Τα διουρητικά στη Χρόνια Νεφρική Νόσο

Ρήγας Καλαϊτζίδης
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Disclosures

Consultant Advisory Board : Astra Zeneca, Winmedica Boehringer Ingelheim,

Speaker's Bureau: Astra Zeneca , Winmedica ,Boehringer Ingelheim ,

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Χρόνια Νεφρική Νόσος

Διουρητικό

Τι γνωρίζουμε μέχρι σήμερα για την επιλογή του διουρητικού;

Τι καινούργιο υπάρχει σήμερα για την επιλογή του διουρητικού στην ΧΝΝ ;

Ποιο διουρητικό της αγκύλης ;

Το Καρδιονεφρικό σύνδρομο

Η αντίσταση στα διουρητικά

Έχουν όλοι οι ασθενείς με Χρόνια Νεφρική Νόσο Την ίδια ανταπόκριση;

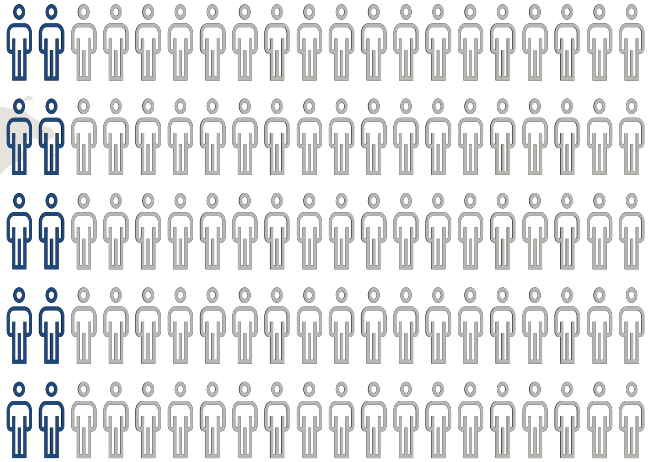
Παρενέργειες των διουρητικών

Χρόνια Νεφρική Νόσος

ΧΝΝ: Μία σιώπηλη απειλή για την παγκόσμια υγεία

~850 εκατ. άτομα

ζοιυν με ΧΝΝ παγκοσμίως[1]

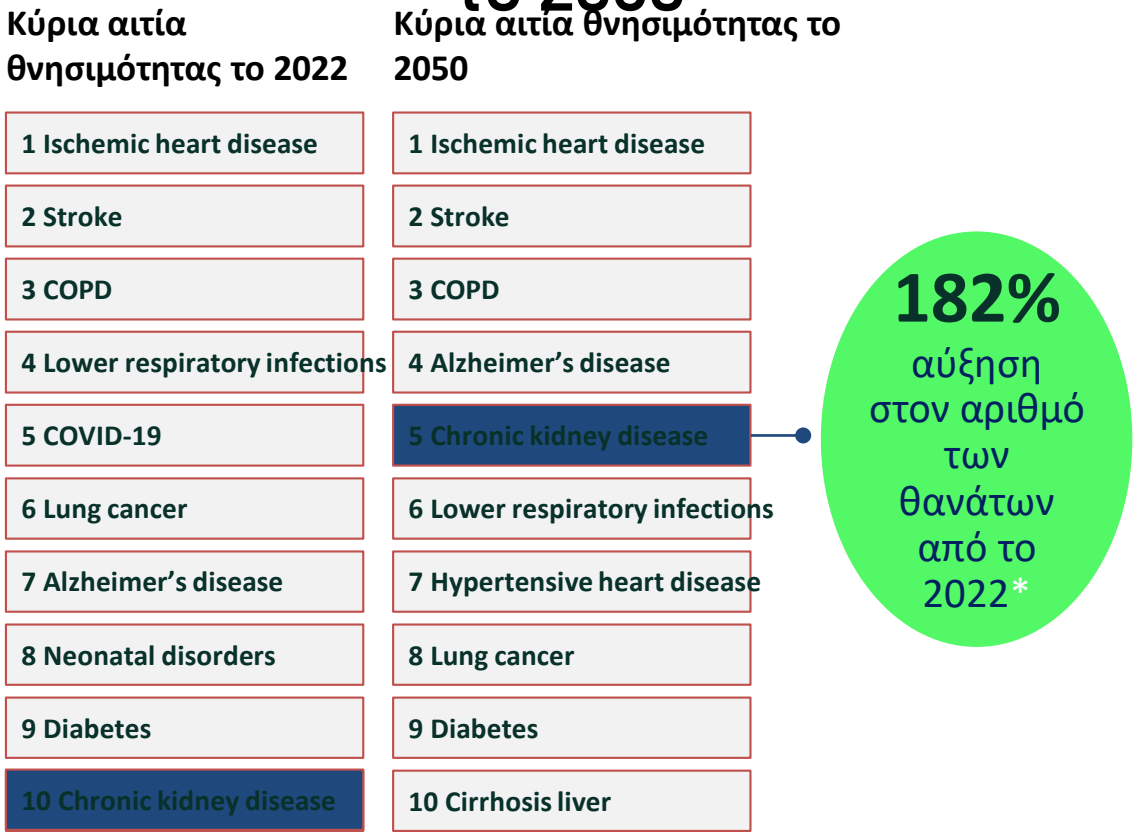


Η **έλλειψη της έγκαιρης ανίχνευσης τόσο και προγραμμάτων προσυμπτωματικού ελέγχου** παγκοσμίως σημαίνει ότι ο **επιπολασμός της ΧΝΝ πιθανότατα υποεκτιμάται**[2]

ΧΝΝ: Χρόνια Νεφρική Νόσος

1. Jager KJ, et al. *Kidney Int.* 2019;96:1048–1050; 2. Francis A, et al. *Nat Rev Nephrol.* 2024; 20:473–485.

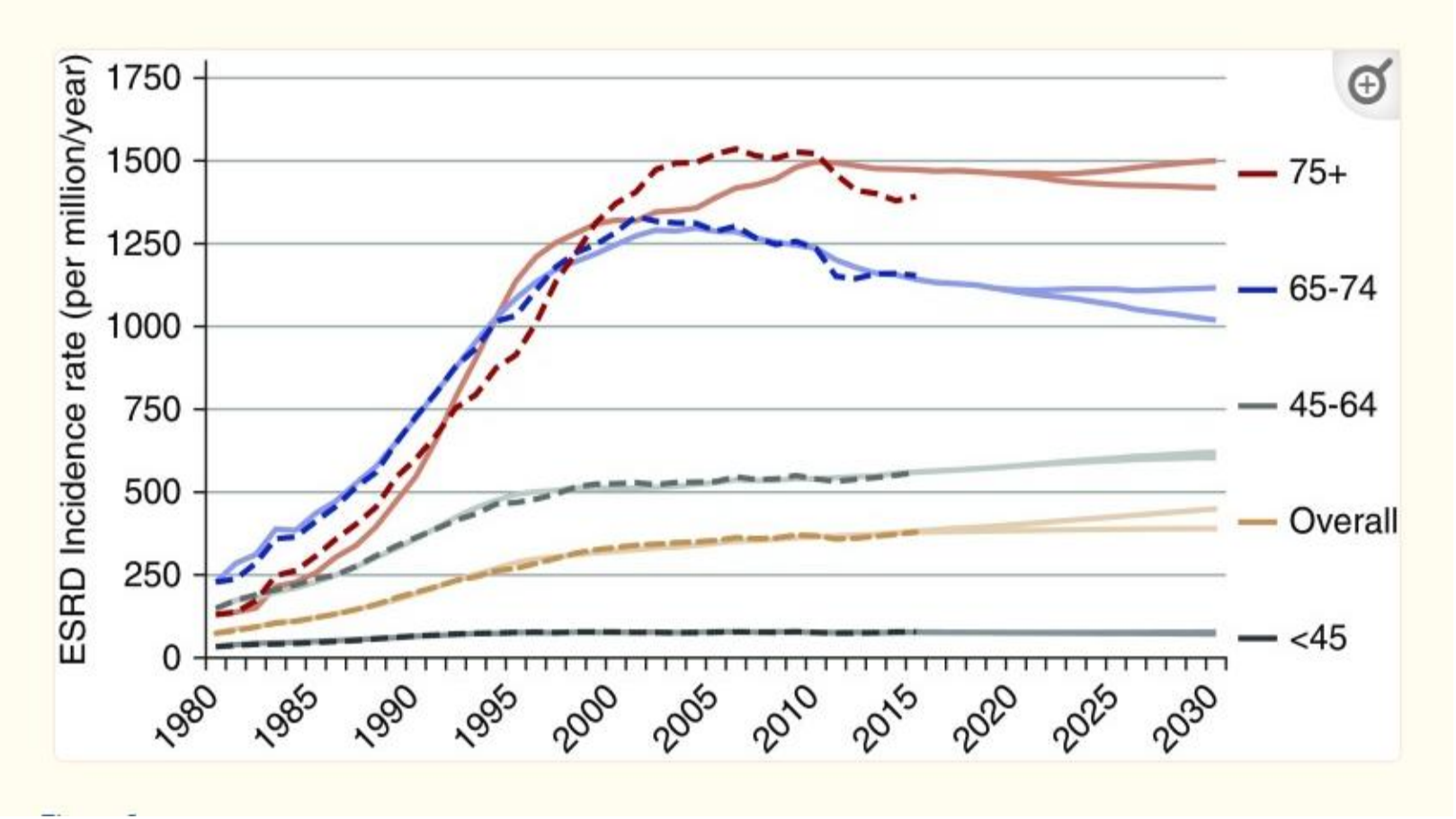
Η ΧΝΝ αναμένεται να ξεπεράσει το Ca πνεύμονα και τον ΣΔ, ως 5η κύρια αιτία θανάτου παγκοσμίως μέχρι το 2050*



*Mean % change.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

GBD 2021 Forecasting Collaborators. *Lancet*. 2024;403:2204–2256.

Age-specific incidence rates have leveled off.



J Am Soc Nephrol. 2019 Jan; 30(1): 127–135.

Typical findings of proteinuria and urine sediment abnormalities in differential diagnosis of common causes of CKD

	Proteinuria	Total albumin/ creatinine ratio	RBC	RBC casts	WBC	WBC casts
Diabetic kidney disease	+	≥30 mg/g	–	–	–	–
Hypertensive kidney disease	±	0–1000 mg/g	–	–	–	–
Myeloma	±	..	–	–	–	–
Cystic kidney disease	-	..	±	–	–	–
Tubulointerstitial/obstructive	±	≤1000 mg/g	–	–	+	+

Chronic kidney disease (CKD) arises from many

Heterogeneous Disease Pathways

Which may influence diuretics action

Table 2: Typical findings of proteinuria and urine sediment abnormalities in differential diagnosis of

www.thelancet.com Vol 389 March 25, 2017


Πανελλήνιο Συνέδριο
27ο Νεφρολογίας
Αλεξανδρούπολη
20-23 Μαΐου 2026 Ξενοδοχείο Astir-Egnatia

Διουρητικά

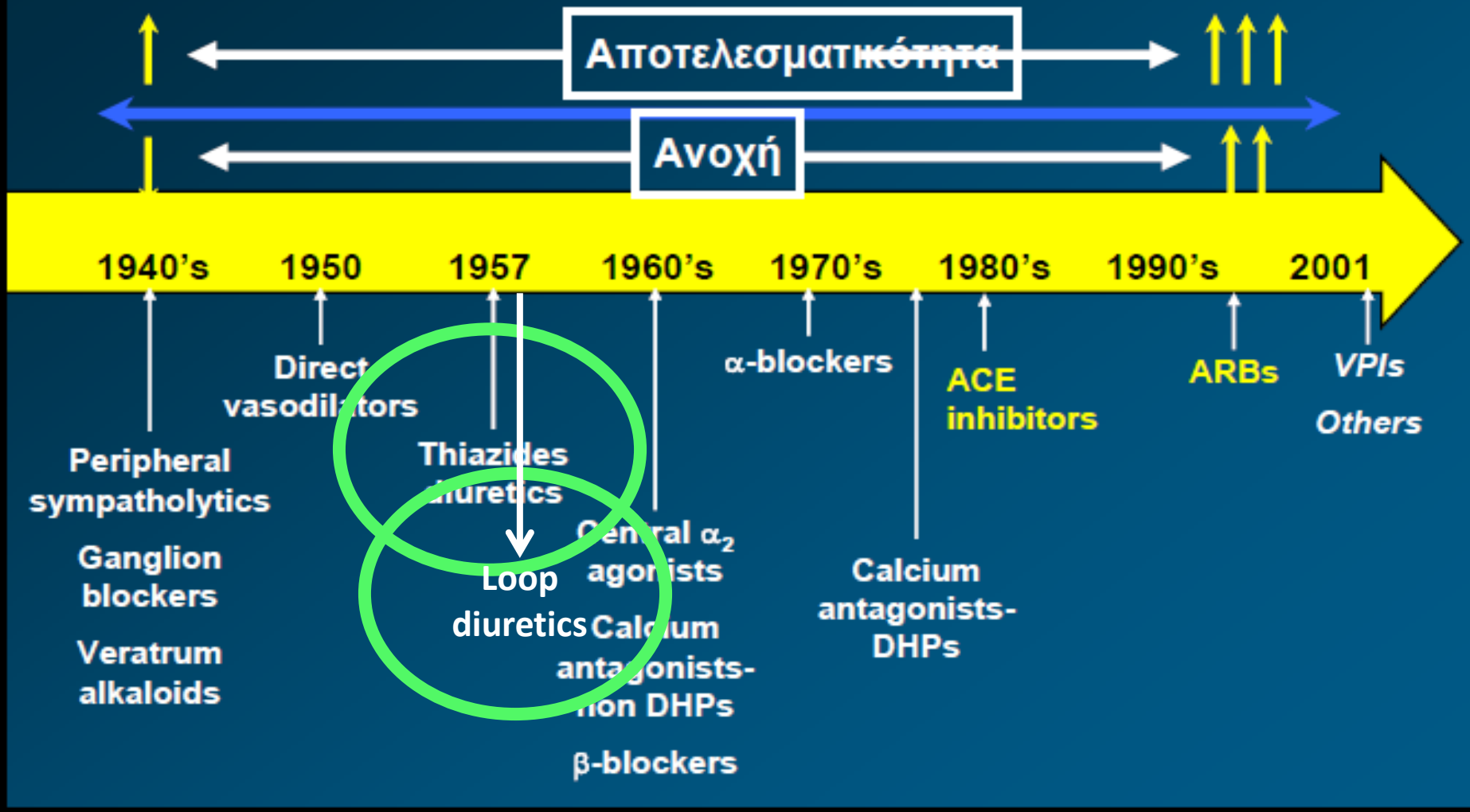
DEFINITIONS

Diuretic: substance that promotes the excretion of urine

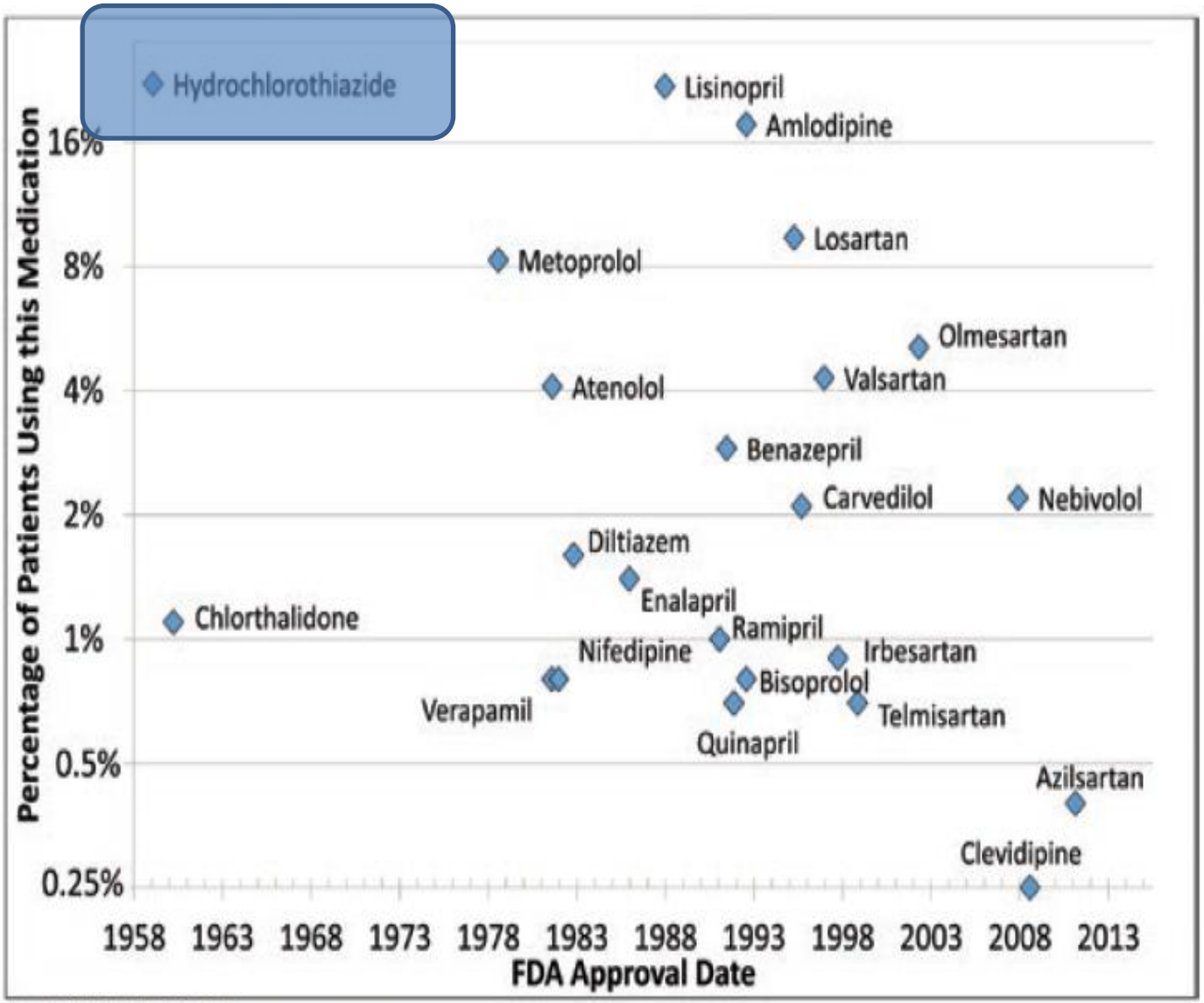
caffeine, yerba mate, nettles, cranberry juice, alcohol

Natriuretic: substance that promotes the renal excretion of Na+

Development of Antihypertensive Therapies



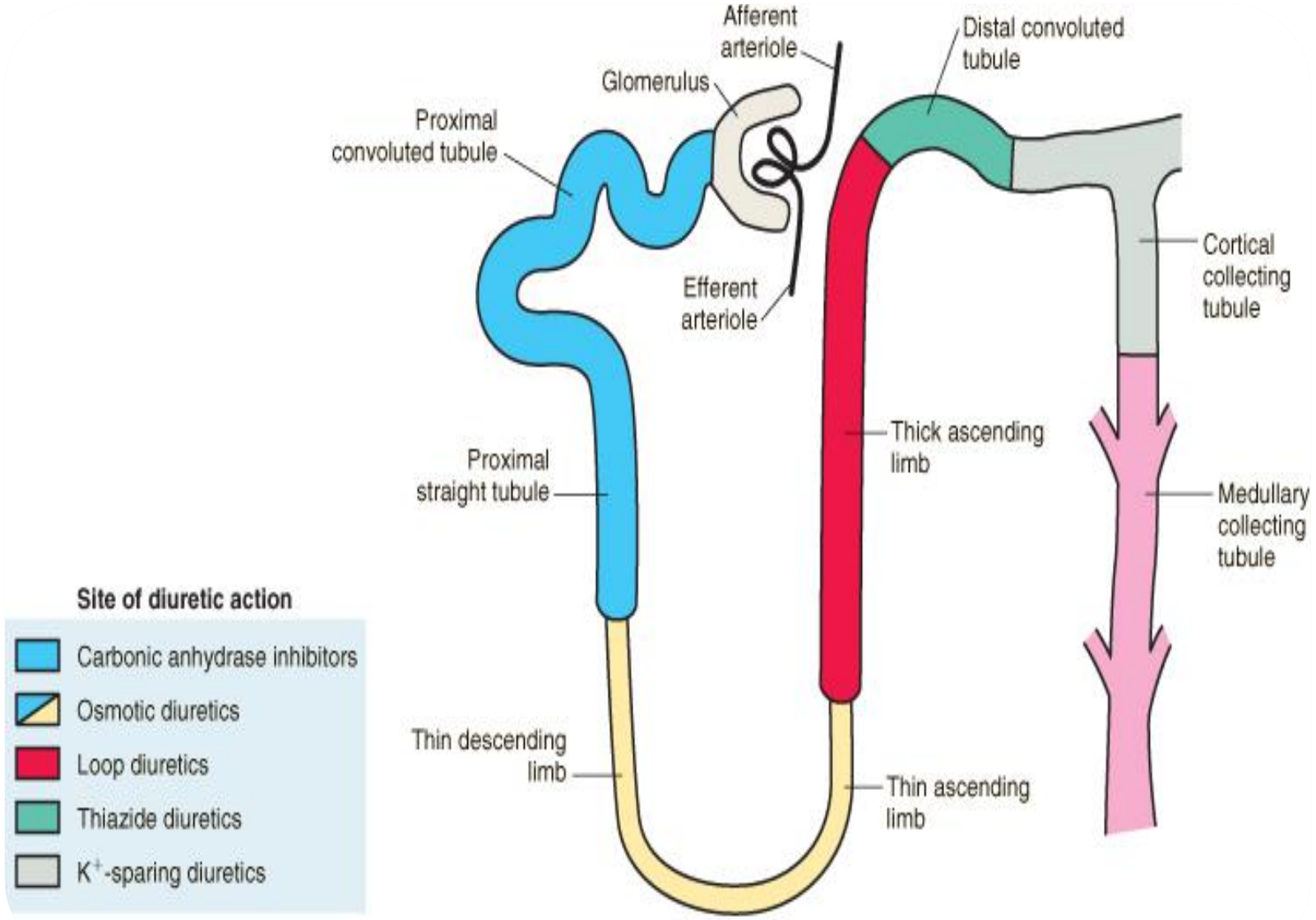
Original approval date of the antihypertensive drugs by prescribing prevalence.



Source: QuintilesIMS, NDTI, 2014.
Approval dates received from the FDA drug database [26]

American Journal of Hypertension, Ltd 2017.

Nephron sites of action of diuretics



Τι γνωρίζουμε μέχρι σήμερα για την επιλογή του διουρητικού;


2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA
Guideline for the Prevention, Detection, Evaluation, and Management
of High Blood Pressure in Adults
A Report of the American College of Cardiology/American Heart Association Task Force on
Clinical Practice Guidelines
WRITING COMMITTEE MEMBERS
Paul K. Whelton, MB, MD, MSc, FAHA, Chair
Robert M. Carey, MD, FAHA, Vice Chair
ACC/AHA TASK FORCE MEMBERS
Glenn N. Levine, MD, FACC, FAHA, Chair
Patrick T. O'Gara, MD, MACC, FAHA, Chair-Elect
Jonathan L. Halperin, MD, FACC, FAHA, Immediate Past Chair
Hypertension
ESC/ESH GUIDELINES
2018 ESC/ESH Guidelines for the management
of arterial hypertension
The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)
ESC GUIDELINES
Guidelines for the management of
elevated blood pressure and hypertension
Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)
KDIGO
KIDNEY DISEASE
GLOBAL OUTCOMES
CLINICAL PRACTICE GUIDELINE
FOR THE EVALUATION AND MANAGEMENT
OF CHRONIC KIDNEY DISEASE

Diuretics

		BA (%)	½ (hours)	DOA (hours)
Thiazide and Thiazide-like Diuretics	Hydrochlorothiazide	65 – 75	3.0 – 10.0	6 – 12
	Chlorothiazide	30 – 50	15.0 – 25.0	6 – 12
	Chlorthalidone	65	24.0 – 55.0	24 – 72
	Bendroflumethiazide	90	2.5 – 5.0	18 – 24
	Indapamide	90	6.0 – 15.0	24 – 36
	Metolazone	65	14	12 – 24
Loop Diuretics	Bumetanide	80 – 90	0.3 – 1.5	4-6
	Furosemide	10 – 100	0.3 – 3.4	6-8
	Torsemide	80 – 100	3.0 – 4.0	6-8
Potassium-Sparing Diuretics	Amiloride	15-20	17.0 – 26.0	24
	Triamterene	83 (55)*	3.0 (3.0)*	7-9
	Spironolactone	>90	1.5 – 15.0†	48-72
	Eplerenone	69	2.2 – 9.4	NA

*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h. BA = bioavailability; $T_{½}$ = half-life; DOA = duration of action: NA = unknown.

Reprinted from Brater DC. In: *Principles of Pharmacology: Based Concepts and Clinical Applications*. 1995:657-672, with permission from Springer Science and Business Media; Delyani JA, et al. *Cardiovasc Drug Rev*. 2001;19:185-200; Rosenberg J, et al. *Cardiovasc Drug Ther*. 2005;19:301-306; Sica DA. *Congest Heart Fail*. 2003;9:100-105.

Drug-treatment strategy for hypertension and CKD

Diuretics are listed in hypertension guidelines as one of three equally weighted first-line treatment options

Initial therapy
Dual combination

ACEi or ARB + CCB
or ACEi or ARB + diuretic (or loop diuretic)[b]

Step 2
Triple combination

ACEi or ARB + CCB + diuretic (or loop diuretic)[b]

Step 3
Triple combination + spironolactone[c] or other drug

Resistant hypertension
Add spironolactone (25-50 mg o.d.)
or other diuretic, alpha-blocker or beta-blocker

Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

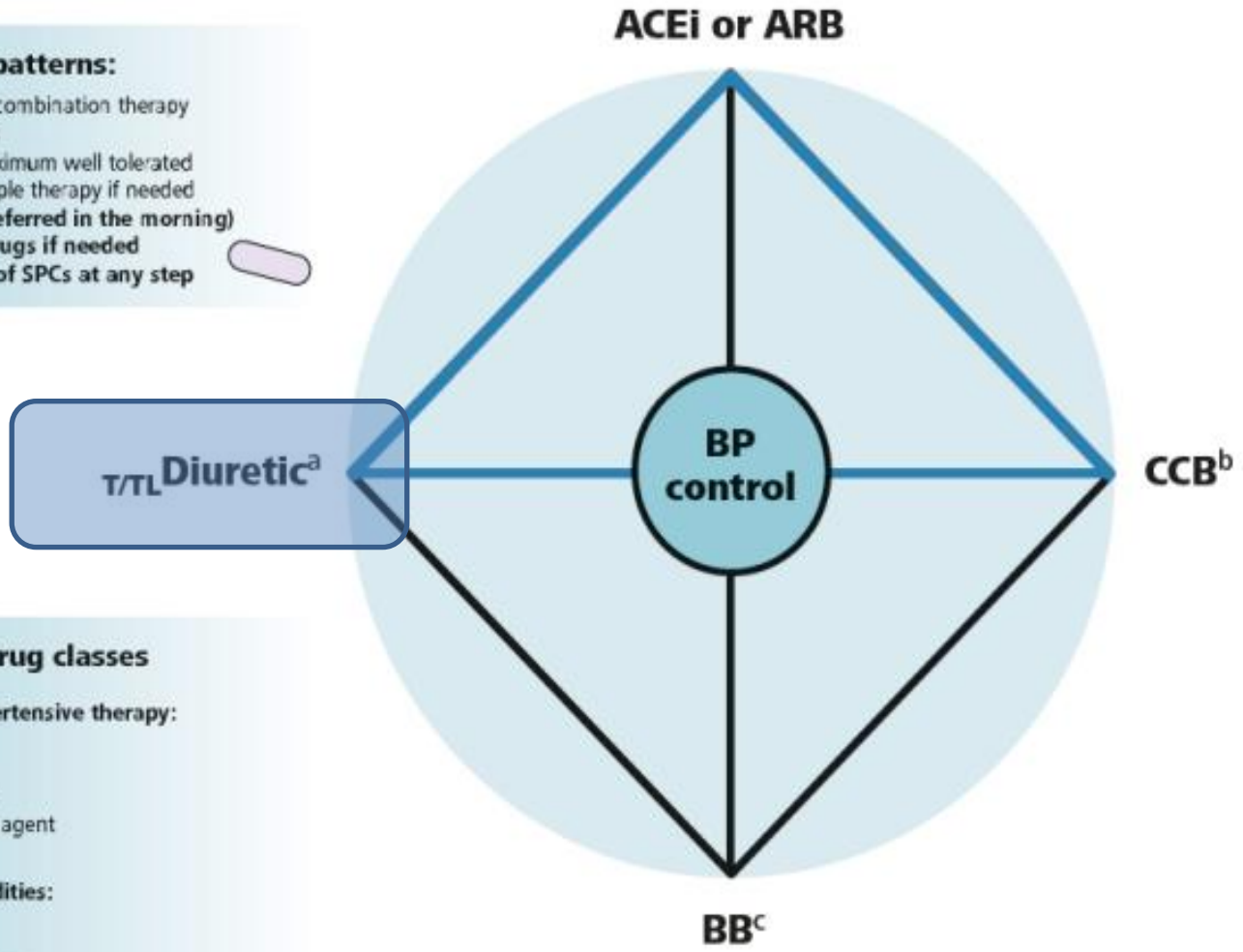
A reduction in eGFR and rise in serum creatinine is expected in patients with CKD[a] who receive BP-lowering therapy, especially in those treated with an ACEi or ARB but a rise in serum creatinine of >30% should prompt evaluation of the patient for possible renovascular disease.

European Society of Hypertension

2023 ESH Guidelines for the management of arterial hypertension

Prescribing patterns:

- Start with dual combination therapy in most patients
- Uptitrate to maximum well tolerated doses and to triple therapy if needed
- **Once daily (preferred in the morning)**
- **Add further drugs if needed**
- **Preferred use of SPCs at any step**



Additional drug classes

General antihypertensive therapy:

- Steroidal MRA
- Loop Diuretic
- Alpha-1 Blocker
- Centrally acting agent
- Vasodilator

Special comorbidities:

- ARNi
- SGLT2i
- Non-Steroidal MRA

European Society of Hypertension

2023 ESH Guidelines for the management of arterial hypertension

Diuretics

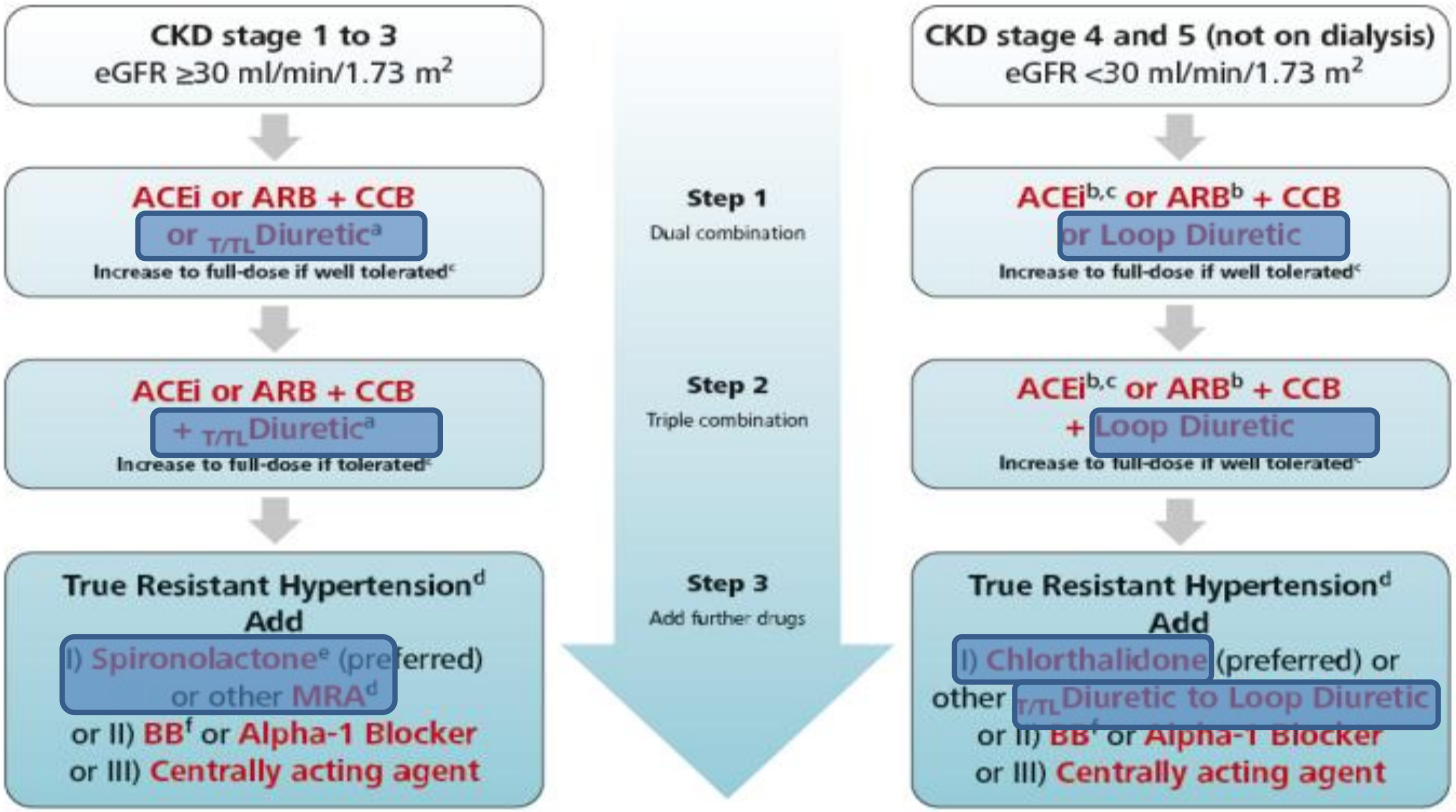
Diureticcs are particularly useful in CKD patients, because these patients are most often **sodium-sensitive (**especially if older, diabetic or obese) and have a high prevalence of treatment-resistant hypertension

Furthermore, diuretics can effectively **reduce proteinuria** when added to RAS blockers in proteinuric CKD [1366].

Thiazide diuretics become less effective, because **they cannot reach their tubular site of action** because of competition for tubular secretion with other substances that accumulate in CKD

European Society of Hypertension

2023 ESH Guidelines for the management of arterial hypertension



Additional therapy: SGLT2i as GDMT in CKD or Finerenone as GDMT in CKD with Type 2 Diabetes mellitus

European Society of Hypertension

Thiazide and Thizide –like Diuretics

Mechanism of action

Diuretics Used to Treat Hypertension

		BA (%)	½ (hours)	DOA (hours)
Thiazide and Thiazide-like Diuretics	Hydrochlorothiazide	65 – 75	3.0 – 10.0	6 – 12
	Chlorothiazide	30 – 50	15.0 – 25.0	6 – 12
	Chlorthalidone	65	24.0 – 55.0	24 – 72
	Bendroflumethiazide	90	2.5 – 5.0	18 – 24
	Indapamide	90	6.0 – 15.0	24 – 36
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*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h. BA = bioavailability; $T_{½}$ = half-life; DOA = duration of action: NA = unknown.

Reprinted from Brater DC. In: *Principles of Pharmacology: Based Concepts and Clinical Applications*. 1995:657-672, with permission from Springer Science and Business Media; Delyani JA, et al. *Cardiovasc Drug Rev*. 2001;19:185-200; Rosenberg J, et al. *Cardiovasc Drug Ther*. 2005;19:301-306; Sica DA. *Congest Heart Fail*. 2003;9:100-105.

Thiazide and Thizide –like Diuetics

Duration of action, potency, and half-life

	Hydrochlorothiazide	Chlorthalidone	Indapamide SR
Half-life [46–48]	6–15 h	40–60 h	14–24 h
Duration of action [49,50]	16–24 h	48–72 h	>24
Equipotency for office SBP [51–53]	25 mg	12.5 mg	1.5 mg
Dose effect for office SBP [53,54]	Yes	Mixed data	No

Journal of Hypertension 2019, 37:1574–1586

Comparison of thiazide-like diuretics *versus* thiazide-type diuretics: a meta-analysis

Study or subgroup	Thiazide-like Mean	SD	Total	Thiazide Mean	SD	Total	Weight	Mean difference IV, Fixed, 95% CI
A.Pareek (2009)	−11.8	13.8	30	−7.8	14.4	30	0.0%	−4.00 [−11.14, 3.14]
Anil K. Pareek *et al.* (2016)	−11.14	12.41	16	−6.02	12.46	18	0.0%	−5.12 [−13.49, 3.25]
Bakris (2012)	−35.1	0.6	295	−29.5	0.6	292	99.2%	−5.60 [−5.70, −5.50]
David *et al.* (1999)	−19.1	18.7	18	−9.05	11.5	21	0.0%	−10.05 [−19.99, −0.11]
Emeriau *et al.* (2001)	−22.7	15.4	178	−19.4	15.5	171	0.1%	−3.30 [−6.54, −0.06]
GERARD *et al.* (1983)	−11	3.6	13	−8	3.6	11	0.1%	−3.00 [−5.89, −0.11]
Kwon *et al.* (2012)	−15	11.5	13	−9	12.8	15	0.0%	−6.00 [−15.00, 3.00]
Michael *et al.* (2006)	−12.4	1.8	13	−7.4	1.7	11	0.5%	−5.00 [−6.40, −3.60]
Pareek *et al.* (2009)	−20.17	12.65	60	−17.63	11.73	60	0.0%	−2.54 [−6.91, 1.83]
Radevski *et al.* (2002)	−20	18.1	20	−8	16.3	22	0.0%	−12.00 [−22.46, −1.54]
Total (95% CI)			**656**			**651**	**100.0%**	**−5.59 [−5.69, −5.49]**

Heterogeneity: $\chi^2 = 10.02$, df = 9 ($P = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 113.33$ ($P < 0.00001$)

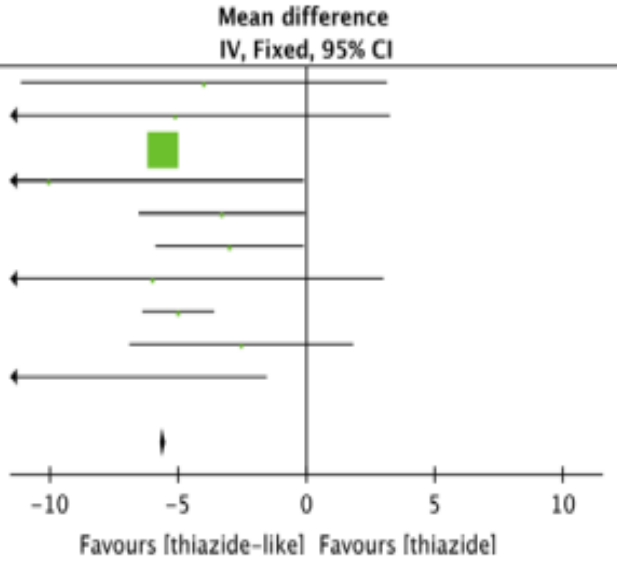


Fig. 2 Forest plot shows the variance of systolic BP reduction by thiazide-like diuretics *versus* thiazide diuretics.

. Cell. Mol. Med. Vol 21, No 11, 2017 pp. 2634-2642

Μηχανισμοί δράσης διουρητικών

- **Υποογκαιμία → μείωση της καρδιακής παροχής**
- **Μείωση των περιφερικών αγγειακών αντιστάσεων**

Διουρητικά

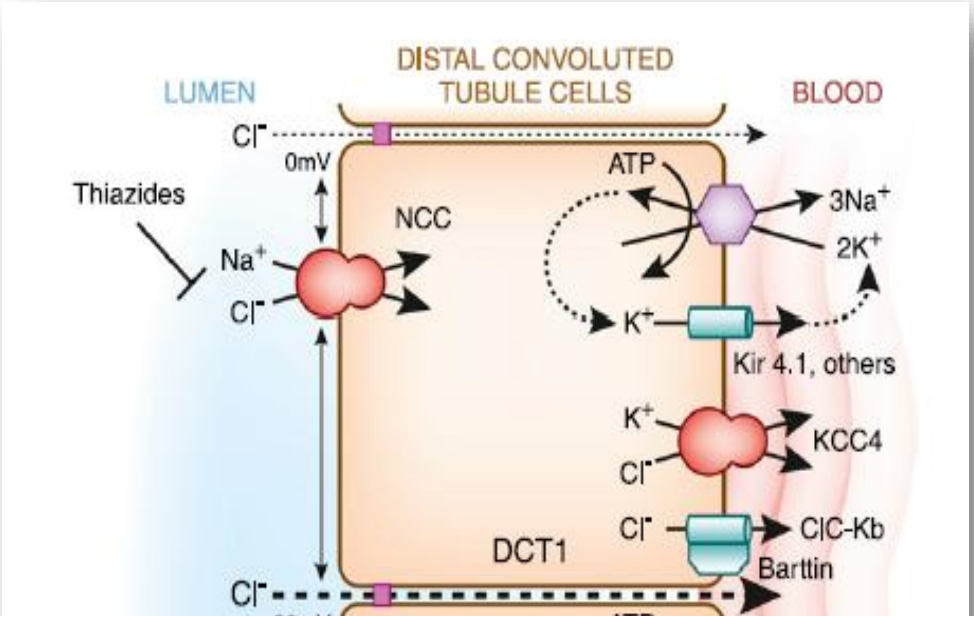
Πλεονεκτήματα

- Μικρό κόστος
- Μεγάλη αποτελεσματικότητα
- Αποδεδειγμένη ωφέλεια

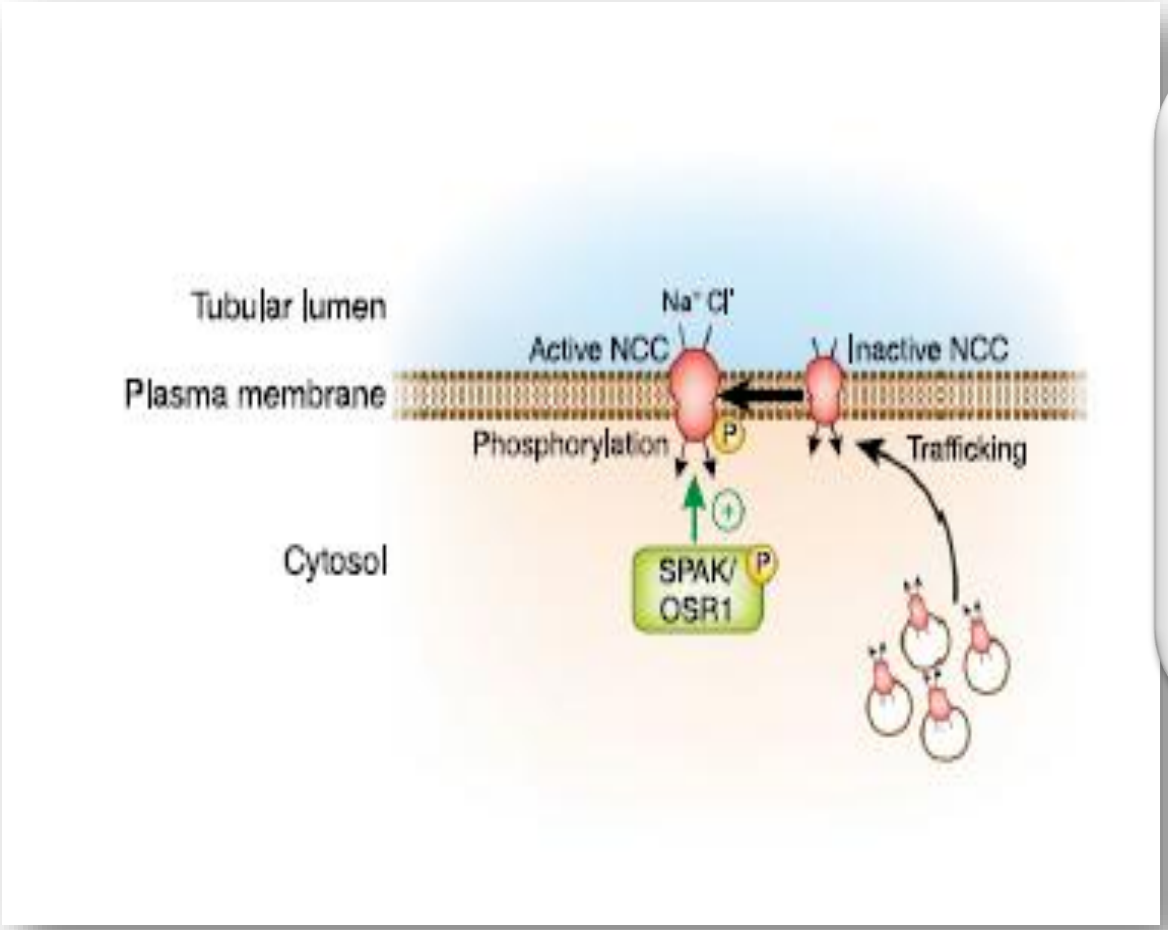
Μειονεκτήματα

- Ηλεκτρολυτικές διαταραχές ($\downarrow K^{+}$, $\downarrow Mg^{++}$, $\downarrow Na^{+}$, $\uparrow Ca^{++}$)
- Διαταραχές του μεταβολισμού των υδατανθράκων
- Διαταραχές του μεταβολισμού των λιπιδίων
- Υπερουριχαιμία

A model of NaCl reabsorption by cells of the early and late DCTs.



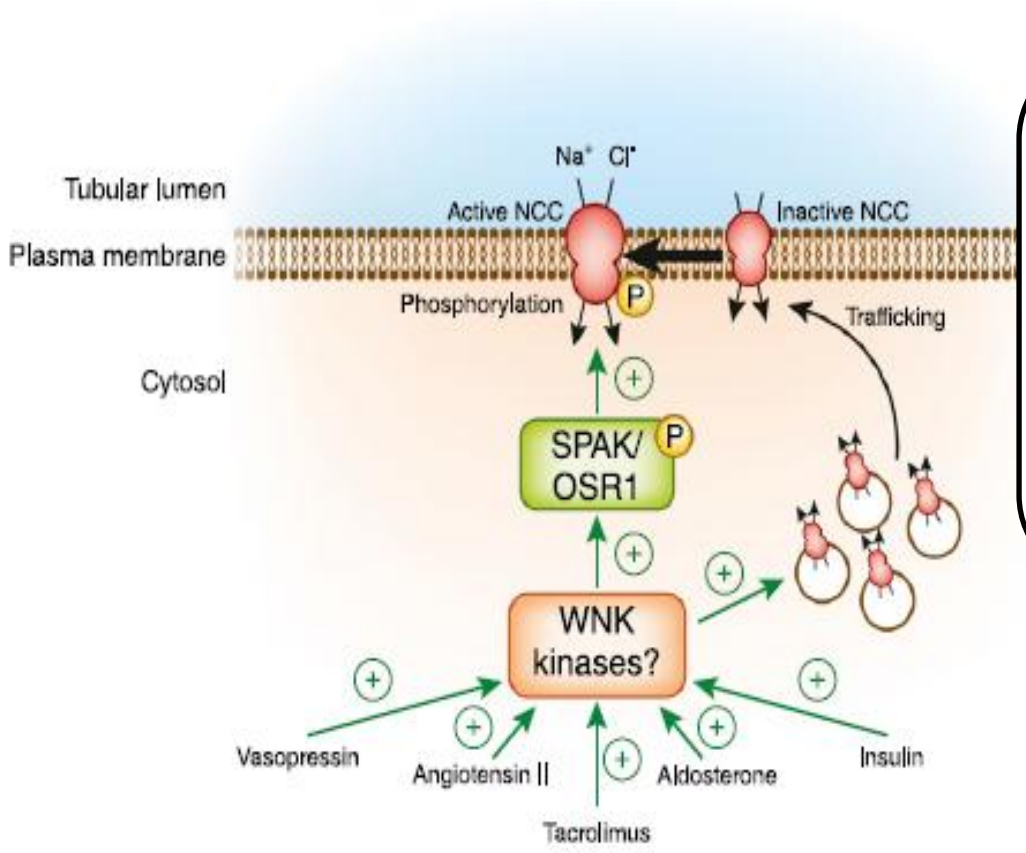
In the early DCT, apical sodium reabsorption is exclusively mediated by **thiazide sensitive** NaCl cotransporter (**NCC)**,



For
NCC to be active, it must traffic to the plasma membrane from an **intracellular storage pool**. After it reaches the surface, it is in an inactive
state until it is **phosphorylated** by two kinases, Ste20-like proline-alanine rich kinase (**SPAK)** and oxidative stress responsive
kinase 1 (**OSR1**).

Clin J Am Soc Nephrol 9: 2147–2163, December, 2014

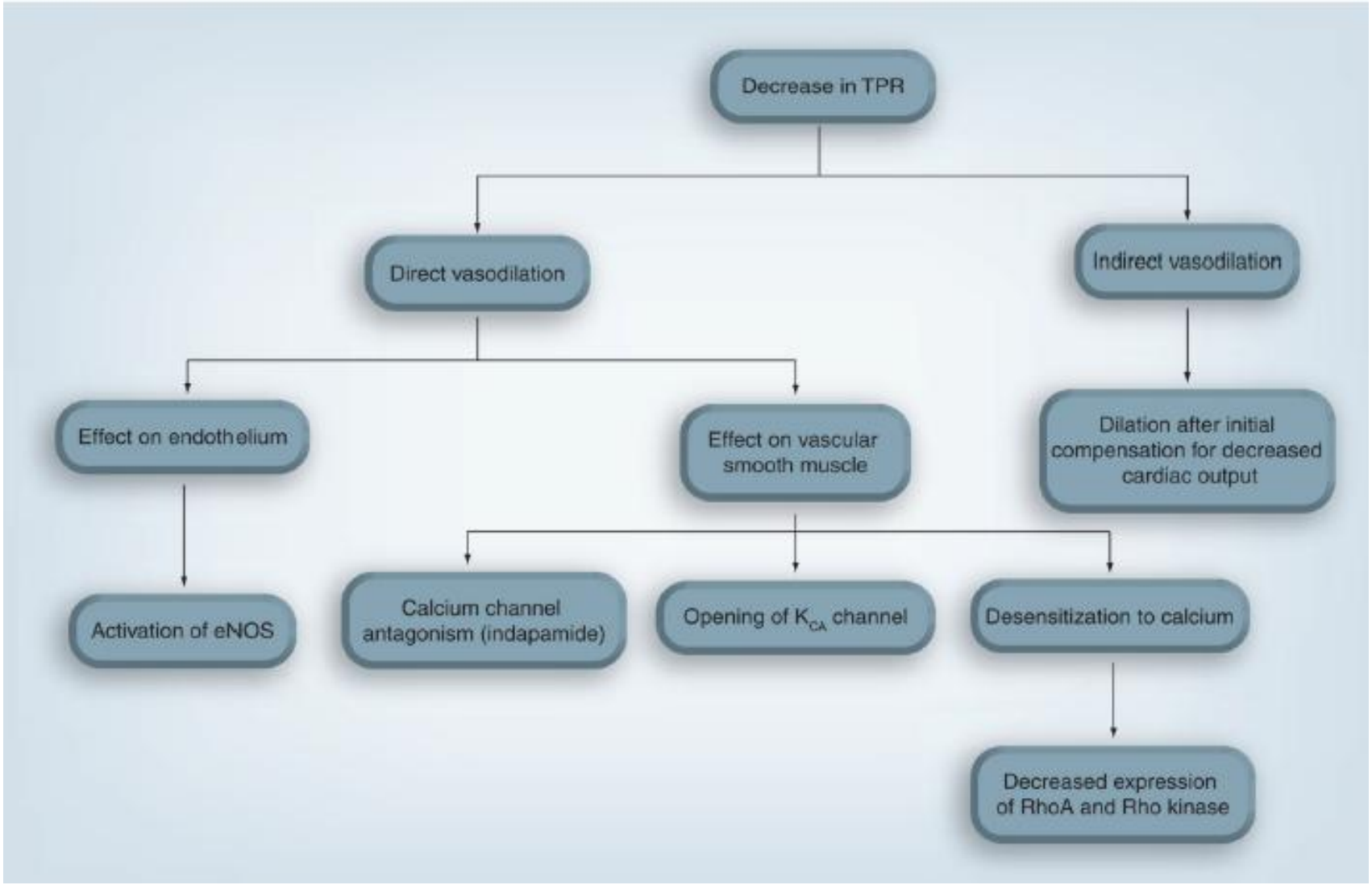
A working model for NCC regulation through the WNK-SPAK/OSR1 signaling cascade



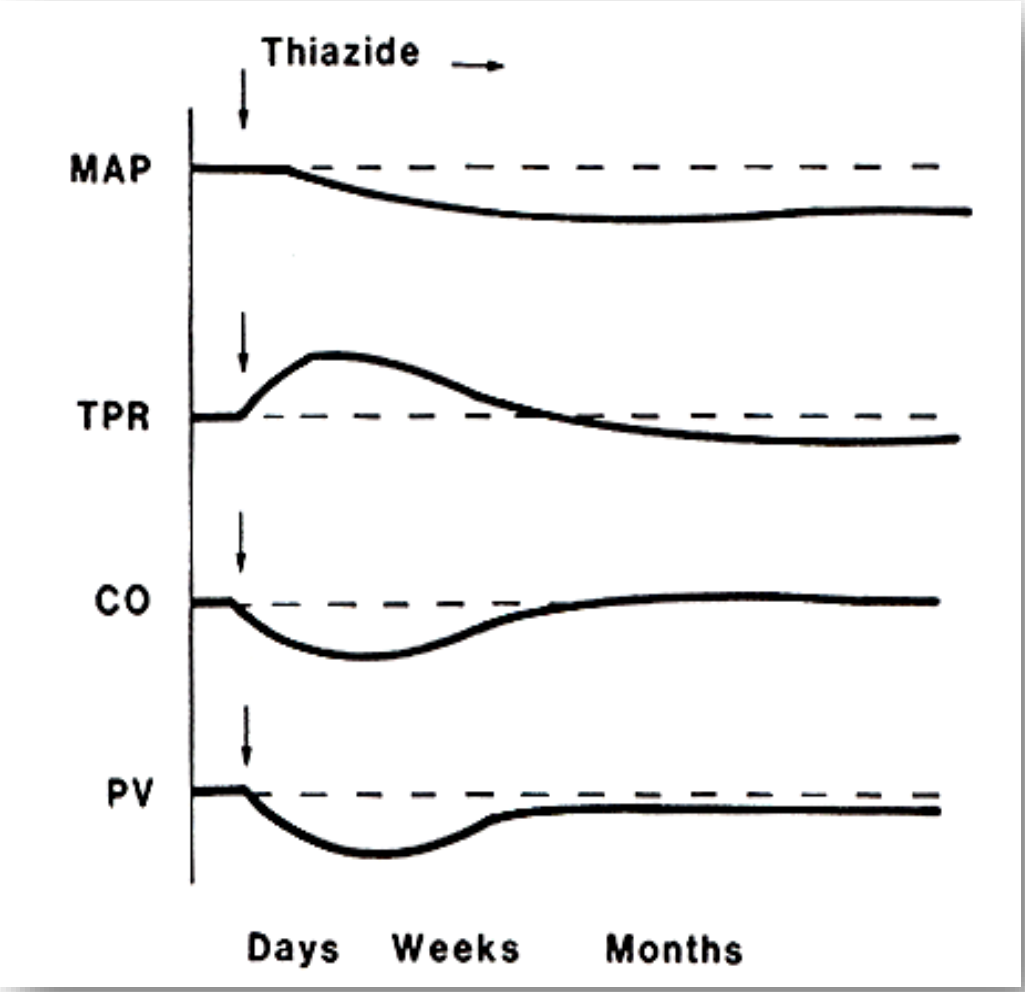
A number of hormones have been shown to **stimulate NCC phosphorylation** at residues that are directly phosphorylated by SPAK and OSR1

Clin J Am Soc Nephrol 9: 2147–2163, December, 2014

Theoretical mechanisms of thiazide-induced chronic blood pressure lowering



Schematic drawing of temporal changes in mean arterial pressure (MAP), total peripheral vascular resistance (TPR), cardiac output (CO) and plasma volume (PV) during thiazide treatment of a hypertensive subject



From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

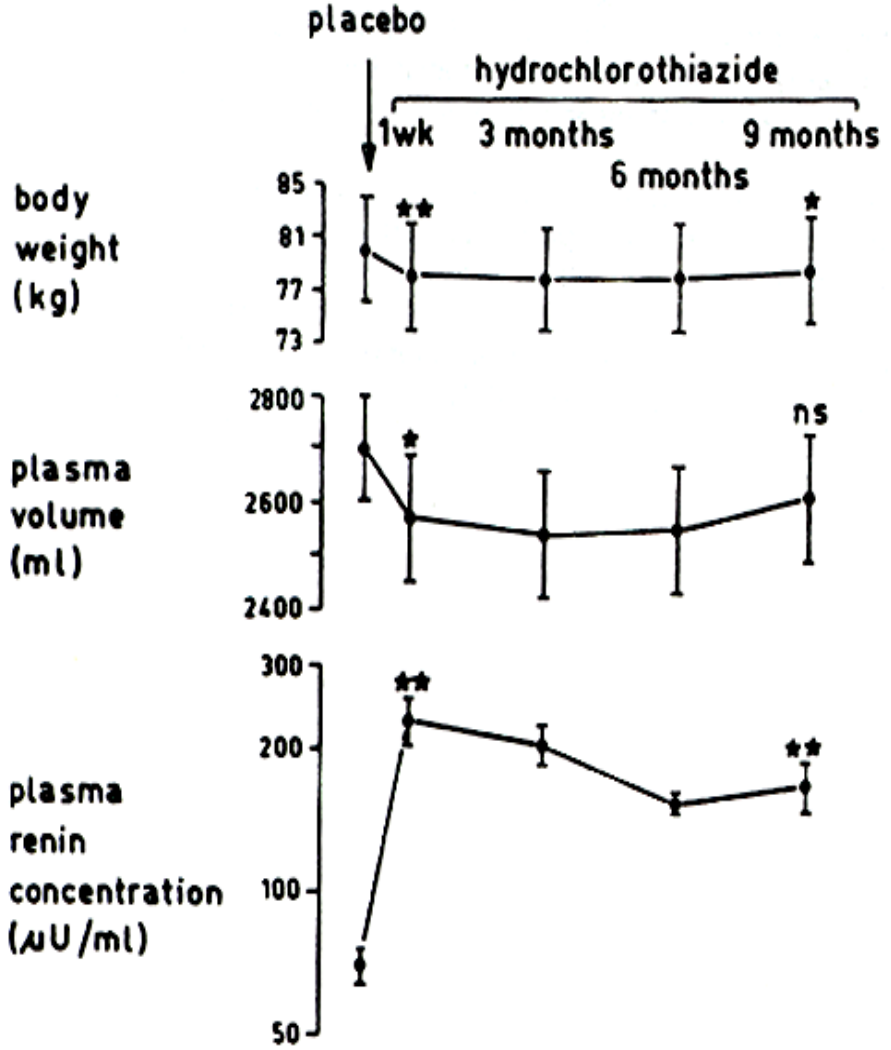


Fig. 4. Persistent elevation of plasma renin concentration in the course of hydrochlorothiazide treatment observed in 10 essential hypertensive patients (adapted from Van Brummelen *et al.* [26]).

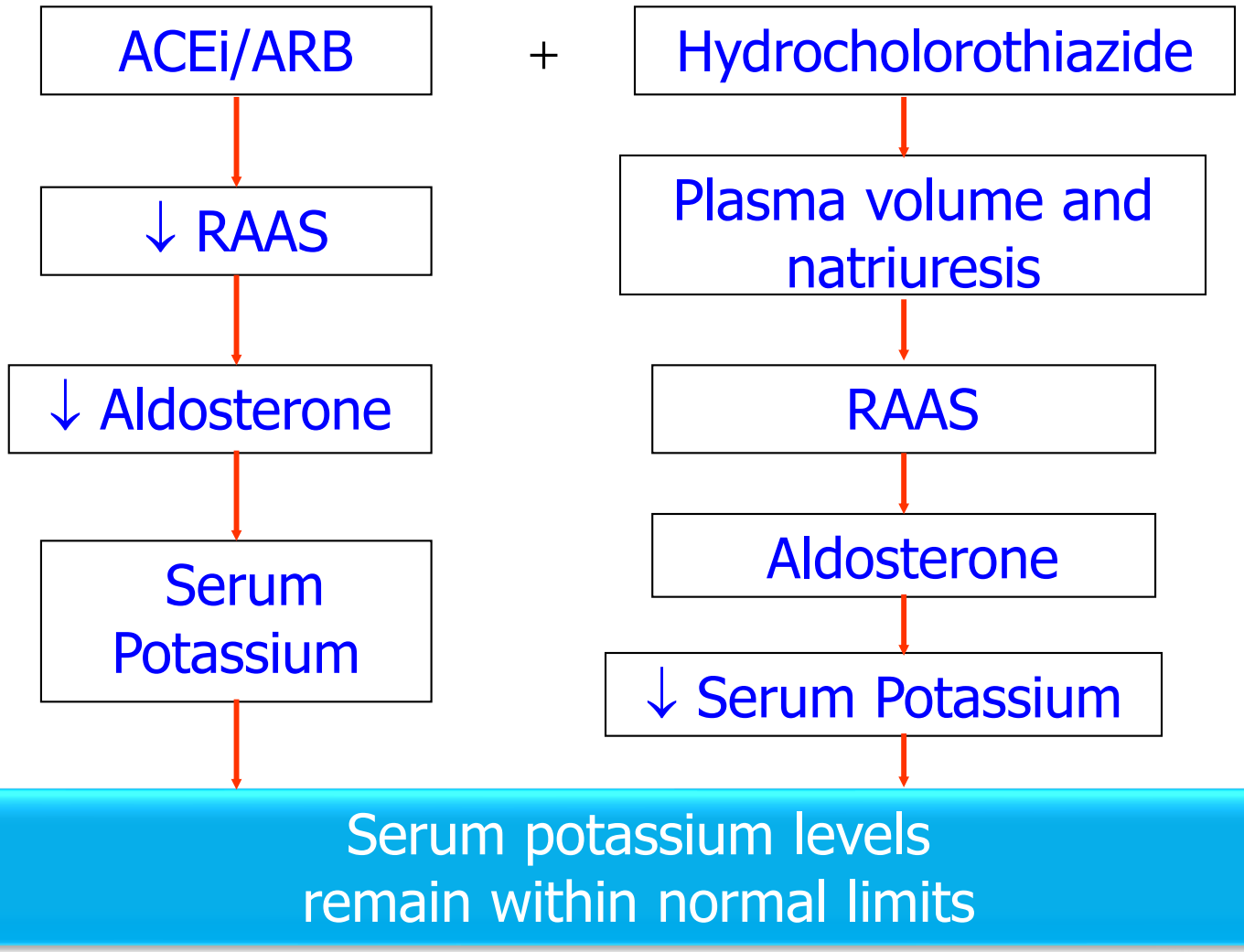
Χρήση διουρητικών

Μείωση του ενδοαγγειακού όγκου

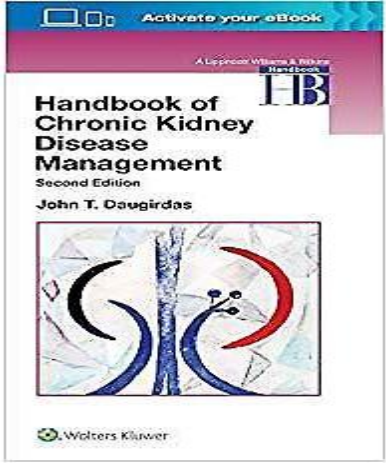
Αύξηση της ρενίνης

From Birkenhäger, WH: Diuretics and blood pressure reduction: physiological aspects. J. Hyperten. 1990, 8 (Suppl 2) S3-S7.

ACEi/ARB - Hydrochlorothiazide Combination: Safety Advantages



Τι γνωρίζουμε για την επιλογή του διουρητικού στην ΧΝΝ ;



Factors Potentially Related to Hypertension in Chronic Kidney Disease

Pre-existing essential hypertension

Extracellular fluid volume expansion

Renin-angiotensin-aldosterone system stimulation

Increased sympathetic activity

Endogenous digitalis-like factors

Prostaglandin/bradykinin

Alterations in endothelium-derived factors (nitric oxide/endothelin)

Increased body weight

Erythropoietin administration

Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia

Calcification of arterial tree

Cyclosporine, tacrolimus, or other immunosuppressive and corticosteroid therapy

Renal artery disease

Rigas Kalaitzidis, M.D., and George L. Bakris, M.D. **Publish date:**9-Oct-2018

Μηχανισμοί αύξησης της ΑΠ στη ΧΝΝ

Ασθενής με ΧΝΝ

Extracellular volume expansion is an important, if not the most important, contributing factor to hypertension seen in

chronic kidney disease

Protection against progression of **renal dysfunction** has two main requirements:

- ❖ Strict blood pressure control
- ❖ Lowering proteinuria to values as near to normal as possible.

Diuretics :have been a useful tool to **manage volume overload** and to achieve **strict blood pressure control** in patients with chronic kidney disease

European Heart Journal (2013) 34, 2159–2219
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

in renal function and hyperkalemia [540]. Loop diuretics should replace thiazides if serum creatinine is 1.5 mg/dL or eGFR is <30 ml/min/1.73 m^2.

Diabetes and Hypertension: A Position Statement by the American Diabetes Association

Diabetes Care 2017;40:1273–1284 | https://doi.org/10.2337/dci17-0026

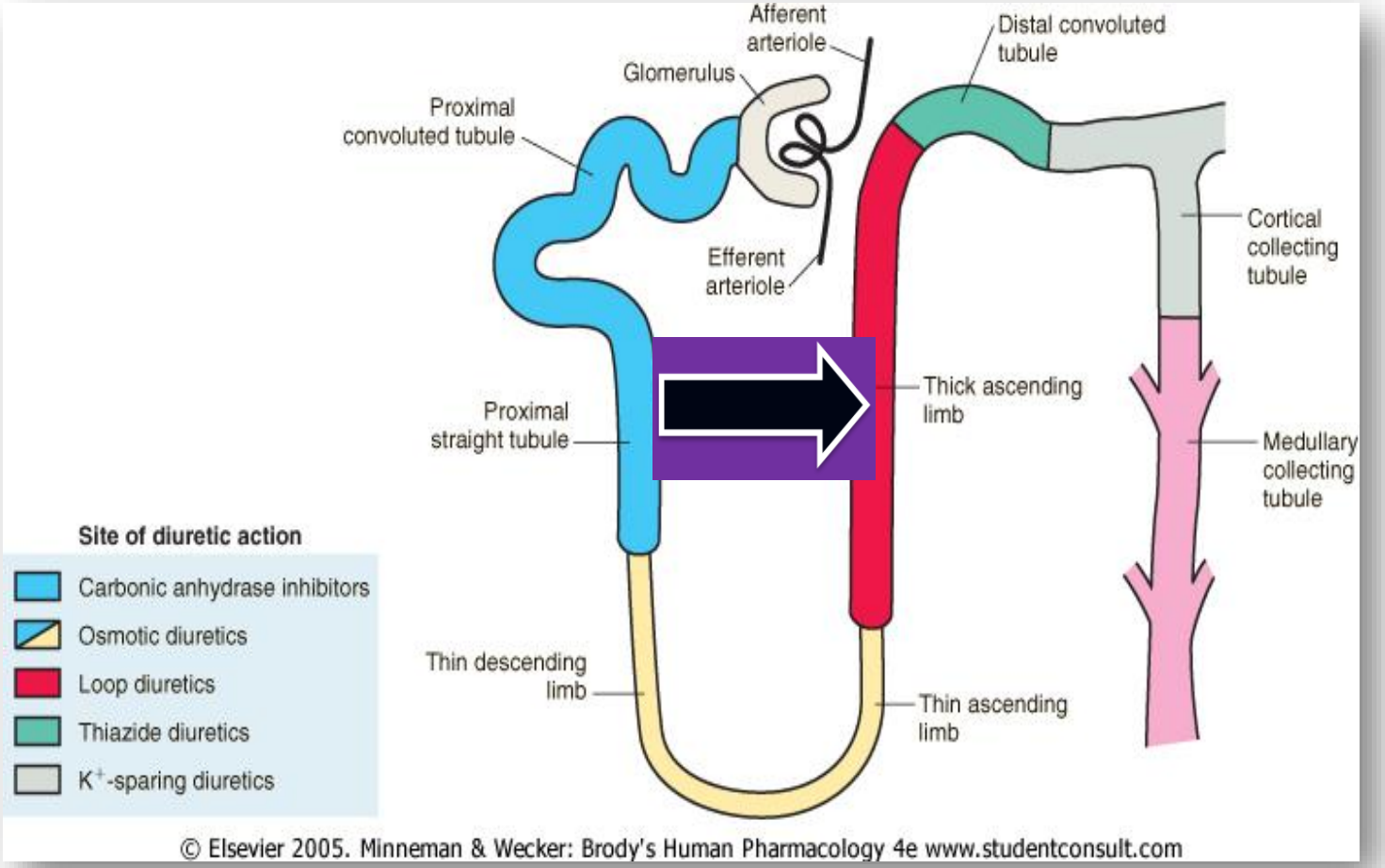
Thiazide-like diuretics are only effective in maintaining volume and reducing the risk of hyperkalemia down to an eGFR of 30 mL/min/1.73 m^2 (86,87). Below an eGFR of 30 mL/min/1.73 m^2, a long-acting loop diuretic, such as torsemide, should be prescribed instead.

2023 ESH Guidelines for the management of arterial hypertension

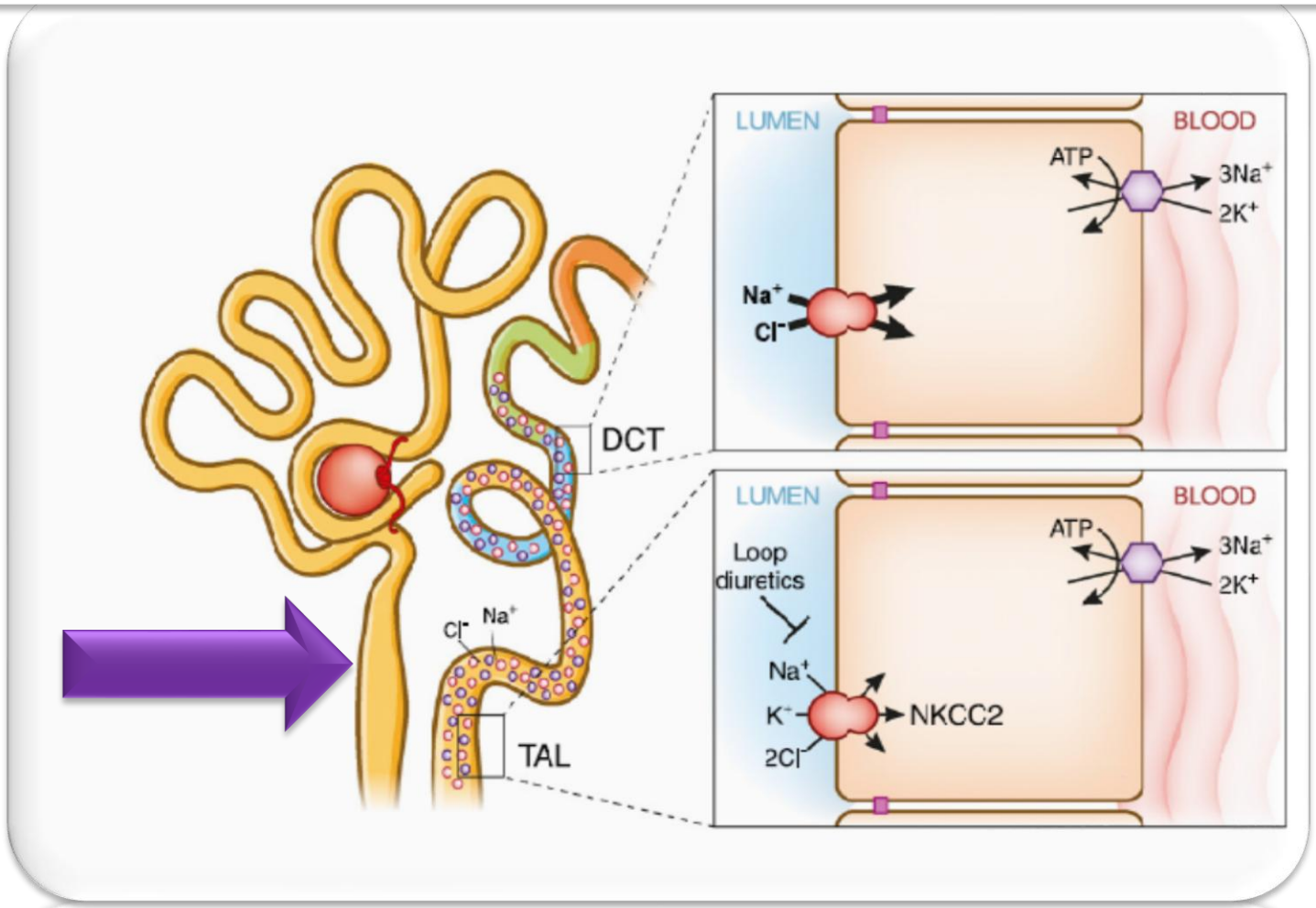
Thiazide/Thiazide-like diuretics are recommended in resistant hypertension if estimated eGFR is ≥ 30 ml/min/1.73 m^2.	I	B
Loop diuretics may be considered in patients with an estimated eGFR < 45 ml/min/1.73 m^2 and should be used if eGFR falls below 30 ml/min/1.73 m^2.	I	B
Chlorthalidone (12.5 to 25 mg once daily) could be used with or without a loop diuretic if eGFR is <30 ml/min/1.73 m^2.	II	B

Loop diuretics
Mechanism of action

Nephron sites of action of loop diuretics



Η επαναρρόφηση που κανονικά διαμεσολαβείται από το παχύ ανιόν σκέλος [Na-K-2Cl] συν μεταφορέα (NKCC2)
μπλοκάρεται από τα διουρητικά της αγκύλης,
όπως η φουροσεμίδη και η τορασεμίδη



Clin J Am Soc Nephrol 9: 2147–2163, December, 2014

Diuretics

		BA (%)	$T_{½}$ (hours)	DOA (hours)
Loop Diuretics	Bumetanide	80 – 90	0.3 – 1.5	4-6
	Furosemide	10 – 100	0.3 – 3.4	6-8
	Torsemide	80 – 100	3.0 – 4.0	6-8

*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h. BA = bioavailability; $T_{½}$ = half-life; DOA = duration of action: NA = unknown.

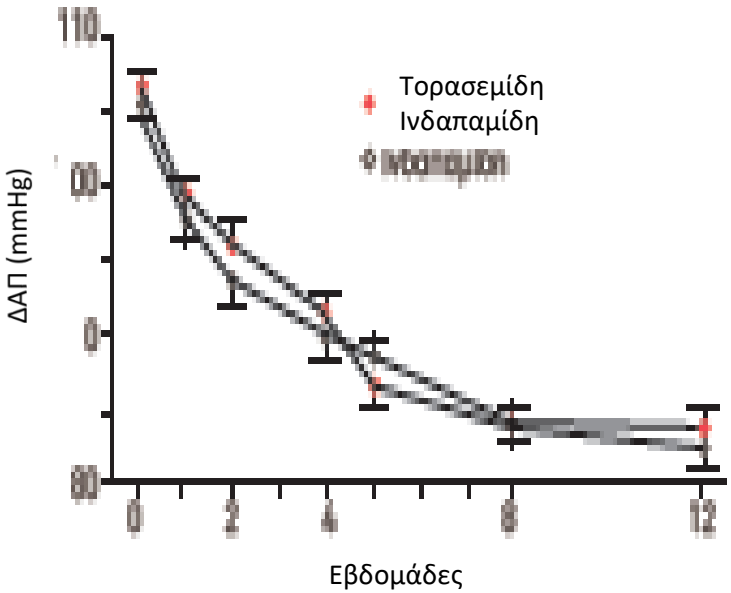
Reprinted from Brater DC. In: *Principles of Pharmacology: Based Concepts and Clinical Applications*. 1995:657-672, with permission from Springer Science and Business Media; Delyani JA, et al. *Cardiovasc Drug Rev*. 2001;19:185-200; Rosenberg J, et al. *Cardiovasc Drug Ther*. 2005;19:301-306; Sica DA. *Congest Heart Fail*. 2003;9:100-105.

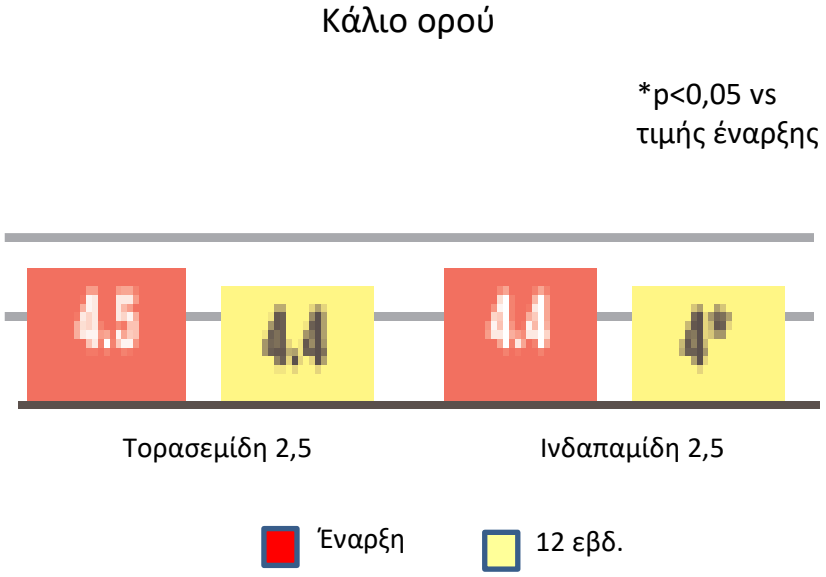
Loop diuretics and hypertension

They lower blood pressure acutely because of their potent natriuretic effect and consequently fall in circulating blood volume

When used alone
loop diuretics may not have useful long-term antihypertensive effect

Υπέρταση – Σύγκριση Τορασεμιδης με Ινδαπαμίδη





Διπλά-τυφλή, τυχαιοποιημένη πολυκεντρική μελέτη σε 66 ασθενείς με ιδιοπαθή υπέρταση [διαστολική αρτηριακή πίεση (ΔΑΠ) κατά την έναρξη 100-115mmHg]. Αρχή με 2,5mg **τορασεμίδη** ή ινδαπαμίδη και δυνατότητα διπλασιασμού μετά από 4 εβδομάδες. Διάρκεια 12 εβδομάδες

Spannbrucker N et al, Arzneim.-Forsch 1988; 38 (1): 191-3

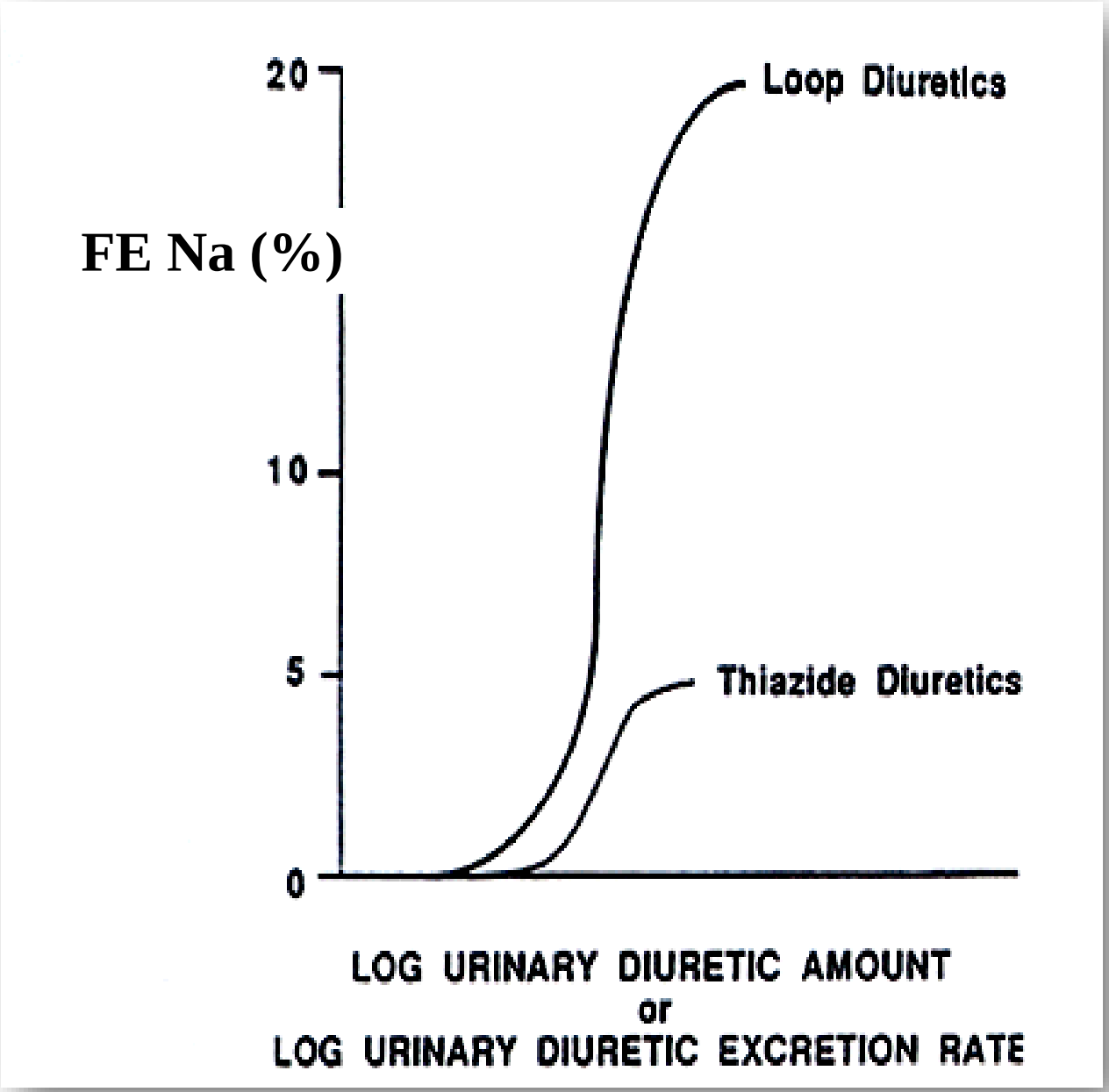
Outcomes of diuretic use in pre-dialysis CKD patients with moderate renal deterioration attending tertiary care referral center

Table 3 Extent of reduction in different parameters from baseline w.r.t diuretic use

Outcomes	Loop diuretics	Thiazide diuretics	Combination	*p* value
Stage 3 ($N=31$)				
Reduction in SBP (mmHg)	−5.9	−3.7	–	0.04
Reduction in DBP (mmHg)	−1.7	−1.6	–	0.8
Reduction in ICW (L)	−0.7	−0.5	–	0.4
Reduction in ECW (L)	−1.9	−2.5	–	0.04
Reduction in TBW (L)	−2.6	−3.0	–	0.06
Decline in eGFR (ml/min/1.73 m2)	−2.2	−1.6	–	0.01
Stage 4 ($N=49$)				
Reduction in SBP (mmHg)	−9.3	−2.8	–	<0.001
Reduction in DBP (mmHg)	−3.0	−1.3	–	0.04
Reduction in ICW (L)	−0.6	−0.4	–	0.5
Reduction in ECW (L)	−1.8	−0.9	–	0.08
Reduction in TBW (L)	−2.5	−1.3	–	0.04
Decline in eGFR (ml/min/1.73 m2)	−2.1	−1.8	–	0.08

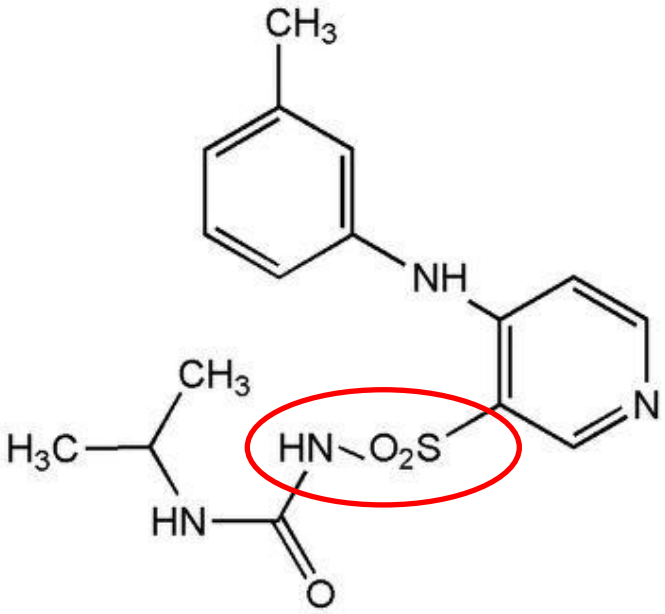
Loop diuretics provided better SBP control than thiazide diuretics
(2) the decline in eGFR was more profound with furosemide in CKD stage 3 and4
(3) combination therapy was most effective in controlling SBP and extracellular water, but had more side effects than single agent diuretic therapy;
(4)side effects were only observed in patients receiving high doses of furosemide and HCTZ.

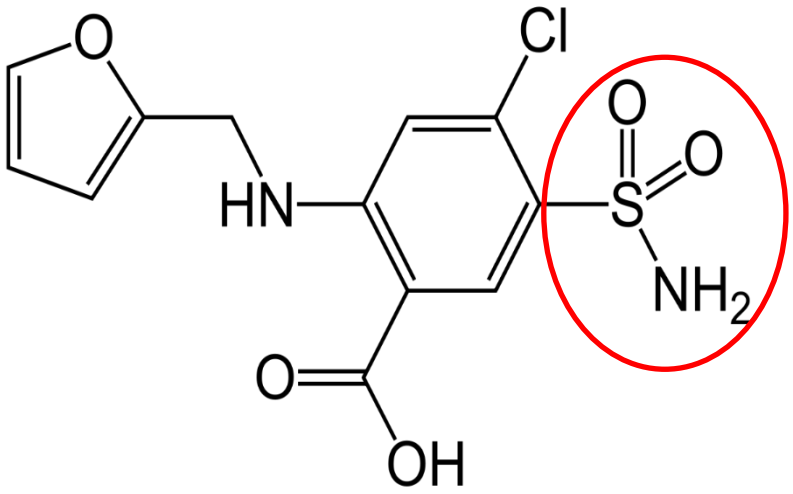
Clin Exp Nephrol (2017) 21:1011–1023



From Brater, DC. Pharmacology of Diuretics. Am. J. Med. Sci. 2000, 319:38-50.

Ποιο διουρητικό της αγκύλης ;





Torasemide Vs Furosemide

Isopropyl-l-methyl-3 phenylamino-4 pyridil-3 sulphonyl- 3-urea

5-(amino sulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] -benzoic acid

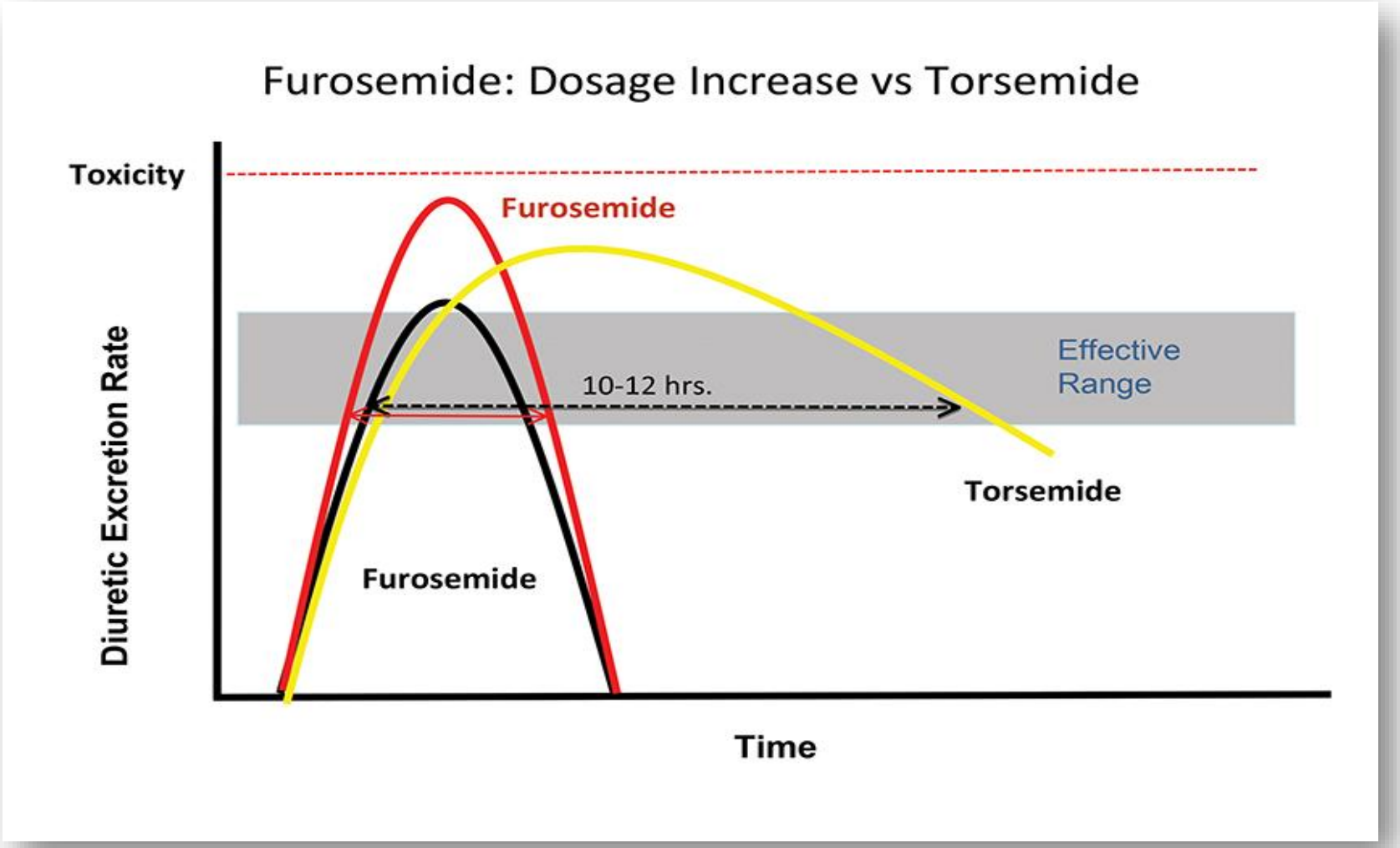
Πλεονεκτήματα Τορασεμίδης έναντι Φουροσεμίδης

	Φουροσεμίδη	Τορασεμίδη
Βιοδιαθεσιμ. (%)	10-100	**80-100**
Μεταβολισμός	50% νεφροί	80% ηπαρ
Σύνδεση με πρωτεΐνες	95%	97-99%
Διάρκεια δράσης (ώρες)	4-6	**18-24**

- Μεγαλύτερη μείωση της θνητότητας στην ΧΚΑ
- Μεγαλύτερη μείωση συχνότητας επανεισαγωγών και διάρκειας νοσηλείας
- Μεγαλύτερη μείωση τάξης κατά NYHA
- Ταχύτερη και πιο αποτελεσματική υποχώρηση συμπτωμάτων

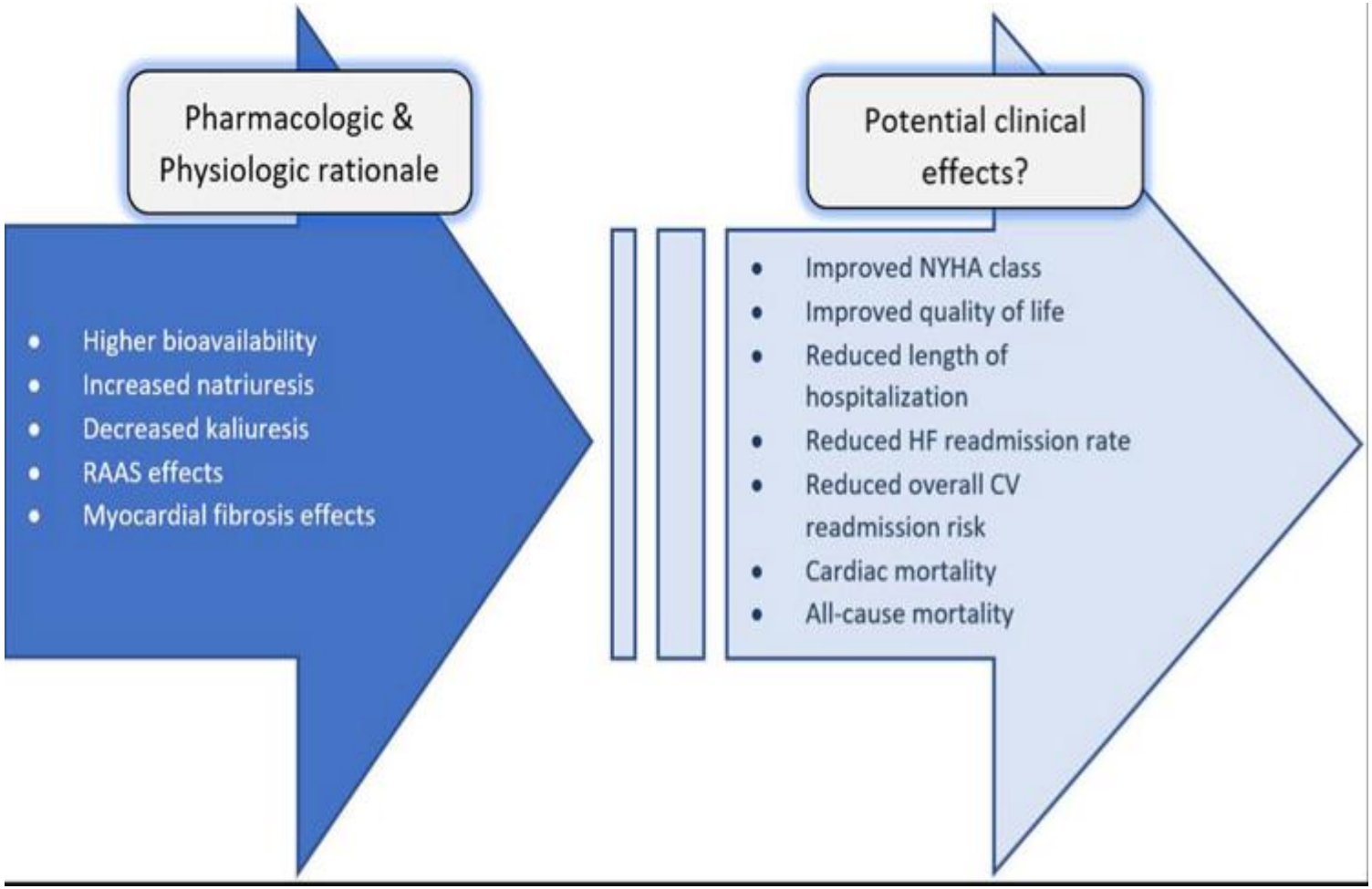
- Βελτίωση αιμοδυναμικών παραμέτρων (LVEF, LVESV, LVEDV)
- Αντι-αλδοστερονική και αντι-ινωτική δράση

- Ισχυρότερη αντι-υπερτασική δράση
- Καλύτερη ποιότητα ζωής (νυκτουρία, μικρουρία)
- Λιγότερη καλλιούρηση


Furosemide: Dosage Increase vs Torsemide
Toxicity
Furosemide
Diuretic Excretion Rate
10-12 hrs.
Effective Range
Torsemide
Furosemide
Time

. 2022 Jan;20(1):5-11. doi: 10.1080/14779072.2022.2022474. Epub 2022 Jan 3

Rationale for torsemide compared to other diuretics



2023 ESH Guidelines for the management of arterial hypertension

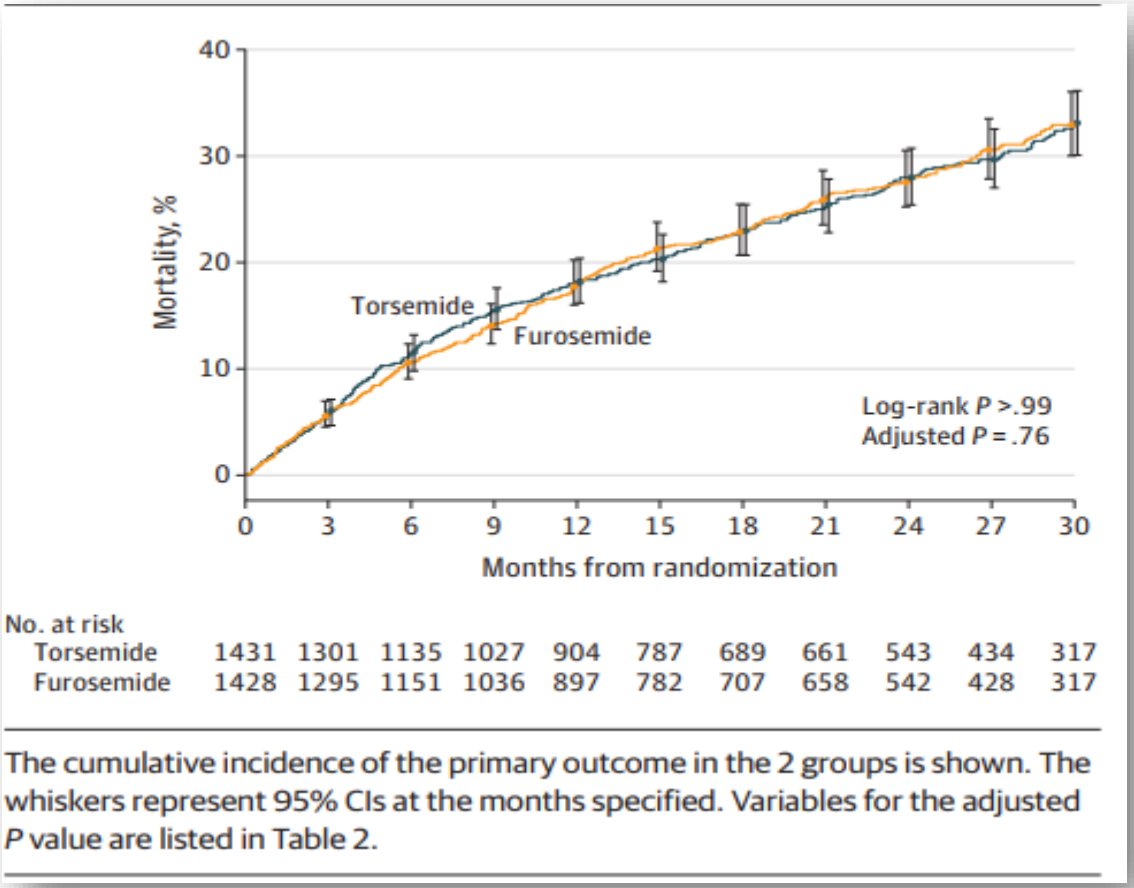
Thiazide should be substituted with a loop diuretic.

Within this class
torasemide might be preferred to furosemide
because of its longer half-life

JAMA | Original Investigation

Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure

The TRANSFORM-HF Randomized Clinical Trial



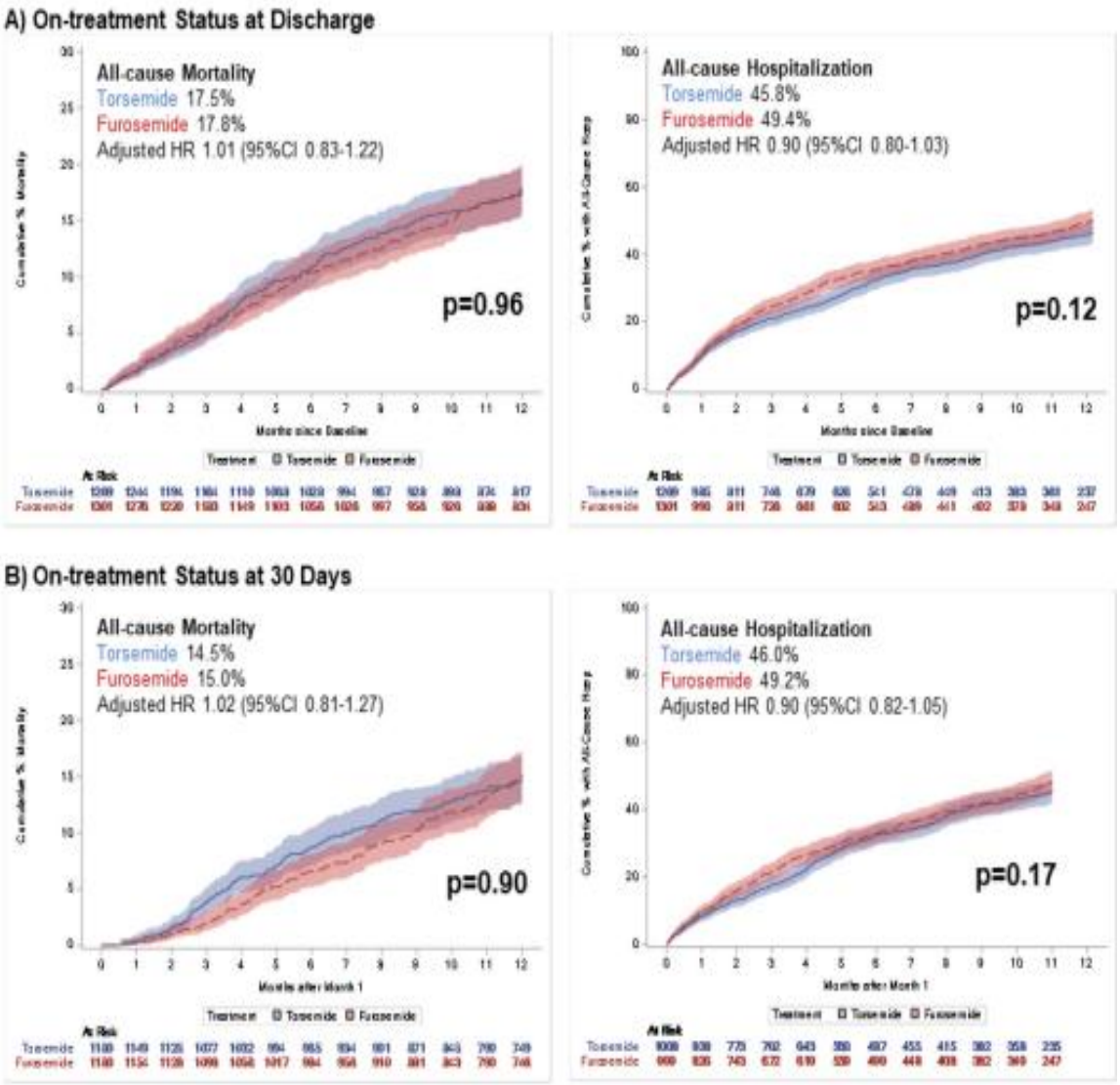
No. at risk											
Torsemide	1431	1301	1135	1027	904	787	689	661	543	434	317
Furosemide	1428	1295	1151	1036	897	782	707	658	542	428	317

The cumulative incidence of the primary outcome in the 2 groups is shown. The whiskers represent 95% CIs at the months specified. Variables for the adjusted *P* value are listed in Table 2.

Primary Outcome of All-Cause Mortality

Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did **not result in a significant difference in all-cause mortality over 12 months.**

JAMA. 2023;329(3):214-223.



In TRANSFORM-HF, a post-hoc on-treatment analysis did not meaningfully differ from the original trial results. Among those deemed compliant with the assigned diuretic, there remained no significant difference in mortality or hospitalization after HF hospitalization with a strategy of torsemide vs furosemide

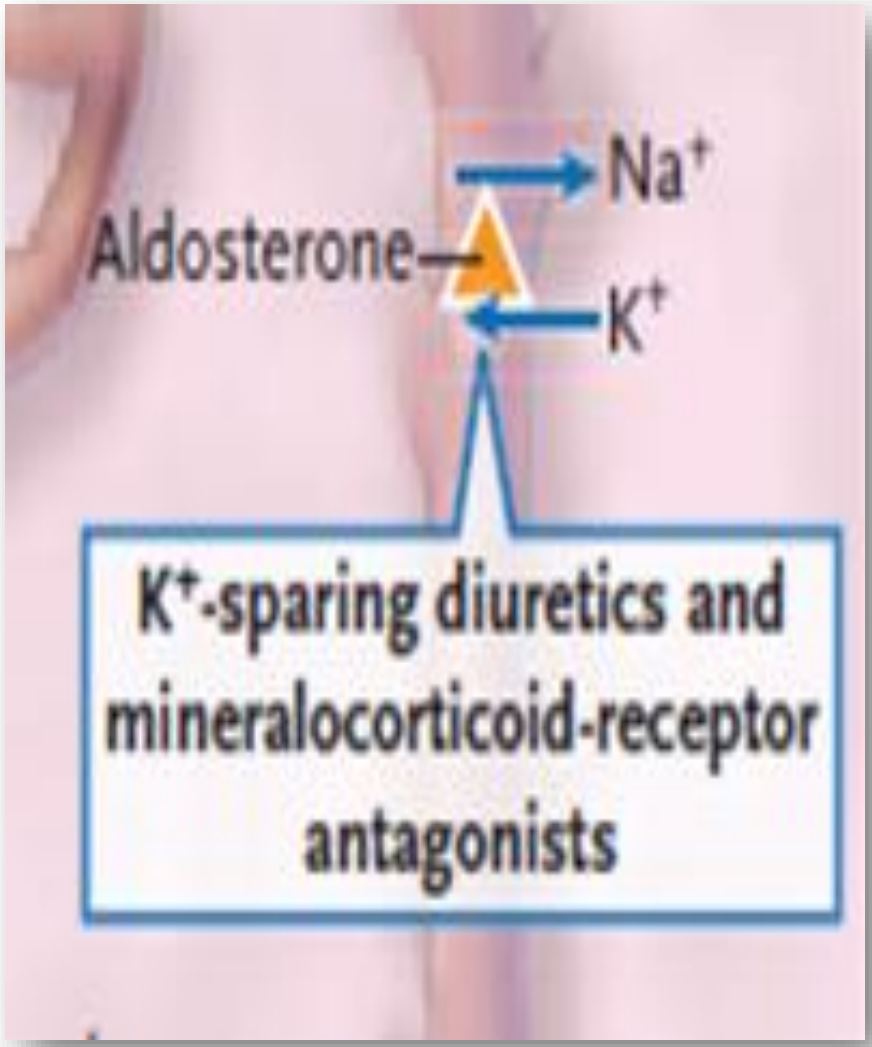
All-cause Mortality and All-Cause Hospitalization by On-treatment Status at Discharge and 30-day Follow-up

Eur J Heart Fail. 2024 July ; 26(7): 1518–1523

Καλιοσυντηρητικά διουρητικά

Παράγωγα της πτεριδίνης
Αμιλορίδη
Τριαμτερένη

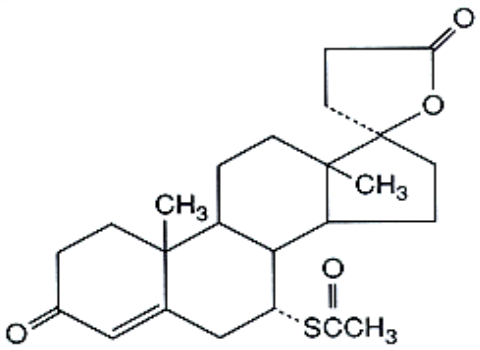
Ανταγωνιστές αλδοστερόνης
Σπιρονολακτόνη
Επλερενόνη



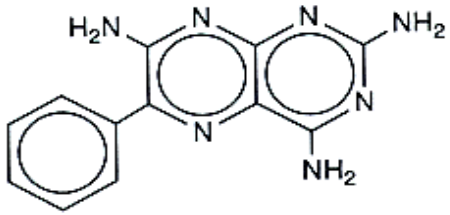
Καλιοσυντηρητικά διουρητικά

Three Groups

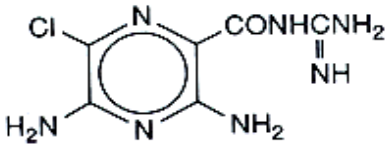
- steroid aldosterone antagonists
- spironolactone, eplerenone
- Pteridines
- triamterene
- Pyrazinoylguanidines
- amiloride



Spironolactone

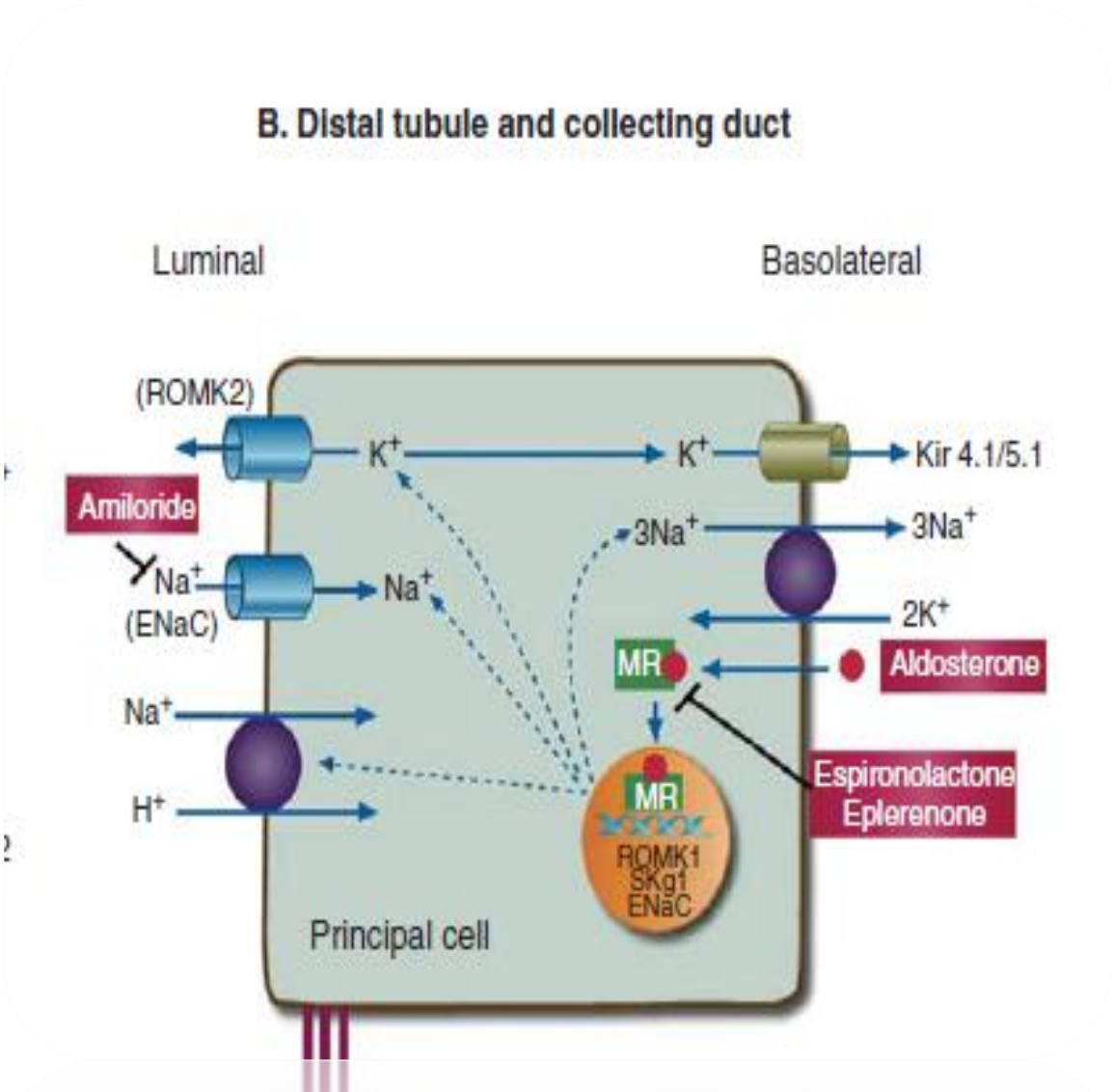


Triamterene



Amiloride

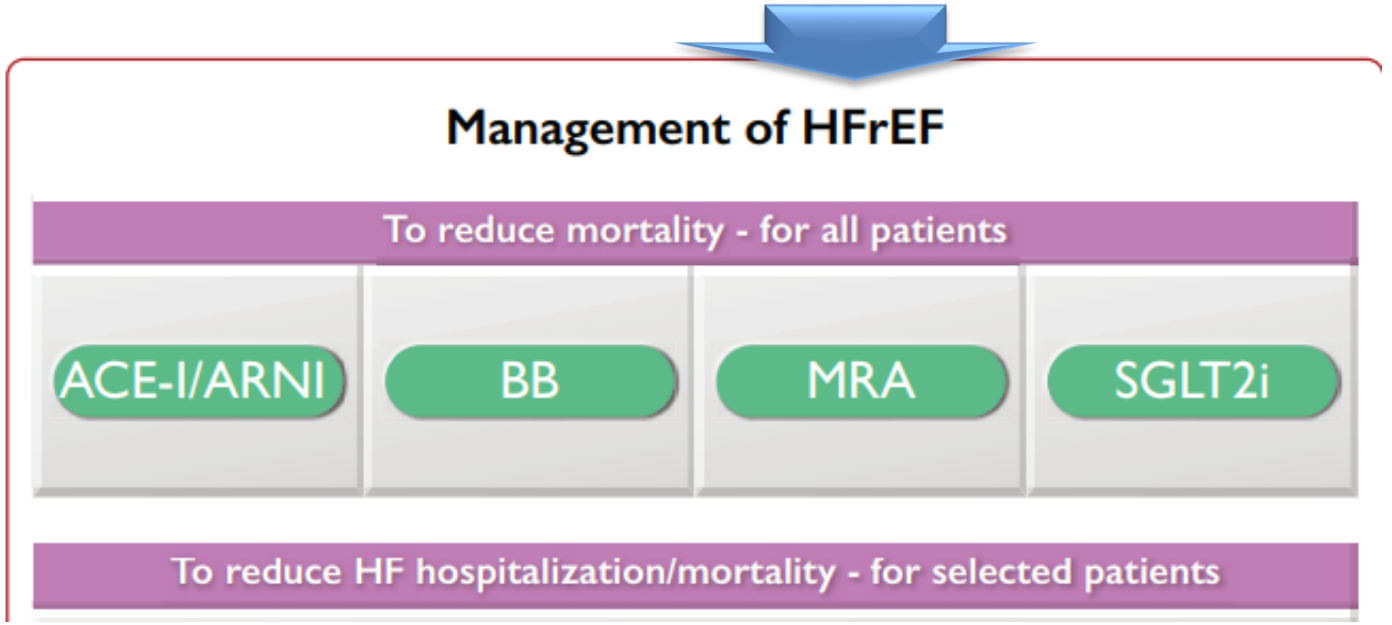
Οι ανταγωνιστές του υποδοχέα των αλατοκορτικοειδών (σπιρονολακτόνη και επλερενόνη)αναστέλλουν ανταγωνιστικά την σύνδεση της αλδοστερόνης στους υποδοχείς αλατοκορτικοειδώνi



Clin J Am Soc Nephrol
9: 2147–2163, December, 2014

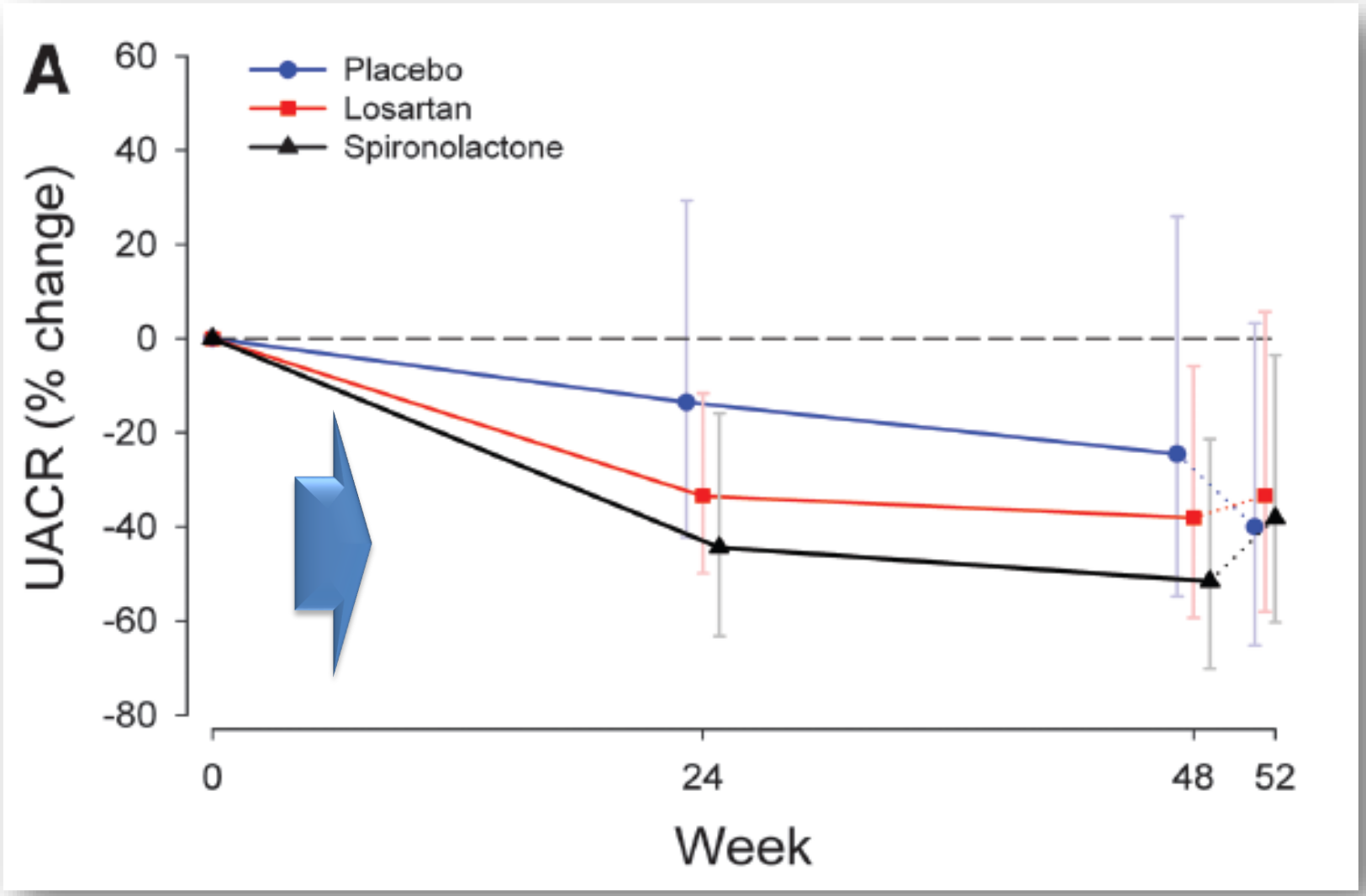
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



European Heart Journal (2021) 42, 35993726

Aldosterone Blockade in Diabetic Nephropathy with Proteinuria



Mehdi et al, J Am Soc Nephrol 2009

Finerenone is the first non-steroidal MRA indicated to reduce risks in patients with CKD associated with T2D

	FIDELIO-DKD[2]	FIGARO-DKD[3]
Primary endpoint	**Composite kidney endpoint** Time to kidney failure, sustained ≥40% eGFR decline, or kidney-related death **18% RRR** NNT=29 HR=0.82; *p*=0.001	**Composite CV endpoint** Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF **13% RRR** ARR=2.1% HR=0.87; *p*=0.03
Key secondary endpoint	Same as primary endpoint in **FIGARO-DKD** **14% RRR** NNT=42 HR=0.86; *p*=0.03	Same as primary endpoint in **FIDELIO-DKD** **13% RRR** NNT=47 HR=0.87; *p*=NS
	N=5674 Median follow up **2.6 years**	**N=7352** Median follow up **3.4 years**

ARR, absolute risk reduction; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; NS, non-significant

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

FIDELIO-DKD FIGARO-DKD

2023 ESH Guidelines for the management of arterial hypertension

Treatment strategies in patients with kidney disease

SGLT-2 inhibitors are recommended for patients with CKD due to type-2 diabetes or some non-diabetic nephropathies and moderately or severely increased albuminuria, independent of eGFR, and in those patients with CKD and eGFR < 45 ml/min/1.73²	I	A
The non-steroidal MRA finerenone can be used, because of its nephroprotective and cardioprotective properties and some BP lowering effect in patients with diabetic CKD and moderately or severely increased albuminuria.	I	A
In CKD patients with hyperkalemia a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue.	II	B

Review

The effects of SGLT2 inhibitors on blood pressure and other cardiometabolic risk factors

Alexandra Katsimardou [1,2], Panagiotis Theofilis [3], Aikaterini Vordoni [3], Michael Doumas [1] and Rigas G Kalaitzidis [3]

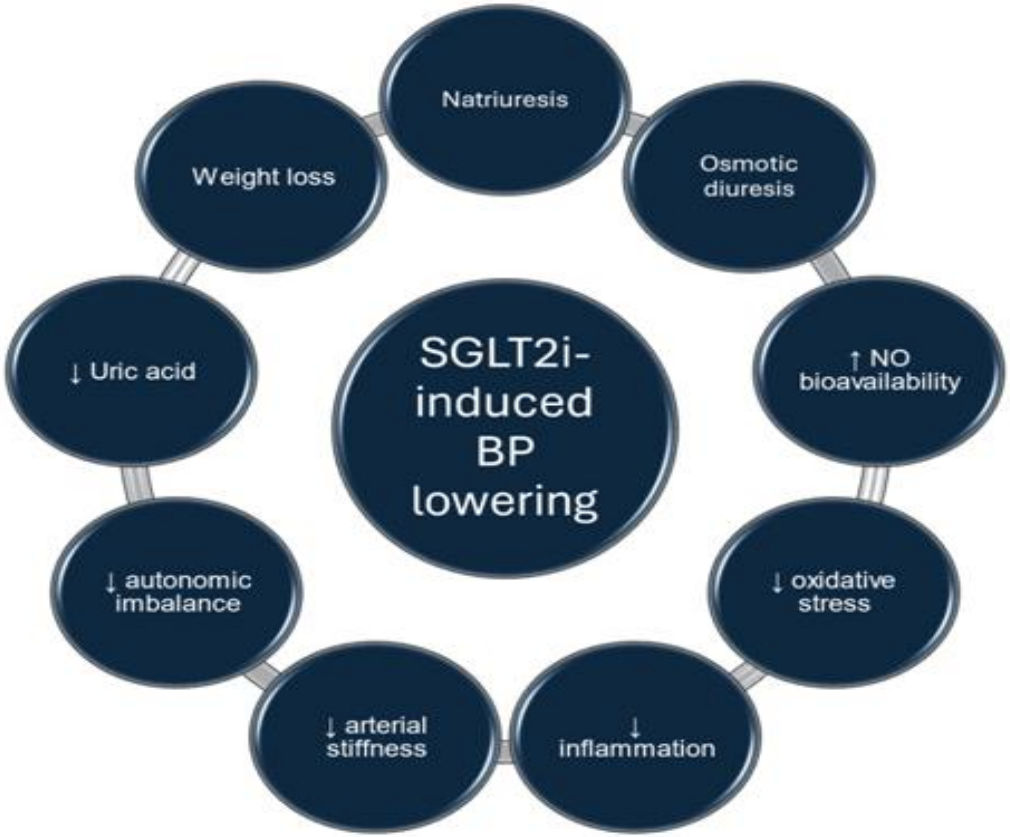
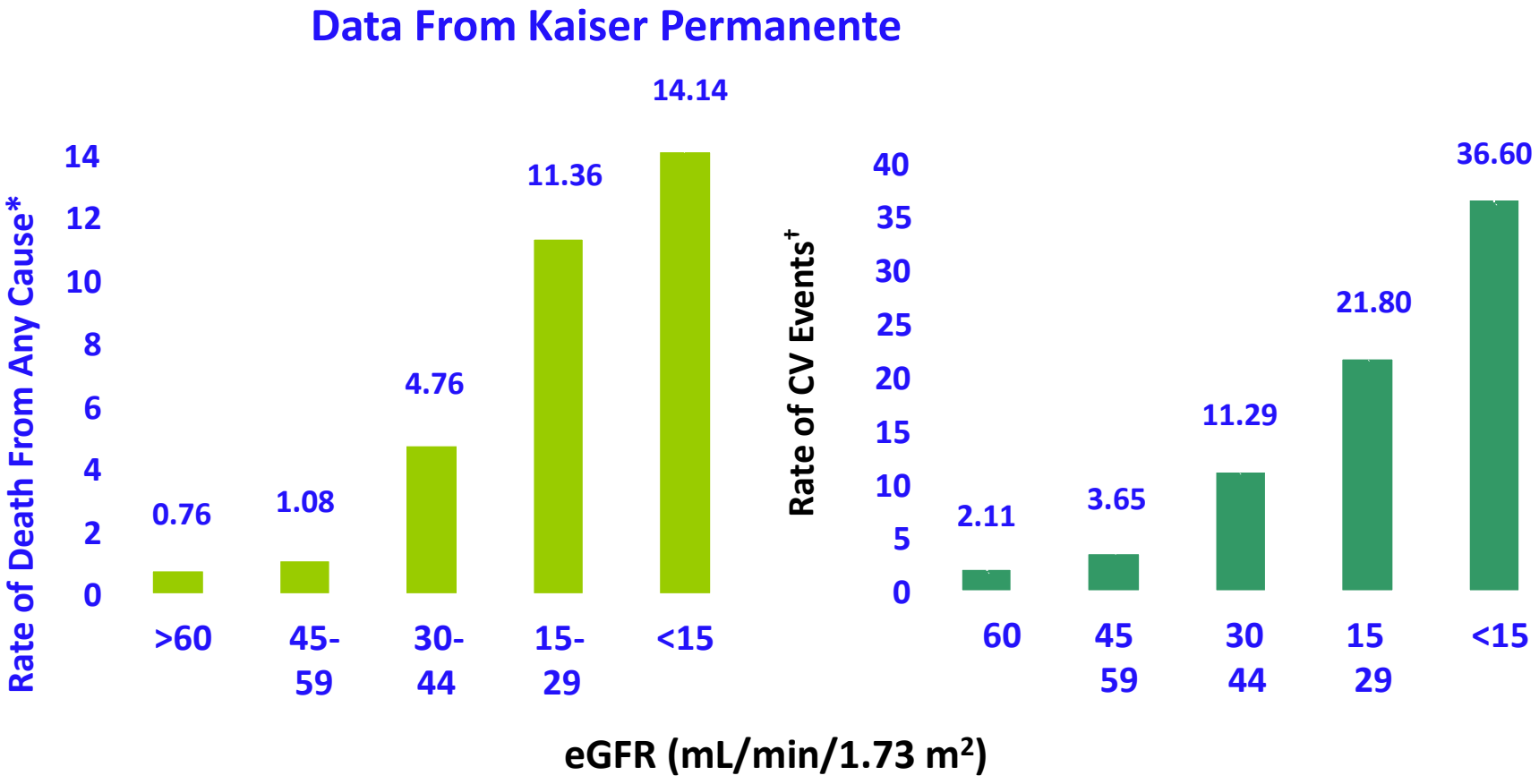


Figure 1. Mechanisms of SGLT2 inhibitor-induced blood pressure lowering.

Καρδιονεφρικό σύνδρομο

Rates of Death and Cardiovascular Events in Patients According to eGFR



N = 1,120,295 adults.

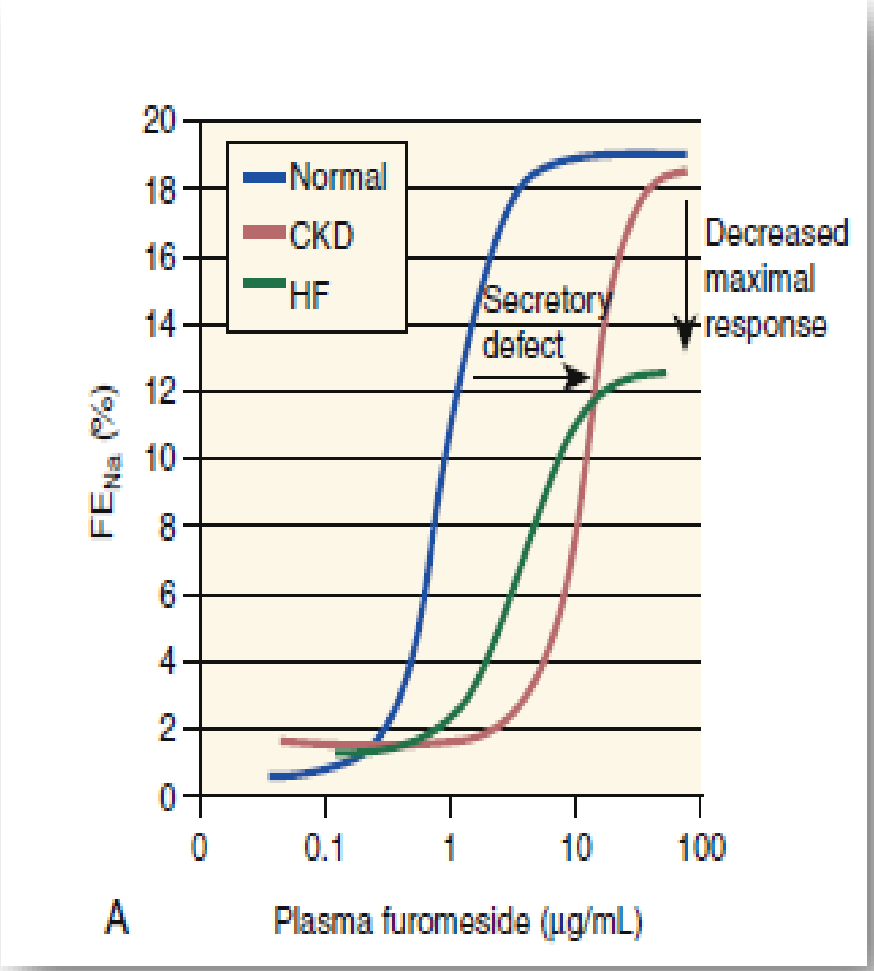
*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.

Go AS, et al. *N Engl J Med.* 2004;351:1296-1305.

XNN & KA

Κλασματική απέκκριση Νατρίου σε φυσιολογικά άτομα σε ασθενείς με XNN

και σε ασθενείς με καρδιακή ανεπάρκεια



The fractional Na+ excretion (FENa)

as a function of plasma loop

diuretic concentration.

Compared

with normal subjects, patients

with chronic kidney disease (CKD)

show a rightward shift in the curve

owing to impaired diuretic secretion.

The maximal response

is preserved when expressed as FENa,

but not when expressed as

absolute Na+ excretion.

Patients with congestive heart failure

demonstrate a rightward and

downward shift, even when

expressed as FENa, and thus

are relatively diuretic resistant

J Pharmacol Exp Ther 215:77, 1980.)

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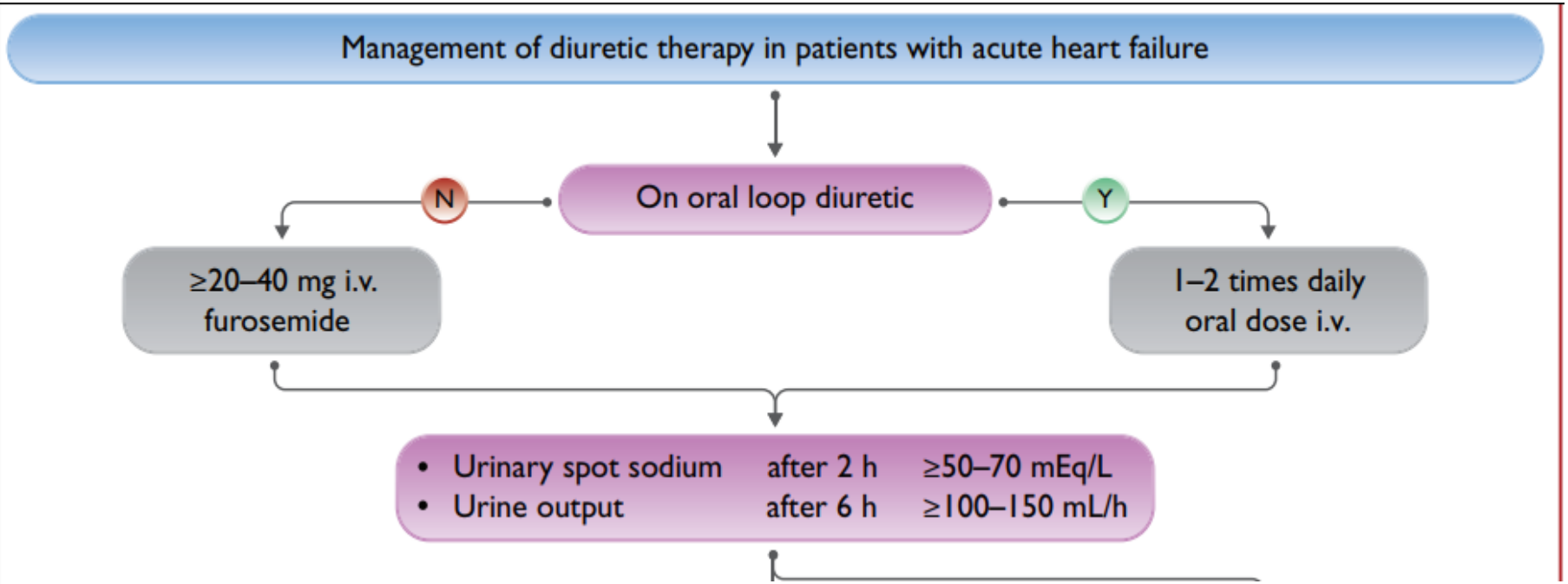

European Heart Journal (2021) 42, 35993726

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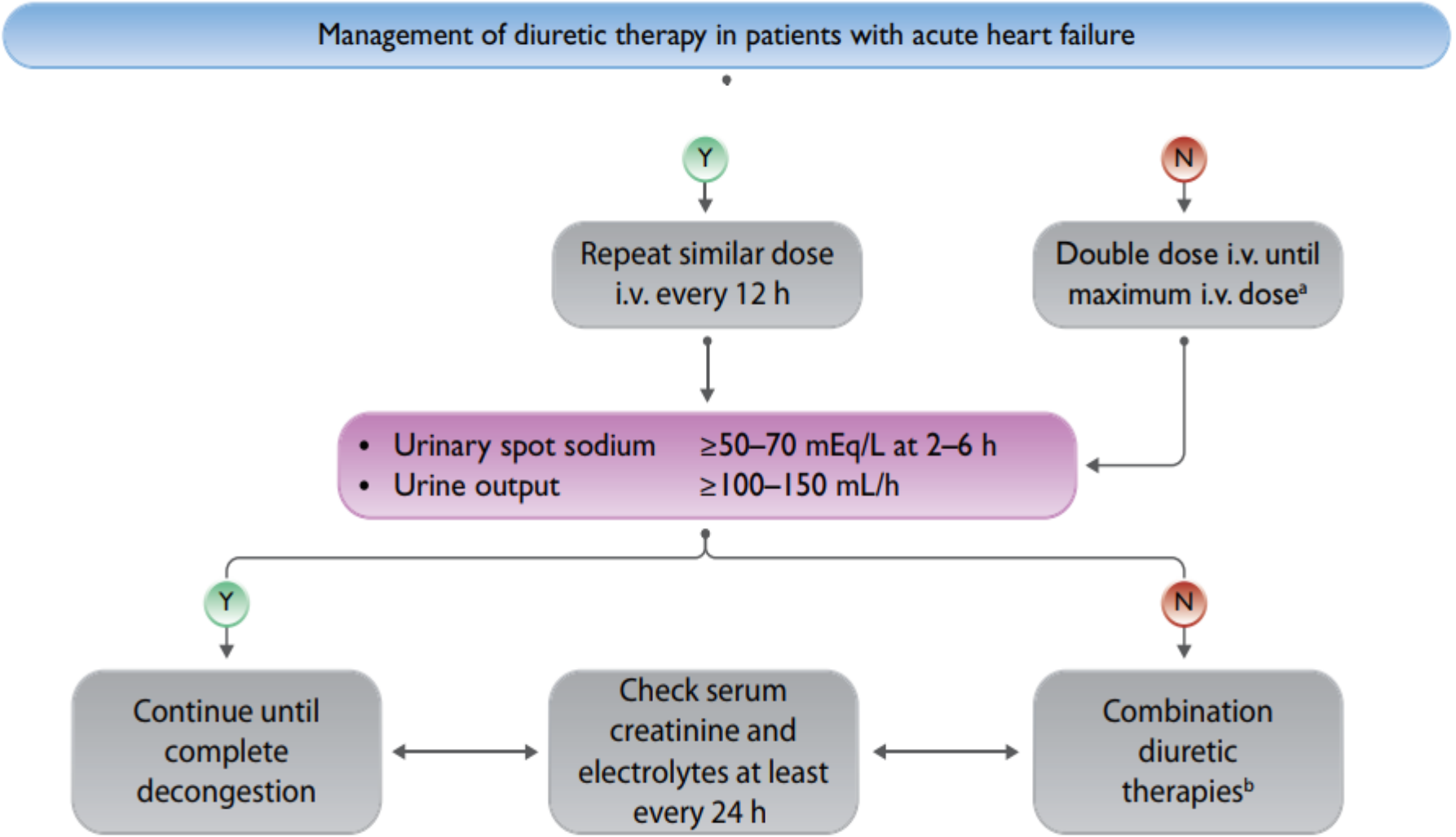


European Heart Journal (2021) 42, 35993726

Congestion associated with worsening HF

Volume overload

Volume redistribution

Diuretic resistance

- Hypoalbuminemia
- HypoNatremia
- HypoCloremia
- Anemia

Clinical Diuretic Resistance

Definition

Persistent signs and/or symptoms of congestion and **minimal weight loss** (<0.5 kg in 24 hours or < 2 kg in 72 hours) often associated with **WRF** (baseline SCr rise ≥ 30% or ≥ 0.3 mg/dl) requiring:

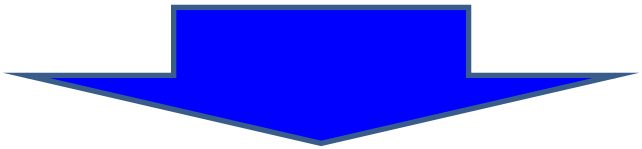
- **High dose intravenous diuretics** (>240 mg furosemide equivalent dose daily in multiple bolus doses or continuous infusion).
- **Addition of distally acting diuretic(s)** (loop diuretic + thiazide ± aldosterone blocker).

Risk factors

- ***Hypotension***
- ***Decreased kidney function***
- ***Severe symptoms of ADHF***
- ***Significant cardiac dysfunction***

McKelvie RS, et al. Can J Cardiol 2011; 27:319-38
Freda B, et al. Am J Kidney Dis 2011; 58:1005-17

Η αντίσταση στα διουρητικά



Αντιμετώπιση

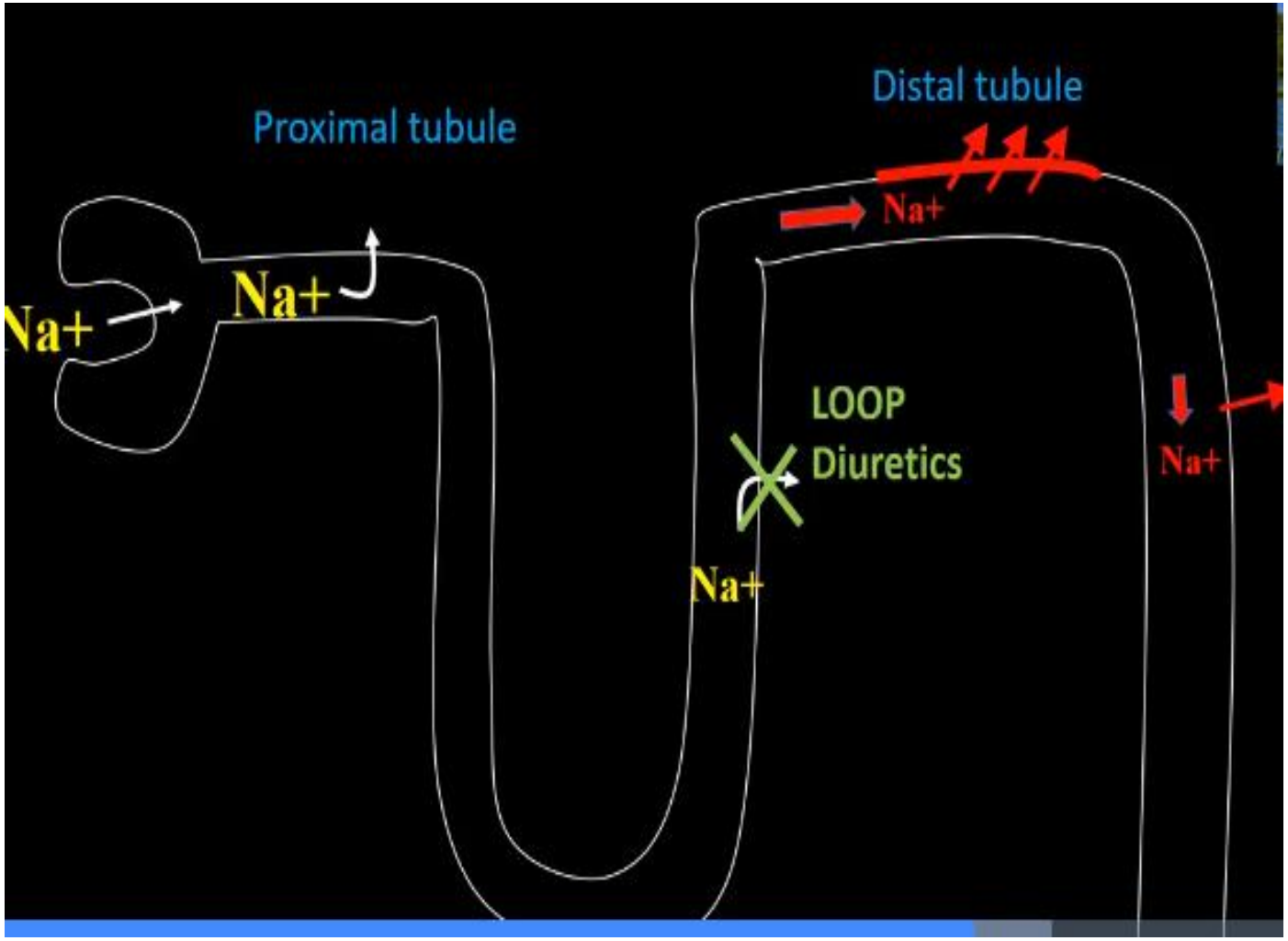
loop diuretic resistance

Αντιμετώπιση

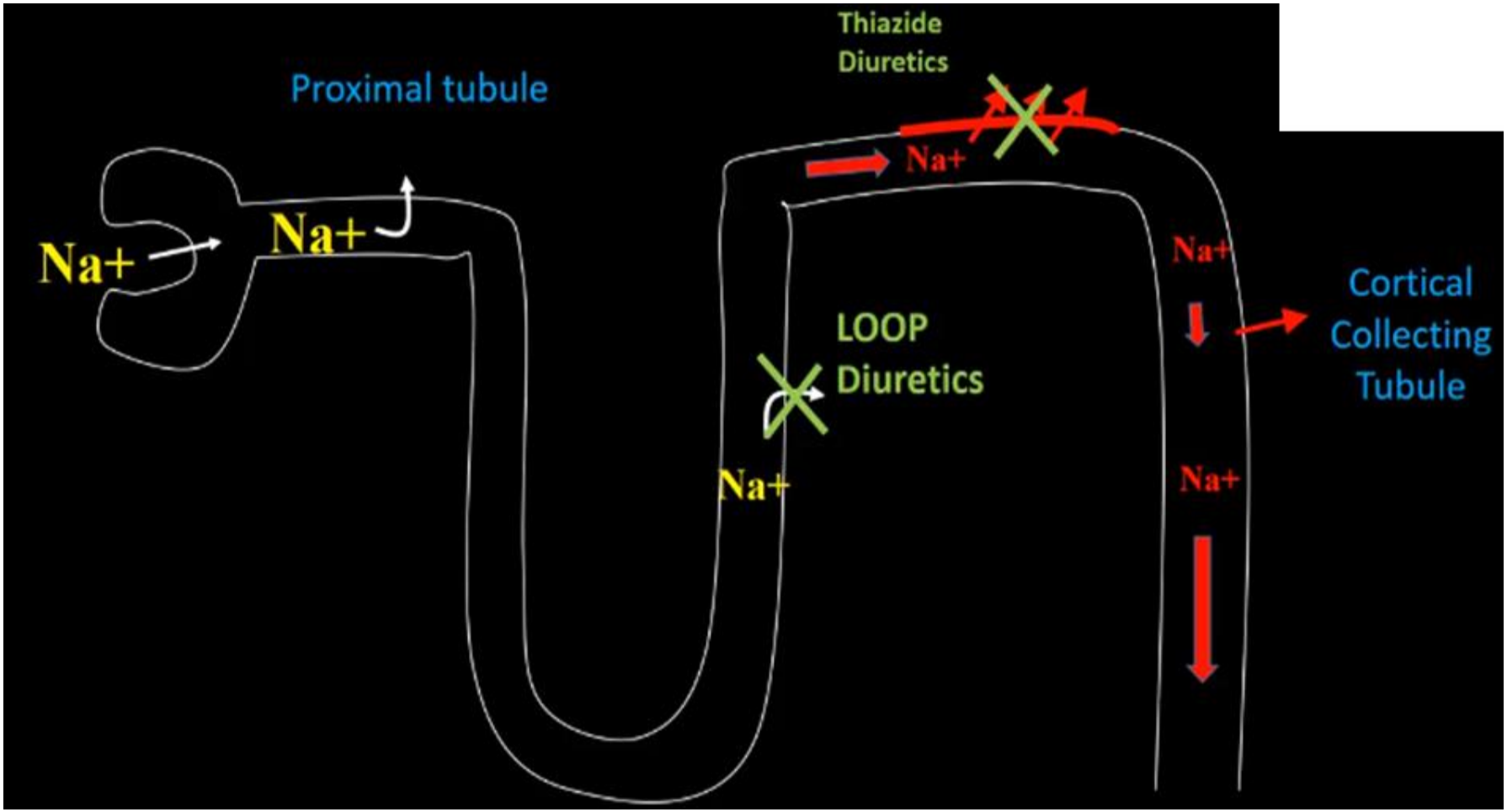
Several approaches to treat diuretic-resistant are available:

- Addition of distal acting thiazide diuretics
- Natriuretic doses of mineralocorticoid receptor antagonist
- Vasoactive drugs
- Slow continuous veno-venous ultrafiltration

Combination therapy–diuretic resistance



Combination therapy-diuretic resistance



Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

BACKGROUND

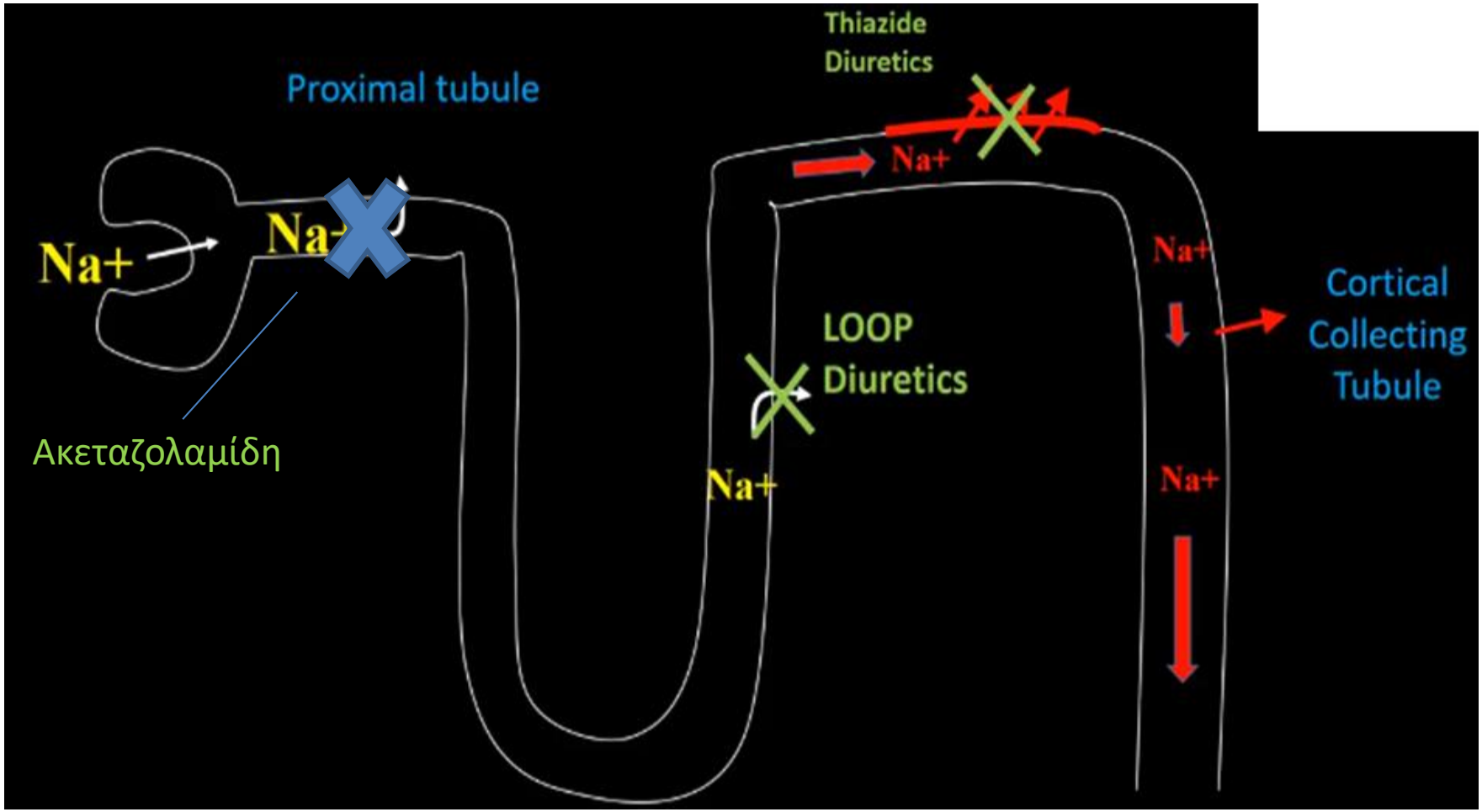
Whether acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, can improve the efficiency of loop diuretics, potentially leading to more and faster decongestion in patients with acute decompensated heart failure with volume overload, is unclear.

CONCLUSIONS

The addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure resulted in a greater incidence of successful decongestion. (Funded by the Belgian Health Care Knowledge Center; ADVOR ClinicalTrials.gov number, NCT03505788.)

N Engl J Med 2022;387:1185-95. DOI: 10.1056/NEJMoa2203094

Combination therapy-diuretic resistance



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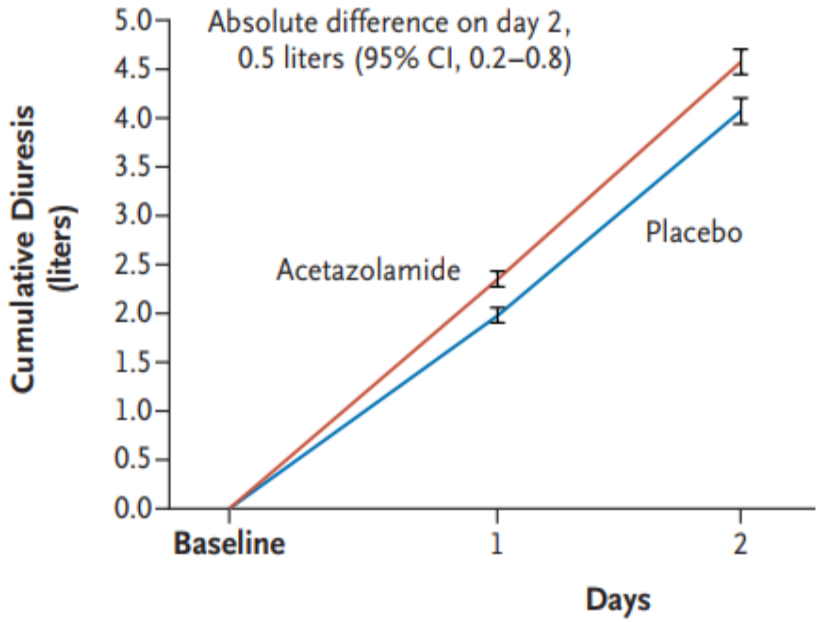
W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*



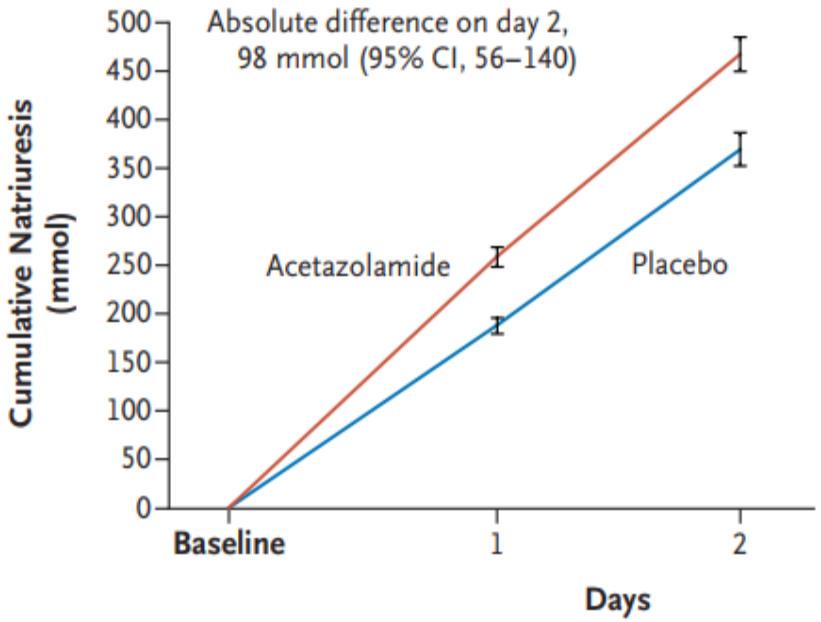


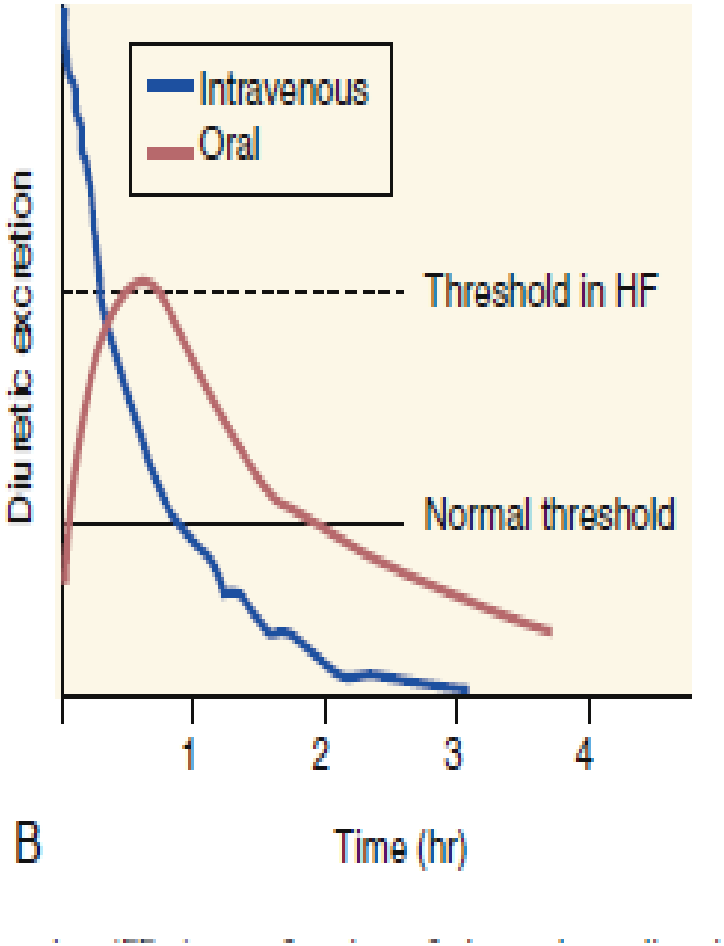
Figure 3. Diuresis and Natriuresis According to Trial Group.

I bars indicate standard errors.

In this placebo-controlled trial, we found that the addition of acetazolamide to standardized intravenous loop-diuretic therapy in patients with acute decompensated heart failure led to a higher incidence of successful decongestion.

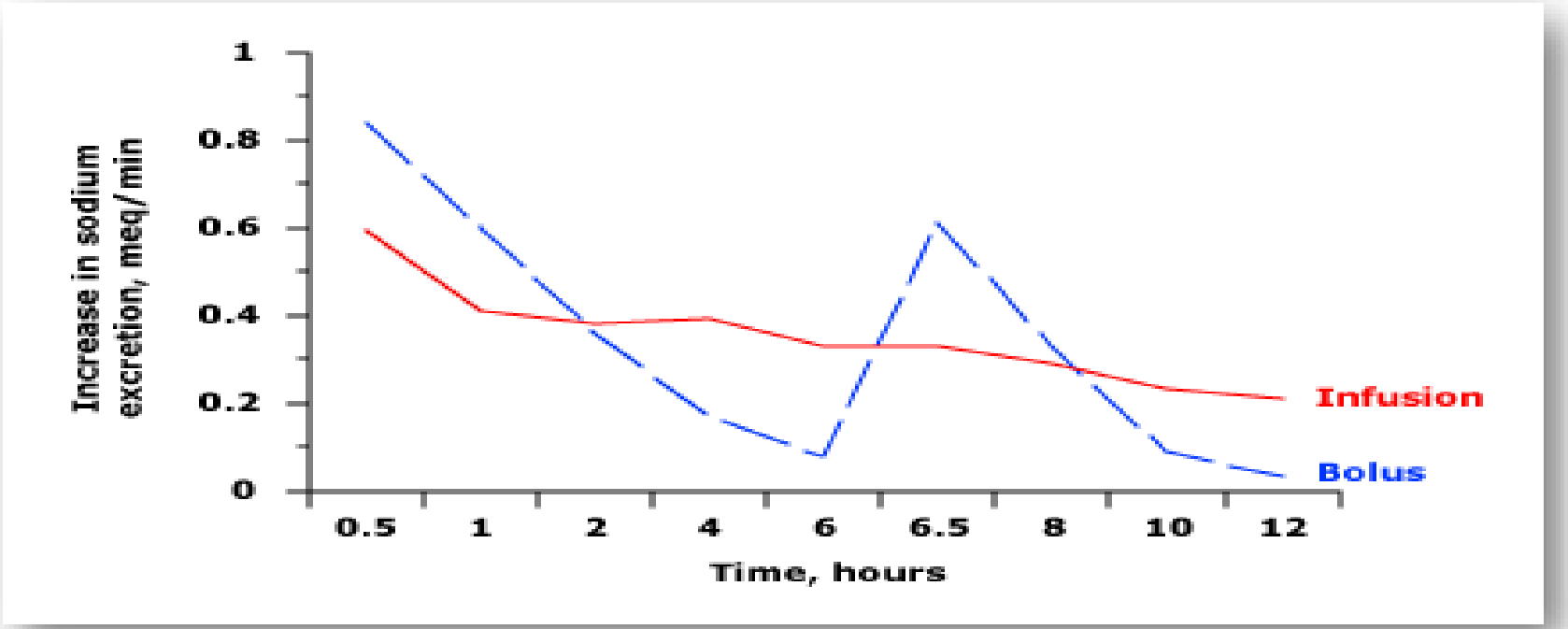
N Engl J Med 2022;387:1185-95. DOI: 10.1056/NEJMoa2203094

Η σύγκριση της ανταπόκρισης στην ενδοφλέβια και την από του στόματος χορήγηση διουρητικών της αγκύλης



A normal individual an oral dose may be as effective as an intravenous dose because the time above the natriuretic threshold (indicated by the *normal threshold line*) is approximately equal. If the natriuretic threshold increased (as indicated by the *threshold* in heart failure *[HF] line*), then the oral dose may not provide a high enough plasma level to elicit natriuresis

Peak diuresis after first dose of loop diuretic



Increase in urinary sodium excretion (UNa) after intravenous bumetanide, given as a continuous infusion (solid line) or as a bolus (dashed line), in patients with stable chronic kidney disease.

The continuous infusion produced a 30 percent greater increase in sodium excretion than bolus therapy due to a more favorable rate of diuretic excretion.

Συνεχής έναντι «bolus» έγχυση φουροσεμίδης

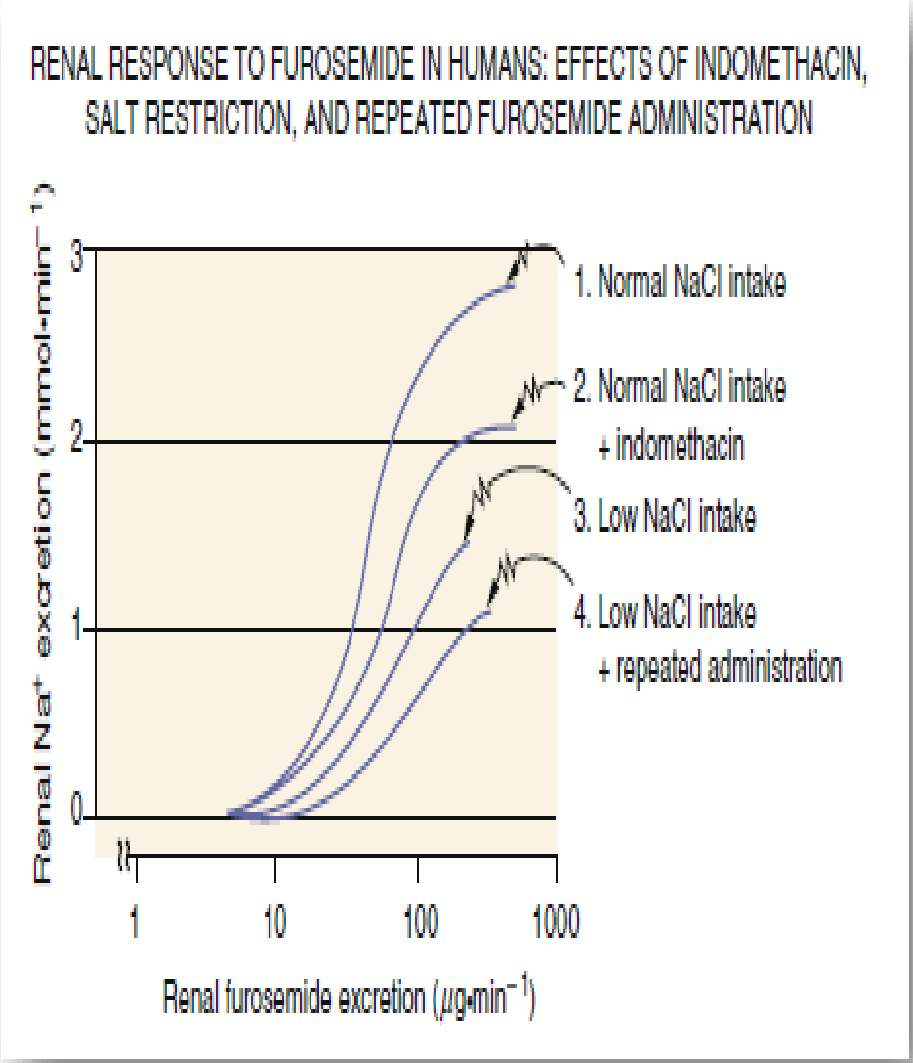
DOSE-HF Study

Bolus

Drip?

	Bolus	Drip?
Median Dose	518 mg	406 mg
Required Dose Increase	21%	11%

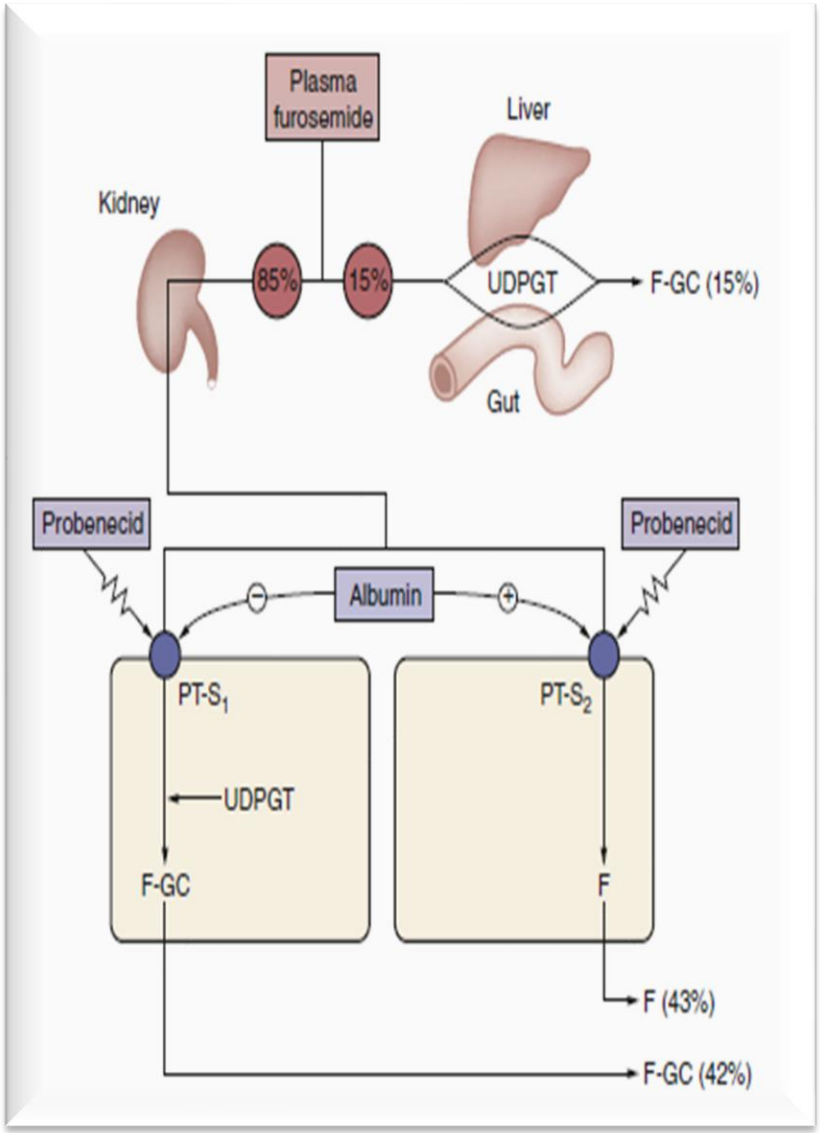
Επίδραση της μειωμένης πρόσληψης άλατος στην δράση της φουροσεμίδης



Relationship between excretion of Na+ and furosemide (log scale) after a bolus intravenous injection of 40 mg furosemide in normal subjects on a normal NaCl intake (1), for a normal NaCl intake after indomethacin (2), for a low Na+ intake (20 mmol/24 hours) (3), and for the third day of furosemide administration on a low Na+ intake

J Pharmacol Exp Ther 215:77, 1980.)

Φαρμακοκινητική φουροσεμίδης



After IV furosemide is administered, **15% is metabolized** by uridine diphosphate glucoronyl transferase (UDPGT) in the liver and gut to the inactive furosemide gluconide (F-GC). Of the remainder, **85% is transported by the kidney**. **Some 42% is taken up in the S1 segment** of the proximal tubule (PT-S1) and metabolized to the inactive gluconide, and **the remainder is taken up by the S2 segment (PT-S2)** and secreted in active form into the lumen.

Br J Pharmacol 119:885, 1996

Maximum Doses of Loop Diuretics

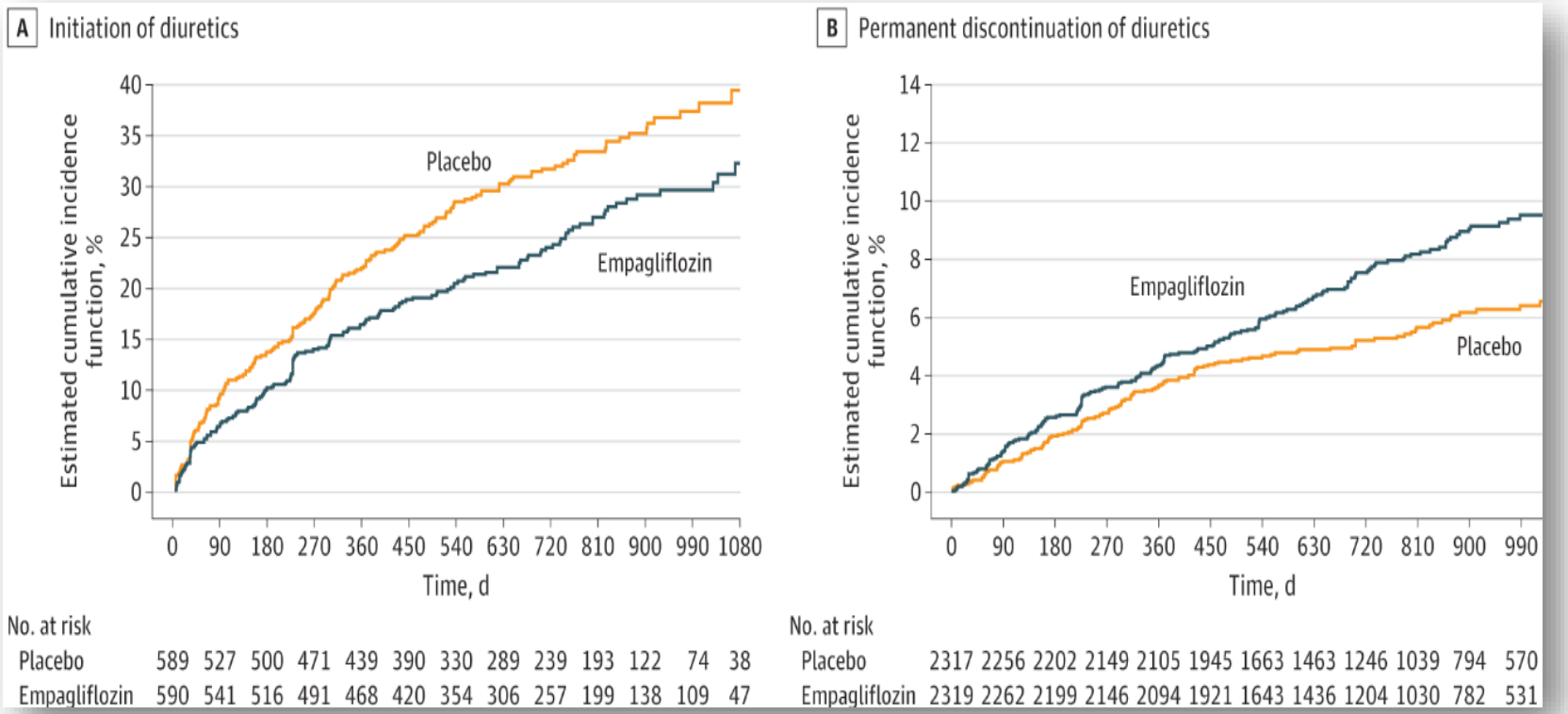
Clinical Condition	Dose of furosemide (mg)	
	intravenous	Oral
Renal Insufficiency $0 < Cl_{Cr} < 50$	80	160
Renal Insufficiency $Cl_{Cr} < 20$	200	400
Nephrotic Syndrome	120	240
Cirrhosis	40	80
Congestive Heart Failure	40-80	80-160

Data from Brater, DC. Pharmacology of Diuretics. Am. J. Med. Sci. 2000, 319:38-50.

May 24, 2023

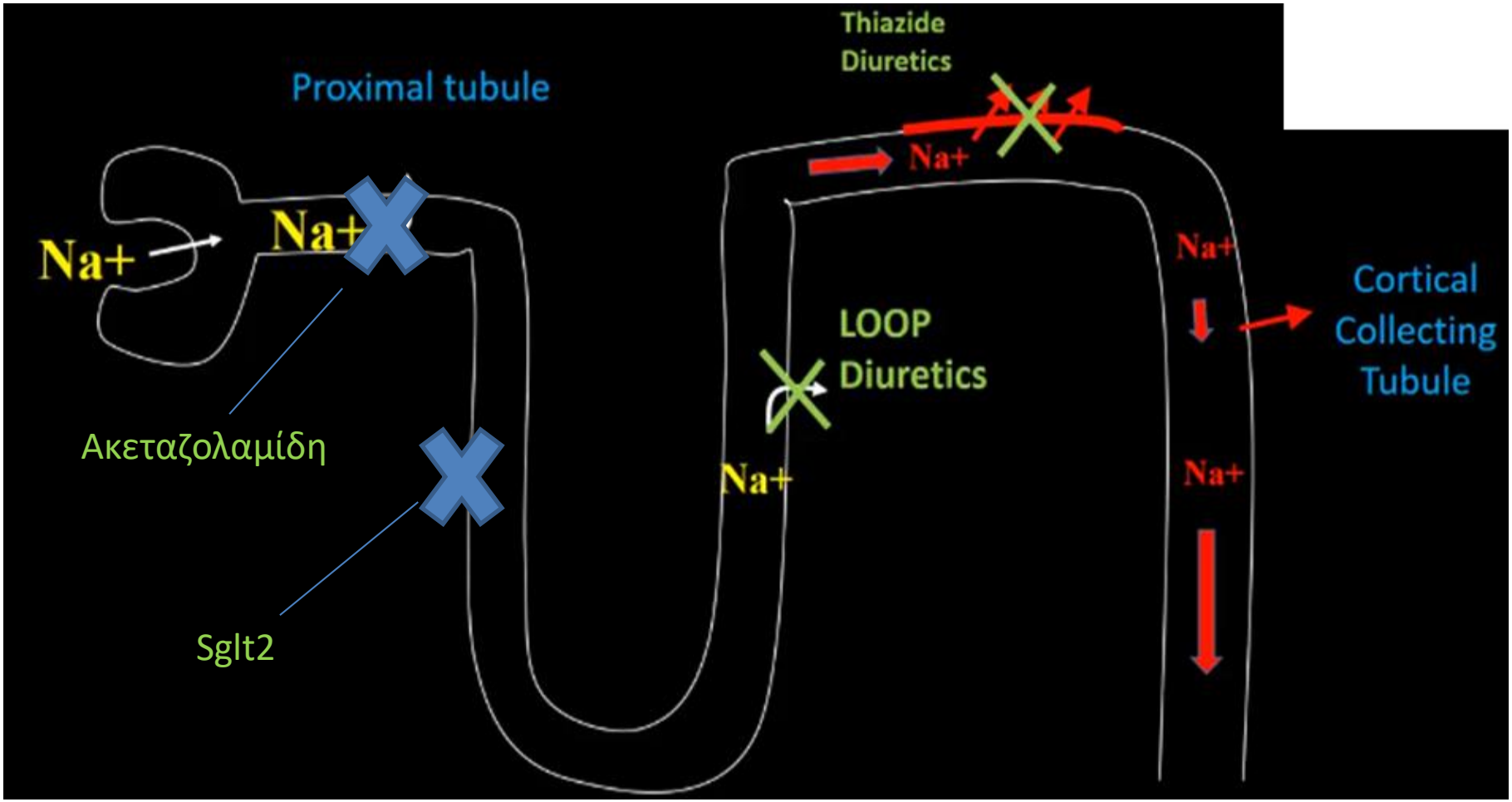
Safety and Efficacy of Empagliflozin and Diuretic Use in Patients with Heart Failure and Preserved Ejection Fraction

A Post Hoc Analysis of the EMPEROR-Preserved Trial



JAMA Cardiol. 2023;8(7):640-649.doi:10.1001/jamacardio.2023.1090

Combination therapy-diuretic resistance



Τι καινούργιο υπάρχει σήμερα
για την επιλογή του διουρητικού στην νεφρική νόσο ;

Review Article

Thiazide diuretics in advanced chronic kidney disease

Rajiv Agarwal, MD* and Arjun D. Sinha, MD

Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, IN

Manuscript received July 12, 2012 and accepted July 24, 2012

Is There a Preferred Thiazide Diuretic in CKD?

Potency followed a log-linear relationship bendroflumethiazide>chlorthalidone>HCTZ.

At ceiling doses of different thiazides, the maximum reduction in systolic BP **was similar**.

Given the higherpotency, long duration of action, and low cost, chlorthalidone may be preferred to other thiazides.

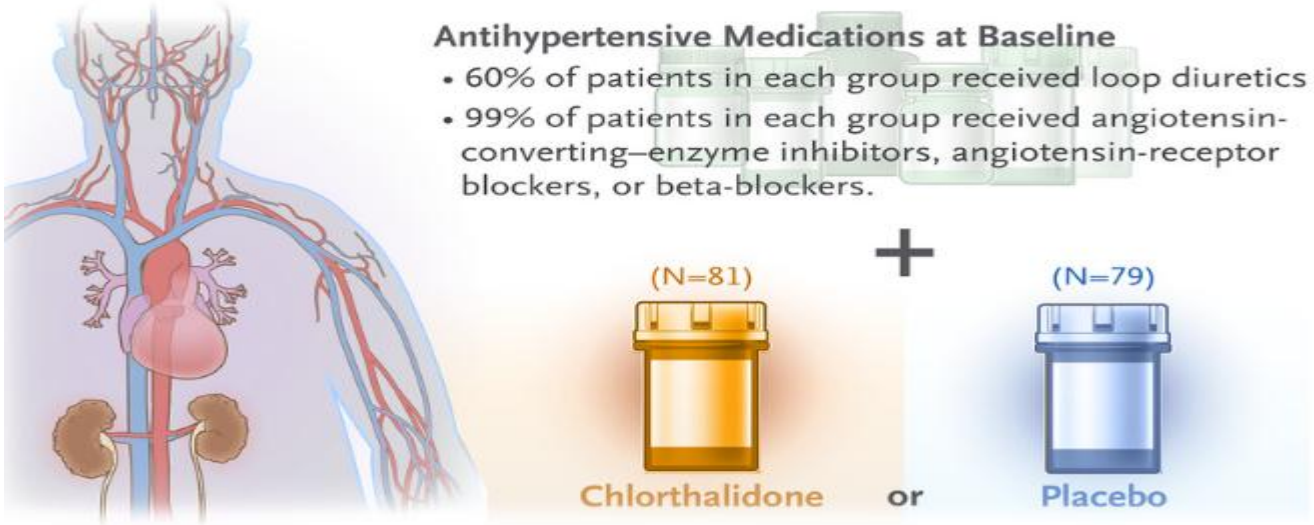
The number of studies using thiazides in advanced CKD is limited to a handful of patients. Using robust methodology, the role of thiazide diuretics in those with advanced CKD needs to be explored further. Nonetheless, existingdata suggest that thiazide diuretics may be useful in causing natriuresis and better BP control in CKD.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 30, 2021 VOL. 385 NO. 27

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Rajiv Agarwal, M.D., Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S., Jazmyn H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D.



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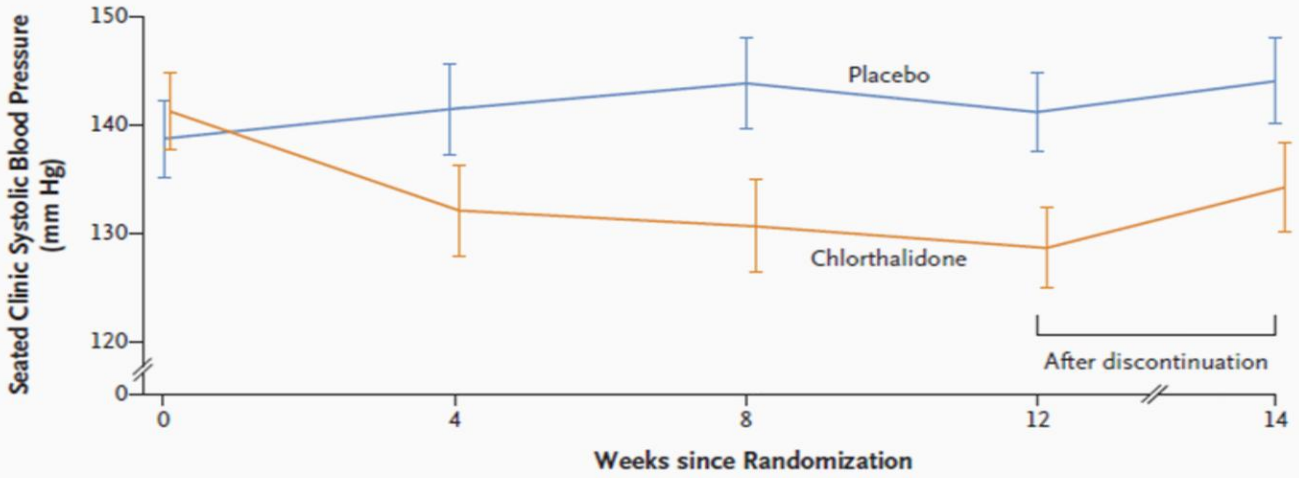
A



Mean Change from Baseline (95% CI) — mm Hg				
Placebo	2.7 (−0.9 to 6.3)	5.1 (1.4 to 8.8)	2.4 (−0.6 to 5.5)	5.3 (1.8 to 8.8)
Chlorthalidone	−9.2 (−12.9 to −5.5)	−10.6 (−14.5 to −6.8)	−12.6 (−15.8 to −9.5)	−7.0 (−10.7 to −3.3)
Difference	−11.9 (−17.1 to −6.7)	−15.7 (−21.0 to −10.5)	−15.1 (−19.4 to −10.7)	−12.3 (−17.5 to −7.2)

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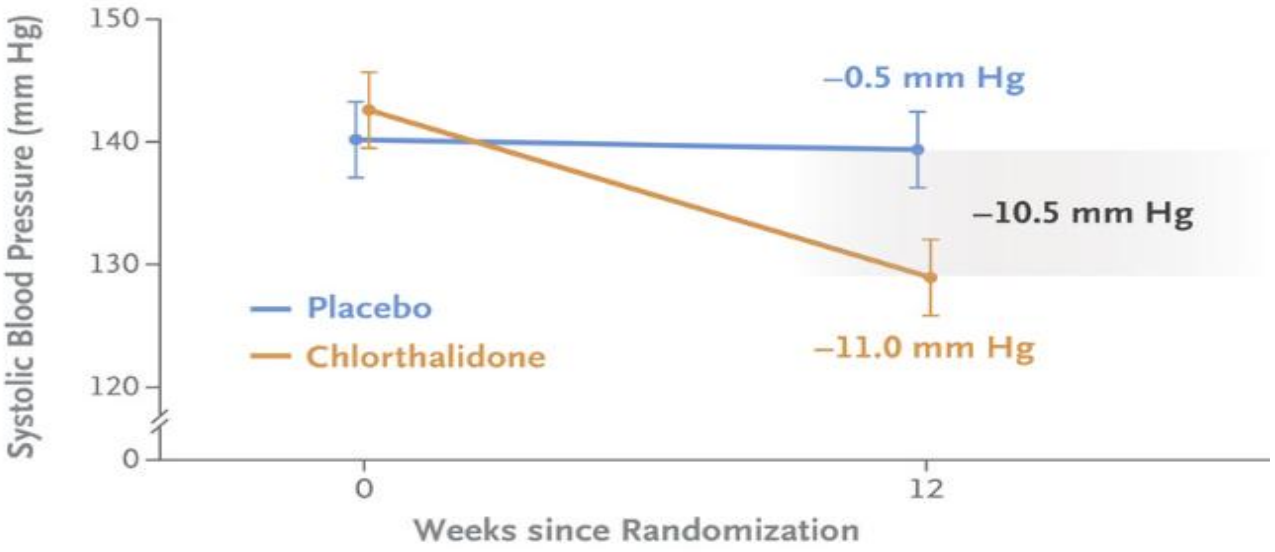
Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

k, M.S.,

Adjusted Change in 24-Hour Ambulatory Systolic Blood Pressure from Baseline to 12 Weeks

Mean difference, −10.5 mm Hg; 95% CI, −14.6 to −6.4; P<0.001



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Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

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Μεταξύ των ασθενών με προχωρημένη νεφρική νόσο, ιδιαίτερα σε εκείνους που λαμβάνουν διουρητικά της αγκύλης προτείνεται η έναρξη της θεραπείας με δόσεις χλωροθαλιδόνης μικρότερες των 12,5mg τρεις φορές την εβδομάδα.

Revisiting diuretic choice in chronic kidney disease

Sehrish Ali[a,b], *Sankar D. Navaneethan*[a,b,c,d]
Salim S. Virani[c,e,f], *and L. Parker Gregg*[a,b,c]

Recent evidence supports expanded indications for diuretics in patients with kidney disease, including chlorthalidone for hypertension in advanced CKD.
Monitoring electrolytes and estimated GFR is critical to ensure patient safety when prescribing these agents for patients with CKD.

Curr Opin Nephrol Hypertens 2022, 31:406–413

N Engl J Med. 2022 Dec 14. doi: 10.1056/NEJMoa2212270. Online ahead of print.

Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events

Areef Ishani [1], William C Cushman [1], Sarah M Leatherman [1], Robert A Lew [1], Patricia Woods [1], Peter A Glassman [1], Addison A Taylor [1], Cynthia Hau [1], Alison Klint [1], Grant D Huang [1], Mary T Brophy [1], Louis D Fiore [1], Ryan E Ferguson [1]; Diuretic Comparison Project Writing Group

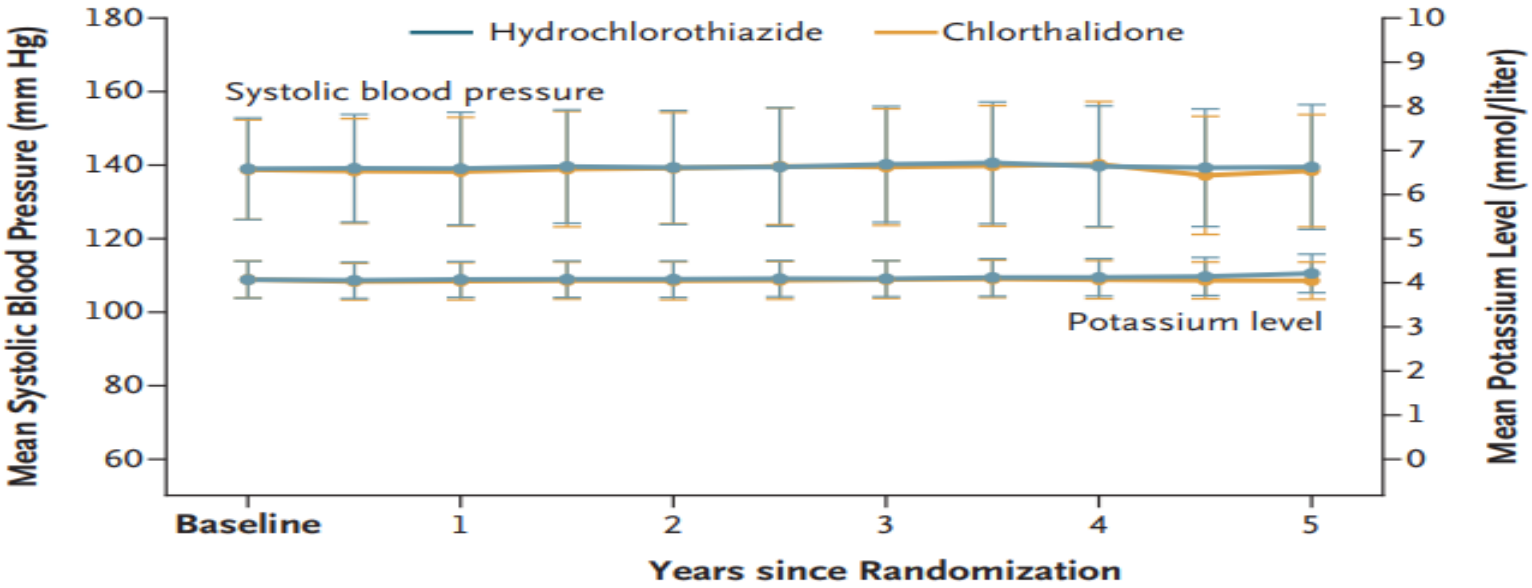
Conclusions: In this large pragmatic trial of thiazide diuretics at doses commonly used in clinical practice, patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non-cancer-related deaths than patients who received hydrochlorothiazide. (Funded by the Veterans Affairs Cooperative Studies Program; ClinicalTrials.gov number, NCT02185417.).

he DCP is the first head-to-head comparison of hydrochlorothiazide and chlorthalidone in a randomized, prospective outcome trial

N engl j med 387;26 nejm.org December 29, 2022

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 29, 2022 VOL. 387 NO. 26

Chlorthalidone vs. Hydrochlorothiazide for Hypertension—Cardiovascular Events



Patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non–cancer-related deaths than patients who received hydrochlorothiazide.

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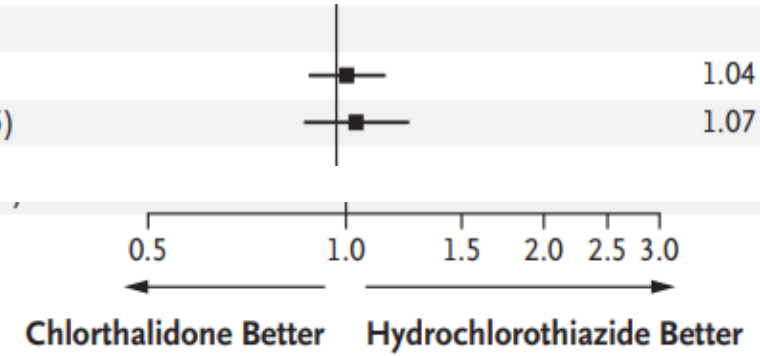
Chlorthalidone vs. Hydrochlorothiazide for Hypertension—Cardiovascular Events

Estimated GFR <60 ml/min/1.73 m² — no. (%)		1550 (22.9)	1547 (22.9)
Estimated GFR			
≥60 ml/min/1.73 m²	843/9660 (9)		1.04 (0.91–1.19)
<60 ml/min/1.73 m²	451/3097 (15)		1.07 (0.89–1.29)



n engl j med 387;26 nejm.org December 29, 2022

Role of Diuretics in CV Events and Mortality in SPRINT: A Post Hoc Analysis

CJASN

SPRINT

Systolic Blood Pressure Intervention Trial

9361 participants

SBP Target <120 mm Hg Intensive grp

SBP Target <140 mm Hg Standard grp

Lower risk of CV end points in the intensive group persisted after adjustment for postrandomization time-varying diuretics use

HR 0.75
(95%CI 0.64-0.89)

HR 0.74
(95%CI 0.62-0.89)
Time-varying Diuretic use

Time-varying diuretics use was not associated with CV end points

Reference
No diuretics

HR 0.89
(95%CI, 0.73-1.10)
Thiazide diuretics

HR 1.29
(95%CI, 0.97-1.73)
Loop/ K+ sparing diuretics

Thiazide-type diuretics use associated with lower risk of CV end points in intensive group

HR 0.62
(95%CI 0.46-0.85)
Intensive group

HR 1.07
(95%CI 0.82-1.39)
Standard group

Effect of intensive intervention on CV end points was not mediated by diuretics use

Mediation analysis

HR 0.66
(95% CI 0.54-0.79)
Total effect

HR 0.67
(95% CI 0.54-0.81)
Direct effect
(not mediated thru diuretics)

HR 0.98
(95% CI 0.88-1.10)
Indirect effect
(mediated thru diuretics)

Results were largely similar for all-cause mortality

Conclusions: The favorable effects of intensive systolic BP lowering on cardiovascular end points and all-cause mortality in SPRINT were independent of and not mediated by time-varying diuretic use.

Sheetal Bansal, Robert Boucher, Jincheng Shen, *et al.* ***Role of Diuretics in Cardiovascular Events and Mortality in Systolic Blood Pressure Intervention Trial: A Post Hoc Analysis.*** CJASN (in): 10.2215/CJN.0000000000000406.
Visual Abstract by Edgar Lanns, MD, FASN

Bansal, Sheetal; Boucher, Robert; Shen, Jincheng; Wei, Guo; Charlow, Glenn M.; Whelton, Paul K.; Cushman, William C.; Cheung, Alfred K.; Seddhu, Srinivasan; , on behalf of SPRINT

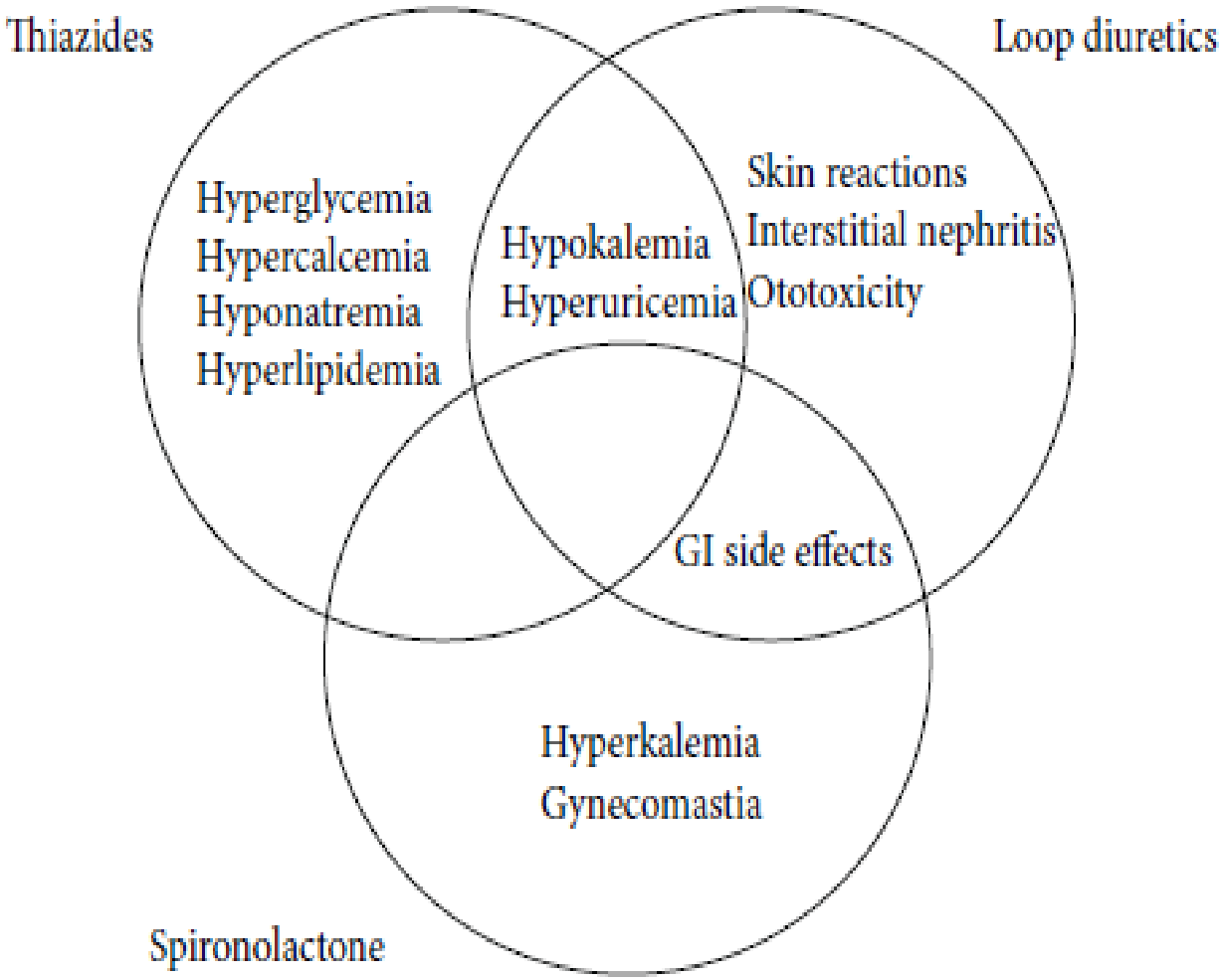
Wolters Kluwer

Clinical Journal of the American Society of Nephrology: January 23, 2024

doi: 10.2215/CJN.0000000000000406

Παρενέργειες των διουρητικών

Adverse effects of major diuretics



Antihypertensive Drug–Induced Iatrogenic Cardiovascular Syndromes

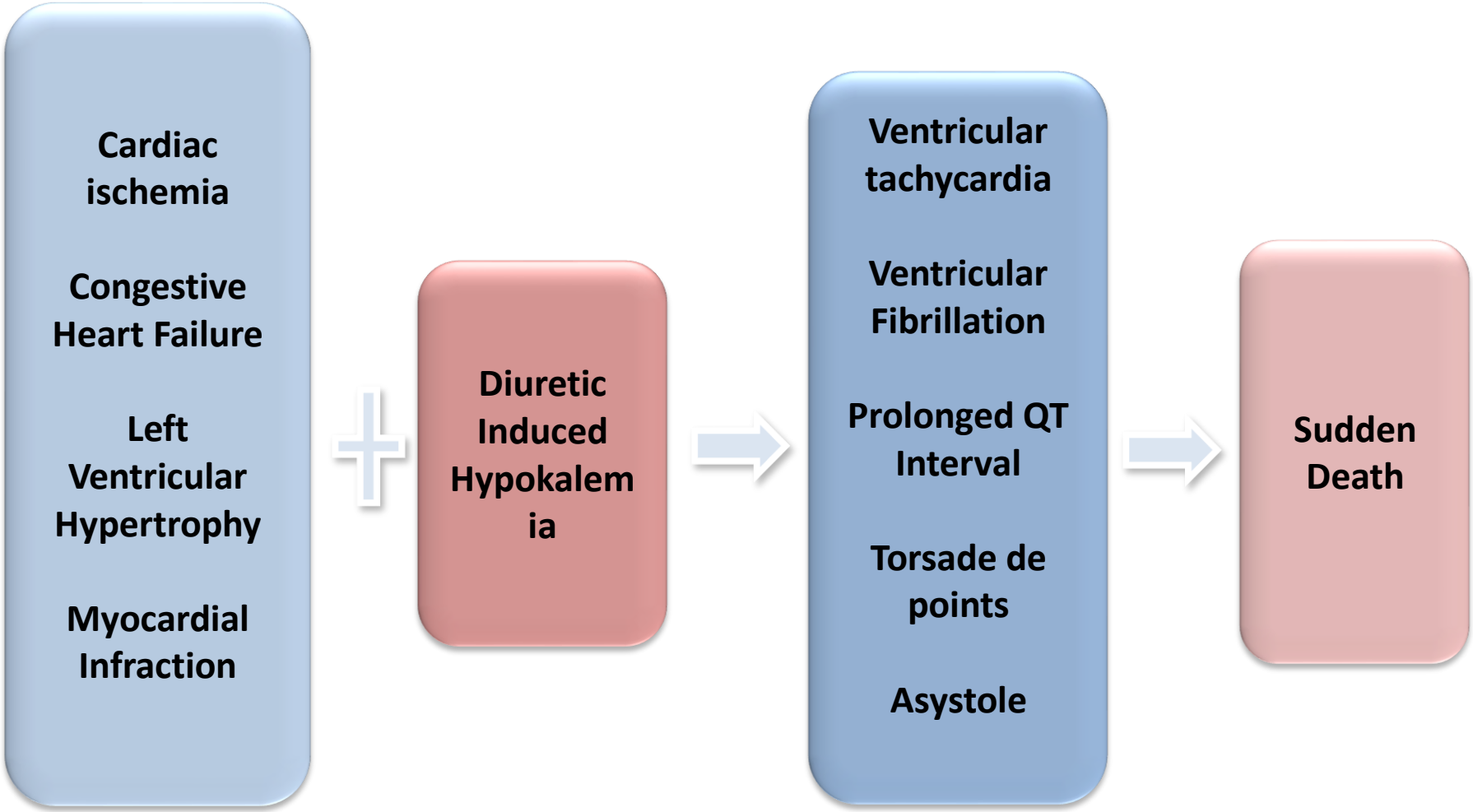
Rigas G. Kalaitzidis and George L. Bakris

Drugs	Side Effects	Cardiovascular Effects
Thiazides and thiazidelike diuretics (e.g., hydroclorothiazide, chlorthalidone, indapamide)	Hypovolemia Hypersensitivity Hypokalemia Hypomagnesemia Hypercalcemia Hyperuricemia	Cardiac arrhythmias Increased ventricular ectopy Sudden death
Loop diuretics (e.g., furosemide, torsemide)	Hypovolemia Hypersensitivity Ototoxicity Hypokalemia Hypomagnesemia	Cardiac arrhythmias
Potassium-sparing diuretics (e.g., spironolactone, [illegible]arenone, amiloride, triamter[illegible])	Hyperkalemia Hypotension, Dizziness Headache Nausea	Cardiac arrhythmias Wide QRS accelerated rhythm Sudden death
Beta-blockers (metopro[illegible], atenolol, carvedilol, nebivolol)	Cold hands and feet Tiredness Fatigue Reduced exercise tolerance Reduced sexual function Increased risk of diabetes with all except (nebivolol and carvedilol)	[illegible] Hypotension Low-output cardiac failure Cardiogenic shock Prolonged QT interval Torsade de pointes Cardiac arrest
RAAS inhibitors (ACE inhibitors, (captopril, enalapril, ramipril, lisinopril)ARBs, (losartan, telmisartan, olmesartan) renin inhibitors) (aliskerin)	Hyperkalemia	Cardiac arrhythmias Bradycardia
Calcium channel blockers (diltiazem, verapamil; dihydropyridines) (amlodipine, nifedipine)	Hypokalemia Hyperglycemia Oliguric renal failure Acute pancreatitis Respiratory distress syndrome	Hypotension Sinus bradycardia Atrioventricular block Vasodilatory shock Pulmonary edema Sinus tachycardia
Alpha-1 blockers (doxazosin, terazosin)	Orthostatic symptoms	Increased risk of cardiac heart failure
Central Alpha-2 Agonists (Moxonidine, clonidine, alpha methyldopa)	Nausea Allergic skin reaction Dry mouth	Increased mortality and morbidity Greater likelihood of hospitalization for heart failure and acute myocardial infarction

Rigas G. Kalaitzidis and George L. Bakris, 2018

Antihypertensive Drug–Induced Iatrogenic Cardiovascular Syndromes

Rigas G. Kalaitzidis and George L. Bakris



Hypokalemia induced sudden death in preexisting heart disease

Thank you


steer.ru