Current conservative treatment of HF - CKD

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The cross-talk between chronic kidney disease and congestive heart failure

Cardiorenal syndrome: definition and classification

General Definition of Cardiorenal Syndromes
Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.

Acute Cardiorenal Syndrome (Type 1)
Acute worsening of cardiac function leading to decreased kidney function.

Chronic Cardiorenal Syndrome (Type 2)
Long-term abnormalities in cardiac function leading to decreased kidney function.

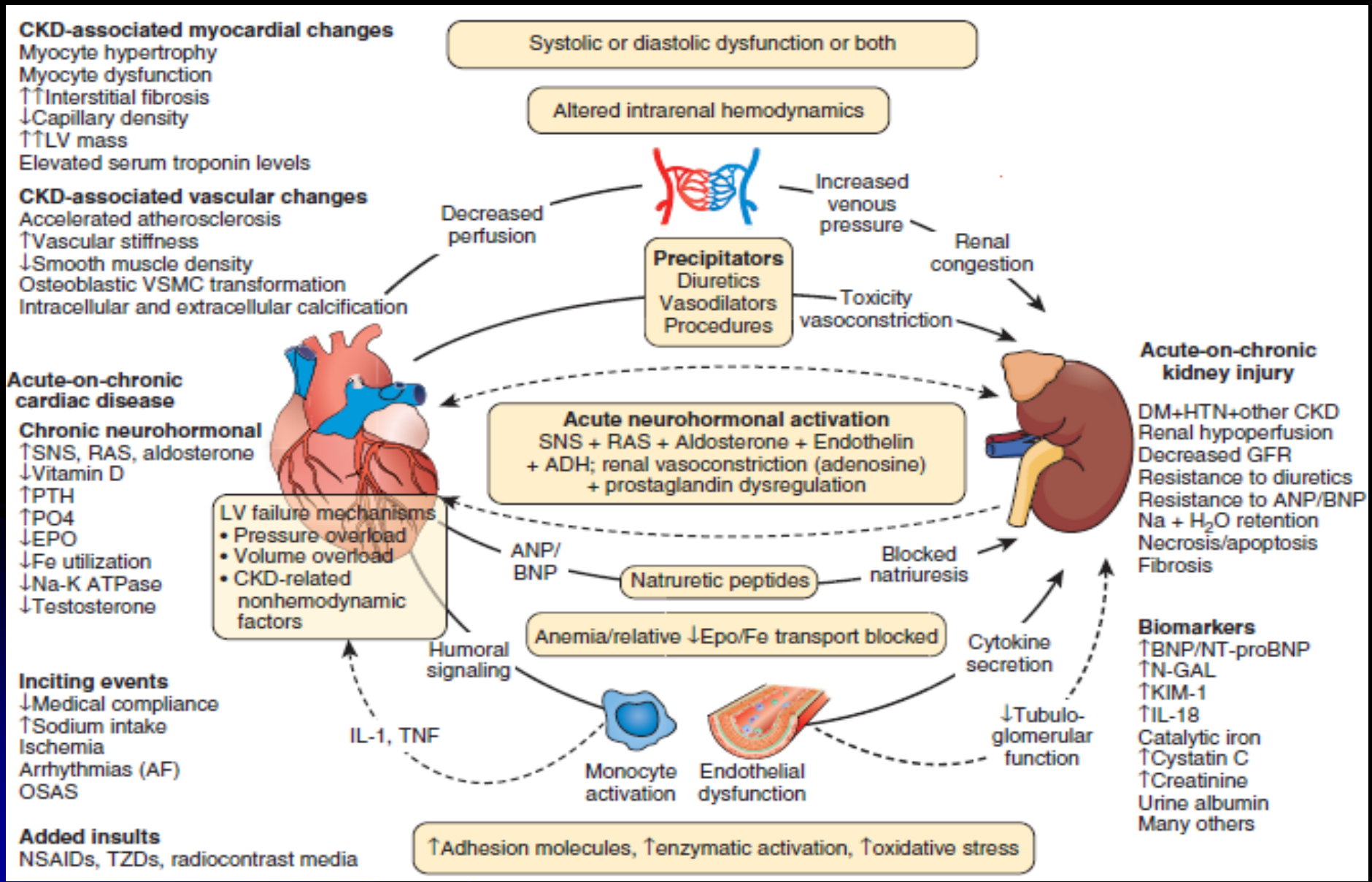
Acute Renocardiac Syndrome (Type 3)
Acute worsening of kidney function causing cardiac dysfunction.

Chronic Renocardiac Syndrome (Type 4)
Long-term abnormalities in kidney function leading to cardiac disease.

Secondary Cardiorenal Syndromes (Type 5)
Systemic conditions causing simultaneous dysfunction of the heart and kidney.

House A. Am J Kidney Dis 2018; 72:284-295.

Cardiorenal syndrome: pathophysiology



Comprehensive Clinical Nephrology 5th Edition.

Prevalence of CKD in patients with HFrEF and HFpEF

Stages of CKD					Levels of Kidney Dysfunction			
		Prevalence				Distribution		
Stage	Description	General Population	HFREF*	HFPEF	GFR (ml/min/1.73 m^2)	General Population	HFREF	HFPEF
1	Kidney damage with normal or ↑ GFR	3.3	2.8	NA	≥90	64.3	8.2	8.2
2	Kidney damage with mild ↓ GFR	3.0	10.6	NA	60–89	31.2	37.2	34.9
3	Moderate ↓ GFR	4.3	45.5	46.1	30–59	4.3	45.5	46.1
4	Severe ↓ GFR	0.2	7.8	8.1	15–29	0.2	7.8	8.1
5	Kidney failure	0.2	1.3	2.7	<15 (or dialysis)	0.2	1.3	2.7
	Albuminuria				**UACR (mg/g creatinine)**			
	Normo-albuminuria				M <17/F <25†	88.3	66.2	60.2
	Micro-albuminuria				M 17–250/F 25–355†	10.6	25.4	28.5
	Macro-albuminuria				M >250/F >355†	1.1	8.4	11.3

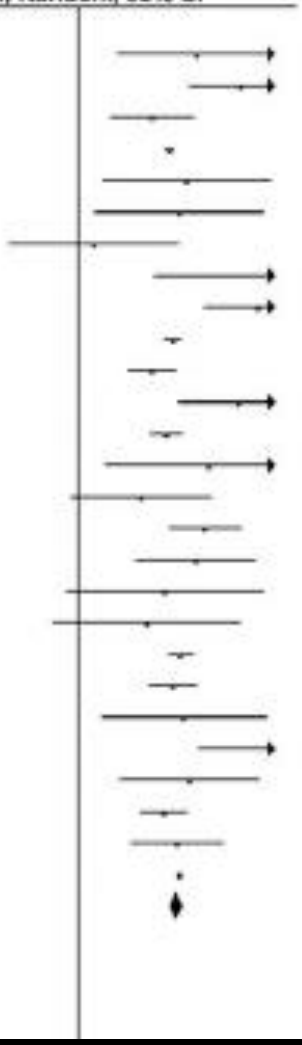
Damman K, et al. J Am Coll Cardiol 2014; 63:853-871.

Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis

Study or Subgroup	CKD Events	CKD Total	no CKD Events	no CKD Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Acute Heart Failure							
Madsen	22	44	38	146	0.7%	2.84 [1.42, 5.71]	1994
Akhter (VMAC)	80	215	33	266	1.2%	4.18 [2.65, 6.61]	2004
Aronson	112	284	65	257	1.6%	1.92 [1.33, 2.78]	2004
Smith (NHCP)	8948	17207	11869	36433	3.4%	2.24 [2.16, 2.33]	2005
Anwaruddin (PRIDE)	17	207	13	392	0.6%	2.61 [1.24, 5.48]	2006
Pimenta	13	44	35	239	0.6%	2.44 [1.17, 5.12]	2007
Petretta	15	51	27	102	0.6%	1.16 [0.55, 2.44]	2007
Filippatos	17	145	3	157	0.2%	6.62 [1.95, 23.79]	2007
Lassus (FINN-AKVA)	94	240	28	240	1.2%	4.87 [3.04, 7.81]	2007
Heywood (ADHERE)	3731	75382	949	43083	3.3%	2.31 [2.15, 2.49]	2007
Patel (GWTG-HF)	384	10074	111	5486	2.5%	1.92 [1.55, 2.38]	2008
Klein (OPTIME-CHF)	69	468	19	469	1.0%	4.10 [2.42, 6.93]	2008
Amsalem	759	2145	331	1648	2.9%	2.18 [1.88, 2.53]	2008
Takagi	14	75	8	119	0.4%	3.18 [1.27, 8.02]	2009
Campbell	32	119	21	121	0.8%	1.75 [0.94, 3.26]	2009
Hamaguchi (JCARE-CARD)	300	1139	50	478	1.8%	3.06 [2.22, 4.22]	2009
Kimura	61	386	20	323	1.0%	2.83 [1.67, 4.79]	2009
Manzano-Fernandez	17	66	10	72	0.5%	2.15 [0.90, 5.12]	2009
Martin-Pfitzenmeyer	28	41	34	63	0.5%	1.84 [0.81, 4.19]	2009
Velavan (Euro HF Survey)	704	3398	700	7303	3.1%	2.47 [2.20, 2.76]	2010
Harjola	165	491	446	2488	2.5%	2.30 [1.86, 2.85]	2010
Vaz Perez	28	54	22	74	0.6%	2.55 [1.23, 5.28]	2010
Carrasco	53	99	17	99	0.7%	5.56 [2.89, 10.70]	2011
Manzano - Fernandez	31	74	31	146	0.8%	2.67 [1.45, 4.92]	2011
Blair (EVEREST)	353	1055	184	966	2.5%	2.14 [1.74, 2.62]	2011
Tarantini (IS-AHF)	104	592	34	416	1.4%	2.39 [1.59, 3.61]	2011
Kao	11847	163402	13383	433054	3.4%	2.45 [2.39, 2.51]	2011
Subtotal (95% CI)		**277499**		**534640**	**39.5%**	**2.39 [2.25, 2.54]**	
Total events	27998		28483				

Heterogeneity: Tau² = 0.01; Chi² = 60.36, df = 26 (P = 0.0001); I^2 = 57%

Test for overall effect: Z = 28.65 (P < 0.00001)



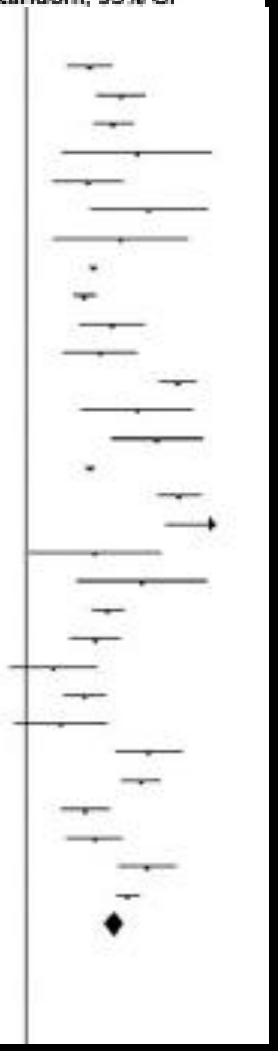
Damman K, et al. Eur Heart J 2014; 35:455-469.

Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis

Study or Subgroup	CKD Events	CKD Total	no CKD Events	no CKD Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Chronic Heart Failure							
Dries (SOLVD Prevention)	167	757	397	2915	2.5%	1.80 [1.47, 2.20]	2000
Hillege (PRIME II)	286	933	146	933	2.4%	2.38 [1.90, 2.98]	2000
Dries (SOLVD Treatment)	363	772	397	1389	2.7%	2.22 [1.85, 2.66]	2000
Marenzi	34	56	33	92	0.7%	2.76 [1.39, 5.48]	2001
McLellan	113	252	130	413	1.8%	1.77 [1.28, 2.45]	2002
Muntwyler	34	118	34	293	1.0%	3.08 [1.81, 5.27]	2002
Pulignano (IN-CHF)	16	47	292	1638	0.8%	2.38 [1.28, 4.41]	2002
Herzog	7083	16633	38104	133367	3.4%	1.85 [1.79, 1.92]	2004
Shlipak (DIG)	1309	3157	1066	3843	3.2%	1.71 [1.55, 1.89]	2004
McAllister	207	419	103	335	1.9%	2.20 [1.63, 2.97]	2004
Bibbins-Domingo (HERS)	159	425	69	297	1.7%	1.98 [1.42, 2.76]	2004
Ezekowitz (APPROACH)	438	2513	196	3914	2.7%	4.00 [3.36, 4.78]	2004
Shlipak (CHS)	107	140	75	139	1.0%	2.77 [1.66, 4.62]	2005
Rolk	67	148	70	350	1.4%	3.31 [2.18, 5.02]	2006
Go (ANCHOR)	11700	24473	10676	31694	3.4%	1.80 [1.74, 1.87]	2006
Hillege (CHARM)	330	966	195	1714	2.5%	4.04 [3.31, 4.94]	2006
Bruch	66	135	17	134	0.8%	6.58 [3.58, 12.12]	2007
Shalaby	49	209	17	121	0.8%	1.87 [1.02, 3.43]	2008
Scrutinio	48	138	20	128	0.8%	2.88 [1.59, 5.21]	2009
Anand (VALHEFT)	703	2916	273	2094	2.8%	2.12 [1.82, 2.47]	2009
Cohen-Solal (SENIORS)	163	704	194	1408	2.3%	1.89 [1.50, 2.38]	2009
Alehagen	76	235	62	229	1.4%	1.29 [0.86, 1.92]	2009
Wali	414	2566	166	1651	2.6%	1.72 [1.42, 2.08]	2010
Hebert	34	338	72	963	1.3%	1.38 [0.90, 2.12]	2010
Damman (COACH)	229	619	69	430	1.9%	3.07 [2.26, 4.17]	2010
Waldum	547	1080	305	1155	2.7%	2.86 [2.40, 3.41]	2010
Damman (CIBIS II)	162	833	220	1797	2.4%	1.73 [1.39, 2.16]	2010
Filippatos (BEST)	160	397	226	863	2.2%	1.88 [1.46, 2.42]	2011
Scrutinio (2011)	237	422	157	529	2.1%	3.04 [2.32, 3.97]	2011
Masson (GISSI-HF)	1035	2566	918	4369	3.1%	[illegible]	[illegible]
Subtotal (95% CI)		**64967**		**198998**	**60.5%**	**2.26 [2.08, 2.47]**	
Total events	26336		54701				

Heterogeneity: Tau² = 0.04; Chi² = 255.62, df = 29 ($P < 0.00001$); I^2 = 89%

Test for overall effect: $Z = 18.68$ ($P < 0.00001$)



Damman K, et al. Eur Heart J 2014; 35:455-469.

Albuminuria as a risk marker for HF

Albuminuria as a Risk Marker for HF

- Progressive continuous relationship with HF
- Prediction power outperforms creatinine based eGFR in HF
- Enhances HF risk prediction models
- Regression of albuminuria associated with reduced risk of HF
- Marker of early kidney damage
- Cost-effective metric to denote CV risk profile

Albuminuria in Progression of HF

- **SOLVD Trial**
  - ↑Albuminuria → ↑1.8 x risk of HHF
- **CHARM Trial**
  - ↑Albuminuria → ↑30-70% risk of HHF
- **GISSI-HF and CHARM Trials**
  - Strong independent predictor of adverse prognosis in HF irrespective of HTN or T2DM

Albuminuria in HF

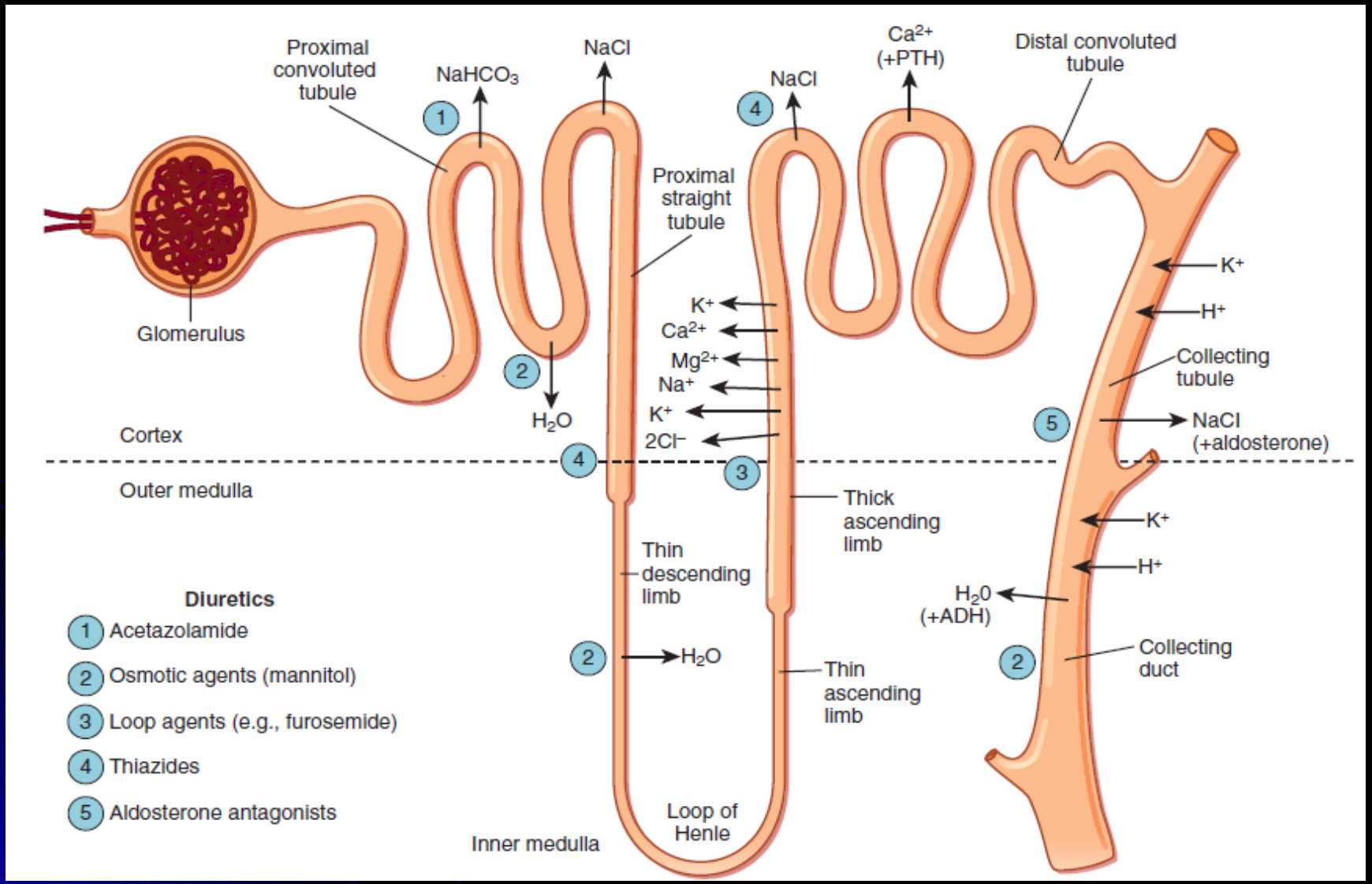
Albuminuria Predicts Risk of Incident HF

- **RENAAL Trial**
  - ↑Albuminuria → ↑2.7 x risk of incident HF
- **FHS Study**
  - ↑Albuminuria → ↑1.7 x risk of incident HF
- **MESA Study**
  - ↑Albuminuria → ↑2.7 x risk of incident HF
- **ARIC Study**
  - ↑Albuminuria → ↑2.5 x risk of incident HF

Khan MS, et al. J Am Coll Cardiol 2023; 81: 270-272.

Principles of diuretic therapy – pharmacokinetic properties of diuretics

Sites of sodium reabsorption and diuretic action



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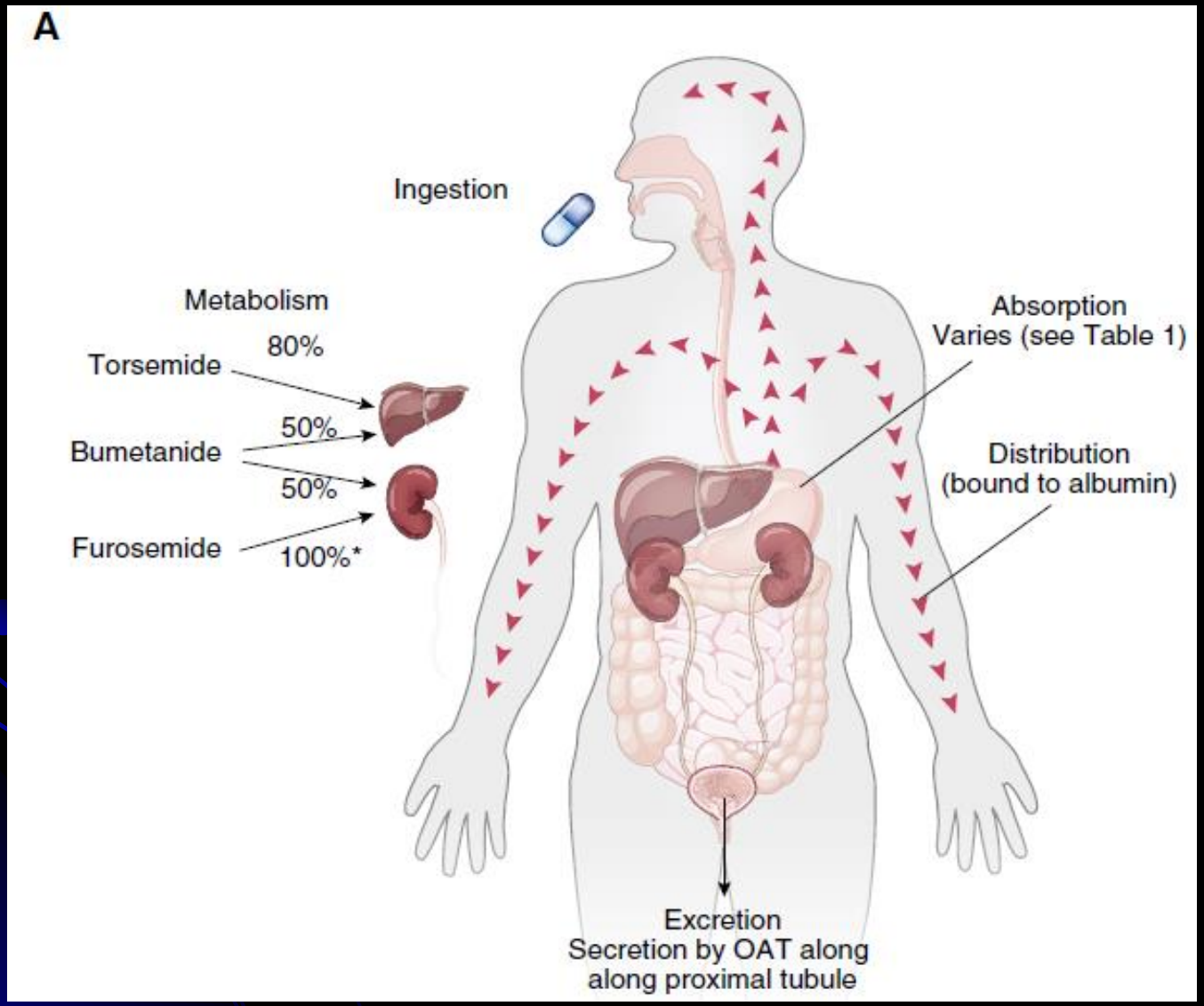
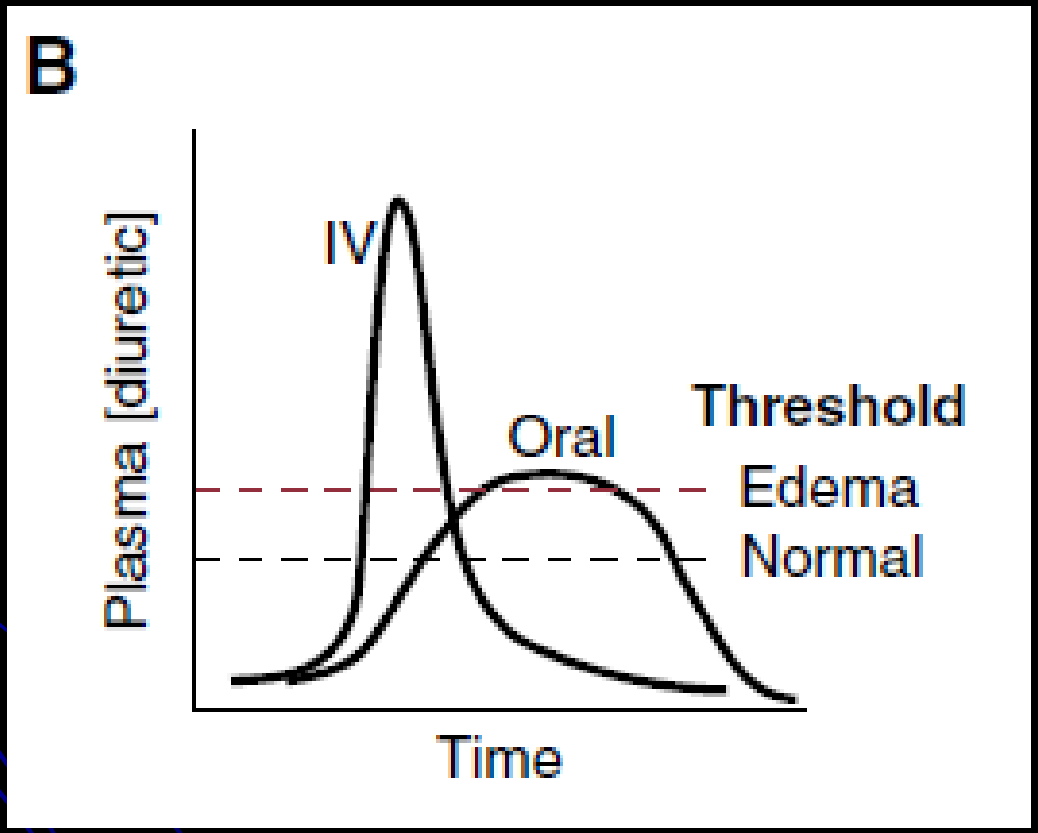
Features of absorption, distribution, metabolism and excretion of diuretics



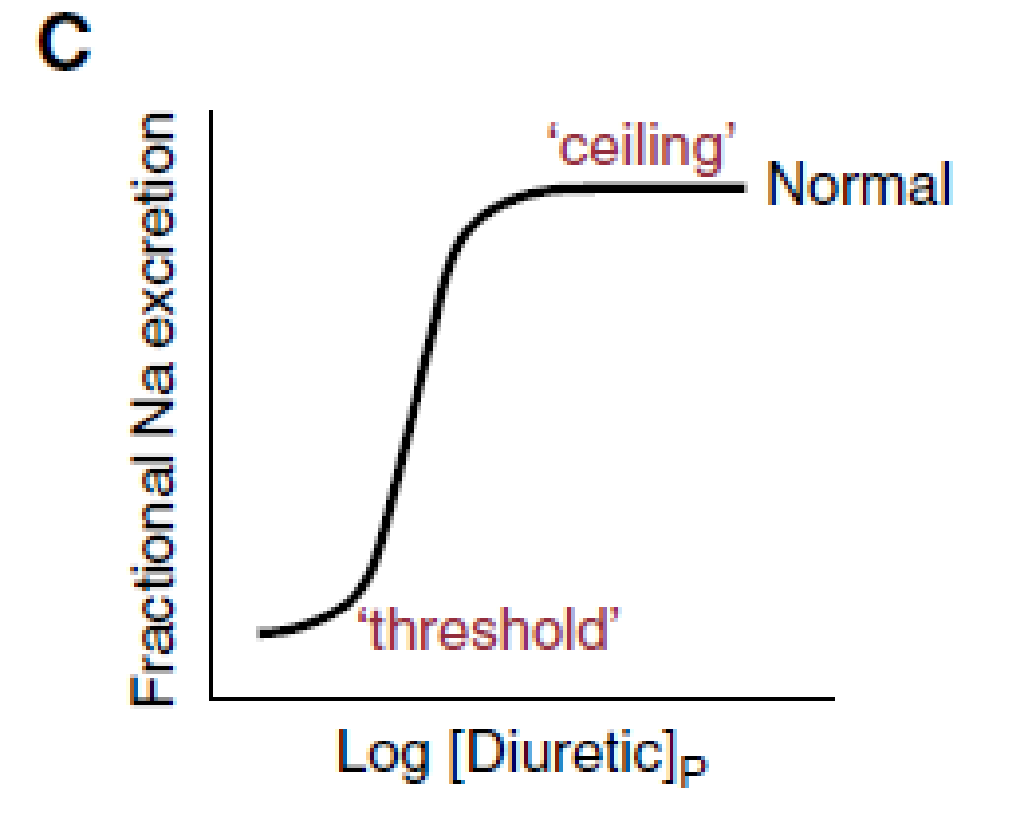
Ellison DH. Clin J Am Soc Nephrol 2019; 14:1248-57.

Plasma diuretic concentration versus time



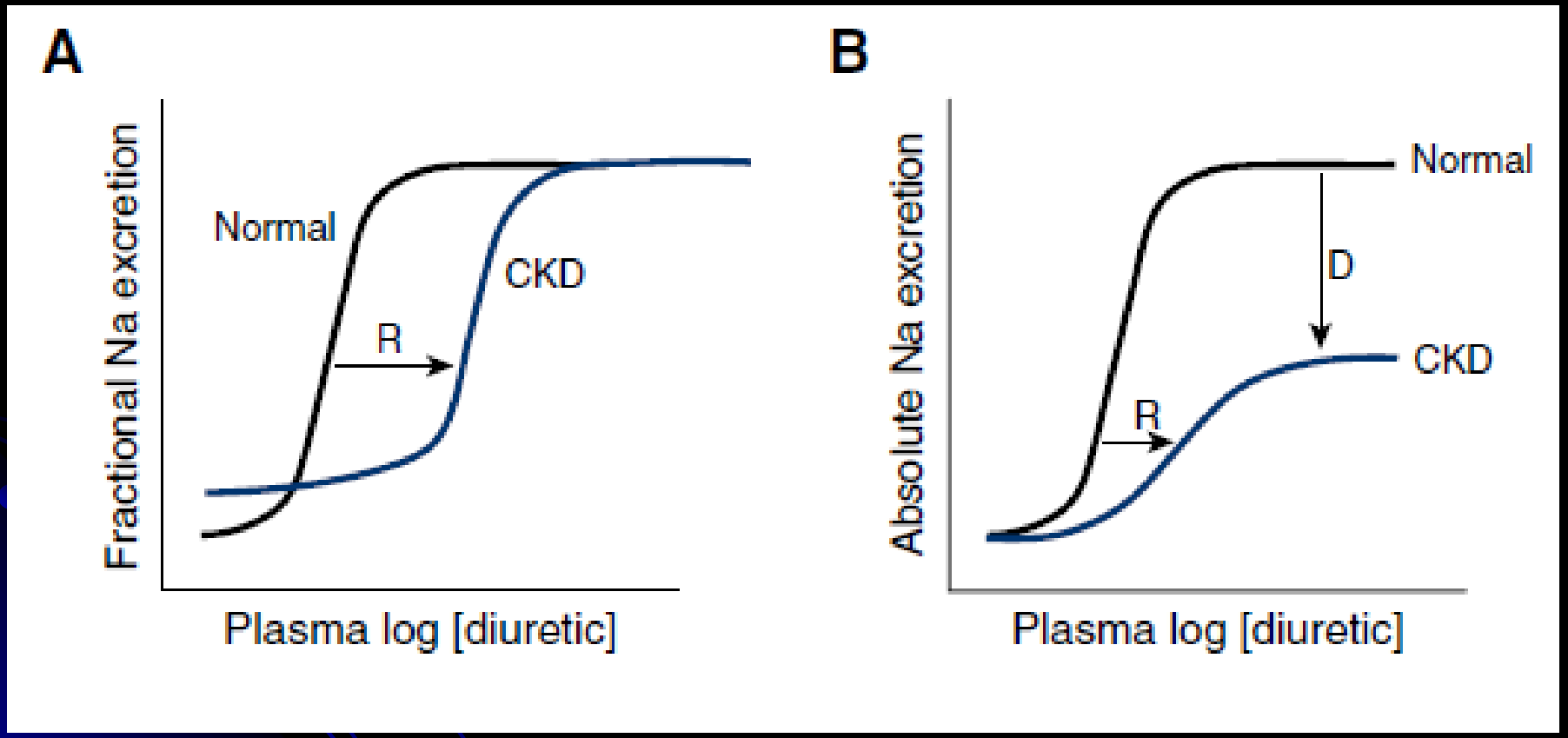
Ellison DH. Clin J Am Soc Nephrol 2019; 14:1248-57.

Dose-response curve for loop diuretic plasma concentration



Ellison DH. Clin J Am Soc Nephrol 2019; 14:1248-57.

Effect of CKD on pharmakodynamic of diuretic action



Ellison DH. Clin J Am Soc Nephrol 2019; 14:1248-57.

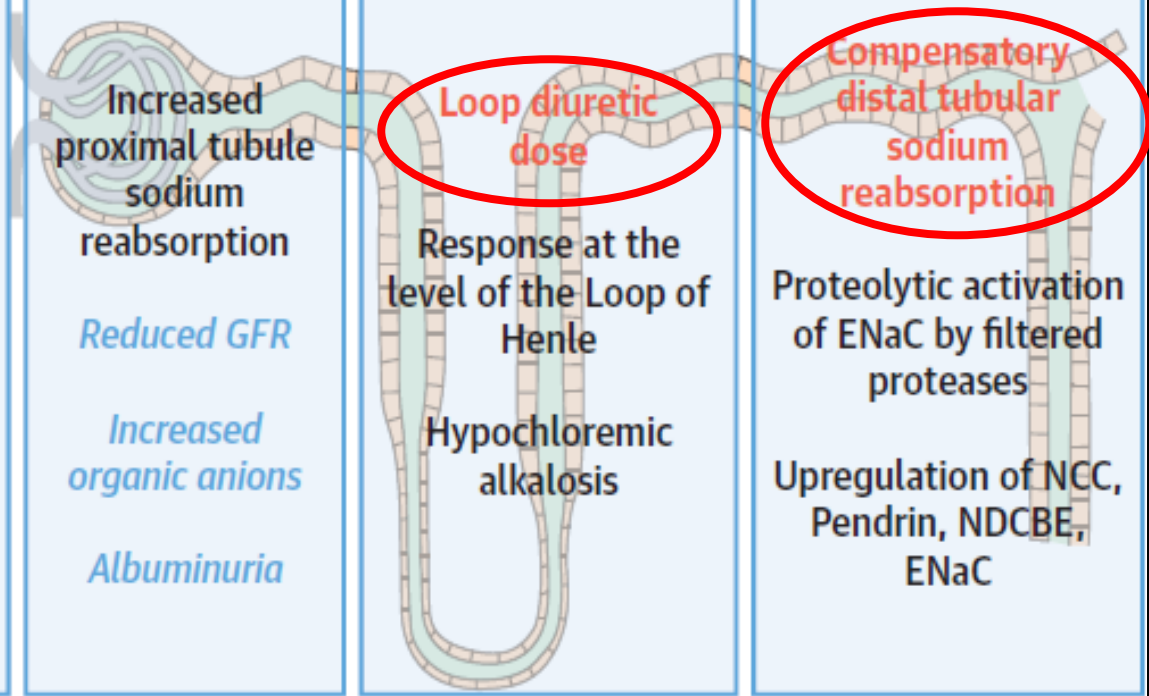
Pharmacokinetics of commonly used diuretics

Diuretic	Bioavailability	Equivalent Dose, mg	Metabolism (Kidney/Liver)	Elimination $t_{1/2}$, h			
				Normal	CKD	CHF	ESLD
Loop							
Furosemide	50%-60% (10%-100%)[a]	40	100%/0%	1.5-2	2.6-2.8	2.7	2.5
Bumetanide	80%-100%	1	50%/50%	1	1.6	1.3	2.3
Torsemide	68%-100%	20	20%/80%	3-4	4-5	6	8
Thiazide							
HCTZ	65%-75%	25	100%/0%	6-15	↑	↔	↔
Chlorthalidone	60%-72%	12.5	100%/0%	40-60	↑	↔	↔
Metolazone	65%-90%	2.5	70%-95%/5%-30%	14-20	↑	↔	↔
Distal							
Amiloride	50%	10	50%/–[b]	6-26	100	?	↔
Triamterene	52%-80%	100	20%/80%	2-5	↑	?	–[c]
Spironolactone	>90%	25	0%/100%	>15[d]	↔	?	↔

Novak JE, Ellison DH. Am J Kidney Dis. 2022. doi: 10.1053/j.ajkd.2021.09.029.

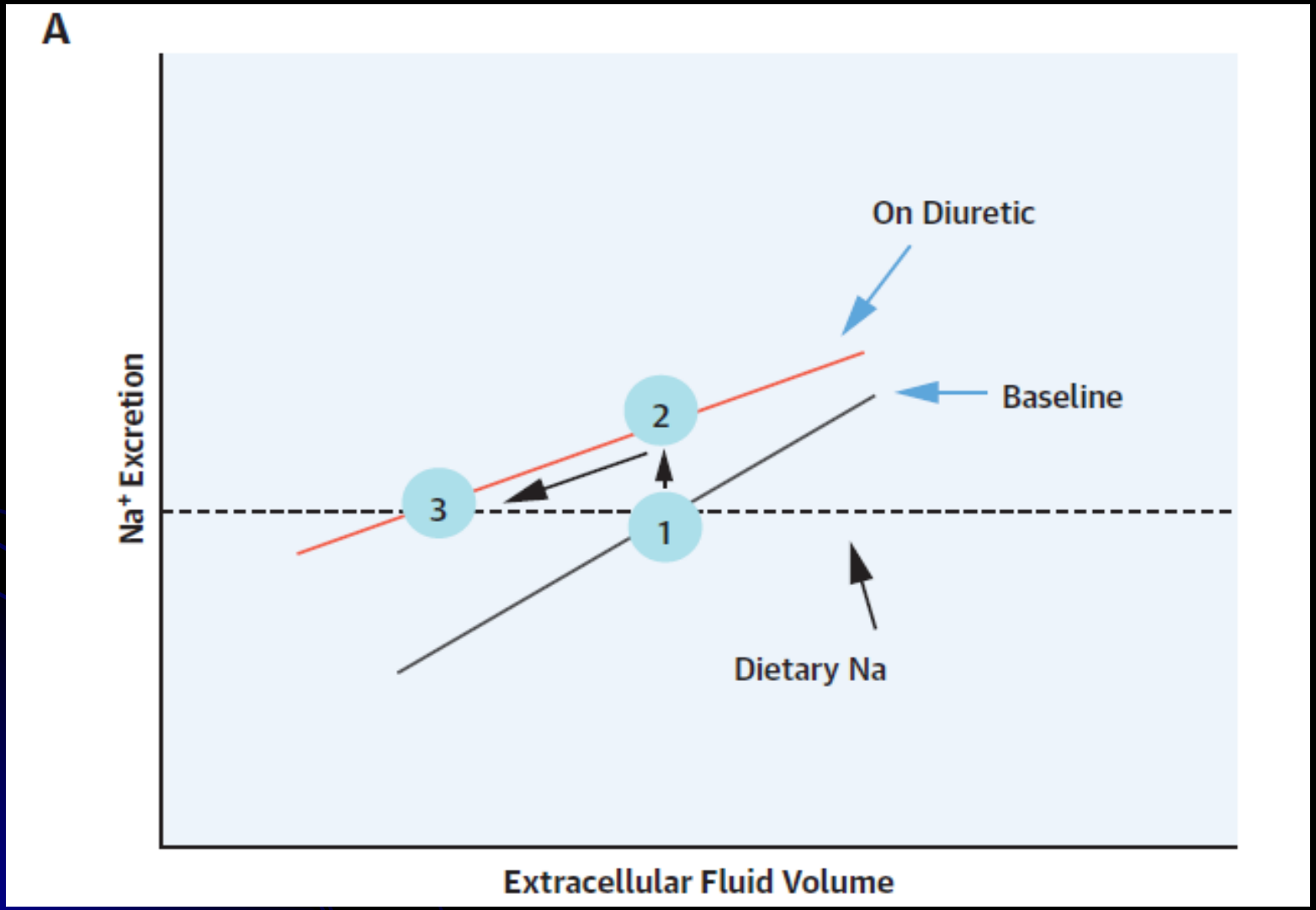
Diuretic resistance

Importance of specific cause/mechanism on diuretic resistance	Diuretic Resistance Categorization			
	Pre-Renal	Intra-Renal		
		Pre-Loop of Henle	Loop of Henle	Post-Loop of Henle
Significant	Venous congestion	Increased proximal tubule sodium reabsorption	Loop diuretic dose	Compensatory distal tubular sodium reabsorption
Unknown but hypothesized to be significant	Increased intra-abdominal pressure	*Reduced GFR*	Response at the level of the Loop of Henle	Proteolytic activation of ENaC by filtered proteases
Not significant with the mild to moderate derangement found in the average HF patient	*Reduced cardiac output*	*Increased organic anions*	Hypochloremic alkalosis	Upregulation of NCC, Pendrin, NDCBE, ENaC
	Hypoalbuminemia	*Albuminuria*		
	High sodium intake			



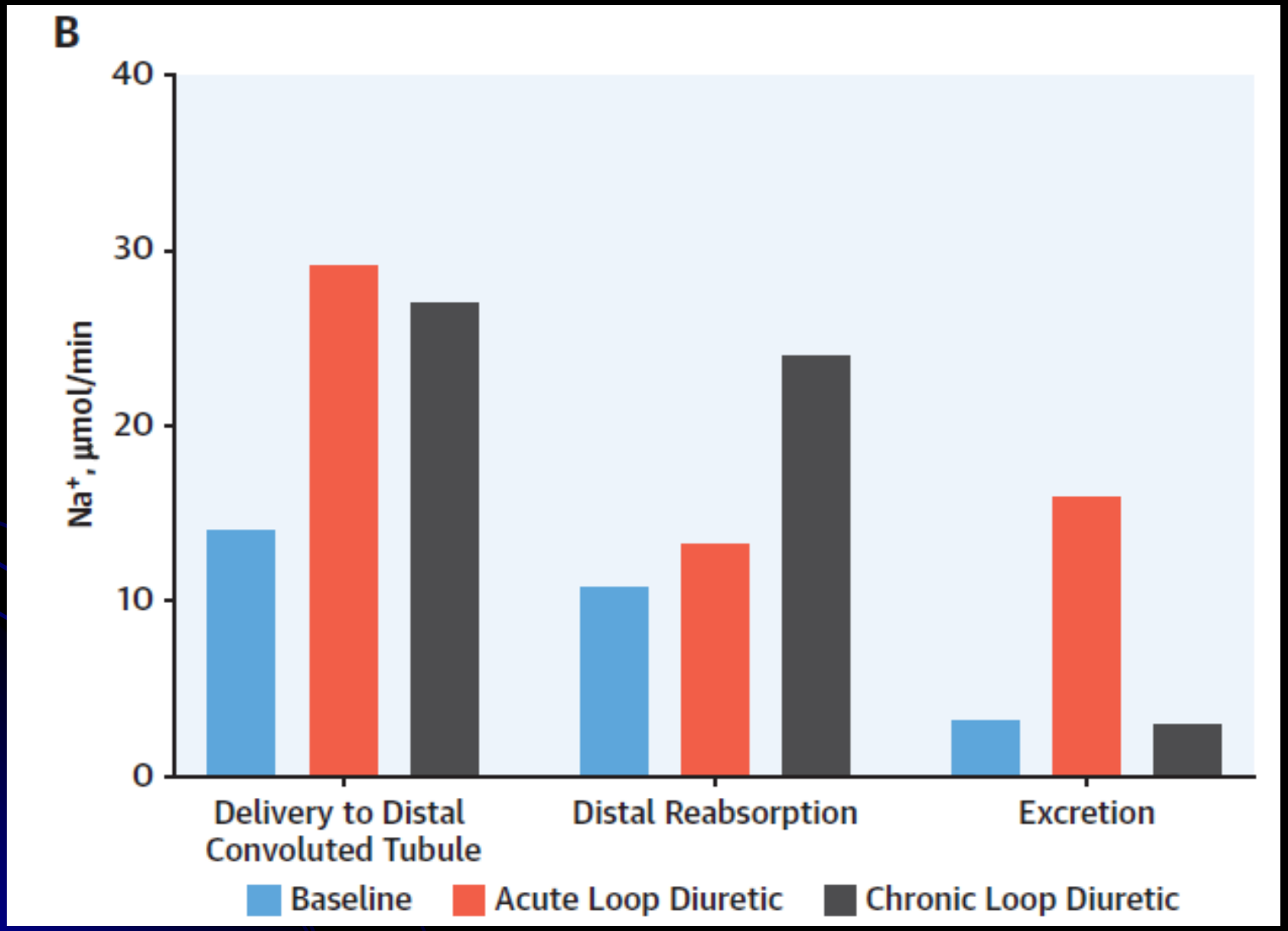
Felker GM, et al. J Am Coll Cardiol. 2020;75(10):1178-1195

Fundamentals of loop diuretic adoption (1)



Felker GM, et al. J Am Coll Cardiol. 2020;75(10):1178-1195

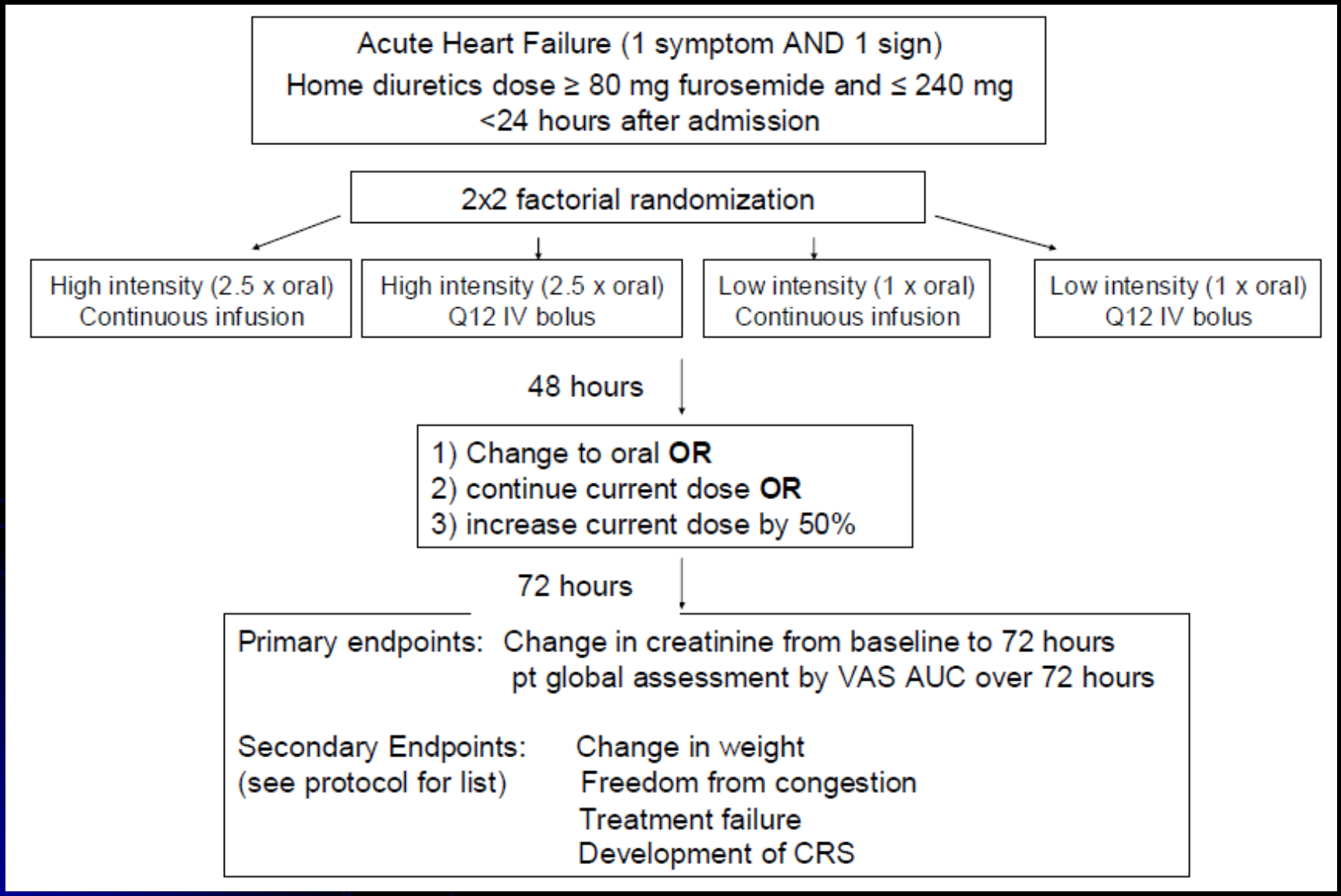
Fundamentals of loop diuretic adoption (2)



Felker GM, et al. J Am Coll Cardiol. 2020;75(10):1178-1195

Diuretics in acute decompensated HF

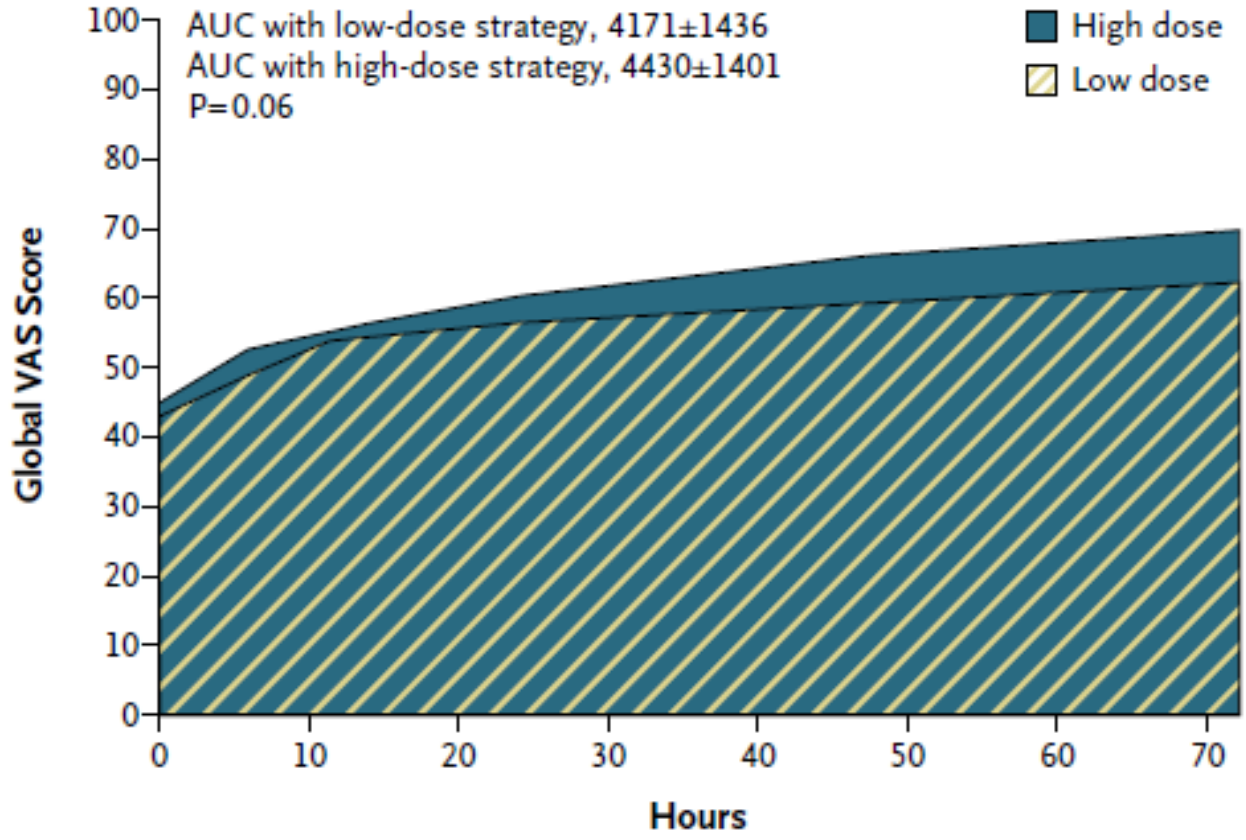
Diuretic Strategies in Patients with Acute Decompensated Heart Failure



Felker GM, et al. N Engl J Med 20112011;364(9):797-805.

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

Figure 1. Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.



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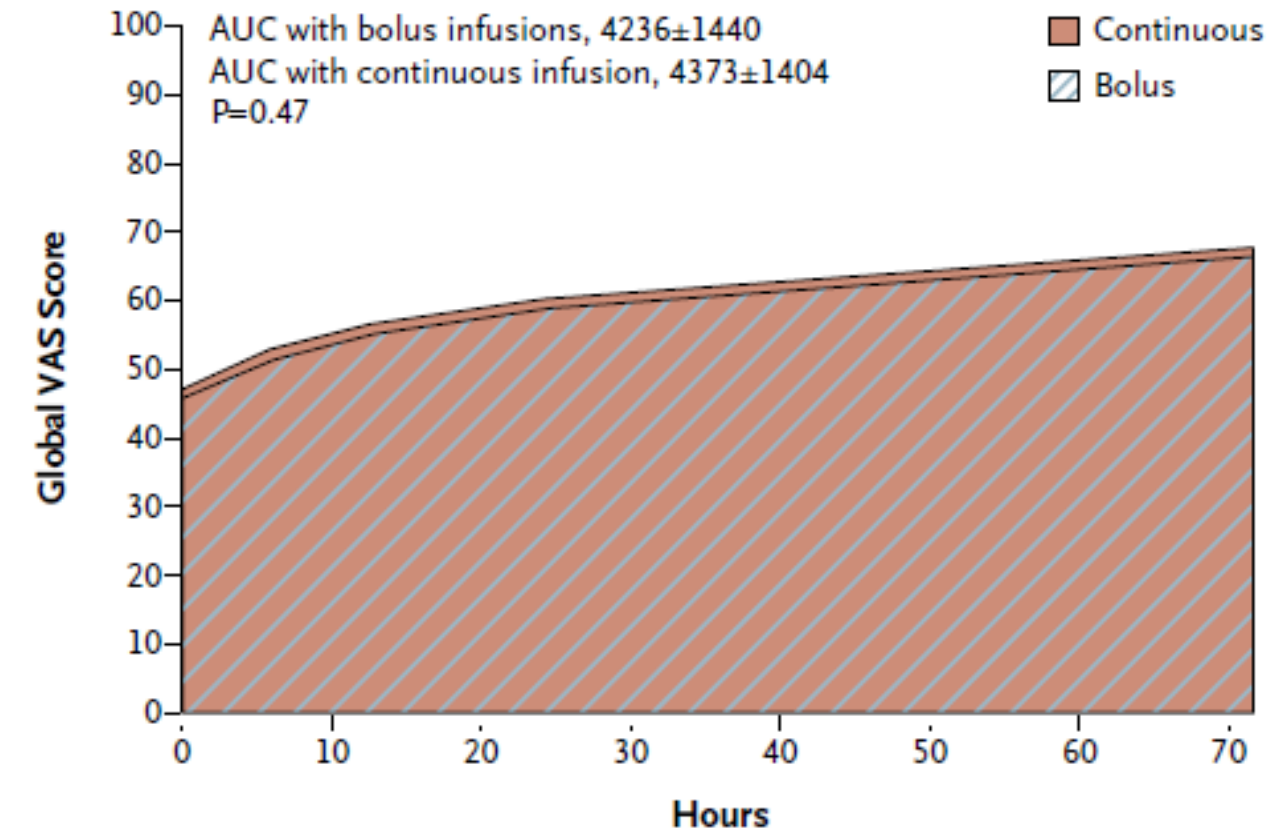
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

Figure 1. Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.



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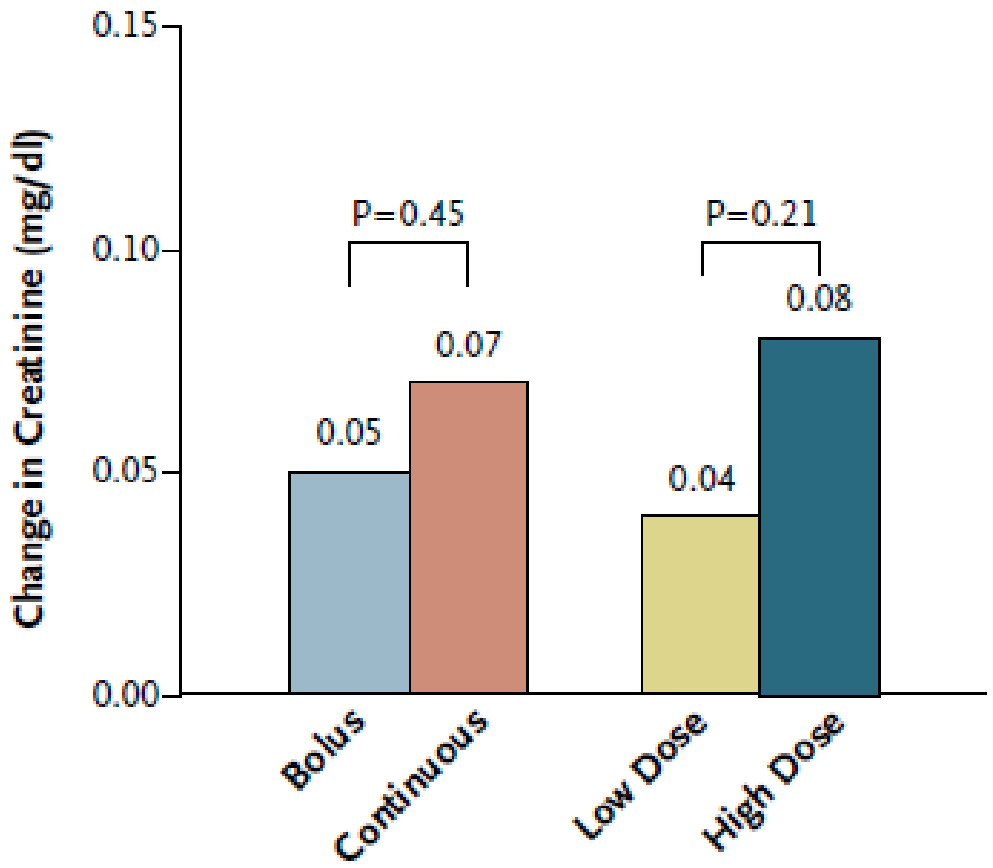
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

Figure 2. Mean Change in Serum Creatinine Level.



Felker GM, et al. N Engl J Med 20112011;364(9):797-805.

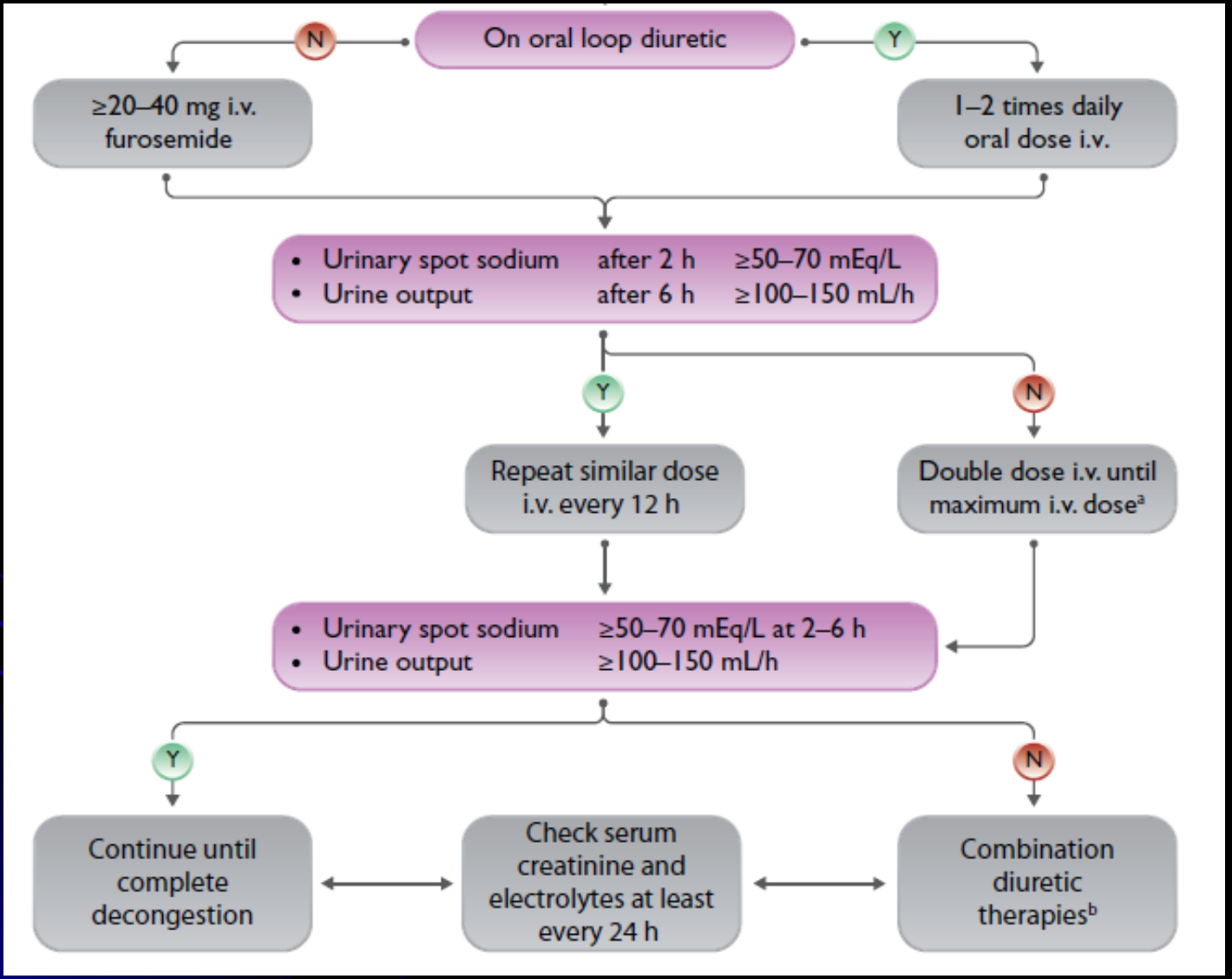
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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	

Felker GM, et al. N Engl J Med 20112011;364(9):797-805.

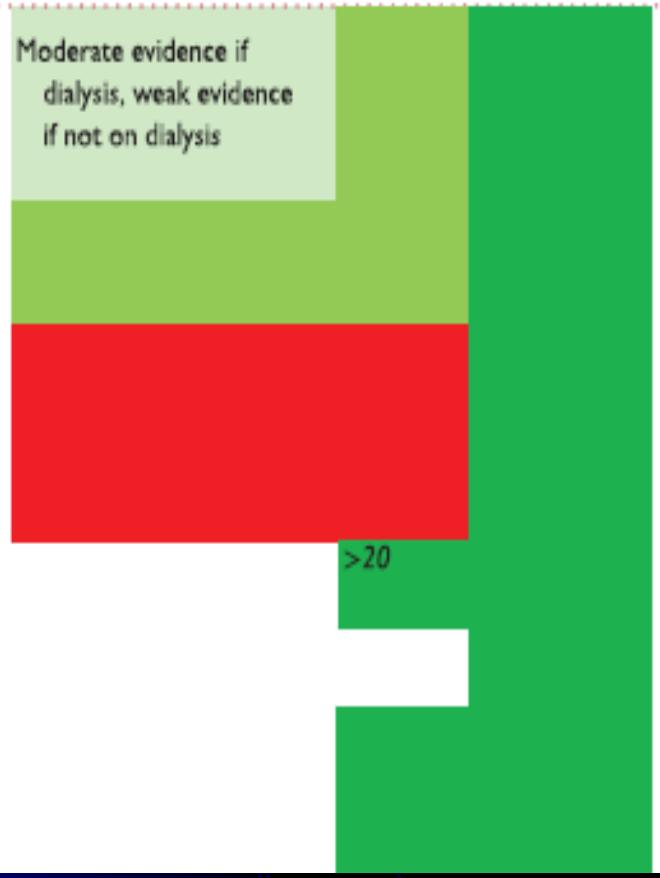
ESC 2021 guideline: diuretic therapy in acute HF



McDonagh TA, et al. Eur Heart J 2021; 42: 3599-3726.

Guideline-directed therapies in chronic HF

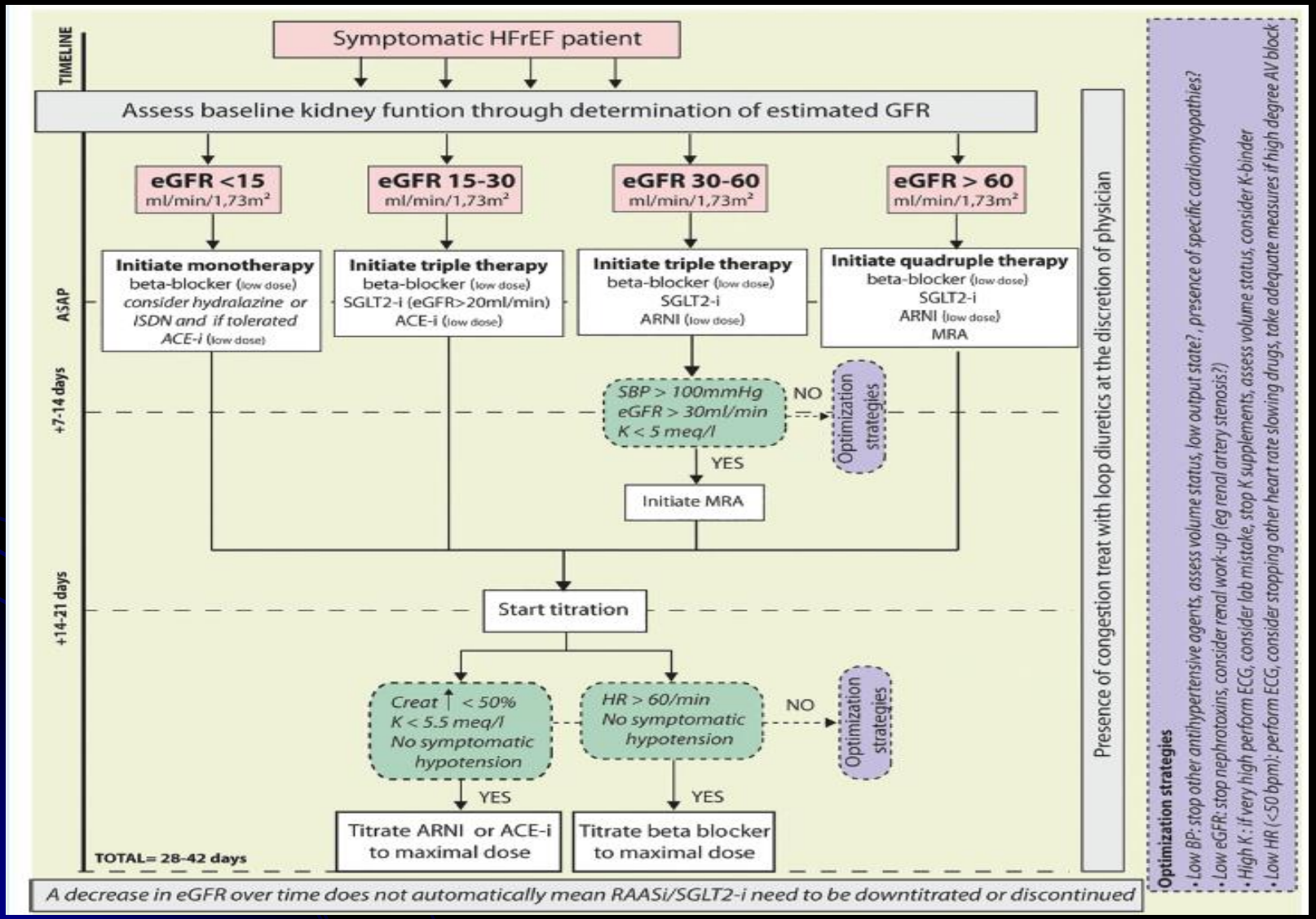
Initiation of HF drugs in relation to CKD status at baseline



Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria	Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
ACE-I/ARB		Yes	No (beneficial effect of around 1–2 ml/min/1.73 m^2 per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers		No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA		Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI		Yes	Yes (around 0.5 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i		Yes	Yes (around 1–2 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
Ivabradine		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Vericiguat		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Omecamtiv mecarbil		No	No	No	Relative benefit: ~ Absolute benefit: ↑

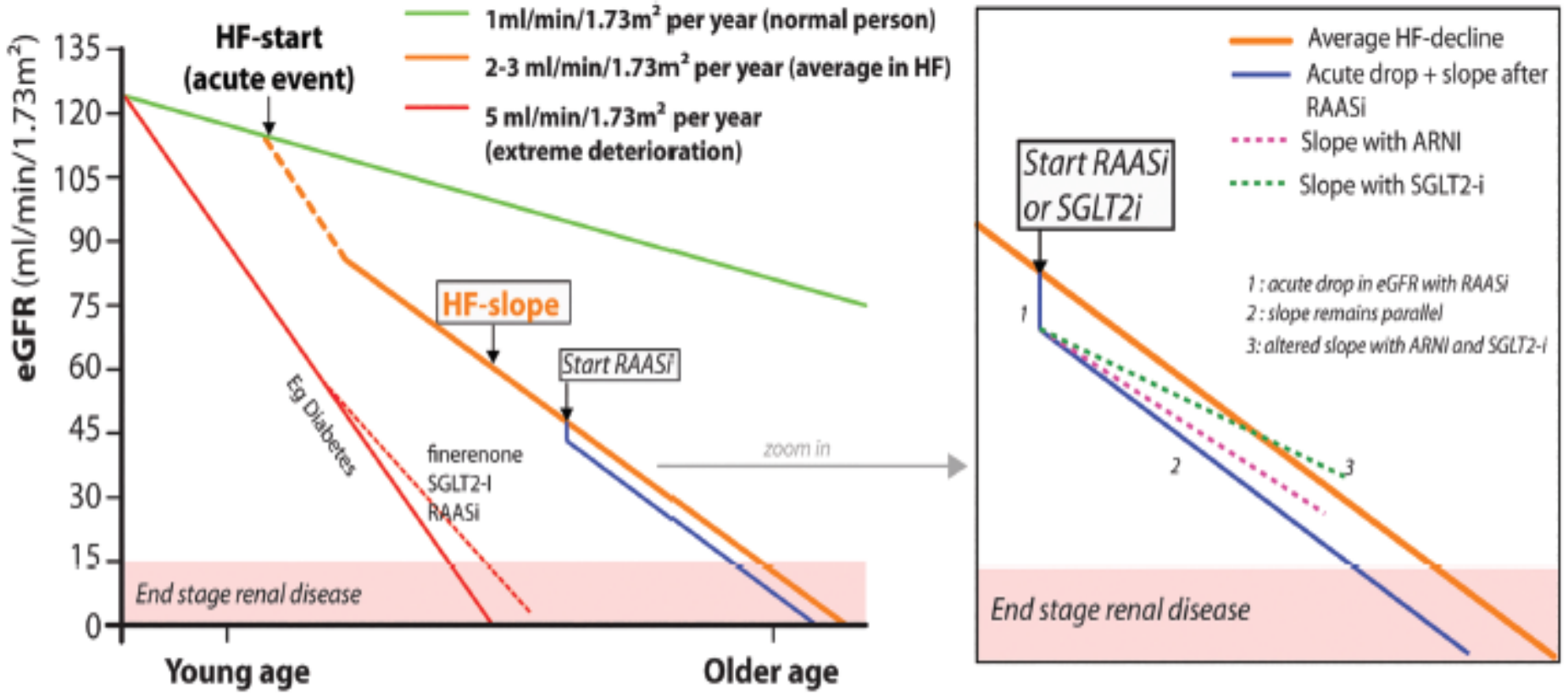
Mullens W, et al. Eur J Heart Fail 2022; 24:603-619.

Renal-based approach to initiation and titration of GDMT in HF



Mullens W, et al. Eur J Heart Fail 2022; 24:603-619.

Effect of drugs on eGFR slope



Key messages

1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HFrEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

Mullens W, et al. Eur J Heart Fail 2022; 24:603-619.

Kidney outcomes with ARNIs and SGLT-2 inhibitors in patients with HF

Trial	N	Design	ESKD events	≥40% or 50% reduction in eGFR	Effect on renal endpoint
Angiotensin receptor–neprilysin inhibitors					
PARADIGM-HF	8442	Sac/val vs. enalapril	Sac/val: 8 (0.2%) Enalapril: 16 (0.4%)	Sac/val: 32 (0.8%) Enalapril: 41 (1.0%)	HR 0.63 (95% CI 0.42–0.95) for ESKD+ ≥50% eGFR decline
PARAGON-HF	4822	Sac/val vs. valsartan	Sac/val: 7 (0.3%) Valsartan: 12 (0.5%)	Sac/val: 27 (1.1%) Valsartan: 60 (2.5%)	HR 0.50 (95% CI 0.33–0.77) for ESKD+ ≥50% eGFR decline or renal death
Sodium–glucose cotransporter 2 inhibitors					
DAPA-HF	4744	Dapagliflozin vs. placebo	Dapagliflozin: 16 (0.7%) Placebo: 16 (0.7%)	Dapagliflozin: 14 (0.6%) Placebo: 23 (1.0%)	HR 0.71 (95% CI 0.44–1.16) for ESKD+ ≥50% eGFR decline or renal death
EMPEROR-Reduced	3730	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 30 (1.6%) Placebo: 58 (3.1%)		Rate of eGFR decline: group difference 1.7 ml/min/year
EMPEROR-Preserved	5988	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 108 (3.6%) Placebo: 112 (3.7%)		Rate of eGFR decline: group difference 1.4 ml/min/year

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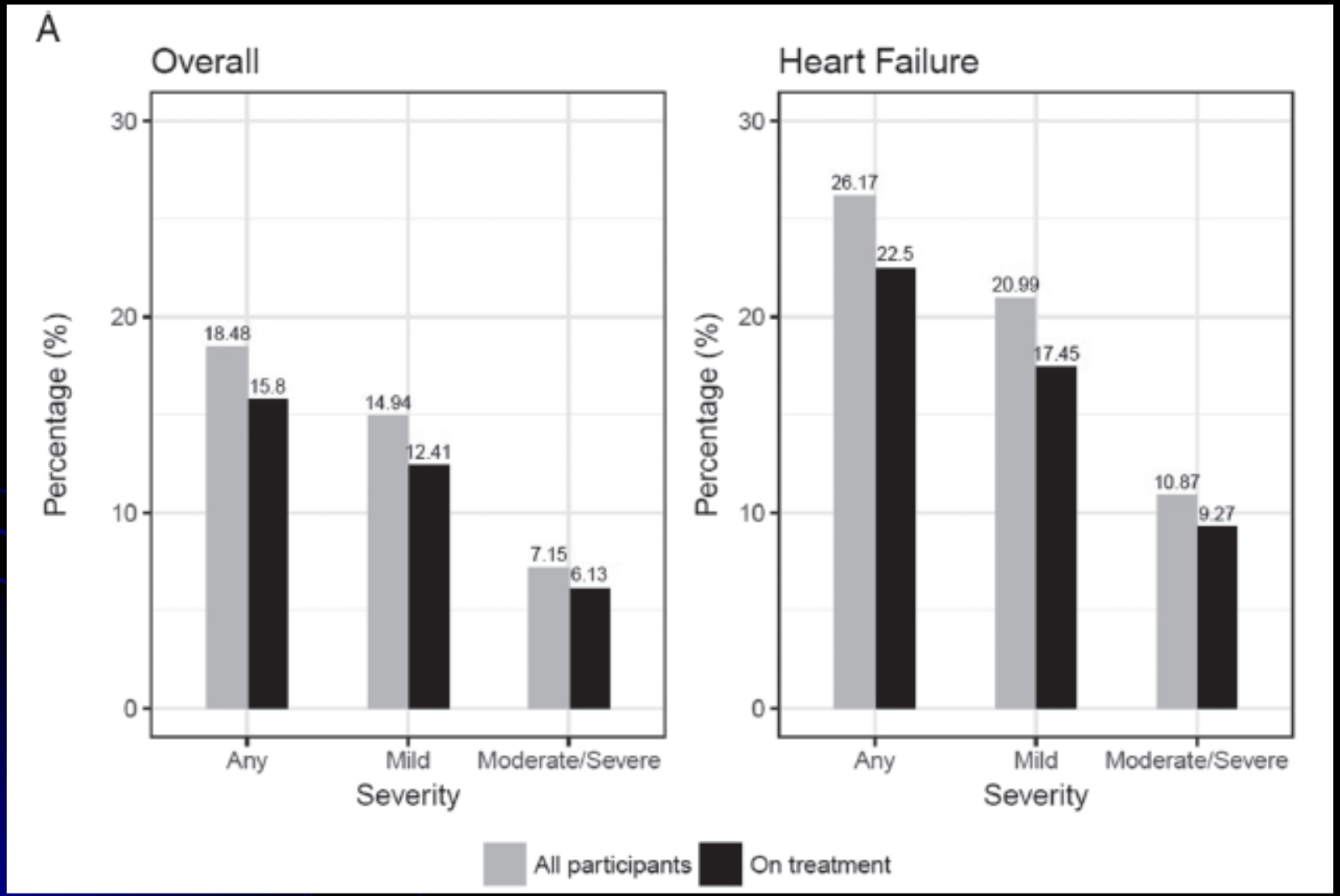
Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists



Trevisan M, et al Eur J Heart Fail 2018;1217-1226

Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists

Table 3 Matrix of drug prescription patterns after hyperkalaemia overall, by event severity and by time since therapy initiation

	Overall ($n = 1761$)	By event severity		By timing	
		Mild hyperkalaemia (K^+ 5.0–5.5 mmol/L) ($n = 1277$)	Moderate/severe hyperkalaemia ($K^+ > 5.5$ mmol/L) ($n = 484$)	<3 mo. of therapy ($n = 1084$)	>3 mo. of therapy ($n = 677$)
MRA continuation	934 (53%)	731 (57%)	203 (42%)	535 (49%)	399 (59%)
Same dose	842 (90%)	668 (91%)	174 (86%)	475 (89%)	367 (92%)
Reduced dose	92 (10%)	63 (9%)	29 (14%)	60 (11%)	32 (8%)
MRA cessation	827 (47%)	546 (43%)	281 (58%)	549 (51%)	278 (41%)
Discontinuation of ACEi/ARBs*	282 (23%)	191 (22%)	91 (26.8%)	194 (25%)	88 (20%)
Prescription of new diuretics†	255 (45%)	171 (42%)	84 (53.2%)	133 (47%)	122 (44%)
Prescription of new SPS	28 (1.6%)	10 (0.8%)	18 (3.7%)	19 (1.8%)	9 (1.3%)

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DIAMOND trial

Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

Study design

1195

Patients with HFrEF and hyperkalemia or a history of hyperkalemia

878

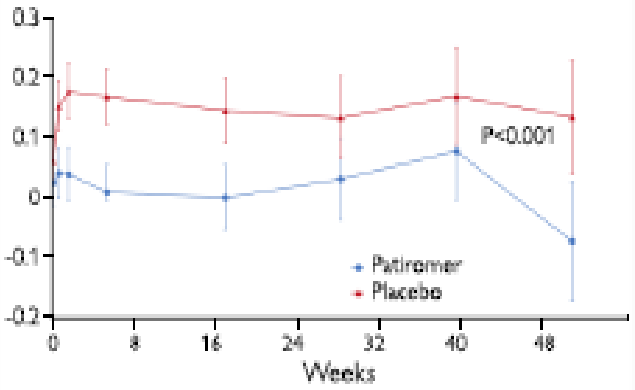
Patients were randomized and completed run-in (where K^+ levels controlled with patiromer and RAASi dose optimized)

439 Placebo

439 Patiromer

Primary endpoint

Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))



	Day 3	Weeks 1	2	6	18	30	42	54
Patiromer	409	406	402	376	273	183	104	66
Placebo	416	409	397	361	270	184	106	74

Secondary endpoints

	Patiromer (n=439)	Placebo (n=439)	Hazard/rate ratio (95% CI)	P-value
Hyperkalemia events with serum K^+ > 5.5 mmol/L	61 (13.9)	85 (19.4)	0.63 (0.45-0.87)	0.006
Maintained MRA target dose	61 (13.9)	83 (18.9)	0.62 (0.45-0.87)	0.006
Total number of hyperkalemia events	225	316	0.66 (0.53-0.81)	<0.001

0.3 1 3.0
RR or HR* (95% CI)
Favours Patiromer Favours Placebo

	Win ratio (95% CI)	P-value
Hyperkalemia-related morbidity-adjusted events*	1.53 (1.23-1.91)	<0.001
Win-ratio for RAASi use score	1.25 (1.003-1.564)	0.048

0.3 1 3.0
Win ratio (95% CI)
Favours Placebo Favours Patiromer

Butler J, et al. Eur Heart J 2022; 43:4362-4373.


ΑΧΕΠΑ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ ΑΧΕΠΑ