האיגוד הישראלי לרפואה פנימית
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המרכז הרפואי קפלן
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בית חולים בילינסון

מקבוצת כללית

מה חדש בנפרולוגיה?

ד"ר חפציבה גרין

אתמול פנימית ב' בלינסון היום פנימית א' בקפלן

- Chronic kidney disease / End-stage kidney disease
- Glomerulonephritis
- Transplantation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

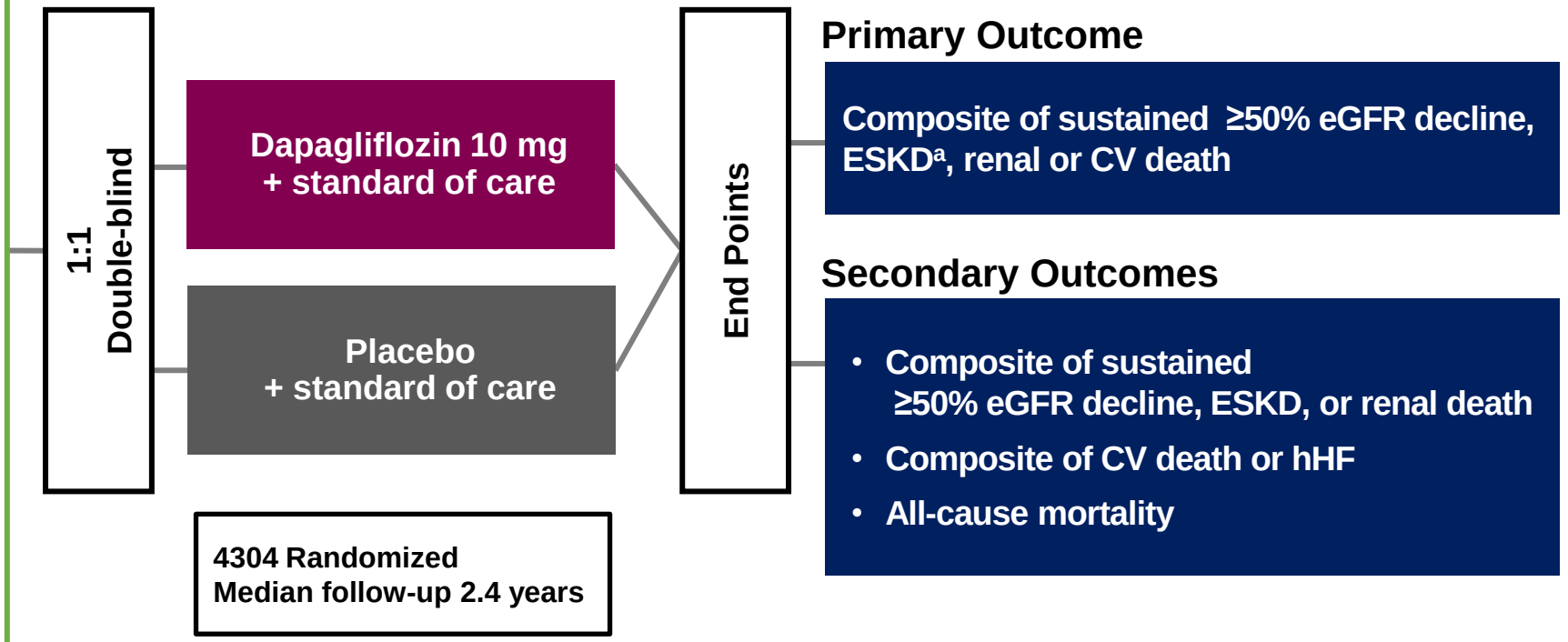
DAPACKD

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

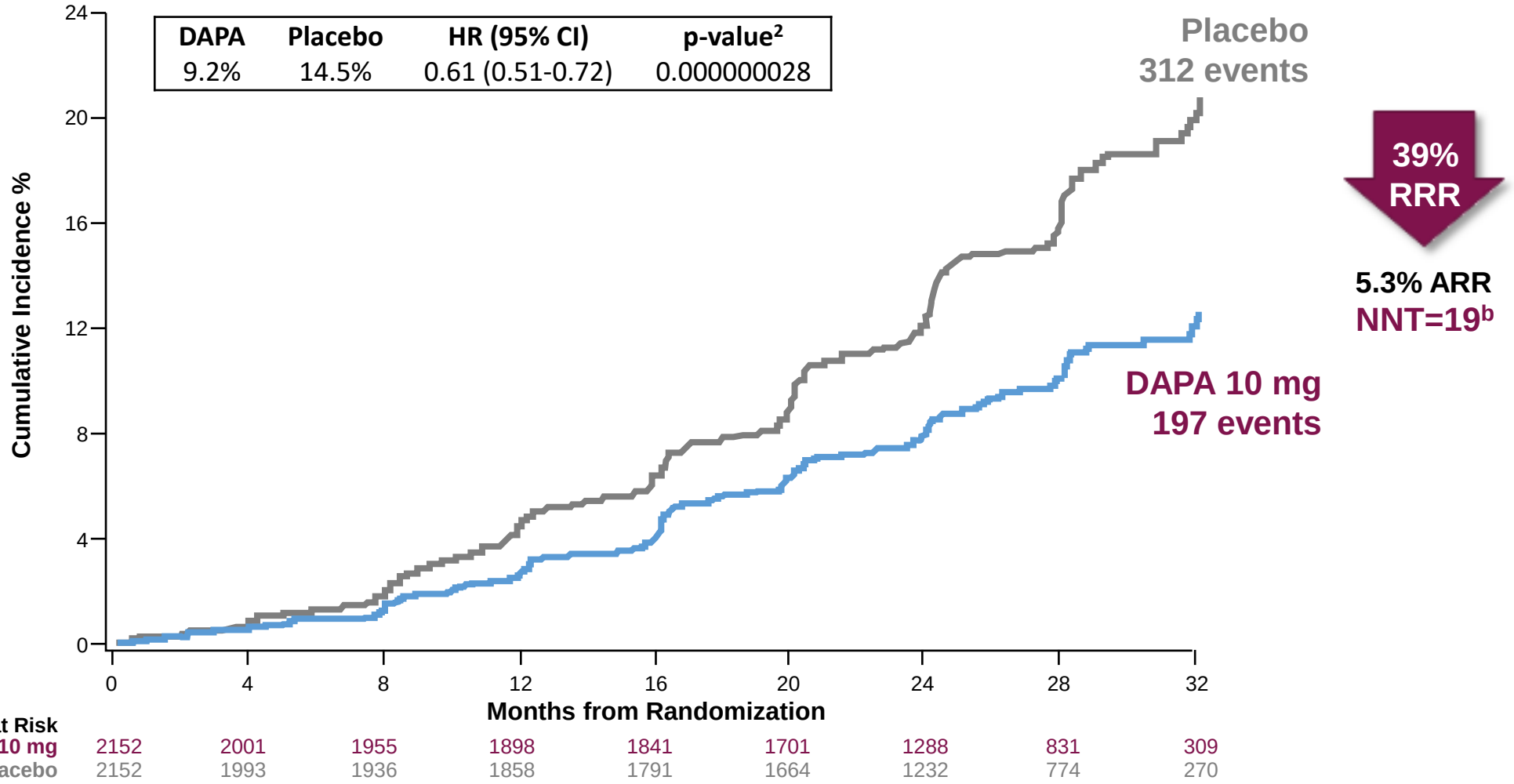
ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

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)
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)
≥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

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a,1]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[3]; [b]95% CI, 15 to 27.

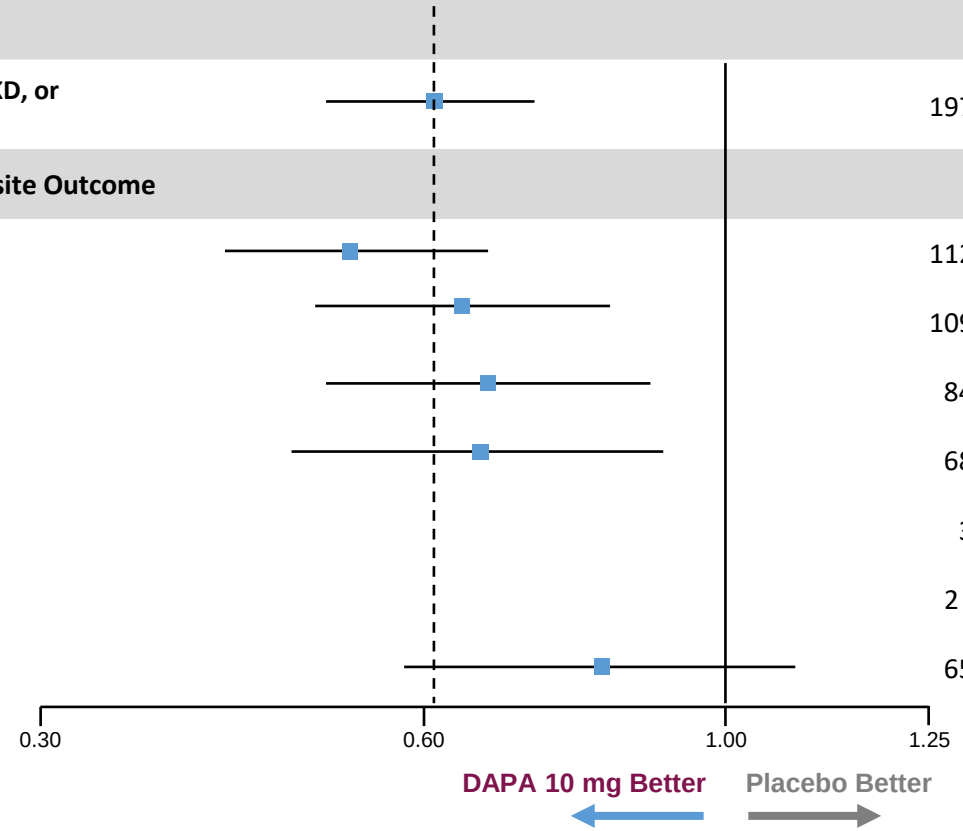
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020;

3. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Primary Composite Outcome: All Components Contributed to the Observed Treatment Effect[1]

	Number of Events (%)				
	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value[2]
Primary Composite Outcome					
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome					
≥50% eGFR Decline	112 (5.2)	201 (9.3)	0.53	(0.42, 0.67)	<0.0001
ESKD	109 (5.1)	161 (7.5)	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2	84 (3.9)	120 (5.6)	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis[a]	68 (3.2)	99 (4.6)	0.66	(0.48, 0.90)	0.0080
Transplantation[a]	3 (0.1)	8 (0.4)	NC		
Renal Death	2 (<0.1)	6 (0.3)	NC		
CV Death	65 (3.0)	80 (3.7)	0.81	(0.58, 1.12)	0.2029



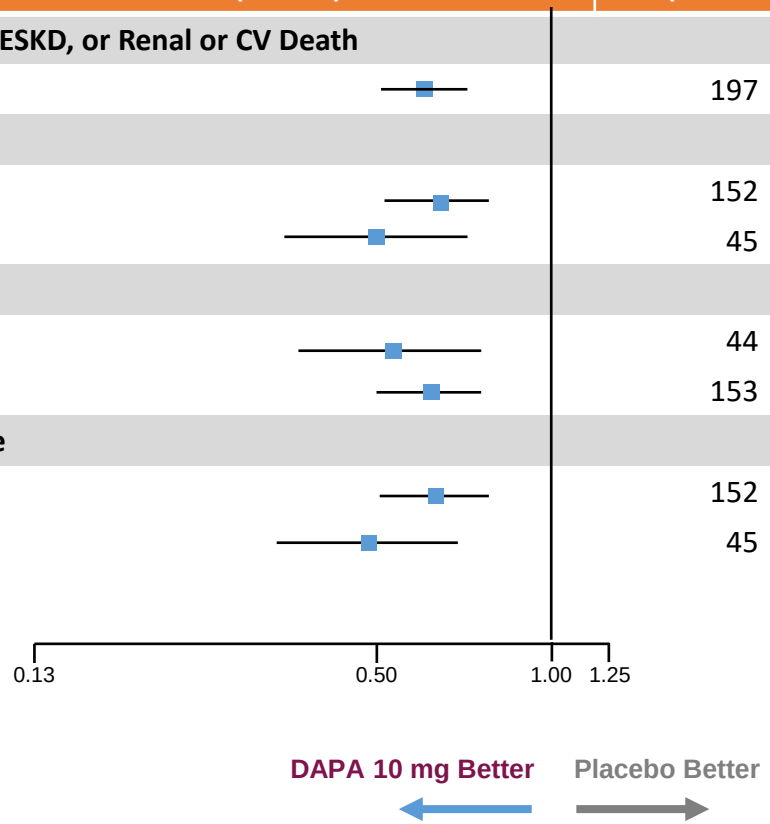
[a]There were 69 endpoint events for dapagliflozin and 100 endpoint events for placebo for the combined chronic dialysis and renal transplantation endpoint (HR 0.66; 95% CI 0.49, 0.90).

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

Primary Composite Outcome: Treatment Benefit Consistent Across Pre-specified Subgroups

	Number of Events				
HR (95% CI)	DAPA 10 mg (n=2152)	Placebo (n=2152)	HR	95% CI	p-value Interaction[2]
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 – September 1, 2020.

פורסיגה וקסיגדו XR זמינים לחולים קרדיורנלים דרך סל התרופות[1], הביטוחים המשלימים וברכישה פרטית מוזלת בסופר פארם

סל נפרולוגיה CKD FORXIGA	סל קרדיולוגיה HF FORXIGA	סל סוכרת T2D FORXIGA / XIGDUO XR*
eGFR 25-75 mL/min/1.73m² וגם UACR ≥ 200 mg/g מטופלים ב ACEi /ARB	EF ≤ 40% וגם eGFR ≥ 30 mL/min/1.73m² NYHA class II-IV לאחר מיצוי טיפול מיטבי (ACEi/ARB & BB)	A1c ≥ 7% ואחד מהבאים: eGFR ≤ 90 mL/min/1.73m² וגם UACR ≥ 30 mg/g או eGFR 45 - 60 mL/min/1.73m² או מחלת לב מוכחת (אוטם, CABG, מחלת לב איסכמית)
28 ₪	**28 ₪**	**פורסיגה 28 ₪/ קסיגדו 37₪**

עדכון סל 2022

משלים/ פרטי מוזל FORXIGA / XIGDUO XR*	למטופל שלא עומד בקריטריוני הסל	מושלם: פורסיגה 94 ₪/ קסיגדו 123₪ סופרפארם: פורסיגה /קסיגדו 150₪

*Xigduo XR מותווה לטיפול בחולי סוכרת סוג 2 החל מ- eGFR 45 ומעלה

EF- ejection fraction . UACR- urinary albumin to creatinine ratio mg/g .eGFR – estimated glomerular filtration rate mL/min/1.73²

1. חוזר מנכ"ל משרד הבריאות, עדכון סל התרופות, ינואר 2022

forxiga (dapagliflozin)

IL-2630

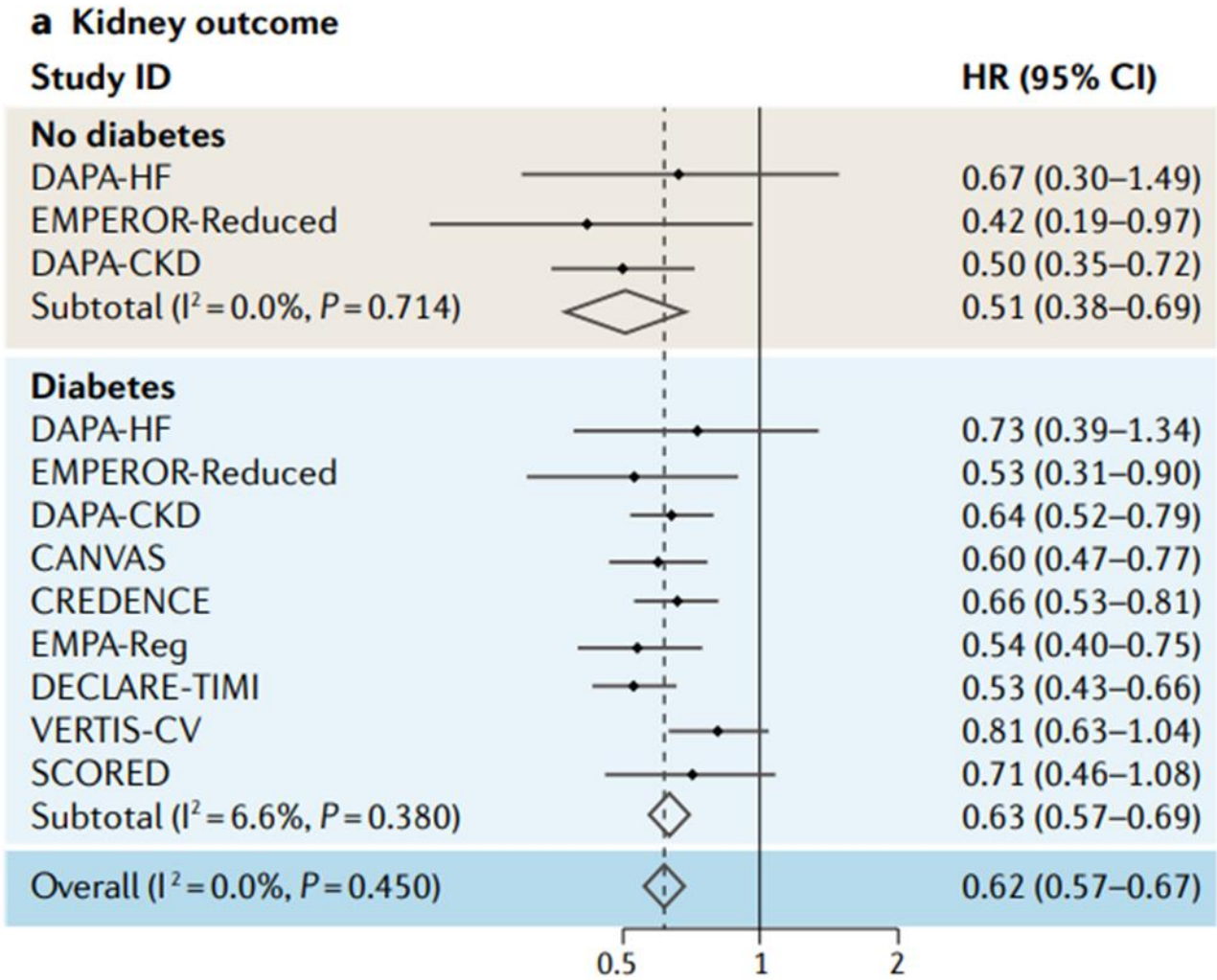
EMPA- KIDNEY

Jardiance® (empagliflozin) Phase III EMPA-KIDNEY trial will stop early due to clear positive efficacy in people with chronic kidney disease

Oxford, UK; Ingelheim, Germany and Indianapolis, U.S. , Wednesday, 03/16/2022 - 13:00

EMPA - KIDNEY

- CKD
- With/without DM
- Non-albuminuric
- 6609 participants
- eGFR ≥20 to <45 or eGFR ≥45 to <90 and UACR ≥ 200 mg/g
- Composite outcome: ESKD, sustained eGFR decline of ≥40% or renal/CV death


a Kidney outcome
Study ID
HR (95% CI)
No diabetes
DAPA-HF
0.67 (0.30–1.49)
EMPEROR-Reduced
0.42 (0.19–0.97)
DAPA-CKD
0.50 (0.35–0.72)
Subtotal (I² = 0.0%, P = 0.714)
0.51 (0.38–0.69)
Diabetes
DAPA-HF
0.73 (0.39–1.34)
EMPEROR-Reduced
0.53 (0.31–0.90)
DAPA-CKD
0.64 (0.52–0.79)
CANVAS
0.60 (0.47–0.77)
CREDENCE
0.66 (0.53–0.81)
EMPA-Reg
0.54 (0.40–0.75)
DECLARE-TIMI
0.53 (0.43–0.66)
VERTIS-CV
0.81 (0.63–1.04)
SCORED
0.71 (0.46–1.08)
Subtotal (I² = 6.6%, P = 0.380)
0.63 (0.57–0.69)
Overall (I² = 0.0%, P = 0.450)
0.62 (0.57–0.67)
0.5
1
2

Finerenone

- Non-steroidal MRA
- FDA approved

- The tissue distribution of non-steroidal MRAs such as finerenone is balanced between the kidney and the heart, whereas steroidal MRAs such as spironolactone and eplerenone accumulate more prominently in the kidney
- Much shorter half-life than steroidal MRAs and has no active metabolites

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

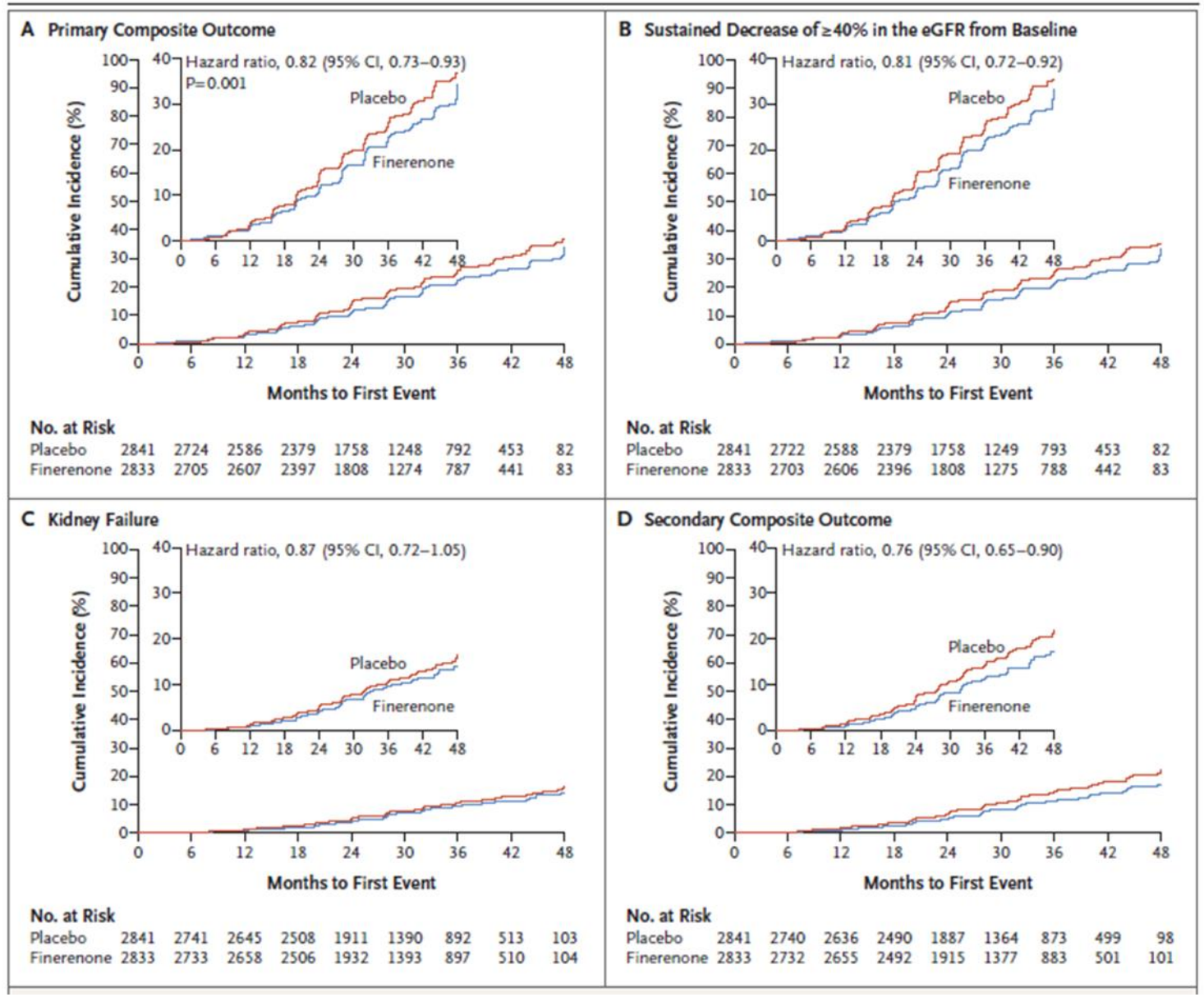
George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

N Engl J Med 2020;383:2219-29

- Composite primary outcome: ESKD, sustained eGFR decline of ≥40% or renal/CV death

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

Urinary albumin-to-creatinine ratio‡			
Median (IQR)	833 (441–1628)	867 (453–1645)	852 (446–1634)
Distribution — no. (%)			
<30	11 (0.4)	12 (0.4)	23 (0.4)
30 to <300	350 (12.4)	335 (11.8)	685 (12.1)
≥300	2470 (87.2)	2493 (87.8)	4963 (87.5)
Missing data	2 (<0.1)	1 (<0.1)	3 (<0.1)
Serum potassium — mmol/liter	4.37±0.46	4.38±0.46	4.37±0.46
Baseline medications — no. (%)			
ACE inhibitor§	950 (33.5)	992 (34.9)	1942 (34.2)
Angiotensin-receptor blocker§	1879 (66.3)	1846 (65.0)	3725 (65.7)
Diuretic	1577 (55.7)	1637 (57.6)	3214 (56.6)
Statin	2105 (74.3)	2110 (74.3)	4215 (74.3)
Potassium-lowering agent¶	70 (2.5)	66 (2.3)	136 (2.4)
Glucose-lowering therapy	2747 (97.0)	2777 (97.7)	5524 (97.4)
Insulin	1843 (65.1)	1794 (63.1)	3637 (64.1)
GLP-1 receptor agonist	189 (6.7)	205 (7.2)	394 (6.9)
SGLT2 inhibitor	124 (4.4)	135 (4.8)	259 (4.6)
<25 ml/min/1.73 m^2	66 (2.3)	69 (2.4)	135 (2.4)


A Primary Composite Outcome
Hazard ratio, 0.82 (95% CI, 0.73–0.93)
P=0.001
Placebo
Finerenone
Cumulative Incidence (%)
Months to First Event
No. at Risk
Placebo 2841 2724 2586 2379 1758 1248 792 453 82
Finerenone 2833 2705 2607 2397 1808 1274 787 441 83
B Sustained Decrease of ≥40% in the eGFR from Baseline
Hazard ratio, 0.81 (95% CI, 0.72–0.92)
Placebo
Finerenone
Cumulative Incidence (%)
Months to First Event
No. at Risk
Placebo 2841 2722 2588 2379 1758 1249 793 453 82
Finerenone 2833 2703 2606 2396 1808 1275 788 442 83
C Kidney Failure
Hazard ratio, 0.87 (95% CI, 0.72–1.05)
Placebo
Finerenone
Cumulative Incidence (%)
Months to First Event
No. at Risk
Placebo 2841 2741 2645 2508 1911 1390 892 513 103
Finerenone 2833 2733 2658 2506 1932 1393 897 510 104
D Secondary Composite Outcome
Hazard ratio, 0.76 (95% CI, 0.65–0.90)
Placebo
Finerenone
Cumulative Incidence (%)
Months to First Event
No. at Risk
Placebo 2841 2740 2636 2490 1887 1364 873 499 98
Finerenone 2833 2732 2655 2492 1915 1377 883 501 101

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—

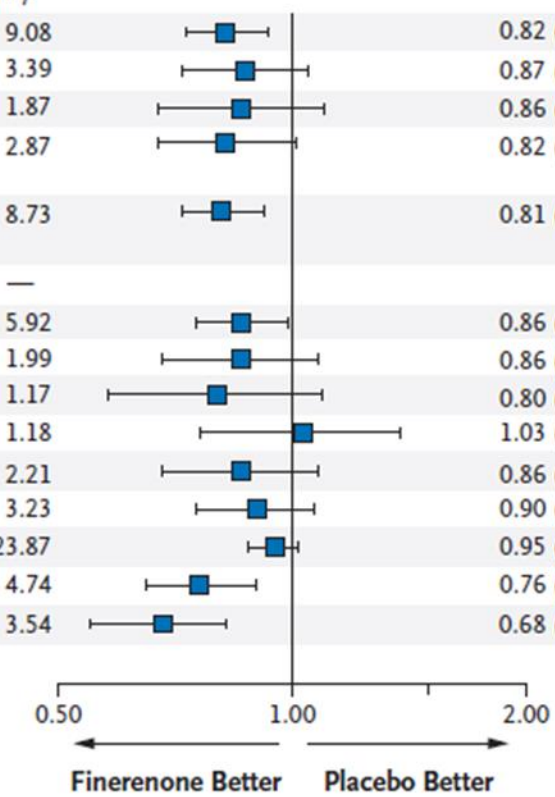
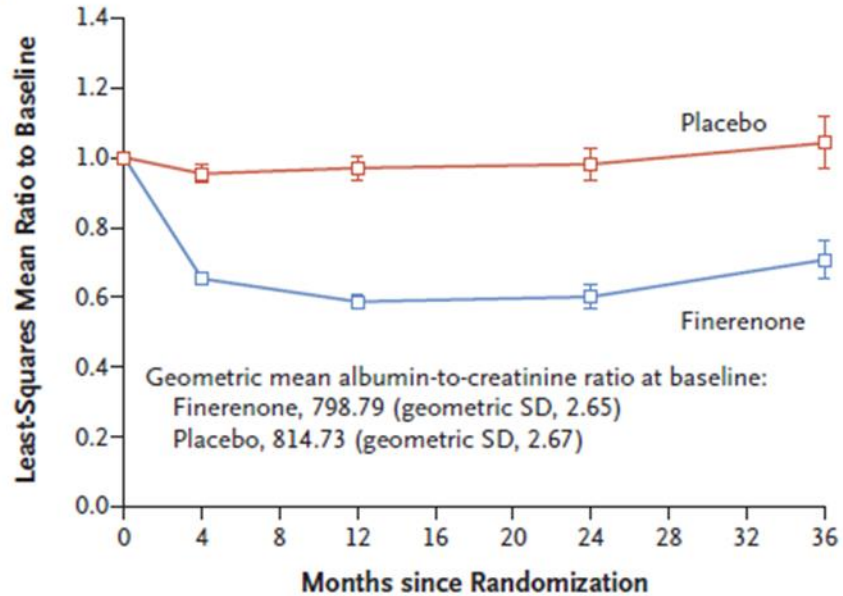


Figure 2. Efficacy Outcomes.

A Urinary Albumin-to-Creatinine Ratio



No. of Patients					
Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834
Mean Change from Baseline (percent)					
Finerenone	Ref.	−34.7	−41.3	−39.9	−29.3
Placebo	Ref.	−4.7	−3.0	−2.0	4.1

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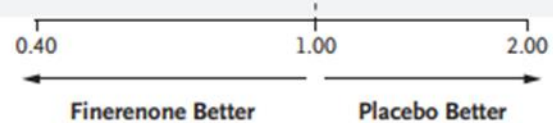
ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

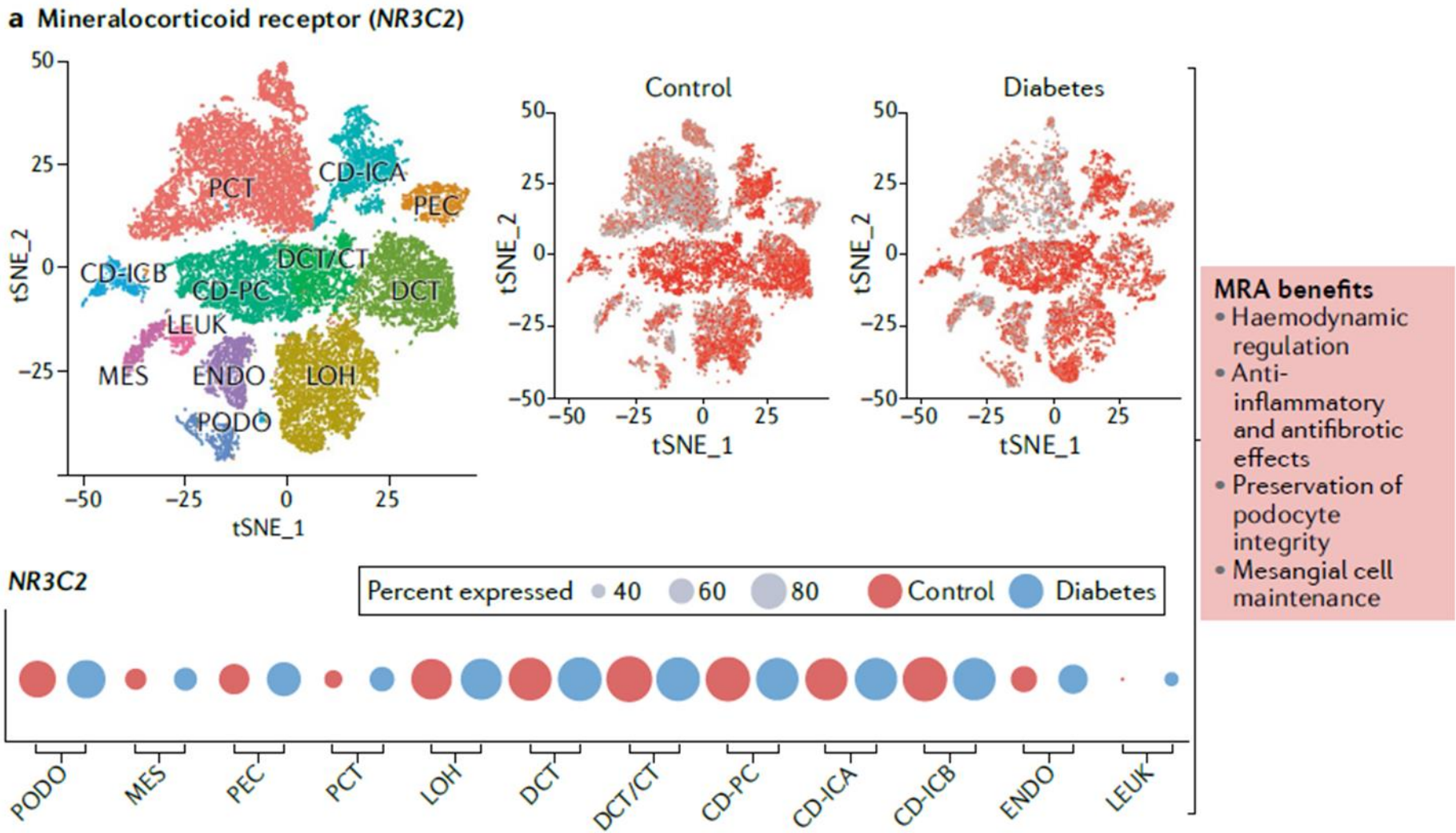
B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

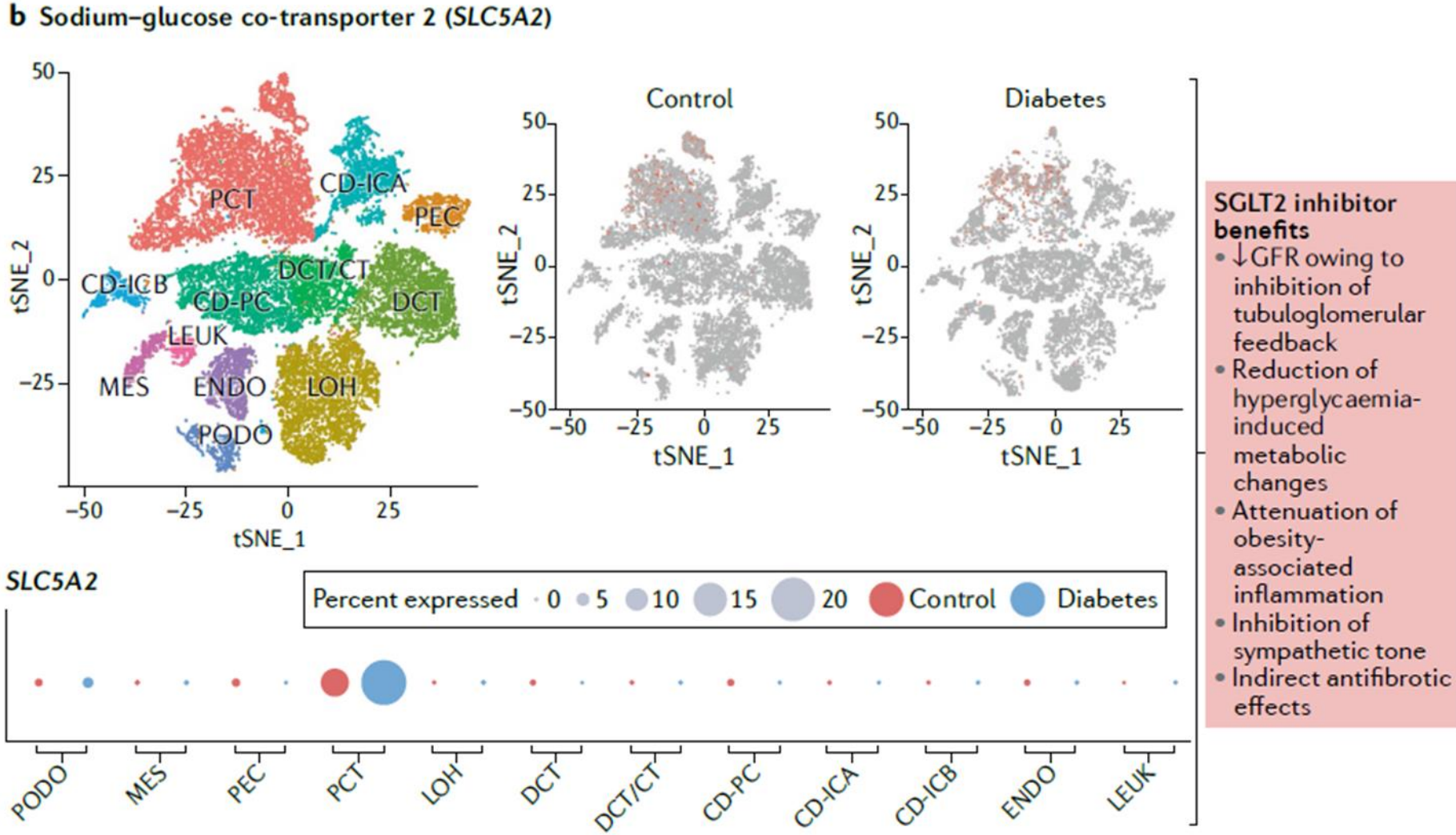
NEJM 385;24 December 9, 2021

Outcome	Finerenone (N=3686)	Placebo (N=3666)	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	458 (12.4)	519 (14.2)	3.87	4.45	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	1.56	1.74	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.85	0.85	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.89	0.92	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.96	1.36	0.71 (0.56–0.90)	—
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.15	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.995)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m^2	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	333 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—



Combining SGLT2 and non-steroidal MRAs?




b Sodium–glucose co-transporter 2 (SLC5A2)
PCT
CD-ICA
PEC
CD-ICB
DCT/CT
CD-PC
DCT
LEUK
MES
ENDO
LOH
PODO
tSNE_1
tSNE_2
Control
Diabetes
SLC5A2
Percent expressed 0 5 10 15 20
Control
Diabetes
PODO
MES
PEC
PCT
LOH
DCT
DCT/CT
CD-PC
CD-ICA
CD-ICB
ENDO
LEUK
SGLT2 inhibitor benefits
• ↓GFR owing to inhibition of tubuloglomerular feedback
• Reduction of hyperglycaemia-induced metabolic changes
• Attenuation of obesity-associated inflammation
• Inhibition of sympathetic tone
• Indirect antifibrotic effects

- Clinical evidence to date does not support the hypothesis that combining SGLT2 inhibitors with MRAs has additional effects in cardiac and/or renal outcomes.

Patiromer

The First Potassium Binder Approved in Over 50 Years

Betty N. Vu, PharmD, Alyssa Mae De Castro, PharmD,† David Shottland, MD,‡ William H. Frishman, MD,§ and Angela Cheng-Lai, PharmD, BCPS†*

(*Cardiology in Review* 2016;24: 316–323)

משרד הבריאות

חוזר המנהל הכללי

י״ז אדר, תשפ״א
1 מרץ, 2021
מס׳: 3/2021

הנדון: הרחבת סל שירותי הבריאות לשנת 2021

הריני להודיעכם, כי שר הבריאות ושר האוצר, מתוקף סמכותם על-פי חוק ביטוח בריאות ממלכתי ובאישור הממשלה, החליטו על בסיס המלצת ועדה ציבורית שמונתה לנושא ולאחר שההמלצה הוצגה בפני מועצת הבריאות, על הוספת תרופות וטכנולוגיות רפואיות אחרות לסל שירותי הבריאות שלפי חוק ביטוח בריאות ממלכתי.

רצ״ב פירוט שירותי הבריאות שנוספו והתוויותיהם.

שם מסחרי	שם גנרי	התוויה
Veltassa	Patiromer	טיפול בהיפרקלמיה - עבור חולי מחלת כליה כרונית (CKD) דרגות 3 עד 5 שאינם מטופלים בדיאליזה, עם מחלה לבבית או יתר לחץ דם עמיד, שרמת האשלגן שלהם בערך 5.5 mEq/L ומעלה, המטופלים במעכבי RAAS, ושמיצו טיפול במשתנים מפרישי אשלגן ודיאטה דלת אשלגן.


ולטסה 8.4 גרם
Patiromer
(as sorbitex calcium) 8.4 g
אבקה ליצירת תרחיף לבליעה
לשימוש דרך הפה.
יש ליטול תוך שעה אחת לאחר הכנת התרחיף.
הרחק מהישג ידם וראייתם של ילדים.
יש לאחסן במקרר (2–8°C). ניתן לאחסן
בטמפרטורה הנמוכה מ-25°C למשך עד 6 חודשים
על-ידי המטופל.
יש לעיין בעלון לצרכן לפני השימוש.
יצרן
Patheon
Ontario, Canada
יבואן ובעל הרישום
CTS Ltd.
4 Haharash st.
Hod Hasharon
VIFOR PHARMA
2000010877
Sf1332-00
LOT: CFWKS
EXP: 07/2023
ולטסה 8.4 גרם
Patiromer
(as sorbitex calcium) 8.4 g
אבקה ליצירת תרחיף לבליעה
לשימוש דרך הפה.
יש לעיין בעלון לצרכן לפני השימוש.
VIFOR PHARMA
30 שקיקים


Veltassa
(patiromer)
For Oral Suspension
30 packets
8.4 g
16.8 g
25.2 g

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 15, 2015 VOL. 372 NO. 3

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

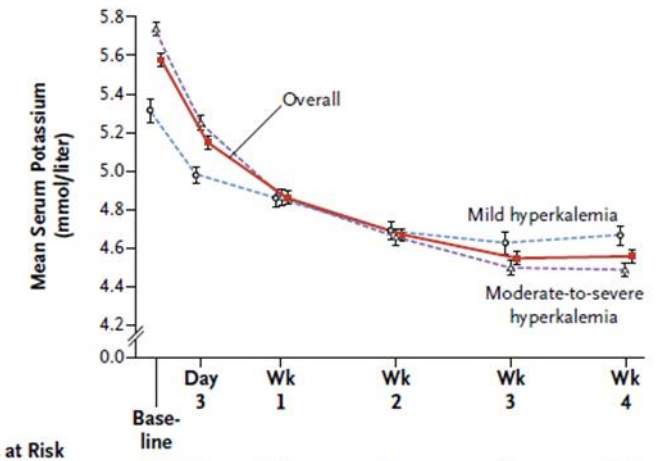
Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

Research

Original Investigation

Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease
The AMETHYST-DN Randomized Clinical Trial

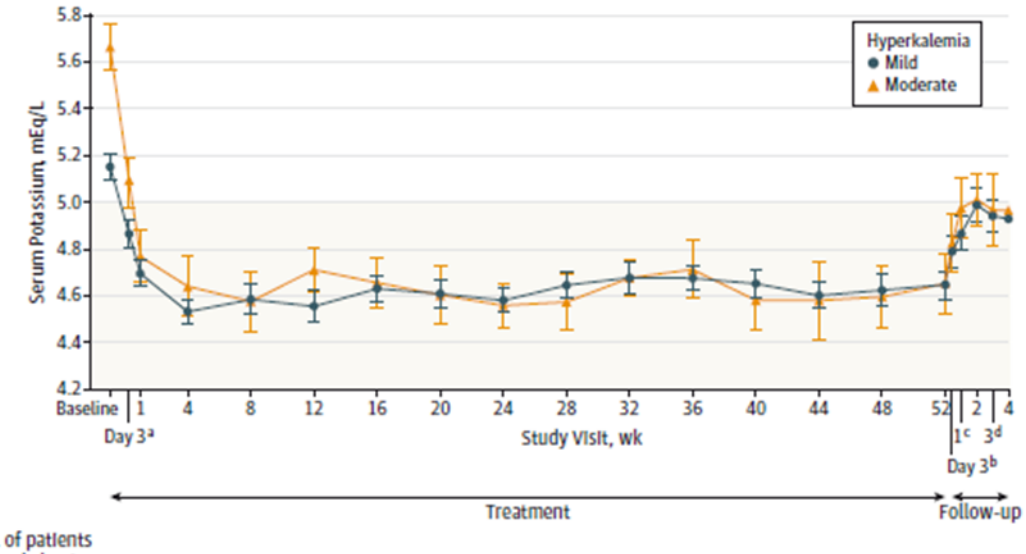
George L. Bakris, MD; Bertram Pitt, MD; Matthew R. Weir, MD; Mason W. Freeman, MD; Martha R. Mayo, PharmD; Dahlia Garza, MD; Yuri Stasiv, PhD; Rezi Zawadzki, DrPH; Lance Berman, MD; David A. Bushinsky, MD; for the AMETHYST-DN Investigators



No. at Risk						
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

Figure 1. Serum Potassium Levels over Time during the Initial Treatment Phase.
Values are the observed mean values as measured in a central laboratory. During the 4-week initial treatment phase, all patients received treatment with patiromer; patients with a potassium level of 5.1 to less than 5.5 mmol per liter (mild hyperkalemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 to less than 6.5 mmol per liter (moderate-to-severe hyperkalemia) received 8.4 g of patiromer twice daily. I bars indicate standard errors. Data points are staggered to make them more legible.

Figure 3. Least Squares Mean (95% CI) Serum Potassium Levels Over 52 Weeks and During Posttreatment Follow-up in Patients With Mild or Moderate Hyperkalemia (Post Hoc Mixed-Effects Models for Repeated-Measures Analysis)



No. of patients																	
Hyperkalemia																	
Mild	218	204	199	192	175	168	161	161	163	158	156	151	148	149	145	131	126
Moderate	83	83	73	70	65	62	62	62	61	53	53	53	52	49	49	48	47

Results: Results of change in potassium, sodium, calcium, and magnesium concentration (percentage change from baseline) at 30 minutes are shown in the Table.

Table: Percentage changes in electrolyte concentrations at the end of 30 minutes with three different doses of Kayexalate and Patiromer

Medication	Kayexalate			Patiromer		
Electrolytes	3.4 g/L	6.8 g/L	13.6 g/L	8.4 g/L	16.8 g/L	33.6 g/L
Potassium	↓15%	↓33%	↓61%	↓7%	↓15%	↓22%
Sodium	↑87%	↑239%	↑300%	↓3%	↓6%	↓9%
Calcium	↓13%	↓19%	↓41%	↑19%	↑37%	↑43%
Magnesium	↓31%	↓46%	↓69%	↓15%	↓30%	↓38%

Conclusions: With the doses utilized in our experiment, Kayexalate was twice as effective in lowering the potassium concentration; however, it increased the sodium content of the formula by almost 100 to 300%, whereas Patiromer did not affect the sodium concentration. Kayexalate also reduced the calcium concentration by as much as 40%, while Patiromer increased the calcium concentration by equivalent amount. Both Kayexalate and Patiromer decreased the magnesium concentration with the decrease being more pronounced with Kayexalate. Knowledge of these electrolyte changes is crucially important in the care of patients with renal disease as not only they lack the normal homeostasis but are also vulnerable to negative consequences of electrolyte imbalance.

Hypoxia-inducible factor–prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease

Volker H. Haase[1,2,3]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden; and [3]Department of Molecular Physiology and Program in Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Erythropoiesis stimulating agents (ESA)

A very short explanation about HIF

- HIF-a is constitutively produced and rapidly degraded under normoxic conditions
- Degradation of HIF-a is mediated by prolyl hydroxylase domain (PHD) 1, PHD2, and PHD3 enzymes, which hydroxylate specific proline residues within HIF-a
- Hydroxylated HIF-a is ubiquitylated, leading to its proteasomal degradation
- Hypoxia or HIF–PHD inhibitors (PHIs) reduce PHD catalytic activity, which leads to cellular accumulation of HIF-a, its nuclear translocation, heterodimerization with HIF-b, and increased transcription of HIF-regulated genes, which are involved in multiple biological processes

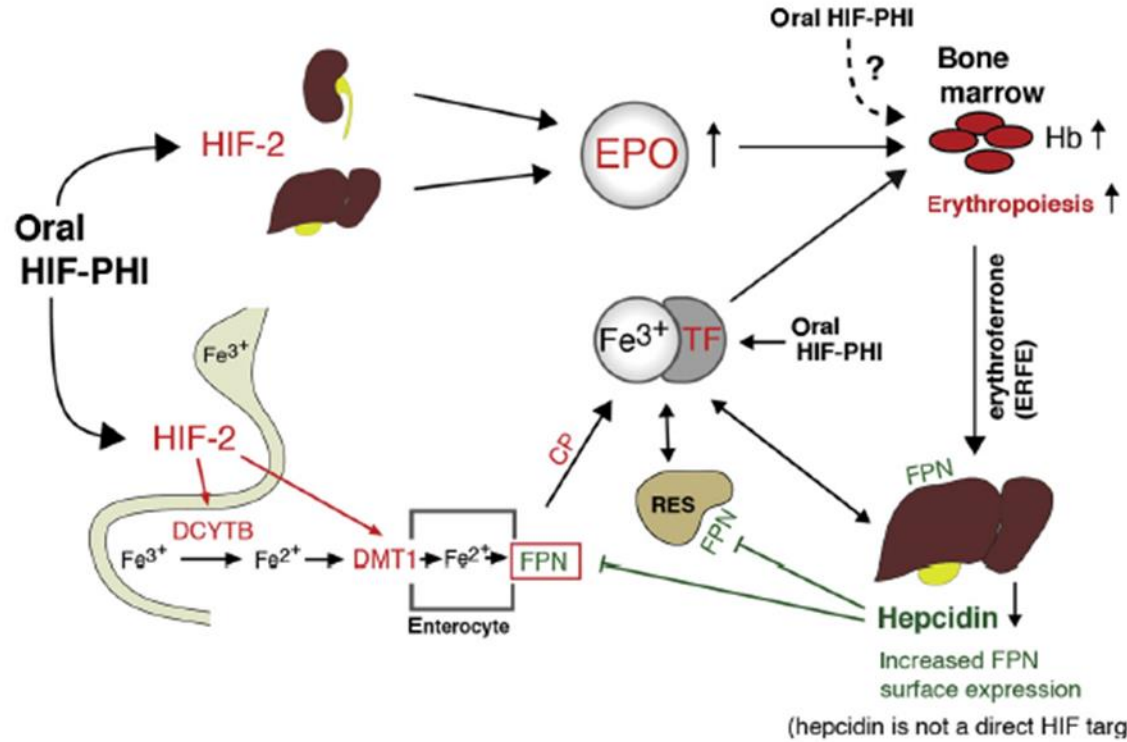


Figure 2 | Overview of hypoxia-inducible factor (HIF) regulation of erythropoiesis. Reprinted from *Advances in Chronic Kidney Disease*, volume 26, issue 4, Sanghani NS, Haase VH, Hypoxia-inducible factor activators in renal anemia: current clinical experience, pages 253–266, Copyright © 2019, with permission from the National Kidney Foundation, Inc.[51] In response to hypoxia or HIF– prolyl-hydroxylase inhibitors (PHIs), HIF-2 stimulates erythropoietin (EPO) production in the kidneys and liver. This promotes erythropoiesis and leads to increased iron demand in the bone marrow. HIF coordinates erythropoisis with iron metabolism, as it regulates genes involved in iron uptake, release from internal stores, and transport (highlighted in red). Absorbed and stored iron is released into the circulation via ferroportin (FPN) and complexed with transferrin (TF) for transport to liver, bone marrow, reticulocyte endothelial system (RES), and other organs. FPN surface expression is regulated by hepcidin, whereas HIF-2 participates in the transcriptional regulation of FPN. Erythroferrone (ERFE) mediates suppression of hepcidin production in the liver under conditions of accelerated erythropoiesis. Ceruloplasmin (CP) is an HIF-regulated copper-carrying ferroxidase that catalyzes the oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) iron. DCYTB, duodenal cytochrome B (cytochrome b reductase 1); DMT1, divalent metal transporter 1; Hb, hemoglobin.

ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 29, 2021 VOL. 384 NO. 17

Vadadustat in Patients with Anemia and Non–Dialysis-Dependent CKD

G.M. Chertow, P.E. Pergola, Y.M.K. Farag, R. Agarwal, S. Arnold, G. Bako, G.A. Block, S. Burke, F.P. Castillo, A.G. Jardine, Z. Khawaja, M.J. Koury, E.F. Lewis, T. Lin, W. Luo, B.J. Maroni, K. Matsushita, P.A. McCullough, P.S. Parfrey, P. Roy-Chaudhury, M.J. Sarnak, A. Sharma, B. Spinowitz, C. Tseng, J. Tumlin, D.L. Vargo, K.A. Walters, W.C. Winkelmayer, J. Wittes, and K.-U. Eckardt, for the PRO$_2$TECT Study Group*

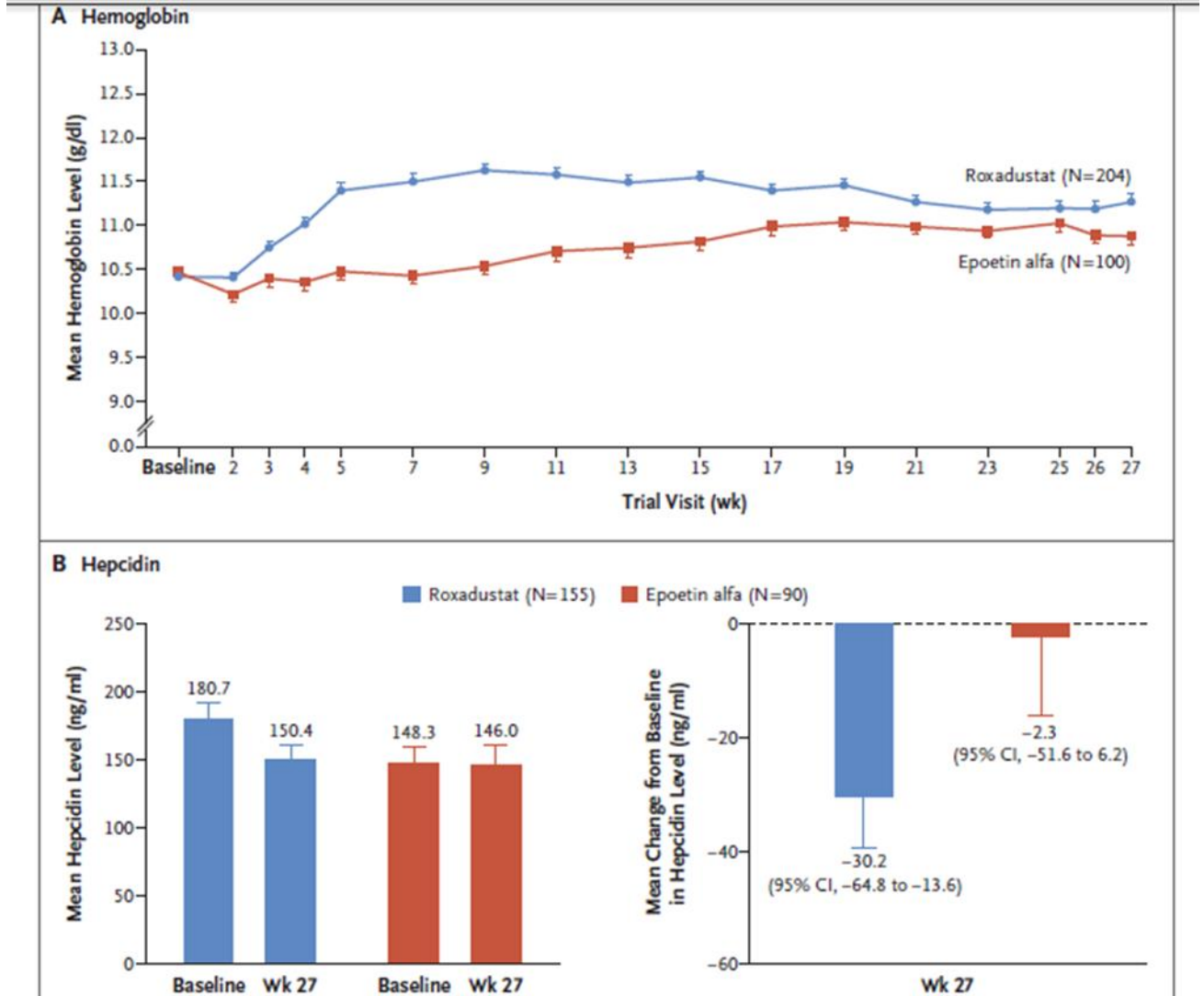
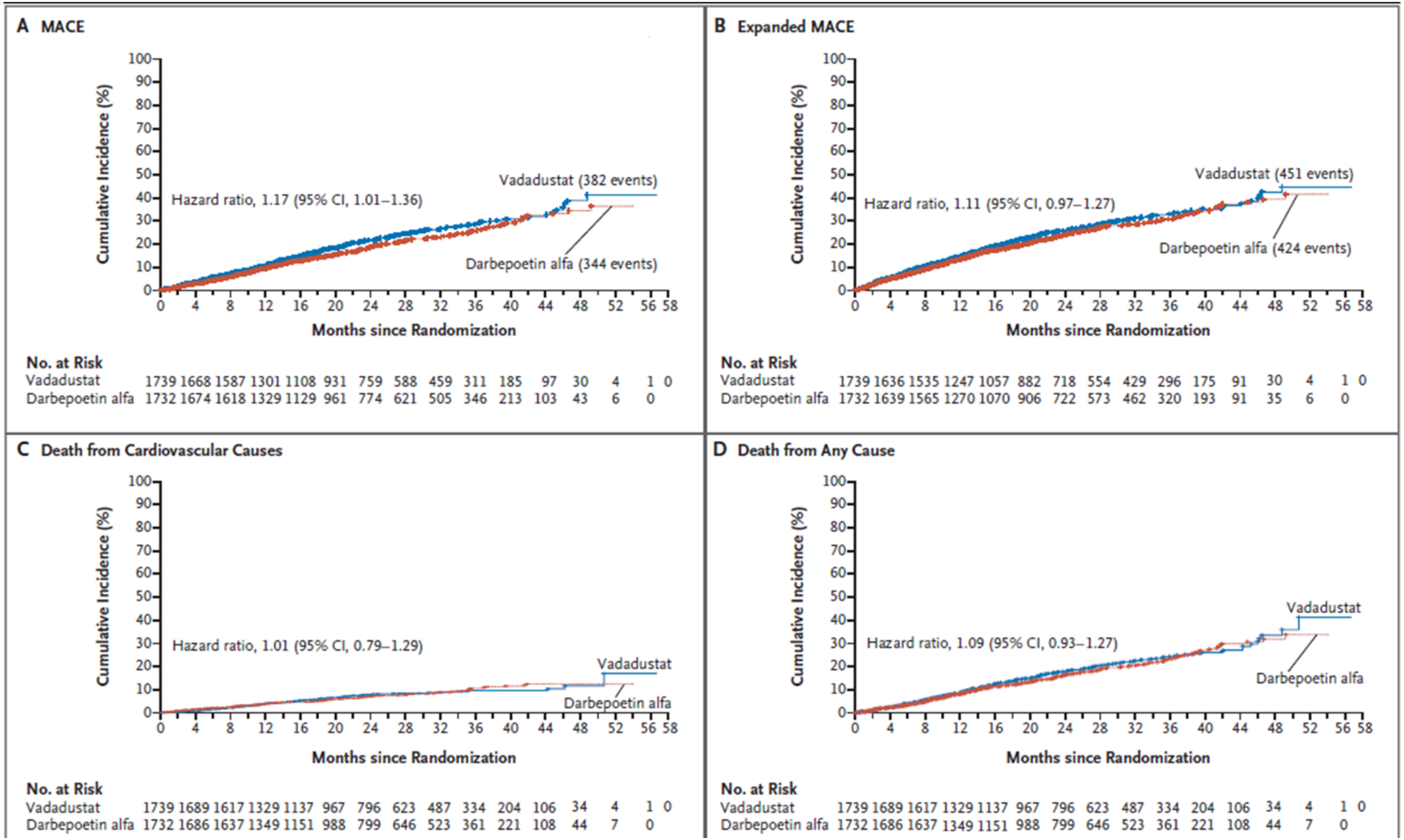


Figure 1. Mean Hemoglobin Levels over Time and Hepcidin Levels and Mean Change from Baseline at Week 27 (Intention-to-Treat Population).

The intention-to-treat population (full analysis set) included all the patients who underwent randomization and had baseline and postbaseline hemoglobin values assessed during treatment. I bars (Panel A) and T bars (Panel B) indicate the standard error.


A MACE
Cumulative Incidence (%)
Hazard ratio, 1.17 (95% CI, 1.01–1.36)
Vadadustat (382 events)
Darbepoetin alfa (344 events)
Months since Randomization
No. at Risk
Vadadustat 1739 1668 1587 1301 1108 931 759 588 459 311 185 97 30 4 1 0
Darbepoetin alfa 1732 1674 1618 1329 1129 961 774 621 505 346 213 103 43 6 0
B Expanded MACE
Cumulative Incidence (%)
Hazard ratio, 1.11 (95% CI, 0.97–1.27)
Vadadustat (451 events)
Darbepoetin alfa (424 events)
Months since Randomization
No. at Risk
Vadadustat 1739 1636 1535 1247 1057 882 718 554 429 296 175 91 30 4 1 0
Darbepoetin alfa 1732 1639 1565 1270 1070 906 722 573 462 320 193 91 35 6 0
C Death from Cardiovascular Causes
Cumulative Incidence (%)
Hazard ratio, 1.01 (95% CI, 0.79–1.29)
Vadadustat
Darbepoetin alfa
Months since Randomization
No. at Risk
Vadadustat 1739 1689 1617 1329 1137 967 796 623 487 334 204 106 34 4 1 0
Darbepoetin alfa 1732 1686 1637 1349 1151 988 799 646 523 361 221 108 44 7 0
D Death from Any Cause
Cumulative Incidence (%)
Hazard ratio, 1.09 (95% CI, 0.93–1.27)
Vadadustat
Darbepoetin alfa
Months since Randomization
No. at Risk
Vadadustat 1739 1689 1617 1329 1137 967 796 623 487 334 204 106 34 4 1 0
Darbepoetin alfa 1732 1686 1637 1349 1151 988 799 646 523 361 221 108 44 7 0

Evrenzo (Roxadustat)

- EMA approved
- For HD patients
- No history of cancer
- P.O(!)
- Appeal for approval in Israel

AJKD

Review

Advances in Understanding of Pathogenesis and Treatment of Immune-Mediated Kidney Disease: A Review

Sam Kant, Andreas Kronbichler, Purva Sharma, and Duvuru Geetha

There continues to be rapid advancement in our understanding of the pathogenesis of immune-mediated kidney disease. This progress has culminated in the development of multiple therapeutic agents that have consistently improved renal and patient outcomes. The focus of this review is to discuss these recent advancements in immune-mediated kidney disease via the lens of direct and indirect immune-mediated mechanisms. In the direct immune-mediated disease, recently described antigens in anti–glomerular basement membrane (GBM) disease and membranous nephropathy are discussed, along with new therapeutic regimens in membranous nephropathy and focal segmental glomerulosclerosis. From an indirect immune-mediated disease standpoint, recent pivotal trials in antineutrophil cytoplasmic antibody vasculitis, lupus nephritis, and IgA nephropathy are examined from a real-world practice perspective. New molecular pathways in various disorders of alternate complement pathway are described, which in turn have led to development of various experimental therapies. In addition, pivotal and ongoing therapeutic trials in the aforementioned diseases are presented.

Complete author and article information provided before references.

Am J Kidney Dis. 79(4):582-600. Published online September 8, 2021.

doi: 10.1053/j.ajkd.2021.07.019

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

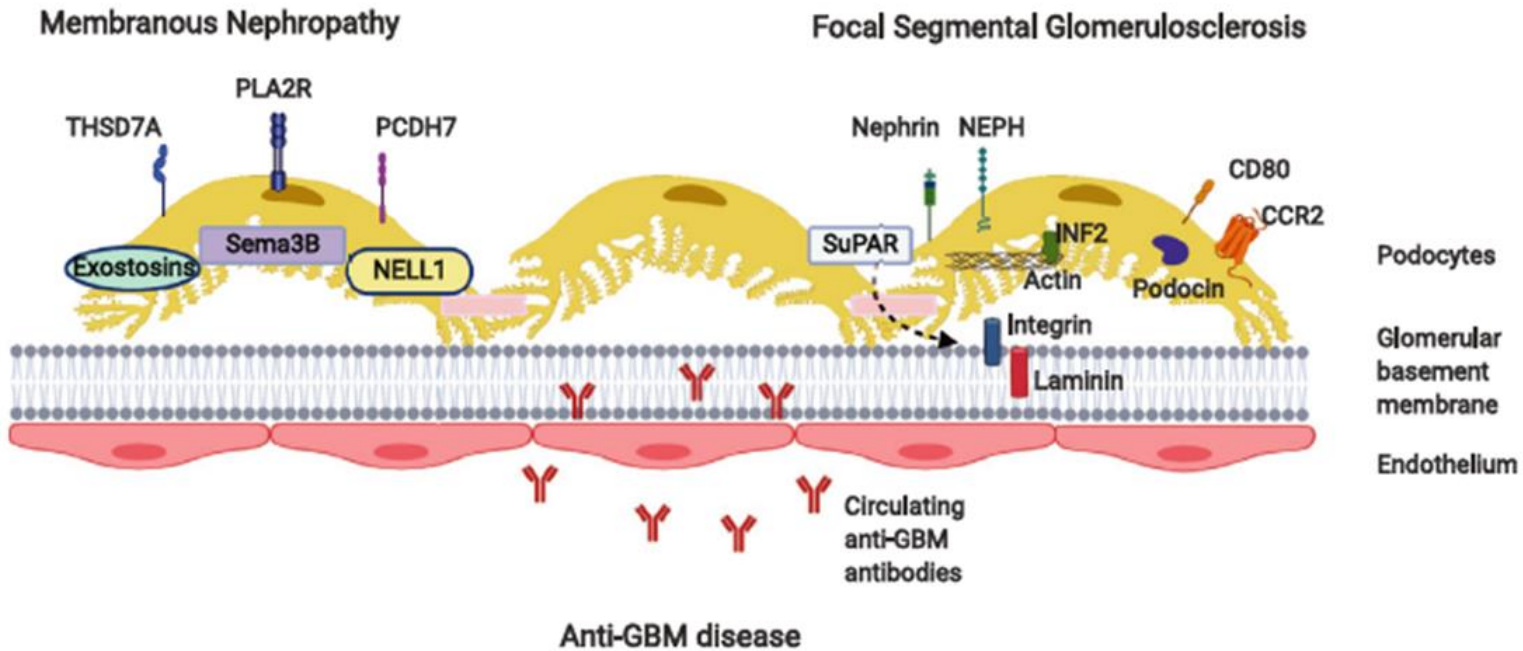
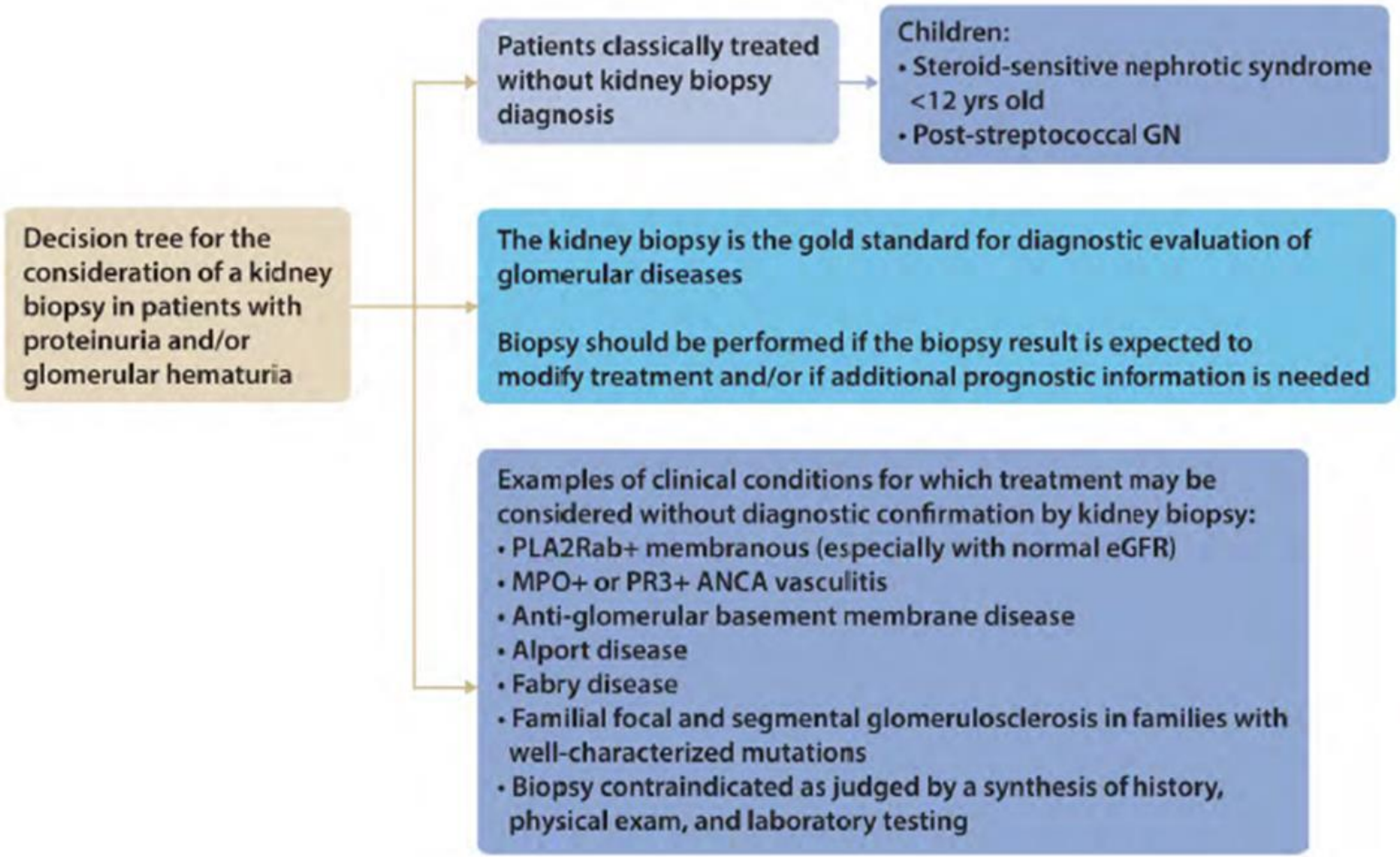


Figure 1. A representation of target antigens of direct immune-mediated kidney diseases—membranous nephropathy, focal segmental glomerulosclerosis (FSGS), and anti–glomerular base membrane disease—with associated antigens and antibodies. Created with BioRender.com. Abbreviations: anti-GBM, anti–glomerular base membrane; CCR2, C-C chemokine receptor type 2; INF-2, inverted formin 2; NELL1, neural EGF-like-1 protein; NEPH, nephrin-like protein; PLA_2R, M-type phospholipase A_2 receptor 1; PCDH7, protocadherin 7; Sema3B, semaphorin 3B; SuPAR, soluble urokinase plasminogen activator receptor; THSD7A, thrombospondin type 1 domain-containing 7A.

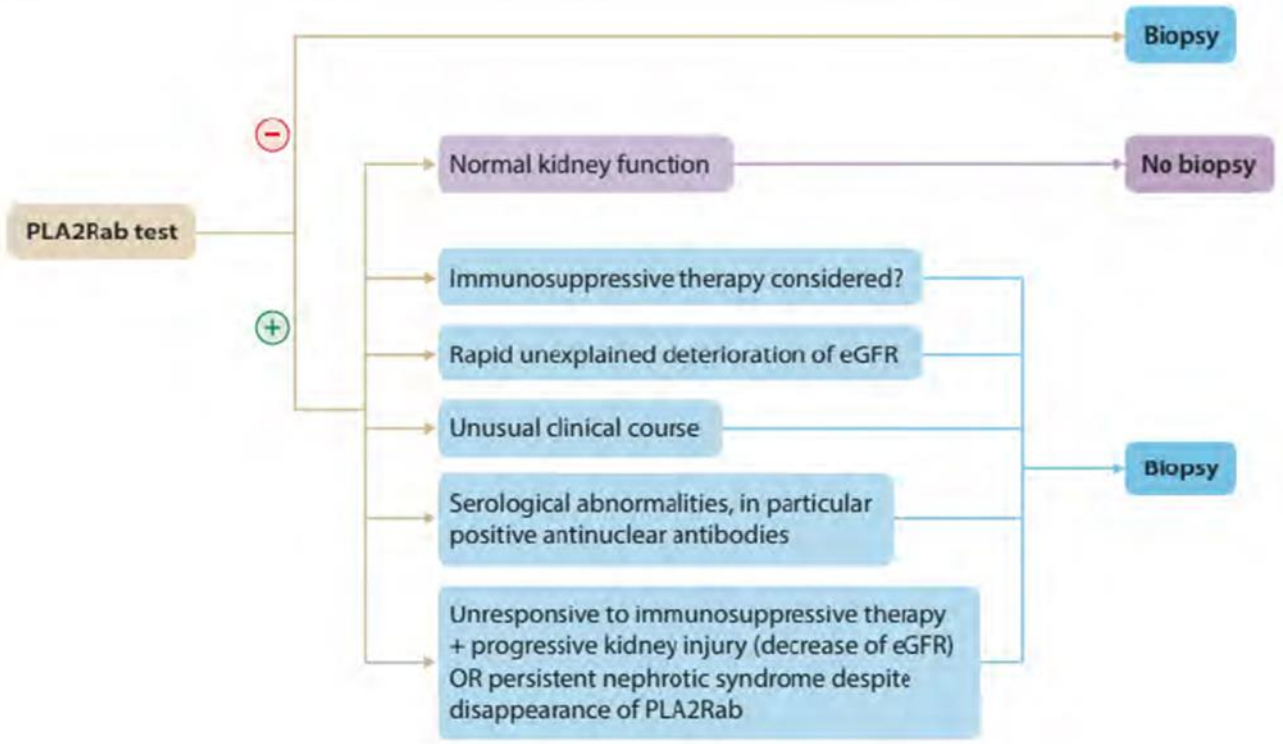
Figure GP1. Considerations for a kidney biopsy in patients with proteinuria and/or glomerular hematuria



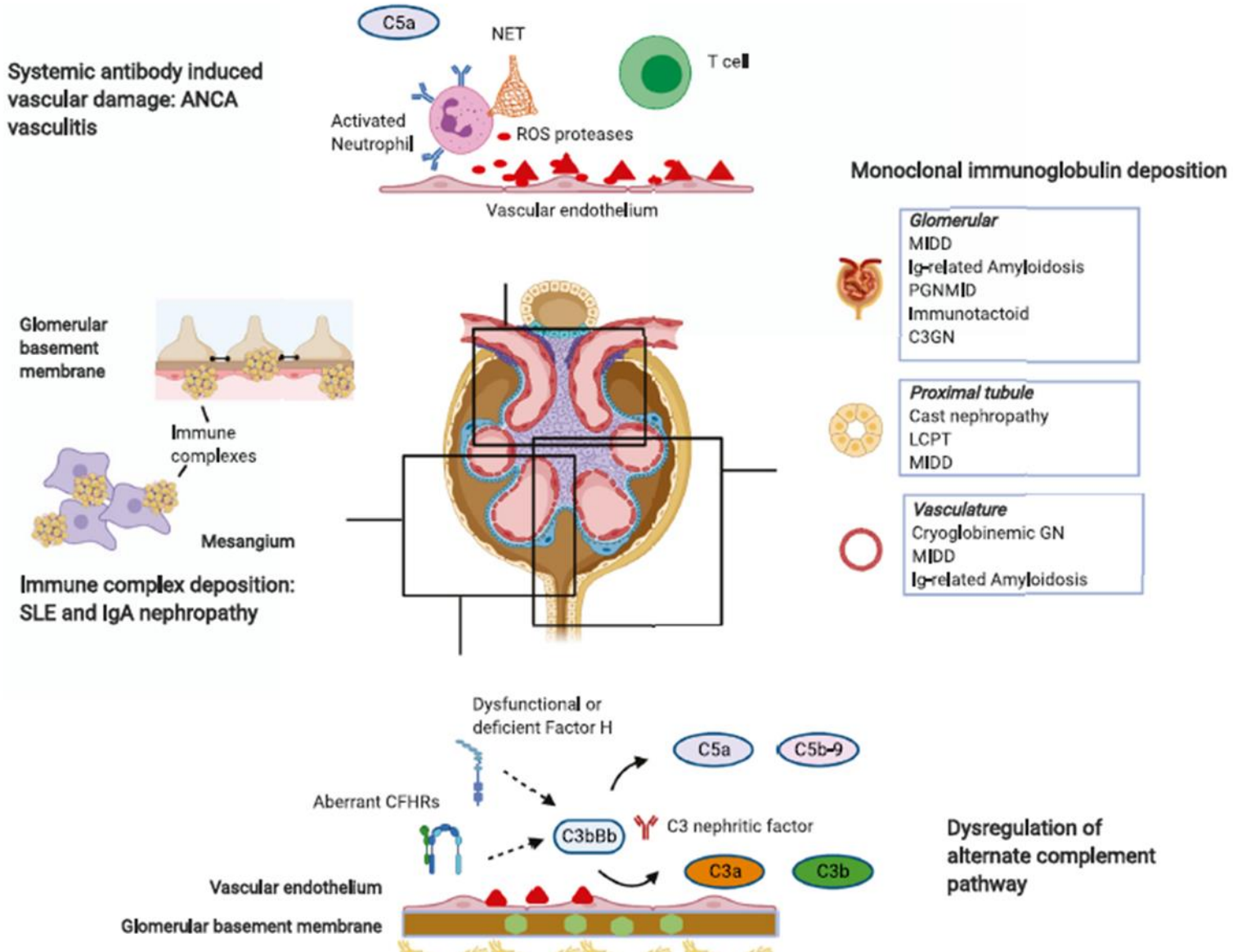
ANCA, anti-neutrophil cytoplasmic antibodies; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; MPO, myeloperoxidase; PLA2Rab+, phospholipase-A2-receptor antibody positive, PR3, proteinase 3

Practice Point 3.1.1. A kidney biopsy may not be required to confirm the diagnosis of MN in patients with a compatible clinical and serological presentation

*Figure MN2. When to consider a kidney biopsy in a PLA2Rab-positive patient**



eGFR, estimated glomerular filtration rate; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor
*In making a decision to perform a kidney biopsy, the risks of a biopsy must be taken into account. The decision is based on patient and physician preferences. This decision to perform a kidney biopsy could be revised in the near future with the development of molecular diagnostics, which could allow for better prediction of outcome for more personalized medicine.


Systemic antibody induced vascular damage: ANCA vasculitis
C5a
NET
T cell
Activated Neutrophil
ROS proteases
Vascular endothelium
Monoclonal immunoglobulin deposition
Glomerular
MIDD
Ig-related Amyloidosis
PGNMID
Immunotactoid
C3GN
Proximal tubule
Cast nephropathy
LCPT
MIDD
Vasculature
Cryoglobinemic GN
MIDD
Ig-related Amyloidosis
Glomerular basement membrane
Immune complexes
Mesangium
Immune complex deposition: SLE and IgA nephropathy
Dysfunctional or deficient Factor H
C5a
C5b-9
Aberrant CFHRs
C3bBb
C3 nephritic factor
C3a
C3b
Vascular endothelium
Glomerular basement membrane
Dysregulation of alternate complement pathway

THE LANCET
Rheumatology

FDA approves avacopan for ANCA-associated vasculitis

Jennifer Thorley

Published: December 03, 2021 • DOI: https://doi.org/10.1016/S2665-9913(21)00391-X •

Article Info

On Oct 8, 2021, the US Food and Drug Administration issued its first new drug approval for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in a decade. The first-in-class approval allows the orally administered complement 5a receptor inhibitor avacopan to be used as an adjunct to standard therapy for the two main forms of ANCA-associated vasculitis (microscopic polyangiitis and granulomatosis with polyangiitis), making avacopan the first drug to be approved with ANCA-associated vasculitis as the primary indication.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

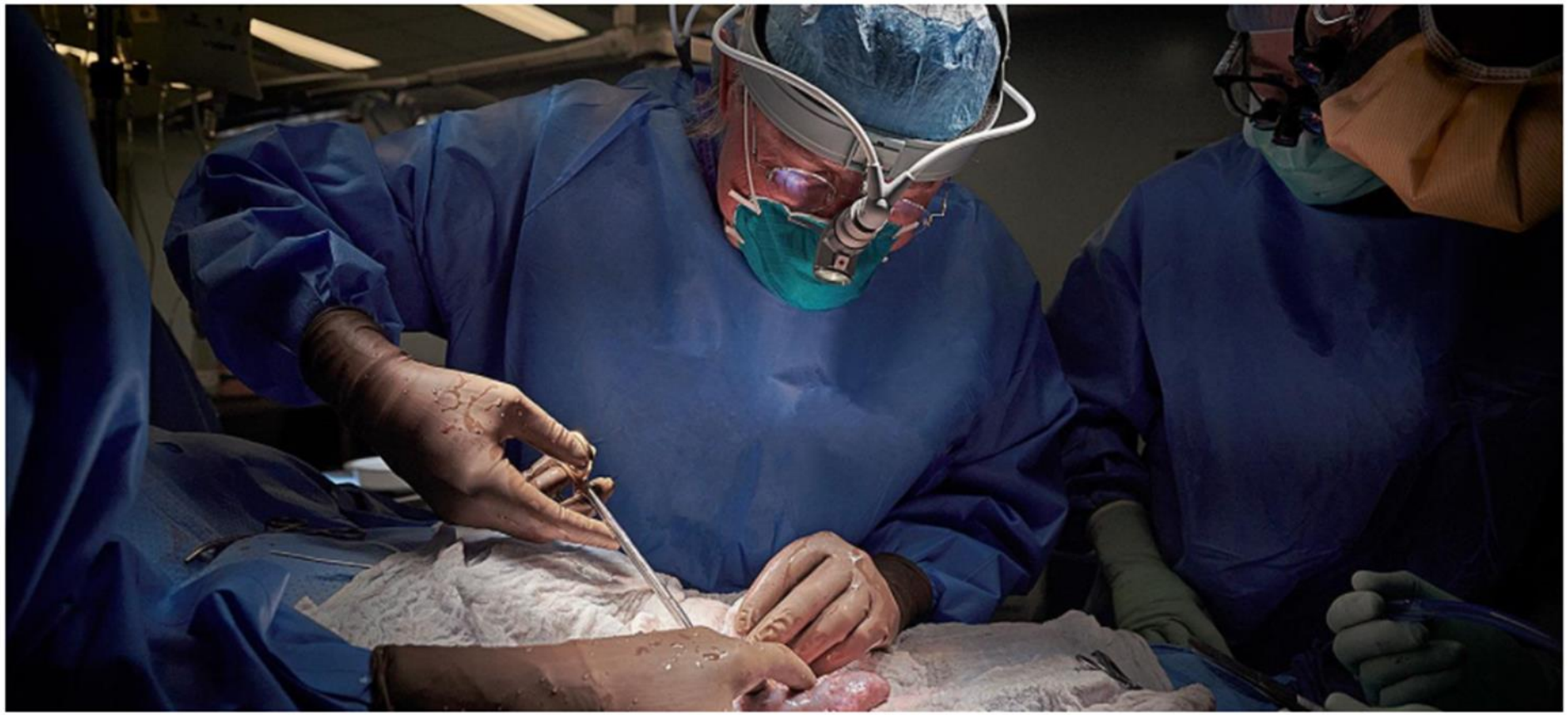
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D.,
for the ADVOCATE Study Group*

Avacopan

- Avacopan noninferior to GC for remission induction at wk 26 (72.3% vs 70.1%) and superior to GC for sustained remission at wk 52 (65.7% vs 54.9%)
- May replace GC in the future

Progress in Xenotransplantation Opens Door to New Supply of Critically Needed Organs



The investigational transplant performed by Dr. Montgomery and his team brings the field one step closer to the goal of an adequate organ supply. PHOTO: JOE CARROTTA

American Journal of Transplantation 2015; 15: 695–704
Wiley Periodicals Inc.

doi: 10.1111/ajt.13091

Chimerism, Graft Survival, and Withdrawal of Immunosuppressive Drugs in HLA Matched and Mismatched Patients After Living Donor Kidney and Hematopoietic Cell Transplantation

J. D. Scandling[1,†], S. Busque[2,†], J. A. Shizuru[3], R. Lowsky[3], R. Hoppe[4], S. Dejbakhsh-Jones[5], K. Jensen[5], A. Shori[2], J. A. Strober[6], P. Lavori[6], B. B. Turnbull[6], E. G. Engleman[7] and S. Strober[5,*]

[1]*Department of Medicine (Nephrology), Stanford University School of Medicine, Stanford, CA*
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[3]*Division of Blood and Marrow Transplantation, Stanford University School of Medicine, Stanford, CA*
[4]*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA*
[5]*Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA*
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[7]*Department of Pathology, Stanford University School of Medicine, Stanford, CA*
[*]*Corresponding author: Samuel Strober, sstrober@stanford.edu*
[†]*These authors contributed equally to this research.*