Brigham and Women's Hospital
Founding Member, Mass General Brigham

What's New, Innovative, and Controversial in Chronic Kidney Disease

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- Clinical focus: CKD, Hemodialysis, Peritoneal Dialysis
- Medical Education

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DISCLOSURES

I have no relevant financial relationships with ineligible companies.

OBJECTIVES

- To highlight recent treatment innovations in chronic kidney disease
- To review recent controversies in chronic kidney disease

Case 1

A 61-year-old man of African descent presents for follow-up. He feels well and has no complaints. His 81-year-old mother has hypertension and end-stage kidney disease on hemodialysis.

Past Medical History

- Hypertension
- Gout
- Obstructive sleep apnea

Case 1-Medications

Amlodipine 5 mg daily

Lisinopril 20 mg daily

Allopurinol 100 mg daily

Case 1: Question 1

Which of the following diagnostic tests is/are appropriate in this patient?

A. Electrolytes
B. Serum creatinine
C. Urine albumin/creatinine
D. All of the above

Case 1 Question 1: Answer

The correct answer is D.
This patient has hypertension and a first-degree relative with end-stage kidney disease. He is therefore at risk for chronic kidney disease, which is usually manifested first by albuminuria. Hence, measuring a serum creatinine and checking for the presence of albuminuria are appropriate. Because he is on an ACE-I, checking an electrolyte panel is also appropriate.

Controversy: Should we routinely screen for chronic kidney disease?

- Chronic kidney disease may remain asymptomatic until advanced
- Is there a role for routine screening of asymptomatic patients?

USPSTF Recommendations for screening asymptomatic adults for CKD

Population	Asymptomatic adults without diagnosed chronic kidney disease
Recommendation	No recommendation
	Grade: I (insufficient evidence)
Risk assessment	There is no generally accepted risk assessment tool for CKD. Diabetes and hypertension are well accepted risk factors with strong links to CKD. Other risk factors for CKD include older age, cardiovascular disease, obesity, and family history.
Screening tests	Although there is insufficient evidence to recommend routine screening, the tests often suggested for screening that are feasible in primary care include testing the urine for protein (microalbuminuria or macroalbuminuria) and testing the blood for serum creatinine to estimate glomerular filtration rate.
Balance of harms and benefits	The USPSTF could not determine the balance between the benefits and harms of screening for CKD in asymptomatic adults.

Moyer, VA Ann Intern Med. 2012;157:567-570

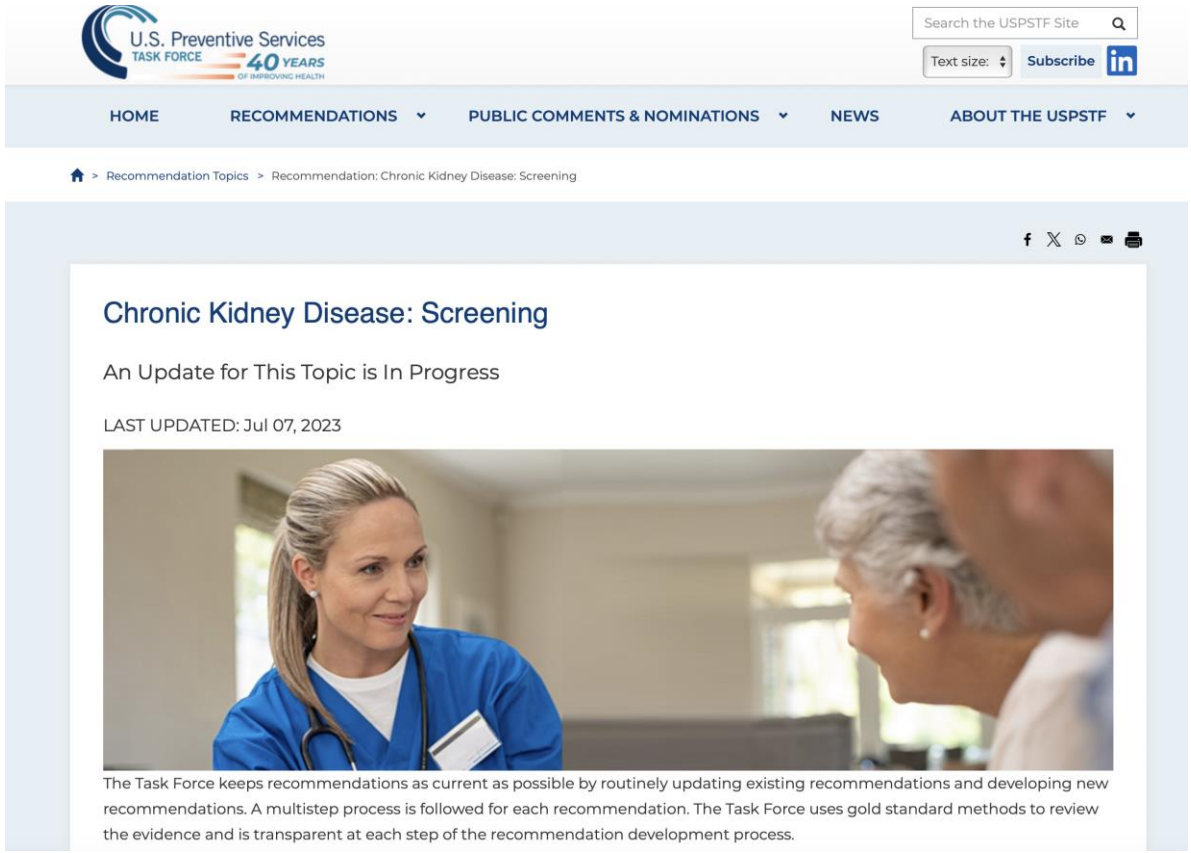
Statement from the National Kidney Foundation on Media Reports of USPSTF Considering Kidney Disease Screening

May 24, 2022, New York, NY —The National Kidney Foundation (NKF) is encouraged by reports the United States Preventative Services Task Force (USPSTF) may consider issuing new guidelines for kidney disease screening. NKF and the Coalition for Kidney Health have long been advocating for USPSTF to revise its CKD recommendations. A statement from Sylvia Rosas, MD, NKF President-elect and Associate Professor of Medicine, Harvard Medical School, and Joseph Vassalotti, MD, Chief Medical Officer for the NKF follows:

"Ultimately, CKD is a health equity issue – African Americans are 3 – 4 times more likely to develop kidney failure than Whites. If we can identify individuals with CKD earlier – at a more manageable stage of their disease – we can slow disease progression and help achieve better outcomes for all populations, but especially those at highest risk for kidney failure. The news that the USPSTF has agreed to review kidney disease screening again, is welcome. However, no timeline for future recommendations has been set. The USPSTF must act and act soon if we ever hope to adequately address inequity in CKD care."

- Sylvia Rosas, MD, NKF President-elect and Associate Professor of Medicine, Harvard Medical School

USPSTF Update for CKD Screening Still in Progress



ISN-KDIGO Early Identification and Intervention in Primary Care

Step 1: Identify those at risk

Main Clinical Risk Factors for CKD:

- Hypertension
- Diabetes
- CVD
- Family history of CKD

Consider Other Factors:

- Systemic diseases that may affect kidneys (SLE)
- Obesity
- Genetic Risk Factors
- Exposure to nephrotoxins
- Demographics (older age, race/ethnicity)
- History of AKI

Case 1: Question 2

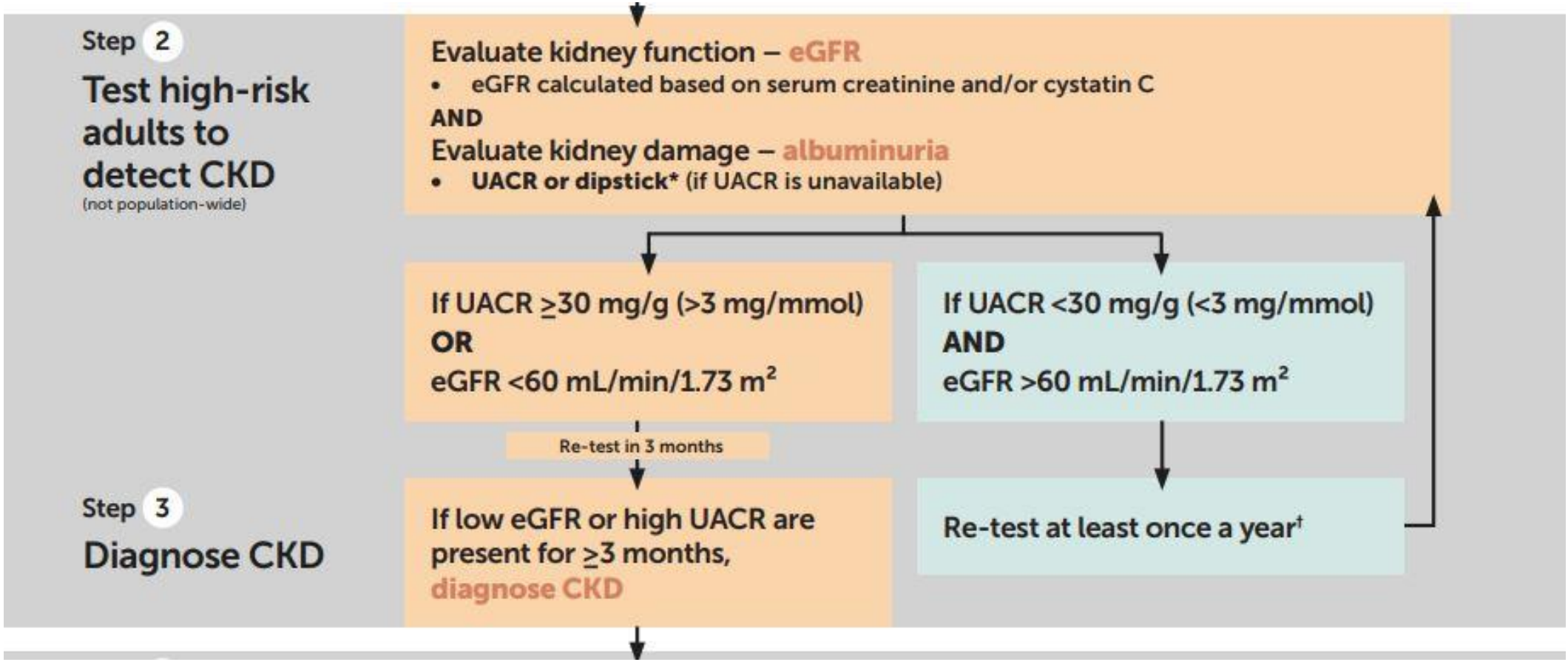
The patient's serum creatinine is 0.91 mg/dL, eGFR 96 mL/min/1.73m2, and urine albumin/creatinine 480 mg/g. Similar values are obtained about 3 months later. Does this patient have CKD?

A. Yes
B. No

Case 1: Question 2 Answer

Yes, this patient meets the definition of CKD because he has albuminuria confirmed on two values 3 months apart.

ISN-KDIGO Early Identification and Intervention in Primary Care



International Society of Nephrology

Overview on Monitoring for Progression of CKD Based upon GFR and ACR Categories

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	**G1**	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

High risk

Very high risk

Innovation: Albuminuria is a treatment trigger, not just a lab abnormality

- The updated CKD framework emphasizes staging by eGFR and albuminuria, and its primary-care takeaways stress that CKD is not defined by creatinine alone. That matters because many patients who “look fine” from a creatinine standpoint still have actionable kidney and cardiovascular risk if albuminuria is present.
- **Order the urine ACR *in addition to* the basic metabolic panel.**

Treat to slow CKD progression, reduce mortality risk, and manage co-morbidities: The ABC approach

ACE-I or ARB	Blood pressure control	CV Risk Reduction Diet Exercise Statins	Diabetes control (A1C < 7%)	Evidence-based therapies SGLT-2s GLP-1s NS MRAs	Follow-up

Adapted from Dr. Xavier Cos

BLOOD PRESSURE CONTROL

Recommendation 3.4.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (2B).

Practice Point 3.4.1: Consider less intensive BP-lowering therapy in people with frailty, high risk of falls and fractures, very limited life expectancy, or symptomatic postural hypotension.

Additional considerations for nephrology consultation

- Unexplained, progressive decline in eGFR ≥5 mL/min/1.73 m^2 over 12 months or sudden decline in eGFR over days to weeks
- Unexplained significant albuminuria/proteinuria or hematuria
- Persistent hyperkalemia, resistant hypertension (defined as uncontrolled hypertension on three antihypertensive agents, including a diuretic), recurring kidney stones, or hereditary kidney diseases (e.g. ADPKD)
- Other complications identified (anemia, mineral and bone disorders, metabolic acidosis, etc.)

Risk Prediction in People with CKD

Recommendation 2.2.1: In people with CKD G3–G5, we recommend using an externally validated risk equation to estimate the absolute risk of kidney failure (1A).

Table 19 | Externally validated risk equations for predicting kidney failure in the general (CKD G3–G5) population

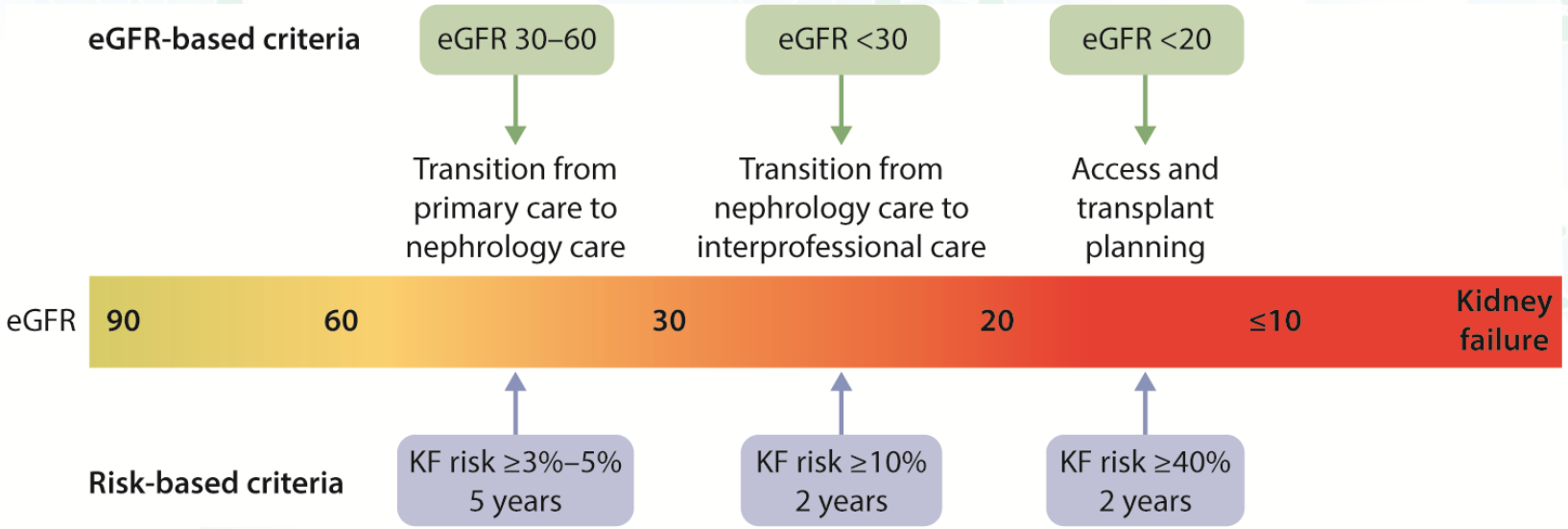
Equation	Variable	Population	Outcome (time horizon)	Discrimination and calibration	Usability
KFRE[9,10,407,408] www.kidneyfailurerisk.com www.ckdpc.org/risk-models.html	Age, sex, eGFR, ACR (4 variable) + calcium, phosphate, bicarbonate, and albumin (8 variables)	>1 million patients, >100,000 events from more than 30 countries	Treated kidney failure (2–5 yr)	0.88–0.91/+	+
KPNW[410]	Age, sex, eGFR, albuminuria, systolic BP, antihypertensive use, diabetes, and diabetes complications	39,013 patients, 1097 events from the Kaiser Permanente Health System (United States)	Kidney failure (5 yr)	0.95/+	+
Landray *et al.*[411]	Sex, SCr, albuminuria, and phosphate	595 patients, >190 events from the CRIB and East Kent cohorts in the United Kingdom	Kidney failure	0.91/+	–
Z6 score[409]	SCr, albumin, cystatin C, urea, hemoglobin, and ACR	7978 patients, 870 events—developed in the German CKD study, validated in 3 additional European cohorts	Kidney failure (5 yr)	0.89–0.92/+	–

ACR, albumin-to-creatinine ratio; BP, blood pressure; CKD, chronic kidney disease; CRIB, chronic renal impairment in Birmingham; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; KPNW, Kaiser Permanente Northwest; SCr, serum creatinine.

Risk Prediction in People with CKD

Practice Point 2.2.1: A 5-year kidney failure risk of 3%–5% can be used to determine need for nephrology referral in addition to criteria based on eGFR or urine ACR, and other clinical considerations.

Practice Point 2.2.2: A 2-year kidney failure risk of >10% can be used to determine the timing of multidisciplinary care in addition to eGFR-based criteria and other clinical considerations.



Case 2

A 39-year-old woman who has been generally healthy complains of intermittent “tea-colored urine” during upper respiratory tract infections.

Past Medical History

- G1P1

Case 2-Medications and Physical Examination

- No medications

- BP 132/82 mm Hg
- Clear lungs
- Regular rate and rhythm
- Benign abdomen
- No peripheral edema
- No rash

Case 2-Labs

- Serum creatinine 0.8 mg/dL
- eGFR 96 mL/min/1.73m^2
- UA: 3+ blood, 2+ protein
- Urine ACR 820 mg/g
- C3 and C4 normal
- ANA negative
- Hepatitis B and C negative

Case 2: Question

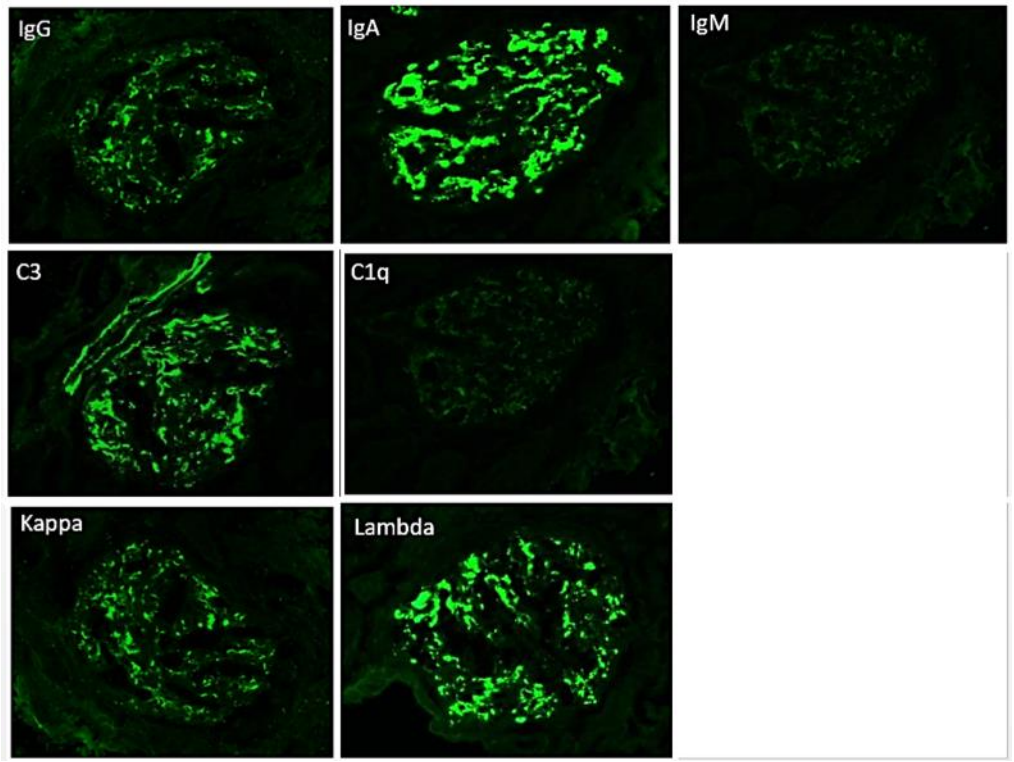
What diagnosis is most consistent with this patient's presentation?

A. Thin basement membranes
B. IgA nephropathy
C. Lupus nephritis
D. ANCA vasculitis

Case 2: Answer

The correct answer is B.
Hematuria occurring in the setting of an upper respiratory tract infection, “synpharyngitic hematuria,” is most suggestive of IgA nephropathy, which worldwide is the most common glomerular disease.

IgA Nephropathy: Immunofluorescence is key to diagnosis



From Renal Fellows Network

Treatment of IgA nephropathy

Treatment of IgA nephropathy has focused on

- Blood pressure control
- Blockade of the renin/angiotensin system
  - –ACE-I
  - –ARB
- Conservative management

Innovation: New disease specific therapies approved by the FDA for treatment of IgA nephropathy

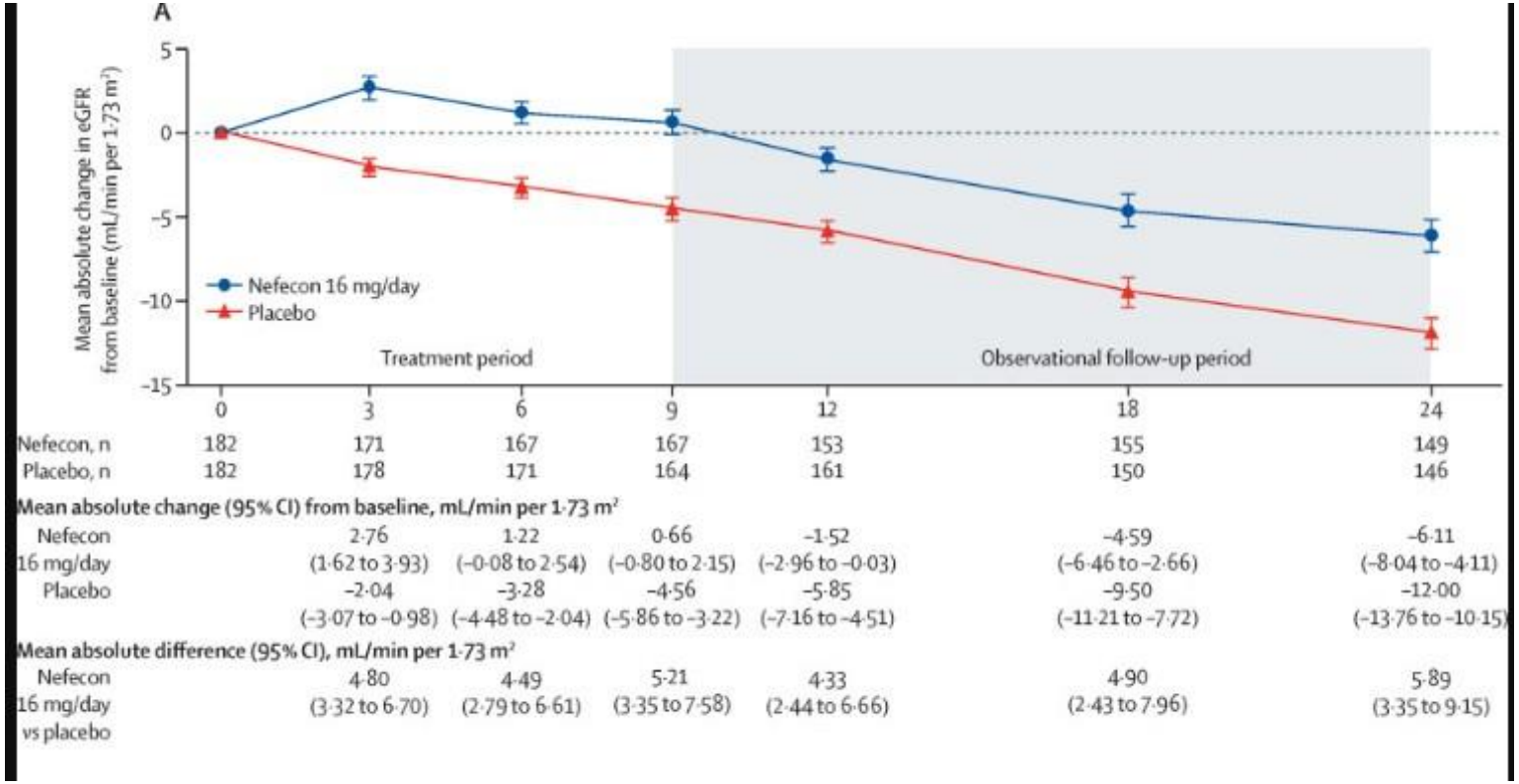
- Nefecon
- Sparsentan
- Iptacopan

Nefecon

- Novel, oral, targeted-release capsule formulation of budesonide
- Designed to be released in the distal ileum for maximal exposure of the B-cell-containing Peyer's patches.
- Due to the high first-pass metabolism of budesonide, only a small amount of active budesonide is systemically available, thereby reducing the potential for systemic glucocorticoid adverse effects.

Lafayette R *et al*, Lancet 2023; 402: 859-870

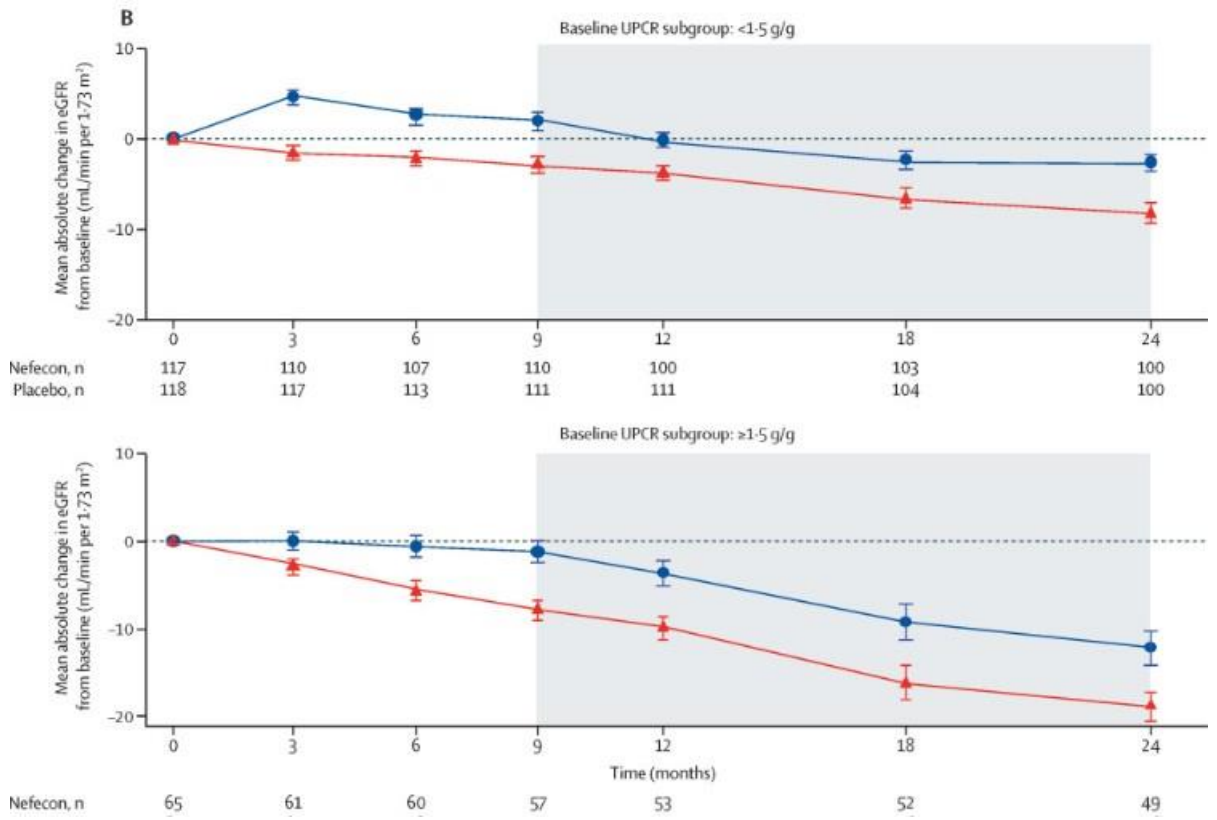
Effect of treatment with Nefecon on GFR



	0	3	6	9	12	18	24
Nefecon, n	182	171	167	167	153	155	149
Placebo, n	182	178	171	164	161	150	146
Mean absolute change (95% CI) from baseline, mL/min per 1·73 m²							
Nefecon 16 mg/day		2·76 (1·62 to 3·93)	1·22 (−0·08 to 2·54)	0·66 (−0·80 to 2·15)	−1·52 (−2·96 to −0·03)	−4·59 (−6·46 to −2·66)	−6·11 (−8·04 to −4·11)
Placebo		−2·04 (−3·07 to −0·98)	−3·28 (−4·48 to −2·04)	−4·56 (−5·86 to −3·22)	−5·85 (−7·16 to −4·51)	−9·50 (−11·21 to −7·72)	−12·00 (−13·76 to −10·15)
Mean absolute difference (95% CI), mL/min per 1·73 m²							
Nefecon 16 mg/day vs placebo		4·80 (3·32 to 6·70)	4·49 (2·79 to 6·61)	5·21 (3·35 to 7·58)	4·33 (2·44 to 6·66)	4·90 (2·43 to 7·96)	5·89 (3·35 to 9·15)

Lafayette R *et al*, Lancet 2023; 402: 859-870

Effect of treatment with Nefecon on proteinuria

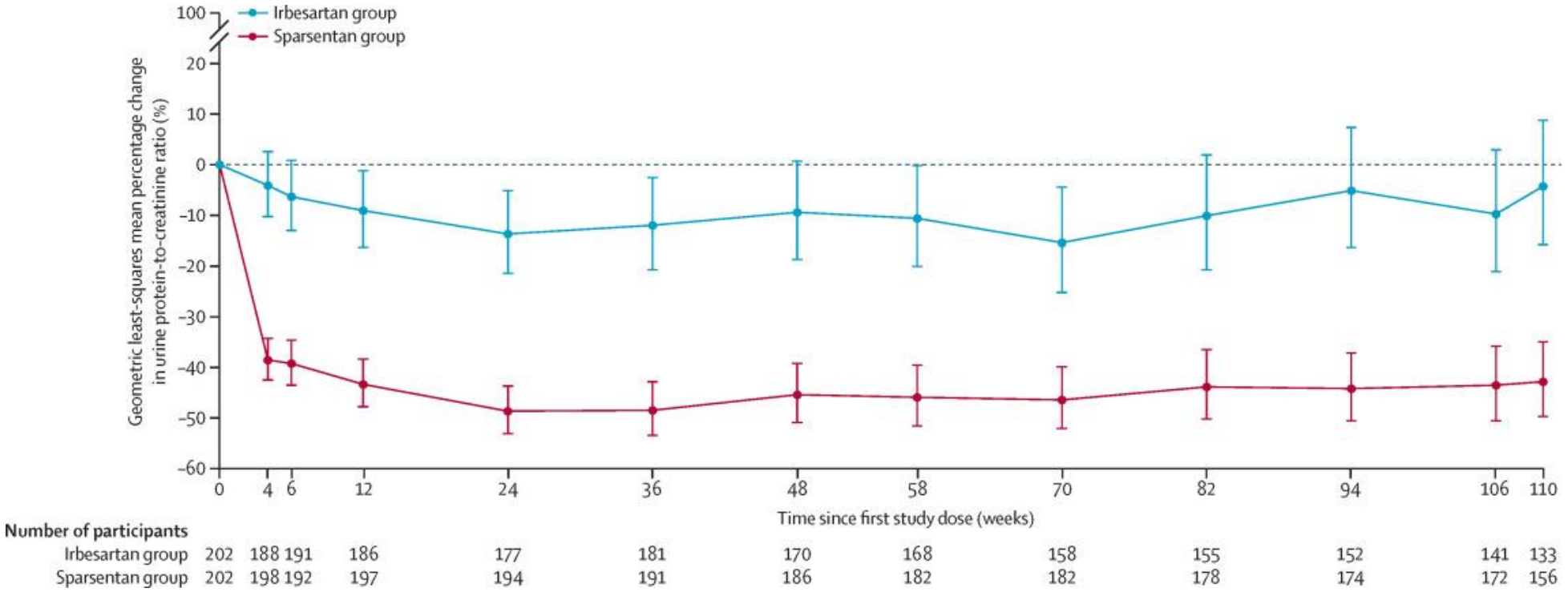


Lafayette R *et al*, Lancet 2023; 402: 859-870

Sparsentan

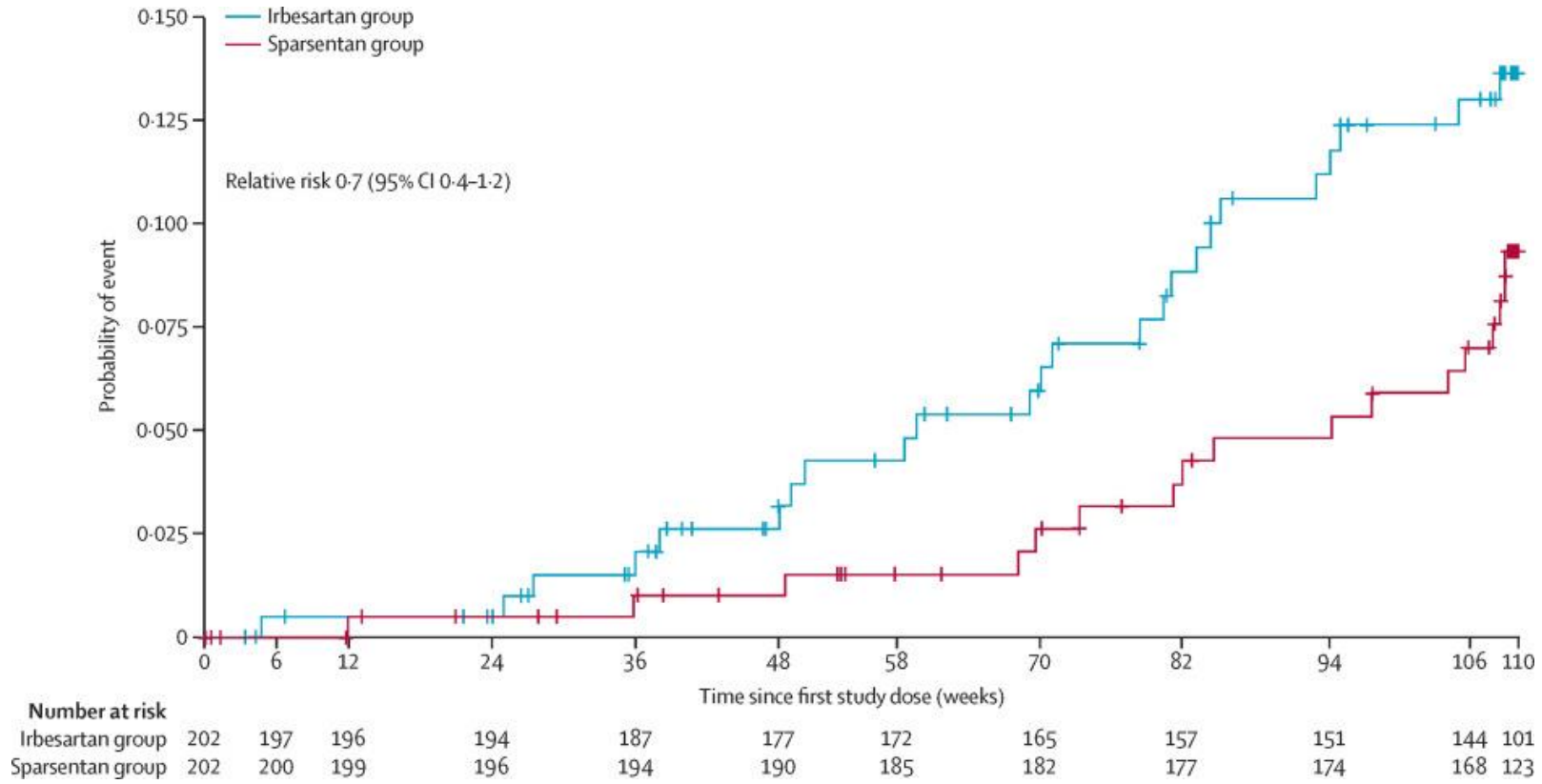
- Dual endothelin receptor antagonist
- Should not be prescribed with an ACE-I or ARB because sparsentan already combines RAS inhibition with an endothelin antagonist in a single drug

Sparsentan reduces proteinuria compared to irbesartan



Rovin, BH et al, Lancet 2023; 402:2077-2090

Sparsentan-treated subjects had lower risk of reaching the composite endpoints

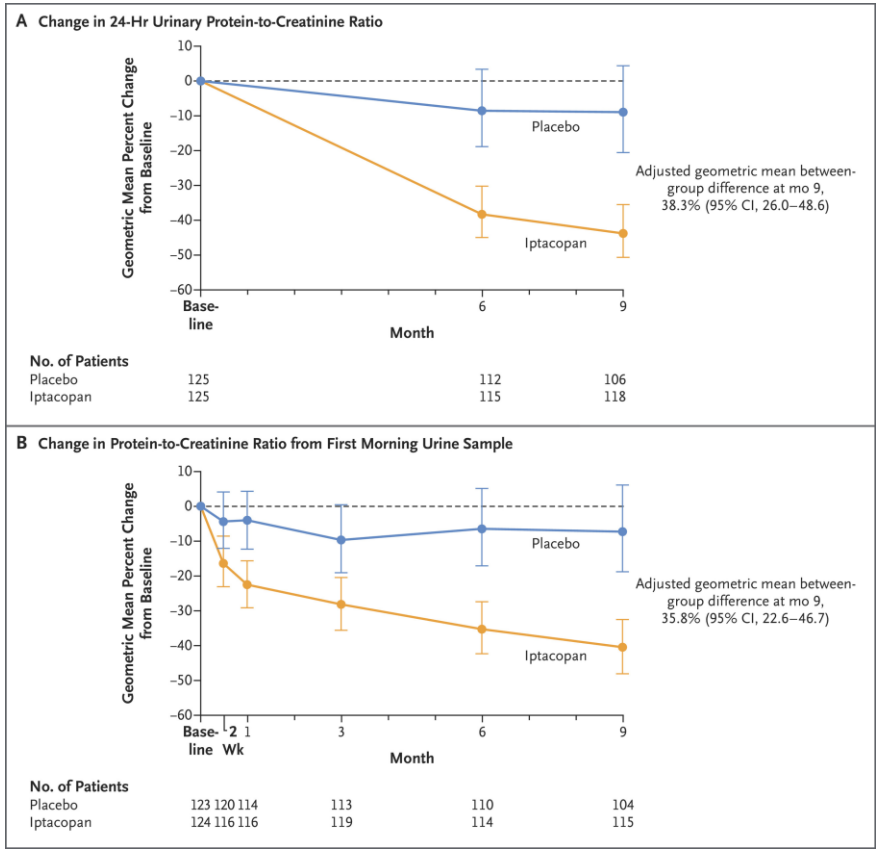


Rovin, BH et al, Lancet 2023; 402:2077-2090

Iptacopan

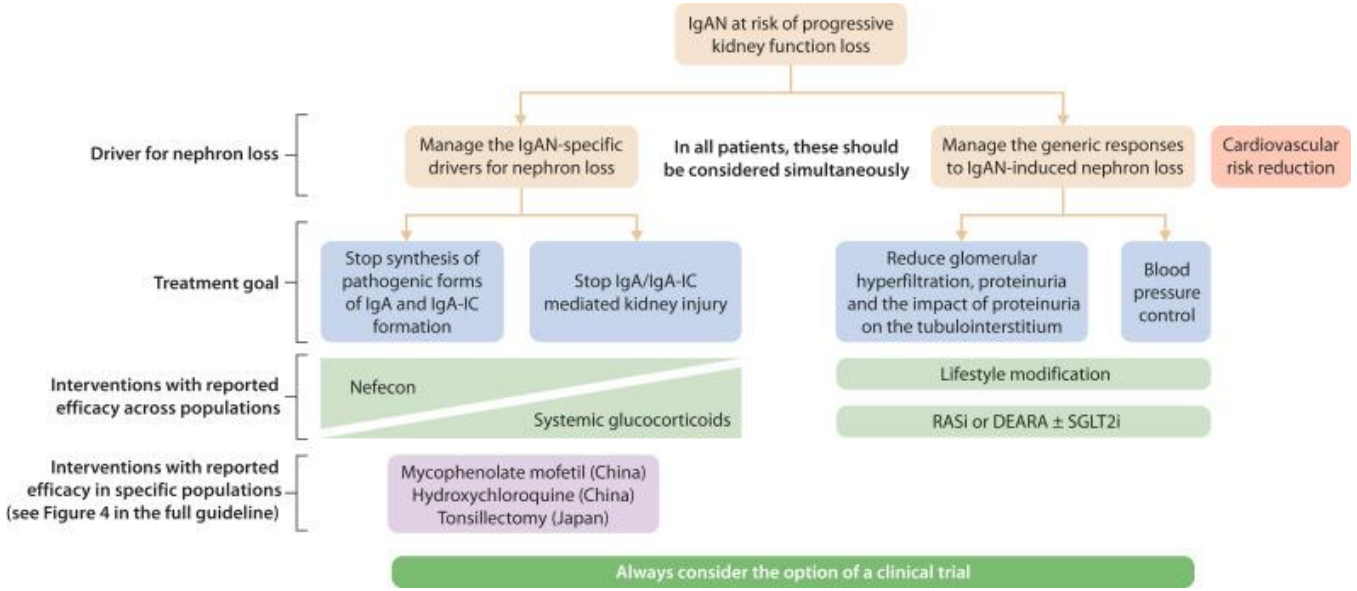
- Iptacopan stops factor B from binding with complement component C3b, preventing the formation of the C3 convertase enzyme.
- By blocking this enzyme, it halts the alternative pathway's feedback loop, preventing downstream complement activation.

Effect of iptacopan on proteinuria



Perkovic V et al, N Engl J Med 2025;392:531-543

KDIGO Guidelines for IgAN



Floege J et al Kidney Int 2025; 108: 548-554

Case 3

A healthy 35-year-old woman donates a kidney to a family member. Two years later she develops pre-eclampsia with her second pregnancy. Following delivery, she has persistent hypertension and proteinuria. Her CKD is managed for ten years until reaching ESKD. She wants to undergo kidney transplantation but has antibodies that will cause immediate rejection of a human kidney. She asks her nephrologist about enrolling in a clinical trial for xenotransplantation.

Innovation: Xenotransplantation: A novel approach to treatment of difficult to transplant patients and the organ shortage

Xenotransplantation: Definition

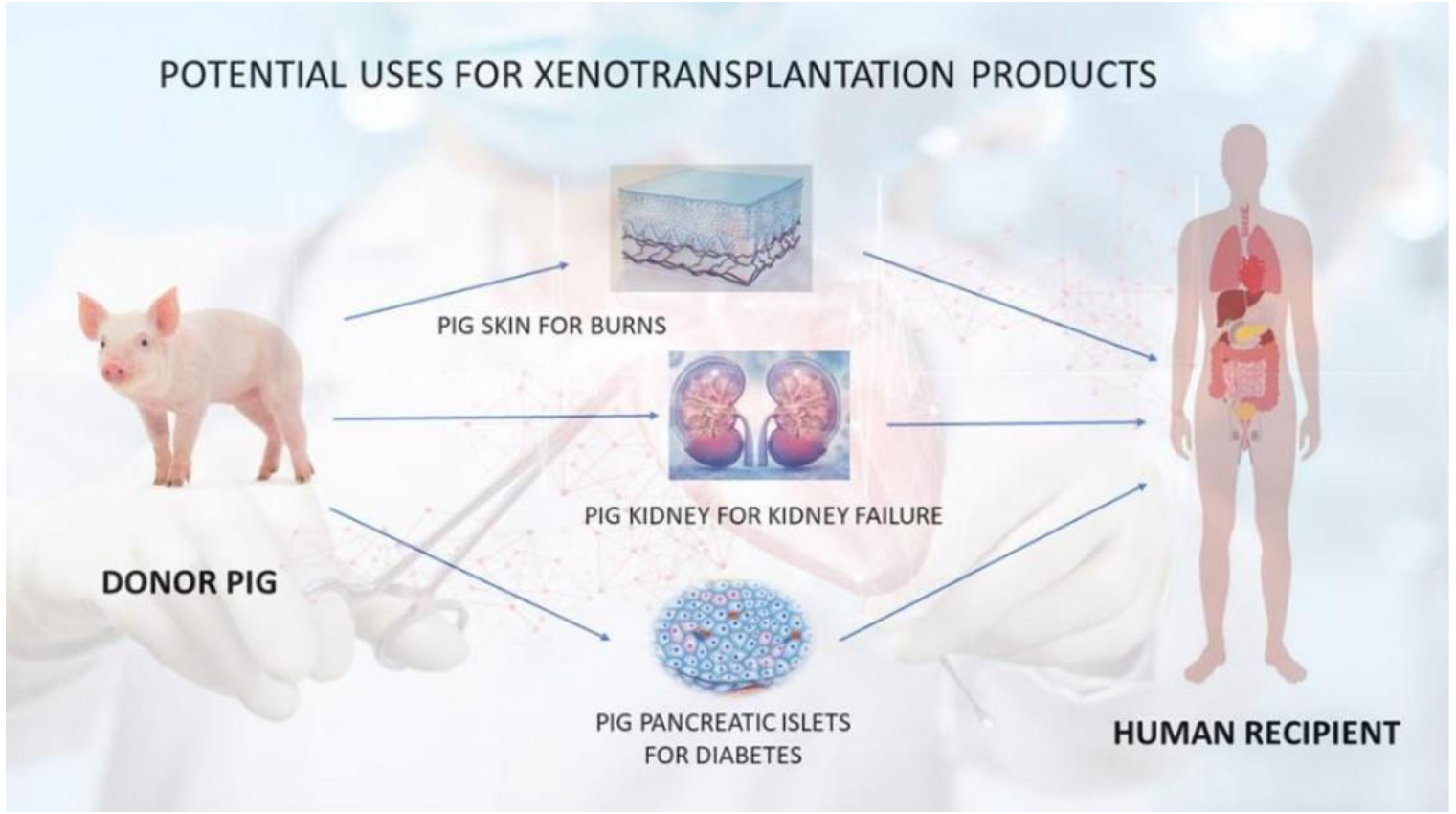
Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs. The development of xenotransplantation is, in part, driven by the fact that the demand for human organs for clinical transplantation far exceeds the supply.

Source: Food and Drug Administration

Addressing the organ shortage

- Currently ten patients die each day in the United States while on the waiting list to receive lifesaving vital organ transplants.
- Recent evidence has suggested that transplantation of cells and tissues may be therapeutic for certain diseases such as neurodegenerative disorders and diabetes, where, again human materials are not usually available.

Potential Uses for Xenotransplantation



Food and Drug Administration

Why pig kidneys for transplantation?

- Similar in size and function to human kidneys
- Able to perform the same metabolic functions as the human kidney
- Similar life expectancy (~30 years) as a human kidney transplant
- Can be genetically modified to make them potentially suitable for human transplantation

National Kidney Foundation

Xenotransplantation in the news

In a first, Mass. General surgeons transplant a pig kidney into a man

The patient is doing well, but many unknowns remain

By **Felice J. Freyer** Globe Staff, Updated March 21, 2024, 7:40 p.m.

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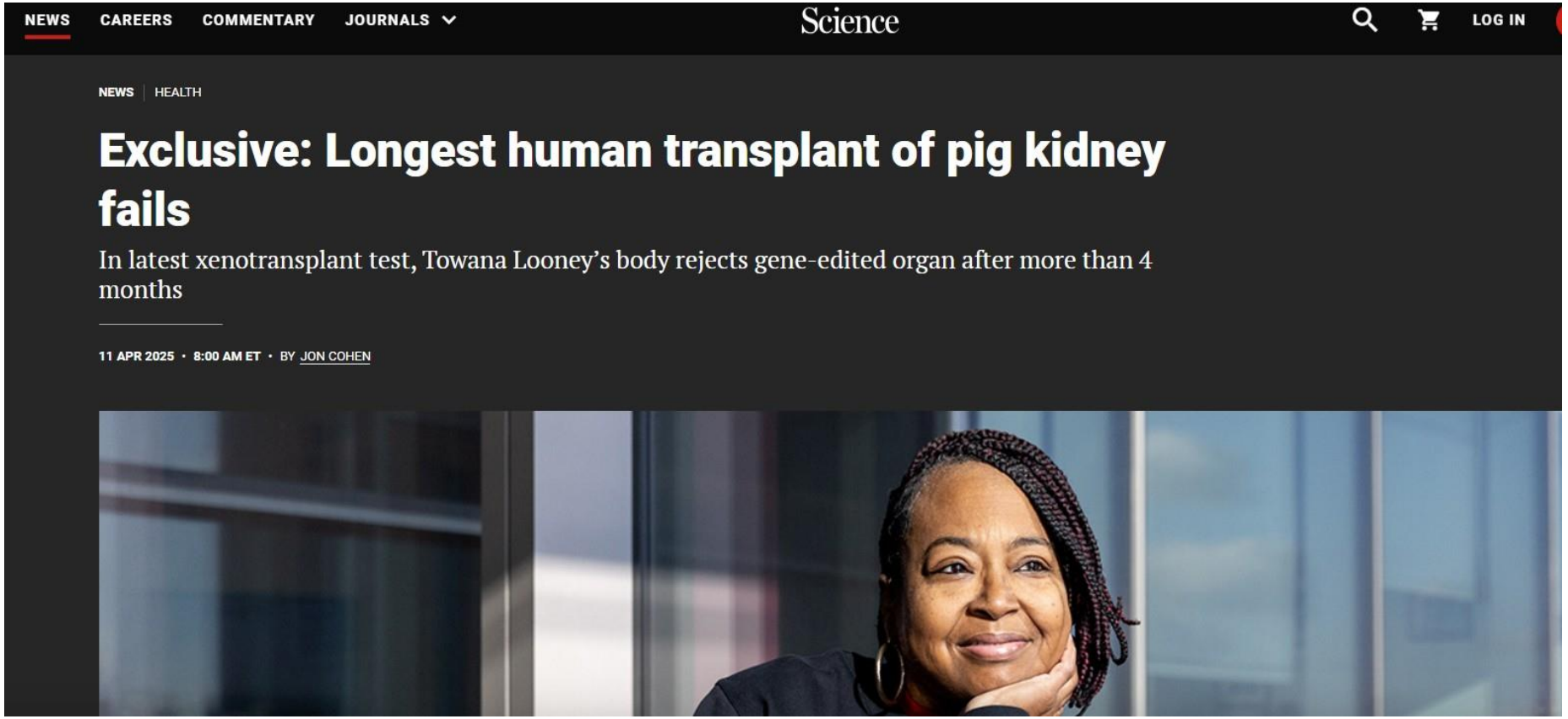
Boston Globe, March 21, 2024

Xenotransplantation in the news



Controversies in Xenotransplantation

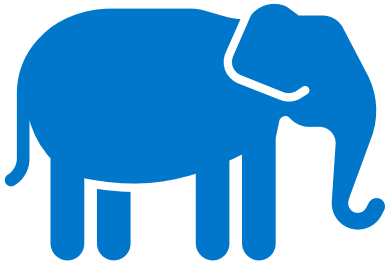
- Ethical considerations
- Safety
- Equity

Ethical considerations

- Religious considerations
- Animal rights

Safety Concerns

Usual transplant safety concerns



Zoonotic infections

Equity concerns

Will the advent of xenotransplantation exacerbate already existing health inequities?

Will xenotransplantation be available only to those who can travel to centers of expertise?

The future: Clinical trials

- NYU Langone
- Massachusetts General Hospital
- Johns Hopkins
- University of Alabama at Birmingham

Case 4

A 72-year-old man with ESRD on HD, diabetes mellitus type 2, and peripheral arterial disease is admitted with a diabetic foot ulcer. He has a hemoglobin of 7.8 g/dL on admission. He has no evidence of GI bleeding.

Case 4
Past Medical History

- ESRD
- Diabetes mellitus type 2
- Hypertension
- Colon cancer s/p partial colectomy 5 year prior; no metastatic disease
- TIA

Case 4
Outpatient Medications

- Amlodipine 10 mg daily
- ASA 81 mg daily
- Calcitriol 0.25 ug 3x/weekly
- Labetalol 300 mg bid
- Lisinopril 10 mg daily
- Pravastatin 40 mg daily
- Nephrocaps 1 daily
- Iron gluconate 125 mg weekly

Anemia Labs

- Hemoglobin 7.8 g/dL
- T-sat 13%
- Ferritin 602 ug/L

Case 4 Question 1

What would you do next in managing this patient's anemia?

A. Do nothing. The patient is asymptomatic.

B. Add an ESA.

C. Transfuse to a hemoglobin of 10-11 g/dL.

D. Give intravenous iron.

Case 4 Question 1 Answer

The patient is anemic but also iron deficient. The goal transferrin saturation in a hemodialysis patient is 30-40%. The first step in management of this patient would be to administer IV iron.

Follow-up

The patient is treated with a course of intravenous iron. His transferrin saturation rises to 35% and his hemoglobin rises to 8.1 g/dL. The patient complains of fatigue with minimal exertion.

Case 4 Question 2

What would you do next in managing this patient's anemia?

A. Do nothing. The patient is asymptomatic.

B. Add an ESA.

C. Transfuse to a hemoglobin of 10-11 g/dL.

D. Refer to hematology.

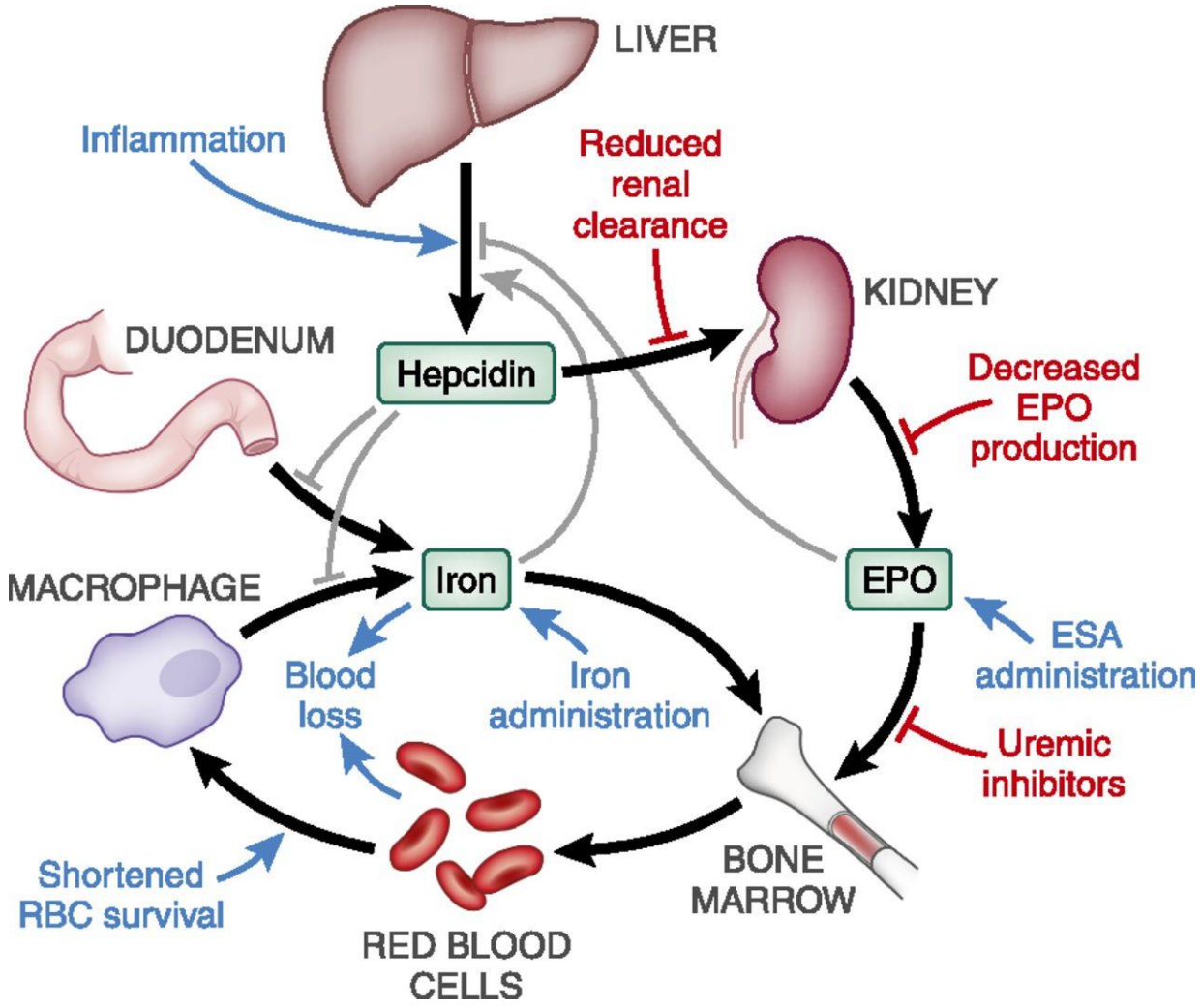
Case 4 Question 2 Answer

The patient has symptomatic anemia with an adequate transferrin saturation. The next best step would be to add an ESA.

Controvery: Use of ESAs in patients with a history of cancer and recent cardiovascular events

Over the last twenty years or so, there has been increasing evidence of the risks of ESAs, particularly in the setting of cancer and recent cardiovascular events, but those studies must be put into the context of how anemia was being managed at the time of those studies.

Mechanisms underlying anemia of chronic kidney disease



Jodie L. Babitt, and Herbert Y. Lin JASN 2012;23:1631-1634

KDIGO Recommendations

In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)

Special considerations with ESAs in dialysis

- Cancer
- Stroke

ESAs and Cancer

Beginning in 2010, the FDA required that ESAs be prescribed to cancer patients under its risk evaluation and mitigation strategy program

- Requires additional education for healthcare providers who prescribe and dispense ESAs
- Requires documentation that patients understand ESA-related risks

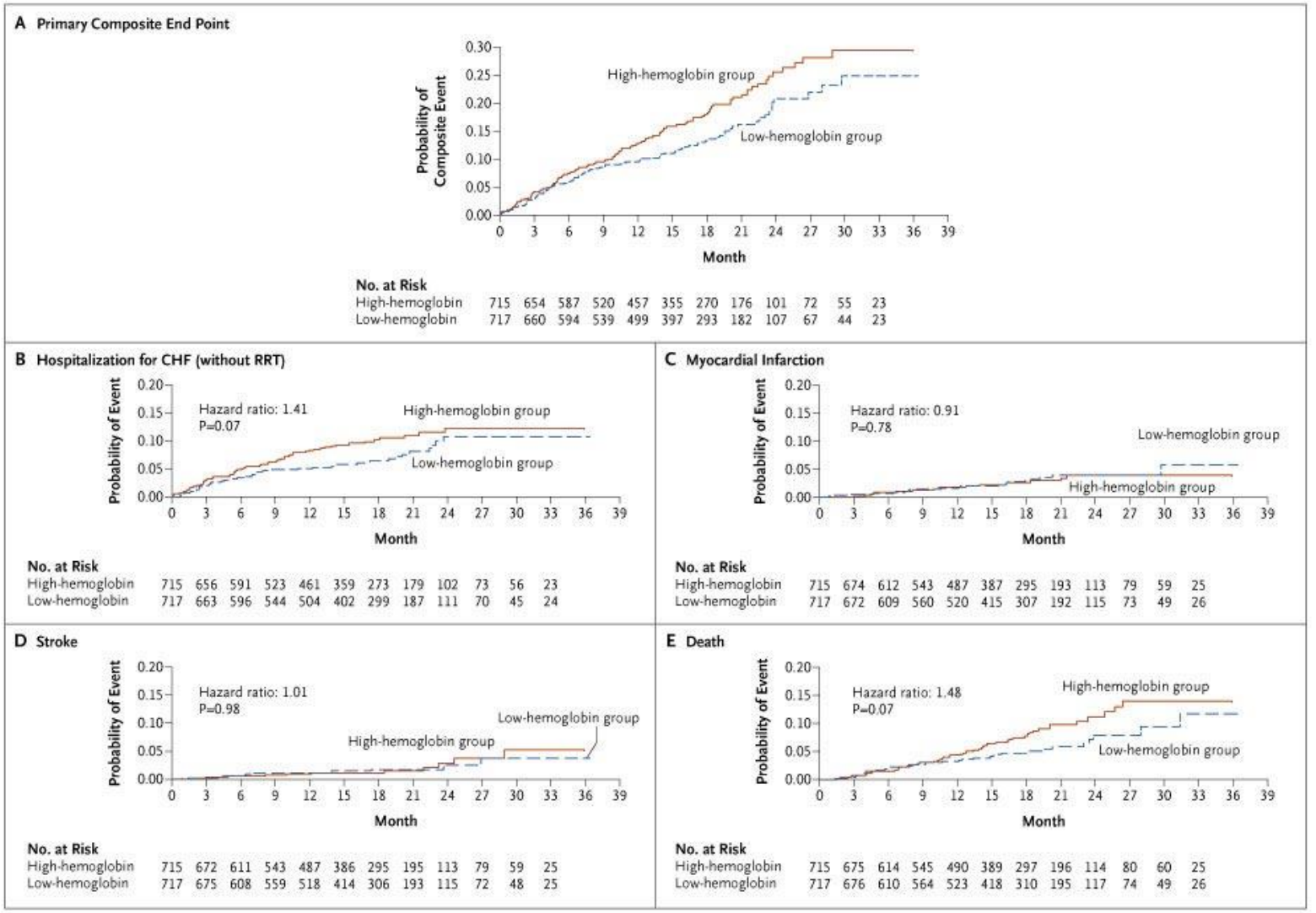
Source	Cancer Type	Concomitant Therapy	# of patients randomized	ESA Treatment	Hemoglobin Stopping Value g/dL	Adverse Outcome
Henke et al 2003	Head and neck	Radiotherapy	351	Epoetin beta (300 IU/kg 3x/week)	≥ 14 (women) ≥ 15 (men)	Locoregional progression
Hedenus et al 2003	Lympho-proliferative cancers	Chemotherapy	349	Darbepoietin alfa (2.25 ug/kg/week)	≥ 14 (women) ≥ 15 (men)	Shortened overall survival
Leyland-Jones et al 2005	Metastatic breast cancer	Chemotherapy	939	Epoetin alfa (40000 U/wk)	> 14	Overall survival vs placebo
Overgaard et al 2007	Locally advanced head and neck	Radiotherapy	522	Darbepoietin alfa (150 ug/week)	> 15.5	Increased risk in local-regional failure
PREPARE	Breast cancer	Chemotherapy	733	Darbepoietin alfa (4.5 ug/kg/2 wk)	≥ 13	Shortened overall survival

Bennett CL *et al* JAMA 2008; 299: 914-924

What is the evidence for an increased risk of cardiovascular events?

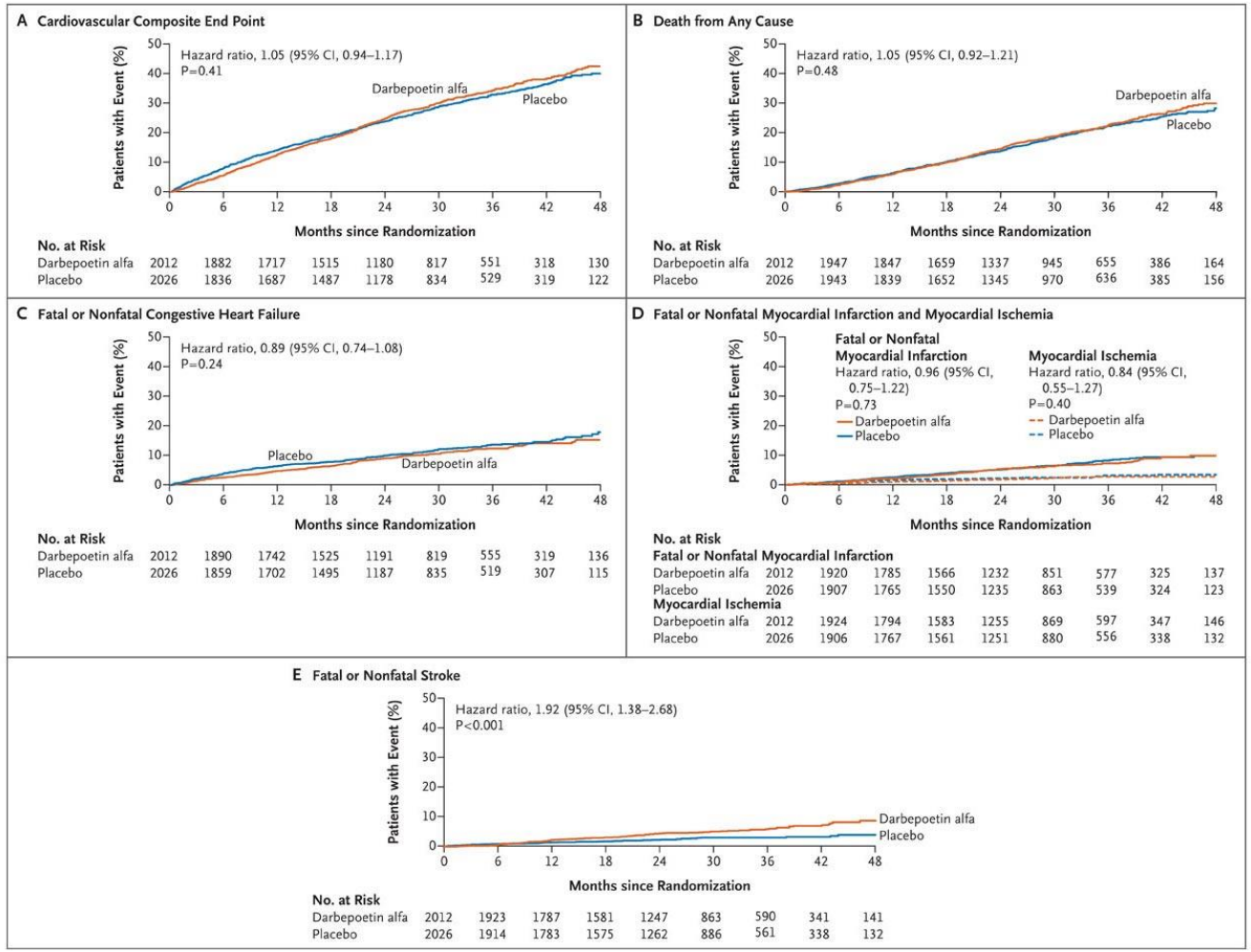
- CHOIR
  - Participants all had CKD and were randomized to two different hemoglobin targets
- TREAT
  - Participants all had CKD and diabetes and were randomized to darbepoietin versus placebo

CHOIR: Probabilities of the Primary and Secondary End Points



Singh AK *et al*. N Engl J Med 2006;355:2085-2098

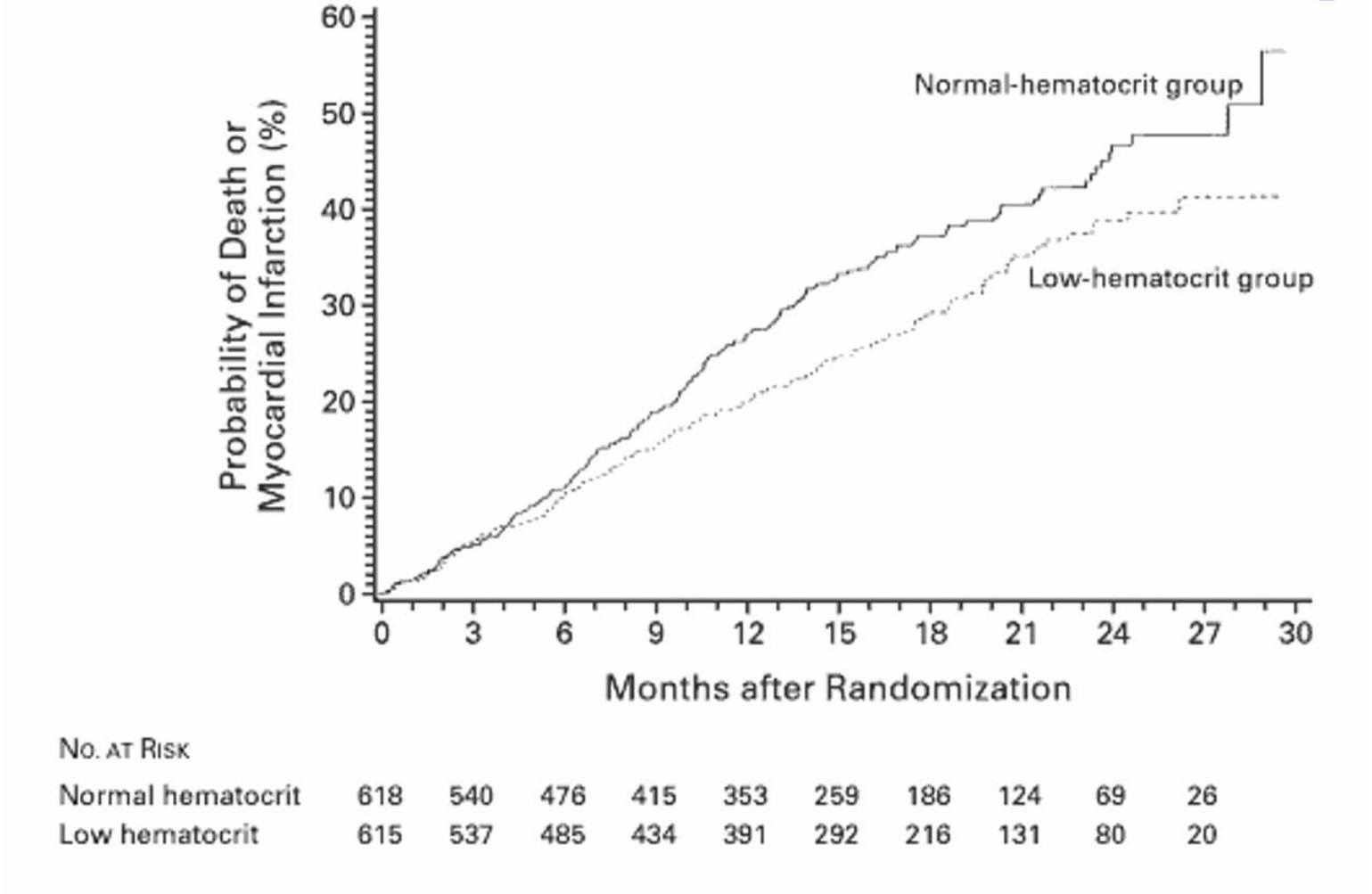
Treat: Kaplan-Meier Estimates of the Probability of the Primary and Secondary End Points (Note Panel E)



Pfeffer M *et al*. N Engl J Med 2009;361:2019-2032

Is a higher hemoglobin better in dialysis patients?

Probability of Death or a First Nonfatal Myocardial Infarction in the Normal-Hematocrit and Low-Hematocrit Groups



No. at Risk										
Normal hematocrit	618	540	476	415	353	259	186	124	69	26
Low hematocrit	615	537	485	434	391	292	216	131	80	20

Besarab A *et al*. N Engl J Med 1998;339:584-590

FDA changes to the ESA label June 2011

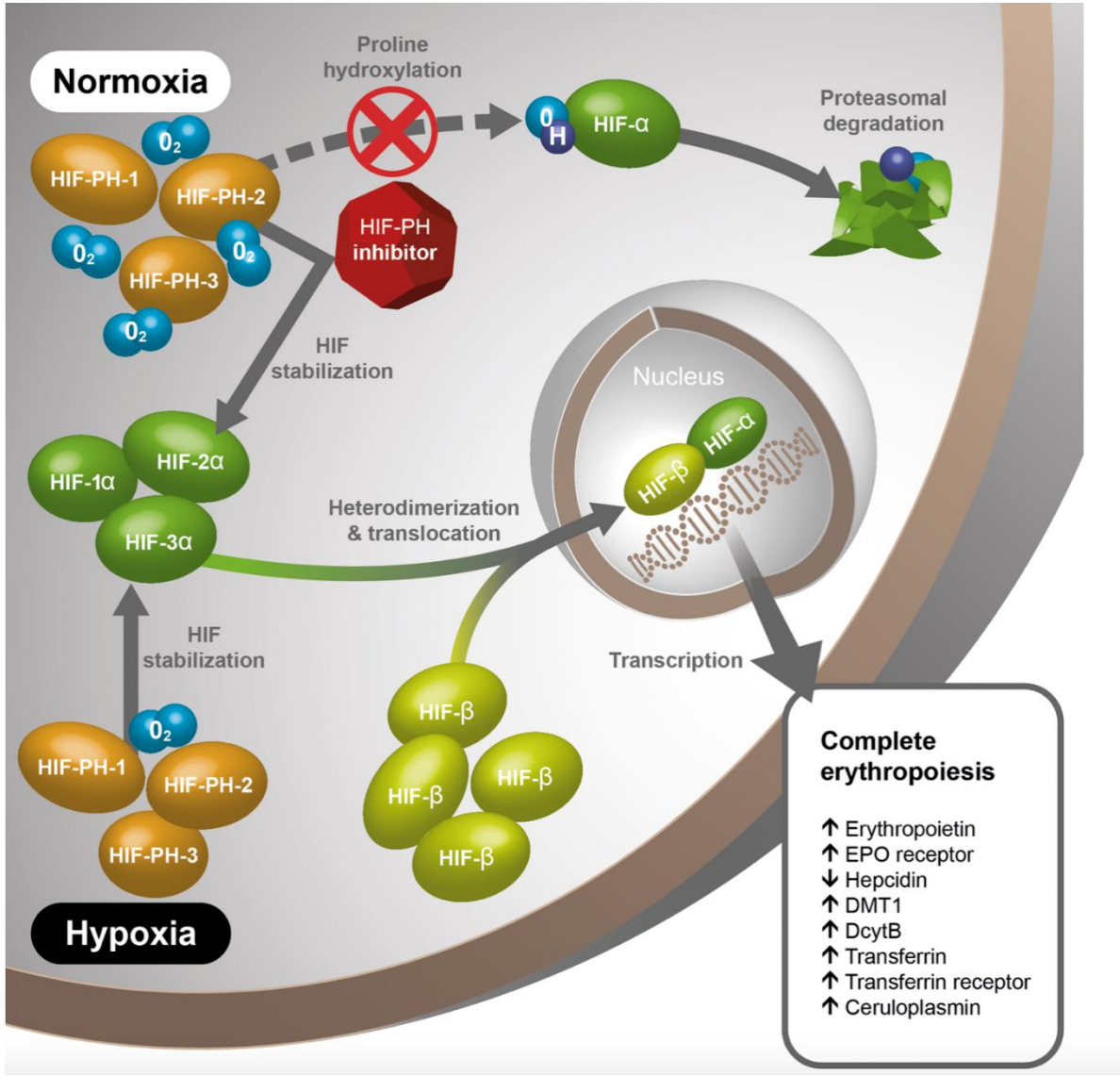
For patients with CKD on dialysis:

- Initiate ESA treatment when the hemoglobin level is less than 10 g/dL
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.
- When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly.
- For patients who do not respond adequately over a 12-week escalation period, increasing the ESA dose further is unlikely to improve response and may increase risks.

Innovation: New drugs to treat anemia of chronic kidney disease

HIF prolyl hydroxylase inhibitors

- Stabilize the HIF complex
- Stimulate endogenous EPO production
- Orally administered



Gupta N and Wish JB. Am J Kidney Dis 2017; 69: 815-826

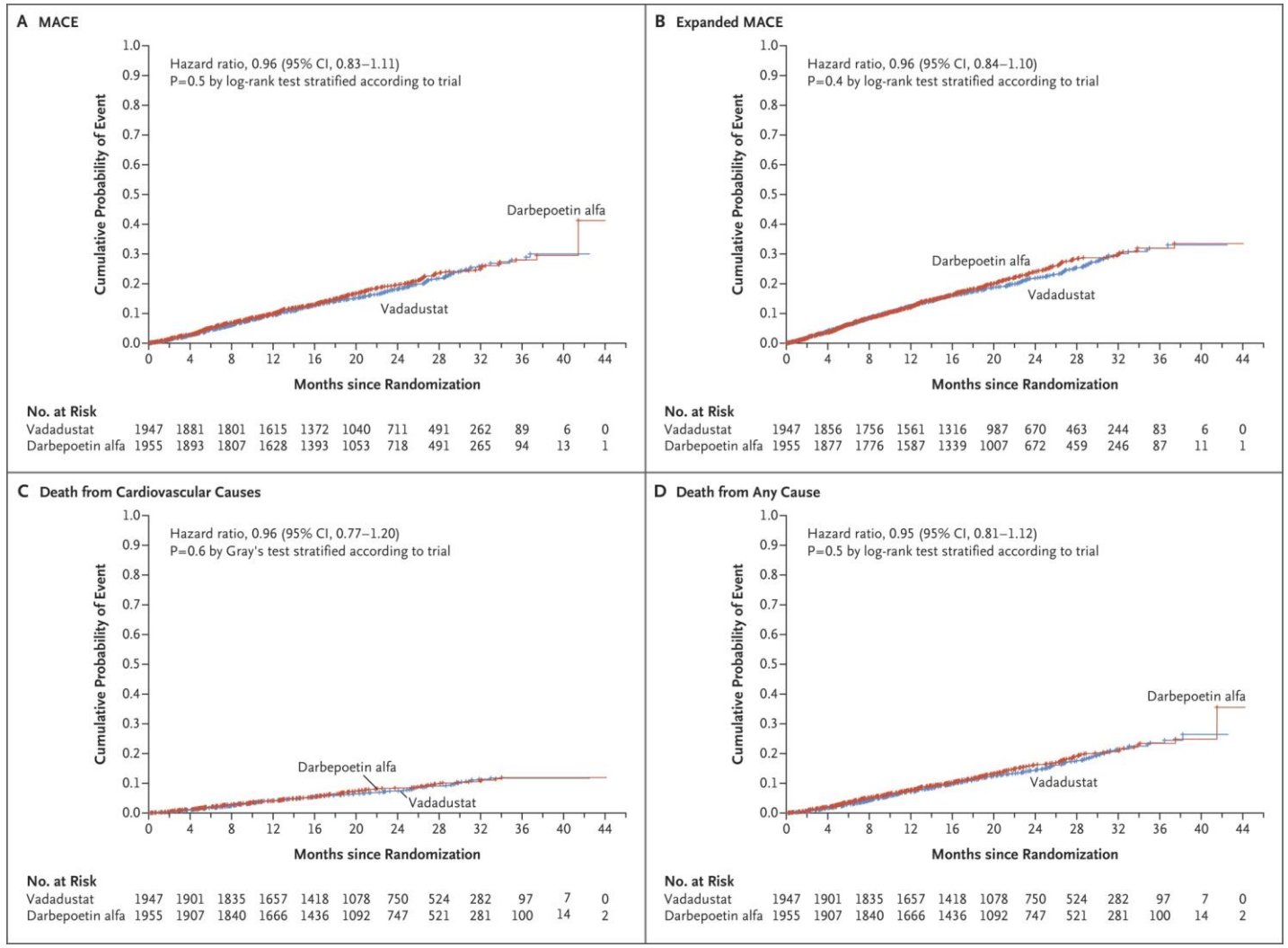
HIF-PH Inhibitors Under Development

Drug	Dosing Frequency
Roxadustat	3x/week
Vadadustat	Daily
Daprodustat	Daily
Molidustat	Daily

Why look for alternatives to erythropoietin?

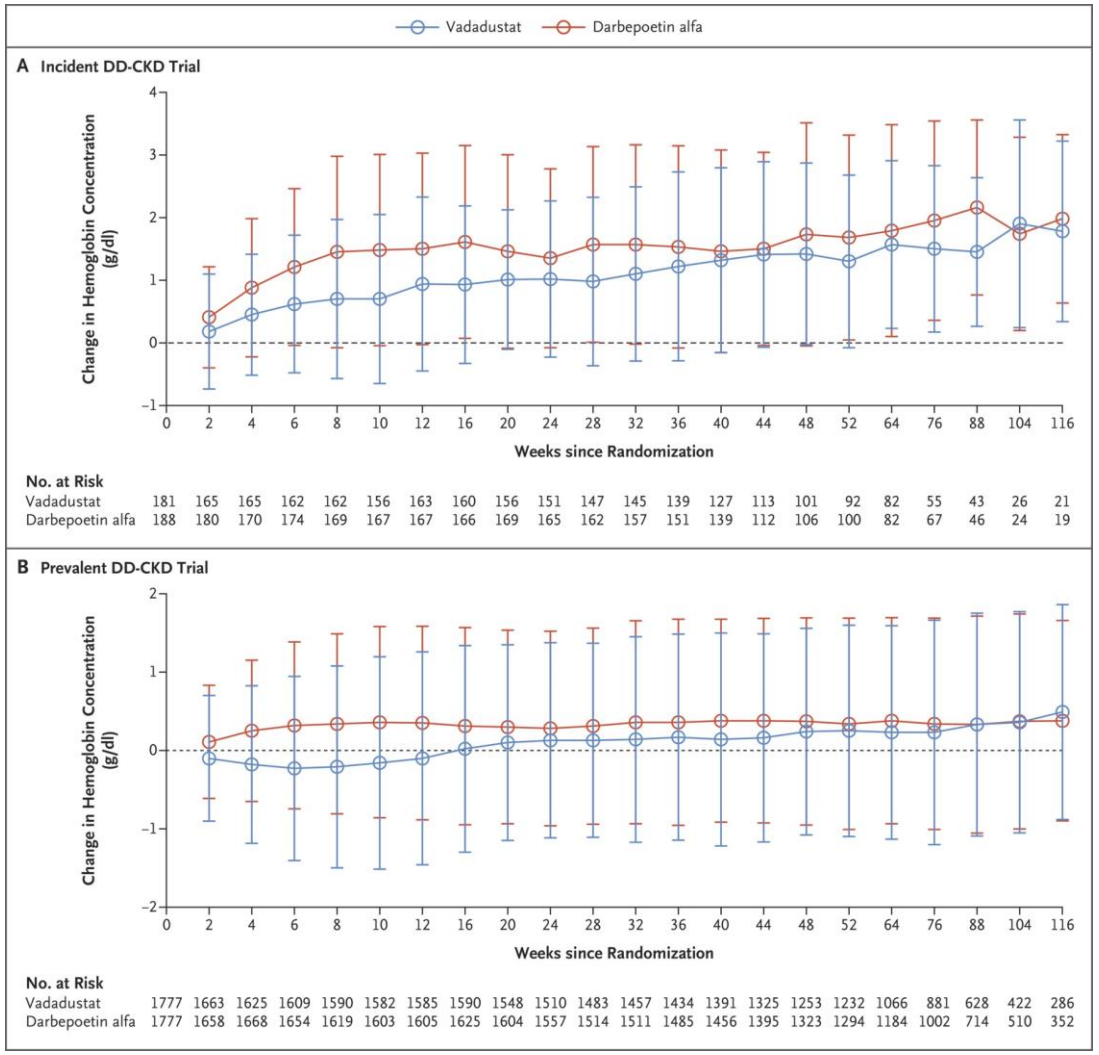
- Cost
- Intravenous or subcutaneous route of administration
- Adverse cardiovascular events
  - CHOIR study: erythropoietin: more CHF in high-hemoglobin group
  - TREAT study: diabetic subjects; more strokes in high hemoglobin group

Cardiovascular Outcomes with Vadadustat



Eckardt K et al N Engl J Med 2021;384:1601-1612

Changes in Hemoglobin with Vadadusat



Eckardt K et al N Engl J Med 2021;384:1601-1612

Vadadustat receives approval for treatment of anemia in ESRD

- FDA approved vadadustat for treatment of anemia in anemia of ESRD in patients *who have been receiving maintenance dialysis for at least three months*
- Currently the only HIF-PH inhibitor available in the United States

MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- Screen patients at high risk for kidney disease
- Albuminuria is as important as GFR in diagnosing CKD
- Nefecon, sparsentan, and iptacopan are newly approved therapies to treat IgA nephropathy based upon proteinuria outcomes
- Iron deficiency is common in CKD and should be corrected before starting an ESA.
- Vadadustat is the only HIF-PH inhibitor available in the US and only for patients on dialysis for at least 3 months.

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