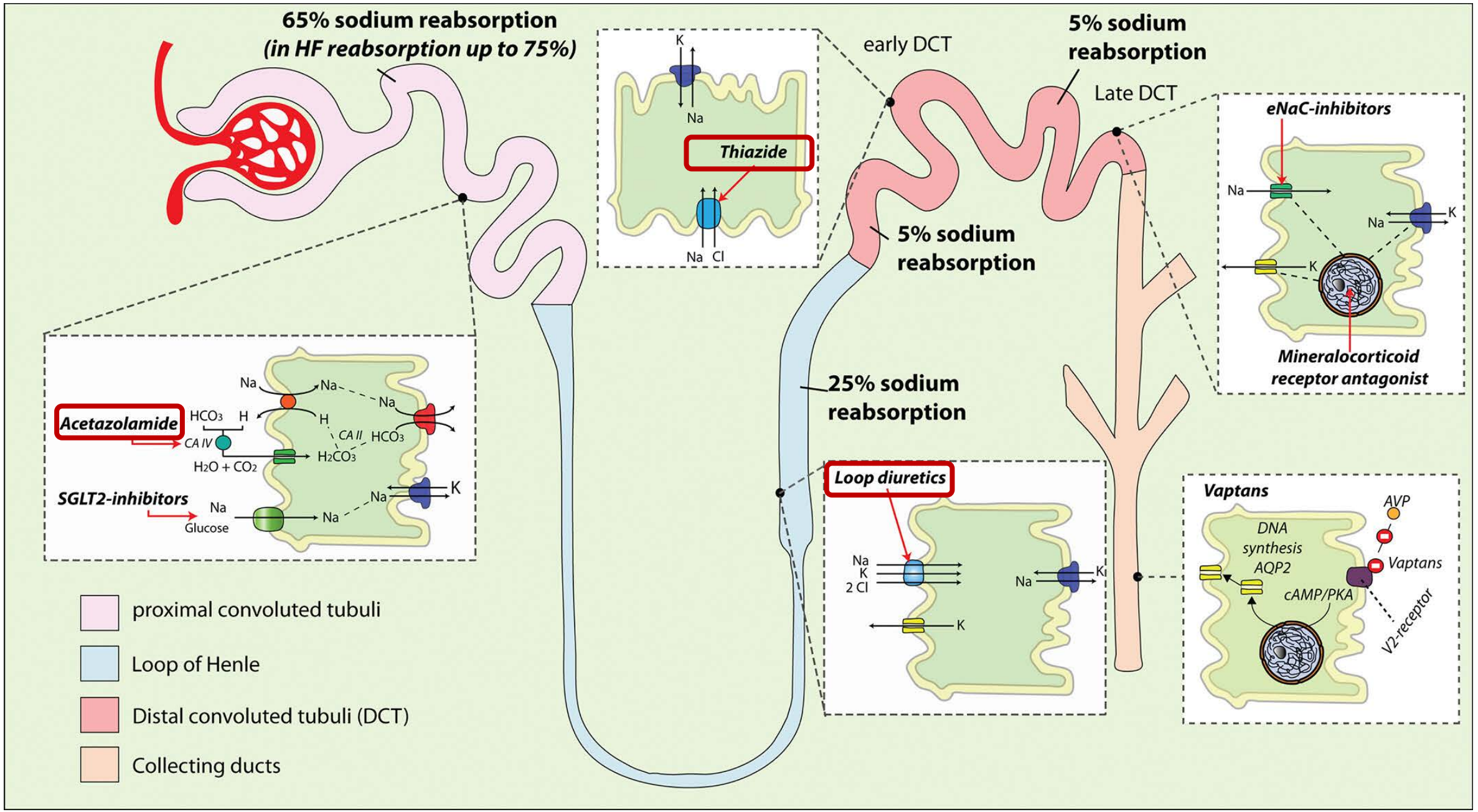
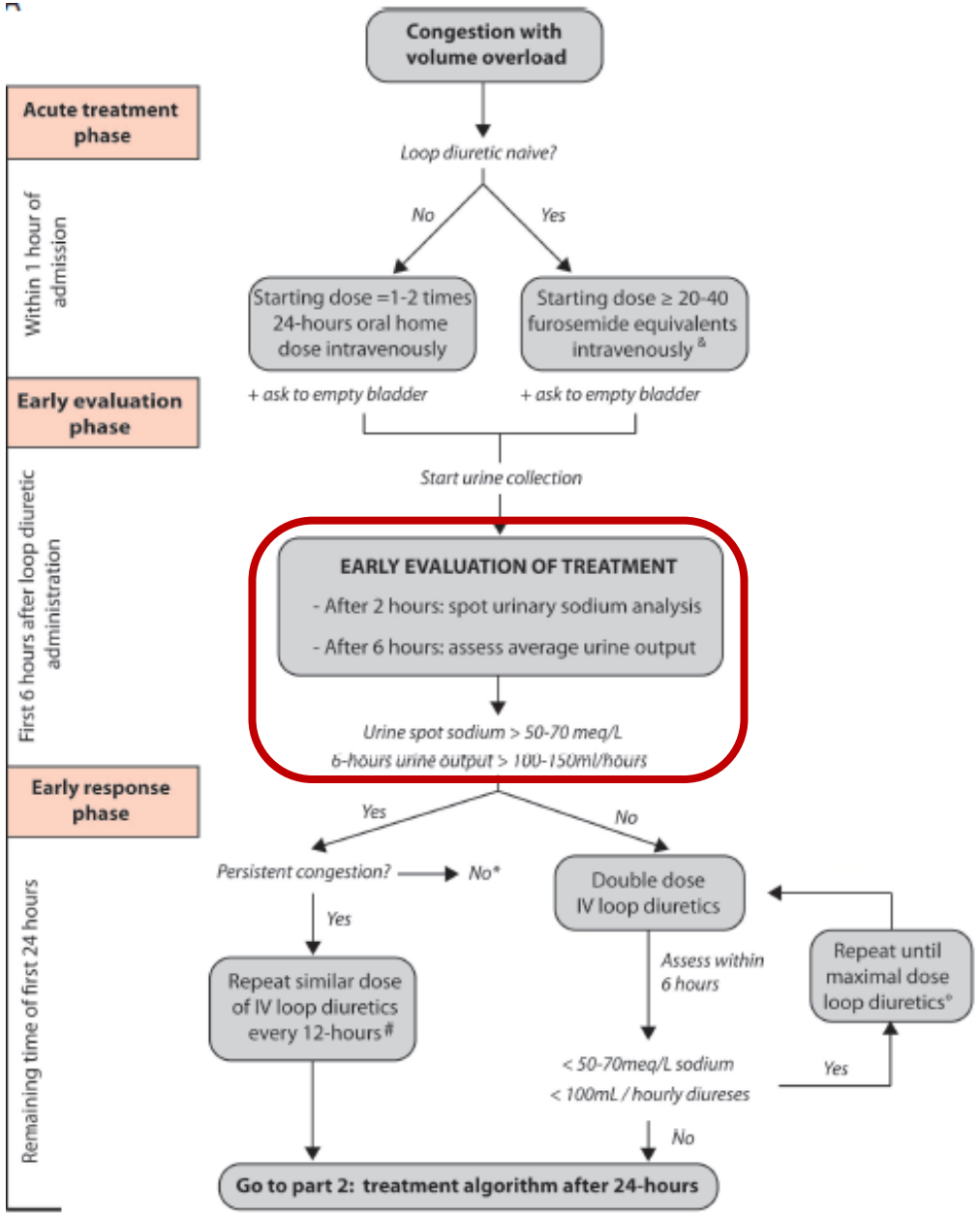
Acetazolamid/chlorthalidone in acute HF related congestion Diuretic Comparison Project (DCP) Study

PROF DILEK URAL, FESC, FHFA
KOÇ UNIVERSITY SCHOOL OF MEDICINE



Mullens W, et al. Eur J Heart Fail 2019;21:137-155.



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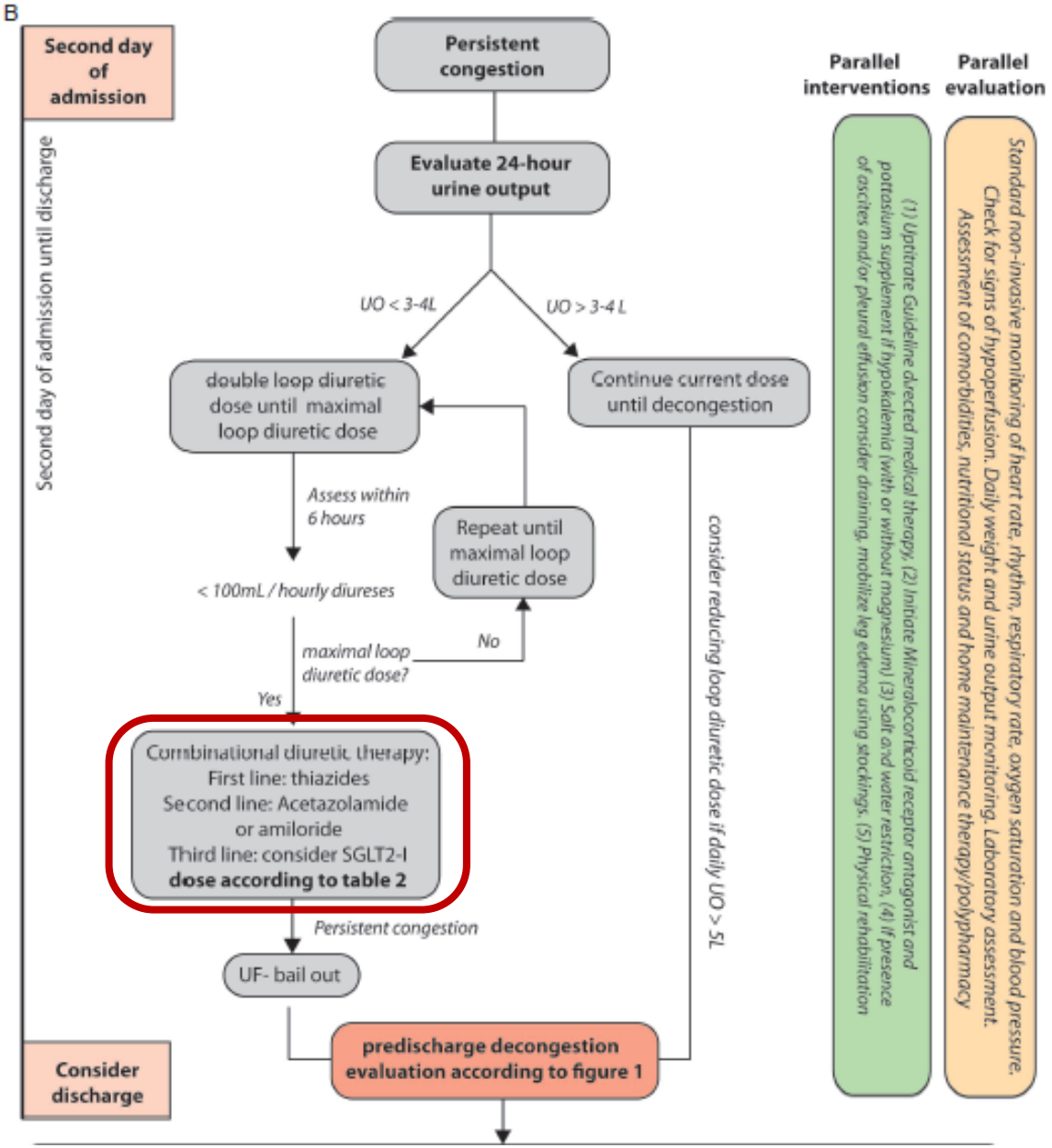
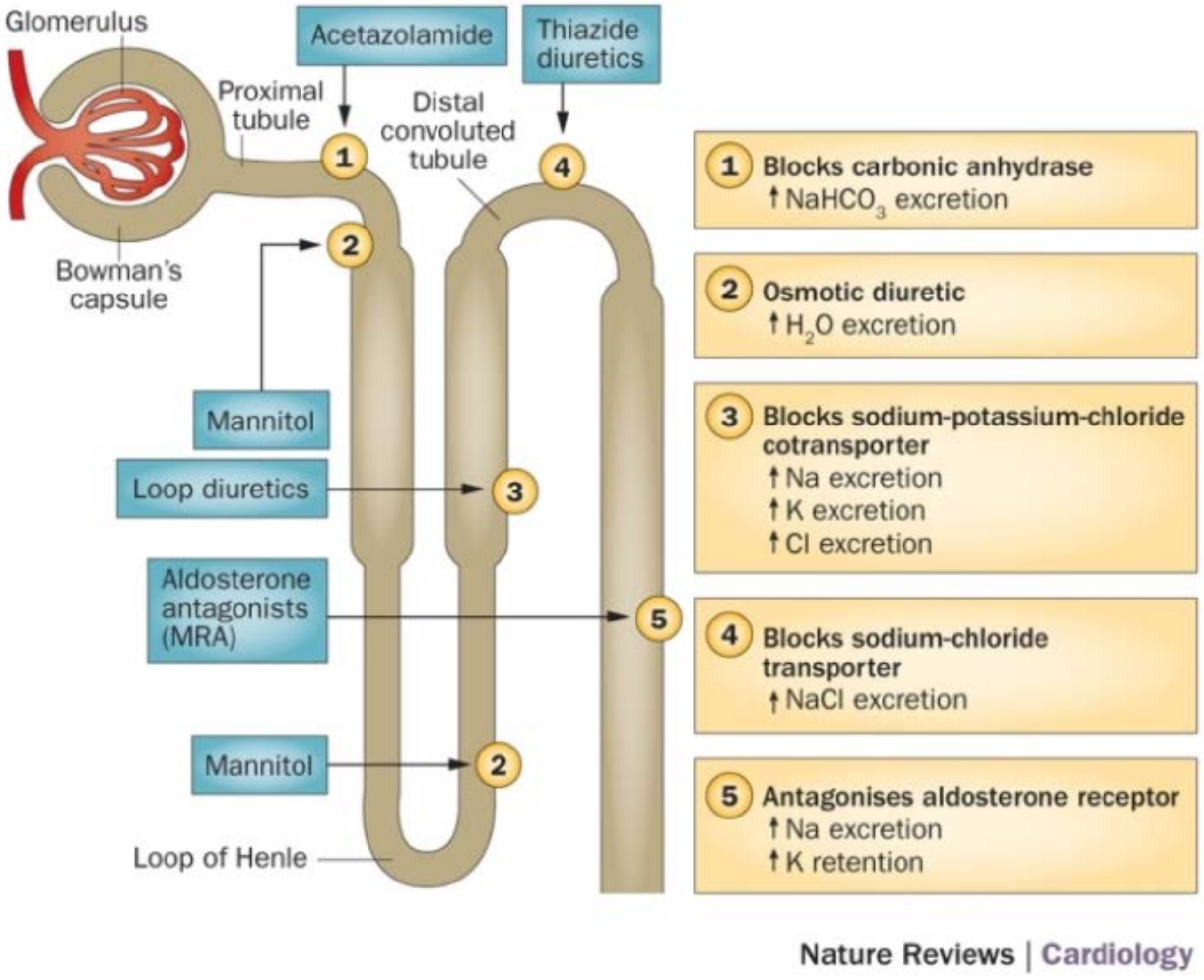


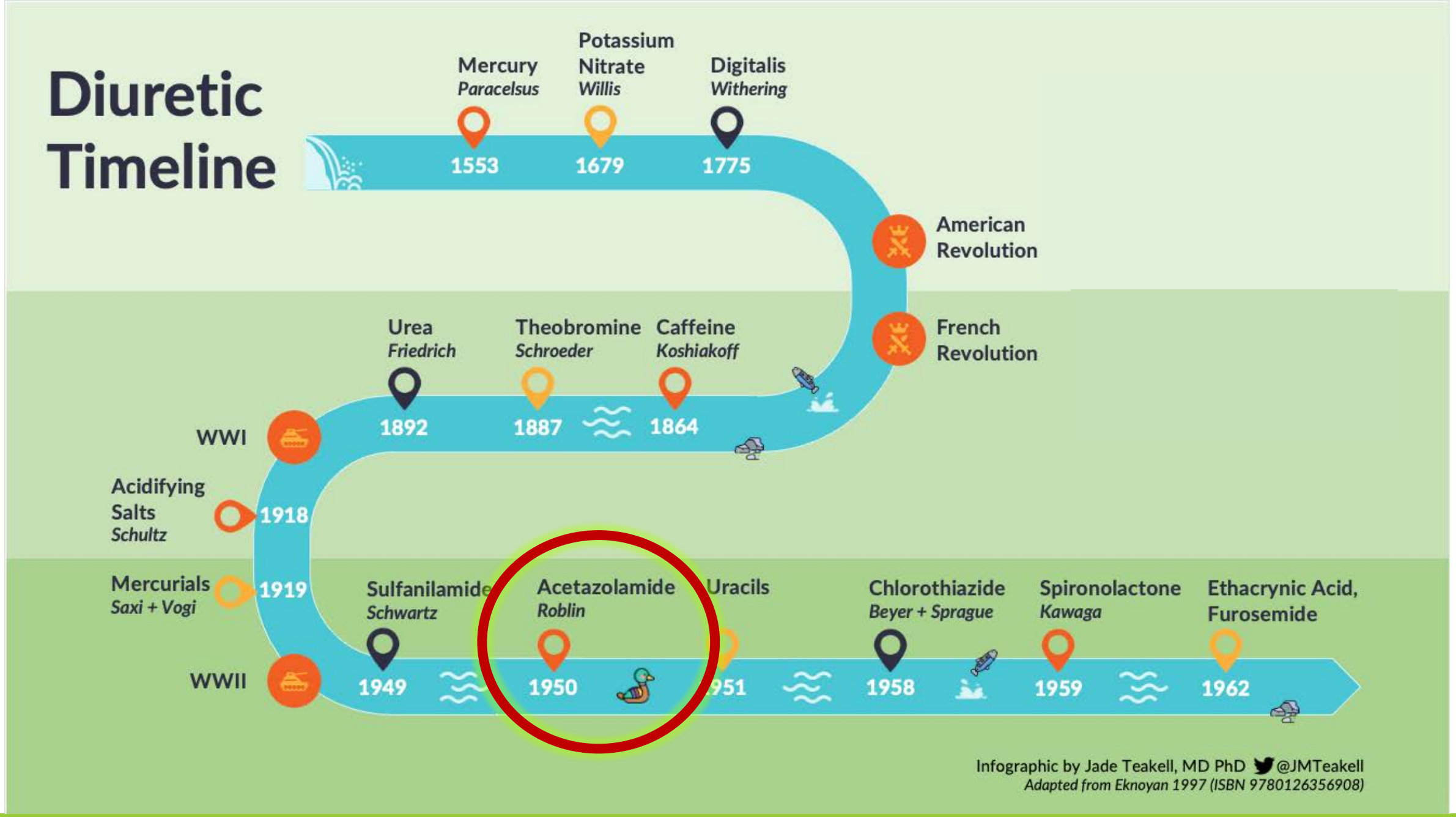
Mullens W, et al. Eur J Heart Fail 2019;21:137-155.

Diüretik kombinasyonu – ardışık nefron blokajı



Konjesyonun Tedavisi
1. 0-6 saat: 2 amp veya Oral x2 furosemit
2. 6-12 saat: Dozu iki katına çıkar
3. 12 + saat: Kombinasyon tedavisine geç 1. adım: + Tiyazid tipi diüretik Yeterli yanıt alınamazsa / veya: 2. adım: + Asetazolamit veya amilorid 3. adım: + MRA veya + Tolvaptan **+ SGLT2i**
4. Renal replasman tedavi

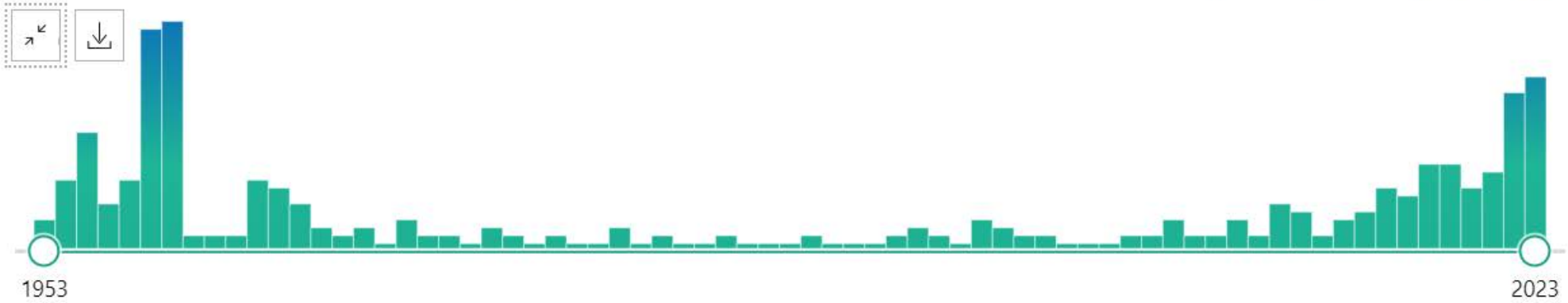
Akut Kalp Yetersizliğinde Asetazolamit


Diuretic Timeline
Mercury
Paracelsus
1553
Potassium Nitrate
Willis
1679
Digitalis
Withering
1775
American Revolution
French Revolution
Urea
Friedrich
1892
Theobromine
Schroeder
1887
Caffeine
Koshiakoff
1864
WWI
Acidifying Salts
Schultz
1918
Mercurials
Saxi + Vogi
1919
WWII
Sulfanilamide
Schwartz
1949
Acetazolamide
Roblin
1950
Uracils
951
Chlorothiazide
Beyer + Sprague
1958
Spironolactone
Kawaga
1959
Ethacrynic Acid, Furosemide
1962
Infographic by Jade Teakell, MD PhD @JMTeakell
Adapted from Eknoyan 1997 (ISBN 9780126356908)

PubMED: acetazolamide «heart failure»

RESULTS BY YEAR

248 results



1 The use of diamox, a carbonic anhydrase inhibitor, as an oral diuretic in patients with congestive **heart failure**.

FRIEDBERG CK, TAYMOR R, MINOR JB, HALPERN M.

N Engl J Med. 1953 May 21;248(21):883-9. doi: 10.1056/NEJM195305212482102.

PMID: 13046634 No abstract available.

Cite

Share

2 Use of a new oral diuretic, diamox, in congestive **heart failure**.

BELSKY H.

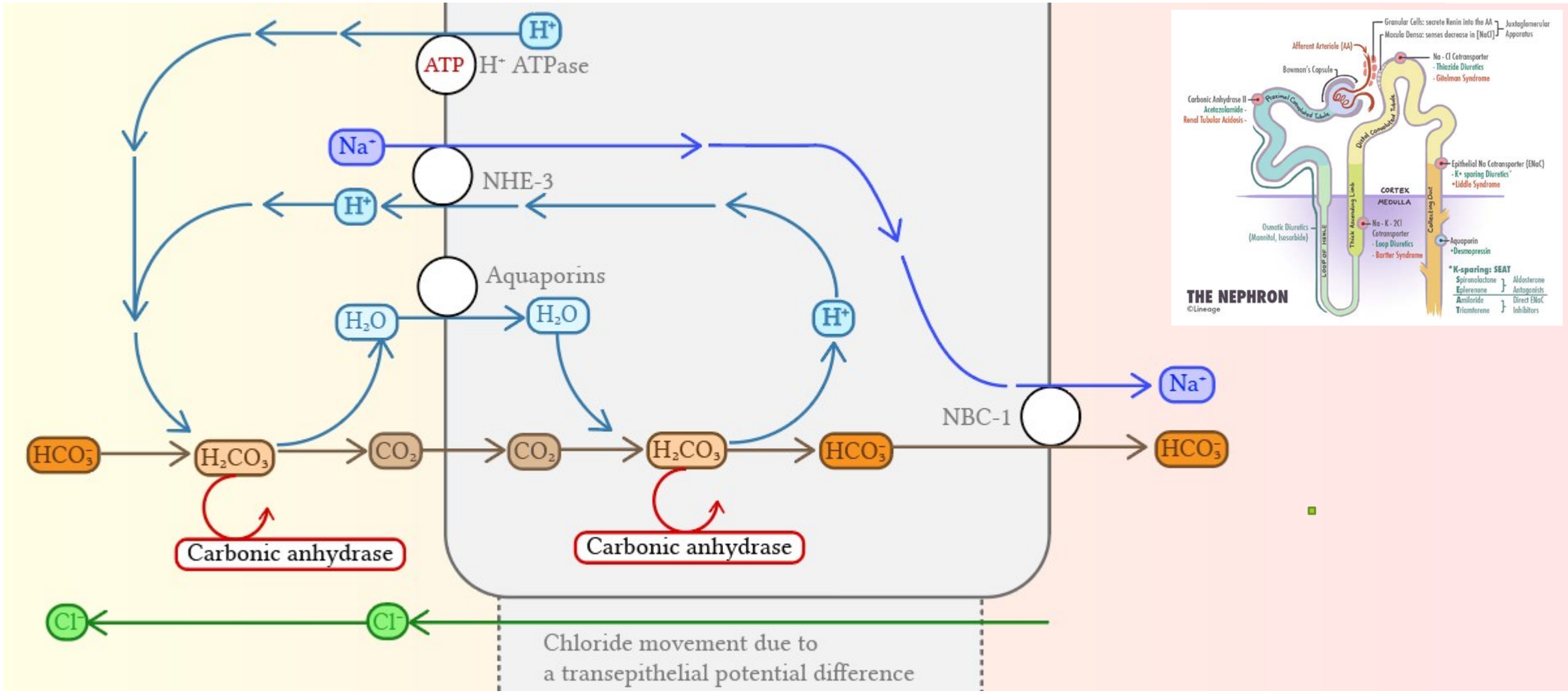
N Engl J Med. 1953 Jul 23;249(4):140-3. doi: 10.1056/NEJM195307232490404.

PMID: 13063701 No abstract available.

Cite

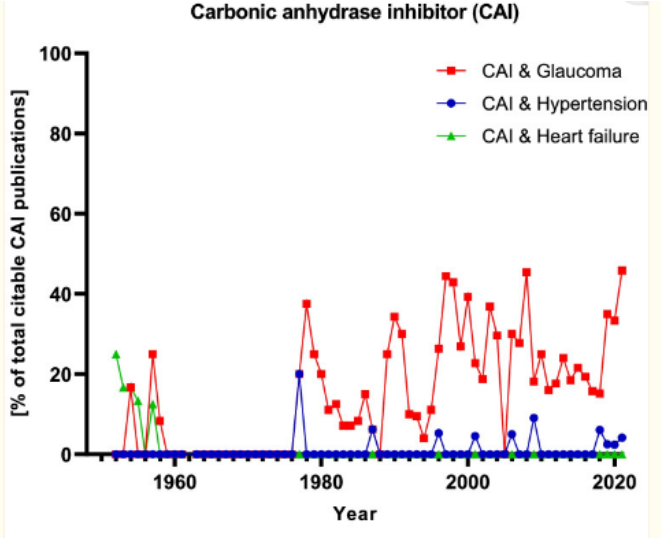
Share

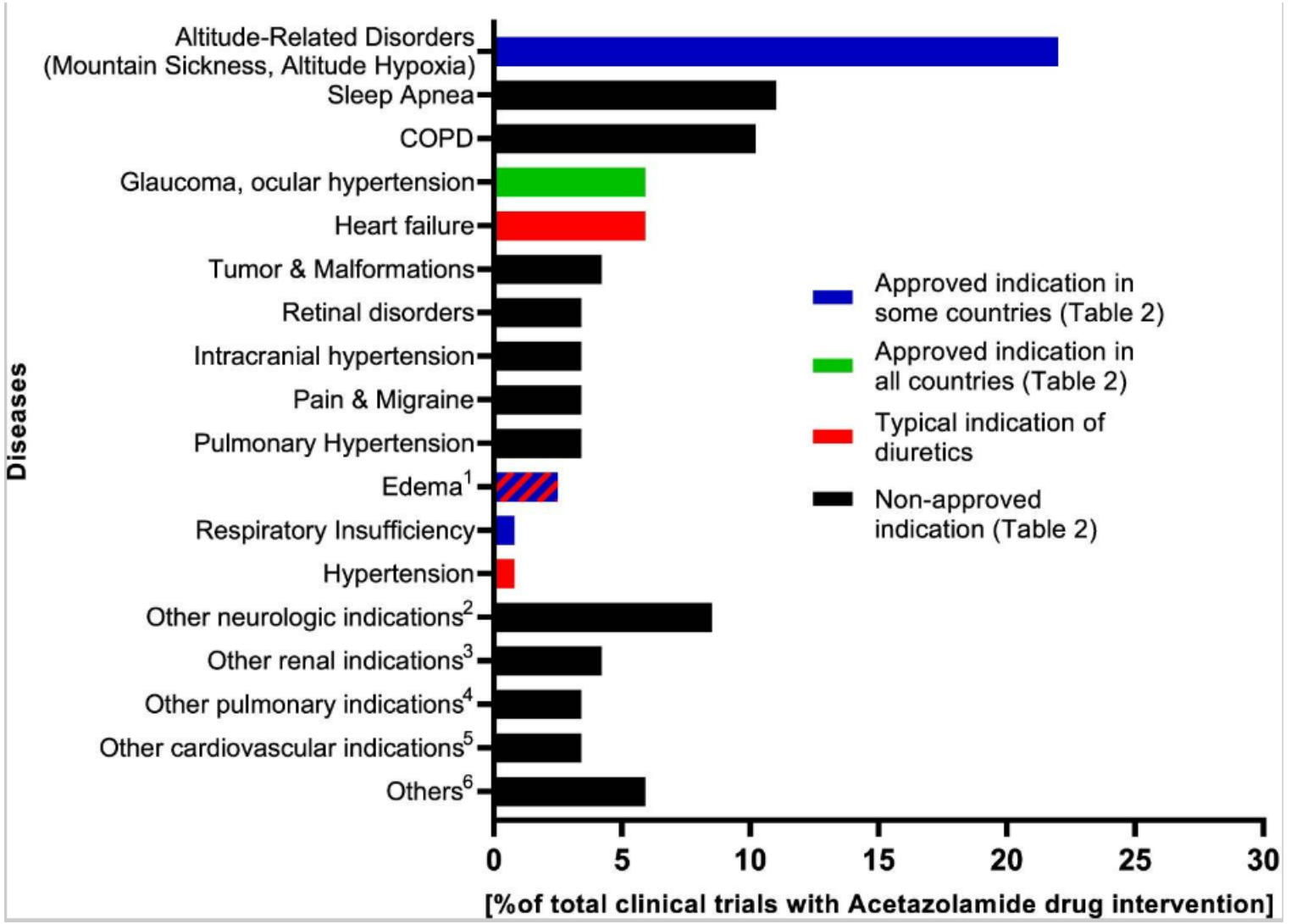
Asetazolamid etki mekanizması



Carbonic anhydrase in the lumen of the proximal tubule of the kidney converts carbonic acid to H2O and CO2. Water and CO2 enter the intracellular space via diffusion. The intracellular carbonic anhydrase enzyme converts water and carbon dioxide back to carbonic acid, which dissociates into H+ and bicarbonate. By inhibition of the enzyme, CAI medications result in the inhibition of the resorption of bicarbonate by the tubular cells, leading to retention of bicarbonate in the tubular lumen.

Klinik kullanım





Kehrenberg MCA, et al. Naunyn Schmiedebergs Arch Pharmacol 2022;395:619-627.

Farmakolojik özellikleri

Yan Etkiler: Metabolik asidoz ve elektrolit değişiklikleri (hipokalemi, hiponatremi), parestezi, yorgunluk, uyuşukluk, depresyon, libido azalması, acı veya metalik tat, mide bulantısı, kusma, karın krampları, ishal, siyah dışkı, poliüri, böbrek taşları.
Az görülen yan etkiler: Stevens-Johnson sendromu, anafilaksi ve kan diskrazileri

Kontrendikasyonlar: Hiperkloremik asidoz, hipokalemi, hiponatremi, adrenal yetmezlik, eGFR <20 ml/dk, asetazolamide veya diğer sülfonamidlere karşı aşırı duyarlılık, ileri karaciğer hastalığı veya fonksiyon bozukluğu

Sürekli kullanımda diüretik etki azalması

Acetazolamide in Decompensated Heart failure with Volume OveRload trial

ADVOR

N = 519

Double-blind, randomized

30 Hospitals in Belgium

Acute heart failure with volume overload

Maintenance loop diuretics for at least 1 month

NTproBNP > 1000 pg/ml

Stratified according to LVEF

High dose loop diuretics + Acetazolamide 500 mg IV

High dose loop diuretics + Matching placebo

Baseline characteristics: elderly heart failure population, well-treated, with a severe degree of volume overload.

Mean age 78 years
63% men
57% LVEF > 40%

Significant degree of volume overload: 78% oedema up to knee or above

Median NT-proBNP 6173 pg/mL

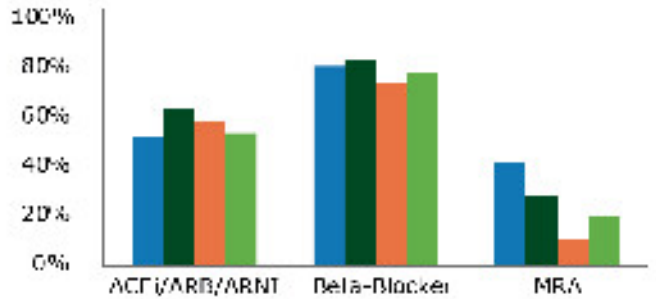
ADVOR
N – 519

DOSE
N = 308

ATHENA
N = 360

CARRESS-HF
N – 188

Overall high baseline heart failure medication prescription, comparable to other large diuretic trials in AHF

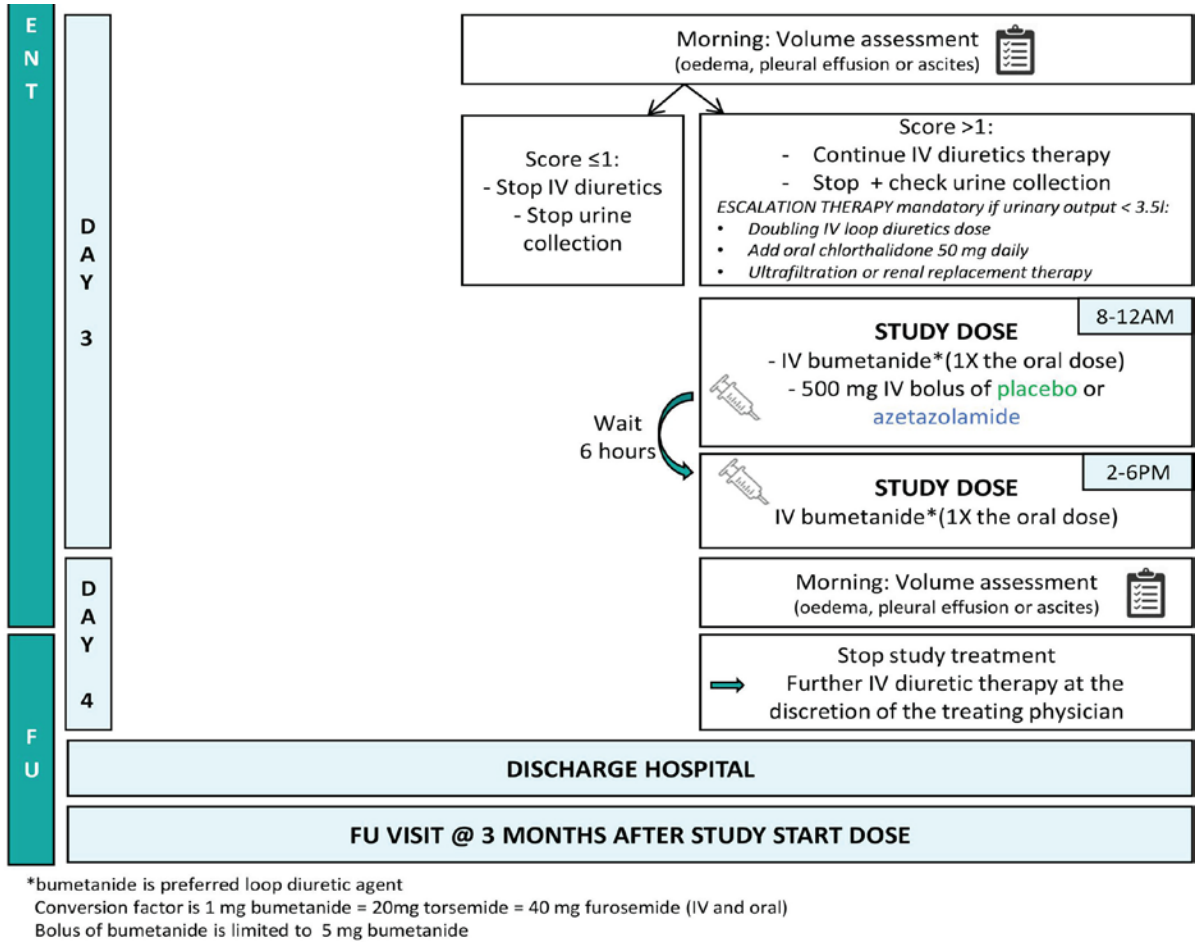


The elderly enrolled population provides a good reflection of the real-world AHF patients in daily clinical practice.

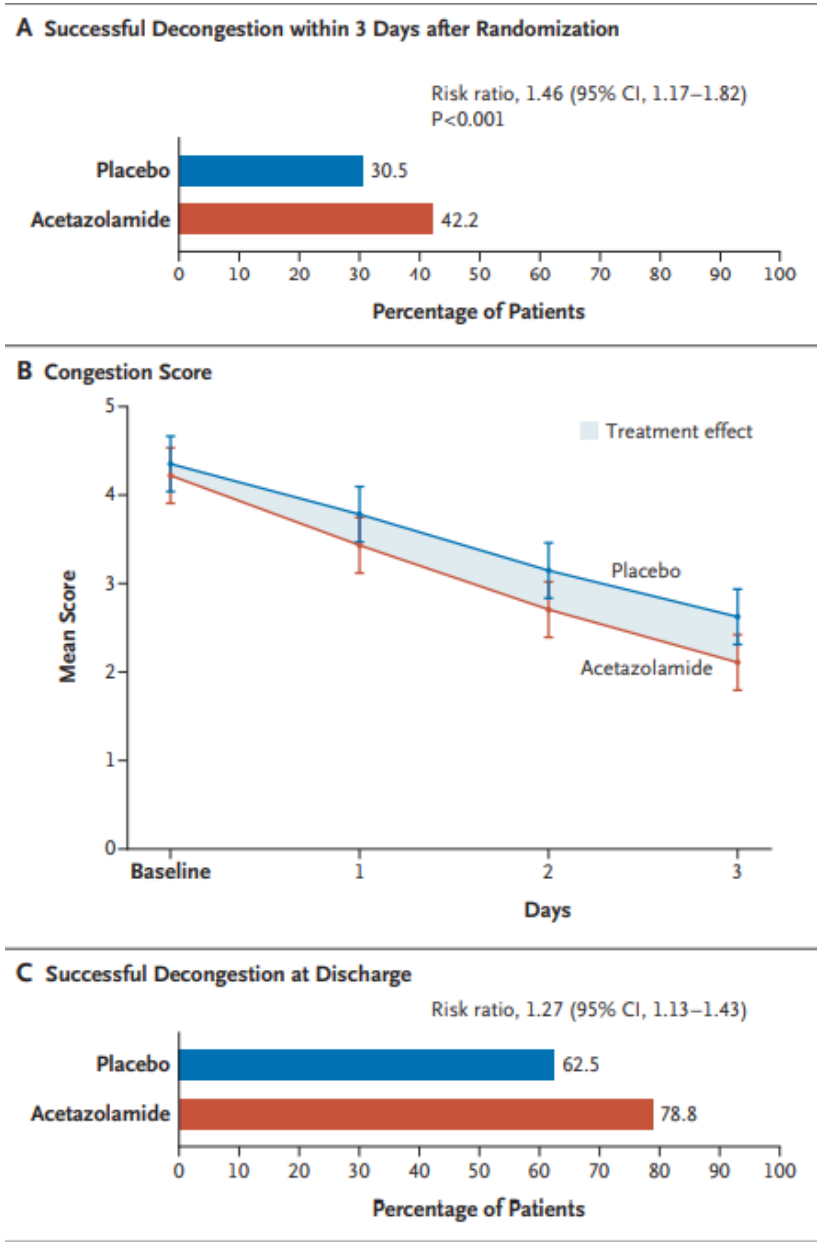
Exclusion: eGFR <20 ml/min

Mullens W, et al. Eur J Heart Fail 2022;24:1601-1610.

Tasarım



All participants received an infusion of 3 grams of magnesium sulfate in 500 ml of 5% dextrose, administered over a period of 24 hours. Additionally, potassium at a dose of 40 mmol was added to the infusions once K < 4 mmol/L - and oral potassium was left to the discretion of the treating team. Similarly, 100 ml of 8.4% $NaHCO_3$ was recommended once HCO_3 was < 20 mmol/L.



Subgroup	Placebo	Acetazolamide	Risk Ratio (95% CI)
	no. of patients/total no.		
Overall	79/259	108/256	1.46 (1.17–1.82)
Age			
≤79 yr	43/130	59/132	1.36 (1.02–1.82)
>79 yr	36/129	49/124	1.56 (1.11–2.21)
Left ventricular ejection fraction			
≤40%	36/111	43/111	1.24 (0.88–1.75)
>40%	43/148	65/145	1.63 (1.22–2.19)
NT-proBNP			
≤6173 pg/ml	51/122	68/132	1.35 (1.06–1.74)
>6173 pg/ml	27/135	38/120	1.61 (1.06–2.44)
Sex			
Female	37/104	36/88	1.21 (0.86–1.71)
Male	42/155	72/168	1.67 (1.24–2.25)
Estimated GFR			
<39 ml/min/1.73 m^2	33/135	53/125	1.77 (1.25–2.50)
≥39 ml/min/1.73 m^2	46/124	55/131	1.23 (0.92–1.65)
Cause of heart failure			
Ischemic	37/113	48/118	1.35 (0.97–1.87)
Nonischemic	42/146	60/138	1.57 (1.16–2.12)
Home maintenance loop diuretic dose			
≤60 mg furosemide equivalent	42/136	67/127	1.78 (1.33–2.36)
>60 mg furosemide equivalent	37/123	41/129	1.08 (0.76–1.55)
Baseline congestion score			
≤4	60/145	82/155	1.38 (1.10–1.74)
>4	19/114	26/101	1.62 (0.96–2.73)
Atrial fibrillation			
No	20/71	31/71	1.76 (1.14–2.72)
Yes	59/188	77/185	1.35 (1.04–1.75)

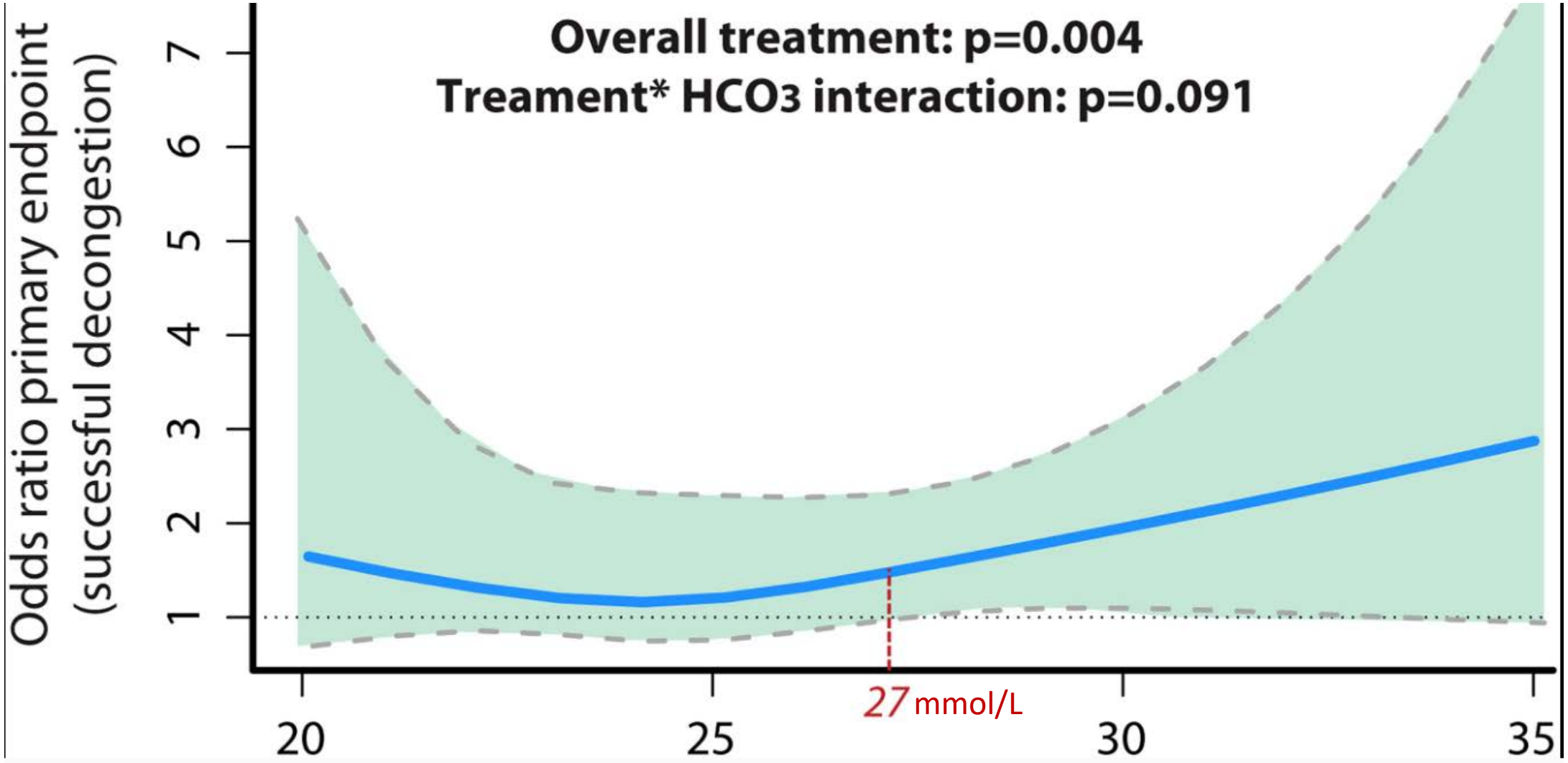
Mullens W, et al. N Engl J Med 2022;387:1185-1195.

Güvenlilik

Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Adverse events				
During treatment phase — no. (%)				
Combined renal safety end point	2 (0.8)	7 (2.7)	—	0.10
Doubling of serum creatinine level from baseline	0	2 (0.8)	—	0.24
≥50% sustained decrease in estimated GFR	1 (0.4)	4 (1.6)	—	0.21
Renal-replacement therapy during index hospitalization	1 (0.4)	4 (1.6)	—	0.21
Severe metabolic acidosis¶	0	0	—	—
Hypokalemia‖	10 (3.9)	14 (5.5)	—	0.39
Hypotension**	9 (3.5)	17 (6.6)	—	0.11
During 3 mo of follow-up — no. (%)				
Serious adverse event	124 (47.9)	123 (48.0)	—	1.00
Adverse event related to placebo or acetazolamide	3 (1.2)	8 (3.1)	—	0.14
Cardiovascular adverse event	122 (47.1)	113 (44.1)	—	0.53

Mullens W, et al. N Engl J Med 2022;387:1185-1195.

Bazal HCO_3^- atılımının etkisi



The treatment response is magnified in patients with baseline or loop diuretic-induced elevated venous HCO3 (marker of proximal nephron NaHCO3 retention) by specifically counteracting this component of diuretic resistance.

Martens P, et al. Eur Heart J 2023 Jun 9;44(22):1995-2005.

Oral ve IV asetazolamid

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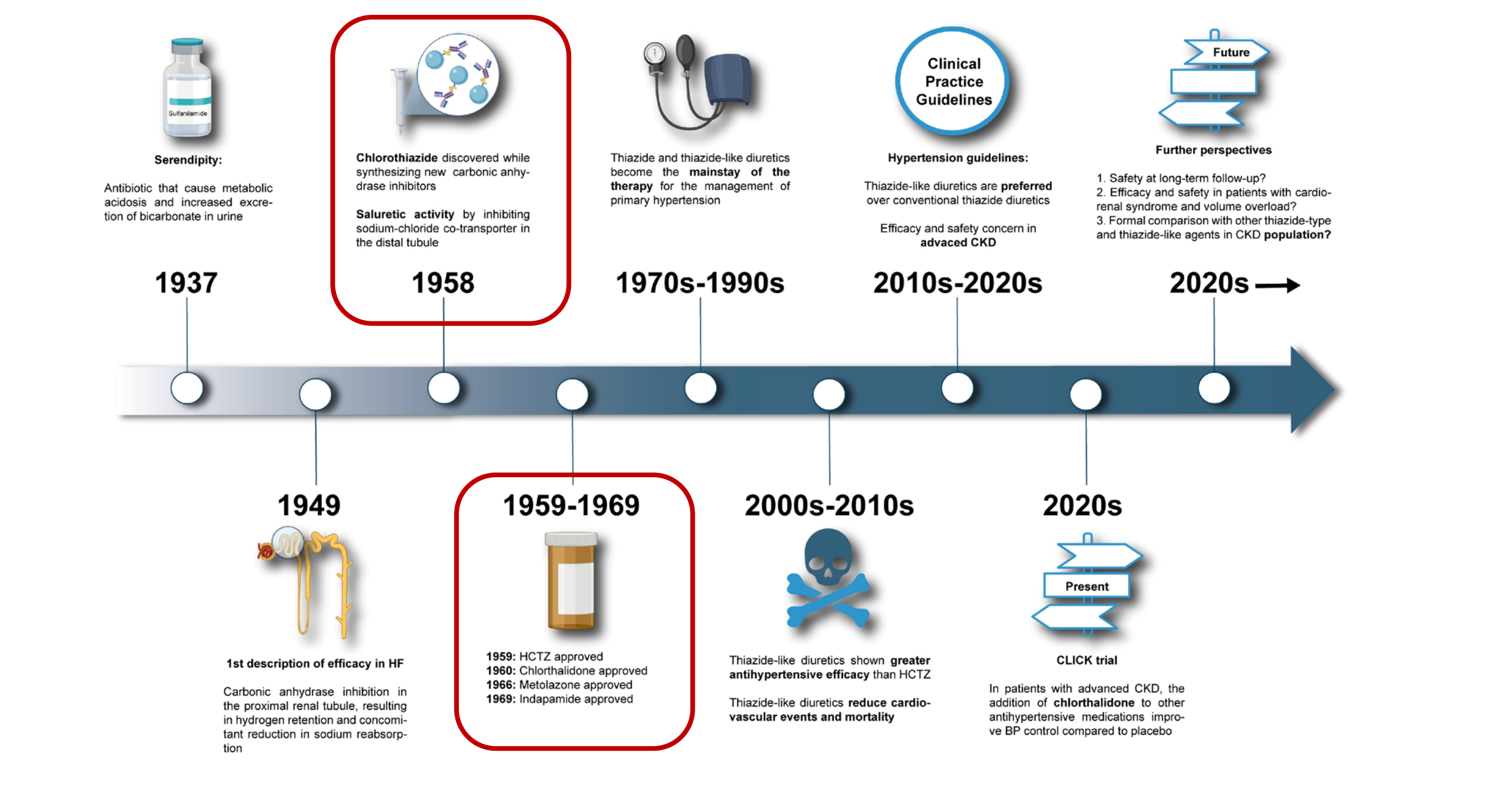
Akut Kalp Yetersizliğinde Tiyazid Grubu Diüretikler



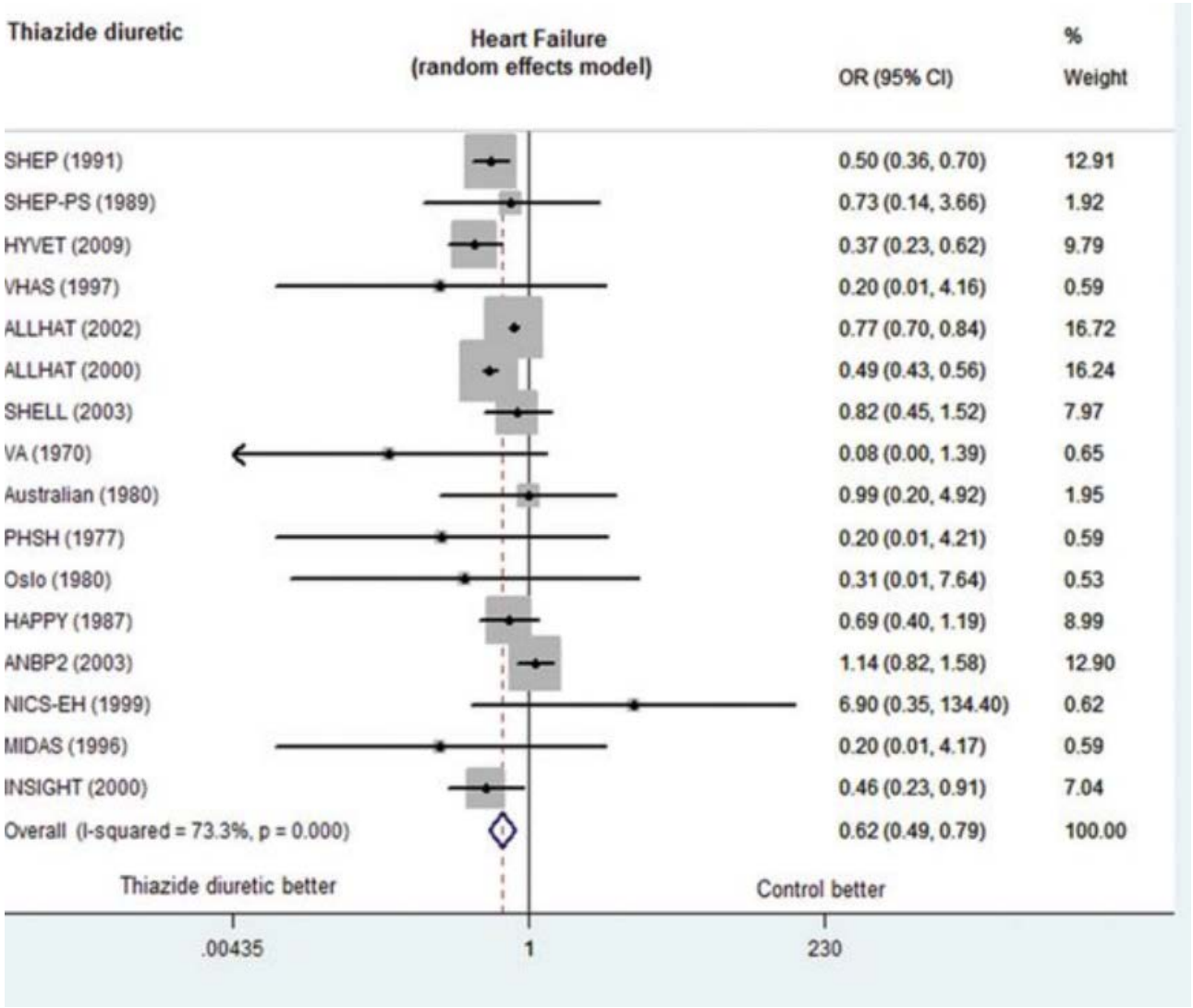
de la Espriella R, et al. Thiazides in chronic kidney disease: "back to the future". Clin Kidney J 2022;16:1-4.

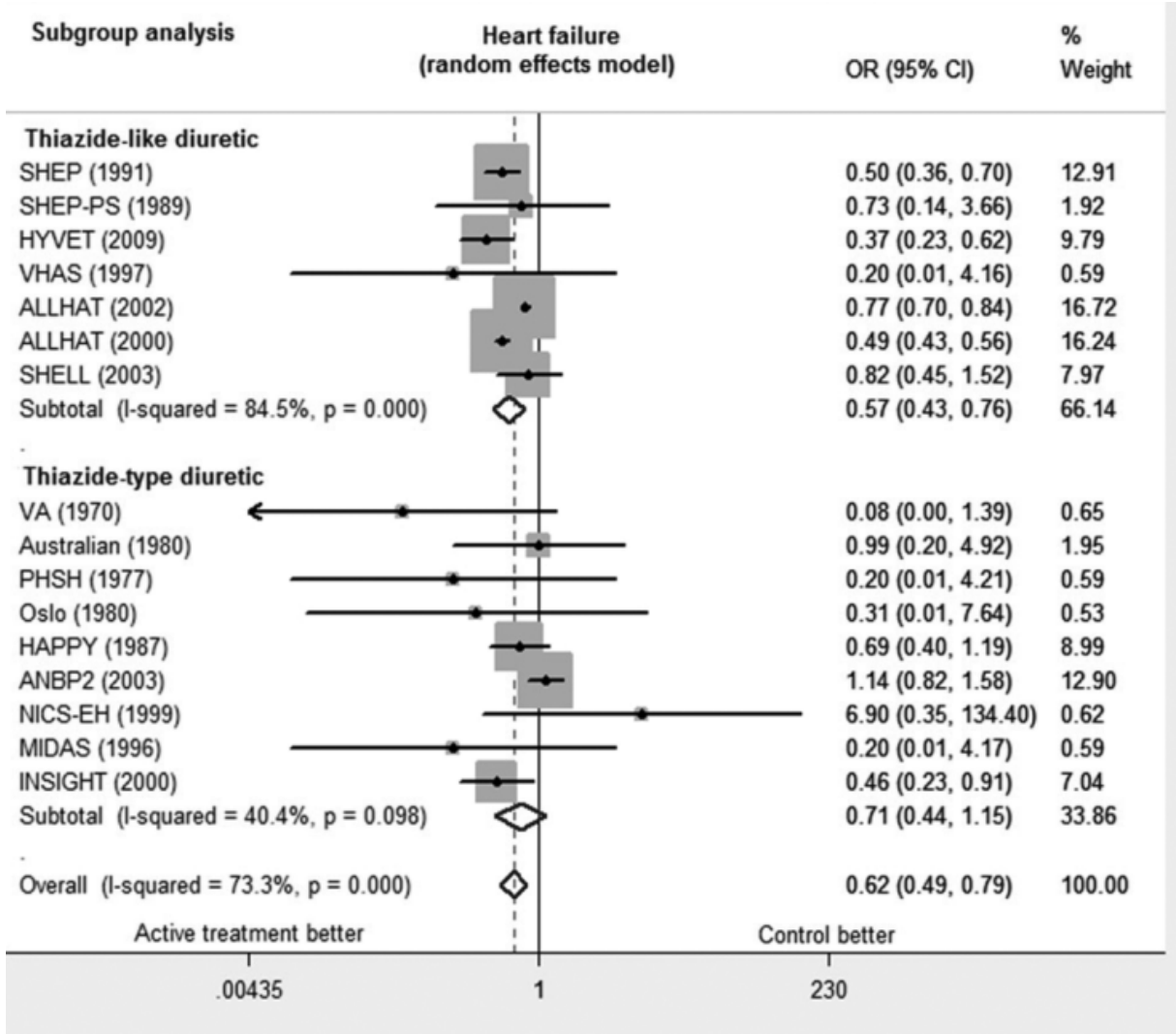
Farmakolojik Özellikler

Thiazide-Type Diuretic	Equipotent Dose, mg	Maximum Daily Dose, mg	Duration of Action
Bendroflumethiazide*	2.5	20	12–24 h (up to 48 h)†
Chlorothiazide	250	1,000	6–12 h (up to 24 h)†
Chlorthalidone	12.5	100	24–72 h†
Hydrochlorothiazide	25	200	6–12 h (up to 24 h)†
Indapamide	2.5	5	36 h
Methylclothiazide	2.5	20	24 h
Metolazone	2.5	20	12–24 h (up to 48 h)†
Quinethazone*	25	200	12–24 h†

Jentzer JC, et al. J Am Coll Cardiol 2010;56:1527-34.

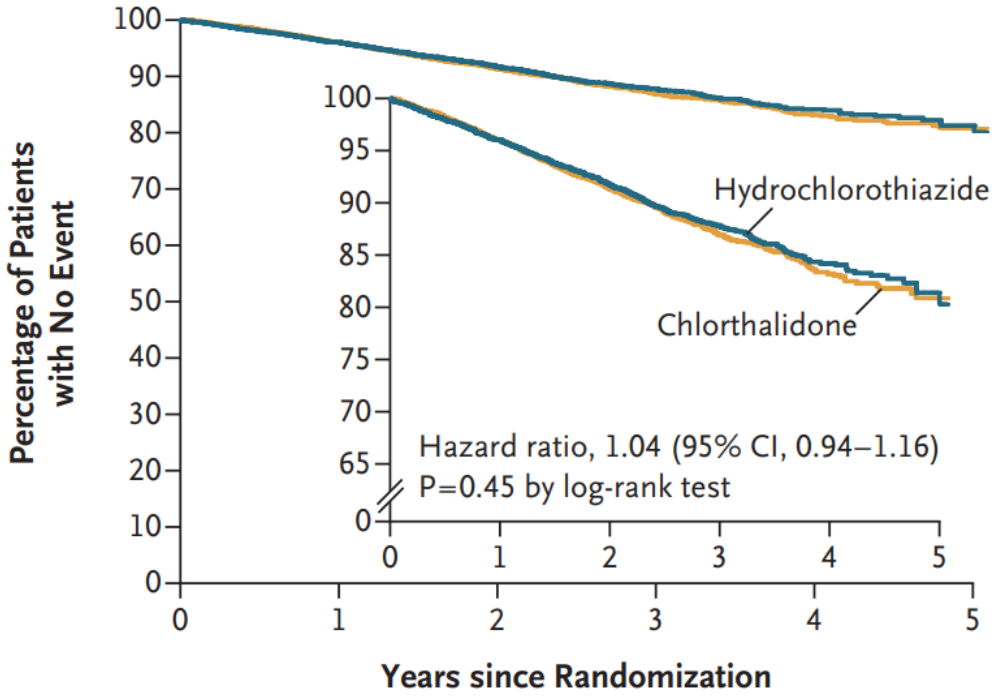
KY gelişimini önlemek için tiyazidler



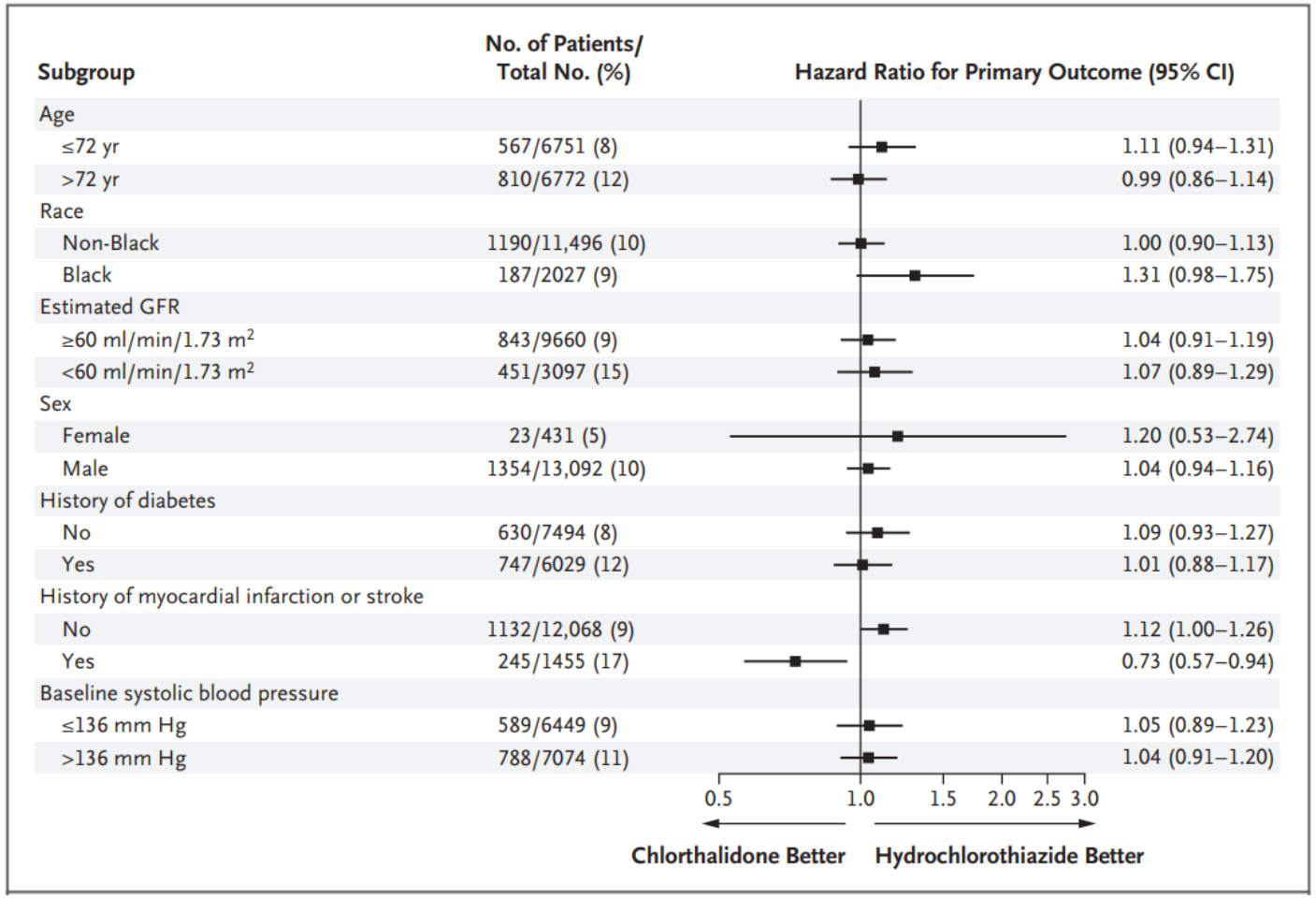


Chen P, et al. Am J Hypertens 2015;28:1453-63.

Diuretic Comparison Project



Yaşı ≥65 yıl (n = 13,523) ve HCTZ 25 – 50 mg/gün kullanan hastalar tedaviye devam etme veya klortalidon 12.5 - 25 mg/güne geçme gruplarına randomize edildi. Birincil sonlanım; nonfatal MI, inme, kalp yetersizliği, acil revaskülarizasyon ve kanser dışı ölüm idi.



Diuretic Comparison Project

Outcome	Chlorthalidone (N=6756)	Hydrochlorothiazide (N=6767)	Hazard Ratio (95% CI)†
Primary composite outcome — no. (%)‡	702 (10.4)	675 (10.0)	1.04 (0.94–1.16)§
Secondary outcomes: components of the primary outcome — no. (%)			
MI	142 (2.1)	140 (2.1)	1.02 (0.80–1.28)
Stroke	83 (1.2)	83 (1.2)	1.00 (0.74–1.36)
Hospitalization due to heart failure	242 (3.6)	232 (3.4)	1.04 (0.87–1.25)
Unstable angina leading to urgent coronary revascularization	20 (0.3)	13 (0.2)	1.54 (0.77–3.10)
Non–cancer-related death	359 (5.3)	354 (5.2)	1.01 (0.88–1.17)
Death from any cause — no. (%)	446 (6.6)	448 (6.6)	1.00 (0.87–1.13)
Expected adverse events — no. (%)			
New allergic or adverse reaction to thiazide-type diuretic	109 (1.6)	21 (0.3)	5.23 (3.28–8.35)
Hypokalemia	406 (6.0)	298 (4.4)	1.38 (1.19–1.60)

Ishani A, et al. N Engl J Med. 2022;387:2401-2410.

CLOROTIC Çalışması

Study population

Randomized, double-blind, placebo-controlled clinical trial

History of chronic heart failure

Treatment with oral furosemide (80-240 mg/day)

Admission for acute decompensation

230 patients were randomized to 5 days of oral treatment with hydrochlorothiazide or placebo

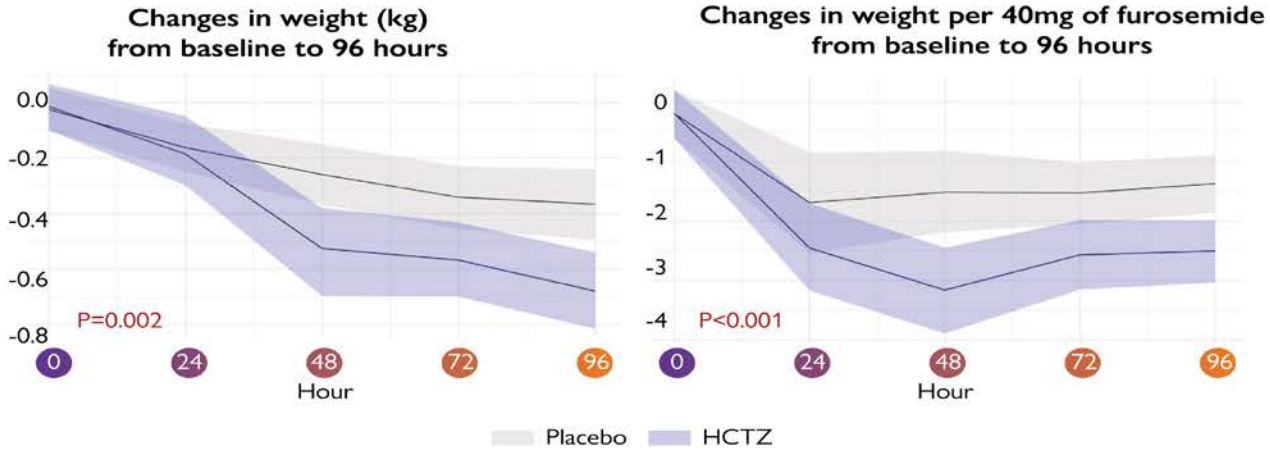
83 years-old

48% women

Comorbidities

HF-PEF 65%

Efficacy



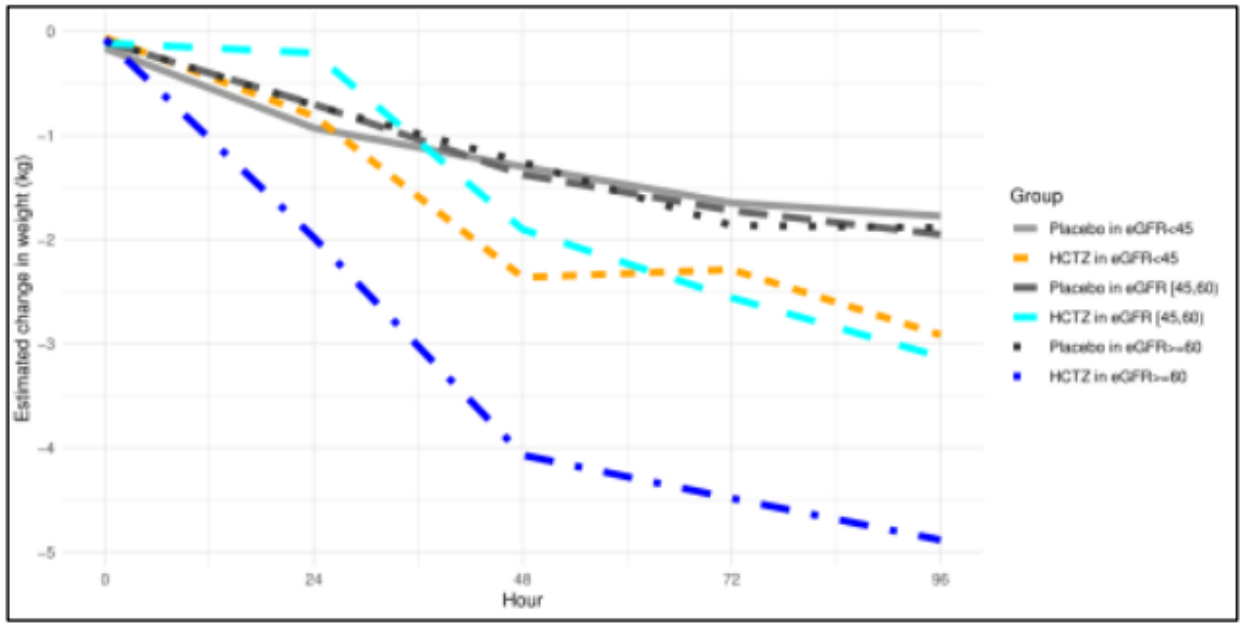
Safety	Placebo	HCTZ	p-value
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Impaired renal function (serum creatinine and eGFR)	20 (17.2%)	53 (46.5%)	<0.001
Hyponatraemia (Na+ ≤ 130 mmol/L) - (Na+ ≤ 125 mmol/L)	6 (5.2%)–2 (1.7%)	10 (8.8%)–3 (2.6%)	0.416–0.682
Hypokalaemia (K+ ≤ 3.0 mmol/L) - (K+ ≤ 2.5 mmol/L)	18 (16.1%)–0 (0.0%)	43 (40.6%)–2 (1.8%)	<0.001–0.245
Serious adverse events	27 (23.3%)	26 (22.8%)	0.93

Oral HCTZ and placebo doses were adjusted according to GFR, estimated using the MDRD formula, as follows:>50 mL/min: 25 mg daily; 20–50 mL/min: 50 mg daily; and <20 mL/min: 100 mg daily. Patients received the same HCTZ (or placebo) dose during the treatment period, and up-titration or down-titration was not permitted at investigators discretion. The dose of HCTZ (or placebo) could only be adjusted based on changes in glomerular filtration rate observed during the treatment period.

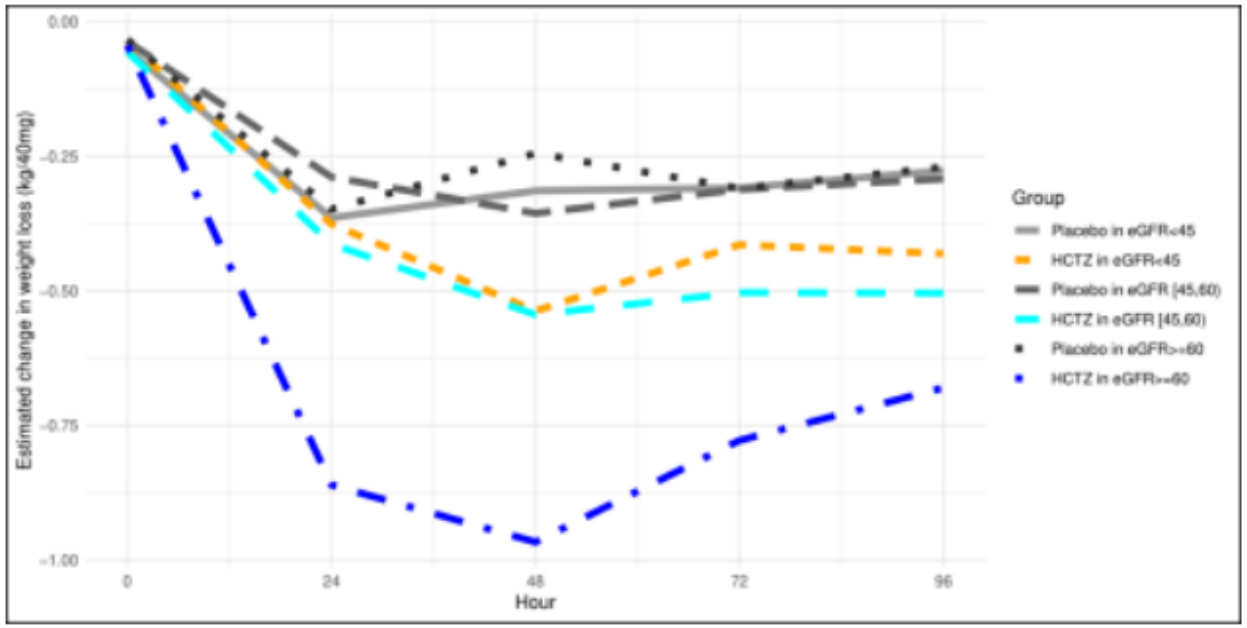
Trulls JC, et al. Eur Heart J 2023;44(5):411-421.

CLOROTIC Çalışmasında Böbrek İşlevleri

Weight loss



Weight loss per 40mg of furosemide



45 to 59 ml/min/1.73m^2	-1.2 [-2.1 to -0.7]	-2.5 [-3.3 to -0.9]	-1.3 [-2.3 to 0.2]	0.246
≥ 60 ml/min/1.73m^2	-1.6 [-2.9 to -1.2]	-3.7 [-4.8 to -2.7]	-2.1 [-3.0 to -0.5]	

Çalışma hastalarının >%50'sinde eGFR < 45 ml/dk idi. HCTZ ile yanıt GFR daha iyi olan hastalarda daha fazlaydı.

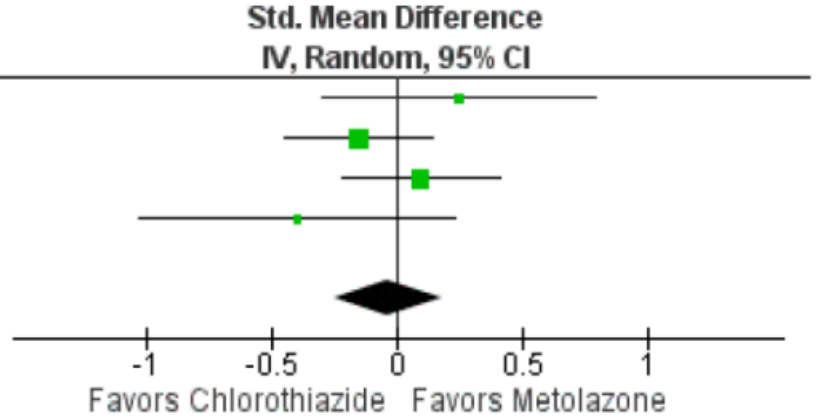
Trullas JC, et al. CLOROTIC Trial. HFA 2023

Metolazone ve klorotiyazid karşılaştırması

Net idrar çıkışı

Study or Subgroup	Weight	IV, Random, 95% CI	Year
Moranville 2015	14.3%	0.25 [-0.30, 0.79]	2015
Shulenberger 2016	39.3%	-0.15 [-0.45, 0.14]	2016
Bohn 2019	35.5%	0.09 [-0.22, 0.41]	2019
Cox 2020	10.9%	-0.40 [-1.02, 0.23]	2020
Total (95% CI)	**100.0%**	**-0.04 [-0.25, 0.18]**	

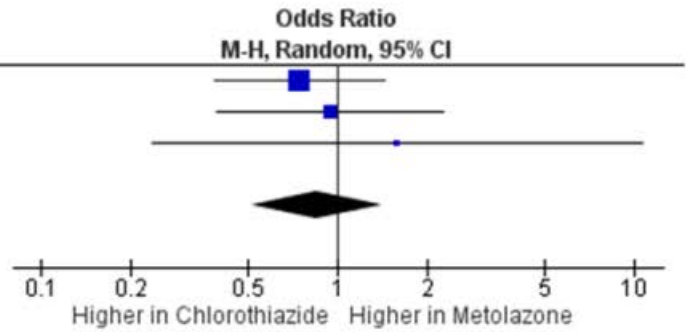
Heterogeneity: Tau² = 0.01; Chi² = 3.56, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 0.32 (P = 0.75)



Hipokalemi

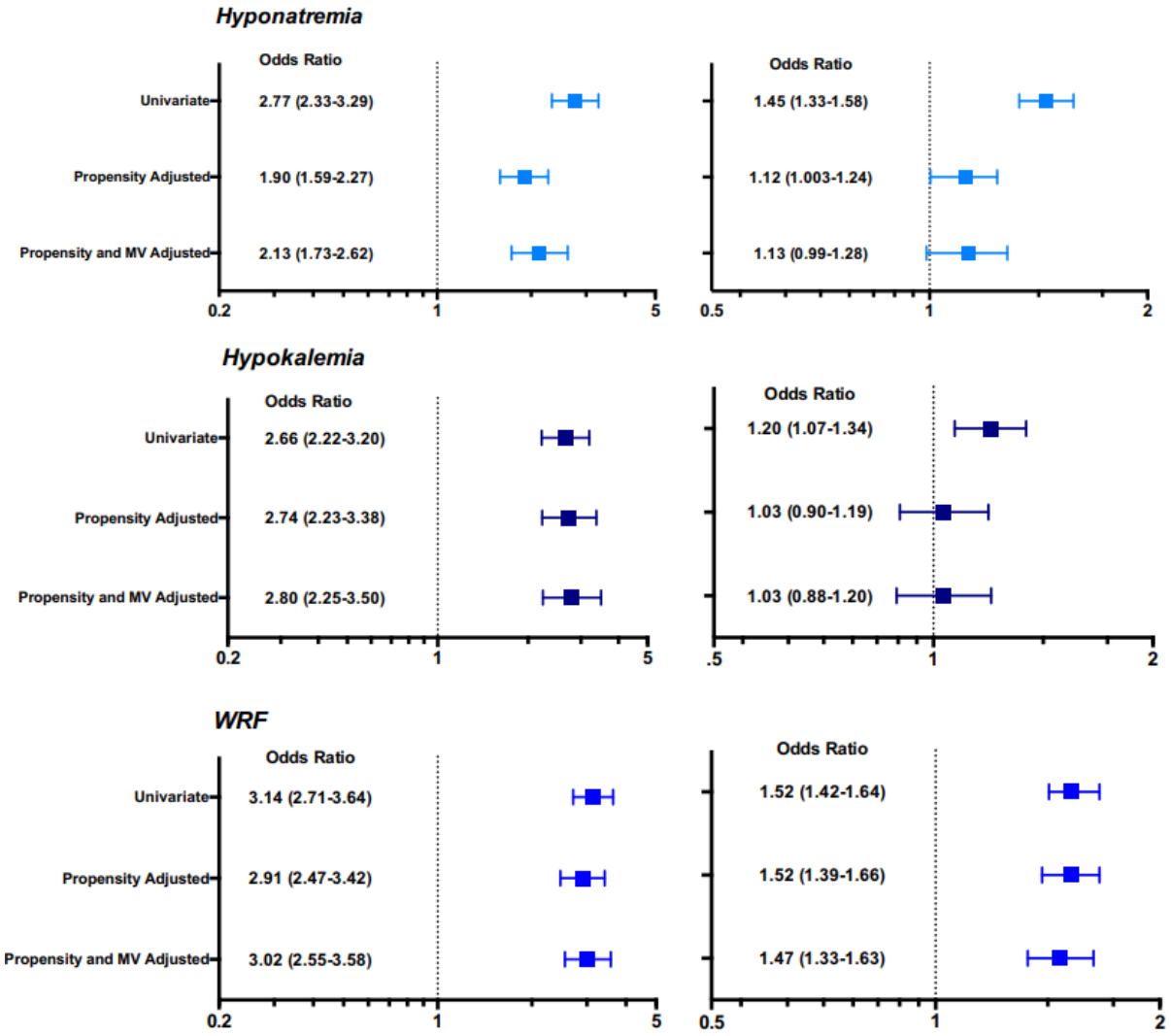
Study or Subgroup	Metolazone Events	Metolazone Total	Chlorothiazide Events	Chlorothiazide Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Shulenberger 2016	22	89	27	88	59.3%	0.74 [0.38, 1.44]	2016
Bohn 2019	9	60	17	108	33.6%	0.94 [0.39, 2.27]	2019
Cox 2020	3	20	2	20	7.1%	1.59 [0.24, 10.70]	2020
Total (95% CI)		**169**		**216**	**100.0%**	**0.85 [0.51, 1.41]**	
Total events	34		46				

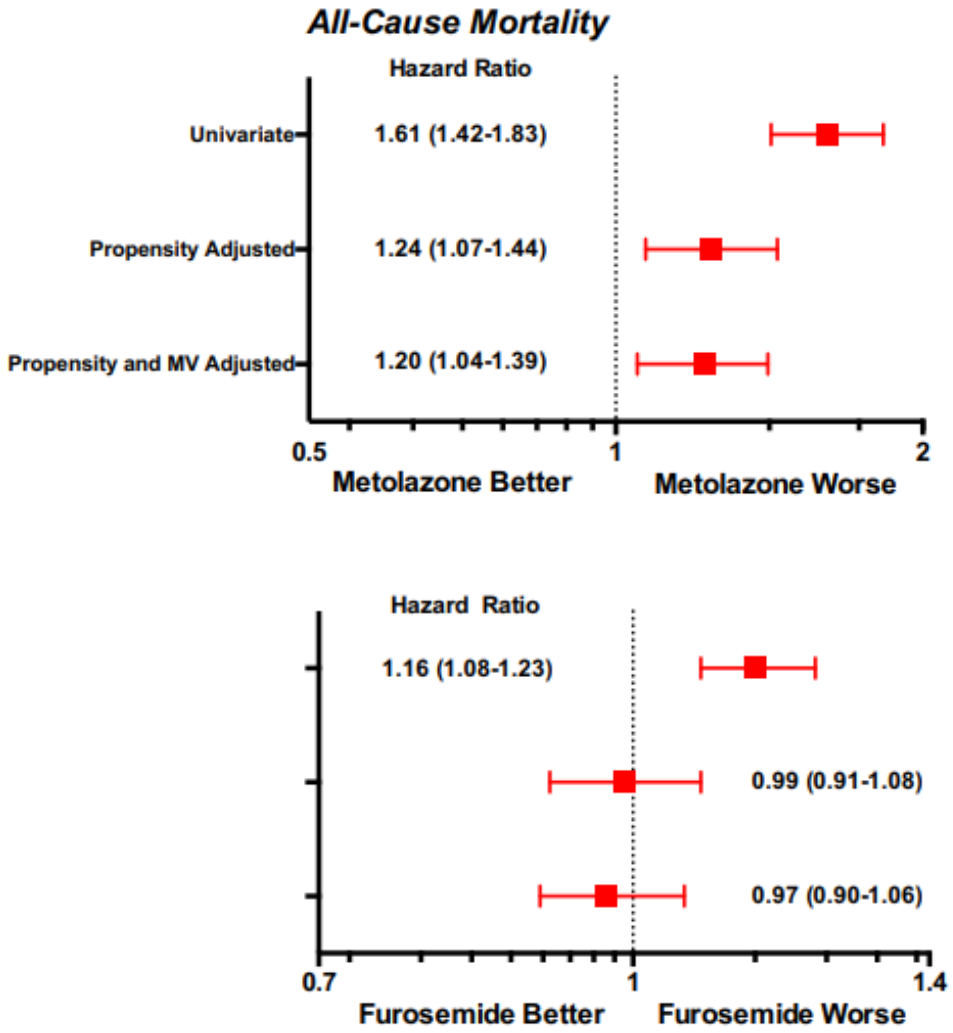
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



Steuber TD, et al. Pharmacotherapy 2020;40:924-935.

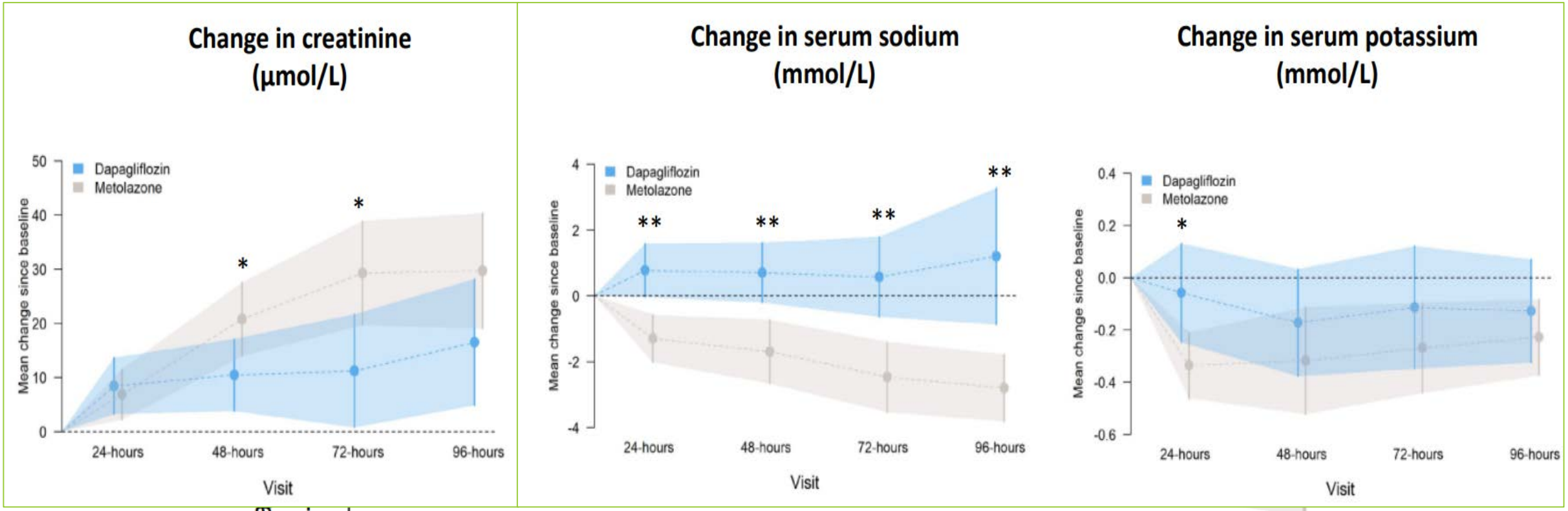
Metalazone





Brisco-Bacik MA, Tet al. J Am Heart Assoc 2018;7:e009149.

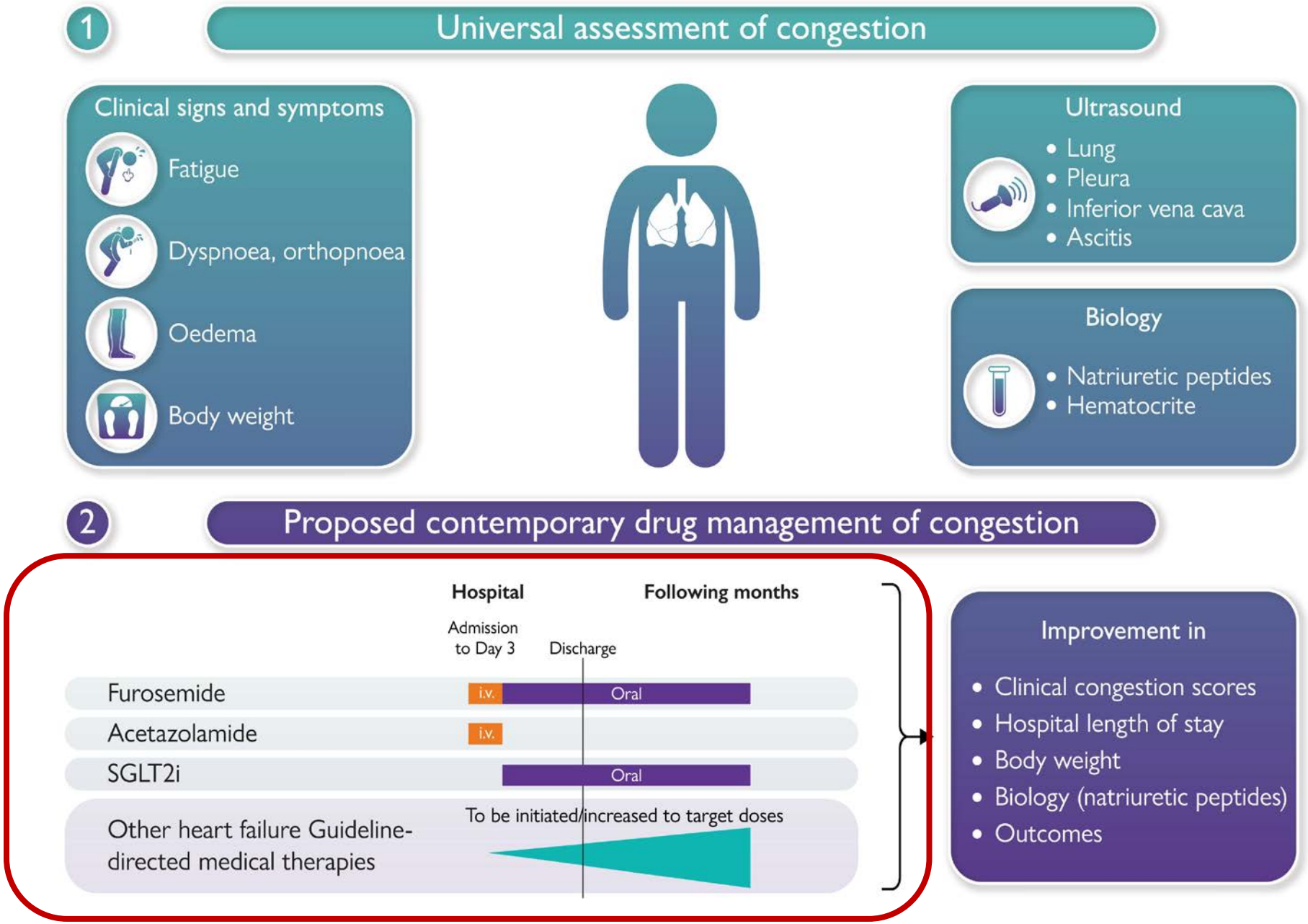
DAPA-RESIST: Metolazone – Dapagliflozin



Dapagliflozin
Metolazone
24-hours
48-hours
72-hours
96-hours

N=61; Ern Yeoh S, et al. Eur Heart J 2023 May 21:ehad341.

Akut KY'de konjesyonun tedavisi



Mebazaa A, et al. Eur Heart J 2023;44:51-53.

ESC 2021

Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[145]	I	C
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[145]	IIa	B

ESC/HFA 2021~~/3~~ ??

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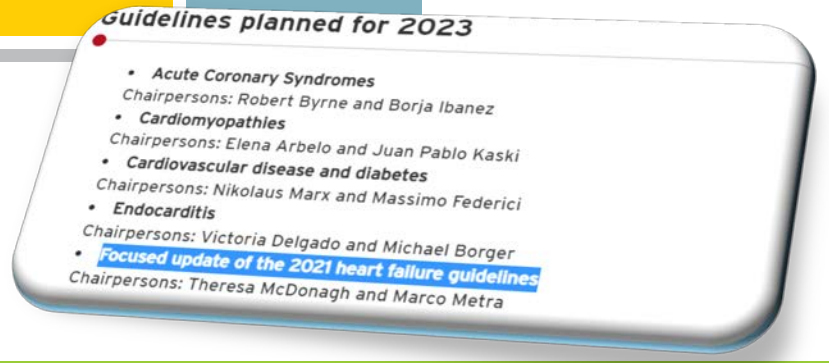
acetazolamide (or thiazide type diuretic, if acetazolamide could not be used)



CONGESTION

THERAPIES

TƏŞƏKKÜRLƏR