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Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART RCT and economic evaluation

Isla S Mackenzie, Christopher J Hawkey, Ian Ford, Nicola Greenlaw, Filippo Pigazzani, Amy Rogers, Allan D Struthers, Alan G Begg, Li Wei, Anthony J Avery, Jaspal S Taggar, Andrew Walker, Suzanne L Duce, Rebecca J Barr, Jennifer S Dumbleton, Evelien D Rooke, Jonathan N Townend, Lewis D Ritchie and Thomas M MacDonald on behalf of the ALL-HEART Study Group



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Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART RCT and economic evaluation

Isla S Mackenzie,[1*] Christopher J Hawkey,[2] Ian Ford,[3] Nicola Greenlaw,[3] Filippo Pigazzani,[1] Amy Rogers,[1] Allan D Struthers,[1] Alan G Begg,[1] Li Wei,[4] Anthony J Avery,[5] Jaspal S Taggar,[5] Andrew Walker,[6] Suzanne L Duce,[1] Rebecca J Barr,[1] Jennifer S Dumbleton,[2] Evelien D Rooke,[1] Jonathan N Townend,[7] Lewis D Ritchie[8] and Thomas M MacDonald[1] on behalf of the ALL-HEART Study Group

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Members of the ALL-HEART study group are listed in *Appendix 1*.

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Abstract

Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART RCT and economic evaluation

Isla S Mackenzie,[1*] Christopher J Hawkey,[2] Ian Ford,[3] Nicola Greenlaw,[3] Filippo Pigazzani,[1] Amy Rogers,[1] Allan D Struthers,[1] Alan G Begg,[1] Li Wei,[4] Anthony J Avery,[5] Jaspal S Taggar,[5] Andrew Walker,[6] Suzanne L Duce,[1] Rebecca J Barr,[1] Jennifer S Dumbleton,[2] Evelien D Rooke,[1] Jonathan N Townend,[7] Lewis D Ritchie[8] and Thomas M MacDonald[1] on behalf of the ALL-HEART Study Group

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Background: Allopurinol is a xanthine oxidase inhibitor that lowers serum uric acid and is used to prevent acute gout flares in patients with gout. Observational and small interventional studies have suggested beneficial cardiovascular effects of allopurinol.

Objective: To determine whether allopurinol improves major cardiovascular outcomes in patients with ischaemic heart disease.

Design: Prospective, randomised, open-label, blinded endpoint multicentre clinical trial.

Setting: Four hundred and twenty-four UK primary care practices.

Participants: Aged 60 years and over with ischaemic heart disease but no gout.

Interventions: Participants were randomised (1 : 1) using a central web-based randomisation system to receive allopurinol up to 600 mg daily that was added to usual care or to continue usual care.

Main outcome measures: The primary outcome was the composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Secondary outcomes were non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, all-cause mortality, hospitalisation for heart failure, hospitalisation for acute coronary syndrome, coronary revascularisation, hospitalisation for acute coronary syndrome or coronary revascularisation, all cardiovascular hospitalisations, quality of life and cost-effectiveness.

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The hazard ratio (allopurinol vs. usual care) in a Cox proportional hazards model was assessed for superiority in a modified intention-to-treat analysis.

Results: From 7 February 2014 to 2 October 2017, 5937 participants were enrolled and randomised to the allopurinol arm (n = 2979) or the usual care arm (n = 2958). A total of 5721 randomised participants (2853 allopurinol; 2868 usual care) were included in the modified intention-to-treat analysis population (mean age 72.0 years; 75.5% male). There was no difference between the allopurinol and usual care arms in the primary endpoint, 314 (11.0%) participants in the allopurinol arm (2.47 events per 100 patient-years) and 325 (11.3%) in the usual care arm (2.37 events per 100 patient-years), hazard ratio 1.04 (95% confidence interval 0.89 to 1.21); p = 0.65. Two hundred and eighty-eight (10.1%) participants in the allopurinol arm and 303 (10.6%) participants in the usual care arm died, hazard ratio 1.02 (95% confidence interval 0.87 to 1.20); p = 0.77.

The pre-specified health economic analysis plan was to perform a 'within trial' cost-utility analysis if there was no statistically significant difference in the primary endpoint, so NHS costs and quality-adjusted life-years were estimated over a 5-year period. The difference in costs between treatment arms was +£115 higher for allopurinol (95% confidence interval £17 to £210) with no difference in quality-adjusted life-years (95% confidence interval −0.061 to +0.060). We conclude that there is no evidence that allopurinol used in line with the study protocol is cost-effective.

Limitations: The results may not be generalisable to younger populations, other ethnic groups or patients with more acute ischaemic heart disease. One thousand six hundred and thirty-seven participants (57.4%) in the allopurinol arm withdrew from randomised treatment, but an on-treatment analysis gave similar results to the main analysis.

Conclusions: The ALL-HEART study showed that treatment with allopurinol 600 mg daily did not improve cardiovascular outcomes compared to usual care in patients with ischaemic heart disease. We conclude that allopurinol should not be recommended for the secondary prevention of cardiovascular events in patients with ischaemic heart disease but no gout.

Future work: The effects of allopurinol on cardiovascular outcomes in patients with ischaemic heart disease and co-existing hyperuricaemia or clinical gout could be explored in future studies.

Trial registration: This trial is registered as EU Clinical Trials Register (EudraCT 2013-003559-39) and ISRCTN (ISRCTN 32017426).

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List of supplementary material

Report Supplementary Material 1	Endpoint adjudication committee charter
Report Supplementary Material 2	Data monitoring committee charter
Report Supplementary Material 3	Statistical analysis plan
Report Supplementary Material 4	Health economic analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/ATTM4092).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

ACS	acute coronary syndrome
CI	confidence interval
CV	cardiovascular
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GP	general practitioner
HF	heart failure
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IDMC	independent data monitoring committee
IHD	ischaemic heart disease
IPCW	inverse probability of censoring weighting
IQR	interquartile range
MI	myocardial infarction
mITT	modified intention to treat
NIHR	National Institute for Health and Care Research
NYHA	New York Heart Association
PROBE	prospective, randomised, open-label, blinded endpoint
QALY	quality-adjusted life-year
SAE	serious adverse event
SD	standard deviation
SUA	serum uric acid
TSC	Trial Steering Committee

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Plain language summary

What was the question?

The purpose of the ALL-HEART study was to determine whether giving allopurinol to people with ischaemic heart disease (also commonly known as coronary heart disease) would reduce their risk of having a heart attack, stroke or of dying from cardiovascular disease. Allopurinol is a medication usually given to patients with gout to prevent acute gout flares. It is not currently used to treat ischaemic heart disease.

What did we do?

We randomly allocated people aged over 60 years with ischaemic heart disease to take up to 600 mg of allopurinol daily (in addition to their usual care) or to continue with their usual care. We then monitored participants for several years and recorded any major health events such as heart attacks, strokes and deaths. We obtained most of the follow-up data from centrally held electronic hospital admissions and death records, making the study easier for participants and more cost-efficient. We asked participants in both groups to complete questionnaires to assess their quality of life during the study. We also collected data to determine whether there was any economic benefit to the NHS of using allopurinol in patients with ischaemic heart disease.

What did we find?

There was no difference in the risk of heart attacks, strokes or death from cardiovascular disease between the participants given allopurinol and those in the group continuing their usual care. We also found no difference in the risks of other cardiovascular events, deaths from any cause or quality-of-life measurements between the allopurinol and usual care groups.

What does this mean?

The results of the ALL-HEART study suggest that we should not recommend that allopurinol be given to people with ischaemic heart disease to prevent further cardiovascular events or deaths.

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Scientific summary

Background

Allopurinol is a xanthine oxidase inhibitor that lowers serum uric acid (SUA) and is widely used in patients with gout to prevent acute gout flares. Xanthine oxidase promotes inflammation and atherosclerosis via the production of reactive oxygen species and xanthine oxidase levels are raised in several conditions including coronary artery disease. The role of SUA in cardiovascular (CV) disease is controversial, with some studies associating higher SUA levels with worse CV outcomes, but more recent genome-wide association studies suggest no major role of uric acid levels in determining CV outcomes. Some observational studies have suggested that allopurinol therapy may improve CV outcomes, while others have not found an association. Small interventional studies have shown that allopurinol therapy improves some CV parameters, including endothelial function, left ventricular hypertrophy, blood pressure, carotid intimal media thickness and arterial stiffness. Allopurinol therapy was also found to improve outcomes after acute coronary syndrome (ACS) in one study and to improve chest pain in patients with chronic stable angina with documented coronary artery disease in another. However, results have not been consistent across different studies. Before the ALL-HEART study, no large, randomised trial of the effects of allopurinol therapy on CV outcomes in patients with ischaemic heart disease (IHD) had been performed.

Objectives

Primary

Does allopurinol therapy added to usual care improve major CV outcomes in patients aged over 60 years with IHD but no gout?

Secondary

Does allopurinol therapy added to usual care improve all-cause mortality or other CV outcomes in patients with IHD?

What is the cost-effectiveness of adding allopurinol up to 600 mg daily to usual care in patients with IHD?

Does allopurinol therapy added to usual care improve quality of life assessed by general health survey [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] or coronary heart disease-specific questionnaire (Seattle angina questionnaire)?

Methods

Design and participants

The ALL-HEART study was a prospective, randomised, open-label, blinded endpoint (PROBE) multicentre trial undertaken in patients with IHD. Participants were primarily recruited from 424 primary care practices via 18 regional centres in the UK, with a small number also referred into the study from secondary care centres. Eligible patients were aged 60 years or over, with a history of IHD [myocardial infarction (MI), angina or other evidence of IHD]. Exclusion criteria were: history of gout; known severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 ml/minute/1.73 m^2]; moderate-to-severe heart failure (HF) [New York Heart Association (NYHA) III–IV]; significant hepatic disease [e.g. alanine transaminase (ALT) > 3 × upper limit of normal, cirrhosis, ascites] (investigator opinion); currently taking part in another interventional clinical trial of an investigational medicinal product or medical

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device (or taken part in one within the last 3 months); previous allergy to allopurinol; previous serious adverse cutaneous (skin) reaction to any drug (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis, hospitalisation due to skin reaction to drug) (investigator opinion); already taking urate-lowering therapy (including allopurinol, febuxostat, sulfinpyrazone, benzbromarone, probenecid, rasburicase); taking azathioprine, mercaptopurine, ciclosporin or theophylline; malignancy (except non-metastatic, non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years (investigator opinion).

The exclusion criterion relating to renal impairment was originally 'known renal impairment eGFR < 60 ml/minute/1.73 m^{2}' for patients recruited from the start of the trial (7 February 2014) until 4 April 2016 when an updated version of the protocol was implemented at all study sites to allow the inclusion of patients with moderate renal impairment in the study with the purpose of making the study results more generalisable. Fifty-two per cent of the target number of patients had been randomised by this date.

Randomisation

At a single screening and randomisation visit usually held at the patient's primary care practice by a research nurse, patients were consented, screened and randomised to receive allopurinol therapy or to continue their usual care. Baseline demographics, medical history, CV risk factors and concomitant medications were recorded. Blood pressure, height and weight were measured. Baseline blood tests were taken for urea, creatinine and electrolytes, full blood count and SUA. Participants were randomised before screening blood results were available. When the screening results were available, a nurse telephoned the patient to advise them to start taking randomised therapy. If the screening visit eGFR result was below the exclusion limit, the participant did not receive any allopurinol and was excluded from the modified intention-to-treat (mITT) analysis population, whichever arm of the study they had been randomised to.

Randomisation was via a web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow, accessed using a web-based application or an interactive voice response system. Randomisation was based on randomised permuted blocks of variable size, stratified by history of MI, history of stroke and primary care practice.

Randomised intervention

Allopurinol 100 or 300 mg tablets were prescribed to participants by their primary care physicians via the usual NHS prescription system. Participants with a screening eGFR result ≥ 60 ml/minute/1.73 m^2 were prescribed allopurinol at 100 mg daily for 2 weeks, then 300 mg daily for 2 weeks then 600 mg daily (given as 300 mg twice daily) thereafter if tolerated for the duration of the study. After 4 April 2016, participants with a screening eGFR result 30–59 ml/minute/1.73 m^2 were prescribed allopurinol at 100 mg daily for 2 weeks, then 300 mg daily thereafter if tolerated for the duration of the study. If there were tolerability issues, the dose could be decreased at the discretion of a physician. Participants who stopped randomised therapy were encouraged to continue with study follow-up. The comparison arm of the study was 'usual care'; no placebo was given as this was a pragmatic open-label study. Randomised therapy was blinded to the endpoint adjudication committee, but not to participants, study staff or treating healthcare professionals. If allopurinol was started in participants randomised to the usual care group at any point in the study (e.g. for clinical reasons such as developing gout), this was recorded.

Other study procedures

At the screening visit, participants completed the EQ-5D-5L questionnaire to assess general health outcomes and the Seattle angina questionnaire to assess coronary artery disease-specific quality of life.

Participants who had taken any allopurinol therapy attended a 6-week study visit. Blood samples were taken for urea, creatinine and electrolytes, full blood count and SUA.

Participants were then followed up remotely by electronic record-linkage with centralised databases of hospitalisations, cancers and deaths held by Public Health Scotland (PHS) and NHS Digital and by annual questionnaires (online, by post or by telephone). Data on adverse events, skin rashes, gout flares and self-reported adherence to randomised therapy were collected at the 6-week visit, then by annual questionnaire (but could also be reported at any time by participants or health professionals). Participants completed the EQ-5D-5L and Seattle angina questionnaires again after 1 year and at the end of the trial.

The trial recruitment period was extended once, and the trial follow-up period was extended twice. Recruitment exceeded the target of 5215 randomised participants to a final total of 5937 randomised participants due to an increase in recruitment rate in the last weeks of recruitment.

The follow-up period of the trial ended on 30 September 2021. After this date, participants stopped randomised therapy and continued to receive their usual care.

Study outcomes

The primary and secondary outcomes were as follows.

Primary outcome:

- Composite of non-fatal MI, non-fatal stroke or CV death.

Secondary outcomes:

- Non-fatal MI.
- Non-fatal stroke.
- CV death.
- All-cause mortality.
- Hospitalisation for ACS.
- Coronary revascularisation.
- Hospitalisation for ACS or coronary revascularisation.
- Hospitalisation for HF.
- All CV hospitalisations.
- Quality of life.
- Cost-effectiveness.

Adverse events

Serious adverse events (SAEs) occurring during the study (until 30 September 2021) were recorded and any events ongoing at that time were followed up for a further 30 days, unless consent had been withdrawn. Treatment-related adverse events (adverse reactions), gout flares and rashes were also recorded. Allopurinol therapy was stopped if participants developed a rash that may have been due to allopurinol.

For any SAEs that were potential study endpoints, detailed information was obtained from medical records and death certificates to support the production of an anonymised endpoint package that was adjudicated by an independent clinical endpoint adjudication committee, blinded to randomised therapy allocation.

Statistical analysis

The power calculation suggested that 5215 participants would need to be randomised 1 : 1 to give 80% power to detect a 20% reduction in the primary outcome for the intervention (allowing for a 4% dropout for withdrawal of consent and non-CV deaths). A primary event rate of 14% over an average of 4 years

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follow-up was estimated from other trials in similar patient groups. The study ended when 631 adjudicated first primary events had occurred.

Baseline characteristics are presented by treatment group as means [standard deviation (SD)] and medians [interquartile range (IQR)] for continuous variables and as numbers (%) for categorical variables.

Clinical outcomes were analysed on a time-to-first event basis using Cox proportional hazards models. Treatment effects (allopurinol vs. usual care) were estimated as hazard ratios (HR) and 95% confidence intervals (CIs) for the Cox models. Analyses were adjusted for the stratification variables history of MI and history of stroke and *p*-values were calculated from Wald statistics. The primary analysis was a mITT analysis.

Health economic analysis

A health economic analysis was planned to determine whether allopurinol was a cost-effective intervention in the context of the NHS setting in the UK in patients with IHD. The analysis plan was based around NHS costs and estimation of quality-adjusted life-years (QALYs) and was to include a 'within trial' cost–utility analysis if the primary outcome was not statistically different between randomised study arms.

Trial approvals and committees

The study was approved by an ethics committee, Medicines and Healthcare Products Regulatory Agency (MHRA) and Health Research Authority (HRA). An Independent Data Monitoring Committee oversaw trial safety. A Trial Steering Committee including independent and patient/lay members oversaw trial progress.

Results

From 7 February 2014 to 29 September 2017, 6134 patients consented to enrol in the trial and were assessed for eligibility. Also, 167 of the 6134 consented participants were not eligible and 30 others were not randomised. The final randomisation was completed on 2 October 2017. Of the 5937 randomised participants, 216 were excluded post randomisation from the mITT analysis population (184 did not meet the eGFR entry criteria once their screening blood results were available; 32 were later found to have not met all of the inclusion/exclusion criteria). Five thousand seven hundred and twenty-one participants (2853 in the allopurinol arm and 2868 in the usual care arm) were included in the mITT analysis population for the efficacy analysis. The population for safety analyses consisted of 2805 participants in the allopurinol arm (excluding the 48 participants in the allopurinol arm who never received any randomised therapy) and 2868 participants in the usual care arm.

The mean duration of follow-up in the trial was 4.8 years. Two hundred and fifty-eight participants (9.0%) in the allopurinol group and 76 participants (2.6%) in the usual care group withdrew consent for all follow-up. One thousand six hundred and thirty-seven participants (57.4%) in the allopurinol arm withdrew from randomised treatment.

Baseline characteristics were well balanced in the two groups. The mean age at study entry was 72.0 years (SD 6.8), 4321 participants (75.5%) were male, 5676 (99.2%) were white and 1241 (21.7%) had a history of diabetes mellitus. The median duration of IHD at study entry was 10.1 years (IQR 5.1–16.1). Three thousand four hundred and sixty-four (60.5%) participants were recruited in England and 2257 (39.5%) participants in Scotland.

The most commonly taken dose of allopurinol was 600 mg daily. In the 2447 participants in the allopurinol arm with both a baseline and 6-week SUA result, SUA fell from a mean of 0.34 (SD 0.08) mmol/l at baseline to a mean of 0.18 (SD 0.09) mmol/l 6 weeks after randomisation. Forty-five participants in the usual care arm started allopurinol therapy during follow-up (for clinical reasons, mainly gout).

Primary and secondary outcomes

There was no significant difference between the randomised treatment groups in the rates of the primary outcome or any of the secondary time-to-event outcomes. Three hundred and fourteen (11.0%) participants in the allopurinol arm (2.47 events per 100 patient-years) and 325 (11.3%) in the usual care arm (2.37 events per 100 patient-years) experienced a primary outcome, HR 1.04 (95% CI 0.89 to 1.21); $p = 0.65$. Two hundred and eighty-eight (10.1%) participants in the allopurinol arm and 303 (10.6%) participants in the usual care arm died, HR 1.02 (95% CI 0.87 to 1.20); $p = 0.77$. Results for the primary outcome were consistent across all pre-specified subgroups. In a supporting on-treatment analysis, results for the time-to-event clinical outcomes were broadly similar to those in the mITT analysis.

There was limited evidence of any effect of allopurinol on quality-of-life outcomes, with no differences in EQ-5D-5L outcomes or Seattle angina questionnaire outcomes at the end of the first year or at the final visit, except for a nominally significant but only slightly greater fall in the physical domain score of the Seattle angina questionnaire at the end of the first year [treatment difference = 1.219 (95% CI 0.027 to 2.410); $p = 0.045$] in the allopurinol arm.

Health economic analysis

There was strong evidence that allopurinol treatment was associated with incremental costs relative to usual care [incremental cost per patient £115.4, 95% CI (£17.0 to £210.2)], with little evidence of improvement in relation to incremental QALYs [incremental QALYs −0.000, 95% CI (−0.061 to 0.060)]. The cost-effectiveness acceptability curve asymptoted at a probability of 0.456, meaning that even with a willingness to pay of an infinite amount, the probability of cost-effectiveness was only 0.465. At a willingness to pay of £20,000 the probability of cost-effectiveness was 0.41.

Adverse events

There was no difference in SAE rates between treatment arms, except for the grouping of endocrine disorders where no events occurred in the allopurinol treatment group but 14 in the usual care group. However, these endocrine events included events with a spread of different types. Fifteen participants had SAEs that were considered potentially treatment related and none of these were fatal. There was no difference between treatment arms in the rates of incident cancers. Adjudicated causes of death were well balanced between the treatment groups, including deaths from COVID-19 and COVID-19 pneumonia.

Conclusions

The ALL-HEART study showed that treatment with allopurinol 600 mg daily did not improve CV outcomes compared to usual care in patients with IHD. There were also no benefits on quality of life. There was no evidence that allopurinol used in line with the study protocol is cost-effective within the NHS system. We conclude that allopurinol should not be recommended for the secondary prevention of CV events in patients with IHD but no gout.

Recommendations for research

1. Future research should explore other therapeutic options for the improvement of CV outcomes and quality of life in patients with IHD.
2. Further exploration of the effects of allopurinol on CV outcomes in patients with co-existing IHD and clinical gout or hyperuricaemia could be considered (patients with gout were excluded from this study).

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Trial registration

The ALL-HEART trial is registered with the EU Clinical Trials Register (EudraCT 2013-003559-39) and ISRCTN (ISRCTN 32017426).

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Chapter 1 Introduction

Background

Ischaemic heart disease (IHD) remains one of the biggest health issues affecting the UK population and is responsible for significant morbidity and mortality. In 2019, 55,064 (10.4%) deaths registered in England and Wales were due to IHD.[2]

Allopurinol is a xanthine oxidase inhibitor that lowers serum uric acid (SUA) levels. It is currently licensed for the treatment of symptomatic hyperuricaemia (gout) and is widely used long term in patients with gout to prevent acute gout flares. Allopurinol is not currently licensed for the treatment of asymptomatic hyperuricaemia, or for the treatment of patients with IHD, unless they also have gout. Xanthine oxidase is an enzyme that promotes inflammation and atherosclerosis via the production of reactive oxygen species and xanthine oxidase activity is raised in several conditions including coronary artery disease.[3]

The role of SUA in cardiovascular (CV) disease is controversial, with some observational studies associating higher SUA levels with worse CV outcomes,[4,5] but more recent Mendelian randomisation approaches suggest no major role of uric acid levels in determining CV outcomes.[6] Some observational studies have suggested that allopurinol therapy may improve CV outcomes,[7,8] while others have not found any beneficial effect.[9] There is significant risk of confounding and bias within observational studies, and a need for evidence generated via prospective randomised trials to guide practice in this area was identified.[10]

Several small interventional studies (with up to 100 participants) have investigated the effects of allopurinol on various CV parameters. Studies have reported improvements in some parameters with allopurinol therapy, including endothelial function,[11–15] flow-mediated dilatation,[16,17] blood pressure,[18–20] left ventricular mass,[16,21,22] carotid intimal media thickness and arterial stiffness.[20] However, other studies have reported no benefit of allopurinol therapy on blood pressure,[17] left ventricular mass,[23,24] myocardial perfusion[25] and flow-mediated dilatation.[26]

In a randomised crossover study in 65 patients with chronic stable angina with angiographically documented coronary artery disease, allopurinol therapy given at 600 mg daily improved time to onset of chest pain and exercise time compared to placebo therapy.[27] In a randomised study of 100 patients presenting with acute coronary syndrome (ACS), allopurinol therapy was found to reduce CV events over a 2-year follow-up period, improve markers of oxidative stress and inflammatory response and reduce angina compared to usual care.[28] Allopurinol given at the time of coronary bypass surgery improved outcomes in one study[29] but not in another.[30]

With regard to possible mechanisms of action, it is not clear whether the potential beneficial CV effects of allopurinol in some of these studies may be a result of urate lowering or due to a reduction in xanthine oxidase-mediated oxidative stress.[11,31]

Given the uncertainties in the results of the observational and small interventional studies to date, there was a clear need to definitively answer the question of whether allopurinol therapy would improve outcomes for patients with IHD in a properly powered prospective randomised trial. If allopurinol were found to be beneficial for patients with IHD in terms of improving CV outcomes or quality of life, it would be a relatively inexpensive and easy to introduce therapy within the UK healthcare system.

The ALL-HEART study was designed to answer this question and was the first large, prospective, randomised trial of the effects of allopurinol therapy on major CV outcomes in patients with IHD.[32]

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Chapter 2 Methods

Study design

The ALL-HEART study was a multicentre, prospective, randomised, open-label, blinded end point (PROBE) trial. The protocol is available at https://njl-admin.nihr.ac.uk/document/download/2031938.

Objectives

The objectives of the ALL-HEART study were to answer the following questions.

Primary objective

Does allopurinol therapy added to usual care improve major CV outcomes in patients aged over 60 years with IHD but no gout?

Secondary objectives

Does allopurinol therapy added to usual care improve all-cause mortality or other CV outcomes in patients with IHD?

What is the cost-effectiveness of adding allopurinol up to 600 mg daily to usual care in patients with IHD?

Does allopurinol therapy added to usual care improve quality of life assessed by general health survey [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] or coronary heart disease-specific questionnaire (Seattle angina questionnaire)?

Participants

Participants were recruited from 424 primary care practices via 18 regional centres in the UK. Primary care records were searched for potentially eligible patients who were then invited by letter from their general practitioner (GP) to participate in the study. In addition, a small number of participants were referred to the study from secondary care centres. Eighty-four Clinical Commissioning Groups (CCGs) in England and 10 Health Boards in Scotland were involved in the study.

The inclusion and exclusion criteria were as follows.

Inclusion criteria

1. Male or female patients aged 60 years and over.
2. Ischaemic heart disease defined as a diagnosis of angina or myocardial infarction (MI) at any time or other evidence of IHD (investigator opinion).

Exclusion criteria

1. History of gout.
2. Known severe renal impairment [estimated glomerular filtration rate (eGFR) < 30 ml/minute/1.73 m^2]. [This was previously 'Known renal impairment eGFR < 60 ml/minute/1.73 m^{2}' for patients recruited

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from the start of the trial (7 February 2014) until 4 April 2016 when protocol v4 was implemented at all study sites. Fifty-two per cent of the target number of patients had been randomised by this date.]

3. Moderate to severe heart failure (HF) [New York Heart Association (NYHA) III–IV].
4. Significant hepatic disease [e.g. alanine transaminase (ALT) > 3 × upper limit of normal, cirrhosis, ascites] (investigator opinion).
5. Patients currently taking part in another interventional clinical trial of an investigational medicinal product or medical device (or taken part in one within the last 3 months).
6. Previous allergy to allopurinol.
7. Previous serious adverse cutaneous (skin) reaction to any drug (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis, hospitalisation due to skin reaction to drug) (investigator opinion).
8. Patients already taking urate-lowering therapy (including allopurinol, febuxostat, sulfinpyrazone, benzbromarone, probenecid, rasburicase).
9. Patients taking azathioprine, mercaptopurine, ciclosporin or theophylline.
10. Malignancy (except non-metastatic, non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years (investigator opinion).

Screening and randomisation visit

At a single screening and randomisation visit held at the patient's primary care practice by a research nurse (or the practice nurse or GP), written informed consent was obtained, then participants were screened and randomised to receive allopurinol therapy or to continue their usual care.

Baseline demographics, medical history, CV risk factors and concomitant medications were recorded. Blood pressure, height and weight were measured. Baseline blood tests were taken for urea, creatinine and electrolytes, full blood count and SUA. Blood tests were sent to local NHS laboratories and results were later entered into the electronic case report form (eCRF) by the nurse. Participants were randomised before screening blood results were available. When the screening blood results were available and had been checked for eligibility, a nurse telephoned those patients randomised to the allopurinol arm of the study to advise them to collect their prescription and start taking randomised therapy. If the screening visit eGFR result was below the exclusion limit, the participant did not receive any allopurinol and was excluded from the modified intention-to-treat (mITT) analysis population, whichever arm of the study they had been randomised to.

Randomisation

Randomisation was carried out using a web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow, accessed using a web-based application or an interactive voice response system. Randomisation was based on randomised permuted blocks of variable size, stratified by history of MI, history of stroke and primary care practice. Participants were randomised 1 : 1 to receive either allopurinol therapy plus usual care or to continue usual care.

Interventions

Allopurinol 100 or 300 mg tablets (various manufacturers and suppliers) were prescribed to participants by their primary care physicians via the usual NHS prescription system and supplied via the patient's local community pharmacy. Participants with a screening eGFR result ≥60 ml/minute/1.73 m^2 were prescribed allopurinol at 100 mg daily for 2 weeks, then 300 mg daily for 2 weeks then 600 mg daily (given as 300 mg twice daily) thereafter if tolerated for the duration of the study (maximum 600 mg daily dose). After the amendment to include patients with moderate renal impairment was implemented

across study sites on 4 April 2016, participants with a screening eGFR result 30–59 ml/minute/1.73 m^2 were prescribed allopurinol at 100 mg daily for 2 weeks, then 300 mg daily thereafter if tolerated for the duration of the study (maximum 300 mg daily dose). If the screening visit eGFR result was below the exclusion criterion limit, the participant did not receive any randomised medication.

If there were tolerability issues, the dose could be decreased at any time at the discretion of a physician, or the allopurinol could be stopped. Participants experiencing any rash, however mild, that could be due to allopurinol were withdrawn from allopurinol therapy as a precaution against the development of a more serious rash such as Stevens–Johnson syndrome or toxic epidermal necrolysis. Participants who stopped randomised therapy were encouraged to continue within the rest of study follow-up. The comparison arm of the study was 'usual care'; no placebo was given as this was a pragmatic open-label study. Randomised therapy was blinded to the endpoint adjudication committee, but not to participants, study staff or treating healthcare professionals. If allopurinol was started in participants randomised to the usual care group at any point in the study (e.g. for clinical reasons such as developing gout), this was recorded along with the date and the reason.

Other study procedures

At the screening visit, participants completed two quality-of-life questionnaires. The EQ-5D-5L[33] was completed to assess general health outcomes and the Seattle angina questionnaire[34] was completed to assess coronary artery disease-specific quality of life.

Participants who had taken any allopurinol therapy attended a 6-week study visit with a research nurse. Blood samples were taken for urea, creatinine and electrolytes, full blood count and SUA. Participants were asked at this visit whether they were still taking their allopurinol therapy.

The participants were then followed up remotely for the rest of the trial, with no further in-person study visits. Follow-up occurred by electronic record-linkage to centralised databases of hospitalisations, cancers and deaths held by Public Health Scotland (PHS) (https://publichealthscotland.scot) and NHS Digital (https://digital.nhs.uk) to capture details of serious adverse events (SAEs) and potential study endpoints. Participants were also asked to complete annual questionnaires (online, by post or by telephone). Data on adverse events, skin rashes, gout flares and self-reported adherence to randomised therapy were collected at the 6-week visit then annually (but could also be reported at any time by participants or health professionals). Participants also self-reported their health resource usage (number of visits to GP, practice nurse, outpatient clinic and physiotherapist in the previous 12-month period) at 1 year, at the end of the study (and annually for a randomly selected 25% of participants) for the purposes of the health economic analysis. Participant-reported data could be clarified or verified where necessary by contacting the participant's primary care practice team or consulting medical records. Participants completed the EQ-5D-5L and Seattle angina questionnaires after 1 year and at the end of the trial. The follow-up period of the trial ended on 30 September 2021. After this date, participants stopped randomised therapy and continued to receive their usual care.

Amendments to protocol during study

The trial recruitment period was extended from 2 years to just over 3.5 years to allow the recruitment target to be reached. Final recruitment exceeded the target of 5215 randomised participants with a final total of 5937 randomised participants reached, due to an increase in recruitment rate in the final weeks of recruitment.

The trial follow-up period was extended twice due to the extended recruitment and lower than predicted CV event rates in the study population. Participants could choose to end their active

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involvement in the study after 5 years' participation (the original study duration) or after 31 March 2021, when these extensions were implemented.

During a temporary shortage of allopurinol 100 mg tablets supply experienced during the year 2014, the protocol was amended temporarily to allow participants to start on 100–150 mg allopurinol for the first 2 weeks so that a half tablet of 300 mg could be administered daily if it was not possible to obtain 100 mg tablets. The dose was then up-titrated to 300 mg, then 600 mg daily as described above. The starting dose of allopurinol for the majority of participants in the study was 100 mg daily.

Originally, only patients with screening eGFR ≥ 60 ml/minute/1.73 m^2 were included in the study. However, the protocol was amended during the second year of recruitment (change implemented at all study sites on 4 April 2016) to allow the inclusion of patients with moderate renal impairment (screening eGFR 30–59 ml/minute/1.73 m^2) in the study with the goal of making the study results more generalisable. Fifty-two per cent of the target number of patients had been randomised by this date.

Outcomes

The primary outcome was the composite of non-fatal MI, non-fatal stroke or CV death.

The secondary outcomes were non-fatal MI; non-fatal stroke; CV death; all-cause mortality; hospitalisation for ACS; coronary revascularisation; hospitalisation for ACS or coronary revascularisation; hospitalisation for HF; all CV hospitalisations; quality of life; cost effectiveness.

Patient-reported healthcare service usage (specifically visits to GP, practice or community nurse, physiotherapist, doctor at a hospital outpatient clinic) were also reported as additional outcomes.

Serious adverse events occurring during the study (until 30 September 2021) were recorded, and any ongoing events were followed up until 30 days after the end of the study follow-up period (until 30 October 2021), unless participants had withdrawn consent. Gout flares, rashes and any treatment-related adverse events were also recorded.

All SAEs were reviewed by a study physician and any potential study endpoints were identified at the time of reporting. For any potential study endpoints, information was collected from medical records and death certificates. An anonymised endpoint package (with details of randomised therapy redacted) was prepared for each potential endpoint. This anonymised endpoint package was adjudicated by an independent clinical events adjudication committee unaware of randomised arm of the study that is blinded to study allocated treatment. The committee adjudicated all the components of the primary composite outcome, all deaths and all secondary CV outcomes (except coronary revascularisations which were confirmed by the Chair of the committee, and any 'cardiovascular hospitalisations' falling outwith one of the other adjudicated categories of CV events, which were confirmed by the study physicians in Dundee); the events are defined in the clinical endpoint adjudication committee charter (see *Report Supplementary Material 1*).

Record-linkage to centralised databases for records of hospitalisations, deaths and cancers was carried out at regular intervals throughout the trial with a final linkage performed after the end of the study follow-up period [PHS (https://publichealthscotland.scot) and NHS Digital (https://digital.nhs.uk)] to capture adverse events and study endpoints.

Approvals, oversight and study committees

The study was approved by the East of Scotland Research Ethics Committee (REC Ref. 13/ES/0104, IRAS ID 135900) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (CTA number 21726/0284/001-0001). NHS R+D and HRA approvals were obtained, as were the relevant permissions to obtain record-linkage data from PHS and NHS Digital.

The study was jointly sponsored by the University of Dundee and NHS Tayside. The chief investigator was Professor Isla Mackenzie, University of Dundee. Principal investigators were appointed at each of the regional study sites. The Clinical Co-ordination Centre was at MEMO Research, University of Dundee. The Data and Biostatistics centre was at the Robertson Centre for Biostatistics, University of Glasgow. Trial monitoring was co-ordinated by the University of Dundee and NHS Tayside, Dundee.

Overall supervision of the study was provided by a Trial Steering Committee (TSC), chaired by Professor Sir Lewis Ritchie, University of Aberdeen. The committee included independent members and two lay/patient members. Trial safety was overseen by an Independent Data Monitoring Committee (IDMC) chaired by Professor Sir Mark Caulfield, Queen Mary University London. An IDMC charter outlined its roles and responsibilities (see *Report Supplementary Material 2*). A study management group led the day-to-day management of the study. All committees and the management group met regularly throughout the trial.

Statistical analysis

The power calculation suggested that 5215 participants would need to be randomised 1 : 1 to give 80% power to detect a 20% reduction in the primary outcome for the intervention (allowing for a 4% dropout for withdrawal of consent and non-CV deaths). A primary event rate of 14% over 4 years average follow-up was estimated from other trials in similar patient groups. The study would end when 631 adjudicated first primary events had occurred.

Baseline characteristics are presented by treatment group as means [standard deviation (SD)] and medians [interquartile range (IQR)] for continuous variables and as numbers (%) for categorical variables.

Clinical outcomes were analysed on a time to first event basis using Cox proportional hazards models. Treatment effects (allopurinol vs. usual care) were estimated as hazard ratios (HRs) and 95% confidence intervals (CIs) for the Cox models. Analyses were adjusted for the stratification variables history of MI and history of stroke and *p*-values were calculated from Wald statistics. Although primary care practice was a stratification variable to avoid potential bias in this open-label trial, because of the large number of practices involved, as is common practice, study site was not adjusted for in the analysis.

The primary analysis was a mITT analysis.

Any participants who had been randomised but were later found to have not met the inclusion/exclusion criteria (e.g. did not meet screening eGFR criteria on screening blood results, or had a history of recent malignancy not fully realised at time of inclusion in the study) were excluded from the mITT analysis. The mITT analysis censored follow-up after death from any cause not included in the endpoint being considered, date of withdrawal of consent to participate any longer in the study, or the end of the study, whichever occurred first. An on-treatment (OT) analysis censored follow-up after permanent stopping of randomised therapy, death from any cause not included in the endpoint being considered, date of withdrawal of consent to participate any longer in the study, or the end of the study, whichever occurred first. Similar analyses were performed for other time-to-event secondary clinical endpoints. Pre-specified subgroup analyses were carried out for the primary endpoint. *p*-values for the test of

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interaction between the variable defining the subgroup and randomised treatment allocation were calculated in each case.

Quality-of-life outcomes at each time point (1-year post randomisation and final visit) were analysed using linear regression models for the change in each quality-of-life measure. Analyses were adjusted for the stratification variables as per the clinical outcomes and the baseline quality-of-life value. Participants with a baseline value available but missing follow-up had a value imputed, with a zero if the participant had died, or using multiple imputation. Ten imputations were generated using SAS PROC MI, with the monotone regression option, using the following variables as predictors: baseline measure, treatment, stratification variables (history of MI and history of stroke) and age. Multiple imputations were combined using SAS PROC MIANALYZE procedure. Selected baseline characteristics were compared between patients with and those without EQ-5D-5L score being available at the end of the study using Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables, for each arm of the study.

Healthcare service usage outcomes for all participants with data at each time point (1 year post randomisation and end of study) were analysed using stratified Wilcoxon tests which account for the stratification variables. The subset of participants with data additionally collected at each interim annual time point were analysed in the same way and the results were similar to those in all participants (with no statistically significant and clinically meaningful differences).

Time-to-event curves are presented as Kaplan–Meier curves for all-cause mortality, and as cumulative incidence functions adjusting for the competing risk of deaths not included in the endpoint being plotted for the other endpoints and are obtained using SAS PROC lifetest. Time to withdrawal of consent from the study and time to discontinuation of allopurinol treatment were described.

The type I error rate was set at 5% for two-sided superiority analyses. Pre-planned interim analyses were carried out for the IDMC (requiring $p < 0.001$ to make a recommendation for early stopping of the trial), but not shared with the study team, after approximately 50% and 75% of the target number of 631 adjudicated study outcomes had been observed. No adjustments were made for multiple statistical comparisons. Analyses other than for the primary endpoint should be considered exploratory.

All participants who were validly randomised and whose baseline eGFR did not exclude them based on their screening visit blood results were included in the mITT and OT analysis populations. The safety analysis population included all participants in the usual care arm, and all participants in the allopurinol arm who took at least one dose of randomised medication (allopurinol). The number of participants with SAEs and crude rates per 100 patient-years are reported by MedDRA system organ class for each treatment arm with rates compared between treatment arms. Rates, rather than percentages with event (as was originally intended), are compared because of the different withdrawal rates and hence length of follow-up in the two treatment arms. Crude rates are calculated as the number of participants with events, divided by the time-to-first event or censoring (years), multiplied by 100.

Analyses and graphical displays were conducted using SAS for Windows version 9.4 and R version 3.6.1. The statistical analysis plan is in *Report Supplementary Material 3*.

Chapter 3 Results

Between 7 February 2014 and 29 September 2017, 6134 patients consented to take part in the trial and were assessed for eligibility. One hundred and sixty-seven were found to be ineligible and 30 did not proceed with randomisation. The final randomisation was completed on 2 October 2017. Of the 5937 randomised participants, 216 were excluded post randomisation due to their screening eGFR blood result being below the limit for the trial or were later found to have not fully met other inclusion or exclusion criteria. Five thousand seven hundred and twenty-one participants (2853 in the allopurinol arm and 2868 in the usual care arm) remained in the mITT population which formed the population for the efficacy analyses. Forty-eight participants in the allopurinol arm of the study never took any of their randomised allopurinol treatment, leaving 2805 participants in the allopurinol arm and 2868 participants in the usual care arm in the safety analysis population. The participant flow is shown in *Figure 1*.

Recruitment occurred in a near-linear fashion throughout the recruitment period of the study, until the last few weeks when the recruitment rate increased (*Figure 2*).

Participants were recruited from primary care practices via 18 regional sites. The breakdown of participant recruitment (consented and randomised) by regional site is given in *Table 1*. Three thousand four hundred and sixty-four (60.5%) participants in the analysis group (n = 5721) were recruited in England and 2257 (39.5%) in Scotland.

Participant follow-up within the study ended on 30 September 2021. Participants were asked to stop taking randomised therapy on that date. Any ongoing SAEs were followed up for outcomes for a further 30 days. Final record-linkage data were obtained from NHS Digital and PHS in December 2021. Supporting information on the remaining potential endpoints was collected over the next few weeks. The trial formally ended on 31 March 2022.

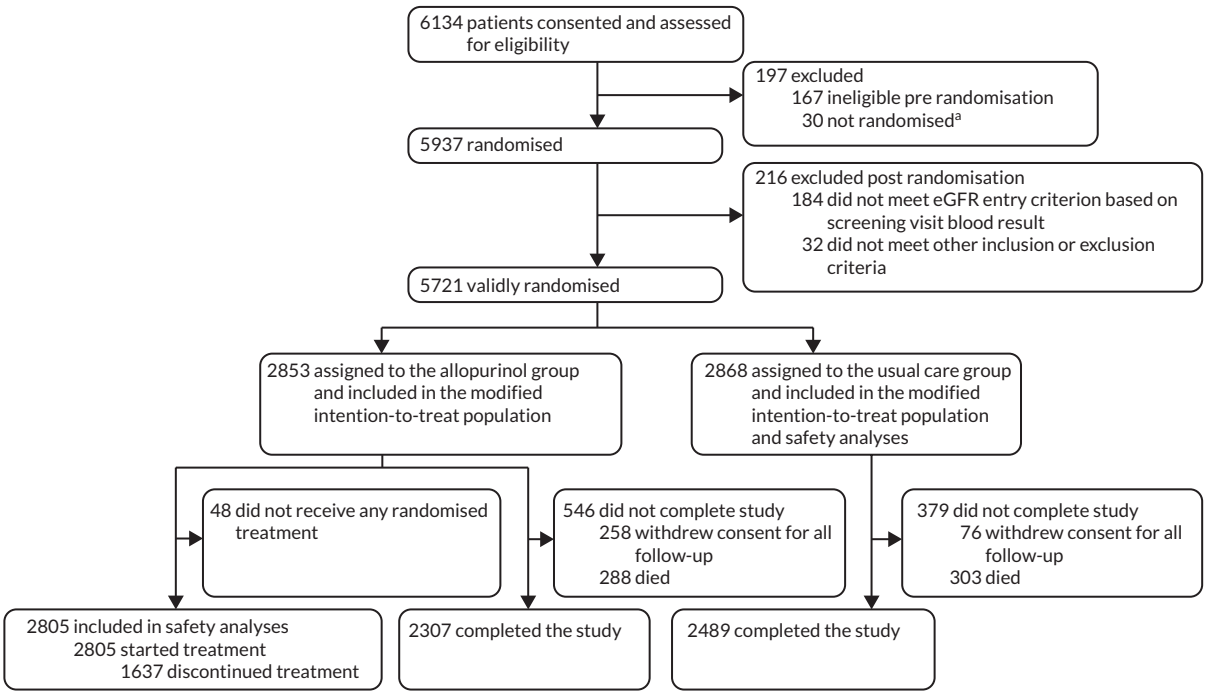


FIGURE 1 Participant flow (CONSORT diagram). a, Screening visit was not completed or participant withdrew consent before randomisation. This figure is reproduced from *The Lancet*, Volume 400, Issue 10359; Mackenzie IS, Hawkey CJ, Ford I Greenlaw N, Pigazzani F, Rogers A, *et al*. Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, PROBE trial. P1195–205, Copyright Elsevier (2022).[1]

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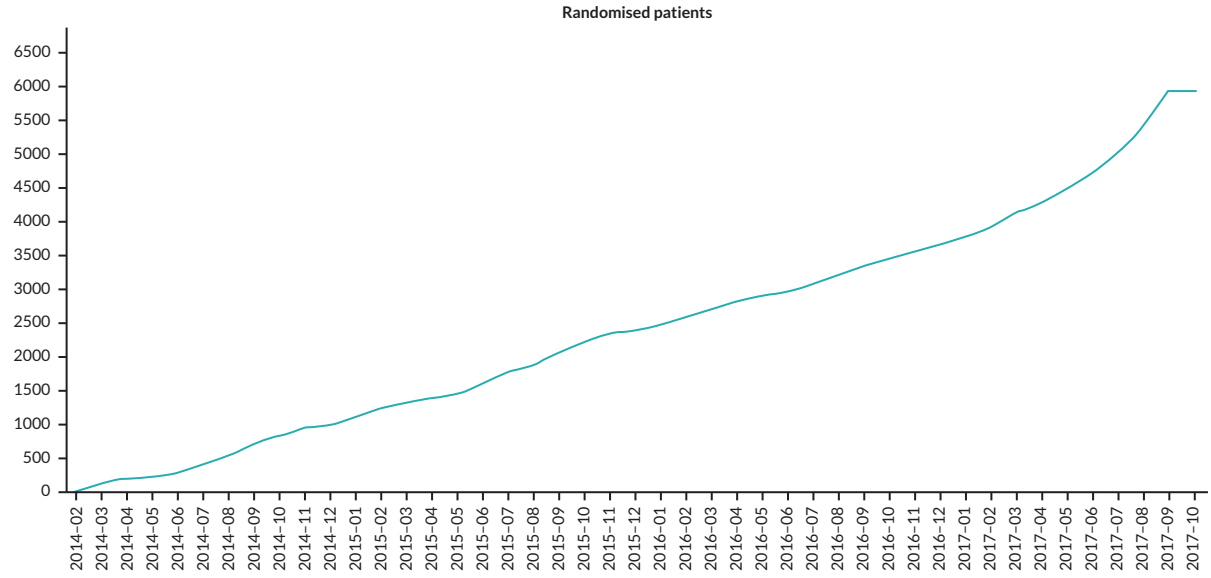


FIGURE 2 Number of participants randomised (*n* = 5937) by month (2014–7).

TABLE 1 Number of participants consented and randomised in each regional site

Regional site	Consented (*n*)	Randomised (*n*)
Dundee	1499	1471
Edinburgh	251	245
Glasgow	119	115
Aberdeen	144	136
Lanarkshire (Hairmyres and Monklands sites)	195	195
Highland	112	111
Ayrshire and Arran	47	46
Dumfries and Galloway	18	18
Nottingham	1069	1038
West Midlands	576	531
Eastern	805	774
Kent, Surrey and Sussex	110	107
South West Peninsula	325	316
North Thames	73	69
North West Coast	436	424
North East and North Cumbria	198	190
Yorkshire and Humber	157	151
Total	**6134**	**5937**

The mean duration of follow-up within the study was 4.8 years (SD 1.5). There were more withdrawals from all follow-up (withdrawals of consent) in the allopurinol group [258 (9.0%) of 2583 participants] than in the usual care group [76 (2.6%) of 2868 participants] (*Figure 3*).

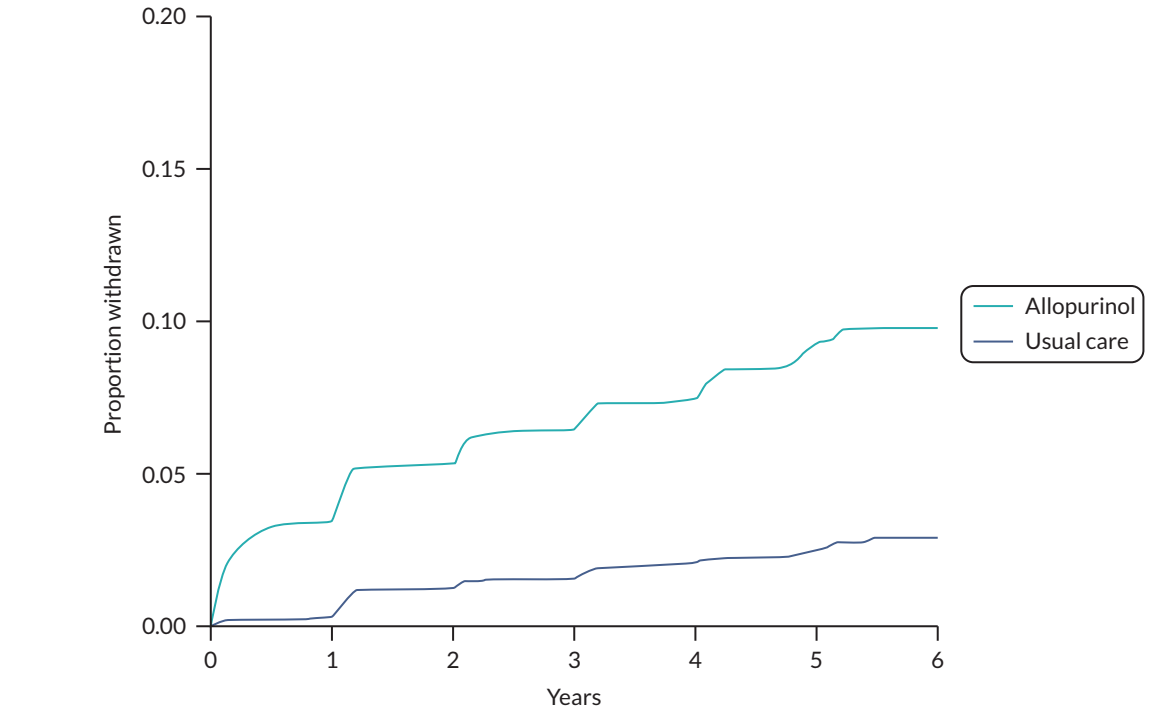


FIGURE 3 Cumulative incidence function – withdrawal of all follow-up (consent) from study. Randomised mITT analysis set (*n* = 5721).

The reasons for withdrawal from all follow-up are given in *Table 2*. The most common reason for withdrawal from all follow-up in both arms of the study was patient preference.

One thousand six hundred and thirty-seven (57.4%) participants in the allopurinol group withdrew from randomised treatment (*Figure 4*).

TABLE 2 Withdrawals from all study follow-up and reasons (randomised set: *n* = 5937)

		Allopurinol (*n* = 2979)	Usual care (*n* = 2958)
Withdrew from study		286 (9.6%)	89 (3.0%)
Reason	Adverse event	23 (0.8%)	3 (0.1%)
	Serious adverse event	13 (0.4%)	2 (0.1%)
	Patient preference	194 (6.5%)	61 (2.1%)
	GP recommendation	12 (0.4%)	1 (0.0%)
	Non-acceptance of randomisation decision	0 (0.0%)	3 (0.1%)
	Blood sample unobtainable	1 (0.03%)	0 (0.0%)
	Limited resource for research	7 (0.2%)	4 (0.1%)
	Relocated and cannot retain	11 (0.4%)	5 (0.2%)
	Protocol violator	20 (0.7%)	8 (0.3%)
	Other	4 (0.1%)	0 (0.0%)
	Screening eGFR is <30 ml/minute/1.73 m^2	1 (0.03%)	2 (0.1%)

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The reasons for withdrawal from randomised treatment (allopurinol) are given in *Table 3*.

The two most common reasons for withdrawal from randomised treatment (allopurinol) were adverse event followed by patient preference.

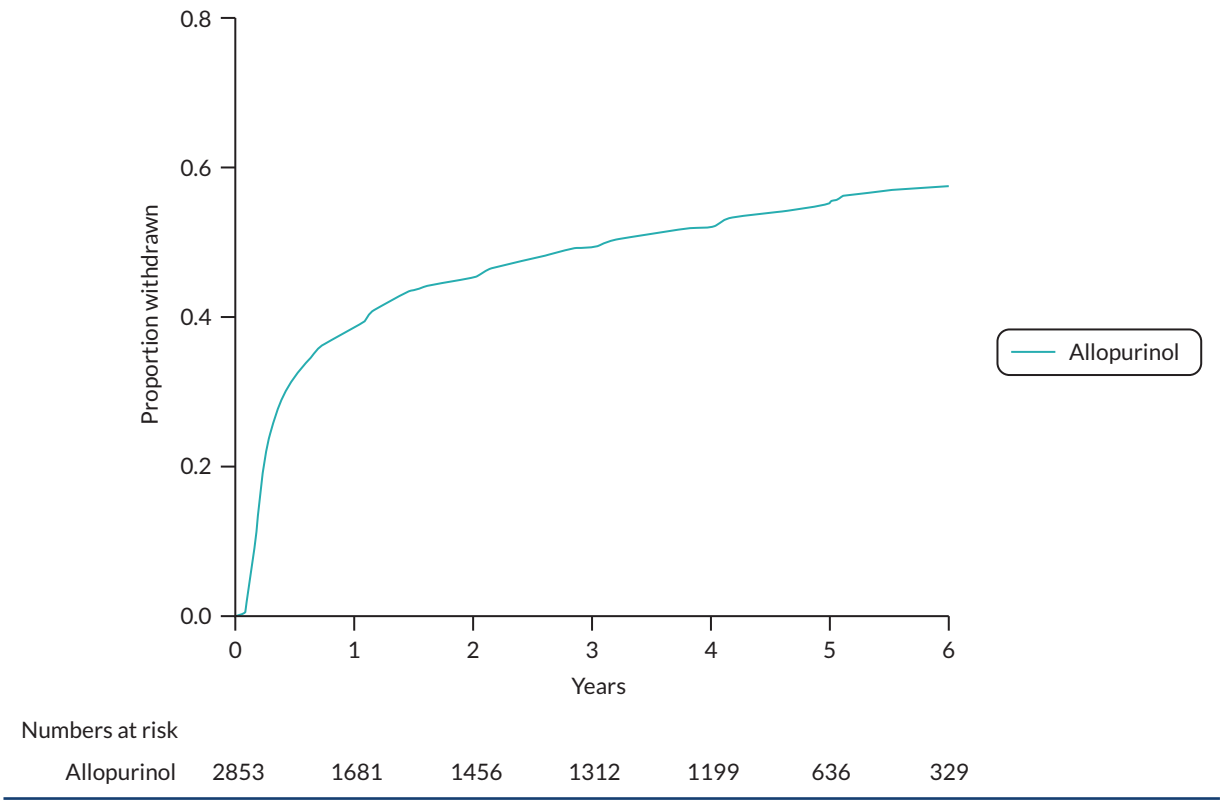


FIGURE 4 Cumulative incidence function – withdrawal from randomised treatment. Randomised mITT analysis set: allopurinol arm (*n* = 2853).

TABLE 3 Reasons for permanent withdrawal from allopurinol in the allopurinol arm [randomised set: allopurinol arm (*n* = 2979)]

		Allopurinol (*n* = 2979)
Permanent withdrawal from allopurinol		1653 (55.5%)
Reason	Adverse event	853 (28.6%)
	Serious adverse event	61 (2.0%)
	Patient preference	448 (15.0%)
	GP recommendation	106 (3.6%)
	Non-acceptance of randomisation decision	1 (0.03%)
	Other	62 (2.1%)
	Screening eGFR is <30 ml/minute 1.73 m^2	0 (0.0%)
	Medical advice	25 (0.8%)
	Not started	75 (2.5%)
	Prescription problem	7 (0.2%)
	Protocol violator	4 (0.1%)
	Unknown	11 (0.4%)

The baseline characteristics of the mITT analysis population (*n* = 5721) are given in *Tables 4–7*. Overall, the mean age at entry to the study was 72.0 years (SD 6.8), 4321 (75.5%) participants were male and 5676 (99.2%) were white.

TABLE 4 Baseline characteristics in all randomised participants in the mITT analysis population (*n* = 5721)

	Allopurinol (*n* = 2853)	Usual care (*n* = 2868)
Age		
Mean (SD), years	71.9 (6.7)	72.0 (6.8)
Sex		
Male	2168 (76.0%)	2153 (75.1%)
Female	685 (24.0%)	713 (24.9%)
Transgender	0 (0.0%)	2 (0.1%)
Ethnicity		
White	2831 (99.2%)	2845 (99.2%)
Asian/Asian British	13 (0.5%)	14 (0.5%)
Black/African/Caribbean/black British	4 (0.1%)	0 (0.0%)
Mixed/multiple ethnic groups	2 (0.1%)	4 (0.1%)
Other	3 (0.1%)	5 (0.2%)
Smoking history		
Current	253 (8.9%)	291 (10.1%)
Former	1644 (57.6%)	1587 (55.3%)
Never	956 (33.5%)	990 (34.5%)
Systolic blood pressure		
Mean (SD), mmHg	132.0 (17.8)	133.2 (17.9)
Diastolic blood pressure[a]		
Mean (SD), mmHg	72.0 (10.5)	72.5 (10.7)
Body mass index		
Mean (SD), kg/m^2	28.9 (4.9)	28.8 (4.9)
Baseline eGFR group		
30–44 ml/minute/1.73 m^2	52 (1.8%)	56 (2.0%)
45–59 ml/minute/1.73 m^2	201 (7.0%)	231 (8.1%)
≥60 ml/minute/1.73 m^2	2600 (91.1%)	2581 (90.0%)
Baseline SUA[b]		
Mean (SD), mmol/l	0.35 (0.08)	0.34 (0.08)

a Based on 2867 patients with data in the usual care group.
b Based on 2841 patients with data in the allopurinol group and 2857 in the usual care group.
c Based on 2807 patients with data in the allopurinol group and 2808 in the usual care group.

Note
Data are mean (SD) or *n* (%).

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TABLE 5 Baseline medical history in all randomised participants in the mITT analysis population (*n* = 5721)

	Allopurinol (*n* = 2853)	Usual care (*n* = 2868)
CV history		
MI	1348 (47.2%)	1356 (47.3%)
Angina	1845 (64.7%)	1824 (63.6%)
CCS Angina grade		
Grade 0	618 (21.7%)	646 (22.5%)
Grade I	755 (26.5%)	702 (24.5%)
Grade II	403 (14.1%)	411 (14.3%)
Grade III	61 (2.1%)	54 (1.9%)
Grade IV	8 (0.3%)	11 (0.4%)
No angina	1008 (35.3%)	1044 (36.4%)
Other evidence of IHD	1972 (69.1%)	2000 (69.7%)
Duration of IHD	10.2 (5.0, 16.3)	10.0 (5.1, 16.0)
Median (IQR), years		
Coronary revascularisation	1612 (56.5%)	1626 (56.7%)
Peripheral arterial revascularisation	144 (5.0%)	159 (5.5%)
Peripheral arterial disease	199 (7.0%)	228 (7.9%)
Cerebrovascular accident/stroke	122 (4.3%)	108 (3.8%)
Transient ischaemic attack	188 (6.6%)	166 (5.8%)
Hypertension	1624 (56.9%)	1663 (58.0%)
HF	146 (5.1%)	149 (5.2%)
NYHA Class I	77 (2.7%)	83 (2.9%)
NYHA Class II	69 (2.4%)	66 (2.3%)
No HF	2707 (94.9%)	2719 (94.8%)
Dyslipidaemia	1817 (63.7%)	1806 (63.0%)
Other medical history		
Chronic obstructive pulmonary disease	244 (8.6%)	251 (8.8%)
Diabetes mellitus	618 (21.7%)	623 (21.7%)
Type I	24 (0.8%)	18 (0.6%)
Type II	594 (20.8%)	605 (21.1%)
No diabetes	2235 (78.3%)	2245 (78.3%)

CCS, Canadian Cardiovascular Society.

Note
Data are *n* (%) or median (IQR).

Allopurinol dose taken and adherence to randomised therapy

The most commonly taken daily dose of allopurinol in the study was 600 mg. The median daily dose of 600 mg was observed at all time points following randomisation when considering all participants,

TABLE 6 Baseline concomitant medications in all randomised participants in the mITT analysis population (*n* = 5721)

	Allopurinol (*n* = 2853)	Usual care (*n* = 2868)
Statins	2583 (90.5%)	2558 (89.2%)
Ezetimibe	93 (3.3%)	87 (3.0%)
Antiplatelet agents	2491 (87.3%)	2504 (87.3%)
Anticoagulants	253 (8.9%)	260 (9.1%)
Beta blockers	1877 (65.8%)	1835 (64.0%)
ACE inhibitors	1356 (47.5%)	1365 (47.6%)
Angiotensin receptor antagonists	530 (18.6%)	543 (18.9%)
Calcium channel blockers	848 (29.7%)	806 (28.1%)
Other anti-anginal medications	1602 (56.2%)	1495 (52.1%)
Loop diuretics	273 (9.6%)	238 (8.3%)
Thiazide/thiazide-like diuretics	214 (7.5%)	201 (7.0%)
Diabetes medication: insulin	110 (3.9%)	80 (2.8%)
Diabetes medication: non-insulin	448 (15.7%)	435 (15.2%)
Non-steroidal anti-inflammatory drugs	118 (4.1%)	141 (4.9%)

ACE, angiotensin converting enzyme.

Note
Data are *n* (%).

TABLE 7 Baseline quality-of-life data in randomised participants in the mITT analysis population (*n* = 5721)

	Allopurinol (*n* = 2853)	Usual care (*n* = 2868)
EQ-5D-5L[a]		
Health state score	0.814 (0.197)	0.821 (0.186)
Visual analogue score	78.9 (16.7)	78.8 (16.2)
Seattle angina questionnaire		
Physical limitation domain[b]	87.8 (19.0)	88.0 (18.5)
Angina stability domain	50.5 (9.7)	50.7 (9.8)
Angina frequency domain	90.8 (17.7)	91.7 (16.7)
Treatment satisfaction domain	95.1 (9.9)	95.0 (10.0)
Disease perception domain	84.8 (18.0)	84.4 (18.2)

a Based on 2846 patients with data in the allopurinol group and 2857 in the usual care group.
b Based on 2495 patients with data in the allopurinol group and 2501 in the usual care group.

Note
Data are mean (SD).

or only those with eGFR ≥ 60 ml/minute/1.7 m^2 at screening visit; a median daily dose of 300 mg was observed at all time points following randomisation in those with eGFR < 60 ml/minute/1.7 m^2 at screening visit. Of those participants still taking allopurinol at each time point after randomisation, 1851 (84.8%) of 2184 participants were still taking the 600 mg daily dose at 6 weeks, 1199 (82.0%) of 1462 participants at 1 year, 1037 (80.4%) of 1290 participants at 2 years, 925 (78.7%) of 1175 participants

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at 3 years and 719 (82.5%) of 871 participants at 4 years. The mean daily allopurinol dose for all participants taking allopurinol was 543.8 mg at 1 year and 532 mg at the end of the study.

The total number of participants who withdrew from allopurinol therapy was 1653 (55.5%), with 853 of these being associated with adverse events, although not all of these were necessarily treatment-related events. The most common adverse event associated with withdrawal from allopurinol therapy was rash. For safety reasons, participants were withdrawn from allopurinol therapy if they experienced a rash that could have been associated with allopurinol treatment.

Two thousand four hundred and forty-seven participants in the allopurinol group had SUA measured at baseline and at 6 weeks after randomisation, and in this group, SUA concentrations decreased from 0.34 mmol/l (SD 0.08) to 0.18 mmol/l (SD 0.09). Forty-five participants assigned to the usual care group started taking allopurinol during follow-up for clinical reasons (e.g. gout).

Primary endpoint

There was no evidence of a difference in the rates of the primary endpoint between the allopurinol and usual care groups (*Figure 5*). Three hundred and fourteen (11.0%) of 2853 participants in the allopurinol group (2.47 events per 100 patient-years) and 325 (11.3%) of 2868 participants in the usual care group (2.37 events per 100 patient-years) had a primary endpoint [HR 1.04 (95% CI 0.89 to 1.21); $p = 0.65$].

Similarly, there was no evidence of a difference between the randomised treatment groups in rates of the secondary time-to-event outcomes of non-fatal MI (*Figure 6*), non-fatal stroke (*Figure 7*), CV death (*Figure 8*) or all-cause mortality (*Figure 9*).

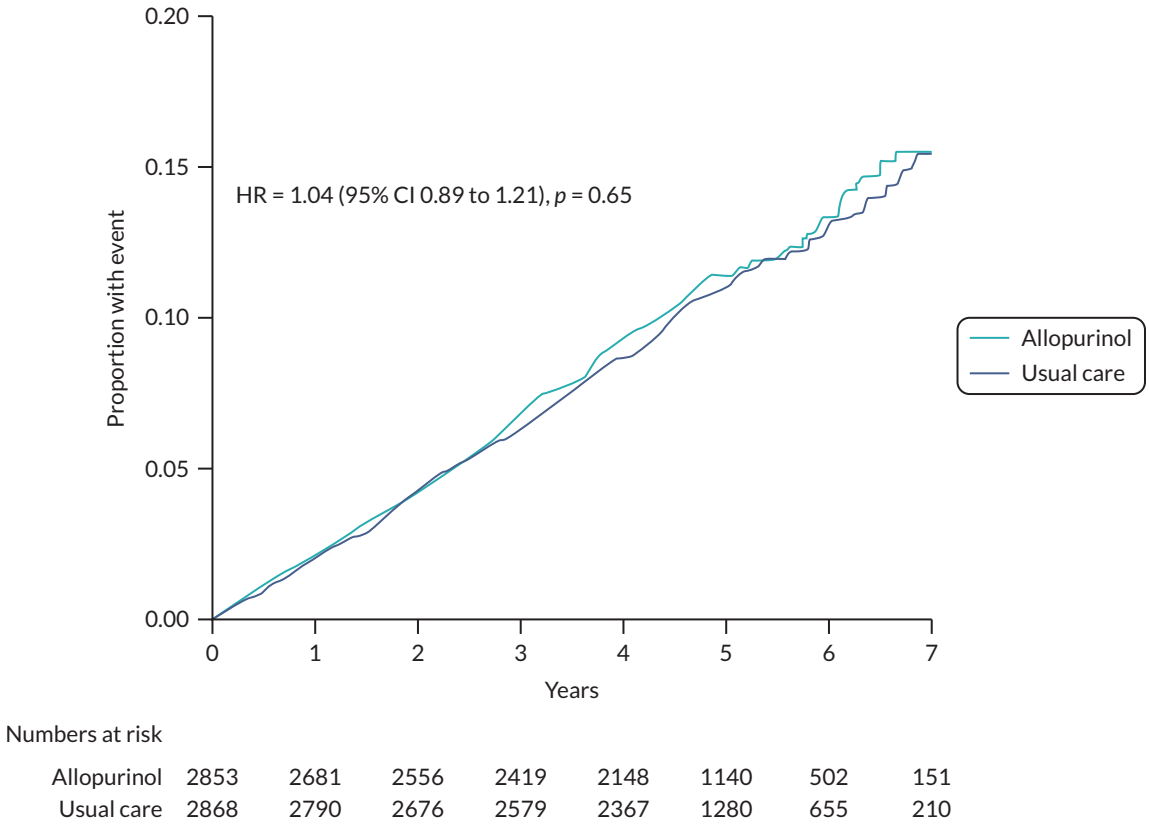
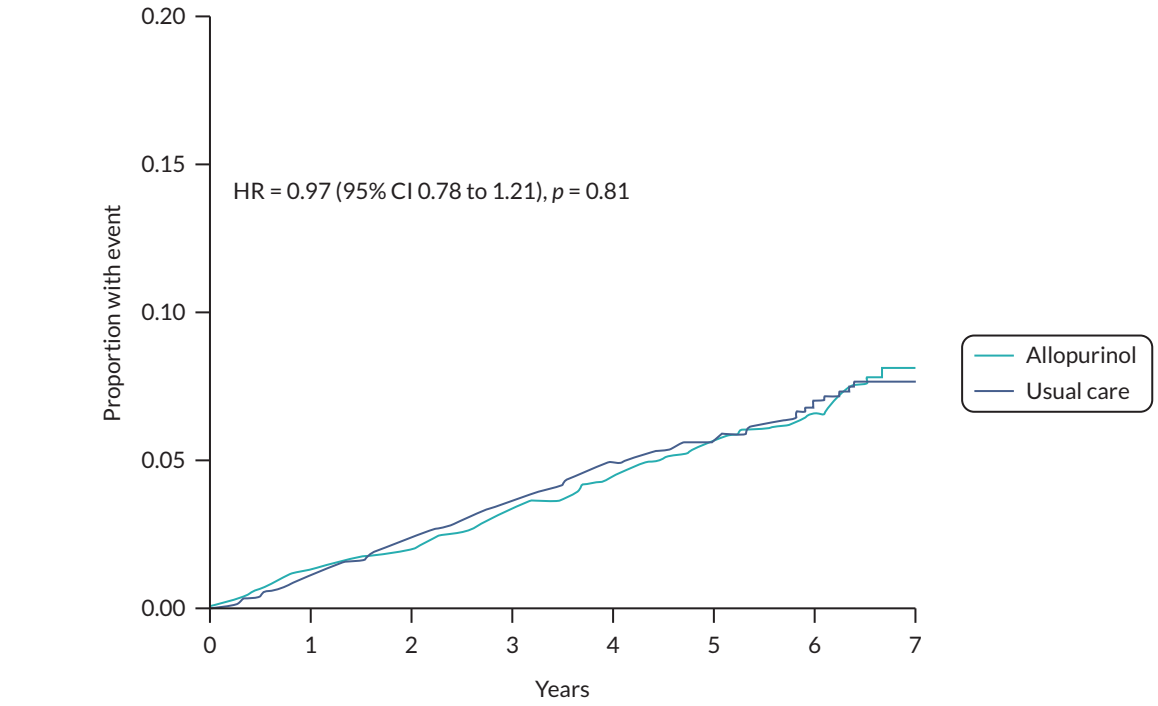


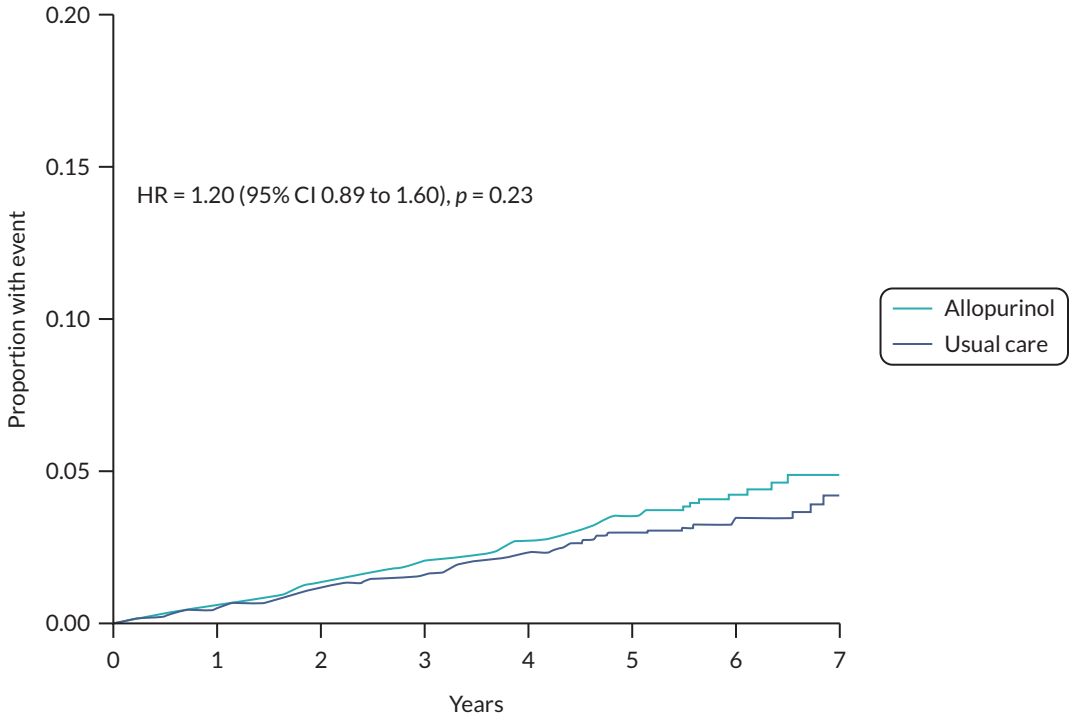
FIGURE 5 Cumulative incidence functions for the primary composite endpoint of non-fatal MI, non-fatal stroke or CV death analysed in the mITT population ($n = 5721$). Note: The figure was adjusted for the competing risk of deaths not included in the endpoint.



Numbers at risk

Allopurinol	2853	2693	2582	2460	2192	1170	520	159
Usual care	2868	2803	2701	2611	2414	1312	671	218

FIGURE 6 Cumulative incidence functions for non-fatal MI analysed in the mITT population (n = 5721). Note: The figure was adjusted for the competing risk of deaths not included in the endpoint.

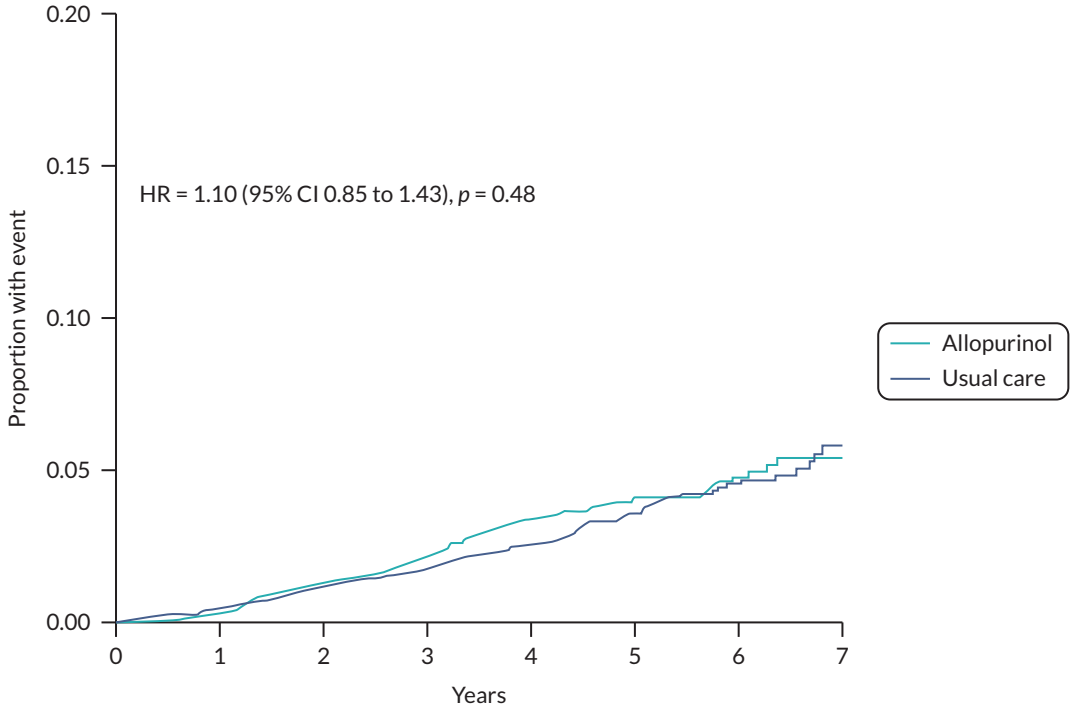


Numbers at risk

Allopurinol	2853	2716	2599	2495	2233	1199	536	161
Usual care	2868	2820	2731	2655	2469	1348	694	225

FIGURE 7 Cumulative incidence functions for non-fatal stroke analysed in the mITT population (n = 5721). Note: The figure was adjusted for the competing risk of deaths not included in the endpoint.

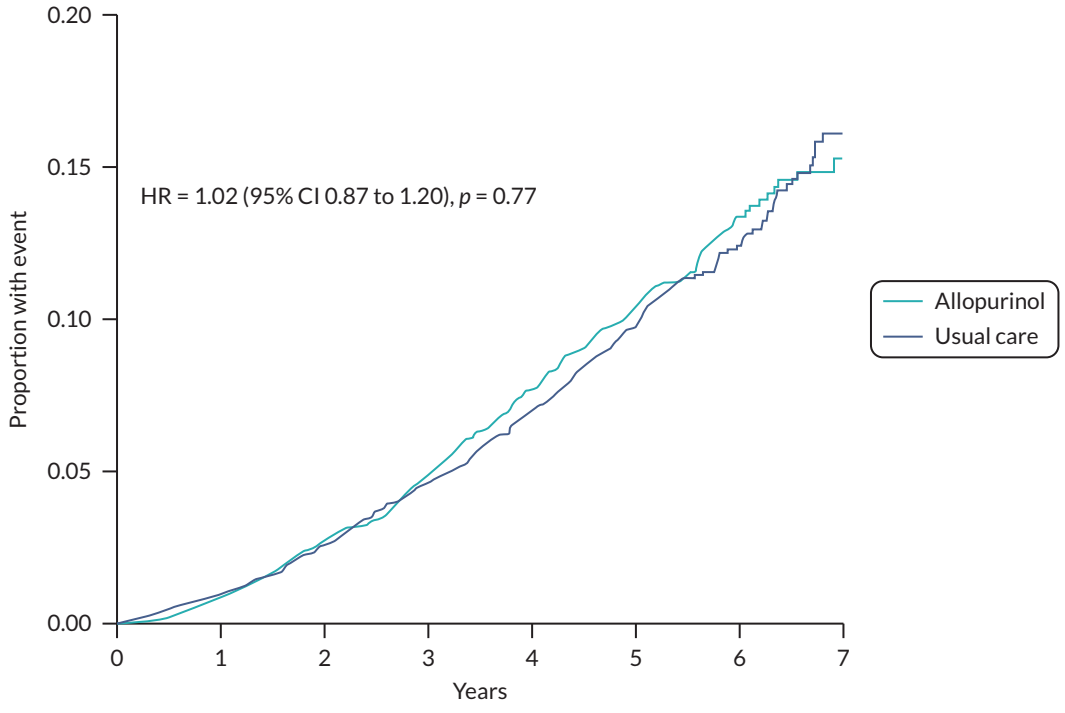
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Numbers at risk

Allopurinol	2853	2730	2629	2540	2283	1232	557	171
Usual care	2868	2834	2760	2694	2521	1381	713	233

FIGURE 8 Cumulative incidence functions for CV death analysed in the mITT population (*n* = 5721). Note: The figure was adjusted for the competing risk of deaths not included in the endpoint.



Numbers at risk

Allopurinol	2853	2730	2629	2540	2283	1232	557	171
Usual care	2868	2834	2760	2694	2521	1381	713	233

FIGURE 9 Kaplan–Meier curve for all-cause mortality analysed in the mITT population (*n* = 5721).

TABLE 8 Primary and secondary time-to-event outcomes in the mITT analysis population (*n* = 5721)

Outcome	Allopurinol group (*n* = 2853)		Usual care group (*n* = 2868)		
	n (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years	HR (95% CI); *p*-value
Primary outcome					
Non-fatal MI, non-fatal stroke or CV death	314 (11.0%)	2.47	325 (11.3%)	2.37	1.04 (0.89 to 1.21); *p* = 0.65
Secondary time-to-event outcomes					
Non-fatal MI	156 (5.5%)	1.21	172 (6.0%)	1.24	0.97 (0.78 to 1.21); *p* = 0.81
Non-fatal stroke	96 (3.4%)	0.74	86 (3.0%)	0.61	1.20 (0.89 to 1.60); *p* = 0.23
CV death	112 (3.9%)	0.85	109 (3.8%)	0.76	1.10 (0.85 to 1.43); *p* = 0.48
All-cause mortality	288 (10.1%)	2.18	303 (10.6%)	2.13	1.02 (0.87 to 1.20); *p* = 0.77
Hospitalisation for ACS	205 (7.2%)	1.61	217 (7.6%)	1.59	1.01 (0.84 to 1.23); *p* = 0.90
Coronary revascularisation	176 (6.2%)	1.38	207 (7.2%)	1.51	0.91 (0.74 to 1.11); *p* = 0.35
Hospitalisation for ACS or coronary revascularisation	267 (9.4%)	2.13	299 (10.4%)	2.22	0.95 (0.81 to 1.13); *p* = 0.57
Hospitalisation for HF	74 (2.6%)	0.57	97 (3.4%)	0.69	0.81 (0.60 to 1.10); *p* = 0.18
All CV hospitalisations	518 (18.2%)	4.32	556 (19.4%)	4.31	1.00 (0.88 to 1.12); *p* = 0.94

Two hundred and eighty-eight (10.1%) participants in the allopurinol group and 303 (10.6%) participants in the usual care group died from any cause [HR 1.02 (95% CI 0.87 to 1.20); *p* = 0.77].

There was no evidence of a difference in rates of any of the other pre-specified secondary time-to-event outcomes (hospitalisation for ACS, coronary revascularisation, hospitalisation for ACS or coronary revascularisation, hospitalisation for HF, and all CV hospitalisations) between randomised treatment groups. All primary and secondary time-to-event outcomes in each randomised treatment group, along with rates of events per 100 patient-years, HRs and *p*-values (calculated with the Wald test) are summarised in the mITT analysis population in *Table 8*.

Subgroup analysis

A pre-specified subgroup analysis showed that results for the primary endpoint were consistent across all subgroups (*Figures 10* and *11*).

On-treatment analysis

A supporting OT analysis showed results for the time-to-event analyses that were broadly similar to those by the mITT analysis (*Table 9*).

Quality-of-life outcomes

No evidence for a difference in quality-of-life outcomes in the treatment groups was found, with no differences in EQ-5D-5L outcomes or Seattle angina questionnaire outcomes at the end of the first year (*Table 10*), except for a nominally significant but only slightly greater fall in the usual care group in the physical domain score of the Seattle angina questionnaire at the end of the first year [treatment difference 1.219 (95% CI 0.027 to 2.410); *p* = 0.045], or at the final visit (*Table 11*).

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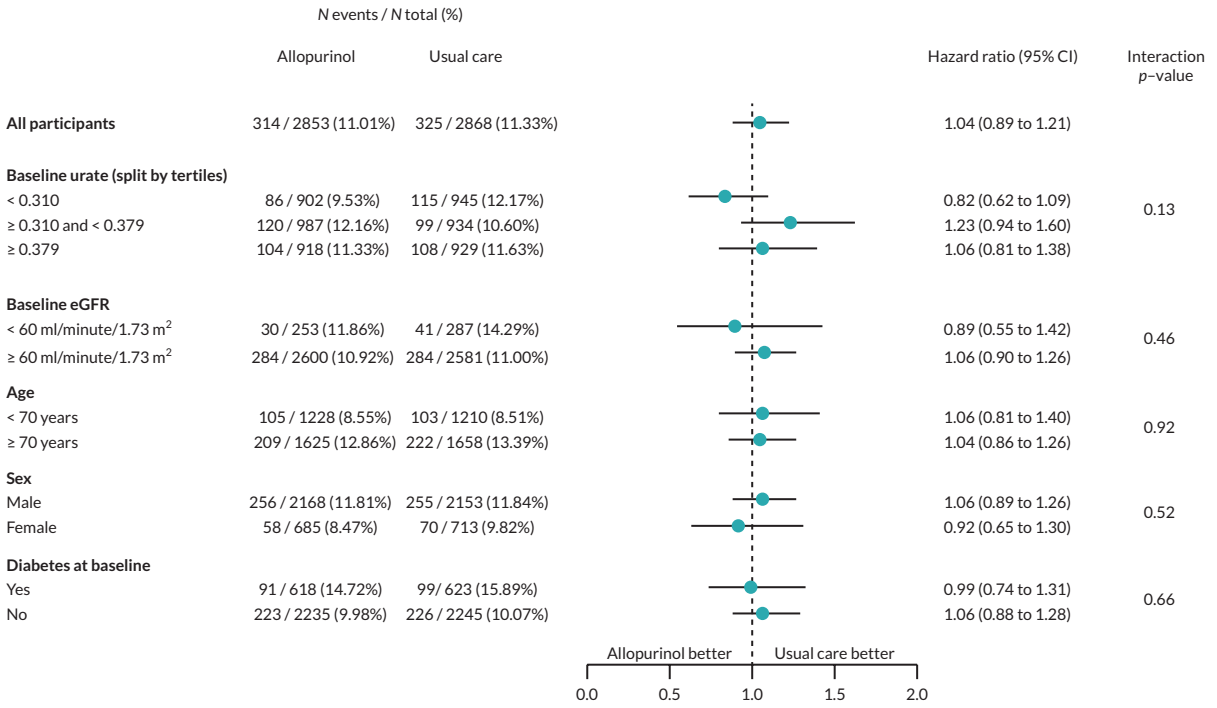


FIGURE 10 Forest plot (1) for primary endpoint for intention-to-treat subgroup analysis – randomised mITT analysis set (*n* = 5721).

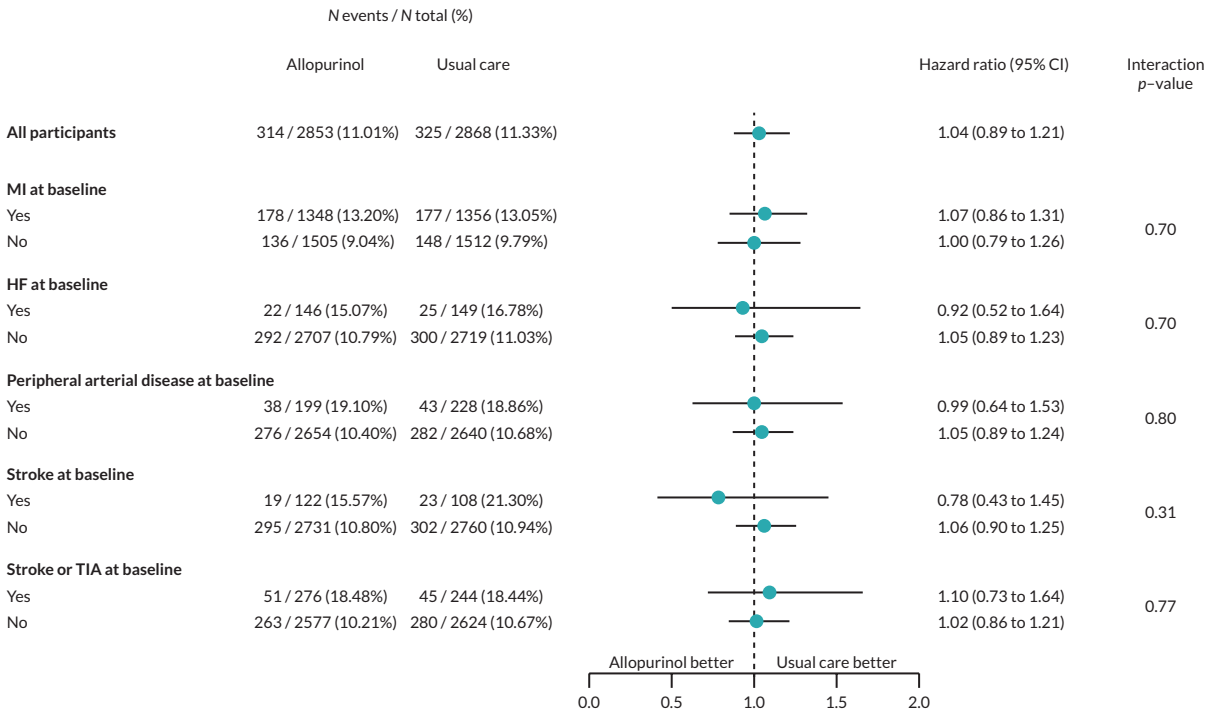


FIGURE 11 Forest plot (2) for primary endpoint for intention-to-treat subgroup analysis – randomised mITT analysis set (*n* = 5721). TIA, transient ischaemic attack.

TABLE 9 Primary and secondary time outcomes – OT analysis, allopurinol relative to usual care [randomised mITT analysis set (*n* = 5721)]

Outcome	Allopurinol group (*n* = 2853)		Usual care group (*n* = 2868)		
	n (%)	Rate per 100 patient-years	*n* (%)	Rate per 100 patient-years	HR (95% CI); *p*-value
Primary outcome					
Primary outcome – non-fatal MI, non-fatal stroke or CV death	172 (6.0%)	2.30	325 (11.3%)	2.37	0.98 (0.81 to 1.18); *p* = 0.81
Secondary time-to-event outcomes					
Non-fatal MI	75 (2.6%)	0.99	172 (6.0%)	1.24	0.80 (0.61 to 1.05); *p* = 0.10
Non-fatal stroke	59 (2.1%)	0.78	86 (3.0%)	0.61	1.27 (0.91 to 1.78); *p* = 0.16
CV death	62 (2.2%)	0.81	109 (3.8%)	0.76	1.10 (0.80 to 1.50); *p* = 0.55
All-cause mortality	153 (5.4%)	1.99	303 (10.6%)	2.13	0.99 (0.82 to 1.20); *p* = 0.93
Hospitalisation for ACS	107 (3.8%)	1.43	217 (7.6%)	1.59	0.88 (0.70 to 1.11); *p* = 0.28
Coronary revascularisation	93 (3.3%)	1.24	207 (7.2%)	1.51	0.81 (0.63 to 1.03); *p* = 0.085
Hospitalisation for ACS or coronary revascularisation	142 (5.0%)	1.91	299 (10.4%)	2.22	0.84 (0.69 to 1.02); *p* = 0.085
Hospitalisation for HF	34 (1.2%)	0.44	97 (3.4%)	0.69	0.66 (0.44 to 0.97); *p* = 0.036
All CV hospitalisations	282 (9.9%)	3.93	556 (19.4%)	4.31	0.90 (0.78 to 1.04); *p* = 0.17

TABLE 10 Secondary quality-of-life outcomes (EQ-5D-5L and Seattle angina questionnaire) in the mITT population at 1 year from randomisation

Outcome	Allopurinol group (*n* = 2853)	Usual care group (*n* = 2868)	
	Change from baseline at 1 year from randomisation [mean (SD)]	Change from baseline at 1 year from randomisation [mean (SD)]	Estimated difference (95% CI); *p*-value
Secondary EQ-5D-5L outcomes			
Health state score[a]	−0.081 (0.205)	−0.094 (0.202)	0.009 (−0.002 to 0.020); *p* = 0.11
Visual analogue score[b]	−4.67 (17.11)	−4.98 (16.96)	0.114 (−0.839 to 1.066); *p* = 0.81
Secondary Seattle angina questionnaire scores			
Physical limitation domain[c]	−12.50 (18.85)	−13.90 (18.84)	1.219 (0.027 to 2.410); *p* = 0.045
Angina stability domain[d]	0.81 (15.90)	0.35 (15.67)	0.194 (−0.669 to 1.057); *p* = 0.66
Angina frequency domain[e]	−0.45 (15.92)	−1.48 (15.42)	0.167 (−0.814 to 1.148); *p* = 0.74
Treatment satisfaction domain[f]	−1.85 (12.27)	−2.39 (13.02)	0.064 (−0.760 to 0.888): *p* = 0.88

continued

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TABLE 10 Secondary quality-of-life outcomes (EQ-5D-5L and Seattle angina questionnaire) in the mITT population at 1 year from randomisation (*continued*)

Outcome	Allopurinol group (*n* = 2853) Change from baseline at 1 year from randomisation [mean (SD)]	Usual care group (*n* = 2868) Change from baseline at 1 year from randomisation [mean (SD)]	Estimated difference (95% CI); *p*-value
Disease perception domain[g]	−4.16 (18.17)	−5.16 (18.35)	0.622 (−0.371 to 1.615); *p* = 0.22

a Changes are based on 2067 participants with data in the allopurinol group and 2237 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
b Changes are based on 2064 participants with data in the allopurinol group and 2248 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
c Changes are based on 1875 participants with data in the allopurinol group and 1996 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
d Changes are based on 2183 participants with data in the allopurinol group and 2354 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
e Changes are based on 2221 participants with data in the allopurinol group and 2419 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
f Changes are based on 2186 participants with data in the allopurinol group and 2392 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
g Changes are based on 2154 participants with data in the allopurinol group and 2349 in the usual care group. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.

Health resource usage

Table 12 shows the results of the self-reported health resource usage in the preceding 12 months (visits to GP, community or practice nurse, physiotherapist, doctor in hospital outpatient clinic) collected at 1 year and at the end of the study in the allopurinol group and the usual care group. There was a lower number of reported visits to the GP at the end of the study in the allopurinol arm and a lower number of reported visits to the physiotherapist at 1 year in the allopurinol arm. However, the mean number of reported visits was generally low, and it is not clear whether these slight differences are meaningful, clinically or economically. Otherwise, self-reported health resource usage was similar in both arms of the study.

TABLE 11 Secondary quality-of-life outcomes (EQ-5D-5L and Seattle angina questionnaire) at final visit in the mITT population

Outcome	Allopurinol Change from baseline at final visit [mean (SD)]	Usual care Change from baseline at final visit [mean (SD)]	Estimated difference (95% CI); *p*-value
Secondary EQ-5D-5L outcomes at final visit			
Health state score[a]	−0.212 (0.338)	−0.219 (0.324)	0.0046 (−0.0110 to 0.0203); *p* = 0.56
Visual analogue score[b]	−6.01 (17.97)	−7.95 (18.69)	−0.356 (−1.823 to 1.110); *p* = 0.63
Secondary Seattle angina questionnaire scores at final visit			
Physical limitation domain[c]	−15.5 (20.77)	−18.2 (22.00)	0.400 (−1.314 to 2.114); *p* = 0.65
Angina stability domain[d]	0.77 (14.00)	−0.03 (15.44)	−0.586 (−1.763 to 0.590); *p* = 0.33

TABLE 11 Secondary quality-of-life outcomes (EQ-5D-5L and Seattle angina questionnaire) at final visit in the mITT population (*continued*)

Outcome	Allopurinol Change from baseline at final visit [mean (SD)]	Usual care Change from baseline at final visit [mean (SD)]	Estimated difference (95% CI); *p*-value
Angina frequency domain[e]	0.23 (16.07)	−1.33 (16.41)	−1.059 (−2.873 to 0.755); $p = 0.25$
Treatment satisfaction domain[f]	−3.84 (14.26)	−4.06 (14.44)	−1.496 (−3.099 to 0.106); $p = 0.067$
Disease perception domain[g]	−4.80 (19.57)	−5.71 (20.33)	−0.668 (−2.442 to 1.106); $p = 0.46$

a Changes are based on allopurinol *N* = 1466, usual care *N* = 1776. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
b Changes are based on allopurinol *N* = 1209, usual care *N* = 1534. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
c Changes are based on allopurinol *N* = 1054, usual care *N* = 1331. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
d Changes are based on allopurinol *N* = 1200, usual care *N* = 1511. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
e Changes are based on allopurinol *N* = 1207, usual care *N* = 1523. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
f Changes are based on allopurinol *N* = 1205, usual care *N* = 1540. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.
g Changes are based on allopurinol *N* = 1186, usual care *N* = 1509. Estimates and CIs are based on 2846 participants in the allopurinol group and 2857 in the usual care group following multiple imputations.

TABLE 12 Self-reported health resource usage in the preceding 12 months at 1 year and at the end of the study in the allopurinol and usual care arms

		Allopurinol (*n* = 2853)		Usual care (*n* = 2868)		*p*-value
Number of GP visits	1 year	*N* = 2223	3.09 (3.30)	*N* = 2427	3.27 (3.89)	
			2 (1, 4)		2 (1, 4)	0.064
	End of study	*N* = 1241	1.46 (2.52)	*N* = 1593	1.66 (2.59)	
			1 (0, 2)		1 (0, 2)	0.016
Number of practice or community nurse visits	1 year	*N* = 2224	2.45 (4.35)	*N* = 2427	2.42 (4.09)	
			1 (1, 3)		2 (1, 3)	0.15
	End of study	*N* = 1238	1.98 (4.71)	*N* = 1593	1.92 (9.14)	
			1 (0, 2)		1 (0, 2)	0.38
Number of physiotherapist visits	1 year	*N* = 2228	0.48 (1.64)	*N* = 2434	0.57 (1.99)	
			0 (0, 0)		0 (0, 0)	0.027
	End of study	*N* = 1240	0.46 (2.06)	*N* = 1592	0.39 (1.82)	
			0 (0, 0)		0 (0, 0)	0.99
Number of visits to doctor at a hospital outpatient clinic	1 year	*N* = 2227	1.24 (2.34)	*N* = 2431	1.26 (2.19)	
			0 (0, 2)		0 (0, 2)	0.44
	End of study	*N* = 1239	1.05 (2.47)	*N* = 1592	0.97 (3.16)	
			0 (0, 1)		0 (0, 1)	0.39

Note
Data are number with data, mean (SD) and median (IQR) of those with data. *p*-value obtained from stratified Wilcoxon test.

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Serious adverse events

There was no evidence of a difference in the rates of SAEs between the allopurinol and usual care groups, except for endocrine disorders, where there were no participants with events in the allopurinol group and 14 in the usual care group (*Table 13*). The endocrine events were of several different types and no pattern of an excess of any one type of endocrine event was seen.

TABLE 13 Serious adverse events during the study, by system organ class, in the safety population

System organ class	Allopurinol (*N* = 2805)	Usual care (*N* = 2868)	Difference in rates (95% CI)
Any SAE	2036 (29.70)	2194 (30.32)	−0.62 (−2.43 to 1.19)
Blood and lymphatic system	99 (0.77)	96 (0.69)	0.09 (−0.12 to 0.29)
Cardiac	577 (4.92)	671 (5.34)	−0.42 (−0.99 to 0.15)
Congenital familial and genetic	24 (0.18)	18 (0.13)	0.06 (−0.04 to 0.15)
Ear and labyrinth	10 (0.08)	21 (0.15)	−0.07 (−0.15 to 0.01)
Endocrine	0 (0.00)	14 (0.10)	–
Eye	357 (2.94)	383 (2.90)	0.05 (−0.38 to 0.47)
Gastrointestinal	538 (4.61)	572 (4.51)	0.10 (−0.44 to 0.64)
General and administration site	288 (2.34)	281 (2.08)	0.26 (−0.10 to 0.63)
Hepatobiliary	79 (0.61)	65 (0.46)	0.15 (−0.02 to 0.33)
Immune system	6 (0.05)	8 (0.06)	−0.01 (−0.06 to 0.04)
Infections and infestations	414 (3.39)	491 (3.72)	−0.33 (−0.79 to 0.13)
Injury poisoning and procedural	251 (2.01)	269 (1.97)	0.05 (−0.30 to 0.39)
Investigations	125 (0.98)	162 (1.17)	−0.19 (−0.43 to 0.06)
Metabolism and nutrition	110 (0.86)	104 (0.74)	0.12 (−0.10 to 0.33)
Musculoskeletal and connective tissue	324 (2.66)	347 (2.62)	0.04 (−0.36 to 0.44)
Neoplasms benign malignant and unspecified	485 (4.04)	561 (4.34)	−0.30 (−0.81 to 0.20)
Nervous system	295 (2.39)	321 (2.37)	0.02 (−0.36 to 0.39)
Product	1 (0.01)	1 (0.01)	0.00 (−0.02 to 0.02)
Psychiatric	41 (0.32)	36 (0.25)	0.06 (−0.07 to 0.19)
Renal and urinary	143 (1.12)	161 (1.16)	−0.04 (−0.29 to 0.22)
Reproductive system and breast	51 (0.39)	64 (0.45)	−0.06 (−0.22 to 0.09)
Respiratory thoracic and mediastinal	236 (1.88)	277 (2.04)	−0.16 (−0.49 to 0.18)
Skin and subcutaneous tissue	40 (0.31)	51 (0.36)	−0.05 (−0.19 to 0.09)
Social circumstances	2 (0.02)	8 (0.06)	−0.04 (−0.09 to 0.00)
Surgical and medical procedures	328 (2.69)	403 (3.07)	−0.38 (−0.79 to 0.04)
Vascular	279 (2.25)	299 (2.21)	0.03 (−0.33 to 0.40)

Note
Data are numbers (rates per 100 patient-years) and differences in rates (95% CIs).

Fifteen participants in the allopurinol group had SAEs that were considered to be potentially treatment-related. There were 278 fatal SAEs in the allopurinol group, none of which were considered to be treatment-related. The rates of incident cancers were not different between treatment groups (*Table 14*).

Adjudicated causes of death were well balanced between the treatment groups (*Table 15*).

COVID-19 and COVID-19 pneumonia deaths and serious adverse events

Nine deaths (0.3%) in the allopurinol group and 11 deaths (0.4%) in the usual care group were adjudicated as being due to COVID-19. Seven deaths (0.2%) in the allopurinol group and seven deaths (0.2%) in the usual care group were adjudicated as being due to COVID-19 pneumonia. There were no differences between treatment groups in the numbers of participants with SAEs related to COVID-19 [30 (1.1%) in the allopurinol group vs. 31 (1.1%) in the usual care group], or COVID-19 pneumonia [9 (0.3%) in the allopurinol group vs. 8 (0.3%) in the usual care group].

TABLE 14 Non-benign incident cancers by type during the study in the safety analysis set (*n* = 5673)

	Allopurinol (*N* = 2805)	Usual care (*N* = 2868)	Difference in rates (95% CI)
Any	400 (3.27)	457 (3.46)	−0.19 (−0.64 to 0.26)
Breast neoplasms (including nipple)	12 (0.09)	14 (0.10)	−0.01 (−0.08 to 0.07)
Endocrine neoplasms	2 (0.02)	2 (0.01)	0.00 (−0.03 to 0.03)
Gastrointestinal neoplasms	53 (0.41)	62 (0.44)	−0.03 (−0.19 to 0.12)
Haematological/blood cancers	32 (0.25)	39 (0.28)	−0.03 (−0.15 to 0.09)
Hepatobiliary neoplasms	9 (0.07)	7 (0.05)	0.02 (−0.04 to 0.08)
Mesotheliomas	3 (0.02)	3 (0.02)	0.00 (−0.03 to 0.04)
Metastases	1 (0.01)	4 (0.03)	−0.02 (−0.05 to 0.01)
Miscellaneous and site unspecified neoplasms	22 (0.17)	33 (0.23)	−0.06 (−0.17 to 0.04)
Nervous system neoplasms	3 (0.02)	4 (0.03)	−0.01 (−0.04 to 0.03)
Ocular neoplasms	9 (0.07)	11 (0.08)	−0.01 (−0.07 to 0.06)
Renal and urinary tract neoplasms	36 (0.28)	33 (0.23)	0.04 (−0.08 to 0.17)
Reproductive cancers	95 (0.74)	82 (0.58)	0.16 (−0.04 to 0.35)
Respiratory and mediastinal neoplasms	40 (0.31)	57 (0.40)	−0.09 (−0.24 to 0.05)
Skeletal neoplasms	0 (0.00)	1 (0.01)	–
Skin neoplasms	126 (0.99)	153 (1.11)	−0.12 (−0.37 to 0.13)
Soft-tissue neoplasms	1 (0.01)	1 (0.01)	0.00 (−0.02 to 0.02)

Note
Data are numbers (rates per 100 patient-years) and differences in rates (95% CIs).

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TABLE 15 Adjudicated causes of death – mITT analysis set (*n* = 5721)

		Allopurinol (*N* = 2853)	Usual care (*N* = 2868)
Cause of death	CV	108 (3.8%)	107 (3.7%)
	Non-CV	176 (6.2%)	194 (6.8%)
	Undetermined cause	4 (0.1%)	2 (0.1%)
CV sub-classification	Acute MI	16 (0.6%)	12 (0.4%)
	Stroke	15 (0.5%)	4 (0.1%)
	Sudden cardiac death	47 (1.6%)	44 (1.5%)
	HF	17 (0.6%)	30 (1.0%)
	CV procedure/operation	2 (0.1%)	3 (0.1%)
	Other CV cause	11 (0.4%)	14 (0.5%)
Non-CV sub-classification	Gastrointestinal	5 (0.2%)	6 (0.2%)
	General and administration site	7 (0.2%)	6 (0.2%)
	Hepatobiliary	3 (0.1%)	1 (0.03%)
	Immune system	0 (0.0%)	2 (0.07%)
	Infections and infestations	64 (2.2%)	67 (2.3%)
	Injury, poisoning and procedural	2 (0.07%)	3 (0.1%)
	Metabolism and nutrition	1 (0.04%)	1 (0.03%)
	Neoplasms benign, malignant and unspecified (including cysts and polyps)	77 (2.7%)	88 (3.1%)
	Nervous system	4 (0.1%)	6 (0.2%)
	Renal and urinary	1 (0.04%)	2 (0.07%)
	Respiratory, thoracic and mediastinal	12 (0.4%)	12 (0.4%)

Gout and skin rashes

At the end of the first year of participation in the study, a similar number of participants in the allopurinol group and the usual care group reported a new attack of gout occurring in the previous 12 months [112 (5.0%) of 2805 vs. 114 (4.6%) of 2868, $p = 0.55$]. At the end of the first year, more participants in the allopurinol group than in the usual care group reported a history of a new skin rash within the previous 12 months [291 (13.1%) vs. 223 (9.1%), $p < 0.0001$]. At the end of the second year of the study, occurrences of gout and skin rash were reported similarly in both groups. At the end of the third and fourth years of the study, both gout and skin rash in the previous 12 months were reported more commonly by participants in the usual care group than in the allopurinol group of the study.

Chapter 4 Health economic analysis

Aim

The aim of the ALL-HEART health economic analysis was to assess the cost effectiveness of allopurinol versus usual care as a treatment to reduce the risk of the primary endpoint of CV death, non-fatal MI or non-fatal stroke for patients with IHD.

Methods

General approach

The health economic analysis plan (HEAP) is available in *Report Supplementary Material 4*. The methods to be used depended on the results of the trial. If the trial failed to demonstrate a statistically significant reduction in its primary endpoint and in the outcome of all-cause mortality, then a within-trial cost-effectiveness analysis was to be carried out. Otherwise, the cost-effectiveness analysis was to be based on a lifetime approach with future costs and benefits based on a Markov model. In fact, the trial did not show evidence of benefit in reducing the risk of the primary endpoint or all-cause mortality. Hence, the analysis presented herein is based on a within-trial assessment of the incremental cost-effectiveness ratio (ICER). Similarly, as there were no meaningful clinical differences between treatment arms, we have not reported subgroup or sensitivity analyses in the health economic analyses. The ICER is defined to be the ratio of the mean 'between treatment group' difference in costs divided by the mean difference in quality-adjusted life-years (QALYs), derived from EQ-5D-5L index. To take account of potential biases due to treatment group-dependent censoring, costs and QALYs were estimated using inverse probability of censoring weighting (IPCW). The primary analysis was to be based on costs associated with the recurrent components of the primary endpoint (hospitalisation for MI or stroke) and death due to CV causes. All of these events were adjudicated by a Clinical Endpoint Committee, blinded to the treatment group assignation. Costs associated with resource use other than hospitalised events (such as GP visits) were patient-reported and were recorded in the eCRF at the end of year 1 and at the end of the study for all patients and at intermediate annual visits for a random sample of 25% of the patients. EuroQol-5 Dimensions, five-level version questionnaires were completed at the end of year 1 and at the end of the study.

Costs and QALYs were calculated for each period of 6 months from the beginning of the trial, up to a maximum of 5 years. Costs for hospitalisations were assigned to the time period associated with the admission to hospital. Results are displayed graphically in the incremental cost-effectiveness plane and in a plot of the probability of cost-effectiveness as a function of ceilings for willingness to pay. Because of the relatively short timeframe of the analysis, we have not applied time preference discounting to costs or benefits. Missing data were handled using multiple imputation with SAS PROC MI and intermediate time-point EQ-5D-5L index values calculated using linear interpolation. The accuracy of mean costs and QALYs was determined using the bootstrap (1000 iterations) to derive 95% CIs. To maximise the efficiency of the programming a single imputation of missing values was generated within each bootstrap iteration.

As hospitalisation costs are based on a cost per event (such as stroke), it was originally intended to present a sensitivity analysis that focused on the costs of length of stay. However, problems arose in ascertaining discharge dates in a significant number of cases. In addition, where data were available there were a number of outliers suggesting that these data might be unreliable. Hence, this sensitivity analysis was not carried out.

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Costs

1. *Drug costs:* The costs of allopurinol treatment are based on the doses in the study until withdrawal, using the costs in *Table 16*. Costs for a given dose were created by combining the costs of 100 and 300 mg doses; for example, a 600 mg dose was costed as twice the cost of a 300 mg tablet. Drug costs in the usual care arm were set to zero.
2. *Clinical event costs:* Costs of hospitalisations for MI and stroke (including all recurrent events) and CV deaths not involving a hospitalisation for stroke or MI were calculated from *Table 16*.
3. *Non-hospital costs:* Costs associated with healthcare resource use outside of the hospital were costed from *Table 16*. Costs recorded at the final study visit were assigned to year 5 if recorded after year 5 or to the nearest year if recorded before year 5. Within each bootstrap replication, SAS PROC MI was used to create a complete data set of annual costs up to 5 years. Half of the annual costs for each year were assigned to the two corresponding 6-month periods. Costs after death or complete withdrawal from the study were set to zero.
4. *Total costs:* Total costs were defined to be the sum of drug costs + clinical event (MI, stroke, CV death) costs + other resource use (GP, practice of community nurse, physiotherapist, doctor at a hospital outpatient clinic) costs (*Table 17*).
5. *QALYs:* Within each bootstrap sample we used one run of SAS PROC MI to generate a complete list of EQ5D scores for baseline, year 1 and end of study (data only captured at baseline, Y1 and end of study). EuroQol-5 Dimensions scores recorded at the final study visit were assigned to year 5 if recorded after year 5 or to the nearest year if recorded before year 5. Six-month scores were calculated by linear interpolation. If the subject was censored before 5 years, scores after the censoring date were set to zero. Quality-adjusted life-years for each 6-month period were calculated as 0.5 × (average of scores at beginning and end of the period). This score was assigned to the beginning of the period. All QALYs for periods after the date of death or censoring were set as equal to zero.
6. *IPCW:* Probability of censoring was calculated using the Kaplan–Meier method treating censoring times as event times and death times as censoring times. Inverse probability of censoring weighting estimates of costs and QALYs were calculated by weighting the costs (or QALYs) associated with each 6-month time period with respect to the inverse of the estimated probability of censoring at the beginning of each time period. Kaplan–Meier estimates of the probability of censoring were recalculated within each bootstrap sample.

TABLE 16 Costs used in the ALL-HEART economic analysis

Item	Cost (£)	Source
Allopurinol 100 mg	0.86 per 28 tablets	British National Formulary[35]
Allopurinol 300 mg	1.20 per 28 tablets	British National Formulary[35]
GP consultation	39	PSSRU[36] page 111
Practice nurse consultation	14	PSSRU[36] page 109 (20 minutes)
Community nurse contact	22	PSSRU[36] page 108 (30 minutes)
Outpatient clinic	140	NICE HTA papers, TA773[37]
Physiotherapy visit	56	https://beta.isdscotland.org/topics/finance/file-listings-fy-2019-to-2020/ and Excel file R046[38]
Acute stroke hospitalisation	8767	Luengo-Fernandez *et al.*[39]
Acute MI hospitalisation	5415	Palmer *et al.*[40]
CV death not occurring during a hospitalisation for stroke or MI	3126	McEwan *et al.*[41]
Cost per day for a CV hospitalisation	919	https://beta.isdscotland.org/topics/finance/file-listings-fy-2019-to-2020/ and Excel file R040[42]

7. *Data analysis:* For each bootstrap sample, data for IPCW costs and QALYs were outputted. Bootstrap estimates with 95% CIs were calculated for each quantity of interest. Incremental costs were plotted against incremental QALYs in the cost-effectiveness plane and a cost-effectiveness acceptability curve created (probability of being cost-effective vs. ceiling of willingness to pay).
8. *Software:* All calculations were carried out in SAS version 9.3 for Windows. Graphics were created in Minitab version 20.3.

Results

Inverse probability of censoring weighting costs and QALYs are given for each treatment arm and as incremental values (difference: allopurinol − usual care). The plot of incremental costs versus incremental QALYs is given in *Figure 12*.

TABLE 17 Estimated 'per patient' drug costs, primary endpoint (MI, stroke, CV death) costs, resource use (GP, practice or community nurse, physiotherapist, doctor at a hospital outpatient clinic) costs, total costs and QALYs with 95% CIs for the allopurinol group, usual care group and difference (allopurinol − usual care)

	Allopurinol (*n* = 2853)	Usual care (*n* = 2868)	Incremental values
Drug costs (£)	64.5 (64.1, 65.0)	0	64.5 (64.1, 65.0)
Primary endpoint costs (£)	532 (482, 582)	499 (451, 548)	35.6 (−39.8, 99.7)
Resource use costs[a] (£)	1188 (1089, 1267)	1174 (1082, 1240)	16.2 (−45.2, 79.4)
Total costs (£)	1782 (1674, 1888)	1669 (1566, 1761)	115.4 (17.0, 210.2)
QALYs	2.541 (2.496, 2.586)	2.543 (2.501, 2.580)	−0.000 (−0.061, 0.060)

a Missing resource use costs were imputed.

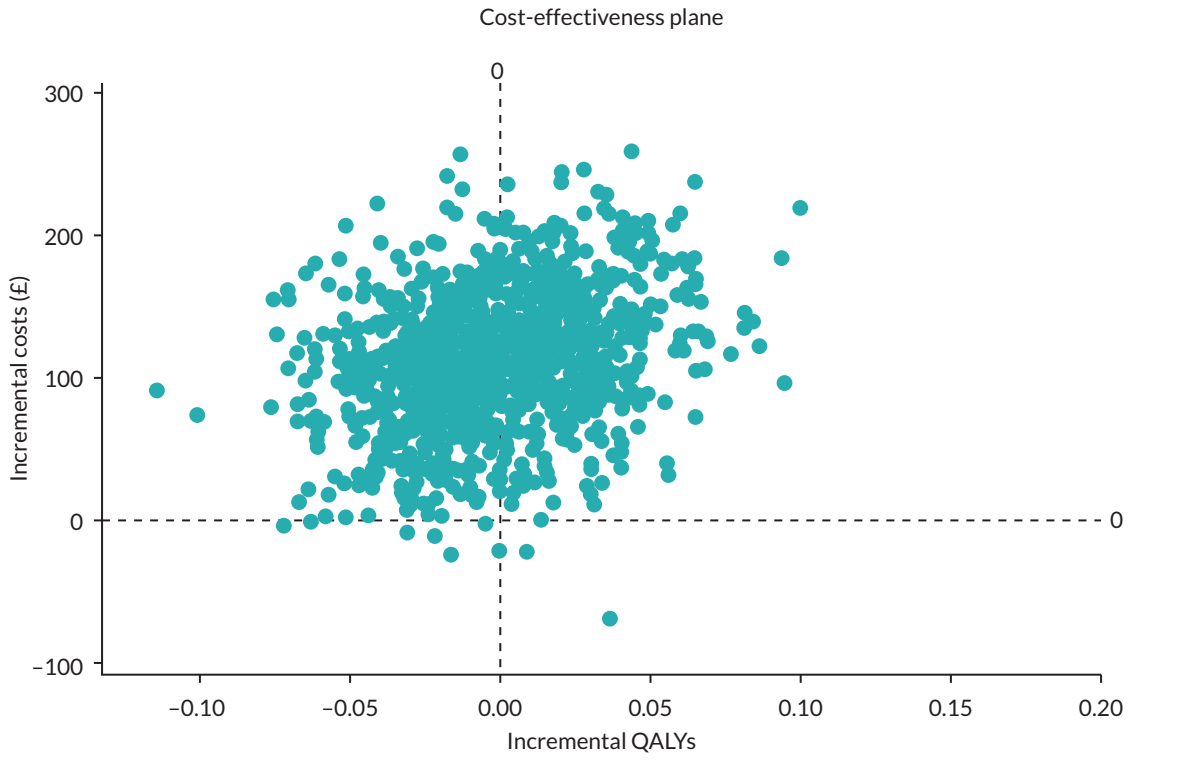


FIGURE 12 Plot of incremental costs vs. incremental QALYs in the cost-effectiveness plane.

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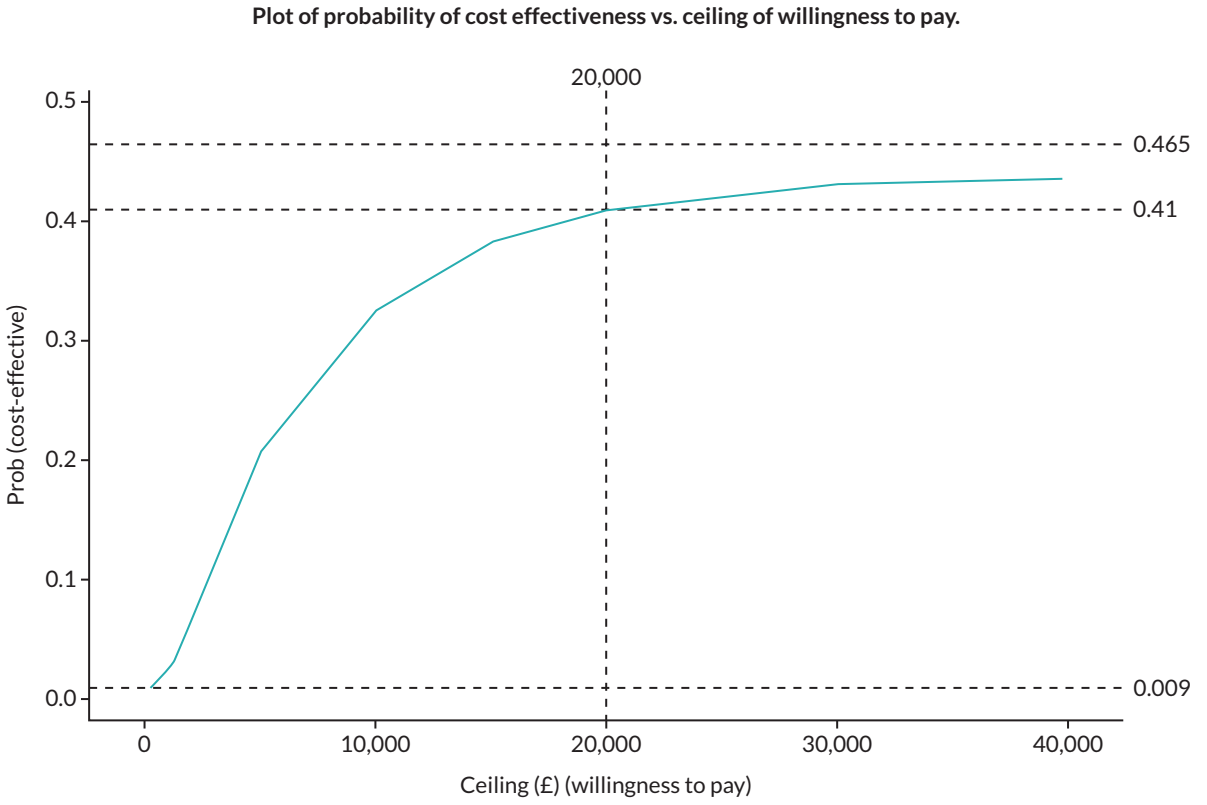


FIGURE 13 Cost-effectiveness acceptability curve.

It is evident from the plot and summary results that there is strong evidence that allopurinol treatment is associated with incremental costs relative to usual care [incremental cost per patient £115.4, 95% CI (£17.0 to £210.2)], with little evidence of improvement in relation to incremental QALYs [incremental QALYs −0.000, 95% CI (−0.061 to 0.060)]. An alternative presentation of these results is given in the cost-effectiveness acceptability curve (*Figure 13*).

This curve asymptotes at a probability of 0.465, meaning that even with a willingness to pay of an infinite amount the probability of cost effectiveness is only 0.465. At a willingness to pay of £20,000 the probability of cost effectiveness is 0.41.

Conclusions of health economic analysis

In keeping with the clinical results of the ALL-HEART trial, the cost-effectiveness analysis provides no evidence to support the use of allopurinol in the treatment of patients with IHD with the objective of reducing the risk of major CV events (MI, stroke and CV death).

Chapter 5 Discussion

Previous smaller interventional and observational studies exploring the impact of urate-lowering therapy on CV outcomes in patients with gout and various CV conditions have given conflicting results, hence the importance of a prospective, randomised trial to determine whether allopurinol improves outcomes in patients with IHD. The ALL-HEART study is the first, large, prospective, randomised outcome trial of allopurinol versus usual care in patients with IHD. It has definitively shown that allopurinol therapy has no benefit on major CV outcomes in patients with IHD, but no gout. The primary intention-to-treat analysis found no difference in rates of the primary or secondary time-to-event clinical outcomes. A similar result was found in the supporting OT analysis, albeit this is likely to be significantly biased due to treatment discontinuation effects. Hospitalisations for HF were significantly lower in the supporting OT analysis in the allopurinol arm, but the numbers were small, in addition to the risk of bias as above, so this finding should be interpreted with caution. The pre-specified subgroup analysis for the primary outcome found no evidence of benefit of allopurinol therapy for any subgroups.

Participants self-reported occurrences of gout at the end of each year of participation in the study. A lower incidence of gout in the previous 12 months was reported by participants in the allopurinol arm than in the usual care arm at the end of the third and fourth years of participation in the study, which might be expected with chronic urate-lowering therapy in a population at risk of gout. However, this may be subject to some reporting bias and would likely not be an indication to start allopurinol prophylactically as it could be started after onset of gout if required. No other clinical, quality-of-life or health economic benefits of allopurinol therapy were demonstrated in the ALL-HEART study.

It is known that allopurinol may cause skin rash in a proportion of patients, and this is most likely to occur during the first few weeks of therapy, in certain ethnic groups with higher prevalence of certain human leucocyte antigen (HLA)-types, and in patients with pre-existing liver or kidney disease. Occasionally, allopurinol therapy may cause serious rashes such as Stevens–Johnson syndrome or toxic epidermal necrolysis, and the risk of these conditions developing or progressing is reduced by stopping allopurinol therapy immediately if any skin rash occurs. To reduce this risk for participants in the ALL-HEART study, it was advised that allopurinol therapy should be stopped immediately if participants reported any rash that might be related to allopurinol. This conservative approach likely resulted in a higher rate of withdrawal from allopurinol therapy than ideal, but it also reflects how allopurinol would be stopped within real-life clinical care in the NHS. Similar rates of withdrawal from therapy have been seen in other trials of urate-lowering therapy. For example, there was a 56.6% withdrawal from randomised therapy in the North American Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES),[43] despite CARES trial participants having a clear clinical indication for urate-lowering therapy (gout). The majority of participants who stopped allopurinol therapy in ALL-HEART continued within study follow-up, so any events occurring following their withdrawal from allopurinol therapy would have been detected. More withdrawals of consent from the study occurred in the allopurinol arm than in the usual care arm, with the difference appearing early in the study. Withdrawals of consent may have been partly driven by the extra study visit for participants in the allopurinol arm at 6 weeks and by withdrawal of consent accompanying early withdrawals from allopurinol therapy. The fact that a placebo or blinding to therapy was not used in the study, instead having an open-label study with a pragmatic usual care arm, may have led to more unbalanced withdrawal from randomised therapy and from the study, as well as some bias in reporting of more subjective adverse events, both participant reported outcomes and those reported by health professionals. However, the components of the primary outcome are objective and were detected from record-linkage hospitalisation data, supported by information from medical records and adjudicated by an endpoint committee blinded to treatment allocation so hopefully free from such biases. Serious adverse events were detected using record-linkage information in addition to participant or health professional reports so should be

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relatively unbiased. The number of missing data for the self-reported quality of life and health resource usage outcomes is acknowledged as a limitation.

No significant safety issues arose with the short- or long-term use of allopurinol in the ALL-HEART study. SAEs, deaths, incident cancers and COVID-19-related deaths and SAEs were found similar in both allopurinol and usual care groups. This is reassuring for those patients with IHD who may require allopurinol therapy for clinical reasons such as gout in the future.

The final approximately 1.5 years of the study follow-up period coincided with the COVID-19 pandemic, which particularly impacted the UK and clinical trials being conducted within the UK, from March 2020 onwards. ALL-HEART was designed from the start as a partly decentralised trial, with remote follow-up processes in place including questionnaires and record-linkage to national databases for outcomes and pharmacovigilance purposes and with no 'in-person' participant visits after the first 6 weeks of participation. This gave the trial added resilience and allowed it to continue without interruption, unlike many other clinical trials, with its processes relatively unaffected during the pandemic. However, despite the use of record-linkage to detect potential endpoints, there may have been some under-reporting of CV endpoints within the trial at the height of the pandemic as fewer patients attended hospitals with acute CV conditions during lockdown periods in early 2020.[44] The decentralised nature of the ALL-HEART trial also resulted in significant cost savings and allowed participants to take part in a major clinical trial lasting several years without the inconvenience of having to travel repeatedly to a central site for trial follow-up visits. The initial screening and randomisation visit and the 6-week visit were carried out locally to participants, usually at their local primary care practice. In recent years, decentralised clinical trial processes have been gaining popularity, having accelerated in their use during the COVID-19 pandemic, and knowledge about the best approaches to optimising participant experiences, inclusivity and study processes is expanding significantly.[45–48]

Allopurinol is generally the first-line urate-lowering therapy for patients with gout. However, a newer and more potent xanthine oxidase inhibitor, febuxostat, also became available a few years ago. Two large, randomised trials of CV outcomes with allopurinol versus febuxostat in patients with gout reported their results during the conduct of the ALL-HEART study. These were the North American Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES)[43] and the Febuxostat versus Allopurinol Streamlined Trial (FAST).[49] The CARES trial, in patients with gout and established CV disease, reported that febuxostat was non-inferior to allopurinol for the primary composite endpoint of death from CV causes, MI, stroke, or unstable angina with urgent revascularisation. However, in the CARES trial, rates of the secondary outcomes of adverse CV outcomes, all-cause death and CV death were significantly higher with febuxostat than with allopurinol. Warnings were issued by regulators against the use of febuxostat in patients with pre-existing CV disease. However, in contrast, the FAST trial, which had better retention in study follow-up and adherence to randomised treatment, found no increased CV risk with febuxostat, and reported a lower rate of all-cause deaths and CV deaths in the febuxostat group than in the allopurinol group. Unlike the ALL-HEART study, the CARES and FAST trials did not include placebo or usual care arms. Although the CARES and FAST trials primarily included patients with gout, both trials included a significant number of patients with co-existing IHD. Patients with pre-existing gout were excluded from participation in the ALL-HEART study, but no selection of patients based on baseline SUA occurred; so, while the mean baseline SUA level in ALL-HEART participants was not particularly high, participants with a wide range of SUA levels were included in the ALL-HEART study. It is possible that some of those patients with IHD with the highest SUA levels would already have expressed some clinical gout symptoms and would therefore not have been included in the ALL-HEART study. It is possible that allopurinol therapy may have had more anti-oxidative activity in patients with higher baseline SUA levels and that in the absence of hyperuricaemia, allopurinol may have had pro-oxidant effects. However, the pre-specified subgroup analysis for the primary outcome in ALL-HEART found no difference in outcomes in patients in the different tertiles of baseline SUA levels. Further analysis of the changes in urate levels with allopurinol therapy and the CV outcomes within the ALL-HEART study may be of interest.

Trials of urate-lowering therapy in patients with asymptomatic hyperuricaemia have not shown positive effects on reducing major CV outcomes. For example, a randomised trial of febuxostat versus control in 1070 elderly patients in Japan with asymptomatic hyperuricaemia at risk for cerebral, CV or renal events, the Febuxostat for Cerebral and CardioRenovascular Events PrEvEntion StuDy (FREED) showed a reduction in the primary composite cardiorenal endpoint in the febuxostat arm, but this was driven by reduced progression of renal dysfunction, rather than an effect on other CV endpoints.[50] Another Japanese trial of febuxostat therapy versus lifestyle modification in 483 patients with asymptomatic hyperuricaemia found no effect on progression of carotid atherosclerosis (carotid-intima medial thickness) over a 2-year treatment period.[51] At present, there remains no clear place for urate-lowering therapy in CV care, outwith certain situations such as clinical gout.

The daily dose of allopurinol given in the ALL-HEART study (600 mg for the majority of participants) was higher than that generally given to patients with gout in the UK (most commonly 100–300 mg daily[40]), but within the licensed dose range of 100–900 mg daily. The 600 mg dose was selected for the ALL-HEART study based on earlier studies that suggested that high doses of allopurinol were needed to achieve beneficial CV effects.[11,27,52] In the ALL-HEART study, SUA levels were approximately halved, to levels well below normal ranges or treatment targets in patients with gout, after 6 weeks of allopurinol therapy. This suggested good adherence to allopurinol therapy in the study, at least in the first few weeks. Adherence to randomised therapy was self-reported at the 6-week visit and annually thereafter, which is a limitation; however, it was possible to check with practices to confirm whether patients were still receiving prescriptions for allopurinol if there was any uncertainty, and generally patient reports and practice records correlated well.

The generalisability of the ALL-HEART study results to the population of patients with IHD is likely to be high. The study was conducted in patients' usual primary care setting, with long-term remote follow-up after the first 6 weeks, so that there would have been minimal impact on participants' usual care during the study. ALL-HEART was a pragmatic study that was a successful example of how a major CV trial could be delivered within the NHS primary care setting in the UK, involving collaborations with several hundred primary care practices, academic institutions, secondary care facilities and research networks. This allowed widespread geographical inclusion of patients, including from some remote and rural practices, and from areas with different levels of social deprivation. Patients with recent-onset coronary disease, or recent ACSs, were not excluded from participation in the ALL-HEART study; however, the median duration of IHD at study entry was 10.1 years, suggesting that most of the participants had chronic, and therefore potentially more stable, IHD. It is possible that different results may have been obtained if a more acute patient population had been recruited to the study. Most participants were taking secondary CV prevention medications including statins and antiplatelet agents at the time of entry to the study, reflecting the high quality of care for patients with IHD in the UK at the time.

Equality, diversity and inclusion

Population characteristics

The mean age of the population included in the study was 72.0 years. A lower age limit of 60 years was selected to ensure the study would have an adequate event rate and that prescriptions for this age group would be free of charge (in England) to avoid issues associated with prescription charges affecting participation. There was no upper age limit for inclusion. Similarly to recruitment into many other CV trials, fewer participants were female (24.5%) than male. All ethnicities were included in the study. However, despite hopes to ensure inclusion of a broad range of ethnicities, 99.2% of participants within the ALL-HEART study reported white ethnicity. The study team recruited from 424 primary care practices across Scotland and England that included city and rural practices, some of which had much higher ethnic diversity than others. We had hoped that the geographical spread of primary care sites would ensure ethnic diversity in the patient populations we were able to recruit from. We had staff from

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a wide range of ethnic backgrounds involved in the study in different roles. Images used on the public study website portrayed people of different genders, ethnicities and with visible disabilities to encourage a culture of inclusivity and diversity. In any future trial, further efforts to recruit from underserved populations, particularly regarding ethnicity with reference to the INCLUDE Ethnicity guidance,[53] should be made to ensure that results are as generalisable as possible. The ALL-HEART study also completed recruitment prior to publication of the INCLUDE framework and guidance,[54] the principles of which should also lead to better diversity in studies in the future. One observation was that no participants suffered severe Stevens–Johnson syndrome within the ALL-HEART study. If the study had been performed in a more diverse ethnic group, the potential risk of Stevens–Johnson syndrome would likely have been higher. The fact that initial visits were generally held in primary care practices and much of the study follow-up was remote could have facilitated the participation of patients with mobility disorders, who may have struggled logistically or physically to attend study visits at central sites some distance from their homes. Options for preferred methods of contact were provided to all participants – e-mails, letters or telephone calls, and options for completion of follow-up questionnaires were also offered – online, paper or by telephone. Participants were able to change their preferences throughout the study follow-up period to adapt to changing circumstances and to aid continuing participation in the study.

Research team and wider involvement

The research team included those from groups who are generally under-represented in CV clinical trials. For example, the chief investigator was female, which is still relatively uncommon in the leadership of major CV trials. Regional principal investigators included both genders and wide ethnic diversity. The research team included senior and junior members, with a wide range of background experience, clinically, academically and in public engagement. The team encouraged and embraced inclusivity regarding neurodiversity, disabilities, caring responsibilities, less than fulltime employees, genders and different ethnicities. Flexibility in working patterns was provided to accommodate individual needs and ensure effective working. National Institute for Health and Care Research allowed flexibility during the two-stage grant application process to accommodate maternity leave of the chief investigator and allowed remote attendance at a monitoring meeting (before the days this was commonplace) to facilitate attendance during maternity leave.

Continuing professional development opportunities were provided to all members of the team, appropriate to their needs at the time. The diversity, flexibility, skill mix and enthusiasm within the study team led to a good working environment and collaborative approach which benefitted the successful conduct of the study and resulted in appropriate problem solving throughout the trial.

Patient and public involvement

Input was obtained at the planning stage of the study from lay people with experience of cardiac disease on the design of the ALL-HEART study and on the acceptability of randomisation to a usual care arm.

The TSC included two patient or lay members throughout the project. Three different patient or lay members held this role during the study, with one member serving on the steering committee from start to end of the study. These members had knowledge of, or personal experience of, cardiac disease, including IHD, and some had been members of local cardiac support groups and other committees previously. The members contributed fully to meetings of the steering committee, also commenting on the extension applications, communications to participants during the study, patient information sheets, end of study letters and dissemination of the results, including communication of the results to participants. Very positive feedback was obtained at the final steering committee meeting, with one lay member reporting that it had been the best experience of patient participation in a committee experienced to date, because their views were always sought and listened to. The commitment and dedication of the patient and lay members throughout the trial were very much appreciated, as it offered a patient perspective on all aspects of the trial and guided the trial team when making important decisions about the conduct and future of the trial.

Patient and public involvement input was obtained into the wording of the plain language summary of this report. Suggested improvements to the wording to improve understanding and readability were incorporated.

The initial study results were presented as a hotline session at the European Society of Cardiology conference in Barcelona in August 2022, then the full paper published in *The Lancet* in October 2022. A lay summary of the study results and a link to the full Lancet paper were disseminated to ALL-HEART study participants by e-mail or letter, according to participant contact preference, within days of the Lancet publication and lifting of the embargo. A lay summary was also published on the ALL-HEART public study website just after the embargo was lifted. Results were disseminated quickly to all participating GP practices and staff involved in the study. Several positive messages of thanks were received back from participants and staff after being sent the study results. Some of these messages were reviewed at the final TSC meeting. Participant feedback included thanking the study team for the concise and clear summary of the results, thanks for sharing the results and feedback that they had been happy to participate in the trial.

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Chapter 6 Conclusions

The ALL-HEART study showed that treatment with allopurinol 600 mg daily did not improve CV outcomes compared to usual care in patients aged over 60 years with IHD. There were no long-term safety issues with allopurinol therapy if it was initially tolerated and continued. There was no evidence that allopurinol used in line with the study protocol is cost-effective within the NHS system. The results of the ALL-HEART study suggest that allopurinol should not be recommended for use for the secondary prevention of CV events in patients with IHD.

Recommendations for research

1. Future research should explore other therapeutic options for the improvement of CV outcomes and quality of life in patients with IHD.
2. Further exploration of the effects of allopurinol on CV outcomes in patients with co-existing IHD and clinical gout or hyperuricaemia could be considered (patients with gout were excluded from this study).

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Contributions of authors

Isla S Mackenzie (https://orcid.org/0000-0002-3680-7127) (Professor of Cardiovascular Medicine) was the chief investigator, with overall responsibility for the design, co-ordination, conduct and delivery of the study. With co-investigators, she led on the conception, design and the original grant application. She drafted the report with input from co-authors.

Christopher J Hawkey (https://orcid.org/0000-0002-6031-1017) (Professor of Gastroenterology) was a regional principal investigator and a co-investigator on the grant application. He contributed to study conduct and reviewed and commented on the final report.

Ian Ford (https://orcid.org/0000-0001-5927-1823) (Senior Research Fellow) was the lead trial statistician and a co-investigator on the grant application. He performed the statistical analysis and contributed to study design, drafting of the statistical analysis plan and drafting of the report. He reviewed and commented on the final report.

Nicola Greenlaw (https://orcid.org/0000-0003-3847-1126) (Consultant Biostatistician) was a trial statistician. She performed the statistical analysis, and contributed to drafting of the statistical analysis plan and drafting of the final report. She performed the health economic analysis and drafted the health economic analysis chapter with support from Andrew Walker and Ian Ford. She reviewed and commented on the final report.

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Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used – #datasaveslives. You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

The data sets generated or analysed are not expected to be made available owing to the limitations of participant consent and approvals in place regarding data sharing between organisations involved in the study. The data will be held in the University of Dundee. Any applications for potential data sharing or collaboration should be made to the corresponding author.

Ethics statement

The study was approved by the East of Scotland Research Ethics Committee (REC Ref. 13/ES/0104, IRAS ID 135900) on 12 September 2013. All participants gave written informed consent.

Information governance statement

The University of Dundee is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Dundee is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.dundee.ac.uk/information-governance/data-protection.

The Robertson Centre for Biostatistics, University of Glasgow was a Data Processor.

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Publications

Mackenzie IS, Hawkey CJ, Ford I, Greenlaw N, Pigazzani F, Rogers A, *et al.*; ALL-HEART study group. Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease: a multicentre, prospective, randomised, open-label, blinded endpoint clinical trial the ALL-HEART study. *Lancet* 2022;**400**:1195–205.

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Appendix 2 Comparisons of EQ-5D-5L data availability at the end of the study by selected baseline characteristics in each arm of the study

	Baseline characteristic	Final visit EQ-5D-5L score available	Final visit EQ-5D-5L score missing	*p*-value
Allopurinol	Age (years)	71.7 (6.70)	72.1 (6.78)	0.15
	Sex			
	Male	1169 (79.6%)	999 (72.2%)	< 0.001
	Female	300 (20.4%)	385 (27.8%)	
	Transgender	0 (0%)	0 (0%)	
	History of MI	739 (50.3%)	609 (44.0%)	< 0.001
	History of stroke	57 (3.9%)	65 (4.7%)	0.31
	History of diabetes	330 (22.5%)	288 (20.8%)	0.30
	Baseline EQ-5D-5L score[a]	0.82 (0.19)	0.80 (0.20)	0.005
Usual care	Age (years)	72.0 (6.69)	72.1 (6.89)	0.55
	Sex			
	Male	1371 (76.8%)	782 (72.3%)	0.012
	Female	414 (23.2%)	299 (27.6%)	
	Transgender	1 (0.06%)	1 (0.09%)	
	History of MI	855 (47.9%)	501 (46.3%)	0.42
	History of stroke	71 (4.0%)	37 (3.4%)	0.48
	History of diabetes	360 (20.2%)	263 (24.3%)	0.010
	Baseline EQ-5D-5L score[b]	0.83 (0.18)	0.80 (0.19)	< 0.001

a EQ-5D-5L missing at baseline in three patients with EQ-5D-5L available at final visit and four participants with EQ-5D-5L missing at final visit.
b EQ-5D-5L missing at baseline in 10 patients with EQ-5D-5L available at final visit and 1 participant with EQ-5D-5L missing at final visit.

Note
Data are *n* (%) or mean (SD). *p*-values provided from Wilcoxon rank sum tests or Fisher's exact tests as required.

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