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# Allopurinol Reduces Left Ventricular Mass in Patients With Type 2 Diabetes and Left Ventricular Hypertrophy

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**Objectives** This study sought to ascertain whether high-dose allopurinol causes regression of left ventricular mass (LVM) in patients with type 2 diabetes mellitus (T2DM).

**Background** Left ventricular hypertrophy (LVH) is common in T2DM and contributes to patients' high cardiovascular (CV) event rate. Oxidative stress (OS) has been implicated in LVH development, and allopurinol has been previously shown to reduce vascular OS. We therefore investigated whether allopurinol causes regression of LVH in patients with T2DM.

**Methods** We conducted a randomized, double-blind, placebo-controlled study of 66 optimally-treated T2DM patients with echocardiographic evidence of LVH. Allopurinol, 600 mg/day, or placebo was given over the study period of 9 months. The primary outcome was reduction in LVM as calculated by cardiac magnetic resonance imaging at baseline and at 9 months' follow-up. Secondary endpoints were change in flow-mediated dilation and augmentation index.

**Results** Allopurinol significantly reduced absolute LVM ($-2.65 \pm 5.91$ g vs. placebo group $+1.21 \pm 5.10$ g [$p = 0.012$]) and LVM indexed to body surface area ($-1.32 \pm 2.84$ g/m$^2$ vs. placebo group $+0.65 \pm 3.07$ g/m$^2$ [$p = 0.017$]). No significant changes were seen in either flow-mediated dilation or augmentation index.

**Conclusions** Allopurinol causes regression of LVM in patients with T2DM and LVH. Regression of LVH has been shown previously to improve CV mortality and morbidity. Therefore, allopurinol therapy may become useful to reduce CV events in T2DM patients with LVH. (Allopurinol in Patients with Diabetes and LVH; UKCRN 8766) (J Am Coll Cardiol 2013;62:2284–93) © 2013 by the American College of Cardiology Foundation

Type 2 diabetes mellitus (T2DM) reduces life expectancy by 8 to 10 years (1–3). It is thought that up to 70% of deaths are due to cardiovascular (CV) disease, due mainly to an excess of CV events (4,5). Left ventricular hypertrophy (LVH) is common (40% to 70% event rate) in T2DM and is a strong independent predictor of CV events, CV deaths, and total mortality (6,7). In the only head-to-head comparison study, LVH was, in fact, a stronger risk factor and accounted for more deaths than multivessel coronary artery disease (8). In fact, the independent risk ratio for LVH is consistently approximately 2.5, irrespective of blood pressure (BP) (9,10). The probable reason that LVH is so adverse is because it pre-dates so many different adverse sequelae. For example, LVH reduces coronary flow reserve and, hence, induces ischemia (11–13). LVH is intrinsically arrhythmogenic, producing ventricular tachycardia and atrial fibrillation (AF) (14–16). LVH impedes left ventricular (LV) filling and, hence, produces diastolic heart failure. Finally, LVH increases left atrial size, which leads to AF and cardioembolic strokes (17,18).

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Despite aggressive treatments for BP, LVH remains a problem in patients with T2DM and is still common when BP is controlled (19,20). Regression of LVH per se is known to reduce CV events over and above BP control, and therefore, CV events may well be reduced further in T2DM patients if

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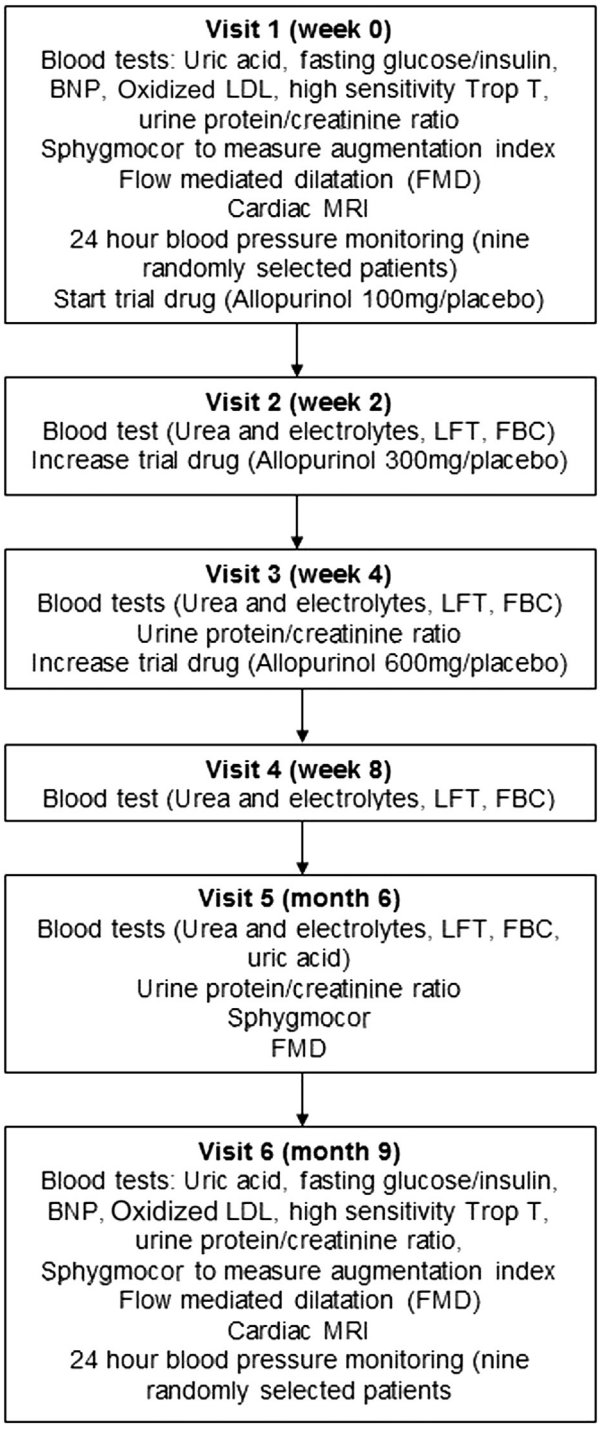


**Figure 1** Outline of Study Visits

Flow chart showing patient involvement in the study. BNP = B-type natriuretic peptide; FBC = full blood count; LDL = low-density lipoprotein; LFT = liver function test; MRI = magnetic resonance imaging; Trop = troponin.

we can find novel ways to regress LVH (21). One new possibility to regress LVH is allopurinol. Previous animal and human studies have suggested that allopurinol might reduce left ventricular mass (LVM). Our group has recently shown that allopurinol can cause regression of LVM in chronic kidney disease patients (22) and in patients with optimally-treated ischemic heart disease (23). Three additional studies have also shown that allopurinol can regress LVH in various experimental models of cardiac disease (24–26). We therefore assessed whether, in T2DM patients with LVH, allopurinol would really cause regression of LVH over and above traditional optimum therapy.

**Abbreviations and Acronyms**

AIx = augmentation index
BP = blood pressure
CMR = cardiac magnetic resonance
CV = cardiovascular
FMD = flow-mediated dilation
LV = left ventricular
LVH = left ventricular hypertrophy
LVMI = left ventricular mass index
MRI = magnetic resonance imaging
T2DM = type 2 diabetes mellitus

## Methods

**Study overview.** The study was carried out as a single-center randomized, double-blind, placebo-controlled trial with 9 months' follow up. The active drug was allopurinol, 600 mg/day, given as 300 mg twice per day. It was approved by the Tayside Research Ethics Committee and was carried out in accordance with the Declaration of Helsinki.

**Study participants.** Patients were identified from the Scottish Diabetes Research Network, the Health Informatics Centre, or the Scottish Primary Care Research Network. Patients with T2DM and office BP <150/90 mm Hg who attended for screening underwent echocardiography. LVH on echocardiography was defined by the American Society of Echocardiography criteria as an LVM index of >115 g/m$^2$ for men and >95 g/m$^2$ for women (using the average of 3 measurements of LVM by 1 trained operator [B.R.S.]) (27). Exclusion criteria included gout, patients currently taking allopurinol, previous adverse reaction to allopurinol, estimated glomerular filtration rate <60 ml/min/1.73 m$^2$, conditions that excluded magnetic resonance imaging (MRI), LV ejection fraction <45%, cancer or other life-threatening illness, pregnancy or breast feeding, and inability to provide consent.

Sixty-six patients were recruited; 33 patients were randomized to receive allopurinol, and 33 were randomized to receive placebo. Patients were allocated by computer-generated treatment code (patients and investigators were blinded). Patients continued all other medications, including antihypertensive and hypoglycemic agents.

**Study visits and drug titration.** After they were recruited, patients attended for 6 visits over a 9-month period. An initial dosage of allopurinol, 100 mg/day, or placebo was dispensed, and this dosage of allopurinol was increased to 300 mg/day, or placebo, after 2 weeks. The dosage was further increased to 600 mg/day, or placebo, at 4 weeks and continued for the duration of the trial. Study visits are outlined in Figure 1. Office BP was measured for all patients at each visit, and

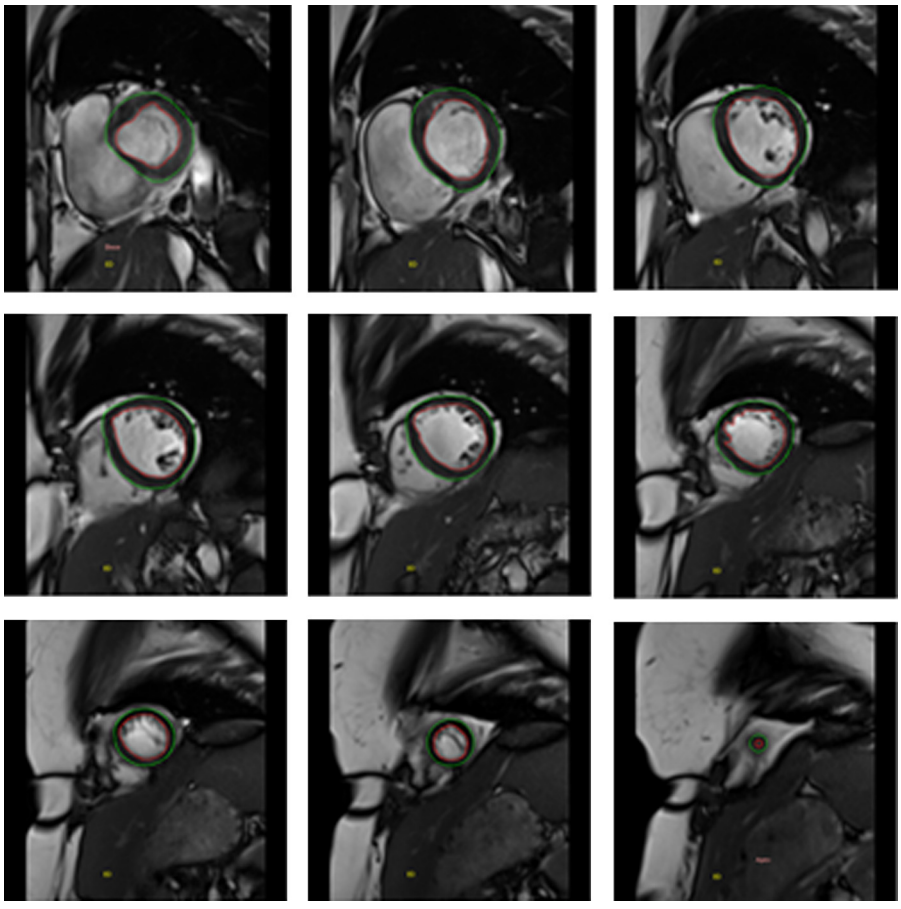

**Figure 2** Cardiac Magnetic Resonance Images for Left Ventricular Mass Estimation

An example of cardiac magnetic resonance images, highlighting typical endocardial and epicardial border region-of-interest contouring from a set of study images. In this example, a total of 9 slices were acquired from the base of the left ventricular myocardium **(top left)** to the apex **(bottom right)**.

9 randomly selected patients had a 24-h ambulatory BP monitor at baseline and final visit. Availability of ambulatory monitors was limited, which is why 24-h BP was only monitored in a random subset.

**Cardiac MRI.** Cardiac MRI was performed at baseline and at 9 months only, using a 3-T Magnetom Trio scanner (Siemens, Erlangen, Germany). Images were analyzed by an independent MRI physicist with cardiac MRI experience, using commercially available software (Argus version B15; Siemens, Erlangen, Germany). Regions of interest were placed around the left ventricular borders at end diastole (Fig. 2) in order to derive LVM. Full details of the MRI protocol are available in the Online Appendix.

**Flow-mediated dilation.** Endothelial function was assessed by measuring flow-mediated dilation (FMD) of the brachial artery. FMD was measured using a Sequoia 512 (Siemens, Camberley, United Kingdom) ultrasonography machine with an 8-MHz linear array probe. FMD was performed at baseline and at 6 and 9 months (Fig. 1). The response to hyperemia and endothelial independent dilation was measured according to International Brachial Artery Reactivity Task Force guidelines and has been performed routinely at our institute (28–30). Our precise methodology has been described in detail previously (22,23,31).

**Applanation tonometry.** Pulse wave analysis and pulse wave velocity were measured at baseline and at 6 and 9 months by a single, trained investigator (B.R.S.) who was blinded to the allocated treatment. Analysis was performed using a SphygmoCor (AtCor, Sydney, Australia) machine using a high-fidelity micromanometer. Our methods were published previously (22,23,31).

**Statistical analysis.** Using published data from Grothues et al. (32), 60 were required patients to provide 90% power to detect a 5-g difference in LVM between active drug and placebo.

Data for continuous variables are presented as mean ± SD. Categorical data are expressed as percentages. Comparison between continuous variables were analyzed using the Student *t* test or Mann-Whitney *U* test, while categorical variables were analyzed using the chi-square test. A multivariate

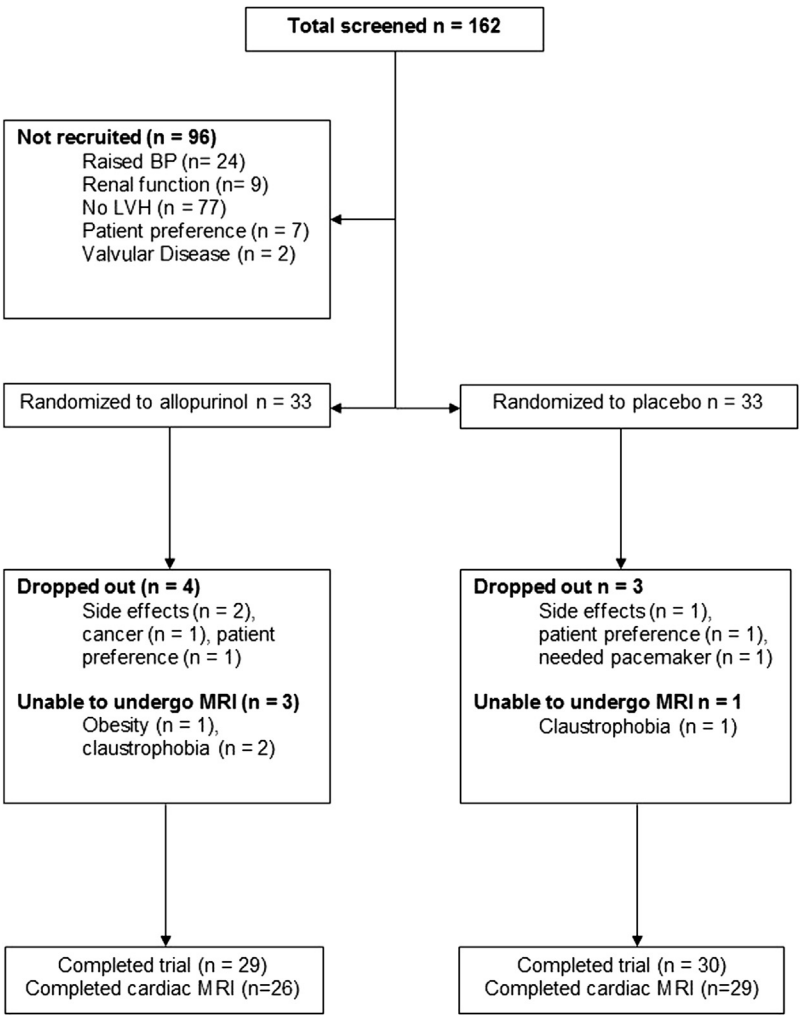


**Figure 3** **CONSORT Diagram**

CONSORT diagram showing study recruitment numbers. BP = blood pressure; CONSORT = CONsolidated Standards of Reporting; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging.

analysis of variance using important covariates was also performed. All statistical analyses were undertaken using SPSS software version 18.0 (SPSS, Inc., Chicago, Illinois). A 2-sided p value $<0.05$ was considered statistically significant.

**Endpoints.** The primary endpoint was to assess whether allopurinol caused regression of LVH in patients with T2DM and controlled BP. The secondary endpoint was to assess whether allopurinol improved parameters of endothelial function. The primary endpoint (LVH) was measured only at 0 and 9 months, whereas the secondary endpoint was measured at 0, 6, and 9 months.

## Results

In total, 66 patients were recruited, and 7 participants withdrew from the study (placebo n = 3, allopurinol n = 4) (Fig. 3). Another 4 participants were unable to undergo cardiac MRI (placebo n = 1, allopurinol n = 3). Therefore, 56 participants completed the cardiac MRI parts of the trial, and 59 completed all other tests. Baseline characteristics are shown in Table 1. There were no significant differences for baseline characteristics other than for baseline body mass index, stroke, and creatinine level.

The main finding from this study is that allopurinol significantly reduced LVM over the 9-month study period, both for absolute LVM and left ventricular mass indexed to body surface area (LVMI). Change in LVM was $-2.65 \pm 5.91$ g and $+1.21 \pm 5.10$ g ($p = 0.012$) for the allopurinol and placebo groups, respectively. Change in LVMI was $-1.32 \pm 2.84$ g/m$^2$ and $+0.65 \pm 3.07$ g/m$^2$ ($p = 0.017$) for the allopurinol and placebo groups, respectively (Table 2, Fig. 4). We performed a multivariate analysis of variance

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**Table 1 Baseline Characteristics**

| Variable | All Patients | Placebo | Allopurinol | p Value |
|---|---|---|---|---|
| Patients, total | n = 59 | n = 30 | n = 29 | |
| Did not have MRI | 4 | 1 | 3 | |
| Completed MRI | 56 | 29 | 26 | |
| Completed FMD | 59 | 30 | 29 | |
| Age, yrs | 64.63 ± 8.79 | 66.03 ± 8.86 | 63.17 ± 8.64 | 0.214 |
| Male | 36 (61.02%) | 21 (70.00%) | 16 (55.17%) | 0.101 |
| BMI baseline | 32.59 ± 4.78 | 31.12 ± 3.93 | 34.13 ± 5.14 | 0.014 |
| 24-h SBP baseline, mm Hg | 121.67 ± 11.55 | 122.25 ± 11.59 | 121.20 ± 12.87 | 0.903 |
| 24-h DBP baseline, mm Hg | 66.22 ± 3.31 | 68.25 ± 2.75 | 64.60 ± 2.97 | 0.101 |
| Office SBP baseline, mm Hg | 139.51 ± 11.33 | 141.63 ± 11.03 | 137.31 ± 11.41 | 0.144 |
| Office DBP baseline, mm Hg | 77.66 ± 8.69 | 76.70 ± 10.18 | 78.66 ± 6.87 | 0.392 |
| Echo LVMI, g/m$^2$ | 126.18 ± 19.04 | 126.39 ± 17.46 | 125.97 ± 20.88 | 0.933 |
| Absolute MRI LVM, g (n = 56) | 122.60 ± 28.32 | 119.92 ± 27.89 | 125.59 ± 29.36 | 0.464 |
| MRI LVMI, g/m$^2$ (n = 56) | 60.67 ± 9.78 | 60.16 ± 10.11 | 61.23 ± 9.56 | 0.691 |
| Hypertension | 53 (89.83%) | 27 (90.00%) | 26 (89.66%) | 0.534 |
| IHD | 6 (10.17%) | 3 (10%) | 3 (10.34%) | 0.534 |
| Stroke | 6 (10.67%) | 5 (16.67%) | 1 (3.45%) | 0.026 |
| Raised cholesterol | 54 (91.52%) | 27 (90.00%) | 27 (93.10%) | 0.056 |
| Smoker | 8 (13.56%) | 6 (20.00%) | 2 (6.90%) | 0.454 |
| Ex-smoker | 26 (44.07%) | 11 (36.66%) | 15 (51.72%) | 0.518 |
| Never smoked | 25 (42.37%) | 13 (43.33%) | 12 (41.38%) | 0.638 |
| Duration of diabetes, yrs | 9.46 ± 6.02 | 8.97 ± 5.36 | 9.97 ± 6.68 | 0.528 |
| ACE inhibitor | 29 (49.15%) | 13 (43.33%) | 16 (55.17%) | 0.363 |
| ARB | 16 (27.12%) | 8 (36.67%) | 8 (27.59%) | 0.937 |
| CCB | 16 (27.12%) | 11 (36.67%) | 5 (17.24%) | 0.093 |
| Thiazide diuretic | 13 (22.03%) | 8 (26.67%) | 5 (17.24%) | 0.383 |
| Furosemide | 4 (6.78%) | 3 (10.00%) | 1 (3.45%) | 0.317 |
| Beta-blocker | 14 (23.73%) | 7 (23.33%) | 7 (24.14%) | 0.942 |
| Metformin | 45 (76.27%) | 20 (66.67%) | 25 (86.21%) | 0.078 |
| Gliclazide | 15 (24.42%) | 7 (23.33%) | 8 (27.58%) | 0.708 |
| TZD | 7 (11.86%) | 3 (10.00%) | 4 (13.79%) | 0.652 |
| Exenatide | 2 (3.39%) | 0 (0.00%) | 2 (6.90%) | 0.143 |
| Insulin | 9 (15.25%) | 4 (13.33%) | 5 (17.24%) | 0.676 |
| Aspirin | 28 (47.46%) | 15 (50.00%) | 13 (44.53%) | 0.691 |
| Clopidogrel | 2 (3.39%) | 0 (0.00%) | 2 (6.90%) | 0.143 |
| Statin | 50 (84.75%) | 25 (83.33%) | 28 (86.21%) | 0.759 |
| Hemoglobin, g/l | 13.73 ± 1.43 | 14.06 ± 1.27 | 13.40 ± 1.53 | 0.076 |
| eGFR, ml/min/1.73 m$^2$ | 86.31 ± 13.75 | 83.21 ± 10.38 | 89.52 ± 16.09 | 0.078 |
| Creatinine, μm/l | 76.88 ± 12.08 | 80.00 ± 11.16 | 73.66 ± 12.33 | 0.043 |
| Fasting glucose, mmol/l | 6.62 ± 1.96 | 6.14 ± 1.66 | 7.11 ± 2.15 | 0.056 |
| Fasting insulin, μU/l | 32.16 ± 25.34 | 34.37 ± 27.74 | 29.88 ± 22.87 | 0.501 |
| $HbA_{1c}$, % | 7.25 ± 0.94 | 7.12 ± 0.83 | 7.39 ± 1.04 | 0.274 |
| Urine PCR, mg/mmol | 13.05 ± 8.26 | 14.13 ± 10.51 | 11.93 ± 4.93 | 0.310 |
| BNP, pg/ml | 29.01 ± 25.81 | 30.01 ± 22.74 | 27.97 ± 29.03 | 0.764 |
| Uric acid, mmol/l | 0.54 ± 0.13 | 0.54 ± 0.10 | 0.55 ± 0.15 | 0.613 |
| HS TropT, ng/l | 7.46 ± 4.85 | 7.90 ± 5.59 | 7.01 ± 3.99 | 0.486 |
| Oxidized LDL, U/l | 28.51 ± 9.90 | 27.58 ± 10.07 | 29.48 ± 9.81 | 0.467 |
| EF, % | 75.15 ± 5.317 | 75.21 ± 4.66 | 75.08 ± 5.78 | 0.927 |
| EDV, ml | 123.52 ± 35.94 | 118.36 ± 36.41 | 129.28 ± 35.23 | 0.264 |
| ESV, ml | 31.17 ± 13.01 | 29.80 ± 12.00 | 32.71 ± 14.12 | 0.412 |
| SV, ml | 92.36 ± 25.42 | 88.57 ± 26.06 | 96.58 ± 24.50 | 0.247 |
| CO, ml | 6.41 ± 1.60 | 6.18 ± 1.70 | 6.66 ± 1.47 | 0.265 |
| FMD, % | 4.11 ± 0.08 | 4.16 ± 0.59 | 4.07 ± 0.64 | 0.578 |
| AIx, % | 11.09 ± 10.07 | 10.47 ± 10.78 | 11.76 ± 9.40 | 0.629 |
| PWV (m/s) | 7.07 ± 1.14 | 6.94 ± 1.03 | 7.19 ± 1.24 | 0.468 |

Values are n, mean ± SD, or n (%). ACE = angiotensin-converting enzyme; AIx = augmentation index; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; CCB = calcium-channel blocker; CO = cardiac output; DBP = diastolic blood pressure; EDV = end-diastolic volume; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESV = end-systolic volume; FMD = flow-mediated dilation; $HbA_{1c}$ = glycosylated hemoglobin; HS = high sensitivity; IHD = ischemic heart disease; LDL = low-density lipoprotein; LVM = left ventricular mass; LVMI = left ventricular mass index; MRI = magnetic resonance imaging; PCR = protein creatinine ratio; PWV = pulsed wave velocity; SBP = systolic blood pressure; SV = stroke volume; TropT = troponin T; TZD = thiazolidinediones.

**Table 2** Change in MRI Parameters Over the 9-Month Study Period

| Change | Placebo | Allopurinol | p Value |
|---|---|---|---|
| LVM, g | +1.21 ± 5.10 | −2.65 ± 5.91 | 0.012 |
| LVMI, g/m$^2$ | +0.65 ± 3.07 | −1.32 ± 2.84 | 0.017 |
| EF, ml | 0.08 ± 7.41 | 1.46 ± 6.10 | 0.458 |
| EDV, ml | 4.45 ± 39.60 | 6.12 ±40.57 | 0.878 |
| ESV, ml | 2.44 ± 21.84 | 0.20 ± 14.60 | 0.660 |
| SV, ml | 2.01 ± 24.83 | 5.89 ± 28.88 | 0.595 |
| CO, l/min | −0.75 ± 1.61 | 0.67 ± 1.45 | 0.081 |

Values are mean ± SD.
Abbreviations as in Table 1.

using covariates of baseline BP, change in BP, and prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, and this still showed a significant difference between allopurinol and placebo ($p = 0.013$ for LVM and $p = 0.021$ for LVMI). Allopurinol-induced LVH regression, however, was concentrated in those with an above-median LVMI at baseline, as might be expected, as shown in Tables 3 and 4 and Figures 5 and 6. Interestingly, in the placebo group, LVH appeared to progress more in the group with the above-median LVH at baseline (i.e., the same group that regressed more with allopurinol). Results are detailed further in Table 2 and in Figures 5 and 6. It is quite common for LVM to increase with ageing in the placebo group of MRI studies, as we saw here and have seen previously (31).

For the other parameters measured on cardiac MRI, there were no significant changes in ejection fraction, end-diastolic volume, end-systolic volume, stroke volume, and cardiac output (Table 2). There was no change in brain natriuretic peptide, oxidized low-density lipoprotein (LDL), or high-sensitivity troponin over the study period (Table 5). There was, as expected, a significant reduction in uric acid levels in the allopurinol group. The allopurinol dosage we used was safe, and there were no changes in urine protein/creatinine ratio or estimated glomerular filtration rate. There were no differences in the change in office or 24-h BP over time (Table 6) and no differences in BP between those with high versus those with low LVM. No significant changes were seen in FMD and augmentation index (AIx) (Table 4).

The reasons for withdrawing from and not completing the trial are outlined in the CONsolidated Standards of Reporting Trials (CONSORT) diagram in Figure 3.

## Discussion

We have shown that allopurinol causes regression of LVH in patients with T2DM and LVH, especially, as might be expected, in those with higher baseline LV masses. These results agree with those of previous studies of ischemic heart disease (23) and chronic kidney disease, in which allopurinol also caused regression of LVH without changing BP (22). This finding is also consistent with 3 experimental studies in animal models that also showed LVH regression with allopurinol (24–26). This would make allopurinol the first "non-antihypertensive drug" conclusively shown to induce regression of LVH in humans in a wide spectrum of diseases, which now includes diabetes mellitus.

Regression of LVH normally decreases CV morbidity and mortality irrespective of BP changes (33). The largest trial to show this is the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial, which studied hypertensive patients with evidence of electrocardiographically-defined LVH (34,35). In the LIFE study, Devereux et al. (35) found that LVH regression per se (independent of BP) was associated with substantial reduction in all-cause mortality, CV mortality, sudden cardiac death, myocardial infarction, new heart failure, new AF, and stroke (36–38).

It is worth considering why allopurinol should regress LVH. Allopurinol reduces tissue oxidative stress (OS) (39), and OS is a mediator of myocardial hypertrophy (40,41). Therefore, hypothetically, the reduction in OS could mediate LVH regression. Furthermore, Cingolani et al. (42) showed that losartan, a uricosuric angiotensin receptor-1 antagonist, is able to reduce pressure overload LVH in mice independently of arterial blood pressure and that this effect was likely the result of a significant reduction in reactive oxygen species. This possibility also was demonstrated in the La Plata study, in which oxypurinol reduced LVH and improved LV ejection fraction in patients with heart failure (43). The results of this present study are aligned with these findings, which suggest that the reduction of reactive oxygen species with allopurinol therapy can exert

**Table 3** Changes in Measured Parameters Analyzed as Subgroups Above and Below Median LVM

| Change | Placebo (LVM Above Median) | Allopurinol (LVM Above Median) | p Value | Placebo (LVM Below Median) | Allopurinol (LVM Below Median) | p Value |
|---|---|---|---|---|---|---|
| LVM, g | 2.67 ± 4.87 | −4.03 ± 6.77 | 0.006 | −0.16 ± 5.10 | −1.27 ± 4.76 | 0.559 |
| LVMI, g/m$^2$ | 1.32 ± 2.13 | −1.93 ± 3.09 | 0.004 | 0.02 ± 2.70 | −0.71 ± 2.52 | 0.552 |
| EF, ml | −0.64 ± 9.17 | 0.26 ± 5.48 | 0.913 | 0.22 ± 5.63 | 2.66 ± 6.67 | 0.303 |
| EDV, ml | −0.75 ± 44.45 | 5.81 ± 40.28 | 0.692 | 9.30 ± 35.34 | 6.43 ± 42.50 | 0.847 |
| ESV, ml | 3.09 ± 30.63 | 1.78 ± 15.00 | 0.889 | 1.83 ± 10.64 | −1.38 ± 14.61 | 0.507 |
| SV, ml | −3.83 ± 21.28 | 3.99 ± 27.90 | 0.418 | 7.47 ± 27.32 | 7.80 ± 30.85 | 0.977 |
| CO, l/min | −0.23 ± 1.65 | 0.68 ± 1.07 | 0.107 | 0.07 ± 1.62 | 0.65 ± 1.81 | 0.373 |

Values are mean ± SD.
Abbreviations as in Table 1.

**Table 4** Changes in Measured Parameters Analyzed as Subgroups Above and Below Median LVMI

| Change | Placebo (LVMI Above Median) | Allopurinol (LVMI Above Median) | p Value | Placebo (LVMI Below Median) | Allopurinol (LVMI Below Median) | p Value |
|---|---|---|---|---|---|---|
| LVM, g | 1.42 ± 5.63 | −4.03 ± 6.77 | 0.025 | 0.95 ± 4.59 | −1.27 ± 4.76 | 0.240 |
| LVMI, g/m$^2$ | 1.58 ± 2.59 | −1.93 ± 3.09 | 0.003 | −0.50 ± 3.31 | −0.71 ± 2.52 | 0.299 |
| EF, ml | −0.13 ± 9.67 | 0.26 ± 5.48 | 0.899 | 0.35 ± 3.36 | 2.66 ± 6.67 | 0.274 |
| EDV, ml | 1.44 ± 41.48 | 5.81 ± 40.28 | 0.778 | 8.16 ± 38.48 | 6.43 ± 42.50 | 0.062 |
| ESV, ml | 3.30 ± 28.47 | 1.78 ± 15.00 | 0.864 | 1.38 ± 9.86 | −1.38 ± 14.61 | 0.110 |
| SV, ml | −1.85 ± 20.38 | 3.99 ± 27.90 | 0.520 | 6.77 ± 29.57 | 7.80 ± 30.85 | 0.932 |
| CO, l/min | −0.18 ± 1.65 | 0.68 ± 1.07 | 0.117 | 0.06 ± 1.63 | 0.65 ± 1.81 | 0.383 |

Values are mean ± SD.
Abbreviations as in Table 1.

beneficial effects on cardiac hypertrophy without the need for decreasing blood pressure. The role of OS in the pathogenesis of diabetes is more controversial. Various studies have suggested a role for OS underlying the development of insulin resistance, β-cell dysfunction, and impaired glucose tolerance (see Wright et al. [44]). Although we did not find a change in oxidized LDL, this does not preclude an effect on OS as plasma biomarkers tend to change very little (if at all) after allopurinol, whereas vascular tissue OS has been shown to change profoundly following exposure to allopurinol (29,30) (i.e., current plasma OS biomarkers may be fairly insensitive in this situation with allopurinol). The second possibility is that LVH might regress because of the reduction in LV afterload, and some studies have found allopurinol reduces AIx. However, we did not find this in our diabetic cohort. The third possibility is that allopurinol might reduce BP. Although allopurinol had no effect on BP in this study, this study was not powered to detect an effect on BP as such, and it remains possible that some of the LVH regression was caused by subtle changes in BP, although no consistent trend was ever seen here (Table 6). Although our study does not clarify the exact mechanism of allopurinol's effect on LVM in T2DM, it demonstrates a potentially useful therapy that might reduce residual CV risk in patients with T2DM.

In contrast to other patient groups, we found no effect of allopurinol on endothelial function. The reason for the lack of effect of allopurinol in this study might be that our T2DM patients were well treated with statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, each of which is known to improve endothelial function. Indeed, this was evident in the baseline measurements of vascular health in our patients. The baseline AIx was only 11%, and therefore, it may have made it difficult to improve it further with allopurinol. This notion is generally supported by a previous study in which allopurinol had no effect on endothelial function in healthy individuals who had normal endothelial function at baseline (45). Another reason why we were able to demonstrate an effect of allopurinol on LVH but not on endothelial function in this study may have been because we pre-selected those with high baseline LVM, whereas abnormal endothelial function

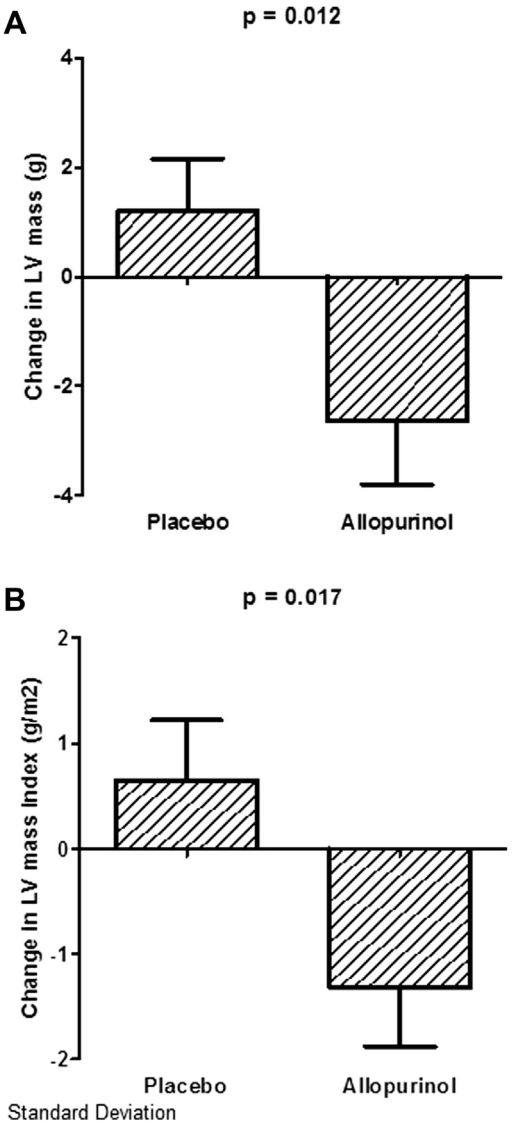


**Figure 4** Overall LV Change

Histogram of changes in **(A)** left ventricular (LV) mass and **(B)** LV mass index in the overall study population.

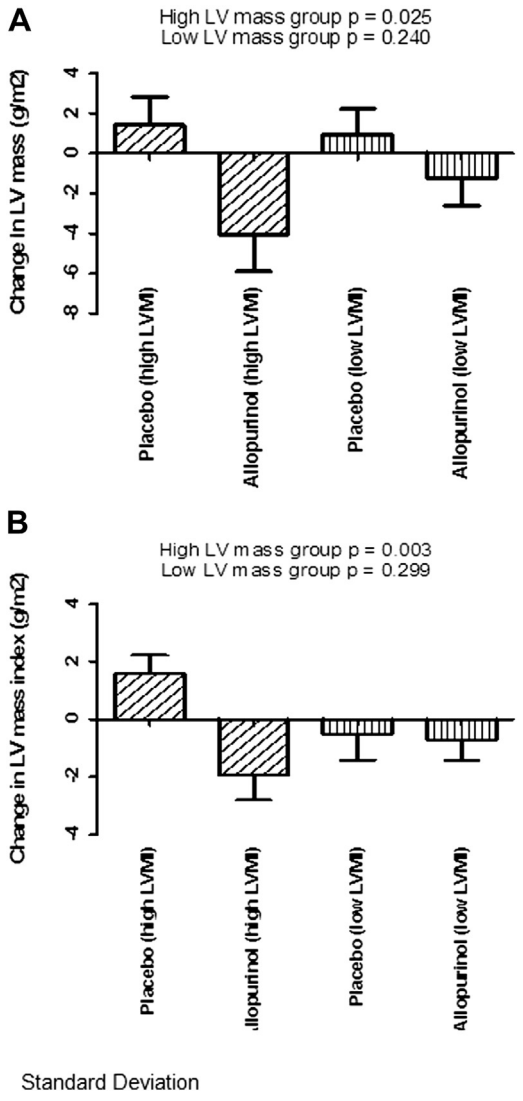


**Figure 5** LV Change by Median LVMI at Baseline

Histogram of change in **(A)** left ventricular mass (LVM) and **(B)** left ventricular mass index (LVMI) in patients with above-median LVMI at baseline. LV = left ventricular.

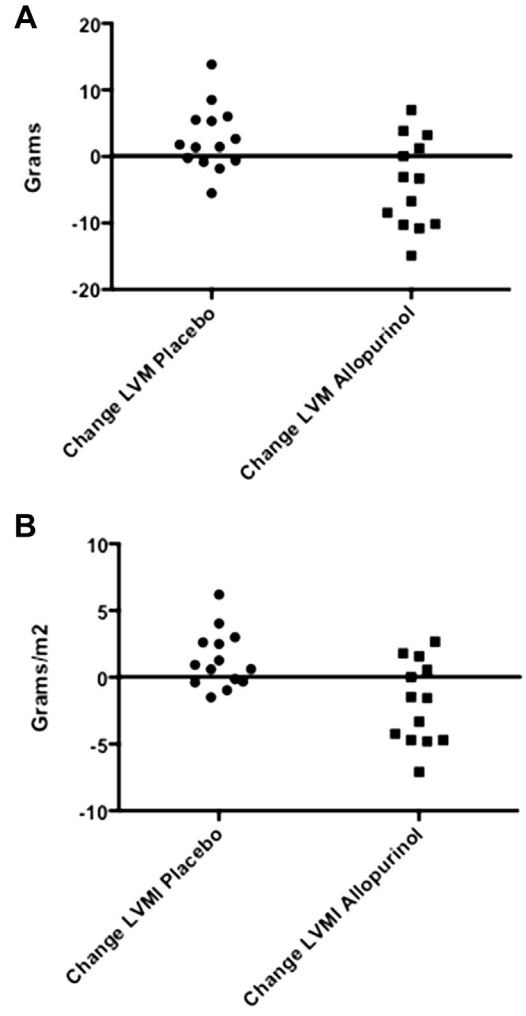


**Figure 6** Individual LV Change by Median LVMI at Baseline

Dot plot of change in **(A)** LVM and **(Bi)** LVMI in patients with above-median LVM or LVMI at baseline. Abbreviations as in Figure 5.

at baseline was not a prerequisite in this study: this was because our primary endpoint was change in LVM.

The magnitude of the LVM changes produced here by allopurinol is modest. We expect that the difference we saw in LVM at 9 months would increase over the first 2 years of treatment, as this is usually the case with LVH regression (46). Furthermore, in this study, LVH regression was greater in those with higher baseline LVM, which suggests that perhaps allopurinol should be focused toward this higher-risk subgroup where its effect was much larger. It is also worth noting that these results are entirely consistent with the only 2 previous human studies, which assessed the effect of allopurinol on LVH (22,23). It is inconceivable that 3 different studies produced the same result by chance.

It is worth noting that the effect of allopurinol on glycemia is controversial. At least 1 case report suggested that allopurinol can induce new T2DM, whereas another large database study suggested exactly the opposite effect (47). Our study is the largest prospective study to date that has investigated the effect of allopurinol on glycemic control in T2DM. We have found that allopurinol has no effect on glycemic control in T2DM.

We used the dosage of 600 mg/day because there appears to be an important dose–response relationship with allopurinol. A lot of previous research with allopurinol used a dose of 300 mg once daily (48). However, 1 study showed that increasing the dose of allopurinol from 300 to 600 mg improved endothelial function by an additional 52%, such that the allopurinol dose of 600 mg improved endothelial function by 143% compared with placebo (29). Previous studies using 300 mg of allopurinol might actually have used

**Table 5** Change in Blood Parameters Over the 9-Month Study Period

| Parameter | Placebo | Allopurinol | p Value |
|---|---|---|---|
| Hemoglobin, g/l | −1.50 ± 3.19 | −1.51 ± 2.99 | 0.993 |
| Creatinine, μm/l | −7.00 ± 13.88 | −7.67 ± 7.39 | 0.910 |
| eGFR over, ml/min/1.73 $m^2$ | 6.57 ± 11.75 | 8.78 ± 10.00 | 0.441 |
| Fasting glucose, mmol/l | 0.84 ± 4.05 | 0.41 ± 3.64 | 0.668 |
| Fasting insulin, μU/l | −6.41 ± 19.26 | −1.64 ± 15.96 | 0.306 |
| $HbA_{1c}$, % | −0.063 ± 0.47 | −0.43 ± 1.80 | 0.279 |
| Urine PCR, mg/mmol | 2.67 ± 12.76 | 5.03 ± 20.13 | 0.590 |
| BNP, pg/ml | −1.49 ± 20.22 | −3.16 ± 20.36 | 0.754 |
| Uric acid (6 months), mmol/l | −0.019 ± 0.12 | −0.27 ± 0.17 | <0.001 |
| Uric acid (9 months), mmol/l | −0.01 ± 0.06 | −0.25 ± 0.18 | <0.001 |
| HS TropT, ng/l | 0.34 ± 2.98 | 0.35 ± 2.25 | 0.656 |
| Oxidized LDL, U/l | −0.11 ± 7.69 | 0.74 ± 8.80 | 0.692 |

Values are mean ± SD.
Abbreviations as in Table 1.

a suboptimal dose of allopurinol. Allopurinol was well tolerated in our study at this high dose. Allopurinol can be given up to 800 or 900 mg/day, according to the U.S. Food and Drug Administration and British National Formulary, respectively. Reassuringly, we have also found that high-dose allopurinol has no adverse effect on renal function in T2DM.

**Study limitations.** The main limitation is the relatively small number of patients recruited. It is almost inevitable with so many demographic parameters that a few parameters will by chance be different at baseline, although few differences were statistically significant. However, because of the relatively small sample size, we cannot exclude the possibility that some subtle demographic differences between the 2 groups might have contributed to our results. The baseline LVMI in this study was low. This was due in part to the segmentation process, where the physicist actively excluded "partial volume" (defined as <50% full thickness myocardium) areas at the extreme basal end of the ventricle. The inclusion or exclusion of a single slice in this region is known to alter the outcome value for the LVMI by typically 10%. However, the emphasis at all stages of this work was to ensure optimized repeatability in order to maximize the potential sensitivity of the primary endpoint (change in LVMI).

**Table 6** Changes in Parameters of Endothelial Function, Blood Pressure, and Body Mass Index

| Parameter | Placebo | Allopurinol | p Value |
|---|---|---|---|
| Office SBP (6 months), mm Hg | −3.17 ± 17.08 | −1.69 ± 11.31 | 0.698 |
| Office SBP (9 months), mm Hg | −6.50 ± 28.67 | 0.52 ± 14.82 | 0.245 |
| Office DBP (6 months), mm Hg | −4.10 ± 14.13 | −8.55 ± 6.88 | 0.132 |
| Office DBP (9 months), mm Hg | −4.53 ± 13.25 | −7.17 ± 8.44 | 0.367 |
| 24hr SBP (9 months), mm Hg | −1.00 ± 0.61 | 0.41 ± 1.72 | 0.129 |
| FMD hyperemia (6 months), % | −0.53 ± 2.93 | −0.079 ± 4.21 | 0.602 |
| FMD hyperemia (9 months), % | 0.48 ± 4.38 | 1.00 ± 6.95 | 0.733 |
| FMD GTN (6 months), % | 1.42 ± 5.43 | 0.11 ± 1.21 | 0.405 |
| FMD GTN (9 months), % | 1.10 ± 4.84 | 0.84 ± 5.95 | 0.856 |
| AIx (6 months), % | −1.88 ± 9.46 | −1.51 ± 11.54 | 0.890 |
| AIx (9 months), % | −1.17 ± 12.67 | −1.36 ± 9.58 | 0.948 |
| PWV (6 months), m/s | −0.32 ± 1.75 | −0.87 ± 2.19 | 0.288 |
| PWV (9 months), m/s | −0.71 ± 2.65 | −0.70 ± 2.22 | 0.987 |
| BMI (9 months) | 0.31 ± 8.11 | 0.04 ± 9.66 | 0.520 |

Values are mean ± SD.
BMI = body mass index; GTN = glycerol tri-nitrate; other abbreviations are as shown in Table 1.

## Conclusions

Allopurinol caused regression of LVH in patients with T2DM and LVH at baseline. Regression of LVH has been shown previously to reduce CV mortality and morbidity. Therefore, allopurinol may become a useful therapy for T2DM patients with LVH, especially in those with the greatest LVH at baseline.

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**Key Words:** allopurinol ■ endothelial function ■ left ventricular hypertrophy ■ type 2 diabetes.

## APPENDIX

**For complete details of the cardiac MRI protocol, please see the online version of this article.**