

Title: Serum urate outcome of treat-to-target urate lowering treatment: results of nationwide cohort study from 1997 to the COVID-19 pandemic using data from the Clinical Practice Research Datalink.

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Despite long-standing recommendations¹⁻³ most gout patients prescribed urate lowering treatment (ULT) do not achieve serum urate (SU) target⁴. The time between treat-to-target (T2T) recommendations and achievement of SU treatment target, and how the latter was impacted by the COVID-19 pandemic has not been evaluated. We used UK-wide nationally-representative primary-care data from the Clinical Practice Research Datalink (CPRD) GOLD to evaluate temporal trends in achievement of T2T-SU levels within 12-month of first ULT prescription in successive years from 1997 to 2020. CPRD contains anonymized healthcare records from >18 million individuals, originating during their routine care in the NHS, a health-care system with universal coverage⁵.

This study spanned 01/01/1997 to 31/12/2021. Prevalent gout cases age ≥ 18 years, first prescribed ULT in the study-period were followed from the first prescription to earliest of prescription end, death, transfer out, last data collection, 12-months after ULT prescription or 31/12/2021. Participants were required to have ≥ 1 -year ULT-prescription free registration prior to study entry to prevent prevalent ULT users appearing as new users. Gout and ULT prescription status were defined using Read and product codes⁶.

Prevalence (95% confidence intervals (CI)) of achieving SU < 360 and < 300 $\mu\text{mol/L}$ within 12-months of ULT initiation were calculated. The latest SU within 12-month of ULT initiation was used to define achievement of target thresholds. Cox proportional hazard ratios (HR) with 95% CI were used to estimate the likelihood of achieving SU target for patients starting ULT in each year compared with those starting in the year 2006 as the first British Society for Rheumatology gout guidelines were published in 2007. Analyses were adjusted for age, time between first primary-care consultation

for gout and first ULT prescription, sex, and region. Sensitivity analysis included additional adjustment for pre-ULT SU. Data were analysed using Stata-MP-v16.

Data for 119,903 gout patients (77.19% men) were included ([Figure-S1](#)). Their mean (standard deviation (SD)) age and time from first gout consultation to ULT prescription was 63.09 (15.06) and 2.54 (5.14) years. 99.32%, 0.50% and 0.18% were prescribed allopurinol, febuxostat and uricosurics respectively. 34,137 (28.47%) and 18,926 (15.78%) achieved SU <360 and <300 $\mu\text{mol/L}$ respectively. Among the 73,657 participants prescribed ULT in 2007 or later, 23,446 (31.83%) and 12,630 (17.15%) achieved SU <360 and <300 $\mu\text{mol/L}$, after mean (SD) 1.05 (1.73) and 1.44 (2.95) years. The median (inter-quartile range (IQR)) allopurinol dose at treatment start was 100(100-300) mg/day (n=107,214). Participants that achieved and did not achieve SU <300 $\mu\text{mol/L}$ by 1-year were prescribed Allopurinol at median (IQR) dose of 300(200-300) and 200(100-300) mg/day ($p < 0.0001$, Wilcoxon rank-sum test). Similarly, participants that achieved and did not achieve SU <360 $\mu\text{mol/L}$ at 1-year were prescribed allopurinol at median (IQR) dose of 300(100-300) and 200(100-300) mg/day ($p < 0.0001$, Wilcoxon rank-sum test). Increasing proportion of gout patients commenced on ULT in calendar years 1997 to 2018 achieved SU target ([Figure 1](#)). The age and SU at start of ULT increased modestly over time ([Table-S1](#)). 5228 (15.31%) and 2979 (15.74%) participants who achieved SU <360 and <300 $\mu\text{mol/L}$ by 12-month consulted their GP for gout flare subsequently, defined as Read code specific for gout flare or any consultation for gout and prescription colchicine, corticosteroids, or NSAIDs on the same or next date.

There was a 5-year lag between EULAR and BSR recommendations to treat gout to target before significant improvement in achievement of recommended SU treatment target was apparent. Compared to those prescribed ULT in 2006, participants

commenced on ULT in the year 2020 were significantly less likely to achieve SU <300 µmol/L (Figure-1, Table-S2).

This study evaluated T2T-ULT in consecutive annual new-prescription cohorts spanning 25-years. There was a sharp reduction in achievement of SU targets among those commenced on ULT in the year 2019 and 2020 potentially due to the impact of the COVID-19 pandemic. This was comparable to 37.2% reduction in healthcare utilisation during the pandemic reported in a systematic review, with 29.6% and 31.4% reduction in therapeutics and diagnostics respectively⁷. T2T-ULT prevents recurrent gout flares and our findings point to a potential epidemic of uncontrolled gout. The modest improvement in SU outcomes pre-pandemic was lost during the COVID-19 pandemic. As the pandemic resolves, additional efforts e.g. engagement with primary-care providers will be required to increase the use of T2T-ULT.

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Contributorship: AA conceived the idea for the study, contributed to the study design, performed the analysis, interpreted the results and critically reviewed the paper. AJA contributed to the study design, interpretation of the results and critically reviewed the paper. EC advised on interpretation of results and critically reviewed the paper. LT contributed to the study design, advised on the analysis and interpretation of the results and critically reviewed the paper. MM contributed to the study design and critically reviewed the paper.

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Data access: Data included in this study are available from the CPRD. The statistical codes may be obtained from the corresponding author on reasonable request.

Patient and public involvement: None.

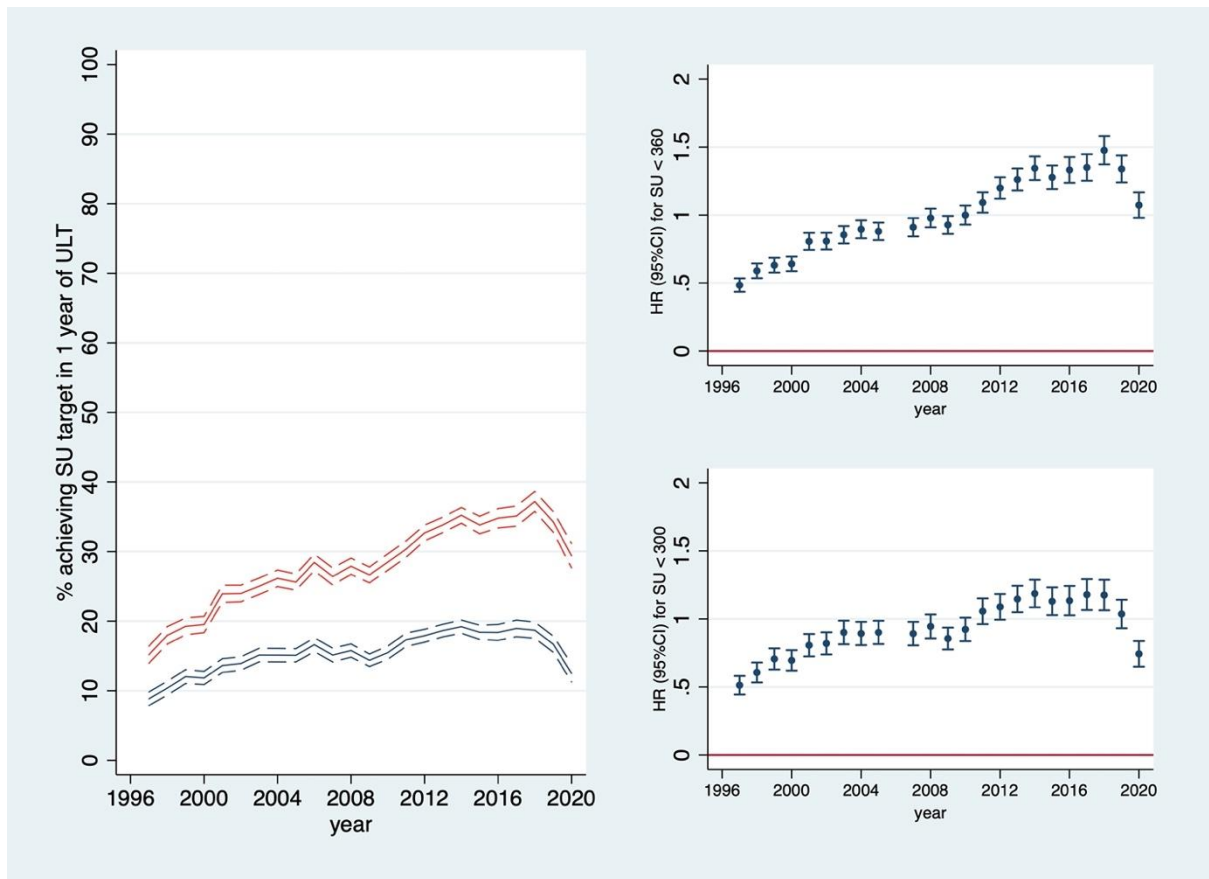


Figure 1: A. Left panel shows the proportion (solid line) and 95% confidence interval (CI, dotted line) of gout cases commenced on urate lowering treatment (ULT) in each calendar year that achieved serum urate (SU) treatment target <360 (red) and <300 (blue) $\mu\text{mol/L}$ within 1 year. B. Right panel adjusted hazard ratios (95% CI) for achieving SU outcomes <360 (top) and <300 (bottom) $\mu\text{mol/L}$ within 1 year in gout cases commenced on ULT in successive years with the year 2006 reference.

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Table S1: Serum urate (SU), age and severe gout at urate lowering treatment (ULT) start in patients commenced on ULT in successive calendar years.

Year	N	N (%) with SU pre-ULT	SU in $\mu\text{mol/L}$ mean (SD)	Age in years mean (SD)	N (%) with severe gout*
1997	3267	634 (19.41)	492.10 (118.18)	61.91 (14.59)	90 (2.75)
1998	3613	849 (23.50)	502.33 (107.09)	62.20 (14.56)	92 (2.55)
1999	4097	1114 (27.19)	509.41 (96.52)	62.18 (14.66)	108 (2.64)
2000	4432	1460 (32.94)	507.59 (100.88)	62.19 (14.74)	101 (2.28)
2001	4596	1792 (38.99)	503.36 (101.90)	62.60 (14.83)	98 (2.13)
2002	4945	2216 (44.81)	510.45 (99.79)	62.72 (14.82)	131 (2.65)
2003	5195	2619 (50.41)	517.85 (95.56)	63.17 (14.95)	131 (2.52)
2004	5259	3088 (58.72)	518.64 (103.28)	63.46 (14.77)	134 (2.55)
2005	5445	3587 (65.88)	524.49 (96.58)	63.21 (15.12)	87 (1.60)
2006	5397	3698 (68.52)	520.18 (96.11)	63.24 (15.04)	95 (1.76)
2007	5037	3460 (68.69)	513.05 (94.19)	63.35 (15.15)	89 (1.77)
2008	5628	3987 (70.84)	516.10 (92.72)	63.58 (15.21)	86 (1.53)
2009	5876	4253 (72.38)	511.82 (94.68)	63.19 (15.21)	109 (1.86)
2010	5608	4177 (74.48)	514.69 (92.81)	63.54 (15.18)	89 (1.59)
2011	5937	4524 (76.20)	515.02 (93.77)	63.12 (15.33)	104 (1.07)
2012	6646	5320 (80.05)	513.72 (91.59)	63.90 (15.25)	103 (1.55)
2013	7125	5788 (81.24)	512.16 (90.28)	63.72 (15.06)	104 (1.46)
2014	6767	5598 (82.72)	507.71 (87.21)	63.47 (15.14)	79 (1.17)
2015	5488	4584 (83.53)	506.74 (88.44)	63.16 (15.15)	69 (1.26)
2016	4460	3621 (81.19)	506.11 (86.70)	63.04 (15.30)	70 (1.57)
2017	4136	3410 (82.45)	505.73 (85.56)	62.91 (14.89)	49 (1.18)
2018	4352	3626 (83.32)	500.30 (83.93)	62.96 (15.26)	38 (0.87)
2019	3958	3244 (81.96)	498.73 (82.61)	62.64 (15.07)	21 (0.53)
2020	2639	2140 (81.09)	503.94 (88.68)	62.27 (15.52)	26 (0.99)

*Defined as present if the following Read codes (med code) were allocated prior to ULT prescription: Gouty tophi of hand (9847), Gouty tophi of other sites (4440), O/E - auricle of ear – tophi (17284), Gouty tophi of ear (36481), Gouty tophi of heart (57334), Gouty arthropathy (10080).

Table S2: Adjusted Hazard Ratio for achieving serum urate (SU) <360 and <300 $\mu\text{mol/L}$ within 1 year in gout patients first prescribed urate lowering treatment (ULT) in successive calendar years.

Year	Adj. Hazard Ratio (95% Confidence Interval)*		Adj. Hazard Ratio (95% Confidence Interval) [§]	
	for SU <360 $\mu\text{mol/L}$	for SU <300 $\mu\text{mol/L}$	for SU <360 $\mu\text{mol/L}$	for SU <300 $\mu\text{mol/L}$
1997	0.49 (0.44-0.53)	0.51 (0.45-0.59)	0.85 (0.72-0.99)	0.80 (0.64-0.99)
1998	0.59 (0.54-0.65)	0.61 (0.54-0.68)	0.99 (0.87-1.13)	0.93 (0.77-1.11)
1999	0.63 (0.58-0.69)	0.71 (0.63-0.79)	1.01 (0.90-1.14)	1.12 (0.96-1.31)
2000	0.64 (0.59-0.70)	0.70 (0.62-0.77)	0.84 (0.75-0.95)	0.89 (0.77-1.04)
2001	0.81 (0.75-0.87)	0.81 (0.73-0.89)	1.02 (0.92-1.24)	0.98 (0.86-1.12)
2002	0.81 (0.75-0.87)	0.82 (0.74-0.91)	1.00 (0.91-1.10)	1.00 (0.89-1.13)
2003	0.86 (0.80-0.92)	0.90 (0.82-0.99)	0.95 (0.87-1.04)	0.99 (0.88-1.12)
2004	0.90 (0.83-0.96)	0.89 (0.81-0.98)	0.96 (0.88-1.04)	0.98 (0.87-1.10)
2005	0.88 (0.82-0.94)	0.90 (0.81-0.99)	0.94 (0.87-1.02)	0.98 (0.88-1.10)
2006	1	1	1	1
2007	0.92 (0.85-0.98)	0.89 (0.81-0.98)	0.90 (0.83-0.98)	0.89 (0.79-0.99)
2008	0.98 (0.91-1.04)	0.94 (0.86-1.04)	0.97 (0.90-1.05)	0.95 (0.86-1.06)
2009	0.93 (0.86-0.99)	0.86 (0.78-0.94)	0.88 (0.82-0.96)	0.82 (0.74-0.92)
2010	1.00 (0.93-1.07)	0.92 (0.84-1.01)	0.93 (0.86-1.00)	0.89 (0.80-0.99)
2011	1.09 (1.02-1.16)	1.06 (0.97-1.16)	1.02 (0.94-1.10)	1.02 (0.92-1.13)
2012	1.20 (1.12-1.28)	1.09 (1.00-1.19)	1.11 (1.03-1.20)	1.05 (0.95-1.15)
2013	1.26 (1.18-1.34)	1.15 (1.05-1.25)	1.18 (1.10-1.27)	1.11 (1.01-1.22)
2014	1.34 (1.26-1.43)	1.19 (1.09-1.29)	1.24 (1.15-1.33)	1.12 (1.02-1.23)
2015	1.28 (1.19-1.37)	1.13 (1.03-1.24)	1.20 (1.11-1.29)	1.08 (0.98-1.19)
2016	1.33 (1.24-1.43)	1.13 (1.03-1.24)	1.21 (1.12-1.31)	1.03 (0.93-1.15)
2017	1.35 (1.26-1.45)	1.18 (1.07-1.30)	1.27 (1.17-1.37)	1.12 (1.00-1.24)
2018	1.48 (1.38-1.58)	1.18 (1.07-1.29)	1.35 (1.25-1.46)	1.08 (0.97-1.20)
2019	1.34 (1.24-1.44)	1.04 (0.94-1.15)	1.25 (1.15-1.35)	0.99 (0.89-1.11)
2020	1.07 (0.98-1.17)	0.74 (0.65-0.84)	0.97 (0.88-1.06)	0.68 (0.59-0.78)

*adjusted for age at start of treatment, disease duration at start of treatment, gender, region. [§]additionally adjusted for SU for participants with serum urate before starting on ULT

Figure S1: Participant flow-chart.

