

# Allopurinol in Patients with Pulmonary Hypertension Associated with Chronic Lung Disease

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**Background:** Oxidative stress (OS) has been implicated in the development of pulmonary hypertension (PH) and ventricular hypertrophy. Xanthine oxidase is a well-recognised source of reactive oxygen species, which lead to OS. The aim of this proof of concept study was to assess whether allopurinol (xanthine oxidase inhibitor) would reduce right ventricular mass (RVM) in patients with PH-associated chronic lung disease (PH-CLD).

**Methods:** We conducted a randomised, double-blind, parallel-group, placebo-controlled trial in patients with PH-CLD (93% COPD, 7% IPF) who were randomly assigned to receive allopurinol or placebo for 12 months. The primary outcome was the mean change in RVM, as assessed by cardiac magnetic resonance imaging (CMRI). Secondary outcomes included quality of life (QOL), spirometry and six-minute walk test (6MWT).

**Results:** Seventy-one patients were recruited: mean age 71 years, mean pulmonary arterial pressure 30 mm Hg, FEV<sub>1</sub> 60% and resting SpO<sub>2</sub> 96%. After 12 months, there was no significant difference in the change in RVM from baseline (allopurinol 1.85g vs placebo 0.97g with mean difference 0.88g, CI -4.77 to 3.01, p = 0.7). There were also no significant changes in other cardiac parameters measured on MRI, in QOL, spirometry and 6MWT. Subgroup analysis showed that allopurinol significantly reduced RVM compared to placebo with -6.16g vs 0.75g and mean difference 6.92g (CI 1.14 to 12.69, p = 0.02) in COPD patients with more severe airflow limitation.

**Conclusion:** Allopurinol had no overall impact on patients with PH-CLD but had potential benefit in COPD patients with more severe airflow limitation.

**Keywords:** pulmonary hypertension, right ventricle, allopurinol, chronic lung disease

## Introduction

The development of pulmonary hypertension (PH) is a well-recognised complication of many chronic lung diseases and is generally mild to moderate in severity. The most common chronic lung diseases associated with PH are chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD).<sup>1</sup> Irrespective of the underlying pulmonary aetiology, the presence of even mild PH is associated with deterioration in exercise capacity, worsening of hypoxaemia and shorter survival.<sup>2,3</sup>

Pulmonary hypertension in hypoxaemic lung diseases is attributed to multiple factors including pulmonary vasoconstriction caused by alveolar hypoxia and the distortion of pulmonary vessels by parenchymal changes.<sup>4</sup> Right ventricular hypertrophy (RVH) is believed to be the consequence of chronic pulmonary hypertension.<sup>5</sup> RVH is the initiating step in the progression to right ventricular (RV) failure in lung disease.

At present, there is no specific therapy recommended for patients with group 3 PH associated with lung disease.<sup>1</sup> The European Respiratory Society advocates

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optimising the treatment of the underlying lung disease and advises that patients should receive long-term oxygen therapy (LTOT) if they are hypoxaemic as LTOT has been shown to partially reduce the progression of PH in COPD.<sup>1</sup>

Allopurinol is a xanthine oxidase inhibitor which decreases both uric acid (UA) and oxidative stress (OS). Five experimental studies have shown that allopurinol inhibits hypoxia-induced pulmonary vasoconstriction, pulmonary hypertension, endothelial dysfunction and vascular remodelling.<sup>6–10</sup> Hypoxia is known from many studies to up-regulate xanthine oxidase and therefore to increase its production of UA and OS.<sup>6</sup> Hypoxia-induced oxidative stress has also been shown to have a direct effect in the development of ventricular hypertrophy.<sup>11</sup> Allopurinol has also been shown in clinical studies to reduce left ventricular mass in patients with chronic kidney disease, optimally treated ischaemic heart disease and type 2 diabetes mellitus.<sup>12–14</sup>

The aim of this proof of concept study was to investigate whether high-dose allopurinol would reduce right ventricular mass in patients with pulmonary hypertension associated with chronic lung disease (PH-CLD).

The hypothesis is that allopurinol would reduce the production of reactive oxygen species, thereby decreasing oxidative stress, which would lead to reduction in right ventricular mass in patients with PH-CLD.

## Methods

### Study Design and Patients

This is a randomised, placebo-controlled, double-blind, parallel-group study conducted over a 12-month treatment period at a single centre in Dundee, Scotland between April 2015 and July 2017. The trial was approved by the East of Scotland Research Ethics Committee (reference: 14/ES/1035) and was carried out in accordance with the Declaration of Helsinki. This study has been registered with the International Standard Randomized Controlled Trial Number register (ISRCTN11081180) and European Clinical Trials Database (EudraCT no: 2014–002305-38).

We recruited patients from the chest clinics at the local hospital, from local respiratory databases, from general practices covering two UK National Health Service boards (Tayside and Fife) via the Scottish Primary Care Research Network, and from the Scottish Health Research Register.

Box 1 shows the study eligibility criteria. All patients provided written informed consent. All their usual medications were continued throughout the study.

### Box 1 Inclusion and Exclusion Criteria

#### Inclusion criteria

- Male or female participants aged 18 years or over
- Known diagnosis of chronic obstructive pulmonary disease or interstitial lung disease
- Stable lung disease medication for at least two weeks prior to consent
- Pulmonary acceleration time < 110 ms and/or right ventricular systolic pressure > 25 mm Hg and/or right ventricular free wall thickness  $\geq$  5.5 mm (on screening echocardiography)

#### Exclusion criteria

- Documented allergy or intolerance to allopurinol
- Active gout (i.e flare up < 2 years) or currently taking allopurinol
- Left ventricular ejection fraction < 45% on echocardiography
- Severe aortic stenosis on echocardiography
- Severe hepatic disease
- Chronic kidney disease class 3B or greater
- Patients taking azathioprine, 6-mercaptopurine, or theophylline
- Malignancy (receiving active treatment) or other life threatening diseases
- Any contraindication to MRI (claustrophobia, metal implants)

## Randomisation and Masking

Eligible patients were randomly assigned by a validated computer-generated random allocation sequence to a study number. The patients were given the trial medication, which was either allopurinol or matched placebo, carrying their unique study number. At baseline visit, they would receive either allopurinol 100 mg/day or matched placebo orally for two weeks. If this was tolerated, the trial medication was increased to 300mg of allopurinol or placebo for four weeks. The dosage was further increased after this four week period to the target dose of 600mg (given as 300 mg twice daily) for the remaining duration of the trial. The intervention and placebo capsules and bottles looked identical and double blinding was maintained throughout. Patients, study investigators and outcome assessors were masked to group allocation. Unmasking was done only after the end of the trial.

## Procedures

All recruited participants underwent screening echocardiography to check if they were eligible. PLSC undertook echocardiography with either Philips iE33 system (Philips, Netherlands) or Philips Epiq7 ultrasound system (Philips

Ultrasound, USA). If the measurements were difficult to obtain using standard acoustic windows, the oblique sub-costal windows were used to assess the pulmonary acceleration time with pulse-wave Doppler.<sup>15</sup> The estimated mean pulmonary arterial pressure (MPAP) was then calculated with Dabestani equation, and/or the right ventricular systolic pressure with the Bernoulli equation.<sup>16</sup>

All participants underwent spirometry, six-minute walk test (6MWT) and cardiac MRI scan at randomisation visit and these measures were repeated at final visit. Spirometry was performed using MicroLoop spirometer (Micro Medical, Rochester, UK) as per ATS/ERS guidelines and 6MWT was performed as per ATS guidelines.<sup>17,18</sup> Patients were allowed to use their usual walking aids but participants on LTOT did their 6MWT off oxygen. Oxygen saturation during the 6MWT was measured using portable pulse oximeter.

Quality of life (QOL) at baseline and final visits was assessed using the St George's Respiratory Questionnaire (SGRQ) and the King's Brief Interstitial Lung Disease (K-BILD) questionnaire. The 36-Item Short Form Survey (SF-36) was also used to assess general QOL measure.

Blood samples were taken at baseline and final visits for N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high-sensitive troponin I (hs-Trop I).

## Cardiac MRI

Cardiac magnetic resonance imaging (CMRI) was performed at baseline and at final visit only. The images were acquired on a 32 RF cardiac receiver channel, 3 Tesla MRI scanner (Prisma, Siemens, Erlangen, Germany) using dedicated cardiac coils as previously described.<sup>19</sup> The images were exported, and analysis performed offline by an independent, blinded radiologist (JWM), with five years experience in CMRI, using CVI 42 (Circle Cardiovascular Imaging software, Calgary, Canada).

The epicardial and endocardial contours were drawn around the right ventricle at end systole and end diastole. Trabeculae were included in the mass measurement and excluded from the volume calculation. The septum was treated as belonging to the left ventricle and was excluded from the right ventricular mass (RVM). Ventricular mass and volumes were indexed to body surface area, which was calculated using the Mosteller formula.<sup>20</sup>

## Outcomes

The primary outcome was the mean difference between the baseline and final right ventricular mass index after 12 months of allopurinol compared to placebo. Secondary outcomes

included change in other cardiac MRI measurements, lung function (spirometry), exercise capacity (6MWT), quality of life measures (SGRQ, K-BILD, SF-36), and blood markers (NT-proBNP, hs-Trop I).

## Statistical Analysis

Bradlow et al,<sup>21</sup> advised that 34 patients are required to have 80% power at  $p < 0.05$  to detect changes in the manually measured outcomes of RV mass of 10g. However, a 10g change in ventricular mass was over ambitious. 66 patients were required to achieve 80% power to detect a 5g change in RVM at a significance level of  $p < 0.05$ , based on previous studies investigating the allopurinol's effect on left ventricular mass using CMRI.<sup>12-14</sup> In order to allow for 10% drop-outs, 72 eligible patients were recruited.

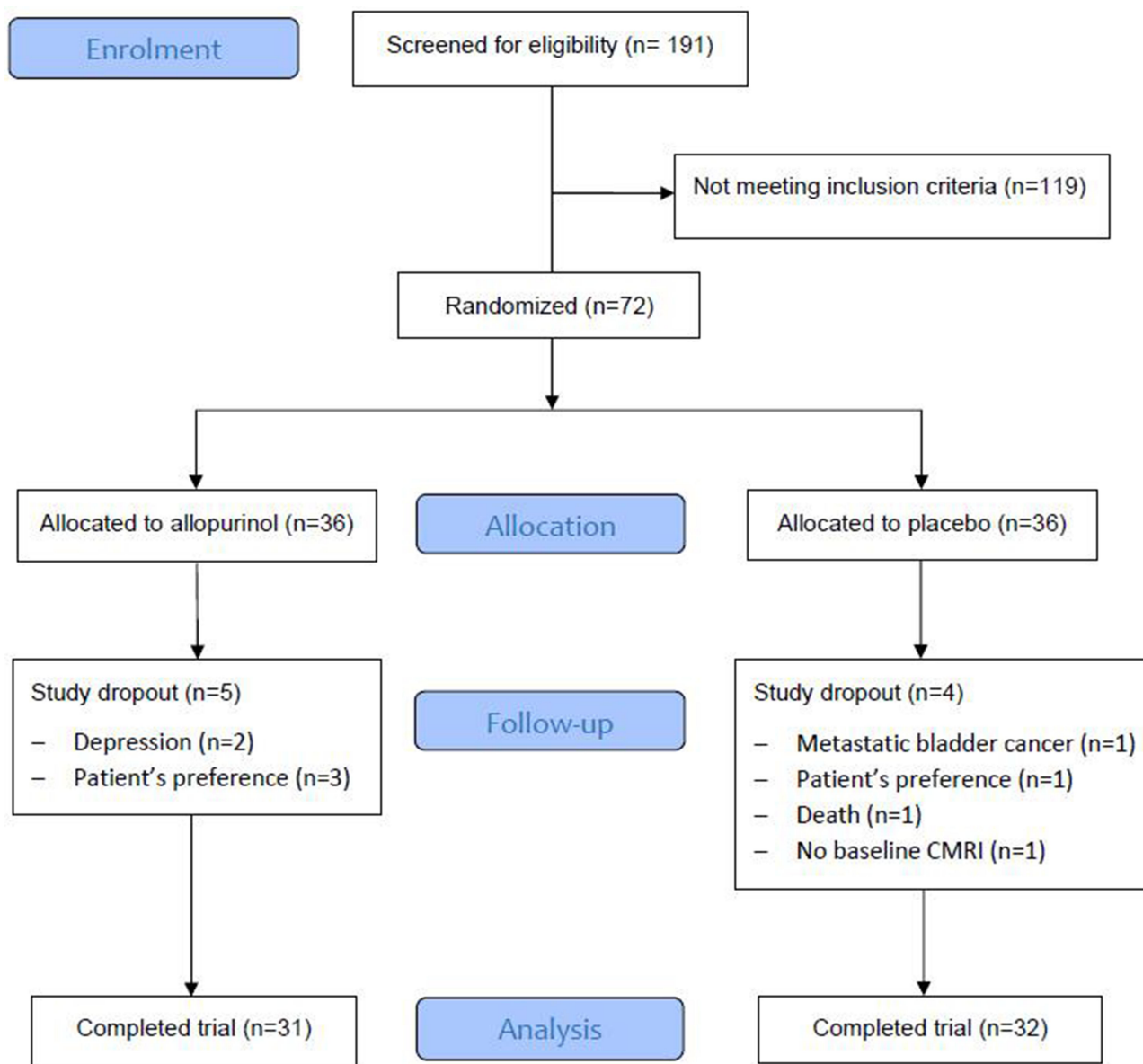
The primary analysis was based on the intention-to-treat principle. The extent of missing data was examined and the reason for drop-out was ascertained. Multiple imputations have been used to impute missing values and where assumptions for missing at random data were met. Complete case analysis where missing patients are excluded was carried out as a secondary analysis.

The data for continuous outcome measures were assessed for normality of distribution prior to analysis. The descriptive statistics was reported in the form of mean  $\pm$  standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and percentages and denominators for categorical variables are tabulated at the baseline visit. The comparison between continuous variables is analysed using paired *t*-tests (to test within group differences), independent *t*-test (to test between group differences), or Mann-Whitney U-test (for non-normally distributed data) whilst categorical variables were analysed using Chi-squared test.

All statistical analyses were undertaken blinded using IBM SPSS Statistics v22.0 (IBM, United States). A two-sided  $p$  value  $< 0.05$  was considered statistically significant.

## Results

The flow of participants is depicted in the CONSORT diagram (Figure 1). A total of 72 participants were recruited for the study. One patient was randomised but excluded from analysis as he was unable to undergo baseline CMRI due to claustrophobia. 36 received allopurinol and 35 received placebo. 63 (89%) participants completed the study per protocol and the average follow-up period



**Figure 1** CONSORT diagram showing participant flow through the study.

was 11.3 months for completers. The compliance from tablet counting was high at 96%. All the participants tolerated a daily dosage of 600 mg of allopurinol except 1 participant who was left on 300 mg as he developed fatigue and lethargy while taking 600 mg.

The baseline characteristics were similar between the two groups (Table 1): mean age 71 years, estimated MPAP 30 mm Hg, mean FEV<sub>1</sub> 60% predicted, resting oxygen saturation (SaO<sub>2</sub>) 96% and predominantly male (62%). 66 (93%) participants had COPD and five (7%) had IPF. Five patients were on LTOT. There were eight study dropouts (allopurinol n = 5, placebo = 3): participant's preference (n = 4), depression (n = 2), metastatic bladder

cancer (n = 1) and death (n = 1). No patient receiving LTOT needed an increase in oxygen dose. One patient in the placebo who was already on ambulatory oxygen was prescribed LTOT during the trial period.

At baseline, RVM and RVMI were similar in both groups (Table 2). In the intention-to-treat analysis (Table 3), there was no significant difference between allopurinol group and placebo group in the change in RVM (allopurinol group  $1.85 \pm 1.56$  g vs placebo group  $0.97 \pm 1.20$  g;  $p = 0.66$ ) and in the change in RVMI (allopurinol group  $0.70 \pm 0.75$  g/m<sup>2</sup> vs placebo group  $0.50 \pm 0.60$  g/m<sup>2</sup>;  $p = 0.83$ ). There was also no significant difference in the change in RVM and RVMI when per-protocol analysis was performed. In the post-hoc

**Table 1** Baseline Characteristics of Study Participants

	Allopurinol (n = 36)	Placebo (n = 35)	p
Age (years)	70 (5)	71 (6)	0.45
Male sex (%)	22 (61)	22 (63)	
Height (m)	1.65 (0.11)	1.68 (0.09)	0.29
Weight (kg)	80.2 (16.6)	82.7 (17.0)	0.54
BMI (kg/m <sup>2</sup> )	29 (5)	29 (5)	0.98
Heart rate (bpm)	79 (14)	78 (13)	0.99
Systolic BP (mm Hg)	138 (16)	140 (19)	0.67
Diastolic BP (mm Hg)	76 (9)	75 (14)	0.93
mMRC dyspnoea scale	2.8 (1.3)	2.7 (1.2)	0.14
WHO Functional class	2.3 (0.8)	2.4 (0.7)	0.48
Smoking status			
• Current smoker	9 (25)	8 (23)	
• Ex-/non-smoker	27 (75)	27 (77)	
Pack-year history	46.9 (27.4)	50.3 (28.6)	0.61
Long-term oxygen	3 (8)	2 (6)	
SaO <sub>2</sub> (%)	96 (3)	96 (3)	0.67
PAT (ms)	94.9 (9.6)	97.1 (12.1)	0.38
COPD	34 (94)	32 (91)	
• FEV <sub>1</sub> (% predicted)	60 (21)	58 (20)	0.64
ILD	2 (6)	3 (9)	

**Notes:** Data are mean (SD), n (%) or median (IQR): Independent samples t-test for normally-distributed continuous variables and Mann-Whitney U-test for non-parametric data.

**Abbreviations:** BMI, body mass index; mMRC, modified medical research council; FEV<sub>1</sub>, forced expiratory volume in 1 sec; SaO<sub>2</sub>, blood oxygen saturation; PAT, pulmonary acceleration time; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 sec; ILD, interstitial lung disease.

exploratory subgroup analysis according to severity of air-flow limitation (Table 4), participants with more severe air-flow limitation (GOLD 3 and 4) showed significant reduction in RVM (allopurinol group  $-6.16 \pm 1.97$  g vs placebo group  $0.75 \pm 1.71$  g;  $p = 0.02$ ) and in RVMI (allopurinol group  $-3.13 \pm 1.00$  g/m<sup>2</sup> vs placebo group  $0.54 \pm 0.85$  g/m<sup>2</sup>;  $p = 0.02$ ). (Figure 2)

For the other parameters measured on CMRI for both right and left ventricles, there were no significant changes in end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF), stroke volume (SV) and their indexed values (Table 3). There were also no statistically significant changes in any of the quality-of-life, 6MWT and spirometric measurements (Table 5). There was no significant change in NT-proBNP and hs-Trop I levels over the study period (Table 6). There was a significant reduction in uric acid level by 59% with allopurinol treatment.

**Table 2** Baseline Cardiac MRI Measurements

	Allopurinol (n = 36)	Placebo (n = 35)	p
RVM (g)	40.27 (1.62)	41.19 (2.06)	0.73
RVMI (g/m <sup>2</sup> )	21.02 (0.68)	20.88 (0.83)	0.90
RVESV (mL)	49.7 (2.9)	55.8 (3.6)	0.19
RVESVI (mL/m <sup>2</sup> )	26.1 (1.6)	28.3 (1.7)	0.33
RVEDV (mL)	118.6 (5.2)	129.1 (5.8)	0.17
RVEDVI (mL/m <sup>2</sup> )	62.2 (2.5)	65.5 (2.3)	0.34
RVSV (mL)	68.8 (3.3)	73.4 (3.8)	0.35
RVEF (%)	57.0 (2.0)	56.5 (1.7)	0.85
RA area (cm <sup>2</sup> )	20.8 (0.9)	21.9 (1.2)	0.45
LVM (g)	106.8 (4.8)	105.9 (4.9)	0.89
LVMI (g/m <sup>2</sup> )	55.5 (1.8)	53.7 (2.0)	0.52
LVSV (mL)	70.9 (3.4)	76.3 (3.3)	0.25
LVEF (%)	52.9 (1.9)	56.8 (1.5)	0.10
LA area (cm <sup>2</sup> )	21.1 (1.1)	22.8 (1.3)	0.35
VMI	0.39 (0.01)	0.39 (0.01)	0.69

**Notes:** Data are mean (SEM); Independent samples t-test for normally-distributed continuous variables and Mann-Whitney U-test for non-parametric data.

**Abbreviations:** RVM, right ventricular mass; RVMI, right ventricular mass index; RVESV, right ventricular end-systolic volume; RVEDV, right ventricular end-diastolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; RA area, right atrial area; LVM, left ventricular mass; LVMI, left ventricular mass index; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LA area, left atrial area; VMI, ventricular mass index.

**Table 3** CMRI Changes After Allopurinol Treatment (Intention-to-Treat Analysis)

	Allopurinol (n = 36)	Placebo (n = 35)	p
Right ventricle			
Change in RVM (g)	1.85 (1.56)	0.97 (1.20)	0.66
Change in RVMI (g/m <sup>2</sup> )	0.70 (0.75)	0.50 (0.60)	0.83
Change in RVESV (mL)	4.8 (2.5)	3.8 (2.8)	0.79
Change in RVESVI (mL/m <sup>2</sup> )	1.9 (1.3)	1.7 (1.4)	0.92
Change in RVEDV (mL)	8.8 (4.2)	5.6 (4.2)	0.59
Change in RVEDVI (mL/m <sup>2</sup> )	4.0 (2.2)	3.1 (2.2)	0.75
Change in RVSV (mL)	3.0 (3.1)	1.6 (2.7)	0.73
Change in RVSVI (mL/m <sup>2</sup> )	1.4 (1.7)	1.1 (1.3)	0.88
Change in RVEF (%)	1.3 (2.4)	1.7 (1.7)	0.91
Change in RA area (cm <sup>2</sup> )	-2.2 (1.5)	-0.6 (1.5)	0.45
Left ventricle			
Change in LVM (g)	0.8 (3.2)	-1.9 (2.8)	0.52
Change in LVMI (g/m <sup>2</sup> )	0.1 (1.5)	-1.1 (1.2)	0.53
Change in LVSV (mL)	5.8 (3.3)	0.4 (2.6)	0.20
Change in LVEF (%)	3.0 (2.0)	0.0 (1.3)	0.20
Change in LA area (cm <sup>2</sup> )	0.6 (0.1)	-0.3 (0.8)	0.49

**Note:** Data are mean (SEM).

**Abbreviations:** RV, right ventricular; LV, left ventricular; MI, mass index; ESV, end systolic volume; EDV, end diastolic volume; SV, stroke volume; EF, ejection fraction.

Another post-hoc exploratory subgroup analysis when stratifying by NT-proBNP level showed that the patients (n = 31) with higher NT-proBNP level (>489 pg/mL) had

**Table 4** CMRI Changes for RV After Allopurinol Treatment in Subgroup GOLD 3 and 4

	Allopurinol (n = 7)	Placebo (n = 13)	p
Change in RVM (g)	-6.16 (1.97)	0.75 (1.71)	0.02
Change in RVMI (g/m <sup>2</sup> )	-3.13 (1.00)	0.54 (0.85)	0.02
Change in RVESV (mL)	-1.4 (6.6)	2.5 (5.8)	0.68
Change in RVESVI (mL/m <sup>2</sup> )	-1.4 (4.1)	1.5 (3.0)	0.59
Change in RVEDV (mL)	4.9 (6.2)	4.7 (6.7)	0.98
Change in RVEDVI (mL/m <sup>2</sup> )	3.7 (3.4)	3.1 (3.6)	0.91
Change in RVSV (mL)	1.0 (9.3)	1.9 (2.8)	0.92
Change in RSVI (mL/m <sup>2</sup> )	1.9 (5.8)	1.4 (1.6)	0.92
Change in RVEF (%)	2.0 (7.7)	0.4 (2.4)	0.81

**Note:** Data are mean (SEM).

**Abbreviations:** RV, right ventricular; LV, left ventricular; MI, mass index; ESV, end systolic volume; EDV, end diastolic volume; SV, stroke volume; EF, ejection fraction.

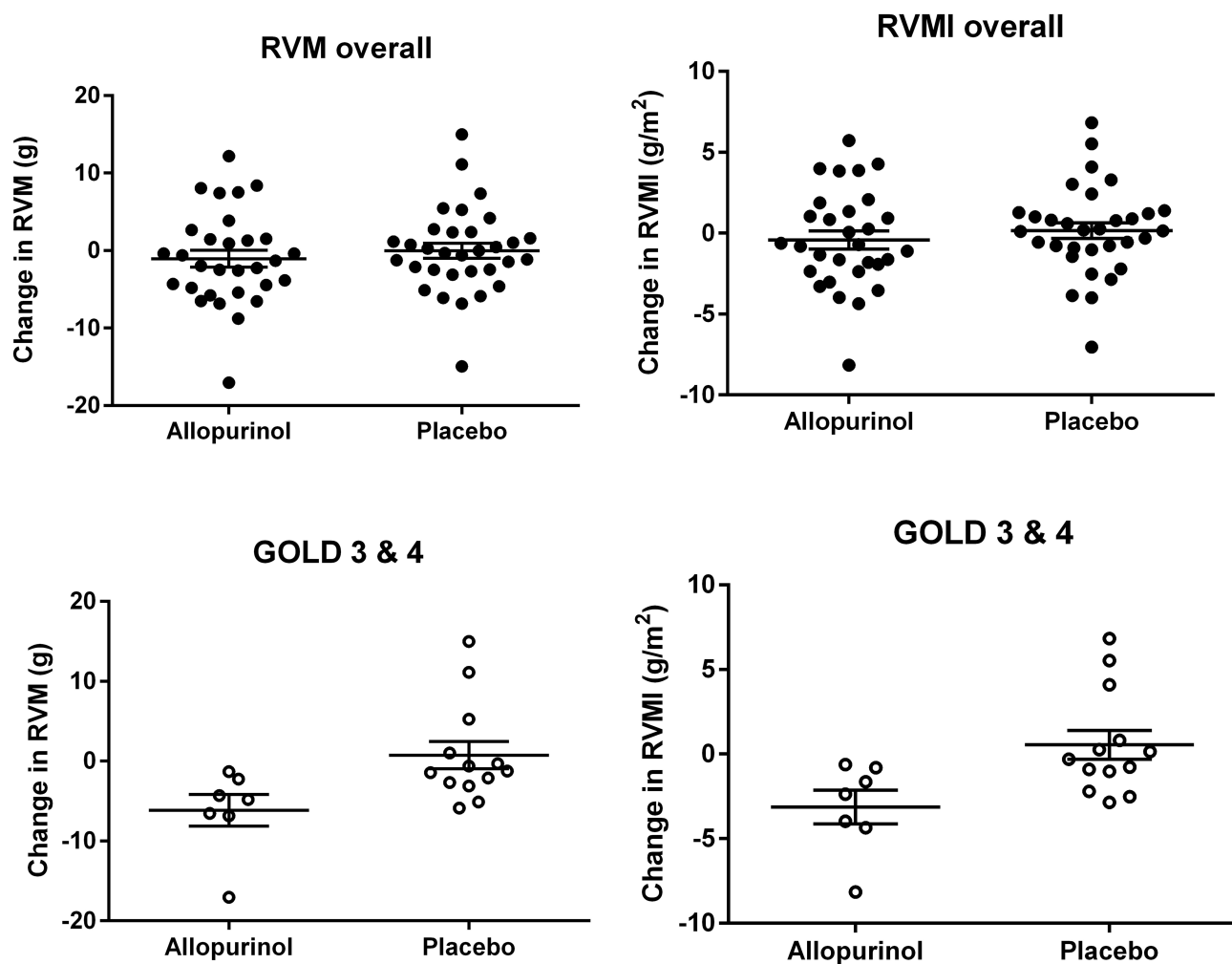
a greater improvement in LVEF with allopurinol  $5.12 \pm 2.36\%$  vs placebo  $-1.62 \pm 1.51\%$  ( $p = 0.02$ ). There was no significant difference in the change in RVM (allopurinol

group  $1.04 \pm 1.33$  g vs placebo  $-0.56 \pm 4.42$  g;  $p = 0.44$ ) and in RVMI (allopurinol group  $0.63 \pm 0.72$  g/m<sup>2</sup> vs placebo group  $-0.05 \pm 0.67$  g/m<sup>2</sup>;  $p = 0.50$ ) in this subgroup.

There was a total of 179 adverse events (AE) recorded with 80 (45%) in the allopurinol group and 99 (55%) in the placebo group. There were 7 serious adverse events (SAE) in the allopurinol group compared to 15 SAE in the placebo group.

## Discussion

High dose allopurinol exhibited no overall effect on the RVM, as measured by cardiac MRI. This could be due to the heterogeneity of severity in chronic lung disease. Recent studies have demonstrated the wide range of phenotypes and heterogeneity of patients suffering from COPD.<sup>22</sup> The overall effect of allopurinol could have



**Figure 2** Scatter plots of RVM and RVMI (mean and SEM) for overall population (allopurinol n=31, placebo n=32) and subgroup GOLD 3 and 4 (allopurinol n=7, placebo n=13). There were significant ( $p = 0.02$ ) differences in RVM and RVMI in the subgroup of GOLD 3/4 patients.

**Table 5** Mean Change in Quality-of-Life Scores, Spirometry and Six-Minute Walk Measurements at 52 Weeks Compared to Baseline (Intention-to-Treat Analysis)

	Allopurinol (n = 36)	Placebo (n = 35)	p
<b>SGRQ</b>			
Total score	-0.89 (1.72)	-1.30 (1.95)	0.88
Symptom score	-2.82 (2.96)	1.55 (3.67)	0.35
Activity score	1.93 (2.31)	-1.31 (2.39)	0.84
Impact score	-1.70 (2.31)	-2.37 (2.41)	0.84
<b>SF-36</b>			
Physical functioning	-1.06 (3.09)	2.92 (2.42)	0.31
Physical role limitations	1.66 (5.74)	8.15 (6.45)	0.45
Emotional role limitations	-5.77 (6.48)	1.45 (8.47)	0.50
Energy or fatigue	-0.81 (2.64)	4.53 (3.81)	0.25
Emotional well-being	4.65 (2.85)	0.29 (3.07)	0.30
Social functioning	-2.43 (3.63)	-1.62 (3.98)	0.88
Pain	-4.08 (3.51)	1.13 (4.67)	0.37
General health	0.12 (2.73)	-0.02 (3.33)	0.97
Health change	5.56 (4.02)	6.96 (5.29)	0.83
<b>Spirometry</b>			
FEV <sub>1</sub>	0.02 (0.03)	-0.01 (0.03)	0.42
FEV <sub>1</sub> %	1.55 (1.31)	0.16 (1.08)	0.41
FVC	0.02 (0.05)	0.02 (0.06)	0.98
FVC%	0.97 (1.41)	1.00 (1.78)	0.99
FEV <sub>1</sub> /FVC	0.97 (1.41)	1.00 (1.78)	0.74
<b>6MWT</b>			
Distance	8.8 (10.0)	-10.0 (12.5)	0.24
Pre-test O <sub>2</sub>	-0.4 (0.3)	-0.8 (0.4)	0.51
Post-test O <sub>2</sub>	-1.3 (0.9)	-0.5 (0.8)	0.52

**Note:** Data are mean (SEM).

**Abbreviations:** SGRQ, St George Respiratory Questionnaire; SF-36, Short Form (36); FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; 6MWT, six-minute walk test.

been different if we had considered only patients with specific phenotypes of the disease. As this was a proof of concept study, it was not possible to restrict to specific phenotypes as there were no previous studies that had already evaluated this.

The right ventricular mass of our study population was relatively not too high compared to studies in patients with idiopathic pulmonary arterial hypertension<sup>23,28</sup> This is probably because pulmonary hypertension in COPD and ILD patients tends to be milder in severity compared to group 1 patients.<sup>1</sup> One could say that because RVM was not high, then our population did not have pulmonary hypertension. However, there was evidence of pulmonary hypertension on CMRI as demonstrated by a higher ventricular mass index (VMI) in our population compared to

**Table 6** Mean Change in Blood Markers at 52 Weeks Compared to Baseline (Intention-to-Treat Analysis)

	Allopurinol (n = 36)	Placebo (n = 35)	p
Baseline NT-proBNP (pg/mL)	916.81 (248.62)	949.31 (275.13)	0.93
Final NT-proBNP (pg/mL)	829.18 (233.20)	1238.68 (376.36)	0.35
Change in NT-proBNP (pg/mL)	-87.6 (127.2)	289.4 (213.3)	0.13
Baseline hs-Trop I (pg/mL)	3.22 (0.55)	3.59 (0.73)	0.69
Final hs-Trop I (pg/mL)	3.03 (0.41)	3.77 (0.79)	0.40
Change in hs-Trop I (pg/mL)	-0.20 (0.48)	0.18 (0.37)	0.53
Baseline Urate (μmol/l)	350.06 (13.54)	342.94 (15.37)	0.73
Final Urate (μmol/l)	144.12 (9.12)	338.34 (15.59)	< 0.001
Change in Urate (μmol/l)	-205.9 (14.9)	-4.6 (8.5)	< 0.001

**Note:** Data are mean (SEM).

**Abbreviations:** NT-proBNP, N-terminal prohormone brain natriuretic peptide; Hs-Trop I, high sensitive troponin I.

similar population of COPD and no PH studied by Johns et al.<sup>29</sup> VMI correlates with invasive measurement of pulmonary artery pressure and has been shown to be a prognostic marker in pulmonary hypertension.<sup>30,31</sup>

Another possible explanation for the negative result for the primary outcome is that the study population consisted mostly of patients with COPD (93%) and a few patients suffering from ILD (7%). It was agreed at the time when the study was designed to include patients suffering from group 3 pulmonary hypertension. However, it is still not completely clear whether the pathophysiology underlying the development of PH and RVH is the same for all the chronic lung diseases.

The heterogeneous study population may have masked a possible effect of allopurinol. This is supported by the finding that there was a statistically significant difference in the allopurinol group amounting to a mean difference of 6.92g in a subgroup of patients with more severe airflow obstruction corresponding to GOLD groups 3 and 4. This in turn suggests that the more severe the degree of airflow limitation, the more likely allopurinol may reduce right ventricular mass. A potential explanation is that such patients are more likely to be more hypoxic on exertion (despite having satisfactory resting oxygen saturation), causing increasing oxidative stress, leading to cardiac hypertrophy and increased pulmonary arterial pressures on exercise. The observed trend towards a reduction in RVESV conferred by allopurinol suggests that offloading the RV may have been the mechanism for the RVH regression, further

supported by similar observations of left ventricular mass reduction and improved systolic function reported by Rekhraj et al study<sup>13</sup> of left ventricular hypertrophy.

The overall negative results in our study may be because the current study population had too mild chronic lung disease. The positive signal that was found in our subgroup analysis suggests that the study needs to be repeated in patients with more severe chronic lung disease to ascertain the benefits of allopurinol in that population who have the greatest need of new treatments.

It is difficult to compare the results of the current study with other randomised clinical trials (RCT) as to date there is no other RCT looking at the cardiac mass, volume and function in patients with group 3 pulmonary hypertension. The closest studies that could be compared with are longitudinal ones in patients with group 1 pulmonary hypertension who received drug therapies already licensed to treat pulmonary hypertension in this group. The results from these studies were mixed: the studies by Michelakis et al,<sup>26</sup> van Wolferen et al,<sup>23</sup> and van de Veerdonk,<sup>28</sup> and the SERAPH study<sup>24</sup> have reported a reduction in RVM from baseline while the study by Roeleveld et al,<sup>27</sup> and the EURO-MR study<sup>25</sup> reported no change in RVM.

Two recent studies<sup>32,33</sup> have reported improvements in ventricular volumes and function in COPD population following treatment with inhaled therapies. However, these studies were looking at a particular phenotype of COPD, namely those with lung hyperinflation which induces cardiac under-filling. Lung hyperinflation or gas trapping was not specifically evaluated in the current study.

We have also found that allopurinol improved left ventricular ejection fraction in a subgroup of patients who had higher NT-proBNP level. A possible mechanism for this finding could be the ability of allopurinol to improve cardiac energetics by improving relative and absolute concentrations of myocardial high-energy phosphates and ATP flux through creatinine kinase, which has been observed in left heart failure.<sup>34</sup>

One of the limitations of this study is that right heart catheterisation (RHC), which is the gold standard for assessing pulmonary haemodynamics, was not performed. RHC is invasive and it would introduce unnecessary risk and reduce the number of patients willing to be recruited, hence potentially making recruits atypical. It is also not routine practice in patients with COPD and suspected borderline or mild pulmonary hypertension. Pulmonary acceleration time is a good alternative and

non-invasive echo measurement that has a correlation coefficient of  $r = 0.88$  with pulmonary pressures.<sup>35</sup>

Another limitation is the lack of data on transfer factor of the lung for carbon monoxide (TLCO). Reduction in TLCO is common in COPD, due to emphysema, while pulmonary hypertension causes a further reduction in the TLCO which would have helped to further characterise the study population. However, as it was not expected that allopurinol would have any beneficial effect on transfer factor and to limit testing burden on the trial participants, it was not included in the current study.

## Conclusion

In conclusion, there was no overall effect of allopurinol on right ventricular mass in patients with pulmonary hypertension associated with chronic lung disease. There was also no overall effect of allopurinol on LV and RV measurements, quality of life, spirometry, six-minute walk test and blood markers.

There was a potential benefit of allopurinol in COPD patients with more severe airflow limitation ( $FEV_1 < 50\%$  predicted) and in patients with higher NT-proBNP levels. Further studies are warranted to assess the longer-term impact of allopurinol in this population.

## Abbreviations

6MWT, six minute walk test; AE, adverse event; CMRI, cardiac magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume;  $FEV_1$ , forced expiratory volume in 1 second; Hs-Trop I, high-sensitive troponin I; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's brief interstitial lung disease; LTOT, long term oxygen therapy; LV, left ventricle; MPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OS, oxidative stress; PH, pulmonary hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease; QOL, quality of life; RCT, randomised controlled trial; RHC, right heart catheterisation; RV, right ventricle; RVH, right ventricular hypertrophy; RVM, right ventricular mass; RVMI, right ventricular mass index; SAE, serious adverse event; SF-36, 36-Item Short Form Survey; SGRQ, St George's Respiratory Questionnaire;  $SpO_2$ , oxygen saturation; SV, stroke volume; TLCO, transfer factor of the lung for carbon monoxide; UA, uric acid; VMI, ventricular mass index.



## Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The trial was approved by the East of Scotland Research Ethics Committee (reference: 14/ES/1035) and was carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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