De-Congestion in Heart Failure
Diuretics *vs* Ultrafiltration

Amir A. Nassiri, M.D, D.I.U

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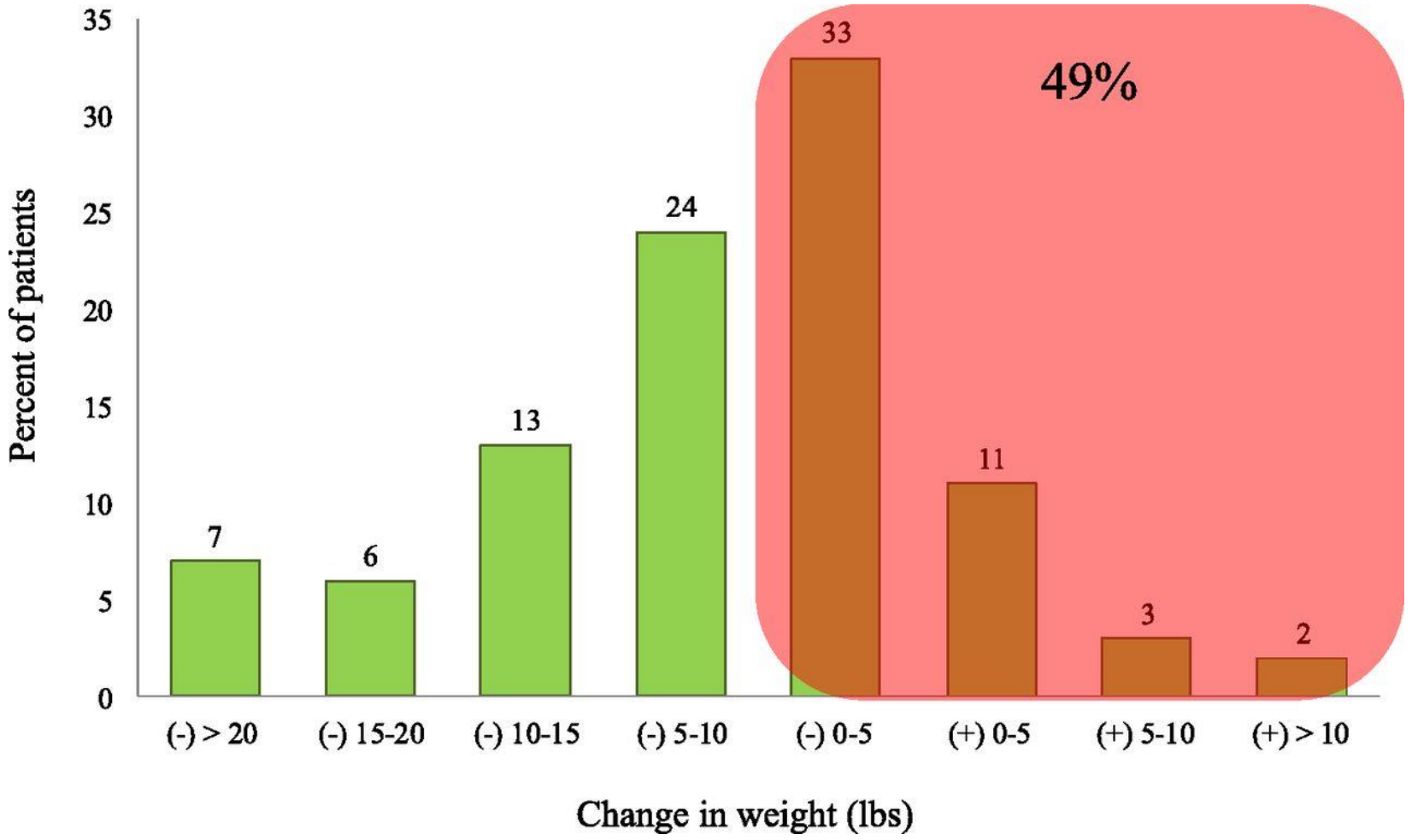
Outlines

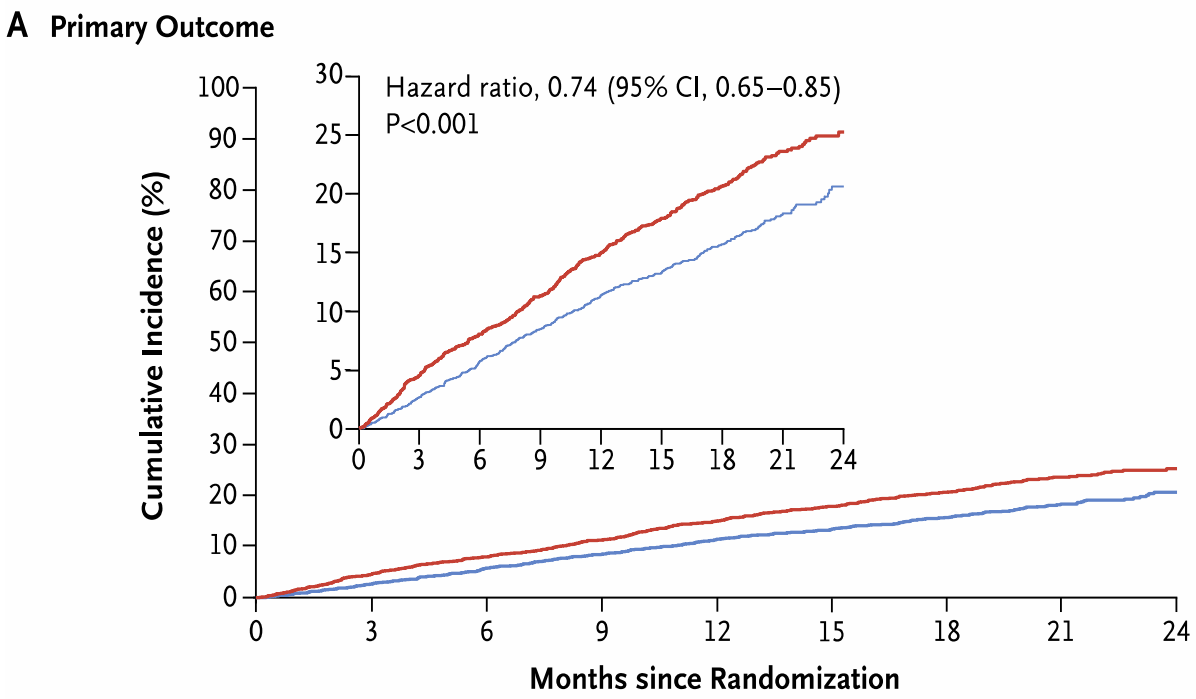
- Congestion & the Kidney
- Congestion & Sodium
- De-congestion
- Diuretic
- Ultra-filtration

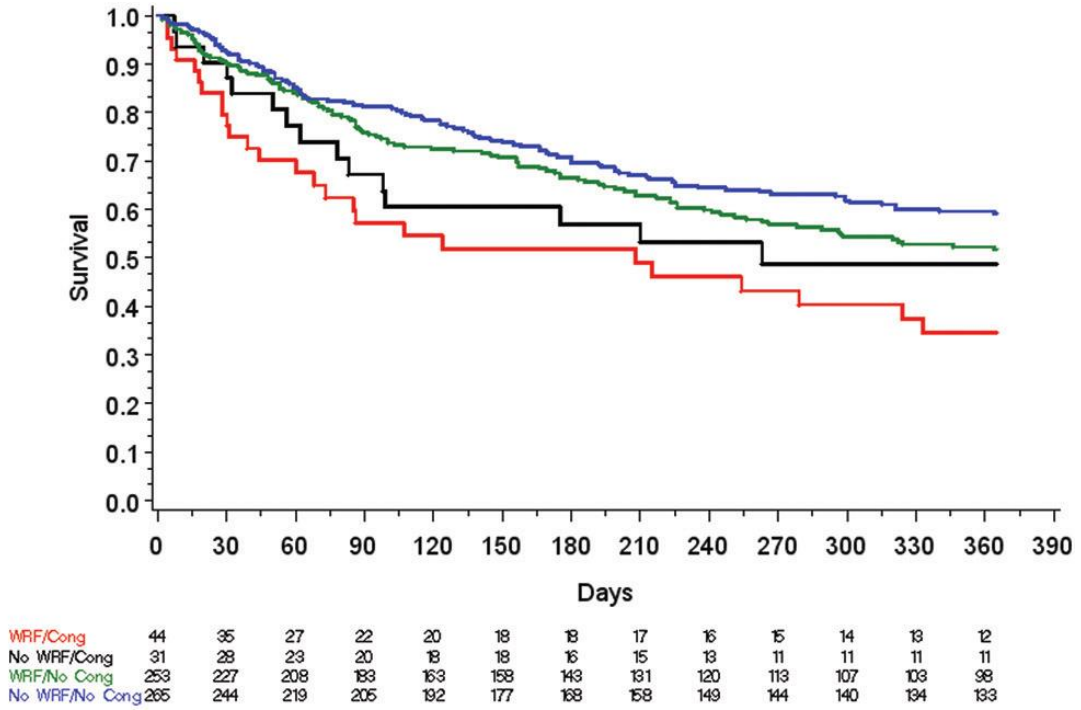
ADHERE

many pts go home w/ residual congestion !



Under-appreciation of congestion

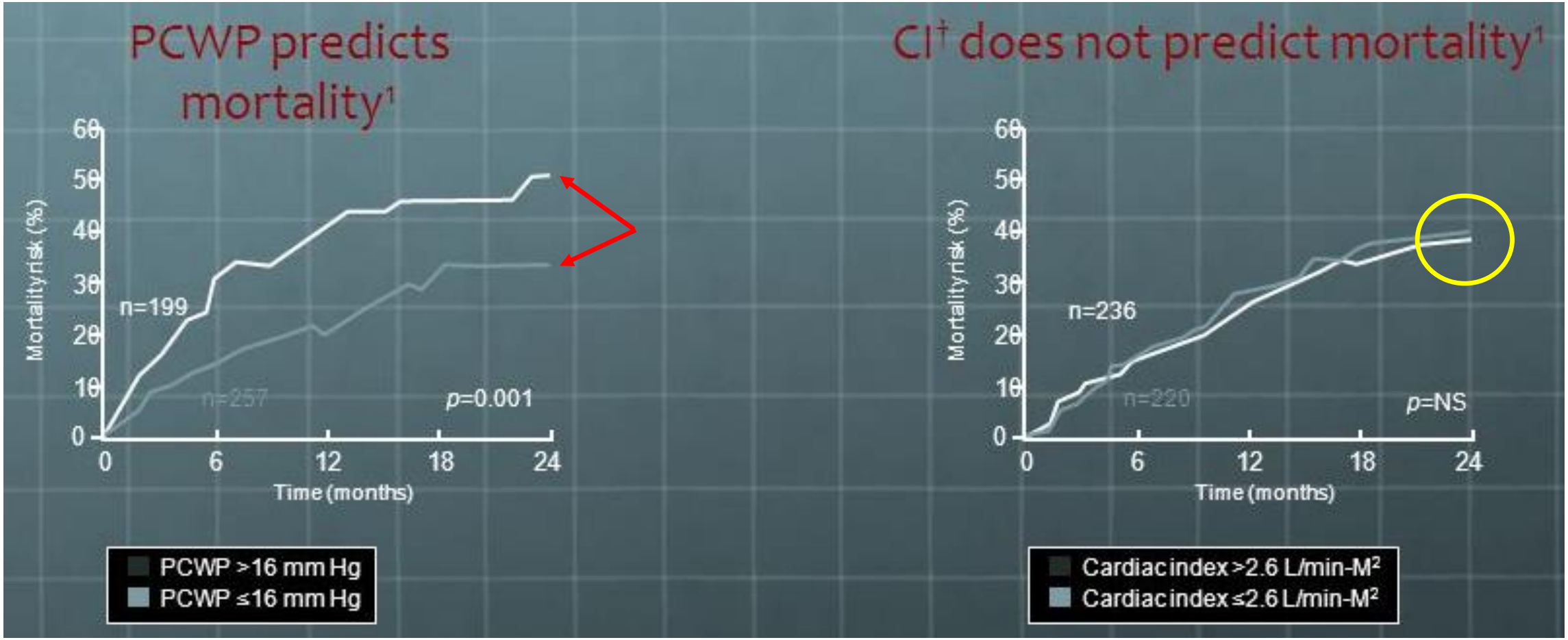




20% of Ambulatory pt w/ AHF have a risk of death or to be re-Hosp within *2 years* >>> clearly under appreciated by most

even worst >>> once admitted by HF & discharged with ongoing congestion ! (ADHERE) >>> *the risk to be re-Hosp or to die >>> 60% at 1 year*

Mortality Predication



“reduction in congestion” is more important than “improving in COP” (in terms of mortality/survival)

RIGHT-SIDED HEART FAILURE

Functional tricuspid regurgitation

Increased central pressure

CONGESTIVE HEPATOPATHY

Decreased hepatic function

CONGESTIVE NEPHROPATHY

Decreased glomerular filtration rate

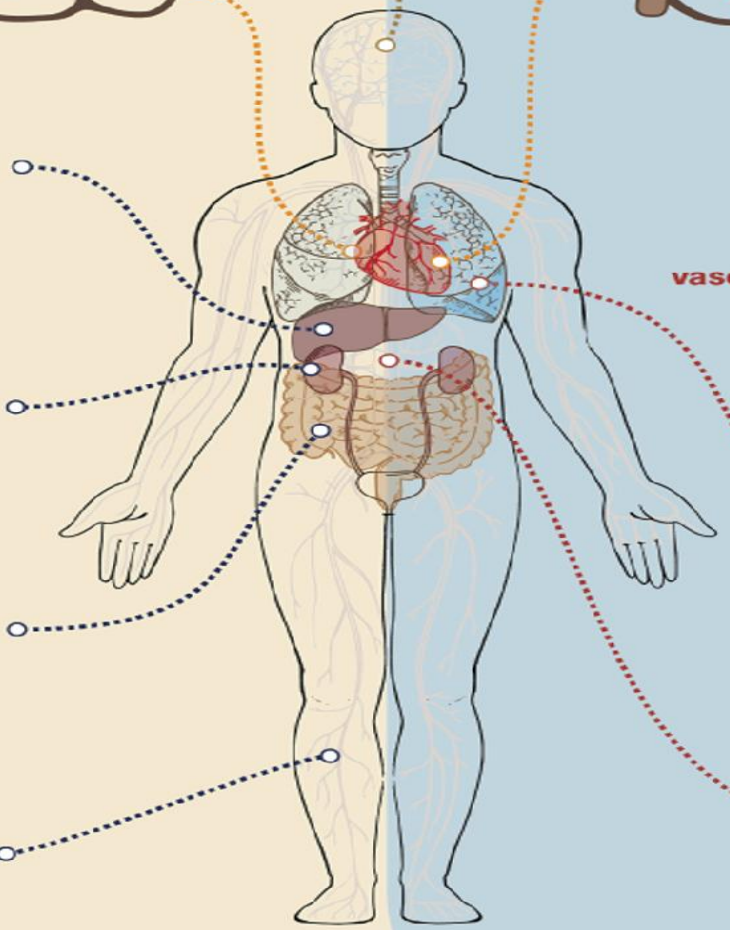
INTESTINAL CONGESTION

Malabsorption
Malnutrition
Proinflammatory state

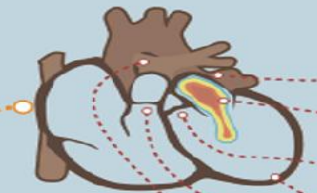
INTERSTITIAL CONGESTION

Interstitial edema

CONFUSION
MENTAL DISTURBANCE



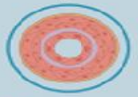
LEFT-SIDED HEART FAILURE



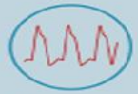
Left atrial remodeling

Functional mitral regurgitation

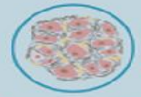
Reduced cardiac output



Pulmonary vascular remodelling



Pulmonary hypertension



Myocardial fibrosis

LUNG CONGESTION

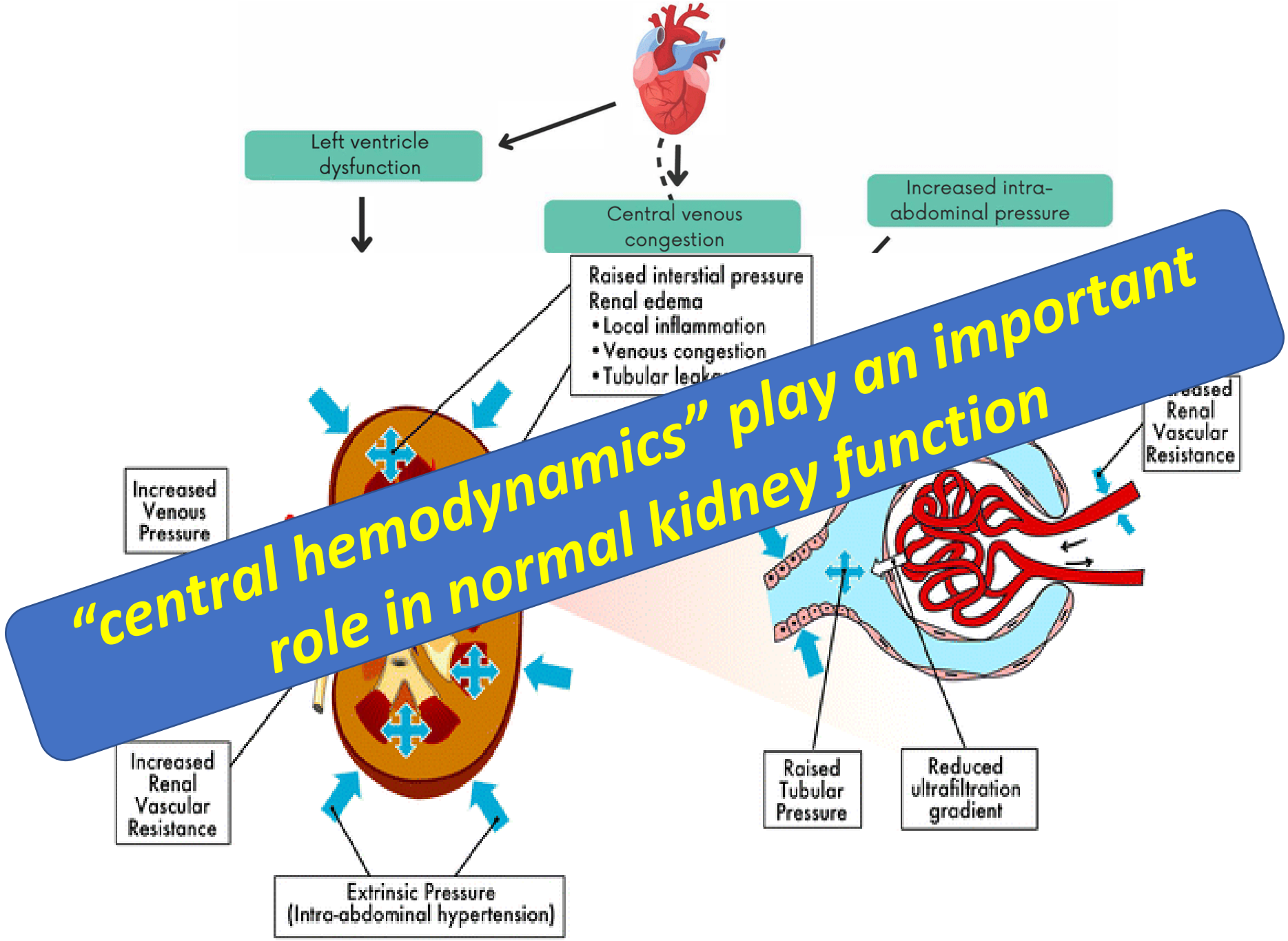
Alveolar edema

Pleural effusion

ARTERIAL VASCULAR REMODELLING

Increased arterial stiffness

increased systemic vascular resistances


Left ventricle dysfunction
Central venous congestion
Increased intra-abdominal pressure
Raised interstial pressure
Renal edema
• Local inflammation
• Venous congestion
• Tubular leak
Increased Venous Pressure
Increased Renal Vascular Resistance
Extrinsic Pressure (Intra-abdominal hypertension)
Renal Vascular Resistance
Raised Tubular Pressure
Reduced ultrafiltration gradient
"central hemodynamics" play an important role in normal kidney function

CVP > 20 mmHg reduces UOP independent of COP

612.463.5:612.144

THE INFLUENCE OF VENOUS PRESSURE ON THE ISOLATED MAMMALIAN KIDNEY.

By F. R. WINTON.
Beit Memorial Fellow.

(*From the Department of Pharmacology, University College, London.*)

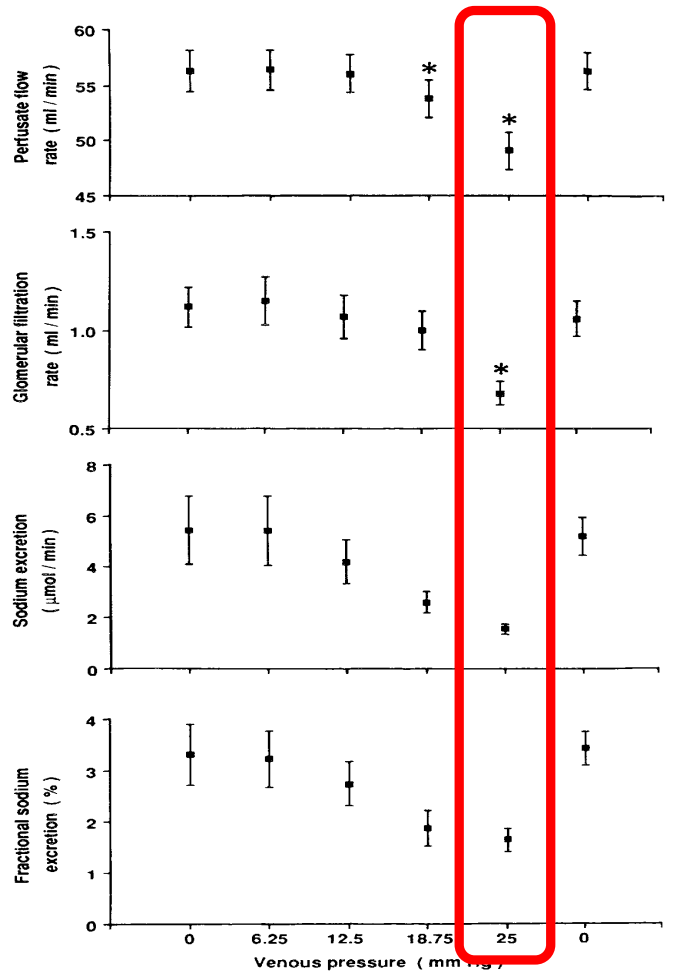
Introduction.

If the blood-pressure in the renal vein is raised beyond about 10 mm. Hg it retards the urine flow. Ludwig [1861] attributed this to mechanical obstruction of the distal part of the uriniferous tubules, due to their compression by the surrounding venules. Heidenhain [1883] endorsed this view in the following terms: "Venöse Stauung hat aber noch besondere Folgungen für die Grenzschicht. Indem ihre Venenbündel sich erweitern, verengern oder verschliessen sie selbst vollständig die zwischen ihn bündelweise gelargerten Harncanälchen, wie Ludwig theils durch anatomische Untersuchungen von Hundenieren mit während des Lebens unterbundenen Venen, theils durch hydraulische Versuche feststellte."

Ludwig also recognized that the effects of increase in capsular pressure due to such obstruction of the tubules would be to some extent neutralized by an increased pressure in the glomerular capillaries, owing to the reduction in the pressure gradient beyond the renal artery when the pressure in the vein is raised.

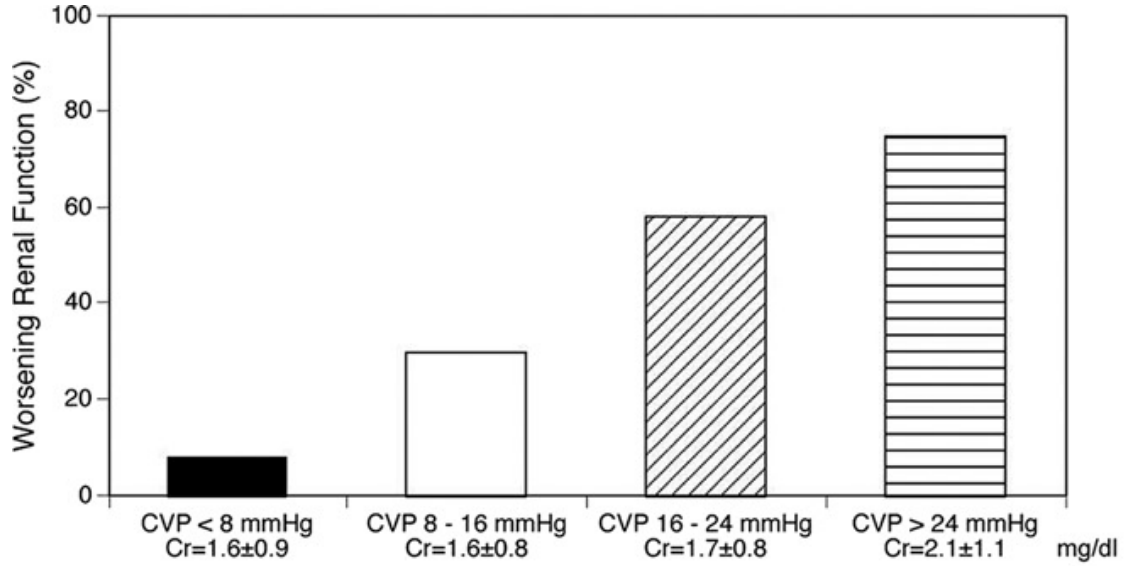
Heidenhain, however, emphasized particularly the reduction in blood flow through the kidney, both when the venous pressure was raised and when the arterial pressure was lowered, and this induced him to attribute the resulting changes in the rate of formation of urine to changes in the velocity of the blood rather than to changes in hydrostatic pressure. Fig. 4, below, incidentally disproves this contention, since it shows that in suitable circumstances an increase of venous pressure which reduces the velocity of blood flow may produce no change, or even an increase, in the rate of urine formation. The observations of these and later authors on the effects of venous obstruction on the kidney have, however, been mainly qualitative.

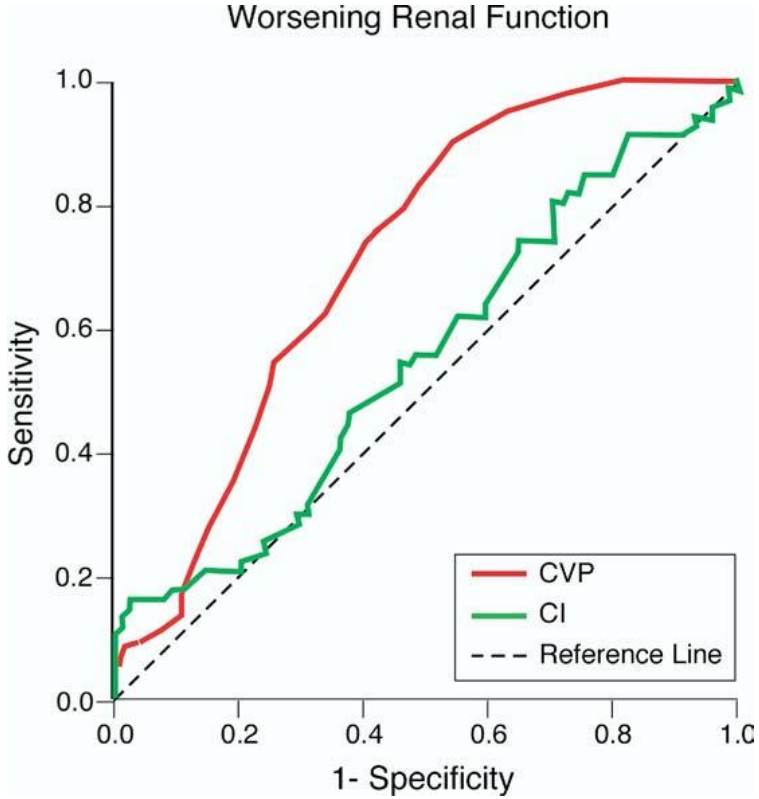
Now the venous pressure, like the arterial pressure and the ureter



Effect of increasing venous pressure on renal perfusate flow rate, glomerular filtration rate, sodium excretion, and fractional sodium excretion in kidneys perfused at constant arterial pressure.

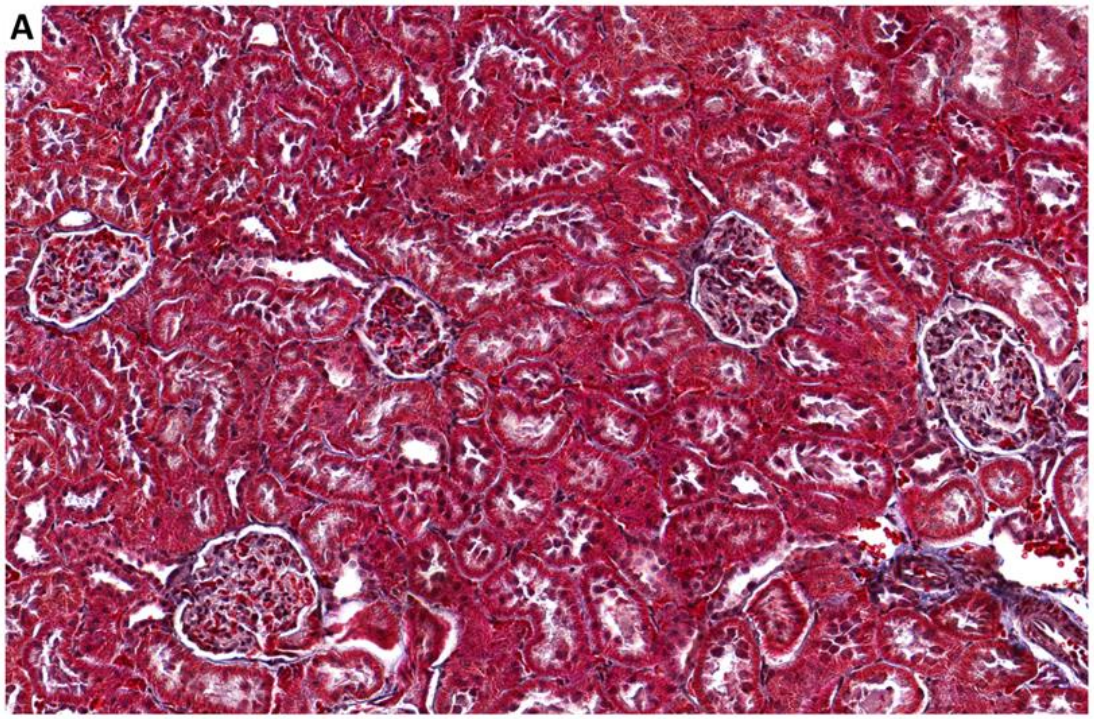
elevated CVP >>> impaired kidney function >>> more Na retention

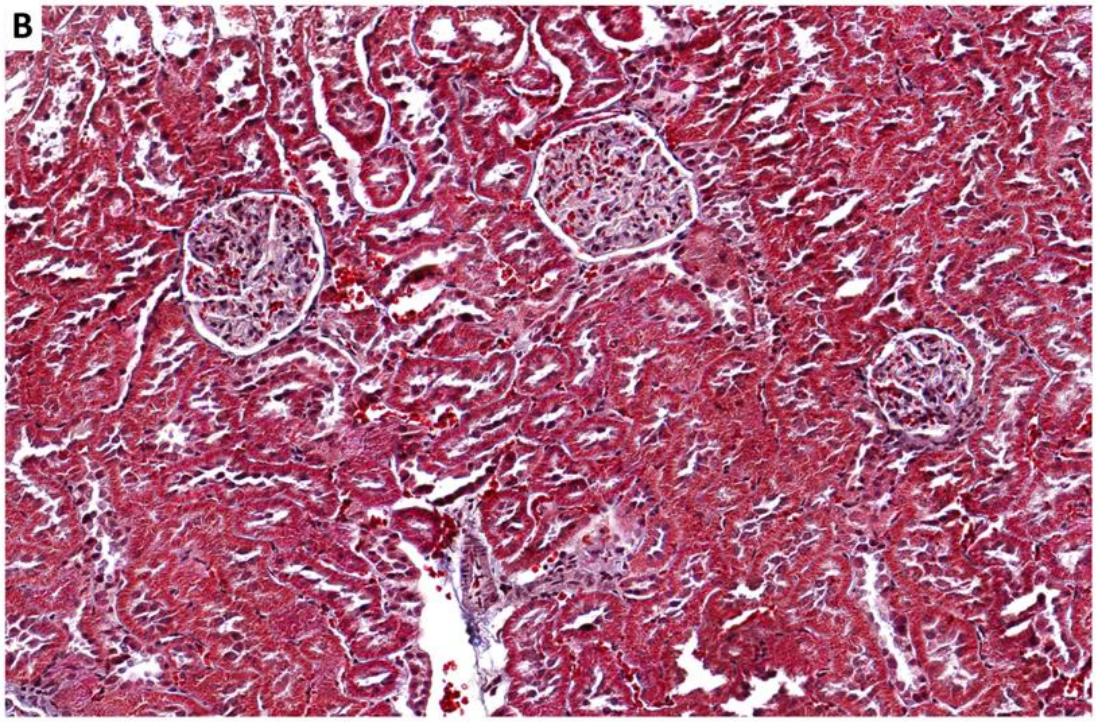




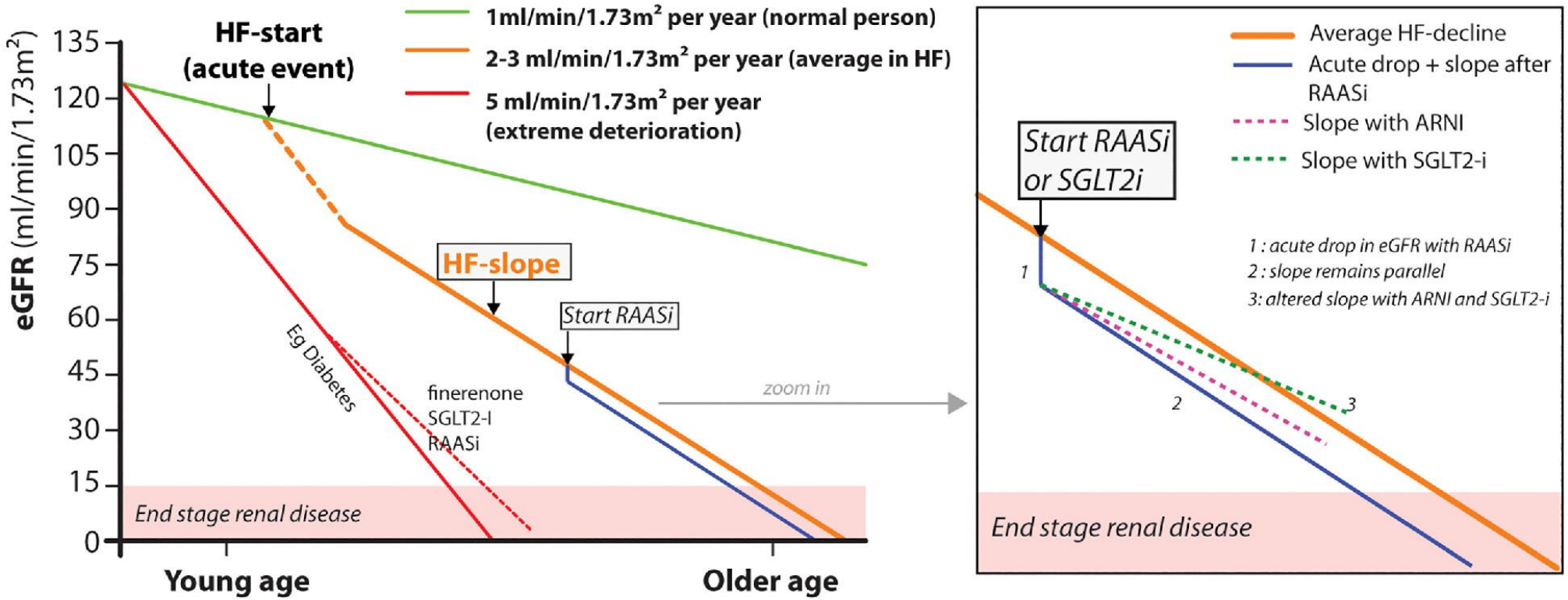
increased CVP contributes "more" to WRF, than a low COP

12 w of partial IVC ligation (increased CVP)
>>> irreversible glomerular changes





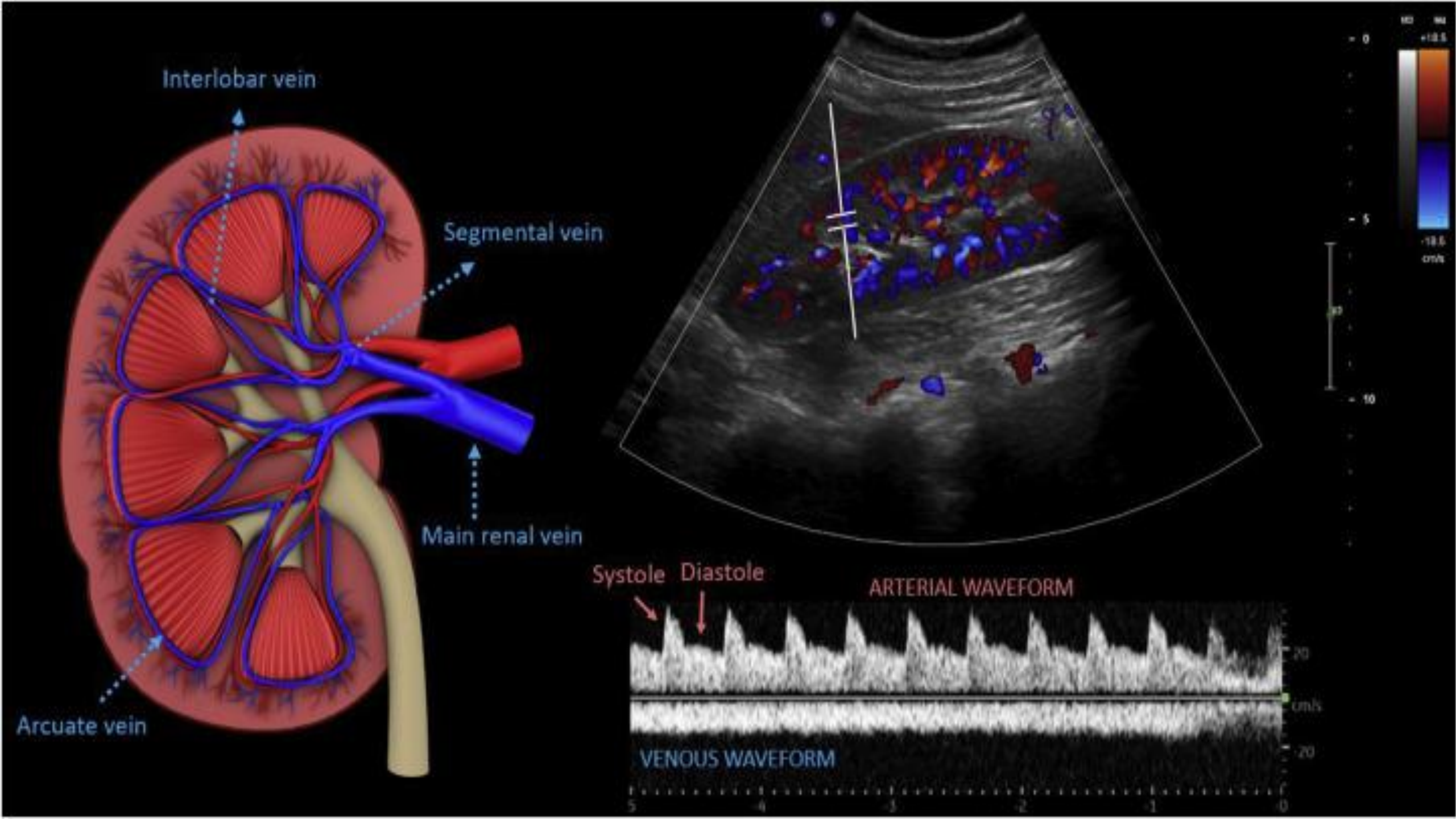
CKD (eGFR<60) affects 50% of HF pts
CKD = x2 of risk for all-cause mortality
CKD = far more stronger predictor than LVEF
CKD pts are more or less HF pts



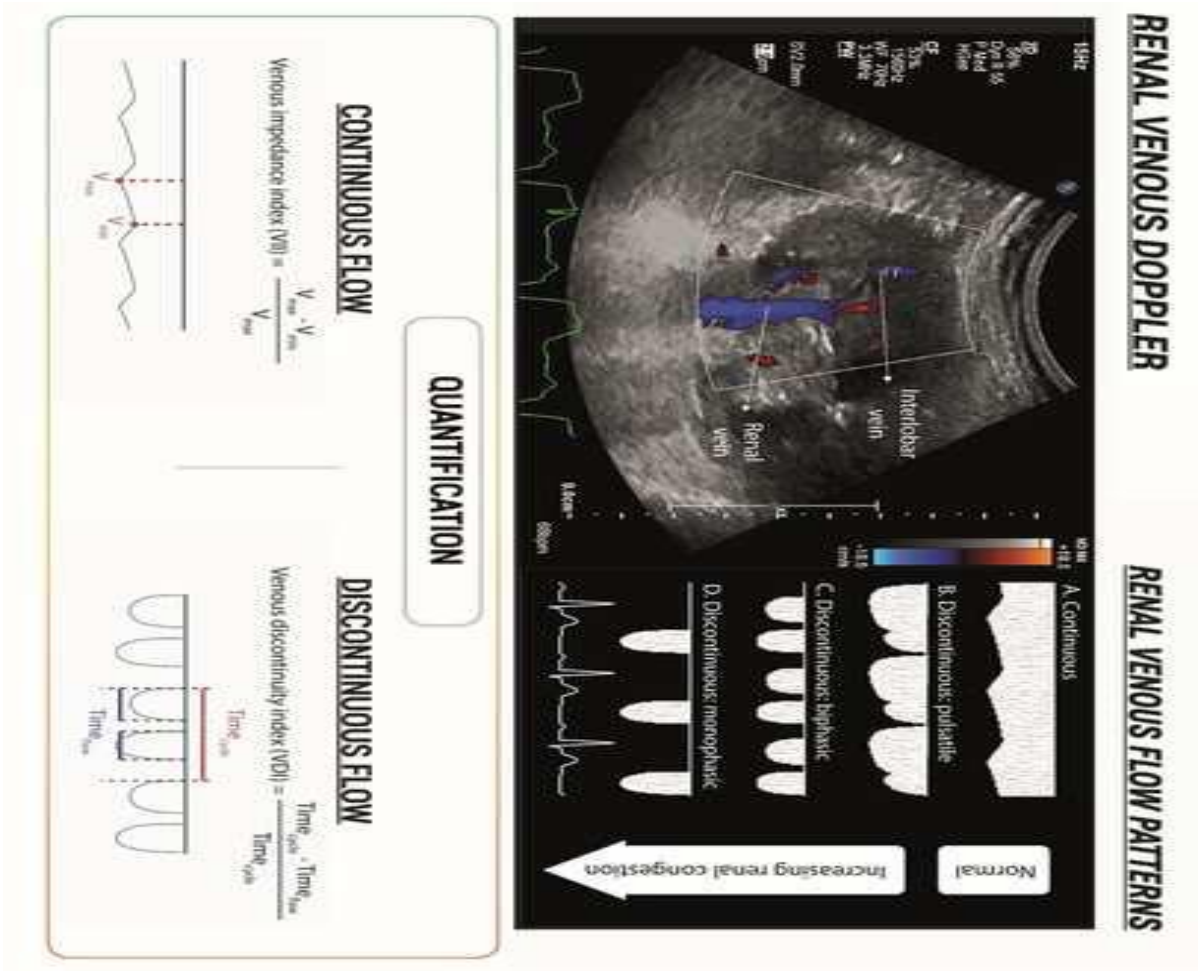
Mullens W Eur J HF, 2020. Mullens W Eur J HF 2022

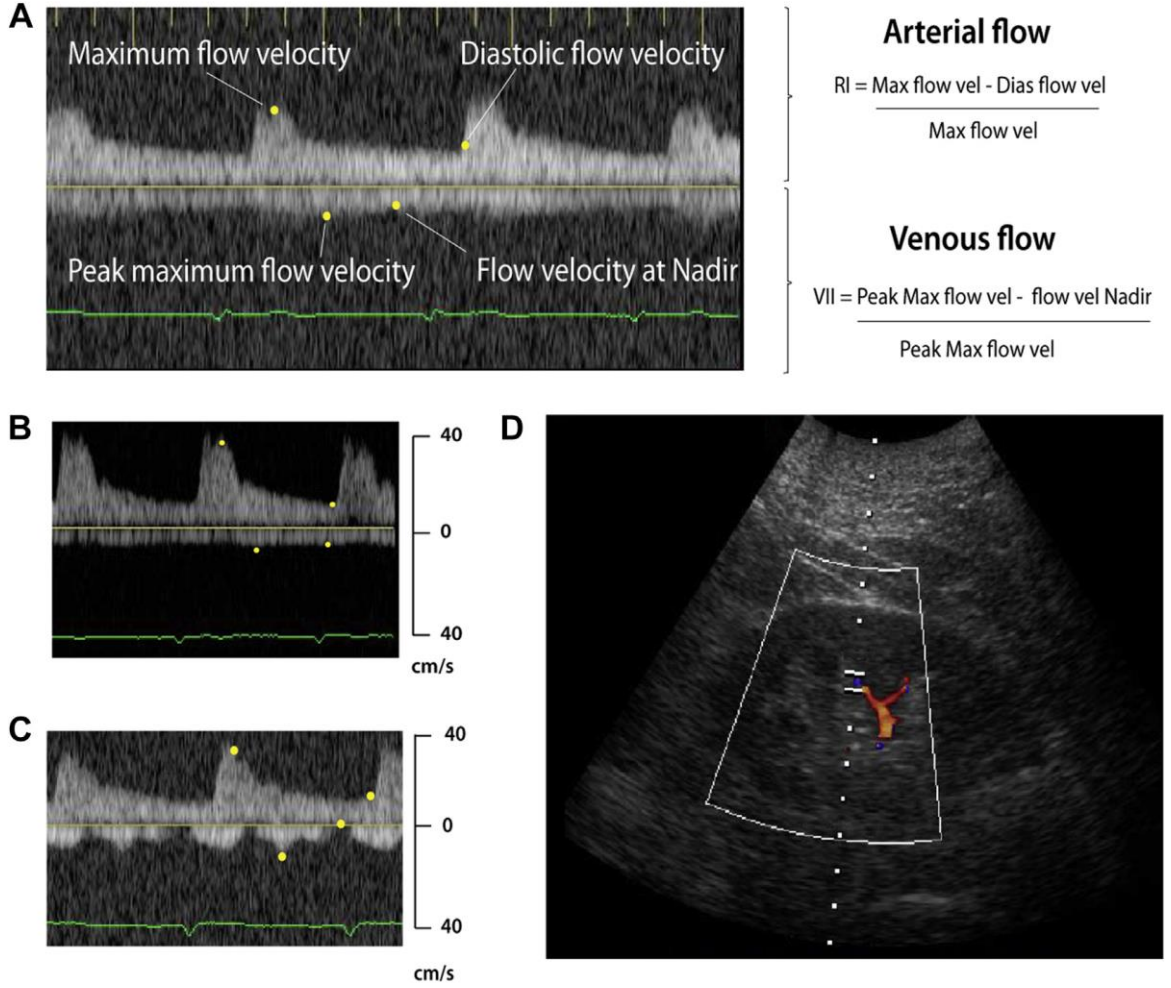
look at the "renal venous flow"

for ***early detection*** of **CONGESTION**

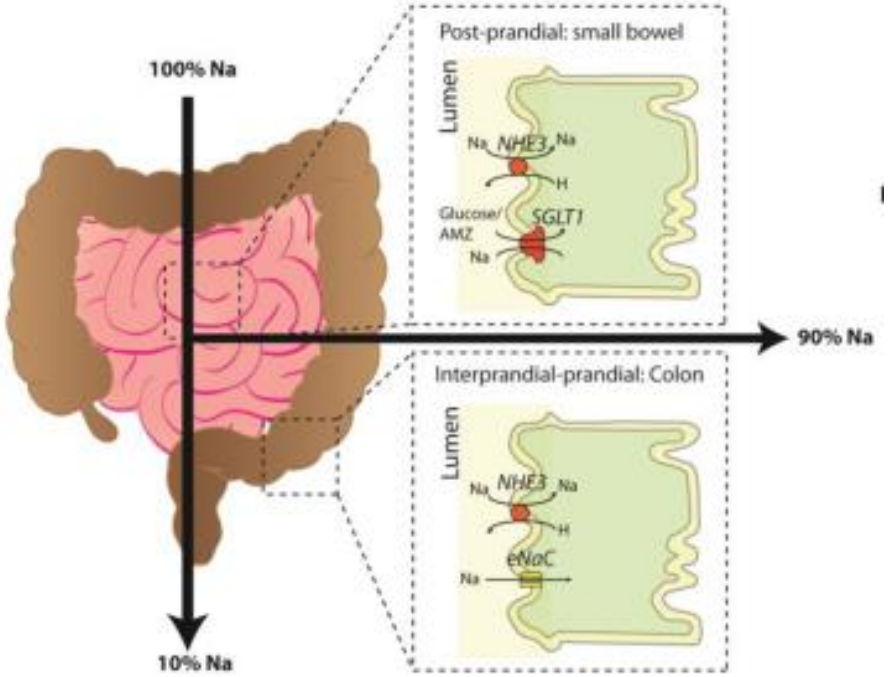

Interlobar vein
Segmental vein
Main renal vein
Arcuate vein
Systole
Diastole
ARTERIAL WAVEFORM
VENOUS WAVEFORM
cm/s

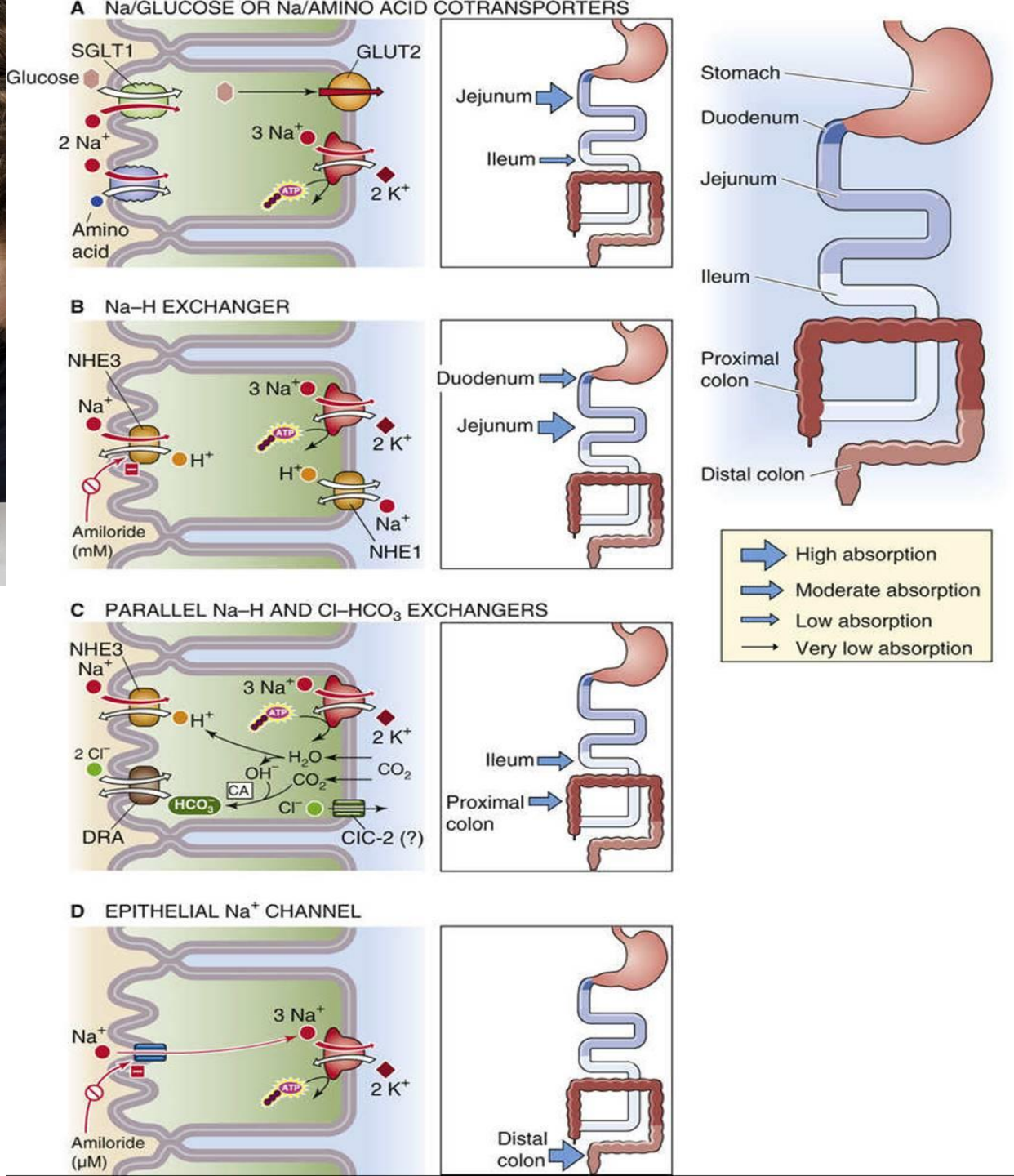
increased CVP >>> the continuous flow of the renal veins >>> *dis-continuous* renal venous flow





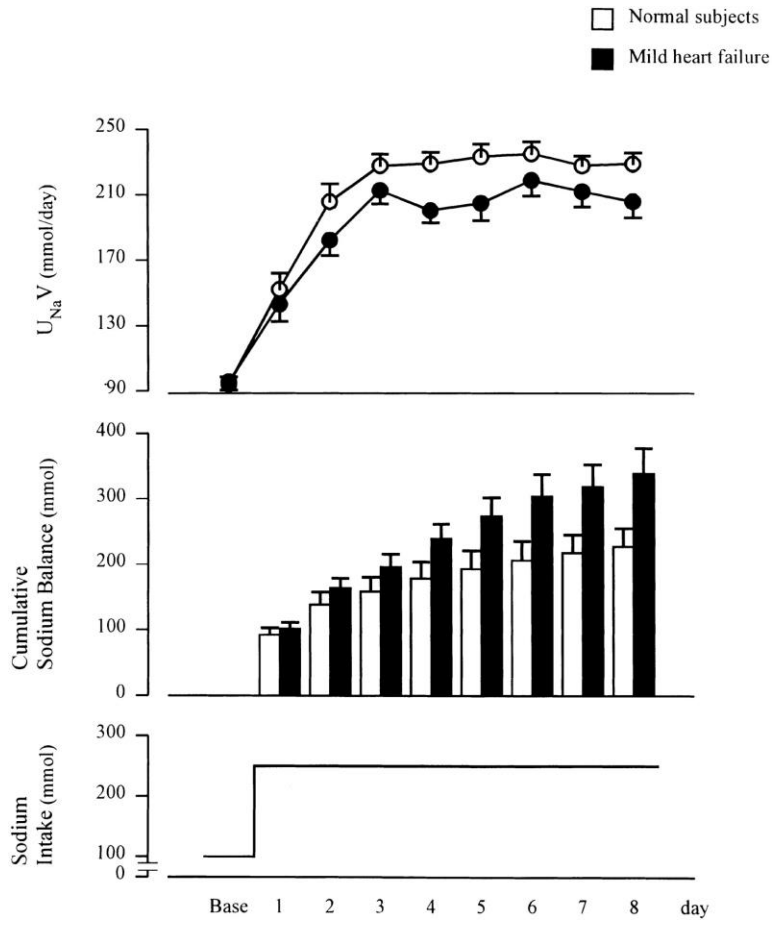

increased RAAS Activity

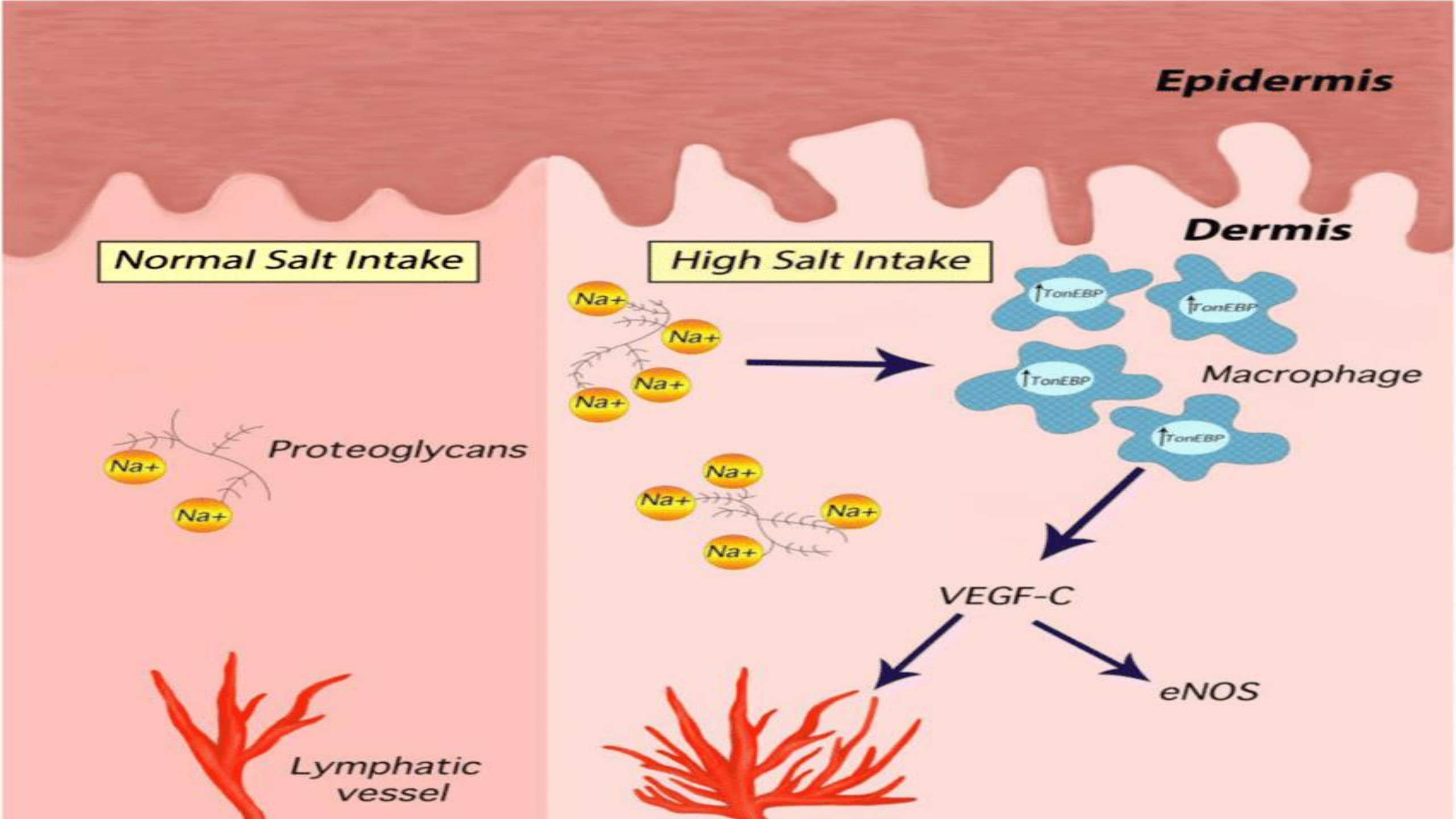

100% Na
90% Na
10% Na
Post-prandial: small bowel
Lumen
Na
NHE3
H
Glucose/
AMZ
SGLT1
Interprandial-prandial: Colon
eNaC

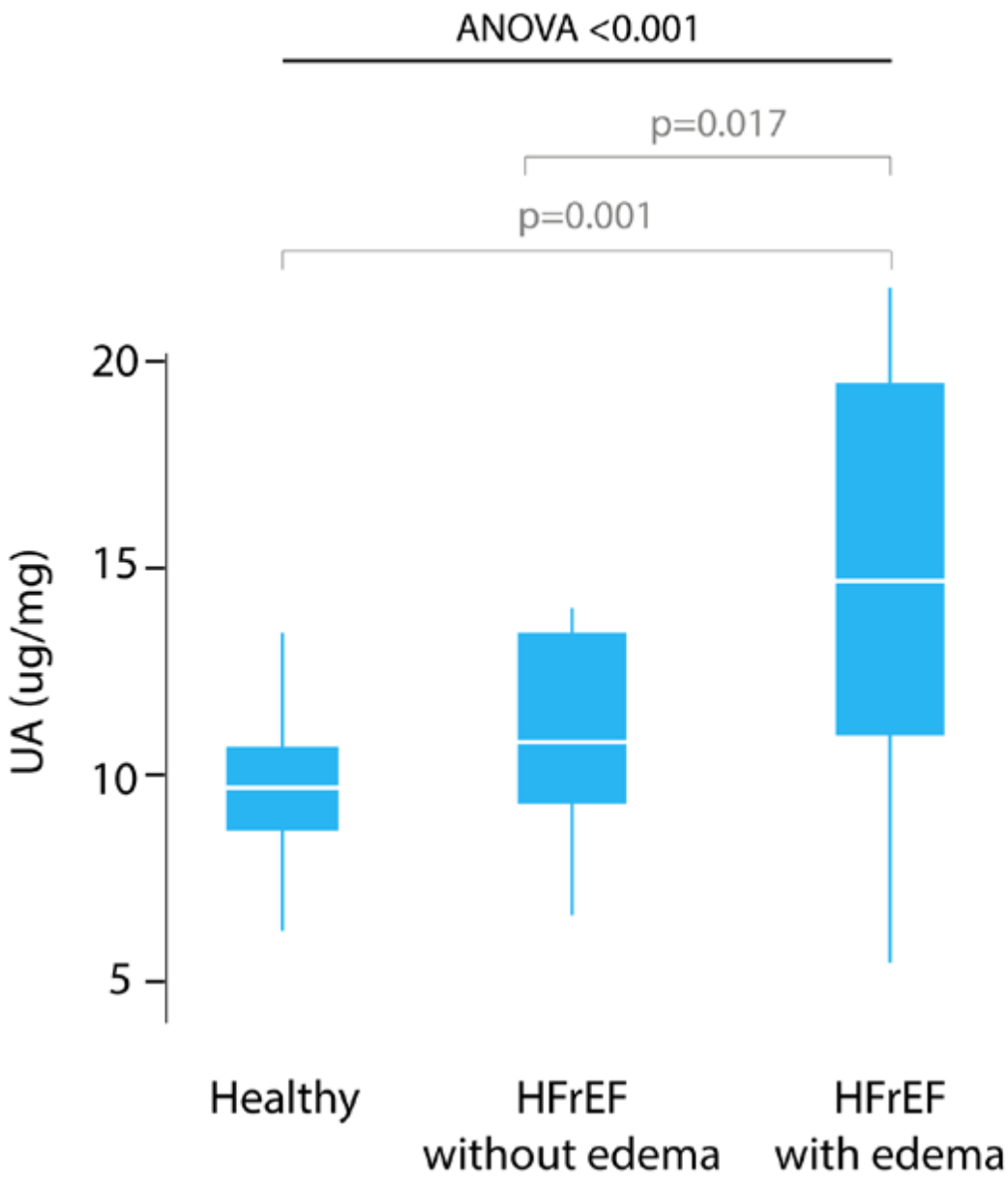

A Na/GLUCOSE OR Na/AMINO ACID COTRANSPORTERS
SGLT1
GLUT2
Glucose
2 Na+
3 Na+
2 K+
ATP
Amino acid
Jejunum
Ileum
B Na–H EXCHANGER
NHE3
Na+
H+
Amiloride (mM)
Na+
NHE1
Duodenum
Jejunum
C PARALLEL Na–H AND Cl–HCO3 EXCHANGERS
2 Cl−
H2O
OH−
CO2
CA
HCO3
Cl−
DRA
ClC-2 (?)
Ileum
Proximal colon
D EPITHELIAL Na+ CHANNEL
Amiloride (μM)
Distal colon
Stomach
Duodenum
Jejunum
Ileum
Proximal colon
Distal colon
High absorption
Moderate absorption
Low absorption
Very low absorption

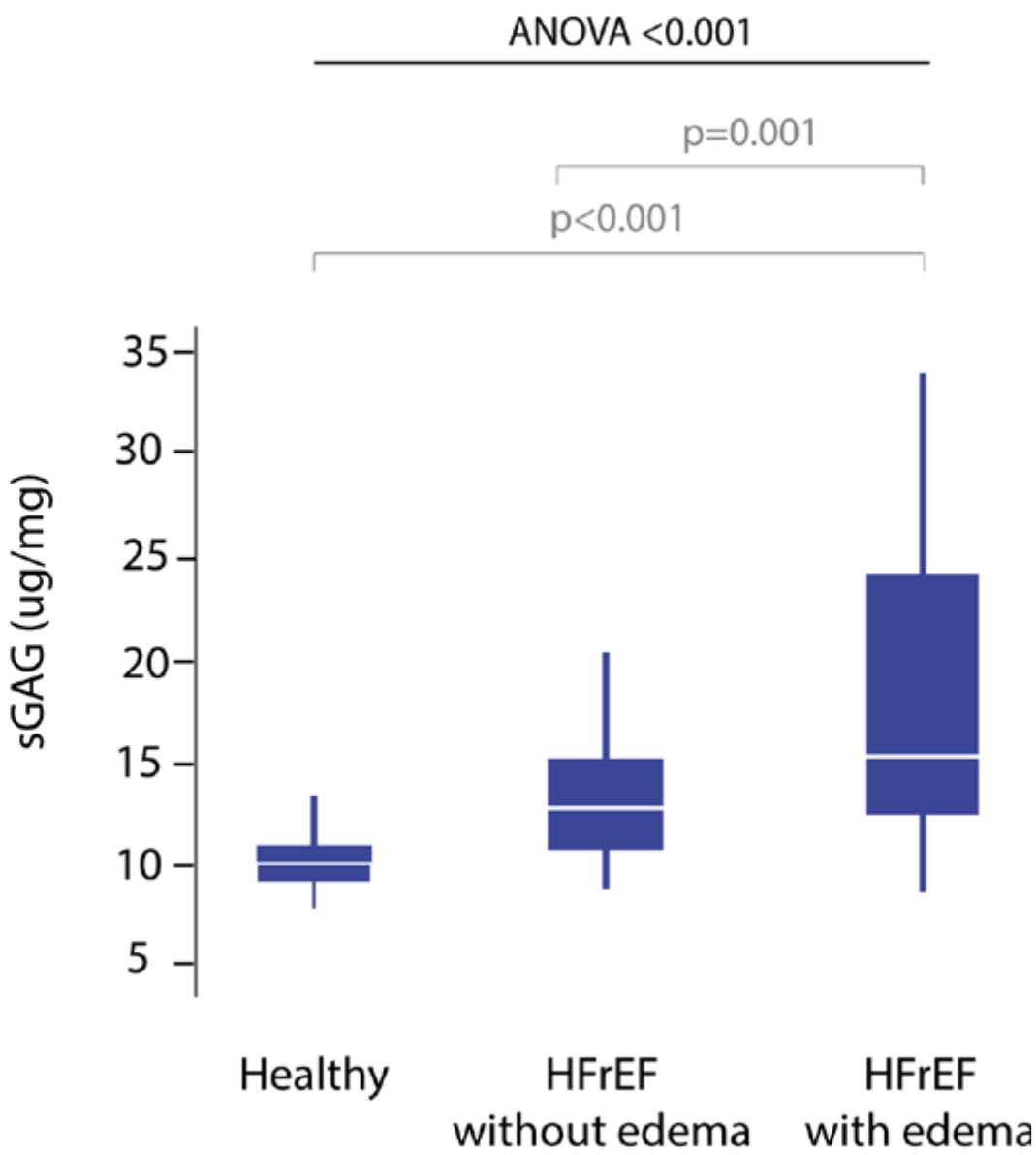
we have a lot of Na stores

positive Sodium balance: very fast !




Epidermis
Dermis
Normal Salt Intake
High Salt Intake
Na+
Na+
Na+
Na+
TonEBP
TonEBP
TonEBP
TonEBP
Macrophage
Proteoglycans
Na+
Na+
Na+
Na+
Na+
Na+
VEGF-C
eNOS
Lymphatic
vessel


ANOVA <0.001
p=0.017
p=0.001
UA (ug/mg)
20
15
10
5
Healthy
HFrEF without edema
HFrEF with edema

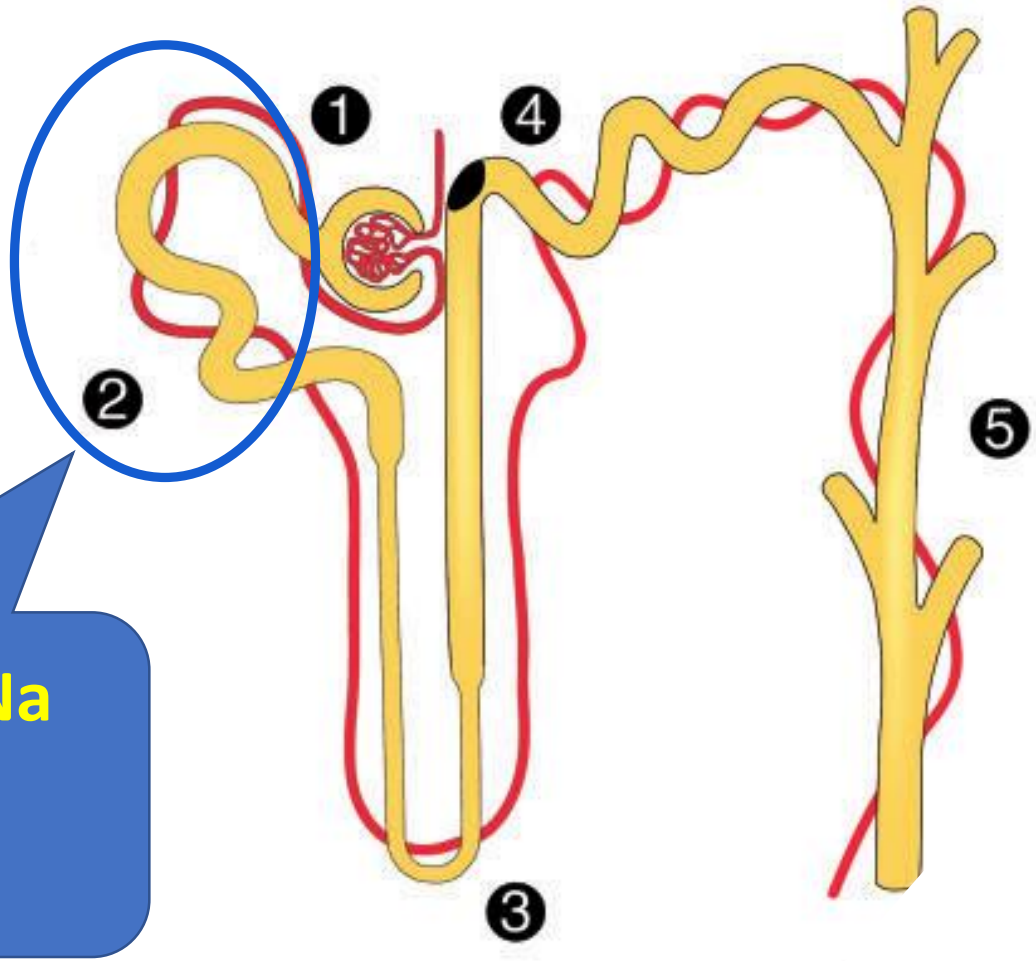

ANOVA <0.001
p=0.001
p<0.001
sGAG (ug/mg)
35
30
25
20
15
10
5
Healthy
HFrEF without edema
HFrEF with edema

GFR = 120-125 mL/min = 170-180 L/day
Plasma [Na+] = 145 mmol/L
180 x 145 = 26,100 mmoL [Na+] filtered each day = ***> 1 kg Na***

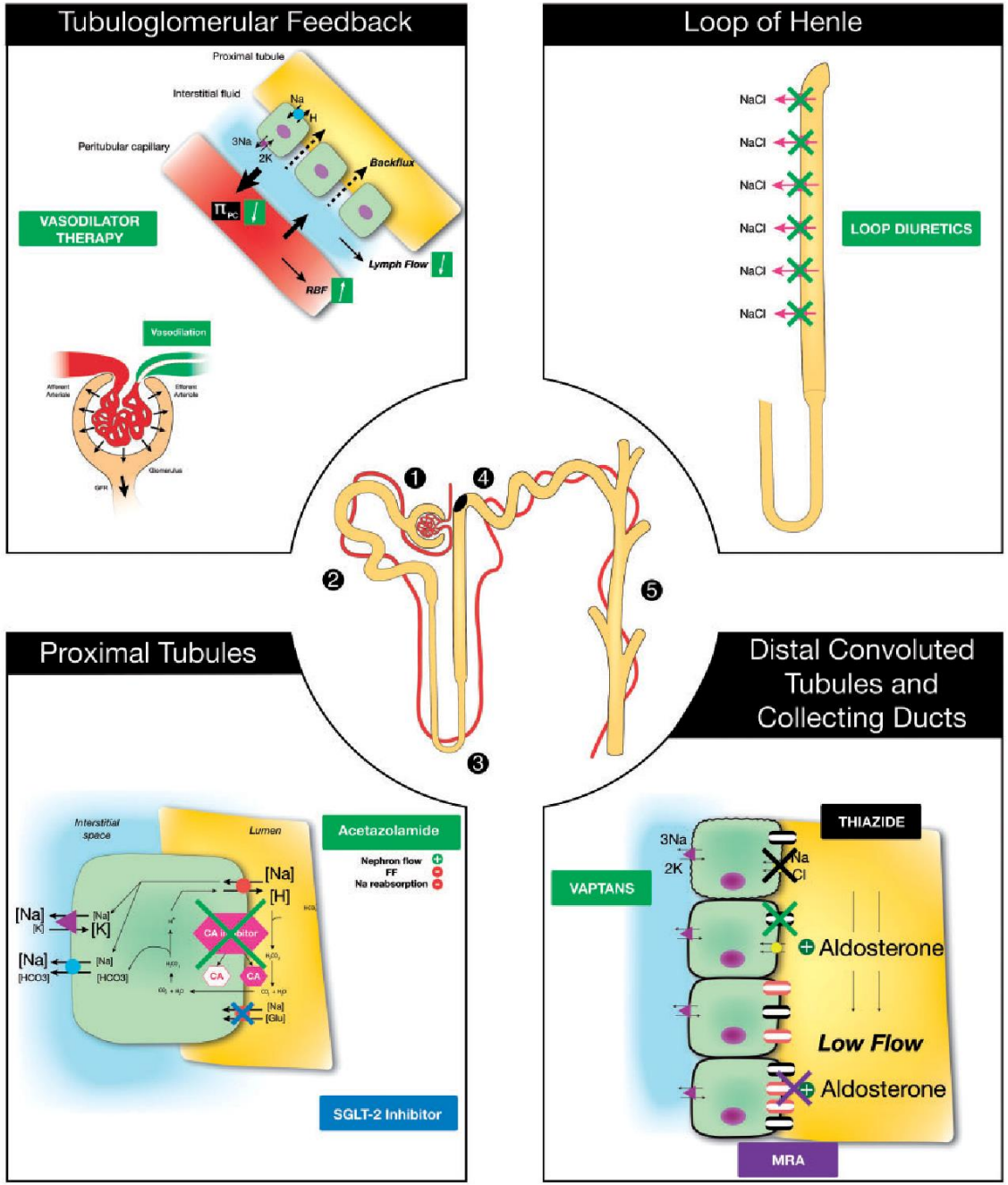
GFR = 10-15 mL/min = 15-20 L/day (need for Dx !)
[Na+] = 145 mmol/L
3,000 mmol Na+ filtered each day = **150 gr Na**

the problem:
reabsorption is stimulated

HF induces an increased renal Na reabsorption, especially in the proximal parts



HF >>> increased Na reabsorption (esp in prox)


Tubuloglomerular Feedback
Proximal tubule
Interstitial fluid
Peritubular capillary
Na
H
3Na
2K
Backflux
TL_{PC}
Lymph Flow
RBF
VASODILATOR THERAPY
Vasodilation
Afferent Arteriole
Efferent Arteriole
Glomerulus
GFR
Loop of Henle
NaCl
NaCl
NaCl
NaCl
NaCl
NaCl
LOOP DIURETICS
1
2
3
4
5
Proximal Tubules
Interstitial space
Lumen
[Na]
[H]
[Na]
[K]
[Na]
[HCO3]
[Na]
[HCO3]
CA Inhibitor
CA
CA
[Na]
[Glu]
Acetazolamide
Nephron flow
FF
Na reabsorption
SGLT-2 Inhibitor
Distal Convoluted Tubules and Collecting Ducts
3Na
2K
Na
Cl
THIAZIDE
VAPTANS
Aldosterone
Low Flow
Aldosterone
MRA

Only Class I rec for Congestion in all HF subgroups

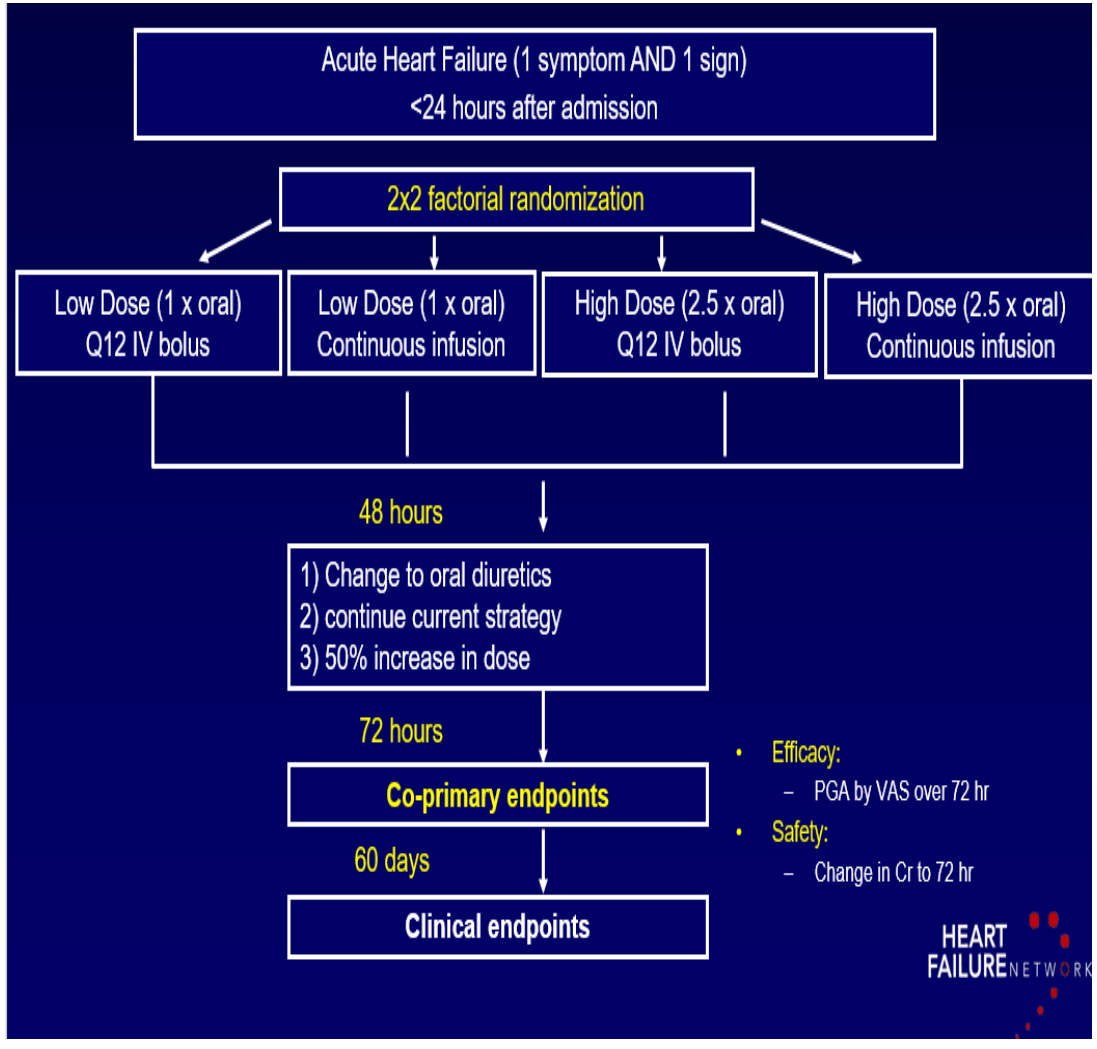
Loop diuretics		
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[137]	I	C
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

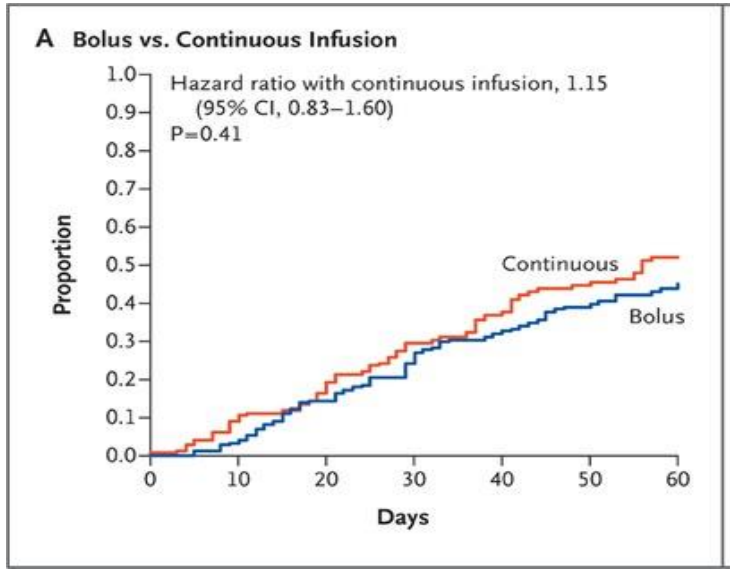
McDonagh T et al. Eur Heart J 2021

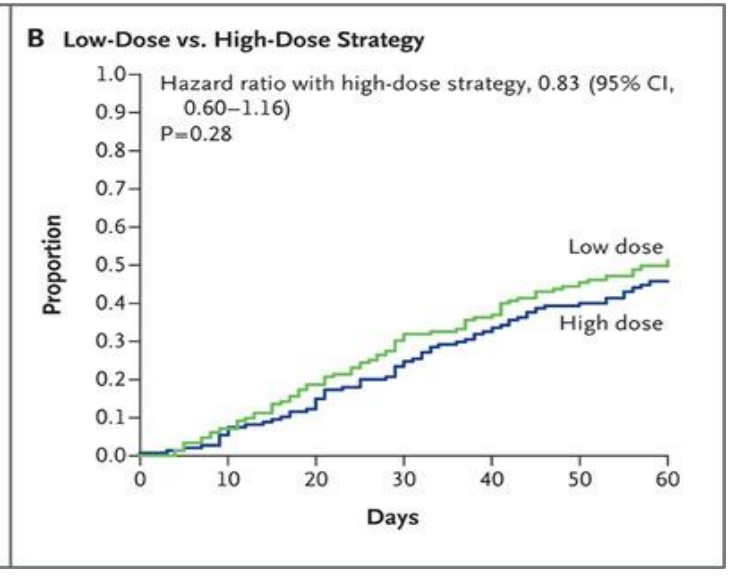
Clinical Trials in Diuretics & Decongestion

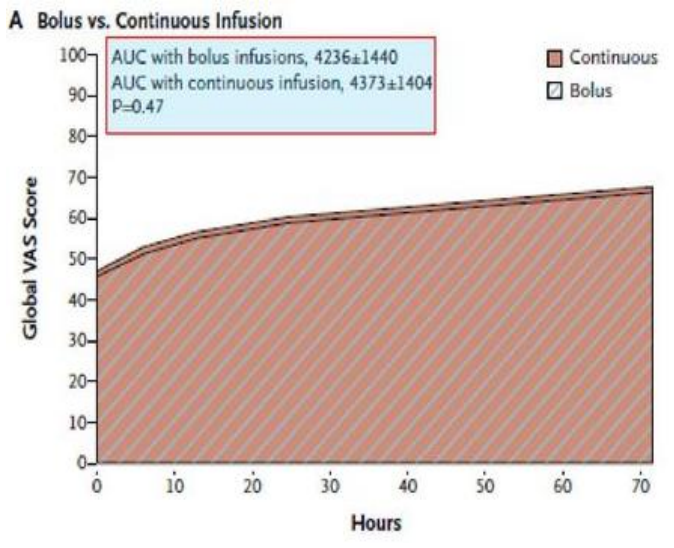
- DOSE-AHF: High Dose Loop Diuretics
- CARRESS: Decongestion Protocol (or Ultrafiltration)
- ENACT-HF: Diuretic Protocols
- ADVOR: Acetazolamide
- CHLOROTIC: Thiazide Diuretics
- ATHENA: MRA
- TRANSFORM-HF: Loop Diuretics
  - Ancillary Study Insights

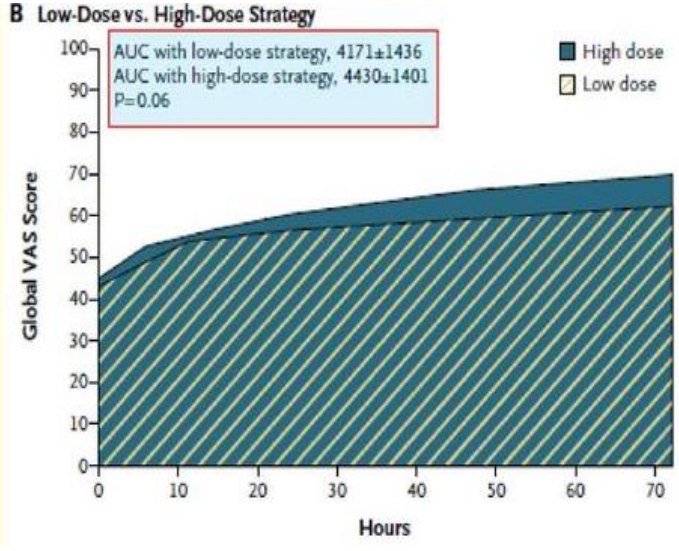
DOSE-AHF











Felker GM *et al*, *NEJM* 2011

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

High-dose IV diuretics

No benefit for primary endpoint of Patient Global Assessment…But

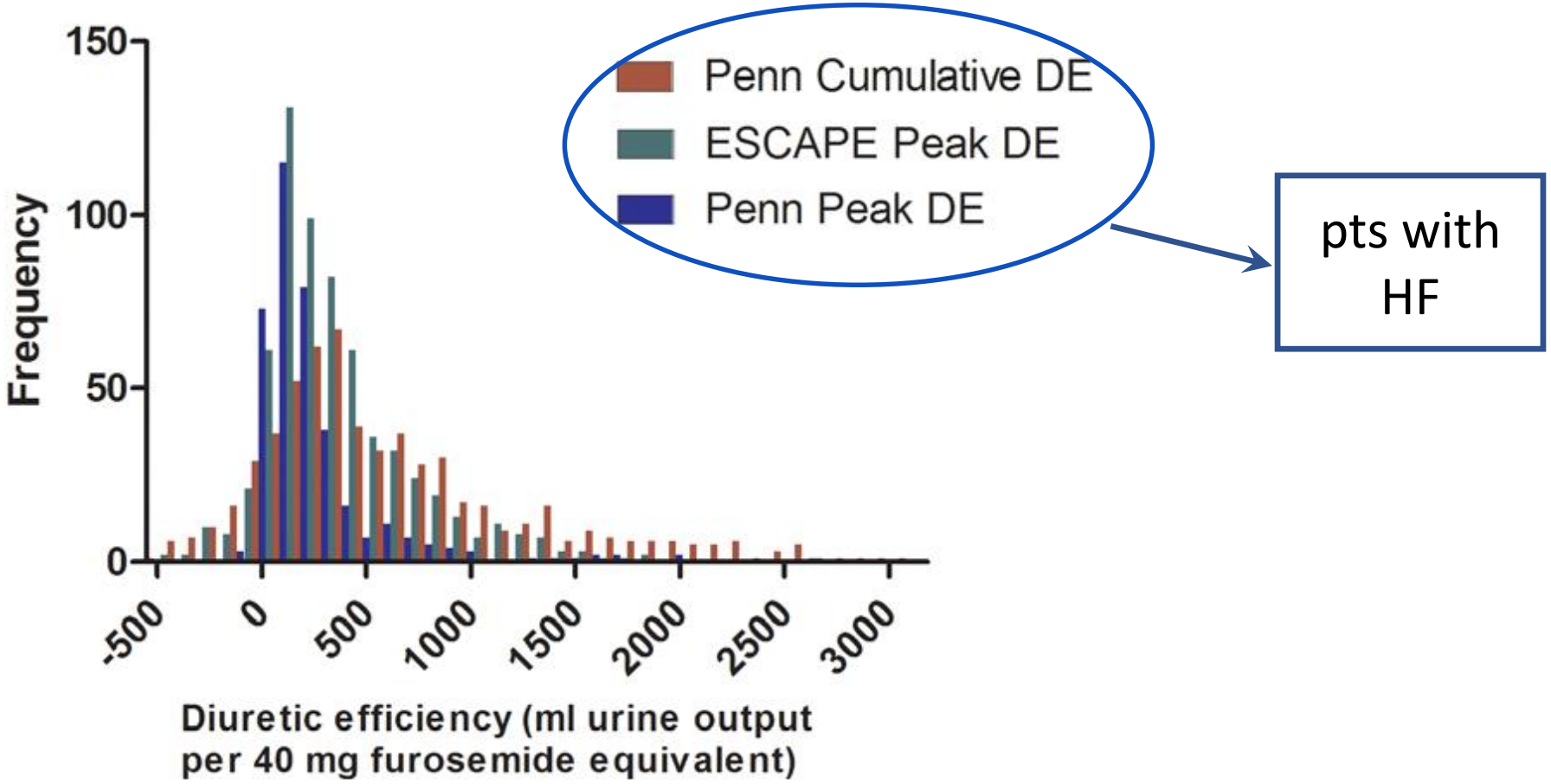
	Low	High	P value
Dyspnea VAS*	4478	4668	0.041
% free from congestion*	11%	18%	0.091
Change in weight*	-6.1 lbs	-8.7 lbs	0.011
Net volume loss*	3575 mL	4899 mL	0.001
Change in NTproBNP* (pg/mL)	-1194	-1882	0.06
% Treatment failure	37%	40%	0.56
% with Cr increase > 0.3 mg/dL*	14%	23%	0.041
Length of stay, days (median)	6	5	0.55

*at 72 hours

Felker GM *et al, NEJM* 2011

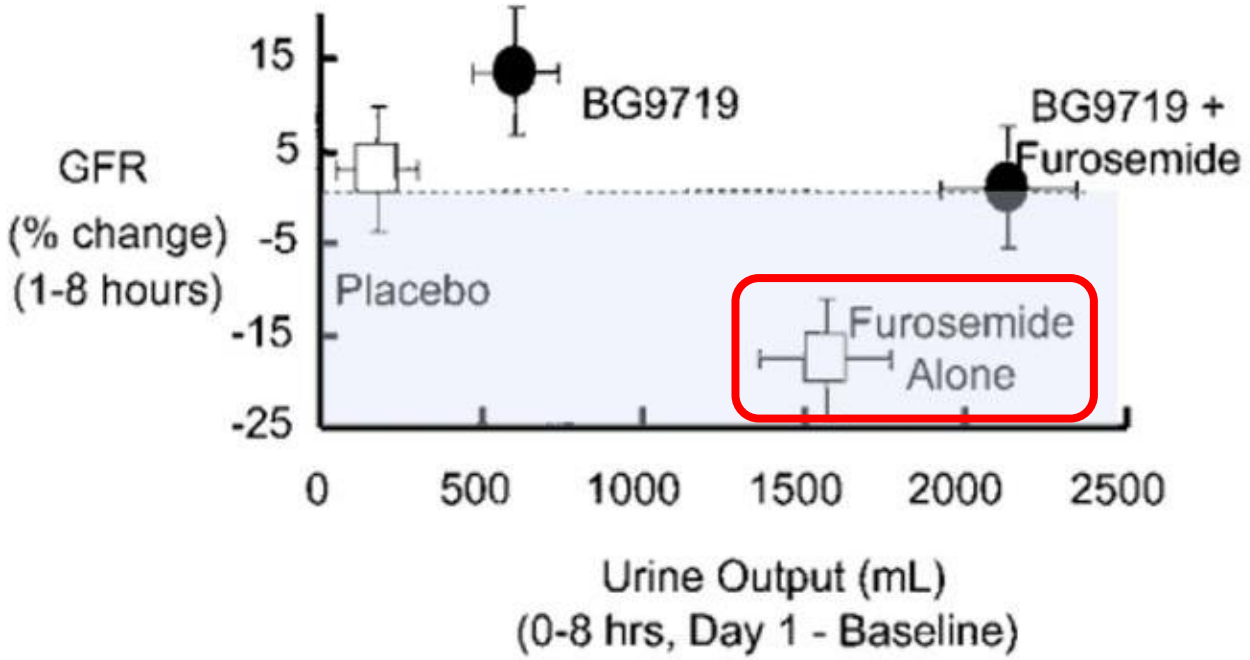
loop diuretics does not really work well in pts w/ HF!
esp if pts are already on Oral Diuretics

Diuretic resistance is omni-present in HF pts



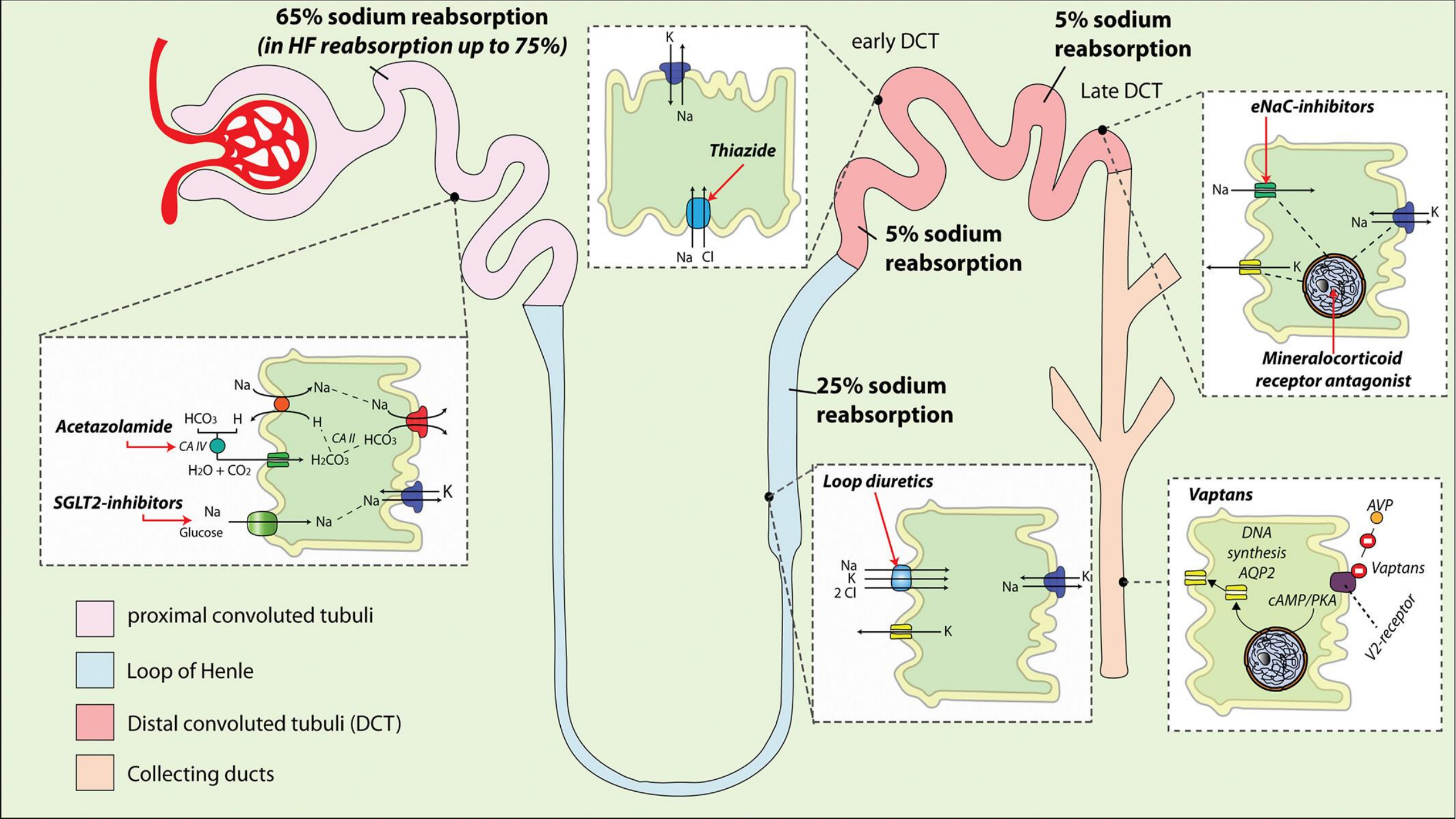
Lazix >>> reduction in GFR

Plasma adenosine raised heart failure – local vasoconstrictor
Locally produced in kidney (stress signal)



Furosemide alone reduces GFR

Gottlieb Circulation. 2002;105:1348-1353


65% sodium reabsorption
(in HF reabsorption up to 75%)
K
Na
Thiazide
Na Cl
early DCT
5% sodium
reabsorption
Late DCT
5% sodium
reabsorption
25% sodium
reabsorption
eNaC-inhibitors
Na
K
Mineralocorticoid
receptor antagonist
Acetazolamide
CA IV
CA II
HCO3
H
H2O + CO2
H2CO3
SGLT2-inhibitors
Glucose
Loop diuretics
2 Cl
Vaptans
AVP
DNA
synthesis
AQP2
cAMP/PKA
V2-receptor
proximal convoluted tubuli
Loop of Henle
Distal convoluted tubuli (DCT)
Collecting ducts

ESC European Society of Cardiology

European Journal of Heart Failure (2019) 21, 137–155
doi:10.1002/ejhf.1369

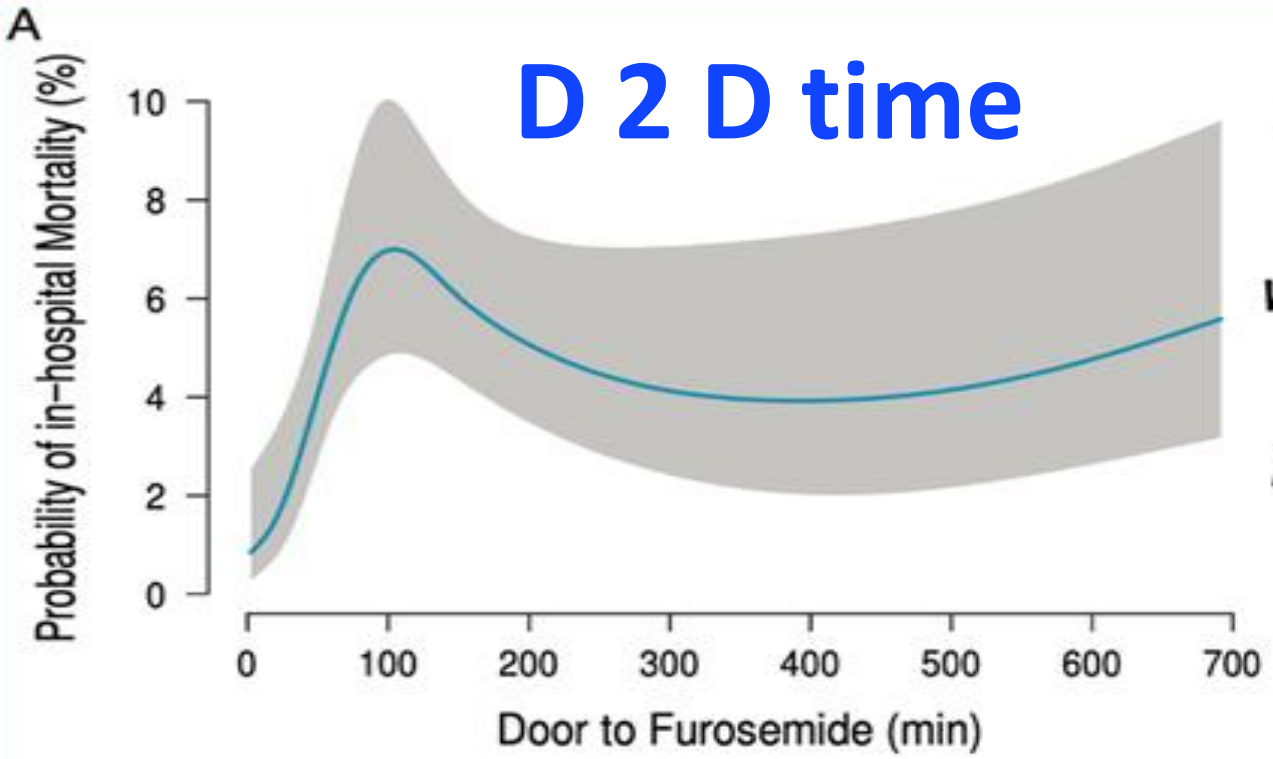
POSITION PAPER

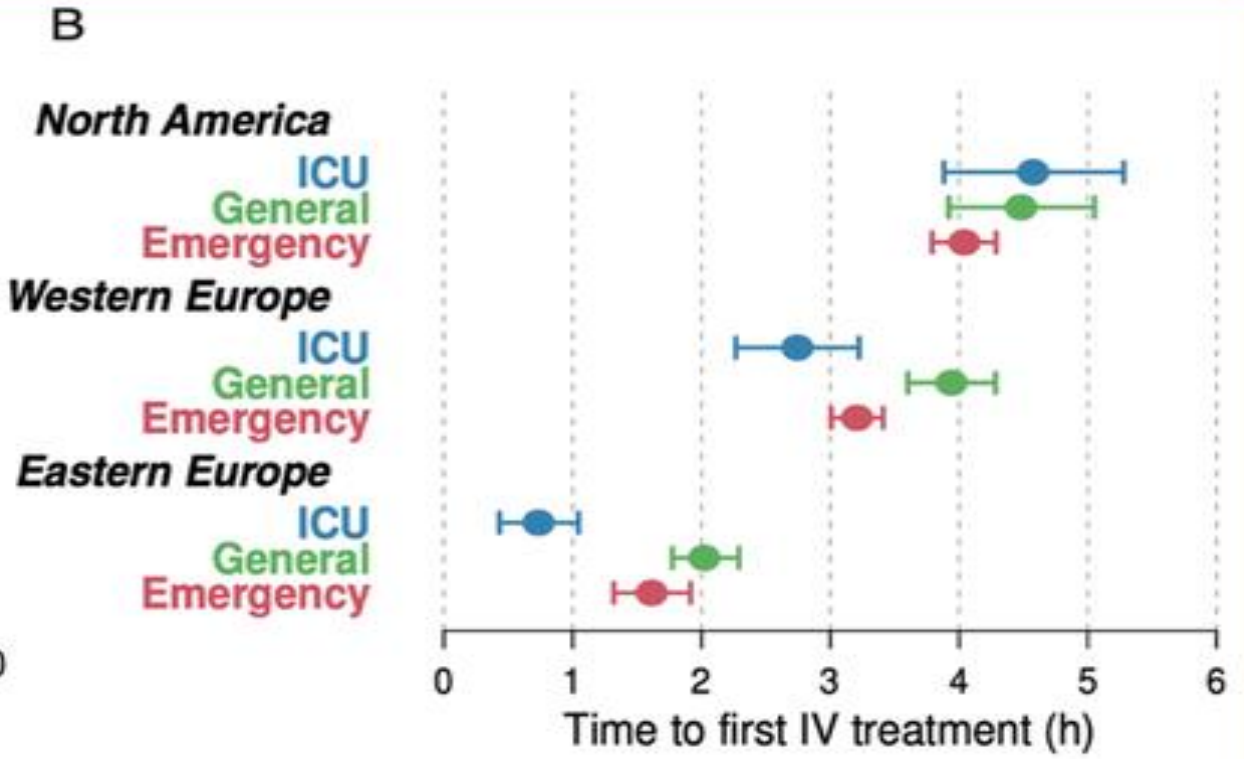
The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

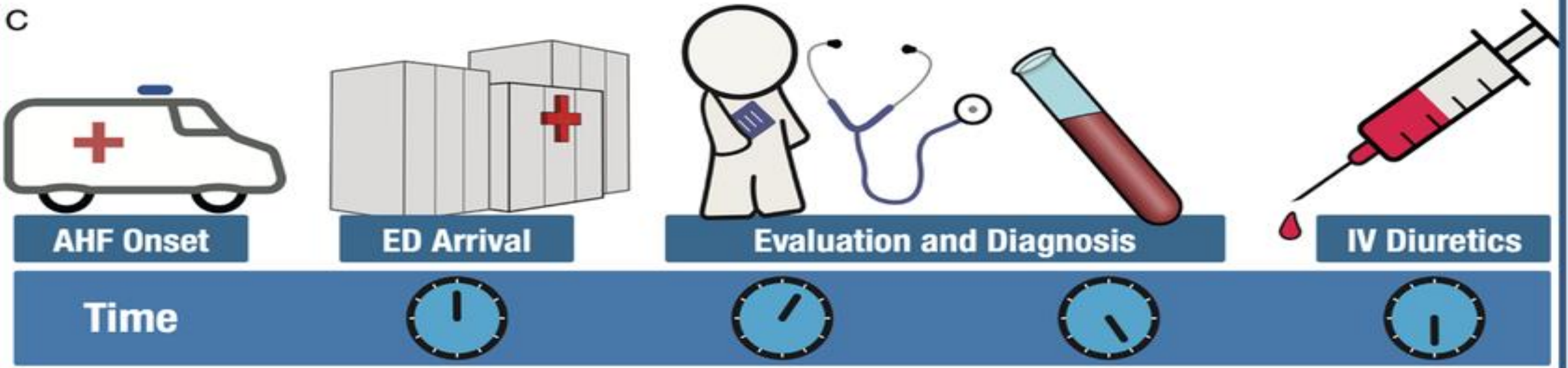
Wilfried Mullens[1,2]*, Kevin Damman[3], Veli-Pekka Harjola[4], Alexandre Mebazaa[5], Hans-Peter Brunner-La Rocca[6], Pieter Martens[1,2], Jeffrey M. Testani[7], W.H. Wilson Tang[8], Francesco Orso[9], Patrick Rossignol[10], Marco Metra[11], Gerasimos Filippatos[12,13], Petar M. Seferovic[14], Frank Ruschitzka[15], and Andrew J. Coats[16]

Mullens W, *et al. Eur J Heart Fail* 2019

D 2 D time


A
Probability of in−hospital Mortality (%)
0
2
4
6
8
10
0
100
200
300
400
500
600
700
Door to Furosemide (min)


B
North America
ICU
General
Emergency
Western Europe
ICU
General
Emergency
Eastern Europe
ICU
General
Emergency
0
1
2
3
4
5
6
Time to first IV treatment (h)


C
AHF Onset
ED Arrival
Evaluation and Diagnosis
IV Diuretics
Time


HOW?

Algorithm

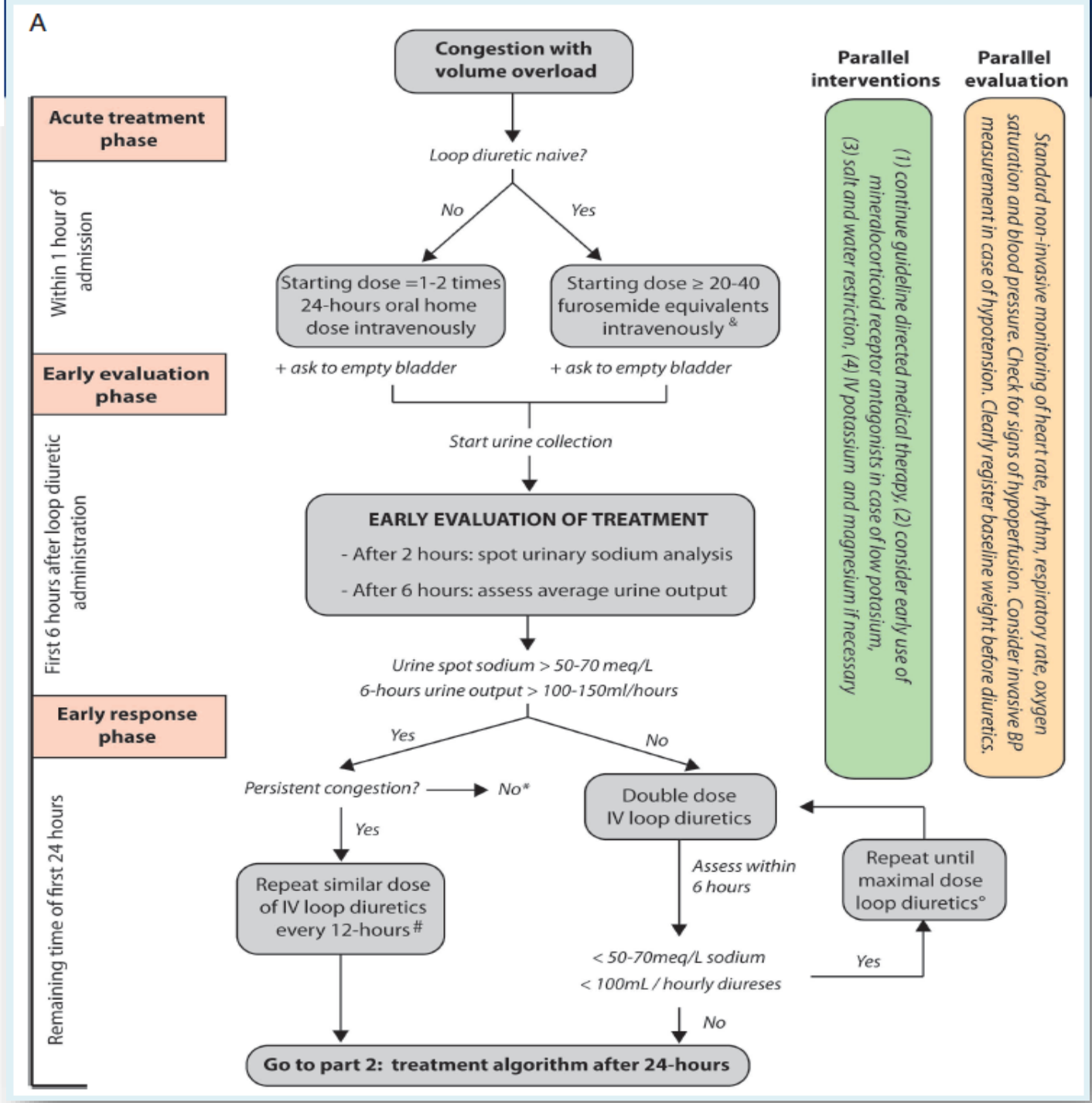
Starting IV Loop Diuretic Dose =
2.5 x Home Dose

Spot U Na
>50-70 mEq/L

Assess UOP
>100-150 mL/hr

If needed, **Double IV Diuretic Dose**

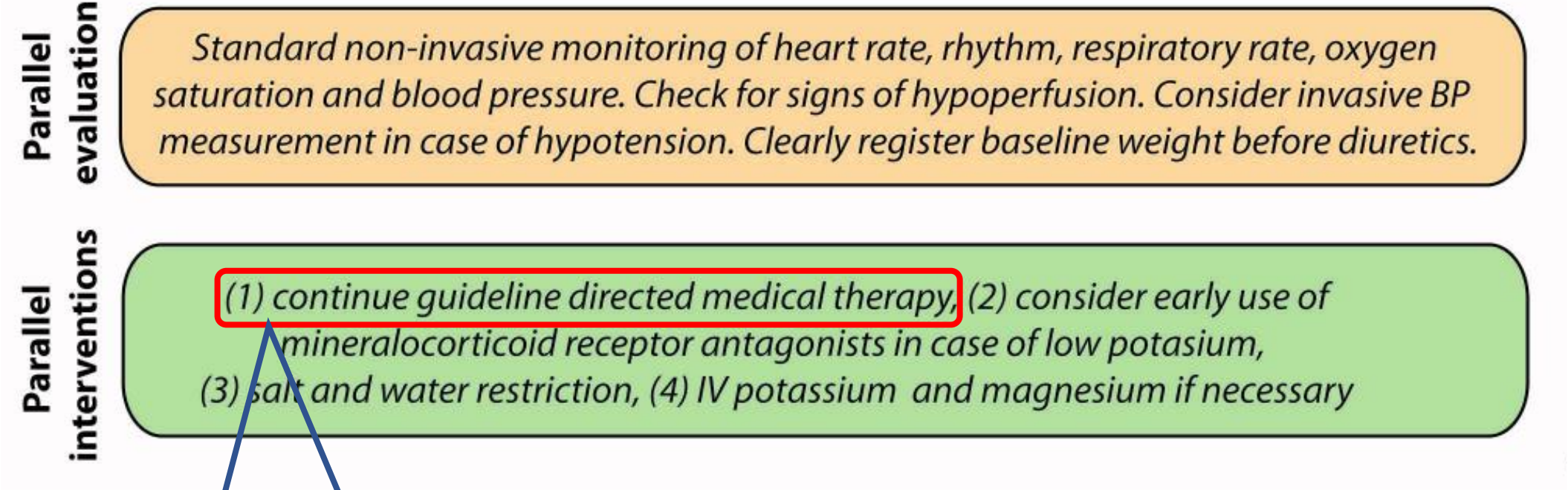
Combination Therapies:
1) Thiazides
2) Acetazolamide
3) Tolvaptan



Mullens W, *et al. Eur J Heart Fail* 2019

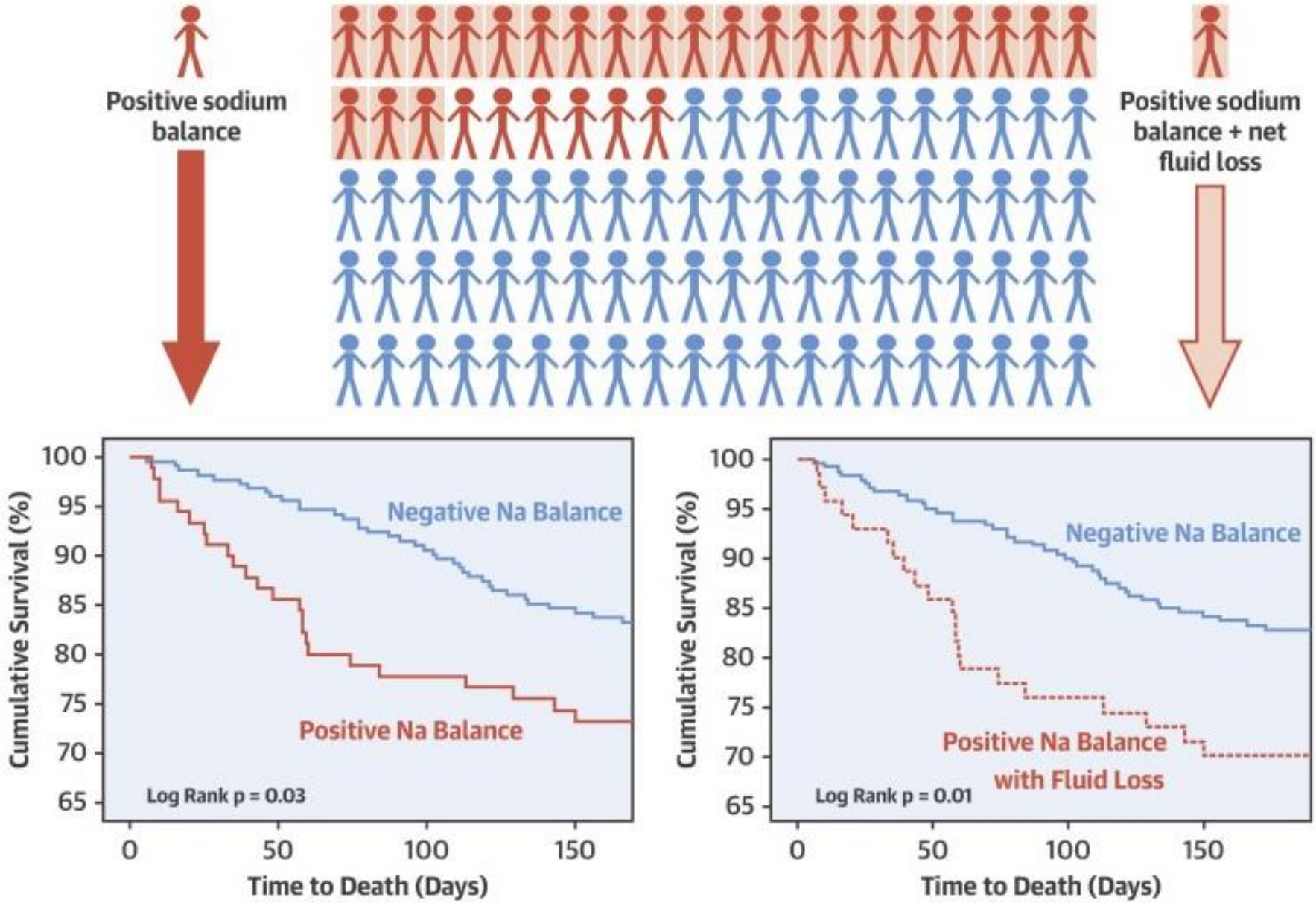
	Variable	EUVOLEMIA → CONGESTED				
Clinical congestion	**Orthopnea**	None		Mild	Moderate	Severe/worst
	JVP (cm)	<8 and no HJR	<8	8-10 or HJR+	11-15	>16
	Hepatomegaly		Absent	Liver edge	Moderate pulsatile enlargement	Massive enlargement and tender
	Edema		None	+1	+2	+3/+4
	6MWT	>400m	300-400m	200-300m	100-200m	<100m
Technical evaluation	**NP (one of both):** **-BNP** **-NT-proBNP**		<100 <400°	100-299 400-1500	300-500 1500-3000	>500 >3000
	Chest X-ray	clear	clear	cardiomegaly	- pulmonary venous congestion* - small pleural effusions*	- Interstitial or alveolar edema
	Vena Cava imaging [45]	**none of two:** - Max diameter >2.2 cm - collapsibility <50%		**One of two:** - Max diameter >2.2 cm - collapsibility <50%		**Both:** - Max diameter >2.2 cm - collapsibility <50%
	Lung Ultrasound [44]	<15 B-lines when scanning 28-sites		15-30 B-lines when scanning 28-sites		>30 B-lines when scanning 28-sites

while we are doing that, we do a parallel evaluation & interventions…



it is very important to continue the guideline Med therapy: including the use of ACEi, BB, MRA

Na loss predicts survivals more than fluid loss

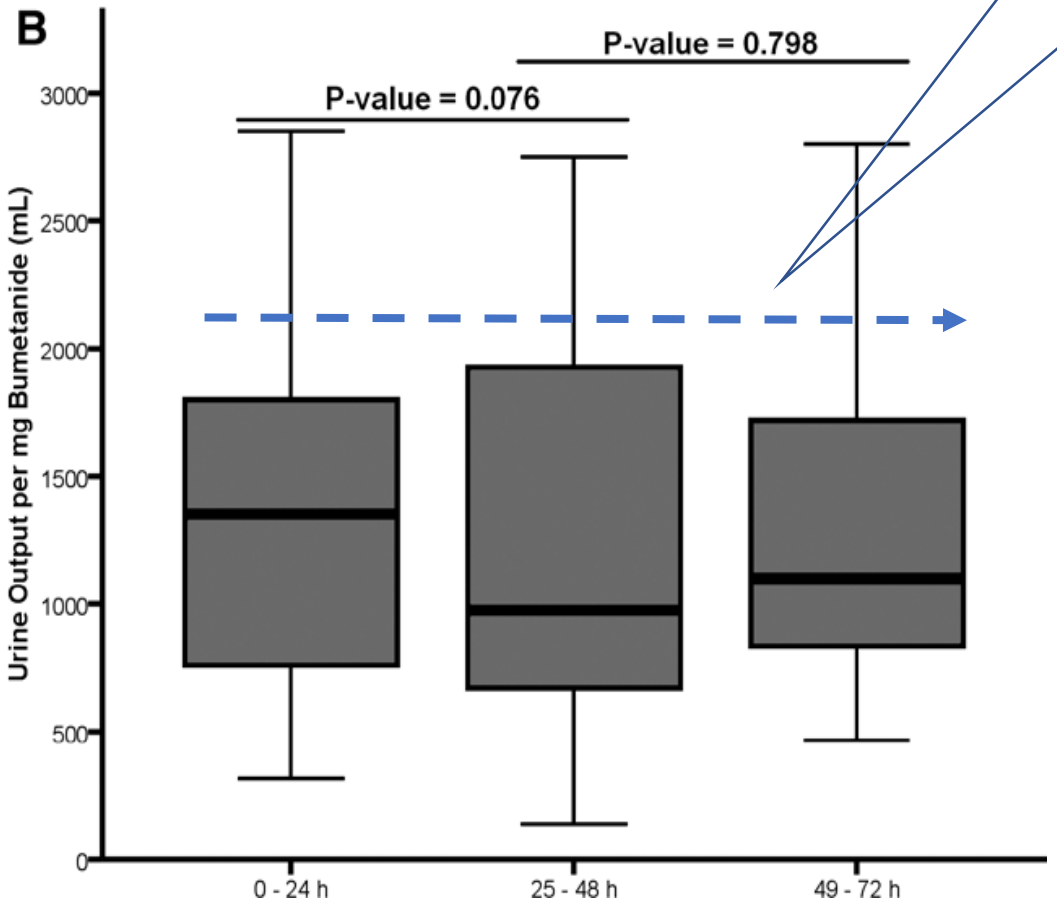


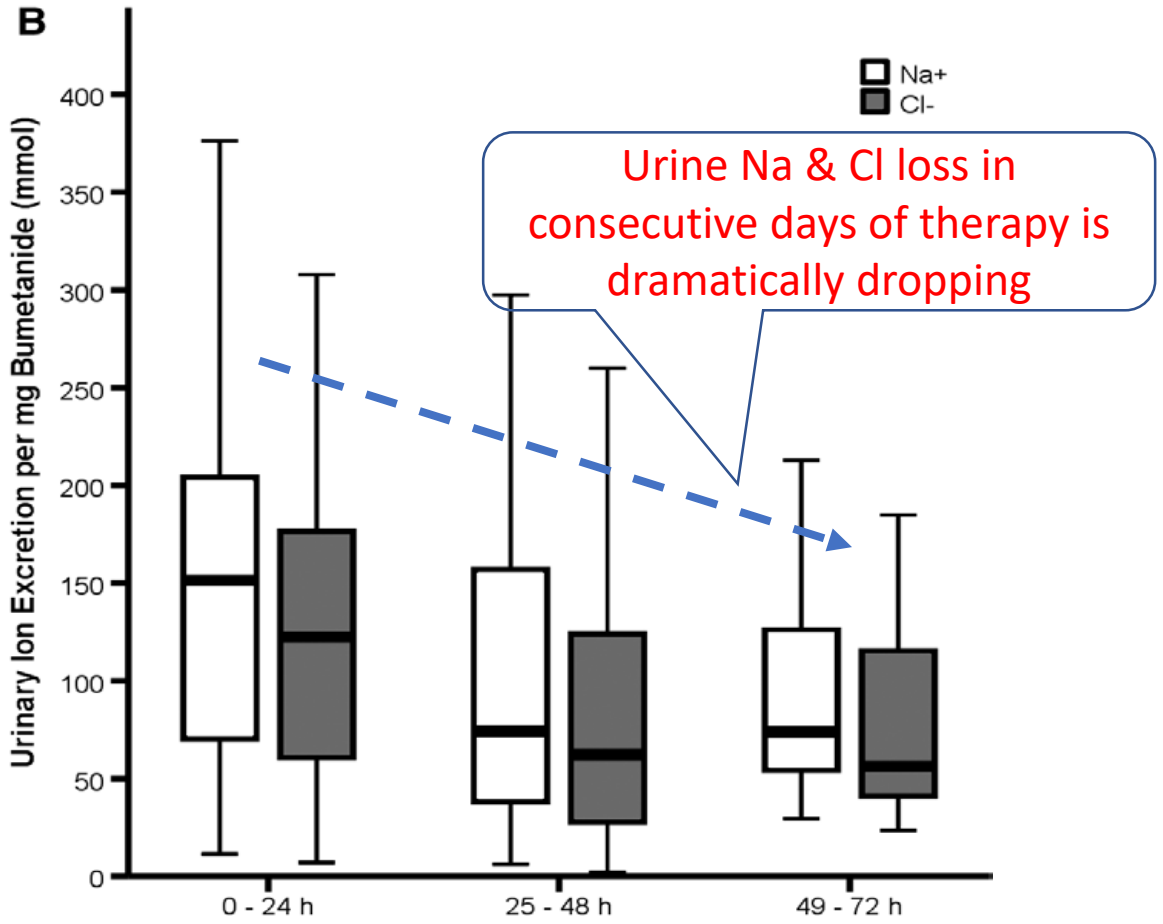
Hodson, D.Z. et al. J Am Coll Cardiol HF. 2019;7(5):383-91.

Urinary Composition During Decongestive Treatment in Heart Failure With Reduced Ejection Fraction

Frederik H. Verbrugge, MD; Petra Nijst, MD; Matthias Dupont, MD; Joris Penders, MD, PhD; W.H. Wilson Tang, MD; Wilfried Mullens, MD, PhD

UOP (urine volume) in consecutive days of therapy is almost the same ***(monotherapy Lazix)***






to get rid of congestion:
pee sodium
(not free water)

ENACT-HF: The Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure

Presenter: J.Dauw, Belgium, May 22, 2023

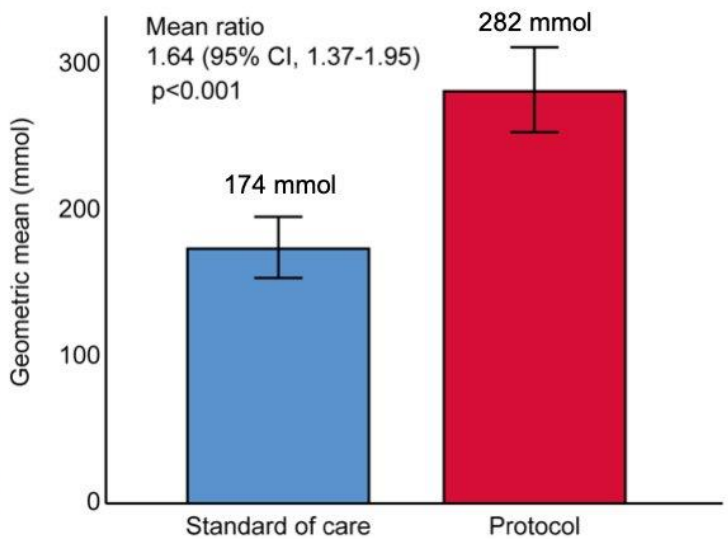
Design: investigator initiated, multi-center, open-label, worldwide (18 countries), non-randomized, SOC vs UNa-guided diuretic strategy in AHF

Endpoints: primary = natriuresis after 1 day, secondary = natriuresis + diuresis after 2 days, LOS

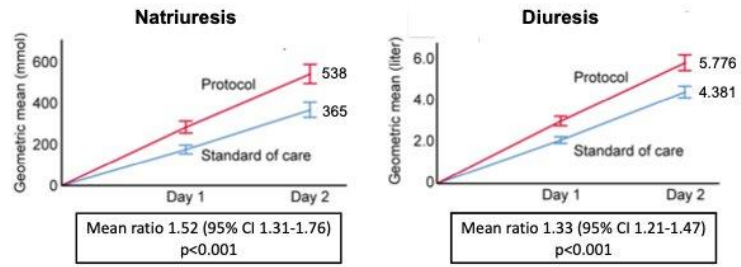
Conclusions: natriuresis-guided protocol compared with local SOC was associated with 64% increase in natriuresis at day 1, increased natriuresis and diuresis after 2 days, and reduction of length of stay

	Standard of care (N=254)	Protocol (N=147)	P value
Age (years)	70 ± 13	69 ± 14	0.618
Sex (female)	96 (37.8%)	55 (37.4%)	0.940
Ischemic etiology	89 (35.0%)	65 (44.2%)	0.069
Chronic kidney disease	127 (50.0%)	74 (50.3%)	0.948
Congestion score	5 (4-7)	5 (3-6)	0.866
NT-proBNP (pg/mL)	5750 (3010-12685)	6137 (3266-11394)	0.761
LVEF categories			0.480
- ≤ 40%	139 (54.7%)	84 (57.1%)	
- 41-49%	36 (14.2%)	25 (17.0%)	
- ≥ 50%	79 (31.1%)	38 (25.9%)	
Creatinine (mg/dL)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	0.836
eGFR (mL/min/1.73m²)	50 (32-74)	48 (32-71)	0.993
Treatment			
- Furosemide equivalent dose (mg)	60 (40-80)	60 (40-100)	0.220
- Thiazide	24 (9.4%)	18 (12.2%)	0.378
- Beta blocker	195 (76.8%)	122 (83.0%)	0.140
- ACE-I/ARB/ARNI	170 (66.9%)	100 (68.0%)	0.821
- MRA	120 (47.2%)	87 (59.2%)	0.021
- SGLT2-inibitor	31 (12.2%)	37 (25.2%)	0.001
- CRT	21 (8.3%)	13 (8.8%)	0.842
- ICD	33 (13.0%)	22 (15.0%)	0.580

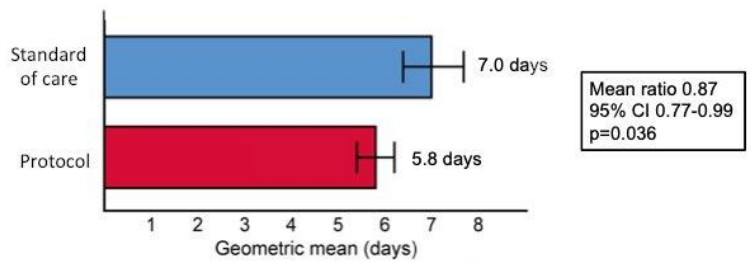
Primary Endpoint: Natriuresis after 1 Day



Secondary Endpoints: Natriuresis and Diuresis after 2 Days



Secondary Endpoints: Duration of Hospitalization



Heart Failure & World Congress on Acute Heart Failure 2023

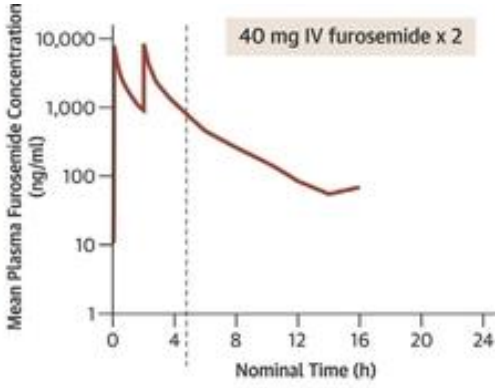
wilfried.mullens@gmail.com

@WilfriedMullens

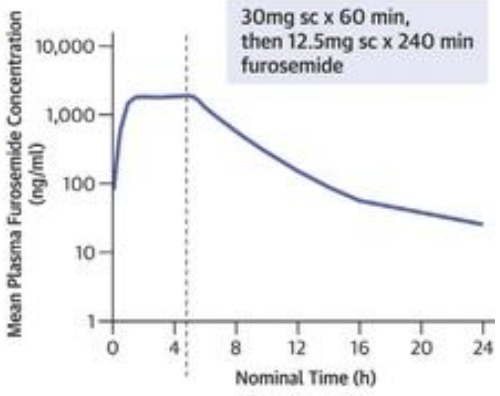
FDA APPROVED

Subcutaneously injected furosemide (Furoscix)

Intravenous bolus



Continuous SC infusion

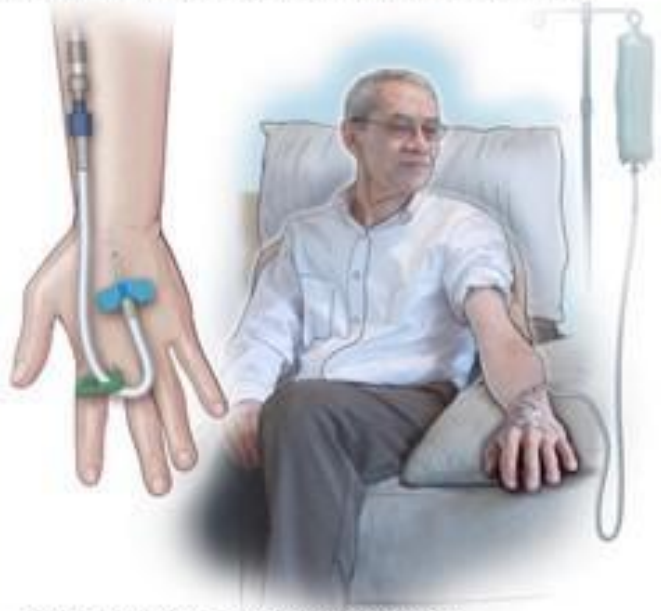


Bioavailability: 99.65%

Similar urine output and natriuresis to IV

Sica, D.A. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(1):25-34.

IV Bolus vs SC Infusion Cross-Over Trial



- 80mg IV bolus vs 80mg SC infusion
- Randomised crossover design
- Stable HF outpatients (n=18)

SUBCUT-HF I Trial

- 80mg SC infusion by patch pump
- Single dose non-comparative design
- Patients hospitalized for worsening HF (n=20)
- Diuresis: 8 hours 1700 mL; 24 hours 2548 mL
- Natriuresis at 8 hours: 97 mmol/L
- 95% report no/minor discomfort

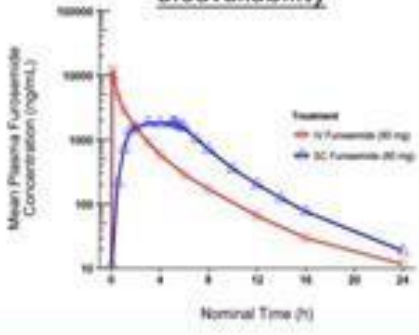
Furosemide IV bolus vs. SC infusion

IV: 80mg Furosemide USP 10m/mL - pH 8.0-9.3

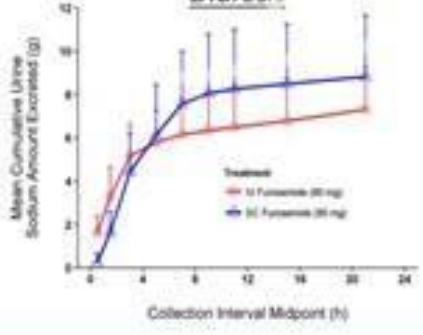
SC: 80mg Furosemide 30mg/mL - pH 7.1-7.8

Bioavailability (SC/IV)	- 112%
Diuresis (SC/IV)	- 115%
Natriuresis (SC/IV)	- 117%

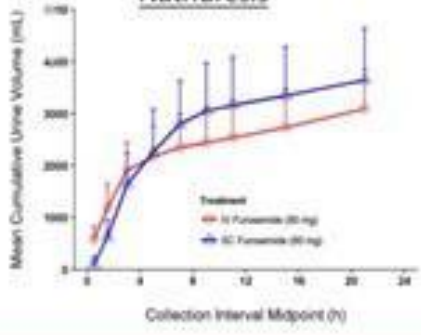
Bioavailability



Diuresis

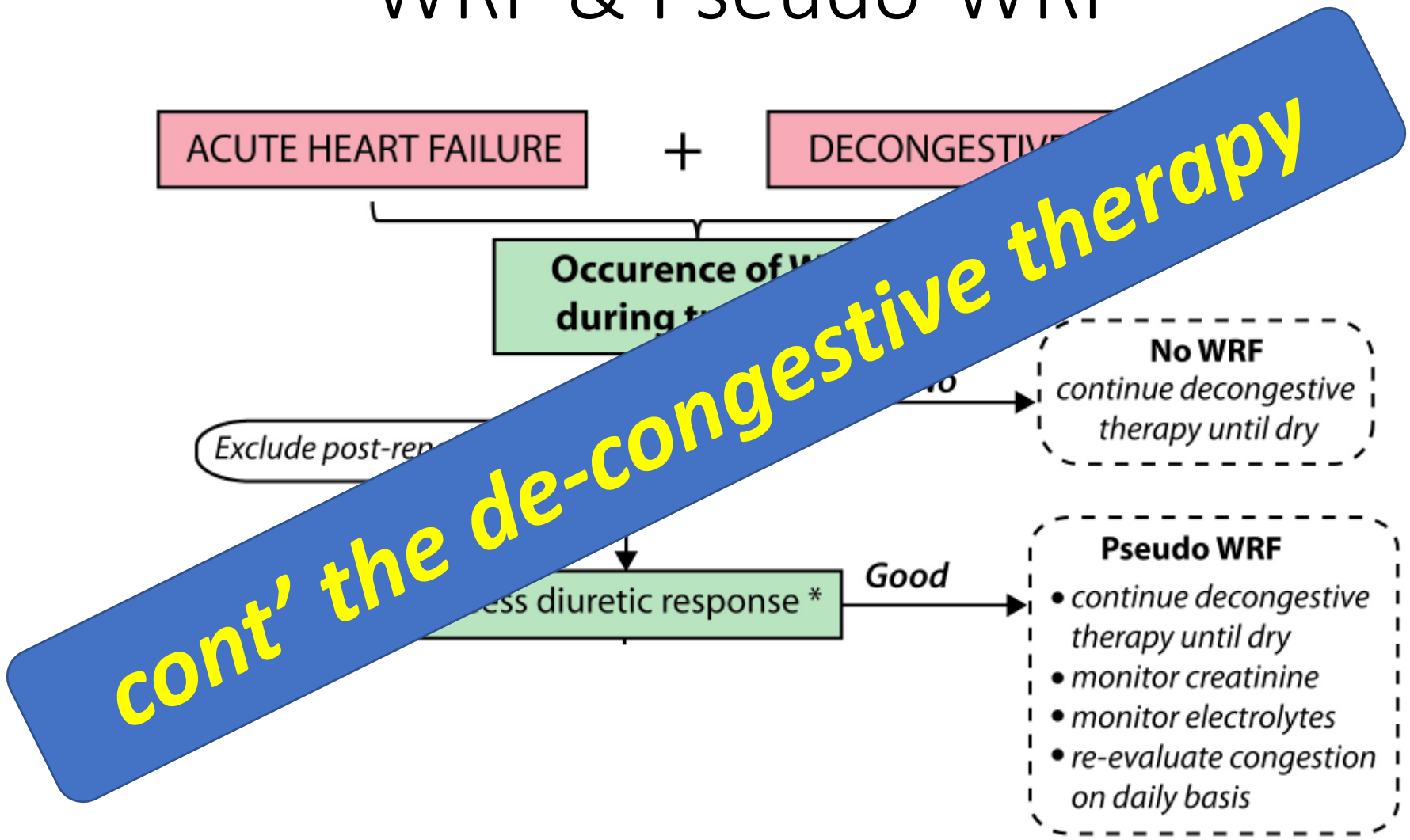


Natriuresis

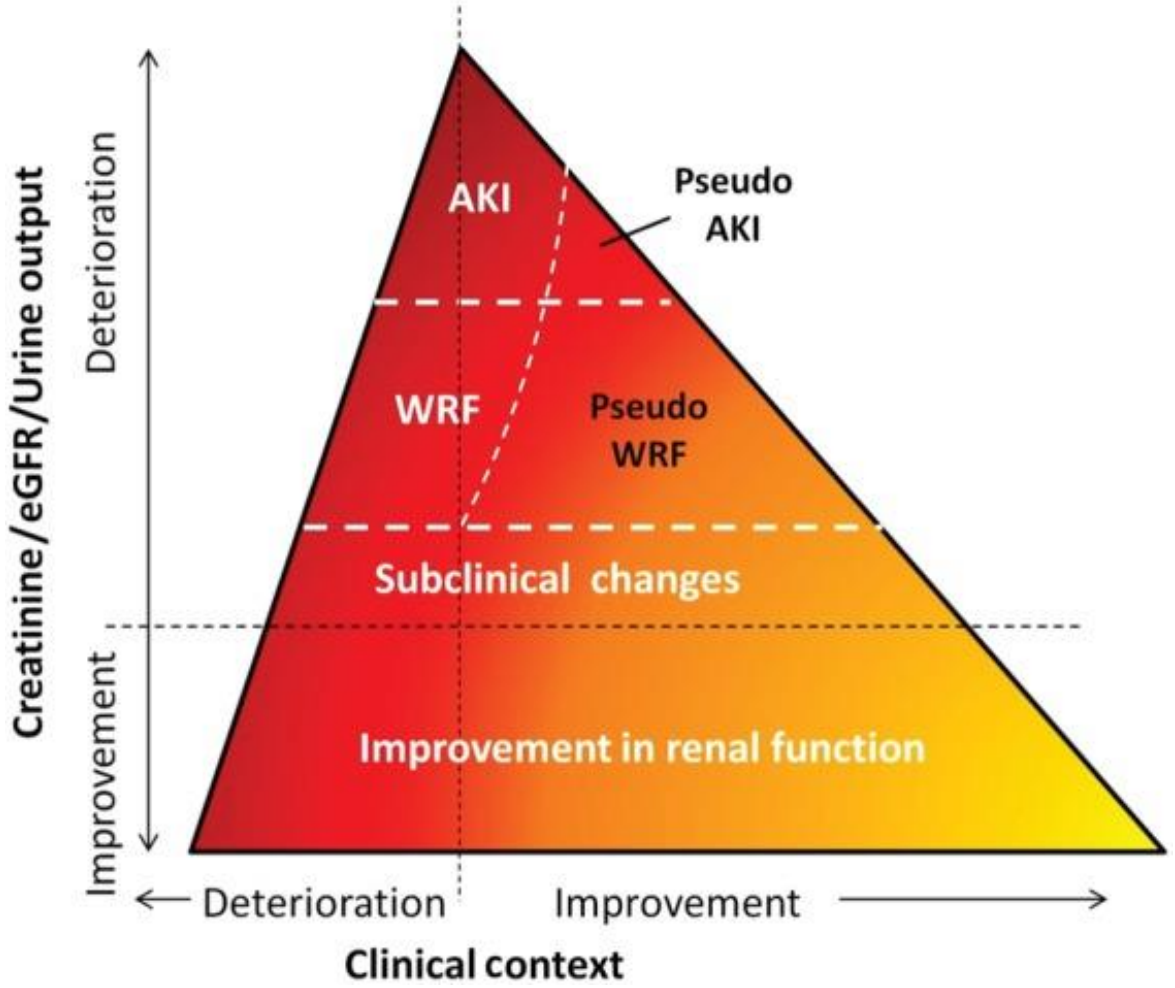


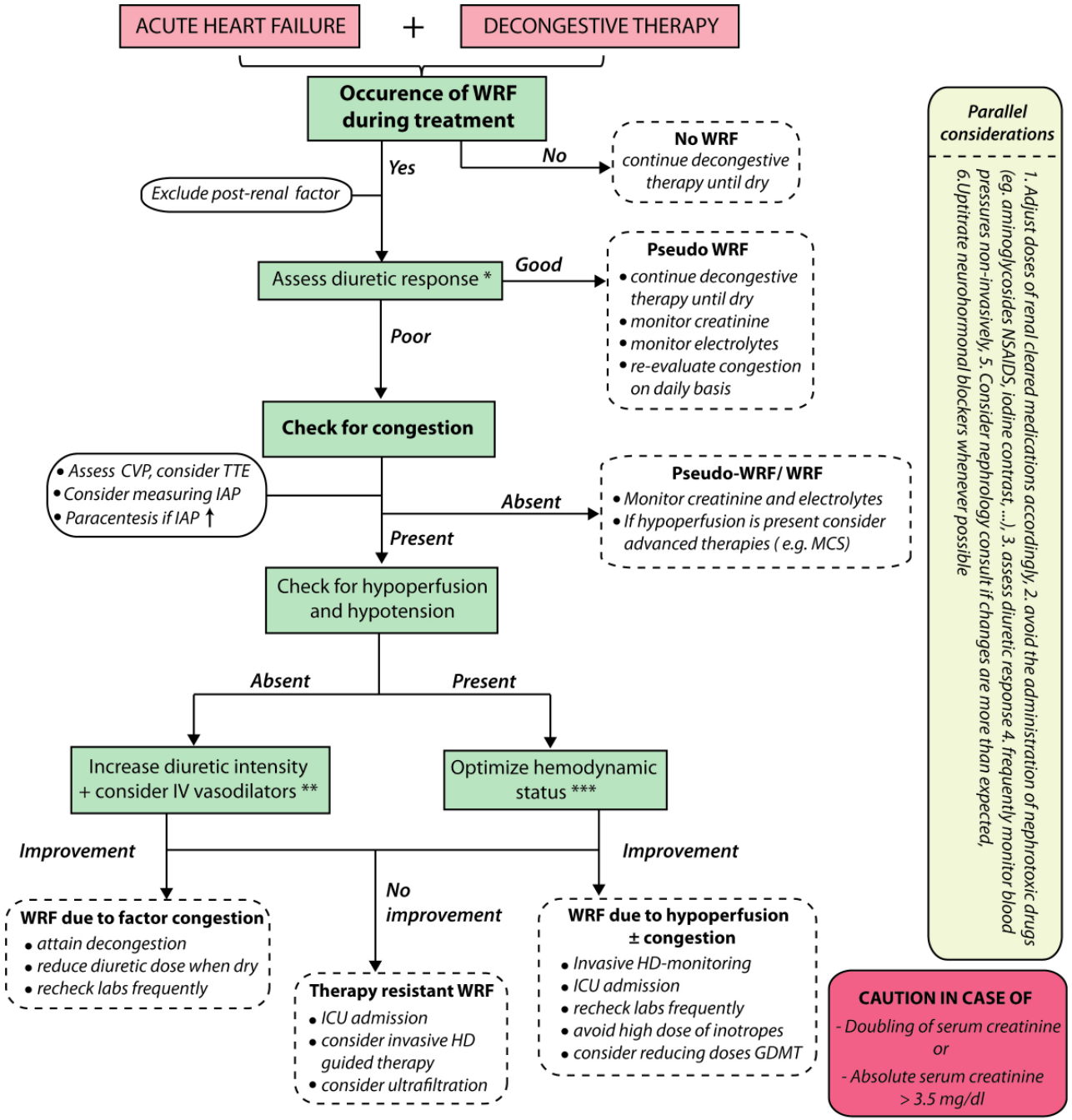
the kidney function often deteriorate during de-congestive therapy

WRF & Pseudo-WRF

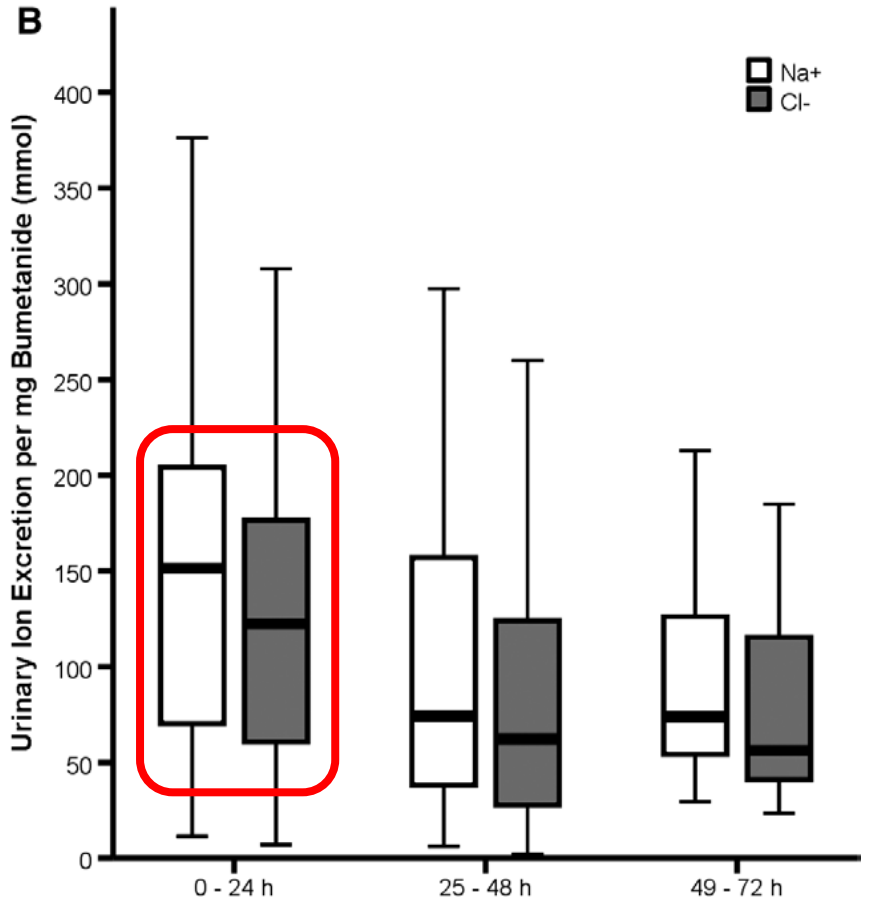


WRF occurs BUT in the context of improvement of clinical S&S

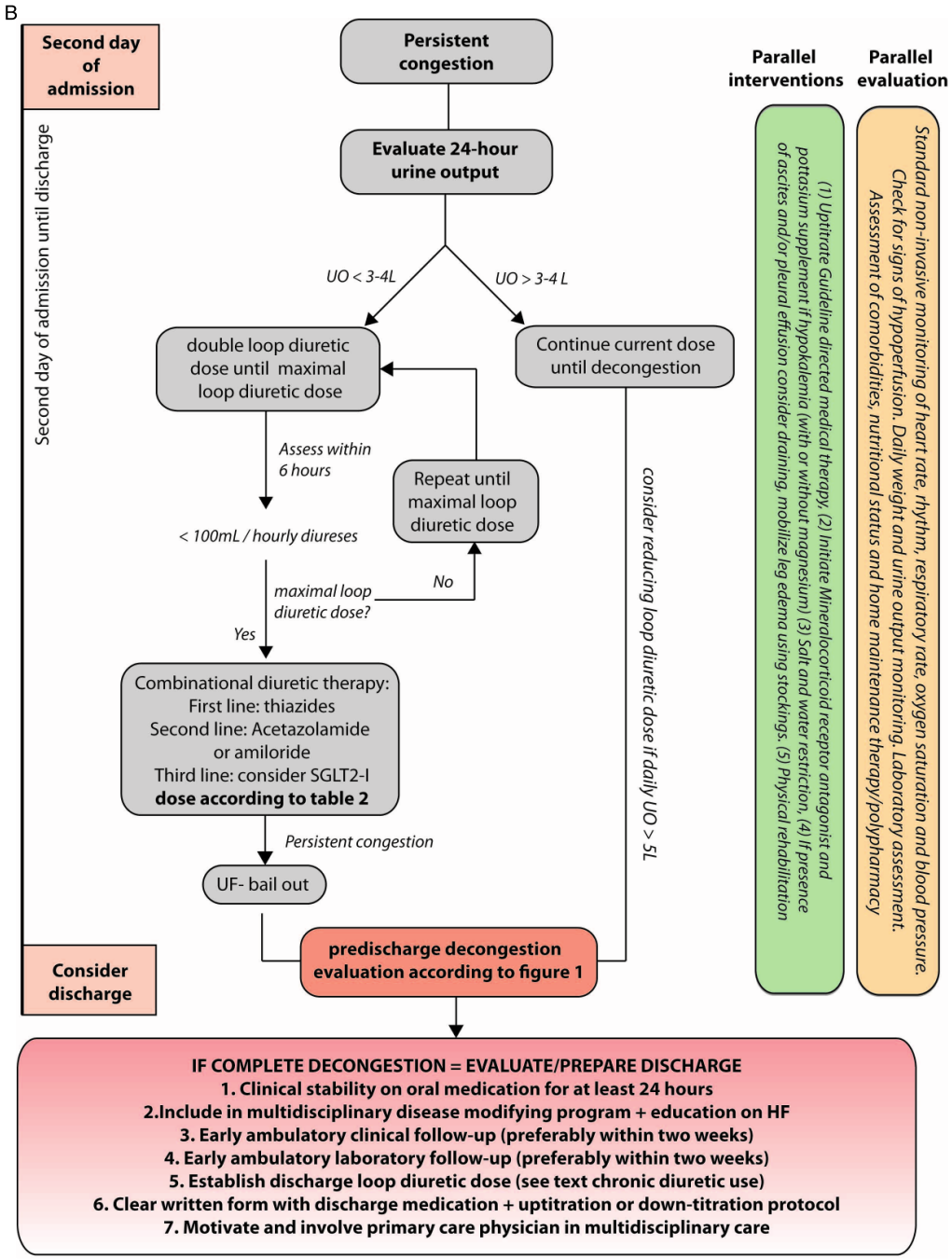



ACUTE HEART FAILURE
+
DECONGESTIVE THERAPY
Occurence of WRF during treatment
No
No WRF
continue decongestive therapy until dry
Yes
Exclude post-renal factor
Assess diuretic response *
Good
Pseudo WRF
• continue decongestive therapy until dry
• monitor creatinine
• monitor electrolytes
• re-evaluate congestion on daily basis
Poor
Check for congestion
• Assess CVP, consider TTE
• Consider measuring IAP
• Paracentesis if IAP ↑
Absent
Pseudo-WRF/ WRF
• Monitor creatinine and electrolytes
• If hypoperfusion is present consider advanced therapies (e.g. MCS)
Present
Check for hypoperfusion and hypotension
Absent
Present
Increase diuretic intensity + consider IV vasodilators **
Optimize hemodynamic status ***
Improvement
Improvement
No improvement
WRF due to factor congestion
• attain decongestion
• reduce diuretic dose when dry
• recheck labs frequently
Therapy resistant WRF
• ICU admission
• consider invasive HD guided therapy
• consider ultrafiltration
WRF due to hypoperfusion ± congestion
• Invasive HD-monitoring
• ICU admission
• recheck labs frequently
• avoid high dose of inotropes
• consider reducing doses GDMT
Parallel considerations
1. Adjust doses of renal cleared medications accordingly, 2. avoid the administration of nephrotoxic drugs (eg. aminoglycosides NSAIDS, iodine contrast, ...), 3. assess diuretic response 4. frequently monitor blood pressures non-invasively, 5. Consider nephrology consult if changes are more than expected, 6.Uptitrate neurohormonal blockers whenever possible
CAUTION IN CASE OF
- Doubling of serum creatinine
or
- Absolute serum creatinine > 3.5 mg/dl

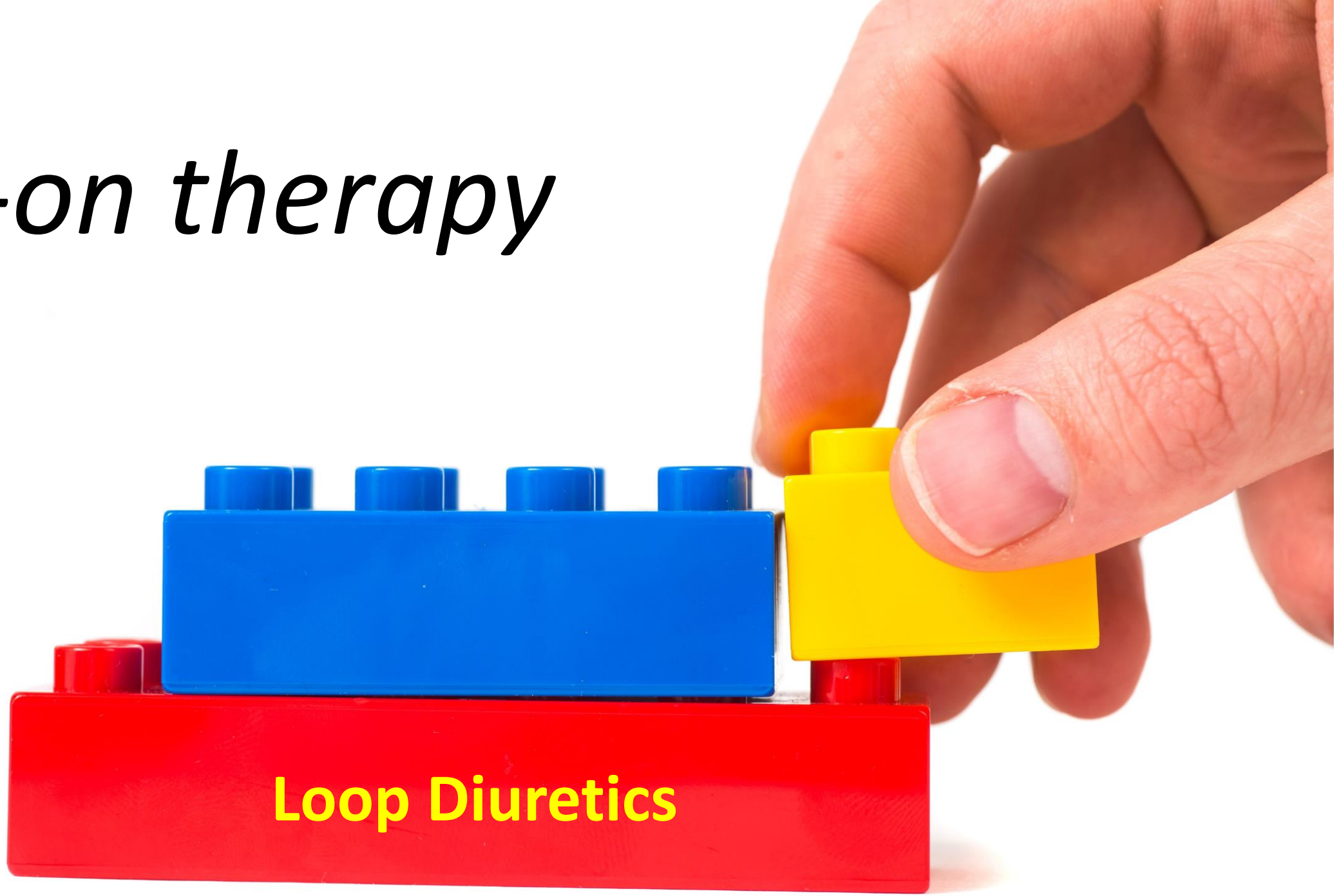
the only moment we get a lot of Na out, is during the first 24 hours



B


Second day of admission
Persistent congestion
Evaluate 24-hour urine output
UO < 3-4L
UO > 3-4 L
double loop diuretic dose until maximal loop diuretic dose
Continue current dose until decongestion
Assess within 6 hours
Repeat until maximal loop diuretic dose
< 100mL / hourly diureses
maximal loop diuretic dose?
No
Yes
Combinational diuretic therapy:
First line: thiazides
Second line: Acetazolamide or amiloride
Third line: consider SGLT2-I
dose according to table 2
Persistent congestion
UF- bail out
predischarge decongestion evaluation according to figure 1
Consider discharge
Second day of admission until discharge
consider reducing loop diuretic dose if daily UO > 5L
Parallel interventions
(1) Uptitrate Guideline directed medical therapy, (2) Initiate Mineralocorticoid receptor antagonist and pottasium supplement if hypokalemia (with or without magnesium) (3) Salt and water restriction, (4) If presence of ascites and/or pleural effusion consider draining, mobilize leg edema using stockings. (5) Physical rehabilitation
Parallel evaluation
Standard non-invasive monitoring of heart rate, rhythm, respiratory rate, oxygen saturation and blood pressure. Check for signs of hypoperfusion. Daily weight and urine output monitoring. Laboratory assessment. Assessment of comorbidities, nutritional status and home maintenance therapy/polypharmacy
IF COMPLETE DECONGESTION = EVALUATE/PREPARE DISCHARGE
1. Clinical stability on oral medication for at least 24 hours
2.Include in multidisciplinary disease modifying program + education on HF
3. Early ambulatory clinical follow-up (preferably within two weeks)
4. Early ambulatory laboratory follow-up (preferably within two weeks)
5. Establish discharge loop diuretic dose (see text chronic diuretic use)
6. Clear written form with discharge medication + uptitration or down-titration protocol
7. Motivate and involve primary care physician in multidisciplinary care

Add-on therapy



Thiazides & Thiazide-likes

Generic Name	Trade Names
Bendroflumethiazide	Naturetin
Benzthiazide	Aquatag, Exna
Chlorothiazide	Diuril
Hydrochlorothiazide	Esidrix, HydroDIURIL
Hydroflumethiazide	Saluron, Diucardin
Methyclothiazide	Enduron, Aquatensen
Polythiazide	Renese
Trichlormethiazide	Naqua, Metahydrin
Chlorthalidone	Hygroton
Indapamide	Lozol
Metolazone	Zaroxolyn, Diulo
Quinethazone	Hydromox

- TZ are the 1st option
- TZ works more distal to the loop diuretics
- TZ may **counter-balance *some*** of the **hypertrophy** that we see with the chronic use of Loop
- **TZ works at low GFR states**
- TZ are **very slowly absorbed** in the gut >>> need to be given hours before loop diuretics >>> a little bit impractical ! >>> esp during the first days of ttt
- TZ >>> **only be used temporarily** >>> increased risk of HF & increased risk of mortality !
- **TZ only for short term** to get rid of congestion (TZ are not used for long term in HF pts) >>> risk of electrolyte disturbances
- TZ >>> longer t ½

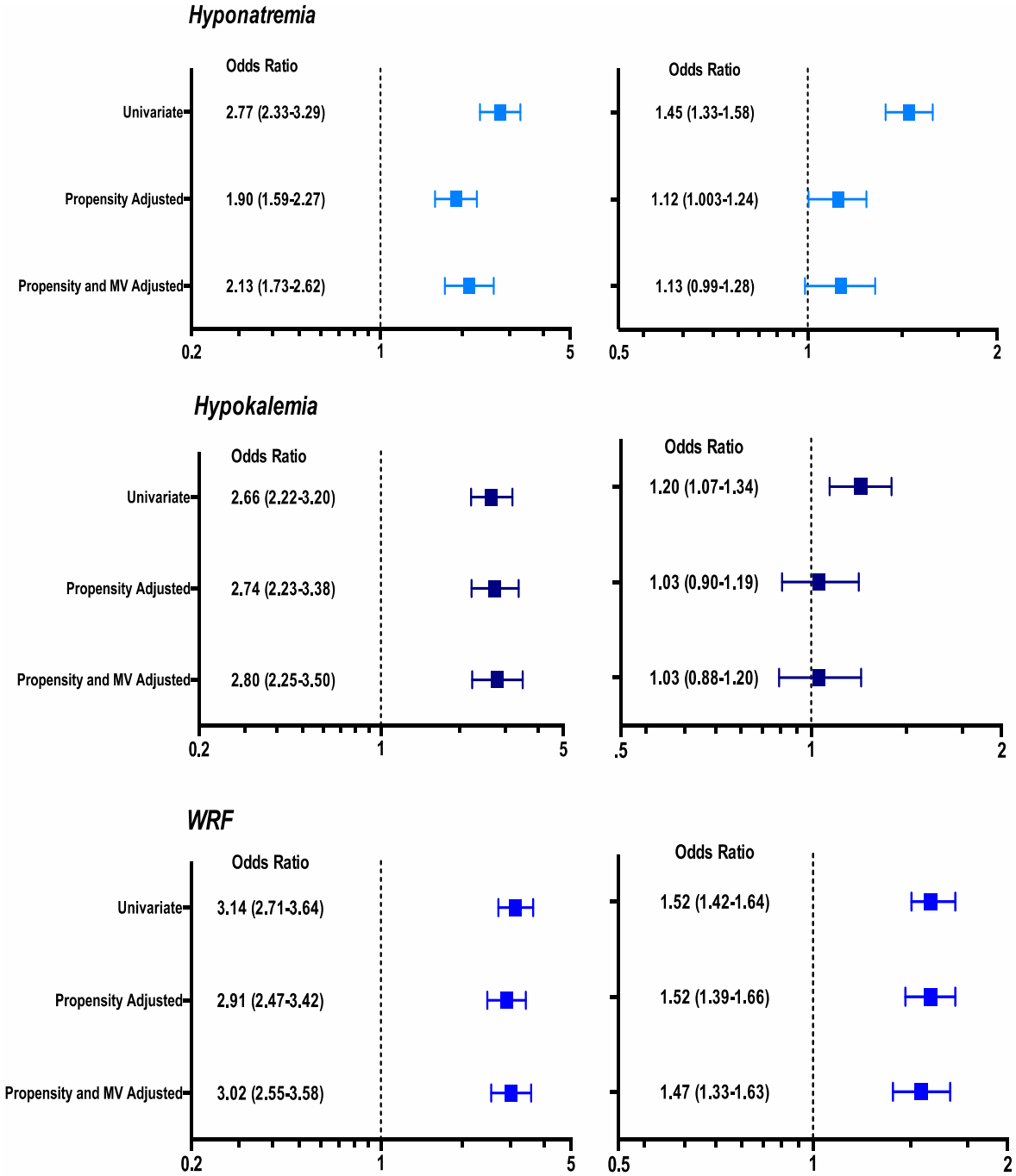
TZD should only be given temporarily

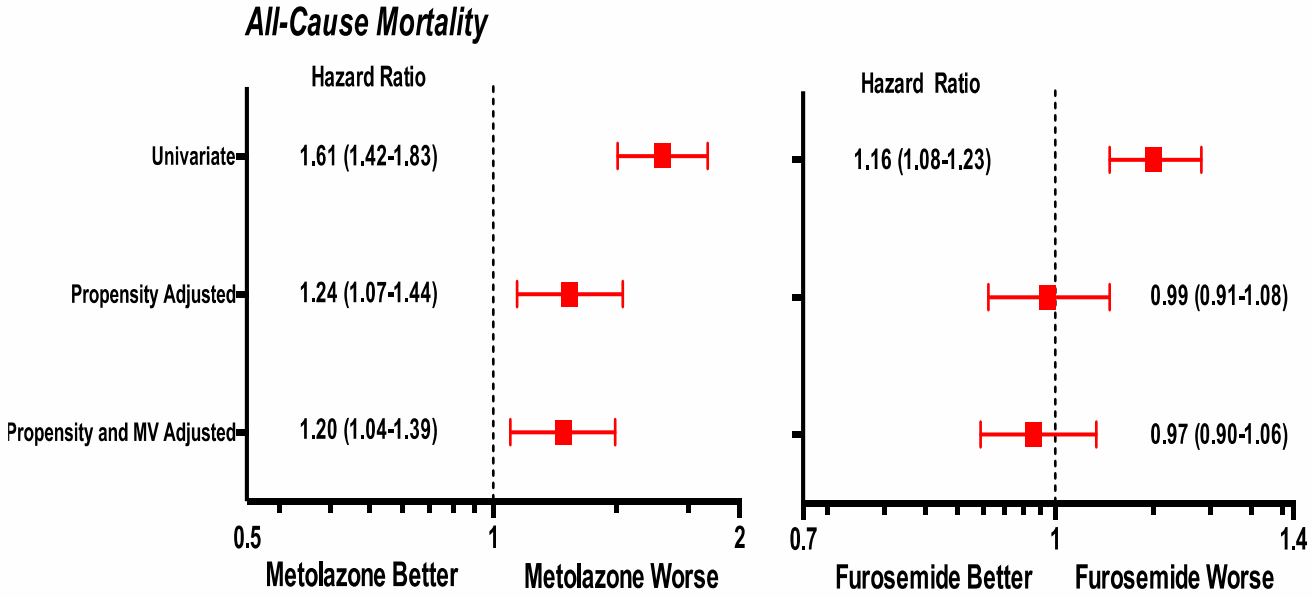
ORIGINAL ARTICLE

American Heart Association | American Stroke Association

Outcomes Associated With a Strategy of Adjuvant Metolazone or High-Dose Loop Diuretics in Acute Decompensated Heart Failure: A Propensity Analysis

Meredith A. Brisco-Bacik, MD, MSCE; Jozine M. ter Maaten, MD; Steven R. Houser, PhD; Natasha A. Vedage, MD; Veena Rao, PhD; Tariq Ahmad, MD, MPH; F. Perry Wilson, MD, MSCE; Jeffrey M. Testani, MD, MTR





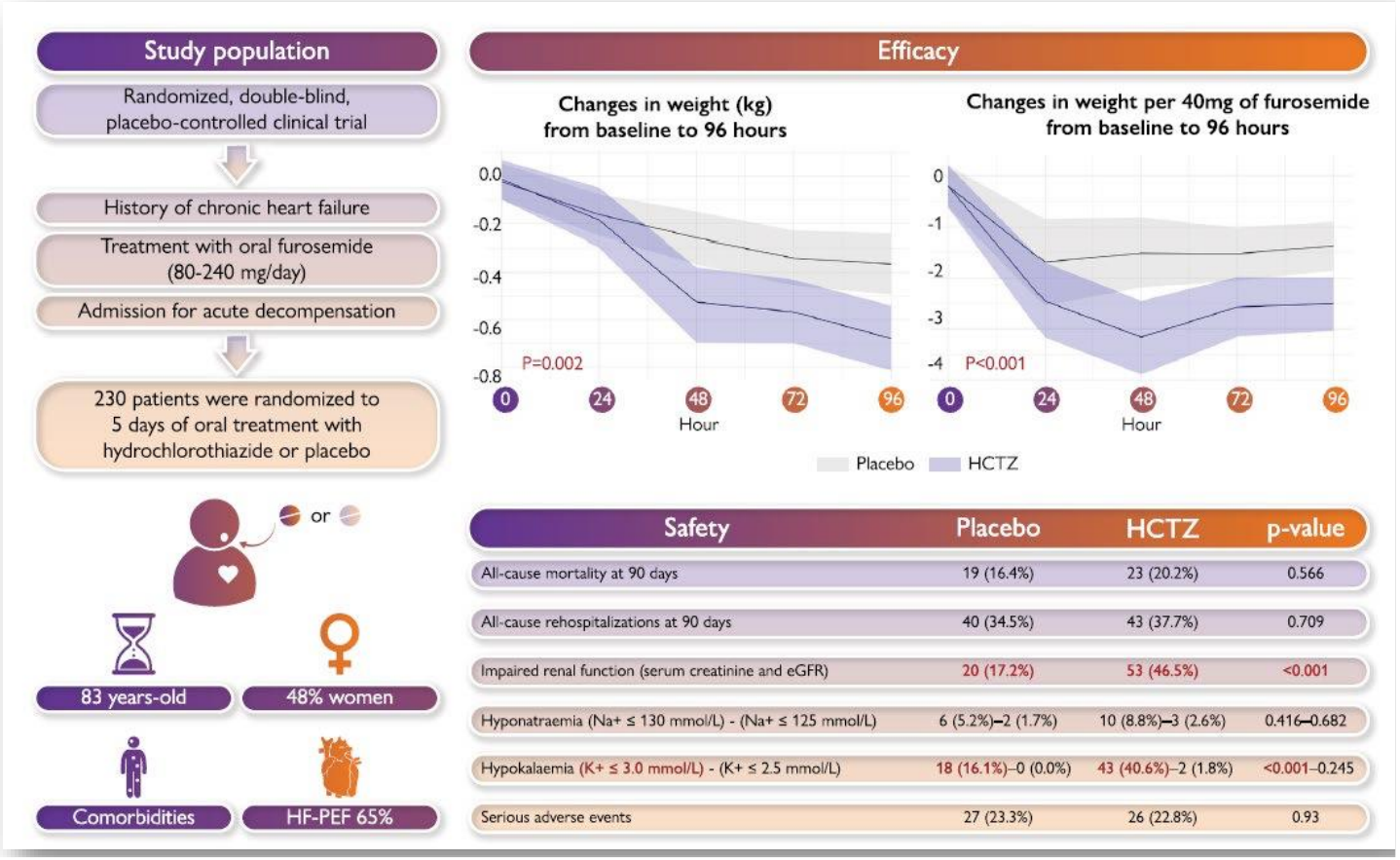
CLOROTIC Trial

HCTZ in AHF

HCTZ PO x 5 d – dose by GFR (25-100 mg)

N = 233
rEF or pEF

72 hr:
More weight loss
No diff in Dyspnea

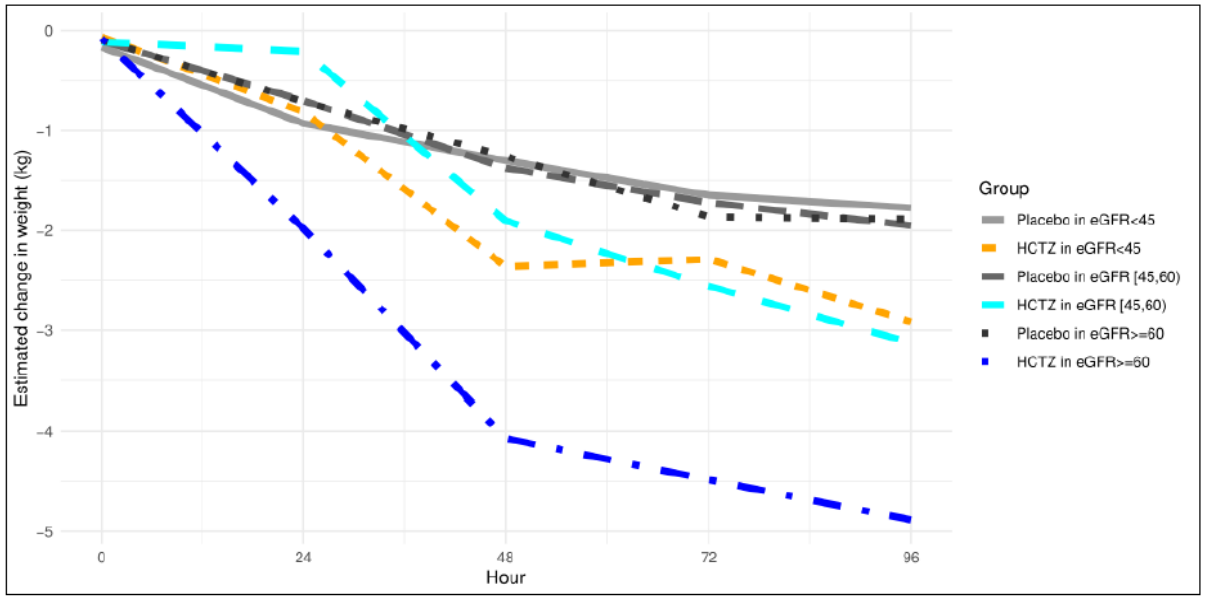


Safety	Placebo	HCTZ	p-value
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Impaired renal function (serum creatinine and eGFR)	20 (17.2%)	53 (46.5%)	<0.001
Hyponatraemia (Na+ ≤ 130 mmol/L) - (Na+ ≤ 125 mmol/L)	6 (5.2%)–2 (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

Trullas JC, *et al. Eur Heart J* 2022

HCTZ: weight loss greater with better GFR

Efficacy endpoints-Weight loss



the addition of oral HCTZ (with doses adjusted to eGFR) to intravenous furosemide improved diuretic response in all patients with AHF regardless of the initial eGFR, but this response was higher in patients with better baseline renal function

Thiazide Diuretics: *Mechanism of Action and Adverse Side Effects*

Authors:
Huneza Nadeem
Reviewers:
Ran (Marissa) Zhang,
Julian Midgley*
** MD at time of publication*

Thiazide diuretics

Block the Na-Cl cotransporter (NCC) in the distal convoluted tubule (DCT) of the nephron

Impaired water excretion, vasopressin release, and ↑ water intake (mechanisms unclear)

Hyponatremia

↓ Na^+ and Cl^- reabsorption into proximal DCT cells

↑ Na^+ in DCT filtrate by ~3-5%

Water follows Na^+ to maintain balanced osmotic pressure

↑ Water available for excretion

Mild Diuresis

↓ Blood volume

Hypotension

↑ Na^+ filtrate delivery to cortical collecting duct (CCD)

Epithelial sodium channels (ENaC)s on principal cells of the CCD transport Na^+ from filtrate into the principal cells

↑ Intracellular Na^+ drives Na/K^+ ATPase activity on principal cells (moves 2 K^+ into cell, 3 Na^+ out into peritubular capillary)

↑ Intracellular K^+ drives H/K^+ ATPase activity on intercalated cells (moves 1 H^+ into cell, 1 K^+ out into tubular filtrate)

↓ K^+ in serum

Hypokalemia

See Hypokalemia: *Clinical Findings* slide

Lack of intracellular Na^+ needed to drive the Na^+/K^+ ATPase (moves 2 K^+ into cell, 3 Na^+ out into peritubular capillary)

↓ Intracellular Na^+ drives Ca-ATPase and 3:Na:Ca exchanger activity (moves 3 Na^+ into cell, 1 Ca+2 out into peritubular capillary)

↑ Ca^{+2} in serum

Hypercalcemia

See Hypercalcemia: *Clinical Findings* slide

Acute response to high dose thiazide diuretics (mechanism unclear)

Hyperlipidemia

Hypokalemia induces hyperpolarization of pancreatic beta cells

↓ Number of voltage gated Ca^{+2} channels open given intracellular charge

↓ Ca^{+2} influx prevents exocytosis mediated insulin release

↓ Glucose uptake in the body

Hyperglycemia

Thiazides in circulation enter the proximal convoluted tubule (PCT) cells by basolateral Organic Acid Transporter 1 (OAT1)

↑ Intracellular thiazide availability for apical OAT4 exchangers

OAT4 reabsorb urate in lumen in exchange for thiazide that is excreted

↑ Urate in serum

Hyperuricemia

Uric acid build up in joints

Gout

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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ATHENA:
High Dose MRA in AHF

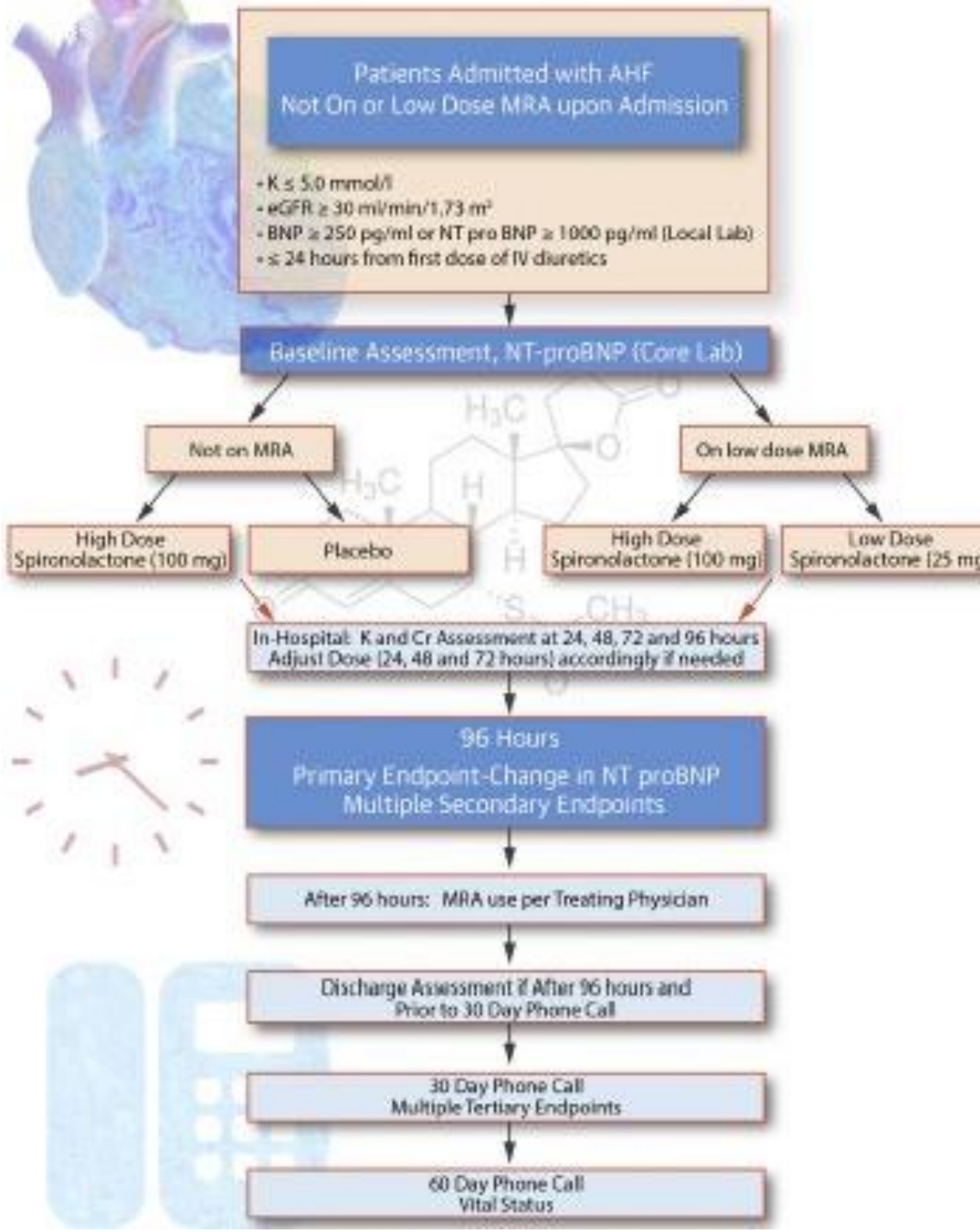
Spiro 100 mg for 96 hours
(vs. placebo or low-dose spiro)

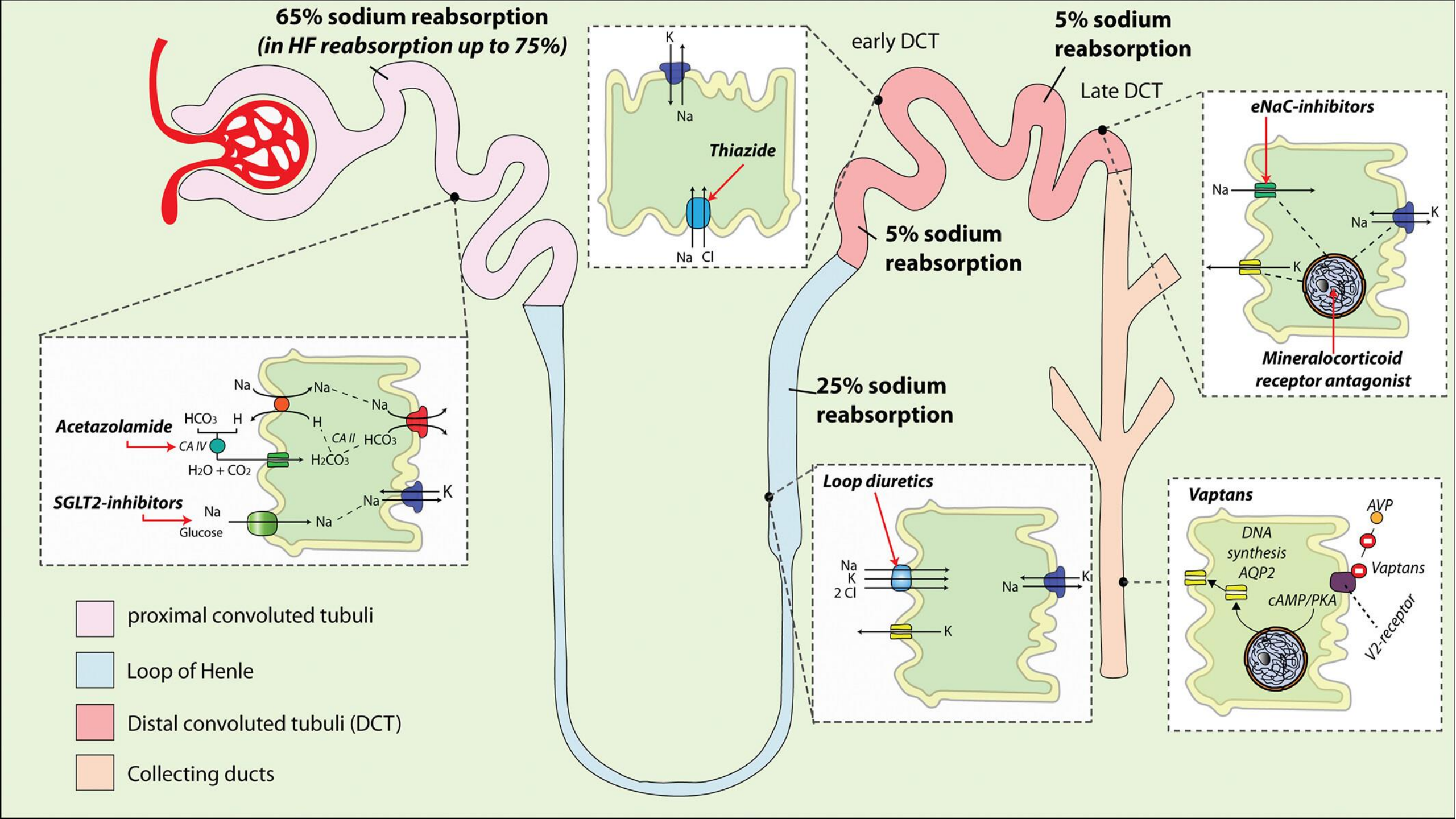
N = 360
rEF or pEF

<u>96 hours</u>
No signif difference in NT-proBNP

Or congestion, dyspnea, UOP, wt change, renal function or clinical outcomes

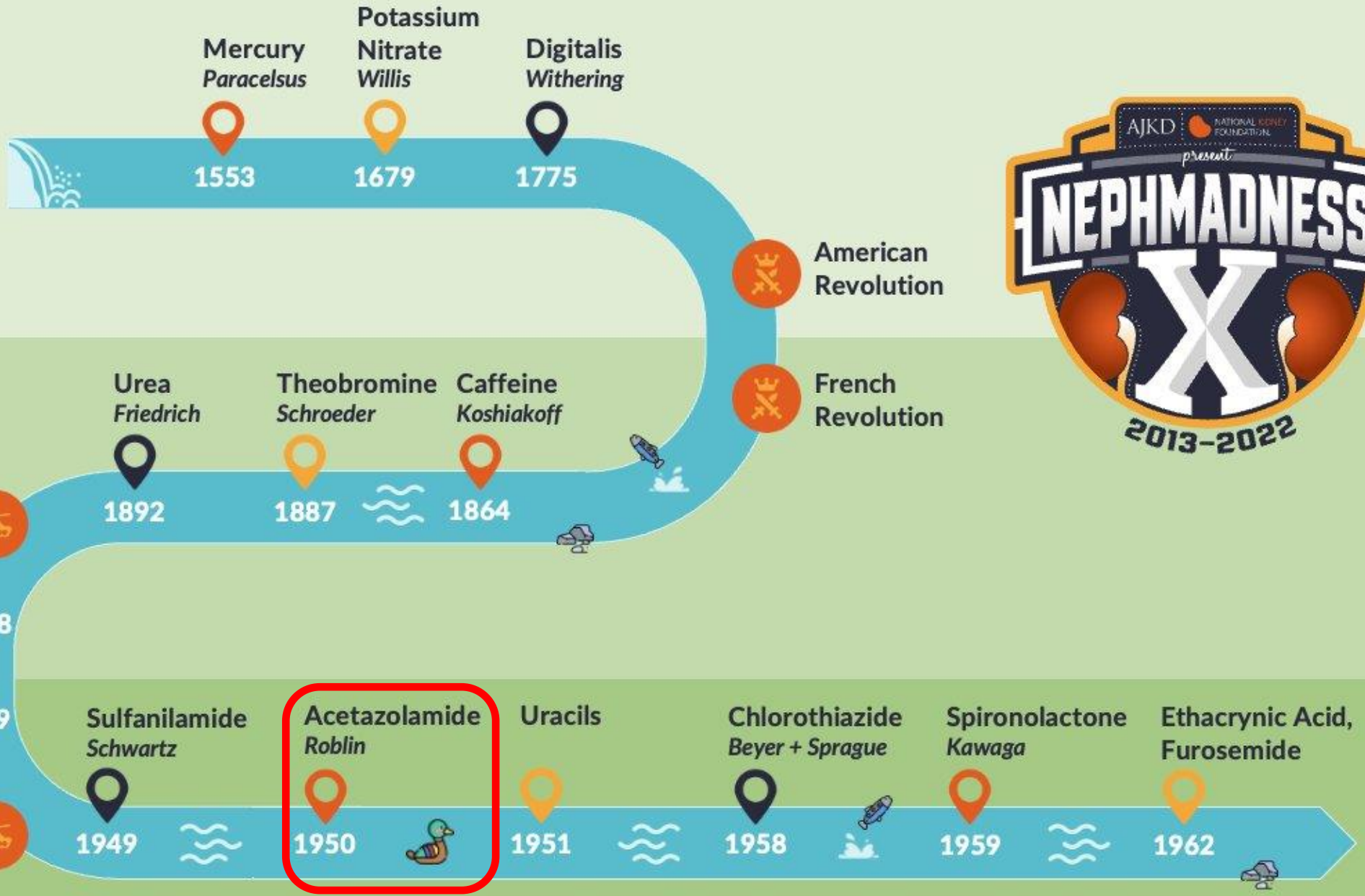
Butler J, *et al. JAMA Cardiol 2017*




65% sodium reabsorption
(in HF reabsorption up to 75%)
K
Na
Thiazide
Na Cl
early DCT
5% sodium
reabsorption
Late DCT
5% sodium
reabsorption
25% sodium
reabsorption
eNaC-inhibitors
Na
K
Mineralocorticoid
receptor antagonist
Acetazolamide
CA IV
CA II
HCO3
H
H2O + CO2
H2CO3
SGLT2-inhibitors
Glucose
Loop diuretics
2 Cl
Vaptans
AVP
DNA
synthesis
AQP2
cAMP/PKA
V2-receptor
proximal convoluted tubuli
Loop of Henle
Distal convoluted tubuli (DCT)
Collecting ducts

PROXIMAL ACTING DIURETICS

Diuretic Timeline

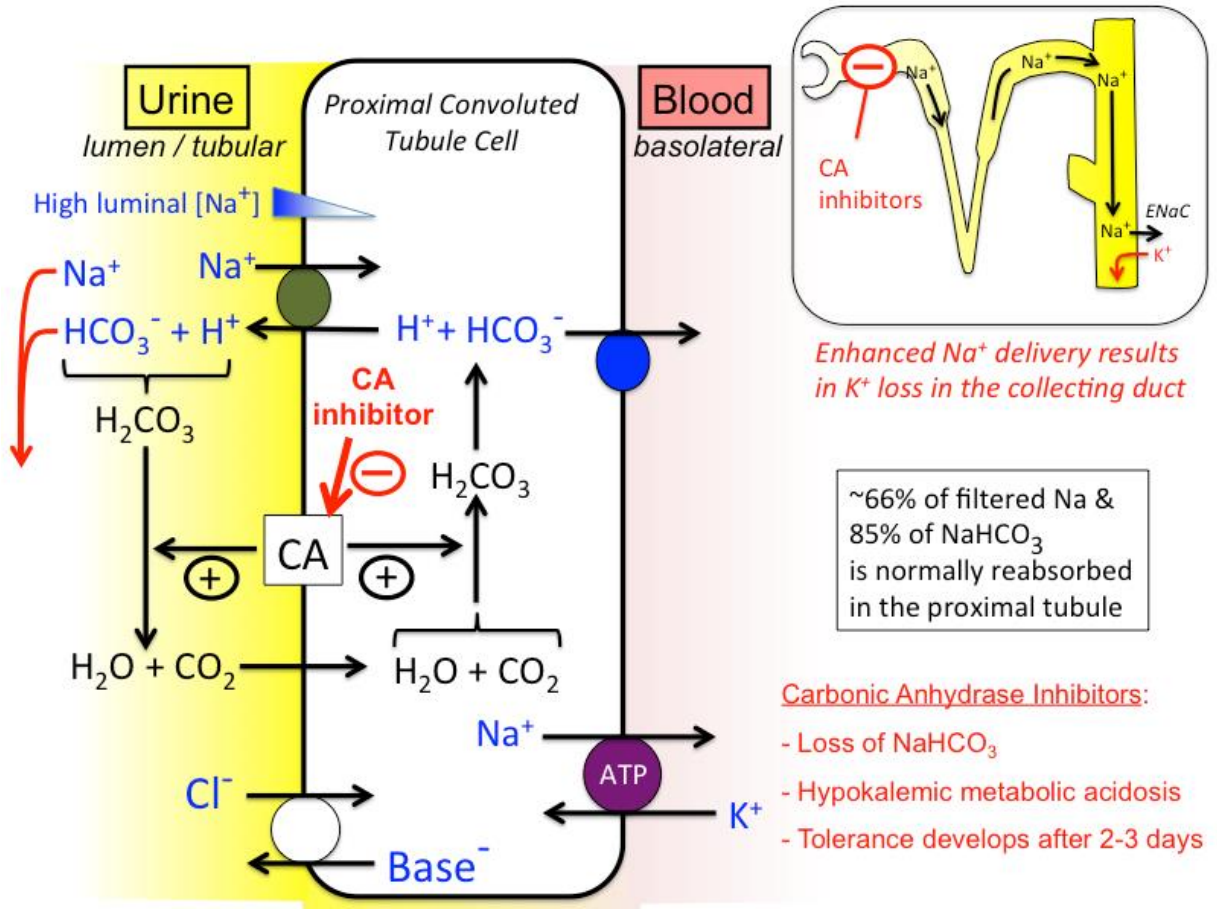


AJKD National Kidney Foundation present NEPHMADNESS X 2013–2022

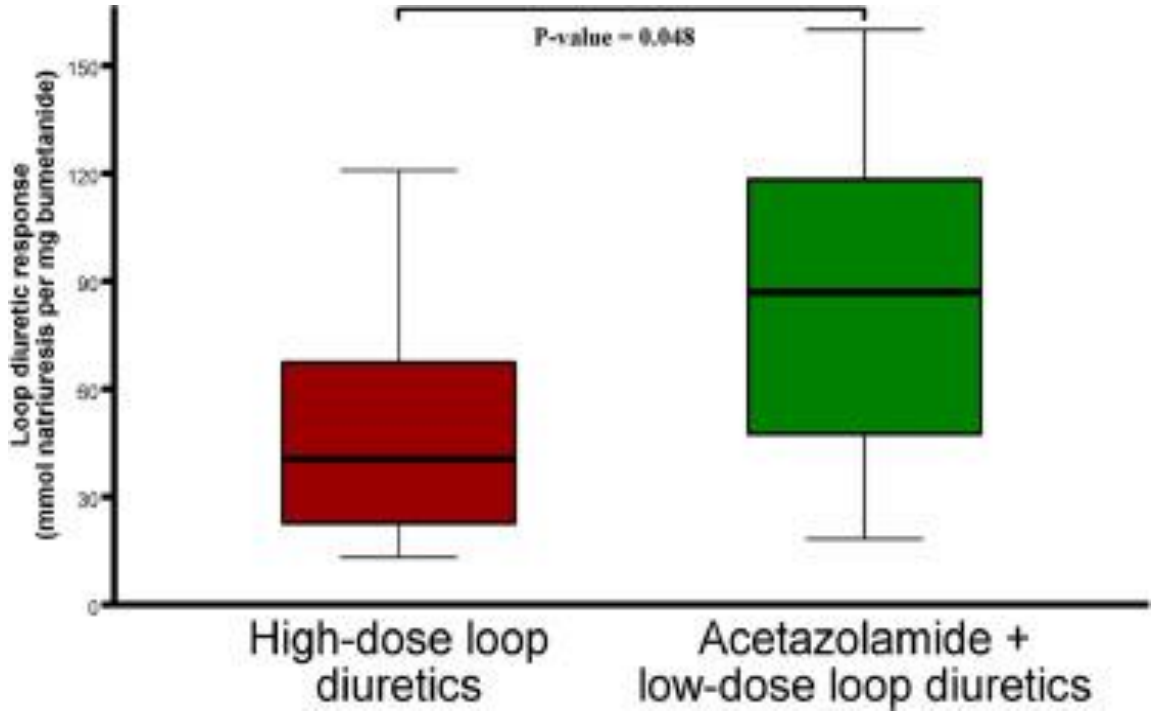
Infographic by Jade Teakell, MD PhD @JMTeakell

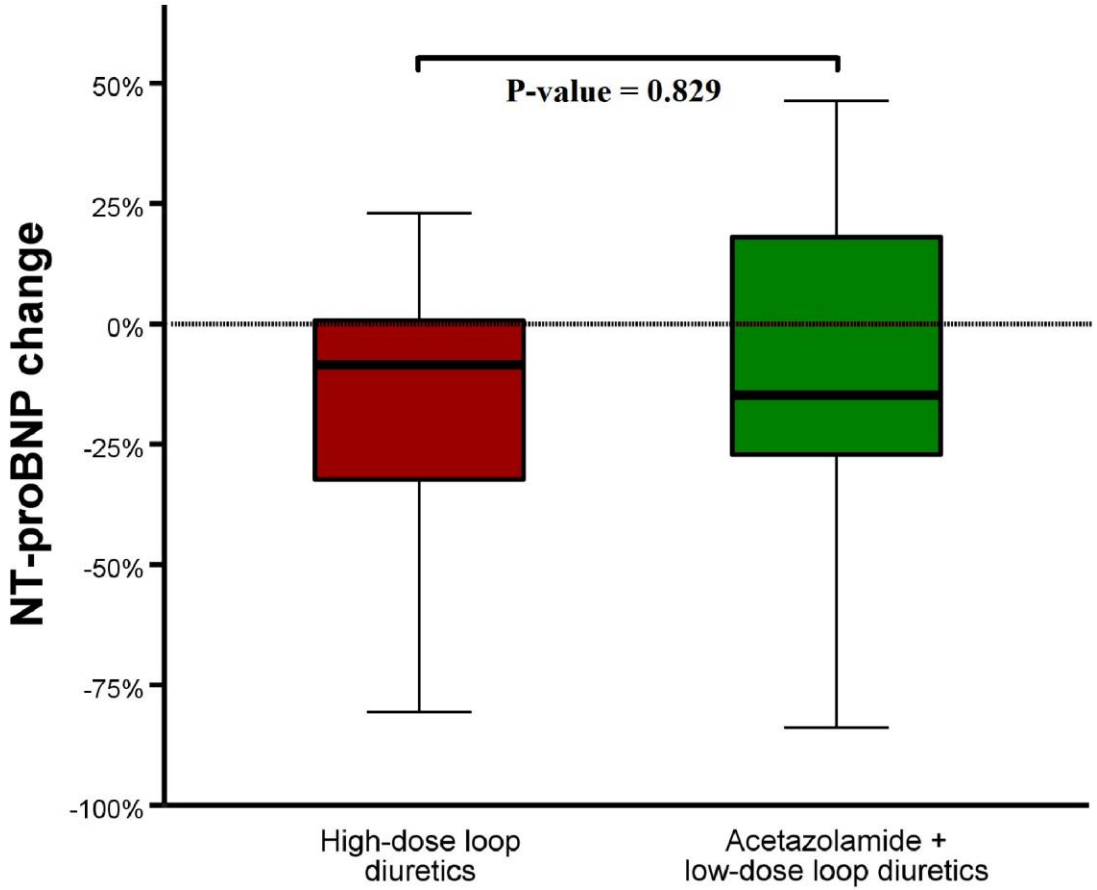
Adapted from Eknoyan 1997 (ISBN 9780126356908)

Acetazolamide



Loop + ACTZ >>> x2 the FeNa
we can get a lot more Na out! (if combined w/ Lazix)



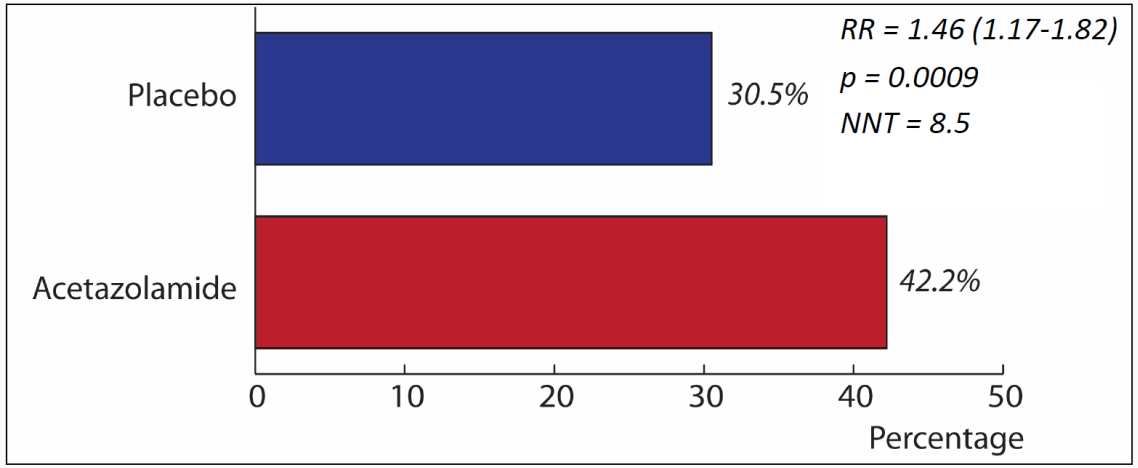


Acetazolamide 500 mg IV x 3 d

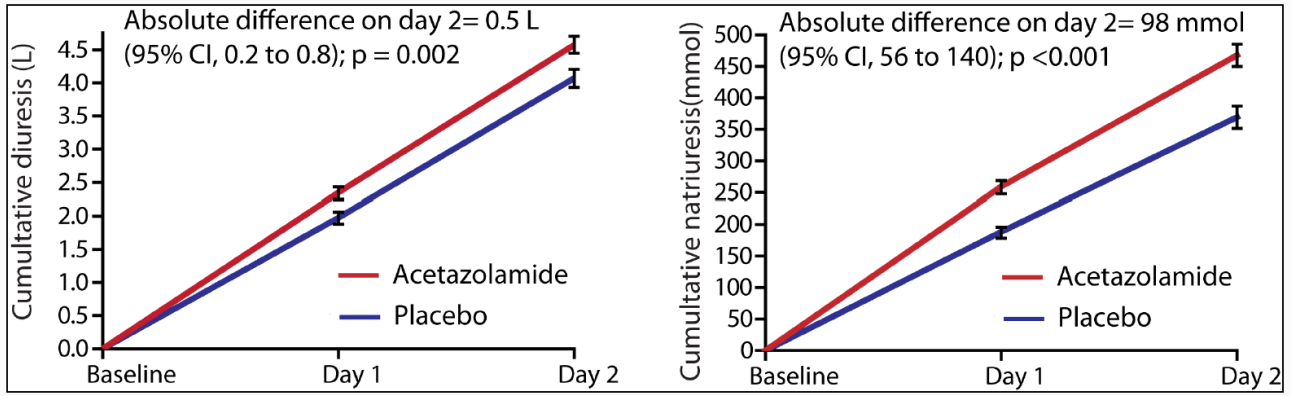
N = 519
rEF or pEF
Exclude: SGLT2i, GFR<20

0.5 L more diuresis
98 mmol more natriuresis

Results: primary end point (successful decongestion within 3 days)



Results: effect of acetazolamide on diuresis and natriuresis



Mullens W, *et al. NEJM* 2022

ADVOR

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

Mullens W, et al. Aug 27, 2022. *NEJM*

QUESTION

Does the addition of acetazolamide to standardized intravenous loop-diuretic therapy improve the incidence of successful decongestion in patients with acute decompensated heart failure?

CRITERIA

Inclusion

- Admitted for acute decompensated HF
- ≥ 1 clinical sign of volume overload
- NT-proBNP >1000pg/mL or BNP >250pg/mL
- Oral maintenance therapy with ≥ 40mg furosemide or equivalent dose

Exclusion

- Acetazolamide or SGLT2i maintenance
- Systolic BP < 90 mm Hg
- GFR < 20mL/min/1.73m^2
- IV loop diuretic >80mg furosemide or equivalent

METHODS

519 patients
27 sites in Belgium
Avg age 78 yrs
63% Male
99% White

Randomized
Double-blinded

Acetazolamide 500mg IV daily

Placebo

For 2 days or until complete decongestion

Administered w/ IV loop diuretic at double maintenance dose

Loop diuretic dose escalated if UOP for 30-48hrs was <3.5L & signs of fluid overload

1° OUTCOME

Successful decongestion:
Absence of signs of volume overload, within 3 days of randomization and without indication for escalation of diuretics

42.2%

30.5%

Risk ratio 1.46
95% CI 1.17-1.82
p < 0.001

2° OUTCOMES

Death from any cause or rehospitalization for HF during 3 months of follow-up

No difference

Duration of index hospital admission

No difference

SAFETY OUTCOMES

Combined renal safety end point, hypokalemia, or hypotension during treatment

No difference

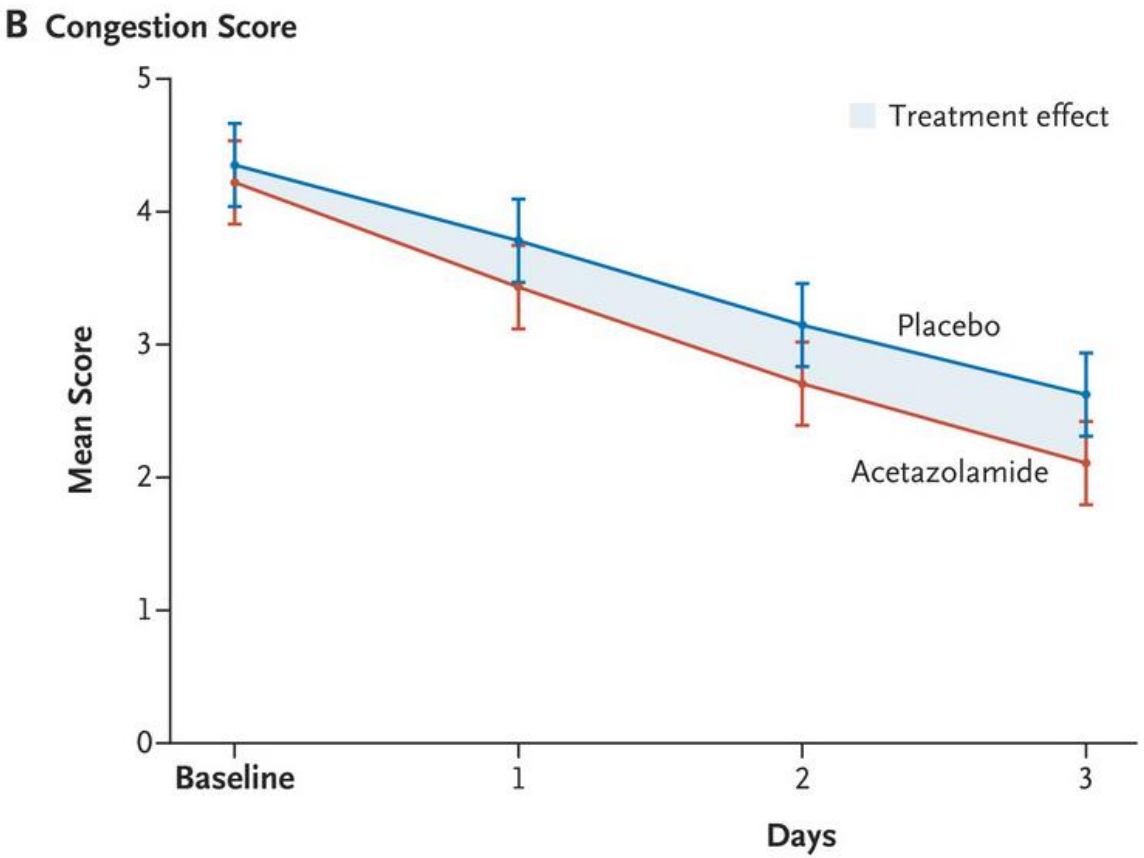
Serious adverse event during 3 month of follow-up

No difference

CONCLUSION

The addition of acetazolamide to standardized IV loop diuretic therapy in patients with acute decompensated heart failure was associated with a higher incidence of successful decongestion.

Created by Gurleen Kaur, MD (@Gurleen_Kaur96)



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)

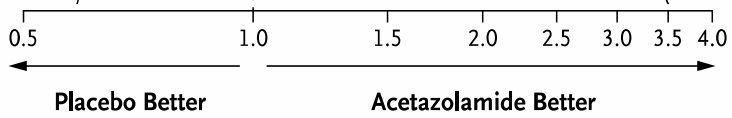


Figure 2. Subgroup Analysis.

Subgroups that were defined according to age, the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, the estimated glomerular filtration rate (GFR), the home maintenance dose of loop diuretic, and the baseline congestion score were based on observed median values at randomization.

ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1713

RESEARCH ARTICL

Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empaglif ozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF)

Kevin Damman[1], Jost C. Beusekamp[1], Eva M. Boorsma[1], Henk P. Swart[2], Tom D.J Smilde[3], Arif Elvan[4], JW. Martijn van Eck[5], Hiddo JL. Heerspink[1,6], and Adriaan A. Voors[1]*

[1]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Antonius Ziekenhuis Sneek, Sneek, The Netherlands; [3]TREANT zorggroep, Emmen, The Netherlands; [4]Department of Cardiology, ISALA, Zwolle, The Netherlands; [5]Jeroen Bosch Ziekenhuis, Den Bosch, The Netherlands; and [6]The George Institute for Global Health, Sydney, Australia

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Aims Inhibition of sodium–glucose co-transporter 2 (SGLT2) reduces the risk of death and heart failure (HF) admissions in patients with chronic HF. However, safety and clinical eff cacy of SGLT2 inhibitors in patients with acute decompensated HF are unknown.

Methods and results In this randomized, placebo-controlled, double-blind, parallel group, multicentre pilot study, we randomized 80 acute HF patients with and without diabetes to either empaglif ozin 10 mg/day or placebo for 30 days. The primary outcomes were change in visual analogue scale (VAS) dyspnoea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of stay. Secondary outcomes included safety and clinical endpoints. Mean age was 76 years, 33% were female, 47% had *de novo* HF and median NT-proBNP was 5236 pg/mL. No difference was observed in VAS dyspnoea score, diuretic response, length of stay, or change in NT-proBNP between empaglif ozin and placebo. Empaglif ozin reduced a combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo [4 (10%) vs. 13 (33%); $P = 0.014$]. Urinary output up until day 4 was signif cantly greater with empaglif ozin vs. placebo [difference 3449 (95% conf dence interval 578–6321) mL; $P < 0.01$]. Empaglif ozin was safe, well tolerated, and had no adverse effects on blood pressure or renal function.

Conclusions In patients with acute HF, treatment with empaglif ozin had no effect on change in VAS dyspnoea, diuretic response, NT-proBNP, and length of hospital stay, but was safe, increased urinary output and reduced a combined endpoint of worsening HF, rehospitalization for HF or death at 60 days.

Keywords Acute heart failure • Empaglif ozin • Sodium–glucose co-transporter 2 • Hospital readmission • Dyspnoea • Diuresis • Renal function • Blood pressure

*Corresponding author. Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9713GZ Groningen, The Netherlands. Tel. +31 50 3611327, Fax: +31 50 3613491, Email: a.a.voors@umcg.nl

SGLT2i

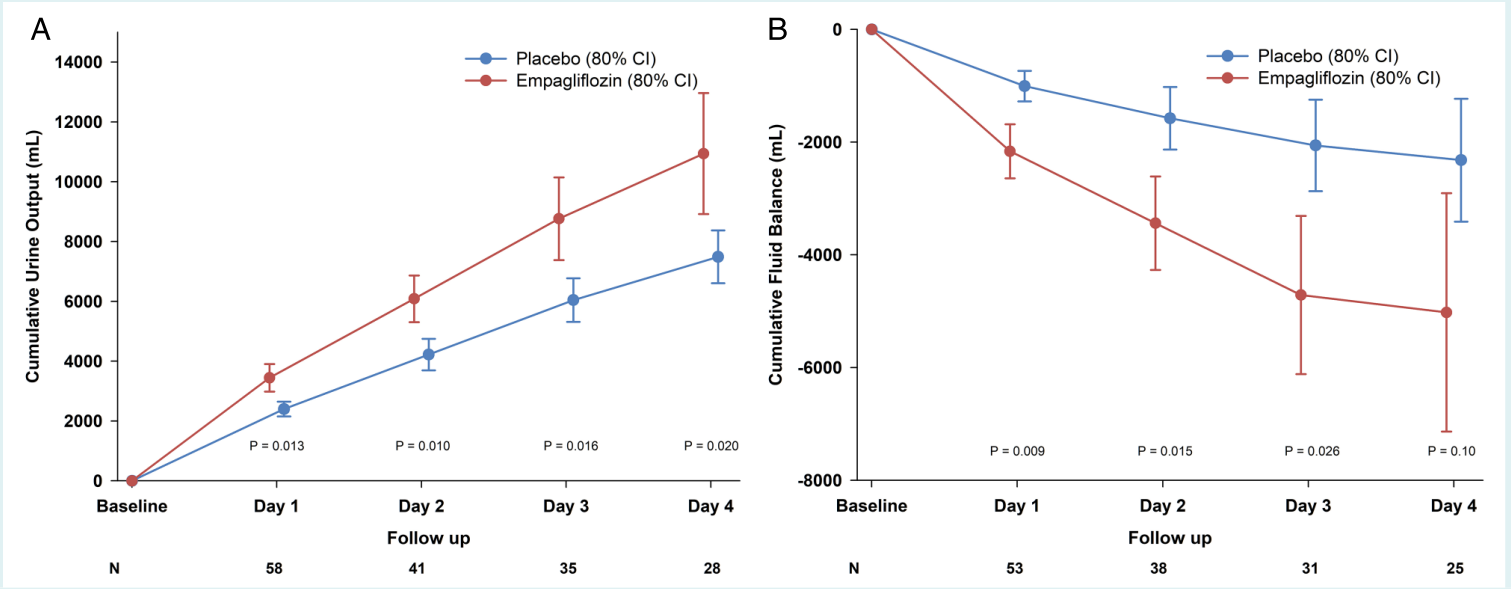
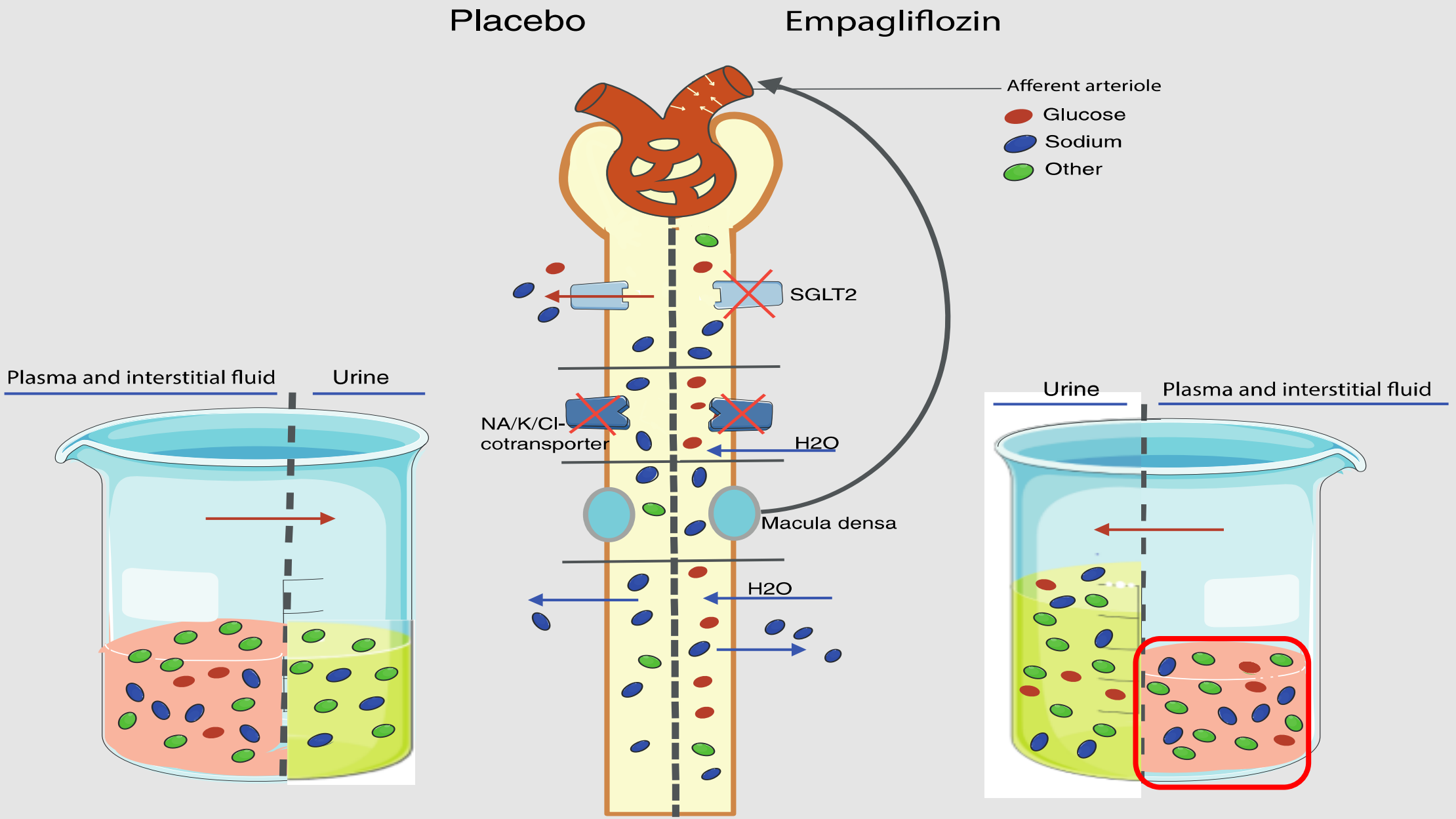
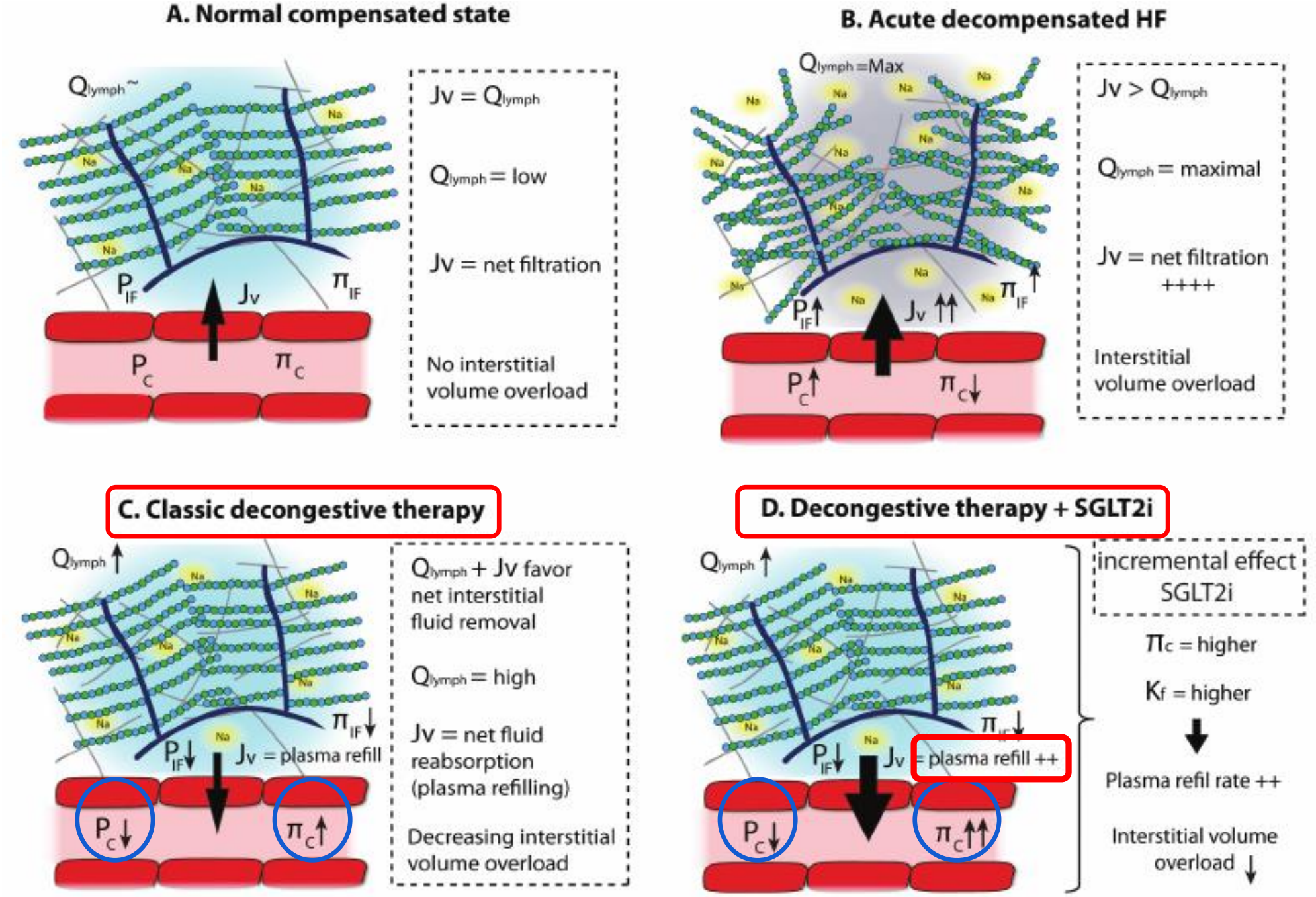


Figure 5 Urinary output and net fluid balance through day 4. (*A*) Cumulative urine output. (*B*) Cumulative net fluid balance. CI, confidence interval.


Placebo
Empagliflozin
Afferent arteriole
Glucose
Sodium
Other
SGLT2
NA/K/Cl-
cotransporter
H2O
Macula densa
H2O
Plasma and interstitial fluid
Urine
Urine
Plasma and interstitial fluid

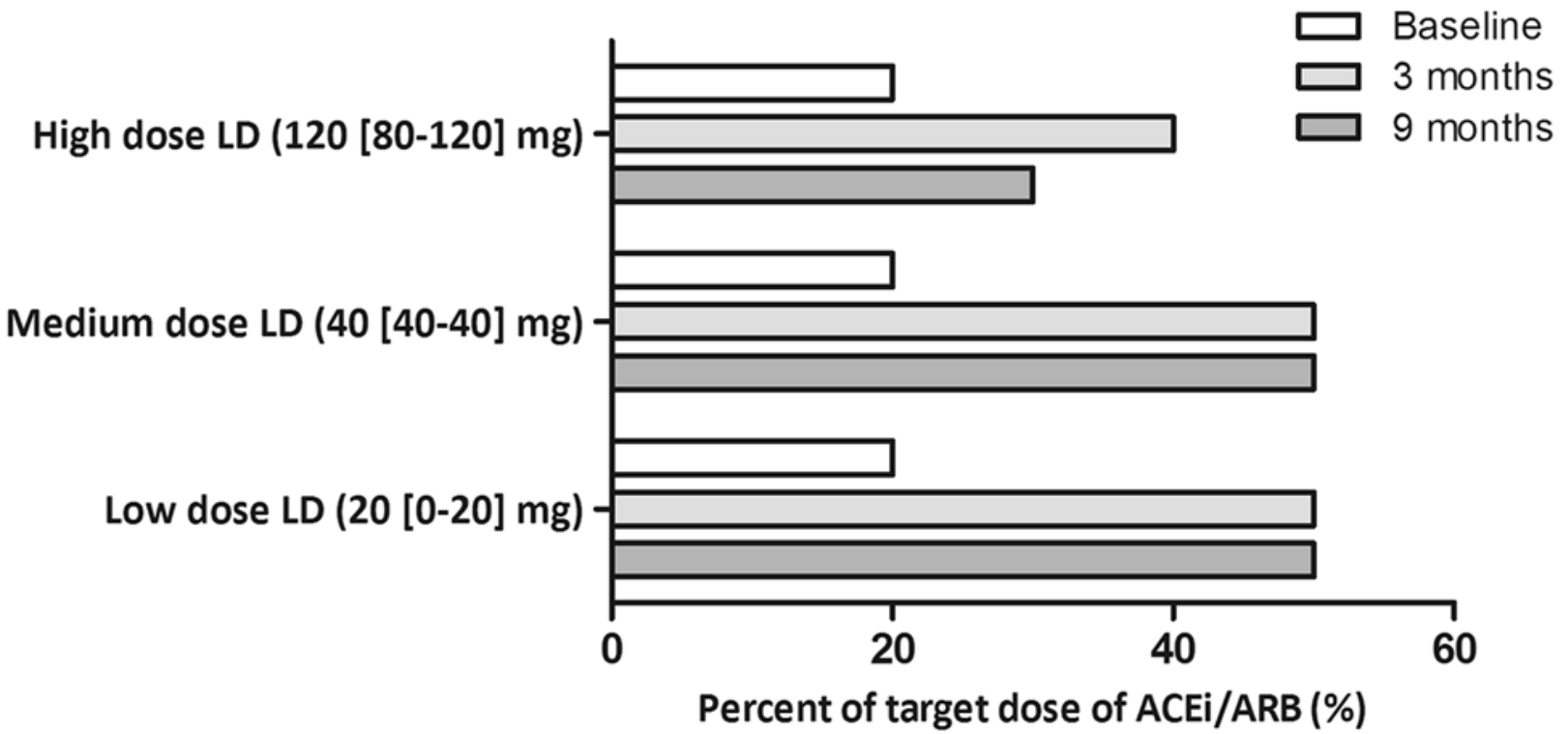

A. Normal compensated state
Qlymph~
Na
PIF
Jv
πIF
PC
πC
Jv = Qlymph
Qlymph = low
Jv = net filtration
No interstitial volume overload
B. Acute decompensated HF
Qlymph =Max
Jv > Qlymph
Qlymph = maximal
Jv = net filtration ++++
Interstitial volume overload
C. Classic decongestive therapy
Qlymph
Jv = plasma refill
Qlymph + Jv favor net interstitial fluid removal
Qlymph = high
Jv = net fluid reabsorption (plasma refilling)
Decreasing interstitial volume overload
D. Decongestive therapy + SGLT2i
Jv = plasma refill ++
incremental effect SGLT2i
πc = higher
Kf = higher
Plasma refil rate ++
Interstitial volume overload

agents that excrete more Na, lead to better/more effective de-congestive therapy

SGLT2i are not AHF de-congesting drugs !
they improve the “prognosis”

the biggest treat for Acute HF pts during Hosp
>>> is the reduction of NH blockers !

Inappropriate High Dose of Loop Diuretics in De-congested Pts, Hampers Up-titration of Disease Modifying Drugs

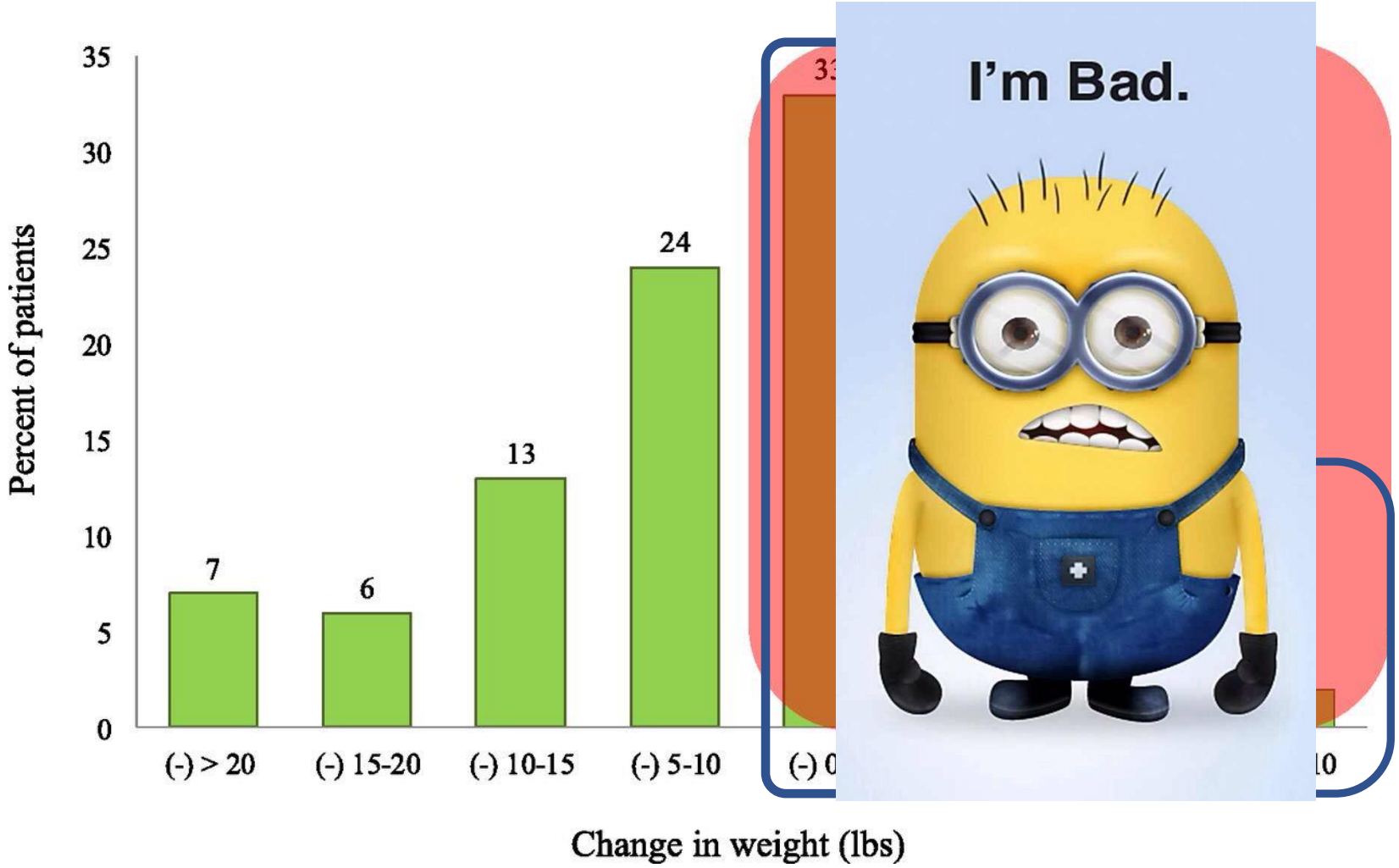


HF = Di[illegible]tt ?

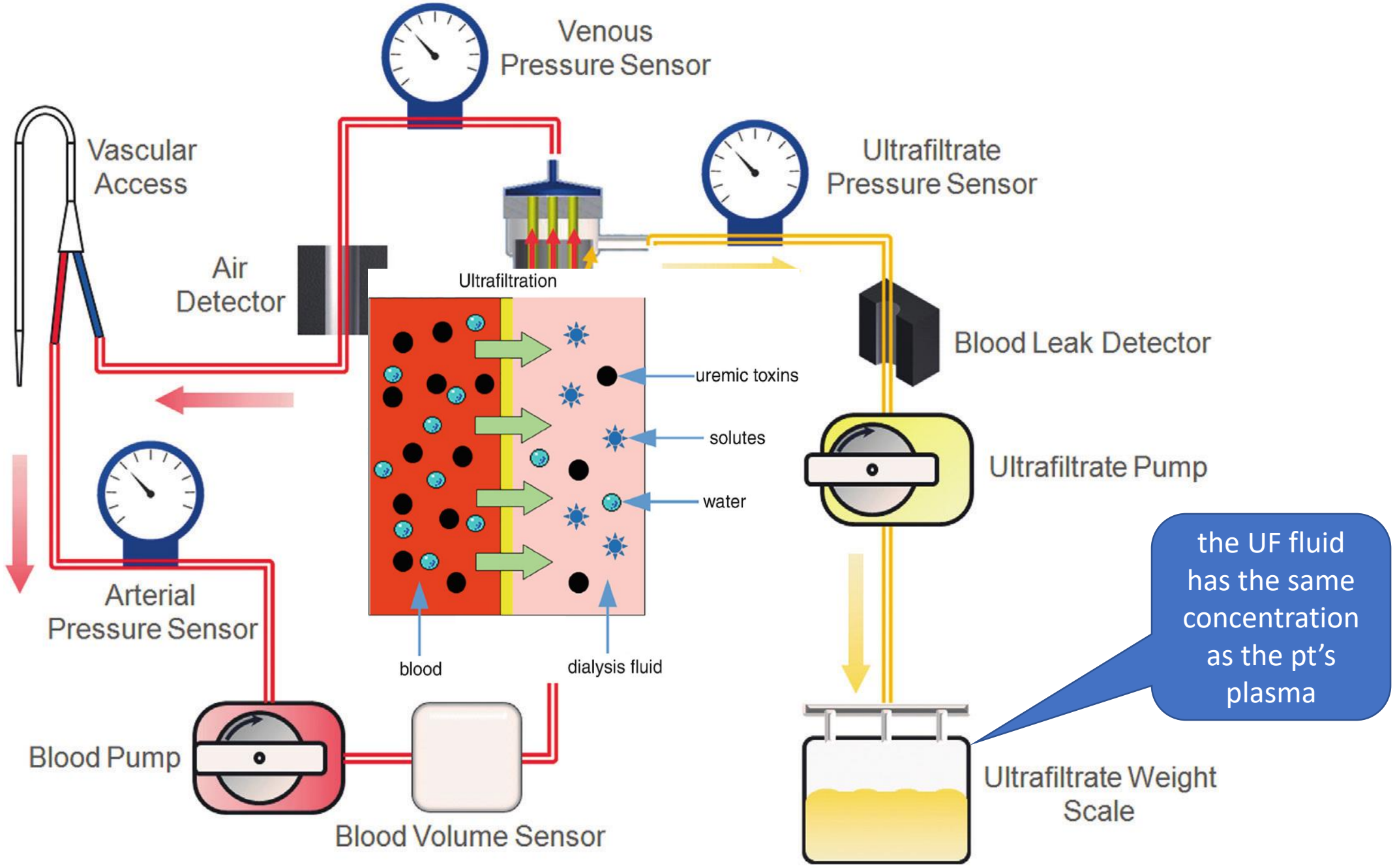
absolutely NO !

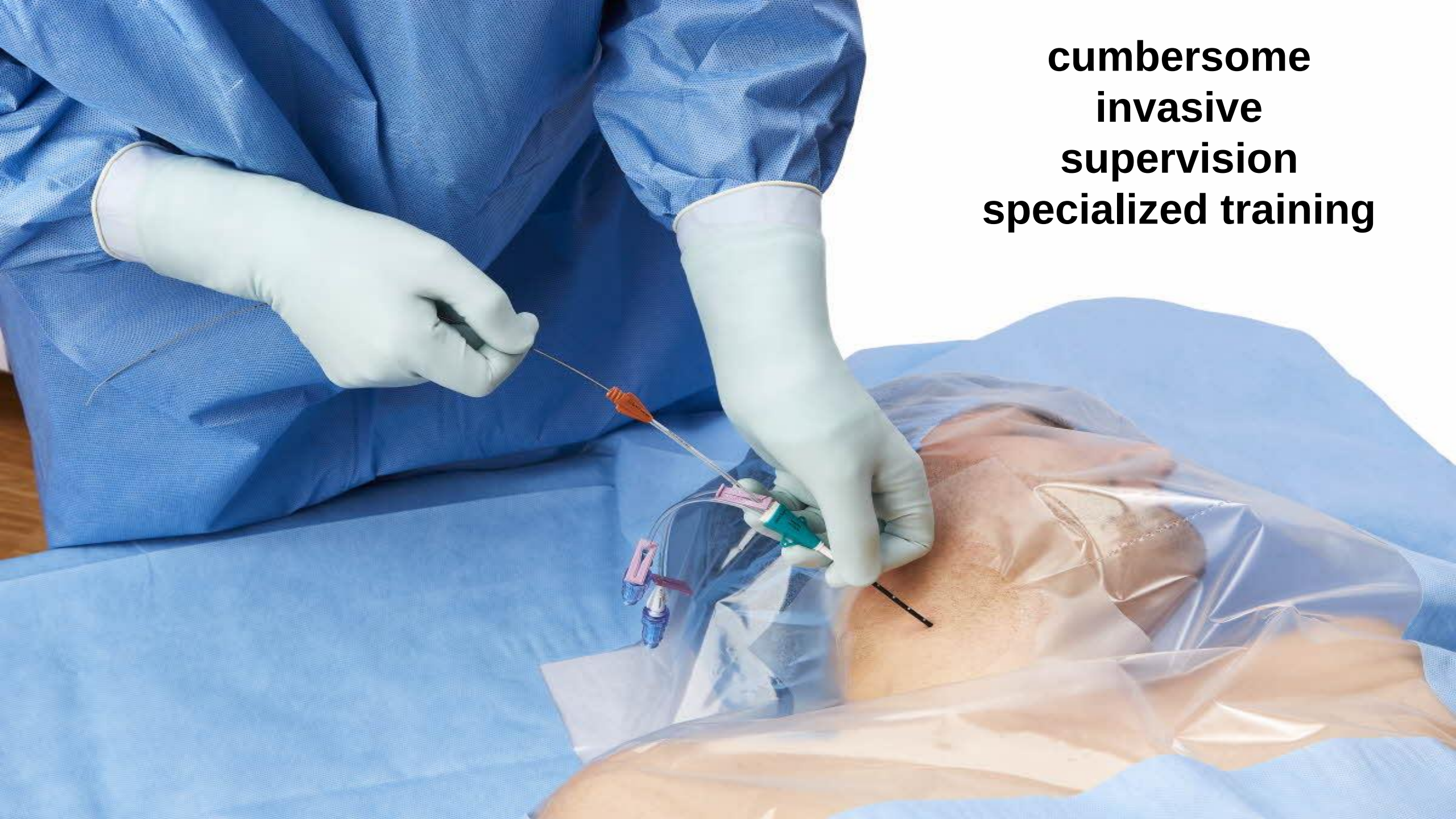

چشم ما را بایست
چو دیگر بایدیدید

Going with ongoing congestion !



Frequently, adequate diuresis is not achievable >>> mechanical strategies


Venous
Pressure Sensor
Vascular
Access
Air
Detector
Ultrafiltration
Ultrafiltrate
Pressure Sensor
Blood Leak Detector
uremic toxins
solutes
water
Ultrafiltrate Pump
Arterial
Pressure Sensor
blood
dialysis fluid
the UF fluid
has the same
concentration
as the pt's
plasma
Blood Pump
Blood Volume Sensor
Ultrafiltrate Weight
Scale

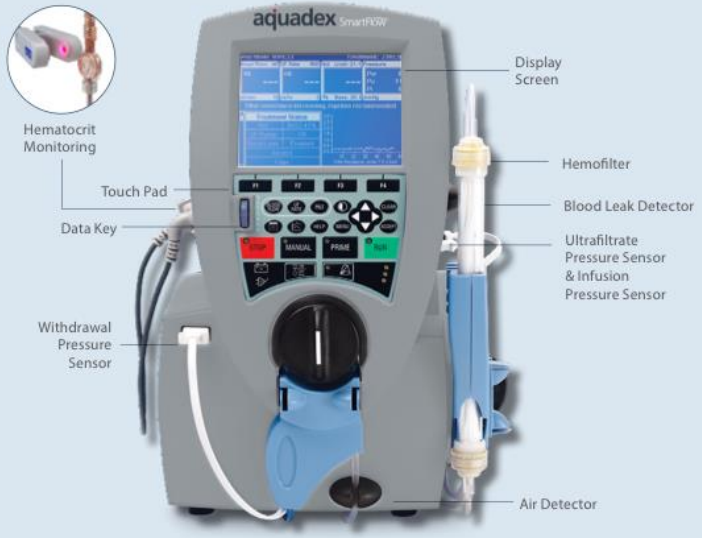


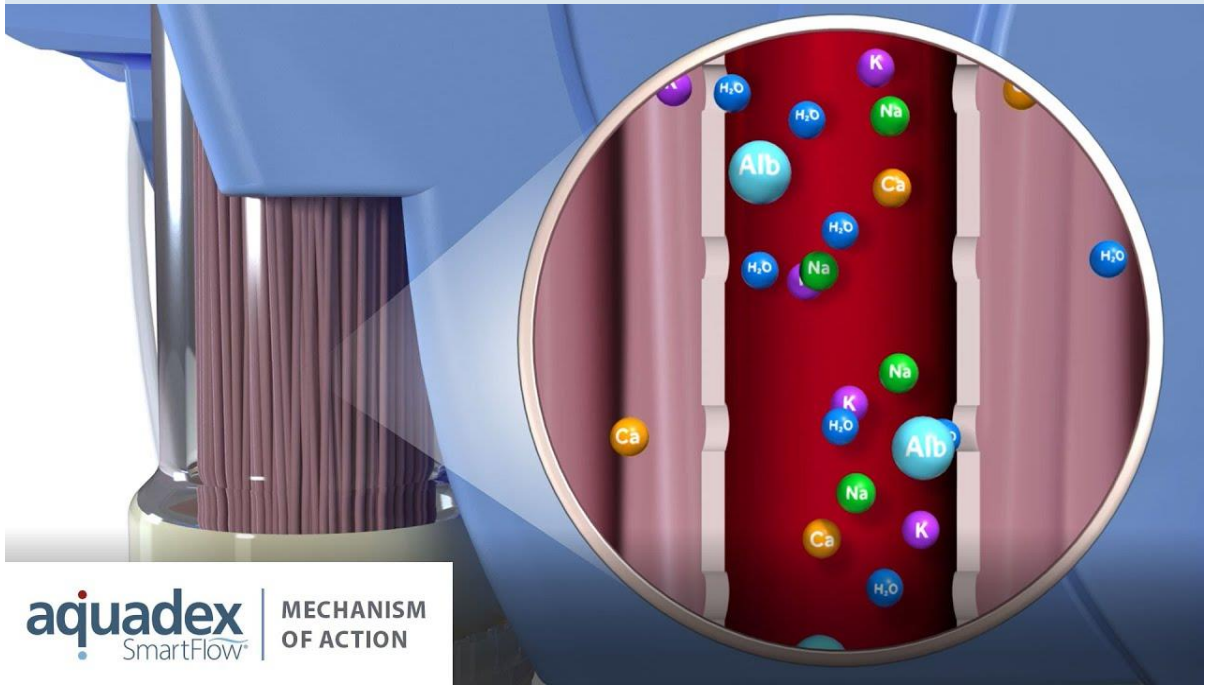
cumbersome
invasive
supervision
specialized training

AQUADEX CONSOLE

EASY TO OPERATE, SAFE TO USE

- Adjustable fluid removal rates for customized therapy
- Perform therapy through peripheral or central venous access
- Highly automated with only one setting required to begin
- Hematocrit sensor provides real-time measurement of % blood volume change
- User defined hematocrit limit
- SvO_2 monitoring provides insights into tissue oxygen delivery



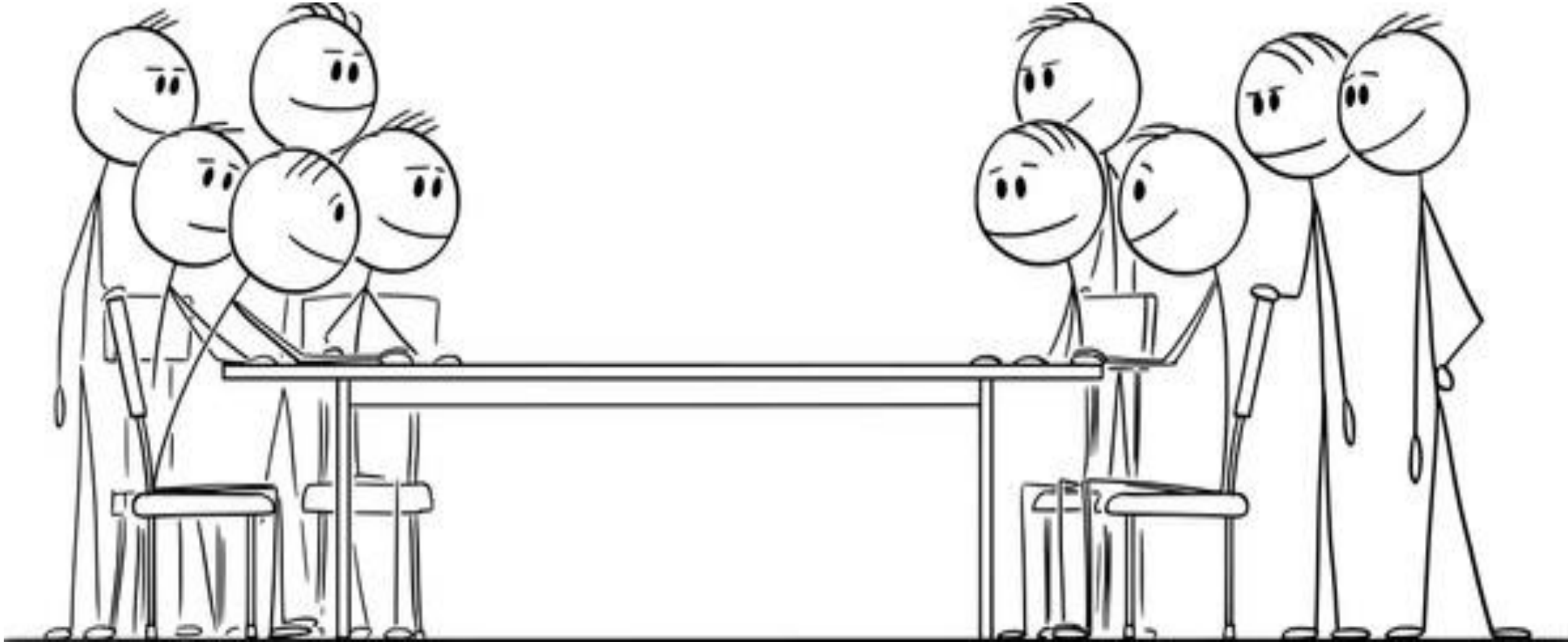


aquadex SmartFlow | MECHANISM OF ACTION

TABLE 1 Comparative Characteristics of Loop Diuretic Agents and Isolated UF

Loop Diuretic Agents	Isolated UF
Direct neurohormonal activation	No direct neurohormonal activation
Elimination of hypotonic urine	Removal of isotonic plasma water
Unpredictable elimination of sodium and water	Precise control of rate and amount of fluid removal
Development of diuretic agent resistance with prolonged administration	Restoration of diuretic agent responsiveness
Risk of hypokalemia and hypomagnesemia	No effect on plasma concentration of potassium and magnesium
Peripheral venous access	Peripheral or central venous catheter
No need for anticoagulation	Need for anticoagulation
No extracorporeal circuit	Need for extracorporeal circuit

Great Debate



Circulation, 2009

UF first

CONTROVERSIES IN HEART FAILURE

Should Ultrafiltration Be Used Preferentially Instead of Diuretics for the Initial Treatment of ADHF Patients?

Treatment of Congestion in Congestive Heart Failure

Ultrafiltration Is the Only Rational Initial Treatment of Volume Overload in Decompensated Heart Failure

Bradley A. Bart, MD

"If you have always done it that way, it is probably wrong."
—Charles F. Kettering, 1876–1958

The morbidity of decompensated heart failure is due to volume overload, a consequence of increased total body sodium.[1,2] Failure to adequately reduce total body sodium contributes to progressive ventricular dysfunction, worsening heart failure, and excess morbidity. Ultrafiltration is the gold standard for sodium-volume removal and is the only intervention shown to improve outcomes in a randomized controlled trial of patients hospitalized with decompensated heart failure.[3] Diuretics are inherently inferior because they produce hypotonic urine[4,5]and undesirable hemodynamic and neurohormonal changes.[6,7] Therefore, ultrafiltration is the preferred initial treatment for patients hospitalized with decompensated heart failure and sodium-volume overload.

Response by Shin and Dec on p 504

Sodium is the Major Determinant of Extracellular Fluid Volume

The earliest descriptions of heart failure date back more than 3500 years to the Egyptian civilization. Even then, symptoms were correctly attributed to volume excess.[8] It was not until the early 20th century that researchers recognized the role of salt in the formation of edema. In 1901, researchers found that salt fed to patients with congestive heart failure could not be recovered as chloride in the urine.[8] This represents one of the earliest descriptions of heart failure as a sodium avid state. Later, it was demonstrated that liberal salt intake increased congestive symptoms and pulmonary edema in patients with heart failure whereas patients on salt-restricted diets could tolerate large amounts of water without any further increases in congestion or edema.[8] Other studies confirmed the primary role of salt, not water, in the formation of edema in heart failure. By 1948, sodium was widely recognized as the major determinant in extracellular fluid volume.[1]

Today, it is understood that sodium retention in heart failure is under the influence of the sympathetic and renin-angiotensin-aldosterone (RAAS) systems.[7] Renin release from the kidneys leads to the production of angiotensin II. Increased angiotensin II levels activate receptors on the epithelium of the proximal tubule enhancing sodium reabsorption in the nephron. Angiotensin II also causes constriction of the efferent arterioles disturbing the usual balance of hydrostatic and osmotic forces in the peritubular capillaries such that sodium reabsorption is increased. In addition to its direct tubular and vascular effects in the kidney, angiotensin II promotes aldosterone secretion. Aldosterone increases sodium reabsorption in the distal nephron. Decreased sodium

From the Division of Cardiology, Hennepin County Medical Center, and the University of Minnesota, Minneapolis, Minn.
Correspondence to Bradley A. Bart, MD, Division of Cardiology, O5 HCMC, 701 Park Ave S, Minneapolis, MN 55415. E-mail bartx006@umn.edu
(*Circ Heart Fail.* 2009;2:499-504.)

Circ Heart Fail is available at http://circheartfailure.ahajournals.org DOI: 10.1161/CIRCHEARTFAILURE.109.863381

Lasix first

CONTROVERSIES IN HEART FAILURE

Should Ultrafiltration Be Used Perferentially Instead of Diuretics for the Initial Treatment of ADHF Patients?

Ultrafiltration Should Not Replace Diuretics for the Initial Treatment of Acute Decompensated Heart Failure

Jordan T. Shin, MD, PhD; G. William Dec, MD

Heart failure (HF) represents a significant and growing health concern in the aging population of the United States. Total HF costs in the United States for 2009 are estimated to be $37.2 billion and account for more than 1 million hospital discharges.[1] Acute decompensated HF (ADHF) represents the most common reason for HF hospitalization. Improvements in HF care would thus have a broad impact on health care delivery.

Response by Bart on p 511

Registry data indicate that the population of patients admitted for HF represents an "at risk" group. Acute in-hospital mortality ranges from 3% to 7% for ADHF and may be as high as 13.5% at 3 months after discharge. Furthermore, surviving patients remain at significant risk for hospital readmission (24% to 31%) within 3 months after their index hospitalization for ADHF.[2] Strategies to understand the mechanisms of disease associated with poor outcomes in HF have identified a clinical syndrome of deteriorating renal function, diuretic unresponsiveness, and impaired natriuresis, which has been called the cardiorenal syndrome (CRS). Chronic renal insufficiency, commonly associated with HF, adversely impacts HF survival, length of stay (LOS), and readmission rates.[3,4] Although no broadly accepted consensus definition of CRS has been adopted,[5] most criteria for CRS include (a) HF and renal insufficiency; (b) worsening renal function during treatment for ADHF; and (c) diuretic resistance.[6] Worsening renal function (defined by an increased serum creatinine [sCr] ≥0.3 mg/dL) is a common feature in patients admitted for volume overload and treatment of ADHF, with some reports identifying a prevalence of >70% in hospitalized patients. Treatments to mitigate diuretic resistance and CRS have been sought to promote better ADHF outcomes.

An emerging literature suggests an important role for venous congestion as a major contributor to CRS. Traditionally cited mechanisms for worsening renal function include (a) systemic and renal hypoperfusion, (b) periodic intravascular or arterial volume depletion, (c) excessive stimulation of vasoconstrictor neurohormones such as angiotensin, and (d) increased interstitial fibrosis associated with the chronic use of furosemide.[7] However, recent data implicate elevated right-sided venous pressures and increased intraperitoneal pressure due to ascites, which commonly accompany right HF in the worsening renal function seen in ADHF.[8–10] Thus, acute therapies directed at relieving venous congestion should be paramount in ADHF.

The pharmacological armamentarium for treating symptomatic volume overload has changed very little during the past 3 decades and remains memorialized in the mnemonic LMNOP (L indicates lasix or loop diuretic; M, morphine; N, nitrates; O, oxygen; and P, positive pressure ventilation)

From the Heart Failure and Transplantation Unit, Cardiology Division, Massachusetts General Hospital Heart Center, Boston, Mass.
Correspondence to Jordan T. Shin, MD, PhD, Heart Failure and Transplantation Unit, Cardiology Division, Massachusetts General Hospital Heart Center, Bigelow 800, 55 Fruit St, Boston, MA 02114. E-mail jshin1@partners.org
(*Circ Heart Fail.* 2009;2:505-511.)

Circ Heart Fail is available at http://circheartfailure.ahajournals.org DOI: 10.1161/CIRCHEARTFAILURE.109.862474

Response to Shin and Dec

Bradley A. Bart, MD

After more than 40 years of loop diuretics, death and rehospitalization rates for patients with acute decompensated heart failure remain unacceptably high. The addition of inotropes, vasodilators, natriuretic peptides, adenosine antagonists, arginine vasopressin antagonists, and invasive hemodynamic monitoring have done nothing to improve outcomes in this patient population. Ongoing faith in this pharmacological alchemy is dangerous testament to what is considered expert opinion. Researchers have known for more than 100 years that sodium is the major determinant of extracellular fluid volume in heart failure. Excess total body sodium is the primary treatment target for hospitalized patients suffering from sodium/volume overload. Loop diuretics, although often effective in removing water, are inherently incapable of predictably reducing total body sodium, whereas ultrafiltration predictably reduces total body sodium in all treatments. Treatment with diuretics may be better than doing nothing, but in controlled trials, ultrafiltration is superior to diuretics with respect to sodium removal, water removal, and rehospitalization rates. Ultrafiltration should be the standard of care for patients with sodium/fluid overload admitted to the hospital with acute decompensated heart failure—other promising therapies should prove safety and efficacy against the standard of ultrafiltration. The ongoing endorsement of diuretics as first-line treatment for sodium/volume overload in the acute decompensated heart failure guidelines pays homage to tradition but ignores new knowledge of the failings and safety concerns of diuretics. With 3-month rehospitalization rates as high as 30%, our patients can no longer afford to suffer from the inertia that resists the use of ultrafiltration—the most effective and reliable method of reducing total body sodium.

Response to Bart

Jordan T. Shin, MD, PhD; G. William Dec, MD

"Le mieux est l'ennemi du bien"
—*Voltaire*

Is ultrafiltration really the only rational treatment of volume overload in acute decompensated heart failure? Current American College of Cardiology/American Heart Assocation guidelines recommend diuretics first (class I) and ultrafiltration second (class IIA for refractory, volume overload) and do not support the statement that ultrafiltration is "the gold standard for sodium/volume removal." Although solid data supports an adverse impact of sodium retention, it remains unclear whether enhanced sodium removal improves outcomes, as is highlighted by questions raised by the use of natriuretic peptides. Whereas some studies suggest that diuresis promotes an adverse neurohormonal milieu, others have demonstrated that acute lowering of ventricular filling pressures is associated with a decline in these measures as well as B-type natriuretic peptide. All positive survival trials in heart failure were done with the background of diuretic therapy. Thus, the argument that diuretics in and of themselves are detrimental should be tested rigorously before being accepted. As we highlight, the association between higher diuretic dose and increased mortality was based on retrospective post hoc analyses that lacked adjustment for severity of illness; these findings have not been borne out (cf. our reference 15). The argument that ultrafiltration provides superior fluid removal, weight loss, and length of stay is inconsistently supported in current trials, and additional trials are needed before these findings should be accepted generally. Although diuretics are an imperfect tool for the treatment of acute decompensated heart failure, they are a "good" therapy and should remain the gold standard until additional evidence proves the "better" approach.

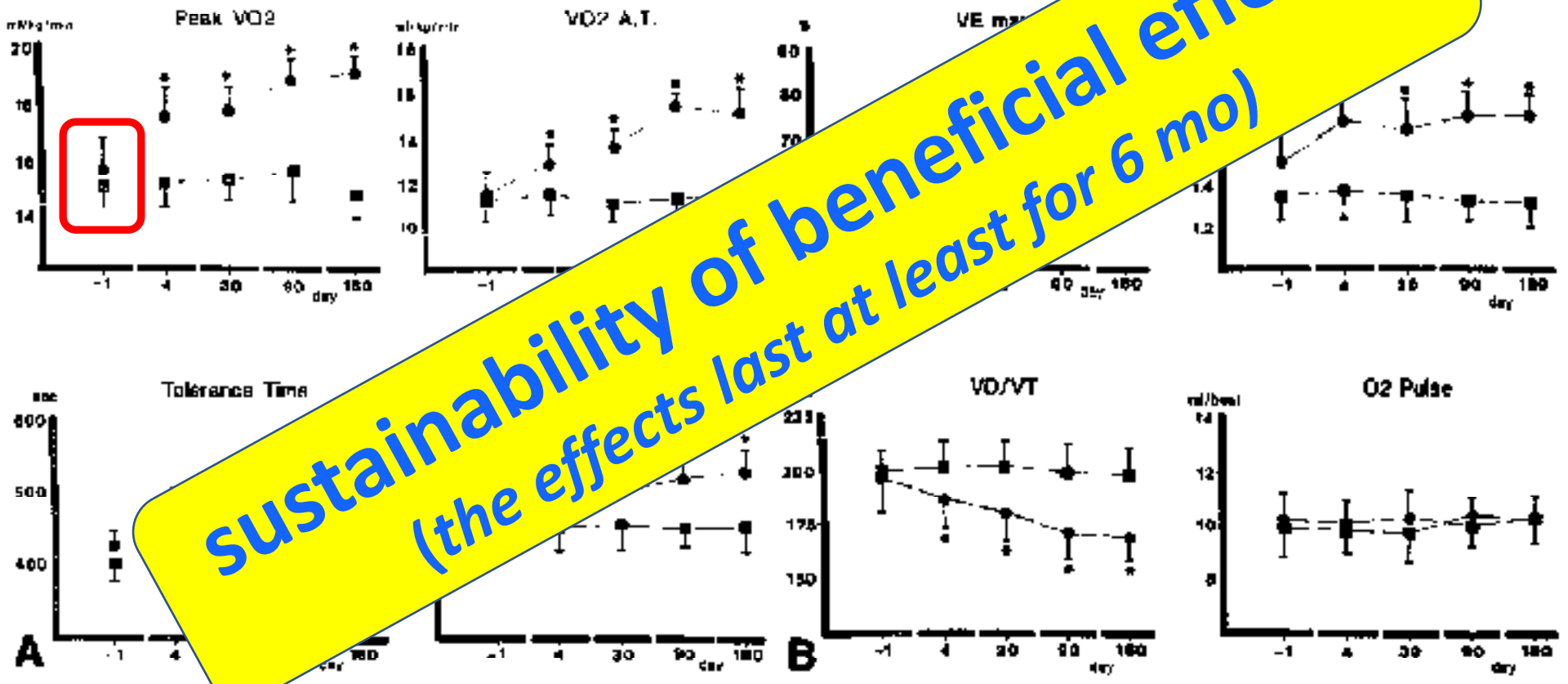
Isolated Ultrafiltration in Moderate Congestive Heart Failure

PIER GIUSEPPE AGOSTONI, MD, GIAN CARLO MARENZI, MD, MAURO PEPI, MD, ELISABETTA DORIA, MD, ALESSANDRO SALVIONI, MD, GIOVANNI PEREGO, MD, GIANFRANCO LAURI, MD, FRANCESCO GIRALDI, MD, SERGIO GRAZI, MD, MAURIZIO D. GUAZZI, MD

Milan, Italy

RCT of 36 pt
& 6 mo F/U
1993

only 1 session of UF



sustainability of beneficial effects
(the effects last at least for 6 mo)

Standard Hemodiafiltration Improves Diuretic Responsiveness in Advanced Congestive Heart Failure

Carmelo Libetta[a, c] Vincenzo Sepe[a] Manuela Zucchi[a, c] Carlo Campana[b] Antonio Dal Canton[a, c]

Units of [a]Nephrology, Dialysis and Transplantation and [b]Cardiology, IRCCS Policlinico 'San Matteo' and [c]University of Pavia, Pavia, Italy

Table 1. Clinical and laboratory data of CHF patients unresponsive (grou… sive (group B) to diuretic treatment

	Group A (HDF) (n = 5)				Group B (n = 5)			
	before		after		before		after	
Weight, kg			5.7[a]		78.68	5.4	70.98	5.7[a]
Fu…			758	38[a]	1258	61	948	38
	1.6		1.68	0.4	1.38	0.5	1.28	0.5
	45.68	48.3	30.78	25.1[a]	39.18	26.9	37.88	24.0
	10.98	4.5	2.38	0.3[a]	8.48	4.0	9.18	5.8
	7068	257	2488	152[a]	3708	188[b]	798	46[a, b]

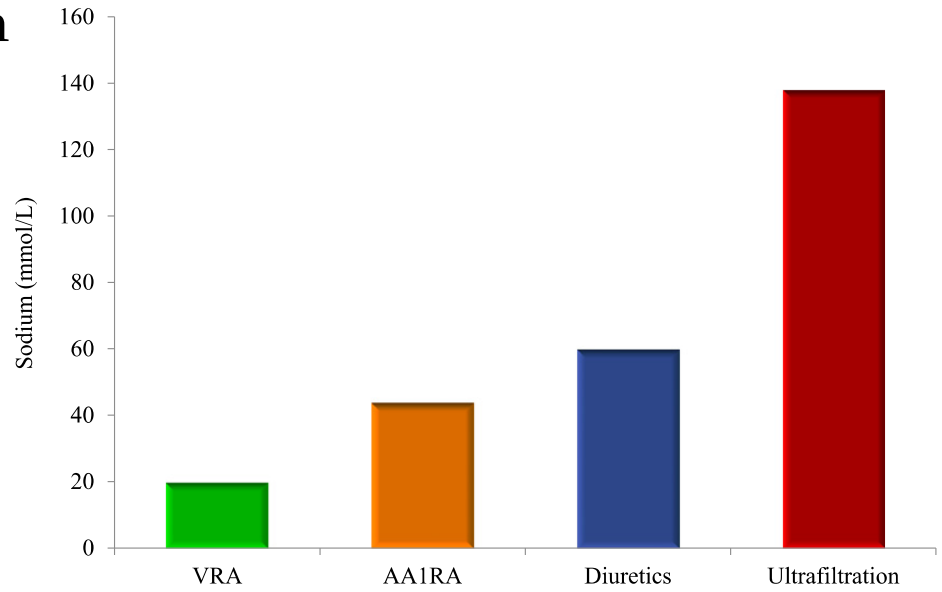
[a] $p < 0.05$ vs. before; [b] $p < 0.05$ vs. group A. Before = just before treatment; after = after 1 month of follow-up from the end of treatment; p.o. = per os (by mouth).

improvement in Diuretic responsiveness

"the effect of UF remains & last for long time"

Advantages

- Reduction in renal venous congestion and improvement in renal hemodynamics
- Rapid and adjustable removal of fluid and improvement in symptoms of congestion
- Higher mass clearance of sodium
- Decreased risk of electrolyte abnormalities (*e.g.*, hypokalemia)
- Lack of neurohormonal activation (SNS, RAAS, and AVP)
- Sustainability of the beneficial effects (*e.g.*, effect on neurohormonal axis)
- Improvement in diuretic resistance, natriuresis, and urine output
- Decreased rate of heart failure–related rehospitalizations
- Decreased hospital length of stay
- Availability of dedicated ultrafiltration devices that are portable, user-friendly, with minimal extracorporeal volume (33 ml), and have the ability of functioning with low blood flow rates (10–40 ml/min)



LANDMARK TRIALS IN

ULTRAFILTRATION FOR HEART FAILURE

SAFE , 21 pt
EUPHORIA, 20 pt
(2005)

2005
RAPID CHF

Diuretics vs UF (n=40)
Median furosemide dose 160 mg
UF for up to 8 hours

No difference in weight in 24h

Diuretics vs UF (n=200)
Average furosemide dose 180 mg
UF for up to 8 hours

UF group - greater weight loss at 48h and lower rehospitalization rates at 90 days

UNLOAD
2007

2012
CARRESS - HF

Stepped Diuretic Approach vs UF (n=188)
Diuretics to achieve 3-5L of UOP
UF with goal of 200ml/h

Stopped early due to lack of benefit + excess of harm

Stepped Diuretic Approach vs Adjustable UF (n=224)
Diuretics to achieve 3-5L of UOP
Tailored UF goal

Study stopped early due to interruption of sponsorship

AVOID - HF
2016

CUORE
2014

LANDMARK NEPHROLOGY

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Heart Failure

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure

Maria Rosa Costanzo, MD, FACC,* Maya E. Guglin, MD, FACC,†
Mitchell T. Saltzberg, MD, FACC,* Mariell L. Jessup, MD, FACC,‡ Bradley A. Bart, MD, FACC,§
John R. Teerlink, MD, FACC,‖ Brian E. Jaski, MD, FACC,¶ James C. Fang, MD, FACC,#
Erika D. Feller, MD, FACC,** Garrie J. Haas, MD, FACC,†† Allen S. Anderson, MD, FACC,‡‡
Michael P. Schollmeyer, DVM,§§ Paul A. Sobotka, MD, FACC,§§ for the UNLOAD Trial Investigators

Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

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Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

Maria Rosa Costanzo, MD,* Daniel Negoianu, MD,† Brian E. Jaski, MD,‡ Bradley A. Bart, MD,§
James T. Heywood, MD,‖ Inder S. Anand, MD, DPHIL (OXON),¶ James M. Smelser, MD,# Alan M. Kaneshige, MD,**
Don B. Chomsky, MD,†† Eric D. Adler, MD,‡‡ Garrie J. Haas, MD,§§ James A. Watts, MD,‖‖ Jose L. Nabut, MS,¶¶
Michael P. Schollmeyer, DVM,¶¶ Gregg C. Fonarow, MD##

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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for the Heart Failure Clinical Research Network

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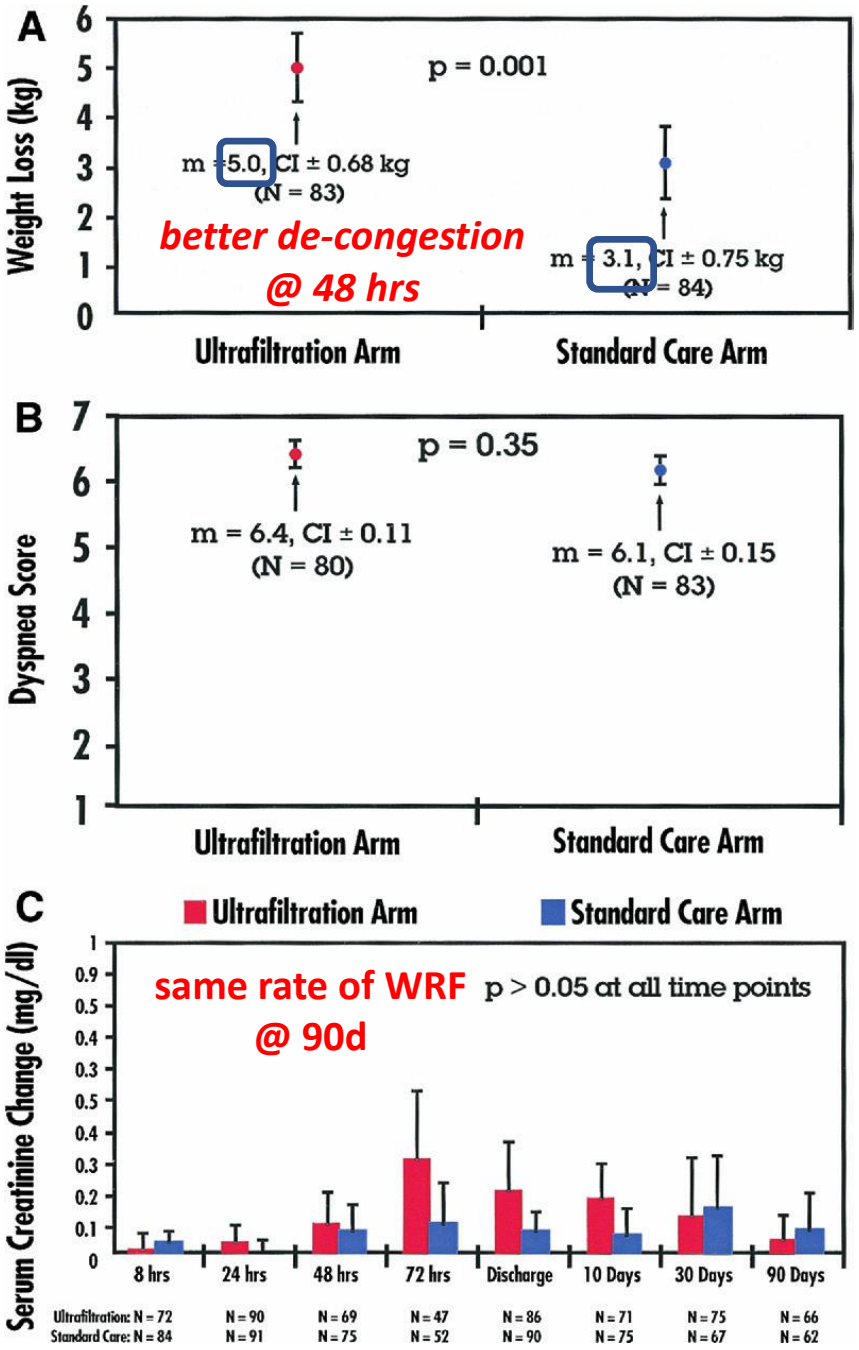
Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

UNLOAD

- Multicenter (28 center) RCT, 2007
- this is a “landmark trial” >>> which address the concerns of “safety profile of VV-UF” over std diuretic therapy.
- also, Qs regarding the effects of UF on renal parameters were taken into consideration in this study.
- ADHF
- UF >>> flexible
- Diuretic = 100 & UF = 100 randomized equally >>
- the primary efficacy endpoints : weight loss & Dyspnea assessment after 48 hrs
- the 2nd endpoints: net fluid loss, re-Hosp fo HF, functional capacity, unscheduled clinic visits in 90 days.
- primary safety endpoints : changes in BUN, SCr, electrolytes and BP @ 8-24-72 hrs



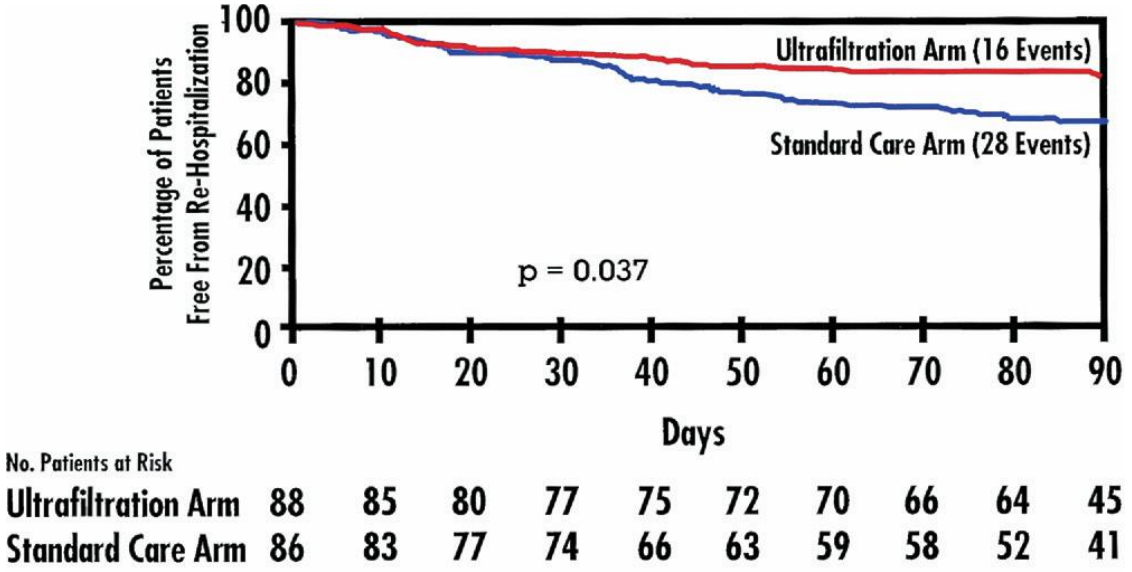


Table 2 Adverse Events

	Ultrafiltration	Standard Care	p Value
Catheter/needle site	3	0	0.156
Filter	5	NA	NA
Infection			
Catheter-related	1	0	0.315
Other	4	9	0.202
Bleeding	1	7	0.032
Hypotension	22	10	0.113
Anemia	3	0	0.080
Dialysis	1	0	0.315
Worsening heart failure	39	63	0.094
Myocardial infarction	3	2	0.988
Arrhythmias	10	7	0.968
Cardiac arrest	4	6	0.987
Neurologic	5	15	0.070

there was a significant increase in Na loss in the ultra-filtrate compared to diuretics (134 mmol/L vs 60 mmol/L) while net loss of K^+ (3.7 mmol/L vs 4.1 mmol/L) and Mg^{2+} (2.9 mg/dL vs 5.2 mg/dL) was reduced.

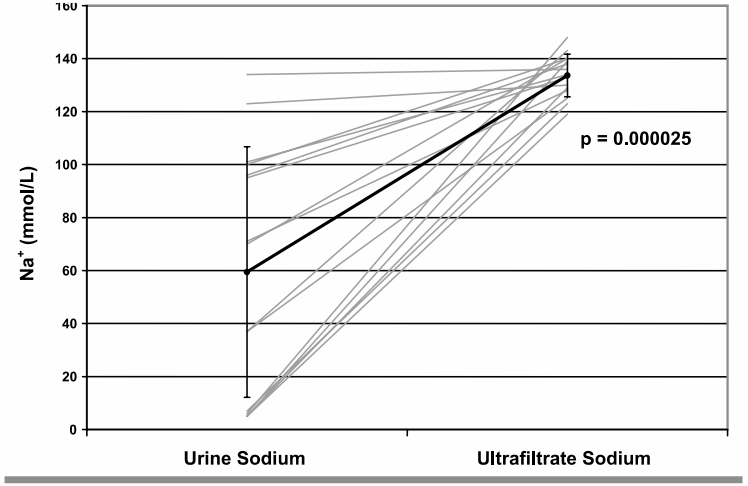


Figure 1. Sodium concentration in urine prior to ultrafiltration (UF) and in the ultrafiltrate 8 hours after initiation of UF.

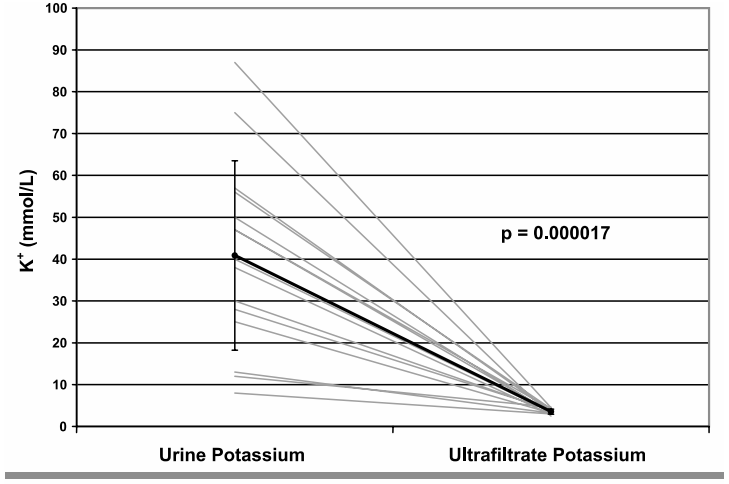


Figure 2. Potassium concentration in urine prior to ultrafiltration (UF) and in the ultrafiltrate 8 hours after initiation of UF.

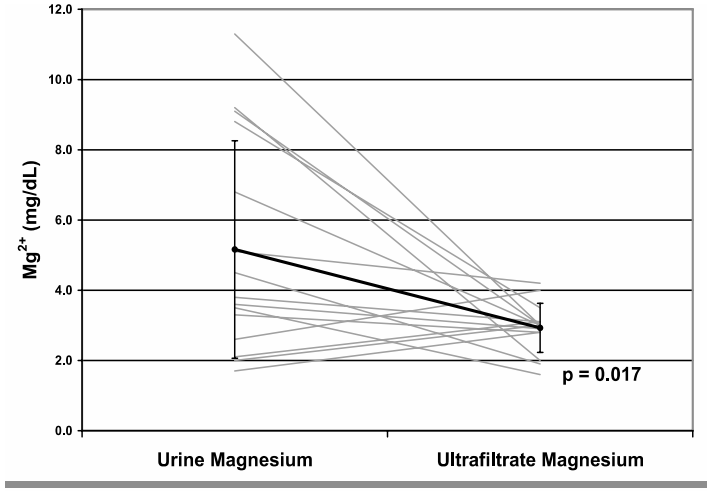


Figure 3. Magnesium concentration in urine prior to ultrafiltration (UF) and in the ultrafiltrate 8 hours after initiation of UF.

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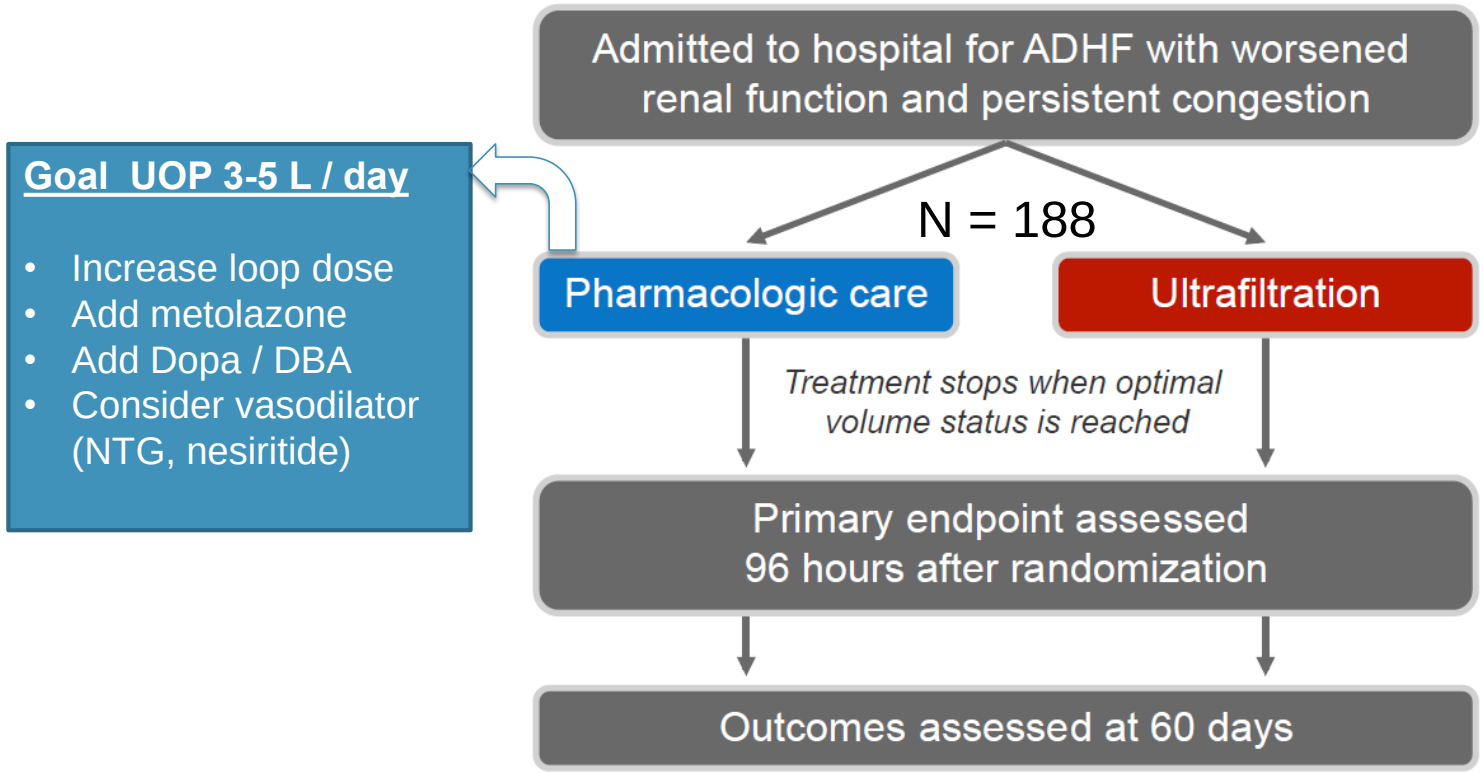
UF vs SPT

Study Design



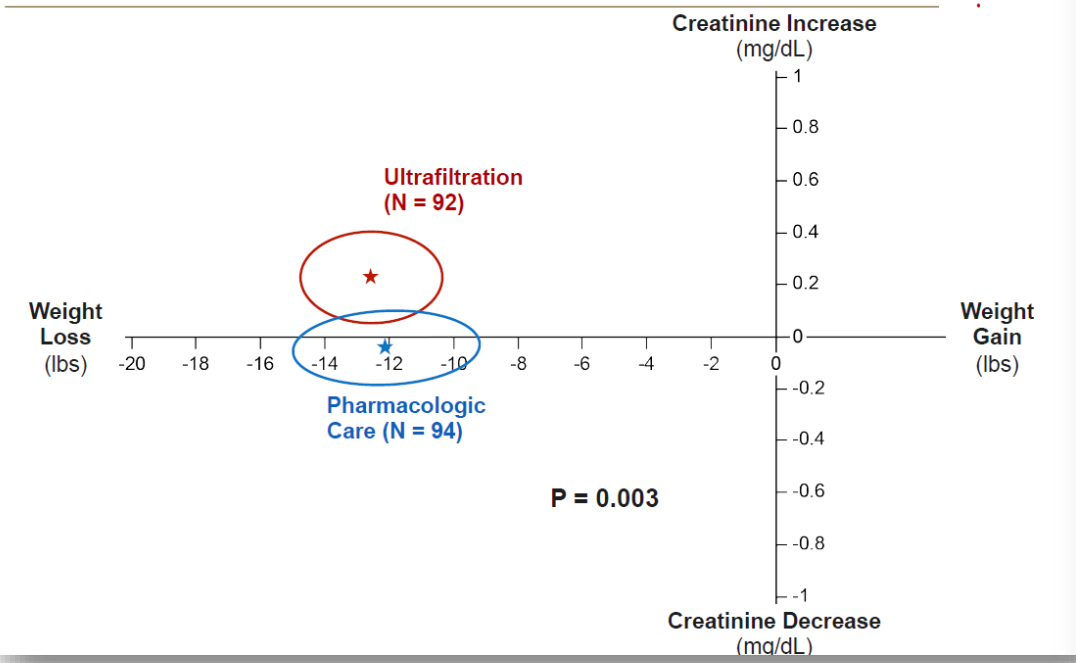
HFrEF + HFpEF

Bivariate Change in Serum Cr and Body Weight

Bart BA *et al. NEJM* 2012

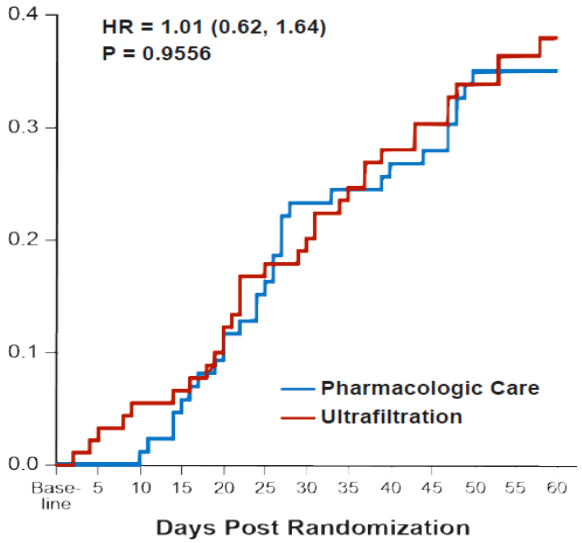
Results: Primary Endpoint

Mean changes in creatinine and weight at 96 hours

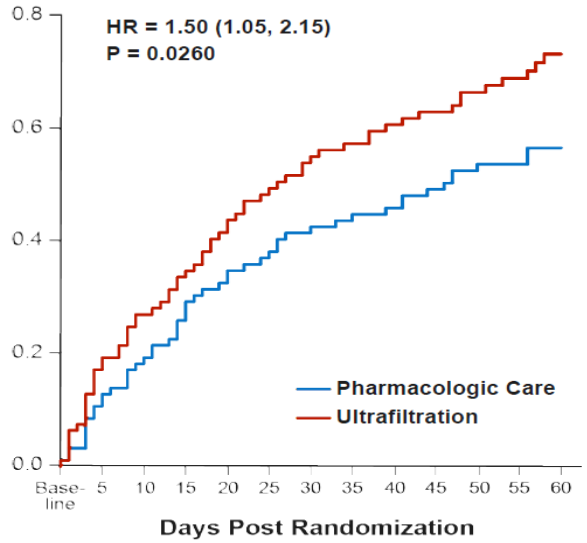


60-day Event Rates

Death or HF Rehospitalization



Death or Serious Adverse Event



Stepped Pharmacologic Care with similar weight loss and less Cr increase

Stepped Pharmacologic Care with fewer SAEs

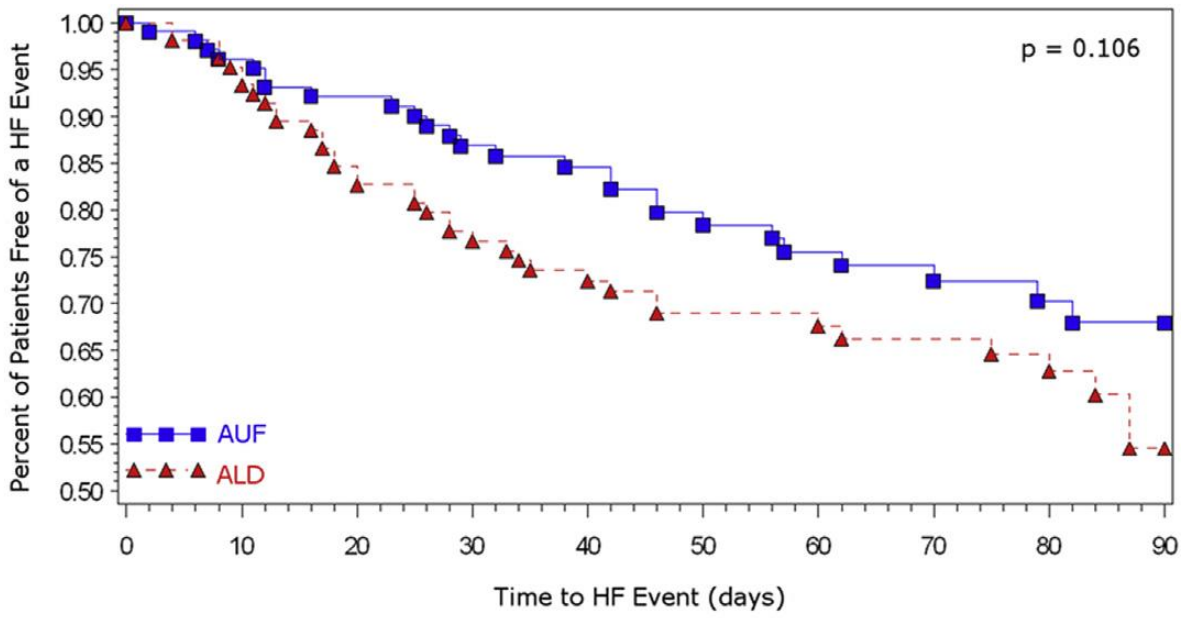
Bart BA *et al. NEJM* 2012


Customized/ Flexible UF (up to 500 mL/h) vs Sub-optimized & unprotocolized (WUW) Medical ttt
UNLOAD (company) 2007
VS
CARRESS-HF (NIH) 2012
Sub-optimal UF (fixed UFR 200 Ml/hr) no matter the BP, the FO,…! vs Customized SPT

AVOID-HF

- Multicenter RCT
- ADHF
- ALD (adjustable LD) = 114
- AUF (adjustable UF) = 110
- **both intervention >>> optimized**

FIGURE 2 Primary Endpoint: Time to Heart Failure Event after Discharge



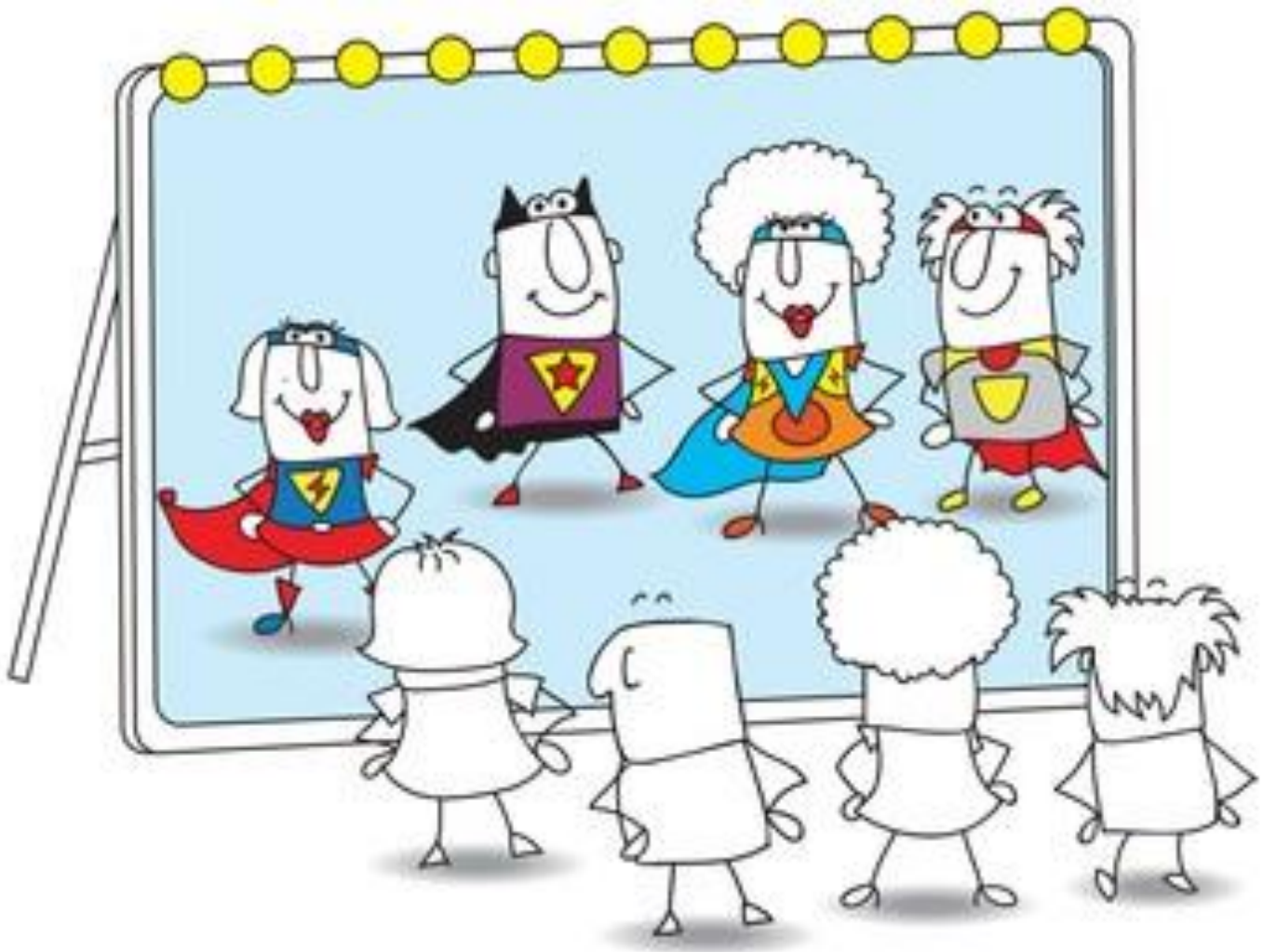
	Baseline	30 Days	60 Days	90 Days
AUF	105	80	52	19
ALD	108	74	49	15

TREND is always for UF !

TABLE 2 Secondary Clinical Endpoints

Endpoint	Days After Discharge	AUF (n = 105)	ALD (n = 108)	p Value
Total number of HF rehospitalizations/ days at risk	30	11/2,876	24/2,882	0.060*
	90	36/6,546	52/6,681	0.182*
Total number of ED or unscheduled office visits with unplanned IV diuretics, vasoactive drugs or, UF/days at risk	30	4/2,869	5/2,863	0.737*
	90	7/6,517	8/6,637	0.840*
Total number of patients with HF rehospitalization	30	10 (9.5)	22 (20.4)	0.034†
	90	27 (25.7)	39 (36.1)	0.106†
Total number of days rehospitalized for HF/days at risk	30	68/2,933	172/3,030	0.029*
	90	338/6,848	460/7,089	0.321*
Total number of CV rehospitalizations/ days at risk	30	17/2,882	33/2,891	0.037‡
	90	46/6,556	66/6,695	0.096 9*
Total number of patients with CV rehospitalization	30	15 (14.3)	27 (25.0)	0.042†
Total number of days for CV rehospitalization/days at risk	30	88/2,953	207/3,065	0.018*
	90	377/6,887	554/7,183	0.154*
All-cause rehospitalization rates/days at risk	30	26/2,891	37/2,895	0.237*
	90	73/6,583	83/6,712	0.571*
Days alive and out of hospital	30	27.3 (5.8)	26.5 (6.3)	0.333§
	90	62.0 (24.6)	61.4 (25.0)	0.803§

re-looking



CARRESS-HF
too much cross over !

European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1158

RESEARCH ARTICLE

Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: a per-protocol analysis of CARRESS-HF

Justin L. Grodin[1,*], Spencer Carter[2], Bradley A. Bart[3], Steven R. Goldsmith[3], Mark H. Drazner[1], and W.H. Wilson Tang[4]

[1]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Division of Cardiology, Department of Medicine, Hennepin County Medical Center, Minneapolis, MN, USA; and [4]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA

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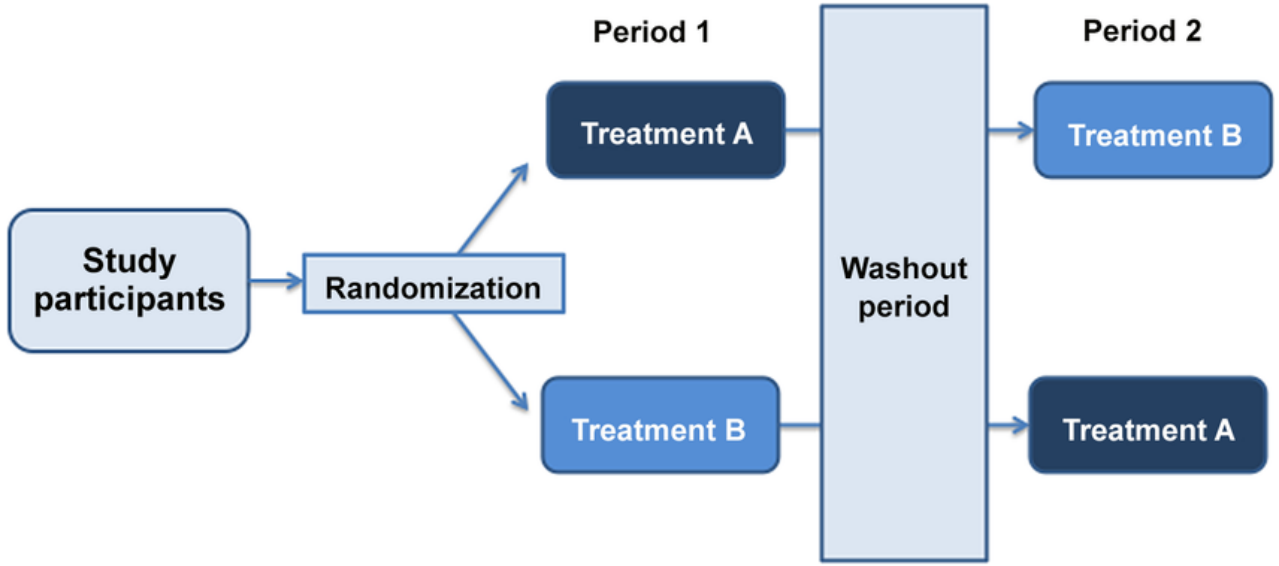
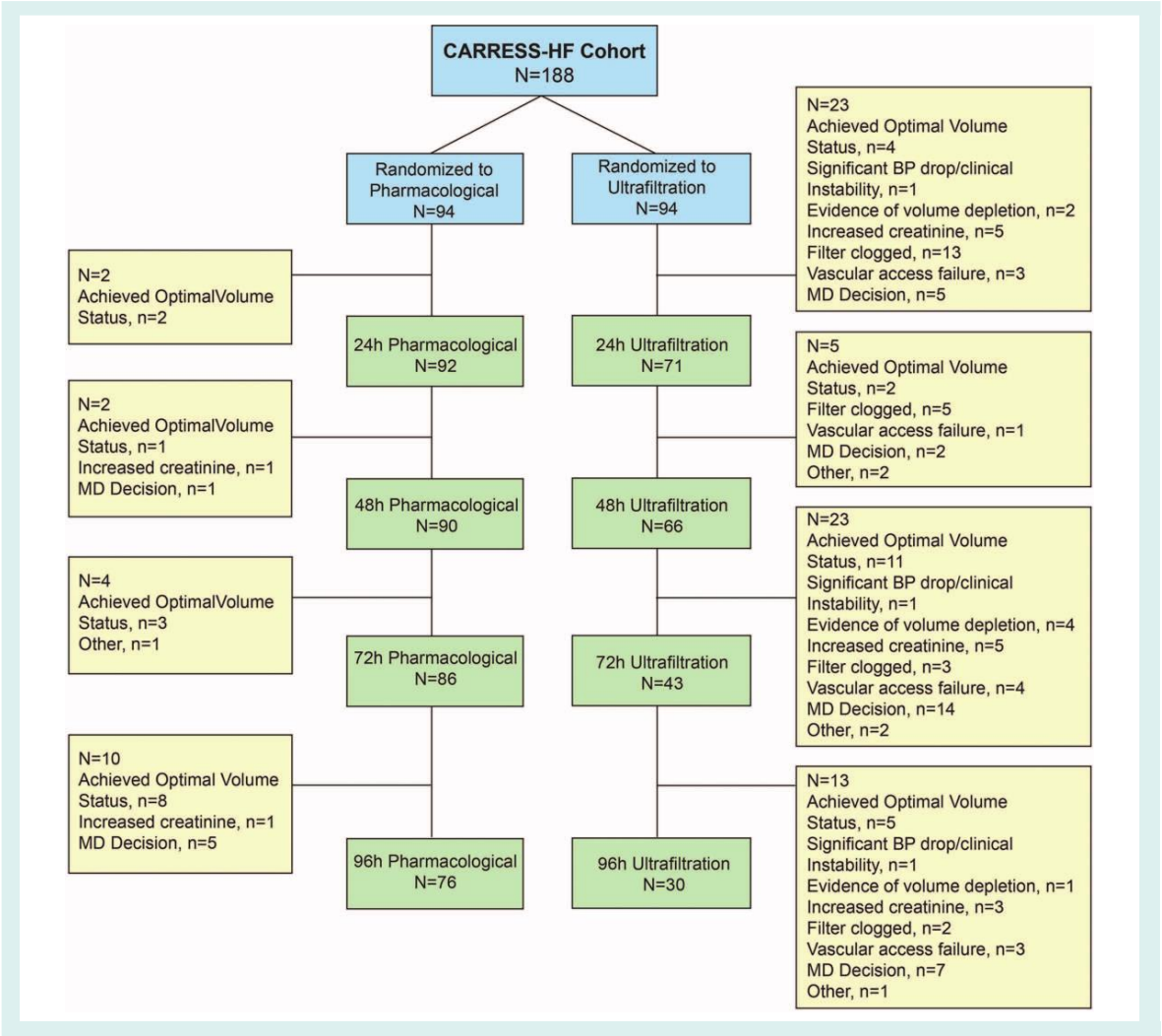


CARESS-HF minus the Cross over !

"per-protocol" analysis & not an "intention to treat"



in contrast to the original trial (intention-to-treat), UF was associated with significantly more fluid loss & weight reduction

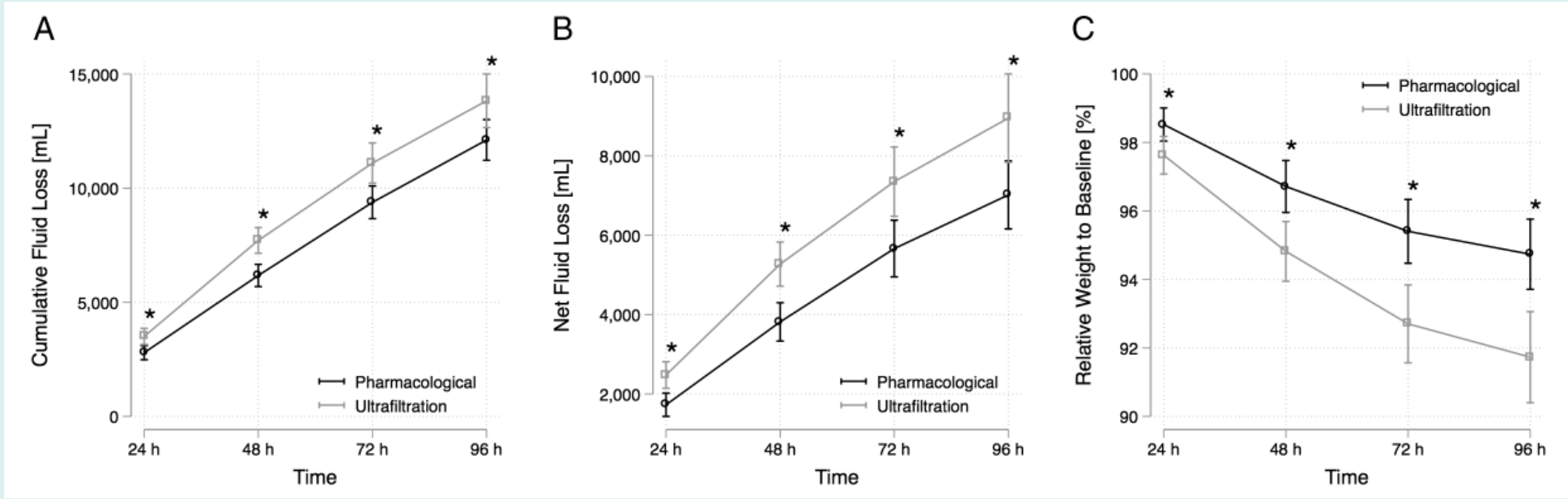
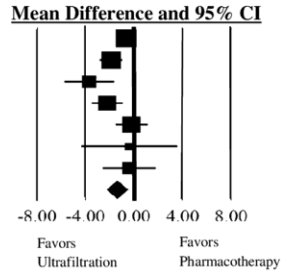


Figure 2 Fluid balance through 96 h by treatment arm. (*A*) Cumulative fluid loss; (*B*) net fluid loss; and (*C*) relative weight to baseline. *$P < 0.05$ for the absolute comparison at each time point.

A : Change in weight (kg)

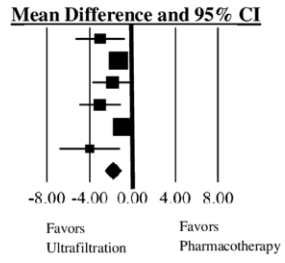
Study	Ultrafiltration Mean	SD	Total	Pharmacotherapy Mean	SD	Total	WMD [95% CI]	p-Value	Weight
RAPID-CHF	2.5	1.2	20	1.86	1.2	20	0.64 [-0.10, 1.38]	0.09	21.89
UNLOAD	5.0	3.1	100	3.1	3.5	100	1.9 [0.98, 2.82]	0.00	20.19
Hanna et al.	4.7	3.5	19	1.0	2.5	17	3.7 [1.69, 5.71]	0.00	10.82
ULTRADISCO	9.1	1.7	15	6.9	1.8	15	2.2 [0.95, 3.45]	0.00	16.85
CARRESS-HF	5.7	3.9	94	5.5	5.1	94	0.2 [-1.10, 1.50]	0.76	16.43
CUORE	7.5	5.6	27	7.9	9.0	29	-0.4 [-4.36, 3.56]	0.84	4.02
AVOID-HF	10.7	7.2	110	10.3	9.2	111	0.4 [-1.78, 2.58]	0.72	9.8
Random			385			386	1.35 [0.49, 2.21]	0.00	



Heterogeneity: Q = 16.20; d.f. = 6 (p = 0.013); Tau² = 0.74; I² = 62.97%
Egger's Test: p (2-tailed) = 0.80
Overall Z = 3.07

B : Fluid removal (L)

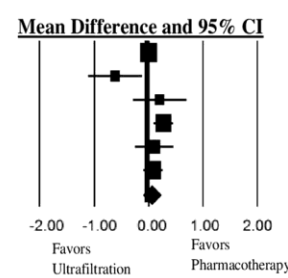
Study	Ultrafiltration Mean	SD	Total	Pharmacotherapy Mean	SD	Total	WMD [95% CI]	p-Value	Weight
RAPID-CHF	8.42	3.65	20	5.38	3.65	20	3.04 [0.78, 5.30]	0.01	9.49
UNLOAD	4.60	2.61	100	3.30	2.61	100	1.3 [0.58,2.02]	0.00	29.27
ULTRADISCO	9.70	2.90	15	7.80	2.00	15	1.9 [0.12,3.68]	0.04	13.28
Hanna et al.	5.22	3.41	19	2.17	2.38	17	3.05 [1.11,4.99]	0.00	11.83
CARRESS-HF	4.70	2.60	94	3.80	2.40	94	0.9 [0.18,1.62]	0.01	29.43
AVOID-HF	12.91	10.70	110	8.91	10.70	111	4.0 [1.18,6.82]	0.01	6.69
Random			358			357	1.81 [1.01,2.62]	0.00	



Heterogeneity: Q = 10.30; d.f. = 5 (p = 0.07); Tau² = 0.44; I² = 51.44%
Egger's Test: p (2-tailed) = 0.01
Overall Z = 4.43

CHANGE IN CREATININE (milligram/deciliter)

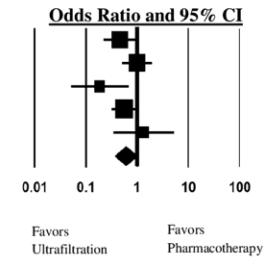
Study	Ultrafiltration Mean	SD	Total	Pharmacotherapy Mean	SD	Total	WMD [95% CI]	p-Value	Weight
UNLOAD	0.1	0.4	69	0.1	0.4	75	0.00 [-0.13, 0.13]	1.00	25.63
ULTRADISCO	-0.55	0.75	15	0.07	0.63	15	-0.62 [-1.12, -0.12]	0.01	8.05
Hana et al.	0.2	0.7	19	0	0.8	17	0.20 [-0.29, 0.69]	0.42	8.19
CARRESS-HF	0.23	0.7	94	-0.04	0.53	94	0.27 [0.09, 0.45]	0.00	22.53
CUORE	0.1	0.63	27	0	0.7	29	0.10 [-0.25, 0.45]	0.58	12.78
AVOID-HF	0.13	0.88	110	0.05	0.3	111	0.08 [-0.09, 0.25]	0.36	22.83
Random			334			341	0.06 [-0.11, 0.22]	0.48	



Heterogeneity: Q = 13.73; d.f. = 5 (p = 0.017); Tau² = 0.023; I2 = 63.57%
Egger's Test: p (2-tailed) = 0.65
Overall Z = 0.70

- **A**: Heart failure rehospitalization

Study	Ultrafiltration Rehospitalization	Total	Pharmacotherapy Rehospitalization	Total	M-H OR [95% CI]	p-Value	Weight
UNLOAD	16	89	28	87	0.46 [0.23,0.93]	0.03	23.88
CARRESS-HF	23	90	24	93	0.99[0.51,1.92]	0.97	25.26
CUORE	4	27	14	29	0.19[0.05,0.68]	0.01	11.09
AVOID-HF	36	105	52	108	0.56[0.32,0.98]	0.04	29.44
Hanna et al.	8	19	6	17	1.33[0.35,5.14]	0.68	10.32
Random	87	330	124	334	0.60[0.37,0.98]	0.04	



Heterogeneity: Q = 7.26; d.f. = 4 (p = 0.12); Tau² = 0.13; I² = 44.90%
Egger's Test: p (2-tailed) = 0.82
Overall Z = -2.05

(current) guidelines for use of UF for ADHF

- **AHA/ACC practice guideline (2009):**
- >>> UF is **reasonable** for pts w/ refractory congestion, ***not responding to medical ttt*** (Class IIa; level of evidence: B)
- **ESC (2008)**:
- >>> UF **should be considered** to "reduce fluid overload" in ***selected pts & to "correct hypo-Na" in symptomatic pts, refractor to diuretics*** (Class IIa; level of evidence: B)
- **HF Society of America (2010):**
- >>> UF **may be considered** when congestion ***fails*** to improve in ***response to diuretics*** (Class IIa; level of evidence: C)

Concluding Thought

- Diuretics are inevitable in AHF
- Heart Failure $\neq$ diuretic therapy
- Good decongestion = Good natri-uresis
- Start Diuretics ASAP (D2D)
- Increase in SCr >>> 20-30% of AHF pts
- Increase in SCr >>> not a problem if the diuretic response is favorable
- Look at the diuretics as a “breakthrough” drugs
- Inappropriately use of high dose of loop diuretics >>> hamper, the up-titration of NH blockade

Concluding Thought

- UF >>> greater weight loss & greater fluid removal
- UF >>> more efficient de-congestion
- UF >>> lower HF re-Hosp rate
- UF >>> lower HF-related cost
- UF >>> w/o negative impact or “renal function”, “mortality” or, “AE”
- UF >>> customized prescription
- Waiting too much for giving lazix, ACTZ,… for a response >>> UF also will not give a result !

MERCI