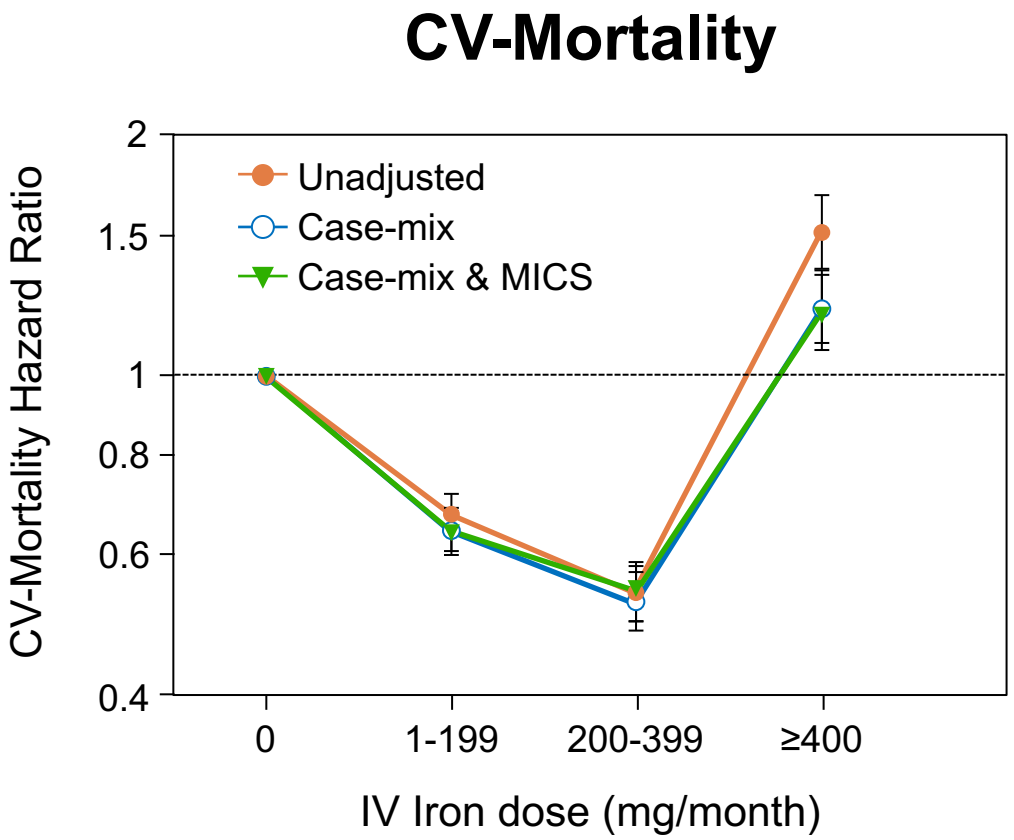
Associations between IV iron dose and mortality

DOPPS



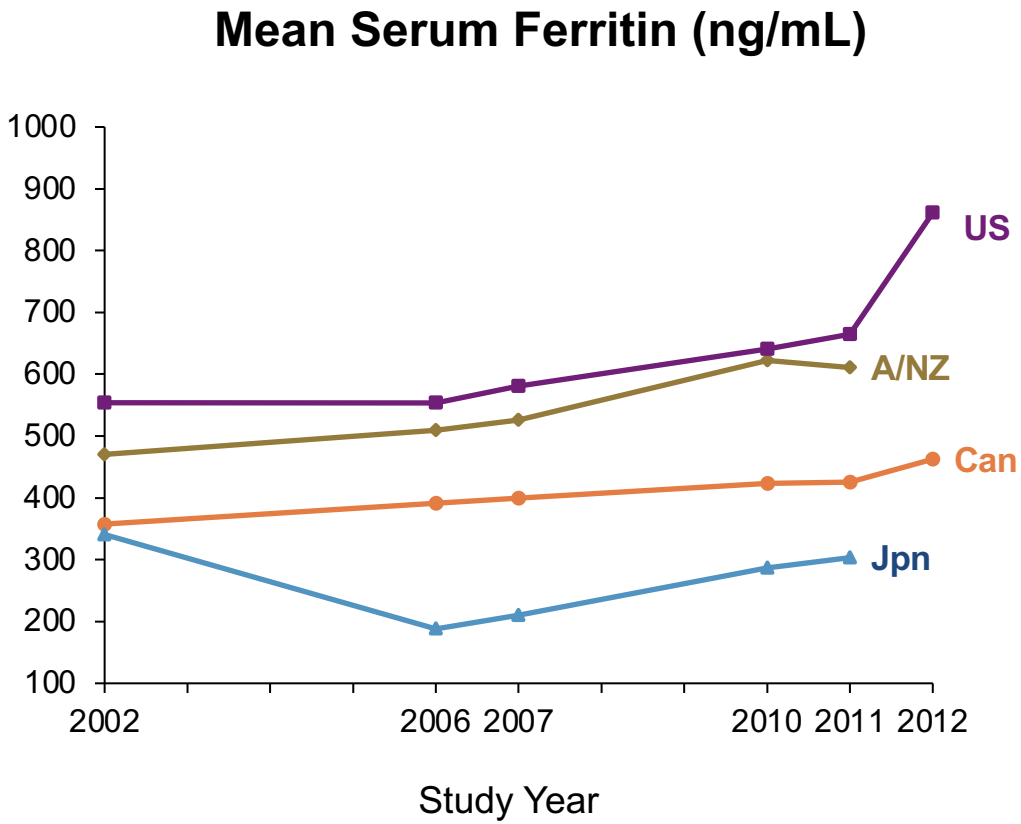
Association of IV Iron dose with Mortality

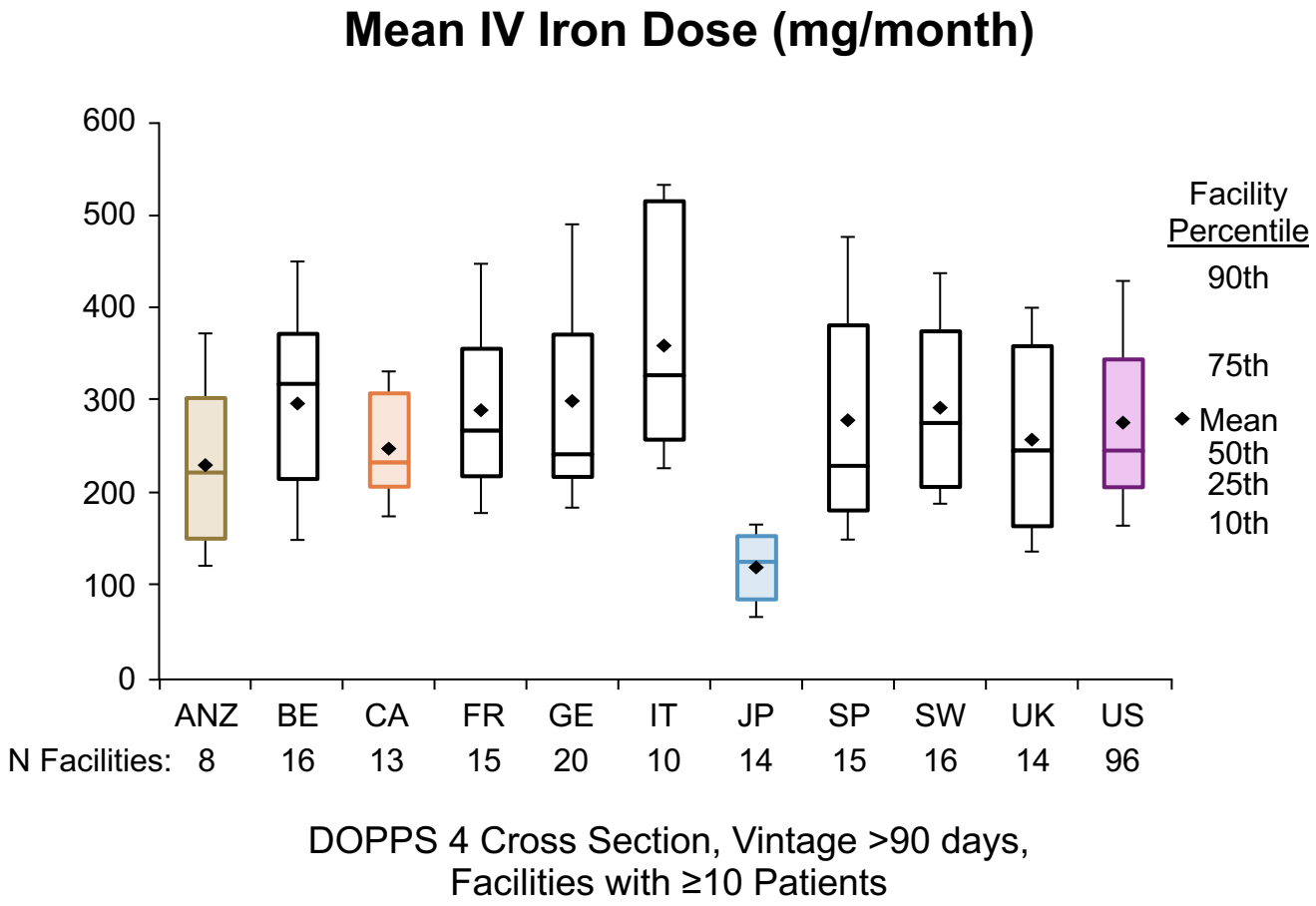




MICS=malnutrition-inflammation-cachexia syndrome.
Kalantar-Zadeh K, et al. *J Am Soc Nephrol.* 2005;16(10):3070-3080.

Ferritin and IV Iron Use in DOPPS





Bailie GR, et al. *Nephrol Dial Transplant.* 2013;28(10):2570-2579.

PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

Proactive IV irOn Therapy in haemodiALysis

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2019
Jan 31;380: 447-458.

ORIGINAL ARTICLE

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Iain C. Macdougall, M.D., Claire White, B.Sc., Stefan D. Anker, M.D., Sunil Bhandari, Ph.D., F.R.C.P., Kenneth Farrington, M.D., Philip A. Kalra, M.D., John J.V. McMurray, M.D., Heather Murray, M.Sc., Charles R.V. Tomson, D.M., David C. Wheeler, M.D., Christopher G. Winearls, D.Phil., F.R.C.P., and Ian Ford, Ph.D., for the PIVOTAL Investigators and Committees*

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Network of Sites

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

N. Ireland
Belfast City Hospital, **Antrim** Area Hospital;
Daisy Hill Hospital,**Newry;** Altnagelvin Hospital, **Derry**

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Hypothesis: Proactive, high-dose IV iron would be non-inferior to reactive, low-dose IV iron for the outcome of all cause mortality and cardiovascular events in haemodialysis patients.

Prospective Randomised, Open label, Blinded Endpoint (PROBE) design

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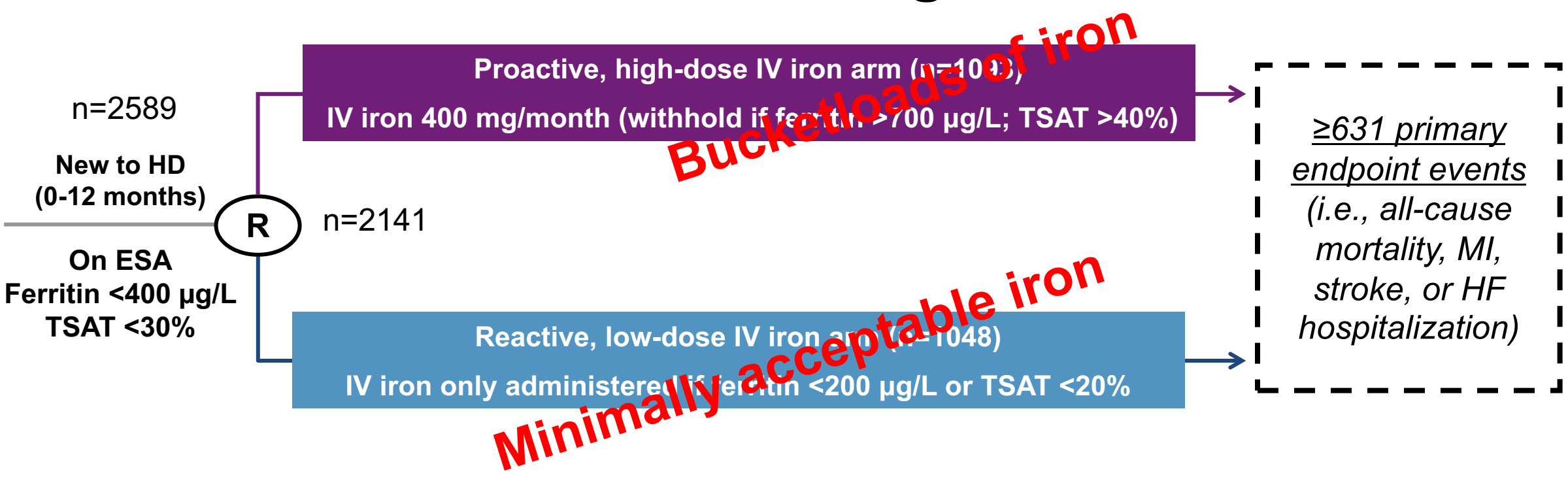
Trial Design



Screening: ≤4 weeks	Follow-up period with monthly visits

Median (maximum) follow-up: 2.1 (4.4) years

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Outcomes

Primary
• Composite of nonfatal MI, nonfatal stroke, hospitalization for HF, or all-cause death, analyzed as time-to-first event

Secondary (efficacy)	Secondary (safety)
• MI, stroke, hospitalization for HF, and deaths (first + recurrent events) • All-cause death • First composite CV event (MI, stroke, and hospitalization for HF) • Fatal or nonfatal MI • Fatal or nonfatal stroke • Hospitalization for HF • ESA dose requirements • Transfusion requirements • Quality-of-life measures	• Vascular access thrombosis • All-cause hospitalization • Hospitalization for infection • Infection episodes

Tertiary	
• Cumulative dose of iron • Hemoglobin concentration • Serum ferritin concentration	• Platelet count • Serum albumin concentration • TSAT

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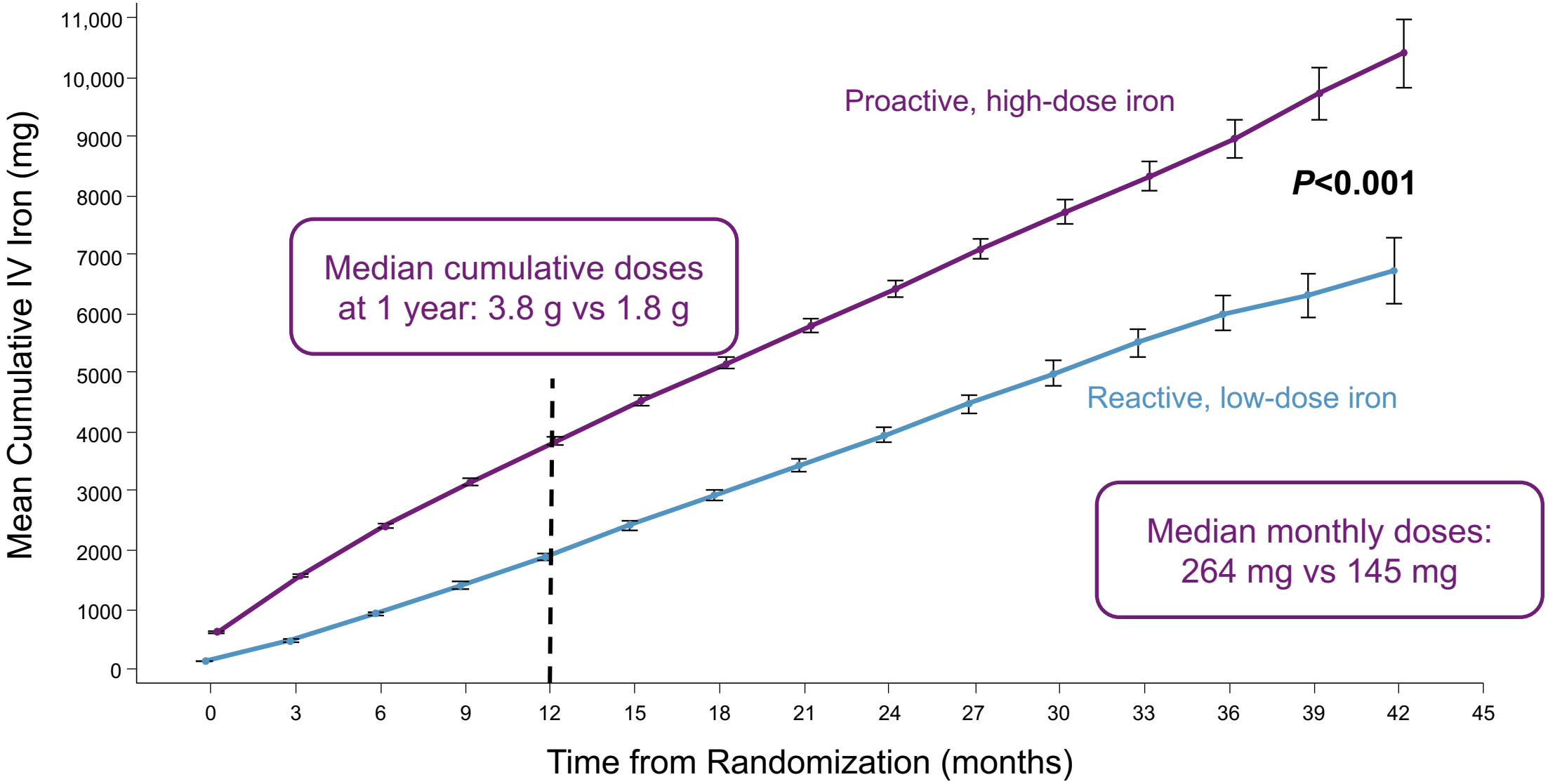
Cumulative Iron Dose



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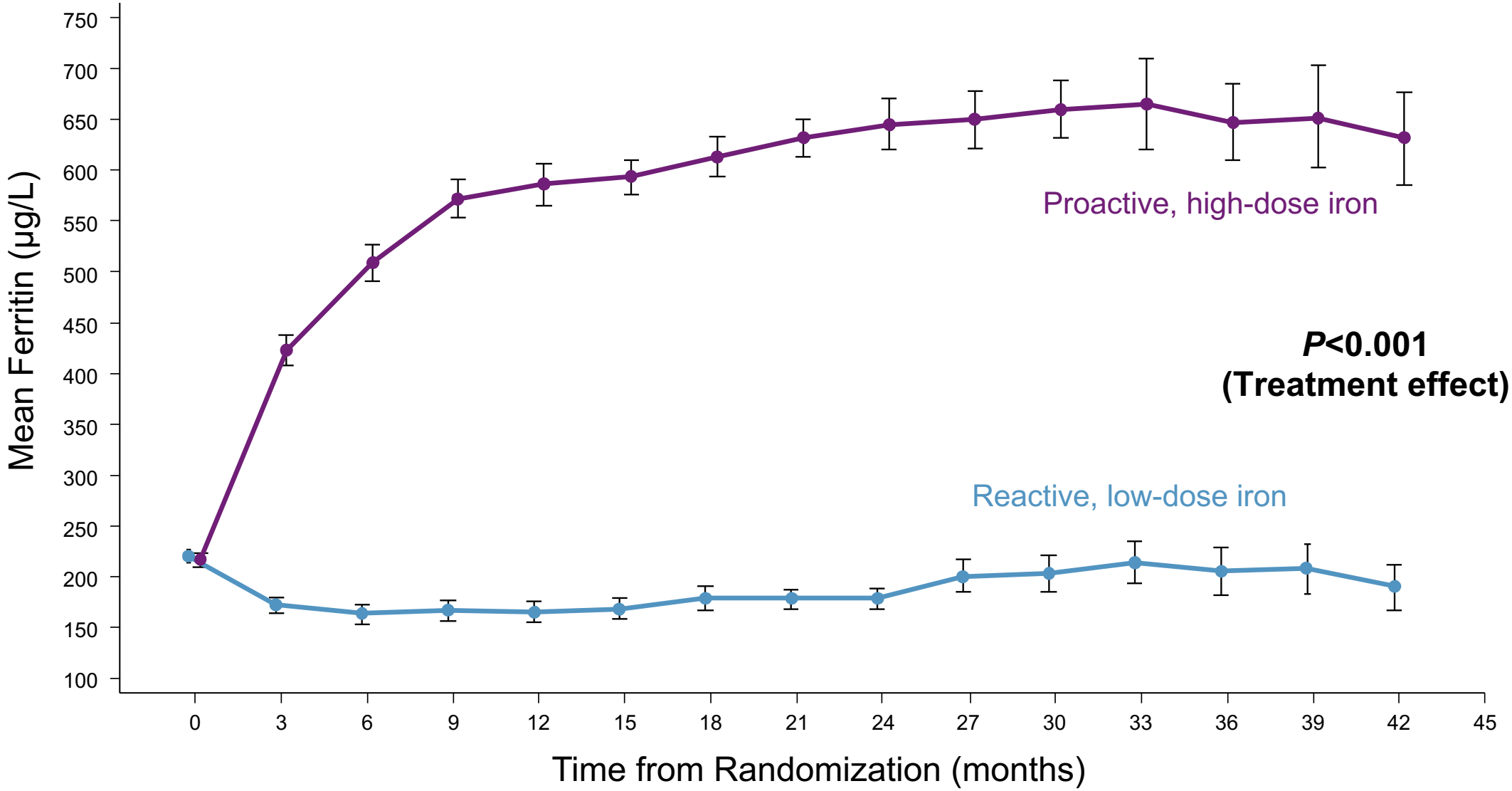
Serum Ferritin Concentration



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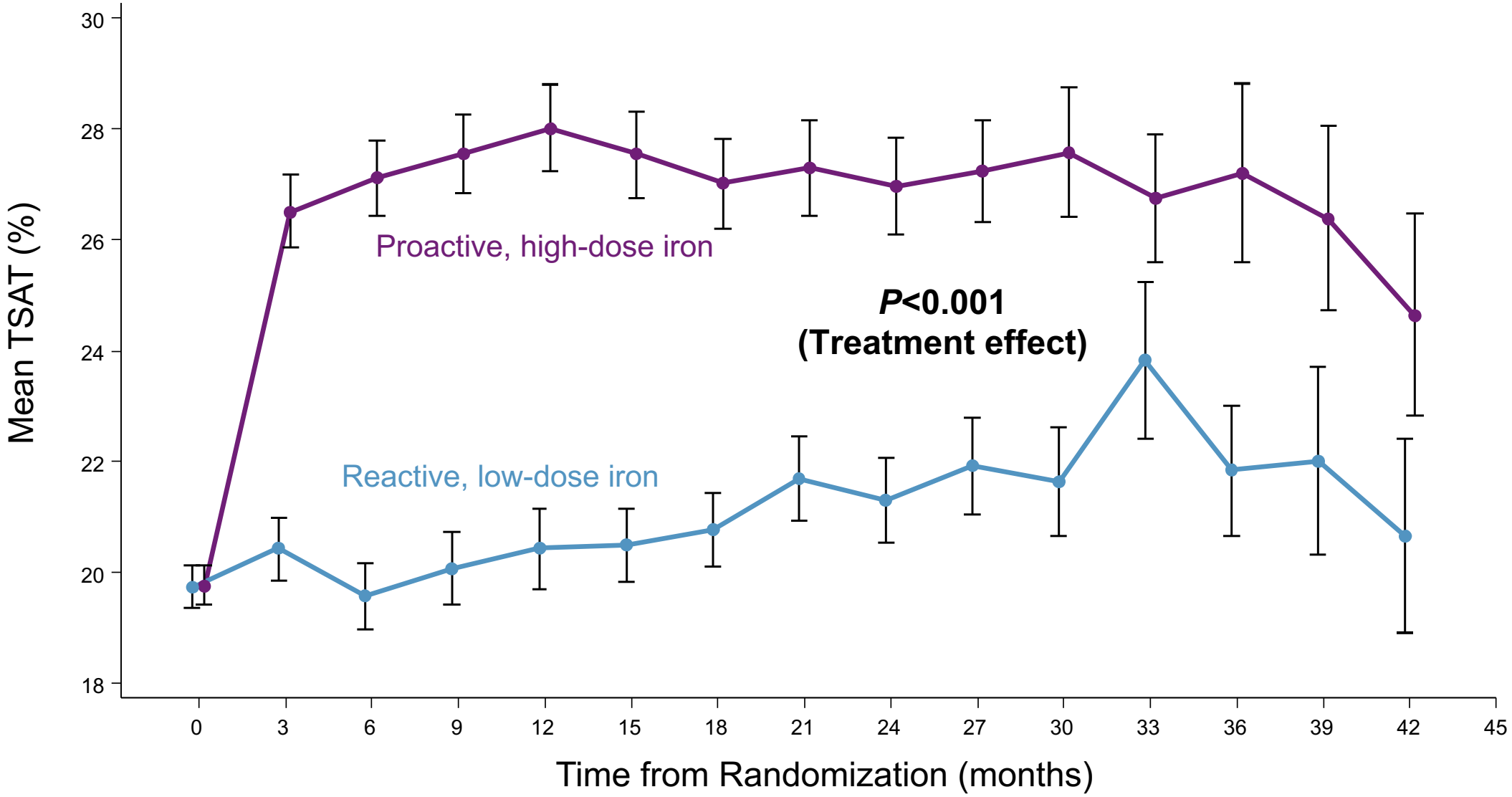
Transferrin Saturation



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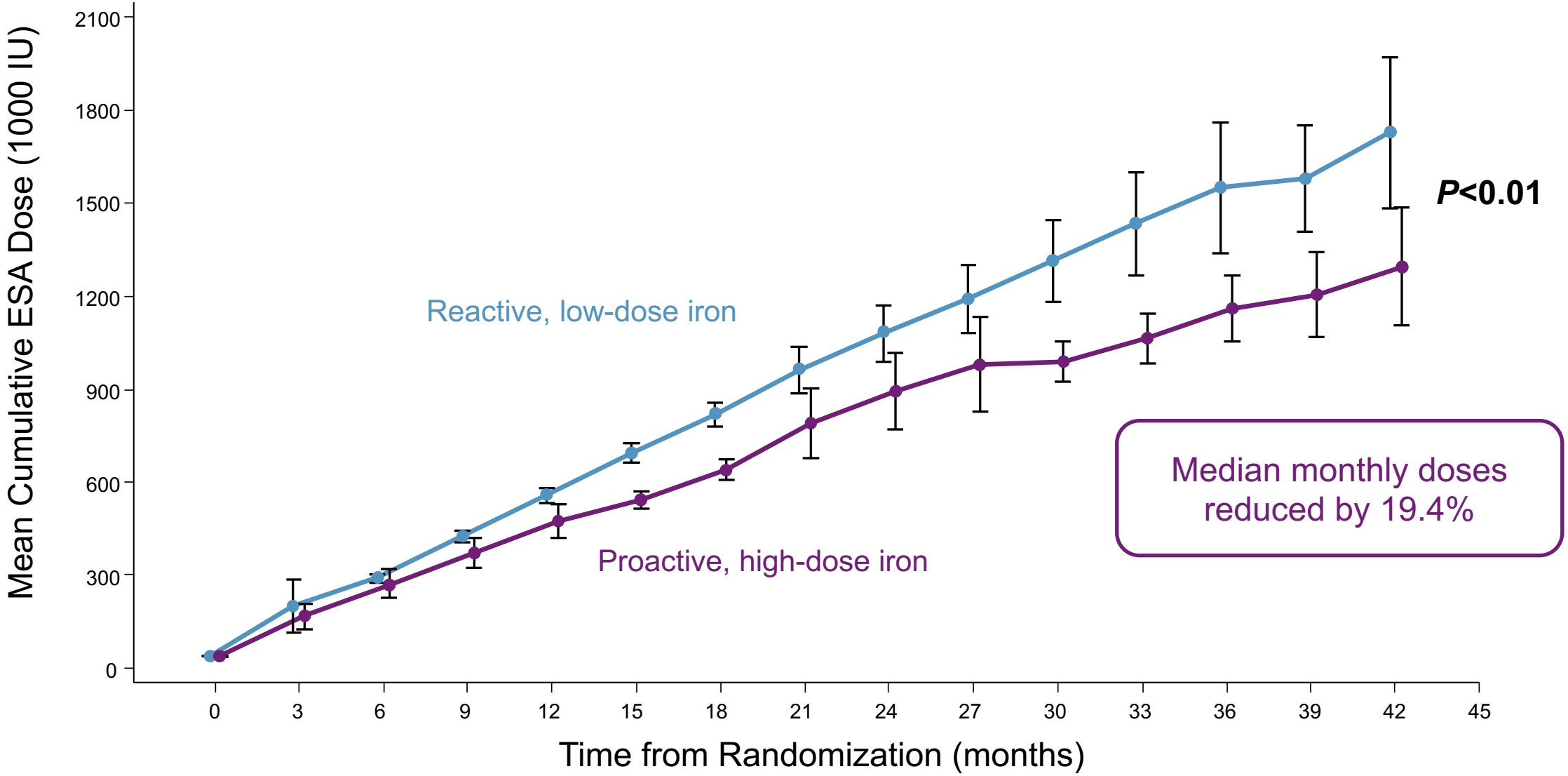
Cumulative ESA Dose



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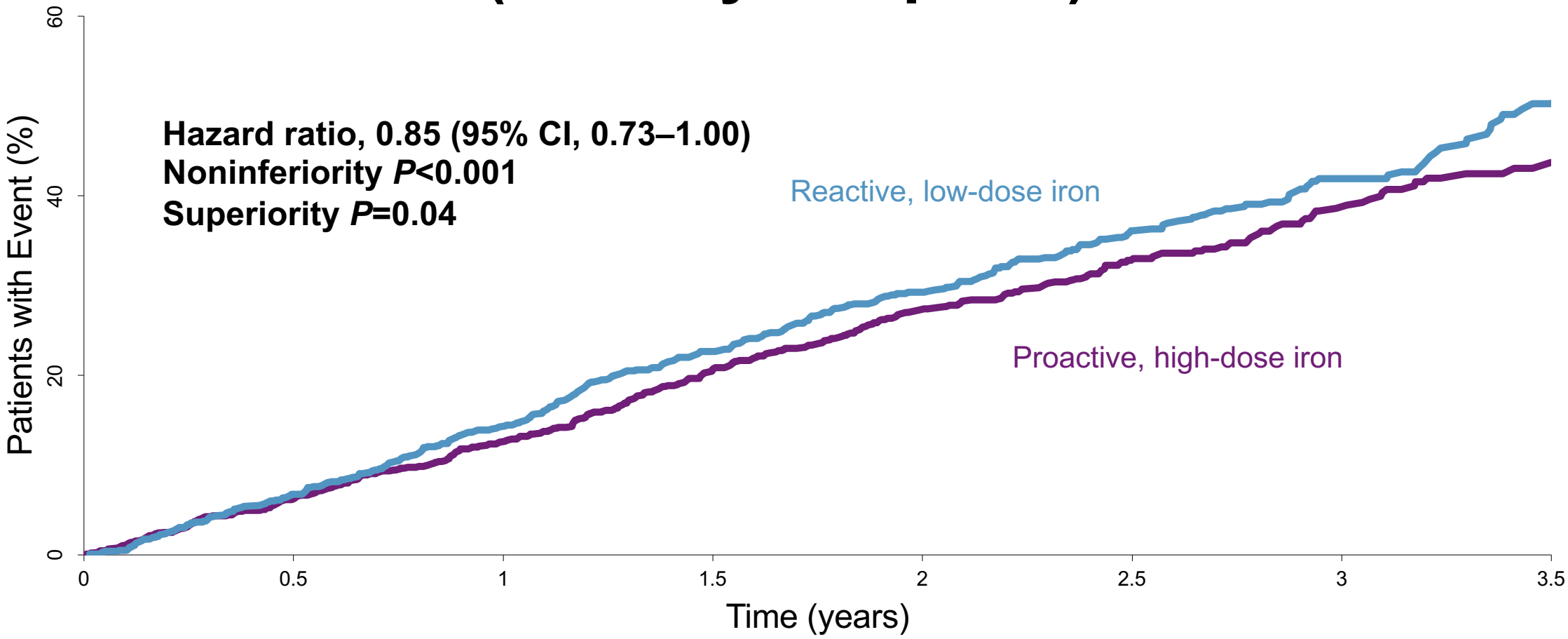
Death, MI, Stroke, or HF Hospitalization (Primary Endpoint)



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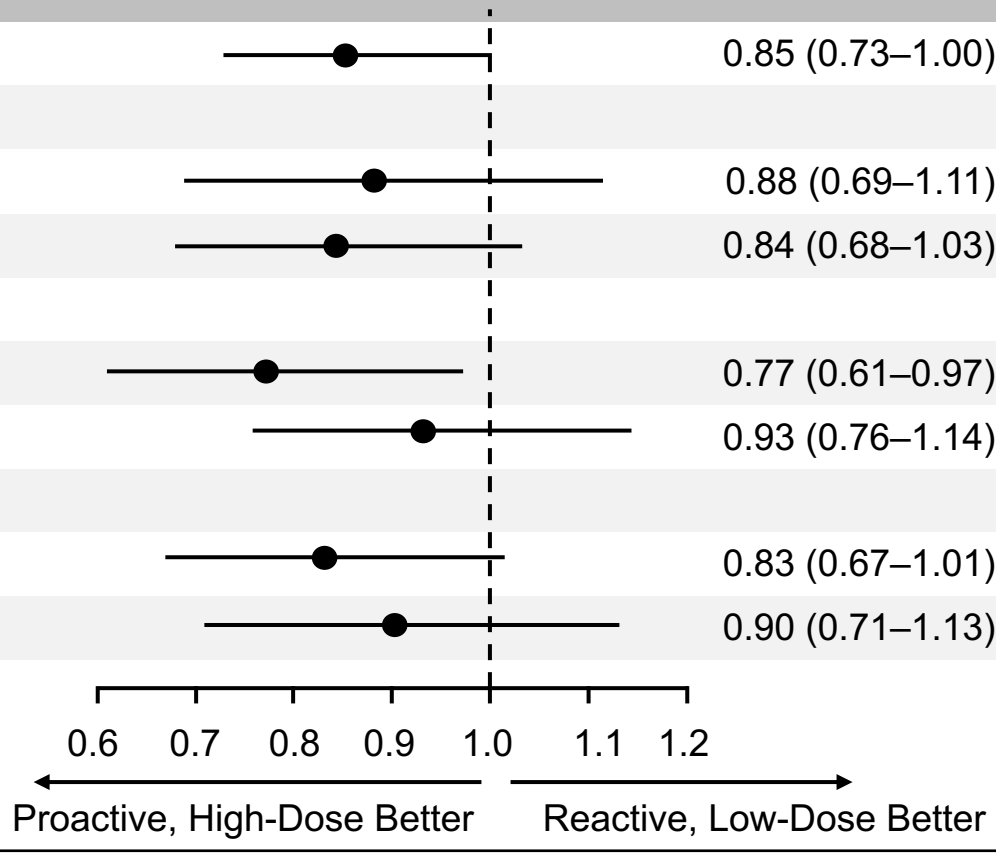
Subgroup Analysis: Primary Endpoint

Subgroup	Proactive, High-Dose Iron	Reactive, Low-Dose Iron	Hazard Ratio (95% CI)	*P* Value for Interaction
	no. of events/total no. (%)			
All participants	320/1093 (29.3)	338/1048 (32.3)	0.85 (0.73–1.00)	
Duration of dialysis treatment at enrollment				0.79
<5 months	139/499 (27.9)	146/487 (30.0)	0.88 (0.69–1.11)	
≥5 months	181/594 (30.5)	192/561 (34.2)	0.84 (0.68–1.03)	
Dialysis access				0.22
Dialysis catheter	137/452 (30.3)	159/432 (36.8)	0.77 (0.61–0.97)	
AV fistula	183/641 (28.6)	179/616 (29.1)	0.93 (0.76–1.14)	
Baseline diabetes				0.62
Yes	182/490 (37.1)	193/453 (42.6)	0.83 (0.67–1.01)	
No	138/603 (22.9)	145/595 (24.4)	0.90 (0.71–1.13)	



AV=arteriovenous.

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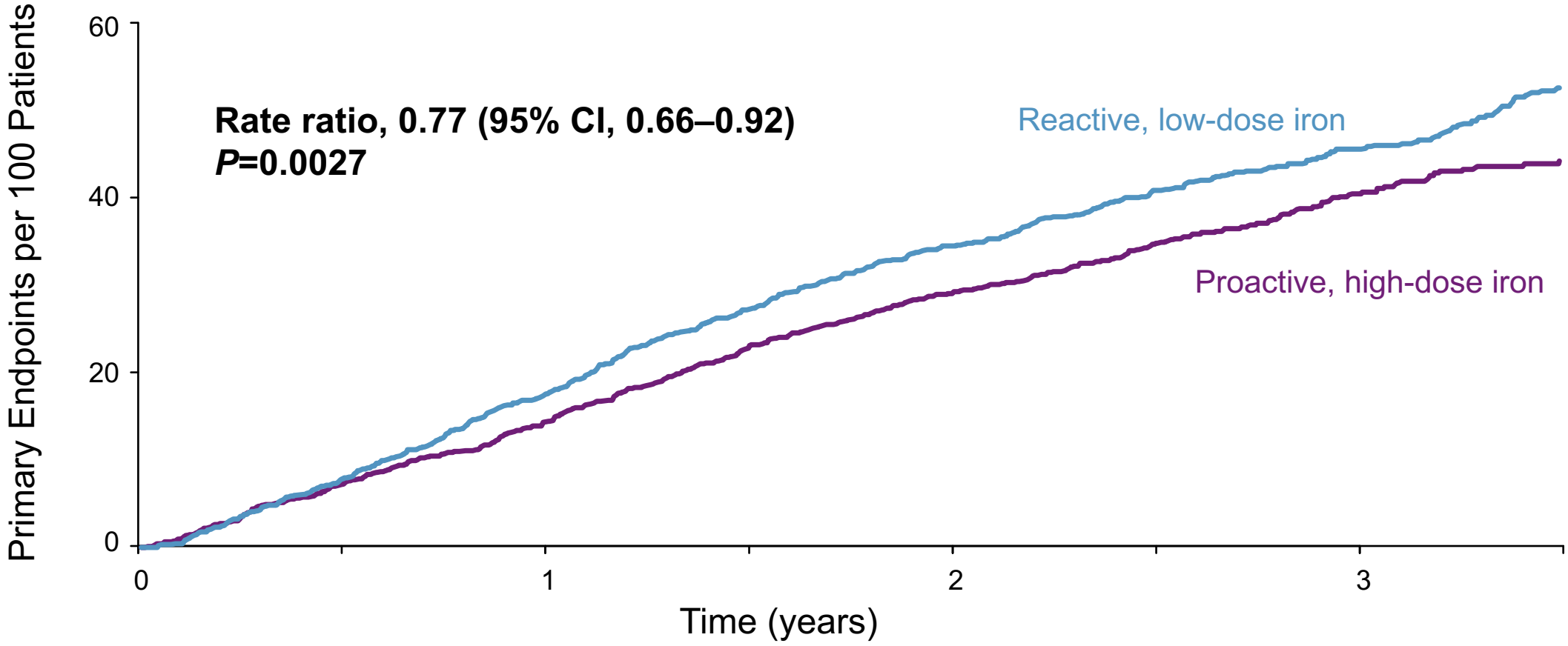
Primary Endpoint Components[a] as Recurrent Events



[a]Death from any cause, MI, stroke, and hospitalization for HF.
Recurrent events plotted in the form of mean frequency functions using the method of Ghosh and Lin (*Biometrics*. 2000;56:554-562.).

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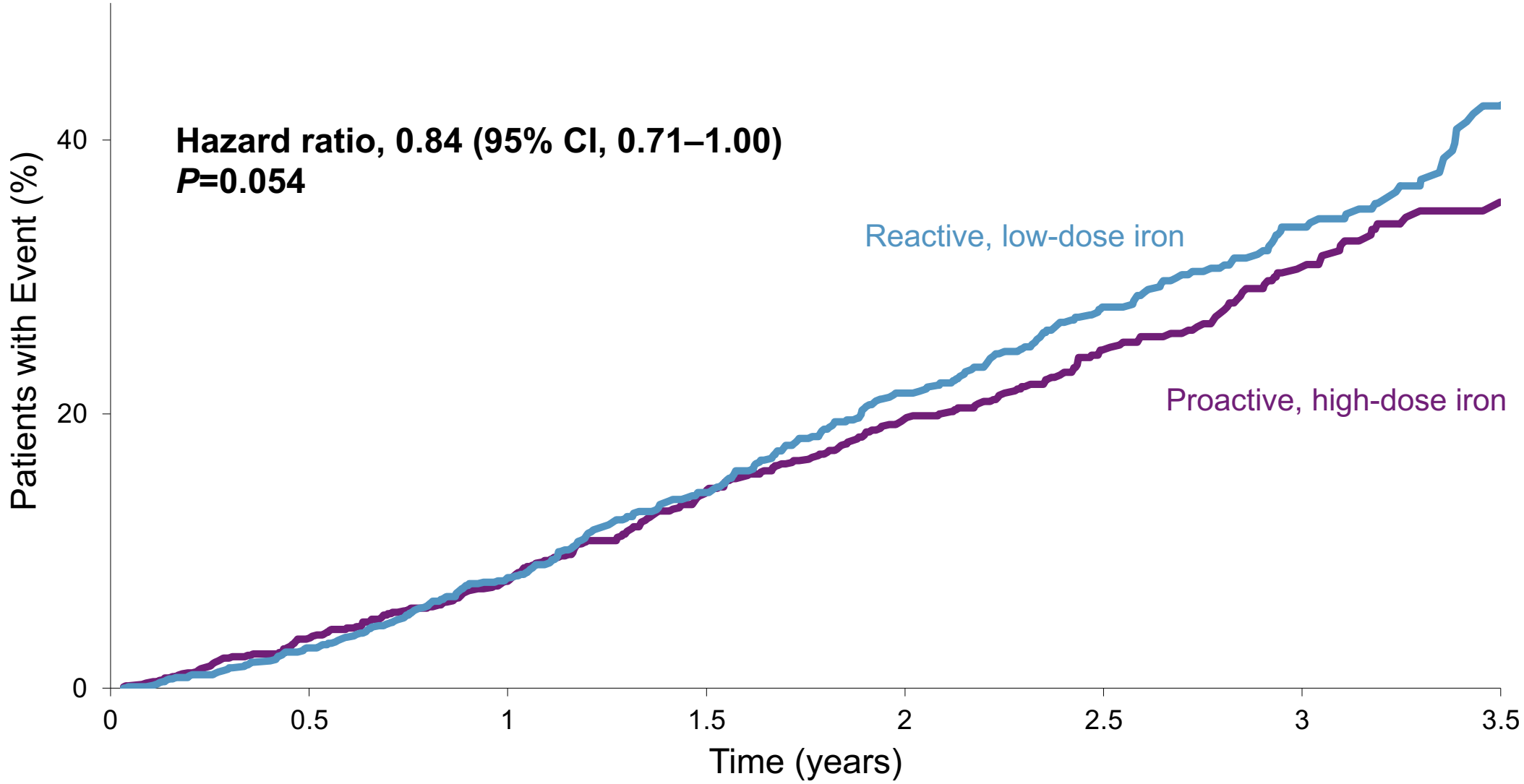
Death from Any Cause



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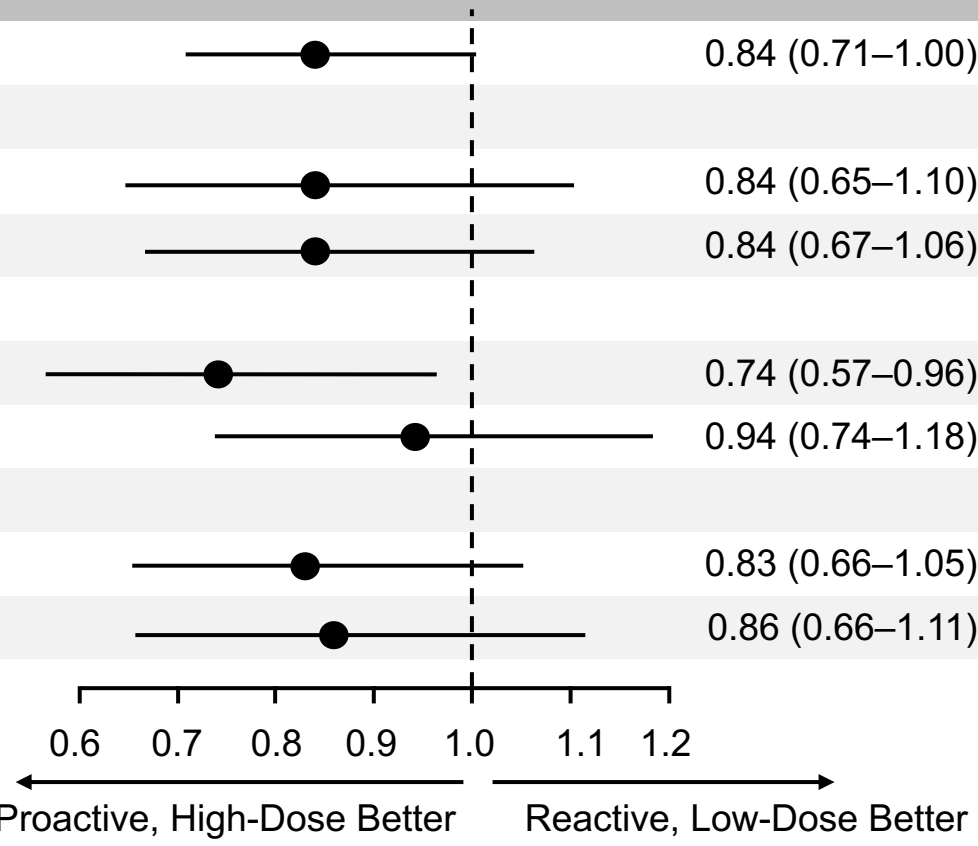
Subgroup Analysis: All-cause Death

Subgroup	Proactive, High-Dose Iron	Reactive, Low-Dose Iron	Hazard Ratio (95% CI)	*P* Value for Interaction
	no. of events/total no. (%)			
All participants	246/1093 (22.5)	269/1048 (25.6)	0.84 (0.71–1.00)	
Duration of dialysis treatment at enrollment				0.99
<5 months	103/499 (20.6)	116/487 (23.8)	0.84 (0.65–1.10)	
≥5 months	143/594 (24.1)	153/561 (27.3)	0.84 (0.67–1.06)	
Dialysis access				0.18
Dialysis catheter	102/452 (22.6)	127/432 (29.4)	0.74 (0.57–0.96)	
AV fistula	144/641 (22.5)	142/616 (23.1)	0.94 (0.74–1.18)	
Baseline diabetes				0.93
Yes	138/490 (28.2)	149/453 (32.9)	0.83 (0.66–1.05)	
No	108/603 (17.9)	120/595 (20.2)	0.86 (0.66–1.11)	



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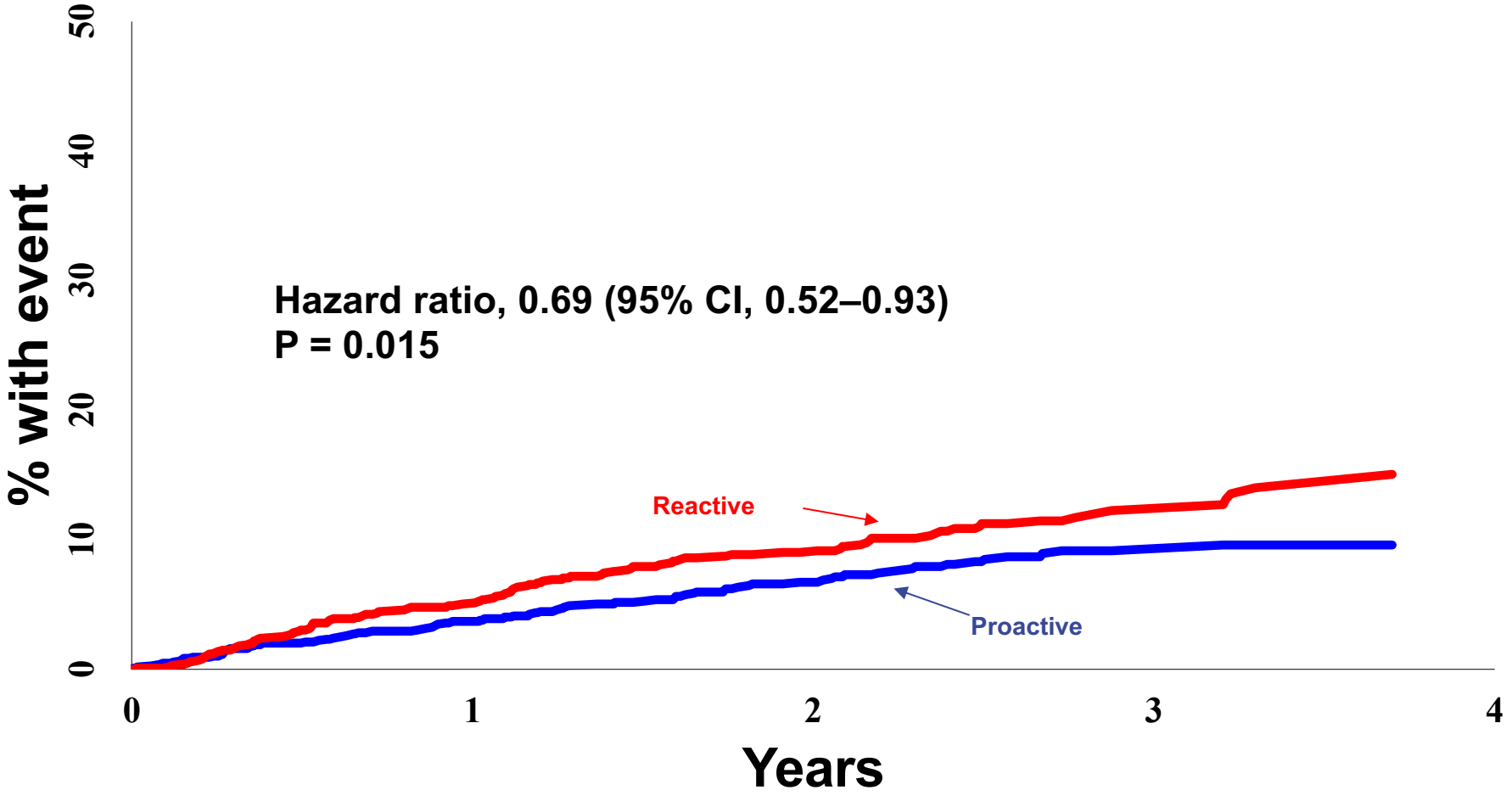
Cardiovascular Events

Outcome	Proactive, High-Dose IV Iron (N=1093) n (%)	Reactive, Low-Dose IV Iron (N=1048) n (%)	Hazard Ratio (95% CI)	*P* Value
Fatal or nonfatal MI, fatal or nonfatal stroke, or hospitalization for HF	149 (13.6)	168 (16.0)	0.80 (0.64–1.00)	0.049
Fatal or nonfatal MI	78 (7.1)	102 (9.7)	0.69 (0.52–0.93)	0.015
Fatal or nonfatal stroke	34 (3.1)	35 (3.3)	0.90 (0.56–1.44)	0.663
Hospitalization for HF	51 (4.7)	70 (6.7)	0.66 (0.46–0.94)	0.023

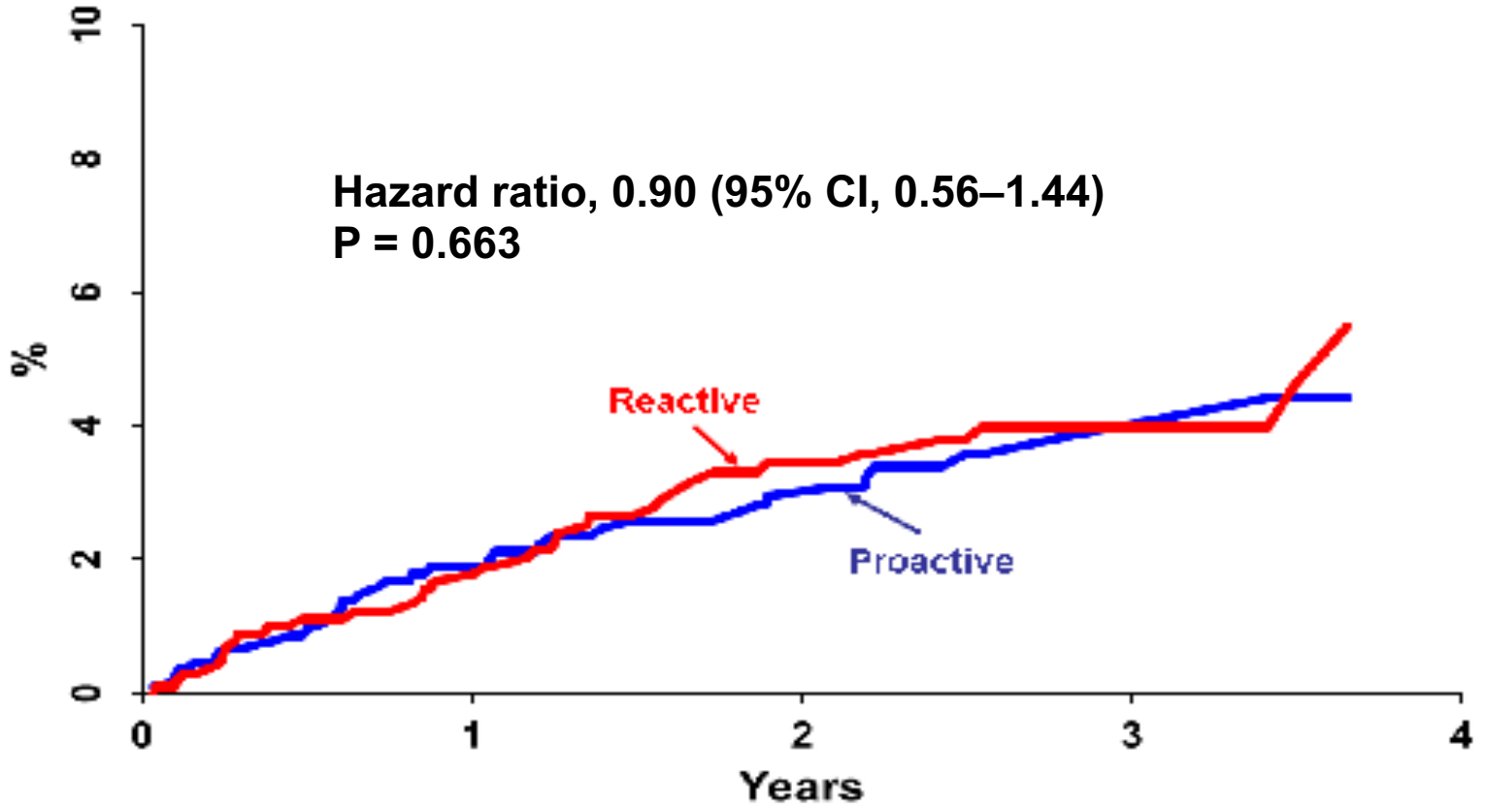
Fatal or nonfatal MI



Numbers at risk:

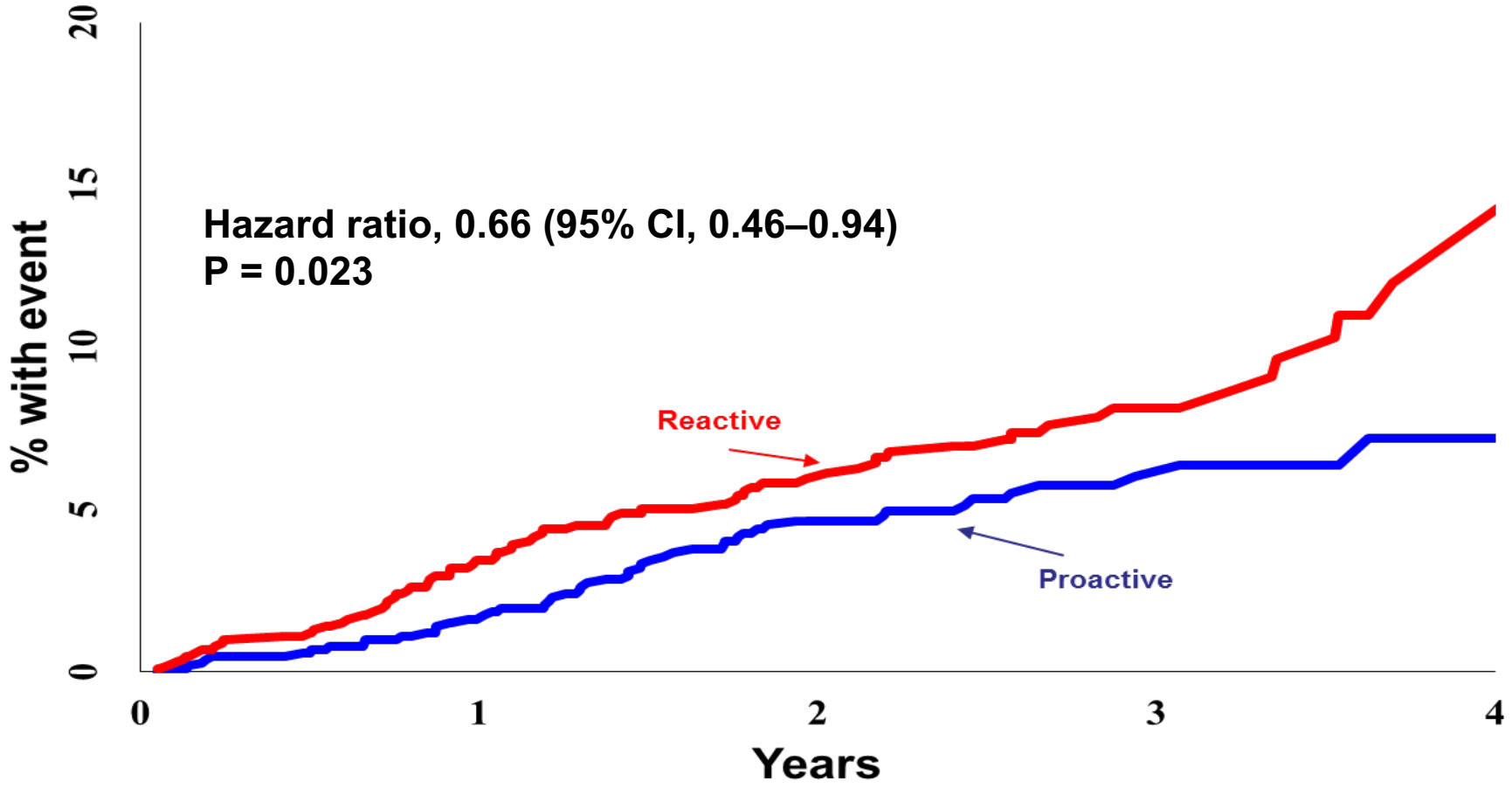
Proactive	1093	819	574	202	30
Reactive	1048	753	517	196	22

Fatal or nonfatal stroke



Numbers at risk:					
Proactive	1093	831	600	219	33
Reactive	1048	778	546	213	22

Heart failure hospitalisation



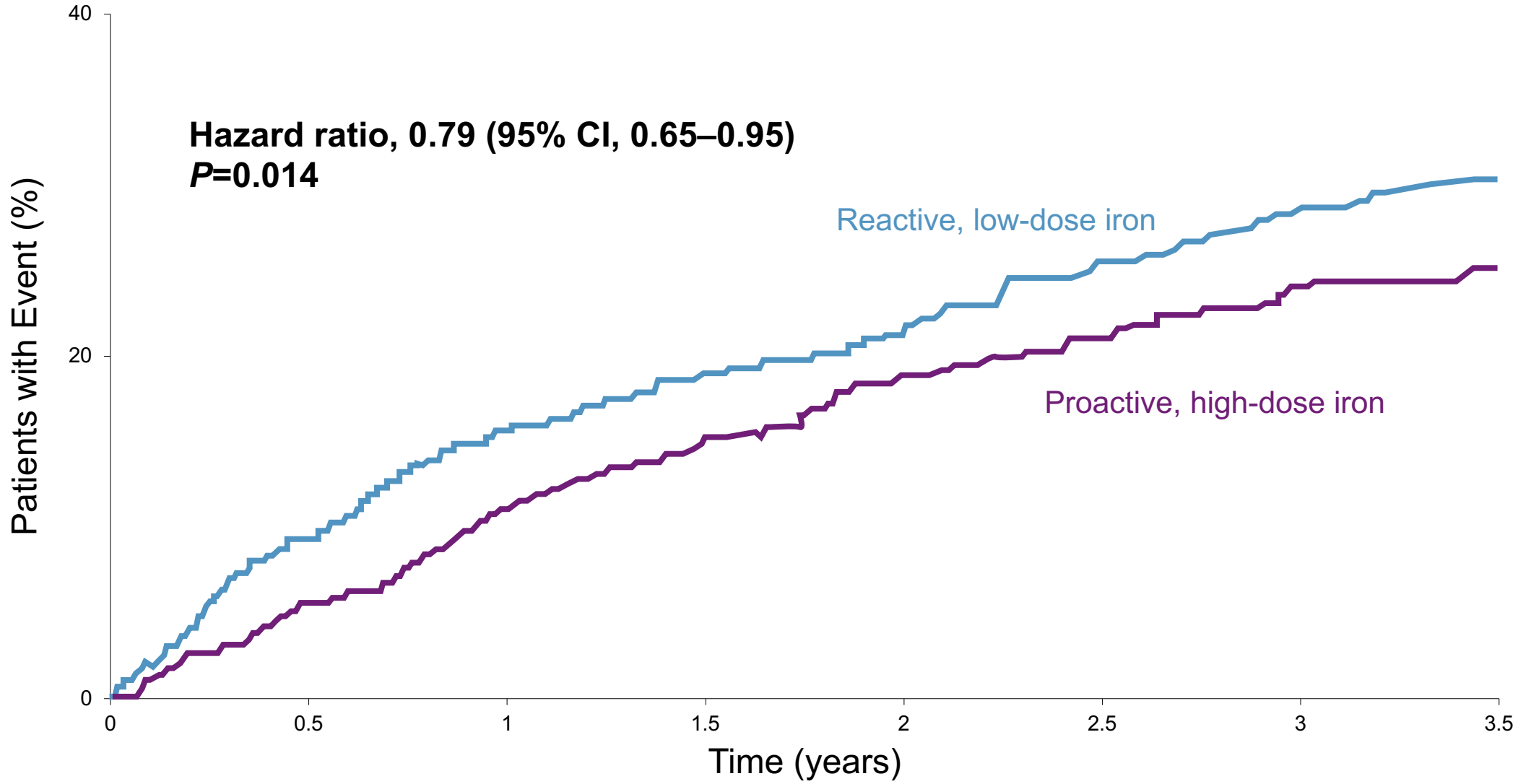
Numbers at risk:

Proactive	1093	834	586	215	32
Reactive	1048	768	532	205	22

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Blood Transfusions

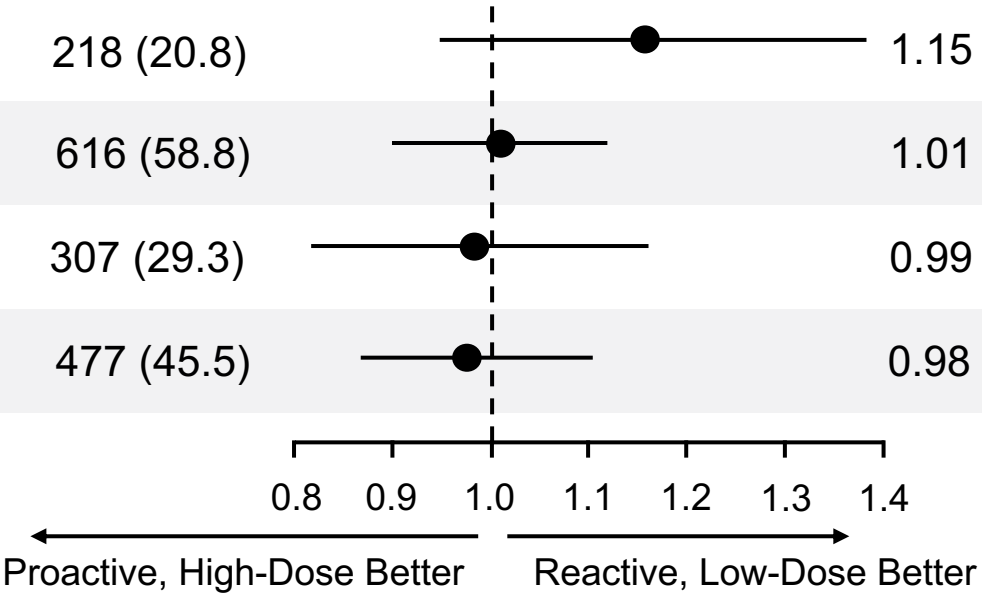


PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Safety

Endpoint	Proactive, High-Dose IV Iron (N=1093) n (%)	Reactive, Low-Dose IV Iron (N=1048) n (%)	Hazard Ratio (95% CI)	*P* Value
Vascular access thrombosis	262 (24.0)	218 (20.8)	1.15 (0.96–1.38)	0.12
All-cause hospitalization	651 (59.6)	616 (58.8)	1.01 (0.90–1.12)	0.90
Hospitalization for infection	323 (29.6)	307 (29.3)	0.99 (0.82–1.16)	0.92
Infection episodes	508 (46.5)	477 (45.5)	0.98 (0.87–1.11)	0.80



PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Conclusions

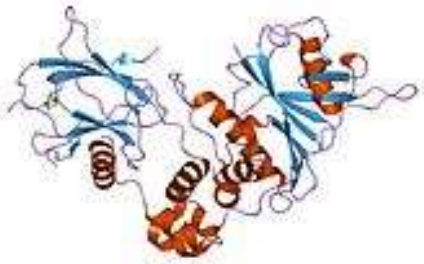
High-dose iron:-

- Significantly reduced the risk of the primary outcome of death or non-fatal CV events
- Reduced the risk of MI and hospitalisation for HF
- Was associated with a significant benefit in a recurrent event analysis
- Reduced ESA dose (19.4%) and transfusion rate (21%)
- Did not cause an increased risk of infection or hospitalisation

HIF Stabilizers: A Viable Option for Managing Renal Anemia in 2021

Steven Fishbane MD

Donald and Barbara Zucker School of Medicine at Hofstra / Northwell



COI

- Astra Zeneca – Research, consulting
- Fibrogen, consulting
- Akebia- Research

Roxadustat – FDA PDUFA Date
March 20, 2021

Introduction

- Anemia remains a common complication of CKD
- Treatment with ESAs has been helpful
  - Concerns about toxicity
- HIF-PHD inhibitors are a promising class of drugs

RCTs on “Normalizing” Hgb with ESAs

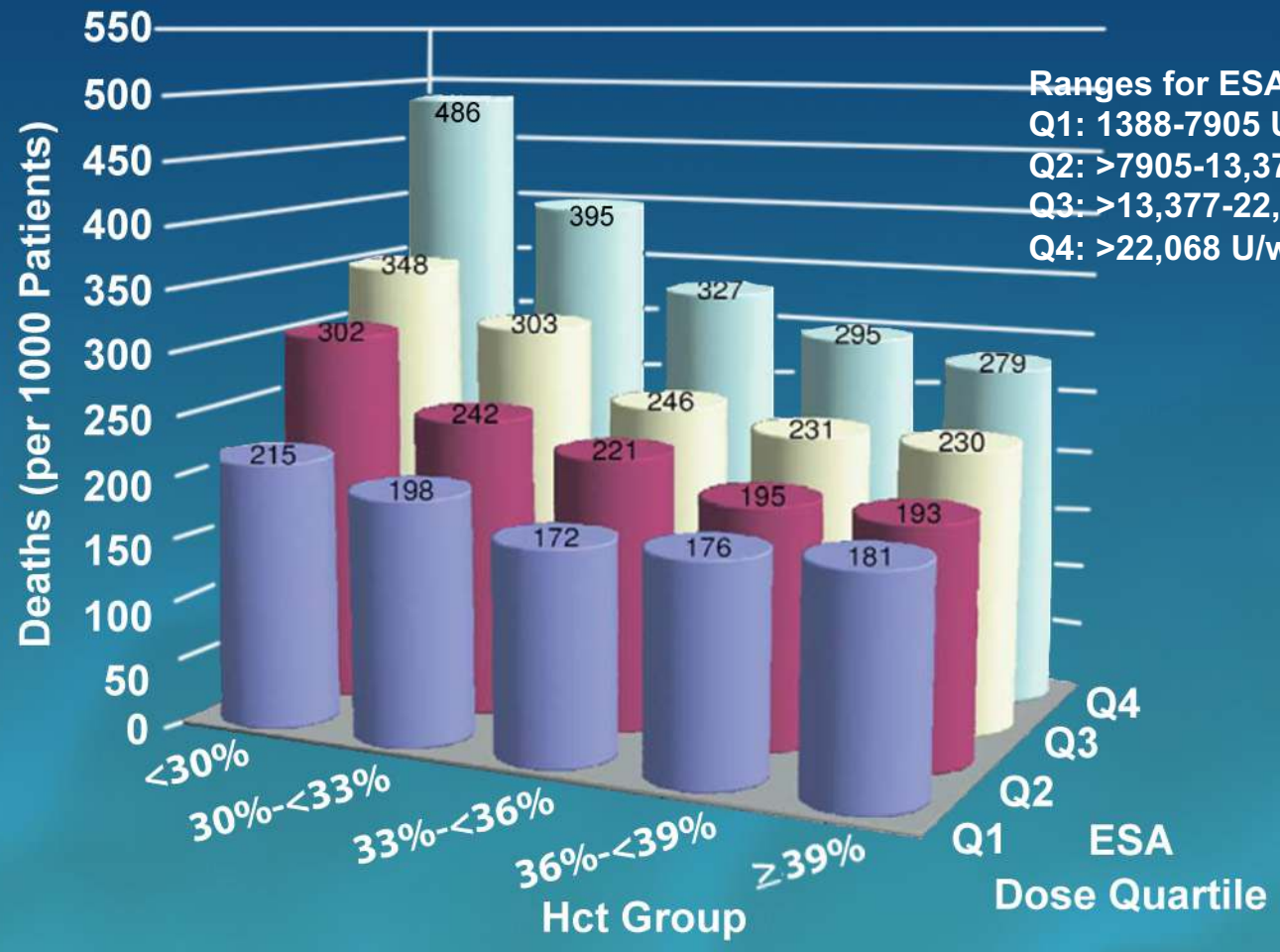
- Parfrey et al (n=596)- hemodialysis
  - increased stroke risk
- Drueke et al (n=600)- CKD
  - trend to increased mortality risk
- Besarab et al- (n=1233)- hemodialysis
  - trend to increased death risk, increased access clotting
- Singh et al (n=1432)- CKD
  - increased cardiovascular risk
- Pfeffer et al (n=4032)- CKD
  - increased risk stroke, cancer deaths

Why is Prolonged EPO Treatment to High Hb Targets Harmful?

- High Hb itself- increased blood viscosity?
- High Hb in patients with vascular disease?
- High EPO doses required to get to normal Hb?
- Other?

- No clear answer

Greater ESA Dose Is Associated With Mortality (Observational Data)



Ranges for ESA quartiles:
Q1: 1388-7905 U/wk
Q2: >7905-13,377 U/wk
Q3: >13,377-22,068 U/wk
Q4: >22,068 U/wk

Zhang et al. *Am J Kidney Dis.* 2004;44:866-876.

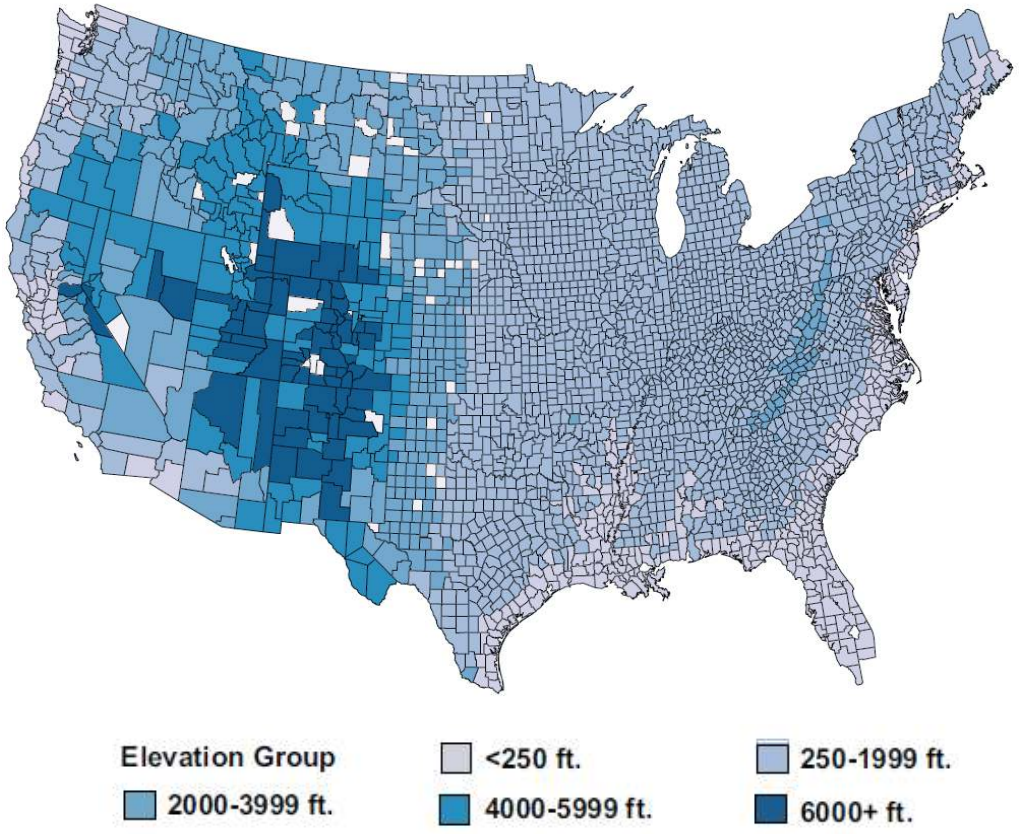
New in Anemia Treatment

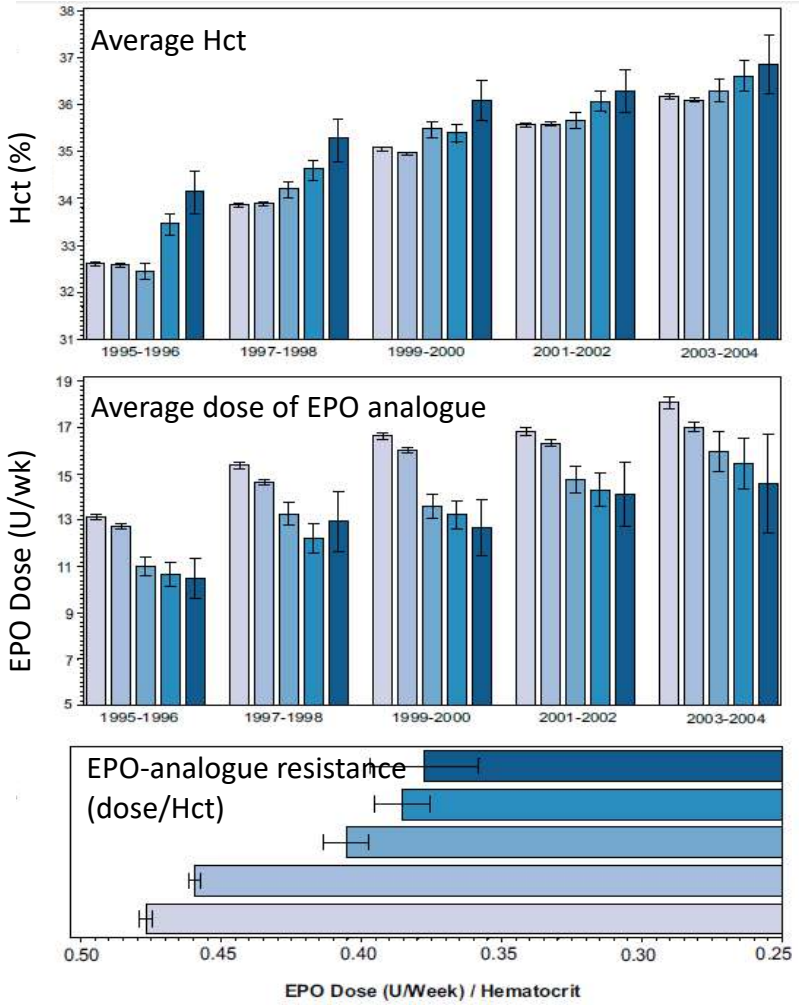
- If higher erythropoietin doses harmful, can anemia be treated with more physiologic changes in serum erythropoietin?

- Prolyl Hydroxylase Inhibitors

Altitude and EPO-Analogue Response

US Renal Data System (N=341,737 incident HD patients) combined with elevation data from the US Geological Survey



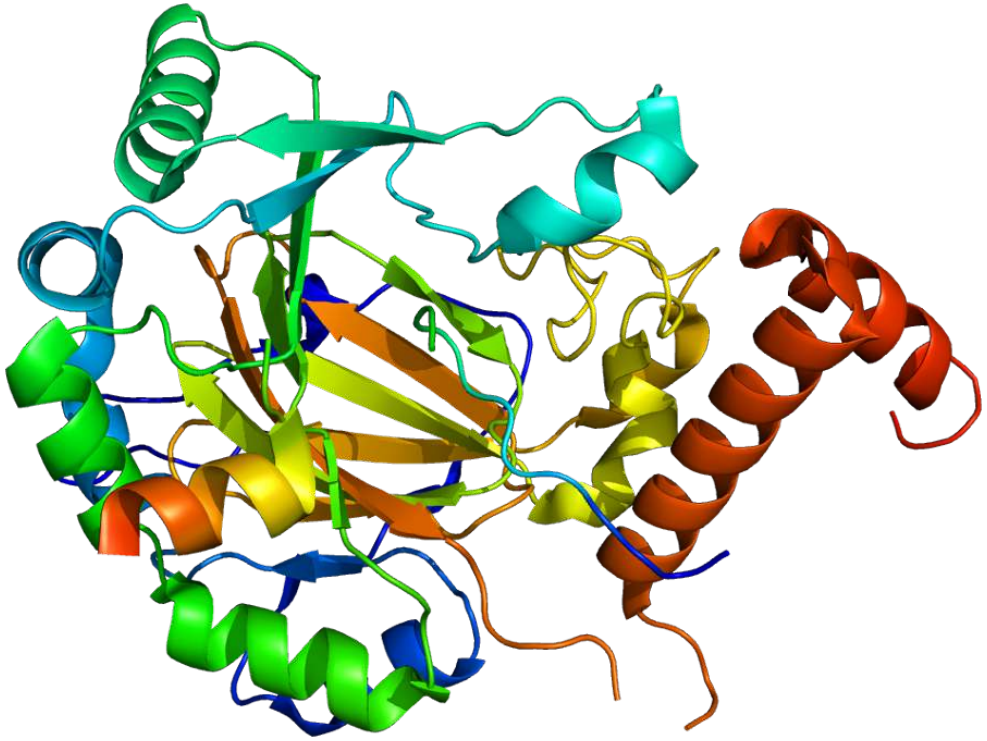


Brookhart MA, et al. *J Am Soc Nephrol*. 2008;19(7):1389-1395.

Hypoxia Inducible Factor (HIF)

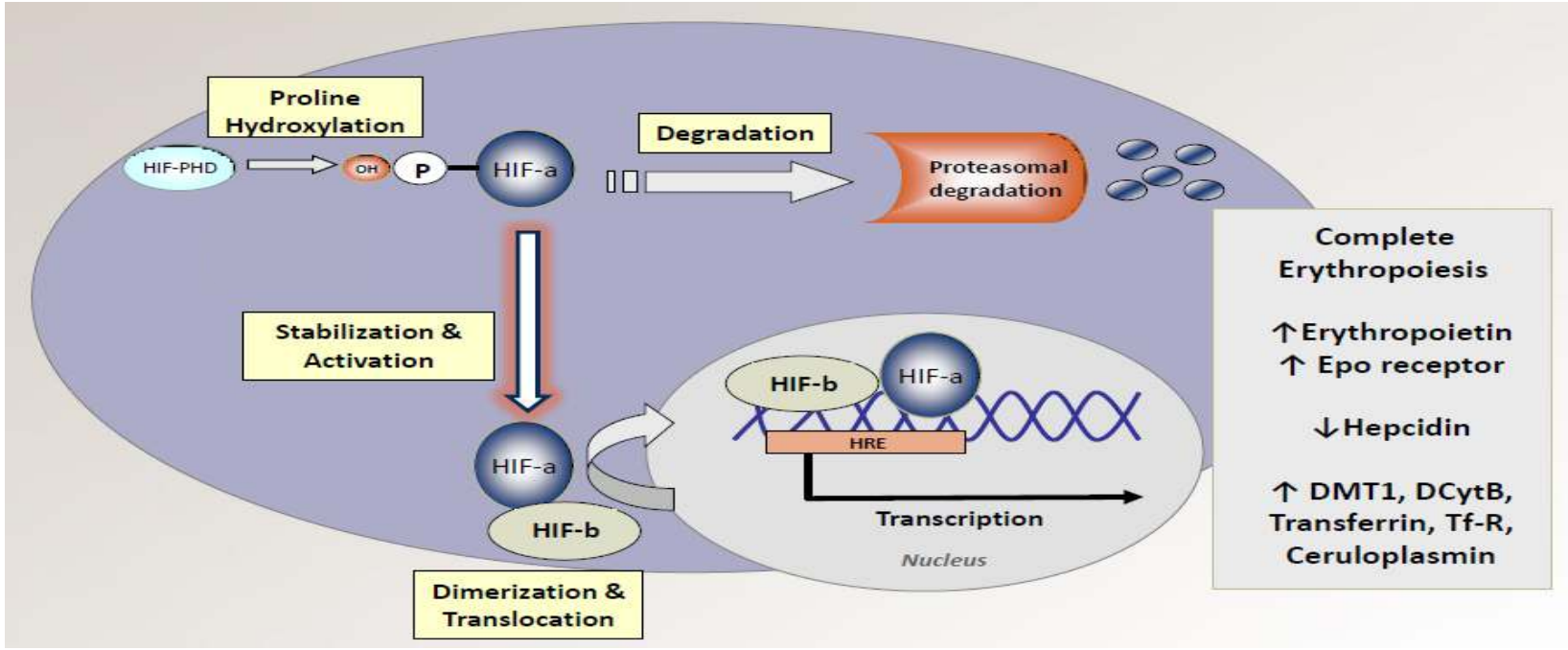
- Oxygen-sensitive transcription factors

Nobel prize 2019



1. Haase VH. *Am J Physiol Renal Physiol*. 2010;299(1):F1-13. 2. Haase VH. *Blood Rev*. 2013;27(1):41-53. 3. Mole DR. *Antioxid Redox Signal*. 2010;12(4):445-458. 4. Yoon D, et al. *J Biol Chem*. 2006;281(35):25703-25711.

HIF Overview



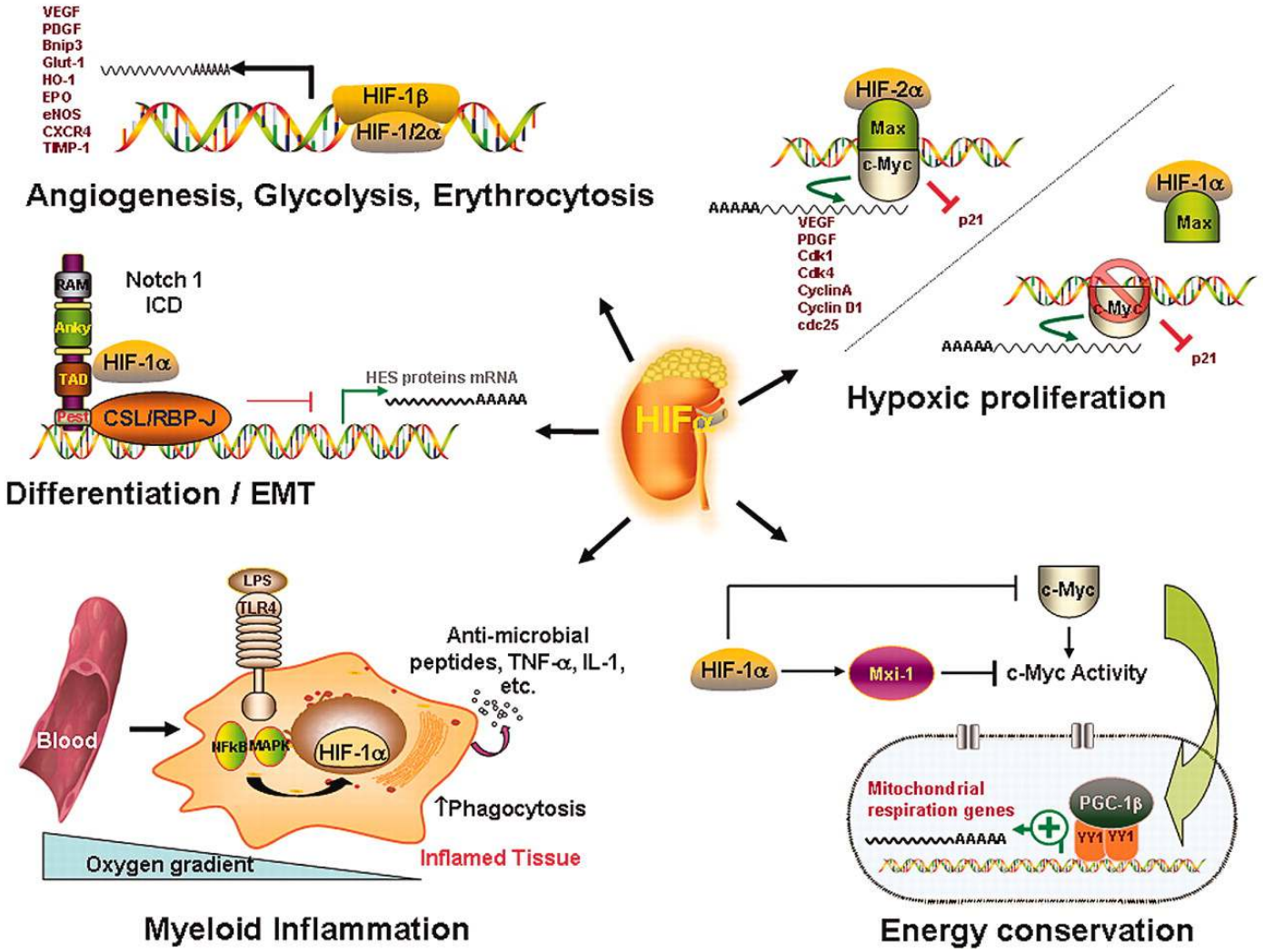
- HIF-α regulated by HIF-PH enzymes that promote its rapid degradation in presence of oxygen

1. Haase VH. *Am J Physiol Renal Physiol*. 2010;299(1):F1-13. 2. Haase VH. *Blood Rev*. 2013;27(1):41-53. 3. Mole DR. *Antioxid Redox Signal*. 2010;12(4):445-458.

HIF Drugs – Potential Benefits

- Oral
- Cause much lower peak EPO levels in blood than ESAs
- Increase iron availability
- May have beneficial effects on BP and Cholesterol
- Other

HIF Activity



Gunaratnam L, et al. *J Am Soc Nephrol.* 2009;20(9):1877-1887.

HIF-PHIs: Pharmacologic Profiles

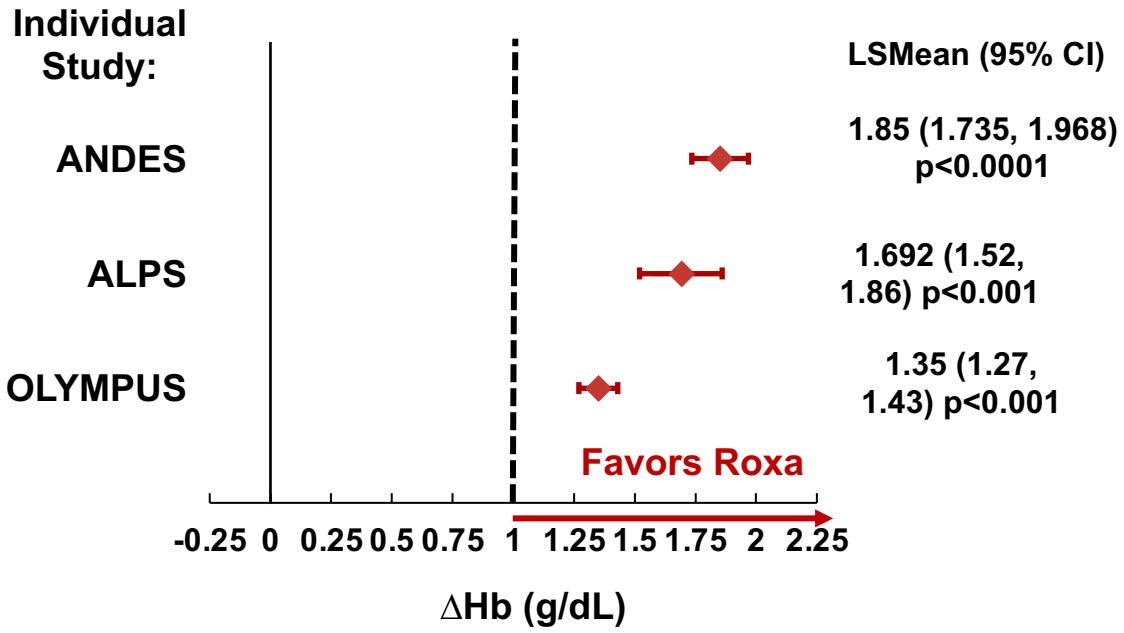
	Roxadustat	Vadadustat	Daprodustat
Effective Daily Oral Doses in Phase II Trials	0.7-2.5 mg/kg	150-600 mg	5-25 mg (50 and 100 mg also examined)
Dosing Schedule	3x weekly	Daily (3x weekly)	Daily
Half-Life (hours)	12-15	4.7-9.1	~1-7
Plasma EPO (IU/L)	113 and 397, 130	32	24.7 and 34.4, 82.4
Metabolism	CYP2C8	NR	CYP2C8 with minor CYP3A4
Rel. Activity, IC50 for PHD2 (μM)	PHD1,2,3 equally, 0.027	PHD3>PHD1>PHD2, 0.029	PHD3>PHD1>PHD2, 0.067

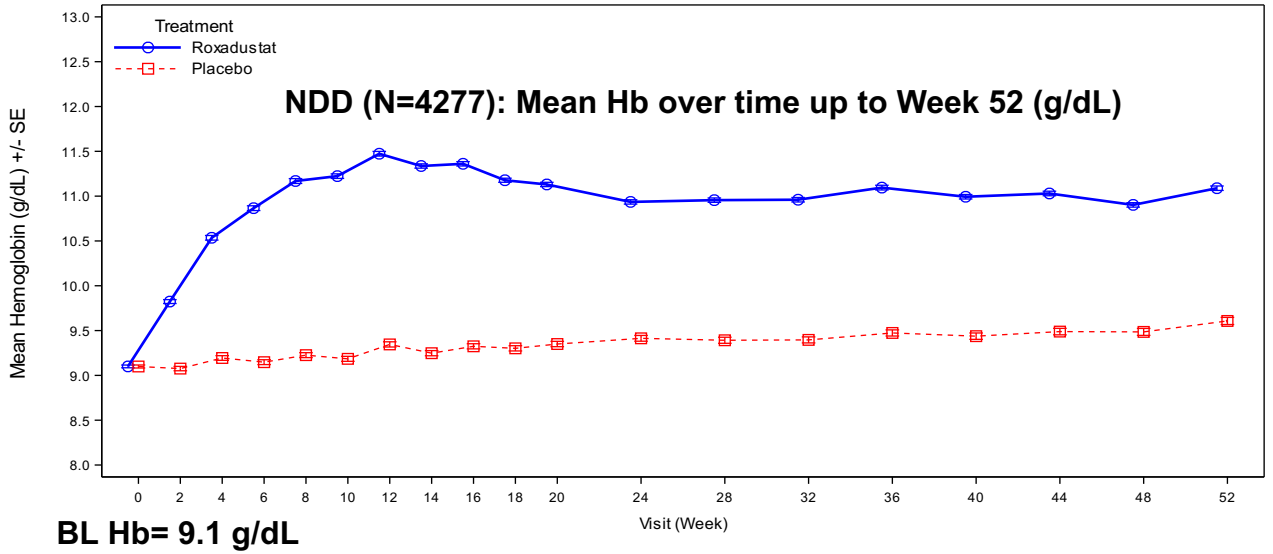
Sanghani NS, Haase VH. *Adv Chronic Kidney Dis*. 2019;26(4):253-266.

HIF-PHI - Study Results

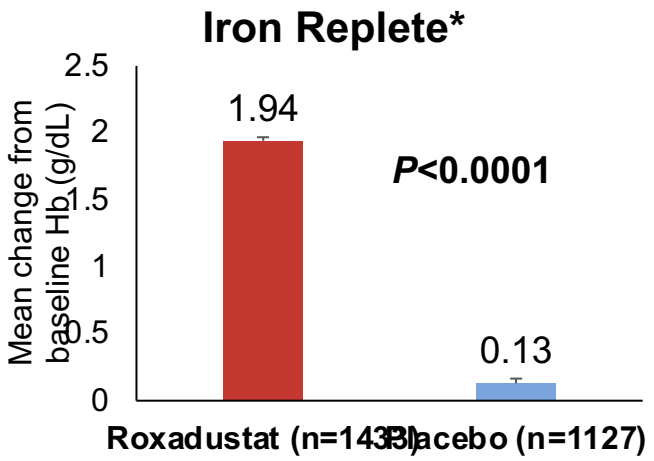
Global Roxadustat Pooled Phase 3 NDD Efficacy

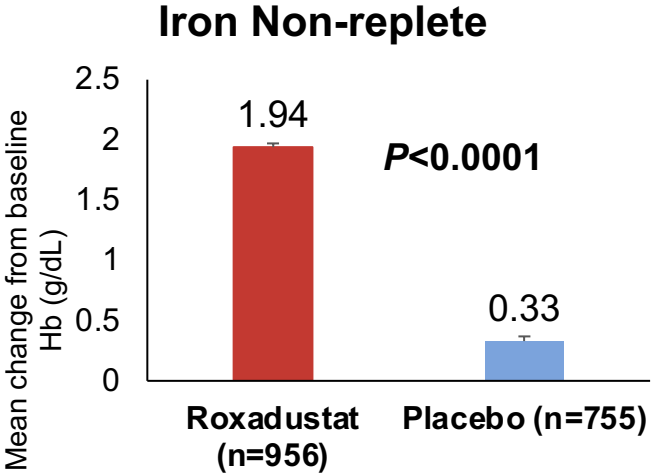
Hb change from baseline to Week 28–52





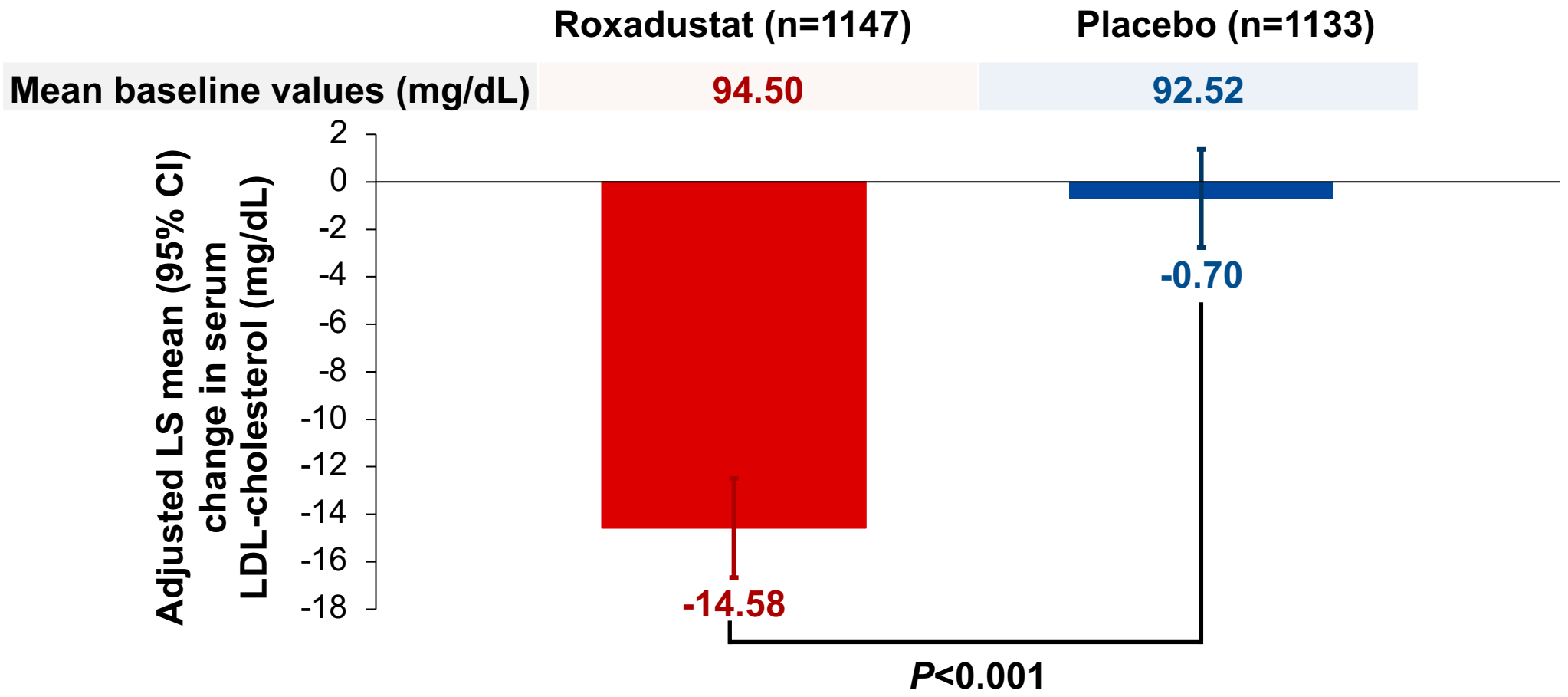
BL Hb= 9.1 g/dL





CI, confidence interval; Hb, hemoglobin;
*Iron Replete: TSAT ≥20% and ferritin ≥100 ng/mL. TSAT, transferrin saturation

Change in Serum LDL-Cholesterol*



*From baseline to Week 24.

Baseline is defined as the last measurement prior to randomization. Intent-to-treat analysis set

CI, confidence interval; LDL, low-density lipoprotein

Common Adverse Events (ITT*)

AE category	Roxadustat (N=1384)			Placebo (N=1377)		
	n	%	Pts w/ Events/ 100 P-Y	n	%	Pts w/ Events/ 100 P-Y
Most reported AEs						
End stage renal disease	209	21.0	**11.7**	282	20.5	**11.8**
Urinary tract infection	177	12.8	**6.8**	110	8.0	**4.2**
Pneumonia	165	11.9	**6.2**	130	9.4	**4.9**
Hypertension	159	11.5	**6.1**	125	9.1	**4.8**
Most reported SAEs						
End stage renal disease	199	14.4	**7.7**	201	14.6	**8.1**
Pneumonia	113	8.2	**4.1**	88	6.4	**3.3**
Azotemia	61	4.4	**2.2**	60	4.4	**2.2**
Sepsis	49	3.5	**1.8**	23	1.7	**0.8**
Acute kidney injury	41	3.0	**1.5**	32	2.3	**1.2**
Hyperkalemia	41	3.0	**1.5**	25	1.8	**0.9**

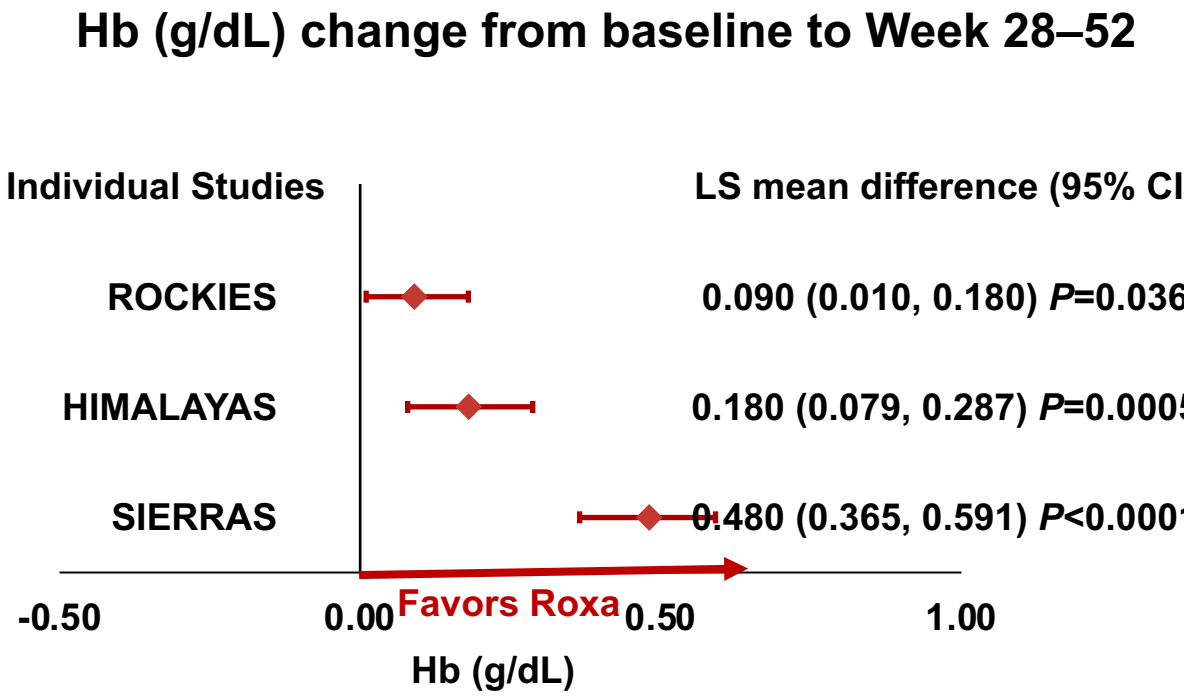
*ITT analysis – include events on treatment + off-treatment in long term follow-up until study end date.

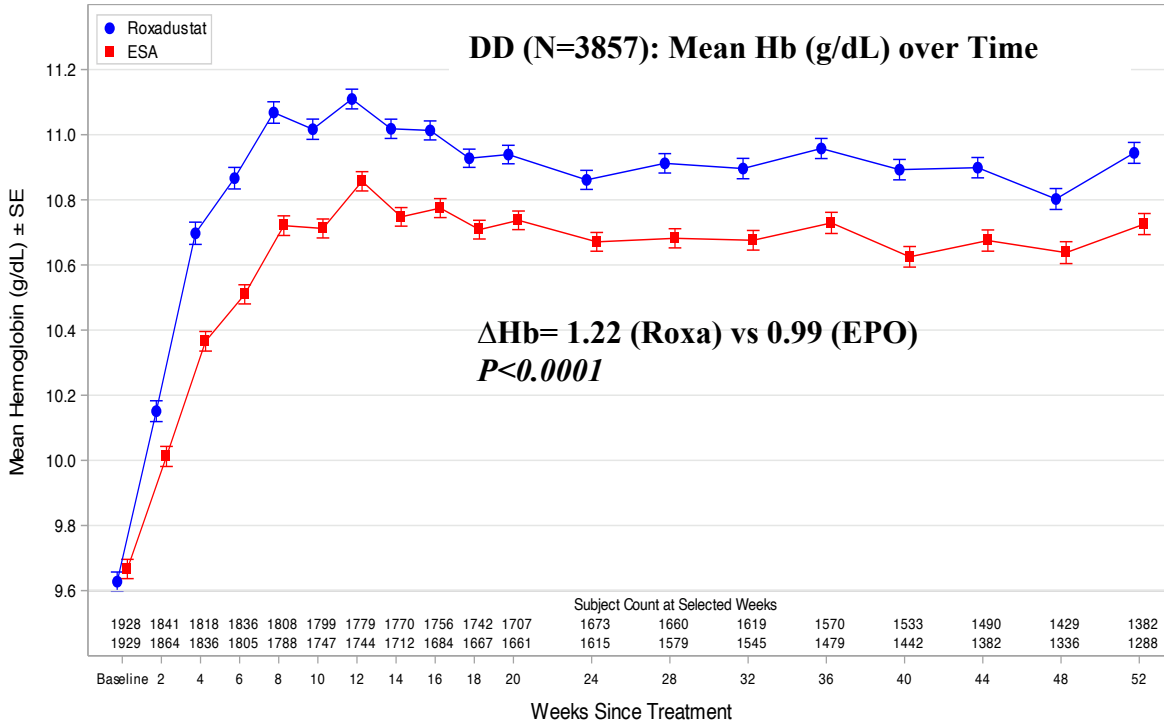
**Pts w/Events/100 PY- Calculated by Follow-up Adjusted Incidence Rate (FAIR).

AE, adverse event; pts, patients; P-Y, patient years

DD: Roxadustat Global Pooled Analysis

Primary efficacy endpoint (change in Hb from baseline to Hb averaged over Weeks 28 to 52):

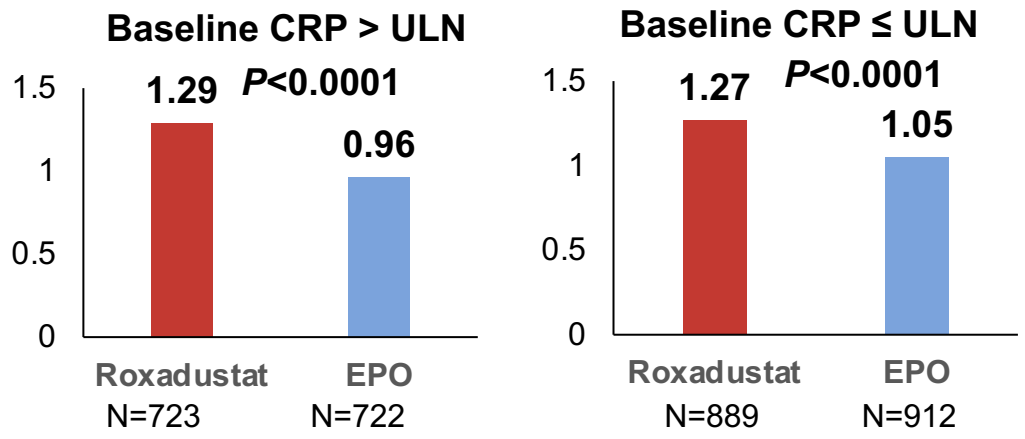




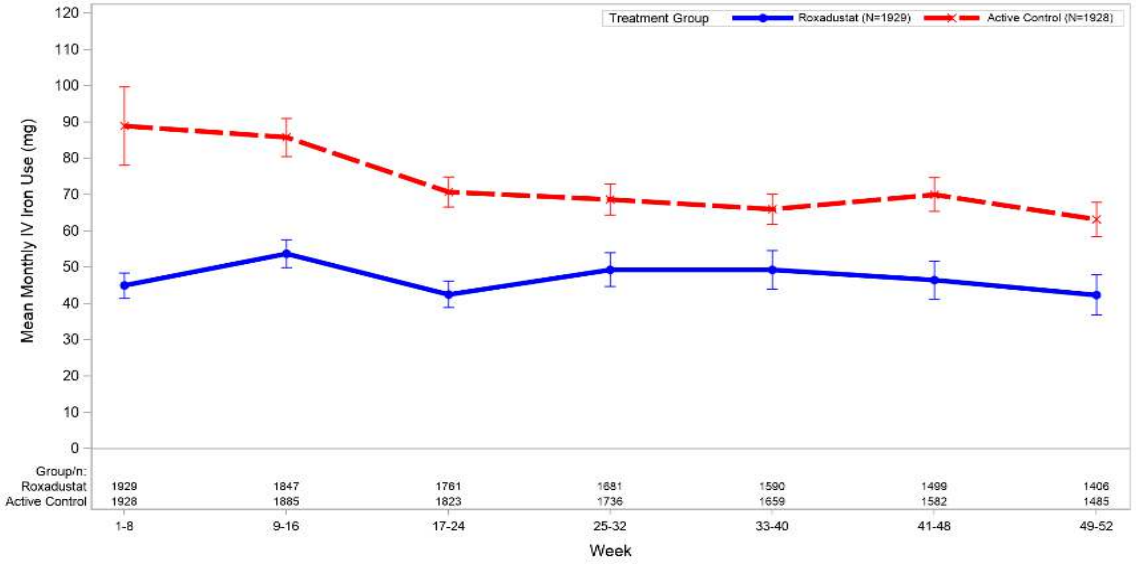
CI, confidence interval; CRP, C-reactive protein; DD, dialysis-dependent; EPO, erythropoietin; Hb, hemoglobin; EPO, epoetin alfa

DD: Roxadustat Efficacy / Inflammation and Iron

DD: Hb (g/dL) change from baseline to Weeks 28–52



DD: Less Monthly IV Iron Use in Roxadustat Patients Than in EPO Patients



CI, confidence interval; CRP, C-reactive protein; DD, dialysis-dependent; EPO, erythropoietin; Hb, hemoglobin; IV, intravenous; TSAT, transferrin saturation; ULN, upper limit of normal

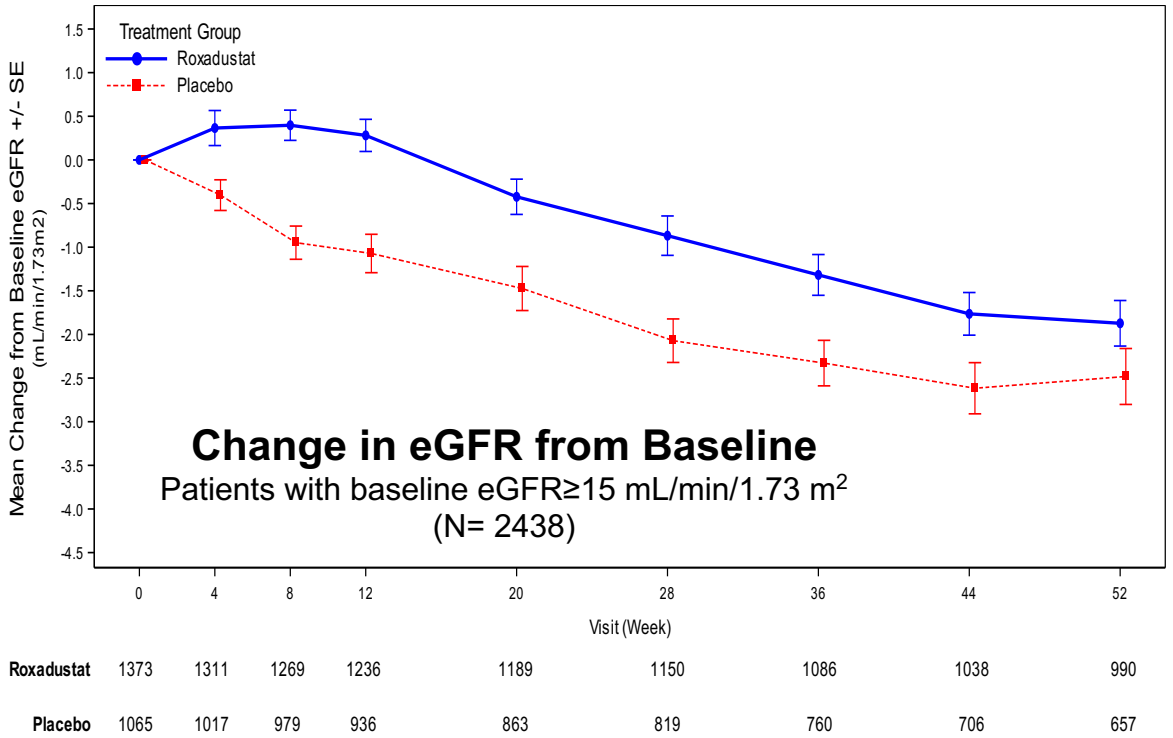
Roxadustat Other Outcomes in NDD

Renal function: NDD

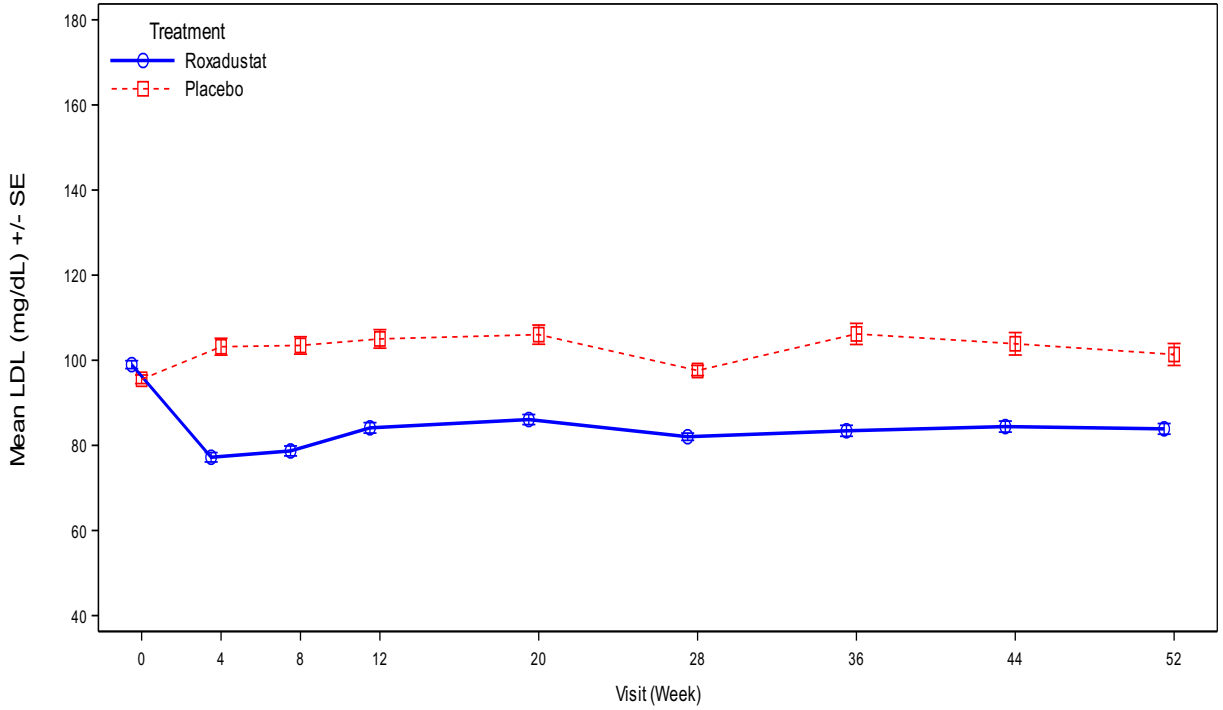
- **Change in eGFR in first year:** -2.8 (Roxa) vs -4.4 (Placebo)
  - Treatment difference: 1.6 mL/min/1.73 m^2, *P* <0.0001

Reduction in LDL cholesterol: NDD

Change in LDL from baseline:
-17.06 (Roxa) vs 1.30 (Placebo)
Treatment difference: -19.83 mg/dL, *P* <0.001

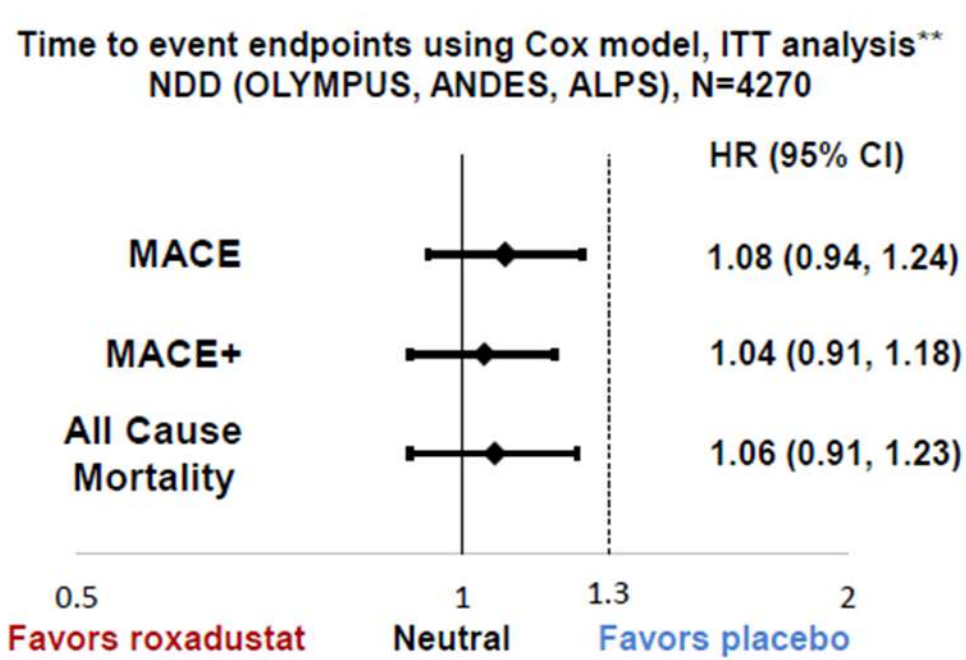


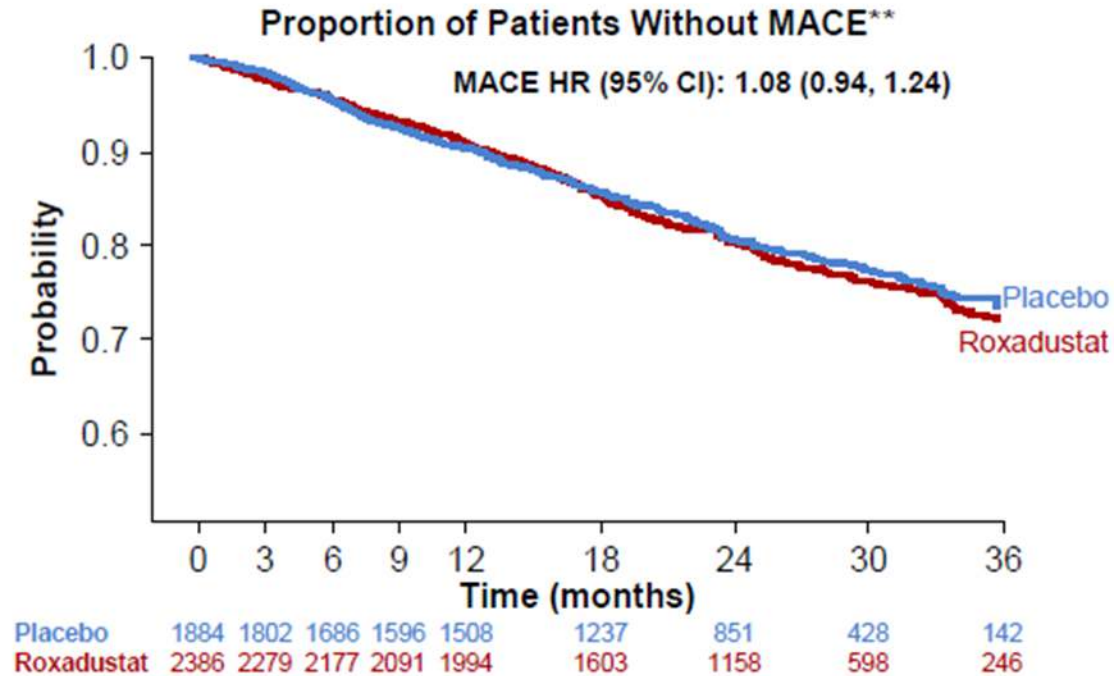
Change in eGFR from Baseline
Patients with baseline eGFR≥15 mL/min/1.73 m^2
(N= 2438)



eGFR, estimated glomerular filtration rate; NDD, non-dialysis-dependent; SE, standard error

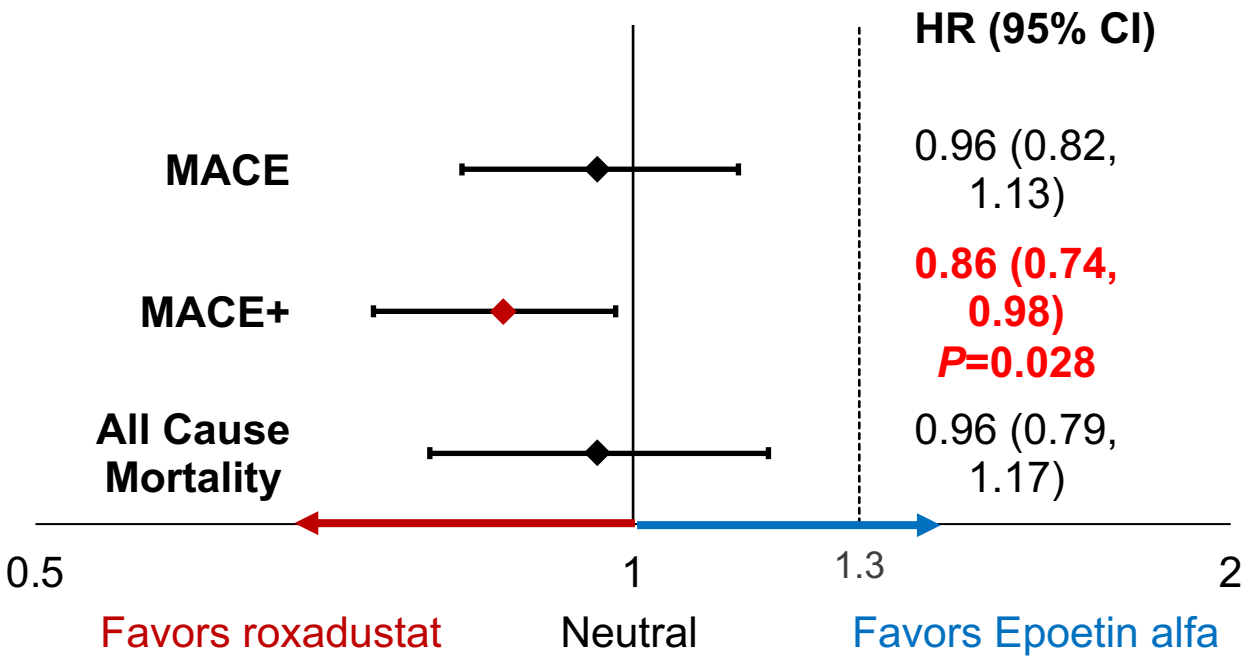
NDD Pool: Cardiovascular Safety Endpoints MACE, MACE+, All-cause Mortality





DD Pooled: Cardiovascular Safety Endpoints

Time to event endpoints using Cox model, DD (ROCKIES, HIMALAYAS, SIERRAS), N=3880

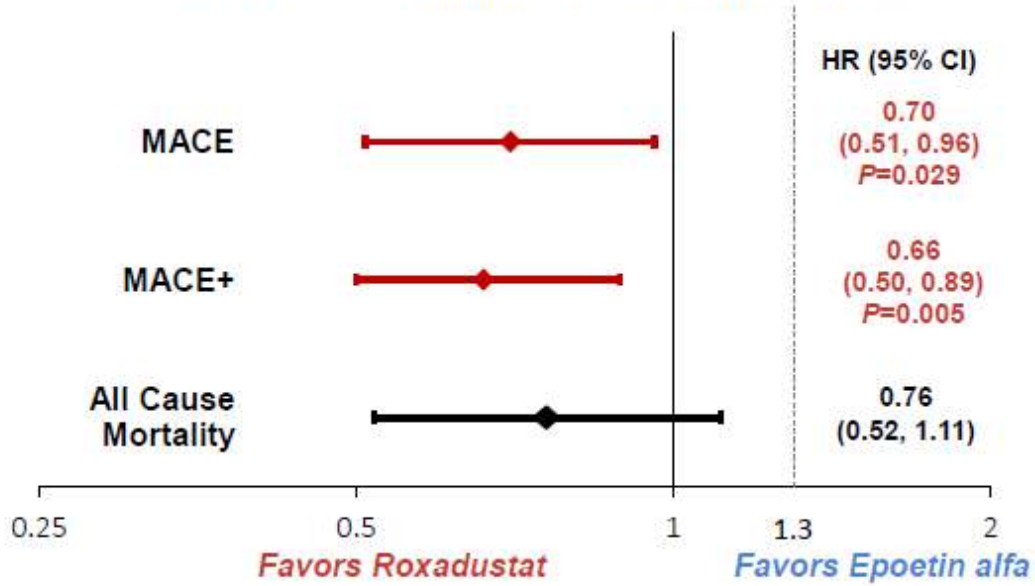


MACE+ Components Incidence Rates, N (%)		
Events	**Roxadustat**	**Epoetin alfa**
n	**1940**	**1940**
Death (all-cause mortality)	**207 (10.7%)**	**232 (12.0%)**
Myocardial Infarction	**103 (5.3%)**	**109 (5.6%)**
Stroke	**45 (2.3%)**	**50 (2.6%)**
Unstable angina	**18 (0.9%)**	**22 (1.1%)**
Congestive heart failure	**120 (6.2%)**	**166 (8.6%)**

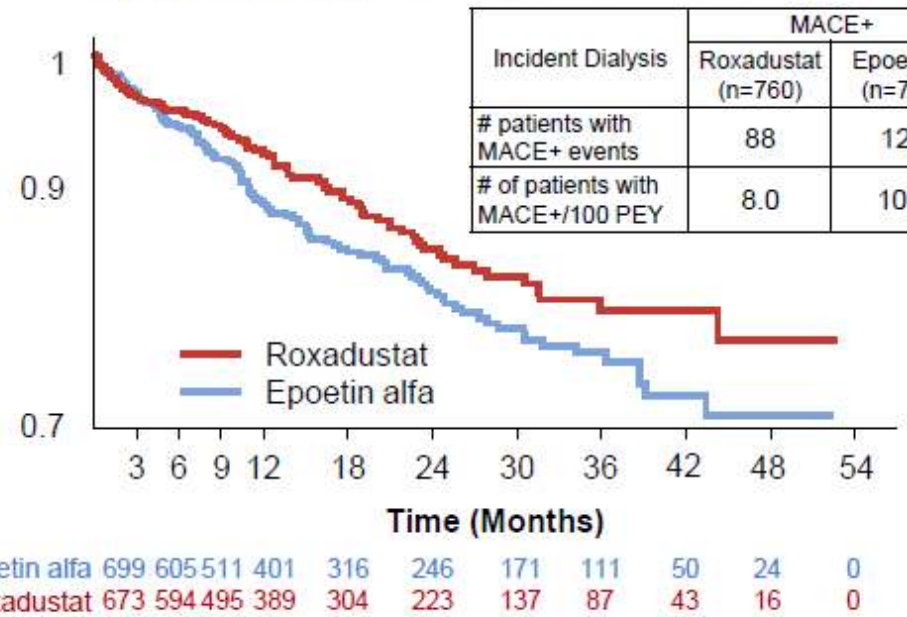
Incident Dialysis Pool: Cardiovascular Safety Endpoints

Roxadustat had 30% lower risk of MACE and 34% lower risk of MACE+ than epoetin alfa* and with a trend towards lower all-cause mortality relative to epoetin alfa, in incident dialysis patients

Time to event endpoints using Cox model †
ID (ROCKIES, HIMALAYAS, SIERRAS), N=1526



Proportion of Patients Without MACE+ Over Time



Incident Dialysis	MACE+	
	Roxadustat (n=760)	Epoetin α (n=766)
# patients with MACE+ events	88	121
# of patients with MACE+/100 PEY	8.0	10.2

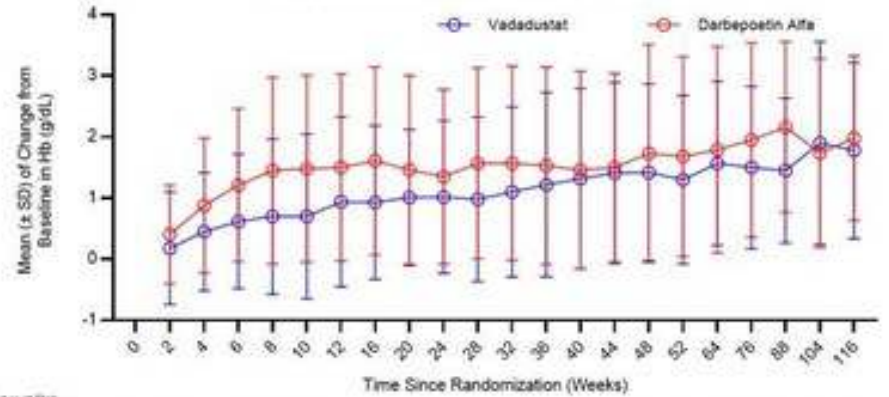
Epoetin alfa	699	605	511	401	316	246	171	111	50	24	0
Roxadustat	673	594	495	389	304	223	137	87	43	16	0

Vadadustat Innovate Dialysis Trial

Primary and Key Secondary Efficacy Endpoint

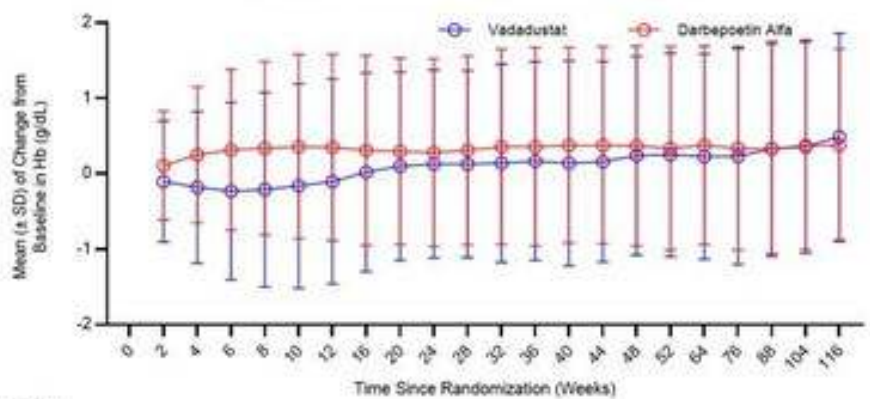
Mean change[a] from baseline in Hb levels in randomized populations

***Incident* DD-CKD Trial**



Mean (SEM) change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	1.26 (0.11)	1.58 (0.11)	**-0.31 (0.11) (95% CI, -0.53 to -0.10)**
Weeks 40-52	1.42 (0.13)	1.50 (0.14)	**-0.07 (0.13) (95% CI, -0.34 to 0.19)**

***Prevalent* DD-CKD Trial**



Mean (SEM) change from baseline, g/dL	Vadadustat	Darbepoetin alfa	Difference (vadadustat - darbepoetin alfa)
Weeks 24-36	0.19 (0.03)	0.36 (0.03)	**-0.17 (0.03) (95% CI, -0.23 to -0.10)**
Weeks 40-52	0.23 (0.03)	0.41 (0.03)	**-0.18 (0.03) (95% CI, -0.25 to -0.12)**

Noninferiority margin: -0.75

→ vadadustat noninferior to darbepoetin alfa

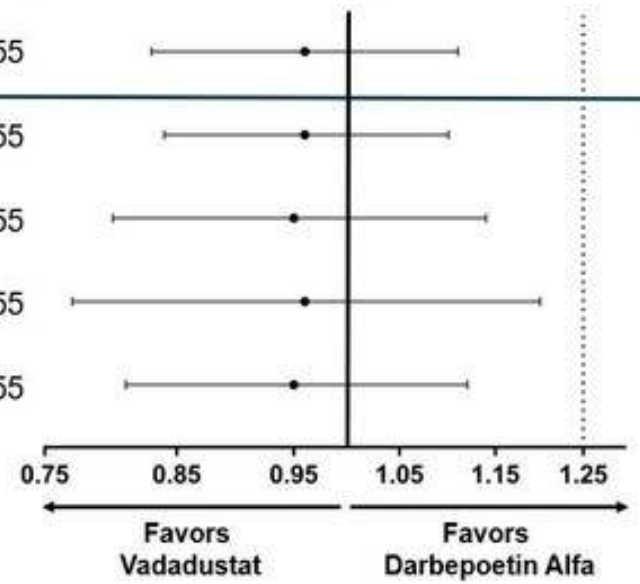
[a]Mean ± SD is presented here to show the extent of variability, given the large sample size.

DD-CKD, dialysis-dependent chronic kidney disease; Hb, hemoglobin; SD, standard deviation; SEM, standard error of the mean.

Vadadustat – ASN Innovate Dialysis Safety

Primary and Key Secondary Safety Endpoints

Safety Endpoint	Vadadustat (n/N)	Darbepoetin Alfa (n/N)	HR (95% CI)
MACE	355/1947	377/1955	0.96 (0.83, 1.11)
Expanded MACE	420/1947	449/1955	0.96 (0.84, 1.10)
Cardiovascular MACE	225/1947	242/1955	0.95 (0.80, 1.14)
Cardiovascular mortality	150/1947	160/1955	0.96 (0.77, 1.20)
All-cause mortality	291/1947	310/1955	0.95 (0.81, 1.12)



→ vadadustat noninferior to darbepoetin alfa

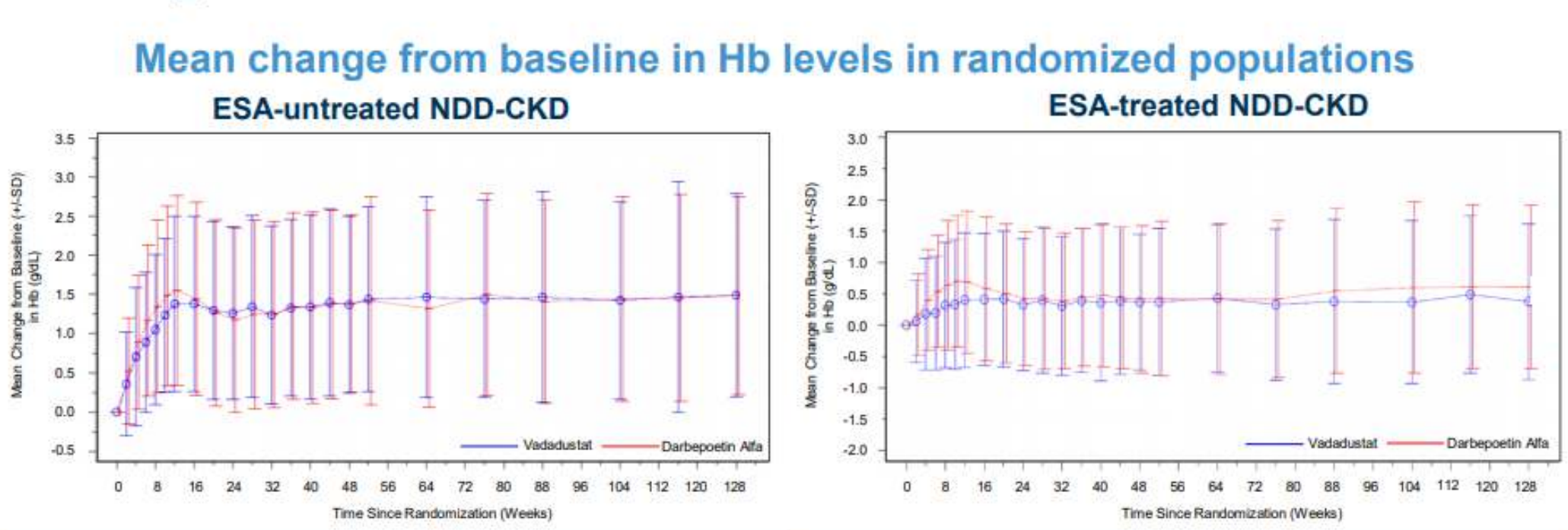
Noninferiority margin: 1.25

MACE: all cause mortality, non-fatal MI or non-fatal stroke
Expanded MACE: MACE plus hospitalisations for heart failure or thromboembolic events (excluding access failure)
Cardiovascular MACE: cardiovascular mortality, non-fatal MI or non-fatal stroke

8

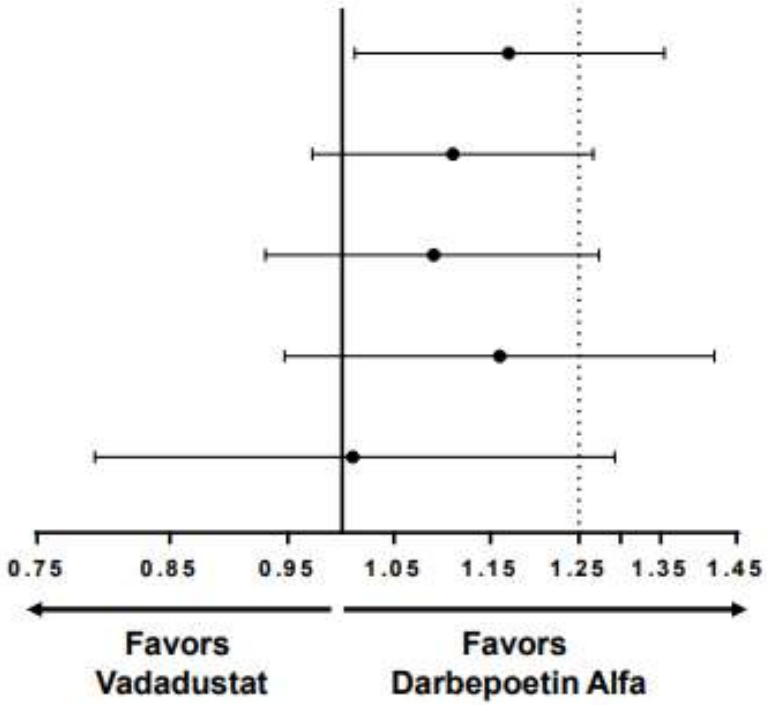
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke).

Vadadustat PROTECT ND-CKD Efficacy



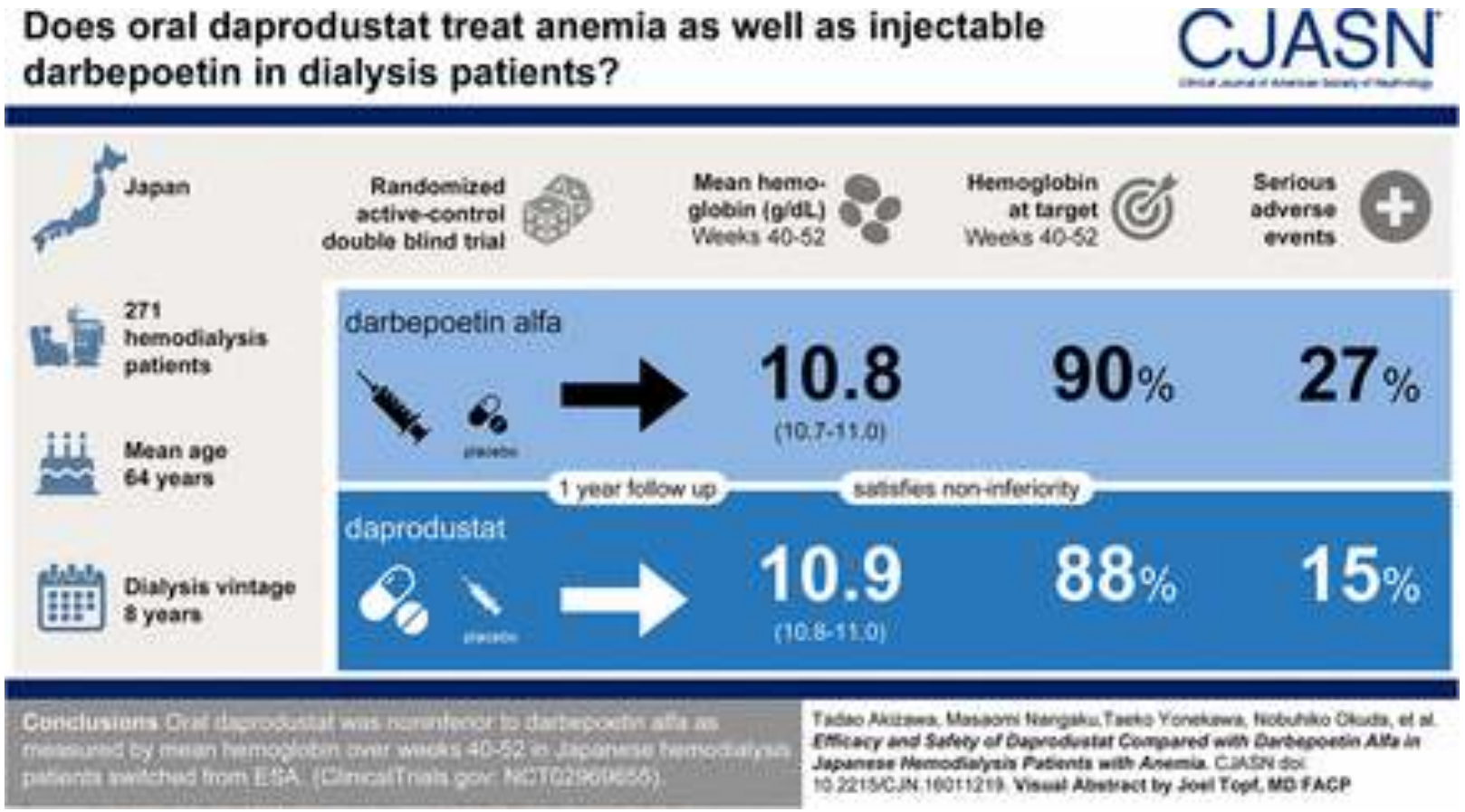
Vadadustat ND-CKD Safety

Safety Endpoint	Vadadustat (n/N)	Darbepoetin Alfa (n/N)	HR (95% CI)
MACE	382/1739	344/1732	1.17 (1.01, 1.36)
Expanded MACE[a]	451/1739	424/1732	1.11 (0.97, 1.27)
All-cause mortality	319/1739	307/1732	1.09 (0.93, 1.27)
Cardiovascular MACE[b]	198/1739	178/1732	1.16 (0.95, 1.42)
Cardiovascular mortality	127/1739	131/1732	1.01 (0.79, 1.29)



Age as a dichotomous variable in the Cox model

Daprodustat Japan Phase 3 Hemodialysis



Summary HIF-PHI

- All HIF-PHI have clearly demonstrated efficacy
  - Side aspects
    - Iron, ESA hyporesponsiveness, LDL
- Safety
  - CV
    - Roxadustat
    - Vadadustat
  - Not fully established
    - Malignancy
    - Other

Practical – Where will HIF-PHIs be used?

- ND-CKD
- HD
- PD
- HHD
- Other

Conclusion

- HIF-PHIs have great potential for improving CKD Anemia treatment
- Not yet proven by published studies to date
- Oral formulation has important practical implications
- Some residual safety concerns