UNIVERSITÀ DEL PIEMONTE ORIENTALE

# Il punto di vista del nefrologo: funzione renale e farmacoterapia

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SCDU Nefrologia e Trapianto

Novara, 13 Settembre 2019

# PROGRAMMA

- **Impiego dei farmaci nella malattia renale cronica (CKD)**
  - **Anticoagulanti**
  - **Bloccanti del sistema renina-angiotensina (RAS)**
- **Conclusione**

# PROGRAMMA

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  - **Anticoagulanti**
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- Conclusione

# CKD STAGES (NKF-DOQI)

| CKD | Description | GFR (mL/min/1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or ↑ GFR | ≥90 |
| 2 | Mild ↓ GFR | 60–89 |
| 3 | Moderate ↓ GFR | 30–59 |
| 4 | Severe ↓ GFR | 15–29 |
| 5 | Kidney failure | <15 or dialysis |
| | ESRD | |

# IL PARADOSSO DELLA CKD

***Elevato rischio sia tromboembolico che emorragico nella CKD avanzata***

- **Frequenti indicazioni a anticoagulazione**

  (FA 12-18% in CKD > 65 anni)

- **Piastrinopatia uremica**
- **Anemia**

# IL PARADOSSO DELLA CKD

***Elevato rischio sia tromboembolico che emorragico nella CKD avanzata***

- **Frequenti indicazioni a anticoagulazione**

  (FA 12-18% in CKD > 65 anni)

- **Piastrinopatia uremica**
- **Anemia**

- **Morte per stroke: 1%**
- **Morte per emorragia: 3%**

# ANTICOAGULAZIONE IN CKD

## Limiti

- **Popolazione con CKD avanzata (GFR< 30 ml/min) esclusa da RCTs**
- Assenza di scores validati per rischio emorragico/trombotico
- Alterazioni farmacocinetiche e farmacodinamiche legate a CKD
- **Metodi variabili per stimare la funzione renale** **Cockcroft CKD-EPI; BIS-1**
- **Nessun consenso sull'impiego di un particolare tipo di anticoagulante orale soprattutto negli stadi 4-5 della CKD**

# ANTICOAGULAZIONE IN CKD

- **Anticoagulanti orali**
- **Eparine**

# ANTICOAGULAZIONE IN CKD

- **Anticoagulanti orali (VKA/DOAC)**
- **Eparine**

# ANTICOAGULANTI ORALI: FARMACOCINETICA

| | | | Pharmacokinetic properties | | |
|---|---|---|---|---|---|
| Oral anticoagulant | Mechanism of action | Prodrug | Metabolism | Dialyzable | Dose adjustment |
| Warfarin | Vitamin K antagonist **VKA** | No | Predominantly via cytochrome P450 type 2C9 (CYP2C9) | No | No |
| Dabigatran | Direct inhibitor of free thrombin and fibrin-bound thrombin | Yes | Renal excretion 80% | Yes | Yes |
| Rivaroxaban | Free and clot-bound Xa factor inhibitor, prothrombinase activity inhibitor | No | Renal excretion 66%, 36% as unchanged drug | No | Yes |
| Apixaban | Free and clot-bound Xa factor inhibitor | No | Metabolized in liver via CYP3A4, renal excretion 27% and in feces | Partial | No |
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VKA

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# WARFARIN IN CKD

**TABLE 1** Estimated Major Bleeding Rates for Patients on Warfarin by Creatinine Clearance

| Kidney Function | Major Bleeding (Events per 100 Patient-Years) |
|---|---|
| CrCl ≥60 ml/min | 6.2 (4.1-8.9) |
| CrCl 30-59 ml/min | 8.3 (5.1-12.8) |
| CrCl <30 ml/min | 30.5 (17.0-50.3) |
| Dialysis | 54-100 |

Data from Limdi et al. (17) and Elliott et al. (64).

CrCl = creatinine clearance.

# WARFARIN IN CKD

## complicanze emorragiche

- **Rischio emorragico** soprattutto nei **primi 3 mesi** dall'avvio

  (sanguinamenti gastroenterici da lesioni uremiche)

- **Riduzione media posologia:**

  - 10% in CKD stadio III (eGFR 30-60 ml/min)

  - **20% in CKD stadio IV (eGFR < 30 ml/min)**

***Polimorfismi genetici:***
CYP2C9 e VKORC1

# WARFARIN IN CKD

## altre complicanze

- **Warfarin-induced nephropathy (WIN)** → AKI
- **Calcificazioni vascolari/calcifilassi** → progressione CKD e incremento del rischio tromboembolico e emorragico

# WARFARIN IN CKD

## Indicazioni differenti in Linee Guida:

- **American Guidelines American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS): in tutti gli stadi CKD** (stage **2-3: class 1** evidence; stage **4-5: class 2** evidence)
- **Canadian Guidelines: preferibile in CKD stadio 4**
- **European Society of Cardiology (ESC): nessuna indicazione** per un particolare tipo di OAC a seconda di stadio CKD

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# ANTICOAGULANTI ORALI: POSOLOGIA

| Recommended oral anticoagulant | CrCl (mL/min) estimated using the Cockroft-Gault equation | | | | |
|---|---|---|---|---|---|
| | ≥50 | 30–49 | 15–29 | <15 | End-stage renal disease on dialysis |
| | DOACs | DOACs | Warfarin/DOACs | Warfarin/DOACs (with caution) | |
| Warfarin | Preferable to adjust the dose function of time in therapeutic range, optimal ≥70% | | | | |
| Dabigatran | 150 mg twice daily<br>110 mg twice daily ≥80 years, or associated with P-glycoprotein inhibitors, or high risk of hemorrhage | Idem | The United States (based only on FDA approval) - 75 mg twice daily<br>Europe - NO | No | |
| Rivaroxaban | 20 mg once daily | 15 mg once daily (dose used by landmark trials recommended by small pharmacokinetic studies) | | No | |
| Apixaban | 5 mg twice daily<br>2.5 mg twice daily if any ≥2 of the following: age ≥ 80 years, body weight ≤ 60 kg and creatinine ≥1.5 mg/dL | Idem | 2.5 mg twice daily | The United States – 2.5 mg twice daily<br>Europe - NO | The United States (FDA) - 5 mg twice daily<br>Europe - NO |
| Edoxaban | 60 mg once daily<br>30 mg once daily when ≥2 of the following criteria are met: body weight ≤ 60 kg, CrCl 30-50 mL/min and therapy with Verapamil, Dronedarone or Quinidine is associated<br>FDA black box warning for CrCl >95 mL/min | 30 mg once daily | | No | |

# DOAC IN CKD

## Linee Guida:

- **American Heart Association (AHA), American College of Cardiology (ACC), European Heart Rhythm Society (EHRS) sconsigliano impiego in presenza di eGFR < 30 ml/min.**
- ***Razionale:*** **pochi RCTs in questa popolazione; tutti DOAC hanno eliminazione renale, sebbene in misura diversa**

# ANTICOAGULANTI ORALI: FARMACOCINETICA

DOAC

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# ANTICOAGULANTI ORALI: POSOLOGIA

| Recommended oral anticoagulant | ≥50<br>DOACs | 30–49<br>DOACs | 15–29<br>Warfarin/DOACs | <15<br>Warfarin/DOACs (with caution) | End-stage renal disease on dialysis |
|---|---|---|---|---|---|
| Warfarin | Preferable to adjust the dose function of time in therapeutic range, optimal ≥70% | | | | |
| Dabigatran | 150 mg twice daily<br>110 mg twice daily ≥80 years, or associated with P-glycoprotein inhibitors, or high risk of hemorrhage | Idem | The United States (based only on FDA approval) - 75 mg twice daily<br>Europe - NO | No | |
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# ANTICOAGULANTI ORALI: POSOLOGIA

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# Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation

## A Systematic Review and Meta-Analysis

- **Minor rischio emorragico rispetto a Dabigatran, Rivaroxaban e Warfarin nella popolazione generale**

Proietti M Stroke 2018

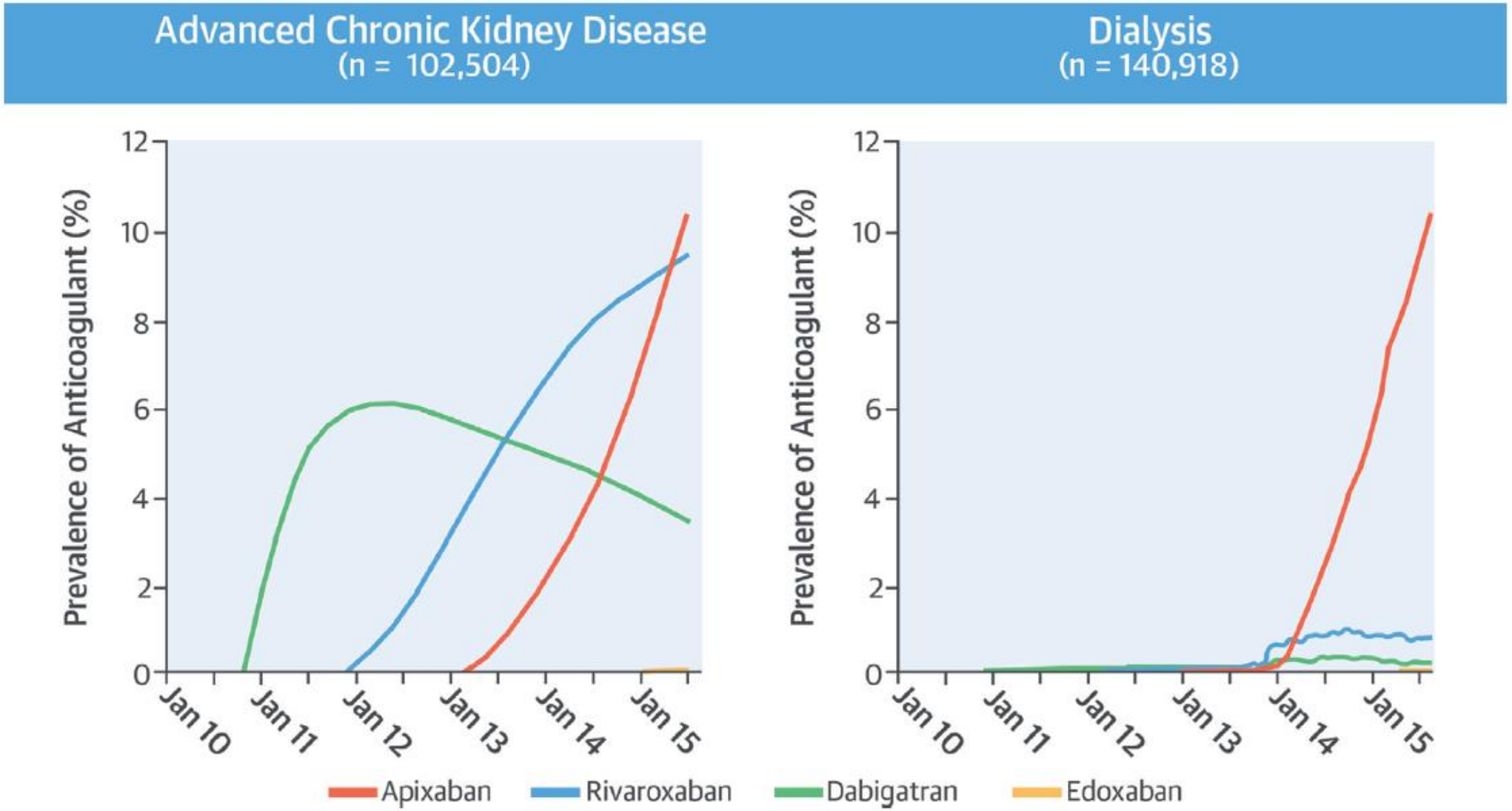
# DOAC vs VKA in CKD (BCrCl 25-50 ml/min)

**TABLE 2** Characteristics of Warfarin and Nonvitamin K-Dependent Oral Anticoagulant Agents

| | Warfarin | Apixaban | Rivaroxaban | Dabigatran | Edoxaban |
|---|---|---|---|---|---|
| Renal clearance of parent drug | <1% | 27% | 36% | 80% | 50% |
| Removal with 4 h of hemodialysis | <1% | 7% | <1% | 50%-60% | 9% |
| Volume of distribution, l (66) | 8 | 21 | 50 | 50-10 | 107 |
| Reversal agent | Vitamin K, FFP, 4F-PCC | 4F-PCC | 4F-PCC | Idarucizumab | 4F-PCC |
| Lowest CrCl drug can be prescribed per FDA label, ml/min | Can be used on dialysis | <15* | 15 | 15 | 15 |
| HR (95% CI) of stroke referent to warfarin, CrCl <50 ml/min | Reference | 0.79 (0.55-1.14) | 0.88 (0.65-1.19) | 0.56 (0.37-0.85) | 0.87 (0.65-1.18)† |
| HR (95% CI) of major bleeding referent to warfarin, CrCl <50 ml/min | Reference | 0.50 (0.38-0.66) | 0.98 (0.84-1.14) | 1.01 (0.79-1.30) | 0.76 (0.58-0.98)† |

*A 5-mg twice-daily dose of apixaban is suggested for patients with CrCl <15 ml/min. This dosing suggestion was based on a small single-dose pharmacokinetic and pharmacodynamic (anti-Xa activity) study. Clinical efficacy and long-term safety studies have not been done in this population; therefore, use apixaban with caution in patients with advanced or end-stage chronic kidney disease. †30-50 ml/min for the comparison of edoxaban versus warfarin (37).

CI = confidence interval; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; FFP = fresh-frozen plasma; 4F-PCC = 4-factor prothrombin complex concentrate; HR = hazard ratio.




Chan KE et al J Am Coll Cardiol 2016

# ANTICOAGULAZIONE IN CKD

- Anticoagulanti orali
- Eparine

# EPARINE IN CKD

# EPARINE: POSOLOGIA

UFH

| Anticoagulant | Dose adjustment function of eGFR (mL/min) | | |
|---|---|---|---|
| | 59-30 | 29-15 | <15 |
| Unfractionated heparin | Not necessary | Not necessary | Dose reduction by 33%: loading dose 60 IU/kg, maintenance 12 IU/kg/h, subsequent aPTT-adjusted dosing |
| Enoxaparin | Not necessary (1 mg/kg/12 hours)<br>VTE 1.5 mg/kg once daily (The United States) | 1 mg/kg once daily<br>anti-Xa adjusted dosing (Anti-Xa:lia ratio 3.9) | |
| Dalteparin | ACS (120 IU/kg/12 hours)<br>VTE (100 IU/kg/12 hours or 200 IU/kg once daily 1 month, then 150 IU/kg once daily 5 months, then oral anticoagulants/LMWH) | - | |
| Tinzaparin | VTE (175 IU/kg once daily) | anti-Xa adjusted dosing to eGFR <20 (Anti-Xa:lia ratio 2.8) | |
| Fondaparinux | VTE: 50% dose compared to the recommended dose per body weight<br>ACS 2.5 mg once daily | VTE: not recommended for eGFR <30<br>ACS: not recommended for eGFR <20 | |
| Argatroban | No dose adjustment is necessary (0.5-2 µg/kg/min) - renal clearance 15% | | |

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# EPARINE: POSOLOGIA

LMWH

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**Nessun dato in CKD severa per Dalteparina, Tinzaparina e Fondaparinux**

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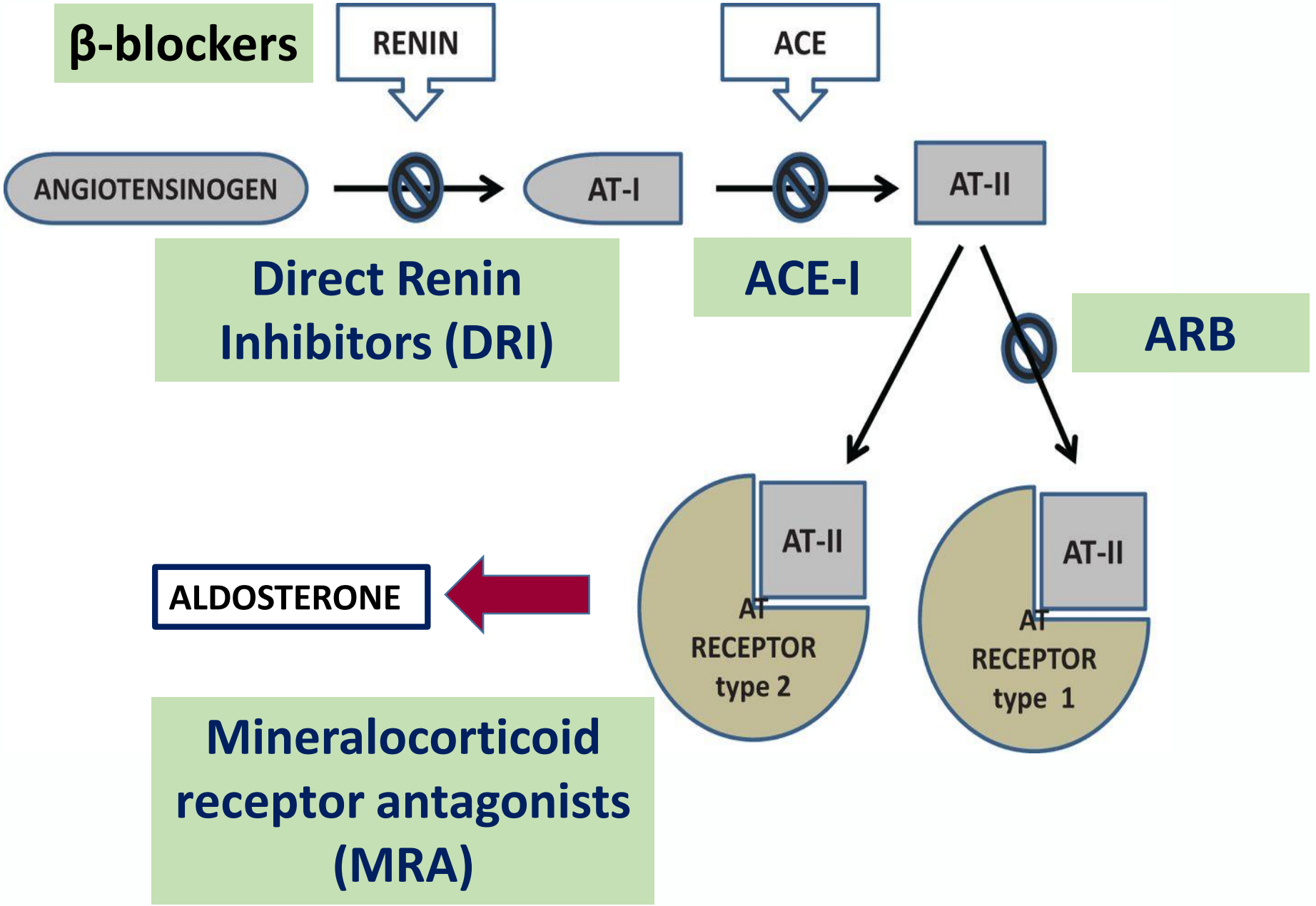
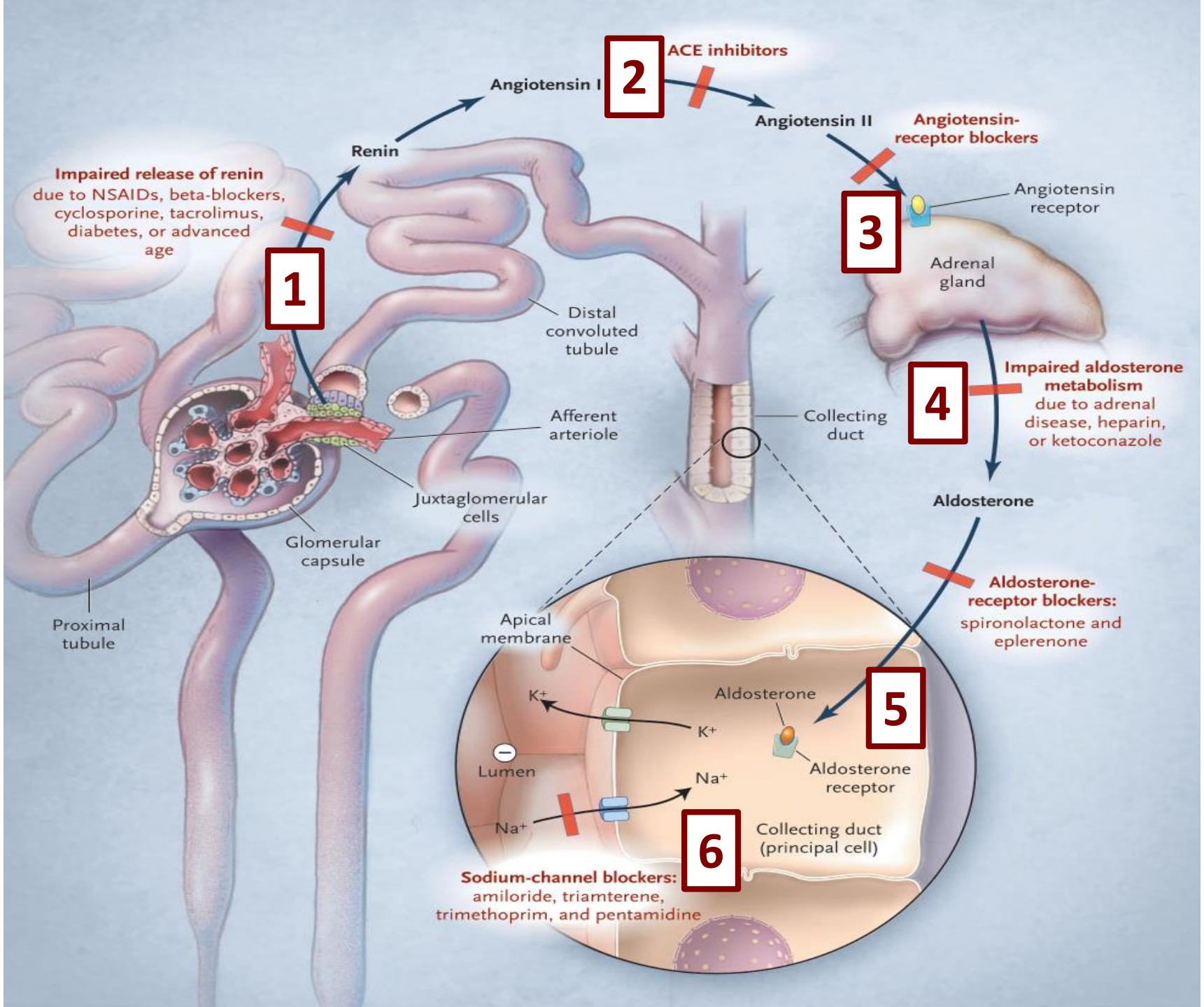
- **Conclusioni**

# ACIDOSI TUBULARE DI TIPO IV IN CKD

*Ipoaldosteronismo ipореninemico*

*Iperkaliemia da farmaci*


β-blockers
RENIN
ACE
ANGIOTENSINOGEN
AT-I
AT-II
Direct Renin Inhibitors (DRI)
ACE-I
ARB
AT-II
AT RECEPTOR type 2
AT-II
AT RECEPTOR type 1
ALDOSTERONE
Mineralocorticoid receptor antagonists (MRA)


Angiotensin I
2
ACE inhibitors
Angiotensin II
Angiotensin-receptor blockers
Renin
Impaired release of renin due to NSAIDs, beta-blockers, cyclosporine, tacrolimus, diabetes, or advanced age
1
3
Angiotensin receptor
Adrenal gland
Distal convoluted tubule
Afferent arteriole
Collecting duct
4
Impaired aldosterone metabolism due to adrenal disease, heparin, or ketoconazole
Juxtaglomerular cells
Aldosterone
Glomerular capsule
Proximal tubule
Aldosterone-receptor blockers: spironolactone and eplerenone
Apical membrane
K+
Aldosterone
5
K+
Lumen
Aldosterone receptor
Na+
Na+
6
Collecting duct (principal cell)
Sodium-channel blockers: amiloride, triamterene, trimethoprim, and pentamidine

# AZIONI DELL'ALDOSTERONE SUL DOTTO COLLETTORE

- Cellule principali
- Cellule intercalate α

# AZIONI DELL'ALDOSTERONE SUL DOTTO COLLETTORE

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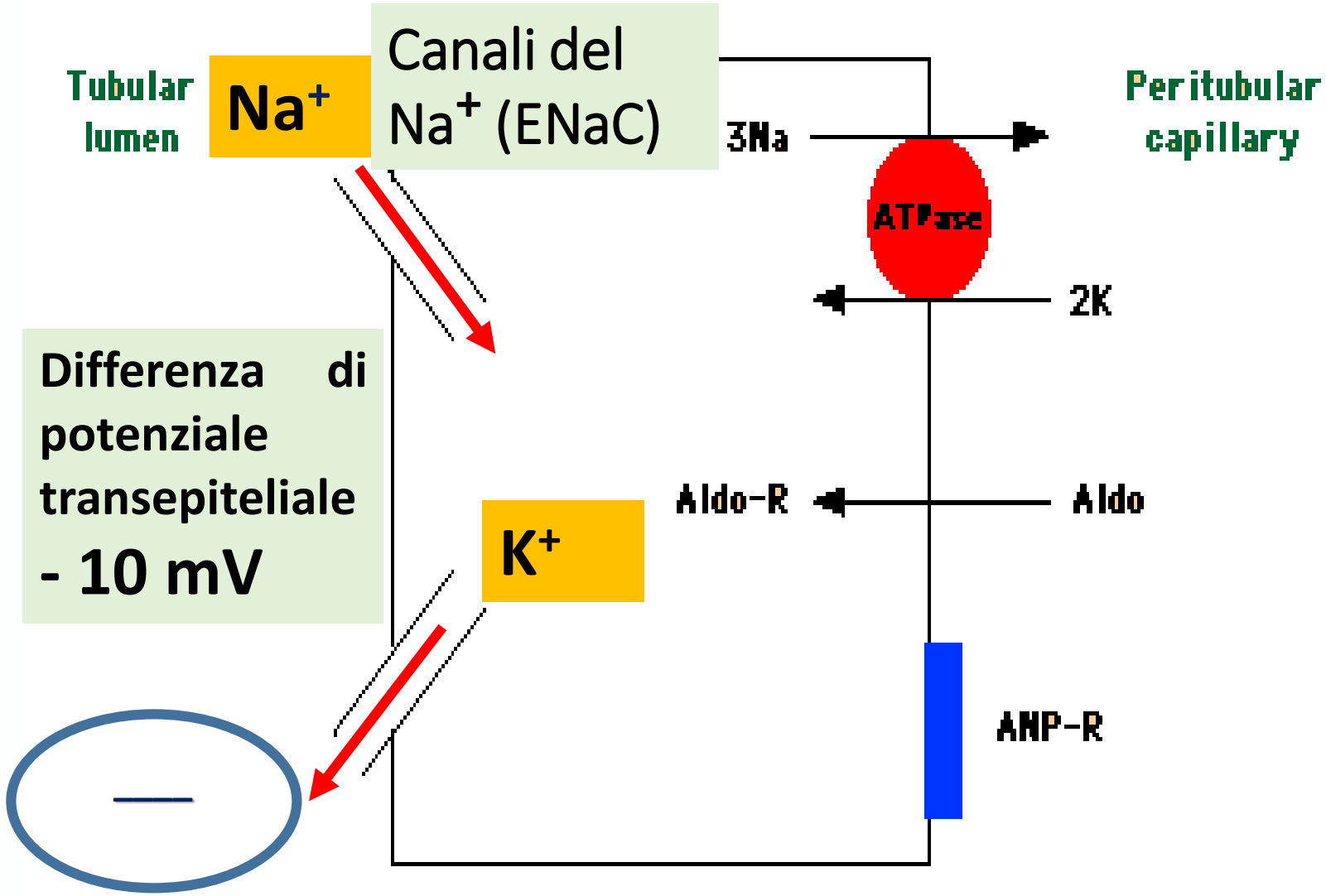
# CELLULE PRINCIPALI



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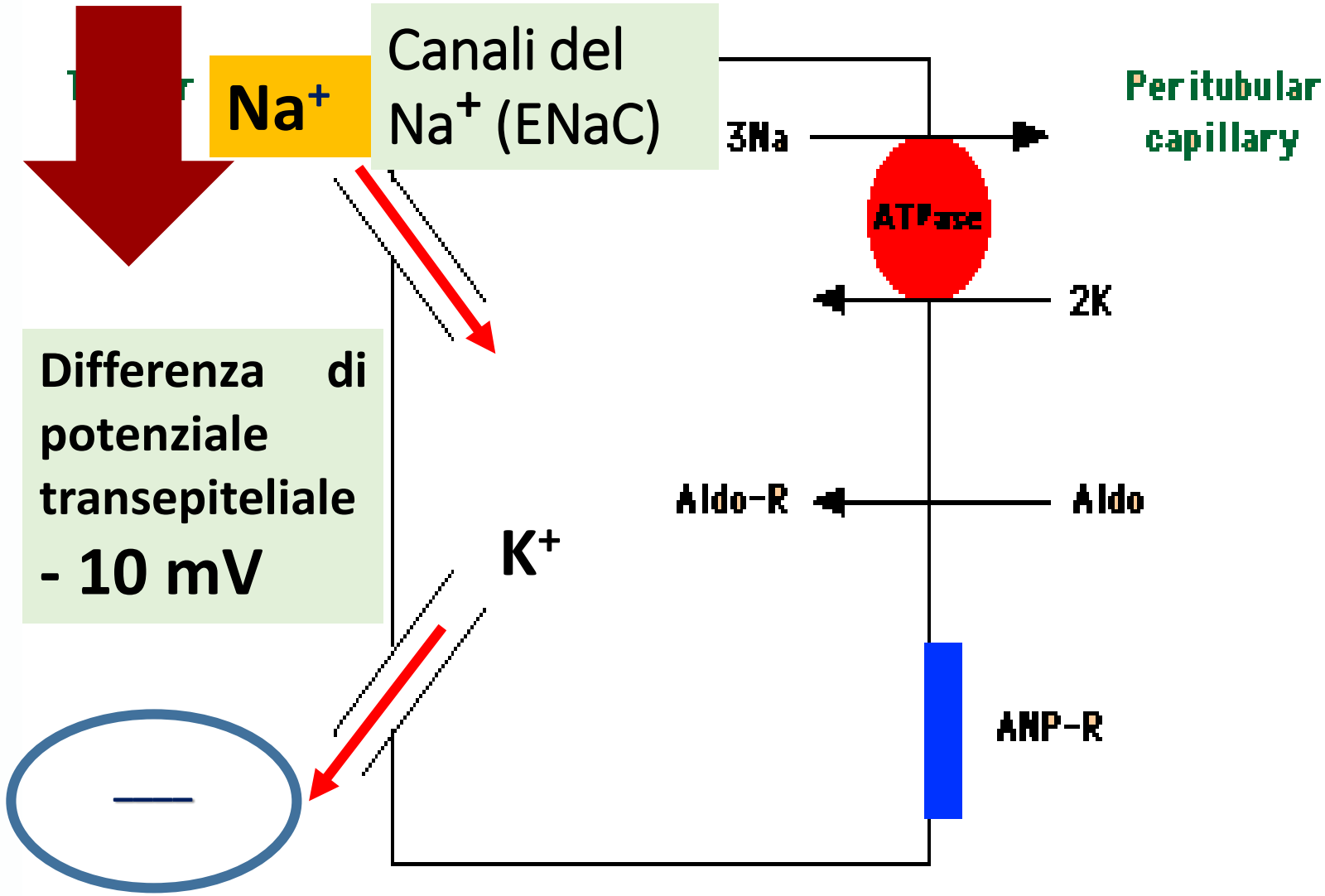

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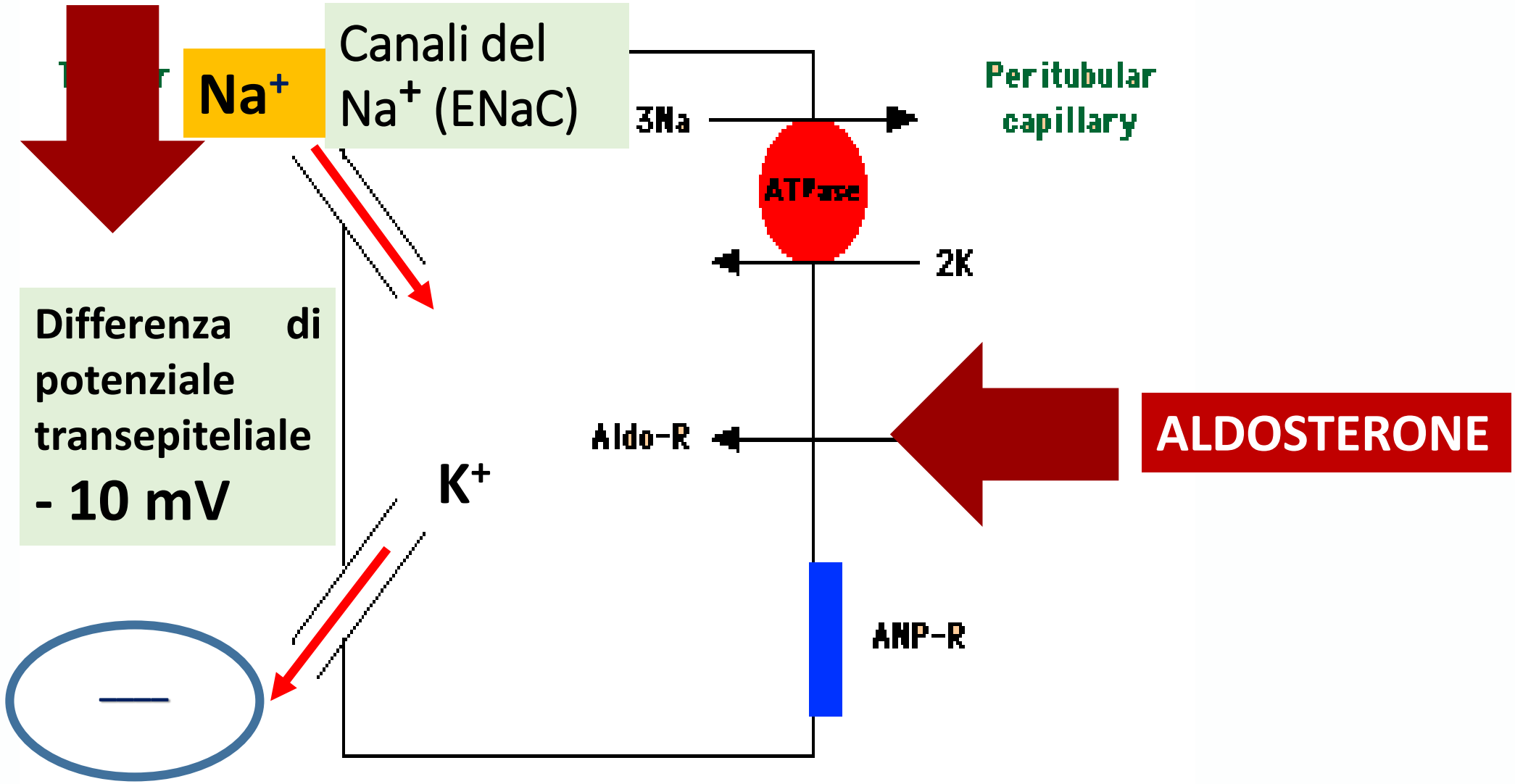
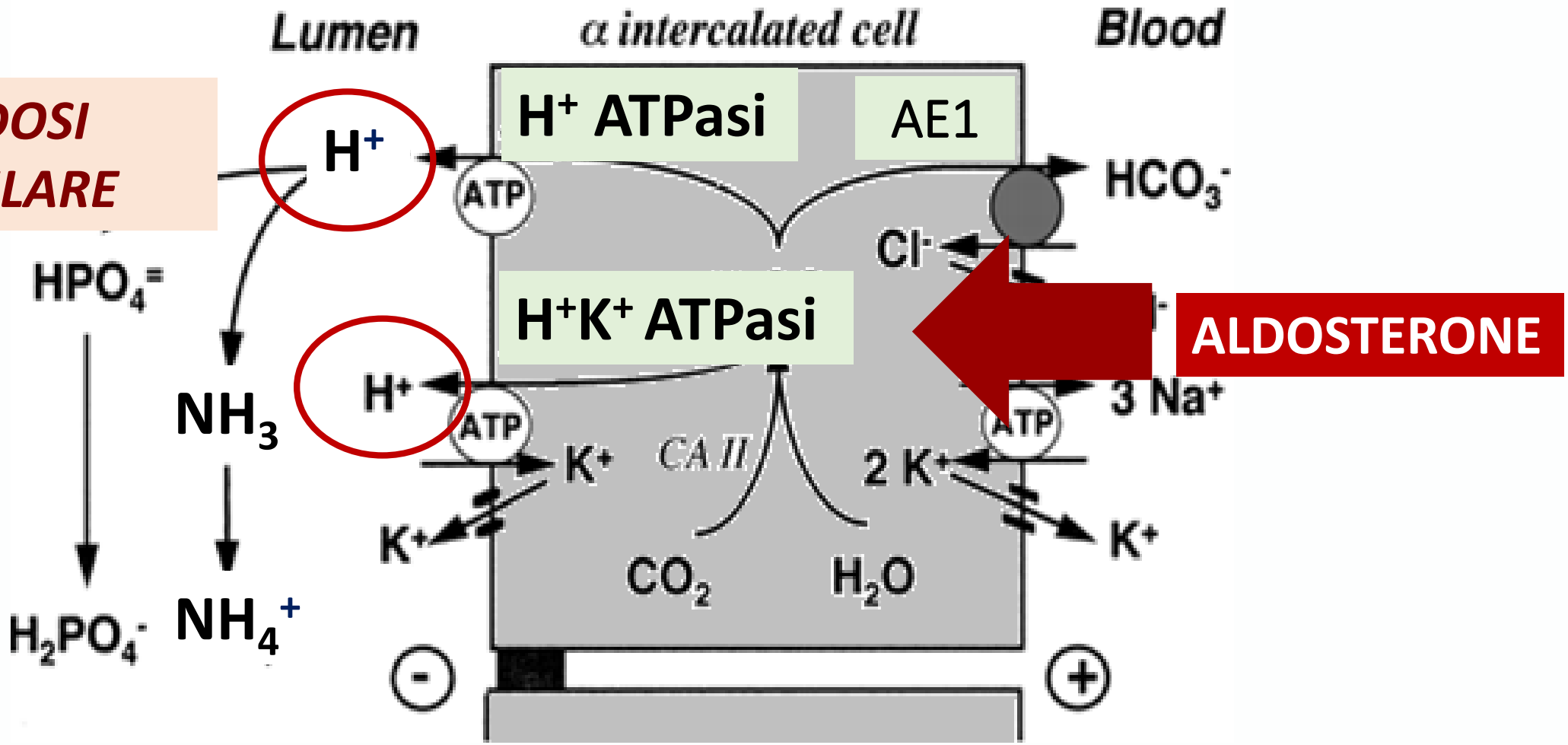


# CELLULE INTERCALATE α

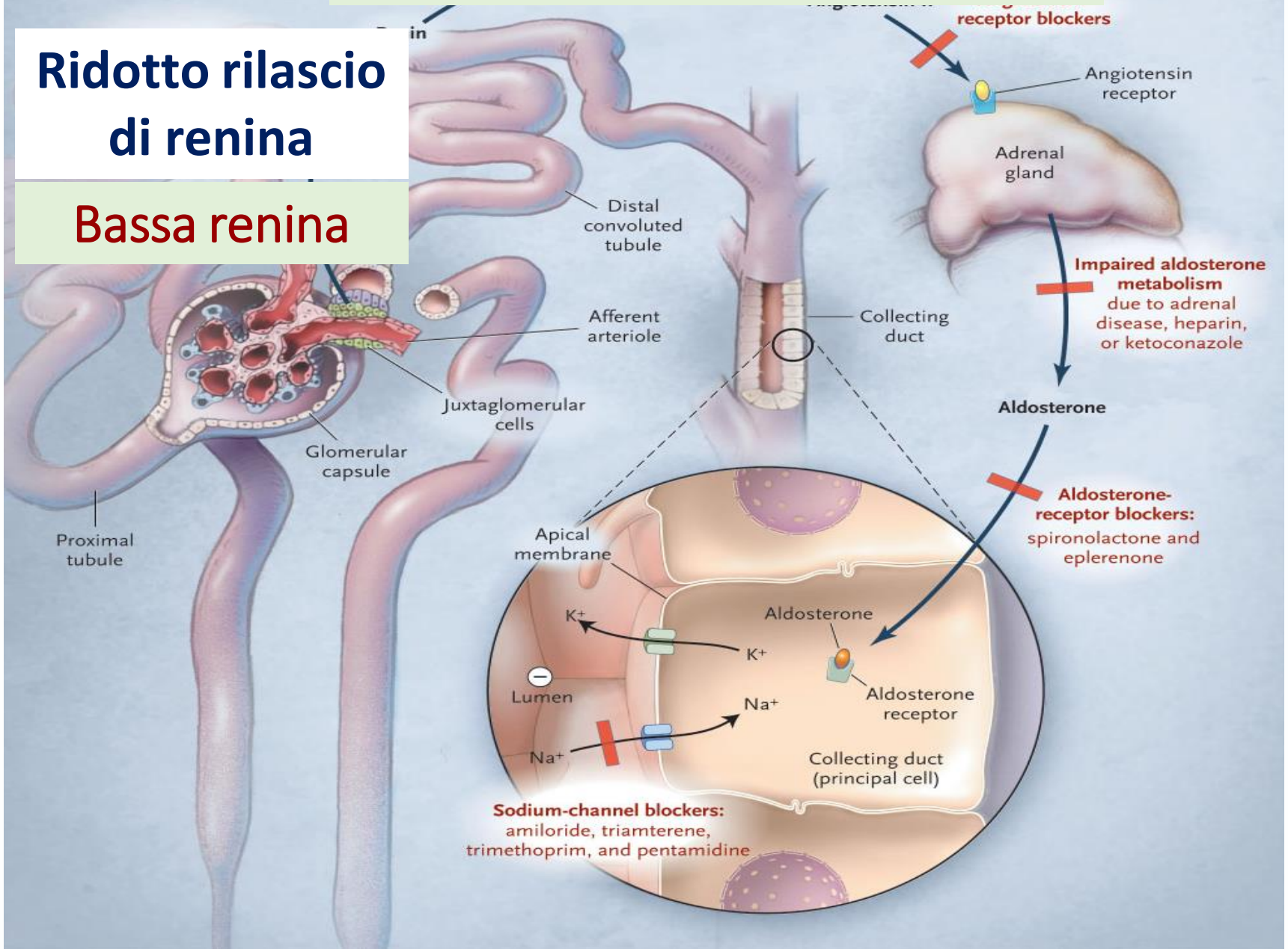
***ACIDOSI TUBULARE***



# Deficit di aldosterone

**Ridotto rilascio di renina**

Bassa renina



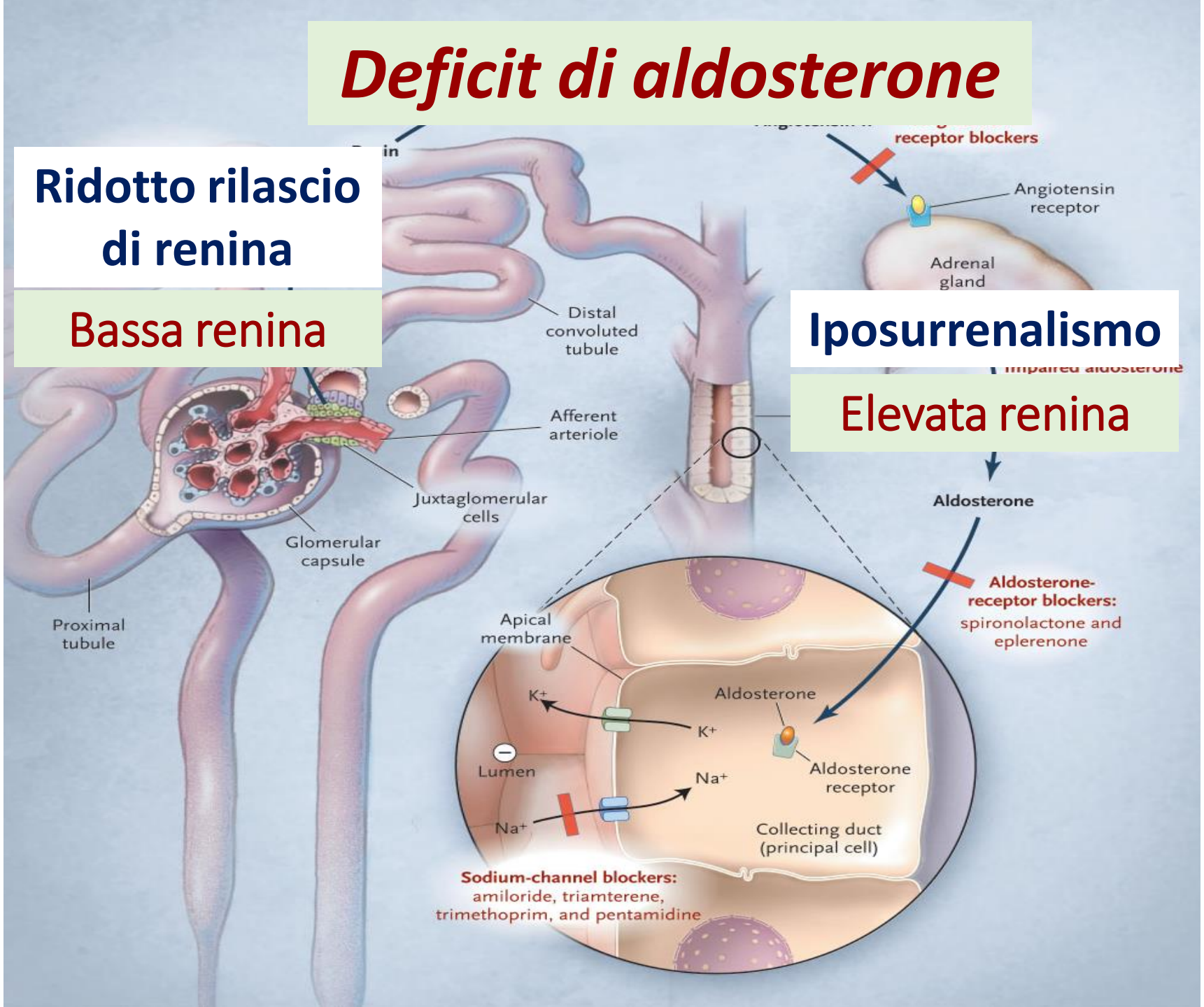
# Deficit di aldosterone

**Ridotto rilascio di renina**

Bassa renina

**Iposurrenalismo**

Elevata renina



# Deficit di aldosterone

**Ridotto rilascio di renina**

Bassa renina

**Iposurrenalismo**

Elevata renina

**Resistenza all'aldosterone**

# Deficit di aldosterone

**Ridotto rilascio di renina**

Bassa renina

**Iposurrenalismo**

Elevata renina

***Carico di $Na^+$***

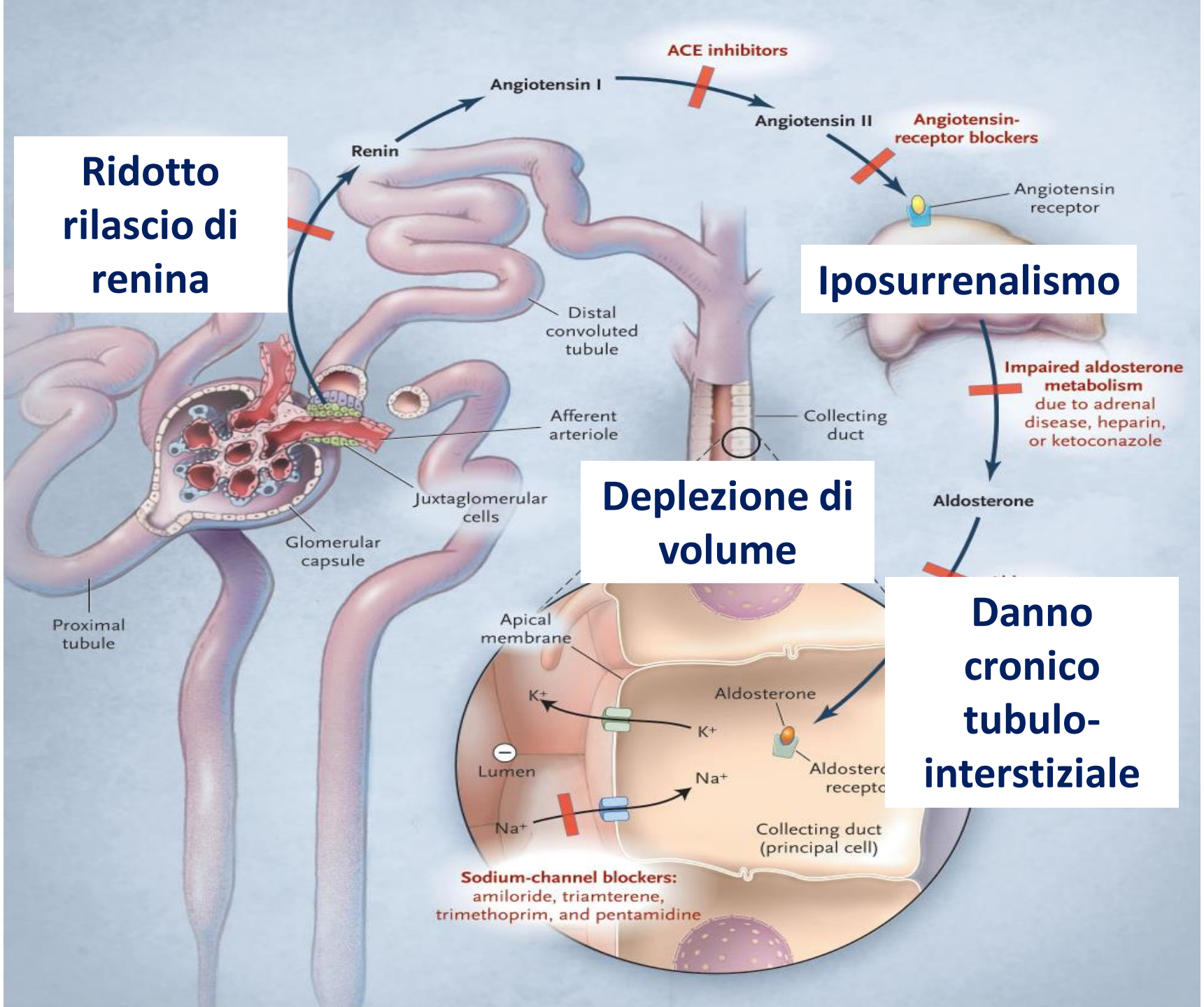
**Resistenza all'aldosterone**

# CONDIZIONI FAVORENTI
# ACIDOSI TUBULARE TIPO IV

- Età avanzata
- Insufficienza renale cronica
- Diabete mellito tipo 2
- Scompenso cardiaco
- Farmaci

# CONDIZIONI FAVORENTI
# ACIDOSI TUBULARE TIPO IV

- Età avanzata
- Insufficienza renale cronica
- Diabete mellito tipo 2
- Scompenso cardiaco
- Farmaci




**Ridotto rilascio di renina**

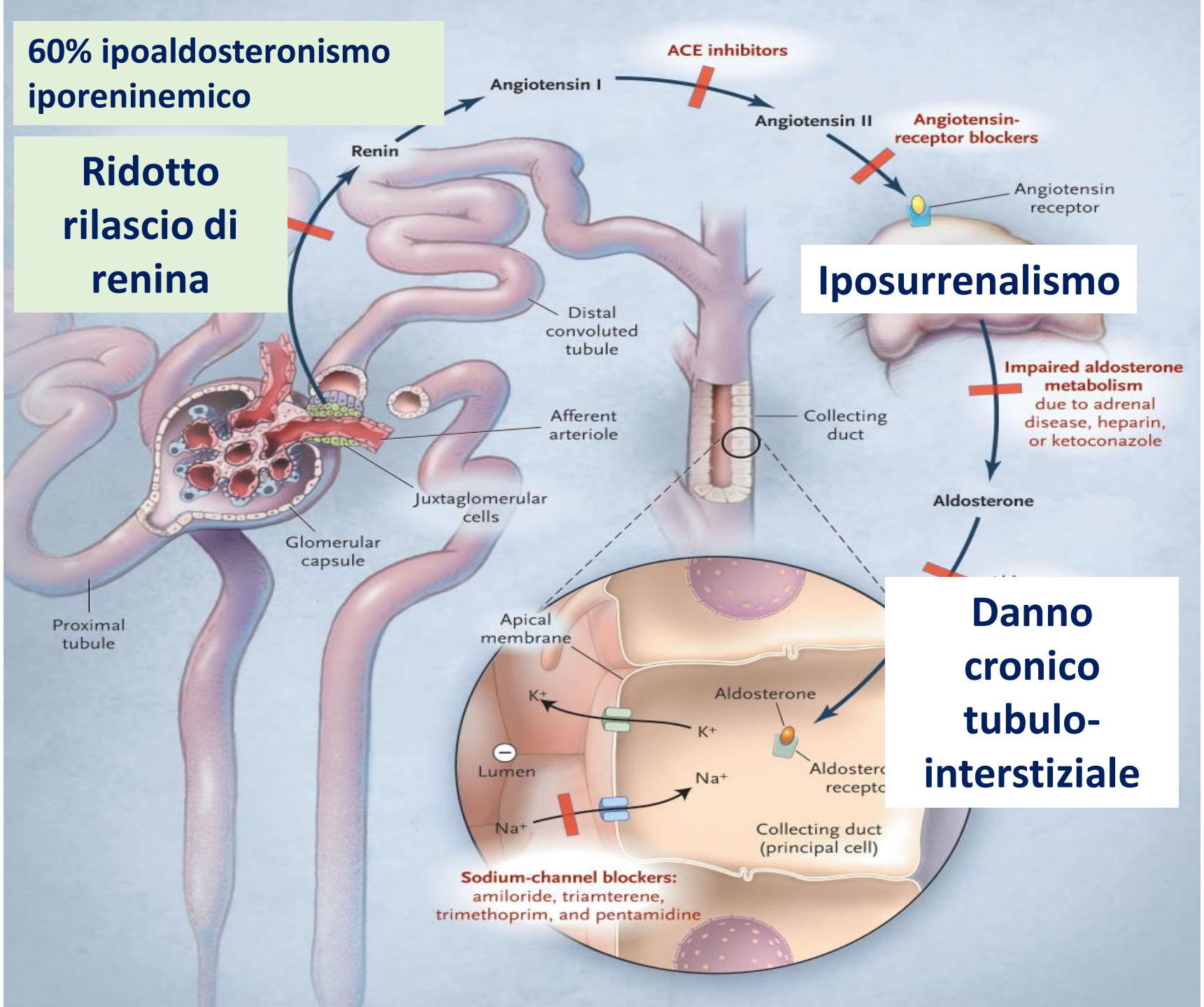
**Iposurrenalismo**

**Deplezione di volume**

**Danno cronico tubulo-interstiziale**

**60% ipoaldosteronismo ipereninemico**

**Ridotto rilascio di renina**

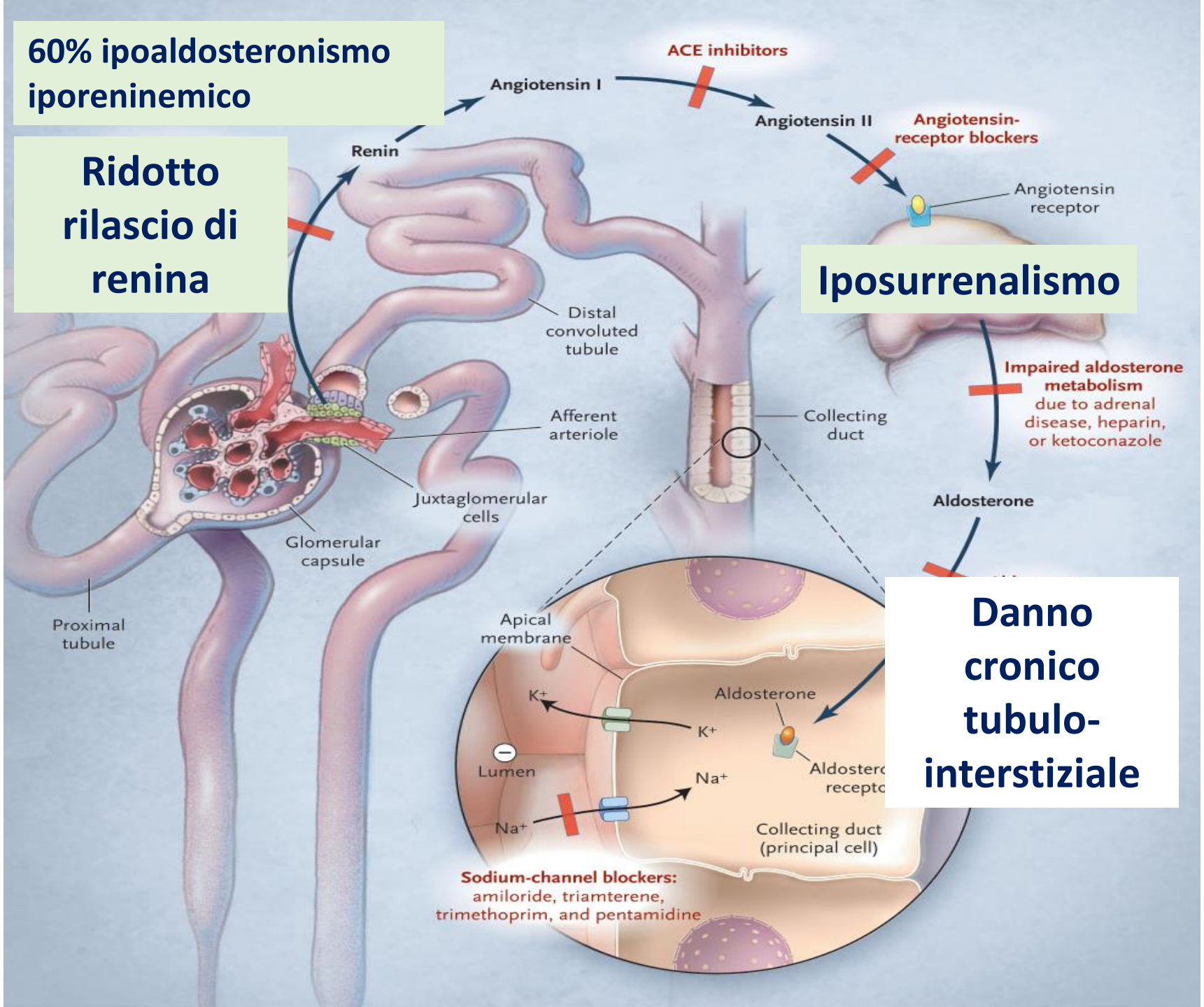



**Iposurrenalismo**

**Danno cronico tubulo-interstiziale**

60% ipoaldosteronismo iporeninemico

Ridotto rilascio di renina




Iposurrenalismo

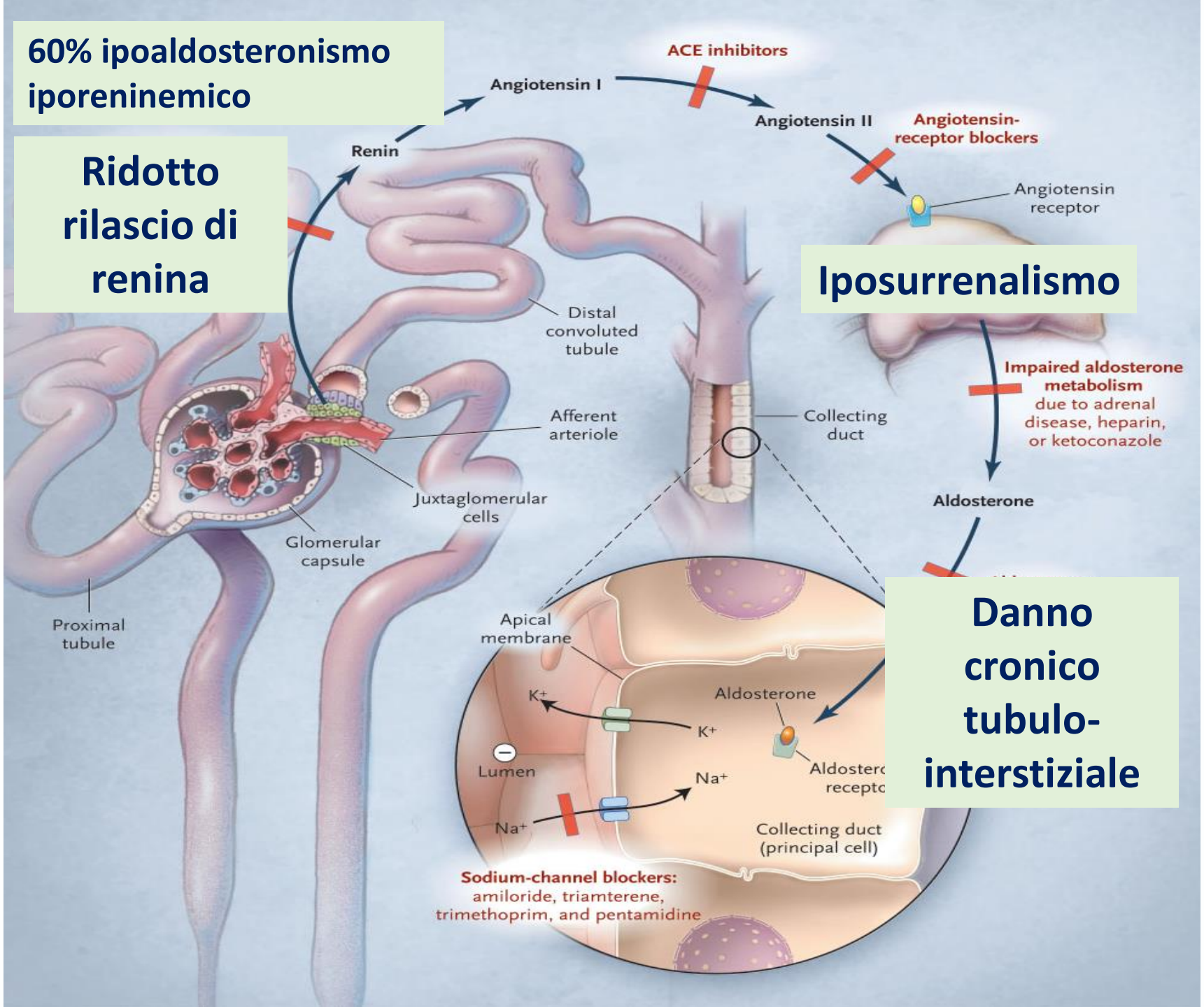
Danno cronico tubulo-interstiziale

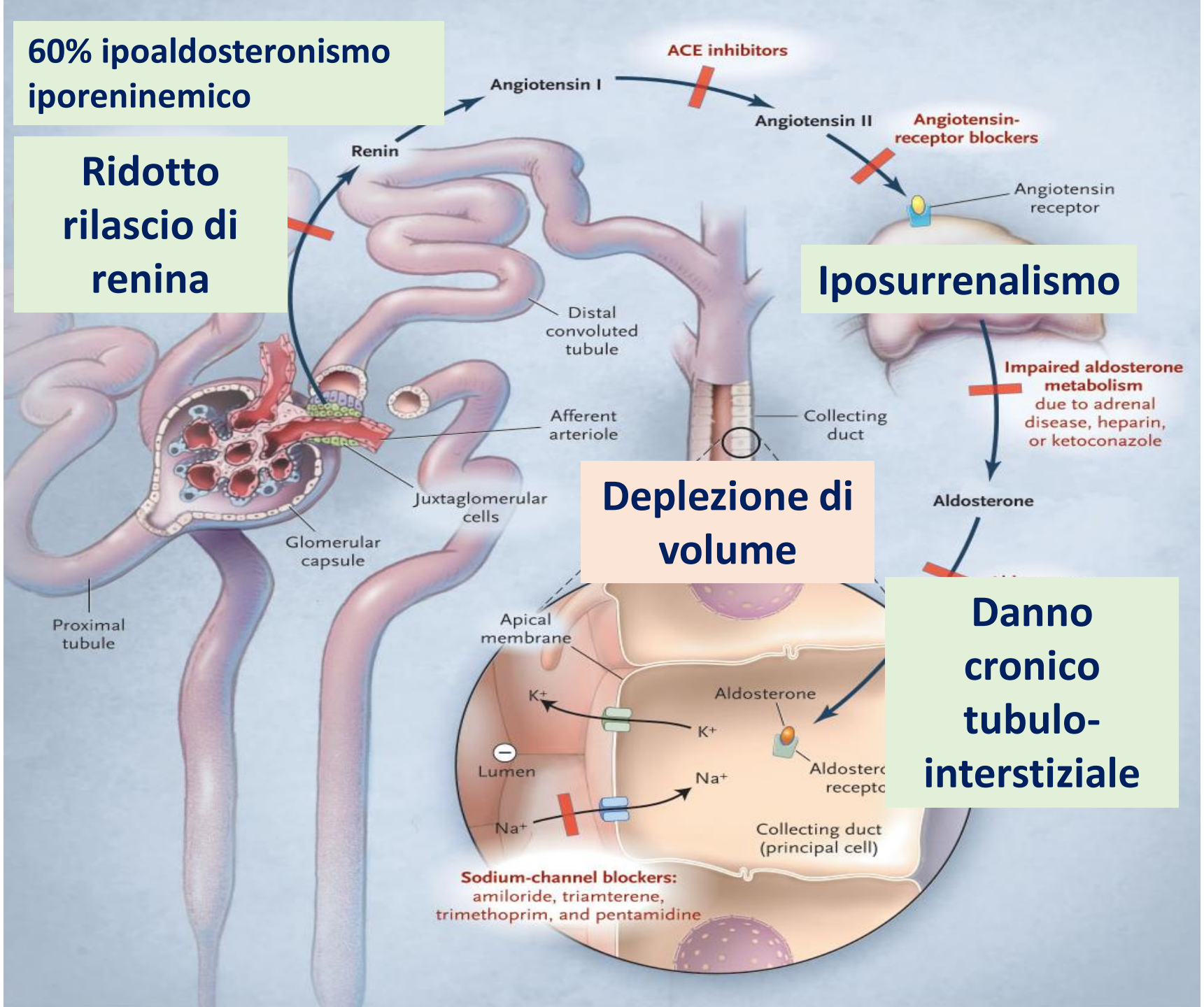
**60% ipoaldosteronismo iporeninemico**

**Ridotto rilascio di renina**

**Iposurrenalismo**

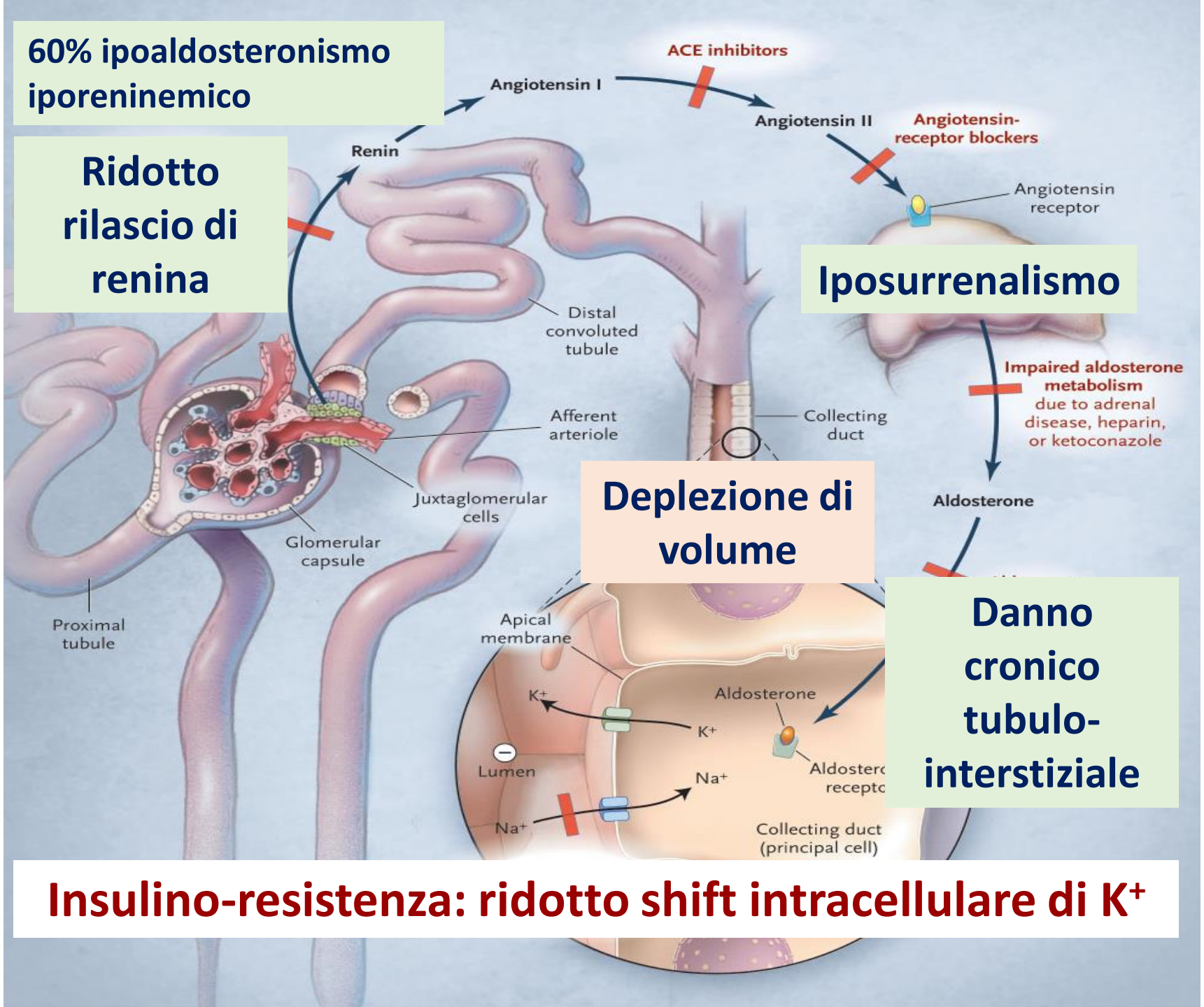
**Danno cronico tubulo-interstiziale**




60% ipoaldosteronismo iporeninemico
Ridotto rilascio di renina
Iposurrenalismo
Deplezione di volume
Danno cronico tubulo-interstiziale
ACE inhibitors
Angiotensin I
Angiotensin II
Angiotensin-receptor blockers
Renin
Angiotensin receptor
Distal convoluted tubule
Afferent arteriole
Collecting duct
Impaired aldosterone metabolism due to adrenal disease, heparin, or ketoconazole
Juxtaglomerular cells
Aldosterone
Glomerular capsule
Proximal tubule
Apical membrane
K+
Aldosterone
Lumen
Na+
Collecting duct (principal cell)
Sodium-channel blockers: amiloride, triamterene, trimethoprim, and pentamidine

60% ipoaldosteronismo iporeninemico

Ridotto rilascio di renina




Iposurrenalismo

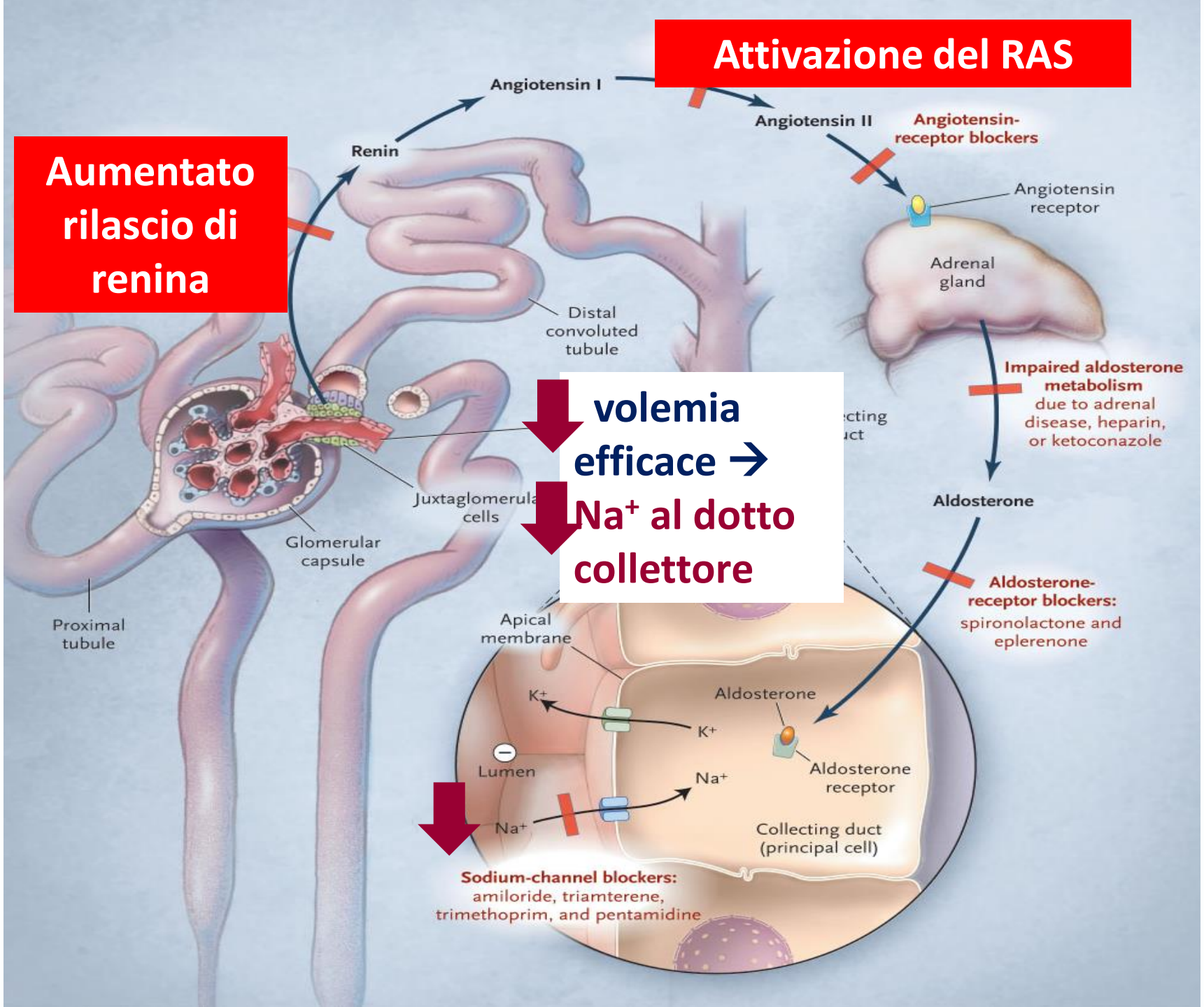
Deplezione di volume

Danno cronico tubulo-interstiziale

Insulino-resistenza: ridotto shift intracellulare di $K^+$

# CONDIZIONI FAVORENTI
# ACIDOSI TUBULARE TIPO IV

- Età avanzata
- Insufficienza renale cronica
- Diabete mellito tipo 2
- Scompenso cardiaco
- Farmaci


Attivazione del RAS
Aumentato rilascio di renina
Angiotensin I
Angiotensin II
Angiotensin-receptor blockers
Renin
Angiotensin receptor
Adrenal gland
Distal convoluted tubule
Impaired aldosterone metabolism due to adrenal disease, heparin, or ketoconazole
volemia efficace →
Na+ al dotto collettore
Juxtaglomerular cells
Glomerular capsule
Aldosterone
Proximal tubule
Aldosterone-receptor blockers: spironolactone and eplerenone
Apical membrane
K+
Aldosterone
K+
Lumen
Na+
Aldosterone receptor
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Collecting duct (principal cell)
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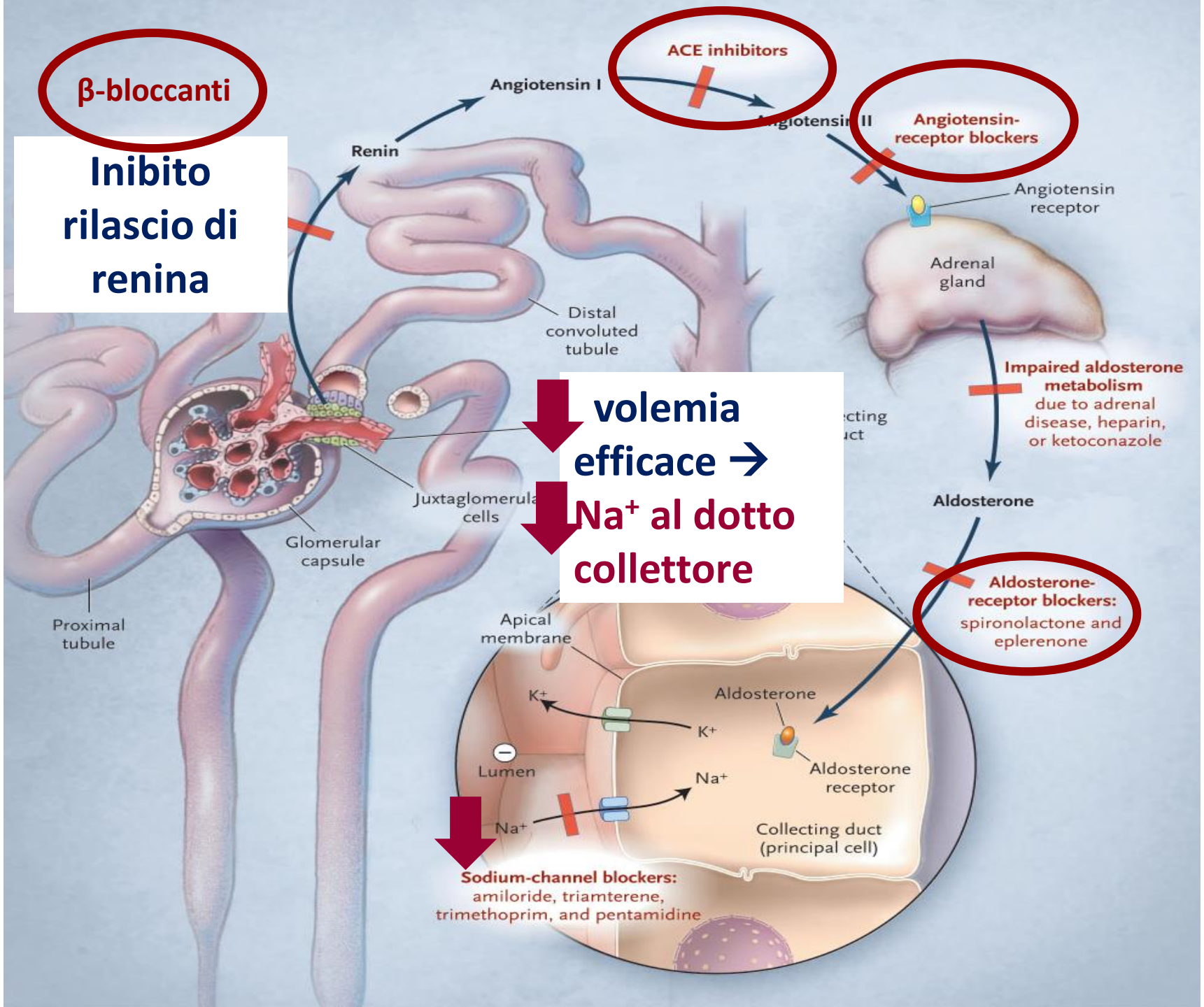
β-bloccanti
Inibito rilascio di renina
ACE inhibitors
Angiotensin I
Angiotensin II
Angiotensin-receptor blockers
Renin
Angiotensin receptor
Adrenal gland
Distal convoluted tubule
Impaired aldosterone metabolism due to adrenal disease, heparin, or ketoconazole
volemia efficace →
Na+ al dotto collettore
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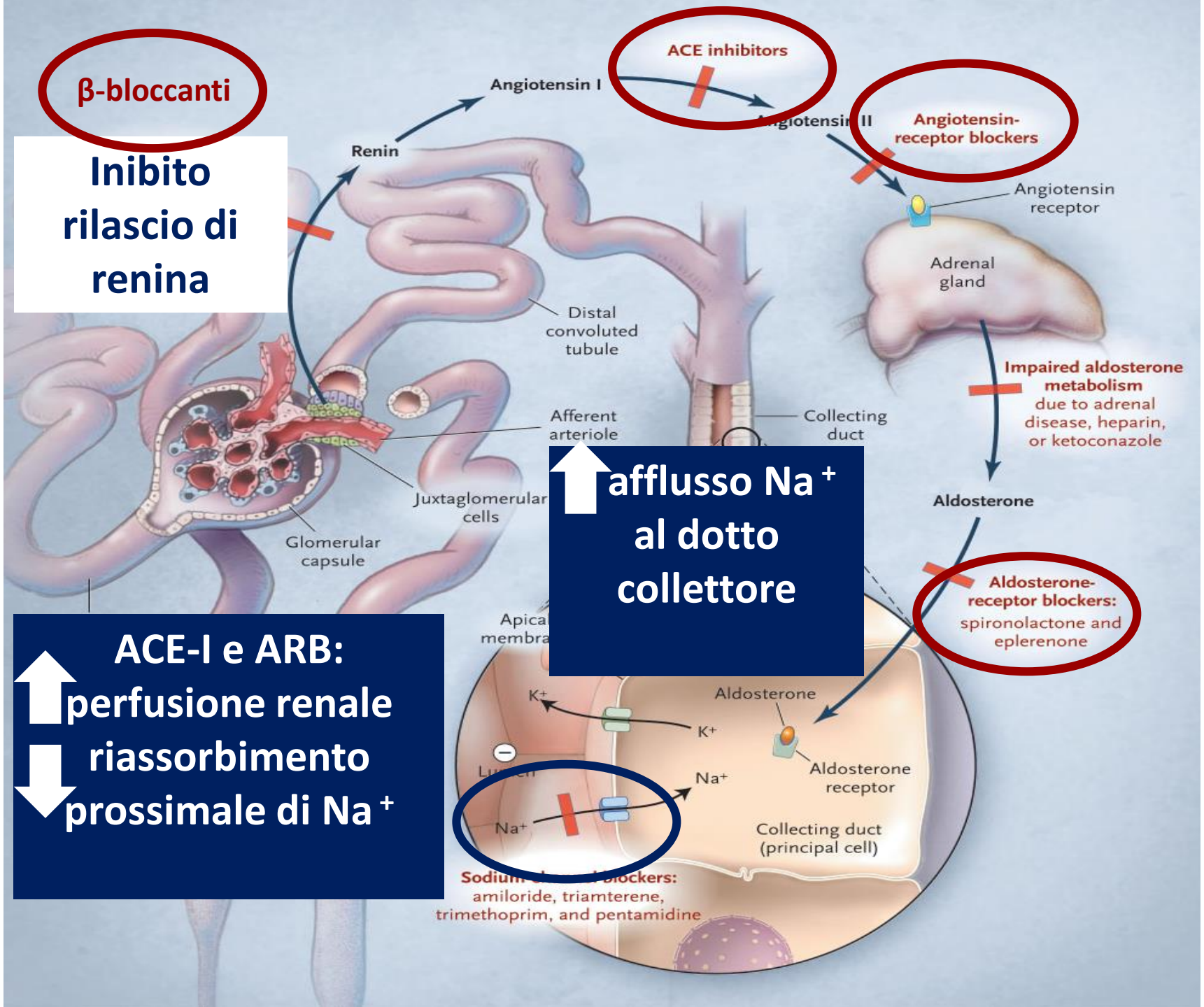
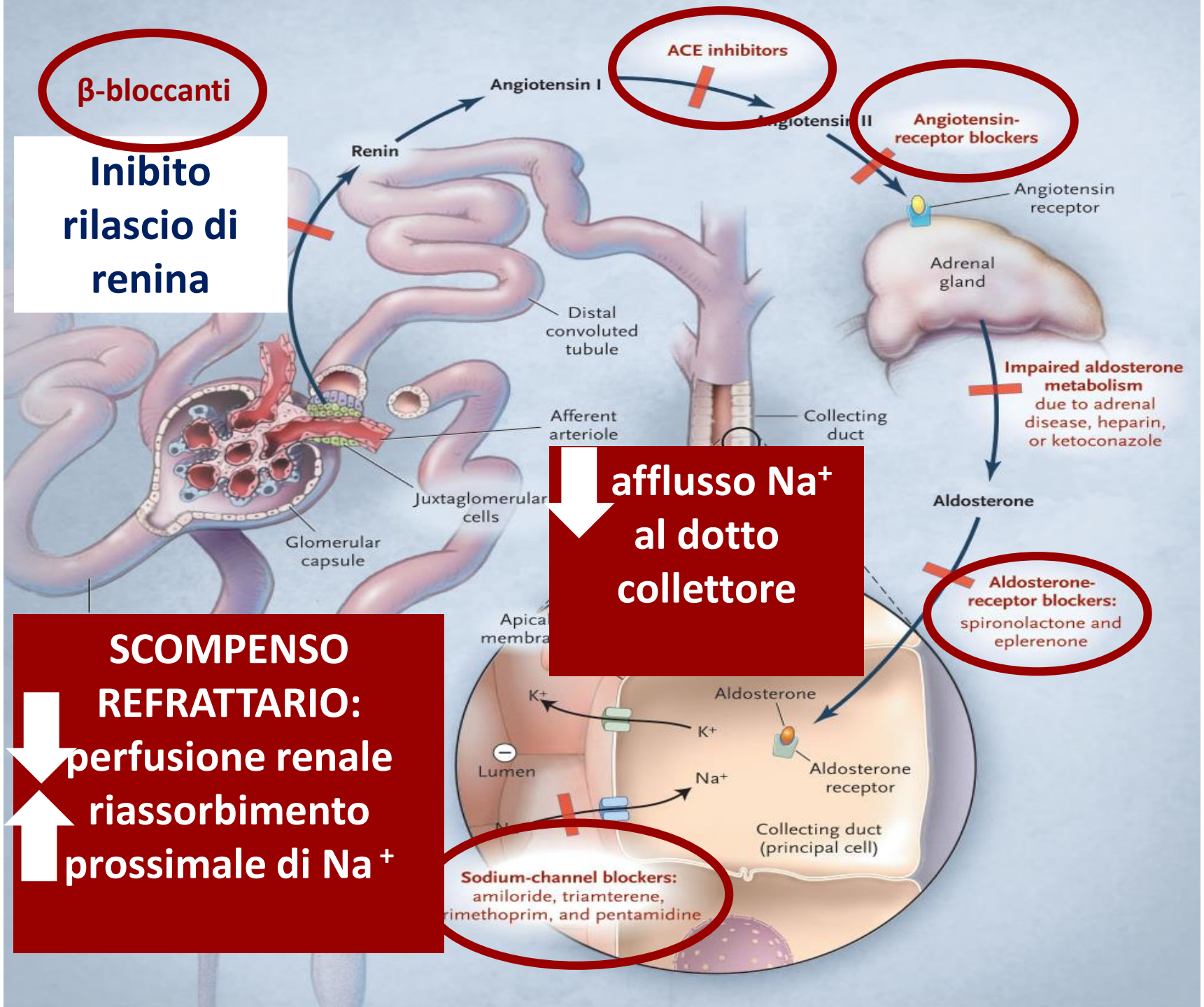

β-bloccanti
Inibito rilascio di renina
ACE inhibitors
Angiotensin I
Angiotensin II
Angiotensin-receptor blockers
Renin
Angiotensin receptor
Adrenal gland
Distal convoluted tubule
Impaired aldosterone metabolism due to adrenal disease, heparin, or ketoconazole
Afferent arteriole
Collecting duct
Juxtaglomerular cells
Glomerular capsule
Aldosterone
afflusso Na+ al dotto collettore
Aldosterone-receptor blockers: spironolactone and eplerenone
ACE-I e ARB: perfusione renale riassorbimento prossimale di Na+
Aldosterone
K+
K+
Na+
Aldosterone receptor
Na+
Collecting duct (principal cell)
amiloride, triamterene, trimethoprim, and pentamidine


β-bloccanti
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ACE inhibitors
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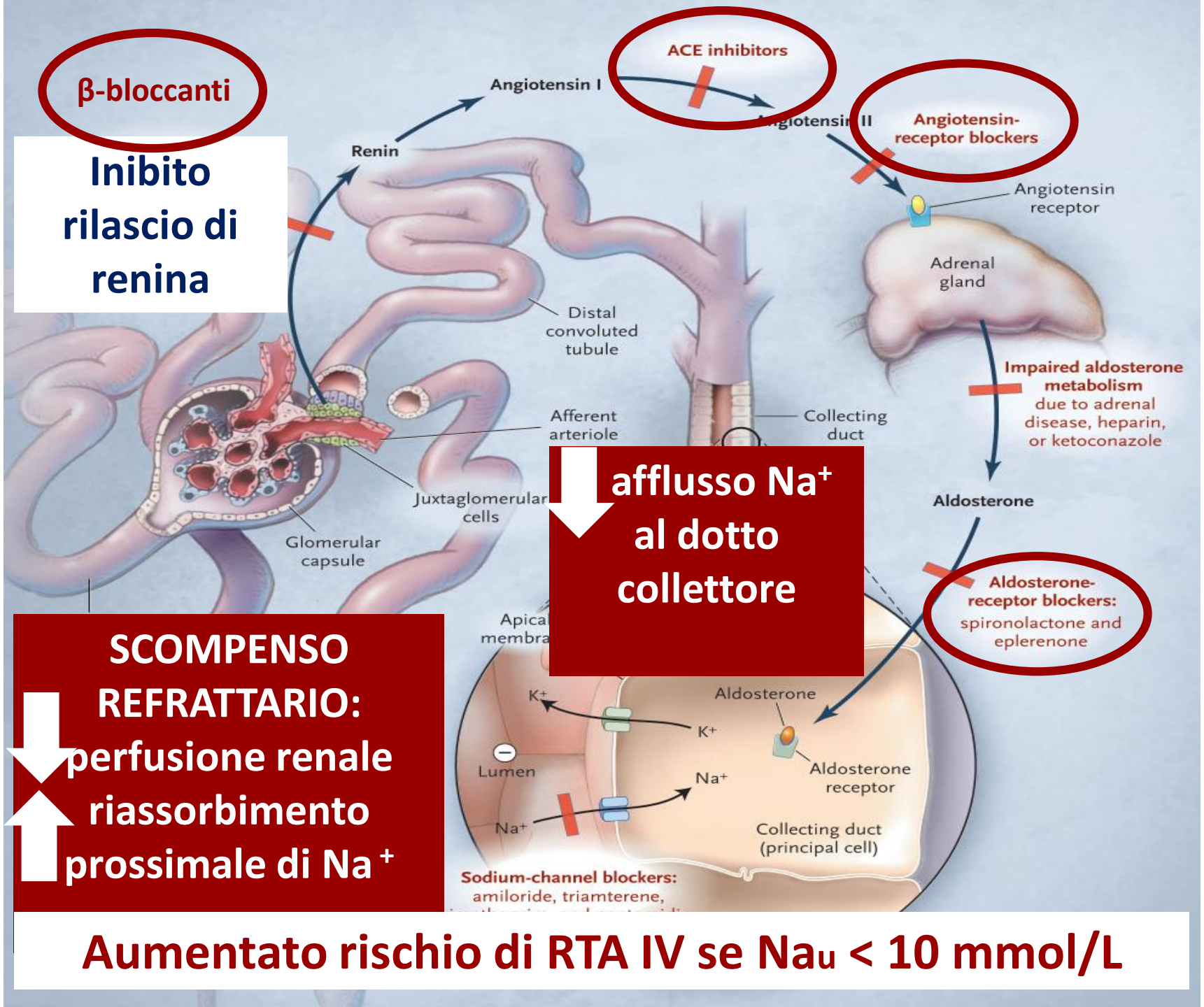
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K+
Lumen
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Aldosterone receptor
Na+
Collecting duct (principal cell)
Sodium-channel blockers: amiloride, triamterene,
Aumentato rischio di RTA IV se Nau < 10 mmol/L

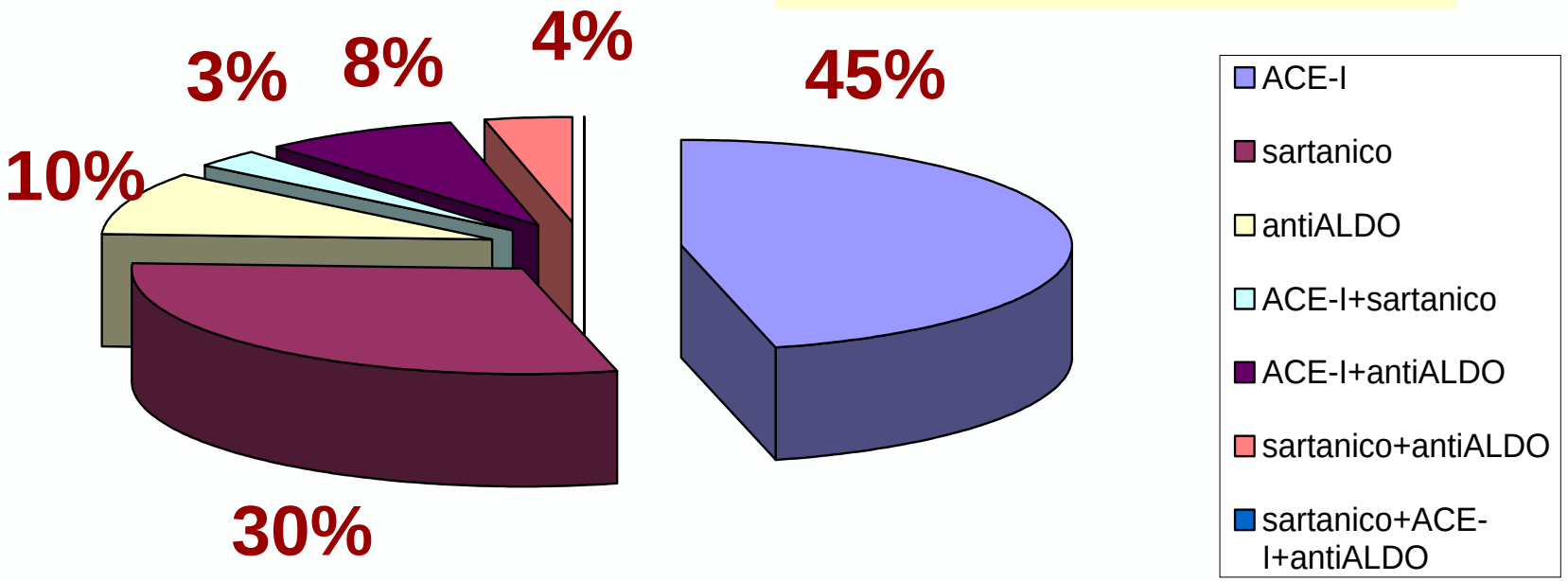
# Accessi al DEA (2007-2009)

**K > 5.5 mmol/l in 459 pazienti**

**= 0,5% degli accessi**

**Età media: 78 anni**

**•42%: ≥ 1 farmaco inibitore del RAS**



# COME PREVENIRE L'ACIDOSI TUBULARE DI TIPO IV?

## Stima del GFR

- Sospensione di altri farmaci iperkaliemizzanti (FANS)
- Dieta a basso contenuto $K^+$
- Tiazidici/diuretici dell'ansa
- Sodio Bicarbonato
- Cautele nella terapia con ACE-I, ARB e anti-aldosteronico

Palmer et al. NEJM 2004

- **GFR < 30 ml/min: forte aumento del rischio di iperkaliemia**
- **GFR < 90 ml/min nel *diabetico* puo' favorire RTA 4.**
- **nell'*anziano* > 70 anni: formula BIS-1**

**(le altre formule sovrastimano GFR!)**

**Palmer et al. NEJM 2004**

- Stima del GFR
- **Sospensione di altri farmaci iperkaliemizzanti (FANS)**
- Dieta a basso contenuto $K^+$
- Tiazidici/diuretici dell'ansa
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Palmer et al. NEJM 2004

- Stima del GFR
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- Dieta a basso contenuto $K^+$
- **Tiazidici/diuretici dell'ansa**
- Sodio Bicarbonato
- Cautele nella terapia con ACE-I, ARB e anti-aldosteronico

Palmer et al. NEJM 2004

- Stima del GFR
- Sospensione di altri farmaci iperkaliemizzanti (FANS)
- Dieta a basso contenuto $K^+$
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- **Sodio Bicarbonato**
- Cautele nella terapia con ACE-I, ARB e anti-aldosteronico

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- Tiazidici/diuretici dell'ansa
- Sodio Bicarbonato
- **Cautele nella terapia con ACE-I, ARB e anti-aldosteronico**

Palmer et al. NEJM 2004

# TERAPIA DI ASSOCIAZIONE

- avvio a basso dosaggio
- controllo kaliemia 1 settimana dopo l'inizio della terapia o dopo una modifica posologica

a) $K^+$ 5-5.5 mEq/L → ridurre dose; sospendere ARB e anti-aldo

b) K+ > 5.5 → sospendere la terapia

Palmer et al. NEJM 2004

# ANTIALDOSTERONICO

## SPIRONOLATTONE + ACE-I/ARB:

- dose non > 25 mg/die
- sospensione se CrCl < 30 ml/min
- controlli potassiemia e sodiemia

Palmer et al. NEJM 2004

# PROGRAMMA

- Impiego dei farmaci nella malattia renale cronica (CKD)
  - Anticoagulanti
  - Bloccanti del sistema renina-angiotensina (RAS)
- Conclusioni

# CONCLUSIONI

# ANTICOAGULAZIONE ORALE E CKD

- eGFR > 50 ml/min: DOAC (dosaggio pieno)

- eGFR 50-30 ml/min: DOAC (dosaggio ridotto)

Rischio/beneficio

- eGFR 30-15 ml/min: VKA/DOAC (Rivaroxaban, Edoxaban; *Ipixaban*)

- eGFR < 15 ml/min: VKA

# BLOCCO DEL RAS E CKD

- Età avanzata
- CKD (eGFR< 30 ml/min)
- Diabete mellito tipo 2
- Scompenso cardiaco

- Inibitore diretto renina (DRI)
- β-bloccante
- ACE-I
- ARB
- Antialdosteronico (MRA)
- Bloccante canale $Na^+$

# BLOCCO DEL RAS E CKD

- Età avanzata
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- ACE-I
- ARB
- Antialdosteronico (MRA)
- Bloccante canale $Na^+$

- FANS….

# BLOCCO DEL RAS E CKD

- Età avanzata
- CKD (eGFR< 30 ml/min)
- Diabete mellito tipo 2
- Scompenso cardiaco

- Inibitore diretto renina (DRI)
- β-bloccante
- ACE-I
- ARB
- Antialdosteronico (MRA)
- Bloccante canale $Na^+$

→ $NaHCO_3$, furosemide…

- FANS…

UNIVERSITÀ DEL PIEMONTE ORIENTALE

# AOU Maggiore della Carità di Novara
# SCDU Nefrologia e Trapianto renale

**Dirigente responsabile**
Prof. Vincenzo CANTALUPPI

**Dirigenti medici**
Dott. Andrea AIROLDI
Dott.ssa Francesca COFANO
Dott.ssa Cristina CORNELLA
Dott.ssa Elisa LAZZARICH
Dott. Claudio MUSETTI
Dott. Angelo NAPPO
Dott.ssa Daniela PALMIERI
Prof. Marco QUAGLIA

**Medici specializzandi**
Dott. Michele BATTISTA
Dott. Simone CORTAZZI
Dott. Gabriele GUGLIELMETTI
Dott. Guido MERLOTTI
Dott.ssa Fabiola PAGANI

# Renal Targeted Therapies of Antihypertensive and Cardiovascular Drugs for Patients With Stages 3 Through 5d Kidney Disease

Dhaybi OI Clin Pharm Ther 2017

# β-BLOCCANTI

| | Half-life (h) | Serum protein binding (%) | Volume of distribution (L/kg) | Dosing for normal renal function[a] | Recommended dosing (eGFR 10–50)[b] |
|---|---|---|---|---|---|
| *Beta Blockers* | | | | | |
| Atenolol | 6–7 | 3 | 1.1 | 50–100 mg q24h | 50% |
| Bisoprolol | 9–13 | 30–35 | 3 | 5 – 20 mg q24h | 75% |
| Carvedilol | 5–10 | 95 | 1.2–1.8 | 6.25–25 mg q12h | 100% |
| Labetalol | 3–9 | 50 | 3.3–7.9 | 200–400 mg q12h | 100% |
| Metoprolol | 3.5 | 11 | 4.2 | 50–400 mg daily | 100% |
| Propranolol | 2–6 | 81–93 | 3.7–4.9 | 80–160 mg q12h | 100% |

Dhaybi OI Clin Pharm Ther 2017

# ACE-INIBITORI

| | Half-life (h) | Serum protein binding (%) | Volume of distribution (L/kg) | Dosing for normal renal function[a] | Recommended dosing (eGFR 10–50)[b] |
|---|---|---|---|---|---|
| Captopril | 2–3 | 25–30 | 0.7–3 | 50–150 mg q8–12h | 75% |
| Cilazapril | 40–50 | unk | 0.5–0.8 | 1.25 mg q24h | 50% |
| Enalapril | 11–24 | 50–60 | 1–2.4 | 5–20 mg q12–24h | 50–100% |
| Fosinopril | 12 | 99 | 0.15 | 10–40 mg q12–24h | 100% |
| Lisinopril | 30 | 0 | 1–3.8 | 20–40 mg q24h | 50–75% |
| Perindopril | 10.9 | 20 | 0.16–0.22 | 2–8 mg q24h | 2 mg q24h |
| Quinapril | 1–3 | 97 | 1.5 | 20–40 mg q12–24h | 2.5–5 mg q24h |
| Ramipril | 8–10 | 55–70 | 1.2 | 5–10 mg q24h | 25–50% |
| Trandolapril | 6–10 | 65–94 | 0.26 | 1 – 4 mg q24h | 50–100% |

Dhaybi OI Clin Pharm Ther 2017

# Clinical and Economic Impact of Hyperkalemia in Patients with Chronic Kidney Disease and Heart Failure

# DIURETICI

| | Half-life (h) | Serum protein binding (%) | Volume of distribution (L/kg) | Dosing for normal renal function[a] | Recommended dosing (eGFR 10–50)[b] |
|---|---|---|---|---|---|
| Acetazolamide | 1.7–5.8 | 70–90 | 0.2 | 250 mg q6–12h | space dosing to q12h |
| Amiloride | 6–21 | 30–40 | 5–5.2 | 5 mg q24h | 50% |
| Bumetanide | 1.2–1.5 | 96 | 0.2–0.5 | 1–2 mg q8–12h | 100% |
| Chlorothiazide | 0.75–2 | unk | unk | 500–1000 mg q12–24h | 100% |
| Chlorthalidone | 44–80 | 76–90 | 3.9 | 25 mg q24h | 100% |
| Ethacrynic acid | 2–4 | 90 | 0.1 | 50–100 mg q8h | space to q8-12h |
| Furosemide | 0.5–2.1 | 95 | 0.07–0.2 | 20–300 mg q12–24h | 100% |
| HTZD | 5.6–15 | 65 | unk | 6.25–100 mg q24h | 100% |
| Indapamide | 14–18 | 76–79 | 0.3–1.3 | 1.25–5 mg q24h | 100% |
| Metolazone | 4–20 | 95 | 1.6 | 5–20 mg q24h | 100% |
| Spironolactone | 10–35 | 98 | unk | 25 mg q6–8h | space to q24h[c] |
| Torsemide | 2–4 | 97–99 | 0.14–0.19 | 5–100 mg q12–24h | 100% |
| Triamterene | 2–12 | 55–81 | 2.2–3.7 | 25–150 mg q12–24h | avoid |

Dhaybi OI Clin Pharm Ther 2017

# The Nephrotoxicity of Vancomycin

Filippone EJ Clin Pharm Ther 2017

**Table 4 Potential risk factors for vancomycin nephrotoxicity**

| | |
|---|---|
| Vancomycin exposure variables | Loading dose |
| | Total daily dose |
| | AUC |
| | Trough level |
| | Duration |
| | Continuous vs. intermittent infusion |
| Patient-specific factors | Obesity |
| | Severity of illness |
| | ICU residence |
| | Chronic kidney disease |
| | Concurrent nephrotoxin exposure |
| | Concurrent aminoglycosides<br>Concurrent piperacillin-tazobactam |

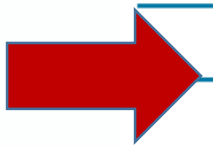

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**Table 5 Approaches to reduce vancomycin nephrotoxicity**

| Recommendation | Comment |
|---|---|
| Weight based dosing of 15–20 mg/kg | Use actual body weight and combine with therapeutic drug monitoring. Consider nomograms in patients with renal insufficiency |
| Consider a loading dose of 25–30 mg/kg for severe infections (bacteremia, endocarditis, pneumonia, osteomyelitis, meningitis) | There is no evidence of increased nephrotoxicity with a loading dose |
| Use intermittent rather than continuous administration | Continuous infusion has limited evidence for reducing toxicity and is cumbersome to use |
| Do not obtain peak vancomycin concentrations | Peak concentrations do not predict efficacy or toxicity |
| Maintain trough concentration 10–15 mg/L for non–severe infections | >15 mg/L correlates weakly with improved efficacy, but at the expense of a clear association with toxicity |
| Maintain tough concentrations 15–20 mg/L for serious infections | Increased potential toxicity balanced against severity of infection |
| Consider cessation of vancomycin should AKI develop after at least 2 days of therapy | Effective but not nephrotoxic alternatives exist e.g., daptomycin for MRSA bacteremia/endocarditis or linezolid for MRSA pneumonia |
| Tailor duration of therapy to efficacy and not to prevent nephrotoxicity | Duration of therapy should be directed to microbiologic control. Toxicity may increase with prolonged therapy, but evidence base is weak |
| Concomitant use with piperacillin-tazobactam or an aminoglycoside should be paired with TDM and ongoing assessment of need for concurrent therapy | There is moderate evidence of synergistic toxicity to be balanced against potential need for efficacy |
| TDM should be used in patients at high risk for toxicity, prolonged therapy or impaired renal function | Toxicity in patients with limited comorbidities treated for less than 10 days is very uncommon |
| Obtain TDM before the fourth dose after starting or adjusting therapy if stable renal function | Assumptions linking trough levels to AUC are based upon a steady state concentration |

Filippone EJ Clin Pharm Ther 2017