Medications for Delaying the Deterioration of Chronic Kidney Disease

延緩慢性腎臟病惡化的藥物治療

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Staging of CKD (Chronic Kidney Disease)

NKF-K/DOQI estimated

Stage	Description	GFR (ml/min/1.73m²)	11% Prevalence rate 11.9% DM/all (USA) vs. all (Taiwan)	
1	Kidney damage with normal or ↑GFR	>90	8.6% / 3.3%	1%
2	Mild ↓GFR	60-89	11.1% / 3.0%	3.8%
3	Moderate ↓GFR	30-59	17.7% / 4.3%	6.8%
4	Severe ↓GFR	15-29	2.3% / 0.4%	0.2%
5	Kidney failure	<15		0.1%

Chronic kidney disease is defined as either kidney damage or GFR <60ml/min/1.73m² for 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

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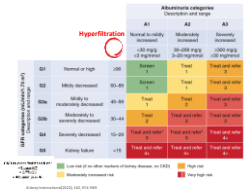
CKD risk of progression and suggested annual visit times

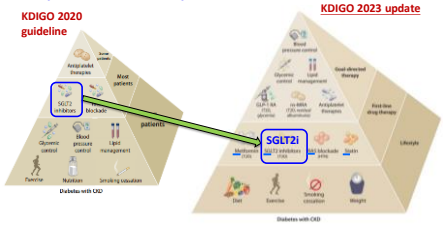


UACR and eGFR are key factors of CKD risk progression

Comprehensive care in patients with diabetes and CKD

KDIGO 2020 guideline

KDIGO 2023 update



Holistic approach for improving outcomes in patients with diabetes and CKD

KDIGO 2022 update

DEWS

Exercise

T2D

T1D and T2D

MeSgR(asi)S(t)

MeSsengeRS

GMA CD

Go to Bed & SLeEPIng

GLP-1 RA

MRA: Finerenone

CCB or Diuretics

Antiplatelets

Glucose

BP

Steroidal MRA

Lipid

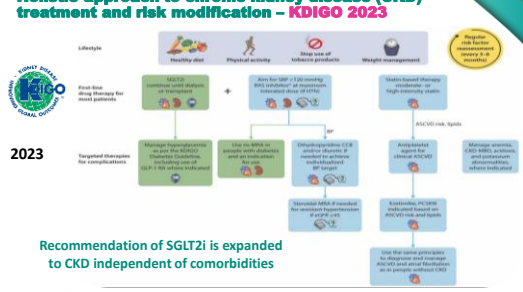
Ezetimibe

PCSK9i

Icosa-pent-ethyl

DEWS on MeSsengeRS for GMA CD, Go to Bed & SLeEPIng

Holistic approach to chronic kidney disease (CKD) treatment and risk modification – KDIGO 2023



Recommendation of SGLT2i is expanded to CKD independent of comorbidities

延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

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KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF CHRONIC KIDNEY DISEASE

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Blood pressure control

Target SBP **< 120 mmHg** (2B)

Entry criteria in the SPRINT trial

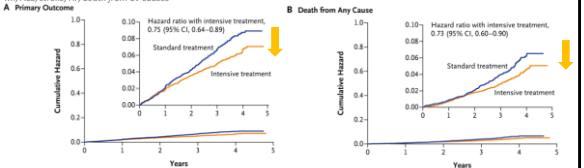
- Age >50 years
- High risk of cardiovascular disease
- Absence of diabetes or previous stroke

Clinician decision

Yes → Blood pressure goal (AOBP) <120 mmHg

No → Continue with current guideline recommendations <140 mmHg

MI, ACS, stroke, HF, death from CV causes



SPRINT Research Group. (2015). A randomized trial of intensive versus standard blood-pressure

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Blood pressure control

Target SBP **< 120 mmHg** (2B)

SPRINT trial

main kidney outcomes：non-significant!!!

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11

SPRINT Research Group. (2015). A randomized trial of intensive versus standard blood-pressure

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Renin-angiotensin system inhibitors

* PP=practice point

Albuminuria category	Diabetes	No diabetes
A1	PP	PP
A2	**1B**	**2C**
A3	**1B**	**1B**

HTN
HFrEF

using the highest approved dose

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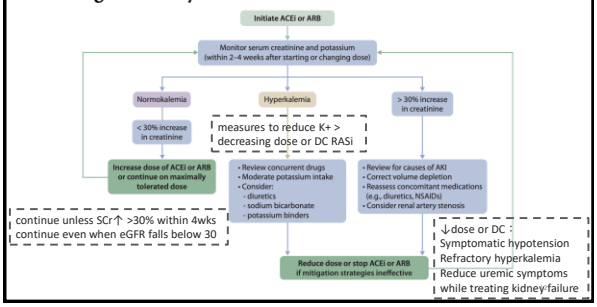
Renin-angiotensin system inhibitors



THE LANCET

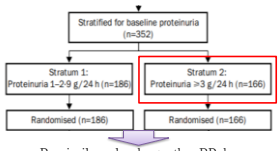
Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy

The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia)*

REIN study - Stratum 2

follow-up 3 years

352 proteinuric CKD, non-DM, eGFR 43~49



Ramipril or placebo + other BP drug
Target DBP< 90 mm Hg

Stratum 2:
166 patients with **proteinuria > 3g/day**

Ramipril group

1. Lower monthly decline in GFR (0.53 vs 0.88 ml/min)
2. Urinary protein excretion significantly decreased (median -55% at 3 years)
3. Less sCr x2 or ESKD

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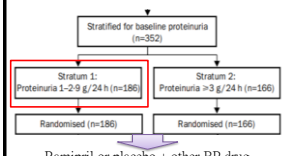
THE LANCET

Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria

Dr Piero Ruggenenti, MD · Annalisa Perna, StatScID · Giulia Gherardi, RN · Giovanni Garini, MD · Carmine Zoccali, MD · Maurizio Salvadori, MD · et al. Show all authors

REIN study - Stratum 1

352 proteinuric CKD, non-DM, eGFR 43~49



Ramipril or placebo + other BP drug
Target DBP< 90 mm Hg

Stratum 1:
186 patients with **proteinuria 1-2.9g/d**

1. Decline in GFR per month was not significantly different(-0.24 vs -0.29)
2. Less ESKD in ramipril group (RR:0.37; 95% CI 0.16–0.82)
3. Less progression to overt proteinuria (>3g/d) (RR:0.42; 95% CI 0.22–0.79)

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Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Fan Fan Hou, M.D., Ph.D., Xun Zhang, M.D., Guo Hua Zhang, M.D., Ph.D., Di Xie, M.D., Ping Yan Chen, M.D., Wei Ru Zhang, M.D., Ph.D., Jian Ping Jiang, M.D., Min Liang, M.D., Ph.D., Guo Bao Wang, M.D., Zheng Rong Liu, M.D., and Ren Wen Geng, M.D.

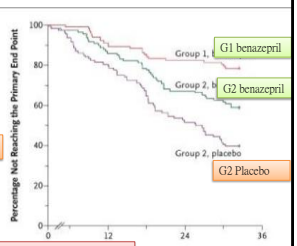
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2006; 354:131-140

422 CKD with Upro~1.6g/d, without DM

Group 1 Cr:1.5-3mg/dl → Benazepril

Group 2 Cr:3.1-5 → Benazepril or Placebo



Benzapril is associated with a **43%** risk **reduction in primary endpoint** in group 2 (independent of BP)

Primary endpoint: Cr x2, ESRD or death

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Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

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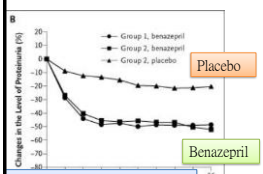

Benazepril : 52% reduction in proteinuria

Table 3. Adverse Events after Randomization.*

Adverse Event	Group 1 (N=104)	Group 2 Benazepril (N=112)	Group 2 Placebo (N=112)
	no. of events		
Death	0	1	0
Nonfatal cardiovascular event			
Myocardial infarction	3	5	8
Heart failure	1	3	5
Stroke	1	2	3
Other adverse events			
Hyperkalemia†	2	6	5
Acute decline in renal function	1	1	1
Dry cough	0	1	0
[illegible]nsion‡	1	0	0
	9	19	22

The incidence of other adverse events similar in the two subgroups of group 2

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Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes

Edmund J. Lewis, M.D., Lawrence G. Hunsicker, M.D., William R. Clarke, Ph.D., Tomas Berl, M.D., Marc A. Pohl, M.D., Julia B. Lewis, M.D., Eberhard Ritz, M.D., Robert C. Atkins, M.D., Richard Rohde, B.S., and Itamar Raz, M.D. for the Collaborative Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

IDNT trial

1715 HTN + CKD + DM → RCT

- Irbesartan (300 mg QD)
- Amlodipine (10 mg QD)
- Placebo

→ Kindy and CV outcomes

IDNT: baseline 2.9 g/d proteinuria, sCr of 1.67 mg/dl

Irbesartan in the primary composite endpoint (**Cr x2, ESRD or death**)

1. 20% risk reduction v.s. placebo (RR: 0.80; 95% CI: 0.66 – 0.97)
2. 23% reduction v.s. amlodipine (RR: 0.77; 95% CI: 0.63 – 0.93)

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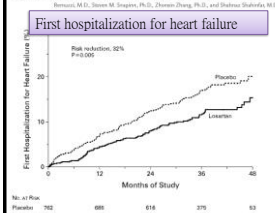
Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy

Barry M. Brenner, M.D., Mark E. Cooper, M.D., Ph.D., Dick de Zeeuw, M.D., Ph.D., William F. Keane, M.D., William E. Mitch, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Steven M. Snapinn, Ph.D., Zhimin Zhang, Ph.D., and Shahnaz Shahinfar, M.D. for the RENAAL Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

RENAAL trial

First hospitalization for heart failure



Secondary endpoint: composite of MI, stroke, first hospitalization for HF or unstable angina, coronary or peripheral revascularization, or CV death

RENAAL: 1513 HTN + CKD + DM
baseline UACR 1237 mg/g, sCr 1.9 mg/dl

Losartan and CV outcome

1. Composite CV outcome was similar in the two groups
2. 16% risk reduction in first hospitalization for HF

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Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).

1. No clear clinical benefits of RASi for CKD progression
2. In HOPE study(DM patients) , CKD subgroup of 3394 patients, Ramipril reduced(vs placebo)
   - ✓ All-cause mortality: 20% (HR: 0.80; 95% CI: 0.67 – 0.96)
   - ✓ MI: 26% (HR: 0.74; 95% CI: 0.61 – 0.91)
   - ✓ **Stroke: 31%** (HR: 0.69; 95% CI: 0.49 – 0.90)

*In the overall HOPE study, 3577 patients had DM, and 2437 of them (roughly 2/3) did not have albuminuria

HOPE Study Investigators. Lancet. 2000;355:253 – 259.
Mann JF et al. Ann Intern Med. 2001;134:629 – 636.

Practice Point 3.2.2: RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

1. The benefits from RASi administered in less than maximally recommended doses are less certain
2. If for whatever reason (e.g., hyperkalemia) the patient cannot tolerate the maximum dose, a smaller dose may still be reasonable

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Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2-4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

1. ACEIs or ARBs → efferent arterioles vasodilatation→ decline of the intraglomerular filtration and GFR
   - ✓ An increase in sCr level, if it occurs, will typically happen during the first 2 weeks of treatment initiation, and it should stabilize within **2 – 4 weeks**
2. RAS blockade → inhibits aldosterone→ risk of hyperkalemia↑
3. A shorter time interval is indicated if the baseline serum creatinine is high, or serum potassium is already high-normal

Practice Point 3.2.4: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

1. Pseudo-hyperkalemia needs to be first ruled out
2. Dietary potassium restriction
3. Discontinuation of potassium supplements(certain salt substitutes) and hyperkalemic drugs
4. Adding potassium-wasting diuretics, and oral potassium binders

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Practice Point 3.2.5: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

1. Expert opinion. No single trial that compared meaningful clinical outcomes in patients who were continuing versus discontinuing versus reducing the dose of RASi upon a fast increase in sCr

Practice Point 3.2.6: Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

1. Discontinue other concurrent BP medications first if symptomatic hypotension
2. Hyperkalemia refractory to medical treatment
3. In advanced CKD with uremic symptoms (eGFR <15), discontinue ACEi and ARB temporarily to allow time for kidney replacement therapy preparation

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Practice Point 3.2.7: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR.

1. The steroidal MRAs spironolactone and eplerenone have been found
   - ✓ Reduce BP in resistant hypertension
   - ✓ Reduce albuminuria in diabetic kidney disease
2. Hyperkalemia and eGFR decline are a concern when added to background therapy with an ACEi, ARB, or diuretic, particularly when eGFR<45

3.3. Role of dual therapy with RASi

Recommendation 3.3.1: We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes *(1B)*.

Dual RASi therapy v.s. monotherapy

1. No CV or renal benefit
2. Increased risk of hypotensive symptoms, syncope, hyperkalemia and renal dysfunction

Mann JF et al. Lancet. 2008; 372:547 – 553
Tobe SW et al. Circulation. 2011;123:1098–1107

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2. Pentoxiphylline
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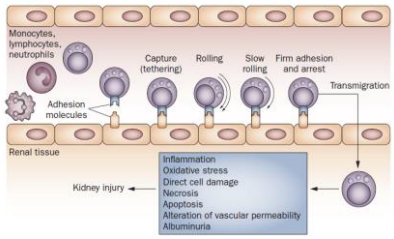
Diabetic kidney disease and inflammatory

1. ↑ Expression of cell adhesion molecules (E-selectin, ICAM-1 and VCAM-1.)
2. ↑ Oxidative stress
3. ↑ Release of inflammatory cytokines (IL-18, IL-1, IL-6, TNF)



Juan F Navarro-González et al. Nat Rev Nephrol . 2011 Jun;7(6):327-40.

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Pentoxiphylline - nonspecific inhibitor of cAMP phosphodiesterase

1. ↑ RBC distensibility
2. ↓ RBC aggregation
3. ↓ platelet aggregation
4. ↓ plasma fibrinogen,
5. ↓ blood viscosity
6. ↓ neutrophil activation
7. ↓ plasma proinflammatory cytokines (TNF-α, IL-1 and IL-6)

→ 1. Improve capillary blood flow
2. Anti-inflammatory and antioxidant effects

→ 1. PAD
2. Alcoholic hepatitis
3. Diabetic kidney disease

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Pentoxiphylline - In vivo animal studies

- Protects mesangial cells from hyperglycemia and angiotensin II-mediated extracellular matrix deposition
- Reduce thickening of the GBM, flattening of podocyte foot processes
- Corrects the diabetes-induced upregulation of TNF, IL-1 and IL-6 in the kidney, decrease urinary cytokine excretion
- Reduce urine albumin excretion

Navarro-González, J. F. *et al. Nat. Rev. Nephrol.* 7, 327 – 340 (2011) 26

7 PTF v.s. 7 control, DKD, f/u 12 months
A trend toward the reduction of proteinuria
no statistical benefit in proteinuria reduction or preservation of renal function

Diskin CJ et al. J Nephrol 20: 410–416, 2007

29 PTF v.s. 27 control, CKD 3-5 (1/3-1/4 DM), f/u 12 months
Pentoxifylline added to losartan therapy decreased proteinuria (UPCR 1,140 to 800 mg/g v.s. 1,410 to 1,810 mg/g)
No significant difference in eGFR decline rate

Lin SL et al. Am J Kidney Dis **52**: 464–474, 2008

22 PTF v.s. 18 control, CKD(1/2 DM), eGFR 20-40, Upro>1g/d, f/u 12 month
Pentoxifylline may slow the eGFR decrease in high-risk CKD patients(-1.2 v.s. -7.2 ml/min/1.73m2/yr) (maybe independent of its antiproteinuric properties)

Perkins RM et al. Am J Kidney Dis **53**: 606–616, 2009

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Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease: The PREDIAN Trial

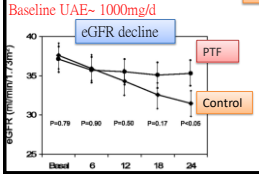
Juan F. Navarro-González, Carmen Mora-Fernández, Mercedes Muros de Fuentes, Jesús Chahin, María L. Méndez, Eduardo Gallego, Manuel Macía, Nieves del Castillo, Antonio Rivero, María A. Getino, Patricia García, Ana Jarque and Javier García
JASN January 2015, 26 (1) 220-229; DOI: https://doi.org/10.1681/ASN.2014010012

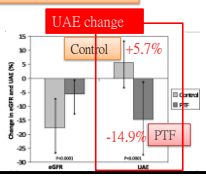
JASN

Single center, open-label
169 stage 3-4 CKD + DM
Baseline UAE~ 1000mg/d

RCT
2 yrs

Pentoxifylline 600mg BID
or
Control
+ RASi





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JASN January 2015, 26 (1) 220-229; DOI: https://doi.org/10.1681/ASN.2014010012

JASN

Single center, open-label
169 stage 3-4 CKD + DM
baseline eGFR ~37ml/min/1.73m2
UAE~ 1000 mg/d

RCT
2 yrs

Pentoxifylline 600mg BID
or
Control
+ RASi

Addition of Pentoxifylline to RASi in DKD **eGFR:+ 2.2** ml/min/ 1.73 m²/year

1. Slowing of the rate of eGFR decline: -2.1±0.4 ml/min/1.73 m² v.s. -6.5±0.4; P<0.001
2. Reducing urine albumin excretion: −14.9% v.s. +5.7%; P=0.001 (**UAE ~20%↓**)
3. Urine TNF-α decreased: from a median 16 ng/g to 14.3 ng/g; no change in placebo group; P<0.01

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Addition of Pentoxifylline to ACEi/ARB may slow eGFR decline rate and reduce proteinuria in CKD patients (especially DKD)

Short follow-up duration(1~2 yrs) and in small sample sizes
A large-scale clinical trial is necessary to confirm this result

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KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

3.4: ACIDOSIS

3.4.1: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (*2B*)

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Metabolic acidosis of CKD

Functioning nephrons declines in CKD

⇩

Increase in the ammonium(NH_4^+) excreted per nephron

⇩ ⇠ NH_4^+ excretion per total GFR(nephron) is 3~4 times above normal

Reduced acid excretion when eGFR<25-40

⇩

Retention of H^+ ⇠ Retained H^+ is buffered by bicarbonate in the extracellular fluid, by tissue buffers, and by bone

⇩

Metabolic acidosis

Jeffrey A Kraut et al. Am J Kidney Dis. 2005 Jun; 45(6):978-93
D G Warnock et al. Kidney Int . 1988 Aug;34(2):278-87

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Consequences of metabolic acidosis in CKD

- Bone resorption and osteopenia
- Increased muscle protein catabolism
- Reduced albumin synthesis
- Aggravation of secondary hyperparathyroidism
- Impair myocardial contractility
- Systemic inflammation
- Progression of CKD
- Mortality

Shah SN et al. Am J Kidney Dis 2009;4:270–7
Menon V et al. Am J Kidney Dis 2010;56:907–14

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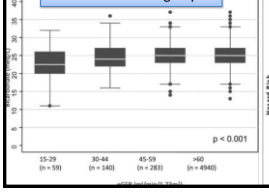
Serum Bicarbonate Levels and the Progression of Kidney Disease: A Cohort Study

Samir N. Shah, MD • Matthew Abramowitz, MD • Thomas H. Hostetter, MD • Michal L. Melamed, MD, MHS

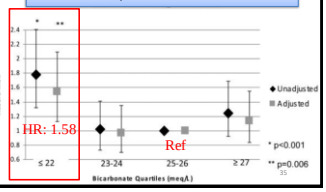
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES
Am J Kidney Dis. 2009 Aug;54(2): 270–277

Single center, n = 5,422 ⟹ f/u ~3.4 years ⟹ Serum HCO_3^- and kidney disease progression

Bicarbonate in GFR groups



Risk for eGFR ↓ 50% or reach eGFR <15



35

Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans

Kalani L. Raphael • Guo Wei • Bradley C. Baird • Tom Greene • Srinivasan Beddhu

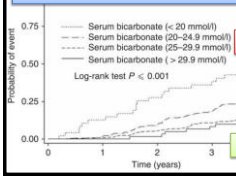
Kidney Int. 2011 Feb;79(3):356-62

kidney INTERNATIONAL

AASK trial

1094 African American HTN + CKD eGFR 20-65 ⟹ f/u ~4 years ⟹ Serum HCO_3^- and kidney disease progression

Event for eGFR ↓ 50% or ↓25 ml/min/1.73m² or ESRD



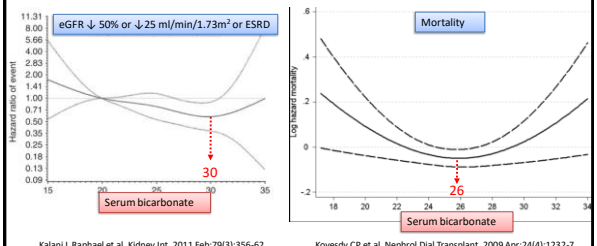
Bicarbonate<20

Each 1 mmol/l increase in serum bicarbonate within 20–30 mmol/l was associated with a 6% lower hazard of ESRD or eGFR event

Bicarbonate>29.9

36

U-shaped association between bicarbonate and renal event/mortality



Kalani L Raphael et al. Kidney Int. 2011 Feb;79(3):356-62

Kovesdy CP et al. Nephrol Dial Transplant. 2009 Apr;24(4):1232-7

Bicarbonate Supplementation Slows Progression of CKD and Improves Nutritional Status

JASN

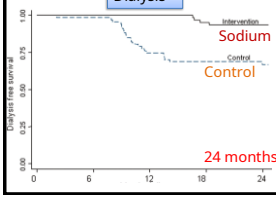
134 CKD stage 4
serum bicarbonate 16 to 20

RCT

Sodium bicarbonate 600 mg TID
↑serum bicarbonate ≥23 mEq/L

Control

Dialysis



A lower risk of ESKD (CrCl <10 ml/min): 6.5 vs 33 %
A lower mean rate of decline of CrCl: 1.88 vs 5.93 mL/min/1.73 m² per year

38

Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study

JOURNAL OF NEPHROLOGY
J Nephrol. 2019; 32(6): 989–1001

740 CKD stage 3-5
serum bicarbonate ~21.5

RCT

Sodium bicarbonate→ target 24–28
Control

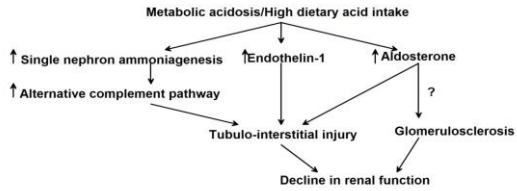
F/u 3 yr

A lower all-cause mortality : 3.1 vs 6.8 %
A lower risk of requiring RRT : 6.9 vs 12.3 %
A lower risk of a doubling of serum Cr : 6.6 vs 17 %

No significant effect of sodium bicarbonate on BP, body weight or hospitalizations

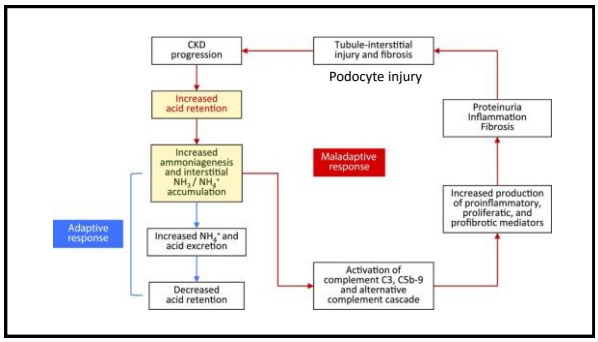
39

Mechanisms of Acidosis-related Decline in Renal Function



Pathogenesis of kidney disease progression due to chronic metabolic acidosis. Metabolic acidosis and/or a high dietary acid load may contribute to progressive kidney disease through multiple mechanisms, including increased ammonia generation per nephron leading to activation of the alternative complement pathway and increased endothelin-1 and aldosterone levels in the kidney. Each of these factors may cause tubulo-interstitial injury leading to a decline in kidney function. Hyperaldosteronism could also accelerate glomerulosclerosis, although glomerular injury due to metabolic acidosis has not been reported in animal models.

Chen and Abramowitz *BMC Nephrology* 2014, 15:55
http://www.biomedcentral.com/1471-2369/15/55

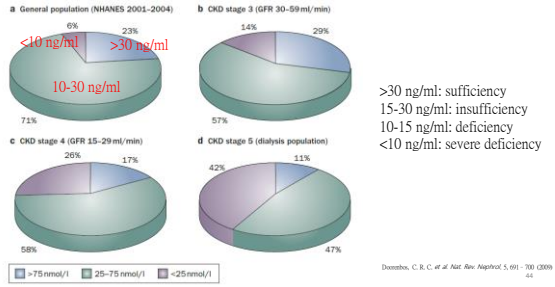


延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

43

Vitamin D deficiency is highly prevalent in CKD patients



>30 ng/ml: sufficiency
15-30 ng/ml: insufficiency
10-15 ng/ml: deficiency
<10 ng/ml: severe deficiency

Doorenbos, C. R. C. *et al. Nat. Rev. Nephrol.* 5, 691 – 700 (2009)

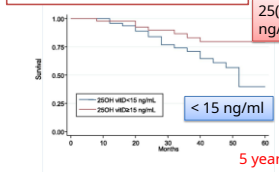
44

Low vitamin D levels are associated with a higher risk of all-cause mortality and faster progression of kidney disease

Cr 50%↑, dialysis, or death

25(OH) vit D > 15 ng/ml

103 DM, CKD stage 2-3, UPCR>300mg/g



< 15 ng/ml

5 year

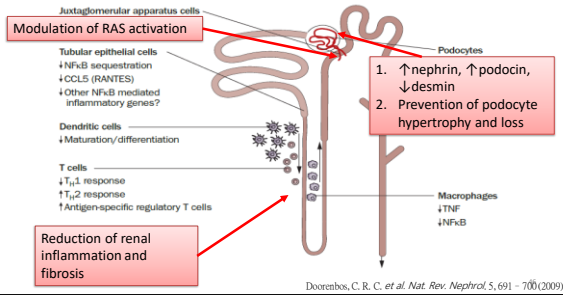
Low vit D level
1. Faster eGFR decline:
   5.8 vs 3.6 ml/min/1.73m^2 per yr
2. High risk of primary endpoint:
   hazard ratio 2.88 (95% CI, 1.84 to 7.67)

No. at Risk									
25(OH) vit D<15 ng/mL	53	49	43	39	37	32	24	20	10
25(OH) vit D≥15 ng/mL	50	45	40	36	33	26	24	20	19

Gema Fernández-Juárez et al. CJASN November 2013, 8 (11) 1870-1876

45

Potential benefits of Vit D on CKD



Doorenbos, C. R. C. *et al. Nat. Rev. Nephrol.* 5, 691 – 700 (2009)

Oral Paricalcitol in the Treatment of Patients With CKD and Proteinuria: A Randomized Trial

Steven Fishbane, MD • Harini Chittineni, MD • Michal Packman, MD • Paula Dutka, RN • Nicole Ali, MD • Nicole Durie, MD

Am J Kidney Dis. 2009 Oct;54(4):647-52

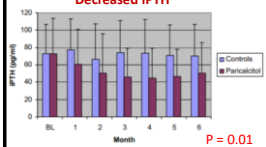
61 CKD patients, eGFR 15 to 90, Upro >400 mg/d

RCT

Paricalcitol 1 ug/d

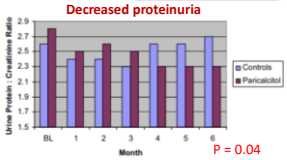
Placebo

Decreased iPTH



P = 0.01

Decreased proteinuria



P = 0.04

But no significant difference in serum Ca and phosphorus

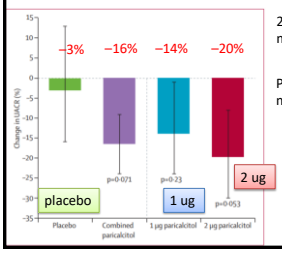
47

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial

THE LANCET

Lancet. 2010 Nov 6;376(9752):1543-51

Prof Dick de Zeeuw, MD • Prof Rajiv Agarwal, MD • Michael Amdahl, MS • Paul Audhya, MD



281 DM, eGFR 15 to 90, median Ualb: 600-800 mg/d. paricalcitol 1ug, 2ug or placebo

Primary efficacy: percentage change in geometric mean UACR from baseline to 6 months later

Paricalcitol lowers albuminuria in patients with DKD

48

Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial

THE LANCET

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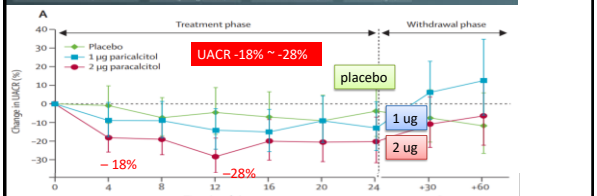

Addition of 2 µg/day paricalcitol to RAAS inhibition lowers albuminuria in patients with DKD(p=0.014)

49

延緩慢性腎臟病惡化的藥物治療

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50

Elevated total cholesterol, non-HDL cholesterol and low HDL → future renal dysfunction(Cr>1.5) in healthy men(n=4483)

- ✓ RR:1.77 (95% CI, 1.10 to 2.86) for total cholesterol ≥ 240 vs <240
- ✓ RR:2.16 (95% CI, 1.22 to 3.80) for non-HDL cholesterol > 196 vs <142
- ✓ RR:2.16 (95% CI, 1.42 to 3.27) for HDL cholesterol < 40 vs ≥ 40

Schaeffner E.S. et al. *J Am Soc Nephrol.* 2003; 14: 2084-2091

High triglycerides and low HDL cholesterol, but not low-density lipoprotein cholesterol, → future renal dysfunction (Cr↑ 0.4mg/dl)(n=12,728, baseline Cr<2 in men, <1.8 in women)

- ✓ RR:1.65 (95% CI, 1.1, 2.5, P = 0.01) for TG >156 vs <78 mg/dl
- ✓ RR:0.47 (95% CI, 0.3, 0.8, P = 0.003) for HDL ≥64 vs ≤41 mg/dl

Paul Muntner et al. *Kidney Int.* 2000 Jul;58(1):293-301

Among 3303 patients with CKD 3-5, high total cholesterol, high non-HDL cholesterol, high LDL → risk for RRT and rapid renal progression (eGFR -6/yr)

- ✓ Lower total cholesterol also increased risk for RRT(malnutrition)

Szu-Chia Chen et al. *PLoS One*. 2013;8(2):e55643

51

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

Prof Colin Baigent, FRCP • Martin J Landray, FRCP • Christina Reith, MRCP • Jonathan Emberson, PhD •

THE LANCET

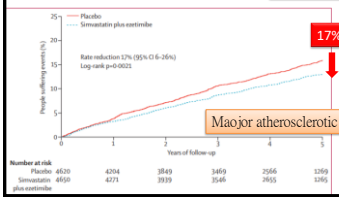
Lancet. 2011 Jun 25;377(9784):2181-92

SHARP study

9270 CKD (3023 on dialysis)
Mean LDL:107 mg/dl

RCT

- Simvastatin 20 mg + ezetimibe 10 mg QD
- Placebo



17%

*non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularisation procedure

Maojor atherosclerotic events

32% mean reduction in LDL-C levels

52

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

Prof Colin Baigent, FRCP • Martin J Landray, FRCP • Christina Reith, MRCP • Jonathan Emberson, PhD •

THE LANCET

Lancet. 2011 Jun 25;377(9784):2181-92

SHARP study

9270 CKD (3023 on dialysis)
Mean LDL:107 mg/dl

RCT

- Simvastatin 20 mg + ezetimibe 10 mg QD
- Placebo

6247 patients not on dialysis,

No significant benefit on CKD progression(6247 not on dialysis):
ESRD(maintenance dialysis or transplantation): 33.9% vs 34.6%; RR 0.97, p=0.41
ESRD or death: 47.4% vs 48.3%; RR 0.97, p=0.34
ESRD or doubling of baseline Cr: 38.2% vs 40.2%; RR 0.93, p=0.09

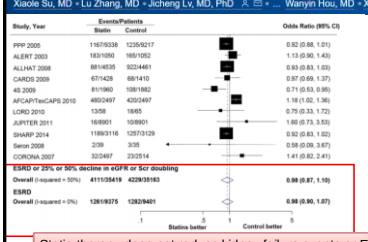
53

Effect of Statins on Kidney Disease Outcomes: A Systematic Review and Meta-analysis

Xiaole Su, MD • Lu Zhang, MD • Jicheng Lv, MD, PhD • ... Wanyin Hou, MD • Xinfang Xie, MD •

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

Am J Kidney Dis. 2016;67(6):881-892



57 RCTs with 143,888 participants, f/u 6-63 months

1. Slower eGFR decline: 0.41 mL/min/1.73 m^2 per year (95% CI, 0.11-0.70)
2. More reduction in proteinuria or albuminuria: SMD −0.65 g (95% CI, −0.94 to −0.37)
3. Lower cardiovascular events: ↓ 31% (OR, 0.69; 95% CI, 0.61-0.79; P < 0.001)

Statin therapy does not reduce kidney failure events or ESRD

54

2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

2.1.1: In adults aged ≥50 years with eGFR <60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination. (*1A*)

2.1.2: In adults aged ≥50 years with CKD and eGFR ≥60 ml/min/1.73 m^2 (GFR categories G1-G2) we recommend treatment with a statin. (*1B*)

2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (*2A*):

- known coronary disease (myocardial infarction or coronary revascularization)
- diabetes mellitus
- prior ischemic stroke
- estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (*2A*)

"fire-and-forget" strategy: do not measure LDL-C unless the results would alter management

55

KDIGO Clinical Practice Guideline for Lipid Management in CKD

18-49 y/o

CKD 1-5 not on dialysis
1. Known coronary disease (MI or coronary revascularization)
2. DM
3. Prior ischemic stroke
4. Estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%

⇩

Statin

≥ 50 y/o

CKD 1-2 → Statin

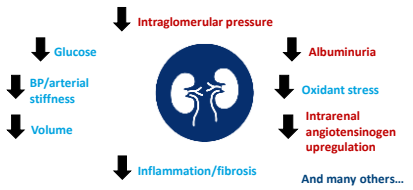
CKD 3-5 not on dialysis → Statin or statin/ezetimibe

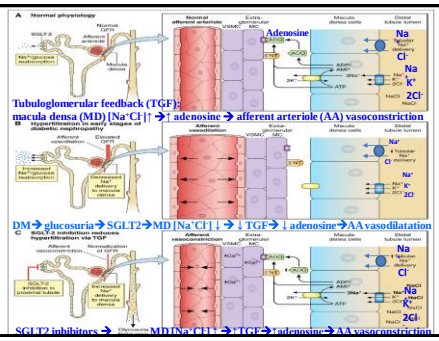
Marcello Tonelli et al. Am J Kidney Dis . 2014 Sep;64(3):375-82

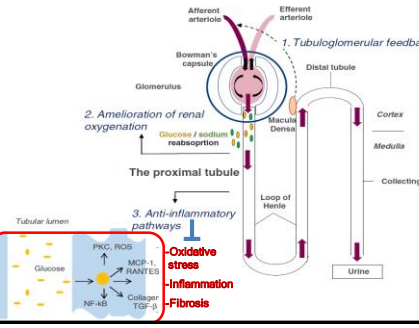
延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

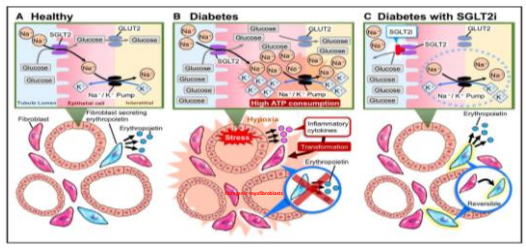
Cardiovascular and Renal Effects of SGLT2 Inhibition





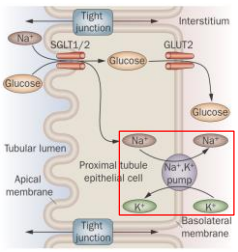


Possible Mechanisms by Which SGLT2i Increase Erythropoietin Production



Circulation. 2019 Apr 23;139(17):1985-1987. doi:10.1161/CIRCULATIONAHA.118.038881.

Oxygen Consumption in the Diabetic Kidney

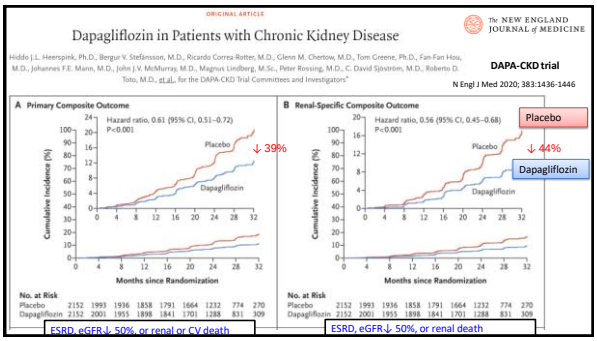


~80% of renal energy consumption fuels sodium reabsorption through the Na^+/K^+ ATPase pump

* High luminal glucose concentrations → ↑ tubular sodium/glucose reabsorption → ↑ intracellular Na^+ concentration → ↑ activation of the Na^+/K^+ ATPase → **↑ O2 consumption**

* **SGLT2i:** direct inhibition of SGLT2-mediated Na reabsorption in the early proximal tubule → **↓ oxygen consumption → ↓ hypoxic stress on the diabetic kidney**

1. Sunder Mudaliar et al. Diabetes Care 2016;39:1115-22
2. Amanda Mather et al. Nat Rev Nephrol. 2010 May;6(5):307-11.



DAPA-CKD trial 和 CREDENCE trial

	DAPA-CKD	CREDENCE
Primary endpoint*	風險下降39% P=0.000000028	風險下降30% P = 0.00001
腎臟預後	風險下降44% P=0.000000018	風險下降34% P <0.001
透析、腎臟移植或死於腎臟病	風險下降34% P= 0.0072	風險下降28%#
末期腎病	風險下降36% P=0.0004	風險下降32% P = 0.002
心衰竭住院或心血管死亡	風險下降29% P=0.0089	風險下降31% P <0.001
總死亡	風險下降31% P=0.0035	風險下降17% HR: 0.83（0.68–1.02）

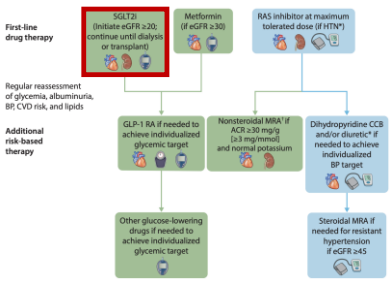
*DAPA-CKD trial的primary endpoint為eGFR持續下降50%、末期腎病(包含持續透析≥28天，腎臟移植或eGFR < 15 ml/min/1.73m² ≥ 28天)或死於腎臟或心血管疾病

CREDENCE trial的primary endpoint為末期腎病(包含透析、腎臟移植或eGFR持續< 15 ml/min/1.73m2、血液肌酸酐變兩倍或死於腎臟或心血管疾病。

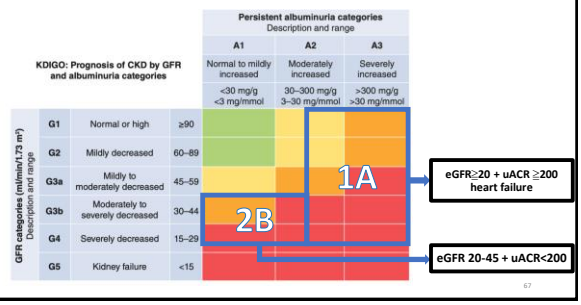
DAPA-CKD trial 和 CREDENCE trial

	DAPA-CKD	CREDENCE
藥物	Dapagliflozin	Canagliflozin
收案人數（人）	4304	4401
非糖尿病患比例（%）	33	0
追蹤時間中位數（年）	2.40	2.62
eGFR平均值（ml/min/1.73m²）	43	56
UACR中位數（mg/g）	965	923

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)



Sodium-glucose cotransporter-2 inhibitors (SGLT2i)



Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

double-blind, placebo-controlled, multicentric RCT (N=4401)
Inclusion：
T2DM,
eGFR 30-<90, uACR >300-≦5000
Canagliflozin VS Placebo

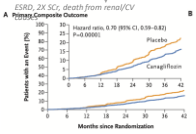
double-blind, placebo-controlled, multicentric RCT (N=4304)
Inclusion：
with or without DM
eGFR 25-75, uACR ≧200-≦5000
Dapagliflozin VS Placebo

double-blind, placebo-controlled, multicentric parallel group RCT (N=6609)
Inclusion：
with or without DM
eGFR 20-45 or 45-90+uACR ≧200-≦5000
Empagliflozin VS Placebo

2019 CREDENCE → **2020 DAPA-CKD** → **2022 EMPA-KIDNEY**

2.62Y

ESRD, 2X SCr, death from renal/CV



primary composite
HR=0.70 (0.59 - 0.82)

renal-specific composite
HR=0.66 (0.53 - 0.81)

68

69

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

double-blind, placebo-controlled, multicentric RCT (N=4401)
Inclusion：
T2DM,
eGFR 30-<90, uACR >300-≦5000
Canagliflozin VS Placebo

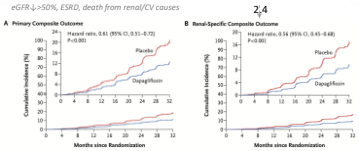
double-blind, placebo-controlled, multicentric RCT (N=4304)
Inclusion：
with or without DM
eGFR 25-75, uACR ≧200-≦5000
Dapagliflozin VS Placebo

double-blind, placebo-controlled, multicentric parallel group RCT (N=6609)
Inclusion：
with or without DM
eGFR 20-45 or 45-90+uACR ≧200-≦5000
Empagliflozin VS Placebo

2019 CREDENCE → **2020 DAPA-CKD** → **2022 EMPA-KIDNEY**

eGFR↓>50%, ESRD, death from renal/CV causes

2.4Y



primary composite
HR=0.61 (0.51 - 0.72)

renal-specific composite
HR=0.56 (0.45 - 0.68)

70

71

Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

double-blind, placebo-controlled, multicentric RCT (N=4401)
Inclusion：
T2DM,
eGFR 30-<90, uACR >300-≦5000
Canagliflozin VS Placebo

double-blind, placebo-controlled, multicentric RCT (N=4304)
Inclusion：
with or without DM
eGFR 25-75, uACR ≧200-≦5000
Dapagliflozin VS Placebo

double-blind, placebo-controlled, multicentric parallel group RCT (N=6609)
Inclusion：
with or without DM
eGFR 20-45 or 45-90+uACR ≧200-≦5000
Empagliflozin VS Placebo

2019 CREDENCE → **2020 DAPA-CKD** → **2022 EMPA-KIDNEY**

2.62Y → 2.4Y → 2Y

renal-specific composite of ESRD, 2×SCr or death from renal cause
HR=0.66 (0.53 – 0.81)

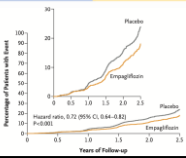
composite of sustained decline in eGFR at least 50%, ESKD, or death from renal cause
HR=0.56 (0.45 – 0.68)

progression of kidney disease *(ESKD, sustained decrease in eGFR to <10/≧40% from baseline , death from renal cause)* or death from CV causes
HR=0.72 (0.64 – 0.82)

CV death, MI, stroke
HR=0.80 (0.67 – 0.95)
hospitalization for heart failure
HR=0.61 (0.47 – 0.80)

composite of death from CV causes or hospitalization for HF
HR=0.71 (0.55 – 0.92)

72



progression of kidney disease or death from CV cause
HR=0.72 (0.64 - 0.82)

延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor / **GLP-1 RA**
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

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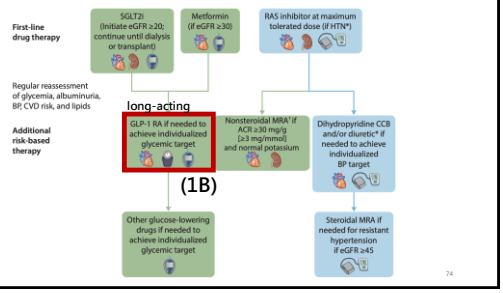
Glucagon-like peptide-1 receptor agonists (GLP-1 RA)



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Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

prioritize agents with documented CV benefits

GLP-1 receptor agonists			primary	albuminuria	GFR loss	
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↓	↔ None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔ GI
Semaglutide[1]	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↔	↔ None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↔	NA Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔ GI
Efpeglenatide	AMPLITUDE-O	eGFR 25–59.9 ml/min per 1.73 m²	MACE	↓	↓↓	↔ GI

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

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Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m²
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m²
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m²
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

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

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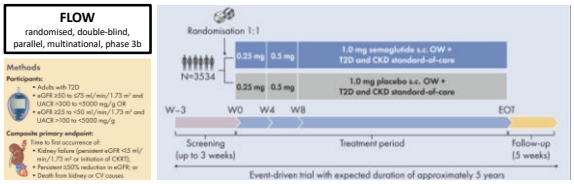
Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

FLOW
randomised, double-blind, parallel, multinational, phase 3b



Methods

Participants:
- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:
- Time to first occurrence of:
- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes

stopped early due to evidence of renal protection

Kidney Events ↓ 24%

Rossing, Peter, et al. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. *Nephrology Dialysis Transplantation* (2023)

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Evidence for GLP-1 receptor agonists to improve kidney outcomes in persons with T2D and high CVD risk

FLOW

Meta-analyses of CVOTs suggested potential kidney-protective effects of GLP-1RAs in study populations with T2D and high CVD risk[1,2]

Figure adapted from Rossing P et al. Nephrol Dial Transplant 2022;38:2041–2052.

The FLOW trial demonstrated broad benefits of semaglutide in participants with T2D and CKD with **reduced risks of the primary kidney outcome by 24%[6]** as well as secondary outcomes of CV events and death from any cause

The **aim of this study** was to assess the effects of semaglutide on **kidney outcomes according to CVD status or risk at baseline** in the FLOW trial population

*p≤0.005.
CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.
1. Kristensen SL et al. *Lancet Diabetes Endocrinol* 2019;7:776–785; 2. Sattar N et al. *Lancet Diabetes Endocrinol* 2021;9:653–662; 3. Mann JFE et al. *N Engl J Med* 2017;377:839–848; 4. Gerstein HC et al. *Lancet* 2019;394:131–138; 5. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 6. Perkovic V et al. *N Engl J Med* 2024;391:109–121.

FLOW trial design

FLOW

A multinational, randomized controlled clinical trial

Key eligibility criteria

- Adults with T2D, HbA_{1c} ≤10%
- RAS inhibitor
- eGFR ≥50 and ≤75 mL/min/1.73 m² and UACR >300 and <5000 mg/g
  OR
  eGFR ≥25 and <50 mL/min/1.73 m² and UACR >100 and <5000 mg/g

R 1:1 N=3533

Once-weekly s.c. **semaglutide** 1 mg + standard of care

Placebo + standard of care

Early trial cessation was recommended at a pre-specified **interim** analysis for efficacy at **~570 events**

eGFR was calculated using the CKD-EPI formula. Randomization was stratified according to SGLT2 inhibitor use at baseline.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; R, randomization; RAS, renin–angiotensin–aldosterone system; s.c. subcutaneous; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes; UACR, urine albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Methods

Primary kidney outcome[1] — **Present analysis**

Time to first occurrence of a composite kidney outcome

- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Kidney failure:
  - Onset of persistent eGFR <15 mL/min/1.73 m²
  - Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Kidney death
- CV death

Participants were categorized at baseline

Prespecified:

- Prior MI or stroke, PAD

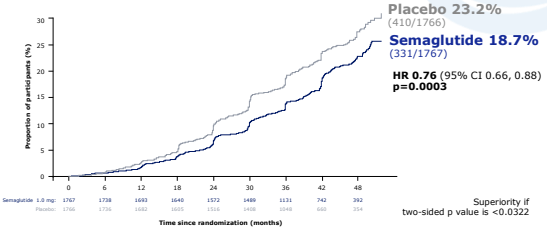
Post-hoc:

- Total CV risk in those without CV disease at baseline (PREVENT score: <20%/≥20%)

There were no specific power calculations for subgroup analyses

eGFR was calculated using the CKD-EPI formula. The PREVENT score estimates the 10-year risk for CVD, ASCVD, and HF as follows: low risk (<5%); borderline risk (5%–7.4%); intermediate risk (7.5%–19.9%); high risk (≥20%). ASCVD, atherosclerotic cardiovascular disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; PREVENT, Predicting Risk of Cardiovascular Disease Events; UACR, urine albumin:creatinine ratio. 1. Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Primary kidney outcome in the overall population

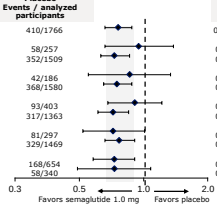


Superiority if two-sided p value is <0.0322

Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk. Event rates: 5.8 and 7.5 per 100 patient-years of follow-up for participants receiving semaglutide and placebo, respectively. CI, confidence interval; HR, hazard ratio. Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Primary kidney outcome by CV status or total CV risk

	Semaglutide 1.0 mg Events / analyzed participants	Placebo Events / analyzed participants	HR (95% CI)	p-interaction
Overall population	331/1767	410/1766	0.76 (0.66, 0.88)*	
Prior MI				
Yes	55/257	58/257	0.95 (0.66, 1.38)	
No	276/1510	352/1509	0.73 (0.63, 0.86)	0.20
Prior stroke				
Yes	37/181	42/186	0.86 (0.55, 1.34)	
No	294/1586	368/1580	0.75 (0.65, 0.88)	0.58
Prior MI or stroke				
Yes	87/405	93/403	0.91 (0.68, 1.22)	
No	244/1362	317/1363	0.72 (0.61, 0.85)	0.17
Prior PAD				
Yes	60/288	81/297	0.72 (0.52, 1.01)	
No	271/1479	329/1469	0.77 (0.66, 0.91)	0.72
Total CV risk (PREVENT score)†				
≥20%	134/675	168/654	0.73 (0.58, 0.91)	
<20%	44/331	58/340	0.73 (0.49, 1.08)	0.99

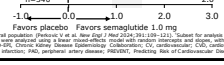


*p<0.001 for semaglutide versus placebo in the overall population (Perkovic V et al. *New Engl J Med* 2024;391:109-121). †Subset for analysis of CV risk score in those without previous CV events or without established CVD. Time to first primary kidney outcome was analyzed using a Cox proportional hazards model with treatment by subgroup as a fixed factor stratified by SGLT2 inhibitor use at baseline. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease; PREVENT, Predicting Risk of Cardiovascular Disease Events; SGLT2i, sodium–glucose co-transporter 2.

Annual change in eGFR by CV status or total CV risk

Estimated treatment difference (ETD) >0.75 mL/min/1.73 m² per year predicts an effect of an intervention to reduce the risk of kidney outcomes

	Participants at baseline Semaglutide 1.0 mg	Placebo	Semaglutide 1.0 mg	Placebo	ETD per year (95% CI)	p-value
Overall population	n=1767	n=1766	−2.2	−3.4	1.2 (0.9,1.5)*	
Prior MI						
Yes	n=257	n=257	−2.2	−3.0	0.8 (−0.0, 1.6)	
No	n=1510	n=1509	−2.2	−3.4	1.3 (1.0, 1.6)	0.29
Prior stroke						
Yes	n=181	n=186	−2.4	−3.3	0.9 (−0.1, 1.9)	
No	n=1586	n=1580	−2.1	−3.4	1.3 (0.9, 1.6)	0.50
Prior MI or stroke						
Yes	n=405	n=403	−2.3	−3.2	0.9 (0.2, 1.5)	
No	n=1362	n=1363	−2.1	−3.4	1.3 (1.0, 1.7)	0.24
Prior PAD						
Yes	n=288	n=297	−1.9	−3.4	1.4 (0.6, 2.2)	
No	n=1479	n=1469	−2.2	−3.4	1.2 (0.8, 1.5)	0.60
Total CV risk (PREVENT score)†						
≥20%	n=675	n=654	−2.0	−3.4	1.4 (0.9, 2.0)	
<20%	n=331	n=340	−2.6	−3.6	1.0 (0.2, 1.7)	0.32

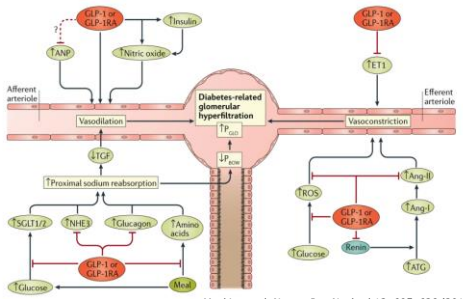


*p<0.001 for semaglutide versus placebo in the overall population (Perkovic V et al. *New Engl J Med* 2024;391:109-121). †Subset for analysis of CV risk score in those without previous CV events or without established CVD. Annual changes in eGFR (CKD-EPI) were analyzed using a shared slope model with random subject-specific intercepts and slopes, with treatment by subgroup as a fixed factor stratified by SGLT2 inhibitor use at baseline. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; MI, myocardial infarction; PAD, peripheral artery disease; PREVENT, Predicting Risk of Cardiovascular Disease Events; SGLT2i, sodium–glucose co-transporter 2.

Semaglutide saves kidneys in persons with CKD and T2D regardless of CV status or risk

Semaglutide similarly reduced risks of the primary kidney outcome or eGFR decline across strata of established CV or CV risk at baseline

CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes.



Muskiet et al. Nature Rev Nephrol 13, 605–628 (2017).

延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

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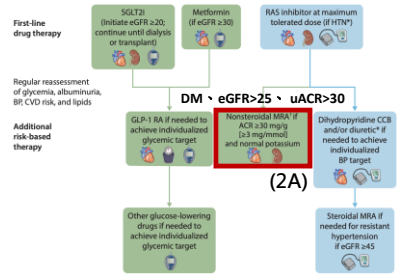
Mineralocorticoid receptor antagonists (MRA)



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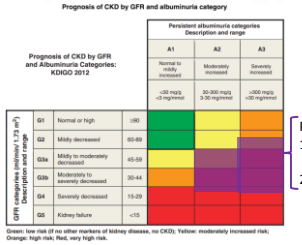
Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

FIDELIO-DKD trial



Patients: 5734 with CKD + DM, all under RASi

1. eGFR 25-60 + UACR 30-300mg/g + DM retinopathy
2. eGFR 25-75 + UACR 300-5000 mg/g

George L Bakris et al. N Engl J Med . 2020 Dec 3;383(23):2219-2229.

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

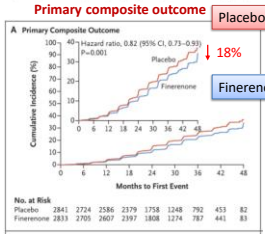
FIDELIO-DKD trial

Primary composite outcome

Placebo

18%

Finerenone



Primary composite outcome: kidney failure(eGFR<15), eGFR decline ≥40%, renal death

Less patients in Finerenone group reached **primary composite outcome** (hazard ratio, 0.82; 95% [CI], 0.73 to 0.93; P=0.001)

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

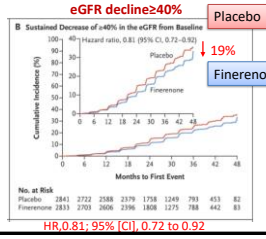
FIDELIO-DKD trial

eGFR decline≥40%

Placebo

19%

Finerenone

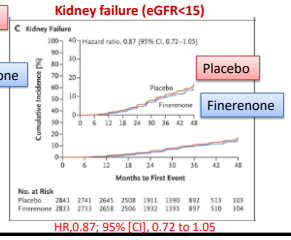


HR,0.81; 95% [CI], 0.72 to 0.92

Kidney failure (eGFR<15)

Placebo

Finerenone



HR,0.87; 95% [CI], 0.72 to 1.05

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

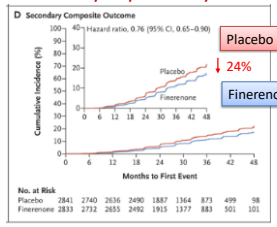
FIDELIO-DKD trial

Secondary composite kidney outcome

Placebo

24%

Finerenone



Secondary composite kidney outcome: kidney failure(eGFR<15), eGFR decline ≥57%, renal death

Less patients in Finerenone group reached **secondary composite kidney outcome** (hazard ratio, 0.76; 95% [CI], 0.65 to 0.90)

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

the NEW ENGLAND JOURNAL of MEDICINE

FIDELIO-DKD trial

Outcome	Finerenone (N=2833) no. of patients with event (%)	Placebo (N=2841) no. of patients with event (%)	Finerenone (N=2833) no. of patients with event per 100 patient-yr	Placebo (N=2841) no. of patients with event per 100 patient-yr	Hazard Ratio (95% CI)	P Value
Key secondary composite outcome	167 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	
Nonfatal myocardial infarction	70 (2.3)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	

0.50 1.00 2.00

Finerenone Better Placebo Better

Less patients in Finerenone group reached **key secondary composite CV outcome**
(CV death, non-fatal MI/stroke, hospitalization for HF) **hazard ratio, 0.86; 95% [CI], 0.75 to 0.99; P=0.03)**

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

the NEW ENGLAND JOURNAL of MEDICINE

FIGARO-DKD trial

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012			Persistent albuminuria categories Description and range		
			A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
			<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90		
	G2	Mildly decreased	60–89		
	G3a	Mildly to moderately decreased	45–59		
	G3b	Moderately to severely decreased	30–44		
	G4	Severely decreased	15–29		
	G5	Kidney failure	<15		

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Patients: 7437 with CKD + DM, all under RASi
1. eGFR 25-90 + UACR 30-300mg/g
2. eGFR ≥60 + UACR 300-5000 mg/g

Bertram Pitt et al. N Engl J Med . 2021 Dec 9;385(24):2252-2263.

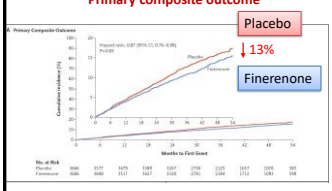
ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

the NEW ENGLAND JOURNAL of MEDICINE

FIGARO-DKD trial

Primary composite outcome



Primary composite CV outcome:
CV death, non-fatal MI/stroke, HHF

Less patients in Finerenone group reached **primary composite outcome** (hazard ratio, 0.87; 95% [CI], 0.76 to 0.98; P=0.03)

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

the NEW ENGLAND JOURNAL of MEDICINE

FIGARO-DKD trial

Outcome	Finerenone (N=3686) no. of patients with event (%)	Placebo (N=3644) no. of patients with event (%)	Finerenone (N=3686) no. of patients with event per 100 patient-yr	Placebo (N=3644) no. of patients with event per 100 patient-yr	Hazard Ratio (95% CI)	P Value
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.13	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.99)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m²	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	331 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—

0.40 1.00 2.00

Finerenone Better Placebo Better

Kidney composite outcome (kidney failure, eGFR decline ≥40%, renal death)
hazard ratio, 0.87; 95% [CI], 0.76 to 1.01

Summary of FIDELIO-DKD and FIGARO-DKD trial

FIDELIO-DKD

Patients: 5734 with CKD + DM, all under RASi
1. eGFR 25-60 + UACR 30-300mg/g + DM retinopathy
2. eGFR 25-75 + UACR 300-5000 mg/g

Finerenone resulted in lower risks of
1. CKD progression (hazard ratio, 0.82; 95% [CI], 0.73 to 0.93; P=0.001)
2. CV events (hazard ratio, 0.86; 95% [CI], 0.75 to 0.99; P=0.03) than placebo

FIGARO-DKD

Patients: 7437 with CKD + DM, all under RASi
1. eGFR 25-90 + UACR 30-300mg/g
2. eGFR ≥60 + UACR 300-5000 mg/g

Finerenone improved CV outcomes as compared with placebo (hazard ratio, 0.87; 95% [CI], 0.76 to 0.98; P=0.03)

George L Bakris et al. N Engl J Med . 2020 Dec 3;383(23):2219-2229.
Bertram Pitt et al. N Engl J Med . 2021 Dec 9;385(24):2252-2263.

nonsteroidal mineralocorticoid receptor antagonist

T2D
CKD
MAX RASi
[K⁺] ≦ 4.8

R

Finerenone 10mg or 20mg QD
Initial dosing of drug based on eGFR at screening; during the study, dosing was guided by serum [K⁺] and eGFR changes
Placebo

FIDELIO – DKD 2.6Y, N=5734
FIGARO – DKD 3.4Y, N=7437

Albuminuria categories[1] (mg albumin/g creatinine)

GFR categories (ml/min/1.73 m²)	A1 Normal to mildly increased 0–29	A2 Moderately increased 30–299	A3 Severely increased ≥300–≤5000
G1	≥90		
G2	60–89		
G3a	45–59		
G3b	30–44		
G4	15–29		
G5	<15		

FIDELIO-DKD FIGARO-DKD Overlapping population

FIDELIO – DKD	FIGARO – DKD
kidney failure sustained eGFR↓ ≥ 40% death from renal causes	death from CV causes nonfatal MI / stroke hospitalization for HF
HR=0.82 (0.65-0.9)	HR=0.87 (0.76-0.98)

nonsteroidal mineralocorticoid receptor antagonist

T2D
CKD
MAX
RASi
[K⁺] ≤ 4.8

R

Finerenone 10mg or 20mg QD
Initial dosing of drug based on eGFR at screening; during the study, dosing was guided by serum [K⁺] and eGFR changes
Placebo

FIDELIO – DKD
2.6Y, N=5734

FIGARO – DKD
3.4Y, N=7437

FIDELITY
prespecific pooled analysis
3Y, N=13026

kidney failure sustained eGFR↓ ≥ 57% death from renal causes	death from CV causes nonfatal MI / stroke hospitalization for HF
HR=0.77 (0.67-0.88)	HR=0.86 (0.78-0.95)

100

nonsteroidal mineralocorticoid receptor antagonist

K⁺ ≤4.8 mmol/l
- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min/1.73 m²
  - 20 mg daily if eGFR ≥60 ml/min/1.73 m²
- Monitor K⁺ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K⁺ now ≤5.0 mmol/l

K⁺ 4.9–5.5 mmol/l
- Continue finerenone 10 mg or 20 mg
- Monitor K⁺ every 4 months

K⁺ >5.5 mmol/l
- Hold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K⁺
- Consider reinitiation if/when K⁺ ≤5.0 mmol/l

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延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

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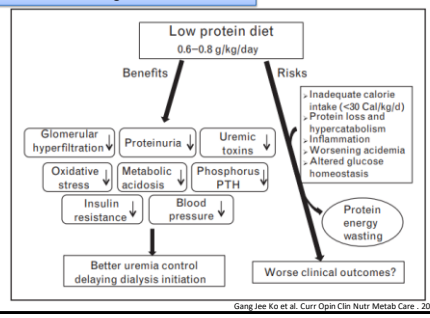
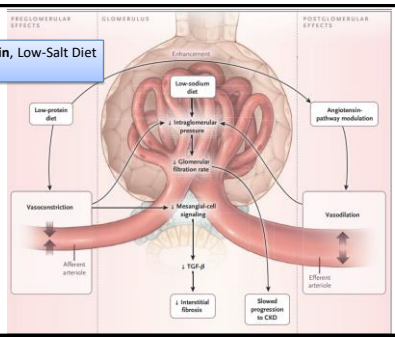
Low Protein Diet in the Management of CKD



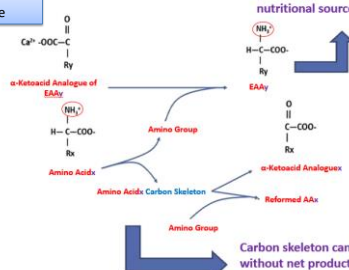
Gang Jee Ko et al. Curr Opin Clin Nutr Metab Care . 2017 Jan;20(1):77-85.

Effects of a **Low-Protein**, Low-Salt Diet on the Glomerulus.



Kamyar Kalantar-Zadeh et al. N Engl J Med . 2017 Nov 2;377(18):1765-1776.

Reversible transamination of a ketoacid (KA) analogue



Anuja P Shah et al. Am J Kidney Dis . 2015 May;65(5):659-73.

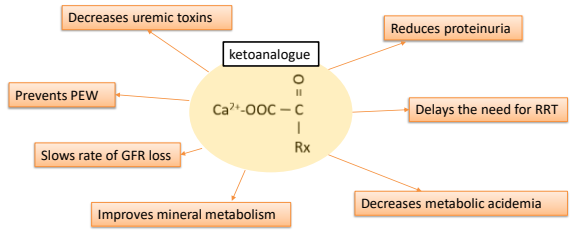
Ketosteril®- composition

1 Ketosteril tablet contains:

67 mg	α-ketoanalogue to isoleucine, Ca-salt
101 mg	α-ketoanalogue to leucine, Ca-salt
68 mg	α-ketoanalogue to phenylalanine, Ca-salt
86 mg	α-ketoanalogue to valine, Ca-salt
59 mg	α-hydroxy-analogue to methionine, Ca-salt
105 mg	lysine-acetate
53 mg	threonine
23 mg	tryptophan
38 mg	histidine
30 mg	tyrosine

Total nitrogen 36mg/tab
Total calcium 50mg/tab

Potential Benefits of KA/EAA-Supplemented Low- or Very-Low-Protein Diets

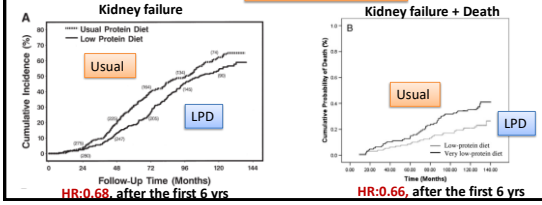


Anuja P Shah et al. Am J Kidney Dis . 2015 May;65(5):659-73.

Effect of dietary protein restriction on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study

AJKD

585 patients, eGFR 25-55
Predominantly non-DKD
RCT
LPD 0.58g/kg/d
Usual protein 1.3g/kg/d
12 yrs f/u
outcome



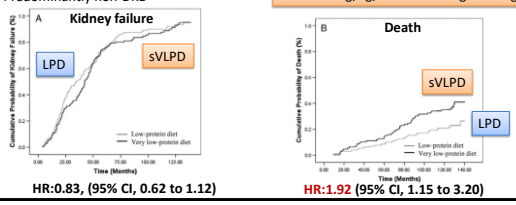
HR:0.68, after the first 6 yrs
HR:0.66, after the first 6 yrs

Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study

AJKD

f/u 12 yrs

225 patients, mainly CKD stage 4
Predominantly non-DKD
RCT
LPD 0.58g/kg/d
sVLPD 0.28g/kg/d + ketoanalogue 0.28g/kg/d

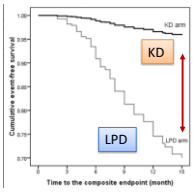


HR:0.83, (95% CI, 0.62 to 1.12)
HR:1.92 (95% CI, 1.15 to 3.20)

Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression

JASN

207 non-diabetic, eGFR<30
RCT
LPD: Conventional LPD
KD: Vegetarian VLPD (0.3 g/kg BW/day) + Ketosteril® (0.125 g/kg BW/day)



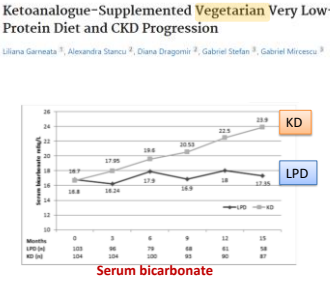
f/u 18 months

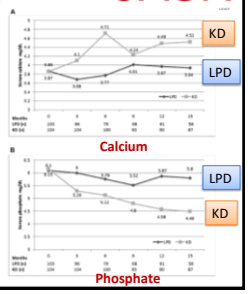
Event-free survival for RRT or ≥50% eGFR↓
HR:0.1 (95% CI, 0.05 to 0.20)

Long-term studies of very low plant protein diets that examine mortality are warranted

Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression

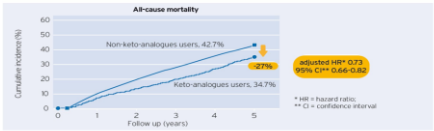
JASN





Ketosteril sLPD reduce all cause mortality in DKD patients

Results from a nationwide population based registry (Taiwan) on CKD patients with DM



Taiwanese National Health Insurance Research Database, **1,001 CKD patients with DM** taking Ketosteril sLPD vs. 14,781 non-KA users for 5 years after reaching CKD stage 5.
Overall adjusted mortality was significantly lower in CKD patients with DM taking Ketosteril sLPD compared to the control group.
This study also reported **slower progression to dialysis** (1.6±1.5 vs. 1.0±1.4 years; HR 0.65, 95% CI 0.61-0.69) as well as a **lower incidence of major adverse cardiovascular events** (MACE; RR 0.76, 95% CI 0.67-0.86) in the Ketosteril sLPD group.

Hsing-Yu Chen, et al. Clin Nutr. 2021 Jun;40(6):4149-4160. *LPD: Low protein diet.

Ketoanalogue supplements reduce mortality in patients with pre-dialysis advanced diabetic kidney disease: A nationwide population-based study

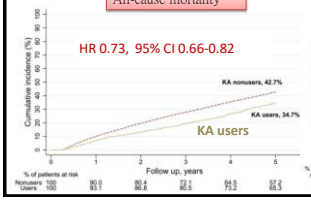
Hsing-Yu Chen • Chiao-Yin Sun • Chin-Chan Lee • ... Yi-Hsuan Lin • Wei-Ching Fang • Heng-Chih Pan

A nationwide cohort retrieved from the **National Health Insurance Research Database in Taiwan**

15,782 with DKD-5-ND Ketoanalogue(KA) users vs nonusers

All-cause mortality

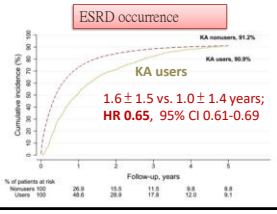
HR 0.73, 95% CI 0.66-0.82



ESRD occurrence

KA users

1.6±1.5 vs. 1.0±1.4 years;
HR 0.65, 95% CI 0.61-0.69



KDOQI
KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE
National Kidney Foundation

KDOQI CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN CKD: 2020 UPDATE | VOLUME 76, ISSUE 3, SUPPLEMENT 1, S1-S107, SEPTEMBER 01, 2020

KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update

T. Alp Ikizler • Jerrilynn D. Burrowes • Laura D. Byham-Gray • ... Daniel Tela • Angela Yee-Moon Wang • Lilian Cuppari • Show all authors

3.0.1 In adults with CKD 3-5 who are metabolically stable, we recommend, under close clinical supervision, protein restriction with or without keto acid analogs, to reduce risk for end-stage kidney disease (ESKD)/death (*1A*) and improve quality of life (QoL) (*2C*):

- a low-protein diet providing 0.55–0.60 g dietary protein/kg body weight/day, or
- a very low-protein diet providing 0.28–0.43 g dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/day)

延緩慢性腎臟病惡化的藥物治療

1. ACEi/ARB
2. Pentoxiphylline
3. Bicarbonate
4. Vitamin D
5. Lipid-lowering agents
6. SGLT2 inhibitor
7. Finerenone
8. Ketosteril
9. Kremezin
10. Summary

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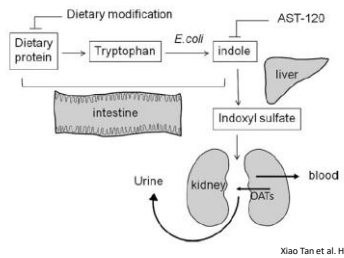
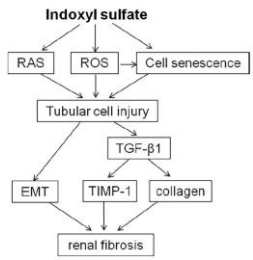
Metabolism of indoxyl sulfate



Xiao Tan et al. Hemodial Int . 2017 Apr;21(2):161-167.

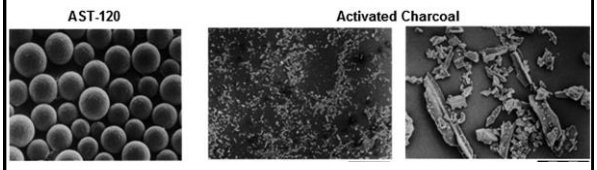
Nephrotoxicity of indoxyl sulfate



RAS: renin-angiotensinsystem
ROS: reactive oxygen species
EMT: epithelial-mesenchymal transition
TIMP1: tissue inhibitor of metalloproteinases 1

Xiao Tan et al. Hemodial Int . 2017 Apr;21(2):161-167.

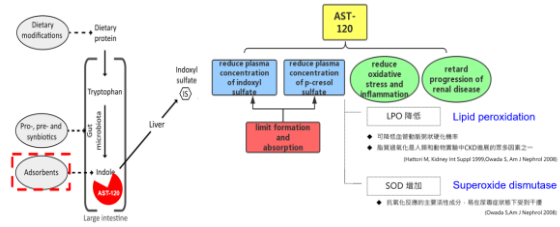
Structural features of AST-120 and activated charcoal



AST-120 differs structurally from activated charcoal

Gerald Schulman et al. J Am Soc Nephrol 2015;26:1732-46

Mechanism of AST-120



Toxin Rev 2016;35(3-4)171-179

ORIGINAL INVESTIGATION PATHOGENESIS AND TREATMENT OF KIDNEY DISEASE AND HYPERTENSION | VOLUME 47, ISSUE 4, P565-577, APRIL 01, 2006

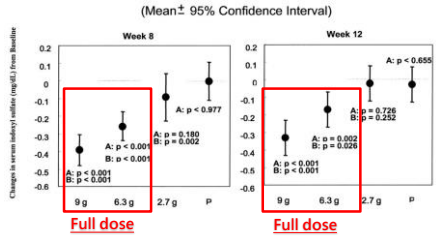
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of AST-120 (Kremezin) in Patients With Moderate to Severe CKD

Gerald Schulman, MD, Rajiv Agarwal, MD, Muralidhar Acharya, MD, Tomas Berl, MD, Samuel Blumenthal, MD, Nelson Kopyt, DO

- A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study
- 29 clinical sites in the United States, 157 CKD patients (SCr 3~6 mg/dL)
- Patients were randomly assigned to 1 of 3 doses of AST-120 (0.9, 2.1, or 3.0 g) or placebo 3 times daily for 12 weeks.

Kremezin® decreased serum indoxyl sulfate levels in a dose-dependent fashion



Schulman G et al. Am J Kidney Dis 2006;47:565-577

Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD

J Am Soc Nephrol 2015;26:1732-46

Gerald Schulman,* Tomas Berl,† Gerald J. Beck,‡ Giuseppe Remuzzi,§ Eberhard Ritz,‖ Kiyoshi Arita,¶ Akira Kato,** and Miho Shimizu¶

(1)

Phase III randomized, double-blind, placebo-controlled study：
Prevention of progression in moderate to severe CKD, EPPIC-2 included QoL assessment

2035 patients

Enrollment 1.5 Y + follow-up 2Y (Total 3.5Y)

Screening

ACEI/ARB use

AST-120 9g/day 300 mg/capsule

Placebo 9g/day

Week 2 Week 6 Week 12 Week 24 Week 36 Every 12 weeks

1020 in EPPIC-1 & 1015 in EPPIC-2 (QoL)

Primary endpoint	: Time to doubling of sCr or dialysis or kidney transplant
Secondary endpoint	: Primary + death, maintain kidney function（eGFR）,safety analyses
Key inclusion criteria	: sCr ; males 2~5mg/dL, females 1.5~5mg/dL, UP/CR: ≥0.5
Sample size 28%, HR=0.72）	: 980 Pts/study (assumptions: drop-out 30%, risk reduction against placebo
Target event	: 291 Events/study
Sites	: Approx. 239sites/study（North America, Latin America, EU, Russia/Ukraine）

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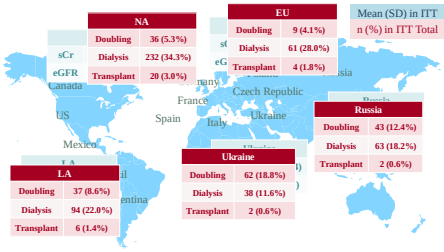
EPPIC studies: global Phase III



Different event rate by regions

Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD

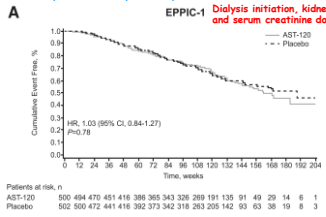
J Am Soc Nephrol 2015;26:1732-46

Gerald Schulman,* Tomas Berl,† Gerald J. Beck,‡ Giuseppe Remuzzi,§ Eberhard Ritz,‖ Kiyoshi Arita,¶ Akira Kato,** and Miho Shimizu¶

(2)

Primary efficacy end point (triple composite end point)

A — EPPIC-1 — Dialysis initiation, kidney transplantation, and serum creatinine doubling



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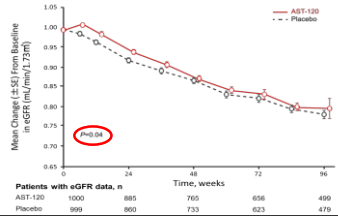
Randomized Placebo-Controlled EPPIC Trials of AST-120 in CKD

J Am Soc Nephrol 2015;26:1732-46

Gerald Schulman,* Tomas Berl,† Gerald J. Beck,‡ Giuseppe Remuzzi,§ Eberhard Ritz,‖ Kiyoshi Arita,¶ Akira Kato,** and Miho Shimizu¶

(3)

Less eGFR decline from baseline



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EPPIC –USA population, post hoc subgroup I

Schulman et al. BMC Nephrology (2016) 17:141

(2)

The primary end point for placebo-treated EPPIC-USA patients was similar to the curve estimated during study planning

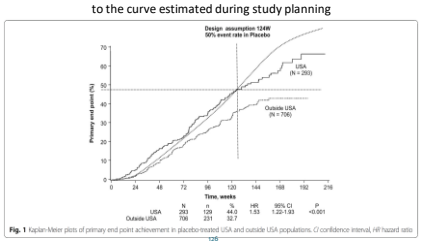

Fig. 1 Kaplan-Meier plots of primary end point achievement in placebo-treated USA and outside USA populations. CI confidence interval, HR hazard ratio

126

USA population, post hoc subgroup I (PP)

The effects of AST-120 on chronic kidney disease progression in the United States of America: a *post hoc* subgroup analysis of randomized controlled trials

Gerald Schulman[1], Tomas Berl[2], Gerald J. Beck[3], Giuseppe Remuzzi[4,5,6], Eberhard Ritz[7], Miho Shimizu[8], Yuko Shobu[9] and Mami Kikuchi[10]*

(1)

- P: 583 pts from per-protocol subgroup from USA, sCr 2-5 mg/dL for men, 1.5-5 mg/dL for women
- I: AST-120 (9g/d) + conventional treatment
- C: Conventional treatment
- O: primary endpoint: doubling of sCr, inititation of dialysis or kidney transplantation

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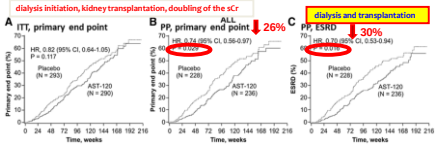
EPPIC –USA population, post hoc subgroup I (2)

Schulman et al. BMC Nephrology (2016) 17:141

dialysis initiation, kidney transplantation, doubling of the sCr

dialysis and transplantation



per protocol (PP) all patients in compliance rate of >67 % (kremezin 6g/day), and/or a treatment period of >8 weeks

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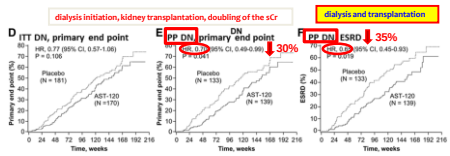
EPPIC –USA population, post hoc subgroup I

Schulman et al. BMC Nephrology (2016) 17:141

(3)

dialysis initiation, kidney transplantation, doubling of the sCr

dialysis and transplantation



per protocol (PP) all patients in compliance rate of >67 % (kremezin 6g/day), and/or a treatment period of >8 weeks

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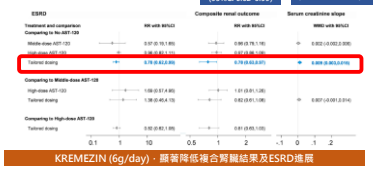
RCT	CKD 病人	治療方式	複合腎臟結果*	ESRD進展
15篇	3,763人	AST-120	RR 0.78 (95%CI 0.62-0.99)	RR 0.78 (95%CI 0.63-0.97)



KREMEZIN (6g/day)：顯著降低複合腎臟結果及ESRD進展

Front. Pharmacol. 12676345.

Risk factors for progression of chronic kidney disease in the EPPIC trials and the effect of AST-120

EPPIC-Subgroup II

Clin Exp Nephrol 2018;22:299-308

Gerald Schulman[1] · Tomas Berl[2] · Gerald J. Beck[3] · Giuseppe Remuzzi[4,5,6] · Eberhard Ritz[7] · Miho Shimizu[8] · Mami Kikuchi[9] · Yuko Shobu[9]

(2)

ACEI/ARB	Hematuria	UP/UCr	AST-120 N	AST-120 n	AST-120 %	Placebo N	Placebo n	Placebo %	HR (95% CI) log scale	HR (95%CI)	P-value
ITT (censored at last contact)			1000	350	35.0	999	360	36.0	Favors AST-120 / Favors Placebo	0.97 (0.83,1.12)	0.64
		All	303	113	37.3	291	139	47.8		0.74 (0.57,0.95)	0.02
	Positive	≥1.0	238	103	43.3	236	124	52.5		0.74 (0.56,0.96)	0.03
Yes		<1.0	65	10	15.4	55	15	27.3		0.58 (0.25,1.36)	0.21
	Negative	All	541	172	31.8	546	156	28.6		1.11 (0.89,1.38)	0.36
		≥1.0	372	141	37.9	354	130	36.7		1.01 (0.79,1.29)	0.94
		<1.0	169	31	18.3	192	26	13.5		1.36 (0.78,2.37)	0.27
	Positive	All	53	31	58.5	51	26	51.0		1.57 (0.85,2.90)	0.15
		≥1.0	41	23	56.1	41	23	56.1		1.95 (0.94,4.05)	0.07
No		<1.0	12	8	66.7	10	3	30.0		0.80 (0.16,4.08)	0.79
	Negative	All	101	34	33.7	106	37	34.9		0.96 (0.59,1.56)	0.87
		≥1.0	64	28	43.8	74	30	40.5		1.33 (0.76,2.34)	0.32
		<1.0	37	6	16.2	32	7	21.9		0.33 (0.08,1.47)	0.15

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EPPIC-Subgroup II (3)

Summary of sub-group analysis

- Results from a sub-group analysis of the EPPIC pooled ITT(intension to treat) population demonstrated the effect of Kremezin (AST-120) on **prolongation of time to the event in CKD patients**
  次分析中，證明AST-120 可有效延緩CKD 惡化
- **Moreover, a greater effect was observed with good drug compliance**
  在服藥順從性高的族群中，效果較佳
- These results suggested that Kremezin (AST-120) has an effect when **added to current standard care** including treatment with **RAS inhibitors** and patients with **hematuria** +/- heavier **proteinuria (UPCR > 1)**
  使用標準治療(ACEI/ARB)外，建議加上 AST-120

Risk factors for progression of chronic kidney disease in the EPPIC trials and the effect of AST-120

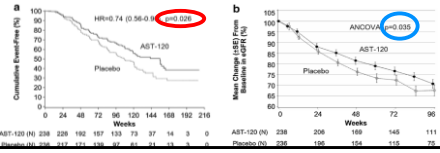
Clin Exp Nephrol 2018;22:299-308

Gerald Schulman[1] · Tomas Berl[2] · Gerald J. Beck[3] · Giuseppe Remuzzi[4,5,6] · Eberhard Ritz[7] · Miho Shimizu[8] · Mami Kikuchi[9] · Yuko Shobu[9]

EPPIC-Subgroup II

(1)

- P: 1999 pts with sCr 2-5 mg/dL for men, 1.5-5 mg/dL for women, and subgroup analysis from UP/Cr>1, hematuria(+) and ACEi/ARB use,
- I: AST-120 (9 g/d) + conventional treatment
- C: Conventional treatment
- O: primary endpoint: doubling of sCr, inititation of dialysis or kidney transplantation



133

EPPIC-Subgroup II

Clin Exp Nephrol 2018;22:299-308

Risk factors for progression of chronic kidney disease in the EPPIC trials and the effect of AST-120

EPPIC-Subgroup II

Gerald Schulman[1] · Tomas Berl[2] · Gerald J. Beck[3] · Giuseppe Remuzzi[4,5,6] · Eberhard Ritz[7] · Miho Shimizu[8] · Mami Kikuchi[9] · Yuko Shobu[9]

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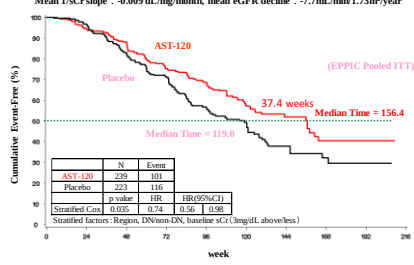
EPPIC-Subgroup II

Secondary endpoint in progressive CKD patients(UP/CR≥1 and hematuria+) with ≥80% compliance of AST-120

(3)

Mean 1/sCr slope : -0.009 dL/mg/month, mean eGFR decline : -7.7mL/min/1.73m²/year



	N	Event
AST-120	239	101
Placebo	223	116

	p value	HR	HR(95%CI)
Stratified Cox	0.035	0.74	0.56 ‖ 0.98

Stratified factors : Region, DN/non-DN, baseline sCr (3mg/dL above/less)

EPPIC-Subgroup II

Summary of sub-group analysis (4)

- Results from a sub-group analysis of the EPPIC pooled ITT(intension to treat) population demonstrated the effect of Kremezin (AST-120) on **prolongation of time to the event in CKD patients**
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  在服藥順從性高的族群中，效果較佳
- These results suggested that Kremezin (AST-120) has an effect when **added to current standard care** including treatment with RAS inhibitors
  使用標準治療(ACEI/ARB)外，建議加上 AST-120

Clinical Study

Effect of an Oral Adsorbent, AST-120, on Dialysis Initiation and Survival in Patients with Chronic Kidney Disease

International Journal of Nephrology 2012

Shingo Hatakeyama,[1] Hayato Yamamoto,[2] Akiko Okamoto,[2] Kengo Imanishi,[3] Noriko Tokui,[2] Teppei Okamoto,[2] Yuichiro Suzuki,[2] Naoaki Sugiyama,[2] Atsushi Imai,[2] Shigemasa Kudo,[3] Takahiro Yoneyama,[3] Yasuhiro Hashimoto,[3] Takuya Kolz,[3] Noritaka Kaminura,[3] Hisao Saitoh,[3] Tomihisa Funyu,[4] and Chikara Ohyama[1,3]

- 572 patients, CKD stage 5 (93%) were retrospective, pair-matched (n = 280 of each group) and enrolled in the study .
  January 1991 ~ December 2010
- Grouped according to whether or not they received AST-120 before dialysis (AST-120 and non-AST-120 groups).
  Dialysis initiation was determined based on scores
- **Lower SBP/DBP in AST-120 group**
- Cumulative dialysis initiation free rate and survival rate were compared.

AJKD American Journal of Kidney Diseases VOL 47, NO 4, APRIL 2006

ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease and Hypertension

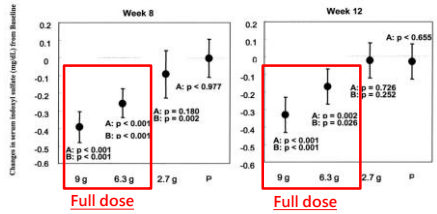
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of AST-120 (Kremezin) in Patients With Moderate to Severe CKD

Gerald Schulman, MD, Rajiv Agarwal, MD, Muralidhar Acharya, MD, Tomas Berl, MD, Samuel Blumenthal, MD, and Nelson Kopyt, DO

- A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study
- 29 clinical sites in the United States, 157 CKD patients (SCr 3~6 mg/dL)
- Patients were randomly assigned to 1 of 3 doses of AST-120 (0.9, 2.1, or 3.0 g) or placebo 3 times daily for 12 weeks.

Kremezin® decreased serum indoxyl sulfate levels in a dose-dependent fashion

(Mean± 95% Confidence Interval)



Full dose Full dose

Schulman G et al Am J Kidney Dis 2006;47:565-577

AST-120 (Kremezin®) initiated in early stage chronic kidney disease stunts the progression of renal dysfunction in type 2 diabetic subjects

Kazunori Konishi, Shigeru Nakano, Shin-ichi Tsuda, Atsushi Nakagawa, Toshikazu Kigoshi, Daisuke Koya *

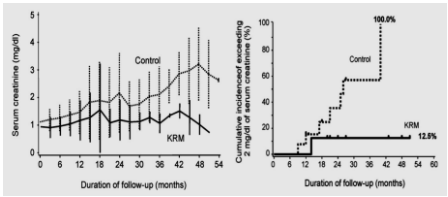
Division of Endocrinology and Metabolism, Department of Internal Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan

- Prospective, randomized, controlled study for subjects with type 2 diabetes (sCr<1.5 mg/dl and urinary protein >0.5 g/day)
- The primary end point : exceeding 2 mg/dl of serum creatinine
- The secondary end point ：entering into hemodialysis.

Diabetes research and clinical practice (2008) 310-315

Kremezin®顯著延緩肌酸酐上升及進入透析比率

eGFR 60-80mL/min



P<0.001 *P*=0.044

Diabetes research and clinical practice (2008) 310-315

Original Article
Nephrology

Predictive Factors for Efficacy of AST-120 Treatment in Diabetic Nephropathy: a Prospective Single-Arm, Open-Label, Multi-Center Study

P: 100 pts with T2DM with sCr 1.5-3.0 mg/ J Korean Med Sci. 2019 Apr 22;34(15):e117
I: AST-120 (6 g/d) + conventional treatment for 24 weeks
C: Conventional treatment
O: primary endpoint: 1/sCr (Ratio change of regression coefficients of 1/sCr after vs. before AST-120 treatment)

sCr 2→ 2.5 → 3 ; eGFR= 60→ 48 → 40 ; Ratio change of regression coefficients of 1/sCr = -8 / -12 = 0.67

Table 2. Efficacy of AST-120 after treatment for 8, 16, and 24 weeks

R*	No. (%)		
	8 wk	16 wk	24 wk
Responders	54/72 = 75%	62/76 = 81.5%	61/76 = 80.3%
≤ 0.30	41 (56.9)	46 (60.5)	50 (65.8)
0.31–0.60	5 (6.9)	8 (10.5)	2 (2.6)
0.61–0.90	8 (11.1)	8 (10.5)	9 (11.8)
Non-responders			
0.91–1.09	0	3 (3.9)	4 (5.3)
≥ 1.10	18 (25)	11 (14.5)	11 (14.5)
Total	72 (100)	76 (100)	76 (100)

*Ratio change of regression coefficients of 1/sCr before and after AST-120 treatment.

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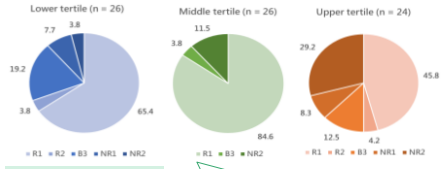

◆ 依照基線 sCr 分組
Lower tertile (L) : 1.45 - 1.7
Middle tertile (M) : 1.71 - 2.09
Upper tertile (U) : 2.10 - 2.94

R1：明顯改善：≤ 0.3
R2：部分改善：0.31–0.6
R3：略有改善：0.61–0.9
NR1：沒有改變：0.91–1.09
NR2：惡化：≥ 1.1

◆ 在三個組別中，經過24周的AST-120治療後，L+M組與U組相比腎功能顯著改善（p=0.024）
◆ sCr < 2.09 使用效果較佳
◆ 降低氧化反應可能為AST-120療效的原因

You-Cheol Hwang ,J Korean Med Sci. 2019 Apr ;22;34(15):e117

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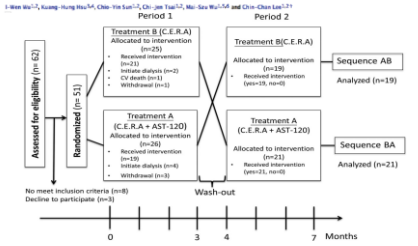
Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on Stage 5 chronic kidney disease patients: a randomized crossover study



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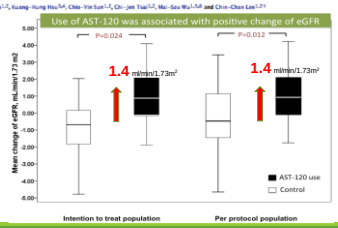
Kremezin®在CKD(Stage 5)患者可延緩eGFR下降速度

Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on Stage 5 chronic kidney disease patients: a randomized crossover study



Wu IW et al, NDT, 320014

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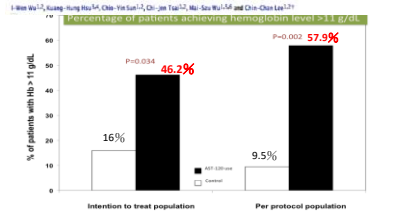
Kremezin®在CKD(Stage 5)患者可提高Hb濃度

Oral adsorbent AST-120 potentiates the effect of erythropoietin-stimulating agents on Stage 5 chronic kidney disease patients: a randomized crossover study



Wu IW et al, NDT, 320014

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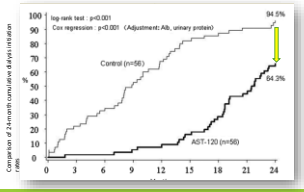
Kremezin® 可降低30%進入透析的比率

為期24 個月的追蹤研究則發現，
有無服用 Kremezin® 的 CKD 患者，累積起始透析率分別為 64.3% 與 94.5%，
顯示 Kremezin® 可顯著延緩開始進行透析的時間（P < 0.001）

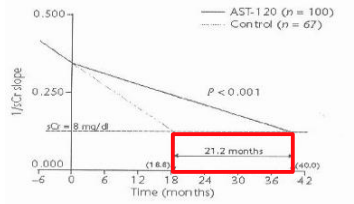


Maeda K, et al. Dialysis & Transplantation 2011;40:212-16

Long-term Effects of Kremezin® in CKD Patients

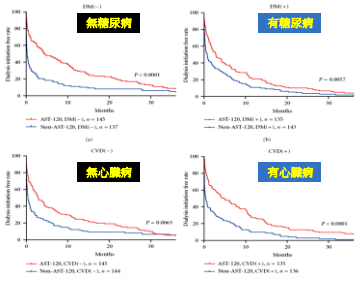
It delayed the initiation of dialysis by 21.2 months

(assuming initiation of dialysis was **sCr level of 8 mg/dl**)

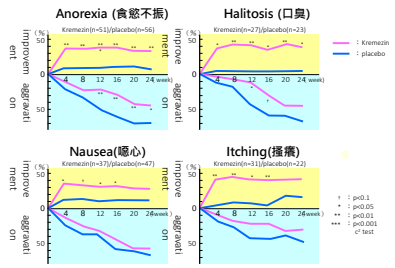


J Int Med Res, 37(1) 2, 2009

Kremezin® delays the cumulative dialysis initiation rate



Kremezin®尿毒素症狀的影響



Kremezin®對粥狀動脈硬化的效果

Non-DM	AST-120 (n=30)	Non AST-120 (n=20)	Healthy controls (n=30)
PWV, cm/s			
Before	1,980 ± 330*	1,940 ± 360*	1,280 ± 240
12 months	1,840 ± 280**	2,020 ± 380	
24 months	1,780 ± 260**	2,140 ± 410**	
IMT, mm			
Before	0.90 ± 0.22*	0.88 ± 0.20*	0.64 ± 0.14
12 months	0.84 ± 0.20	0.90 ± 0.24	
24 months	0.78 ± 0.18**	0.93 ± 0.26	

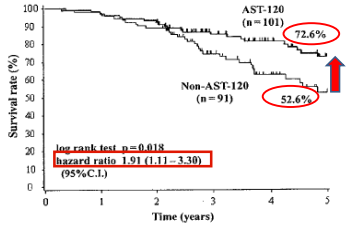
*Versus healthy controls, p<0.01. **versus before, p<0.05

PWV: pulse wave velocity脈波傳導速度

IMT: intima-media thickness 頸動脈內膜中層厚度

Kidney Blood Pressure Research 2004;27:121-126

Kremezin®改善洗腎病人的5年存活率達20%



Renal Failure, 30:856-60, 2008

食品級植物碳不得宣稱具有療效

法規	臺灣 TFDA	美國 FDA
活性碳	**活性碳**：則因製程複雜，需要經過「碳化」與「活化」的步驟，因此不屬於「天然食品顏色添加劑」，依規定不得添加於食品中。	**禁止**將碳粉、活性碳作為食品顏色添加劑
植物碳	**植物碳**：以竹子、木、纖維素、泥炭、椰子殼及果殼等原料，經高溫（800- 1000度）碳化製成。 • 僅可做為食品顏色添加劑用途	

• 衛福部藥事法第69條：非藥物不得宣稱療效；違反者處新台幣六十萬元以上，二千五百萬元以下罰鍰。

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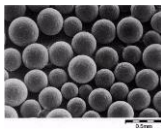
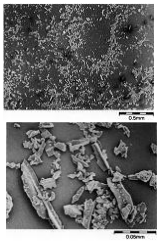
Difference between AST-120 and Activated Charcoal



AST-120



Activated Charcoal

Case Sharing

155

Case 1: ID: 260xxxx 曾oo

- 78 y/o male, first visited on 8/18/2015
  - **Chief complaint**: Renal function impairment
  - **Past history**: Hypertension since 2006 with medication control; Chronic sinusitis s/p ENT surgery on 9/2014; Severe headache since 4/2015;peptic ulcer.
    - Baseline BP: 152/92 mmHg
    - Started treatment since 2006/03:Fosinipril 1# QD(LMD)
    - Changed medication on 2016/02: Coniel + Edarbi
    - Changed medication on 2016/03: Edarbi
  - **Symptoms**: Creat.:1.05➔> NSAID + Lasix ➔Cr:1.4 on 06/11/2015 (LMD)
  - **Impression**: MCD/FSGS (focal segmental glomerulosclerosis) with nephrotic syndrome and hypoalbuminemia
    - s/p prednisolone since 2016
    - s/p temporal cyclosporin use in 2016
    - s/p pulse therapy with MTP 1000mg on 9/13-9/15/2017
    - s/p long-term prednisone treatment
  - **Renal biopsy**: 1. Minimal change disease on 9/9/2016
    2. Widespread foot process effacement c/w FSGS on 7/16/2018

Current Medications

For hypertension	Nifedipine 30 mg	1	Q12H
	Micardisl 80 MG	1	QD
	Doxazosin 4 mg	1	QN
For CKD	Ketosteril	2	TIDCC
	Kremezin 500 mg(4's/wp)	1	TIDPC
	Pentoxiphylline (400mg)	1	BIDPC
For hyperlipidemia	Zulitor 4 mg	1	QN
For anemia	Mircera 50 mcg	SC	QM
For hypokalemia	K-Glu oral soln 20 mEq/15 ml	0.5 AMP	QD
Miscellaneous symptoms control	Macalol 0.25 mcg	1	QD
	Eltroxin 50mcg	1.5	QDAC
	Prednisolone 5 mg	0.5	QD
	Through 20 mg	3	HS

Laboratory Data

	BUN	Cr	eGFR	ΔeGFR	Kremezin	K	HbA1c	LDL	TG	Hb	UPCR	Notice
2015/08	14	1.05	70.03			3.3	5.2	107	68	13.7	0.098	
2016/09	13	1.11	65.49			3.8	5.1			12.7	2.659	*Progressive proteinuria
2017/09	18	1.25	56.94			3.1	5.8			10.9	1.838	*Pulse therapy with methyl-prednisolone
2018/08	15	1.17	61.28	-37.43		3.7	5.7	172	134	12.2	1.985	NSAID from LMD 2018/9-11
2018/12	47	2.65	23.85	-1.52		3.3	-			8.2	3.834	
2019/09	44	2.80	22.33	-3.17		3.2	5.7	182		9.9	2.996	
2020/07	61	3.19	19.16	-1.65	1	3.8	5.6	125	98	9.2	3.013	*started Kremezin 0.5P BID since 2020/7/28
2021/08	52	3.44	17.51	-3.6	1 ~ 0	3.52	5.9			9.6	1.693	*COVID-19(+) loss F/U
2022/09	53	4.19	13.91	+3.74	3	3.3	5.4			10.4	2.34	Kremezin 1P TID
2023/09	40	3.40	17.65	-0.68	2	4.1	-	69	-	8.4	1.183	Kremezin 1P BID
2024/10	49	3.51	16.97	-0.45	3	3.8	-	72	54	10.8	1.175	Kremezin 1P TID
2025/02	46	3.63	16.52		3	4.2	-	84	94	10.7	1.252	Kremezin 1P TID

Case 2: ID: 28XX35XXX 李o秋

- 47 y/o male, First visited the nephrology clinic in 2009.
  - Chief complaint: proteinuria and liver dysfunction were noted recently
  - Past history: Hypertension with medication control
- Diagnosis
  - Chronic kidney disease, stage 4 (severe)
  - Recurrent and persistent hematuria with unspecified morphologic changes
  - Systemic disorders of connective tissue in other diseases classified elsewhere
  - Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrh
  - r/o IgA nephropathy with CKD stage 3, R/O autoimmune nephritis
- Started taking Kremezin in 2012/11

Current Medications

For hypertension	Zanidip 10 mg	1	BIDAC
	Aprovel 300 mg	1	QD
For CKD	**Kremezin** 500mg (4's/wp)	1	TIDPC
	Pentoxiphylline (400 mg)	1	BIDPC
For hyperuricemia	EURICON 50 mg	1	QD
For Anemia	NESP 20 mcg	20 ug	Q2W
	Folirromin 50 mg	2	QDPC
For hyperlipidemia	Mevalotin protect 40 mg	1	QN
For hypertriglyceride	Omacor 1000mg	1	QD
For acidemia	Sod bicarbonate 300mg	2	TIDPC
Miscellaneous symptoms control	Methylone 4 mg	4.5	QD
	Macalol 0.25 mcg	1	QN

Laboratory Data

	BUN	Cr	eGFR	UA	Na	K	HbA1c	LDL	TG	Hb	UPCR
2009-09	24	1.32	**44.6**	6.4	134	4.1	5.5	128	146	12.4	1.423
2012-11	27	1.82	**32.8**	6.8	135	4.3	5.5	142	135	11.8	0.891
2016-08	28	1.92	**30.7**	6.2	131	4.3	5.6	149	106	11.4	0.309
2017-02	28	1.68	35.7	5.4	133	4.1	5.6	147	98	10.5	0.52
2018-01	27	1.76	33.7	6	131	4.4	5.6	118	79	10.2	0.403
2019-02	27	1.81	32.4	5.3	133	4.9	5.6	97	81	10.1	0.259
2020-03	30	1.93	30	6.2	128	3.95	5.4	123	101	9.7	0.26
2021-04	37	2.07	27.5	6.1	126	5.68	5.3	125	122	11.1	0.3
2022-02	35	1.96	29.2	5.5	126	5.24	5.7	128	64	11.2	0.492
2022-08	28	1.92	29.9	6.2	127	4.5	5.7	127	119	10.7	0.287
2023-01	33	1.93	29.6	5.5	127	5.1	5.7	114	39	11.3	0.488
2023-07	30	1.91	29.9	5.5	127	5	5.8	111	108	11	0.635
2023-12	35	1.84	31.3	5.1	126	5.4	5.7	122	63	11.1	2.28
2024-03	32	2.06	27.3	5.2	127	5.3	5.7	117	86	10.2	1.112
2024-06	33	2.04	**27.6**	5.3	126	5	5.6	94	65	10	0.80
2025-03	34	2.14	**26.3**	5.8	129	5.2	5.7	98	95	10.2	1.021

Case 3: Profile

- **Age:** 96 y/o
- **Name:** 林碧**O**
- **Gender:** female

Case 3: Hx

- **Past medical history:**
  - Chronic interstitial nephritis in CKD stage 3-4
  - Dizziness and giddiness
  - Hyperlipidemia
  - Vestibular neuritis

  Personal history:
  - Smoking: None
  - Alcohol drinking: None

Case 3: Medication Hx

- **2015-2:**

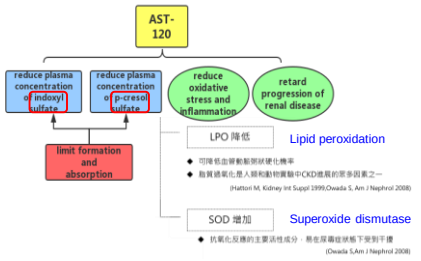
Sod bicarbonate tab 300mg	6	TAB	BID
NESP * inj 20 mcg	20	MCG	Q2W
Pentoxiphylline 100 mg	1	TAB	TID
Lipitor FC * tab 10 mg	1	TAB	QD

- **2015-3: Kremezin 1 pack 1 hour after dinner → bid since 2015-4-21**

Case 3 : Lab data

Biochemistry study							
	2015-2	2015-4	2016-10	2021-6	2022-5-7	2024-10	2025-1-16
BUN/Cr	47/1.8	-/1.37	25/1.34	36/1.42	34/1.33	51/1.37	46/1.39
eGFR	27	36	38	34.52	36.7	35.7	35.2
Na/K	142/4.5	-/-	140/4.6	140/4.1	140/4.1	140/4.2	141/4.5
UA	5.8	5.3	5.6	5.6	5.5	5.4	5.7
TC/TG	188/86	196/103	224/111	151/76	139/79	134/75	188/85
FBS	91	90	97	78	91	92	96
HbA1c	-	5.4	5.5	5.4	5.6	5.6	-
UPt/Cr	0.26	0.15	0.11	0.353	0.296	0.18	0.16
Hb/Hct	10.7/31.6	-/-	11.7/34.5	11.7/35.2	12.1/36.7	12.0/36.2	11.1/31.4

Summary of Therapeutic Mechanisms



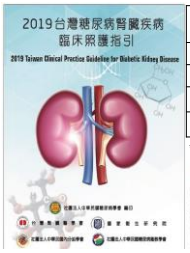
2015 Taiwan Chronic Kidney Disease Clinical Guidelines

早期 CKD 病人使用AST-120 可能可延緩腎絲球過濾率下降速度。
建議強度 B 證據等級 1-

2018 日本 CKD 診療指引

CKD的治療目前沒有特異性藥物, Kremezin 可延緩腎功能惡化的速度,是可以考量推薦使用的藥物。

2019 Taiwan Clinical Practice Guideline for Diabetic Kidney Disease & Personal Experience



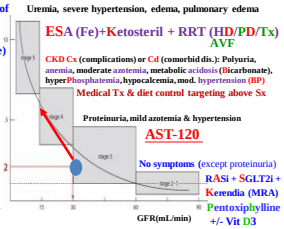
CKD Stage	Starting dose: PPD	Maximal dose: PPD
3A	1	2~3
3B	1~2	3
4	1~3	3
5	2~3	3~4

** According to my personal experience & opinion

Therapeutic Strategy for Progressive CKD Patients

ASK-- PhDSCI -- AST – BP-- BP– ESKD (Tx- AVF- PD) 高糖蛋白免

- CKD 1-2: Combination Tx of RAS inhibitor ; SGLT2 inhibitor ; Kerendia (MRA:finerenone) Pentoxiphylline Vit D3 Statin CCB IS: Immunosuppression
- CKD 3: Oral carbonaceous adsorbent (AST-120)
- CKD4: Meds + diet control for CKD Cx or Cd (A to Z)
- CKD 5: Erythropoietin stimulating agent (ESA) + Ketosteril + RRT



Uremia, severe hypertension, edema, pulmonary edema

ESA (Fe)+Ketosteril + RRT (HD/PD/Tx) AVF

CKD Cx (complications) or Cd (comorbid dis.): Polyuria, anemia, moderate azotemia, metabolic acidosis (bicarbonate), hyperPhosphatemia, hypocalcemia, mod. hypertension (BP)

Medical Tx & diet control targeting above Sx

Proteinuria, mild azotemia & hypertension

AST-120

No symptoms (except proteinuria)

RASi + SGLT2i + Kerendia (MRA) Pentoxiphylline +/- Vit D3 Statin, CCB,IS

(Tomino Y, Ed. Essential Nephrology, 2019, in Japanese)