IN THE NAME OF GOD

Heme Pigment-Induced Acute Kidney Injury and Uric Acid Nephropathy

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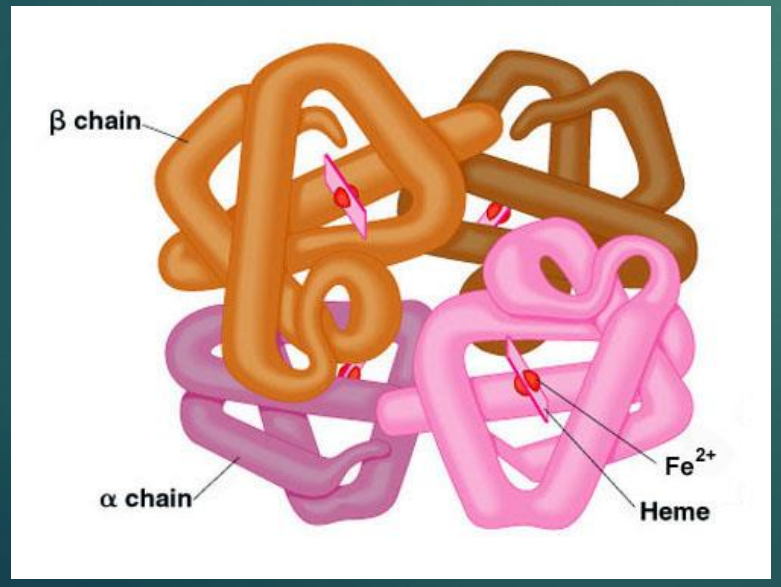
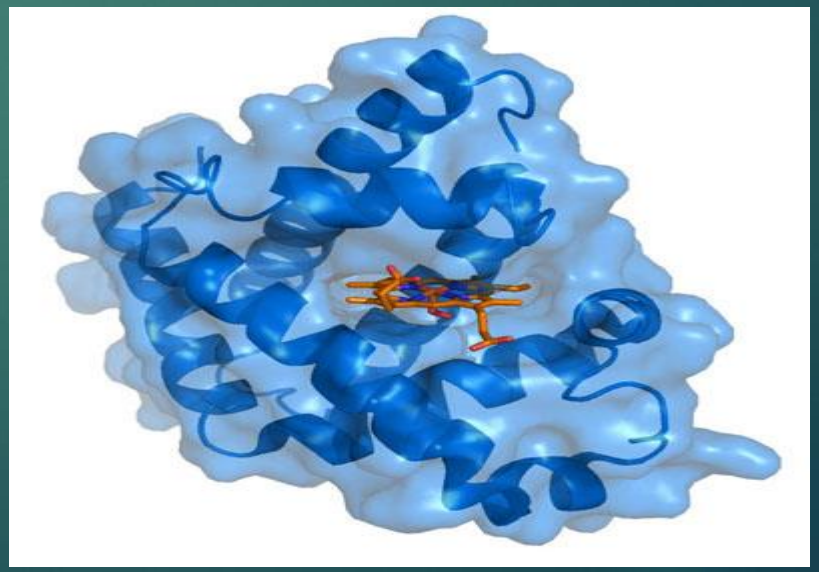
Heme pigment-induced acute kidney injury

- hemoglobin and myoglobin are a cytoplasmic protein that binds oxygen on a heme group. It harbors only one globulin group, whereas hemoglobin has four. Although its heme group is identical to those in Hb, Mb has a higher affinity for oxygen than does hemoglobin. This difference is related to its different role: whereas hemoglobin transports oxygen, myoglobin's function is to store oxygen.





Heme pigment-induced acute kidney injury
Rhabdomyolysis-induced AKI (RIAKI)

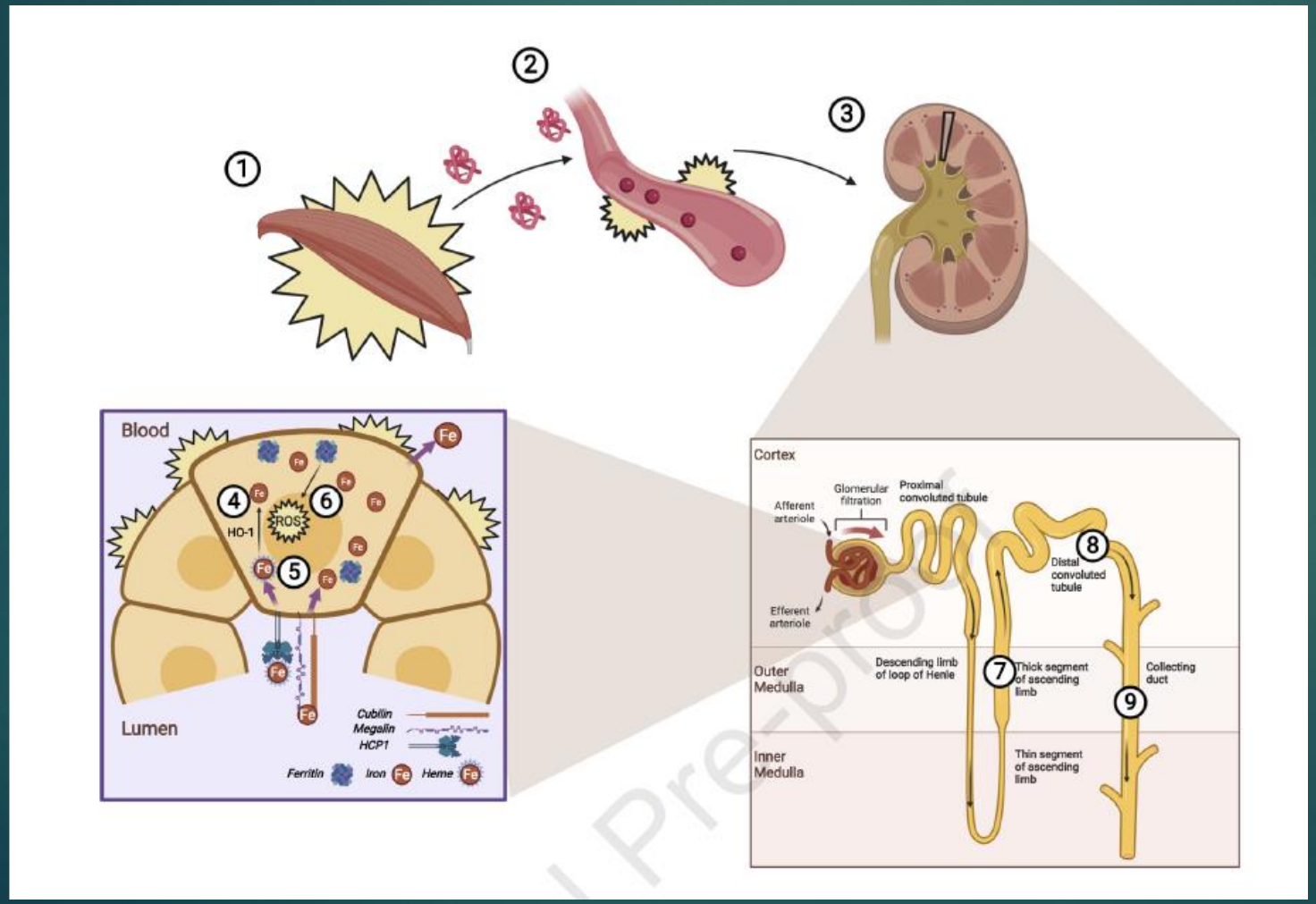
- Rhabdomyolysis-induced AKI (RIAKI), is a common complication affecting up to 46% of patients hospitalized and 80% of those requiring ICU for rhabdomyolysis. Even with excellent care, mortality is greater than 15%.
- The incidence of RIAKI has increased 10-fold in the last decade , fueled in part by popular interest in studio fitness training, significant comorbidity for injured soldiers who are are 3-4 times more likely to develop rhabdomyolysis than civilians . It is also common in critically ill patients with COVID-19, as COVID-AKI shares many features with RIAKI even without specific markers of RIAKI .
- RIAKI takes on greater importance as the leading cause of death in immediate survivors of earthquakes.

Nielsen FE, et al *Clin Epidemiol*. 2020;12:989-95.

Mechanis of renal injury and urgent need for Developing mechanism-based treatments for RIAKI

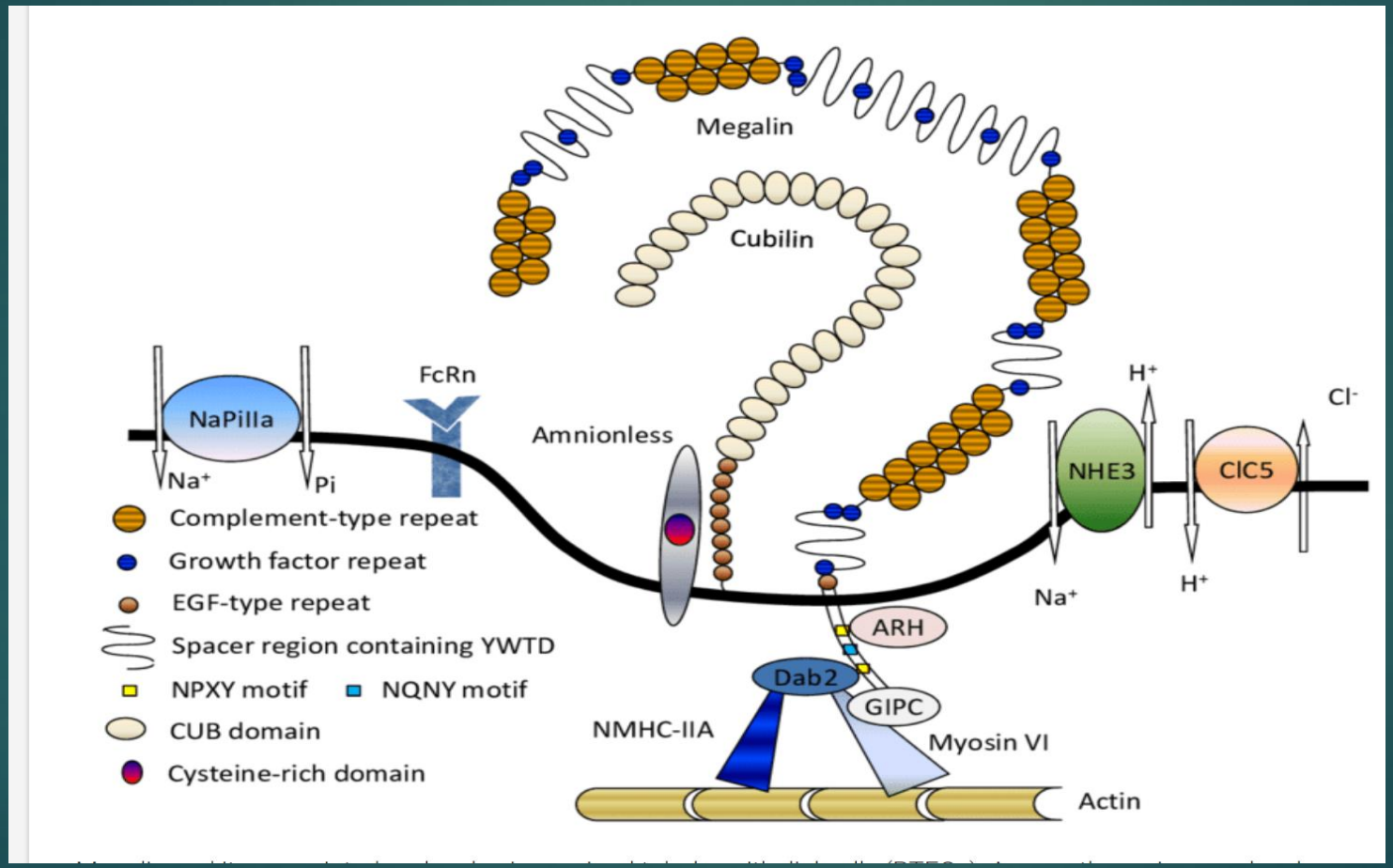
- Myoglobin and its oxygen-carrying moiety heme play a key role in RIAKI through: (i) renal vasoconstriction; (ii) direct injury of proximal tubular cells through oxidative stress, lipid peroxidation, and macrophage activation;(iii) myoglobin precipitation with uromodulin, forming pigmented casts in distal tubules(iiii) Immune-Mediated Mechanisms.
- In addition to processes directly related to myoglobin toxicity, products released from skeletal muscle and tubular epithelial cell damage act as immunogenic damage-associated molecular patterns (DAMPs), activating resident macrophages and recruiting circulating immune cells into the kidney interstitium.

Mechanis of renal injury and urgent need for Developing mechanism-based treatments for RIAKI



Receptor-Mediated Endocytosis

Megalin and its associated molecules in proximal tubule epithelial cells



Cilastatin Ameliorates Acute Kidney Injury Due to Rhabdomyolysis in Mice

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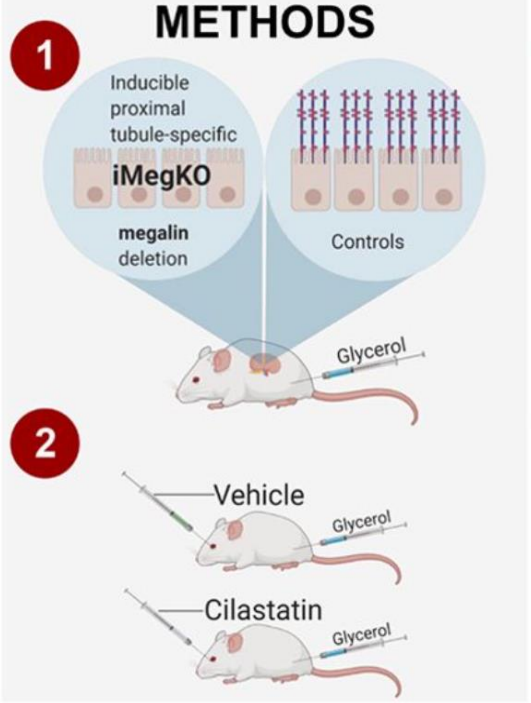
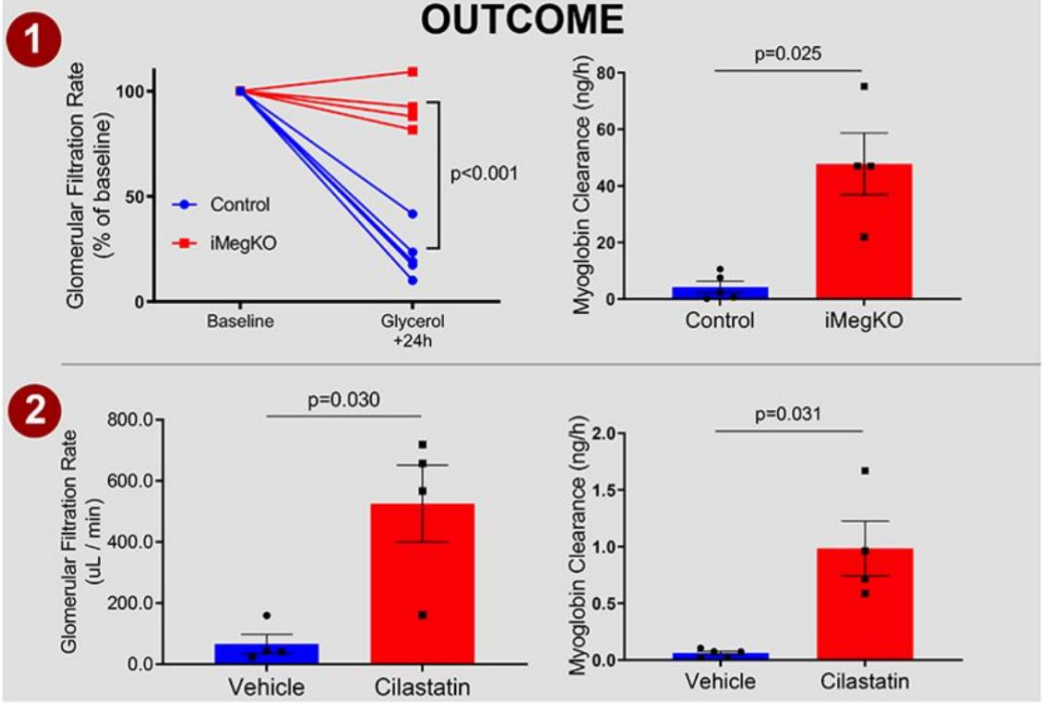
METHODS



OUTCOME



Conclusion

Cilastatin, a pharmacologic inhibitor of megalin, is renoprotective in rhabdomyolysis-induced acute kidney injury, in a megalin-dependent fashion.

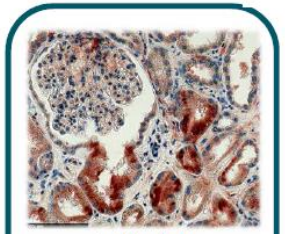
doi: 10.1681/ASN.2020030263

Cilastatin

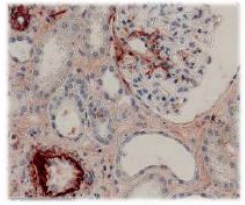
- Cilastatin is a chemical compound which inhibits the human enzyme dehydropeptidase. Renal dehydropeptidase degrades the antibiotic imipenem. Cilastatin is therefore combined intravenously with imipenem in order to protect it from dehydropeptidase and prolong its antibacterial effect.

Complement activation is a crucial driver of acute kidney injury in rhabdomyolysis

10 human RIAKI biopsies

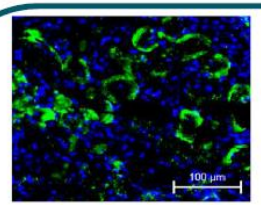


Tubular C3d deposit

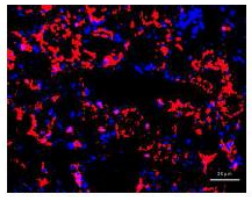


Vascular C5b-9 deposits

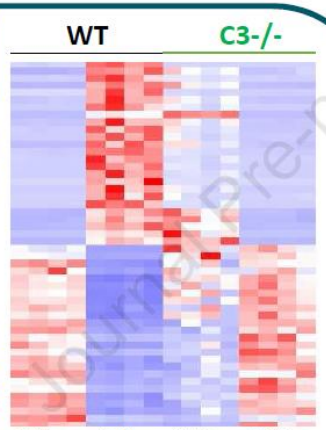
Glycerol induced rhabdomyolysis RIAKI mouse model



Tubular C3b/iC3b deposits



C5aR1 on tubular and interstitial cells



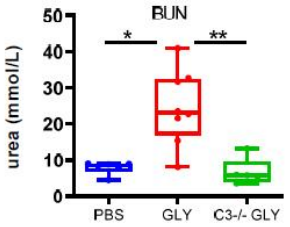
C3 knockout reverses RIAKI transcriptomic signature

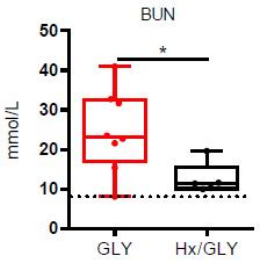
C3-/-

+ Hemopexin

WT

Kidney Protection





CONCLUSION: Complement system is activated in rhabdomyolysis induced acute kidney injury (RIAKI).

Complement blocking and heme scavenging are promising therapeutic strategies.

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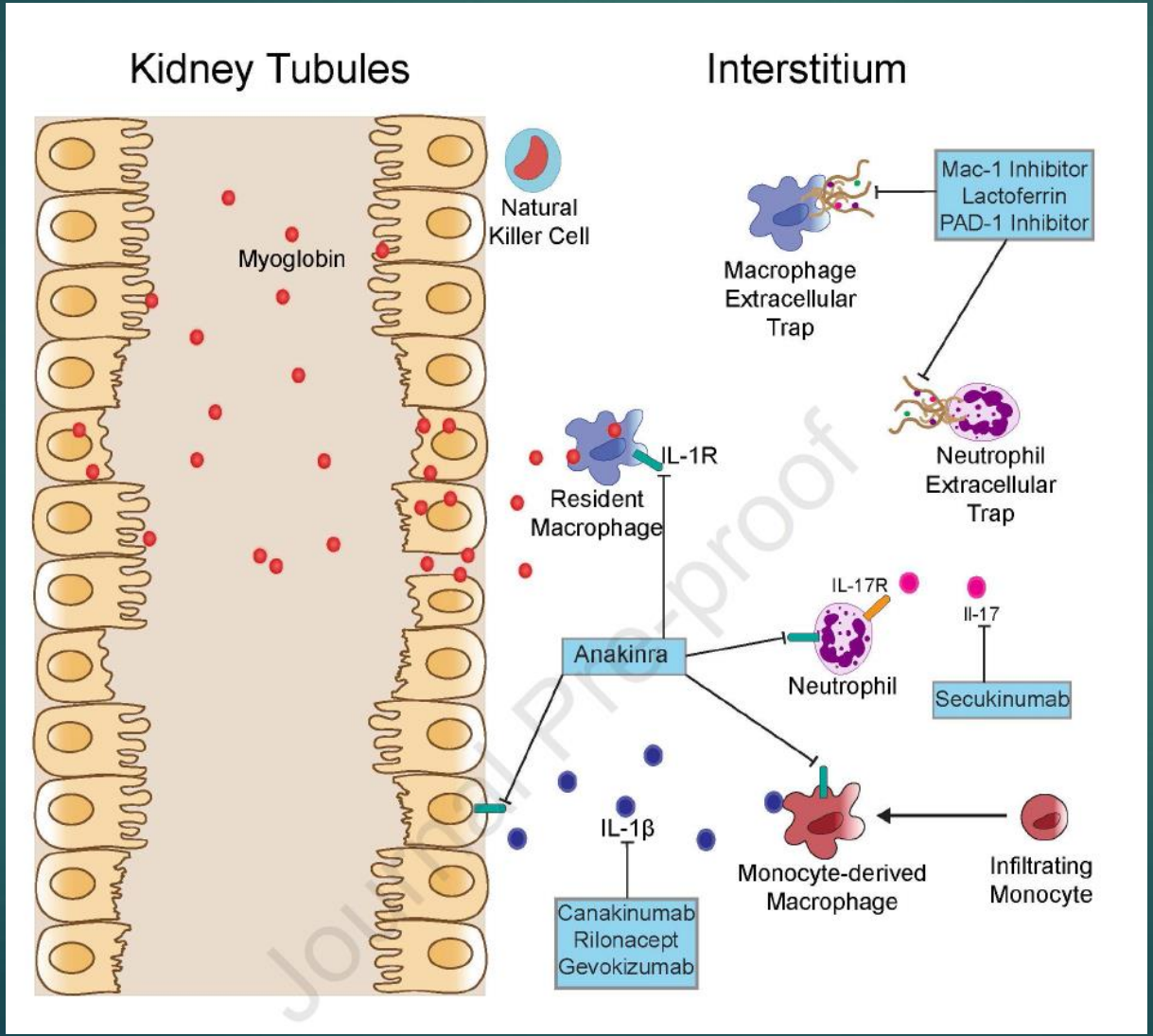
Boudhabhay, 2020

A close look to the Kidney inflammation during RIAKI and associated molecular targets



RIAKI treatments (current and proposed) and their molecular targets

Current Therapies				
Treatment	**Molecular Target**	**Investigated in RIAKI?**	**Investigation Stage**	**Reference(s)**
Intravenous Fluid	Tubular flow	Y	Current Recommended Treatment	(76)
Sodium Bicarbonate	Tubular pH, myoglobin precipitation	Y	Current Treatment at some centers	(76, 80)
Mannitol	Tubular flow, ROS	Y	Current Treatment at some centers	(76, 80)

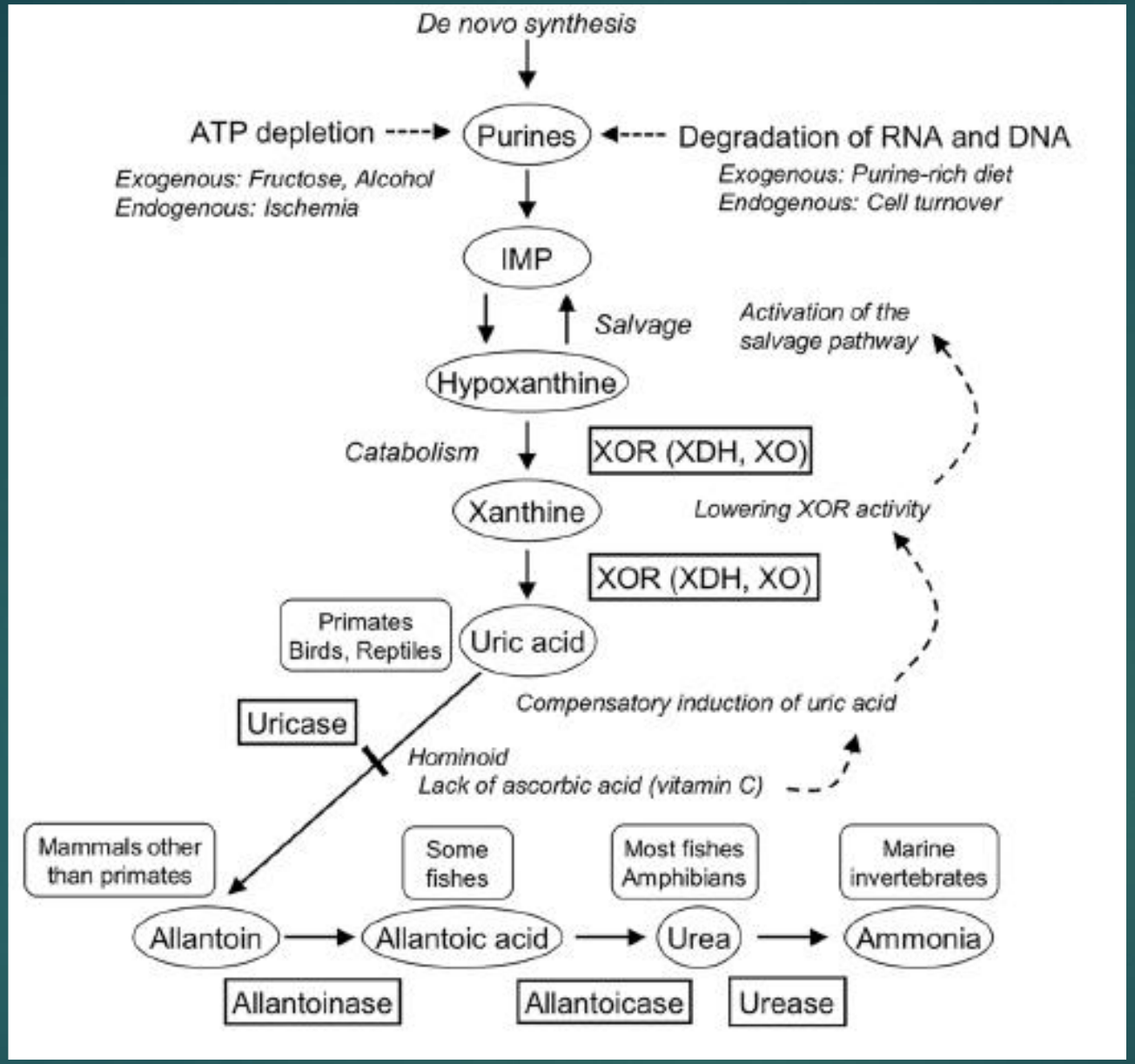
Jessica F., et al, *Kidney International Reports 2022*

RIAKI treatments (current and proposed) and their molecular targets

Treatment	Molecular Target	Investigated in RIAKI?	Investigation Stage	Reference(s)
Cilastatin	Megalin/Tubular Endocytosis	Y	Preclinical	(89, 90)
High Flux Dialysis	Myoglobin	Y	Phase I - NCT01467180	(129)
N Acetylcystine	Reactive oxygen species	Y	Phase II - NCT00391911	(94-96)
CytoSorb Device	Myoglobin	Y	Phase II - NCT02111018	(130, 131)
Peptidyl Arginine Deaminase	NET/MET formation	N - lupus	Preclinical	(132)
Brensocatib	Dipeptidyl peptidase-1	N - brochiectasis	Phase II - NCT03218917	(113)
Secukinumab	IL-17A	N - rheumatoid diseases	FDA approved for rheumatoid diseases	(133)
Lactoferrin	MET formation	Y	Preclinical	(134)
Anti-Mac-1 antibody	Mac-1	Y	Preclinical	(134)
Canakinumab	IL-1B	N - CKD	Phase III - NCT01327846	(104)
Anakinra	IL-1B	N - inflammation in CKD	Phase II - NCT00420290, Phase II - NCT02278562	(135)
Rilonacept	IL-1B	N - inflammation in CKD	Phase II - NCT00897715	(136)
Gevokizumab	IL-1B	N - Type 2 diabetic kidney disease	Phase II - EudraCT2013–003610–41	(137)

Uric Acid and the Kidney-Intruduction

- The end product of metabolism by which nitrogen sources are excreted is dependent on the animal species and can be in the form of ammonia, urea, or uric acid. For most mammals, urea is the final end product to excrete their nitrogen, but humans and certain primates still have relatively high uric acid levels due to the loss of uricase .
- Humans have higher serum uric acid levels compared to most mammals due to a mutation in the uricase gene. Uricase is an enzyme that degrades uric acid, and most mammals that express uricase maintain serum uric acid levels in the 1 to 3 mg/dl range. However, the great apes and humans lost uricase through a series of mutations that progressively reduced activity of uricase until it was completely silenced around 15 million years ago . The consequence was an increase in serum uric acid to the 3 to 4 mg/dl range, which then has subsequently increased with western diets rich in fructose-laden sugars and purines.
- It has been hypothesizedthat uric acid might confer benefits of being neuroprotective and hold antioxidant properties. In addition, high levels have other implications for human clinical health.



Furuhashi M. New insights into purine metabolism in metabolic diseases: role of xanthine oxidoreductase activity. Am J Physiol Endocrinol Metab. 2020 Nov

Hyperuricemia and CKD

- From a pathophysiological standpoint, the dual relationship between increasing serum uric acid values and GFR reduction makes for a complex scenario, wherein hyperuricemia may be botha promoter and simply a result of kidney damage.
- the nephroprotective effect of treating hyperuricemia has been debated in the last years. In fact, until recently, available literature on this issue was limited to small size, often non-randomized single-centre trials, with a limited follow-up time.

Observational studies of hyperuricemia and CKD

Country	Population	Design (follow-up yr)	Finding	Study
Japan	6,403 Adults, healthy	Prospective cohort (6.75)	SUA >6.0 mg/dL was an independent predictor of ESRD in women (HR, 5.77)	Iseki et al. (2004) [99]
Thailand	3,499 Adults, healthy	Prospective cohort (12)	SUA >6.3 mg/dL associated with risk of development of decreased kidney function (OR, 1.82)	Domrongkitchaiporn et al. (2005) [90]
USA	5,808 Adults, healthy	Prospective cohort (6.9)	SUA was strongly associated with prevalence but weakly with progression of CKD (OR, 1.49)	Chonchol et al. (2007) [91]
Austria	21,457 Adults, healthy	Prospective cohort (7)	SUA >7 mg/dL increased CKD risk (OR, 1.74), >9.0 mg/dL (OR, 3.12)	Obermayr et al. (2008) [92]
USA	675 Type 1 DM	Cross-sectional	SUA in the high-normal range is associated with impaired renal function	Rosolowsky et al. (2008) [88]
USA	177,570 Adults, healthy	Prospective cohort (25.7)	Higher quartile of SUA conferred 2.14-fold increased risk of ESRD	Hsu et al. (2009) [93]
Italy	900 Adults, healthy	Prospective cohort (5)	Each 1 mg/dL increase in SUA increased risk of reduced eGFR (HR, 1.28)	Bellomo et al. (2010) [94]
Japan	7,078 Adults, healthy	Prospective cohort (5)	SUA level is an independent predictor of CKD onset (OR, 1.15)	Sonoda et al. (2011) [95]
Italy	1,449 Type 2 DM	Prospective cohort (5)	1-SD increment in SUA was associated with a 21% increased risk of CKD.	Zoppini et al. (2012) [89]
Japan	803 Adults, CKD stage 3–4	Retrospective cohort (4) Propensity score analysis	UA >6.5 mg/dL increased ESRD risk (HR, 2.39)	Uchida et al. (2015) [96]
USA	627 Children, CKD (median GFR 58.1 mL/min/1.73 m^2)	Prospective cohort (5)	SUA >7.5 mg/dL is an independent risk factor for faster progression of CKD in children and adolescents	Rodenbach et al. (2015) [97]
Korea	2,042 Adults, CKD stage 1–5	Prospective cohort (2.12)	Each 1 mg/dL increase in SUA increased the risk of progression to renal failure (HR, 1.277)	Oh et al. (2019) [98]

RCTs on the effectiveness of urate-lowering treatment on renal function in patients with chronic kidney disease

Study	Study design	Study drug	Population	Duration (months)	Change in renal function in T group	Change eGFR in C group	P	Other renal outcomes
Siu *et al.* 2006 [10]	Parallel, placebo RCT	Allopurinol ($n = 25$) *versus* usual therapy ($n = 26$)	Hyperuricemic patients with CKD defined as proteinuria >0.5 g and/or an sCr >1.35 mg/dL)	12	sCr +1.03 mg/dL	sCr +0.35 mg/dL	0.08	Combined endpoint of significa deterioration in renal function a dialysis: 16% in T and 46.1% in C ($P = 0.015$)
Malaguarnera *et al.* 2009 [11]	Parallel, placebo RCT	Rasburicase ($n = 20$) *versus* placebo ($n = 18$)	Hyperuricemic elderly patient	2	ClCr +12.7 mL/min	ClCr −0.9 mL/min	<0.001	
Goicoechea *et al.* 2010 [12]	Parallel RCT	Allopurinol ($n = 57$) *versus* usual therapy ($n = 56$)	CKD (eGFR <60 mL/min × 1.73 m^2)	24	eGFR +1.3 mL/min × 1.73 m^2	eGFR −3.3 mL/min × 1.73 m^2	0.018	
Momeni *et al.* 2010 [13]	Parallel, placebo RCT	Allopurinol ($n = 20$) *versus* placebo ($n = 20$)	Diabetic patients with nephropathy (proteinuria >500 mg/d and sCr <3 mg/dL)	4	sCr +0.00 mg/dL	sCr +0.3 mg/dL	0.180	
Shi *et al.*, 2012 [14]	Parallel, RCT	Allopurinol (n=21) *versus* usual therapy ($n = 19$)	Hyperuricemic IgAN patient, non-nephrotic, sCr <3 mg/dL	6	eGFR +3.7 mL/min × 1.73 m^2	eGFR +5.3 mL/min × 1.73 m^2	0.200	
Goicoechea *et al.* 2015 [15]	Post-hoc follow-up RCT	Allopurinol ($n = 56$) *versus* usual therapy ($n = 51$)	CKD (eGFR <60 mL/min × 1.73 m^2)	84	eGFR −6.5 mL/min × 1.73 m^2	eGFR −13.3 mL/min × 1.73 m^2	0.001	Renal event (defined as starting dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in eGFR) [hazard ratio 0.32 (95% confidence interval 0.15–0.69) P = 0.004]
Tani *et al.* 2015 [16]	Prospective, Open-label study	Febuxostat ($n = 30$) *versus* no treatment ($n = 30$)	Hyperurecemic patients with hypertension	6	eGFR +3.7 mL/min × 1.73 m^2	eGFR −3.4 mL/min × 1.73 m^2	0.006	
Sircar *et al.* 2015 [17]	Parallel, placebo RCT	Febuxostat ($n = 45$) *versus* no treatment ($n = 48$)	Adults 18–65 years with CKD stages 3 and 4, with asymptomatic hyperuricemia	6	eGFR + 3.2 mL/min × 1.73 m^2	eGFR −4.4 mL/min × 1.73 m^2	0.05	>10% decline in eGFR: 38% in T and 54% in C ($P < 0.004$)
Tanaka *et al.* 2015 [18]	Parallel, open-label RCT	Febuxostat ($n = 21$) *versus* usual therapy ($n = 19$)	Hyperuricemic patients with CKD stage 3	3	eGFR −1.3 mL/min × 1.73 m^2	eGFR −0.4 mL/min × 1.73 m^2	NS	
Saag *et al.* 2016 [19]	Parallel, placebo RCT	Febuxostat 30 mg BID ($n = 17$) *versus* Febuxostat (40–80 mg/d ($n = 25$) *versus* placebo ($n = 15$)	Hyperuricemic patients with gout and moderate-to-severe renal impairment (eGFR 15–50 mL/min × 1.73 m^2), gout and hypertension	12	sCr +0.09 mg/dL (T 30 mg BID)	sCr +0.19 mg/dL	0.459	

Goicoechea *et al.* 2015 [15]	Post-hoc follow-up RCT	Allopurinol ($n = 56$) *versus* usual therapy ($n = 51$)	CKD (eGFR <60 mL/min × 1.73 m^2)	84	eGFR −6.5 mL/min × 1.73 m^2	eGFR −13.3 mL/min × 1.73 m^2	0.001	Renal event (defined as starting dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in eGFR) [hazard ratio 0.32 (95% confidence

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

Hyperuricemia

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)

The NEW ENGLAND JOURNAL of MEDICINE

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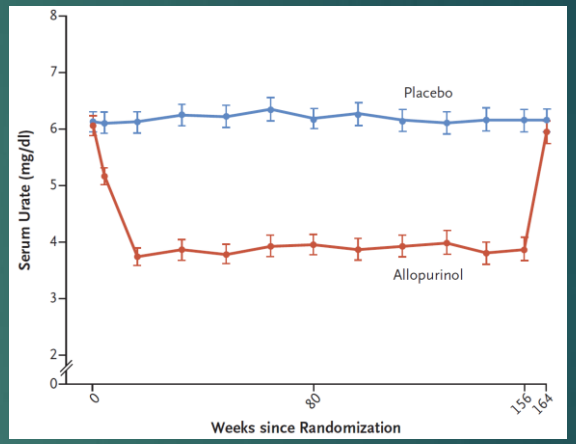
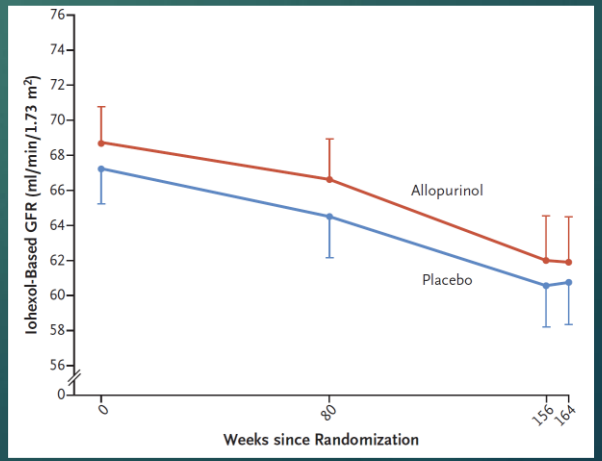
Serum Urate Lowering with Allopurinol and Kidney Function in Type 1 Diabetes

- **Preventing Early Renal Loss in Diabetes (PERL) Trial**
- **USA, CANADA,DENMARK**
- A total of 267 patients were assigned to receive allopurinol and 263 to receive placebo(530). The mean age was 51.1 years, the mean duration of diabetes 34.6 years,and the mean glycated hemoglobin level 8.2%.
- The mean baseline iohexol-based GFR was 68.7 ml per minute per 1.73 m2 in the allopurinol group and 67.3 ml per minute per 1.73 m2 in the placebo group.
- During the intervention period, the mean serum urate level decreased from 6.1 to 3.9 mg per deciliter with allopurinol and remained at 6.1 mg per deciliter with placebo.
- After washout, the between-group difference in the mean iohexol-based GFR was 0.001 ml per minute per 1.73 m2 (95% confidence interval [CI], −1.9 to 1.9; P = 0.99).
- We found no evidence of clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with type 1 diabetes and early-to-moderate diabetic kidney disease.



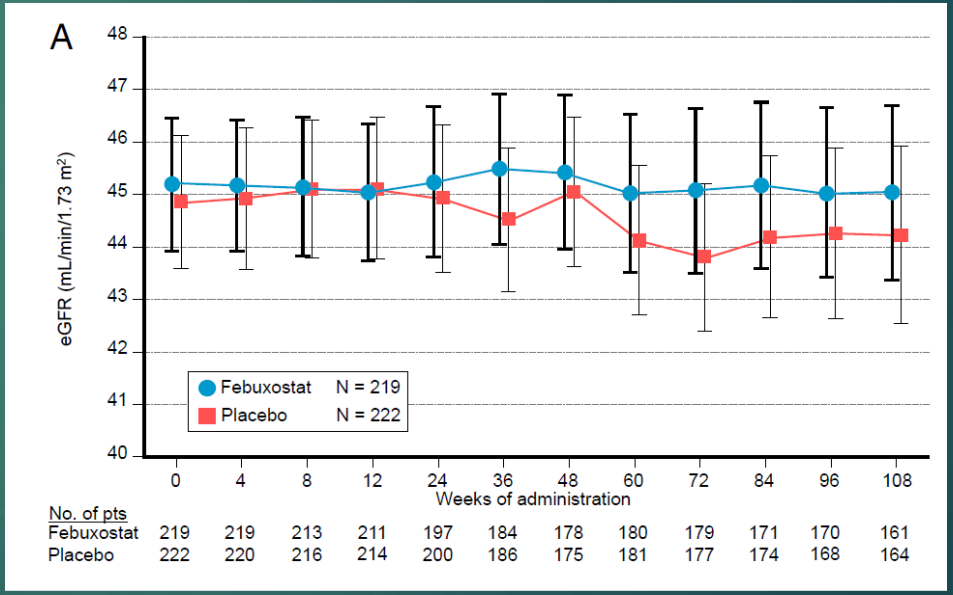


AJKD

Original Investigation

Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

- on behalf of the FEATHER Study(2012)
- Of 443 patients who were randomly assigned, 219 and 222 assigned to febuxostat and placebo, respectively, were included in the analysis.
- There was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; P = 0.1).



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ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

The Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase **(CKD-FIX)**

- **Population (363) (AUSTRALIA)**

• CKD stage 3 or 4 (eGFR 15 to 59 ml/min/1.73 m2)

• UACR 265 mg/g

- **Intervention**

Oral placebo or Allopurinol: minimum of 100 mg/day

- Increased every 4 weeks to a maximum of 3 tablets daily

- **Mean baseline urate level**

8.2 — 1.8 mg/dl

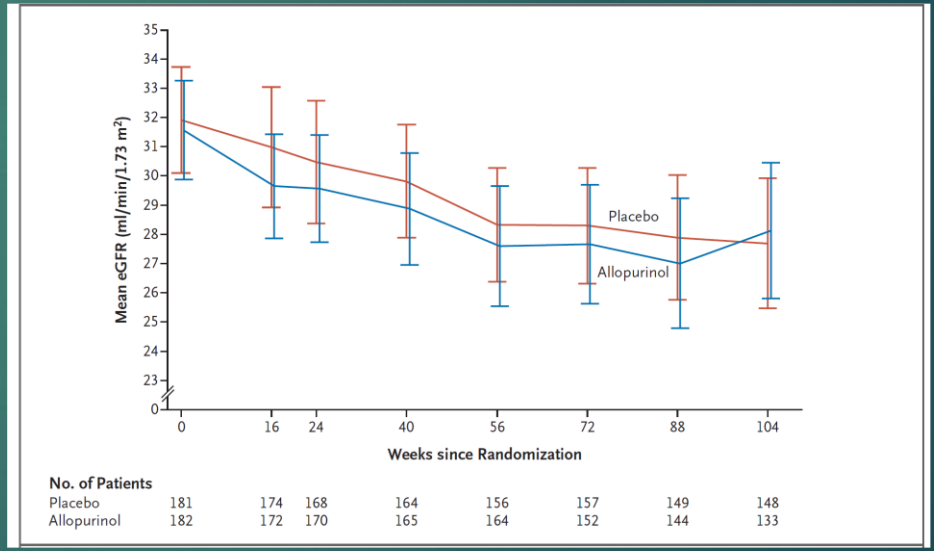
- **Serum urate level post-allopurinol**

5.1 mg/dl (300 µmol/l)

- **Change in GFR**

• Placebo\: − 3.23 ml/min/1.73 m2/ year

• Allopurinol\: − 3.33 ml/min/1.73 m2/year



ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

- **However, initiating ULT is conditionally recommended for patients with comorbid moderate-to-severe CKD (stage ≥3), SU concentration >9 mg/dl, or urolithiasis.**
- **The choice of pegloticase as a first-linetherapy is strongly recommended *against.***
- **Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD[stage ≥3]) and febuxostat (≤40 mg/day) with subsequentdose titration over starting at a higherdose is strongly recommended.**
- **Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is conditionally recommended.**