The PREVENT Study: Preventing hospital admissions attributable to gout

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The PREVENT Study: Preventing hospital admissions attributable to gout

Thesis incorporating publications, submitted for the degree of Doctor of Philosophy

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Abstract

Background

Gout is the most common form of inflammatory arthritis, affecting 1 in 40 people in the UK. Despite highly effective treatments, hospital admissions for gout flares have doubled in England over the last 20 years. Many of these admissions may have been prevented if optimal gout management had been delivered to patients.

Objectives

1. Describe the epidemiology of gout management in primary and secondary care in the UK.
2. Develop an intervention package for implementation during hospitalisations for gout flares, with the aim of improving care and reducing hospitalisations.
3. Implement and evaluate this intervention in people hospitalised for gout.

Methods

I used population-level health datasets (CPRD, OpenSAFELY, NHS Digital Hospital Episode Statistics) to evaluate outcomes for people with incident gout diagnoses over a 20-year period. I used multivariable regression and survival modelling to analyse factors associated with outcomes, including: i) initiation of urate-lowering therapies (ULT); ii) attainment of serum urate targets; and iii) hospitalisations for gout flares.

With extensive stakeholder input, I developed an evidence-based intervention package to optimise hospital gout care. This incorporated the findings of a systematic literature review and process mapping of the admitted patient journey in a cohort of hospitalised gout patients. My intervention consisted of a care pathway, based upon British (BSR), European (EULAR) and American (ACR) gout management guidelines, which encouraged ULT initiation prior to discharge, followed by a nurse-led, post-discharge review to facilitate handover to primary care. I implemented this intervention in patients hospitalised for gout flares at King's College Hospital over a 12-month period, and evaluated outcomes including ULT initiation, urate target attainment and re-admission rates.

Results

In the UK, between 2004 and 2020, I showed that only 29% of patients with gout were initiated on ULT within 12 months of diagnosis, while only 36% attained urate targets. No significant improvements in these outcomes were observed after publication of updated BSR and EULAR gout management guidelines. Comorbidities, including chronic kidney disease, heart failure and obesity, associated with increased odds of ULT initiation but decreased odds of attaining urate targets.

For patients who were diagnosed with gout during the COVID-19 pandemic, I showed that ULT initiation improved modestly, relative to before the pandemic, while urate target attainment trends were similar. Underlying these trends was a 31% decrease in incident gout diagnoses in England during the first year of the pandemic.

Using linked primary and secondary care data, I showed that the risk of hospitalisations for gout flares is greatest within the first 6 months after diagnosis. ULT initiation is associated with more hospitalisations for flares within the first 6 months of diagnosis, but a reduced risk of hospitalisations beyond 12 months; particularly when urate targets are attained.

After process mapping the admitted patient journey and systematically appraising the evidence base, I developed and implemented a multi-faceted intervention at King's College Hospital, with the aim of improving hospital gout care. Following implementation of this intervention, the proportion of hospitalised gout patients who initiated ULT increased from 49% to 92%; more patients achieved serum urate targets; and there were 38% fewer repeat hospitalisations for gout flares.

Conclusions

At a population level, ULT initiation and urate target attainment remain sub-optimal for people with gout in the UK, despite updated management guidelines. Initiation of ULT is associated with long-term reductions in hospitalisations for flares; however, only a minority of patients hospitalised for gout flares are initiated on ULT. After designing and implementing a strategy to optimise hospital gout care, over 90% of patients were initiated on ULT, urate target attainment improved, and repeat hospitalisations decreased. My findings suggest that improved primary-secondary care integration is essential if we are to reverse the epidemic of gout hospitalisations.

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Publications

Incorporated into this thesis

- **Russell MD**, Rutherford AI, Ellis B, *et al*. Management of gout following 2016/2017 European (EULAR) and British (BSR) guidelines: an interrupted time-series analysis in the United Kingdom. *The Lancet Regional Health Europe*. 2022;18:July 01.
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- **Russell MD**, Stovin C, Alveyn E, *et al*. JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. *Annals of Rheumatic Diseases*. 2023;82(8):1059-1067.
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Presentations

Presentations directly related to this thesis

- **Russell MD**. Unleashing the potential of in-patient admissions to optimise the management of gout. *British Society for Rheumatology Conference* (2023).
- **Russell MD**, Rutherford A, Ellis B, *et al*. Sub-standard care for patients with gout, despite updated guidelines: a UK-wide, population-based cohort study. *EULAR Congress* (2022).
- **Russell MD**, Ellis B, Clarke B, *et al*. Process Mapping Gout Hospitalizations: A Deep Dive into an Avoidable Epidemic. *American College of Rheumatology Conference* (2021).

Other presentations during my PhD Fellowship

- **Russell MD**. Developments in capturing information for national data sets. *British Society for Rheumatology Conference* (2023).
- **Russell MD**, Galloway JB, Andrews CD, *et al*. Incidence and management of inflammatory arthritis in England before and during the COVID-19 pandemic - a population-level cohort study using OpenSAFELY. *British Society for Rheumatology Conference* (2023).
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Prizes

I was winner of the **Royal Society of Medicine, Eric Bywaters Prize** for my Doctoral research highlighting the sub-optimal management of gout.

The Royal Society of Medicine

Section of Rheumatology and Rehabilitation

Eric Bywaters Prize

This is to certify that

Dr Mark Russell

was awarded first place oral presentation for their submission

'Inadequate management of gout in the UK despite updated guidelines: A population-based cohort study' on Monday 20 June 2022

Professor Humphrey Scott
Dean,
Royal Society of Medicine

I was also winner of the **King's College London Postgraduate Research Excellence Prize** for my Doctoral research.

Personal Contribution

This thesis is a compilation of studies performed during my time working as a Doctoral Research Fellow at the Centre for Rheumatic Diseases, Department of Inflammation Biology, King's College London. I was awarded an NIHR Doctoral Fellowship to undertake this work.

The conception and development of my thesis aims were my own, with assistance from my supervisory team: Professor James Galloway, Professor Andrew Cope and Dr Jo Hudson.

The epidemiological analyses of the Clinical Practice Research Datalink and OpenSAFELY datasets (Chapters 3, 4, 5) were my own work. I led the design, methodology, analysis and write-up of these studies. I received methodological support and feedback from my supervisory team and the co-authors listed in the manuscripts.

I designed, conducted and wrote my systematic review of hospital gout management (Chapter 6), my retrospective analyses of gout management (Chapter 7), and my care pathway implementation study at King's College Hospital (Chapter 8). The co-authors listed in the manuscripts assisted me with data collection, and provided feedback on the manuscripts.

The interviews of healthcare professionals and thematic analysis of the resulting data (Chapter 8) were conducted by María A de la Puente, a psychology MSc student at King's College London, under the supervision of Dr Jo Hudson.

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This PhD has been an incredible learning opportunity for me, and I have thoroughly enjoyed all aspects of it. The skills I have developed will provide me with the best possible opportunity of achieving my goal of becoming a leading health researcher.

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Finally, I would like to thank Kim, Max and Holly, and my parents and sister for their unwavering support and encouragement throughout my studies.

Glossary of Terms

ABCG2: ATP Binding Cassette Subfamily G Member 2
aβ: adjusted β-coefficient
ACR: American College of Rheumatology
ACTH: adrenocorticotropic hormone
ACU: ambulatory care unit
aHR: adjusted hazard ratio
aOR: adjusted odds ratio
APC: admitted patient care
axSpA: axial spondyloarthritis
A&E: accident and emergency department
BD: twice daily
BNF: British National Formulary
BSR: British Society for Rheumatology
CCG: clinical commissioning group
CKD: chronic kidney disease
CI: confidence interval
CPPD: calcium pyrophosphate deposition disorder
CPRD: Clinical Practice Research Datalink
CrCl: creatinine clearance
CRP: C-reactive protein
CVA: cerebrovascular accident
DAS28: disease activity score at 28 joints
DECT: dual-energy computed tomography
DRESS: drug reactions with eosinophilia and systemic symptoms
ECDS: Emergency Care Data Set
ED: emergency department
EHR: electronic health record
EMIS: primary care software provider
ERIC: Expert Recommendations for Implementing Change
ESR: erythrocyte sedimentation rate
EULAR: European Alliance of Associations for Rheumatology
FBC: full blood count
GFR: glomerular filtration rate
GIFRT: The Getting It Right First Time recommendations in the UK
GLUT9: glucose transporter 9
GP: general practitioner
GSTT: Guy's and St Thomas' Hospital NHS Foundation Trust
HCP: healthcare practitioner
HES: Hospital Episodes Statistics

HLA: human leukocyte antigen
HR: hazard ratio
ICD-10: International Classification of Diseases version 10
IMD: Index of Multiple Deprivation
IHD: ischaemic heart disease
IL: interleukin
IM: intramuscular
IPTW: inverse probability of treatment weighting
IQR: interquartile range
ITSA: interrupted time-series analysis
KCH: King's College Hospital
LFTs: liver function tests
MAR: missing at random
MCAR: missing completely at random
MC&S: microscopy, culture and sensitivity
MNAR: missing not at random
MSc: Master of Science
NEIAA: National Early Inflammatory Arthritis Audit
NHANES: National Health and Nutrition Examination Survey
NICE: National Institute for Health and Care Excellence
NOS: Newcastle-Ottawa Scale
NHS: National Health Service, UK
NLRP3: NLR family pyrin domain containing 3
NPT1: nicotinate phosphoribosyltransferase 1
NSAID: non-steroidal anti-inflammatory drug
NUTS: Nomenclature of Territorial Units for Statistics
OD: once daily
OMERACT: Outcome Measures in Rheumatology
OPCS: UK Office of Population, Census and Surveys classification
OR: odds ratio
OT: occupational therapist
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROPSERO: prospective register of systematic reviews
PRUH: Princess Royal University Hospital
PsA: psoriatic arthritis
RA: rheumatoid arthritis
RCT: randomised-controlled trial
RoB-2: Cochrane Risk of Bias 2 tool
RR: risk ratio
SCAR: severe cutaneous adverse reaction
SF-36: 36-Item Short Form Survey

SJS: Stevens–Johnson syndrome
SNOMED-CT: Systematized Nomenclature of Medicine Clinical Terms
SpR: specialty registrar doctor
SU: serum urate
SUS: Secondary Uses Service
TDS: three times daily
TEN: toxic epidermal necrolysis
TIA: transient ischaemic attack
TPP: primary care software provider
ULT: urate-lowering therapy
URAT1: urate transporter 1
U&Es: renal function, urea and electrolytes
VAS: visual analogue scale
@home team: at-home treatment outreach team

1 Background

The overarching goal of my thesis is to improve the quality of care for people with gout, particularly patients who have been hospitalised for flares. To achieve this goal, first we must understand what standard of care is currently provided to people with gout. Then, we must review the evidence base that underpins the optimal management of gout. Finally, we need to implement strategies that bridge the gap between what care *is* provided and what care *should* be provided to people with gout.

To provide context for my results chapters, I will begin by outlining the condition, gout, its pathophysiology, epidemiology and treatment.

1.1 Gout

Gout is the most prevalent form of inflammatory arthritis worldwide. It affects 2.5% of the UK population and 3.9% of adults in the United States.[1,2] Gout is characterised by the deposition of monosodium urate crystals in the joints, leading to recurrent flares of joint pain and swelling, which can require hospital admission when severe.

Hospitalisations for gout flares have increased markedly in recent years. In a previous study, I demonstrated that hospitalisations with primary admission diagnoses of gout had increased by 58% in England between 2006 and 2017.[3] The increase in gout hospitalisations contrasted a decrease in hospitalisations for rheumatoid arthritis (RA), which halved over the same time period.[3]

There are likely to be several factors that have contributed to an increase in hospitalisations for gout. The incidence and prevalence of gout have increased in recent years, on a background of an epidemic of the metabolic syndrome and an ageing population.[4] Additionally, previous studies have shown that gout is poorly managed in both community and hospital settings, despite highly effective treatments for the prevention of gout flares.[1,5]

In recent years, there have been concerted efforts to improve the management of gout. Updated guidelines have been published by the British Society for Rheumatology (BSR), European Alliance of Associations for Rheumatology (EULAR), and American College of Rheumatology (ACR).[6-8] These guidelines encourage the initiation and titration of urate-lowering therapies (ULT), such as allopurinol, using a treat-to-urate-target approach.[6-8] Whether publication of these guidelines has translated into improved care for patients is not yet fully understood, and I will investigate this in my thesis.

To date, there has been very little focus on how to improve the management of gout in hospitalised patients, or how to counter the rising number of admissions for gout. Hospital admissions provide unique opportunities to engage patients in shared decision-making and begin the process of establishing optimal ULT. I will investigate whether strategies to optimise the management of gout can be implemented during hospitalisations for flares, and I will

analyse whether these strategies can improve outcomes for patients and prevent avoidable admissions.

1.1.1 Clinical features

Gout is a chronic disease characterised by recurrent flares of joint pain and swelling, which can progress to a persistent arthritis and erosive joint damage if undertreated. Gout flares can affect many different joint sites, but often have a predilection for specific joints – most commonly the first metatarsophalangeal joint ("podagra"), mid-foot or ankle.

Flares are typically very acute in onset, peaking in intensity within 24 hours, before subsiding over days to weeks. They are often followed by intercritical periods, during which joint symptoms are quiescent despite the continued deposition of urate crystals.[9] Intercritical periods may vary considerably in duration, from weeks to years. The frequency of recurrent flares depends on a number of factors, including serum urate concentrations and patient characteristics; male sex, higher body mass index, higher alcohol intake and comorbid cardiovascular disease are all associated with more frequent flares.[10] Flares can be spontaneous in onset, or triggered by factors such as intercurrent illness, dehydration, medications (e.g. diuretics), dietary purine intake or alcohol intake.

In the context of sustained hyperuricaemia, flares often become more frequent and polyarticular over time. Flares may evolve to affect not only the lower limb joints, but also the upper limb joints, the axial skeleton, and peri-articular tissues including bursae and entheses. Flares - particularly polyarticular flares - may be accompanied by constitutional symptoms, such as fevers, and elevated markers of systemic inflammation, such as C-reactive protein (CRP).

Gout flares are intensely painful, with patients often being unable to weight bear or perform activities of daily living. Gout is strongly associated with reduced quality of life, chronic disability and work impairment.[11,12] In approximately 15% of patients, a chronic arthritis develops.[13] Erosive joint damage and deformity can arise due to a combination of direct crystal-mediated effects on osteoblasts and osteoclasts, and cytokine-mediated effects. Extra-articular sequelae may also occur, including tophus formation (subcutaneous deposits of urate crystals with surrounding granulomatous inflammatory tissue, most commonly over the extensor surfaces of joints, tendons or bursae, or the ears), urolithiasis and chronic kidney disease (CKD).

Gout is strongly associated with other comorbidities, many of which form part of the metabolic syndrome. These comorbidities include diabetes mellitus, hypertension, dyslipidaemia, CKD and cardiovascular disease, which can contribute to morbidity and mortality in people with gout. However, even when these associations are adjusted for, gout remains an independent risk factor for all-cause and cardiovascular mortality.[14] Furthermore,

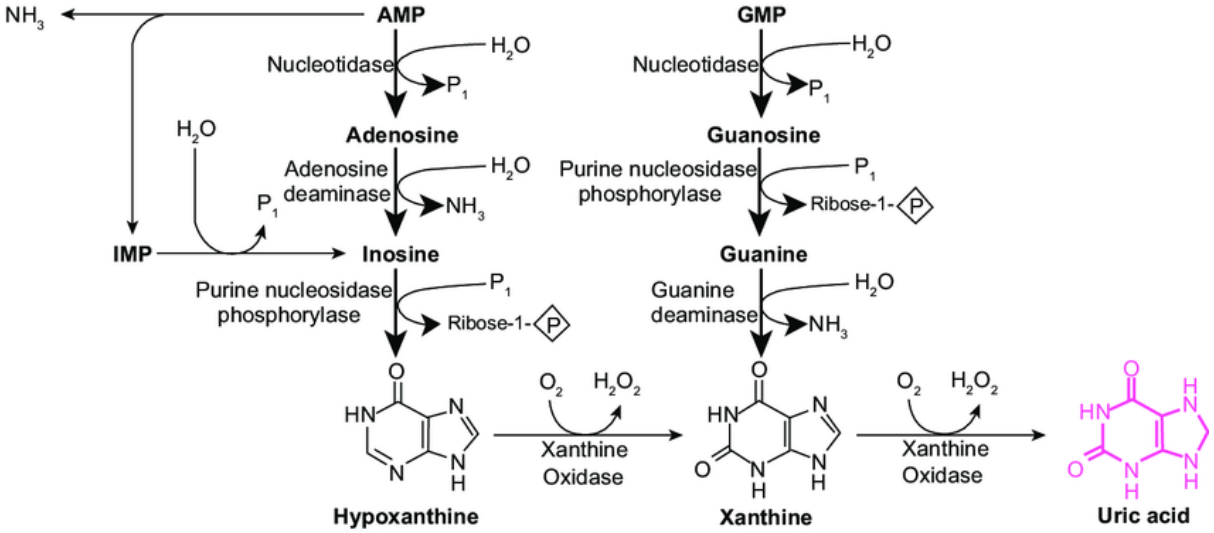
in contrast to RA, excess mortality for people with gout, relative to the general population, has not improved over the last two decades.[15]

1.1.2 Pathophysiology

Gout arises in the presence of chronically elevated serum levels of urate (hyperuricaemia). Urate has low solubility in blood, and supersaturation and crystallisation occurs at serum urate concentrations above 360 micromol/L (6mg/dL) at 35°C.[16] Deposits of monosodium urate crystals in the joints and other tissues (e.g. kidneys) act as damage-associated molecules, inducing potent innate inflammatory responses. Key mediators of the inflammatory response include pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6, and NLR family pyrin domain containing 3 (NLRP3) inflammasome activation by resident macrophages that have consumed complement-coated crystals.[9] Proinflammatory cytokine and chemokine signalling leads to the recruitment of neutrophils and other inflammatory cells to sites of crystal deposition, which, in turn, result in acute pain and swelling.

Urate is the final oxidation product of purine degradation (Figure 1). In humans, urate is predominantly excreted in the urine; this contrasts other mammals, where the enzyme, uricase, oxidases urate to soluble allantoin. Hyperuricaemia can arise as a consequence of overproduction or underexcretion of urate, or a combination of both. Renal underexcretion of urate is the primary driver of hyperuricaemia in the majority of people with gout.[17] Four putative urate transporters are involved in the renal excretion (GLUT9, URAT1, ABCG2, NPT1) and intestinal transportation of urate (ABCG2). Single nucleotide polymorphisms have been identified in the genes encoding these transporters, and genetic predisposition, rather than dietary purine intake, is thought to be the key contributing risk factor for hyperuricaemia in most patients with gout.[9,18] In a genome-wide association study of serum urate levels in over 450,000 individuals, there were extensive genetic correlations between serum urate levels and cardiometabolic traits, with the kidney and liver being key target tissues.[19] Renal underexcretion of urate is also exacerbated by CKD and the use of diuretics, both of which are recognised risk factors for gout. Additionally, elevated circulating levels of insulin reduces the renal excretion of urate, which may, in part, explain the association between diabetes, the metabolic syndrome and gout.[20]

Figure 1. Purine degradation pathway



Schematic outlining the purine degradation pathway. Reproduced from Berry CE, Hare JM. Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. J Physiol. 2004; 555(Pt 3):589-606. Copyright: Blackwell Publishing.

Other contributing factors to hyperuricaemia include excessive dietary intake of purine-rich foods, including certain types of seafood (e.g. anchovies, shellfish, tuna), red meat and alcohol (e.g. dark ales and distilled spirits). Increased consumption of fructose (present in sweetened drinks) is strongly associated with an increased risk of gout.[21] Dietary purine intake and alcohol also increase levels of free fatty acids, which activate toll-like receptors on macrophages and contribute to the inflammatory cascade.[9]

Increased cell turnover (e.g. in the context of myeloproliferative/lymphoproliferative disorders or following the use of cytotoxic agents) is another predisposing factor for hyperuricaemia and gout. Monogenic disorders such as Lesch-Nyhan syndrome - an X-linked disorder associated with absent or reduced activity in hypoxanthine-guanine phosphoribosyltransferase - are rare causes of hyperuricaemia and gout, with symptoms typically presenting from a young age.[22]

The greater the extent of hyperuricaemia, the more likely an individual is to develop gout. In people with serum urate levels of 600 micromol/L or greater, the cumulative incidence of gout is 50% over a 15-year period.[23] It is important to note, however, that a large proportion of people with sustained hyperuricaemia do not go on to develop gout, suggesting additional as yet poorly understood factors are necessary to drive the transition from hyperuricaemia into clinical gout. As such, empirical treatment of asymptomatic hyperuricaemia with ULT is not currently recommended in the UK.[8]

1.1.3 Diagnosis

The gold standard diagnostic test for gout is the identification of monosodium urate crystals within synovial fluid or tophi. On polarised microscopy, monosodium urate crystals are seen as negatively birefringent, needle-shaped crystals. Their presence is highly specific for the diagnosis of gout in the context of typical symptoms.[24] In addition to investigating for the presence of urate crystals, joint aspiration is strongly recommended to help exclude alternative diagnoses that can mimic a gout flare, such as septic arthritis or calcium pyrophosphate deposition disorder (CPPD).

In situations where joint aspiration is not feasible, many patients can be diagnosed with gout on the basis of typical clinical features: for example, a history of recurrent episodes of acute-onset joint pain and swelling on a background of predisposing risk factors and/or other suggestive clinical features (e.g. tophi). Serum urate testing can provide important diagnostic information, with some important caveats. Hyperuricaemia is present in up to 20% of the general population; far greater than the prevalence of gout.[25] As such, the presence of hyperuricaemia alone should not be seen as diagnostic of gout in the absence of suggestive symptomology. Additionally, serum urate levels can decrease during acute flares, possibly due to inflammation-mediated urinary excretion of urate; a normal serum urate during a flare does not therefore exclude a diagnosis of gout.[26]

Imaging can provide useful diagnostic and prognostic information in people with gout. While plain radiographs are typically normal early in the disease course, characteristic erosions ("punched-out" erosions with sclerotic margins and overhanging edges) may be evident in patients with more advanced gout. Ultrasonography can be used to detect the presence of urate crystal deposits on the cartilage surface of joints (the "double-contour" sign), as well as tophi within soft tissues. Dual-energy computed tomography (DECT) is an advanced imaging technique that has become increasingly available in recent years. DECT is able differentiate between materials with differing spectral absorptions with high specificity and sensitivity – for example, urate crystal deposits vs. non-urate-based materials – making it a useful imaging modality for cases of diagnostic uncertainty or where urate burden quantification is required.[27]

1.1.4 Treatment of flares

The immediate priority when managing acute flares of gout is to control pain and suppress inflammation. Flares are treated with anti-inflammatory medications, which should be commenced as soon as possible after the onset of symptoms.[6] Recommended flare treatments include colchicine (which abrogates NLRP3-mediated inflammation), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. naproxen), and corticosteroids.[6-8]

Previous studies have demonstrated comparable efficacy between the recommended flare treatment options.[28,29] In a double-blind randomised-controlled trial (RCT) of primary care

patients with gout (n=120), comparable reductions in pain were demonstrated for participants treated with oral prednisolone 35 mg daily vs. naproxen 500 mg twice daily, with no significant differences in adverse effects.[29] In an open-label trial of naproxen (750 mg immediately, then 250 mg three-times daily for 7 days) vs. colchicine (500 micrograms three-times daily for 4 days), there were no significant differences in pain reductions between the treatments: 67% of participants in each arm had complete pain resolution by 7 days; while diarrhoea and headache were reported in more patients with colchicine than naproxen.[28]

In view of comparable efficacy, the choice of flare treatment typically depends on individual risk factors, such as the presence of comorbidities and medication interactions, as well as patient preference. For example, NSAIDs may be relatively contraindicated in patients with comorbid CKD, hypertension or heart failure. Steroids may be relatively contraindicated in patients with poorly-controlled diabetes or hypertension. Colchicine has a number of drug interactions that must be taken into consideration, including statins and macrolides.

The provision of rescue packs of flare treatment for people with gout is recommended in several guidelines.[8,24] Not only does this approach enable patients to treat their flares at the first sign of symptom onset, but it also empowers patients to self-manage their condition. This, in turn, reduces the reliance upon healthcare services during flares. As well as prescribing medications used to treat flares, patients should also be advised to rest and elevate the affected joints where possible, and use ice-packs to help alleviate the symptoms.[30]

In monoarticular or oligoarticular flares, joint aspiration and intra-articular injection of corticosteroid is an effective treatment option. Combination therapy (e.g. colchicine with corticosteroids) can also be utilised in flares that are severe and/or resistant to monotherapy. IL-1 inhibitors (e.g. anakinra and canakinumab) are highly effective in the treatment of flares resistant to standard therapy; however, no IL-1 inhibitors are currently licenced for use for gout in the UK.[6]

1.1.5 Prevention of flares

Gout is unique amongst the inflammatory arthritides in that it is curable when preventative treatments (ULT; e.g. allopurinol and febuxostat) are taken long-term. The goal of ULT is to drive down the serum concentration of urate to below the saturation threshold for crystal formation. When prescribed at effective doses, ULT prevents gout flares and new crystal formation, leads to dissolution of pre-existing crystals, improves quality of life, and limits the progression of associated comorbidities such as CKD.[6,31,32]

Allopurinol is the first-line recommended ULT in the BSR, EULAR and ACR gout management guidelines.[6-8] Allopurinol was first synthesized by Roland Robins in 1956, and further investigated by Gertrude Elion in the early 1960s, during a search for effective anti-cancer therapies. Allopurinol is a structural analogue of hypoxanthine (a purine molecule), which in turn is hydroxylated by xanthine oxidase to its active metabolite, oxypurinol. Oxypurinol acts

as a potent inhibitor of xanthine oxidase, thereby leading to a reduction in urate formation (Figure 1).

It is recommended that allopurinol is initiated at a low dose (100 mg once daily in normal renal function) and uptitrated incrementally (every 2-4 weeks) until a target serum urate level is reached.[6-8] Gradual titration of allopurinol reduces the risk of hypersensitivity reactions and decreases the likelihood of flares arising from sudden changes in urate levels.[33] The maximum recommended dose of allopurinol in patients with normal renal function is 900 mg daily.[6] In patients with renal impairment, a lower maximum dose is recommended; however, there remains conflicting guidance on ULT prescribing in renal impairment, primarily due to the limited number of trials that have been conducted in patients with gout and CKD.[34]

Guidelines differ in their recommendations for target serum urate levels: the BSR guideline recommends a target serum urate level of ≤300 micromol/L; the EULAR guideline and National Institute for Health and Care Excellence (NICE) guideline recommend a target ≤360 micromol/L (or ≤300 micromol/L in patients with severe gout); and the ACR guideline recommends a target ≤360 micromol/L.[6-8] All of these target urate levels are below the saturation threshold for crystal formation, thereby preventing new crystal formation and facilitating dissolution of pre-existing crystals. Once initiated, ULT should be continued lifelong, as most patients will experience flares after stopping ULT.[8]

In the BSR, EULAR and ACR guidelines, febuxostat is the second-line recommended ULT for patients who cannot tolerate allopurinol, or for patients who continue to experience flares despite maximally-tolerated doses of allopurinol.[6-8] In the NICE guideline, febuxostat is included as a co-first-line ULT medication, alongside allopurinol.[35] As with allopurinol, febuxostat exerts its urate-lowering effect through the inhibition of xanthine oxidase. Febuxostat is typically commenced at a dose of 80mg daily, followed by an increase to 120 mg daily should the target serum urate level not be achieved.

In a phase 3 RCT, a greater proportion of patients attained target urate levels with febuxostat 80 mg daily (48%) or 120 mg daily (65%) than with allopurinol (22%), highlighting its potent urate-lowering effect.[36] Of note, however, this study limited the dose of allopurinol to 300 mg once daily (or 100 mg once daily in patients with renal impairment), and, thus, many patients in the allopurinol cohort did not receive sufficient doses to achieve target serum levels (460 mg was the mean dose of allopurinol required to achieve target urate levels in Doherty *et al*.'s RCT, mentioned below).[36] In the STOP-Gout RCT, allopurinol at doses of up to 800 mg per day was non-inferior to febuxostat 80-120 mg per day for flare prevention and lowering of serum urate, with 81% and 78% of allopurinol and febuxostat-treated patients, respectively, achieving urate targets by 48 weeks.[13]

Unlike allopurinol, febuxostat is predominantly metabolised by the liver, providing clinicians with an alternative to allopurinol in moderate-to-severe CKD.[37] Increased cardiovascular event rates were reported with febuxostat, relative to allopurinol, in the CARES trial; a randomised, non-inferiority study that compared the cardiovascular safety of febuxostat with

allopurinol.[38] In this study, the primary endpoint - a composite measure of cardiovascular events and mortality - was not significantly different between the cohorts; however, all-cause and cardiovascular mortality were significantly higher with febuxostat than with allopurinol (hazard ratios (HR) of 1.22 and 1.34, respectively). There was, however, a high discontinuation rate (approximately 50%) in this study, and the majority (85%) of deaths occurred after discontinuation of ULT.[39] Furthermore, subsequent analyses found that mortality differences between febuxostat and allopurinol were no longer statistically significant when efforts were made to trace the outcomes of participants who had discontinued the study.[38] A subsequent RCT (the FAST study) demonstrated that febuxostat was non-inferior to allopurinol with respect to cardiovascular outcomes and mortality.[40]

In patients with recurrent flares despite the use of maximally-tolerated doses of allopurinol or febuxostat, a uricosuric agent such as benzbromarone or sulfinpyrazone can be considered, either alone or in combination with a xanthine oxidase inhibitor.[6] Uricosuric medications exert their urate-lowering effects by promoting the renal excretion of urate, and thus are contraindicated in patients with a history of urolithiasis.

International gout guidelines differ substantially in their recommendations on when ULT should be initiated. The BSR guideline, published in 2017, recommends that ULT should be discussed and offered to all patients with a diagnosis of gout, including patients presenting with their first flares.[6] Additionally, the BSR guideline recommends that ULT should be strongly encouraged in patients with additional risk factors: recurrent flares (≥2/year), tophi, chronic gouty arthritis, joint damage, CKD, urolithiasis, diuretic use, and in those diagnosed with gout at a young age. The EULAR guideline, published in 2016, differs subtly from the BSR guidelines in their recommendations.[7] They state that ULT should be considered and discussed with every patient with gout from the first presentation, without explicitly stating that ULT should be offered to every patient. They state that ULT is indicated in all patients with recurrent flares (≥2/year), tophi, urate arthropathy, renal stones, those presenting at a young age (<40 years), or with a very high serum urate level (>480 µmol/L), and/or in the presence of comorbidities (CKD, hypertension, ischaemic heart disease (IHD), heart failure). In contrast, the ACR guideline, published in 2020, conditionally recommends against initiating ULT in patients who have experienced their first flare, while acknowledging the importance of shared decision-making when reaching this decision. They conditionally recommend ULT initiation in patients who have previously experienced ≥2 flares, and strongly recommend ULT for patients with more frequent flares, tophi or evidence of radiographic damage attributable to gout.[8] The NICE guideline, published in 2022, recommends offering ULT to people with gout who have multiple or troublesome flares, CKD, diuretic therapy, tophi and/or chronic gouty arthritis, while recommending discussion of ULT with patients who do not meet these criteria (e.g. patients experiencing their index flares).[35]

There are widely varying opinions on whether ULT should be initiated during flares or deferred until after resolution of flares. The latter approach has been common practice

historically, due to concerns that sudden changes in urate levels could prolong and/or worsen flares. This is reflected in the BSR and NICE guidelines, which recommend deferring ULT initiation until after flare resolution, where possible.[6] The EULAR guideline did not make a recommendation about the timing of ULT initiation, highlighting the limited body of evidence at the time.[7] The ACR guideline challenged the status quo by conditionally recommending that ULT be initiated during flares, alongside treatment for the flare itself.[8] This recommendation stemmed from an increasing body of evidence to suggest that immediate commencement of ULT does not prolong or worsen flares, when compared with delayed initiation of ULT, provided treatment for the flare is given concurrently.[41-43] Additionally, these studies found that an early initiation approach reduced the time to achieve target urate levels, thereby potentially improving outcomes for patients.

When initiating and titrating ULT, it is recommended to consider concurrent prescription of prophylactic, low-dose, anti-inflammatory medications until urate targets are achieved (typically 3-6 months). This approach has been shown to reduce the risk of flares due to changes in urate levels.[6-8] Colchicine, at a dose of 500 micrograms once or twice daily, is the first-line recommended medication for prophylaxis against flares during ULT titration. Of note, low-dose colchicine has also been shown to reduce cardiovascular mortality in patients with cardiovascular risk factors, highlighting a potential additional benefit of colchicine use in the longer term.[44,45]

A well-recognised adverse effect of xanthine oxidase inhibitors is the development of rashes and severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS). While rashes requiring cessation of allopurinol occur in approximately 1-2% of patients, SCARs in the context of allopurinol use are rare (0.1-0.4%).[9] SCARs are idiosyncratic in origin, and typically occur within the first 9 weeks of therapy.[6,33] All patients initiating xanthine oxidase inhibitors should be advised to monitor for the development of a new rash or constitutional symptoms after commencing allopurinol or febuxostat, and withdraw treatment should this occur.

Patients carrying the human leukocyte antigen (HLA)-B*58:01 allele are predisposed to the development of SCARs with allopurinol. The HLA-B*58:01 allele is present in a greater proportion of people of Han Chinese, Korean and Thai descent (6-12%), relative to those of White ethnicity. Screening for the HLA-B*58:01 allele has been recommended in these ethnic groups prior to consideration of allopurinol;[6,46] however, testing for this allele is not widely available in many healthcare settings.

The incidence of hypersensitivity reactions to febuxostat has been reported to be similar to allopurinol.[47] In a study of patients sequentially initiating febuxostat after hypersensitivity reactions to allopurinol, the odds of cutaneous reactions to febuxostat were increased (odds ratio (OR) 3.85), compared with patients without prior cutaneous reactions to allopurinol. However, the increase in risk was lower than would be expected if there was true cross-

reactivity between the allopurinol and febuxostat, and therefore likely represents the presence of general risk factors for hypersensitivity reactions in such patients.[48] Additional risk factors for allopurinol hypersensitivity reactions include higher starting doses of allopurinol, renal impairment (oxypurinol is renally excreted and accumulates in renal disease), and the use of diuretics.[49] As such, in patients with renal impairment, lower starting doses of allopurinol are recommended.

In addition to ULT, it is recommended that patients with gout should be provided with dietary and lifestyle advice.[6] Patients should be advised to adopt a diet low in purine-rich food and drinks, and high in fruit, vegetables and fibre. Fructose should be avoided due to its strong association with incident gout.[21] Of note, however, the evidence base supporting the urate-lowering effects of dietary modification is limited. A meta-analysis of cross-sectional data from the United States showed that dietary variation accounted for ≤0.3% of variance in serum urate concentrations, whereas 23.9% of variance in serum urate levels was explained by common, genome-wide single nucleotide variations.[50] This contrasts the commonly-held belief that gout is a disease attributable to diet, but instead suggests it is a genetically-determined chronic disease.

Exercise and maintaining a healthy weight should also be encouraged in patients with gout. Weight loss associates with a reduction in urate levels, and also helps to reduce the risk of comorbidities that are strongly associated with gout, including diabetes mellitus, cardiovascular disease, dyslipidaemia, hypertension and CKD. Annual screening for these comorbidities is recommended, with risk factor modification as appropriate.[6] Where possible, the use of diuretics should be avoided, as they are strongly associated with incident gout.

1.1.6 Incidence and prevalence

Gout is the most common form of inflammatory arthritis worldwide, far exceeding RA, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).[4,51] Estimates from the Global Burden of Disease Study indicate that there were 55.8 million prevalent cases of gout in 2020, with a corresponding age-standardised prevalence of 693 cases per 100,000 population.[52] The global prevalence of gout increased by 22.5% from 1990 to 2020. By 2050, there are expected to be 95.8 million prevalent cases of gout.[52]

The incidence and prevalence of gout vary considerably between geographical regions and between different ethnic groups. For example, the prevalence of gout in Māori and Pacific people in New Zealand is 8.5% and 13.9%, respectively.[53] In contrast, the prevalence of gout in Japan and South Korea is 0.5% and 0.4%, respectively.[54] Data from the United States National Health and Nutrition Examination Survey (NHANES) reported a prevalence of gout in US adults of 3.9% in 2015-16, corresponding to 9.2 million affected US adults.[2]

As well as regional, ethnic, dietary and genetic differences, other demographic factors can influence the risk of gout.[4] The prevalence of gout rises markedly with increasing age. In an

UK-based study, the prevalence of gout was 9% in people aged 80 years and above, compared with <1% in people below 40 years of age.[1] Across all age ranges, men are at a considerably greater risk of gout than women. At ages of 80 years above, the incidence of gout in men in the UK is close to 15%, while in women it is 6%.[1] Of note, gout is very uncommon in pre-menopausal women, possibly due to the uricosuric effects of oestrogen.[4]

In many countries worldwide, the incidence and prevalence of gout have increased considerably in recent decades.[4] In a UK-based study that utilised the Clinical Practice Research Datalink (CPRD), the prevalence of gout increased by 63.9% between 1997 and 2012 (from 1.5% to 2.5%, respectively).[1,4] The incidence of gout in the UK increased by 29.6% over this time period (from 1.4 cases per 1000 person-years in 1997 to 1.8 cases per 1000 person-years in 2012). There are likely to be multiple contributing factors to the increasing burden of gout worldwide, including population growth, an ageing population, higher rates of obesity and the metabolic syndrome, dietary factors, and sub-optimal management.[1,4,52]

While population growth and population ageing are thought to be primary drivers of increasing gout burden worldwide,[52] recent data suggest that the incidence of gout may have begun to plateau or even decline in some countries. A UK-based study, utilising CPRD, showed a reduction in the standardised incidence of gout from 2013 to 2021 (from 1.97 per 1000 person-years to 0.98 per 1000 person-years, respectively).[55] A large proportion of this decrease in incidence corresponded to the onset of the COVID-19 pandemic; however, the underlying pattern of declining gout incidence predated the onset of the pandemic. Data beyond 2021 are lacking, and I will investigate this further in my thesis.

1.1.7 Epidemiology of gout management

Despite the widespread availability of low cost, highly effective treatments, numerous studies have shown that gout is poorly managed in both primary and secondary care settings.[1,4,5] In a UK-based primary care study utilising CPRD, only 27.3% of patients newly diagnosed with gout were prescribed ULT within 12 months of diagnosis, with no significant improvement observed between 1997 and 2012.[1] Of patients who were prescribed ULT, only 39.7% were adherent to treatment.[1] This corroborated the findings of a previous study, which reported that drug adherence among patients with gout was the lowest of seven common chronic health conditions, including diabetes and hypertension.[56]

Similar findings of sub-optimal ULT prescribing have been reported in many other countries. In a study utilising Australian primary care data, allopurinol was prescribed to only 42.6% of patients with a coded gout diagnosis during the 5-year study period; 54.6% of patients had a serum urate tested during the 5-year period, of whom only 40.9% attained a serum urate ≤360 micromol/L.[57] In a study utilising NHAHES data from the United States between 2007 and 2014, only 33% of patients with gout had ULT prescribed, with no improvement in ULT

initiation over the study period.[58] Comparably low rates of ULT initiation have been reported in other countries, including Canada and Sweden.[59,60]

Sub-optimal gout management is not limited to patients managed in primary care settings. A national audit of gout management by UK rheumatologists, published in 2018, reported relatively higher ULT use (76% of patients) when compared with primary care; however, only 45% and 25% of patients, respectively, achieved target urate levels of ≤360 micromol/L and ≤300 micromol/L by 12 months.[5]

The reasons underlying sub-optimal gout management are manyfold. A UK-based qualitative study highlighted numerous patient and provider-related barriers to optimal care.[61] Negative stereotypes and stigma were associated with the diagnosis of gout, with a reluctance to seek medical attention due a common perception that gout is a self-inflicted condition linked to poor diet, alcohol excess and an unhealthy lifestyle. In turn, this resulted in the emphasis being placed on dietary modification and lifestyle modification, at the expense of evidence-based treatments such as ULT.[61] Gout was viewed by many patients as an alternative and/or less serious rheumatic disease, rather than a form of arthritis. The episodic nature of flares resulted in a common misconception that urate crystals were only deposited during flares, rather than continuously. The consequences of undertreatment – for example, erosive joint damage – were often not appreciated. Patients also reported limited understanding of the differences between preventative treatments and flare treatments, leading to cessation of ULT following flares. This corroborates the results of an observational study, which found that only 43% of patients continued ULT beyond 1 year of initiation.[62] Furthermore, patients often reported concerns about the long-term use of medications such as ULT, such as the potential for cumulative side effects.[61]

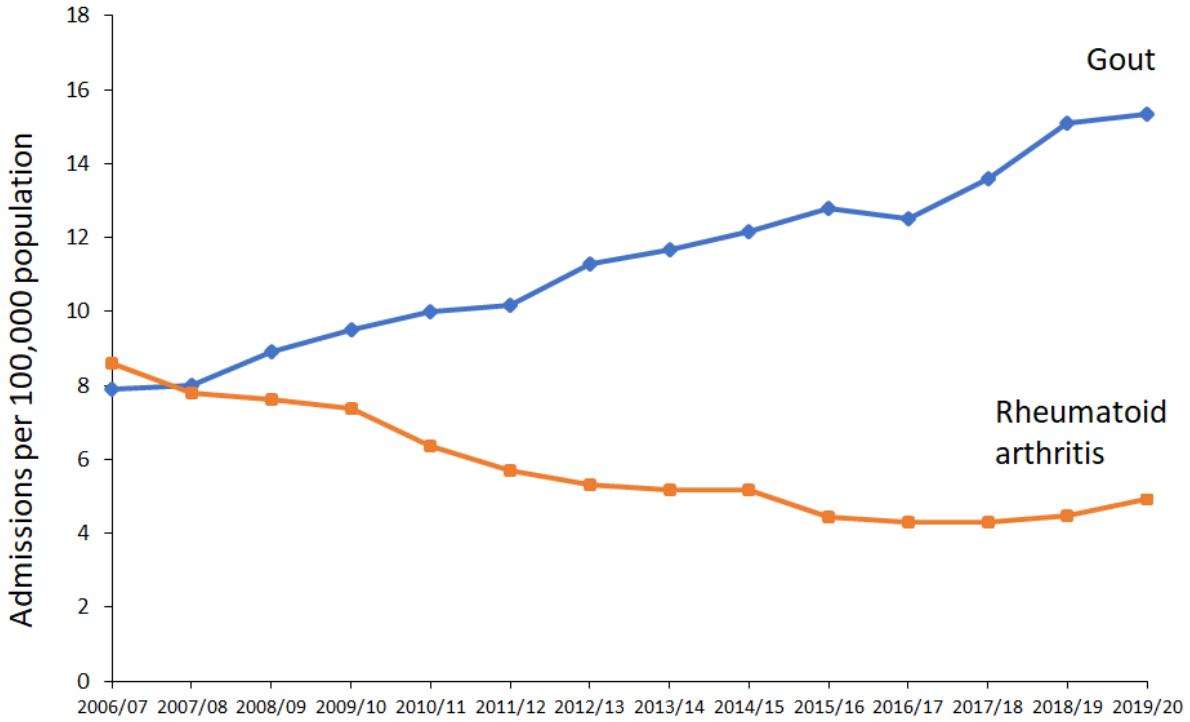
Healthcare providers also reported numerous barriers to optimal gout care.[61] This included poor understanding of the condition and its treatment. As with patients, most providers perceived gout to be a disease of poor lifestyle, rather than a genetically-determined condition. Healthcare providers often overemphasised the treatment of flares (e.g. with anti-inflammatory medications), rather than preventing flares and complications using ULT. Guidelines for the optimal management of gout (e.g. the BSR guideline) were underutilised. ULT was commonly reserved for patients with very frequent gout flares and/or complications. Insufficient information was provided to patients on the importance of ULT in preventing long-term complications associated with gout, with the perception that patients would prefer not to take long-term medications. There was also a reluctance to prescribe doses of allopurinol higher than 300 mg daily, despite data suggesting that this dose is insufficient for the majority of patients to achieve urate targets.[31] Additionally, the absence of financial incentives, meant that there was limited urgency to achieve urate targets.

1.1.8 Hospitalisations

An important consequence of sub-optimal gout management and a rising disease prevalence is an increasing burden of hospital admissions and emergency department (ED) attendances for gout flares. While the majority of gout patients are managed predominantly in primary care, some patients require hospitalisations for flares. This can include patients who are presenting with their index gout flare, as well as patients presenting with recurrent flares in the context of sub-optimally managed gout. Flares can be primary or secondary admission diagnoses, with the latter occurring in the context of other diagnoses (e.g. heart failure or infection). Additionally, patients can present to hospital with complications of gout, for example infected tophi or urolithiasis.

In previous analyses of aggregate NHS Digital data, I reported that hospitalisations with primary admission diagnoses of gout had increased by 58% in England between 2006 and 2017, from 7.9 admissions to 12.5 admissions per 100,000 population, respectively ($p<0.0001$).[3] Since 2017, hospitalisations for gout flares have continued to increase, contrasting RA, for which unplanned admissions have halved since 2006 (Figure 2).[3]

Figure 2. Incidence of hospital admissions with primary admission diagnoses of gout in England, compared with rheumatoid arthritis, between 2006 and 2020



The pattern of increasing hospitalisations for gout flares, contrasting decreases in hospitalisations for other inflammatory arthritides, has been reported in many other countries.[63-67] A study performed in the United States, reported an increase in the annual hospitalisation rate for gout from 4.4 to 8.8 per 100,000 adults, respectively, between 1993 and 2011; this contrasted RA, where hospitalisations decreased from 13.9 to 4.6 per 100,000 adults.[63] In a Canadian study, hospitalisations for gout doubled between 2000 and 2011, while hospitalisations for RA decreased by 50%.[64] In a registry study performed in Sweden, gout hospitalisations doubled between 1998 and 2015, whereas RA hospitalisations decreased by 79%.[65] In South Korea, the number of ED visits for gout increased by more than 3-fold between 2010 and 2017, from 6.3 to 21 per 100,000 adults.[68]

Hospitalisations are highly unpleasant for patients and costly for healthcare services. In previous analyses, I showed that the mean and median lengths of stay for primary gout admissions were 6 days and 3 days, respectively, in 2017.[3] Admissions with primary diagnoses of gout accounted for 349,768 hospital bed-days, cumulatively, in England between 2006 and 2017.[3] Furthermore, these figures do not take into consideration bed-days resulting from secondary gout admissions. The cost to the NHS of a non-elective admission for a gout flare ranges from £999 to £6,601, depending on the number of comorbidities a patient has and the length of stay.[69] In the US, the charges attributable to ED visits with primary gout diagnoses were $287 million in 2012.[70] As such, there a huge potential for cost savings if avoidable hospitalisations for gout flares can be prevented.

There are several plausible explanations for the increasing number of gout hospitalisations. The prevalence of gout has increased markedly in recent years, which increases the pool of patients in whom admissions and ED attendances can occur. More generally, the number of hospital admissions from any cause has increased substantially over the last two decades.[71] This, in turn, could contribute to an increase in gout admissions, along with other diagnoses. Of note, however, in my previous analyses of NHS Digital data, I showed that gout admissions had increased as a proportion of all-cause hospital admissions between 2006 and 2017.[3] This suggests that the increase in gout admissions cannot be attributed solely to increasing numbers of all-cause admissions.

The marked decrease in RA hospitalisations over the last two decades despite an increase in RA prevalence suggests that rising numbers of gout hospitalisations are unlikely to be driven by increases in gout prevalence and population growth alone.[51] Sub-optimal gout management is likely to be a key contributing factor. For autoimmune-mediated inflammatory arthritis diagnoses, such as RA, there have been extensive efforts to ensure prompt, target-driven treatment.[72] Experience suggests that when a patient with RA is hospitalised for a flare, they are likely to receive specialist input during their stay, as well as secondary care follow-up after discharge (e.g. outpatient clinics and rheumatology helpline access). This contrasts the care provided to patients who have been hospitalised for gout flares, where patients often do not see a rheumatologist during or after their admission; ULT

is rarely commenced; and a breakdown in communication with primary care frequently occurs.[73]

In recent years, there has been a concerted effort in the UK to manage gout in primary care. The Getting It Right First Time (GIRFT) recommendations, published in 2021, state that:

"*Care for patients with non-inflammatory painful MSK conditions such as back pain, fibromyalgia and hypermobility, as well as gout, polymyalgia rheumatica, osteoarthritis and soft tissue musculoskeletal conditions, should be provided in primary and community care settings*."

While the GIRFT recommendations recognise that complex cases of gout and patients who are not responding to treatment could be managed in a secondary care setting, the emphasis placed on primary care management is likely to have reinforced the belief that gout is not a problem for secondary care, but rather a problem for primary care.

1.1.9 Strategies to optimise gout management

Much of the existing data on how to optimise gout management has been obtained from community-based studies.[74] A large RCT, led by Professor Doherty at the University of Nottingham and published in The Lancet in 2018, demonstrated the benefits of a nurse-led approach that combined patient education and treat-to-target ULT.[31] Primary care patients with gout (n=517) were randomised to receive usual general practitioner (GP) care or a nurse-led intervention that incorporated individualised patient education, shared decision-making and follow-up visits to optimise ULT using a treat-to-target approach. 95% of the cohort receiving the nurse-led treat-to-target approach attained a serum urate level ≤360 micromol/L by 2 years, compared with 30% in the usual care group (88% vs. 17%, respectively, attained a serum urate ≤300 micromol/L by 2 years). The intervention reduced flare frequency beyond the first year of treatment, reduced the presence of tophi, improved quality of life, and was cost-effective when assessed against NICE criteria. Notably, in this study, there was an average of 17 study visits per participant over a 24-month period, the majority of which occurred within the first 6 months of ULT initiation.

An outpatient-based study, performed in Singapore, evaluated a pragmatic, nurse-led intervention, which incorporated: i) self-management training of patients by a nurse; ii) dietetic referral and dietary advice; iii) treat-to-target ULT, flare treatment and prophylaxis via a Gout Action Plan; iv) provision of a nurse helpline; and v) follow-up calls and visits.[75] Of 126 enrolled patients, the median time to achieve a serum urate ≤360 micromol/L was 37 weeks, with 56% of patients achieving target urate levels by the median follow-up duration of 40 weeks. Target attainers were seen on average every 2 months, and required a mean of 2.5 visits over the study period. A higher frequency of visits associated with better attainment of urate targets in univariate and multivariate regression models.

Another study, published in 1984, investigated different educational strategies in patients with gout.[76] 63 patients were randomised to four different educational groups: i) education via a rheumatology clinical fellow; ii) provision of a leaflet on gout; iii) intensive nurse-led education; or iv) monthly telephone calls from a nurse. Patients assigned to the first two educational groups had no significant changes in serum urate levels at the end of the 24-month study period. In contrast, individuals randomised to the nurse-led approaches (iii and iv) had improvements in urate levels, from 8.8 mg/dL to 6.4 mg/dL.[76] The benefits of nurse-led education have also been shown in a qualitative study. Compared with usual primary care-led gout education, nurse-educated patients reported better understanding and engagement with ULT, and enhanced treatment adherence.[77]

In addition to nurse-led strategies, pharmacist-led approaches have been explored as a means of optimising gout management. In a US-based, site-randomised study of 1,463 patients receiving new prescriptions for allopurinol, a pharmacist-led approach that encouraged treat-to-target optimisation of allopurinol (delivered primarily via telephone-based, interactive voice system) was compared with usual care.[78] At one year, patients who received the pharmacist-led intervention were more likely to have been adherent to allopurinol (50% vs. 37%; OR 1.68; p<0.001), and more likely to have achieved serum urate targets (30% vs. 15%; OR 2.37; p<0.001) than those receiving usual care. Despite the intervention, the majority of patients did not achieve urate targets or receive allopurinol dose increases, which suggests that a more intensive intervention incorporating patient education (similar to that implemented by Doherty *et al.*[31]) is required.

A US-based observational study evaluated an intervention whereby a trained clinical pharmacist implemented treat-to-target ULT and provided education to patients via telephone. Of 95 patients, 78 attained a serum urate ≤360 micromol/L using this approach.[79] However, when the same intervention was tested in an RCT setting, absolute levels of target attainment were lower: 35% of participants (13/37) in the intervention group achieved a serum ≤360 micromol/L by 26 weeks, compared with 13% (5/40) in the usual care comparator group.[80]

Electronic health record (EHR)-based tools have also been evaluated as means of enhancing ULT initiation and target attainment. A study in US primary care, implemented a strategy that incorporated EHR changes (gout order sets, smart phrases, and notification lists of patients with gout who were not receiving ULT and/or at target), educational programmes for primary care clinicians, and clinician feedback (leaderboards of performance, relative to peers).[81] After implementation, the proportion of patients who were prescribed ULT, had their urate levels monitored, and achieved urate targets all improved significantly. Of the possible intervention components, in-person education sessions, EHR reminders, and economic incentives were felt to be the most effective by primary care providers.[81] Improving the quality of gout care was reported as being the main motivation for participating in the project.

In a US-based study conducted in a rheumatology outpatient setting, an electronic visit tool was used to enhance patient-clinician interactions after the initiation of ULT in patients with gout.[82] This tool provided educational information for patients, reminders on when urate tests were required, and facilitated ULT dose titrations under the supervision of a physician. With this approach, significantly more patients achieved target urate levels ≤360 micromol/L within 6 months, relative to a historical cohort (64% vs. 34%, respectively; $p<0.01$). The mean number of electronic visits and in-person visits were 1.6 and 0.8, respectively, in a 6-month period, compared with 1.1 in-person visits in the comparator group.

For there to be sustained reductions in admissions for gout flares, strategies are needed to optimise care for patients during and after their hospitalisations. Despite this need, there have been no studies to date that have systematically reviewed approaches to improving hospital gout care and preventing admissions. I will address this knowledge gap in my thesis.

To develop a strategy, I will adapt components of the aforementioned, community-based strategies for implementation in a hospitalised setting. The basis for my strategy will be the highly successful, nurse-led approach utilised in Doherty *et al.*'s study.[31] Not only was this the most effective intervention, to date, at ensuring patients achieved urate targets, but it was also shown to be cost-effective in a UK primary care setting, making it more easily translatable to my study setting.

1.2 Aims and objectives

This chapter has highlighted a number of knowledge gaps that align with the aims of my thesis:

1.2.1 Aim 1: Has gout management in UK primary care improved following the publication of updated gout management guidelines?

Previous studies, with data up to 2012, highlighted the sub-optimal management of gout in UK primary care.[1] However, more recent data are lacking. Recognising the need for improvements in gout care, the BSR, EULAR, ACR and NICE have all introduced updated gout management guidelines since 2016.[6-8,35] These guidelines lowered the threshold for the initiation of ULT, and specifically recommended a treat-to-target approach.

What is not clear is whether the recommendations contained within these updated guidelines have been implemented in practice, and whether this has translated into better care for patients. I will investigate this using population-level, routinely-collected data sources: CPRD (Chapter 3) and OpenSAFELY (Chapter 4).

1.2.2 Aim 2: How have the incidence, prevalence and management of gout been impacted by the COVID-19 pandemic?

The COVID-19 pandemic has had an enormous impact on healthcare systems worldwide, with abrupt changes to healthcare utilisation, re-deployment of staff, and a rapid transition to virtual consultations.[83-85] The extent to which these changes and accompanying system-wide pressures have affected care for people with gout is not understood.

Data from early in the pandemic suggested that decreases had occurred in the incidence of gout and urate target attainment in the UK, relative to before the pandemic, while ULT prescriptions did not appear to be impacted.[55,86] Whether these patterns continued beyond 2021 is not known. Similarly, it remains unclear how the pandemic has impacted upon hospitalisations for gout flares. Contemporaneous primary and secondary care data are needed to answer these important questions; I will address this using the OpenSAFELY platform (Chapter 4).

1.2.3 Aim 3: What proportion of incident gout patients are hospitalised for flares, and how is the risk of hospitalisation affected by ULT initiation and urate target attainment?

Previous analyses of aggregate NHS Digital data showed that gout hospitalisations increased markedly at a population-level in the UK between 2006 and 2017.[3] However, no studies to date have utilised individual-level data to describe the incidence of hospitalisations for flares in people with gout, or the risk factors for hospitalisations. I will analyse this using linked primary and secondary care data in CPRD (Chapter 5).

Additionally, while the long-term benefits of ULT in community settings have been demonstrated, few studies have investigated the impact of ULT and urate target attainment on hospitalisations for flares. It remains unclear whether ULT initiation associates with more hospitalisations in the short-term (due to exacerbations of flares); whether colchicine prophylaxis mitigates this risk; or whether attaining target serum urate levels influences the risk of hospitalisations following ULT initiation. I will investigate these questions in CPRD (Chapter 5).

1.2.4 Aim 4: What is the evidence base for interventions in patients hospitalised for gout flares?

If the epidemic of gout hospitalisations is to be addressed, strategies are needed to optimise care for hospitalised gout patients and prevent avoidable admissions. Studies in community settings have evaluated strategies to optimise gout care: for example, by combining nurse- or pharmacist-led, treat-to-target ULT and individualised patient education.[31,79] In contrast, there have been no systematic appraisals of evidence for interventions in patients hospitalised for gout flares. I will conduct a systematic review to evaluate this (Chapter 6).

1.2.5 Aim 5: What are the barriers and facilitators of optimal gout care in hospitalised patients?

To improve outcomes for hospitalised gout patients, we need to describe the barriers and facilitators of optimal gout care in the hospital setting. Only then can strategies be implemented to address these barriers and bridge the evidence-practice gap.

I will perform detailed, retrospective analysis of gout care in the emergency department and inpatient setting at King's College Hospital NHS Foundation Trust over a 4-year period. I will process map the patient journey, to identify barriers and facilitators of optimal hospital gout care (Chapter 7). This will form the basis of a strategy to improve care and prevent avoidable admissions.

1.2.6 Aim 6: Can a strategy centred on treat-to-target ULT and individualised patient education be implemented effectively during hospitalisations for flares?

Professor Doherty's study demonstrated the benefits of treat-to-target ULT and nurse-led, individualised patient education in a primary care setting.[31] No studies to date have evaluated similar strategies in the hospitalised setting.

I will work with stakeholders to develop a care pathway and implementation strategy for hospitalised gout patients. This will be modelled on the nurse-led intervention that was shown to be highly effective in a community setting in Professor Doherty's study.[31] My intervention will incorporate the findings of my systematic review (Chapter 6), and retrospective analyses and process mapping of hospital gout care (Chapter 7). I will

implement this strategy at King's College Hospital NHS Foundation Trust, and evaluate outcomes including ULT initiation, urate target attainment, and re-hospitalisation rates (Chapter 8). Semi-structured interviews with patients and healthcare professionals will be used to obtain more granular feedback on outcomes. I will collaborate with stakeholders to adapt the pathway for implementation at other hospital sites (Chapter 8).

2 Methodology and data sources

This section provides a general summary of the methodologies and data sources utilised in my thesis. More specific summaries of the methods used are detailed within each of my results chapters.

2.1 Methodologies

2.1.1 Regression models

Regression models are used to explore the relationship between dependent (outcome) variables and one or more independent (predictor) variables. By modelling the relationship between these variables, it enables one to make inferences and/or predictions based upon that relationship when certain assumptions are met.[87,88]

Linear regression is used to model linear relationships between variables. This assumes that a linear relationship exists between independent and dependent variables. A linear equation ($y = \beta0 + \beta1x + \varepsilon$) is fitted to the observed data, whereby the resulting regression line shows the expected value of the dependent variable for all values of the independent variable; $\beta1$ (the regression coefficient) depicts the amount y changes per unit increase in x.[87,88] If the linear assumption is not met, one or more variables can be transformed (e.g. log transformed), or additional independent variables can be added to the model (e.g. the square of a predictor variable if the relationship with the outcome variable is parabolic in nature) to try and meet this assumption. Additional assumptions for linear regression modelling include: the requirement for residuals (errors) to be normally distributed; independent variables should not be highly correlated (multi-collinearity); the variance of the residuals should be constant across all values of the independent variable (homoscedasticity); and the sample should be of sufficient size to permit reliable estimates to be derived from the model (typically at least 5-10 observations for each independent variable).[87,88]

Logistic regression is performed for binary outcome variables. This contrasts linear regression, where the outcome is continuous in nature. A logistic function is fitted to the data, to model the probability of the binary outcome occurring for a given value of the independent variable(s).[87,88] The strength of this association is represented with an odds ratio (OR), which is the exponential function of the log-odds of the outcome occurring per unit increase in the predictor variable. Logistic regression requires observations to be independent of one other (e.g. not repeated measurements from the same individual). As with linear regression, independent variables should not be highly correlated (multicollinearity). Additionally, the sample should be of sufficient size to permit reliable estimates to be derived from the model.[87,88]

In the epidemiological analyses within my thesis, I employ both univariable and multivariable regression modelling. Univariable analysis is used to provide a measure of association between the outcome variable and one predictor variable. With multivariable regression,

measures of association take into account multiple predictor variables. This is useful when investigating and controlling for potential confounding variables, such as the effects of age and sex on hospitalisations. There are several different approaches to selecting which covariates should be included in multivariable analysis models.[87,88] One of the most commonly used approaches, which I adopted for my analyses, is the *a priori* selection of variables that are hypothesised to be potential confounders on the basis of the investigator's knowledge and previous data. Other approaches include stepwise regression, with forwards selection or backwards elimination of all candidate variables using an iterative process, and retention of variables that influence the effect-size estimates. A problem with this approach is that some variables that may have relevant causal effects can be excluded on the basis of not meeting a particular significance threshold, whereas other less relevant variables may be included on the basis of coincidentally meeting that significance threshold.[89]

It is important to emphasise that the effect-size estimates derived from regression models are measures of association, and causality should not be inferred directly from this. This is of particular relevance to my analyses of ULT initiation and hospitalisations (Chapter 5); for example, a positive association between ULT initiation and admissions could either mean that ULT causes hospitalisations, or that people who are hospitalised for gout are more likely to receive ULT (reverse association) – I discuss this further in Chapter 5.

2.1.2 Survival analysis

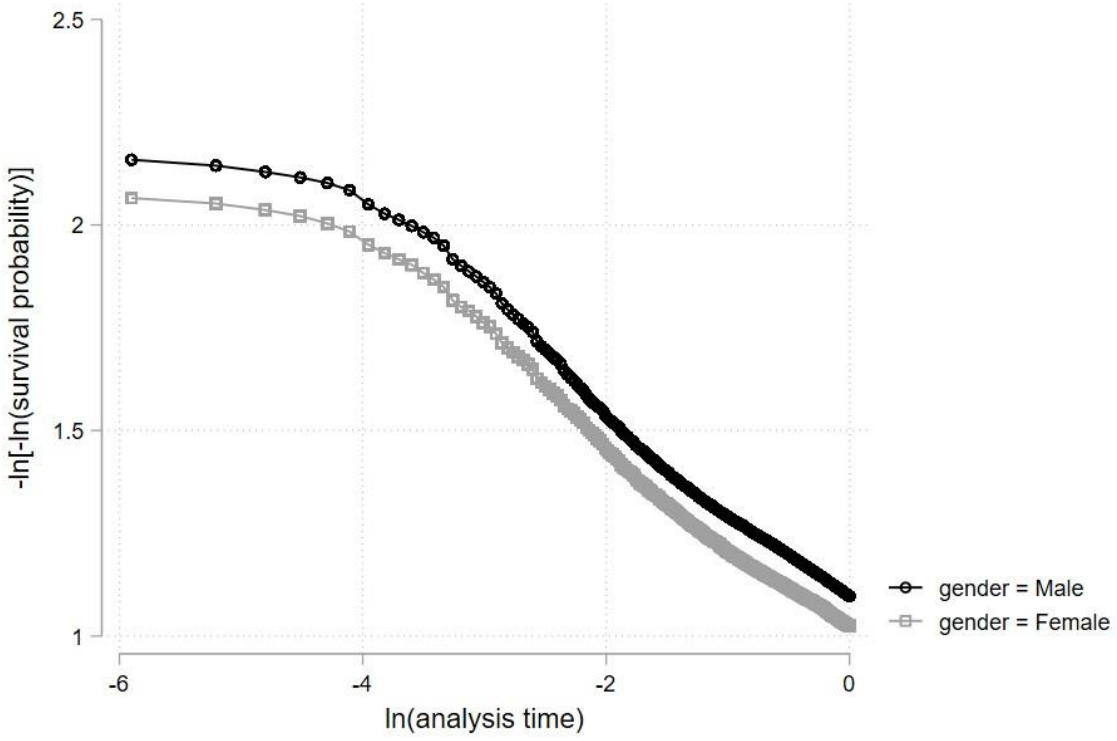
In contrast to logistic regression, where the objective is to predict whether an outcome occurs or not, survival analysis also takes into consideration the time until that event of interest occurs. This is particularly relevant to my thesis, for example when analysing predictors of hospitalisation for gout flares. In these cases, I care not only about whether a hospitalisation has occurred (which could be analysed using logistic regression), but also how long it took for the hospitalisation event to occur (e.g. after starting ULT).

In survival analysis, subjects become at risk of the event from a defined study entry point, and are observed until they experience the event of interest or leave the study period for other reasons (e.g. lost to follow-up or death). Models (e.g. Cox regression) can be used to estimate the association between the dependent variable (time to the event of interest) and one or more predictor variables.[90] Observations can be censored to take into account incomplete information about survival time. Right censoring refers to when events occur beyond the end of the observation period. Left censoring refers to when an event has occurred, but the elapsed time to event is not known (e.g. at risk before the observation window began). Interval censoring refers to when an event is observed, but the individual has been intermittently observed, and therefore the exact time to event is not known. Censoring assumes that the subjects who drop out have the same hazard of an event as those that remain in the study.[90]

In survival analysis, a survival function can be used to describe the probability of surviving (i.e. not experiencing the event of interest) beyond a specific time point. This can be represented graphically using survival curves. Kaplan-Meier estimates and curves are non-parametric statistics that are commonly utilised, as they do not make assumptions about the underlying distribution of the data (e.g. censorship).[90] The hazard function refers to the instantaneous rate of the event of interest occurring at a specific time point. A related concept is the hazard rate, which refers to the probability of an event occurring within a specified time interval (instantaneous event rates).[90]

Hazard rates can be compared between groups of individuals (e.g. according to treatment assignment), to provide estimates of relative risk, depicted as a hazard ratio. Cox proportional-hazards regression is a commonly employed method of investigating the effect of numerous predictor variables on hazard rates.[90] Cox regression assumes that the effects of the predictor variables upon survival are constant over time (i.e. that the hazard ratio should be constant over time). The proportional hazards assumption can be tested graphically using Nelson-Aalen and log-log plots (Figure 3), and via the Schoenfeld test.[90]

Figure 3. Example of a log-log plot



Shown is a log-log plot used to test proportionality assumptions in a survival model that evaluated the impact of gender on the time taken to initiate ULT. Survival plots on a logarithmic scale are compared for the different genders, to evaluate whether the effects on survival (i.e. ULT prescribing) are proportional over time. In this case, proportionality assumptions appear to be valid.

2.1.3 Propensity modelling

Channelling bias is an issue of particular relevance to my analyses of hospitalisation risk in people who started vs. do not start ULT. In this case, treatment selection may be influenced by the characteristics of a patient. For example, a patient who is more likely to be prescribed ULT may have certain shared characteristics that makes them more likely to be hospitalised for gout flares (e.g. more severe gout, more flares, and higher serum urate levels). This, in turn, could lead to an apparent association between the use of ULT and hospitalisations. One must therefore try to account for differences in baseline characteristics when estimating the effect of a treatment on outcomes, for example by performing multivariable adjustment or propensity modelling.

In propensity modelling, a summary metric known as the propensity score is generated using methods such as logistic regression. This score describes the likelihood on an individual being allocated to the treatment on the basis of their observed baseline characteristics. Individuals can be matched on the basis of their propensity scores, so that baseline covariates that determine whether an individual is allocated to the treatment are balanced evenly between the treatment groups.[91] There are different approaches to balancing in propensity modelling. The approach I adopted was to use inverse probability of treatment weighting (IPTW). In IPTW, individuals are assigned weights that are inversely proportional to their propensity score, thereby balancing characteristics across the groups.[92] Alternative approaches include propensity score matching, where individuals in the treatment and controls are matched on the basis of the propensity scores, and stratification by propensity scores. An advantage of IPTW is that is utilises all the available data, whereas propensity score matching utilises only a subset of data.[91,92]

Propensity models can have several advantages over multivariable adjustment when balancing multiple potential confounders. By collapsing multiple covariates into a single propensity score (dimensionality reduction), it can preserve degrees of freedom and reduce the likelihood of overfitting. Propensity models can be more flexible in handling non-linear relationships and interactions between covariates. Additionally, it possible to visualise the balancing of covariates between treatment allocation groups (Figure 4).

Figure 4. Diagnostics of balance in propensity models

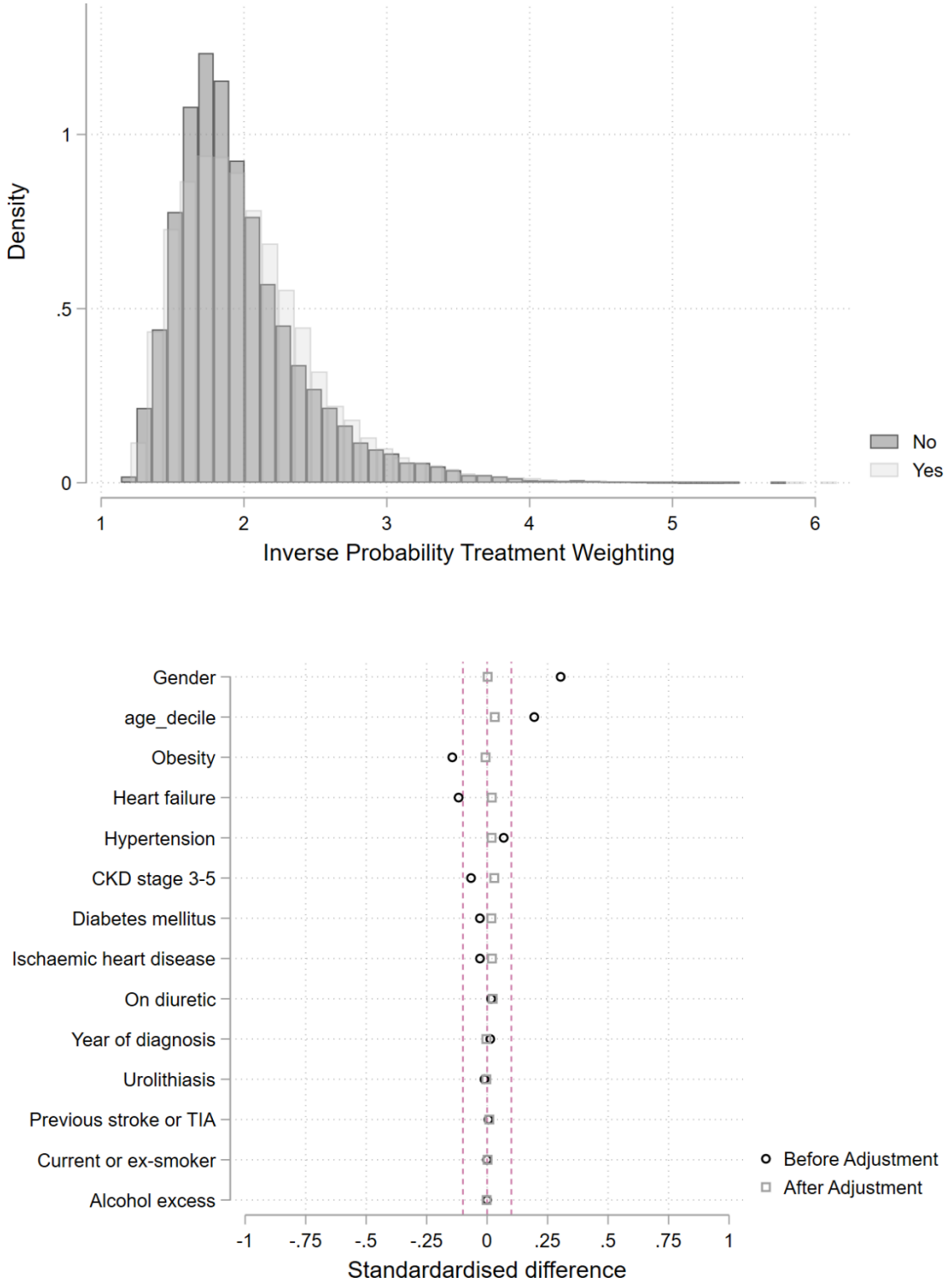


Figure showing the balancing of covariates in the propensity models I used to explore the impact of ULT initiation on the risk of hospitalisations for gout flares.

There are also potential limitations with propensity modelling approaches. A key assumption is that the treatment assignment (and balancing on the basis of this) can be accounted for on the basis of the observed variables used to generate the propensity score.[91-93] If crucial variables have been omitted, the groups may remain imbalanced. Another potential issue with propensity modelling arises when there is minimal overlap in propensity scores between treatment allocation groups. This, in turn, results in residual imbalance and the potential for biased estimates. Additionally, if trimming approaches have been used to retain only individuals with common support (i.e. overlap in propensity score distributions), then a large number of patients can be excluded if there is substantial imbalance. I encountered this issue when analysing whether colchicine prophylaxis mitigates the risk of hospitalisations in people who have initiated ULT. In this case, individuals who were prescribed colchicine were markedly different to those who were not prescribed colchicine (e.g. more severe disease), with only minimal common support.

2.1.4 Missing data and multiple imputation

A key issue that often arises when analysing real-world, observational data is missing data. This has the potential to introduce bias, depending on the pattern of missingness:[94]

- **Missing completely at random (MCAR)**: missingness is not related to the individual being studied but, instead, data are missing based upon chance events. One example would be a participant accidentally missing a question at random. In these cases, complete case analyses can be performed and unbiased estimates returned, albeit with reduced precision due to fewer data points.
- **Missing at random (MAR)**: missingness relates to the individual being studied, and can be predicted by observed variables within the data but not by unobserved data. For example, an individual with depression might be less likely to complete a survey on diet than someone without depression. The missing data that result from this can be explained by the presence of the diagnosis of depression, which is an observed variable within the dataset. Assuming variables that explain missingness are included within the analysis dataset, statistical methods such as multiple imputation can be used to account for this.[95] Multiple imputation generates multiple plausible datasets with imputed values for missing data on the basis of other observed variables, and combines the results. Rubin's rules are employed to reduce the uncertainty associated with the missing values.[96-98]
- **Missing not at random (MNAR)**: missingness is dependent on unobserved data. For example, a person with gout might be less likely to fill in a survey on gout due to stigma associated with diagnosis. To reduce the potential for bias, the missing data should be considered *non-ignorable* and must be accounted for as part of the analysis,[99] such as by using selection models and/or collecting additional data.

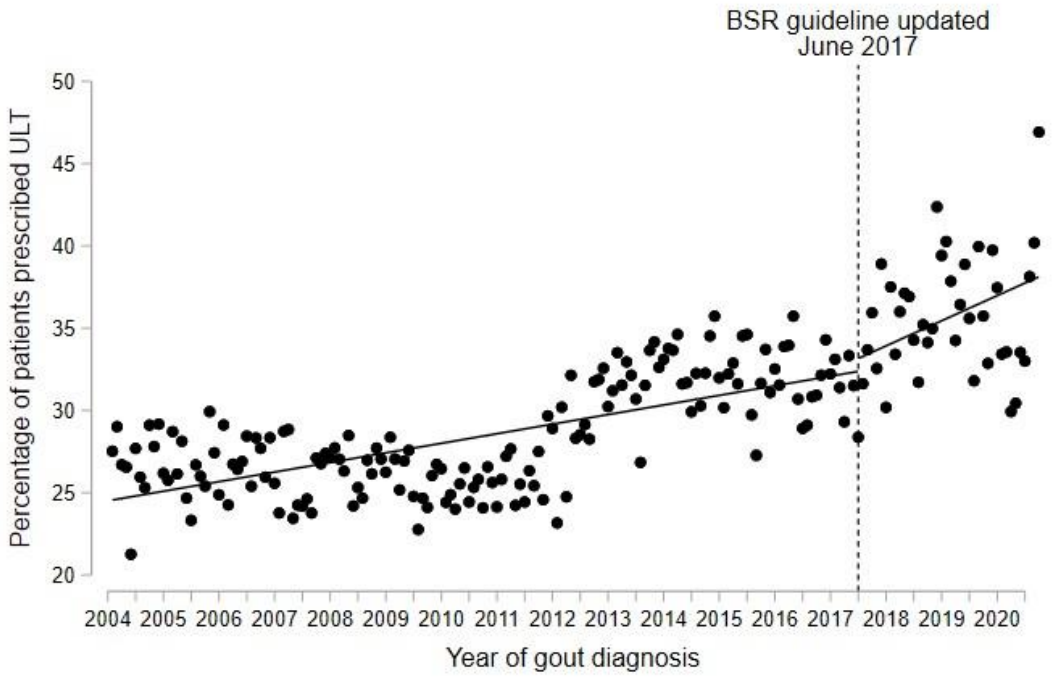
In Chapter 5 of my thesis, I wanted to determine whether attainment of serum urate targets was associated with a lower risk of hospitalisations for flares in people with gout who initiated

ULT, relative to those who did not attain urate targets. A substantial proportion of patients who initiated ULT did not have a serum urate level recorded subsequently; it was not therefore possible to determine whether these individuals achieved target or not. If we assumed that the data were MCAR, then complete case analyses could be performed. If we assumed that the data were MAR (i.e. the missingness of the serum urate levels related to observed variables, e.g. age, sex, receipt of ULT), then techniques such as multiple imputation could be performed to estimate the missing values on the basis of the observed variables. However, if the data were MNAR, the missingness of the serum urate levels would relate to the serum urate levels themselves. For example, patients with less severe gout and lower serum urate levels, might be less likely to have serum urate levels checked by their GP. A key question would then be whether we are able to accurately predict missing serum urate levels on the basis of other observed data, such as baseline serum urate levels, receipt of ULT, and hospitalisation frequency - all of which could be seen as markers of disease severity. In my results chapter, I presented multiple sensitivity analyses to try and account for these different possibilities, including: i) complete case analyses; ii) analyses using multiple imputation that incorporated a range of possible predictors of target attainment, such as age, sex, comorbidities, number of hospitalisations, receipt of ULT, and baseline urate; and iii) propensity models with IPTW.

2.1.5 Interrupted time-series analysis

Interrupted time-series analysis (ITSA) is a statistical method used to estimate the effect of an intervention on an outcome by analysing changes in that outcome before and after the intervention. This method is useful for evaluating the impact of large-scale (e.g. population-level) interventions, where the outcome in question is reported at an aggregate level over time.[100] In my thesis (Chapter 3), I sought to determine whether the introduction of updated BSR and EULAR gout management guidelines (published in June 2017 and July 2016, respectively) had influenced the prescription of ULT and/or attainment of urate targets at a population level. Using population-level data (CPRD), I calculated monthly averages of the attainment of these outcomes in people with incident gout. I could then use ITSA to compare trends in these outcomes before and after publication of the BSR and EULAR guidelines (Figure 5).

Figure 5. Example of an ITSA graph, evaluating the impact of the 2017 BSR Gout Guideline on ULT prescribing in the UK



Percentage of newly-diagnosed gout patients who were prescribed ULT within 12 months of diagnosis, comparing trends before and after the introduction of the updated BSR gout management guideline. Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of ULT initiation.

ITSA can be performed as single group analyses, where there is a single population under study (as was true of my analyses), or in multiple groups, where there are other groups to compare with. Regression models are fitted to the time-series data, to quantify the effect of the intervention on the outcome, and to test whether any changes in trends after the intervention point are statistically significant, relative to before the intervention.[101] ITSA typically utilises ordinary least-squares regression-based approaches, with modifications made to account for autocorrelation between observation periods. Prais-Winston transformation and Newey-West standard errors are two commonly used methods to account for autocorrelation in ITSA,[101] both of which I used in my analyses.

There are several limitations with ITSA.[102] When interpreting the findings, one must consider other events that might have influenced changes in the outcome. For example, changes in ULT prescribing corresponding to the introduction of a guideline might also have coincided with a price reduction in the cost of ULT. Unlike randomised controlled trials, ITSA relies upon observational data without randomisation. As such, bias can result from changes over time in the characteristics of the pre- and post-intervention cohorts. Another major limitation of ITSA relates to the choice of the intervention point (or "cut point"). An intervention might occur

on a specific date but take time to disperse. This can lead to an underestimate of the impact of the intervention if this is not taken into consideration.

2.1.6 Systematic literature review

Systematic literature reviews are a commonly used method of systematically collating and evaluating the evidence base for a specific question.[103] I used this approach in Chapter 6 of my thesis, to evaluate the evidence base for interventions in patients hospitalised for gout flares. The question being answered in a systematic review should be clearly defined – for example, by using the PICO framework to specify the Population/Problem (e.g. people hospitalised for gout), Intervention/Exposure (e.g. pharmacological and non-pharmacological interventions or exposures), Comparator (e.g. the absence of that intervention or exposure), and Outcome (e.g. re-admission for gout flares).

Once the research question has been defined, a systematic search of relevant literature sources is performed to gather as much of the relevant data as possible. These data sources can include literature databases (e.g. PubMed and Embase), trials registration repositories (e.g. clinicaltrials.gov), and manual searching of reference lists (so called "grey literature" searches). Search strategies and screening of manuscripts should be as systematic as possible, to ensure relevant evidence is not missed. Similarly, data extraction should be systematic, using data extraction spreadsheets to extract pre-defined variables and outcomes. Recommended practice is for there to be at least two independent researchers who perform screening and extraction, with involvement of additional reviewers as needed to resolve discrepancies.[104] Research questions and detailed methods should be documented in advance in a protocol, which should be made publicly available (e.g. in databases such as PROSPERO).

Eligible studies should be assessed for potential sources of bias. There are several tools available to assist risk of bias assessments, depending on the study type. For my systematic literature review, I opted for two widely used tools: the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs,[105] and the Newcastle-Ottawa Scale for non-randomised studies.[106]

Once eligible studies have been identified and relevant data extracted, the results need to be synthesised. Depending on the research question, number and heterogeneity of eligible studies and outcomes, approaches can include narrative synthesis of the results, where eligible studies are described, or meta-analysis, where data from relevant studies are pooled to provide a summary effect-size estimate.[103] In my systematic literature review, the relatively small number of eligible studies with differing interventions and outcome measures meant that meta-analysis was not feasible; I therefore adopted a narrative synthesis approach.

2.1.7 Process mapping

A primary objective in Chapter 7 of my thesis was to describe what happens to patients during and after hospitalisations for gout flares. This can be analysed at a population level, for example by using large health datasets, such as the CPRD/NHS Digital analyses (Chapter 5). However, there are downsides to population-level analyses: some data are not adequately captured in population-level health datasets, such as granular data on hospital processes. which can only be captured from other sources of data (e.g. case-note reviews and stakeholder input); aggregated, population-level data are also susceptible to the ecological fallacy, whereby assumptions made on the basis of relationships at a group level may not hold true at an individual level.[107]

To capture more granular information on the processes involved in managing hospitalised patients at a local level, I used several approaches. I manually reviewed the health records of a retrospective sample of patients hospitalised for gout flares at King's College Hospital NHS Foundation Trust. I then process mapped a typical patient journey, taking into account what I had gathered from the case-note reviews, and incorporating input from multiple stakeholders (including multi-disciplinary healthcare professional and patients). This enabled me to define, in detail, what happens to a typical patient with gout, from attendance at ED with symptoms of a gout flare, through to discharge from hospital and subsequent community follow-up.

Process mapping is a method of systematically documenting the activities, process steps and decision steps that occur during a process - in this case, the process of being hospitalised for gout flares.[108] Process mapping enables one to better understand and communicate the barriers and facilitators involved in a complex process, which in turn can help identify areas for improvement. There are several different approaches to process mapping.[108] In consultation with my supervisory team, I adopted a process flowchart method that incorporated principles from the Six Sigma methodology.[109] Six Sigma was developed by Motorola in the 1980s, with the aim of minimising variation and errors in processes. It incorporates five key steps: defining the processes and related problems to be solved; measuring the baseline performance of the process; analysing each step of the process to identify possible reasons for failure; implementing changes to improve performance; and adding controls so that any changes are sustainable.[109]

When process mapping hospital gout care, I collaborated with stakeholders from multiple disciplines to ensure a broad range of views were considered. Any potential sources of delay and/or sub-optimal care were highlighted on a process flowchart. In consultation with stakeholders, I then considered potential solutions that might address the barriers to optimal hospital gout care. Potential solutions mapped to barriers on the flowchart, and grouped according to whether they primarily addressed one of several key themes (diagnostic delay; inadequate flare treatment; inadequate flare prevention; inadequate follow-up arrangements; and prevention of re-admissions).

2.1.8 Qualitative interviews

After implementing a pathway to optimise care for hospitalised gout patients, I wanted to capture granular feedback on facilitators and barriers when using the pathway. To achieve this, I designed a topic guide with interview questions for both patients who received the pathway and healthcare professionals who delivered the pathway (see appendix for interview topics).[110] I conducted individual interviews with patients who had been treated under the pathway. I also collaborated with Maria, a health psychology MSc student, who conducted individual interviews with healthcare professionals who had treated patients using the pathway.

Two different analytical approaches were used to evaluate the patient and healthcare professional interviews. The focus of the patient interviews was to gain stakeholder feedback from the perspective of those who had "received" the pathway. This work was viewed as user-centred design,[111] and is consistent with guidance provided by the Medical Research Council Complex Intervention Development Framework.[112] The aim was to identify necessary changes to the pathway to optimise it further from the patient perspective. I conducted these interviews because I had the best knowledge of the pathway. The analysis strategy focussed on comparing patients' experience of the pathway, relative to its planned implementation. The focus of the healthcare professional interviews was also to explore how best to optimise the pathway. A more in-depth, thematic analysis was performed for healthcare professionals, to understand barriers and facilitators of its use from their perspective, because they are key to its implementation, as outlined below.

Thematic analysis is a qualitative research method that involves systematically identifying and analysing themes within data.[113] This enables researchers to form a more detailed interpretation and understanding of patterns within complex, qualitative datasets. Thematic analysis can be seen as an umbrella term for several different approaches to identifying common themes within data, including inductive thematic analysis, deductive thematic analysis, reflexive thematic analysis, and mixed-methods thematic analysis.[113] In inductive thematic analysis, there are no pre-determined themes; these emerge following analysis of the data. In contrast, with deductive thematic analysis, the researcher utilises pre-existing hypotheses to guide the identification of themes.

In consultation with my supervisory team, Maria adopted a reflexive thematic analysis approach to analyse the healthcare professional interview data.[114] Central to this approach is the concept of reflexivity, whereby researchers reflect upon their own perspectives and assumptions whilst interpreting and analysing themes. This, in turn, can contribute a more nuanced understanding of the data, and improve the validity of the analyses by exploring possible biases in interpretation. In reflexive thematic analysis, there are a series of steps that are typically followed iteratively to develop themes from the data.[114] Firstly, the researcher familiarises themselves with the interview transcripts by reading them several times and formulating notes. Semantic codes (textual information) and latent codes (implicit

information) are generated, and organised into initial themes according to the identified patterns. The initial themes are reviewed, modified, and thematic maps built. The finalised themes are named and defined, in order to convey data patterns. Finally, the research questions, codes, themes and definitions are verified. Throughout this process, the researcher reflects upon how their own experiences and perspectives can influence their interpretation of the data and the selection of themes.[114]

There are limitations of reflexive thematic analysis, and thematic analysis more broadly, that need to be taken into consideration.[114] The identification and interpretation of themes is a highly subjective process. This has the potential to introduce bias, depending on the researcher's personal experiences. Reflexive thematic analysis can help improve the transparency of such interpretations, by acknowledging the researcher's individual interpretations of the data; this does not, however, eliminate the potential for bias. Inconsistent findings can result from this subjectivity, with different researchers reaching different conclusions from the data. Another potential limitation is limited generalisability of the findings, whereby identified themes are specific to the research setting or individual experiences of the researchers.

2.2 Data sources

In my thesis, I utilised three real-world, health datasets for my population-level analyses of primary and secondary care management of gout, and to evaluate changes in disease incidence and prevalence.

2.2.1 Clinical Practice Research Datalink

CPRD is a longitudinal health dataset, containing anonymised health data from people registered with over 2,000 primary care practices in the UK.[115] CPRD was established more than 30 years ago, and has contributed to over 3,000 peer-reviewed publications during this period.[115] Data including demographic characteristics, coded medical diagnoses, prescriptions and test results are available for over 60 million patients previously or currently registered with CPRD-contributing general practices in the UK, of whom over 18 million are currently registered. Eligible practices can choose whether to participate (and contribute data to) CPRD for public health and research purposes. There are strict privacy safeguards in place to preserve the privacy and confidentiality of patient data.[116,117] No identifiable characteristics (e.g. name, address, NHS number, exact date of birth) are transferred from practices or sent to researchers. All CPRD projects require approval via the CPRD Research Data Governance Panel, to ensure the proposed research is of benefit to patients and the public. As no identifiable data are transferred to researchers, informed consent is not required from patients to analyse data in CPRD after project approval is obtained; however, data opt-outs must be respected.[116]

CPRD data are separated into two datasets: CPRD GOLD, which contains data contributed by practices using Vision® EHR software, and CPRD Aurum, which contains data contributed by practices using EMIS® EHR software. There are advantages and disadvantages of each dataset. CPRD GOLD data has been in use for more than 20 years, and has excellent historical data coverage throughout the nations of the UK. There is mean follow-up of 14 years for currently registered patients in CPRD GOLD, compared with 11 years in CPRD Aurum.[118,119] There are also a large number of previous CPRD GOLD-based studies available to researchers, in addition to libraries of codelists (Vision® uses the Read coding system, in contrast to SNOMED coding in EMIS®).

A key benefit of CPRD Aurum is the number of registered practices and patients: there are over 13 million currently registered patients in CPRD Aurum, corresponding to 20% of the UK population, compared with 3 million currently registered patients in CPRD GOLD (4.5% of the UK population).[118,119] 99% of patients in CPRD Aurum are registered with practices in England, whereas only 2% of currently-registered patients in CPRD GOLD are registered with practices in England. NHS Digital Hospital Episode Statistics data linkage are only available in England, which means that there are many more currently registered patients eligible for linkage in CPRD Aurum than GOLD.

For my analyses of primary care gout management (Chapter 3), I opted to use CPRD GOLD. I wanted a dataset with coverage throughout the UK, which made CPRD GOLD more suitable than CPRD Aurum, particularly as linked hospital data were not essential. In contrast, for my analyses of gout hospitalisations (Chapter 5), I required linked primary and secondary care data. I therefore used CPRD Aurum for these analyses.

2.2.2 Hospital Episode Statistics

In England, data on all hospital admissions, emergency department attendances and outpatient attendances at NHS hospitals are captured and managed by the Secondary Uses Service (SUS) via NHS England. These data are essential for healthcare planning, commissioning, audit, research and other non-direct care purposes.[120] From SUS, Hospital Episodes Statistics (HES) datasets are curated on an annual basis. HES data are then made available for the purposes of research and other secondary uses following an approval process. HES data can also be linked with other data sources, including primary care data sources, via platforms such as CPRD and OpenSAFELY.

Within HES, there are several datasets, covering hospital admissions, emergency department attendances, critical care stays, and outpatient activity. The quantity and quality of data captured within each dataset varies widely. By far the most comprehensive dataset within HES is the Admitted Patient Care (APC) dataset, which contains coded data on all admission episodes to hospitals in England, including private patients treated in NHS Hospitals and NHS treatment delivered in the private sector.[71] Within HES APC, coded data is captured on primary and secondary admission diagnoses (using the International Classification of Diseases

version 10 (ICD10) coding frame), patient demographics, dates and methods of admission and discharge, length of stay, specialist input and procedures (using the UK Office of Population, Census and Surveys classification (OPCS) 4.6). These data can be linked to primary care data and other data sources using unique NHS numbers and other identifiers.[121]

Data capture within the other HES datasets is more limited than HES APC. Historically, the HES Accident and Emergency (A&E) dataset has relied upon a unique coding system that is much less granular than the ICD10 coding system. In 2020, HES A&E transitioned to the Emergency Care Data Set (ECDS), which captures new data fields and information on other urgent care visits (e.g. Hot clinics).[122] Importantly, ECDS utilises Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) terms, which greatly improves the granularity of information on coded diagnoses.

Only limited information is captured in the HES Outpatient dataset. Unlike HES APC, it is not mandatory for hospitals to record diagnostic information for outpatient visits using ICD-10 codes. As such, diagnostic information is often missing within the HES Outpatient dataset, which limits is diagnostic utility. Data are captured on outpatient visit date, treatment speciality and other appointment metrics, which makes these data more useful for service-related projects. I have previously utilised these data to highlight changes in service delivery during the COVID-19 pandemic for people with autoimmune rheumatic diseases.[123]

A key strength of HES lies in its data coverage, which allows one to capture nearly all admission episodes to hospitals in England. This is particularly helpful when trying to analyse the admission burden of conditions such as gout (Chapter 5). Historically, the reliability of coding within HES had been a concern; however, with the introduction of Payment by Results (where funding is based upon diagnostic coding), there has been a greater emphasis on data quality and completeness.[124] Of note, the quality of diagnostic coding can vary substantially between diagnoses and depending on whether the condition was a primary or non-primary admission diagnosis.[124] Primary admission diagnoses are typically more reliably coded that secondary admission diagnoses. As such, for my analyses of gout hospitalisations, I made an *a priori* decision to include only admissions with primary admission diagnoses of gout. While improving the robustness of my analyses, this will be an underestimate of the overall hospital burden of gout, as it does not capture admissions in which gout occurred as a secondary diagnosis (e.g. during an admission for heart failure). I acknowledge this as a limitation in my analyses. With the introduction of the ECDS dataset, it may be also possible to reliably capture emergency department attendances with diagnoses of gout in future analyses.

2.2.3 OpenSAFELY

There are some key limitations with existing datasets, such as CPRD. Firstly, data are available for only a subset of the population - around 25% of the UK in CPRD. While this may provide sufficient analytical power for relatively common conditions such as gout, it can be an issue for rare conditions, such as autoimmune or genetic diseases. Additionally, there is substantial

regional variation the proportion of practices that contribute data to platforms such as CPRD, which can lead to poor data coverage in certain regions of the country.

Secondly, there are issues with delays in accessing data. For primary care data in CPRD, there is typically a 1 to 2-month lag between events being recorded in primary care and being made available to researchers for analysis. For secondary care data, however, this lag is often more than a year. While less problematic for historical analyses, such as diagnostic incidence trends, this is a major issue when trying to analyse contemporaneous events. For example, my analyses of pandemic-related changes in gout incidence, prevalence and hospitalisation events (Chapter 4) requires data that are closer to real-time.

Another major criticism of platforms such as CPRD and HES is the potential for data breaches and disclosure of sensitive information. While safeguards are in place to limit the potential for disclosure of sensitive information (e.g. de-identification of patient data), there still remains a potential for disclosure. As an example, medical conditions and events (e.g. operations) are frequently reported in the news for prominent individuals, such as politicians and celebrities. This information could be combined to identify an individual's record within a pseudonymised dataset, leading to disclosure of other sensitive information. In addition, at present, de-identified data are physically transferred to individuals for analysis via CPRD and HES. This increases the likelihood of data breaches occurring.

To overcome the aforementioned barriers with existing health datasets, the OpenSAFELY platform was created by the Bennett Institute at the University of Oxford, in collaboration with the London School of Hygiene and Tropical Medicine, TPP and EMIS (primary care software providers), and NHS England. It was created at the start of the COVID-19 pandemic, to support urgent research into the pandemic. Primary care data for all general practices in England that use TPP and EMIS software (>99% of all practices in England) are available for analysis via the OpenSAFELY platform. Primary care data are linked with multiple other health datasets via the OpenSAFELY platform, including SUS/HES data, Office for National Statistics death registry data, COVID-19 test results, and high-cost drug data.[125]

As well as its unparalleled data coverage, the lags in data availability are much shorter with OpenSAFELY than with other datasets. Primary care data are typically available within a week of the events being coded in primary care. SUS data are typically available within 1-2 months of hospital events occurring.[125] This enables researchers to conduct analyses closer to real time, which, in turn, opens up the potential for dashboarding and feedback to clinicians (e.g. via the OpenSAFELY reports website: https://reports.opensafely.org/).

A major benefit of OpenSAFELY lies in its privacy safeguards. OpenSAFELY acts as a Trusted Research Environment, through which approved researchers can analyse linked patient data without physically being sent those data. In OpenSAFELY, no individual-level data leaves the environments in which it already resides: the servers of primary care software providers (TPP and EMIS). Instead, researchers write their analysis code against dummy data, similar in format to real patient data. Once written, they then submit their analysis code behind a

firewall, to run against the real patient data.[125] Researchers can only access the summary/aggregate outputs from these analyses, not the individual data. These outputs are only released once they have had statistical disclosure techniques applied and been checked by at least two qualified output checkers. This approach not only reduces the likelihood of sensitive data disclosure, but also reduces the potential for "data fishing". Additionally, all analysis code is made publicly available via GitHub, which reduces redundant analysis code between projects.

The current legal basis for collecting and processing confidential patient data without consent via OpenSAFELY requires that there is COVID-19-related purpose for the project.[126] This basis includes research that improves our understanding of the impact of COVID-19 on health services. This provided justification for analyses of the impact of COVID-19 on the incidence, prevalence and management of gout in England (Chapter 4).

3 Epidemiology of gout management in UK primary care (*Lancet Regional Health Europe, 2022*)

3.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 1: Has gout management in UK primary care improved following the publication of updated gout management guidelines?

Previous epidemiological studies have highlighted the sub-optimal management of gout in the UK.[1] Kuo *et al.* used CPRD data, up to 2012, to demonstrate that only 27% of people with gout in UK primary care received prescriptions for ULT within 12 months of diagnosis.[1] Recognising the need for improvement, the BSR (2017), EULAR (2016), ACR (2020) and NICE (2020) have all introduced updated gout management guidelines.[6-8,35] These guidelines substantially lowered the threshold for the initiation of ULT, and recommended a treat-to-target approach.

However, no studies to date have investigated whether these guideline recommendations have been widely implemented in UK clinical practice, or analysed whether ULT initiation and urate target attainment have improved since previous analyses were performed in 2012.[1] Additionally, both the BSR and EULAR guidelines strongly recommend that ULT should be initiated in patients with comorbidities such as CKD; yet, it remains unclear whether these recommendations have been implemented. I investigated these important questions using population-level, primary care data in CPRD.

Management of gout following 2016/2017 European (EULAR) and British (BSR) guidelines: an interrupted time-series analysis in the United Kingdom

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3.2 Abstract

Background: Following studies reporting sub-optimal gout management, EULAR and BSR guidelines were updated to encourage the prescription of ULT with a treat-to-target approach. We investigated whether ULT initiation and urate target attainment has improved following publication of these guidelines, and assessed predictors of these outcomes.

Methods: We used the CPRD to assess attainment of the following outcomes in people (n=129,972) with index gout diagnoses in the UK from 2004-2020: i) initiation of ULT; ii) serum urate ≤360 µmol/L and ≤300 µmol/L; iii) treat-to-target urate monitoring. Interrupted time-series analyses were used to compare trends in outcomes before and after updated EULAR and BSR management guidelines, published in 2016 and 2017, respectively. Predictors of ULT initiation and urate target attainment were modelled using logistic regression and Cox proportional hazards.

Findings: 37,529 (28.9%) of 129,972 people with newly-diagnosed gout had ULT initiated within 12 months. ULT initiation improved modestly over the study period, from 26.8% for those diagnosed in 2004 to 36.6% in 2019 and 34.7% in 2020. Of people diagnosed in 2020 with a serum urate performed within 12 months, 17.1% attained a urate ≤300 µmol/L, while 36.0% attained a urate ≤360 µmol/L. 18.9% received treat-to-target urate monitoring. No significant improvements in ULT initiation or urate target attainment were observed after updated BSR or EULAR management guidance, relative to before. Comorbidities, including CKD, heart failure and obesity, and diuretic use associated with increased odds of ULT initiation but decreased odds of attaining urate targets within 12 months: CKD (adjusted OR 1.61 for ULT initiation, 95% CI 1.55 to 1.67; adjusted OR 0.51 for urate ≤300 µmol/L, 95% CI 0.48 to 0.55; both p<0.001); heart failure (adjusted OR 1.56 for ULT initiation, 95% CI 1.48 to 1.64; adjusted OR 0.85 for urate ≤300 µmol/L, 95% CI 0.76 to 0.95; both p<0.001); obesity (adjusted OR 1.32 for ULT initiation, 95% CI 1.29 to 1.36; adjusted OR 0.61 for urate ≤300 µmol/L, 95% CI 0.58 to 0.65; both p<0.001); and diuretic use (adjusted OR 1.49 for ULT initiation, 95% CI 1.44 to 1.55; adjusted OR 0.61 for urate ≤300 µmol/L, 95% CI 0.57 to 0.66; both p<0.001).

Interpretation: Initiation of ULT and attainment of urate targets remain poor for people diagnosed with gout in the UK, despite updated management guidelines. If the evidence-practice gap in gout management is to be bridged, strategies to implement best practice care are needed.

3.3 Introduction

Gout is the most common form of inflammatory arthritis, with a prevalence of 2.5% in the UK and 3.9% of adults in the United States.[1,2] In the context of chronic hyperuricaemia and urate crystal deposition, gout is characterised by recurrent flares of joint pain and swelling, erosive joint damage, and extra-articular sequelae such as renal impairment.

Gout is also the only curable form of inflammatory arthritis: flares are preventable with ULT, of which allopurinol is the first-line recommended treatment.[6] Despite this, in 2012, only 27% of people with gout in UK primary care received prescriptions for ULT within 12 months of diagnosis.[1] Moreover, only a minority achieve the serum urate levels necessary to prevent gout flares and morbidity.[5,31] Studies in other countries, including the United States, Australia, New Zealand, Sweden and Taiwan have also reported sub-optimal levels of ULT initiation and target attainment.[53,57,58,60,127-129]

Recognising the need for improvement, the EULAR and BSR updated their gout management guidelines in 2016 and 2017, respectively.[6,7] The BSR guideline recommends that all patients with gout should have ULT discussed and offered to them, while EULAR guidance recommends that ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. The prescription of ULT is strongly encouraged in people with gout who have risk factors that include CKD, cardiovascular comorbidities (hypertension, IHD and heart failure), urolithiasis, diuretic use, or gout diagnosis at a young age.[6,7] Once initiated, it is recommended that the dose of ULT is uptitrated to achieve a serum urate level that is below the saturation threshold, thereby preventing new crystal formation and helping to dissolve pre-existing crystals. The target urate level is ≤300 µmol/L in the BSR guideline, and ≤300 µmol/L or ≤360 µmol/L, depending on gout severity, in the EULAR guideline.[6]

Whether gout management has improved, particularly following the publication of updated guidelines, is not known. In this study, we performed analyses of people diagnosed with gout in the UK between 2004 and 2020, to assess the following objectives: i) temporal trends in the initiation of ULT, and predictors thereof; ii) trends in the implementation of a treat-to-target approach with regards to serum urate levels and monitoring; and iii) predictors of attaining target serum urate levels.

3.4 Methods

Data source

The CPRD is a longitudinal, representative health database containing anonymised demographic, clinical and prescription data from people registered with over 2000 primary care practices in the UK.[115] In this study, we used the CPRD GOLD dataset, containing data on over 20 million people from general practices using Vision® electronic health record software.

Study population and case definition

We conducted a population-level, observational cohort study of people aged ≥18 years, currently or previously registered with a CPRD GOLD practice, with index gout diagnoses between 1st January 2004 and 21st October 2020. The start date of 2004 corresponds to the more widespread availability of laboratory-linked data with the incorporation of the Quality and Outcomes Framework into UK primary care contracts.

An index gout diagnosis was defined as a new diagnostic code for incident gout in people without previous gout diagnostic codes. A minimum of 12 months of registration with a CPRD practice prior to the first gout diagnostic code was required to ensure only incident cases were detected, in addition to a minimum of 12 months of follow-up post-diagnosis.

Outcomes and predictor variables

Primary outcome measures assessed were: i) a new prescription for ULT (allopurinol, febuxostat, benzbromarone, probenecid or sulfinpyrazone) within 12 months of the index gout diagnosis date; ii) a recorded serum urate level ≤360 µmol/L within 12 months of index diagnosis; iii) a recorded serum urate level ≤300 µmol/L within 12 months of index diagnosis; and iv) treat-to-target urate monitoring, which we defined as two or more serum urate levels performed within 12 months of index diagnosis and/or one or more urate levels ≤300 µmol/L within the same time period (i.e. representing a minimum threshold for treat-to-target monitoring). Attainment of these outcomes within 24 months of the index gout diagnosis date were also reported as secondary outcome measures for people with at least 24 months of follow-up with a CPRD practice after diagnosis.

Predictor variables were selected *a priori* on the basis of whether they were felt to be important potential confounders of outcome measures, as follows: age at gout diagnosis; sex; year of gout diagnosis; country within the United Kingdom where patients' registered primary care practices were located (England, Wales, Scotland or Northern Ireland); comorbidities (CKD stages 3-5, hypertension, diabetes mellitus, IHD, heart failure, previous stroke or transient ischaemic attack (TIA), and obesity); current or previous history of urolithiasis; smoking status (current/previous smoker vs. never smoker); alcohol excess; and diuretic therapy at gout diagnosis. Definitions of comorbidities are shown below:

- CKD: ever or current diagnostic code (see below) for CKD stages 3 to 5, renal failure, dialysis or a renal transplant at the time of index gout diagnosis, and/or two consecutive estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m2 closest to the gout index diagnosis date (assuming they were within 5 years of diagnosis).
- Hypertension, diabetes mellitus, IHD, heart failure, urolithiasis, alcohol excess: ever or current diagnostic code for that condition at the time of index gout diagnosis. Absence of the comorbidity was assumed if a diagnostic code was not present.
- Obesity: recorded body mass index ≥30 kg/m2 on the reading closest to the index gout diagnosis date (assuming this reading was within 5 years before or after the diagnosis date).
- Smoking status: ever or current diagnostic code for being an ex-smoker or current smoker at the time of index gout diagnosis.

- Diuretic therapy: prescription issued for a diuretic medication (furosemide, bendroflumethiazide, spironolactone, bumetanide, indapamide, hydrochlorothiazide, eplerenone, metolazone, amiloride, torasemide, chlortalidone, benzthiazide or xipamide) within 4 months of the index gout diagnosis date.

Statistical analysis

Baseline characteristics were tabulated and described without inferential statistics. Attainment of outcome measures by year of gout diagnosis were described graphically using two-way plots.

ITSA were used to estimate the effect of the introduction of updated BSR and EULAR gout management guidelines (published in June 2017 and July 2016, respectively) on: i) the prescription of ULT, and ii) target urate attainment within 12 months of index gout diagnosis. Monthly averages of these outcomes were compared in the periods before and after the introduction of the updated guidelines using single-group ITSA. Autocorrelation between observation periods was accounted for using a Prais-Winsten approach, whereby the generalised least-squares method is used to estimate parameters in a regression model, in which standard errors are assumed to follow a first-order autoregressive process.[101] Robust standard errors were used to allow for practice-level clustering.

Logistic regression was used to estimate the strength of associations between predictor variables and outcomes measures. Robust standard errors were estimated to account for clustering of patients within practices. Age and sex-adjusted models and fully-adjusted models (adjusted for all predictor variables, including year of gout diagnosis) were presented with odds ratios and 95% confidence intervals (CI).

Cox proportional hazards models with robust standard errors were used to describe associations between predictor variables and the time to initiation of ULT following new gout diagnoses (single failure models). Age and sex-adjusted models and fully-adjusted models (adjusted for all predictor variables, including year of gout diagnosis) were presented with hazard ratios and 95% CI. Assumptions regarding proportional hazards were tested graphically using Nelson-Aalen and log-log plots.

Statistical analyses were performed in Stata version 17.1.

Study approval and ethics

The study protocol was approved by the CPRD Research Data Governance committee (approval number: 21_000680). No further ethical approval was required.

3.5 Results

Baseline demographics and comorbidities

Within the cohort, 129,972 people from 905 practices had new diagnoses of gout between January 2004 and October 2020. The mean and median durations of follow-up were 6.3 years and 5.4 years, respectively. The mean age of patients at diagnosis was 62 years; 72.8% were

male. 53.2% of patients were registered with a practice in England; 21.7% in Wales; 20.1% in Scotland; and 5.0% in Northern Ireland. Patient demographics, comorbidities and diuretic use at gout diagnosis are summarised in Table 1. The number of patients with newly-diagnosed gout, separated by year of diagnosis, is shown in Table 2.

At diagnosis, 72.5% of patients had one or more of the following comorbidities: hypertension (47.6%); CKD stages 3-5 (25.3%); diabetes mellitus (12.1%); IHD (15.5%); heart failure (6.8%); previous stroke or TIA (6.0%); and/or obesity (38.9%). 36.2% of patients were receiving diuretic therapy at diagnosis, and 2.1% of patients had a current or previous history of urolithiasis. 61.6% of patients had a baseline serum urate performed, with a mean level of 472 µmol/L. Baseline urate levels were higher in male than female patients (480 µmol/L vs. 452 µmol/L, respectively) and in patients with a greater comorbidity burden at presentation (440 µmol/L vs. 612 µmol/L, respectively, in patients with no comorbidities vs. seven comorbidities at presentation).

Table 1. Baseline demographics, comorbidities and diuretic use in people newly diagnosed with gout

	Total N=129,972	**Male N=94,610**	**Female N=35,362**
Age at diagnosis, years	62 (15)	59 (15)	69 (14)
Country:			
England	69,129 (53.2%)	50,897 (53.8%)	18,232 (51.6%)
Wales	28,180 (21.7%)	20,387 (21.5%)	7,793 (22.0%)
Scotland	26,154 (20.1%)	18,706 (19.8%)	7,448 (21.1%)
Northern Ireland	6,509 (5.0%)	4,620 (4.9%)	1,889 (5.3%)
Number of comorbidities at diagnosis	1.5 (1.4)	1.3 (1.3)	2.0 (1.4)
CKD stages 3-5			
No	97,103 (74.7%)	76,665 (81.0%)	20,438 (57.8%)
Yes	32,869 (25.3%)	17,945 (19.0%)	14,924 (42.2%)
Hypertension			
No	68,106 (52.4%)	55,387 (58.5%)	12,719 (36.0%)
Yes	61,866 (47.6%)	39,223 (41.5%)	22,643 (64.0%)
Diabetes mellitus			
No	114,309 (87.9%)	85,144 (90.0%)	29,165 (82.5%)
Yes	15,663 (12.1%)	9,466 (10.0%)	6,197 (17.5%)
Ischaemic heart disease			
No	109,817 (84.5%)	80,348 (84.9%)	29,469 (83.3%)
Yes	20,155 (15.5%)	14,262 (15.1%)	5,893 (16.7%)
Heart failure			
No	121,084 (93.2%)	88,836 (93.9%)	32,248 (91.2%)
Yes	8,888 (6.8%)	5,774 (6.1%)	3,114 (8.8%)
Previous stroke or TIA			
No	122,200 (94.0%)	89,570 (94.7%)	32,630 (92.3%)
Yes	7,772 (6.0%)	5,040 (5.3%)	2,732 (7.7%)
Obesity			
No	79,364 (61.1%)	60,044 (63.5%)	19,320 (54.6%)
Yes	50,608 (38.9%)	34,566 (36.5%)	16,042 (45.4%)
Urolithiasis			
No	127,259 (97.9%)	92,432 (97.7%)	34,827 (98.5%)
Yes	2,713 (2.1%)	2,178 (2.3%)	535 (1.5%)
Current/ex-smoker			
No	48,550 (37.4%)	34,953 (36.9%)	13,597 (38.5%)
Yes	81,422 (62.6%)	59,657 (63.1%)	21,765 (61.5%)
Alcohol excess			
No	121,975 (93.8%)	87,823 (92.8%)	34,152 (96.6%)
Yes	7,997 (6.2%)	6,787 (7.2%)	1,210 (3.4%)
Diuretic therapy			
No	82,986 (63.8%)	67,916 (71.8%)	15,070 (42.6%)
Yes	46,986 (36.2%)	26,694 (28.2%)	20,292 (57.4%)
Baseline serum urate level, µmol/L	472	480	452

Data are presented as mean (standard deviation) for continuous measures, and n (%) for categorical measures. Baseline serum urate levels were available for 80,054 patients (male patients: n=56,963; female patients: n=23,091).

Table 2. Number of patients with newly-diagnosed gout, separated by sex, year of diagnosis and serum urate data availability

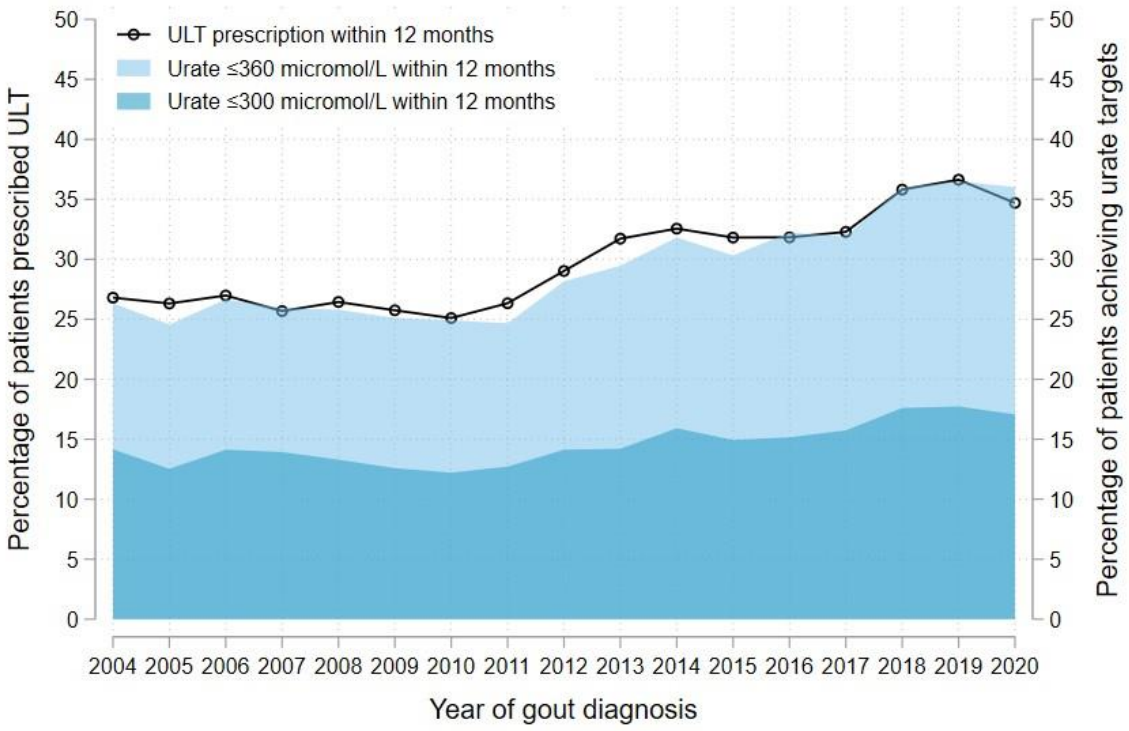
Year of gout diagnosis	All Patients			Patients with post-diagnosis serum urate		
	Total N=129,972	Male N=94,610	Female N=35,362	Total N=65,127	Male N=47,012	Female N=18,115
2004	7,682	5,515	2,167	3,557	2,523	1,034
2005	8,889	6,540	2,349	4,081	2,972	1,109
2006	8,927	6,444	2,483	4,182	2,958	1,224
2007	8,990	6,588	2,402	4,081	2,919	1,162
2008	9,517	6,906	2,611	4,465	3,206	1,259
2009	9,580	7,052	2,528	4,382	3,204	1,178
2010	9,381	6,871	2,510	4,434	3,211	1,223
2011	9,716	7,155	2,561	4,730	3,473	1,257
2012	9,746	6,979	2,767	4,995	3,582	1,413
2013	9,553	6,941	2,612	5,142	3,725	1,417
2014	8,376	6,037	2,339	4,541	3,254	1,287
2015	6,670	4,838	1,832	3,640	2,630	1,010
2016	5,834	4,250	1,584	3,211	2,323	888
2017	5,482	4,001	1,481	3,060	2,229	831
2018	5,043	3,678	1,365	2,986	2,153	833
2019	4,583	3,340	1,243	2,627	1,915	712
2020	2,003	1,475	528	1,013	735	278

Data are shown in the right-hand side of the table for patients with newly-diagnosed gout who had at least one serum urate level performed within 12 months of diagnosis.

Prescription of ULT after diagnosis

Overall, 37,529 (28.9%) of 129,972 people with newly-diagnosed gout received prescriptions for ULT within 12 months of diagnosis. The proportion of people initiated on ULT within 12 months of diagnosis improved modestly over the study period, from 26.8% for those diagnosed in 2004 to 36.6% in 2019, decreasing slightly to 34.7% for people diagnosed in 2020 (Figure 6).

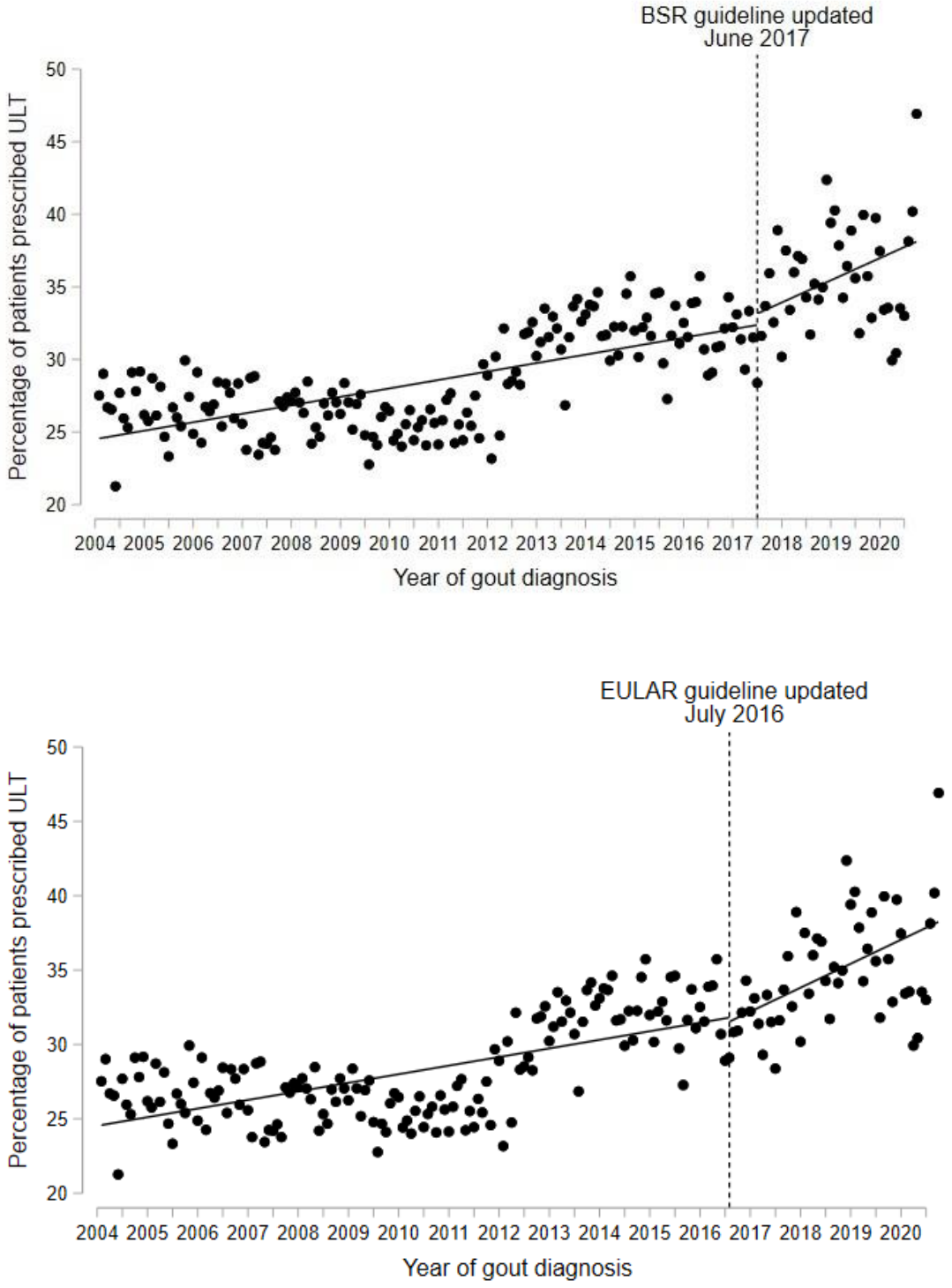
Figure 6. Initiation on ULT and attainment of serum urate targets in new gout patients



Proportion of patients newly diagnosed with gout (n=129,972), separated by year of diagnosis, who: i) were initiated on ULT within 12 months of diagnosis (black line); or ii) had a serum urate performed (n=65,127) and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 12 months of diagnosis.

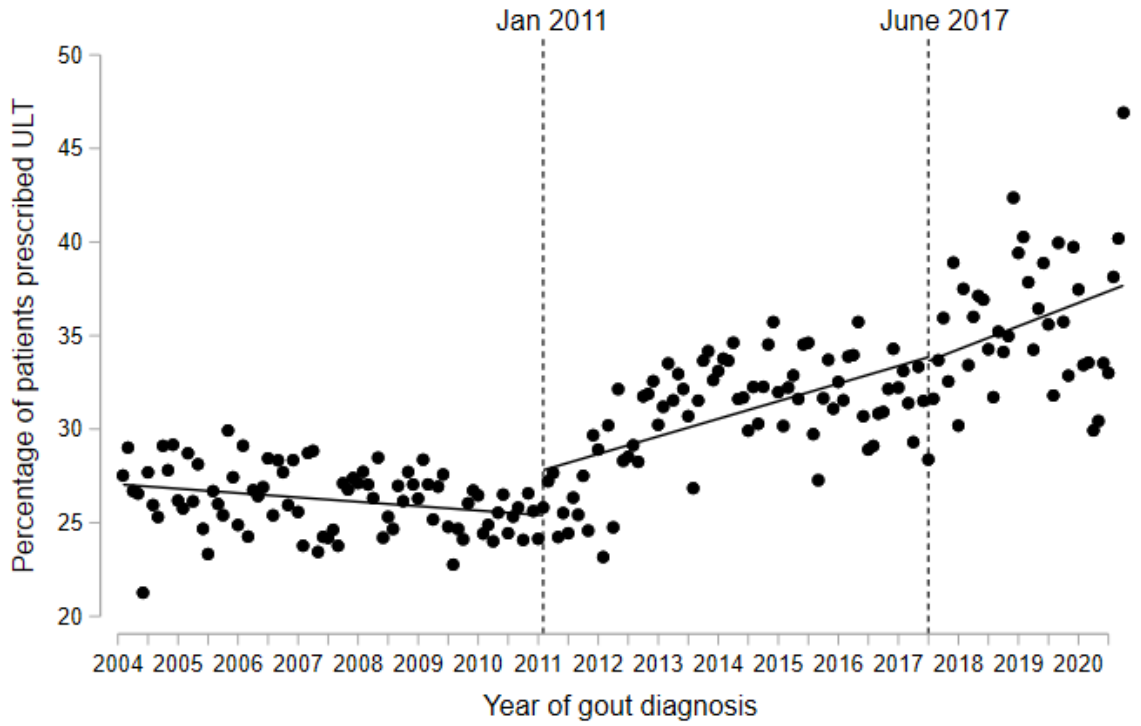
We estimated the effect of publication of updated BSR and EULAR gout management guidelines (in June 2017 and July 2016, respectively) on the initiation of ULT, using ITSA models. The trend in ULT initiation after publication of the BSR guideline was not significantly different to prior to publication (rate of improvement post-guideline: 1.53% per year; pre-guideline: 0.58% per year; difference: 0.95% per year: 95% CI -1.13 to 3.02, p=0.37) (Figure 7). Similarly, no statistically significant differences in ULT initiation were observed after publication of the EULAR guideline (rate of improvement post-guideline: 1.61% per year; pre-guideline: 0.58% per year; difference: 1.03% per year: 95% CI -0.14 to 2.21, p=0.09) (Figure 7). As sensitivity analyses, ITSA were performed with an additional cut point in January 2011 (i.e. before an apparent improvement in ULT initiation between 2011 and 2014); this demonstrated improvements in ULT initiation after 2011, relative to before 2011, but showed no significant changes after the publication of BSR or EULAR guidelines (Figure 8 and Figure 9).

Figure 7. Trends in ULT initiation, before and after the introduction of the BSR and EULAR gout guidelines



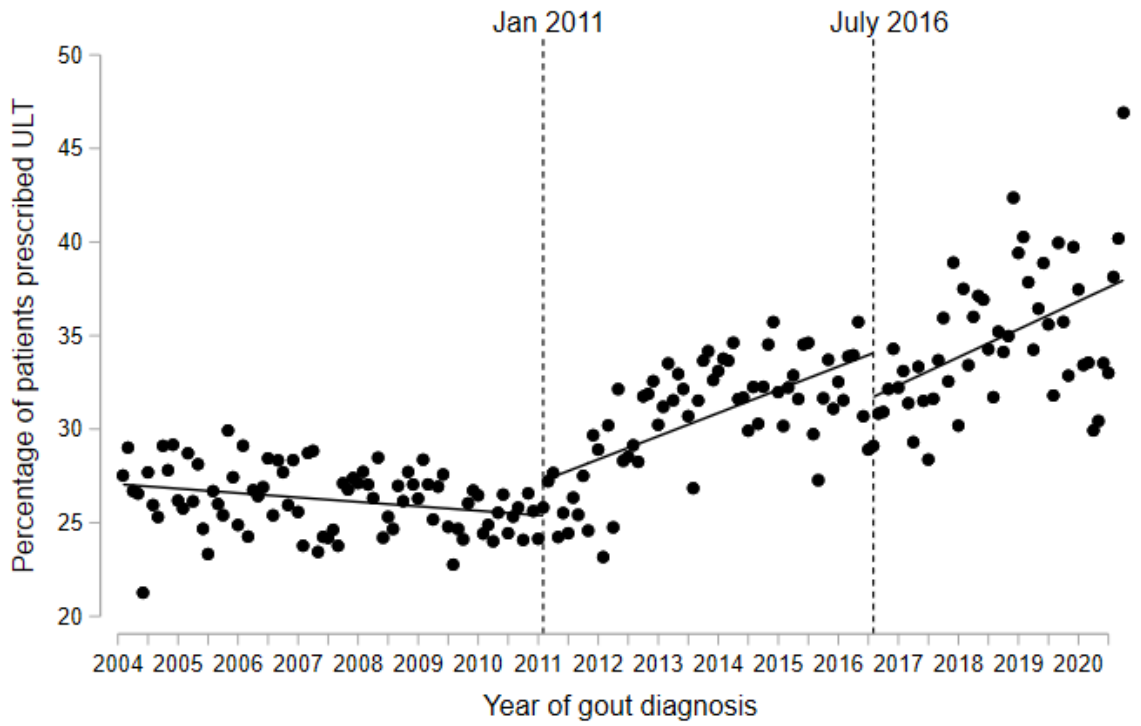
Percentage of newly-diagnosed gout patients (n=129,972) who were prescribed ULT within 12 months of diagnosis, comparing trends before and after the introduction of the updated BSR gout management guideline, published in June 2017 (top panel), and the EULAR gout management guideline, published in July 2016 (bottom panel). Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of ULT initiation.

Figure 8. Trends in ULT initiation, before and after the introduction of the BSR gout guideline, with an additional change point in 2011



Percentage of patients newly diagnosed with gout (n=129,972) who were prescribed ULT within 12 months of gout diagnosis, comparing trends before and after two time points: i) January 2011 (i.e. before an apparent period of improvement in ULT initiation between 2011 and 2014), and ii) after the introduction of updated BSR gout management guidelines in June 2017. Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of ULT prescription rates. Trend change after June 2017, relative to between Jan 2011 and June 2017: 0.30% improvement per year, 95% CI -1.50 to 2.10, p=0.74. Trend change between Jan 2011 and June 2017, relative to pre-2011: 1.17% improvement per year, 95% CI 0.71 to 1.63, p<0.001.

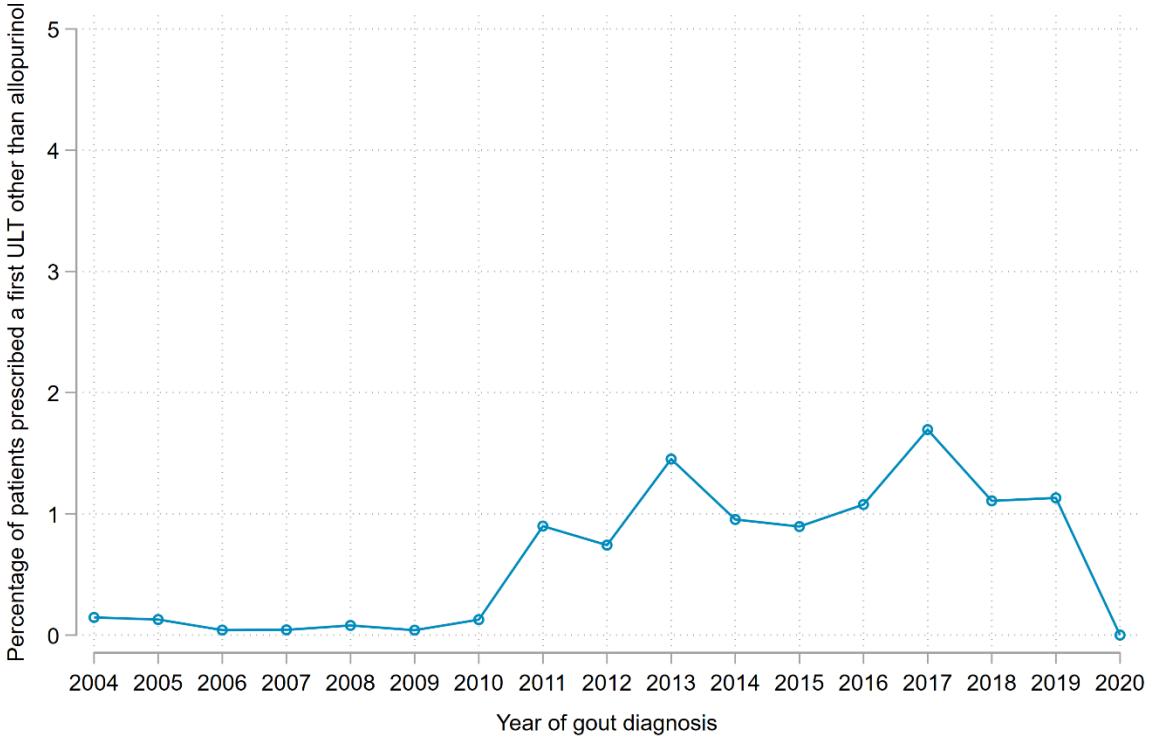
Figure 9. Trends in ULT initiation, before and after the introduction of the EULAR gout guideline, with an additional change point in 2011



Percentage of patients newly diagnosed with gout (n=129,972) who were prescribed ULT within 12 months of gout diagnosis, comparing trends before and after two time points: i) January 2011 (i.e. before an apparent period of improvement in ULT initiation between 2011 and 2014), and ii) after the introduction of updated EULAR gout management guidelines in July 2016. Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of ULT prescription rates. Trend change after July 2016, relative to between Jan 2011 and July 2016: 0.26% improvement per year, 95% CI -0.85 to 1.36, p=0.65. Trend change between Jan 2011 and July 2016, relative to pre-2011: 1.48% improvement per year, 95% CI 0.94 to 2.02, p<0.001.

Of first ULT prescriptions, 37,293 (99.4%) were for allopurinol, while 222 (0.6%) were for febuxostat. The proportion of first ULT prescriptions for medications other than allopurinol increased from <0.15% prior to 2011, to 1.7% in 2017, before decreasing slightly to 1.1% in 2019 (Figure 10). There were no first ULT prescriptions for medications other than allopurinol in 2020.

Figure 10. Initiation of ULT medications other than allopurinol, by year of diagnosis

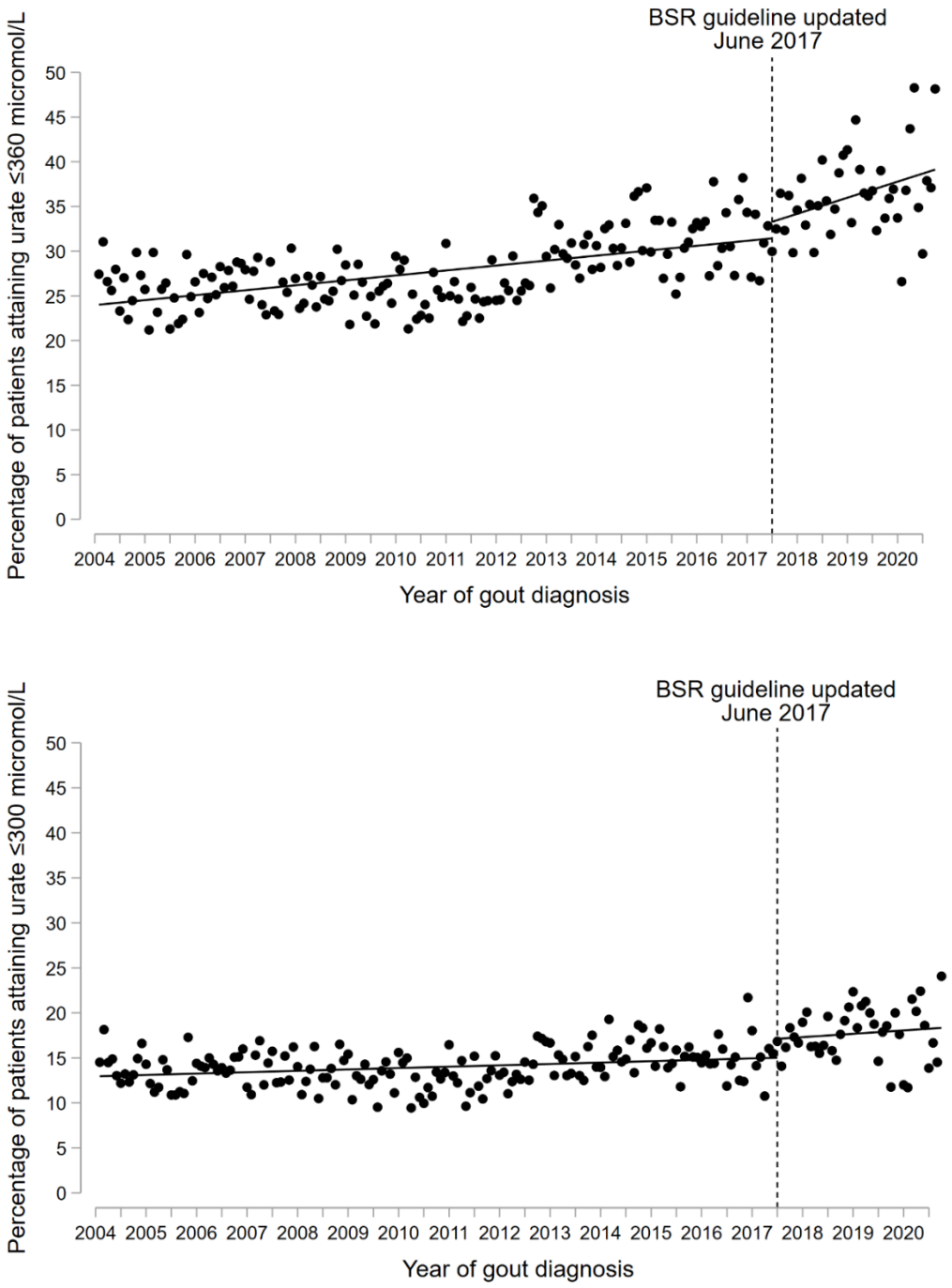


Percentage of patients newly diagnosed with gout (n=129,972) who received first ULT prescriptions for medications other than allopurinol within 12 months of diagnosis, separated by year of diagnosis

Target serum urate attainment and monitoring

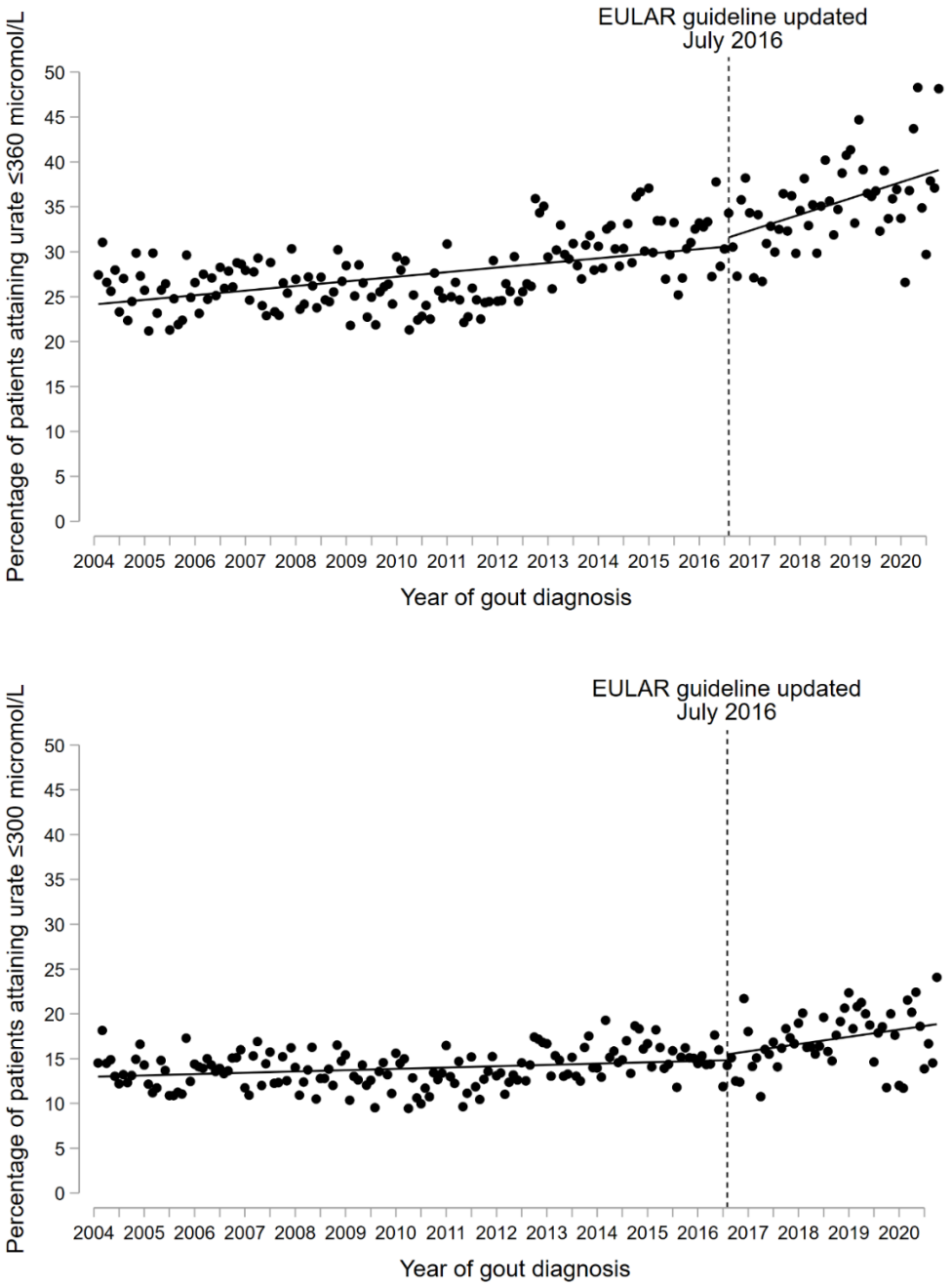
65,127 (50.1%) of 129,972 people with newly-diagnosed gout had at least one serum urate level performed within 12 months of diagnosis, of whom 9,304 (14.3%) attained a serum urate level ≤300 µmol/L and 18,523 (28.4%) attained a level ≤360 µmol/L. Target urate attainment increased modestly over the study period, from 14.2% in 2004 to 17.7% in 2019 and 17.1% in 2020 (for ≤300 µmol/L), and from 26.3% in 2004 to 36.5% in 2019 and 36.0% in 2020 (for ≤360 µmol/L (Figure 6). In ITSA models, trends in the attainment of urate targets after publication of updated EULAR and BSR guidelines were not significantly different to prior to the publication of these guidelines (Figure 11 and Figure 12).

Figure 11. Attainment of target urate levels before and after the introduction of updated BSR guidelines



Percentage of patients newly diagnosed with gout who had a serum urate level performed within 12 months of diagnosis (n=65,127) and attained a urate ≤360 µmol/L (top panel) and ≤300 µmol/L (bottom panel), comparing trends before and after the introduction of the updated BSR gout management guideline (published in June 2017). Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of urate target attainment rates. For urate ≤360 µmol/L, rate of improvement post-guideline: 1.80% per year; pre-guideline: 0.55% per year; difference 1.25% per year, 95% CI -0.68 to 3.17, p=0.20. For urate ≤300 µmol/L, rate of improvement post-guideline: 0.37% per year; pre-guideline: 0.15% per year; difference: 0.22% per year, 95% CI -0.99 to 1.43, p=0.72.

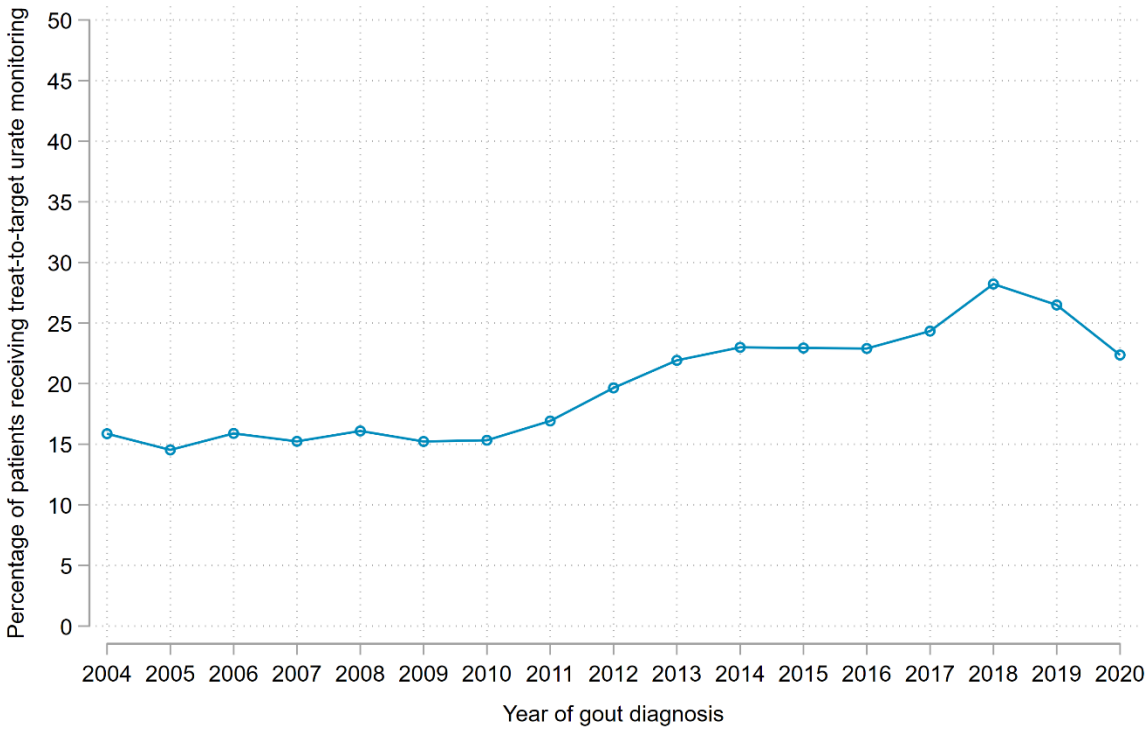
Figure 12. Attainment of urate levels before and after the introduction of updated EULAR guidelines



Percentage of patients newly diagnosed with gout who had a serum urate level performed within 12 months of diagnosis (n=65,127) and attained a urate ≤360 µmol/L (top panel) and ≤300 µmol/L (bottom panel), comparing trends before and after the introduction of the updated EULAR gout management guideline (published in July 2016). Trends were assessed using interrupted time-series analysis, with single time point dots representing monthly average percentages of urate target attainment rates. For urate ≤360 µmol/L, rate of improvement post-guideline: 1.80% per year; pre-guideline: 0.51% per year; difference 1.28% per year, 95% CI -0.08 to 2.66, p=0.07. For urate ≤300 µmol/L, rate of improvement post-guideline: 0.81% per year; pre-guideline: 0.15% per year; difference 0.66% per year, 95% CI -0.28 to 1.60, p=0.17.

24,593 (18.9%) of 129,972 patients received treat-to-target serum urate monitoring, which we defined as two or more serum urate levels performed within 12 months of diagnosis and/or one or more serum urate levels ≤300 µmol/L within the same period. Treat-to-target monitoring increased from 15.9% of patients in 2004 to 28.2% of patients in 2018, before decreasing to 22.4% in 2020 (Figure 13).

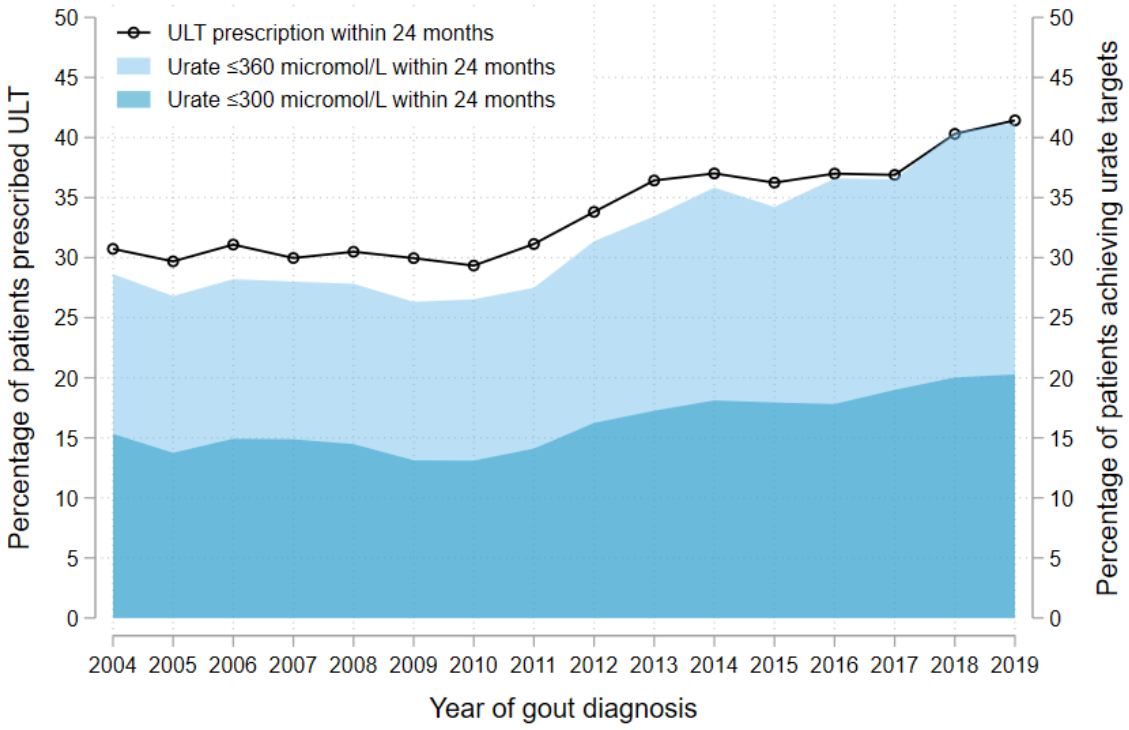
Figure 13. Treat-to-target urate monitoring within 12 months of gout diagnosis



Proportion of newly diagnosed gout patients (n=129,972) who received treat-to-target serum urate monitoring within 12 months of diagnosis, by year of gout diagnosis. Treat-to-target monitoring was defined as two or more urate levels performed within 12 months of diagnosis and/or one or more urate levels ≤300 µmol/L within the same period.

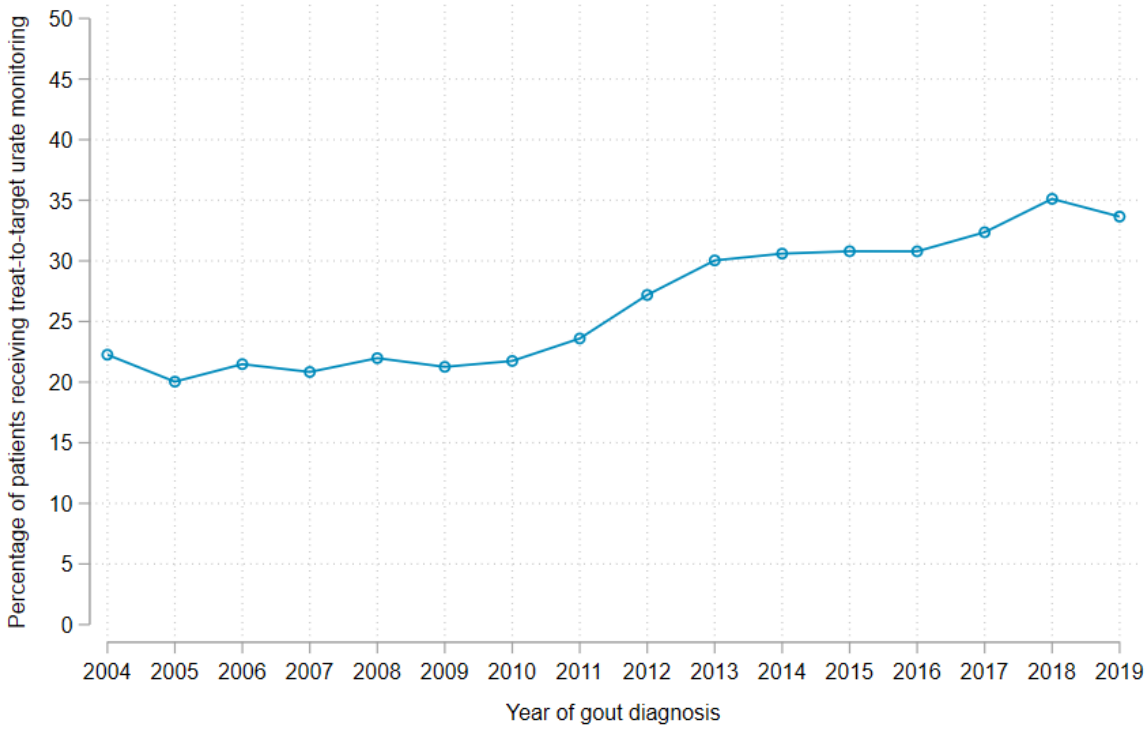
Trends in the attainment of serum urate targets, initiation of ULT, and treat-to-target urate monitoring within 24 months of gout diagnosis were comparable to those observed within 12 months of diagnosis, as shown in Figure 14 and Figure 15. Temporal trends in ULT initiation and urate target attainment, comparing male and female patients, are shown in Figure 16.

Figure 14. Initiation of ULT and attainment of urate targets within 24 months of gout diagnosis



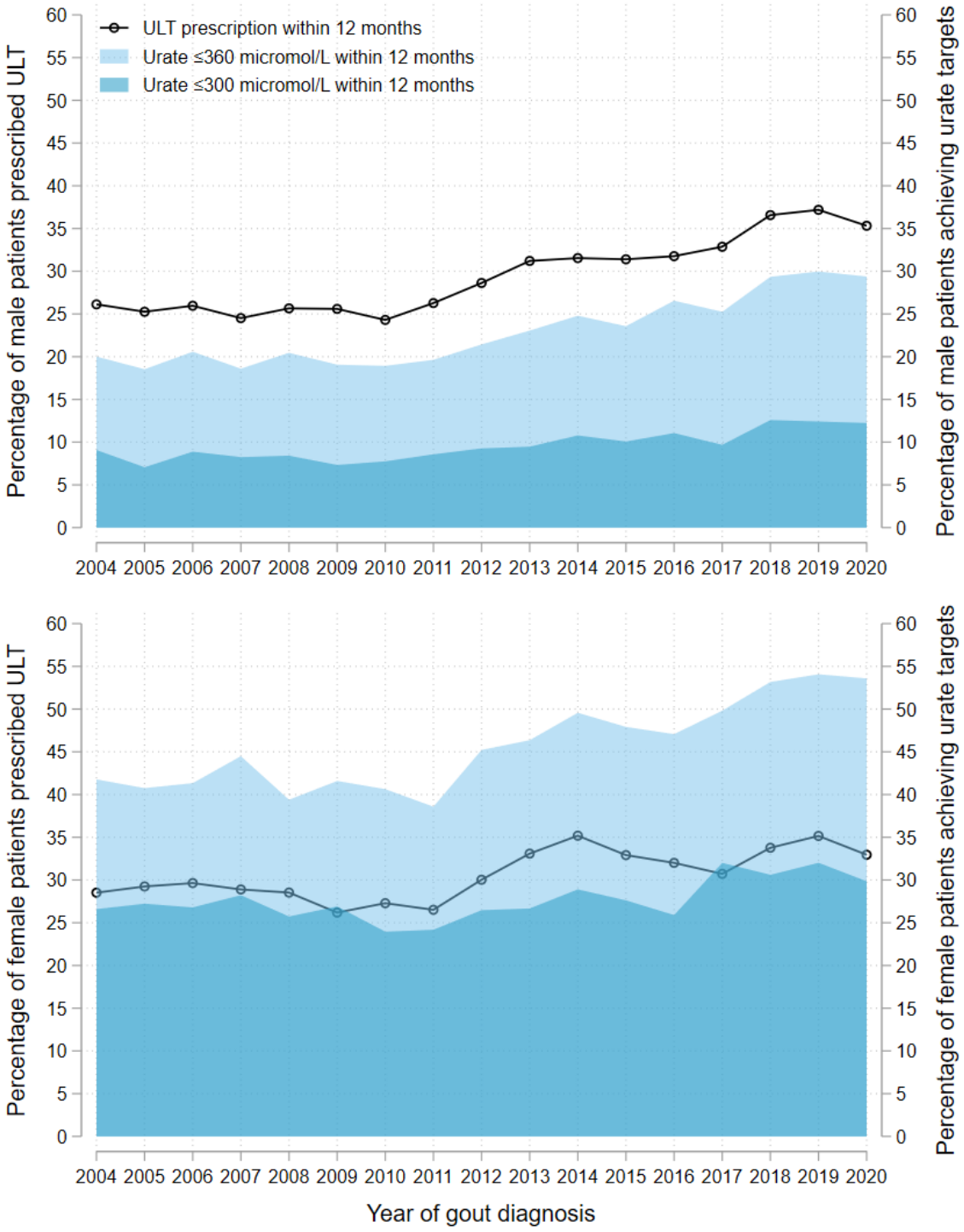
Proportion of patients newly diagnosed with gout, separated by year of diagnosis, who: i) were initiated on ULT within 24 months of diagnosis (black line); or ii) had a serum urate performed and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 24 months of diagnosis.

Figure 15. Treat-to-target urate monitoring within 24 months of gout diagnosis



Proportion of newly-diagnosed gout patients who received treat-to-target serum urate monitoring within 24 months of diagnosis, separated by year of gout diagnosis. Treat-to-target monitoring was defined as two or more urate levels performed within 24 months of diagnosis and/or one or more urate levels ≤300 µmol/L within the same period.

Figure 16. Trends in the initiation of ULT and attainment of urate targets within 12 months of diagnosis for male and female patients with gout



Proportion of male patients (top panel; n=94,610) and female patients (bottom panel; n=35,362) newly diagnosed with gout who: i) were initiated on ULT within 12 months of diagnosis (black line); or ii) had a serum urate performed (male: n=47,012; female: n=18,115) and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 12 months of diagnosis, separated by year of diagnosis.

Predictors of ULT prescription and target urate attainment

Univariable and multivariable logistic regression was performed to analyse predictors of ULT prescription (Table 3) and attainment of serum urate levels ≤300 µmol/L (Table 4) or ≤360 µmol/L (Table 5) within 12 months of gout diagnosis.

People with gout and CKD stages 3-5 at baseline were more likely to be prescribed ULT within 12 months of diagnosis than patients without CKD (adjusted mean difference 9.83%, adjusted OR 1.61, 95% CI 1.55 to 1.67, p<0.001); however, they were less likely to achieve serum urate levels ≤300 µmol/L within 12 months of diagnosis (adjusted mean difference -6.74%, adjusted OR 0.51, 95% CI 0.48 to 0.55, p<0.001).

Similar findings of increased ULT prescription but decreased urate target attainment were observed for people with the following comorbidities at baseline: heart failure (ULT prescription: adjusted mean difference 9.32%, adjusted OR 1.56, 95% CI 1.48 to 1.64, p<0.001; target attainment: adjusted mean difference -1.72%, adjusted OR 0.85, 95% CI 0.76 to 0.95, p<0.001); hypertension (ULT prescription: adjusted mean difference 1.22%, adjusted OR 1.06, 95% CI 1.03 to 1.10, p<0.001; target attainment: adjusted mean difference -1.95%, adjusted OR 0.84, 95% CI 0.79 to 0.89, p<0.001); obesity (ULT prescription: adjusted mean difference 5.53%, adjusted OR 1.32, 95% CI 1.29 to 1.36, p<0.001; target attainment: adjusted mean difference -5.29%, adjusted OR 0.61, 95% CI 0.58 to 0.65, p<0.001); and in patients receiving diuretic therapy at baseline (ULT prescription: adjusted mean difference 8.03%, adjusted OR 1.49, 95% CI 1.44 to 1.55, p<0.001; target attainment: adjusted mean difference -5.27%, adjusted OR 0.61, 95% CI 0.57 to 0.66, p<0.001). Comparable findings were observed for the attainment of target urate levels ≤360 µmol/L within 12 months of diagnosis (Table 5).

Table 3. Predictors of ULT initiation within 12 months of gout diagnosis

Variables	Odds ratio (univariable)	95% CI	p-value	Odds ratio (multivariable)	95% CI	p-value
Age at diagnosis (per 10-year increase)	1.03	(1.02 - 1.04)	<0.001	0.90	(0.89 - 0.91)	<0.001
Female sex	1.06	(1.03 - 1.09)	<0.001	0.90	(0.88 - 0.93)	<0.001
Year of gout diagnosis	1.03	(1.03 - 1.04)	<0.001	1.03	(1.02 - 1.03)	<0.001
Country:						
England	Reference			Reference		
Wales	1.00	(0.92 - 1.10)	0.91	0.93	(0.85 - 1.01)	0.09
Scotland	1.87	(1.71 - 2.05)	<0.001	1.65	(1.50 - 1.81)	<0.001
Northern Ireland	1.84	(1.58 - 2.15)	<0.001	1.65	(1.42 - 1.92)	<0.001
CKD stages 3-5	1.96	(1.89 - 2.02)	<0.001	1.61	(1.55 - 1.67)	<0.001
Hypertension	1.37	(1.33 - 1.41)	<0.001	1.06	(1.03 - 1.10)	<0.001
Diabetes mellitus	1.31	(1.26 - 1.36)	<0.001	1.01	(0.98 - 1.05)	0.49
Ischaemic heart disease	1.34	(1.30 - 1.39)	<0.001	1.08	(1.04 - 1.12)	<0.001
Heart failure	2.07	(1.97 – 2.18)	<0.001	1.56	(1.48 - 1.64)	<0.001
Previous stroke or TIA	1.14	(1.09 - 1.20)	<0.001	0.98	(0.93 - 1.03)	0.34
Urolithiasis	1.20	(1.10 - 1.30)	<0.001	1.08	(0.99 - 1.18)	0.07
Obesity	1.46	(1.42 - 1.49)	<0.001	1.32	(1.29 - 1.36)	<0.001
Current/ex-smoker	1.04	(1.01 - 1.07)	0.01	0.98	(0.95 - 1.01)	0.19
Alcohol excess	1.27	(1.20 - 1.34)	<0.001	1.10	(1.04 - 1.17)	<0.001
Diuretic therapy	1.81	(1.76 - 1.87)	<0.001	1.49	(1.44 - 1.55)	<0.001

Univariable logistic regression outputs are shown (adjusted for age at diagnosis and sex), in addition to multivariable logistic regression outputs (with adjustment for all predictor variables, including year of diagnosis). Robust standard errors were estimated to account for clustering of patients within practices.

Table 4. Predictors of attainment of serum urate levels ≤300 µmol/L within 12 months of gout diagnosis

Variables	Odds ratio (univariable)	95% CI	p-value	Odds ratio (multivariable)	95% CI	p-value
Age at diagnosis (per 10-year increase)	0.91	(0.89 - 0.93)	<0.001	1.05	(1.03 - 1.07)	<0.001
Female sex	3.99	(3.77 - 4.23)	<0.001	5.18	(4.86 - 5.53)	<0.001
Year of gout diagnosis	1.02	(1.02 - 1.03)	<0.001	1.02	(1.01 - 1.02)	<0.001
Country:						
England	Reference			Reference		
Wales	1.02	(0.95 - 1.10)	0.60	1.00	(0.92 - 1.08)	0.95
Scotland	1.20	(1.11 - 1.30)	<0.001	1.24	(1.14 - 1.35)	<0.001
Northern Ireland	1.52	(1.32 - 1.75)	<0.001	1.59	(1.37 - 1.85)	<0.001
CKD stages 3-5	0.47	(0.44 - 0.51)	<0.001	0.51	(0.48 - 0.55)	<0.001
Hypertension	0.60	(0.57 - 0.64)	<0.001	0.84	(0.79 - 0.89)	<0.001
Diabetes mellitus	0.89	(0.82 - 0.95)	<0.001	1.19	(1.10 - 1.28)	<0.001
Ischaemic heart disease	0.84	(0.78 - 0.90)	<0.001	1.00	(0.93 - 1.08)	0.99
Heart failure	0.62	(0.56 - 0.69)	<0.001	0.85	(0.76 - 0.95)	<0.001
Previous stroke or TIA	0.90	(0.81 - 1.00)	0.04	1.02	(0.92 - 1.13)	0.66
Urolithiasis	1.19	(1.02 - 1.38)	0.02	1.25	(1.07 - 1.46)	<0.001
Obesity	0.58	(0.55 - 0.61)	<0.001	0.61	(0.58 - 0.65)	<0.001
Current/ex-smoker	1.14	(1.08 - 1.20)	<0.001	1.18	(1.12 - 1.24)	<0.001
Alcohol excess	1.19	(1.08 - 1.32)	<0.001	1.05	(0.95 - 1.17)	0.32
Diuretic therapy	0.47	(0.44 - 0.50)	<0.001	0.61	(0.57 - 0.66)	<0.001

Univariable logistic regression outputs are shown (adjusted for age at diagnosis and sex), in addition to multivariable logistic regression outputs (with adjustment for all predictor variables, including year of diagnosis). Robust standard errors were estimated to account for clustering of patients within practices.

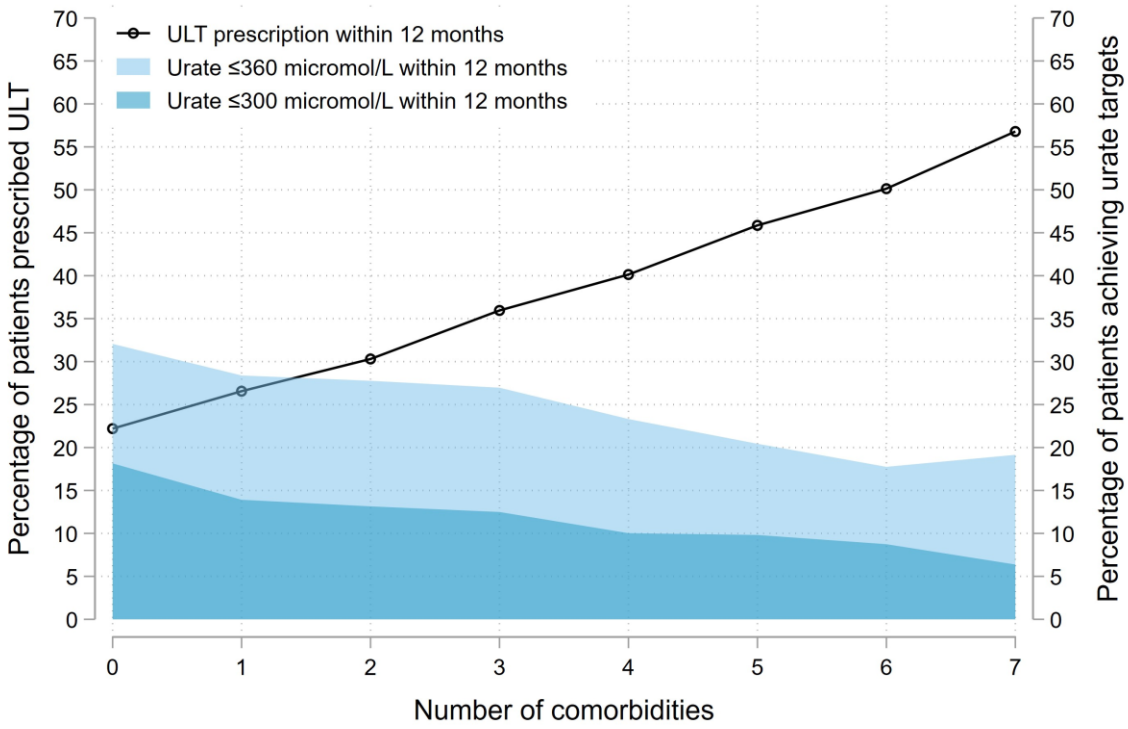
Table 5. Predictors of attainment of serum urate levels ≤360 µmol/L within 12 months of gout diagnosis

Variables	Odds ratio (univariable)	95% CI	p-value	Odds ratio (multivariable)	95% CI	p-value
Age at diagnosis (per 10-year increase)	0.97	(0.96 - 0.98)	<0.001	1.11	(1.10 - 1.13)	<0.001
Female sex	2.93	(2.80 - 3.06)	<0.001	3.68	(3.50 - 3.87)	<0.001
Year of gout diagnosis	1.04	(1.03 - 1.04)	<0.001	1.03	(1.02 - 1.04)	<0.001
Country:						
England	Reference			Reference		
Wales	1.07	(1.01 - 1.14)	0.02	1.01	(0.94 - 1.08)	0.83
Scotland	1.36	(1.26 - 1.47)	<0.001	1.31	(1.21 - 1.42)	<0.001
Northern Ireland	1.48	(1.30 - 1.68)	<0.001	1.48	(1.30 - 1.69)	<0.001
CKD stages 3-5	0.49	(0.46 - 0.52)	<0.001	0.52	(0.49 - 0.55)	<0.001
Hypertension	0.70	(0.67 - 0.73)	<0.001	0.92	(0.88 - 0.97)	<0.001
Diabetes mellitus	0.98	(0.92 - 1.04)	0.48	1.23	(1.16 - 1.31)	<0.001
Ischaemic heart disease	0.80	(0.76 - 0.85)	<0.001	0.96	(0.90 - 1.01)	0.12
Heart failure	0.60	(0.56 - 0.65)	<0.001	0.82	(0.75 - 0.89)	<0.001
Previous stroke or TIA	0.86	(0.80 - 0.93)	<0.001	0.97	(0.90 - 1.05)	0.49
Urolithiasis	1.17	(1.05 - 1.31)	0.01	1.21	(1.08 - 1.36)	<0.001
Obesity	0.73	(0.70 - 0.76)	<0.001	0.75	(0.73 - 0.78)	<0.001
Current/ex-smoker	1.10	(1.05 - 1.14)	<0.001	1.13	(1.09 - 1.18)	<0.001
Alcohol excess	1.21	(1.13 - 1.31)	<0.001	1.05	(0.98 - 1.14)	0.16
Diuretic therapy	0.51	(0.49 - 0.54)	<0.001	0.63	(0.60 - 0.67)	<0.001

Univariable logistic regression outputs are shown (adjusted for age at diagnosis and sex), in addition to multivariable logistic regression outputs (with adjustment for all predictor variables, including year of diagnosis). Robust standard errors were estimated to account for clustering of patients within practices.

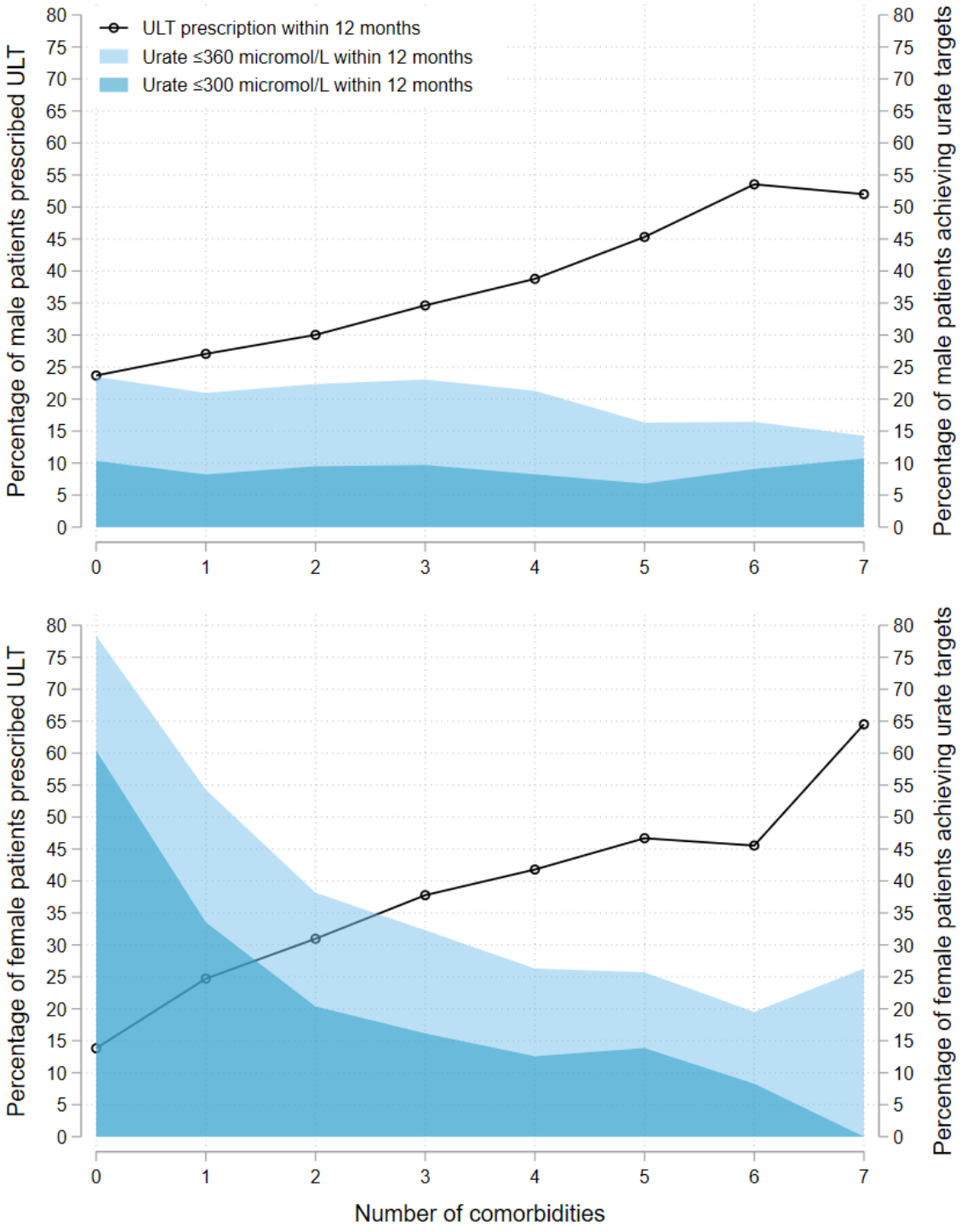
The associations of multimorbidity on ULT prescription and urate target attainment were additive: each additional comorbidity present at gout diagnosis increased the likelihood of ULT prescription, but decreased the likelihood of urate target attainment within 12 months of diagnosis (Figure 17). The effect of multimorbidity on ULT initiation and urate target attainment was more pronounced for female than male patients (Figure 18).

Figure 17. Impact of multimorbidity on ULT initiation and urate target attainment



Impact of the number of comorbidities present at diagnosis on the proportion of newly-diagnosed gout patients (n=129,972) who: i) were initiated on ULT within 12 months of diagnosis (black line); or ii) had a serum urate performed (n=65,127) and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 12 months of diagnosis. Comorbidities assessed at baseline were chronic kidney disease stages 3-5, hypertension, diabetes mellitus, IHD, heart failure, previous stroke/TIA and obesity.

Figure 18. Impact of multimorbidity on ULT initiation and urate target attainment for male vs. female gout patients



Impact of number of comorbidities at gout diagnosis on the proportion of male patients (top panel; n=94,610) and female patients (bottom panel; n=35,362) who: i) were initiated on ULT within 12 months of diagnosis (black line); or ii) had a serum urate performed (male: n=47,012; female: n=18,115) and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 12 months of diagnosis.

Female patients were much more likely than male patients to attain urate levels ≤300 µmol/L (adjusted mean difference 23.0%, adjusted OR 5.18, 95% CI 4.86 to 5.53, p<0.001) and ≤360 µmol/L (adjusted mean difference 27.2%, adjusted OR 3.68, 95% CI 3.50 to 3.87, p<0.001). In unadjusted analyses, slightly more female than male patients were initiated on ULT within 12 months of diagnosis (30.2% vs. 28.4%, respectively). However, after adjusting for other predictors, female patients were slightly less likely to be initiated on ULT than male patients, with the same true of older patients relative to younger patients (Table 3); this was primarily due to interaction effects between age, sex, CKD and diuretic use at baseline.

Patients registered with practices in Scotland or Northern Ireland were more likely to be initiated on ULT (Table 3) and to achieve target urate levels (Table 4 and Table 5) within 12 months of diagnosis, relative to patients registered with practices in England.

Survival modelling was performed to analyse predictors of the time to first ULT prescription following new gout diagnoses (Table 6), with results highly comparable to those observed in univariable and multivariable logistic regression models (Table 3).

Table 6. Predictors of time to ULT initiation following new gout diagnoses, using Cox proportional hazards.

Variables	Hazard ratio (univariable)	95% CI	p-value	Hazard ratio (multivariable)	95% CI	p-value
Age at diagnosis (per 10-year increase)	1.02	(1.01 - 1.03)	<0.001	0.91	(0.91 - 0.92)	<0.001
Female sex	1.06	(1.03 - 1.08)	<0.001	0.93	(0.91 - 0.96)	<0.001
Year of gout diagnosis	1.03	(1.02 - 1.03)	<0.001	1.02	(1.02 - 1.03)	<0.001
Country:						
England	Reference			Reference		
Wales	1.00	(0.93 - 1.08)	0.99	0.94	(0.87 – 1.01)	0.08
Scotland	1.67	(1.55 - 1.80)	<0.001	1.49	(1.38 - 1.60)	<0.001
Northern Ireland	1.65	(1.46 - 1.87)	<0.001	1.49	(1.33 - 1.68)	<0.001
CKD stages 3-5	1.70	(1.66 - 1.75)	<0.001	1.44	(1.40 - 1.48)	<0.001
Hypertension	1.29	(1.26 - 1.32)	<0.001	1.05	(1.03 - 1.08)	<0.001
Diabetes mellitus	1.24	(1.21 - 1.28)	<0.001	1.02	(0.99 - 1.05)	0.22
Ischaemic heart disease	1.26	(1.23 - 1.30)	<0.001	1.06	(1.03- 1.09)	<0.001
Heart failure	1.74	(1.68 - 1.81)	<0.001	1.38	(1.32 - 1.43)	<0.001
Previous stroke or TIA	1.11	(1.07 - 1.16)	<0.001	0.98	(0.95 - 1.02)	0.43
Urolithiasis	1.15	(1.08 - 1.23)	<0.001	1.06	(0.99 - 1.13)	0.08
Obesity	1.36	(1.33 - 1.39)	<0.001	1.25	(1.22 - 1.27)	<0.001
Current or ex-smoker	1.03	(1.01 - 1.05)	0.03	0.98	(0.96 - 1.01)	0.13
Alcohol excess	1.22	(1.16 - 1.27)	<0.001	1.08	(1.03 - 1.13)	<0.001
Diuretic therapy	1.61	(1.57 - 1.65)	<0.001	1.36	(1.32 - 1.40)	<0.001

Outputs from univariable models (adjusted for age at diagnosis and sex) and multivariable models (adjusting for all predictor variables, including year of diagnosis) are presented. Robust standard errors were estimated to account for clustering of patients within practices.

3.6 Discussion

In this UK-wide study, we show that the initiation of ULT, monitoring and attainment of target urate levels following new gout diagnoses remain poor, with only marginal improvements in these outcomes between 2004 and 2020. Even after the introduction of updated British and European gout management guidelines, only one in three people with gout are prescribed ULT within 12 months of diagnosis, and only one in six achieve a urate ≤300 µmol/L. These findings are a stark warning about the quality and success of gout care.

A previous study of UK gout management showed that, in 2012, 27% of people with gout were prescribed ULT within 12 months of diagnosis.[1] Studies in other countries, including the United States,[58,127,128] Australia,[57] New Zealand,[53] Sweden,[60] and Taiwan[129] also reported sub-optimal ULT initiation and target attainment. [1] In 2016 and 2017, respectively, EULAR and BSR gout management guidelines were updated to encourage the prescription of ULT, with titration of the dose of ULT until a target serum urate level is achieved.[6,7] Despite this, in time-series analyses, we showed that trends in the prescription of ULT and the attainment of urate targets after publication of these guidelines were not significantly different to before publication. We also observed reductions in the prescription of ULT and in urate monitoring in people diagnosed in 2020, relative to 2019. This is likely, at least in part, to reflect reduced access to care as a consequence of the COVID-19 pandemic, which has been reported for other chronic diseases.[130] The pandemic is also likely to have impacted on clinician uptake of new guidance. Given the relatively short timeframe between the publication of updated BSR and EULAR guidelines and the start of the pandemic, future analyses will provide more insight into the impact of the COVID-19 pandemic on gout care and guideline implementation.

Our findings suggest that, for there to be a step-change in the quality of gout care, implementation strategies are needed to complement guidelines and encourage the uptake of treat-to-target ULT by clinicians. The failure to adopt new guidance in primary care should not be seen as a failure of primary care itself, but rather as a systems failure. Patient and clinician education programmes are needed to disseminate key guidance and raise awareness about inequities in care. Enhanced modules within EHRs could automatically flag those in need of ULT initiation, titration, and monitoring. Financial incentives to encourage ULT prescription and target attainment could be explored, as has been done for other conditions (e.g. the Quality and Outcomes Framework in the UK). New models of care for people with gout may be needed: for example, engaging allied health professionals (e.g. nurses and pharmacists) from primary care or community pharmacies in ULT titration and monitoring, which has been shown to be effective. Point-of-care urate meters are also widely available, providing reliable estimates of urate levels to facilitate remote monitoring,[131,132] while empowering patients to be in control of their condition.

Guidelines strongly advise initiation of ULT in people with gout who have risk factors that include CKD, hypertension, heart failure, and diuretic use.[6,7] We found that patients with these risk factors were indeed more likely to be prescribed ULT within 12 months of diagnosis than patients without these risk factors; however, they were less likely to achieve target urate levels, leaving them at risk of ongoing flares and morbidity. The effects of multimorbidity on ULT prescription and urate target attainment were additive, suggesting that it is not only

individual risk factors that influence whether ULT is titrated adequately, but also the comorbidity burden at diagnosis. Clear guidance is needed on the management of gout in the presence of comorbidities, to ensure that patients most at risk of poor outcomes receive adequate ULT titration. This is particularly true of CKD, in view of conflicting guidance on the maximum recommended doses of allopurinol in renal impairment.[6,7,133] Conditions including cardiovascular disease, CKD and obesity have been shown to be associated with a greater urate burden.[134,135] In our study, we showed that a greater comorbidity burden at diagnosis was associated with higher baseline serum urate levels, which may be contributing to the failure to adequately suppress urate levels in these patients. Although not specifically addressed in our study, it is also true that comorbidities, particularly renal impairment, influence clinicians' willingness to dose-escalate ULT.[136] Additionally, medications used to manage comorbidities, for example diuretics, impact upon the relative efficacy of ULT.[137]

Further research is needed to explore our finding that patients in Scotland and Northern Ireland are more likely to be prescribed ULT and achieve urate targets than patients in England or Wales. In 2012, Scotland and Northern Ireland had the lowest prevalence of gout in the UK,[1] suggesting that the improved outcomes observed in these countries are not due to increased clinician exposure to the underlying condition. The differences in gout care are more likely to reflect better attainment of care quality indicators more generally in Scotland and Northern Ireland, relative to the rest of the UK: reports published by the National Audit Office and The Heath Foundation showed that practices in Scotland and Northern Ireland achieved the highest quality indicator scores in the UK.[138,139]

Our finding that female patients were five times more likely than male patients to obtain a target urate level ≤300 μmol/L also warrants further investigation. This finding was not explained by differences in ULT initiation, with female patients being relatively less likely to be initiated on ULT than male patients after adjustment for other covariates. The differences may relate to lower serum urate levels at baseline in female than male patients, contributing to easier attainment of target urate levels. Additionally, there may be differences in how male and female patients respond to ULT; in medication adherence; and other aspects of given care, which should be explored in future studies.

The strengths of our study include its population-level data coverage, large sample size, high quality and comprehensive data source,[140,141] and study period of greater than 15 years. In addition to analysing trends in ULT prescription, we also investigated trends in urate target attainment and monitoring, as well as predictors of these outcomes. Our statistical models accounted for multiple potential confounders, including year of diagnosis, recognising that clinical practice evolves with changing guidance over time.

Our study had limitations. The study was performed on a UK-based primary care cohort and, although comparable results have been reported in many countries,[4] the findings should not be assumed to be generalisable to other countries or settings. For example, the American College of Physicians recommended a "treat-to-avoid-symptoms" approach rather than a "treat-to-urate-target" approach,[142] while the ACR guidelines conditionally recommended against ULT initiation after first gout flares in the absence of specific risk factors.[8] While BSR guidance recommends offering ULT to all patients with gout and EULAR guidance

recommends considering and discussing ULT with gout patients from the first presentation, our analyses did not account for cases where ULT was offered to patients but declined or investigate prescription trends in patients with vs. without definite indications for ULT (e.g. urolithiasis).

The case definition for gout used in our analyses was based upon clinical codes entered by GPs, rather than classification criteria or urate crystal identification. As such, there is the potential for diagnostic misclassification inherent to analyses of clinically-coded data without case verification. Similarly, there is the potential for misclassification with clinical coding of comorbidities and missing data. Previous studies have, however, demonstrated the high validity of diagnostic coding in CPRD, including gout coding.[140,141] Our analyses did not account for the potential impact of gout flares on urate levels (i.e. lowering of urate levels during flares) or the impact of symptoms on medication adherence and/or attendance for blood tests, both of which are important areas for future study. Whilst we adjusted for multiple predictor variables in our models, the potential for unmeasured confounding must be considered when interpreting associations; for example, we did not have access to data on ethnicity or socioeconomic indices. Although practice region was adjusted for in our models, one must consider the potential impact of changes in the regional composition of CPRD on temporal trends in ULT prescription and target attainment, with reducing numbers of CPRD GOLD-contributing practices from England since 2004 and increasing relative proportions of Welsh, Scottish and Northern Irish-contributing practices.

In conclusion, only a minority of people with gout in the UK are initiated on ULT or attain target urate levels within 12 months of diagnosis. This is despite the introduction of guidelines that lowered the threshold for ULT initiation and recommended titration of ULT dosing until target urate levels are achieved. If the evidence-practice gap in gout management is to be bridged successfully, implementation strategies that incorporate multiple complementary approaches are required, integrating primary and secondary care, and including education programmes and incentivisation.

4 Changes in the incidence, prevalence and management of gout during the COVID-19 pandemic (*Lancet Rheumatology, 2023*)

4.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 2: How have the incidence, prevalence and management of gout been impacted by the COVID-19 pandemic?

My analyses of gout management in CPRD (Chapter 3) covered a period up to the start of the COVID-19 pandemic. Another key aim of my thesis was to evaluate the impact of the pandemic on the management of gout in UK. Additionally, I sought to evaluate how the pandemic had influenced the incidence and prevalence of gout diagnoses, as well as gout-associated hospitalisations. For other rheumatological diagnosis, such as RA, I had previously shown a sharp reduction in new diagnoses in the early pandemic, without a substantial impact on other metrics of care, such as time to first disease-modifying anti-rheumatic drug.[123] Whether this was also true of gout, which is primarily diagnosed and managed in primary care, was not yet understood.

For this Chapter, I used the OpenSAFELY data analytics platform to answer these important questions. As detailed in my methodology section, a limitation of using CPRD for these analyses would have been the lag in data availability, particularly for linked secondary care data. The OpenSAFELY platform has many advantages in this regard, with data being updated much closer to real-time. There are also numerous other advantages in terms of data coverage and privacy, as highlighted in my methodology section.

Trends in Gout Incidence and Management during the COVID-19 Pandemic: A Nationwide Study in England via OpenSAFELY

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4.2 Abstract

Background: Gout is the most prevalent inflammatory arthritis, yet one of the worst managed. Our objective was to assess how the COVID-19 pandemic impacted on incidence and care quality for people with gout in England.

Methods: With the approval of NHS England, we conducted a population-level cohort study using primary care and hospital data for 17.9 million adults via the OpenSAFELY platform. We analysed the following outcomes between 1 March 2015 and 28 February 2023: 1) incidence and prevalence of recorded gout diagnoses; 2) incidence of gout hospitalisations; 3) initiation of ULT; and 4) serum urate target attainment.

Findings: From 17,865,145 adults, there were 246,695 incident gout diagnoses. The mean age of diagnosed patients was 61.3 years (SD 16.2), 66,265 (26.9%) were female, and 189,035 (90.9%) of 208,050 with available ethnicity data were White. Newly recorded gout diagnoses decreased by 31.0% in the year beginning March 2020, compared with the preceding year (1.23 vs. 1.78 diagnoses per 1,000 adults). Gout prevalence was 3.07% in 2015/16 and 3.21% in 2022/23. Gout hospitalisations decreased by 30.1% in the year commencing March 2020, relative to the preceding year (9.58 vs. 13.7 admissions per 100,000 adults). Of 228,095 people with incident gout and available follow-up, 66,560 (29.2%) were prescribed ULT within 6 months. Of 65,305 ULT initiators with available follow-up, 16,790 (25.7%) attained a urate ≤360 micromol/L within 6 months of ULT initiation. In interrupted time-series analyses, ULT prescribing improved modestly during the pandemic, relative to pre-pandemic, while urate target attainment was similar.

Interpretation: Using gout as an exemplar disease, we demonstrated the complexity of how healthcare was impacted during the pandemic. We observed a reduction in gout diagnoses but no impact on treatment metrics. Importantly, we showed how country-wide, routinely-collected data can be used to map disease epidemiology and monitor care quality.

4.3 Introduction

Gout is the most prevalent inflammatory arthritis worldwide, but one of the worst managed.[4] Guidelines recommend discussing and/or offering preventative ULT (e.g. allopurinol) to all patients with gout, followed by titration of ULT dosing until serum urate targets are achieved.[6,35] Despite this, studies from prior to the COVID-19 pandemic had shown persistently low uptake of ULT and poor attainment of urate targets.[1,4,143]

The COVID-19 pandemic has had an enormous impact on service delivery throughout healthcare systems worldwide, with abrupt changes to healthcare utilisation, re-deployment of staff, and a rapid transition to virtual consultations.[83-85] The extent to which this has affected care for people with long-term conditions, such as gout, is not understood.

The OpenSAFELY data analytics platform provides a unique opportunity to address this question. Through OpenSAFELY, pseudonymised EHR for up to 99% of England's population can be analysed in a highly-secure environment in near real-time. In a recent proof-of-concept study, a 20% reduction in autoimmune inflammatory arthritis diagnoses was observed during the first year of the pandemic in England; however, for people who sought medical attention, the impact of the pandemic on the delivery of care for diagnoses such as RA was less marked than might have been expected.[123]

Our objective was to assess how the COVID-19 pandemic has impacted on diagnostic incidence and care quality for people with gout in England.

4.4 Methods

Study design and data source

We performed a population-level, observational cohort study using EHR data via the OpenSAFELY platform. Due to data availability, we piloted our approach in OpenSAFELY-TPP, which contains data for 23 million people, including 17.9 million adults (approximately 40% of the population of England). OpenSAFELY-TPP is representative of England's population in terms of age, sex, Index of Multiple Deprivation (IMD), ethnicity and causes of death.[144] Primary care records managed by the GP software provider, TPP, were linked to NHS SUS data through OpenSAFELY.

Incident and prevalent case definitions

The study period was from 1 March 2015 to 28 February 2023. Incident gout diagnoses were defined as people aged 18-110 years, registered with TPP practices in England for at least 12 months, who had index diagnostic codes for incident gout. At least 12 months of continuous registration prior to diagnosis was required for incident diagnoses, to ensure only index diagnoses were captured. People with incident gout codes who had received prescriptions for ULT more than 30 days before diagnosis were deemed not to be incident diagnoses.

The incidence of gout was defined as the number of newly recorded gout diagnoses within the study population during each study year (from 1 March to 28 February). The study

population was defined as people registered with TPP practices for at least 12 months at the mid-point of each study year (1 September); this assumed individuals were registered for the full study year. We calculated the point prevalence of gout by dividing the number of people with prevalent diagnostic codes for gout at a fixed time point - chosen as the mid-point of each study year (1 September) - by the number of people currently registered with TPP practices at that time point. No age or sex standardisation of incidence or prevalence was performed due to the relatively short study period, with only minimal differences in age or sex distribution observed over this time period.

Incidence of gout hospitalisations

Linked data on hospitalisations were available from 1 April 2016 to 31 March 2022. The incidence of gout hospitalisations was defined as the number of hospitalisations with primary admission diagnoses of gout (ICD10 code: M10) within the study population during each year (from 1 April to 31 March). The study population was defined as the number of people registered with TPP practices at the mid-point of each study year.

ULT initiation and serum urate target attainment

NICE guidelines recommend discussing the option of ULT with all people diagnosed with gout, followed by titration of ULT dosing until a serum urate ≤360 micromol/L (≤6mg/dL) is achieved.[35] For people with incident gout who had at least 6 months of available follow-up after diagnosis, we reported the proportion who received a prescription for ULT (allopurinol or febuxostat) within 6 months of diagnosis. Primary care prescriptions were captured, but prescriptions dispensed by hospital pharmacies were not.

For people with incident gout prescribed ULT within 6 months of diagnosis who had at least 6 months of available follow-up after initiating ULT, we reported the proportion who attained a serum urate ≤360 micromol/L within 6 months of ULT initiation.

Statistical methods

Baseline sociodemographic characteristics and comorbidities were described without inferential statistics for people with incident gout (presented overall and by diagnosis year) and for the reference population (at 1 March 2019).

ITSA were performed to estimate the impact of the pandemic on the proportion of incident gout patients, averaged by month, who were: i) prescribed ULT within 6 months of diagnosis; ii) prescribed ULT within 6 months of diagnosis and attained a serum urate ≤360 micromol/L within 6 months of ULT initiation. Trends were compared before and after the first COVID-19 lockdown in England (March 2020) using single-group ITSA.[101] Autocorrelation between observation periods was accounted for using Newey-West standard errors with 5 lags.[101] Outcomes were also presented by region of England (categorised into the 9 Nomenclature of Territorial Units for Statistics (NUTS) Level 1 regions[145]) using horizontal bar charts.

Python 3.8 was used for data management and Stata 16 for statistical analyses. All code for data management and analysis, as well as codelists, are shared openly for review and re-use under MIT open license (*https://github.com/opensafely/gout*). As our analyses were primarily

descriptive, no correction for multiple hypothesis testing was performed. For statistical disclosure control, frequency counts were rounded to the nearest 5 and non-zero counts below 8 were redacted.

Diagnostic codelists and comorbidity definitions

The first appearance of an incident gout diagnostic code in the primary care record was deemed an incident gout diagnosis, assuming the patient had been registered with a TPP practice in England for at least 12 months prior to this code. Patients with a ULT prescription more than 30 days prior to their index code were deemed not to be incident diagnoses. Similarly, patients with recorded hospital admission(s) and/or ED attendance(s) for gout flares more than 30 days before the index code were deemed not to be incident diagnoses.

We defined a gout flare as any of the following (adapted from a previously published definition[146]): 1) presence of a non-index diagnostic code for gout flare; 2) non-index admission with a primary gout diagnostic code; 3) non-index ED attendance with a primary gout diagnostic code; or 4) any non-index gout diagnostic code and a prescription for a flare treatment (colchicine, NSAID and/or corticosteroid) on same day as that code. Flares that occurred within 14 days of one another were excluded, to prevent double counting of the same flare.

We defined the presence of a comorbidity as a current or ever-recorded diagnostic code for that condition on or before the index diagnosis date (for the gout cohort) or 1 March 2019 (for the reference population). A comorbidity was assumed not to be present if diagnostic codes for that condition were absent from the medical record.

For people with diabetes mellitus, the most recent HBA1c reading in the 2 years prior to the index inflammatory arthritis diagnosis date was captured and categorised according to whether it was above or below 58 mmol/mol.

Chronic kidney disease was defined as an eGFR <60 ml/min/1.73 m^2 (calculated from the most recent creatinine reading using the CKD-EPI formula with no ethnicity) and/or the presence of a diagnostic code for end-stage renal failure.

Obesity/being overweight was defined according to the most recent BMI reading, assuming this reading was within 10 years of the index diagnosis date and the person was aged ≥16 at the time of the reading.

Individual codelists are available at https://codelists.opensafely.org including:

- Incident gout diagnoses: https://www.opencodelists.org/codelist/user/markdrussell/gout/7a2a1f9e/
- Prevalent gout diagnoses: https://www.opencodelists.org/codelist/user/markdrussell/gout-prevalent/048d1131/
- Gout admissions: https://www.opencodelists.org/codelist/user/markdrussell/gout-admissions/07a7df6d/

- Gout flare: https://www.opencodelists.org/codelist/user/markdrussell/gout-flaresattacks/5334de55/
- Tophaceous gout: https://www.opencodelists.org/codelist/user/markdrussell/gouty-tophi/41df05b9/
- Ethnicity: https://www.opencodelists.org/codelist/opensafely/ethnicity/2020-04-27/
- Smoking status: https://www.opencodelists.org/codelist/opensafely/smoking-clear/2020-04-29/
- Chronic cardiac disease: https://www.opencodelists.org/codelist/opensafely/chronic-cardiac-disease/2020-04-08/
- Diabetes mellitus: https://www.opencodelists.org/codelist/opensafely/diabetes/47ac0884/
- Hypertension: https://www.opencodelists.org/codelist/opensafely/hypertension/2020-04-28/
- Chronic respiratory disease: https://www.opencodelists.org/codelist/opensafely/chronic-respiratory-disease/2020-04-10/
- Chronic liver disease: https://www.opencodelists.org/codelist/opensafely/chronic-liver-disease/2020-06-02/
- Stroke: https://www.opencodelists.org/codelist/opensafely/stroke-updated/2020-06-02/
- Haematological cancer: https://www.opencodelists.org/codelist/opensafely/haematological-cancer/2020-04-15/
- Lung cancer: https://www.opencodelists.org/codelist/opensafely/lung-cancer/2020-04-15/
- All other cancers: https://www.opencodelists.org/codelist/opensafely/cancer-excluding-lung-and-haematological/2020-04-15/
- Renal replacement therapy: https://www.opencodelists.org/codelist/opensafely/renal-replacement-therapy/2020-04-14/

Study approval and ethics

Approval to undertake this study under the remit of service evaluation was obtained from King's College Hospital NHS Foundation Trust. No further ethical approval was required as per UK Health Research Authority guidance. This study was supported by Dr Joanna Ledingham as senior sponsor.

Patient and public involvement

This analysis relies on the use of large volumes of patient data. Ensuring patient, professional and public trust is therefore of critical importance. Maintaining trust requires being transparent about the way OpenSAFELY works, and ensuring patient voices are represented in the design of research, analysis of the findings, and considering the implications. For transparency purposes, OpenSAFELY have developed a public website (*https://opensafely.org/*) which provides a detailed description of the platform in language suitable for a lay audience; they have participated in two citizen juries exploring public trust in OpenSAFELY;[147] they are currently co-developing an explainer video; they have 'expert by experience' patient representation on the OpenSAFELY Oversight Board; they have partnered with Understanding Patient Data to produce lay explainers on the importance of large datasets for research; they have presented at a number of online public engagement events to key communities; and more. To ensure the patient voice is represented, OpenSAFELY are working closely with appropriate medical research charities.

Data availability and sharing

All data were linked, stored and analysed securely within the OpenSAFELY platform (*https://opensafely.org/*). Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. All code for data management and analysis, as well as codelists, are shared openly for review and re-use under MIT open license (*https://github.com/opensafely/gout*). Detailed pseudonymised patient data are potentially re-identifiable and therefore not shared. Access to the underlying identifiable and potentially re-identifiable pseudonymised EHR data is tightly governed by various legislative and regulatory frameworks and is restricted by best practice. The data in OpenSAFELY are drawn from general practice data across England where TPP is the data processor. TPP developers (Chris Bates, Jonathan Cockburn, John Parry, Frank Hester, and Sam Harper) initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. Bennett Institute for Applied Data Science developers and PIs (Ben Goldacre, Liam Smeeth, Jon Massey, Seb Bacon, Alex J Walker, William Hulme, Helen J Curtis, David Evans, Peter Inglesby, Simon Davy, George Hickman, Krishnan Bhaskaran, and Christopher T Rentsch) hold contracts with NHS England and have access to the OpenSAFELY pseudonymised data tables as needed to develop the OpenSAFELY tools. These tools in turn enable researchers with OpenSAFELY Data Access Agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline—from raw data to completed results for this analysis—and for the OpenSAFELY platform as a whole is available for review at *https://github.com/OpenSAFELY*. The data management and analysis code for this paper was led by MDR and JBG.

Information governance

NHS England is the data controller for OpenSAFELY-TPP; TPP is the data processor; all study authors using OpenSAFELY have the approval of NHS England. This implementation of

OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant.[148] Patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.[149] The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation and the Data Protection Act 2018. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent.[126] This was extended in November 2022 for the NHS England OpenSAFELY COVID-19 research platform.[150] In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group.[151] Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform. This study was supported by Dr Joanna Ledingham (clinical director for the National Early Inflammatory Arthritis Audit) as senior sponsor.

4.5 Results

Baseline characteristics

From a reference population of 17.9 million adults, there were 246,695 incident gout diagnoses between 1 March 2015 and 28 February 2023. A study flowchart is shown in Figure 19. Relative to the reference population, people with incident gout were older (mean age 61.3 vs. 49.7 years; standard deviation 16.2 vs. 18.7 years, respectively), more likely to be male (73.1% vs. 49.8%), and have more comorbidities including obesity (45.4% vs. 27.9%), hypertension (47.0% vs. 21.4%), diabetes mellitus (18.5% vs. 9.6%), chronic cardiac disease (19.9% vs. 6.8%), CKD (24.0% vs. 6.5%), and diuretic use (26.1% vs. 5.9%) (Table 7).

Figure 19. Flow diagram of study populations utilised in analyses

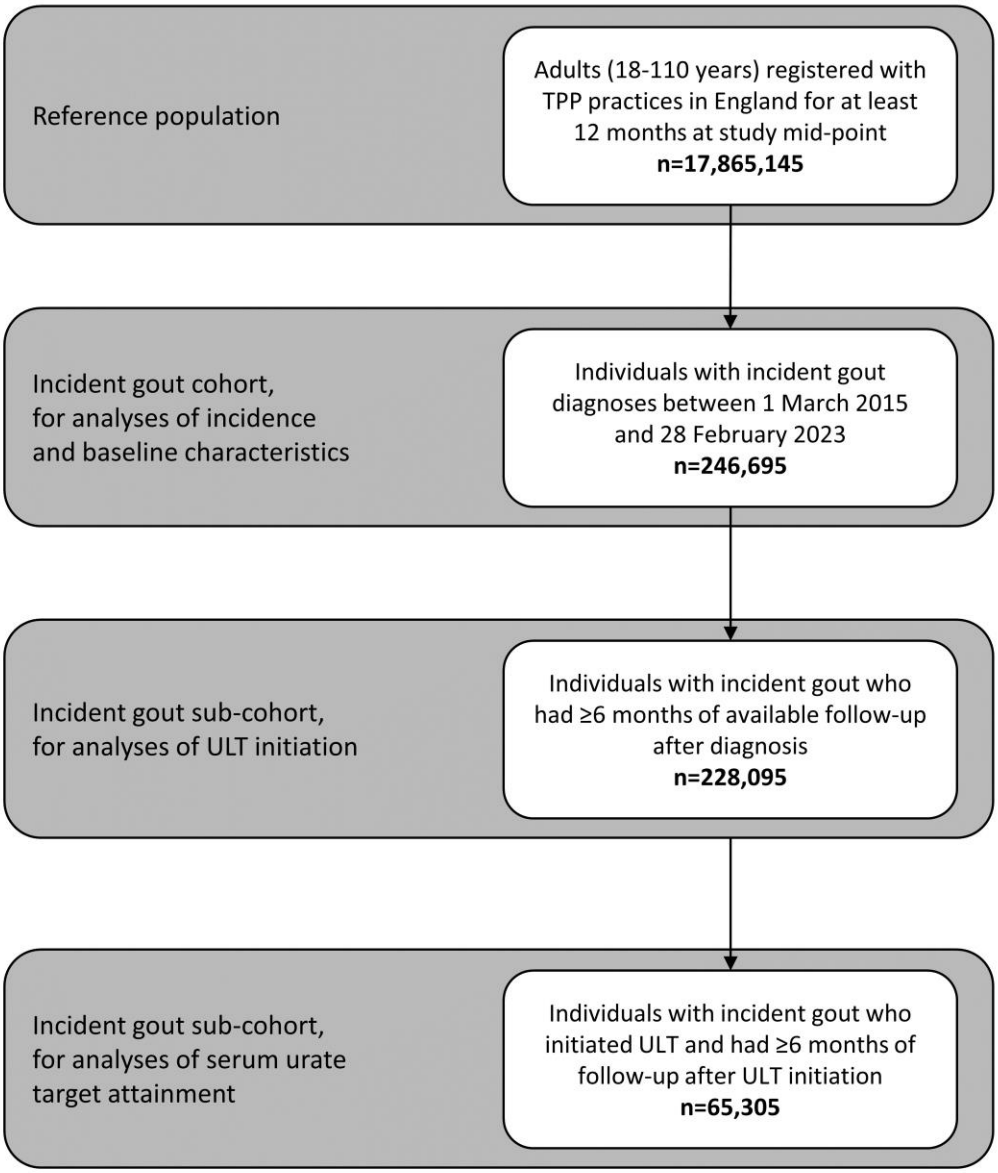


Table 7. Baseline demographics and comorbidities of people with incident gout diagnoses during the study period

	General population n=17,865,145	Gout (all years) n=246,695	Gout (2015/16) n=35,400	Gout (2016/17) n=34,675	Gout (2017/18) n=34,295	Gout (2018/19) n=34,415	Gout (2019/20) n=32,245	Gout (2020/21) n=22,775	Gout (2021/21) n=25,775	Gout (2022/23) n=27,140
Age group										
18-39	6,100,895 (34.1%)	26,900 (10.9%)	3,385 (9.6%)	3,410 (9.8%)	3,585 (10.5%)	3,715 (10.8%)	3,520 (10.9%)	2,720 (11.9%)	3,210 (12.5%)	3,360 (12.4%)
40-49	2,969,050 (16.6%)	34,785 (14.1%)	5,055 (14.3%)	4,770 (13.8%)	4,685 (13.7%)	4,700 (13.7%)	4,410 (13.7%)	3,320 (14.6%)	3,835 (14.9%)	4,005 (14.8%)
50-59	3,155,635 (17.7%)	49,090 (19.9%)	6,710 (19.0%)	6,765 (19.5%)	6,690 (19.5%)	6,825 (19.8%)	6,465 (20.0%)	4,710 (20.7%)	5,310 (20.6%)	5,625 (20.7%)
60-69	2,485,900 (13.9%)	50,970 (20.7%)	7,800 (22.0%)	7,625 (22.0%)	7,275 (21.2%)	6,935 (20.2%)	6,450 (20.0%)	4,515 (19.8%)	5,045 (19.6%)	5,330 (19.6%)
70-79	1,989,240 (11.1%)	50,325 (20.4%)	7,375 (20.8%)	7,115 (20.5%)	7,195 (21.0%)	7,280 (21.2%)	6,695 (20.8%)	4,385 (19.3%)	5,030 (19.5%)	5,255 (19.4%)
80+	1,164,425 (6.5%)	34,625 (14.0%)	5,075 (14.3%)	4,990 (14.4%)	4,865 (14.2%)	4,960 (14.4%)	4,705 (14.6%)	3,125 (13.7%)	3,345 (13.0%)	3,565 (13.1%)
Sex										
Female	8,962,935 (50.2%)	66,265 (26.9%)	9,665 (27.3%)	9,530 (27.5%)	9,290 (27.1%)	9,180 (26.7%)	8,750 (27.1%)	5,910 (26.0%)	6,820 (26.5%)	7,120 (26.2%)
Male	8,902,210 (49.8%)	180,430 (73.1%)	25,730 (72.7%)	25,145 (72.5%)	25,000 (72.9%)	25,230 (73.3%)	23,495 (72.9%)	16,860 (74/0%)	18,950 (73.5%)	20,020 (73.8%)
Ethnicity										
White	12,704,335 (87.0%)	189,035 (90.9%)	26,970 (92.1%)	26,535 (91.6%)	26,235 (91.3%)	26,365 (91.0%)	24,810 (90.7%)	17,625 (90.8%)	19,750 (89.8%)	20,740 (89.0%)
Asian/Asian British	1,042,195 (7.1%)	11,470 (5.5%)	1,450 (4.9%)	1,505 (5.2%)	1,520 (5.3%)	1,615 (5.6%)	1,520 (5.6%)	1,020 (5.3%)	1,325 (6.0%)	1,520 (6.5%)
Black	349,105 (2.4%)	3,455 (1.7%)	425 (1.5%)	435 (1.5%)	480 (1.7%)	455 (1.6%)	475 (1.7%)	345 (1.8%)	400 (1.8%)	440 (1.9%)
Mixed/Other	506,960 (3.5%)	4,090 (2.0%)	450 (1.5%)	500 (1.7%)	510 (1.8%)	540 (1.9%)	540 (2.0%)	425 (2.2%)	530 (2.4%)	595 (2.6%)
Missing	3,262,550	38,645	6,105	5,700	5,550	5,440	4,900	3,355	3,760	3,840
Index of multiple deprivation										
1 most deprived	3,370,640 (19.1%)	41,135 (17.0%)	6,035 (17.4%)	5,725 (16.8%)	5,750 (17.1%)	5,705 (16.9%)	5,415 (17.1%)	3,785 (17.0%)	4,235 (16.8%)	4,485 (17.0%)
2	3,466,375 (19.7%)	44,650 (18.5%)	6,365 (18.4%)	6,270 (18.4%)	6,310 (18.7%)	6,330 (18.7%)	5,840 (18.4%)	4,120 (18.5%)	4,645 (18.5%)	4,775 (18.1%)
3	3,804,745 (21.6%)	53,505 (22.1%)	7,560 (21.8%)	7,645 (22.5%)	7,315 (21.7%)	7,490 (22.1%)	7,125 (22.5%)	4,885 (21.9%)	5,550 (22.1%)	5,945 (22.5%)
4	3,610,825 (20.5%)	52,265 (21.6%)	7,575 (21.8%)	7,360 (21.7%)	7,320 (21.7%)	7,320 (21.6%)	6,800 (21.5%)	4,790 (21.5%)	5,475 (21.8%)	5,630 (21.3%)
5 least deprived	3,355,730 (19.1%)	50,030 (20.7%)	7,140 (20.6%)	6,995 (20.6%)	6,985 (20.7%)	6,975 (20.6%)	6,475 (20.5%)	4,680 (21.0%)	5,235 (20.8%)	5,545 (21.0%)
Missing	256,830	5,110	725	685	610	595	590	505	635	765
BMI										
Underweight (<18.5)	321,610 (2.3%)	1,195 (0.6%)	145 (0.5%)	155 (0.5%)	170 (0.6%)	165 (0.5%)	175 (0.6%)	120 (0.6%)	130 (0.6%)	140 (0.6%)
Normal (18.5-24.9)	4,895,895 (35.2%)	34,250 (15.9%)	4,955 (16.0%)	4,865 (16.0%)	4,730 (15.8%)	4,760 (15.8%)	4,665 (16.5%)	3,050 (15.4%)	3,480 (15.6%)	3,745 (16.0%)
Overweight (25-29.9)	4,817,025 (34.6%)	82,360 (38.2%)	12,260 (39.5%)	11,885 (39.0%)	11,505 (38.4%)	11,695 (38.7%)	10,645 (37.6%)	7,325 (37.1%)	8,385 (37.6%)	8,660 (37.0%)
Obese I (30-34.9)	2,428,140 (17.4%)	59,255 (27.5%)	8,530 (27.5%)	8,365 (27.5%)	8,325 (27.8%)	8,215 (27.2%)	7,735 (27.3%)	5,525 (27.9%)	6,070 (27.2%)	6,495 (27.7%)

Obese II (35-39.9)	927,655 (6.7%)	24,345 (11.3%)	3,295 (10.6%)	3,340 (11.0%)	3,395 (11.3%)	3,420 (11.3%)	3,215 (11.3%)	2,355 (11.9%)	2,625 (11.8%)	2,695 (11.5%)
Obese III (40+)	527,595 (3.8%)	14,120 (6.6%)	1,835 (5.9%)	1,850 (6.1%)	1,875 (6.3%)	1,965 (6.5%)	1,910 (6.7%)	1,395 (7.1%)	1,615 (7.2%)	1,685 (7.2%)
Missing	3,947,225	31,170	4,380	4,220	4,290	4,195	3,900	2,995	3,470	3,720
Smoking status										
Never	8,225,665 (47.9%)	95,495 (39.0%)	13,560 (38.5%)	13,520 (39.2%)	13,185 (38.7%)	13,315 (39.0%)	12,440 (38.9%)	8,780 (39.0%)	9,965 (39.0%)	10,735 (40.0%)
Former	5,880,190 (34.2%)	121,020 (49.4%)	17,490 (49.7%)	17,010 (49.3%)	16,920 (49.7%)	16,975 (49.7%)	15,845 (49.5%)	11,100 (49.2%)	12,535 (49.1%)	13,150 (49.0%)
Current	3,075,465 (17.9%)	28,285 (11.6%)	4,155 (11.8%)	3,955 (11.5%)	3,945 (11.6%)	3,875 (11.3%)	3,730 (11.7%)	2,660 (11.8%)	3,020 (11.8%)	2,945 (11.0%)
Missing	683,825	1,895	195	190	240	250	230	230	255	310
Hypertension	3,817,990 (21.4%)	115,960 (47.0%)	17,640 (49.8%)	16,950 (48.9%)	16,460 (48.0%)	16,315 (47.4%)	15,130 (46.9%)	10,220 (44.9%)	11,360 (44.1%)	11,885 (43.8%)
Diabetes										
No diabetes	16,153,210 (90.4%)	201,085 (81.5%)	29,615 (83.7%)	28,825 (83.1%)	28,255 (82.4%)	28,015 (81.4%)	25,860 (80.2%)	18,360 (80.6%)	20,565 (79.8%)	21,590 (79.6%)
Diabetes with HbA1c <58 mmol/mol	1,084,050 (6.1%)	32,850 (13.3%)	3,930 (11.1%)	4,090 (11.8%)	4,335 (12.6%)	4,640 (13.5%)	4,685 (14.5%)	3,180 (14.0%)	3,800 (14.7%)	4,185 (15.4%)
Diabetes with HbA1c >58 mmol/mol	481,580 (2.7%)	10,530 (4.3%)	1,525 (4.3%)	1,410 (4.1%)	1,405 (4.1%)	1,470 (4.3%)	1,440 (4.5%)	1,025 (4.5%)	1,115 (4.3%)	1,135 (4.2%)
Diabetes with no HbA1c measure	146,305 (0.8%)	2,230 (0.9%)	325 (0.9%)	345 (1.0%)	295 (0.9%)	285 (0.8%)	265 (0.8%)	205 (0.9%)	285 (1.1%)	230 (0.8%)
Chronic cardiac disease	1,207,230 (6.8%)	49,190 (19.9%)	7,300 (20.6%)	7,060 (20.4%)	6,850 (20.0%)	6,945 (20.2%)	6,530 (20.3%)	4,460 (19.6%)	4,970 (19.3%)	5,080 (18.7%)
Stroke	375,200 (2.1%)	11,360 (4.6%)	1,690 (4.8%)	1,635 (4.7%)	1,575 (4.6%)	1,555 (4.5%)	1,600 (5.0%)	1,005 (4.4%)	1,120 (4.3%)	1,180 (4.3%)
Cancer	961,885 (5.4%)	22,155 (9.0%)	3,035 (8.6%)	3,070 (8.9%)	3,085 (9.0%)	3,125 (9.1%)	3,005 (9.3%)	2,070 (9.1%)	2,320 (9.0%)	2,445 (9.0%)
Chronic respiratory disease	721,065 (4.0%)	21,255 (8.6%)	3,135 (8.9%)	2,940 (8.5%)	2,970 (8.7%)	3,055 (8.9%)	2,825 (8.8%)	1,975 (8.7%)	2,190 (8.5%)	2,170 (8.0%)
Chronic liver disease	98,645 (0.6%)	2,490 (1.0%)	325 (0.9%)	285 (0.8%)	290 (0.8%)	315 (0.9%)	350 (1.1%)	300 (1.3%)	315 (1.2%)	310 (1.1%)
Chronic kidney disease	1,152,460 (6.5%)	59,195 (24.0%)	9,140 (25.8%)	8,840 (25.5%)	8,375 (24.4%)	8,320 (24.2%)	7,600 (23.6%)	5,170 (22.7%)	5,700 (22.1%)	6,050 (22.3%)
Diuretic at diagnosis	1,056,465 (5.9%)	64,325 (26.1%)	10,630 (30.0%)	9,855 (28.4%)	9,395 (27.4%)	8,935 (26.0%)	8,140 (25.2%)	5,365 (23.6%)	6,025 (23.4%)	5,970 (22.0%)
Tophaceous gout	N/A	2,535 (1.0%)	340 (1.0%)	400 (1.2%)	355 (1.0%)	355 (1.0%)	305 (0.9%)	180 (0.8%)	280 (1.1%)	325 (1.2%)
At least one additional flare within 6 months of diagnosis	N/A	24,755 (10.0%)	3,630 (10.3%)	3,615 (10.4%)	3,570 (10.4%)	3,565 (10.4%)	3,220 (10.0%)	2,275 (10.0%)	2,505 (9.7%)	-
Serum urate at diagnosis, micromol/L	N/A	466 (100)	470 (101)	468 (100)	466 (101)	462 (100)	461 (101)	467 (101)	470 (102)	463 (98)

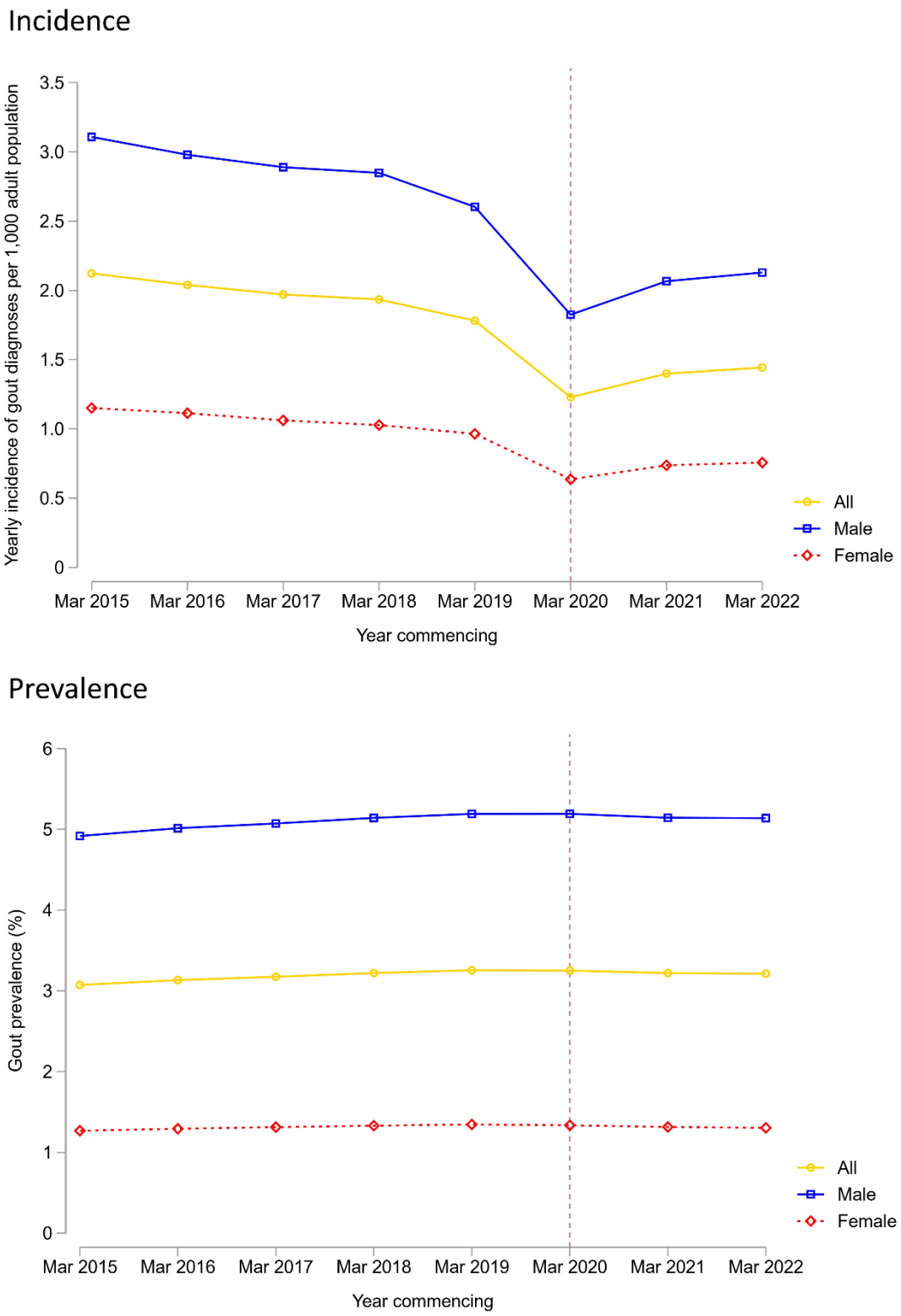
Characteristics for the general population represent all adults registered with TPP practices in England as of 1 March 2019 (the mid-point of the study). Counts have been rounded to the nearest 5, to reduce the risk of disclosure; as such, column totals may differ from the sum of the individual variables. Data on additional gout flares were not available for the 2022/23 cohort, as insufficient follow-up time had elapsed. Mean (standard deviation) serum urate levels are shown for patients who had urate levels performed at baseline (157,590/246,695; 63.9%).

Incidence and prevalence

The incidence of newly recorded gout diagnoses decreased from 2.12 per 1,000 adults in 2015/16 to 1.78 per 1,000 adults in 2019/20 (Figure 20 and Figure 21). A marked decrease in recorded gout diagnoses was observed in the year beginning March 2020, compared with the year preceding the pandemic, corresponding to a 31.0% decrease in incidence (from 1.78 to 1.23 diagnoses per 1,000 adults). This was driven primarily by a 39.0% decrease in recorded diagnoses between February 2020 and April 2020 (from 2,475 to 1,510 monthly diagnoses, respectively). The incidence of recorded gout diagnoses increased in the years commencing March 2021 and March 2022 (1.40 and 1.44 diagnoses per 1,000 adults, respectively), but remained below pre-pandemic incidence.

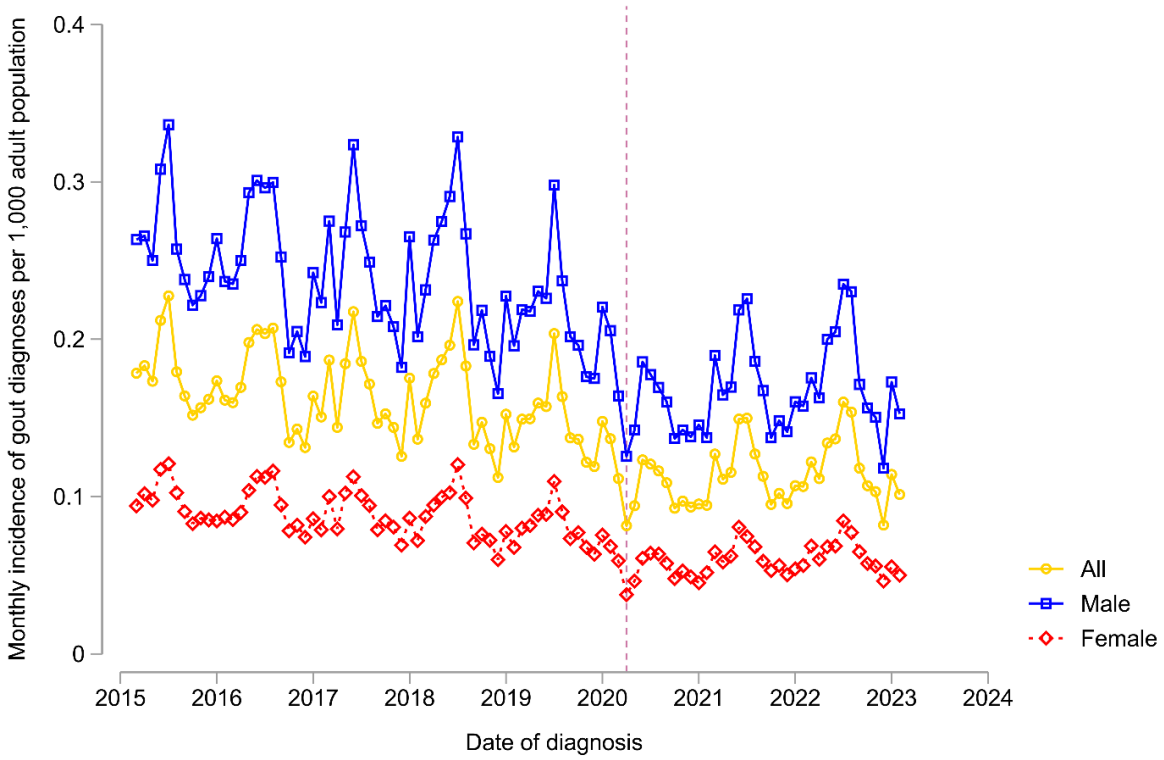
Gout prevalence remained relatively stable over the study period, at 3.07% of adults in 2015, 3.25% in 2019, and 3.21% in 2022 (Figure 20). Hospitalisations with primary admission diagnoses of gout increased from 12.2 per 100,000 adults in 2016/17 to 13.7 per 100,000 adults in 2019/20, before decreasing by 30.1% during the first year of the pandemic, to 9.58 admissions per 100,000 adults (Figure 22). A modest increase in admissions was observed in the year commencing March 2021 (10.7 admissions per 100,000 adults), but this remained before pre-pandemic levels.

Figure 20. Incidence and prevalence of gout diagnoses recorded in primary care in England between 2015 and 2023



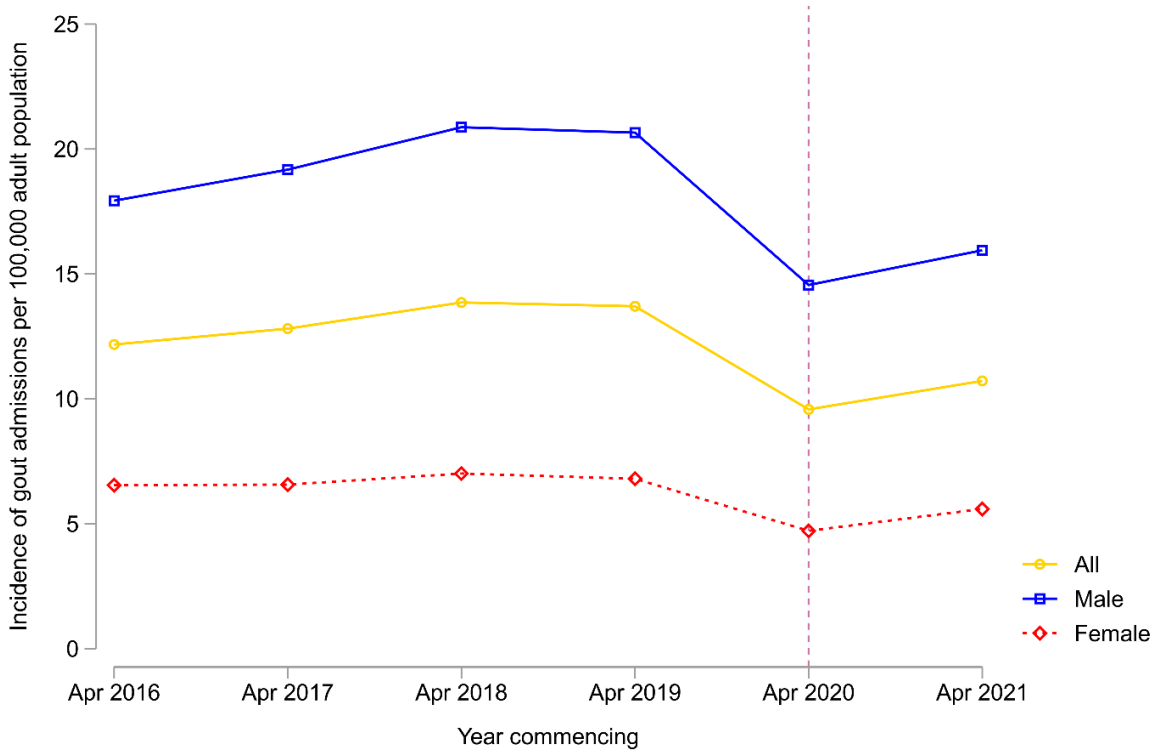
The vertical dashed line corresponds to the onset of the first COVID-19 lockdown in England (March 2020).

Figure 21. Monthly incidence of gout diagnoses newly recorded in primary care in England between 2015 and 2023



The vertical dashed line corresponds to the onset of the first COVID-19 lockdown in England (March 2020).

Figure 22. Yearly incidence of hospitalisations with primary admission diagnoses of gout in England between and 2022

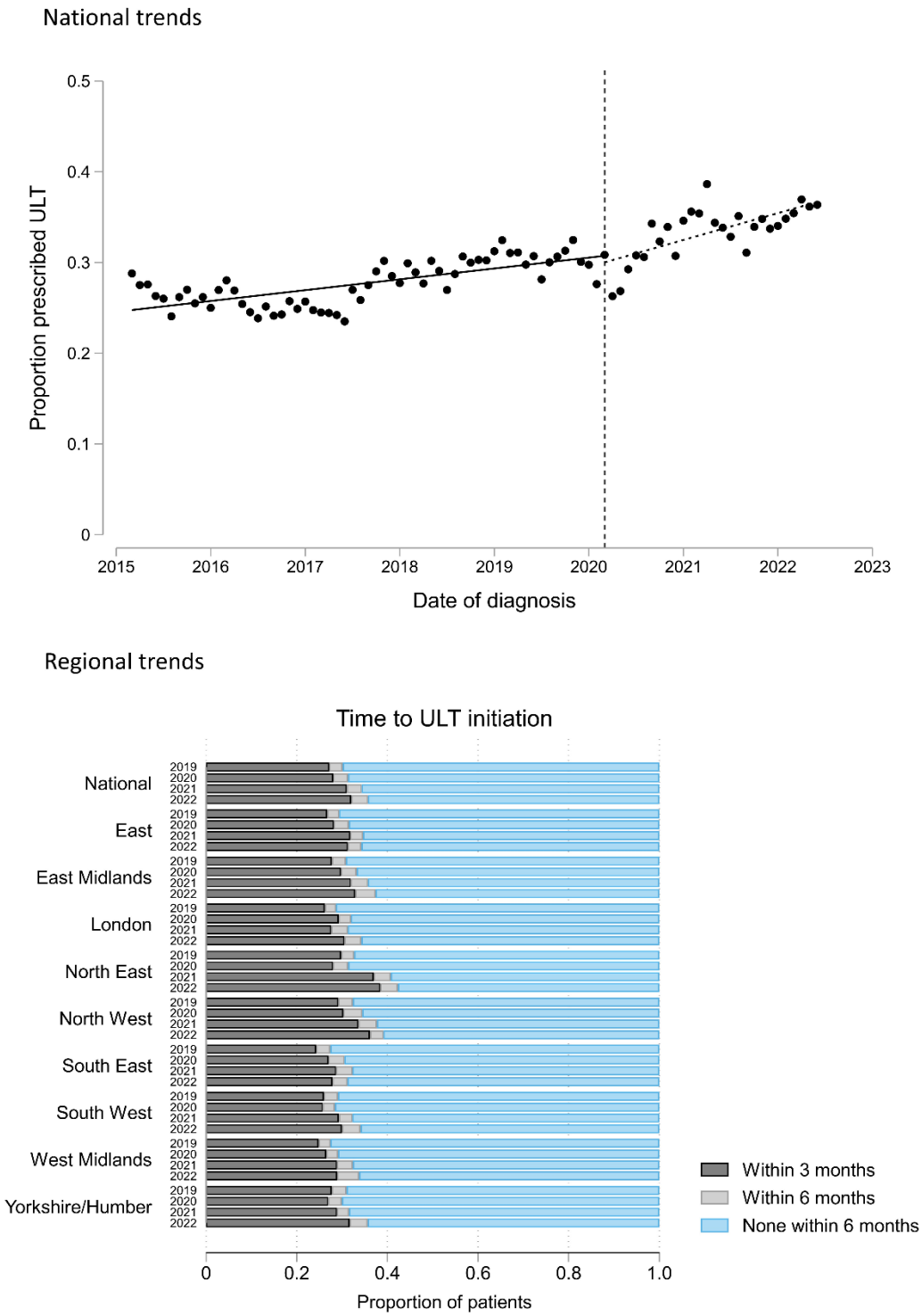


The vertical dashed line corresponds to the onset of the first COVID-19 lockdown in England (March 2020).

Trends in urate-lowering therapy

Of 246,695 new gout diagnoses during the study period, 228,095 (92.5%) had at least 6 months of available follow-up, 66,560 (29.2%) of whom were prescribed ULT within 6 months of diagnosis (65,680/206,890 [31.8%] within 12 months of diagnosis). In ITSA models, modest improvements in ULT initiation were observed over the study period (Figure 23). Small, statistically significant improvements in ULT prescribing trends were seen after March 2020, relative to pre-pandemic trends: trend pre-March 2020: 1.19% improvement per year (95% CI 0.69 to 1.70); trend post-March 2020: 2.96% improvement per year (95% CI 1.58 to 4.35); difference in trends: 1.77% improvement per year (95% CI 0.23 to 3.30; p=0.025). Improvements in ULT initiation during the pandemic were observed throughout most regions of England, albeit to varying degrees (Figure 23).

Figure 23. Trends in the proportion of patients with incident gout who were initiated on ULT

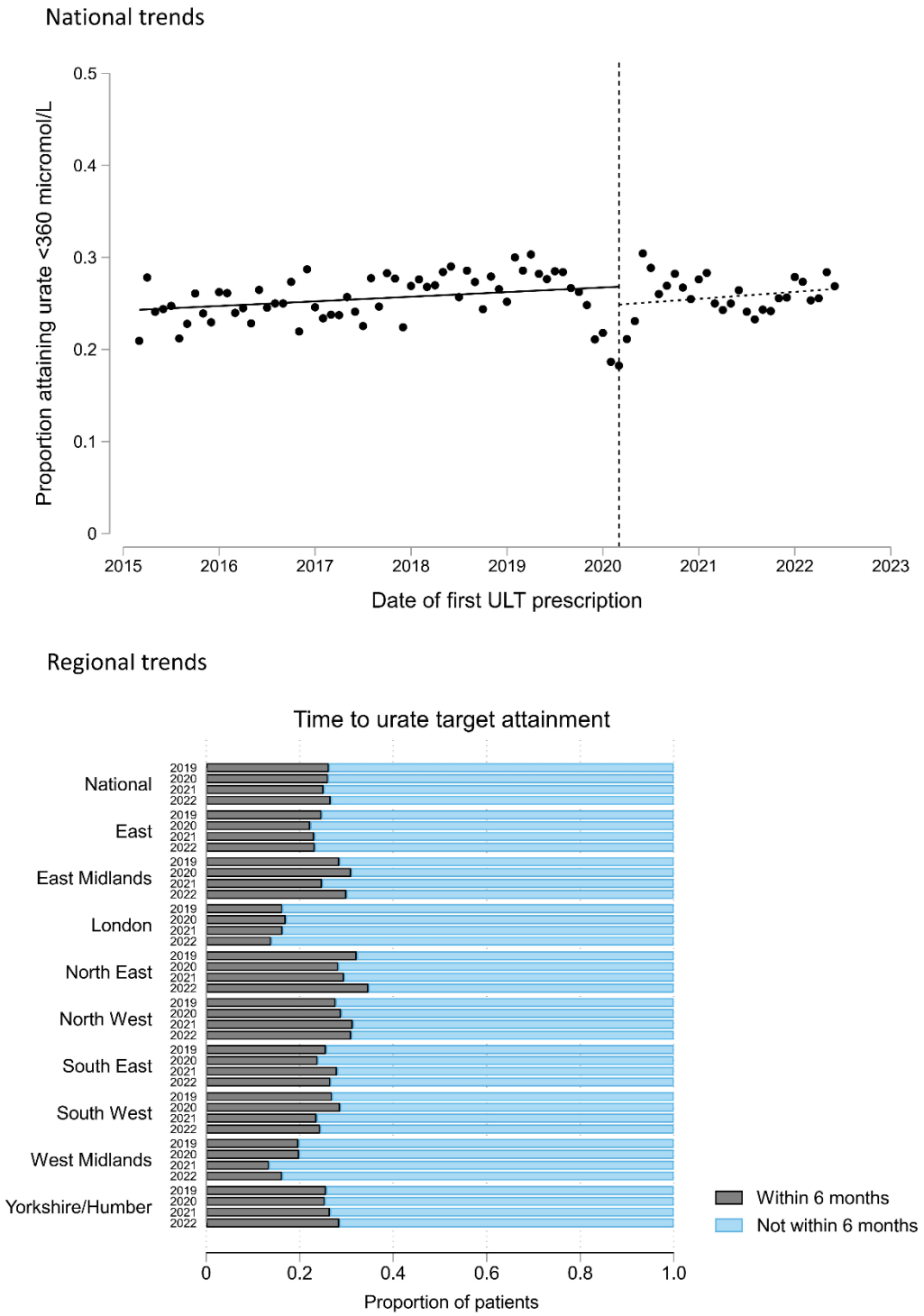


In the top panel, an interrupted time series analysis shows national trends in the mean monthly proportion of patients who initiated ULT within 6 months of diagnosis. The vertical dashed line corresponds to the onset of the first COVID-19 lockdown in England (March 2020). The bottom panel shows the proportion of patients who were prescribed ULT within 3, 6, or >6 months of diagnosis, separated by region of England and by year (March 2019/20; March 2020/21; March 2021/22; March 2022/23).

Trends in serum urate target attainment

Of 66,560 patients with incident gout who initiated ULT within 6 months of diagnosis, 65,305 (98.1%) had at least 6 months of available follow-up after ULT initiation. 36,245/65,305 (55.5%) patients had at least one serum urate level performed within 6 months of initiating ULT, while 12,990/65,305 (19.9%) had two or more urate levels performed. 16,790/65,305 (25.7%) attained a serum urate ≤360 micromol/L within 6 months of ULT initiation (18,170/58,455 [31.1%] within 12 months). Urate target attainment remained relatively stable over the study period, aside from a temporary decrease in attainment for people initiating ULT in late 2019 and early 2020 (nadir of 18.2% in March 2020), before recovering by June 2020 (Figure 24). Overall, there were no significant differences in urate target attainment trends before and after the onset of the pandemic: trend pre-March 2020: 0.50% improvement per year (95% CI -0.31 to 1.31); trend post-March 2020: 0.75% improvement per year (95% CI -1.18 to 2.69); difference in trends: 0.25% improvement per year (95% CI -2.21 to 2.71; p=0.84). Urate target attainment varied considerably throughout England during the pandemic, with the lowest attainment seen in London (185/1,155; 16.0%) and highest attainment seen in North-East England (555/1,800; 30.8%) (Figure 24).

Figure 24. Trends in the proportion of incident gout patients who attained serum urate levels ≤360 micromol/L within 6 months of initiating ULT



In the top panel, an interrupted time series analysis shows national trends in the mean monthly proportion of patients who attained target within 6 months of ULT initiation. The vertical dashed line corresponds to the onset of the first COVID-19 lockdown in England (March 2020). The bottom panel shows the proportion of incident gout patients who attained a urate ≤360 micromol/L within 6 months of ULT initiation, separated by region of England and by year (March 2019/20; March 2020/21; March 2021/22; March 2022/23).

Characteristics of people presenting before and after pandemic onset

Differences in patients presenting with new gout diagnoses during each year of the pandemic, relative to before the pandemic, were investigated (Table 7). The age, sex, ethnicity, and sociodemographic composition of patients presenting during the pandemic were comparable to patients presenting before the pandemic. Proportionately fewer patients presenting with gout during the pandemic had comorbid hypertension, CKD or diuretic use, relative to before the pandemic. The proportion of patients with tophi at diagnosis was comparable before and after the onset of the pandemic, as was early flare burden. Serum urate levels at diagnosis were also comparable in patients presenting before vs. during the pandemic.

4.6 Discussion

In this study, we used the OpenSAFELY platform to demonstrate a marked reduction in recorded gout diagnoses during the COVID-19 pandemic in England. No increase in gout diagnoses above pre-pandemic levels has been observed as of 3 years after the pandemic's onset, suggesting a substantial burden of undiagnosed disease. For people presenting with new gout diagnoses during the pandemic, small improvements in ULT initiation were seen, relative to pre-pandemic trends, while trends in serum urate target attainment were comparable. Irrespective of the pandemic, ULT initiation and urate target attainment remain far below an acceptable standard.

This study demonstrates the potential to transform monitoring of chronic diseases using routinely-collected health data. Unlike existing national audits (e.g. the National Early Inflammatory Arthritis Audit in England and Wales),[152] the use of routinely-collected health data in Trusted Research Environments obviates the need for manual data entry by clinicians, increases case ascertainment, and reduces the potential for bias.[123,153] Rates of ULT initiation and urate target attainment in our study were comparable to studies utilising other data sources (e.g. CPRD), supporting the validity of our approach.[55,143] In contrast to these other data sources, however, analyses using OpenSAFELY can be updated in near real-time and do not require any sharing of potentially identifiable patient data, minimising the risk of sensitive data disclosure.

The 40% decrease in incident gout diagnoses observed in the early months of the pandemic is comparable to what has been described for autoimmune inflammatory arthritis diagnoses, such as RA.[123] This highlights the wide-ranging impact of the pandemic on both primary care and secondary care-led rheumatological conditions, with service provision disrupted across many parts of the country due to redeployment of staff. National data show that 10% fewer primary care appointments occurred in England between April 2020/2021, relative to the preceding year, which is likely to have contributed to some but not all of the observed reduction in recorded gout diagnoses during the pandemic.[154] Similarly, our finding of a 30% reduction in gout hospitalisations during the first year of the pandemic needs to be considered in the wider context of a 16% reduction in all-cause emergency admissions in England between April 2020/2021, relative to April 2019/2020.[155] In addition to the marked reduction in recorded gout diagnoses observed during the pandemic, we also observed a background decrease in gout incidence over the full study period. This supports the findings

of a recent observational study, utilising CPRD, that reported a decreasing incidence of gout that predated the COVID-19 pandemic, with a potential link to changes in alcohol intake and dietary modification over time.[55]

As was reported for autoimmune inflammatory arthritis diagnoses, the absence of a rebound increase in recorded gout diagnoses above pre-pandemic levels suggests many people remain undiagnosed as a consequence of the pandemic.[123] It remains to be seen the degree to which this represents people who have yet to seek medical attention (e.g. due to altered health-seeking behaviour) or people yet to be diagnosed due to ongoing system-wide pressures. Gout is characterised by episodic flares early in the disease course, with intercritical periods that can last several months or years. As such, it is possible that patients who did not seek medical attention for index gout flares during the pandemic may not yet have experienced further flares and/or re-presented to primary care; this may have contributed to the absence of a rebound increase in gout diagnoses over the relatively short study period.

Our findings highlight the remarkable adaptation of the health service to the pandemic; for example, in being able to deliver modest improvements in ULT initiation despite unprecedented pressures. This reflects what has been reported for other inflammatory arthritis diagnoses, including RA, where time to first rheumatology assessment and DMARD initiation were comparable or better than before the pandemic.[123] The rapid transition to virtual consultations during the pandemic may have favoured conditions such as gout, for which remote titration of urate-lowering therapies is possible. Despite this, absolute levels of ULT initiation and urate target attainment remained sub-optimal at the end of the study period (at 34% and 29%, respectively), while only 20% of patients had more than one urate level performed within 6 months of initiating ULT. This demonstrates the pressing need for strategies to encourage uptake of treat-to-target ULT.

In addition to benchmarking national standards of care, our data highlight marked regional variation in gout care. Urate target attainment in certain regions of England (e.g. North East England) was close to double that of other regions (e.g. London). Regional disparities in care were evident before the pandemic and, in some cases, have become more pronounced since the pandemic. Further research incorporating qualitative methodology is needed to better understand the reasons behind such disparities. This could help tailor the implementation of strategies towards addressing regional facilitators and barriers to better care, which, in turn, could be monitored over time using electronic dashboards based upon near real-time updates of these data.

In contrast to other inflammatory arthritis diagnoses, where some markers of disease severity (e.g. DAS28) captured by specialist clinics are not currently available for analysis in OpenSAFELY, we were able explore differences in patients presenting with gout during vs. before the pandemic. We hypothesised that patients presenting during the pandemic were more likely to be those with more severe disease, particularly in the context of increased weight gain and alcohol consumption during the pandemic.[156,157] Our findings did not support this hypothesis. The proportion of patients who had tophi at baseline (a marker of disease severity) was similar during and before the pandemic, as was the proportion of patients who experienced recurrent flares after diagnosis (a marker of disease burden). Serum urate levels at baseline were also comparable. Of note, proportionately fewer patients presenting with

gout during the pandemic had comorbidities such as CKD. This could represent altered health-seeking behaviour in such patients; for example, in response to government recommendations for high-risk patients to stay at home ('shield') during the pandemic.[158]

Our study had limitations. Although our estimates of gout incidence and prevalence are in line with other studies utilising EHR data,[1,55] there is a potential for diagnostic misclassification inherent to studies using coded health data, which can lead to overestimates of incidence and prevalence. With EHR studies, one must also acknowledge the challenges in determining whether observed differences in diagnostic incidence over time represent true changes in underlying disease incidence or changes in the recording of diagnoses. While the marked decrease in gout diagnoses observed during the pandemic is likely to primarily reflect delays in presentation and the recording of diagnoses, further research is needed to determine whether longer-term trends reflect true decreases in disease incidence. As our analyses centred on gout diagnoses coded in primary care in England, they may not be representative of secondary care gout management during the pandemic or generalisable to other countries. Additionally, we could only capture primary care-issued prescriptions for ULT in OpenSAFELY, not secondary care-issued prescriptions;[159] however, as the majority of patients with gout are managed in primary care, this is unlikely to have meaningfully altered our findings.

When interpreting the observed changes in ULT prescribing, it is important to acknowledge changes in guideline recommendations that have occurred over time, which may have influenced prescribing behaviour. In the 2017 BSR gout management guidelines, it is recommended that all patients with gout should be offered ULT, including those presenting with their first flare.[6] In the NICE gout guideline, introduced in 2022, there is a recommendation to discuss the option of ULT with all patients with gout, but there is no specific recommendation to offer ULT unless additional factors are present (e.g. multiple flares, tophi or CKD).[35] If the NICE criteria were applied over the full study period, then the proportion of patients who should have been offered ULT and were prescribed ULT would have been relatively higher. Similarly, we could not account for patient preference in our analyses; for example, patients who were offered ULT by their clinician but declined to start it. Finally, we were unable to describe other important aspects of gout care in our analyses, such as patient-reported outcomes and the provision of disease education.

In conclusion, we showed that newly recorded gout diagnoses decreased by a third during the first year of the pandemic, with no rebound increase in incidence observed as of early 2023. For patients who presented with incident gout, ULT initiation improved modestly during the pandemic, while urate target attainment was comparable to before the pandemic. Despite this, absolute levels of ULT initiation and urate target attainment remain below an acceptable standard. Importantly, this study demonstrates the potential for routinely-captured health data to revolutionise the monitoring of chronic diseases at both national and regional levels.

5 Epidemiology of gout management in UK secondary care (*Rheumatology, 2023*)

5.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 3: What proportion of incident gout patients are hospitalised for flares, and how is the risk of hospitalisation affected by ULT initiation and urate target attainment?

Previous studies from numerous countries worldwide have shown marked increases in hospitalisations for gout flares in recent decades. In England, gout hospitalisations increased by nearly 60% between 2006 and 2017.[3] These studies utilised aggregate data to highlight population-level trends; however, no studies had used individual-level data to describe the incidence of hospitalisations in people with gout.

In addition, few studies had examined the risk factors for hospitalisations. In particular, it remained unclear what impact treat-to-target ULT had on hospitalisations. On the one hand, ULT initiation and titration can precipitate flares in the short-term; potentially leading to an increase in hospitalisations. On the other hand, community-based studies had shown that urate target attainment prevents flares in the long-term.[31] In this chapter, I use linked primary and secondary care data in CPRD to address these questions.

Treat-to-target urate-lowering therapy and hospitalisations for gout: results from a nationwide cohort study in England

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5.2 Abstract

Objective: To investigate associations between treat-to-target ULT and hospitalisations for gout.

Methods: Using linked CPRD and NHS Digital Hospital Episode Statistics data, we described the incidence and timing of hospitalisations for flares in people with index gout diagnoses in England from 2004-2020. Using Cox proportional hazards and propensity models, we investigated associations between ULT initiation, serum urate target attainment, colchicine prophylaxis, and the risk of hospitalisations for gout.

Results: Of 292,270 people with incident gout, 7,719 (2.64%) had one or more hospitalisations for gout, with an incidence rate of 4.64 hospitalisations per 1000 person-years (95% CI 4.54 to 4.73). There was an associated increased risk of hospitalisations within the first 6 months after ULT initiation, when compared with people who did not initiate ULT (adjusted Hazard Ratio (aHR) 4.54; 95% CI 3.70 to 5.58; p<0.001). Hospitalisations did not differ significantly between people prescribed vs. not prescribed colchicine prophylaxis in fully-adjusted models. From 12 months after initiation, ULT associated with a reduced risk of hospitalisations (aHR 0.77; 95% CI 0.71 to 0.83; p<0.001). In ULT initiators, attainment of a serum urate <360 micromol/L within 12 months of initiation associated with a reduced risk of hospitalisations (aHR 0.57; 95% CI 0.49 to 0.67; p<0.001) when compared with people initiating ULT but not attaining this target.

Conclusion: ULT associates with an increased risk of hospitalisations within the first 6 months of initiation but reduces hospitalisations in the long-term, particularly when serum urate targets are achieved.

5.3 Introduction

Hospitalisations for gout flares have increased markedly in recent years, on a background of an increasing prevalence of gout and sub-optimal management.[1,3,143] In England, hospitalisations for gout doubled between 2006 and 2020.[71] Hospitalisations due to gout also doubled in the United States, Canada and Sweden, contrasting large decreases in admissions for RA.[63-65] Despite this, few studies have investigated strategies to prevent avoidable gout admissions.[160]

Gout is unique among the inflammatory arthritides, in that there are curative medications that prevent flares: ULT, such as allopurinol and febuxostat. The benefits of ULT are well recognised in primary care settings. A large, RCT demonstrated that ULT, when titrated to achieve a serum urate below the saturation threshold for crystal formation (<360 micromol/L), significantly reduced the frequency of gout flares at 2 years compared with usual care (risk ratio (RR) 0.33; 95% CI 0.19 to 0.57).[31] However, in the short-term, initiation and titration of ULT can precipitate flares: the frequency of gout flares with treat-to-target ULT in the first year of this trial exceeded that observed with usual care (RR 1.36; 95% CI 1.05 to 1.77).

What is not known is whether treat-to-target ULT prevents hospitalisations for gout. Using a population-level dataset with over 290,000 people with incident gout, we investigated two primary objectives: 1) the impact of ULT, with and without colchicine prophylaxis, on the risk of hospitalisations for gout; and 2) whether attaining target serum urate levels influences the risk of hospitalisations following ULT initiation.

5.4 Methods

Data source

The CPRD is a longitudinal health database with pseudonymised demographic, clinical and prescription data from people registered with over 2,000 UK primary care practices.[115] We used CPRD Aurum, containing data on 41 million people currently or previously registered with general practices that use EMIS Web® health record software. Currently registered patients (13.3 million) in CPRD Aurum cover 20% of the UK population, with 99% of contributing practices registered in England.[118]

Primary care data in CPRD Aurum was linked to NHS Digital HES APC data. HES APC contains pseudonymised data on all admissions and attendances at English NHS providers, including acute hospital trusts.

Study population and case definition

We conducted a population-level, observational cohort study of people aged ≥18 years, currently or previously registered with a CPRD Aurum practice, who had index gout diagnoses between 1st January 2004 and 31st December 2020, and who were eligible for linkage to secondary care data. The start date of 2004 corresponds to the more widespread availability of laboratory-linked data with the incorporation of the Quality and Outcomes Framework into

UK primary care contracts. Linked secondary care data was available to 31st March 2021, with 98% of patients being eligible for linkage.

We defined an index gout diagnosis as a new diagnostic code for gout in people without previous gout diagnostic codes. At least 12 months of registration with a CPRD Aurum practice prior to the first gout code was required, to ensure only incident cases were detected, in addition ≥12 months of follow-up post-diagnosis.

Definition of hospitalisations

We defined a hospitalisation for gout flare as an admission episode with a primary gout diagnosis (ICD10 code: M10). We did not include admissions with only secondary diagnoses of gout or ED-only attendances, due to less reliable coding.[161] We excluded admissions that occurred within 7 days of another gout admission, to reduce capture of re-admissions for single flares. Only admission episodes within patients' CPRD registration windows were included. People newly diagnosed with gout during a hospitalisation will typically have a gout code entered in primary care following receipt of the discharge notification; in these cases, we selected the admission date as the index diagnosis date.

We classified gout hospitalisations into: i) index diagnosis events – i.e. first recorded diagnosis of gout made during or within 7 days of a hospitalisation for flare; and ii) non-index events – hospitalisations ≥7 days after the initial diagnosis.

Incidence rate of hospitalisations

We reported the proportion of patients who had one or more hospitalisations for gout, and the number of hospitalisations during the study period. We described patients' characteristics at diagnosis (without inferential statistics) for the whole study cohort and, separately, for patients who had one or more hospitalisations for gout. We calculated an incidence rate of hospitalisations by dividing the number of admission episodes by person-time exposure. In tabular and graphical form, we described the incidence rate of hospitalisations over time since first gout diagnosis, using restricted cubic splines to fit a regression line.

Treatment, urate monitoring and target attainment

For people hospitalised for gout during the study period who had a minimum of 12 months of CPRD registration after their first hospitalisation, we described the number and proportion who: i) were already prescribed ULT (allopurinol, febuxostat, benzbromarone, probenecid or sulfinpyrazone) at the time of their first hospitalisation; ii) initiated ULT within 12 months of their first hospitalisation; iii) had ≥1 serum urate level performed within 12 months of hospitalisation; iv) had treat-to-target urate monitoring, which we defined ≥2 serum urate levels within 12 months of hospitalisation and/or ≥1 serum urate level <360 micromol/L (i.e. representing a minimum threshold for treat-to-target monitoring); and v) had ≥1 recorded serum urate level <360 micromol/L or <300 micromol/L within 12 months. We described these outcomes for the hospitalised cohort as a whole, and for the subset of patients first diagnosed with gout during an admission episode. For the latter cohort, we compared attainment of these outcomes to patients first diagnosed with gout outside of an admission

using two-proportions Z-tests, and described time trends in outcome attainment graphically using two-way plots.

Factors associated with hospitalisations

We used Cox proportional hazards models with robust standard errors to describe factors associated with hospitalisations in people with incident gout. Patients were defined as at-risk from gout diagnosis until their first hospitalisation, death, or date of de-registration, whichever came first. We selected covariates *a priori* on the basis of whether they were felt to be important potential confounders of hospitalisations: age at diagnosis; sex; calendar year of diagnosis; comorbidities (CKD stages 3-5, hypertension, diabetes mellitus, IHD, heart failure, previous stroke or TIA, obesity, current or previous history of urolithiasis); smoking status (current/previous smoker vs. never smoker); alcohol excess; and diuretic therapy at gout diagnosis. Age and sex-adjusted models and fully-adjusted models (adjusted for all covariates) were presented with hazard ratios and 95% CI. In a sensitivity analysis, adjustment was performed for baseline serum urate levels in patients who had these data available (baseline serum urate level was defined as the test closest to diagnosis, assuming this was within 6 months before/after diagnosis and not post-ULT commencement). Nelson-Aalen and log-log plots were performed to ensure assumptions regarding proportional hazards were met.

Using a similar approach, we explored associations between the following factors and non-index hospitalisations: 1) ULT initiation within 12 months of diagnosis; 2) serum urate target attainment within 12 months of ULT initiation. We defined the at-risk date for hospitalisations as when ULT was initiated or serum urate targets were attained, respectively. For individuals who did not initiate ULT or did not attain serum urate targets, dummy dates were imputed using hot deck imputation to account for the greater initial risk of hospitalisations after diagnosis and ULT initiation. When exploring associations between serum urate target attainment and hospitalisations, we presented complete case analyses (i.e. individuals who had serum urate levels performed within 12 months of ULT initiation) and imputed models (i.e. all individuals who initiated ULT, with 20-cycle multiple imputation of target attainment for individuals who did not have serum urate levels performed within 12 months of ULT initiation). In all models, multivariable adjustment was performed for the covariates described above. As sensitivity analyses, we presented outputs from: i) Cox proportional hazard models with inverse probability of treatment weighting of covariates; and ii) Cox proportional hazard models including adjustment for time from diagnosis to ULT initiation.

We also explored the effect of colchicine prophylaxis when initiating ULT on hospitalisations. Individuals initiating ULT were categorised according to whether they did/did not receive ≥90 tablets of colchicine within 90 days of ULT initiation. As a sensitivity analysis, we excluded individuals who were prescribed ≥90 tablets of NSAID (naproxen, ibuprofen, diclofenac, indomethacin, celecoxib, etoricoxib) or corticosteroids (prednisolone, prednisone, methylprednisolone, methylprednisone) within 90 days of ULT initiation.

A summary of our primary models and sensitivity analyses is included in Table 8. All analyses were performed in Stata version 17.1.

Study approval and ethics

The study protocol was approved by the CPRD Research Data Governance committee (approval number: 21_000680). No further ethical approval was required.

Table 8. Summary of prediction models used in the study

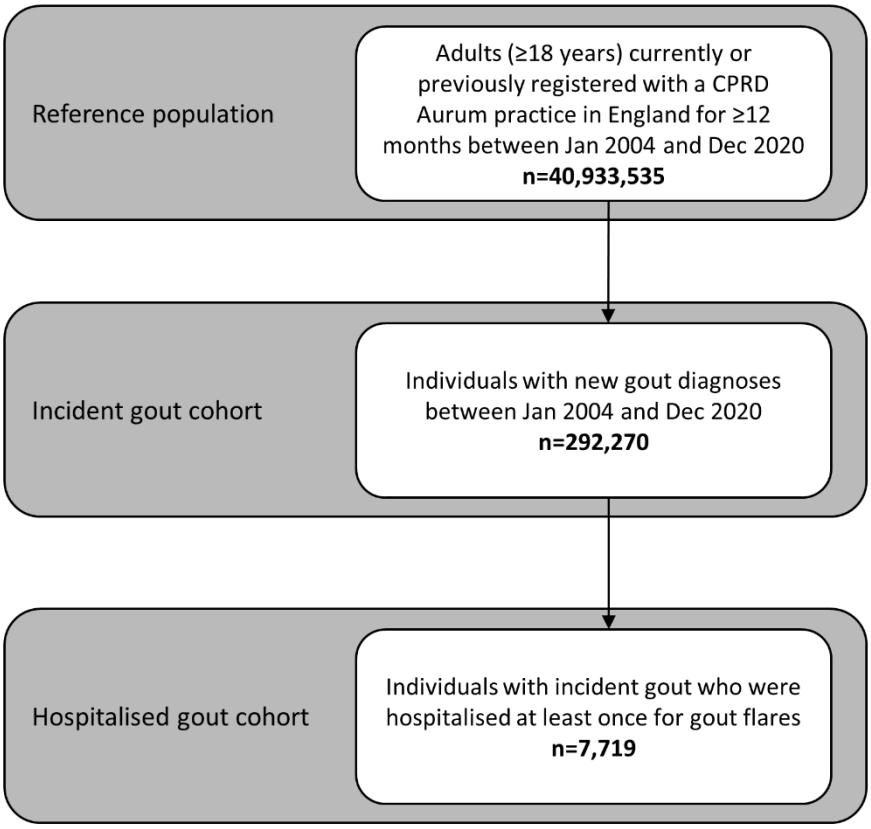
Study population	Exposure group	Comparison group	Primary model	At-risk date	Covariates	Sensitivity analyses
People with incident gout	People with gout who were hospitalised for gout flares	People with gout who were not hospitalised for gout flares	Cox proportional hazards	From gout diagnosis	Age, sex, calendar year of diagnosis, CKD, hypertension, diabetes mellitus, IHD, heart failure, previous CVA, obesity, urolithiasis; smoking status, alcohol excess, diuretic therapy	1. Adjustment for serum urate level at diagnosis
People with incident gout	ULT initiated within 12 months of diagnosis	No ULT initiated within 12 months of diagnosis	Cox proportional hazards	From ULT initiation (dummy date imputed for ULT non-initiators)		1. Adjustment for serum urate level at diagnosis 2. Propensity model with IPTW 3. Adjustment for time from diagnosis to ULT initiation
People with gout who initiated ULT	Colchicine prophylaxis prescribed for ≥3 months	Colchicine prophylaxis not prescribed for ≥3 months	Cox proportional hazards	From ULT initiation		1. Exclusion of individuals prescribed NSAID or corticosteroid prophylaxis
People with gout who initiated ULT	Urate <360 micromol/L achieved within 12 months of ULT initiation	Urate <360 micromol/L not achieved within 12 months of ULT initiation	Cox proportional hazards with multiple imputation of target attainment in those without urate levels	From target attainment (dummy date imputed for target non-attainers)		1. Complete case analysis (unimputed) 2. Propensity model with IPTW
People with gout who initiated ULT	Urate <300 micromol/L achieved within 12 months of ULT initiation	Urate <300 micromol/L not achieved within 12 months of ULT initiation	Cox proportional hazards with multiple imputation of target attainment in those without urate levels	From target attainment (dummy date imputed for target non-attainers)		1. Complete case analysis (unimputed) 2. Propensity model with IPTW

5.5 Results

Study population and baseline characteristics

292,270 people had new gout diagnoses in a CPRD Aurum-contributing practice in England between 1st January 2004 and 31st December 2020. From this cohort, 7,719 people (2.64%) had one or more hospitalisations for gout flares during the study period, with 8,920 admissions in total. 6,805 people (88.2%) had one admission; 914 people (11.8%) had multiple admissions. A flowchart of the study populations used in our analyses is shown in Figure 25. The mean duration of admissions was 6 days (median: 3 days). Cumulatively, 56,857 bed-days were occupied due to gout admissions over the study period.

Figure 25. Flowchart of study populations



The baseline characteristics (at diagnosis) of people with and without hospitalisations for gout are shown in Table 9. Individuals hospitalised for gout were older, had more comorbidities, were more likely to be on diuretics, and had higher serum urate levels at diagnosis than those without hospitalisations.

Of 8,920 admissions, 713 (7.99%) occurred in patients after prior attainment of a serum urate level <360 micromol/L, while 325 admissions (3.64%) occurred after prior attainment of a serum urate level <300 micromol/L.

Table 9. Baseline characteristics of people with newly-diagnosed gout, with and without hospitalisations

	All patients with gout N=292,270	Patients with no admissions N=284,551	Patients with one admission N=6,805	Patients with multiple admissions N=914
Age at diagnosis	62 (16)	61 (16)	67 (16)	66 (16)
Sex				
Male	216,630 (74.1%)	211,066 (74.2%)	4,881 (71.7%)	683 (74.7%)
Number of comorbidities at diagnosis	1.6 (1.4)	1.6 (1.4)	2.3 (1.6)	2.5 (1.7)
CKD stage 3-5				
No	214,809 (73.5%)	210,617 (74.0%)	3,748 (55.1%)	444 (48.6%)
Yes	77,461 (26.5%)	73,934 (26.0%)	3,057 (44.9%)	470 (51.4%)
Hypertension				
No	149,422 (51.1%)	146,398 (51.4%)	2,681 (39.4%)	343 (37.5%)
Yes	142,848 (48.9%)	138,153 (48.6%)	4,124 (60.6%)	571 (62.5%)
Diabetes mellitus				
No	252,057 (86.2%)	246,066 (86.5%)	5,309 (78.0%)	682 (74.6%)
Yes	40,213 (13.8%)	38,485 (13.5%)	1,496 (22.0%)	232 (25.4%)
Ischaemic heart disease				
No	243,893 (83.4%)	238,311 (83.7%)	4,957 (72.8%)	625 (68.4%)
Yes	48,377 (16.6%)	46,240 (16.3%)	1,848 (27.2%)	289 (31.6%)
Heart failure				
No	271,441 (92.9%)	265,105 (93.2%)	5,624 (82.6%)	712 (77.9%)
Yes	20,829 (7.1%)	19,446 (6.8%)	1,181 (17.4%)	202 (22.1%)
Previous CVA				
No	273,241 (93.5%)	266,444 (93.6%)	6,008 (88.3%)	789 (86.3%)
Yes	19,029 (6.5%)	18,107 (6.4%)	797 (11.7%)	125 (13.7%)
Obesity				
No	180,143 (61.6%)	175,692 (61.7%)	3,947 (58.0%)	504 (55.1%)
Yes	112,127 (38.4%)	108,859 (38.3%)	2,858 (42.0%)	410 (44.9%)
Urolithiasis				
No	284,996 (97.5%)	277,490 (97.5%)	6,621 (97.3%)	885 (96.8%)
Yes	7,274 (2.5%)	7,061 (2.5%)	184 (2.7%)	29 (3.2%)
Current or ex-smoker				
No	87,442 (29.9%)	85,350 (30.0%)	1,852 (27.2%)	240 (26.3%)
Yes	204,828 (70.1%)	199,201 (70.0%)	4,953 (72.8%)	674 (73.7%)
Alcohol excess				
No	273,060 (93.4%)	266,041 (93.5%)	6,210 (91.3%)	809 (88.5%)
Yes	19,210 (6.6%)	18,510 (6.5%)	595 (8.7%)	105 (11.5%)
On diuretic				
No	194,681 (66.6%)	190,924 (67.1%)	3,346 (49.2%)	411 (45.0%)
Yes	97,589 (33.4%)	93,627 (32.9%)	3,459 (50.8%)	503 (55.0%)
Serum urate at diagnosis, micromol/L	471 (100)	470 (99)	523 (117)	558 (126)

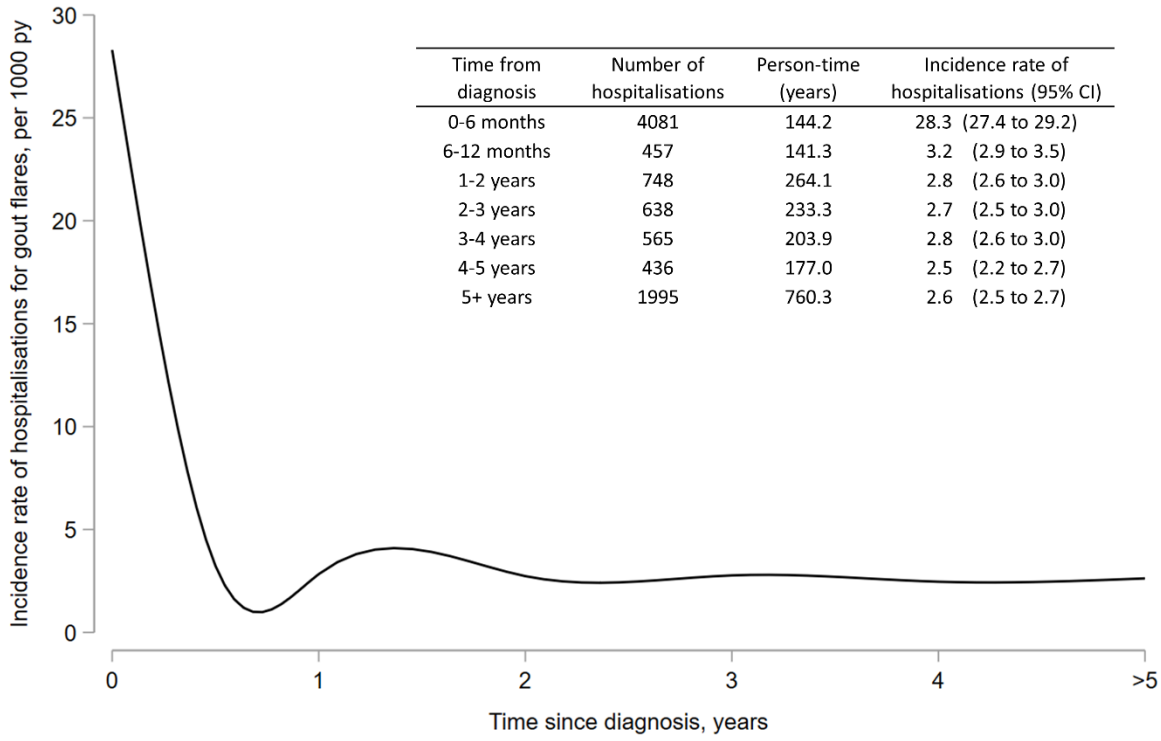
Baseline demographics and comorbidities in people with newly-diagnosed gout, separated into those who had hospitalisations for gout flares (single vs. multiple) during the study period and those who had no hospitalisations. Data are presented as mean (standard deviation) for continuous measures, and n (%) for categorical measures. Baseline serum urate levels were available for 184,185 patients.

Incidence rate of hospitalisations

Of 8,920 admissions, 3,316 (37.2%) were index diagnosis events (i.e. first recorded diagnosis of gout made during a hospitalisation for flare), while 5,604 occurred ≥7 days after first diagnosis.

The incidence rate of hospitalisations for flares in people with gout was 4.64 per 1,000 person-years (95% CI 4.54 to 4.73). The incidence rate of hospitalisations was greater within 6 months of diagnosis (28.3 admissions per 1,000 person-years; 95% CI 27.4 to 29.2) than beyond 6 months (2.71 admissions per 1,000 person-years; 95% CI 2.64 to 2.80), as shown in Figure 26.

Figure 26. Incidence rate of hospitalisations for flares in people with gout, in relation to time since diagnosis



Time from diagnosis	Number of hospitalisations	Person-time (years)	Incidence rate of hospitalisations (95% CI)
0-6 months	4081	144.2	28.3 (27.4 to 29.2)
6-12 months	457	141.3	3.2 (2.9 to 3.5)
1-2 years	748	264.1	2.8 (2.6 to 3.0)
2-3 years	638	233.3	2.7 (2.5 to 3.0)
3-4 years	565	203.9	2.8 (2.6 to 3.0)
4-5 years	436	177.0	2.5 (2.2 to 2.7)
5+ years	1995	760.3	2.6 (2.5 to 2.7)

Restricted cubic splines were used to fit a regression line

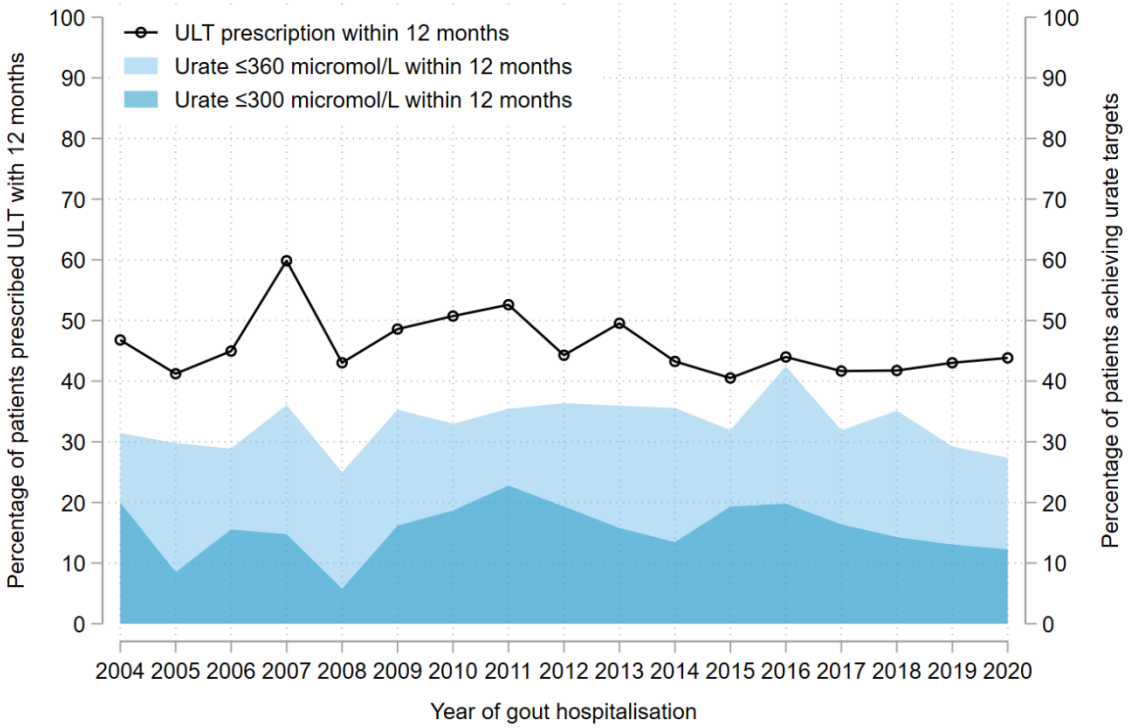
ULT initiation and urate target attainment

Of 7,719 patients hospitalised for gout, 7,040 (91.2%) had ≥12 months of available follow-up after their first hospitalisation, to facilitate analyses of post-discharge ULT initiation and serum urate target attainment. 1,734/7,040 people (24.6%) were already prescribed ULT at the time of their first hospitalisation; 2,560 (36.4%) commenced ULT within 12 months of hospitalisation; and 2,746 (39.0%) remained off ULT 12 months after their first hospitalisation.

3,360/7,040 people (47.7%) had ≥1 serum urate level performed within 12 months of their first hospitalisation; 1,956 (27.8%) had treat-to-target urate monitoring. Of 3,360 hospitalised patients who had ≥1 serum urate level performed, 1,184 (35.2%) attained a serum urate <360 micromol/L within 12 months, while 581 (17.3%) attained a serum urate <300 micromol/L.

Of the subset of patients first diagnosed with gout during hospitalisations for flares (n=3,316), 1,504 (45.4%) were prescribed ULT within 12 months of diagnosis. In comparison, people diagnosed with gout outside of a hospitalisation (n=288,954) were less likely to initiate ULT within 12 months of diagnosis (27.9%; p<0.001). People first diagnosed with gout during a hospitalisation were also more likely to receive treat-to-target urate monitoring (25.7% vs. 22.0%, respectively; p<0.001) and to attain serum urate levels <300 micromol/L (15.8% vs. 13.2%; p<0.001) and <360 micromol/L (33.4% vs. 27.4%; p<0.001) within 12 months of diagnosis than those diagnosed outside of an admission. Time trends in post-discharge ULT initiation and serum urate target attainment are shown in Figure 27.

Figure 27. Trends in ULT initiation and urate target attainment following new gout diagnoses made during hospitalisations



Time trends are shown in the proportion of patients newly diagnosed with gout during hospitalisations for flares (n=3,316) who: i) were initiated on ULT within 12 months of hospitalisation (black line); or ii) had a serum urate performed (n=1,529) and attained a level ≤360 µmol/L (light blue) or ≤300 µmol/L (dark blue) within 12 months of hospitalisation.

Baseline factors associated with hospitalisations

In Cox proportional hazard models with multivariable adjustment, the following factors at diagnosis associated with hospitalisations for flares in people with gout: older age, male sex, diuretic use, comorbidities (CKD, heart failure, alcohol excess, IHD, diabetes mellitus, previous CVA, and obesity), and later calendar year of diagnosis (Table 10). Following adjustment for serum urate level at diagnosis in the subset of patients who had levels performed (n=184,185), these variables remained significant predictors of hospitalisations, albeit with a reduced effect size for several comorbidities (Table 11).

Table 10. Factors associated with hospitalisations for flares in people with gout

Variables	Hazard ratio (age/sex-adjusted)	95% CI	p-value	Hazard ratio (fully-adjusted)	95% CI	p-value
Age at diagnosis (per 10-year increase)	1.32	(1.29 - 1.34)	<0.001	1.10	(1.08 - 1.13)	<0.001
Female sex	0.90	(0.85 - 0.94)	<0.001	0.82	(0.78 - 0.86)	<0.001
Later calendar year of diagnosis	1.02	(1.02 – 1.03)	<0.001	1.03	(1.02 - 1.03)	<0.001
CKD stages 3-5	2.03	(1.91 - 2.14)	<0.001	1.68	(1.59 - 1.79)	<0.001
Hypertension	1.24	(1.18 - 1.31)	<0.001	0.96	(0.91 - 1.02)	0.19
Diabetes mellitus	1.67	(1.58 - 1.76)	<0.001	1.32	(1.25 - 1.39)	<0.001
Ischaemic heart disease	1.58	(1.50 - 1.67)	<0.001	1.15	(1.09 - 1.22)	<0.001
Heart failure	2.66	(2.50 - 2.83)	<0.001	1.89	(1.77 - 2.02)	<0.001
Previous CVA	1.62	(1.51 - 1.73)	<0.001	1.37	(1.28 - 1.47)	<0.001
Urolithiasis	1.05	(0.92 - 1.21)	0.46	0.98	(0.85 - 1.13)	0.77
Obesity	1.27	(1.21 - 1.33)	<0.001	1.11	(1.06 - 1.17)	<0.001
Current/ex-smoker	1.08	(1.03 - 1.14)	<0.001	0.97	(0.92 - 1.02)	0.19
Alcohol excess	1.74	(1.60 - 1.89)	<0.001	1.72	(1.59 - 1.87)	<0.001
Diuretic therapy	1.71	(1.63 - 1.80)	<0.001	1.33	(1.25 - 1.42)	<0.001

Age and sex-adjusted Cox proportional hazard model outputs are shown, in addition to multivariable Cox proportional hazard model outputs (with adjustment for all covariates, including calendar year of diagnosis). Robust standard errors were estimated to account for clustering of patients within practice/region.

Table 11. Factors associated with hospitalisations for flares in people with gout, with and without adjustment for baseline serum urate

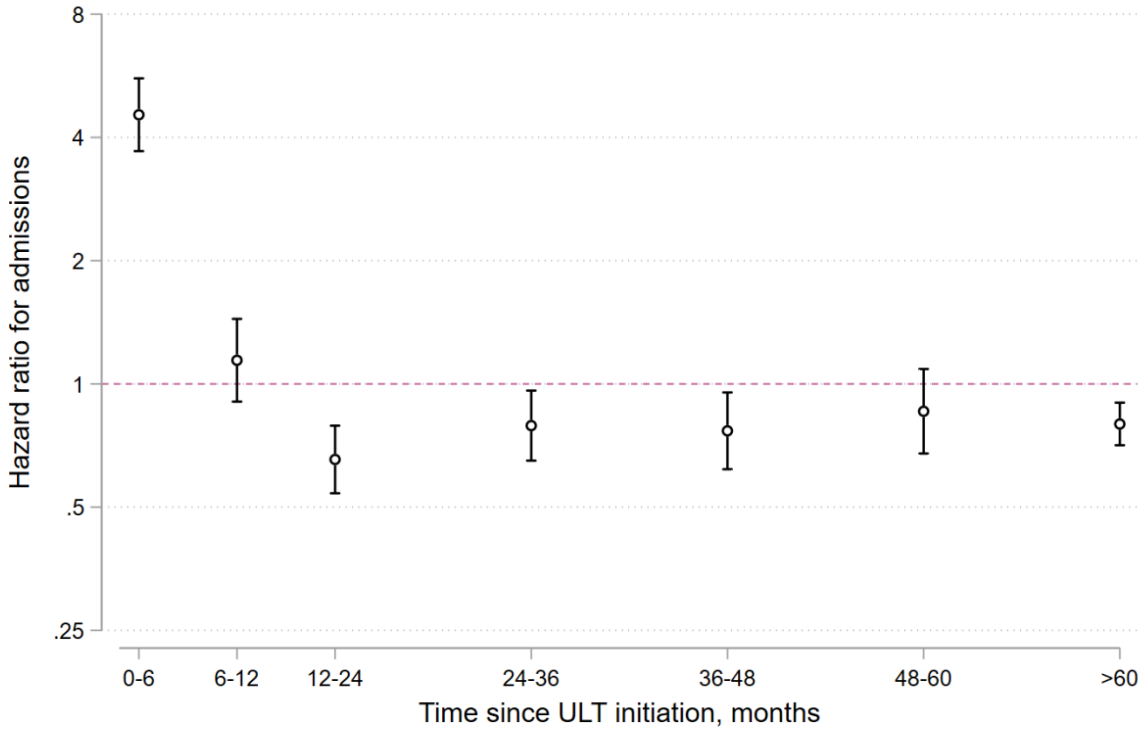
	Without adjustment for baseline urate			With adjustment for baseline urate		
Variables	**Hazard ratio**	**95% CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Age at diagnosis (per 10-year increase)	1.11	(1.07 - 1.15)	<0.001	1.15	(1.11 - 1.19)	<0.001
Female sex	0.76	(0.71 - 0.82)	<0.001	0.83	(0.77 - 0.89)	<0.001
Year of gout diagnosis	1.03	(1.02 - 1.04)	<0.001	1.03	(1.02 - 1.04)	<0.001
CKD stages 3-5	1.67	(1.53 - 1.81)	<0.001	1.43	(1.31 - 1.56)	<0.001
Hypertension	0.99	(0.91 - 1.08)	0.86	1.00	(0.92 - 1.08)	0.97
Diabetes mellitus	1.22	(1.13 - 1.33)	<0.001	1.23	(1.14 - 1.34)	<0.001
Ischaemic heart disease	1.15	(1.06 - 1.25)	<0.001	1.15	(1.06 - 1.25)	<0.001
Heart failure	2.05	(1.87 - 2.26)	<0.001	1.89	(1.71 - 2.08)	<0.001
Previous CVA	1.31	(1.18 - 1.45)	<0.001	1.30	(1.17 - 1.44)	<0.001
Urolithiasis	1.00	(0.83 - 1.22)	0.97	1.00	(0.83 - 1.22)	0.97
Obesity	1.13	(1.05 - 1.21)	<0.001	1.08	(1.01 - 1.16)	0.03
Current/ex-smoker	0.95	(0.88 - 1.02)	0.14	0.94	(0.88 - 1.01)	0.11
Alcohol excess	1.74	(1.54 - 1.96)	<0.001	1.68	(1.49 - 1.90)	<0.001
Diuretic therapy	1.30	(1.20 - 1.42)	<0.001	1.12	(1.03 - 1.22)	0.01
Baseline serum urate level (>480 micromol/L)	-	-	-	1.90	(1.77 - 2.05)	<0.001

Baseline serum urate data available for 184,185 patients. Multivariable Cox proportional hazard model outputs are shown, with (right-hand side) and without (left-hand side) adjustment for serum urate level at diagnosis. Serum urate was included as a binary variable (above/below 480 micromol/L) corresponding to the threshold specified in the EULAR gout management guideline. Outputs were adjusted for all other covariates shown, including calendar year of diagnosis. Robust standard errors were estimated to account for clustering of patients within practice/region.

Associations between ULT initiation and hospitalisations

In Cox proportional hazard models with multivariable adjustment, an increased risk of hospitalisations for flares was observed within the first 6 months of initiating ULT, compared with people with gout who did not initiate ULT: adjusted Hazard Ratio (aHR) 4.54; 95% CI 3.70 to 5.58; p<0.001. Between 6 and 12 months after ULT initiation, there was no significant association with hospitalisations (aHR 1.14; 95% CI 0.91 to 1.44; p=0.26). Beyond 12 months after ULT initiation, there was a reduced risk of hospitalisations associated with ULT initiation (aHR 0.77; 95% CI 0.71 to 0.83; p<0.001), when compared with patients who did not initiate ULT (Figure 28).

Figure 28. Risk of hospitalisation for flares in people with gout who initiated ULT within 12 months of diagnosis, compared with people who did not initiate ULT



Outputs from Cox proportional hazards models are shown, highlighting the change in hazard ratio for hospitalisations in relation to time elapsed following initiation of ULT. Adjustment was performed for the following covariates: age, sex, calendar year of gout diagnosis, diuretic use and comorbidities at diagnosis (hypertension, CKD, IHD, heart failure, diabetes mellitus, prior CVA, obesity, smoking status, alcohol excess, history of urolithiasis). A logarithmic y-axis was used, to reflect the exponential distribution of hazard functions.

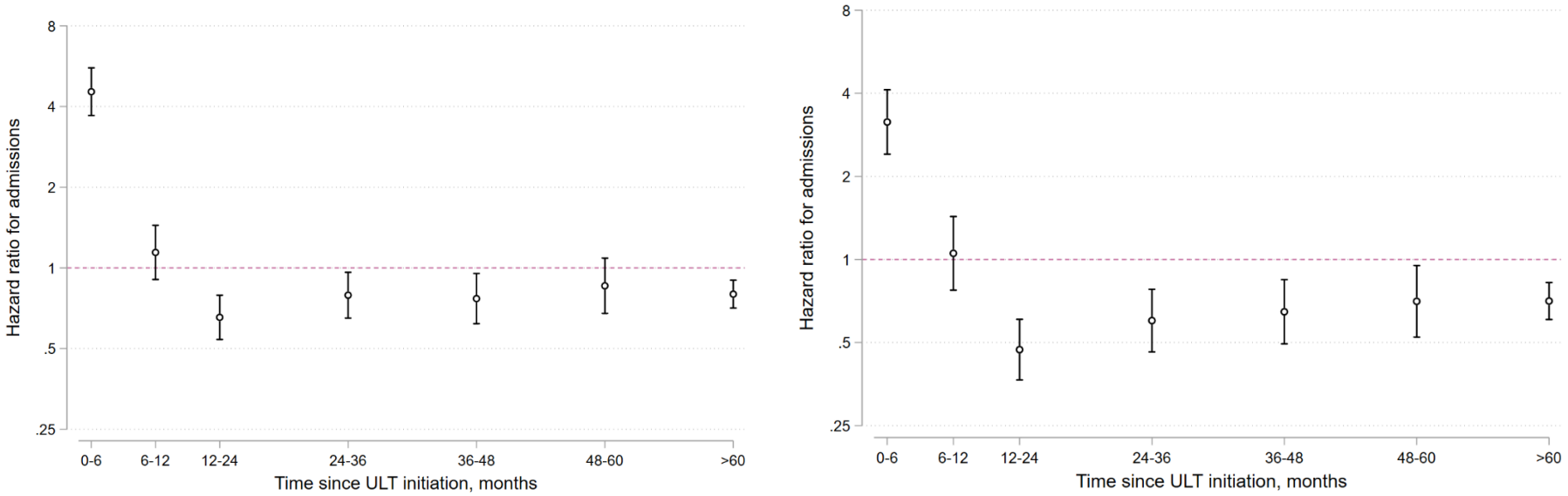
Following adjustment for serum urate level at diagnosis in the subset of patients who had these levels performed (n=184,185), the association between ULT and increased hospitalisations within 6 months of initiation remained but reduced in effect size (aHR 3.15; 95% CI 2.41 to 4.12; p<0.001), while the association between ULT and fewer hospitalisations beyond 12 months increased in effect size (aHR 0.63; 95% CI 0.57 to 0.70; p<0.001) (Figure 29). In sensitivity analyses comparing our primary Cox model to a propensity model with IPTW, the results were very similar (Figure 30), as were Cox models that included adjustment for time from diagnosis to ULT initiation (Figure 31 and Figure 32).

We explored whether prescription of colchicine prophylaxis during ULT initiation impacted upon hospitalisation risk. Of 81,994 people initiating ULT, 8,026 (9.8%) received ≥90 tablets of colchicine in the 3 months after ULT initiation. In age and sex-adjusted Cox models, there was an associated increased risk of hospitalisations within 6 months after ULT initiation in people prescribed vs. not prescribed colchicine prophylaxis (HR 1.41; 95% CI 1.02 to 1.94; p=0.038). In fully-adjusted Cox models, however, there were no statistically significant differences between these groups (aHR 1.31; 95% CI 0.95 to 1.82; p=0.10). In sensitivity analyses excluding individuals prescribed NSAID prophylaxis or corticosteroid prophylaxis (n=9,559), colchicine prophylaxis did not associate with significant differences in hospitalisations within 6 months of ULT initiation (aHR 1.32; 95% CI 0.93 to 1.87; p=0.12).

Associations between urate target attainment and hospitalisations

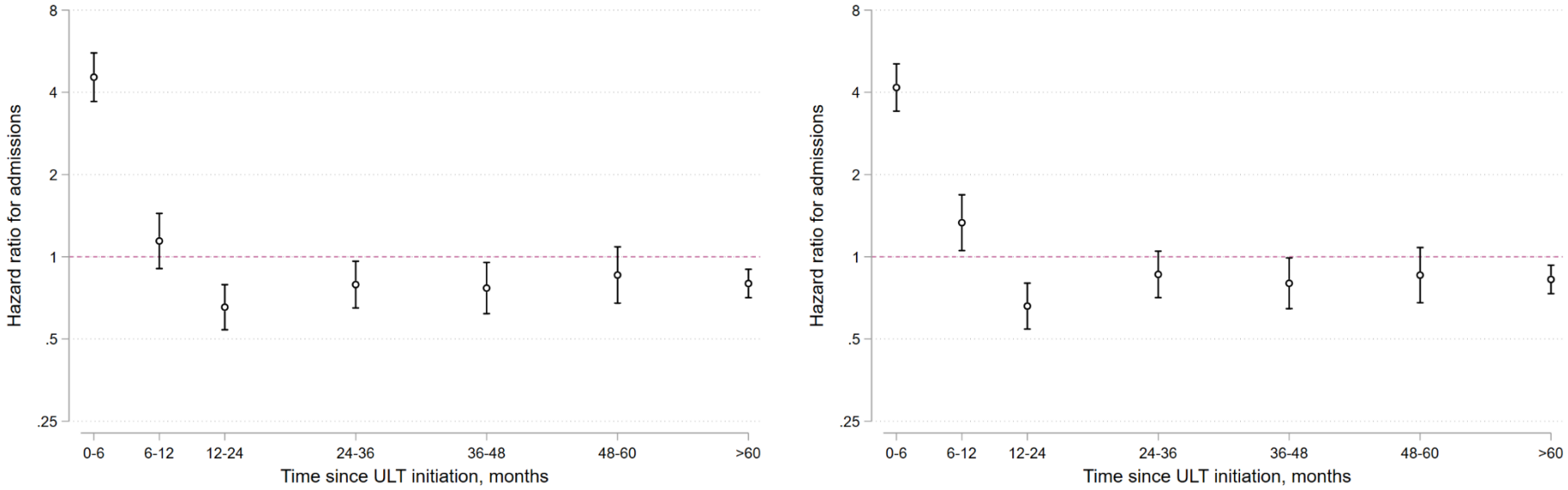
Finally, we investigated associations between serum urate target attainment in people initiating ULT (n=81,994) and hospitalisations. Using Cox proportional hazards with multiple imputation for people with no serum urate levels performed within 12 months of ULT initiation (n=36,704), attainment of a serum urate <360 micromol/L associated with a reduced risk of hospitalisations after target attainment (aHR 0.57; 95% CI 0.49 to 0.67; p<0.001) when compared with people initiating ULT but not attaining target. For those attaining a serum urate <300 micromol/L, the adjusted hazard ratio for hospitalisations was 0.69 (95% CI 0.57 to 0.84; p<0.001). In complete case analyses – restricted to people initiating ULT who had ≥1 serum urate level performed within 12 months of initiation (n=45,290) - the hazard ratios for hospitalisations were 0.39 (95% CI 0.32 to 0.47; p<0.001) for attaining <360 micromol/L and 0.47 (95% CI 0.37 to 0.59; p<0.001) for attaining <300 micromol/L. Similar findings were observed in propensity models with IPTW: <360 micromol/L (HR 0.39; 95% CI 0.32 to 0.47; p<0.001) and <300 micromol/L (HR 0.48; 95% CI 0.37 to 0.61; p<0.001).

Figure 29. Risk of hospitalisations for flares in people with gout who initiated ULT within 12 months of diagnosis, relative to those who did not initiate ULT



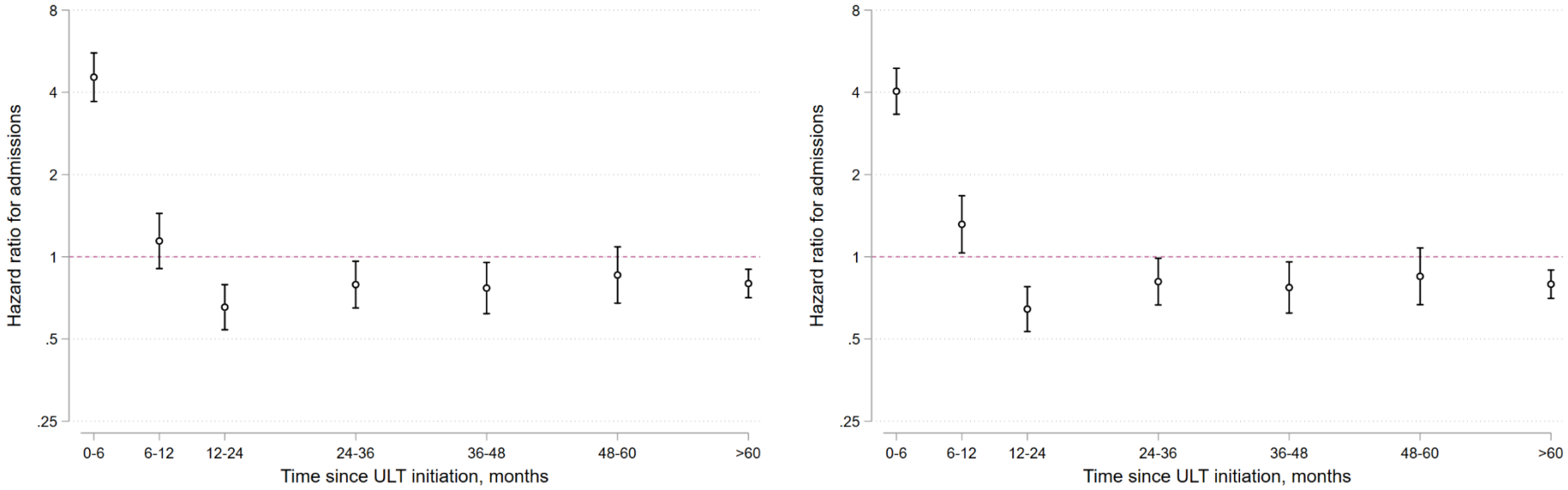
Outputs are shown from Cox proportional hazard models: i) without adjustment for serum urate levels at diagnosis (left panel; primary model); and ii) with adjustment for serum urate levels at diagnosis (right panel; sensitivity analysis). In both models, the following covariates were adjusted for: age, sex, calendar year of gout diagnosis, diuretic use and comorbidities at diagnosis (hypertension, CKD, IHD, heart failure, diabetes mellitus, prior CVA, obesity, smoking status, alcohol excess, history of urolithiasis). A logarithmic y-axis was used, to reflect the exponential distribution of hazard functions.

Figure 30. Comparison of Cox proportional hazards model and propensity model, to explore risk of hospitalisations in people with gout who initiated ULT within 12 months of diagnosis, relative to those who did not initiate ULT



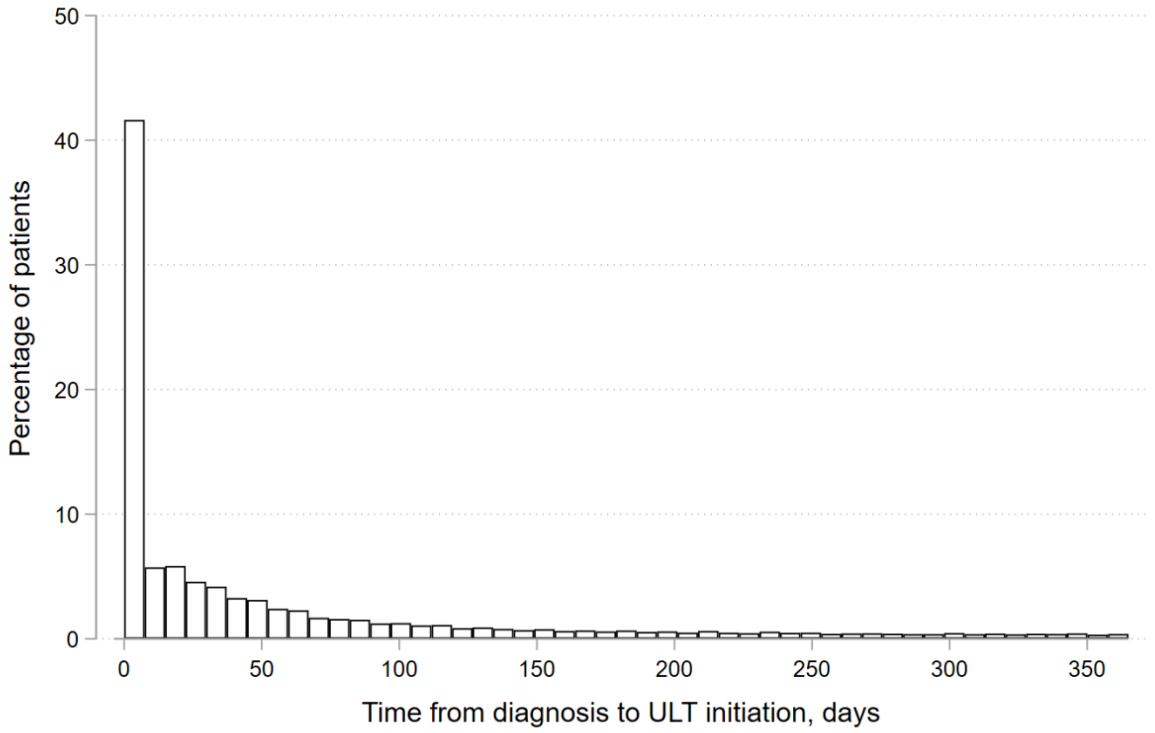
Outputs from my primary Cox proportional hazard model (left panel) are compared to a propensity model with inverse probability treatment weighting (right panel). In both models, adjustment/weighting was performed for the following covariates: age, sex, calendar year of gout diagnosis, diuretic use and comorbidities at diagnosis (hypertension, CKD, IHD, heart failure, diabetes mellitus, prior CVA, obesity, smoking status, alcohol excess, history of urolithiasis). A logarithmic y-axis was used, to reflect the exponential distribution of hazard functions.

Figure 31. Comparison of Cox proportional hazards models for hospitalisations, with and without adjustment for time from gout diagnosis to ULT initiation



Hazard ratio of hospitalisations for flares in people with gout who initiated ULT within 12 months of diagnosis, relative to those who did not initiate ULT. Outputs from our primary Cox proportional hazard model (left panel) are compared to a sensitivity analysis that included adjustment for time from gout diagnosis to ULT initiation (right panel). A histogram of time from gout diagnosis to first prescription of ULT is shown in Figure 32. In both models, adjustment/weighting was performed for the following covariates: age, sex, calendar year of gout diagnosis, diuretic use and comorbidities at diagnosis (hypertension, CKD, IHD, heart failure, diabetes mellitus, prior CVA, obesity, smoking status, alcohol excess, history of urolithiasis). A logarithmic y-axis was used, to reflect the exponential distribution of hazard functions.

Figure 32. Histogram of time from gout diagnosis to first prescription of ULT in patients who initiated ULT within 12 months of diagnosis



5.6 Discussion

In this study, we described the incidence of hospitalisations for gout and the impact of treat-to-target ULT in over 290,000 people with gout. We observed an increased risk of hospitalisations in the first 6 months after ULT initiation, and a reduced risk of hospitalisations beyond 12 months. In people initiating ULT, attainment of target serum urate levels associated with a 30-60% lower risk of hospitalisations for flares. Despite this, only a third of patients achieved a serum urate target within a year of hospitalisation.

Previous studies from the US, UK and Europe have used aggregated health data to demonstrate large increases in hospitalisations for gout over the last 20-30 years.[3,63-65] Our study is the first to use individual-level, linked primary and secondary care data to describe the incidence and pattern of hospitalisations in a nationwide cohort of incident gout patients. For every 1,000 people with gout, there were 4.6 hospitalisations with primary diagnoses of gout per year between 2004 and 2020. There was a 10-fold increased incidence of hospitalisations during the first 6 months after diagnosis. Older patients, those with comorbidities, diuretic users, and people with higher serum urate levels at diagnosis were most at risk of being hospitalised.

Previously, two small retrospective analyses (≤250 patients each) reported associations between ULT and reduced risks of hospitalisations or ED attendances for gout.[162,163] The time-varying relationship between ULT and hospitalisations, and the impact of achieving serum urate targets, were not known. Our finding that serum urate target attainment after ULT initiation associates with fewer hospitalisations demonstrates the importance of treat-to-target ULT in the long-term prevention of admissions. Hospitalisations with primary diagnoses of gout cost the English NHS more than £10 million per year.[164] Additional costs are attributable to ED attendances, hospitalisations with secondary diagnoses of gout (e.g. in the context of heart failure), repeated primary care attendances, and work disability due to flares.[165,166] In our study, 63% of admissions occurred in people already diagnosed with gout; however, only 25% of admitted patients were receiving ULT; 40% remained on no ULT at 12 months after their first hospitalisation; and only a third of patients achieved a serum urate <360 micromol/L within 12 months. Despite the publication of British, European and American guidelines that encourage treat-to-target ULT,[6-8] we observed no improvements ULT initiation or urate target attainment between January 2004 and December 2020. Together, these findings emphasise the need for implementation strategies that promote the uptake of treat-to-target ULT, particularly for patients most at risk of hospitalisation.

Our finding that ULT associates with an increased risk of flares requiring hospitalisation in the first 6 months after initiation is in keeping with the results of studies in community settings. In a UK primary care-based RCT of people with gout (n=517), treat-to-target ULT increased the frequency of gout flares within the first year when compared with usual care, but reduced flares at 2 years.[31] In the NOR-Gout study of treat-to-target ULT, flares were more frequent

during the first year after initiation (particularly at 3-6 months after initiation), but reduced greatly in the second year.[167]

Changes in serum urate levels when initiating ULT may precipitate flares through dissolution and remodelling of intra-articular urate crystal deposits.[168] Guidelines recommend considering prescription of prophylaxis against flares when initiating and titrating ULT, with low-dose colchicine (500 micrograms once or twice daily for ≥3 months) recommended as first-line prophylaxis.[6,7] In our cohort, only 10% of people initiating ULT were prescribed the equivalent of colchicine 500 micrograms once daily for ≥3 months. In age and sex-adjusted models, we observed an association between increased hospitalisations and the prescription of colchicine prophylaxis; however, this association was not statistically significant following multivariable adjustment. Our finding contrasts RCTs that have reported fewer flares when initiating ULT with colchicine prophylaxis.[169] The differences may represent confounding by indication in our cohort; for example, prescription of colchicine to people with more severe gout at greater risk of hospitalisation. We explored the use of propensity models to account for differences in colchicine-receiving vs. non-receiving groups; however, differences between these groups precluded this. Other potential contributing factors could include repeated acute prescriptions for colchicine for flares being misclassified as prophylaxis, and low adherence to prophylaxis during ULT titration.

Our study had several strengths. We used validated, population-level data sources containing pseudonymised data on 41 million people, covering a period of 17 years.[124,140,141] Linked secondary care data on all admissions to NHS hospitals in England were available for 98% of the study cohort, facilitating accurate estimates of hospitalisations. We used several statistical approaches to explore identified associations, including propensity models, and accounted for multiple possible confounders.

Our study also had limitations. There is a potential for diagnostic misclassification inherent to studies using coded healthcare data. We defined hospitalisations for gout flares as admissions with primary diagnoses of gout using the ICD-10 coding system. Although most primary admissions for gout will have been due to flares, other factors may have contributed to these admissions; for example, associations between gout flares and cardiovascular events were recently reported.[146] We were unable to infer the directionality of reported associations. Reverse causality may have contributed to the increased risk of hospitalisations observed within 6 months of ULT initiation; supported by our finding that people first diagnosed with gout during an admission were 65% more likely to be prescribed ULT than those diagnosed outside of an admission. Additionally, our analyses do not take into account the impact of medication adherence or persistence on outcomes.

We did not include ED attendances or secondary admission diagnoses of gout, due to the less granular/reliable coding of these episodes.[161] This will have substantially underestimated the true burden of gout, noting that 76% of unplanned hospital attendances for gout in a recent UK-based study were ED attendances that did not require admission.[170] Furthermore, as our

analyses were performed in a cohort of incident gout patients in England, the findings are not necessarily generalisable to other healthcare services or to people with longstanding gout.

In conclusion, the prescription of ULT in people with gout associates with an increased risk of hospitalisations for flares within the first 6 months of initiation, but reduces hospitalisations from 12 months onwards particularly when serum urate targets are achieved. Despite this, only a third of patients achieved serum urate targets within a year of discharge from hospital, and 40% remained on no ULT. If avoidable admissions are to be prevented in the long term, treat-to-target ULT must be implemented.

6 Systematic literature review of hospitalised gout management (*Rheumatology, 2021*)

6.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 4: What is the evidence base for interventions in patients hospitalised for gout flares?

Numerous studies in community settings have evaluated strategies to optimise care for people with gout.[74] For example, nurse-led, treat-to-target ULT combined with individualised education has been shown to reduce flares and improve quality of life for patients.[31,79] In contrast, there have been no systematic appraisals of interventions in patients hospitalised for gout flares. These data are essential to inform strategies that improve care for hospitalised patients and prevent avoidable admissions.

In this chapter, I performed a systematic review to evaluate the evidence base for interventions in patients hospitalised for gout flares. I incorporated evidence for both pharmacological and non-pharmacological treatments, and included a range of clinical outcomes.

Improving outcomes for patients hospitalised with gout: a systematic review

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6.2 Abstract

Objectives

Hospital admissions for gout flares have increased dramatically in recent years, despite widely available, effective medications for the treatment and prevention of flares. We conducted a systematic review to evaluate the effectiveness and implementation of interventions in patients hospitalised for gout flares.

Methods

A search was conducted in MEDLINE, Embase and the Cochrane library, from database inception to 8th April 2021, using the terms gout and hospital and their synonyms. Studies were included if they evaluated the effectiveness and/or implementation of interventions during hospital admissions or ED attendances for gout flares. Risk of bias assessments were performed for included studies.

Results

Nineteen articles were included. Most studies were small, retrospective analyses performed in single centres, with concerns for bias. Eleven studies (including five RCTs) reported improved patient outcomes following pharmacological interventions with known efficacy in gout, including allopurinol, prednisolone, NSAIDs and anakinra. Eight studies reported improved outcomes associated with non-pharmacological interventions: inpatient rheumatology consultation and a hospital gout management protocol. No studies to date have prospectively evaluated strategies designed to prevent re-admissions in patients hospitalised for gout flares.

Conclusion

There is an urgent need for high quality, prospective studies of strategies to improve uptake of urate-lowering therapies in hospitalised patients, incorporating prophylaxis against flares and treat-to-target optimisation of serum urate levels. Such studies are essential if the epidemic of hospital admissions from this treatable condition is to be countered.

6.3 Introduction

Gout is characterised by recurrent flares of joint pain and swelling, which can necessitate hospital admission when severe. Highly effective, low-cost medications are available for the treatment of gout flares: colchicine, NSAIDs and corticosteroids.[6-8] Flares can be prevented by ULT, of which allopurinol is most widely used.[6-8] BSR and EULAR guidelines recommend offering ULT to all patients with gout, with up-titration to achieve serum urate levels of 300-360 micromol/L (5-6 mg/dL), to facilitate crystal dissolution.[6,7] The ACR gout management guideline was recently updated to conditionally recommend initiation of ULT during flares, rather than delayed initiation of ULT after flare resolution.[8]

Despite effective treatments, hospitalisations for gout flares have increased dramatically, doubling in the United States between 1993 and 2011, from 4.4 to 8.8 admissions per 100,000 adults, respectively;[63] doubling in Canada between 2000 and 2011, from 3.8 to 7.6 admissions per 100,000 adults;[64] and increasing by 58.4% in England between 2006 and 2017, from 7.9 to 12.5 admissions per 100,000 adults.[3] This contrasts with the decline in hospitalisations from RA.[3,63,64] There are multiple contributing factors to the epidemic of gout hospitalisations: the prevalence of gout has increased in Western countries in recent years on a background of an ageing population with rising prevalences of obesity and the metabolic syndrome;[1,4] the management of gout is frequently sub-optimal in primary care, rheumatology clinics and inpatient settings, and only a minority of patients achieve the serum urate levels required to prevent flares.[1,5]

Hospital admissions provide a unique opportunity to engage patients in shared decision-making and begin the process of establishing optimal ULT. What is not known is how best to implement evidence-based treatments during hospitalisations for gout. Such strategies are essential if the rising number of gout admissions is to be countered. The objective of this systematic review was to evaluate the evidence of effectiveness of interventions in patients hospitalised with gout.

6.4 Methods

Database search strategy and eligibility criteria

A systematic literature search was conducted using the MEDLINE, Embase and Cochrane library databases. Studies were eligible if they evaluated the effectiveness and/or implementation of interventions in patients aged ≥18 years during hospital admissions or ED attendances for gout flares. Studies involving patients with secondary admission diagnoses of gout were also eligible for inclusion. Search terms utilised included (gout OR crystal arthritis) AND (hospital* OR hospitalised OR hospitalized OR inpatient OR admit* OR admitted OR admission OR emergency OR unplanned). Interventions could be pharmacological or non-pharmacological, for example implementation of a management protocol.

Outcomes were selected following consensus discussion around measures felt to be important in the management and follow-up of hospitalised gout patients. Primary outcome measures were the frequency of admission to hospital and/or ED attendances for gout flares, the frequency of gout flares following the intervention, and length of stay in hospital. Additional outcomes of interest were time to resolution of the initial gout flare, time to initiation of treatment, time to first flare re-occurrence, change in pain scores, change in inflammatory markers (CRP, ESR), adverse event rates, the proportions of patients undergoing joint aspiration and/or steroid injection during admission, with a serum urate level measured during admission, prescribed ULT on or after discharge, with discharge plans and/or outpatient follow-up for gout, and attaining target serum urate levels.

An initial search of databases was performed on 10th February 2021, followed by a re-run of the search on 8th April 2021 to ensure additional relevant studies were included. Eligible study types were RCTs, non-randomised controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, and case series reporting at least five patients. Case reports were excluded.

The study was performed in accordance with the preferred reporting system for systematic reviews (PRISMA),[104] and was registered with the international prospective register of systematic reviews (PROSPERO registration ID: CRD42021245672).

Data extraction

Two reviewers (MR and BC) screened manuscript titles and abstracts. Full texts of relevant studies were reviewed against the eligibility criteria. Data extraction was performed by two reviewers (MR and BC). Study characteristics extracted included study type, participant numbers, demographics, disease characteristics, interventions and outcome measures, as detailed above. Discrepancies arising between reviewers during study selection or data extraction were resolved through consensus discussion, with involvement of a third reviewer (JG) where necessary.

Risk of bias determination

A bias assessment was conducted by two reviewers (MR and BC). The Cochrane Risk of Bias 2 (RoB 2) tool was used for RCTs;[105] the Newcastle-Ottawa Scale (NOS) was used for non-randomised studies.[106] Discrepancies were resolved through consensus discussion, with involvement of a third reviewer (JG) where necessary.

Data synthesis

A narrative synthesis was performed due to the small number of eligible studies with differing interventions and outcome measures; meta-analysis was not possible for these reasons.

6.5 Results

Study characteristics

The systematic literature search identified 4,197 studies, of which 19 were included (Figure 33 and Table 12). Of the included studies, five were RCTs, one was a prospective cohort study and 13 were retrospective analyses. Eleven studies assessed outcomes after pharmacological interventions: ULT (six studies), prednisolone versus indomethacin (two studies), indomethacin versus ketorolac (one study), anakinra (one study), and adrenocorticotropic hormone (ACTH) (one study). Eight studies assessed outcomes after non-pharmacological interventions: inpatient rheumatology consultation (seven studies), and an inpatient gout management protocol (one study). Of the five included RCTs, one was deemed to be at high risk of bias,[171] three had some concerns for bias,[41,172,173] and one was at low risk of bias (Figure 34).[43] All non-randomised studies had potential sources of bias (Figure 35).

Figure 33. PRISMA flowchart of studies identified from the systematic literature search

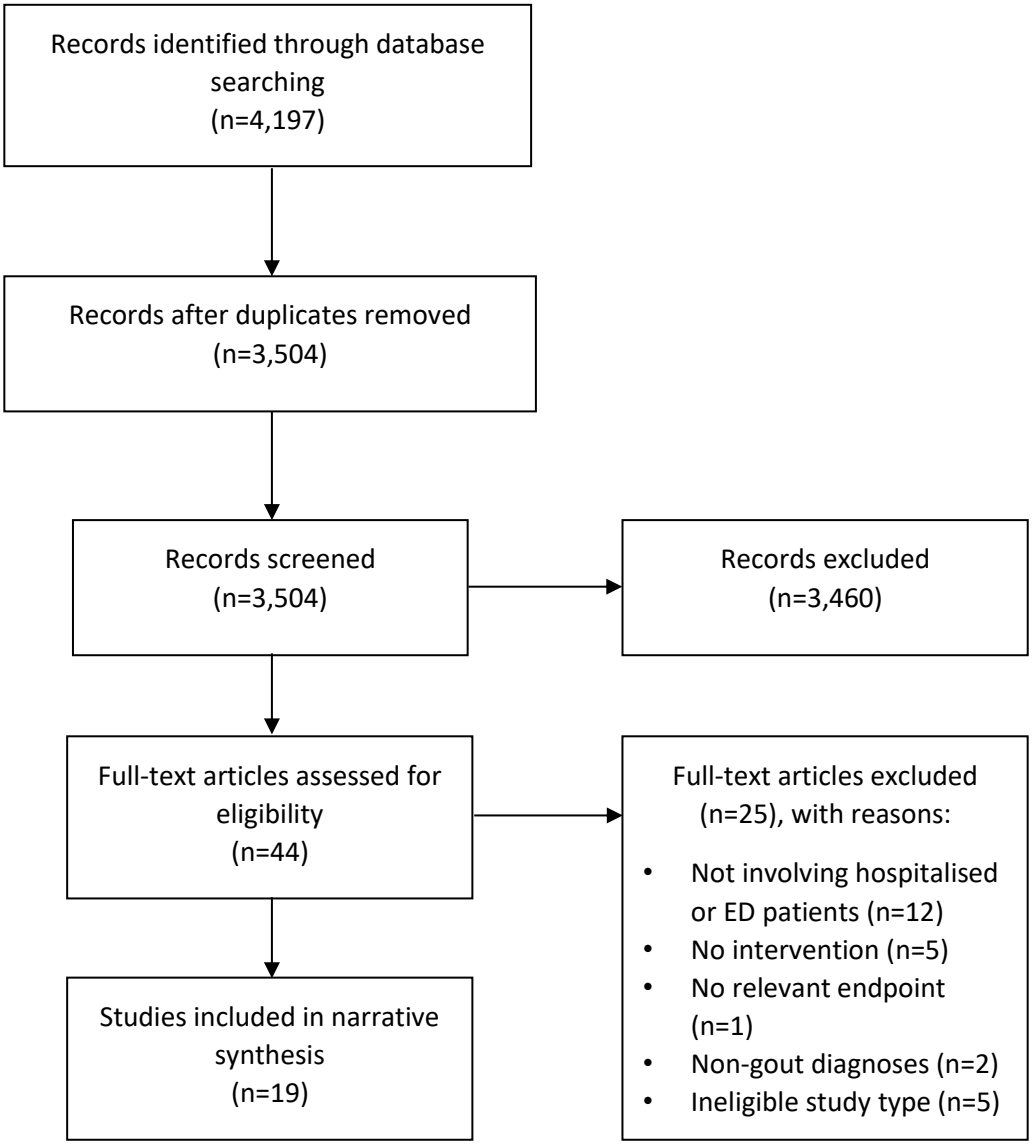


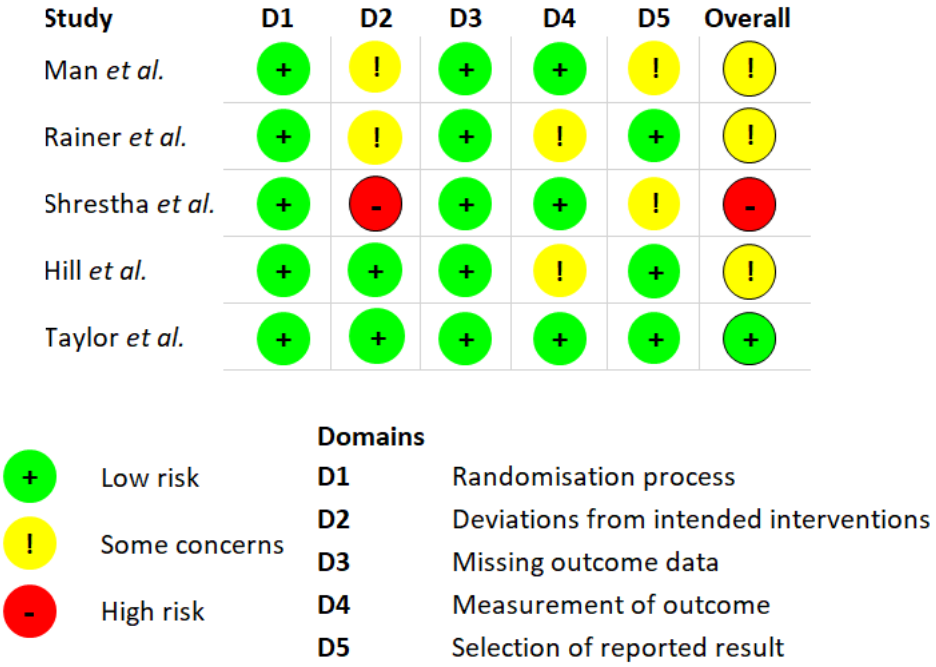
Table 12. Summary of studies included within the systematic review

Study author/year /country	Study design	Participants	Intervention	Comparator	Outcomes measures	Findings
Rainer, 2016, Hong Kong[172]	RCT	416 patients presenting to EDs (four centres) with gout flares	Prednisolone 30mg OD orally for 5 days	Indomethacin 50mg TDS orally for 2 days then 25mg TDS for 3 days	Improvement in pain (VAS); adverse events; time to resolution of symptoms; length of ED stay; return visits to ED	Equivalent reductions in pain at rest and on activity for prednisolone and indomethacin; no major adverse events; more minor adverse events with indomethacin than prednisolone ($p<0.001$); no differences in length of ED stay or return visits to ED within 14 days
Man, 2007, Hong Kong[173]	RCT	90 patients presenting to ED (single centre) with suspected gout flares	Prednisolone 30mg OD orally for 5 days	Indomethacin 50mg TDS orally for 2 days then 25mg TDS for 3 days	Improvement in pain (VAS); adverse events	Rate of decrease in pain on activity greater for prednisolone than indomethacin ($p=0.0026$); more adverse events with indomethacin than prednisolone ($p<0.05$)
Shrestha, 1995, United States[171]	RCT	20 patients presenting to EDs (two centres) with gout flares	Indomethacin 50mg OD orally single dose	Ketorolac 60mg IM single dose	Improvement in pain (Wong-Baker Faces Rating Scale); adverse events	Equivalent reductions in pain between the study arms at 2 hours; more rebound increases in pain with ketorolac at 6 hours ($p<0.05$); no adverse events
Ghosh, 2013, United States[174]	Retrospective	26 patients hospitalised for gout flares; flares resistant to standard treatments and/or contraindications to these treatments	Anakinra, multiple dosing regimens	None	Pain response (VAS <3/10 and able to weight bear); time to resolution of flare; adverse events	Pain response observed in 67% of patients within 24 hours and 85% by 48 hours; complete resolution of presenting symptoms in 73% by day 5; no attributable adverse events
Daoussiset, 2012, Greece[175]	Retrospective	181 patients hospitalised for gout flares (primary or secondary admission diagnoses)	ACTH 1mg IM single dose, followed by repeat dose if indicated	None	Response to treatment (attenuation of inflammation and no requirement for acute gout medications for 2 days); adverse events	78% of patients responded to the initial ACTH dose; 83% responded to a further dose; few attributable adverse events
Pattanaik, 2019, United States[162]	Retrospective	250 patients (US veterans) attending ED with gout flares	ULT	No ULT	Frequency of ED visits	Use of ULT associated with fewer ED visits than no use of ULT ($p=0.02$)

Hutton, 2009, New Zealand[163]	Case-control	48 patients hospitalised for gout at least twice in the preceding year (cases); 48 matched patients with gout but without hospital admissions (controls)	Allopurinol; Colchicine prophylaxis	No allopurinol; no colchicine prophylaxis	Hospital admissions	Patients who had been hospitalised were less likely to be on allopurinol than non-hospitalised patients (OR 0.06; p<0.0001) and less likely to have been prescribed colchicine prophylaxis (OR 0.39; p=0.039)
Huang, 2020, United States[176]	Retrospective	59 patients with active prescriptions for allopurinol who had been admitted for gout flares	Continuation of ULT/dose increase	Discontinuation of ULT/dose reduction	Frequency of gout flares in the 3 months post-discharge	Dose reduction/discontinuation of allopurinol associated with more repeat gout flares within 3 months of discharge (p=0.03)
Hill, 2015, United States[41]	RCT	31 patients with gout meeting ACR criteria for ULT commencement, recruited from EDs and rheumatology clinics within 72 hours of initial therapy for gout flares	Allopurinol 100mg OD orally (days 0-14) then 200mg daily (days 15-28)	Placebo	Time to resolution of acute flare	No significant difference between allopurinol arm (15.4 days) or placebo arm (13.4 days) (p=0.50)
Taylor, 2012, United States[43]	RCT	57 patients with crystal-proven gout flares, recruited from EDs, wards and outpatient clinics within 7 days of flare onset.	Allopurinol 300mg OD orally from day 0 onwards	Placebo (days 0-10) then allopurinol 300mg OD orally (days 11-30)	Improvement in pain (VAS) by day 10; new or recurrent flares by day 30	Rapid decrease in pain in both study arms, with no significant differences; flares reported in 7.7% of early initiation group and 12.0% of delayed initiation group (p=0.61); rapid decreases in serum urate levels by day 10 in the early initiation group
Feng, 2015, China[177]	Retrospective	123 patients with gout initiating ULT during acute flares in ward and outpatient settings versus 457 patients initiating ULT after flares	ULT initiation during acute flares	Delayed ULT initiation after flare resolution	Proportion attaining target serum urate levels; time to attainment of serum urate target; flare rates	No difference in serum urate attainment rates (66.7% vs. 65.6%); quicker attainment of target serum urate with immediate ULT (2.5 months vs. 3.8 months; p=0.004); numerically more flares with immediate ULT vs. delayed ULT in first 12 weeks but not subsequently
Kamalaraj, 2012, Australia[178]	Retrospective	Patients with gout flares in hospital before (n=118) and after (n=89) the introduction of management protocol	Introduction of a gout management protocol	No gout management protocol	Length of stay; treatment delays; proportion continuing ULT on admission	After introduction of protocol, more patients continued baseline allopurinol (p=0.01), treatment delays reduced (p<0.001), length of stay non-significantly shorter (10 vs. 11.5 days; p=0.3).
Kapadia, 2019, UK[73]	Retrospective	55 patients with crystal-proven gout flares admitted to a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Proportion with discharge plan to initiate ULT	More patients receiving rheumatology consultation had a discharge plan to initiate ULT (OR 22.25; p=0.007)

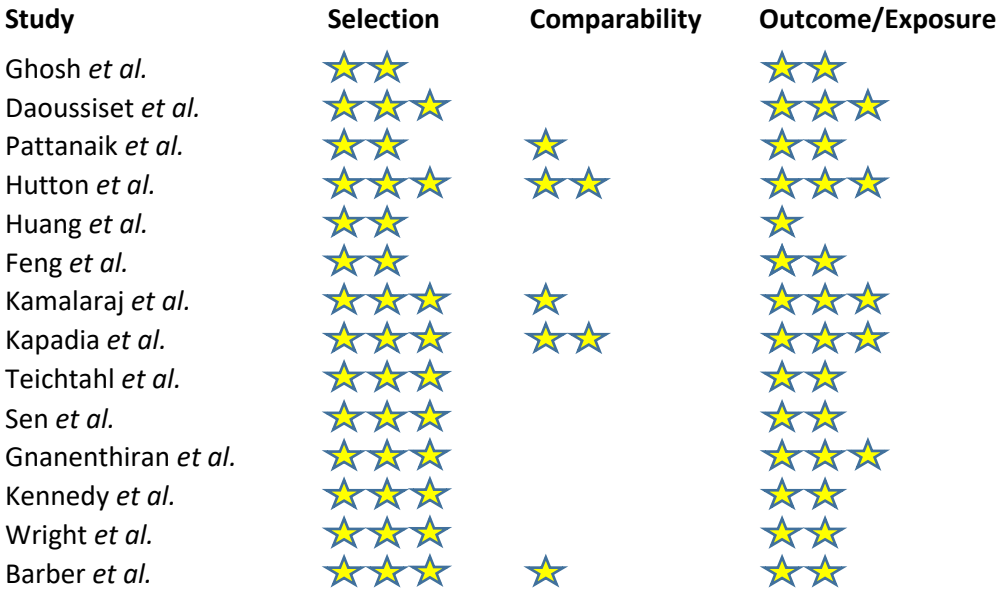
Teichtahl, 2014, Australia[179]	Prospective cohort	58 patients hospitalised with gout flares (primary or secondary admission diagnoses) in a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Proportion on ULT at discharge; proportion receiving gout discharge plans or outpatient follow-up	Rheumatology consultation associated with non-significantly more ULT on discharge (42% vs. 27%; p=0.27); more gout discharge planning (92% vs. 24%; p<0.001); more rheumatology outpatient follow-up (42% vs. 0%; p<0.001)
Sen, 2019, United States[180]	Retrospective	200 hospitalised patients with diagnoses of gout in a single centre, 27% of whom flared during admission	Inpatient rheumatology consultation	No rheumatology consultation	Length of stay; proportion discharged on ULT or colchicine; proportion with outpatient follow-up	No difference in length of stay (4.7 days vs, 5.8 days); more patients with rheumatology input were discharged on ULT or colchicine (100% vs. 79%; p<0.04); more patients received outpatient follow-up (62% vs. 12%; p<0.002)
Gnanenthiran, 2011, Australia[181]	Retrospective	134 patients admitted for gout flares (primary or secondary admission diagnoses) in a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Length of stay; treatment delays; proportion with outpatient follow-up	Length of stay not significantly different (19 vs. 17 days; p=0.6); treatment delay not significantly different (2.0 vs. 1.7 days; p=0.05); more rheumatology follow-up for those with inpatient rheumatology consult (53% vs. 0%; p<0.001)
Kennedy, 2015, New Zealand[182]	Retrospective	90 admissions for gout flares (primary or secondary admission diagnoses) in a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Length of stay; proportion initiating ULT +/- treat-to-target therapy	Length of stay not significantly different (7.1 vs. 7.6 days; p=0.81); more patients with rheumatology input commenced allopurinol (53% vs. 23%; p=0.04); no difference in treat-to-target therapy (17% vs. 7%; p=0.15)
Wright, 2017, New Zealand[183]	Retrospective	235 admissions for gout flares (primary or secondary admission diagnoses) in a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Length of stay; proportion undergoing joint aspiration, serum urate measurement or ULT dose adjustment	Length of stay not significantly different (5.3 vs. 6.7 days; p=0.44); more joint aspirations, serum urate measurement and ULT adjustment with rheumatology input (all p<0.001)
Barber, 2009, Canada[184]	Retrospective	138 patients hospitalised with gout flares (primary or secondary admission diagnoses) in a single centre	Inpatient rheumatology consultation	No rheumatology consultation	Proportion initiating ULT +/- treat-to-target therapy; proportion receiving prophylaxis while initiating ULT	Non-significantly more patients consulted by rheumatology commenced ULT during/after admission (81% vs. 65%; p=0.08); non-significantly more patients received a treat-to-target approach (53% vs. 30%; p=0.06); more patients received prophylaxis while initiating ULT (61% vs. 29%; p=0.03)

Figure 34. Risk of bias assessment for included randomised-controlled trials



Graphical display of study bias assessed using the Cochrane RoB 2 tool for randomised-controlled trials included within the systematic review. Further information on RoB 2 scoring is available at: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

Figure 35. Risk of bias assessment for included non-randomised studies



Graphical display of study bias for non-randomised studies included within the systematic review, assessed using the NOS. Studies are assessed on three categories: selection (maximum score: 4 stars), comparability (maximum score: 2 stars), and outcome/exposure for cohort/case-control studies (maximum score: 3 stars). Further information on NOS scoring is available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Pharmacological treatments for gout flares in hospitalised patients

Two RCTs compared NSAIDs and corticosteroids in patients presenting to EDs with gout flares.[172,173] In both studies, participants were randomised to receive prednisolone 30 mg daily for 5 days or indomethacin 50 mg three times daily for 2 days followed by indomethacin 25 mg daily for 3 days. All participants received concomitant paracetamol (acetaminophen) 1 gram, up to 4 times daily as required.

In the larger of the two studies, 416 participants from four EDs were recruited and randomised, of whom 376 participants completed the study.[172] In intention-to-treat and per-protocol analyses, reductions in pain scores were similar between the prednisolone and indomethacin arms, both in ED and by day 14. No serious adverse events occurred with either intervention. Minor adverse events were more frequent with indomethacin than prednisolone during the ED stays (19% vs. 6%; p<0.001) but not subsequently. Length of stay in ED was not different between the study arms (5 hours in both cohorts). There were no significant differences in the proportion of participants returning to ED within 14 days.

In the second RCT (n=90), the rate of decrease in pain on activity from day 1 to 14 of follow-up was greater for prednisolone than indomethacin (-2.9 mm/day vs. -1.7 mm/day, respectively; mean difference: 1.2 mm/day; 95% CI: 0.4, 2.0 mm/day; p=0.003);[173] however, the absolute differences in pain scores between the interventions were modest, and both cohorts reached the same VAS score by day 14. The indomethacin arm experienced more adverse events than the prednisolone arm (63% vs. 27%, respectively; p<0.05), particularly gastrointestinal bleeding events requiring hospitalisation (5 vs. 0 events, respectively). Flare rates were not significantly different between the indomethacin and prednisolone arms (8 vs. 5 flares, respectively).

An additional RCT compared the analgesic efficacy of two NSAIDs – oral indomethacin 50 mg, single dose, and intramuscular ketorolac 60 mg, single dose - in patients (n=20) presenting to two EDs with gout flares.[171] Analgesic efficacy was not significantly different between the treatments at two hours after administration (64% vs. 68% reduction in pain scores, respectively). With indomethacin, pain scores remained low at 24 hours after treatment. With ketorolac, mean pain scores rebounded after 6 hours (from 1.4 to 2.8 on a 0 to 5 Wong-Baker scale; p<0.05), followed by improvements thereafter, such that scores were not significantly different between indomethacin and ketorolac by 24 hours after treatment. No adverse effects were reported with either treatment.

A single-centre retrospective study reported outcomes for 26 hospitalised patients receiving anakinra for treatment-resistant flares, defined as an inadequate response to colchicine, NSAIDs or steroids and/or contraindications to these medications.[174] Several anakinra dosing regimens were used, depending on patients' weight, renal function, extent of joint involvement and response to initial treatment. Multiple courses of anakinra were administered in seven patients, five of whom received the additional courses during different hospital admissions. There was no comparator group. Improvements in pain scores to below 3 on a 10-point scale were observed in 67% of anakinra courses within 24 hours of treatment and in 85% by 48 hours. Symptom resolution occurred in 73% of patients by day 5; by day 10,

all but one patient had fully responded. Anakinra was well tolerated, with no attributable adverse events.

Another single-centre retrospective study reported on the use of intramuscular ACTH 1mg in 181 hospitalised gout patients.[175] There was no comparator group. 78% of participants responded to ACTH, defined as attenuation of signs of inflammation and no requirement for steroids, NSAIDs, colchicine or analgesics for two days. Most non-responders were re-treated with a further injection of ACTH, of whom 83% responded. 11% of participants suffered a repeat flare after a median of 4 days. Few attributable adverse events were reported, with local injection site reactions observed in 2% of participants.

ULT for the prevention of gout flares in hospitalised patients

The benefits of ULT on hospitalisations and ED attendances have been evaluated in retrospective analyses. In a single-centre study of US veterans (n=250) attending ED for gout flares, use of ULT associated with fewer ED visits for gout flares (determined retrospectively), relative to no use of ULT (p=0.02; effect size not provided).[162]

In a case-control study, patients (n=48) hospitalised for gout at least twice in the preceding year were less likely to have received allopurinol than age, sex and ethnicity-matched controls with gout but without hospital admissions (OR 0.06; 95% CI: 0.02, 0.20; p<0.0001).[163] Median allopurinol dosages were lower in patients with recurrent admissions than the comparator group (200mg vs. 300mg, respectively; p=0.0019), and hospitalised patients were less likely to have been prescribed colchicine prophylaxis (OR 0.39; 95% CI: 0.17, 0.89; p=0.039). Relative to those without recurrent admissions, patients with recurrent admissions had more comorbidities (6.5 vs. 5.1; p=0.011), more comorbid heart disease (71% vs. 46%; p=0.013), higher rates of erosive gout (89% vs. 46%; p=0.0007) and more tophaceous disease (65% vs. 42%; p=0.038). Patients with recurrent hospital admissions for gout were also more likely to have been admitted for other conditions in the preceding year (5.8 vs. 0.6 admissions; p<0.0001).

In a retrospective study of patients hospitalised for gout flares while receiving allopurinol (n=59), dose-reductions or discontinuations of allopurinol during admissions were associated with higher rates of flares in the three months following discharge than admissions where allopurinol doses were unchanged or increased (53% vs. 22%; p=0.03).[176] The primary reason provided for the allopurinol dose-reductions/discontinuations was acute kidney injury, which was present in a higher proportion of this group than the comparator group (60% vs. 36%). Patients in the dose-reduced/discontinued cohort were less likely to have received flare prophylaxis at discharge than the dose-unchanged/increased cohort (60% vs. 27%; p-value not specified), which may have contributed to the observed differences in post-discharge flares.

Whether to initiate ULT during a gout flare has been evaluated in three studies that included participants recruited from EDs and inpatient settings.[41,43,177] In an RCT, 31 participants were recruited from EDs and rheumatology clinics within 72 hours of initial therapy for a gout flare and randomised to receive allopurinol 100mg daily (up-titrated to 200mg daily after 14 days) or placebo.[41] Treatment for the flare was determined by the treating physician, with

corticosteroids utilised in over 80% of participants. Both study arms received prophylactic low-dose colchicine. The primary endpoint of time to resolution of the flares was not significantly different between the allopurinol or placebo arms (15.4 days vs. 13.4 days, respectively; p=0.50). Of note, however, post-hoc power calculations suggested 116 subjects per arm were required to have demonstrated a significant difference in this endpoint. Pain and physician global assessment scores declined rapidly in both study arms. As might be expected, serum urate levels were significantly lower with allopurinol than placebo (6.4 mg/dL vs. 8.3 mg/dL; p=0.012).

In another single-centre RCT, 57 participants recruited from EDs, wards and outpatient clinics within 7 days of onset of gout flares were randomised to receive allopurinol 300mg daily or placebo for 10 days.[43] After day 10, all participants received open-label allopurinol 300mg daily. All participants received indomethacin 50mg three times daily for 10 days and colchicine 0.6mg twice daily for 90 days. The co-primary endpoint of participant-reported joint pain normalised rapidly in both study arms, with no significant differences between arms from days 1 to 10. Self-reported new or recurrent gout flares did not differ significantly between study arms by day 30 (7.7%, early initiation group vs. 12.0%, delayed initiation group; p=0.61), despite rapid decreases in serum urate levels in the early initiation group. Similarly, in a retrospective study involving patients recruited from hospital or outpatient settings, more rapid attainment of target serum urate levels was observed with immediate versus delayed initiation of ULT (2.5 vs. 3.8 months, respectively; p=0.004).[177] Repeat flares occurred more frequently in the immediate commencement cohort than the delayed commencement cohort in the 12 weeks after the initial flare but were comparable beyond this point.

Non-pharmacological interventions for hospitalised gout patients

Gaps in healthcare providers' knowledge of gout are an important barrier to optimal care.[61] To address this, one study retrospectively analysed outcomes before and after the introduction of an evidence-based protocol for non-rheumatologists treating hospitalised patients with gout flares;[178] this included recommendations to continue baseline ULT, initiate anti-inflammatory medications, perform joint aspiration, and involve rheumatologists in cases of diagnostic uncertainty. Following introduction of the protocol, more patients continued their baseline allopurinol (56% vs. 20%; p=0.01), treatment delays reduced (5% vs. 33%; p<0.001) and rheumatology consults increased (52% vs 34%; p=0.01). Admission durations were numerically shorter following introduction of the protocol, albeit non-significantly (10 days vs. 11.5 days; p=0.3).

Six retrospective studies and one prospective cohort study have reported outcomes for gout admissions involving inpatient rheumatology consultation, relative to those without rheumatology consultation.[73,179-184] The proportion of admissions with rheumatology input varied widely between studies, from 17% to 76%, averaging 40% across all studies. Rheumatology input consistently associated with more intra-articular joint aspirations and/or steroid injections.[179-184] Those receiving rheumatology input were more likely to have had serum urate levels measured,[181,183,184] and more likely to have received outpatient rheumatology follow-up,[179-181] relative to patients without rheumatology input. Four studies reported significant associations between rheumatology consultation and increased

utilisation of ULT.[73,180,182,183] No studies reported significant associations between rheumatology consultation and length of stay in hospital.[180-183]

6.6 Discussion

In this systematic review, we identified 19 studies reporting associations between interventions and improved outcomes for patients hospitalised with gout. Most were small, retrospective analyses performed in single centres, with concerns for bias. The majority reported on pharmacological interventions known to be effective in the treatment and prevention of gout flares. However, no prospective studies to date have evaluated packages of care designed specifically to prevent further admissions in patients hospitalised for gout flares. There is an urgent need for such studies if the inexorable rise in hospitalisations from this treatable condition is to be stopped.

Hospitalisations provide an opportunity for clinicians to educate patients about gout, engage them in shared decision-making, facilitate self-management and introduce optimal ULT. Sustained reductions in serum urate levels with optimal use of ULT halts crystal formation and causes dissolution of existing crystals, thereby preventing flares, shrinking tophi and protecting against long-term joint damage.[6,31] We identified two retrospective analyses that reported associations between the use of ULT and the prevention of hospitalisations and ED attendances.[162,163] Despite this, most patients do not receive ULT prior to, during or after their admissions.[73,183] Initiation of ULT is frequently deferred until after discharge, due to concerns that initiation of ULT will prolong or worsen the existing flare.[43] Post-discharge recommendations to commence ULT are frequently not acted upon,[73] leaving patients at risk of re-admission. The recently updated ACR gout management guideline challenged this practice by conditionally recommending initiation of ULT during flares, supported by their patient panel who advised that the flare may provide additional motivation for patients to commence ULT, although also highlighting the potential for information overload, which could conflate flare management and long-term ULT.[8] ACR's recommendation is backed by the findings of four studies,[41-43,177] three of which recruited hospitalised patients or patients attending ED. These studies demonstrated ways of mitigating the risk of flare aggravation while commencing ULT, including gradual up-titration of ULT from a low starting dose and concomitant use of anti-inflammatory medications. Widespread implementation of ACR's recommendation in patients hospitalised for gout could greatly improve uptake of ULT in this high-risk population and prevent recurrent admissions. Admission affords the time to provide information to patients about both flare management and ULT, addressing the concern of the ACR guideline patient panel.

Only a minority of patients who commence ULT achieve the target serum urate levels necessary to prevent flares and hospitalisations.[1,5] Very few studies identified in our search reported on the attainment of target serum urate levels, and no studies directly evaluated approaches to achieving target serum urate levels after discharge. Seven studies reported improved outcomes with involvement of rheumatologists during hospitalisations, emphasising the importance of specialist input in facilitating appropriate diagnosis and management. However, rheumatology consultation does not necessarily equate to the attainment of target serum urate levels; a recent UK national audit of gout management in

outpatient rheumatology clinics reported that target serum urate levels were achieved in less than half of patients.[5] Furthermore, of the relevant studies in our review, rheumatology input occurred in only 40% of admissions for gout flares, suggesting strategies are needed to increase consultation rates.

Several studies in community settings have evaluated interventions aimed at increasing attainment of target serum urate levels,[31,75,79,82,185] many of which could be applied to hospitalised patients. In an RCT of 517 patients with gout in primary care, research nurses were trained to deliver an individualised package of care, incorporating patient education, shared decision-making and follow-up visits to guide ULT dose escalation.[31] At one year, 95% of patients who received the intervention achieved target serum urate levels, compared to 30% receiving usual GP care. Gout flares were less frequent following the intervention and patients' quality of life improved significantly. In a site-randomised study of 1,463 patients receiving new prescriptions for allopurinol, pharmacist-led treat-to-target optimisation of allopurinol was compared to usual care.[78] The intervention was delivered through an interactive voice-response system, incorporating reminders and encouragement for patients. At one year, patients receiving the pharmacist-led intervention were more likely to have been adherent to allopurinol (50% vs. 37%; OR 1.68; p<0.001) and more likely to have achieved serum urate targets (30% vs. 15%; OR 2.37; p<0.001) than those receiving usual care. In another study, an electronic visit tool was used to facilitate patient-clinician interaction, treat-to-target ULT, and education for outpatients.[82] Significantly more patients achieved target serum urate levels following this intervention, relative to a historical cohort (64% vs. 34%, respectively; p<0.01). Aspects of all of these interventions could be incorporated into a care package, delivered by non-medical practitioners such as nurses or pharmacists, with the aim of establishing patients on dose-optimised ULT following discharge from hospital.

Many interventions that associated with improved outcomes for hospitalised patients are already included within international gout management guidelines.[6-8] Poor healthcare provider understanding of the long-term health consequences of gout and the importance of treatment are important barriers to optimal care.[61] Strategies to improve implementation of evidence-based interventions in hospitalised patients are needed if outcomes are to be improved and re-admissions prevented. In their study of an inpatient gout management protocol based upon EULAR guidelines, Kamaralaj *et al.* utilised three implementation approaches: educational sessions for clinicians, EHR prompts and advertising in clinical settings.[178] Multi-pronged implementation approaches are essential if interventions known to be effective in the management of gout are to be assimilated into clinical practice.[186] Case reviews and process mapping will help to identify barriers and facilitators of optimal admitted gout care and the necessary behavioural changes.[187] Only then can interventions be selected to address these barriers, alongside implementation approaches tailored to the inpatient setting.[188]

Our systematic review has several limitations, many of which reflect the paucity of available data. Most included studies had small participant numbers, with concerns for bias. The majority of studies reported positive findings, suggesting a degree of publication bias. Many were single centre analyses, which limits the generalisability of the findings. Outcome

measures varied widely between studies, precluding direct comparisons and meta-analysis. This is also reflected in the range of outcome measures selected for our review, which were chosen on the basis of consensus discussion rather than using specific criteria, such as the OMERACT criteria;[189] although some outcomes align with those within the OMERACT criteria, adoption of these criteria in future studies would facilitate comparisons of study outcomes. Similarly, diagnostic and inclusion criteria varied substantially between studies, while verification of diagnosis was not possible, which may have resulted in a degree of misclassification bias. Many of the included studies reported pooled results for primary and secondary admission diagnoses of gout, despite differences between these populations, and separate reporting of outcomes in future studies may highlight the need for different management strategies in these populations.

This systematic review highlights an urgent need for prospective studies of strategies to prevent hospitalisations from gout. Gout is a highly treatable yet poorly managed condition, and many admissions from gout are likely to be preventable with better use of existing treatments. Effective implementation of strategies designed to improve uptake of ULT in hospitalised patients, alongside prophylaxis against flares and treat-to-target ULT optimisation, is essential if the epidemic of hospital admissions from this treatable condition is to be countered.

7 Identifying barriers and facilitators of optimal hospitalised gout care (*Journal of Rheumatology, 2022*)

7.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 5: What are the barriers and facilitators of optimal gout care in hospitalised patients?

To help me design and implement a strategy that improves outcomes for hospitalised gout patients, first I need to understand the barriers and facilitators of optimal hospital gout care at a local level. This information is vital if interventions, such as those highlighted in Chapter 6, are to be tailored to the individual hospital setting.

To achieve this aim, I utilised several complementary approaches. I performed detailed, retrospective analyses of gout care at the emergency department and inpatient wards of King's College Hospital NHS Foundation Trust. Using this information and the experiences of multiple stakeholders, I process mapped the patient journey, to identify barriers and facilitators of optimal hospital gout care and potential solutions. This will form the basis of a strategy to improve hospital gout care and prevent avoidable admissions (Chapter 8).

Hospitalisations for acute gout: process mapping the inpatient journey and identifying predictors of admission

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7.2 Abstract

Objectives

To identify predictors of admission following emergency attendances for gout flares, and describe barriers to optimal inpatient gout care.

Methods

ED attendances and hospital admissions with primary diagnoses of gout were analysed at two UK-based hospitals between 1st January 2017 and 31st December 2020. Demographic and clinical predictors of ED disposition (admission or discharge) and re-attendance for gout flares were identified using logistic regression and survival models, respectively. Case-note reviews (n=59), stakeholder meetings and process mapping were performed to capture detailed information on gout management and identify strategies to optimise care.

Results

Of 1,220 emergency attendances for gout flares, 23.5% required hospitalisation (median length of stay: 3.6 days). Recurrent attendances for flares occurred in 10.4% of patients during the study period. In multivariate logistic regression models, significant predictors of admission from ED were older age, overnight ED arrival time, higher serum urate, higher CRP and higher total white cell count at presentation.

Detailed case-note reviews showed that only 22.6% of patients with pre-existing gout were receiving ULT at presentation. Initial diagnostic uncertainty was common, yet rheumatology input and synovial aspirates were rarely obtained. By six months post-discharge, 43.6% were receiving ULT; however, few patients had treat-to-target dose optimisation, and only 9.1% achieved a urate ≤360 micromol/L.

Conclusion

We identified multiple predictors of hospitalisation for acute gout. Prescription of ULT and treat-to-target optimisation following hospitalisation remain inadequate, and must be improved if admissions are to be prevented.

7.3 Introduction

Gout is the most common form of inflammatory arthritis, affecting 3.2% of UK adults and 3.9% of US adults, respectively.[1,2] Hospital admissions for gout flares have increased substantially in recent years, doubling in the US between 1993 and 2011, doubling in Canada between 2000 and 2011, and increasing by 58.4% in England between 2006 and 2017.[3,63,64]

There are likely to be multiple factors driving the growth in hospitalisations for gout flares. This includes an increasing incidence of gout in many countries worldwide, ageing populations, and the epidemic of the metabolic syndrome.[1,4] Previous analyses of hospitalised gout patients in the US have reported predictors of admission following ED attendances for gout flares, including increasing age, higher comorbidity burden, socioeconomic and insurance provider status.[190,191]

Hospitalisations for gout flares are unpleasant for patients and costly for healthcare services.[64] Many hospitalisations for gout flares could be prevented with more widespread use of existing treatments at effective doses. ULT (e.g. allopurinol and febuxostat), when titrated to target serum urate levels (300-360 micromol/L; 5-6 mg/dL), is highly effective at preventing flares and improving quality of life.[31] Associations between the use of ULT and fewer ED visits and hospitalisations for gout flares have been reported.[162,163] Despite this, previous studies have shown that only a minority of patients hospitalised for gout receive ULT.[73,183] Moreover, post-discharge recommendations to commence ULT are rarely provided by secondary care and/or acted on by primary care.[73,183]

If hospitalisations are to be prevented, we need to understand what barriers exist to optimal inpatient gout care. Only then can strategies be implemented to address these barriers and improve patient outcomes. The objective of this study was to perform detailed analyses of gout care in EDs and inpatient wards at two UK-based hospitals over a four-year period. We sought to identify predictors of admission, and utilise process mapping to identify barriers to optimal gout care.

7.4 Methods

Study sample

All ED attendances and hospital admissions at two hospitals in London, UK, with primary admission diagnoses of gout between 1st January 2017 and 31st December 2020 were eligible for inclusion. Gout attendances were identified using primary admission diagnostic billing codes: ICD-10 code: M10; SNOMED code: 90560007. Manual case verification was performed to verify that the final diagnosis made by the treating clinician was a gout flare rather than an alternative diagnosis. The diagnosis of gout flare could be made on clinical grounds alone or via crystal analysis of synovial fluid. Cases were not eligible for inclusion if the primary cause

of a patient's joint symptoms was deemed by the treating clinician to be a diagnosis other than a gout flare. There were no other exclusion criteria.

Variables

Co-primary outcomes for the analyses were: i) ED disposition (admission or discharge) and ii) re-attendance for gout flares (vs. no re-attendance) during the study period.

Covariates were selected *a priori* on the basis of whether they were felt to be important potential predictors of outcome measures, as follows: age; sex; time of arrival at ED (9am to 9pm vs. 9pm to 9am); day of arrival at ED (Saturday/Sunday vs. Monday to Friday); CRP (mg/L); serum urate level (micromol/L); total white cell count ($x10^9$/L); and serum creatinine (micromol/L). For laboratory data, the result of the first test performed during the attendance was captured for analysis, where available.

Statistical analyses

Baseline characteristics were tabulated and described without inferential statistics. Logistic regression was used to assess the strength and significance of associations between predictor variables and ED disposition. For patients with multiple ED presentations during the study period, only the first presentation was included in these models. Unadjusted models and models adjusted for all covariates (age, sex, time of arrival at ED, day of arrival at ED, CRP, serum urate level, total white cell count, and serum creatinine at baseline) were presented with odds ratios and 95% CIs.

Cox proportional hazards models were used to assess associations between predictor variables (age, sex, serum urate, and serum creatinine at presentation) and the risk of re-attendance for gout flares during the study period (single failure models). Unadjusted models and models adjusted for age, sex, serum urate, and serum creatinine at baseline were presented with hazard ratios and 95% CIs. Assumptions were tested graphically using Nelson-Aalen plots.

Differences were considered statistically significant if $p<0.05$. As these were exploratory analyses, correction for multiple hypothesis testing was not performed. Statistical analyses were performed in Stata version 16.1.

Case-note review

To capture detailed information on the processes involved during hospital attendances for gout flares, alongside patient outcomes, we adopted a mixed methodological approach to interrogate the medical records of patients with attendance start dates between 1st October 2020 and 31st December 2020. Information was captured manually from every entry in the clinical records, irrespective of who had entered it. Quantitative and qualitative approaches were used to review the data, including transcription of binary outcomes for pre-specified variables (see below for further information on captured variables) and identification of

common themes arising during patients' ED attendances, inpatient stays and post-discharge follow-up.

Information captured during the detailed case-note review.

- Did the patient have a pre-existing gout diagnosis at the time of attendance?
- Was the patient in receipt of ULT at the time of presentation?
- Was there initial diagnostic uncertainty as to the cause of the presenting joint symptoms?
- Was septic arthritis in the initial differential diagnosis?
- Was rheumatology consultation (telephone advice or in-person) sought in the ED?
- Was joint aspiration performed in ED and/or during admission?
- Was treatment initiated for the gout flare? If so, which medications were used (NSAIDs, colchicine, oral corticosteroids and/or intra-articular corticosteroids)?
- Was the patient receiving diuretic therapy during their attendance and, if so, were the diuretics reviewed in light of the presentation for gout flare?
- Was there documentation of education (verbal or written) provided to patients on the diagnosis and/or treatment of gout?
- Were there delays in receiving care during the attendance and/or delays in discharge from hospital?
- Was the patient provided with a discharge plan that specified treatment recommendations and/or follow-up for gout?
- Was ULT initiated and/or uptitrated during the ED attendance/admission?
- Was ULT initiated and/or uptitrated within six months of discharge from hospital?
- Median time from discharge to ULT initiation or first ULT dose titration (if patient already receiving ULT at the point of discharge)?
- Was prophylaxis co-prescribed during ULT initiation and/or uptitration.
- Was there evidence of treat-to-target ULT titration within six months of discharge from hospital (defined as testing of serum urate levels on more than one occasion with titration of ULT if urate >360 micromol/L)?
- Did the patient attain serum urate targets of i) ≤360 micromol/L (6 mg/dL) or ii) ≤300 micromol/L (5 mg/dL) within six months of discharge from hospital?
- Did the patient re-present to the ED for a gout flare within six months of discharge and, if so, what was the median time to re-attendance?

Process mapping

Process mapping was performed to document the process steps and decision points in a typical patient journey, from attendance at ED with symptoms of a gout flare, through to discharge from hospital and subsequent community follow-up. A process flowchart approach based upon Six Sigma methodology was employed,[109] incorporating the findings of the case-note reviews and semi-structured discussions (n=32) with multiple stakeholders. Stakeholders from multi-disciplinary backgrounds were selected, with and without personal

experience of managing hospitalised gout patients, to ensure a broad range of views were considered:

- Patients with gout.
- Rheumatology consultants, trainees and nurse specialists.
- Primary care physicians.
- Internal and acute medical consultants and trainees.
- ED doctors and nurse practitioners.
- Elderly care clinicians.
- Pharmacists in primary and secondary care.
- Allied health professionals, including physiotherapists.
- Hospital at home clinicians.
- Hospital management executives.
- Clinical commissioning group members.
- Qualitative methodologists.
- Charity representatives.

Sources of delay and/or sub-optimal care were highlighted on the process map. Discussions were then held with stakeholders around potential solutions to address the key barriers to optimal hospitalised gout care that had been identified through case-note reviews and process mapping. Potential solutions were grouped according to whether they primarily addressed the following barriers: diagnostic delay; inadequate flare treatment; inadequate flare prevention; inadequate follow-up arrangements; and prevention of re-admissions.

Study approval

This study was performed as part of a service evaluation project (Preventing Hospital Admissions Attributable to Gout), with the objective of improving care for patients hospitalised for gout flares. Approval to undertake this service evaluation project was obtained from King's College Hospital NHS Foundation Trust. National research ethical approval was not required under current Health Research Authority guidance.

7.5 Results

Characteristics of gout attendances during the study period

Between 1st January 2017 and 31st December 2020, there were 1,220 attendances with primary diagnoses of gout in 1,065 patients; 287 attendances (23.5%) required admission to hospital from ED (median length of stay: 3.6 days; mean length of stay: 6.8 days); 933 attendances (76.5%) were discharged from ED without an inpatient stay. Inpatient stays for primary admission diagnoses of gout accounted for 1,944 hospital bed-days across the study period.

Patient characteristics for gout flare attendances during the study period are summarised in Table 13. The mean age of patients was 59 years; 81.6% were male. 1,018 attendances (83.4%) occurred at King's College Hospital (urban location), and 202 attendances (16.6%) at Princess Royal University Hospital (suburban location). 385 attendances (31.6%) had an ED arrival time of between 9pm and 9am. 320 attendances (26.2%) began on a Saturday or Sunday. The mean serum urate level at presentation was 478 micromol/L, mean CRP was 66.1 mg/L, mean white cell count was 9.0 $x10^9$/L, mean neutrophil count was 6.3 $x10^9$/L, mean lymphocyte count was 1.8 $x10^9$/L, and mean serum creatinine level was 127 micromol/L.

Table 13. Characteristics of emergency and inpatient attendances for gout flares at two London hospitals from January 2017 to December 2020

	Total N=1,220	**ED N=933**	**Inpatient N=287**
Age, years	59 (17)	55 (16)	71 (16)
Sex			
Female	225 (18.4%)	145 (15.5%)	80 (27.9%)
Male	995 (81.6%)	788 (84.5%)	207 (72.1%)
Location			
King's College Hospital	1,018 (83.4%)	829 (88.9%)	189 (65.9%)
Princess Royal University Hospital	202 (16.6%)	104 (11.1%)	98 (34.1%)
ED arrival time			
9am to 9pm	835 (68.4%)	685 (73.4%)	150 (52.3%)
9pm to 9am	385 (31.6%)	248 (26.6%)	137 (47.7%)
ED arrival day			
Mon-Fri	900 (73.8%)	680 (72.9%)	220 (76.7%)
Sat-Sun	320 (26.2%)	253 (27.1%)	67 (23.3%)
Serum urate, micromol/L	478 (137)	464 (119)	508 (166)
CRP, mg/L	66.1 (78.0)	40.5 (52.9)	109.8 (93.1)
White cell count, $x10^9$/L	9.0 (3.0)	8.6 (2.5)	9.9 (3.5)
Neutrophil count, $x10^9$/L	6.3 (2.7)	5.8 (2.3)	7.4 (3.2)
Lymphocyte count, $x10^9$/L	1.8 (0.8)	2.0 (0.8)	1.6 (0.7)
Serum creatinine, micromol/L	127 (104)	116 (86)	148 (129)

Data for ED-only attendances and attendances requiring inpatient admission are shown in separate columns. For this table, patients could contribute multiple attendances; limiting to just the first attendance made no meaningful difference to patterns. For laboratory data, the result of the first test performed during the attendance was captured for analysis. Data are presented as mean (standard deviation) for continuous measures, and n (%, by column) for categorical measures.

Predictors of admission to hospital from ED

In unadjusted and adjusted logistic regression models, there were statistically significant associations between the following predictor variables and the odds of admission to hospital from ED for gout flares (relative to discharge from ED): older age; overnight ED arrival; higher serum urate levels; higher CRP; and higher total white cell counts at presentation (Table 14). Female sex predicted admission from ED in unadjusted models but not in adjusted models. This was due to an interaction between age and sex: the mean age of female patients presenting with gout flares was older than for male patients (66 vs. 57 years, respectively). There was no significant association between the day of arrival at ED (weekend vs. weekday) and the odds of admission for gout flares.

Table 14. Associations between pre-specified predictor variables and the odds of admission to hospital for a gout flare, relative to discharge from ED without admission

Variables	Unadjusted β-coefficient	Unadjusted odds ratio	95% CI	p-value	Adjusted β-coefficient	Adjusted odds ratio	95% CI	p-value
Age (per 10-year increase)	0.58	1.78	(1.61 - 1.96)	<0.001	0.38	1.47	(1.25 - 1.72)	<0.001
Female sex	0.65	1.91	(1.37 - 2.67)	<0.001	0.48	1.62	(0.86 - 3.03)	0.13
ED arrival time (9pm to 9am)	0.91	2.48	(1.85 - 3.33)	<0.001	0.87	2.39	(1.40 - 4.08)	0.001
ED arrival day (Saturday/Sunday)	-0.16	0.85	(0.61 - 1.19)	0.36	0.20	1.22	(0.70 - 2.13)	0.49
Serum urate (per 100 micromol/L increase)	0.23	1.25	(1.08 - 1.45)	0.003	0.23	1.25	(1.05 - 1.50)	0.01
CRP (per 10 mg/L increase)	0.14	1.15	(1.11 - 1.18)	<0.001	0.11	1.12	(1.07 - 1.16)	<0.001
Total white cell count (per $1x10^9$/L increase)	0.16	1.17	(1.11 - 1.24)	<0.001	0.13	1.14	(1.04 - 1.25)	0.007
Serum creatinine (per 10 micromol/L increase)	0.03	1.03	(1.01 - 1.05)	0.003	0.02	1.02	(0.99 - 1.04)	0.16

Outputs from adjusted and unadjusted Cox proportional hazards models are shown. Adjustment was performed for: age, sex, ED arrival time, ED arrival day, serum urate, CRP, total white cell count, and serum creatinine at baseline. Outputs are reported with clinically meaningful units.

Predictors of re-attendance

Of 1,065 patients, 111 (10.4%) had more than one attendance for gout flares at King's College Hospital or PRUH during the study period: 85 patients had two attendances, 14 patients had three attendances, seven patients had four attendances, four patients had five attendances, and one patient had six attendances. In unadjusted survival models, associations were present between the risk of recurrent attendance for gout flares during the study period (relative to no recurrent attendance) and male sex and higher serum urate levels; however, following adjustment for other covariates, these associations were not statistically significant (Table 15). There were no statistically significant associations between the risk of recurrent attendance for gout flares and age or serum creatinine level at presentation.

Table 15. Associations between pre-specified predictor variables and the risk of recurrent attendances for gout flares during the study period, relative to no recurrent attendance

Variables	Unadjusted hazard ratio	95% CI	p-value	Adjusted hazard ratio	95% CI	p-value
Age (per 10-year increase)	1.05	(0.94 - 1.17)	0.37	1.09	(0.93 - 1.28)	0.30
Male sex	1.81	(1.01 - 3.22)	0.04	1.29	(0.62 – 2.67)	0.50
Serum urate (per 100 micromol/L increase)	1.19	(1.00 - 1.42)	0.04	1.19	(0.98 - 1.43)	0.07
Serum creatinine (per 10 micromol/L increase)	1.01	(0.99 - 1.03)	0.53	1.00	(0.96 - 1.03)	0.80

Outputs from adjusted and unadjusted Cox proportional hazards models are shown. Adjustment was performed for: age, sex, serum urate and serum creatinine at baseline. Variables are reported with clinically meaningful units.

Detailed review of inpatient gout management

To provide an in-depth understanding of current practice during hospital attendances for gout flares, detailed case-note reviews were performed for patients with attendances between 1st October 2020 and 31st December 2020. Of 59 attendances, 13 (22.0%) required inpatient stays and 46 (78.0%) were ED-only attendances. Thirty-one patients (52.5%) had pre-existing diagnoses of gout, of whom only seven (22.6%) were on ULT at the time of presentation (all at sub-optimal doses).

There was initial diagnostic uncertainty in 29/59 patients (49.2%), with septic arthritis considered in eight patients (13.6%), five of whom received antibiotic cover while diagnostic tests were performed. Despite diagnostic uncertainty being prevalent, rheumatology consultation was sought in ED in only eight cases (13.6%), while joint aspiration was attempted in only six patients (10.2%).

Fifty-four patients (91.5%) received anti-inflammatory treatment for their flare: NSAIDs (n=30; 50.8%); colchicine (n=27; 45.8%); oral corticosteroids (n=7; 11.9%); or intra-articular steroids (n=1; 1.7%). Fifteen patients (25.4%) were on diuretic therapy, of whom one patient had their diuretics reviewed. Four patients (6.8%) had ULT initiated during their inpatient stay or ED attendance (allopurinol 100mg once daily in all cases). Documented education on the diagnosis and/or treatment of gout was provided to 19 patients (32.2%); however, specific advice on how to self-manage gout flares was provided to only one patient.

Of the 13 patients who required admission, ten (76.9%) experienced delays in discharge from hospital (i.e. beyond that needed for treatment of the gout flare itself), with the following reasons: investigation/treatment of non-gout diagnoses (n=8); delayed referral for rheumatology consultation (n=4); input from physiotherapists, occupational therapists and/or social workers (n=4); and/or delayed decisions on when to stop antibiotic therapy commenced as cover for septic arthritis (n=3).

On discharge from hospital, 38 patients (64.4%) were provided with a discharge plan specifying treatment recommendations and/or follow-up for gout: 33 patients (55.9%) had primary care follow-up recommended; 10 patients (16.9%) had rheumatology follow-up recommended; while 16 patients (27.1%) had recommendations to initiate and/or uptitrate ULT after discharge from hospital, three of whom had a treat-to-target approach advised.

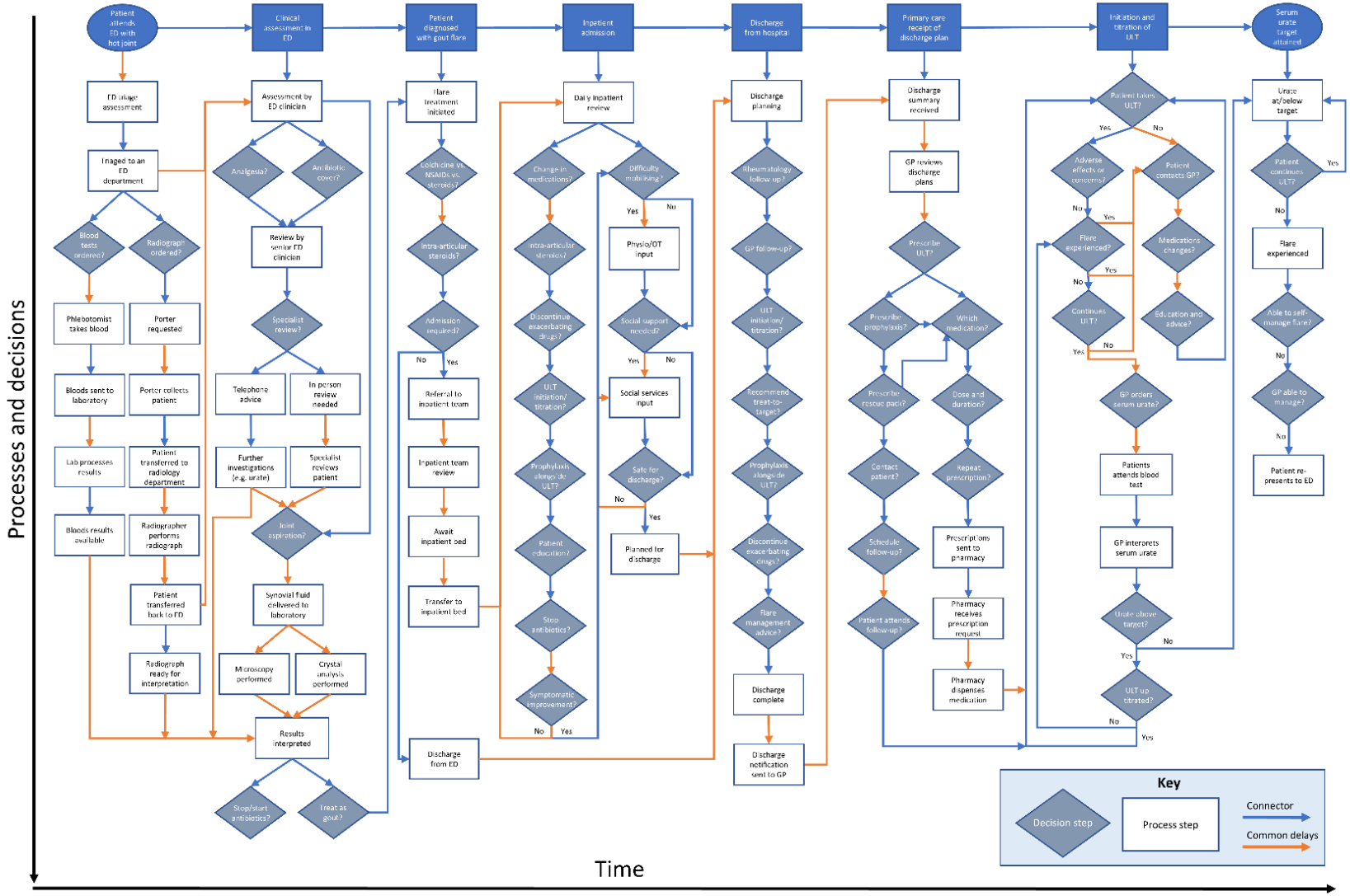
Of 55 patients with six-month post-discharge follow-up data available, 19 patients (34.5%) initiated ULT or had their pre-admission ULT uptitrated within six months of discharge. The median time to initiation or first titration of ULT was 30 days (IQR: 17 to 69 days). In total, 24 patients (43.6%) were receiving ULT by six months post-discharge. Fourteen patients were co-prescribed prophylaxis during ULT initiation/titration. Nine patients (16.4%) had evidence of treat-to-target ULT titration during the six-month post-discharge period; however, only five patients (9.1%) achieved a serum urate level of ≤360 micromol/L, while one patient (1.8%) achieved a serum urate level of ≤300 micromol/L. Four patients (7.3%) re-presented to

hospital for gout flares within six months of discharge, with a median time to re-attendance of 73 days (IQR: 33 to 139 days).

Process mapping

Process mapping was performed to describe a typical patient journey, from attendance at ED with symptoms of a gout flare, to discharge from hospital and subsequent community follow-up. The processes, decision steps and sources of delay are summarised in Figure 36. Process map of a typical patient journey during and after an emergency department attendance for a gout flare. In consultation with stakeholders, strategies were identified to address key barriers to optimal admitted gout care and re-admission prevention (Table 16).

Figure 36. Process map of a typical patient journey during and after an emergency department attendance for a gout flare



Process steps are shown as rectangles; decision steps are shown as diamonds; ovals represent start/stop points. A high-level process map is shown in blue. Arrows depict flow between processes and decisions steps; orange arrows highlight common sources of delay.

Table 16. Barriers to optimal care of patients attending hospital for gout flares and potential solutions to overcome these barriers

Problem	**Potential solutions**
Diagnostic delay	• Early involvement of rheumatology specialists • Prompt aspiration of joint effusions • Provision of training in point-of-care crystal analysis
Inadequate treatment of flares	• Timely initiation of flare treatments at therapeutic doses • Use of combination therapy for severe and/or polyarticular flares • Therapeutic aspiration of joint effusions to dryness • Use of intra-articular corticosteroids where appropriate
Inadequate flare prevention	• Initiation/titration of ULT during the flare • Education for patients and clinicians on the benefits of ULT • ULT titration using a treat-to-target approach
Inadequate follow-up	• Rheumatology follow-up after discharge • Guidance for primary care clinicians on when to review patients • Use of remote monitoring/consultations, e.g. for ULT titration • Involvement of multi-disciplinary professionals, e.g. pharmacists
Re-admission for flare	• Education for patients on how to self-manage flares • Rescue packs of anti-inflammatory medications for patients • Prescription of flare prophylaxis during ULT initiation/titration • Provision of a helpline for patients to contact in the event of flare • Use of admission-avoidance pathways, e.g. hot clinics

7.6 Discussion

In this study, we described the characteristics and management of patients hospitalised for gout flares in one of most detailed analyses to-date. We identified demographic and clinical predictors of hospitalisation from ED, including older age, overnight ED arrival, and higher serum urate levels. Through detailed case-note reviews and process mapping, we highlighted barriers to optimal care and identified strategies to prevent avoidable admissions.

Many of the ED attendances and hospital admissions in our cohort could have been prevented with better use of existing treatments. Over half of the attendances detailed in our case-note review involved patients with pre-existing gout; however, only 23% of these patients were receiving ULT at the time of presentation, and less than half were prescribed ULT by six months post-discharge. In patients receiving ULT, attainment of target serum urate levels was poor, leaving patients at risk of re-admission.

Our findings support previously published reports of sub-optimal gout care in other hospitalised cohorts.[73,183] They are consistent with studies reporting inadequate prescription of ULT in primary care and infrequent attainment of target serum urate levels in rheumatology clinics.[1,5] The reasons behind the inadequate prescription and titration of ULT are manyfold, and include poor understanding of the benefits of ULT, both from a provider and patient perspective [61] In our cohort, education was provided to only a third of patients during their hospital attendance. Strategies to encourage the provision of education and increase prescription/titration of ULT for hospitalised patients are likely to have a beneficial impact on outcomes: in a randomised controlled trial of primary care patients with gout (n=517), nurse-delivered patient education and treat-to-target ULT were highly effective at improving attainment of serum urate targets, reducing flares and improving quality of life.[31] A similar approach, adapted for implementation during hospitalisations for gout flares, may help prevent avoidable admissions. This should include guidance for patients on how to self-manage flares, prescription of rescue packs to enable prompt flare treatment, and access to admission-avoidance pathways for treatment-resistant or severe flares. To reduce the impact of post-discharge recommendations not being acted upon, ULT should be initiated during hospitalisations and ED attendances where possible; this is in line with recently updated ACR guidance, which conditionally recommends initiating ULT during flares, alongside treatment for the flare.[8] Once initiated, patients and primary care clinicians should be provided with clear guidance on ULT titration, to ensure target serum urate levels are achieved, with rheumatology input as required.

In our cohort, discharge delays were common, which contributed to a mean length of stay of over 6 days; this is in keeping with the mean length of stay observed for gout admissions at a national level.[3] In many cases, delays occurred in the context of the management of non-gout diagnoses and/or a need for allied health professional input; reflective of the older age of patients requiring admission. Delays in referral for rheumatology consultation were not uncommon, and, in the majority of cases, rheumatology input was not sought in ED, despite

initial diagnostic uncertainty in half of patients. Strategies to encourage timely referral for rheumatology input, joint aspiration, and use of intra-articular corticosteroids could reduce diagnostic and treatment delays; supported by studies demonstrating associations between inpatient rheumatology consultation and improved outcomes for patients attending hospital for gout flares.[73,179,180,182-184]

Our finding that older age predicts inpatient admission following ED attendances for gout flares is supported by previously published studies.[190,191] In our cohort, the risk of admission was also greater in patients presenting to ED overnight, and in patients with higher serum urate, CRP and total white cell counts at presentation. Many of these predictors are likely to reflect more general predictors of hospital admission (e.g. older age, greater burden of disease, overnight presentation). Validation of these predictors in population-level datasets could facilitate development of admission-risk calculators for patients presenting with gout flares. This, in turn, may have utility in directing resources (e.g. rheumatology consultation and admission-avoidance pathways) towards patients most at risk of admission.

Our study has limitations. Our analyses were restricted to gout attendances at two hospitals and, although consistent with the findings of other studies,[1,73,183] our findings cannot be assumed to be generalisable to other locations. Indeed, the primary purpose of this work was to inform local service transformation and quality improvement. Our quality improvement methodology could, however, be adapted for use at other locations, with the aim of improving inpatient and post-discharge care. The subset of patients for whom we performed detailed case-note reviews attended hospital during the COVID-19 pandemic, and, as such, their care may not be fully reflective of other time points. Re-attendance for gout flare occurred in only 10% of our cohort over the study period; therefore, our analyses of predictors of re-attendance lacked statistical power. A number of factors known to affect gout management (e.g. medication adherence, comorbidities, and diuretic use) were not included within our prediction models. Additionally, our cohort did not include attendances with secondary diagnoses of gout (for example, gout flares occurring during admissions for heart failure) or capture data on re-admissions to hospitals outside of South-East London (i.e. right censorship), and, thus, our analyses will be an underestimate of the true inpatient burden of gout. Further analyses utilising national datasets with linked primary and secondary care data are needed to provide a more complete picture of this avoidable epidemic.

8 Implementing a care pathway to optimise hospital gout care (*Rheumatology, 2023*)

8.1 Relevance to this thesis

This chapter addresses the following aim:

Aim 6: Can a strategy centred on treat-to-target ULT and individualised patient education be implemented effectively during hospitalisations for flares?

Using the information gathered from the preceding chapters of my thesis, my final aim was to develop and implement a strategy to improve hospitalised gout care and prevent avoidable admissions.

My first objective was to develop a care pathway, based upon recommendations contained within the BSR, EULAR and ACR gout management guidelines,[6-8] but tailored to the hospital setting. I wanted a central pillar of this pathway to be nurse-led, treat-to-target ULT and individualised patient education, which was shown to be highly effective in Professor Doherty's primary-care based RCT.[31] In order to maximise the chances of success, I wanted the pathway to address as many barriers highlighted in Chapter 7 as possible. The pathway would need to be tailored to the individual hospital setting, but adaptable for use in other hospitals.

My second objective was to develop an implementation strategy for use alongside the pathway. Multi-faceted implementation strategies are essential if complex interventions are to be assimilated into clinical practice.[186] To devise this implementation strategy, I worked with multiple stakeholders and implementation experts.

My third objective was to implement the pathway at King's College Hospital NHS Foundation Trust. I evaluated a range of outcomes, including rates of ULT initiation, urate target attainment and re-hospitalisation. Semi-structured patient and healthcare professional interviews were used to obtain more granular feedback on patient and provider outcomes. Finally, I addressed whether the pathway could be adapted for use at other hospital sites, in preparation for a wider roll-out.

8.2 Developing a hospital care pathway

8.2.1 Pathway objectives

My first objective was to develop a care pathway that optimised the management of patients who had been hospitalised for gout flares. The primary objectives of the care pathway were to be:

- Based upon best practice care, as detailed in the BSR, EULAR and ACR gout management guidelines;[6-8]
- Modelled on the intervention used in Doherty *et al.*'s primary care-based RCT of nurse-delivered, treat-to-target ULT and individualised patient education,[31] which was highly effective in community settings;
- Implementable in the hospital setting;
- Usable by specialists and non-specialists alike;
- Adaptable for use in different hospitals;
- Sustainable within the existing resource envelope.

8.2.2 Stakeholder input

To develop an initial framework for the care pathway, I held individual and small-group meetings with multiple stakeholders (32 meetings in total), including:

- Patients;
- Rheumatology doctors;
- Rheumatology specialist nurses;
- General practitioners;
- General medicine doctors;
- Acute medicine and ambulatory care doctors;
- Emergency medicine doctors;
- Emergency medicine nurse practitioners;
- Hospital-based pharmacists;
- Primary care-based pharmacists;
- Physiotherapists;
- Clinical commissioning group representatives;
- Hospital executives and medical director;
- Community support teams;
- Charity representatives;
- Health policy experts.

The experiences of individual stakeholders helped to identify key barriers and facilitators of optimal gout care, as detailed in Chapter 7 of my thesis. We discussed potential solutions to

the identified barriers, and reviewed interventions that had previously been used in the setting of hospitalised gout flares (Chapter 6).

Patient input was essential throughout the intervention design process. During initial stakeholder meetings, the focus had been on solitary interventions which might target specific barriers: for example, providing patients with point-of-care urate meters after discharge from hospital. Whilst possibly effective at facilitating titration to target, patients highlighted that single intervention components would not address the multiple barriers to optimal hospital gout care (Figure 36). Instead, strategies incorporating several intervention components, aligned to best practice care, would be needed to address multiple barriers. In turn, these interventions would need to be accompanied by a multi-faceted implementation strategy if they were to be assimilated successfully into clinical practice.

In addition to virtual and in-person stakeholder meetings, I visited the community outreach ('@home') team in South-East London, to investigate methods of reducing admissions in people attending hospital for gout flares. The @home team support the management of complex patients in the community, including patients with multiple comorbidities and severe pain (as is true of many patients with gout). In Chapter 7 of my thesis, I showed that the management of comorbidities was a primary reason for discharge delays in people hospitalised for gout flares. In many patients, these comorbidities could be managed in a non-hospital setting (e.g. via referral to the @home team or in ambulatory care clinics). Admission-avoidance pathways therefore formed key components of my care pathway.

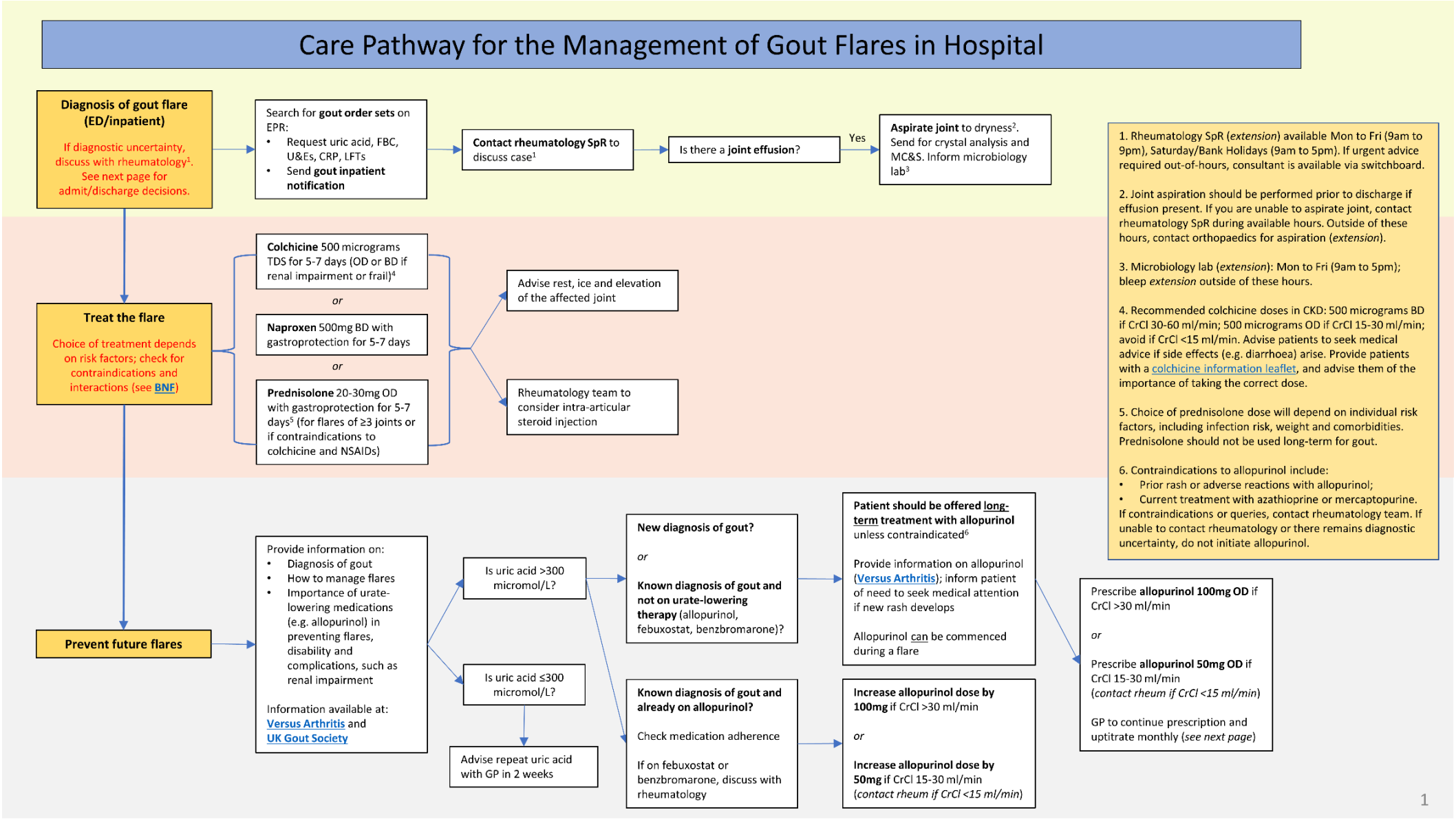
After holding individual meetings, I convened a large stakeholder meeting with representation from many of the stakeholders above. The objectives of this meeting were to:

- Review the findings of my systematic literature review (Chapter 6), case-note reviews and process mapping of hospital gout care (Chapter 7);
- Define the evidence-practice gap (i.e. the gap between what we *should* be doing and what we *are* doing in practice);
- Identify interventions that could address barriers to optimal care and bridge the evidence-practice gap;
- Evaluate the practicality of embedding these interventions at the interface between primary and secondary care;
- Determine whether these interventions could be sustained within the existing resource envelope;
- Discuss implementation strategies.

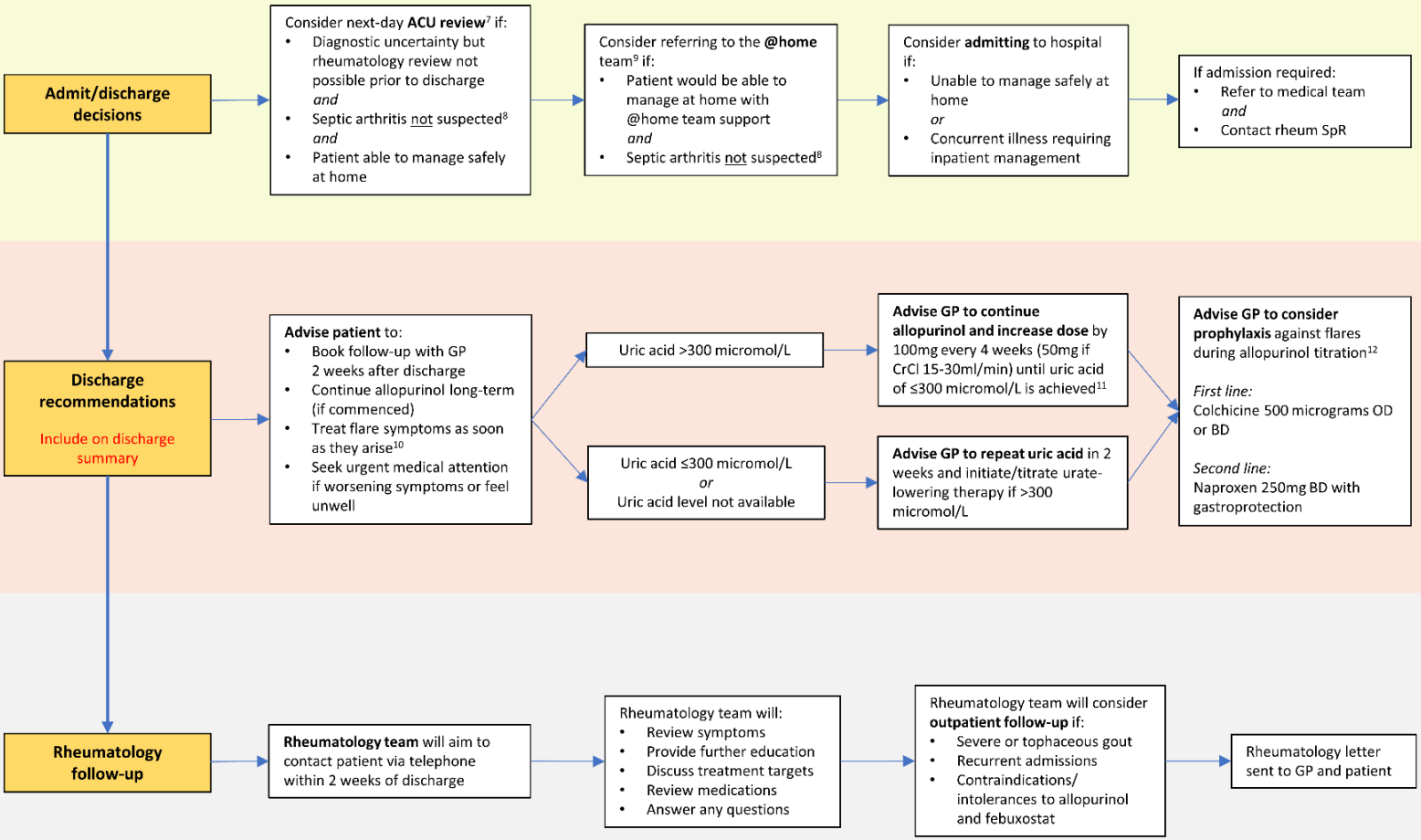
The stakeholder meeting was transcribed, to enable re-review of the content after the meeting. Using the information gathered, I formulated a care pathway, which was then circulated to stakeholders. This pathway was modified to its finalised form (Figure 37) in light of stakeholder feedback, which included: providing guidance on what to do in the event of

diagnostic uncertainty; clear definitions of renal dosing thresholds for colchicine and allopurinol; stressing the importance of taking the colchicine dose as advised, due to toxicity in overdose; guidance on prednisolone dosing; and guidance on how to transition to colchicine/NSAID prophylaxis.

Figure 37. Pathway for the management of patients attending emergency department and/or admitted for gout flares at King's College Hospital



Care Pathway for the Management of Gout Flares in Hospital



7. Discuss ACU referrals with ACU team (*extension*) in-hours or medical SpR (*extension*) out-of-hours.

8. Patients with suspected septic arthritis or joint effusions should be assessed/aspirated prior to discharge: contact rheumatology SpR (*extension*) Mon to Fri (9am to 9pm), Saturday (9am to 5pm); contact orthopaedics (*extension*) outside of these hours.

9. Referrals to @home team via *extension*(8am to 6pm); also complete an @home team referral on EPR.

10. See page 1 for flare treatment options. Consider prescribing a rescue pack for patients or asking GP to prescribe a rescue pack.

11. Allopurinol doses >300mg OD are often required to achieve target urate levels. Maximum recommended dose is 900mg in normal renal function. If CrCl 20-60 ml/min, maximum recommended dose is 300mg daily. If CrCl <20 ml/min, refer to rheumatology.

12. Prophylaxis with colchicine or naproxen should commence after treatment for the acute flare is complete, and usually continues for 3-6 months. Choice of medication depends on risk factors; check for contraindications and interactions (see BNF).

8.2.3 Pathway components

There were 6 key components to the care pathway I developed (Figure 37):

1. **Timely diagnosis**: encouraging appropriate blood tests on arrival; notifying and discussing the case with the rheumatology team; and joint aspiration, where appropriate.
2. **Flare treatment**: several first-line treatment options, with choice dependent on the presenting symptoms, risk factors and patient preference; recommendation to consider intra-articular steroid injection.
3. **Flare prevention**: education on the diagnosis and long-term treatment of gout; initiation of ULT during the flare (alongside flare treatment); dose-adjustment according to renal function (thresholds were chosen in consultation with experts and stakeholders, in view of limited trial evidence).
4. **Admission prevention**: utilisation of ambulatory care units (ACU) and/or @home community support teams, to reduce the need for admission when safe to do so.
5. **Discharge recommendations**: provision of clear recommendations to patients and their primary care teams on ULT titration-to-target, urate monitoring, flare prophylaxis, and follow-up.
6. **Post-discharge follow-up**: all patients to be reviewed in a nurse-led clinic, delivered via telephone within 2 weeks of discharge, followed by handover to primary care; option of ongoing rheumatology outpatient follow-up for patients with severe gout (e.g. tophaceous gout and/or multiple admissions).

A key component of my pathway was a nurse-led, post-discharge clinic, designed to facilitate the review of patients shortly after discharge from hospital. This was modelled on the successful, nurse-led approach utilised in Doherty's *et al.*'s community-based RCT, with several important differences.[31] As with Doherty's *et al.*'s intervention, the aims of our post-discharge clinic were to review patients' symptoms after discharge, deliver individualised education on the diagnosis and treatment of gout, coordinate treat-to-target optimisation of ULT, review potential adverse effects of treatments, and answer any questions or concerns. In contrast to Doherty's *et al.*'s intervention - where there was an average of 17 study visits per patient over a 24-month period - our post-discharge clinic was delivered as a single telephone appointment within 2 weeks of discharge, followed by handover of care to patients' primary care teams. This approach was chosen to reflect resource availability in a typical NHS hospital; our department had nursing capacity for up to 5 post-discharge appointments per week, with each appointment lasting approximately 30 minutes. By adopting this approach, we would be able to compare how well a single post-discharge follow-up appointment performed, in comparison to the more intensive approach used in Doherty's *et al.*'s study.

Verbal information delivered by nurse specialists during the post-discharge clinic was summarised in clinic letters, which were provided to patients and their primary care teams. These letters included clear guidance on titration of ULT to achieve urate targets, urate monitoring, recommendations for flare prophylaxis, and follow-up recommendations (Figure 37). Patients were provided with links to the Versus Arthritis and UK Gout Society websites, containing further information on the diagnosis and treatment of gout. Additionally, I created prompt sheets for use in clinic, as well as a standard operating procedure and clinic letter templates (see Supplementary Appendix). SMS reminders were sent to patients to ensure they were aware of their appointments after discharge from hospital.

8.2.4 Implementation strategy

For complex healthcare interventions to be successfully adopted in clinical practice, effective implementation strategies are needed.[186,187,192] These strategies typically consist of multiple, complementary implementation approaches, tailored to the intervention and setting. The Expert Recommendations for Implementing Change (ERIC) guidelines provide a comprehensive summary of implementation strategies that can be adopted for interventions.[192] In collaboration with my supervisory team and stakeholders, I explored which implementation approaches were most likely to be effective in maximising the uptake of my care pathway. We took into consideration whether the implementation approach was likely to be: i) appropriate for the intervention components within my care pathway and the barriers identified in Chapter 7 of my thesis; ii) feasible to implement at King's College Hospital NHS Foundation Trust and other Trusts; iii) acceptable to patients and clinicians; and iv) sustainable in the long-term.

The following implementation approaches were selected:

- **Digital enablers** – in collaboration with the King's College Hospital IT team, I created electronic order sets for relevant investigations (Figure 38; e.g. serum urate and synovial fluid crystal analysis) and medications (Figure 39; e.g. flare treatment options and ULT). Additionally, I created an eNotification system (Figure 40), whereby clinicians completed an electronic order form to notify the rheumatology team when a patient had been hospitalised for gout.
- **Study champions** – clinicians from several specialties, including the emergency medicine, general medicine and rheumatology departments, were provided with the opportunity to take part in developing the pathway and in supporting its implementation within their department. This was particularly important for disseminating the pathway within the ED, due to high rates of staff turnover.
- **Educational sessions** – I delivered training sessions for frontline clinicians in multiple departments, including emergency medicine, acute medicine, general medicine and rheumatology. The aim of these sessions was to provide guidance on optimal gout management, go through the components of the pathway, discuss how

implementation would work in practice, and answer any questions. I used face-to-face and virtual sessions staggered over time (>10 sessions in total), to enable as many clinicians as possible to attend.

- **Executive approval** – I involved hospital executives, including the chief executive and clinical directors, in the development of the pathway and implementation strategy. Once finalised, I submitted the pathway for review and approval by the rheumatology clinical governance committee, ED and general medicine clinical governance committees, and the drug and therapeutics committee at King's College Hospital. Once approved, the pathway was submitted to the King's College Hospital patient outcomes team for review and publication on the Trust clinical guidelines webpage. Approval to implement the pathway was obtained from King's College Hospital under the remit of service evaluation (see supplementary appendix).
- **Advertising** – information on the pathway, training sessions and electronic order sets was uploaded to the hospital website and circulated to all staff in the Trust (Figure 41, Figure 42, Figure 43). Additionally, tailored emails were sent to individual departments, notifying them of the pathway and its implementation.
- **Medication availability** – in collaboration with the pharmacy team, pre-packs of commonly-used gout medications (e.g. colchicine) were ordered and stocked within the ED, so that patients could be provided with these prior to discharge.
- **Clinical supervision** – rheumatology specialists with expertise in gout management were made available to support frontline clinicians managing hospitalised gout patients.
- **Quality monitoring and clinician feedback** – outcomes (detailed below) were monitored prospectively throughout the intervention period. Opportunities for clinician feedback were provided; however, no changes were made to the pathway itself during the study period.

Figure 38. Investigations order set

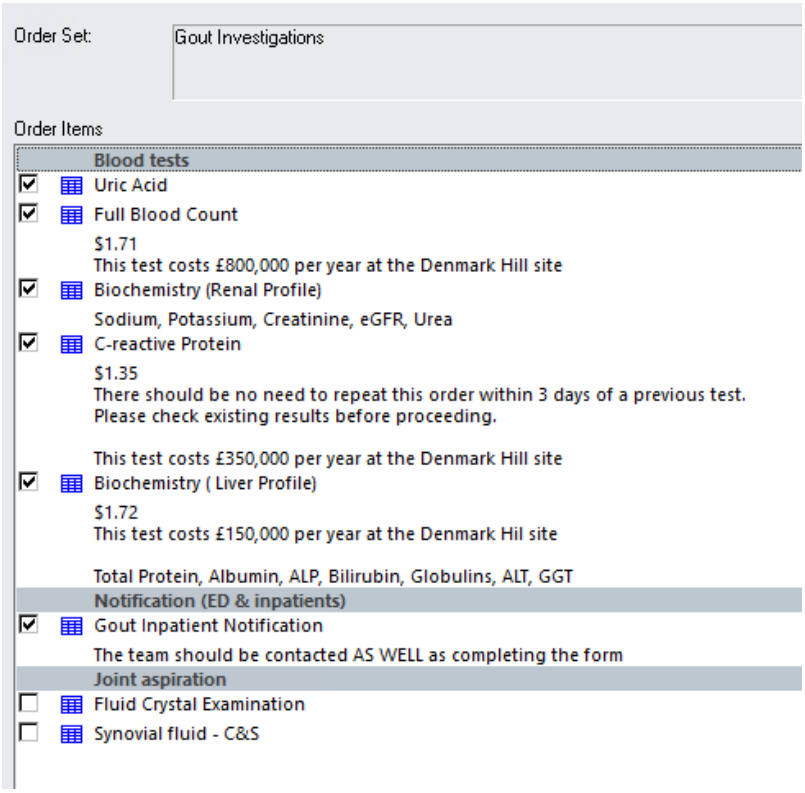


Figure 39. Prescribing order set

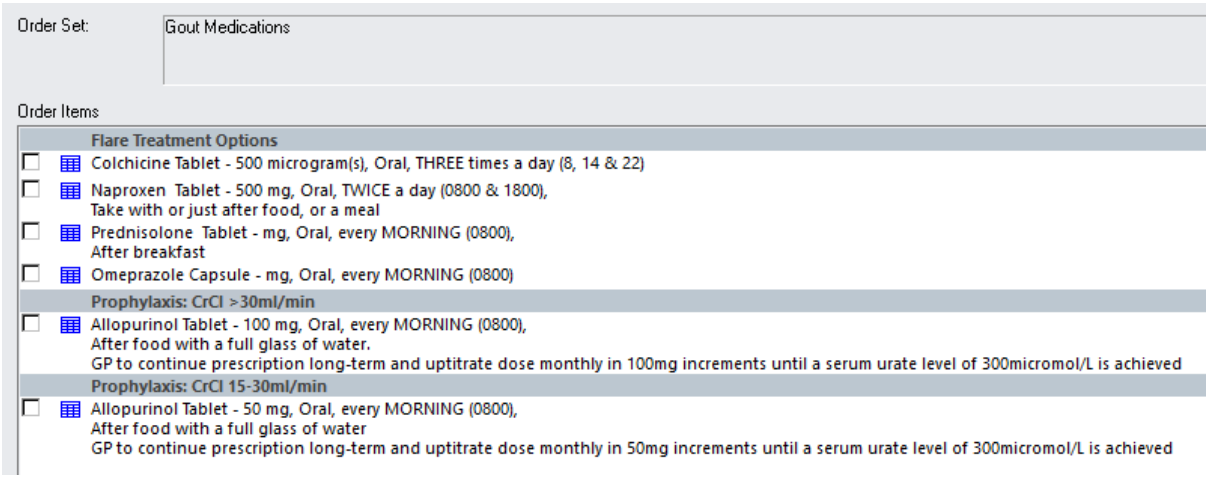


Figure 40. Inpatient gout notification

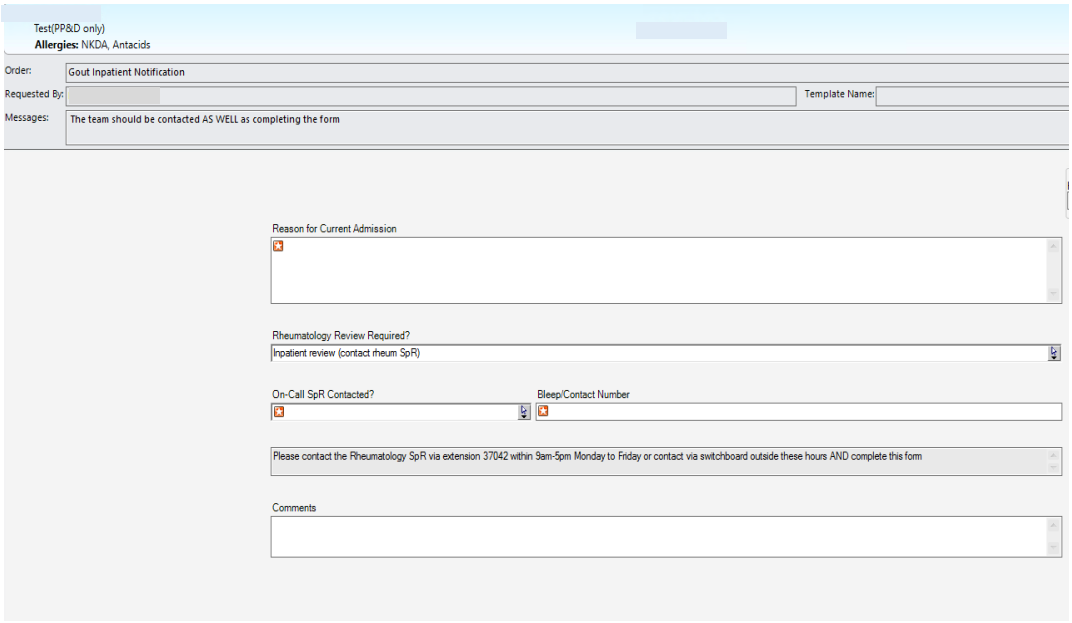


Figure 41. Pathway access via Emergency department guideline portal

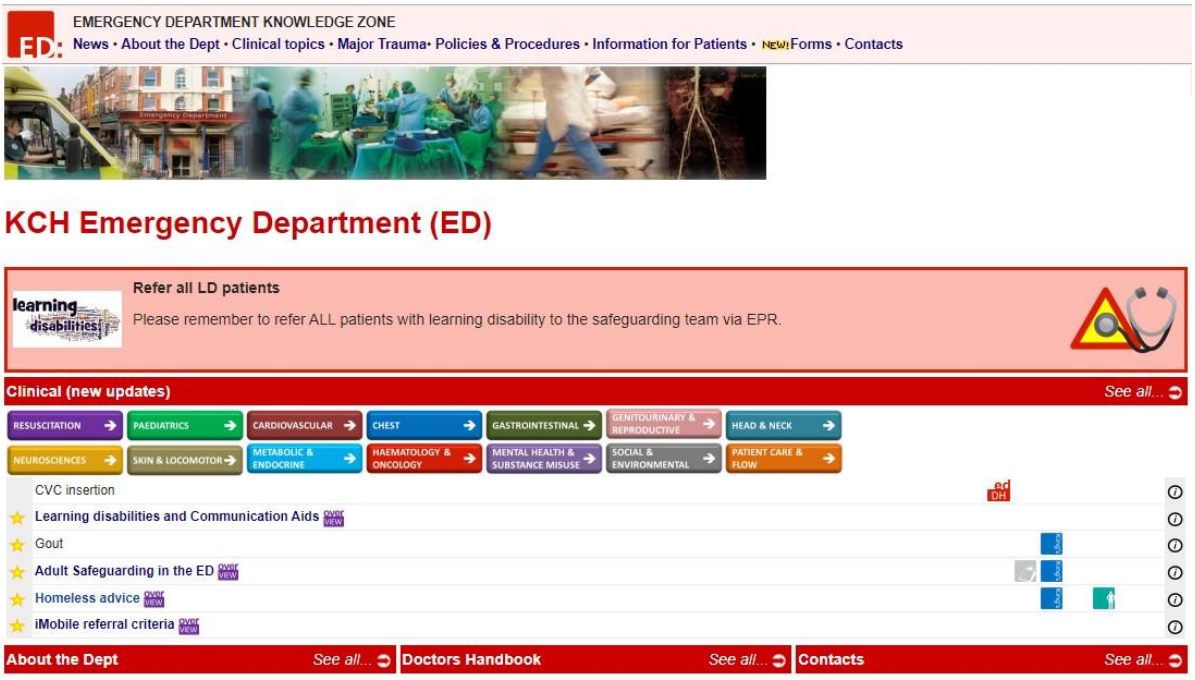
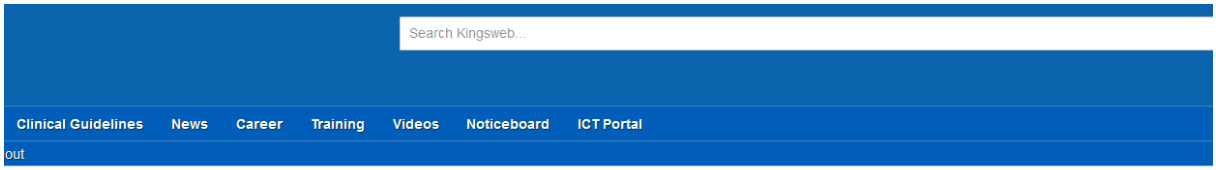


Figure 42. Emergency department news bulletin

Figure 43. Hospital news bulletin



Improving management of gout

A new pathway has launched at Denmark Hill to help improve the management of gout.

We speak to Mark Russell, a Rheumatology Specialist Registrar Doctor and Research Fellow, about how the pathway was developed and what it is hoping to improve.

Hi Mark, can you tell us a bit about your role?

I'm a Rheumatology Specialist Registrar Doctor and Research Fellow at King's.

I do a mixture of clinical work – seeing patients with inflammatory arthritis and other rheumatic conditions – and clinical research.

Lots of my work focuses on how we can improve outcomes for patients attending hospital with gout flares and how to prevent avoidable hospital admissions.

A new care pathway for the management of gout in the emergency department and inpatient wards has recently been developed. Why was the new pathway needed?

Gout is the most common form of inflammatory arthritis worldwide. It is characterised by flares of joint pain and swelling, which can require admission to hospital when severe.

There are very effective medications available to treat and prevent gout flares (for example, allopurinol), yet previous studies have shown that these medications are not used frequently enough or at appropriate doses.

One consequence of this is increasing numbers of hospital admissions. Hospitalisations for gout flares have doubled in England since 2006.

At King's, there are over 300 emergency department and hospital admissions a year for gout flares, many of which might have been prevented with more widespread use of treatments such as allopurinol.

We have developed a quick-reference care pathway, which incorporates national recommendations for best practice gout care.

Our aim is to improve care for patients and reduce avoidable admissions. The pathway includes the following key components:

- i) education for patients on the diagnosis of gout and treatment options;
- ii) flare treatment plans;
- iii) prevention against future flares; and
- iv) follow-up coordinated between the hospital and GPs.

How was it developed, and what are you hoping it achieves?

To develop the pathway, first we mapped the patient journey, to explore what happens from when patients attend the emergency department with flare symptoms, through to when they are discharged back to the care of their GP.

This enabled us to identify barriers to optimal care. We then held discussions with multiple stakeholders at King's and the local area (including patients, nurses, doctors, pharmacists and Trust executives), to identify strategies to overcome these barriers and improve uptake of guideline-recommended treatments.

We hope that the new care pathway will directly benefit patients, with fewer painful gout flares, fewer hospital attendances, and reduced accumulation of disability.

For clinicians managing patients with gout, it will provide them with an easy reference guide on optimal gout management.

For the Trust, we hope that the pathway will produce cost savings, reduce bed pressures, and improve integration between primary and secondary care

Is there anything else you think we should know about the pathway or the new EPR gout order sets you have created?

The new care pathway is now available on the King's Clinical Guidelines – search for "gout".

We have also created new EPR order sets for gout investigations and medications – search for "gout" under the EPR orders tab.

We will be delivering teaching sessions on the management of gout and hot joints in the coming weeks.

Another potential issue I considered was to how to reach patients who presented to hospital for gout flares without the rheumatology team being notified. For example, if a patient was reviewed by an ED clinician who was not aware of the pathway, they would not necessarily know to send a gout eNotification and/or contact the rheumatology team. These patients would not therefore receive follow-up as per the gout pathway. To address this, I collaborated with the Business Investigation Unit at King's College Hospital to generate an automated, weekly list of patients who had been hospitalised or attended ED with diagnostic codes for gout. This list was used to flag patients who had attended hospital for gout flares, but who had not been referred to the rheumatology team and/or had a gout eNotification sent. These patients could then be contacted and booked into the follow-up gout clinic for review, and have their outcomes reviewed as part of the project.

8.2.5 Study design

I considered whether it would be ethical to randomise patients to treatment under the pathway vs. a control group (e.g. usual gout care). This was the approach adopted in Doherty *et al.*'s RCT.[31] In consultation with my supervisory team, we opted against this approach for several reasons:

i. My pathway was based upon best practice care and national/international guidelines, and therefore represents the standard of care that we should be offering to all patients with gout;
ii. Data from Doherty *et al.*'s RCT had shown that treat-to-target ULT and individualised patient education was highly effective; therefore, it may have been unethical/impractical to randomise patients to a sub-optimal approach;
iii. My pathway was part of a service evaluation project to improve care for patients hospitalised for gout; a study in which randomisation was performed would likely fall under the remit of research, and would require substantially more resources than was available.

For the above reasons, I opted to implement the care pathway for all patients attending hospital for acute gout flares after the implementation launch date. Outcomes after implementation launch would then be compared with a historical control group – patients who had been hospitalised for gout flares prior to the implementation of the care pathway.

I designed pragmatic eligibility criteria for treatment under the pathway, so that it could be implemented for the vast majority of patients presenting to hospital with gout flares:

- Patients aged ≥18 years who presented to ED and/or were admitted with a clinical diagnosis of a gout flare;
- Flares could be the primary attending diagnosis or a secondary attending diagnosis (e.g. in the context of admissions for other diagnoses);
- Crystal analysis of a joint aspirate was recommended in the pathway but not mandatory, as reflects clinical practice;

- Patients with either new or pre-existing gout diagnoses were eligible for treatment under the pathway.

The pathway was designed to act as a guide for the optimal management of gout, rather than a definitive pathway. All clinical decisions were at the discretion of the primary clinical team, and care was delivered by the patients' primary medical team, in consultation with the rheumatology team where appropriate.

8.2.6 Study outcomes

Another aspect of my study that required extensive stakeholder input was the selection of study outcomes. This needed to capture both effectiveness and implementation outcomes. In consultation with my supervisors, I mapped these outcomes to the individual components of the study intervention, including:

Outcomes during hospitalisation:

- Was rheumatology input sought during the attendance;
- Was a serum urate level performed;
- Was a joint aspiration performed;
- Was a flare treatment (NSAID, colchicine and/or corticosteroid) initiated;
- Was disease education provided to patients and documented in the medical records;
- Was ULT initiated and/or up-titrated prior to discharge;
- Was a prescription for prophylaxis against flares provided during ULT initiation/titration;
- Were gout-specific recommendations and/or follow-up provided on discharge.

Outcomes within 6 months of discharge from hospital:

- Was ULT initiated and/or up-titrated in the community;
- How many serum urate levels were performed;
- Were serum urate targets ≤360 micromol/L and/or ≤300 micromol/L achieved;
- Did the patient receive follow-up in the nurse-led, post-discharge clinic;
- Did the patient receive follow-up in a rheumatology outpatient clinic;
- Did the patient re-attend ED and/or were they re-admitted with a gout flare.

Importantly, the above outcomes can be captured using routinely-collected clinical data available in the EHR at King's College Hospital NHS Foundation Trust. This ensured that robust data collection could be performed prospectively, in line with the service evaluation remit of the project, and without large amounts of additional data capture burden. In-hospital data were extracted from EHRs, while post-discharge data were extracted from local care records, containing primary and secondary care data for patients with linked NHS identifiers.

The 6-month follow-up period was chosen pragmatically to reflect the time available within my project. If monthly ULT titration is followed appropriately, then 6 months should be sufficient for the majority of patients to achieve urate targets; acknowledging that, for some

patients, more time will be needed. Many re-admissions occur within the first few months of ULT initiation (Chapter 5), which would be captured within this outcome; however, the longer-term benefits of ULT on re-admission prevention may require a longer follow-up period. These were potential limitations that I needed to consider when interpreting my study outcomes.

8.2.7 Primary care guideline

Although the primary objective of my care pathway was to optimise the management of patients who had been hospitalised for gout flares, it is important to note that a large proportion of gout care is provided in primary care. This includes the ongoing follow-up of patients who have been hospitalised for flares.

Data from my previous chapters had shown that the recommendations contained within specialist guidelines (e.g. BSR and EULAR gout management guidelines are not widely followed in primary care (Chapter 3). To try and address this barrier, I developed a quick-reference guide for the management of gout in primary care (Figure 44). A key objective of this guide was to provide primary care clinicians in South-East London with advice on how to optimally manage patients with gout, including patients who had been discharged from hospital. As with the hospital care pathway, this guideline reflected best practice care, as defined in BSR, EULAR and ACR guidelines.[6-8]

During the primary care pathway development process, I consulted rheumatologists, pharmacists, patients and primary care clinicians, as well as members of the South-East London Clinical Commissioning Group (CCG). Once finalised, the pathway was submitted for ratification at the South East London Integrated Medicines Optimisation Committee Rheumatology Pathway sub-group and South-East London Medicines and Pathways Review Group.

Figure 44. Care pathway for the management of gout in primary care

South East London Guideline for the Management of Gout in Primary Care

Diagnosis

Clinical diagnosis is important. Common presenting features include:

- Typical joint sites (hallux, mid-foot, ankle)
- One or few joints affected (can be polyarticular in longstanding gout or patients on diuretics)
- Onset of symptoms over hours
- Episodic flares, often with resolution between flares
- Presence of tophi

Serum urate testing is important for diagnosis and therapeutic monitoring, with the following caveats:

- Urate levels can be normal during flares; if normal, consider repeat testing 2 weeks after the flare
- Hyperuricaemia without clinical features of gout does not equate to a diagnosis of gout, and is not an indication for urate-lowering therapy.

Refer to rheumatology if diagnostic uncertainty. Atypical presentations are common, particularly in elderly patients and women. Gout is highly unlikely in pre-menopausal women.

Red flags

- Consideration must always be given to **septic arthritis** in any patient presenting with an acutely painful, swollen joint.
- Risk factors for septic arthritis include:
  - Prior joint replacement
  - Pre-existing joint damage
  - Recent intra-articular injection
  - Intravenous drug use
  - Immunosuppression.
- Joint aspiration is the gold standard for diagnosis of gout and exclusion of septic arthritis, but may not be possible in primary care.
- Refer to A&E for same-day joint aspiration if septic arthritis is suspected or being considered.

Treatment of flares

Colchicine 500 micrograms TDS (OD/BD if CKD or elderly), typically for 5-7 days.

or

NSAID (e.g. naproxen 500mg BD) with gastroprotection, typically for 5-7 days.

or

Prednisolone 20-30mg OD with gastroprotection, typically for 5-7 days; for polyarticular or resistant flares or if contraindications to colchicine and NSAIDs.

- *Choice of treatment depends on risk factors and patient preference.*
- *Colchicine use in clinical practice and as recommended in guidelines often exceeds the maximum 6mg per course referenced in the BNF.*
- *Suggested colchicine doses in CKD: 500 micrograms BD if GFR 30-60 ml/min; 500 micrograms OD if GFR 15-30 ml/min; avoid if GFR <15 ml/min.*
- *Check for medication interactions with colchicine, e.g. statins, macrolides.*
- *Choice of prednisolone dose depends on individual risk factors, including infection risk, patient weight and comorbidities.*
- ***Do not stop urate-lowering therapy (ULT) during flares.***
- *Advise patient to return if symptoms worsen or if no improvement in 1-2 days.*
- *Advise patients to commence treatment as soon as possible after the onset of symptoms; consider providing patients with a **rescue pack**, to be initiated at the onset of flare symptoms.*
- ***Adjunct measures** include rest, ice and elevation of the affected joint.*
- *Combination therapy can be considered in treatment-resistant flares.*

Advice for patients and self-care

- **Education** should be provided for all patients on the diagnosis, how to manage flares, and the importance of ULT in preventing flares, disability and gout-associated comorbidities, such as renal impairment.
- Provide written information on gout and commonly used medications; available at Versus Arthritis and UK Gout Society.
- Provide lifestyle advice: **reduce consumption of purine-rich foods** (e.g. shellfish, red meat), fructose (e.g. sweetened drinks) and alcohol
- Advise good intake of fruit, vegetables, fibre and low-fat dairy products.
- Advise maintaining a healthy weight (reduces urate levels).
- **Screen patients for comorbidities** annually, including diabetes mellitus, dyslipidaemia, hypertension and renal impairment.
- **Limit the use of diuretics**, where possible.

Prevention of flares: urate-lowering therapy

First line: Initiate **allopurinol** 100mg OD (50mg OD if renal impairment), then uptitrate in 100mg increments (50mg increments if renal impairment) every 4 weeks until a serum urate **≤300 micromol/L** is achieved.

Second line: Initiate **febuxostat** 80mg OD instead of allopurinol, if allopurinol contraindicated or ongoing flares despite maximally tolerated allopurinol. Increase to 120mg OD after 4 weeks if required to achieve serum urate **≤300 micromol/L**.

Third line: Refer to rheumatology if ongoing flares despite maximally tolerated doses of allopurinol or febuxostat, or if contraindications to both.

Consider prophylaxis against flares during ULT initiation and uptitration (typically for 3-6 months)**.** *First line*: colchicine 500 micrograms OD or BD. *Second line*: low-dose NSAID with gastroprotection, unless contraindicated.

- *ULT should be offered to **all patients** with gout, including first flares.*
- *ULT should be strongly encouraged if any of the following: recurrent flares, tophi, persistent arthritis, joint damage, renal impairment, urolithiasis, diuretic use, comorbidities or diagnosis of gout at a young age.*
- ***ULT can be initiated during flares**, alongside treatment for the flare.*
- ***Allopurinol doses >300mg OD are frequently required to achieve urate targets.** Maximum recommended dose is 900mg daily in normal renal function (doses above 300mg should be split). If GFR 20-60 ml/min, max. recommended dose is 300mg daily. If GFR <20 ml/min, seek rheumatology advice.*
- *Seek rheumatology advice if GFR <30 ml/min and febuxostat being considered.*
- *Check renal function before initiating ULT. Check LFTs before initiating febuxostat and periodically during treatment (e.g. after dose changes or if signs of liver dysfunction).*
- *Consider referral to a **practice pharmacist**, if available, to facilitate ULT titration.*
- *Patient information leaflets are available for allopurinol and febuxostat.*
- *Patients initiating ULT should be advised to **monitor for a new rash**; stop medication and seek medical attention if so. Severe cutaneous reactions are rare (0.1-0.4%) but more common in patients of Asian and Black ethnicity. Patients with previous hypersensitivity reactions to allopurinol are at increased risk of hypersensitivity reactions to febuxostat.*
- *Do not initiate allopurinol or febuxostat in patients taking azathioprine or mercaptopurine (risk of fatal myelosuppression).*
- *Avoid febuxostat in patients with pre-existing major cardiovascular disease.*
- ***ULT should continue lifelong**; most patients flare within 5 years of stopping. Consider annual monitoring of urate levels to ensure patients remain at target.*

References: BSR Guideline for the Management of Gout, 2017; ACR Guideline for the Management of Gout, 2020; EULAR evidence-based recommendations for the management of gout, 2016; Dalbeth N, *et al*. Gout. Nat Rev Dis Primers, 2019.

8.3 Implementing the care pathway at King's College Hospital

Implementing treat-to-target urate-lowering therapy during hospitalisations for gout flares

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8.4 Abstract

Objectives: To evaluate a strategy designed to optimise care and increase uptake of ULT during hospitalisations for gout flares.

Methods: We conducted a prospective cohort study to evaluate a strategy that combined optimal in-hospital gout management with a nurse-led, follow-up appointment, followed by handover to primary care. Outcomes, including ULT initiation, urate target attainment, and re-hospitalisation rates, were compared between patients hospitalised for flares in the 12 months post-implementation and a retrospective cohort of hospitalised patients from 12 months pre-implementation.

Results: 119 and 108 patients, respectively, were hospitalised for gout flares in the 12 months pre- and post-implementation. For patients with 6-month follow-up data available (n=94 and n=97, respectively), the proportion newly initiated on ULT increased from 49.2% pre-implementation to 92.3% post-implementation (age/sex-adjusted OR (aOR) 11.5; 95% CI 4.36-30.5; p<0.001). After implementation, more patients achieved a serum urate ≤360 micromol/L within 6 months of discharge (10.6% pre-implementation vs. 26.8% post-implementation; aOR 3.04; 95% CI 1.36-6.78; p=0.007). The proportion of patients re-hospitalised for flares was 14.9% pre-implementation vs. 9.3% post-implementation (aOR 0.53, 95% CI 0.22 to 1.32; p=0.18).

Conclusion: Over 90% of patients were initiated on ULT after implementing a strategy to optimise hospital gout care. Despite increased initiation of ULT during flares, recurrent hospitalisations were not more frequent following implementation. Significant relative improvements in urate target attainment were observed post-implementation; however, for the majority of hospitalised gout patients to achieve urate targets, closer primary-secondary care integration is still needed.

8.5 Introduction

Hospitalisations for gout flares have increased markedly over the last 20 years, doubling in the United States, England and Canada.[3,63,64,71] These increases have occurred despite widespread availability of ULT, such as allopurinol and febuxostat. When titrated to achieve serum urate targets ≤360 micromol/L, ULT prevents flares, improves quality of life, and leads to long-term reductions in hospitalisations.[31,167,193] International guidelines have been updated to encourage the uptake of treat-to-target ULT.[6-8,35] However, population-level data continue to show that ULT is initiated in only a minority of patients, while few patients achieve the urate targets necessary to prevent flares and hospitalisations.[1,55,143,193]

For avoidable gout admissions to be prevented, strategies are needed to optimise care and increase uptake of treat-to-target ULT in hospitalised patients. A recent systematic review found a paucity of high-quality studies in people hospitalised for gout.[160] Specifically, no prospective studies to date had evaluated strategies designed to encourage ULT uptake and prevent re-admissions in hospitalised patients.[160] We sought to address this knowledge gap.

In this study, we evaluated a strategy designed to optimise hospital gout care and increase uptake of ULT. Our strategy was modelled on a nurse-led intervention shown to be highly effective at optimising gout management in primary care.[31] We adapted this strategy for implementation during hospitalisations for flares, and assessed outcomes including ULT initiation, serum urate target attainment, and rates of re-hospitalisation.

8.6 Methods

Study design and intervention

We performed a prospective cohort study at a large teaching hospital in South London, UK, which serves a population of over 1 million people. We evaluated outcomes after implementation of a strategy designed to optimise care for people hospitalised for gout flares, and compared these outcomes with a retrospective cohort of hospitalised patients from before implementation.

The intervention package consisted of two key components: 1) an in-hospital gout management pathway (Figure 37), based on BSR, EULAR and ACR gout management guidelines;[6-8] and 2) a nurse-led telephone appointment performed two weeks after discharge.

The intervention was developed with extensive stakeholder input, following a systematic literature review,[160] audit and process mapping of gout care at our hospital.[170] The management pathway was designed as a quick-reference guide on optimal gout care for use by frontline clinicians and rheumatologists. This included recommendations on: diagnostic tests (including serum urate levels and joint aspiration); rheumatologist input; flare treatments (NSAIDs, colchicine and/or corticosteroids, where appropriate); offering ULT

(allopurinol first-line) to all patients unless contraindicated; initiating ULT during the acute flare; considering prophylaxis against flares during ULT initiation and titration; admission-avoidance strategies (e.g. ACUs); disease education; and post-discharge advice (including treat-to-target ULT optimisation, as recommended in the BSR gout management guideline[6]).

A nurse-led telephone clinic was established to provide patients with a single follow-up appointment within two weeks of discharge. This clinic was delivered on a weekly basis by a specialist rheumatology nurse, trained in gout management, with appointments lasting approximately 30 minutes per patient. Objectives were to review symptoms, provide disease education, discuss flare management strategies, and provide advice to patients and their primary care team on ULT dose optimisation using a treat-to-target strategy.[6] After this appointment, care was handed over to the patient's primary care team via a clinical letter. For patients with severe gout and/or recurrent admissions, additional rheumatology outpatient follow-up could be considered.

To maximise uptake of the intervention, a multi-pronged implementation strategy was developed with implementation experts. This incorporated strategies from the ERIC guidance,[192] which were tailored to the specific hospital environment.

Study period

The study period was from 30 October 2020 to 29 April 2023. The intervention was launched on 30 October 2021. Data were collected prospectively on all patients hospitalised with gout flares in the 12-month period after intervention launch (30 October 2021 to 29 October 2022). Post-implementation outcomes were compared with outcomes for patients hospitalised with gout in the 12-month period prior to launch (30 October 2020 to 29 October 2021). All patients with linked primary care data were followed up for 6 months after discharge to review post-discharge outcomes (detailed below).

Case definitions

All ED attendances and admission episodes for gout flares (collectively referred to as hospitalisations) in the pre- and post-implementation periods were included. Both primary and secondary admission diagnoses of gout (e.g. flares occurring during hospitalisations for other reasons) were eligible, assuming gout was deemed the likely cause of the acute joint symptoms by the primary clinical team. Although recommended in our pathway, confirmatory joint aspiration and/or rheumatology input were not mandated, as reflects local clinical practice. Patients managed solely in an urgent care centre (primarily staffed by GPs rather than ED clinicians) were excluded, as the urgent care centre facility at our hospital was transferred to another institution prior to intervention launch.

Data sources

All data used in these analyses were routinely captured during clinical care. In-hospital data were extracted from EHRs. Post-discharge data were extracted from local care records,

containing primary and secondary care data for patients with linked NHS identifiers who had not opted out of this service.[194] All data were manually validated by a rheumatologist, and pseudonymised for the purposes of analysis. Outcomes were selected *a priori* with stakeholder input.

Baseline characteristics

Baseline data were collected as follows: age; sex; admission type (ED attendance-only vs. hospital admission); day/time of presentation (defined as out-of-hours if occurring between 9pm-9am or on a Saturday/Sunday); pre-existing gout diagnosis; pre-existing prescription for ULT (allopurinol, febuxostat, benzbromarone, sulfinpyrazone or probenecid); and baseline blood tests, if performed during the presentation (serum urate, CRP, white cell count, neutrophil count, lymphocyte count and serum creatinine).

Outcomes during hospitalisation

Data were captured to ascertain whether the following outcomes occurred during the hospitalisation episode: rheumatology input sought; serum urate level performed; joint aspiration performed; flare treatment(s) prescribed (NSAID, colchicine and/or oral, intramuscular, intravenous or intra-articular corticosteroids); disease education provided to patients; ULT initiated (if patient not already receiving ULT) or up-titrated (if patient already receiving ULT at a sub-optimal dose); prophylaxis prescribed (low-dose colchicine, NSAIDs or corticosteroids); gout-specific recommendations and/or follow-up on discharge.

Outcomes after hospitalisation

For patients with available follow-up data, we ascertained whether the following outcomes occurred within 6 months of discharge: ULT initiation and/or up-titration; prescription of prophylaxis against flares during ULT initiation/titration; number of serum urate levels performed; attainment of serum urate targets ≤360 micromol/L and/or ≤300 micromol/L; follow-up in the gout telephone clinic and/or rheumatology outpatient clinic; re-attendance at ED and/or re-admission with a subsequent gout flare (occurring more than 7 days after discharge from the initial presentation).

Statistical methods

Baseline characteristics were tabulated, and between-cohort differences estimated using Chi-squared tests for categorical variables and independent T-tests for continuous variables. Logistic regression, with adjustment for age and sex, was used to estimate differences in categorical outcomes between pre- and post-implementation cohorts, expressed as adjusted OR with 95% CI. Linear regression, with adjustment for age and sex, was used to estimate differences in continuous outcomes, expressed as adjusted β-coefficients (aβ) with 95% CI. Kaplan-Meier survival curves were presented for repeat hospitalisations. Univariable logistic regression was performed to explore a differential impact of the intervention on patient subgroups, categorised by age, sex, admission type, time of presentation, whether the gout

diagnosis was pre-existing, or whether rheumatology input was sought during hospitalisation. Stata v17 was used for all analyses. No adjustment was performed for multiple hypothesis testing, as this was an exploratory study.

Study approval and ethics

Approval to undertake this study under the remit of service evaluation was obtained from King's College Hospital NHS Foundation Trust. No further ethical approval or written informed patient consent were required, as per UK Health Research Authority guidance.

Patient and public involvement

Patients have been closely involved in all stages of this project. Patient feedback was instrumental in conceptualising this project, and in designing the intervention. In particular, patients emphasised the importance of a holistic, multi-faceted intervention and implementation strategy, recognising that a single intervention was unlikely to address the multiple barriers to optimal hospital gout care. Patients will be closely involved in disseminating the findings of this study, and in developing follow-on projects.

8.7 Results

Baseline characteristics

In the 12 months prior to implementation of the intervention, 119 people attended ED with gout flares, of whom 63 (52.9%) required admission to hospital. In the 12 months after implementation, 108 attended ED with gout flares, of whom 53 (49.1%) required admission. A study flowchart is shown in Figure 45.

Baseline characteristics are shown in Table 17. Pre- and post-implementation cohorts had similar mean ages (62 vs. 64 years, respectively). There were proportionally more female patients in the pre- than post-implementation cohort (26.9% vs. 15.7%). The proportion of patients who had pre-existing gout diagnoses was similar in the pre- and post-implementation cohorts (66.4% vs. 67.6%); 41.8% and 27.4% of known gout patients in the pre- and post-implementation cohorts, respectively, were receiving ULT prior to hospitalisation. Mean serum urate levels at baseline were comparable (485 micromol/L vs. 487 micromol/L).

Figure 45. Study flowchart depicting the pre- and post-implementation study cohorts

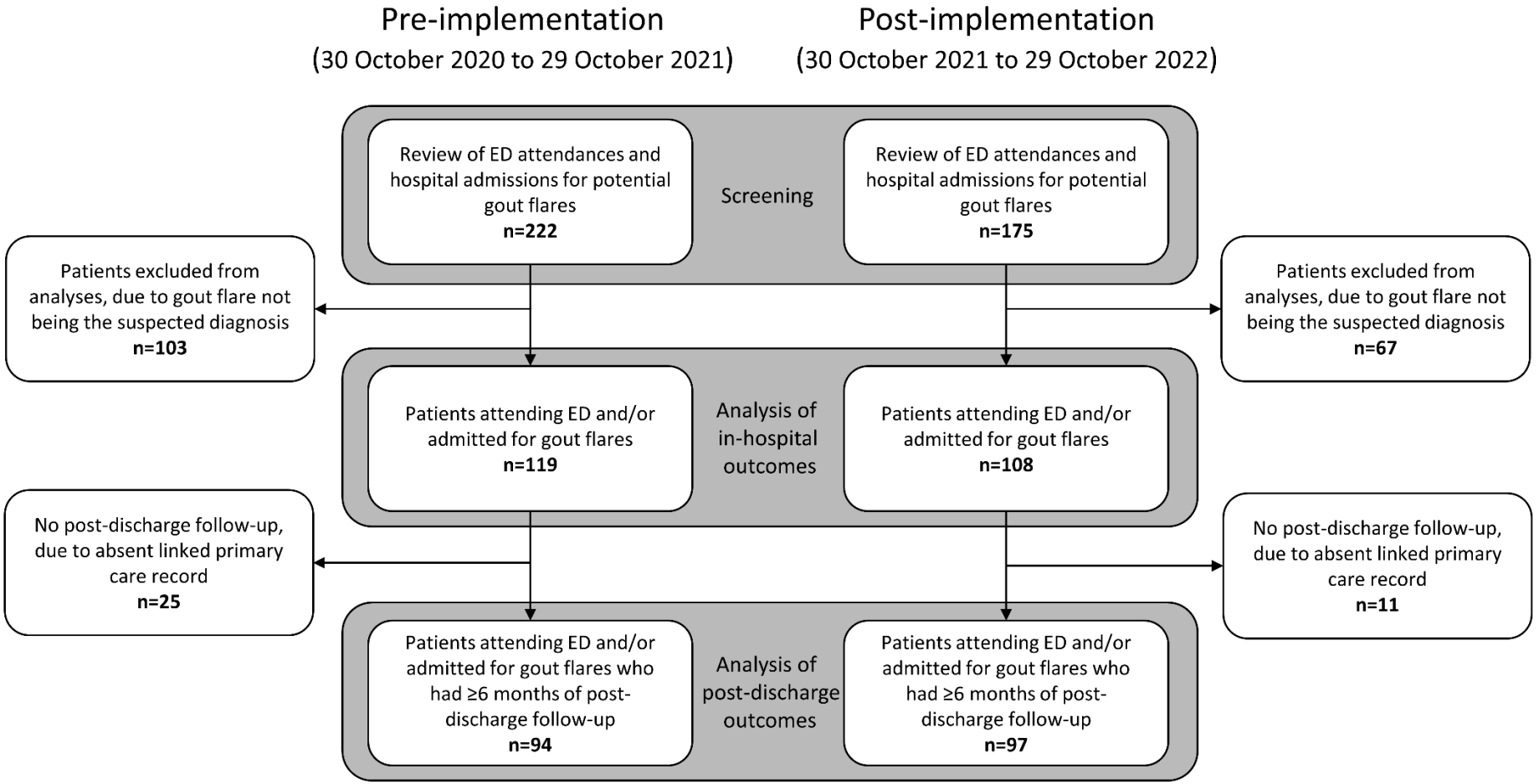


Table 17. Baseline characteristics of the pre- and post-implementation cohorts

Characteristic	Pre-implementation N=119	Post-implementation N=108	p-value
Age, years	62 (16)	64 (16)	0.31
Sex			
Female	32 (26.9%)	17 (15.7%)	0.041
Male	87 (73.1%)	91 (84.3%)	
Admission type			
Discharged from ED	56 (47.1%)	55 (50.9%)	0.56
Admitted to hospital	63 (52.9%)	53 (49.1%)	
Presented out-of-hours	59 (49.6%)	43 (39.8%)	0.14
Pre-existing gout diagnosis	79 (66.4%)	73 (67.6%)	0.85
Receiving ULT prior to hospitalisation	33 (41.8%)	20 (27.4%)	0.063
Not on ULT prior to hospitalisation	46 (58.2%)	53 (72.6%)	
Serum urate at baseline, micromol/L	485 (185)	487 (125)	0.94
CRP at baseline, mg/L	89 (84)	76 (79)	0.28
White cell count at baseline, $x10^9$/L	9.3 (3.5)	9.5 (4.6)	0.76
Neutrophil count at baseline, $x10^9$/L	6.6 (3.1)	6.5 (3.9)	0.79
Lymphocyte count at baseline, $x10^9$/L	1.6 (0.8)	1.8 (0.9)	0.14
Creatinine at baseline, micromol/L	165 (161)	142 (116)	0.24

Blood test results are shown as means with standard deviations, and represent the first tests performed during the hospitalisation. Inferential statistics for between-cohort differences were obtained from independent T-tests for continuous variables and Chi-squared tests for categorical variables.

Outcomes during hospitalisations

In-hospital outcomes were compared before and after implementation (Table 18). Following implementation, specialist rheumatology input was obtained more frequently in hospital (54.6% pre-implementation vs. 75.9% post-implementation; aOR 2.48, 95% CI 1.37 to 4.52; p=0.003); serum urate levels were performed in more patients (66.4% vs. 92.6%; aOR 6.32, 95% CI 2.75 to 14.5; p<0.001); and joint aspiration was performed more frequently (19.3% vs. 47.2%; aOR 3.44, 95% CI 1.88 to 6.27; p<0.001).

93.3% and 98.1% of pre- and post-implementation cohorts, respectively, received a guideline-recommended flare treatment. After implementation, more patients were prescribed colchicine (62.2% vs. 79.6%; aOR 2.30, 95% CI 1.23 to 4.31; p=0.009), corticosteroids (21.0% vs. 37.0%; aOR 2.20, 95% CI 1.21 to 4.02; p=0.010), or multiple flare treatments (17.6% vs. 45.4%; aOR 4.10, 95% CI 2.20 to 7.67; p<0.001). Use of intra-articular corticosteroids increased modestly from a low baseline (1.7% vs. 8.3%; aOR 5.53, 95% CI 1.15 to 26.7; p=0.033). There was no significant difference in the use of NSAIDs (31.9% vs. 31.5%; aOR 1.18, 95% CI 0.61 to 2.28; p=0.63).

The proportion of patients initiated and/or up-titrated on ULT prior to discharge increased markedly following implementation, from 17.6% to 62.0% (aOR 7.69, 95% CI 4.12 to 14.4; p<0.001). After implementation, more patients were provided with gout-specific management recommendations on discharge (58.8% vs. 86.1%; aOR 4.33, 95% CI 2.21 to 8.48; p<0.001). Documented evidence of disease education provision prior to discharge was low in both cohorts (22.7% vs. 22.2%; aOR 1.00, 95% CI 0.53 to 1.90; p=0.99).

Table 18. Outcomes during hospitalisations for gout flares, comparing the pre- and post-implementation cohorts

Outcome	Pre-implementation N=119	Post-implementation N=108	Odds ratio (95% CI)	p-value
Rheumatology input during hospitalisation	65 (54.6%)	82 (75.9%)	2.48 (1.37 to 4.52)	0.003
Serum urate level performed	79 (66.4%)	100 (92.6%)	6.32 (2.75 to 14.5)	<0.001
Joint aspiration performed	23 (19.3%)	51 (47.2%)	3.44 (1.88 to 6.27)	<0.001
Flare treatment prescribed	111 (93.3%)	106 (98.1%)	4.46 (0.91 to 21.8)	0.065
NSAIDs	38 (31.9%)	34 (31.5%)	1.18 (0.61 to 2.28)	0.63
Colchicine	74 (62.2%)	86 (79.6%)	2.30 (1.23 to 4.31)	0.009
Corticosteroids	25 (21.0%)	40 (37.0%)	2.20 (1.21 to 4.02)	0.010
Multiple flare treatments prescribed	21 (17.6%)	49 (45.4%)	4.10 (2.20 to 7.67)	<0.001
Intra-articular steroid injection	2 (1.7%)	9 (8.3%)	5.53 (1.15 to 26.7)	0.033
Disease education documented prior to discharge	27 (22.7%)	24 (22.2%)	1.00 (0.53 to 1.90)	0.99
ULT initiated and/or titrated during hospitalisation	21 (17.6%)	67 (62.0%)	7.69 (4.12 to 14.4)	<0.001
Gout recommendations documented on discharge	70 (58.8%)	93 (86.1%)	4.33 (2.21 to 8.48)	<0.001
Recommendation to initiate and/or titrate ULT after discharge	18 (15.1%)	42 (38.9%)	3.26 (1.71 to 6.19)	<0.001
Recommendation for prophylaxis while titrating ULT	23 (19.3%)	13 (12.0%)	0.54 (0.26 to 1.15)	0.11
Recommendation for target serum urate level	13 (10.9%)	28 (25.9%)	2.56 (1.23 to 5.36)	0.012
Recommendation for primary care follow-up	53 (44.5%)	43 (39.8%)	0.82 (0.48 to 1.41)	0.47
Recommendation for rheumatology/gout clinic follow-up	11 (9.2%)	73 (67.6%)	19.8 (9.34 to 42.0)	<0.001

Odds ratios from logistic regression models are shown, with adjustment for age and sex.

Outcomes after hospitalisations

94/119 (79.0%) and 97/108 (89.8%) patients in the pre- and post-implementation cohorts, respectively, had primary care follow-up data available to facilitate analyses of post-discharge outcomes (Table 19). By 6 months post-discharge, 91/97 (93.8%) of the post-implementation cohort were prescribed ULT, compared with 61/94 (64.9%) pre-implementation (aOR 7.68, 95% CI 3.02 to 19.6; p<0.001). When restricted to patients not receiving ULT prior to hospitalisation, the proportion of patients who newly initiated ULT in hospital or within 6 months of discharge increased markedly after implementation, from 49.2% to 92.3% (aOR 11.5, 95% CI 4.36 to 30.5; p<0.001). Of all patients receiving ULT by 6 months, 57/61 (93.4%) and 90/91 (98.9%) of the pre- and post-implementation cohorts, respectively, were prescribed allopurinol. There was no significant difference in prophylaxis use between patients newly initiating ULT in the pre- vs. post-implementation periods (25.0% vs. 29.2%; aOR 1.12, 95% CI 0.42 to 2.98; p=0.81).

Following implementation, more patients achieved a serum urate ≤360 micromol/L within 6 months of discharge: 10/94 (10.6%) pre-implementation vs. 26/97 (26.8%) post-implementation (aOR 3.04; 95% CI 1.36 to 6.78; p=0.007). There was no significant difference in the proportion of patients achieving a serum urate ≤300 micromol/L within 6 months (5.3% pre-implementation vs. 13.4% post-implementation; aOR 2.65, 95% CI 0.89 to 7.84; p=0.079). Mean reductions in serum urate at 6 months, relative to baseline, were 29.7 micromol/L pre-implementation vs. 96.8 micromol/L post-implementation (aβ -64.3; 95% CI -128.0 to -0.64; p=0.048). The mean number of serum urate levels performed within 6 months increased from 0.5 tests pre-implementation to 1.1 tests post-implementation (aβ 0.55; 95% CI 0.14 to 0.96; p=0.009).

79/97 (81.4%) of the post-implementation cohort were reviewed in the nurse-led, gout telephone clinic (median time to review: 12 days), while 16/97 (16.5%) patients received rheumatology outpatient follow-up within 6 months. Prior to implementation, 8/94 (8.5%) patients received rheumatology outpatient follow-up within 6 months of discharge.

The number of patients who re-attended ED and/or were re-admitted for gout flares within 6 months of discharge was 14/94 (14.9%) pre-implementation vs. 9/97 (9.3%) post-implementation (aOR 0.53, 95% CI 0.22 to 1.32; p=0.18). Survival curves for repeat hospitalisations are shown in Figure 46.

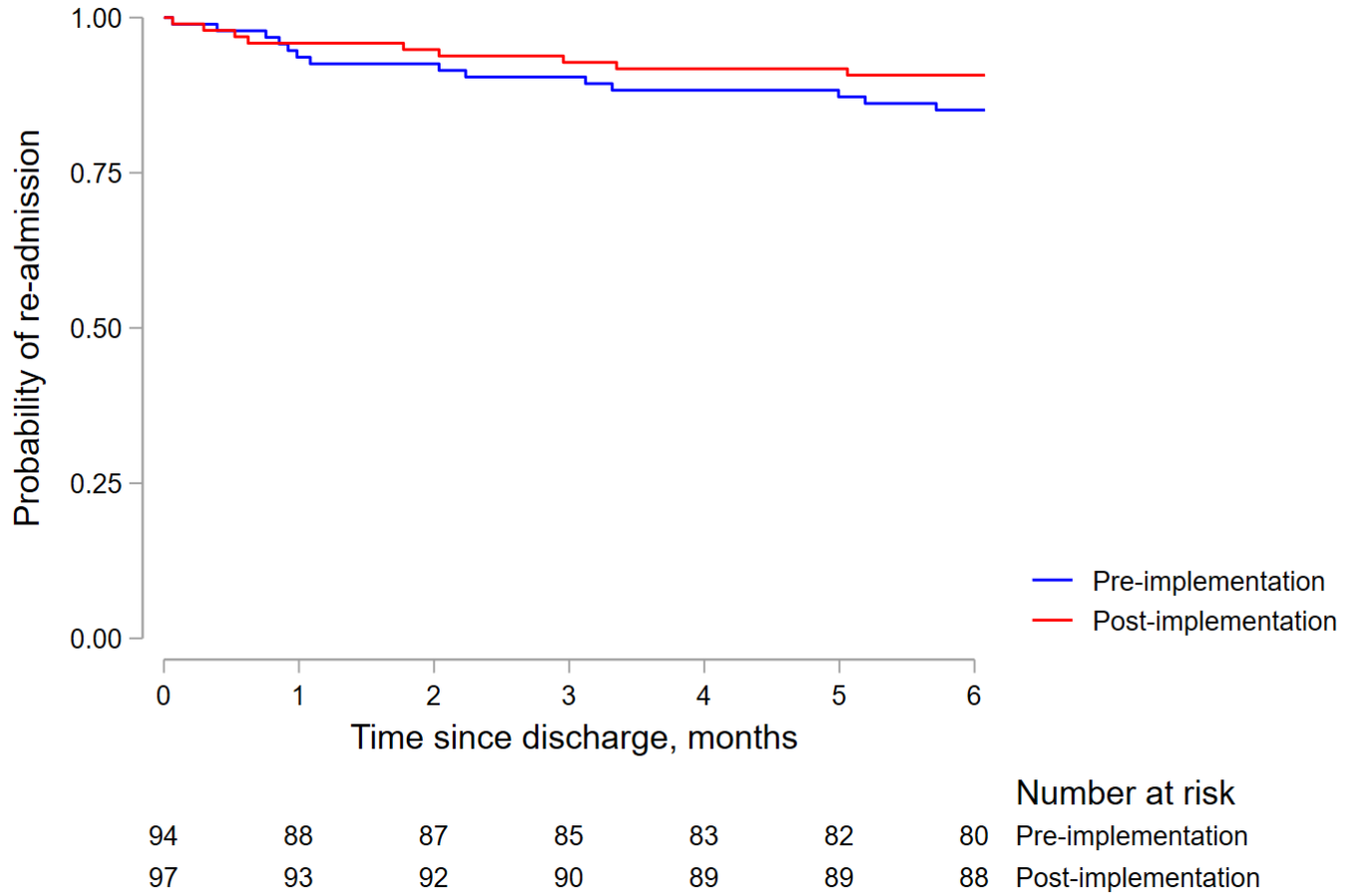
Further analyses were performed to explore the impact of the intervention on different subgroups of patients (Figure 47, Figure 48, Figure 49, Figure 50). Odds of ULT initiation were significantly higher in the post-implementation than pre-implementation cohort, irrespective of age, sex, admission type, time of presentation, whether the gout diagnosis was pre-existing, or whether rheumatology input was sought during hospitalisation (Figure 47).

Table 19. Outcomes in the 6-month period after hospitalisations for gout flares, comparing the pre- and post-implementation cohorts

Outcome	Pre-implementation N=94	Post-implementation N=97	Odds ratio (95% CI)	p-value
Receiving ULT by 6 months	61 (64.9%)	91 (93.8%)	7.68 (3.02 to 19.6)	<0.001
ULT initiated in hospital or within 6 months of discharge				
Yes	32 (49.2%)	72 (92.3%)	11.5 (4.36 to 30.5)	<0.001
No	33 (50.8%)	6 (7.7%)		
Receiving ULT pre-admission	29	19		
Prophylaxis prescribed while initiating ULT				
Yes	8 (25.0%)	21 (29.2%)	1.12 (0.42 to 2.98)	0.81
No	24 (75.0%)	51 (70.8%)		
Not newly initiated on ULT	62	25		
Serum urate performed at least once within 6 months	30 (31.9%)	56 (57.7%)	2.88 (1.58 to 5.25)	0.001
Serum urate ≤360 micromol/L within 6 months	10 (10.6%)	26 (26.8%)	3.04 (1.36 to 6.78)	0.007
Serum urate ≤300 micromol/L within 6 months	5 (5.3%)	13 (13.4%)	2.65 (0.89 to 7.84)	0.079
Rheumatology outpatient clinic within 6 months	8 (8.5%)	16 (16.5%)	2.08 (0.82 to 5.28)	0.12
Gout telephone clinic within 6 months	N/A	79 (81.4%)	N/A	N/A
Re-presented to hospital within 6 months	14 (14.9%)	9 (9.3%)	0.53 (0.22 to 1.32)	0.18

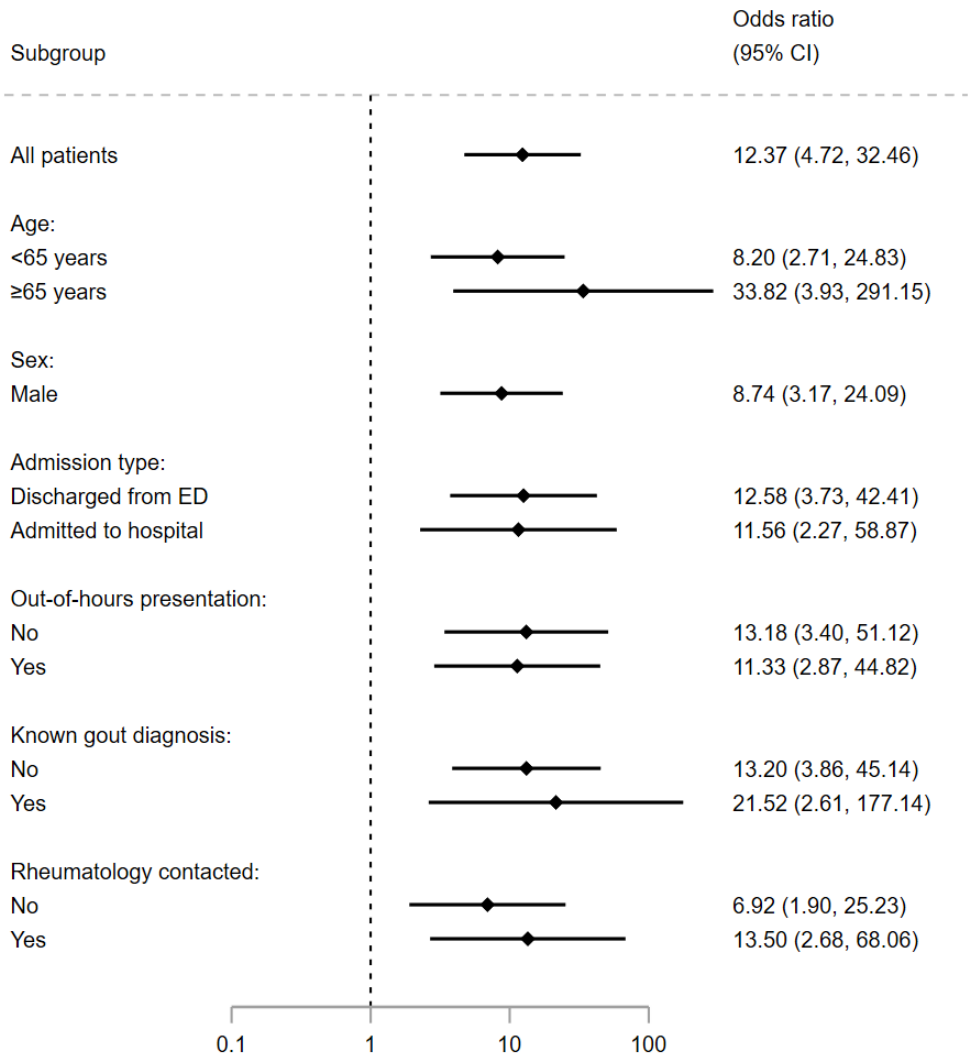
Odds ratios from logistic regression models are shown, with adjustment for age and sex. A gout telephone clinic was established as part of the intervention package, and therefore was not available to patients in the pre-implementation cohort.

Figure 46. Survival curve showing the probability of re-attendance at ED and/or re-admission to hospital for gout flares following discharge



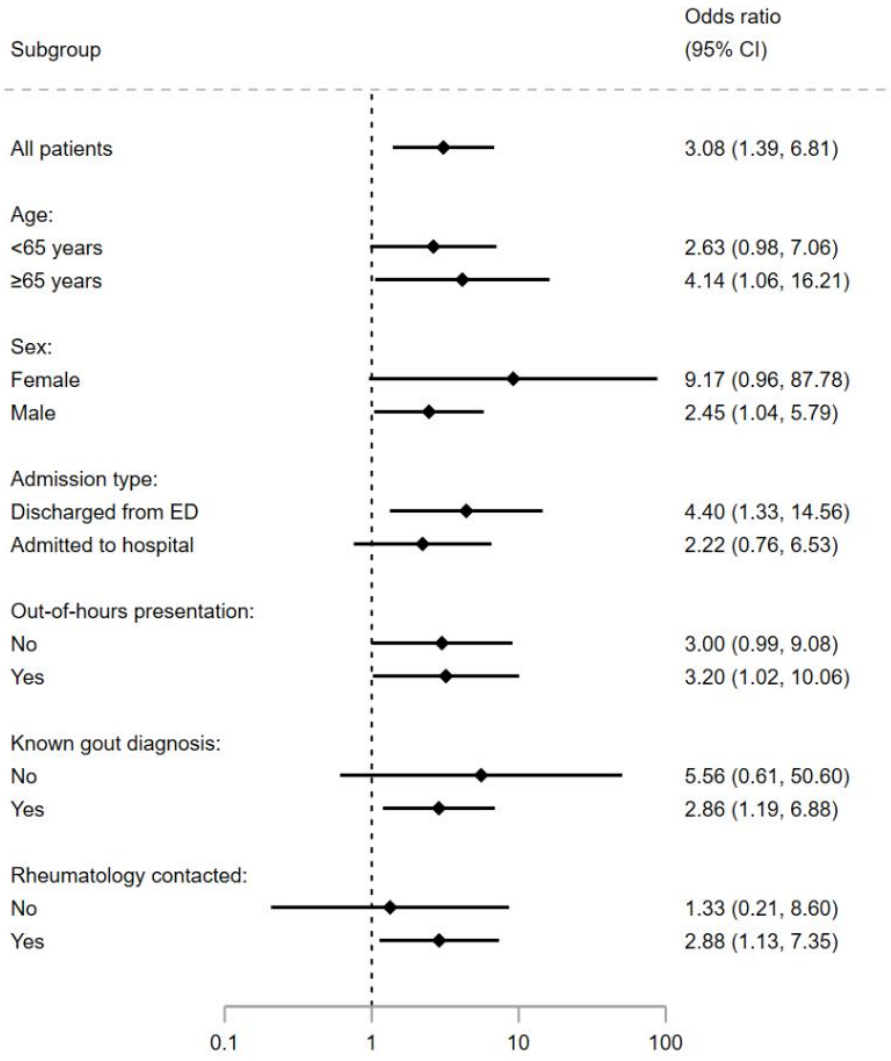
Pre-implementation (blue line) and post-implementation (red line) cohorts are shown. The number of patients at risk at each time point is shown in a risk table.

Figure 47. Odds of being initiated on ULT during hospitalisation or within 6 months of discharge in the post-implementation cohort relative to the pre-implementation cohort



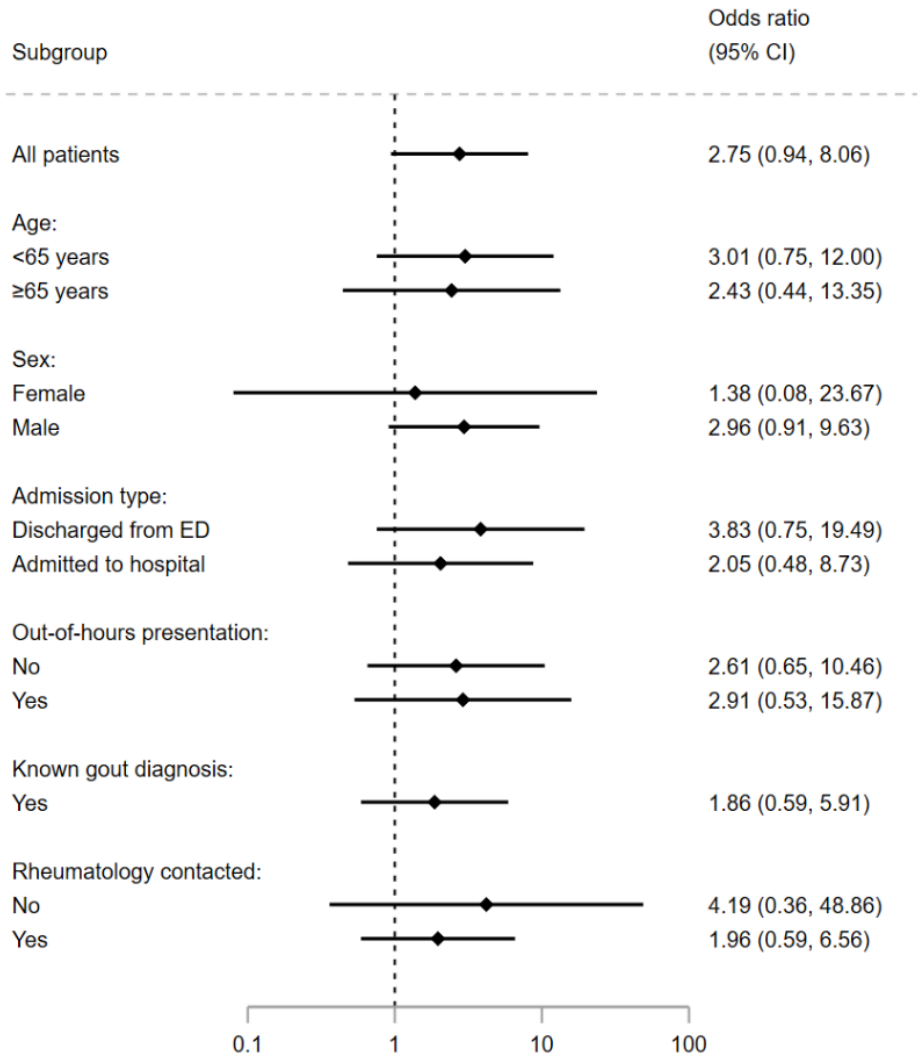
Outputs shown are from univariable logistic regression models. Female sex is omitted, as all female patients were receiving ULT by 6 months post-discharge.

Figure 48. Odds of achieving a serum urate ≤360 micromol/L within 6 months of discharge in the post-implementation cohort relative to the pre-implementation cohort



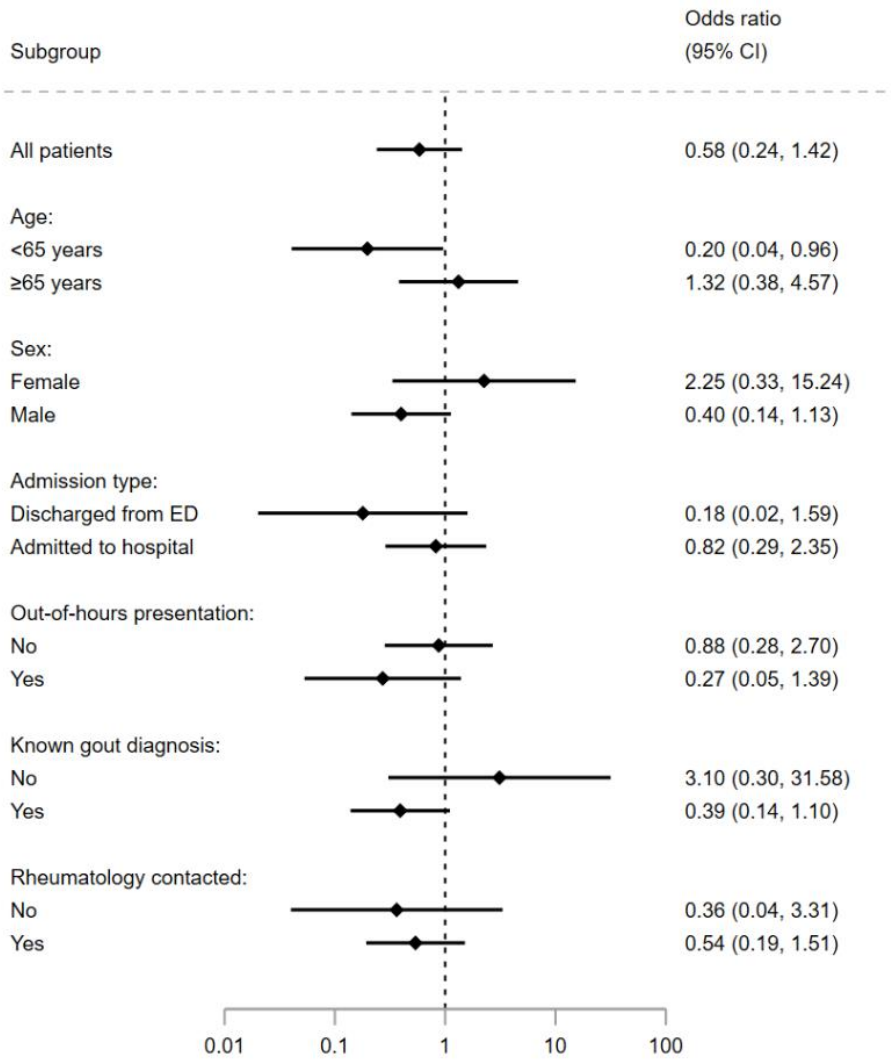
Outputs shown are from univariable logistic regression models.

Figure 49. Odds of achieving a serum urate ≤300 micromol/L within 6 months of discharge in the post-implementation cohort relative to the pre-implementation cohort



Outputs shown are from univariable logistic regression models.

Figure 50. Odds of re-attending hospital for a gout flare within 6 months of discharge in the post-implementation cohort relative to the pre-implementation cohort



Outputs shown are from univariable logistic regression models.

8.8 Discussion

Following implementation of a strategy designed to optimise care during gout hospitalisations, more than 90% of ULT-naïve patients were initiated on ULT - nearly double the pre-implementation baseline. Many other aspects of care improved, including urate target attainment and post-discharge follow-up. The initiation of ULT during flares did not increase recurrent hospitalisations, supporting the use of ULT in this setting.

Our intervention was modelled on one shown to be highly effective in a primary care setting. In a large RCT in the UK, nurse-delivered patient education and treat-to-target ULT resulted in 95% of patients achieving serum urate targets within 1 year, compared with 26% with usual care.[31] Flare frequency, tophi, and quality of life all improved, and the intervention was shown to be cost-effective. We adapted this intervention for implementation in a hospital setting. As well as optimising care during patients' hospital stays, we established a nurse-led, post-discharge clinic to facilitate disease education and provide advice on ULT optimisation. This appointment was delivered as a single telephone appointment, recognising that in-person appointments can be challenging for patients to attend after hospitalisations for flares. Care was then handed over to patients' primary care teams for ongoing management.

Following implementation of this strategy, many aspects of hospital gout care improved: joint aspirations increased; serum urate levels were performed more frequently; use of guideline-recommended flare treatments increased (particularly combination therapy); and gout-specific follow-up was provided to more patients. Rheumatologist input also increased: specialist support for frontline clinicians was felt to be an important facilitator of optimal gout care during our stakeholder consultations,[170] supported by previous analyses demonstrating that rheumatology input associates with improvements in care for hospitalised gout patients.[73,180,182,183]

The biggest change observed following implementation of our strategy was increased initiation of ULT. By 6 months post-discharge, 94% of patients had been prescribed ULT. This is comparable to ULT initiation rates in the Nottingham primary care-based study,[31] and substantially better than the 61% of patients who were receiving ULT within 12 months of hospitalisation in a recent UK-wide analysis.[193] In particular, there was a 3-fold increase in the proportion of patients initiating and/or up-titrating ULT prior to discharge. There has been extensive debate around the relative benefits and harms of early ULT initiation (vs. deferred initiation of ULT after flare resolution), with international guidelines varying widely in this regard.[6,8,35] We advocated for early ULT initiation for several reasons. First, hospitalisations provide unique opportunities for clinicians to optimise care for people with long-term conditions, such as gout. Second, accumulating evidence suggests that upfront initiation of ULT does not prolong or worsen intercurrent flares, provided it is initiated alongside flare treatment.[41,43,195,196] Third, earlier initiation of ULT leads to more timely reductions in serum urate levels.[41,43,195,196] Finally, this approach can help to mitigate a breakdown in

communication between secondary care and primary care, whereby post-discharge recommendations to initiate ULT are not acted on.[73]

Despite the marked increase in ULT initiation during flares, we did not observe an increase in hospitalisations for recurrent flares after implementing this strategy. These real-world data support those obtained from trial settings.[41,43,195,196] Although not statistically significant, proportionately fewer re-hospitalisations occurred after implementation, relative to before (37.6% relative reduction; 5.6% absolute reduction), suggesting a potential for benefit with this approach. One contributory factor might have been the post-discharge follow-up appointment, which gave patients an opportunity to have any ongoing symptoms reviewed. Advice on flare management was provided within this appointment, empowering patients to self-manage flares. With longer follow-up, there is the potential for more admissions to be prevented with this strategy: observational data show that ULT associates with a significantly reduced risk of recurrent hospitalisations from 12 months after initiation, particularly when urate targets are attained.[193] Future work will also help to determine whether primary care workload is also reduced following implementation of better hospital gout care.

Prior to implementation, only 10% of patients achieved a serum urate ≤360 micromol/L within 6 months of discharge. After implementation, urate target attainment more than doubled, to 26.8%. Despite this relative improvement, absolute levels of urate target attainment remained far below those seen in the Nottingham primary care trial (95% attainment by 12 months).[31] Similarly, target attainment was below that reported in the BSR National Audit of outpatient gout management by UK rheumatologists (45% attainment by 12 months),[5] and only modestly better than what was reported in a UK-wide analysis of post-discharge gout care (1,184/7,040 [16.8%] patients attaining urate ≤360 micromol/L within 12 months of hospitalisation[193]). There are several possible reasons for this. Follow-up in our study was relatively short at only 6 months. Patients in our study were all hospitalised for gout, and therefore are likely to represent a more severe cohort. Perhaps most importantly, in the Nottingham study there were an average of 17 study visits per participant over a 24-month period. In contrast, our gout follow-up clinic was delivered as a single telephone appointment, followed by handover of care to patients' primary care teams. Indeed, target attainment in our study was comparable to that seen in the usual care group of the Nottingham trial (26.8% vs. 26.2%, respectively). Thus, our findings strongly suggest that our intervention, while effective at facilitating ULT initiation, is insufficient for the majority of people hospitalised for gout flares to achieve target urate levels.

There are several ways in which our intervention could be altered to promote urate target attainment. Rheumatologists could take greater ownership of hospitalised gout patients by providing outpatient follow-up until urate targets are achieved. Alternatively, training could be provided for healthcare professionals in primary care (e.g. nurses and/or pharmacists) to deliver optimal treat-to-target ULT, which was shown to be highly effective in the Nottingham study,[31] NOR-Gout study,[167] and many other studies.[79,197] Strategies could be modelled on other integrated care services, which proactively identify patients in hospital before

transferring them to primary care-based pathways with secondary care support, such as fracture liaison services.[198] Future strategies should also encourage adherence to ULT, which although not assessed in our study, is often sub-optimal and may have contributed to our finding of infrequent urate target attainment despite high levels of ULT initiation;[199] this could incorporate patient education programmes, self-management tools, and point-of-care urate testing.[198]

A key strength of our study was the close involvement of stakeholders, patients and methodologists when developing our intervention and implementation strategy. Our intervention was based on best practice care from national and international gout management guidelines,[6-8,35] and was modelled on the highly successful intervention used in the Nottingham primary care trial.[31] We adopted a multi-faceted implementation strategy to maximise intervention uptake. This incorporated several implementation strategies recommended in the ERIC guidance,[192] including digital enablers, study champions, education sessions and clinician feedback. Adopting a multi-faceted strategy is particularly important when implementing complex interventions in healthcare settings. For example, an implementation strategy involving only educational sessions for clinicians in EDs may not succeed, given the challenges of reaching all frontline staff.

Our study also had limitations. Follow-up was only 6 months, which may have been too short to ascertain differences in post-discharge outcomes such as urate target attainment and recurrent hospitalisations. While the numerical reductions in re-hospitalisations we observed following implementation of our strategy might have been clinically meaningful, our study was underpowered to detect significant differences in these relatively rare events. Use of prophylaxis against flares whilst initiating/titrating ULT remained infrequent despite the intervention, particularly when compared with national data,[5] and future studies should encourage the use of prophylaxis, given the benefits on flare reduction.[6] Data on comorbidities and other clinical outcomes (e.g. flare frequency or tophus burden) were unavailable. We included all hospitalisations where gout was deemed the likely diagnosis; crystal analysis and rheumatologist input were recommended, but not mandated. These pragmatic inclusion criteria reflect real-world clinical practice, although there remains a potential for diagnostic misclassification. Additionally, we utilised a retrospective comparator, rather than a prospective comparator. This was an *a priori* decision, to reflect resource availability and the service evaluation remit of this project; however, it is possible that some of the changes observed may represent changes in practice over time, rather than a direct result of the intervention (e.g. changes in service delivery during the COVID-19 pandemic). Our findings should therefore be seen as exploratory, rather than definitive. Finally, as our analyses were conducted at a single UK centre, the findings cannot be assumed to be generalisable to other healthcare settings.

In conclusion, after implementing a strategy designed to optimise care for people hospitalised with gout flares, more than 90% of patients were initiated on ULT. In the context of a single, nurse-led follow-up appointment, relative improvements in urate target attainment were

observed; however, for the majority of hospitalised gout patients to achieve target urate levels, better in-hospital gout care needs to be accompanied by strategies that embed and support optimisation of ULT in primary care.

8.9 Qualitative interviews

In order to obtain more granular feedback on the pathway I had implemented at King's College Hospital, I devised a series of semi-structured interviews with my PhD supervisor, Dr Joanna Hudson. My goal was to gather feedback from stakeholders on the implementation of the pathway, which I would not otherwise have been able to capture from quantitative data alone.

I developed a series of semi-structured interview questions (see appendix) for patients and healthcare professionals who had received or delivered care, respectively, using the pathway. A semi-structured format was chosen to ensure important topics were covered, whilst also providing flexibility to the interviewer.

With my supervisory team, I discussed who should conduct the interviews. We agreed that it would be reasonable for me to conduct the patient interviews, as I had detailed knowledge of the pathway and had not had prior contact with patients who were being interviewed. In contrast, I had a close working relationship with many of the healthcare professionals who had treated patients using the pathway. My direct involvement in interviewing these professionals would have made it challenging to obtain an objective assessment of the pathway's implementation. To help overcome this, I collaborated with Maria de la Puenta Rojas, a psychology MSc student, who conducted the interviews with healthcare professionals. Maria was not known to any of the healthcare professionals prior to the interviews, and had a qualitative methodology background, which enabled her to perform thematic analysis on the transcribed interview content.

8.9.1 Methods

Permission to qualitatively evaluate the care pathway was obtained under the remit of service evaluation from King's College Hospital.

Recruitment

Consecutive patients who had been treated for gout flares at King's College Hospital between April 2022 and June 2022 were identified for approach from their medical notes. A target recruitment of 5-10 patients was defined, as this is deemed appropriate to optimise an intervention during its initial development and testing.[111] Likewise, healthcare professionals were identified for recruitment from either: i) the rheumatology department, who provide support in managing patients with gout flares, or ii) the emergency medicine, acute and general medicine departments, who had evidence of administering care for patients with gout flares following implementation of the pathway. It was not possible to identify primary care clinicians from the local care records for approach for interview, and thus this aspect of the care pathway was not evaluated. All healthcare professionals identified as having managed patients with gout flares during the period of January 2023 – March 2023 were approached for interview via email or verbally. A target sample size of 10-15 healthcare professionals was

defined, as this is considered an appropriate sample size for qualitative interviews.[200] Patients and healthcare professionals consented to being interviewed, and were aware that all personal identifiable information would be removed from written transcription of the interviews and recordings deleted once transcribed.

Data collection

An interview topic guide was devised and followed for the interviews (see appendix). Interviews were conducted via Microsoft Teams or via telephone, and were audio-recorded and transcribed using Microsoft Teams transcription software. For the patient user engagement, 50% were conducted via telephone and, on these occasions, field notes were taken. For transcriptions, their accuracy was checked against the recordings. Interview durations ranged from 30 minutes to 1 hour.

Data analysis

As discussed in my general methodology section (Chapter 2), patient interviews were examined to evaluate patients' reflections on receipt of care, compared with that of the proposed implementation plan. Healthcare professional interviews were analysed by adhering to the principles of thematic analysis (see general methodology section, Chapter 2, for a more detailed description).

8.9.2 Patient feedback

A total of 14 patients were approached for interview, of whom ten consented. Table 20 summarises the patient feedback, indicative quotes, and key learning points identified from the interviews. Patient experiences were grouped according to in-hospital experiences and post-discharge experiences.

Table 20. Patient experiences of the pathway and key learning points

Stakeholder experiences	**Example quotes**	**Key Learning Points**
In-hospital experiences		
Education on disease management: • Variability in the amount and quality of information provided. • Lack of clarity on the need to attend for monthly blood tests whilst titrating ULT.	*"I am happy with what's been provided and to be quite honest, you see, if I didn't get the information then I'd be in limbo."* *"I wasn't given much verbal information on allopurinol during my admission."*	• Congruent with quantitative findings – e.g. disease education during hospital stays was poorly documented in the medical records, which likely reflects implementation challenges.

	"*I don't remember being told about the need for blood tests out of hospital, but I'm happy to do them if needed."*	• Need to explore how equitable education on disease management can be achieved for all in-patients (e.g. via information leaflets). • Consider the use of "action planning" to improve clarity on need for blood tests.[201]
Post-discharge experiences		
Confidence in the self-management of flares: • Some patients reported greater confidence and a reduced likelihood of attending the emergency department, whilst others reported decreased confidence levels and a need to use urgent care if a flare occurred.	*"I am much happier with how to manage things by myself now."* *"If I had a further flare and it was bad, I would come to the hospital – if I need to come, I need to come"*	• Congruent with quantitative findings – there was not a statistically significant difference in re-hospitalisations for gout flares post-implementation, relative to pre-implementation. • Consider use of "action planning" to provide clear steps on the management of flares and when urgent care is needed.[201]
Diet • Perception that gout is caused by diet and thus management via dietary modification is used, reducing the perceived need for ULT.	*"It all boiled down to my diet."* *"I ran away from fish and organ meat. I don't take any now. So I've been trying to be more vegetarian. I'm not there yet, but more most of my diet now are just greens."* "*My long-term goal is to change my lifestyle to see if I can stop allopurinol."*	• Need for greater emphasis on the role of ULT for the management of gout. • Adopt the necessity concerns framework from the medication adherence literature.[202]
Adherence	*"The doctor told me that [allopurinol] is probably*	• Use of necessity concerns framework

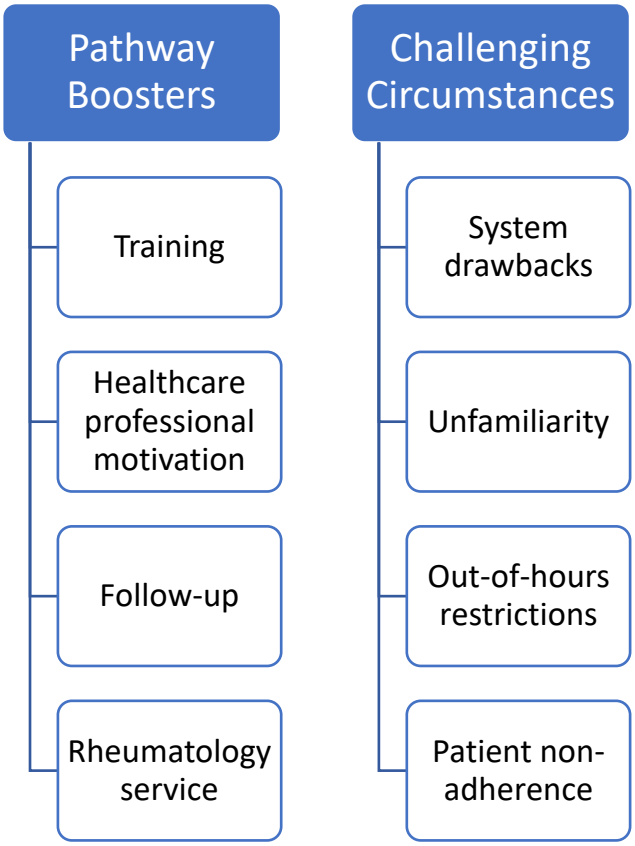
• No practical barriers were identified other than the effort needed to attend blood tests. • Minority of patients reported a concern of being on medications long-term for their gout; however, a majority of patients experienced benefits from doing so.	*going to be a kind of forever medication and I got scared about that. I don't know. I'm just very scared of taking tablets."* *"I'm happy to do this as it helps the pain and swelling."*	from the medication adherence literature to reinforce benefits of ULT, relative to costs.[202] • Explore in more detail what specific concerns patients have about long-term ULT use.
Nurse telephone review • Valued by all patients, including the method of telephone delivery. • Helped patients understand the need for ULT, dose titration, and flare treatments	*"I felt more informed [about my gout] and more able to manage."* *"It was nice having someone explain the information clearly to me."*	• No specific revisions needed to the format of the interview.

8.9.3 Healthcare professional feedback

Twelve healthcare professionals from the rheumatology, emergency medicine, acute and general medicine departments were initially invited to participate in the interviews. There was a more limited response than expected to the initial invitation emails; therefore, a gift card (£10) was offered to healthcare professionals who participated in the interviews. Six of 12 invited healthcare professionals (50%) completed a semi-structured interview: 3 rheumatology doctors, 1 rheumatology nurse specialist, and 2 ED doctors.

From Maria's thematic analysis of the transcribed healthcare professional interview data, two overarching themes and four nested sub-themes were identified, as shown in Figure 51, to reflect factors that facilitated and restricted the implementation of the pathway. Each theme and sub-theme are summarised below.

Figure 51. Themes and sub-themes identified in the thematic analysis of healthcare professional interviews



Overarching theme 1: Pathway Boosters

This overarching theme ("Pathway Boosters") incorporated a wide range of factors that healthcare professionals perceived to be facilitators of implementation of the gout pathway. The overarching theme consisted of four sub-themes: training; healthcare professional motivation; follow-up; and the rheumatology service.

Sub-theme 1: Training

Healthcare professionals believed that training in the gout treatment pathway provided them with useful information on gout management, which allowed them to adhere to the pathway appropriately.

> *"That teaching was really good. I think he did about an hour on the gout pathway and then he did an hour on general rheumatology…. Before we did this pathway, I didn't realise you could give allopurinol at the same time as your acute treatment, so that's educational for me."* (healthcare professional (HCP) 4, Emergency doctor)

> *"He did a presentation to our rheumatology weekly teaching meeting about the pathway and how it was intended to be used. So that was quite useful introduction to the pathway…. it was very good to have that introduction before we started using it*." (HCP3, Rheumatology doctor)

Additionally, healthcare professionals mentioned that the setting in which the training was provided was appropriate.

> "*We have got protected teaching. The mornings are the least busy times. There are not many patients, so actually there's no obstacle [to attending teaching] then."* (HCP5, Emergency doctor)

Sub-theme 2: Healthcare professionals' motivation

Healthcare professionals mentioned that they were motivated to continue using the pathway, as they considered it helpful when treating patients with gout. In particular, the inpatient gout notifications were felt to be a key component of the pathway, as they provided a means of communicating the need for rheumatology review and follow-up. The gout electronic order sets were also felt to be helpful. The healthcare professionals expressed their desire to learn about the pathway, and then, in turn, helped to disseminate this learning to other staff members.

> "*I am more than happy to help with the intra-departmental education, like hanging the pathway on the wall, spreading the word, and doing some [training for] the other doctors*." (HCP5, Emergency doctor)

Sub-theme 3: Follow-up

The healthcare professionals considered the follow-up provided as part of the pathway as crucial to optimising gout management. Specifically, rheumatologists perceived the follow-up appointment as the most appropriate setting to educate patients on their condition and its management.

> "*Either we may not have enough time [during a hospitalisation] or we don't explain it well enough, or the patient doesn't understand it because they haven't looked so much…. It's really useful to then have that follow-up appointment with a nurse, and have the appropriate time allocated to speak about what the condition is, how to prevent it, and how to do things going forward."* (HCP2, Rheumatology doctor)

Sub-theme 4: Rheumatology Service

Rheumatology clinicians mentioned that they felt that rheumatology specialist input was essential to providing optimal management to patients with gout. Additionally, clinicians from other specialities found the rheumatology team to be approachable when referring patients.

"…and to be honest, rheumatology is one of the most helpful specialties. Actually, they're always very keen on seeing the patient and very constructive." (HCP5, Emergency doctor)

Overarching theme 2: Challenging circumstances

The second overarching theme describes a series of barriers that healthcare professionals faced when trying implement the gout treatment pathway. Within this overarching theme, there was four sub-themes: system drawbacks; unfamiliarity; out-of-hours restrictions; and patient non-adherence.

Sub-theme 1: System drawbacks

Healthcare professionals referred to a series of complexities related to the healthcare system itself, which were barriers to implementation of the pathway. This included having to train all clinicians in how to use the new gout pathway; made more challenging by the frequent turnover of staff, particularly within the ED.

"In hospital, there are thousands of employees; hundreds within each department; and the changeover of staff will happen every 4-6 months [depending on the department]. So, keeping people up-to-date will be difficult…" (HCP2, Rheumatology doctor)

Additionally, although many healthcare professionals reported sufficient knowledge to treat gout, they perceived system workload as an obstacle to providing patients with the standard of care that they would have liked to have provided.

"…patients are in the corridors, I'm literally running around, trying to sort out all the things. All the juniors are coming to discuss patients and stuff. So, I don't think I have enough time to slow down to really discuss that…" (HCP5, Emergency doctor)

Technological errors were also deemed to have interfered with implementation of the pathway. For example, patients were not always notified about their appointments, and there were sometime delays in GPs receiving the clinic letters. Additionally, some staff members reported having difficulty opening the pathway on the Trust intranet.

"*Sometimes [the patients] were not expecting the call, but that might be due to an admin booking system [error].*" (HCP1, Rheumatology nurse)

"*I was trying to access [the pathway] today through the King's website, and I was struggling to get through and access the link*." (HCP3, Rheumatology doctor).

Suggestions were provided by healthcare professionals on how to address some of the system drawbacks:

- Repeat training for healthcare professionals periodically at Trust inductions and services meetings, both online and in-person;
- Make the pathway available in different workspaces and platforms;
- Have an online recording of the training available to disseminate to new staff;
- Provide patients with written documentation, explaining that they are going to be referred to the pathway and what this process entails;
- Encourage patients to book follow-up with their GP;
- Perform periodic assessments of how the pathway is performing, to check for implementation issues;
- Programme an alert in the Trust EHR software to notify the team when patients are hospitalised with gout flares.

Sub-theme 2: Unfamiliarity

Healthcare professionals also mentioned aspects of the pathway that they were not familiar with. This included uncertainty about how to aspirate joints; how to provide patients with information on medications used to treat gout; and where to access the pathway on the Trust intranet. One ED clinician also mentioned being entirely unaware of the pathway.

> "*…I don't have understanding the long-term management of gout, and how to optimise urate levels and those kinds of things. We don't really have much mind space for that*." (HCP5, Emergency doctor)

> *"I'm still not quite sure where to look for [the pathway] on the King's webpage…so when I want to access the pathway, I guess I go into clinical guidelines, and I look under documents…. I mean, personally, I don't really need the guideline, cause I kind of know what to do with my gout patients…*" (HCP6, Rheumatology doctor)

Some healthcare professionals offered potential suggestions to address aspects of the pathway that they (and others) might be unfamiliar with:

- Educate staff on where to find the pathway;
- Encourage senior staff to disseminate the pathway with their junior staff;
- Attract staff to training sessions with food;
- Emphasise the effectiveness of the pathway, to encourage staff to engage with it;
- Train emergency doctors on how to perform joint aspirations;
- Educate nurses and phlebotomists about the gout order sets;
- Add the urate blood test to the ED order set;
- Add the BSR logo on the pathway flow chart.

Sub-theme 3: Out-of-hours restrictions

Healthcare professionals referred to barriers to implementation of the pathway that related to out-of-hours restrictions. For example, in ED they were unable to provide patients with

some of the medications recommended in the pathway (e.g. allopurinol) prior to discharge. Instead, patients needed to return to hospital to collect the medications. Additionally, the local biochemistry laboratory would not process synovial fluid crystal samples out-of-hours, resulting in patients needing to wait for their results. Emergency doctors also mentioned difficulties in performing joint aspirations out-of-hours, either because they did not feel comfortable performing the procedure or because the orthopaedics team rejected their request to perform the procedure.

> "*If the outpatient pharmacy isn't open at the time that you see the patient, that means they can't go and get their medication straight away."* (HCP3, Rheumatology doctor)

> *"If it's after 9:00 PM, the medical team aren't happy to do the joint aspiration... In theory, I think orthopaedics are meant to…they usually say no, not us… and if you aspirate a joint out-of-hours, you're stuck with the fluid."* (HCP4, Emergency doctor)

Some potential suggestions were offered to address out-of-hours restrictions:

- Clarify how the pathway works out-of-hours in the ED;
- Familiarise the orthopaedics team with the pathway;
- Train doctors in how to analyse synovial fluid for crystals;
- Inform patients to come back to the department to collect their medication;
- Order a prescription for delivery for patients that live faraway.

Sub-theme 4: Patient non-adherence

Healthcare professionals also considered that patients' belief systems influenced treatment adherence and/or affected the success of implementation of the pathway.

> "*...and especially with young people, older people, sometimes there's denial; I don't want to take tablets for the rest of my life…I had one patient say to me 'better the devil you know than the angel you don't know', referring to taking medication."* (HCP1, Rheumatology nurse)

Suggestions offered to tackle patient non-adherence included:

- Providing patients with written educational information;
- Reinforce education on allopurinol with an additional follow-up appointment;
- Provide emergency doctors with a refresher session on the gout patient education.

8.9.4 Discussion

The feedback received from patients and healthcare professionals provided valuable information on the implementation of the pathway, which I would not have been able to gather from my quantitative data alone.

It was rewarding to hear that patients were satisfied with the care they had received under the pathway, and that they felt more confident in managing their gout as a consequence. Patient feedback highlighted that the fidelity of the intervention during patients' admissions had been variable, which may relate to differing levels of confidence in managing gout amongst frontline healthcare professionals and/or familiarity with the pathway. However, the involvement of the rheumatology team had been a key facilitator in "standardising" the quality of gout care that patients had received during and after their admission. In particular, patients were consistently happy with the nurse-led, post-discharge review, which provided them with an opportunity to go through important information about their condition, and provided clarity on preventative urate-lowering medications and titration. These data corroborate the findings of several other studies that have reported improved outcomes when inpatient rheumatology consultation was obtained during gout hospitalisations.[73,179-184]

Similarly, healthcare professionals from multiple specialties found the pathway helpful when treating patients for gout. They valued the training provided on the pathway, and felt more motivated to improve the care they offered to patients with gout as a consequence. They considered the digital enablers I developed as part of my implementation strategy helpful, such as the electronic order sets and eNotification system. Healthcare professionals emphasised that the nurse-led, follow-up appointment was an ideal environment through which to educate patients on the management of gout.

Importantly, the interviews also highlighted several barriers to effective implementation of the pathway. There was inconsistency around the delivery of education to patients during their hospital stays, despite being recommended in the pathway. This may relate to inadequate documentation of education having been provided; however, the lack of improvement following implementation of the pathway suggests additional changes are needed to try and overcome this barrier. This could include the provision of written information to all patients (e.g. via the pharmacy department on receipt of discharge medications). Importantly, the nurse-led post-discharge review was a key "backstop" in ensuring most patients received disease education after discharge from hospital.

From a patient perspective, despite emphasising the importance of urate-lowering medications in improving long-term disease control, many patients remained focused on dietary modification, for which the evidence base is limited. Additionally, some patients reported concerns with taking long-term preventative treatments for their gout. One potential solution to try and address these concerns would be to include training on the necessity concerns framework for clinicians reviewing gout patients. The necessity concerns

framework postulates that adherence to treatment is influenced by the balance between judgements of personal need for the treatment (necessity beliefs) and concerns about the adverse effects of taking the treatment.[203] Interventions to improve adherence are often more effective when they are tailored to the individual beliefs and concerns of the patients.[203] This is particularly relevant for gout, which has a lower adherence rate than many other chronic conditions.[56] The post-discharge review clinic would be an ideal setting in which to explore patients' beliefs and concerns about their treatment, and future iterations of my pathway could be strengthened by including training based upon the necessity concerns framework within these post-discharge reviews. The use of action planning could also facilitate behaviour change.[201] Using this approach, a patient has an *a priori*-determined plan to implement the necessary behaviour changes which, in the context of gout management, include optimising adherence to ULT, attending for blood tests, and managing flares.

The barriers identified by healthcare professionals may be interpreted within the context of the COM-B framework.[187] COM-B provides a useful framework for understanding behaviours, and identifying what needs to happen to enact behaviour change. COM-B specifies three conditions that interact to generate a particular behaviour: capability (an individual's psychological and physical capability to perform the activity), motivation (an individual's willingness and decision to perform the activity), and opportunity (the physical and social elements outside the individual that influence their behavioural achievement).[187] My interviews demonstrated that most healthcare professionals were motivated to use the pathway after training, with a desire to improve care for their patients. Notwithstanding the challenges in delivering training to departments with high staff turnover (e.g. the emergency department), many healthcare professionals reported sufficient knowledge to deliver effective gout care after receiving training (capability). However, the interviews with healthcare professionals noted several barriers to following the pathway due to the system-wide issues (opportunity). These included heavy workload, technical errors in accessing the pathway, and obstacles related to out-of-hours restrictions. While some of these issues are difficult to address, an understanding of these barriers is essential for when I develop the pathway for wider implementation in other healthcare settings, as discussed in my final chapter.

It is also important to recognise the limitations of the qualitative approaches used. No formal qualitative analysis was performed on patient interviews, as the focus of the interviews was on user-centred design. A more in-depth thematic analysis may have provided the opportunity to interview more patients and probe them specifically on their adherence-related concerns in relation to the behavioural changes they needed to make (e.g. adherence to medications, attendance at blood tests, and appropriate management of flares). Furthermore, whilst 12 healthcare professionals were approached for interview, only half consented to be interviewed, of whom the majority were from a rheumatology background. Pragmatic limitations including time constraints prevented further recruitment, and data saturation was not achieved (i.e. the identification of no new barriers or facilitators to the

pathway).[200] With further time and resources, efforts could be made to recruit more healthcare professionals and, indeed, explore ways of identifying staff who did not implement the gout pathway, with an additional focus on recruiting primary care clinicians. This would likely prove beneficial in informing future adaptations to my pathway. Despite these limitations, the rich information gleaned from the interviews provides clear avenues to address in future revisions, as discussed in my next chapter.

8.10 Implementing the care pathway at other hospitals

In parallel to developing the hospital care pathway for King's College Hospital, I began adapting the pathway for implementation at other hospital sites. The aim of doing so was two-fold: firstly, it would help to improve care for hospitalised gout patients at other hospitals; and, secondly, it would outline a process for more widespread implementation of my pathway.

While many of the core components of the pathway remained unchanged at the other hospital sites (e.g. individualised patient education and early ULT initiation), I had to adapt several other aspects to the specific hospital site. Resource availability, in particular, was a key determinant of which in-hospital and post-discharge consultation arrangements were feasible in each hospital. In all cases, I worked closely with multiple stakeholders at each hospital site to adapt the pathway, and to develop an implementation strategy.

Due to the time required for pathway development and approval at each hospital site (at least 6 months), I made the pragmatic decision to adapt the pathway for use at other hospitals alongside implementation of the King's College Hospital pathway. As such, data on outcomes following implementation at King's College Hospital were not available to inform the adaptation process. While these data would have been helpful, it would not have been possible within my project timescale. Future adaptations will be able to benefit from these data, however.

8.10.1 Princess Royal University Hospital

Princess Royal University Hospital (PRUH) is the second major hospital site within King's College Hospital NHS Foundation Trust, alongside King's College Hospital. While the hospitals share many similarities (e.g. common IT infrastructure), there are several key differences: PRUH is smaller; has a sub-urban location; an older patient demographic; and fewer consultant rheumatologists, registrars and specialist nurses than King's College Hospital. Additionally, whereas at King's College Hospital I was able to directly oversee implementation of the pathway, this was less feasible at the PRUH. These differences made the PRUH an ideal site for me to evaluate how the pathway could be adapted and implemented.

Using the pathway and implementation framework I had developed for King's College Hospital, I collaborated closely with the rheumatology, acute medicine and ED teams at PRUH to adapt the pathway (Figure 52). There were unique challenges when implementing the pathway at the PRUH, which primarily reflected the availability of in-hospital rheumatology support. Three key differences between the PRUH pathway and the King's College Hospital pathway were:

- The recommendation to contact the rheumatology team for all hospitalised gout cases was changed to a recommendation that rheumatology should be contacted when advice was needed (e.g. diagnostic uncertainty). This change reflected resource

availability at the PRUH. Whereas at King's there are multiple rheumatology trainees who provide on-site cover until 10pm, at PRUH there is only one rheumatology registrar available, with no on-site, out-of-hours cover.

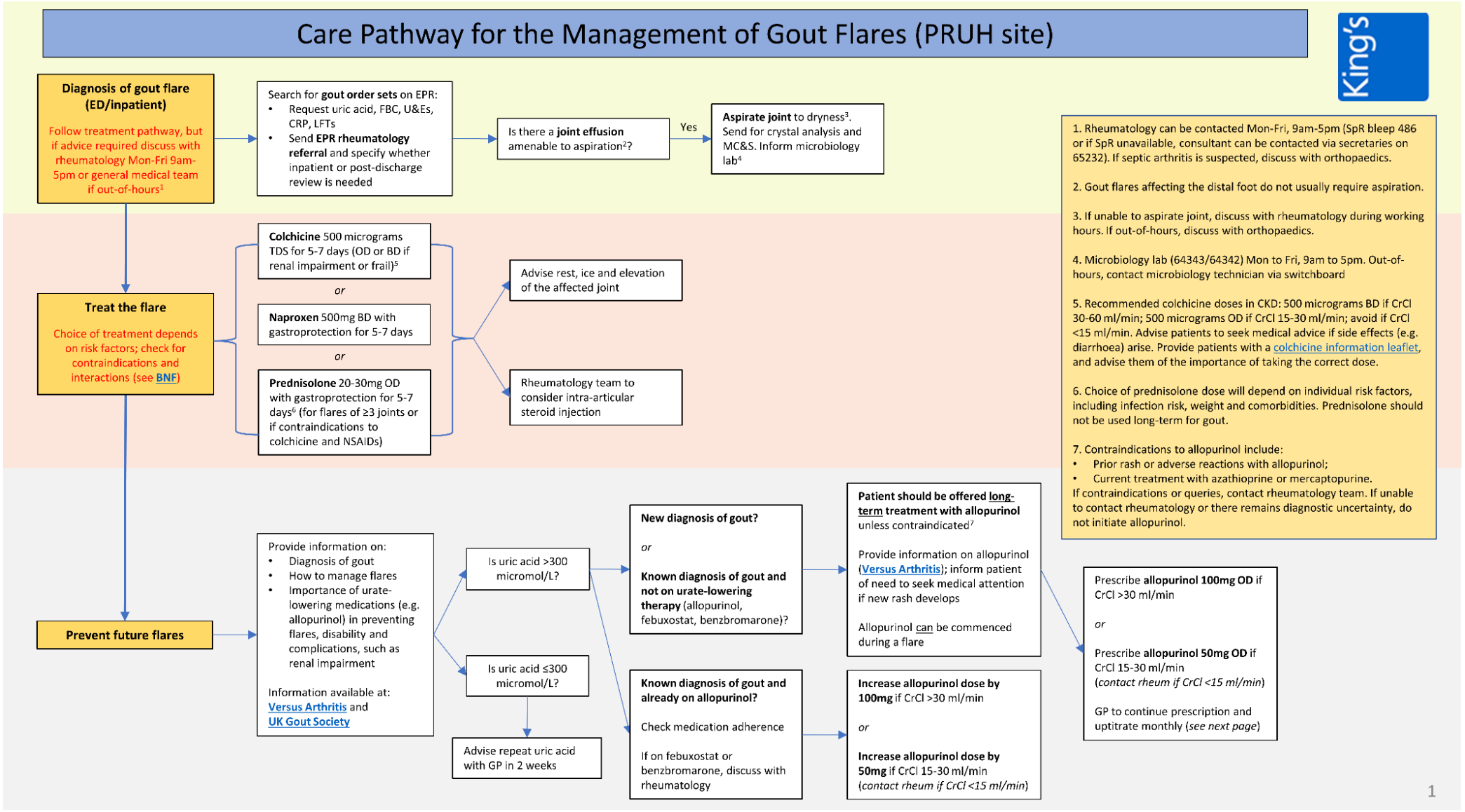
- At PRUH, there was insufficient nursing capacity to enable routine post-discharge, nurse-led review for all hospitalised gout patients. Instead, the rheumatology registrar offered to lead the post-discharge reviews.
- There is no "@home" community support service available at the PRUH, therefore admission-avoidance pathways centred on utilisation of ACU services.

I developed a comparable, multi-faceted implementation strategy for use with the PRUH pathway, which included:

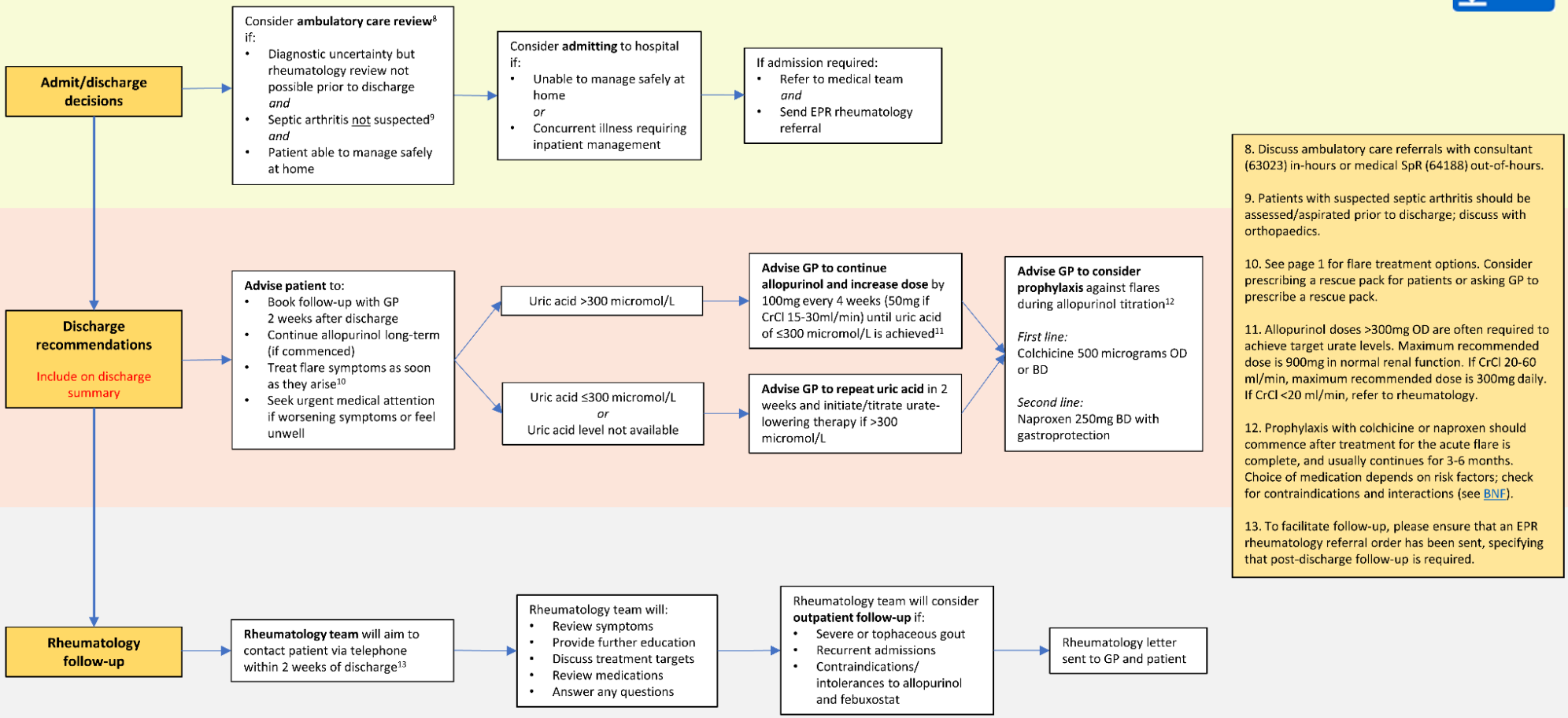
- **Digital enablers** – electronic order sets for relevant investigations (Figure 38; e.g. serum urate and synovial fluid crystal analysis) and medications (Figure 39; e.g. flare treatment options and ULT).
- **Study champions** – the rheumatology registrar at PRUH was instrumental in supporting implementation of the pathway, and in disseminating the guidance amongst other members of staff.
- **Educational sessions** – I delivered training sessions on the pathway and optimal gout management for clinicians in relevant departments, including emergency medicine, acute medicine, general medicine and rheumatology. I staggered these sessions over time, to enable as many clinicians as possible to attend.
- **Executive approval** – As for King's College Hospital, the PRUH pathway went through numerous approval and review steps, followed by sign-off by the clinical governance teams and drug and therapeutics committee. The pathway became the official gout management pathway at the PRUH.
- **Advertising** – information on the pathway was uploaded to the hospital website and circulated to all staff in the Trust. Additionally, tailored emails were sent to individual departments, notifying them of the pathway and its implementation.

The pathway was launched at the PRUH in August 2022. Implementation is ongoing currently, and outcomes will be reviewed after a 12-month intervention period, with 6 months of follow-up for each patient.

Figure 52. Pathway for the management of patients attending emergency department and/or admitted for gout flares at Princess Royal University Hospital



Care Pathway for the Management of Gout Flares (PRUH site)



8. Discuss ambulatory care referrals with consultant (63023) in-hours or medical SpR (64188) out-of-hours.

9. Patients with suspected septic arthritis should be assessed/aspirated prior to discharge; discuss with orthopaedics.

10. See page 1 for flare treatment options. Consider prescribing a rescue pack for patients or asking GP to prescribe a rescue pack.

11. Allopurinol doses >300mg OD are often required to achieve target urate levels. Maximum recommended dose is 900mg in normal renal function. If CrCl 20-60 ml/min, maximum recommended dose is 300mg daily. If CrCl <20 ml/min, refer to rheumatology.

12. Prophylaxis with colchicine or naproxen should commence after treatment for the acute flare is complete, and usually continues for 3-6 months. Choice of medication depends on risk factors; check for contraindications and interactions (see BNF).

13. To facilitate follow-up, please ensure that an EPR rheumatology referral order has been sent, specifying that post-discharge follow-up is required.

8.10.2 Guy's and St Thomas' Hospital NHS Foundation Trust

I chose Guy's and St Thomas' Hospital NHS Foundation Trust (GSTT) as the third site to adapt and implement my pathway. GSTT is a separate hospital Trust to King's College Hospital NHS Foundation Trust. While some aspects of the hospitals are aligned (e.g. academia, via King's College London), there are many differences – for example, separate IT systems, management pathways, and approval systems. This made GSTT an ideal third site to adapt and implement my gout pathway.

I encountered some challenges when adapting the pathway for use at GSTT. Despite being a large rheumatology service (>15 consultant rheumatologists), staffing resources were very stretched. This made it difficult to replicate some aspects of the pathway that had worked well at King's College Hospital – particularly the nurse-led, post-discharge reviews.

In collaboration with the rheumatology, ED and general medicine teams at GSTT, we made the following substantial changes to the pathway (Figure 53):

- As with the PRUH, the recommendation to contact the rheumatology team was reserved for cases where advice was required (e.g. diagnostic uncertainty), rather than recommending discussion for all cases. This reflected the absence of on-site rheumatology cover beyond 5pm. As many emergency gout presentations occur out-of-hours, the lack of rheumatology cover during these hours was felt to be a barrier to providing rheumatology input for all gout patients.
- At GSTT, nursing and doctor capacity was too limited to enable routine post-discharge review of all hospitalised gout patients. Rheumatology outpatient follow-up was reserved for patients who had severe disease (e.g. tophaceous gout and/or multiple re-admissions).
- The rheumatology team at GSTT felt it would be important to provide guidance on febuxostat titration (i.e. to increase the dose to 120 mg daily if the patient was sub-optimally managed on febuxostat 80 mg daily). In contrast, at King's College Hospital, we advised that the clinical team should contact the rheumatology team for advice in such cases. This reflected that rheumatology support was available out-of-hours at King's College Hospital.

I developed an implementation strategy for use with the GSTT pathway, based upon the one used at King's College Hospital, including:

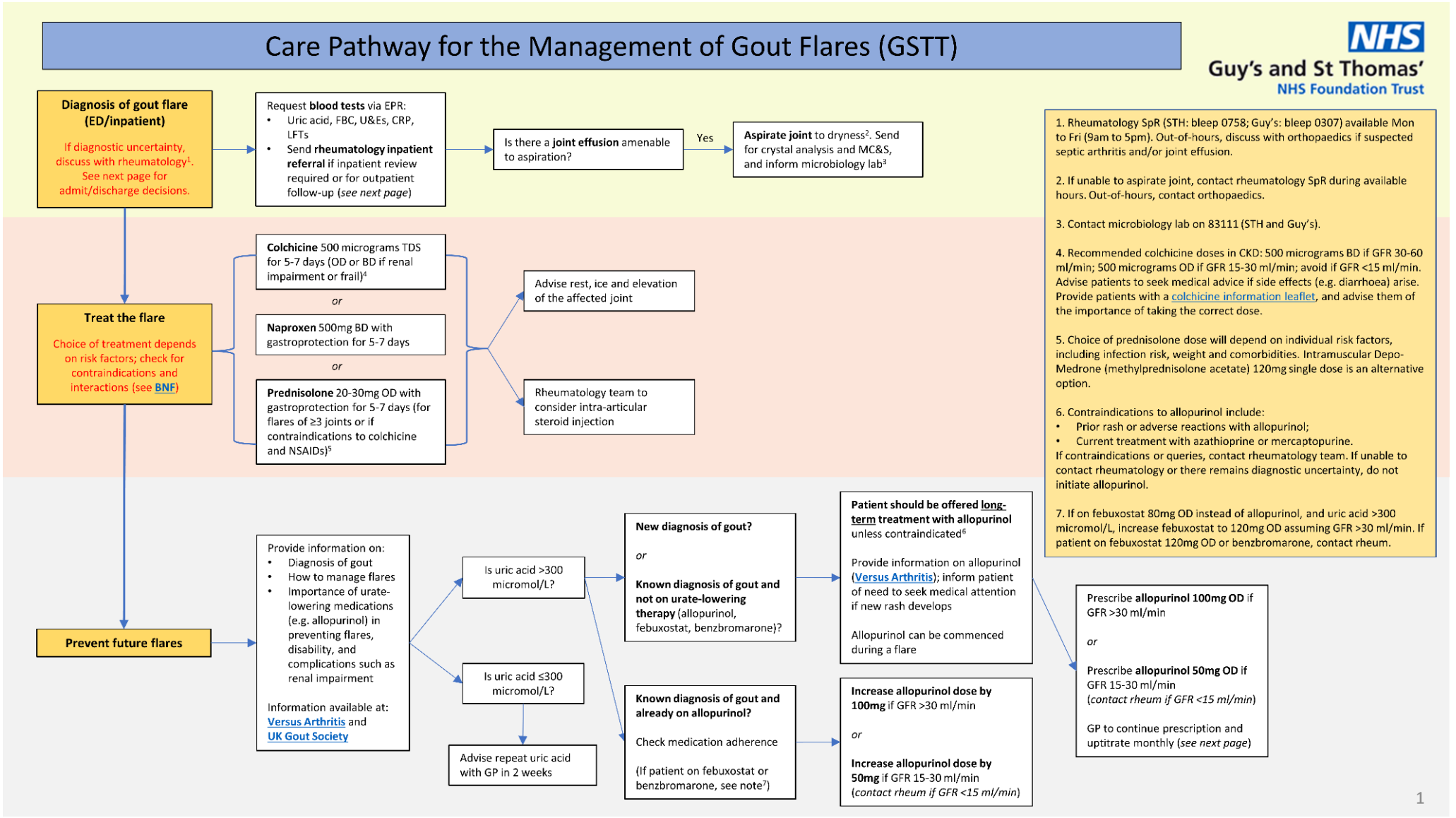
- **Educational sessions** – I delivered training sessions on the pathway and optimal gout management for clinicians in relevant departments, including emergency medicine, acute medicine, general medicine and rheumatology. I staggered these sessions over time, to enable as many clinicians as possible to attend.
- **Executive approval** – the GSTT pathway went through numerous approval and review steps, followed by sign-off by the clinical governance teams and drug and therapeutics committee. The pathway became the official gout management pathway at GSTT.

- **Advertising** – information on the pathway was uploaded to the hospital website. Additionally, tailored emails were sent to individual departments, notifying them of the pathway and its implementation.

There were challenges in replicating some of the other implementation approaches I had used at King's College Hospital. It was not possible to generate electronic order sets at the time of pathway launch at GSTT, due to the impending roll-out of new EHR system. As such, I could only recommend which investigations and medications should be ordered/prescribed via the pathway, rather than by creating easy-to-use order sets.

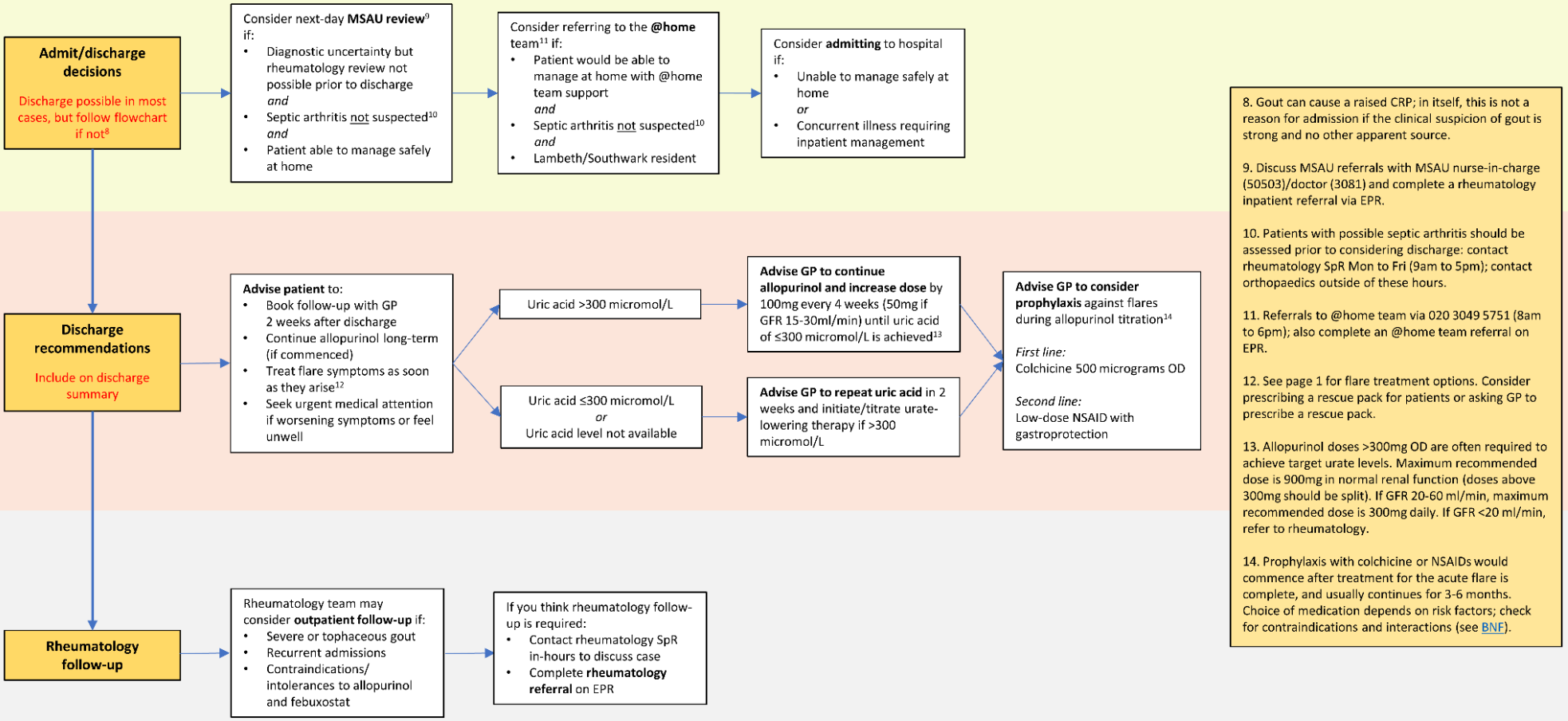
The GSTT pathway was launched in May 2023. Implementation is currently ongoing, and outcomes will be reviewed after a 12-month period, with 6 months of follow-up for each patient.

Figure 53. Pathway for the management of patients attending emergency department and/or admitted for gout flares at Guy's and St Thomas' Hospital



Care Pathway for the Management of Gout Flares (GSTT)

Guy's and St Thomas' NHS Foundation Trust



8. Gout can cause a raised CRP; in itself, this is not a reason for admission if the clinical suspicion of gout is strong and no other apparent source.

9. Discuss MSAU referrals with MSAU nurse-in-charge (50503)/doctor (3081) and complete a rheumatology inpatient referral via EPR.

10. Patients with possible septic arthritis should be assessed prior to considering discharge: contact rheumatology SpR Mon to Fri (9am to 5pm); contact orthopaedics outside of these hours.

11. Referrals to @home team via 020 3049 5751 (8am to 6pm); also complete an @home team referral on EPR.

12. See page 1 for flare treatment options. Consider prescribing a rescue pack for patients or asking GP to prescribe a rescue pack.

13. Allopurinol doses >300mg OD are often required to achieve target urate levels. Maximum recommended dose is 900mg in normal renal function (doses above 300mg should be split). If GFR 20-60 ml/min, maximum recommended dose is 300mg daily. If GFR <20 ml/min, refer to rheumatology.

14. Prophylaxis with colchicine or NSAIDs would commence after treatment for the acute flare is complete, and usually continues for 3-6 months. Choice of medication depends on risk factors; check for contraindications and interactions (see BNF).

8.10.3 Stockport NHS Foundation Trust

During my PhD, I was contacted by a fourth hospital site, Stockport NHS Foundation Trust, who were interested in adapting my pathway for implementation at their hospital. This provided me with an insight into how I could remotely support implementation of the pathway at entirely separate hospital Trusts. In contrast to implementation at King's College Hospital, PRUH and GSTT, I acted as more of a collaborator then a project lead for this Stockport NHS Foundation Trust. I supported the rheumatology team in tailoring the pathway for their service, but I was not directly involved in the day-to-day running of the pathway after its implementation.

A key difference between the pathway developed for Stockport NHS Foundation Trust and the pathway I had implemented at King's College Hospital, was that a specialist rheumatology pharmacist was chosen to lead the post-discharge reviews. This was opted for because of resource availability at Stockport NHS Foundation Trust. Additionally, there is an evidence-base to support the benefits of pharmacist-led ULT titration to target.[78-80] In a US-based, site-randomised study of 1,463 patients, a pharmacist-led approach that encouraged treat-to-target optimisation of allopurinol resulted in more patients achieving urate targets, compared with usual care.[78] However, no studies to date have assessed the benefits of pharmacist-led approach in a hospitalised gout setting, and so this site will provide novel information in this regard once implementation and evaluation is complete (currently ongoing).

9 Discussion and future directions

9.1 Aim 1: Has gout management in UK primary care improved following the publication of updated management guidelines?

In my population-level analyses of CPRD data, I showed that only very modest improvements occurred in ULT initiation and urate target attainment between 2004 and 2020. In 2020, only 35% of patients with gout were initiated on ULT within 12 months of diagnosis; 36% achieved a serum urate ≤360 micromol/L; and 22% had two or more urate levels performed. In time-series analyses, I showed that trends in ULT prescription and urate target attainment did not improve significantly after the publication of the 2016 EULAR or 2017 BSR gout management guidelines, relative to before publication of these guidelines.

Together, my findings suggest that the publication of specialist guidelines alone has not substantially improved gout management at a population level in the UK, and that additional strategies are required to implement treat-to-target recommendations. Such strategies need to address the multiple barriers to optimal gout care that have been highlighted in qualitative studies, at both patient and provider levels.[61] These barriers include stigma surrounding the diagnosis of gout, a perception that gout is a diet-driven disease rather than a genetic disease, and a reluctance to initiate and adhere to long-term ULT.[61]

Historically, ULT was reserved for patients with severe disease and/or recurrent gout flares.[204,205] The threshold for ULT initiation was lowered substantially in the updated 2016 EULAR and 2017 BSR management guidelines. In the 2017 BSR guidelines, it is recommended that all patients with gout should have ULT offered to them, including patients presenting with their first flares.[6] If these guidelines were followed in clinical practice, the majority of patients with gout in my analyses should have been initiated on ULT within 12 months of diagnosis; acknowledging that some patients will have been offered ULT but declined to initiate it.

The 2016 EULAR gout management guidelines differed subtly from the 2017 BSR guidelines. They recommend that ULT be considered and discussed with all patients with gout, but only explicitly recommend that ULT is indicated in patients with additional risk factors: recurrent flares (≥2/year), tophi, urate arthropathy and/or renal stones, those presenting at a young age (<40 years), or with a very high urate level (>8 mg/dL; 480 µmol/L) and/or comorbidities (renal impairment, hypertension, IHD, heart failure). Although I could not capture all of these risk factors in my analyses, I could demonstrate that they majority of patients had at least one risk factor: 50% of my CPRD cohort had hypertension, 25% had CKD, 15% had IHD, and the mean serum urate level at diagnosis was 472 µmol/L (i.e. close to the high urate threshold). As such, the majority of patients I analysed in CPRD should have been initiated on ULT if the EULAR guidance was followed.

One possible explanation for why BSR and EULAR guidelines were not followed for the majority of gout patients in UK primary care could be that clinicians were unaware of these

updated guidelines. Primary care clinicians have to manage thousands of medical conditions in limited time slots, and it would be near impossible to stay appraised of all specialist guideline updates. In UK primary care, NICE guidelines are widely used by clinicians. The first NICE gout management guideline was introduced in June 2022.[35] This was beyond the study period examined in Chapter 3 of my thesis. In Chapter 4 of my thesis, I showed that ULT initiation remained low in late 2022; however, guidelines take time to be assimilated into clinical practice, and therefore it is likely to be too early to determine how much impact these guidelines have had.

An important finding from my regression analyses in Chapter 3 was that patients with risk factors for poor outcomes (e.g. CKD, heart failure, hypertension, and diuretic users) were less likely to achieve urate targets than patients without these risk factors, despite being more likely to be initiated on ULT. Furthermore, I showed that the greater the number of comorbidities a patient had, the less likely they were to achieve urate targets. The fact that patients with these risk factors were more likely to be initiated on ULT is in line with BSR and EULAR guidance; however, it is concerning that these risk factors associated with poorer urate target attainment, given these patients are likely to be at increased risk of adverse outcomes from their gout.

Sub-optimal urate target attainment in patients with comorbidities could potentially be explained by it being harder to attain urate targets in the presence of these risk factors. I showed that mean baseline serum urate level was 612 µmol/L in patients with seven comorbidities vs. 440 µmol/L in patients with no comorbidities. It may also be that clinicians are more reluctant to titrate ULT in patients with comorbidities.[136] This is compounded by inconsistent guidance on ULT dosing in the presence of comorbidities, such as CKD.[6,7,133] In the British National Formulary (BNF) it states:

"*Allopurinol should be used with caution in people with renal impairment, due to the risk of accumulation. Maximum initial dose is 100 mg daily, increased only if response inadequate; in severe impairment, reduce daily dose below 100 mg, or increase dose interval; if facilities available, adjust dose to maintain plasma-oxypurinol concentration below 100 micromol/litre.*"

Oxypurinol monitoring is not widely available in UK clinical practice, which makes it challenging for clinicians to titrate allopurinol adequately in the presence of CKD if the BNF guidance is followed. This emphasises the need for clear guidance on the management of gout in the presence of comorbidities, to ensure that patients most at risk of poor outcomes receive optimal ULT dosages.

CPRD was an ideal dataset in which to address the aims of this chapter. CPRD has UK-wide, population-level data coverage, with data spanning a period of more than 15 years. There is detailed coded information on diagnoses, tests and prescriptions. There have been previous studies that have validated the diagnosis of gout in CPRD,[140,141] which reduces the likelihood of diagnostic misclassification.

There were also some important limitations that must be considered. I was unable to account for patient preference when reporting trends in ULT initiation and urate target attainment. Some patients will have been offered ULT by their primary care clinicians, but declined to start it. As such, my findings will be an underestimate of the proportion of patients who were offered ULT. I was unable to account for subtle differences in the BSR and EULAR gout management guidelines, which could have influenced a healthcare provider's decision to initiate ULT. Many of these issues pertain more generally to analyses of coded health datasets; while excellent at highlighting population-level trends, they may not always capture granular information on patient and provider behaviour.

9.2 Aim 2: How have the incidence, prevalence and management of gout been impacted by the COVID-19 pandemic?

In Chapter 4, I performed analyses of gout care using the OpenSAFELY platform – one of the most compreshensive health data platforms available globally. Using OpenSAFELY, I showed that newly-recorded gout diagnoses decreased by a third in the first year of the pandemic. The magnitude of decrease in gout diagnoses during the pandemic was greater than for RA, PsA or axSpA.[123] Additionally, I showed that hospitalisations for gout flares decreased by a third in the first year of the pandemic. Together, my findings highlight the wide-ranging impact of the pandemic on both primary care and secondary care-led rheumatological conditions.

The marked decrease in incident gout diagnoses and hospitalisations may be explained by fewer patients seeking medical attention for non-COVID-19 diagnoses during the pandemic and/or difficulties in obtaining appointments. This hypothesis is supported by national data, which show that there were 10% fewer primary care appointments and 16% fewer emergency admissions for all causes in the first year of the pandemic.[154,155] Of note, however, these national trends accounted for less than half of the decrease in gout diagnoses and hospitalisations that was observed in my analyses. This suggests that additional factors contributed to a disproportionate impact on gout care during the pandemic.

I showed that the decrease in gout diagnoses during the pandemic was not explained by patients with less severe disease avoiding seeking medical attention or by sociodemographic factors, which were comparable in the pre- and peri-pandemic cohorts. Interestingly, I found that patients who presented with gout during the pandemic had proportionately fewer comorbidities, such as CKD, than those presenting before the pandemic. This could have been influenced by stay-at-home advice for those at high risk of adverse COVID-19 outcomes.[158]

While incident gout diagnoses partly recovered after the first year of the pandemic, there was no subsequent evidence of a rebound increase in gout diagnoses above pre-pandemic levels. This suggests that a substantial number of people with gout in the UK remain undiagnosed as a consequence of the pandemic. Delays in diagnosis and treatment can worsen outcomes for patients with gout, due to an accumulation of damage and comorbidities, as well as impacting

on quality of life and work impairment.[11,12] Future analyses will help to determine whether gout diagnoses go on to rebound above pre-pandemic levels as the post-pandemic recovery continues.

In addition to marked decreases in incident gout diagnoses during the pandemic, I showed that there has been a gradual decrease in gout incidence that predated the pandemic. This finding corroborates those of a recently published study using CPRD, which reported a decrease in gout incidence since 2013.[55] These data suggest that the incidence of gout may have peaked in the UK, following decades of increasing incidence. The reasons behind this gradual decrease in incidence are not fully understood. Changes in diet and alcohol comsumption have been hypothesised as potential causes;[55] however, this would not necessarily account for the fact that gout is predominantly a genetically-determined disease.[9,18]

For people who did seek medical attention with gout during the pandemic, I showed that metrics of care were comparable or even marginally improved, relative to before the pandemic. Small, statistically significant improvements in ULT prescribing were seen after March 2020, relative to pre-pandemic trends. Urate target attainment remained relatively stable over the study period, aside from a temporary decrease in attainment for people initiating ULT in late 2019 and early 2020. Underlying these national trends was marked regional variation in urate target attainment, with patients in some regions of England being more than twice as likely to achieve urate targets than other regions of England.

Despite modest improvements in ULT initiation during the pandemic, absolute rates of ULT initiation and urate target attainment remained low at the end of the study period. For patients diagnosed with gout in 2022, I showed that only 34% of patients were prescribed ULT within 12 months of diagnosis, while 29% of patients achieved a serum urate ≤360 micromol/L within 12 months of initiating ULT. These findings corroborate those from Chapter 3 of my thesis, and suggest that multi-faceted strategies are needed to implement guideline recommendations.

More generally, my analyses in Chapter 4 are amongst the first to demonstrate that routinely-collected health data, accessed via the OpenSAFELY platform, can be used to benchmark care for chronic diseases in the UK. The OpenSAFELY platform has been groundbreaking for facilitating research into the COVID-19 pandemic, but few studies had evaluated whether the platform could be used to drive improvements in routine clinical care. My findings complement those from my previous analyses of autoimmune inflammatory arthritis diagnoses using OpenSAFELY.[123] In that proof-of-concept study, I was able to replicate several key metrics from the National Early Inflammatory Arthritis Audit (NEIAA) using routinely-collected data in OpenSAFELY.

Use of routinely-collected health data can overcome many of the issues with existing national audits (e.g. NEIAA), which rely upon manual data collection and entry by clinicians. The need for manual data collection can lead to low levels of case ascertainment, clinician

disengagement, and a potential for bias.[153] I was able to show that the use of routinely-collected health data in OpenSAFELY resulted in much higher case capture than existing audits, with monitoring possible in near real-time.[123] In turn, these data can be relayed to departments via dashboards (https://reports.opensafely.org/reports/incidence-and-management-of-inflammatory-arthritis-in-england-before-and-during-the-covid-19-pandemi/), facilitating audit and quality improvement.

While there is not currently a national audit programme for gout in the UK, my analyses of OpenSAFELY data could serve as a basis for benchmarking care across the UK. This would be beneficial for several reasons. At a national level, the data could be used to ascertain whether national guidelines (e.g. the NICE gout management guideline[35]) are being implemented in practice, and evaluate the impact of implementation strategies on patient care. For example, if my admission-prevention pathway (Chapter 8) was rolled out across multiple sites in the UK, data in OpenSAFELY could be used to monitor the impact on hospitalisations for gout flares. Additionally, routinely-collected data can highlight inequities in care at regional and local levels (as detailed above), which can be used to direct resources towards improving care.

The OpenSAFELY platform has numerous advantages over other datasets. The privacy safeguards in OpenSAFELY far exceed those in other platforms, such as CPRD.[125] This not only protects against disclosure of sensitive data, but also makes use of sensitive data more acceptable to patients and the public.[147] Data coverage in OpenSAFELY is greater than for any other platform in the UK (and, indeed, many other countries); linked primary and secondary care health data are available for 99% of England's population. Data are updated in close to real-time, making OpenSAFELY well-suited for analyses of pandemic-related care.

There are also limitations with OpenSAFELY. While coded health data are useful for highlighting trends in disease management and epidemiology, they cannot tell you with certainty whether the trends were caused by a specific intervention, background changes or changes in coding practices. Similarly, trends in diagnostic incidence could result from changes in underlying disease incidence or delays in the recording of diagnoses. As with CPRD, prescription and laboratory data from secondary care are not currently captured in OpenSAFELY. These data are important for analysing the secondary care management of gout, and efforts are underway to incorporate them.[159] Additionally, other important outcome measures - e.g. patient-reported outcomes - are not currently captured in routine primary and secondary care data. Until these caveats are addressed, routinely-collected data in platforms such as OpenSAFELY will be helpful for augmenting existing national audits, rather than replacing them.

9.3 Aim 3: What proportion of incident gout patients are hospitalised for flares, and how is the risk of hospitalisation affected by ULT initiation and urate target attainment?

At a population level, hospitalisations for gout flares have increased markedly over the last two decades.[3] In England, hospitalisations with primary admission diagnoses of gout cost the NHS more than £10 million per year.[164] Additional costs are attributable to ED attendances, hospitalisations with secondary diagnoses of gout (e.g. in the context of heart failure), and work disability due to hospitalisations.[165,166] However, few studies have investigated the incidence, timing and risk factors for gout hospitalisations at an individual-level. Moreover, the time-varying relationship between ULT initiation and hospitalisations was not known, nor was the impact of achieving urate targets on hospitalisations. I investigated these questions using linked primary and secondary data in CPRD.

I showed that there are 4.6 hospitalisations for gout flares per 1000 person-years in people diagnosed with gout. A third of hospitalisations are index diagnosis events (i.e. the first recorded diagnosis of gout is made during a hospitalisation for flare), with the remainder occurring more than a week after diagnosis. The risk of hospitalisations is greatest within the first 6 months of diagnosis (28 admissions per 1,000 person-years), then stablises beyond 6 months (2.7 admissions per 1,000 person-years). Morever, I showed that many of the risk factors that associate with sub-optimal gout management (Chapter 3) are also risk factors for hospitalisations. Individuals hospitalised for gout are more likely to be male, have more comorbidities, be on diuretics, and have higher serum urate levels at diagnosis than those without hospitalisations. These risk factors were more common still in patients hospitalised multiple times for gout.

As is true of gout management in primary care (Chapters 3 and 4), I showed that patients hospitalised for gout are often sub-optimally managed. Only 25% of patients had been prescribed ULT by the time of their first gout hospitalisation, while 39% remained on no ULT by 12 months after their first hospitalisation. Of patients who had at least one serum urate level performed within 12 months of discharge, only 35% achieved a urate ≤360 micromol/L. I hypothesised that many admissions could have been prevented had more patients received optimal gout management before, during or after their hospitalisations. Community-based studies have shown that treat-to-target ULT reduces flares in the long-term.[31] However, it is also true that ULT initiation and titration can precipitate flares in the short-term.[168]

The relative impact of ULT and urate target attainment on the risk of hospitalisations is a question that had not be studied before in detail, and one that I tried to address using CPRD. These were some of most complex analyses in my thesis, both to perform and to intepret. Firstly, as described above, the impact of ULT on flares varies over time, which breaks the proportional hazards assumption of Cox regression. To overcome this, I performed time-split analyses, whereby I analysed the effects of ULT on hospitalisations at multiple time-points. Using this approach, I showed that ULT initiation associates with fewer hospitalisations in the

long-term, compared with people who did not initiate ULT, particularly when urate targets are achieved. In contrast, within the first 6 months of ULT initiation, there were nearly 5-times more hospitalisations for flares, relative to people who did not initiate ULT.

On the one hand, the association between ULT and hospitalisations in the short-term could be interpreted as meaning ULT causes hospitalisations, e.g. by precipitating flares. Alternatively, it could be that patients who are at greater risk of hospitalisations are those more likely to be prescribed ULT (i.e. a reverse association). In Chapter 3 of my thesis, I showed that male patients, those with comordidites, and diuretic users were more likely to be initiated on ULT than those without these risk factors. Similarly, I demonstrated that these characteristics are risk factors for hospitalisations for gout flares. This raises the possibility of a reverse association; however, when I performed adjustment for these risk factors in my Cox models, the association between ULT initiation and early hospitalisations remained. The same was true when I adjusted for baseline serum urate levels - a marker of disease severity – and in my propensity models. Taken together, these findings may suggest a causative relationship between ULT and hospitalisations in the short-term. It is also possible that residual confounding could explain the differences between these cohorts. Randomised controlled trial data would help to clarify these questions, although it may be unethical to randomise patients to no ULT, given the well-established benefits. Real-world data from my implementation study (Chapter 8; discussed below) provide some reassurance that ULT does not associate with more hospitalisations in the short-term, provided appropriate post-discharge care is delivered.

To further investigate the association between ULT initiation and hospitalisations in the short-term, I performed modelling to evaluate the impact of colchicine prophylaxis alongside ULT. My rationale for doing so was that there are data to support the benefits of colchicine prophylaxis in preventing flares when ULT is initiated and titrated.[206] Interestingly, in my multivariable-adjusted Cox models, co-prescription of colchicine did not associate with fewer hospitalisations, relative to patients who initiated ULT but did not have colchicine co-prescribed. Indeed, effect sizes were towards more hospitalisations when colchicine was prescribed. This did not seem logical in view of real-world and RCT data that supports the benefits of colchicine on flare reduction. I hypothesised that my findings were more likely to be due to residual confounding, supported by the fact that the propensity models I attempted had very limited common support between colchicine initiators and non-initiators. From clinical experience, I know that I am more inclined to prescribe colchicine prophylaxis to patients who I believe to be at greatest risk of flares/hospitalisations (e.g. patients with severe gout, tophi or previous hospitalisations). These analytical conundrums highlight the potential limitations of observational data when trying to answer such questions.

Another interesting and challenging analytical question I encountered was how to evaluate the impact of urate target attainment on hospitalisations. I showed that in patients who initiated ULT, urate target attainment was associated with fewer hospitalisations than when urate targets were not achieved; lending support to the treat-to-target approach in the

prevention of hospitalisations. Of note, however, 45% of patients who initiated ULT did not have a serum urate level performed within 12 months of ULT initiation. It was not therefore possible to know whether these patients had achieved urate targets or not. If these data were assumed to be missing completely at random, then it would be reasonable to perform complete case analyses. When I did so, the hazard ratio for hospitalisations was 0.39 in those attaining urate levels ≤360 micromol/L, relative to those not attaining these urate levels. If these data were assumed to be missing at random, then the missingness of the serum urate levels would relate to other observed variables (e.g. age, sex, receipt of ULT) but not the missing data itself. To investigate this assumption, I performed multiple imputation to estimate the missing values. After doing so, attainment of a urate ≤360 micromol/L still associated with fewer hospitalisations, relative to those who did not attain target (aHR 0.57).

Finally, if I assumed that the serum urate data were missing not at random, then the missingness of the serum urate levels would relate to the serum urate levels themselves. For example, patients with less severe gout and lower serum urate levels might be less likely to see their GP and have serum urate levels performed. I could partly account for this by adjusting for variables known to be associated with disease severity (e.g. CKD); however, this adjustment may be have been incomplete. This is a potential limitation of my analyses, and one that is challenging to model.

Despite the challenges with these analyses, there were several strengths. The dataset I used, CPRD Aurum, contains pseudonymised data on 41 million people in the UK, with linked hospitalisation data available for 98% of the cohort. By exploring findings from multiple different statistical models, as detailed above, it provided me with more robust estimates.

Taken together, my analyses from this chapter have an important take-home message. They suggest that ULT with a treat-to-target approach associates with a long-term reduction in hospitalisations for flares. Coupled with a wealth of data from non-hospitalised settings,[74] this demonstrates the importance of treat-to-target strategy in tackling the epidemic of gout hospitalisations.

9.4 Aim 4: What is the evidence base for interventions in patients hospitalised for gout flares?

In Chapter 6, I presented the findings from my systematic literature review, which summarised the evidence base for interventions in people hospitalised for gout flares. These data were essential for informing the strategy I developed and implemented in Chapter 8 of my thesis.

Given the scale of the problem with increasing gout hospitalisations, it was somewhat surprising to find only 19 published studies of interventions in patients hospitalised for gout flares. The majority of these studies were small, retrospective analyses conducted in single centres, with concerns for bias. When devising the protocol for my systematic review, I had hoped to perform meta-analysis on the extracted data. Unfortunately, the limited number of

studies with comparable interventions and outcomes precluded this. Instead, I adopted a narrative synthesis approach. While not a limitation per se, this highlights the need for more studies in patients hospitalised for gout flares.

Several of the studies I identified evaluated pharmacological interventions that are already known to be effective at treating flares in non-hospitalised settings (NSAIDs, corticosteroids and IL-1 inhibitors). All of these treatments were shown to be effective at controlling pain in the setting of hospitalised flares, with relatively few adverse effects. NSAIDs and corticosteroids were both included as flare treatment options in my care pathway (Chapter 8); IL-1 inhibitors were not as they are not routinely used for the treatment of gout flares in the UK.

Three small, observational studies evaluated the flare-prevention benefits of ULT in patients hospitalised for gout, demonstrating associations with fewer hospitalisations and ED attendances. These findings support those from Chapter 5 of my thesis, and emphasise the importance of ULT in strategies to prevent hospitalisations. A more controversial treatment decision is whether to initiate ULT during flares, or wait until the flare has resolved. Historically, the latter has been common practice, due to concerns that upfront ULT initiation could prolong or worsen flares. In my systematic review, I identified three studies that challenged this dogma.[41,43,177] Two studies were RCTs, comparing upfront allopurinol with deferred initiation of allopurinol, alongside treatment of the flare itself. No differences were seen between the study arms in the time to flare resolution, pain reduction or recurrent flares. Additionally, more timely reductions in urate levels were observed when ULT was initiated early. Together, these data, coupled with data from non-hospitalised settings,[195] support the benefits of initiating ULT during flares, alongside flare treatment. I recommended this approach in my hospital gout pathway. Hospitalisations provide unique opportunities to improve care for people with severe gout. By initiating ULT prior to discharge, it helps to ensure patients get the treatment they need to prevent flares and recurrent admissions in the long-term. This approach also helps to overcome the breakdown in communication that frequently occurs between secondary care and primary care, whereby discharge recommendations are not acted upon.[73]

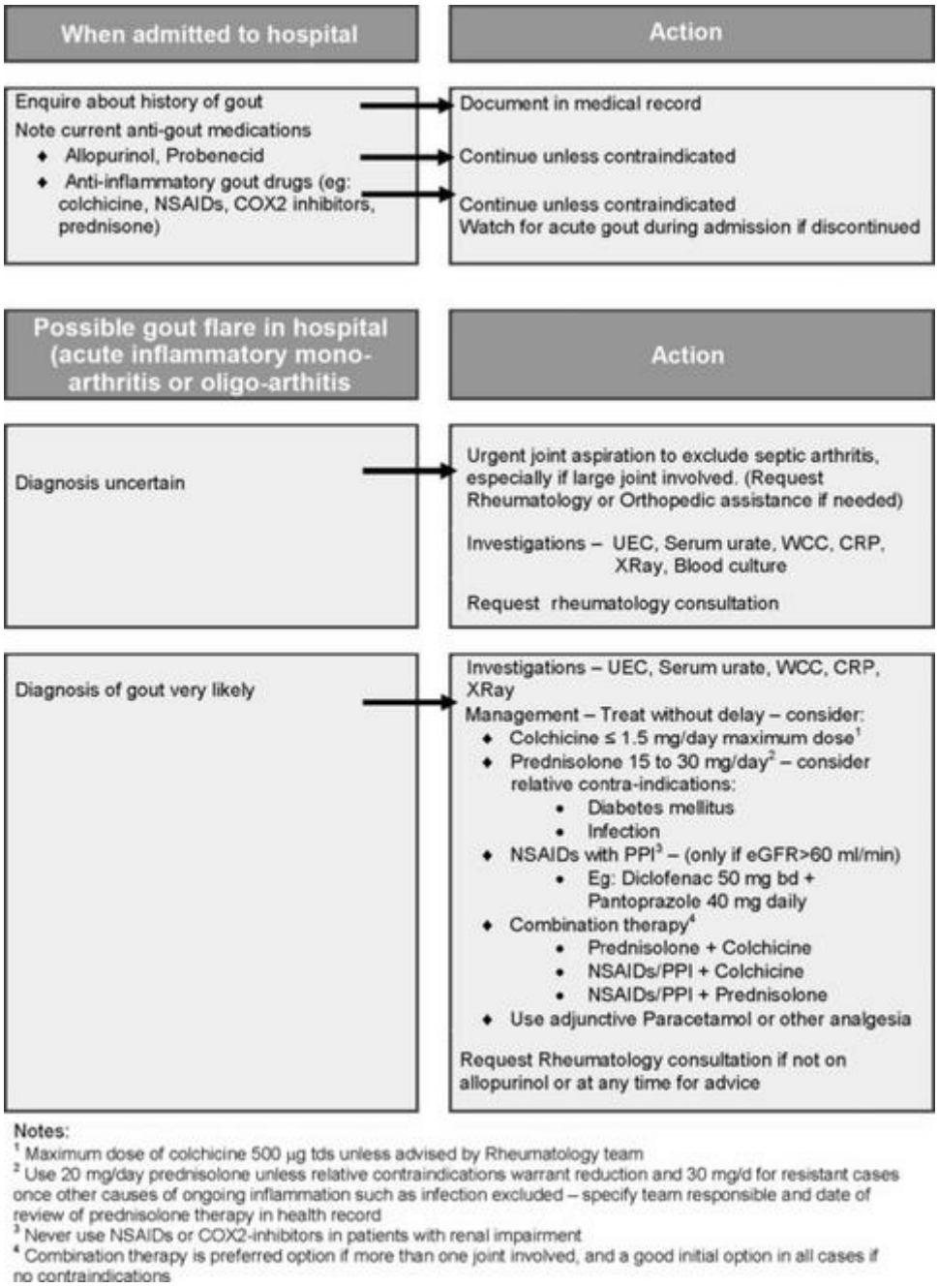
Seven studies in my systematic review evaluated the impact of rheumatology consultations on hospitalised gout care. Rheumatology input associated with more joint aspirations, more frequent measurement of urate levels, increased utilisation of ULT, and more post-discharge follow-up. During my pathway development process (Chapter 8), stakeholders agreed strongly that rheumatology consultation was an important facilitator of optimal gout care. In the pathway I implemented at King's College Hospital, I recommended that all patients hospitalised for gout flares should be discussed with a rheumatologist prior to discharge, where possible. Doing so can facilitate optimal care if the treating clinician is less familiar with gout management. While this was feasible in many cases at King's College Hospital, it was challenging to implement in hospitals with more limited rheumatology cover (e.g. PRUH). In those situations, a pragmatic decision was made to seek rheumatologist advice when there

was uncertainty around the diagnosis or management of gout. Future data will indicate whether this approach provides as much benefit as more consistent rheumatology input.

The study most directly comparable to the intervention I implemented in Chapter 8 of my thesis was a retrospective analysis of an inpatient gout management protocol in an Australian hospital.[178] This protocol was based upon EULAR guidelines, and included recommendations to continue baseline ULT, initiate anti-inflammatory medications, perform joint aspiration, and involve rheumatologists in cases of diagnostic uncertainty (Figure 54). Following the introduction of this protocol, more patients continued their baseline allopurinol, treatment delays decreased, and rheumatology consults increased. Admission durations were also numerically shorter following the introduction of the protocol. Many of the components from this protocol were incorportated into my gout treatment pathway. There were, however, several key differences. The Australian protocol did not advocate for early ULT initiation. There were no recommendations to utilise admission-avoidance pathways, or to encourage a treat-to-target approach. Additionally, there were no specific post-discharge follow-up arrangements made as part of this protocol. These were all key components that were identified during my stakeholder consultation work as being important for optimising hospital gout care.

Perhaps the most important finding of my systematic review was that there had been no prospective studies of interventions designed to increase attainment of urate targets and/or prevent re-admissions in hospitalised gout patients. Such data are essential if avoidable gout admissions are to be prevented. In Chapter 8 of my thesis, I implemented a strategy with these specific aims.

Figure 54. Protocol implemented by Kamalaraj et al. in Australia



9.5 Aim 5: What are the barriers and facilitators of optimal gout care in hospitalised patients?

As described above, my analyses in Chapter 5 demonstrated that treat-to-target ULT is rarely implemented at a population level following hospitalisations for gout flares. My systematic literature review in Chapter 6 highlighted the evidence base for interventions to optimise hospital gout care. However, for me to implement a strategy incorporating this evidence, the

barriers and facilitators of optimal care needed to be understood at a local level. This was the aim of Chapter 7 of my thesis, and I used several approaches to achieve this aim.

Firstly, I performed a retrospective case-note review to evaluate care in over 1,200 emergency attendances for gout flares at King's College Hospital NHS Foundation Trust over a 4-year period. 75% of these hospitalisation episodes were ED attendances that did not require admission. This indicated that my strategy would have to be applicable to an ED setting, as well as an inpatient setting. I showed that older patients, those with higher inflammatory markers and urate levels, and patients arriving out-of-hours were more likely to be admitted than those without these risk factors. The latter finding, in particular, emphasised the need for my pathway to be usable out-of-hours by ED clinicians.

In line with my population-level findings (Chapters 3, 4 and 5), I showed that only 23% of people presenting to King's with known gout diagnoses were receiving ULT at the time of their hospitalisation; 7% initiated ULT during their attendance; and 44% of patients were prescribed ULT by 6 months post-discharge. Treat-to-target recommendations were provided to only a small minority of patients, while only 9% of patients attained a serum urate ≤360 micromol/L within 6 months of discharge. I showed that initial diagnostic uncertainty was present in 50% of gout hospitalisations, yet rheumatology input was rarely sought, while joint aspiration was attempted in only 10% of patients. Corticosteroids were rarely prescribed as flare treatment (12% of patients), despite evidence of their efficacy.[6] Discharge delays were common, with common reasons including delayed rheumatology referral and management of comorbid diagnoses. Education on the diagnosis and/or treatment of gout was documented in only a third of cases, and only one patient was provided with advice on how to manage future flares.

These data showed that, despite being recommended in guidelines, optimal gout care was not being provided to hospitalised gout patients locally. These barriers, in turn, would need to be addressed in any strategy I implemented.

The complexity of hospitalisations for gout flares became evident when I process mapped the admitted patient journey. In doing so, I identified nearly 100 process steps and decision points during a typical patient journey, many of which were common sources of delay and/or sub-optimal care. It became apparent that trying to overcome all of these barriers would be very challenging, particularly as many barriers related to wider issues in the health service (e.g. difficulties in getting appointments). It was therefore essential to try and identify which barriers I could address, and which were a priority for my optimal care strategy. To achieve this, I involved multiple stakeholders. Five overarching themes were identified from these meetings, along with potential solutions:

i) **Diagnostic delay**, with potential solutions being early involvement of rheumatology specialists and prompt joint aspiration;

ii) **Inadequate flare treatment**, with recommendations including early initiation of guideline-recommended flare treatments, combination therapy, and intra-articular corticosteroid injections;

iii) **Inadequate flare prevention**, with solutions including ULT initiation prior to discharge, adopting a treat-to-target approach, and education for clinicians and patients on the benefits of ULT;

iv) **Inadequate follow-up**, with recommendations for multi-disciplinary team input (e.g. nurse and pharmacist-led titration), guidance for primary care clinicians on ULT titration and urate monitoring, rheumatology support for primary care clinicians, and the use of remote consultations to support ULT titration;

v) **Re-admissions**, with solutions including self-management advice for patients, rescue packs of flare treatment, flare prophylaxis during ULT titration, post-discharge support, and use of admission-avoidance pathways.

All of these solutions were incorporated into the care pathway I implemented in Chapter 8 of my thesis. The extensive stakeholder input was a major strength of this development process, as it enabled me to capture the views of patients and many of the team members involved in caring for people with hospitalised gout. A limitation of this process was the generalisability of the results to other hospitals. While many of the barriers I identified are applicable to other hospitals, the potential solutions can differ substantially depending on the individual hospital and resource availability. For example, a nurse-led post-discharge clinic may be ideally suited to a well-resourced hospital, whereas it could be challenging to implement in an under-resourced hospital. I go on to describe these challenges in more detail when addressing my next aim.

9.6 Aim 6: Can a strategy centred on treat-to-target ULT and individualised patient education be implemented effectively during hospitalisations for flares?

My final aim was to develop and implement a strategy to improve hospitalised gout care and prevent avoidable admissions. To achieve this, I incorporated the findings from the earlier chapters of my thesis, and collaborated extensively with stakeholders and patients.

My intervention package consisted of two key components: an in-hospital gout management pathway (Figure 37), based upon BSR, EULAR, and ACR gout management guidelines; and a nurse-led, post-discharge review, followed by handover to primary care for ongoing management. I implemented this intervention at King's College Hospital for all patients who attended ED and/or were admitted for gout flares. To maximise uptake of the pathway, I designed a multi-faceted implementation strategy, incorporating education sessions, advertising and digital solutions. I prospectively collected data on numerous effectiveness and implementation outcomes over a 12 month-period. In line with the service evaluation remit

of my project, my comparator group was patients who had been treated for gout flares at King's College Hospital in the 12 months prior to implementation.

A key component of my pathway that was successfully implemented was ULT initiation. After implementation, 94% of hospitalised gout patients received ULT by 6 months post-discharge, compared with 65% of patients before implementation. As recommended in the pathway, many more patients initiated and/or uptitrated ULT prior to discharge from hospital. I advocated for this approach (vs. deferred ULT initiation after discharge) for several reasons. Firstly, RCT evidence suggests that upfront initiation of ULT does not prolong or worsen intercurrent flares, provided it is initiated alongside flare treatment.[41,43,195,196] Secondly, earlier initiation of ULT leads to more timely reductions in serum urate levels.[41,43,195,196] Perhaps most importantly, this approach also helps to mitigate against the breakdown in communication that commonly occurs between secondary and primary care after discharge.[73] This is something that I have encountered frequently in practice, particularly for patients who attend ED without seeing a rheumatologist. In many such cases, the focus of the ED attendance is on treating the acute flare, with little/no attention paid to longer-term flare prevention.[73]

A key effectiveness outcome I evaluated was whether my care pathway impacted on re-admissions for gout flares. My population-level analyses (Chapter 5) had shown an association between ULT initiation and more hospitalisations for flares within the first 6 months of initiation. As discussed previously, it was unclear whether this represented a causative effect of ULT on hospitalisations or a reverse association. The findings from my implementation study suggest that the latter may be true: after implementing the care pathway, I observed no increase in hospitalisations for recurrent flares within 6 months of discharge, despite a marked increase in ULT initiation. Indeed, although not statistically significant, 38% fewer re-hospitalisations occurred after implementation, relative to before. A larger study, with longer follow-up, is needed to more definitively determine whether upfront ULT initiation associates with fewer hospitalisations in the short and long-term; however, even modest reductions in hospitalisations could produce large cost savings.

An aspect of my intervention that was less successfully implemented was titration to urate targets. Pre-implementation, the baseline was very low: only 10% of patients achieved urate targets within 6 months of discharge. After implementation, this increased significantly, to 27% of patients. However, this remained far below the 95% target attainment obtained in Doherty *et al.*'s RCT, which implemented nurse-led, treat-to-target ULT and individualised patient education in a primary care setting.[31] There are several possible explanations for the less successful urate target attainment in my study. Firstly, for pragmatic reasons, I opted for a follow-up period of 6 months post-discharge. While 6 months might be sufficient for many patients to achieve urate targets if guidelines are followed appropriately, outside of an RCT setting there are often delays in appointments, blood tests and prescriptions, which can preclude urate target attainment within this timeframe. Secondly, the patients in my study were all hospitalised for gout, and therefore are likely to represent a more severe cohort of

patients that those in a primary care setting; in Chapter 5, I showed that hospitalised patients have higher baseline urate levels than non-hospitalised patients, as well as more comorbidities, which can make it harder to attain urate targets.

One of the biggest differences between my intervention and the intervention in Doherty *et al.*'s RCT was the number of patient-clinician contacts. In my study, there was typically only one contact (via telephone) between the patient and a rheumatology nurse specialist after discharge. Care was then handed over to primary care, via a clinic letter. In contrast, in Doherty *et al.*'s RCT there were an average of 17 contacts per participant over a 24-month period, many of which occurred within the first 6 months.[31] These differences partly reflect resource availability – at King's College Hospital, we had nursing capacity for up to 5 appointments per week. It also reflects differences in study design. Doherty *et al.*'s RCT had a primary outcome of urate target attainment at 2 years. In contrast, the main objective of my study was to optimise the early management of patients hospitalised for gout flares, followed by handover to primary care for ongoing management.

Irrespective of these differences, my findings suggest that a single post-discharge follow-up appointment, followed by virtual handover to primary care, is insufficient for the majority of hospitalised gout patients to achieve target urate levels by 6 months. Moreover, my findings suggest that recommendations to titrate ULT to target are often not followed in practice. Over 80% of the patients in my study were reviewed in a specialist nurse gout clinic after discharge, all of whom had a letter sent to their primary care team recommending monthly urate monitoring and ULT titration. Despite this, the mean number of urate levels performed within 6 months of discharge was one (a modest increase from 0.5 tests pre-implementation). This highlights the real-world challenges of delivering treat-to-target ULT outside of a trial setting.

In part, the challenges I observed are likely to reflect patient and/or healthcare provider barriers to optimal gout care, including the stigma surrounding the diagnosis, the episodic nature of flares, and the perception that ULT should be reserved for people with severe gout.[61] One way to try and overcome these barriers would be to deliver training and education on the diagnosis and management of gout to primary care clinicians. My study showed that if you provide training to secondary care clinicians on optimal gout management, and deliver individualised education for patients, most will opt to initiate ULT. The challenge at a population level is reaching the majority of clinicians who manage people with gout (i.e. GPs in primary care). In the UK, clinical update days (e.g. Red Whale and Hot Topics) are widely attended by GPs, and recent sessions have included information on the NICE gout guideline. Similarly, during my PhD I have delivered educational sessions on optimal gout management to over 1,500 GP trainees in the UK. Whether educational interventions lead to sustained improvements in clinical practice is more controversial, however: previous studies have shown that educational interventions alone are one of the least effective means of enacting behaviour change ("often necessary but rarely sufficient").[207,208] Further qualitative research is needed to determine the barriers to delivering optimal gout care following hospitalisations for flares. Qualitative interviews with primary care clinicians will help to clarify the barriers

that prevent the majority of patients from receiving optimal urate monitoring and ULT titration after discharge from hospital. Once these barriers are better understood, my intervention can be modified to address the barriers to optimal gout care at the primary/secondary care interface.

Service-related factors are also likely to have contributed to the real-world challenges I encountered in urate monitoring and target attainment. Pressures on the NHS have increased in recent years, with record waiting lists and difficulties in obtaining appointments.[209] These challenges have been compounded by the COVID-19 pandemic.[84,154] To follow treat-to-target guidelines correctly requires monthly urate monitoring and titration of ULT dosing. Additionally, flares and adverse effects must be treated if they arise. While the pressures on the NHS are unlikely to abate soon, there are potential solutions to this problem.

One evidence-based solution is to utilise allied health professionals in the titration of ULT. Doherty *et al.*'s RCT demonstrated clearly that nurse-delivered, treat-to-target ULT is effective in a primary care setting.[31] A further primary care-based RCT is currently underway in the UK, which utilises a range of primary care professionals (including practice nurses and pharmacists) to deliver treat-to-target ULT.[210] Other studies have demonstrated improvements in urate target attainment with pharmacist-led, treat-to-target ULT.[74] The majority of general practices in the UK have at least one practice nurse and/or pharmacist, who manage chronic conditions such as asthma, hypertension and diabetes mellitus. This could be extended to include gout, the management of which can be highly protocolised. Additionally, there are networks of community-based pharmacists, who are being increasingly utilised to manage common conditions.[211] A viable option to reduce pressure on GPs would therefore be to handover gout management after hospitalisations for flares to community/practice-based pharmacists and/or nurses. While it may not be feasible to deliver 17 visits over a 24-month period (as per Doherty *et al.*'s RCT), there is likely to be a middle ground between this approach and the single post-discharge visit used in my study. This could incorporate adapted self-management and educational approaches that have been shown to be highly effective in other conditions – for example, the Dose Adjustment for Normal Eating (DAFNE) course for people with Type 1 diabetes mellitus.[212] These programmes can be delivered in group and/or online format, which can reduce costs and improve scalability.

An alternative to the one-stop, post-discharge clinic used in my study would be to follow-up all hospitalised gout patients in a rheumatology outpatient clinic (e.g. until urate targets are achieved). While many gout patients can be successfully managed in primary care, more complex patients (e.g. those hospitalised for flares and/or with comorbidities) may benefit from secondary care input. I explored this approach with stakeholders, but there was a reluctance to do so due to resource/capacity issues. There remains a perception that gout is the remit of primary care, rather than secondary care; perhaps compounded by guidance such as GIRFT.[213] A pragmatic solution to address capacity concerns might therefore be to provide as-needed secondary care support to primary care clinicians managing complex gout patients (e.g. patients hospitalised for flares). For example, rheumatologists could provide virtual

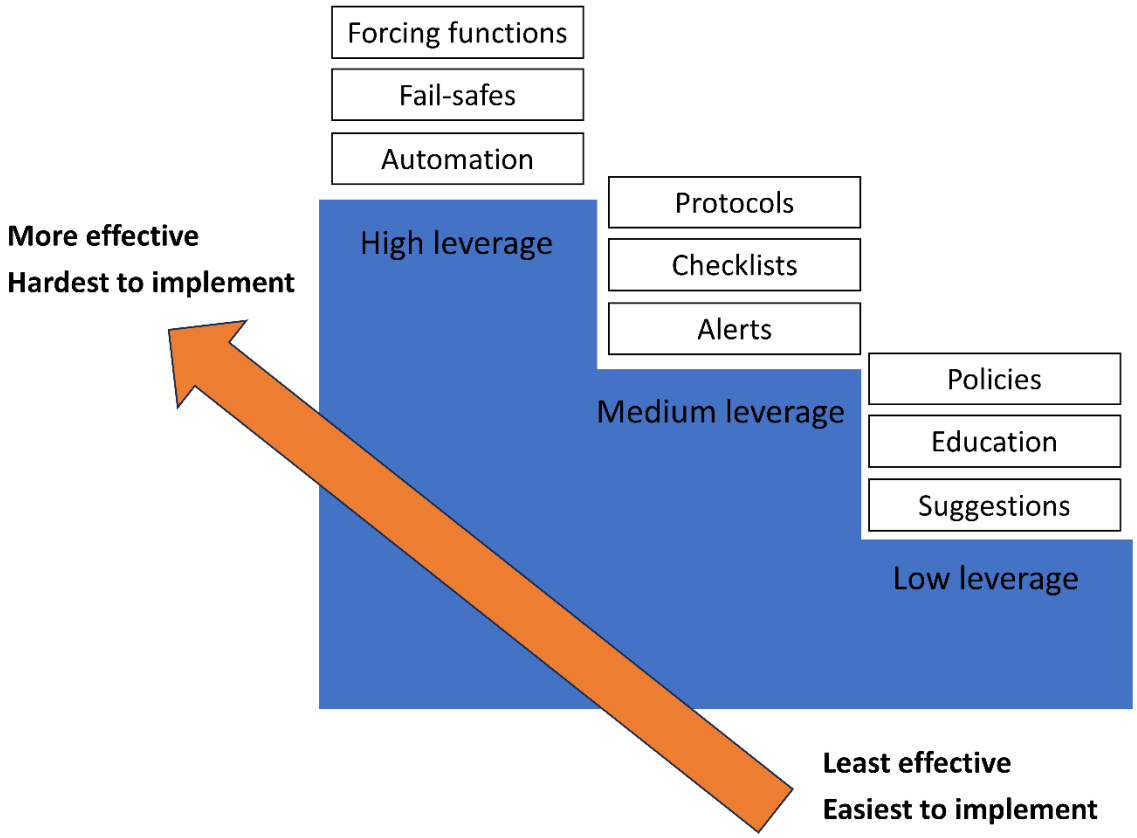
support to guide urate target attainment in the community, with face-to-face input provided in the event of recalcitrant flares or adverse effects. This would align with NHS England's drive to provide patients with flexibility in their appointments ("Patient initiated follow-up").[214]

To further reduce the burden on primary care clinicians, and empower patients, point-of-care urate meters and smartphone apps/health diaries could be used to facilitate ULT titration, as is done for conditions such as diabetes. Previous studies have validated point-of-urate meters, in relation to serum urate testing.[215] Additionally, a feasibility study performed in 60 patients in the UK, demonstrated that self-management that combined a point-of-care urate meter and a smartphone app resulted in a significantly greater proportion of patients achieving urate targets, compared with usual GP care (73% vs. 15%, respectively).[216]

There are other strategies to enact behaviour change that could potentially be applied to ULT optimisation after hospitalisations for flares. Some of the most effective strategies are those that make it easier for clinicians to do their job correctly, and harder for them to do it incorrectly (Figure 55).[217] For example, modules in electronic health record systems could be used to ensure urate levels are ordered and/or acknowledged when prescriptions for ULT are issued. This, in turn, could link directly to a treat-to-target protocol, with automated reminders sent to patients to facilitate monitoring and/or titration. Electronic dashboards (e.g. utilising the OpenSAFELY platform in Chapter 5 of my thesis) could be used benchmark outcomes such as urate target attainment between clinicians, practices and regions, and encourage behaviour change at local, regional and national levels.

To succeed in getting the majority of hospitalised patients to target, a combination of the above strategies is likely to be needed. These strategies could be based upon other models of integrating primary and secondary care. For example, fracture liaison services have been widely implemented throughout the UK.[198] These services proactively identify patients with fragility fractures, and utilise nurse-delivered interventions (e.g. education, anti-osteoporotic medications and falls prevention), followed by handover to primary care. Implementation toolkits are available to help establish these services at hospitals throughout the UK.[198]

Figure 55. Implementation strategies to enact behaviour change



Adapted from the Institute for Safe Medication Practices (https://www.ismp.org/)

Perhaps the most important strength of my study was the extensive stakeholder and patient involvement during the pathway development process. This resulted in an intervention that was strongly evidence-based and closely aligned to the barriers I had identified in Chapter 7. The involvement of study champions, who were motivated to bring about change, helped to ensure the success of the intervention. My study outcomes used routinely-collected data, which facilitated the monitoring of performance without overly burdensome data collection.

While a strength in the above regard, the reliance on a few motivated individuals to sustain the intervention could also be a barrier to the wider implementation of my strategy. For example, the rheumatology nurse specialist who delivered the post-discharge clinics in my study was highly motivated and proficient at optimising gout care. Had she become unavailable to deliver the pathway, the success of the project would have relied upon finding a suitable replacement. This was a barrier I encountered when implementing the pathway at other hospitals, where there was insufficient nursing capacity to deliver the post-discharge clinic. Time will tell how successful implementation has been at these other sites; however, the experience from this study has taught me that a post-discharge review is an important initial step in optimising care and bridging the secondary/primary care interface.

As project lead, I was not only heavily involved in designing the intervention, but also in sustaining the pathway at King's College Hospital. I designed the intervention so that care was delivered by patients' primary clinical teams; however, I remained closely involved in other aspects of the pathway. I delivered education and training sessions to relevant staff members; I reviewed gout eNotifications and hospital discharges on a weekly basis to ensure patients were booked into the post-discharge clinic; and I provided clinical support to the post-discharge clinic. While important to ensure the success of the project, it remains unclear whether a more hands-off approach would have resulted in the same outcomes. Similarly, the intervention likely benefitted from having a relatively large pool of rheumatology consultants and trainees available to support frontline clinicians in managing gout patients. Whether the outcomes would be the same at less well-resourced hospitals remains to be seen.

Another important limitation that needs to be acknowledged is the use of a historical comparator in my study. While this was chosen over a prospective, randomised control group for pragmatic reasons, it could potentially introduce bias. For example, temporal changes in service provision due to the COVID-19 pandemic could have influenced performance in the pre- vs. post-implementation periods. Of note, however, my findings from Chapters 4 and 5 highlight that hospitalised gout care was inadequate at a population level throughout this time period; any improvements observed post-implementation are therefore unlikely to be due to background temporal changes alone.

9.7 Future directions

Utilising the findings and skills I have gained from my thesis, there are several avenues I would like to explore in my post-doctoral work.

9.7.1 Real-world monitoring of gout care using the OpenSAFELY platform

By harnessing the power of routinely-collected health data, we have the potential to transform the monitoring of chronic diseases. In my thesis, I showed that the OpenSAFELY platform can be used to evaluate the epidemiology and management of gout in the UK on a near-real time basis. While important from an epidemiological perspective, this has even greater potential in routine clinical care.

Using OpenSAFELY, I could benchmark performance against national standards of care, such as those contained within the NICE gout management guideline.[35] Feedback is a powerful tool for change, and performance against NICE standards could be relayed to clinicians and patients at local, regional and national levels to encourage behaviour change. OpenSAFELY has in-built tools to facilitate dashboarding, which I have implemented for autoimmune inflammatory arthritis diagnoses (https://reports.opensafely.org/reports/incidence-and-management-of-inflammatory-arthritis-in-england-before-and-during-the-covid-19-pandemi/). I plan to expand this work further for gout, by mapping numerous guideline-aligned metrics, including ULT titration, urate monitoring, target attainment, and prophylaxis

use. In turn, this information could be used to highlight regional disparities in care, and direct resources to where they are most needed.

In addition to benchmarking performance against care standards, I hope to use the OpenSAFELY platform to evaluate interventions designed to improve gout care. For example, if I were to launch a national strategy to reduce gout hospitalisations, I would be able to monitor the number of hospitalisations and the quality of care delivered at intervention sites, and compare this with non-intervention sites. Furthermore, from a public health perspective, the near-real time data availability in OpenSAFELY will allow me to monitor the changing epidemiology of gout in the coming years. This will help to elucidate whether incident gout diagnoses start to rebound as the post-pandemic recovery continues, or whether the trend in decreasing gout diagnoses in the UK continues.[55]

9.7.2 Launching a national strategy to improve hospitalised gout care

In my thesis, I showed that it is possible to implement a strategy based upon best practice care for patients hospitalised for gout flares. When implemented at King's College Hospital, this strategy was associated with large improvements in ULT initiation and many other aspects of gout care. I intend to adapt this strategy for implementation at other hospitals throughout the UK.

While the core components of my intervention are likely to remain the same (e.g. timely ULT initiation, education, and promotion of self-management), there are several aspects that require further evaluation in a follow-on study. In particular, it remains unclear how best to facilitate urate target attainment following hospitalisations for gout flares. While intensive, nurse-led strategies can support high levels of urate target attainment in RCT settings,[31] clinical pressures mean that a comparable approach is unlikely to be deliverable in routine care. In my study, I showed that a single post-discharge review can help to navigate the transition from secondary care to primary care management; however, a single post-discharge review was insufficient for the majority of hospitalised patients to achieve urate targets. Qualitative interviews also identified key areas for improvement in the pathway: namely, a need to include clear actions plans and further targeting of patients' perceived necessity and concerns for taking ULT. From the healthcare professional perspective, there is a need to explore how to sustain training, possibly using remote delivery and contingencies to address the delivery of optimal gout care in the out-of-hours setting.

Using a hybrid implementation-effectiveness study design, I could evaluate different strategies for optimising gout care at the primary/secondary care interface. Strategies could include the direct handover of care to primary care-based nurses and/or pharmacists for ongoing ULT titration. This approach could be compared against one where hospitalised patients are followed up in secondary care until urate targets are achieved. Another approach would be to provide "light-touch" secondary care support to primary care clinicians, in addition to self-management approaches, such as point-of-care urate meters and smartphone apps. Each approach would need to be pragmatic and tailored to the individual needs of the patient and resources of the hospital/community. As demonstrated in my study,

the interventions would need to be accompanied by a multi-faceted implementation strategy to ensure the intervention is sustainable. If successful, these models of care could serve as frameworks for other chronic diseases where there is a critical transition from secondary care to primary care.

9.8 Summary

Hospitalisations for gout flares have doubled in the UK over the last 20 years. Many of these admissions might have been preventable had optimal gout care been provided to patients; however, no studies to date had evaluated strategies designed to improve hospital gout care and prevent avoidable admissions.

In my thesis, I used routinely-collected, population-level, health data to show that gout care remains sub-optimal in primary and secondary care in the UK, despite updated BSR and EULAR gout management guidelines. I showed that only a minority of patients are prescribed ULT or achieve urate targets after diagnosis. Patients most at risk of poor outcomes – for example, those with multi-morbidity – are the least likely to achieve urate targets.

Using linked primary and secondary care data, I demonstrated that the risk of hospitalisations for gout flares is greatest within the first 6 months after diagnosis. I showed that the initiation of ULT associates with long-term reductions in hospitalisations for flares. The risk of hospitalisations is lower still when urate targets are attained. This emphasises the importance of a treat-to-target strategy in the prevention of gout admissions. Despite this, I showed that urate targets are achieved in only a minority of patients after discharge from hospital; highlighting the need for improvement.

Via the OpenSAFELY platform, I evaluated the epidemiology and management of gout during the COVID-19 pandemic. I highlighted a sharp decrease in incident gout diagnoses during the early pandemic; greater than had been observed for RA, PsA or axSpA. I found that no rebound increase in gout diagnoses had occurred by early 2023, suggesting that there remains a substantial burden of undiagnosed gout as a consequence of the pandemic. Reassuringly, for patients who did present with gout during the pandemic, the standard of care provided was comparable or better than before the pandemic.

To develop an evidence-based strategy to improve hospital gout care, I conducted a systematic literature search, detailed case-note reviews and process mapping, combined with extensive stakeholder involvement. The intervention I developed consisted of an evidence-based care pathway that encouraged ULT initiation prior to discharge from hospital, followed by a nurse-led, post-discharge review to facilitate handover to primary care. After implementing this strategy at King's College Hospital, more than 90% of patients were initiated on ULT, and many other aspects of care improved significantly. Attainment of urate targets also improved following the implementation of my strategy, but not to the same extent as intensive, nurse-led interventions in a primary-care based RCT setting. A larger follow-on study is therefore essential to evaluate strategies to optimise urate target attainment after hospitalisations for flares. Only then can we truly reduce the burden of avoidable gout admissions.

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Appendices

Media interviews and publicity related to my thesis

Interview and article in The Times newspaper, 26 May 2022

https://www.thetimes.co.uk/article/gout-sufferers-are-denied-effective-pills-as-cases-rise-p0lpmbjxj

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https://www.telegraph.co.uk/health-fitness/body/gout-like-having-foot-full-glass-shards/

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https://www.dailymail.co.uk/health/article-11228333/Suddenly-gout-rise-patients-treatment-need.html

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Interview for BBC Radio 4, Inside Health, 27 July 2022

https://www.bbc.co.uk/programmes/m0019jyy

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Interview for the Rheumatology Journal Podcast, 16 March 2022

https://academic.oup.com/rheumatology/pages/podcast-archive-2020-2022

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Article on the NIHR website, 27 May 2022

https://www.nihr.ac.uk/news/just-one-in-three-people-with-gout-prescribed-preventative-medication/30697

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Institutional approvals

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15th November 2021

To Whom It May Concern

I hereby confirm that King's College Hospital NHS Foundation Trust has reviewed the study documentation and REC (research ethical committee) approval is not required as this project is deemed to be a service evaluation.

Study title: Preventing Hospital Admissions Attributable to Gout

IRAS: N/A

EudraCT no: N/A

Service Evaluation Lead: Mark Russell

Service Evaluation Supervisor: James Galloway

Research & Innovation Governance Manager
King's College Hospital NHS Foundation Trust

Appendix 1: Approval for service evaluations at KCH

Action	Responsibility	Completed – sign and date (NB: Note if 'not applicable')
1. Honorary contract obtained, if required	Service Evaluation Lead	7/7/2021
2. Service Evaluation Supervisor identified	Service Evaluation Lead	7/7/2021
3. Relevant Trust policies read and understood	Service Evaluation Lead	7/7/2021
4. Advice provided by Patient Experience Team, if required	Patient Experience Manager	22/7/2021
5. Approval to proceed obtained	Service Evaluation Supervisor	22/7/21

Letter template for use in gout follow-up clinics

Dear Patient and GP,

Diagnosis: Gout

Recommendation to GP: Please continue prescribing allopurinol (details below)

I reviewed you regarding your recent hospital attendance for a gout flare. We discussed your diagnosis and the reasons for recommending treatment. Without treatment, gout can not only damage your joints, but also affect other organs, such as your kidneys. We talked about diet and lifestyle changes that can help. We discussed how medicines such as allopurinol can help prevent flares, joint damage and complications.

If you would like to read more about these topics, I would recommend two excellent online resources on the Versus Arthritis (https://www.versusarthritis.org/about-arthritis/conditions/gout/) and UK Gout Society websites (http://www.ukgoutsociety.org/).

Monitoring your condition:

Gout is caused by urate crystals in your joints. We can measure your urate levels with a blood test. Your recent urate level was INSERTVALUE micromol/L. We recommend that you should aim for a target level of below 300.

Treatment advice:

We recommend starting allopurinol to help lower your urate levels. Allopurinol is a long-term medication and should not be stopped if you experience a gout flare. We can provide your initial prescription, but your GP will be able to supply you with ongoing prescriptions. The dose of your medicine may need to be increased to achieve your target urate level.

Things to watch out for:

Rash: Should you notice any new skin rashes after starting allopurinol, please stop allopurinol and speak to your doctor.

Flares: Some patients experience gout flares in the first few months after starting or increasing allopurinol. This is normal and does not mean the medicine is not working. The benefits of allopurinol can take several months to become noticeable, and stopping and starting allopurinol can make things worse. Attacks of joint pain should become less frequent when you reach the target urate level.

Managing gout flares:

If you experience a gout flare, you should start a medicine to treat the inflammation as soon as possible. We have asked your GP to prescribe you a rescue pack of flare treatment. This can be taken at the same time as allopurinol. During a flare, stay well hydrated, rest the inflamed joint(s), elevate them where possible, and apply ice-packs. If your flare symptoms do not improve within 1-2 days of starting treatment, or should you feel unwell, speak to a doctor.

Recommendations to your GP:

1. Please continue allopurinol. An initial prescription for allopurinol INSERTVALUE once daily for 28 days has been provided.
2. Please increase the dose of allopurinol by INSERTVALUE every 4 weeks until the target serum urate of ≤300 micromol/L has been achieved. The maximum recommended dose of allopurinol is 900mg daily in normal renal function or 300mg if GFR 20-50ml/min.
3. We advise co-prescribing colchicine 500 micrograms once daily until the target urate is achieved (usually 3-6 months). Exceptions include renal impairment (GFR <45ml/min) or interacting medications (e.g. statins).
4. Should there be ongoing gout flares despite maximally-tolerated allopurinol, consider switching allopurinol to febuxostat.
5. We recommend prescribing a rescue pack of flare treatment (colchicine, NSAID or prednisolone, depending on risk factors) for patients to take at the first sign of flare.
6. We advise annual screening for comorbidities associated with gout, including renal impairment, diabetes mellitus, hypertension and hyperlipidaemia.
7. We HAVE/HAVENOT arranged a further appointment in the rheumatology clinic. Please contact us should there be any management queries.

Prompt sheet for use in gout follow-up clinic

In this document, we highlight some key topics that we recommend discussing with patients in the gout follow-up clinic. It is not an exhaustive list but can hopefully provide some useful prompts (see the SOP for further information). This prompt sheet has been adapted from the education information used in Doherty *et al.*'s study (Lancet, 2018).[31]

Discussion around current symptoms and medications:

- Review flare symptoms following recent hospital attendance
- Prior history of flares (how frequent; required hospitalisation?)
- Review current flare treatments and urate-lowering medications
- Check if any side effects experienced with these medications
- Review previous use of urate-lowering medications, doses taken, and any side effects (if any)

Clear verbal explanation about the diagnosis of gout, backed up by written information (e.g. Versus Arthritis booklet), including:

- We know its cause - it is due to deposition of urate crystals in and around the joints
- Crystals form when serum urate levels rise above a critical "saturation point"
- When sufficient crystals have formed in joint cartilage, some "spill out" into the joint cavity, triggering severe inflammation of the joint lining and presenting as a gout flare
- During flares, patients often experience severe pain, warmth and swelling of affected joints
- Can affect their ability to work and mobilise
- Over years, flares may increase in frequency, spread to other joints, and cause joint damage
- Continuing deposition may result in hard, slowly expanding lumps of crystals ("tophi") that can damage joint cartilage and bone, and appear as lumps under the skin
- Additionally, there is increasing concern that persistently high urate levels increase the risk of heart disease, chronic kidney disease and dying younger
- Reduction and maintenance of urate levels below the saturation point stops production of new crystals and encourages existing crystals to dissolve – so, eventually there are no crystals and, therefore, no gout
- The target serum urate level we aim for in most patients is 300 (micromol/L) or below – we can check this on a routine blood test

Individualised explanation of relevant risk factors that elevate urate above the saturation point, including:

- Hereditary factors, which result in inefficient excretion of urate by the kidneys
- A high body mass – most urate in the body is made by the body's cells by breaking down "purines", and this production increases with obesity
- Chronic kidney impairment
- Certain medications, such as diuretics (water tablets)

A diet containing foods that are high in purines

Individualised advice on preventative urate-lowering medications (ULT):

How these medications work – by lowering serum urate levels to below the level (300 micromol/L) where crystals form and gout flares occur

The importance of these medications in preventing flares, joint damage, disability and other gout-associated complications, such as kidney damage

Recommendation that all patients with gout are offered ULT

ULT medications are long-term treatments and are continued for life in most patients; gout flares usually return if they are stopped

First-line recommended ULT is allopurinol (Versus Arthritis booklet)

How we start allopurinol and uptitrate dose monthly (under guidance of GP) until the target urate level is reached

Initially, this requires regular (usually monthly) blood tests with GP to check urate levels; once target level achieved, usually only an annual blood test is required

Check for previous reactions with ULT (e.g. rashes), other contraindications (e.g. use of azathioprine/mercaptopurine) and renal function

If commencing ULT, discuss the potential side effects, including the risk of rash

Warn patients to monitor for a new rash after starting (if this occurs, stop medication and seek medical attention)

Warn patients that ULT can trigger flares when first starting or changing doses – important to continue the medication and take flare treatment – this does not mean the ULT is not working (takes time to reach optimal dose)

Consideration of prophylaxis to reduce risk of provoking flares when starting and titrating ULT (vs. rescue pack approach)

Individualised advice on management of a gout flare:

Which treatment options are available (colchicine, NSAIDs, corticosteroids)

Choice depends on patient preference and individual risk factors

Aim to start as soon as the first flare symptom is noticed (consider rescue packs)

Unlike urate-lowering medications, these are not long-term medications (although in some patients, we use low-dose anti-inflammatories to prevent flares when starting ULT)

Can be used at the same time as ULT medications – do not stop ULT during flares

Check for contraindications and interactions before prescribing/recommending a medication

Advise patients on side effects to monitor for (e.g. diarrhoea with colchicine)

Other approaches that can help flares (rest, ice, elevation)

Safety netting – if a flare does not improve within 24-48 hours; worsens despite treatment; or they feel unwell – seek urgent medical attention

Individualised advice on ways to reduce urate levels by lifestyle modification, if appropriate:

Reducing weight if overweight or obese

Reduction in excessive intake of alcohol and sugary drinks

Reduce intake of purine-rich foods (dietary advice sheet)

Healthy diet/lifestyle important for reducing urate levels and other complications; however, most patients will still require ULT to prevent flares and complications from gout

Next steps:

Request blood tests if required (see gout order sets on EPR)

Obtain prescriptions if needed (advise that ongoing prescriptions should come from GP)

Recommend that patients book a follow-up appointment with their GP (if ULT has been commenced, they will need to obtain a repeat prescription from GP before this runs out)

Determine whether ongoing outpatient rheumatology follow-up is required (see SOP)

If no rheumatology follow-up required, advise that this is a single appointment only, but that recommendations will be sent via letter to them and their GP (see EPR letter template).

Interview topic guide

Information for all participants

- We would like to invite you to participate in this questionnaire as part of a quality improvement project.
- We have developed a care pathway for patients who attend hospital for gout flares.
- Gout is a common, treatable form of arthritis. It is characterised by episodes of joint pain, which can require admission to hospital when severe. There are highly effective medications available to treat and prevent gout flares, yet previous studies have shown that hospital admissions for gout flares have increased substantially in recent years.
- The aim of the care pathway is to improve the quality of care for patients, and reduce avoidable hospital admissions.
- We are interviewing patients and staff members, to gather their thoughts on the pathway and how to improve care for patients. This information will be used to modify the pathway.
- The results of this study, along with the care pathway and its development process, will be communicated to the public and health professionals via research articles, presentations, and a dissertation.
- Your participation in this interview is entirely optional. The information will be collected anonymously. You are free to withdraw from the study at any time and without giving a reason.
- If you have any questions, please do not hesitate to contact the principal investigator: Dr Mark Russell; mark.russell@kcl.ac.uk

Questions for all participants

- Are you willing to participate in this interview?
    - Check informed consent form has been signed
- Are you a patient, ED doctor, ED nurse, rheumatology doctor, rheumatology nurse specialist, general medicine doctor, elderly care doctor, GP, junior doctor (i.e. pre-specialty training)?

Questions for patients

First section focuses on what happened during the hospital admission:

- Tell me about your most recent admission/ED attendance for a gout flare?
- We are looking to understand how gout was explained to you during your attendance: tell me about any gout education you received during your attendance?
    - Happy with the content/how it was explained?
    - Anything you would do to change/improve?
- Was the importance of preventative urate-lowering medications (e.g. allopurinol or febuxostat) discussed with you during your attendance?
    - If yes, what were the key bits of information you took away from this?
- If you were prescribed any urate-lowering medications, did you take them after discharge?
    - Describe how you are taking these medications?
    - Were you told how to get a further supply of the medication?
    - Tell me your thoughts on taking this medication long-term?
        - If barriers, what would help improve this?

- Were you told about the need for blood urate tests and/or increasing the dose of the preventative medication?
    - What are your thoughts on having to have blood tests until your target blood levels are achieved?
    - Did you/are you planning to do so?
    - Any "costs" of regular appointments?
    - If barriers, what would help to improve this?
- What advice were you provided with on discharge from hospital?
- Were you told what to do if you suffer from a further gout flare?
    - What were you told to do?
- Is there any additional you have liked to have been done to improve the care you received during your attendance?

Next, focus on follow-up telephone call (if follow-up telephone call received):

- Tell me about your experience of the gout follow-up appointment?
    - What was helpful/not helpful?
- Could anything be done differently to improve this?
- Was the format (i.e. telephone call) acceptable to you? Would in-person have been preferable?
- Did the call change how you plan to manage your gout?
    - Why/why not

Finally, focus on other follow-up and post-discharge care:

- Did you receive any other follow-up (e.g. GP or rheumatology) for your gout after discharge?
    - Tell me more about this
    - Was it helpful?
- Did this follow-up change how you managed your gout?
- Do you have any further appointment scheduled?
    - Do you plan to make any further appointments?
- Have you experienced any further gout flares since your hospital attendance?
    - If so, how many? What did you do?
- Do you think your gout flares are more or less frequent, or no different, than prior to your attendance?
- Do you think you are more or less likely, or no different, to need to come to hospital for a gout flare, relative to before?
- Overall, how positive or negative would you say you feel about the management of your gout?
    - More or less than before?
- Do you have any other suggestions, comments or improvements?

Questions for clinicians

- What is your clinical role?

First, general pathway-related questions:

- Are you aware of the gout care pathway? Have you used it?
- If yes, tell me about your experiences of using the pathway

    - Which aspects of the care pathway were most helpful/worked well?
    - Which aspects of the care pathway were least helpful/do not work as well?
- Anything you would do to change/improve the pathway?
- How do you access the pathway?
    - Easy to access? Any improvements?
- Did you receive any training/education on gout management or use of the pathway?
    - Was this useful?
    - Anything you would do to change how the education was delivered/the content?
- Do you use the EPR gout order sets?
    - Helpful?
    - Could they be improved?
- What are your thoughts on requesting a blood test for all patients presenting with gout flares?
    - In-hours vs. out-of-hours
- Do you send an "inpatient gout notification" on all patients, including ED discharges?
- Approximately, what proportion of patients with gout flares do you discuss with rheumatology?
    - Which patients? Why?
- Are you happy managing a patient out-of-hours (e.g. when rheumatology not available)?
    - What would you do if there was diagnostic uncertainty and out-of-hours?
    - What if a joint aspiration was required out-of-hours?
- Do you think the admission avoidance pathways are helpful in avoiding admissions in people with gout flares?
- Do you think gout follow-up calls/clinics are helpful?
    - Do you think they should be telephone or in-person, or mixture?
- How likely are you to continue using the pathway going forward?
    - Why? Why not?
    - Barriers to using it? How could we overcome these?
- Do you think the pathway improves care for patients? Do you think it will reduce the number of gout presentations to ED/hospital?
    - Why? Why not?
- Any other barriers to implementation of the pathway that you can think of?
- What do you think would motivate clinicians to engage with the care pathway going forward?
    - Any other implementation strategies you would recommend?
- Do you think there are any cost implications?
    - Do the benefits outweigh these costs?

Finally, gout education and management questions:

- Do you feel confident providing education to patients on gout?
    - Anything you are not confident with?
- When discussing the potential benefits of preventative urate-lowering therapies (e.g. allopurinol), what information do you typically provide to patients?
    - Prevention of flares, quality of life, comorbidities e.g. kidney impairment?
- What safety information (if any) do you provide to patients before/after prescribing urate-lowering medications?
- Are you comfortable initiating/titrating urate-lowering medications in an acute setting (i.e. during a flare)?
- What would you do if you weren't sure whether to start a urate-lowering medication?

    - In-hours vs. out-of-hours?
- What information do you typically provide to patients and GPs about dose titration of ULT and target urate levels?
- Do you think there are barriers to patients receiving optimal care in this regard?
    - How to overcome?
- What discharge advice do you typically provide to patients?
- What do you advise patients to do in the event of future flares?
- What follow-up do you recommend to patients?
    - GP follow-up? How long after discharge?
    - Do you inform patients to expect gout follow-up clinics?
- What discharge advice do you typically provide to GPs?
- Do you have any other suggestions, comments or improvements?