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งานประชุมวิชาการ Contemporary Review in Pharmacotherapy 2023
25 สิงหาคม 2566 เวลา 9.30-10.30 น. ห้องประชุมราชเทวี 2 ชั้น 3 โรงแรมเอเชีย ราชเทวี กทม.

The Blockage of RAAS and SGLT2 for Nephroprotection

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Disclosure

- The author of this presentation has no actual or potential conflicts of interest

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Outline

- Mechanism of RAAS pathway and drugs involved RAAS
- Role of RAAS inhibitors in kidney disease
- How to use RAAS inhibitors safety in kidney disease
- Key takeaways

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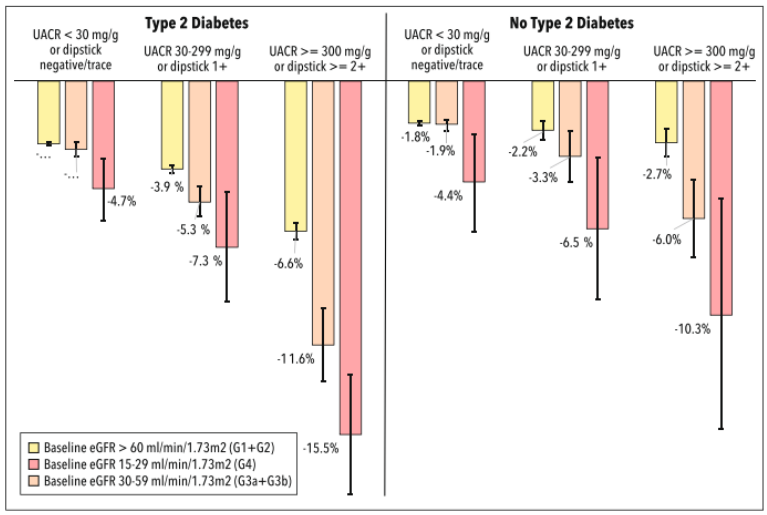
Risk for CKD progression



Nichols et al. BMC Nephrology (2020) 21:167.

- Main factors related to CKD progression
  - Level of eGFR (staging of CKD)
  - Level of albuminuria
  - Having type 2 DM

Anti-hypertensive use in CKD

Hypertension and CKD

Proteinuria

ACEI/ARB +/- CCB

Uncontrolled?

Add on:

- CCB if not already prescribed
- Thiazide/thiazide-like diuretic
- MRA
- Beta-blocker
- Alpha-blocker

No-Proteinuria

One or two of:

- ACEI/ARB
- CCB
- Thiazide/thiazide-like diuretic

Add on:

- ACEI/ARB
- CCB
- Thiazide/thiazide-like diuretic
- MRA
- Beta-blocker
- Alpha-blocker

Drugs. 2019 Mar;79(4):365-379.

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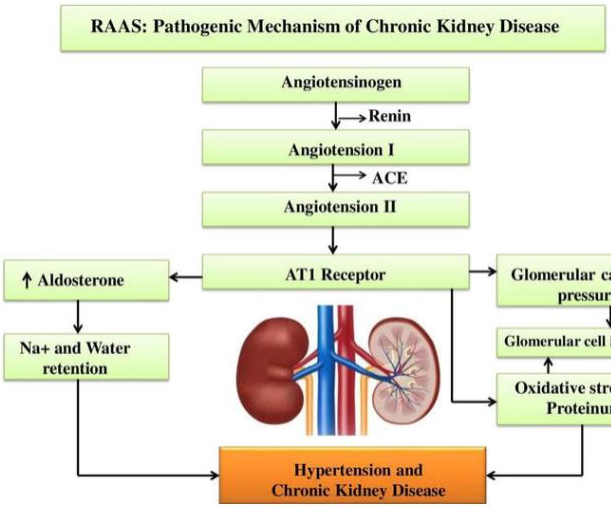

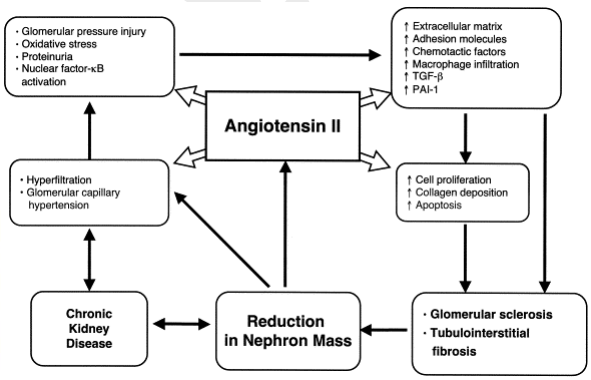

Renin-angiotensin aldosterone system Edited by Samy I. McFarlance. 2021. Am J Med. 2004 Feb 15;116(4):263-72.

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KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease *(Public review draft July 2023)*

ACEI/ARB

ระยะของโรคไตเรื้อรัง (CKD staging)	ภาวะความดันโลหิตสูง (hypertension)	ภาวะเบาหวาน	ระดับอัลบูมินในปัสสาวะ			น้ำหนักคำแนะนำ และคุณภาพหลักฐานทางวิชาการ
			A1 (<30 มิลลิกรัม/วัน)	A2 (30-300 มิลลิกรัม/วัน)	A3 (>300 มิลลิกรัม/วัน)	
G1-G4	√				√	1B
G1-G4	√			√		2C
G1-G4	√	√		√	√	1B

- Avoiding any combination of ACEI, ARB, direct renin inhibitors (1B)
- RAASi (ACEI/ARB) should be administered using the highest approved dose

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Drug	Starting dose	Max daily dose	Dosage adjustment in kidney impairment
Enalapril	5 mg OD	40 mg	CrCL < 30 mL/min, reduced initial dose to 2.5 mg OD
Fosinopril	10 mg OD	80 mg	No dosage adjustment necessary
Lisinopril	10 mg OD	40 mg	CrCL 10-30 mL/min, reduced initial se by 50% for adult CrCL < 10 mL/min, reduced initial do ng PO
Perindopril	2 mg OD	8 mg	CrCL < 30 mL/min, not mended
Quinapril	10 mg OD	80 mg	CrCL 30-6 in, rt at ng OD CrCL 10 mL/ , s at 2 mg OD < 1 mL/mi insu cient data for dosage recommendation
Ramipril	2.5 mg OD	20 mg	CrC 40 in, administer 25% of normal dose
Trandolapril	1 mg OD	ig	rCL < 30 mL/min, reduced initial dose to 0.5 mg/day
Azilzartan	20-80 mg	8 g	Dose adjustment is not required
Candesartan	1 mg	32 mg	CrCL < 30 mL/min, AUC and Cmax were doubled
Irbesartan	15 g	300 mg	No dosage adjustment necessary
Losartan	0 mg OD	100 mg	No dosage adjustment necessary
Olmesartan	20 mg OD	40 mg	No initial dosage adjustment necessary
Telmisartan	40 mg OD	80 mg	No dosage adjustment necessary
Valsartan	80 mg OD	320 mg	No dosage adjustment available for CrCL < 30 mL/min

Ref: KDIGO 2021 guideline

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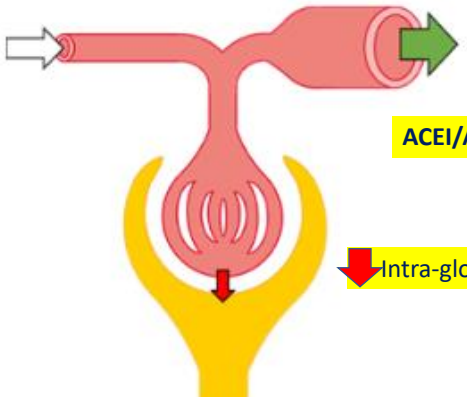
ACEIs/ARBs and proteinuria



RAASi **reduced** intra-glomerular pressure (IGP)

↓

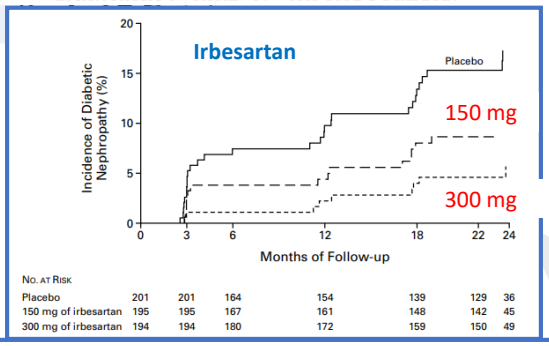
Decrease proteinuria/albuminuria

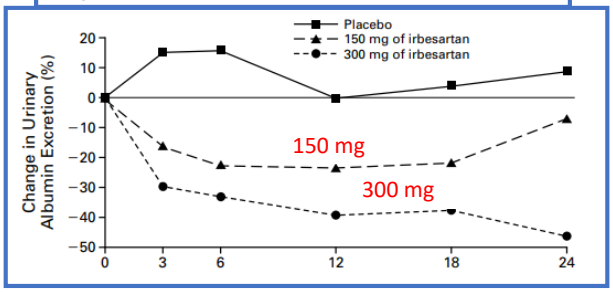
Albuminuria-lowering effect is dose-dependent

Drugs. 2022 Feb;82(2):97-108.

The New England Journal of Medicine

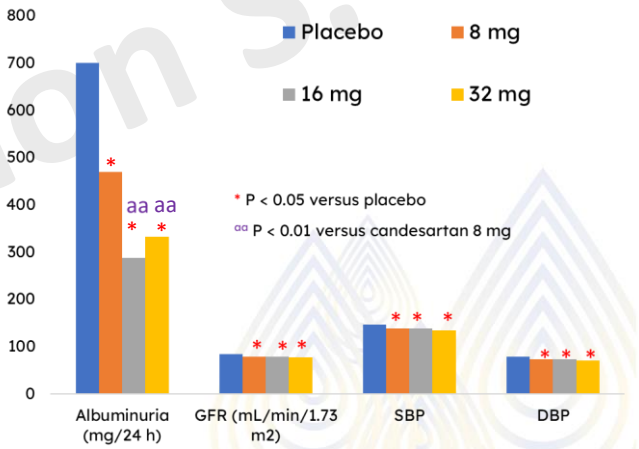
THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES





Optimal Dose of Candesartan for Renoprotection in Type 2 Diabetic Patients With Nephropathy

A double-blind randomized cross-over study



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Key clinical questions?

- When to start/stop RAASi in kidney disease patients?
- What are the current evidence of RAASi in advanced CKD?
- How to use RAASi safely in CKD patients?

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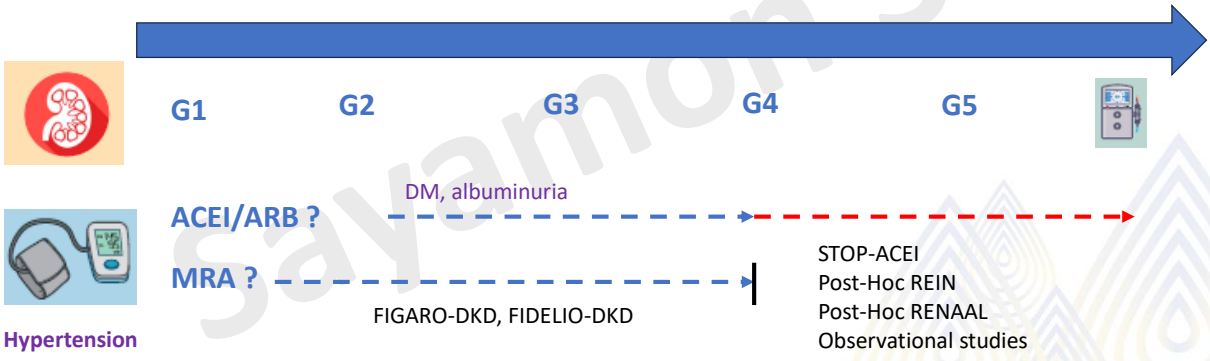
Different CKD patient scenario

Who should receive RAASi?



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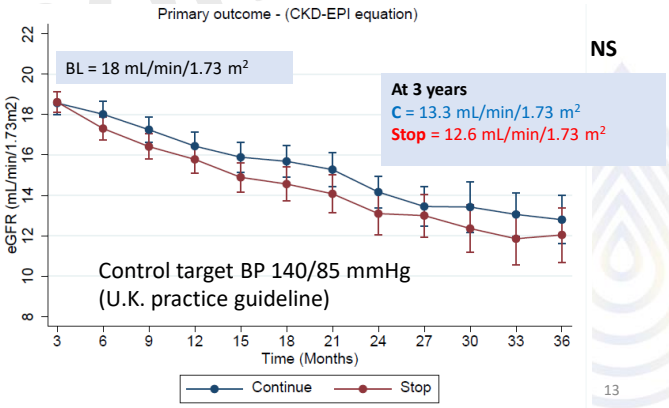
STOP ACEi Trial (2022)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2022 VOL. 387 NO. 22

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

Sunil Bhandari, Ph.D., Samir Mehta, M.Sc., Arif Khwaja, Ph.D., John G.F. Cleland, M.D., Natalie Ives, M.Sc., Elizabeth Brettell, B.Sc., Marie Chadburn, Ph.D., and Paul Cockwell, Ph.D., for the STOP ACEi Trial Investigators*

- **P** = 411 patients receiving RAASi (ACEI/ARB = 50%/50%)
  - Mean eGFR 18 mL/min/1.73 m^2
  - DM 30%, A2
  - Controlled BP (136/77 mmHg) CCB 65%, loop 33%, aa 30%, Beta-blocker 30%, no. of anti-HTN = 2.7 items
- **I** = D/C RAASi
- **C** = continue RAASi
- **O** = eGFR at 3 years



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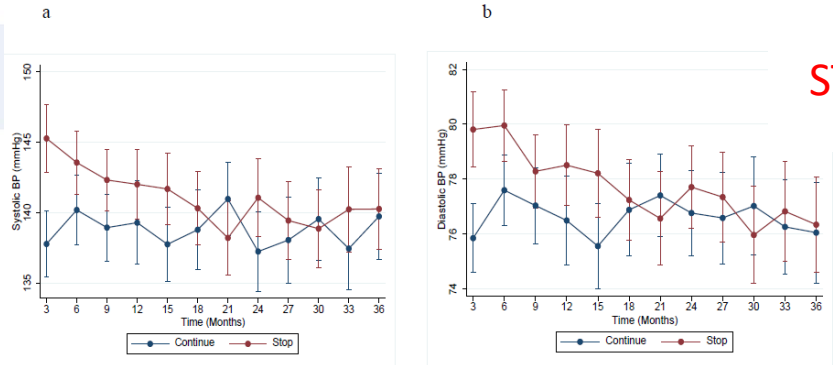
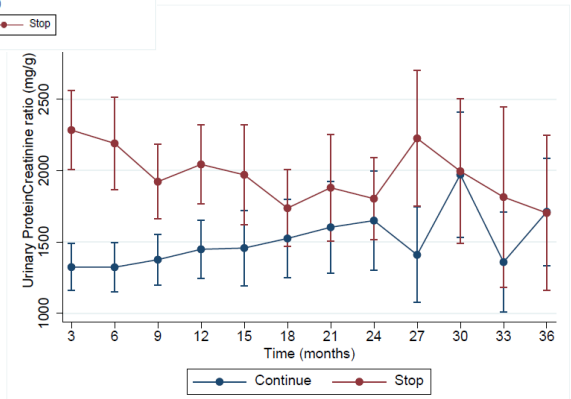
STOP ACEi Trial (2022)

BP



UPCR



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RAASi in advanced kidney disease

	Post Hoc REIN (2001)	Post Hoc RENAAL (2004)	Ahmed AK (2010)
P			
• Age • CKD staging • Albuminuria • Cause of CKD • BP	• 50 years • G4 (CrCL 29-30 mL/min/1.73 m^2) • **A3 (proteinuria 3-4 g/day)** • GN 35%, other or unknown 54%, APKD/interstitial nephritis 11% • **150/90 mmHg**	• 60 years • G4 (CrCL 28 mL/min/1.73 m^2) • **A3 (UACR 1800 mg/g)** • **All T2DM,** A1C = 8 • **155/80 mmHg**	• 73 years • G4 (eGFR 16 mL/min/1.73 m^2) • **A1 (proteinuria 77 mg/mmol)** • DM 50%, other causes (GN, tubulointerstitial nephritis, obstructive nephropathy, no known etiology 50%) • HTN 77% (BP 137/70 mmHg)
I	Ramipril (N = 52)	Losartan (N = 2448)	All STOP RAASi and changed to other anti-BP medication (N = 52)
C	Conventional anti-BP (N = 55)	Placebo (N = 263)	No

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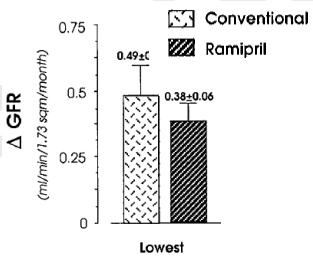
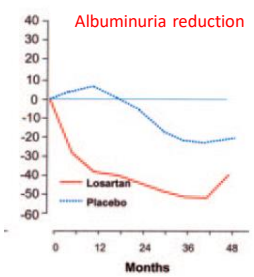
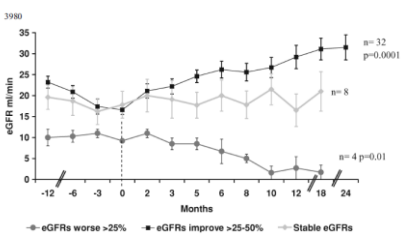
	Post Hoc REIN (2001)	Post Hoc RENAAL (2004)	Ahmed AK (2010)
O			
• Primary endpoint • Others	• Change in eGFR at 3 years • Progression to ESKD	• Progression to ESKD (need for HD, KT)	• Change in eGFR at 12 mo
Results	**For ramipril, eGFR declined 4 mL/min/1.73 m^2/year**. For conventional, eGFR declined 6 mL/min/1.73 m^2/year	**Losartan decreased the risk of ESKD by 24.6%** (95% CI 0.2-43.1, P = 0.048)	The eGFR after stopping RAASi for 12 mo was 26 mL/min/1.73 m^2 (P = 0.001)



Highest quartile
(Scr > 2 mg/dL)





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Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcomes: A Nationwide Study

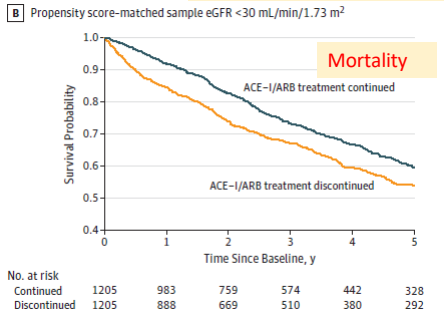
Edouard L. Fu,[1] Marie Evans,[2] Catherine M. Clase,[3] Laurie A. Tomlinson,[4] Merel van Diepen,[1] Friedo W. Dekker,[1] and Juan J. Carrero[5]

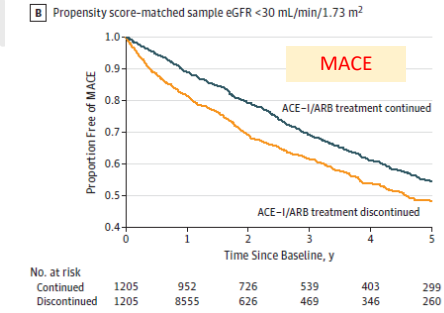
Due to the number of contributing authors, the affiliations are listed at the end of this article.

Table 2. The 5-year RMST, RMST differences, absolute risks, and risk differences associated with stopping RASi and continuation on mortality, MACE, and KRT in advanced CKD patients with eGFR <30 ml/min per 1.73 m²

Outcome and Treatment Strategy	Weighted Persons, *n*	Weighted Events, *n*	5-yr RMST, mo (95% CI)	5-yr RMST Difference, mo (95% CI)	5-yr Absolute Risk, % (95% CI)	5-yr Risk Difference, % (95% CI)
All-cause mortality						
Continuing RASi	7971	3258	47.9 (46.2 to 49.7)	Reference	40.9 (38.9 to 42.8)	Reference
Stopping RASi	7078	3852	44.3 (43.8 to 44.8)	−3.6 (−5.4 to −1.8)	54.5 (48.5 to 61.2)	13.6 (7.0 to 20.3)
MACE						
Continuing RASi	8127	3870	44.7 (42.8 to 46.5)	Reference	47.6 (45.9 to 49.4)	Reference
Stopping RASi	7623	4543	41.4 (40.8 to 41.9)	−3.3 (−5.3 to −1.4)	59.5 (53.8 to 66.1)	11.9 (5.7 to 18.6)
KRT						
Continuing RASi	8329	3007	48.1 (46.5 to 49.7)	Reference	36.1 (34.7 to 37.7)	Reference
Stopping RASi	8808	2458	48.9 (48.3 to 49.5)	0.8 (−0.8 to 2.5)	27.9 (23.5 to 32.5)	−8.3 (−12.8 to −3.6)

JASN 32: 424–435, 2021





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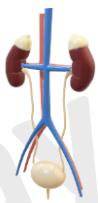
Identify advance CKD patients who should continue with RAASi

- Albuminuria
- DM
- Hypertension



CONT RAASi

MI
Stroke
HFrEF

- Mortality
- MACE

Acute kidney injury

Hyperkalemia

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Key clinical questions?

- When to start/stop RAASi in kidney disease patients?
- What are the current evidence of RAASi in advanced CKD?
- How to use RAASi safely in CKD patients?

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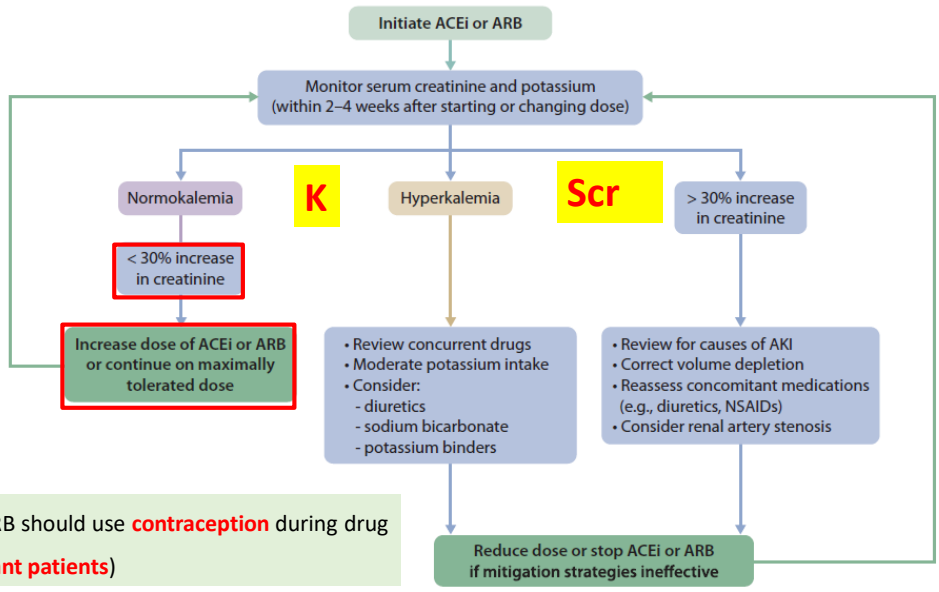
KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

Monitoring Scr, K after initiating ACEI/ARB



Patients receiving ACEI/ARB should use **contraception** during drug used **(and avoid in pregnant patients)**

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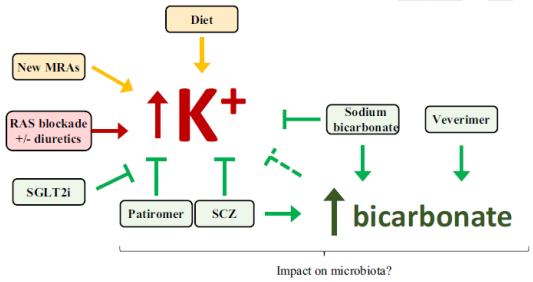
Hyperkalemia in CKD

Contributors of hyperkalemia

- Increased K+ load from food
- Transcellular shift K out of cells
- Decreased kidney K excretion



Recommendation when using RAASi in CKD

- Monitor serum K within 2-4 weeks of initiation of RAASi (KDIGO 2020)
  - In patients at high risk of hyperkalemia, monitoring should start within 1 week
- Avoid initiation/up titration when K level > 5 mEq/L (Larive e NL, 2023)

1. Expert Opin Investig Drugs. 2021;30(2):139-151. 2. KDIGO. Clinical practice guideline for diabetes management in chronic kidney disease.
2. 3. Kidney Int. 2020;98(4s):S1-s115. Cardiol Ther (2023) 12:35–63.

When patients taking RAASi

K

- **HOLD** RAASi and sent patient to ER for urgent management

K+ level (mEq/L)

5.0 5.5 5.8 6.0 6.5

- **No change of RAASi dose**
- Consider K binder to lower K level to ≤ 5 mmol/L

- Consider **HOLDING** RAASi
- Initiate potassium binder to lower K level to ≤ 5 mmol/L

- Before reintroducing RAASi, repeat K level within 1 week

Kidney Int. 2020;98(4s):S1-s115. Cardiol Ther (2023) 12:35–63.

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Evaluation of Drug-Related Problems in Patients Attending a Chronic Kidney Disease Clinic

Sathaporn Khananthai[1], Angsunid Porncatatak[1], Malinporn Jampong[2], Natchaya Ingpongpun[3], Supattra Pinsamsay[3], Supatat Chumnumwat[3], Sayamon Sukkha[3]

[1] Clinical Pharmacy, Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Nakhon Pathom, Thailand

[2] Division of Nephrology, Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Nakhon Pathom, Thailand

[3] Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

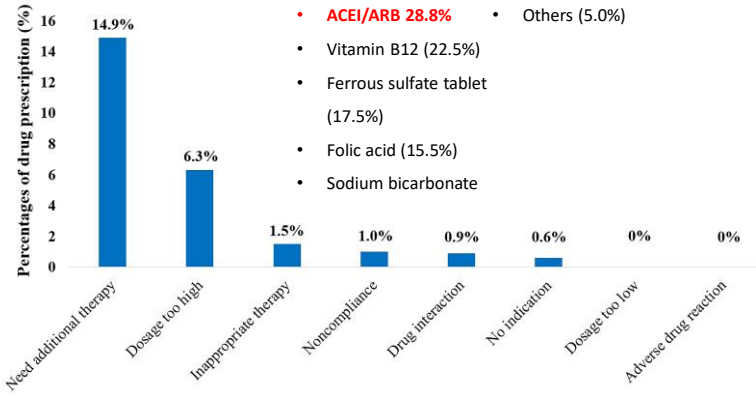
The manuscript is currently being submitted

Inclusion criteria

1. Male of female aged > 18 years
2. Stage 1-4 CKD
3. Attended CKD clinic at the Golden Jubilee Medical Center between Jan 2020 to June 2021

Exclusion criteria

1. Patients with dialysis
2. Patient with insufficiency information



Need additional therapy (10.6%)

- **ACEI/ARB 28.8%**
- Vitamin B12 (22.5%)
- Ferrous sulfate tablet (17.5%)
- Folic acid (15.5%)
- Sodium bicarbonate
- Others (5.0%)

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Pharmacist role for hyperkalemia in chronic setting

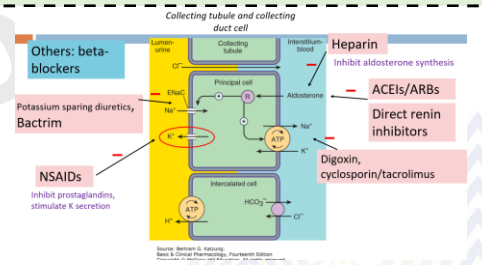
Counseling potassium-restricted diets

Application

Using sodium bicarbonate when indicated (for treatment of metabolic acidosis)

Medications tx to prevent severe metabolic acidosis (HCO < 16 mmol/L (KDIGO 2023, draft version)

Screening for concomitant medications that cause hyperkalemia



Suggesting of increasing potassium excretion (loop or thiazide diuretics and/or potassium binders)

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Key Takeaways

Role of RAASi in CKD patients

- G1-4, Albuminuria, hypertension, DM
- Increased dose of ACEI/ARB on maximally tolerated dose

Contraindications /precautions

- Consider planned D/C of ACEI/ARB in the 48-72 hours prior to elective surgery or acute management due to AEs (CKD 2023, draft version)
- Advise contraception in women who are receiving ACEI/ARB and D/C in those who are considering pregnancy

Monitoring

- Scr within 1-2 week after starting/increasing dose (AKI)
- Potassium (hyperkalemia)

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