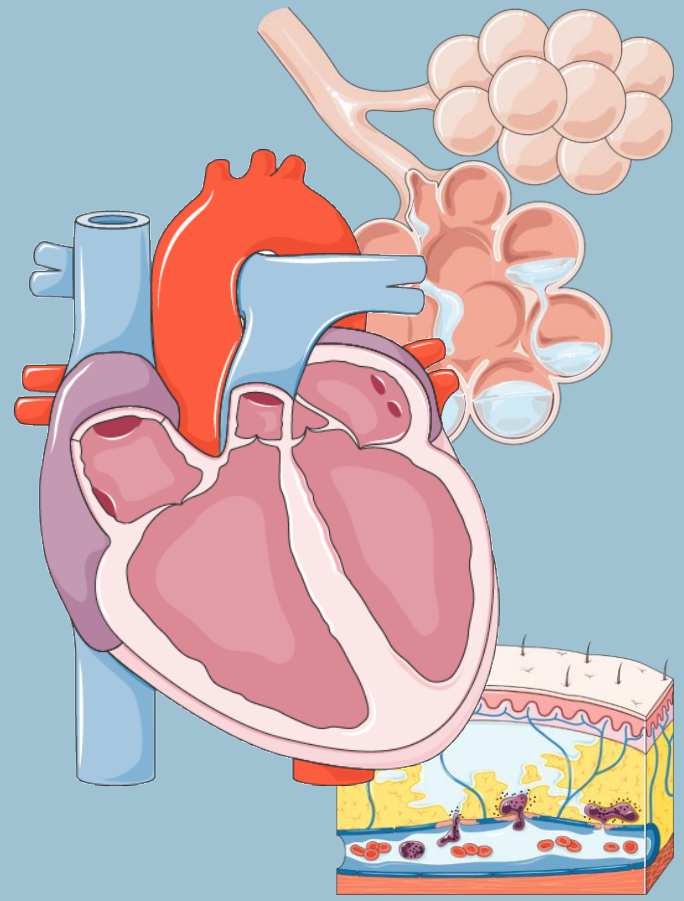
The decompensated patient. Game over?

Dr. Jozine ter Maaten

The decompensated patient

Game over?

Jozine ter Maaten
Cardioloog UMCG



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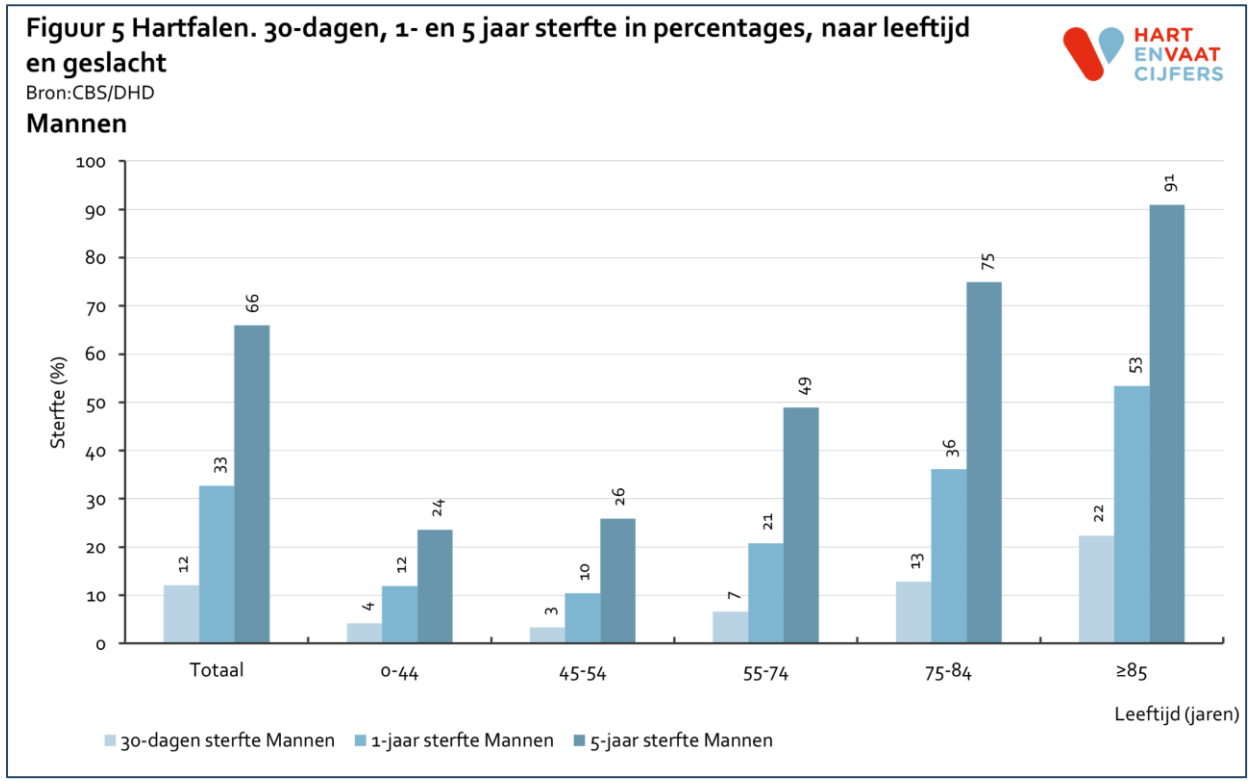
Disclosures

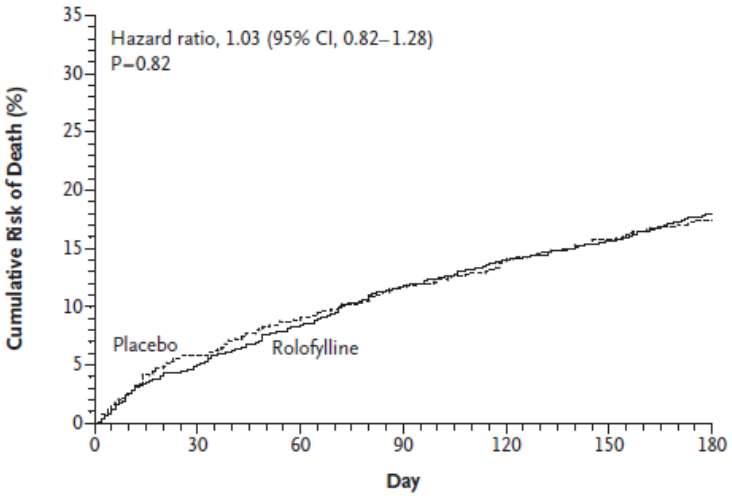
(Potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• Sprekers kosten betaald aan het UMCG door Novartis en Boehringer Ingelheim • Gesponsord door een Dekker beurs van de Hartstichting, Off Road grant en Veni van NWO

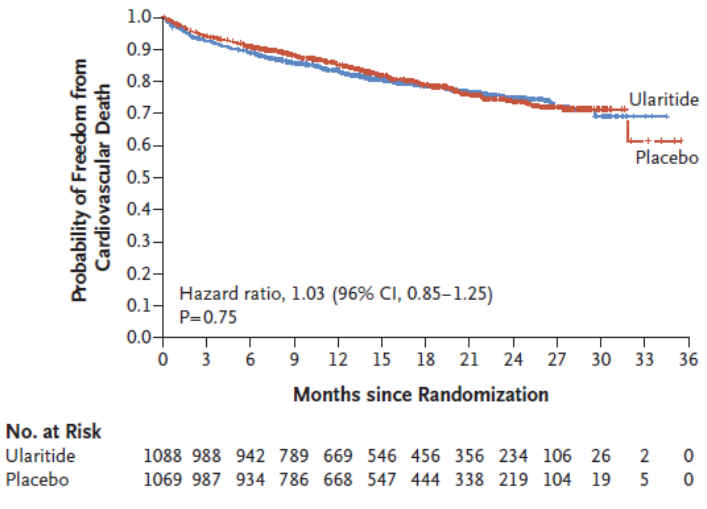
The decompensated patient – game over?

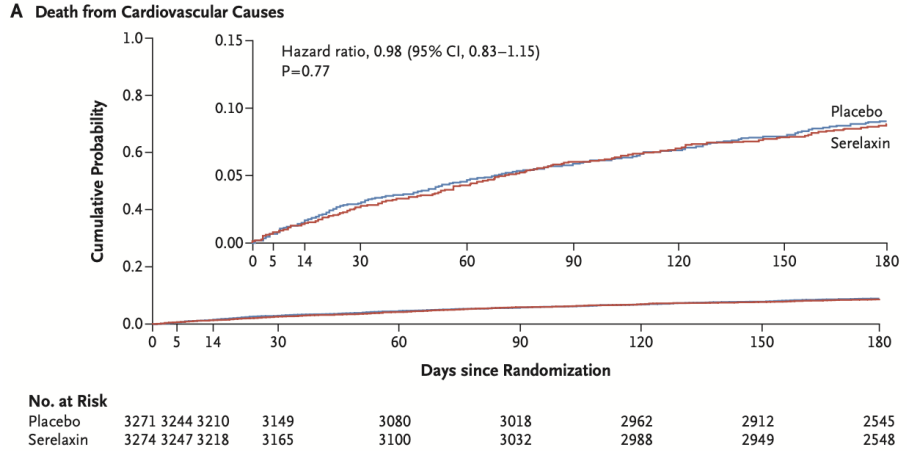
- Voornaamste reden ziekenhuisopnames bij 65+
  - In 2017 30.000 HF opnames
  - Neemt alleen maar toe
- HF zorg 1-2% van **totale** gezondheidszorgbudget (€ 817 miljoen 2017)
  - HF opnames verantwoordelijk voor 50-70% van dit bedrag



AHF = neutrale trials?







PROTECT

TRUE AHF

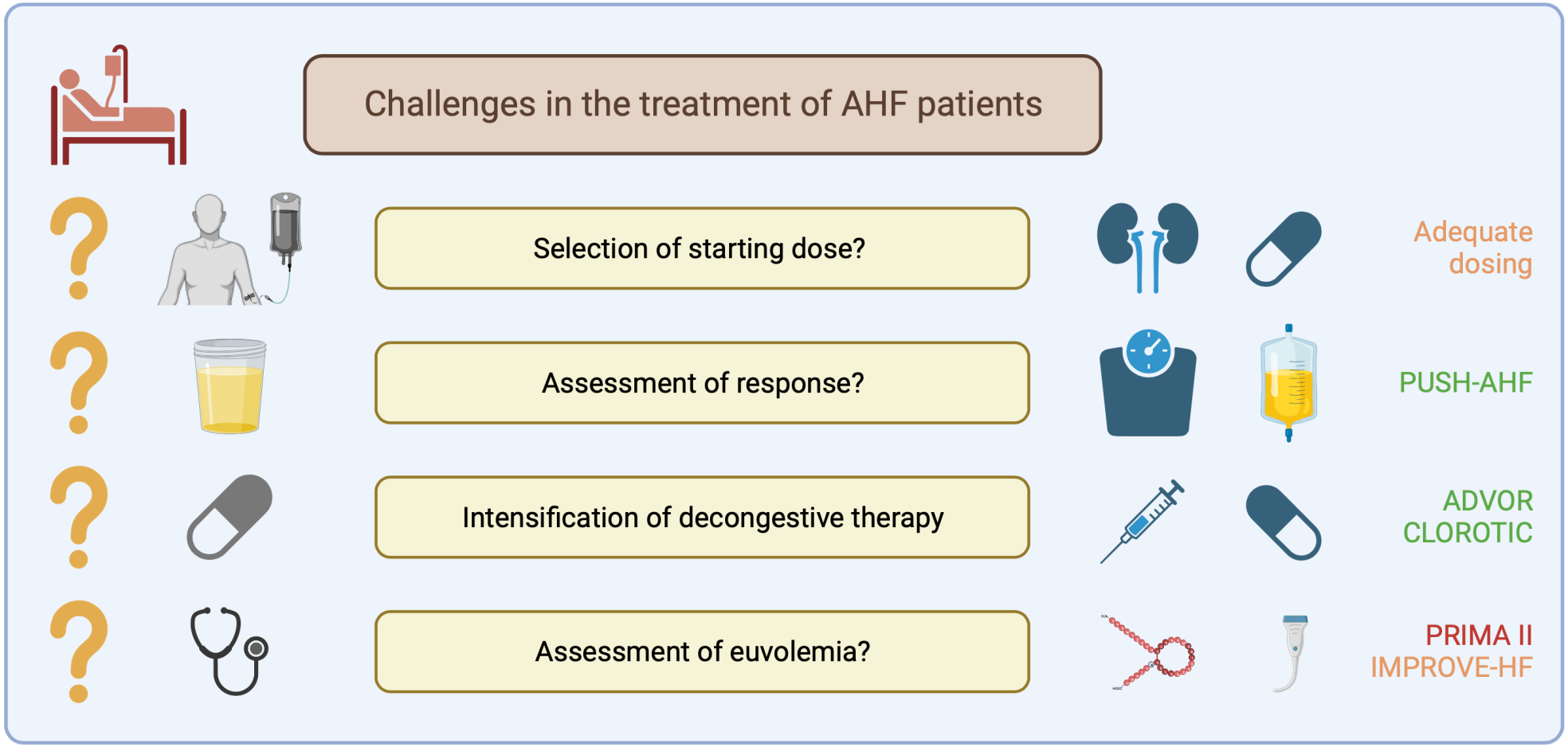
RELAX2

Dus alleen diuretica?

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

Massie et al. NEJM 2010; Packer et al. NEJM 2017; Metra et al. NEJM 2019

Hoe kunnen we acuut hartfalen toch beter behandelen?



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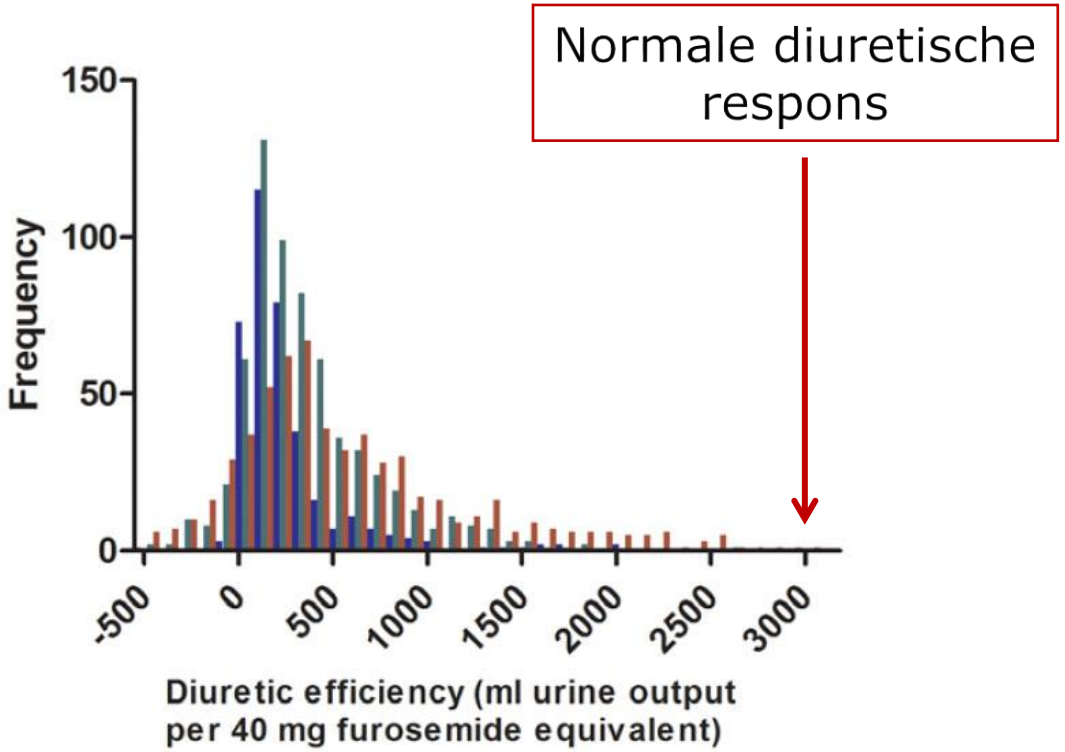
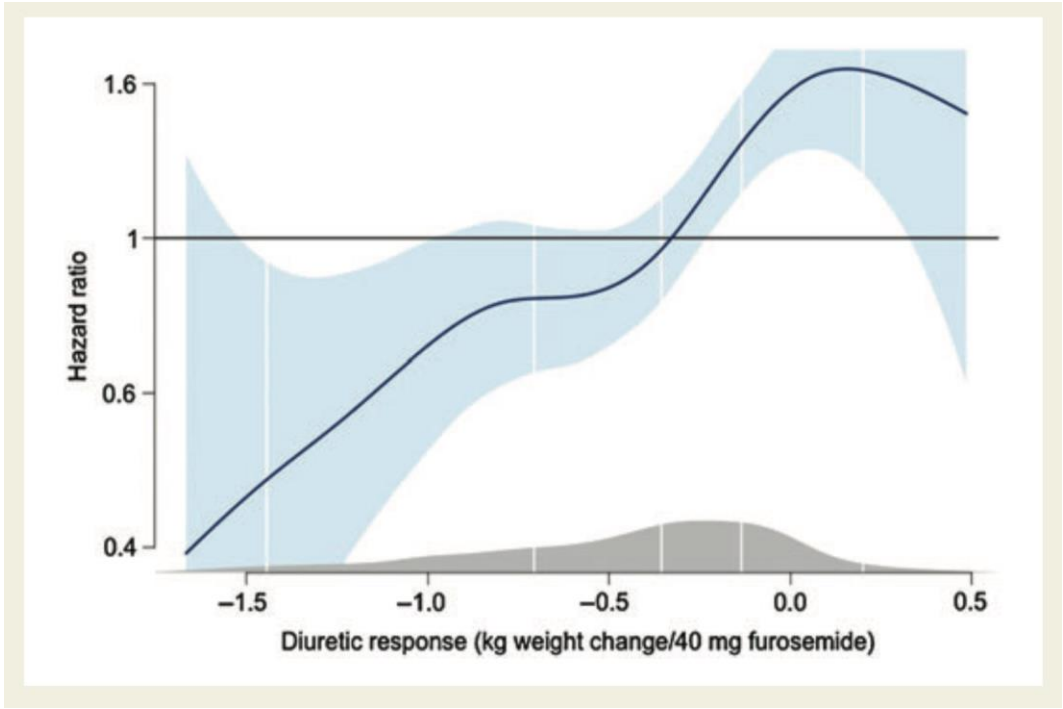
ter Maaten et al. Submitted

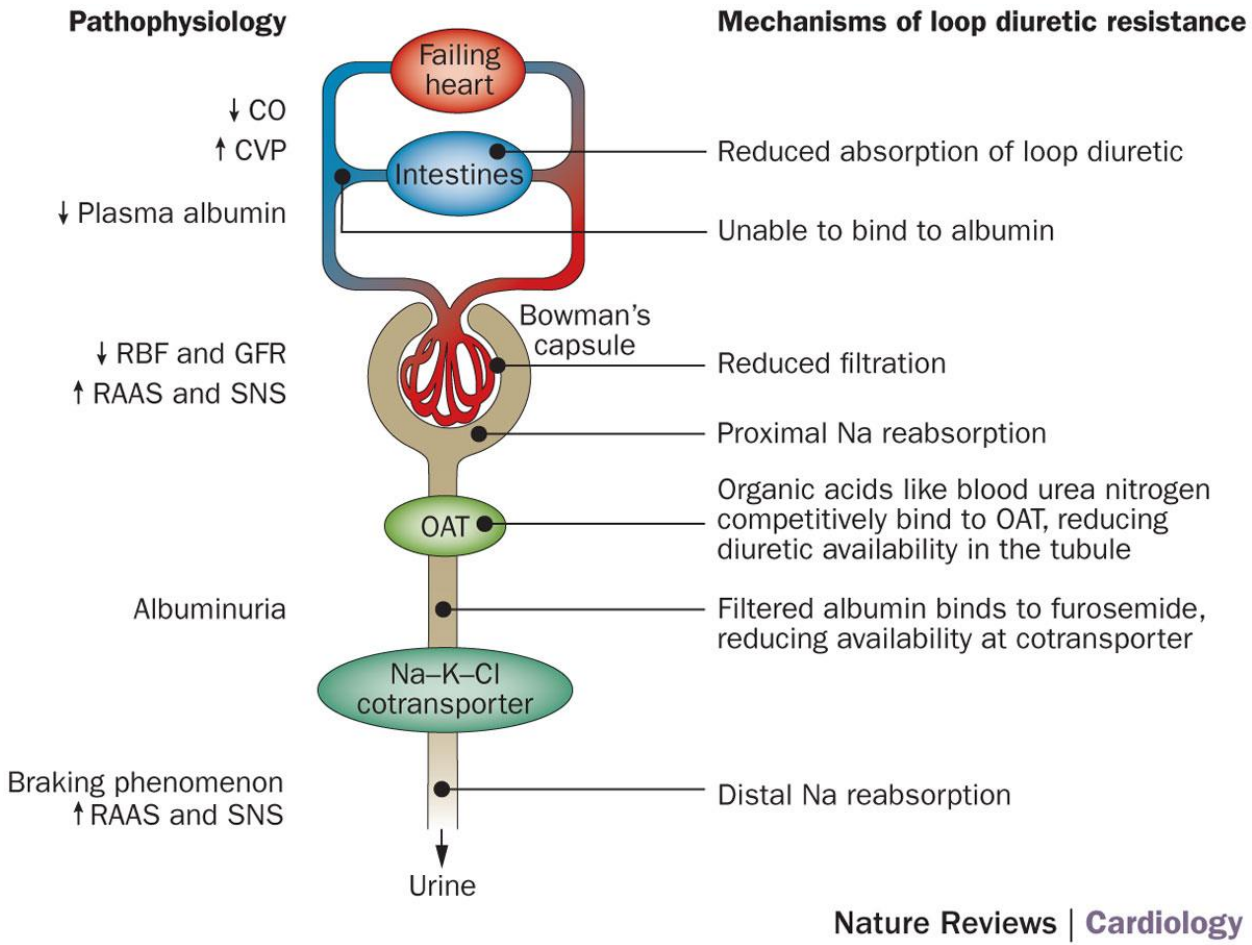
Diuretische respons

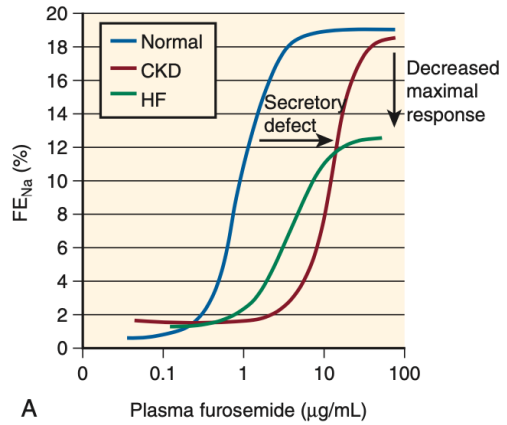


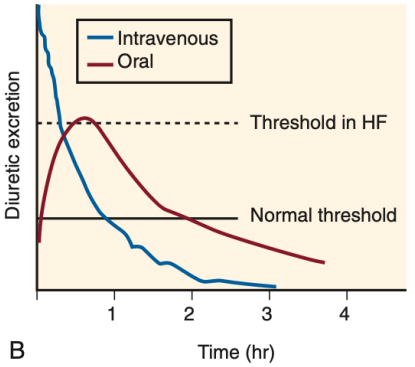


Testani et al. Circ 2014; Valente et al. EHJ 2015

Etiologie verminderde respons





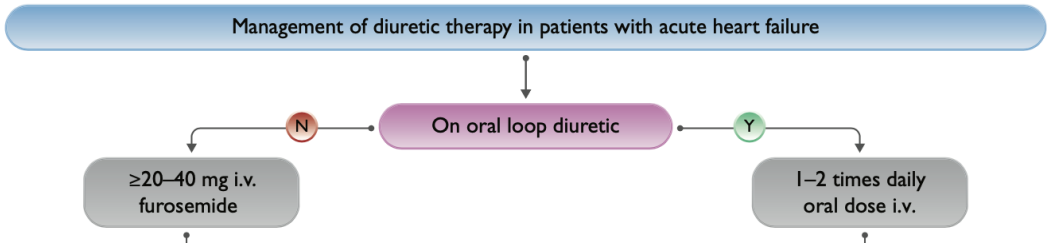


ter Maaten et al. Nat Rev Cardiol 2015; Brenner & Rector the Kidney

Selectie van (adequate) start dosering

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

End Point	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	20/147 (14)	35/154 (23)	0.04



High dose = 2,5 * de totale orale lisdiuretica dosering thuis

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Felker et al. NEJM 2011; McDonagh et al. EHJ 2021

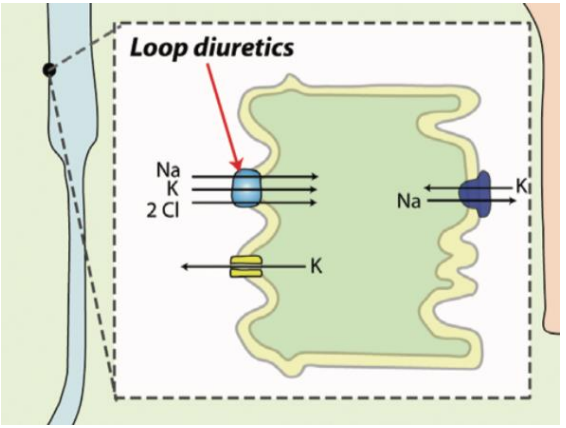
Slechte respons voorspellen?

Onmogelijk om van tevoren te beoordelen hoe een patiënt reageert op diuretica

- Veel markers van respons zijn onbetrouwbaar of laat beschikbaar

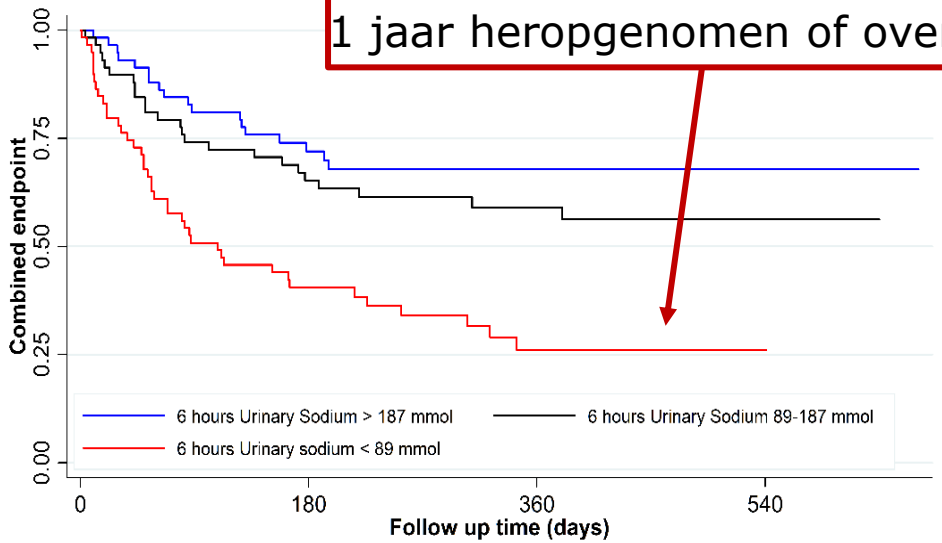
Risicofactoren slechte diuretische response:

- Nierinsufficiëntie en verminderde renale perfusie
- Hypochloremie
- Slechte diuretische response in eerste 24 uur
- Zoutexcretie na eerste gift diuretica

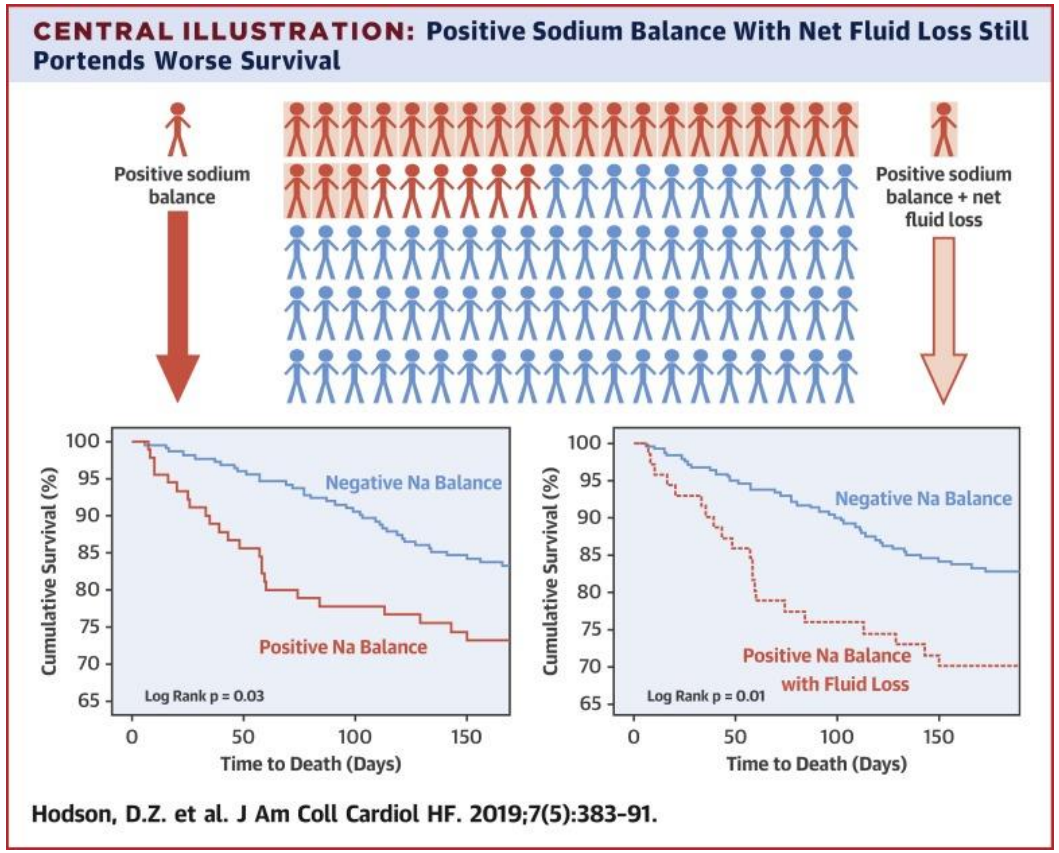


Is natriurese niet een betere marker voor response?

Bij slechte natriurese is 75% binnen 1 jaar heropgenomen of overleden!

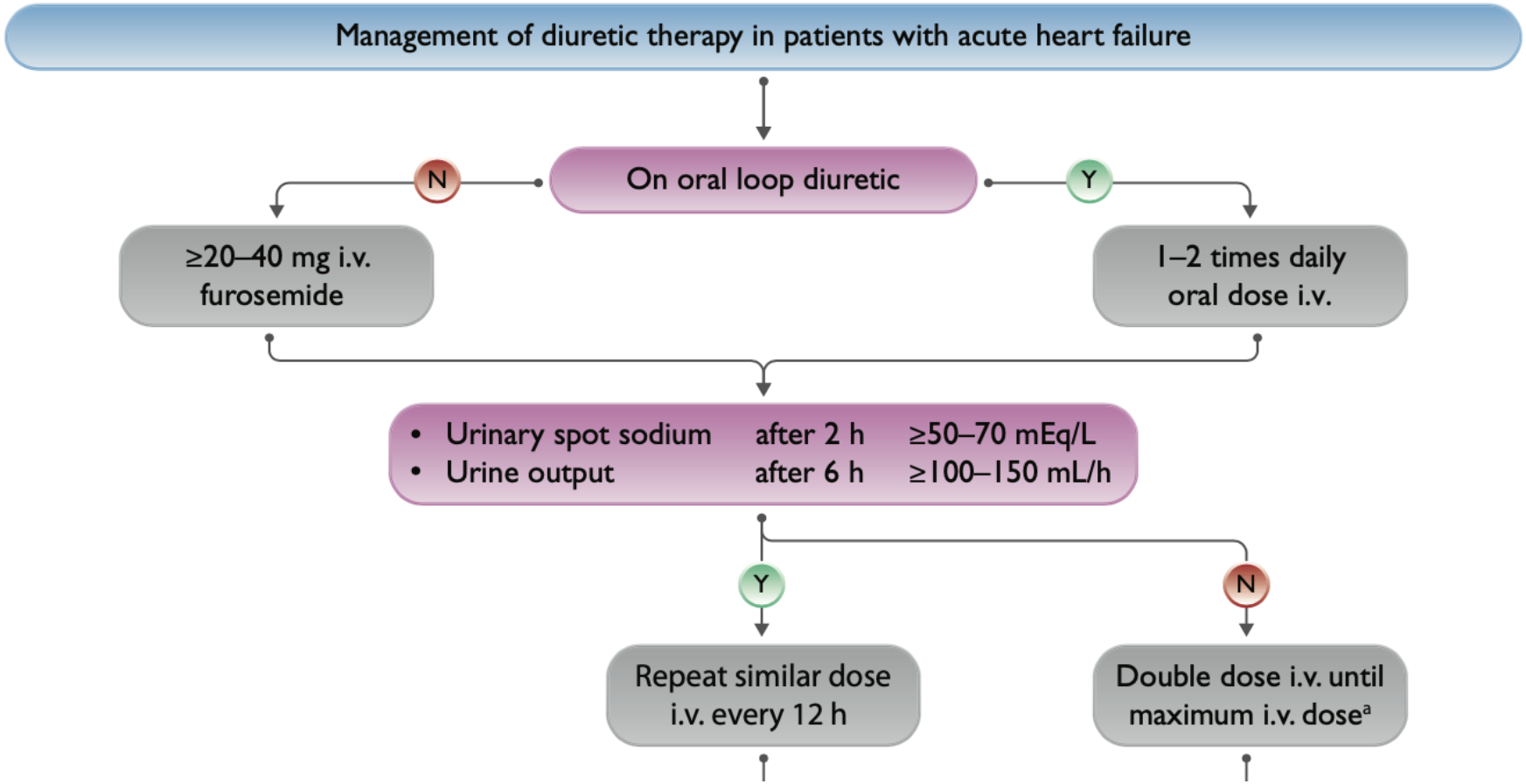


Number of Patients				
6 hours Urinary Sodium > 187 mmol	58	35	18	5
6 hours Urinary Sodium 89-187 mmol	58	36	22	5
6 hours Urinary sodium < 89 mmol	59	22	9	1



Damman et al. EJHF 2021; Hodson et al. JACC HF 2019

Natriuresis guided therapy – ready for implementation?



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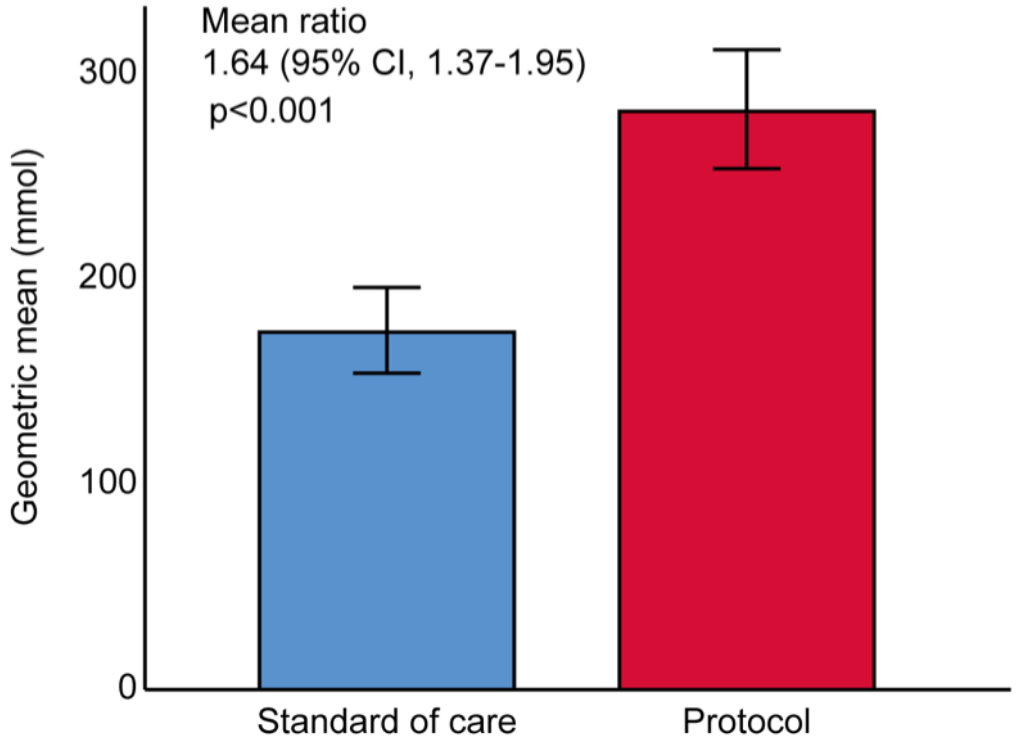
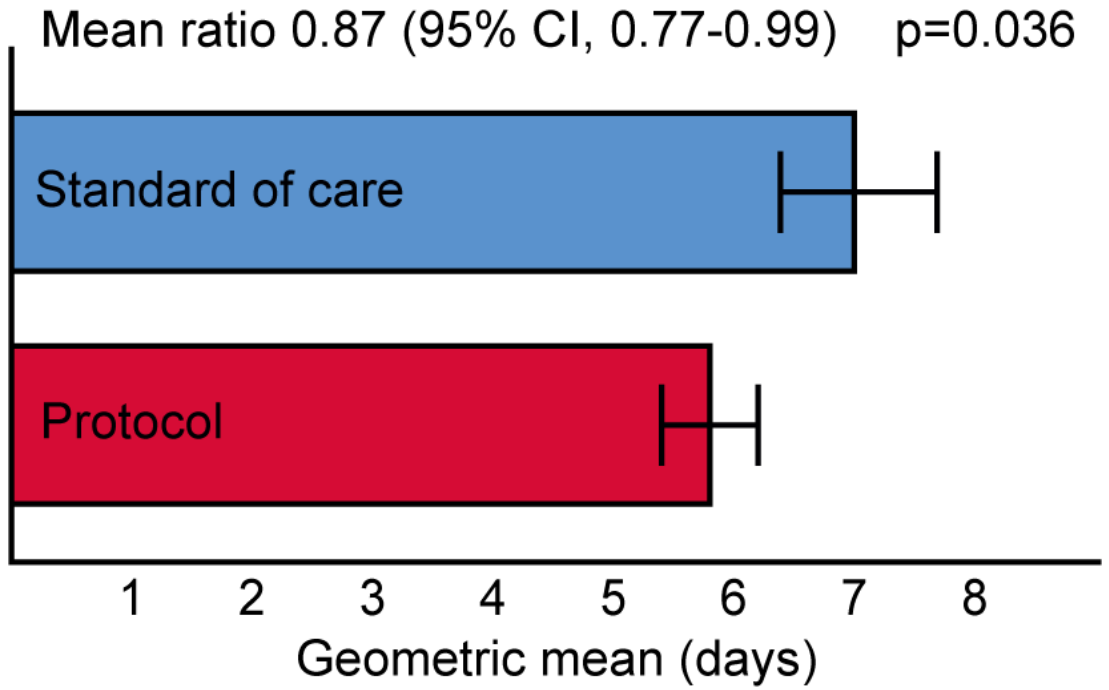
McDonagh et al. EHJ 2021

ENACT-HF – pre/post studie (254/147 pt)

24-uur natriurese



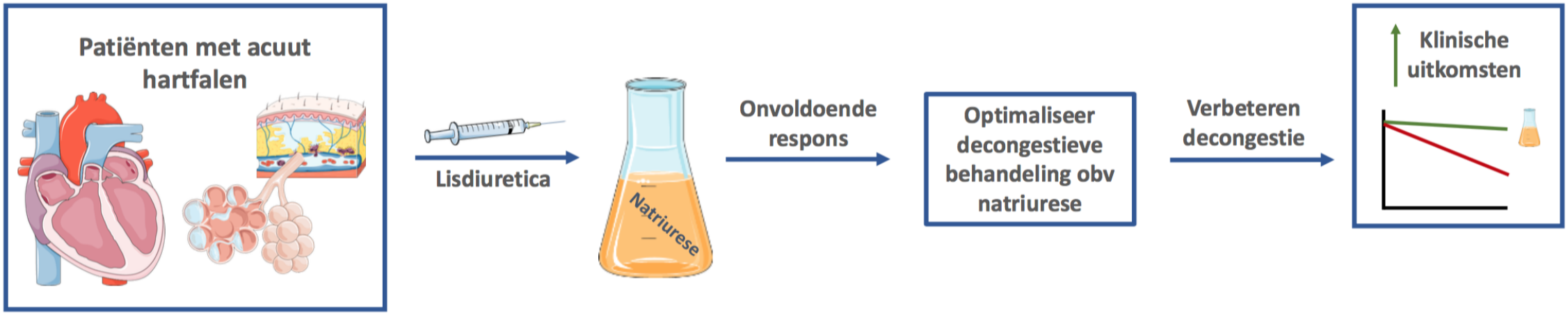
Opnameduur



Dauw et al. Submitted

Pragmatic Urinary Sodium based treatment algoritHm in Acute Heart Failure

Natriurese gestuurde therapie in patiënten met acuut hartfalen leidt tot een verbetering van diuretische respons, decongestie, en klinische uitkomsten



ter Maaten et al. EJHF 2022

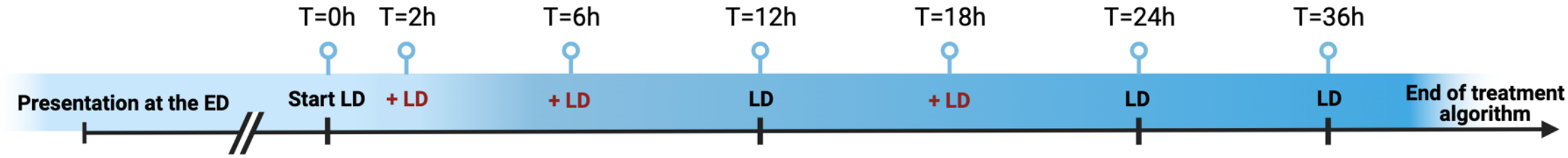
PUSH AHF study design

Presentation at the ED with AHF:
Signs and symptoms of congestion
Requiring treatment with intravenous loop diuretics (LD)

Randomization in EHR to natriuresis guided therapy or standard of care

Enrollment:
First administered iv loop diuretic dose (deferred consent)

Standardized starting dose of loop diuretic based on:
- Renal function and
- Outpatient loop diuretic dose



Insufficient response:
- Urinary sodium < 70 mmol/L
- Diuresis < 150 mL/hour

Treatment algorithm if insufficient:
1. Double previous bolus dose
2. Combination diuretic therapy
   a. Add hydrochlorothiazide
   b. Add second line: acetazolamide or SGLT2i

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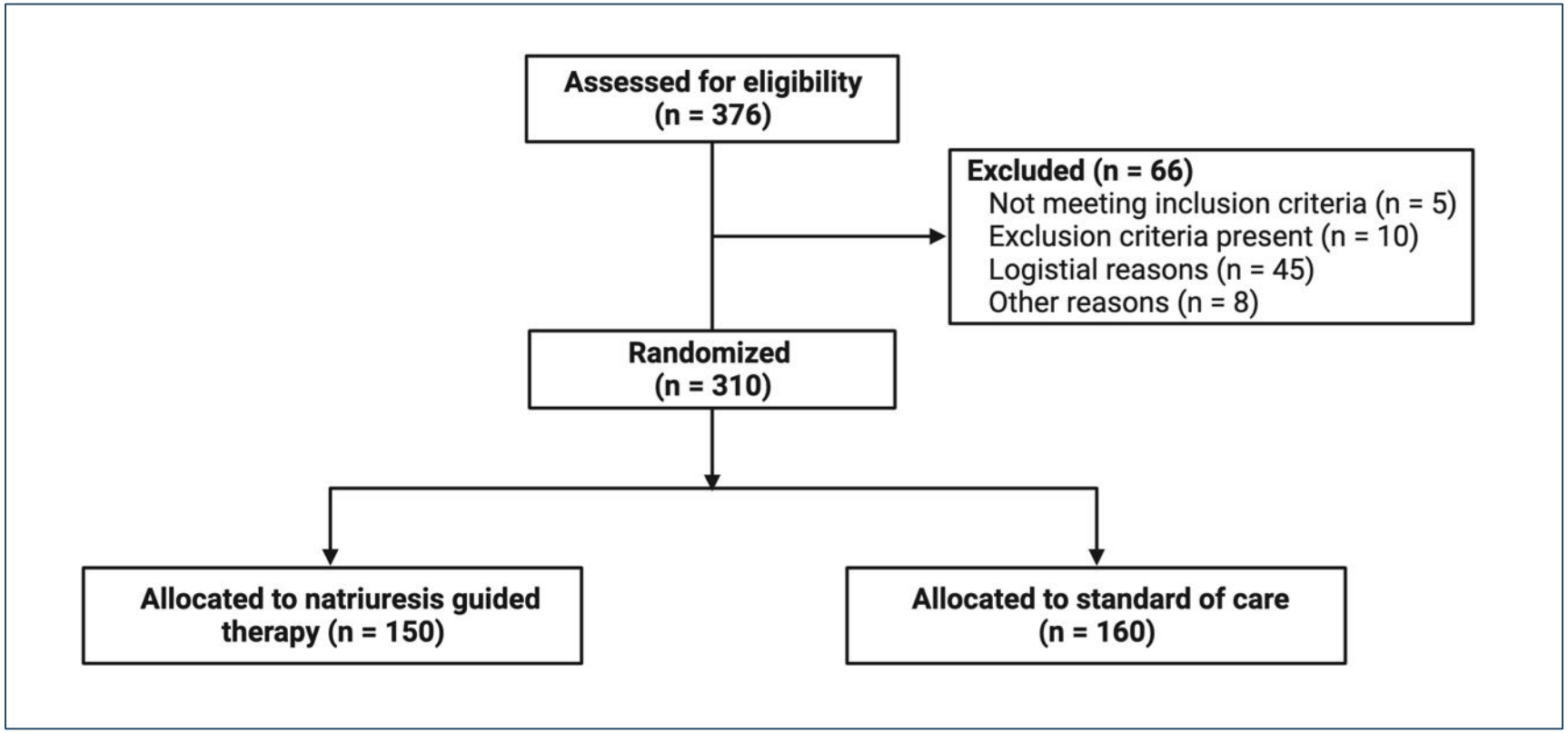
ter Maaten et al. Nat Med 2023

PUSH study flow chart



ter Maaten et al. Nat Med 2023

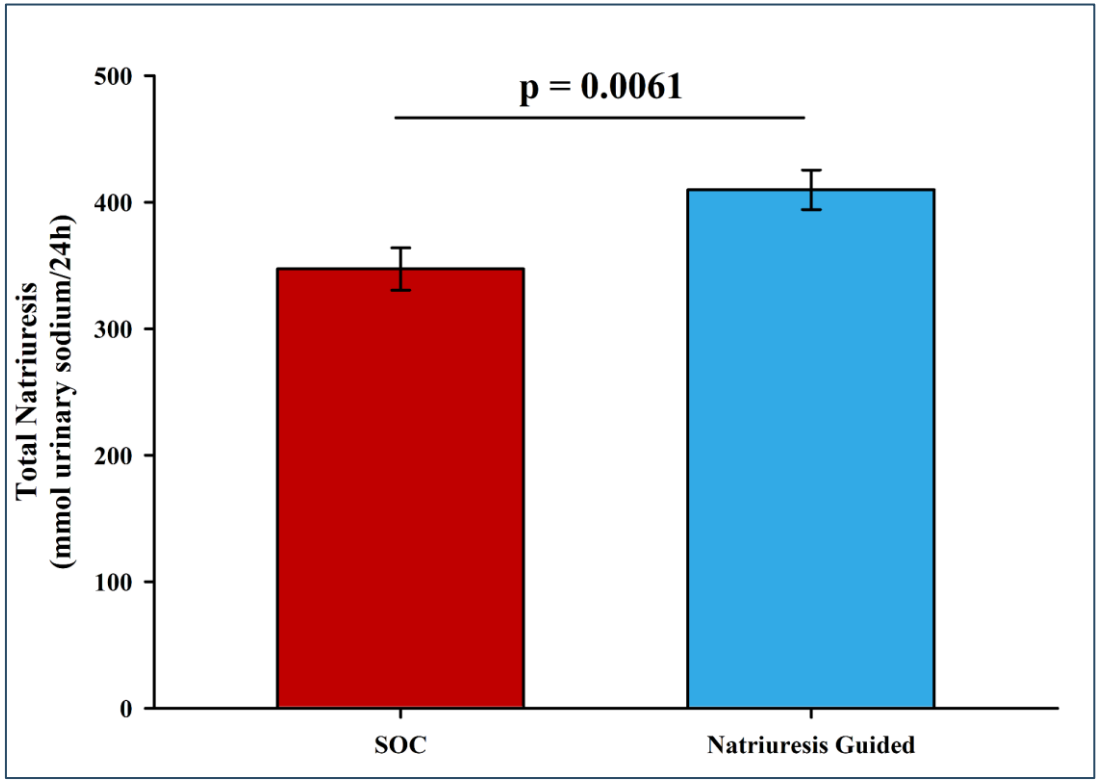
Baseline tabel

	Natriuresis guided therapy (n=150)	Standard of Care (n=160)
Demographics		
Age (years)	74 [66-82]	74 [65-81.2]
Sex (n (%) female)	61 (41%)	77 (48%)
Race (n (%) white)	142 (96%)	155 (98%)
Physical examination at presentation		
NYHA Class (n (%))		
II	5 (3%)	11 (7%)
III	39 (26%)	29 (18%)
IV	106 (71%)	120 (75%)
Heart failure		
LVEF (%)	35 [25-53]	38 [28-48]
HFpEF (n (%))	30 (26%)	21 (18%)
New-onset heart failure (n (%))	66 (44%)	69 (43%)
Ischemic etiology (n (%))	56 (37%)	55 (34%)
Laboratory values at baseline		
eGFR (ml/min/1.73m2)	54 [35-72]	53 [34.8-73.2]
NT-proBNP (ng/L)	4390 [2554-8226]	4947 [2607-9809]

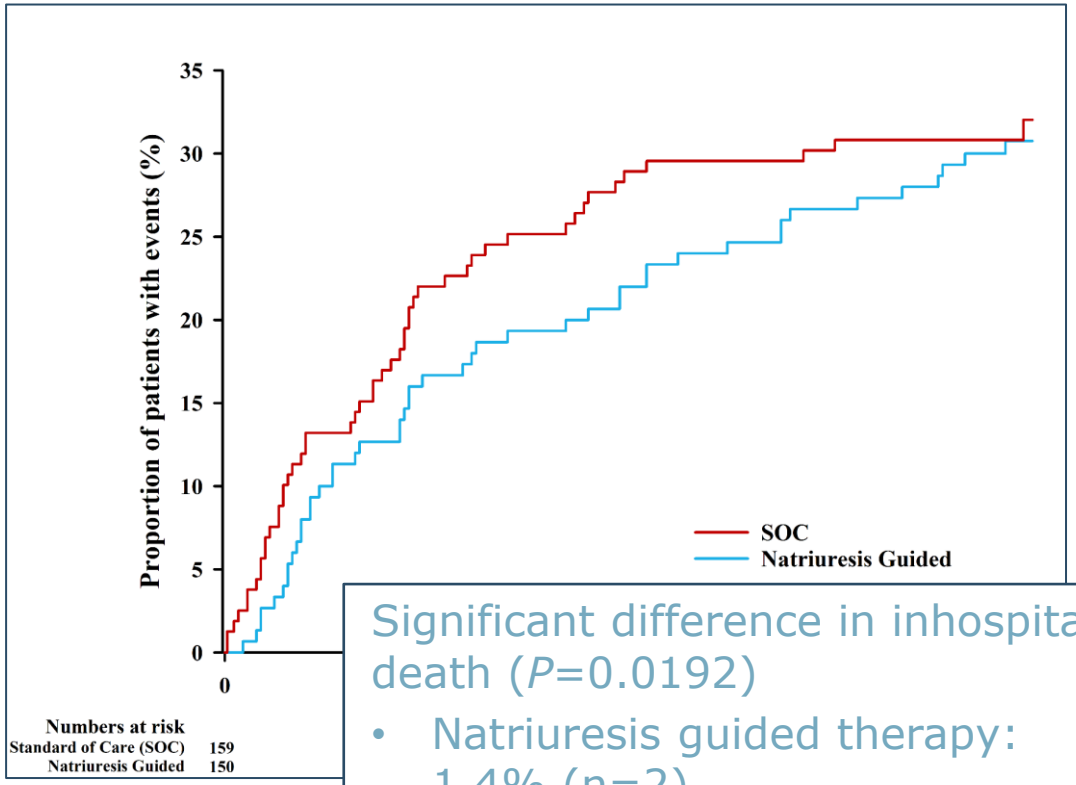
ter Maaten et al. Nat Med 2023

Dual primary endpoint

24-hours natriuresis



180 days ACM & HF hosp



Significant difference in inhospital death (*P*=0.0192)

- Natriuresis guided therapy: 1.4% (n=2)
- Standard of care: 7.5% (n=14)

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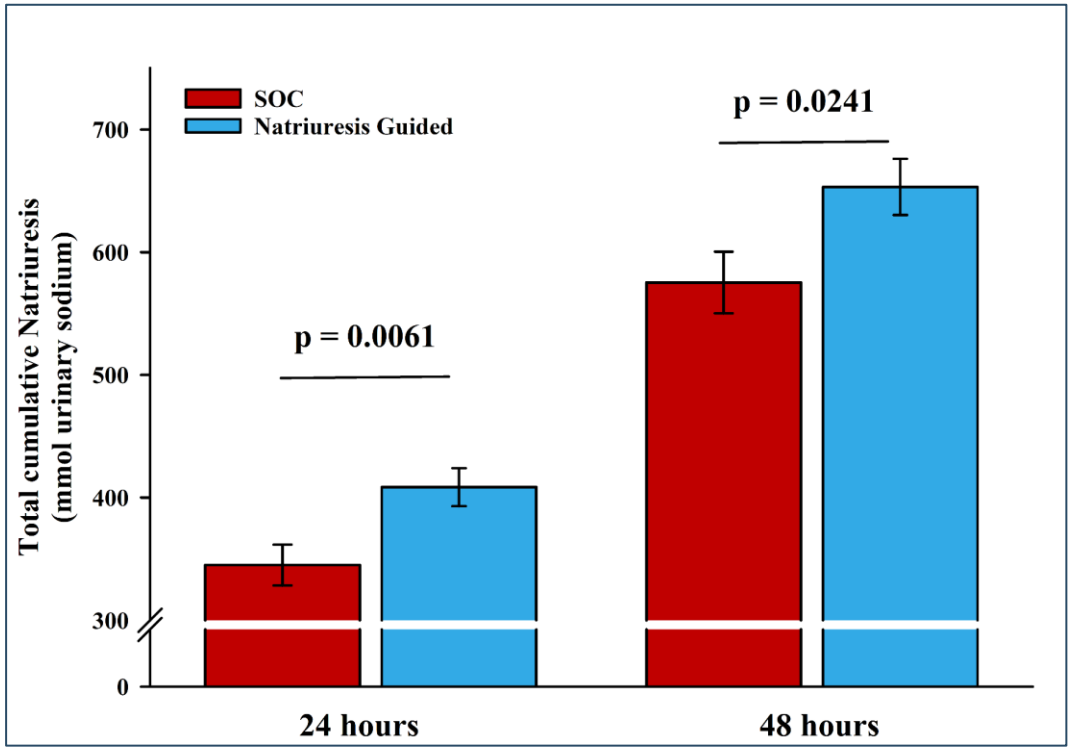
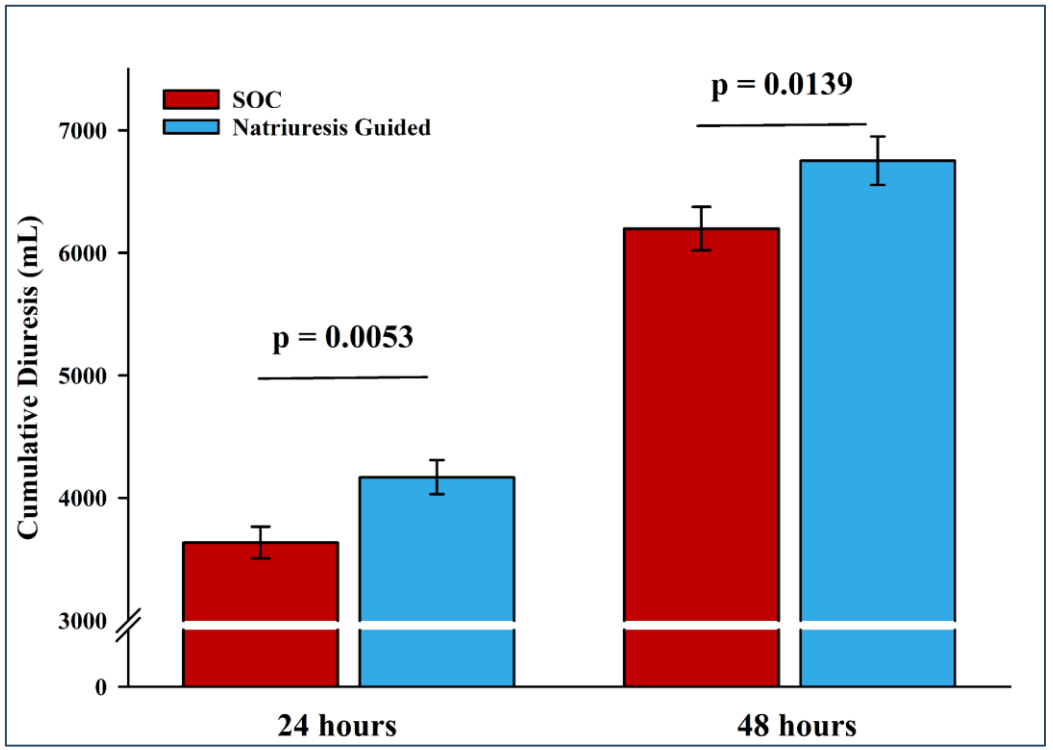
ter Maaten et al. Nat Med 2023

Secondary endpoint – natriuresis and diuresis

Natriuresis



Diuresis



ter Maaten et al. Nat Med 2023

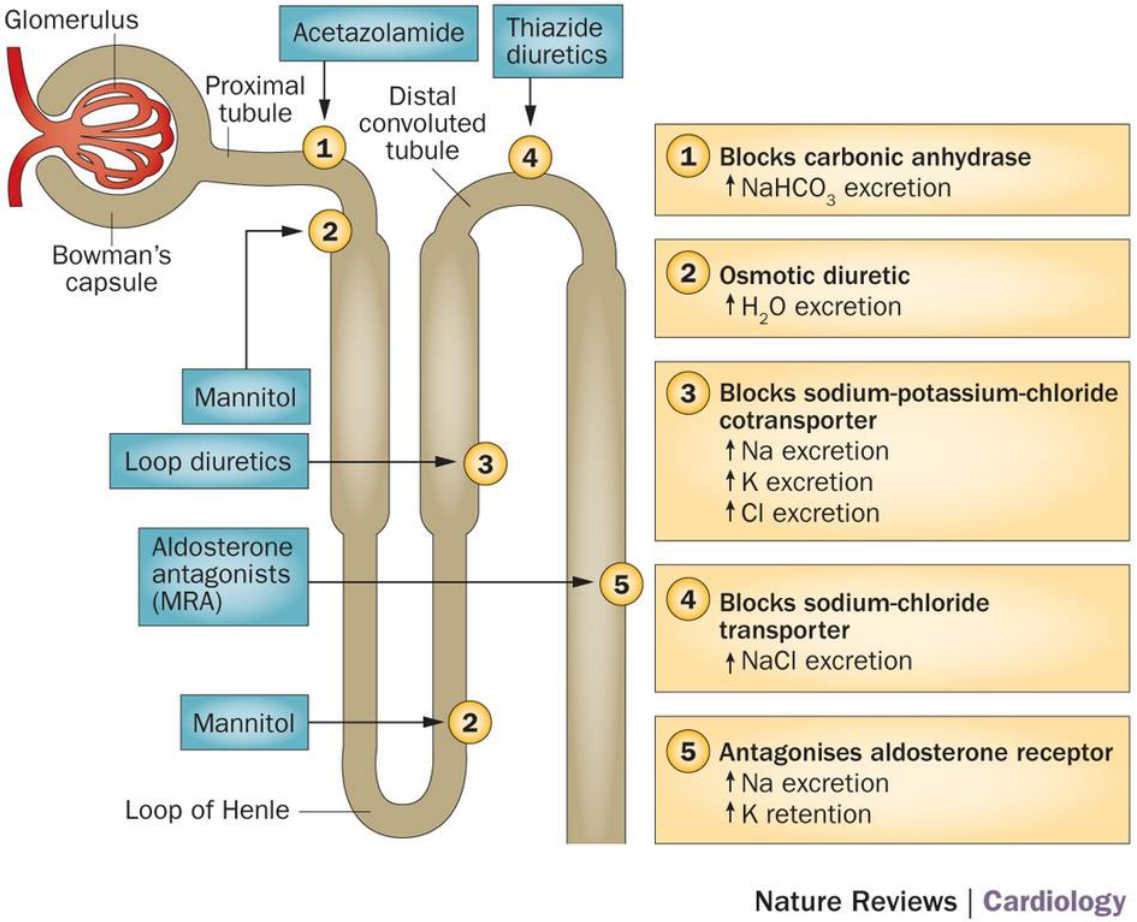
Natriurese gestuurde decongestieve therapie

- Is een eerste stap naar een gepersonaliseerd behandeling van AHF
  - Om natriurese en diurese te verbeteren
  - Geen effect op lange termijn uitkomsten
- Natriuresis gestuurde therapie is veilig
- Kan direct geïmplementeerd worden

	Natriuresis-guided therapy	SOC	*P* value
Safety endpoints			
Serious adverse events (% (*n*))	40 (60)	44 (70)	0.5799
Adverse events (% (*n*))	57 (86)	60 (96)	0.7180
Renal safety events			
Doubling of serum creatinine at 24 h from baseline (% (*n*))	0 (0)	1 (1)	1.0000
Doubling of serum creatinine at 48 h from baseline (% (*n*))	1 (1)	1 (2)	1.0000
Worsening HF (% (*n*))	6 (9)	9 (15)	0.3689
True worsening renal function (% (*n*))	1 (1)	1 (2)	1.0000

ter Maaten et al. Nat Med 2023

Onvoldoende respons – wat nu?



Werkt 'niet':

- Spironolacton (ATHENA HF)
- Dopamine (ROSE en DAD HF)
- Rolofylline (PROTECT)
- Nesiritide (ROSE en ASCEND HF)
- Serelaxine (RELAX 2)
- Ularitide (TRUE)

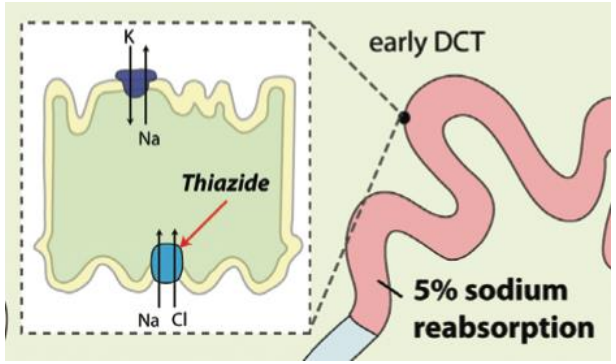
NB lisdiuretica voldoende doseren

ter Maaten et al. Nat Rev Cardiol 2015

HCT – CLOROTIC trial

Thiazide diuretica

- Distale tubulus
- Risico op WRF en elektrolyt#



Study population

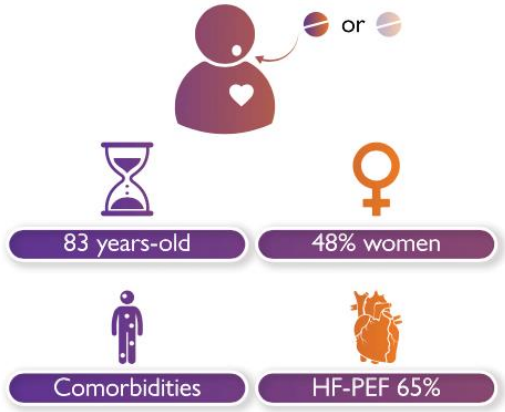
Randomized, double-blind, placebo-controlled clinical trial

History of chronic heart failure

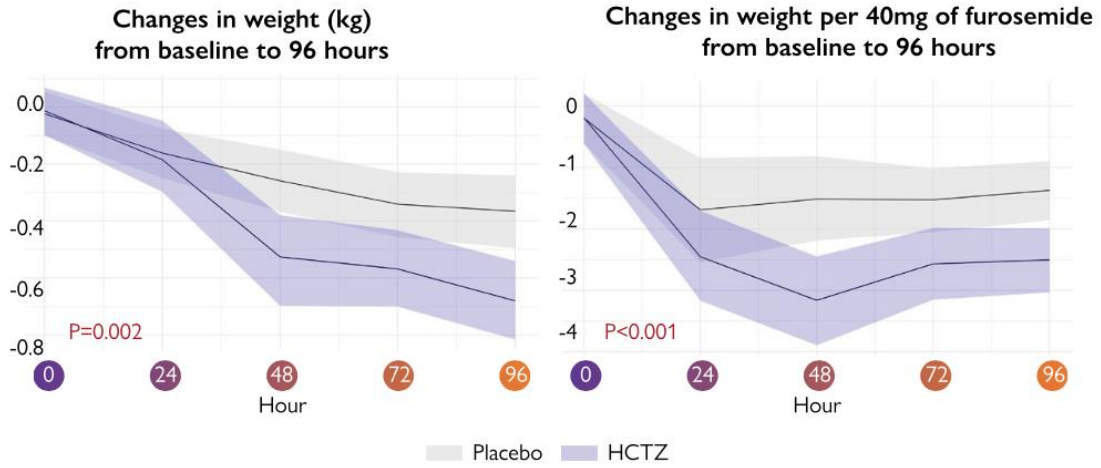
Treatment with oral furosemide (80-240 mg/day)

Admission for acute decompensation

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



Efficacy



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

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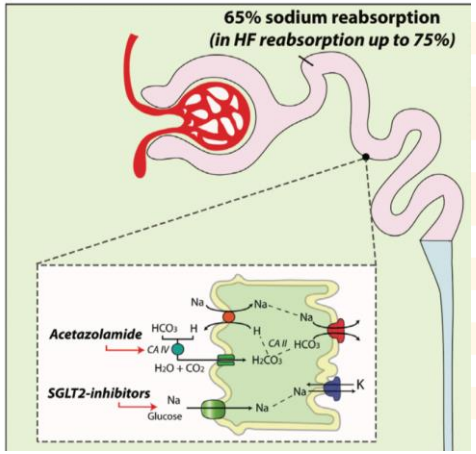
Trullas et al. Eur Heart J 2022

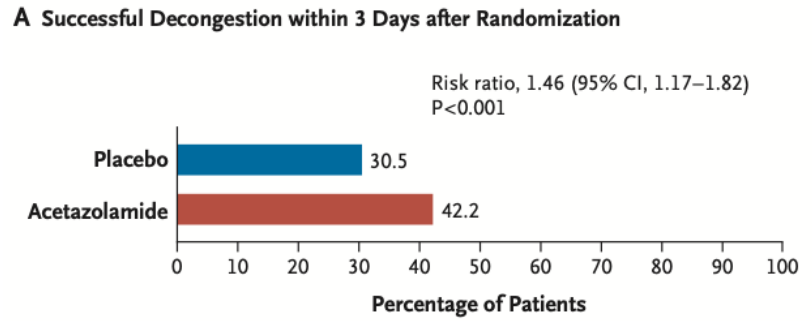
Acetazolamide – ADVOR trial

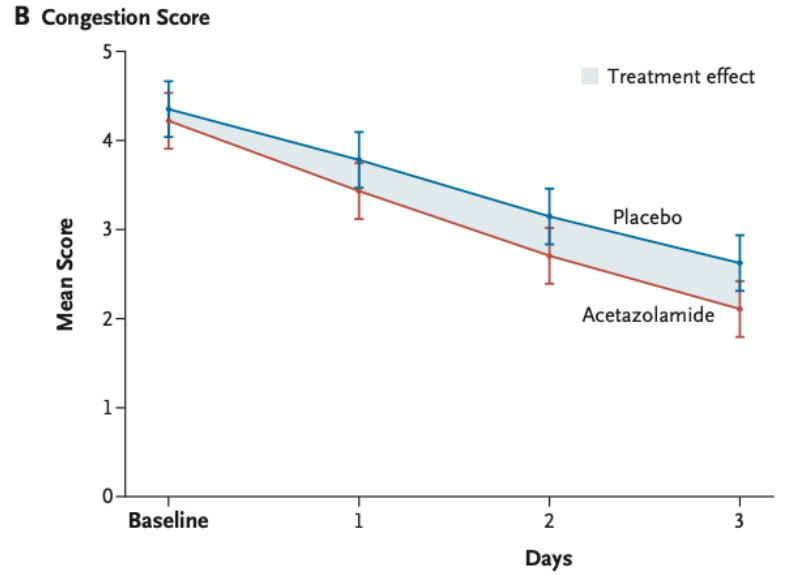
519 patiënten met AHF
1:1 acetazolamide:placebo

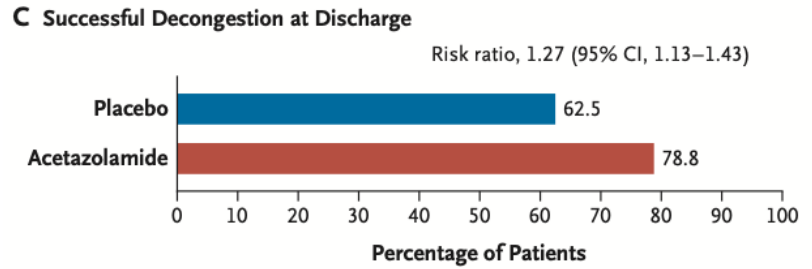
Primaire eindpunt: succesvolle decongestie binnen 3 dagen zonder escalatie therapie

Adverse events		
During treatment phase — no. (%)		
Combined renal safety end point	—	0.10
Doubling of serum creatinine level fr line	—	0.24
≥50% sustained decrease in estimat	—	0.21
Renal-replacement therapy during in hospitalization	—	0.21
Severe metabolic acidosis¶	—	—
Hypokalemia‖	—	0.39
Hypotension**	—	0.11
During 3 mo of follow-up — no. (%)		
Serious adverse event	—	1.00
Adverse event related to placebo or acet	—	0.14
Cardiovascular adverse event	—	0.53









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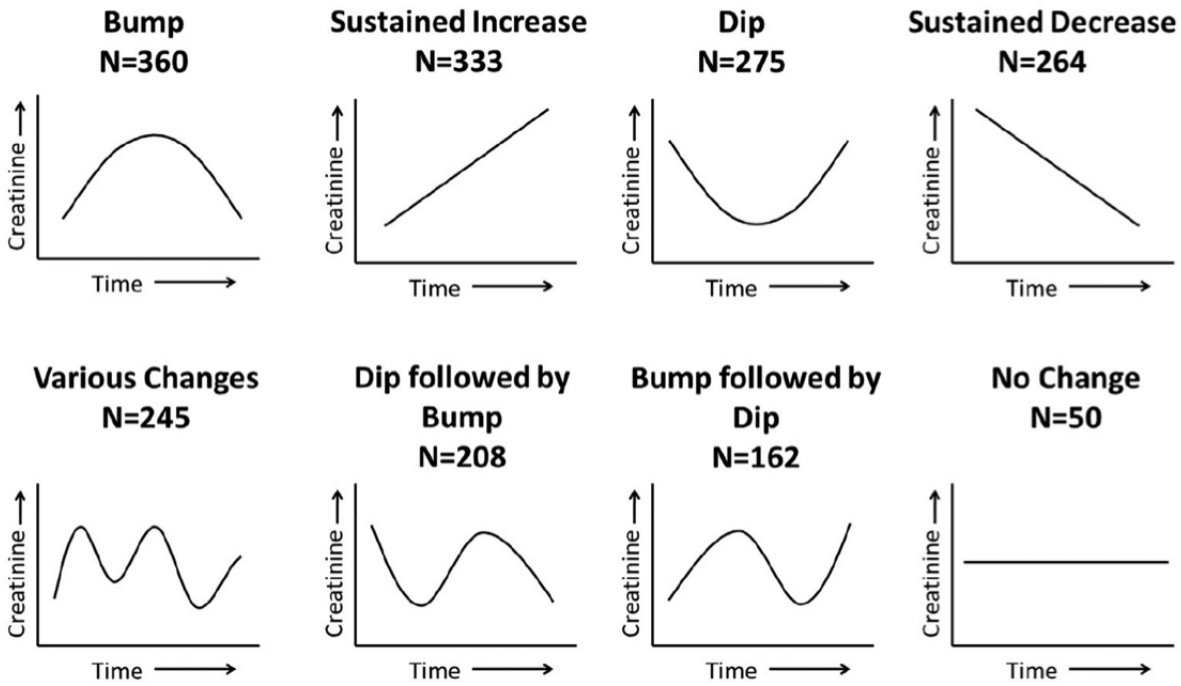
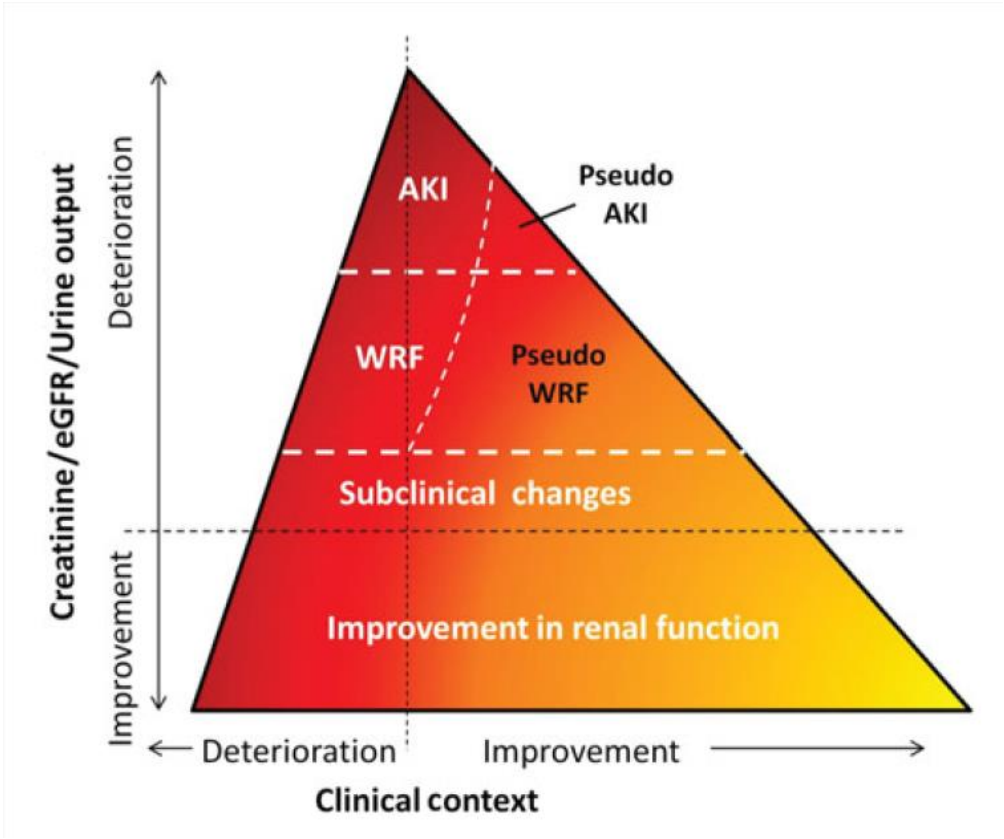
ADVOR

Mullens et al. NEJM 2022

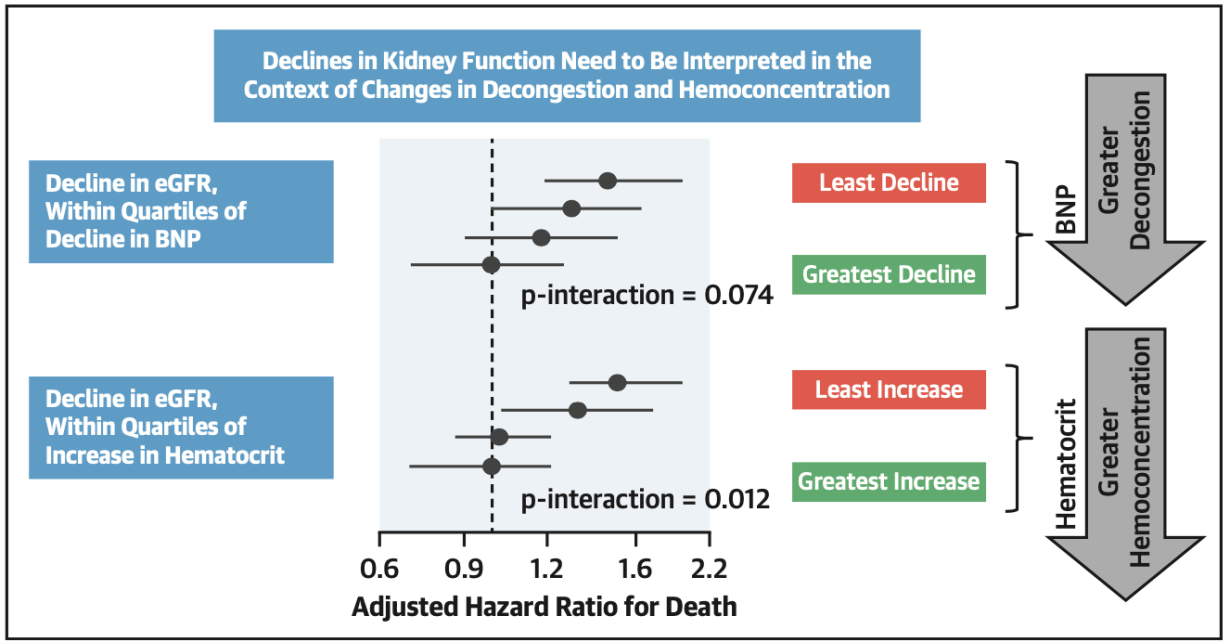
Nierfunctie tijdens decongestie

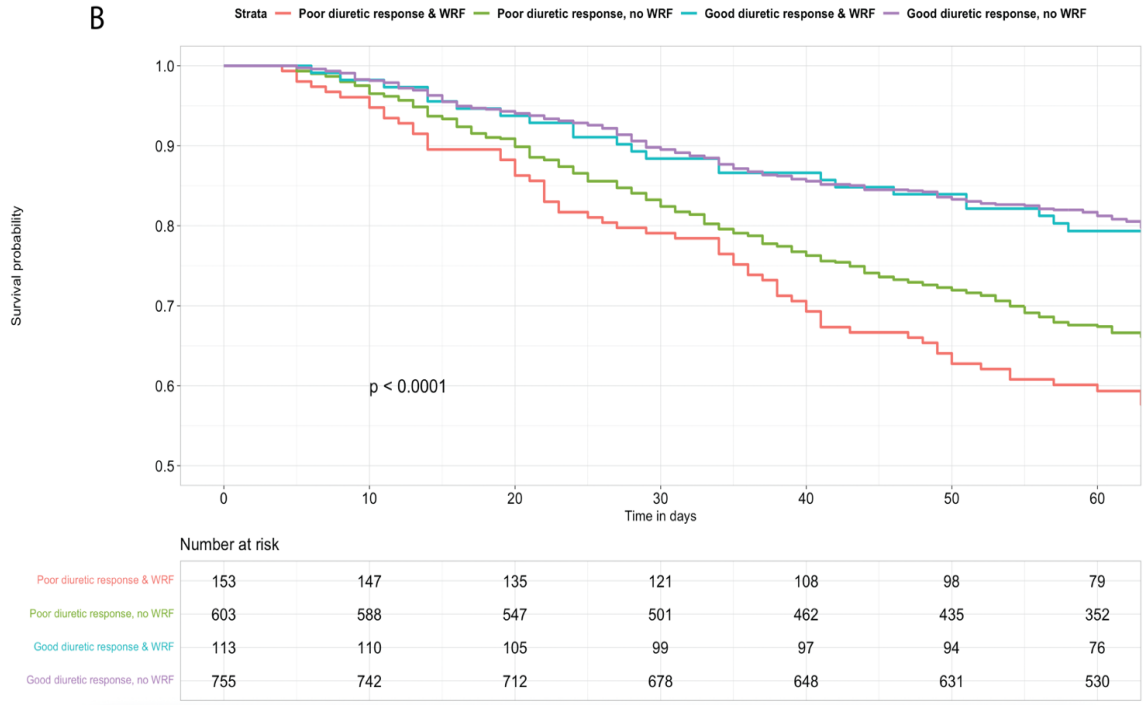




Beldhuis et al. JCF 2018; Damman et al. EHJ 2015

Nierfunctie tijdens decongestie





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McCallum et al. JACC HF 2020; Emmens et al. EJHF 2022

The decompensated patient – game on!

1. Start met adequate dosering lisdiureticum

2. Bepaal respons middels natriurese

3. Bij onvoldoende response: optimaliseer lisdiuretica/start combinatie diuretica therapie
    - Voor combinatie therapie acetazolamide eerste keus (ADVOR)

Tot slot: initiatie van GDMT tijdens hospitalisatie (PIONEER, EMPA RESPONSE) en recent STRONG HF

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Vragen?

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