# Management of congestion in heart failure

Eric Klug

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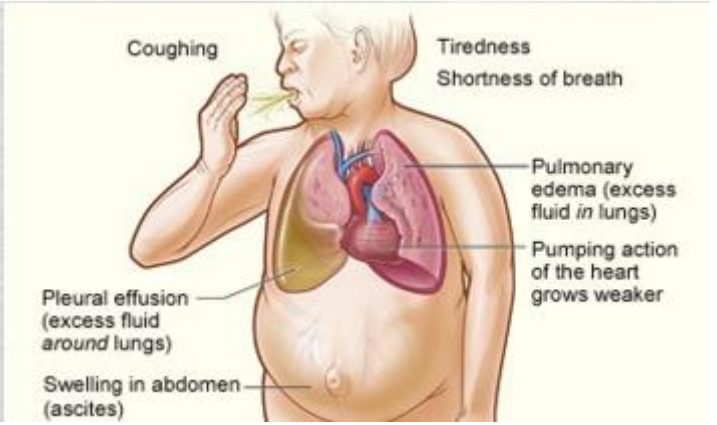
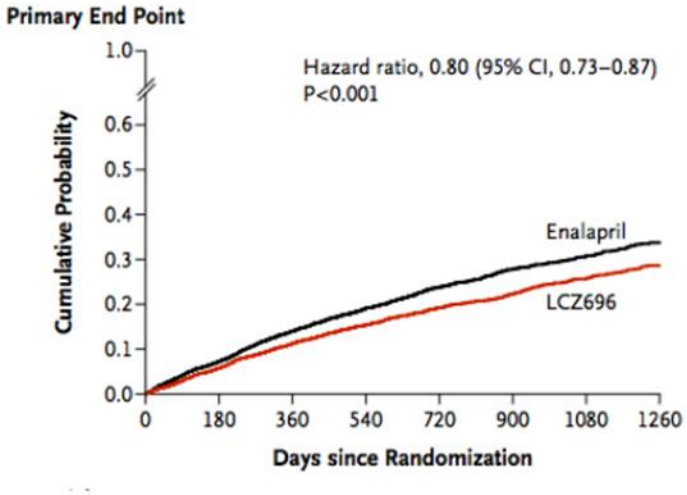
# Fluid Overload

- Congestion is a primary cause of worsening heart failure and HF hospitalisation
- Residual congestion at the time of discharge is a strong predictor of poor clinical outcomes and hospital readmission
- Diuretic therapy targets the intravascular space, allowing lymphatics to drain the interstitial space

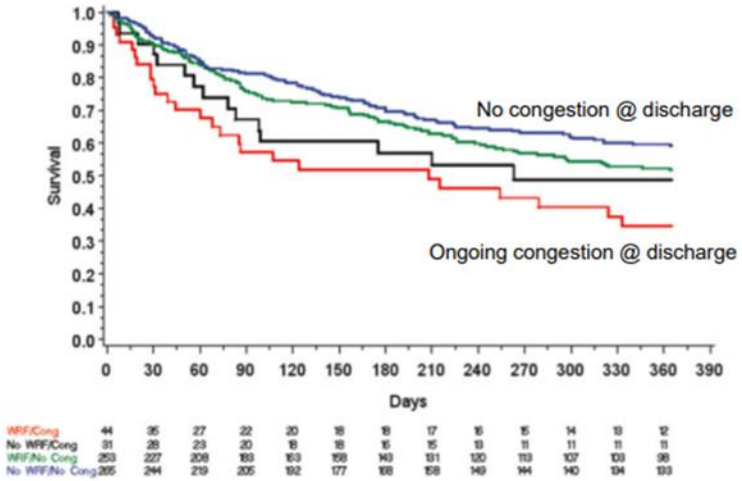


# Underappreciated risk for hospitalization/death linked to residual congestion in HFpnts

Ambulatory: 20% risk at 2 years




Recently Hospitalized: 60% risk at 1 year




McMurray, Packer et al NEJM 2014
Metra M et al. Circ Heart Fail. 2012;5:54-62

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| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[427,472] | I | C |

+ also in ambulatory HF



*McDonagh T et al. Eur Heart J 2021*

# Diuretics only class I recommended therapy for all HF classes

| 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 |

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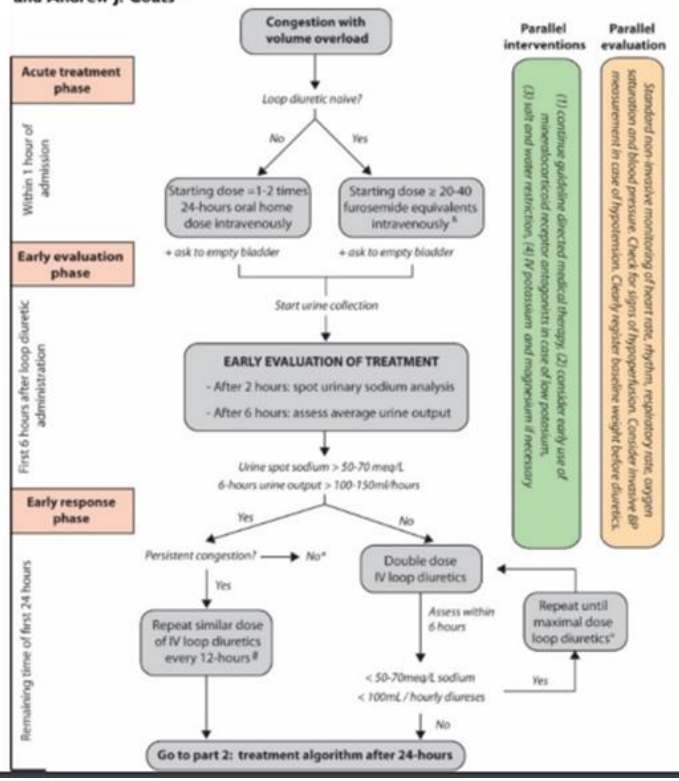
*McDonagh T et al. Eur Heart J 2021*

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
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]




Incorporated

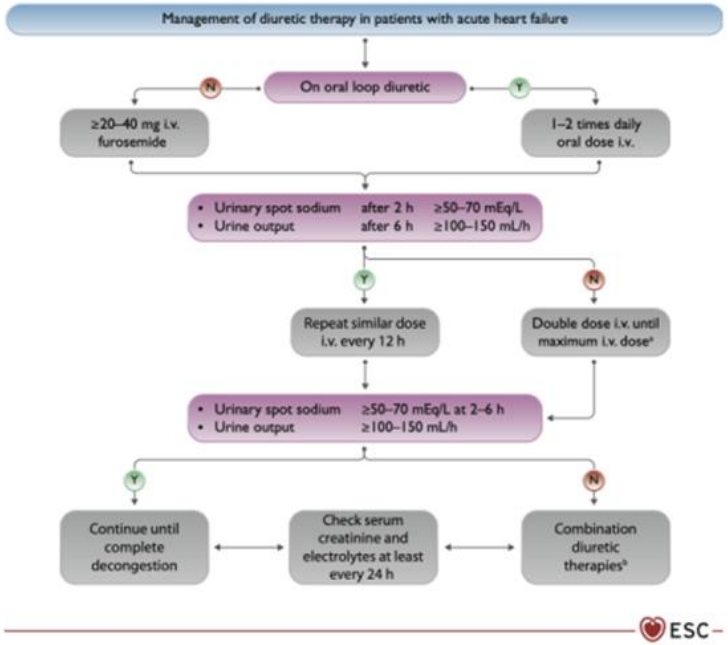
ESC European Society of Cardiology
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

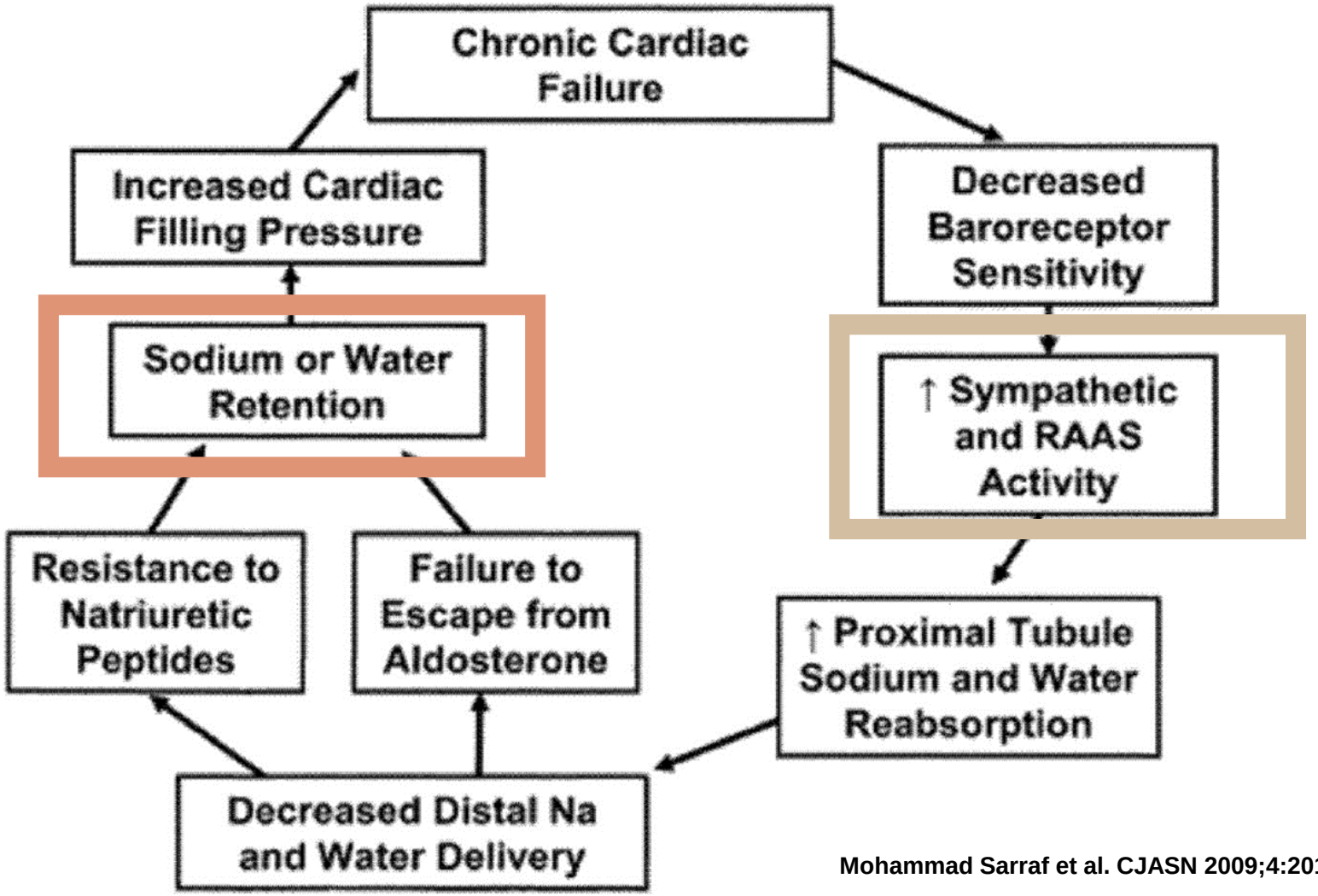
ESC GUIDELINES

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

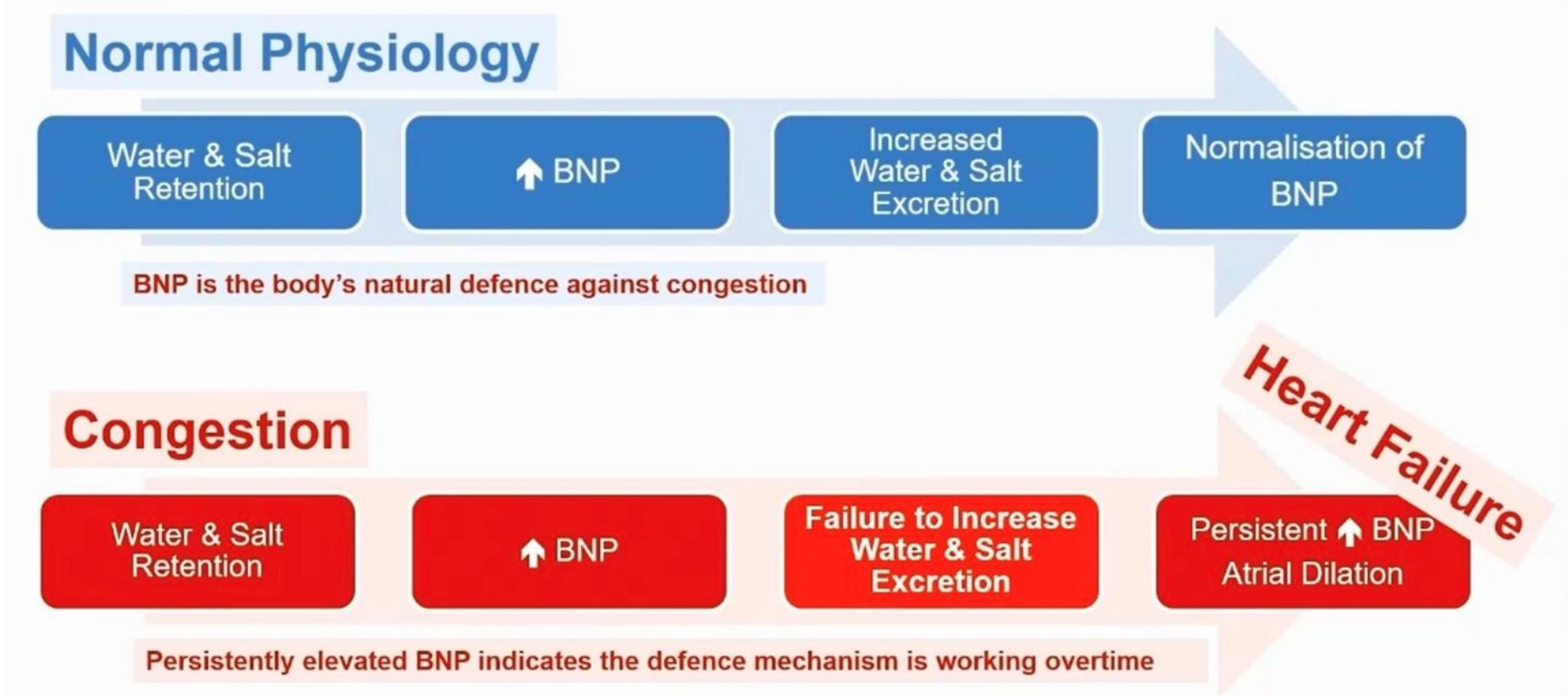
**Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)**

**With the special contribution of the Heart Failure Association (HFA) of the ESC**






Mohammad Sarraf et al. CJASN 2009;4:2013-2026

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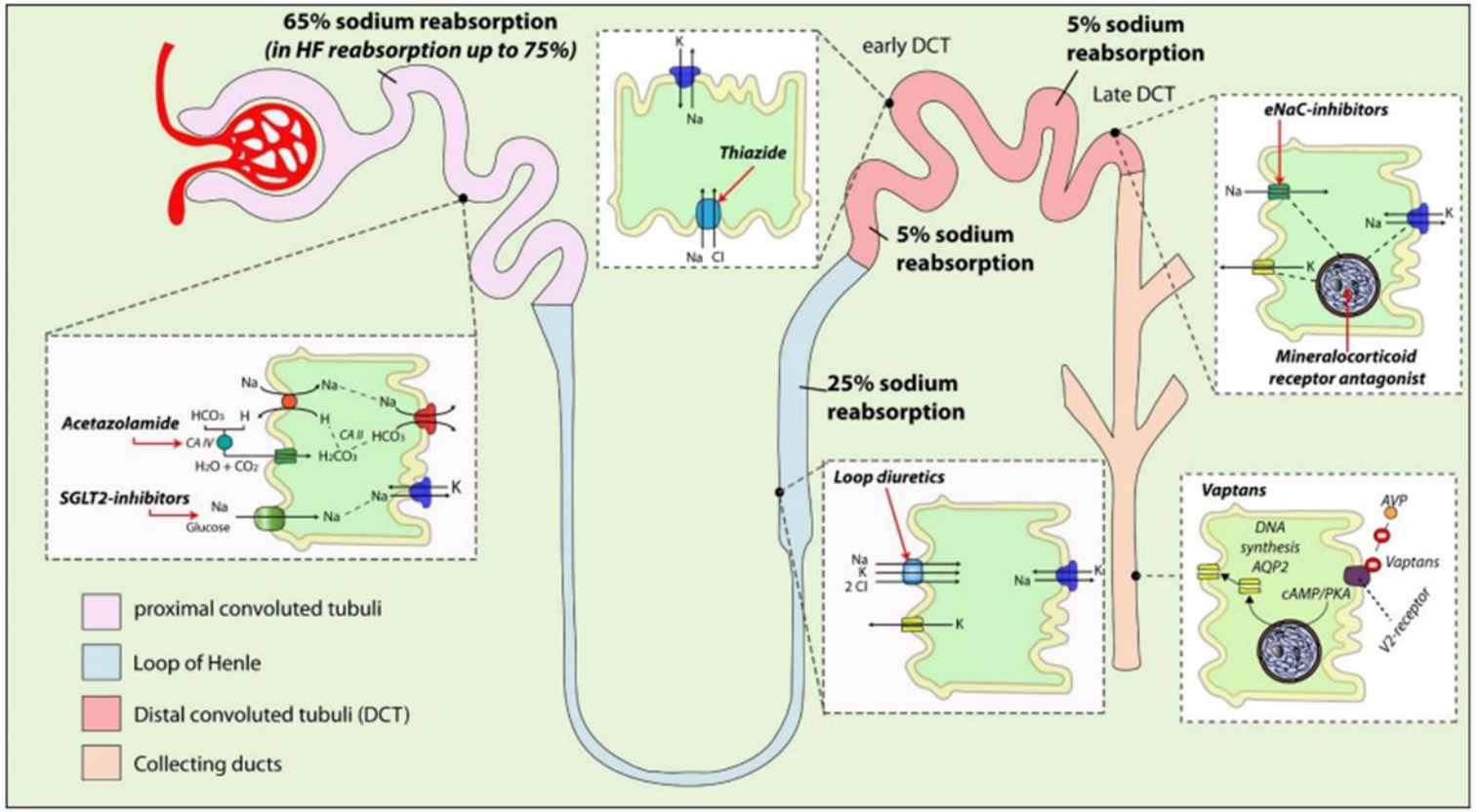
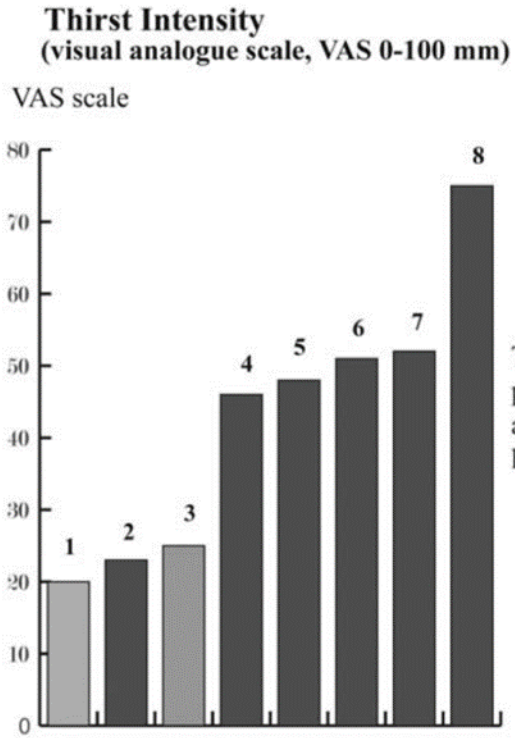
Cleland & Pellicori Circ J (in press)

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




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

# Thirst




Thirst in healthy volunteers (1), patients with heart failure (2, 4-8) and in acutely ill elderly without heart failure (3).

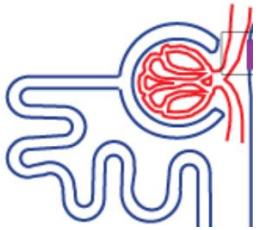
**1** Healthy volunteers; Hahn & Waldréus (2012) submitted.
**2** Stable heart failure with liberal fluid inatake; Holst et al. (2008).
**3** Acutely ill elderly without heart failure; Waldréus et al. (2011).
**4** Stable heart failure with fluid and salt restriction; Philipson et al. (2010).
**5** Stable heart failure with liberal fluid and salt intake; Philipson et al. (2010).
**6** Stable heart failure with fluid restriction; Holst et al. (2008).
**7** Stable heart failure; Philipson et al. (2010).
**8** Worsening heart failure; Waldréus et al. (2011).


# Pharmacokinetics

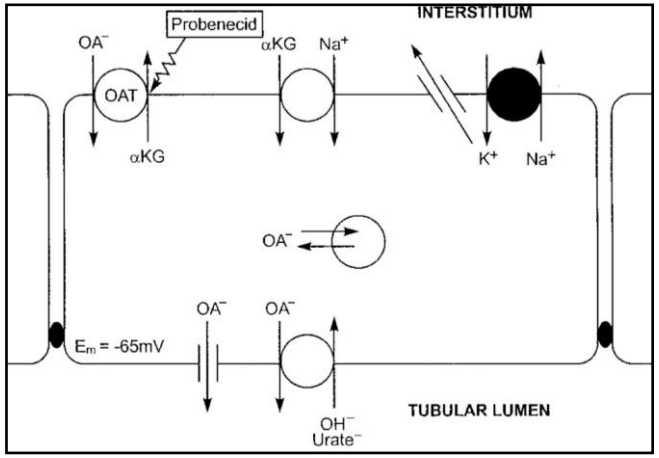
**Loop diuretics must enter the tubular fluid in order to exert their diuretic effect**


**Diuretics have a significant binding to albumin, and thus a limited amount is freely filtered**

RBF



**Decreased diuretic secretion into the tubular lumen results from decreased renal perfusion**




OAT and the PCT

**Loop diuretics are highly (≥95%) protein bound; consequently, they primarily enter the tubular lumen by secretion by the proximal tubule, not by glomerular filtration**

**Use of dugs that impair diuretic responsiveness (NSAIDS)**

# Benefit from a supine posture

- Diuretic responsiveness can be influenced by posture, although the effects of posture have not been specifically studied in patients with refractory oedema (better outcomes, improved renal perfusion and presumably urinary diuretic delivery with supine position)

- Supine position associated with improved creatinine clearance, diuretic response and lower plasma norepinephrine, renin, and aldosterone

# Salt

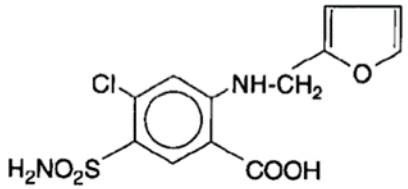
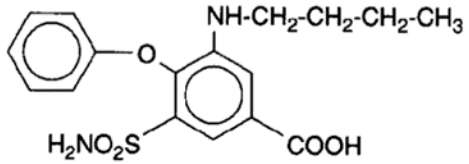
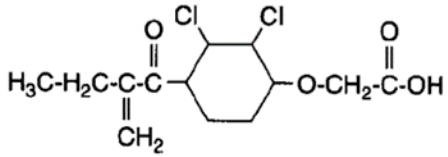
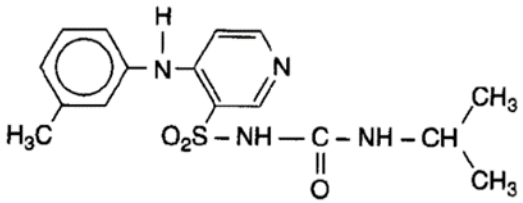
- A very low sodium diet is associated with worse outcomes, and may lead to hyponatremia and hypochloraemia, which may themselves be responsible for the diuretic resistance.

- Furthermore, a chronic low sodium diet may lead to a sodium, calcium and magnesium depletion within the extracellular matrix and the bones, with resulting osteoporosis



HFSA. J Card Fail 2010;16:475-539.
Ponikowski P, et al. Eur Heart J 2016;18(8):891-975.

# Loop diuretics

| DRUG | STRUCTURE | RELATIVE POTENCY | ORAL ABSORPTION | $t_{1/2}$ |
|---|---|---|---|---|
| Furosemide |  | 1 | 11–90% | 0.3–3.4 |
| Bumetanide |  | 40 | 59–89% | 0.3–1.5 |
| Ethacrynic acid |  | 0.7 | Nearly complete | 0.5–1 h |
| Torsemide |  | 3 | 79–91% | 0.8–6.0 |

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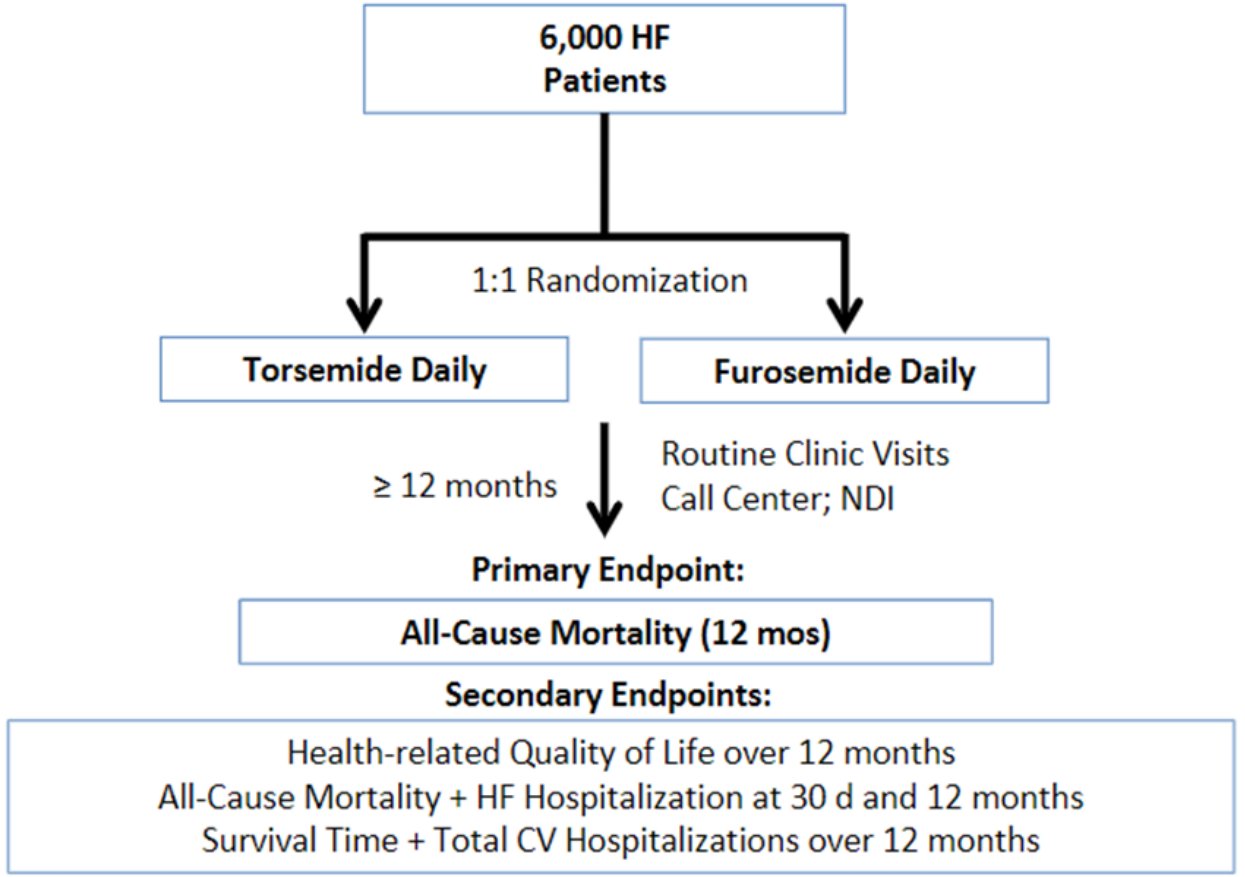
# The TRANSFORM-HF Trial




Recruitment began in June 2018. Following a routine DSMB meeting on February 18, 2022, the DSMB recommended stopping recruitment because the sample size was sufficient to answer the primary research question. The trial sponsor (National Heart, Lung, and Blood Institute) reviewed and accepted these recommendations with determination that the trial should execute an orderly closeout.

JAMA

**QUESTION** Does torsemide reduce all-cause mortality compared with furosemide in patients with heart failure following hospitalization?

**CONCLUSION** This clinical trial found that torsemide vs furosemide did not result in a significant difference in all-cause mortality; however, interpretation of these findings is limited by loss to follow-up and participant crossover and nonadherence.

## POPULATION

1804 Men
1055 Women

Adults hospitalized for heart failure and could have had either de novo heart failure or worsening of chronic heart failure

Median age: 65 years

## LOCATIONS

60 Hospitals in the US

## INTERVENTION


2859 Patients randomized


1431
**Torsemide**
Investigator-selected dosage, with 2:1 to 4:1 furosemide to torsemide conversion as a guide

1428
**Furosemide**
Investigator-selected dosage, with 2:1 to 4:1 furosemide to torsemide conversion as a guide

## PRIMARY OUTCOME

All-cause mortality through 30 months of follow-up

## FINDINGS

All-cause mortality

**Torsemide**
373 of 1431 patients


**Furosemide**
374 of 1428 patients


Torsemide vs furosemide did not result in a significant difference:
Hazard ratio, 1.02 (95% CI, 0.89 to 1.18)



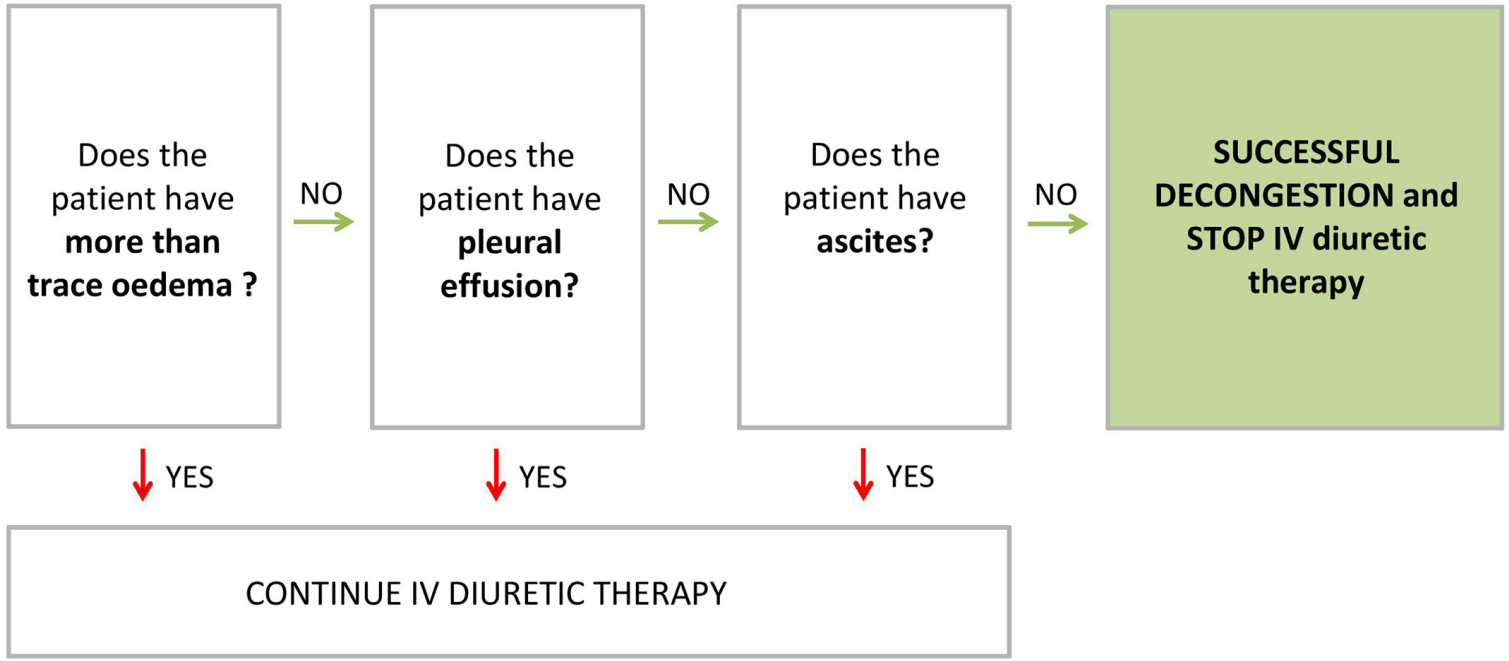
Mentz RJ, Anstrom KJ, Eisenstein EL, et al; TRANSFORM-HF Investigators. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA*. Published January 17, 2023. doi:10.1001/jama.2022.23924

The trial reached the target event count of 721 death events with a sample size approximately half that initially planned

Median NTproBNP = 3913 pg/ml (DAPA-HF:1437 pg/ml)

# IV THERAPY

| | | |
|---|---|---|
| Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[145] | I | C |




**The initial dose of IV loop diuretic should be approximately 2 or 2.5 times the patient's total maintenance daily oral dose**

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**Table 16** Doses of diuretics commonly used to treat heart failure (with and without a preserved ejection fraction, chronic and acute)

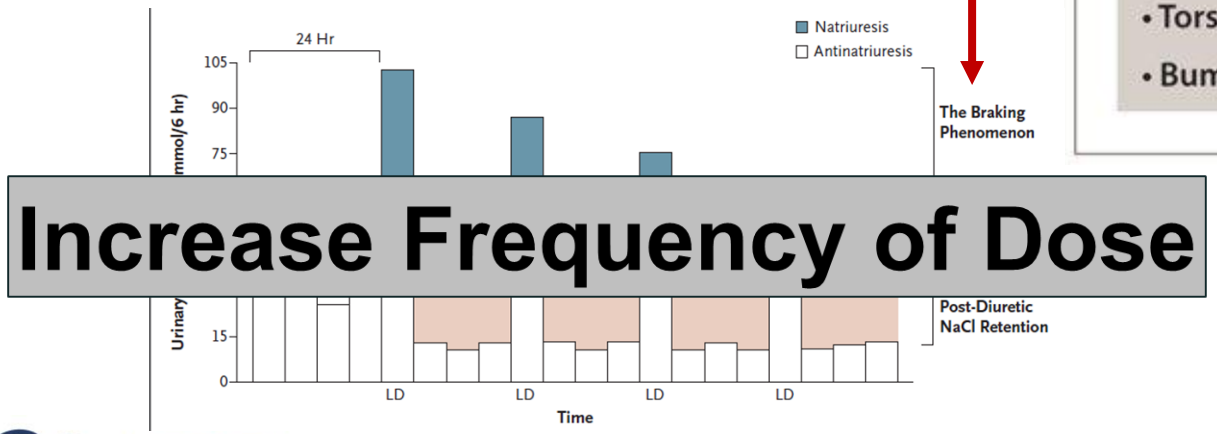
| Diuretics | Initial dose (mg) | | Usual daily dose (mg) | |
|---|---|---|---|---|
| **Loop diuretics**[a] | | | | |
| Furosemide | 20–40 | | 40–240 | |
| Bumetanide | 0.5–1.0 | | 1–5 | |
| Torasemide | 5–10 | | 10–20 | |
| **Thiazides**[b] | | | | |
| Bendroflumethiazide | 2.5 | | 2.5–10 | |
| Hydrochlorothiazide | 25 | | 12.5–100 | |
| Metolazone | 2.5 | | 2.5–10 | |
| Indapamide[c] | 2.5 | | 2.5–5 | |
| **Potassium-sparing diuretics**[d] | | | | |
| | +ACEi/ ARB | −ACEi/ ARB | +ACEi/ ARB | −ACEi/ ARB |
| Spironolactone/ eplerenone | 12.5–25 | 50 | 50 | 100–200 |
| Amiloride | 2.5 | 5 | 5–10 | 10–20 |
| Triamterene | 25 | 50 | 100 | 200 |

## Causes of diuretic resistance

1. Medication nonadherence
2. Dietary NA+ indiscretion
3. NSAID or steroid use
4. Impaired oral absorption
5. The "braking phenomenon"
6. Post-diuretic NA+ retention

## Equipotent doses of oral loop diuretics

- Furosemide 40 mg
- Torsemide 10 mg to 20 mg
- Bumetanide 1 mg




**Increase Frequency of Dose**

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N Engl J Med 2017;377:1964-75

# Diuretic resistance

Diuretic resistance may be overcome by:

1. Increasing **doses** of loop diuretic
2. **Adding** second and third diuretics from different classes

| | | |
|---|---|---|
| Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[145] | IIa | B |

*To an effective or maximal safe dose of a loop diuretic add:*

*Distal convoluted tubule diuretics*
Metolazone 2.5-10 mg per os daily (duration or frequency adjusted based on the target weight)
Hydrochlorothiazide (or equivalent) 25-100 mg per os daily
Chlorothiazide 500-1000 mg intravenously

*Proximal tubule diuretics*
Acetazolamide 250-375 mg daily or up to 500 mg intravenously

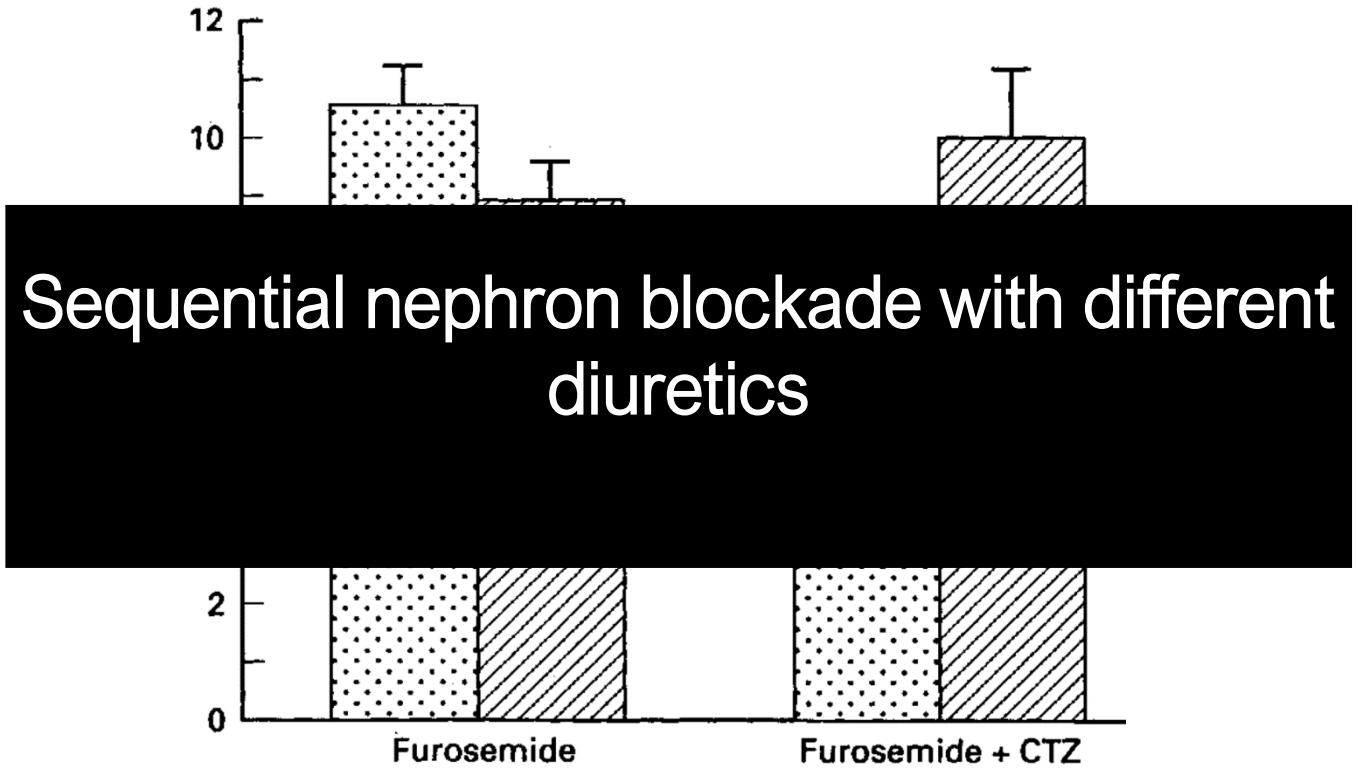
*Potassium-sparing diuretics*
Spironolactone 100-200 mg daily
Amiloride 5-10 mg daily

Almeshari K, et al. J Am Soc Nephrol 1993;3(12):1878-1883.
Rudy DW, et al. Ann Intern Med 1991;115(5):360-366.

*McDonagh T et al. Eur Heart J 2021*

# Combining different diuretics

## Diuretic synergy




Sequential nephron blockade with different diuretics

Kidney International 1991: 39:336-352

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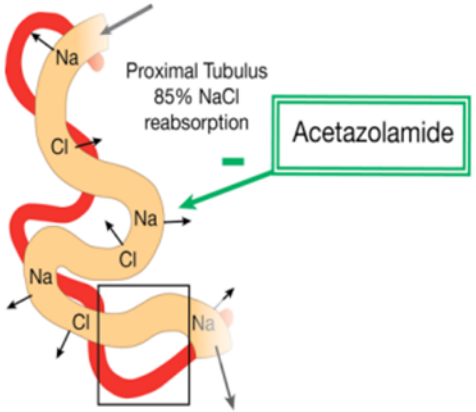
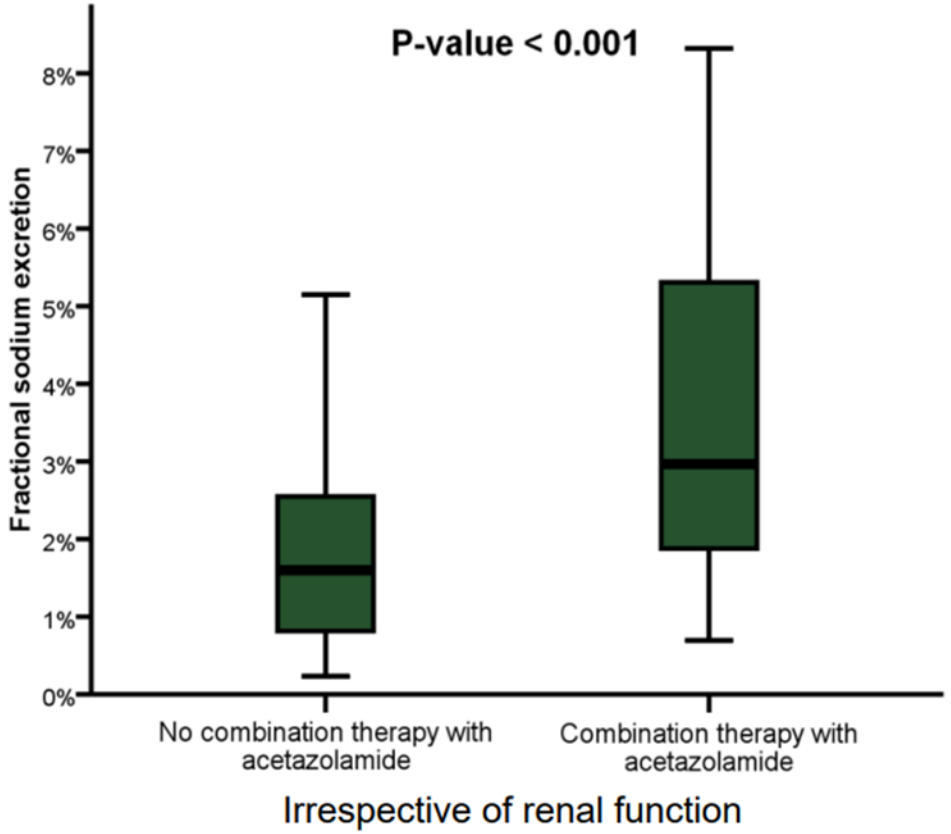
# Loop diuretics vs Loop diuretics + Acetazolamide

(500 mg IV bolus once daily on top of loop diuretics)



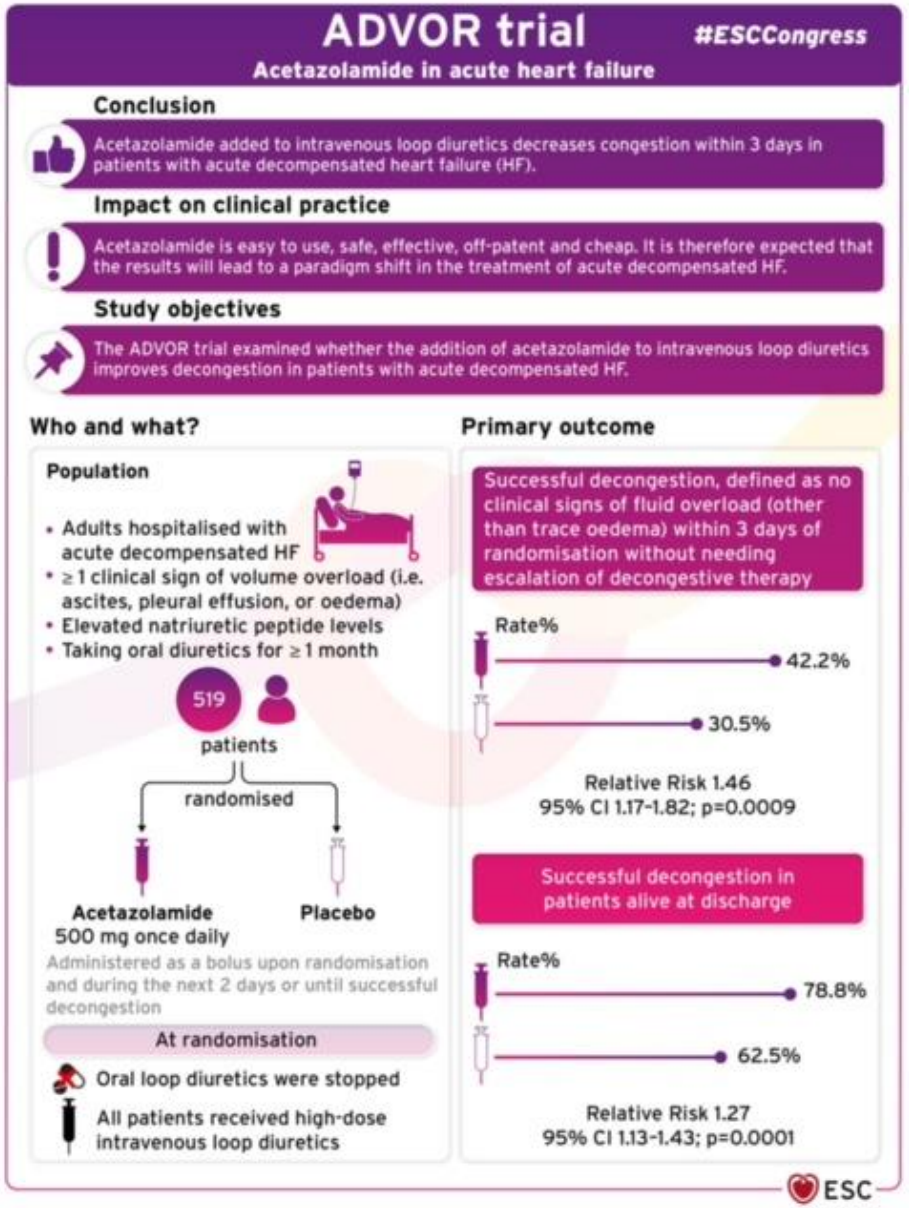




Irrespective of renal function

*Verbrugge F, Mullens W. Acta Cardiol 2015*
*Verbrugge F, Mullens W. Eur J Heart Fail 2019*

# ADVOR study

A double blind, randomized, placebo controlled, phase IV, prospective multi-center clinical study to examine if acetazolamide in decompensated heart failure with volume overload patients will lead to a better decongestion

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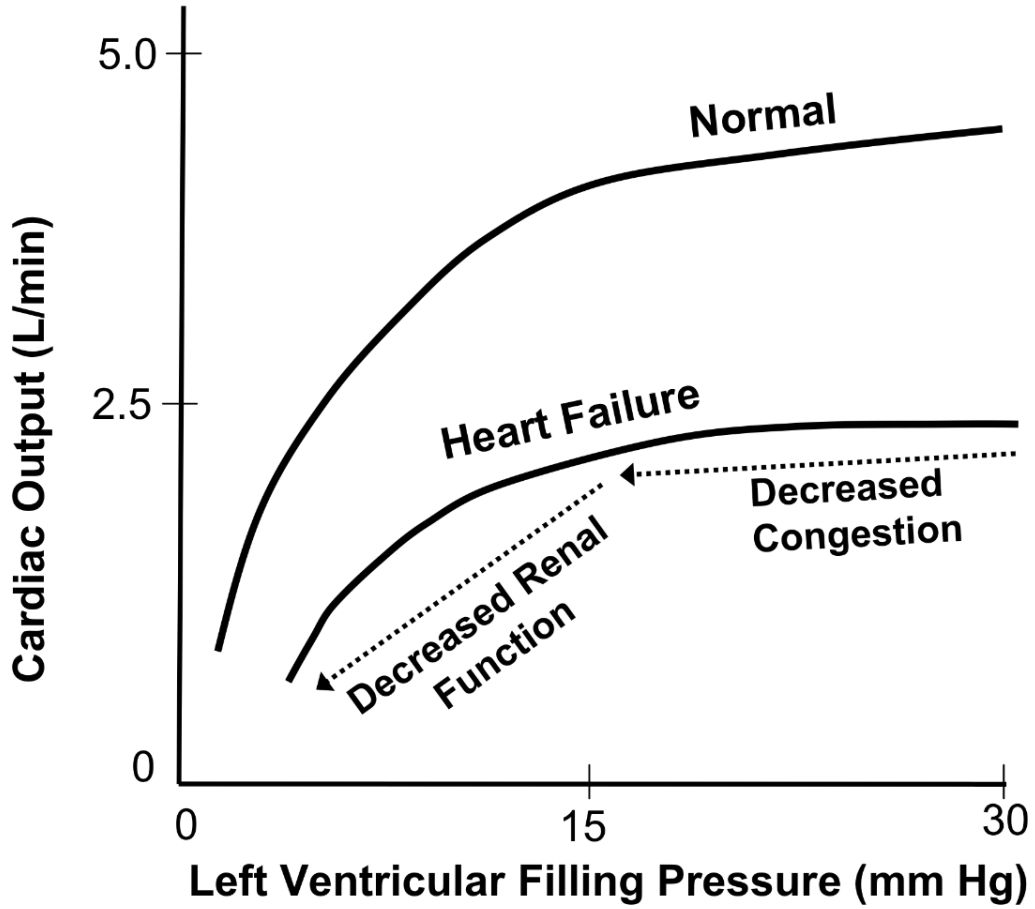
The CLOROTIC Trial: Combination of Loop Diuretics with Hydrochlorothiazide in Acute Heart Failure

# Potential for worsening renal function

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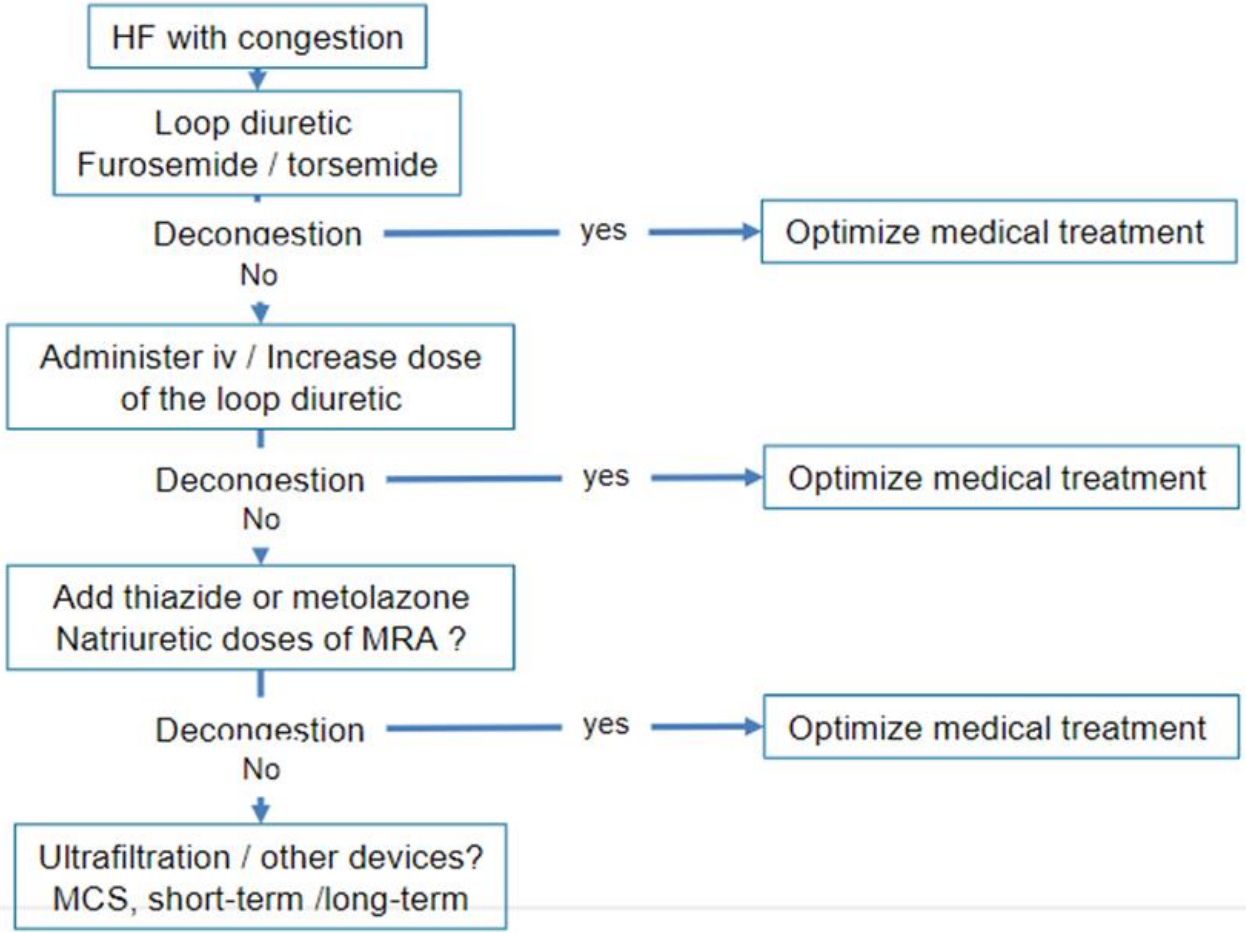
Circ Heart Fail. 2008;1:2-5.

# Management of refractory oedema in HF

1. Fluid restriction
   - Aim for 1 to 1.5L/day
2. Avoid drugs that may interfere with diuretic responsiveness
3. Daily weight diary
   - Should be performed at the same time each day, usually in the morning, prior to eating and after voiding
4. Patient education and reporting of adverse events

# Stepped care strategy for decongestion in HF

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nature medicine

Article

https://doi.org/10.1038/s41591-023-02532-z

# Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial

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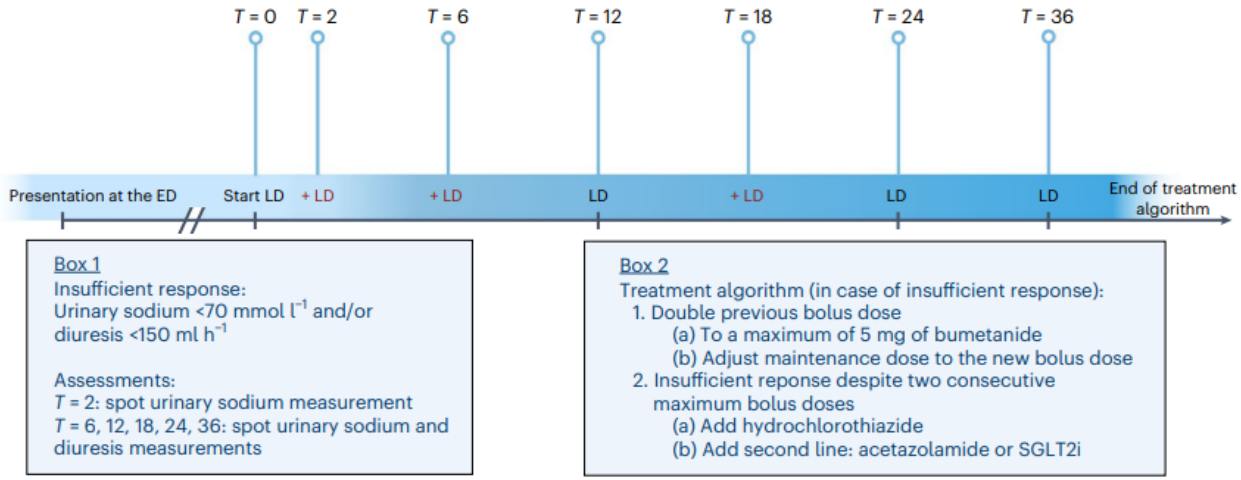
Accepted: 3 August 2023

Published online: 28 August 2023

Jozine M. ter Maaten[1], Iris E. Beldhuis[1], Peter van der Meer[1], Jan A. Krikken[1], Douwe Postmus[2], Jenifer E. Coster[1], Wybe Nieuwland[1], Dirk J. van Veldhuisen[1], Adriaan A. Voors[1] & Kevin Damman[1]

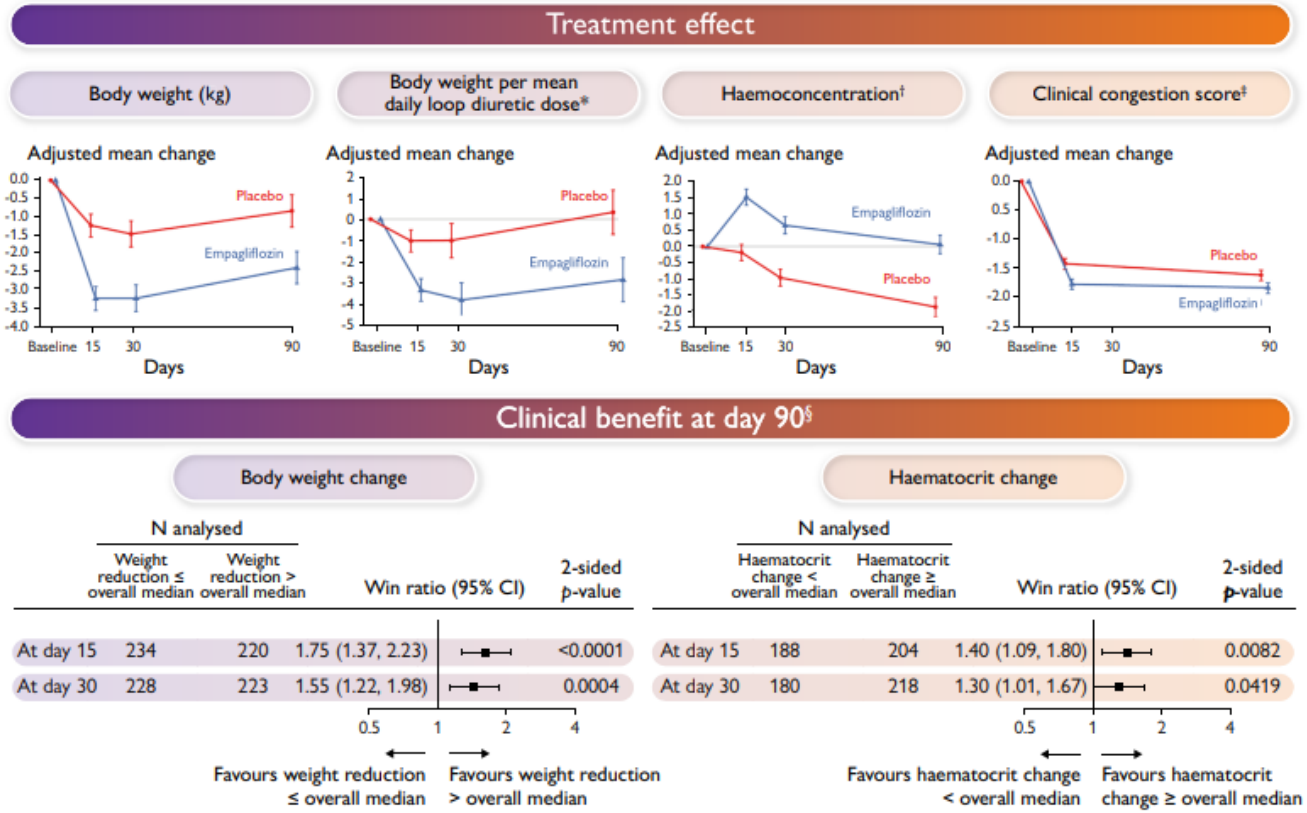



24 h urinary sodium excretion: natriuresis in the natriuresis-guided and SOC arms was 409 ± 178 mmol arm versus 345 ± 202 mmol, respectively (P = 0.0061)

No significant differences between the two arms for the combined endpoint of time to all-cause mortality or first heart failure rehospitalization, which occurred in 46 (31%) and 50 (31%) of patients in the natriuresis-guided and SOC arms

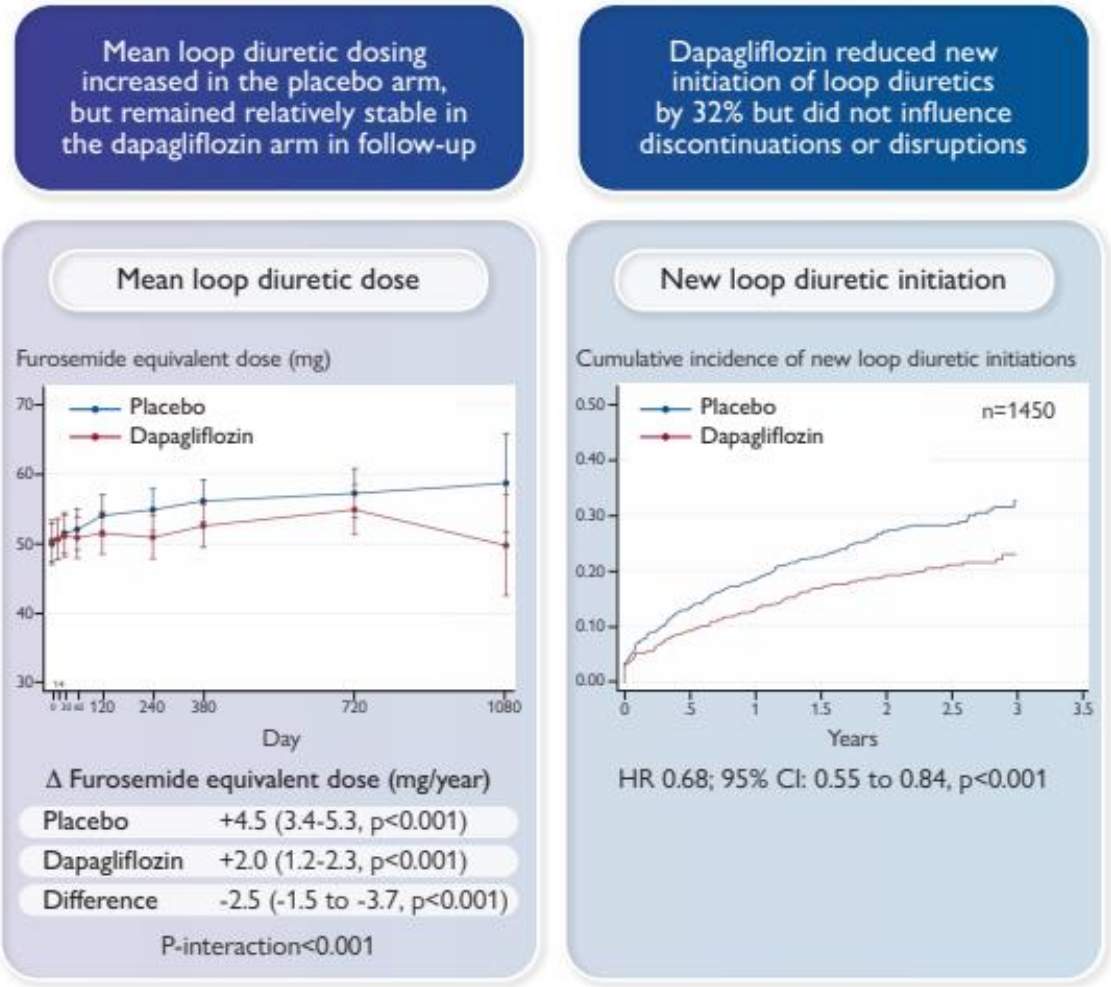
**These findings suggest that natriuresis-guided therapy could be a first step towards personalized treatment of AHF**

# EMPULSE trial




European Heart Journal (2023) 44, 41–50

# DELIVER trial




European Heart Journal (2023) 44, 2930–2943

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# Dapagliflozin vs. metolazone in heart failure resistant to loop diuretics

The mean decrease in weight at 96 h was 3.0 kg with dapagliflozin compared to 3.6 kg with metolazone


Cumulative dose of furosemide at 96 h was 977 mg in the dapagliflozin group and 704 mg in patients assigned to metolazone

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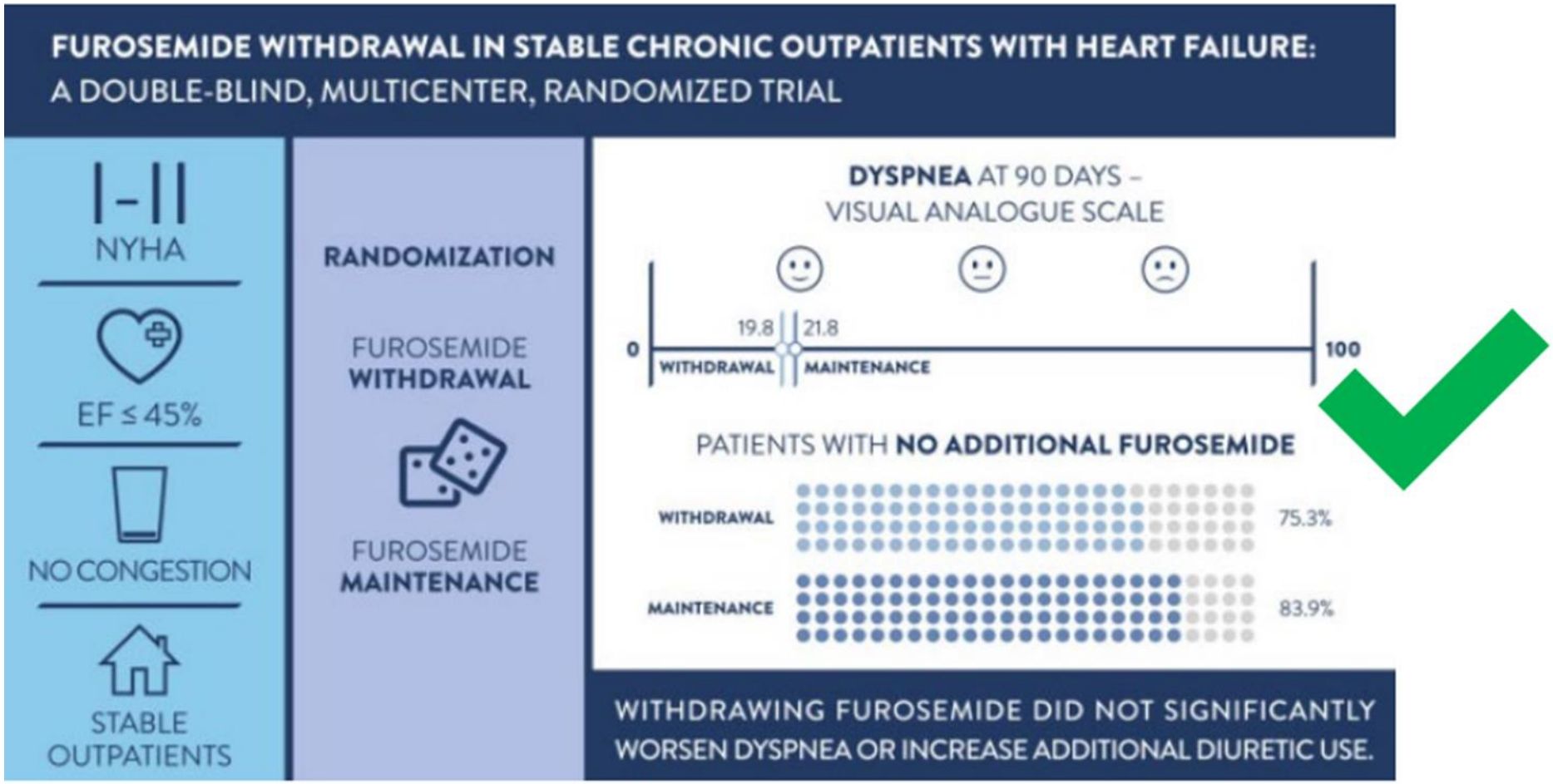
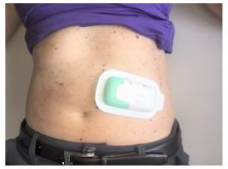
European Heart Journal (2023) 44, 2966–2977




Eur Heart J. 2019 Nov 21;40(44):3605-3612

# Conclusion

- Remaining congestion carries a worse prognosis in HF
- The HF kidney is sodium and water avid
- Thirst needs management, rest/supine position helps initially with diuresis, salt limitation not preferred
- Tubular secretion of loop diuretics required and be aware of offending organic acids/other drugs competing
- No proven difference in efficacy of various loop diuretics
- Chronic diuretic therapy may require increased doses, increased frequency of dose and combinations (Thiazide, CA inhibitor- ADVOR), and change in route of administration (IV or Subcutaneously)
- Renal dysfunction may be a consequence
- SGLT2 inhibitors decongest, reduce loop diuretic doses, preserve the kidney



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# Thank you for attending!

Please complete the online confirmation of attendance emailed to you post meeting to receive a CPD certificate.

# HF ACADEMY COURSE OVERVIEW

This **free CPD accredited educational program** was developed by cardiologists who are members of the Heart Failure Society of South Africa and is aimed at those who are interested in improving services for people with heart failure, including **not only doctors, but also nurses and pharmacists**. The course comprises 5 modules that provide a basic review of heart failure care and each module is individually **CPD accredited for 5 CPD points** with the HPCSA. Following the completion of all 5 modules, a **Certificate of Competency** in basic heart failure management will be awarded by HeFSSA.

## COURSE LEARNING OBJECTIVES

- ✓ Raise the awareness of heart failure among health care professionals
- ✓ Improve the prevention, diagnosis, treatment and long – term management of heart failure
- ✓ Ensure equity of care for all patients with heart failure
- ✓ Support and empower patients with heart failure and their families or other caregivers to engage proactively in long – term care

**COURSE DIRECTORS**


Prof Nash Ranjith
City Hospital
University of KwaZulu Natal

Dr Martin Mpe
Mediclinic Heart Hospital

Prof Nqoba Tsabedze
University of the Witwatersrand

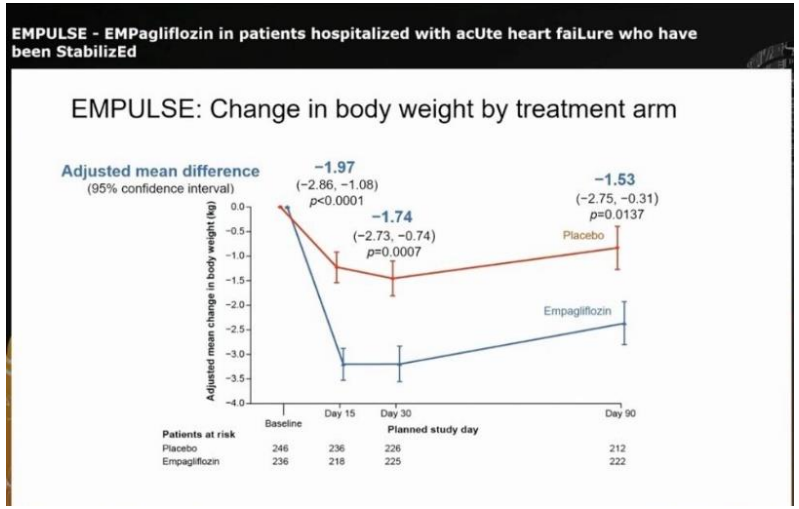
Dr Tony Lachman
Victoria Hospital

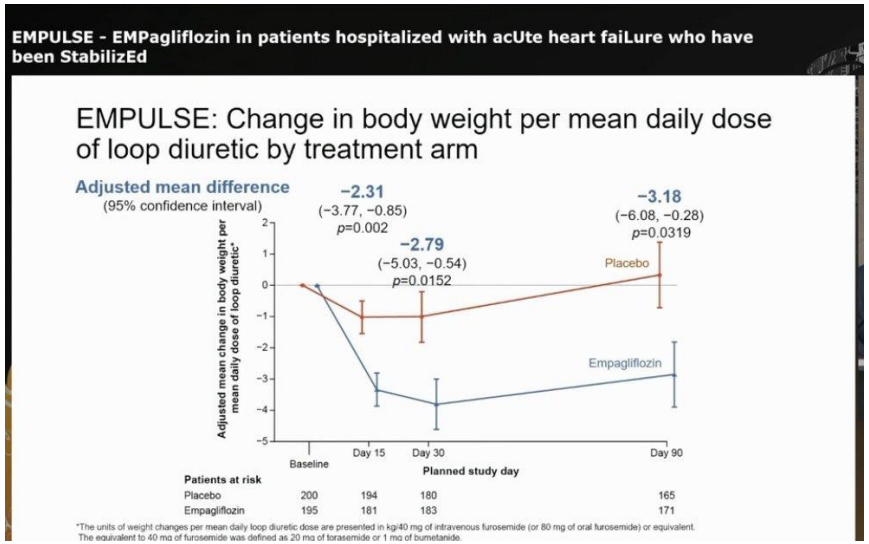
Prof Mpiko Ntsekhe
University of Cape Town


**Click on the link below**
**www.hefssa.org**

# The Impact of Empagliflozin on Decongestion in Patients Hospitalized for Acute Heart Failure:

# Analysis from the EMPULSE Trial

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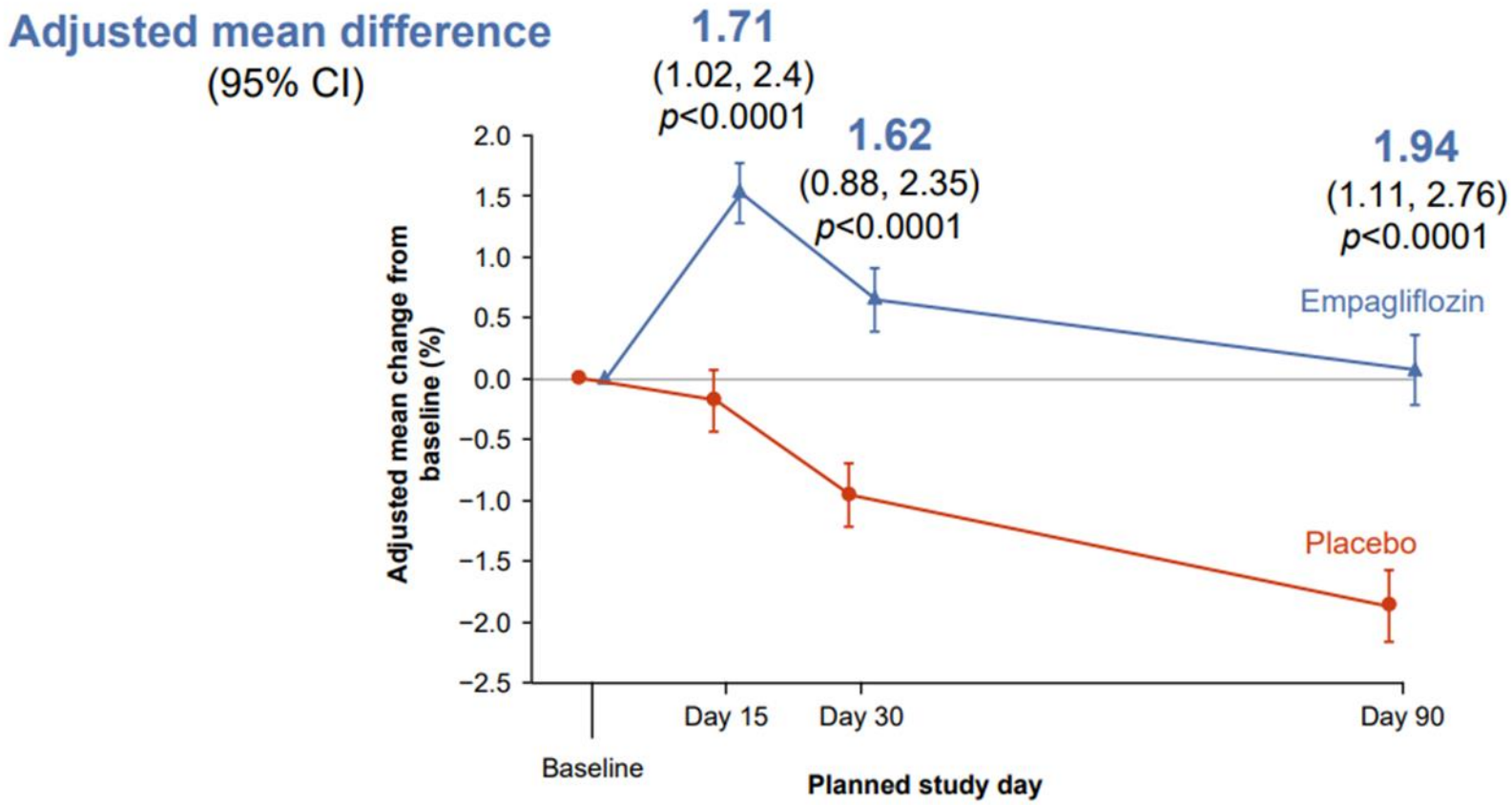
# EMPULSE: Haemoconcentration*




*Measured as changes in haematocrit (%)

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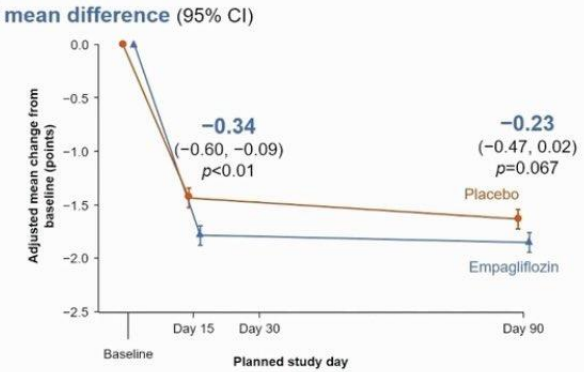
**EMPULSE - EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd**

EMPULSE: Change in clinical congestion score (dyspnoea, orthopnoea and fatigue*)




* 0–3 point scale has been used, where points were allocated for: absence (0 points), seldom (1 point), frequent (2 points) and continuous (3 points) based on frequency of the clinical sign

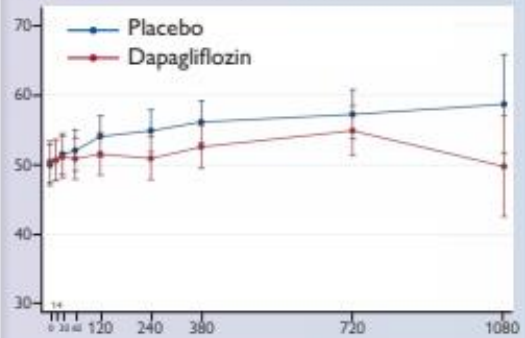
1. Initiation of ***empagliflozin*** in patients hospitalized for acute HF resulted in an ***early*** (seen already at the first assessment at day 15), ***clinically meaningful and sustainable*** (present until day 90) ***decongestion.***
2. Compared with placebo, treatment with empagliflozin resulted in ***an uniform pattern*** of significantly greater changes in all studied markers of decongestion at all time-points.
3. The ***magnitude of decongestion*** (as evidenced by greater weight loss) was associated with ***clinical benefit.***

**Mean loop diuretic dosing increased in the placebo arm, but remained relatively stable in the dapagliflozin arm in follow-up**

**Dapagliflozin reduced new initiation of loop diuretics by 32% but did not influence discontinuations or disruptions**

**Mean loop diuretic dose**

Furosemide equivalent dose (mg)



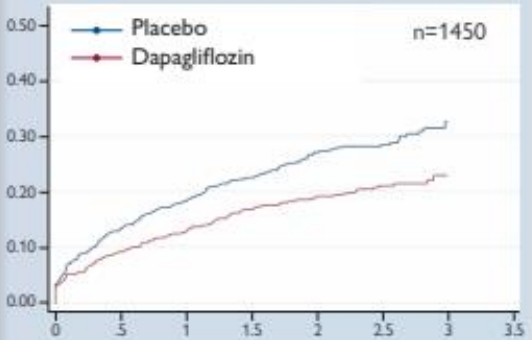

Δ Furosemide equivalent dose (mg/year)

| | |
|---|---|
| Placebo | +4.5 (3.4-5.3, p<0.001) |
| Dapagliflozin | +2.0 (1.2-2.3, p<0.001) |
| Difference | -2.5 (-1.5 to -3.7, p<0.001) |

P-interaction<0.001

**New loop diuretic initiation**

Cumulative incidence of new loop diuretic initiations




HR 0.68; 95% CI: 0.55 to 0.84, p<0.001

European Heart Journal (2023) 44, 2930–2943

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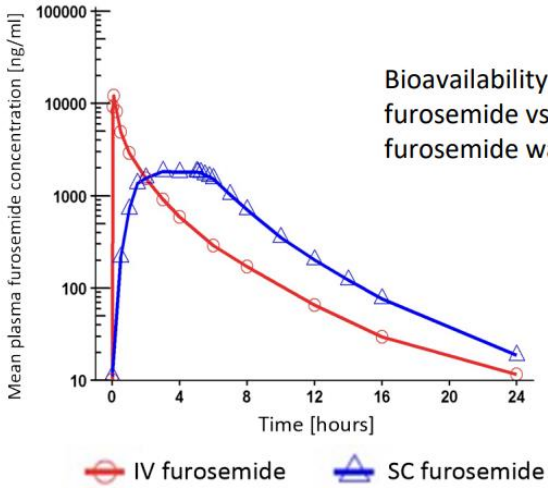
# Subcutaneous furosemide – the future?

University of Glasgow

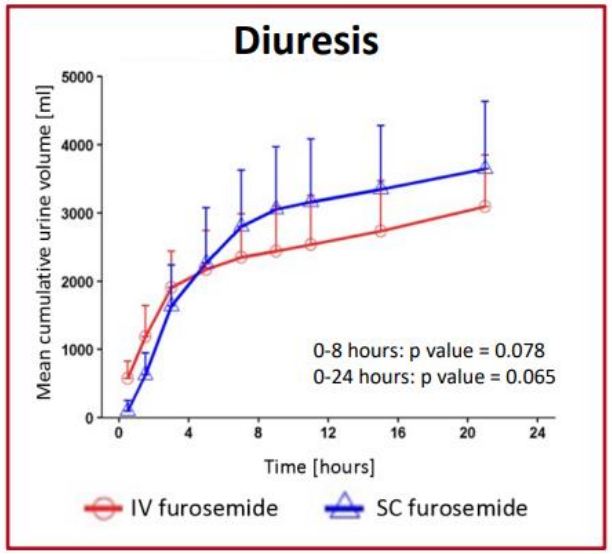
**A novel, small-volume subcutaneous furosemide formulation delivered by an abdominal patch infusor device in patients with heart failure: results of two phase I studies**

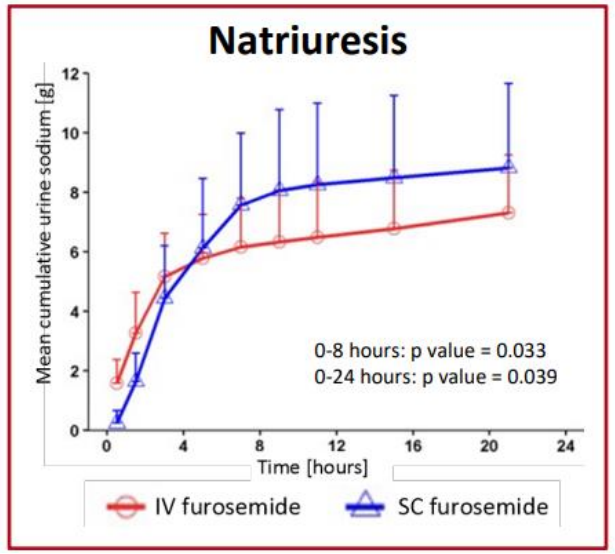
October 11, 2022

**FDA Approves Wearable Furosemide Delivery System Furoscix for Outpatient Use**




Bioavailability of subcutaneous furosemide vs intravenous furosemide was 112%

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