New advances in Hyperkalaemia management in Diabetic Kidney Disease and beyond

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Disclosures

AstraZeneca:
Grant holder from company
Honoraria :Advisory boards, presentations at meetings, Congress attendance

Vifor Fresenius
Honoraria :Advisory boards, presentations at meetings, Congress attendance

Overview

- Hyperkalaemia: prevalence and associations
- 3 decades of RAASi therapy for the Heart and Kidney
- Hyperkalaemia: a barrier to guideline-recommended RAASi therapy
- Current treatment options for Hyperkalaemia have limitations
- Current/future Potassium binders
- Summary

Hyperkalaemia† is often associated with cardio-renal disease and patients typically suffer from multiple comorbidities

†defined as serum potassium >5.0 mmol/L

Up to 40-50% of patients with advanced CKD experience hyperkalaemia, occurring more commonly in those with diabetes.[1]

Up to 16% of patients with diabetes develop with hyperkalaemia over a 4-year period.†[3]

†defined as serum potassium >5.0 mmol/L

Up to ~40% of patients with HF experience hyperkalaemia over a mean 2.2 year period.†[2]

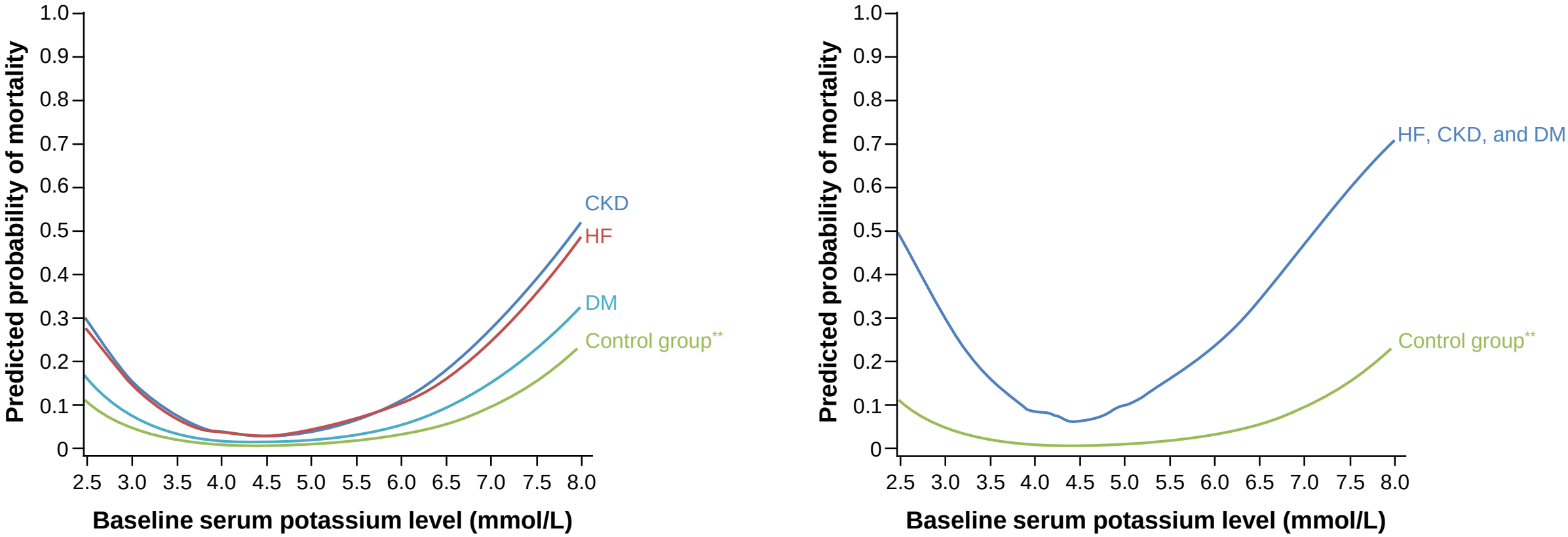
†defined as serum potassium >5.0 mmol/L

CKD, Chronic Kidney Disease; HF Heart Failure; HK, hyperkalaemia

1. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nat Rev Nephrol 2014;10:653–662; **2.** Thomsen RW, Nicolaisen SK, Hasvold P, Garcia-Sanchez R, Pedersen L, Adelborg K, et al. Elevated Potassium Levels in Patients With Congestive Heart Failure: Occurrence, Risk Factors, and Clinical Outcomes. J Am Heart Assoc. 2018;7(11).; **3.** Thomsen R, Nicolaisen S, Adelborg K, Svensson E, Hasvold P, Palaka E, et al. Hyperkalaemia in people with diabetes: occurrence, risk factors and outcomes in a Danish population-based cohort study. Diabetic Medicine. 2018.

Higher serum K^+ levels and comorbidities increase the mortality risk associated with HK.

Risk of all-cause mortality by serum K^+ level and comorbidities (N=911,698)*

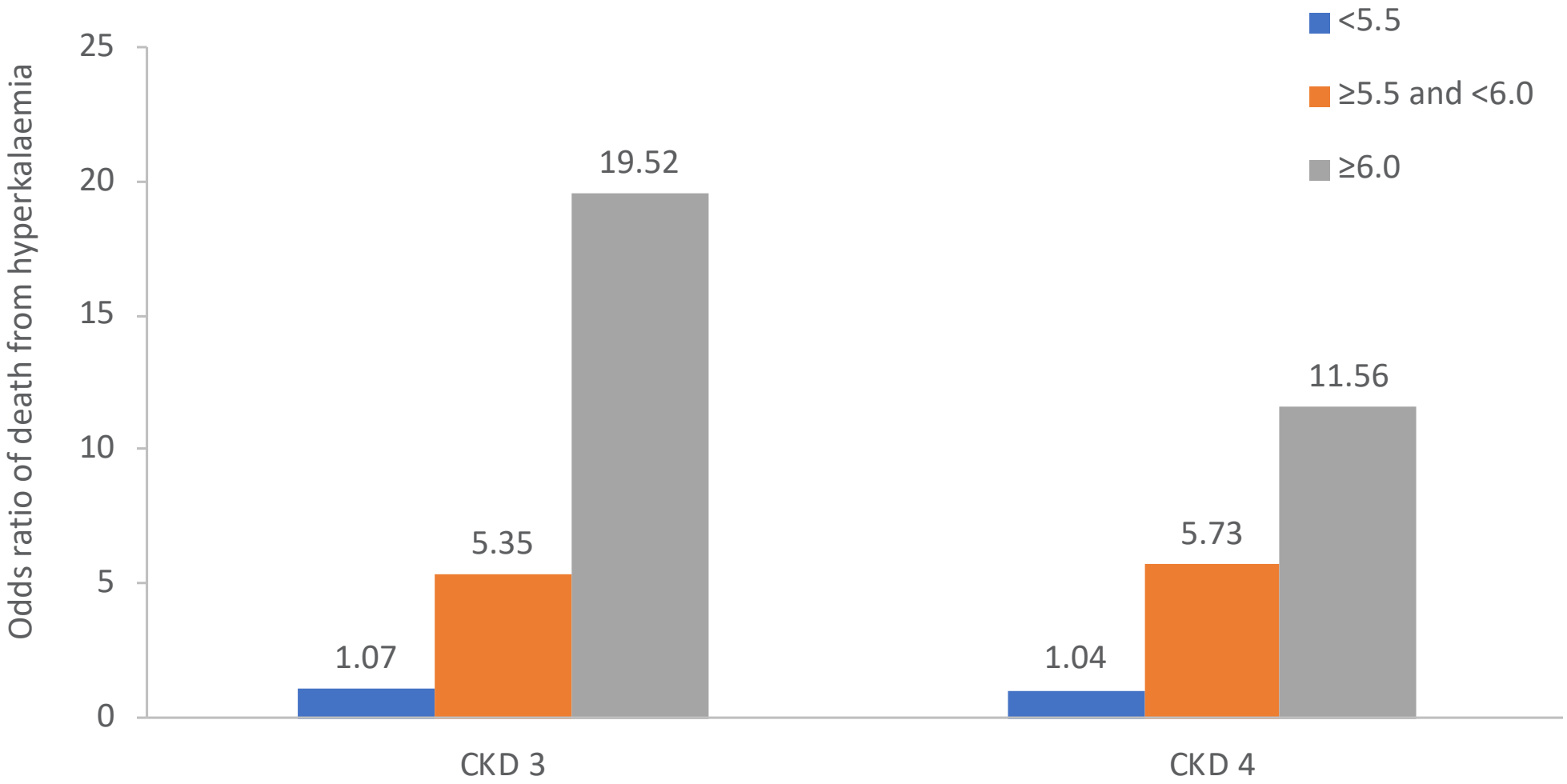


Adapted from: Collins AJ, et al. (2017)

* Retrospective analysis of medical records from a geographically diverse population in the US; **Control group comprised of individuals without known HF, CKD, DM, CVD, or HTN .
CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HK, Hyperkalaemia; HTN, hypertension

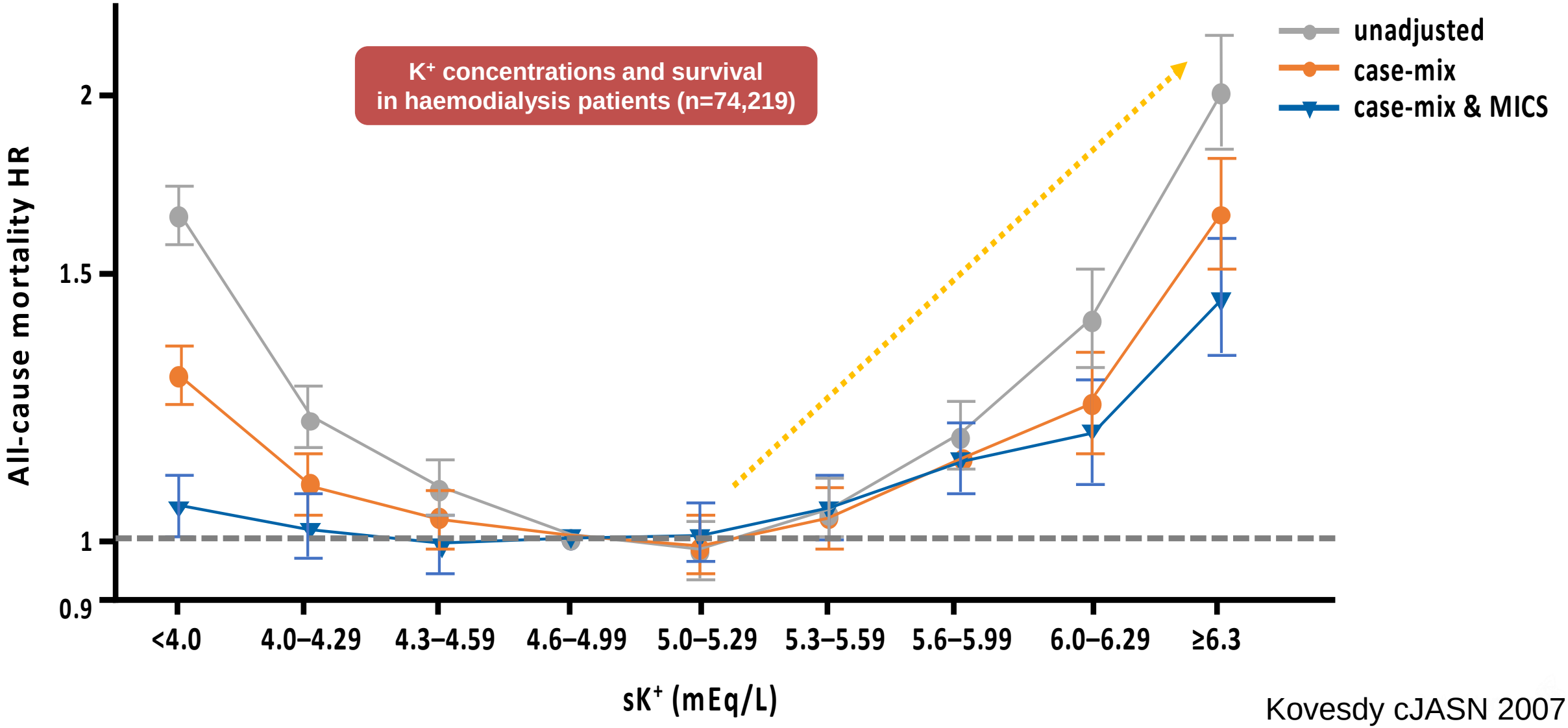
Collins AJ, et al. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *Am J Nephrol* 2017;46:213–221

CKD patients with hyperkalaemia have significantly increased 24-h mortality



Einhorn LM, et al. *Arch Intern Med.* 2009

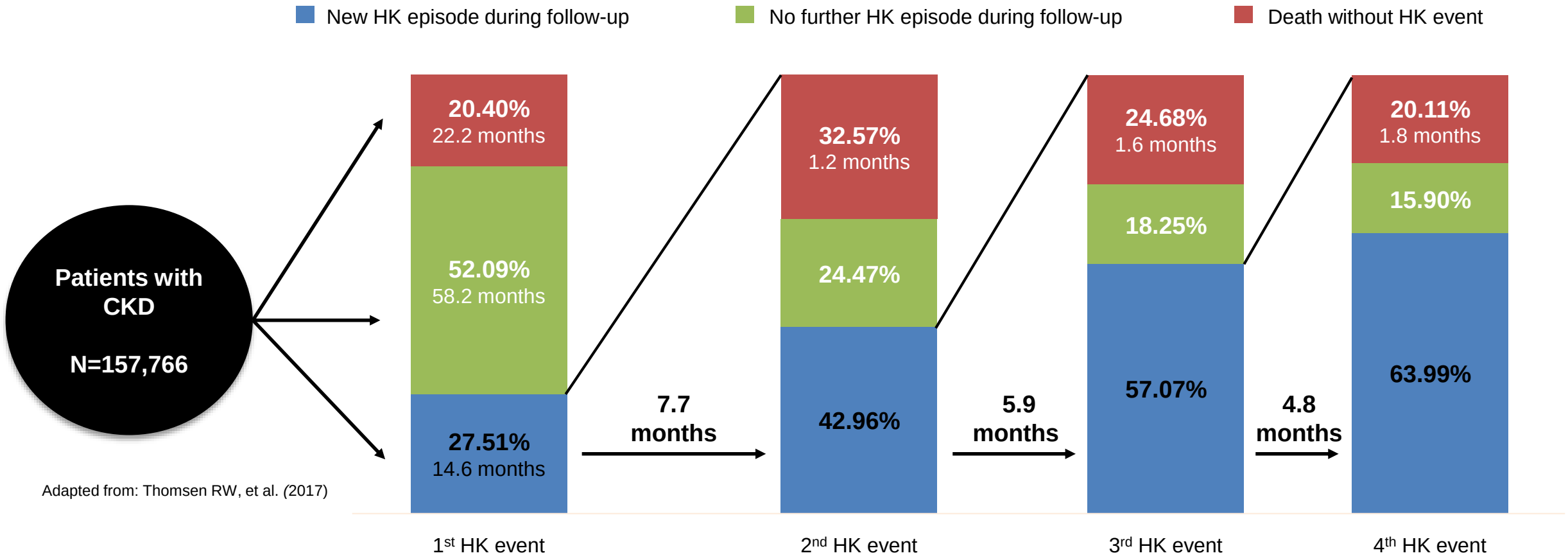
Higher serum potassium levels are associated with an increased risk of mortality in haemodialysis patients



Kovesdy cJASN 2007

Many patients with CKD have recurrent episodes of hyperkalaemia, with successively shorter time between episodes.

Median follow-up time for CKD patients (n=157,766) with recurrent hyperkalaemia events in the Danish National Patient Registry.



Adapted from: Thomsen RW, et al. (2017)

Population-based cohort study linking individual data from mandatory hospital, prescription, and laboratory databases in Northern Denmark (population 1.8 million) during 2000–2012 (N=157,766)

CKD, chronic kidney disease; HK, hyperkalaemia

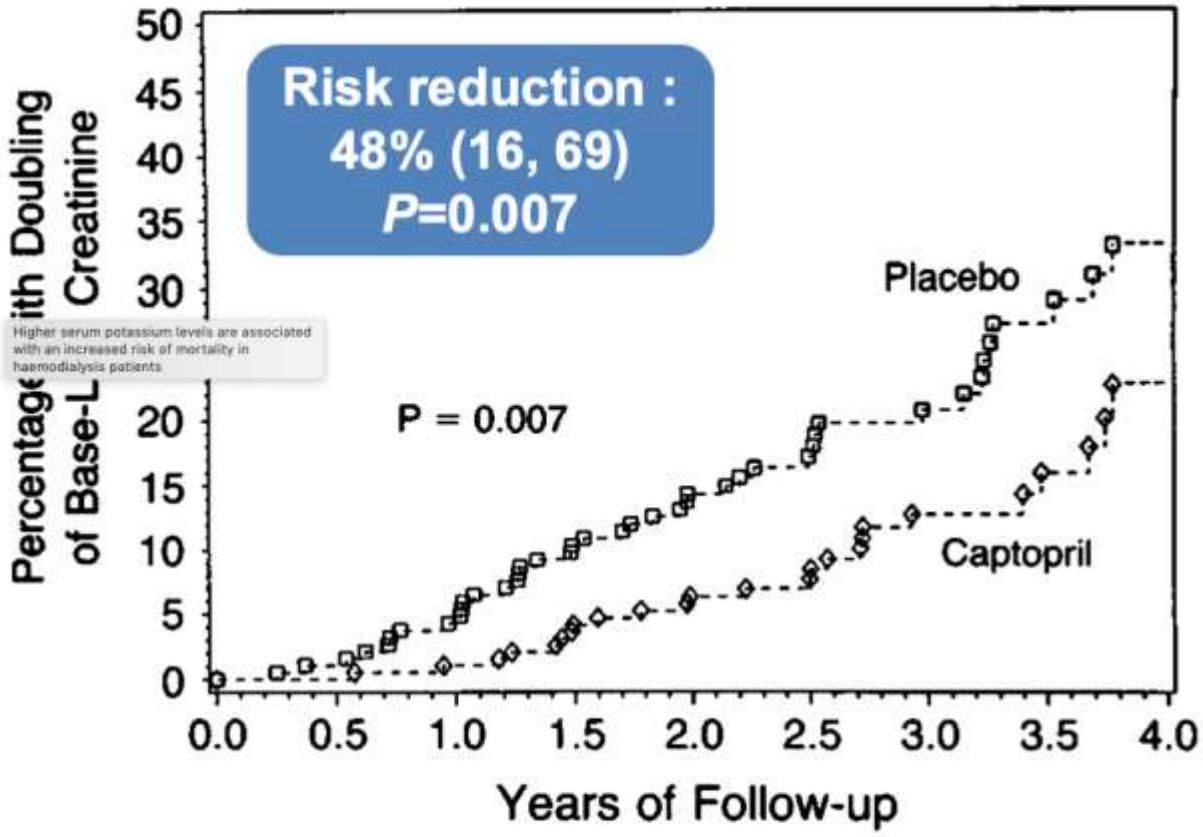
From the source population of all individuals living in northern Denmark between 2000 and 2012, a cohort of patients were identified with an incident CKD diagnosis, defined as the first occurrence of one of the following: (i) a second creatinine measurement, >90 days following a prior measurement, corresponding to a second estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2; (ii) an incident hospitalisation with a diagnosis of CKD or (iii) hospital-based codes for renal dialysis. The severity of CKD was further classified according to CKD stage, based on the lowest eGFR recorded (or presence of dialysis) up to the date of meeting the CKD definition (the index date), as follows: Stages 1 and 2: eGFR 60 mL/min/1.73m^2; Stage 3A: eGFR 45–59; Stage 3B: eGFR 30–44; Stage 4: eGFR 15–29; Stage 5: eGFR <15 or dialysis

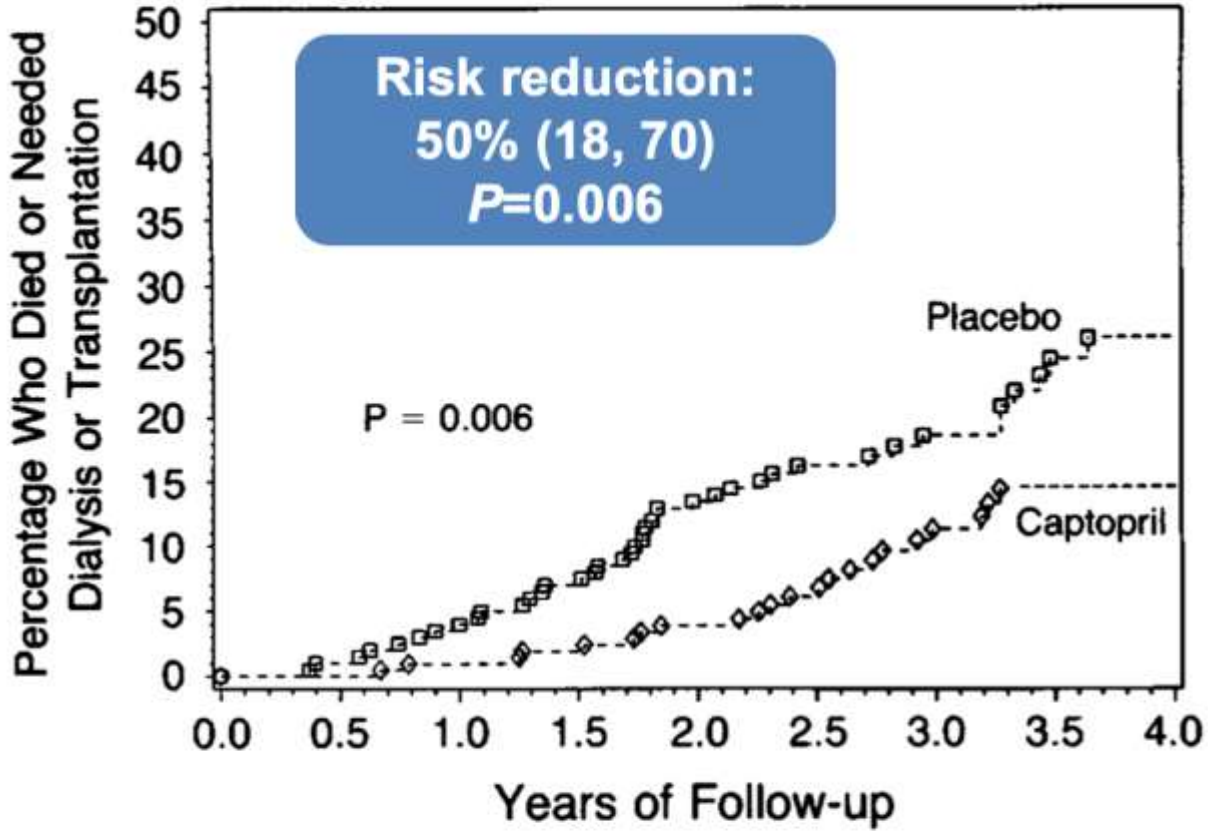
Thomsen RW, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes— a Danish population-based cohort study. *Nephrol Dial Transplant* 2017;33:1610–1620

25 years of RAASi therapy in renoprotection

THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D., AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*



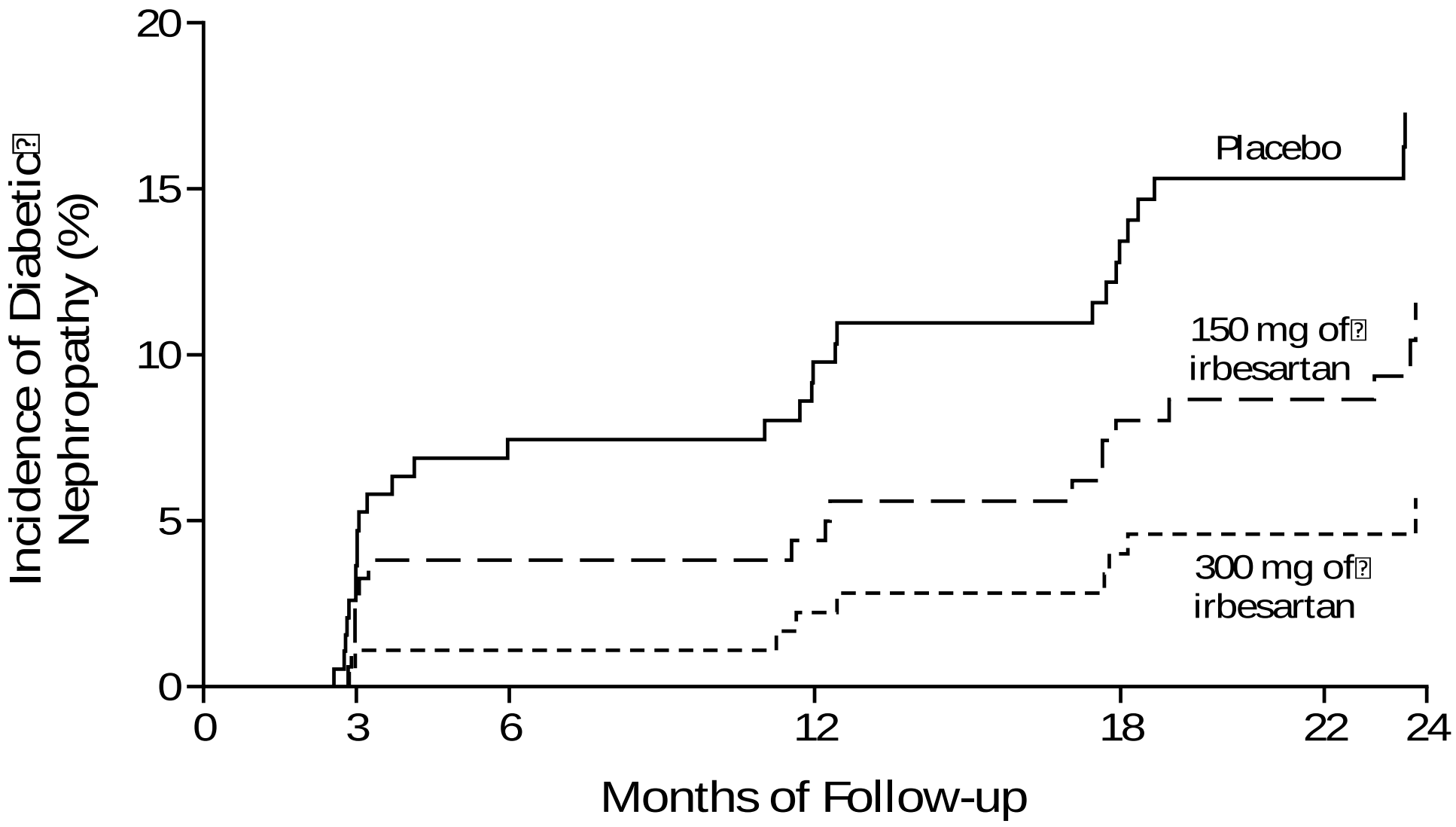


400 patients with Type 1 DM and Cr <221
Received Captopril versus placebo

The Collaborative Study Group

N Engl J Med. 1993 Nov 11;329(20):1456-62.

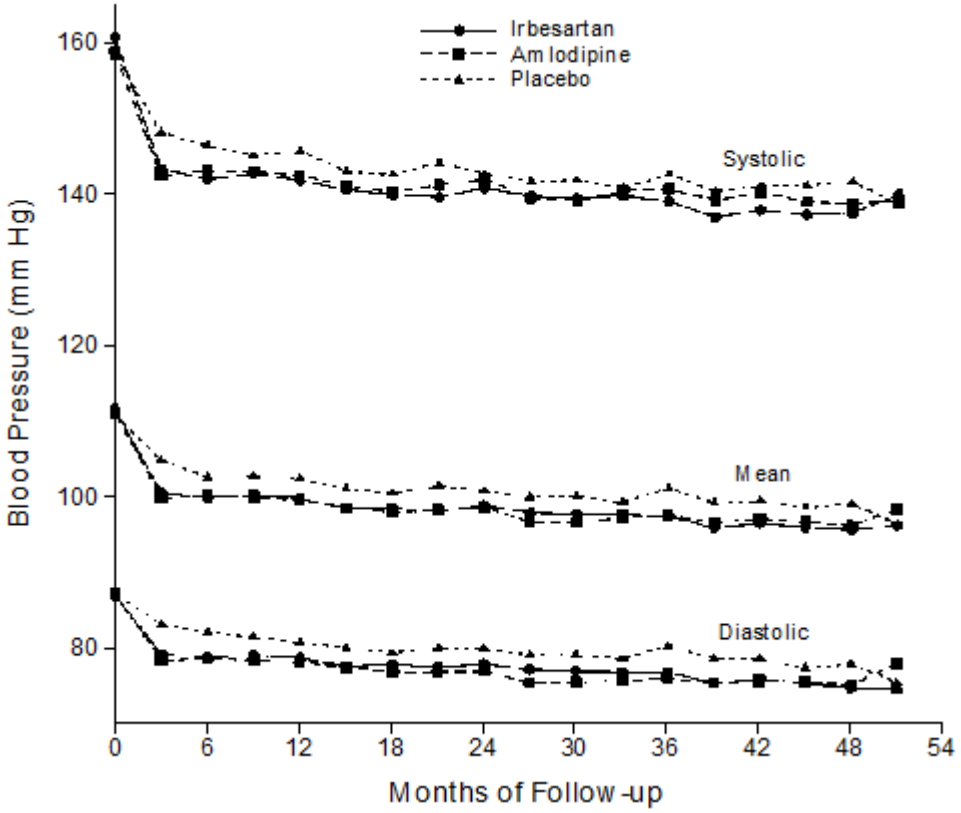
EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

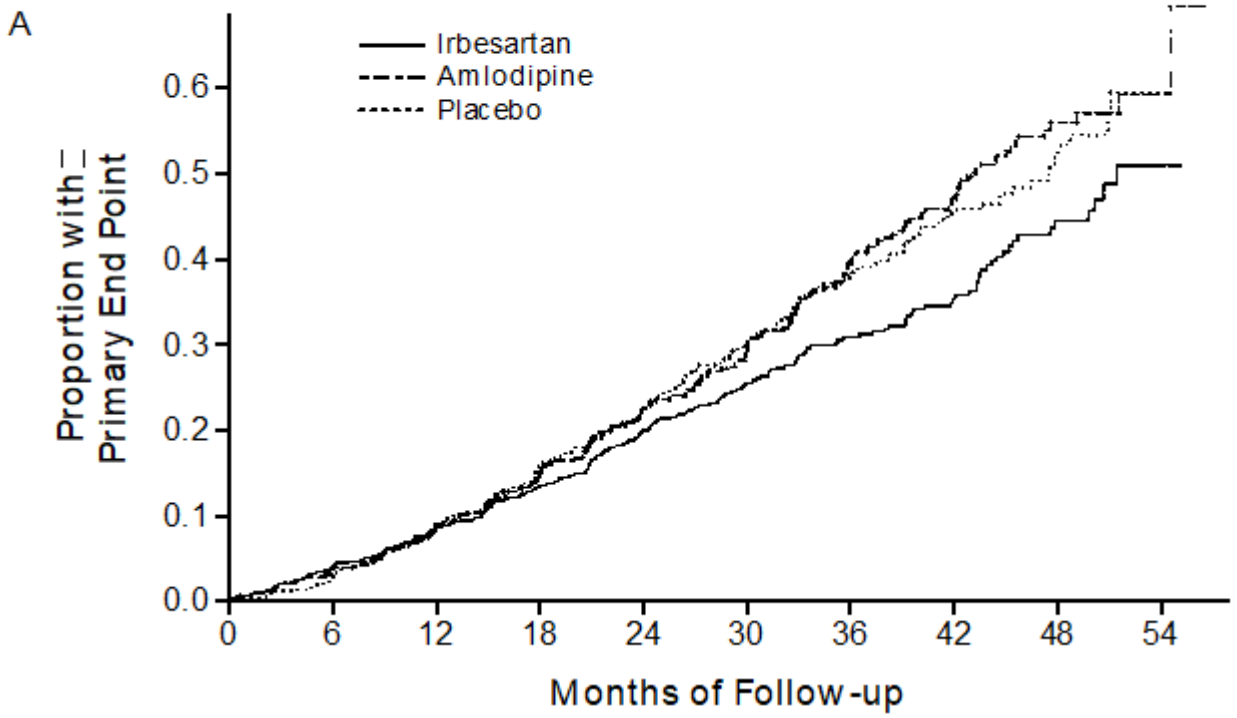


N=590, hypertensive, type 2 DM and microalbuminuria

N Engl J Med. 2001 Sep 20;345(12):870-8.

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

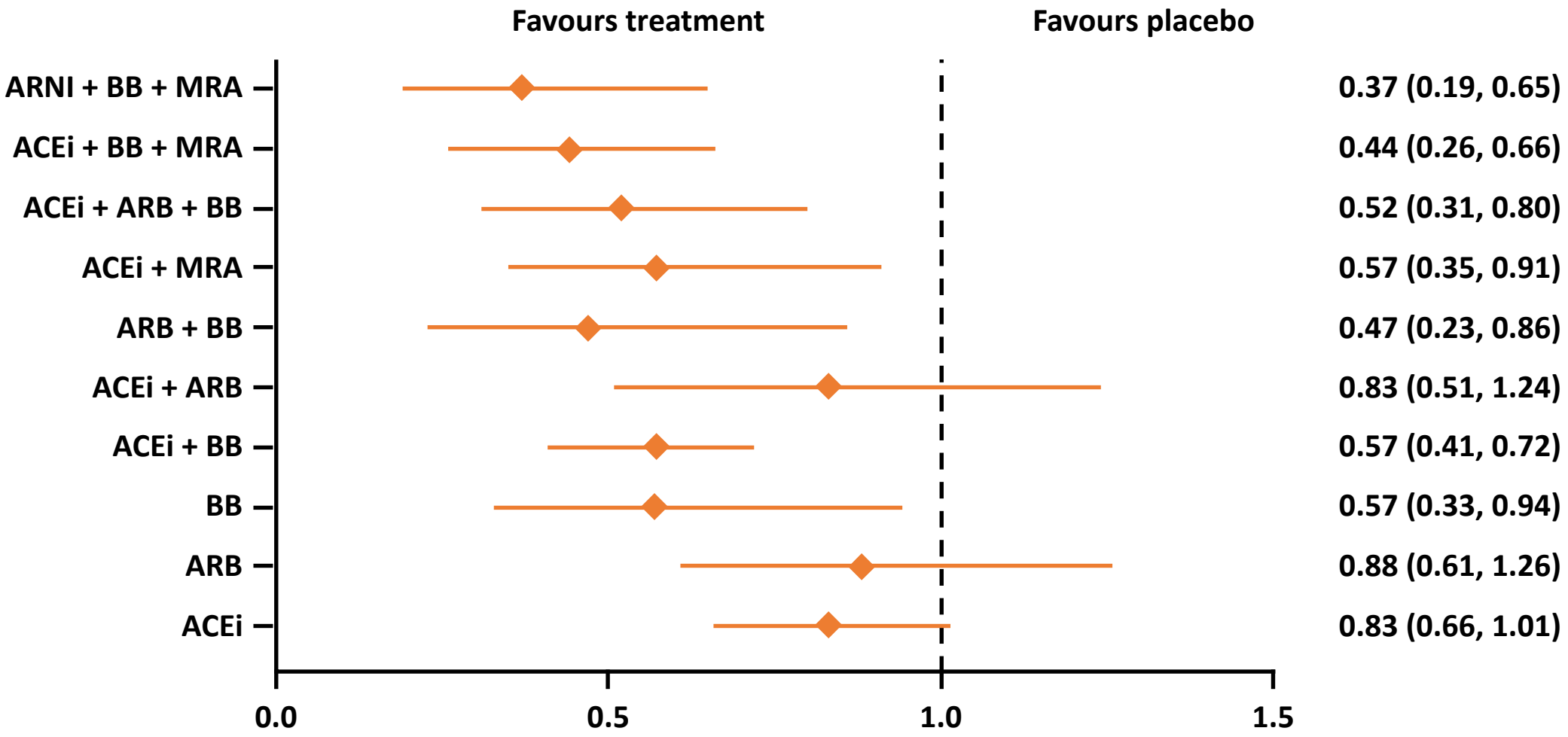




IDNT study N=1715
33% reduction in doubling serum creatinine
23% reduction in development of ESRD

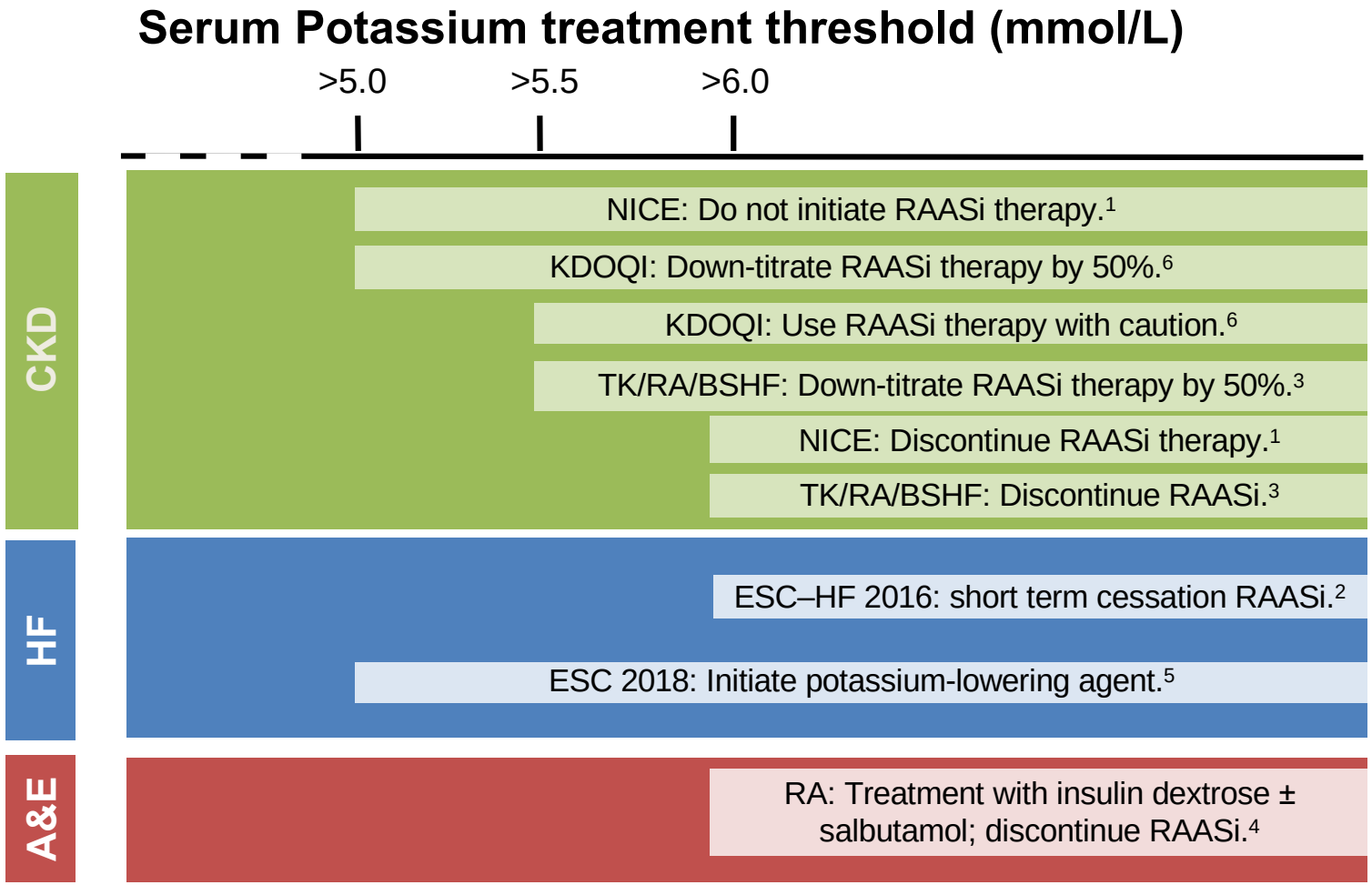
N Engl J Med. 2001 Sep 20;345(12):851-60.

3 decades of HFrEF Studies in 1 slide…

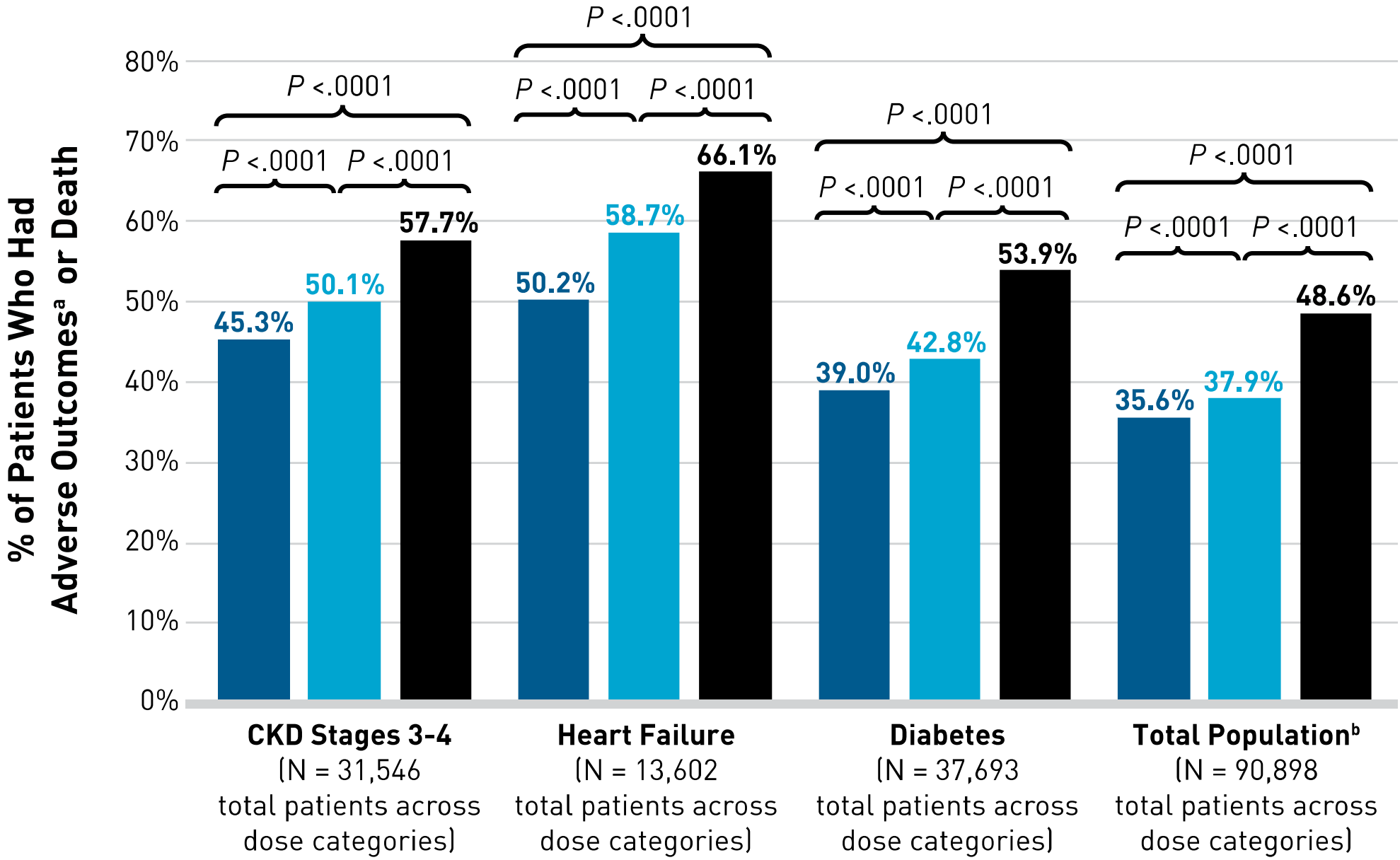


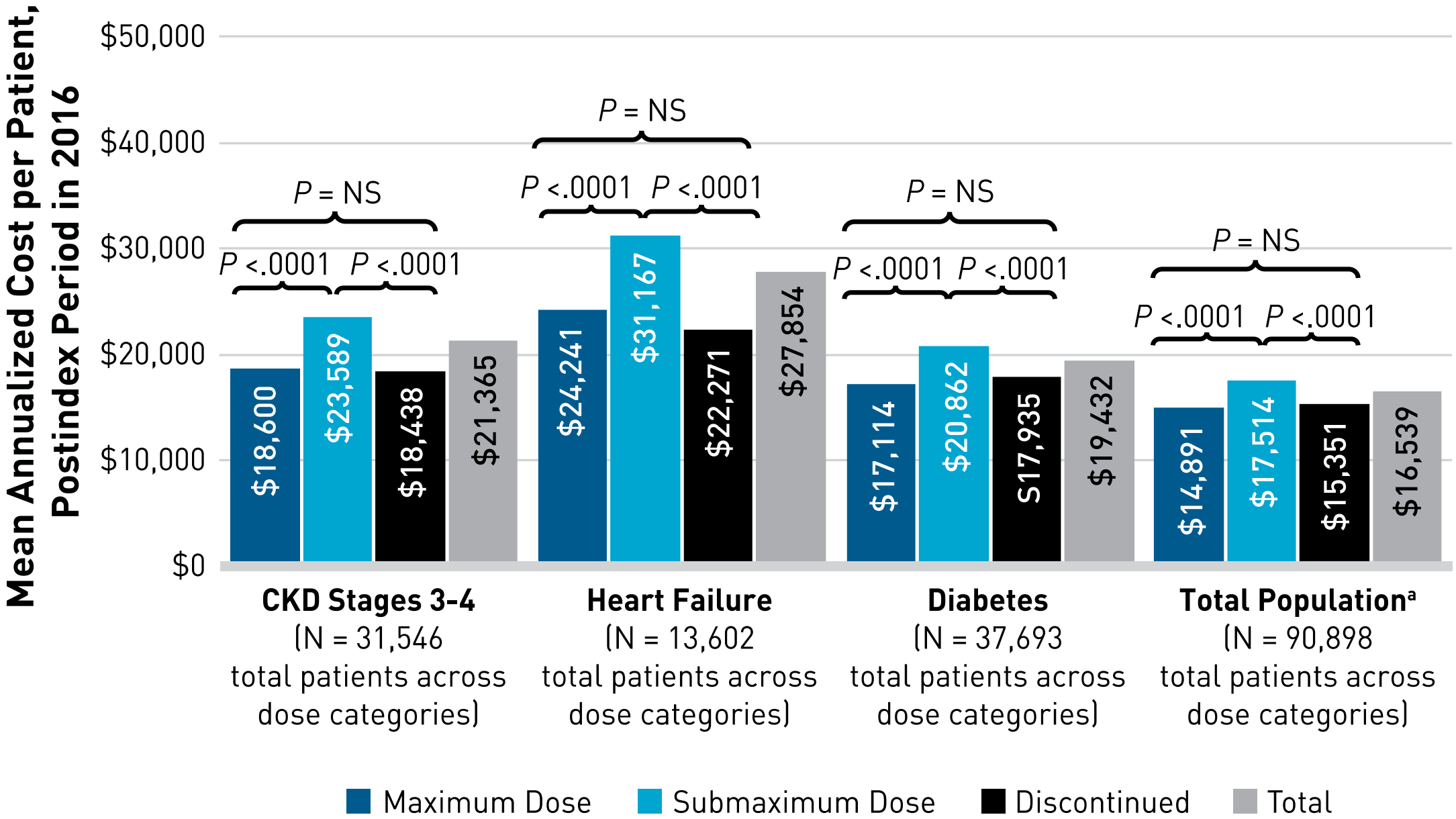
Burnett H *et al.2017 Circ Heart Fail*,

However, due to RAASi-induced hyperkalaemia, guidelines also recommend discontinuation of RAASi therapy.



1. National Institute of Clinical and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management [CG182] 2015 [Available from: https://www.nice.org.uk/guidance/cg182; Accessed April 2019. **2**. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200; **3**. British Society of Heart Failure, Renal Association UK, Think Kidneys . Changes in kidney function and serum potassium during ACEI/ARB/diuretic treatment in primary care, A position statement from Think Kidneys, the Renal Association and the British Society for Heart Failure. 2017; **4**. Alfonzo A, Soar J, MacTier R, Fox J, Shillday I, Nolan J, et al. Clinical Practice Guidelines, Treatment of Acute Hyperkalaemia in Adults, UK Renal Association 2014 [Available from: https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf;] Accessed April 2019. **5**. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. European heart journal Cardiovascular pharmacotherapy. 2018;4(3):180-8; **6**. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-290.

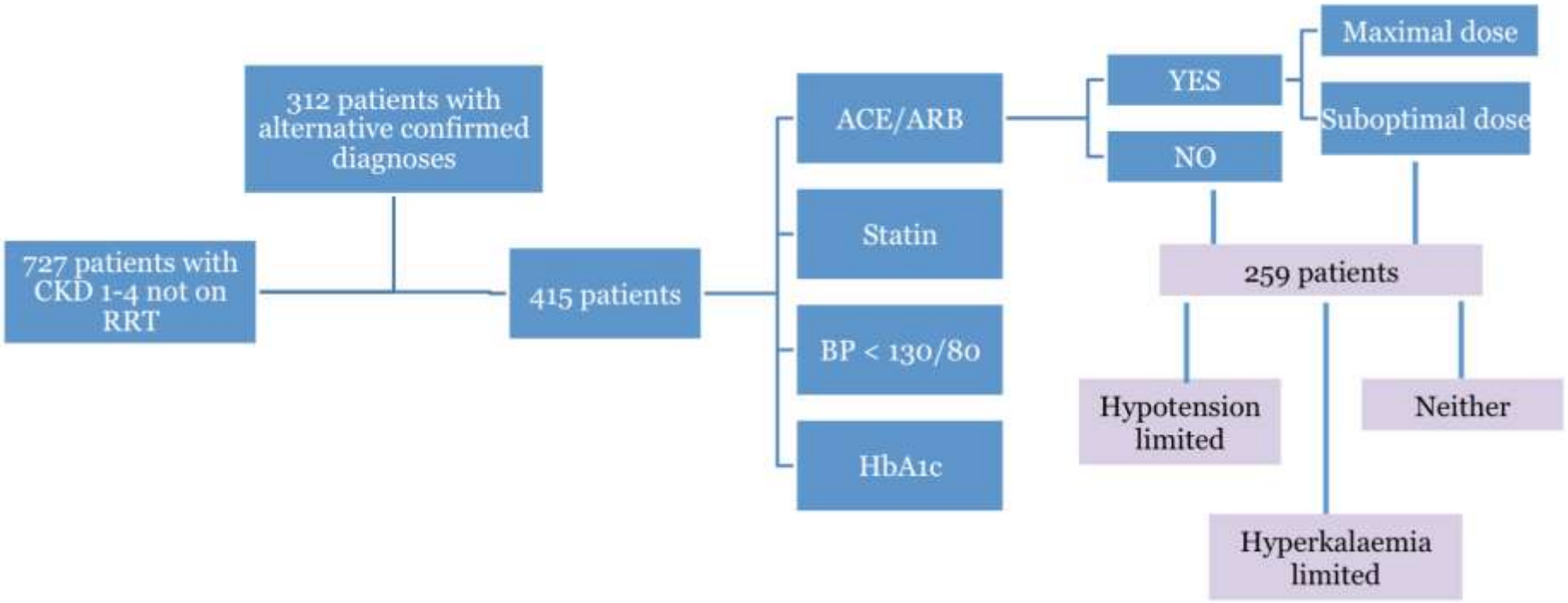

% of Patients Who Had Adverse Outcomes[a] or Death
80%
70%
60%
50%
40%
30%
20%
10%
0%
P <.0001
P <.0001
P <.0001
P <.0001
P <.0001
P <.0001
P <.0001
P <.0001
P <.0001
45.3%
50.1%
57.7%
50.2%
58.7%
66.1%
39.0%
42.8%
53.9%
35.6%
37.9%
48.6%
CKD Stages 3-4 (N = 31,546 total patients across dose categories)
Heart Failure (N = 13,602 total patients across dose categories)
Diabetes (N = 37,693 total patients across dose categories)
Total Population[b] (N = 90,898 total patients across dose categories)
Maximum Dose
Submaximum Dose
Discontinued



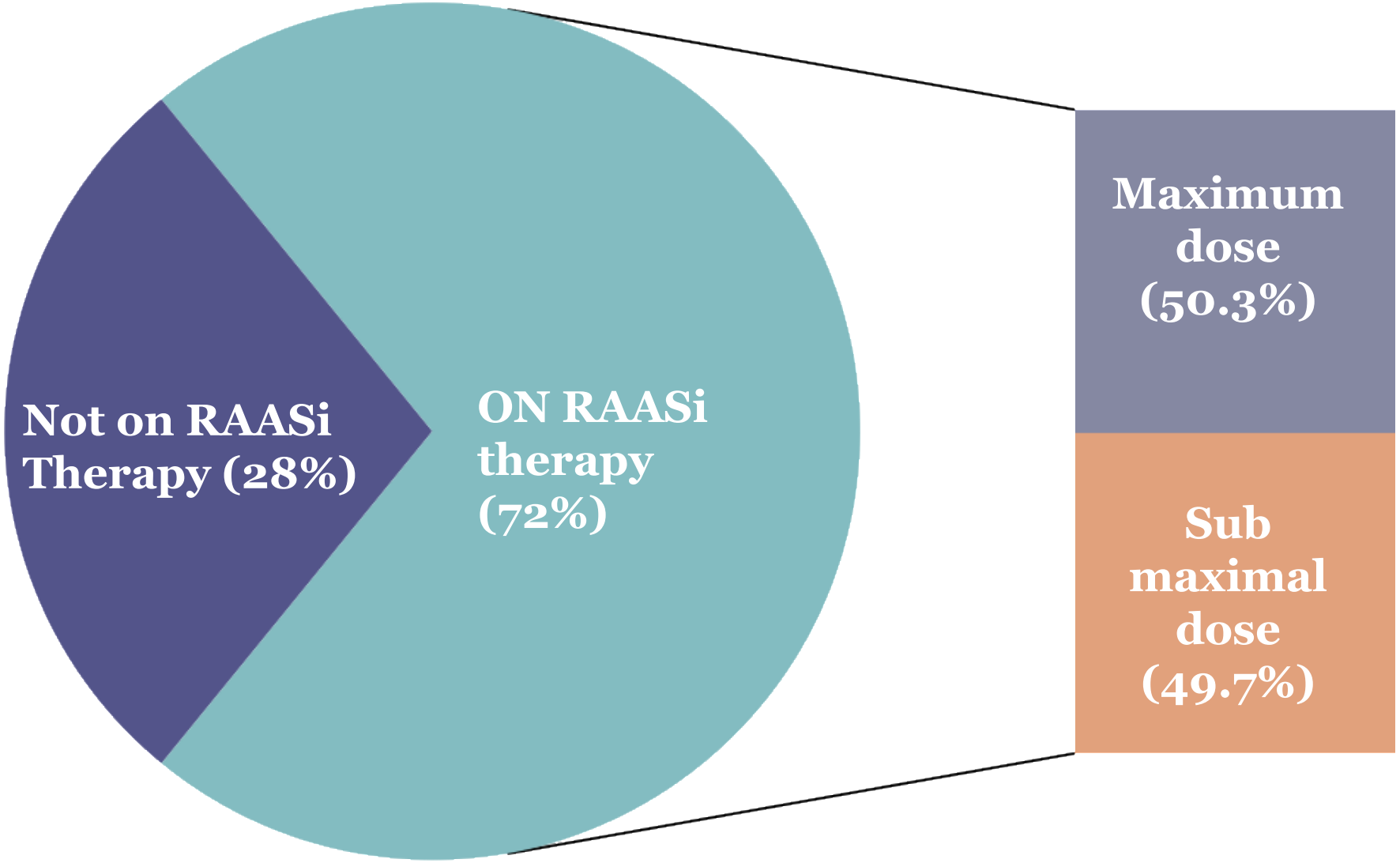
In 2013 over 70,000 ED visits due to hyperkalaemia.
>50% admitted to hospital. Mean stay of 3.1 days. Mean inpatient cost of $**27,802**

Barriers to ACEi/ARB use and optimization

- Retrospective observational study
- Identified all patients with Type 2 diabetes as a cause of their CKD and excluded those on dialysis/renal transplant.
- Examined those patients for maximum ACE/ARB, and the barriers to this.



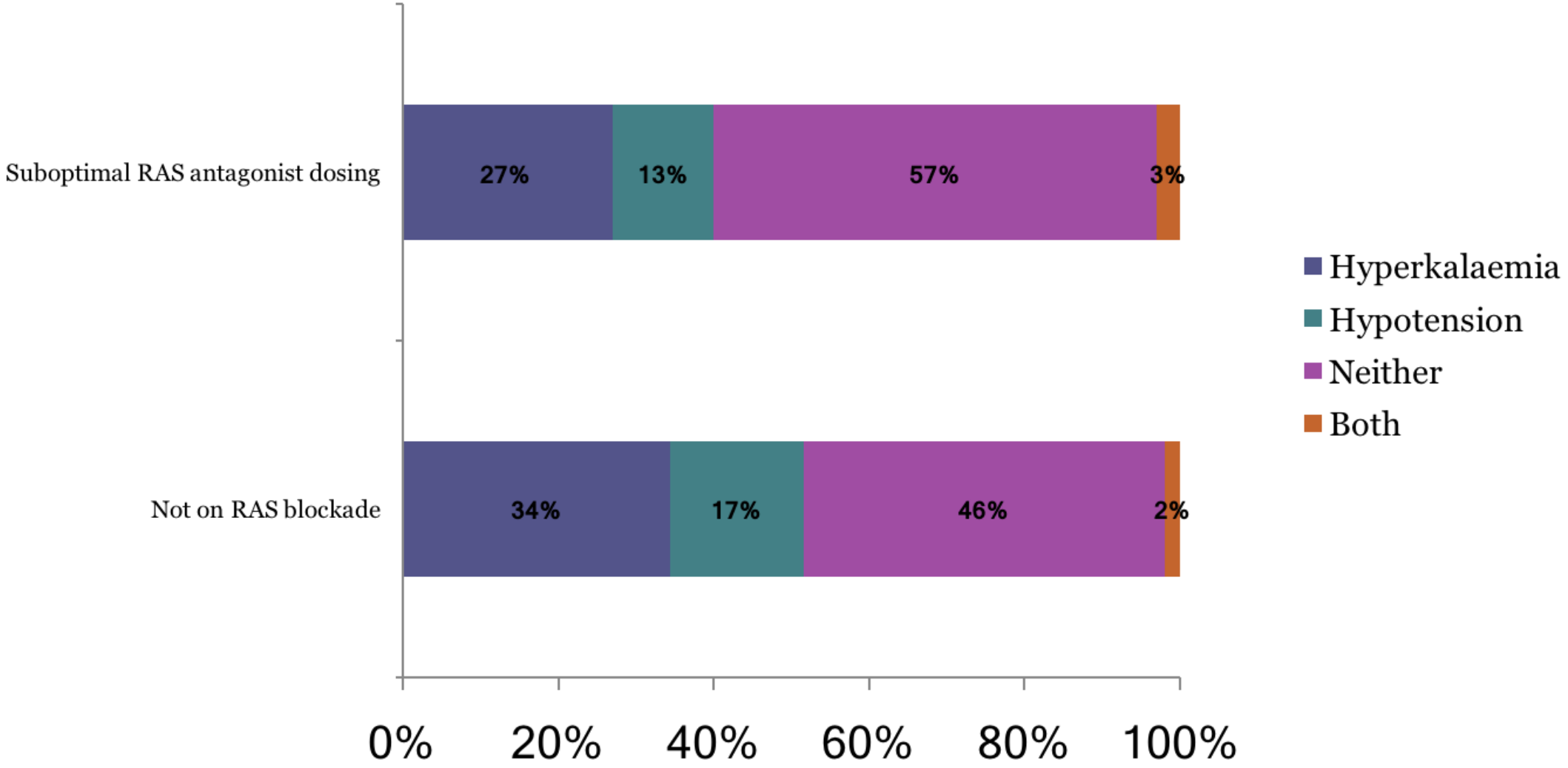
Chong et al ASN 2017 (poster)



A total 259 (62.9%) were on suboptimal doses of ACE/ARB or not on these agents at all

Chong et al ASN 2017 (poster)

Reasons for ACEi/ARB suboptimal dosing



Chong et al ASN 2017 (poster)

Current treatment options for managing hyperkalaemia are limited

Current treatment options for the management of hyperkalaemia†

Temporising agents[1-3]	Other pharmacological interventions[4]	Diet [5,6]	Modification of current therapies[1,5,7,8]
iv insulin dextrose ± salbutamol	**Calcium resonium**	**Low potassium diets**	**Down-titration / discontinuation of RAASi**
• Temporising agent only (i.e. shifts potassium into the cells). • Significant risk of hypoglycaemia. • May require >1 dose. • Occasions of suboptimal management, highlighted by an NHS Improvement Safety Alert in 2018.[3]	• There are few studies demonstrating evidence of efficacy. • Gastric irritation, anorexia, nausea, vomiting, constipation and occasionally diarrhoea may occur. • Potential non-compliance due to GI tolerability.[9] • Concerns of bowel necrosis and poor tolerability may limit chronic use.	• Low potassium diet falls outside what is generally recommended as a healthy diet.[6] • Dietary restrictions are difficult to adhere to.[10] • However, it can offer a level of empowerment to patients to control their health condition. • A low potassium intake may increase blood pressure.[11]	• See next slide

A&E / inpatient setting

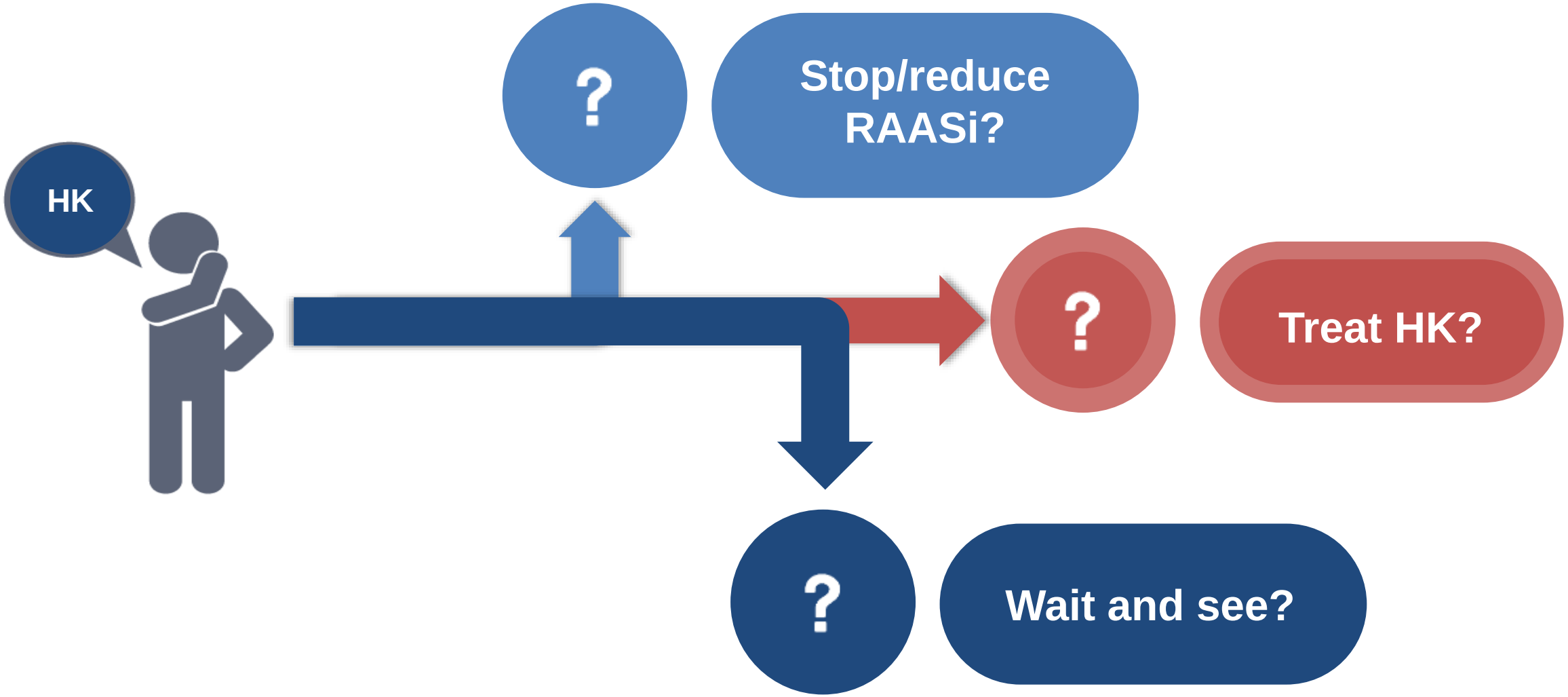
Outpatient setting

Insulin Dextrose

- Is not a benign therapy…
- Large retrospective cohort of general medical admissions with insulin dextrose:
  - 9% became hypoglycaemic <4
  - Almost 3% had blood sugars 2.2 or below[1]
- In non diabetic dialysis patients: 10U of Insulin and 50ml of 50% Dextrose, led to hypoglycaemia (glucose<3) in 75% of patients at 1h[2]

1. Schafers *et al*, 2012. *Journal of hospital medicine*, 7(3), 239-242.
2. Allon *et al*, 1990. *Kidney international*, *38*(5), 869-872.

Are we optimally managing patients with HK?



HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor

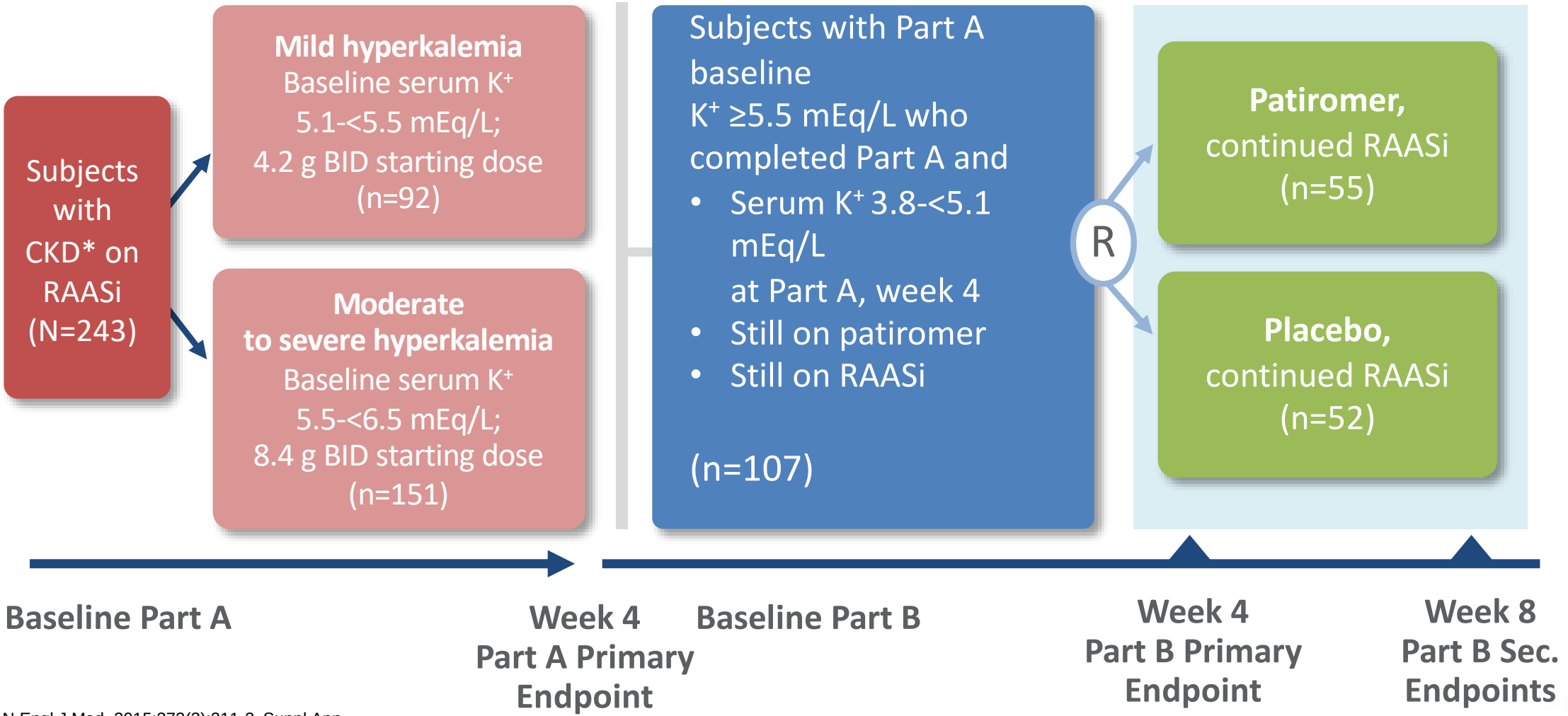
Novel Potassium binders

- **Patiromer/Veltassa**
- **LokeIma/SZC**

OPAL-HK Phase 3 Patients With CKD on RAASi

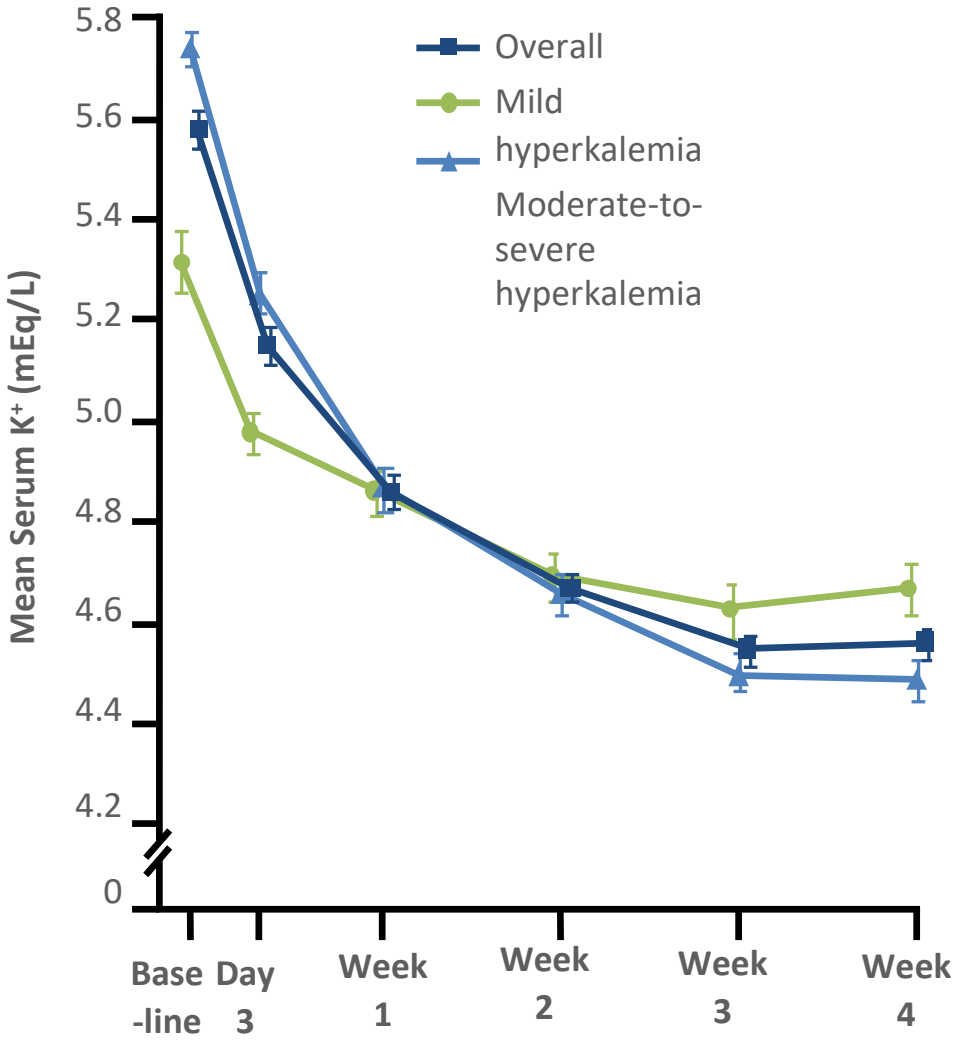
Part A:
Treatment Phase (Single-Blind)

Part B:
Randomized Withdrawal Phase (Single-Blind)

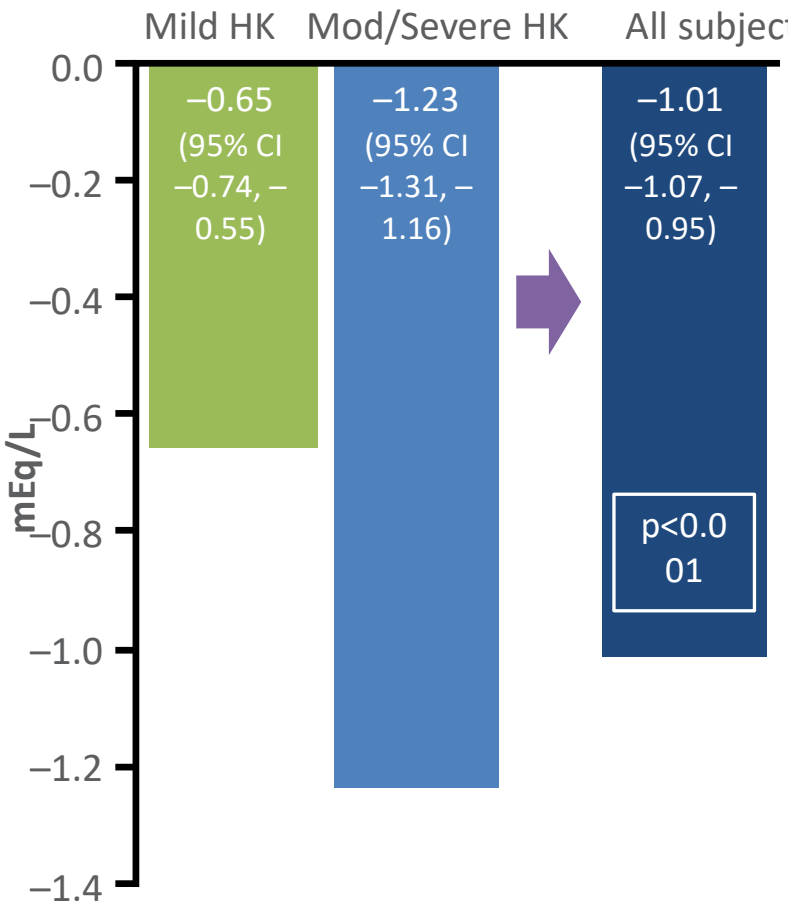


Weir et al, N Engl J Med, 2015;372(3):211-2. Suppl App

Primary and Secondary Efficacy Endpoints



Primary efficacy endpoint:
mean change from baseline to Week 4 (all subjects)

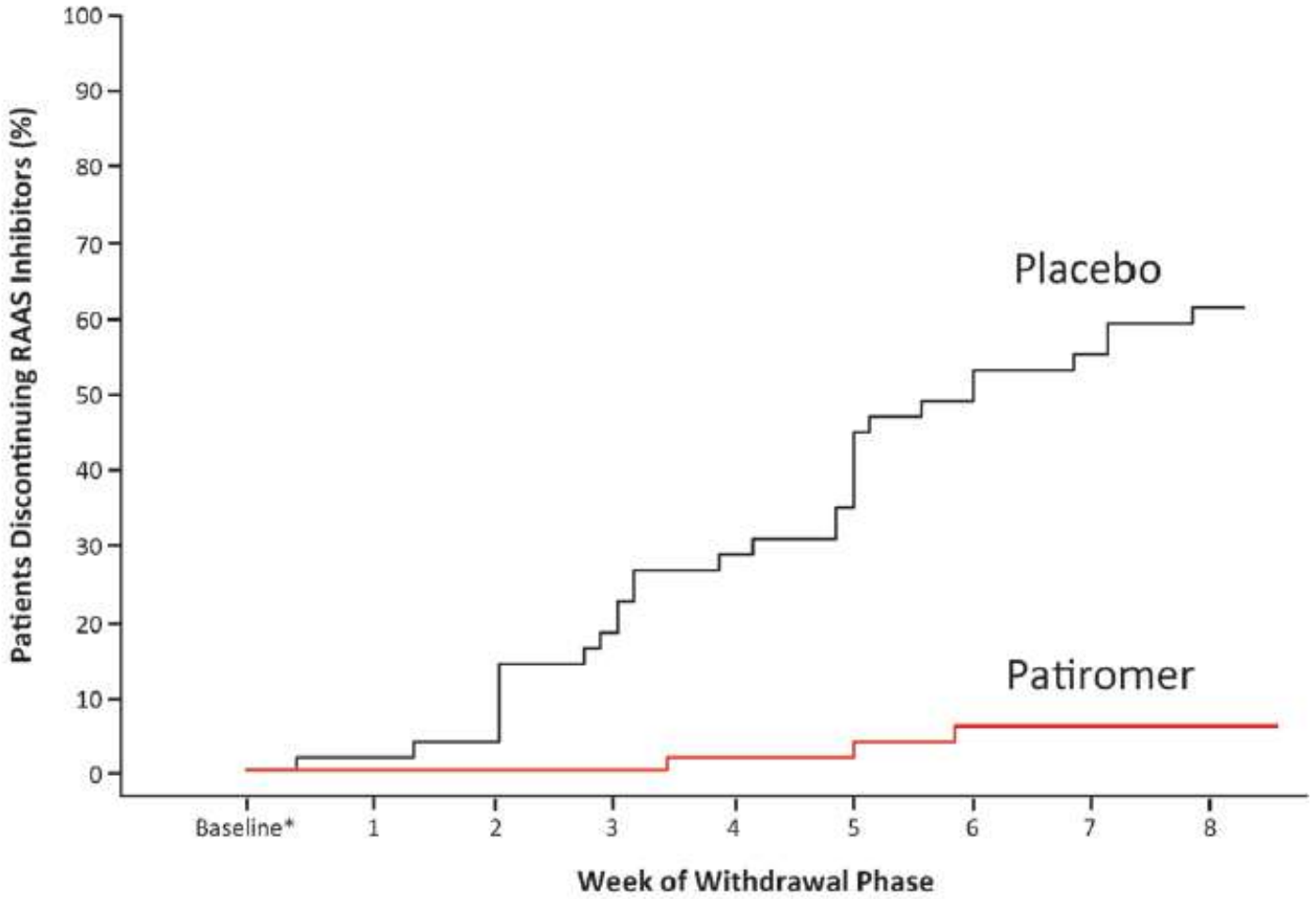


*Depicts potassium between 4.0-6.0 in line with the normal reference range for potassium

Secondary Efficacy Endpoint: 76% of subjects had serum K^+ in the target range (3.8 to <5.1 mEq/L) at week 4

Weir MR, et al. *N Engl J Med.* 2015;372(3):211-221.

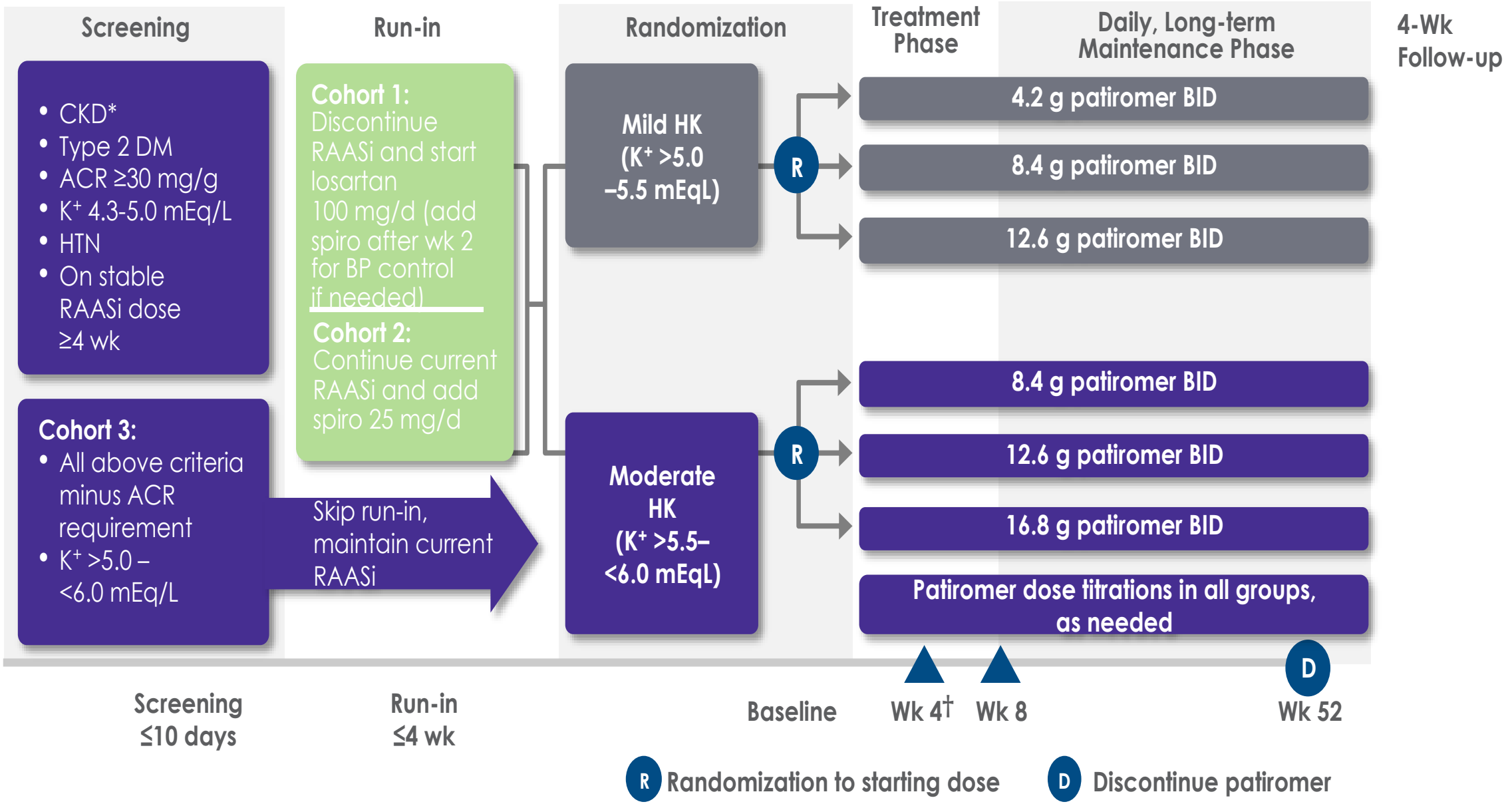
Exploratory end point: effect of Patiromer on the proportion of patients discontinuing RAASi therapy



No. of Patients									
Placebo	52	49	47	40	35	32	25	22	14
Patiromer	55	54	52	51	50	48	44	44	34

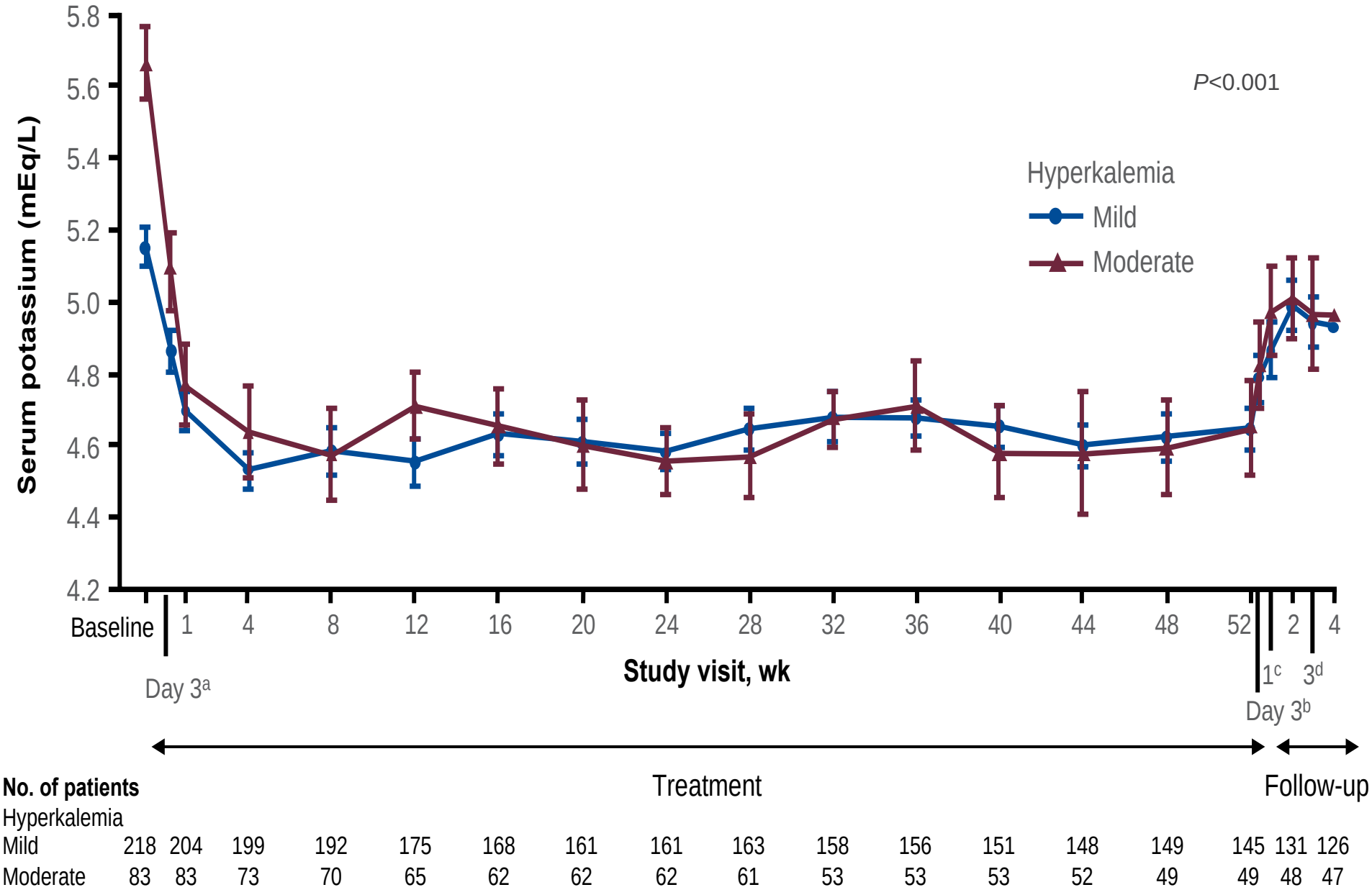
Weir et al, N Engl J Med, 2015;372(3):211-2. Suppl App

AMETHYST-DN: Study Design



*eGFR 15-60 mL/min/1.73 m^2. †Primary endpoint. ACR: albumin-creatinine ratio, DM: diabetes mellitus, GFR: glomerular filtration rate, HTN: hypertension, RAASi: renin-angiotensin-aldosterone system inhibitor, spiro: spironolactone.

- Bakris G, et al. *JAMA*. 2015;314(2):151-161



All serum K^+ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K^+ value at baseline and therefore are not included in the analysis at this timepoint. *At all timepoints, *P*<0.001 (2-sided *t*-test) for least-squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study).

- Bakris G, et al. *JAMA*. 2015;314(2):151-161.

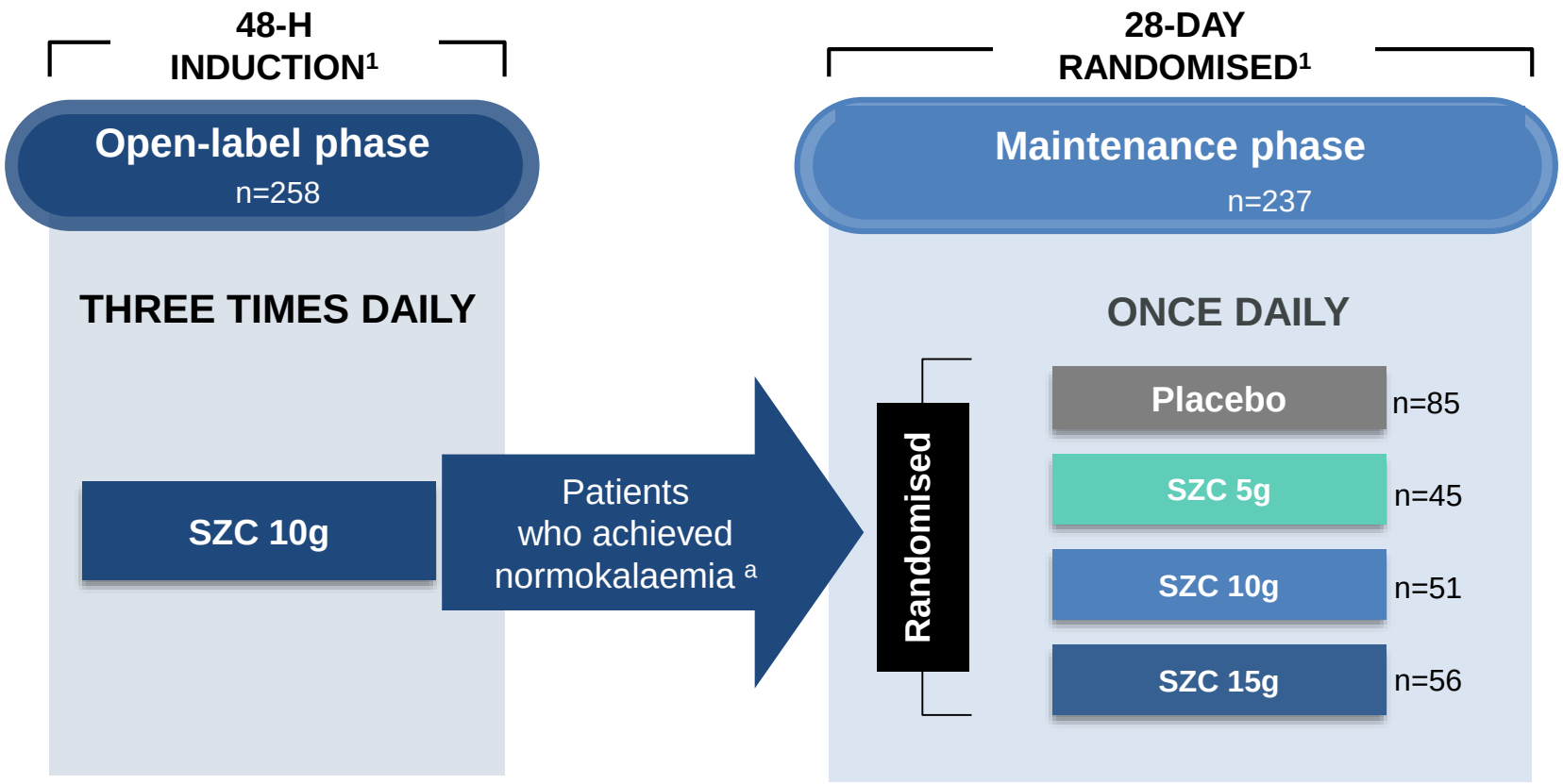
Novel Potassium binders

- Patiromer/Veltassa
- **Lokelma/SZC**

HARMONIZE (004): Study design

Primary efficacy endpoint

The primary endpoint is the comparison of mean potassium levels between placebo and each treatment arm during days 8 through to 29 of randomised phase. Population: 258 patients with hyperkalaemia (K^+ ≥5.1mmol/L, baseline average 5.6 mmol/L).[1]



SZC: Reduction of serum potassium levels·

In the 48 hour open label phase of the study, one dose (10g) of SZC significantly reduced the mean serum K^+ level after 1 hour.[1,2]

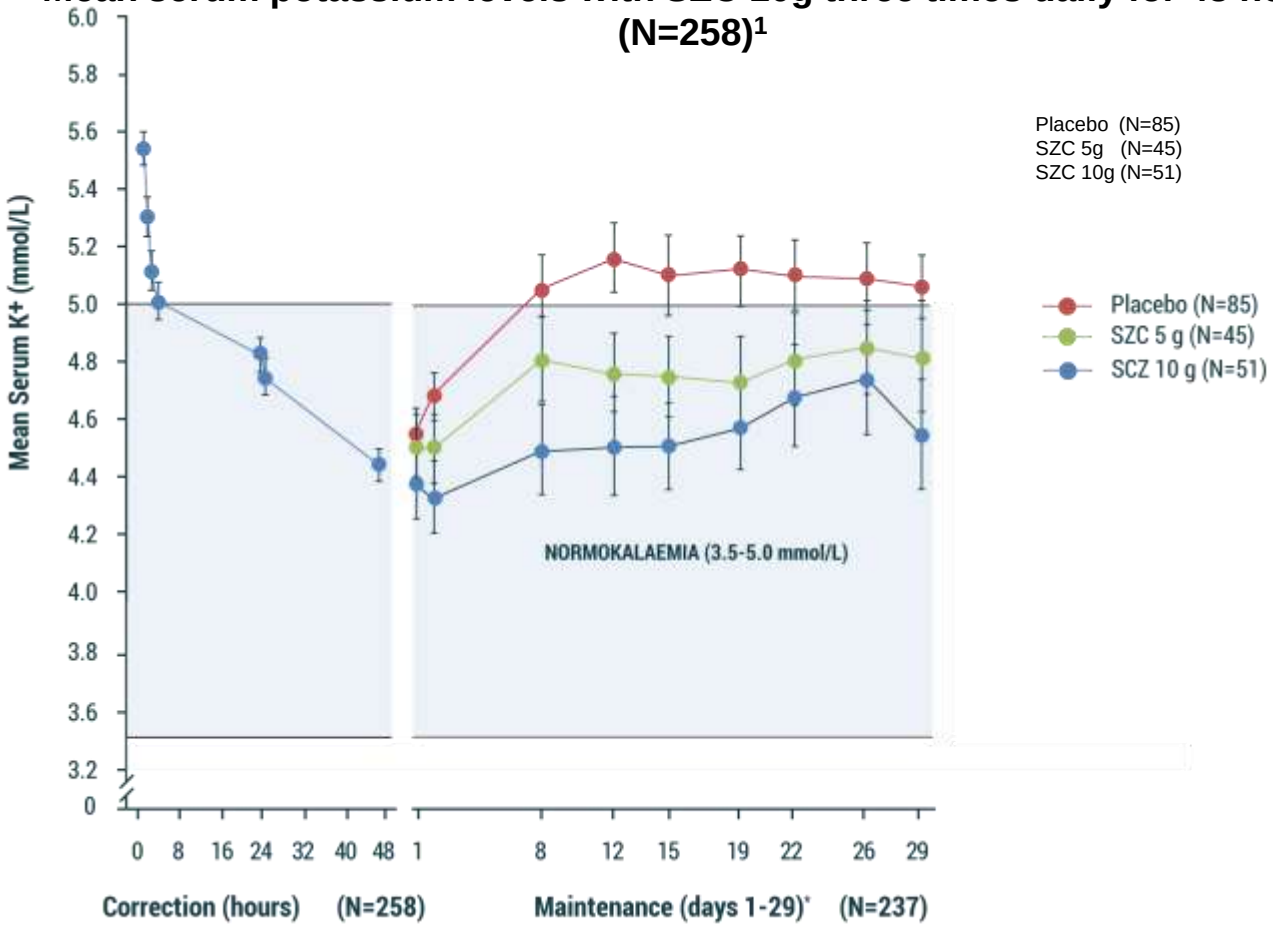
-0.2 mmol/L compared to baseline. 95% CI: -0.3 to -0.2.[2]

In an emergency situation, standard of care should be used in line with local or national guidelines.

Results of open label induction phase (absolute change in K^+ and proportion of patients achieving normokalaemia) are secondary endpoints.

88% of patients achieved normokalaemia at 48 hours.[1]

Mean serum potassium levels with SZC 10g three times daily for 48 hours (N=258)[1]

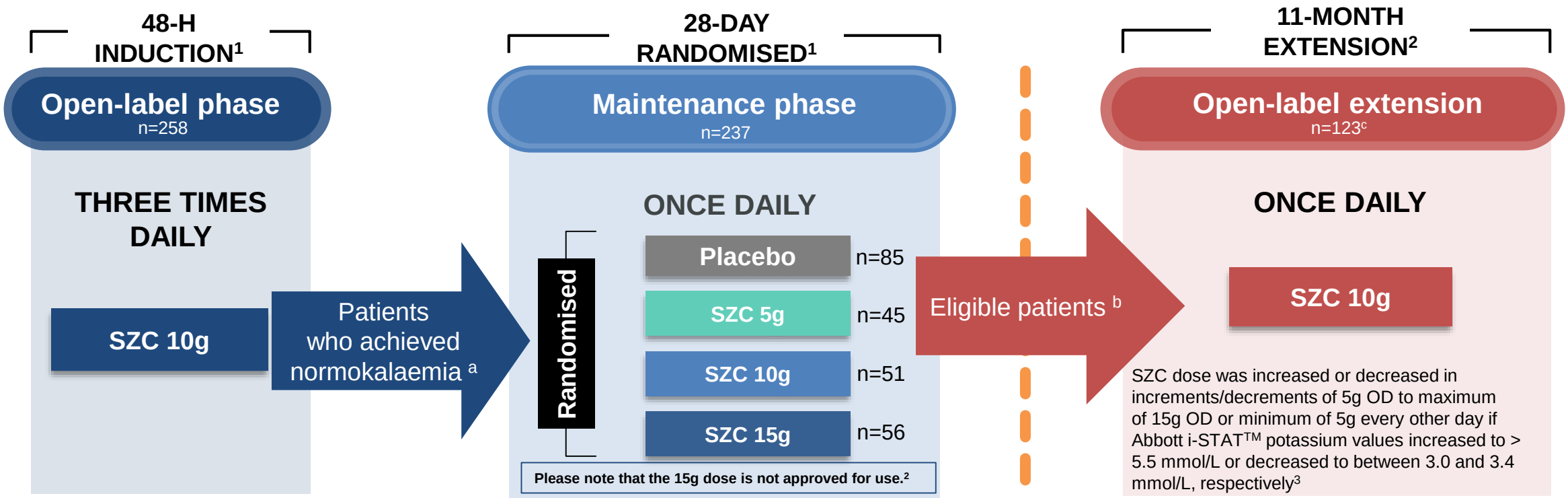


Adapted from Kosiborod et al., 2014[2]

HARMONIZE (004): Open-label extension

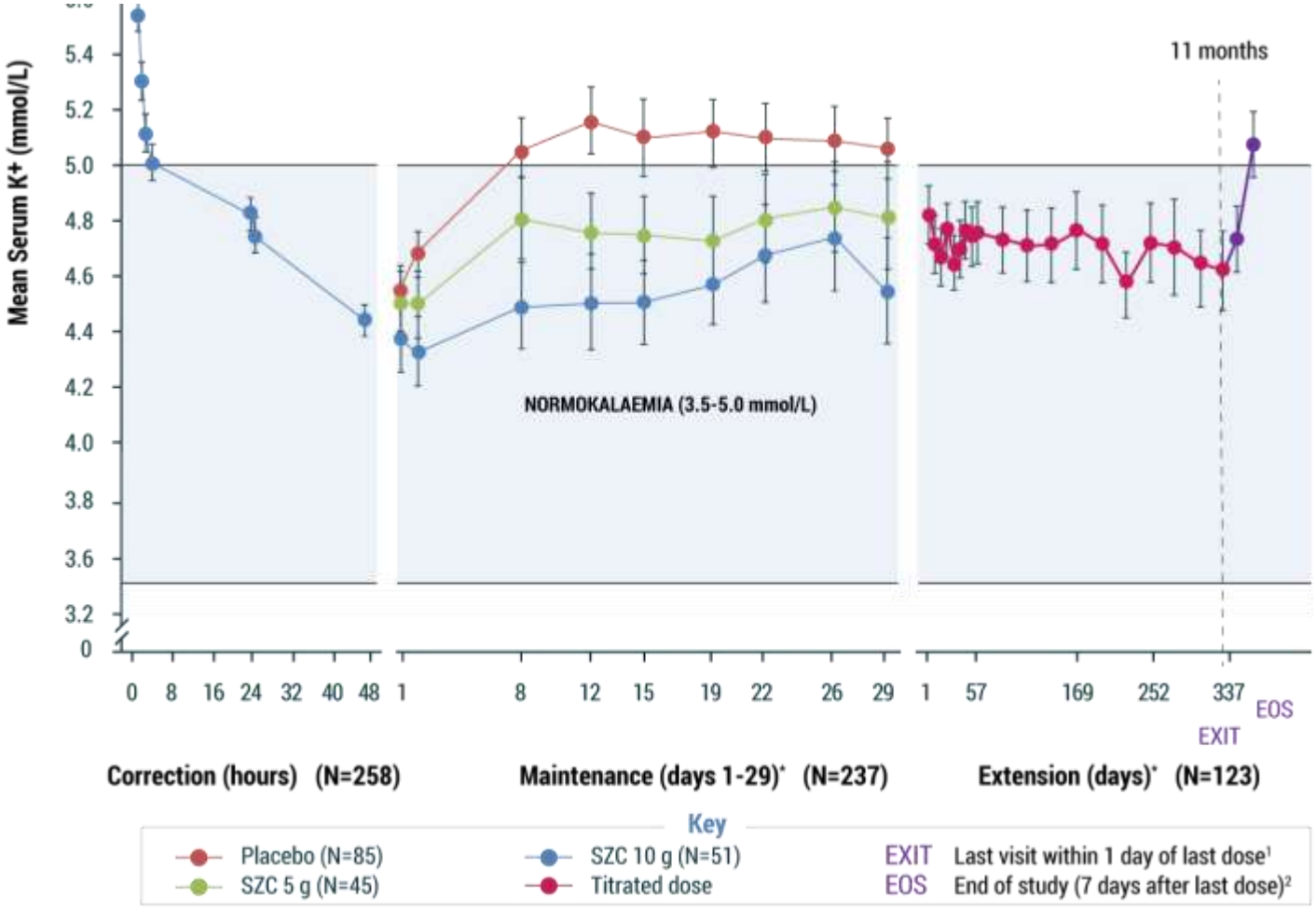
Primary efficacy endpoint

The primary endpoint is the comparison of mean potassium levels between placebo and each treatment arm during days 8 through to 29 of randomised phase. Population: 258 patients with hyperkalaemia (K^+ ≥5.1mmol/L, baseline average 5.6mmol/L).[1]



SZC: Sustained serum K^+ control for up to 1 year when used as maintenance therapy.

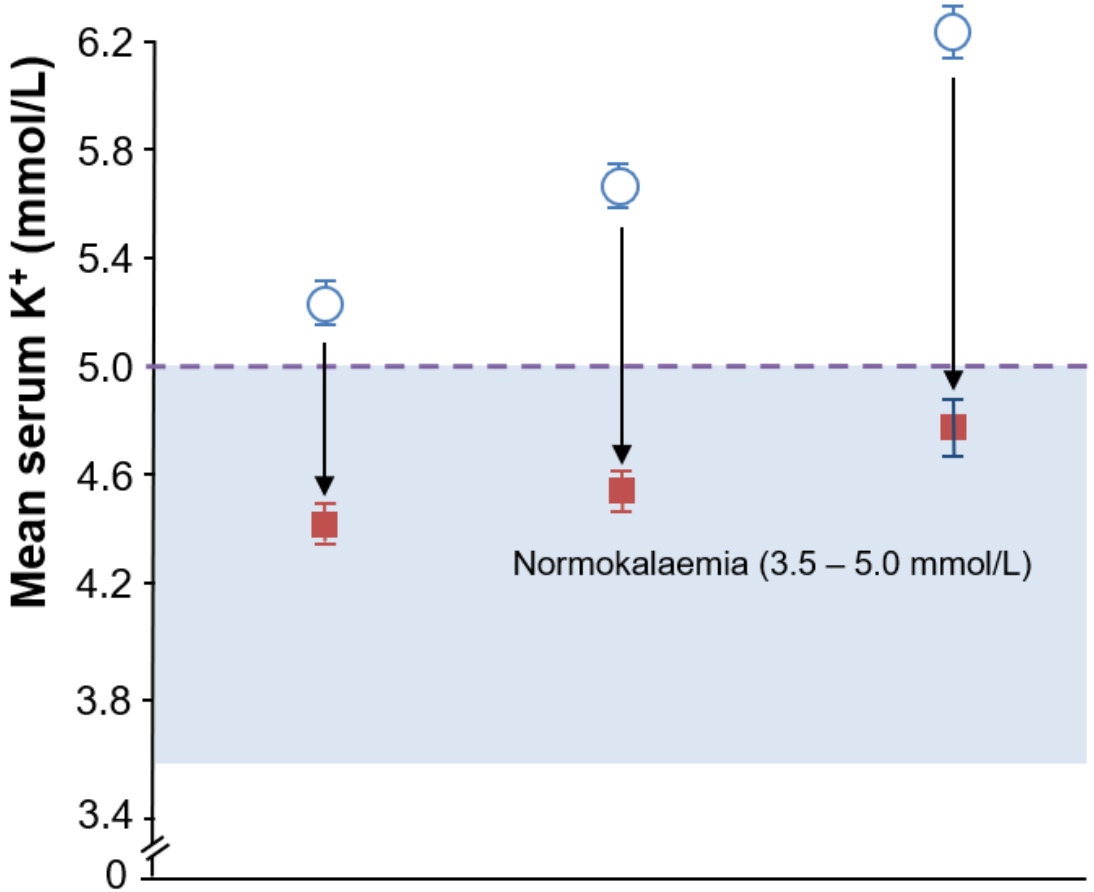
- **Once-daily maintenance dosing of SZC sustains normokalaemia (3.5 – 5.0 mmol/L) for up to one year.**[1,2]
- **88% of patients in the Extension Phase receiving SZC maintained an average serum K^+ of <5.1 mmol/L over 11 months.**[1,2]
- **No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations.**[1,2]



SZC: consistent serum K^+ reduction in all studied patient groups.

Subgroup analysis performed on data from the open label induction phase showed:

- **SZC consistently reduced serum K^+, regardless of comorbidities*, use of RAASi therapy, or baseline K^+ level.**[2]
- **Greater reductions in serum K^+ were observed in patients with higher baseline serum K^+ levels.**[2]



Baseline K^+ level (mmol/L)	<5.5	5.5 to <6.0	≥6.0
No. of patients:			
Baseline	119	100	39
48 hours	115	99	37

Statistical analysis of differences between baseline and 48 hours was not reported in Kosiborod et al (2014).[2]

Adapted from: Kosiborod M, et al. (2014)[2]

Drug-drug interactions.

- As SZC is not absorbed or metabolised by the body, and does not meaningfully bind other medicinal products
- SZC can transiently increase gastric pH by absorbing hydrogen ions and can lead to changes in solubility and absorption kinetics for co-administered medicinal products with pH-dependent bioavailability.

However, SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability.
Examples of medicinal products that should be administered 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are:

azole antifungals (ketoconazole, itraconazole and posaconazole),

anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir and rilpivirine) and

tyrosine kinase inhibitors (erlotinib, dasatinib and nilotinib).

SZC dosage and methods of administration

Recommended dosing of SZC to achieve and sustain normokalaemia

Correction phase

Recommended starting dose:
10g three times daily for up to 48 hours until normokalaemia is achieved.*

In an emergency situation, standard of care should be used in line with national or local guidelines

Maintenance phase

1×  **/day****

5g for up to 1 year

To establish minimum effective dose, SZC may be titrated

- Up to **10g once daily** or
- Down to **5g once every other day**

No more than **10g once daily** should be used for maintenance therapy

Mix SZC with 3 tablespoons (45 mL) of water for oral administration[1]

- ✓ Tasteless and odourless[1,2]
- ✓ May be taken with most other medication ǂ
- ✓ May be taken with or without food
- ✓ No special conditions for storage

NICE approval 4th September 2019

- Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults only if used:
- In emergency care for acute life-threatening hyperkalaemia alongside standard care or
- In outpatient care for people with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, if they:
  - have a confirmed serum potassium level of at least 6.0 mmol/litre
  - are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and
  - are not on dialysis.

In outpatient care, stop sodium zirconium cyclosilicate if RAAS inhibitors are no longer suitable.

Comparison of novel K binders

Lokelma

- Inorganic crystalline zirconium silicate compound, swapping Na for K
- Dose: 5g-10g
- Cost: £7.12 for 5g
- Onset of Action: 1 hour
- Data on safety and effectiveness out to 1 year
- No effect on Ca/Mg
- Interactions: avoid administration within 2h of drugs affected by gastric pH bioavailability: some azole antifungals, anti-HIV drugs and tyrosine kinase inhibitors.
- Can be taken with food
- Most frequent adverse reactions reported from trials oedema related events (5.7%), constipation (2.9%), nausea (1.6%) diarrhoea (0.9%), abdominal pain/distension (0.5%), and vomiting (0.5%)
- Chronic treatment fall in around 0.8-1.2mmol K
- NICE approved

Patiromer

- Cation exchange polymer containing a calcium-sorbitol complex as a counterion
- Dose 8.4g-25.2g
- Cost: £10 for 8.4g
- Onset of action: 4-7 hours
- Data on safety and effectiveness out to 1 year
- May lower calcium/magnesium by a small amount
- Interactions: Concomitant administration of Patiromer showed reduced bioavailability of ciprofloxacin, levothyroxine and metformin.

- Avoid food/other medications within 3h
- Most frequent adverse reactions reported from trials constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%)

- Chronic treatment fall in around 0.8-1.2mmol K
- Not currently NICE approved

Summary

- Hyperkalaemia is common in patients with CKD, HF, diabetes, and hypertension, and is associated with clinical burden and increased healthcare costs.
- Hyperkalaemia treatment options may be associated with limitations:
  - Low-potassium diets, diuretics, lowering RAASi dosing, older potassium binders.
- Novel K binders represent a leap forward in hyperkalaemia management: both appear safe and effective in the short and long term (up to 1 year).