

University of Dundee

## Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART)

Mackenzie, Isla S.; Hawkey, Christopher J.; Ford, Ian; Greenlaw, Nicola; Pigazzani, Filippo; Rogers, Amy

*Published in:*  
The Lancet

*DOI:*  
[10.1016/S0140-6736\(22\)01657-9](https://doi.org/10.1016/S0140-6736(22)01657-9)

*Publication date:*  
2022

*Licence:*  
CC BY

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Mackenzie, I. S., Hawkey, C. J., Ford, I., Greenlaw, N., Pigazzani, F., Rogers, A., Struthers, A. D., Begg, A. G., Wei, L., Avery, A. J., Taggar, J. S., Walker, A., Duce, S. L., Barr, R. J., Dumbleton, J. S., Rooke, E. D., Townend, J. N., Ritchie, L. D., MacDonald, T. M., & ALL-HEART study group (2022). Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. *The Lancet*, *400*(10359), 1195-1205. [https://doi.org/10.1016/S0140-6736\(22\)01657-9](https://doi.org/10.1016/S0140-6736(22)01657-9)

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.



# Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial

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, Thomas M MacDonald, on behalf of the ALL-HEART Study Group\*



## Summary

**Background** Allopurinol is a urate-lowering therapy used to treat patients with gout. Previous studies have shown that allopurinol has positive effects on several cardiovascular parameters. The ALL-HEART study aimed to determine whether allopurinol therapy improves major cardiovascular outcomes in patients with ischaemic heart disease.

**Methods** ALL-HEART was a multicentre, prospective, randomised, open-label, blinded-endpoint trial done in 18 regional centres in England and Scotland, with patients recruited from 424 primary care practices. Eligible patients were aged 60 years or older, with ischaemic heart disease but no history of gout. Participants were randomly assigned (1:1), using a central web-based randomisation system accessed via a web-based application or an interactive voice response system, to receive oral allopurinol up-titrated to a dose of 600 mg daily (300 mg daily in participants with moderate renal impairment at baseline) or to continue usual care. The primary outcome was the composite cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The hazard ratio (allopurinol vs usual care) in a Cox proportional hazards model was assessed for superiority in a modified intention-to-treat analysis (excluding randomly assigned patients later found to have met one of the exclusion criteria). The safety analysis population included all patients in the modified intention-to-treat usual care group and those who took at least one dose of randomised medication in the allopurinol group. This study is registered with the EU Clinical Trials Register, EudraCT 2013-003559-39, and ISRCTN, ISRCTN32017426.

**Findings** Between Feb 7, 2014, and Oct 2, 2017, 5937 participants were enrolled and then randomly assigned to receive allopurinol or usual care. After exclusion of 216 patients after randomisation, 5721 participants (mean age 72.0 years [SD 6.8], 4321 [75.5%] males, and 5676 [99.2%] white) were included in the modified intention-to-treat population, with 2853 in the allopurinol group and 2868 in the usual care group. Mean follow-up time in the study was 4.8 years (1.5). There was no evidence of a difference between the randomised treatment groups in the rates of the primary endpoint. 314 (11.0%) participants in the allopurinol group (2.47 events per 100 patient-years) and 325 (11.3%) in the usual care group (2.37 events per 100 patient-years) had a primary endpoint [hazard ratio [HR] 1.04 [95% CI 0.89–1.21],  $p=0.65$ ]. 288 (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 0.87–1.20],  $p=0.77$ ).

**Interpretation** In this large, randomised clinical trial in patients aged 60 years or older with ischaemic heart disease but no history of gout, there was no difference in the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death between participants randomised to allopurinol therapy and those randomised to usual care.

**Funding** UK National Institute for Health and Care Research.

**Copyright** © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

## Introduction

The xanthine oxidase inhibitor, allopurinol, is a urate-lowering medication licensed for the prophylaxis of gout or symptomatic hyperuricaemia and prophylaxis of hyperuricaemia associated with cancer chemotherapy; its chronic use reduces the likelihood of acute flares of gout. Allopurinol is not currently indicated for the treatment of people with asymptomatic hyperuricaemia or in patients with ischaemic heart disease unless they also have gout.

High serum uric acid concentrations have been associated with adverse cardiovascular outcomes, and

some observational studies have suggested that urate-lowering therapy reduces cardiovascular risk,<sup>1,2</sup> whereas others have not found such benefits.<sup>3</sup> However, the risk of confounding and bias within such observational studies is significant, and the need for prospective randomised trials in this area has been identified.<sup>4</sup>

Several previous small interventional studies have reported benefits of allopurinol therapy on cardiovascular parameters, including endothelial function,<sup>5–9</sup> flow-mediated dilatation,<sup>10,11</sup> blood pressure,<sup>12–14</sup> left ventricular mass,<sup>10,15,16</sup> carotid intima-media thickness progression,

*Lancet* 2022; 400: 1195–205

See [Comment](#) page 1172

\*Other members of the ALL-HEART Study Group, investigators, and contributors are listed in the appendix (pp 14–19)

**MEMO Research, Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK** (Prof I S Mackenzie PhD, F Pigazzani PhD, A Rogers MD, Prof A D Struthers MD, A G Begg MBChB, S L Duce PhD, R J Barr PhD, E D Rooke MBChB, Prof T M MacDonald MD); **Nottingham Digestive Diseases Centre** (Prof C J Hawkey FMedSci, J S Dumbleton BSc), **Centre for Academic Primary Care, School of Medicine** (Prof A J Avery DM, J S Taggar PhD), **University of Nottingham, Nottingham, UK**; **The Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK** (Prof I Ford PhD, N Greenlaw MSc); **School of Pharmacy, University College London, London, UK** (Prof L Wei PhD); **Salus Alba, Glasgow, UK** (A Walker PhD); **Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK** (Prof J N Townend MD); **Academic Primary Care, University of Aberdeen, Aberdeen, UK** (Prof Sir L D Ritchie MD)

Correspondence to: Prof Isla S Mackenzie, MEMO Research, Division of Molecular and Clinical Medicine, University of Dundee, Dundee DD1 9SY, UK [i.s.mackenzie@dundee.ac.uk](mailto:i.s.mackenzie@dundee.ac.uk)  
See [Online](#) for appendix

### Research in context

#### Evidence before this study

On July 8, 2022, we searched PubMed, with no date or language restriction, using the search terms “allopurinol” and “cardiovascular disease” and “cardiovascular outcomes”, then “allopurinol” and “ischaemic heart disease” and “cardiovascular outcomes”. We searched for any randomised clinical trials with more than 500 participants comparing allopurinol with placebo or usual care in terms of cardiovascular outcomes. Apart from the published protocol paper for the ALL-HEART study, we found no other relevant results. We found no randomised clinical trials comparing allopurinol with placebo or usual care for cardiovascular outcomes with more than 100 participants.

#### Added value of this study

The ALL-HEART study was a large, multicentre, prospective, randomised, open-label, blinded-endpoint study comparing cardiovascular outcomes in patients aged 60 years or older with ischaemic heart disease, but no history of gout, treated with allopurinol therapy versus usual care. This is the first large prospective outcome study of its kind. The doses of allopurinol used in the ALL-HEART study are higher than those generally used in the treatment of most patients with gout, but still within the licensed dose range for treatment of gout (100–900 mg daily in the UK). In the modified intention-to-treat population, only 5·8% of participants withdrew from all follow-up, but 57·4% of participants in the allopurinol group withdrew from randomised

treatment during the trial, most commonly due to adverse event or participant preference. ALL-HEART used record linkage to national health-care databases to complement other methods of reporting for the detection of hospitalisations, cancers, and deaths. We found no difference between the allopurinol and usual care groups for the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death during a mean follow-up period of 4·8 years. There was also no significant difference in any of the secondary time-to-event outcomes between the allopurinol and usual care groups. Results for the primary endpoint were consistent across all prespecified subgroups, including baseline serum uric acid. There were no significant safety concerns in the allopurinol group. Incident cancer rates in both treatment groups were similar.

#### Implications of all the available evidence

Although previous smaller studies have found cardiovascular benefits of allopurinol therapy, this large, prospective, randomised outcome trial found no benefit of allopurinol therapy on the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death in patients with ischaemic heart disease, without a history of gout. The results of this study do not support use of allopurinol for prevention of adverse cardiovascular outcomes in patients with ischaemic heart disease without symptomatic hyperuricaemia (gout), whatever their baseline concentration of serum uric acid.

and arterial stiffness.<sup>14</sup> However, other studies have reported no benefit of allopurinol therapy on blood pressure,<sup>11</sup> left ventricular mass,<sup>17,18</sup> myocardial perfusion,<sup>19</sup> and flow-mediated dilatation.<sup>20</sup> A clinical crossover study that randomly assigned patients with angina and angiographically documented coronary artery disease to 600 mg daily allopurinol versus placebo found that allopurinol therapy increased exercise time and reduced chest pain.<sup>21</sup> Furthermore, a study in 100 patients with acute coronary syndrome randomly assigned to allopurinol or usual care reported reduced angina, improvements in markers of oxidative stress and inflammatory response, and fewer cardiovascular events after 2 years of follow-up in the allopurinol group compared with the usual care group.<sup>22</sup> The mechanistic hypothesis for why allopurinol might be beneficial in patients with ischaemic heart disease includes its effects on reducing xanthine oxidase-mediated vascular oxidative stress, potentially unrelated to its effects on lowering serum uric acid concentrations.<sup>5,23</sup> Until now, no large, prospective, randomised outcome trial of allopurinol therapy in patients with ischaemic heart disease had been performed.

The ALL-HEART study aimed to determine whether allopurinol therapy improved cardiovascular outcomes in patients with ischaemic heart disease, but no history of gout.<sup>24</sup>

## Methods

### Study design and participants

A multicentre, prospective, randomised, open-label, blinded-endpoint trial was done in 18 regional centres in England and Scotland. Patients were primarily recruited from 424 primary care practices in England and Scotland (by search of primary care records for potentially eligible patients), but a small number were also referred from secondary care centres via the primary care practices. Eligible patients were aged 60 years or older, with a history of ischaemic heart disease (myocardial infarction, angina, or other evidence of ischaemic heart disease, such as a positive coronary angiogram). Patients with a history of gout, known moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] of <60 mL/min per 1·73 m<sup>2</sup>), moderate-to-severe heart failure, significant hepatic disease, previous severe adverse skin reaction to any drug, or significant malignancy within the past 5 years were excluded. On April 4, 2016, an amendment to the protocol was implemented allowing the inclusion of patients with moderate renal impairment in the study. The full list of inclusion and exclusion criteria is in the appendix (p 13).

The study Clinical Co-ordination Centre was MEMO Research at the University of Dundee (Dundee, UK), and the study Data and Biostatistical Centre was at the Robertson Centre for Biostatistics at the University of

Glasgow (Glasgow, UK). Trial monitoring was carried out or subcontracted by the University of Dundee and NHS Tayside. The study protocol (appendix pp 20–59) was approved by an ethics committee and regulatory authorities in the UK. All participants gave written informed consent.

### Randomisation and masking

Participants were randomly assigned (1:1) to receive allopurinol or continue usual care using a central web-based randomisation facility located at the Robertson Centre for Biostatistics. The randomisation system could be accessed via a web-based application or an interactive voice response system. The randomisation list was created by a statistician (who had no role in the final analysis) in the Robertson Centre for Biostatistics based on randomised permuted block sizes of four and six, stratified according to primary care practice, history of myocardial infarction, and history of stroke. Randomised therapy was not masked to participants, site staff, and treating physicians but was masked to the clinical endpoint adjudication committee. Placebo was not given in this study because it was designed to be a pragmatic, open-label clinical trial.

### Procedures

At the screening visit, informed consent was obtained, inclusion and exclusion criteria checked, and then baseline demographics, medical history, cardiovascular risk factors, medications, blood pressure, and height and weight data were collected by the research nurse. Baseline blood tests were taken, including serum uric acid, urea, creatinine and electrolytes, and full blood count, and participants were randomly assigned (before screening blood results were available). When the screening blood results were available, a nurse telephoned the participant to advise them to start taking their randomised therapy. If the screening visit eGFR was below the exclusion criterion limit, the participant did not receive any randomised medication and was excluded from the modified intention-to-treat analysis population, regardless of the group to which they had been randomly assigned.

100 mg or 300 mg allopurinol tablets (various manufacturers and suppliers) were prescribed to participants by their primary care physician. For participants with a screening eGFR of 60 mL/min per 1.73 m<sup>2</sup> or more, allopurinol was prescribed at 100 mg for 2 weeks, then 300 mg for 2 weeks, and then 600 mg daily (given as 300 mg twice daily) thereafter if tolerated.

From April 4, 2016, when a protocol amendment was implemented that allowed the inclusion of patients with moderate renal impairment in the study, participants with a screening eGFR of 30–59 mL/min per 1.73 m<sup>2</sup> were prescribed oral allopurinol at 100 mg for 2 weeks and then 300 mg daily thereafter if tolerated (300 mg was the maximum daily dose given to these participants).

Two different quality-of-life questionnaires were completed at the screening visit: the EQ-5D to assess general

health outcomes and the Seattle Angina Questionnaire<sup>25</sup> to assess coronary artery disease-specific quality of life.

Participants who took any allopurinol attended a week 6 visit at which blood samples were taken for serum uric acid, urea, electrolytes and creatinine, and full blood count. If there were tolerability issues at any time, participants could continue in the study on a lower-than-maximal dose of allopurinol at the discretion of their physician. Allopurinol was stopped in patients with a rash that could have been due to allopurinol, but they could continue in the trial. Participants who stopped randomised therapy were encouraged to complete study follow-up. If allopurinol was later started for clinical reasons in participants randomly assigned to the usual care group, the start date and reason for therapy were recorded.

The remainder of study follow-up was remote, with follow-up for events by electronic record linkage to records of hospitalisations, cancers, and deaths. Participants also completed annual questionnaires (by post, online, or by telephone). Data on adverse events, skin rashes, gout flares, and self-reported continuing adherence to randomised therapy were collected at the 6-week visit and then annually (but could also be reported at any time by participants or health professionals). Clarifications of self-reported data could be obtained where necessary by research nurses contacting the participant's primary care practice for details of events or confirmation of continued prescribing of randomised medication and dose. Participants completed the EQ-5D and Seattle Angina Questionnaire after 1 year and at the end of the trial.

Record linkage to centralised databases (Public Health Scotland and NHS Digital) for records of hospitalisations, deaths, and cancers was carried out at regular intervals. Because recruitment took longer than predicted and the primary event rates were lower than predicted, the trial recruitment period was extended and the follow-up period was also extended twice. Participants could choose to discontinue their active involvement in the study after 5 years (the original intended trial duration) or after March 31, 2021, when these extensions were implemented.

During a temporary shortage of the 100 mg allopurinol tablet supply in 2014, the protocol was amended temporarily to allow participants to start on 100–150 mg allopurinol for the first 2 weeks. The dose was then up-titrated as described previously.

At the end of the follow-up period of the trial (Sept 30, 2021), participants stopped allopurinol and continued to receive usual care.

### Outcomes

The primary outcome was the composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The secondary outcomes were non-fatal myocardial infarction; non-fatal stroke; cardiovascular death; all-cause mortality; hospitalisation for acute coronary syndrome; coronary revascularisation; hospitalisation for

For **Public Health Scotland** see [publichealthscotland.scot](http://publichealthscotland.scot)

For **NHS Digital** see [digital.nhs.uk](http://digital.nhs.uk)

For the EQ-5D see [www.euroqol.org](http://www.euroqol.org)

acute coronary syndrome or coronary revascularisation; hospitalisation for heart failure; all cardiovascular hospitalisations; quality of life; and cost-effectiveness. The cost-effectiveness analysis will be reported separately in the NIHR Journals report for the ALL-HEART study.

Serious adverse events occurring during the study (until Sept 30, 2021) were recorded and then summarised by treatment group, system organ class, and preferred term as classified by the Medical Dictionary for Regulatory Activities (MEDDRA), and were followed up until 30 days after the end of the study follow-up period, unless participants had withdrawn consent. Gout flares, rashes, and any treatment-related adverse events were also recorded. For serious adverse events that were potential study endpoints, more detailed information was collected from medical records and death certificates. An anonymised endpoint package was prepared for each potential endpoint for adjudication by an independent clinical events adjudication committee that was unaware of the trial group assignments. This committee was led by JNT and assessed all the components of the primary composite outcome, secondary cardiovascular outcomes, and deaths; these events are defined in the clinical endpoint adjudication committee charter (appendix pp 60–99).

### Statistical analysis

It was originally calculated that 5215 participants would need to be randomly assigned 1:1 to give 80% power to detect a 20% reduction in the primary outcome for the intervention (allowing for 4% dropout for withdrawal of consent to follow-up and non-cardiovascular deaths). A primary event rate of 14% over an average of 4 years of follow-up was initially estimated from previous trials in similar patient groups. The study would end when 631 adjudicated first primary events had occurred. Baseline characteristics are shown according to treatment groups as means (SD) or medians (IQR) for continuous variables and as numbers and percentages for categorical variables.

We analysed clinical outcomes on a time-to-first-event basis using Cox proportional hazards models. Treatment effects (allopurinol *vs* usual care) were estimated in the form of hazard ratios (HRs) and 95% CIs for the Cox models. Analyses were adjusted for the stratification variables: history of myocardial infarction and history of stroke. We calculated *p* values from Wald statistics. The primary analysis was a modified intention-to-treat analysis. Participants who were randomised but later found to have met one of the exclusion criteria or not met an inclusion criterion were not included in the modified intention-to-treat analysis. The modified intention-to-treat analysis censored follow-up after death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, or the end of the study, whichever occurred first. A prespecified on-treatment analysis censored follow-up after permanent discontinuation from randomised therapy, death from any cause not included in the endpoint being

considered, date of withdrawal of all consent to participate further in the study, or the end of the study, whichever occurred first. We did similar prespecified analyses for other time-to-event secondary endpoints. Prespecified subgroup analyses (urate split by tertiles, eGFR, age, sex, diabetes, myocardial infarction, heart failure, peripheral arterial disease, stroke, and stroke or transient ischaemic attack at baseline) were carried out for the primary endpoint. We calculated *p* values for the test of interaction between the variable defining the subgroup and randomised treatment allocation.

We analysed quality-of-life outcomes at each timepoint (1 year after randomisation and the final visit) using linear regression models for the change in each quality-of-life measure. Analyses were adjusted for the stratification variables as for 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.

Time-to-event curves are presented as cumulative incidence functions, adjusting for the competing risk of deaths not included in the endpoint being plotted, for the primary endpoint and secondary endpoints of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Kaplan-Meier curves are presented for all-cause mortality. Time to discontinuation from the study and time to discontinuation from allopurinol are described.

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

All validly randomly assigned participants who satisfied the eGFR entry criterion based on their screening visit blood results were included in the modified intention-to-treat and on-treatment analyses. The safety analysis population included all participants in the modified intention-to-treat usual care group and those who took at least one dose of randomised medication in the allopurinol group. The number of serious adverse events and rates of serious adverse events per 100 patient-years of follow-up are summarised by treatment group. Comparisons (post hoc) between treatment groups for the rates of any serious adverse event and for each system organ class were made assuming binomial distributions.

Estimates of the difference in rates between groups and corresponding 95% CIs are presented. The numbers and percentages of COVID-19 and COVID-19 pneumonia deaths and serious adverse events (coded by preferred term) are summarised by treatment group. The numbers of patients at each annual visit with at least one event within the previous 12 months (new skin rash and attack

of gout) are summarised by treatment group. These analyses were compared using the  $\chi^2$  test (post hoc).

Analyses and graphical displays were done with SAS for Windows (version 9.4) and R (version 3.6.1). The statistical analysis plan is in the appendix (pp 112–124). All cardiovascular outcomes were adjudicated by an independent clinical endpoint adjudication committee (appendix p 14), except coronary revascularisations, which were reviewed and confirmed by the chair of the committee, and cardiovascular hospitalisations (other than those reviewed by the committee), which were confirmed by the clinical team at the University of Dundee.

Trial safety was overseen by an independent data monitoring committee (appendix p 14). A trial steering committee, including lay and patient members, was in place throughout the trial (appendix p 14). This trial is registered with the EU Clinical Trials Register, EudraCT 2013-003559-39, and ISRCTN, ISRCTN32017426.

#### Role of the funding source

The funder had no role in study design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

#### Results

Between Feb 7, 2014, and Sept 29, 2017, 6134 patients consented to be enrolled in the trial and were assessed for

eligibility (figure 1). Of the 5937 participants randomised, 216 were excluded after randomisation (184 due to not meeting the eGFR entry criterion based on screening visit eGFR blood results [which were only obtained after randomisation since screening and randomisation were usually carried out during the same single visit] and 32 were found to have not met other inclusion or exclusion criteria), leaving 5721 (2853 in the allopurinol group and 2868 in the usual care group) in the modified intention-to-treat population which forms the population for efficacy analyses. 48 participants in the allopurinol group never received randomised treatment, resulting in 2805 participants in the allopurinol group and 2868 in the usual care group in the safety population (figure 1).

The final randomisation took place on Oct 2, 2017. Participants stopped randomised treatment at the final end of follow-up on Sept 30, 2021. Time to receive final record-linkage data and supporting information on endpoints resulted in the trial completion date being March 31, 2022. The mean duration of follow-up was 4.8 years (SD 1.5). 258 (9.0%) of 2853 participants in the allopurinol group and 76 (2.6%) of 2868 in the usual care group withdrew from all follow-up (appendix p 10). Reasons for withdrawal from all follow-up (withdrawal of consent) are given in the appendix (p 4). 1637 (57.4%) participants in the allopurinol group withdrew from randomised treatment (appendix p 11). Reasons for

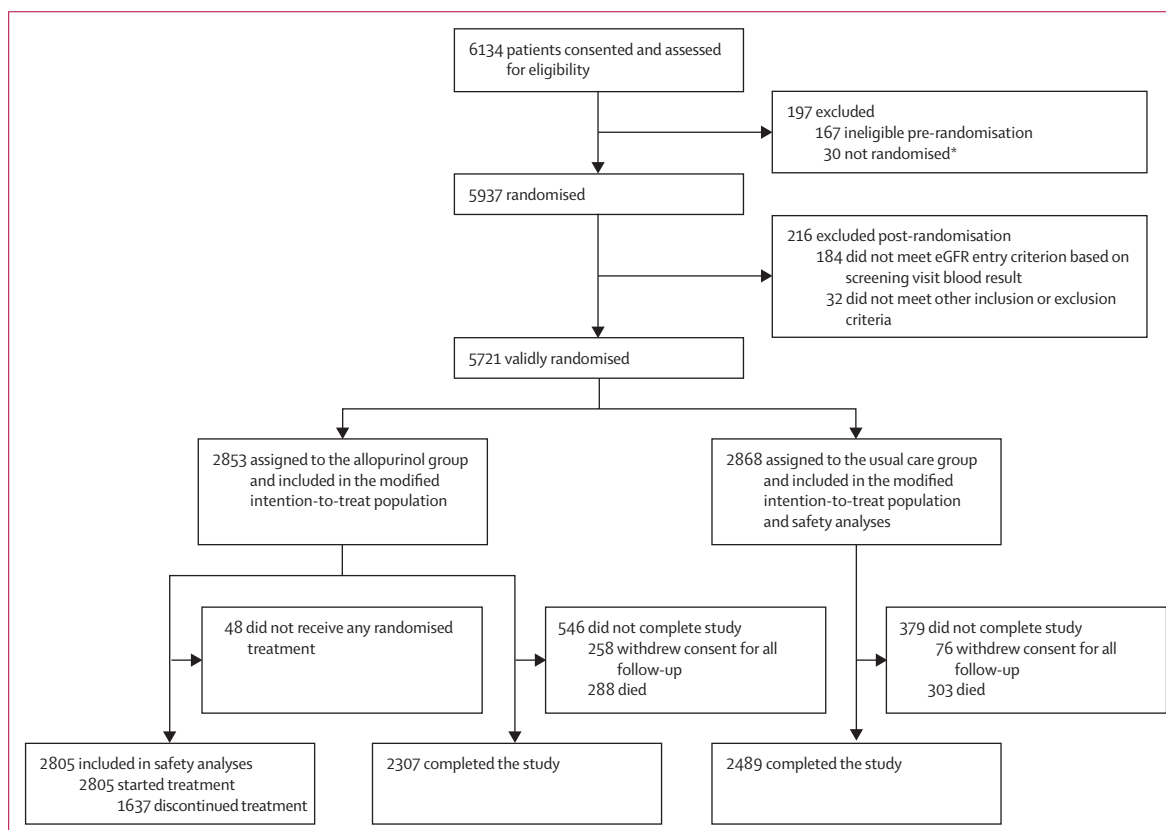


Figure 1: Trial profile

eGFR=estimated glomerular filtration rate. \*Screening visit was not completed or participant withdrew consent before randomisation.

	Allopurinol group (n=2853)	Usual care group (n=2868)
Age, years	71.9 (6.7)	72.0 (6.8)
Gender		
Male	2168 (76.0%)	2153 (75.1%)
Female	685 (24.0%)	713 (24.9%)
Transgender	0	2 (0.1%)
Ethnicity		
White	2831 (99.2%)	2845 (99.2%)
Asian or Asian British	13 (0.5%)	14 (0.5%)
Black, African, Caribbean, or Black British	4 (0.1%)	0
Mixed or 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*, mm Hg	132.0 (17.8)	133.2 (17.9)
Diastolic blood pressure*, mm Hg	72.0 (10.5)	72.5 (10.7)
Body-mass index†, kg/m <sup>2</sup>	28.9 (4.9)	28.8 (4.9)
Baseline eGFR group		
30–44 mL/min per 1.73 m <sup>2</sup>	52 (1.8%)	56 (2.0%)
45–59 mL/min per 1.73 m <sup>2</sup>	201 (7.0%)	231 (8.1%)
≥60 mL/min per 1.73 m <sup>2</sup>	2600 (91.1%)	2581 (90.0%)
Baseline serum uric acid‡, mmol/L	0.35 (0.08)	0.34 (0.08)
Cardiovascular history		
Myocardial infarction	1348 (47.2%)	1356 (47.3%)
Angina	1845 (64.7%)	1824 (63.6%)
CCS angina grade 0	618 (21.7%)	646 (22.5%)
CCS angina grade I	755 (26.5%)	702 (24.5%)
CCS angina grade II	403 (14.1%)	411 (14.3%)
CCS angina grade III	61 (2.1%)	54 (1.9%)
CCS angina grade IV	8 (0.3%)	11 (0.4%)
No angina	1008 (35.3%)	1044 (36.4%)
Other evidence of ischaemic heart disease	1972 (69.1%)	2000 (69.7%)
Duration of ischaemic heart disease, years	10.2 (5.0–16.3)	10.0 (5.1–16.0)
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%)
Stroke	122 (4.3%)	108 (3.8%)
Transient ischaemic attack	188 (6.6%)	166 (5.8%)
Hypertension	1624 (56.9%)	1663 (58.0%)
Heart failure	146 (5.1%)	149 (5.2%)
New York Heart Association class I	77 (2.7%)	83 (2.9%)
New York Heart Association class II	69 (2.4%)	66 (2.3%)
No heart failure	2707 (94.9%)	2719 (94.8%)
Dyslipidaemia	1817 (63.7%)	1806 (63.0%)

(Table 1 continues in next column)

	Allopurinol group (n=2853)	Usual care group (n=2868)
(Continued from previous column)		
Other medical history		
Chronic obstructive pulmonary disease	244 (8.6%)	251 (8.8%)
Diabetes	618 (21.7%)	623 (21.7%)
Type 1	24 (0.8%)	18 (0.6%)
Type 2	594 (20.8%)	605 (21.1%)
No diabetes	2235 (78.3%)	2245 (78.3%)
Concomitant medication ongoing at inclusion		
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%)
β-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 or 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%)
EQ-5D§		
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¶	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)

Data are mean (SD), n (%), or median (IQR). ACE=angiotensin-converting enzyme. CCS=Canadian Cardiovascular Society. eGFR=estimated glomerular filtration rate. \*Based on 2867 patients with data in the usual care group. †Based on 2841 patients with data in the allopurinol group and 2857 in the usual care group. ‡Based on 2807 patients with data in the allopurinol group and 2808 in the usual care group. §Based on 2846 patients with data in the allopurinol group and 2857 in the usual care group. ¶Based on 2495 patients with data in the allopurinol group and 2501 in the usual care group.

**Table 1: Baseline characteristics of the modified intention-to-treat analysis population**

withdrawal from randomised treatment are given in the appendix (p 5). The most common reason for withdrawal from treatment was an adverse event.

Baseline characteristics are shown in table 1. The overall mean age at study entry was 72.0 years (SD 6.8). 4321 (75.5%) participants were male, 5676 (99.2%) were white, and 544 (9.5%) were current smokers.

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

HR=hazard ratio. \*Calculated with the Wald test.

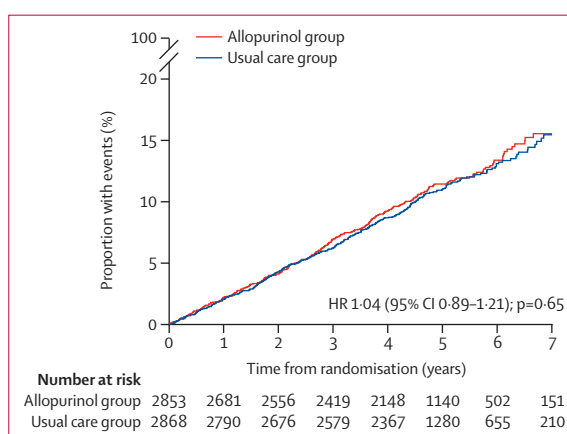
**Table 2: Primary and secondary time-to-event outcomes in the modified intention-to-treat population**

2257 (39.5%) participants were recruited in Scotland and 3464 (60.5%) in England.

The most commonly taken dose of allopurinol was 600 mg daily, with 1851 (84.8%) of 2184 participants still taking this dose at 6 weeks from randomisation, and 1199 (82.0%) of 1462 at 1 year, 1037 (80.4%) of 1290 at 2 years, 925 (78.7%) of 1175 at 3 years, and 719 (82.5%) of 871 at 4 years from randomisation. In the 2447 participants in the allopurinol group who had serum uric acid measured at baseline and 6 weeks after randomisation, serum uric acid concentrations decreased from a mean of 0.34 mmol/L (SD 0.08) to 0.18 mmol/L (SD 0.09). 45 participants randomly assigned to the usual care group started allopurinol treatment (for clinical reasons such as gout) during follow-up.

There was no evidence of a difference between the randomised treatment groups in the rates of the primary endpoint or for any of the secondary time-to-event outcomes (table 2; figures 2, 3). 314 (11.0%) of 2853 participants in the allopurinol group (2.47 events per 100 patient-years) and 325 (11.3%) of 2868 in the usual care group (2.37 events per 100 patient-years) had a primary endpoint (HR 1.04 [95% CI 0.89-1.21],  $p=0.65$ ; table 2; figure 2). 288 (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 0.87-1.20],  $p=0.77$ ; table 2; figure 3).

Results for the primary endpoint were consistent across all subgroups (appendix p 12). In an on-treatment analysis, results for the time-to-event analyses were broadly similar to those by modified intention to treat (appendix p 6). There was limited evidence of any treatment effect on quality of life, with no differences in EQ-5D outcomes or Seattle Angina Questionnaire outcomes at the end of the first year (table 3) or at the final visit (appendix p 9), with the exception of a nominally significant but only slightly greater fall in the usual care group in the physical domain



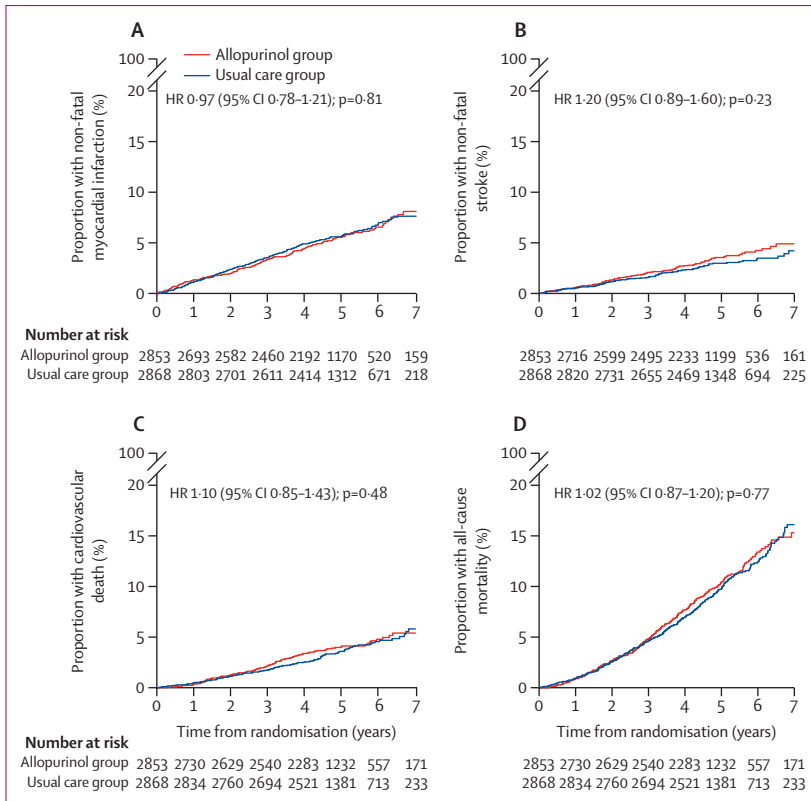
**Figure 2: Cumulative incidence functions for the primary composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death analysed in the modified intention-to-treat population**

The figure was adjusted for the competing risk of deaths not included in the endpoint. HR=hazard ratio.

score at the end of the first year (treatment difference 1.219 [95% CI 0.027-2.410],  $p=0.045$ ; table 3).

There was no evidence of a difference in the rates of serious adverse events between treatment groups, with the exception of endocrine disorders, where there were no patients with events in the allopurinol group and 14 in the usual care group (table 4). However, the endocrine disorders were spread across several different types (preferred terms; data not shown). 15 participants in the allopurinol group had serious adverse events that were considered to be potentially treatment related. None of the 278 fatal serious adverse events in the allopurinol group were considered to be treatment related. There was no difference between treatment groups in the rates of incident cancers (appendix p 7). Adjudicated causes of death (appendix p 8) were also well balanced between the





**Figure 3:** Cumulative incidence functions for non-fatal myocardial infarction (A), non-fatal stroke (B), and cardiovascular death (C), and Kaplan-Meier curves for all-cause mortality (D) analysed in the modified intention-to-treat population

Figures of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death were adjusted for the competing risk of deaths not included in the endpoint. HR=hazard ratio.

number adjudicated as being due to COVID-19 pneumonia was seven (0.2%) in the allopurinol group and seven (0.2%) in the usual care group. There were also no differences between the treatment groups in the numbers of participants with serious adverse events related to COVID-19 (30 [1.1%] in the allopurinol group vs 31 [1.1%] in the usual care group) or COVID-19 pneumonia (nine [0.3%] in the allopurinol group vs eight [0.3%] in the usual care group).

At the end of their first year in the study, a similar number of participants in the allopurinol group and in 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, a history of a new skin rash during the previous 12 months was reported more commonly by participants in the allopurinol group than in the usual care group (291 [13.1%] vs 223 [9.1%], p<0.0001). Occurrences of gout and skin rash reported at the end of the second year of the study were similar in both groups. At the end of the third and fourth years of the study, both skin rash and gout in the previous 12 months were reported more commonly by participants in the usual care group than in the allopurinol group of the study.

**Discussion**

The ALL-HEART study is the first large, prospective, randomised outcome trial of allopurinol in patients with ischaemic heart disease. In more than 5000 patients with ischaemic heart disease, but no gout, it showed no benefit of allopurinol on major cardiovascular outcomes. This was shown in the primary modified intention-to-treat analysis, and a similar result was found in the supporting on-treatment analysis, although the on-treatment analysis is likely to be considerably biased due to treatment discontinuation effects. There was no evidence of increased serious adverse events in participants in the allopurinol group compared with the usual care group, and the number of deaths in both groups of the study was also similar. There was no difference in incident cancers between participants in the allopurinol group and those in the usual care group. Apart from a lower incidence of gout reported in the participants in the allopurinol group after the second year of the study, which might be subject to some reporting bias and which might be expected with chronic urate-lowering therapy in a population at higher than average risk of gout, no other clinical or quality-of-life benefits of allopurinol were demonstrated in this study. As there was no significant effect of allopurinol on the primary endpoint, cardiovascular hospitalisations, or quality-of-life outcomes, no health economic benefit of allopurinol in this study is plausible.

Previous smaller interventional and observational studies exploring the effect of urate-lowering therapy on cardiovascular outcomes in patients with gout and various cardiovascular conditions have shown conflicting results, hence the importance of this prospective randomised trial in determining whether allopurinol provided benefits to

	Mean (SD) change from baseline at 1 year from randomisation		Estimated difference (95% CI)	p value
	Allopurinol group (n=2853)	Usual care group (n=2868)		
<b>Secondary EQ-5D outcomes at 1 year from randomisation*</b>				
Health state score	-0.081 (0.205)	-0.094 (0.202)	0.009 (-0.002 to 0.020)	0.11
Visual analogue score	-4.67 (17.11)	-4.98 (16.96)	0.114 (-0.839 to 1.066)	0.81
<b>Secondary Seattle Angina Questionnaire scores at 1 year from randomisation</b>				
Physical limitation domain†	-12.50 (18.85)	-13.90 (18.84)	1.219 (0.027 to 2.410)	0.045
Angina stability domain	0.81 (15.90)	0.35 (15.67)	0.194 (-0.669 to 1.057)	0.66
Angina frequency domain	-0.45 (15.92)	-1.48 (15.42)	0.167 (-0.814 to 1.148)	0.74
Treatment satisfaction domain	-1.85 (12.27)	-2.39 (13.02)	0.064 (-0.760 to 0.888)	0.88
Disease perception domain	-4.16 (18.17)	-5.16 (18.35)	0.622 (-0.371 to 1.615)	0.22

\*Based on 2846 patients with data in the allopurinol group and 2857 in the usual care group. †Based on 2495 patients with data in the allopurinol group and 2501 in the usual care group.

**Table 3:** Secondary quality-of-life outcomes in the modified intention-to-treat population

two study groups. The number of deaths adjudicated as being due to COVID-19 was nine (0.3%) in the allopurinol group and 11 (0.4%) in the usual care group, and the

patients with ischaemic heart disease. In recent years, two large randomised trials, the North American Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES)<sup>26</sup> and the Febuxostat versus Allopurinol Streamlined Trial (FAST),<sup>27</sup> reported on cardiovascular outcomes in patients with gout randomly assigned to treatment with allopurinol or the newer xanthine oxidase inhibitor, febuxostat. The CARES trial reported that, in patients with gout and established cardiovascular disease, febuxostat was non-inferior to allopurinol for the primary endpoint of the study (composite of death from cardiovascular causes, myocardial infarction, stroke, or unstable angina with urgent revascularisation). However, rates of the secondary outcomes of adverse cardiovascular outcomes, all-cause death, and cardiovascular death were significantly higher with febuxostat than with allopurinol. This finding led to regulators issuing warnings against the use of febuxostat in patients with pre-existing cardiovascular disease. However, by contrast, the FAST trial, with better retention in study follow-up and adherence to randomised treatment, found no increased cardiovascular risk with febuxostat, and reported a lower rate of all-cause deaths and cardiovascular deaths in the febuxostat group than in the allopurinol group. There were no placebo or usual care groups in the CARES or FAST trials, and results of the ALL-HEART study were eagerly awaited to assist with better understanding of the findings of the CARES and FAST trials. The ALL-HEART study results show that treatment with allopurinol was not different to usual care in patients with ischaemic heart disease but no gout regarding major cardiovascular outcomes.

It would be interesting to understand whether febuxostat might have given a different result to allopurinol if it had been used instead in the ALL-HEART study. A randomised trial of febuxostat therapy versus control in 1070 patients aged 65 years or older in Japan with asymptomatic hyperuricaemia and at risk of cerebral, cardiovascular, or renal events, the Febuxostat for Cerebral and Cardio-renalovascular Events Prevention Study (FREED), found a reduction in the primary composite cardiorenal endpoint in the febuxostat group, but this was driven by reduced progression of renal dysfunction rather than an effect on other cardiovascular endpoints.<sup>28</sup> Another trial in Japan of febuxostat therapy versus non-pharmacological lifestyle modification as a control group in 483 patients with asymptomatic hyperuricaemia found no effect on progression of carotid atherosclerosis (carotid-intima medial thickness) over a 2-year treatment period.<sup>29</sup> Currently, there remains no clear place for urate-lowering therapy in cardiovascular care, except in certain situations in which it is already indicated, such as clinical gout.

The COVID-19 pandemic started during the late follow-up period of the study and had a major effect in the UK, where the study was based, during approximately the last 18 months of the study follow-up period. Because the ALL-HEART study had decentralised elements in its

	Allopurinol group (n=2805)	Usual care group (n=2868)	Difference in rates (95% CI)
Any serious adverse event	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)

Data are number (rate per 100 patient-years) unless otherwise stated.

**Table 4: Serious adverse events during the study, by system organ class, in the safety population**

design, including remote participant follow-up, the effect of the COVID-19 pandemic on this study was not as large as it might otherwise have been. There were no differences in rates of COVID-19 or COVID-19 pneumonia serious adverse events or deaths between the allopurinol and usual care groups. Despite the use of record linkage to detect potential endpoints, there might have been some under-reporting of cardiovascular endpoints at the height of the pandemic because fewer patients attended hospitals with acute coronary syndromes and other cardiovascular conditions during lockdown periods in early 2020.<sup>30</sup>

The dose of allopurinol chosen for the ALL-HEART study (600 mg daily for most participants) was within the licensed dose range for treatment of gout but higher than the daily dose generally used in clinical practice in patients with gout in the UK (most commonly 100–300 mg daily).<sup>27</sup> The daily dose of 600 mg was chosen for the ALL-HEART study on the basis of earlier studies that had suggested higher doses of allopurinol might be needed to achieve beneficial cardiovascular effects.<sup>5,21,31</sup> Serum uric acid concentrations were significantly reduced (halved) after 6 weeks of allopurinol, achieving concentrations well

below normal laboratory ranges or treatment targets in patients with gout. A limitation of the study is that adherence to randomised therapy was self-reported at the week 6 visit and annually, but in general any clarifications and checks made with prescribing practices correlated with patient reports of whether they were still taking randomised therapy. The marked reduction in serum uric acid concentrations from baseline at the 6-week visit also suggests good adherence to allopurinol, at least initially. Patients were included in the study whatever their baseline concentration of serum uric acid, but were excluded if they had a history of gout, which might have excluded the people with ischaemic heart disease with the highest concentrations of serum uric acid from the study. It is possible that allopurinol might have shown more anti-oxidative activity in patients with higher serum uric acid concentrations and that, in the absence of hyperuricaemia, allopurinol might have had pro-oxidant effects. However, our prespecified subgroup analysis according to tertiles of baseline serum uric acid concentration showed no significant effect on the primary outcome.

Allopurinol is known to cause rash in a proportion of patients, especially soon after starting therapy. To avoid the rare, but potentially serious, complication of severe rashes such as Stevens-Johnson syndrome developing in study participants, allopurinol was stopped immediately if participants reported any rash that might be related to allopurinol. This low threshold for stopping allopurinol might have resulted in a higher withdrawal from therapy rate than would have been ideal within the study, but it also reflects real-life practice if allopurinol were to be used in clinical care. Similar rates of withdrawal from randomised treatment were seen within the CARES trial, with 56.6% of participants in CARES discontinuing randomised treatment before the end of the trial, and that was in a population who had a clear clinical indication (gout) for urate-lowering therapy. Most patients who withdrew from allopurinol in ALL-HEART remained within the study follow-up, so events occurring after their withdrawal from allopurinol would have been detected.

There were more withdrawals of consent from the study in the allopurinol group than in the usual care group. This difference appeared early in the study and might have been partly driven by the extra study visit for participants in the allopurinol group at 6 weeks and by withdrawal of consent accompanying early withdrawals from allopurinol. Because of the high treatment discontinuation rate, the on-treatment analysis is likely to be biased, although the results were consistent with the primary modified intention-to-treat analysis. Likewise, results for participant-reported outcomes should be treated with caution due to potential reporting bias in this open-label study. The absence of a placebo, instead using a pragmatic usual care group, might have led to more unbalanced withdrawal from therapy and from the study, as well as more bias in reporting of more subjective adverse events. 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 masked to treatment allocation. Serious adverse events were also detected using record-linkage information in addition to participant reports, so should be relatively unbiased.

The generalisability of the ALL-HEART study findings to the population of patients with ischaemic heart disease is likely to be high. Patients were recruited from, and treated within, their usual primary care setting. It was designed as a pragmatic study that could be delivered successfully within the UK National Health Service primary care setting. The final number of participants randomised (5937) exceeded the target of 5215 randomised participants due to a significant increase in the recruitment rate in the final weeks of recruitment. Follow-up was entirely remote after the first 6 weeks of the study, with a minimal effect on participants' usual care environment. Better ethnic diversity in recruitment could have improved the generalisability to non-white populations. 99.2% of participants within the ALL-HEART study reported white ethnicity. 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. Most of the participants had long-term ischaemic heart disease, with a median duration of ischaemic heart disease of 10.2 years at study entry, although patients with recent coronary events were not excluded. It is possible that different results might have been obtained if a more acute patient population had been recruited.

In summary, we found that treatment with allopurinol 600 mg daily did not improve cardiovascular outcomes compared with usual care in patients with ischaemic heart disease. Based on the results of the ALL-HEART study, allopurinol should not be recommended for secondary prevention of cardiovascular events in patients with ischaemic heart disease.

#### Contributors

The idea for the study was conceived by ISM and TMM. ISM, TMM, IF, AJA, and AW participated in the design of the study. NG and IF did the statistical analysis and directly accessed and verified the underlying data reported in the manuscript. ISM wrote the first draft of the manuscript with input from IF, TMM, and NG. All authors participated in the interpretation of the data, and critical review of the manuscript. All authors read and approved the final version. ISM, TMM, IF, and NG had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

#### Declaration of interests

ISM reports research grants from Menarini, EMA, Sanofi, Health Data Research UK, the British Heart Foundation, and Innovative Medicines Initiative; institutional consultancy income from AstraZeneca outside the submitted work; and personal income from AstraZeneca and Amgen outside the submitted work. TMM reports grants from Menarini/Ipsen/Teijin and Merck Sharp & Dohme outside the submitted work, and personal income for consultancy from Novartis and AstraZeneca outside the submitted work, and is a trustee of the Scottish Heart Arterial Risk Prevention Society. AGB reports personal income from Novartis, Mylan, AstraZeneca, Bayer, Daiichi-Sankyo, Boehringer, Pfizer, Galderma, Zambon, and Novo-Nordisk outside the submitted work. ADS and the University of Dundee hold a European patent for the use of xanthine

oxidase inhibitors in treating chest pain in angina pectoris. AW declares personal income for consultancy from AbbVie, Akcea, Albireo, Alexion, Allergan, Amarin, Apsara, Arena, Astellas, AstraZeneca, Autolus, Bayer, Biocryst, Biogen, Biomarin, Bristol Myers Squibb, Boehringer Ingelheim, Calico, Celgene, Chiesi, Daiichi Sankyo, Diurnal, Elsay, Eli Lilly, Ferring, Galapagos, Gedeon Richter, Gilead, GlaxoSmithKline, GW Pharma, Idorsia, Incyte, Intercept, Ionis, Ipsen, Janssen, Jazz, Jcyte, Kite Gilead, LEK, Leo Pharma, Les Laboratoires Servier, Lundbeck, Merck (Merck Sharp & Dohme), Merck-Serono, Mitenyi, MundibioPharma, Mustang Bio, Mylan, Myovant, Norgine, Novartis, Novo Nordisk, Orchard, Paion, Pfizer, Pierre Fabre, PTC, RegenXBio, Rhythm, Sanofi, Santen, Sarepta, SeaGen, Shionogi, Sigmatec, SOBI, Takeda, Tanaya, UCB, and Vertex outside the submitted work. JST declares research funding from the UK National Institute for Health and Care Research (NIHR) and NHS England outside the submitted work and membership of a UK National Institute for Health and Care Excellence guideline committee on management of atrial fibrillation. All other authors declare no competing interests.

#### Data sharing

The datasets generated or analysed during the current study 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 and will be considered.

#### Acknowledgments

This study was funded by the NIHR Health Technology Assessment programme (HTA 11/36/41 to ISM, IF, CJH, LW, ADS, AGB, AJA, AW, JST, and TMM). The views expressed are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care. The study was supported by the Scottish Primary Care Research Network, Support for Science Scotland (Grampian, Highlands, Tayside, Fife, Forth Valley, Greater Glasgow and Clyde, Lothian, Ayrshire and Arran, Dumfries and Galloway, and Lanarkshire), and the NIHR Local Clinical Research Networks (East Midlands, West Midlands, Eastern, North Thames, Yorkshire and Humber, North East and North Cumbria, North West Coast, Kent, Surrey and Sussex, and South West Peninsula), which assisted with recruitment and other study activities. We thank Public Health Scotland and NHS Digital for providing data linkage. We thank all the participants, physicians, nurses, and other staff who participated in the ALL-HEART study.

#### References

- Weisman A, Tomlinson GA, Lipscombe LL, Perkins BA, Hawker GA, Hawker GA. Association between allopurinol and cardiovascular outcomes and all-cause mortality in diabetes: a retrospective, population-based cohort study. *Diabetes Obes Metab* 2019; **21**: 1322–29.
- Lai S-W, Lin C-L, Liao K-F. Case-control study examining the association between allopurinol use and ischemic cerebrovascular disease. *J Investig Med* 2019; **67**: 48–51.
- Ju C, Lai RWC, Li KHC, et al. Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users. *Rheumatology* 2020; **59**: 2340–49.
- Suissa S, Suissa K, Hudson M. Effectiveness of allopurinol in reducing mortality: time-related biases in observational studies. *Arthritis Rheumatol* 2021; **73**: 1749–57.
- George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 2006; **114**: 2508–16.
- Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105**: 2619–24.
- Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002; **106**: 221–26.
- Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. *Hypertension* 2000; **35**: 746–51.
- Guthikonda S, Sinkey C, Barenz T, Haynes WG. Xanthine oxidase inhibition reverses endothelial dysfunction in heavy smokers. *Circulation* 2003; **107**: 416–21.
- Rekhras S, Gandy SJ, Szejewski BR, et al. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. *J Am Coll Cardiol* 2013; **61**: 926–32.
- Gaffo AL, Calhoun DA, Rahn EJ, et al. Effect of serum urate lowering with allopurinol on blood pressure in young adults: a randomized, controlled, crossover trial. *Arthritis Rheumatol* 2021; **73**: 1514–22.
- Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008; **300**: 924–32.
- Morgan BJ, Teodorescu M, Pegelow DF, et al. Effects of losartan and allopurinol on cardiorespiratory regulation in obstructive sleep apnoea. *Exp Physiol* 2018; **103**: 941–55.
- Higgins P, Walters MR, Murray HM, et al. Allopurinol reduces brachial and central blood pressure, and carotid intima-media thickness progression after ischaemic stroke and transient ischaemic attack: a randomised controlled trial. *Heart* 2014; **100**: 1085–92.
- Szejewski BR, Gandy SJ, Rekhras S, et al. Allopurinol reduces left ventricular mass in patients with type 2 diabetes and left ventricular hypertrophy. *J Am Coll Cardiol* 2013; **62**: 2284–93.
- Kao MP, Ang DS, Gandy SJ, et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1382–89.
- Gingles CR, Symon R, Gandy SJ, et al. Allopurinol treatment adversely impacts left ventricular mass regression in patients with well-controlled hypertension. *J Hypertens* 2019; **37**: 2481–89.
- Rutherford E, Ireland S, Mangion K, et al. A randomized, controlled trial of the effect of allopurinol on left ventricular mass index in hemodialysis patients. *Kidney Int Rep* 2020; **6**: 146–55.
- Pop-Busui R, Stevens MJ, Raffel DM, et al. Effects of triple antioxidant therapy on measures of cardiovascular autonomic neuropathy and on myocardial blood flow in type 1 diabetes: a randomised controlled trial. *Diabetologia* 2013; **56**: 1835–44.
- Lim TK, Noman A, Choy AMJ, Khan F, Struthers AD, Lang CC. The APEX trial: effects of allopurinol on exercise capacity, coronary and peripheral endothelial function, and natriuretic peptides in patients with cardiac syndrome X. *Cardiovasc Ther* 2018; **36**: e12311.
- Noman A, Ang DSC, Ogston S, Lang CC, Struthers AD. High dose allopurinol prolongs exercise in chronic stable angina: a randomised placebo controlled trial. *Lancet* 2010; **375**: 2161–67.
- Huang Y, Zhang C, Xu Z, et al. Clinical study on efficacy of allopurinol in patients with acute coronary syndrome and its functional mechanism. *Hellenic J Cardiol* 2017; **58**: 360–65.
- Rajendra NS, Ireland S, George J, Belch JJ, Lang CC, Struthers AD. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. *J Am Coll Cardiol* 2011; **58**: 820–28.
- Mackenzie IS, Ford I, Walker A, et al. Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study. *BMJ Open* 2016; **6**: e013774.
- Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995; **25**: 333–41.
- White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018; **378**: 1200–10.
- Mackenzie IS, Ford I, Nuki G, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet* 2020; **396**: 1745–57.
- Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for cerebral and cardiorenovascular events prevention study. *Eur Heart J* 2019; **40**: 1778–86.
- Tanaka A, Taguchi I, Teragawa H, et al. Febuxostat does not delay progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia: a randomized, controlled trial. *PLoS Med* 2020; **17**: e1003095.
- Mafham MM, Spata E, Goldacre R, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020; **396**: 381–89.
- MacIsaac RL, Salatzki J, Higgins P, et al. Allopurinol and cardiovascular outcomes in adults with hypertension. *Hypertension* 2016; **67**: 535–40.