DOCTOR OF MEDICINE

Renal and Blood Pressure Effects of Xanthine Oxidase Inhibitors in the FAST trial

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Declaration

I confirm that I, Claudine Jennings, am the sole author of this thesis. I confirm that unless otherwise stated, all references cited have been consulted and this thesis is a true record of work completed. This thesis has not been previously accepted for a higher degree.

Signature: _____
Dr Claudine Jennings

Date: _____

Abbreviations

ACS	Acute coronary syndrome
APTC	Anti-Platelet Trialists' Collaboration
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EULAR	European League Against Rheumatism
FAST	Febuxostat versus Allopurinol Streamlined Trial
MDRD	Modification of Diet in Renal Disease Study Equation
MI	Myocardial infarction
NAFLD	Non Alcoholic Fatty Liver Disease
PVD	Peripheral vascular disease
RAS	Renin-Angiotensin System
sUA	Serum Urate
TIA	Transient ischaemic attack
ULT	Urate Lowering Therapy
XOi	Xanthine oxidase inhibitor

Tables and Figures

Chapter 1

Summary

1) Summary

Hyperuricaemia and Human Disease

In humans, uric acid is the end product of purine metabolism and is predominantly excreted via the kidneys. Evidence is emerging that hyperuricaemia is not just a risk factor for the development of gout but is also an independent cardiovascular risk factor and is associated with systemic detrimental health effects including the metabolic syndrome, development of essential hypertension and renal function decline. Establishing a causal link between hyperuricaemia and cardiovascular morbidity is challenging as they share common risk factors (eg. aging, obesity, dietary factors, smoking) and evidence is lacking that treating hyperuricaemia has an impact on cardiovascular outcomes.

Xanthine oxidase inhibitors in the management of hyperuricaemia

Management of hyperuricaemia is predominantly undertaken in the context of symptomatic gout and there are three main strategies which include increasing urinary urate excretion with uricosuric agents, blocking formation of uric acid with xanthine oxidase inhibitors or breaking down uric acid into more soluble waste products with urokinase. In current clinical practice, the treatment of hyperuricaemia is mainly with the xanthine oxidase inhibitors: allopurinol and febuxostat. Inhibition of xanthine oxidase effectively block formation of uric acid and lower serum urate (sUA). They are readily available, relatively inexpensive and generally well tolerated however, their use is not risk

free due to an extremely rare but potentially life threatening side effect of a Stevens-Johnson like skin reaction which potentially limits their widespread use.

The Febuxostat versus Allopurinol Streamlined Trial (FAST)

The Febuxostat versus Allopurinol Streamlined Trial (FAST) is a cardiovascular safety study comparing febuxostat and allopurinol, in patients over the age of 60 who are already treated for gout. The FAST trial protocol ensures that urate levels are controlled to meet European League against Rheumatism (EULAR) targets (sUA ≤357 µmol/L) at randomisation. Patient data is collected at a screening visit, an up-titration visit (if required), at 3-monthly nurse follow up and at an annual review. Patients in the FAST trial are followed up for a minimum of 3 years and therefore provide an opportunity to study the additional effects on blood pressure and renal function of both currently available xanthine oxidase inhibitors.

Objectives of this Thesis

1. To review gout management with titration of allopurinol dose.
2. To establish whether urate control with either febuxostat or allopurinol lowers the blood pressure of patients in the FAST trial.
3. To establish whether changes in serum urate over one year impact on renal function as measured by creatinine clearance in FAST patients.

Studies Presented

1) Up-Titration of Allopurinol in Patients with Gout

Patients recruited into the FAST trial have their sUA levels measured at the screening visit and patients with sUA >357 µmol/L require up-titration of their allopurinol dose to achieve EULAR recommended sUA levels prior to randomisation. The up-titration process in FAST involves increasing allopurinol dose by 100mg and re-checking sUA after 2 weeks. Dose increases of 100mg are repeated every fortnight until sUA is ≤357 µmol/L or the patient is taking their maximum tolerated dose of allopurinol. This analysis of FAST patients looked at the proportion of patients who required up-titration, the number of up-titrations required and any associated side effects.

2) FAST Blood Pressure Sub-Study

Home monitored blood pressure was measured in FAST patients who were recruited into a blood pressure sub-study between December 2012 and January 2014. Patients recorded home blood pressure measurements after randomisation, after optimisation of urate lowering therapy (if applicable), after a washout period and after 8 weeks of randomised treatment. Analysis was undertaken looking at changes in blood pressure between patients randomised to allopurinol and those randomised to febuxostat and changes in blood pressure in relation to changes in sUA.

3) Interim Analysis of Renal Function at Annual Follow Up in FAST patients

Renal function is measured in all FAST patients with blood tests taken at screening and at every annual visit. Serum creatinine is used with screening data (age, sex, height and weight) to calculate an estimated glomerular filtration rate (eGFR) and creatinine clearance (CrCl) for every patient. The renal function interim analysis looked at data from consecutively randomised FAST patients recruited between 1st January 2012 and 31st May 2013 and assessed how changes in sUA related to changes in CrCl over 1 year.

Chapter 2

Introduction to the FAST Trial and Literature Reviews

2a) Introduction to the Febuxostat versus Allopurinol Streamlined Trial

The Febuxostat versus Allopurinol Streamlined Trial (FAST) [ISRCTN72443728] is a prospective, randomised, open-label, blinded endpoint trial comparing the cardiovascular safety of febuxostat and allopurinol [1]. FAST is funded by Menarini, Ipsen and Teijin and is sponsored by the University of Dundee.

Background to FAST – Gout and Gout Management

The current prevalence of gout in the UK in men over 40 years is 2.5%, making it the commonest inflammatory arthropathy [2]. The symptoms of gout develop when there is deposition of monosodium urate crystals in joints and tissues and include a painful and potentially destructive arthropathy and formation of gouty tophi. The risk of gout flares and the development of complications including joint destruction can be effectively reduced by lowering serum urate (sUA) levels. Historically this involved advising a low purine diet and use of uricosuric agents to increase urinary excretion of uric acid, however gout management was revolutionised in the 1960's with the introduction of the xanthine oxidase inhibitor (XOi), allopurinol. Allopurinol works in the purine metabolism pathway by inhibiting the xanthine oxidase enzyme and blocking formation of uric acid. This leads to a very effective reduction in sUA levels and associated improvements in gout prognosis and joint symptoms [3].

For decades allopurinol remained the only available XOi until the emergence of febuxostat, a non-purine based and more selective XOi which entered clinical trials in 2003. The APEX [4], FOCUS [5], EXCEL [6] and FACT [7] trials demonstrated the clinical effectiveness and safety of febuxostat in the management of hyperuricaemia. Comparative studies with allopurinol established the potency of febuxostat and final phase III trials demonstrated that 80mg febuxostat was superior to 300mg allopurinol for achieving and maintaining sUA levels within recommended guideline levels [8]. Febuxostat was licensed for urate lowering in patients with symptomatic hyperuricaemia in 2008.

Current UK clinical guidelines for management of gout suggest urate lowering therapy (ULT) with xanthine oxidase inhibitors is discussed and offered to all patients with a diagnosis of gout. Allopurinol remains the first line option for symptomatic hyperuricaemia. ULT is particularly advised in patients with more than 2 gout flares per year, those with evidence of tophi or destructive arthritis, patients with impaired renal function, diuretic use or a history of uric acid renal calculi [9]. UK Guideines recommend targeting a serum urate level <300 µmol/L whereas European and American guidelines suggest a target sUA <357 µmol/L [10, 11]. The serum urate targets in rheumatology guidelines prevent crystal formation and dissolve away existing crystals and effectively reduce the risk of gout flares and gout complications (arthropathy and gouty tophi). There are no guidelines or accepted clinical thresholds for measuring or targeting serum urate levels outside of the management of gout.

Background to FAST - Cardiovascular Safety

The study populations involved in the febuxostat trials were predominantly male patients with gout who generally had a high burden of risk factors for cardiovascular disease. Cardiovascular events were therefore likely to be relatively common in this patient population and the phase III febuxostat trials showed a numerical, but non-statistically significant increase in investigator reported cardiovascular events in patients taking febuxostat compared with those taking allopurinol [8]. No causal relationship was established but due to this finding, the European Medicines Agency imposed a post-licensing commitment on the manufacturers of febuxostat to undertake a cardiovascular safety study (European Union Risk Management Plan for febuxostat Version 2.0; 19 February 2008). The FAST trial was devised to fulfil this post-licensing requirement and formed part of the pharmacovigilance plan for febuxostat.

Overview of FAST Protocol

FAST began recruitment in January 2012 at study centres in the UK and Denmark. Recruited patients are aged over 60 years, already prescribed allopurinol for symptomatic hyperuricaemia (gout) and have at least one additional cardiovascular risk factor (listed in FAST protocol paper, Appendix 3). FAST exclusion criteria include eGFR <30 ml/min, significant liver impairment, life-threatening co-morbidity, significant heart failure and active malignancy. Patients are mainly recruited from primary care.

Invited patients are seen at a screening visit where eligibility is confirmed and medical history and baseline measurements are recorded by a FAST research nurse. If eligible, patients undergo an allopurinol lead-in phase (detailed below) and are then randomised 1:1 to either allopurinol or febuxostat. Patients are followed up for a minimum of 3 years.

The primary endpoint of the FAST trial is the first occurrence after randomisation of any event included in the Anti-Platelet Trialists' Collaboration (APTC) composite endpoint of hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation) or death due to a cardiovascular event [12]. Secondary and exploratory endpoints will be evaluated using a time to event analysis. Secondary endpoints include all-cause mortality and hospitalisation for any of the following conditions: heart failure, unstable angina, coronary revascularisation, cerebral revascularization, TIA, non-fatal cardiac arrest, vascular thrombotic event and arrhythmia with no evidence of ischaemia.

A total of 456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms and the power calculation requires recruitment of 2282 patients in each treatment arm (allowing for 20% drop-outs, recruitment target is 2853 patients in each treatment arm equaling 5706 patients in total). Potential endpoints are reported by research nurses and study doctors and final endpoint data is collected via

record linkage [13]. Endpoint data is adjudicated by an independent endpoint committee blinded to randomised treatment.

The allopurinol lead-in phase, prior to randomisation allows optimisation of the allopurinol dose to control sUA to the recommended European League Against Rheumatism (EULAR) target of ≤357 µmol/L (<6.0 mg/dL) [10]. This lead-in phase is required to ensure comparison of equally potent urate lowering treatment (as standard dose febuxostat lowers sUA more than smaller (100-200mg) doses of allopurinol). Approximately one-third of FAST patients require up-titration of allopurinol during this lead in phase [14]. If screening sUA is >357µmol/L the daily dose of allopurinol is increased by 100mg and sUA levels re-checked after 2 weeks. This process is repeated until EULAR urate target is reached or the patient is taking their maximum tolerated dose of allopurinol. After randomisation there is a minimum 7 day washout period during which the patient stops taking allopurinol prior to starting their randomised therapy.

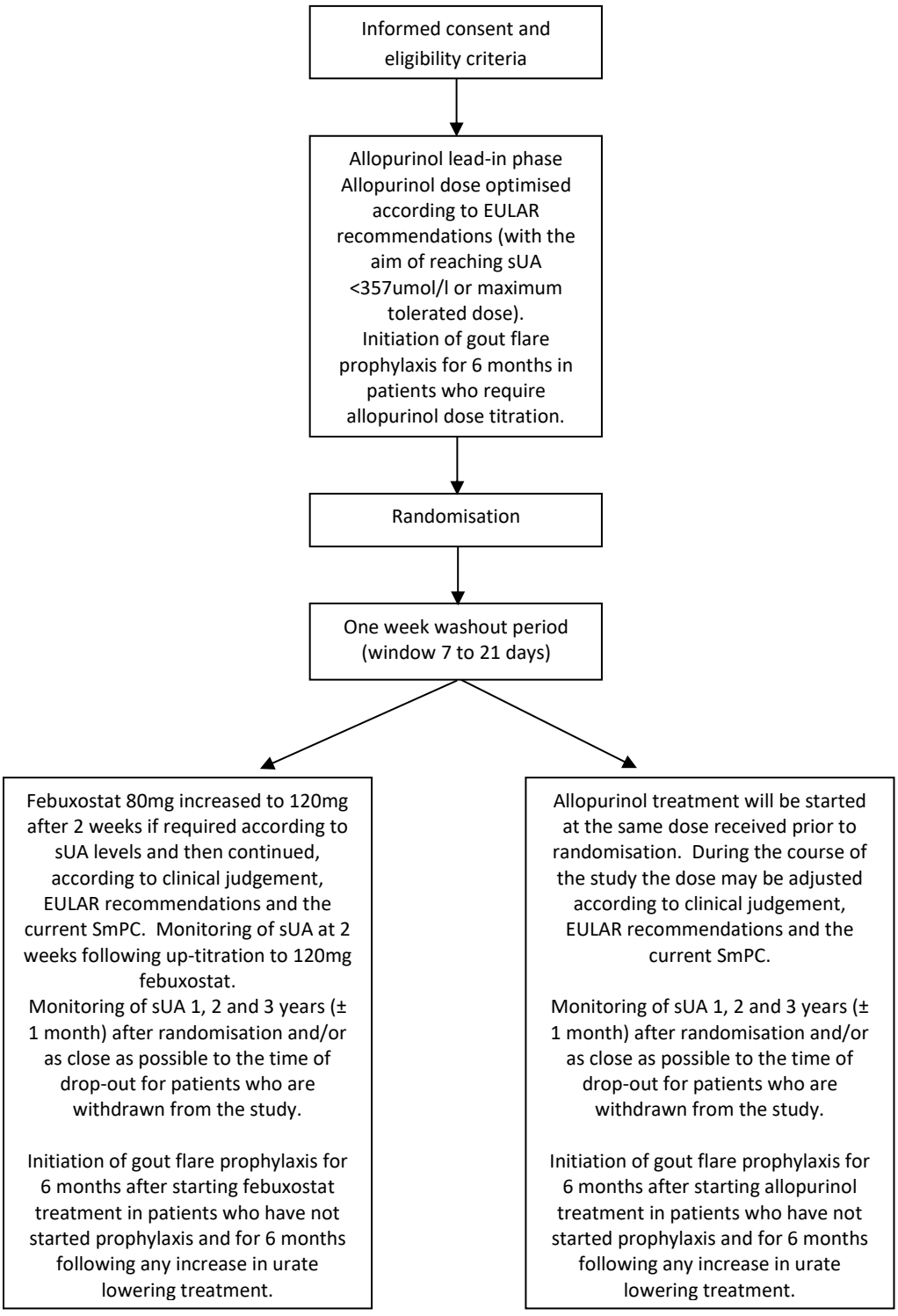
Gout flare prophylaxis with either low dose colchicine or NSAID with gastric protection is offered to all patients during the allopurinol lead in phase and for 6 months post randomisation. Post randomisation, allopurinol dose is continued at the dose determined during the allopurinol lead-in phase and febuxostat is commenced at 80 mg daily with potential to increase to 120 mg daily if sUA is above the EULAR target at a two week check. All trial medication is open label and supplied directly to each patient by post from the Dundee University research pharmacy [15].

A flow diagram summarising the FAST trial is shown in Figure 2.1.

FAST Trial – Research Opportunities

The data collected in FAST includes extensive demographics and screening data on a group of patients with increased burden of cardiovascular risk. The length of follow up and access to patients provided the opportunity to investigate other potential benefits in management of serum urate levels with use of XOi's. Blood pressure was chosen to investigate as a sub-study as hypertension is common and widely treated however many patients do no regularly achieve target levels and even modest improvement in blood pressure have a significant impact in reducing risk of stroke and heart disease. Whether urate lowering affects blood pressure is therefore an important clinical question. Regular contact with FAST patients and the research nurses facilitated delivery of a blood pressure sub-study and using patient recorded home measurements was an efficient and cost effective method of data collection. The renal function interim analysis used data already collected and stored in the FAST database. Although only one year of data is presented in this thesis, when FAST completes there will be 3-5 years of follow up data in a large population of high risk patients. This would provide a very significant data set adding to current small interventional trials and large observational studies investigating management of hyperuricaemia in the context of preventing and managing renal impairment.

Figure 2.1: Flow diagram summarising the FAST trial



2b) Biology of Uric Acid

Uric acid is a compound of carbon, nitrogen and hydrogen with the formula $C_5H_4N_4O_3$. The terms urate and uric acid are often used interchangeably however the difference is due to the charge of the molecule which can vary according to temperature and pH. At physiological pH the majority or uric acid exists as hydrogen urate ion so is simply referred to and measured as serum urate.

Uric acid is the end product of purine metabolism in humans and higher primates as these species lack the active uricase enzyme and therefore cannot further break down uric acid into more soluble waste products. In the purine metabolism pathway, xanthine oxidase enables the conversion of xanthine to hypoxanthine and finally to uric acid. This conversion is associated with the production of oxidants including superoxide anion and hydrogen peroxide. However, uric acid itself can act as an anti-oxidant as under physiological pH the donation of an electron to form urate means that electron can interact with other substances including hydrogen peroxide, hydroxyl radical, peroxynitrite, and nitric oxide and reduce oxidative stress. This is a highly complex system as some of these reactions then in turn also produce free radicals and alkylating species that may be damaging [16].

Evolutionary theories developed with advances in paleogenetics help to determine when mutations occurred in the human genome and this can then be compared with climate and anthropological data to evaluate the driving forces behind genetic evolution. The

evolutionary path leading to loss of function of the uricase enzyme provides some insight into the mechanisms by which levels of uric acid affect human health. There must have been a reason why humans evolved without the ability to break down uric acid and therefore higher serum urate levels must have conferred a survival advantage to our early ancestors. A number of theories have attempted to explain this phenomenon. One theory centers on the increased anti-oxidant potential of higher levels of uric acid which would potentially confer longevity, improved brain function and a better innate immune system to fight infection and protect against cancer. An alternative theory relates to blood pressure and insulin resistance. The ability to maintain blood pressure, particularly on a salt poor, hunter/gatherer diet and reduce the effects of insulin to enable fat storage in times of famine would clearly have provided a survival advantage to early man [17, 18].

Humans have significantly higher serum urate levels than most other mammals due to the lack of the uricase enzyme and this can lead to problems when animal (particularly rodent) models are used to research human disease. The mechanism by which hyperuricaemia raises blood pressure has been investigated in rat models which show that if the uricase enzyme is blocked there is elevation in blood pressure associated with reductions in endothelial nitric oxide and stimulation of RAS. Uric acid is also linked to microvascular damage in the kidneys due to effects of uric acid on vascular smooth muscle and endothelial cells. This microvascular damage preferentially targets salt retention which exacerbates hypertension and increases overall risk of cardiovascular events[17].

The potential role of uric acid to increase insulin resistance leading to obesity and the metabolic syndrome has also been studied. The mechanism is likely due to uric acid blocking the action of insulin by reducing endothelial nitric oxide and direct effects on adipocytes. The phenomenon of high fructose diets linking to high uric acid levels and inducing the metabolic syndrome has been widely researched [19]. High intake of fructose alters usual energy metabolism and links to ATP depletion in the liver, this is exacerbated by high uric acid levels and ATP depletion in the liver affects how cells transfer and store energy and increases the risk of NAFLD and the metabolic syndrome [16]. The link between uric acid and inflammation may be due to urate acting as a physiological substrate for myeloperoxidase. Urate is readily oxidised by myeloperoxidase and the products of this interaction include reactive hydroperoxide and enhanced depletion of nitric oxide both of which have the potential to exacerbate inflammation [20].

Uric acid has a complex role in the human body and its potential involvement in oxidative stress, systemic inflammation and intrahepatic fructose metabolism have been extensively studied. Lowering urate levels with xanthine oxidase inhibitors is highly effective in lowering measured serum urate however the wider implications of this in terms of microvascular effects are gradually being better understood however this is an ongoing area of research.

2c) Review of Hypertension and Hyperuricaemia: A Target for Treatment

Abstract

Hypertension is a significant cardiovascular risk factor with multifactorial aetiology. The link between hypertension and hyperuricaemia has been noted for over a century however determining whether this link is causal and whether there is a role for management of hyperuriaemia in the context of hypertension has been more problematic. Over the past two decades research in this area has dramatically increased with development of animal models of hyperuricaemia and use of large observational cohorts. There is an emerging body of evidence that hyperuricaemia should be considered an independent risk factor for the development of essential hypertension and that further research into the management of hyperuricaemia is required.

Introduction

Hypertension is a leading risk factor for cardiovascular disease and worldwide prevalence of hypertension is increasing. In 2000 26% of the world's adult population (over 1 billion people) were considered to have hypertension and in 2009 the WHO reported that hypertension had a causative role in the deaths of over 7.5million people [21, 22]. Prevalence of hypertension in adults of 16 years or older in the UK was 31.5% in men and 29.0% in women in 2010 [23]. The majority of hypertension is considered to be essential hypertension which develops due to a complex interplay of genetic, lifestyle and environmental factors. Cardiovascular risk associated with increasing blood pressure is

continuous with 7% increase in mortality from ischaemic heart disease and 10% increased risk of mortality from stroke for every 2mmHg rise in population blood pressure [24]. Therefore even small improvements in population blood pressure control are likely to have a significant impact on long term public health. Significant efforts are directed at addressing hypertension as a cardiovascular risk factor and one area that has fallen in and out of favour over the years is the role of hyperuricaemia in the development of hypertension and as a potentially modifiable cardiovascular risk factor. There is a growing body of evidence supporting the association between hyperuricaemia and the metabolic syndrome [25], chronic kidney disease [26] and atherosclerosis [27] as well as hypertension which will be the focus of this review. The question that now needs to be answered is whether there is a role for actively lowering serum urate (sUA) levels to better manage these associated conditions. Small trials have been conducted looking at whether reduction of sUA levels influences blood pressure control and there is now a growing consensus that a large randomised controlled trial is needed to finally answer this question [28].

PubMed, Web of Science and Medline databases were searched using the terms hyperuricaemia, uric acid, urate, hypertension, blood pressure, cardiovascular, xanthine oxidase inhibitor, uricosuric, allopurinol and febuxostat in English language publications from 1975 to July 2013. Abstracts were reviewed by category and references retrieved for papers meeting relevance criteria, reference lists of selected papers were scrutinised for relevant papers and data synthesised by themes [29].

Definition of Hyperuricaemia

Uric acid is the end product of purine metabolism in humans and increased sUA levels may be seen due to high dietary purine intake (particularly shellfish, red meat and beer), in conditions of increased cell turnover or cell death (for example following cytotoxic chemotherapy) and if renal function is impaired (urate is approximately 70% renally excreted). Urate levels generally rise with increasing age and hyperuricaemia is also seen in the metabolic syndrome partly due to hyperinsulinaemia impairing urate excretion [19]. The definition of hyperuricaemia varies but is generally considered to be levels above the serum saturation point of uric acid (approximately 6.8 mg/dL). Above this level uric acid may precipitate out of solution and be deposited in joints and tissues causing the recognised complication of gout. Guidelines for the management of gout recommend achieving sUA levels below 6mg/dL in order to reduce gout flares and complications [30]. There are currently no guidelines or recommendations for the management of asymptomatic hyperuricaemia.

Hyperuricaemia and Evolution

Hyperuricaemia is an almost uniquely human problem due to the fact that humans have a loss of function mutation affecting the uricase enzyme which prevents further breakdown of uric acid into more soluble waste products. This mutation occurred over 15 million years ago, during a time of intense climatic upheaval when food, water and salt supplies were scarce, and resulted in significantly higher sUA levels in humans than in most other mammals. This mutation is thought to have conferred an evolutionary advantage by

enabling our early ancestors to retain sodium, maintain blood pressure with a salt poor diet and augment fat storage from fructose found in fruits [31, 32]. Unfortunately, in the modern world with increasingly sedentary lifestyles and the plentiful availability of high salt, energy dense food this evolutionary adaptation for survival is now potentially one of the factors contributing to the current worldwide epidemic of hypertension, obesity and the metabolic syndrome [18].

Historical Association of Hyperuricaemia and Hypertension

Hyperuricaemia is currently viewed solely as an important risk factor in the development of gout but is not otherwise routinely measured or monitored. Historically, however, hyperuricaemia has been closely associated with elevated blood pressure, for example, a paper published in the Lancet in 1879 noted that many gout patients were hypertensive and a subsequent BMJ review of "arterial tension" in 1889 recommended a low purine diet for the management of hypertension [33, 34]. Hyperuricaemia fell out of favour as a cardiovascular risk factor in the 1970's and 80's (and consequently measurement of sUA was removed from many standard blood testing panels) partly due to the lack of evidence of a causal association and partly due to concerns regarding side effects of medication used to manage what was considered to be an asymptomatic condition.

The establishment of plausible biological mechanisms for the relationship between hyperuricaemia and hypertension has been facilitated by the development of animal models of hyperuricaemia. This information, coupled with large observational studies in

human populations have provided a growing body of evidence pointing strongly to a causal relationship between hyperuricaemia and the development of hypertension [35].

Biological Mechanisms for Hyperuricaemia Induced Hypertension

The first animal models of hyperuricaemia were developed in the 1990's and used oxonic acid as a uricase inhibitor. Initial work in rats showed that after 2 weeks exposure to mild increases in urate levels, there was activation of the renin angiotensisin system and decrease in plasma nitrates leading to vasoconstriction and hypertension [36]. This hypertension was reversible by either stopping the oxonic acid (allowing the uricase enzyme to function normally) or by lowering urate levels with either xanthine oxidase inhibitors or uricosuric agents. This early hypertension was also responsive to treatment with blockade of the renin-angiotensin system [37]. When hyperuricaemia was induced in normal and remnant kidney rats it resulted in renal cortical vasoconstriction, glomerular hypertension and inflammatory cell infiltration, and the vascular damage recorded was much more severe in the remnant kidney rats. It was surmised that in this model, hyperuricaemia impaired the auto-regulatory responses of afferent arterioles resulting in glomerular hypertension and vascular wall thickening to produce renal hypoperfusion. This led to renal ischaemia and subsequent tubulointerstitial inflammation, fibrosis and arterial hypertension [38]. Importantly these effects were not seen in rats treated with allopurinol which prevented the rise in urate levels.

A two stage hypertension theory has emerged from this experimental work in rats. The initial vascular changes and subsequent hypertension seen in response to hyperuricaemia can be reversed, however, after prolonged exposure to high urate levels there is a second phase of hypertension with evidence of altered intra-renal architecture [39]. The pattern of renal microvascular damage is similar to that seen in patients with essential hypertension where, over time, there is evidence of tubular ischaemia, interstitial inflammatory cell infiltration, oxidant generation and local vasoconstriction resulting in reduction of sodium filtration, enhanced sodium reabsorption and hypertension that is mainly salt sensitive [32, 40]. In both cases these vascular changes become irreversible over time which may explain the observation that the link between hyperuricaemia and hypertension appears stronger in younger people [41].

Evidence from Epidemiological studies

Since the revival of interest in the role of hyperuricaemia in the development of hypertension and as a potential independent cardiovascular risk factor, there has been an exponential rise in the number of papers published demonstrating and discussing this link [42]. Two recent meta-analyses looking specifically at hyperuricaemia and hypertension have concluded that higher urate levels predict the development of hypertension. Meta-analysis by Zhang and colleagues in 2009 included their prospective cohort study of 7220 normotensive Chinese patients with 4 years follow up. The adjusted relative risk of developing hypertension was 1.55 in men and 1.91 in women for the highest quartiles of sUA compared with the lowest quartiles. When included with 7 other studies in the meta-

analysis (total 28,657 participants) there was a pooled relative risk of 1.55 for development of hypertension in those with the highest quartiles of sUA. In Zhang's original study the association between hyperuricaemia and hypertension appeared to be partly mediated by abdominal obesity and it was postulated that this was due to hyperinsulinaemia enhancing uric acid reabsorption [43]. In 2011 Grayson conducted a meta-analysis of 18 published, prospective cohort studies (including the 8 studies used by Zhang) comprising a total of 55,607 patients (Table 2.1) [43-60]. This meta-analysis showed that hyperuricaemia was associated with an increased risk for incident hypertension (adjusted risk ratio 1.41) and for every 1mg/dL increase in sUA the pooled risk ratio for incident hypertension (after correcting for confounding factors) was 1.13. The risk appeared to be more significant in younger people and in women [41]. These two meta-analyses included studies from Europe, China, Japan, Israel and the USA indicating that this relationship is seen across ethnic groups.

Other studies not included in the above meta-analyses include the Bogalusa Heart study which looked at 577 US children, followed up for a mean of 11.4 years and showed that childhood urate levels significantly predicted hypertension in adult life [61]. The Taiwanese Health Survey from 2012 comprising 3257 patients showed that high sUA was an independent predictor of blood pressure progression (HR 1.78) and incident hypertension (HR 1.68) [62]. A small Turkish study looking at 112 hypertensive patients with 24hr ABPM measurements, categorised patients as dippers or non-dippers depending on blood pressure fall during the night. Loss of nocturnal blood pressure

dipping is associated with worse cardiovascular outcomes and in this study the non-dippers had significantly higher urate levels than the dippers (OR 2.28) [63].

The epidemiological evidence to date does indicate a strong association between hyperuricaemia and hypertension and the diversity of ages and ethnic groups studied and the length of follow up lend weight to the argument that this association is causal, rather than representative of two conditions that share the same risk factors. However, epidemiological evidence does not provide conclusive proof of causality and further experimental work and evidence from interventional trials are required to firmly establish the nature of this relationship.

Table 2.1: Studies used in Grayson meta-analysis linking hyperuricaemia and hypertension

Author	Population	Risk	Ref
Forman 2009	Nurses Health Survey (US), n=1496	OR for incident hypertension 1.89; 95% CI 1.26-2.82	[45]
Zhang 2009	Qingdao Port Health and Nutrition 7220 Examination Survey in China, mean age 37	Adjusted RR for incident hypertension men 1.55; 95% CI 1.10-2.19 and women 1.91; 95% CI 1.12-3.25)	[43]
Forman 2007	Health Professionals Follow up Study (US), n=1454 (men only)	Adjusted RR 1.24; 95% CI 0.93 to 1.66	[46]
Krishnan 2007	Multiple Risk Factor Intervention Trial (US), n=3073	Hazard ratio 1.81; 95% CI: 1.59 to 2.07 for incident hypertension	[47]
Mellen 2006	Atherosclerosis Risk in Communities (ARIC) study (US), n= 9104	Adjusted hazard ratio for incident hypertension for each SD of higher uric acid 1.10; 95% CI1.04 to 1.15	[48]
Perlstein 2006	Normative Aging Study (US), n=2062	Age adjusted RR 1.10; 95% CI: 1.06 to 1.15	[49]
Shankar 2006	Beaver Dam Population Cohort (US), n=2520	RR for incident hypertension 1.65; 95% CI 1.41-1.93	[50]
Sundstrom 2005	Framingham (US), n=3329	Adjusted OR for incident hypertension 1.17; 95% CI 1.02-1.33 for every 1 SD increase in sUA	[44]
Nagahama 2004	Okinawa General Health Maintenance Association (OGHMA) cohort (Japan), n=4489	Adjusted OR for incident hypertension, men 1.48; 95% CI 1.08-2.02, women 1.90; 95% CI 1.03-3.51	[51]
Nakanishi 2003	Male office workers (Japan), n=2310	Adjusted RR for incident hypertension 1.58; 95% CI 1.26-1.99	[52]
Taniguchi 2001	Osaka Health Survey (Japan), n=6356	Adjusted RR incident hypertension 2.01; 95% CI 1.56-2.59	[53]
Imazu 2001	Hawai, Los Angeles Hiroshima Study (US/Japan), n=159	Adjusted RR for incident hypertension 2.03; 95% CI 1.02-3.90	[54]
Dyer 1999	Coronary Artery Risk Development in Young Adults (CARDIA) study (US), n=4747	Multivariate OR for incident hypertension, black men 1.21; 95% CI 1.03-1.41, white men 1.16; 95% CI 0.96-1.40	[55]
Jossa 1994	Olivettic Heart Study (Italy), n=505	Adjusted RR for incident hypertension 1.23; 95% Cl1.07-1.39	[56]
Hunt 1991	Utah Cardiovascular Genetics Study (US), n=1482	Adjusted RR for incident hypertension 2.16 ($p<0.10$)	[57]
Selby 1990	Kaiser Permanente Multiphasic Health Checkup (US), n=2062	RR for incident hypertension 2.19; 95% CI 1.2-3.98	[58]
Fessel 1973	Target population and screening program (US), n=335	Data not available	[59]
Kahn 1972	The Israel Ischaemic Heart Disease Study, n=2904	RR for incident hypertension 1.82; 95% CI 1.3-2.54	[60]

[Abbreviations: RR = relative risk, OR = odds ratio, HR = hazard ratio, CI = confidence interval, sUA = serum uric acid level]

Management of Hyperuricaemia – Clinical Trial Data

If hyperuricaemia is accepted as a potential causal factor for the development of essential hypertension then does reducing sUA levels protect against the development of hypetension? A number of clinical trials over the past decade have sought to answer this question through either lowering urate levels with xanthine oxidase inhibitors or through use of uricosuric agents. The method by which urate lowering is achieved is important when looking at outcomes. Uricosuric agents such as probenecid act via the renal tubules and lower urate levels by increased renal excretion. Xanthine oxidase inhibitors (XOi) act by blocking the conversion of hypoxanthine to xanthine (the precursor of uric acid) and generally have a more potent effect on lowering urate levels than uricosuric agents. Allopurinol is the most commonly used XOi and is non-selective so not only reduces levels of uric acid but also inhibits other reactions in the purine/pyrimidine metabolism pathways thereby preventing production of oxidants generated during this process [64]. It is hypothesised that allopurinol improves vascular outcomes due to this non-selectivity and by reducing oxidative stress rather than simply through reduction of urate levels. Febuxostat is a non-purine XOi and therefore more selective than allopurinol resulting in greater reductions in urate levels but with potentially less anti-oxidant effect [65]. It remains to be seen whether different cardiovascular effects will be found with febuxostat compared to allopurinol due to their selectivity of action.

Small pilot studies have been undertaken using allopurinol in hypertensive patients and particularly striking results have been seen in obese and newly diagnosed adolescents

with hypertension. A randomised, placebo controlled trial in US adolescents with newly diagnosed essential hypertension showed that allopurinol 200mg twice daily resulted in a mean 24hr blood pressure change of -6.3 mmHg systolic and -4.6 diastolic compared to 0.8 systolic and -0.3 diastolic for the placebo group. These changes were significant although limited by the small sample size of only 30 adolescents [66]. A further study in 60 pre-hypertensive obese 11-17 year olds found that those treated with urate lowering therapy saw a reduction in clinic BP compared with the placebo group (-10.3/-8.0 mmHg adjusted with allopurinol and -10.2/-8.8 mmHg adjusted with probenecid). They concluded that uric acid contributed to the development of hypertension in adolescents and this effect could be mitigated by urate lowering therapy [67].

There have also been small trials in adults looking at the effect of allopurinol on patients with asymptomatic hyperuricaemia. 48 patients treated for 3 months with 300 mg allopurinol daily showed decreased urate levels, decreased CRP, increase in eGFR and decreased blood pressure (-3.9/-1.9 mmHg) compared with control groups [68]. Another trial compared 30 asymptomatic hyperuricaemic patients treated with allopurinol with 37 asymptomatic hyperuricaemic controls and 30 normouricaemic controls and showed that systolic blood pressure after 4 months decreased by 8mmHg in treated patients compared with controls [69]. Therefore asymptomatic patients with no prior history of hypertension responded to allopurinol treatment with a reduction in blood pressure.

A recent systematic review and meta-analysis of allopurinol use in reducing blood pressure looked at 10 studies, comprising a total of 738 participants. The authors found that, compared with the control group, treatment with allopurinol lowered systolic blood pressure by 3.3 mmHg and diastolic blood pressure by 1.3 mmHg. They concluded that allopurinol had a small but significant effect in lowering blood pressure that could be exploited in managing hypertension in hyperuricaemic patients [70].

The majority of interventional studies to date have looked at using allopurinol to lower urate levels however there are alternative treatment options available. One drug that is particularly interesting in this field is losartan as it has a mildly uricosuric action which is unique in the angiotensin II receptor blocker (ARB) class. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that a losartan based regimen was superior to an atenolol based regimen for reduction of cardiovascular mortality and morbidity despite comparable blood pressure reduction [71]. It was hypothesised that this could have been due to the uricosuric action of losartan and a further analysis concluded that over the 4.8 year follow up in LIFE the increase in sUA seen over time was attenuated by losartan and this appeared to explain 29% of the treatment effect on the primary endpoint (cardiovascular death, MI or stroke) [72]. The association between sUA and cardiovascular events was again noted to be stronger in women in this study.

The main concern with widespread use of allopurinol to manage hyperuricaemia in asymptomatic patients is the potential for side effects. Approximately 1% of patients

prescribed allopurinol will develop a rash and in a very small proportion this can develop into the potentially life threatening allopurinol hypersensitivity reaction. Dose reductions of allopurinol are also recommended in renal impairment. An alternative XOi, febuxostat, has been lincensed since 2008 and is more selective and more potent at lowering urate than 300 mg of allopurinol [8]. Febuxostat shares some cross reactivity with allopurinol and similar rates of side effects have been reported however, febuxostat undergoes mainly biliary excretion and therefore does not require dose reductions in renal impairment [8, 73]. The impact of febuxostat on blood pressure in humans has yet to be established and it will be interesting to see if more potent urate lowering has a more significant effect on blood pressure or whether the increased selectivity of febuxostat will make it less effective than allopurinol in this context.

Hyperuricaemia and Cardiovascular Outcomes

Following over a decade of intensive research in this area what has emerged is broad acceptance of a correlation between hyperuricaemia and hypertension and a clearer picture of a causal link, particularly for a subset of patients. There is however ongoing scepticism about the significance of hyperuricaemia induced hypertension in determining cardiovascular outcomes and more importantly whether modifying sUA levels will influence these outcomes in a substantial way. The evidence looking at hyperuricaemia and cardiovascular outcomes shows mixed results. The European Working Party on High Blood Pressure in the elderly found no relationship between urate levels and cardiovascular outcomes however the patients studied were enrolled in a trial of diuretics

which may have confounded the results [74]. Data from the Framingham Heart study which included 6763 Framingham participants with measurements of sUA taken between 1971 and 1976 showed that after adjusting for other risk factors, urate levels did not predict adverse cardiovascular outcomes. The authors concluded that elevated sUA does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes [75]. A meta-analysis of 11 trials involving 21,373 participants looking at changes in sUA and cardiovascular events found that there was no relationship between changes in urate levels and outcomes [76]. The authors acknowledged that hyperuricaemic patients are at increased risk of cardiovascular events however as many of the risk factors for hyperuriaemia are the same risk factors as for cardiovascular disease the difficulty remains in separating out the individual effect of hyperuricaemia [76-78]. This also confirms the ongoing doubt surrounding the best management of hyperuricaemia as evidence that aggressive treatment of hyperuricaemia improves overall cardiovascular outcomes is lacking.

Conclusion

Undoubtedly the effect of hyperuricaemia in the human body is complex. At present evidence is accumulating that hyperuricaemia could be a significant factor in the development of hypertension in some people, and importantly, hyperuricaemia is also a potentially reversible risk factor. Hypertension is a significant global health problem and a key contributor to increased risk of cardiovascular events, therefore any intervention that could improve the management of hypertension requires careful examination. There

remains an unanswered question over whether aggressive management of hyperuricaemia can reduce blood pressure and improve cardiovascular outcomes significantly enough to be cost effective and outweigh the potential side effects of the urate lowering therapies required. Large randomised controlled trials are needed to answer this question, and it is possible that in the future management of hyperuricaemia will be as routine as management of cholesterol in the context of modifying cardiovascular risk.

2d) Review of Renal Function and Hyperuricaemia

Abstract

Uric acid is a product of the metabolic breakdown of purines. It is freely filtered at the glomerulus and predominantly excreted via the kidneys, therefore, hyperuricaemia is an inevitable consequence of renal function decline. However, the relationship between hyperuricaemia and renal function is complex and hyperuricaemia is increasingly being viewed as a potentially significant independent risk factor for the development and progression of chronic kidney disease. Historically the association between hyperuricaemia and renal function decline centred on the idea of direct deposition of uric acid crystals in the kidney leading to inflammation, scarring and eventual fibrosis. It is increasingly apparent that chronic renal damage due to hyperuricaemia occurs by more subtle mechanisms such as endothelial dysfunction and impaired renal blood flow autoregulation. There is ongoing debate over whether we should view hyperuricaemia as a significant contributor towards renal function decline and whether active management of hyperuricaemia in patients with or at risk of chronic kidney disease should be considered. This review considers the currently available evidence and presents arguments for and against the treatment of hyperuricaemia with the aim of preserving renal function.

Introduction

The terms uric acid and urate are used interchangeably as uric acid and urate exist in equal ratio in the circulation. Uric acid is relatively insoluble in plasma and humans lack the uricase enzyme which breaks down uric acid into more soluble waste products. The loss of function mutation affecting the uricase gene is thought to have occurred in humans approximately 15 million years ago and resulted in adaptations in human renal handling of urate allowing increased urate excretion [79].

Hyperuricaemia is generally defined as serum urate (sUA) levels greater than 400 µmol/l (6.8 mg/dL) as this is the concentration at which uric acid becomes insoluble in plasma. Epidemiological data shows that population urate levels have been rising over recent decades. In the UK mean urate levels in men increased from 330 µmol/L (5.5 mg/dL) in the 1960's to 390 µmol/L (6.5 mg/dL) by the late 1970's. The third US National Health and Nutritional Examination Survey (NHANES III, 1988–1994) showed that urate levels >7mg/dL (> 420 µmol/L) in men and >5.7mg/dL (> 340 µmol/L) in women were found in 18.4% of the US population. Increasing prevalence of hyperuricaemia is multi-factorial and contributing factors include ageing populations, increased use of medications such as low dose aspirin and diuretics and the role of diet, particularly purine rich foods and increased fructose consumption [80]. There are also genetic as well as environmental influences and across the globe urate levels differ between ethnic groups with higher levels seen in Aboriginal peoples in Australia and Taiwan and in African-Americans compared with Caucasian Americans [81].

Hyperuricaemia is currently recognised mainly as the dominant risk factor for gout where uric acid crystals precipitate out of solution and are deposited in tissues and joints causing gouty tophi and a painful and destructive inflammatory arthritis. European guidelines suggest urate levels should be kept below 360 µmol/L in patients with symptomatic hyperuricaemia (i.e. gout) as above this level the risk of gout flares and complications significantly increase [10]. There are currently no guidelines or recommendations for the management of asymptomatic hyperuricaemia.

Renal Handling of Uric Acid

Uric acid in the body is derived approximately 30% from dietary purines and 70% from endogenous production in the liver, muscles and intestines [82]. The kidneys are responsible for approximately 70% of uric acid clearance therefore sUA levels are predominantly determined by renal excretion. Uric acid is freely filtered at the glomerulus and then undergoes a complex process of filtration, re-absorption, secretion and excretion. Advances in molecular biochemistry over the past two decades, aided by information from the human genome project have allowed identification of over 30 different urate transporters in the kidney. There are large numbers of genetic polymorphisms which may affect these urate transporters and which can predispose certain individuals and ethnic groups to hyperuricaemia. Some of the most convincing data so far has emerged for Urate Transporter 1 (URAT1) and Glucose Transporter-like protein 9a (GLUT9), both of which are inhibited by uricosuric agents such as probenicid and losartan and both are considered targets for development of new drugs in

management of hyperuricaemia. GLUT9 is expressed on the basolateral cell membrane and appears to be the principal pathway for urate to exit proximal tubule cells [79]. URAT1 is located on the luminal side of the proximal tubule and is one of the major luminal pathways for urate reabsorption. Patients with inactivated mutations of URAT1 excrete the majority of filtered urate and therefore have idiopathic hypouricaemia [79].

Hyperuricaemia and Renal Disease

Hyperuricaemia has traditionally been thought of as causing renal problems in three ways, namely acute kidney injury with acute severe hyperuricaemia, uric acid renal stones and chronic urate nephropathy. Acute severe hyperuricaemia occurs where there is massive purine release from cell breakdown (for example following treatment of bulky tumours in the tumour lysis syndrome). The excess production of uric acid overwhelms the kidneys ability to filter and excrete uric acid which then blocks the renal tubules. This used to be associated with significant morbidity however the use of recombinant urate oxidase (rasburicase) [83] coupled with better awareness and renal protection with rehydration in those undergoing chemotherapy for bulky tumours means this is now largely preventable. Uric acid renal stones account for only 5-10% of renal stones in the UK (although are significantly more common in locations such as the Middle East) [84]. When associated with infection and/or obstruction uric acid stones may play a part in deteriorating kidney function but are not normally associated with significant chronic renal function decline.

Chronic urate nephropathy was the term previously used to describe deteriorating renal function in patients with hyperuricaemia and gout. It was presumed that uric acid crystals were deposited in the renal medulla causing local inflammation and eventual fibrosis and this was considered to be an extra-articular manifestation of gout. The evidence for uric acid crystals in the kidney on renal biopsy and at autopsy were less convincing and the vast majority of patients who had renal biopsies because of deteriorating renal function in the context of gout showed non-specific changes of tubulosinterstitial fibrosis, arteriolosclerosis and glomerulosclerosis [85, 86]. Monosodium urate crystals were seen and appeared to cause a local inflammatory reaction however this was not associated with significant decline in renal function and did not explain the more diffuse biopsy findings. One autopsy series from Switzerland included 11,408 autopsies of which only 37 (0.3%) were identified as having chronic urate nephropathy in the form of crystal deposition evident in the kidney and of those patients who had impaired renal function at death all but 3 cases had other significant co-morbidity that would better explain their renal impairment. The authors concluded that renal tophi may be present in the kidneys of hyperuricaemic patients however they were not usually associated with renal function decline [85]. Therefore, the concept of chronic urate nephropathy or gouty nephropathy as a disease of crystal deposition has been replaced by the idea that hyperuricaemia can potentially lead to renal impairment by more subtle mechanisms associated with hypertension, endothelial dysfunction, renal vasoconstriction and impaired renal blood flow autoregulation [87].

There is also interesting research emerging in the development of diabetic nephropathy which shows that patients with the highest levels of sUA are more likely to progress from micro to macroalbuminuria and to end stage renal disease [88, 89]. Further research is required in this area but hyperuricaemia may be one factor in explaining why some diabetic patients progress to end stage renal disease while others do not.

Hyperuricaemia and Chronic Renal Disease – Epidemiological Evidence

The pivotal role of the kidneys in urate homeostasis means that determining whether deteriorating renal function is causing the hyperuricaemia or occurring as a consequence of hyperuricaemia is difficult to unravel. Evidence from epidemiological studies cannot establish causality however there are a number of very large population screening studies which show that baseline hyperuricaemia appears to be a risk factor for future development of renal impairment. One of the largest studies was published in 2009 and comprised 177,570 people in northern California who participated in a health testing services program between 1964 and 1973 and were followed up over a 25 year period. The data confirmed the importance of traditional risk factors for chronic kidney disease including hypertension and proteinuria but also identified hyperuricaemia as a novel risk factor. The hazard ratio (HR) for development of end stage renal disease comparing the lowest and the highest quartile of baseline sUA was 2.14 [90].

Another large retrospective cohort study in Taiwan included 94,422 patients enrolled in a screening program and followed up for a mean of 3.5 years. Higher uric acid levels were

found to be an independent risk factor for incident chronic kidney disease with an adjusted HR of 1.15 [91]. A further retrospective cohort of 63,785 Taiwanese patients showed that patients with hyperuricaemia had significantly greater eGFR decline annually after adjustment for known risk factors (HR 1.28 for accelerated eGFR decline >3mL/min/1.73 m^2 per year and HR 1.52 for CKD progression at the end of follow-up) [92]. Evidence from European populations include 21, 475 healthy volunteers from the Vienna screening project who were followed up for a median of 7 years and after adjustment for baseline eGFR, a urate level 7.0 - 8.9 mg/dL nearly doubled the risk of incident CKD (OR 1.74) and urate > 9 mg/dL trebled the risk (OR 3.12). This increased risk remained significant after correction for known risk factors and the authors concluded that elevated urate levels independently increase the risk for new-onset kidney disease [93]. The strengths of these retrospective cohort studies are their size and duration of follow up. Results were also corrected for known risk factors including age, sex, baseline eGFR, diabetes mellitus, hypertension and hypercholesterolaemia.

Animal Studies Linking Hyperuricaemia and CKD

In order to support the association seen in epidemiological studies evidence is required to show plausible mechanisms by which hyperuricaemia can cause renal damage. Traditionally this would be gathered from animal models however, there are some significant limitations in the use of animal models for investigation of hyperuricaemia because traditional animal models such as rodents have a functioning gene for the uricase enzyme and therefore no natural hyperuricaemic state. Hyperuricaemia has to be

induced by using uricase knockout animals or uricase inhibitors and the rodent kidney cannot deal with the excessive urate load. This may be one reason why promising work in animal studies has not always translated into advances in human disease.

The eventual development of rodent models using oxonic acid as an uricase inhibitor within the past two decades has allowed modelling of a chronic hyperuicaemic state and therefore research in this area to progress. Early work using this rat model showed that rats with mild hyperuricaemia demonstrated renal vasoconstriction and glomerular hypertension as well as high renin systemic hypertension [38, 94]. Other studies with rats showed that hyperuricaemia induced renal arteriolopathy independent of blood pressure [37].

Evidence for Treatment of Hyperuricaemia to Prevent or Slow Progression of Renal Disease

With strong epidemiological evidence linking hyperuricaemia and development or progression of CKD as well as plausible mechanisms by which this could occur, the key question that remains is whether intervention in hyperuricaemia could improve renal outcomes. To date there is only limited evidence from small clinical trials with limited follow up to answer this question. There are several options for managing hyperuricaemia, including recombinant uricase, xanthine oxidase inhibitors and uricosuric agents. It is also not known whether the method of urate reduction or the amount of urate reduction is more important.

Losartan is recognised to have a uricosuric effect which is unique amongst the angiotensin II receptor blockers. The RENAAL study enrolled 1513 patients with type 2 diabetes, proteinuria and renal impairment and compared losartan 50 mg or 100 mg against placebo. sUA was reduced by 160 µmol/L in the losartan group and there was a reduction of the composite renal endpoint with 6% reduction in risk of renal events. The difficulty with this study was whether this improvement in renal outcomes could be explained by better blood pressure control and management of proteinuria in the losartan group rather than by changes in sUA [95].

Xanthine oxidase inhibitors are generally more potent at lowering sUA levels than uricosuric agents and the two currently available drugs are allopurinol and febuxostat. There have been a number of small trials using xanthine oxidase inhibitors and looking at renal outcomes. One study used 54 patients with mild to moderate CKD given 100 - 300 mg allopurinol or no additional treatment and followed for 1 year. The results did not meet statistical significance but there was a trend towards better outcomes in the treated group with 16% of the allopurinol group meeting study endpoints (>40% rise in creatinine, dialysis or death) compared with 46% in the non-treated group [96]. Another study published in 2010 randomised 113 patients with eGFR < 60 ml/min to either 100 mg allopurinol or to continue on their usUAl treatment and found that after 24 months treatment serurm urate and CRP were significantly decreased in the allopurinol group and eGFR had improved by 1.3 ml/min (compared to a decrease of 3.3 ml/min in the usUAl treatment group) [97]. An abstract presented at the European Renal Association meeting

in May 2013 showed that 56 CKD 2/3 patients with asymptomatic hyperuricaemia, treated with either febuxostat, allopurinol or nothing showed mean 12 ml/min increase in eGFR and lower blood pressure (mean -8/-3 mmHg) in the two treatment arms after 14 months follow up [98]. The NU-FLASH trial compared allopurinol and febuxostat in hyperuricaemic patients post cardiac surgery and found that febuxostat not only reduced sUA more than allopurinol but also that febuxostat had a renoprotective effect and inhibited oxidative stress [99].

A meta-analysis looking at the effect of urate lowering with allopurinol on renal outcomes was published in 2014 and included 8 studies with 476 patients in total. The authors concluded that "allopurinol may retard the progression of CKD, however, adequately powered randomised trials are required" [100]. There are now at least two large trials beginning recruitment to answer this question. The CKD-FIX trial (ACTRN12611000791932) is a randomised, double blind, placebo controlled study to assess the effect of allopurinol on renal function decline in 620 CKD 3/4 patients in Australia and New Zealand [100]. The FEATHER trial is also a double blind, placebo controlled trial, recruiting in Japan which plans to enrol 400 patients with CKD stage 3 and asymptomatic hyperuricaemia (sUA 7.1 – 10.0 mg/dL). Participants are randomised to either febuxostat or placebo and followed up for 2 years with the primary outcome being change in eGFR [101].

Treatment of Hyperuricaemia to Preserve Renal Function

The arguments for and against active treatment of hyperuricaemia are presented in Box 2.1. More research is required and hopefully the CKD-FIX and FEATHER trials will go some way towards answering these questions. The burden of CKD is expected to rise exponentially over coming decades and any intervention that may slow progression of renal function decline particularly slowing development of end stage kidney disease would have significant health and economic benefits.

Conclusion

The current interest in hyperuricaemia is recycling ideas that have been around for many decades. Technological advances in recent years including the ability to perform epidemiological studies of hundreds of thousands of people, improved laboratory techniques, development of animal models and the impact of the human genome project have all led to renewed interest in hyperuricaemia. We have moved on from viewing hyperuricamia as a problem of crystal deposition towards seeing it as a systemic impactor on human microvasculature and therefore a potentially modifiable risk factor for cardiovascular and renal disease. With a 21st century global health epidemic of obesity, hypertension, chronic renal disease, diabetes and the metabolic syndrome any intervention to improve outcomes will receive attention. The evidence currently being gathered will hopefully finally answer the question of whether hyperuricaemia is something we should be looking for and treating outwith the context of patients with gout.

Box 2.1: Arguments for and against treatment of hyperuricaemia in the context of renal disease

Why we should treat hyperuricaemia

- Strong evidence from epidemiological studies that higher urate levels increase risk of subsequent development of chronic kidney disease
- Plausible biological mechanisms demonstrated in animal models showing how hyperuricaemia can cause microvascular renal damage
- Some evidence from small interventional studies that treatment of hyperuricaemia can slow decline of renal function in the short term
- Allopurinol is relatively inexpensive
- Global burden of chronic kidney disease is rapidly increasing

Why we should not treat hyperuricaemia

- Association with incident CKD may be due to hyperuricaemia indicating subtle renal damage not detected by creatinine based estimations of renal function
- Evidence showing improvement in hard endpoints (end stage renal failure and mortality) from large randomised controlled trials is currently lacking
- Potential side effects from treatment of an asymptomatic condition (e.g. risk of allopurinol hypersensitivity reaction)
- Additional treatment burden for patients
- Concerns that inducing significant hypouricaemia may have unforeseen consequences [102, 103]

Chapter 3

Optimisation of Serum Urate Control with Allopurinol

3a) Up-Titration of Allopurinol in Patients with Gout

i) Introduction

Gout is a common condition with an overall prevalence in the UK of 1.4% rising to over 6% in the over 65 age group [2, 104]. Incidence of gout in the UK has been stable for the past two decades, however, the disease burden of gout is expected to increase due to increasing life expectancy and a predicted rise in the UK population over 60 years of age from 14 million in 2010 to 18.6 million by 2026 [105, 106]. The European League against Rheumatism (EULAR) published guidelines in 2006 making a series of recommendations for the management of gout including titration of urate lowering therapy (ULT) to achieve a serum urate target (sUA) <6 mg/dL [10]. The American College of Rheumatology guidelines published in 2012 recommend a sUA target <6.0 mg/dL in all patients, but recognised that lowering sUA below 5.0 mg/dL may be required for durable improvements in severe disease manifestations such as tophaceous deposits [30].

Allopurinol is currently the first line ULT prescribed in patients with chronic gout and guidelines recommend starting at a low dose and titrating this upwards until target sUA level is reached. In the UK approximately 30% of patients with gout are regularly prescribed allopurinol [107] and it is recognised that a significant proportion of these patients do not achieve the EULAR sUA target of <6.0 mg/dL. A postal survey in UK primary care practices showed that 23% of patients with gout taking allopurinol had sUA levels >6.0 mg/dL [108]. In a US review of 15,596 patients with gout, only 30% met the

specified sUA target and of those prescribed allopurinol, 40% did not have a sUA level checked after completing their first allopurinol prescription [109]. In UK General Practices <1% of 34,000 patients with gout had an annual measurement of sUA[2] although a survey of UK GP's found that 86% of GP's felt confident in their diagnosis and management of gout [110]. In addition to inadequate patient education and patient adherence to prescribed therapy, poor achievement of sUA targets in patients with gout may also be attributable to a lack of awareness of appropriate targets for therapy in General Practice, concerns about risks of side effects associated with increasing doses of allopurinol and infrequent monitoring of sUA levels [111].

The Febuxostat versus Allopurinol Streamlined Trial (FAST) [ISRCTN72443728] was designed to compare the cardiovascular safety of febuxostat with allopurinol, as well as to fulfil a Eurpoean Medicines Agency requirement for a post-licensing cardiovascular safety study of febuxostat. Patients with gout recruited for the trial were already taking allopurinol as ULT. Previous phase III trials had shown that only a minority of gout patients receiving allopurinol at a dose of 300mg daily achieved target reduction of sUA when compared with those treated with febuxostat [8, 112]. It was therefore thought to be appropriate to up-titrate the dose of allopurinol when necessary, to lower the sUA to the EULAR target of 6.0 mg/dL (357 µmol/L) prior to randomisation to allow a fair comparison of cardiovascular safety of the two xanthine oxidase inhibitors at therapeutic doses. An exact conversion of 6.0 mg/dL is 357 µmol/L and this was the cut off urate level used in FAST.

Analysis of patients recruited into FAST provides data on the current use of allopurinol in this population of patients with gout in primary care and adds to currently sparse information on patients' response to allopurinol dose increases, how this therapy is tolerated, and what factors might influence the patients' response

ii) Methods

FAST patients were recruited in Scotland, England and Denmark. Potential patients were identified by searches of primary care databases undertaken by study nurses. Eligible patients were those aged over 60 years, with a clinical diagnosis of gout, prescribed allopurinol for ULT and who had at least one additional cardiovascular risk factor. Patients with significantly impaired renal function (eGFR <30 mL/min) were excluded. Patients meeting the inclusion criteria attended for a screening visit and progression from screening to randomisation was determined by the sUA level at screening. If the sUA at screening was already below the EULAR target of <357 µmol/L patients could proceed directly to randomisation; however if the initial sUA level was ≥357 µmol/L then the daily dose of allopurinol was increased by 100 mg and sUA levels were re-checked after 2 weeks on the higher allopurinol dose. This up-titration process was repeated until EULAR sUA target levels were achieved or the patient reached their maximum tolerated dose of allopurinol. The maximum possible dose of allopurinol that could be prescribed was 900 mg daily, as specified by the British National Formulary (BNF).

Patient data was stored on an electronic clinical report form, and patients were randomised via a central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow. Randomisation was 1:1 to take either the optimised dose of allopurinol or to take febuxostat (initially 80mg with potential to increase to 120mg to maintain sUA levels below the EULAR target). Gout flare prophylaxis with colchicine, or second line prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) with gastric protection was offered to patients who required allopurinol up-titration, and to all patients following randomisation. All patients were encouraged to take and continue gout flare prophylaxis for 6 months, but the decision as to whether or not to do so was left to each patient's discretion.

Data Collection and Analysis

The first 400 FAST patients were randomised by January 2013. Data collected from the screening visit and during the up-titration process are presented in this paper. Anonymised data were extracted from the FAST database and analysed using SPSS v. 19. Data describing patient characteristics are shown as mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. Independent t-tests and Chi-squared (or Mann-Whitney U if appropriate) analysis were used to compare characteristics of patients with sUA levels <357 μmol/L with those who were not at target at screening.

iii) Results

144 of the 400 patients (36%) had urate levels ≥357µmol/L at screening and therefore required up-titration of their allopurinol dose. The baseline characteristics of these two groups are shown in Table 3.1.

Patients who required up-titration of allopurinol were significantly more likely to be male ($p=0.002$), have a higher body mass index (BMI) ($p=0.026$), have higher alcohol intake ($p<0.05$), be prescribed a diuretic ($p=0.015$) and were taking a lower dose of allopurinol ($p<0.005$) compared with those who were at target at the screening visit.

At screening, the maximum prescribed allopurinol dose in this patient population was 600mg daily. The most commonly prescribed daily doses of allopurinol were 100 mg (in 32% of patients) and 300 mg (in 51% of patients) with only 2% of patients prescribed a daily dose greater than 300 mg (Figure 3.1). 67% of the 129 patients prescribed allopurinol 100 mg daily required up-titration, compared with 16% of the 203 patients prescribed 300mg. The number of up-titrations required to achieve sUA <357 µmol/L ranged from one to five (median 1, mean 1.5). 65% of up-titrated patients required one dose increase, 24% required two dose increases, 9% required three dose increases and only 1% required more than three dose increases. The maximum final dose of allopurinol required by any patient in this cohort of 400 patients was 700 mg daily. Figure 3.2 shows the range of allopurinol doses prescribed at screening and after up-titration for the 144 patients who required up-titration. 97% of up-titrated patients achieved the EULAR sUA

target requiring a mean allopurinol dose of 309 mg daily. Of the five patients who failed to achieve sUA levels <357 µmol/L three did not tolerate further allopurinol dose increases and the other two patients had sUA levels of exactly 357 µmol/L at the time of randomisation, and hence no further up-titrations were attempted.

The mean fall in sUA after a 100 mg daily dose increase of allopurinol was 71 µmol/L (± 49 µmol/L). For those patients controlled after a single 100 mg dose increase the mean fall in sUA was 90 µmol/L (± 43 µmol/L). Patients requiring only one up-titration had a lower mean baseline urate of 406 µmol/L compared to 448 µmol/L for those requiring more than one up-titration ($p<0.05$). The number of up-titrations required was also related to baseline factors which influenced initial sUA levels, including gender, BMI and diuretic use.

There were no serious adverse events reported following up-titration of allopurinol, and no patients discontinued allopurinol during the up-titration process. Three patients were unable to tolerate further dose increases and reported idiosyncratic side effects including gastric reflux, paresthesiae and generalised fatigue. Other side effects reported during up-titration included dry skin and mildly deranged liver function tests, but these were not deemed to require dose adjustment by the responsible physician. There were no reported cases of rash or allopurinol hypersensitivity. Three patients (2%) experienced a flare of gout during the up-titration process. All three patients with a gout flare were receiving flare prophylaxis (2 patients with colchicine and 1 patient with diclofenac). The low rate of gout flares is speculated to be due to having a population pre-exposed to

allopurinol and good uptake and compliance with flare prophylaxis for patients requiring up-titration.

68 of the 400 patients had eGFR <60 mL/min on their screening blood tests. 25 patients had eGFR 30-44 mL/min of whom 10 (40%) required up-titration and 43 patients had eGFR 45-60 mL/min of whom 17 (40%) required up-titration. In both groups median allopurinol dose at screening was 200 mg and the median allopurinol dose following up-titration was 300 mg. The maximum allopurinol dose given to a patient with eGFR <60 mL/min was 500mg daily and there was one patient on this dose in each eGFR category (30-44 mL/min and 45-60 mL/min).

Table 3.1: Baseline characteristics of the first 400 patients randomised into FAST

Patient Characteristic	Required Up-Titration (n=144)	At target (n=256)	p value
Age, years, mean (SD)	69.3 (6.0)	70.5 (6.8)	0.93
Male sex, n (%)	133 (92%)	207 (81%)	0.002
Female sex, n (%)	11 (8%)	49 (19%)	
BMI kg/m^2, mean (SD)	32.1 (4.9)	30.9 (4.8)	0.026
Initial Urate µmol/L, mean (SD)	421 (45)	286 (44)	<0.001
Initial Allopurinol Dose mg, median (IQR)	100 (100-200)	300 (200-300)	<0.05
Alcohol Use, n (%):			0.77
Never	8 (6%)	22 (9%)	
Former	12 (8%)	25 (10%)	
Current	124 (86%)	209 (82%)	
Alcohol Intake units/week, Median (IQR)	12.0 (3-22)	7.5 (0-22)	<0.05
Renal Function, n (%):			0.98
eGFR >60ml/min	117 (81%)	215 ((84%)	
eGFR 45-60ml/min	18 (12%)	25 (10%)	
eGFR 30-44ml/min	10 (7%)	15 (6%)	
Co-morbidities, n (%):			
Hypertension	115 (80%)	209 (82%)	0.70
Diabetes	31 (21%)	71 (28%)	0.43
MI	15 (10%)	27 (11%)	0.94
Angina	22 (15%)	35 (14%)	0.84
Other ACS	14 (10%)	26 (10%)	0.94
CKD	26 (18%)	39 (15%)	0.65
Stroke	9 (6%)	13 (5%)	0.86
Prescribed Diuretic, n (%)	50 (35%)	60 (23%)	0.015

Figure 3.1: Bar graph to show the number of patients achieving target EULAR urate level at FAST screening visit by daily allopurinol dose (n=400)

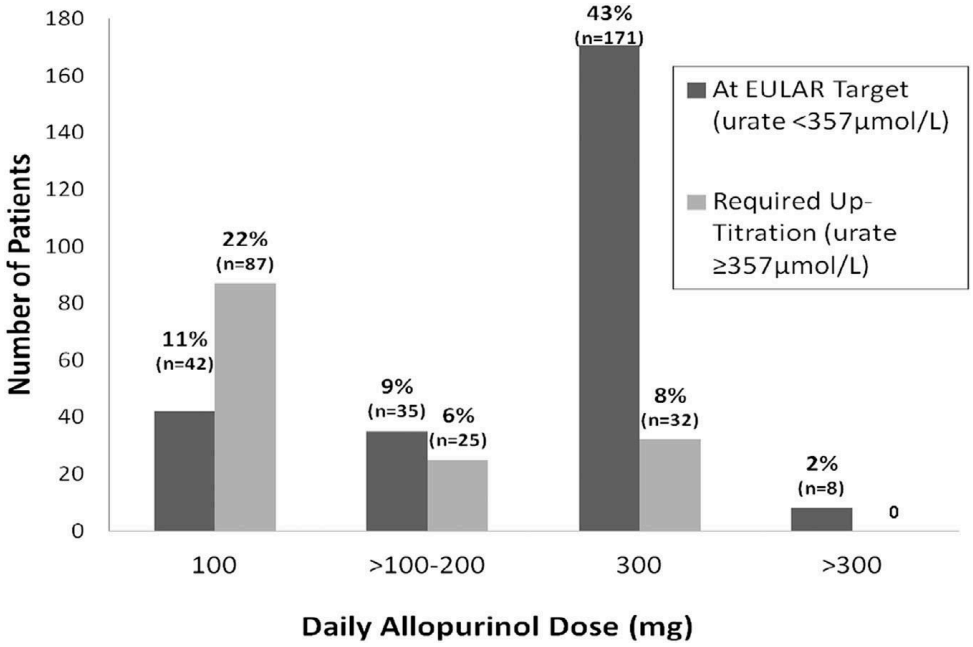
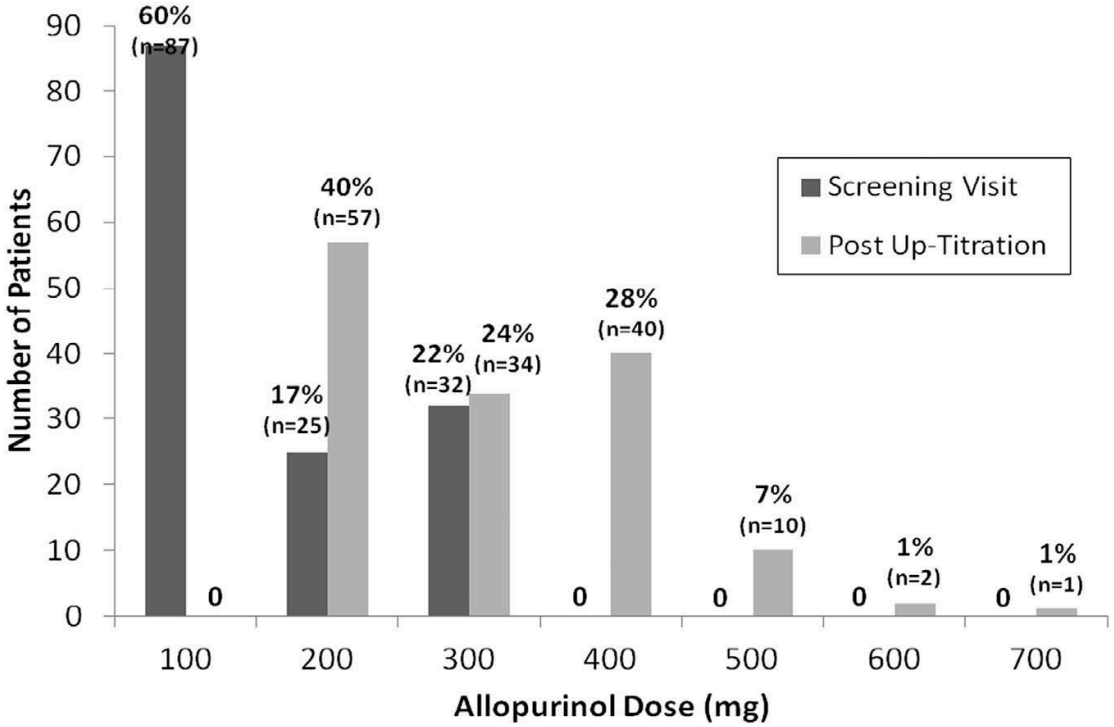


Figure 3.2: Bar graph to show screening and post up-titration allopurinol dose for those patients who required up-titration (n=144)



iv) Discussion

Current evidence-based expert guidelines for the management of gout from EULAR [10], the British Society for Rheumatology (BSR) [113] and the American College of Rheumatology (ACR) [30] all recommend allopurinol as first line ULT. Epidemiological studies have shown that allopurinol is the most widely used ULT in Europe [2] and North America [30]. There is consensus that allopurinol should be started at a low dose (100 mg daily) with increase in the daily dose of 100 mg every 1-2 weeks as required until the sUA is lowered to a target of 6.0 mg/dL (357 μmol/L) or the more stringent BSR target of 5.0 mg/dL (300 μmol/L). Controversially the more recently published guideline from the ACR [30] recommends up-titration of allopurinol in order to achieve the sUA target even in patients with renal impairment where there has previously been reluctance to prescribe higher doses [10, 113, 114]. Unfortunately, however, despite the availability of evidence-based, expert and updated guidelines for the management of gout there is a growing body of studies which clearly show that the management of gout is seriously suboptimal in practice [107, 111, 115-117].

Analysis of the first 400 patients randomised into FAST shows that, at baseline, only 64% of patients had their sUA controlled to EULAR target levels on their current dose of allopurinol. For those patients not controlled at baseline, 65% achieved target sUA levels with a single 100 mg daily dose increase of allopurinol and 90% were controlled after two 100 mg up-titrations of allopurinol. Known risk factors for gout include advancing age, male sex, being overweight, diuretic use and high alcohol intake [104] and this was

reflected in our data, as these known risk factors were associated with higher baseline sUA levels and the need for more up-titrations.

Not surprisingly one of the most significant factors influencing the baseline sUA level was the prescribed dose of allopurinol and all the current guidelines on gout management emphasise the importance of reduction of sUA levels to defined targets. While diet and lifestyle changes are frequently indicated in gout management, their impact on reducing sUA levels to therapeutic target levels is modest compared with the use of ULT. Optimal management of gout should combine all these approaches and Rees et al have recently demonstrated in a proof-of-principle study, that 92% of gout patients under review in secondary care achieved therapeutic sUA targets with a complex intervention combining patient education, individualised lifestyle advice and appropriate ULT [118]. The results of the present study provide further evidence to suggest that adherence to key elements of current guidelines can be highly effective in improving management of this common disease.

The most commonly prescribed doses of allopurinol at the screening visit were 100 mg and 300 mg reflecting a “fixed dose” approach to allopurinol prescribing rather than prescribing a dose based on sUA levels. An audit of UK general practice in 2000 found that 62% of patients did not have their urate levels checked at all after prescription of allopurinol.[119] If guidelines were being appropriately followed with a “treat-to-target” approach, one would expect that a much broader range of allopurinol doses would be

prescribed. The fact that allopurinol is only available in 100 mg and 300 mg tablets may also strongly influence the dose prescribed as other dose choices would increase the number of tablets to be taken daily by a patient.

Data from the EULAR guidelines suggested that a 100 mg dose increase in allopurinol should reduce sUA levels by 60 µmol/L (approximately 1 mg/dL). Our results indicate that this may be an underestimate of the sUA reduction that can be expected, as overall levels in our study fell by 71 µmol/L (1.2mg/dL) after one dose increase. This result may, however, be confounded by the lack of a placebo-controlled arm and by improved adherence following recruitment into the trial.

One of the main deterrents to up-titration of allopurinol is anxiety about the possibility of an increased risk of side effects with higher doses. It is estimated that around 1-2% of patients prescribed allopurinol will have a reaction to the drug, mostly in the form of a minor rash [120, 121]. Very rarely patients may develop a much more serious allopurinol hypersensitivity syndrome (AHS) with potentially life-threatening Stevens-Johnson syndrome or toxic epidermal necrosis. These reactions may occur weeks to months after starting allopurinol. The risk of AHS appears to be linked to a higher starting dose, but not to the maximal maintenance dose of allopurinol [122]. AHS is also significantly more likely in people with the HLA-B5801 allele (common in Korean, Thai and Han-Chinese populations), which has led to routine testing for this in high risk populations in the USA before commencing allopurinol [30, 123]. However, this is not yet current practice in

Europe. In our patient population side effects associated with increasing doses of allopurinol were rare and mild. It is important to remember however, that all patients recruited into FAST had already taken allopurinol for at least 60 days to be eligible for inclusion, and are therefore a group of patients already known to be tolerant of allopurinol.

The risk of precipitating a flare of gout by up-titration of allopurinol is also a concern to both doctors and patients and all patients entering FAST were offered gout flare prophylaxis during the up-titration process. This risk appears to be minimal with only 2% of patients experiencing a gout flare during up-titration of allopurinol, all of whom were taking flare prophylaxis. This is considerably less frequent than the 21% incidence of gout flares in patients newly treated with allopurinol who participated in a randomised trial of allopurinol versus febuxostat [112]. This demonstrates that the risk of flare is much lower when up-titrating allopurinol therapy in partially treated patients and may indicate that prolonged courses of prophylactic therapy might not be necessary under these circumstances.

Management of gout in patients with renal impairment is an additional matter of particular concern as allopurinol is rapidly metabolised into oxypurinol, which is predominantly renally excreted. As the half-life of oxypurinol is significantly prolonged in advanced renal impairment, lower doses of allopurinol are generally required. Previous treatment recommendations have suggested following the Hande guidelines [114] which

advocate progressive reduction of allopurinol dosage according to creatinine clearance in patients with renal impairment. Unfortunately, following this strategy results in inadequate reduction of sUA in many patients with gout and renal insufficiency. The recent ACR guidelines recommend that the dose of allopurinol can be up-titrated even in patients with renal impairment, as long as this is accompanied by adequate patient education and monitoring for drug toxicity such as pruritis, rash and elevated transaminases. However, the evidence supporting this needs to be considered carefully, taking into account the relatively small numbers of patients studied with renal impairment that had their dose of allopurinol escalated without adverse events, the rarity, but potentially life-threatening severity, of serious cutaneous reactions to allopurinol, and the availability of alternative ULTs such as febuxostat and benzbromarone for the treatment of gout patients with mild or moderate renal insufficiency.

Patients with eGFR <30 mL/min were excluded from FAST and patients with mild renal impairment (eGFR 30-60 mL/min) constituted only 17% of the first 400 patients recruited into FAST so the quantity of data was limited. In this small group, 40% of patients required up-titration, and the doses of allopurinol they were prescribed before and after up-titration were comparable with those prescribed to patients with eGFR >60 mL/min.

This analysis has some limitations, as it represents the first portion of a much larger ongoing study and was performed in open-label conditions. In addition, patients were already on treatment with allopurinol for at least 2 months prior to study entry and were

selected to meet certain other entry criteria so they may not be fully representative of the wider, particularly younger, gout population. FAST is a multi-centre trial and therefore includes a large and diverse patient population, and there were some regional differences in prescribing. Adherence to prescribed medication was not assessed and no adjustments were made for the potential of improved compliance with medication after entry into the study.

v) Conclusion

Analysis of pre-randomisation data for the first 400 FAST patients has shown that only 64% of patients were controlled on their baseline dose of allopurinol. 144 patients required one or more up-titrations of allopurinol and 97% of these patients ultimately achieved a reduction of sUA to the EULAR target of <357µmol/L. Historical guidelines advocate caution with higher doses of allopurinol, however our data shows that, in patients already taking allopurinol, generally only modest dose increases are required and these appear to be well tolerated and effective.

Chapter 4

The Effect of Xanthine Oxidase Inhibitors on Blood Pressure

An eight week sub-study of the Febuxostat versus Allopurinol Streamlined Trial (FAST)

4a) FAST Blood Pressure Sub-Study

i) Background

The link between hyperuricaemia and hypertension has been recognised for centuries and the hypertension and hyperuricaemia literature review in Chapter 2 highlights the extent of current research into this area. Laboratory data, observational data and small clinical trials have all contributed to our current knowledge of the links between blood pressure and hyperuricaemia however a number of questions remain unanswered.

Further randomised controlled trials in this area are potentially limited by design, ethical approval, expense and difficulties in recruitment. Therefore, using a population already enrolled in a clinical trial provided a good opportunity to recruit a large number of patients with established hyperuricaemia who are treated with XOi into a study on blood pressure.

ii) Aims

The primary aim of this study was to determine the effect of taking xanthine oxidase inhibitors (allopurinol and febuxostat) on the home monitored blood pressure of patients in the FAST trial.

Secondary aims were to investigate other factors that could influence blood pressure control including pre-existing hypertension, changes in serum urate and dose increases of allopurinol.

iii) Materials and Methods

Recruitment

298 patients who randomised into the FAST trial between December 2012 and January 2014 were consented for the blood pressure sub-study. Patient recruitment to the sub-study was confined to the UK and undertaken by FAST research nurses from the Dundee, Edinburgh, Glasgow, Nottingham and Highland study centres. Patients were recruited into the sub-study at their FAST screening visit.

Ethics

Ethical approval for the sub-study was sought from the Scotland Research Ethics committee (REC reference 11/AL/0311) and granted as part of amendment 8 to the FAST protocol.

Equipment – Blood Pressure Monitors

Home blood pressure measurements were measured using a Kinetik BPM1 blood pressure monitor (validated for home use by the British Hypertension Society in accordance with

the European Society of Hypertension International Protocol 2010 [124]). Standard and large blood pressure cuffs were available and a measure of the upper arm determined which cuff was given to the patient. Randomised patients were also provided with an instruction booklet for taking measurements (see Appendix 1) and blood pressure measurements were recorded in a monitoring diary (see Appendix 2).

Patient Selection

All UK patients invited to attend a screening visit for FAST during the study recruitment period were sent a patient information sheet for the blood pressure sub-study. Those patients eligible for FAST who wished to participate in the sub-study were asked to sign an additional consent form at the screening visit. If participating in the sub-study a measurement of the circumference of the upper arm was taken to allow selection of the appropriate size of blood pressure cuff. The patient was provided with a home blood pressure monitor (Kinetik BPM1), an instruction book and a monitoring diary. Every patient received a short tutorial in use of the home blood pressure monitor from the FAST research nurse.

Table 4.1: Inclusion and Exclusion Criteria for Blood Pressure Sub-Study

Inclusion criteria: - Eligible for entry into FAST Exclusion criteria: - Unable to effectively use a home blood pressure monitor - Systolic blood pressure >200mmHg at screening visit (to be reviewed at the investigators discretion) - Unstable blood pressure control or expectation that changes will be made to existing anti-hypertensive medication (patients taking anti-hypertensive medication should have been on stable medication for 1 month prior to entering the sub-study) - Commenced on NSAID as gout flare prophylaxis within the FAST protocol

Taking and Recording Blood Pressure Measurements

All patients were required to take a minimum of 3 sets of blood pressure measurements:

1) On receiving the blood pressure monitor [referred to as Initial measurements]
2) At the end of the 7 day allopurinol washout period [referred to as Washout measurements]
3) After 8 weeks of randomised therapy [referred to as 8 Week measurements]

Those patients who required up-titration of allopurinol during the allopurinol lead in phase took a further set of measurements when their urate level was controlled to ≤357 µmol/L or they reached their maximum tolerated dose of allopurinol [referred to as Additional measurements].

Each set of measurements was taken over 4 consecutive days. Blood pressure and pulse measurements were taken morning and evening 3 times and written down in the monitoring diary. Patients were asked to take morning and evening measurements at similar times each day and to leave at least 1 minute between each of the 3 measurements. Morning measurements were to be taken before any regular morning medication.

Instructions for home blood pressure monitoring (Appendix 2) followed the NICE Hypertension guidelines [24] and included use of an appropriate cuff size, being seated and at rest for 5 minutes with both feet on the floor prior to taking measurements, having the blood pressure cuff at the level of the heart and no exercise, food or caffeinated drinks for 30 minutes prior to taking blood pressure measurements. Patients were asked to use their non-dominant arm where possible for the blood pressure cuff and to ensure they always used the same arm for taking measurements. Heart rate was also recorded with each blood pressure reading.

At the end of the study patients kept the blood pressure monitor and returned the monitoring diary in a postage paid envelope to the Dundee FAST study centre.

Study Endpoints

Primary Endpoint:

1. Difference in mean home systolic and diastolic blood pressure from Washout to 8 Week measurements between patients randomised to allopurinol and those randomised to febuxostat.

Secondary Endpoints:

1. Change in mean home systolic and diastolic blood pressure from Washout to 8 Week measurements in hypertensive patients (systolic BP ≥ 135 mmHg) and non-hypertensive patients (systolic BP < 135 mmHg). Hypertension determined by mean blood pressure of Initial measurements.
2. Change in mean home systolic and diastolic blood pressure from Washout to 8 Week measurements in patients whose serum urate decreased by > 60 µmol/L (~ 1 mg/dL), either due to up-titration of allopurinol or following randomisation to febuxostat (n=117).
3. Effect of up-titration of allopurinol during allopurinol lead in phase for patients whose urate was not controlled to EULAR standards at screening visit (n=77).

The primary endpoint of blood pressure change after 8 weeks of randomised treatment was chosen as a pragmatic compromise between enough time to see a blood pressure effect against a short enough period to enable timely data collection and limit patient drop outs. The mechanism by which blood pressure reduction could be achieved with use of xanthine oxidase inhibitors is mediated by changes in nitric oxide and the renin angiotensin system and therefore 8 weeks should be sufficient exposure to the drugs to see a blood pressure effect.

Sample Size

Sample size for primary endpoint was calculated based on detecting a 4 mmHg change in blood pressure from Washout to 8 week measurements with SD 10 mmHg for home blood pressure measurements, α 0.05 and β 0.1. This required a sample size of 133 patients in each group. Allowing for 15% drop out, incomplete and non-return of monitoring diaries, planned recruitment was 150 patients randomised to allopurinol and 150 patients randomised to febuxostat giving a total of 300 patients.

The pre-specified secondary endpoints were exploratory and to generate hypotheses about possible contributing factors to blood pressure change including pre-existing hypertension, changes in serum urate and the dose of allopurinol. No formal power calculation was undertaken for secondary endpoints.

Data Collection

Screening data was collected from the FAST database (held by the Robertson Centre for Biostatistics, University of Glasgow) and included patient demographics, medication, co-morbidities and measurements of blood pressure, height and weight. Screening blood results were available for renal function and sUA levels. Additional sUA results were available for those patients who required up-titration of allopurinol or who were randomised to febuxostat.

Blood pressure data was received as a paper monitoring diary containing either 3 or 4 sets of measurements and identifiable by the FAST patient number only. For each set of measurements (Initial, Washout, 8 Week and Additional (if applicable)) patients recorded blood pressure three times, morning and evening for 4 consecutive days (total 24 systolic and 24 diastolic measurements). All blood pressure measurements were dual entered into an Excel spreadsheet.

For analysis, day 1 measurements and the first of each set of three measurements for days 2, 3 and 4 were discarded. Therefore, for each 4 day set of measurements there were 12 systolic and 12 diastolic blood pressure measurements used in analysis. A minimum data set was defined as 6 systolic and 6 diastolic measurements (from at least two consecutive days).

Clinically implausible measurements where the difference between systolic and diastolic measurements was < 15 mmHg were excluded. Patients whose blood pressure medication was changed during the study period were also excluded (medication changes were self-reported or recorded by FAST research nurses).

iv) Analysis

Patient demographics and baseline data is presented in a frequency table comparing those randomised to allopurinol and those randomised to febuxostat. Data is presented as percentage for categorical data and compared using Chi-squared test and mean and standard deviation for continuous data and compared using independent t-tests.

The primary analysis compared the change in blood pressures from Washout to 8 Week measurements for patients taking allopurinol and those taking febuxostat by dependent samples t-test. Secondary outcomes including change in blood pressure for patients whose sUA decreased by > 60 µmol/L, the effect of up-titration of allopurinol during the allopurinol lead in phase and change in BP with hypertension at screening were also analysed using dependent samples t-test. Predictors of change in blood pressure were estimated for all patients and for patients with baseline hypertension using generalised linear models. All analysis was undertaken by SPSS version 22.

v) Results

298 patients were consented into the blood pressure sub-study. Complete data sets were available from 223 participants and these were included in the final analysis. Figure 4.1 shows the breakdown of consented patients including withdrawals and patients with incomplete data. Of the 223 patients included in analysis, 104 were randomised to allopurinol and 119 were randomised to febuxostat.

Table 4.2 shows demographics and baseline measurements. As expected in the population of the FAST trial, patients were older with a mean age of nearly 70 years. predominantly male and overweight with mean BMI > 31. There was a high burden of cardiovascular disease with history of hypertension and high cholesterol being the most common risk factors followed by renal disease, diabetes and angina. The majority of patients were prescribed at least 2 anti-hypertensive medications. Screening measurements show that FAST patients had good renal function with mean creatinine clearance > 90mls/min. There were no statistically significant differences in baseline characteristics between the allopurinol group and the febuxostat group.

Blood pressure data for the different sets of blood pressure measurements is presented in Table 4.3. Overall mean change in blood pressure from Washout to 8 Week measurements was - 0.10/0.50 mmHg in the allopurinol group and - 0.77/- 0.41 mmHg in the febuxostat group (Table 4.4). These changes in blood pressure were not significant.

Reduction in sUA by > 60 μmol/L showed a very small, non-significant reduction in blood pressure (Table 4.5). Up-titration of allopurinol prior to randomisation showed a non-significant reduction in blood pressure (Table 4.6). Mean effect of up-titration during allopurinol lead in phase was - 1.15/-0.62 mmHg.

Multivariate analysis for all patients (Table 4.7) and for patients with hypertension at screening (Table 4.8) demonstrate that the only variable that did predict a reduction in both systolic and diastolic blood pressure from Washout to 8 Week measurements was female gender, however there were only 22 women in the study overall which limits further interpretation.

Figure 4.1: Patients consented into blood pressure sub-study

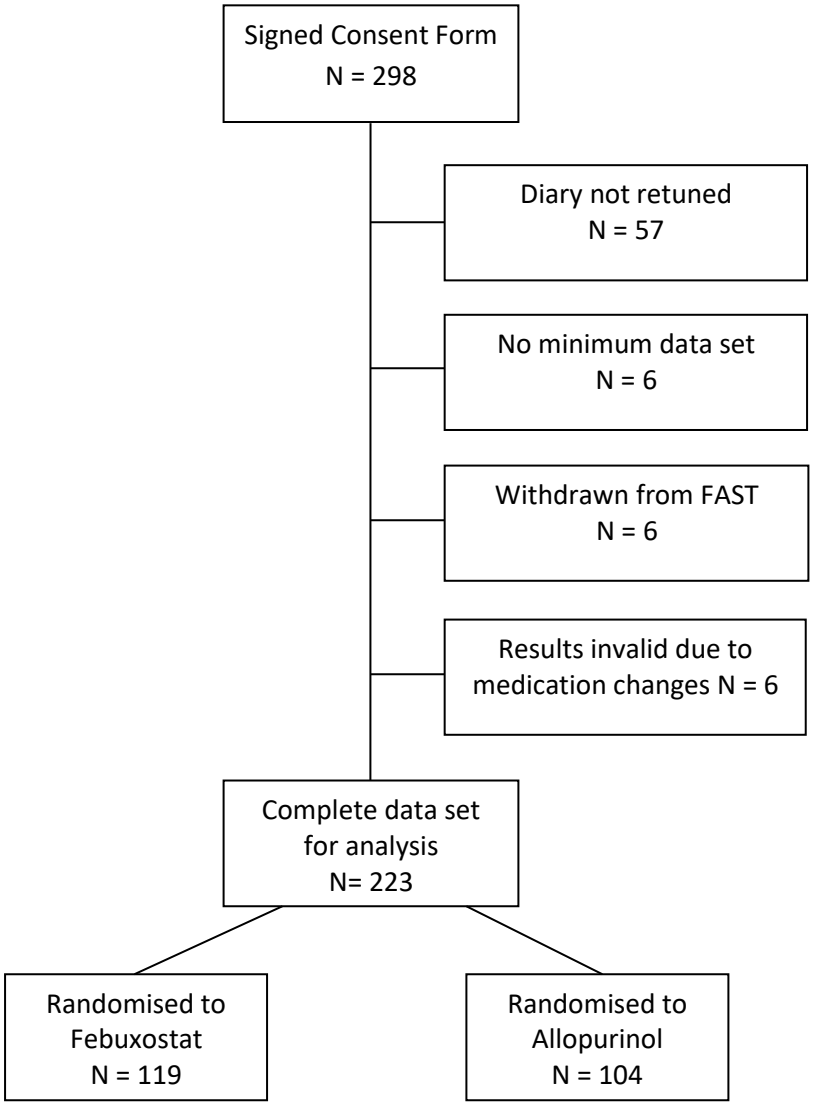


Table 4.2: Patient demographics and baseline data [mean (SD) or percentage]

		Allopurinol (n=104)	Febuxostat (n=119)	p value
Demographics	Age	69.6 (5.93)	69.9 (5.24)	0.87
	Gender (male)	85.6%	94.1%	0.35
Smoking Status	Current	5.8%	2.5%	0.34
	Former	54.8%	61.3%	
	Never	39.4%	36.1%	
Alcohol Consumption	Units per week	16.6 (16.8)	19.3 (18.4)	0.38
Number up titrations of allopurinol	0	70.2%	60.5%	0.21
	1	18.3%	30.3%	
	2	10.6%	9.2%	
	3	1.0%	-	
Allopurinol dose at screening (mg)	100	10.6%	9.2%	0.74
	200	26.0%	31.9%	
	250	-	1.7%	
	300	51.9%	46.2%	
	400	8.7%	6.7%	
	500	-	2.5%	
	600	1.9%	1.7%	
	900	1.0%	-	
Medical History	MI	8.7%	10.9%	0.56
	Stroke	1.9%	3.4%	0.50
	TIA	4.8%	4.2%	0.84
	PVD	2.9%	4.2%	0.59
	Hypertension	77.9%	76.5%	0.65
	ACS	9.6%	11.8%	0.59
	Coronary revascularisation	13.5%	11.8%	0.72
	Angina	14.4%	16.0%	0.73
	Heart failure	1.9%	6.7%	0.08
	High cholesterol	73.1%	68.9%	0.46
	Renal disease	21.2%	18.5%	0.63
	Asthma	15.4%	12.6%	0.33
	COPD	4.8%	6.7%	0.71
	Diabetes	19.2%	16.8%	0.65

Number of anti-hypertensives	0	20.2%	24.4%	0.20
	1	25.0%	31.1%	
	2	35.6%	28.6%	
	3	13.5%	10.1%	
	4	4.8%	4.2%	
	5	1.0%	1.7%	
Taking ACE/ARB	Yes	65.4%	55.5%	0.17
	No	14.4%	20.2%	
	N/A	20.2%	24.4%	
Taking Diuretic	Yes	20.2%	20.2%	0.63
	No	59.6%	55.5%	
	N/A	20.2%	24.4%	
Screening measurements	Systolic BP (mmHg)	137.1 (15.7)	136.5 (16.6)	0.30
	Diastolic BP (mmHg)	74.0 (11.0)	74.4 (11.8)	0.30
	BMI (Kg/m^2)	31.2 (7.6)	31.7 (6.3)	0.35
	Creatinine clearance (ml/min)	95.3 (29.3)	98.0 (28.3)	0.18
	eGFR > 60 ml/min	86.5%	89.1%	0.32
Urate (µmol/L)	Screening	318.2 (74.1)	329.3 (72.5)	0.27
	Randomisation	292.1 (46.8)	295.3 (47.3)	0.47
	On febuxostat	n/a	213.8 (53.7)	

Table 4.3: Summary table of blood pressure measurements from FAST Sub-study

BP measurements		Mean (SD)		p value
		Allopurinol	Febuxostat	
Initial (n=223)	Systolic	134.6 (13.4)	136.5 (14.3)	0.30
	Diastolic	80.7 (8.4)	82.2 (9.1)	0.29
Washout (n=223)	Systolic	134.2 (12.2)	133.8 (13.8)	0.84
	Diastolic	80.4 (8.2)	81.0 (8.5)	0.56
8 Week (n=223)	Systolic	134.1 (12.0)	133.0 (13.1)	0.55
	Diastolic	80.9 (8.7)	80.6 (8.3)	0.82
Additional (n=77)	Systolic	134.6 (14.8)	137.2 (13.2)	0.43
	Diastolic	79.2 (8.0)	82.5 (8.7)	0.09

Table 4.4: Primary outcome of change in blood pressure from Washout to 8 week measurements by randomised treatment

BP Measurements		Allopurinol		Febuxostat	
		Mean ΔBP (95% CI)	p value	Mean ΔBP (95% CI)	p value
Washout to 8 Week (n = 223)	Systolic	-0.10 (-1.76, 1.56)	0.903	-0.77 (-4.20, 2.67)	0.766
	Diastolic	0.50 (-1.82, 2.81)	0.672	-0.41 (-2.56, 1.73)	0.706

Table 4.5: Change in blood pressure from washout to 8 week measurements for patients whose serum urate reduced by > 60 µmol/L (secondary outcome 2)

BP measurements		Change in BP (mmHg) Mean (95% CI)	p value
Washout to 8 Week (n=115)	Systolic	-0.29 (-1.27,1.84)	0.715
	Diastolic	-0.17 (-0.71,1.07)	0.699

Table 4.6: Effect of up-titration of allopurinol on blood pressure (secondary outcome 3)

BP measurements		Change in BP (mmHg) Mean (95% CI)	p value
Initial* to Additional (n = 77)	Systolic	-1.15 (-3.10, 0.81)	0.246
	Diastolic	-0.62 (1.63, 0.40)	0.229

*initial measurements only from patients who required up-titration as serum urate not controlled at screening visit

Table 4.7: Multivariate analysis of change in systolic and diastolic blood pressure between Washout and 8 Week measurements

		Systolic BP		Diastolic BP	
Predictor	Level	Effect (95% CI)	p-value	Effect (95% CI)	p-value
Treatment gp (vs allopurinol)	Febuxostat	-1.58 (-3.96, 0.81)	0.20	-1.31 (-2.73, 0.11)	0.07
Gender (vs Men)	Female	-3.97 (-7.55,-0.39)	0.03	-3.27 (-5.40,-1.14)	0.003
Smoking Hx	Current	-0.27 (-5.32, 4.77)	0.92	-0.27 (-3.27, 2.74)	0.86
	Former	2.27 (0.18, 4.36)	0.03	1.15 (-0.07, 2.37)	0.07
Units of alcohol/week		-0.03 (-0.09, 0.02)	0.24	-0.02 (-0.05, 0.02)	0.33
BMI at Screening		0.14 (-0.01, 0.28)	0.06	0.06 (-0.03, 0.14)	0.21
Up titrated	Yes	2.15 (-0.54, 4.83)	0.12	-0.37 (-1.97, 1.23)	0.65
History of MI	Yes	-1.19 (-5.14, 2.74)	0.55	-0.46 (-2.81, 1.89)	0.70
History of Stroke	Yes	-5.11 (-11.2, 0.98)	0.10	-0.24 (-3.85, 3.37)	0.90
History of TIA	Yes	-0.39 (-5.33, 4.55)	0.88	0.79 (-2.16, 3.73)	0.60
History of PVD	Yes	4.55 (-0.67, 9.78)	0.08	-0.28 (-3.38, 2.82)	0.86
History hypertension	Yes	2.28 (-1.54, 6.09)	0.24	0.28 (-2.00, 2.55)	0.81
History of ACS	Yes	-0.83 (-4.54, 2.87)	0.66	-0.21 (-2.41, 1.99)	0.85
History of revascularisation	Yes	-2.24 (-6.27, 1.79)	0.28	-1.59 (-4.00, 0.81)	0.19
History of angina	Yes	-1.26 (-4.65, 2.12)	0.47	-0.54 (-2.60, 1.53)	0.61
History of heart failure	Yes	-3.01 (-8.53, 2.34)	0.26	-0.57 (-3.80, 2.66)	0.73
History of high cholesterol	Yes	0.04 (-2.14, 2.22)	0.97	0.43 (-0.87, 1.73)	0.51
History renal disease	Yes	0.54 (-2.09, 3.17)	0.69	0.05 (-1.52, 1.62)	0.95
History of asthma	Yes	3.10 (0.27, 5.93)	0.03	0.79 (-0.90, 2.47)	0.36
History of COPD	Yes	0.60 (-3.81, 5.01)	0.79	0.35 (-2.28, 2.98)	0.79
History of diabetes	Yes	0.62 (-2.05, 3.29)	0.65	-1.02 (-2.61, 0.57)	0.21
Antihypertensive drugs (vs none)	1	-4.22 (-8.57, 0.14)	0.06	-1.07 (-3.66, 1.53)	0.42
	2	-3.58 (-8.22, 1.07)	0.13	-0.81 (-3.57, 1.95)	0.56
	3	-2.02 (-7.84, 3.79)	0.50	0.49 (-2.97, 3.95)	0.78
Taking ACE/ARB	yes	-0.58 (-3.37, 2.22)	0.69	0.04 (-1.61, 1.69)	0.96
Taking any diuretic	yes	-2.21 (-5.39, 0.97)	0.17	-1.85 (-3.73, 0.04)	0.06
eGFR >60 ml/min	Yes	0.40 (-2.93, 3.72)	0.82	2.33 (0.35, 4.32)	0.02

Table 4.8: Multivariate analysis of change in systolic and diastolic blood pressure between Washout and 8 Week measurements in patients with hypertension (systolic BP ≥ 135mmHg) at screening visit (secondary outcome 1)

		Systolic		Diastolic	
Predictor	Level	Effect (95% CI)	p-value	Effect (95% CI)	p-value
Treatment gp (vs allopurinol)	Febuxostat	0.07 (-4.07, 4.20)	0.98	-0.72 (-2.94, 1.51)	0.53
Gender (vs Men)	Female	-8.02 (-14.0,-2.03)	0.01	-5.70 (-8.92,-2.47)	<.001
Smoking Hx	Current	-4.58 (-12.7, 3.49)	0.27	-4.11 (-8.45, 0.23)	0.06
	Former	2.74 (-0.85, 6.32)	0.14	2.24 (0.31, 4.17)	0.02
Units of alcohol/week		-0.04 (-0.14, 0.06)	0.42	-0.04 (-0.10, 0.01)	0.10
BMI at Screening		0.29 (0.04, 0.53)	0.02	0.05 (-0.08, 0.18)	0.45
Up titrated	Yes	2.44 (-1.78, 6.67)	0.26	0.50 (-1.77, 2.78)	0.67
History of MI	Yes	-6.13 (-12.9, 0.69)	0.08	-1.08 (-4.75, 2.59)	0.56
History of Stroke	Yes	14.71 (-3.75, 33.17)	0.12	6.87 (-3.06,16.80)	0.18
History of TIA	Yes	-2.46 (-12.5, 7.59)	0.63	0.65 (-4.76, 6.06)	0.81
History of PVD	Yes	2.57 (-4.57, 9.70)	0.48	-0.34 (-4.18, 3.50)	0.86
History hypertension	Yes	3.77 (-4.03,11.56)	0.34	-1.02 (-5.21, 3.18)	0.64
History of ACS	Yes	-2.72 (-8.18, 2.75)	0.33	-1.56 (-4.50, 1.38)	0.30
History of revascularisation	Yes	-0.35 (-7.51, 6.81)	0.93	-1.07 (-4.93, 2.78)	0.59
History of angina	Yes	1.72 (-4.31, 7.74)	0.58	2.82 (-0.42, 6.06)	0.09
History of heart failure	Yes	-1.63 (-9.97, 6.71)	0.70	-2.61 (-7.10, 1.88)	0.25
History of high cholesterol	Yes	-1.74 (-5.48, 2.01)	0.36	-0.41 (-2.43, 1.60)	0.69
History renal disease	Yes	-1.43 (-6.04, 3.17)	0.54	0.40 (-2.08, 2.88)	0.75
History of asthma	Yes	2.64 (-1.57, 6.84)	0.22	-0.17 (-2.43, 2.10)	0.89
History of COPD	Yes	-1.33 (-8.41, 5.75)	0.71	-0.77 (-4.58, 3.04)	0.69
History of diabetes	Yes	-1.25 (-5.79, 3.30)	0.59	-2.68 (-5.13,-0.24)	0.03
Antihypertensive drugs (vs none)	1	-8.09 (-16.9, 0.76)	0.07	-2.55 (-7.31, 2.22)	0.30
	2	-10.7 (-19.8,-1.57)	0.02	-1.79 (-6.68, 3.10)	0.47
	3	-7.99 (-18.6, 2.65)	0.14	-0.43 (-6.15, 5.29)	0.88
Taking ACE/ARB	yes	-1.47 (-6.72, 3.77)	0.58	0.65 (-2.17, 3.47)	0.65
Taking any diuretic	yes	-2.24 (-6.89, 2.42)	0.35	-1.20 (-3.70, 1.31)	0.35
eGFR >60 ml/min	Yes	-5.49 (-11.2, 0.25)	0.06	-0.61 (-3.70, 2.48)	0.70

vi) Discussion

The blood pressure sub-study of FAST patients (who are older patients, with treated gout) demonstrated no significant change in home monitored blood pressure over an 8 week period for patients randomised to either allopurinol or febuxostat. Up-titration of allopurinol, reduction in sUA and baseline hypertension did not alter this result or predict a blood pressure response.

The finding that female gender predicted a small but statistically significant reduction in blood pressure over the study period is intriguing however the very small number of females included limits further interpretation of this result. Gout is significantly less common in pre-menopausal women (due to uricosuric effects of oestrogen) but incidence rises to match that of men in post-menopausal women. It could be postulated therefore that women have more capacity to respond to the extended effects of urate lowering as they have less cumulative exposure to the detrimental effects of hyperuricaemia. Further research may look into particular groups of patients that could be targeted for treatment either due to particularly high risk or likelihood of response and certainly a difference between gender responses warrants further investigation.

There were a number of limitations to this sub-study. Firstly, the study was ultimately underpowered with return of only 223 monitoring diaries out of the 266 that were required. As there was virtually no change in blood pressure demonstrated it appears

unlikely that greater numbers would have altered the result to the extent that significant change in blood pressure was seen.

The study population is a limitation as the patients from the FAST trial were older and predominantly male with high burden of cardiovascular risk factors, a background history of gout and already treated with allopurinol. The potential for urate lowering to influence blood pressure control has been demonstrated in a number of small studies outlined in the review in chapter 2. In these studies, the most positive blood pressure lowering effects were seen in young patients and those not previously exposed to urate lowering therapy. Therefore, the impact of newly initiated allopurinol on blood pressure in patients with hyperuricaemia may not be evident in this study. To mitigate this to some extent we used measurements after a 7 day washout period as the half-life of oxypurinol (the active metabolite of allopurinol) is approximately 15 hours so all active metabolites should have been removed during this washout period however, urate levels were not re-checked therefore we cannot estimate the effect of this washout period.

The short duration of follow up is potentially a limiting factor however previous studies have used relatively short follow up to demonstrate an effect. For example blood pressure lowering of -6 mmHg systolic and -4 mmHg diastolic was seen in adolescents with newly diagnosed essential hypertension and sUA > 6 mg/dL taking 200mg allopurinol twice daily for only 4 weeks [66]. Blood pressure lowering was also seen in patients with asymptomatic hyperuricaemia where mean fall in BP was -4 mmHg systolic and -2 mmHg

diastolic in those taking 300mg allopurinol daily for 12 weeks [68]. A Korean study comparing blood pressure effects of febuxostat and allopurinol in men with gout ran for only 4 weeks and a significant fall in diastolic blood pressure was seen in the treated groups compared to control. This effect was not significant after correcting for baseline characteristics but this study does demonstrate that a short duration of follow up is feasible to demonstrate a blood pressure effect [125]. These studies looked at different populations to FAST patients however the doses of allopurinol and febuxostat used and relatively short duration of follow up were not too dissimilar to those used in this sub-study. The 8 week follow up period was chosen as a compromise between a short enough period to allow timely data collection and optimise patient retention and diary return against a long enough period to see any effects of medication on blood pressure. The postulated mechanism by which XOi would be expected to lower blood pressure would be due to reduction of the detrimental effects of hyperuricaemia such as inhibition of nitric oxide and RAS activation. Other studies used longer follow up periods (between 3 to 12 months) and it may be that the beneficial effect of controlling hyperuricaemia with XOi only becomes measureable over time as some microvascular damage is reversed. Ideally a longer duration of follow up would be preferred.

Other limitations to this study, include patient controlled data collection process and compliance with medication. Patient controlled data collection involved blood pressure measurements taken and recorded by patients at home after a single short tutorial on use of the monitor from the recruiting nurse. A comprehensive instruction book was also

provided aiming to ensure that patient technique was as accurate and consistent as possible however there was no way of checking what patients were actually doing, or how carefully they were taking and recording measurements. The research nurses ensured that patients were supplied with the correctly sized cuff for their arm diameter. The blood pressure monitor used (Kinetik BPM1) is validated for home use and NICE guidelines suggest home monitored blood pressure is accurate and acceptable for research use. The major limitation of this method of data collection was non-return of 57 blood pressure monitoring diaries despite prompting and telephone reminders. Data recording by patients was overall very good and only 6 of the returned diaries did not have the minimum data set required for analysis.

Compliance with study medication was not formally monitored and assessment relied on self-report only. Patients were posted study medication from the FAST research pharmacy and they returned empty packaging to the research pharmacy. Patients and research nurses were also asked to report any changes in their background medication, particularly anti-hypertensive medication during the study period however again we had no way of verifying patient compliance with background medication.

vii) Conclusion

Overall, although no blood pressure lowering effect was seen in the specific population used in this sub-study and with the limitations outlined above, the potential for

management of hyperuricaemia to modify cardiovascular risk factors including hypertension remains an attractive proposition and research in this area will continue. One positive outcome from this sub-study was the use of home monitored blood pressure measurement as a research tool. This method was well accepted by participants in the study and patient recording of blood pressure data was generally good. Incentives to improve data collection could be considered for future studies.

Chapter 5

Impact of Xanthine Oxidase Inhibitors on Renal Function of FAST Patients

5a) Interim analysis of FAST trial data

i) Background

Uric acid is predominantly renally excreted therefore the relationship between sUA levels and renal function is complex. Urate levels inevitably rise as renal function declines and evidence is emerging that raised sUA is also an independent risk factor for decline in renal function. Routine measurement of sUA is rarely undertaken outside of patients with symptomatic hyperuricaemia as while there is postulated to be a causal link between hyperuricaemia and other conditions, including renal function decline, at present the evidence to support active intervention in lowering sUA to modify outcomes in these other conditions is lacking.

Declining renal function occurs as a natural consequence of aging and while there are many factors that will affect this process, in general, in patients over the age of 60 with no history of chronic kidney disease, glomerular filtration will decline by an average of 1-3 ml/min/year [126-128]. This rate of decline will potentially be faster in those who are older and those with co-morbidities including pre-existing renal dysfunction, hypertension, diabetes, obesity and hypercholesterolaemia.

The review of hyperuricaemia and renal function in Chapter 2 highlights the difficulties in determining whether hyperuricaemia is a cause or a consequence of renal function decline. Large, interventional trials are currently taking place to answer the question of

whether nephrologists should routinely monitor and treat high serum urate with the sole intent of slowing decline in renal function. FAST is a large, multi-centre trial which already collects the data required to monitor renal function in a high risk population receiving optimal urate lowering treatment. Data collected from participants in the FAST trial provide an opportunity to observe the effects of optimal urate lowering on renal function in this population over one year and results of this analysis will determine whether further studies with FAST data are warranted in this area.

ii) Aim

The aim of this interim analysis of FAST data was to look at how changes in serum urate (sUA) due to use of xanthine oxidase inhibitors affected renal function measured by creatinine clearance (CrCl) at annual follow up of patients in the FAST trial.

iii) Materials and Methods

Consecutive patients from all study centres in the UK and Denmark who randomised into FAST between 1st January 2012 and 31st May 2013 were included. Those who had stopped taking study medication, had not completed an annual review or did not have complete annual blood results available at the time of data collection (end of July 2014) were then excluded from the analysis.

Screening blood tests included sUA level, renal function (urea and creatinine with derived estimated glomerular filtration rate (eGFR) and CrCl), liver function tests, full blood count and coagulation screen. Annual blood tests included sUA, renal function and liver function only. eGFR was calculated by the central study laboratory in Ninewells Hospital, Dundee using serum creatinine, patient gender and age using the abbreviated MDRD equation [129] and uploaded to the electronic patient record. eGFR was given as a number for values up to 60 ml/min and as >60 ml/min for all values greater than 60 ml/min. CrCl was calculated using serum creatinine, patient gender, age and the patient's weight measured by the FAST nurses from screening and annual visits. Calculation was made using the Cockcroft-Gault formula [130] and this formula was embedded in the electronic patient record. CrCl was used in the analysis as it provided specific results for patients with preserved renal function (eGFR above 60 ml/min).

There are well documented limitations to all methods of renal function estimation, particularly in patients at extremes of body weight, patients with diabetes and older patients. As the primary outcome for the renal function interim analysis compares change in CrCl over time in the same patient and the vast majority (85%) of patients had no history of chronic kidney disease use of the Cockcroft gault formula was felt to be a reasonable method for estimation of renal function [131, 132].

All blood samples from screening and follow up as part of the FAST trial were sent to a central lab in Ninewells Hospital, Dundee for analysis. This ensured comparability of results from patients in all study centres.

Baseline data (in addition to blood tests) collected at the screening visit included age, gender, BMI, blood pressure, smoking history, alcohol history, baseline dose of allopurinol, number of up-titrations required, past medical history (MI, stroke, PVD, ACS, coronary revascularisation, angina, heart failure, raised cholesterol, asthma, COPD, cancer, diabetes and CKD) and medication at screening. This data was captured by FAST research nurses using measurements obtained at the screening visit, patient history and GP records. Data was extracted from the FAST database (Robertson Centre for Biostatistics, University of Glasgow) for analysis.

iv) Analysis

Analysis was undertaken using SPSS version 22. Values are expressed as mean and standard deviation (SD) or number and percentage. Categorical data were compared by Chi-squared test and continuous variables by independent samples t-test with 95% confidence intervals (CI) provided. Further analysis of treatment effect of change in CrCl from baseline was estimated using a generalised linear model with baseline CrCl, BP, BMI and change in sUA as continuous covariates and gender, smoking status and medical history as categorical covariatesStatistical significance was defined as two-tailed $p < 0.05$.

Primary Analysis: Patients were categorised into two main groups according to how sUA changed over the 12 month follow up period and mean change in CrCl was compared by independent t-test. The two main groups were:

sUA Decreased	Patients whose sUA fell by more than 10%
sUA Unchanged	Patients whose sUA either increased or remained within 10% of screening value.

Additional analysis of mean change in CrCl divided patients into five groups:

Group 1 – sUA increased by > 10%

Group 2 – sUA unchanged (± ≤ 10% of screening value)

Group 3 – sUA decreased by > 10% and ≤ 25%

Group 4 – sUA decreased by > 25% and ≤ 50%

Group 5 – sUA decreased by > 50%

Secondary analysis included comparison of change in CrCl between patients randomised to febuxostat and those randomised to allopurinol.

v) Results

757 patients were randomised between 1st January 2012 and 31st May 2013 (and therefore had annual follow up data available at time of data collection in July 2014). 100 patients were excluded from final analysis (12 due to incomplete blood results at annual follow up, 2 withdrawn completely from the study and 86 who had stopped taking randomised therapy) leaving 657 patients in the final analysis.

Demographics and baseline characteristics are shown in Table 5.1.

As expected in a study recruiting patients with symptomatic hyperuricaemia the majority were male with a mean age of 70 years at the time of screening (FAST excluded patients under the age of 60 years). FAST is a cardiovascular safety study therefore all recruited patients had to have at least one additional cardiovascular risk factor and the study population has a high overall cardiovascular disease burden particularly for hypertension, hypercholesterolaemia, ischaemic heart disease and diabetes. FAST excluded patients with eGFR < 30 ml/min on screening bloods and therefore only a small proportion of patients had established chronic kidney disease at screening.

There was a significant difference between screening and annual sUA confirming that sUA was significantly decreased in the sUA Decreased group over the study interval. There were also significant differences between the groups for allopurinol dose at screening, requirement for up-titration and randomised therapy which reflects the FAST protocol as

those with higher screening sUA would be up-titrated to control sUA to within EULAR guideline recommendations. Febuxostat is also a more potent xanthine oxidase inhibitor than lower doses of allopurinol and would potentially be expected to lower sUA by a greater amount, therefore the majority of patients randomised to febuxostat were in the sUA Decreased group. Screening CrCl was lower in the sUA Decreased group which correlates with higher screening sUA and it may be expected that those with poorer baseline renal function had higher sUA due to the predominantly renal excretion of uric acid.

Table 5.1: Demographics and Baseline Characteristics

	Mean (SD) or n (%)			p value*
	Overall (n=657)	sUA Unchanged (n=233)	sUA Decreased (n=424)	
Age (years)	70.1 (6.4)	70.0 (6.5)	70.1 (6.3)	0.910
Gender (male)	561 (85.4%)	197 (84.5%)	364 (85.8%)	NS
BMI	31.5 (5.4)	31.3 (5.6)	31.5 (5.3)	0.715
Screening Blood Pressure:				
Systolic (mmHg)	137.0 (17.5)	138.4 (17.0)	136.3 (17.8)	0.144
Diastolic (mmHg)	74.4 (11.6)	74.2 (11.2)	74.4 (11.8)	0.798
Allopurinol dose at screening (median)	300mg	300mg	200mg	<0.001
Allopurinol up-titration	252 (38.4%)	27 (11.6%)	225 (53.1%)	<0.001
Screening sUA (µmol/L)	336.8 (82.4)	287.0 (62.3)	364.2 (79.3)	<0.001
Annual sUA (µmol/L)	262.8 (71.6)	300.7 (64.6)	241.9 (66.5)	<0.001
Screening CrCl (ml/min)	98.4 (34.5)	102.1 (36.6)	96.4 (33.1)	0.040
Annual CrCl (ml/min)	93.8 (34.3)	95.6 (35.0)	92.7 (34.0)	0.299
Randomised to Febuxostat	301 (45.8%)	36 (15.5%)	265 (62.5%)	<0.001
Past Medical History:				
Hypertension	508 (77.3%)	189 (81.1%)	319 (75.2%)	
Chronic Kidney Disease	97 (14.8%)	30 (12.9%)	67 (15.8%)	
Previous Myocardial Infarction	73 (11.1%)	29 (12.4%)	44 (10.4%)	
Stroke	36 (5.5%)	11 (4.7%)	25 (5.9%)	
Peripheral Vascular Disease	39 (5.9%)	14 (6.0%)	25 (5.9%)	
Acute Coronary Syndrome	66 (10.0%	17 (7.3%)	49 (11.6%)	
Coronary revascularisation	91 (13.9%)	33 (14.2%)	58 (13.7%)	
Angina	94 (14.3%)	33 (14.2%)	61 (14.4%)	
Heart failure	34 (5.2%)	19 (8.2%)	15 (3.5%)	
Raised cholesterol	446 (67.9%)	147 (63.1%)	299 (70.5%)	
Asthma	91 (13.9%)	33 (14.2%)	58 (13.7%)	
COPD	42 (6.4%)	20 (8.6%)	22 (5.2%)	
Diabetes	173 (26.3%)	61 (26.2%)	112 (26.4%)	NS
Smoking history:				
Current	51 (7.8%)	20 (8.6%)	31 (7.3%)	
Former	390 (59.4%)	131 (56.2%)	259 (61.1%)	
Never	216 (32.9%)	82 (35.2%)	134 (31.6%)	NS
Alcohol:				
None	154 (23.4%)	55 (23.6%)	99 (23.3%)	
No. units/week (n=502)	18.6 (16.7)	18.9 (18.7)	18.8 (16.5)	NS

NS = Not significant *comparison of sUA Unchanged and sUA Decreased

For all patients there was a significant change in CrCl from screening to annual review with a mean fall in CrCl of 4.6 ml/min (95% CI -3.7, -5.6), p<0.001.

Results of the primary analysis comparing mean change in CrCl for the two main groups of change in sUA are shown in Table 5.2.

The difference in change in CrCl for the two groups was -2.9 ml/min (95% CI -4.8, -0.9) p=0.004, confirming a significantly lesser fall in CrCl in sUA Decreased group. This relationship remains significant after correcting for screening CrCl (p=0.012)

Further analysis using the 5 groups of change in sUA shows a similar trend with a significantly greater mean fall in CrCl of 8.6 ml/min in those whose sUA increased over the follow up period compared to a mean fall of only 2.2 ml/min in those whose sUA decreased by over 50% (p<0.001). Results shown in table 5.3 and Figure 5.1.

Table 5.2: Change in sUA (µmol/L) and CrCl (ml/min) from baseline to annual visit

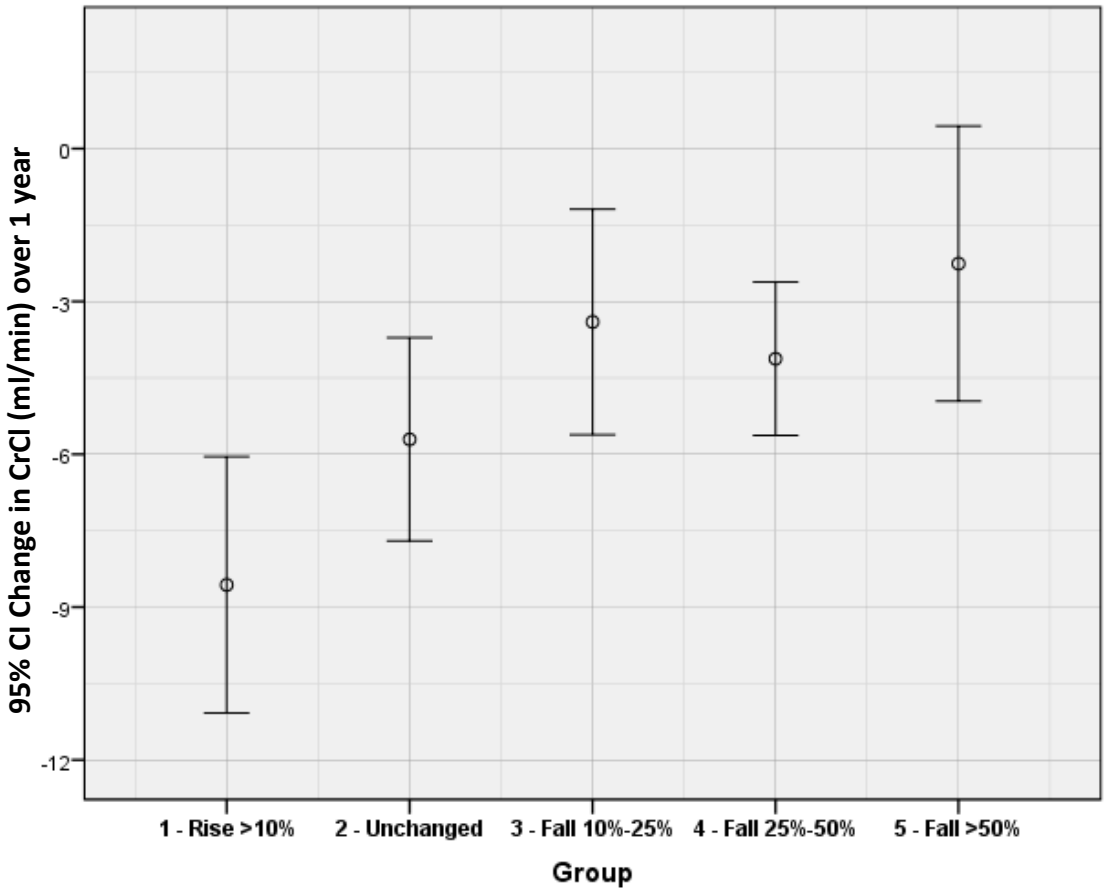
	Serum Urate (µmol/L) Mean (SD)			Creatinine Clearance (ml/min) Mean (SD)		**Δ CrCl (95% CI)**	**p value**
	Screening	Annual	Δ sUA	Screening	Annual		
sUA Unchanged (n=233)	287.0 (62.3)	300.7 (64.6)	13.7 (35.9)	102.1 (36.6)	95.6 (35.0)	**-6.5 (-8.1, -4.9)**	**0.004**
sUA Decreased (n=424)	364.2 (79.3)	241.9 (66.5)	-122.3 (63.3)	96.4 (33.1)	92.7 (34.0)	**-3.6 (-4.8, -2.5)**	

Table 5.3: Changes in sUA (µmol/L) and CrCl (ml/min) from baseline to annual visit.

	Serum Urate (µmol/L) Mean (SD)			Creatinine Clearance (ml/min) Mean (SD)		**Δ CrCl (95% CI)**
	Screening	Annual	Δ sUA	Screening	Annual	
sUA increased by ≥10% (n=62)	266.5 (63.8)	322.2 (73.9)	55.8 (41.0)	100.6 (30.4)	92.0 (27.8)	**-8.6 * (-11.2, -6.1)**
sUA unchanged (± ≤10% of screening value) (n=171)	294.5 (60.3)	293.0 (59.2)	-1.5 (16.8)	102.7 (38.7)	97.0 (37.2)	**-5.7 (-7.7, -3.7)**
sUA decreased by >10% and ≤25% (n=139)	344.5 (68.4)	282.5 (55.0)	-62.0 (22.0)	98.6 (34.7)	95.2 (35.5)	**-3.4 (-5.6, -1.2)**
sUA decreased by >25% and ≤50% (n=223)	370.5 (81.9)	236.7 (57.8)	-133.9 (40.4)	97.5 (32.3)	93.4 (33.1)	**-4.1 (-5.6, -2.6)**
sUA decreased by >50% (n=62)	385.7 (84.2)	169.7 (50.7)	-216.0 (55.5)	87.2 (31.0)	85.0 (33.1)	**-2.2 * (-4.9, -0.6)**

* sUA increased by ≥10% vs sUA decreased by >50% p=<0.001

Figure 5.1: Change in CrCl (ml/min) with 95% CI by sUA group



Estimates from a generalised linear model using both continuous and categorical variables are shown in Table 5.4 demonstrating that baseline CrCl, systolic BP and BMI are also significant predictors of change in CrCl as well as change in sUA and the treatment effect of allopurinol or febuxostat. Change in CrCl due to change in sUA remains significant after adjusting for baseline renal function, blood pressure and BMI.

Figure 5.1 shows a scatter plot comparing change in CrCl against change in sUA and comparing those randomised to allopurinol and those randomised to febuxostat with independent regression lines fitted according to which type of xanthine oxidase inhibitor the patients were randomised to. Formal analysis of this relationship shows that change in urate is a significant predictor of change in CrCl ($p<0.001$), the slope of this relationship is not significantly different in the two treatment groups ($p=0.465$) and a treatment difference remains after adjusting for it ($p<0.001$). As expected patients taking febuxostat (blue dots) tended to have greater overall reduction in sUA compared to those taking allopurinol (red dots). This analysis suggests that the relationship between change in sUA and change in CrCl has a similar slope within each treatment group but change in sUA does not account for the treatment difference between the two XOi's.

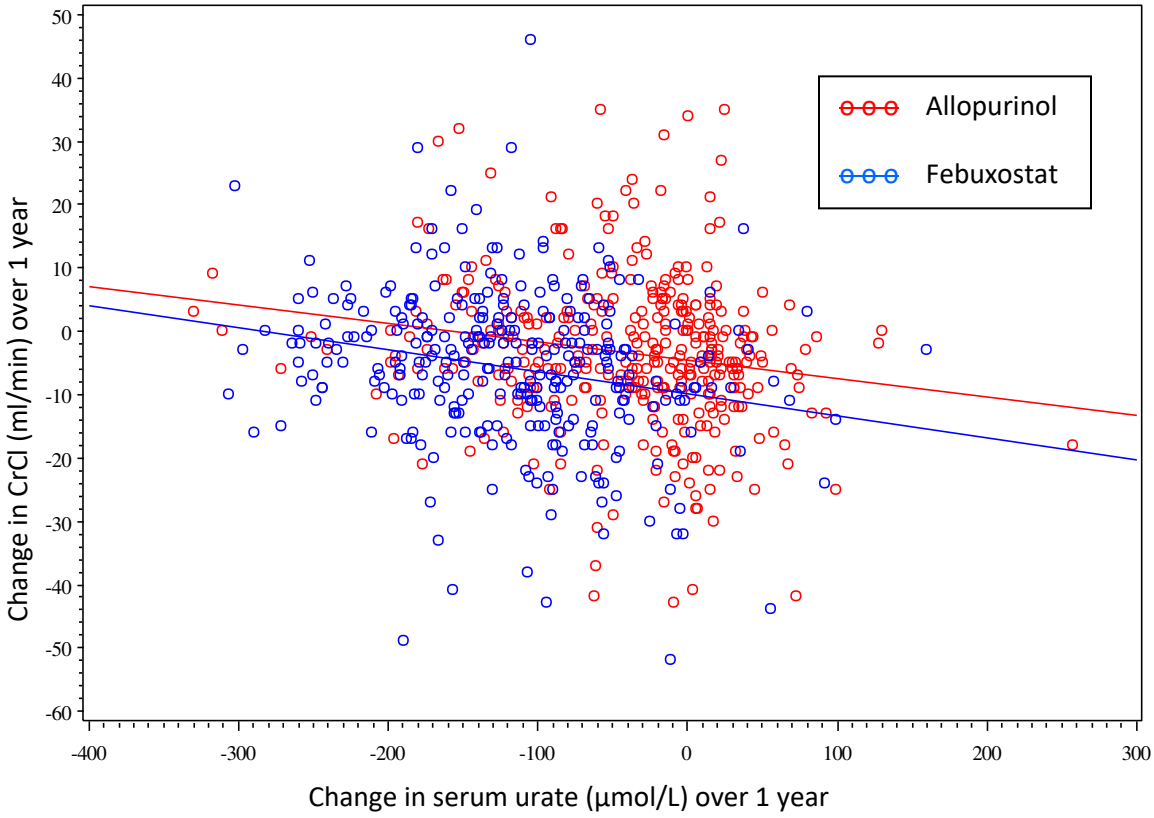
An interesting observation is that overall, patients taking febuxostat achieved a greater mean reduction in sUA compared to those taking allopurinol (-116 µmol/L vs -38 µmol/L) but patients randomised to febuxostat also saw a greater fall in CrCl of -5.9 ml/min

compared to -3.5 ml/min for those taking allopurinol. This observation may be explained by the differences in action of the two XOi's.

Table 5.4: Generalised linear model with baseline CrCl, systolic BP, BMI and change in sUA as continuous covariates, and gender, smoking status and past medical history as categorical covariates.

		P value
Predictor	Effect (95% CI)	
Screening Cr clearance	-0.104 (-0.137,-0.071)	<.0001
Change in urate over 1 year	-0.027 (-0.039,-0.015)	<.0001
Febuxostat vs Allopurinol	-4.851 (-6.819,-2.883)	<.0001
Systolic BP at screening	-0.083 (-0.135,-0.032)	0.0016
BMI at Screening	0.337 (0.134, 0.541)	0.0011
Men vs Women	1.323 (-1.391, 4.037)	0.3394
Smoking: Current vs Never	-2.034 (-5.542, 1.474)	0.2557
Smoking: Former vs Never	-0.824 (-2.782, 1.133)	0.4091
History renal disease	-3.482 (-6.180,-0.784)	0.0114
History hypertension	-0.493 (-2.612, 1.626)	0.6483
History of MI	1.522 (-1.888, 4.932)	0.3817
History of Stroke	-2.101 (-6.112, 1.909)	0.3045
History of TIA	-3.079 (-6.906, 0.748)	0.1148
History of PVD	0.287 (-3.521, 4.095)	0.8825
History of ACS	-0.567 (-3.747, 2.612)	0.7265
History of coronary revascularisation	-0.288 (-3.549, 2.974)	0.8628
History of angina	-3.145 (-6.033,-0.258)	0.0328
History of heart failure	-2.391 (-6.621, 1.840)	0.2680
History of high cholesterol	1.022 (-0.975, 3.019)	0.3158
History of asthma	-0.309 (-2.940, 2.321)	0.8176
History of COPD	1.415 (-2.293, 5.124)	0.4545
History of diabetes	0.569 (-1.543, 2.682)	0.5974

Figure 5.2: Scatter plot of change in CrCl against change in sUA with independent regression lines fitted for patients in each treatment group.



vi) Discussion

This interim analysis of FAST data looking at changes in renal function measured by CrCl over one year in relation to changes in sUA shows that the overall mean decline in CrCl for FAST patients over one year was - -4.6 ml/min. This may be a greater decline than would be seen in the general population but likely reflects the age, increased co-morbidity and high overall cardiovascular disease burden seen in the FAST population [133]. This patient group also has a history of symptomatic hyperuricaemia and therefore potential exposure to high levels of sUA for many years which may be a key factor in predisposing them to more rapid renal function decline.

The main result of this analysis shows that in those patients whose sUA decreased by at least 10%, the decline in CrCl was significantly less than in those whose sUA did not change or increased. Importantly, the data also demonstrated a trend that the greater the reduction in sUA, the smaller the fall in CrCl. This data would therefore appear to provide further evidence that active intervention with XOi's to lower sUA can slow the progression of renal function decline.

This is an important finding as chronic renal impairment affects approximately 10% of the world's population and jumped from 27th to 18th in just two decades in the Global Burden of Disease study that ranked causes of death worldwide [134]. Measurement of serum urate is straightforward and a low cost, well tolerated intervention that preserves renal function and potentially reduces cardiovascular risk would be an important contribution

to global health. In a questionnaire survey of Japanese nephrologists, 86% would actively treat hyperuricaemia with xanthine oxidase inhibitors in CKD stages 3-5 with the aim of slowing renal function decline [135]. This is not standard practice elsewhere but may change in the future as more convincing evidence emerges.

Further analysis by generalised linear model demonstrated that blood pressure, baseline renal function and BMI were also predictors of change in renal function. Analysis of covariance accounting for these factors still demonstrates a significant change in CrCl with change in sUA over the year of follow up. It is interesting that the age of the patient was not a significant predictor of change in CrCl however this is likely due to the patient selection for FAST and the relatively small spread of age groups represented in the data. Higher systolic blood pressure and higher BMI were associated with a greater fall in CrCl over the year of follow up which may be expected as hypertension and obesity are risk factors for renal function decline. The relationship between higher screening CrCl and greater fall in CrCl may reflect the use of Cockcroft-Gault formula and increased error with higher baseline function. It would be interesting to see if these factors remain as predictors for change in renal function in a larger analysis of FAST data.

When the data was split according to the randomised treatment of either allopurinol or febuxostat, the somewhat unexpected outcome was that while febuxostat is the more potent drug in terms of sUA lowering with a mean urate reduction of 116 µmol/L it was also associated with greater fall in CrCl. Therefore, while the overall trend is consistent

(greater reduction in sUA associates with less reduction in CrCl) and it could be suggested from this data that allopurinol has superior renal function protective properties than febuxostat despite its more modest reductions in sUA. This potentially reflects the different actions of the xanthine oxidase inhibitors, with febuxostat being a more selective inhibitor while allopurinol blocks urate production and formation of by-products including free radicals which may increase oxidative stress and microvascular damage. It may be that these by-products are potentially more damaging to the microvasculature and therefore there is a benefit to a non-selective xanthine oxidase inhibitor above purely absolute reduction in sUA.

Another important observation is that the group whose urate fell by greater than 50% over the year had significantly higher screening sUA and lower CrCl at baseline. This is consistent with the renal excretion of uric acid and that higher urate levels are expected with poorer excretory renal function. The findings remained significant after correcting for baseline CrCl and the assumption was made that renal function declines in a linear fashion, therefore the rate of decline remains constant. In our data, the group with the lowest baseline CrCl, saw the greatest reduction in sUA and the least decline in CrCl. We have attributed this to the change in sUA and the data set is too small to allow further analysis however it is possible that the rate of renal decline is slower when starting from a lower baseline. This is another area where further data is needed to confirm a direct impact of sUA reduction on renal function decline.

These findings add to an increasing body of published work including two meta-analyses published by Bose et al in 2014 and Kanji et al in 2015 [100, 136] both of which reviewed currently available trial data looking at the effect of uric acid lowering therapy on renal outcomes. The conclusion reached in both papers was that there may be a role for allopurinol in retarding progression of chronic kidney disease however further randomised controlled trials are required**.** Neither of these meta-analyses included any trials with febuxostat reflecting the much greater number of research trials undertaken with allopurinol compared to febuxostat as febuxostat is still relatively new to the market (licensed in 2008). A large retrospective cohort study using Medicare claims in the United States did look at prescribing of allopurinol compared to febuxostat and the incidence of new renal disease. This study found that allopurinol was associated with a lower risk of incident renal disease in elderly patients compared to febuxostat and the authors concluded that further research into the different mechanisms of action of the xanthine oxidase inhibitors was warranted [137]. There are currently two large RCT's (CKD-FIX and FEATHER) in follow up looking specifically at febuxostat in relation to renal outcomes. Further evidence will emerge to confirm whether management of hyperuricaemia to protect renal function is a class effect of xanthine oxidase inhibitors or an effect only seen with allopurinol.

There are a number of limitations with the data used for this analysis, the main one being the very select population eligible for FAST. Older, predominantly male patients with gout and additional cardiovascular risk factors who have prior exposure to allopurinol are both

an interesting, high risk population as well as having a number of factors that may confound results. Alternatively, this high risk population may demonstrate the greatest renal benefit from reduction in sUA and these changes may not be replicated in a younger, less co-morbid population. Also the estimation of renal function from a single creatinine measurement may not truly reflect actual change in renal function over the follow up period and could be significantly influenced by changes in medication or concurrent illness. Longer term follow up of this population would reduce the potential impact of this limitation.

vii) Conclusion

The interim renal function analysis shows a significant correlation between lowering sUA with XOi and reduction of decline in renal function. Whether this relationship is causative cannot be proven from this data. There is ongoing interest from nephrologists in managing sUA with the aim of preserving renal function but further randomised controlled trial evidence is required before this would be considered routine practice. Evidence is also required to determine whether this reduced decline in CrCl translates into improved hard endpoints in terms of end stage renal failure and mortality and whether this is a class effect for xanthine oxidase inhibitors or limited to allopurinol.

Chapter 6

Conclusions

Limitations

Clinical Implications and Future Research

6a) Conclusions

The xanthine oxidase inhibitors, allopurinol and febuxostat, are effective treatments for lowering serum urate in the management of gout. In current clinical practice allopurinol is the most widely used XOi and the up-titration protocol in FAST demonstrates that dose titration is safe and effective at achieving control of serum urate to within recommended guideline levels.

Beneficial effects of XOi's in addition to the management of gout have been under investigation for a number of years and continue to present an intriguing question for clinicians. The studies presented in this thesis include the FAST blood pressure sub-study which did not demonstrate a reduction in blood pressure with either allopurinol or febuxostat. However, this study did demonstrate that patient use of home blood pressure monitoring is a feasible and useful research method.

The interim analysis of renal function in FAST patients did show that lowering sUA was associated with a significantly smaller fall in CrCl over a follow-up period of one year. This finding adds to data already accumulating which shows that urate lowering may be renal protective and slow the progression of renal function decline. Larger, randomised controlled trials are in progress to further test this hypothesis which, if proven, will have significant clinical implications given the growing burden of chronic kidney disease worldwide. FAST recruitment is ongoing and patients will have longer follow-up data

available at the end of the trial. A final analysis of changes in CrCl over the course of the FAST study to see if the relative preservation of renal function is sustained will be eagerly anticipated.

In the renal function interim analysis, the patient population overall had a greater than expected fall in CrCl over one year and had risk factors associated with development of chronic kidney disease. Therefore, this patient population could be considered at high risk for renal function decline during follow up and any positive finding from the study warrants further investigation in this high risk population.

6b) Limitations

Both studies used data collected from patients in the FAST trial and therefore the findings relate only to a very specific population of predominantly older male patients with a background of gout, significant cardiovascular co-morbidity and who are already taking allopurinol. This was likely to be a significant limitation, particularly for the blood pressure sub-study as with the relatively short duration of follow up in patients who were not xanthine oxidase inhibitor naïve it would be difficult to show a significant result. The majority of studies that have shown blood pressure effects with urate lowering have been in younger patients, not previously exposed to XOi. Other limitations of the blood pressure sub-study include potential errors in patients taking their own blood pressure at

home and 26% non-return of monitoring diaries which led to the study being under-powered.

Limitations of the renal function interim analysis are mainly to do with data collection and the inherent problem of using a single blood test result to extrapolate overall renal function. The relatively large number of patients allowed results to reach statistical significance however, in this group of patients with significant co-morbidity and polypharmacy it would be expected that some degree of fluctuation in renal function would be seen over the course of a year and therefore analysis of a longer period of follow up would be required.

A further limitation to the data available to present in this thesis was slow recruitment of patients into the FAST trial. Patient recruitment and retention is widely recognised as one of the most significant limitations to any randomised controlled trial and recruitment to FAST was significantly slower than expected despite a number of initiatives to increase recruitment. These included newspaper advertising [138], incentive payments to patients [139], a trial information DVD that was posted to potentially suitable patients and use of GP research networks in the UK. Faster recruitment would have provided a larger data set for all studies presented in this thesis.

6c) Clinical Implications and Future Research

The clinical significance of managing hyperuricaemia with the aim of lowering blood pressure and preserving renal function to modify cardiovascular risk is potentially huge given the prevalence and associated morbidity of cardiovascular disease. Studies in this area have increased exponentially over recent decades and will continue to do so until this question is answered. The potential beneficial effects of using xanthine oxidase inhibitors to modify cardiovascular risk need to be balanced against the risk of side effects, the cost effectiveness of treatment and the patient burden of additional medication. FAST patients are a population with particularly high cardiovascular disease burden and future research would also need to consider if treatment should be targeted only at those with the highest risk.

The tolerability of XOi is an important factor when considering broadening their clinical use. Inclusion criteria for FAST require that patients are already established on allopurinol so we have only studied a population known to be tolerant of allopurinol. The commonest side effects seen with both allopurinol and febuxostat are mild GI upset however the concern is a severe hypersensitivity skin reaction which can be potentially life threatening. Incidence of this is estimated at 0.4% of new allopurinol users (lower in febuxostat users) and is significantly more common in those with a HLA-B*5801 haplotype. Risk of a skin reaction can be reduced by screening for this haplotype and starting at low doses with immediate discontinuation if a rash occurs. This risk cannot be

eliminated completely and approximately 1 in 10 of those who suffer a skin reaction will have a severe, potentially life threatening reaction [140]. These risks are important to recognise if XOi's are to be used in a much larger population.

FAST will complete recruitment and follow up and final analysis of change in renal function over the course of the study will add a valuable and large data source to current evidence. The currently recruiting RCT's including CKD-FIX and FEATHER [101] which are looking specifically at febuxostat in the context of renal function will complete and publish over the next few years. Further trials using allopurinol to modify cardiovascular risk include the allopruinol and cardiovascular outcomes in patients with ischaemic heart disease (ALL-HEART) trial, (ISRCTN32017426) which is currently recruiting and will help to answer the question of whether allopurinol reduces cardiovascular morbidity and mortality. A further study, currently recruiting in the UK is XILO-FIST (NCT02122718) which is looking at use of xanthine oxidase inhibitors to improve outcomes after stroke and TIA. This trial is using 300mg allopurinol for 2 years in patients post stroke and outcomes are additional brain injury, heart size and blood pressure.

It is expected that over the next decade, as these large randomised trials report, we should have a more definitive answer to the question of whether urate lowering with xanthine oxidase inhibitors should become a mainstream therapy for modification of cardiovascular risk and all its associated co-morbidities.

Chapter 7

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Chapter 8

Appendices

Appendix 1 FAST Blood Pressure Sub-study Instruction book

FAST

BLOOD PRESSURE STUDY

HOW TO USE YOUR *KINETIK* BLOOD PRESSURE MONITOR

Thank you for participating in this blood pressure study.

In addition to this instruction booklet you should have received your *Kinetik* home blood pressure monitor and a blood pressure monitoring diary.

Please read this instruction booklet carefully before you begin to take your blood pressure and pulse readings.

Please Note: The *Kinetik* blood pressure monitor also has an instruction manual included. Some of the instructions are not relevant to this study therefore please use the instructions here first. If you are struggling to work the monitor then the *Kinetik* instruction manual may provide useful information.

If you have any problems with the blood pressure monitor or recording diary or any questions regarding this study please contact:

Dr Claudine Jennings
Clinical Research Fellow
Telephone: 01382 383390
Email: claudine@memo.dundee.ac.uk

A pre-paid envelope has been supplied to return the monitoring diary at the end of the study. The address for return is:

Medicines Monitoring Unit
Ninewells Hospital
Dundee DD1 9SY

How to Use your Blood Pressure Monitor

1) Unpacking

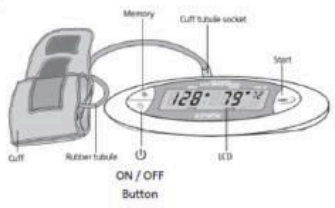
Remove your monitor from the packaging.

You should have a monitor and a blood pressure cuff.

The blood pressure monitor requires 4 AAA batteries which are supplied and have been checked prior to postage.

2) Assembly

To assemble the blood pressure monitor you need to plug the blood pressure cuff into the monitor using the rubber tubing as shown.



The blood pressure monitor will record both your blood pressure and your pulse (heart rate).

3) Getting ready to take blood pressure readings

It is very important that the blood pressure and pulse readings you take are accurate.

Please follow these simple rules when taking your readings:

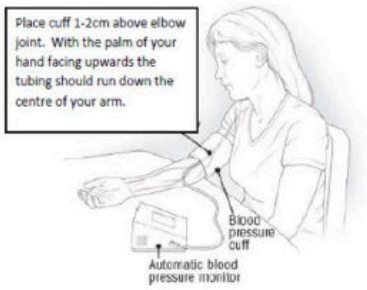
- You must be seated comfortably and at rest for five minutes before taking your readings.
- Both feet should be on the floor.
- Do not exercise, eat a large meal, have a drink containing caffeine or smoke a cigarette for 30 minutes before taking your readings.
- Morning blood pressure readings should be taken BEFORE you take your usual morning medication.
- Remove any tight fitting clothing from your upper arm.
- The arm you put the blood pressure cuff on should be your non-dominant arm (i.e. if you are right handed you should use your left arm). It is very important to use the same arm for all your blood pressure readings.
- Your arm should be supported on an arm rest if you are sitting in a chair or on the table if you are sitting at a table. This means the blood pressure cuff should be approximately level with your heart.
- Each time you take a set of blood pressure and pulse readings you need to take three separate readings. You should leave at least 30 seconds between each blood pressure reading.

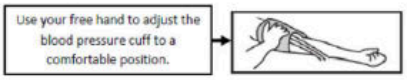
4) Placement of the blood pressure cuff

The blood pressure cuff should sit comfortably around your upper arm.

It should sit approximately 2 fingers above the bend in your elbow and you should be able to slide a finger between the cuff and your arm.

The tubing that connects to the machine should sit on the inside of your arm along the crease in your elbow as shown.





5) Taking a Blood Pressure Reading

Ensure you are sitting comfortably with the blood pressure cuff on your arm in the correct position. Have your monitoring diary and a pen ready.

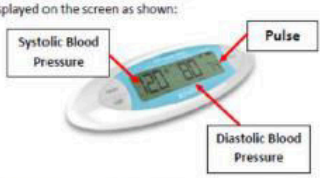
Press the "On" button once. Wait a few seconds the screen will flash and you will hear a beeping noise. The screen will show 0mmHg (as shown below). When ready press the "Start button" and the blood pressure cuff will start to inflate.

As the blood pressure cuff inflates it will feel tight on your arm and this is uncomfortable. It should not be painful and will only last for a few seconds. The cuff will begin to deflate and then the first reading will appear on the monitor.

For example:

6) Recording your readings

When the cuff has finished deflating, three numbers will be displayed on the screen as shown:



Blood pressure is recorded as "Systolic blood pressure / "Diastolic blood pressure" e.g. 120 / 80 in the picture above.

Record blood pressure and pulse readings in your monitoring diary.

Example Diary Entry: Day 1 – Monday 15th June
Time (Morning): 8am

Reading Number	Blood Pressure	Pulse
1	120/80	74
2	/	
3	/	

Wait for at least 30 seconds after your first reading and take the second reading. Wait for at least another 30 seconds and take the third reading.

Remove the blood pressure cuff and switch off the blood pressure monitor.

7) Completing your Monitoring Diary

You need to record blood pressure and pulse readings morning and evening for 4 consecutive days for each set of blood pressure readings.

There are 4 sections in your monitoring diary for 4 sets of blood pressure readings. Most FAST patients will only use 3 sections (the additional section is only used if you have required an increase in the dose of your allopurinol).

1st set of readings:
To be taken as soon as you receive the blood pressure monitor and diary. You should be taking your usual dose of allopurinol.

Additional readings (NOT TAKEN BY EVERY PATIENT):
If your allopurinol dose was increased you will take a second set of blood pressure readings on the final higher dose of allopurinol (your study nurse will advise you on this).

2nd set of readings:
To be taken at the end of the allopurinol washout period. You will be asked to stop taking your allopurinol for 7 days before starting on the FAST trial medication. At the end of this 7 day period you take a set of readings.

3rd set of readings:
To be taken after you have been on FAST trial medication (either allopurionl OR febuxostat) for 8 weeks.

Please refer to your monitoring diary for further instructions on recording your blood pressure and pulse readings.

Problems:

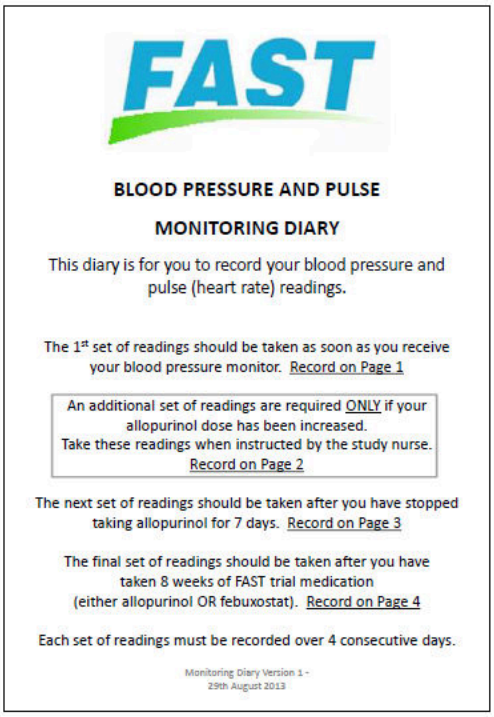
- The *Kinetik* blood pressure monitor has an instruction manual included. Some of the instructions are not relevant to this study but if you are having problems with your monitor it may be useful to refer to this manual.
- Sometimes the blood pressure cuff will inflate and deflate several times, this is the machine trying to get the best possible reading. Just check that the cuff is in the correct position and you are sitting comfortably.
- As the cuff inflates it will feel tight on your arm. This is uncomfortable but should not be very painful. If it is painful switch off the monitor and the cuff will automatically deflate.
- If the blood pressure machines fails to take a reading you will see an error message (ERR). Just relax, check the position of the blood pressure cuff on your arm and then take the reading again. If this happens three times then remove the cuff and try to take a further set of readings later that morning/evening. If on two occasions you are unable to get any blood pressure readings please contact the study centre.
- If you get a very unusual reading for you – either very high or very low then please record this reading but then wait a few minutes and repeat the reading. If you are feeling unwell and getting unusual readings you should contact your GP.

- If you get several readings with the systolic (the top number) blood pressure >200 you should inform your GP as this may need further assessment. If you get readings >200 and have any symptoms such as headache or visual problems then please seek medical attention urgently.

If you have any problems with the blood pressure monitor or recording diary or any questions regarding this study please contact:

Dr Claudine Jennings
Clinical Research Fellow
Telephone: 01382 383390
Email: claudine@memo.dundee.ac.uk

Appendix 2 FAST Blood Pressure Sub-study Monitoring Diary



FAST

BLOOD PRESSURE AND PULSE

MONITORING DIARY

This diary is for you to record your blood pressure and pulse (heart rate) readings.

The 1st set of readings should be taken as soon as you receive your blood pressure monitor. Record on Page 1

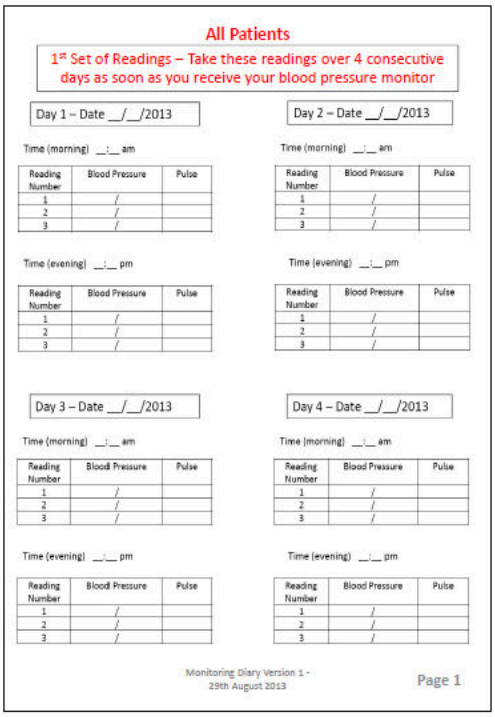
An additional set of readings are required ONLY if your allopurinol dose has been increased.
Take these readings when instructed by the study nurse.
Record on Page 2

The next set of readings should be taken after you have stopped taking allopurinol for 7 days. Record on Page 3

The final set of readings should be taken after you have taken 8 weeks of FAST trial medication (either allopurinol OR febuxostat). Record on Page 4

Each set of readings must be recorded over 4 consecutive days.

Monitoring Diary Version 1 - 29th August 2013



All Patients

1st Set of Readings – Take these readings over 4 consecutive days as soon as you receive your blood pressure monitor

Day 1 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 2 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 3 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 4 – Date __/__/2013

Time (morning) __:__ am

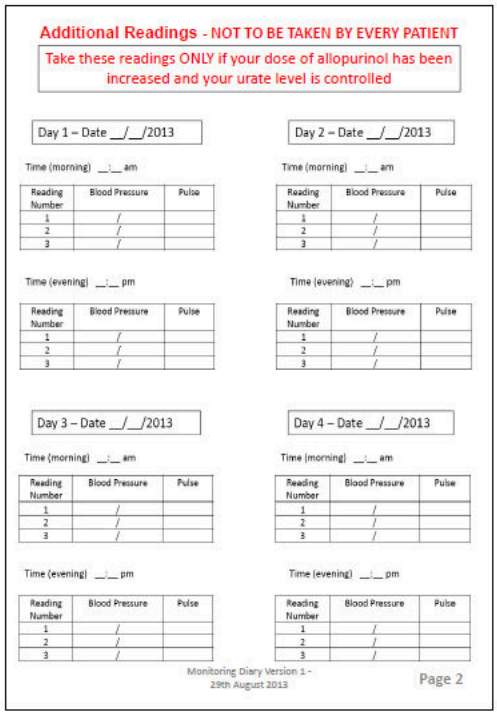
Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Monitoring Diary Version 1 - 29th August 2013

Page 1



Additional Readings - NOT TO BE TAKEN BY EVERY PATIENT

Take these readings ONLY if your dose of allopurinol has been increased and your urate level is controlled

Day 1 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 2 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 3 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 4 – Date __/__/2013

Time (morning) __:__ am

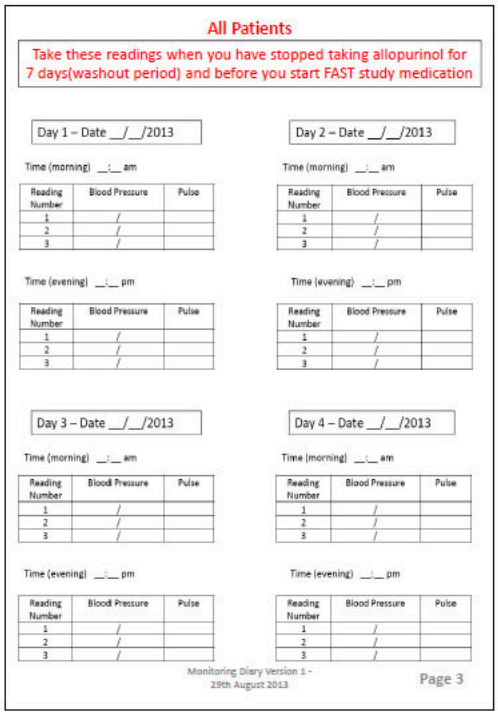
Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Monitoring Diary Version 1 - 29th August 2013

Page 2



All Patients

Take these readings when you have stopped taking allopurinol for 7 days(washout period) and before you start FAST study medication

Day 1 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 2 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 3 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 4 – Date __/__/2013

Time (morning) __:__ am

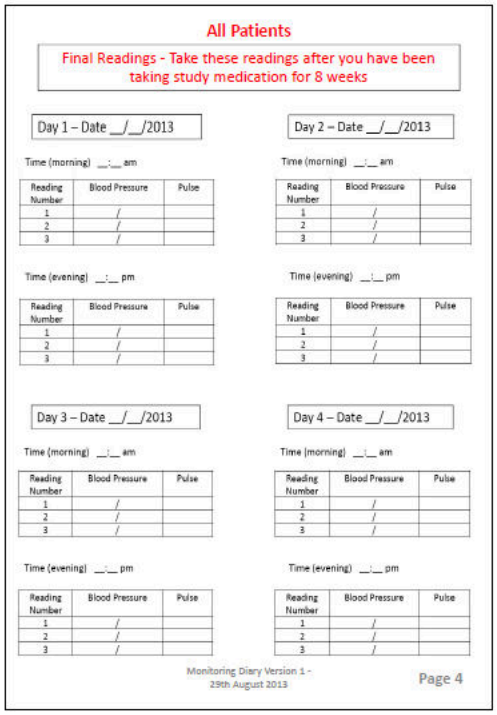
Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Monitoring Diary Version 1 - 29th August 2013

Page 3



All Patients

Final Readings - Take these readings after you have been taking study medication for 8 weeks

Day 1 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 2 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 3 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Day 4 – Date __/__/2013

Time (morning) __:__ am

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Time (evening) __:__ pm

Reading Number	Blood Pressure	Pulse
1	/	
2	/	
3	/	

Please report any problems with the blood pressure monitor or any comments about any of your readings.

-
-
-
-
-

Please record any changes to your regular medication while you have been taking blood pressure readings.

-
-
-
-
-

Appendix 3

Publications (Copies of three published papers are included at the end of the thesis)

Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia. TM MacDonald, I Ford, G Nuki et al. BMJ Open 2014;4:e005354 doi:10.1136/bmjopen-2014-005354

Up-titration of allopurinol in patients with gout. CG Jennings, IS Mackenzie, R Flynn et al. Seminars in Arthritis and Rheumatism 2014; 44 (1): 25 – 30.

Review of Hyperuricaemia and Hypertension: A Target for Treatment. CG Jennings, IS Mackenzie and TM MacDonald. Journal of Hypertension 2014 3:4.

Oral Presentations

Scottish Society of Physicians General Meeting, Glasgow October 2013

- Up-Titration of Allopurinol in Patients with Gout

Scottish Renal Association Annual Meeting, Dundee October 2015

- Urate Lowering with Xanthine Oxidase Inhibitors – Impact on Renal Function

Poster Presentations

Dundee University Student Symposium, June 2015

- Renal and Blood Pressure Effects of Xanthine Oxidase Inhibitors for Patients in the FAST Trial

International Society of Pharmacoepidemiology (ISPE) Conference, Taiwan, 2014

- Prevalence of Cardiovascular Risk Factors and Estimated 10 year Cardiovascular Risk for patients in the Febuxostat versus Allopurinol Streamlined Trial (FAST)
- Cardiovascular risk management of patients in the Febuxostat versus Allopurinol Streamlined Trial (FAST)

International Society of Pharmacoepidemiology (ISPE) Conference, Montreal 2013

- Up-Titration of Allopurinol in the Febuxostat versus Allopurinol Streamlined Trial (FAST)
- Demographics of the Patient Population Recruited into the Febuxostat versus Allopurinol Streamlined Trial (FAST)
- Prevalence of Treated Gout in Scotland, England and Denmark and Summary of Recruitment into the Febuxostat versus Allopurinol Streamlined Trial (FAST)

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Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia

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ABSTRACT

Introduction: Gout affects 2.5% of the UK's adult population and is now the most common type of inflammatory arthritis. The long-term management of gout requires reduction of serum urate levels and this is most often achieved with use of xanthine oxidase inhibitors, such as allopurinol. Febuxostat is the first new xanthine oxidase inhibitor since allopurinol and was licensed for use in 2008. The European Medicines Agency requested a postlicensing cardiovascular safety study of febuxostat versus allopurinol, which has been named the Febuxostat versus Allopurinol Streamlined trial (FAST).

Methods and analysis: FAST is a cardiovascular safety study using the prospective, randomised, open, blinded endpoint design. FAST is recruiting in the UK and Denmark. Recruited patients are aged over 60 years, prescribed allopurinol for symptomatic hyperuricaemia and have at least one additional cardiovascular risk factor. After an allopurinol lead-in phase where the dose of allopurinol is optimised to achieve European League against Rheumatism (EULAR) urate targets (serum urate <357 µmol/L), patients are randomised to either continue optimal dose allopurinol or to use febuxostat. Patients are followed-up for an average of 3 years. The primary endpoint is first occurrence of the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Secondary endpoints are all cause mortality and hospitalisations for heart failure, unstable, new or worsening angina, coronary or cerebral revascularisation, transient ischaemic attack, non-fatal cardiac arrest, venous and peripheral arterial vascular thrombotic event and arrhythmia with no evidence of ischaemia. The primary analysis is a non-inferiority analysis with a non-inferiority upper limit for the HR for the primary outcome of 1.3.

Ethics and dissemination: FAST (ISRCTN72443728) has ethical approval in the UK and Denmark, and results will be published in a peer reviewed journal.

Trial Registration number: FAST is registered in the EU Clinical Trials Register (EUDRACT No: 2011-001883-23) and International Standard Randomised Controlled Trial Number Register (ISRCTN No: ISRCTN72443728).

Strengths and limitations of this study

- Use of technology including an electronic case report form, web portal and record linkage to identify potential endpoints provides efficient data management.
- The open-label design provides good external validity as the trial is conducted in the normal care setting. The endpoint committee is blinded to randomised treatment.
- A minor study limitation will be the non-inclusion of younger populations with hyperuricaemia.

INTRODUCTION

Gout is the commonest inflammatory arthropathy in men over the age of 40, and current prevalence is estimated at 1–2% of the adult population in western countries with UK prevalence of 2.5%.[1–4] Gout is characterised by the deposition of monosodium urate

crystals in joints and other tissues, causing an acutely painful inflammatory arthritis that can progress to a chronic and disabling destructive arthropathy. Crystal deposition in soft tissues may also be seen as gouty tophi. Although serum urate levels correlate poorly with disease activity, hyperuricaemia is the most significant risk factor for the development of symptomatic gout. Hyperuricaemia is generally defined as urate above approximately 400 µmol/L (6.8 mg/dL), as this is the concentration at which uric acid becomes insoluble in plasma.[5]

It is well recognised that patients with gout have increased cardiovascular morbidity and mortality compared with the general population, and urate levels are increasingly believed to be an independent predictor of cardiovascular mortality. Theories as to the specific causal relationship between hyperuricaemia and cardiovascular disease/mortality vary; however, the correlation between the two is widely recognised. It is also not clear whether lowering urate levels would improve the cardiovascular event rate of patients with hyperuricaemia.[6–9]

Management of gout was revolutionised in the 1960s with the introduction of allopurinol, the first xanthine oxidase inhibitor, which reliably reduced urate levels, gout flares and long-term complications of gout.[10] The current European League against Rheumatism (EULAR) guideline for the management of gout recommends that urate lowering therapy (ULT) is indicated in patients with recurrent acute flares, arthropathy, tophi or radiographic changes of gout. The therapeutic goal of ULT is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum urate level (SUA) below the saturation point for monosodium urate, and the target level recommended is <357 µmol/L (<6 mg/dL).[11] Allopurinol is currently the first-line ULT in the UK and Europe. It is licensed in the dose range of 100–900 mg; however, patients with renal impairment are recommended to take the minimum effective dose required to achieve urate control.[12] In the UK, the majority of patients are prescribed between 100 and 300 mg of allopurinol daily, and primary care surveys have shown that the EULAR guideline target for urate is achieved in less than 50% of patients with gout receiving 300 mg of allopurinol.[13]

Febuxostat is a novel xanthine oxidase inhibitor which was licensed in 2008 for the treatment of chronic hyperuricaemia in conditions where urate deposition has occurred. The febuxostat Phase III randomised controlled trials demonstrated that 80 mg febuxostat was superior to allopurinol 300 mg in achieving and maintaining the target urate level of <357 µmol/L.[14] Febuxostat can also be prescribed to patients with mild-to-moderate renal insufficiency without the need for dose adjustment, and therefore provides an important alternative in the treatment of hyperuricaemia in patients with gout with renal impairment.

In the Phase III and long-term clinical extension studies of febuxostat, there was a numerical increase in investigator-reported cardiovascular events with febuxostat when compared to allopurinol. However, no statistically significant differences were found, no causal relationship was established and 60% of the patients in these trials had ≥2 risk factors for cardiovascular disease. The European Union Risk Management Plan for febuxostat (V.2.0; 19 February 2008) indicated that a postmarketing study to evaluate cardiovascular safety of febuxostat was to be conducted as part of the febuxostat pharmacovigilance plan. To fulfil this postlicensing obligation, a large safety study of febuxostat versus standard ULT with allopurinol for patients with symptomatic hyperuricaemia (gout) is being undertaken. The study is named the FAST.

METHODS

Trial design

Overall trial design

FAST is a prospective, randomised, open-label, blinded endpoint evaluation (PROBE) design trial to compare the cardiovascular safety of febuxostat and allopurinol. The PROBE design allows the real-world use of the two drugs to be compared, and also allows for dose adjustments during the study, if required.[15] Recruited patients are randomised to either allopurinol or febuxostat and followed-up for a minimum of 3 years.

Study population

FAST has study centres in Scotland, England and Denmark. Each centre identifies regional general practices to act as study sites and potential study patients are recruited from these study sites. General practice patient lists are searched for patients aged 60 years or more who are taking chronic allopurinol (defined as 60 days or 2 or more prescriptions for allopurinol in the last 6 months). Patients meeting these selection criteria have their case records reviewed by appropriately trained staff to determine eligibility according to inclusion and exclusion criteria (detailed in boxes 1 and 2). Patients identified as potentially suitable are provided with written study information and invited to attend a screening visit.

Consent

Written, informed consent is obtained at the screening visit for all patients who wish to proceed in the study. Screening visits are conducted by research nurses with appropriate training in obtaining informed consent.

Randomisation

Randomisation is performed through a central web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow. Randomisation is stratified according to previous cardiovascular events (myocardial infarction (MI), stroke or hospitalisation for congestive heart failure or peripheral vascular disease).

Data storage—electronic clinical report form

Patient data are entered via a secure web-based electronic clinical report form (eCRF) with a central database at the Robertson Centre for Biostatistics, University of Glasgow.

Trial treatments

Trial treatments are allopurinol or febuxostat. Allopurinol dose is determined during the allopurinol lead-in phase (see below) and febuxostat is started at 80 mg daily with potential to increase to 120 mg daily if SUA is above the EULAR target at a 2 week check. The allopurinol lead-in phase is required because febuxostat 80 mg is a more potent urate lowering therapy than low dose allopurinol. A study overview is shown in figure 1.

Trial medication is supplied directly to each patient by post from the Dundee University Research Pharmacy. All trial medication is supplied open-label.

Allopurinol lead-in phase

An allopurinol lead-in phase precedes randomisation. If the SUA exceeds the EULAR recommended target of <357 µmol/L on screening blood tests, the daily allopurinol dose is increased by 100 mg. SUA levels are rechecked after 2 weeks on the higher dose and this process is repeated until the EULAR target is achieved or the maximum tolerated dose of allopurinol is reached. If SUA at screening is <357 µmol/L then no dose titrations are required and the patient proceeds straight to randomisation. Patients with renal impairment (estimated-glomerular filtration rate 30–60 mL/

Box 1 FAST inclusion criteria

Inclusion criteria

1. Male or female patients aged 60 years or older with at least one additional cardiovascular risk factor:
   - Age ≥70 years (male) or ≥75 years (female)
   - Smoking (current or within the last 2 years)
   - Diabetes mellitus
   - Impaired glucose tolerance
   - Hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) or receiving treatment to lower blood pressure
   - Dyslipidaemia (investigator assessment)
   - Chronic kidney disease
   - Microalbuminuria or proteinuria
   - Family history of coronary heart disease or stroke in first-degree relative at age <55 years
   - Inflammatory arthritis (investigator assessment—including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis)
   - Chronic non-steroidal anti-inflammatory drugs therapy (investigator assessment)
   - Previous cardiovascular event (myocardial infarction, cerebrovascular accident or transient ischaemic attack)
   - Peripheral vascular disease (investigator/clinical assessment)
   - Chronic obstructive pulmonary disease
   - Body mass index >30 kg/m^2
2. Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy.
3. Patients who have received ≥60 days treatment with allopurinol, or ≥2 allopurinol prescriptions, within the previous 6 months.
4. Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat.
5. Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators.
6. Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (eg, for adverse event assessment and to determine whether an episode of acute gout has occurred).

Box 2 FAST exclusion criteria

Exclusion criteria

1. Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations.
2. Patients who are not receiving allopurinol as urate lowering therapy.
3. Patients with severe renal impairment (estimated-glomerular filtration rate <30 mL/min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight).
4. Patients with moderate or severe hepatic impairment, that is, cirrhosis with clinical and/or biological decompensation (ie, alanine aminotransferase or aspartate aminotransferase >3× reference value, ascites, lower limb oedema, icterus or increased prothrombin time >2× reference value).
5. Patients with a life-threatening comorbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol.
6. Patients with a diagnosis of, or receiving treatment for, malignancy (excluding minor skin cancer) in the previous 5 years.
7. Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit.
8. Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV.
9. Patients whose behaviour or lifestyle would render them less likely to comply with study medication (ie, abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
10. Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare.
11. Patients currently participating in another clinical trial or who have participated in a non-interventional clinical trial in the previous 1 month or an interventional clinical trial in the previous 3 months.

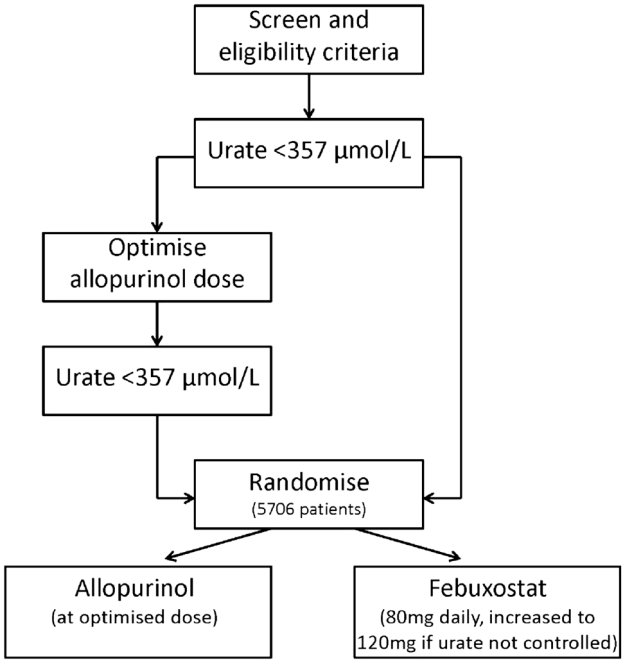

Figure 1 Overview of the FAST trial.

min) have their allopurinol dose titrated in exactly the same manner as those without renal impairment. This reflects published guidance on allopurinol titration in renal impairment which recommends starting at a low dose and titrating to achieve urate target.[16]

Allopurinol washout

Once patients are randomised and prior to start of randomised treatment all patients have an allopurinol washout period of at least 7 days (window 7–21 days).

Gout flare prophylaxis

Patients requiring up-titration of allopurinol during the allopurinol lead-in phase and all patients postrandomisation are offered gout flare prophylaxis. First-line prophylaxis is with colchicine (0.5 mg once or twice daily) and second-line alternatives are non-steroidal anti-inflammatory drugs (NSAID's; naproxen, diclofenac or meloxicam) with gastric protection. Prophylaxis postrandomisation is offered for 6 months. Patients may decline prophylaxis or discontinue prophylaxis at any time and prophylaxis may be tailored by the patients' primary care physician, particularly if there are concerns with long-term NSAID use. General practitioners (GPs) are left to manage gout flares according to local guidelines.

Postrandomisation treatment

Patients randomised to allopurinol continue to receive allopurinol at the dose determined before randomisation (ie, the dose required to achieve SUA level <357 µmol/L or the maximum tolerated dose). Patients randomised to febuxostat will start with 80 mg daily with potential to increase the dose to 120 mg if the SUA is ≥357 µmol/L after 2 weeks.

All drugs supplied to randomised patients from the Dundee University Research Pharmacy are recorded on the patient's eCRF, providing a cumulative record of supplied and returned medications.

Efficacy

If therapeutic efficacy is judged to be inadequate, physicians have the option to increase the dose of study medication according to their clinical judgment and EULAR recommendations provided this remains in line with the current summary of product characteristics for allopurinol and febuxostat. GPs are also free to decrease the dose of either drug if appropriate. Changes in dose are recorded in the eCRF.

Tolerability

Patients who experience any treatment-related adverse events may have their dosage adjusted or trial medication stopped according to clinical judgment. Study personnel report such events as adverse reactions (with severity assessment) as appropriate.

Follow-up

Patients will be followed-up for an average of 3 years from randomisation. Contact will be made by study nurses every 2 months by phone, letter or visit to the patient. Every patient will be seen annually and annual visits will include clinical review and annual blood testing for SUA level, renal and liver function. Recruiting physicians and the patients' GP may also report any significant events and adverse events thought to be related to study medication at any time during the follow-up period.

Record linkage is available in Scotland, England and Denmark and refers to the method by which patient-specific information that is stored separately can be linked to provide comprehensive patient data for hospitalisations and deaths.[17] Record linkage will be performed at regular intervals during FAST follow-up.

Trial endpoints

Primary endpoint

The primary endpoint is the first occurrence after randomisation of any event included in the Anti-Platelet Trialists' Collaboration (APTC) composite endpoint (hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome, non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation) or death due to a cardiovascular event).[18]

Secondary endpoints and further planned exploratory analysis are detailed in box 3.

Assessment of endpoints, adverse events and serious adverse events

All observed or volunteered adverse events that are considered to be either serious or related to study treatment (or both) are recorded in the eCRF. Physicians assess

Box 3 FAST secondary and exploratory endpoints

Secondary endpoints

The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis:

- Hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred *during* a hospitalisation)
- Cardiovascular death
- All cause mortality
- Hospitalisation for heart failure
- Hospitalisation for unstable, new or worsening angina
- Hospitalisation for coronary revascularisation
- Hospitalisation for cerebral revascularisation
- Hospitalisation for transient ischaemic attack
- Hospitalisation for non-fatal cardiac arrest
- Hospitalisation for venous and peripheral arterial vascular thrombotic event
- Hospitalisation for arrhythmia with no evidence of ischaemia

The following endpoints will be evaluated as an incidence rate:

- Cardiovascular mortality
- Anti-Platelet Trialists' Collaboration events in each treatment arm

Exploratory efficacy endpoint

The proportion of patients whose urate level is ≥6.0, <6.0 and <5.0 mg/dL after 1, 2 and 3 years of treatment.

the causality and expectedness of any event thought to be related to one of the study medications. An event is deemed serious if it results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability/incapacity or any other important medical event that requires medical or surgical intervention to prevent serious outcomes (whether or not the event was related to study medication). Serious adverse events (SAEs) are reported by study personnel without delay and are also collected regularly where appropriate using record-linkage methods. SAEs are followed up until resolved or the patient has died. Events that are neither serious nor related to study medication are not required to be reported. Primary and secondary study endpoints and their associated symptoms or laboratory abnormalities are not reported as suspected unexpected serious adverse reactions (SUSARs).

If a reported SAE is a potential study endpoint, more detailed information is collected and an anonymised endpoint package is prepared. Endpoint data are adjudicated by an independent endpoint committee blinded to randomised treatment.

DATA ANALYSIS AND STATISTICAL METHODS

Sample size

A total of 456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming non-inferiority limit for the HR (febuxostat vs allopurinol) of 1.3, with 80% power and a one-sided α of 0.025. Non-inferiority will be claimed if the upper limit of the 95% CI for the HR is ≤1.3 for the per-protocol analysis.

Assuming a cardiovascular event rate at 3 years in the allopurinol treatment arm is estimated at 10%,[i] then 2282 patients will be required in each treatment arm to detect the 456 events. Allowing for a loss of follow-up due to non-cardiovascular death, withdrawal of consent or other loss to follow-up, we intend to recruit an additional 20% of patients to a total of 5706 patients with 2853 patients in each treatment arm.

Primary analysis

A full statistical plan is developed for the primary analysis. Time to event analysis will involve Cox proportional hazards models including the randomised treatment group and randomisation strata (previous cardiovascular events (yes/no) as covariates). Statistical significance for effect will be based on the Wald statistic with associated 95% CIs for the estimated HR comparing febuxostat to allopurinol.

The first analysis to be carried out will be a non-inferiority analysis of the primary outcome based on the per-protocol population (those patients remaining on randomised therapy) with a supporting non-inferiority analysis based on the intention-to-treat (ITT) population. Per-protocol analysis will exclude patients who discontinued trial therapy, deaths from non-cardiovascular causes and patients lost to follow-up. If non-inferiority is demonstrated, a superiority analysis will be carried out based on the ITT population.

Sensitivity analysis

A sensitivity analysis will be performed by censoring patient follow-up at 90 days beyond the per-protocol period or end of study, whichever comes first. This will be performed for primary and secondary endpoints.

To adjust for the possibility of differential drop-out in the per-protocol analysis, a further analysis will be carried out adjusting for age, sex, LDL-cholesterol levels and HDL-cholesterol levels, systolic blood pressure, smoking status and histories of diabetes, hypertension and cardiovascular disease.

ETHICS AND DISSEMINATION

Steering Committee and Independent Data Monitoring Committee

A Steering Committee oversees the conduct of the trial. An independent Data Monitoring Committee receives unblinded data and has the power to recommend modifications to the conduct of the study, including early

[i]Cardiovascular event rate was calculated using cohorts of patients from the Tayside Medicines Monitoring Unit database who were dispensed allopurinol in Scotland between 1994 and 2002 and cardiovascular events and deaths occurring in these patients up to 2002 from the Scottish Morbidity Record One and General Registrar Office database.

discontinuation based on a risk/benefit assessment of the study data.

Study sponsorship: monitoring, audit, quality control and quality assurance

The study sponsor is the University of Dundee which undertakes monitoring and quality assurance. The trial is funded by Menarini in partnership with Ipsen and Tejin.

Access to data

The completed, original eCRF data will be the joint property of the University of Dundee and the University of Glasgow. Data will be available for authorised representatives of the universities or regulatory authorities or to third parties with express written permission from the universities.

Ethics

FAST is registered as ISRCTN72443728. The trial is performed in line with Good Clinical Practice guidelines and International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice guidance.[19]

Dissemination

The results of the trial will be published in a peer-reviewed scientific journal and presented at a major conference.

DISCUSSION

The trial design of FAST allows a large safety study to be undertaken with efficient use of resources by maximising the benefits of modern technology including use of an eCRF and following up patients using record linkage. The trial design has good external validity by comparing drugs in a real-world setting and evaluating outcomes in the patient population most likely to be taking these drugs.

The Dundee University Research Pharmacy is the first purely research pharmacy in the UK and allows all trial medication to be posted directly to patients in the UK and Denmark. This is advantageous for the patient and their primary care physician, and allows tracking of drug supply and drug return.

When completed, FAST will help to establish the cardiovascular safety of febuxostat and allopurinol in a population with high cardiovascular risk. Efficacy endpoints will also help to define the role of febuxostat in the management of patients with gout.

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Contributors The idea was conceived by TMM. The initial draft of the manuscript was created by CGJ and ISM and circulated among the authors for critical revision. The Chief Investigator of FAST is TMM. All authors approved the final version of the manuscript.

Competing interests TMM holds research grants from Novartis, Pfizer, Ipsen and Menarini, is currently or has been the principal investigator on trials paid for by Pfizer, Novartis, Ipsen and Menarini and TMM has been paid consulting or speakers fees by Pfizer, Novartis, Kaiser Permanante, Takeda, Recordati, Servier, Menarini, and AstraZeneca in the previous 3 years. ISM holds research grants from Novartis, Ipsen and Menarini.

Ethics approval The trial has been approved by the UK Multi-Centre Research Ethics Committee (Reference number: 2011-001883-23) and the Medicines and Healthcare Products Regulatory Agency (Reference number: 11/AL/0311) as well as the relevant authorities in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

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Up-titration of allopurinol in patients with gout

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ABSTRACT

Objectives: European League against Rheumatism (EULAR) gout management guidelines recommend achieving a target urate level <6.0 mg/dL (<357 μmol/L). Allopurinol is the most widely used urate-lowering therapy; however, many gout patients who are prescribed allopurinol do not have urate levels optimally controlled. The objective of this analysis was to review the efficacy and tolerability of allopurinol up-titration in achieving the EULAR target levels.

Method: The Febuxostat versus Allopurinol Streamlined Trial (FAST) is an ongoing multi-centre study comparing the cardiovascular safety of febuxostat and allopurinol (target recruitment: 5706 patients). Recruited patients were already taking allopurinol and the protocol required up-titration of daily allopurinol dose, in 100 mg increments, to achieve the EULAR urate target level prior to randomisation. We reviewed pre-randomisation data from the first 400 recruited and subsequently randomised FAST patients.

Results: Of 400 patients, 144 (36%) had urate levels ≥ 357 μmol/L at screening and required allopurinol up-titration. Higher urate levels were significantly associated with lower allopurinol dose, male sex, increased BMI, increased alcohol intake and diuretic use. Mean fall in urate levels after a single 100-mg dose increase was 71 μmol/L. The number of up-titrations required ranged from one to five (median = 1) with 65% of patients controlled after one 100-mg up-titration. Overall, 97% of up-titrated patients achieved target urate levels with median final allopurinol dose of 300 mg daily. Side effects and complications of up-titration were minimal.

Conclusion: Overall, 36% of FAST patients were not at target urate levels and required up-titration. Allopurinol up-titration was effective in achieving urate target levels and was generally well tolerated by patients.

Introduction

Gout is a common condition with an overall prevalence in the UK of 1.4% rising to over 6% in the over 65 years age group [1,2]. Incidence of gout in the UK has been stable for the past two decades; however, the disease burden of gout is expected to increase due to increasing life expectancy and a predicted rise in the UK population that is over 60 years of age from 14 million in 2010 to 18.6 million by 2026 [3,4]. The European League against Rheumatism (EULAR) published guidelines in 2006, making a series of recommendations for the management of gout, including titration of urate-lowering therapy to achieve a serum urate target level <6.0 mg/dL [5]. The American College of Rheumatology guidelines published in 2012 recommend a target serum urate level <6.0 mg/dL in all patients but recognised that lowering serum urate level below 5.0 mg/dL may be required for durable improvements in severe disease manifestations such as tophaceous deposits [6].

Allopurinol is currently the first-line urate-lowering therapy prescribed for patients with chronic gout, and guidelines recommend starting at a low dose and titrating this upwards until a

All listed authors fulfil the requirements for authorship and agree to submission of the manuscript in its current form.

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target urate level is reached. In the UK, approximately 30% of patients with gout are regularly prescribed allopurinol [7], and it is recognised that a significant proportion of these patients do not achieve the EULAR target of serum urate level <6.0 mg/dL. A postal survey in UK primary care practices showed that 23% of patients with gout taking allopurinol had urate levels >6.0 mg/dL [8]. In a US review of 15,596 patients with gout, only 30% met the specified urate target level, and of those prescribed allopurinol, 40% did not have the urate level checked after completing their first allopurinol prescription [9]. A survey of UK GPs found that 86% of GPs felt confident in the diagnosis and management of gout [10], but despite this confidence, achievement of the EULAR target levels remains poor. This is potentially due to a lack of awareness of the targets for therapy, concerns about side effects of allopurinol dose increases and infrequent monitoring of urate levels.

The Febuxostat versus Allopurinol Streamlined Trial (FAST) [ISRCTN72443728] fulfils a European Medicines Agency requirement for a post-licensing cardiovascular safety study of febuxostat and compares the cardiovascular safety of febuxostat with allopurinol. Febuxostat is a more potent urate-lowering treatment than 300 mg of allopurinol [11,12]. Therefore, as recruited patients were already taking allopurinol, in order to allow a fair comparison of cardiovascular safety, the study design forced up-titration of allopurinol dose until the serum urate level was below the EULAR target prior to randomisation. An exact conversion of 6.0 mg/dL is 357 μmol/L and this was the cutoff urate level used in FAST.

Analysis of patients recruited into FAST gives an insight into the use of allopurinol in this population and provides important information on the response to allopurinol dose increases, how this therapy is tolerated and what factors might influence patients' response to allopurinol.

Methods

FAST patients were recruited in Scotland, England and Denmark. Potential patients were identified by searches from primary care databases undertaken by study nurses. Eligible patients were aged over 60 years, prescribed allopurinol for symptomatic hyperuricaemia (clinical diagnosis) and had at least one additional cardiovascular risk factor. Patients with significantly impaired renal function (eGFR $<$ 30 mL/min) were excluded. Patients meeting the inclusion criteria attended for a screening visit, and progression from screening to randomisation was determined by the urate level at screening. If the screening urate level was <357 μmol/L (meeting the EULAR urate target level), patients could proceed straight to randomisation; however, if the initial urate level was ≥ 357 μmol/L, then the daily dose of allopurinol was increased by 100 mg and urate levels were re-checked after 2 weeks on the higher dose. This up-titration process was repeated until the EULAR target urate levels were achieved or the patient reached their maximum-tolerated dose of allopurinol. The maximum possible dose of allopurinol was 900 mg daily, as specified by allopurinol-prescribing guidelines.

Patient data was stored on an electronic clinical report form, and patients were randomised via a central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow. Randomisation was 1:1 to take either optimal-dose allopurinol or febuxostat (initially 80 mg with potential to increase to 120 mg to maintain urate levels within the EULAR target range). Patients who required up-titration and all patients for 6 months post-randomisation were offered gout flare prophylaxis with colchicine [second-line prophylaxis was a non-steroidal anti-inflammatory drug (NSAID) with gastric protection]. All patients were encouraged to take 6 months of gout flare prophylaxis; however, it was left to individual patients to decide whether or not to take flare prophylaxis.

The first 400 FAST patients were randomised by January 2013. Data collected from the screening visit and during the up-titration process are presented here. Anonymised data were extracted from the FAST database and analysed using SPSS v. 19. Data describing patient characteristics are shown as mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. Independent *t*-tests and chi-squared (or Mann–Whitney *U* test if appropriate) analysis were used to compare characteristics of patients with urate levels <357 μmol/L with those who were not at target levels at screening.

Results

Of the 400 patients, 144 (36%) had urate levels ≥ 357 μmol/L at screening and therefore required up-titration of their allopurinol dose. The baseline characteristics of these two groups are shown in the Table.

Patients who required up-titration of allopurinol were significantly more likely to be male ($p = 0.002$), have a higher body mass index (BMI) ($p = 0.026$), have higher alcohol intake ($p < 0.05$), be prescribed a diuretic ($p = 0.015$) and were taking a lower dose of allopurinol ($p < 0.005$) compared with those who were at target levels at the screening visit.

At screening, the maximum prescribed allopurinol dose in this patient population was 600 mg daily. The most commonly prescribed daily doses of allopurinol were 100 mg (in 32% of patients) and 300 mg (in 51% of patients) with only 2% of patients prescribed a daily dose greater than 300 mg (Fig. 1). Overall, 67% of the 129 patients who were prescribed allopurinol 100 mg daily required up-titration compared with 16% of the 203 patients who were prescribed 300 mg. The number of up-titrations required to achieve urate level <357 μmol/L ranged from one to five (median $= 1$, mean $= 1.5$). Overall, 65% of up-titrated patients required one dose increase, 24% required two dose increases, 9% required three dose increases and only 1% required more than three dose increases. The maximum final dose of allopurinol required by any patient was 700 mg daily. Figure 2 shows the range of allopurinol doses prescribed at screening and after up-titration for the 144 patients who required up-titration. Overall, 97% of up-titrated patients achieved the EULAR urate target levels. Of the five patients who failed to achieve urate levels <357 μmol/L, three did not tolerate further allopurinol dose increases and the other two patients had urate levels of exactly 357 μmol/L at the time of randomisation, and here no further up-titrations were attempted.

The mean fall in urate level after a 100 mg daily dose increase of allopurinol was 71 μmol/L (± 49 μmol/L). For those patients controlled after a single 100 mg dose increase, the mean fall in urate level was 90 μmol/L (± 43 μmol/L). Patients requiring only one up-titration had a lower mean baseline urate level of 406 μmol/L compared to 448 μmol/L for those requiring more than one up-titration ($p < 0.05$). The number of up-titrations required was also associated with baseline factors influencing initial urate level, including gender, BMI and diuretic use.

There were no serious adverse events reported for up-titrations of allopurinol, and no patients discontinued allopurinol during the up-titration process. A total of three patients were unable to tolerate further dose increases and reported idiosyncratic side effects, including gastric reflux, paraesthesia and generalised fatigue. Other reported side effects of up-titration included dry skin and mildly deranged liver function tests, but these did not require dose adjustment according to the responsible physician. There were no reported cases of rash or allopurinol hypersensitivity. Overall, three patients (2%) experienced a flare of gout

Table
Baseline characteristics of the first 400 patients randomised into FAST

Patient characteristic	Required up-titration (n = 144)	At target (n = 256)	p Value
Age (years), mean (SD)	69.3 (6.0)	70.5 (6.8)	0.93
Male sex, n (%)	133 (92)	207 (81)	**0.002**
Female sex, n (%)	11 (8)	49 (19)	
BMI (kg/m^2), mean (SD)	32.1 (4.9)	30.9 (4.8)	**0.026**
Initial urate (μmol/L), mean (SD)	421 (45)	286 (44)	< **0.001**
Allopurinol dose at screening visit (mg), median (IQR)	100 (100–200)	300 (200–300)	< **0.005**
Alcohol use, n (%)			
Never	8 (6)	22 (9)	0.77
Former	12 (8)	25 (10)	
Current	124 (86)	209 (82)	
Alcohol intake (units/week), median (IQR)	12.0 (3–22)	7.5 (0–22)	< **0.05**
Renal function, n (%)			
eGFR > 60 mL/min	117 (81)	215 (84)	0.98
eGFR 45–60 mL/min	18 (12)	25 (10)	
eGFR 30–44 mL/min	10 (7)	15 (6)	
Co-morbidities, n (%)			
Hypertension	115 (80)	209 (82)	0.70
Diabetes	31 (21)	71 (28)	0.43
MI	15 (10)	27 (11)	0.94
Angina	22 (15)	35 (14)	0.84
Other ACS	14 (10)	26 (10)	0.94
CKD	26 (18)	39 (15)	0.65
Stroke	9 (6)	13 (5)	0.86
Prescribed diuretic, n (%)	50 (35)	60 (23)	**0.015**

Statistically Significant differences are highlighted in bold.
Abbreviations: SD = standard deviation; IQR = inter-quartile range; BMI = body mass index; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; ACS = acute coronary syndrome; CKD = chronic kidney disease.

during the up-titration process. All three patients with a gout flare were receiving flare prophylaxis (two patients with colchicine and one patient with diclofenac).

Of the 400 patients, 68 had eGFR < 60 mL/min on their screening blood tests; 25 had eGFR 30–44 mL/min, of whom 10 (40%) required up-titration; and 43 patients had eGFR 45–60 mL/min, of whom 17 (40%) required up-titration. In both groups median allopurinol dose at screening was 200 mg and the median allopurinol dose following up-titration was 300 mg. The maximum allopurinol dose given to a patient with eGFR < 60 mL/min was 500 mg daily and there was one patient on this dose in each eGFR category (30–44 mL/min and 45–60 mL/min).

Discussion

The 2006 EULAR guidelines proposed 12 key recommendations to improve the management of patients with gout, including three recommendations for urate-lowering therapy [5]. Allopurinol is recommended as first-line urate-lowering therapy and should be started at a low dose (100 mg daily) with the daily dose to be increased by 100 mg every 1–2 weeks as required. The British Rheumatology Society published guidelines in 2007 with similar recommendations except advising an even lower target urate level of < 300 μmol/L [13]. The American College of Rheumatology guidelines published in 2012 also recommended starting at a

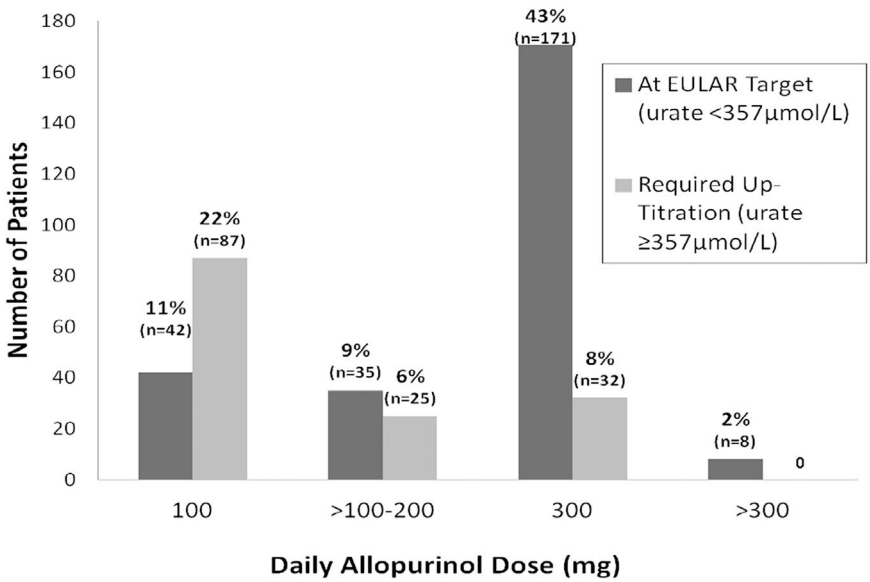

Fig. 1. Bar graph to show the number of patients achieving the EULAR urate target level at the FAST screening visit by daily allopurinol dose (n = 400).

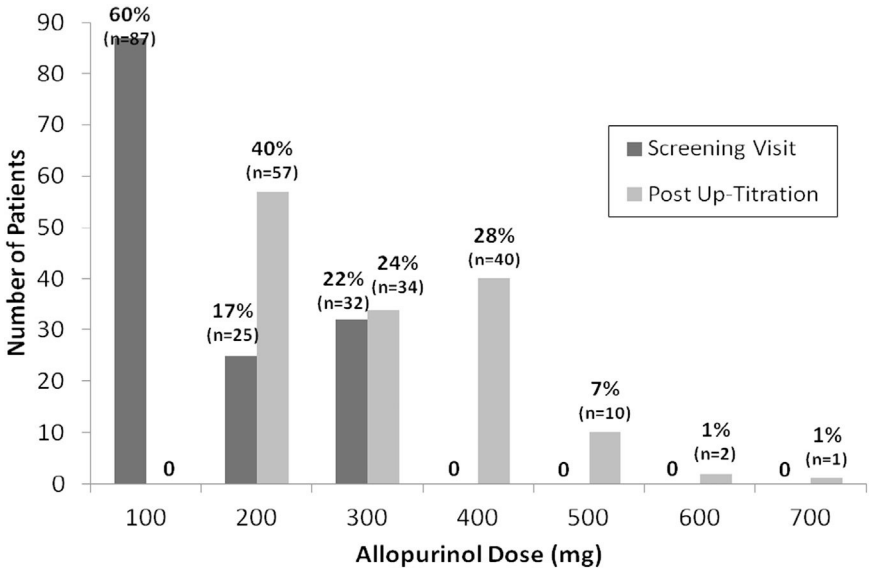

Fig. 2. Bar graph to show screening and post-up-titration allopurinol dose for those patients who required up-titration ($n = 144$).

low dose of allopurinol and titrating the dose to reach a urate target level of <6.0 mg/dL. Importantly, the American guidelines state that allopurinol doses greater than 300 mg daily may be needed and should be used even in patients with renal impairment, where there has previously been reluctance to prescribe higher doses. This recent flood of gout management guidelines reflects a general feeling that this controllable form of inflammatory arthritis could be better managed [14].

Analysis of the first 400 patients randomised into FAST shows that at baseline, only 64% of patients had urate levels controlled to the EULAR target levels on their current dose of allopurinol. For those patients not controlled at baseline, 65% achieved target urate levels with a single 100 mg daily dose increase of allopurinol, and 90% were controlled after two 100 mg up-titrations of allopurinol. Known risk factors for gout include advancing age, male sex, being overweight, diuretic use and high alcohol intake [2], and this was reflected in our data as these known risk factors were associated with higher baseline urate levels and the need for more up-titrations.

One of the most significant factors influencing the baseline urate level was the prescribed dose of allopurinol. This is obviously not surprising as the reason for prescribing allopurinol is to reduce urate levels. However, it is extremely important to highlight that current guidelines on gout management increasingly emphasise reduction of urate levels to particular targets. It is recognised that diet and lifestyle changes are important in gout management but their impact on reducing urate levels to the targets required is modest compared with the use of urate-lowering medications. Optimal management of gout should combine all these approaches, and Rees et al. [15] demonstrated in a recent proof-of-principle study that 92% of gout patients under review in secondary care achieved therapeutic target levels with a complex intervention combining patient education, individualised lifestyle advice and appropriate urate-lowering therapy. The results of this study, when taken in conjunction with our results, suggest that adherence to key elements of the current guidelines can be highly effective in improving management of this common disease.

The most commonly prescribed doses of allopurinol at the screening visit were 100 mg and 300 mg, reflecting a "fixed-dose" approach to allopurinol prescribing rather than prescribing a dose based on urate levels. An audit of UK general practice in 2000 found that 62% of patients did not have their urate levels checked at all once they were prescribed allopurinol [16]. Current guidelines advocate a "treat-to-target" approach; therefore, if guidelines were being appropriately followed, a much broader range of allopurinol doses should be seen. The fact that allopurinol is only available in 100 mg and 300 mg tablets will also strongly influence the dose prescribed as other dose choices would increase the number of tablets to be taken daily by a patient.

Data from the EULAR guidelines suggested that a 100-mg dose increase in allopurinol should reduce urate levels by 60 μmol/L (approximately 1 mg/dL). Our results indicate that this potentially underestimates the urate level reduction that can be expected as overall levels in our study fell by 71 μmol/L (1.2 mg/dL) after one dose increase. However, this result may be confounded by the lack of a placebo-controlled arm and by improved compliance once these patients were recruited into the trial.

One of the main concerns regarding up-titration of allopurinol is the increased risk of side effects with higher doses. It is estimated that around 1–2% of patients who are prescribed allopurinol will have a reaction to the drug, mostly in the form of a minor rash [17,18]. Very occasionally, patients will develop more severe skin reactions, which are globally referred to as the allopurinol hypersensitivity syndrome (AHS) and include potentially life-threatening conditions, such as Stevens–Johnson syndrome and toxic epidermal necrosis. These reactions may occur weeks to months after starting allopurinol. The risk of AHS appears to be linked to a higher starting dose but not to the maximal maintenance dose of allopurinol [19]. AHS is also significantly more likely in people with the HLA-B5801 allele (common in Korean, Thai and Han-Chinese populations), which has led to routine testing for this in high-risk populations in the USA before commencing allopurinol [6,20]. This is not yet a current practice in Europe. In our patient population, side effects of increasing doses of allopurinol were rare and mild; however, it should be remembered that patients recruited into FAST had to have taken allopurinol for at least 60 days to be eligible for inclusion and therefore represent a group of patients already known to be tolerant to allopurinol.

The risk of precipitating a flare of gout by up-titration of allopurinol is also a concern to both doctors and patients, and all patients in FAST were offered gout flare prophylaxis during the up-titration process. This risk appears to be minimal with only 2% of patients experiencing a gout flare during the up-titration of allopurinol, all of whom were taking flare prophylaxis. This is considerably less frequent than the 21% incidence of gout flares in patients newly treated with allopurinol who participated in a randomised trial of allopurinol versus febuxostat [12]. This

demonstrates that the risk of flare is much lower when up-titrating allopurinol therapy in partially treated patients and indicates that prolonged courses of prophylactic therapy might not be necessary under these circumstances.

Management of gout in patients with renal impairment is another area of particular concern as allopurinol is rapidly metabolised into oxypurinol, which is predominantly renally excreted. The half-life of oxypurinol is significantly prolonged in advanced renal impairment; therefore, lower doses of allopurinol are generally required. Previous guidelines including the Hande criteria published in 1984 [21] recommended extremely cautious doses of allopurinol in patients with renal impairment due to concerns about oxypurinol toxicity and increased risk of AHS. This has contributed to under-treatment of a number of patients with gout. The current guidance of starting at a low dose and titrating to target levels should also be applied in patients with all stages of renal impairment. Patients with eGFR <30 mL/min were excluded from FAST, and patients with mild renal impairment (eGFR $=30$–60 mL/min) constituted only 17% of the first 400 patients recruited into FAST; therefore, data were limited. In this small group, 40% of patients required up-titration, and the doses of allopurinol they were prescribed before and after up-titration were comparable to what was prescribed to patients with eGFR >60 mL/min. While these small numbers cannot be over-interpreted, these results are reassuring that perhaps the historical caution used in prescribing allopurinol to patients with chronic kidney disease could be overcome.

This analysis has some limitations as it represents the first portion of a much larger ongoing study and was performed in open-label conditions. In addition, patients were already on treatment with allopurinol for at least 2 months prior to study entry and were selected to meet certain other entry criteria so they may not be fully representative of the wider, particularly younger, gout population. FAST is a multi-centre trial and therefore includes a large and diverse patient population, and there were some regional differences in prescribing that are beyond the scope of this article to explore. Compliance with medication was not assessed, and no adjustments were made for the potential of improved compliance with medication after entry into the study.

Conclusion

Analysis of pre-randomisation data for the first 400 FAST patients has shown that only 64% of patients were controlled on their baseline dose of allopurinol. A total of 144 patients required one or more up-titrations of allopurinol and 97% of these patients ultimately achieved the EULAR urate target level of <357 μmol/L. Historical guidelines advocate caution with higher doses of allopurinol; however, our data shows that in patients already taking allopurinol, generally only modest dose increases are required and these appear to be well tolerated and effective.

The FAST study group

Steering committee

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FAST recruiting centres

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Ethical approval

The FAST trial has ethical approval in the UK and Denmark (REC Ref: 11/AL/0311). All participants in the FAST trial provided written informed consent.

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Review Article Open Access

Review of Hyperuricaemia and Hypertension: A Target for Treatment

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Abstract

Hypertension is a significant cardiovascular risk factor with multifactorial aetiology. The link between hypertension and hyperuricaemia has been noted for over a century however determining whether this link is causal and whether there is a role for management of hyperuriaemia in the context of hypertension has been more problematic. Over the past two decades research in this area has dramatically increased with development of animal models of hyperuricaemia and use of large observational cohorts. There is an emerging body of evidence that hyperuricaemia should be considered an independent risk factor for the development of essential hypertension and that further research into the management of hyperuricaemia is required.

Keywords: Hypertension; Hyperuricaemia; Cardiovascular risk

Introduction

Hypertension is a leading risk factor for cardiovascular disease and worldwide prevalence of hypertension is increasing. In 2000 26% of the world's adult population (over 1 billion people) were considered to have hypertension and in 2009 the WHO reported that hypertension had a causative role in the deaths of over 7.5 million people [1,2] Prevalence of hypertension in adults of 16 years or older in the UK was 31.5% in men and 29.0% in women in 2010 [3]. The majority of hypertension is considered to be essential hypertension which develops due to a complex interplay of genetic, lifestyle and environmental factors. Cardiovascular risk associated with increasing blood pressure is continuous with 7% increase in mortality from ischaemic heart disease and 10% increased risk of mortality from stroke for every 2 mmHg rise in population blood pressure [4].

Therefore even small improvements in population blood pressure control are likely to have a significant impact on long term public health. Significant efforts are directed at addressing hypertension as a cardiovascular risk factor and one area that has fallen in and out of favour over the years is the role of hyperuricaemia in the development of hypertension and as a potentially modifiable cardiovascular risk factor. There is a growing body of evidence supporting the association between hyperuricaemia and the metabolic syndrome [5], chronic kidney disease [6] and atherosclerosis [7] as well as hypertension which will be the focus of this review. The question that now needs to be answered is whether there is a role for actively lowering serum urate levels to better manage these associated conditions. Small trials have been conducted looking at whether reduction of serum urate levels influences blood pressure control and there is now a growing consensus that a large randomised controlled trial is needed to finally answer this question [8].

PubMed, Web of Science and Medline databases were searched using the terms hyperuricaemia, uric acid, urate, hypertension, blood pressure, cardiovascular, xanthine oxidase inhibitor, uricosuric, allopurinol and febuxostat in English language publications from 1975 to July 2013. Abstracts were reviewed by category and references retrieved for papers meeting relevance criteria, reference lists of selected papers were scrutinised for relevant papers and data synthesised by themes [9].

Definition of Hyperuricaemia

Uric acid is the end product of purine metabolism in humans and increased serum urate levels may be seen due to high dietary purine intake (particularly shellfish, red meat and beer), in conditions of increased cell turnover or cell death (for example following cytotoxic chemotherapy) and if renal function is impaired (urate is approximately 70% renally excreted). Urate levels generally rise with increasing age and hyperuricaemia is also seen in the metabolic syndrome partly due to hyperinsulinemia impairing urate excretion [10]. The definition of hyperuricaemia varies but is generally considered to be levels above the serum saturation point of uric acid (approximately 6.8 mg/dL). Above this level uric acid may precipitate out of solution and be deposited in joints and tissues causing the recognised complication of gout. Guidelines for the management of gout recommend achieving serum urate levels below 6 mg/dL in order to reduce gout flares and complications [11]. There are currently no guidelines or recommendations for the management of asymptomatic hyperuricaemia.

Hyperuricaemia and Evolution

Hyperuricaemia is an almost uniquely human problem due to the fact that humans have a loss of function mutation affecting the uricase enzyme which prevents further breakdown of uric acid into more soluble waste products. This mutation occurred over 15 million years ago, during a time of intense climatic upheaval when food, water and salt supplies were scarce, and resulted in significantly higher serum urate levels in humans than in most other mammals. This mutation is thought to have conferred an evolutionary advantage by enabling our early ancestors to retain sodium, maintain blood pressure with a salt poor diet and augment fat storage from fructose found in fruits

[12,13]. Unfortunately, in the modern world with increasingly sedentary lifestyles and the plentiful availability of high salt, energy dense food this evolutionary adaptation for survival is now potentially one of the factors contributing to the current worldwide epidemic of hypertension, obesity and the metabolic syndrome [14].

Historical Association of Hyperuricaemia and Hypertension

Hyperuricaemia is currently viewed solely as an important risk factor in the development of gout but is not otherwise routinely measured or monitored. Historically, however, hyperuricaemia has been closely associated with elevated blood pressure, for example, a paper published in the Lancet in 1879 noted that many gout patients were hypertensive and a subsequent BMJ review of "arterial tension" in 1889 recommended a low purine diet for the management of hypertension [15,16]. Hyperuricaemia fell out of favour as a cardiovascular risk factor in the 1970's and 80's (and consequently measurement of serum urate was removed from many standard blood testing panels) partly due to the lack of evidence of a causal association and partly due to concerns regarding side effects of medication used to manage what was considered to be an asymptomatic condition.

The establishment of plausible biological mechanisms for the relationship between hyperuricaemia and hypertension has been facilitated by the development of animal models of hyperuricaemia. This information, coupled with large observational studies in human populations have provided a growing body of evidence pointing strongly to a causal relationship between hyperuricaemia and the development of hypertension [17].

Biological Mechanisms for Hyperuricaemia Induced Hypertension

The first animal models of hyperuricaemia were developed in the 1990's and used oxonic acid as an uricase inhibitor. Initial work in rats showed that after 2 weeks exposure to mild increases in urate levels, there was activation of the renin angiotensisin system and decrease in plasma nitrates leading to vasoconstriction and hypertension [18]. This hypertension was reversible by either stopping the oxonic acid (allowing the uricase enzyme to function normally) or by lowering urate levels with either xanthine oxidase inhibitors or uricosuric agents. This early hypertension was also responsive to treatment with blockade of the renin-angiotensin system [19].

When hyperuricaemia was induced in normal and remnant kidney rats it resulted in renal cortical vasoconstriction, glomerular hypertension and inflammatory cell infiltration, and the vascular damage recorded was much more severe in the remnant kidney rats. It was surmised that in this model, hyperuricaemia impaired the auto-regulatory responses of afferent arterioles resulting in glomerular hypertension and vascular wall thickening to produce renal hypoperfusion. This led to renal ischaemia and subsequent tubulointerstitial inflammation, fibrosis and arterial hypertension [20]. Importantly these effects were not seen in rats treated with allopurinol which prevented the rise in urate levels.

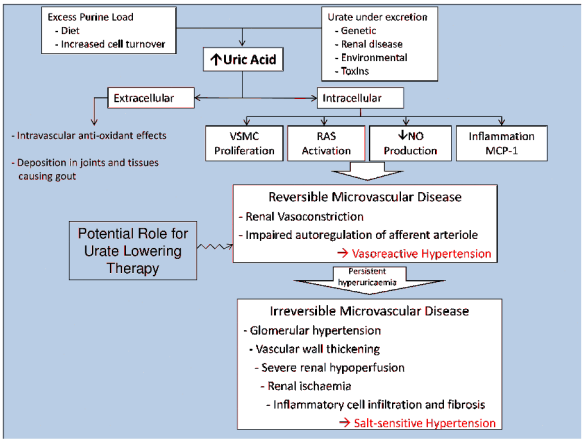

Figure 1: Hyperuricaemia induced hypertension

A two stage hypertension theory has emerged from this experimental work in rats. The initial vascular changes and subsequent hypertension seen in response to hyperuricaemia can be reversed, however, after prolonged exposure to high urate levels there is a second phase of hypertension with evidence of altered intra-renal architecture [21]. The pattern of renal microvascular damage is similar to that seen in patients with essential hypertension where, over time, there is evidence of tubular ischaemia, interstitial inflammatory cell infiltration, oxidant generation and local vasoconstriction resulting in reduction of sodium filtration, enhanced sodium reabsorption and hypertension that is mainly salt sensitive [13,22]. In both cases these vascular changes become irreversible over time which may explain the observation that the link between hyperuricaemia and hypertension appears stronger in younger people [23].

Evidence from Epidemiological studies

Since the revival of interest in the role of hyperuricaemia in the development of hypertension and as a potential independent cardiovascular risk factor, there has been an exponential rise in the number of papers published demonstrating and discussing this link [24]. Two recent meta-analyses looking specifically at hyperuricaemia and hypertension have concluded that higher urate levels predict the development of hypertension. Meta-analysis by Zhang and colleagues in 2009 included their prospective cohort study of 7220 normotensive Chinese patients with 4 years follow up. The adjusted relative risk of developing hypertension was 1.55 in men and 1.91 in women for the highest quartiles of serum urate compared with the lowest quartiles. When included with 7 other studies in the meta-analysis (total 28,657 participants) there was a pooled relative risk of 1.55 for development of hypertension in those with the highest quartiles of serum urate. In Zhang's original study the association between hyperuricaemia and hypertension appeared to be partly mediated by abdominal obesity and it was postulated that this was due to hyperinsulinaemia enhancing uric acid reabsorption [25]. In 2011 Grayson conducted a meta-analysis of 18 published, prospective cohort studies (including the 8 studies used by Zhang) comprising a total of 55,607 patients (Table 1) [25-42]. This meta-analysis showed that hyperuricaemia was associated with an increased risk for incident hypertension (adjusted

risk ratio 1.41) and for every 1 mg/dL increase in serum urate the pooled risk ratio for incident hypertension (after correcting for confounding factors) was 1.13. The risk appeared to be more significant in younger people and in women [23]. These two meta-analyses included studies from Europe, China, Japan, Israel and the USA indicating that this relationship is seen across ethnic groups.

Author	Population	Risk
Forman [29]	Nurses Health Survey (US), n=1496	OR for incident hypertension 1.89; 95% CI 1.26-2.82
Zhang [27]	Qingdao Port Health and Nutrition 7220 Examination Survey in China, mean age 37	Adjusted RR for incident hypertension men 1.55; 95% CI 1.10-2.19 and women 1.91; 95% CI 1.12-3.25)
Forman [30]	Health Professionals Follow up Study (US), n=1454 (men only)	Adjusted RR 1.24; 95% CI 0.93 to 1.66
Krishnan [31]	Multiple Risk Factor Intervention Trial (US), n=3073	Hazard ratio 1.81; 95% CI: 1.59 to 2.07 for incident hypertension
Mellen [32]	Atherosclerosis Risk in Communities (ARIC) study (US), n=9104	Adjusted hazard ratio for incident hypertension for each SD of higher uric acid 1.10; 95% CI1.04 to 1.15
Perlstein [33]	Normative Aging Study (US), n=2062	Age adjusted RR 1.10; 95% CI: 1.06 to 1.15
Shankar [34]	Beaver Dam Population Cohort (US), n=2520	RR for incident hypertension 1.65; 95% CI 1.41-1.93
Sundstrom [28]	Framingham (US), n=3329	Adjusted OR for incident hypertension 1.17; 95% CI 1.02-1.33 for every 1 SD increase in SUA
Nagahama [35]	Okinawa General Health Maintenance Association (OGHMA) cohort (Japan), n=4489	Adjusted OR for incident hypertension, men 1.48; 95% CI 1.08-2.02, women 1.90; 95% CI 1.03-3.51
Nakanishi [36]	Male office workers (Japan), n=2310	Adjusted RR for incident hypertension 1.58; 95% CI 1.26-1.99
Taniguchi [37]	Osaka Health Survey (Japan), n=6356	Adjusted RR incident hypertension 2.01; 95% CI 1.56-2.59
Imazu [38]	Hawai, Los Angeles Hiroshima Study (US/Japan), n=159	Adjusted RR for incident hypertension 2.03; 95% CI 1.02-3.90
Dyer [39]	Coronary Artery Risk Development in Young Adults (CARDIA) study (US), n=4747	Multivariate OR for incident hypertension, black men 1.21; 95% CI 1.03-1.41, white men 1.16; 95% CI 0.96-1.40
Jossa [40]	Olivettic Heart Study (Italy), n=505	Adjusted RR for incident hypertension 1.23; 95% CI1.07-1.39
Hunt [41]	Utah Cardiovascular Genetics Study (US), n=1482	Adjusted RR for incident hypertension 2.16 (p<0.10)
Selby [42]	Kaiser Permanente Multiphasic Health Checkup (US), n=2062	RR for incident hypertension 2.19; 95% CI 1.2-3.98
Fessel [43]	Target population and screening program (US), n=335	Data not available
Kahn [44]	The Israel Ischaemic Heart Disease Study, n=2904	RR for incident hypertension 1.82; 95% CI 1.3-2.54

Table 1: Studies used in Grayson meta-analysis linking hyperuricaemia and hypertension, [Abbreviations: RR: Relative Risk, OR: Odds Ratio, HR: Hazard Ratio, CI: Confidence Interval, SUA: Serum Uric Acid Level]

Other studies not included in the above meta-analyses include the Bogalusa Heart study which looked at 577 US children, followed up for a mean of 11.4 years and showed that childhood urate levels significantly predicted hypertension in adult life [43]. The Taiwanese Health Survey from 2012 comprising 3257 patients showed that high serum urate was an independent predictor of blood pressure progression (HR 1.78) and incident hypertension (HR 1.68) [44]. A small Turkish study looking at 112 hypertensive patients with 24 hr ABPM readings, categorised patients as dippers or non-dippers depending on blood pressure fall during the night. Loss of nocturnal blood pressure dipping is associated with worse cardiovascular outcomes and in this study the non-dippers had significantly higher urate levels than the dippers (OR 2.28) [45].

The epidemiological evidence to date does indicate a strong association between hyperuricaemia and hypertension and the diversity of ages and ethnic groups studied and the length of follow up lend weight to the argument that this association is causal, rather than representative of two conditions that share the same risk factors. However, epidemiological evidence does not provide conclusive proof of causality and further experimental work and evidence from interventional trials are required to firmly establish the nature of this relationship.

Management of Hyperuricaemia – Clinical Trial Data

If hyperuricaemia is accepted as a potential causal factor for the development of essential hypertension then does reducing serum urate levels protect against the development of hypertension? A number of clinical trials over the past decade have sought to answer this question through either lowering urate levels with xanthine oxidase inhibitors or through use of uricosuric agents. The method by which urate lowering is achieved is important when looking at outcomes. Uricosuric agents such as probenecid act via the renal tubules and lower urate levels by increased renal excretion. Xanthine oxidase inhibitors (XOi) act by blocking the conversion of hypoxanthine to xanthine (the precursor of uric acid) and generally have a more potent

effect on lowering urate levels than uricosuric agents. Allopurinol is the most commonly used XOi and is non-selective so not only reduces levels of uric acid but also inhibits other reactions in the purine/pyrimidine metabolism pathways thereby preventing production of oxidants generated during this process [46]. It is hypothesised that allopurinol improves vascular outcomes due to this non-selectivity and by reducing oxidative stress rather than simply through reduction of urate levels. Febuxostat is a non-purine XOi and therefore more selective than allopurinol resulting in greater reductions in urate levels but with potentially less anti-oxidant effect [47]. It remains to be seen whether different cardiovascular effects will be found with febuxostat compared to allopurinol due to their selectivity of action.

Small pilot studies have been undertaken using allopurinol in hypertensive patients and particularly striking results have been seen in obese and newly diagnosed adolescents with hypertension. A randomised, placebo controlled trial in US adolescents with newly diagnosed essential hypertension showed that allopurinol 200mg twice daily resulted in a mean 24 hr blood pressure change of -6.3 mmHg systolic and -4.6 diastolic compared to 0.8 systolic and -0.3 diastolic for the placebo group. These changes were significant although limited by the small sample size of only 30 adolescents [48]. A further study in 60 pre-hypertensive obese 11-17 year olds found that those treated with urate lowering therapy saw a reduction in clinic BP compared with the placebo group (-10.3/-8.0 mmHg adjusted with allopurinol and -10.2/-8.8 mmHg adjusted with probenecid). They concluded that uric acid contributed to the development of hypertension in adolescents and this effect could be mitigated by urate lowering therapy [49].

There have also been small trials in adults looking at the effect of allopurinol on patients with asymptomatic hyperuricaemia. 48 patients treated for 3 months with 300 mg allopurinol daily showed decreased urate levels, decreased CRP, increase in eGFR and decreased blood pressure (-3.9/-1.9 mmHg) compared with control groups [50]. Another trial compared 30 asymptomatic hyperuricaemic patients treated with allopurinol with 37 asymptomatic hyperuricaemic controls and 30 normouricaemic controls and showed that systolic blood pressure after 4 months decreased by 8 mmHg in treated patients compared with controls [51]. Therefore asymptomatic patients with no prior history of hypertension responded to allopurinol treatment with a reduction in blood pressure.

A recent systematic review and meta-analysis of allopurinol use in reducing blood pressure looked at 10 studies, comprising a total of 738 participants. The authors found that, compared with the control group, treatment with allopurinol lowered systolic blood pressure by 3.3 mmHg and diastolic blood pressure by 1.3 mmHg. They concluded that allopurinol had a small but significant effect in lowering blood pressure that could be exploited in managing hypertension in hyperuricaemic patients [52].

The majority of interventional studies to date have looked at using allopurinol to lower urate levels however there are alternative treatment options available. One drug that is particularly interesting in this field is losartan as it has a mildly uricosuric action which is unique in the angiotensin II receptor blocker (ARB) class. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showed that a losartan based regimen was superior to an atenolol based regimen for reduction of cardiovascular mortality and morbidity despite comparable blood pressure reduction [53]. It was hypothesised that this could have been due to the uricosuric action of losartan and a further analysis concluded that over the 4.8 year follow up in LIFE the increase in serum urate seen over time was attenuated by losartan and this appeared to explain 29% of the treatment effect on the primary endpoint (cardiovascular death, MI or stroke) [54]. The association between serum urate and cardiovascular events was again noted to be stronger in women in this study.

The main concern with widespread use of allopurinol to manage hyperuricaemia in asymptomatic patients is the potential for side effects. Approximately 1% of patients prescribed allopurinol will develop a rash and in a very small proportion this can develop into the potentially life threatening allopurinol hypersensitivity reaction. Dose reductions of allopurinol are also recommended in renal impairment. An alternative XOi, febuxostat, has been licensed since 2008 and is more selective and more potent at lowering urate than 300 mg of allopurinol [55]. Febuxostat shares some cross reactivity with allopurinol and similar rates of side effects have been reported however, febuxostat undergoes mainly biliary excretion and therefore does not require dose reductions in renal impairment [55,56]. The impact of febuxostat on blood pressure in humans has yet to be established and it will be interesting to see if more potent urate lowering has a more significant effect on blood pressure or whether the increased selectivity of febuxostat will make it less effective than allopurinol in this context.

Hyperuricaemia and Cardiovascular Outcomes

Following over a decade of intensive research in this area what has emerged is broad acceptance of a correlation between hyperuricaemia and hypertension and a clearer picture of a causal link, particularly for a subset of patients. There is however ongoing scepticism about the significance of hyperuricaemia induced hypertension in determining cardiovascular outcomes and more importantly whether modifying serum urate levels will influence these outcomes in a substantial way. The evidence looking at hyperuricaemia and cardiovascular outcomes shows mixed results. The European Working Party on High Blood Pressure in the elderly found no relationship between urate levels and cardiovascular outcomes however the patients studied were enrolled in a trial of diuretics which may have confounded the results [57]. Data from the Framingham Heart study which included 6763 Framingham participants with measurements of serum urate taken between 1971 and 1976 showed that after adjusting for other risk factors, urate levels did not predict adverse cardiovascular outcomes. The authors concluded that elevated serum urate does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes [58]. A meta-analysis of 11 trials involving 21,373 participants looking at changes in serum urate and cardiovascular events found that there was no relationship between changes in urate levels and outcomes [59]. The authors acknowledged that hyperuricaemic patients are at increased risk of cardiovascular events however as many of the risk factors for hyperuricaemia are the same risk factors as for cardiovascular disease the difficulty remains in separating out the individual effect of hyperuricaemia [59-61]. This also confirms the ongoing doubt surrounding the best management of hyperuricaemia as evidence that aggressive treatment of hyperuricaemia improves overall cardiovascular outcomes is lacking.

Conclusions

Undoubtedly the effect of hyperuricaemia in the human body is complex. At present evidence is accumulating that hyperuricaemia could be a significant factor in the development of hypertension in some people, and importantly, hyperuricaemia is also a potentially

reversible risk factor. Hypertension is a significant global health problem and a key contributor to increased risk of cardiovascular events, therefore any intervention that could improve the management of hypertension requires careful examination. There remains an unanswered question over whether aggressive management of hyperuricaemia can reduce blood pressure and improve cardiovascular outcomes significantly enough to be cost effective and outweigh the potential side effects of the urate lowering therapies required. Large randomised controlled trials are needed to answer this question, and it is possible that in the future management of hyperuricaemia will be as routine as management of cholesterol in the context of modifying cardiovascular risk.

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