TRANSLATIONAL LECTURE
AGING KIDNEY E ANEMIA: ERITROPOIETINE E OLTRE

68° CONGRESSO NAZIONALE SIGG

FIRENZE, 13-16 DICEMBRE 2023

PALAZZO DEI CONGRESSI

Giuseppe Spatoliatore, MD

UO NEFROLOGIA & DIALISI,
OSPEDALE SAN GIOVANNI DI DIO,
USLCENTRO - FIRENZE

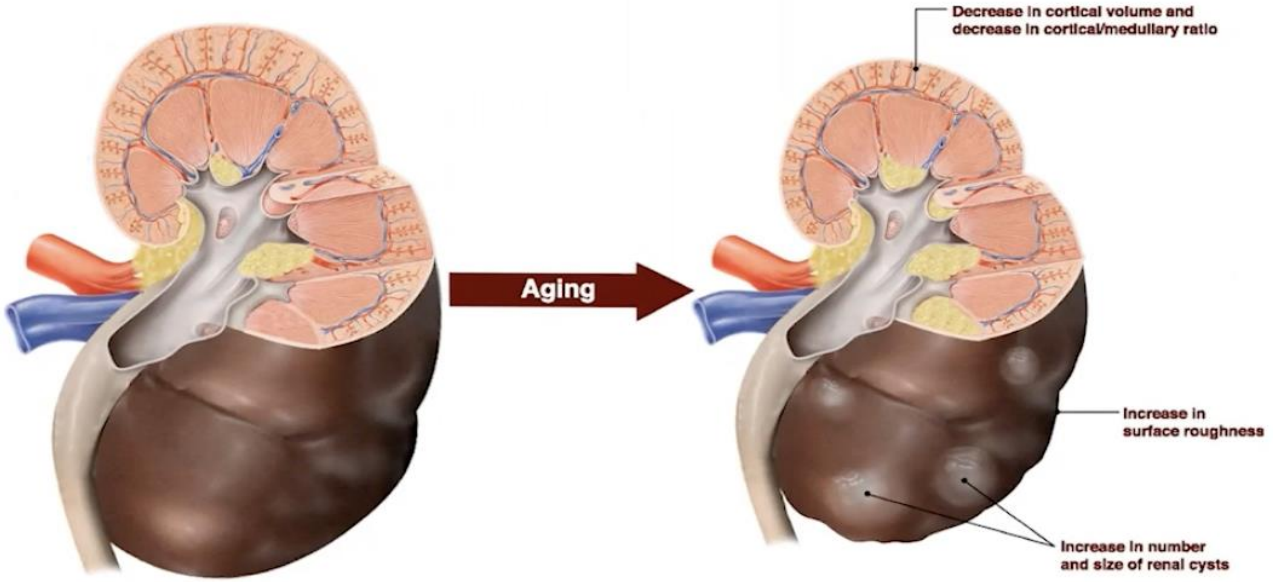
Disclosures

Nothing to disclose

Learning objectives

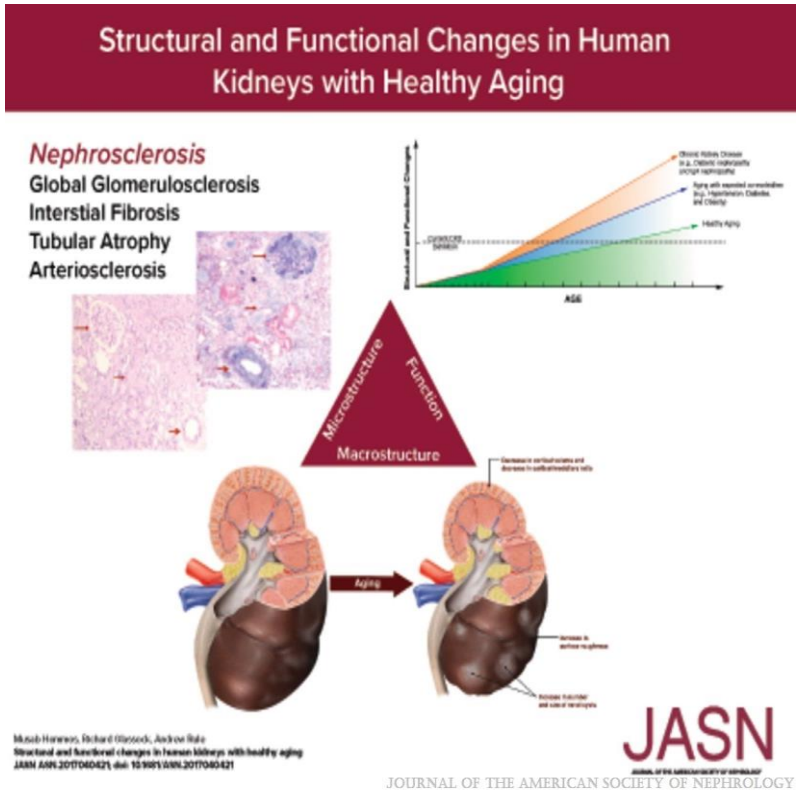
- Describe recent progress in delineating the signal pathway regulating «**Accelerated Cellular Senescence**» in CKD
- Anemia in CKD : What's new in the present ?
- **Erythropoietin** vs **Hypoxia-inducible factor 1-alpha inhibitors** (HIF-PHIs): pros & cons

Aging kidneys and CKD



Cellular senescence

Definition: It is a form of irreversible arrest of cell growth after exposure to some insults, which was described by Leonard Hayflick in early 1960



Structural and Functional Changes With the Aging Kidney

Aleksandar Denic, Richard J. Glassock, and Andrew D. Rule

Senescence or normal physiologic aging portrays the expected age-related changes in the kidney as compared to a disease that occurs in some but not all individuals. The microanatomical structural changes of the kidney with older age include a decreased number of functional glomeruli from an increased prevalence of nephrosclerosis (arteriosclerosis, glomerulosclerosis, and tubular atrophy with interstitial fibrosis), and to some extent, compensatory hypertrophy of remaining nephrons. Among the macroanatomical structural changes, older age associates with smaller cortical volume, larger medullary volume until middle age, and larger and more numerous kidney cysts. Among carefully screened healthy kidney donors, glomerular filtration rate (GFR) declines at a rate of 6.3 mL/min/1.73 m^2 per decade. There is reason to be concerned that the elderly are being misdiagnosed with CKD. Besides this expected kidney function decline, the lowest risk of mortality is at a GFR of ≥75 mL/min/1.73 m^2 for age <55 years but at a lower GFR of 45 to 104 mL/min/1.73 m^2 for age ≥65 years. Changes with normal aging are still of clinical significance. The elderly have less kidney functional reserve when they do actually develop CKD, and they are at higher risk for acute kidney injury.

Key Words: Aging, Nephrosclerosis, Glomerulosclerosis, Kidney function, Glomerular filtration rate

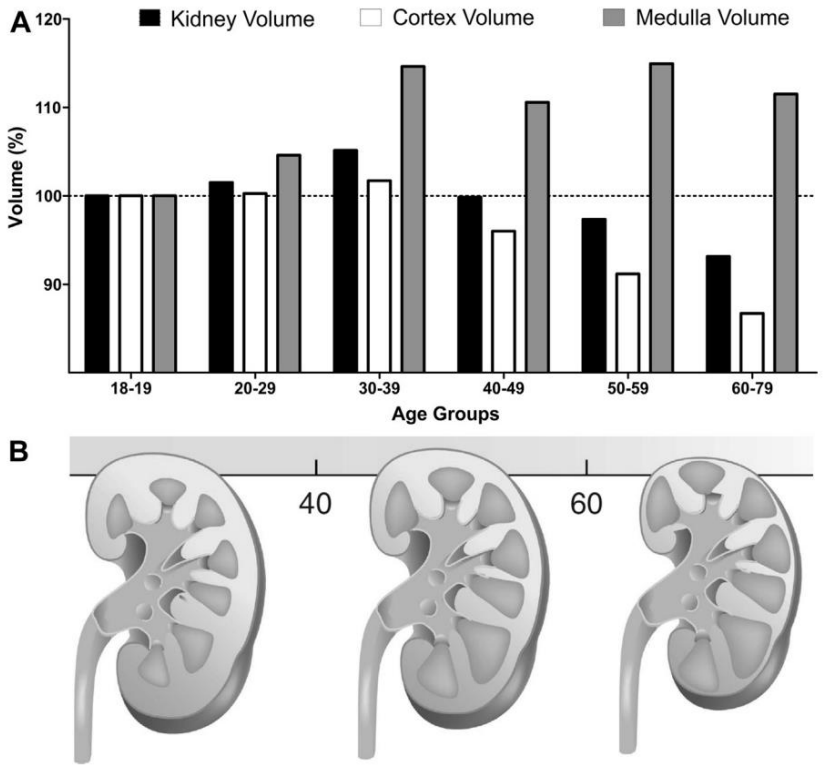


Figure 2. Effect of age on total kidney, cortical, and medullar volumes. (A) Among 1281 living kidney donors, cortical volume declines, whereas medullary volume increases, making total kidney volume relatively stable until about 50 years of age. After which, medullary volume does not increase anymore, and total kidney volume begins to decline. Results were normalized to the total kidney, cortical, or medullar volumes in 18-19-year age group. (B) Schematic illustration of cortical and medullary volume changes with aging. Modified with permission from Kidney International.[48]

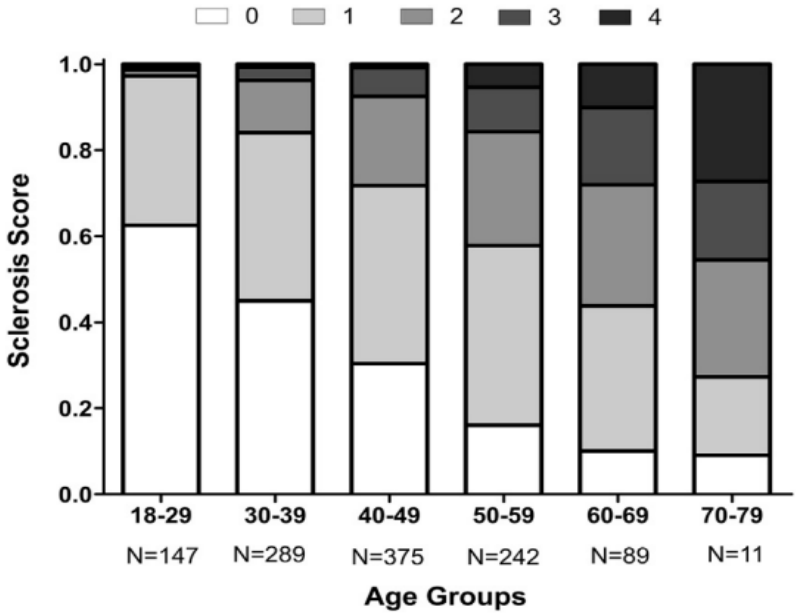


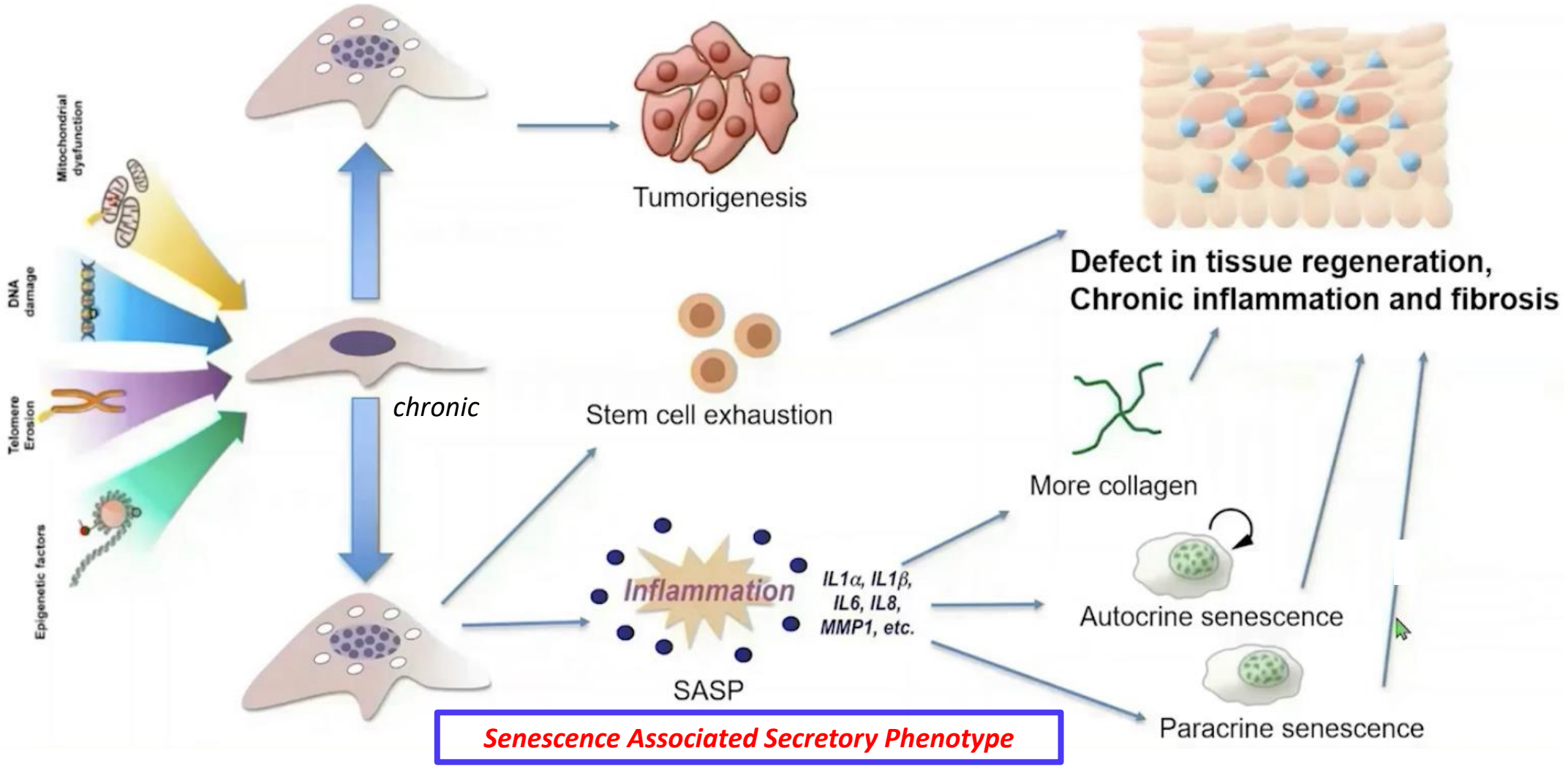
Figure 1. Sclerosis score by age group among 1203 living kidney donors. Sclerosis score is defined as the total number of chronic histological abnormalities between any global glomerulosclerosis, any tubular atrophy, interstitial fibrosis > 5%, and any arteriosclerosis. In the figure, a score of 0 (absence of any abnormality) is white, a score of 4 (presence of all 4 pathological abnormalities) is black, and intermediate scores are on a gray scale.

Advances in Chronic Kidney Disease, Vol 23, No 1 (January), 2016: pp 19-28

CLINICAL SUMMARY

- There is a rising prevalence of nephrosclerosis with aging, from 2.7% for healthy individuals younger than 29 years up to 73% for healthy individuals aged more than 70 years.
- Total kidney volume remains stable through about age 50 years due to declining cortical volume and a compensatory medullary volume increase, but decreases with aging beyond 50 years.
- Glomerular filtration rate (GFR) declines with normal aging, and mortality data support the use of a lower range of GFR to define normal in the elderly compared to younger adults.
- There are substantial reasons to be concerned that a fixed GFR threshold of <60 mL/min/1.73 m^2 to define CKD leads to overdiagnosis in the elderly and underdiagnosis in younger adults.

Induction and outcomes of cellular senescence



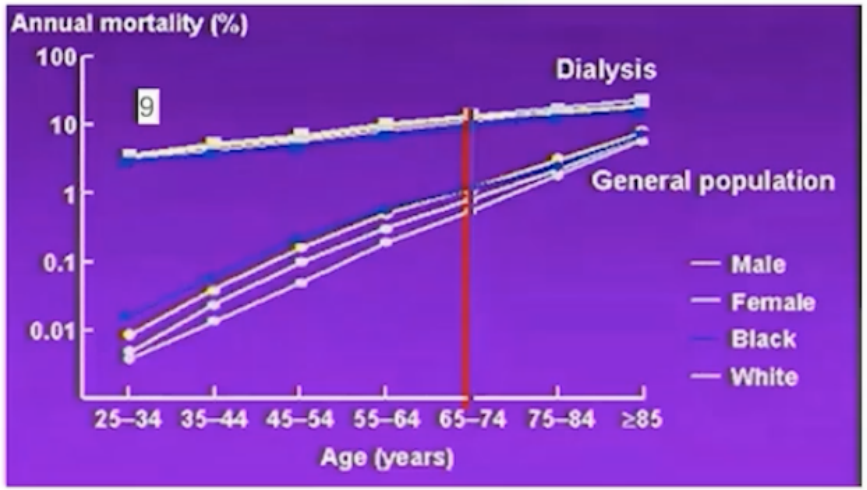
Senescence Associated Secretory Phenotype

CKD is a state of accelerating aging

CKD is associated with high mortality & shorter life expectancy

ESRD vs general population

>10



Foley et al. AJKD, 1998;32(Suppl 3):S112

ESRD vs Non-ESRD (2018)

Age (Years)	Sex	ESRD Dialysis	ESRD Transplant	Non-ESRD All	
66-74	Male	257.0	67.5	25.0	>10
	Female	244.8	56.4	16.3	>15
75+	Male	362.5	138.5	85.6	
	Female	344.0	137.5	77.2	

Medicare beneficiaries (>66 yrs) 2020 Annual Data Report | USRDS

Cellular senescence contributes to CVD and CKD

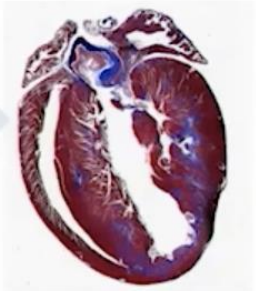
Senescence inducers

CKD

Non-CKD

↑ Pi,
↓ Klotho
Indoxyl sulfate
P-cresyl sulfate
ROS,
Chronic inflammation
Advanced glycation end products (AGE)

Endothelial cells
Myocytes
Myofibroblasts

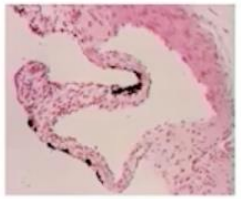


Hypertrophy
fibrosis

Macrophages
Endothelial cells
VSMCs

Atherosclerosis

Endothelial cells
VSMCs



Vascular calcification

CVD

Endothelial cells
Kidney tubules

Atrophy
fibrosis

CKD

CKD/Senescence: a contributor to cardiovascular disease

Traditional risk factor
- Anemia
- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Age
- Low physical activity
- Inflammation
- Volume overload

→ **Cardiovascular disease** ←

Nontraditional risk factor
- Systemic Inflammation
- Systemic oxidative stress
- RAS activation
- Abnormal mineral metabolism (Pi, Mg...)
- Abnormal hormones: PTH, FGF23, Klotho...
- Abnormal autophagy activity
- Abnormal senescence

Klotho: an endogenous senescence inhibitor

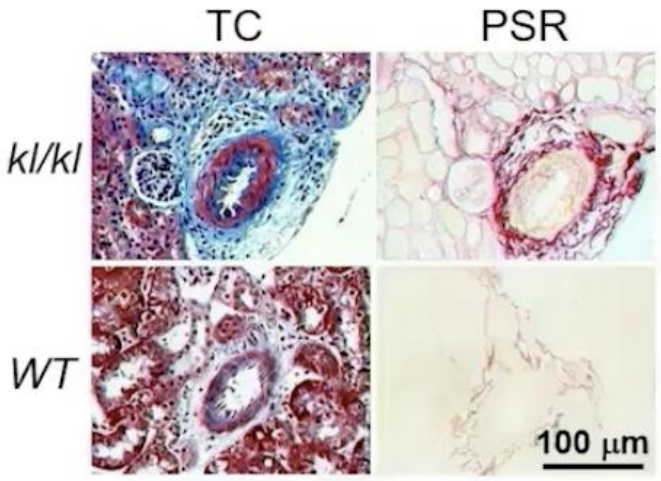
1. Klotho is an anti-aging membrane type 1 protein (N-terminal faces the outside of the cell)
2. Klotho absence induces accelerating ageing
3. Most types of kidney diseases are associated with Klotho deficiency
4. Klotho deficiency reduces autophagy flux and induces apoptosis
5. The association between Klotho and cellular senescence is relatively less reported

Maique et al. Front Pharmacol, 2020; 11:1273

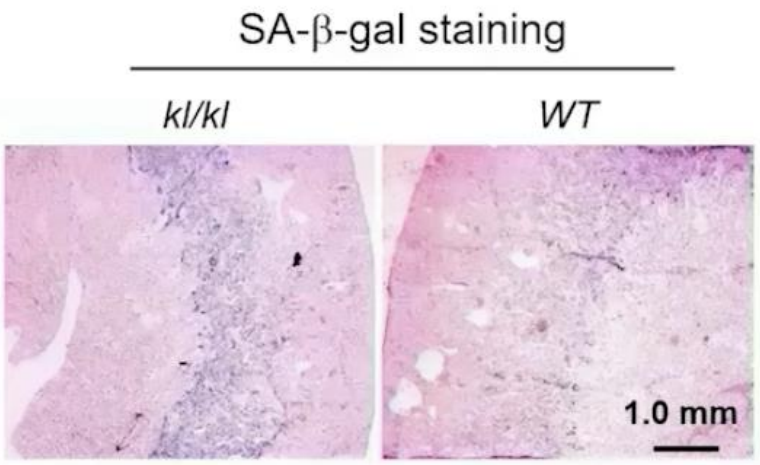
Klotho: an endogenous senescence inhibitor

Low Klotho induces senescence in kidney tubules

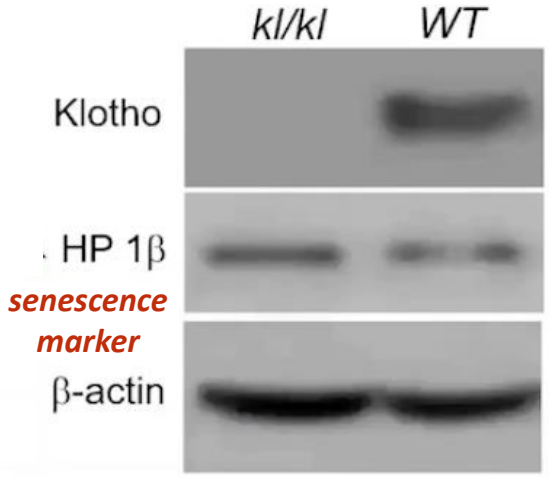
Collagen staining by
Trichrome Picrosirius Red



Senescence-associated $\mathcal{B}$ galactosidase staining



Immunoblot of kidney lysate

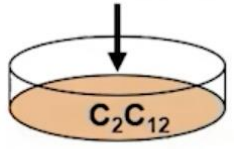


Maique et al. Front Pharmacol, 2020; 11:1273

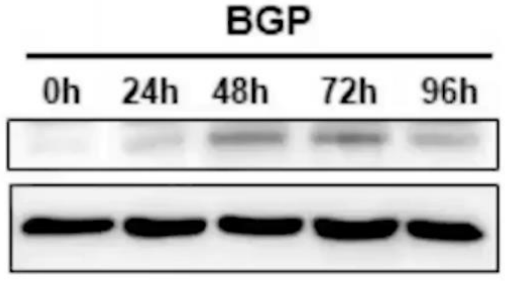
High phosphate induces cellular senescence

High Pi induces senescence in myoblast

BGP 10 mM

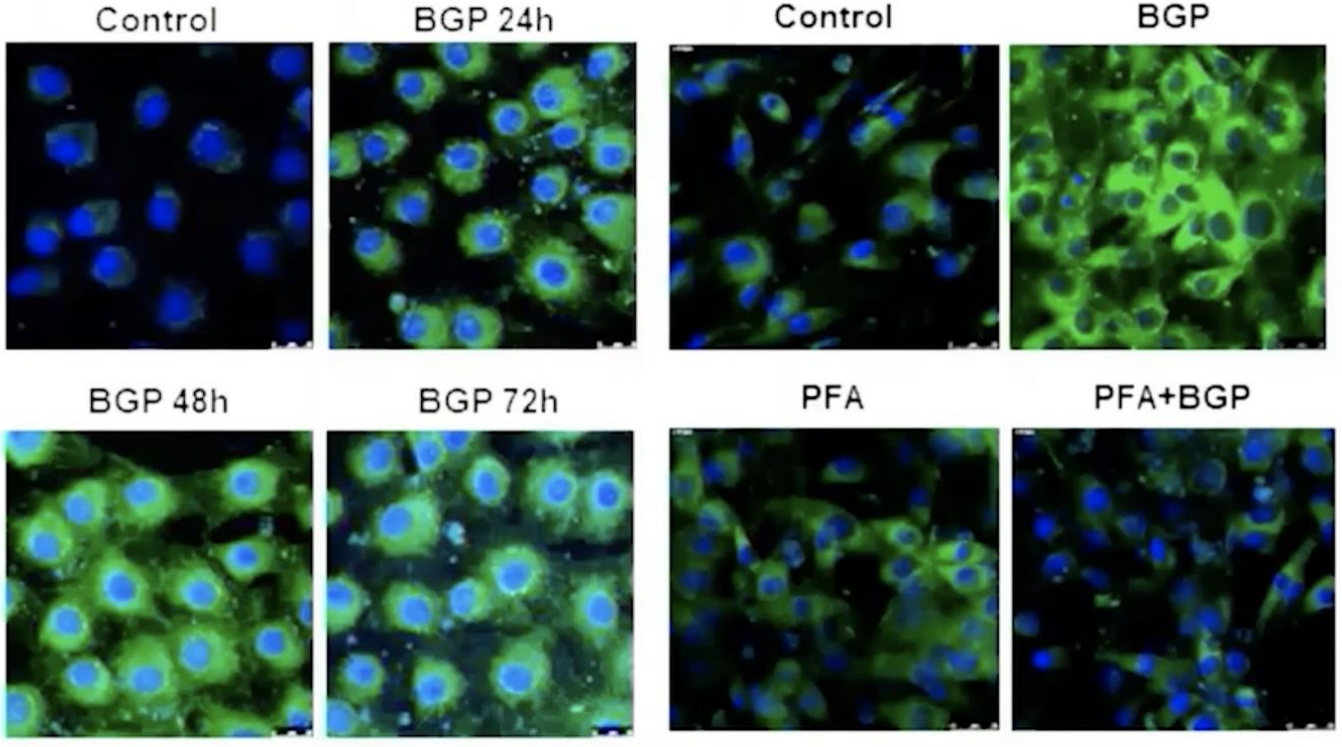


Beta-glycerole phosphate (BGP)



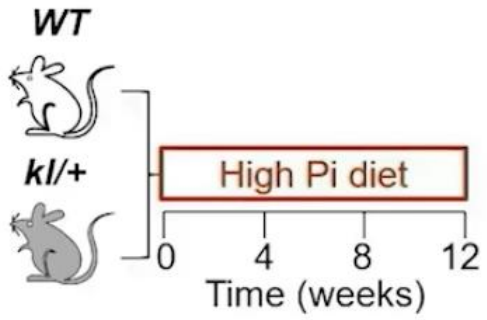
endogenous energy control

ICC with fluorogenic substrate C12FDG, SA-ß-GAL probe



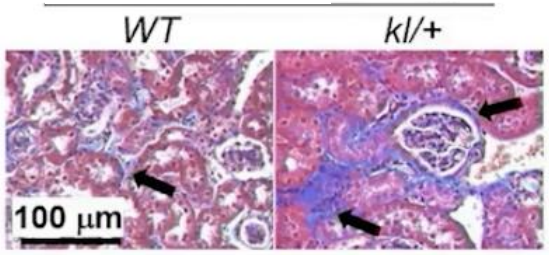
Sosa, et al. Aging Dis, 2018; 9:769

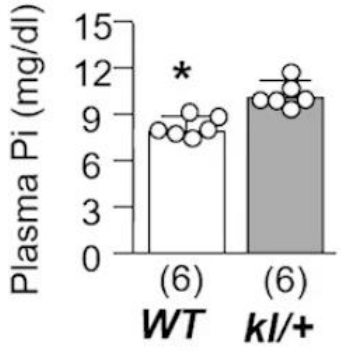
Low Klotho exacerbates high Pi-induced senescence



Collagen staining by

Trichrome Picrosirius Red





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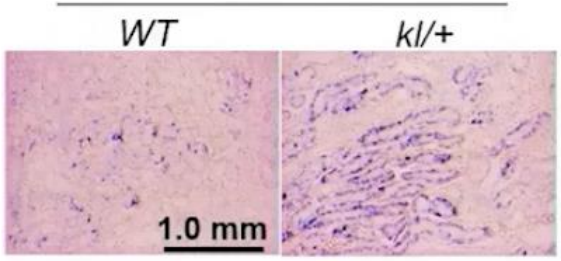
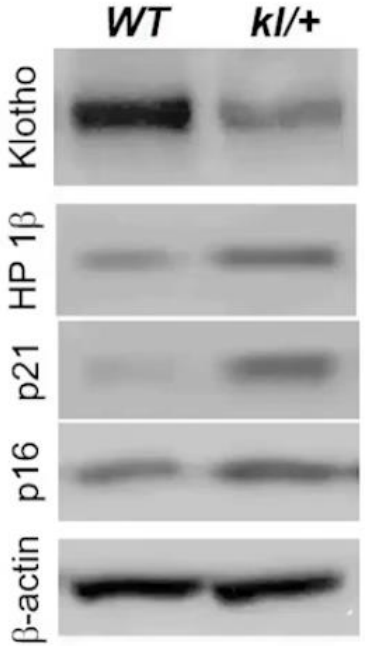
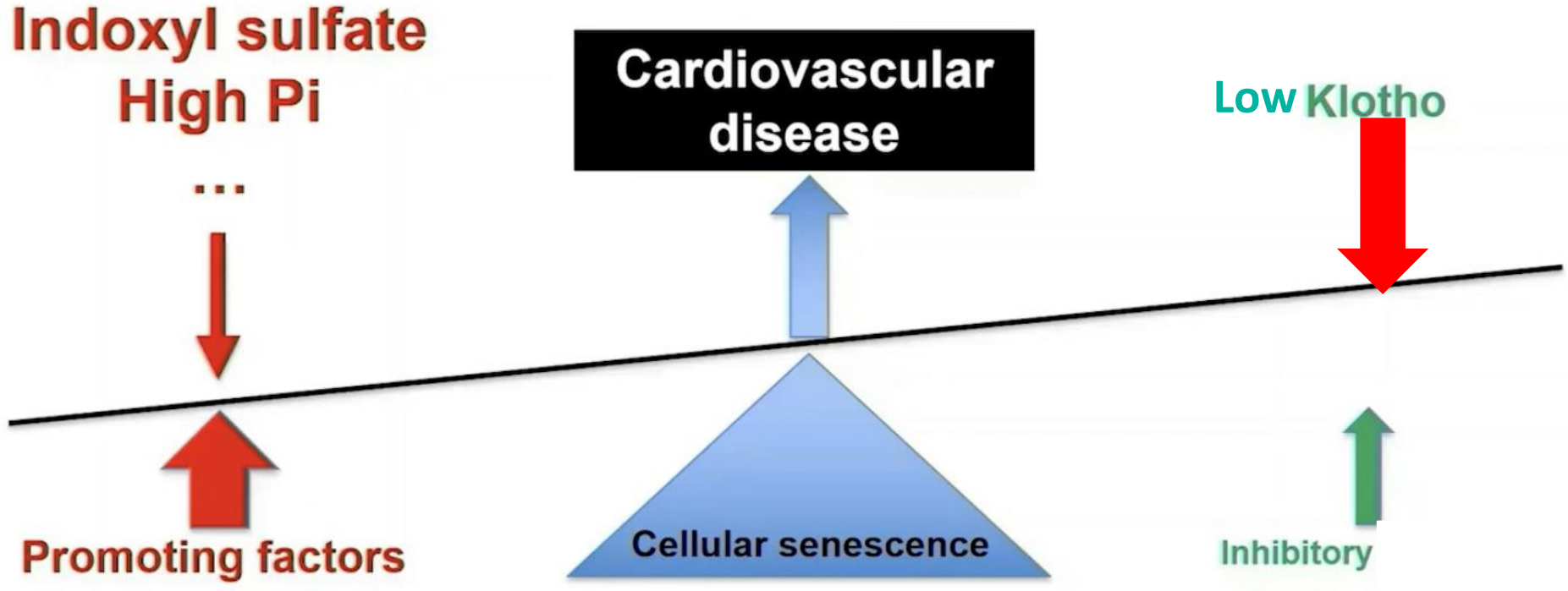




Maique et al. Front Pharmacol, 2020; 11:1273

CKD/Senescence: a contributor to cardiovascular disease



Tsirpanlis. Am J Kidney Dis, 2007; 51:131; Amudhala et al. eLife, 2021; 10:e62678

AKI (even mild) predisposes to CKD

- AKI leads to new CKD
- AKI leads to progression of pre-existing CKD
- AKI predisposes to increased risk of ESRD and excess mortality

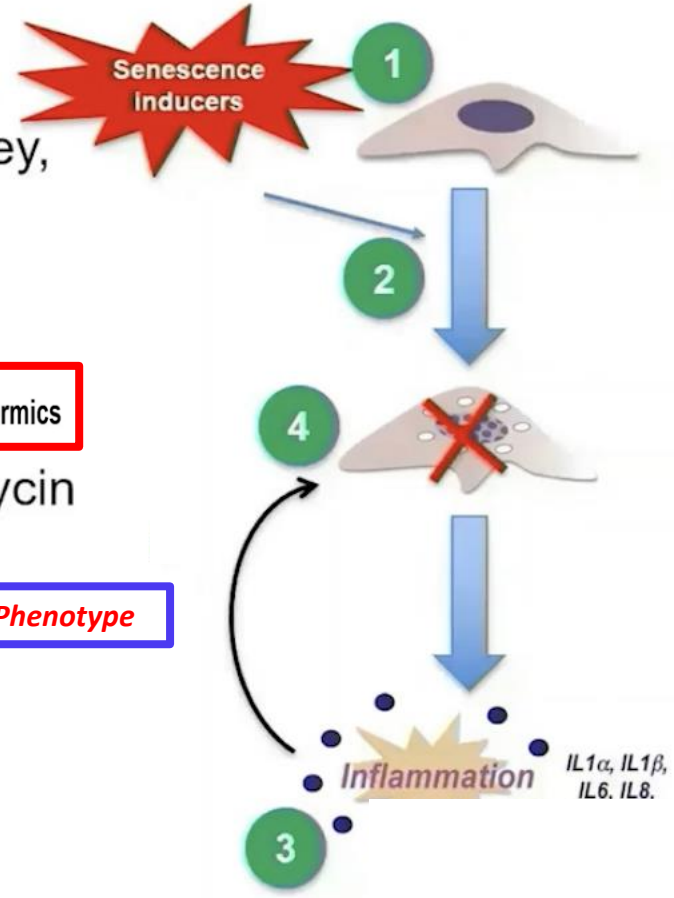
- Tubule cell senescence is a common and early event after AKI
- Tubule innate immunity signaling controls senescence amplification and fibrosis after AKI
- Tubule innate immunity signaling controls early-stage tubule proliferation after AKI, possibly through chromatin remodeling
- Senolysis decreases inflammation and fibrosis, but not tubular damage after AKI

Innate Immunity and Tubular Cell Senescence After Kidney Injury

Massimo Attanasio, MD
University of Iowa Carver College of Medicine

Senotherapy: targeting senescent cells

Goals	Approaches
Prevent senescence 1	Remove risk factors to heart and kidney, Treat original diseases Reduce uremic toxin (Pi, indoxyl…) Increase Klotho
Inhibit senescence activation 2	Senescence suppressor **Senostatics or senophormics** Fucoidan, Klotho, Metformin, rapamycin
Interrupt senescence propaganda 3	Neutralize/block ***Senescence Associated Secretory Phenotype*** Intermediates of SASP
Clean senescent cells 4	Induce apoptosis Use **senolytics**: Dastinib/Quercetin



Tanara. JAMA, 2018; 320:1319; Xu. Front Pharmacol, 2020; 11:601325; Franzi. Front Pharmacol, 20201; 12:630419

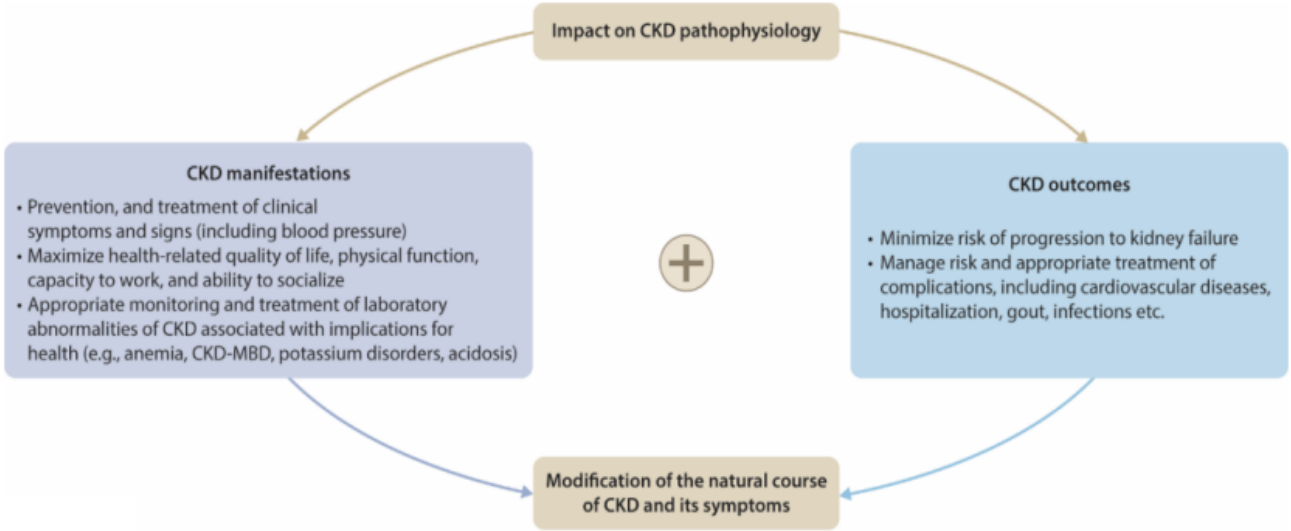
UT Southwestern Medical Center

KDIGO: KIDNEY DISEASE IMPROVING GLOBAL OUTCOME

DELAYING CKD PROGRESSION AND MANAGING ITS COMPLICATIONS

3.1. CKD treatment and risk modification

Practice Point 3.1: Treat people with CKD with a comprehensive treatment strategy to reduce risks of progression of CKD and its associated complications



Chronic kidney disease (CKD) treatment and risk modification. CKD-MBD, chronic kidney disease-mineral and bone disorders

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES
KDIGO

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

PUBLIC REVIEW DRAFT
JULY 2023

ANEMIA: TRADITIONAL RISK FACTOR FOR CHONIC KIDNEY DISEASE, A STATE OF ACCELERATING AGING

Traditional risk factor

- Anemia
- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Age
- Low physical activity
- Inflammation
- Volume overload

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES ®

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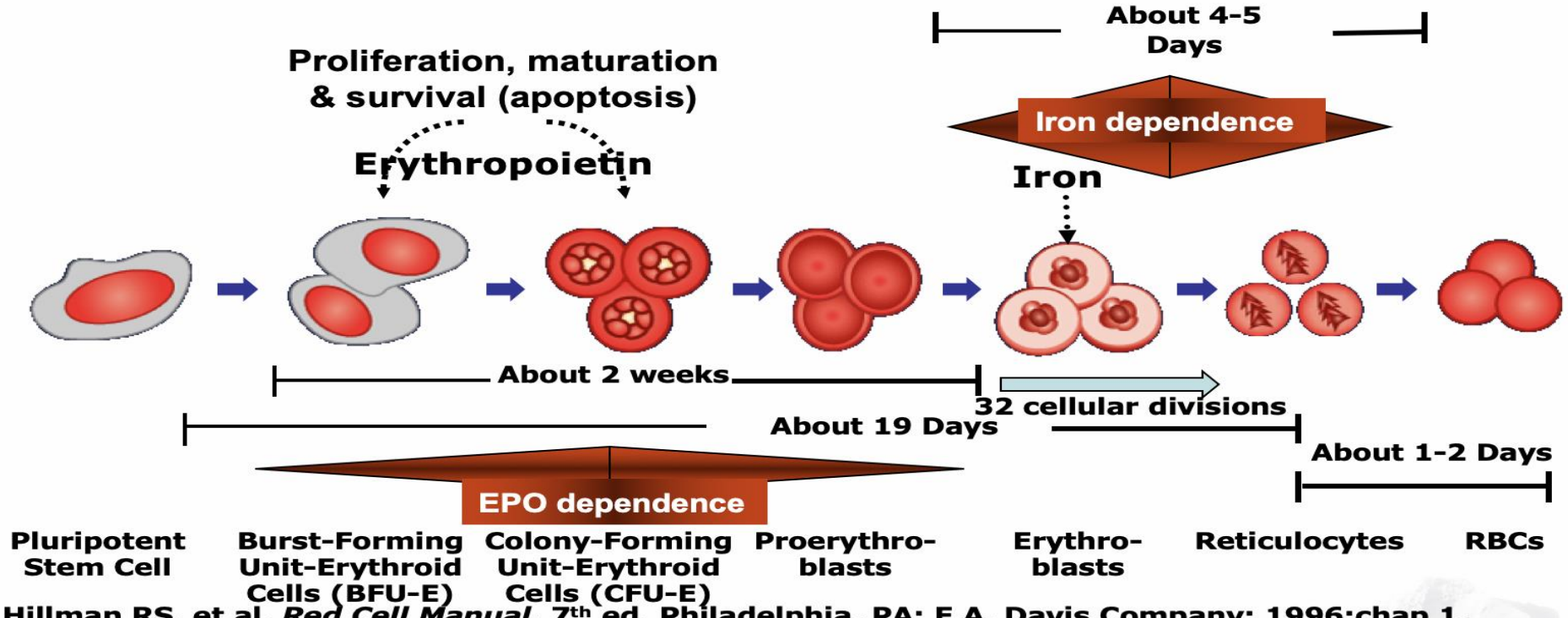
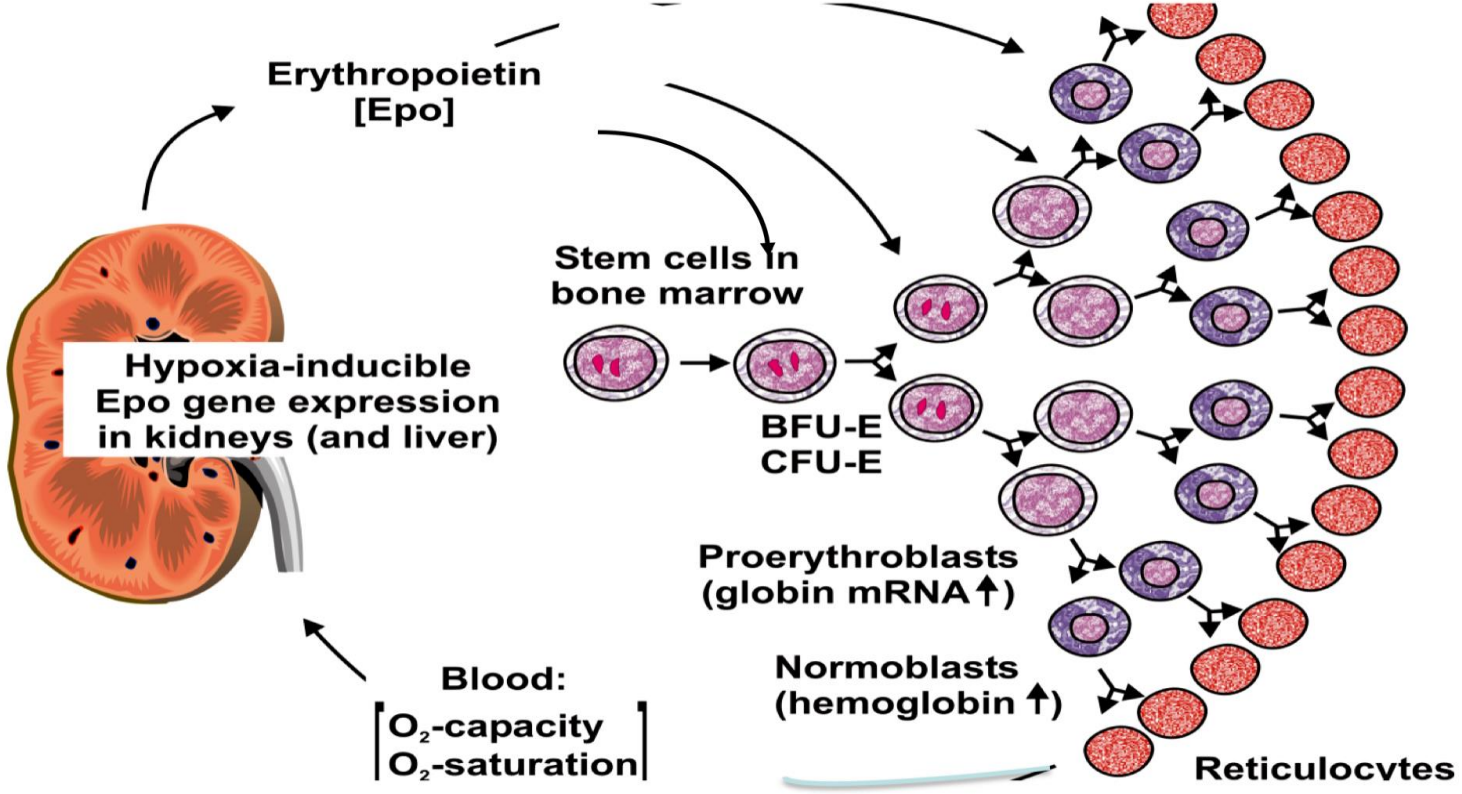
Erythropoiesis is a beautifully orchestrated process requiring many "switches to be turned on", not just one!



Hillman RS, et al. *Red Cell Manual*, 7th ed. Philadelphia, PA: F.A. Davis Company; 1996:chap 1. Papayannopoulou T, et al. In: Hoffman R, et al. eds. *Hematology: Basic Principles and Practice*, 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:chap 20. Brock. *Iron Metabolism in Health and Disease*. W.B. Saunders Co; 1994

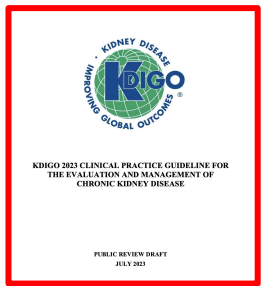
Erythropoiesis



3.11. Anemia

The *KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease* will be updated in 2024.[59]

Mean hemoglobin is, on average, lower in both men and women with an eGFR <60 ml/min per 1.73 m^2 compared to health adults and progressively falls with decreasing GFR (Table 30; Figure 29). For example, adults with CKD G3, A1 in the general and high-risk population cohorts contributing to the CKD Prognosis Consortium had an adjusted prevalence of anemia (hemoglobin <12 g/dl in men; <11 g/dl in women) of 14.9% and 11.5% in those with and without diabetes, respectively. Increasing to 60.7% and 57.4% by CKD G5, A3. Note that a drop in Hb is expected in pregnancy (physiologic anemia) and may not warrant treatment (although the cutoff at which treatment is desirable is unclear and requires


KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

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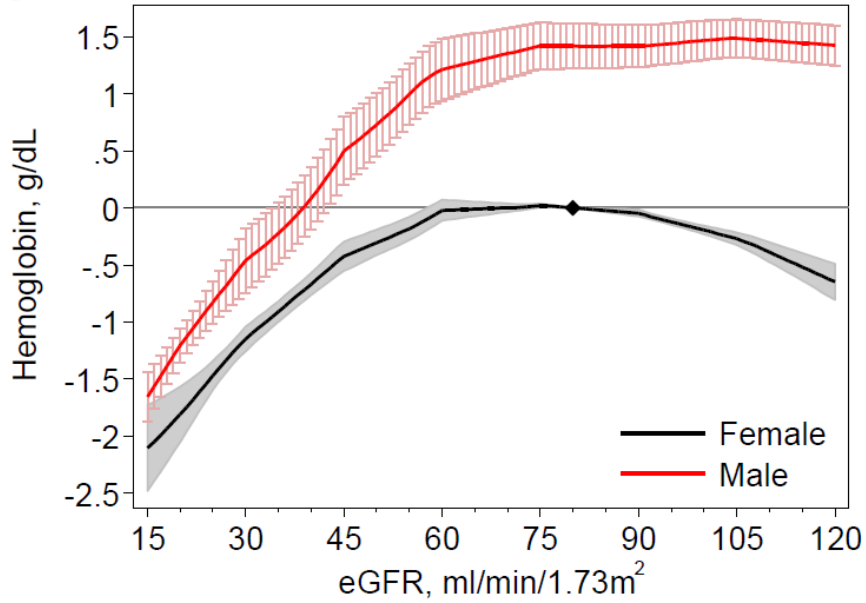
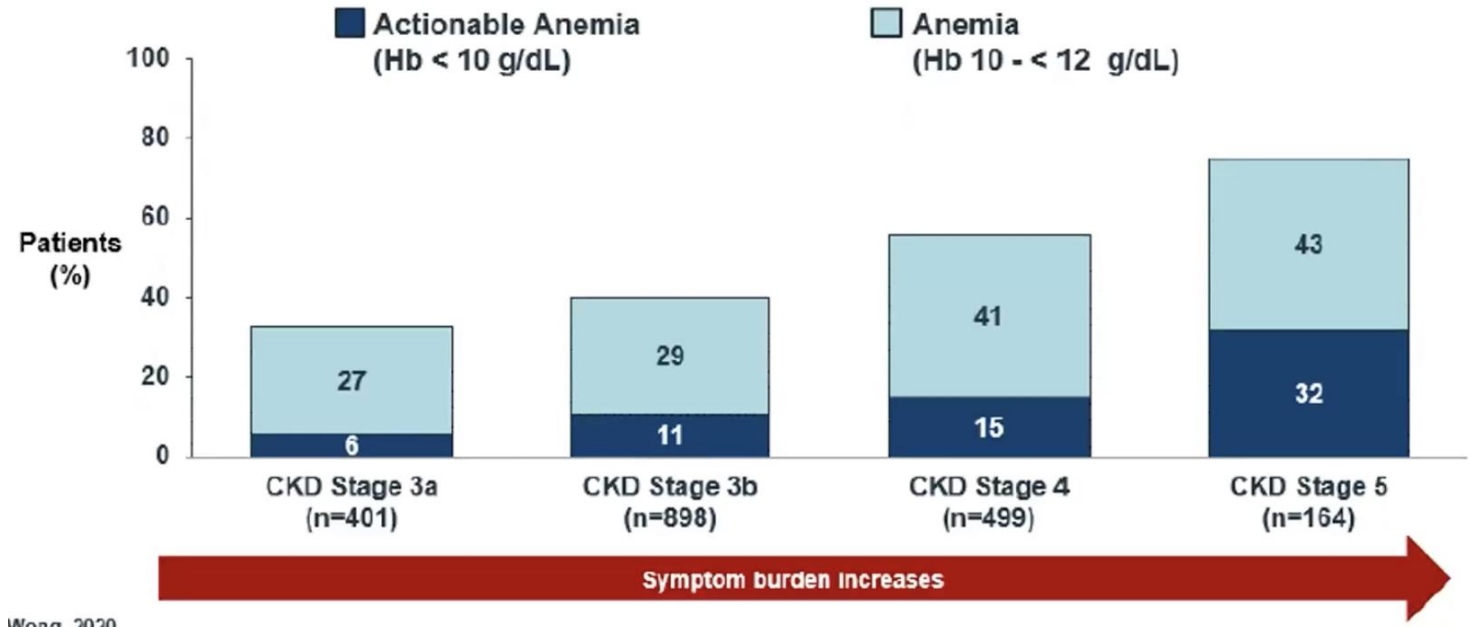


Am J Kidney Dis 2019; **73:** 206-217

Anemia Becomes More Prevalent as CKD Progresses



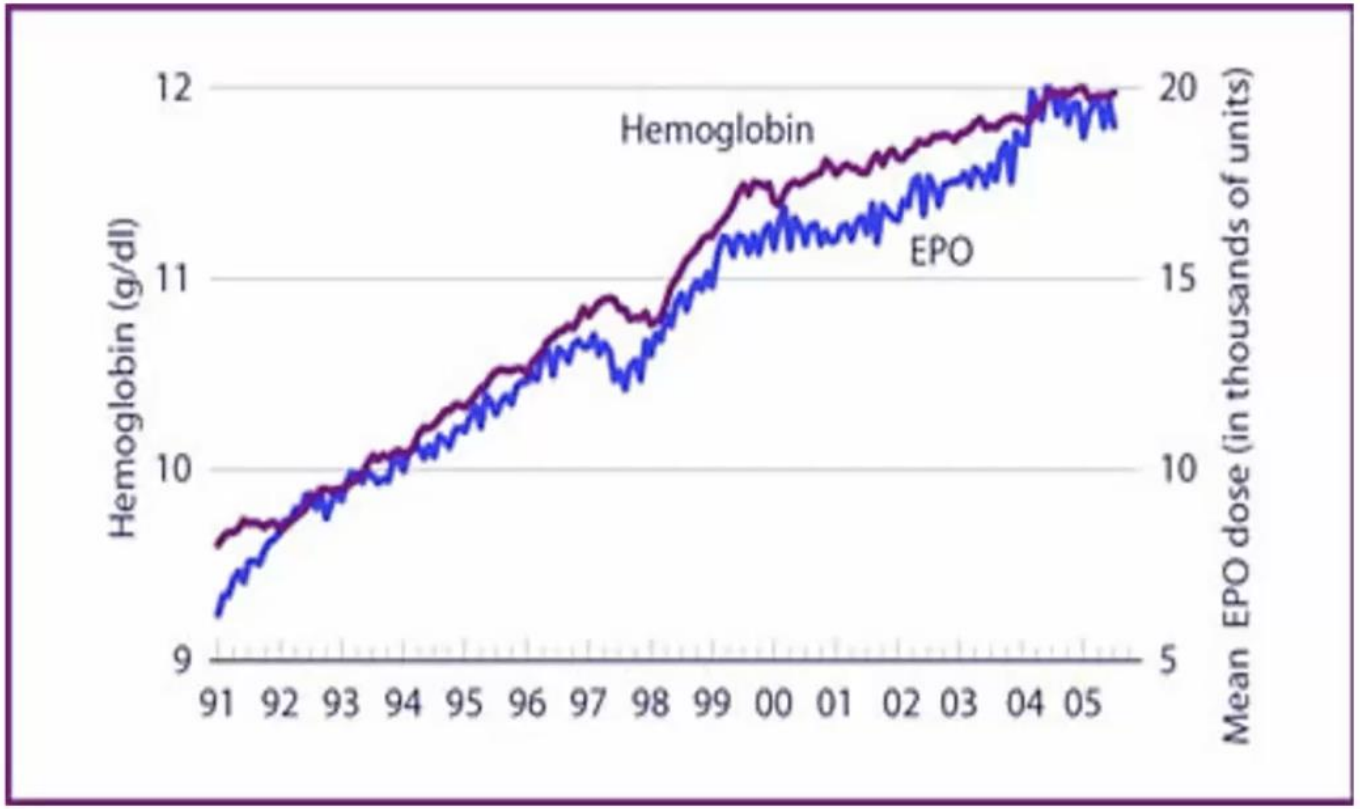
Wong, 2020

Discovery of Recombinant EPO

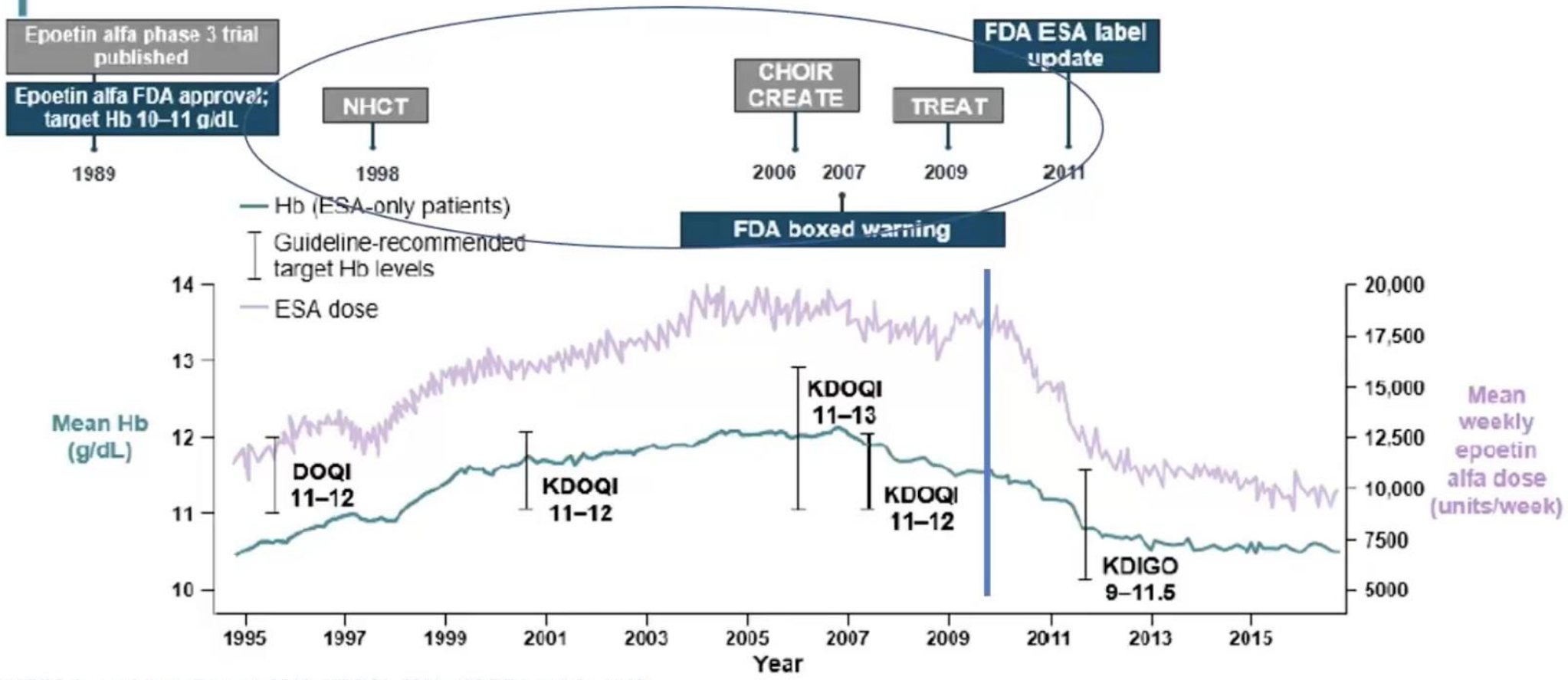
- Gene cloned 1985
- Recombinant protein produced 1989
- Eschbach first test in a human December, 1989
- FDA approval late 1989

Joseph W. Eschbach

Hemoglobin and EPO Dosing in the U.S. 1991 - 2005



CV Safety Trials Led to ESA Labeling Changes and Decreased Hb Target Levels



USRDS Annual Data Report, 2018; KDOQI, 2006; US FDA Safety, 2017

FDA EPO Label – "Black Box Warning"

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

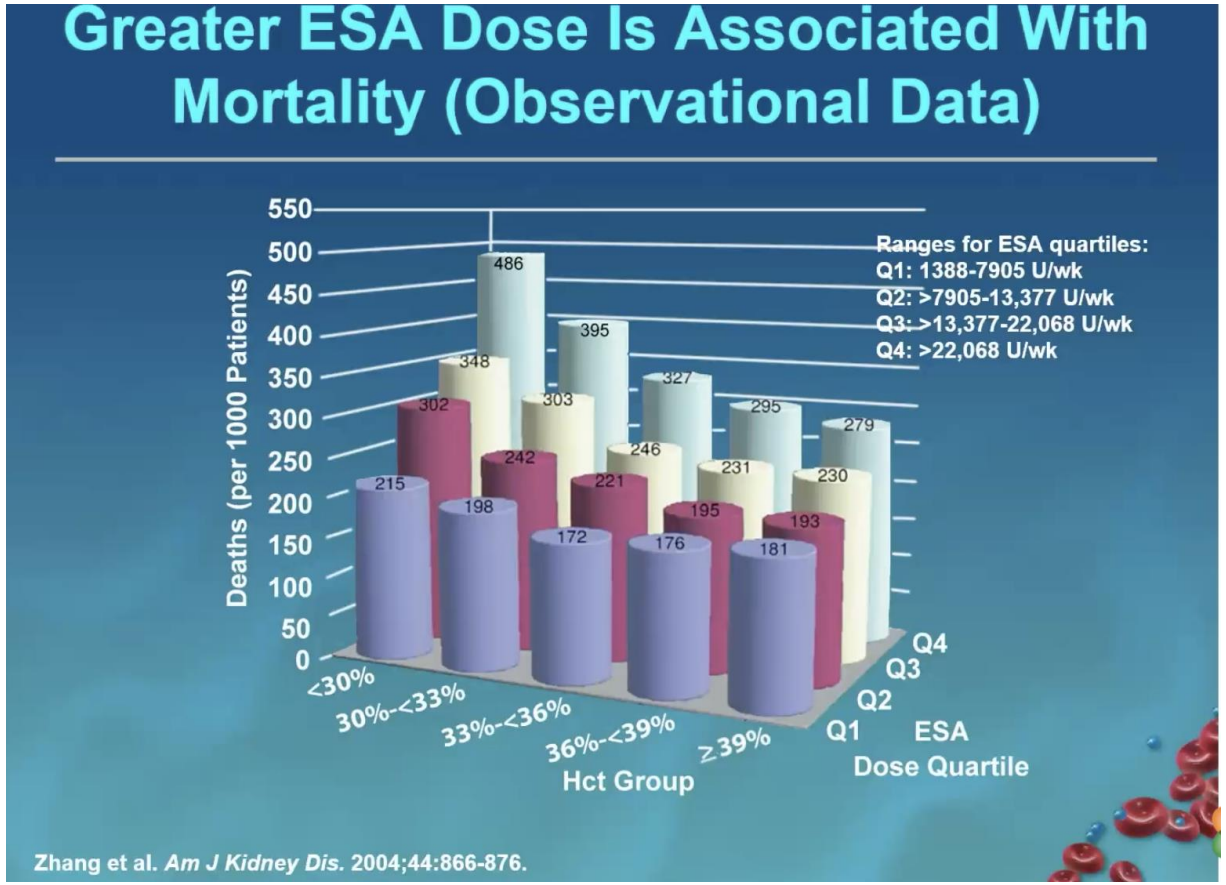
See full prescribing information for complete boxed warning.

Chronic Kidney Disease:

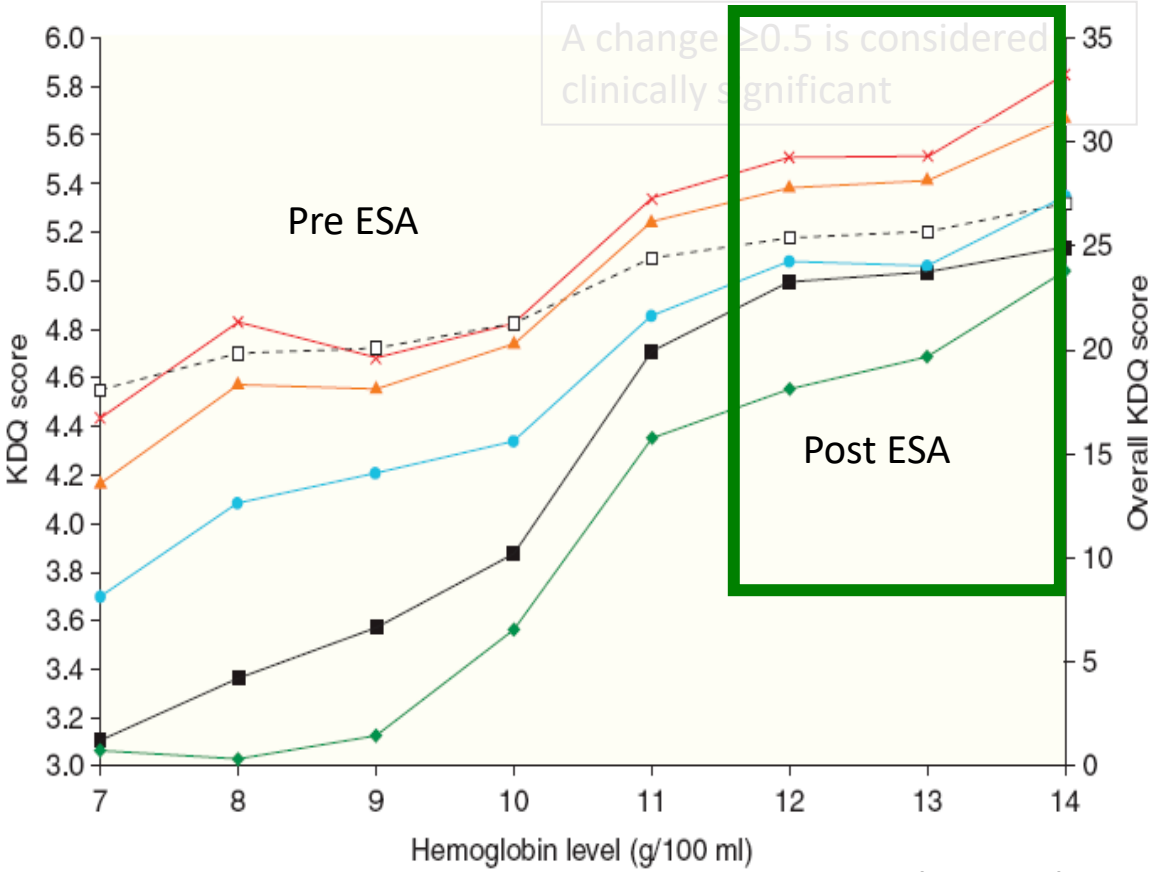
- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks (2.2).**
- **Use the lowest Epogen dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Why are Higher Hb Targets Harmful?

- No definite answer
- High Hb / increased blood viscosity [in patients with atherosclerosis]?
- Higher ESA doses?
  - Normal serum EPO around 10 IU/L, post-IV dose can rise to 500 IU/L
- Other?



Meta-analysis of Relationship of HRQoL to Mean Hb in CKD & Dialysis Trials



Key
- Physical symptoms
- Fatigue
- Depression
- Relationship with others
- Frustration
- Overall KDQ

Spearman correlation coefficients:	
Physical symptoms	$r = 0.46$; $P < 0.0001$
Fatigue	$r = 0.42$; $P < 0.0001$
Depression	$r = 0.24$; $P < 0.0001$
Relationship with others	$r = 0.29$; $P < 0.0001$
Frustration	$r = 0.21$; $P < 0.0001$
Overall KDQ	$r = 0.38$; $P < 0.0001$

Most improvement occurs within a Hb range of 9.5 to 12 g/dL

Leaf and Goldfarb Kidney International 75: 15–24, 2009

HRQoL: Health-Related Quality of Life

Current Status of Anemia and its Treatment in CKD

- Chronic kidney disease (CKD) is associated with excessive cardiovascular morbidity and mortality
- Anemia is common in CKD (particularly in stage 3b-5) and contributes to poor patient outcomes
- Observational studies indicate that low Hb levels in CKD patients may increase risk for progression of kidney disease, cardiovascular morbidity and mortality[5]. No definitive proof. RCTs have not shown this effect
- Controlled clinical trials of anemia treatment with erythropoietin stimulating agents (ESAs) to reasonable Hb levels (10-13 g/dL) have improved symptoms but have not demonstrated improved outcome
- ESA treatment to higher Hb levels (> 13 g/dL) in NHCT and CCT studies (HD patients) and CREATE, CHOIR, and TREAT studies (non dialysis CKD patients) is associated with worse outcomes (hypertension, thrombosis, cerebrovascular risk)

Can Anemia Treatment be Improved?

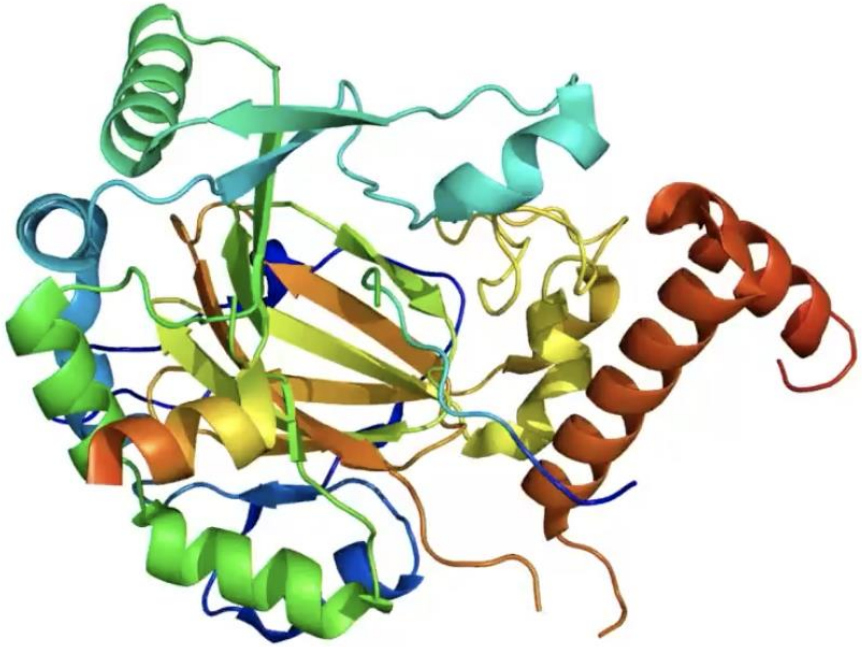
- Treat symptoms and improve quality of life without CV risks
- Hypothesis- Traditional ESAs -very high serum erythropoietin concentrations - and this may be the cause of the increased risk
- Hypoxia Inducible Factor – Prolyl Hydroxlase Inhibitors (HIF-PHIs)
  - Increase in serum erythropoietin that does not rise beyond physiologic levels
  - Would that allow for anemia correction without CV / Thrombotic risk?

Quick Primer: Hypoxia Inducible Factor (HIF)

- Oxygen-sensitive transcription factors

Nobel Prize, Medicine and Physiology 2019

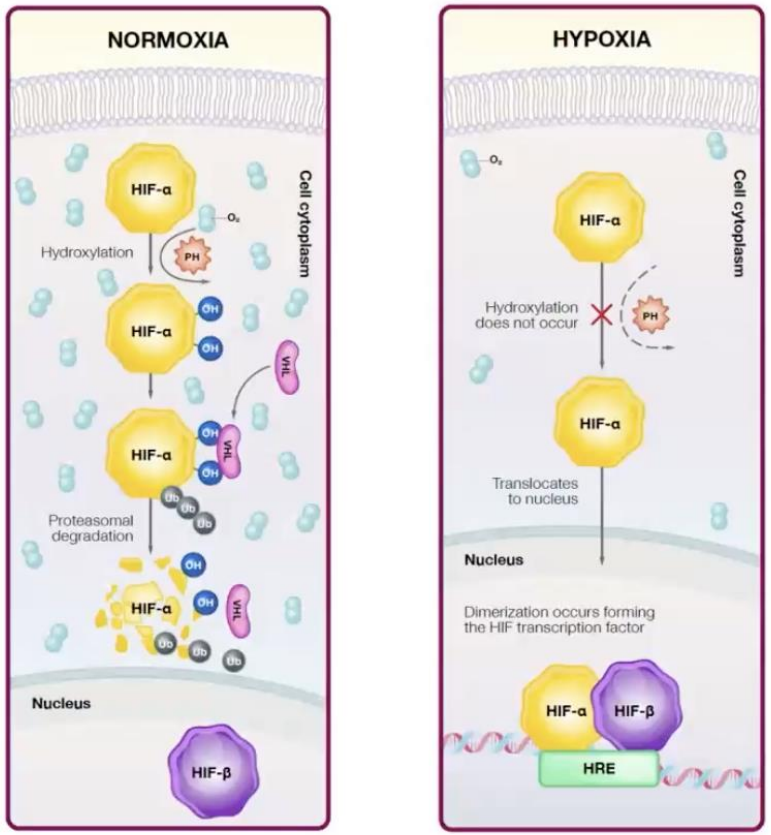
William Kaelin | Gregg Semenza | Peter Ratcliffe



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.

Challenges of translating basic research into therapeutics

The HIF Pathway is the Key Oxygen-Sensing Pathway in all Cells

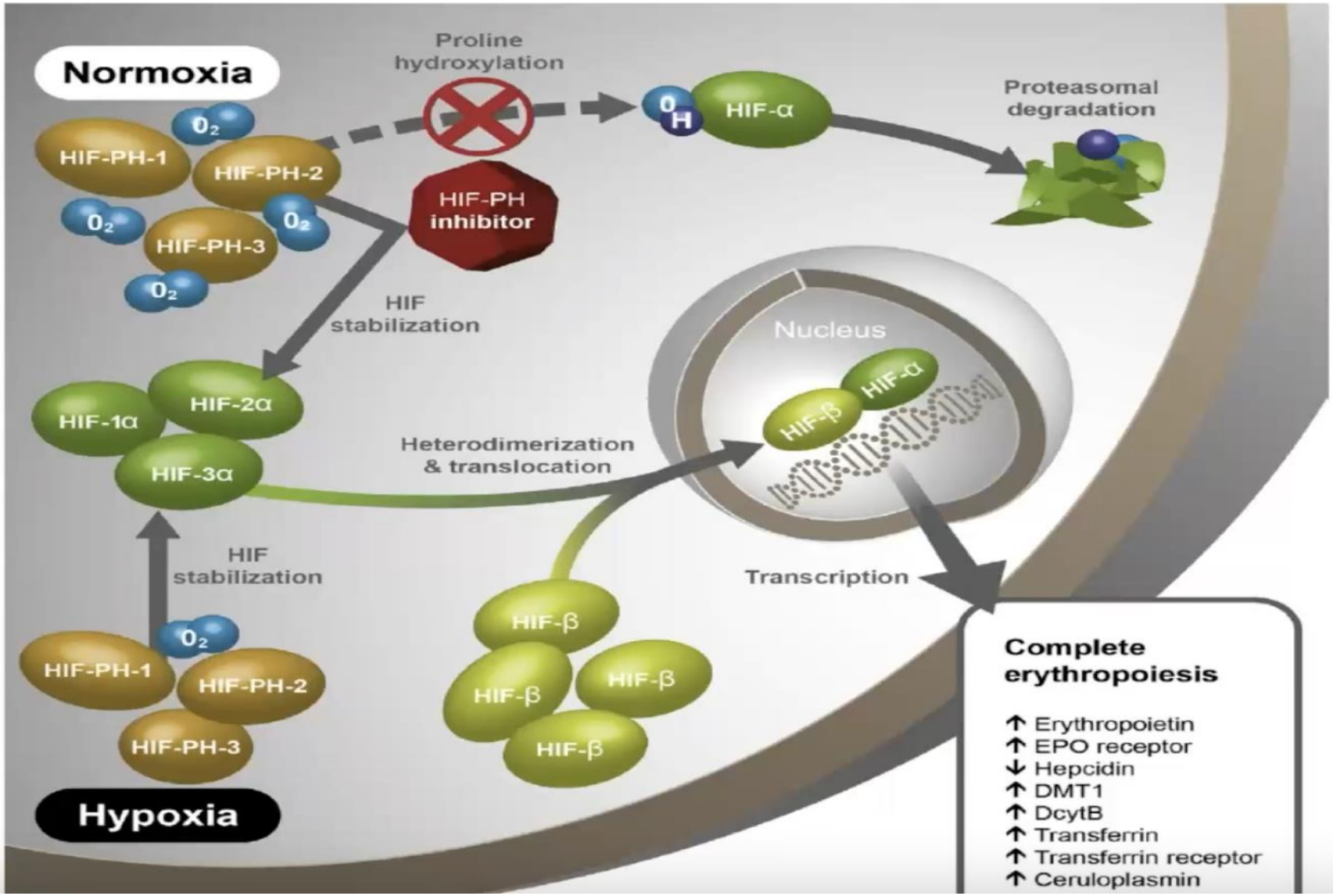


- HIF-PHIs
  - Drugs block PHs
  - HIF-α not degraded
  - Increase production of proteins that protect against hypoxia
    - EPO
    - Iron stabilizing
    - Many others

Note: Figures based on in vitro studies and animal models.

HRE = hypoxia response element; OH = hydroxyl; PH = prolyl hydroxylase; Ub = ubiquitin; VHL = Von Hippel-Lindau.

1. Kaelin WG Jr et al. *Mol Cell*. 2008;30:393-402; 2. Koury MJ et al. *Nat Rev Nephrol*. 2015;11:394-410; 3. Haase VH. *Blood Rev*. 2013;27:41-53; 4. Wenger RH et al. *Am J Physiol* 2010;298:F1287-F1296.


Normoxia
Proline hydroxylation
HIF-α
Proteasomal degradation
HIF-PH-1
HIF-PH-2
HIF-PH-3
HIF-PH inhibitor
HIF stabilization
Nucleus
HIF-1α
HIF-2α
HIF-3α
HIF-β
Heterodimerization & translocation
Transcription
HIF stabilization
Hypoxia
Complete erythropoiesis
↑ Erythropoietin
↑ EPO receptor
↓ Hepcidin
↑ DMT1
↑ DcytB
↑ Transferrin
↑ Transferrin receptor
↑ Ceruloplasmin

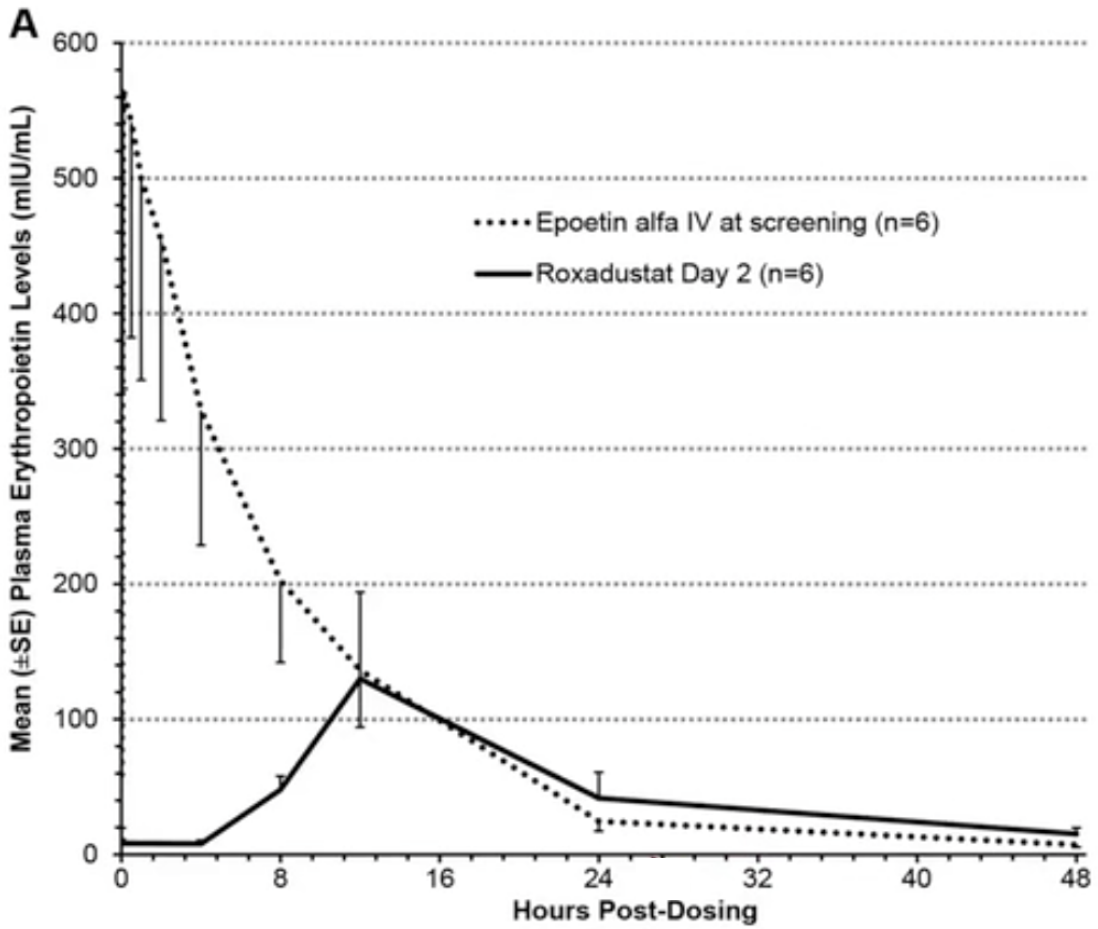
Hypoxia Inducible Factor – Prolyl Hydroxylase Inhibitors (HIF-PHs):

A new class of oral drugs for the treatment of renal anemia

- **ROXADUSTAT/Evrenzo/Ai Ruizho/Rosasat --- Fibrogen/AstraZeneca/Astellas**
- **DAPRODUSTAT/Duvroq --- GlaxoSmithKlein/GSK – Kyowa Kirin**
- **VADADUSTAT/Vafseo. --- Otsuka Pharmaceutical/Akebia Therapeutics**

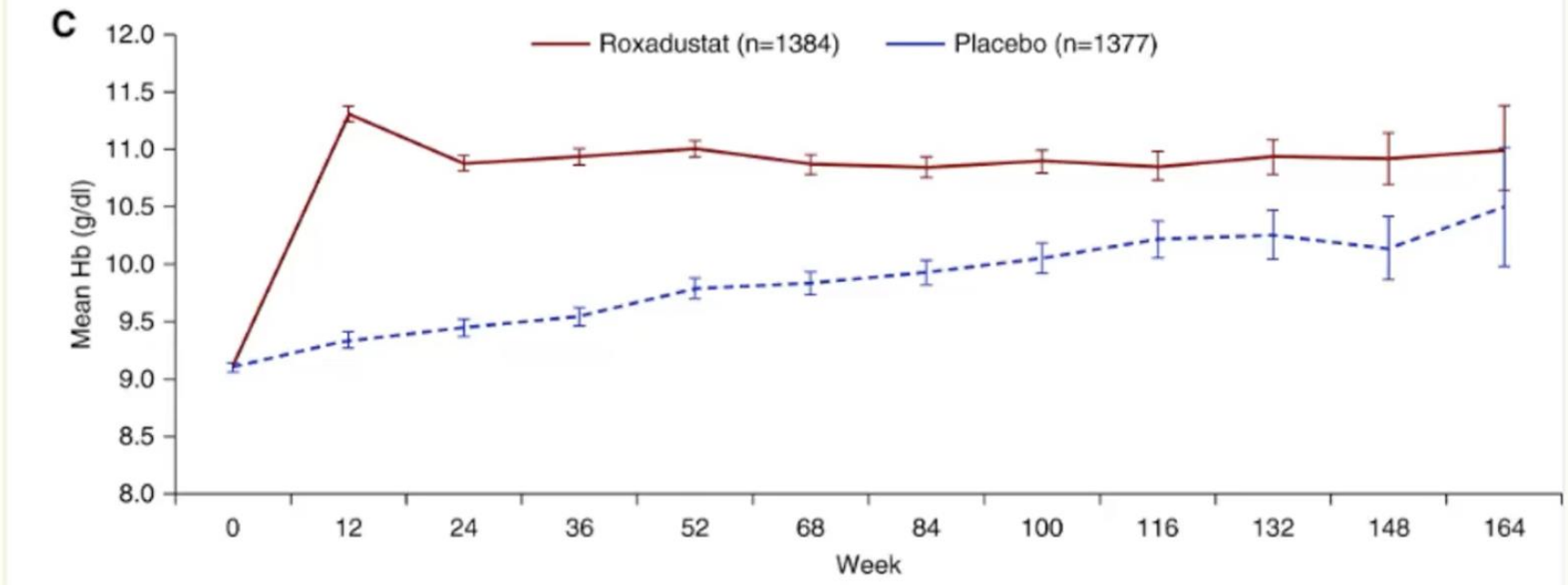
- **Molidustat**
- **Desidustat/Oxemia**
- **Enarodustat/Enaroy (Japan)**

HIF-PHIs and Serum Erythropoietin



Provenzano et al. Am J Kidney Dis . 2016 Jun;67(6):912-24

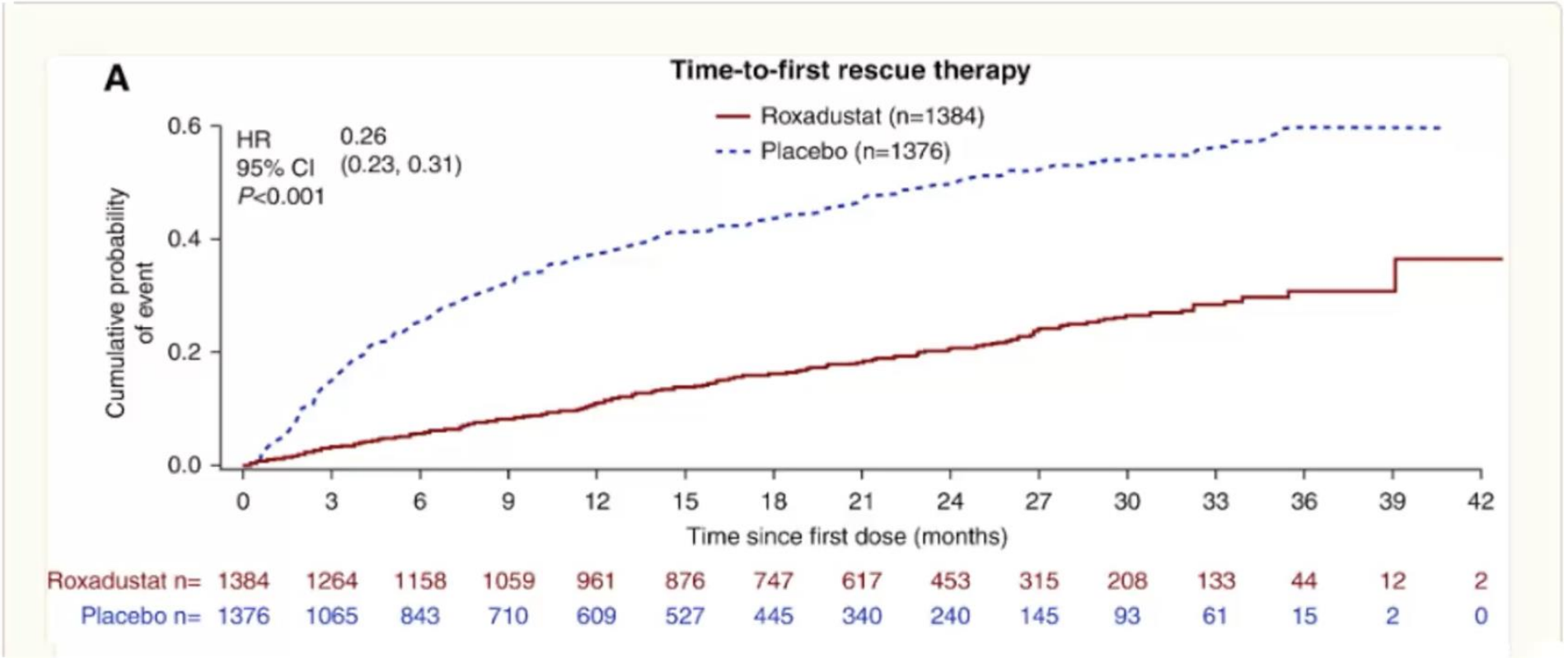
Roxadustat Efficacy – Nondialysis CKD vs. Placebo



Roxadustat n=	1384	1237	1203	1121	1081	999	866	695	490	308	166	49
Placebo n=	1377	1200	1121	1046	977	899	765	591	411	254	148	33

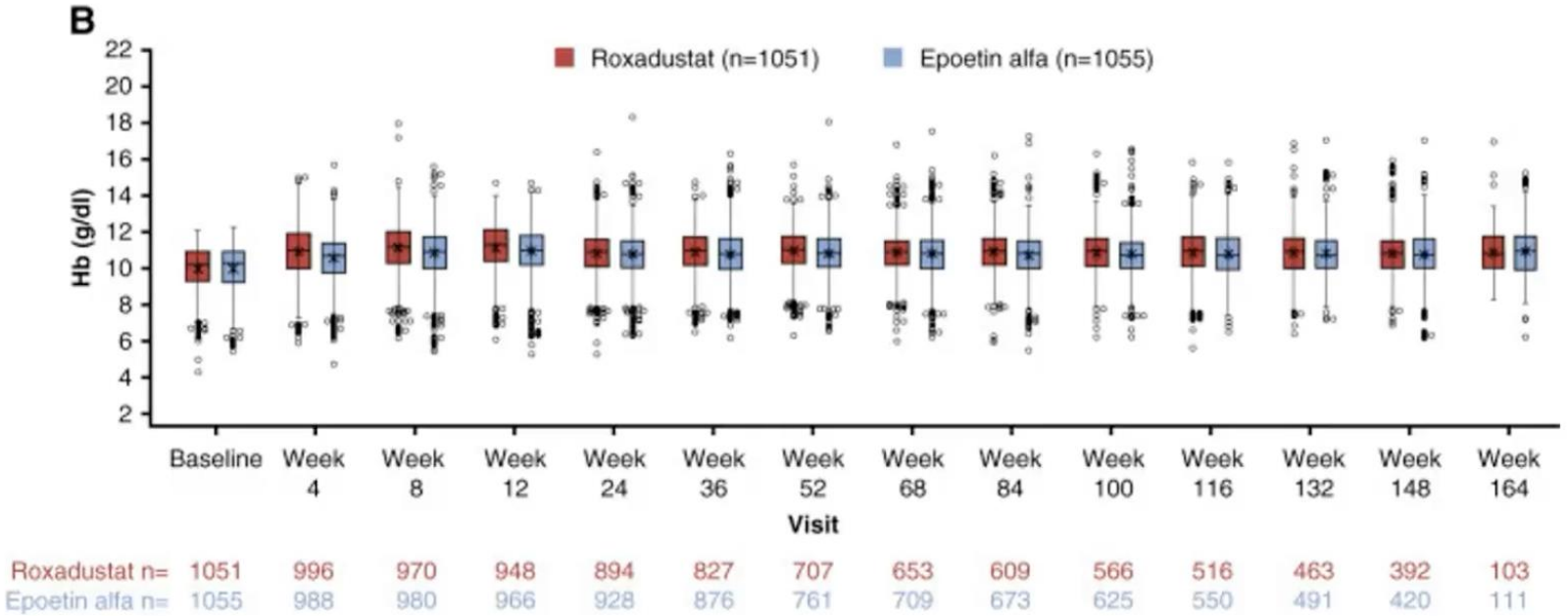
Fishbane et al. J Am Soc Nephrol . 2021 Mar;32(3):737-755.

Roxadustat Efficacy – Nondialysis CKD vs. Placebo



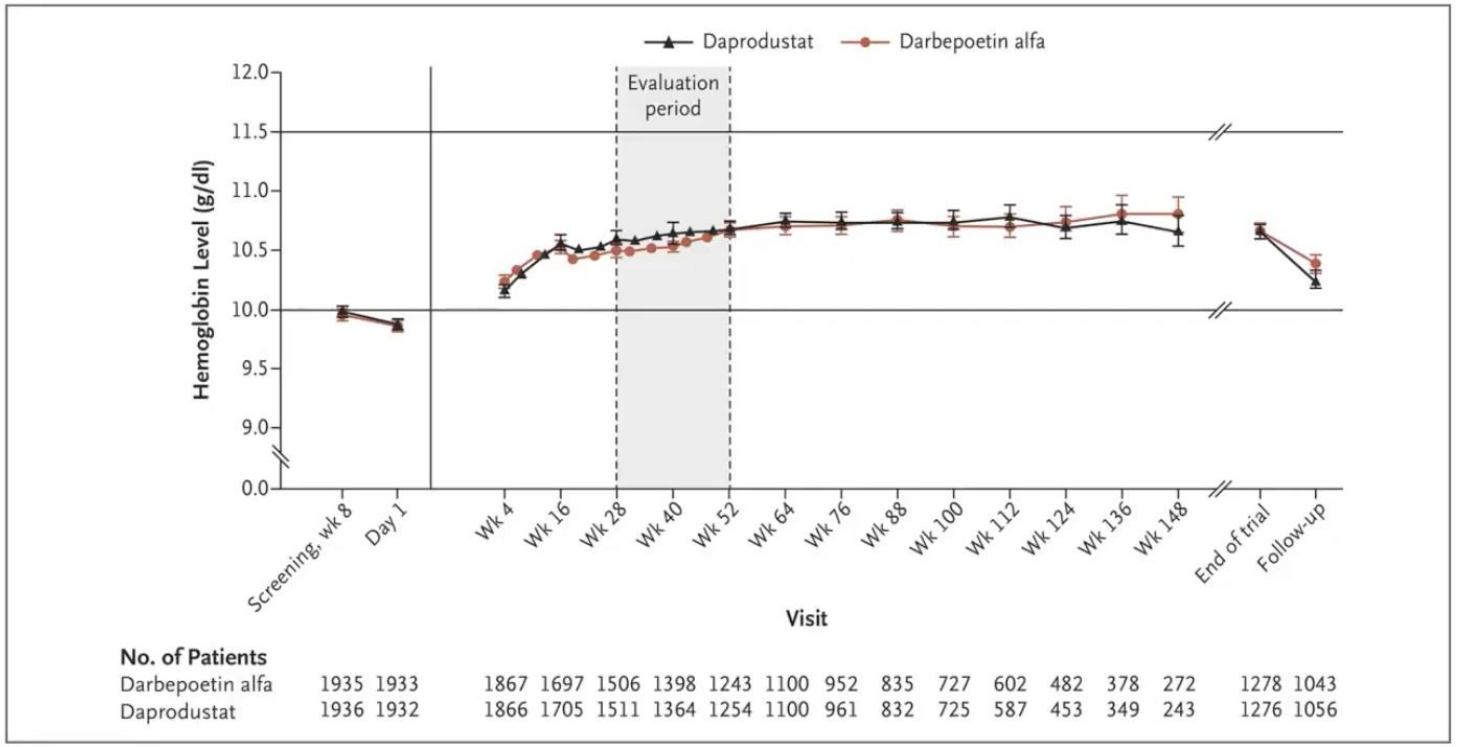
Fishbane et al. J Am Soc Nephrol . 2021 Mar;32(3):737-755.

Roxadustat Efficacy – Dialysis vs. ESA



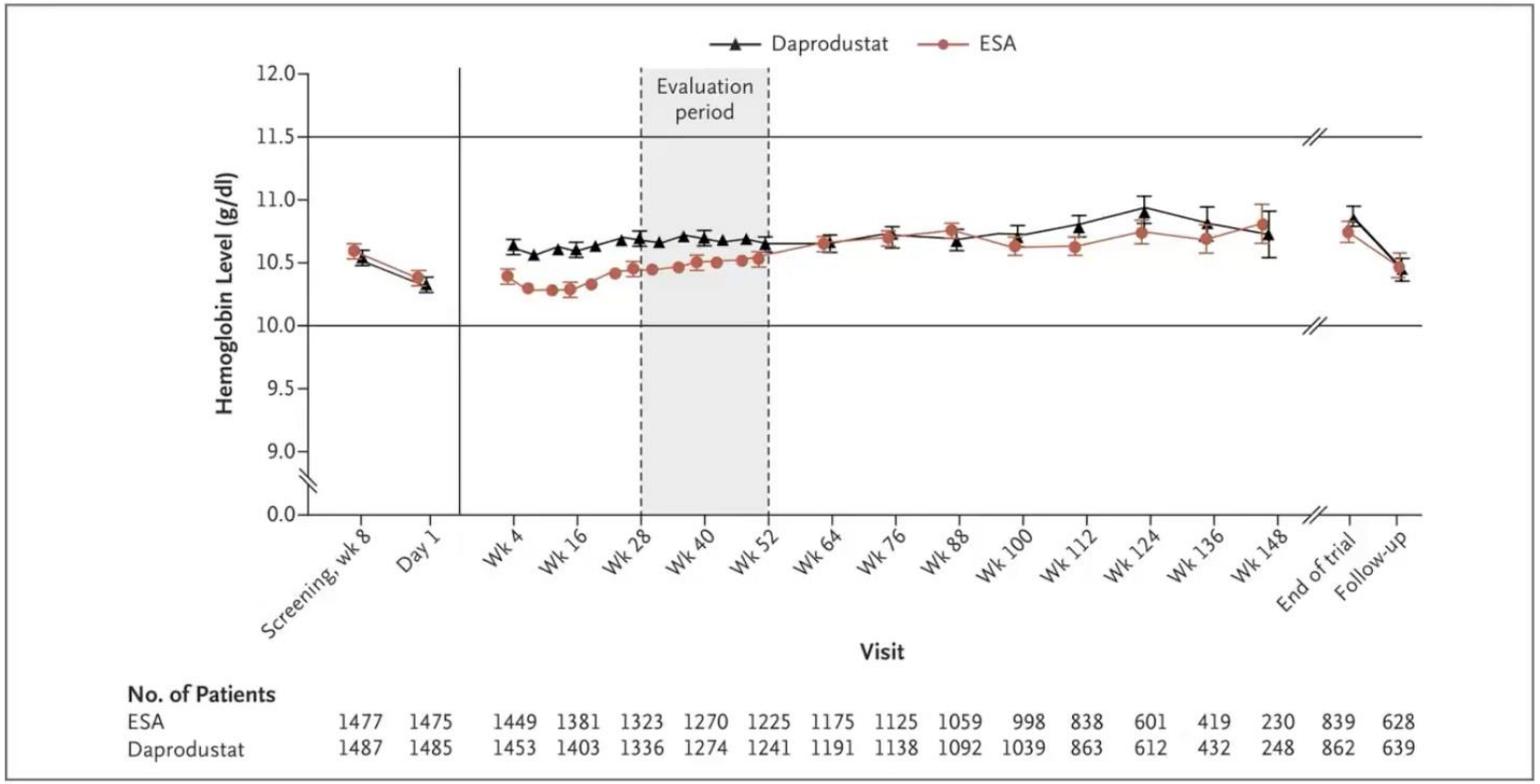
Fishbane et al. J Am Soc Nephrol. 2022 Apr;33(4):850-866.

Daprodustat in Nondialysis CKD (vs. Darbepoetin Alfa)



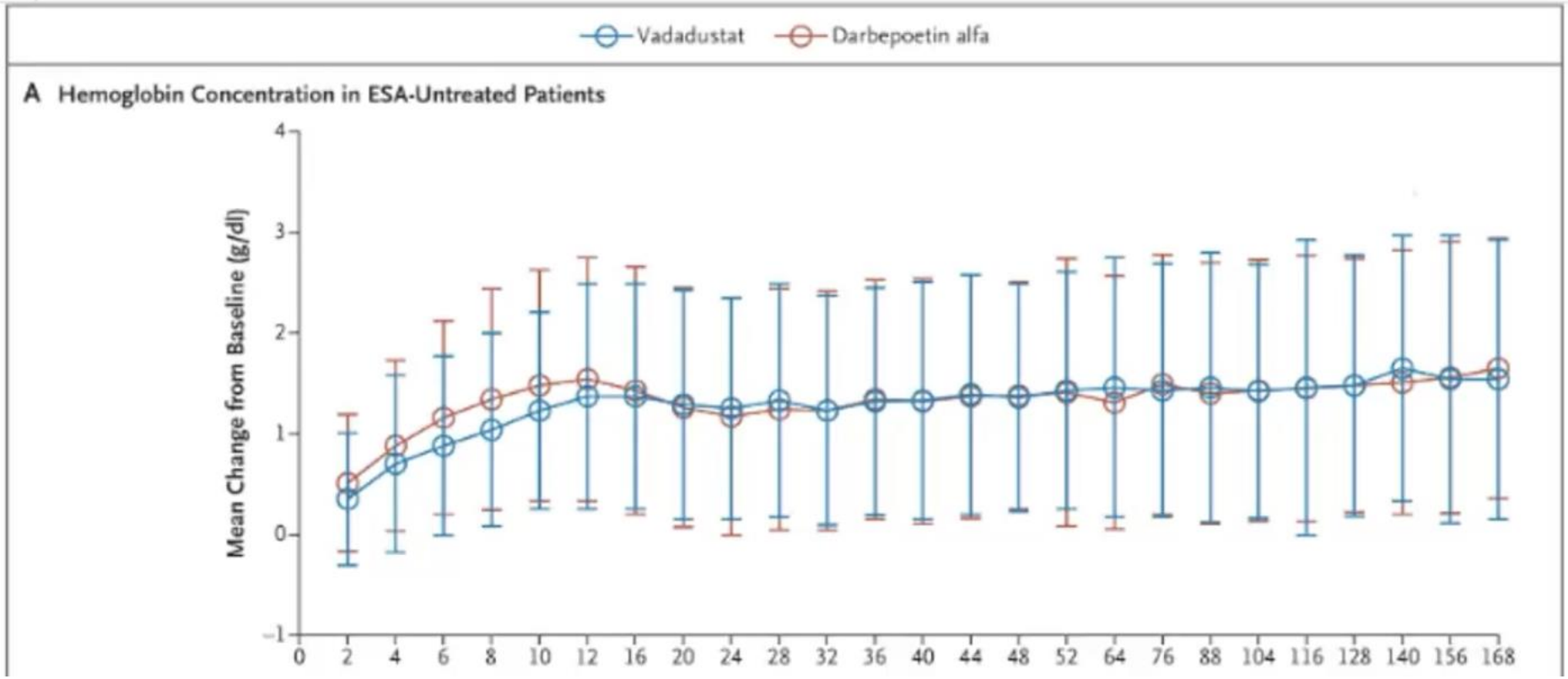
Singh et al. N Engl J Med . 2021 Dec 16;385(25)

Daprodustat in Dialysis (vs. Darbepoetin Alfa)

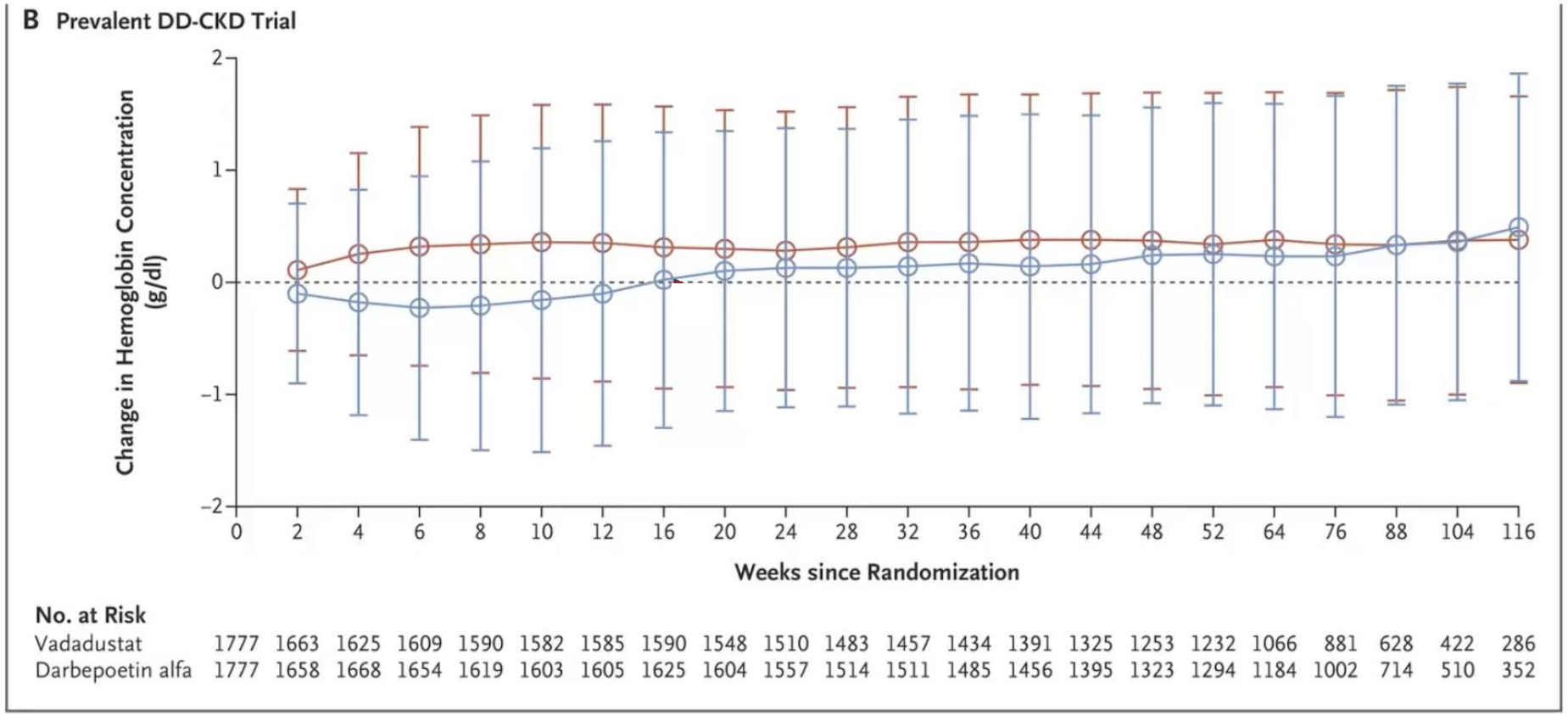


Singh et al. N Engl J Med 2021; 385:2325

Vadadustat – Nondialysis (vs. Darbepoetin Alfa)



Vadadustat – Dialysis (vs. Darbepoetin Alfa)



Eckhardt et al. N Engl J Med. 2021 Apr 29;384(17)

HIF-PHIs and Iron

- HIF-PHIs cause production of a large number of proteins that improve iron availability
  - And result in reduced serum hepcidin

- Are these effects clinically meaningful?

HIF-PHIs and Iron (Cont.)

- Meta-analysis included 12 RCTs, involving 6 HIF-PHIs and 1,382 patients
- Compared with placebo, HIF-PHIs:
  - Increased TIBC - transferrin
  - Did not change serum iron, so lower TSAT
  - Decreased serum ferritin, and hepcidin

- Does improved cellular iron availability improve health?
- Is there decreased need for IV Iron?

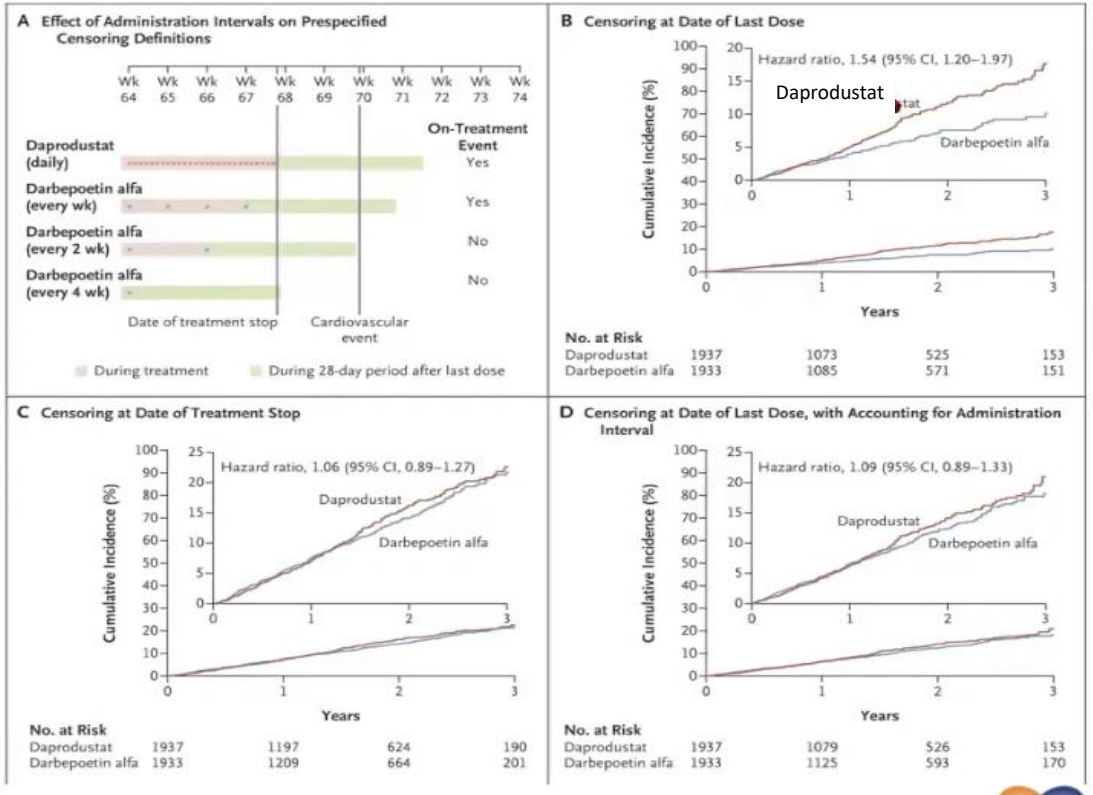
Li, Haase, Hao. Kidney Dis (2023) 9 (1)

Effect of Censoring Time on MACE in ASCEND-ND

Major Adverse Cardiovascular Events

…the on-treatment MACE analysis, which censored data on patients at 28 days after the date of the last dose, showed a higher incidence of a first MACE during the treatment period in the daprodustat group (14.1%) than in the darbepoetin alfa group (10.5%) (hazard ratio, 1.40; 95% CI, 1.17 to 1.68).

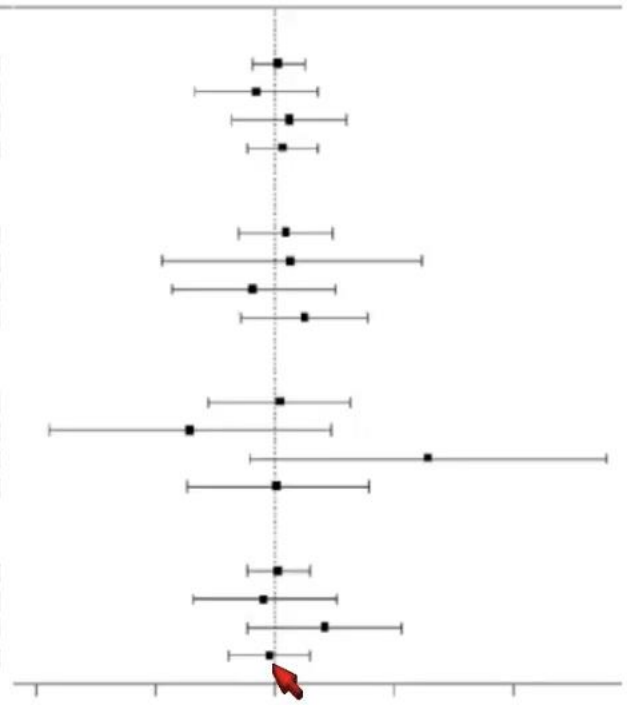
Singh, et al. NEJM 2021



McCausland, e… EJ…

Figure 11: MACE and its Components for Studies in the DD Population (OT+7 Analysis)

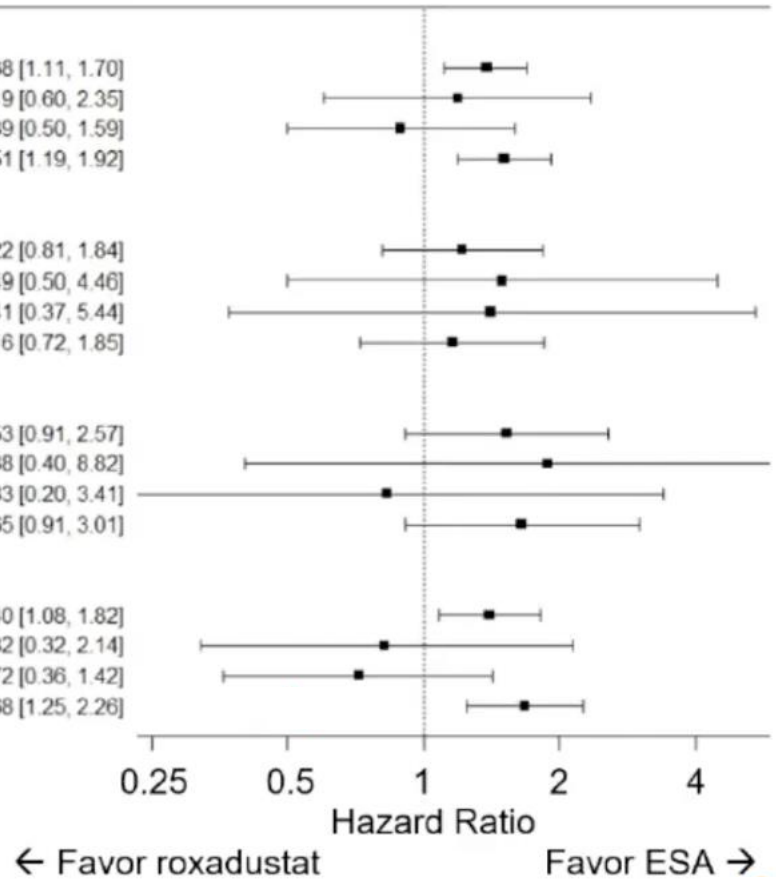
	Number of Events/ PY/ Rate		HR [95% CI]
	Roxadustat (N = 1,940)	ESA (N = 1,940)	
MACE			
All Studies	306/ 3261/ 9.4	339/ 3660/ 9.3	1.02 [0.88, 1.20]
063	57/ 886/ 6.4	66/ 938/ 7.0	0.90 [0.63, 1.28]
064	68/ 608/ 11.2	76/ 722/ 10.5	1.09 [0.78, 1.52]
002	181/ 1767/ 10.2	197/ 2001/ 9.8	1.05 [0.85, 1.28]
Myocardial Infarction			
All Studies	103/ 3279/ 3.1	109/ 3690/ 3.0	1.07 [0.81, 1.40]
063	14/ 889/ 1.6	13/ 948/ 1.4	1.10 [0.52, 2.36]
064	31/ 611/ 5.1	39/ 731/ 5.3	0.88 [0.55, 1.42]
002	58/ 1779/ 3.3	57/ 2011/ 2.8	1.19 [0.82, 1.72]
Stroke			
All Studies	45/ 3330/ 1.4	50/ 3746/ 1.3	1.03 [0.68, 1.55]
063	9/ 896/ 1.0	15/ 950/ 1.6	0.61 [0.27, 1.39]
064	10/ 628/ 1.6	6/ 755/ 0.8	2.44 [0.86, 6.89]
002	26/ 1807/ 1.4	29/ 2040/ 1.4	1.01 [0.60, 1.73]
All-Cause Mortality			
All Studies	207/ 3350/ 6.2	232/ 3777/ 6.1	1.02 [0.85, 1.23]
063	41/ 900/ 4.6	47/ 961/ 4.9	0.94 [0.62, 1.43]
064	40/ 631/ 6.3	39/ 766/ 5.1	1.34 [0.85, 2.10]
002	126/ 1818/ 6.9	146/ 2051/ 7.1	0.97 [0.76, 1.23]



Source: FDA Analysis

Figure 9: MACE and its Components for Studies in the NDD Population (OT+7 Analysis)

	Number of Events/ PY/ Rate		
	Roxadustat (N = 2,386)	Placebo (N = 1,884)	HR [95% CI]
MACE			
All Studies	277/ 3843/ 7.2	131/ 2332/ 5.6	1.38 [1.11, 1.70]
060	40/ 1124/ 3.6	11/ 382/ 2.9	1.19 [0.60, 2.35]
608	40/ 470/ 8.5	18/ 201/ 9.0	0.89 [0.50, 1.59]
001	197/ 2249/ 8.8	102/ 1749/ 5.8	1.51 [1.19, 1.92]
Myocardial Infarction			
All Studies	72/ 3869/ 1.9	37/ 2340/ 1.6	1.22 [0.81, 1.84]
060	18/ 1133/ 1.6	4/ 382/ 1.0	1.49 [0.50, 4.46]
608	11/ 473/ 2.3	3/ 201/ 1.5	1.41 [0.37, 5.44]
001	43/ 2264/ 1.9	30/ 1757/ 1.7	1.16 [0.72, 1.85]
Stroke			
All Studies	48/ 3888/ 1.2	21/ 2350/ 0.9	1.53 [0.91, 2.57]
060	9/ 1138/ 0.8	2/ 383/ 0.5	1.88 [0.40, 8.82]
608	6/ 477/ 1.3	3/ 202/ 1.5	0.83 [0.20, 3.41]
001	33/ 2273/ 1.5	16/ 1765/ 0.9	1.65 [0.91, 3.01]
All-cause Mortality			
All Studies	183/ 3914/ 4.7	85/ 2358/ 3.6	1.40 [1.08, 1.82]
060	18/ 1146/ 1.6	6/ 383/ 1.6	0.82 [0.32, 2.14]
608	24/ 480/ 5.0	14/ 202/ 6.9	0.72 [0.36, 1.42]
001	141/ 2287/ 6.2	65/ 1773/ 3.7	1.68 [1.25, 2.26]



Source: FDA analysis

Cancer Risk in ASCEND-ND

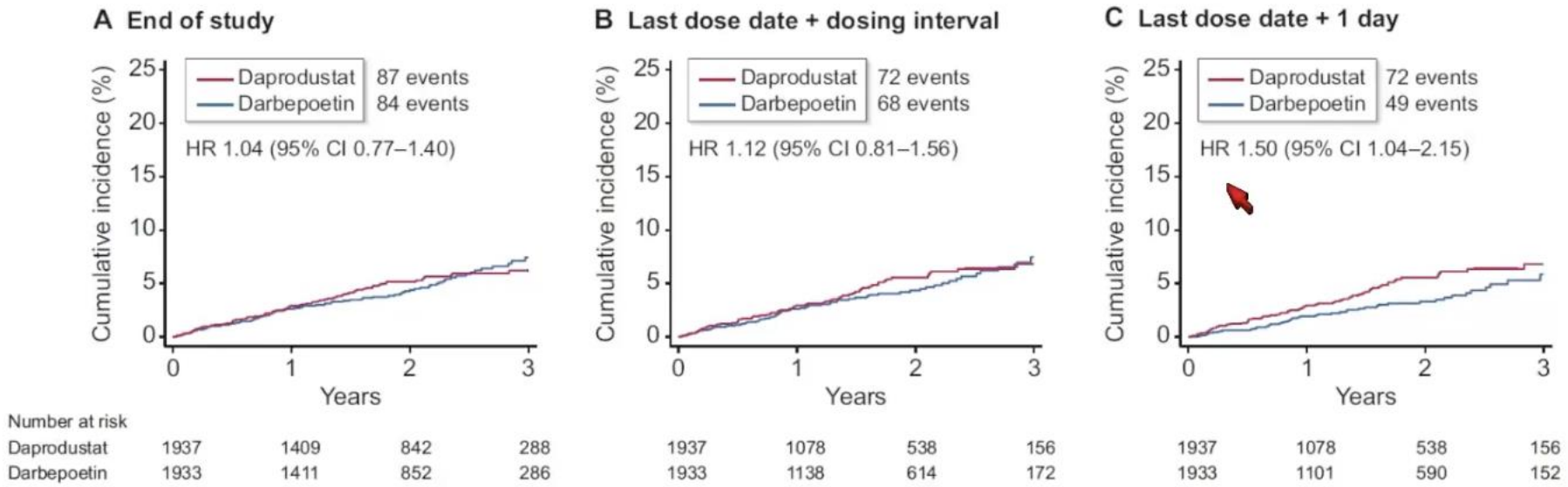


Figure 2: Kaplan–Meier curves for on-treatment cancer-related AE analyses of the ASCEND-ND trial according to various censoring times.

Singh, et al. NDT 2023

---------- CONTRAINDICATIONS ----------

- Strong cytochrome P450 2C8 (CYP2C8) inhibitors such as gemfibrozil. (4)
- Uncontrolled hypertension. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Hospitalization for Heart Failure: Increased in patients with a history of heart failure. (5.2)
- Hypertension: Worsening hypertension, including hypertensive crisis may occur. Monitor blood pressure. Adjust anti-hypertensive therapy as needed. (5.3)
- Gastrointestinal Erosion: Gastric or esophageal erosions and gastrointestinal bleeding have been reported. (5.4)
- Not indicated for treatment of anemia of CKD in patients who are not dialysis-dependent (5.5)
- Malignancy: May have unfavorable effects on cancer growth. Not recommended if active malignancy. (5.6)

Hyperkalemia more common than with placebo in some studies

FDA

ESA Hyporesponsiveness

- In ASCEND-D 12% of subjects were identified as being ESA-hyporesponsive and were reported as having similar Hb response as others

- Some dialysis patients will have a partial Hb response to a HIF-PHI but many remain below target and need higher doses than most subjects in clinical trials received

HIF-PHIs for Anemia Treatment in Kidney Disease The PRO Position

Steven Fishbane

Zucker School of Medicine at Hofstra / Northwell Health

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN American Society of Nephrology

HIF-PHIs for Treatment of Anemia: Con

Jeffrey S. Berns, MD, FASN

University of Pennsylvania Health System;
Hospital of the University of Pennsylvania

KIDNEY WEEK 2023

ASN American Society of Nephrology

The PRO side of HIF-PHIs

- The importance of anemia has gone from overemphasized (1990s) to grossly underappreciated (now)
- Anemia in nondialysis CKD is undertreated

- 40% of patients receive transfusions in the 2 years prior to dialysis
  - Harming subsequent transplantation opportunity
    - Increasing risk of subsequent graft failure
  - Oral agents would facilitate effective treatment and may reduce the high number of blood transfusions

Efficacy

- HIF-PHIs raise Hb as effectively as ESAs
- They reduce blood transfusions compared to placebo

- They accomplish this despite being administered orally
- There may be secondary beneficial effects

Conclusion

- HIF-PHIs allow for anemia treatment without the potentially harmful large surges in serum erythropoietin induced by ESAs
- Global Phase 3 studies indicate the clear efficacy of these agents
  - There may be secondary beneficial effects of treatment
- The oral route of administration creates significant opportunities
- As with all medical treatments, benefits must be weighed against risks
  - **The safety of HIF-PHIs proved complex to analyze in phase 3 studies**

- **November, 2023- HIF-PHIs approved in many countries in Europe and Asia**
  - **In U.S., only daprodustat is approved- and only for patients on dialysis for at least 4 months**

The CON side of HIF-PHIs

Daprodustat in the US

- Retail price about $125-130 for 1 mg pill (all prices from GoodRx website)
  - About half of patients treated on study with ≤ 6 mg, half 8-24 mg
  - $425 for 150 mcg of methoxy polyethylene glycol-epoetin beta
  - $800 for 25 mcg darbepoetin

- In-center HD---why switch from IV to pill unless given in HD unit for financial reasons?
- Home dialysis---perhaps as alternative to IV or SC ESA depending on patient preference
- ESA-hyporesponsive patients---perhaps a short trial

- Drug-drug interactions (metabolized mainly by CYP2C8)
  - Clopidogrel and TMP are CYP2C8 inhibitors ; increase daprodustat levels
  - Rifampicin decreases circulating levels of daprodustat by induction of CYP2C8
  - Note: Other HIF-PHIs have other drug-drug interactions

The CON side of HIF-PHIs

Conclusions

- Proven to be [more] effective and at least as safe ✗ ??????
- Proven to be safer and sufficiently effective ✗
  - HIF-PHIs have a "safety profile that seems, in sum, no better than the existing ESAs" McCallum, Weiner. CJASN 2022
  - "In terms of cardiovascular safety, HIF-PHIs are inferior to, or at best similar to conventional ESAs. Different safety signals were observed for different HIF-PHIs across large phase 3 trial programs, and concerns surrounding cardiovascular and thrombotic risks persist" KDIGO Controversies Conference 2023
- Preferred route of administration ✓ for some
- Less expensive ??????
  - Approved 10/1/2023 for TDAPA (1 mg)
- Patient preference ??????

Clinical Kidney Journal

Clinical Kidney Journal, 2023, vol. 16, no. 5, 776–779

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Editorial Comment

EDITORIAL COMMENT

Hypoxia-inducible factor stabilizers: 27 228 patients studied, yet a role still undefined

Steven Fishbane, Deepa A. Malieckal and Ji H. Ng

Zucker School of Medicine at Hofstra / Northwell, Great Neck, NY, USA

Other approaches being taken: present & future

1. Increasing late stage erythrocyte survival [Activin Traps].

- **Ligand-trapping fusion protein** (ACE-536, Setercept) containing the extracellular domain of human activin receptor type IIB (ActRIIB, TGF-β superfamily) modified **to reduce activin binding**
- They may also increase BFU-E and CFU-E via Erythropoietin
- They increase the number of daughter cells that mature from 32 to 36-40 by preventing “apoptosis”
- Might be very effective in MDS, thalassemias
- Effect in humans being evaluated
- Also has effects on metabolic bone disease to increase cortical bone thickness (mass)

2. Targeting the Hepcidin-Ferroportin Axis

- Direct inhibitors of hepcidin function (Direct Hepcidin Antagonists]
- Prevent the transcription of hepcidin (Hepcidin Production Inhibitors

1. Promote resistance of ferroportin to hepcidin action (Ferroportin agonists/ stabilizers)

3. SGLT2 Innibitori