ESC European Society of Cardiology

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POSITION PAPE

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

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DR.F.MIRBOLOOK

INTERVENTIONAL CARDIOLOGIST

Congestion in heart failure

Congestion in heart failure is defined as
signs and symptoms of extracellular fluid accumulation that result in increased cardiac filling pressures.

Filling pressures are the integrated result of the cardiac systolic and diastolic function, plasma volume, and venous capacitance/compliance.

Increased sympathetic output leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume.

This increases the effective circulating volume by redistribution, in a state where volume expansion is already present.

Venous capacitance function becomes compromised during states of longstanding venous congestion and/or increased sympathetic activation in acute heart failure

Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study in comparison to **serial clinical assessment**, despite signifcantly improving haemodynamics.

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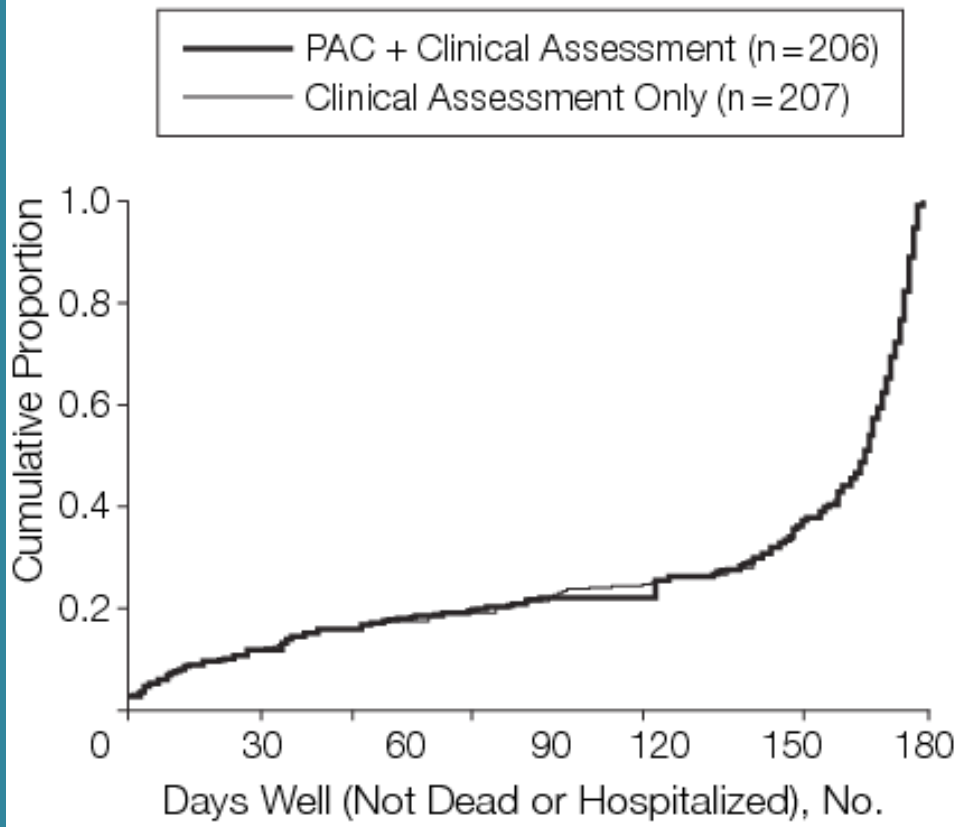
The diagnostic accuracy of non-invasive clinical and technical assessments of congestion has been validated against invasive haemodynamic evaluation and shown a variable sensitivity and specifcity (*Table 1*)



Cumulative proportion of patients contributing each possible numeric outcome for the number of days neither dead nor hospitalized during the 180 possible days of follow-up. Patients at the far left side of the curve represent early deaths, while those counted as 180 days survived for 6 months without rehospitalization. The curves for the treatment groups, pulmonary artery catheter (PAC) plus clinical assessment and clinical assessment only are superimposed.

Table 3. Impact of Interventions on Discharge Status*

	PAC Group (n = 215)			Clinical Assessment Group (n = 218)		
	Baseline	Discharge	Mean Change	Baseline	Discharge	Mean Change
Weight, kg	85.7 (21.8)	80.8 (20.3)	−4.0 (5.4)†	85.6 (20.3)	82.2 (20.4)	−3.4 (4.2)†
Systolic blood pressure, mm Hg	106 (17)	102 (15)	−4 (17)†	106 (15)	102 (15)	−4 (17)†
Estimated jugular venous pressure, mm Hg	12.1‡	6.7‡	45%†	12.5‡	7.3‡	42%†
Edema§	134 (67)	41 (20)	−93 (46)†	139 (68)	42 (21)	−97 (48)†
Creatinine, mg/dL‖	1.5 (0.6)	1.5 (0.6)	0.0 (0.4)	1.5 (0.6)	1.6 (0.9)	0.1 (0.8)†
Urea nitrogen, mg/dL	34 (21)	37 (21)	2 (18)	36 (24)	39 (23)	4 (21)†
Sodium, mEq/L	136.5 (4.4)	135.2 (3.9)	−1.3 (3.9)†	136.7 (4.4)	135.4 (4.6)	−1.4 (4.4)†
Symptom score (global)	43 (22)	68 (20)	25 (25)†	41 (21)	65 (20)	24 (24)†
Orthopnea (0-4 scale)	3.3 (1.1)	1.9 (1.0)	−1.4 (1.2)†	3.4 (1.0)	2.1 (1.1)	−1.2 (1.2)†

Abbreviation: PAC, pulmonary artery catheter.
SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; urea nitrogen to mmol/L, multiply by 0.357.
*Data are expressed as mean (SD) unless otherwise indicated.
†Significant ($P<.05$) change from baseline to discharge.
‡Indicates estimated geometric means assuming a grouped log normal distribution, all geometric SDs were 1.4.
§Edema refers to the number of patients with edema; change indicates the fraction improving from baseline to discharge.
‖Significant ($P<.05$) change between treatments.

Table 1 Sensitivity and specificity of different clinical and technical parameters to detect congestion

Parameter	Sensitivity	Specificity	Comparator	Comment
Clinical evaluation				
Right-sided				
JVP > 8 cm	48%	78%	RAP > 7 mmHg	Difficult in obese patient
Jugular venous reflux	50%	75%	RAP > 7 mmHg	Difficult in obese patient
Hepatomegaly	51%	62%	RAP > 7 mmHg	Difficult in obese patient, non-HF causes
Bilateral leg oedema	94%	10%	RAP > 7 mmHg	Non-HF oedema gives false positive
Left-sided				
Dyspnoea	50%	73%	PCWP > 18 mmHg	Multiple reasons for dyspnoea
Dyspnoea on exertion	66%	52%	PCWP > 18 mmHg	Multiple reasons for dyspnoea on exertion
Orthopnoea	66%	47%	PCWP > 18 mmHg	May be non-cardiac in origin or absent
S3	73%	42%	PCWP > 18 mmHg	Intra-observer variability
Rales	13%	90%	PCWP > 18 mmHg	May be non-cardiac in origin or absent
Echocardiographic evaluation				
Right-sided				
Collapse (< 50%) IVC	12%	27%	RAP > 7 mmHg	Difficult to use in positive pressure ventilated patients
Inspiratory diameter IVC < 12 mm	67%	91%	RAP > 7 mmHg	Cannot be used in positive pressure ventilated patients
Left-sided				
Mitral inflow E-wave velocity > 50 (cm/s)	92%	28%	PCWP > 18 mmHg	Difficult when fusion of E and A wave
Lateral E/e' > 12	66%	55%	PCWP > 18 mmHg	Less accurate in advanced heart failure and CRT
Deceleration time < 130 ms	81%	80%	PCWP > 18 mmHg	Difficult when fusion of E and A wave
Pulmonary vein S/D < 1	83%	72%	PCWP > 18 mmHg	Intra-observer variability in Doppler measurements of the vein
Diffuse B-lines on lung ultrasound[a]	85.7%	40%	PCWP > 18 mmHg	B-lines might be present in non-cardiac conditions

CRT, cardiac resynchronization therapy; HF, heart failure; IVC, inferior vena cava; JVP, jugular venous pulsation; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; S/D, systolic diastolic velocity.

[a]More than three B-lines in more than two intercostal spaces bilaterally.

Adapted from Gheorghiade,[22] Nagueh,[24] Mullens,[25] Parrinello[26] and Volpicelli.[27]

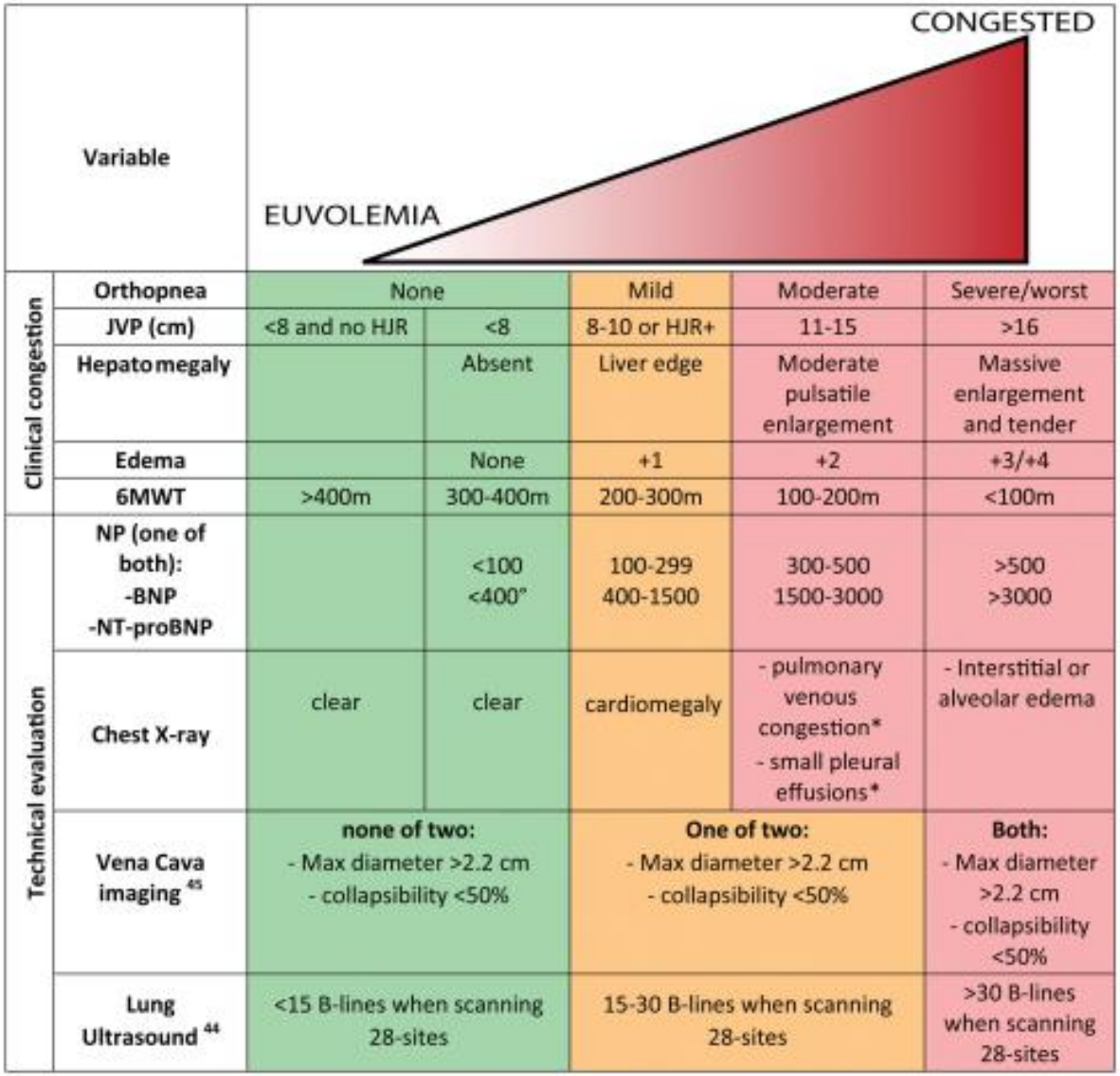
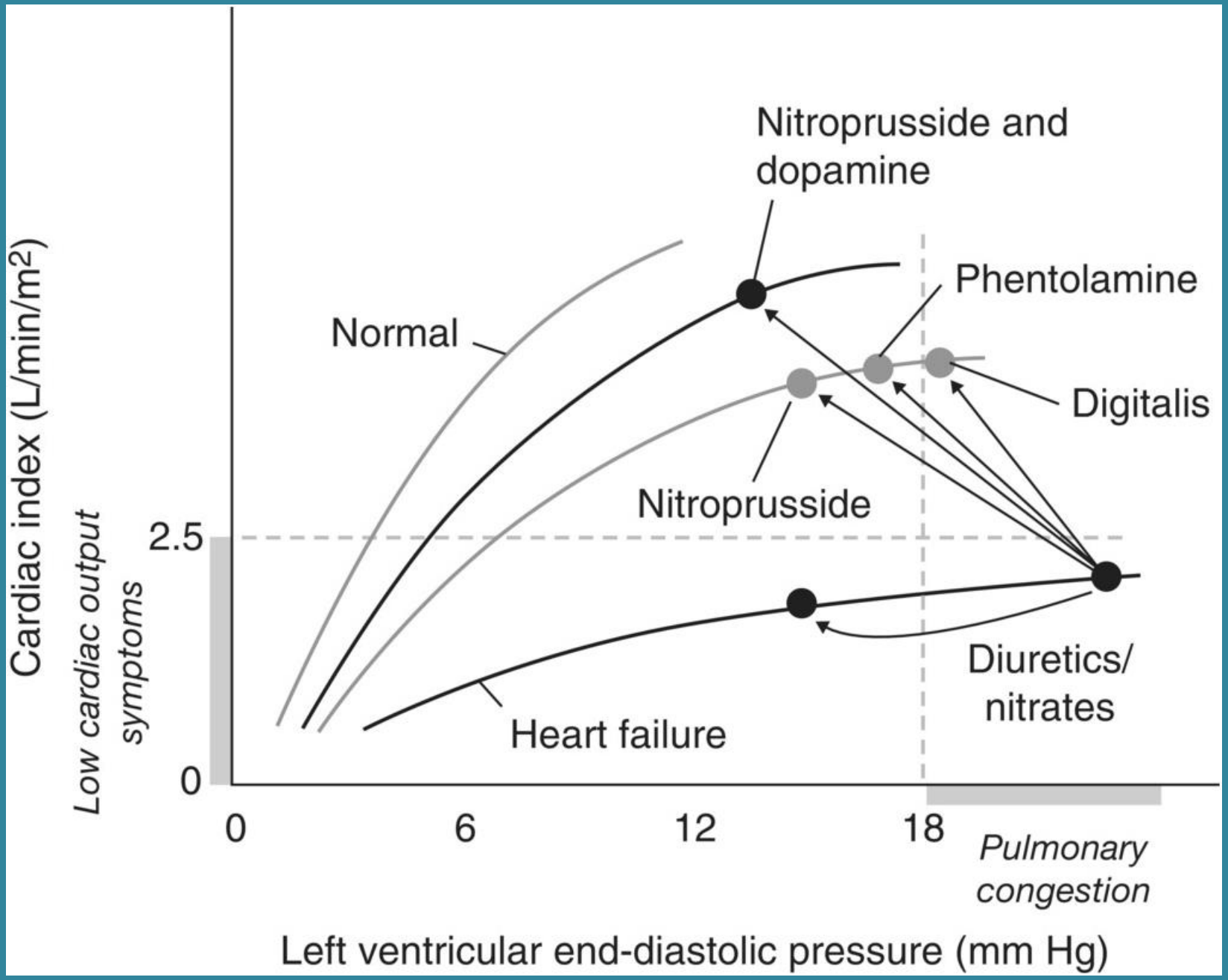


Figure 1 Integrative euvolaemia/congestion evaluation at discharge. 6MWT, 6-minute walk test; BNP, B-type natriuretic peptide; HJR, hepato-jugular reflux; HR, heart rate; JVP, jugular venous pulsation; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic


Nitroprusside and dopamine
Phentolamine
Normal
Digitalis
Nitroprusside
Diuretics/ nitrates
Heart failure
Cardiac index (L/min/m²)
Low cardiac output symptoms
2.5
0
0
6
12
18
Pulmonary congestion
Left ventricular end-diastolic pressure (mm Hg)

Mechanisms of action of diuretics in heart failure

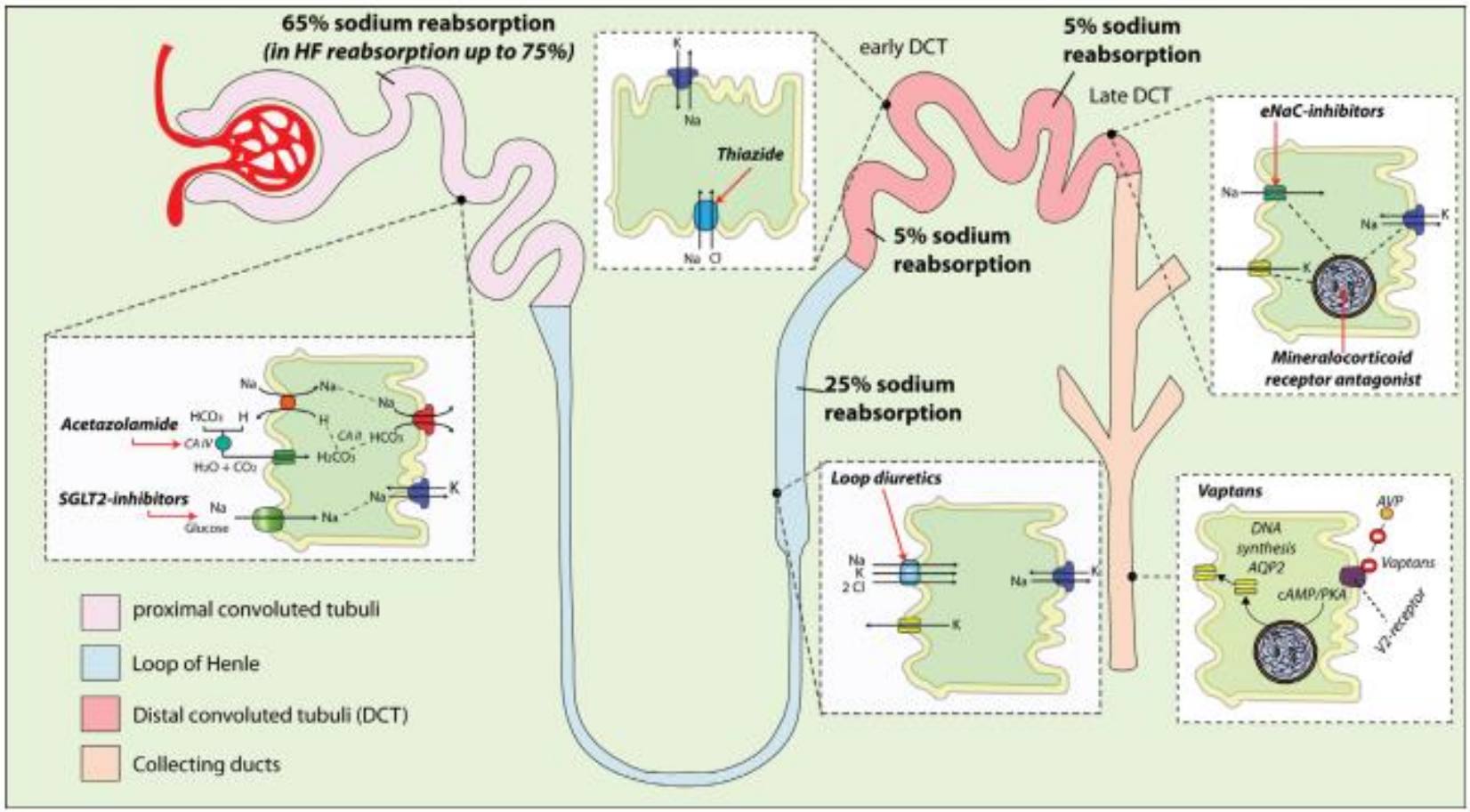


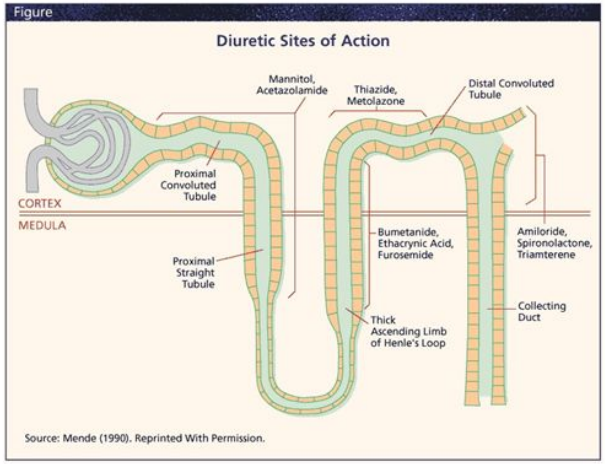
Figure 2 Sites and mode of action and effects on sodium reabsorption in the nephron of different diuretics. AQP2, aquaporin-2; AVP, arginine vasopressin; cAMP, cyclic adenosine monophosphate; eNaC, epithelial sodium channel; HF, heart failure; PKA, protein kinase A; SGLT2, sodium–glucose linked transporter-2.

The DOSE Trial

Diuretic Optimization Strategies Evaluation

DOSE Trial

- 308 patients with ADHF
- Low vs High Dose Furosemide
- Continuous vs a12 hour dosing



- Overall no significant difference among all groups
  - Patients symptoms
  - Creatinine
  - High Dose group had a greater diuresis with transient increases in creatinine

N Engl J Med. 2011 Mar 3;364(9):797-805.

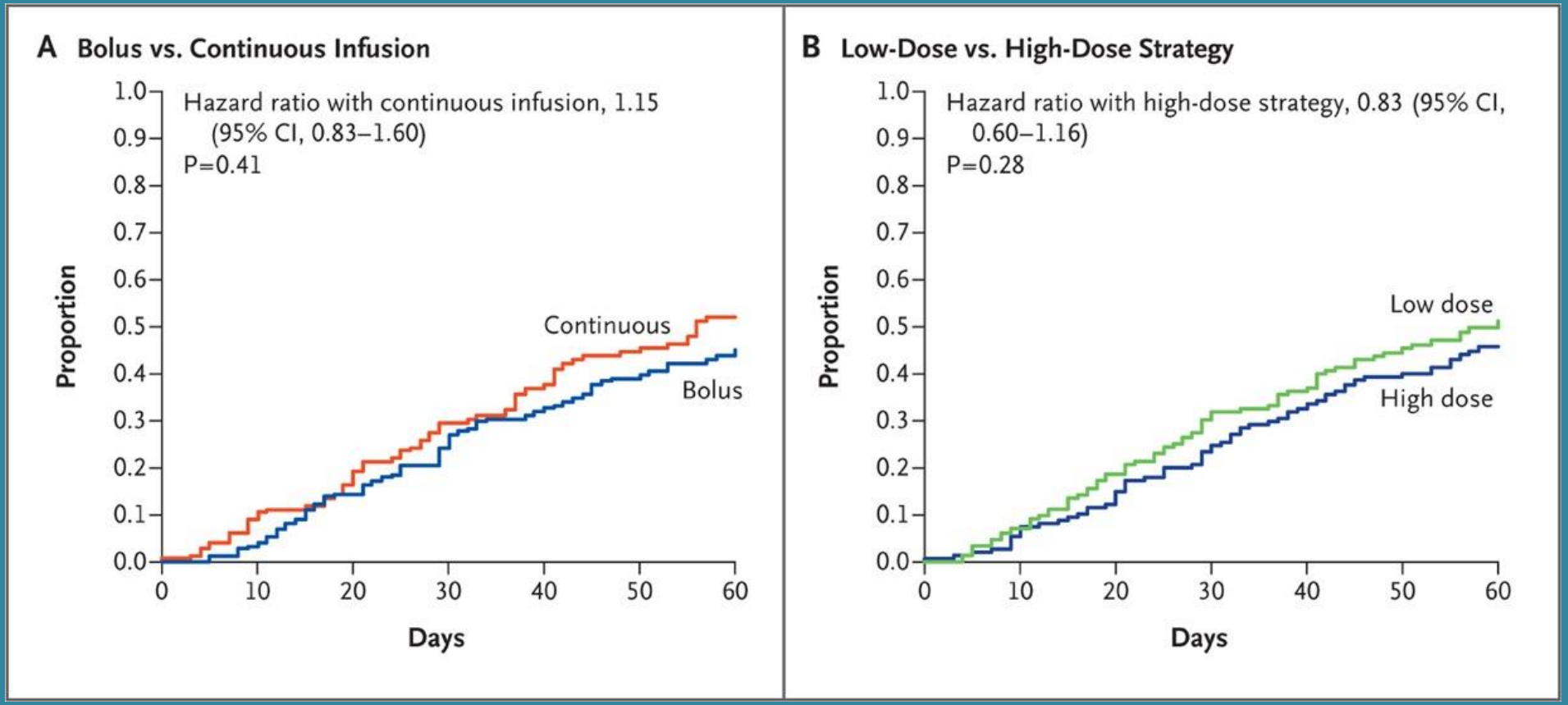


Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit. Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced Executive Committee, Trial Committees, Investigators and Coordinators

- In DAPA-HF, dapagliflozin improved outcomes in patients with heart failure and a reduced ejection fraction (with or without diabetes), largely those mild-to-moderate LV systolic dysfunction and increases in natriuretic peptides.

- In the **EMPEROR-Reduced trial**, we evaluated the effects of empagliflozin in a broad population of patients with chronic heart failure and a reduced ejection fraction (with and without diabetes) that was enriched for patients with more severe left ventricular systolic dysfunction and marked increases in natriuretic peptides.

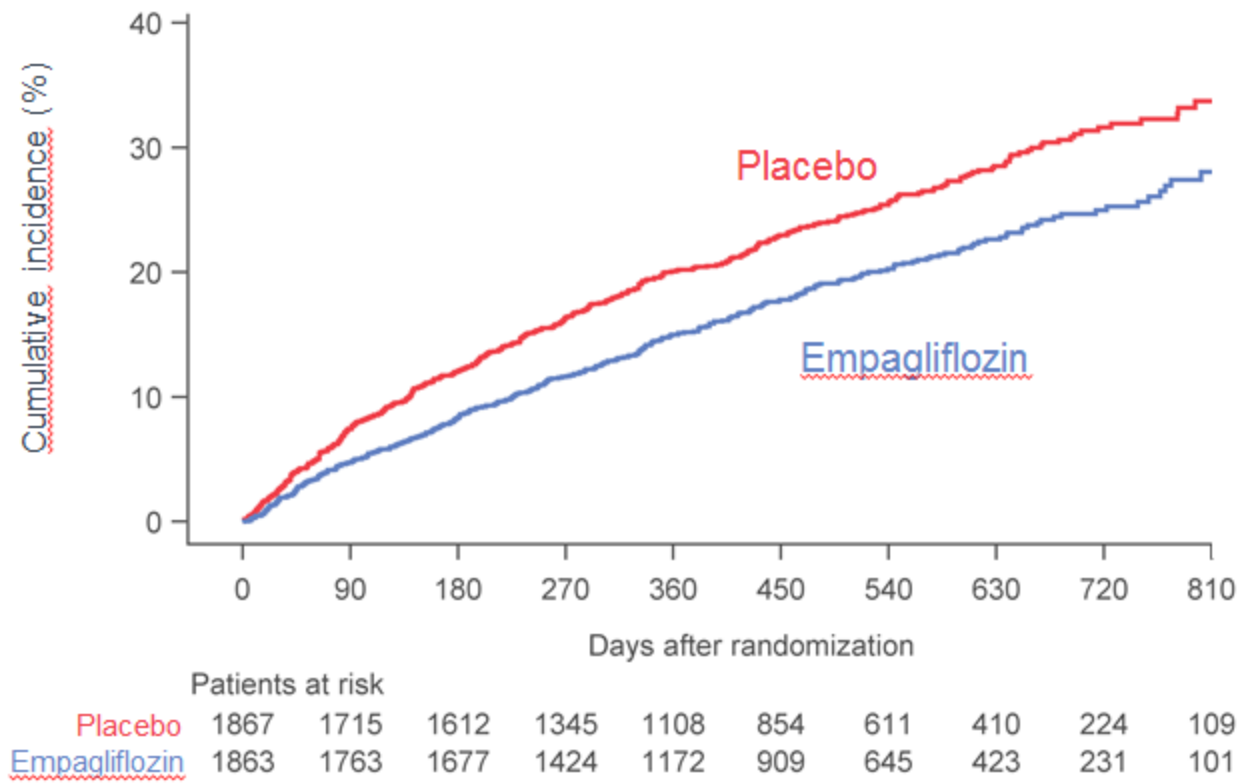
- Our goal was to enroll a patient population that was particularly enriched for those with an ejection fraction ≤ 30%. If the ejection fraction was > 30%, eligible patients were required to show very high levels of NTproBNP or a hospitalization for heart failure within 12 months.

- Eligible patients were randomized double-blind (1:1 ratio) to empagliflozin 10 mg once daily or placebo, in addition to their usual therapy.

EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

Primary Endpoint Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
First Secondary Endpoint Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
Second Secondary Endpoint Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)

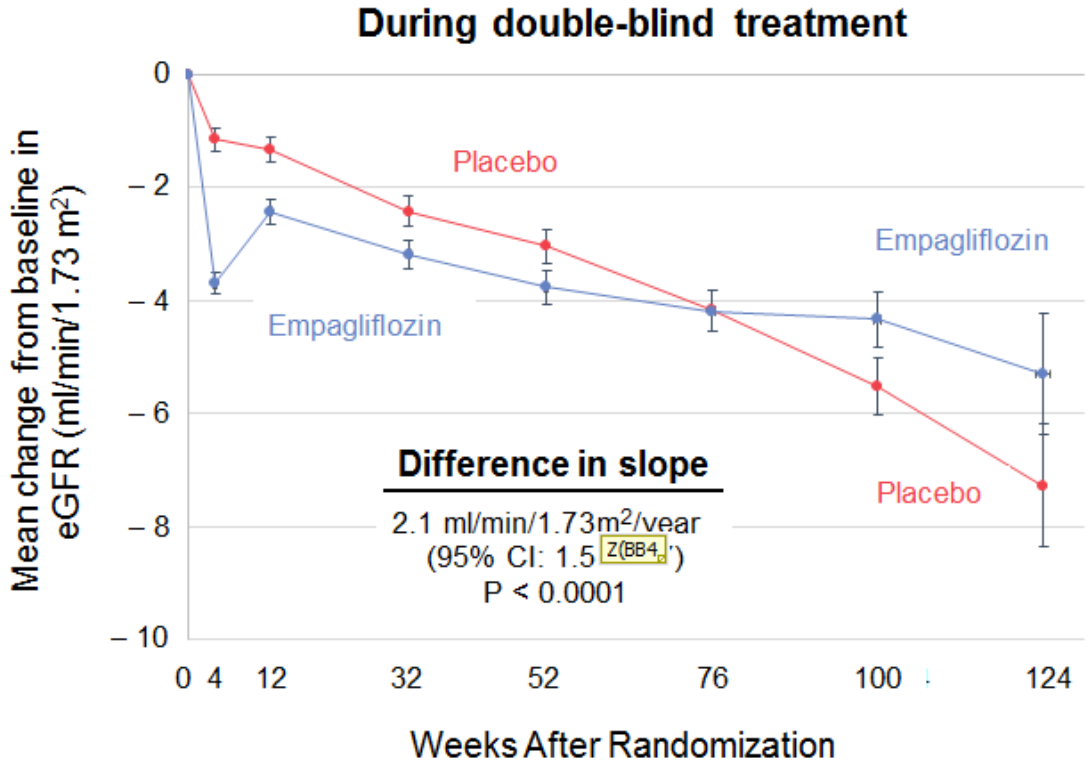


462 patients with event
Rate: 21.0/100 patient-years

361 patients with event
Rate: 15.8/100 patient-years

HR 0.75
(95% CI 0.65, 0.86)
P < 0.0001

EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint



In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

– 4.2 ml/min/1.73 m² on placebo

– 0.9 m/min/1.73 m² on empagliflozin

P < 0.0001

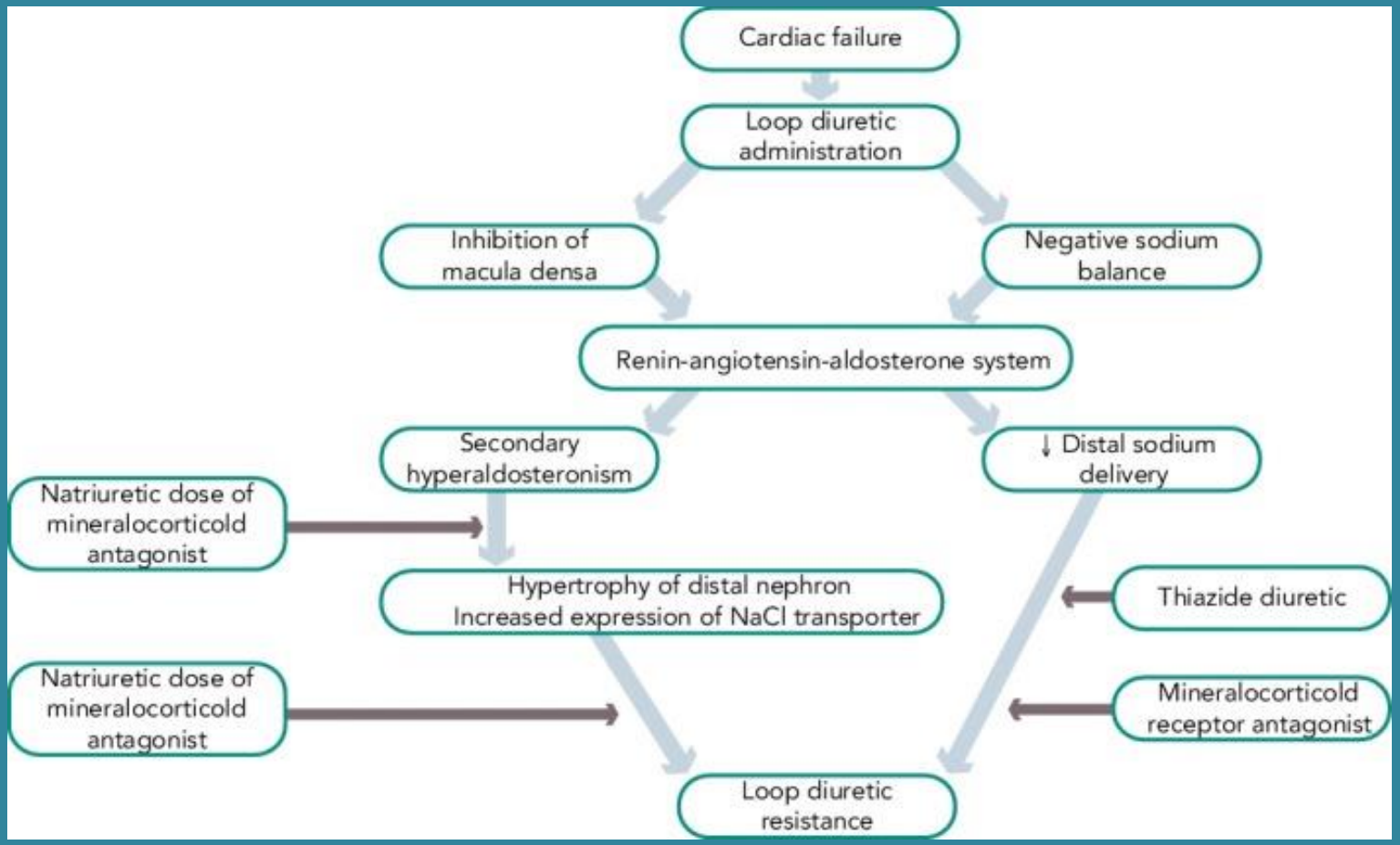
Diuretic response and resistance in heart failure

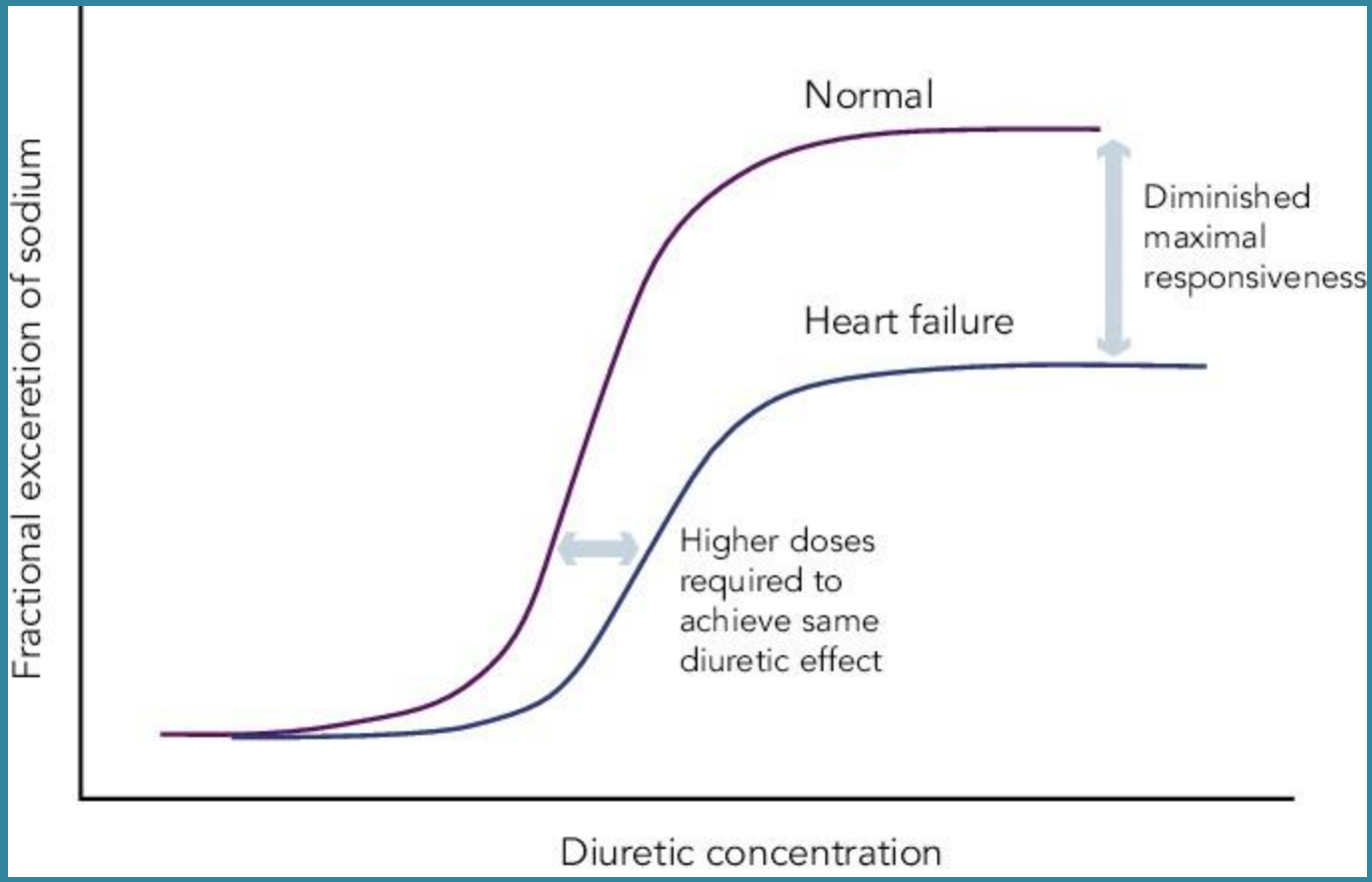
Urinary sodium content has recently experienced a renewed interest as an **indicator for diuretic response**

In addition to measuring sodium in a Continuous urinary collection, a **spot urine sample 1–2 h** following loop diuretic administration has recently demonstrated an excellent correlation with total urine sodium output in a 6 h urine collection.

Despite persistent increased urinary volume output (diuresis), **renal sodium output (natriuresis) diminishes over time.** Therefore, increasingly hypotonic urine is produced during consecutive days of loop diuretic therapy, which might relate to numerous factors including altered renal haemodynamics, differential substrate delivery (sodium and/or diuretics), neurohormonal factors and structural kidney alterations.

The pathophysiology of **diuretic resistance** is multi-factorial and involves sympathetic nervous system activation, renin– angiotensin–aldosterone system (RAAS) activation, nephron remodelling, pre-existing renal function alterations, disrupted pharmacokinetics and dynamics of diuretics and intravascular fluid depletion due to slow plasma refilling





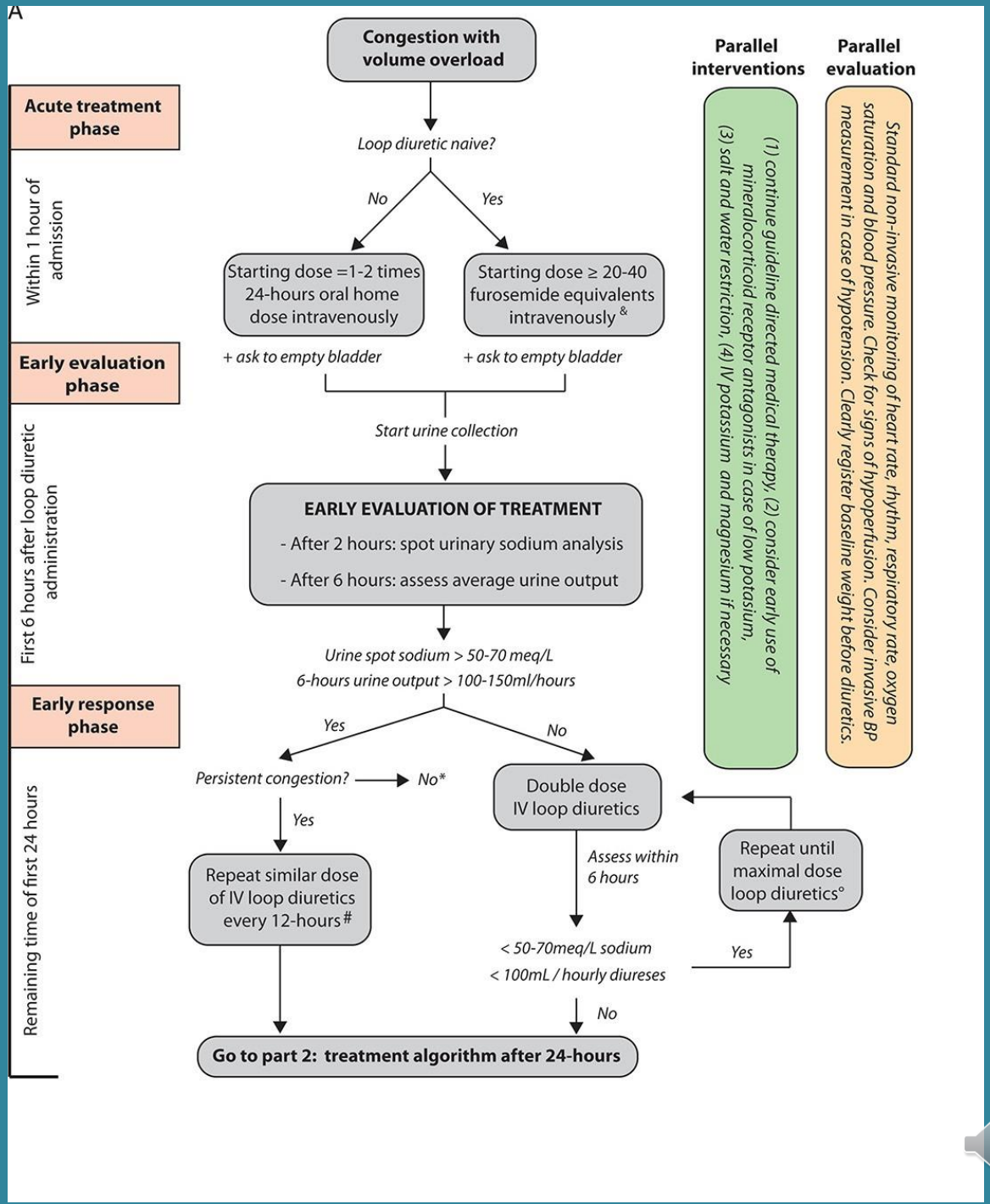
Schematic of a Dose-response Curve of Loop Diuretics in Heart Failure Patients Compared with Controls

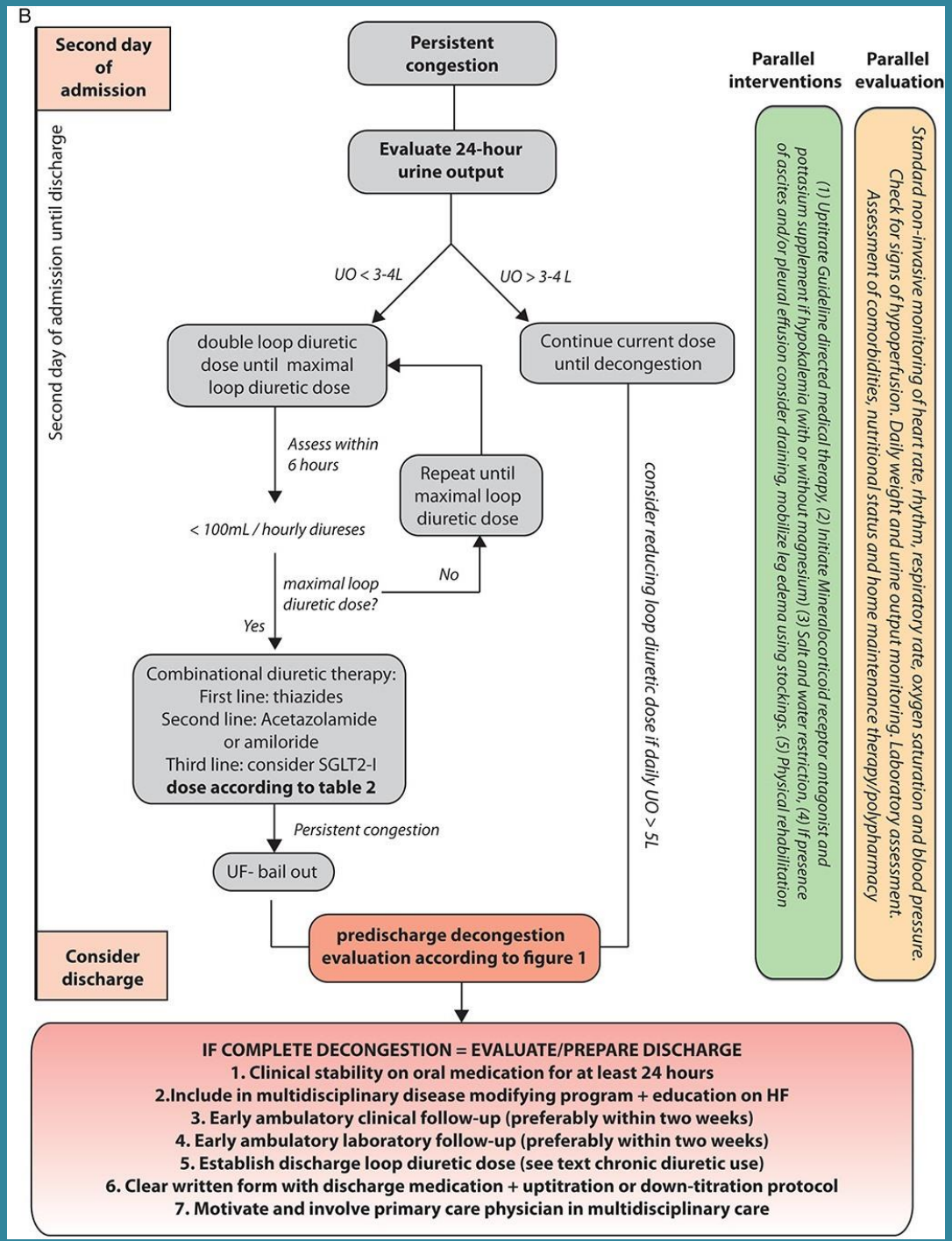
Table 2 Pharmacology of diuretics

	Acetazolamide	Loop diuretics	Thiazide-like diuretics	MRA[a]	Amiloride
Site of action	Proximal nephron	Ascending loop of Henle	Early distal convoluted tubule	Late distal tubuie	Late distal tubule
Starting dose/usual chronic dose	Oral: 250–375 mg Intravenous: 500 mg	Furosemide: 20–40/40–240 mg[b] Bumetanide: 0.5–1.0/1–5 mg[b] Torsemide: 5–10/10–20 mg[b]	HCTZ: 25/12.5–100 mg[c] Metolazone: 2.5/2.5–10 mg[c] Chlorthalidone: 25/25–200 mg[c] Chlorothiazide: 500–1000 mg (IV formulation available)	Spironolactone: 25/25–50 mg Eplerenone: 25/25–50 mg Potassium canrenoate: 25–200 mg/not for chronic use	5/10 mg
Maximum recommended total daily dose	Oral: 500 mg 3x/day Intravenous: 500 mg 3x/day	Furosemide: 400–600 mg Bumetanide: 10–15 mg Torsemide: 200–300 mg	HCTZ: 200 mg Metolazone: 20 mg Chlorthalidone: 100 mg Chlorothiazide: 1000 mg	50–100 mg (doses up to 400 mg are used in hepatology)	20 mg
Half-life	2.4–5.4 h	Furosemide: 1.5–3.0 h Bumetanide: 1–1.5 h Torsemide: 3–6 h	HCTZ: 6–15 h Metolazone: 6–20 h Chlorthalidone: 45–60 h	Canrenone: 16.5 h[d] Eplerenone: 3–6 h	Normal GFR: 6–9 h GFR < 50 mL/min: 21–144 h
Onset	PO: 1 h IV: 15–60 min	PO: 0.5–1 h[e] IV: 5–10 min[e] SC: 0.5 h[e]	PO: 1–2.5 h IV: Chlorothiazide is IV available, onset action: 30 min	PO: 48–72 h[d] IV: potassium canrenoate; 2.5 h	PO: 2 h IV: not available
Oral bioavailability	Absorption is dose-dependent, dose >10 mg/kg exhibit variable uptake	Furosemide: 10–100% Bumetanide: 80–100% Torsemide: 80–100%	HCTZ: 65–75% Metolazone: 60–65%[f] Chlorthalidone: unknown Chlorothiazide: 9–56%	Spironolactone: ~90% Eplerenone: 69%	30–90%
Enteral absorption affected by food	May be taken with food. Food decreases symptoms of GI upset.	Furosemide: yes (slowed) Bumetanide: yes (slowed) Torsemide: no	HCTZ: unknown Metolazone: unknown Chlorthalidone: unknown	Spironolactone: bioavailability increase with high fat food Eplerenone: unknown	Unknown
Potency (FENa%)[g]	4%	20–25%[e]	5–8%	2%	2%

FENa, fractional excretion of sodium; GFR, glomerular filtration rate; GI, gastrointestinal; HCTZ, hydrochlorothiazide; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; PO, per oral; SC, subcutaneous.
Diuretic agents are reflected from the site of action; from proximal nephron to distal nephron.
[a]Minimal diuretic effect.
[b]Dose of intravenous and oral loop diuretics are similar.
[c]Only PO use in acute HF, thiazides are not recommended for daily ambulatory use in chronic stable HF.

Flowchart to diuretic use in acute heart failure. (*A*) Congestion with volume overload. (*B*) Treatment algorithm after 24 h. Total loop diuretic dose can be administered either as continuous infusion or bolus infusion. Higher dose should be considered in patients with reduced glomerular fltration rate. *Consider other reasons for dyspnoea given the quick resolution of congestion. ◦The maximal dose for IV loop diuretics is generally considered furosemide 400–600 mg or 10–15 mg bumetanide. #In patients with good diuresis following a single loop diuretic administration, once a day dosing can be considered.




B
Second day of admission
Second day of admission until discharge
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
consider reducing loop diuretic dose if daily UO > 5L
predischarge decongestion evaluation according to figure 1
Consider discharge
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


Thank You
For Your Atten