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

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Scientific summary

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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

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

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).

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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