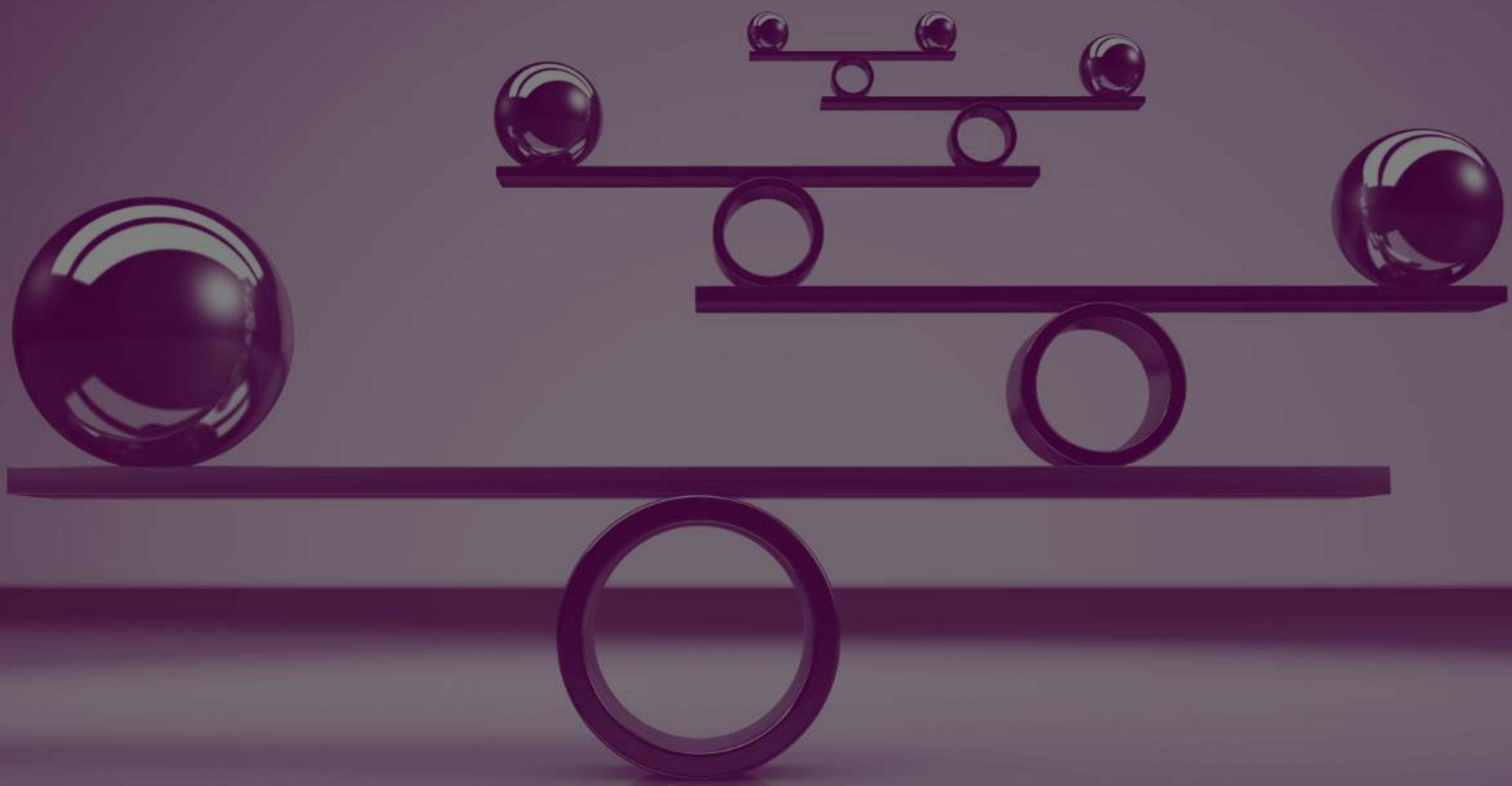
I° BRIXIA DP MEETING

CORSO DI FORMAZIONE IN DIALISI PERITONEALE
Brescia, 4-6 Aprile 2024

Gli inibitori HIF-PHi e gli anti-iperkaliemici.

Le indicazioni e i possibili effetti collaterali dei nuovi farmaci: come usarli con sicurezza anche nei pazienti in dialisi peritoneale.

Silvio Borrelli
Università Vanvitelli - Napoli



Part I: **HIF-PH inhibitors**

Adaptation to hypoxia: a Nobel biological process!

The Nobel Prize in Medicine or Physiology 2019

for their discoveries of how cells sense and adapt to oxygen availability

© Nobel Media. Photo: A. Mahmoud

William G. Kaelin Jr

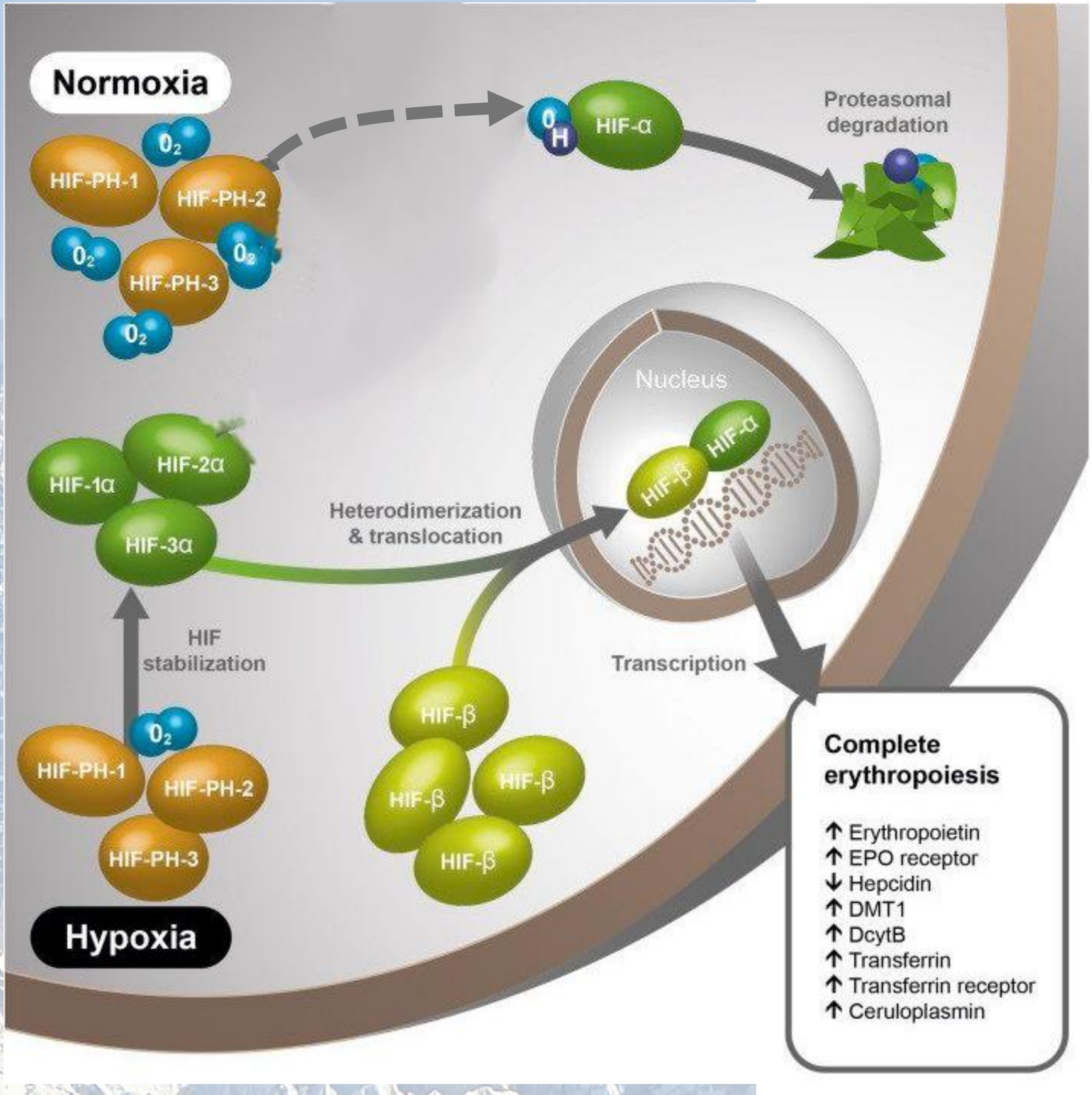
© Nobel Media. Photo: A. Mahmoud

Sir Peter J. Ratcliffe

© Nobel Media. Photo: A. Mahmoud

Gregg L. Semenza

HIF PATHWAY REGULATION

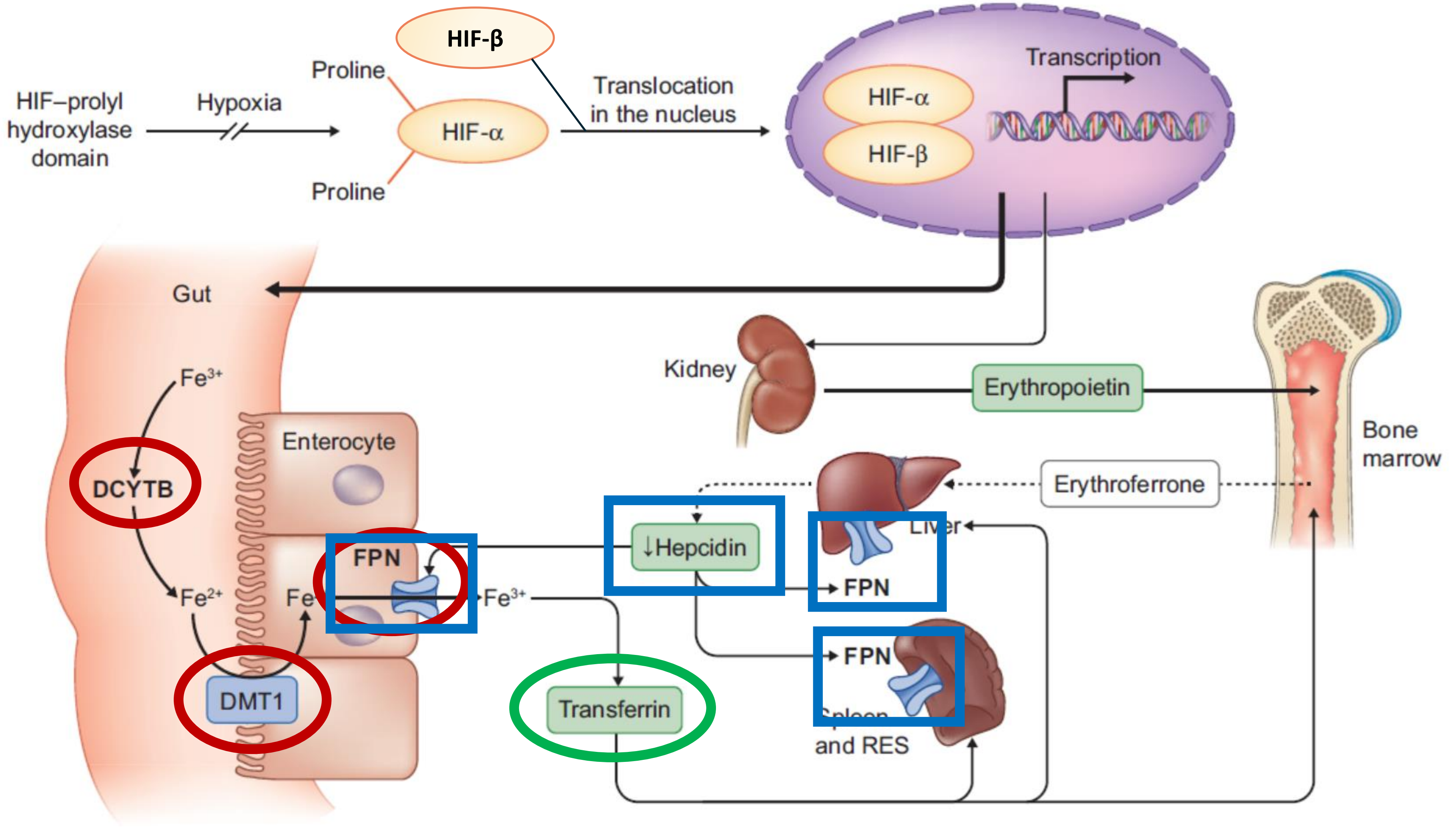


HIF pathway activation induces a coordinated erythropoietic response

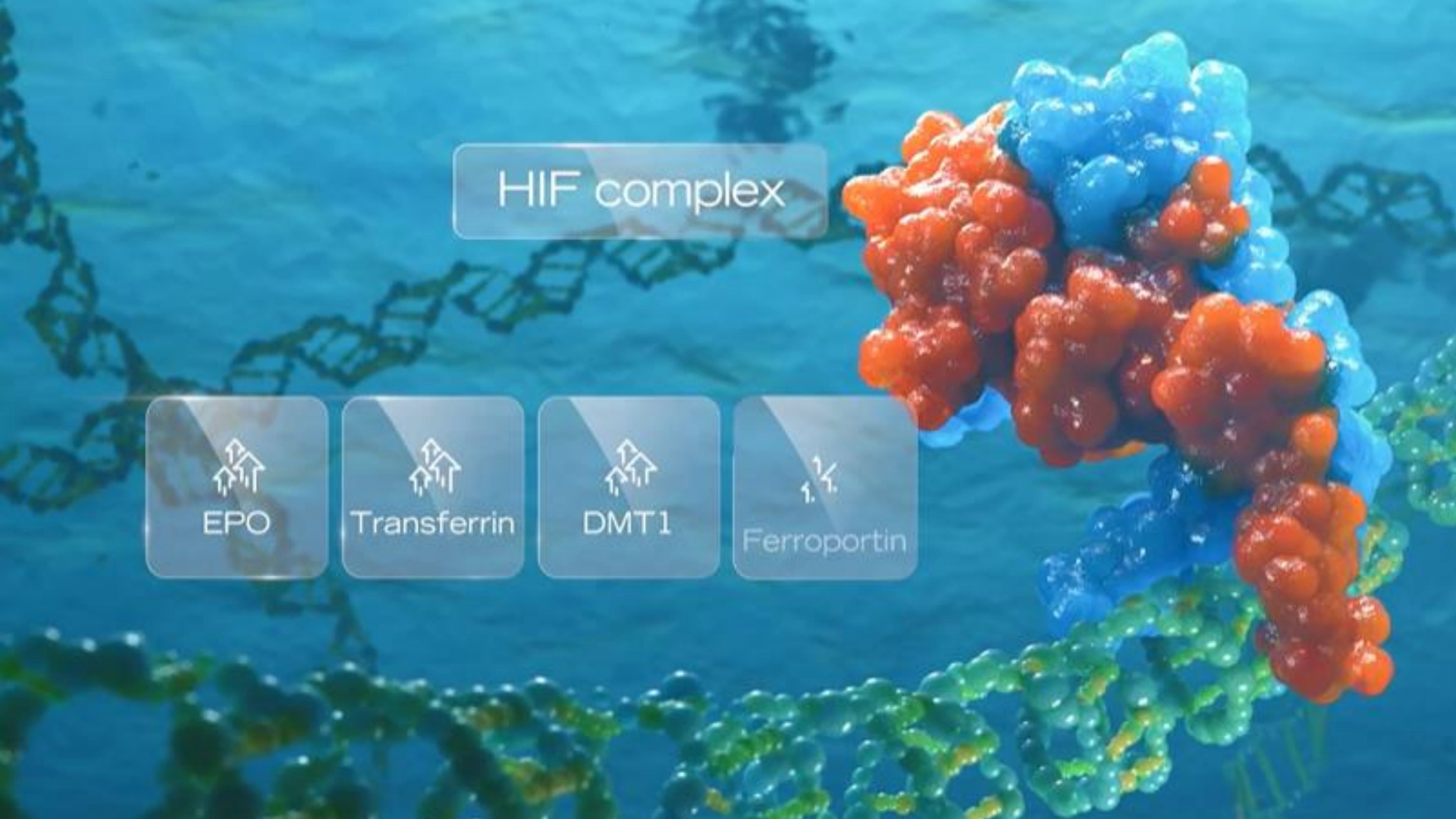
1. Increases of intestinal absorption of iron inducing duodenal cit. B, DMT-1 and ferroportin

2. Improves peripheral iron delivery by up-regulating transferrin and its receptor (TFr)

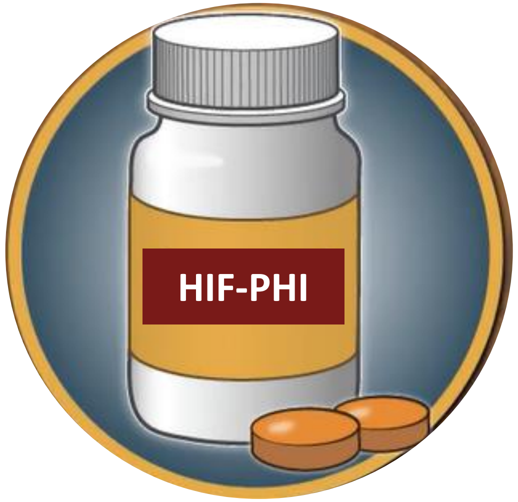
3. Increases iron mobilization suppressing hepcidin which induces FPN expression



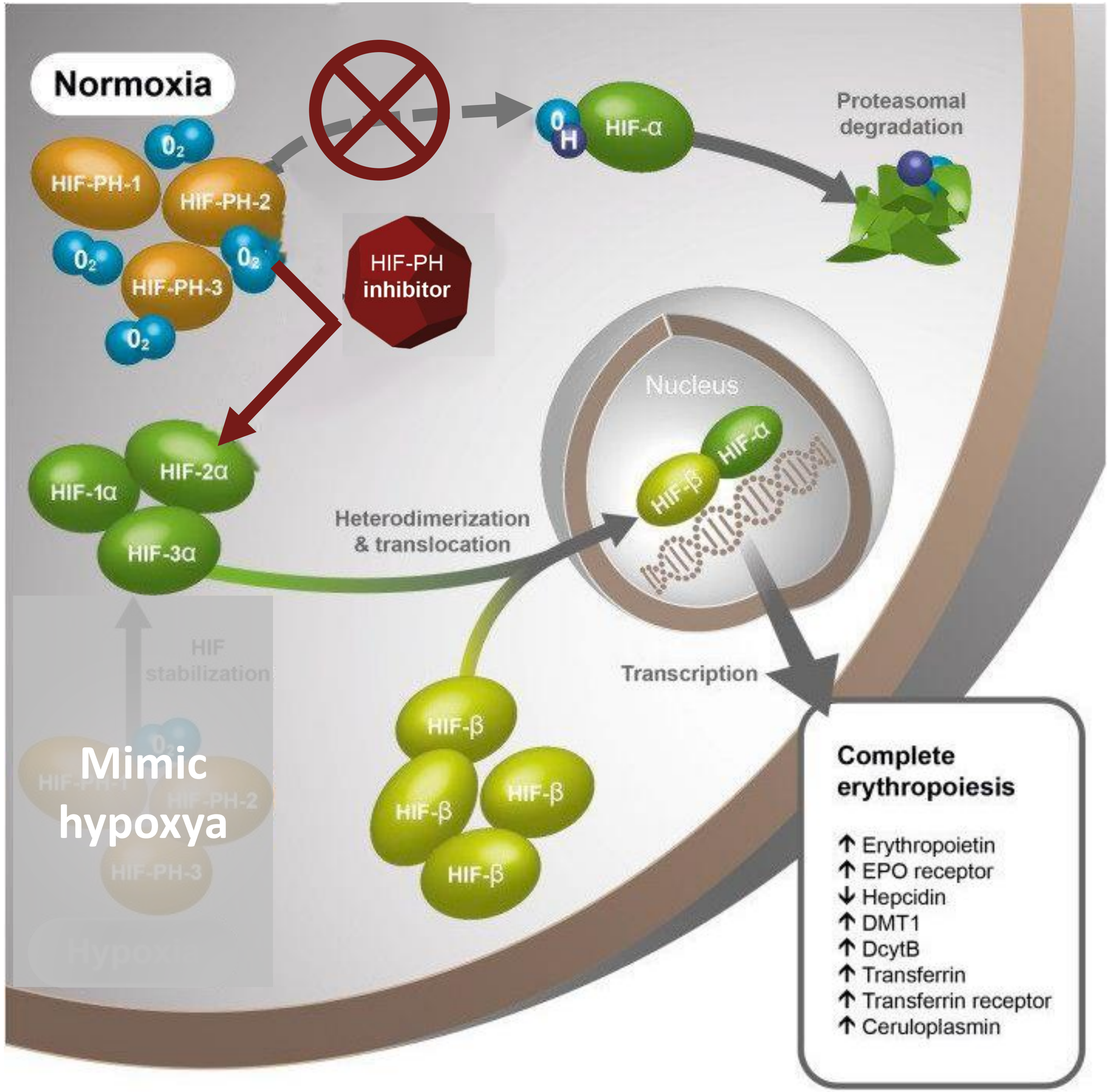
Locatelli, F, Del Vecchio L, De Nicola L, Minutolo R. Nephrol Dial Transplant 2021


HIF complex
EPO
Transferrin
DMT1
Ferroportin

HIF-PHIs



ROXADUSTAT (in Italy)
DAPRODUSTAT (in US only in hemodialysis)
VADADUSTAT (in Japan and in Europe)
ENARODUSTAT
MOLIDUSTAT
DESIDUSTAT



Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials.

Minutolo R, Liberti ME, Simeon V, Sasso FC, Borrelli S, De Nicola L, Garofalo C.

Meta-analysis

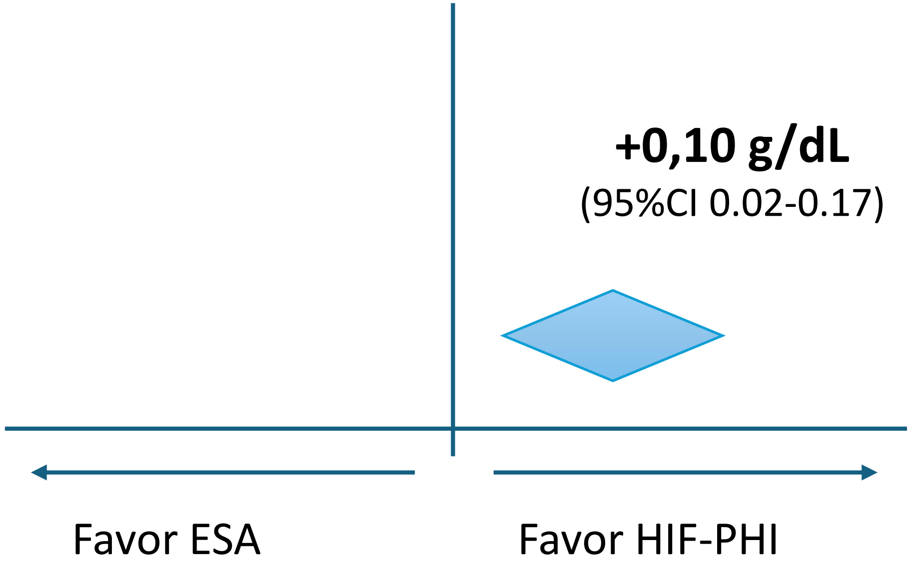
- 26 RCT (phase-3)
- 24387 CKD patients (59% dialysis)

Treatment period: 16.5 months(range 6–42)

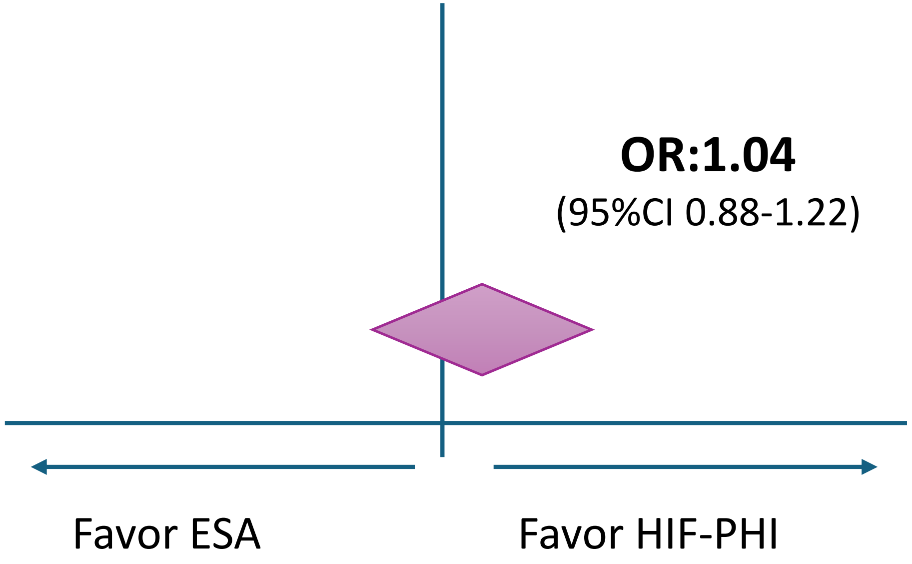
ROXADUSTAT

ESA (long acting, N= 17; short-acting, N=9)

Hb change from baseline (HIF-PHIs vs ESA):



Hb target achievement (HIF-PHIs vs ESA):

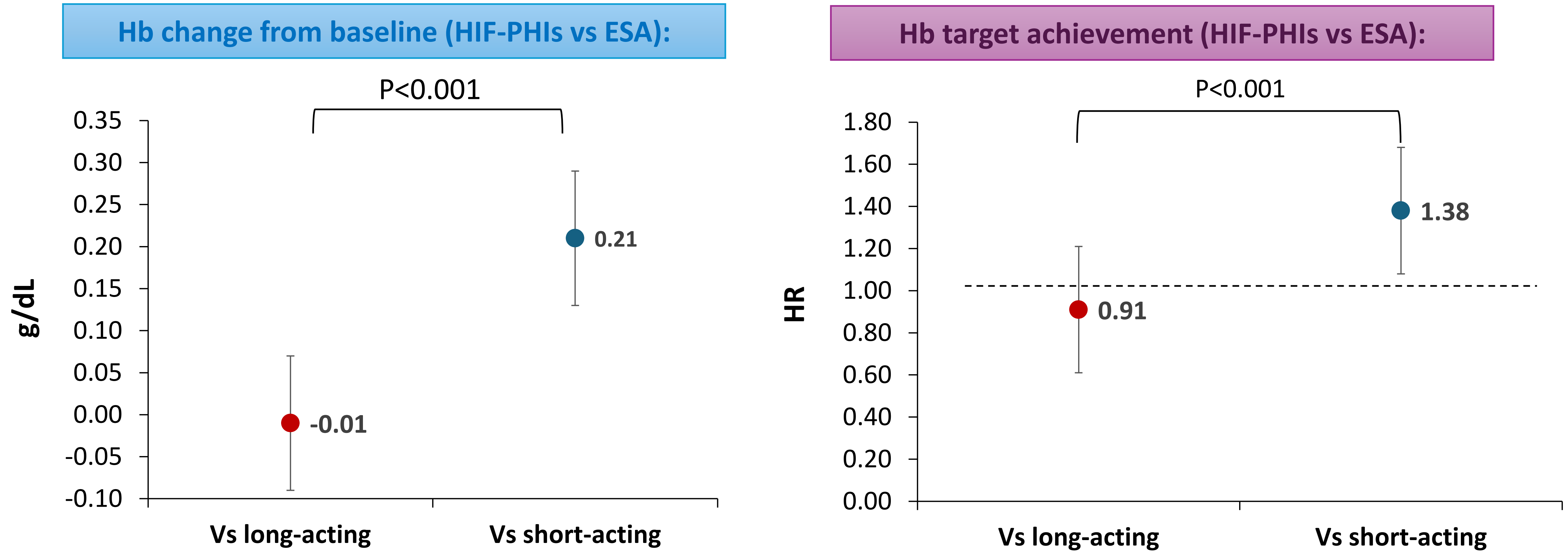


Clin Kidney J. 2023 Jun 22;17(1):sfad143.

Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials.

Minutolo R, Liberti ME, Simeon V, Sasso FC, Borrelli S, De Nicola L, Garofalo C.

Long-acting vs short acting

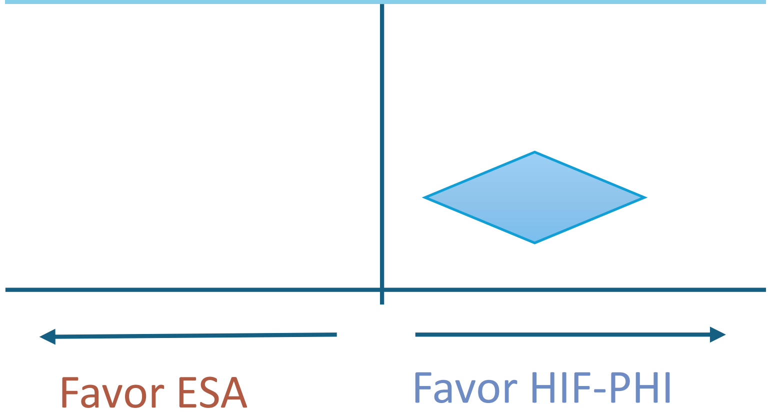


Clin Kidney J. 2023 Jun 22;17(1):sfad143.

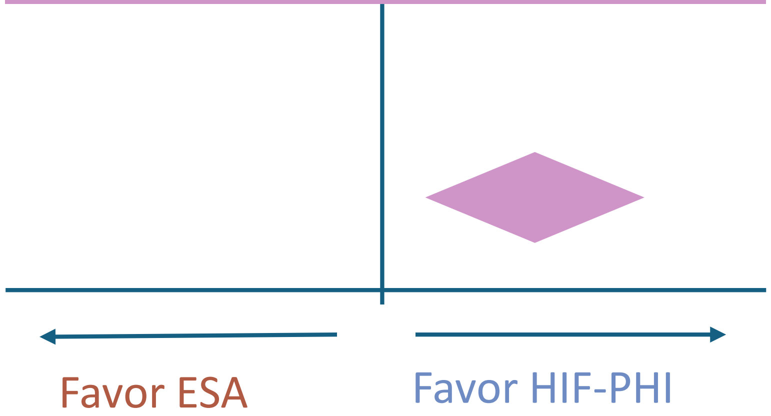
Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials.

Minutolo R, Liberti ME, Simeon V, Sasso FC, Borrelli S, De Nicola L, Garofalo C.

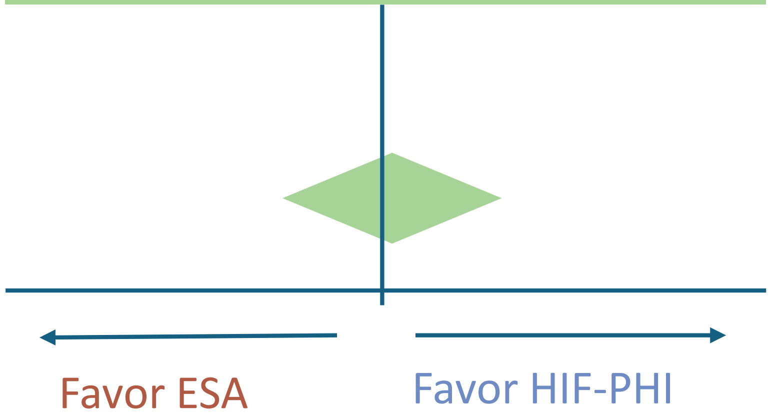
Hepcidin (HIF-PHIs vs ESA):
-19.2 g/dL (95%CI 28.4-10.0)



Ferritin (HIF-PHIs vs ESA):
-16.8 g/dL (95%CI –32.4; -1.3)



TSAT (HIF-PHIs vs ESA):
-0.33 g/dL (95%CI -1.67- 0.02)



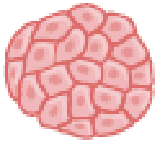
3.14 mg/week i.v. IRON dose

Clin Kidney J. 2023 Jun 22;17(1):sfad143.

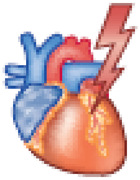
Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials.

Minutolo R, Liberti ME, Simeon V, Sasso FC, Borrelli S, De Nicola L, Garofalo C.

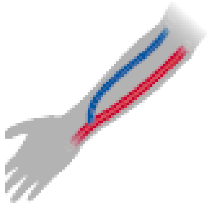
Safety (HIF-PHI vs ESA)



Rate ratio of cancer
0.93 (95% C.I. :0.76-1.13)



Rate ratio of MACE
1.00 (95% C.I. :0.94-1.07)

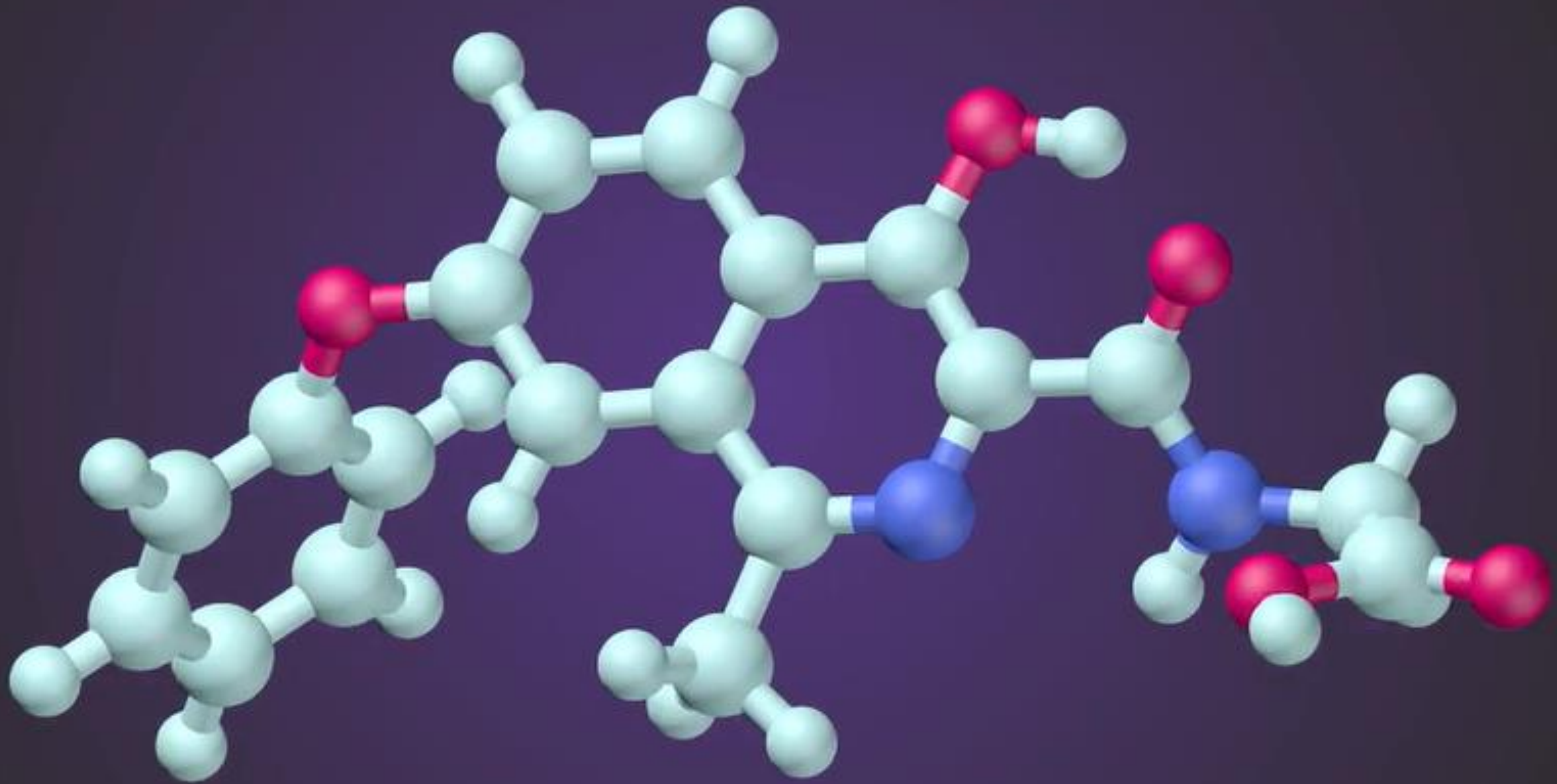


Rate ratio of AVF thrombosis
1.00 (95% C.I. :0.94-1.07)

Rate ratio of all-cause detah
1.02 (95% C.I. :0.95-1.09)

Clin Kidney J. 2023 Jun 22;17(1):sfad143.

ROXADUSTAT



Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis.

Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, Tao Y, Liang X, Liu Z, Xing C, Chen J, Luo L, Zuo L, Liao Y, Liu BC, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP.

RCT

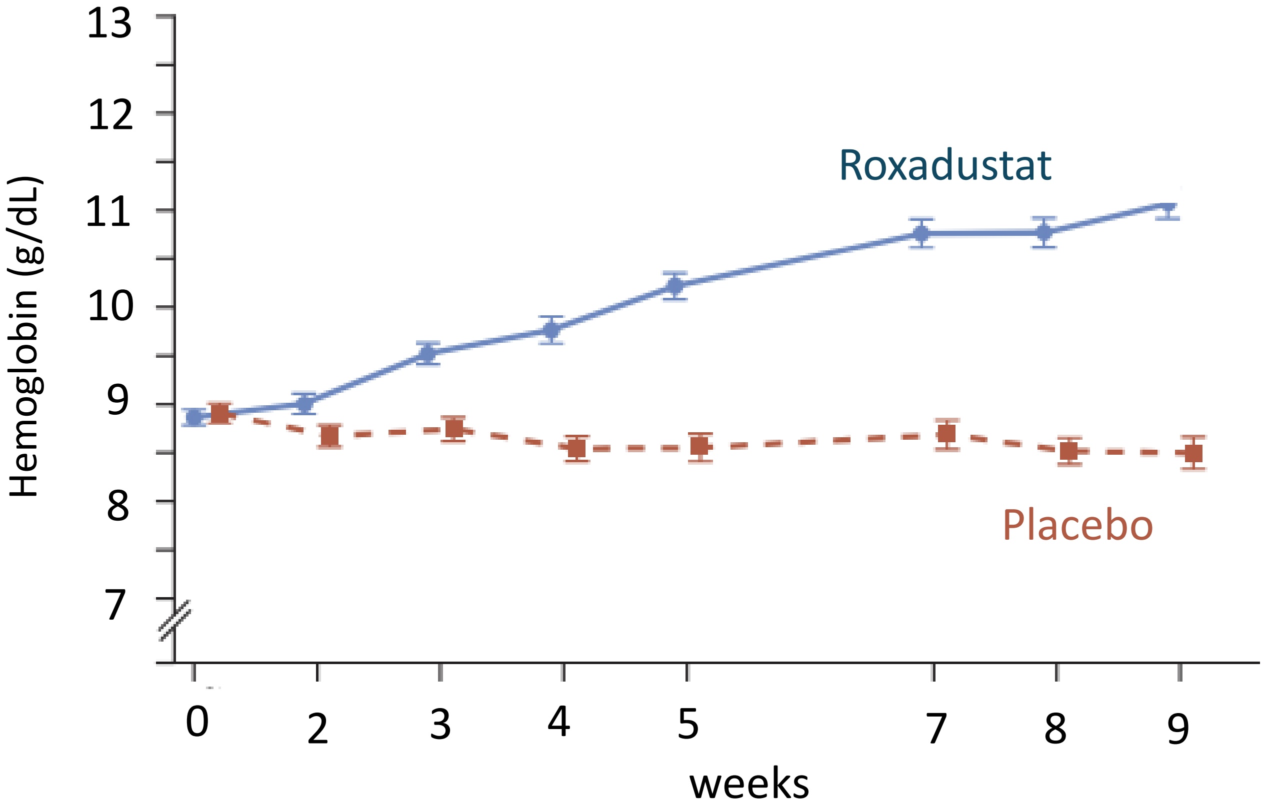
- Patients CKD

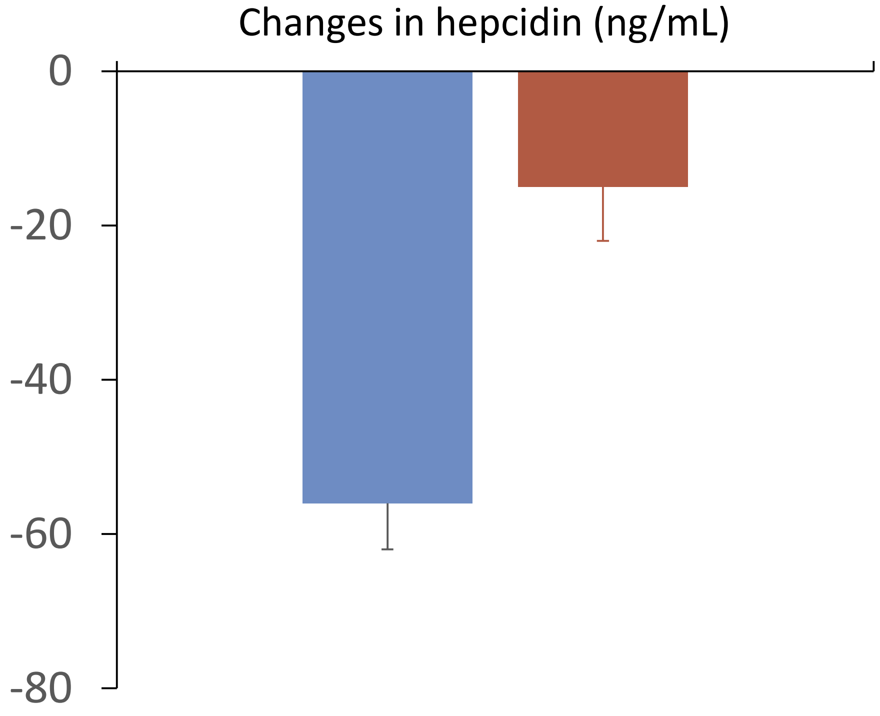
N
152
1:2

Treatment period: 9 week

ROXADUSTAT (n = 101)

PLACEBO (n = 51)





N Engl J Med. 2019 Sep 12;381(11):1001-1010.

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, Liang X, Jiang G, Liu Z, Li X, Zuo L, Luo L, Wang J, Zhao MH, Liu Z, Cai GY, Hao L, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP.

RCT

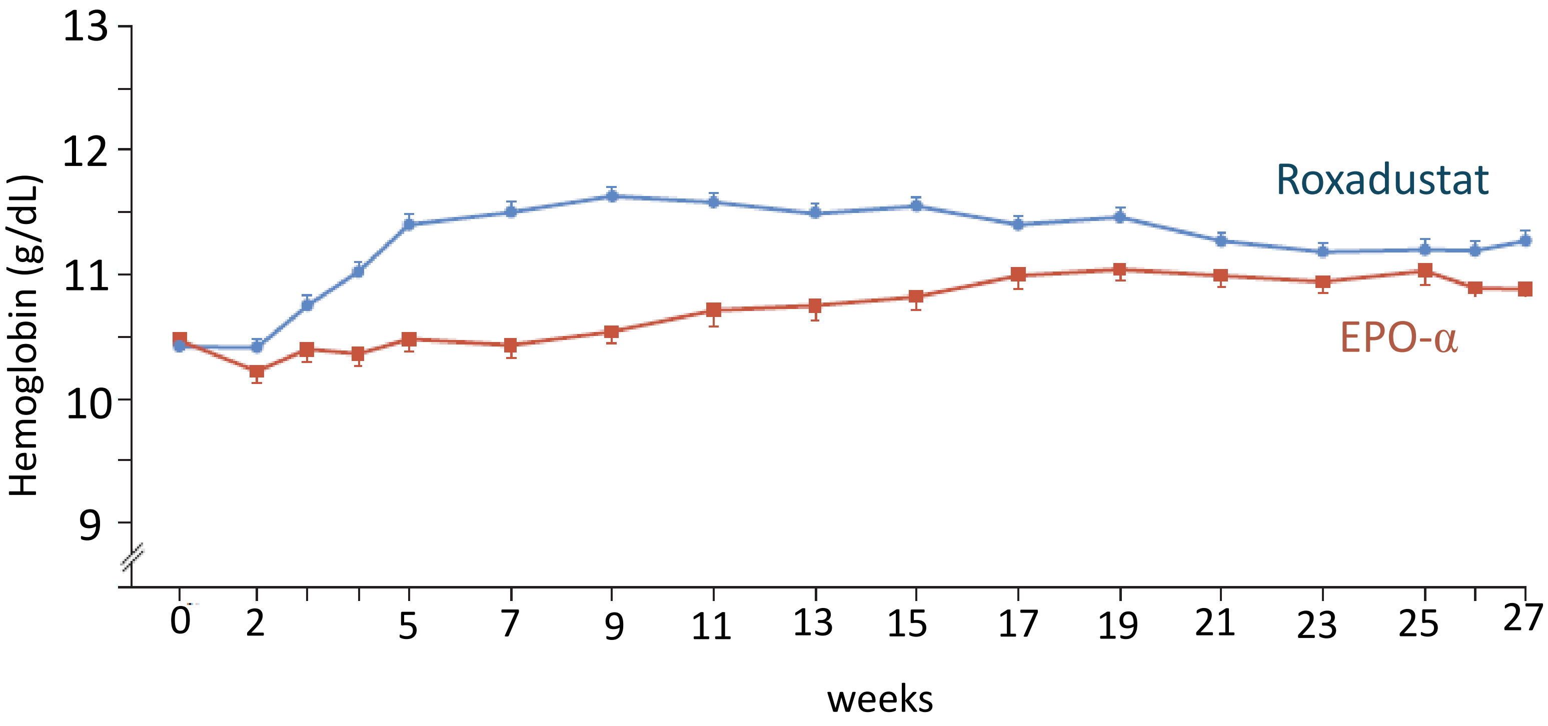
- Patients in chronic dialysis

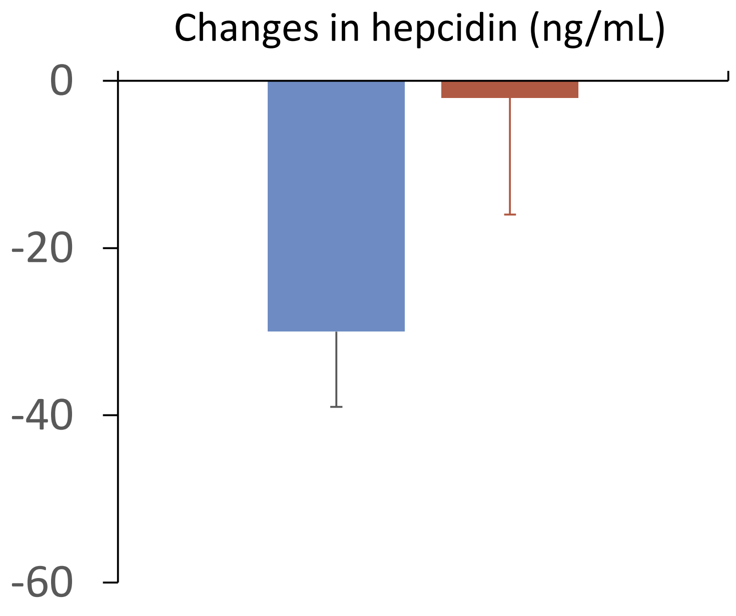
N
305
1:2

Treatment period: 27 week

ROXADUSTAT (n = 204)

PLACEBO (n = 101)

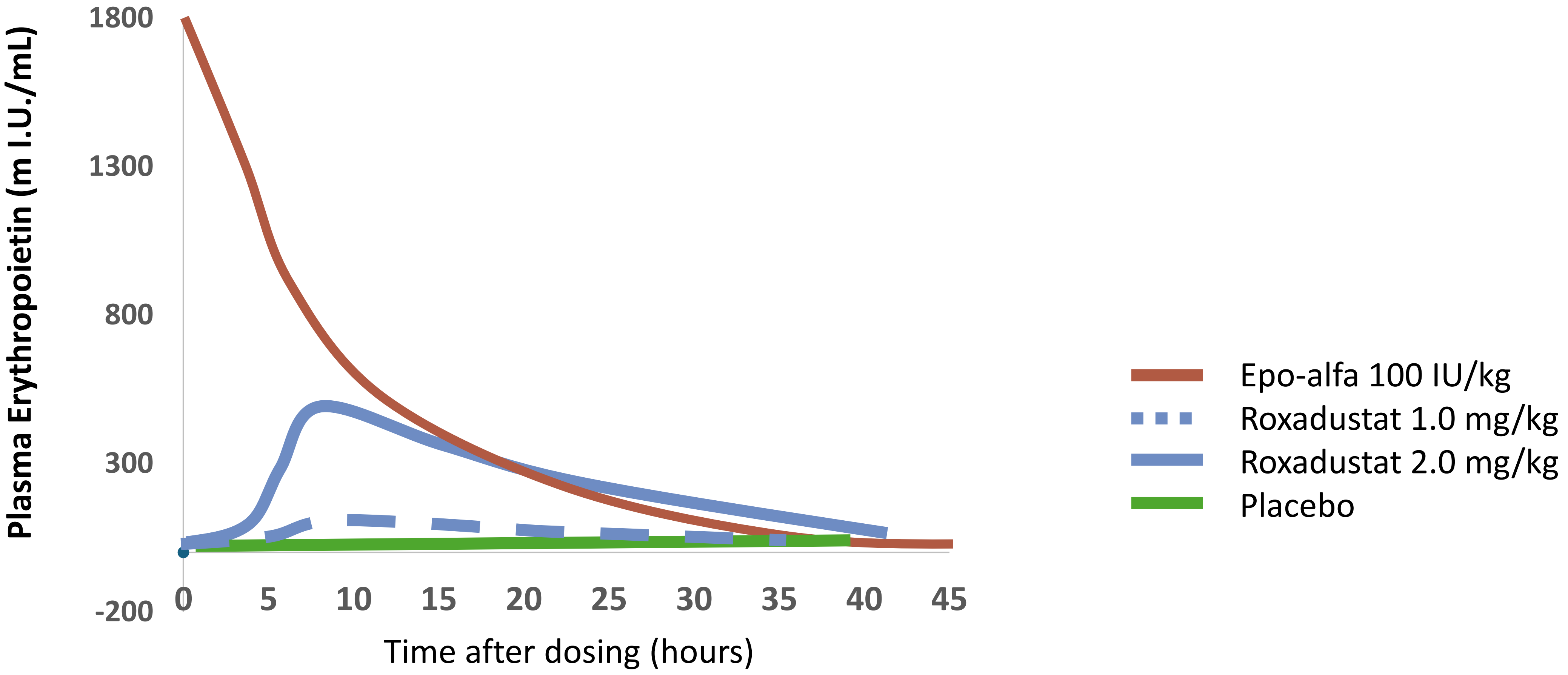




N Engl J Med. 2019 Sep 12;381(11):1011-1022.

Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat (FG-4592) for Treatment of Anemia in Chronic Kidney Disease: A Placebo-Controlled Study of Pharmacokinetic and Pharmacodynamic Profiles in Hemodialysis Patients.

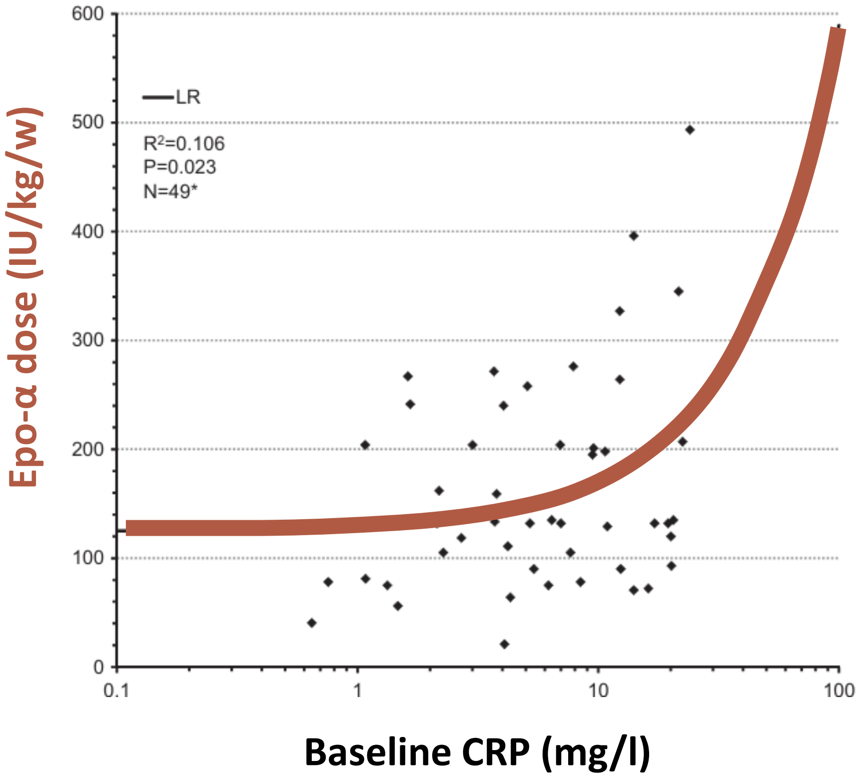
Provenzano R, Tumlin J, Zabaneh R, Chou J, Hemmerich S, Neff TB, Yu KP.

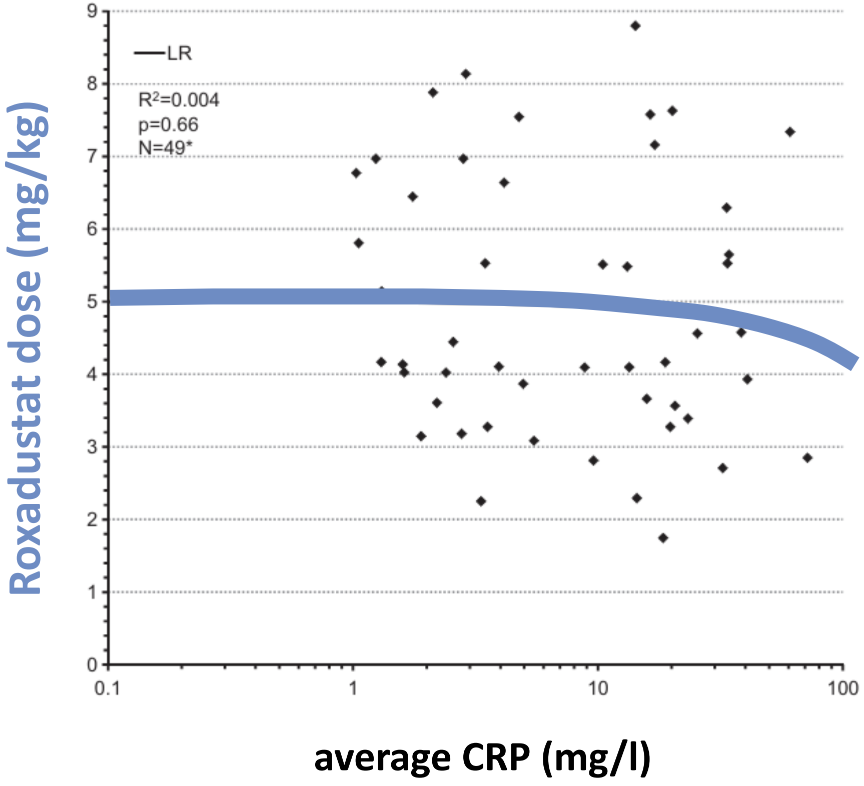


J Clin Pharmacol. 2020 Nov;60(11):1432-1440.

Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study.

Provenzano R, Besarab A, Wright S, Dua S, Zeig S, Nguyen P, Poole L, Saikali KG, Saha G, Hemmerich S, Szczech L, Yu KH, Neff TB.





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

Roxadustat in peritoneal dialysis

Roxadustat treatment for anemia in peritoneal dialysis patients: A randomized controlled trial.

Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, Li B.

Patients

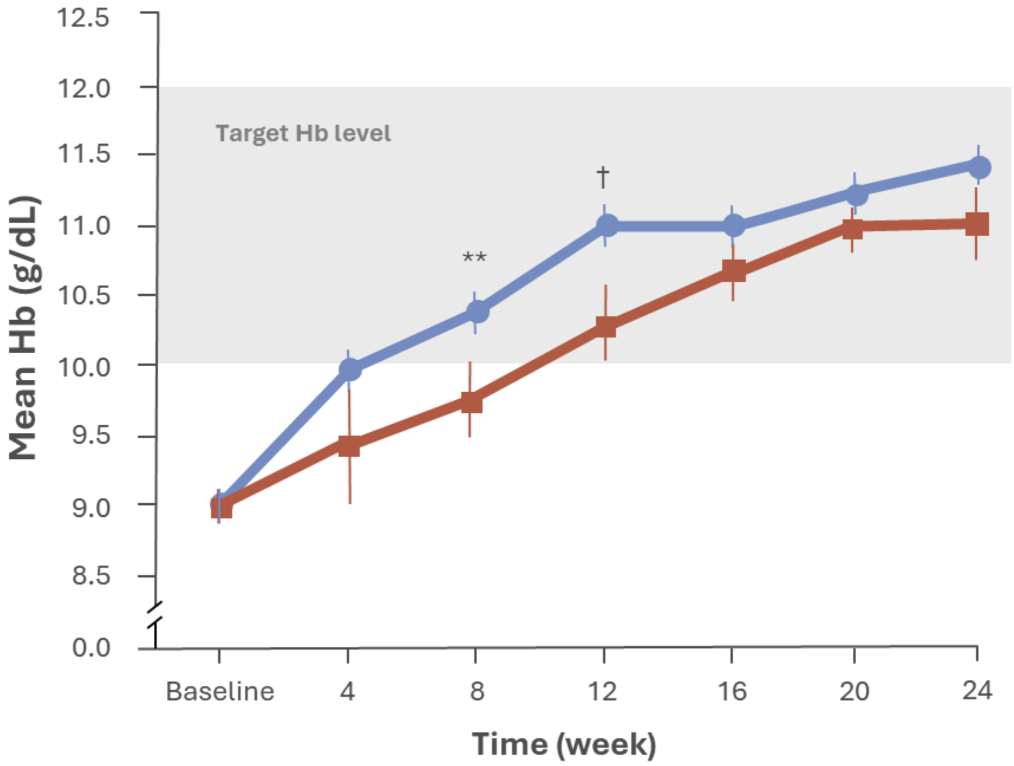
- Patients undergoing PD
- Hb < 12 g/dL
- +/- ESA treatment

N
129
2:1

Treatment period: 24 weeks

ROXADUSTAT (n = 86)

EPO-α (n = 43)



Cumulative response rate at week 24:

ROXADUSTAT 96%

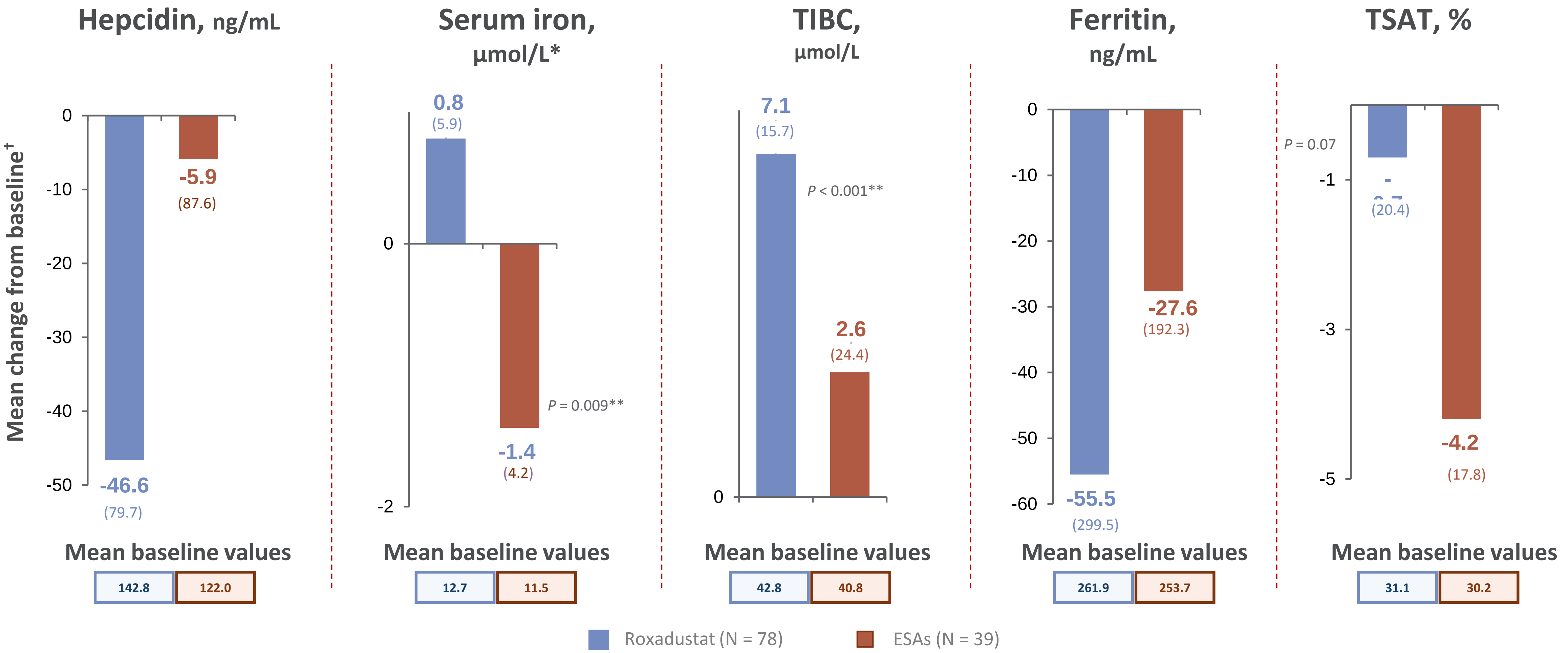
EPO-α 92%

J Formos Med Assoc. 2022 Feb;121(2):529-538.

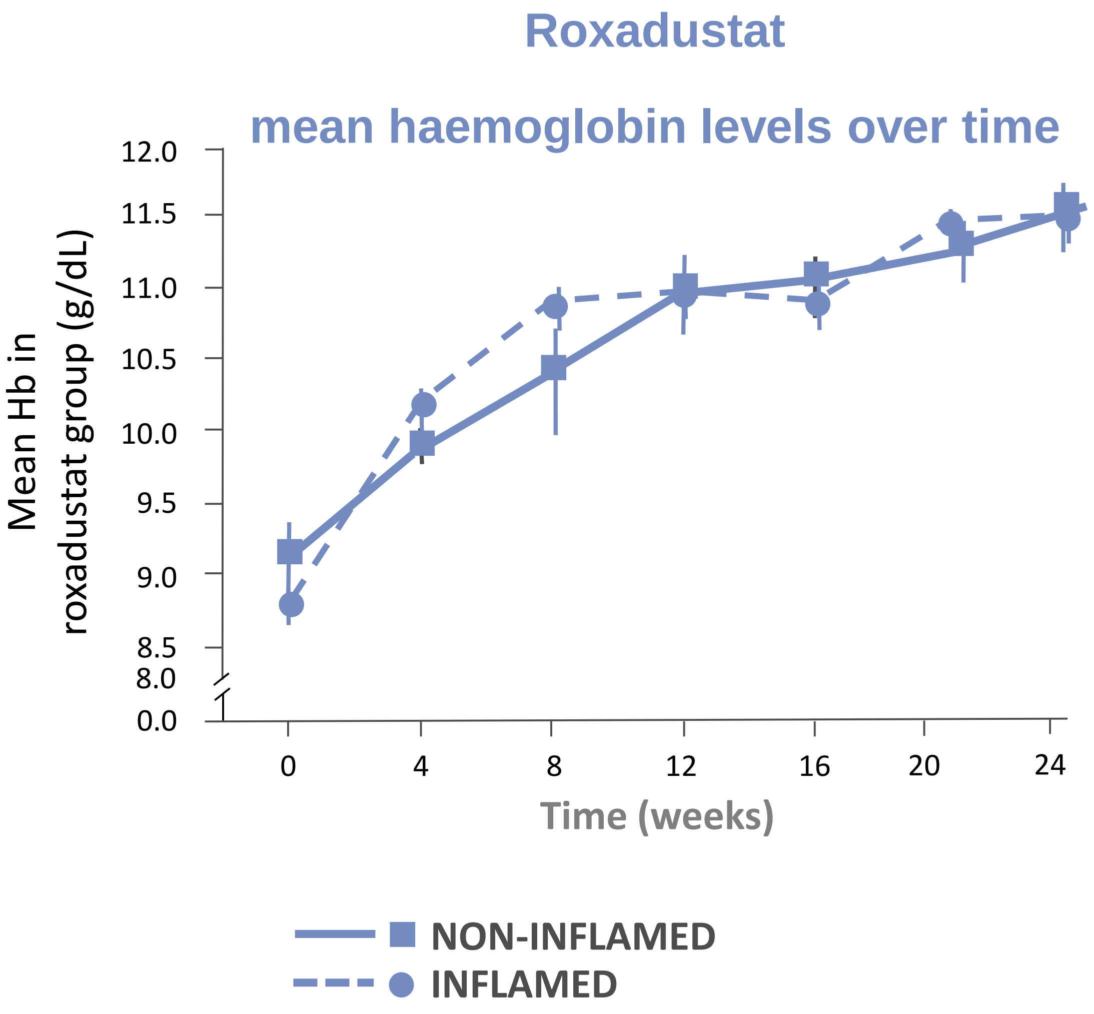
Roxadustat treatment for anemia in peritoneal dialysis patients: A randomized controlled trial.

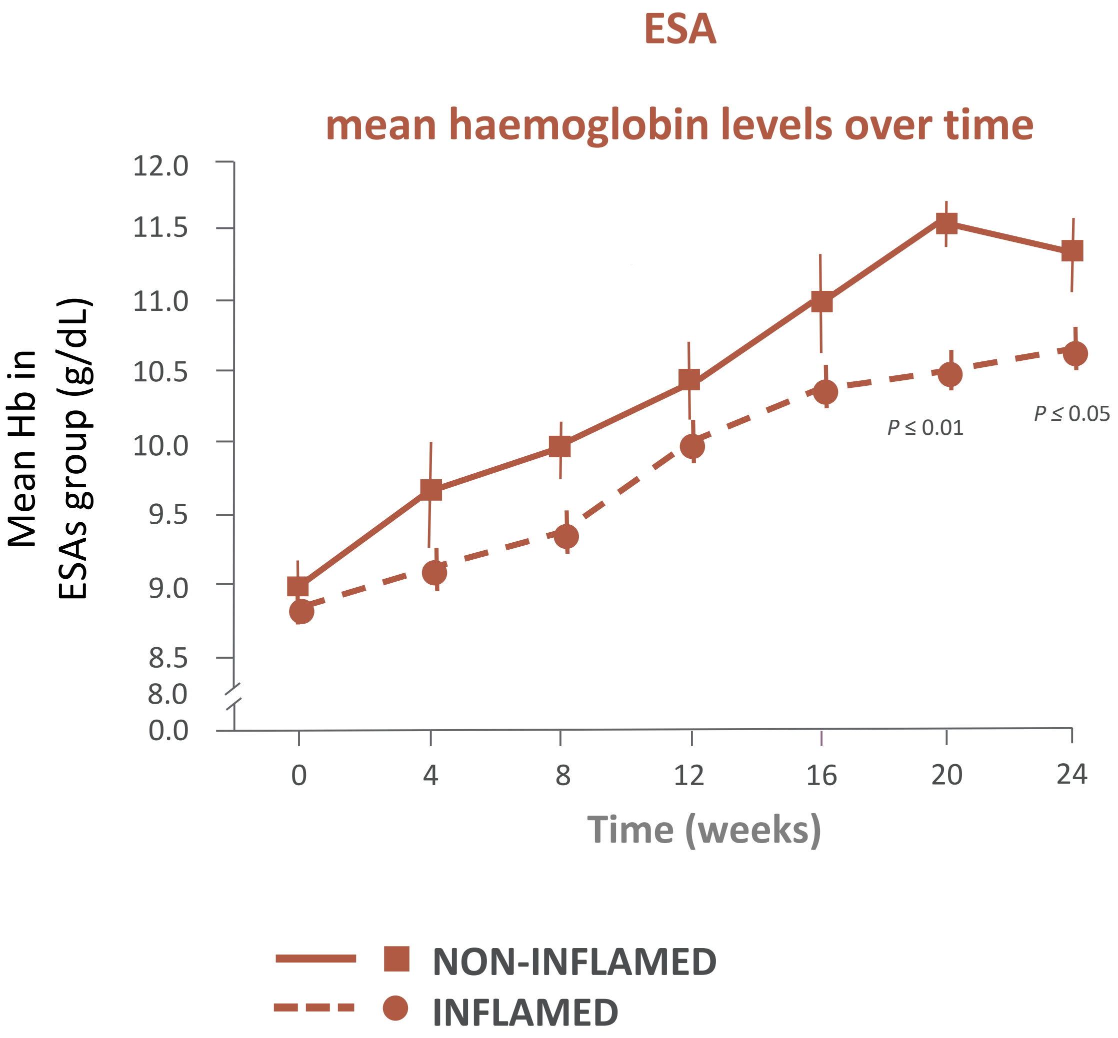
Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, Li B.

Mean change from baseline of iron biomarker levels to Week 12

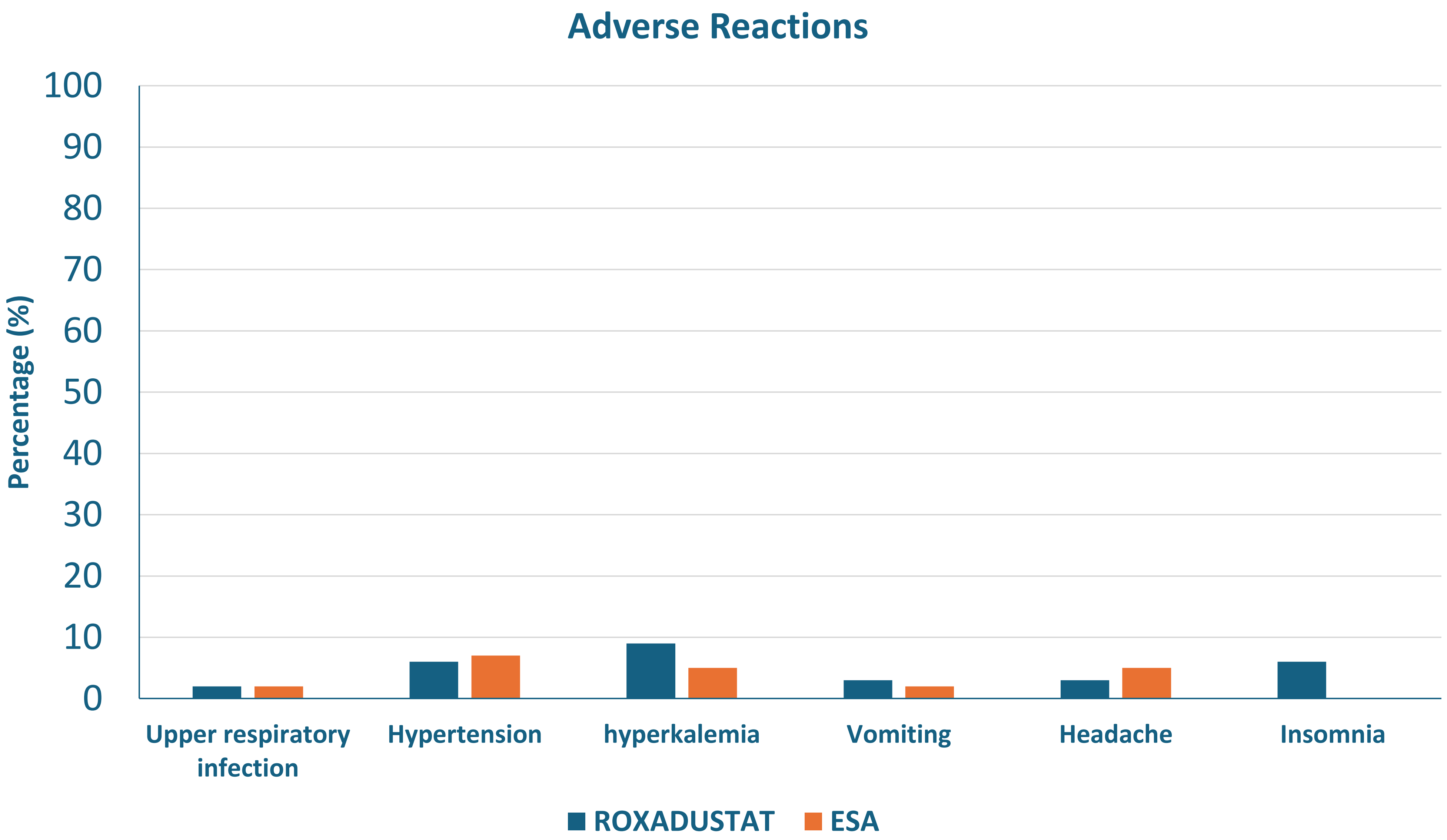


Roxadustat treatment for anemia in peritoneal dialysis patients: A randomized controlled trial.
Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, Li B.





Roxadustat treatment for anemia in peritoneal dialysis patients: A randomized controlled trial.
Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, Li B.



J Formos Med Assoc. 2022 Feb;121(2):529-538.

Effects of Roxadustat on the Anemia and Iron Metabolism of Patients Undergoing Peritoneal Dialysis.

Hirai K, Nonaka H, Ueda M, Morino J, Kaneko S, Minato S, Mutsuyoshi Y, Yanai K, Ishii H, Matsuyama M, Kitano T, Aomatsu A, Miyazawa H, Ito K, Ueda Y, Ookawara S, Morishita Y.

Retrospective analysis

- Patients undergoing PD
- ESA treatment

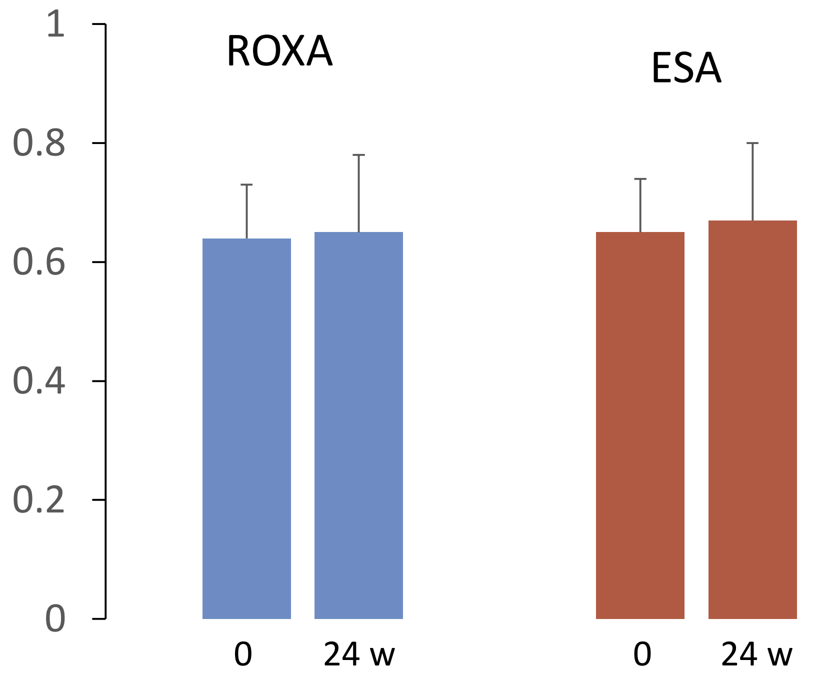
N 39

Treatment period: 24 weeks

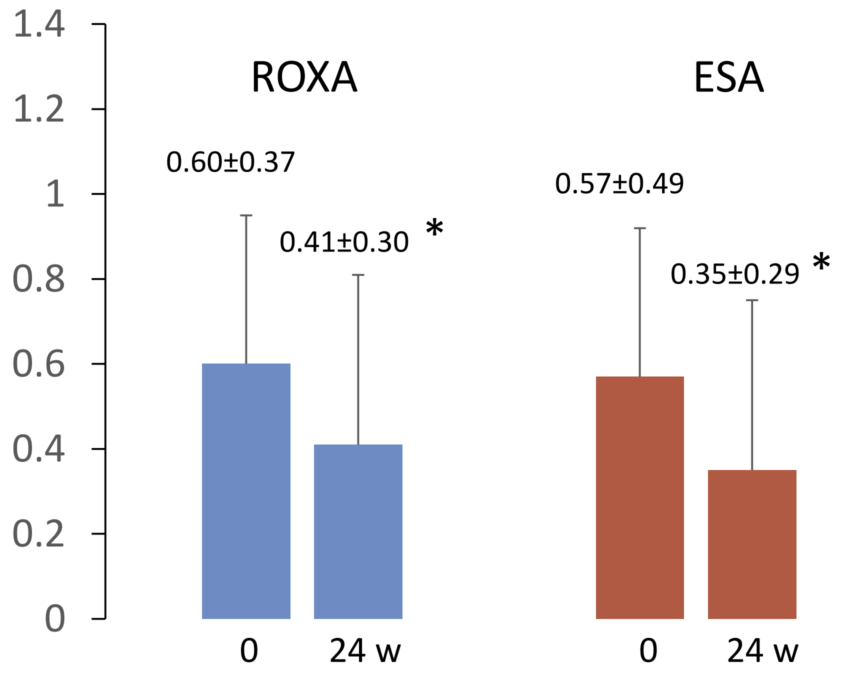
Roxadustat (n = 16)

ESA (n = 23)

Changes in D/P creatinine



Changes in renal Kt/V



Front Med (Lausanne). 2021 Jul

CONCLUSIONS – PART 1

HIF-PH inhibitors mimics the body’s natural response to hypoxia

HIF-PH inhibitors stimulates a coordinated erythropoietic response that not only increases erythropoietin (EPO) levels, but also increases iron availability as well as helping to overcome the effects of inflammation by suppressing hepcidin.

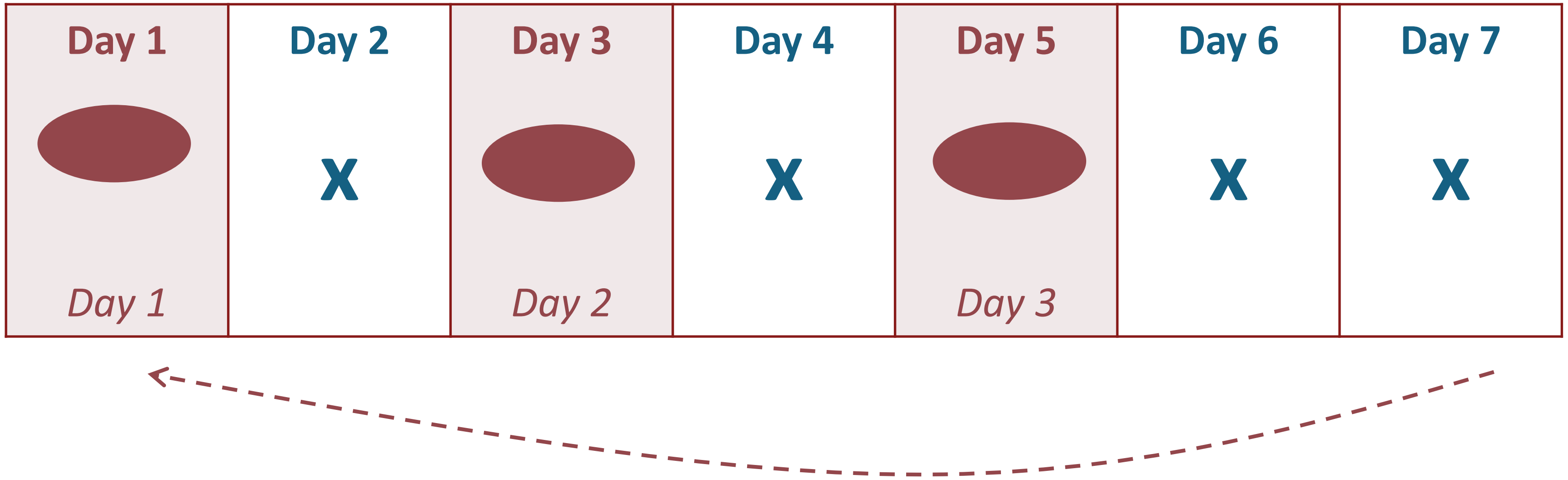
In patients treated by peritoneal dialysis, the use of HIF-PH is associated with:

1. **Sustained haemoglobin control, irrespective of inflammation**
2. **Improved iron regulation and reduced use of IV iron compared with exogenous EPO**

Long-term surveillance from post-marketing data are, however, of fundamental importance to definitely confirm the lack of safety signals.

Appendix –prescription ROXADUSTAT

- 70 mg per three times a week (B.W. < 100 kg)
- 100 mg per three times a week (B.W. > 100 kg)



Repeat on the same each week

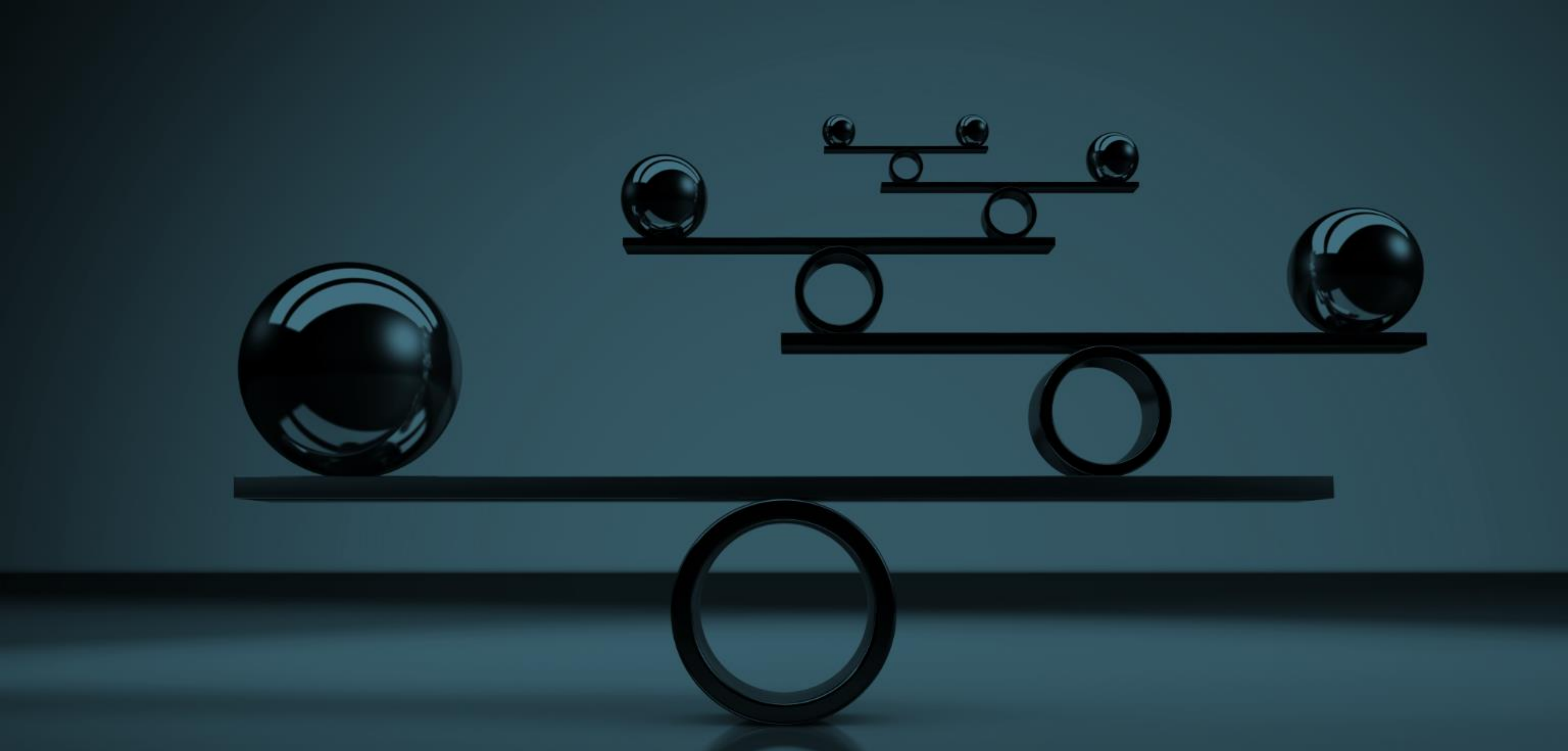
150 mg

100 mg

70 mg

50 mg

20 mg



Part II: K binders

Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort.

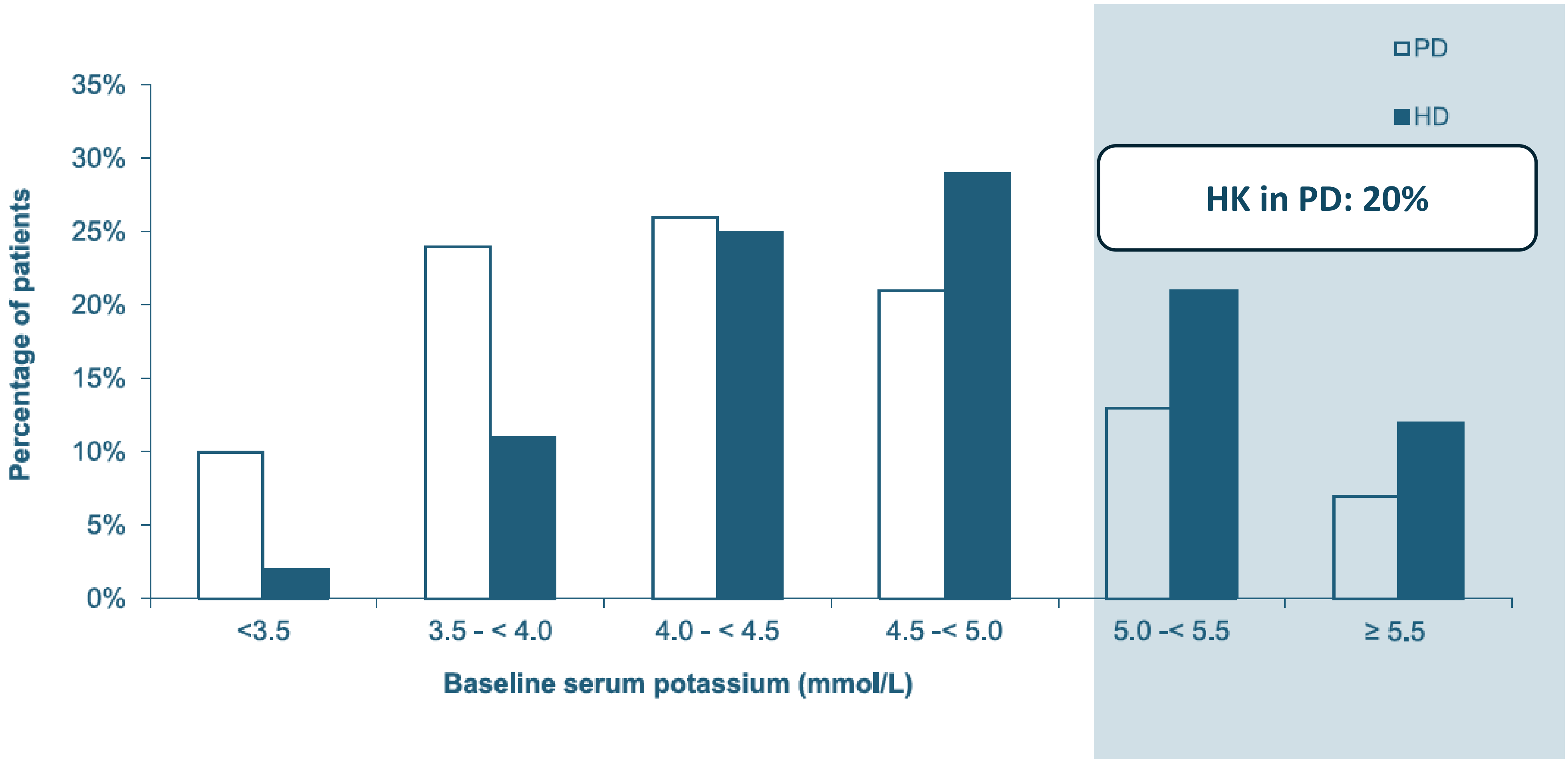
Torlén K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R.

Cohort study (Da Vita facilities) 2001 – 2006

Maintenance dialysis patients N=122,219

PD:10,468

HD=111,651



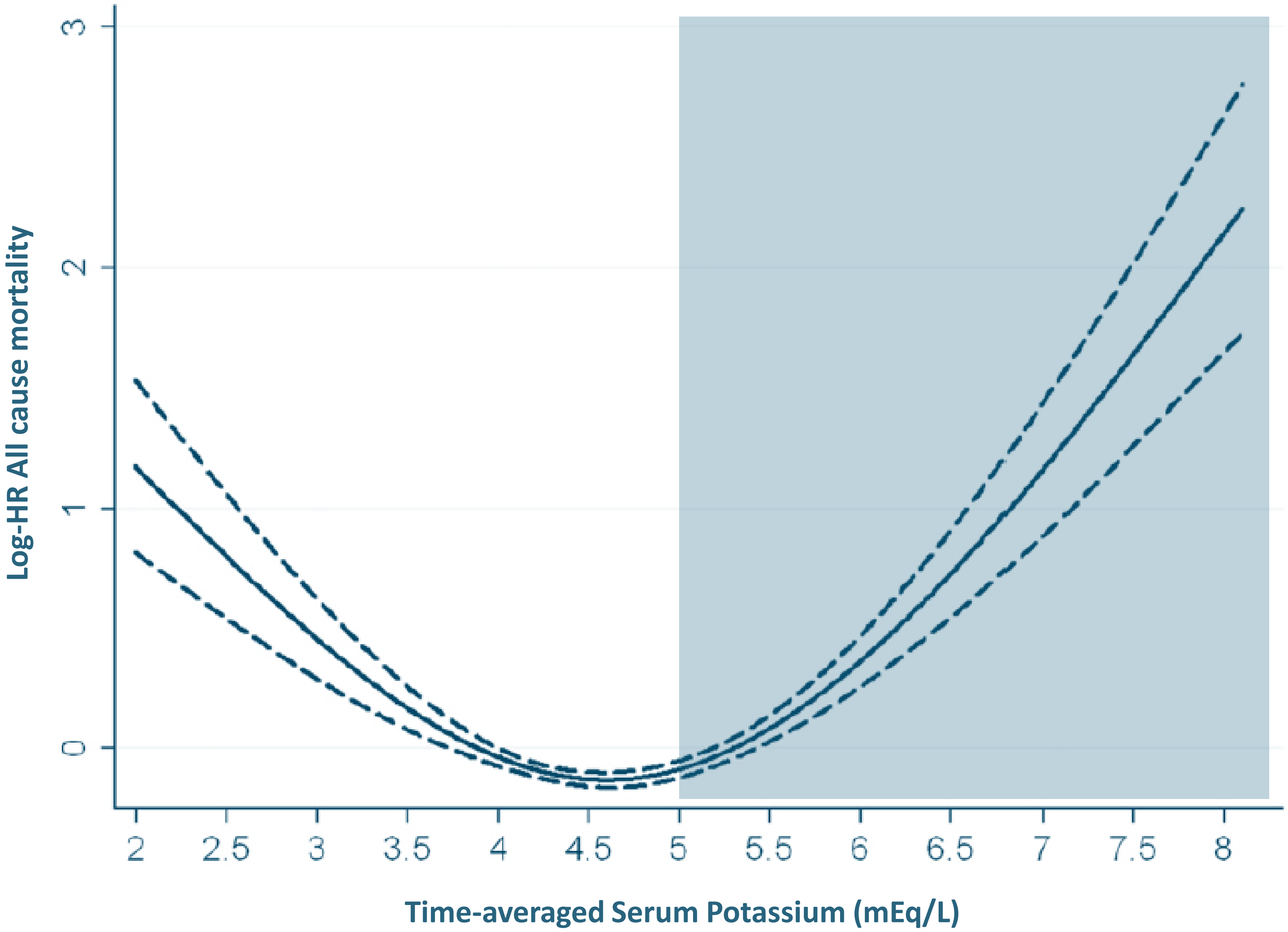
Clin J Am Soc Nephrol. 2012 Aug;7(8):1272-84.

Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort.

Torlén K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R.

PD:10,468

Association of serum K and mortality in PD



Clin J Am Soc Nephrol. 2012 Aug;7(8):1272-84.

INDIRECT EFFECTS OF HYPERKALEMIA

RAASi-MRA SUSPENSION (or dose reduction)

SPS (*Kayexalate*)

REDUCTION IN INTAKE of K-RICH FOOD

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for preserving residual kidney function in peritoneal dialysis patients.

Zhang L, Zeng X, Fu P, Wu HM.

Meta-analysis

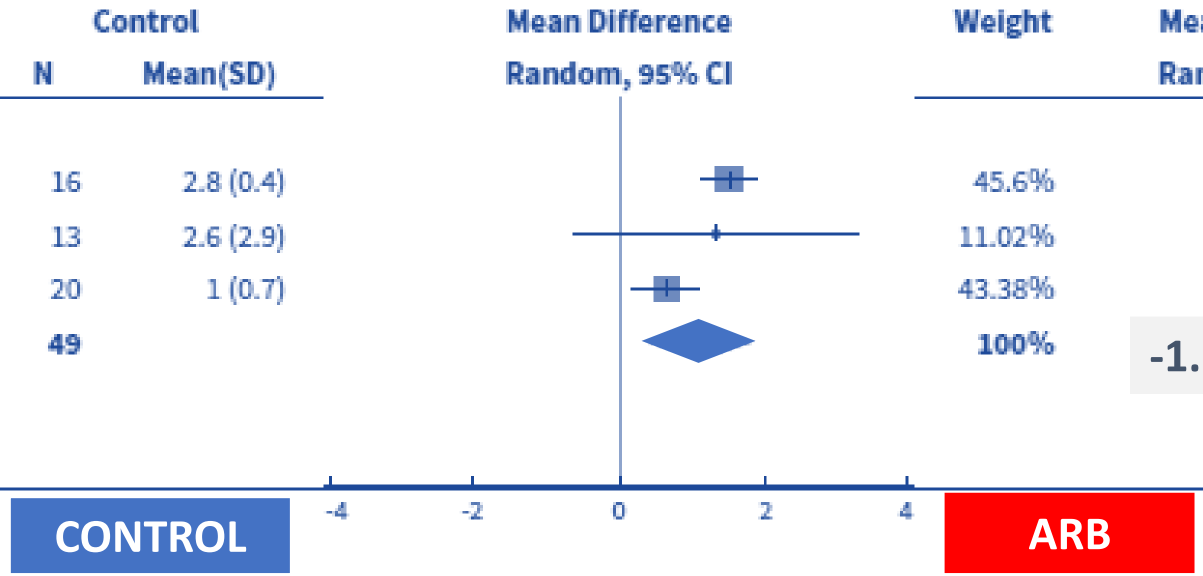
- 3 RCT (phase-3)
- 110 PD patients

Treatment period: > 12months

CONTROL (N=49)

ARB (N=61)

Study or subgroup	ARB N	ARB Mean(SD)	Control N	Control Mean(SD)	Weight	Mean Difference Random, 95% CI
1.1.5 12 to 24 months						
Suzuki 2004	18	4.3 (0.7)	16	2.8 (0.4)	45.6%	1.5[1.12,1.88]
Wang 2005d	19	3.9 (2.6)	13	2.6 (2.9)	11.02%	1.31[-0.63,3.25]
Zhong 2007a	24	1.7 (0.9)	20	1 (0.7)	43.38%	0.64[0.19,1.09]
Subtotal ***	**61**		**49**		**100%**	**-1.11** (0.38; 1.38)
Heterogeneity: Tau²=0.26; Chi²=8.26, df=2(P=0.02); I²=75.79%						
Test for overall effect: Z=2.99(P=0)						



ARBs therapy is associated with a better preservation of residual kidney function in peritoneal dialysis patients -1.11 (0.38;1,38) *ml/min/1.73 m²*

Cochrane Database Syst Rev. 2014 Jun 23;2014(6):CD009120.

Long-term effects of spironolactone in peritoneal dialysis patients.

Ito Y, Mizuno M, Suzuki Y, Tamai H, Hiramatsu T, Ohashi H, Ito I, Kasuga H, Horie M, Maruyama S, Yuzawa Y, Matsubara T, Matsuo S; Nagoya Spiro Study Group.

Open label RCT

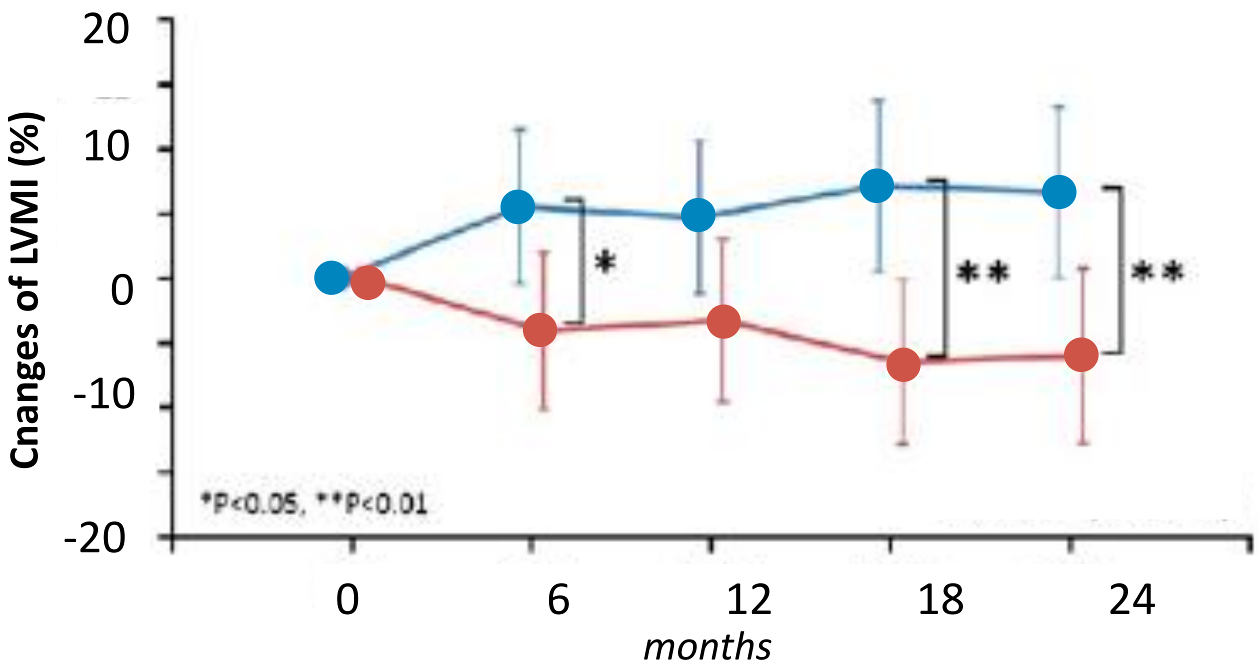
- Patients undergoing PD
- RAASi

N
158
1:1

Treatment period: 24 months

PLACEBO (n = 78)

SPIRONOLACTONE (n = 80)



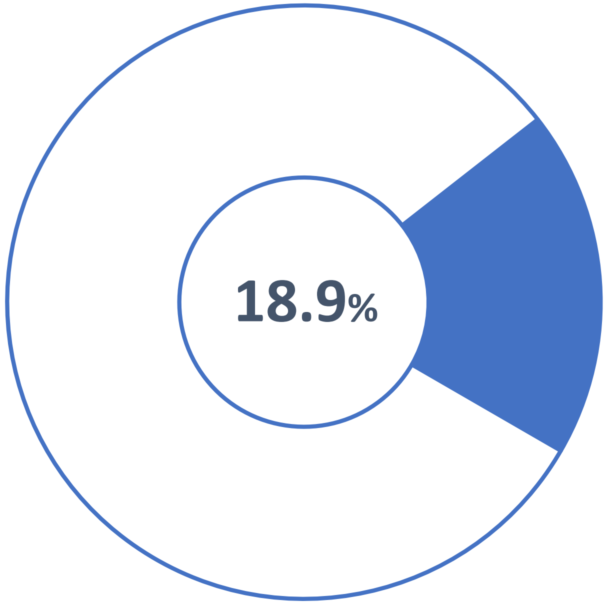
J Am Soc Nephrol. 2014 May;25(5):1094-102.

Initiation of sodium polystyrene sulphonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study

Laureati P, Xu Y, Trevisan M, Schalin L, Mariani I, Bellocco R, Sood MM, Barany P, Sjölander A, Evans M, Carrero JJ.

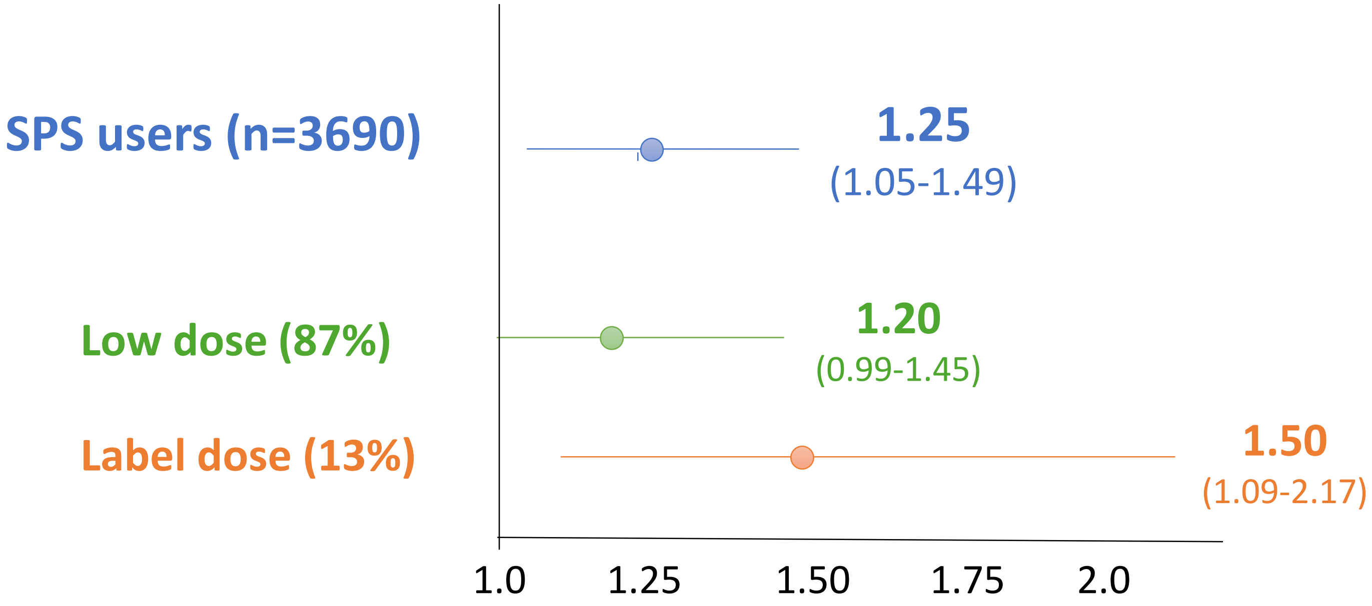
Population-based retrospective – 2006 -2016
Swedish CKD registry n=19530 (13.9% dialysis)

SPS users (%)



21% risk of lassative use

Adjusted risk of severe gastro-intestinal events

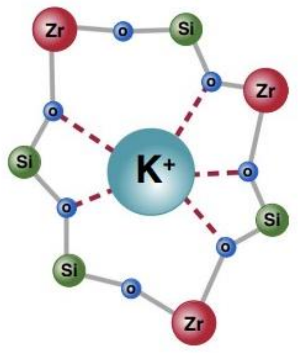


Nephrol Dial Transplant. 2020;35(9):1518-26

The restriction of K-rich food reduces intake of essential nutrients

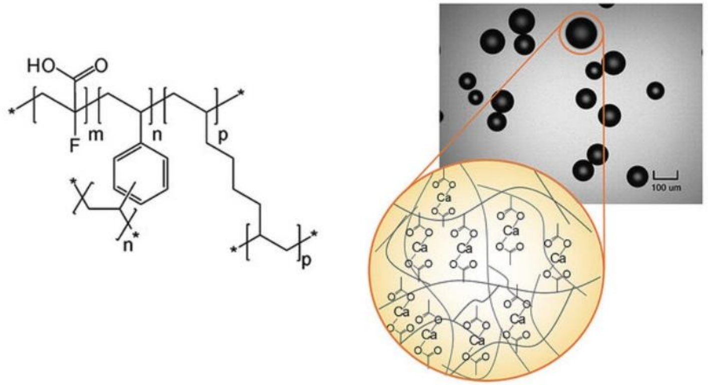
New kids on the block…

Sodium Zirconium Cyclosilicate (SZC)
LOKELMA ®

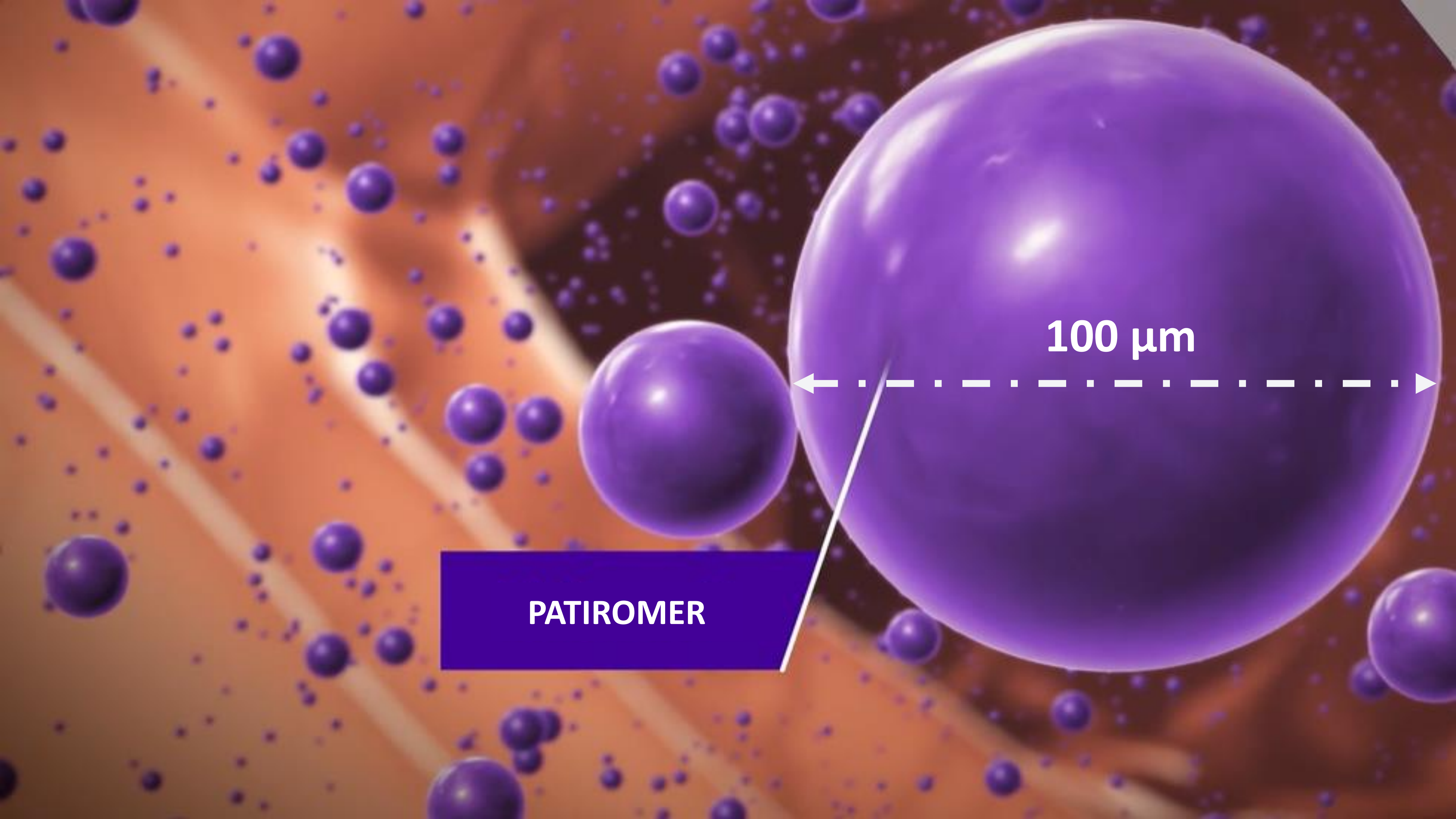


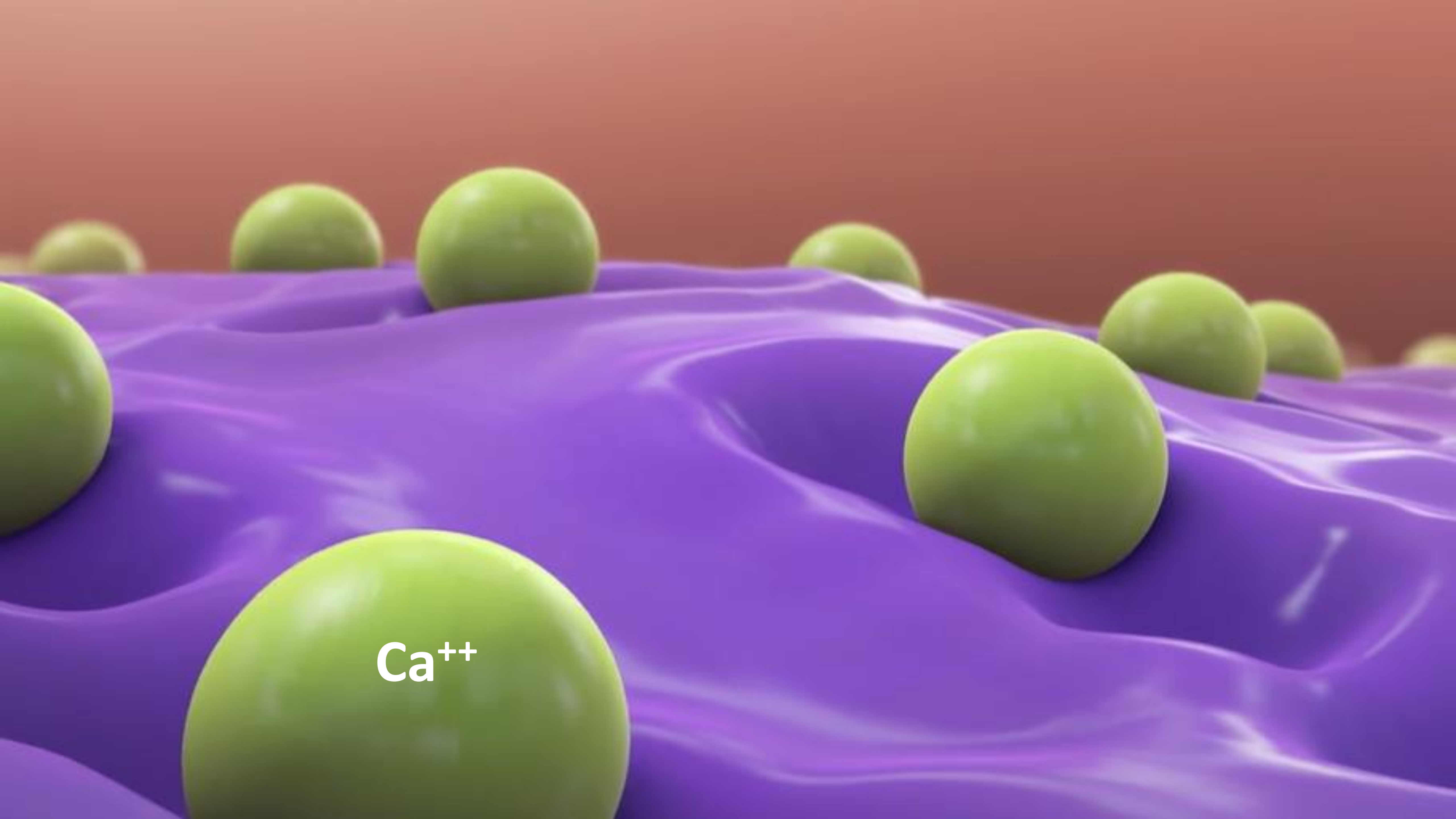
Non-absorbable, non-polymer inorganic cation-exchange crystalline compound highly selective for monovalent cations, specifically potassium and ammonium ions.

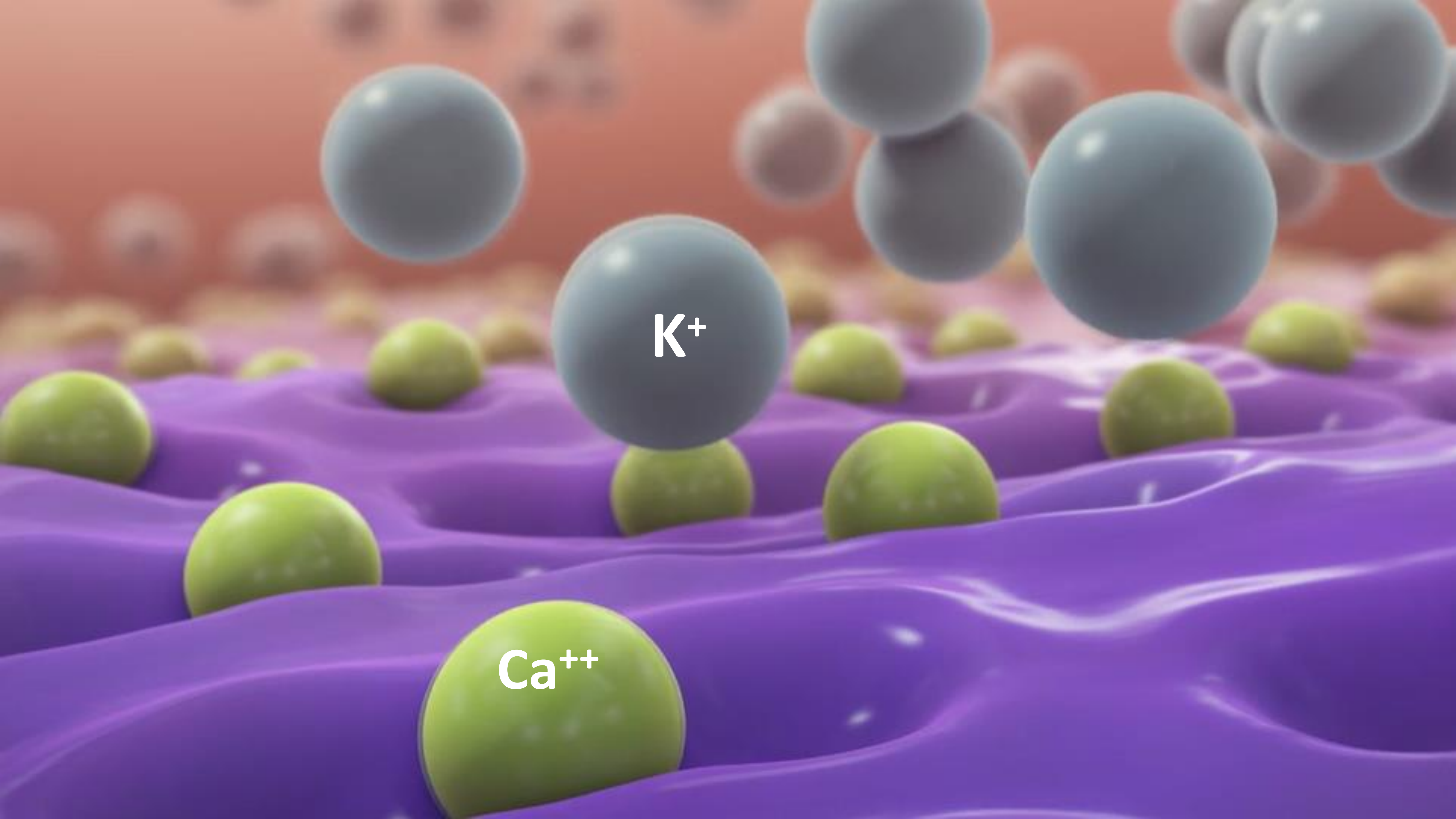
Patiromer
VELTASSA ®

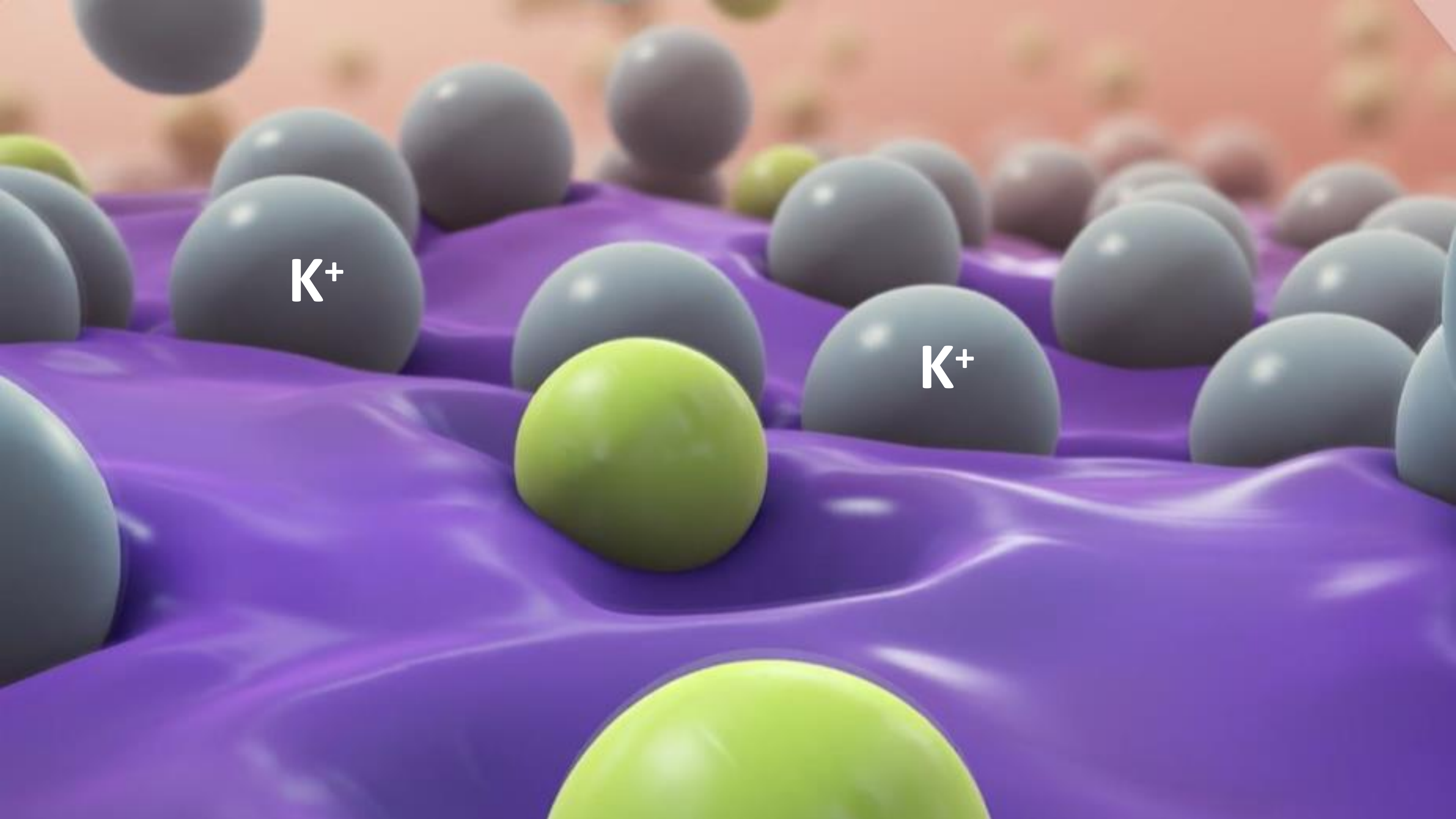


Non-absorbable synthetic polymer made of smooth spherical 100 µm beads. It is a calcium based-resin that exchanges calcium ions for potassium.


100 µm
PATIROMER


Ca++

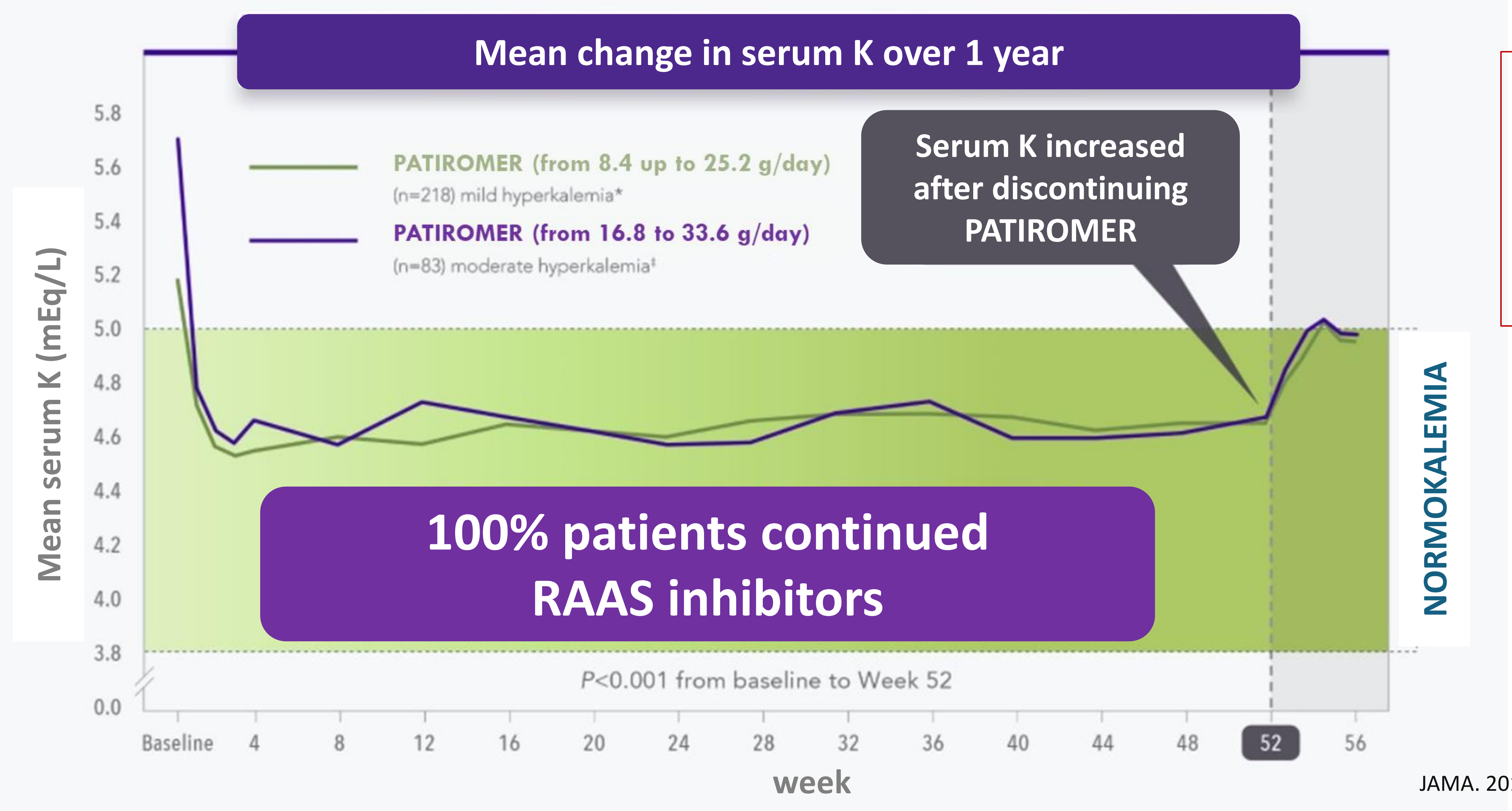

K^{+}
Ca^{++}


K^+
K^+

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

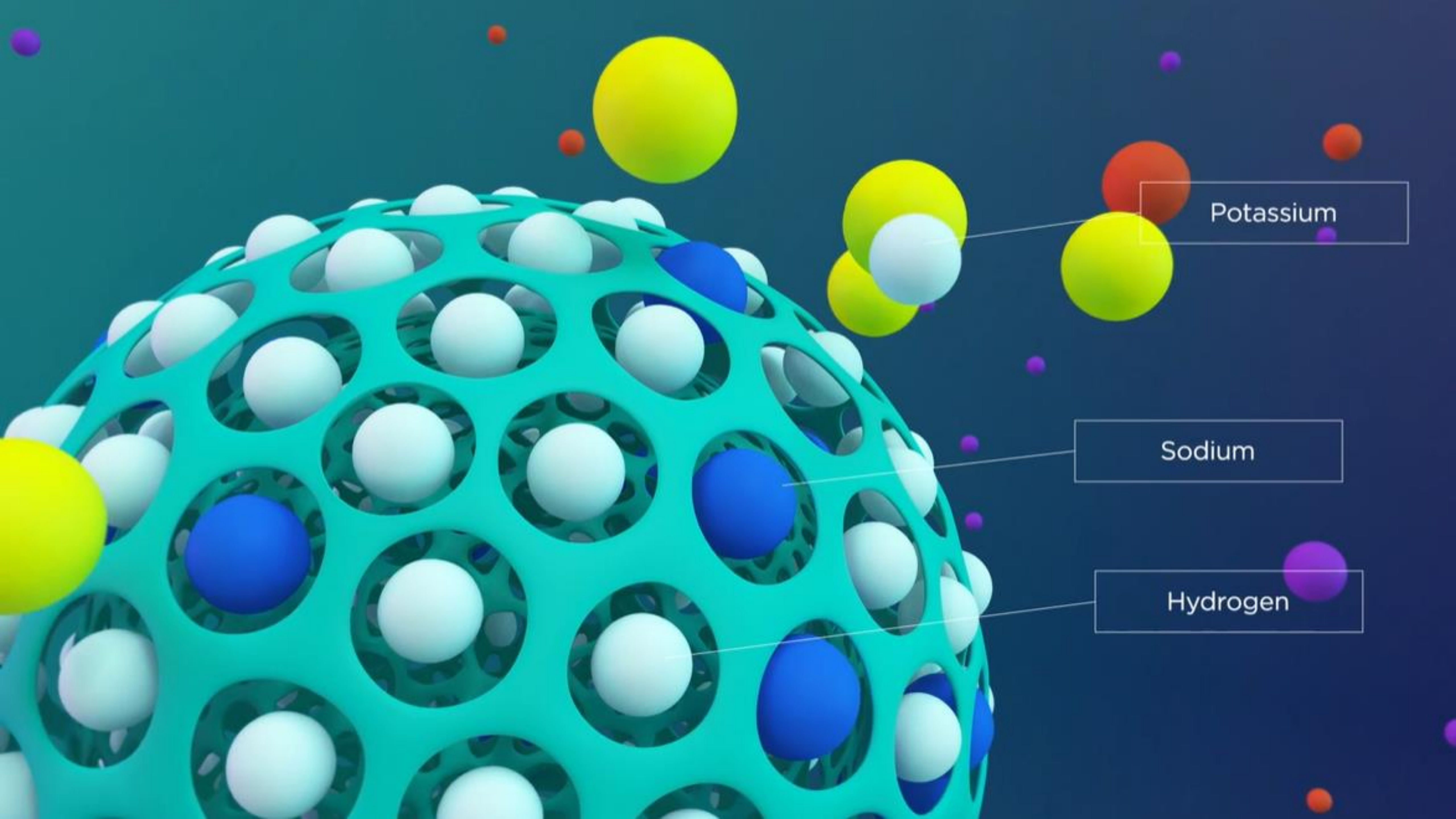
Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, Stasiv Y, Zawadzki R, Berman L, Bushinsky DA; AMETHYST-DN Investigators.

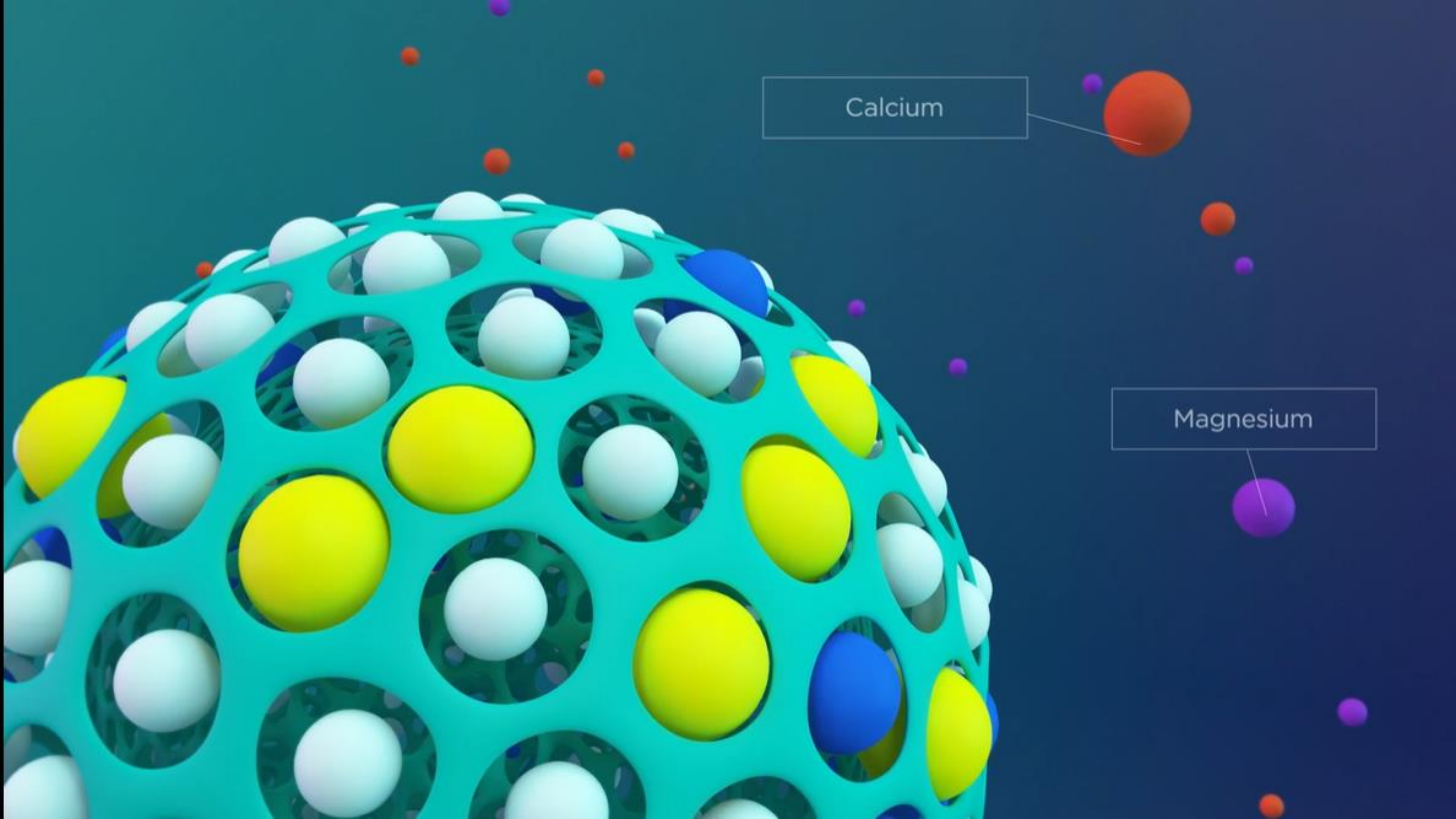
306 Diabetic CKD patients (stage 3-5) under RAAS inhibitors with serum K > 5.0 mEq/L

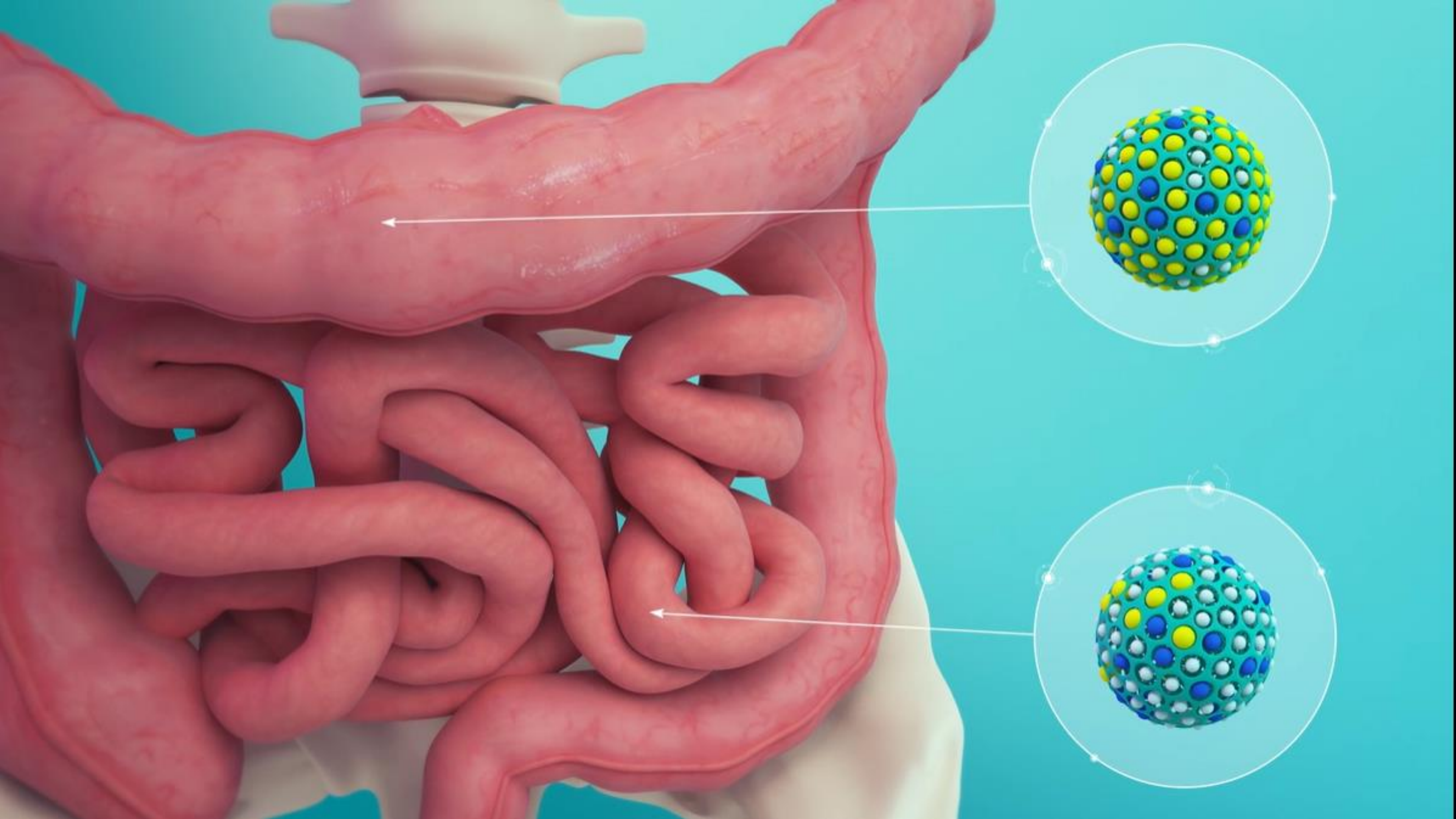


6.3% Stipsis
7.2% HypoMg
5.6% HypoK

JAMA. 2015 Jul 14;314(2):151-61.


Potassium
Sodium
Hydrogen

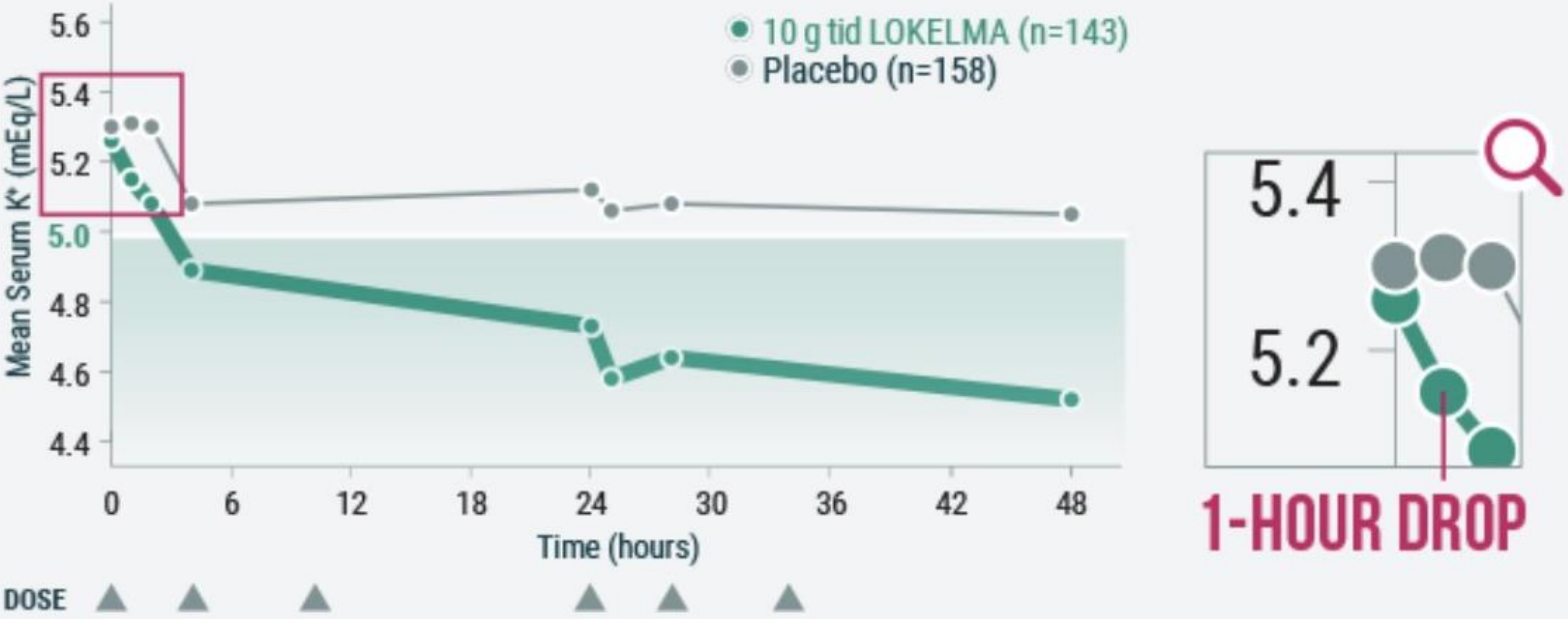

Calcium
Magnesium



Sodium zirconium cyclosilicate in hyperkalemia.

Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B.

Adults under RAAS inhibitors with serum K > 5.0 mEq/L

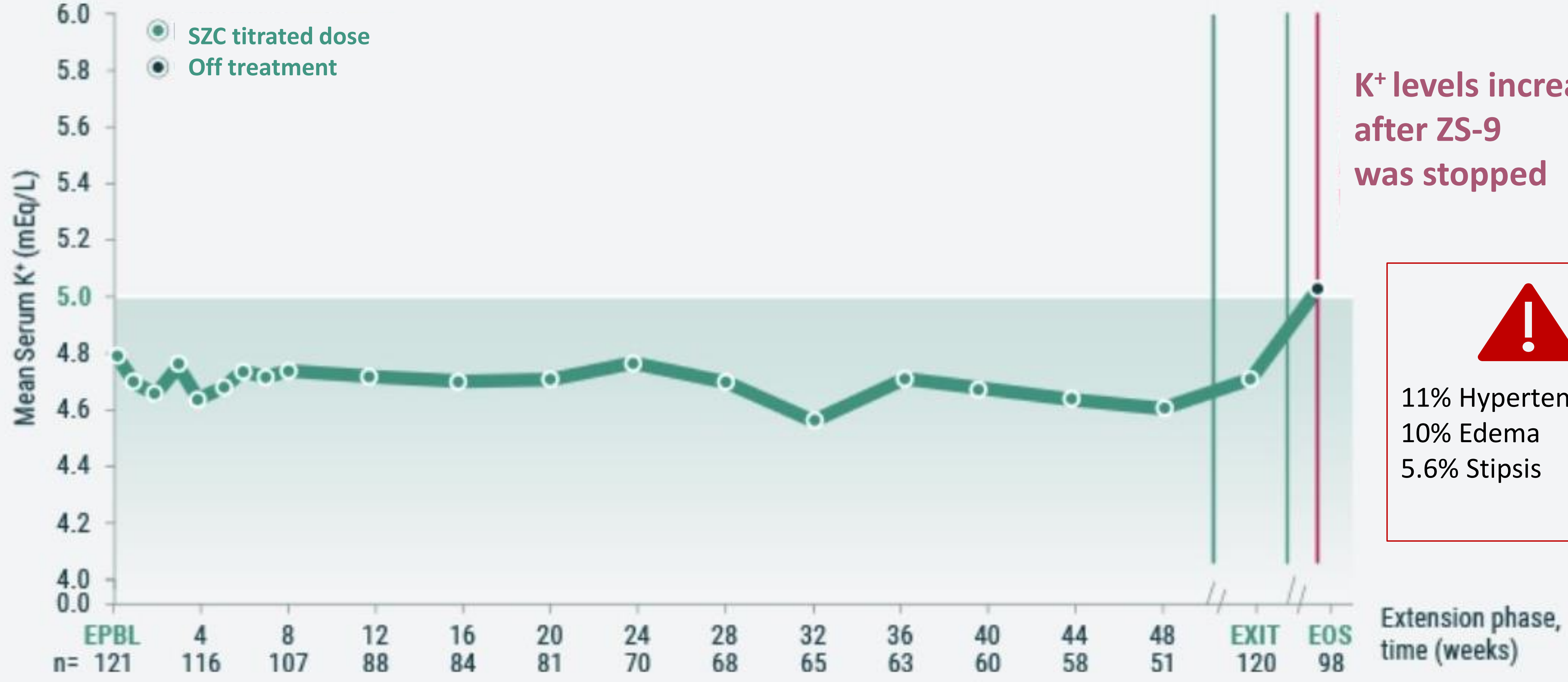


N Engl J Med. 2015 Jan 15;372(3):222-31.

Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia: A 12-Month Phase 3 Study.

Spinowitz BS, Fishbane S, Pergola PE, Roger SD, Lerma EV, Butler J, von Haehling S, Adler SH, Zhao J, Singh B, Lavin PT, McCullough PA, Kosiborod M, Packham DK; ZS-005 Study Investigators.

751 Adults under RAAS inhibitors with serum K > 5.0 mEq/L



K⁺ levels increased after ZS-9 was stopped

11% Hypertension
10% Edema
5.6% Stipsis

Clin J Am Soc Nephrol. 2019 Jun 7;14(6):798-809.

Characteristics	SPS	Patiromer	SZC
Approval date	1958	U.S.2015; E.U.2017	U.S.2015; E.U.2017
Mechanism of action	K binding in exchange for Na in GI tract	K binding in exchange for Ca2 in GI tract	K-binding in exchange for H and Na in GI tract
Site of action	Colon	Colon	Small and large intestines
Selectivity for K^+	Non-selective, also binds Ca^{2+} and Mg^{2+}	Non-selective, also binds Na^+ and Mg^{2+}	High selective, also binds $NH4^+$
Onset of action	Variable; several hours	7 hours	1 hours
Na content	1500 mg per 15 g	None	400 mg per 5 g
Ca content	None	1.6 g per 8.4 g	None
Dosing	15 g 1-4 times (oral); 30-50 g 1-2 times (rectal)	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (30 g) for initial correction of hyperkalemia (for 48 h), then 5 g QOD to 15 g QD for maintenance
Serious AEs	Cases of fatal GI injury	None reported	None reported
Most common AEs	GI disorders (diarrhea/stypsis/gastric irritation); hypomagnesemia, hypocalcemia, alkalosis	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema

A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia.

Fishbane S, Ford M, Fukagawa M, McCafferty K, Rastogi A, Spinowitz B, Staroselskiy K, Vishnevskiy K, Lisovskaja V, Al-Shurbaji A, Guzman N, Bhandari S.

RCT

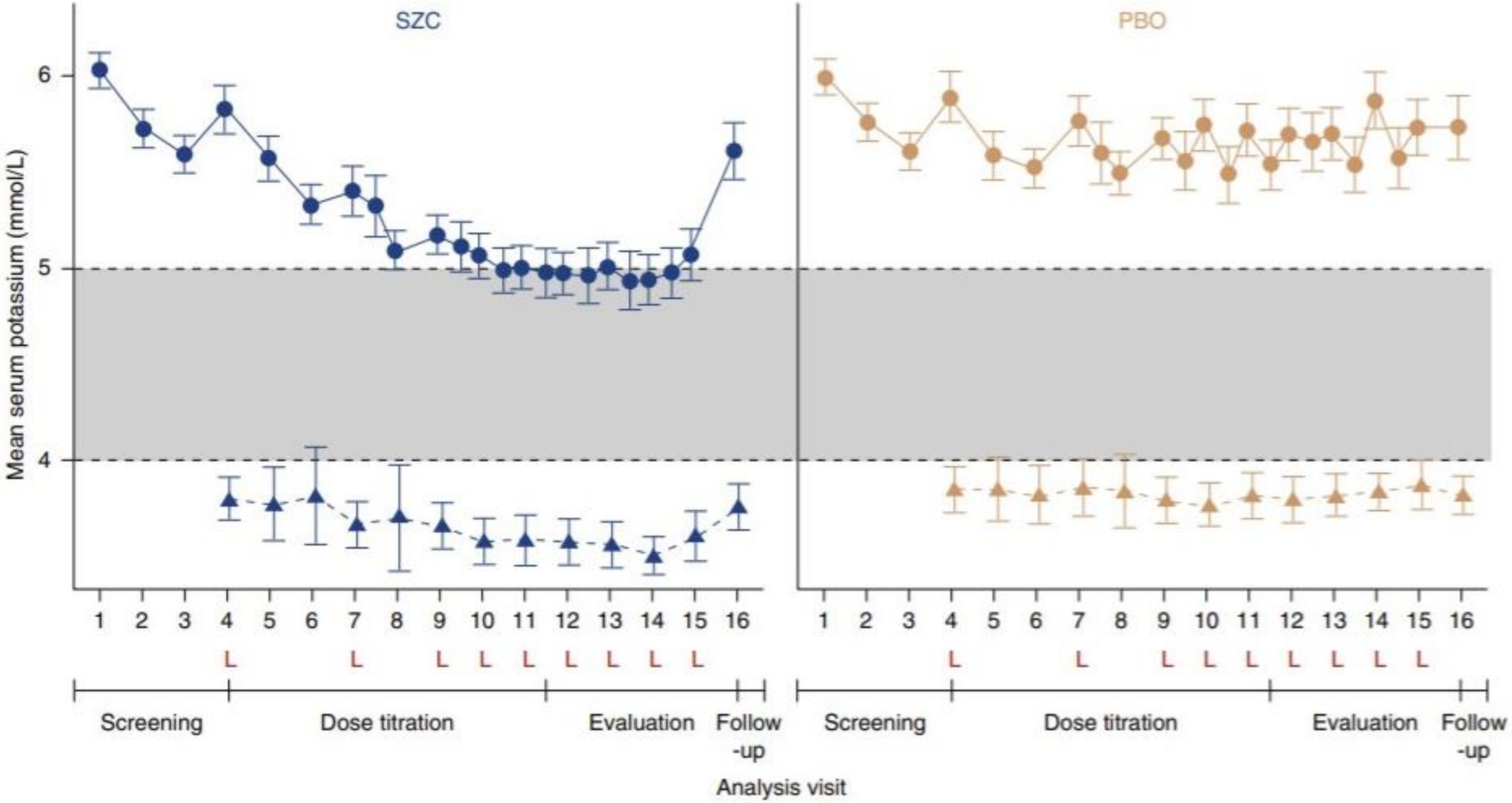
- Patients HD

N
196
1:1

Treatment period: 8 weeks

SZC 5 g / non-HD day (n = 97)

PLACEBO/ non-HD dau (n = 99)



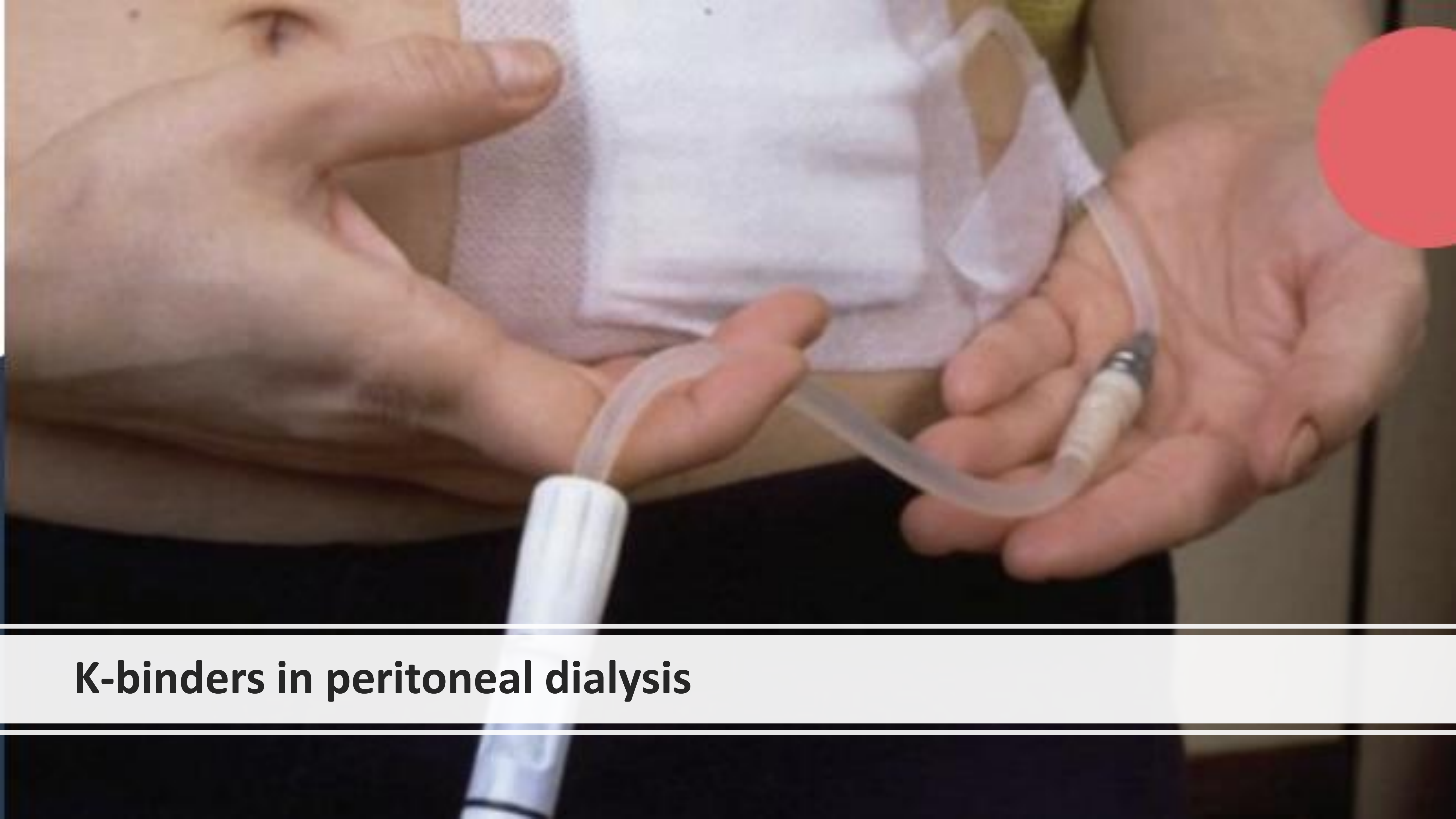
SAEs were similar:

SZC: 7.3% vs Placebo: 8.1%

Interdialytic weight gain was similar:

SZC: 0.2kg vs Placebo: -0.1kg

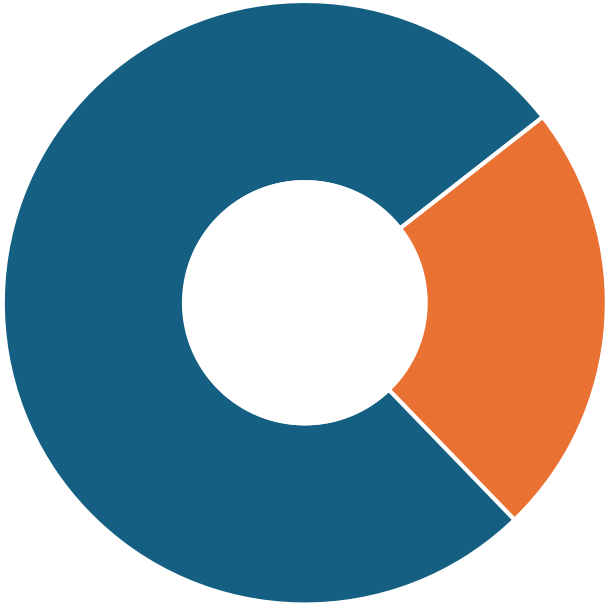
J Am Soc Nephrol. 2019 Sep;30(9):1723-1733.



K-binders in peritoneal dialysis

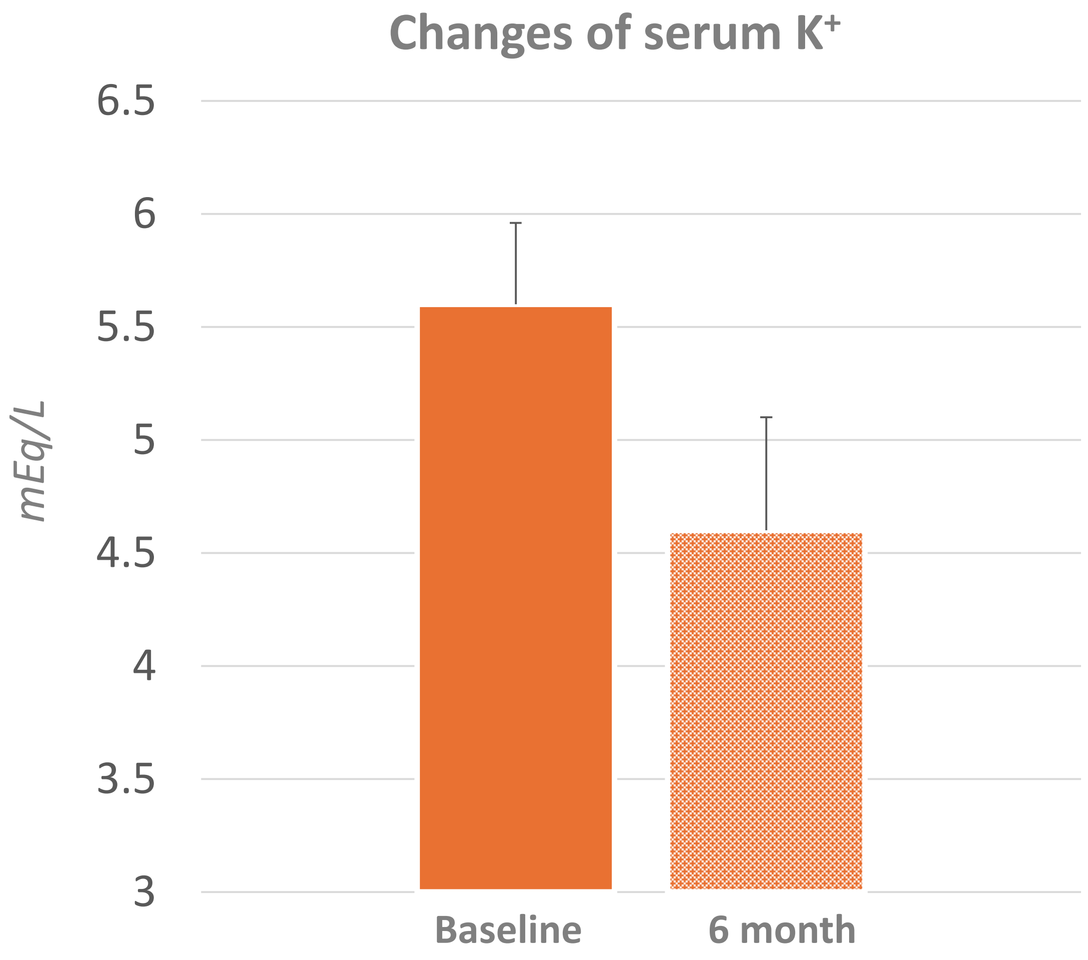
Our experience with K binders in PD

From June 2022 to June 2023:
35 patients prevalent in PD
20% *serum K* > 5.0 mmol/L



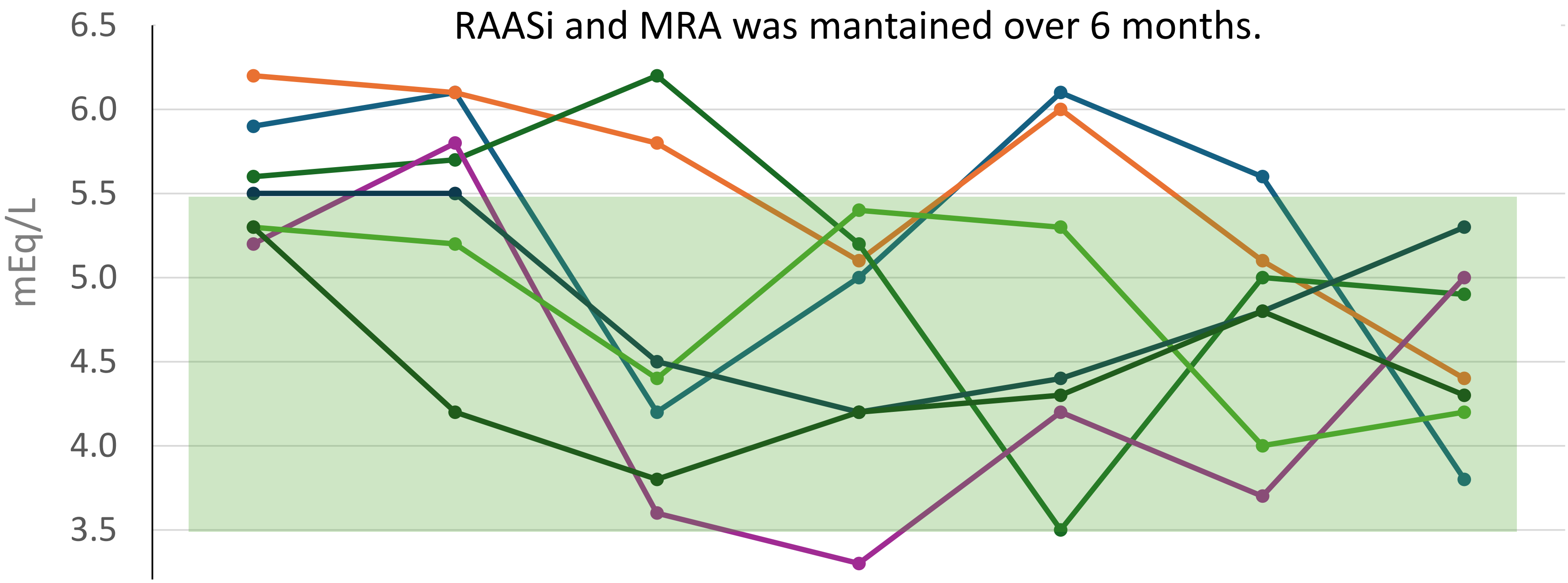
- 71% males
- 43% diabetes
- 100% under RAASi
- 43% under MRA
- KtV adeguato

HK patients treated SZC 5 g/day



All patients mantained RAASi/MRA therapy over 6 mo.

Our experience with K-binders in PD



	Baseline	1	2	3	4	5	6
Paziente 1	ZSC 5g	ZSC 10g	ZSC 10g	stop	stop	ZSC 5g	ZSC 5g
Paziente 2	ZSC 5g	ZSC 10g	stop	stop	stop	ZSC 5g	ZSC 5g
Paziente 3	ZSC 5g	ZSC 5g	ZSC 10g	ZSC 10 g	stop	ZSC 5g	ZSC 5g
Paziente 4	ZSC 5g	ZSC 10g	ZSC 5g	stop	ZSC 5g	ZSC 5g	ZSC 5g
Paziente 5	ZSC 5g	ZSC 5g	ZSC 5g	ZSC 5g	ZSC 5g	ZSC 5g	ZSC 5g
Paziente 6	ZSC 5g	ZSC 10g	ZSC 10g	ZSC 10g	ZSC 10g	ZSC 10g	ZSC 5g
Paziente 7	ZSC 5g	ZSC 5g	ZSC 5g	stop	stop	stop	ZSC 5g

Controversies in Nephrology

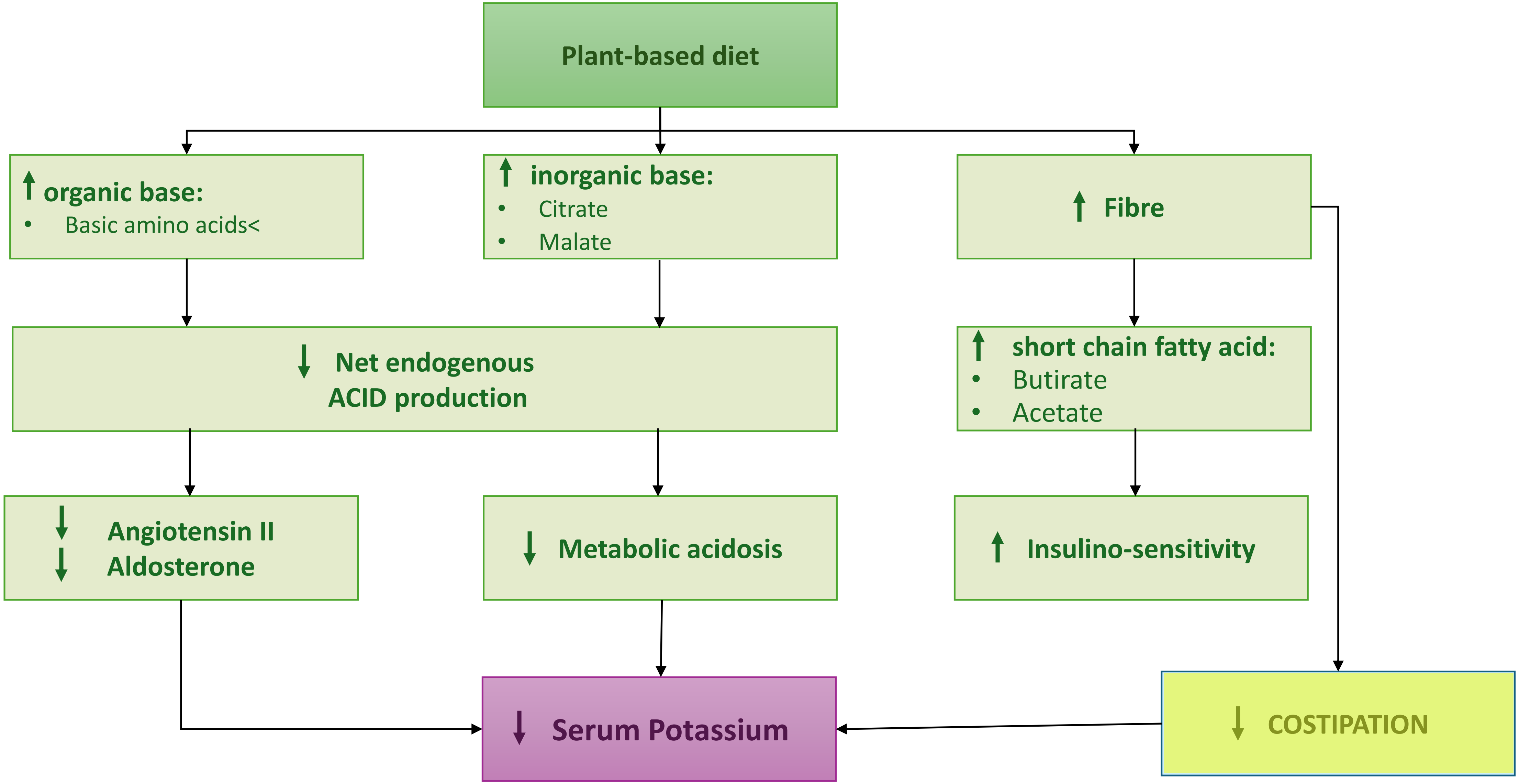
Recommendations on nutritional intake of potassium in CKD: It's now time to be more flexible!

Luca De Nicola, Carlo Garofalo, Silvio Borrelli and Roberto Minutolo

Nephrology Dialysis Unit-Dept. of Advanced Medical and Surgical Sciences at University of Campania "Luigi Vanvitelli", Naples (Italy)

Not all food is equal

Plant based diet improves metabolic acidosis and hyperkalemia



Modified from **Juan J Carrero**, et al. Nat Rev Nephrol. 2020;16(9):525-542

Effects of Short-Term Potassium Chloride Supplementation in Patients with Chronic Kidney Disease

Gritter M, Wouda RD, Yeung SMH, Wieërs MLA, Geurts F, de Ridder MAJ, Ramakers CRB, Vogt L, de Borst MH, Rotmans JI, Hoorn EJ; on behalf of Konsortium.

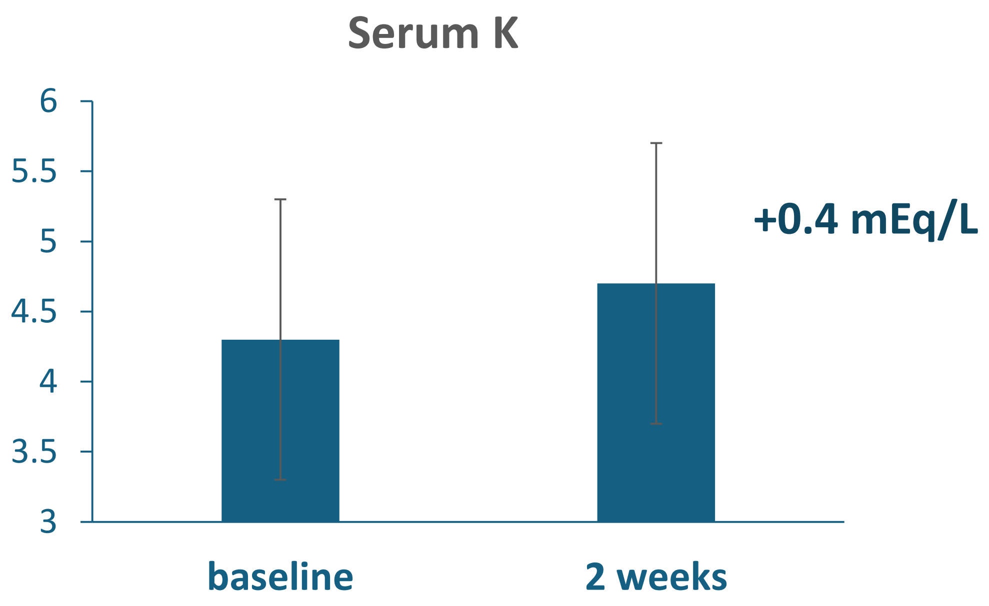
Run-in RCT

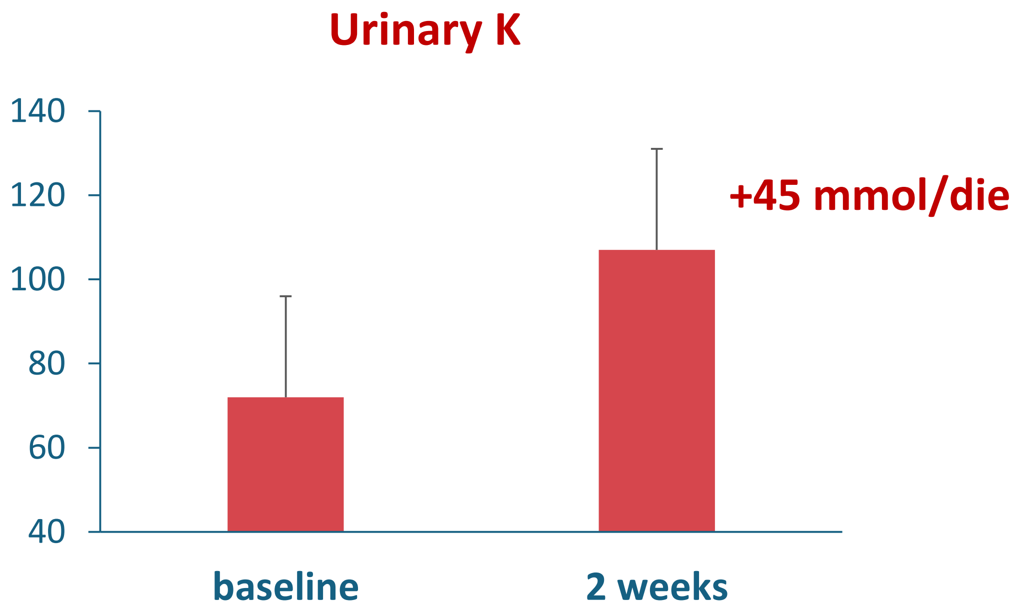
- CKD STAGE 3-4

N 191

Treatment period: 2 weeks

KCL 40 mmol/day (n = 80)





J Am Soc Nephrol. 2022 Sep;33(9):1779-1789.

CONCLUSIONS – PART 2

The new K+-binder drugs provide adequate and safe therapeutic options to reduce serum potassium in patients with CKD enabling to maintain RASI treatment and potentially an adequate intake of fruit and vegetables in CKD patients

In patients treated by peritoneal dialysis, the use of new K+ binders could enable to maintain RAAS inhibition therapy essential for cardio-renal protection.

Furthermore, the use of new K+ binders could favor a normal potassium intake while avoiding excessive loading as well as severe restrictions.

Currently, there is no studies on the use of K binders in PD patients


Solo i più saggi o i più stupidi degli uomini non cambiano mai
Confucio