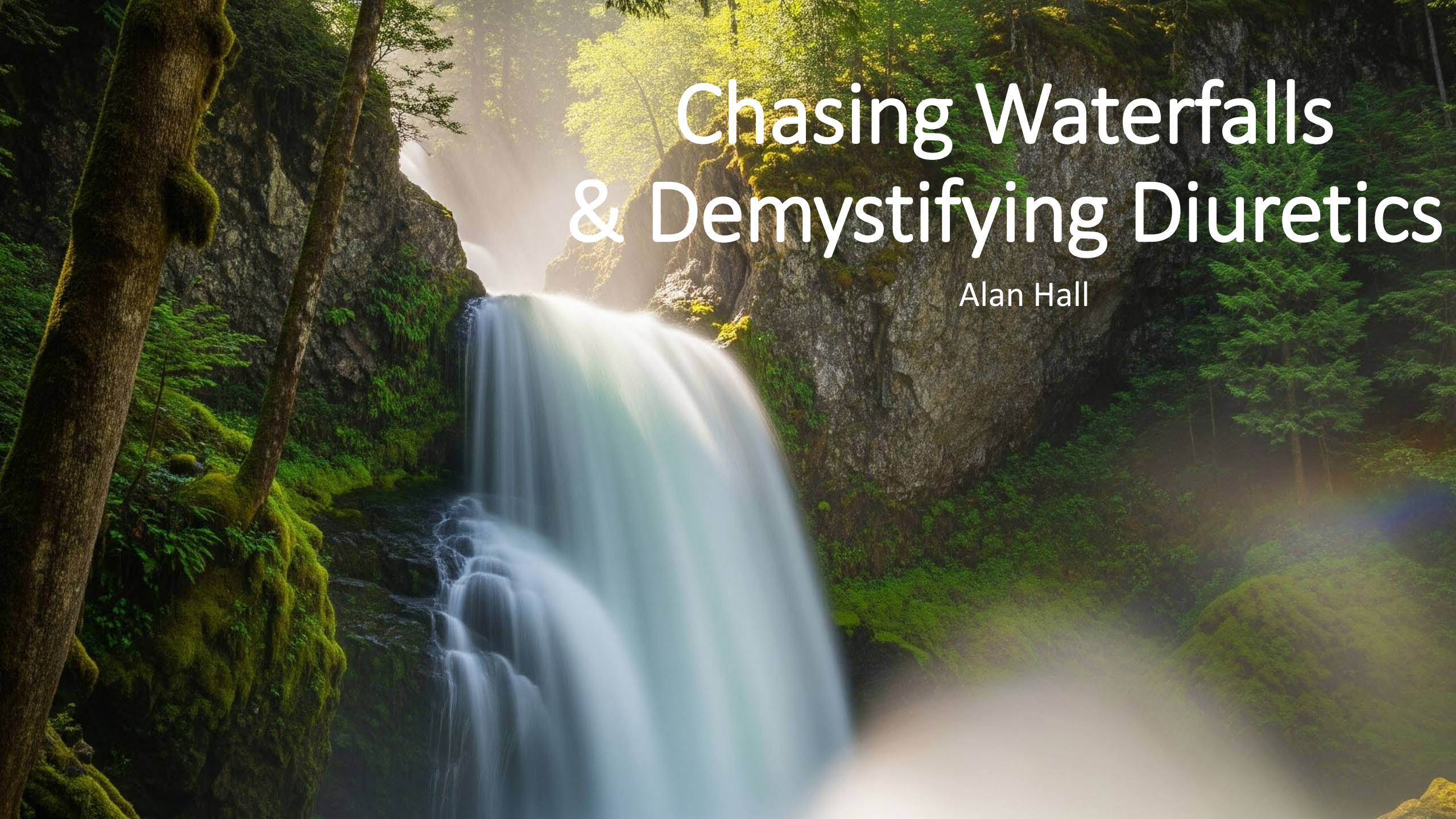


Chasing Waterfalls & Demystifying Diuretics

Alan Hall

Learning Objectives

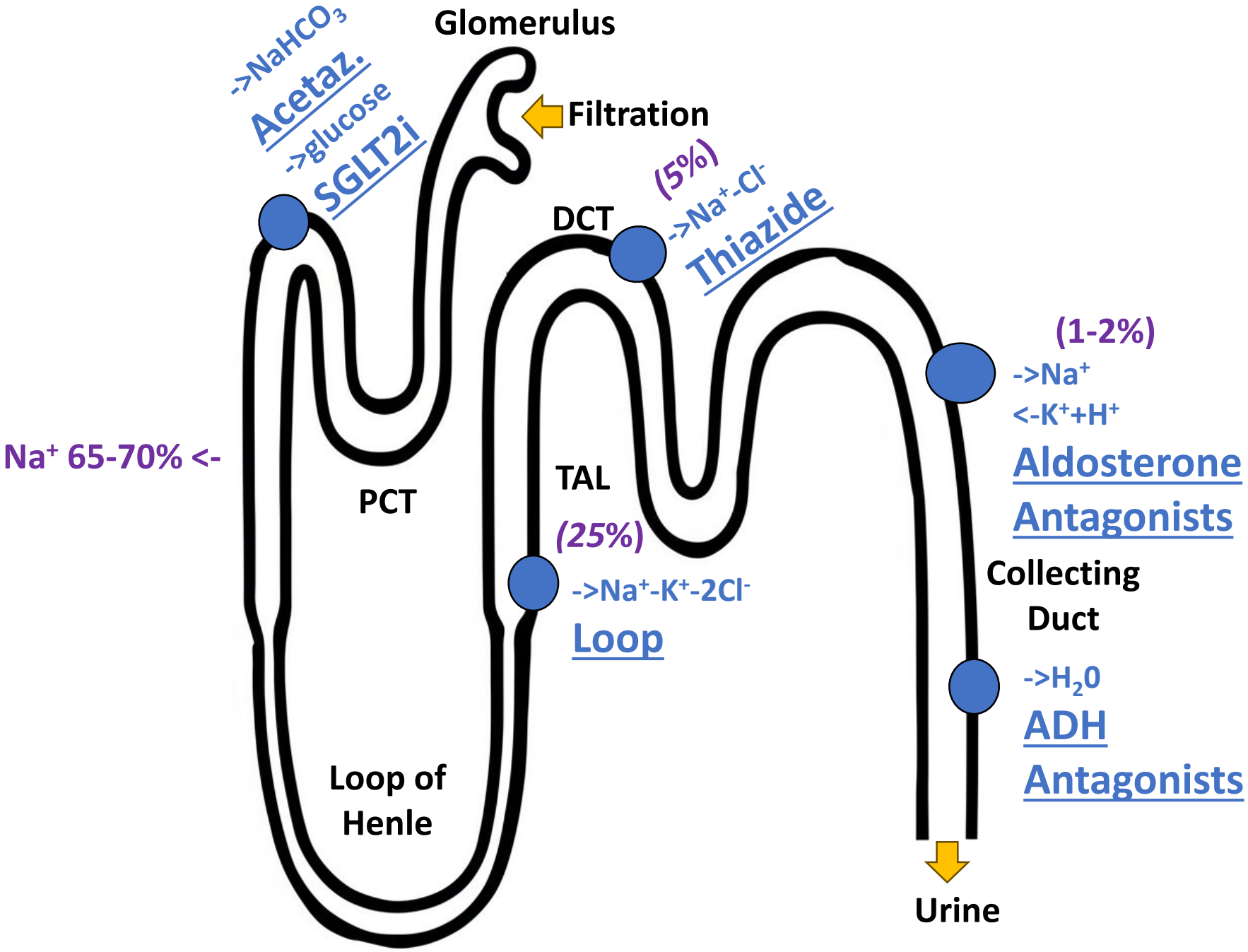
Compare and contrast diuretic agents within each class

Use guideline-supported and evidenced-based diuretics for acute CHF in the hospital

Manage patients with refractory volume overload

Introducing…

Loop
Thiazide
Aldosterone antagonists/MRA
Carbonic anhydrase Inhibitor
SGLT2-inhibitor
ADH Antagonist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Acetaz.
->glucose
SGLT2i
Filtration
(5%)
->Na+-Cl-
Thiazide
DCT
(1-2%)
->Na+
<-K+ +H+
Aldosterone
Antagonists
Na+ 65-70% <-
PCT
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(25%)
->Na+-K+-2Cl-
Loop
Collecting
Duct
->H20
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Antagonists
Loop of
Henle
Urine

Chasing the waterfall loop

Waterfall = Decongestion Goal

- No peripheral edema*
- No crackles
- No dyspnea on minimal exertion
- No hepatomegaly/congestive GI symptoms
  - No hepatojugular reflex
- No orthopnea or bendopnea
- JVD <6-8 cm H20

Chasing the Waterfall

- 65-year-old woman with hypertension, atrial fibrillation, dyslipidemia, type 2 diabetes, CKD (b/l Cr 2.2) HFpEF admitted with shortness of breath and increased lower extremity edema.

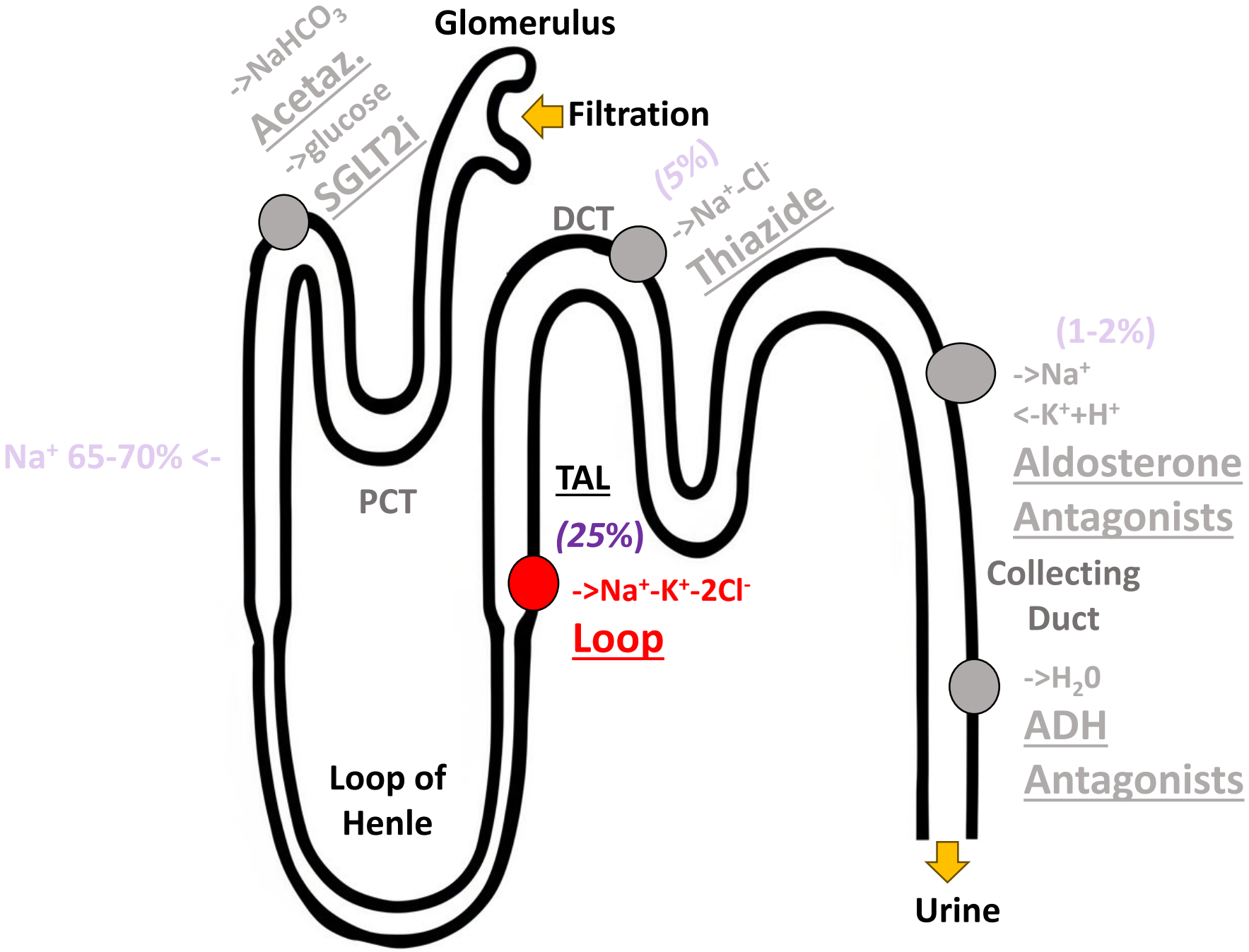
- On exam, O2 sat: 85% RA, RR 22, +JVD, 3+ lower extremity edema above knees, +orthopnea.

- Labs: Na 136, Cl 100, K 4.2, HCO3 22, Cr 3.5, Pro-BNP: Very high
- CXR: Fluffy bilateral infiltrates

- What loop diuretic do you reach for first?

Which loop diuretic do you reach for first?

A. Furosemide
B. Bumetanide
C. Torsemide
D. Ethacrynic acid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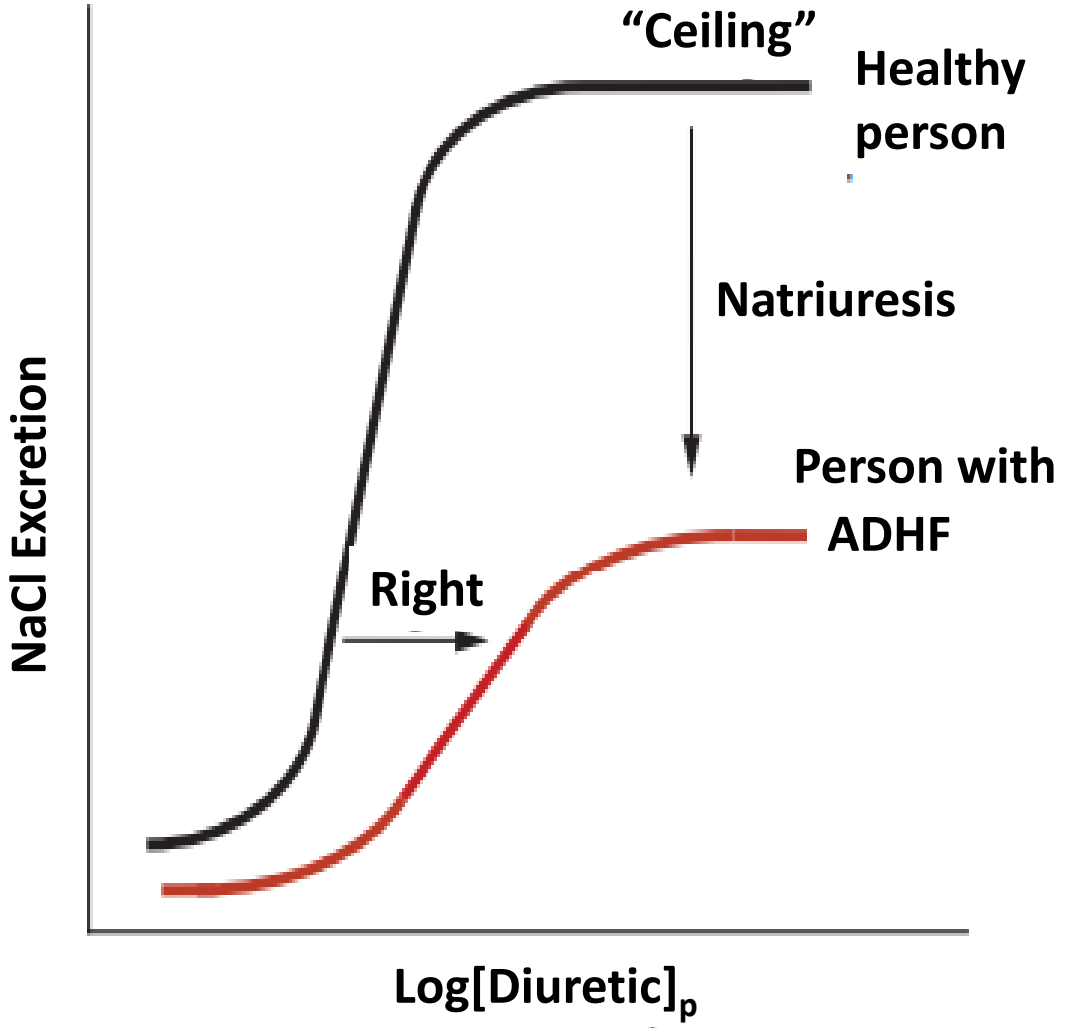

PMID: 29141174

Loop Diuretic, max daily dose	PO Equivalence	Usual Inpatient Dosing (IV)	PO Bioavailability	Duration (hours)	Half-life (hours)
Furosemide, 600mg	40mg (20mg IV)	40-160mg	~50% (10-90%)	6-8	0.5-2
Bumetanide, 10mg	1mg	1-4mg	80-100%	4-6	1-1.5
Torsemide, 200mg	20mg	20-40mg	80%	12-16	3.5

(PMID 7781259, 39127954, Lexidrug, https://www.ncbi.nlm.nih.gov/books/NBK589894/table/michiganmedicine.t2/)

IV Bolus Vs. Infusion

- 2024 Cochrane Review with 7 RCTs -> no clear difference

PMID: 38775253,

IV Bolus Dose

	Intervention	Outcome
2011 RCT 308 pts	IV home oral dose vs. **2.5x** home oral dose	2.5x dose -> 37% more fluid loss + 43% more weight loss + greater dyspnea relief @ 72 hr

- Bolus up to ~3x day (trying to allow for sleep)

PMID: 39127954, 21366472

Urine Na

- Urine Na <50-70 mEq/L at 2-6 hours suggest poor diuretic response
  - Early dose escalation if low

	Intervention	Primary Outcome
2023 open label trial, 310 pts	Urine Na (2 hrs +) vs. standard care **2x dose bumetanide (max 5mg) if Urine Na <70* *-> 1) HCTZ, 2) Acetaz/SGLT2*	• ↑ 24 h urinary Na excretion • = combined all-cause mortality + heart failure rehospit. @ 180 days

PMID: 39127954, 37640861, 28829876

NT-proBNP Daily?

- Serial measurements of NT-proBNP to guide diuresis does not help

PMID: 39127954

Which loop diuretic?

Study	Comparison	Patients	Primary Outcome	Secondary Outcome
Open label RCT (2001)	PO F vs. T	234	**+Torsemide lower readmission for CHF**	No difference in readmission, quality of life

PMID: 11705426, 30874955, 36648467, 39196651

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PMID: 11705426, 30874955, 36648467, 39196651

Does the loop choice matter?

- Likely not in the hospital
  - High enough dose may matter the most

- Likely similar at discharge
  - Maybe torsemide decreases readmissions (limited bumetanide studies)

Risk with loop diuretic doses

- HypoK, HypoNa, Met. Alkalosis, Hyperuricemia, Overdiuresis/AKI
- Sulfonamides -> hypersensitivity reactions, even AIN
  - ↓ cross-reactivity to sulfa antibiotics
- Ototoxicity
  - High dose (furosemide >240mg/hr up to 21,600mg/d) if nml kidney function
    - Lower doses if low GFR
  - Aminoglycosides ↑ risk
  - Maybe ↑ risk with bolus vs. infusion

PMID: 496112

What’s the deal with ethacrynic acid?

- More ototoxic
- Only used if loop sulfonamide allergy

Goal Waterfall?

- Limited data -> tailor to patient, not standard goal (1-2L/d)

- Evidence that UOP >150mL/hr 3hr post initial diuretic improves LOS
  - *Extrapolated -> 3.6L/d*

PMID: 40414113

Lab Frequency?

- Daily Cr + electrolytes for most per guidelines
  - Maybe BID when morning labs require supplementation

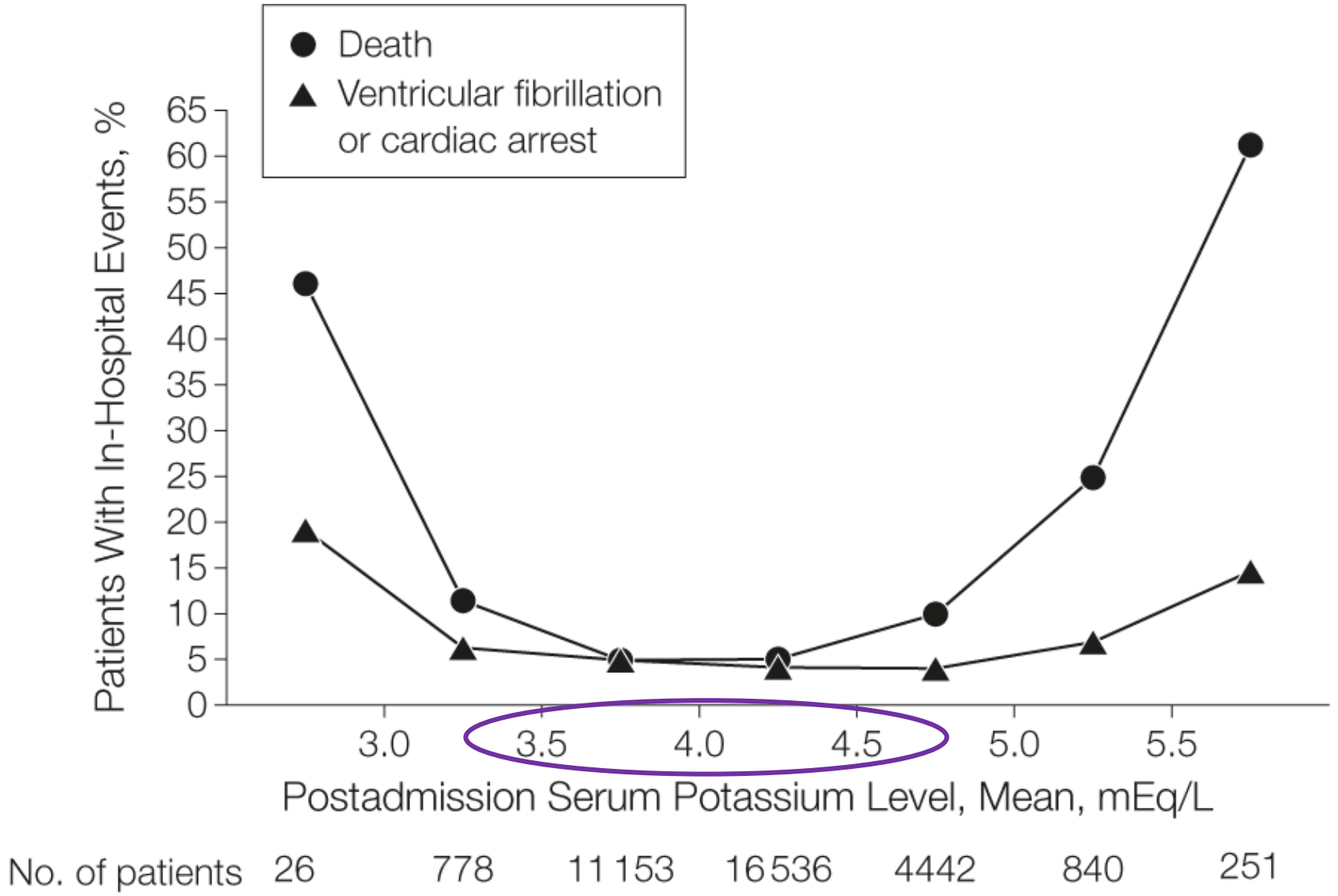
PMID: 35363499

K^+ Supplementation Target?

- 2010 Propensity Matched Study of Digoxin Trial CHF Data
  - Association of K >4 with improved mortality

PMID: 20103777

2012 Retrospective cohort of 38,689 patients with acute MI



PMID: 2223508

K^+ Supplementation Target?

	Intervention	Outcome
2019 Retrospective CHF study, 5000 pts	K < 4 mEq/L vs. 4-4.5 vs. > 4.5	<u>> 4.5 =</u> ↑ LOS ↑ mortality trend (p=0.07)

PMID: 31339844

K^+ Supplementation Target?

- No guidelines

- Supplement to normal
  - May need to be aggressive to avoid hypoK^+ with significant loop diuresis

Mg^{2+} Supplementation Target

- No guidelines/consensus
  - Probably normal range

- To maintain >2mg/dL in hospital -> ~2g BID of IV mag

PMID: 38112279

Loop Diuretic Summary

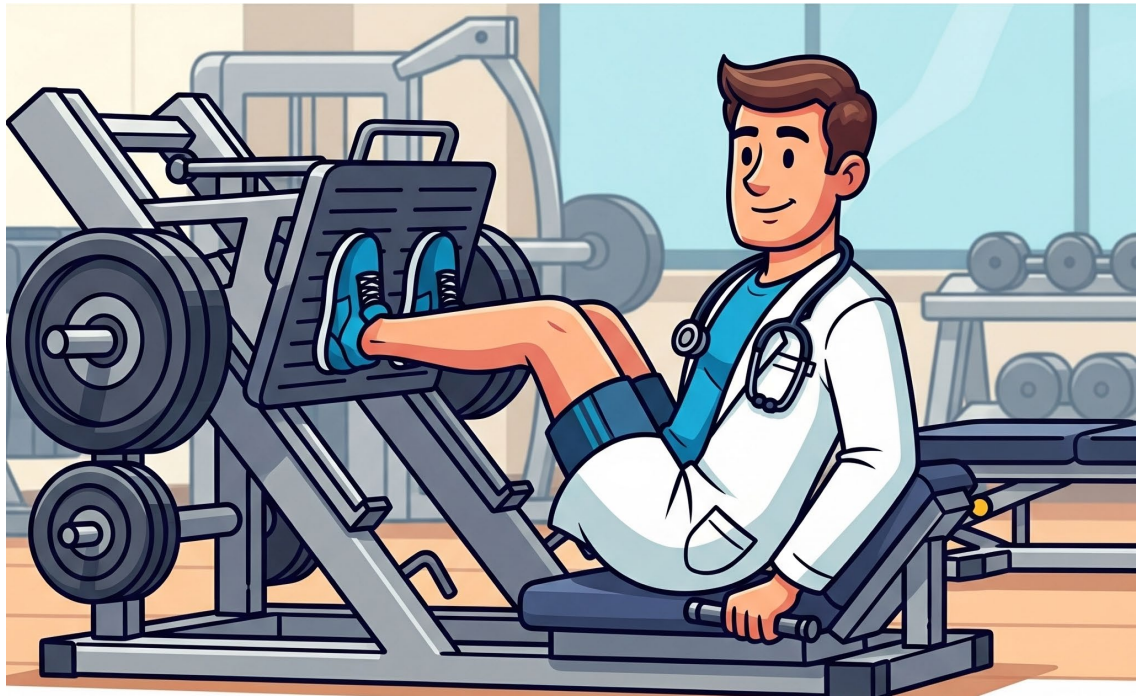
- Bolus ≡ Gtt
- Dose > Loop Diuretic Choice
  - Urine Na may help
- Goal = Big Waterfall
- Daily Electrolytes
- K/Mg Normal

BP during Weight-Lifting

Arterial blood pressure response to heavy resistance exercise

J. D. MACDOUGALL, D. TUXEN, D. G. SALE, J. R. MOROZ, AND J. R. SUTTON
Departments of Physical Education and Medicine, McMaster University, Hamilton, Ontario L8S 4K1, Canada

- Blood pressures as high as **480/350 mmHg** with leg press
- **Avoid IV hydralazine**



MacDougall JD, Tuxen DS, Sale DG, Moroz JR, Sutton JR. Arterial blood pressure response to heavy resistance exercise. Journal of applied Physiology. 1985 Mar 1;58(3):785-90.

Dry Waterfall

- 65-year-old woman admitted with acute CHF -> on hospital day 2, urine output has been about 500 mL, weight unchanged.

- Labs: Na 136, Cl 100, K 3.9, HCO3 22, Cr 3.5->3.8
  - Urine Na 30 mEq/L

- What do you do next to aid fluid removal?

What do you do next to aid fluid removal?

A. Increase the loop dose
B. Loop + thiazide
C. Loop + acetazolamide
D. Loop + SGLT2 inhibitor
E. Loop + MRA
F. Loop + hypertonic saline
G. Dialysis

When the Cr rises…

- Assess for other causes (meds, obstruction, etc.)

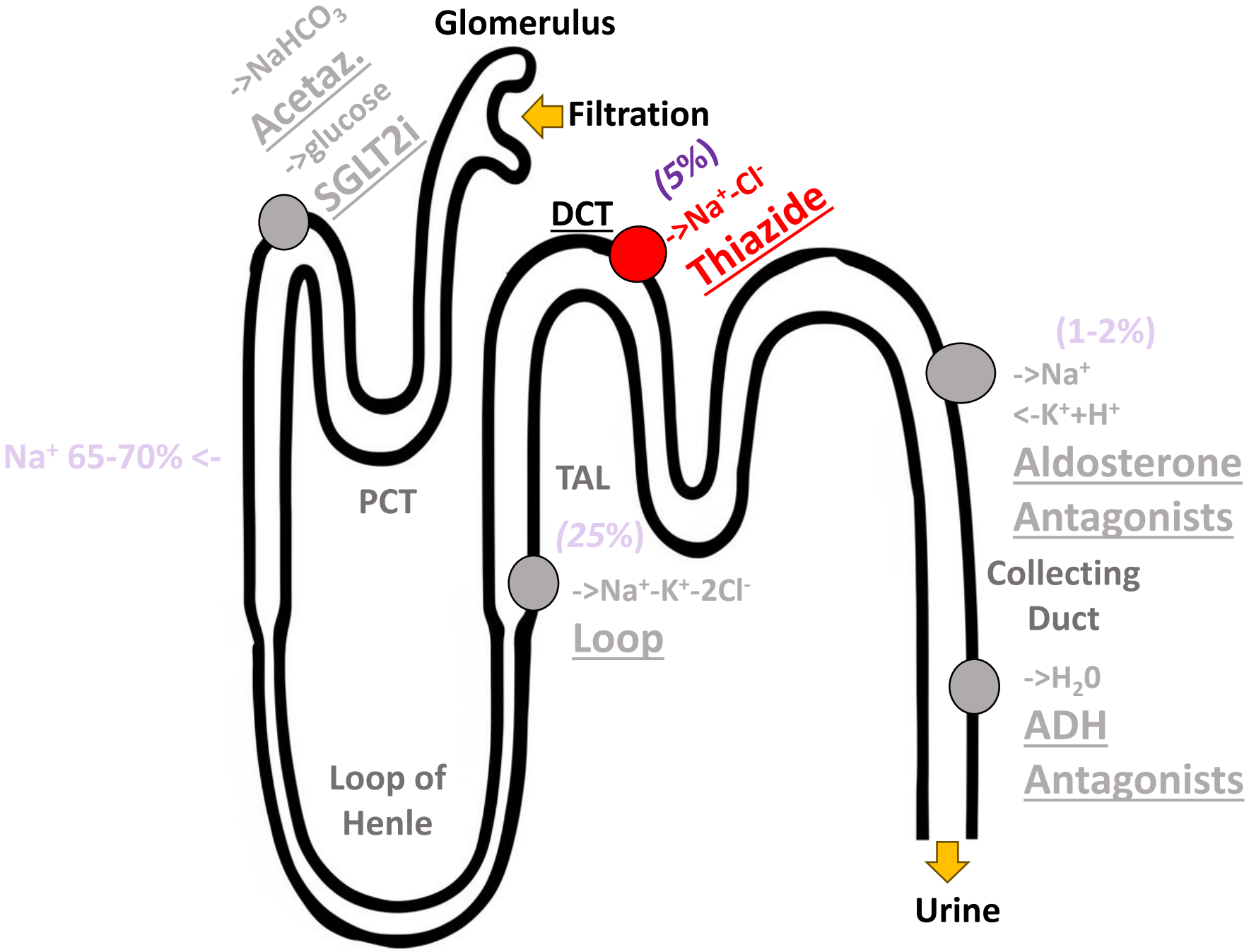
- If continued signs of congestion-> continue fluid removal
  - Cr should (hopefully) ↓ with ↑ diuresis
  - Persistent congestion at d/c = higher mortality/readmissions

- If not congested-> hold fluid removal

PMID: 29544928; 35363499

When there’s no waterfall

Combination Therapy, Sequential Nephron Blockade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Thiazide in acute CHF

Thiazide Diuretic	Initial Daily Dose	Duration
Chlorothiazide (PO/IV)	250–1000 mg once or twice	6–12 h
Metolazone (PO)	2.5-5mg mg once	12–24 h
Chlorthalidone (PO)	12.5–25 mg once	24–72 h
Hydrochlorothiazide (PO)	25-50 mg once or twice	6–12 h
Indapamide (PO)	*2.5 mg once*	*36 h*

PMID: 39127954, 32639593, 35363499

Loop + Thiazide vs. Increase Loop

- 2022 AHA/ACA/HFSA Guidelines =

  “Metolazone/chlorothiazide may be added to loop diuretics in patients with refractory edema unresponsive to loop diuretics alone”

PMID: 35363499, 35363499

Evidence of Loop + Thiazide

	Intervention	Outcome
2018 Observational study, ~14,000pts	Metolazone vs. high-dose loop alone	Metolazone -> ↑mortality*, ↓K^+, ↓Na^+, ↑ Cr

PMID: 30371181, 36423214

Evidence of Loop + Thiazide

	Intervention	Outcome
2023 CLORITIC RCT, 230pts	Furosemide + HCTZ or placebo in acute CHF	<u>Primary</u> ↑ wt. loss (2.3 vs. 1.5 kg) @ 72 hrs = reported dyspnea @ 72 hrs <u>Secondary</u> ↑ diuresis (~275mL) @ 24hr + Cr = mortality, rehosp., hypoK, hypoNa

PMID: 30371181, 36423214

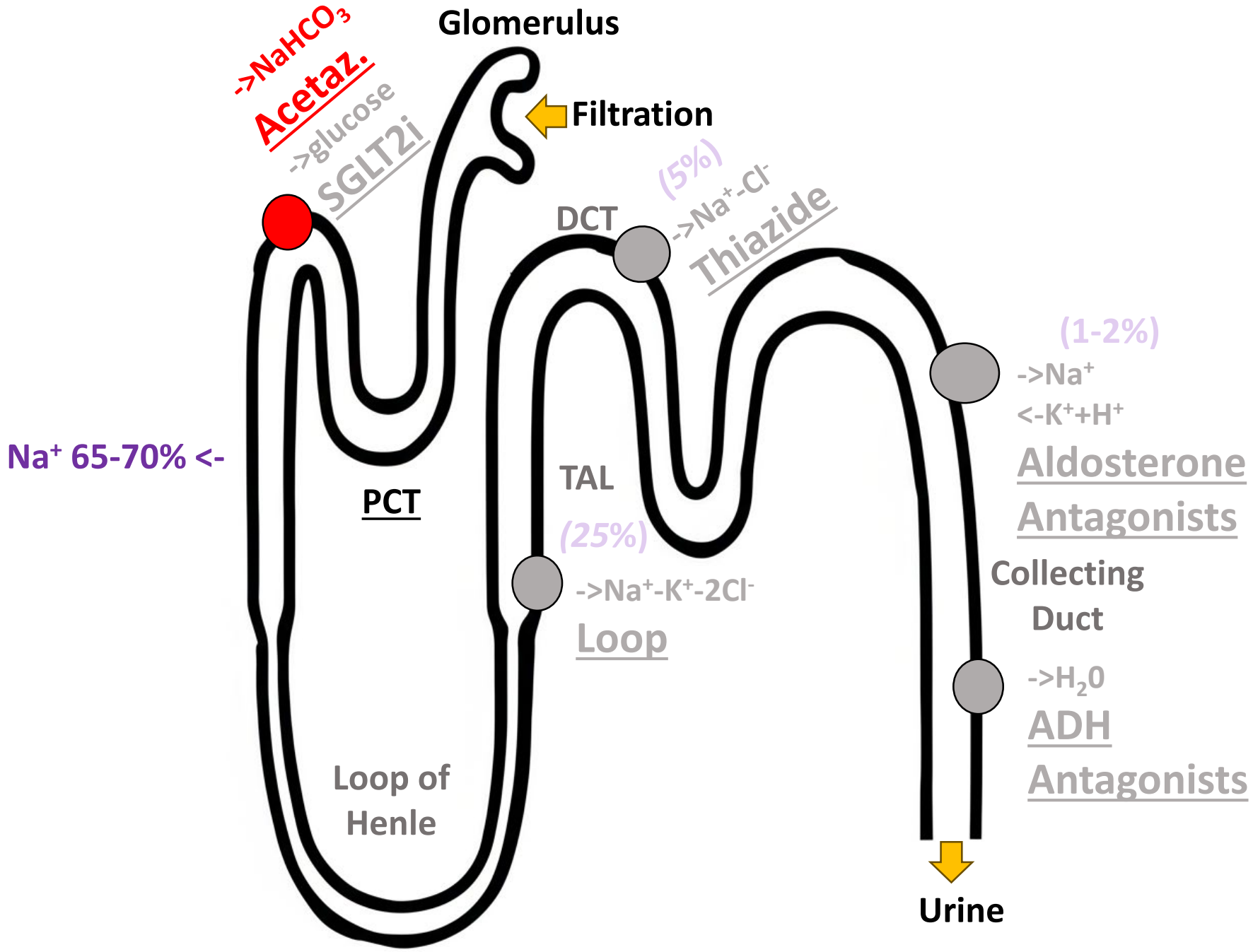
Loop + Thiazide Choice

- Meta-Analysis (3 retrospective + 1 small RCT)
  - IV Chlorothiazide ($) ≡ PO Metolazone: 24-hour UOP

PMID: 3568840, 32639593, 21029871

Loop + Thiazide Summary

- Consider + thiazide if limited response to escalating loop
- Commonly thiazide given 30 min - 1 hr prior to loop (?)
  - Metolazone slow and variable absorption
- ?Primary diuretic benefit continued diuresis when loop wears off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Acetazolamide in acute CHF

Diuretic	Initial Daily Dose	Duration
Acetazolamide (PO/IV)	250-500 mg once daily	IV 4-5 hours

PMID 39127954

	Intervention	Outcome
2019 Meta-analysis (9 studies, 3 RCTs), 229 pts	Acetazolamide use in CHF	• ↓ pH, & bicarb • ↑ natriuresis

PMID: 30871038, 36027559

	Intervention	Outcome
2019 Meta-analysis (9 studies, 3 RCTs), 229 pts	Acetazolamide use in CHF	↓ pH, PCO2, & bicarb ↑ natriuresis
2023 ADVOR RCT, 519 pts	Loop (2x home) + Acetazolamide 500mg vs. Placebo x3d	<u>Primary</u> ↑ 'successful decongestion' (42.2% vs. 30.5%) ↓ LOS (8.8 vs. 9.9 days) <u>Secondary</u> = in death + rehosp. at 3 mo

**Aggressive supplements: $HCO3^-$ < 20 -> 100 ml of NaHCO3 8.4% IV.*

PMID: 30871038, 36027559

Loop + acetazolamide vs. thiazide

- Unpublished abstract: single center retrospective study
  - 144 patients: Loop + thiazide
  - 105 patients: Loop + acetazolamide
  - 91 patients: Loop + thiazide + acetazolamide
- No difference in urine output/day
- Loop + acetazolamide less AKI

Loop + Acetazolamide Summary

- Consider acetazolamide addition if no/limited response to escalating, high-dose loop

- May be most helpful with elevated bicarb levels

PMID: 38645830

Urine output

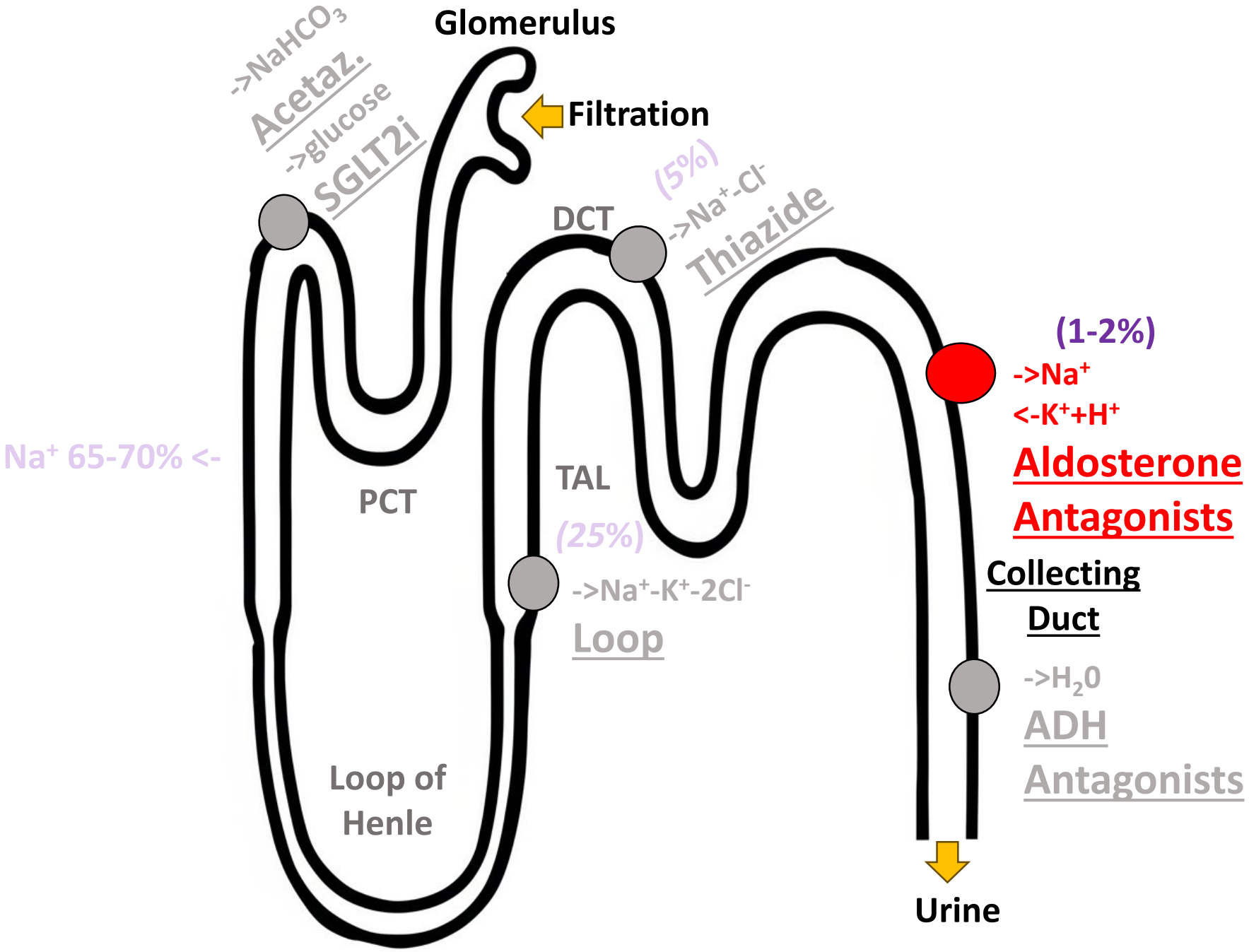
BMJ

RESEARCH

CHRISTMAS 2010: THE LIVES OF DOCTORS

Urine output on an intensive care unit: case-control study

- Urine outputs of pts vs. residents
  - ICU patients: 15% of shifts with < 0.5mL/kg/hr
  - Residents: 25%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Loop + Aldosterone Antagonists

Diuretic	Initial Daily Dose	Half Life (Duration)
Spironolactone* (PO)	25mg/day	1.4 hrs (2-3 days)
Finerenone (PO) $$$	10mg/day	2-3 hrs
Eplerenone (PO)	25mg/day	3-6 hrs

*Onset to full effect days

Aldosterone/Mineralocorticoid Receptor Antagonists

- ↑ K^+
- ↑ Mg^{2+}
- ↓ $HCO3^-$
- Spironolactone/eplerenone -> gynecomastia
  - Not finerenone

PMID: 27434136

Loop + Spironolactone

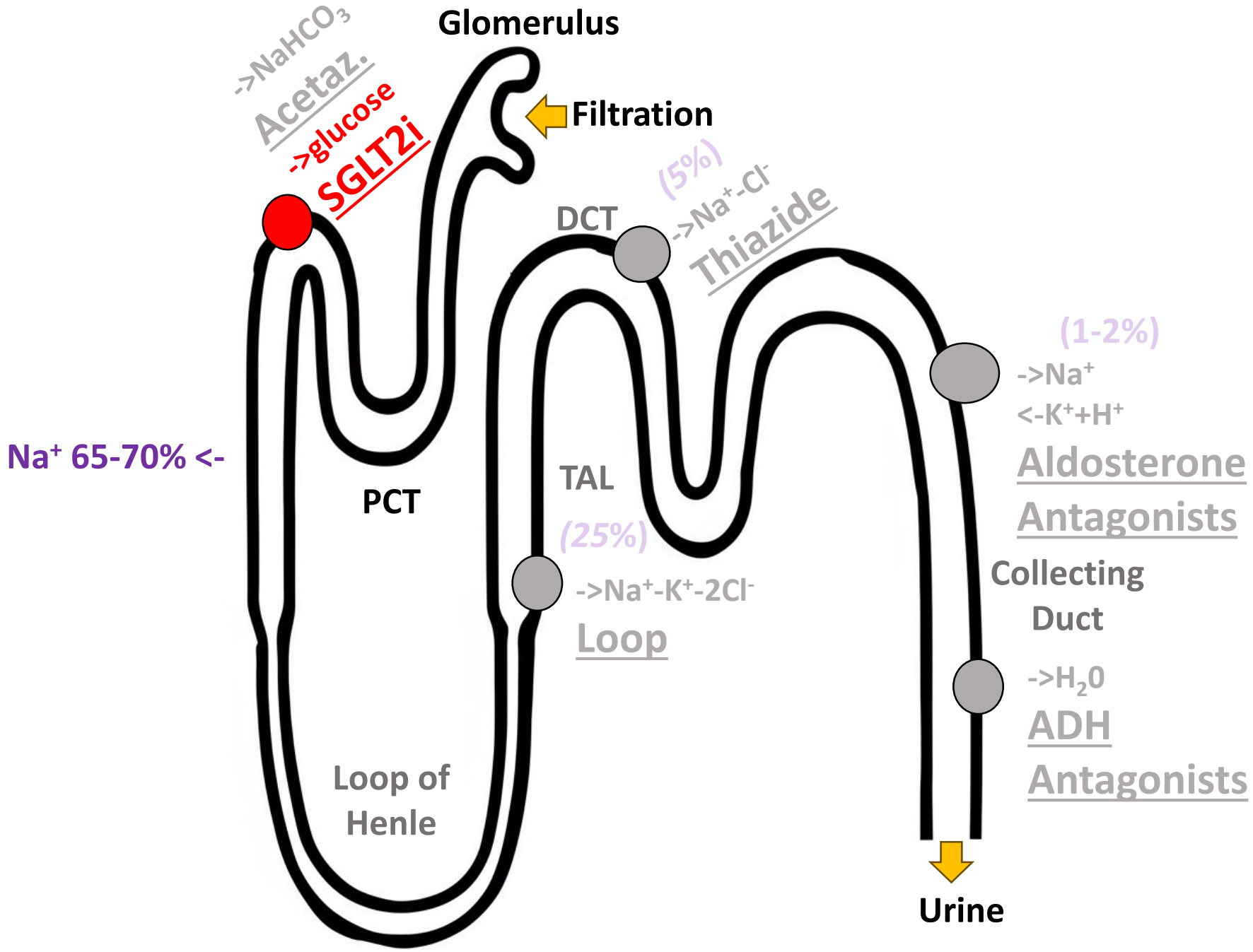
	Intervention	Outcome
2017 Athen-HF RCT, 360 pts	Loop + 100mg spiro. vs. placebo/25mg spiro. in hospital	Primary = NT-proBNP Secondary = Urine output, weight change, mortality

- Why less impact?
  - 1-2% of Na resorption
  - Spironolactone takes ~2 days to have diuretic effect
    - Amiloride, K-sparing diuretic with faster onset (but not GDMT)

PMID: 28700781

Loop + Aldosterone/Mineralocorticoid Receptor Antagonist Summary

- Can try to start inpatient for long-term benefit
- Likely doesn’t significantly improve diuresis
- ↑ K/Mg may be helpful with loop diuresis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SGLT2i

- Mechanism osmotic diuresis + next to Na^+/H^+ exchanger which promotes natriuresis
- Renal protective but may increase GFR (~up to 30%)
- ↓ uric acid levels
- ↑ magnesium levels

PMID: 34654997, 37194077

SGLT2i

Diuretic	Initial Daily Dose	Half Life (Duration)
Empagliflozin (PO)	10mg/day	12.4 hrs (3 days)
Dapagliflozin (PO)	10mg/day	12.9 hrs (3 days)

Bexagliflozin, Canagliflozin, Ertugliflozin, Sotagliflozin…

Loop + SGLT2i

	Intervention	Outcome
2024 Single Center RCT, 1366 pts • 1st 24 hrs of decompensation->increased furosemide dose	After 24 hours • Continued ↑ furosemide dose vs. back to pre-admit dose + empagliflozin	<u>Primary Outcome</u> ↓ readmission (28.7% vs. 40.2%) <u>Secondary Outcome</u> ↑ 6 min walk distance, heart rate, weight, NT-proBNP, eGFR

PMID: 38864970

Loop + SGLT2i Summary

- Add Early for GDMT unless contraindication
- Increases diuresis
- Renal protective, but may increase GFR
- ↓ uric acid/↑magnesium

Maternal Kisses

Maternal kisses are not effective in alleviating minor childhood injuries (boo-boos): a randomized, controlled and blinded study

The Study of Maternal and Child Kissing (SMACK) Working Group

- No change in pain scores
  - Mom's kisses vs. 'Sham kisses" vs. nothing

Loop + Salt

- Hypertonic saline...how does it work?
  - Pulls fluid from interstitial spaces so loop more effective removing fluid
  - Raising Cl^- -> ↓RAS pathway + ↓ Na-avid state of kidney
    - *L-lysine Monohydrochloride supplementation reduced diuretic resistance*

PMID: 40618742, 13759316, 14439868, 37340592, 3416628, https://emcrit.org/pulmcrit/pulmcrit-hyperdiuresis-using-hypertonic-saline-to-facilitate-diuresis/

Loop + Salt

- 150mL hypertonic bolus (~3%) + high dose IV furosemide

PMID: 40618742, 13759316, 14439868, 37340592, 3416628, https://emcrit.org/pulmcrit/pulmcrit-hyperdiuresis-using-hypertonic-saline-to-facilitate-diuresis/

Loop + Salt

	Intervention	Outcome
2023 Metanalysis of 10 RCTs, 3013 pts	In refractory acute HFrEF: furosemide vs. 3% + furosemide	↓ LOS (-3.6 days) ↓ weight (-2.34kg) ↓ creatinine ↓ hypoNa ↑ urine output (~500mL/24 hrs)

PMID: 40618742, 13759316, 14439868, 37340592, 3416628, https://emcrit.org/pulmcrit/pulmcrit-hyperdiuresis-using-hypertonic-saline-to-facilitate-diuresis/

Loop + Salt

	Intervention	Outcome
2025 Metanalysis, 14 RCTs (1 PO) + 2 non-randomized studies, 3544 pts	Prescribed Na intake in decompensated CHF in hospital	Salt: ↓ serum Cr + BNP ↓ weight ↓ LOS (-2.68 days) ↑ Na (6 mEq/L in 24 hr) No pulmonary edema, hypoxia

PMID: 40450575

Loop + PO Salt

	Intervention	Outcome
2023 RCT, 65 pts	IV furosemide gtt + 2g PO NaCl TID vs. placebo (~13g NaCl given)	Primary: = weight + Cr

- At least NaCl did not make thing worse

PMID: 37044281

Loop + Salt Summary

- Hypertonic saline + Loop seems effective
  - Reduced length of stay by 2-3 days
- Should we be using this more/earlier?

Loop + Albumin

	Intervention	Outcome
Meta-analysis 2014, 343 pts 2021, 422 pts	Loop vs. Loop + Albumin	• Modest improvement in urine output in short-term • Transient + limited clinical significance + $$$

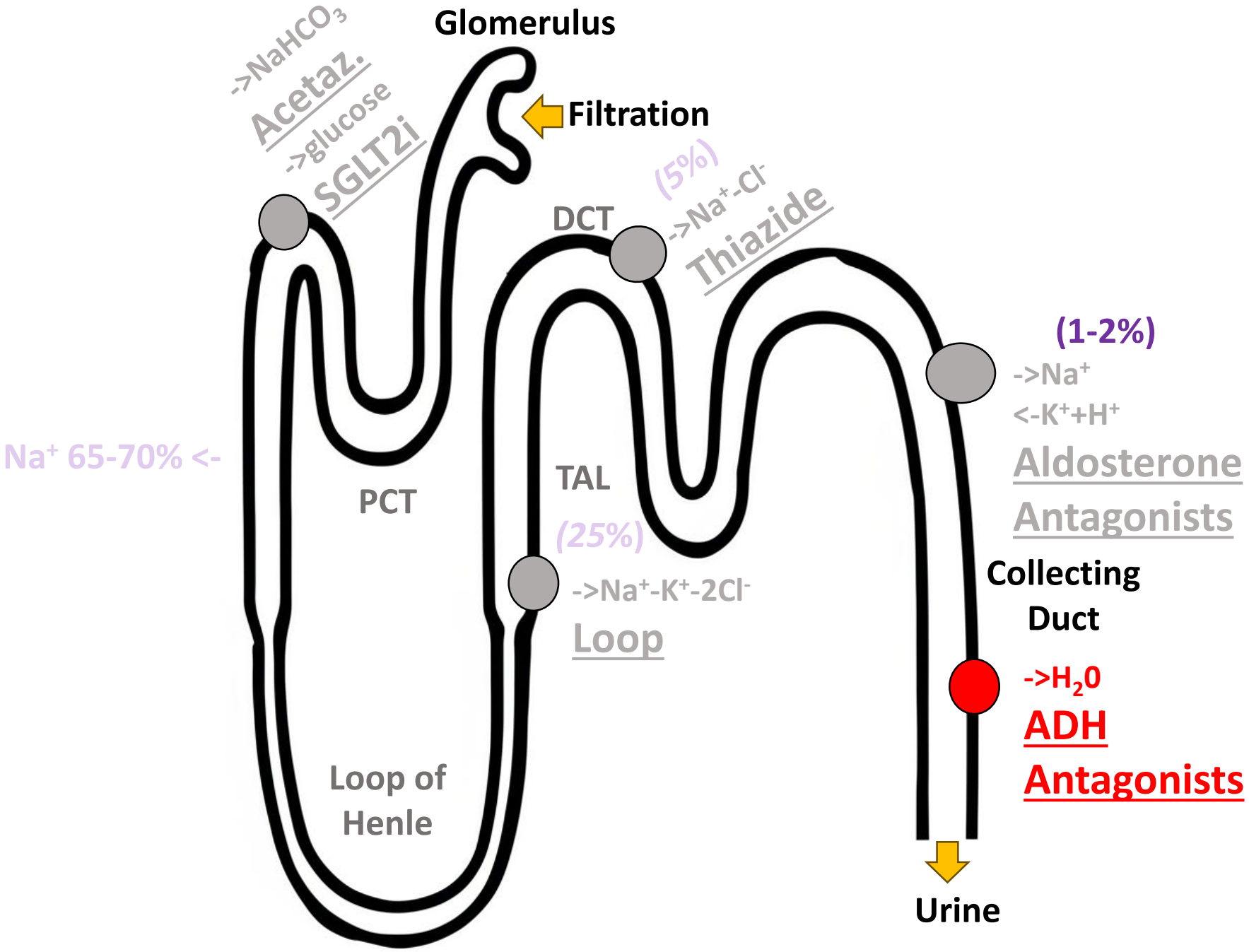
- Serum albumin level doesn't correlate with loop response
- Not recommended in guidelines

PMID: 31010938, 24268626, 34851962

Loop + Albumin Summary

- Not needed

- $$$ and only short-term benefit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ADH V2 Antagonists: Tolvaptan

	Intervention	Outcome
2007 RCT, 4133 pts	Tolvaptan 30mg daily vs. placebo x min 60 days + standard therapy	<u>Primary</u> = mortality, CV death or hospit. for CHF <u>Secondary</u> ↓ day 1 dyspnea + body weight & day 7 edema ↑ serum Na

PMID: 17384437

ADH Antagonist: Tolvaptan

- 2022 AHA/ACC/HFSA Guidelines
  - “If reversing potential causes & free H_20 restriction do not improve hyponatremia, vasopressin antagonists may be helpful…to decrease congestion while maintaining serum sodium.”
- May worsen liver disease
- Risk of rapid correction of hypoNa^+
  - Vs. increased thirst may counteract impact
- > $400/tablet

ADH Antagonist: Tolvaptan

- $$$

- Role limited: fluid overload + refractory hypoNa^+

Patient-centered Waterfall Approach in CHF

Loop Diuretic Summary

- Bolus ≡ Gtt
- Dose > Loop Diuretic Choice
  - Urine Na may help
- Goal = Big Waterfall
- Daily Electrolytes
- K/Mg Normal

Chasing Waterfalls

- Start with loop & ↑ dose early (UOP/Urine Na)
  - Add SGLT2i early = long-term + improve diuresis + counteract ↓ Mg/uric acid
  - Add MRA early = long-term + may counteract ↓ K/Mg & ↑ in HCO3

- If not responding, then:
  - If bicarb ↑ = acetazolamide
  - If bicarb normal = thiazide
  - If Cl/Na ↓ = hypertonic saline

- Consider Hypertonic saline/acetazolamide earlier with loop
- Tolvaptan only fluid overload + refractory hypoNa^+