Approach to the patient with hyperkalaemia

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Outline

- Definition
- Physiological basis
- Evaluation
- Management

Definitions

Definitions

Hyperkalemia is defined as a serum potassium level above the normal/reference range (3.0 - 5.0 mEq/L*)

Various cutoffs, such as >5.0, >5.5, or >6.0 mEq/L have been used to indicate different levels of severity

Severe hyperkalemia is most often defined as serum levels >6 mEq/L

Viera A, Wouk N. *Am Fam Physician*. 2015;92:487-495.

Epstein M, et al. *Am J Manag Care*. 2015;21(11 Suppl):S212-S220.

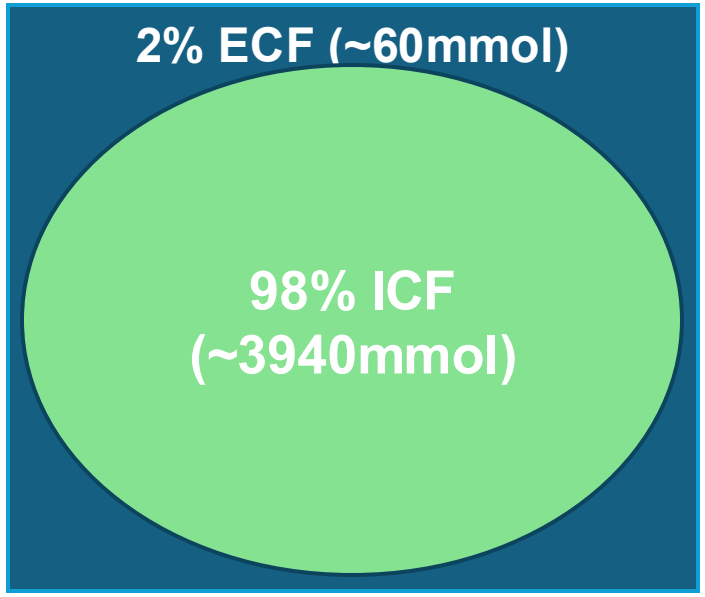
Acute Versus Chronic Hyperkalemia

Acute Hyperkalemia	Chronic Hyperkalemia
Requires immediate attention (e.g., cardiac monitoring, acute medical interventions, possibly dialysis)	Requires ongoing management to correct underlying disturbances in potassium balance (i.e., nonpharmacological and pharmacological interventions)

Kovesdy C. *Nat Rev Nephrol*. 2014;10:653-662.
Viera A, Wouk N. *Am Fam Physician*. 2015;92:487-495.

Physiological basis

- K^+ most abundant Cation
- Distribution:



ICF:ECF [K^+] reflects RMP

Skeletal Muscle: ⅔ Body K^+

Potassium Homeostasis

- 2 Important Regulatory Systems:

i) *SHIFTS*: Intracellular ⟺ Extracellular

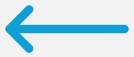
ii) *Intake and EXCRETION*:

EXCRETION:
- 90-95% by Kidneys
- 5-10% by Gut

Potassium secretion

The degree of potassium secretion is primarily stimulated by three factors:

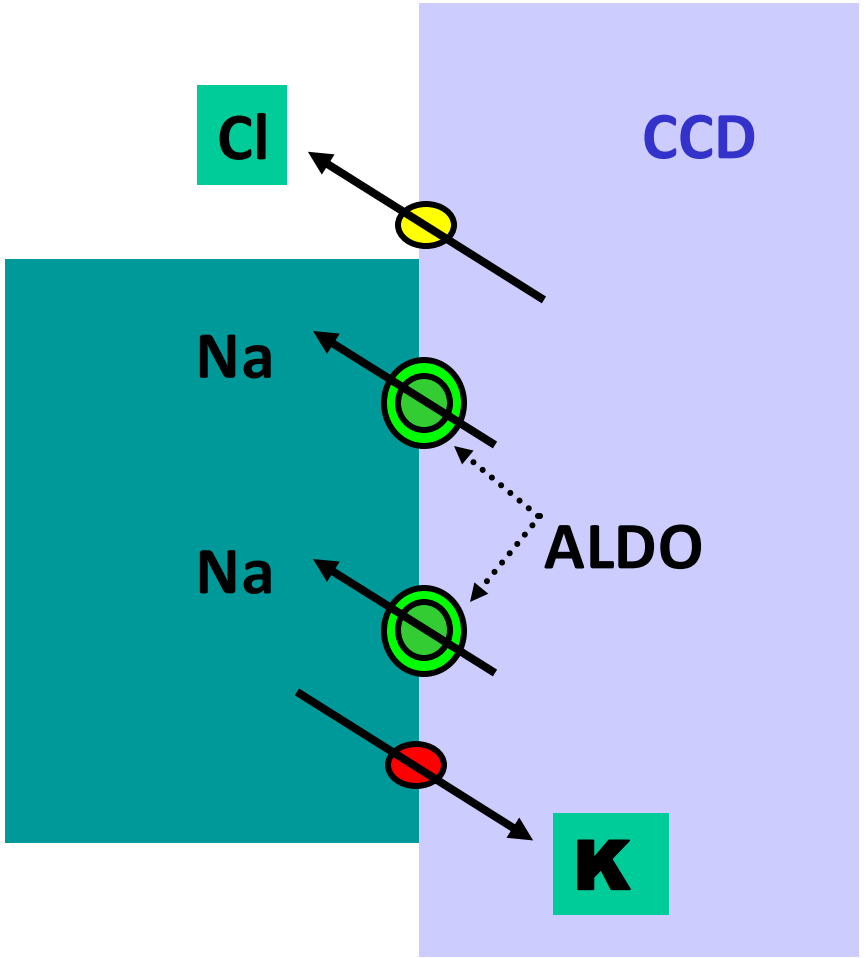
An increase in the serum potassium concentration



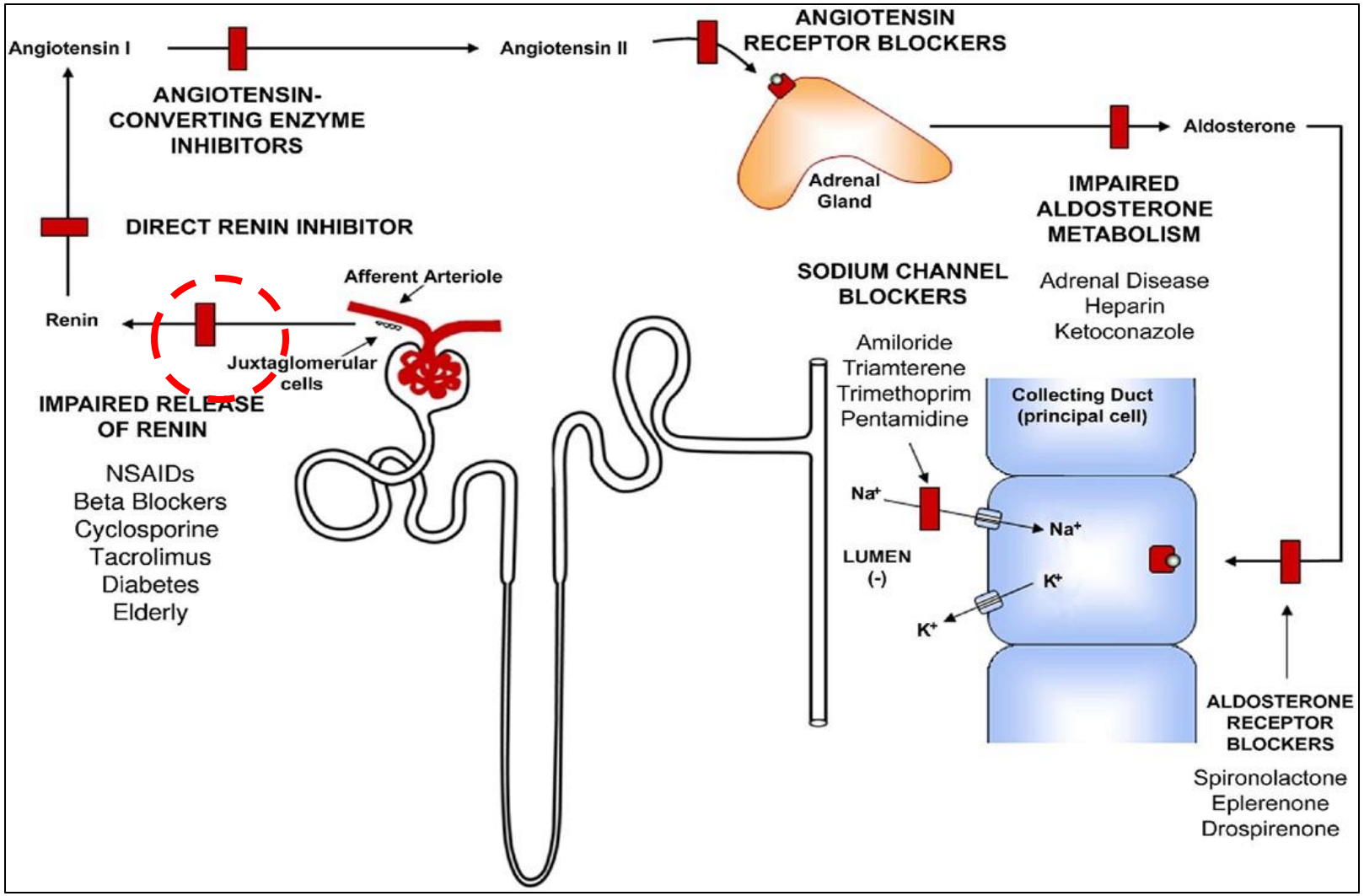
A rise in the plasma aldosterone concentration

Enhanced delivery of sodium and water to the distal secretory site

K^+ secretion in the CCD



Pathogenesis of Hyperkalemia: RAAS and Potassium Excretion



RAAS, renin-angiotensin-aldosterone system

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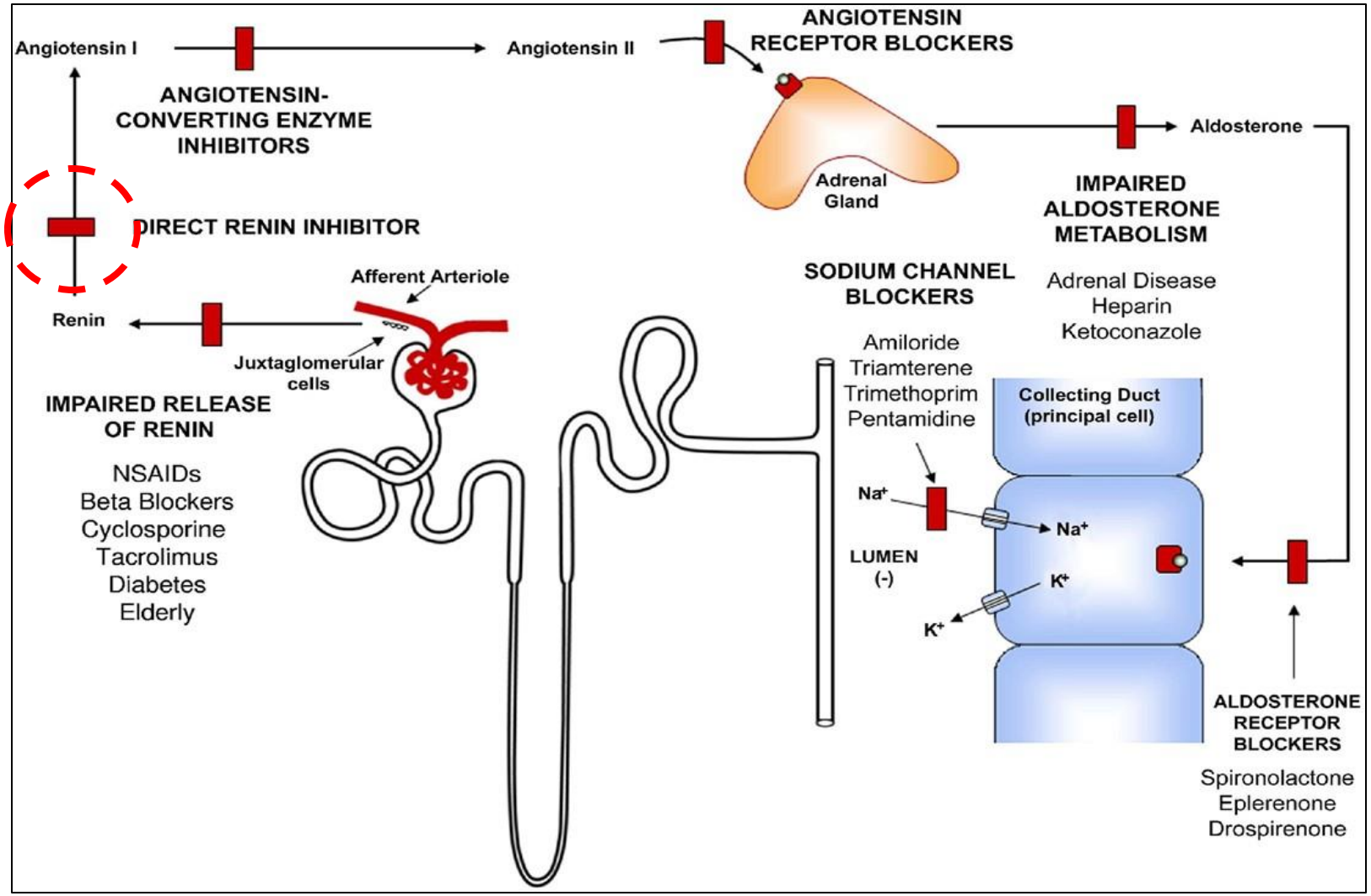

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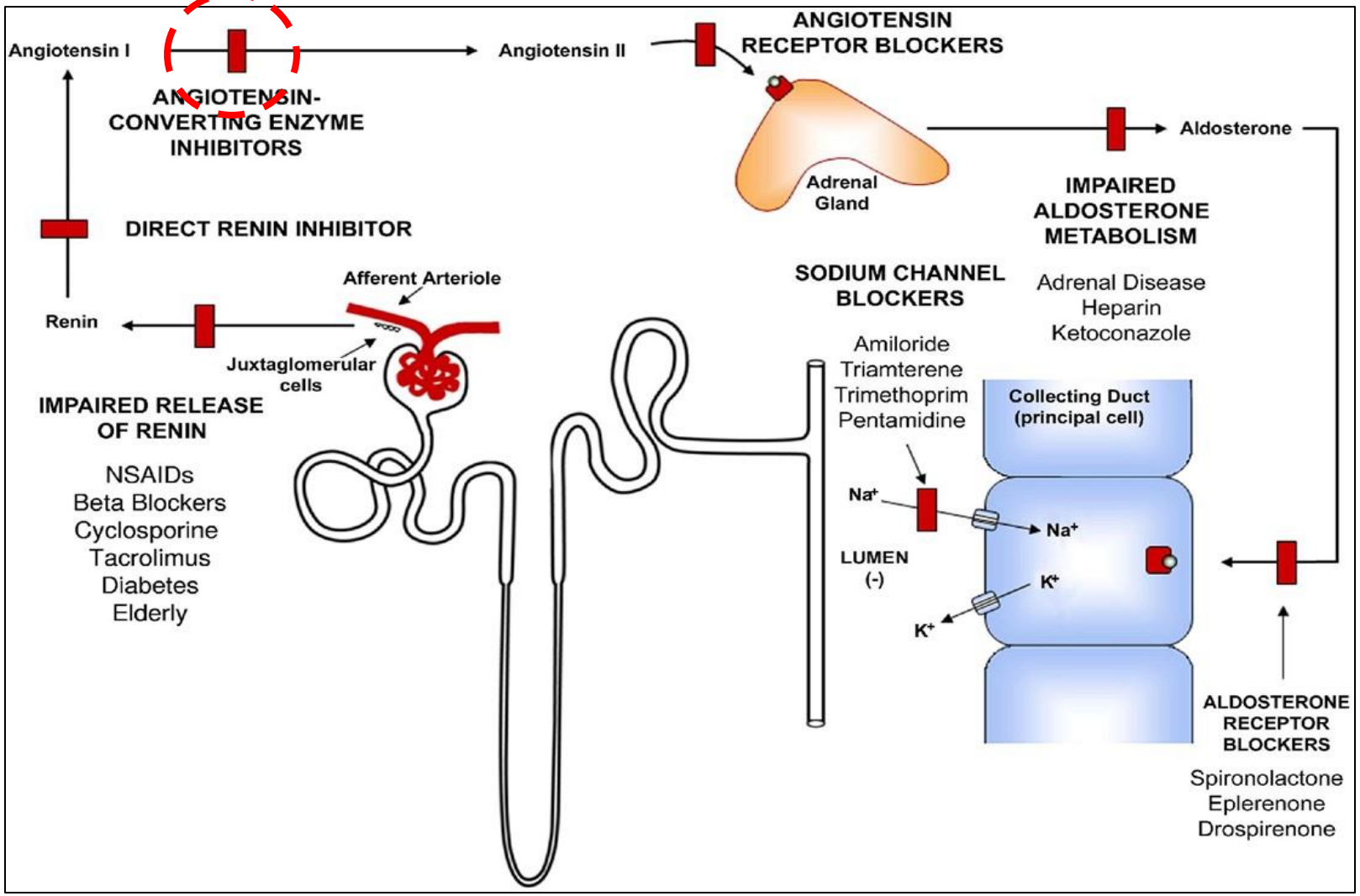

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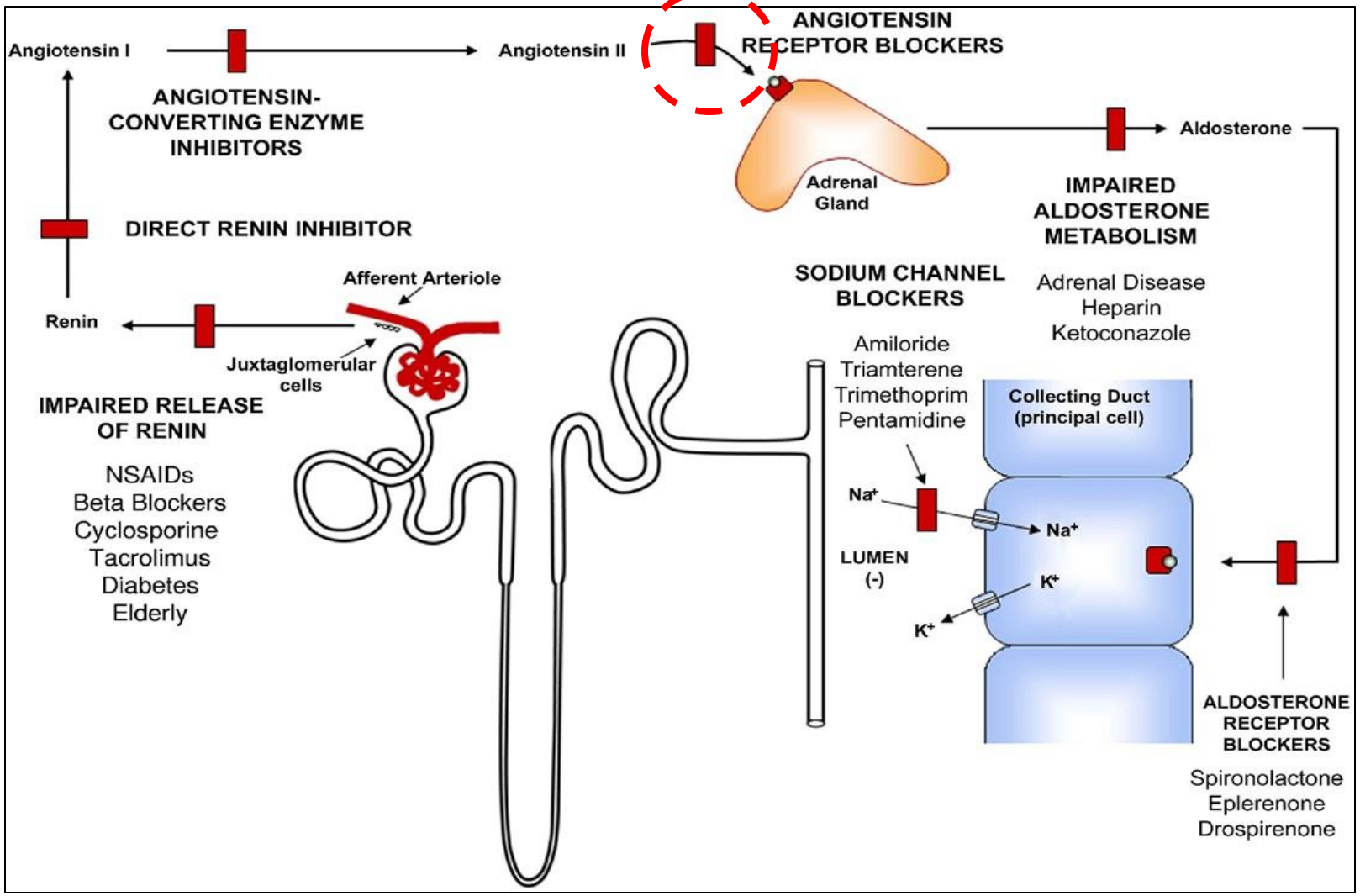

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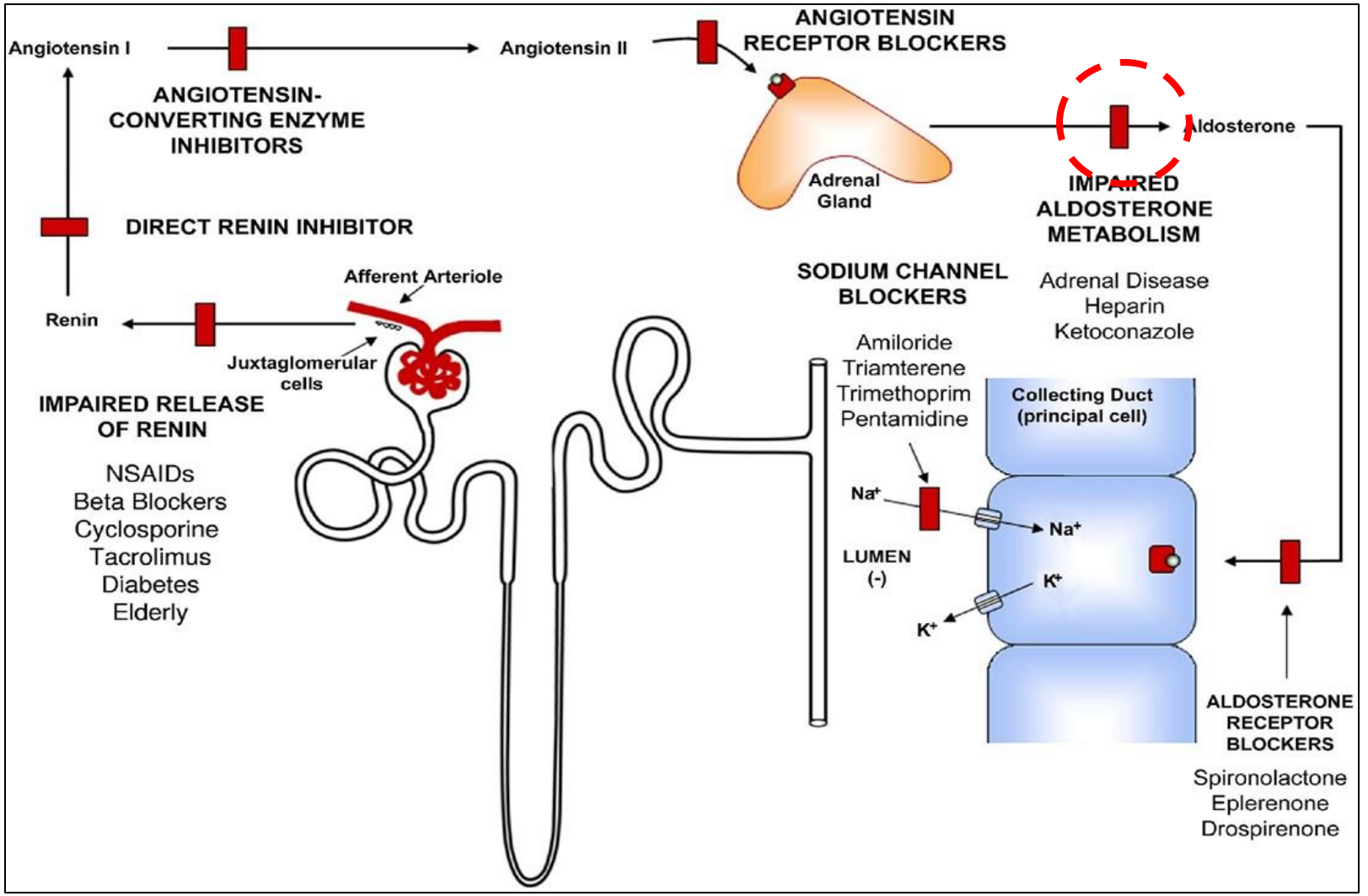

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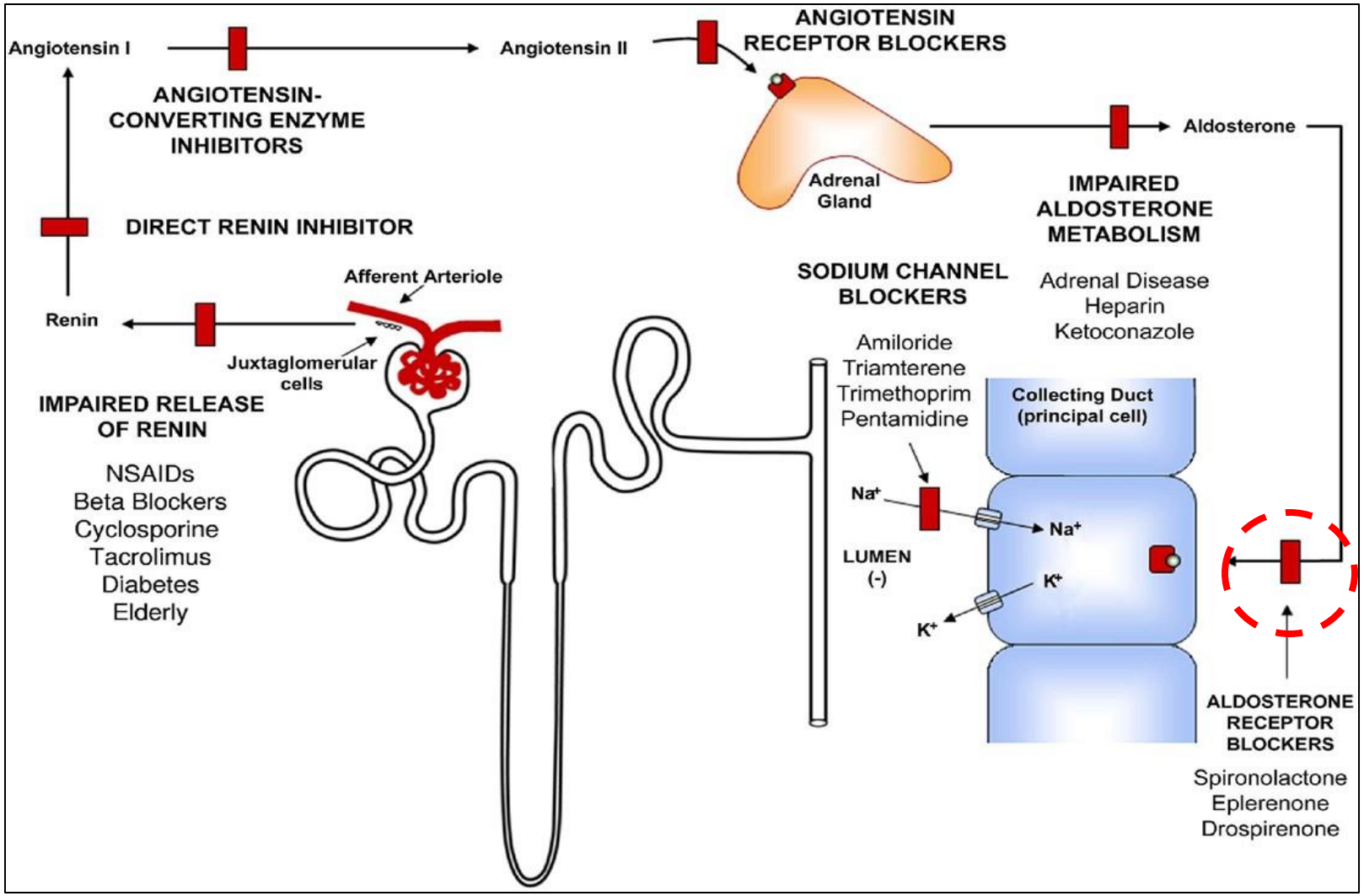

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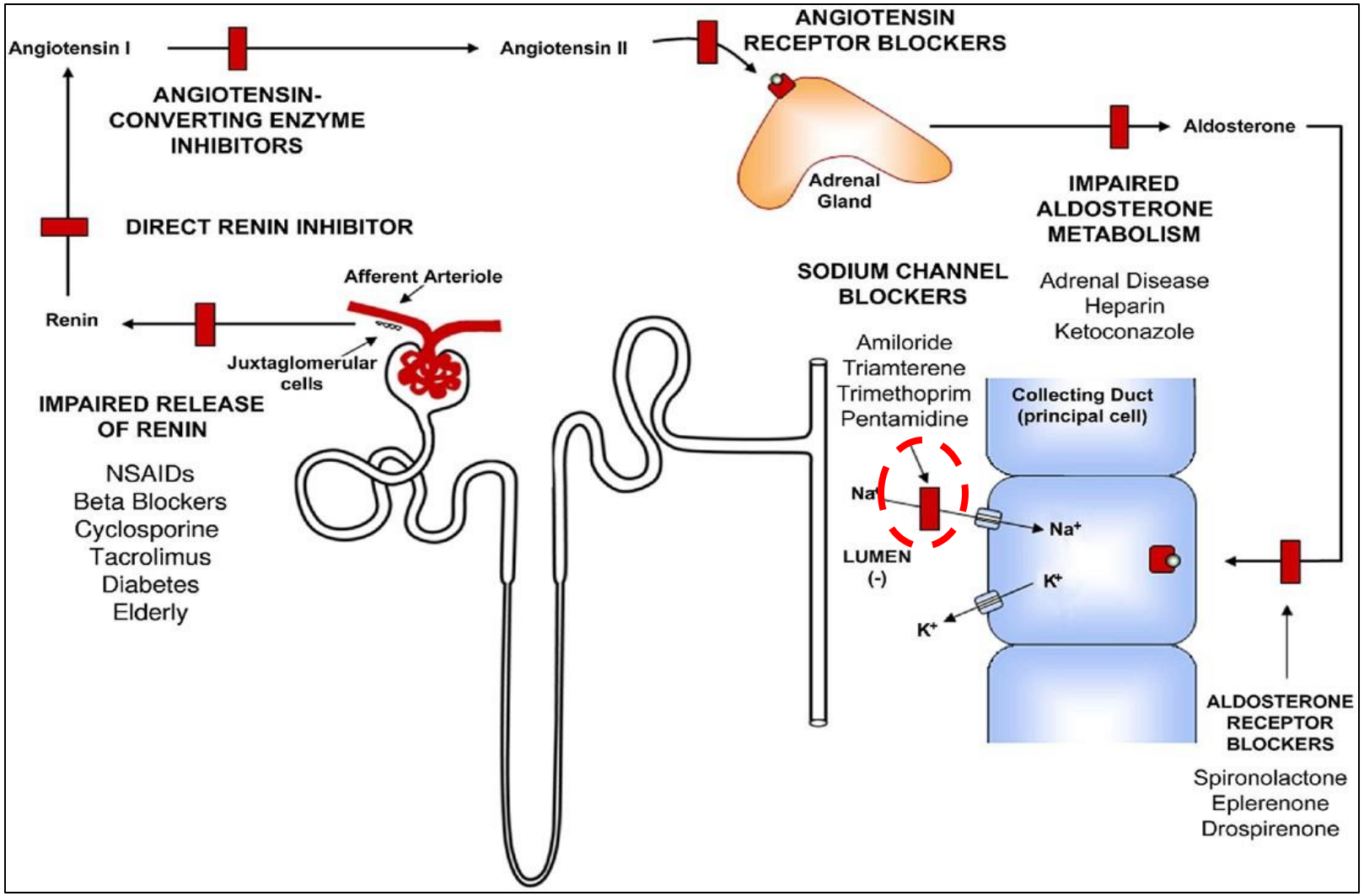

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Drugs Known to Induce Hyperkalemia

Method of Induction	Examples
Drug-inducing transmembrane potassium movement	Non-selective beta blockers Digoxin intoxication Intravenous cationic amino acids Mannitol Suxamethonium
Drugs that affect aldosterone secretion	ACE inhibitors ARBs Direct renin inhibitors NSAIDs and COX-2 inhibitors Calcineurin inhibitors
Drugs that cause tubular resistance to the action of aldosterone	Aldosterone antagonists Potassium-sparing diuretics Trimethoprim, pentamidine
Potassium-containing agents	Salt substitutes and alternatives Penicillin G, stored blood products

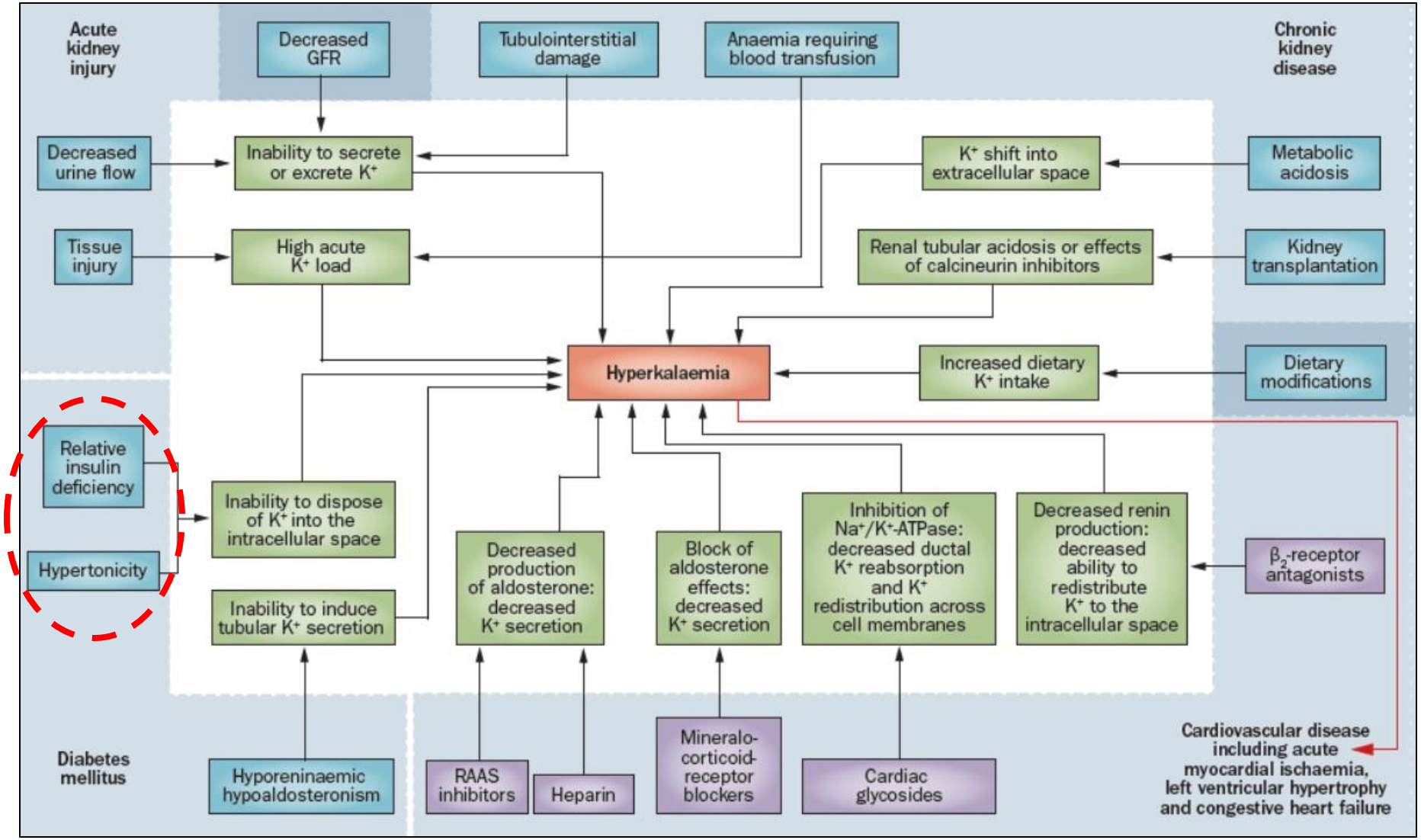
Ben Salem C, et al. *Drug Saf*. 2014;37:677-692.

Causes of Hyperkalemia

- **Pseudohyperkalemia**
  - Hemolysis
  - Thrombocytosis
  - Severe Leukocytosis
  - Fist clenching (venipuncture)
- **Abnormal Potassium Distribution**
  - Insulin Deficiency
  - Beta-blockers
  - Metabolic or respiratory acidosis
  - Familial hyperkalemic periodic paralysis
- **Abnormal Potassium Release from Cells**
  - Rhabdomylosis
  - Tumor Lysis syndrome
- **Decreased Renal Excretion**
  - Acute or Chronic kidney disease
  - Diseases that impact kidney function (e.g., lupus)
  - Aldosterone deficiency
  - Adrenal insufficiency
  - Heart failure
  - Drugs that inhibit potassium excretion

Modified from Allon M. NKF Primer on Kidney Diseases. 2014.

Mechanisms of Hyperkalemia in CKD



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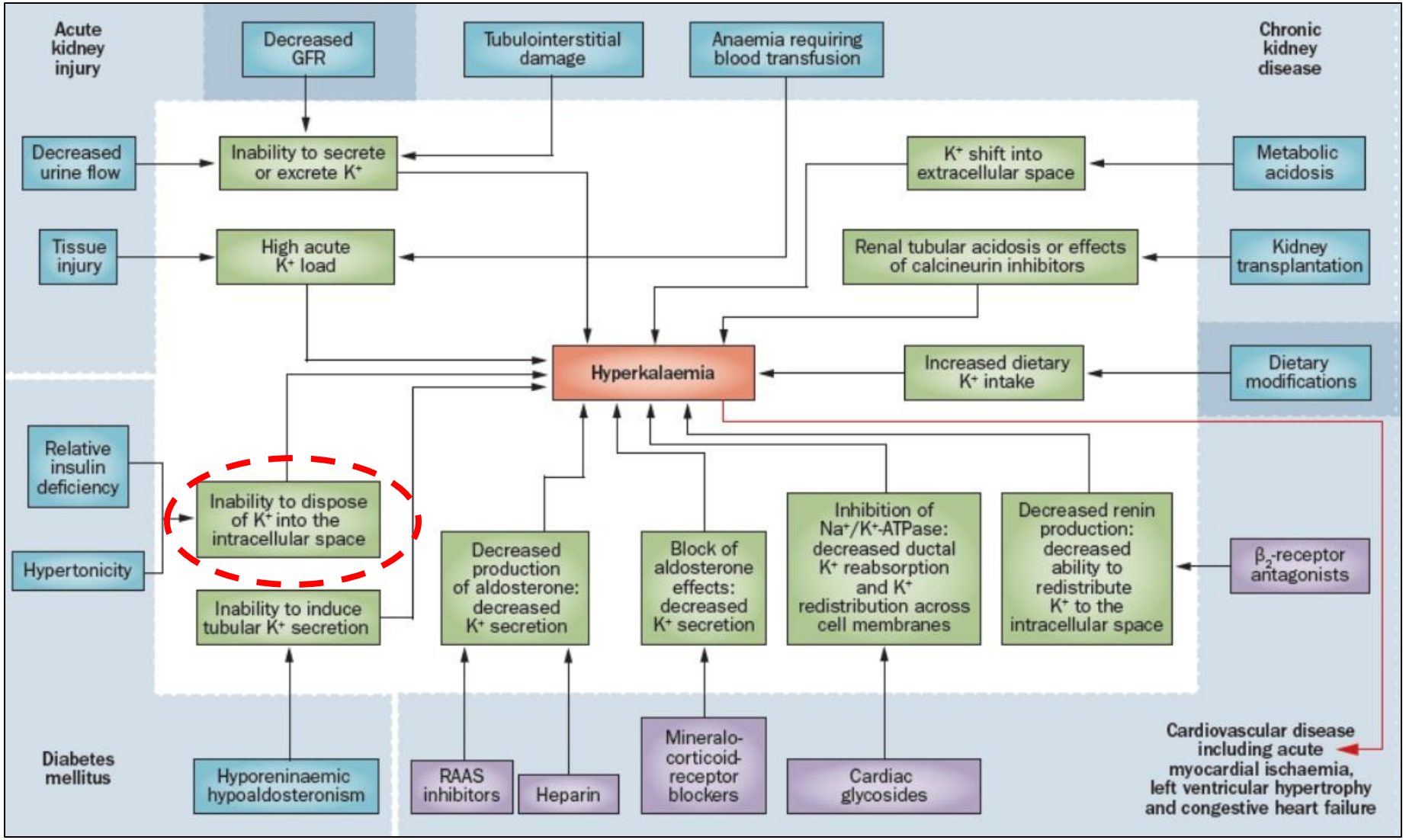

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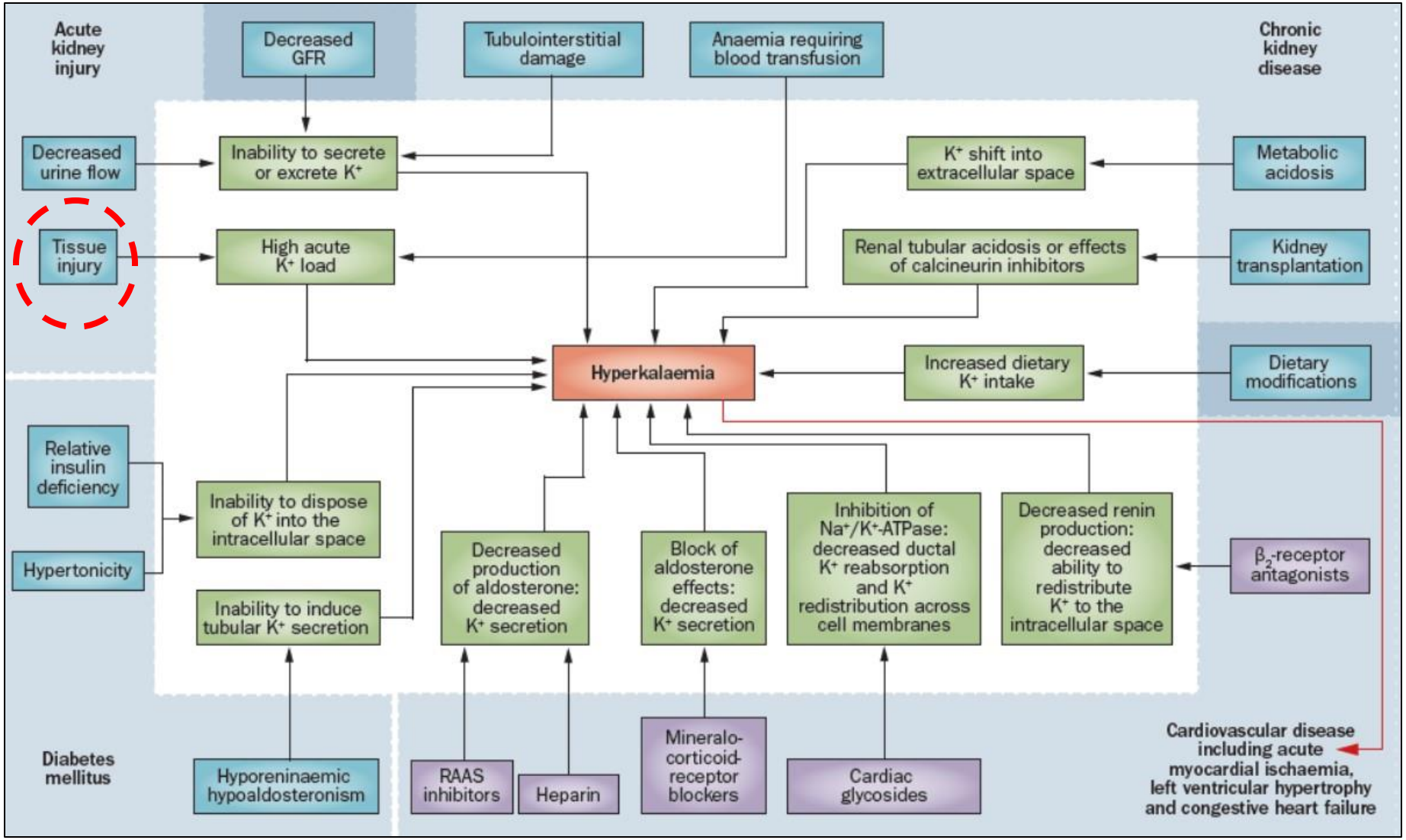

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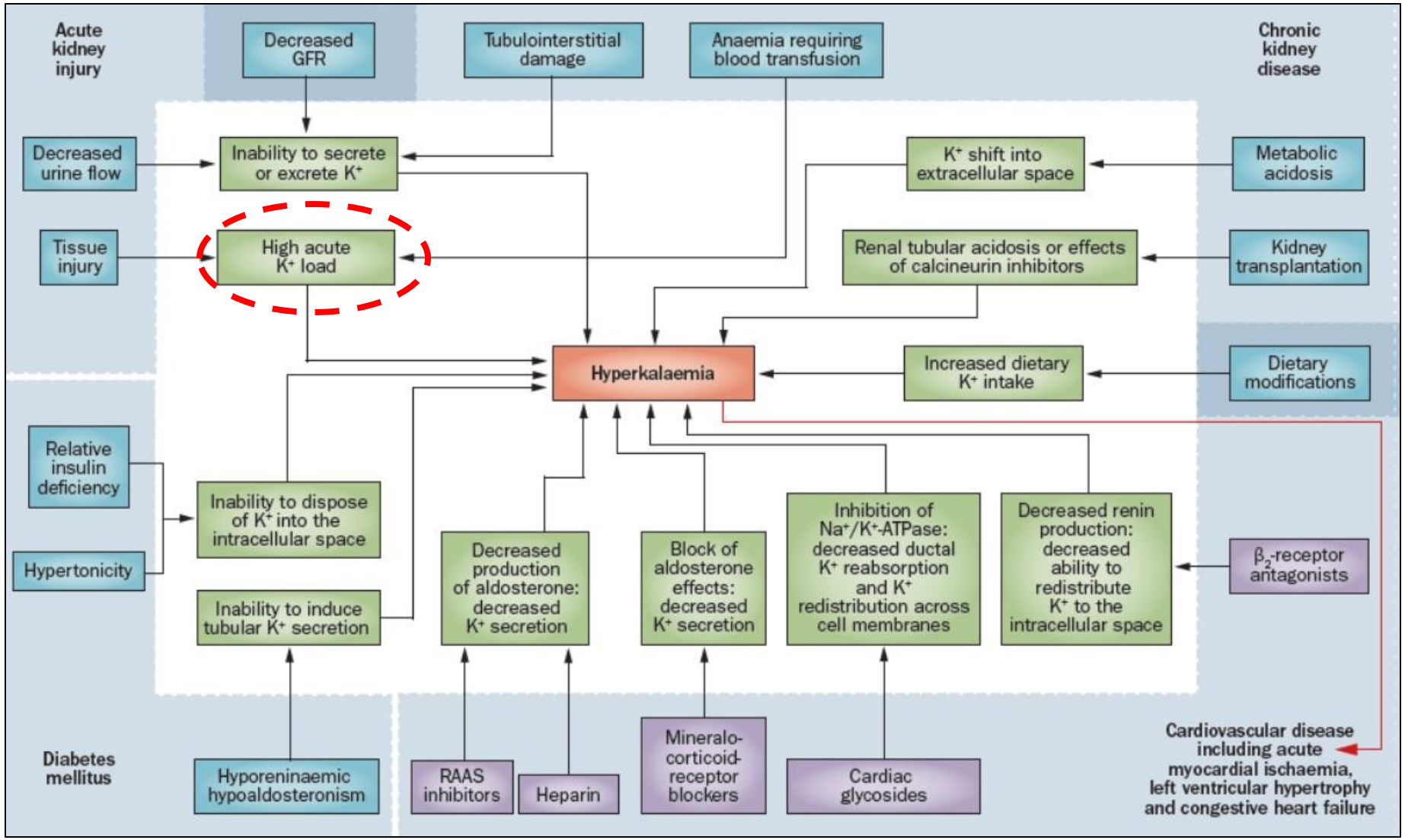

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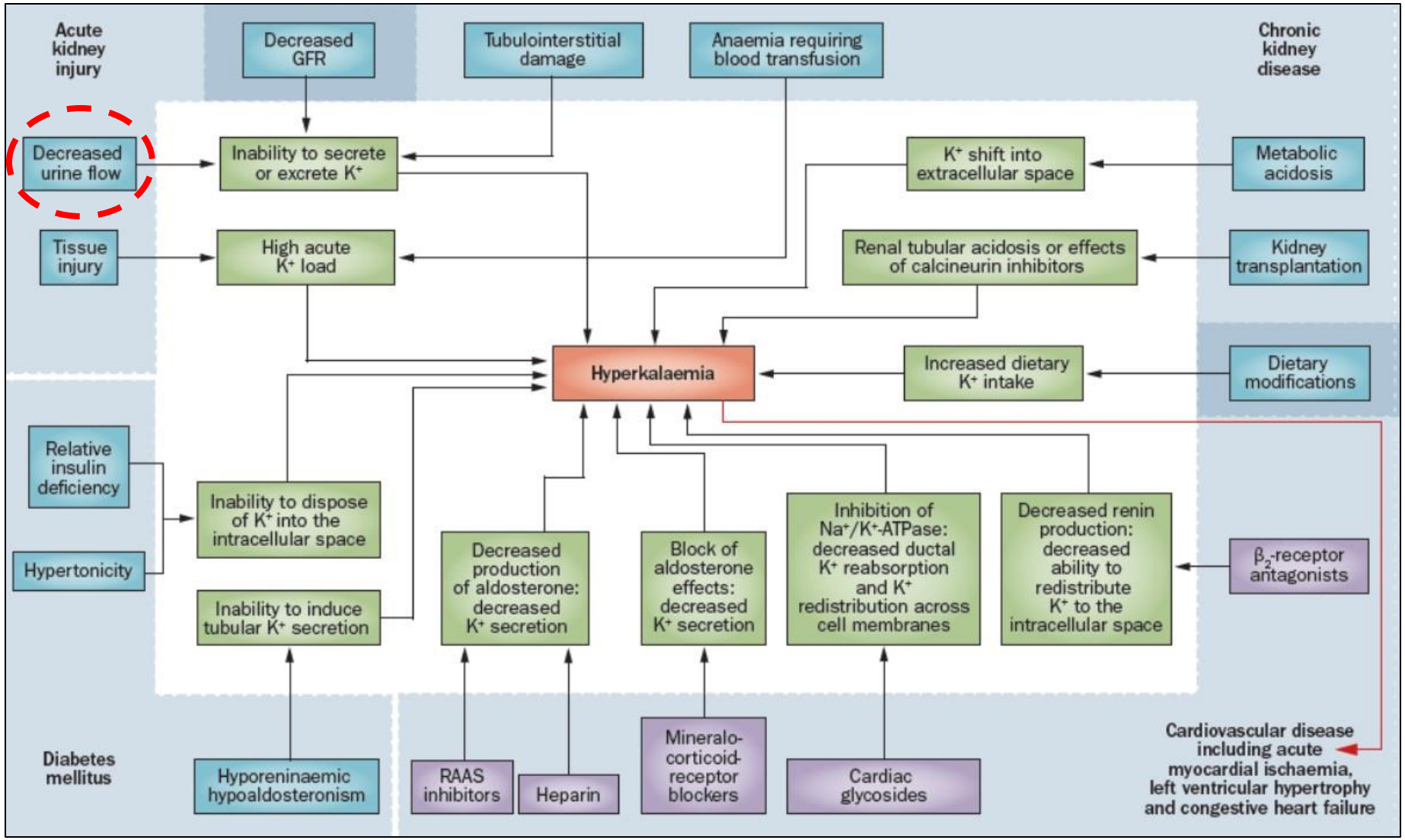

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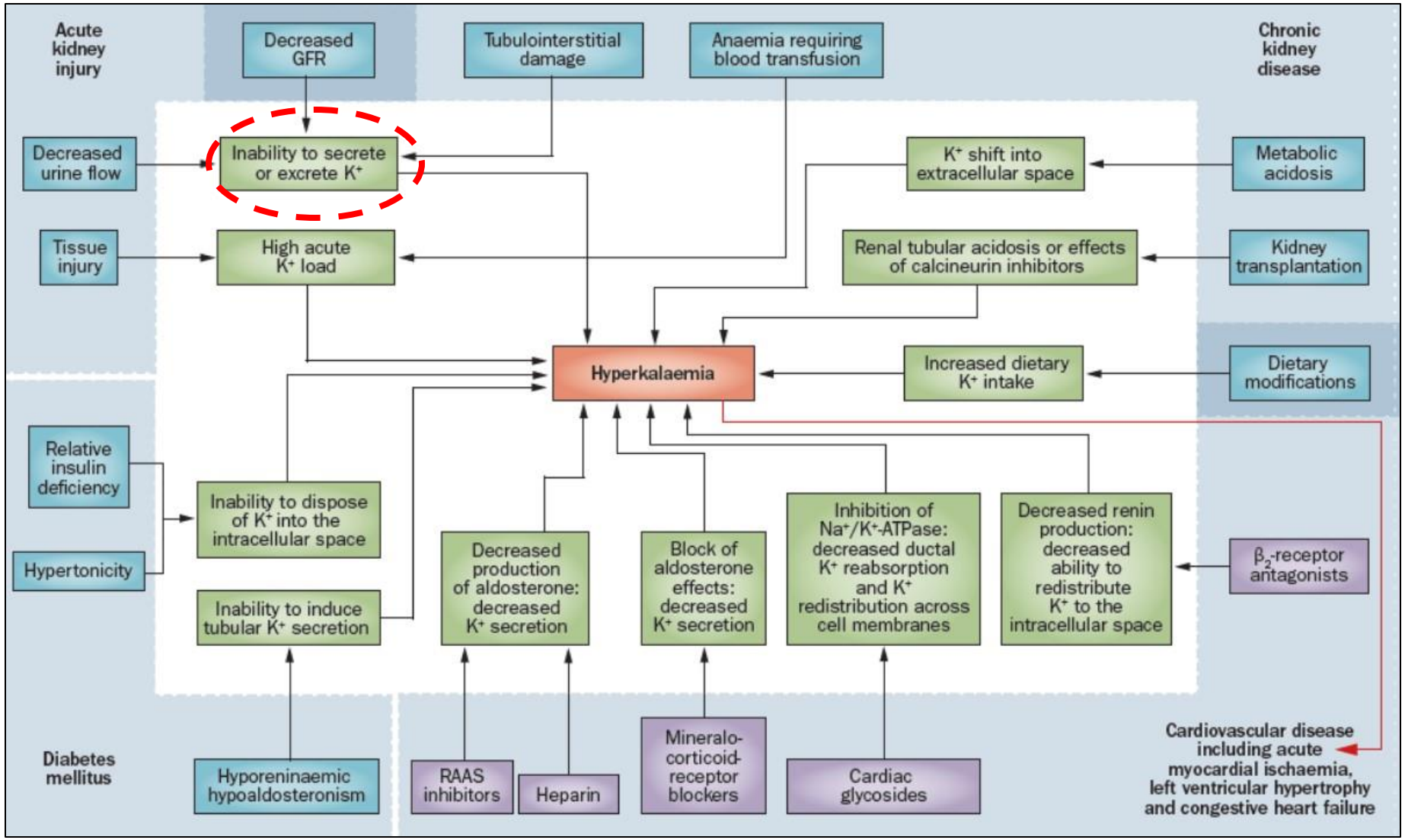

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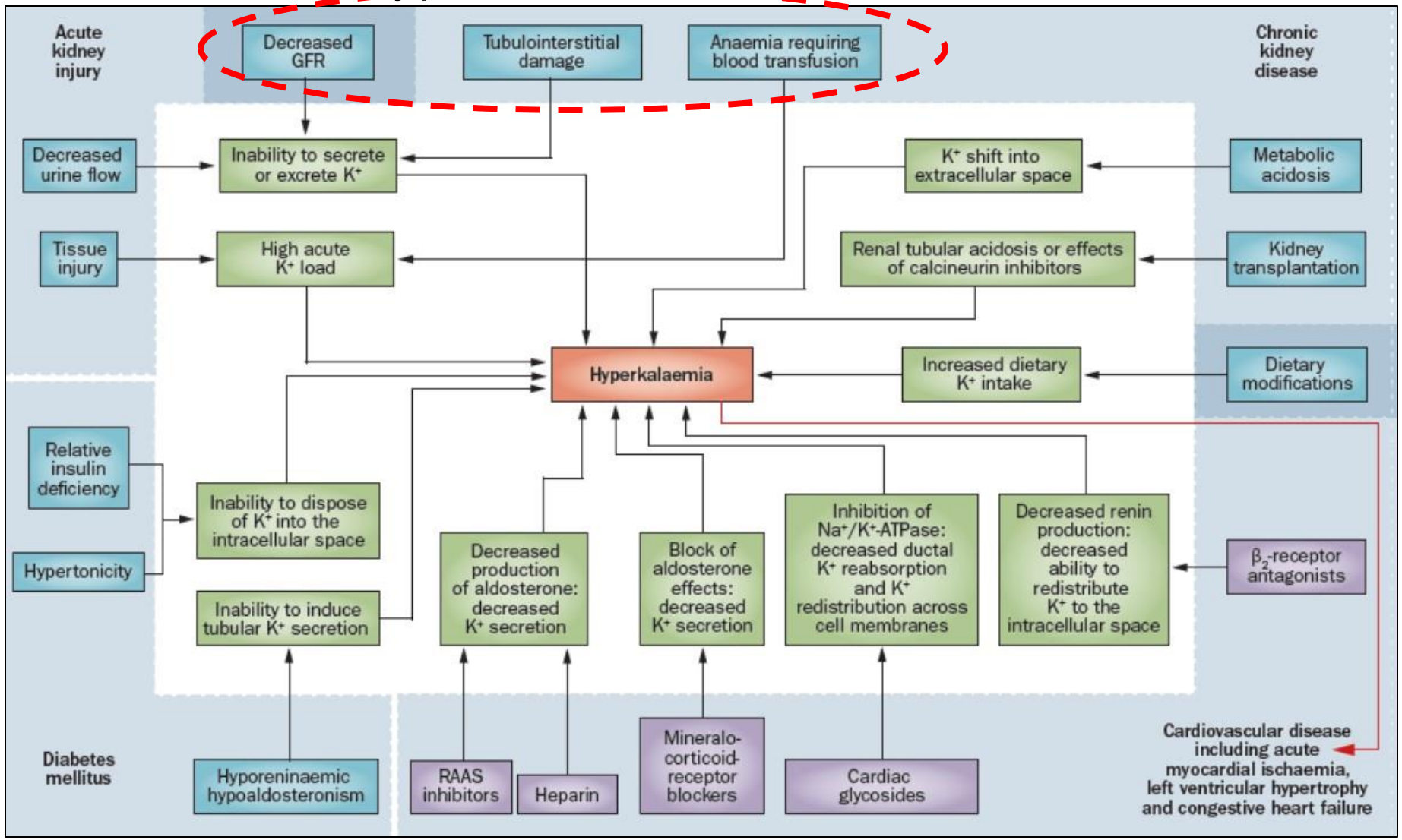

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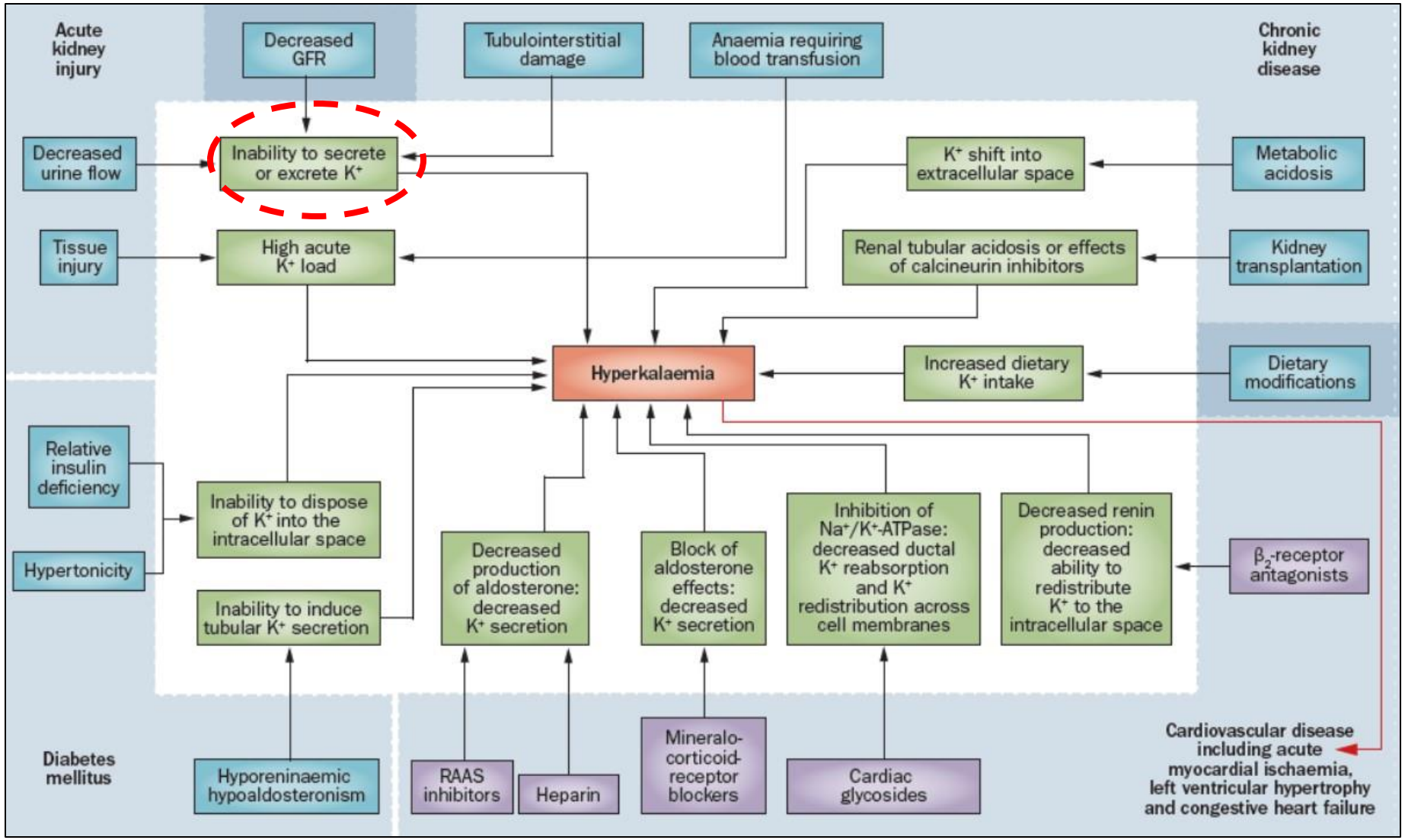

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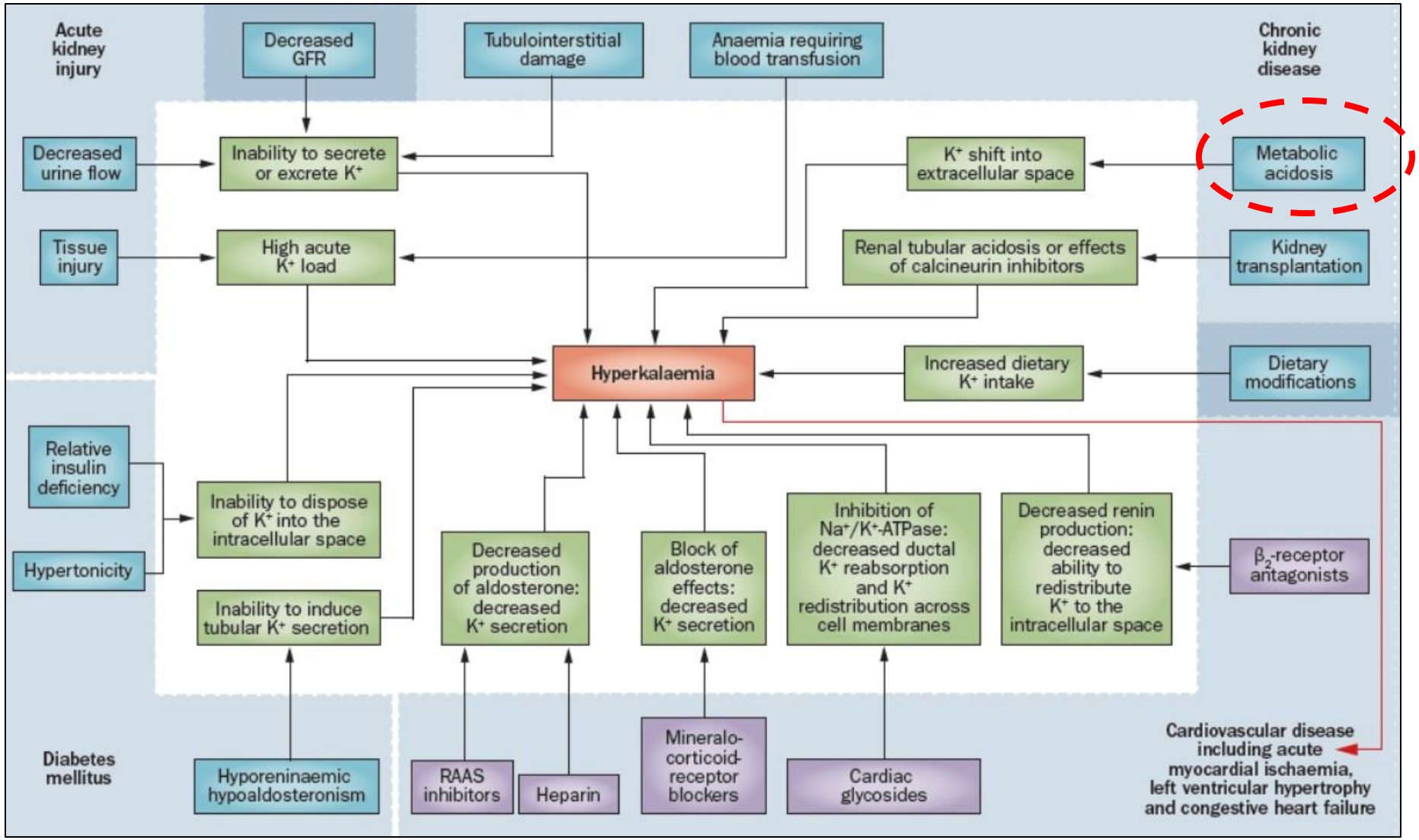

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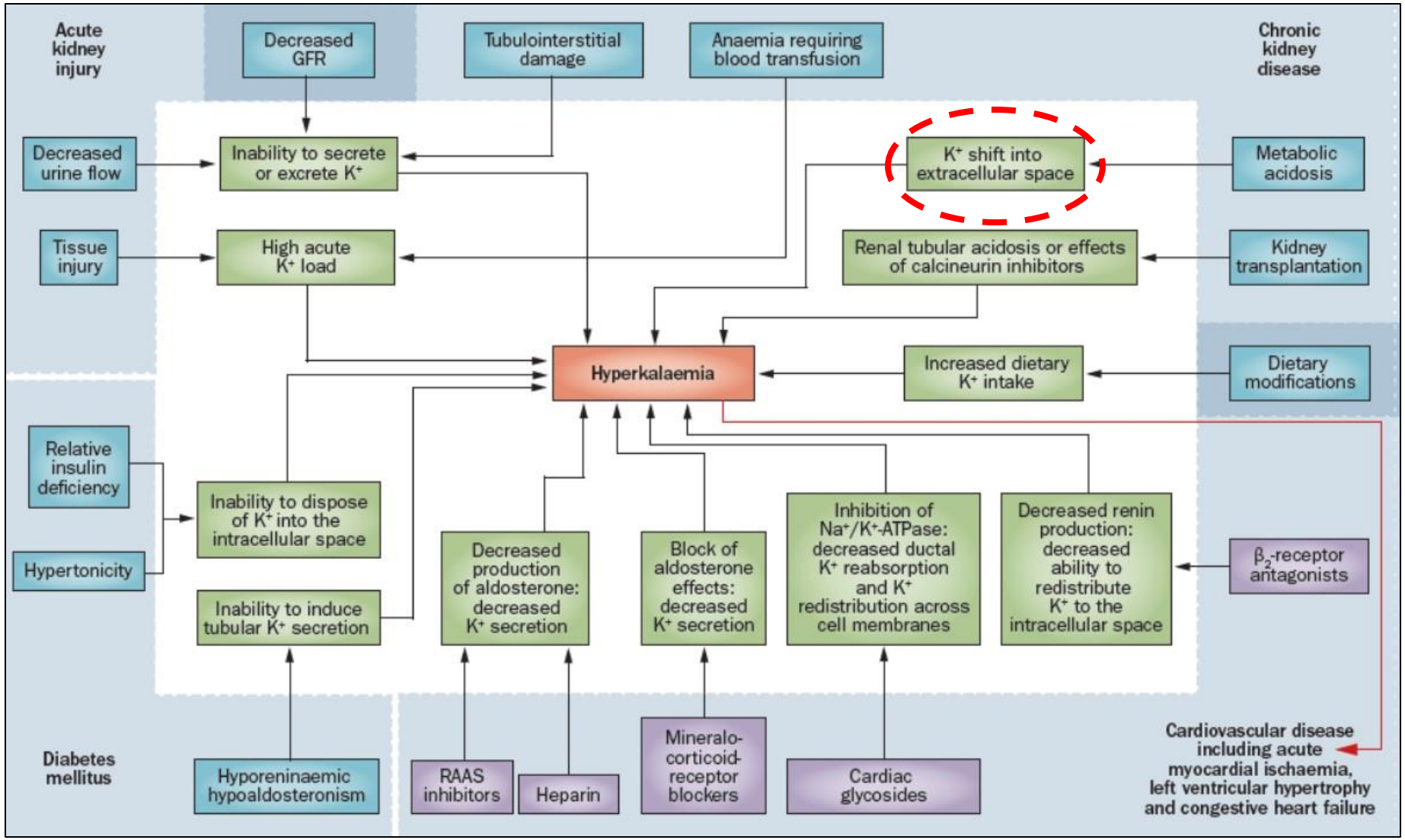

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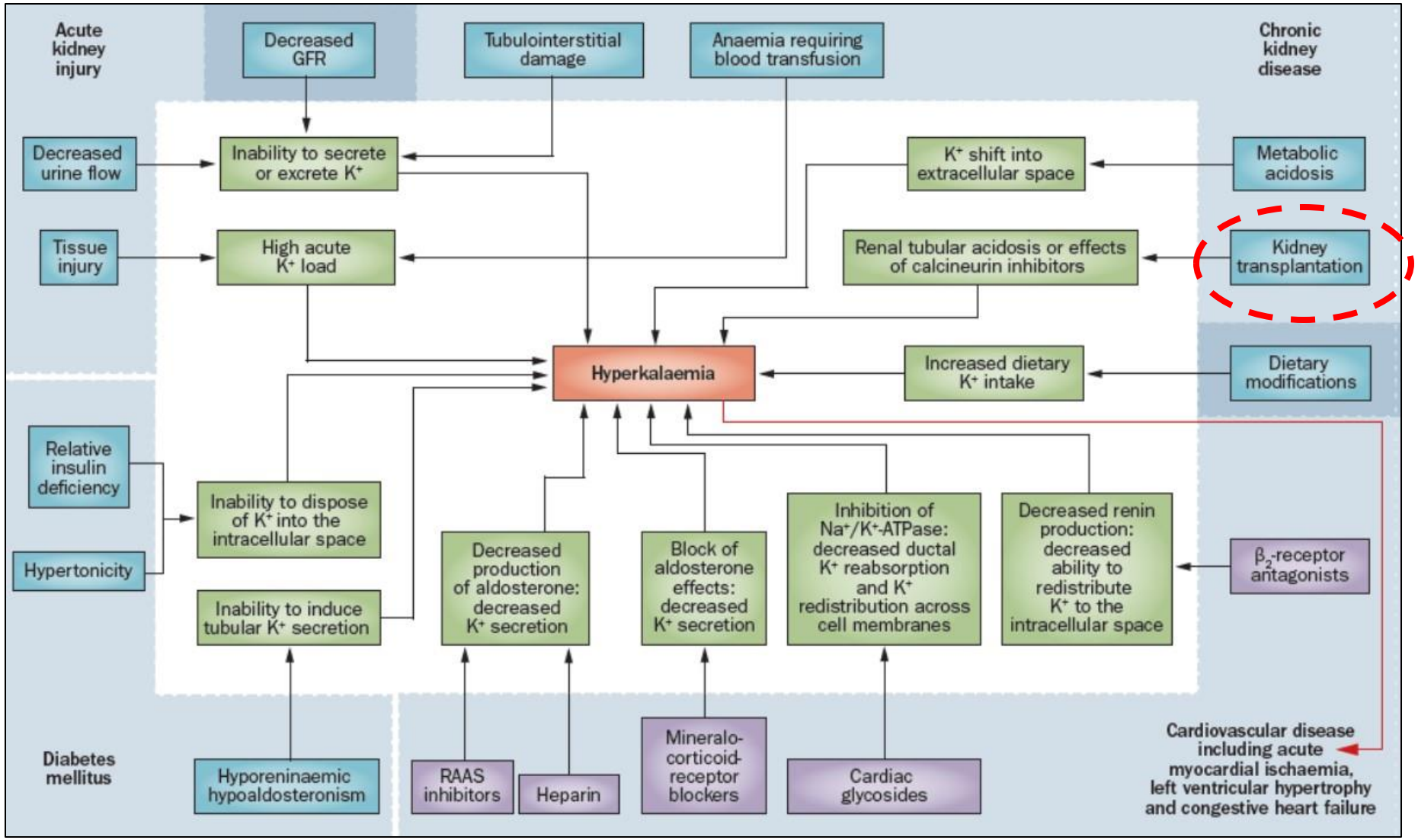

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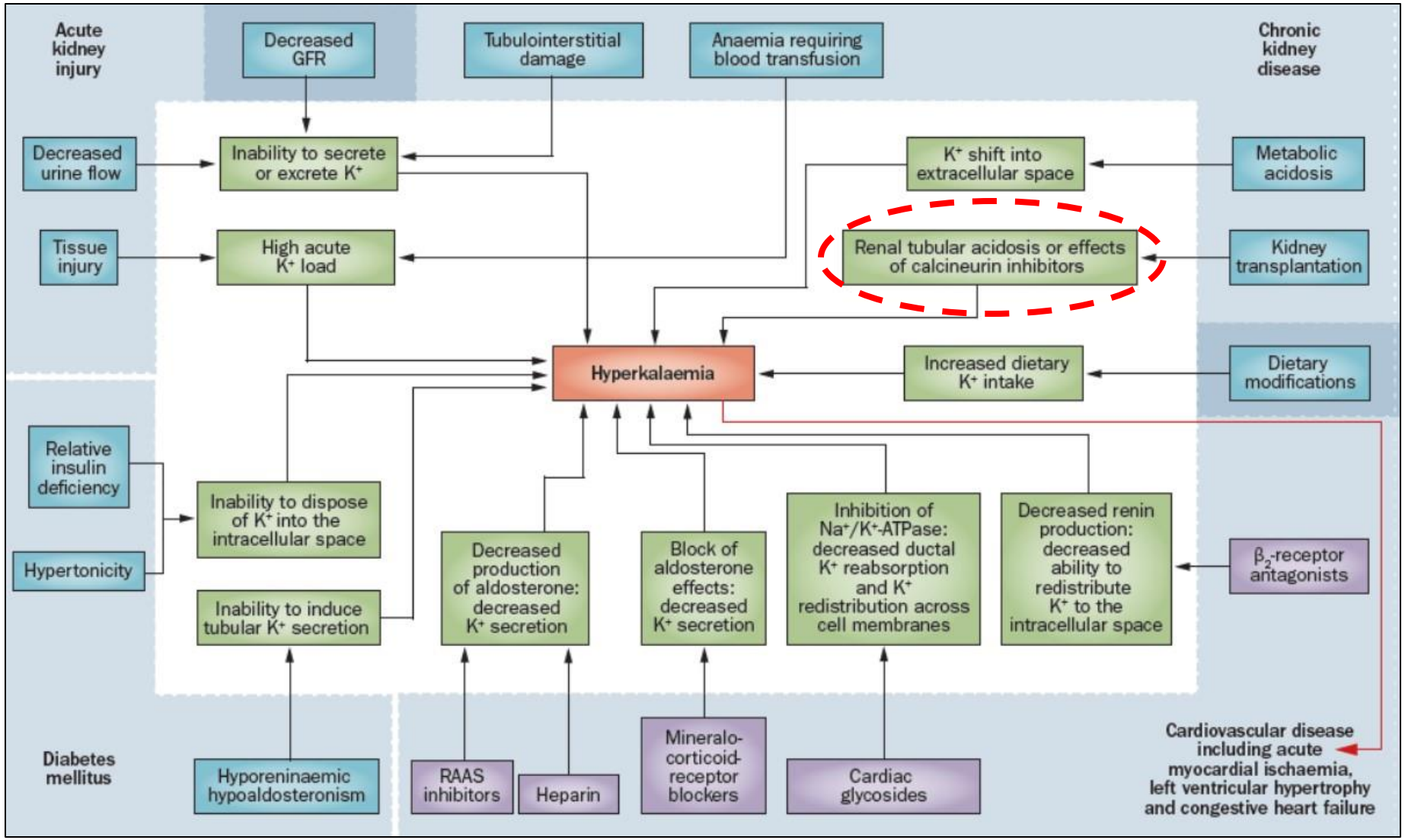

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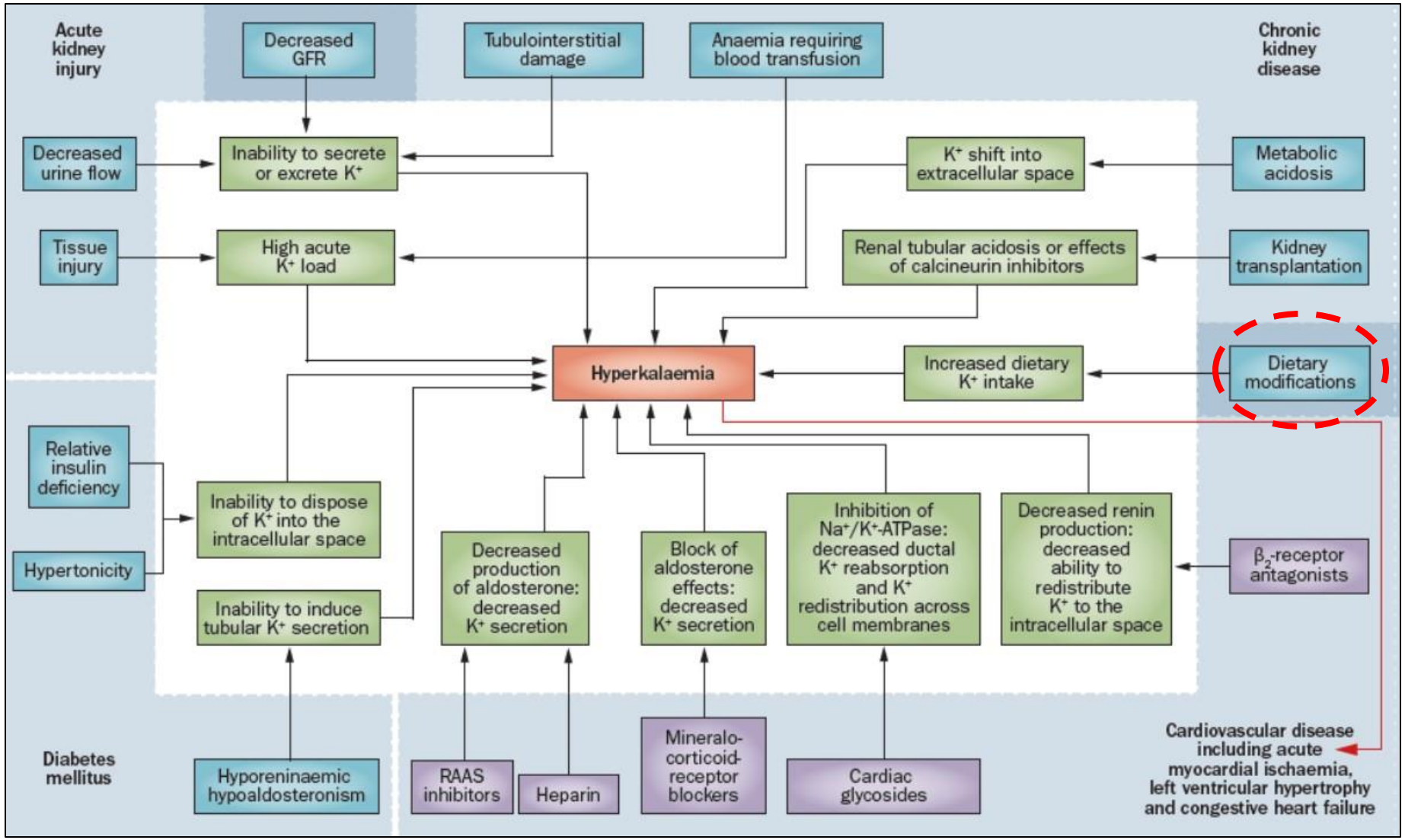

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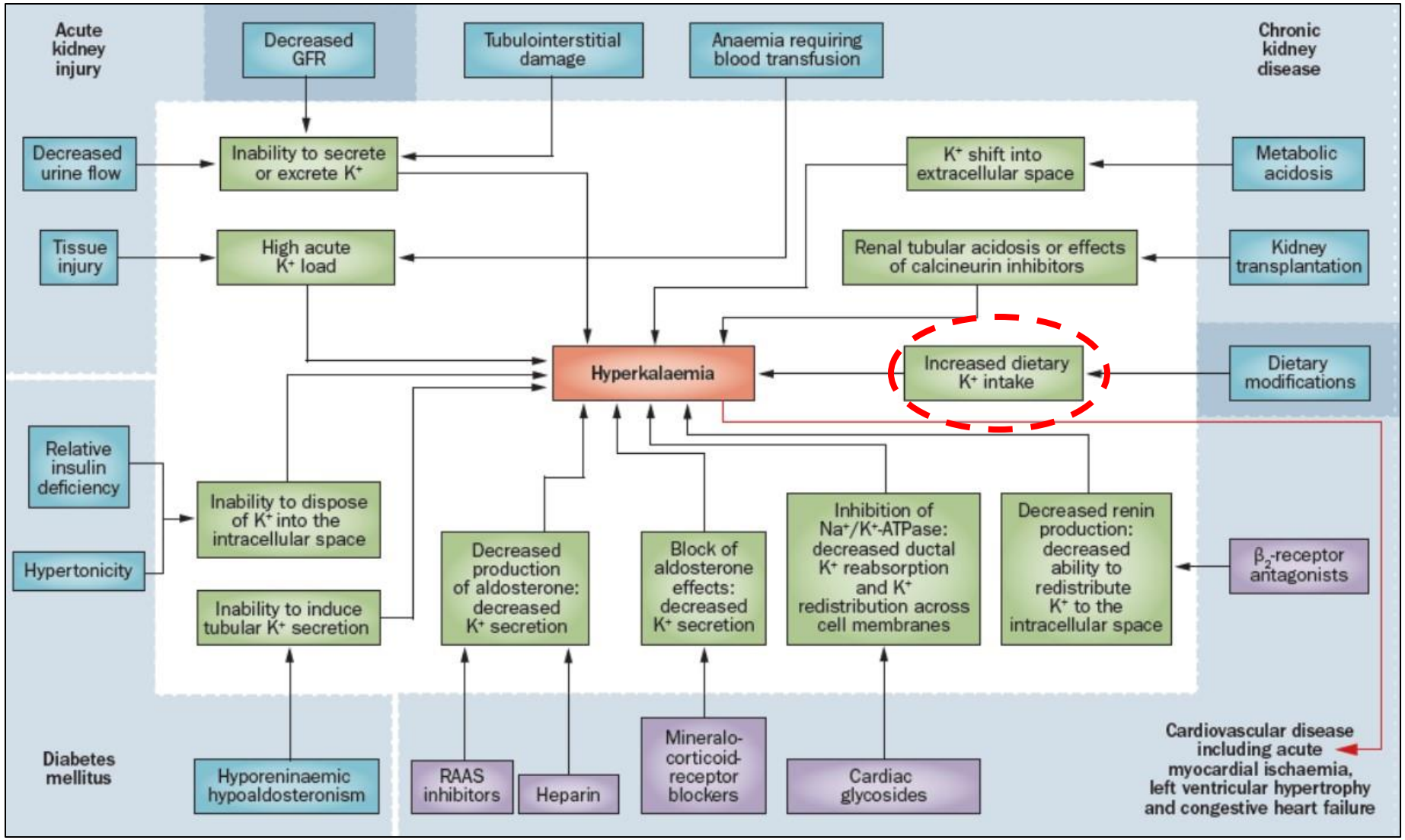

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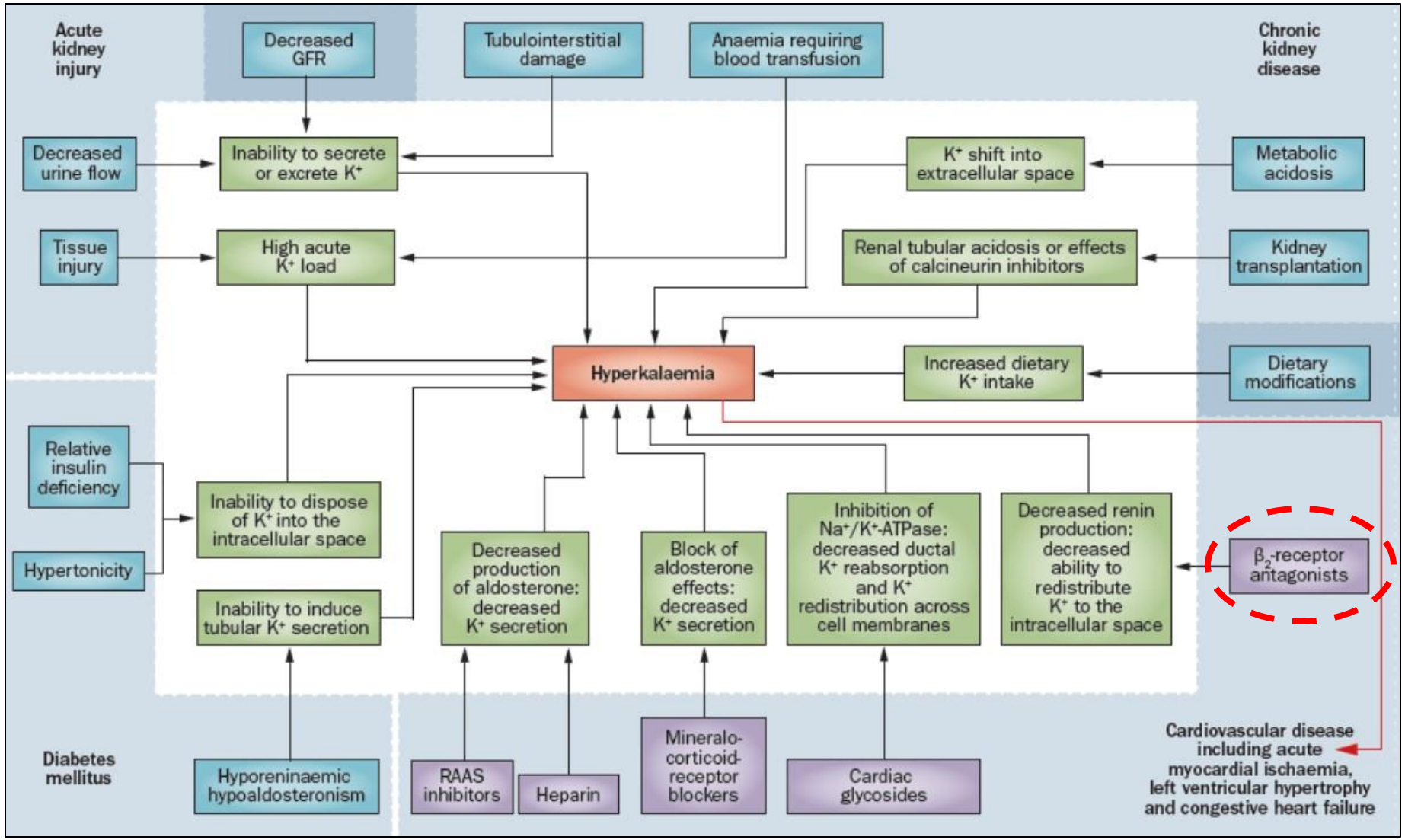

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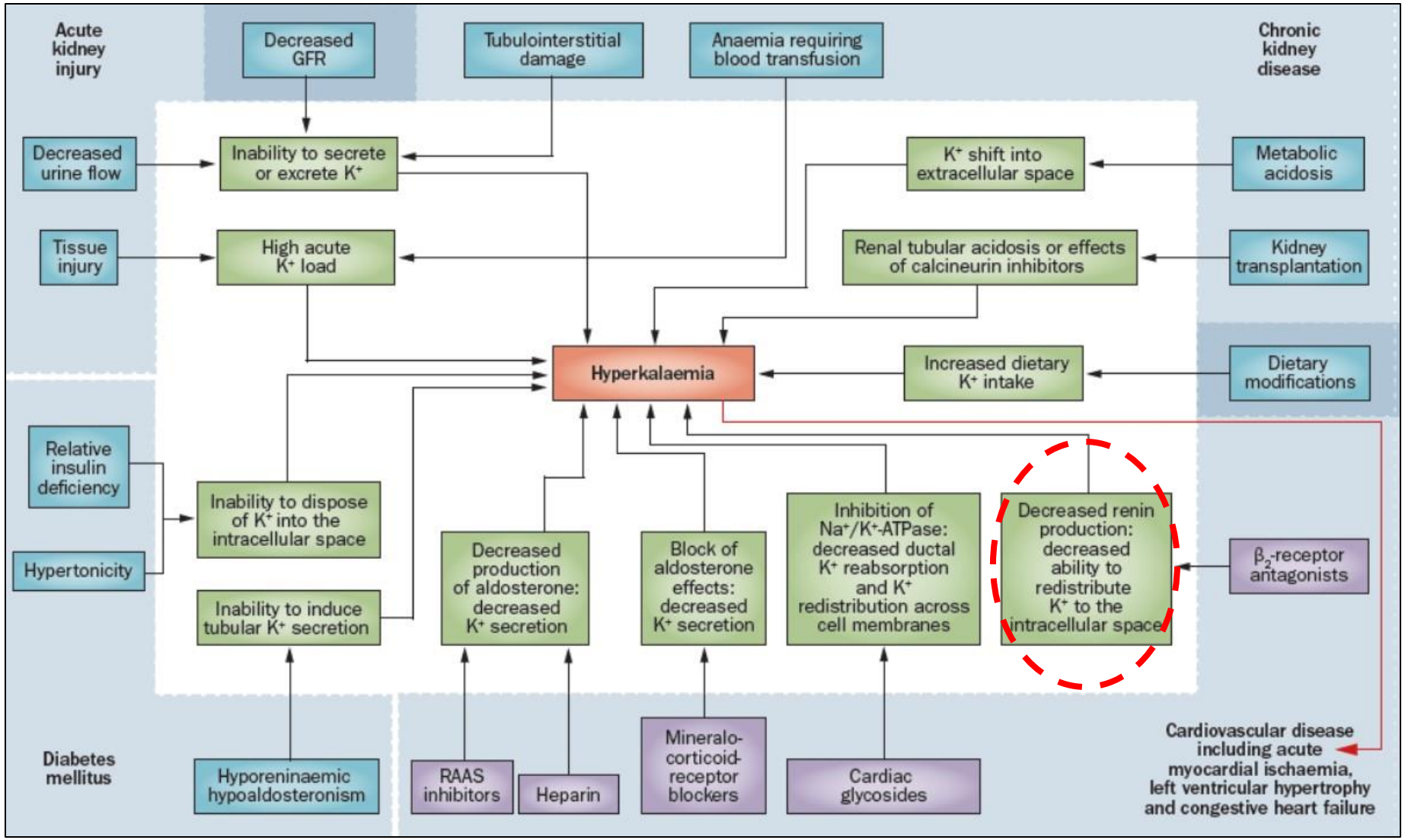

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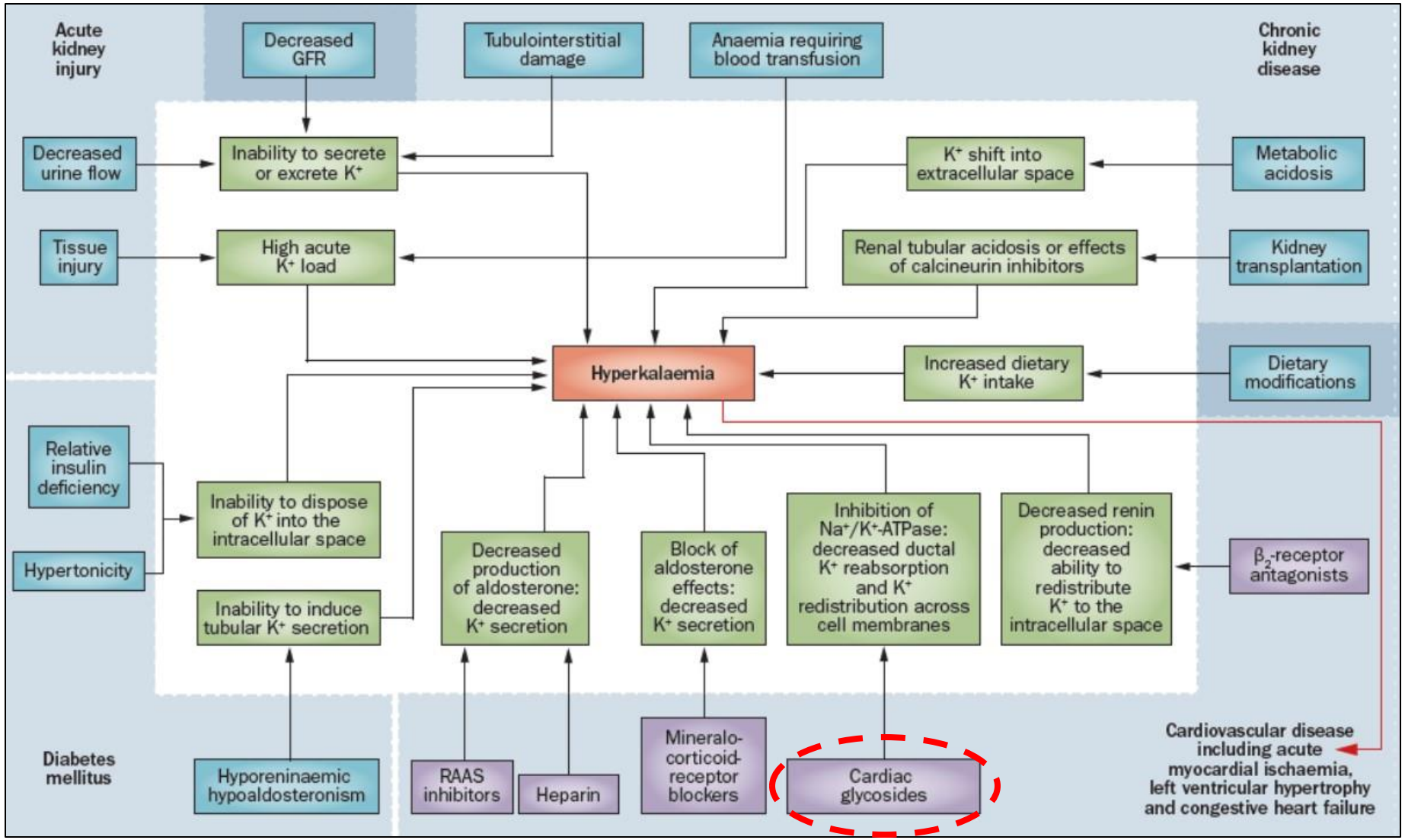

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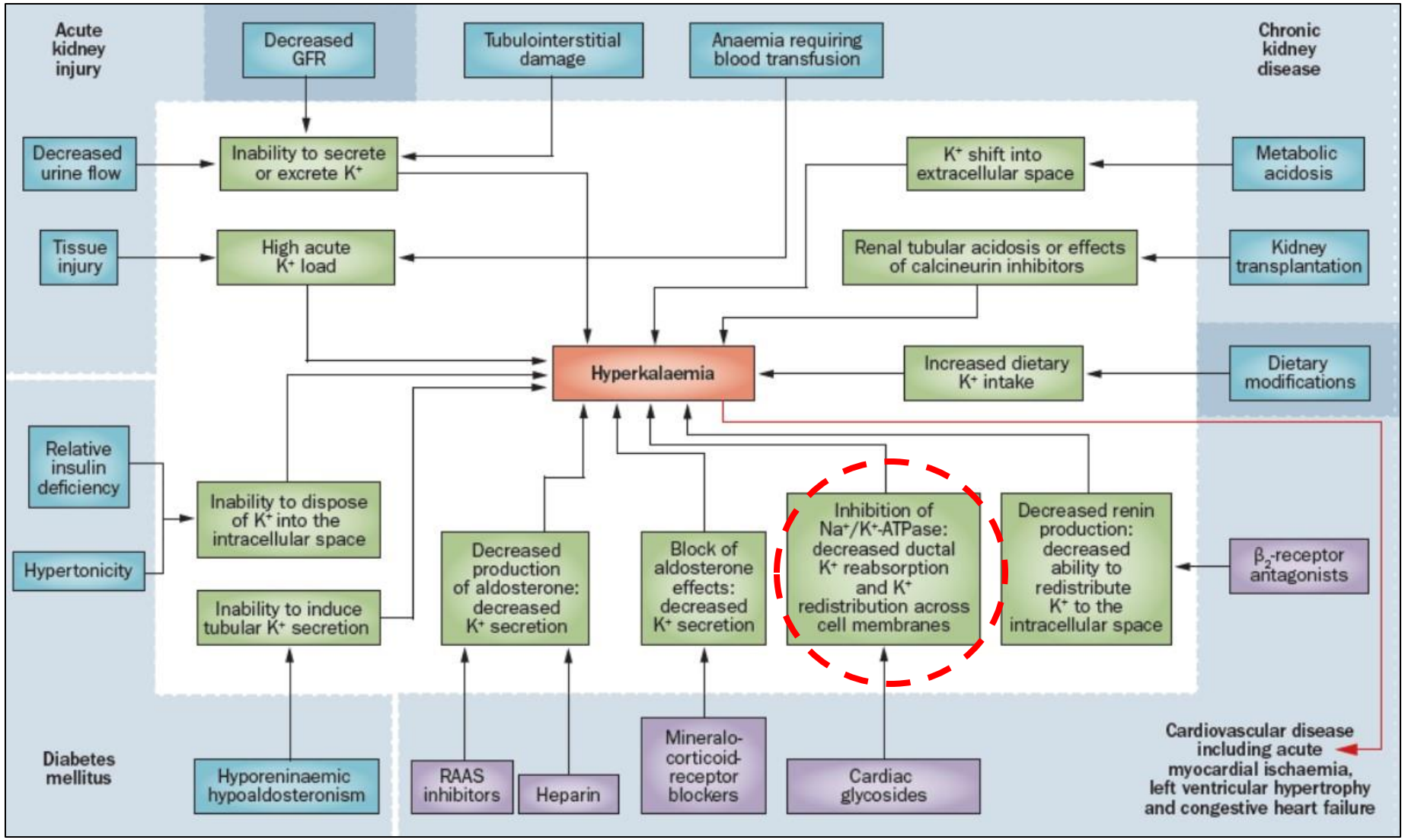

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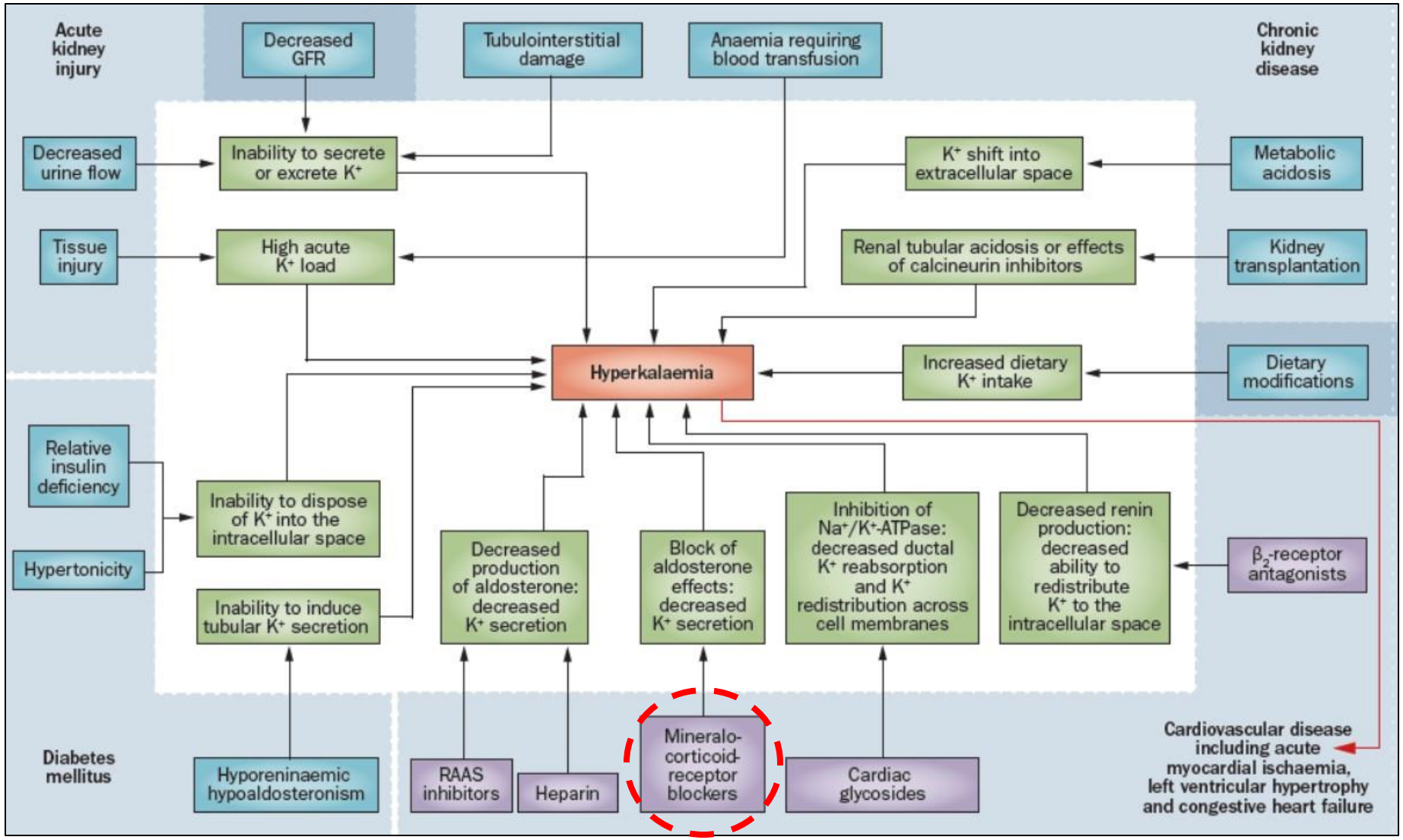

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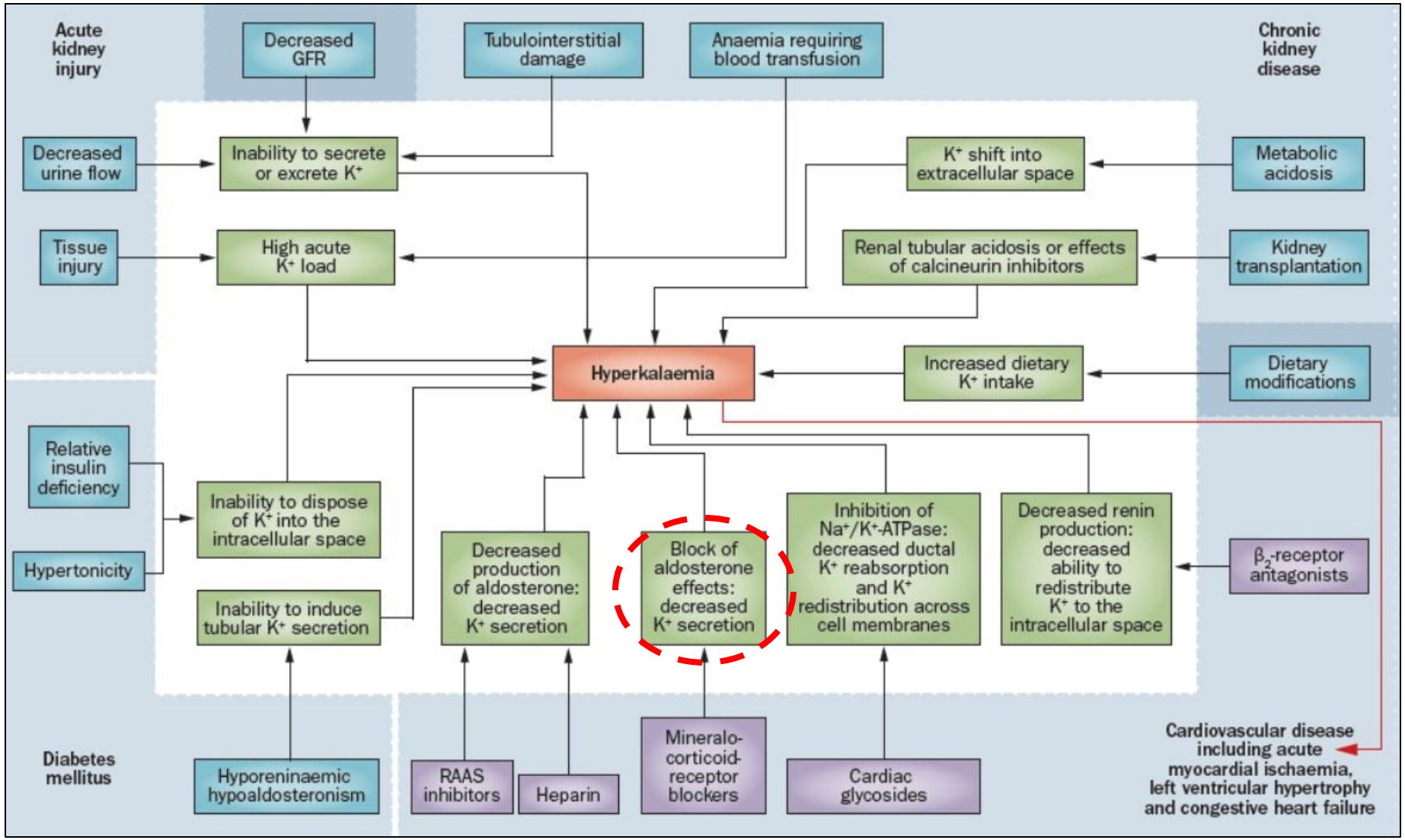

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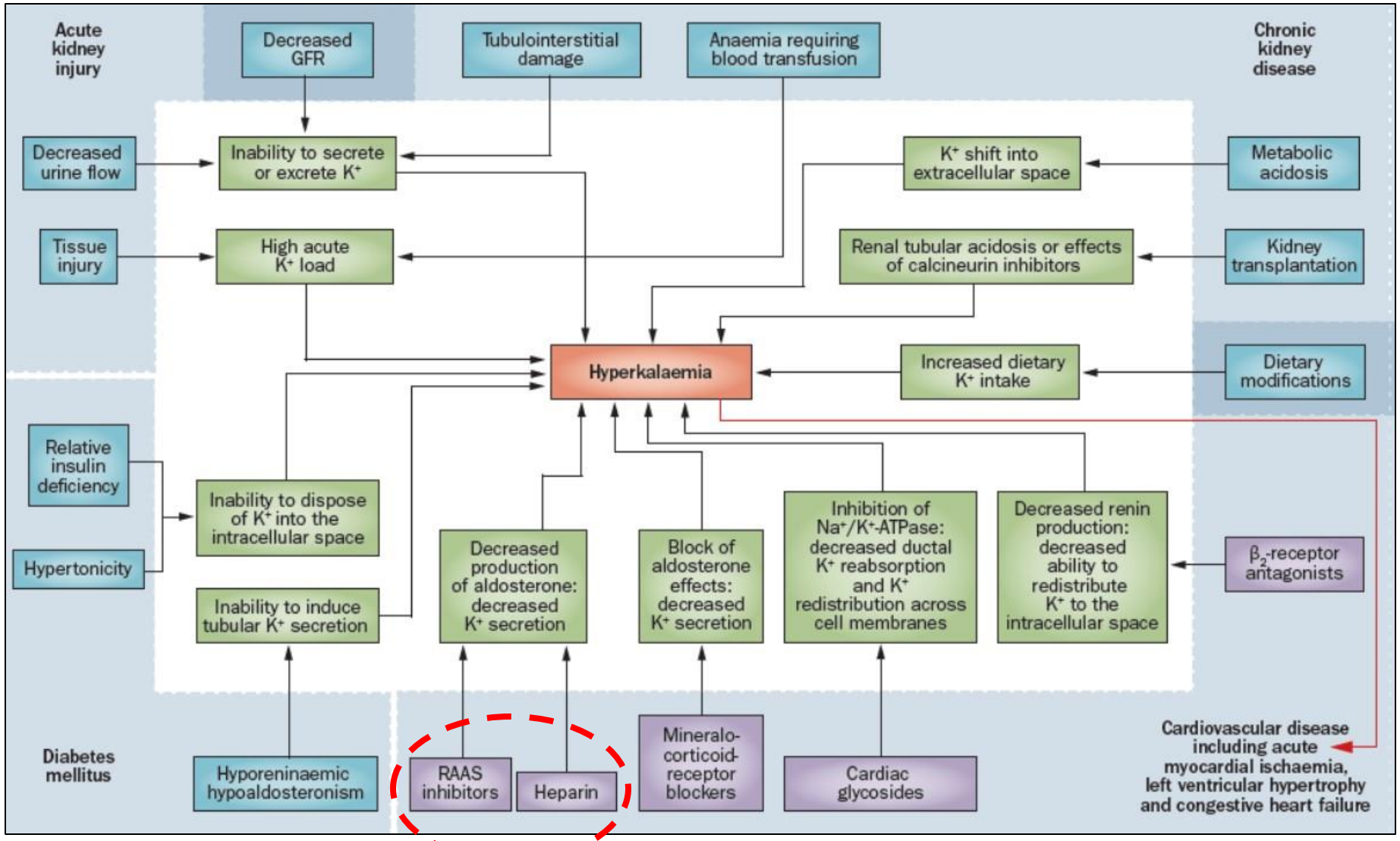

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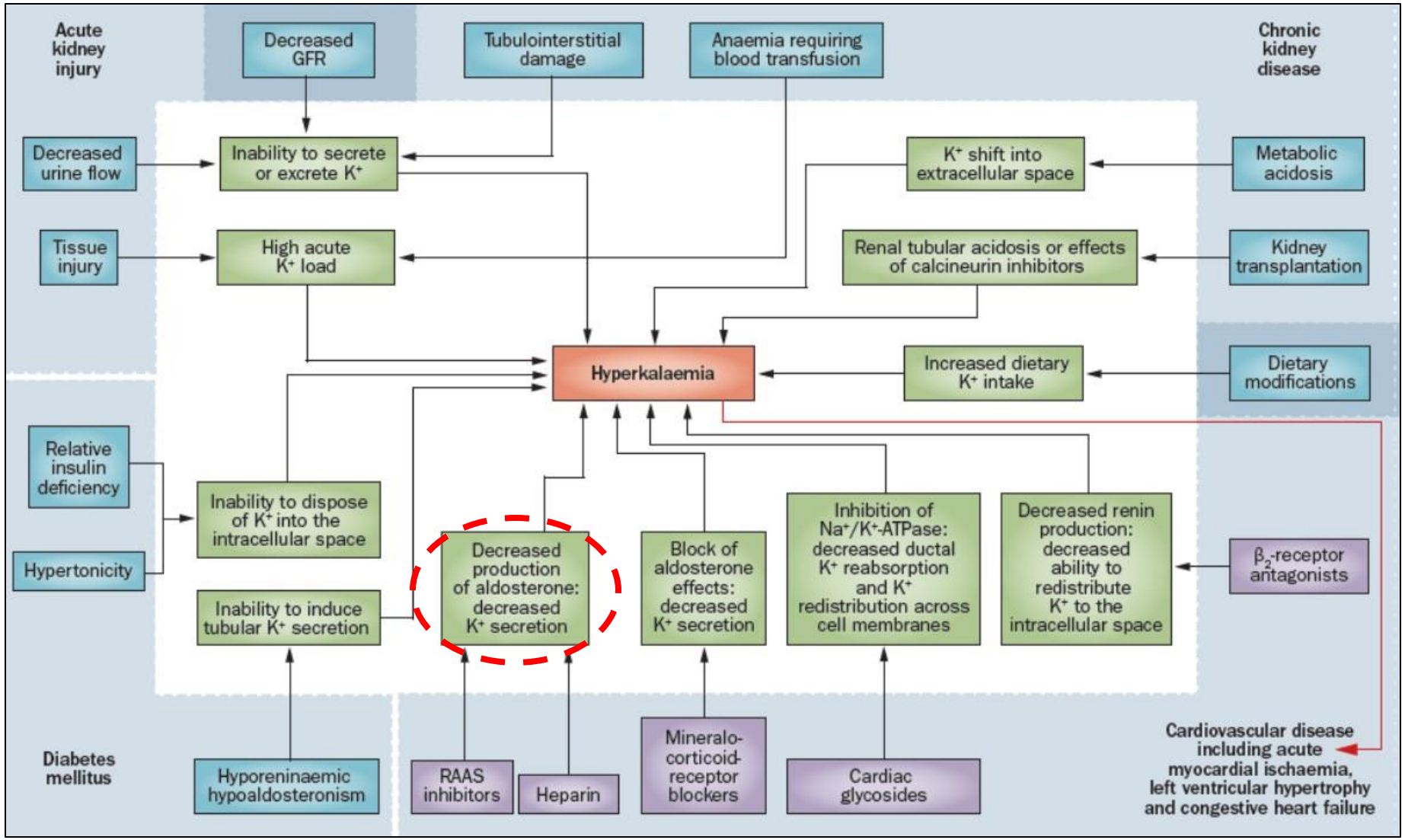

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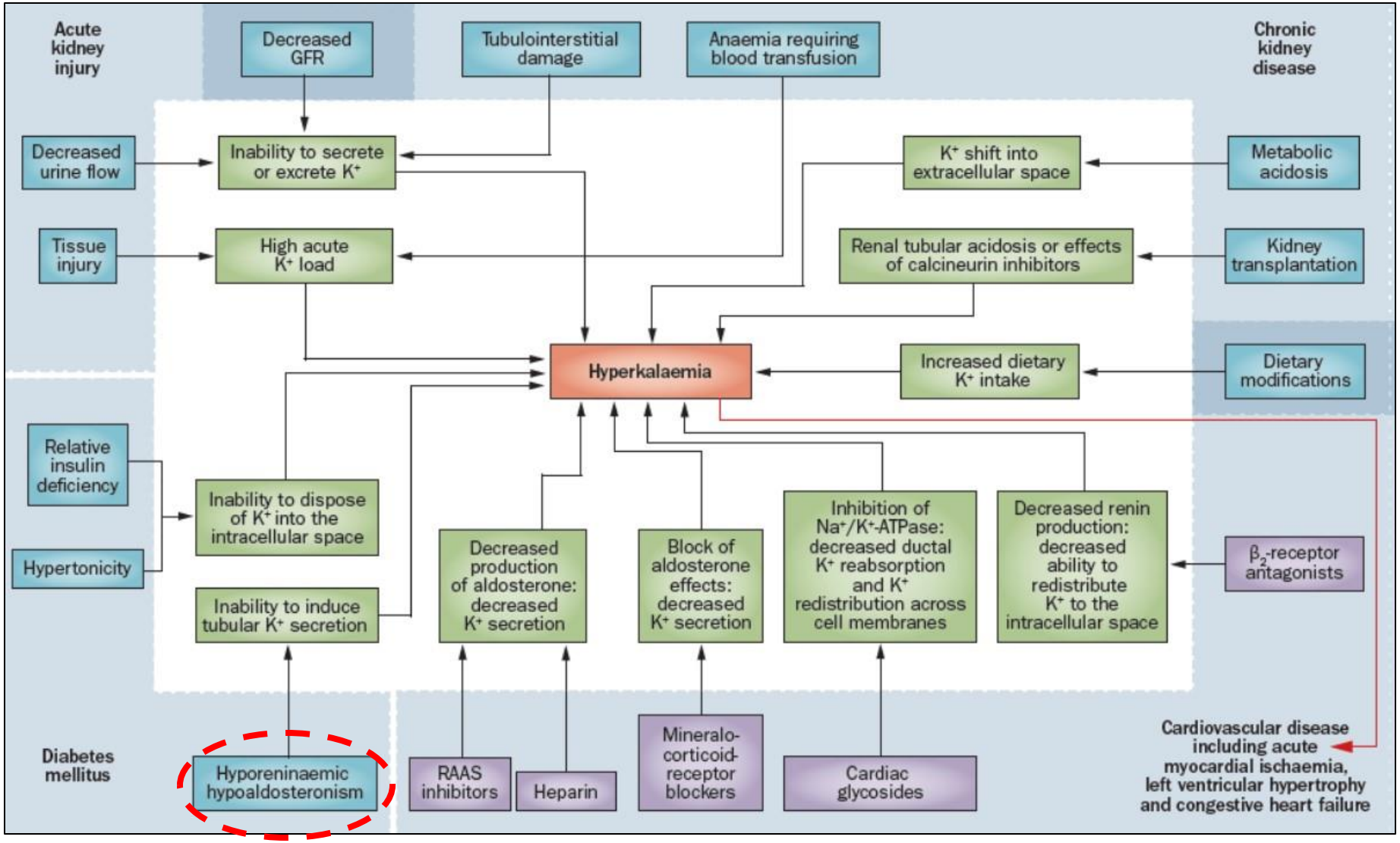

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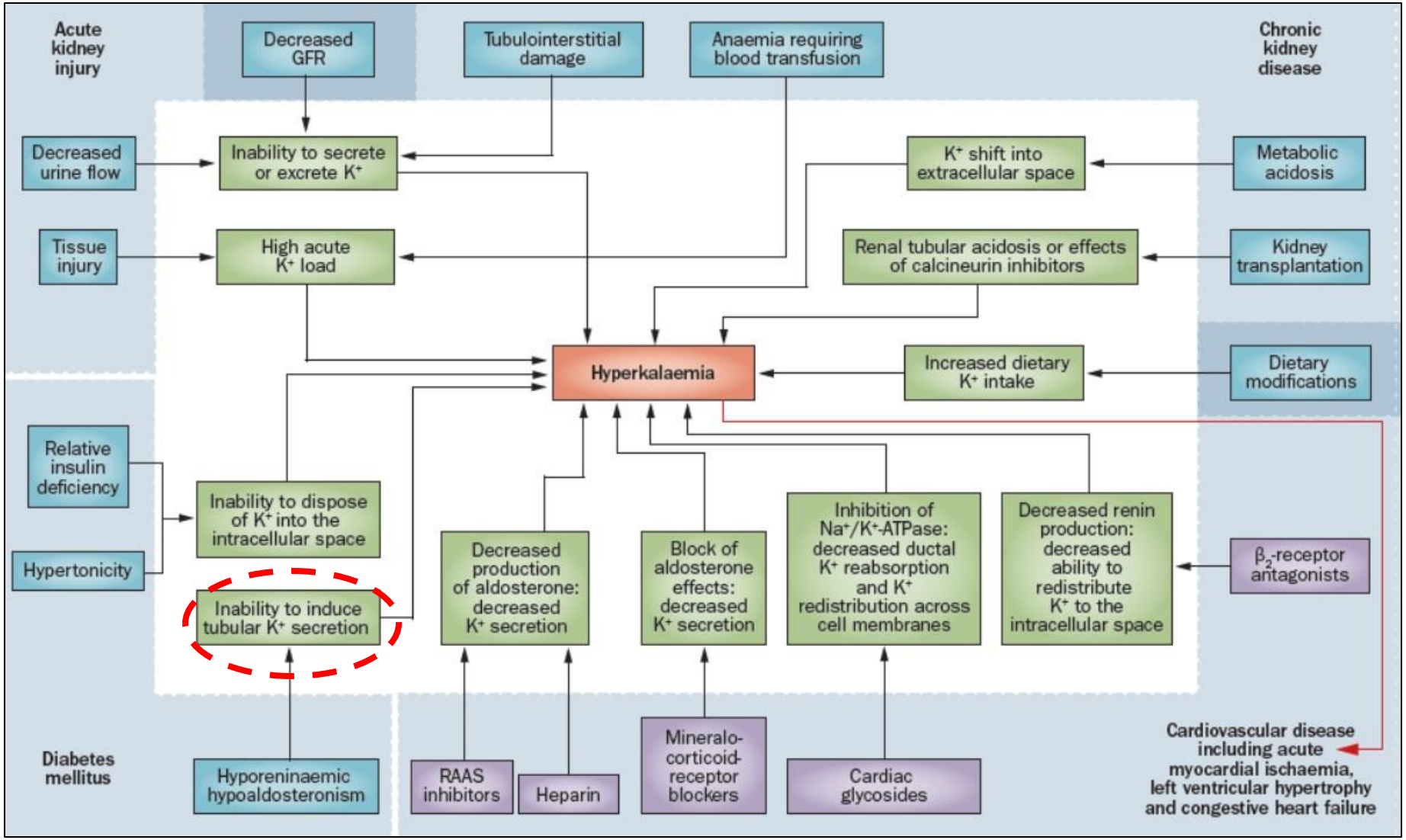

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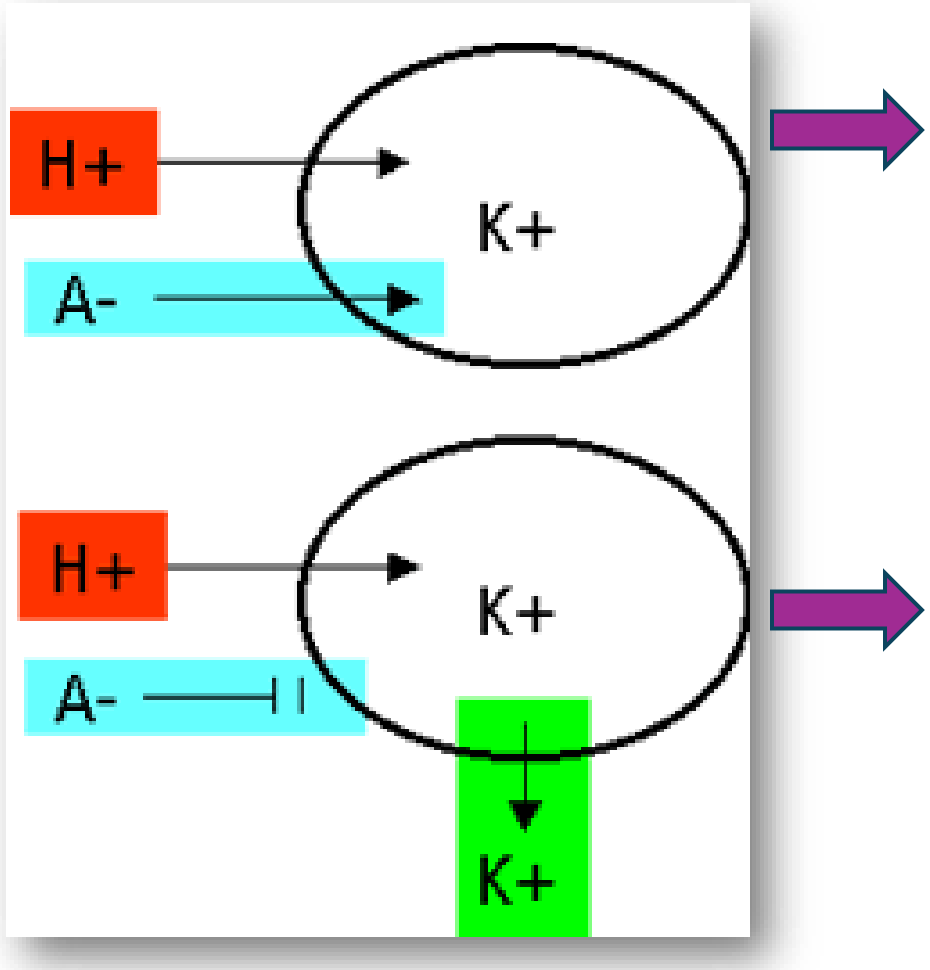
Acidosis and Potassium



If anion of acid **CAN** enter cell with H^+:
NO K^+ shift = NO hyperkalaemia

eg. Non-mineral or organic acidosis
(anion= lactate, acetate)

If anion of acid **CAN'T** enter cell with H^+:
K+ moves out to maintain neutrality
= hyperkalaemia

eg. Mineral acidosis
(anion= chloride, sulfate or phosphates)

Evaluation

Hyperkalemia: Symptoms

Often asymptomatic, but patients may report non-specific symptoms, including palpitations, nausea, muscle pain, weakness, dyspnea, or paresthesia

Hyperkalemia can lead to disturbances of cardiac rhythm, which can be fatal

Viera A, Wouk N. *Am Fam Physician*. 2015;92:487-495.
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Definitions

Hyperkalemia is defined as a serum potassium level above the normal/reference range (3.0 - 5.0 mEq/L*)

Various cutoffs, such as >5.0, >5.5, or >6.0 mEq/L have been used to indicate different levels of severity

Severe hyperkalemia is most often defined as serum levels >6 mEq/L

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Acute Versus Chronic Hyperkalemia

Acute Hyperkalemia	Chronic Hyperkalemia
Requires immediate attention (e.g., cardiac monitoring, acute medical interventions, possibly dialysis)	Requires ongoing management to correct underlying disturbances in potassium balance (i.e., nonpharmacological and pharmacological interventions)

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Hyperkalemia Diagnosis

- Clinical history
- Physical examination
- Review of medications
- Assessment of cardiac function, kidneys, and urinary tract
- Assessment of hydration status
- Electrocardiogram
- Comprehensive laboratory workup

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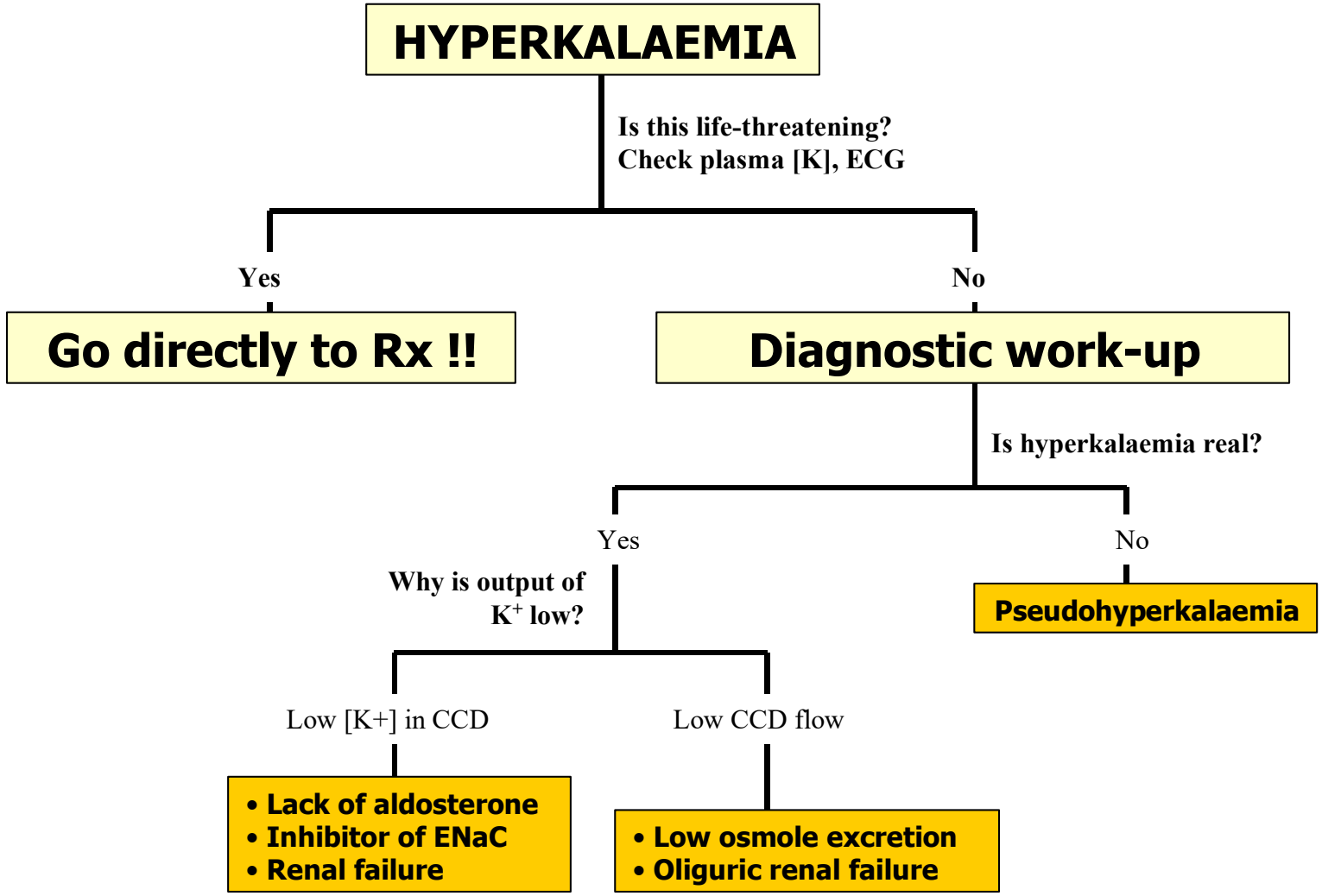
DIAGNOSTIC APPROACH TO HYPERKALAEMIA

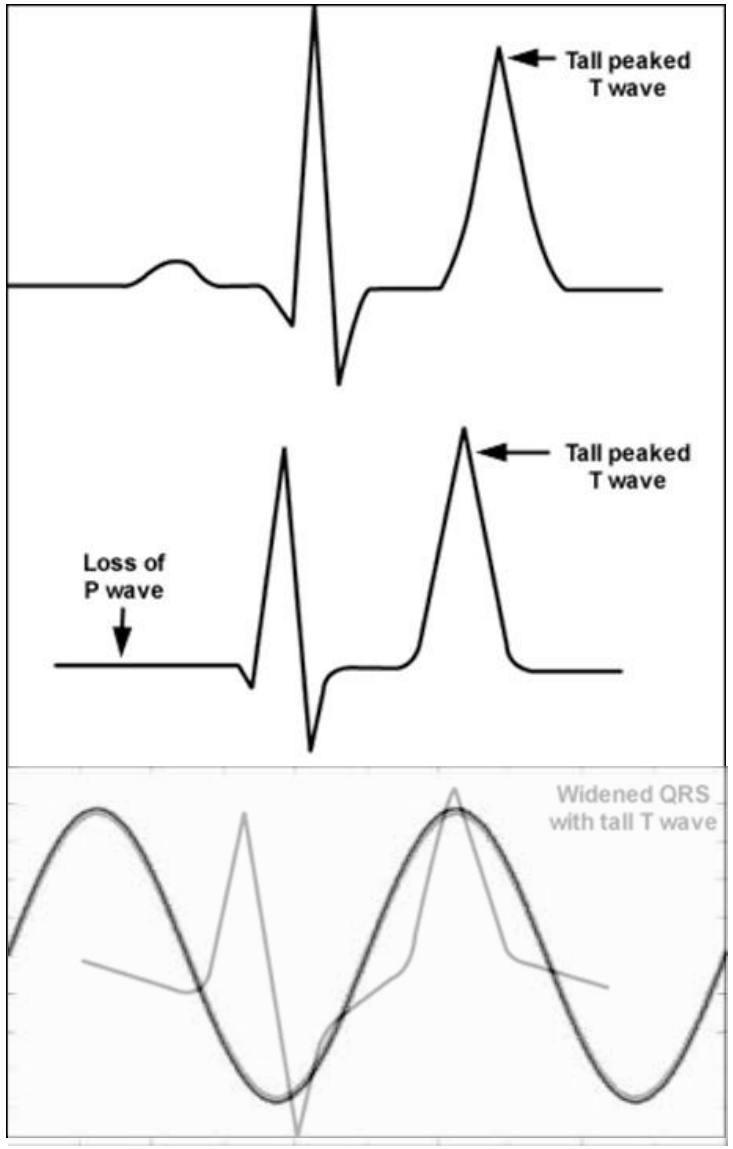


Electrocardiograph Changes Seen in Patients With Hyperkalemia*

EKG features of hyperkalemia:[1]

- 5.5-6.5 mEq/L: Tall peaked T waves
- 6.5-7.5 mEq/L: Loss of P waves
- 7.0-8.0 mEq/L: Widening of QRS complexes
- 8.0-10.0 mEq/L: Sine wave, ventricular arrhythmias, asystole

*EKG changes not always present



1. Slovis C, Jenkins R. *BMJ*. 2002;324:1320.

Management

Management Goals: Acute Versus Chronic Hyperkalemia

Acute Hyperkalemia	Chronic Hyperkalemia
• Prevent potentially life-threatening cardiac conduction and neuromuscular disturbances • Shift potassium into cells • Eliminate excess potassium • Resolve underlying disturbance	• Prevent the development or recurrence of hyperkalemia • Correct underlying defects in potassium homeostasis • Increase potassium excretion (e.g., diuretics, potassium binders)

Dunn J, et al. *Am J Manag Care*. 2015;21:s307-s315.
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Management Approaches to Hyperkalemia

Acute Management

- *Stabilize:* Evaluate patient for life-threatening toxicities
  - Initiate EKG monitoring
  - Ca-Gluconate
- *Shift:* Augment the shift of potassium from extra- to intracellular space
  - Dextrose and/or insulin infusion
  - Beta-adrenergic agonists
  - Sodium bicarbonate
- *Remove:* Renal replacement therapy
  - Hemodialysis
  - CKRT
  - Potassium binders

Chronic Management

- *Remove or manage* any ongoing contributors to hyperkalemia
  - Diet
  - Medications
  - Co-morbid conditions
- *Increase excretion* of potassium
  - Loop diuretics (furosemide)
  - Mineralocorticoid accentuation
  - Potassium binders

CKRT, Continuous Kidney Replacement Therapy

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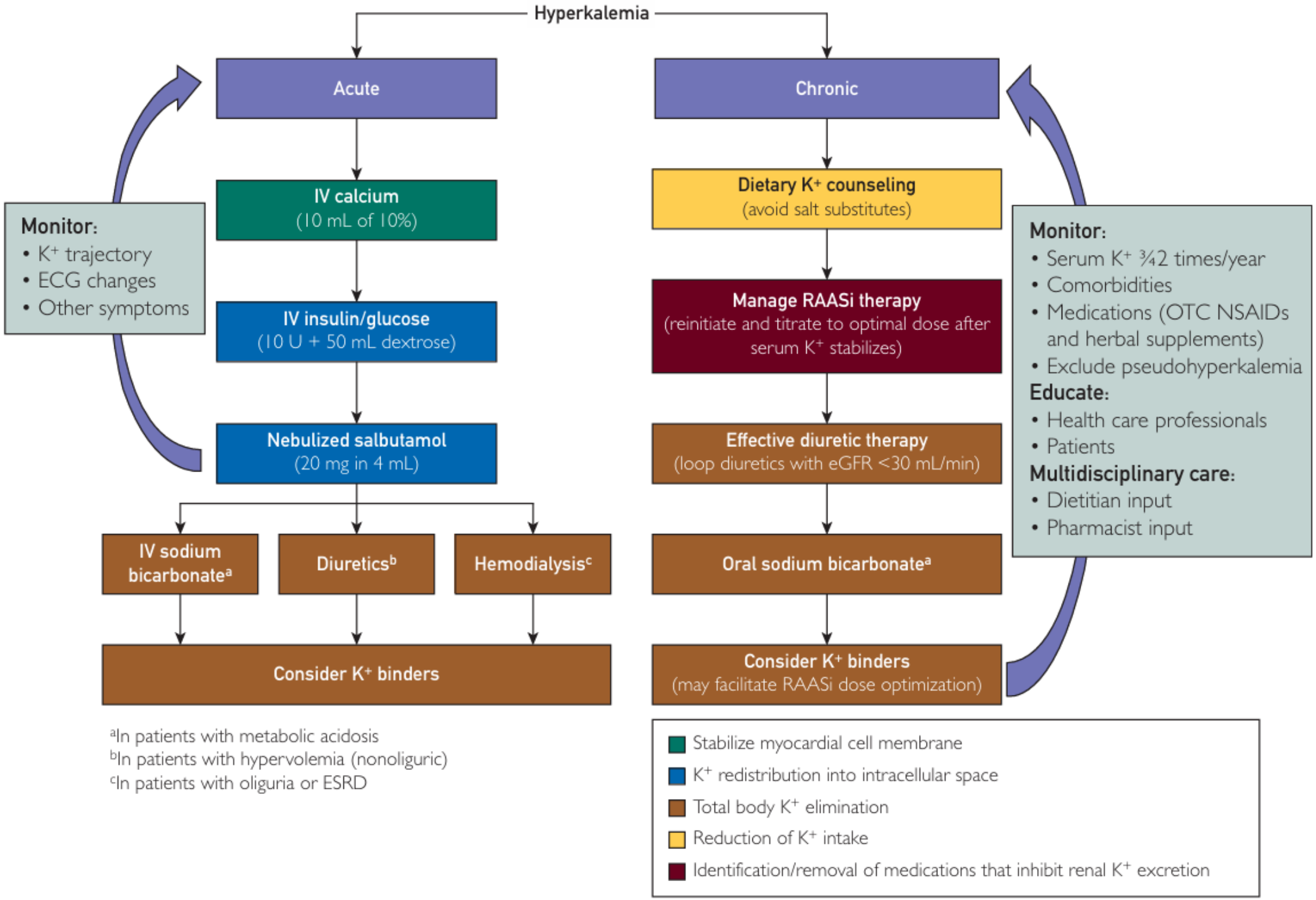
Viera A, Wouk N. *Am Fam Physician*. 2015;92:487-495.
Dunn J, et al. *Am J Manag Care*. 2015;21:s307-s315.


Hyperkalemia
Acute
IV calcium
(10 mL of 10%)
IV insulin/glucose
(10 U + 50 mL dextrose)
Nebulized salbutamol
(20 mg in 4 mL)
IV sodium bicarbonate[a]
Diuretics[b]
Hemodialysis[c]
Consider K+ binders
Monitor:
• K+ trajectory
• ECG changes
• Other symptoms
Chronic
Dietary K+ counseling
(avoid salt substitutes)
Manage RAASi therapy
(reinitiate and titrate to optimal dose after serum K+ stabilizes)
Effective diuretic therapy
(loop diuretics with eGFR <30 mL/min)
Oral sodium bicarbonate[a]
Consider K+ binders
(may facilitate RAASi dose optimization)
Monitor:
• Serum K+ ¾2 times/year
• Comorbidities
• Medications (OTC NSAIDs and herbal supplements)
• Exclude pseudohyperkalemia
Educate:
• Health care professionals
• Patients
Multidisciplinary care:
• Dietitian input
• Pharmacist input
[a]In patients with metabolic acidosis
[b]In patients with hypervolemia (nonoliguric)
[c]In patients with oliguria or ESRD
Stabilize myocardial cell membrane
K+ redistribution into intracellular space
Total body K+ elimination
Reduction of K+ intake
Identification/removal of medications that inhibit renal K+ excretion

Mechanism of β-2 Agonists:

- **β-2 adrenergic agonists** stimulate Na^+/K^+ ATPase pump= K^+ movement **into** cells= ↓ Serum K^+
- Non-selective β-Blockers BLOCK this action

- **α-adrenergic agonists**= K^+ movement **out of** cells = ↑ serum K^+

- **Adrenaline = mixed α and β agonist**:

Normal individuals: **β-2** effect predominates(↓ serum K)

Severe RF: **α** effect predominates(therefore ineffective)

Management of chronic hyperkalaemia

- Correct amendable factors:
  - Decrease excessive potassium intake, review medication, correct metabolic acidosis

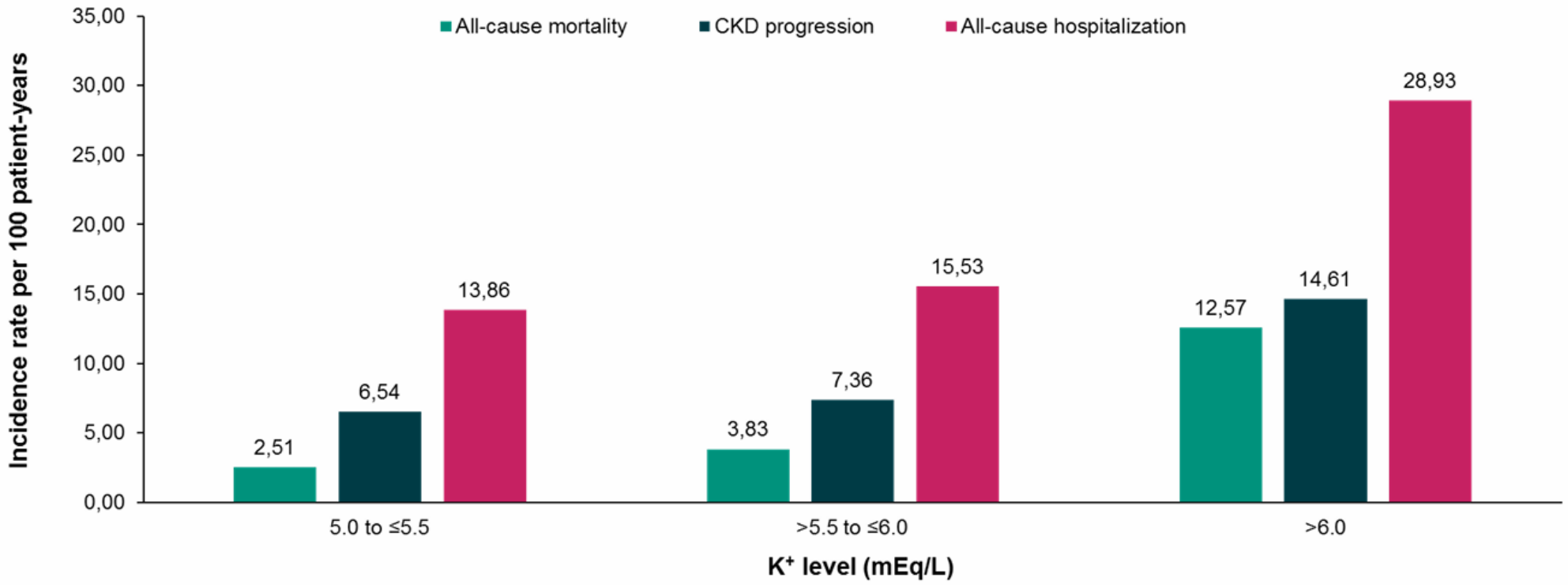
- Maintain/increase cardioprotective and nephroprotective treatment
  - a) Attempt to maintain RAS blockade and MRA, if indicated
  - b) Consider adding diuretics and/or SGLT2 inhibitors
    - Heart failure
    - Type 2 diabetes,
    - chronic kidney disease

- Removing potassium from the body:
  - Sodium zirconium cyclosilicate (SZC)
  - Patiromer
  - Calcium polystyrene sulfonate

	Sodium Polystyrene Sulphonate	Patiromer	Sodium Zirconium Cyclosilicate
MOA	Nonspecific cation binding in exchange for sodium	Polymer exchange resin	Selective K+ binding in exchange for sodium and hydrogen
Time to Normokalemia	Unconfirmed	Within 1 week[2]	Within 24 hours for 84% of patients[3]
Onset of action	Unknown (generally hours to days)	7 hours after first dose[4]	1 hour following the first dose[3]
Drug–drug Interactions	With antacids, laxatives, digitalis, sorbitol, lithium, and thyroxine[5]	FDA: Must be taken 3 hours apart from other oral drugs[6]	Should be given 2 hours apart from oral medication with gastric pH dependent bioavailability[7]
Location of K+ Binding	Colon	Predominantly distal colon	Likely entire GI tract
Safety / Tolerability	Associated with: Safety and tolerability concerns[8] Electrolyte disturbances	Hypomagnesaemia[9] GI side effects, e.g. mild-to-moderate constipation	Mild-to-moderate GI effects[10] Oedema

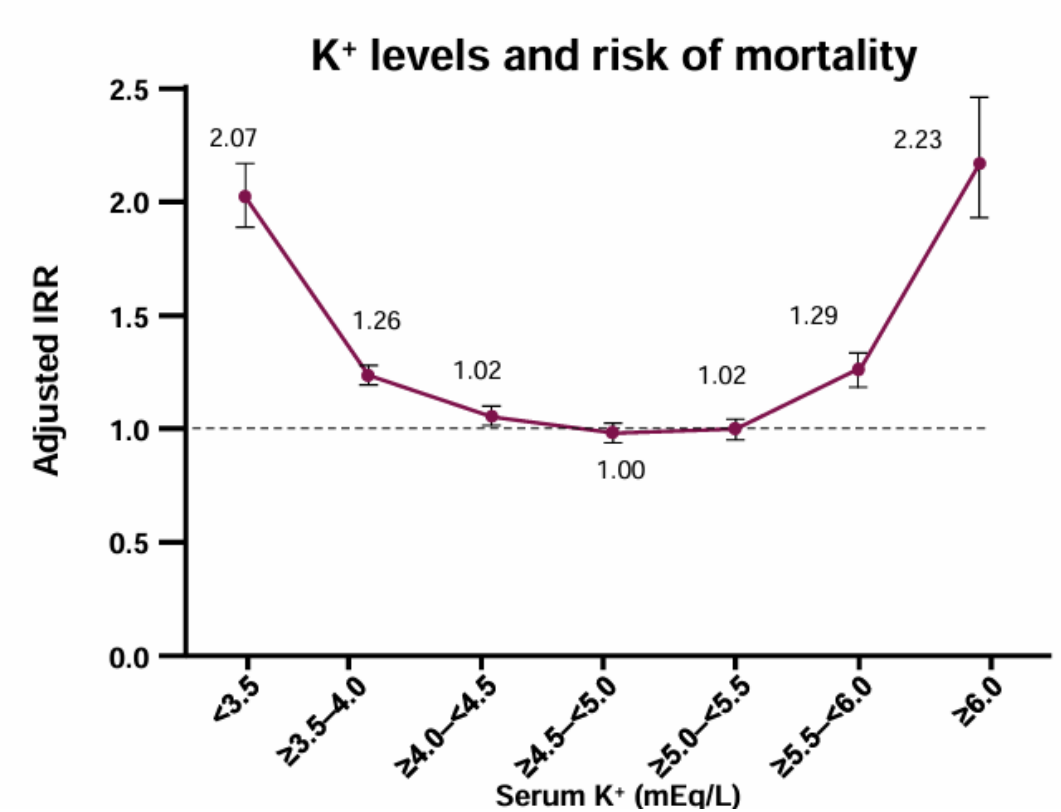
FDA, US Food and Drug Administration; GI, gastrointestinal; MOA, mechanism of action; SPS, sodium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate 1.Garimella PS, et al. Am J Kidney Dis 2016;67:545–547; 2. Weir MR, et al. N Engl J Med 2015;372:211–221; 3. Kosiborod M, et al. JAMA 2014;312:2223–2233; 4. Bushinsky DA, et al. Kidney Int 2015;88:1427–1433; Sanofi-Avents. Kayexalate Prescribing information 2009; 6. Patiromer Prescribing Information 2016; 7 AstraZeneca. Sodium Zirconium Cyclosilicate Summary of Product Characteristics 2018;; 8. Lepage L, et al. Clin J Am Soc Nephrol 2015;10:2136–2142; 9. Bakris GL, et al. JAMA 2015;314:151–161; 10. Packham DK, et al. N Engl J Med 2015;372:222–231

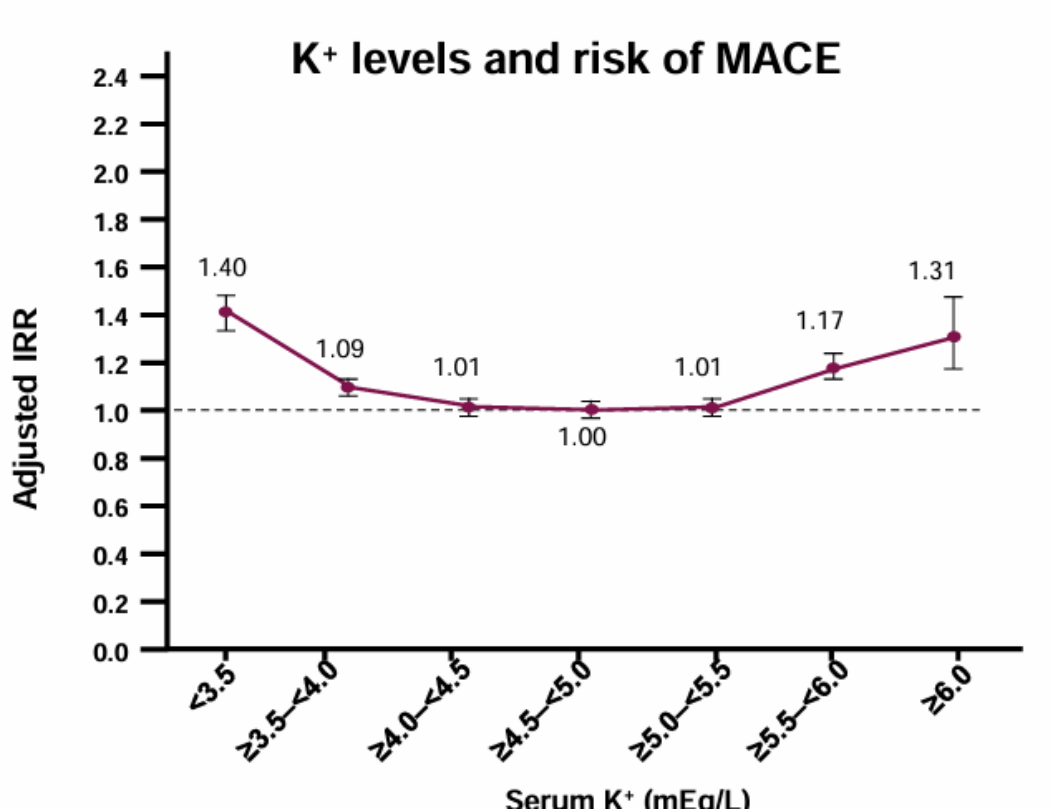
Rates of adverse clinical outcomes increase with severity of hyperkalemia



CKD, chronic kidney disease

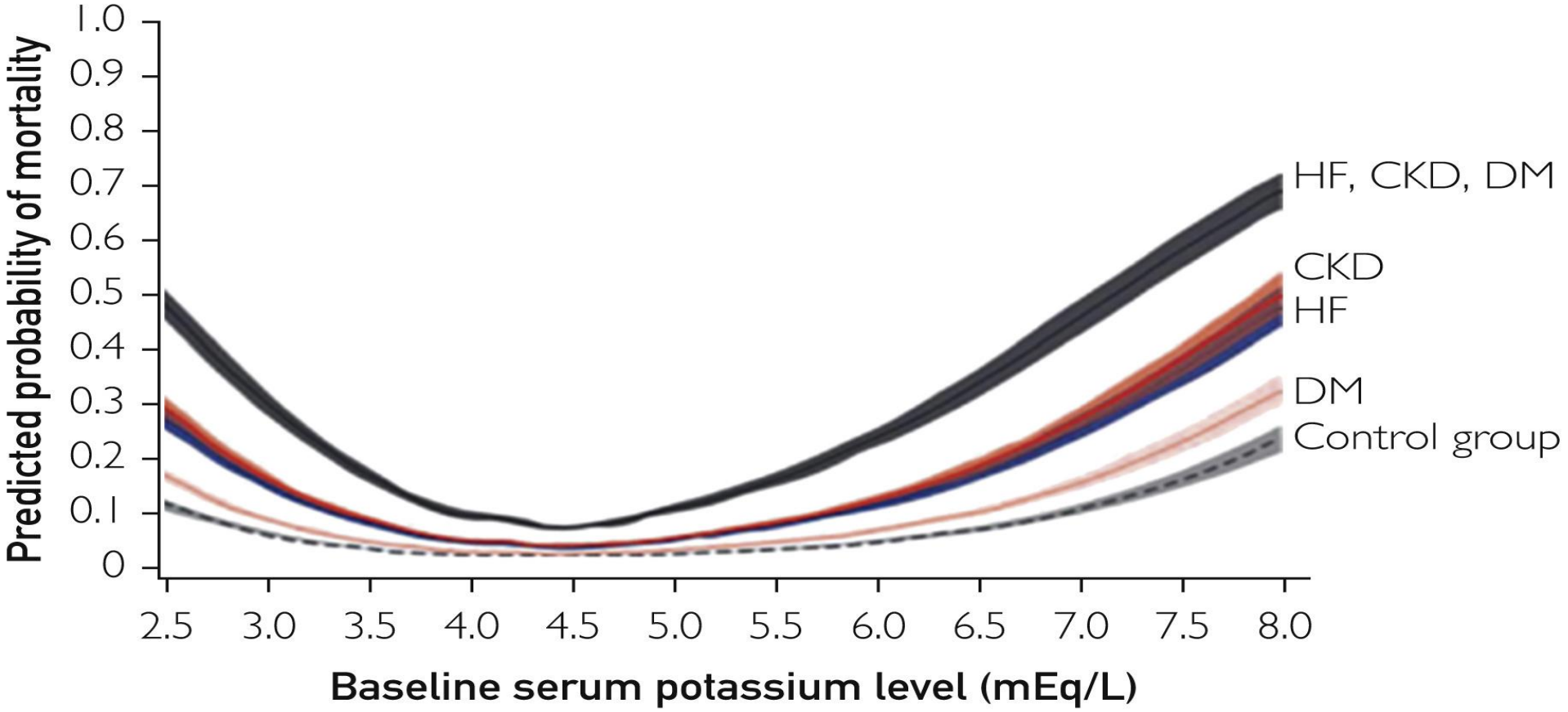
Horne L, et al. Presented at 54th European Renal Association – European Dialysis and Transplant Association Congress; June 3rd–6th, 2017; Madrid, Spain; poster MP380 (retrospective analysis





Recent studies confirm high serum K+ levels are associated with increased risk of mortality and MACE in CKD – U shape association

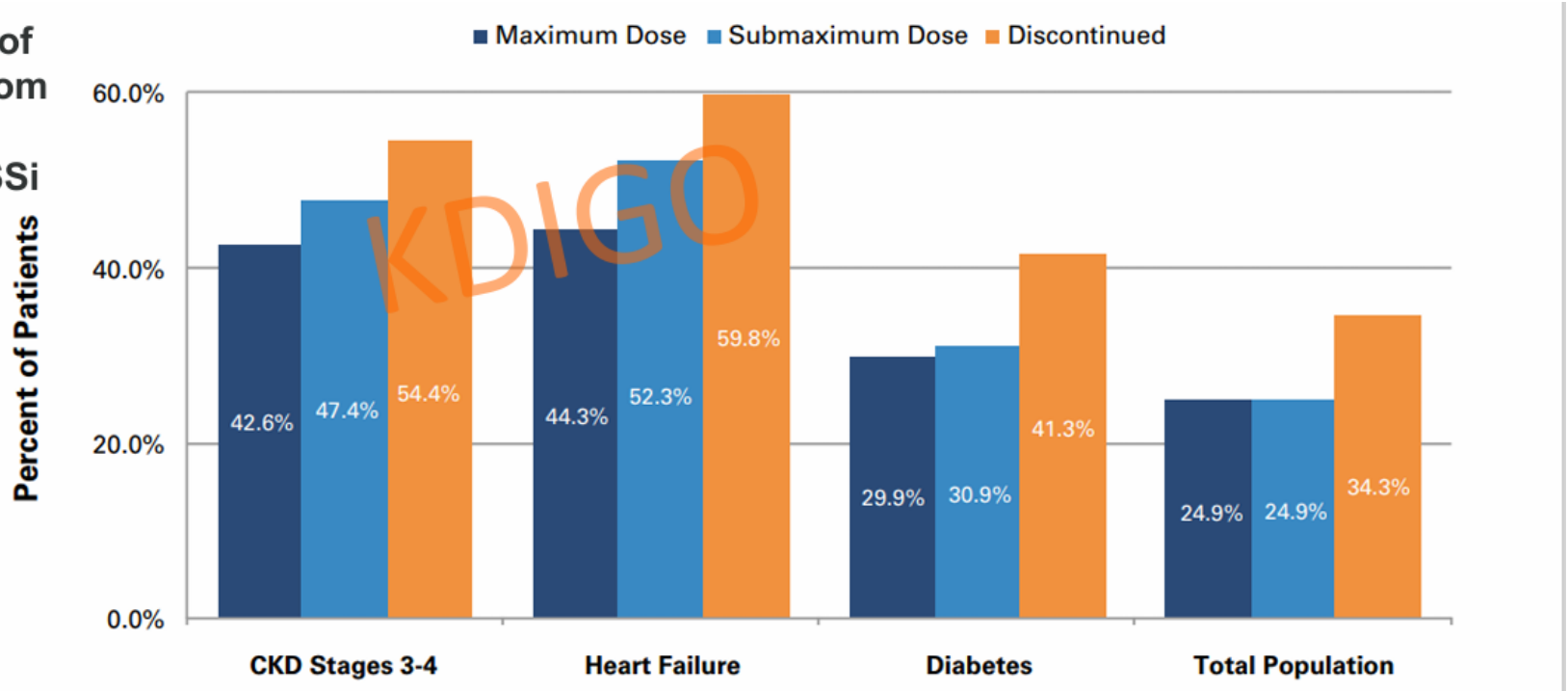
CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HES, hospital episode statistics; IRR, incident risk ratio; MACE, major adverse cardiovascular events Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S; MO067. The Relationship Between Serum K+ and Incidence Rates of Major Adverse Cardiovascular Events and Mortality in UK Patients With CKD. Nephrol Dial Transplant. 2017;32(Suppl 3):iii73–iii74, by permission of the European Renal Association–European Dialysis and Transplant Association.



The risk of hypokalemia- or hyperkalemia-associated mortality in patients with chronic kidney disease (CKD) and other comorbidities over

Palmer BF, et al. Clinical Management of Hyperkalemia. Mayo Clinic Proceedings. 2021;96(3):744-62.

Retrospective study of 205,108 patients from the Humedica database on a RASSi



HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor

Epstein M, et al. *Am J Manag Care* 2015;21(Suppl 11):S212–S220

Conclusion

Recognition:

- Hyperkalemia rates are high in real-world CKD populations
- Elevated serum potassium is associated with increased mortality in non-dialysis and dialysis CKD populations

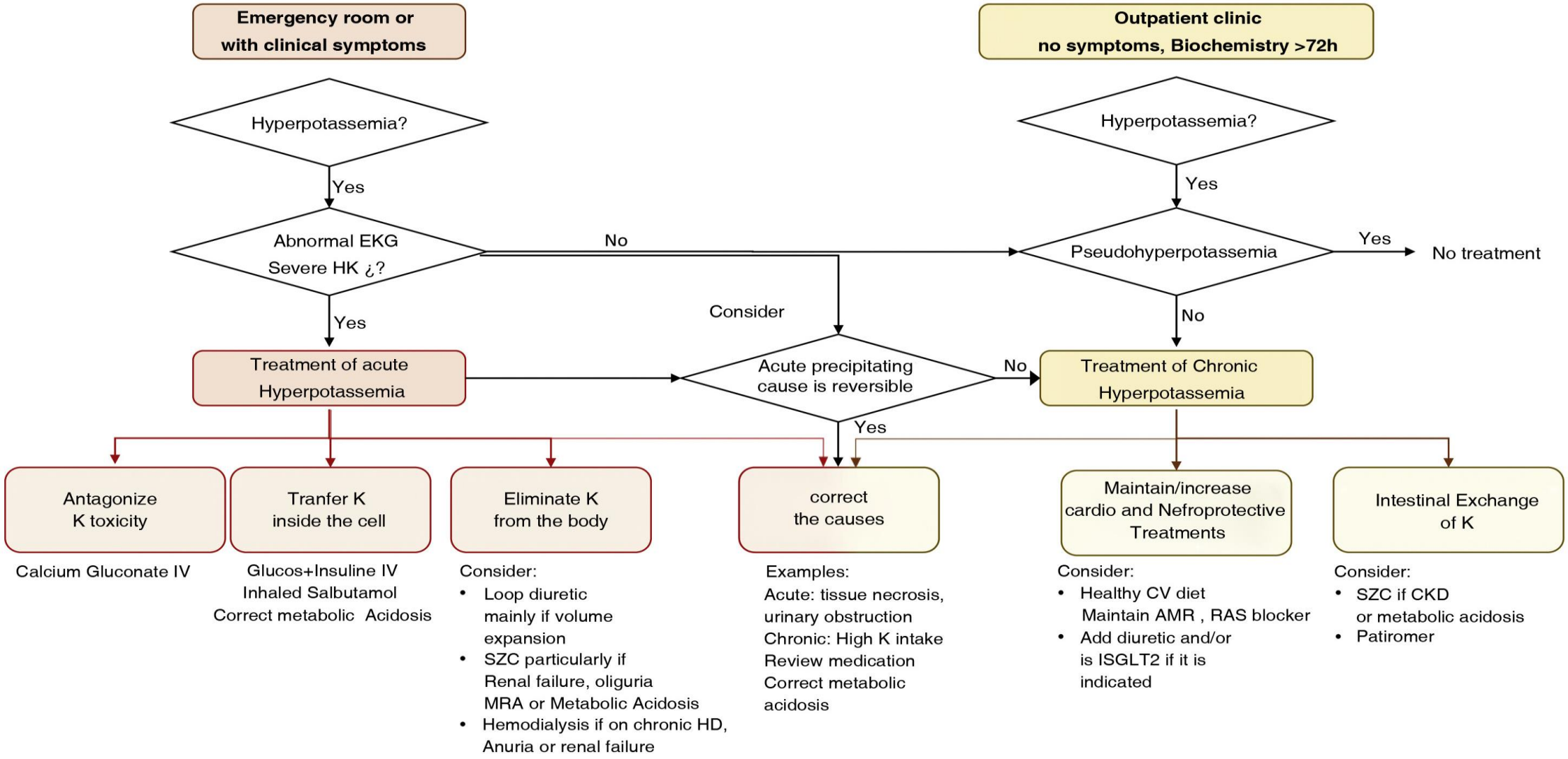
Management:

- Long-term strategies to minimize the risk of hyperkalemia, including dietary restrictions or reduction of RAAS therapy, have significant limitations
- Down-titration or discontinuation of RAAS therapy is a common consequence of hyperkalemia
- Recognize acute hyperkalaemia and manage appropriately

Treatment:

- Sodium polystyrene sulfonate, calcium resonium
- Patiromer and SZC are newer agents with well described safety and tolerability profile

Merci d'avoir écouté



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