Diuretic resistance

Dr. András Tislér

Semmelweis University Department. of Internal Medicine and Oncology
August, 2023

SEMMELWEIS
EGYETEM 1769

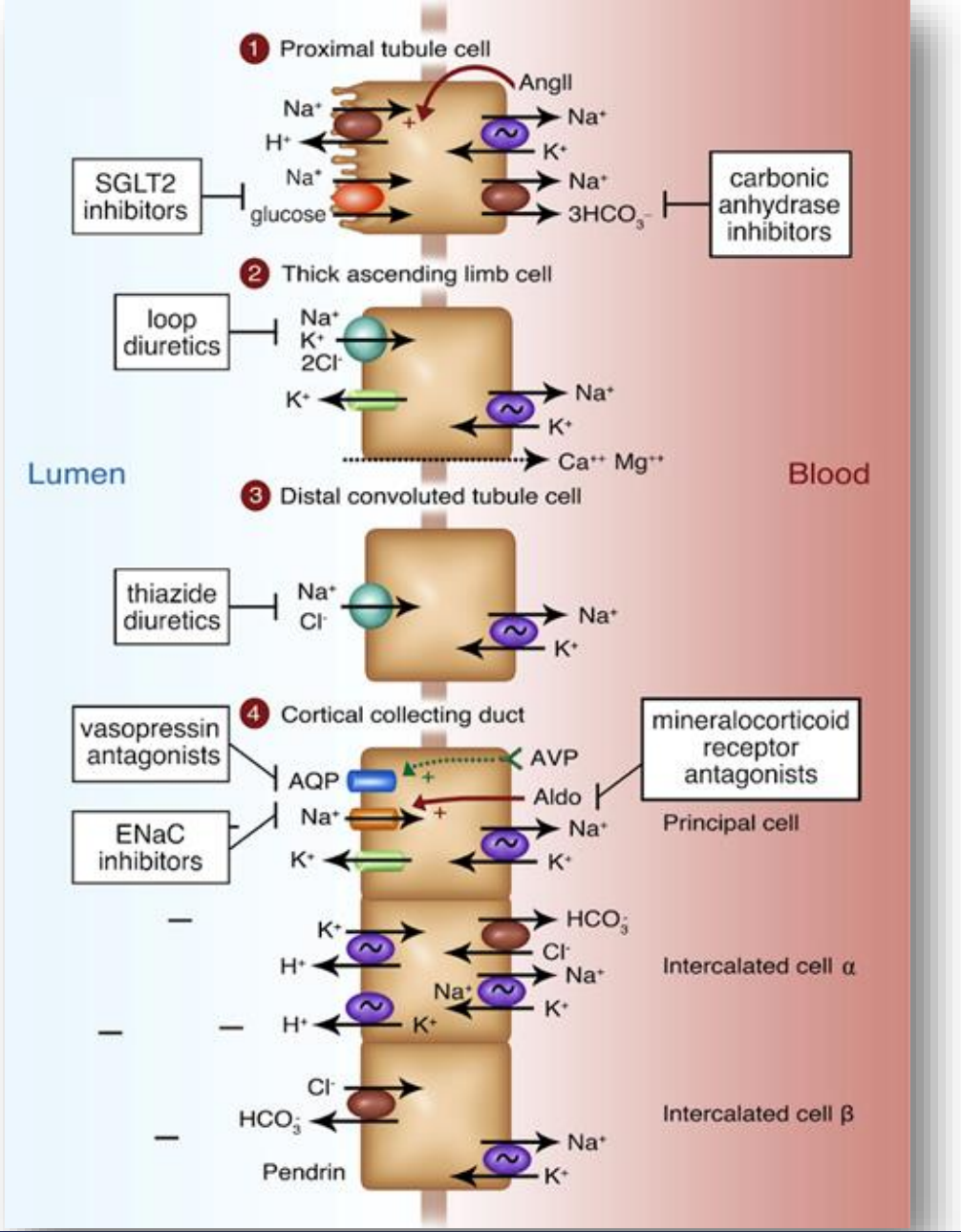
Overview

- **Diuretics**
  - Mode of action
  - Pharmacokinetics
- **Evaluation a volume overload/congestion**
- **Diuretic resistance (DR)**
  - Definition, evaluation
  - Causes of DR
- **Management strategies**
- **Special situations**
  - ESLD/ascites
  - Chronic kidney disease
  - Nephrotic syndrome

Diuretics

	DRUG CLASS	Examples
saluretic	**Loop diuretic**	Furosemide, bumetanide, torsemide, ethacrynic acid
saluretic	**Thiazide, thiazide like**	Hydrochlorothiazide, chlortalidon, indapamide, metolazone
saluretic	**Mineralocorticoid receptor antagonist**	Spironolactone, eprelenone, finerenone, esaxerenone..
saluretic	**Epithelial sodiam channel (ENaC) blocker**	Amiloride, triamterene
saluretic	**Carbonic anhydrase inhibitor**	Acetazolamide
aquaretic	**Vasopressin V2 antagonist**	Tolvaptan, conivaptan
aquaretic	**Osmotic diuretic**	Mannitol, urea
	SGLT2 inhibitor	Canaglifozin, dapagliflozin, empagliflozin…
	Neprilysin inhibitor	Sacubitril

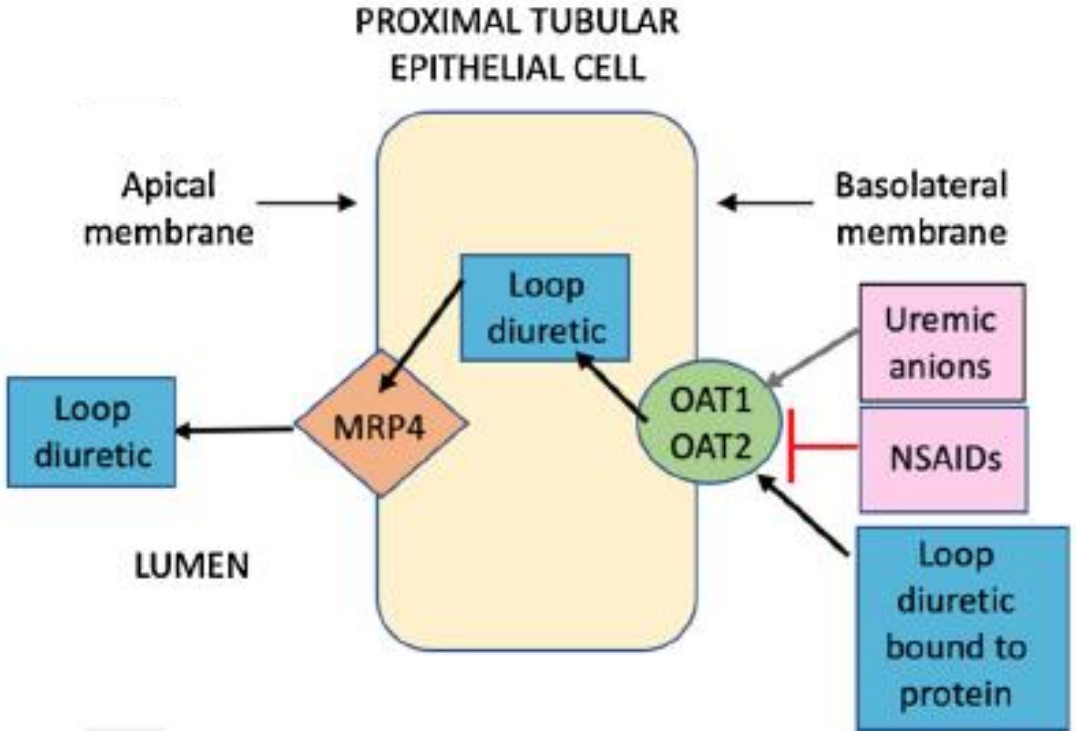
Mode of action



AJKD Nephmadness 2022

Steps in the action of loop diuretics

- Absorption
- Albumin binding
- Delivery to the poximal tubule
- Secretion into the proximal tubule lumen
- Delivery to the site of Na^+ reabsorption in the TALH



Curr Heart Fail Rep 2019;16:57

Pharmacokinetics of diuretic agents

Diuretic	Bioavailability	Equivalent Dose, mg	Metabolism (Kidney/Liver)	Elimination $t_{1/2}$, h	
				Normal	CKD
Loop					
Furosemide	50%-60% (10%-100%)[a]	40	100%/0%	1.5-2	2.6-2.8
Bumetanide	80%-100%	1	50%/50%	1	1.6
Torsemide	68%-100%	20	20%/80%	3-4	4-5
Thiazide					
HCTZ	65%-75%	25	100%/0%	6-15	↑
Chlorthalidone	60%-72%	12.5	100%/0%	40-60	↑
Metolazone	65%-90%	2.5	70%-95%/5%-30%	14-20	↑
Distal					
Amiloride	50%	10	50%/–[b]	6-26	100
Triamterene	52%-80%	100	20%/80%	2-5	↑
Spironolactone	>90%	25	0%/100%	>15[d]	↔
Indapamide		**1.5-2.5**	**70%**	**18**	

Am J Kidney Dis 2022;80:264

Overview

- **Diuretics**
  - Mode of action
  - Pharmacokinetics
- **Evaluation a volume overload/congestion**
- **Diuretic resistance (DR)**
  - Definition, evaluation
  - Causes of DR
- **Management strategies**
- **Special situations**
  - ESLD/ascites
  - Chronic kidney disease
  - Nephrotic syndrome

Volume overload, congestion

- **Congestion (in heart failure) is the combination of signs and symptoms of extracellular fluid accumulation that results in increased filling pressure**
  - Congestion ≠ volume overload

- **Refractory congestion: presence of symptoms despite optimal treatment including chronic diuretics**
  - Expected response in healthy individuals to iv. 40 mg FSD: 3-4l/day, 200-300 mmol/day of sodium

Front Physiol 2022,13:art 913580

Evaluation of volume overload, congestion

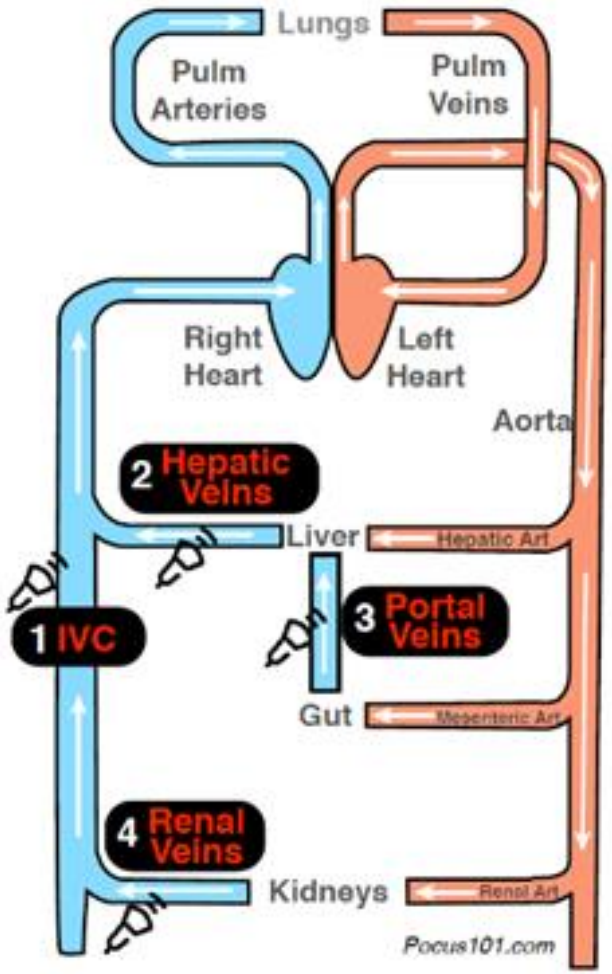
- **Physical examination**
  - edema, rales, elevated jugular venous pressure, hepatojugular reflux, S3
- **Biomarkers:**
  - BNP, NT-proBNP, CA125
- **Imaging**
  - chest X-Ray,
  - multi organ ultrasound
    - chest B-lines (comets)
    - IVC diameter (>2cm) and no collapsibility: RAP >20 mmHg
    - Venous flow characteristics
      - Hepatic vein
      - Portal vein
      - Renal interlobal vein
    - ECHO: E/e' >15

- **Bioimpedance analysis**

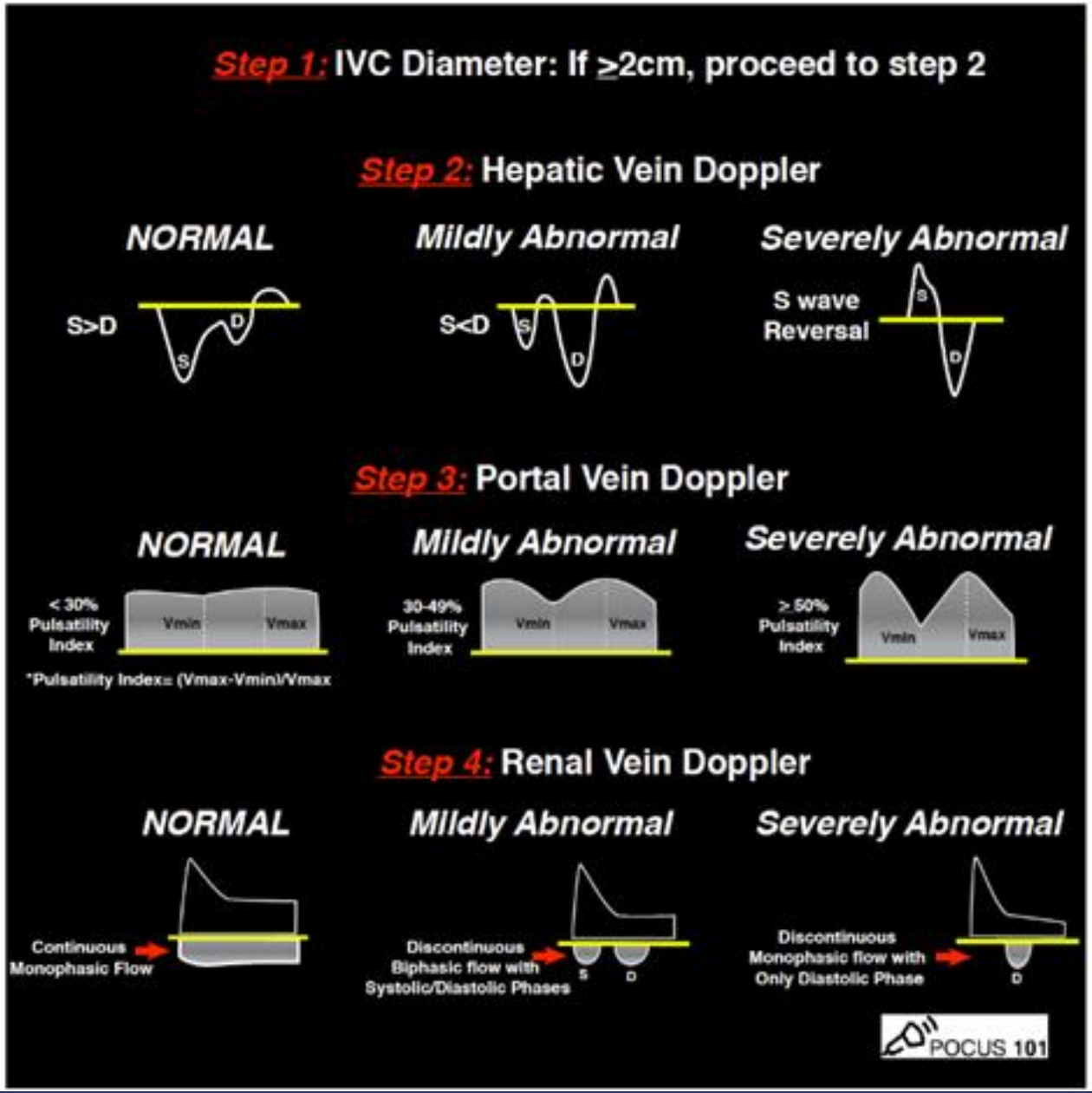
- **Right heart catheterisation**
  - Right atrial pressure
  - Pulmonary capillary wedge pressure

Front Physiol 2022,13:art 913580

Venous Excess Ultrasound VExUS



https://www.pocus101.com/



Interpretation

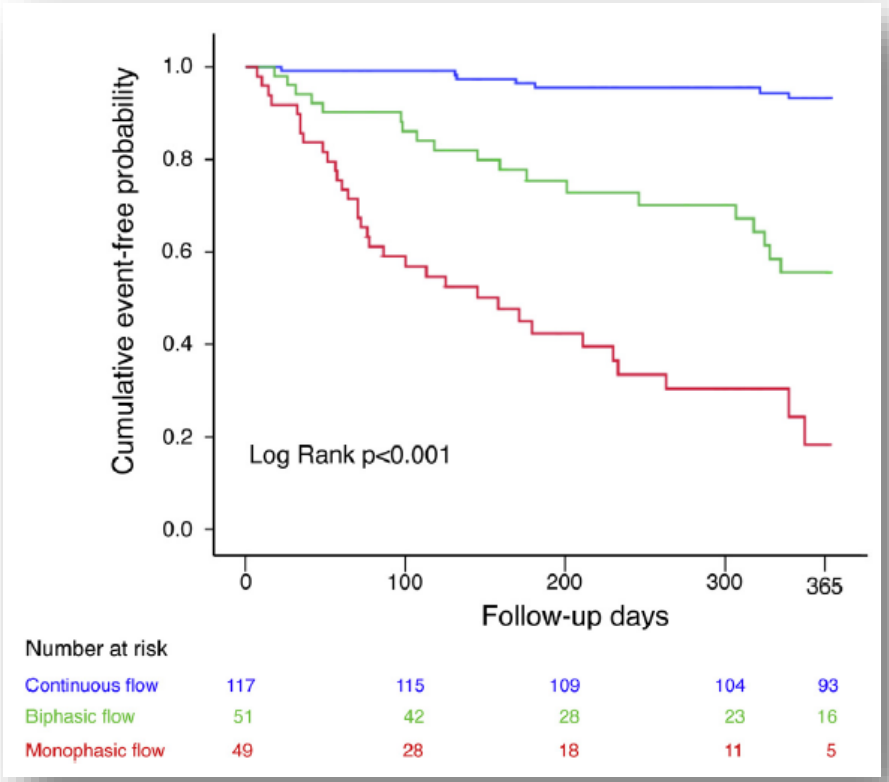
Grade 0
(no congestion)
IVC < 2cm

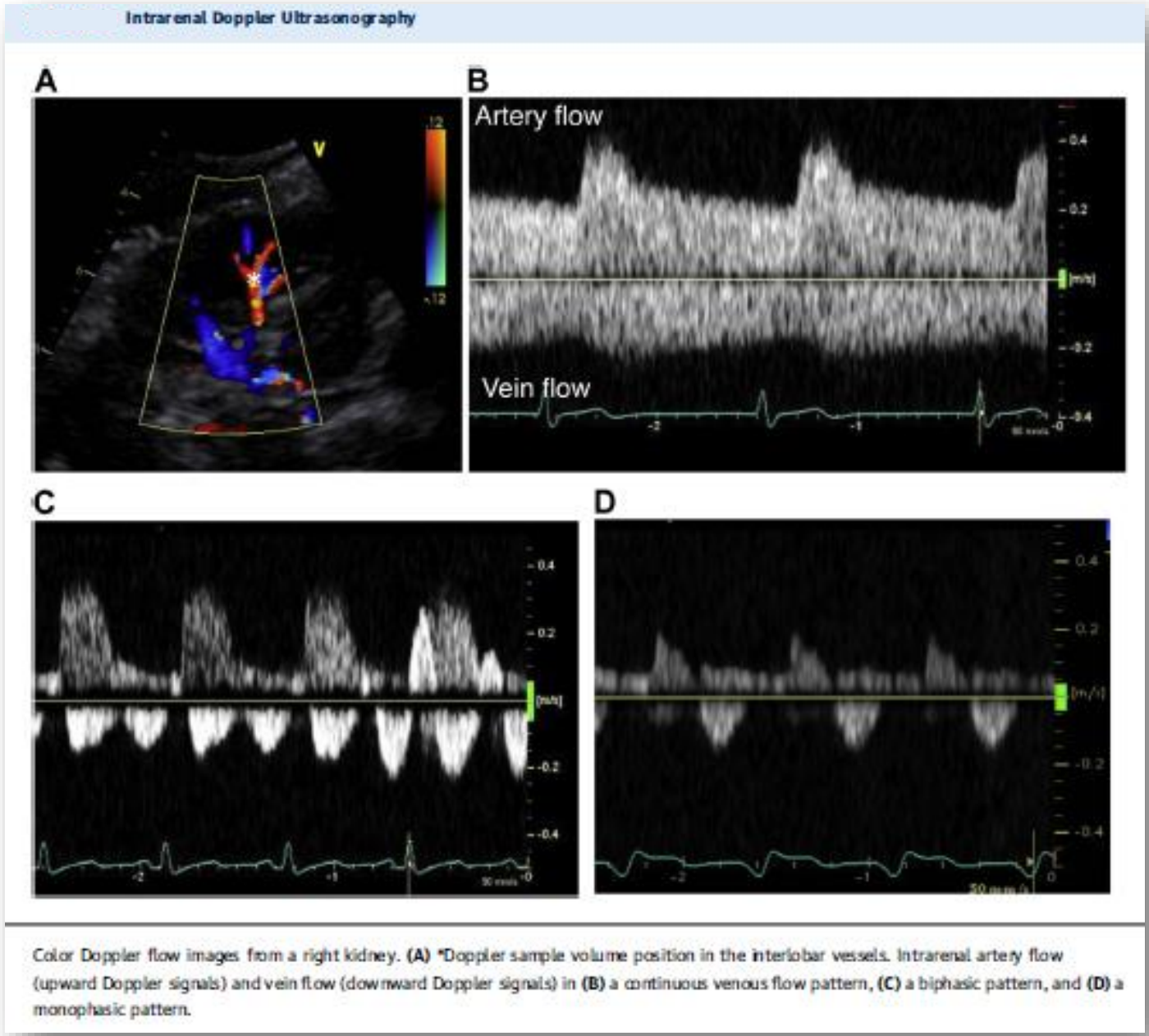
Grade 1
(Mild congestion)
IVC >2cm and any combo of Normal or Mildly Abnl Patterns

Grade 2
(Moderate congestion)
IVC >2cm and ONE Severely Abnl Pattern

Grade 3
(Severe congestion)
IVC >2cm and > 2 Severely Abnl Patterns

Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure





Color Doppler flow images from a right kidney. **(A)** *Doppler sample volume position in the interlobar vessels. Intrarenal artery flow (upward Doppler signals) and vein flow (downward Doppler signals) in **(B)** a continuous venous flow pattern, **(C)** a biphasic pattern, and **(D)** a monophasic pattern.

N=224 HF, 1 year, CV death HF hosp, JACC: Heart Failure 2016; 4:674

Overview

- **Diuretics**
  - Mode of action
  - Pharmacokinetics
- **Evaluation a volume overload/congestion**
- **Diuretic resistance (DR)**
  - Definition, evaluation
  - Causes of DR
- **Management strategies**
- **Special situations**
  - ESLD/ascites
  - Chronic kidney disease
  - Nephrotic syndrome

(loop) diuretic resistance

does not have a standard well-accepted definition

- **Failure to eliminate extracellular fluid despite adequate trial of diuretics** (Nat Rev Card. 2015;12:184)
- **Failure to decongest despite adequate and escalating doses of diuretics** (Cardiology. 2001;96:132)

- **Fractional excretion of Na <0,2% while on diuretic**
- **Spot urine Na <50mmol/l**

- **Prevalence in HF 20-50% of hospitalised patients with HF**

Urinary sodium (UNa) measurements as a predictor of natriuretic resposiveness and clinical outcome

Study	Time point of measurement of urine sample	*N*	Measurements	Predictive value/outcome
Singh, et al. 2014	Spot sample at steady state during continuous loop diuretic infusion	52	UNa < 50 mmol	Less weight loss and decreased net fluid output over 24 h
			UNa: urine furosemide ratio < 2 mmol/mg	Above, and worse clinical outcomes
Ferreira, et al. 2016	Spot sample on day 3 of therapy with loop diuretic ± spironolactone	100	UNa > 60 mmol/L and UNa: urine potassium > 2	Fewer adverse clinical outcomes
Testani, et al. 2016	1–2 h after loop diuretic administration	50	UNa < 60 mmol/L cumulative in 6 h by equation	Worse cumulative 6-h sodium output/poor natriuretic response
Luk, et al. 2018	1st urine void after loop diuretic administration	103	UNa < 60 mmol/L	More adverse clinical outcomes
Brinkley, et al. 2018	1st urine void after loop diuretic administration	176	UNa < 60 mmol/L	Greater rates of 30-day hospitalization or emergency room visit
Collins, et al. 2018	1 h after loop diuretic administration	61	UNa < 35 mEq/L	Worsening heart failure

Current Heart Failure Reports (2019) 16:57–66

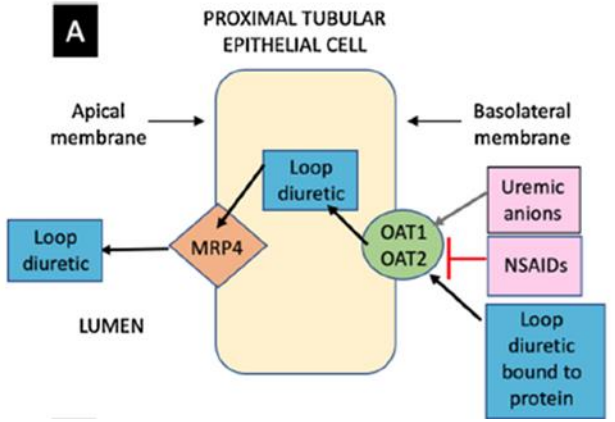
Causes of loop diuretic resistance

1. insufficient delivery of loop diuretics to the lumen of thick ascending limb of the loop of Henle

2. reabsorption of sodium *at other nephron segments* due to heightened sodium avidity

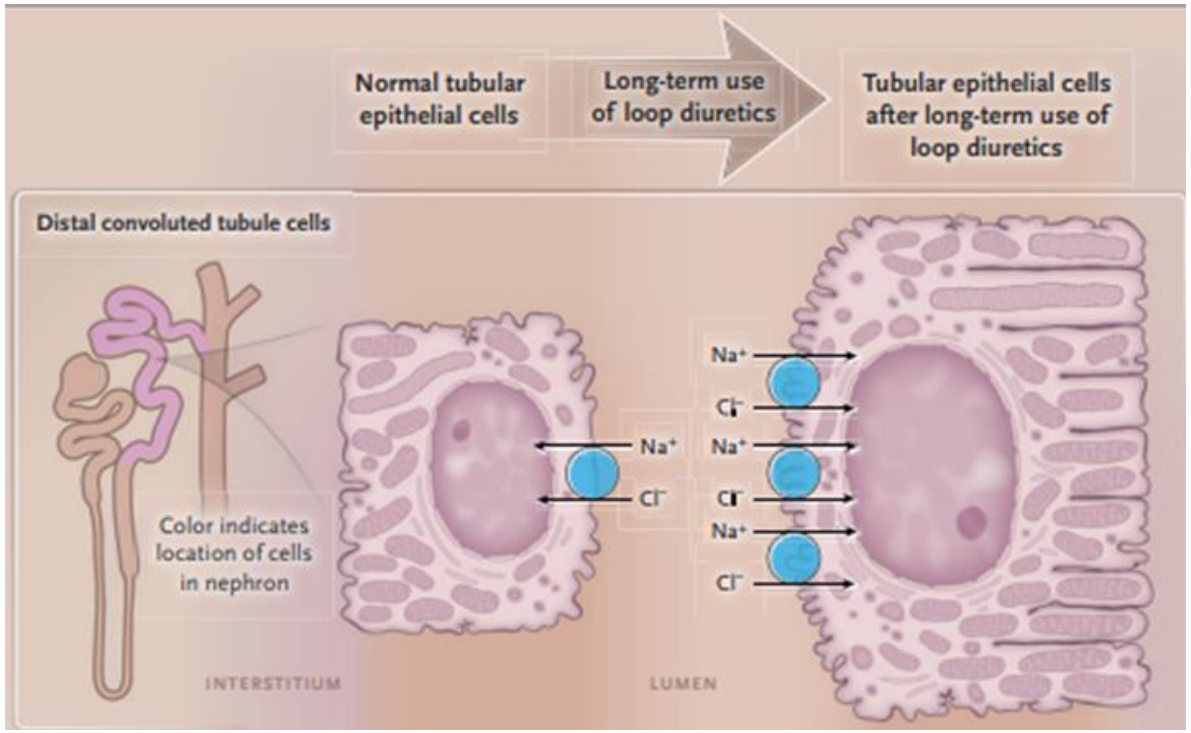
Causes of diuretic resistance

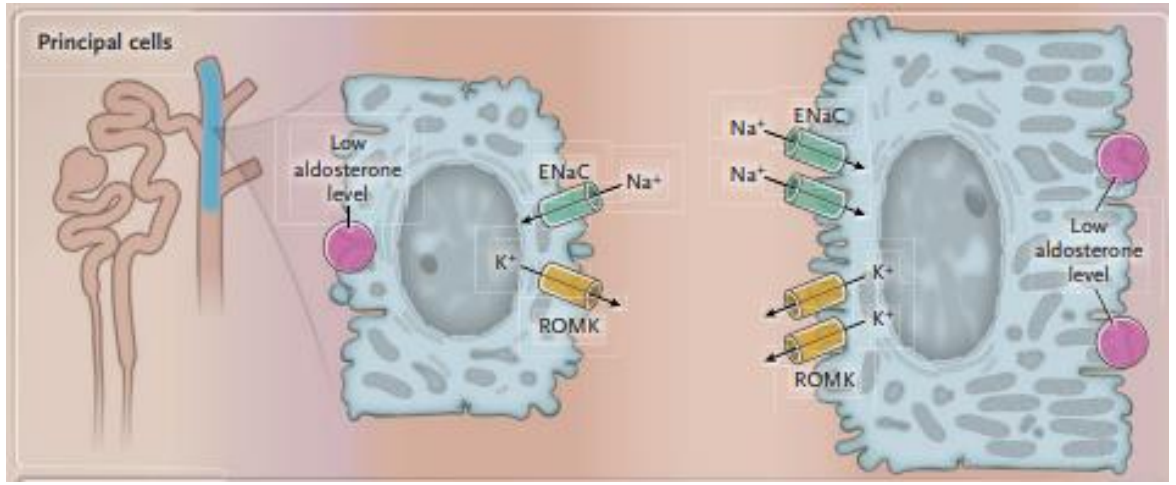
- Decreased drug delivery to the tubules
  - Decreases absorption (gut edema)
  - Inadequate dose/frequency
  - Hypoalbuminemia
- Decreased drug secretion in the proximal tubule
  - Decreased kidney blood flow
    - decreased effective arterial blood volume
    - „renal tamponade”- renal congestion
  - Tubular transport inhibition: bile acids, organic acids, NSAI, indoxyl sulphate, p-cresyl sulphate
  - Decreased kidney mass
- Increased Na avidity/reabsorption at other nephron segments
  - RAAS activation, sympathetic nervous system activity
  - Distal tubular hypertrophy

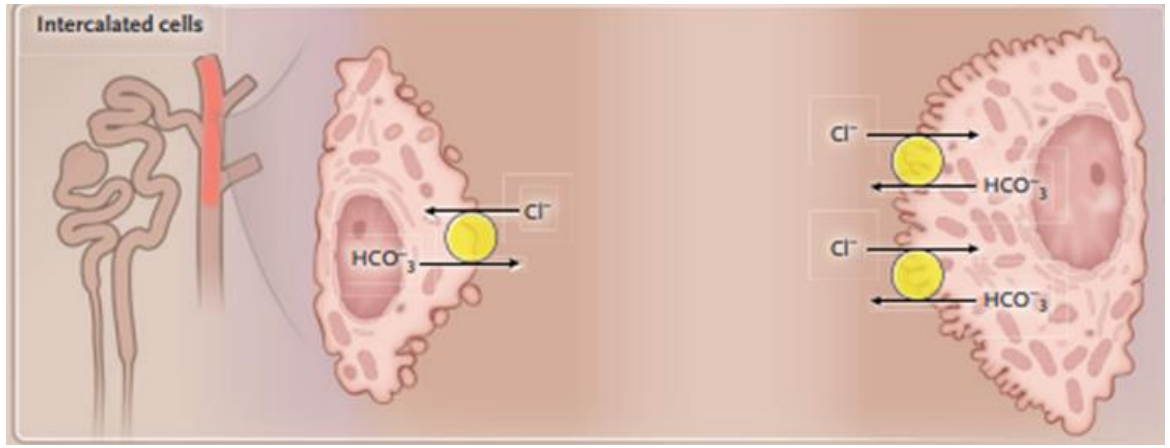


AJKD 2022;80:264

Nephron remodelling as a mechanism of diuretic resistance

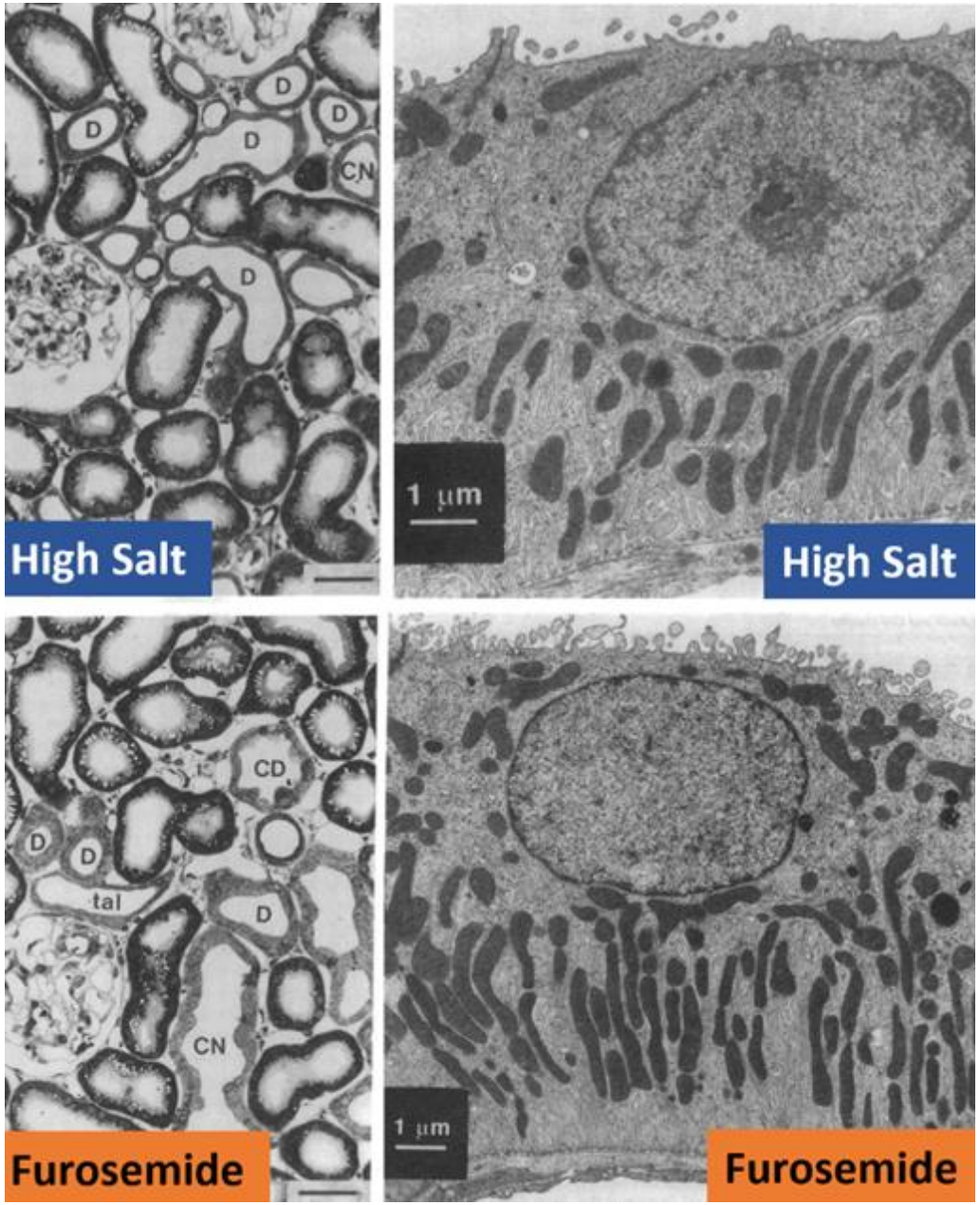






NEJM 2017;377:1964

Adaptation of the distal tubule to chronic diuretic infusion



J Clin Invest 1989;83:113

Compensatory Distal Reabsorption Drives Diuretic Resistance in Human Heart Failure

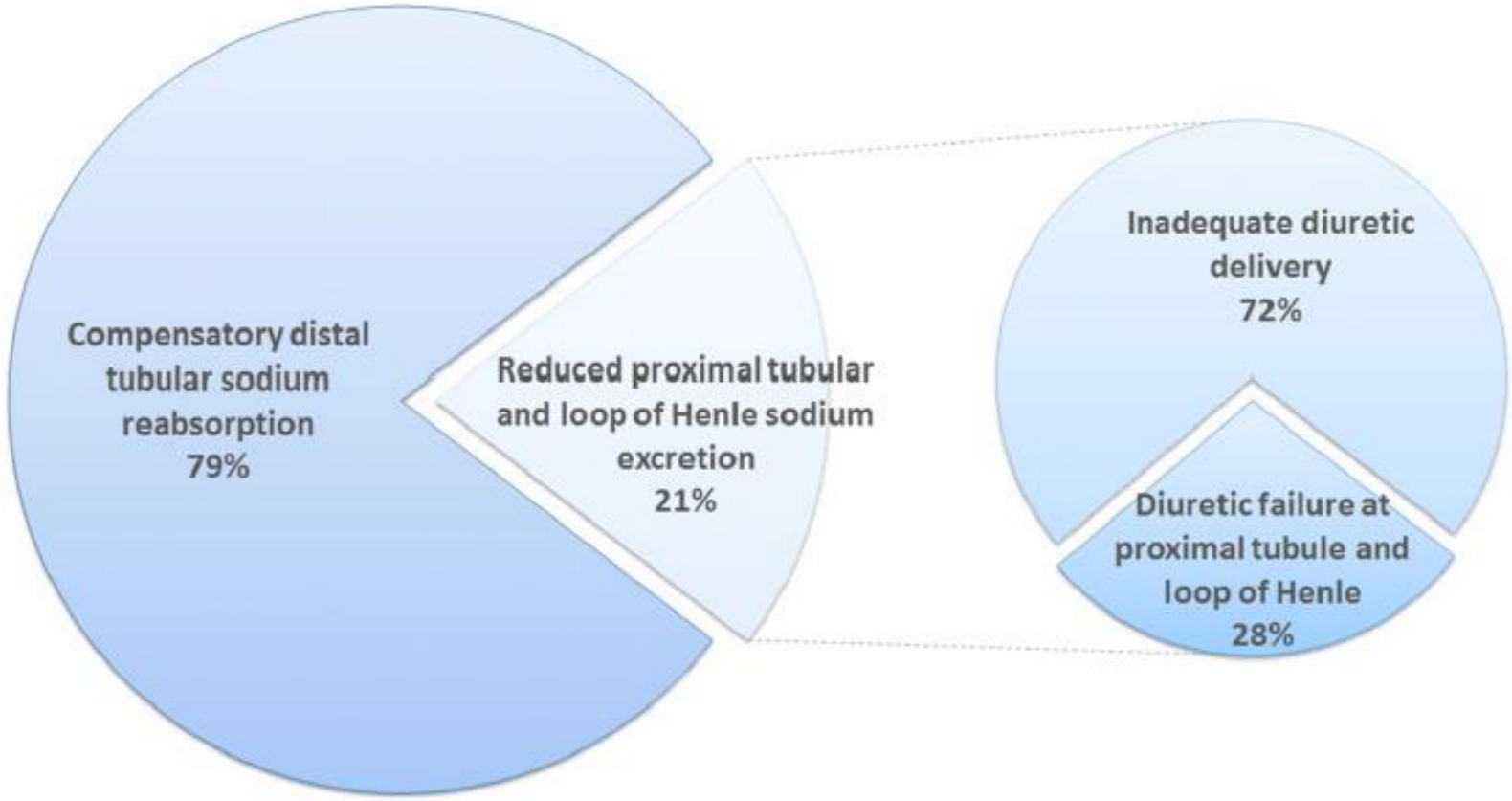


Figure 4. Relative contribution of different intrarenal mechanisms to diuretic-induced increase in FENa. Compensatory distal tubular sodium reabsorption makes the largest relative contribution to diuretic induced increase in FENa. Of the proximal tubular contribution to diuretic response, the major factor driving poor response was inadequate diuretic delivery rather than primary failure at the loop of Henle.

JASN 2017;28:3414

Overview

- **Diuretics**
  - Mode of action
  - Pharmacokinetics
- **Evaluation a volume overload/congestion**
- **Diuretic resistance (DR)**
  - Definition, evaluation
  - Causes of DR
- **Management strategies**
- **Special situations**
  - ESLD/ascites
  - Chronic kidney disease
  - Nephrotic syndrome

Causes of loop diuretic resistance

1. insufficient delivery of loop diuretics to the lumen of thick ascending limb of the loop of Henle

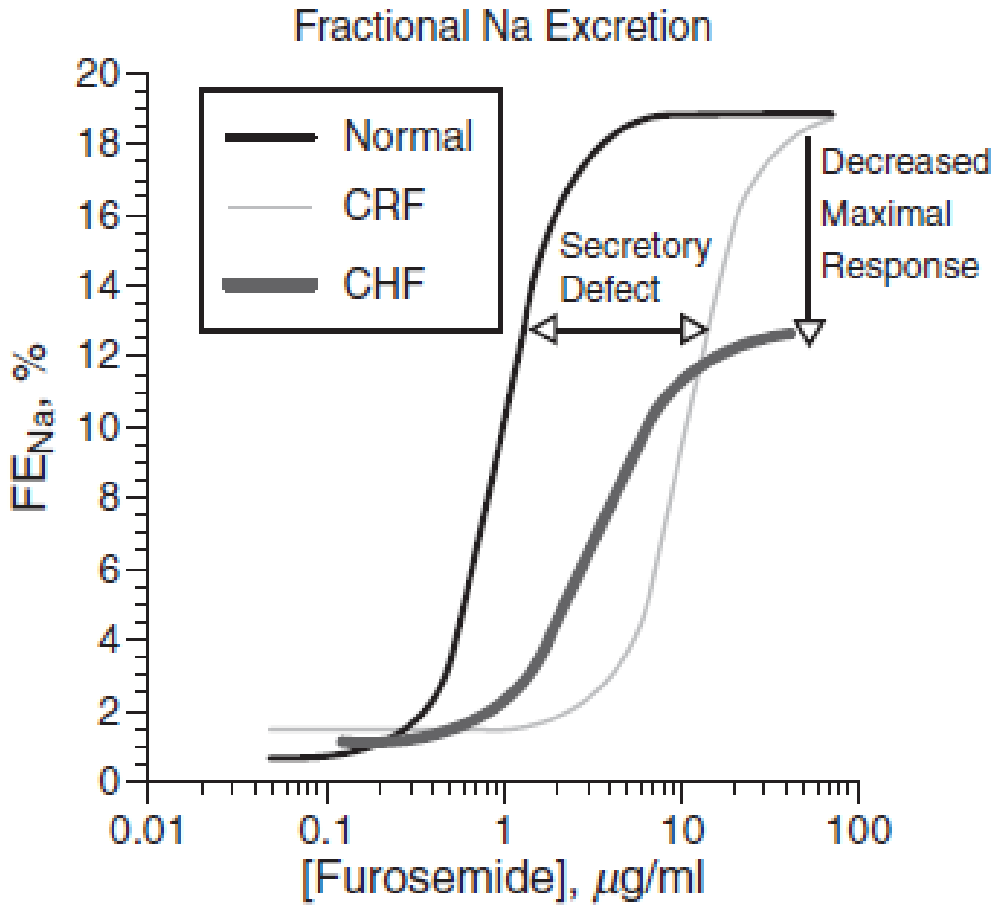
2. reabsorption of sodium *at other nephron segments* due to heightened sodium avidity

1. Maximizing loop diuretic efficacy

- **Change the type, route and dose**
  - Torsemide v.s. furosemide*
  - i.v. versus p.o.
    - i.v. 2-2,5 times the oral dose BID or TID
    - evaluate urine sodium (>50mmol/L) for efficacy
    - natriuretic response prediction equation (JACC 2021;77:695)
  - Continuous infusion v.s. intravenous

- **Albumin infusion (?)**
  - If albumin <25g/L,
  - higher dose >30g used

- **Improve renal perfusion**
  - Dopamine? nesiritide?



*Transform HF trial, n=2859, tor v.s. FSD at discharge (HF) , mortality 26 vs 26% at a median of 17 months, *JAMA*. 2023;329(3):214-223.
J Am Coll Cardiol 2021;77:695, Cardiology 2001;96:132, PLOS ONE | https://doi.org/10.1371/journal.pone.0260312 December 1, 2021,

2. Sequential nephron blockade to prevent distal sodium reabsorption

Co-administration of:

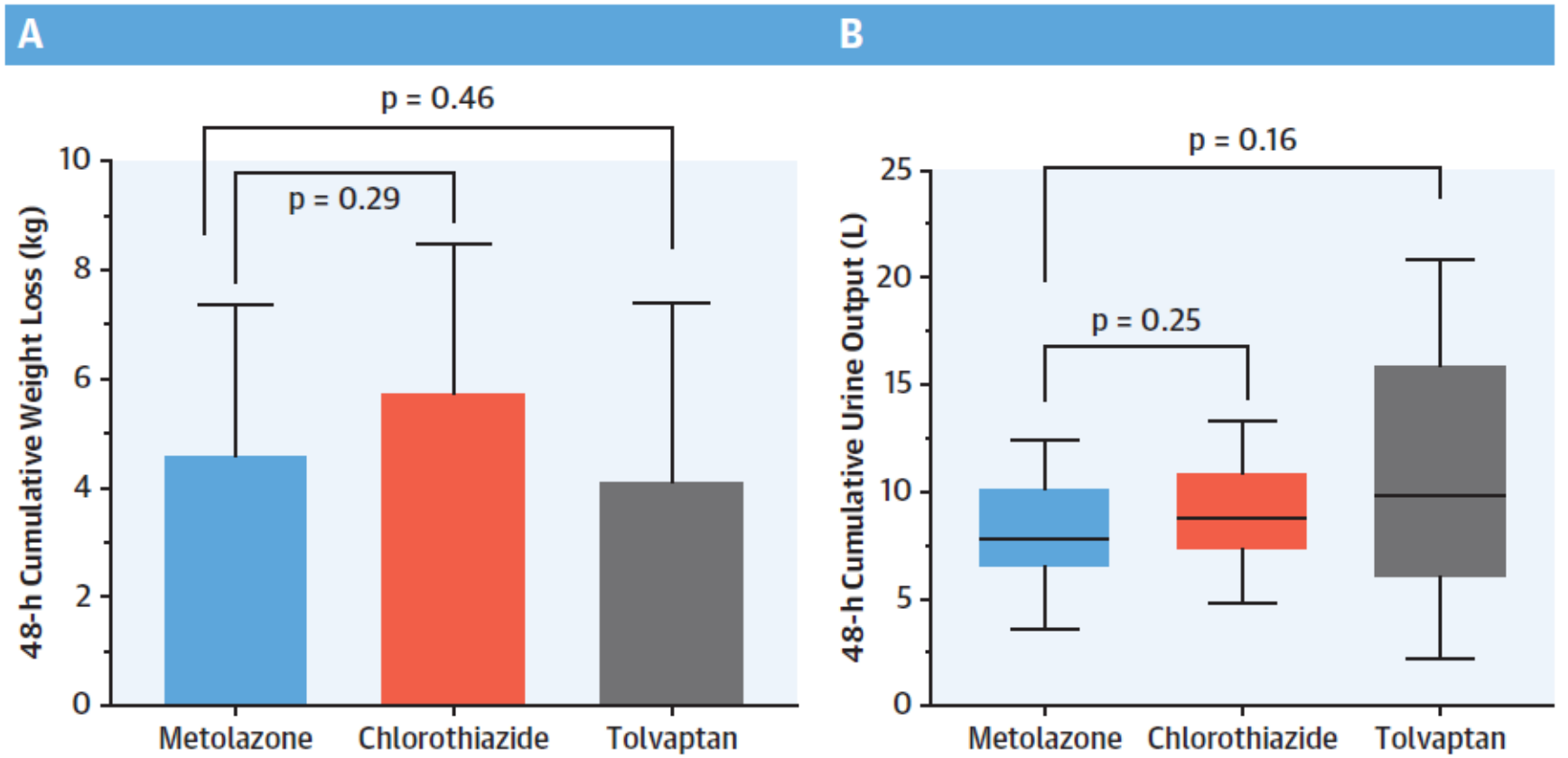
- **Thiazide and thiazide-like diuretics**
  - Blocking the distal Na^+Cl^- transporter and pendrin system
  - May work in advanced kidney disease also
  - K↓, pH↑

Front Physiol July 2022;13,art 913580

Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure

The 3T Trial

CENTRAL ILLUSTRATION 48-Hour Diuretic Efficacy



N760 AHF, DR FSD dose 612 mg/d JACC Heart Failure 2020;8:157

Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

Study population

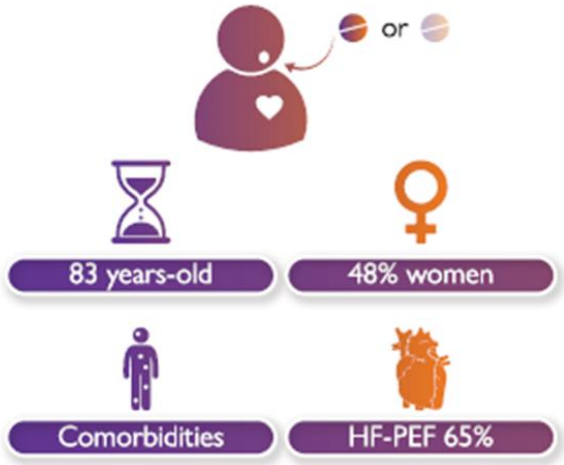
Randomized, double-blind, placebo-controlled clinical trial

History of chronic heart failure

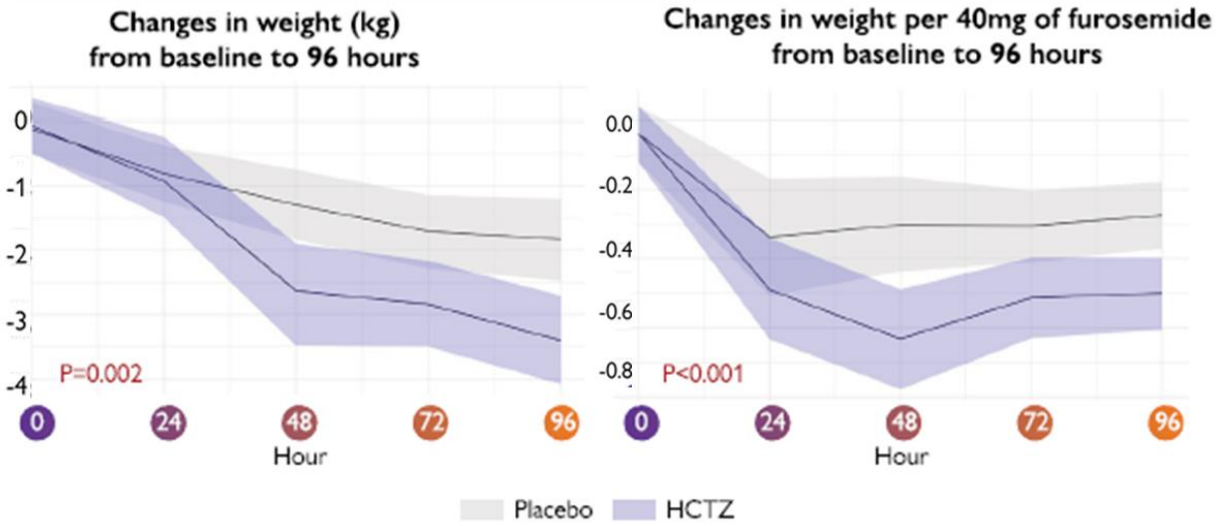
Treatment with oral furosemide (80-240 mg/day)

Admission for acute decompensation

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



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

Eur Heart Journal (2023) 44, 411–421
Dose adjusted for GFR

2. Sequential nephron blockade to prevent distal sodium reabsorption

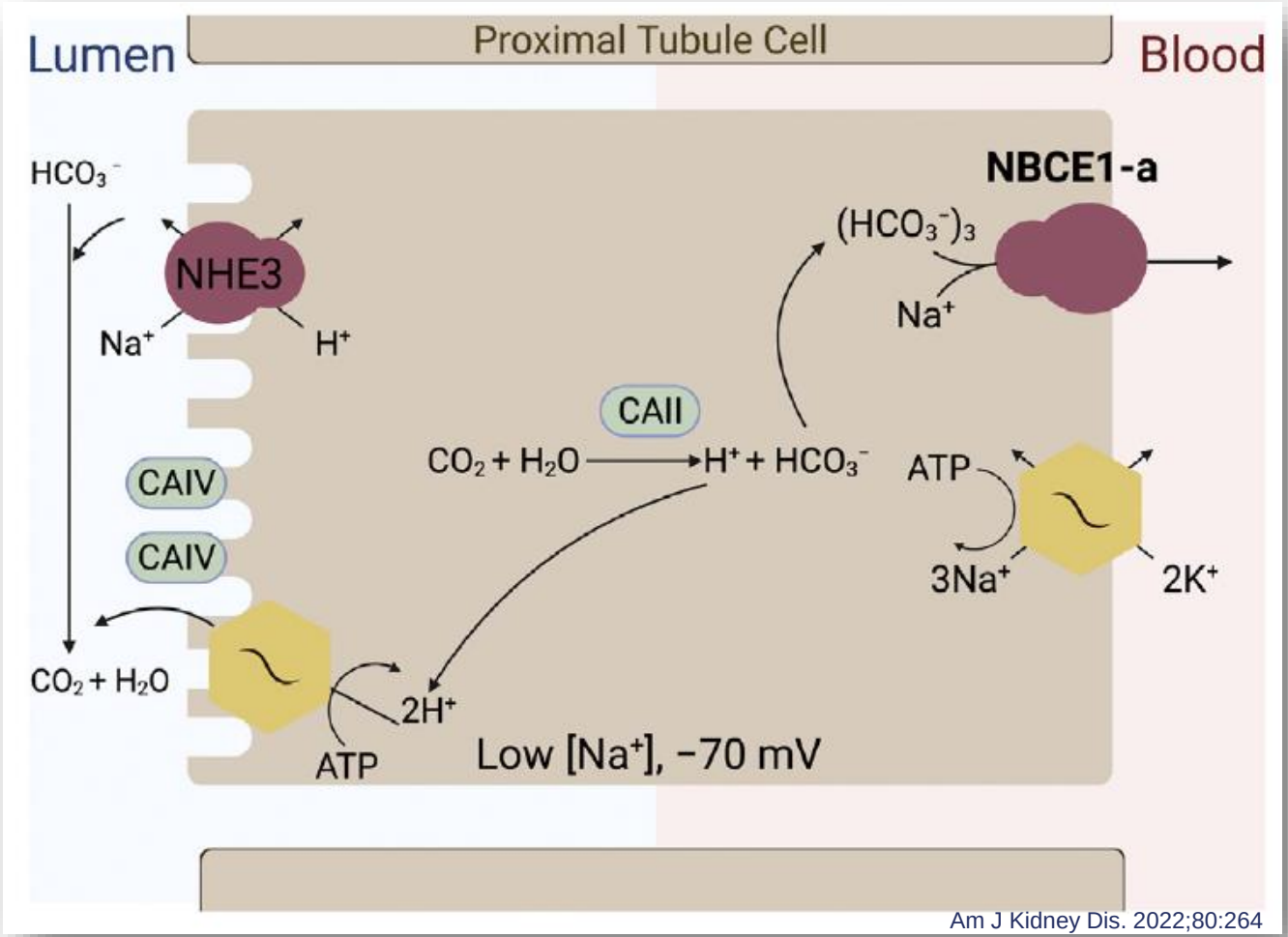
Co-administration of:

- **Thiazide and thiazide-like diuretics**
  - Blocking the distal NaCl transporter and pendrin system
  - May work in advanced CKD also
  - K↓, pH↑
- **Mineralocorticoid receptor antagonists**
  - Blocking MRA (and ENaC)
  - 25mg vs 100mg (?)
  - K↑
- **Amiloride, triamterene**
  - less recommended
- **Acetazolamide**

Front Physiol July 2022;13,art 913580

Acetazolamide

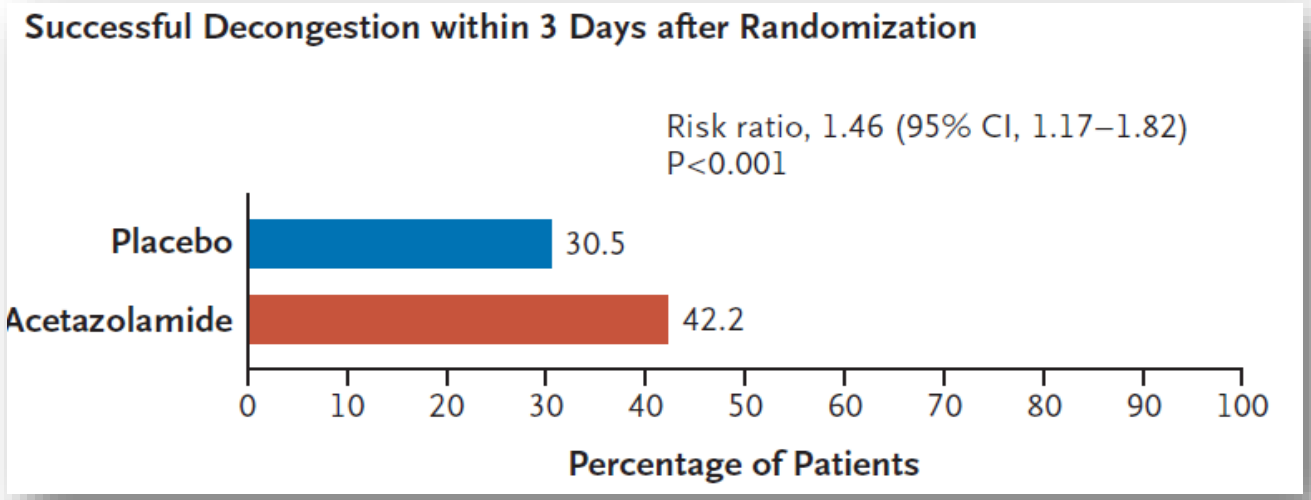
- Carbonic anhydrase II and IV. inhibitor in the tubules (prox and distal)
- Na^+-H^+ exchange ↓, natriuresis
- Weak diuretic
- Bicarbonaturia, metabolic acidosis
- Hypokalemia, hypercalciuria
- Hypocitraturia

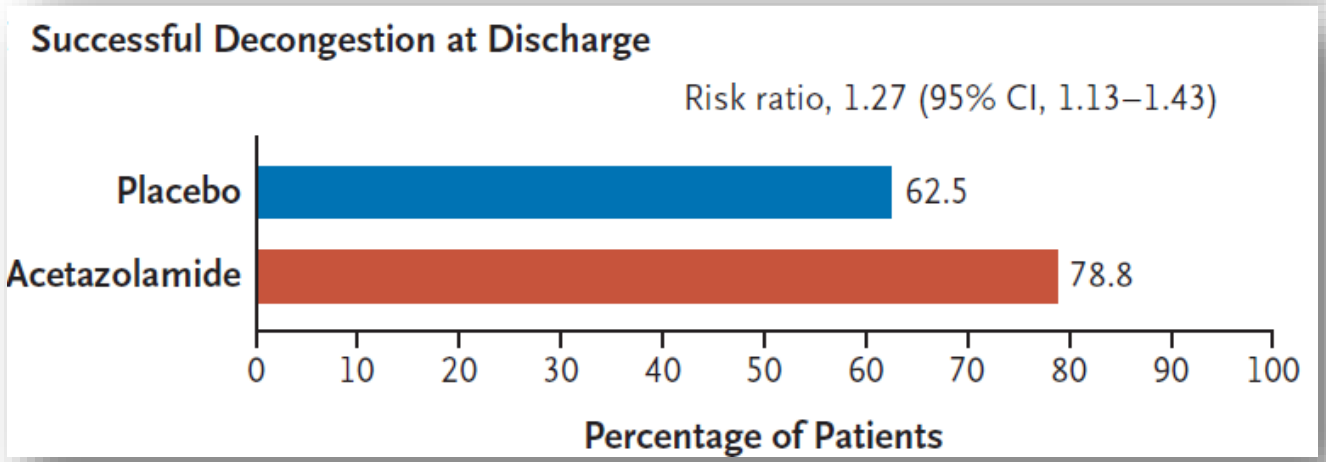


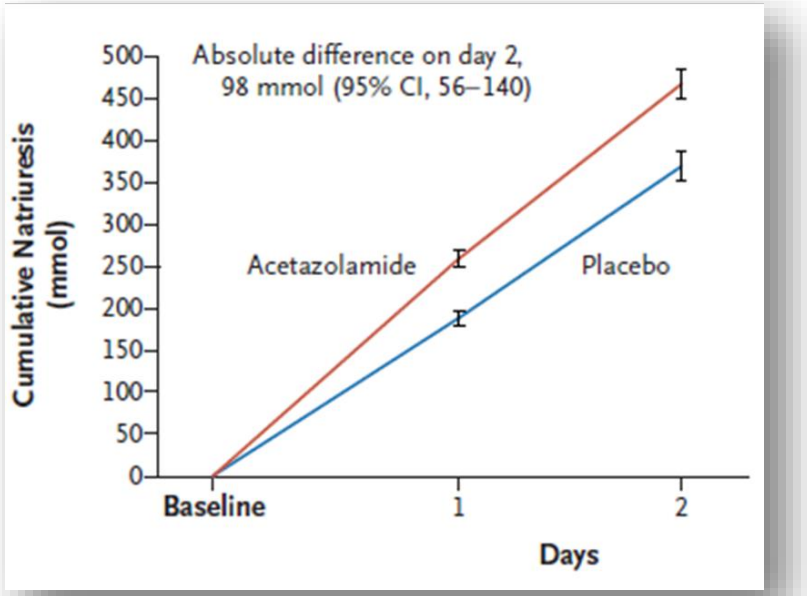
Am J Kidney Dis. 2022;80:264

NEJM Aug 27 2022

ADVOR trial: primary end point: successful decongestion

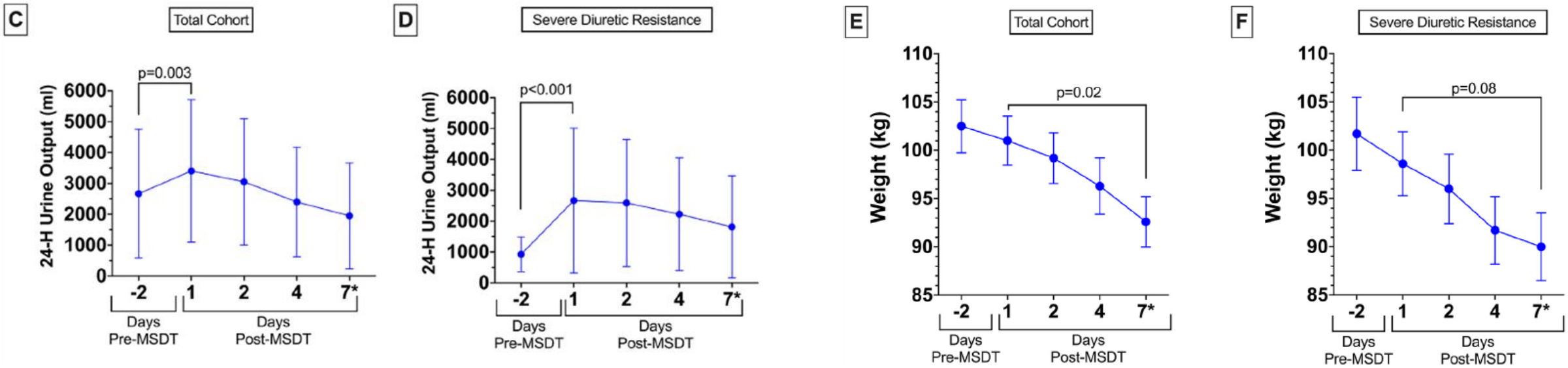






N=519, ADHF, acetazolamide 500mg iv 3 days v.s plac, FSD iv. bid, NEJM Aug 27 2022

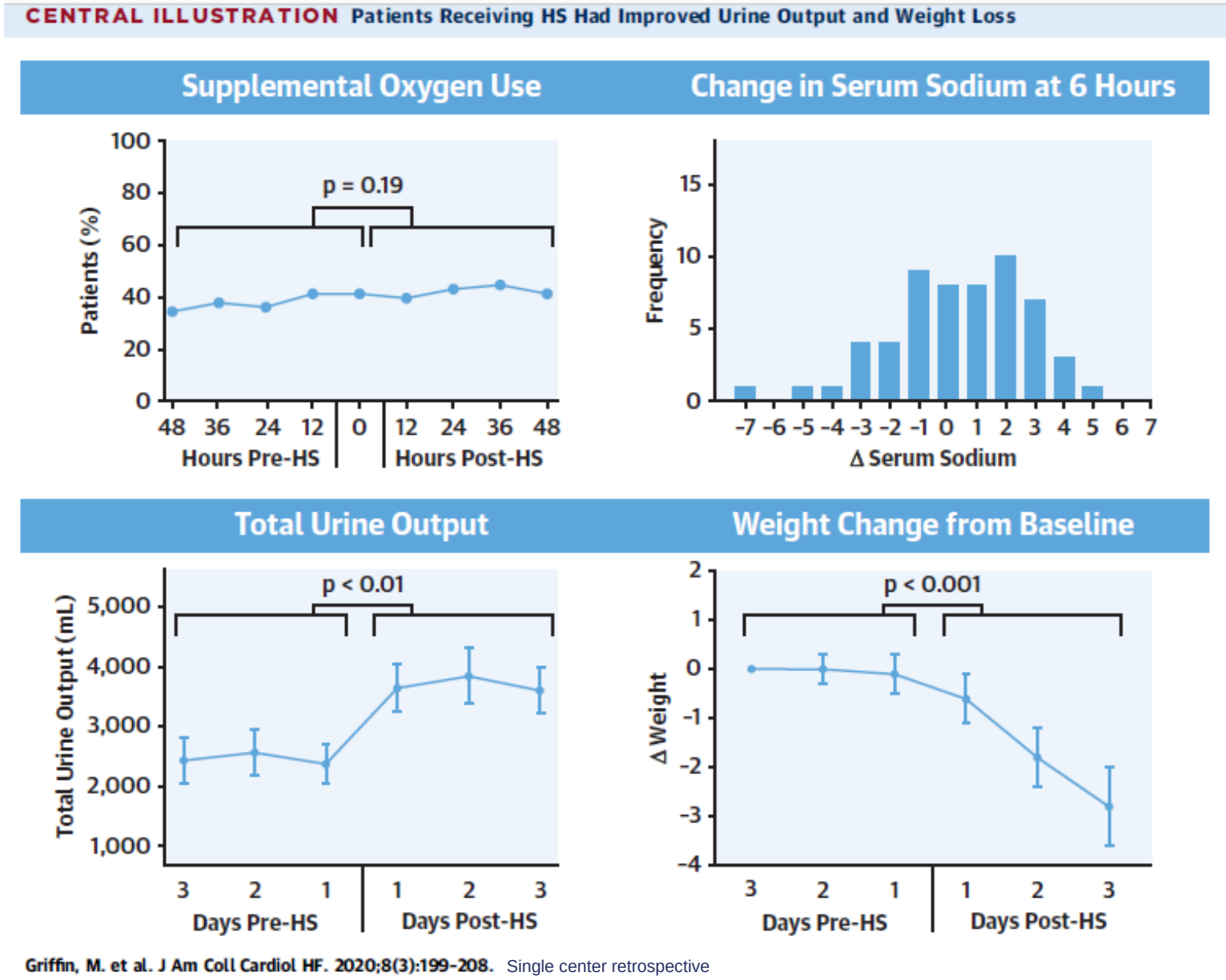
Multinephron Segment Diuretic Therapy to Overcome Diuretic Resistance in Acute Heart Failure: A Single-Center Experience



Retrospective, N=167 AHF DR , Acet 250mgx3 iv, FSD 200mgx4 iv., metolazone 10mgx2 po, sipron 100mgx2 po. J Cardiac Fail 2022;28:21

3. „Hyperdiuresis” with hypertonic sodium chloride infusion

- **150ml 3% NaCl over 30 min with loop diuretic**
  - Osmotic effect
  - Effect of distal nephron WNK kinases
  - Blunting RAAS activity
  - The role of Cl^-?

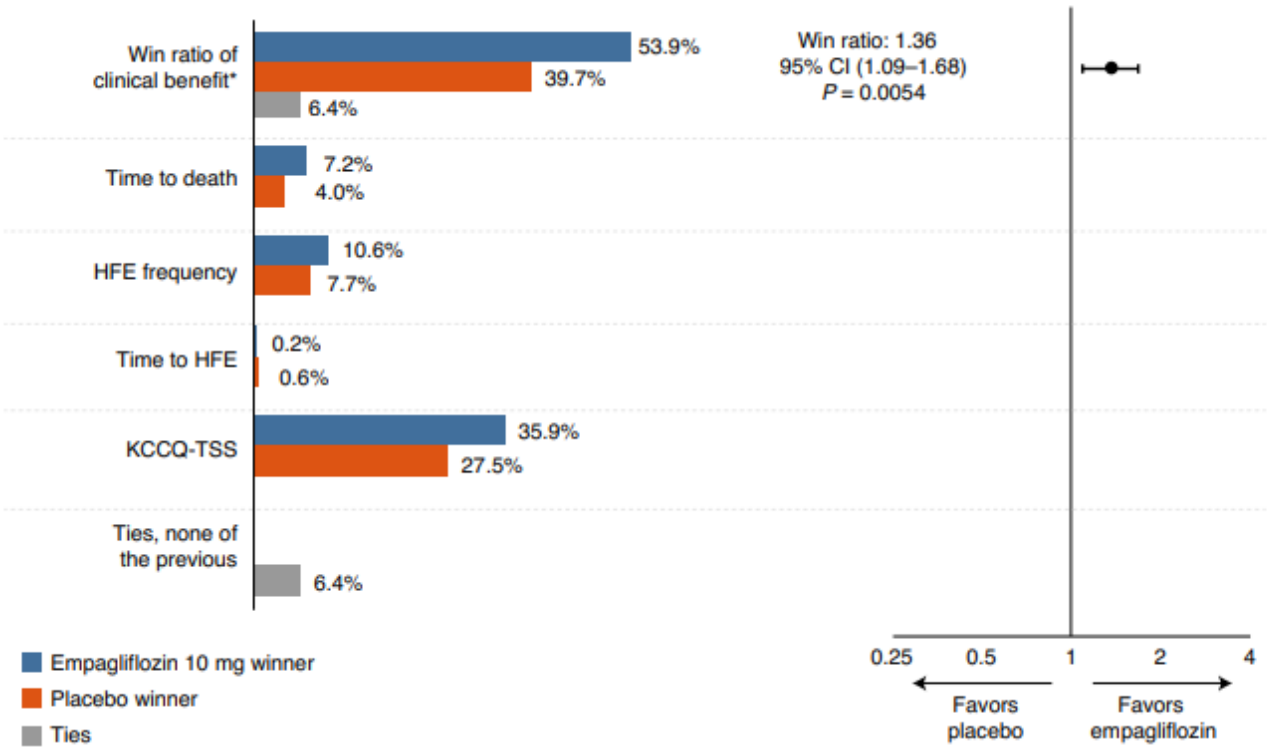


Griffin, M. et al. J Am Coll Cardiol HF. 2020;8(3):199-208. Single center retrospective

4. Other interventions for diuretic resistance

- **SGLT2 inhibitors**
  - Do have cardiorenal protective effects
  - Weak diuretic in the PT, but may synergize with loop diuretics (Hypertension. 2020;75:894)
  - EMPULSE trial in ADHF (Nature Medicine 2022;28:568)

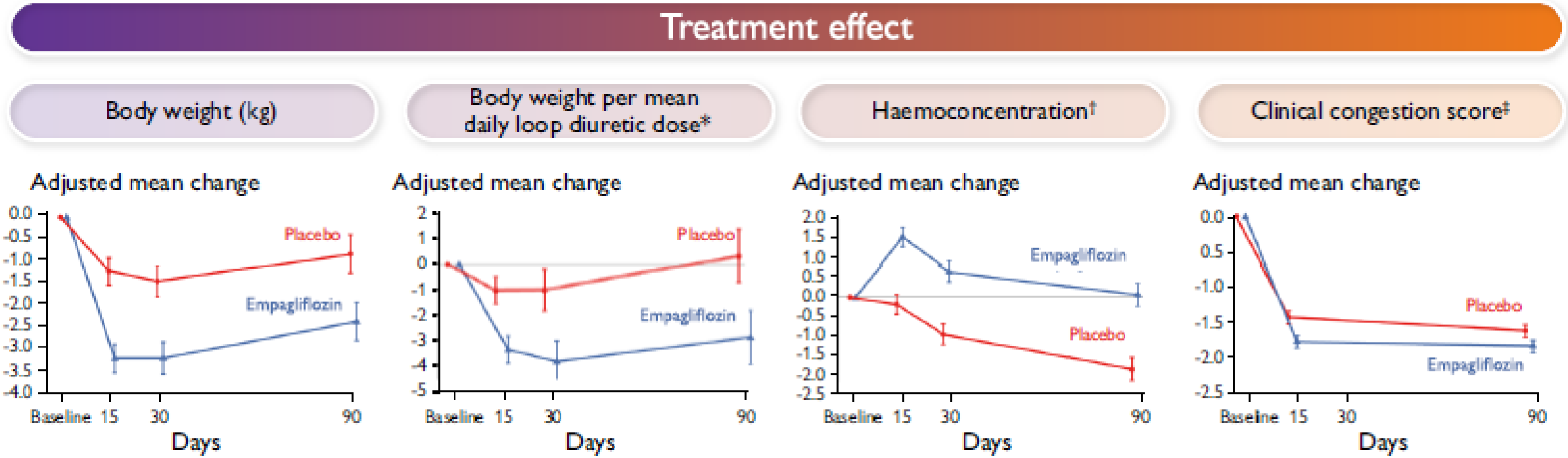
- ? Vasopressin V2 receptor antagonists
- Nesiritide (BNP)
- Ralofylline (A1 antagonist)
- ? Neprilysin inhibitors
- ? Inotropic agents
- Ultrafiltration
- Peritoneal dialysis



Front Physiol July 2022;13,art 913580

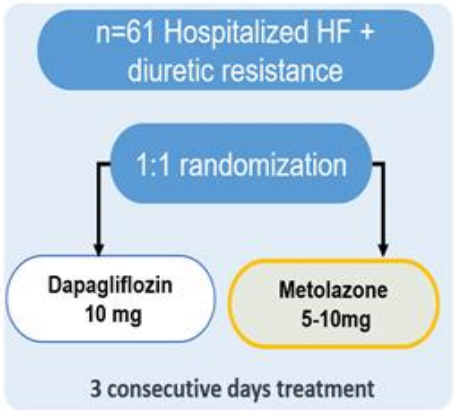
N=530 ADHF new+recurrent, Empa vs. Plac after stablisation, F/U 90 days, Nature Medicine 2022;28:568

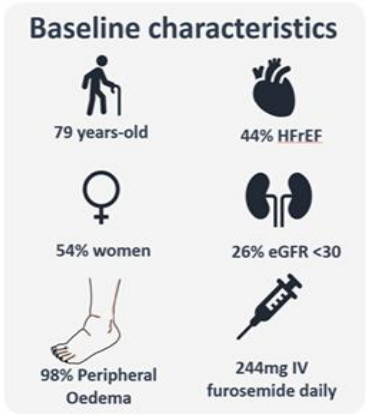
Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial



N=530 ADHF new+recurrent, Empa vs. Plac after stablisation, F/U 90 days, Eur heart J 2023;44:41

Dapagliflozin versus metolazone in heart failure resistant to loop diuretics DAPARESIST

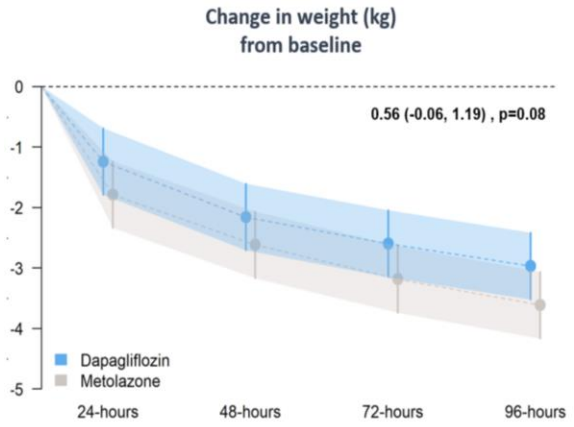


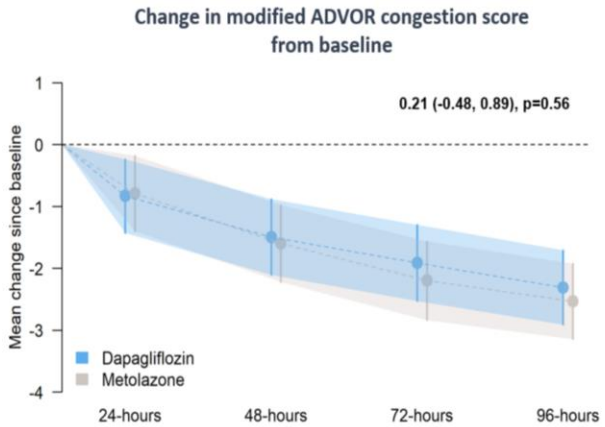


Conclusion

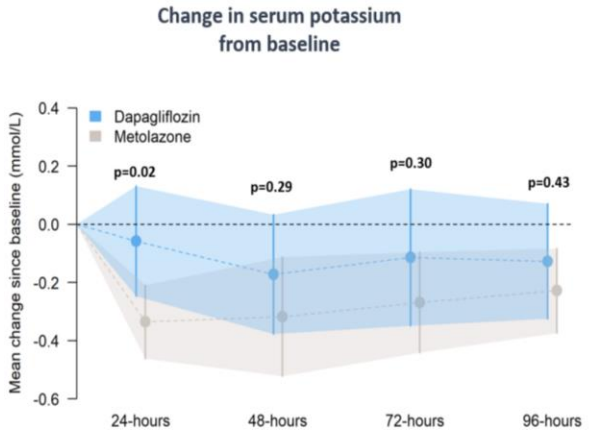
In patients with heart failure and loop diuretic resistance, dapagliflozin was not more effective at relieving congestion than metolazone. Patients assigned to dapagliflozin received a larger cumulative dose of furosemide but experienced less biochemical upset than those assigned to metolazone.

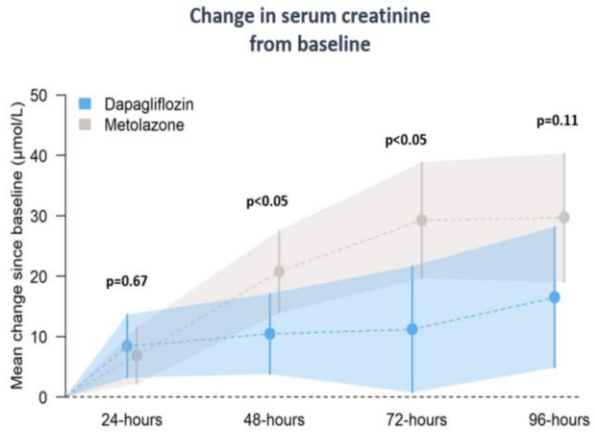
EFFICACY





SAFETY





European Heart Journal, ehad341, https://doi.org/10.1093/eurheartj/ehad341

4. Other interventions for diuretic resistance

- **SGLT2 inhibitors**
  - Do have cardiorenal protective effects
  - Weak diuretic in the PT, but may synergize with loop diuretics (Hypertension. 2020;75:894)
  - EMPULSE trial in ADHF (Nature Medicine 2022;28:568)

- **? Vasopressin V2 receptor antagonists**
- **Nesiritide (BNP)**
- **Ralofylline (A1 antagonist)**
- **? Neprilysin inhibitors**
- **? Inotropic agents**
- **Ultrafiltration**
- **Peritoneal dialysis**

Front Physiol July 2022;13,art 913580

Overview

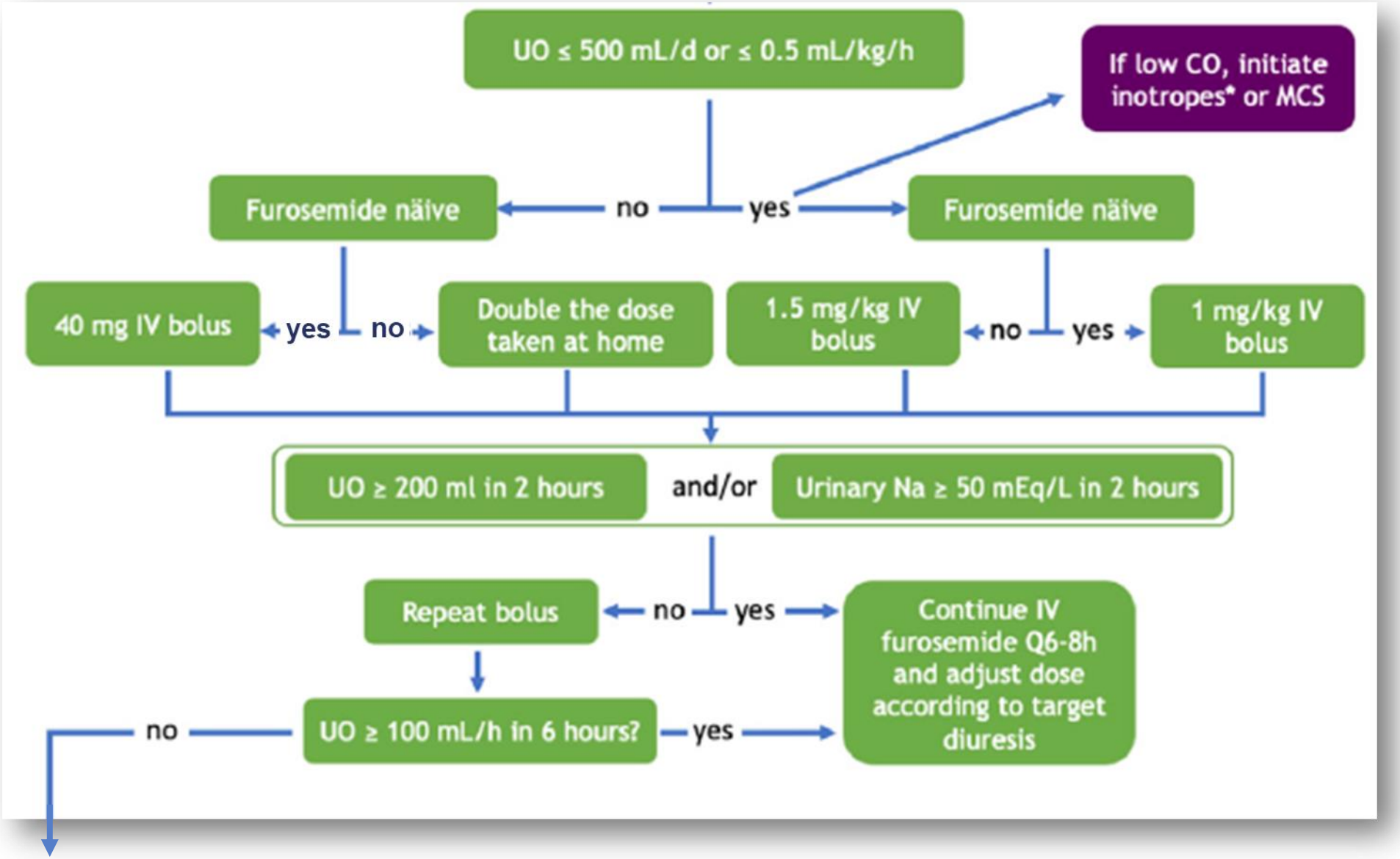
- **Diuretics**
  - Mode of action
  - Pharmacokinetics
- **Evaluation a volume overload/congestion**
- **Diuretic resistance (DR)**
  - Definition, evaluation
  - Causes of DR
- **Management strategies**
- **Other situations**
  - ESLD/ascites
  - Chronic kidney disease
  - Nephrotic syndrome

Other situations with volume overload/congestion

- **End stage liver disease/ascites**
  - Sodium restriction (<2g/day)
  - MRA among the most effective diuretics (50-200mg/d spironolactone) with addition of loop diuretic
  - Avoid hypovolemia
- **Chronic kidney disease**
  - Luminal concentration of loop diuretic is less – dose increase is needed
  - Thiazides (chlorthalidon) are effective at GFR <30
- **Nephrotic syndrome**
  - „Overfill" vs. „underfill" hypothesis
  - Decreased absorption, delivery, secretion of loop diuretics
  - ENaC blockers?

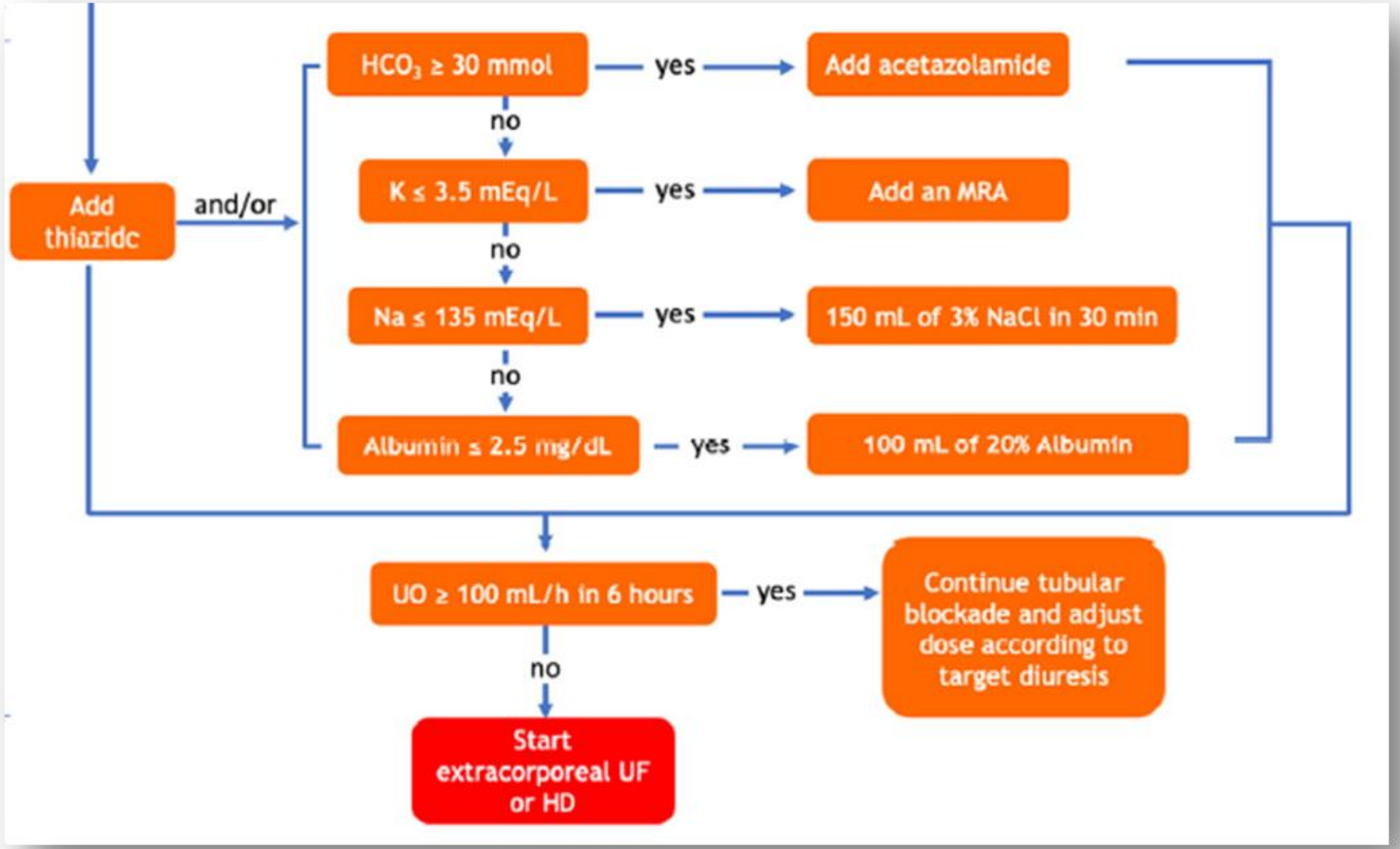
AJKD 2022;80:264

Summary: flow-chart



Front Physiol July 2022;13,art 913580

Summary: flow-chart



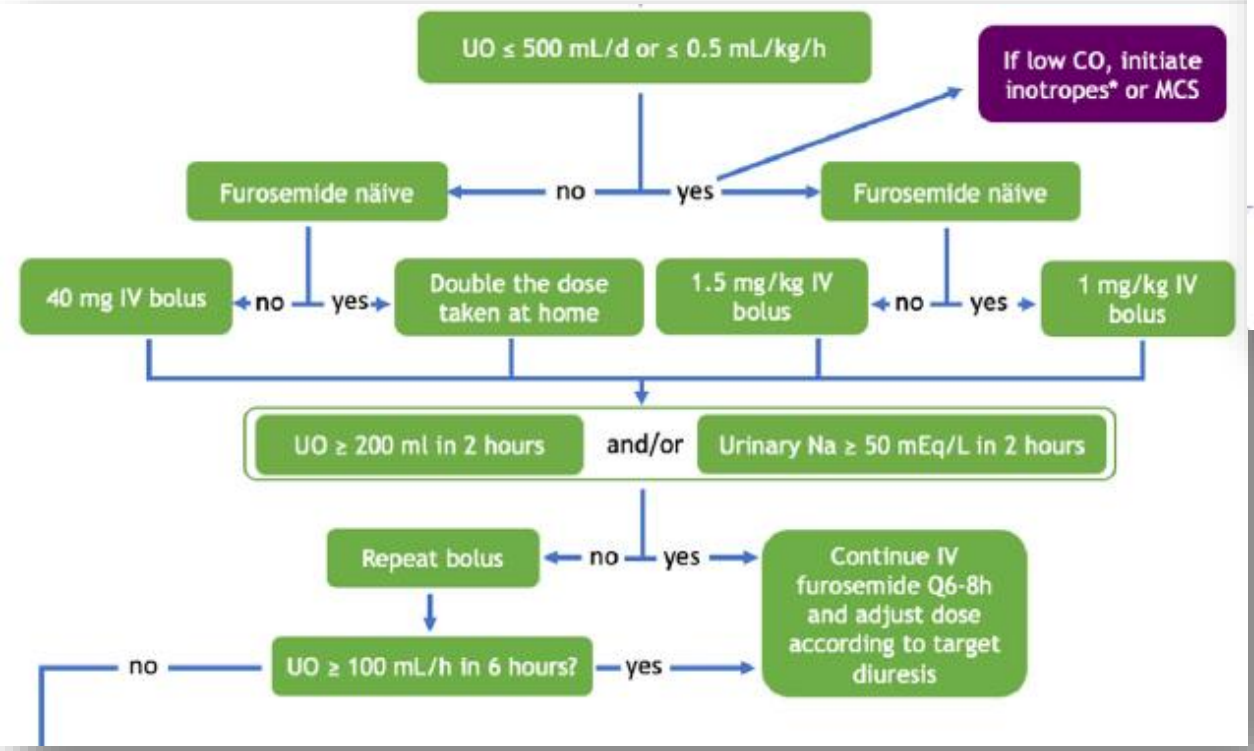
Front Physiol July 2022;13,art 913580

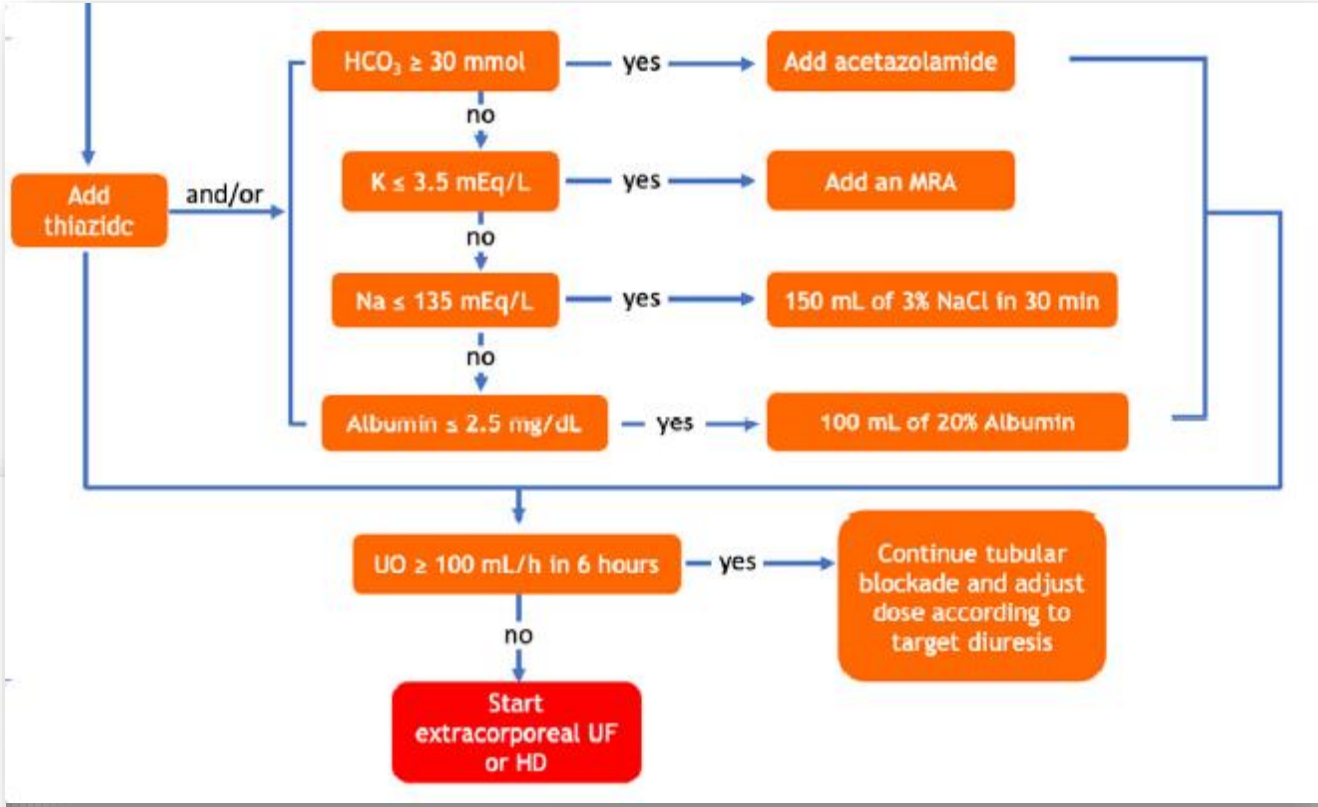
Overview and summary

- **Diuretics**
  - Mode of action
  - Comparision of pharmacokinetics
- **Evaluation a volume overload/congestion**
  - Novel ultrasound measurements
- **Diuretic resistance**
  - Definition, evaluation
  - Causes: decreased delivery to the PT, increased distal reabsorption
- **Management strategies**
  - Increase delivery to the PT
  - Sequential nephron blocade
  - Short hypertonic NaCl infusion

Summary: flow chart

Front Physiol July 2022;13,art 913580





Mecha
rationa

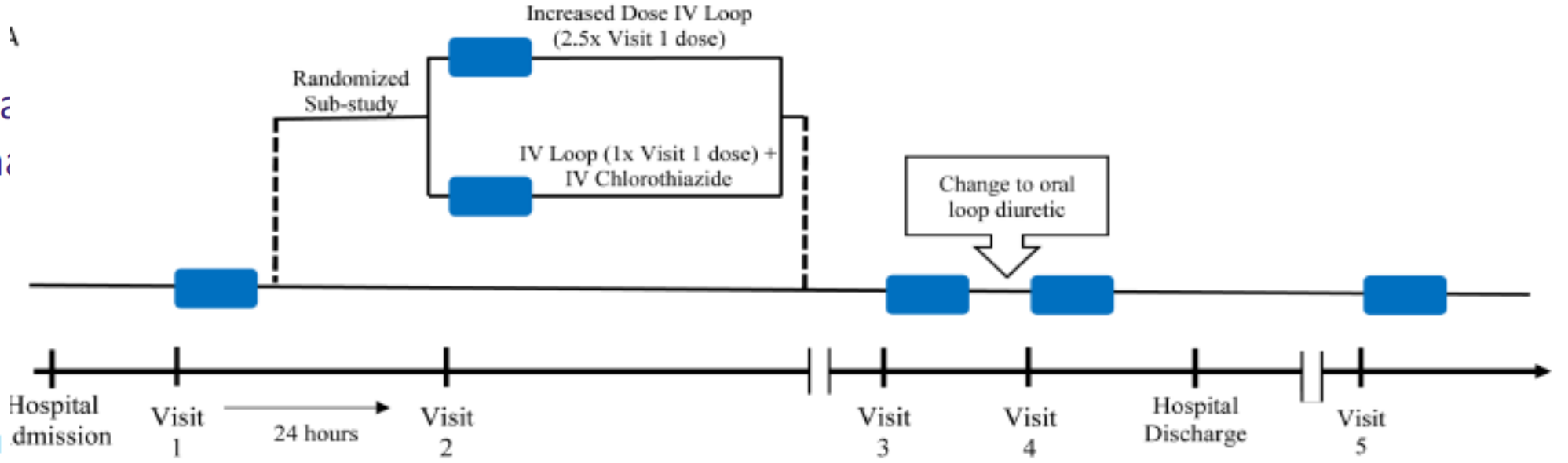
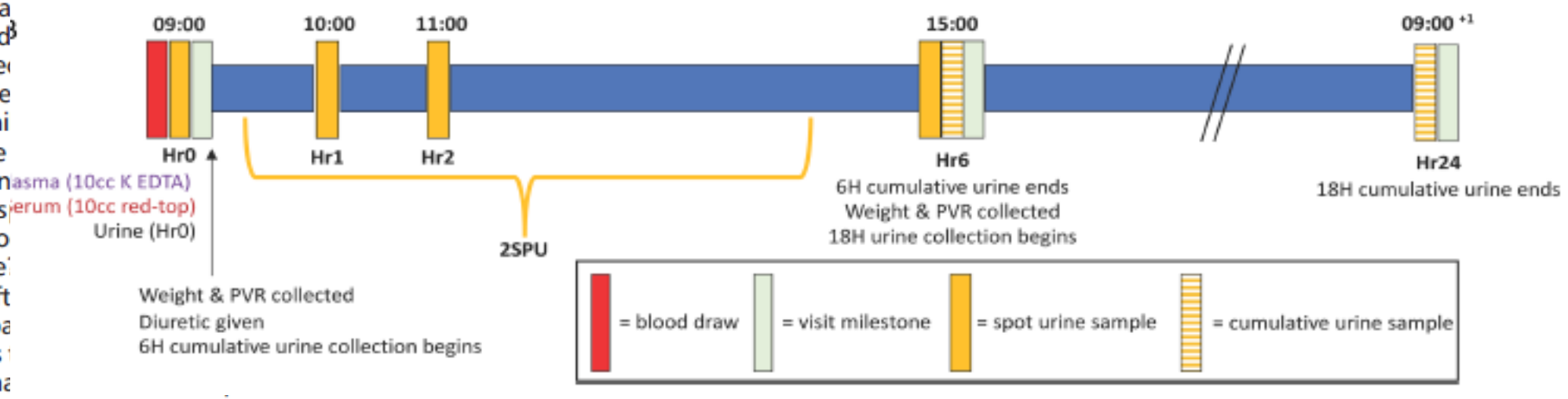


Table 1

What va
Can wid
Are spe
therapie
Does tai
Can the
Which n
Which s
How do
episode
How oft
What pa
What is
combina



ESC Heart Failure 2020;7:4458