



Mass General Brigham

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

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Disclosures

None



Objectives

- To highlight recent treatment innovations in chronic kidney disease
- To review recent controversies in chronic kidney disease
- To understand innovative strategies to eliminate disparities in kidney health



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

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: 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



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 > Recommendation Topics > Recommendation: Chronic Kidney Disease: Screening

Chronic Kidney Disease: Screening

An Update for This Topic is In Progress

LAST UPDATED: Jul 07, 2023



The Task Force keeps recommendations as current as possible by routinely updating existing recommendations and developing new recommendations. A multistep process is followed for each recommendation. The Task Force uses gold standard methods to review the evidence and is transparent at each step of the recommendation development process.

ISN-KDIGO Early Identification and Intervention in Primary Care

Step 1:
Identify those at risk

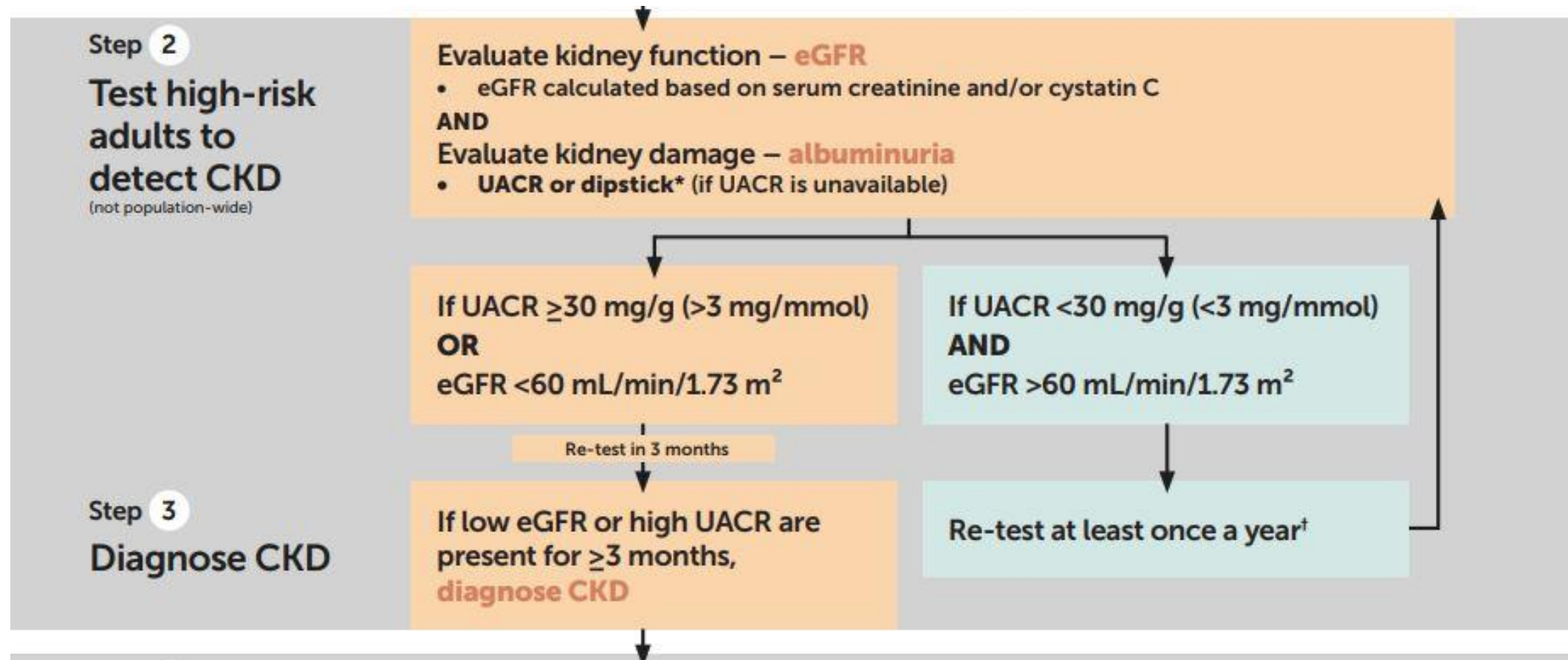
Main Clinical Risk Factors for CKD:

- 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

ISN-KDIGO Early Identification and Intervention in Primary Care



International Society of Nephrology



ISN-KDIGO Early Identification and Intervention in Primary Care: Step 4, Stratify and Treat

Range	A1 <30 mg/g	A2 30-299 mg/g	A3 >300 mg/g
≥90 G1	Monitor	Treat	Treat and Consult
60-89 G2	Monitor	Treat	Treat and Consult
45-59 G3a	Treat	Treat	Treat and Consult
30-44 G3b	Treat	Treat and Consult	Treat and Consult
15-29 G4	Treat and Consult	Treat and Consult	Treat and Consult
< 15 G5	Treat and Consult	Treat and Consult	Treat and Consult



Treat to slow CKD progression, reduce mortality risk, and manage co-morbidities

- Lifestyle modification
 - Smoking cessation
 - Regular exercise
 - Well balanced diet
 - Avoiding excessive protein intake
 - Avoiding processed foods
 - Limiting sodium intake to < 2 grams/day
- Pharmacologic therapies

Monitor for CKD Progression and Comorbidities

CKD Progression and comorbidities	What to monitor
CKD Monitoring	eGFR, UACR, urinalysis (urine sediment)
CVD and Dyslipidemia	Blood pressure, cardiovascular risk stratification, lipid status
Diabetes	Blood glucose, hemoglobin A1C

Additional considerations for nephrology consultation

- Unexplained, progressive decline in eGFR ≥ 5 mL/min/1.73 m² 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.)



Blood pressure control guidelines (KDIGO)

- Target systolic blood pressure of < 120 mm Hg when tolerated
- Start ACE-I or ARB in individuals with hypertension, CKD, and moderate to severe albuminuria with or without diabetes
- Avoid any combination of ACE-I, ARB, and direct renin inhibitor therapy in patients with CKD, with or without diabetes



Case 2

A 57-year-old woman with type 2 diabetes, hypertension, PAD, and CKD presents for follow-up.

Past Medical History

- Diabetes mellitus type 2
- Chronic kidney disease
- Hypertension
- Peripheral arterial disease



Case 2-Medications and Labs

- Amlodipine 10 mg daily
- Lisinopril 20 mg daily
- Chlorthalidone 25 mg daily
- Metformin 500 mg bid
- K^+ 4.8 mEq/L
- Bicarbonate 23 mmol/L
- Creatinine 1.2 mg/dL
- Hemoglobin A1C 8.0%
- Urine albumin/creatinine 400 mg/g



Case 2: Question

What additional medication(s) may be beneficial in improving her cardiorenal outcomes?

- A. Glipizide
- B. Saxtagliptin
- C. Canagliflozin
- D. Insulin



Case 2: Answer

The correct answer is C.

The only one of the medications listed with proven benefits in retarding progression of chronic kidney disease is canagliflozin.



Diabetes and Kidney Disease

Treatment of diabetic kidney disease has focused on

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

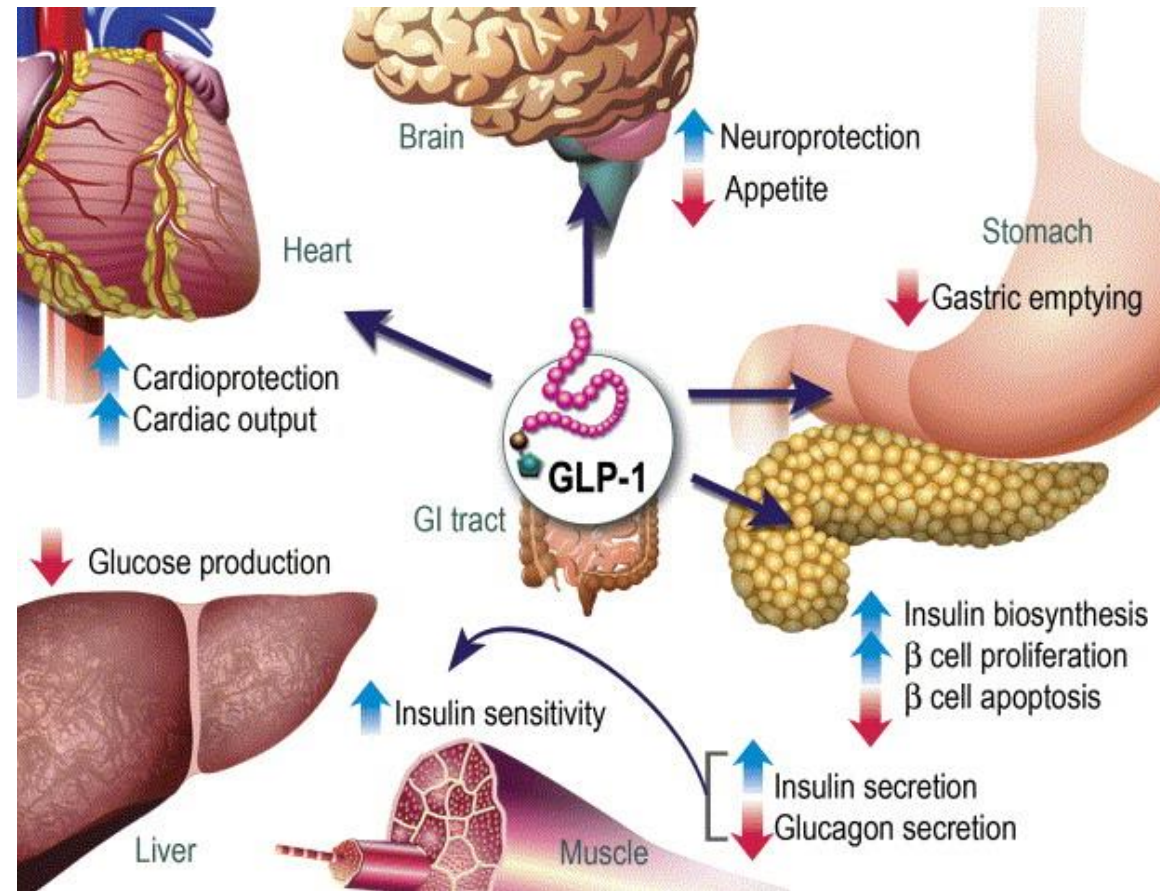


Innovation: Drug class matters

- Despite widespread use of RAS inhibitors, diabetes remains the leading cause of ESRD in the United States
- Some glucose-lowering agents appear to have glucose-independent effects on diabetic nephropathy and its progression
 - GLP-1 analogues
 - Sodium-glucose cotransporter-2 (SGLT-2) inhibitors



GLP-1 Agonists: Dulaglutide, Semaglutide and others



Drucker DJ Cell Metab 2006

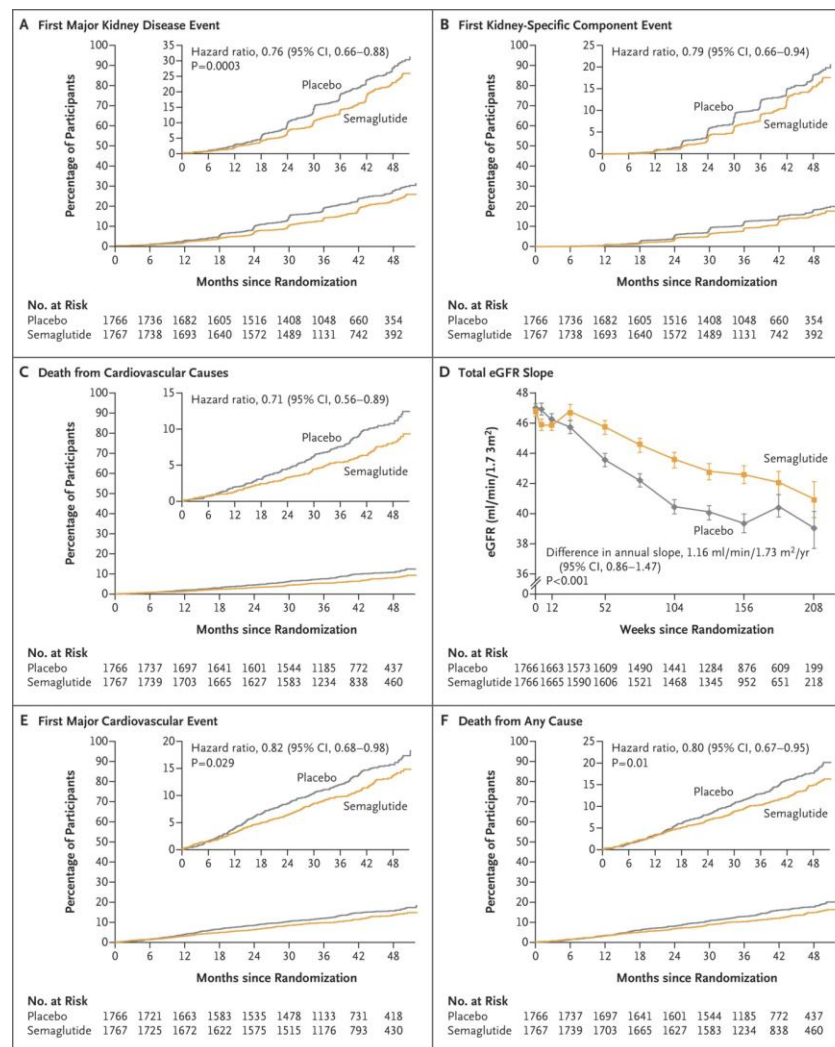
The FLOW Trial

- In patients with type 2 diabetes and chronic kidney disease, weekly semaglutide significantly reduced risks of major kidney events, cardiovascular events, and death from any cause while slowing loss of kidney function.



Primary and Secondary Outcomes in FLOW

24% reduction
in risk of first
major kidney
disease event



SGLT-2 Inhibitors

- Sodium-glucose transporter blockers
- Block the reabsorption of glucose at the proximal tubule
- Effective in individuals across stages of CKD
- Lower weight and blood pressure (diuretic effect)
- Low risk of hypoglycemia



CREDENCE: A game changer

Randomized trial of canagliflozin 100 mg daily versus placebo
4401 patients randomized

Inclusion criteria:

- Albumin/creatinine > 300 to 5000
- eGFR 30 to < 90
- Treatment with RAS blockade

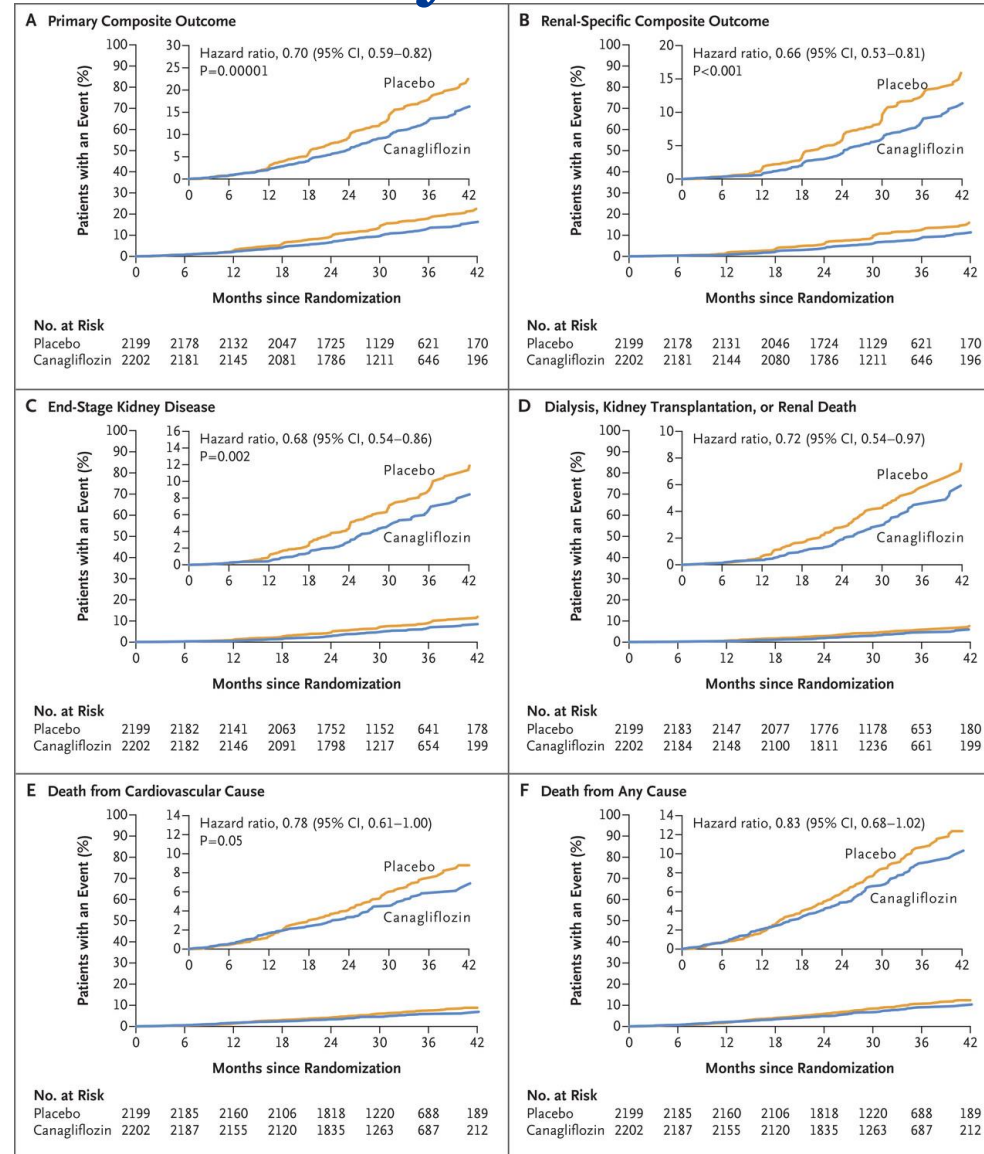
Primary outcomes:

- Composite of ESRD and
- Doubling of the serum creatinine
- Death from renal or cardiovascular causes

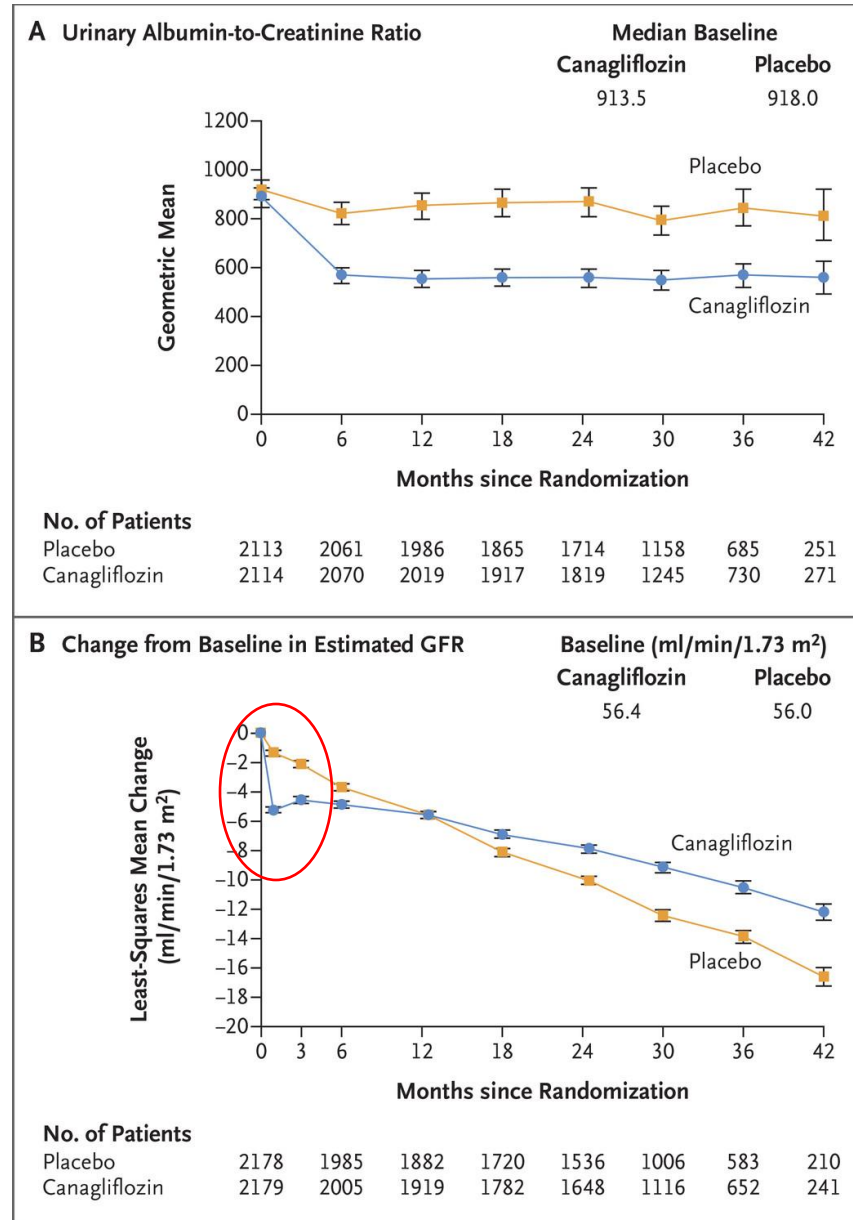


Primary Composite, Renal, and Mortality Outcomes

30% reduction in risk of primary outcome



Effects on Albuminuria and Estimated GFR



Note the acute drop in GFR

SGLT-2 inhibitors in non-diabetic kidney disease



Newer trials have shown SGLT-2 inhibitors to retard progression in *non-diabetic* kidney disease

- DAPA-CKD
- EMPA-KIDNEY



DAPA-CKD

- Randomized trial of dapagliflozin 10 mg daily versus placebo
- 4304 subjects *with or without diabetes* randomized
- Inclusion criteria:
 - Albumin/creatinine > 200 to 5000
 - eGFR 25-75 mL/min/1.73 m²
 - Treatment with RAS blockade
- Primary outcomes:
 - Composite of sustained decline in eGFR of at least 50% and
 - End-stage kidney disease and
 - Death from renal or cardiovascular causes



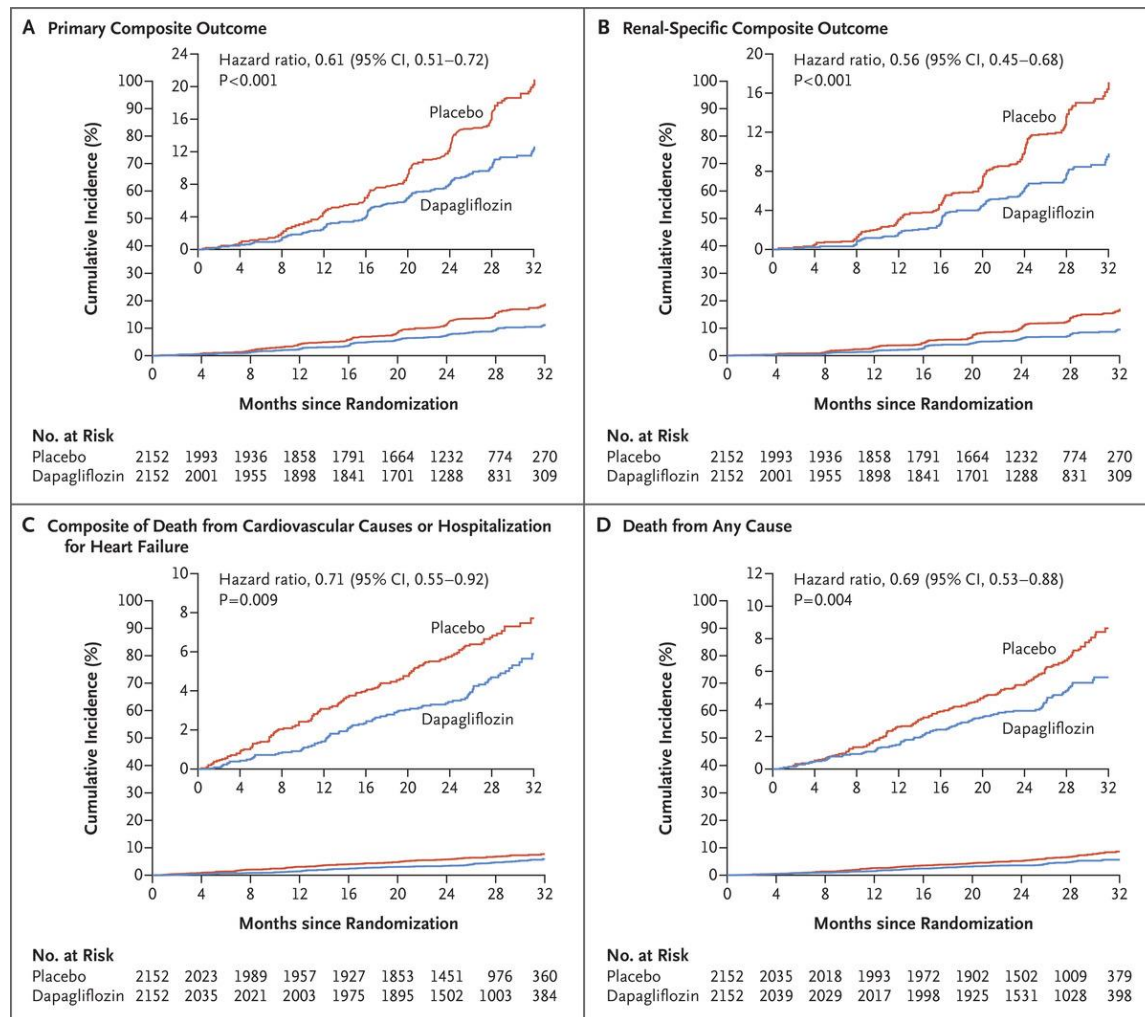
Demographic and Clinical Characteristics of the Participants at Baseline

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

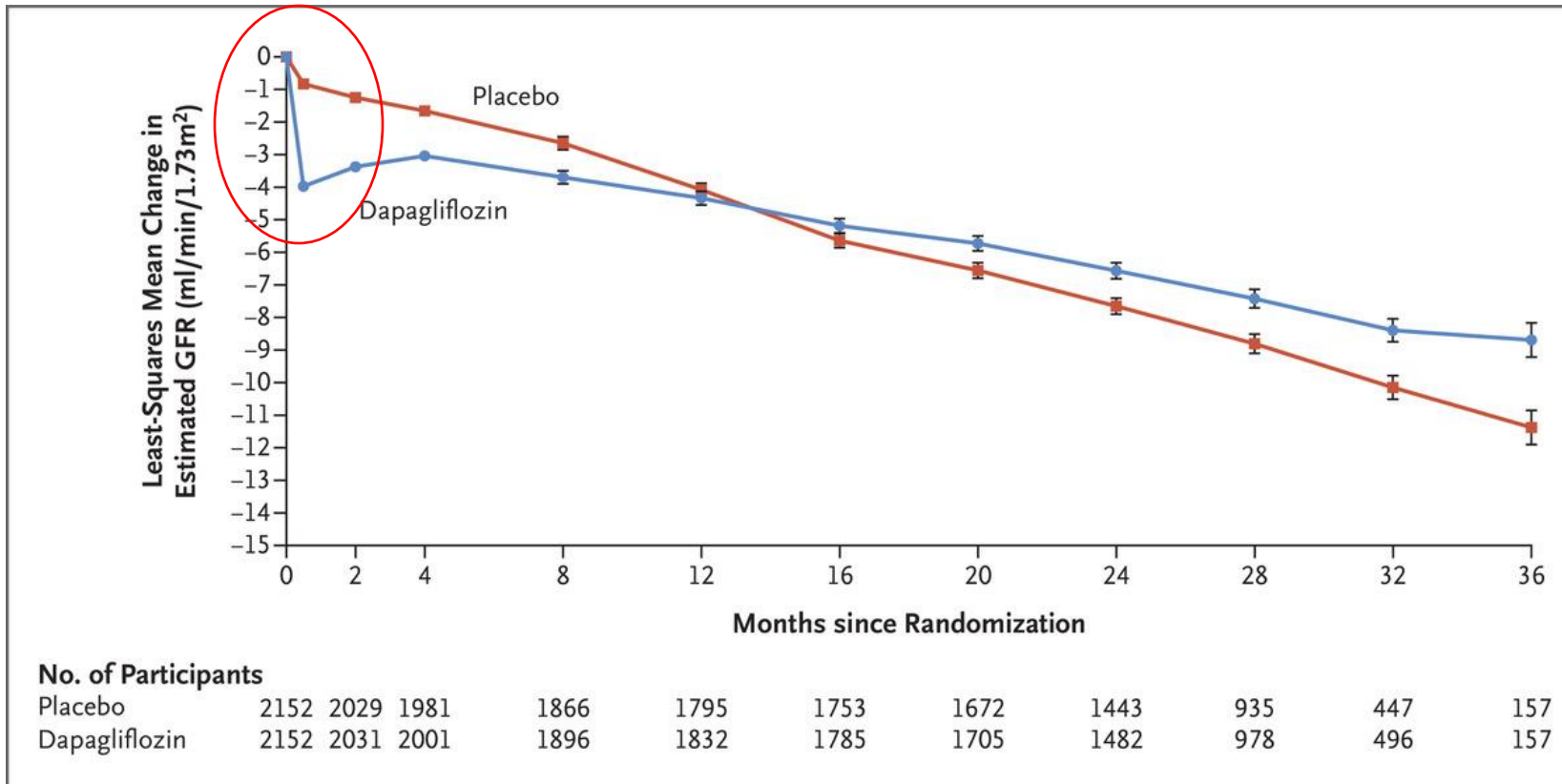
Characteristic	Dapagliflozin (N = 2152)	Placebo (N = 2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m ²	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m ²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m ²	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m ²	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m ²	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)



DAPA-CKD Outcomes



Change in GFR from Baseline



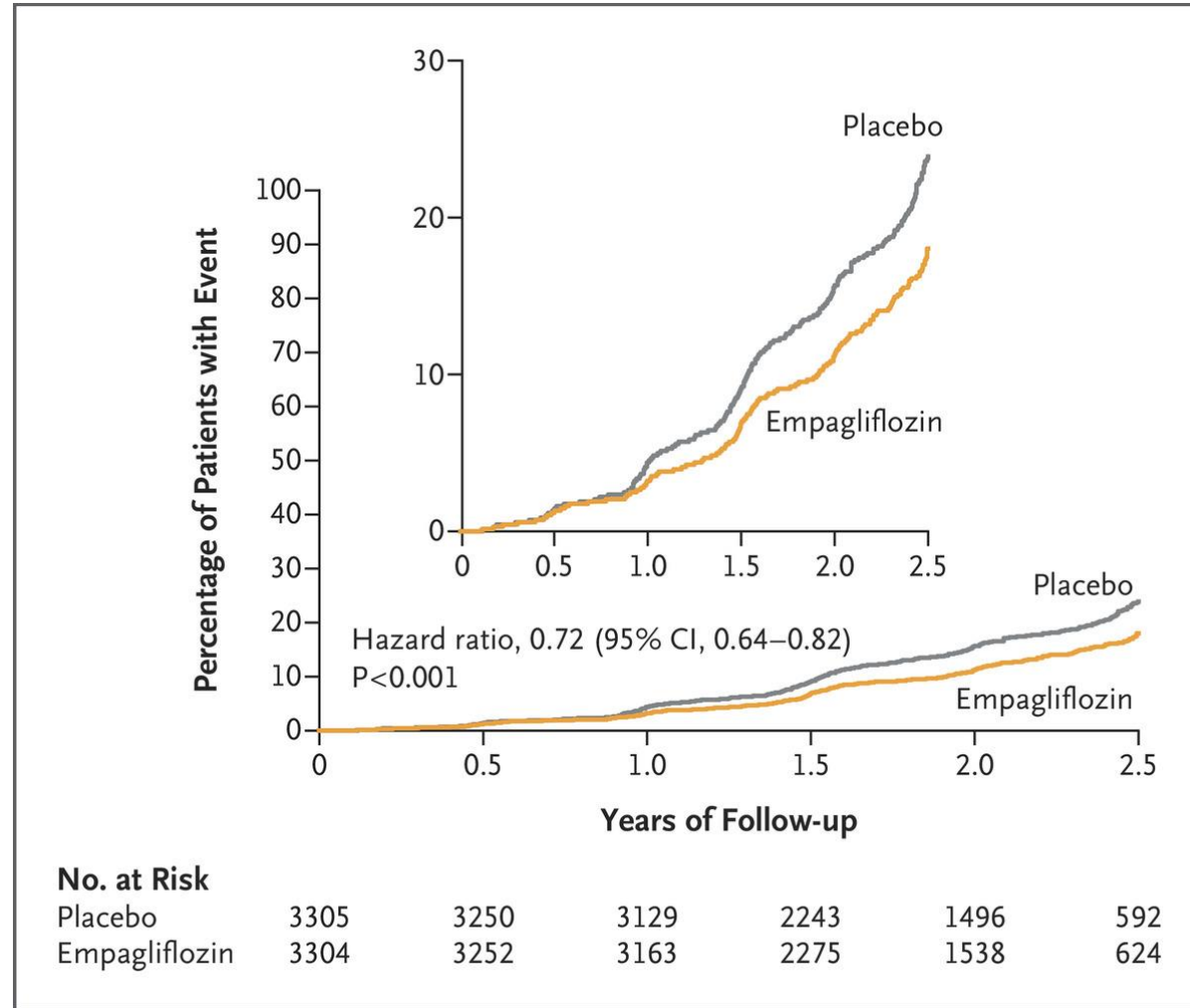
Acute drop in
GFR

EMPA-KIDNEY

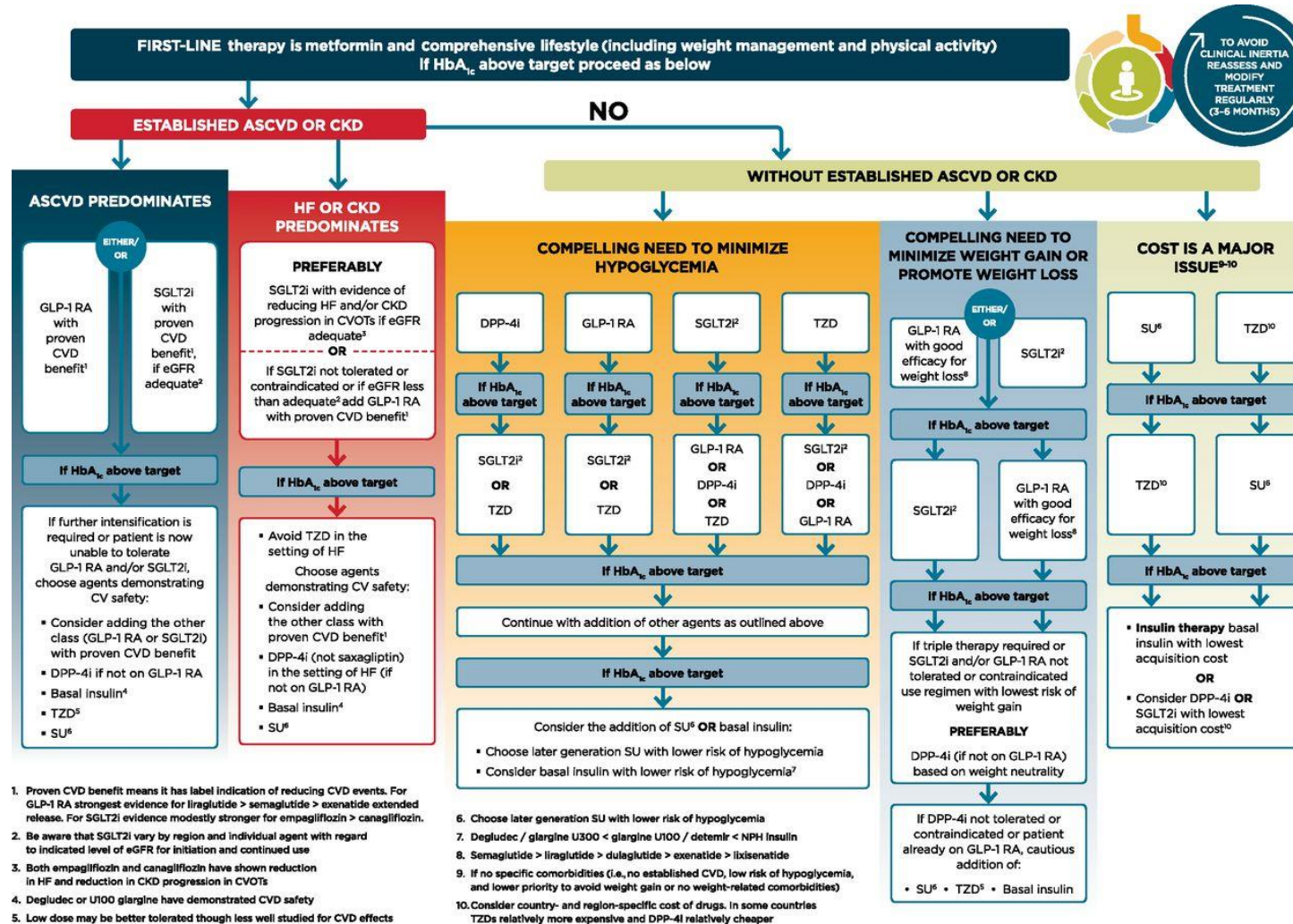
- Randomized trial of empagliflozin 10 mg daily versus placebo
- 6609 subjects *with or without diabetes* randomized
- Inclusion criteria:
 - Albumin/creatinine > 200 to 5000
 - eGFR $\geq 20 < 45$ mL/min/1.73 m² regardless of level of albuminuria
 - eGFR $\geq 45 < 90$ mL/min/1.73 m² with UACR at least 200
 - Treatment with RAS blockade
- Primary outcomes:
 - Progression of kidney disease
 - Death from cardiovascular causes



EMPA-KIDNEY Outcomes



Glucose-lowering medication in type 2 diabetes: overall approach



Mineralocorticoid receptor blockade

- Among patients with type 2 diabetes and urine albumin/creatinine 30-300 mg/g, eGFR 25-60 and diabetic retinopathy, *or* urine albumin/creatinine 300-5000 mg/g and eGFR 25-75
 - Finerenone lowered risk of CKD progression and cardiovascular events compared to placebo (FIDELIO-DKD)
- Among patients with type 2 diabetes and urine albumin/creatinine 30-300 mg/g and an eGFR 25-90 mL/min or a urine albumin/creatinine of 300-5000 mg/g and an eGFR ≥ 60 mL/min:
 - Finerenone improved cardiovascular outcomes compared to placebo (FIGARO-DKD)



Optimal therapies for patients with (type 2) diabetic kidney disease

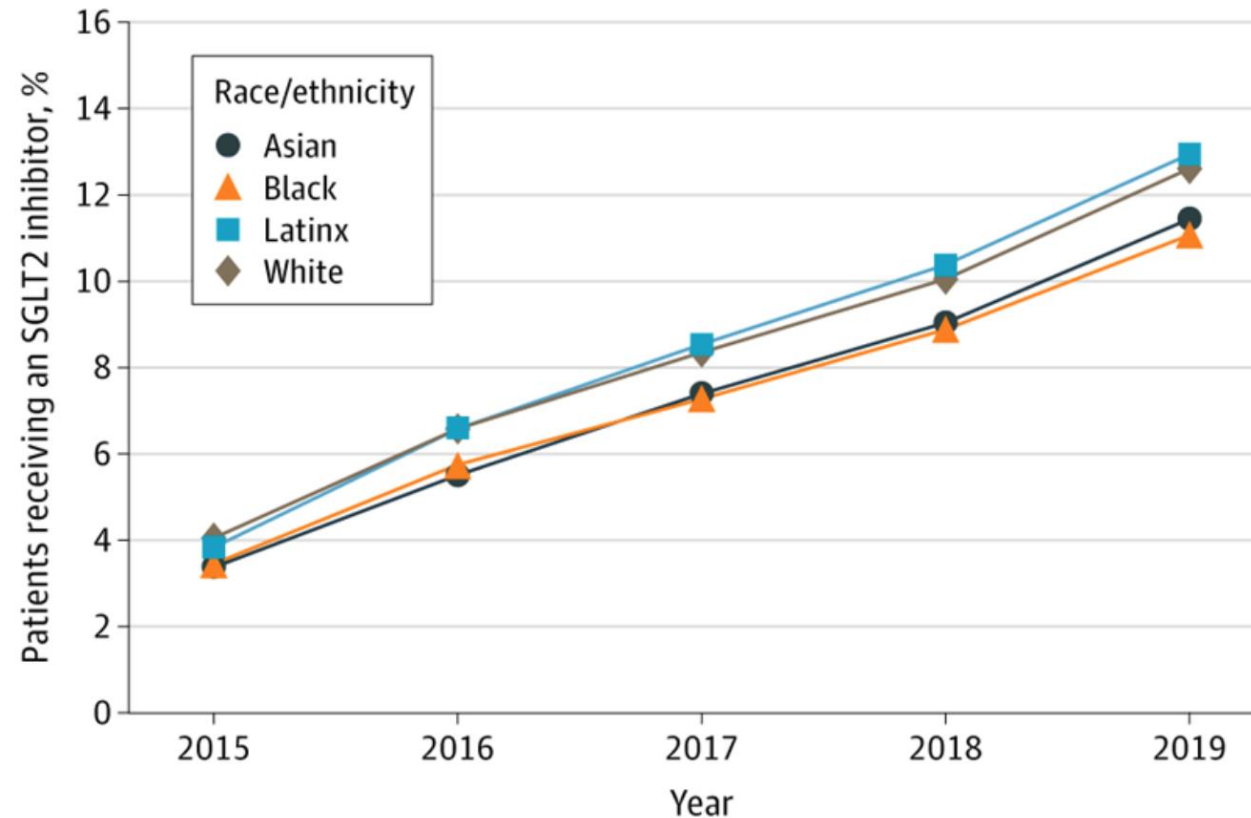
- ACE-I/ARB
- SGLT-2 Inhibitors
- GLP-1 agonists
- Finerenone
- Loop or thiazide diuretics
- Statins
- β -blockers



Are all patients offered
advanced therapies at
the same rates?



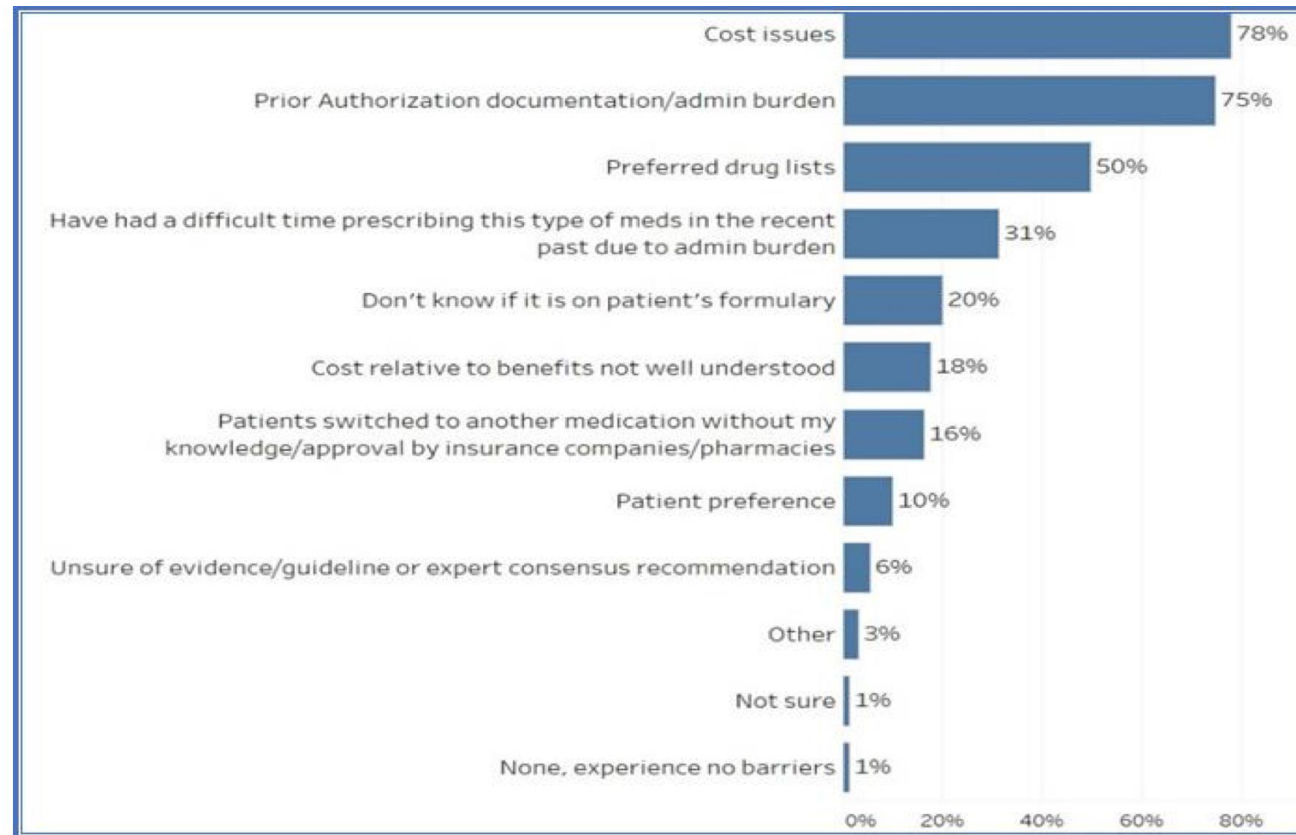
Racial/ethnic differences in use of SGLT-2 inhibitors among patients with diabetes in the United States



Eberly LA et al. JAMA Network Open 2021; 4(4):e216139. doi:10.1001/jamanetworkopen.2021.6139



Barriers to prescribing newest evidence based cardiovascular care



Association of Black Cardiologists, 2019



Case 3

A 59-year-old woman with ESKD secondary to diabetes mellitus, on hemodialysis for 13 years, presents to her primary care provider with complaints of itching.



Case 3-Medications

- Sevelamer carbonate 1600 mg po qAC
- Hydroxyzine 10 mg po qhs
- Gabapentin 300 mg po three times weekly after dialysis
- Calcitriol 0.5 ug three times weekly
- Amlodipine 10 mg po daily
- Erythropoietin 6000 units IV three times weekly



Case 3 Labs

- spKt/V 1.4 (indicating adequate dialysis)
- Calcium 8.5 mg/dL
- Phosphorous 5.1 mg/dL
- PTH 251 pg/mL
- Hemoglobin 10.9 g/dL



Case 3: Physical Examination



Case 3: Question

Which of the following is the most likely diagnosis of her skin lesion?

- A. Calciophylaxis
- B. Shingles
- C. Acquired perforating dermatosis
- D. Calcinosis cutis



Case 3: Question Answer

The correct answer is C.

This patient has a crater-shaped nodular eruption occurring in the setting of diabetes mellitus and ESKD. The most likely diagnosis is therefore acquired perforating dermatosis.



Pruritus and skin disorders in CKD

- Pruritus and other skin disorders are common in chronic kidney disease
- Minor annoyance for some patients but may be debilitating in others
- Preferred nomenclature: “CKD-aP” not “uremic pruritus”
- Co-management with primary care is critical for patients with ESKD
 - Not possible to do a full skin examination in the dialysis clinic



Risk factors for CKD-aP

- Inadequate dialysis
- Metabolic derangements
 - Hyperphosphatemia
 - Hyperparathyroidism
- Malnutrition/Inflammation
 - Low serum albumin
 - High ferritin
 - High CRP
- Hepatitis B
- Hepatitis C

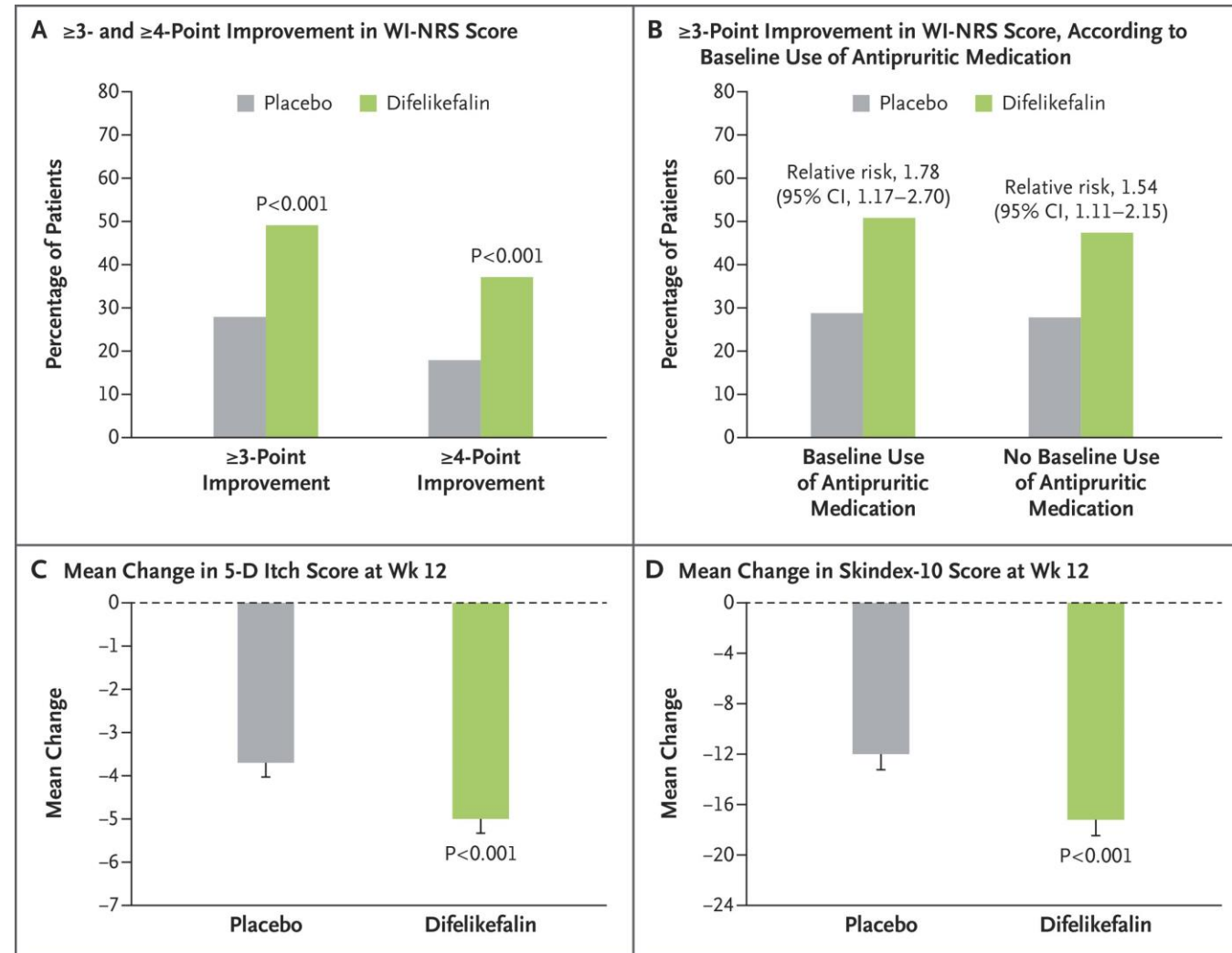


Treatments for CKD-aP

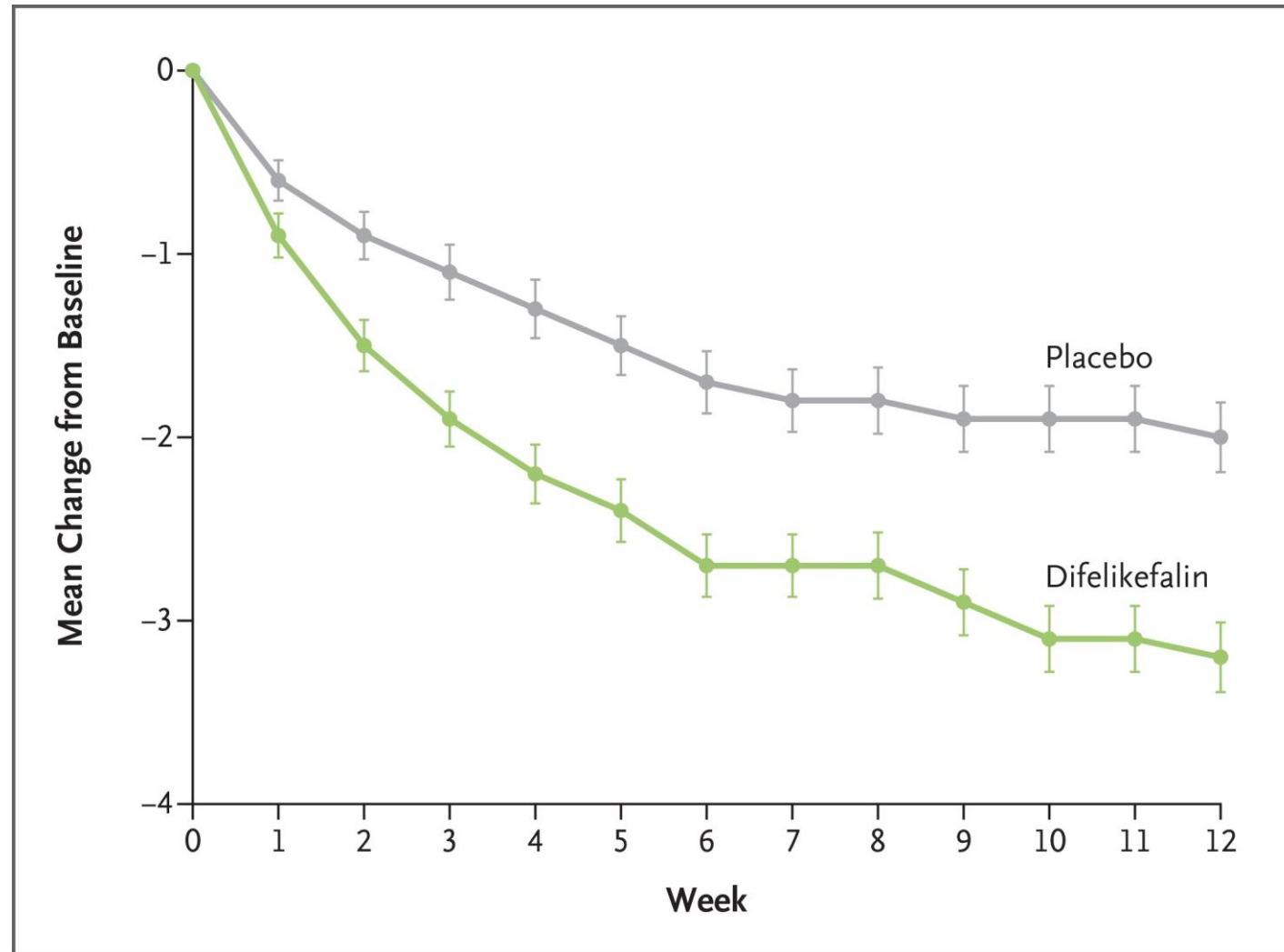
- Emollients
 - Should be applied to the wet or damp skin after bathing
- Topical analgesics
 - Pramoxine
- Antihistamines
 - Diphenhydramine
 - Hydroxyzine
 - Cetirizine
- Cromolyn sodium
- Gabapentinoids
 - Gabapentin
 - Pregabalin
- Opioid agonists and antagonists



Innovation: Treatment with Difelikefalin



Difelikefalin: Mean Change in WI-NRS Score



Fishbane S et al. N Engl J Med 2020; 382: 222-232



Acquired perforating dermatosis

- Presents with pruritic to painful nodules in a patient with known risk factors
- Primary risk factors: Diabetes mellitus and CKD
- Lesions may be precipitated or worsened by scratching
 - Treating pruritus is key in preventing the development of APD



Treatment of APD

- Adequate dialysis
- Phosphate control
- Glycemic control
- Topical therapies
 - Emollients
 - Topical or intralesional corticosteroids
 - Keratolytics
 - Salicylic acid (2-10%)
 - Urea (10-40%)
 - Topical retinoids
- Antihistamines
- Systemic retinoids
- Allopurinol
- UV phototherapy



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.

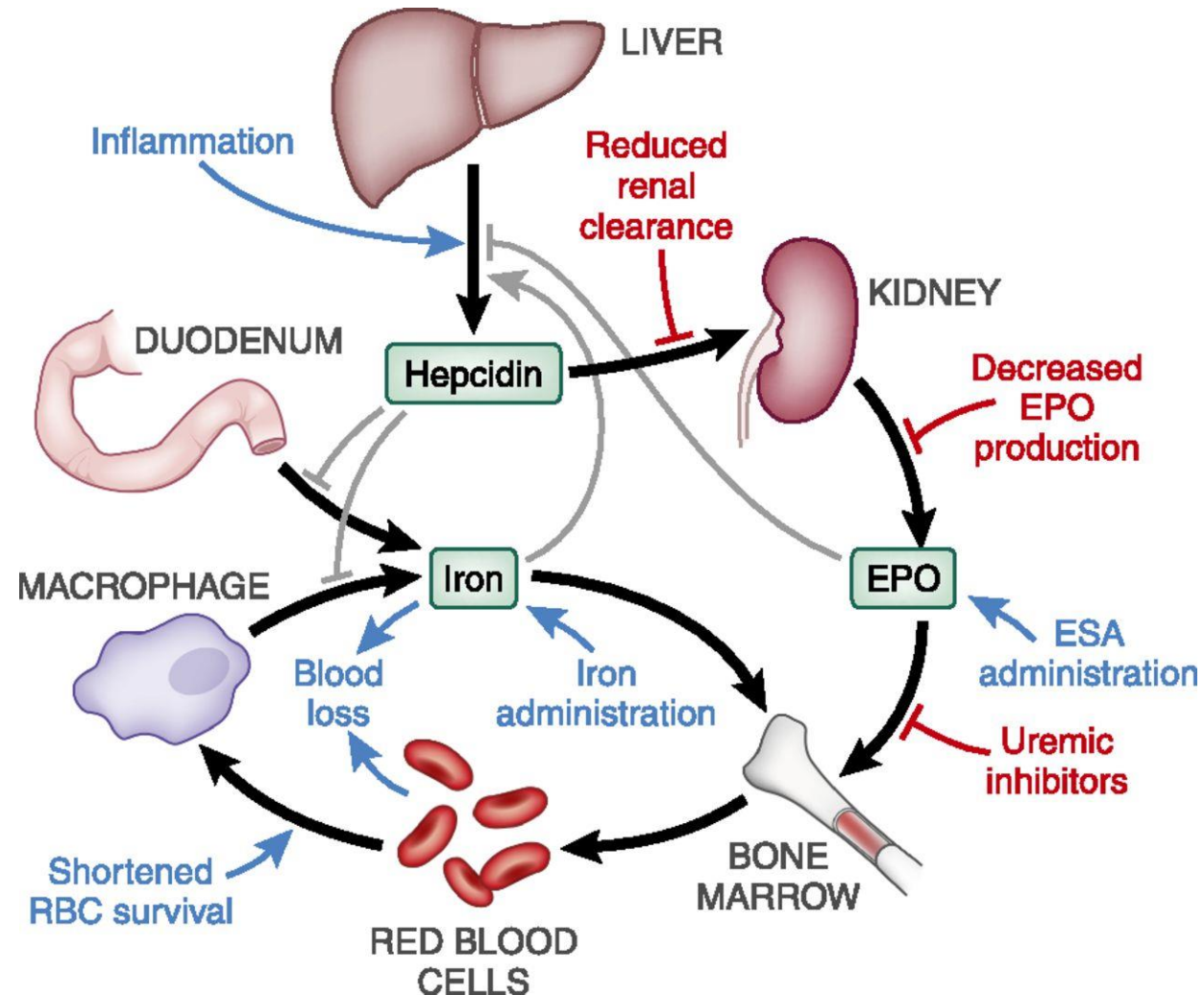


Controversy: Use of ESAs in patients with a history of cancer and recent cardiovascular events

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



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

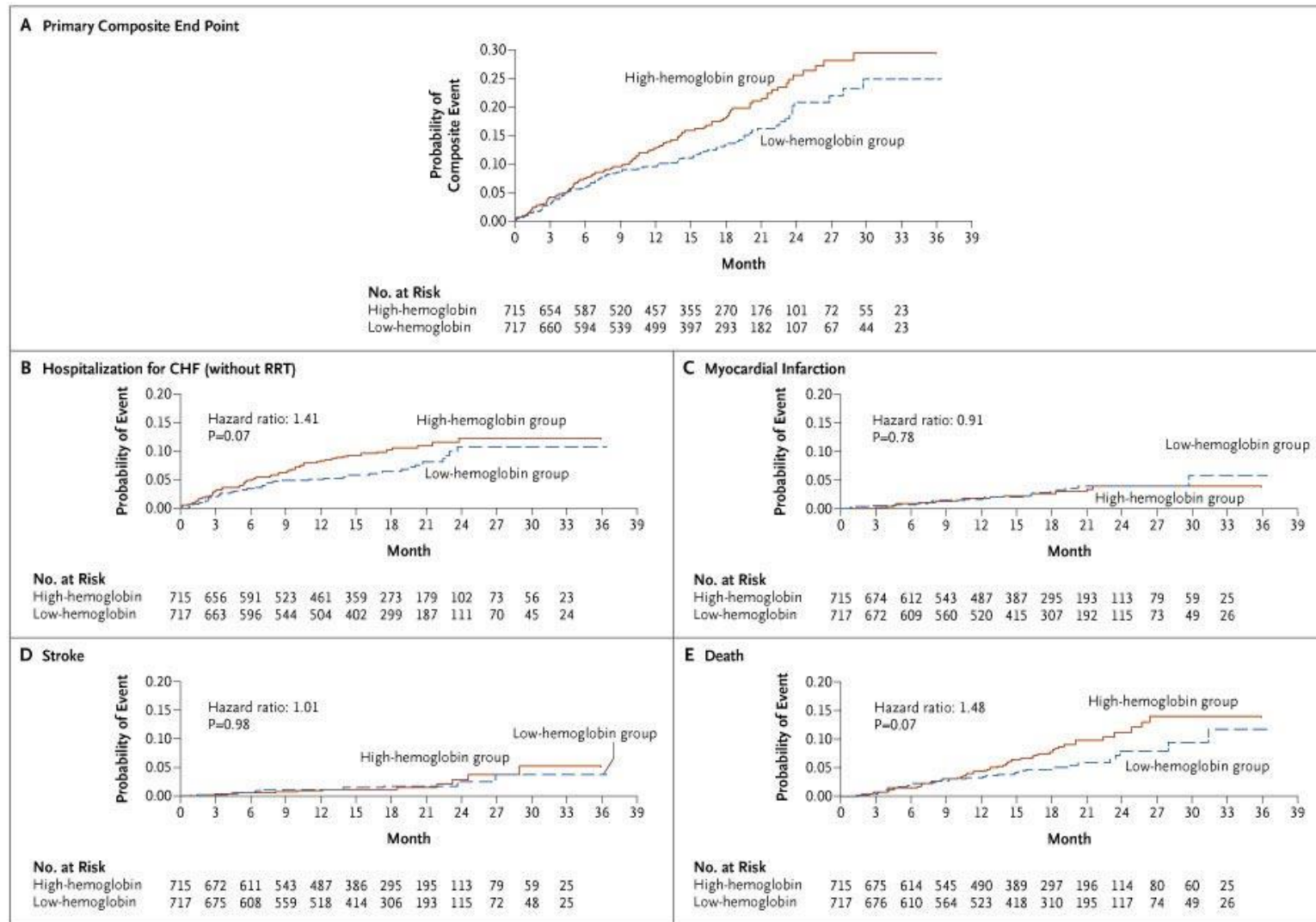


What is the evidence for an increased risk of cardiovascular events?

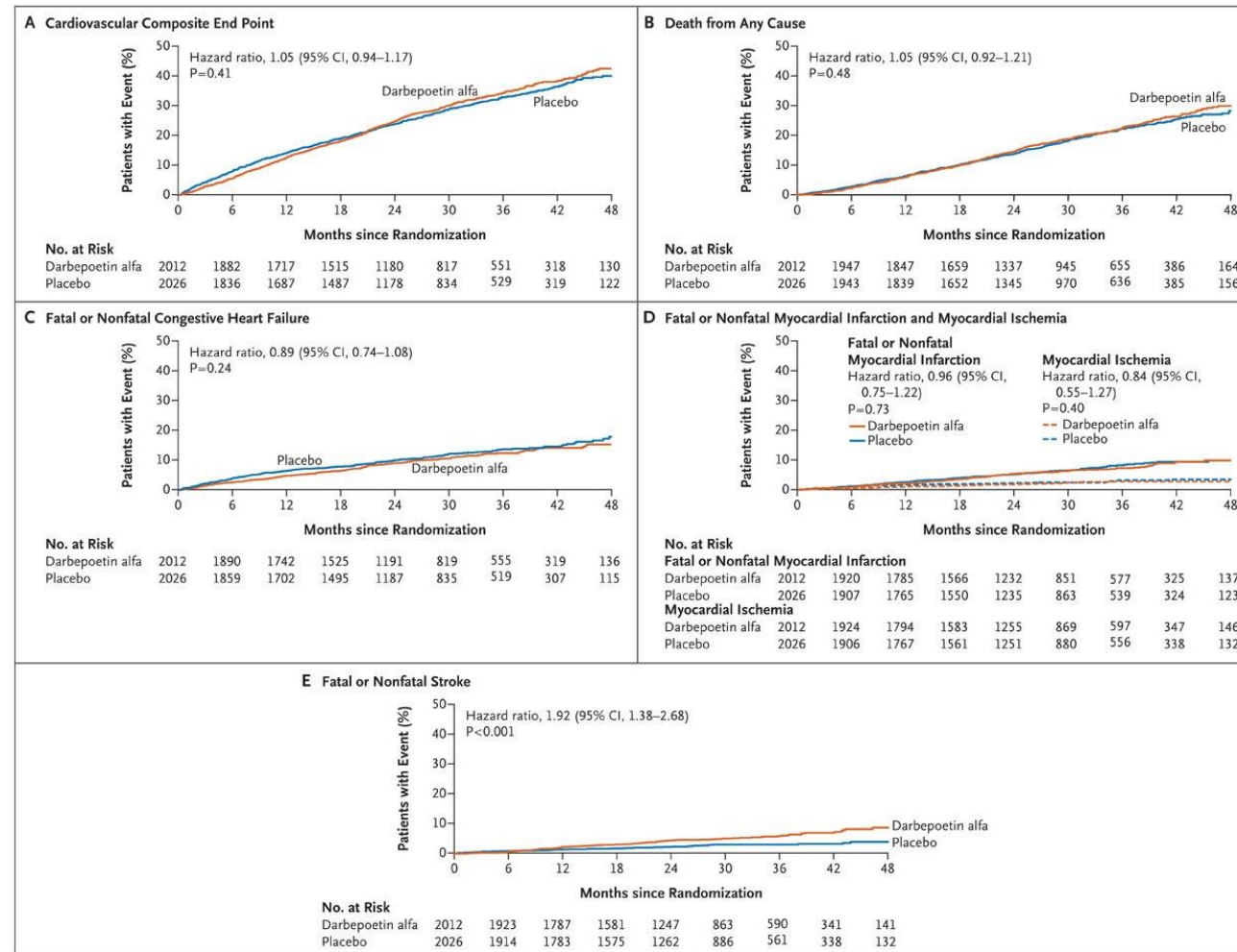
- CHOIR
 - Participants all had CKD and were randomized to two different hemoglobin targets
- TREAT
 - Participants all had CKD and diabetes and were randomized to darbepoietin versus placebo



CHOIR: Probabilities of the Primary and Secondary End Points



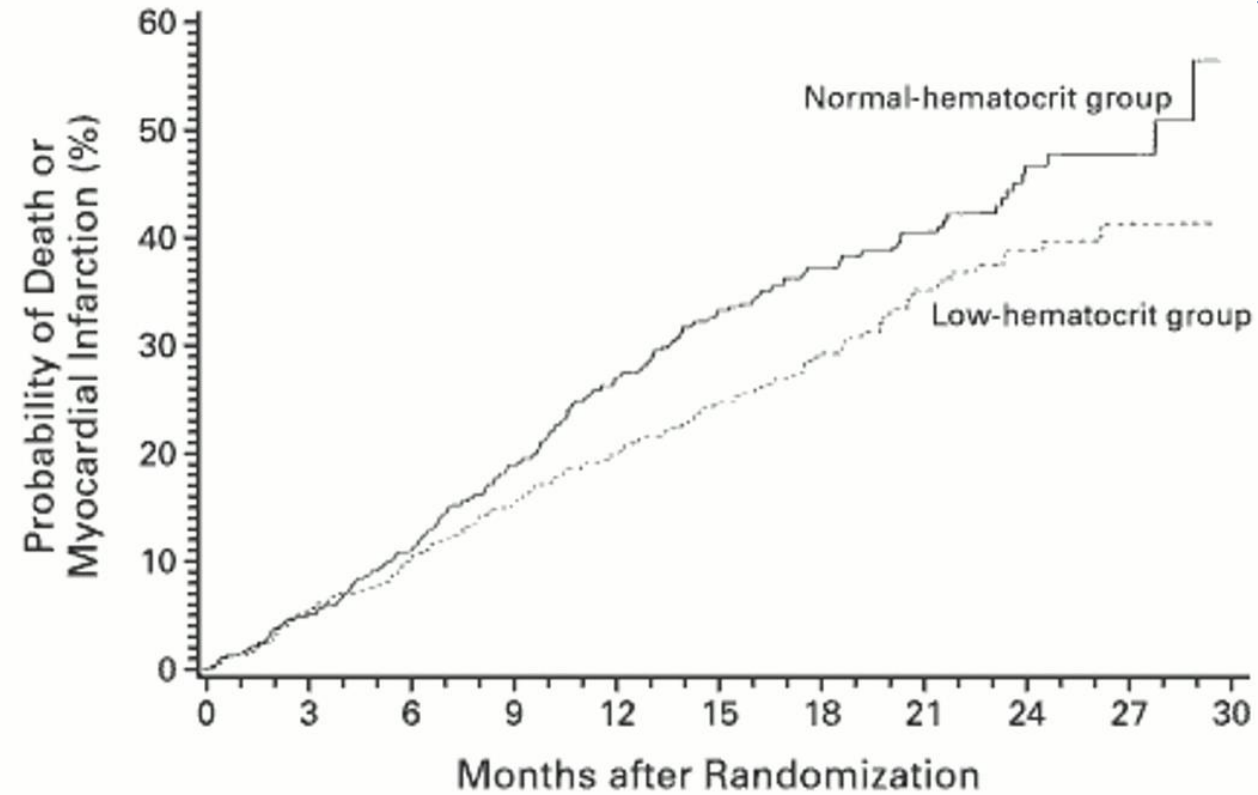
Treat: Kaplan-Meier Estimates of the Probability of the Primary and Secondary End Points (Note Panel E)



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



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.

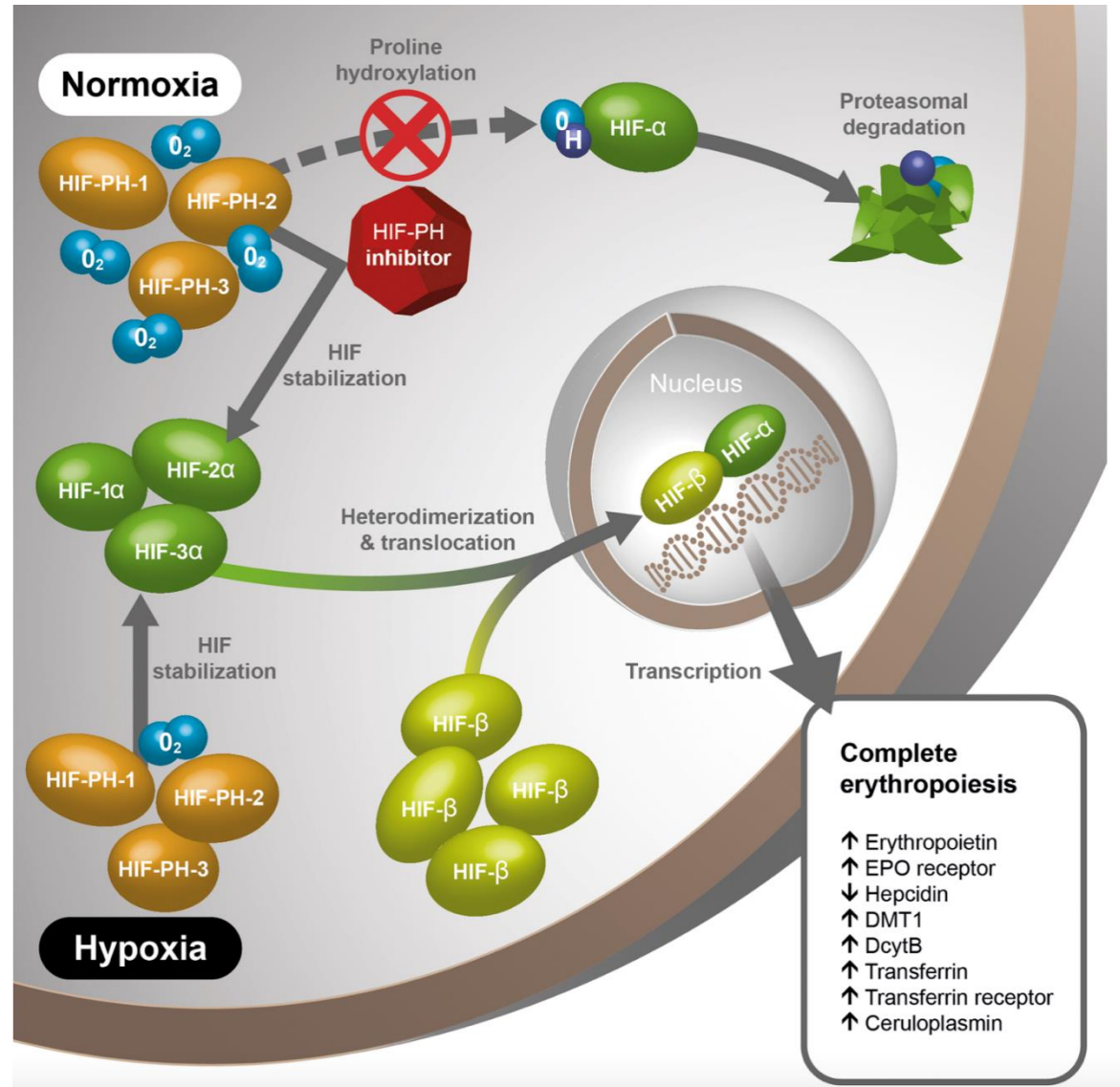


Innovation: New drugs to treat anemia of chronic kidney disease

HIF prolyl hydroxylase inhibitors

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





HIF-PH Inhibitors Under Development

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

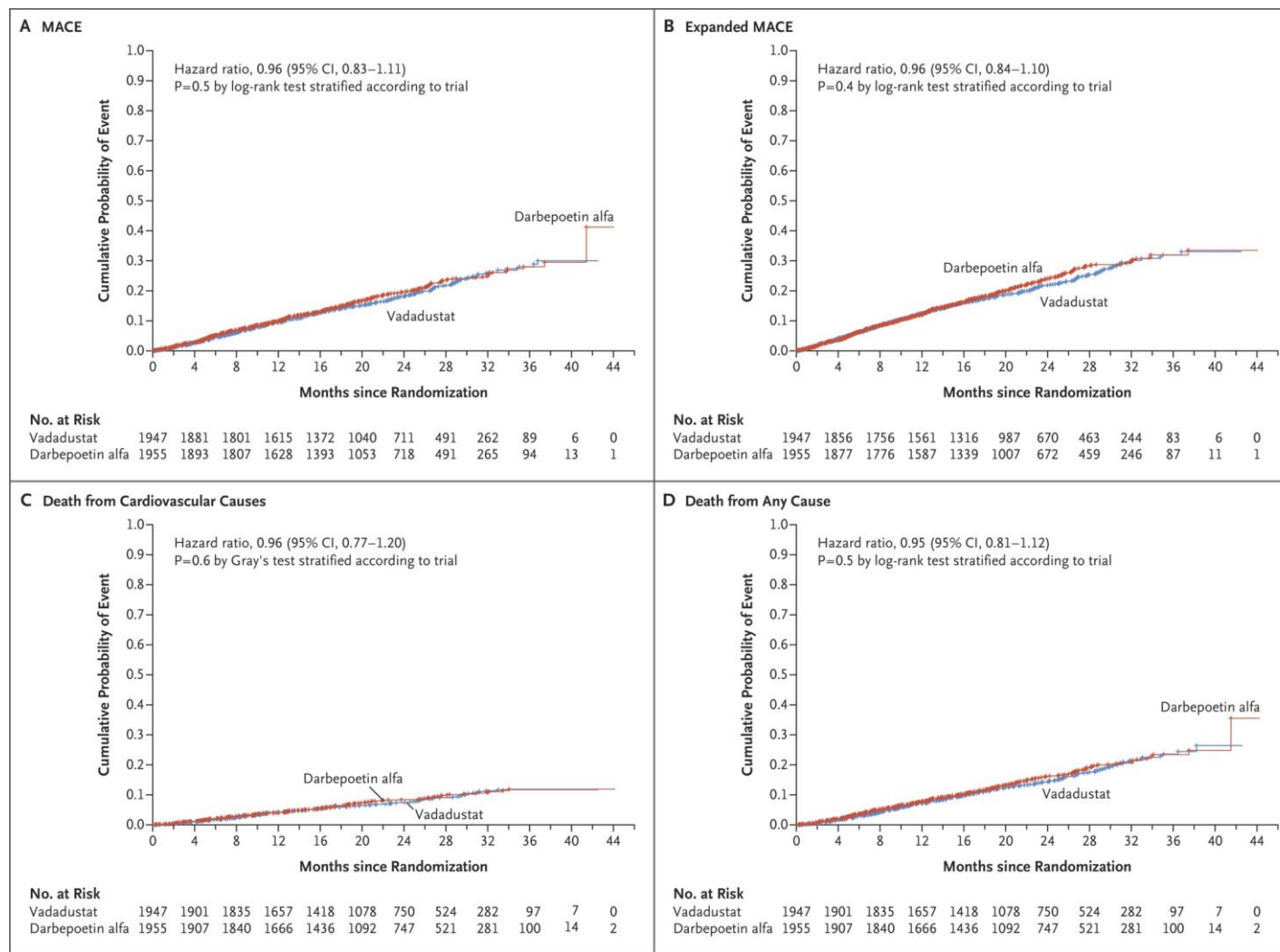


Why look for alternatives to erythropoietin?

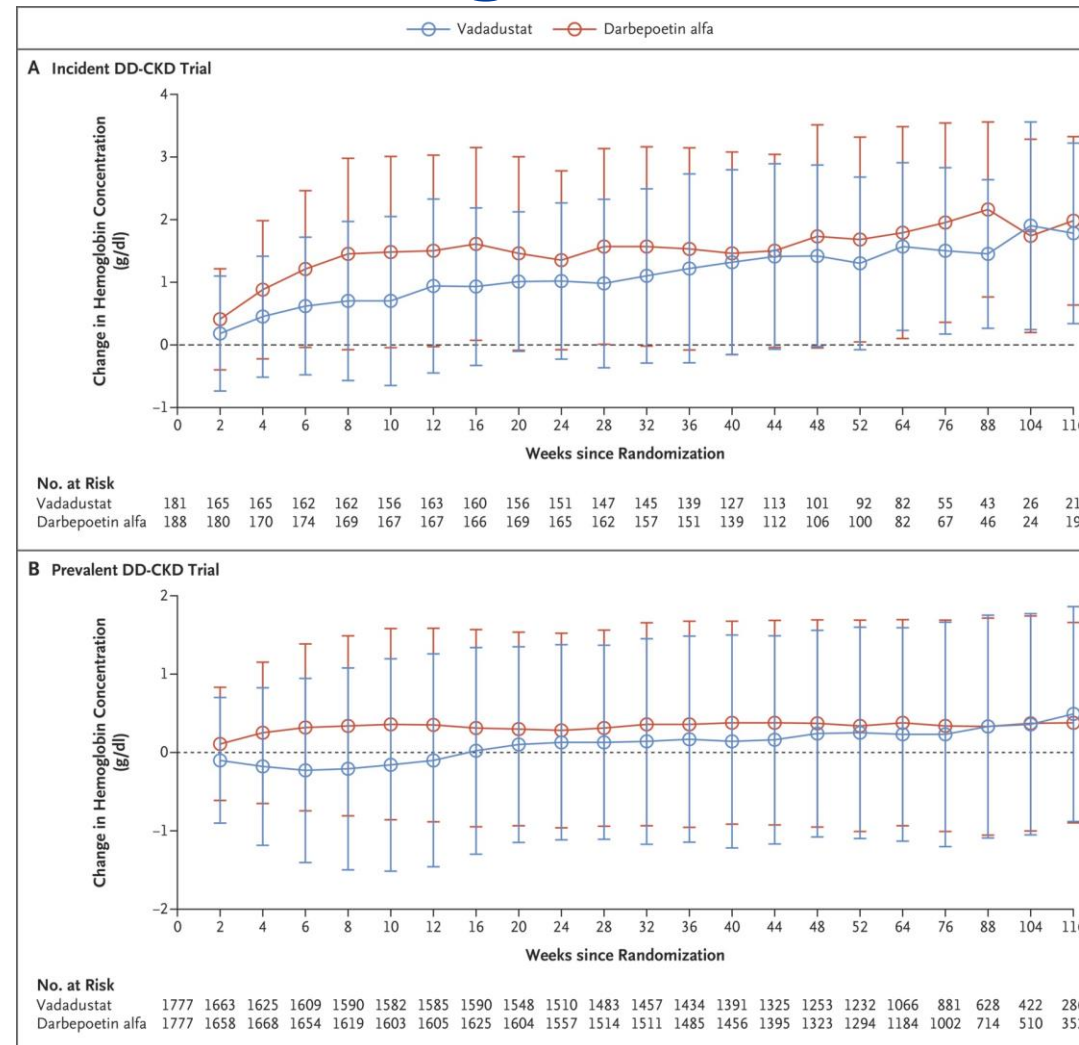
- Cost
- Intravenous or subcutaneous route of administration
- Adverse cardiovascular events
 - CHOIR study: erythropoietin: more CHF in high-hemoglobin group
 - TREAT study: diabetic subjects; more strokes in high hemoglobin group



Cardiovascular Outcomes with Vadadustat



Changes in Hemoglobin with Vadadusat



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



Key Points

- Screen patients at high risk for kidney disease
- SGLT-2 inhibitors and GLP-1 agonists are key medications in retarding progression of diabetic kidney disease.
- SGLT-2 inhibitors may be useful in retarding progression of non-diabetic kidney disease
- Difelikefalin may be useful in treating pruritus associated with ESKD
- Iron deficiency is common in CKD and should be corrected before starting an ESA.
- Daprodustat is the first FDA-approved HIF-PH inhibitor for treatment of anemia of CKD



Next best steps

- Endocrine consultation may be helpful in management of poorly controlled type 2 diabetic patients given the number of new diabetic medications and the complexity of some regimens.





Mass General Brigham