

Supplementary Table S1. Probability of incident and worsening frailty using IPTW

Variables	HR	95% CI	<i>P</i> value
<i>Incident frailty</i>			
Non-users	1.000		
Febuxostat users	1.604	1.462 – 1.760	<i><0.001</i>
Non-users	1.000		
Allopurinol users	0.963	0.684 – 1.357	<i>0.831</i>
<i>Worsening frailty</i>			
Non-users	1.000		
Febuxostat users	1.045	1.003 – 1.089	<i>0.036</i>
Non-users	1.000		
Allopurinol users	1.127	0.988 – 1.287	<i>0.076</i>

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting

Supplementary Table S2. Negative outcome (urinary tract infection) incidence and probability analysis

Variables	Events	P	PYs	Cumulative incidence	Incidence density*	Crude		Model [#]	
						HR	95% CI	HR	95% CI
<i>UA-lowering treatments</i>									
Non-users	2,292	16,147	50,839.0	14.19%	45.08	1.000	-	1.000	-
Febuxostat users	313	2,485	5,984.8	12.60%	52.30	1.069	0.950-1.203	1.004	0.884-1.139
Allopurinol users	109	598	2,275.9	18.23%	47.89	1.118	0.923-1.355	1.122	0.923-1.364
Both users	26	159	576.0	16.35%	45.13	1.050	0.713-1.545	1.122	0.760-1.654

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; P, population; PY, person-year; UA, uric acid

* per 1000 patient-year

[#] Incorporating demographic, comorbidities, medications, FRAIL results, and laboratory data (eGFR and UA)

Supplementary Table S3. Incidence and probability of frailty development and worsening frailty according to the duration of UA-lowering treatment used

Variables	Events	P	PYs	Cumulative incidence	Incidence density*	Crude		Model [#]	
						HR	95% CI	HR	95% CI
<i>Frailty development</i>									
<i>Febuxostat</i>									
Non-users	698	16,147	54,754.5	4.32%	12.75	1.000	-	1.000	-
≤ median duration ^a	81	1,333	3,528.8	6.08%	22.95	1.895	1.504-2.387 ⁺⁺⁺	1.152	0.908-1.463
> median duration ^a	81	1,311	3,414.1	6.18%	23.72	1.965	1.559-2.475 ⁺⁺⁺	1.287	1.008-1.643 ⁺
						<i>P for trend <0.001</i>		<i>P for trend 0.0287</i>	
<i>Allopurinol</i>									
Non-users	698	16,147	54,754.5	4.32%	12.75	1.000	-	1.000	-
≤ median duration ^b	25	416	1,694.6	6.01%	14.75	1.128	0.757-1.682	0.852	0.570-1.275
> median duration ^b	19	341	1,420.9	5.57%	13.37	1.011	0.641-1.596	0.626	0.395-0.992 ⁺
						<i>P for trend 0.7538</i>		<i>P for trend 0.0351</i>	
<i>Worsening frailty</i>									
<i>Febuxostat</i>									
Non-users	4,328	16,147	47,337.0	26.80%	91.43	1.000	-	1.000	-
≤ median duration ^a	344	1,333	3,049.3	25.81%	112.81	1.237	1.109-1.381 ⁺⁺⁺	0.995	0.889-1.115
> median duration ^a	368	1,311	2,955.0	28.07%	124.54	1.367	1.229-1.521 ⁺⁺⁺	1.102	0.984-1.234
						<i>P for trend <0.001</i>		<i>P for trend 0.1451</i>	
<i>Allupurinol</i>									

Non-users	4,328	16,147	47,337.0	26.80%	91.43	1.000	-	1.000	-
≤ median duration ^b	135	416	1,451.8	32.45%	92.99	1.014	0.854-1.204	0.843	0.709-1.003
> median duration ^b	138	341	1,139.0	40.47%	121.15	1.325	1.118-1.570 ^{††}	1.016	0.855-1.206
<i>P for trend 0.0037</i>							<i>P for trend 0.4874</i>		

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; P, population; PY, person-year; UA, uric acid

^{*} per 1000 patient-year

[#] Incorporating demographic, comorbidities, medications, FRAIL results, and laboratory data (eGFR and UA)

^a161 days; ^b140 days

[†] $p < 0.05$; ^{††} $p < 0.01$; ^{†††} $p < 0.001$

Supplementary Table S4. Incidence and probability of frailty development and worsening frailty

Variables	Incidence density*	Crude		Model 2 [@]		Model 3 [%]		Model 4 ^{&}	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
<i>Frailty development</i>									
Non-users	12.75	1.000	-	1.000	-	1.000	-	1.000	-
Febuxostat users	23.74	1.992	1.668-2.381 ⁺⁺⁺	1.183	0.977-1.433 ^a	1.187	0.981-1.435 ^b	1.086	0.894-1.320
Allopurinol users	12.85	0.974	0.684-1.389	0.642	0.448-0.919 [†]	0.638	0.445-0.913 [†]	0.713	0.493-0.999 [†]
Both users	19.21	1.479	0.836-2.617	1.259	0.708-2.239	1.262	0.710-2.243	1.310	0.735-2.335
<i>Worsening frailty</i>									
Non-users	91.43	1.000	-	1.000	-	1.000	-	1.000	-
Febuxostat users	118.97	1.307	1.203-1.420 ⁺⁺⁺	1.041	0.953-1.138	1.017	0.930-1.111	0.972	0.888-1.064
Allopurinol users	103.06	1.126	0.982-1.293	0.917	0.797-1.054	0.902	0.784-1.037	0.933	0.814-1.069
Both users	114.49	1.250	0.969-1.612	1.019	0.788-1.317	0.997	0.772-1.288	1.047	0.820-1.337

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UA, uric acid

* per 1000 patient-year

[@] Incorporating Model 1 variables, with blood pressure-lowering drugs divided according to types

[%] Incorporating Model 1 variables, but eGFR calculated using the CKD-EPI formula

[&] Incorporating Model 1 variables, using death as competing risk event, in combination with Models 2 and 3 variables

[†] $p < 0.05$; ⁺⁺⁺ $p < 0.001$

$$^ap = 0.085; ^bp = 0.077; ^cp = 0.062$$