The impact of UA-lowering therapies on the risk of frailty among nephrology patients

Jui Wang, PhD, Chia-Ter Chao, MD, PhD

National Taiwan University

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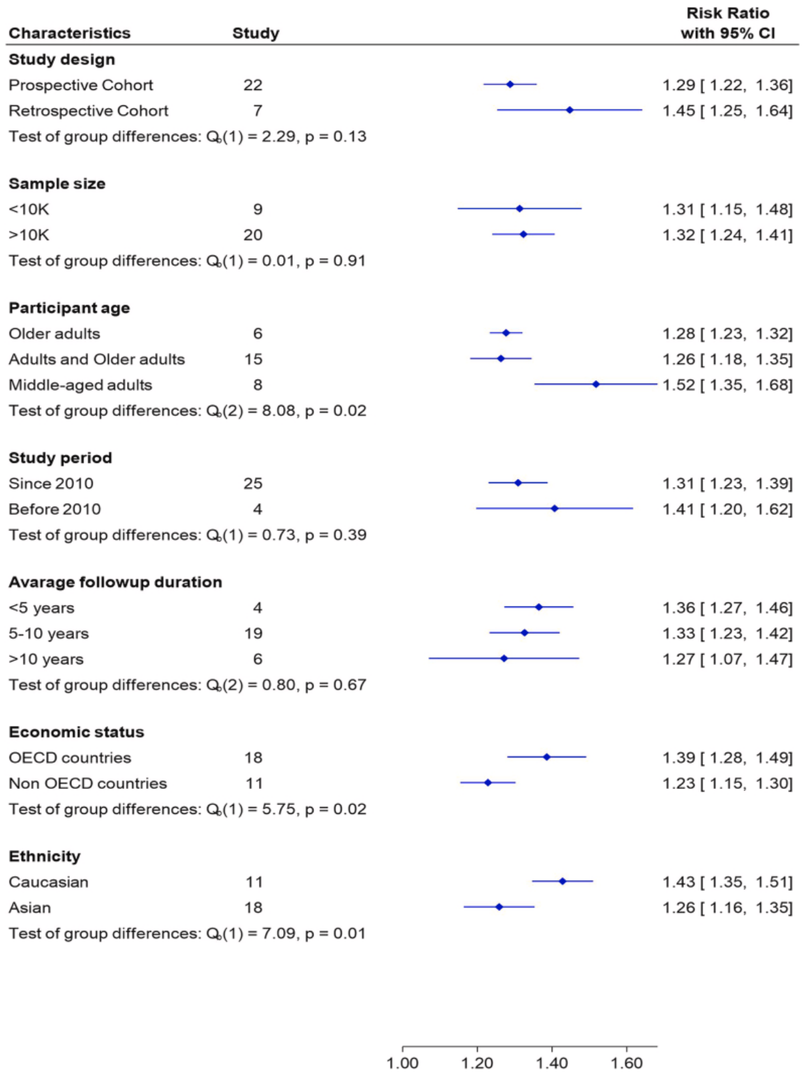
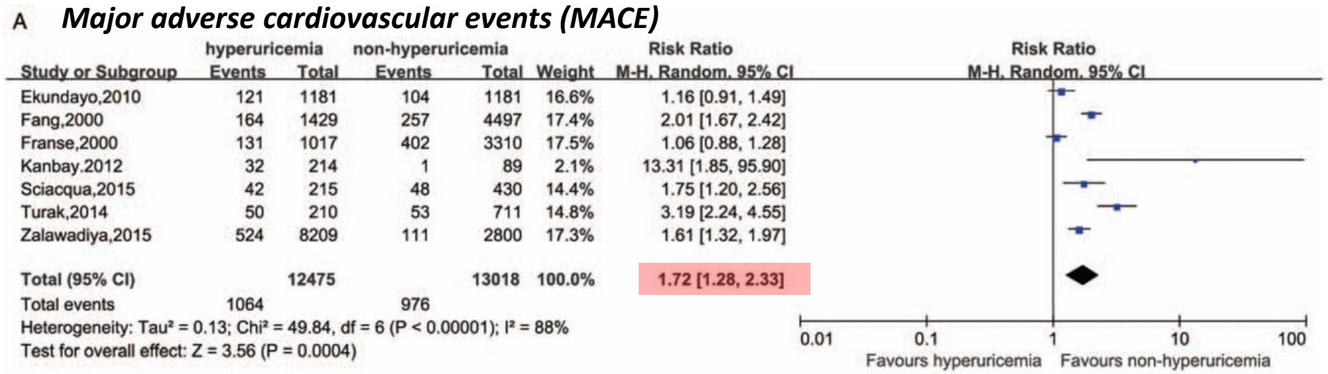
Hyperuricemia is associated with higher mortality and CV risk



Rabbani MG et. al. Metabol Open. 2025 May 16;26:100371.

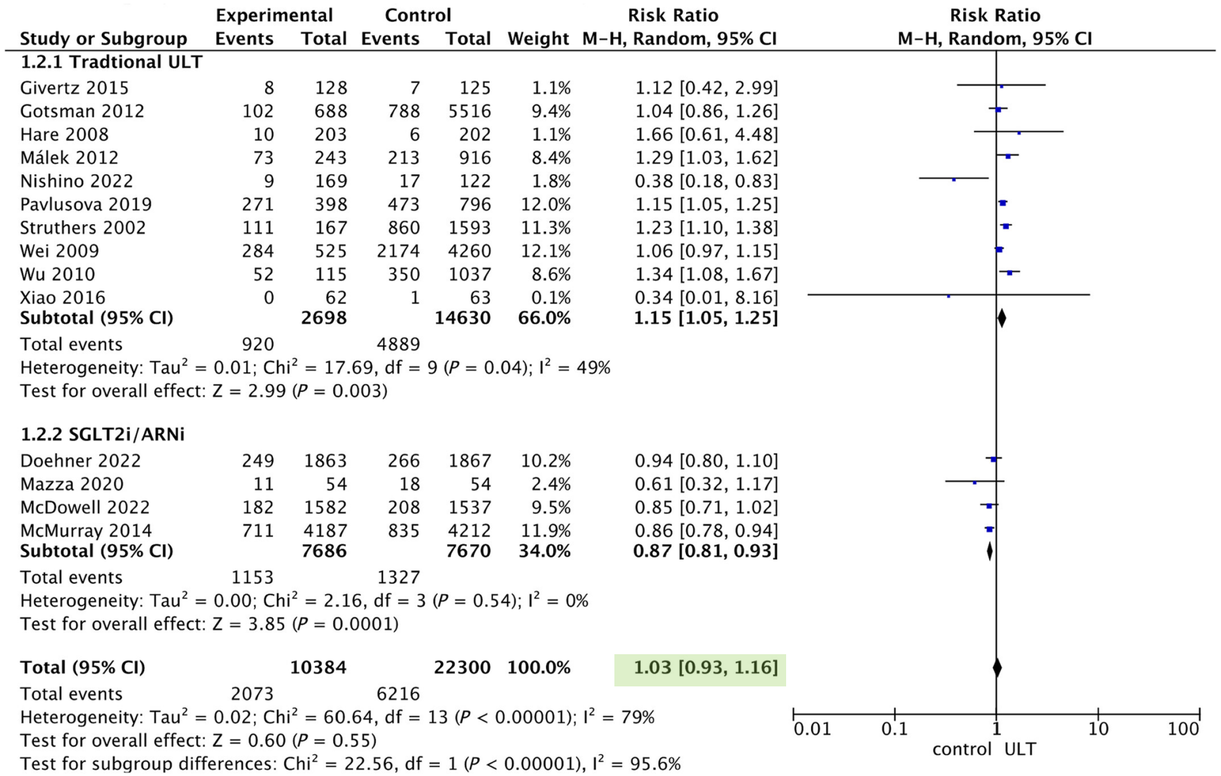
Meta-analysis of 29 studies reported that higher serum uric acid (SUA) levels were significantly associated with an increased risk of all-cause mortality.



Meta-analysis of 7 prospective cohort studies reported that hyperuricemia was associated with a higher risk of MACE.

Zhao L. et. al. Chin Med J (Engl). 2020 Apr 20;133(8):982-993.

However, UA-lowering does not always improve outcomes…



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Tradtional ULT						
Givertz 2015	8	128	7	125	1.1%	1.12 [0.42, 2.99]
Gotsman 2012	102	688	788	5516	9.4%	1.04 [0.86, 1.26]
Hare 2008	10	203	6	202	1.1%	1.66 [0.61, 4.48]
Málek 2012	73	243	213	916	8.4%	1.29 [1.03, 1.62]
Nishino 2022	9	169	17	122	1.8%	0.38 [0.18, 0.83]
Pavlusova 2019	271	398	473	796	12.0%	1.15 [1.05, 1.25]
Struthers 2002	111	167	860	1593	11.3%	1.23 [1.10, 1.38]
Wei 2009	284	525	2174	4260	12.1%	1.06 [0.97, 1.15]
Wu 2010	52	115	350	1037	8.6%	1.34 [1.08, 1.67]
Xiao 2016	0	62	1	63	0.1%	0.34 [0.01, 8.16]
Subtotal (95% CI)		**2698**		**14630**	**66.0%**	**1.15 [1.05, 1.25]**
Total events	920		4889			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 17.69$, df = 9 ($P = 0.04$); $I^2 = 49\%$						
Test for overall effect: Z = 2.99 ($P = 0.003$)						
1.2.2 SGLT2i/ARNi						
Doehner 2022	249	1863	266	1867	10.2%	0.94 [0.80, 1.10]
Mazza 2020	11	54	18	54	2.4%	0.61 [0.32, 1.17]
McDowell 2022	182	1582	208	1537	9.5%	0.85 [0.71, 1.02]
McMurray 2014	711	4187	835	4212	11.9%	0.86 [0.78, 0.94]
Subtotal (95% CI)		**7686**		**7670**	**34.0%**	**0.87 [0.81, 0.93]**
Total events	1153		1327			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.16$, df = 3 ($P = 0.54$); $I^2 = 0\%$						
Test for overall effect: Z = 3.85 ($P = 0.0001$)						
Total (95% CI)		**10384**		**22300**	**100.0%**	**1.03 [0.93, 1.16]**
Total events	2073		6216			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 60.64$, df = 13 ($P < 0.00001$); $I^2 = 79\%$						
Test for overall effect: Z = 0.60 ($P = 0.55$)						
Test for subgroup differences: $Chi^2 = 22.56$, df = 1 ($P < 0.00001$), $I^2 = 95.6\%$						

Uric acid–lowering therapies have been proposed as a strategy to improve outcomes.

However, results remain inconsistent: some studies suggest modest cardiovascular benefit, while others report neutral effects.

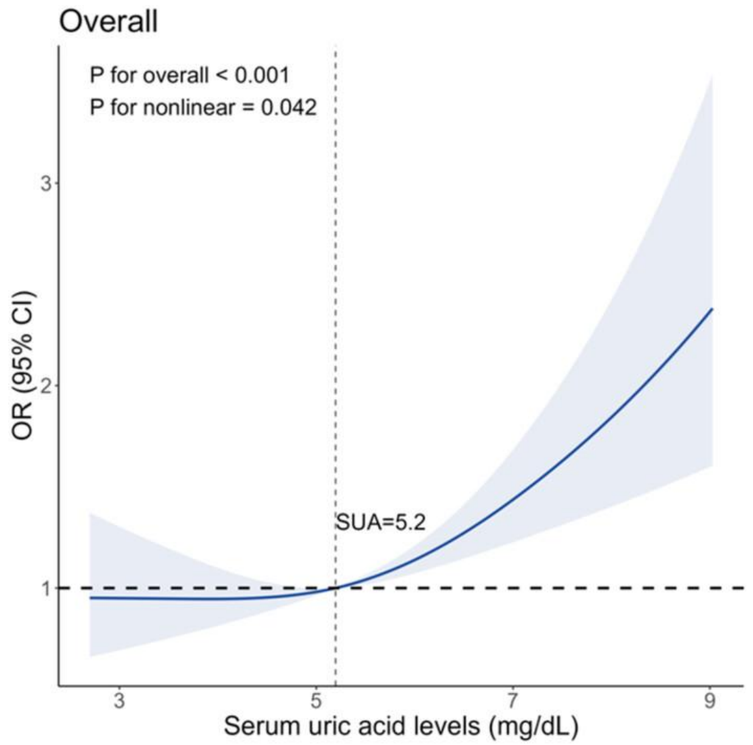
Qin S. et. al. ESC Heart Fail. 2024 Feb;11(1):78-90.

Higher SUA independently correlate with muscular loss

Beyond cardiometabolic outcomes, hyperuricemia may also influence musculoskeletal health.

Elevated uric acid has been implicated in muscle, joint, and bone degeneration through oxidative stress, crystal deposition, and inflammation.

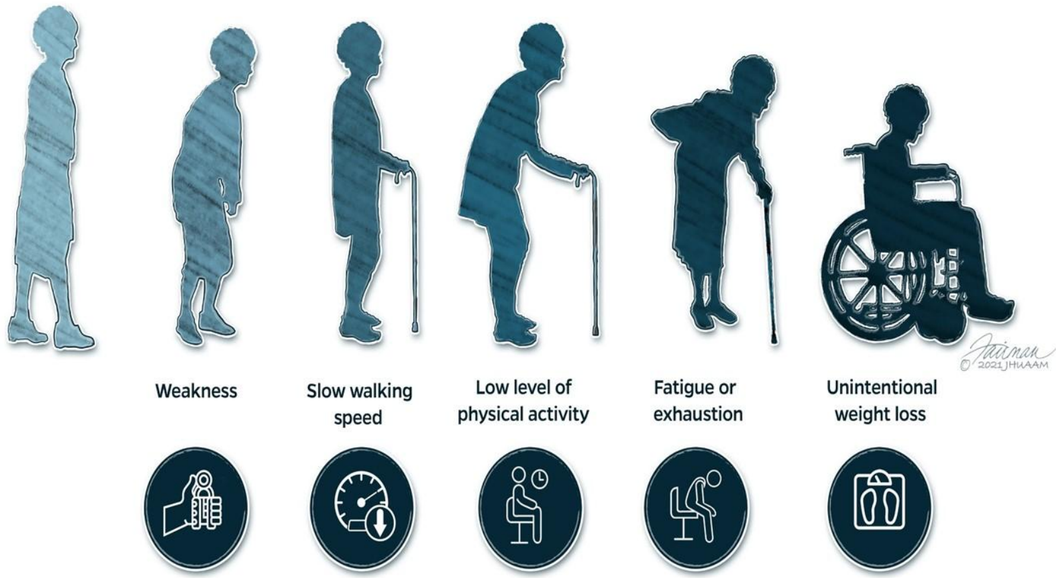
Preliminary studies suggest that UA-lowering therapies may reduce these harmful processes and possibly support muscle recovery.



Wang F. et. al. J Cachexia Sarcopenia Muscle. 2025 Jun;16(3):e13867.

Frailty

- Given that musculoskeletal function is closely related to frailty, a geriatric syndrome describing an individual's increased vulnerability and the associated adverse outcome influences, may serve as a surrogate for physical function.



- Frailty and cardiovascular disease are strongly interrelated. CVD contributes to frailty through physiological, structural, and lifestyle pathways.

https://www.hopkinsmedicine.org/news/newsroom/news-releases/2021/03/multisystem-failure-regarding-frailty-necessitates-multisystem-intervention

Study hypothesis

- Higher serum uric acid strongly associated with low muscle mass, and possibly lower grip strengths.

- Whether UA-lowering treatment confers benefit for frailty remains unknown.

- We hypothesized that UA-lowering therapies might affect frailty risk. Given that CKD and other kidney disorders increase the likelihood of abnormal UA levels, we used a large cohort of nephrology patients to test this hypothesis.

Methods and Results

Study population

Population:

Patients from the NTUH integrated Medical Database (NTUH-iMD) who attended general medicine clinics between 2006 and 2021

Exclusion:

Individuals who never attended a nephrology clinic

Individuals who first visited a nephrology clinic before January 1, 2013

Individuals who had frailty, the primary outcome of interest, before the index date

Individuals who lacked available estimated glomerular filtration rate (eGFR) or UA data

Individuals who had no follow-up after the index date

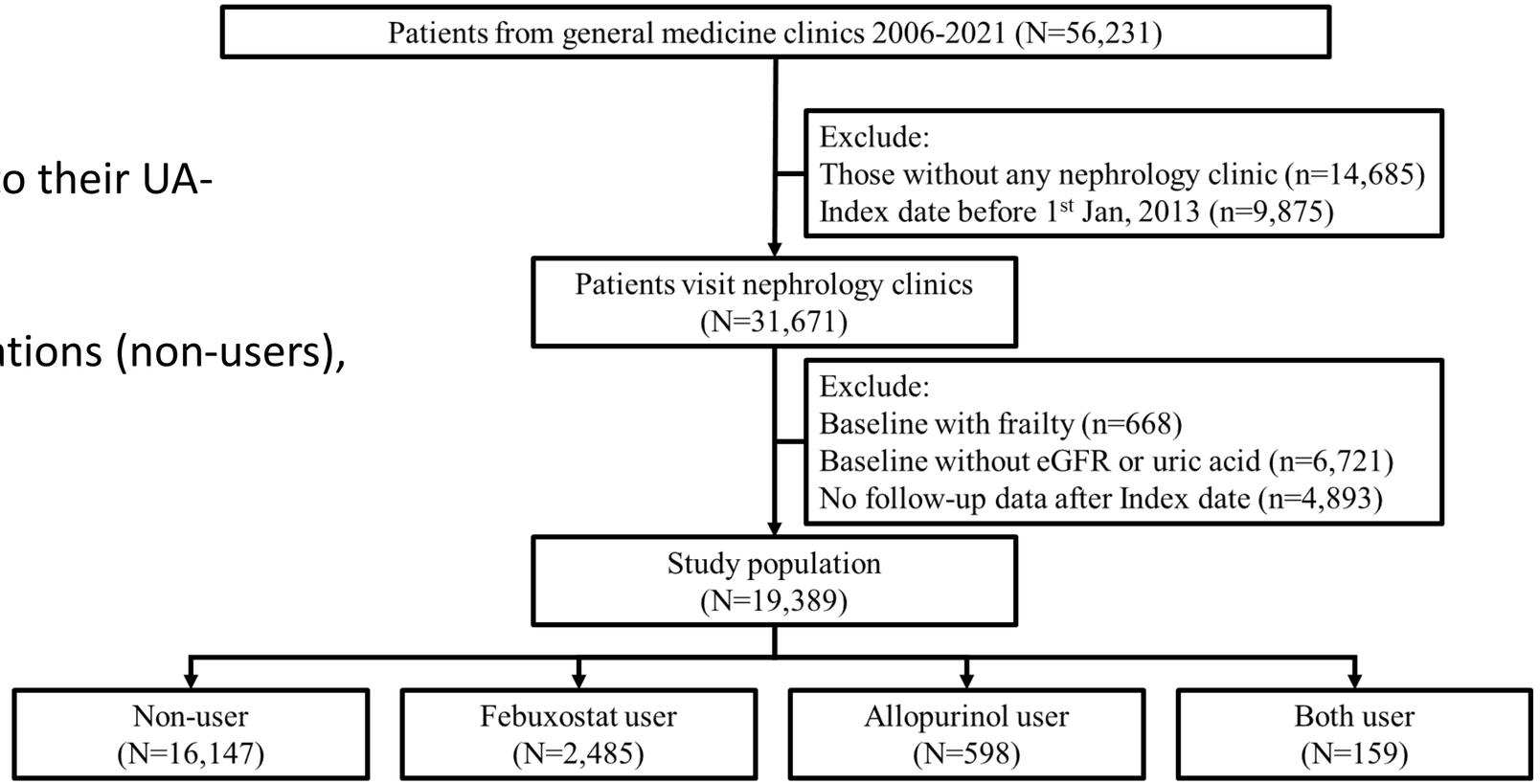
Study flow

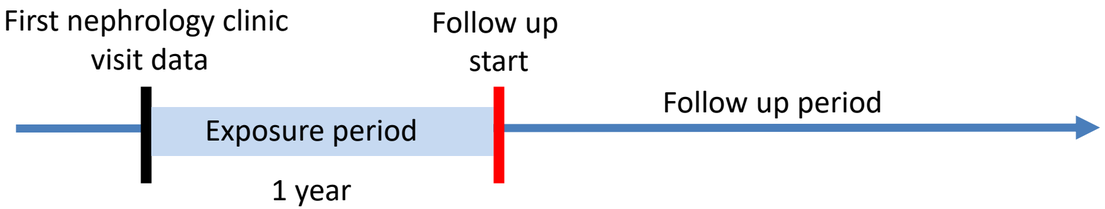
Exposures:

We divided participants according to their UA-lowering regimens, into those who

1. did not receive any such medications (non-users),
2. febuxostat users
3. allopurinol users
4. concurrent users

before the index date.





Outcomes

Outcomes:

The outcomes were incident frailty and worsening frailty during follow up.

Frailty was defined by the fatigue, resistance, ambulation, illness, and loss of weight (FRAIL) scale, a well-established frailty-assessing instrument among older adults and individuals with chronic diseases.

Individuals with ≥3 out of a total 5 are deemed frail, whereas those with ≥1-point increase during follow-up compared to baseline were considered to have worsening frailty.

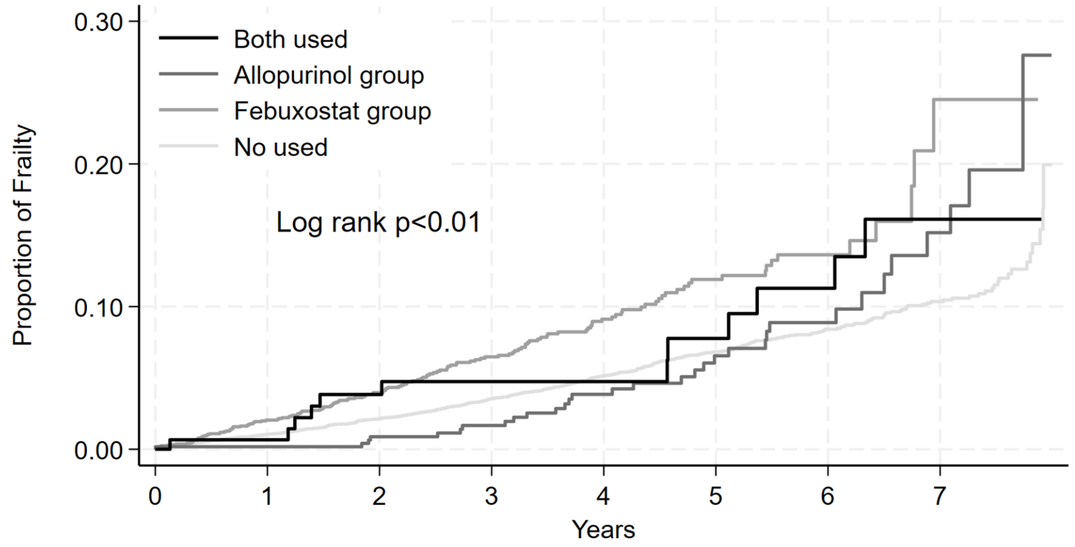
FRAIL Scale	
Fatigue	How much time during the previous 4 weeks did you feel tired? (all of the time, most of the time = 1 points)
Resistance	Do you have any difficulty walking up 10 steps alone without resting and without aids? (Yes = 1 point)
Ambulation	Do you have any difficulty walking several hundred years alone with without aids? (Yes = 1 point)
Illness	How many illnesses do you have out of a list of 11 total? (5 or more = 1 point)
Loss of weight	Have you had weight loss of 5% or more? (Yes = 1 point)
(The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease).	

Comparison of clinical features

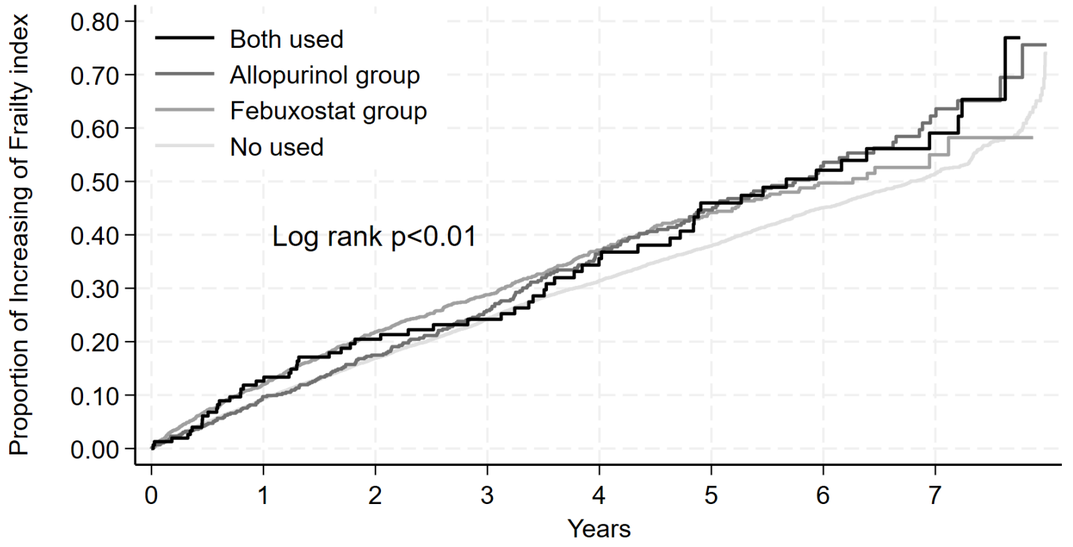
	Total population		Uric acid medication								
			No used		Febuxostat user		Allopurinol user		Both user		
	N=19389		N=16147		N=2485		N=598		N=159		
	n	%	n	%	n	%	n	%	n	%	p-value
Age (mean±SD)	64.70	15.55	64.08	15.66	67.91	14.58	67.59	14.78	66.32	15.02	<.0001
<50	3439	17.74	3037	18.81	314	12.64	66	11.04	22	13.84	<.0001
50-64	5601	28.89	4765	29.51	619	24.91	170	28.43	47	29.56	
>=65	10349	53.38	8345	51.68	1552	62.45	362	60.54	90	56.60	
BMI (mean±SD)	25.04	4.55	24.89	4.54	25.82	4.57	25.71	4.32	25.45	4.23	<.0001
Gender											<.0001
Women	8803	45.40	7850	48.62	767	30.87	151	25.25	35	22.01	
Men	10586	54.60	8297	51.38	1718	69.13	447	74.75	124	77.99	
Comorbidities											
Hypertension	15794	81.46	12760	79.02	2336	94.00	550	91.97	148	93.08	<.0001
Diabetes	8314	42.88	6550	40.56	1388	55.86	301	50.33	75	47.17	<.0001
Hyperlipidemia	9778	50.43	7785	48.21	1564	62.94	344	57.53	85	53.46	<.0001
Cardiovascular disease	6411	33.07	4970	30.78	1098	44.19	272	45.48	71	44.65	<.0001
Kidney stone	2482	12.80	2059	12.75	319	12.84	83	13.88	21	13.21	0.877
Chronic kidney disease											<.0001
Stage 1	3779	19.49	3719	23.03	24	0.97	33	5.52	3	1.89	
Stage 2	4895	25.25	4617	28.59	173	6.96	87	14.55	18	11.32	
Stage 3a	2883	14.87	2445	15.14	317	12.76	95	15.89	26	16.35	
Stage 3b	2848	14.69	2082	12.89	591	23.78	135	22.58	40	25.16	
Stage 4	2231	11.51	1388	8.60	670	26.96	125	20.90	48	30.19	
Stage 5	2753	14.20	1896	11.74	710	28.57	123	20.57	24	15.09	
Number of Frail index (mean±SD)	0.45	0.62	0.42	0.61	0.62	0.68	0.50	0.60	0.46	0.55	<.0001
Laboratory Tests (mean±SD)											
eGFR	57.83	37.57	63.06	37.88	29.70	20.14	39.30	27.07	35.98	21.04	<.0001
UA	6.40	2.25	6.41	2.21	6.06	2.45	7.42	1.85	6.84	2.46	<.0001
Medications											
Antihypertensive agents	12666	65.33	9960	61.68	2079	83.66	491	82.11	136	85.53	<.0001
Antidiabetic agents	6174	31.84	4741	29.36	1143	46.00	232	38.80	58	36.48	<.0001
Antidyslipidemic agents	5871	30.28	4508	27.92	1064	42.82	237	39.63	62	38.99	<.0001
Antiplatelet agents	5175	26.69	4019	24.89	869	34.97	235	39.30	52	32.70	<.0001
Anticoagulant agents	879	4.53	667	4.13	171	6.88	34	5.69	7	4.40	<.0001
NSAIDs	1546	7.97	1335	8.27	152	6.12	46	7.69	13	8.18	0.003

The no-use group had a younger age and a lower proportion of comorbidities and medication use.

Regression findings



Number at risk								
Both used	153	130	106	85	69	55	40	20
Allopurinol group	556	485	415	355	254	184	103	48
Febuxostat group	2484	1826	1339	915	582	329	134	18
No used	15570	12694	10146	7707	5385	3627	1893	838



Number at risk								
Both used	155	117	92	74	53	40	27	14
Allopurinol group	568	457	366	290	184	130	65	28
Febuxostat group	2485	1681	1136	742	439	233	97	16
No used	15764	11949	9037	6491	4305	2759	1398	596

	No. of event	Person years	Incidence density(1000 P-Ys)	HR	Model[a] 95%CI		p-value
Uric acid medication							
No used	698	54754.5	12.75	1.000	ref		
Febuxostat user	150	6318.4	23.74	1.221	1.010	1.477	0.039
Allopurinol user	32	2490.9	12.85	0.652	0.455	0.933	0.019
Both user	12	624.6	19.21	1.290	0.726	2.293	0.385

a.Adjusted for age, gender, comorbidities, medications, eGFR and UA

	No. of event	Person years	Incidence density(1000 P-Ys)	HR	Model[a] 95%CI		p-value
Uric acid medication							
No used	4328	47337.0	91.43	1.000	ref		
Febuxostat user	652	5480.2	118.97	1.051	0.962	1.148	0.273
Allopurinol user	213	2066.8	103.06	0.919	0.800	1.057	0.239
Both user	60	524.1	114.49	1.019	0.788	1.316	0.888

a.Adjusted for age, gender, comorbidities, medications, eGFR and UA

Main finding

- **In this large cohort of nephrology patients, we investigated whether UA-lowering therapies affect their risk of incident and worsening frailty.**

- **Febuxostat use was independently associated with an increased risk of incident frailty, whereas allopurinol use was associated with a reduced risk, after extensive confounder adjustment.**

Clinical implications

- **The link between febuxostat and incident frailty**
  - **Evidence suggests that febuxostat may be associated with an increased risk of frailty and cardiovascular issues, indicating the need for cautious use in vulnerable populations.**

- **The link between allopurinol and incident frailty**
  - **Allopurinol may confer multiple benefits, including ROS reduction, anti-inflammation, endothelial function improvement…**

- **A Potential Renaissance for Allopurinol in an Aging Society?**

Thank You

For Your Attention