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ALLOPURINOL INITIATION AND CHANGE IN BLOOD PRESSURE IN OLDER ADULTS WITH HYPERTENSION

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Abstract

Hypertension is a key risk factor for cardiovascular disease and new treatments are needed. Uric acid reduction lowers blood pressure in adolescents suggesting a direct pathophysiological role in development of hypertension. Whether the same relationship is present in older adults is unknown. We explored change in blood pressure after allopurinol initiation using data from the UK Clinical Practice Research Datalink.

Data were extracted for patients with hypertension aged >65-years who were prescribed allopurinol with pre and during treatment blood pressure readings. Data from comparable controls were extracted. The change in blood pressure in patients with stable blood pressure medication was the primary outcome and was compared between groups. Regression analysis was used to adjust for potential confounding factors and a propensity-matched sample was generated.

365 patients who received allopurinol and 6678 controls were included. Blood pressure fell in the allopurinol group compared to controls (between group difference in systolic and diastolic blood pressure 2.1 mmHg (95%CI -0.6 to 4.8) and 1.7 mmHg (95%CI 0.4 to 3.1), respectively). Allopurinol use was independently associated with a fall in both systolic and diastolic blood pressure on regression analysis (p<0.001). Results were consistent in the propensity-matched sample. There was a trend toward greater fall in blood pressure in the high dose allopurinol group but change in blood pressure was not related to baseline uric acid level.

Allopurinol use is associated with a small fall in blood pressure in adults. Further studies of the effect of high dose allopurinol in adults with hypertension are needed.

Key Words – Hypertension, uric acid, xanthine oxidase, allopurinol, therapeutics
INTRODUCTION

Hyperuricaemia is associated with incident hypertension [1] and preclinical studies support a role for hyperuricaemia in the development of hypertension. Hyperuricaemia has been shown to raise blood pressure (BP) in normotensive rats and this rise is attenuated by urate lowering drugs [2]. Further, sustained hyperuricaemia has been shown to induce a primary renal arteriolopathy and a salt sensitive rise in BP in experimental models [3].

Recently, randomised placebo controlled and blinded clinical trials have shown that urate lowering drugs reduce BP in hyperuricaemic, hypertensive adolescents and in obese adolescents with pre-hypertension [4,5]. In one study, both allopurinol (a xanthine oxidase inhibitor which reduces formation of uric acid) and probenecid (a uricosuric drug) were studied [5]. For similar reductions in uric acid, both agents were associated with significant reduction in systolic BP, suggesting the effect is mediated by uric acid reduction per se.

Whether serum uric acid has a direct pathophysiological role in the sequelae of hypertension in older adults is less clear. A recent analysis of 6984 patients undergoing treatment for hypertension showed no relationship between baseline serum uric acid level and long term BP change, although it did show an association between high uric acid level and decline in renal function [6]. Equally, it is less clear whether drugs that lower uric acid lower BP in adults with hypertension. A meta-analysis of the effect of allopurinol on BP, combining data from 10 clinical studies with 738 participants, found a small reduction in BP in allopurinol treated patients (3.3mmHg (95% CI: -1.4 to -5.3mmHg) for systolic BP [7].

We hypothesised that, similar to in adolescents, the initiation of allopurinol would be associated with a fall in BP in older adults with hypertension and that higher doses would have a greater effect. We extracted data from the UK Clinical Practice Research Datalink (CPRD) to test this hypothesis.
MATERIALS AND METHODS

The CPRD (formally GPRD) is the world’s largest computerized database of anonymized longitudinal clinical records from primary care [8]. It contains data on demographic characteristics, diagnoses, prescriptions, referrals to secondary care and medical history [9]. Information is collected from over 500 practices giving details of over 3.4 million patients and the information contained within the database has been shown to be accurate and representative of the UK population [10,11].

Approval was granted by the Independent Scientific Advisory Committee of the CPRD for access to the database for this study. Ethical approval for all purely observational studies using CPRD data has been granted by the National Research Ethics Service.

Study Cohort

Data on 44,406 patients were obtained from the CPRD. The cohort included all patients with hypertension aged 65 years or older who were registered with the CPRD on 1 January 1996 with two or more years of up to standard follow-up data prior to this date. Hypertension was defined as a documented record of hypertension with onset within 10 years prior to cohort entry or at least two BP readings of more than 160/90mmHg within the same period. Age was derived from date of birth records in the CPRD. It was decided to include patients aged 65 years or more as they are exempt from prescription charges in the UK which reduces the risk of income-based confounding and our aim was to explore the effect of allopurinol in older adults with established hypertension.

Patients with a diagnosis of renal impairment, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis or migraine were excluded as these could confound antihypertensive and other medication choices.

From this initial cohort of 44,406 patients, two groups were extracted for inclusion in this study (an allopurinol group and a control group). Patients were included in the allopurinol
group if they were prescribed allopurinol and had a BP measured before and during allopurinol treatment. Control patients had at least two BP measures recorded at least 30 days apart. A pre-allopurinol treatment serum uric acid level was extracted for allopurinol treated patients.

**Allopurinol exposure**

Allopurinol is identified by the British Formulary Classification as class 10.1.4. Allopurinol use was defined as > 3 prescriptions of allopurinol after 1st January 1996. The number of prescriptions, the date of the prescriptions and the dosages of the prescriptions were extracted.

The dosages were used to calculate the number of mg of allopurinol received and this was used to classify participants into high (≥300 mg daily) and low dose (<300 mg daily) allopurinol groups.

**Blood pressure readings**

For both groups, two BP readings were extracted; a baseline measurement and a subsequent measurement. For the allopurinol group the baseline (pre-treatment) BP was defined as the BP reading on the day of or closest to and within one calendar year of the first allopurinol prescription date. The second measure was at least 30 days after starting (but still during) the allopurinol treatment. The difference between these measurements was calculated.

For the patients not receiving allopurinol the baseline BP was the first measurement obtained after 1 January 1996 and the second BP reading was taken at least 30 days thereafter. The difference between these BP measurements was calculated.

**Antihypertensive drug exposure**

Data regarding patient’s antihypertensive medication use was also obtained. The dates and number of prescriptions were obtained for drugs belonging to the following drug classes: angiotensin-converting enzyme inhibitors (BNF class 2.5.5.1), angiotensin receptor blockers...
(BNF class 2.5.5.2), calcium channel blockers (BNF class 2.6.2), any diuretic class (BNF class 2.2), beta blockers (BNF class 2.4) and alpha blockers (BNF class 2.5.4).

Based on this study subjects were organised into two groups; those receiving ‘new antihypertensive treatment’ (if their first prescription above was received within 30 days before the (pre-allopurinol) baseline BP or between baseline and the on-allopurinol BP reading) and those with ‘no antihypertensive treatment or continued unchanged antihypertensive treatment’ (if the patients were not prescribed any antihypertensive treatment at all or continued on the same treatment as when the baseline BP was measured).

Outcomes of interest

The primary outcome was the change in SBP between the baseline and subsequent BP readings. The secondary outcome was the change in DBP between baseline and subsequent BP readings. Our primary analysis included patients in the no or continued unchanged antihypertensive group.

Statistical analysis

A p value of <0.05 was used to define a statistically significant difference for all analyses. The change in SBP and DBP was compared between the allopurinol and control group using a 2 sample t test (data were normally distributed). One way analysis of variance was used to compare the change in BP in the high dose and low dose allopurinol patients. A 2 sample t-test was then used to compare those with low dose and high dose allopurinol.

Regression analysis was used to determine if allopurinol was independently associated with the change in BP. Variables that were related to either the change in BP or the treatment group (allopurinol vs. control) were identified by either correlation analysis for two continuous variables or chi squared analysis.

Analyses were performed separately in the no or continued unchanged antihypertensive treatment group (the primary analysis) and then in the new antihypertensive treatment group.
In order to further assess the potential for confounding we used nearest neighbour propensity matching to refine the control group and repeated the above analyses. Patients were matched on the variables that differed between the treatment groups (age, BMI, diabetes, IHD, days between BP measurements and for antihypertensive treatment group but not baseline BP as this was used to calculate the outcome measures). In the regression models, all matching variables, as well as those that differed between the treatment groups or were related to the change in BP were included.

A sensitivity analysis was performed including only patients whose baseline BP was measured ≤ 30 days before the initial allopurinol prescription. This was to reduce the effects any confounding factors may have during the time between the baseline (pre-treatment) BP being obtained and the patient starting allopurinol.

Finally, we explored the relationship between baseline serum uric acid level and change in BP (in the whole group and in males and females separately). We did not have sufficient data to calculate a change in uric acid level following allopurinol treatment.

**RESULTS**

From the 44,406 patients included in the CPRD data extract 1412 were exposed to allopurinol. Of these, 1047 did not have BP data meeting the above criteria. This left 365 patients included in the allopurinol study group (Figure 1). Of these, 262 (71.9%) received no or continued unchanged antihypertensive treatment and 103 (28.1%) started new antihypertensive treatment between their BP readings. A total of 133 (36.4%) of patient took allopurinol at a dose of 300 mg daily (no patient took a dose higher than this). Pre-treatment serum uric levels were available for 202 allopurinol treated patients. The median time between the baseline BP measurement and commencing allopurinol was 98 days [Interquartile range (IQR) 21-271 days]. 308 (84.4%) patients began allopurinol within
6 months and 133 (36.4%) within 1 month of their BP measurement (these 133 patients were included in the aforementioned sensitivity analysis).

A total of 6678 patients met the criteria for inclusion in the control group. Baseline characteristics for both groups are shown in Table 1. The allopurinol and control groups differed significantly for BMI, diabetes, ischaemic heart disease, baseline BP and numbers assigned to the two antihypertensive medication groups.

Blood pressure change during allopurinol treatment

In those receiving no or continued unchanged antihypertensive treatment SBP fell by 2.60mmHg [(95%CI: -5.43 to 0.22mmHg) p=0.071] and DBP fell by 2.26mmHg [(95%CI: -3.81 to -0.71mmHg) p=0.019]. In the new antihypertensive treatment group, SBP decreased by 7.82mmHg [(95%CI: -13.4 to -2.26mmHg) p=0.006] and DBP decreased by 4.26mmHg [(95%CI: -6.87 to -1.65mmHg) p=0.002].

Comparison Between Treatment Groups

Compared to controls, SBP fell by 2.08mmHg [(95%CI: -0.59 to 4.75mmHg) p=0.127] and DBP fell by 1.72mmHg [(95%CI: 0.38 to 3.07mmHg) p=0.032] in the allopurinol group for those receiving no or continued unchanged antihypertensives. In those receiving new antihypertensives SBP fell to a greater extent in the control group [-4.81mmHg (95%CI: -10.21 to 0.60mmHg) p=0.081], as did DBP [-2.56mmHg (95%CI: -5.36 to 0.24mmHg) p=0.073] (Table 2). However, regression analysis showed allopurinol use to be associated with an independent fall in both systolic and diastolic BP in both the “no or continued” and in the new anti-hypertensive treatment groups (Table 3a). Age, smoking, BMI, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, baseline BP, days between BP measurements and allopurinol use were included in the regression models.

BP Change, Allopurinol Dosage and Serum Uric Acid Level
One way analysis of variance showed no relationship between the change in SBP and receiving no dose, low dose or high dose allopurinol \([p=0.312]\) but did show a significant relationship for the change in DBP \([p=0.040]\). However, the fall in BP in high dose allopurinol and low dose allopurinol patients was similar (for SBP high dose: \(-2.59\text{mmHg} (95\% \text{CI: } -7.58 \text{ to } 2.40 \text{ mmHg})\), low dose: \(-2.61\text{mmHg} (95\% \text{CI: } -6.07 \text{ to } 0.847 \text{ mmHg})\)] and for DBP high dose: \(-2.63\text{mmHg} (95\% \text{CI: } -5.49 \text{ to } 0.227 \text{ mmHg})\), low dose: \(-2.06\text{mmHg} (95\% \text{CI: } -3.91 \text{ to } -0.22\text{mmHg})\)).

There was no relationship between baseline serum uric acid and either change in SBP or DBP in either the whole group \((r=0.01, p=0.84 \text{ and } r=-0.04, p=0.60 \text{ respectively})\) or when males \((r=0.01, p=0.94 \text{ and } r=-0.00, p=0.97)\) and females \((r=0.02, p=0.86 \text{ and } r=-0.00, p=0.99)\) were considered separately.

**Propensity Matched Data**

Propensity matching yielded two groups with 313 patients in each; 52 patients from the original allopurinol treatment group could not be matched (Table 1).

In the allopurinol group, SBP fell by \(2.09\text{mmHg} [(95\% \text{CI: } -5.14 \text{ to } 0.95 \text{ mmHg}) p=0.177]\) and DBP fell by \(2.0\text{mmHg} [(95\% \text{CI: } -3.69 \text{ to } -0.30 \text{ mmHg}) p=0.021]\) in those receiving no or continued unchanged antihypertensive treatment. In those receiving new antihypertensive treatment SBP fell by \(5.67\text{mmHg} [(95\% \text{CI: } -11.7 \text{ to } 0.36 \text{ mmHg}) p=0.065]\) and DBP fell by \(3.33\text{mmHg} [(95\% \text{CI: } -6.08 \text{ to } -0.59) p=0.018]\) (Table 2).

Comparison of the propensity matched groups showed SBP to fall by \(3.02\text{mmHg} (95\% \text{CI: } -1.24 \text{ to } 7.26 \text{ mmHg}, p=0.165)\) and DBP by \(1.71\text{mmHg} (95\% \text{CI: } -0.51 \text{ to } 3.93 \text{ mmHg}, p=0.130)\) more in the allopurinol group than in the control group for those receiving no or continued unchanged antihypertensive treatment (table 3). In patients receiving new antihypertensive treatment the fall in SBP and DBP were greatest in the control groups (table
3), However, regression analysis again showed allopurinol treatment to be associated with a statistically significant and independent drop in BP across all conditions of use (Table 3b). One way analysis of variance showed no relationship between the change in systolic or diastolic BP and receiving no dose, low dose or high dose allopurinol [SBP change p=0.227, DBP change p=0.252]. However, there was a trend towards the fall in both systolic and diastolic BP being greater in patients receiving high dose allopurinol (on line supplement).

**Sensitivity Analysis**

The results were compatible with the main study analysis (data not shown).

**DISCUSSION**

This study sought to determine whether the initiation of allopurinol is associated with a fall in BP in a hypertensive population aged 65 years and older. Allopurinol initiation was independently associated with a fall in both systolic and diastolic BP across all conditions of use in regression analysis. There was a trend toward a greater fall in BP with high dose treatment. The fall in BP was modest (3 mmHg in the propensity matched sample) but was independent of adjustment for potential confounding variables and high dose treatment may be associated with a higher fall in BP. Although the fall in BP appeared less in patients receiving new BP drugs, allopurinol was also associated with a greater fall in BP in this group on regression analysis.

Epidemiological studies have already shown that uric acid level is associated with incident hypertension [1] and a role for uric acid in the development of hypertension has been shown in clinical trials in adolescents and obese adolescents [4,5]. A meta-analysis of small studies that was limited by heterogeneity suggests allopurinol may lower BP in adults [7] and a recent clinical trial in patients with stroke found a BP lowering effect [12]. However, this has not been demonstrated in trials designed for this purpose, nor in adults with hypertension.
The current study suggests, but cannot prove, that allopurinol has a modest effect on BP and that higher doses may be particularly effective.

Uric acid is produced from the metabolism of purines by xanthine oxidase [13,14,15]. Uric acid has been shown to cause hypertension and arteriolopathy in rats through activation of the renin system and inhibition of nitric oxide synthase [4,5]. In addition, uric acid stimulates vascular smooth muscle cell proliferation and acts as a pro-inflammatory mediator. Xanthine oxidase activity also produces reactive oxygen species (ROS), namely superoxide, hydrogen peroxide and the hydroxyl radical. ROS cause tissue damage and inactivate nitric oxide leading to endothelial dysfunction, a precursor for atherosclerosis and vascular injury [13,14,15]. Allopurinol inhibits xanthine oxidase activity, thus lowering ROS and improving the bioavailability of NO. Treatment with allopurinol has been shown to improve endothelial function, measured by forearm blood flow in patients with HF [16] and type 2 diabetes with mild hypertension [17].

Thus, there are two mechanisms by which allopurinol may lower BP; the reduction in uric acid or the reduction in ROS. This dual action makes it an obvious choice for hypertension trials. The almost identical reductions in BP from allopurinol and probenicid in obese adolescents with prehypertension might suggest that uric acid reduction is responsible for the fall in BP [5], confirming that high uric acid is a risk factor for development of hypertension in this group. Whether this is the case in older adults with established hypertension is unclear and our study cannot confirm this. We did not see a relationship between baseline serum uric acid and change in BP but head to head comparator studies of xanthine oxidase inhibitors and uricosuric drugs would be needed to establish the pathophysiological importance of uric acid in this group. Were allopurinol to have no effect on BP, it still has other established benefits. These benefits are related to xanthine oxidase inhibition and the subsequent decrease in oxidative stress and increase in available oxygen and energy. Oxidative stress is associated
with the development of left ventricular hypertrophy (LVH). High dose allopurinol has been shown to reduce LVH in patients with renal disease [18]. In addition, allopurinol has also been shown to improve oxygen consumption in the myocardium [19] and increase the delivery of ATP during heart failure [20].

The dose used in the clinical trials in adolescents was 200mg twice daily [4,5]. In this study, patients were prescribed between 100mg and 300mg daily with 58% being prescribed only 100mg. Previous studies show a steep dose-response relationship for the action of allopurinol and suggest higher doses of allopurinol (300 mg twice daily) are needed to exert effects on endothelial function and left ventricular hypertrophy [18]. It may be that these doses are required for a beneficial BP effect. Allopurinol for the treatment of gout can be given up to 900mg daily in patients without impaired renal function [21]. Although our study did not conclusively show a greater effect of higher doses, we believe the totality of evidence supports use of doses of 300 mg daily and above in future studies. The modest fall in BP observed could also reflect the older population with established hypertension included in this study. The Framingham study showed the association between hypertension and uric acid level to weaken as age and duration of hypertension increased [22] and our previous analyses support this [6].

There are several limitations in this to consider. There is a risk of selection bias in this study – only 3.18% of patients from the extracted cohort were prescribed allopurinol treatment. Reassuringly, this is in keeping with a primary care study from the General Practice Hypertension Study Group which found the prevalence of gout to be 3.1% in patients with hypertension [23]. This suggests the cohort obtained is broadly representative of the wider allopurinol treated primary care population. Unfortunately only 25.8% of these patients had the required BP readings but analysis found few differences between this group and all allopurinol exposed patients (data not shown). Adjustment was made for potential
confounding variables but a concealed confounder cannot be excluded. In order to further limit these factors we included a secondary analysis of a propensity matched sample which, while smaller, confirmed an independent fall in BP following allopurinol initiation. The baseline BP differed between groups and was higher in controls. This difference persisted after matching but was adjusted for in all analyses. This could confound results, particularly as it may influence BP treatments, but we are reassured that results were consistent in the subgroup with no medication changes. The time between BP measurements is an important potential confounder and differed between groups but this was also adjusted for in the regression models. One further potential confounder is non-steroidal anti-inflammatory drug (NSAID) use. As would be expected, NSAID use was highly prevalent in the allopurinol group. NSAID use increases the BP [24] and this would likely bias the results towards the null and attenuate the fall in BP seen. Although we explored the relationship between baseline uric acid level and change in BP, the sample size was small and we could not assess change in uric acid level. The effect of allopurinol on BP in hyperuricaemic and normouricaemic patients warrants further study. We used clinic BP, which are highly variable rather than the gold standard ambulatory BP monitoring. Further, although the CPRD is accurate in recording prescriptions issued, it is not possible to confirm patient adherence to therapy, although our results were consistent in patients taking no BP drugs. We also did not include a group of patients who withdrew BP medication, nor did we explore the effect of allopurinol initiation across different classes of BP lowering drugs and we were unable to study the effect of changes in BP medication doses. We have not explored use of other xanthine oxidase inhibitors such as Febuxostat. All of these areas warrant further study.

**Perspectives**
Hypertension is a key risk factor for coronary heart disease and stroke and hyperuricaemia is known to have a role in the development of hypertension in adolescents. New treatments are needed to control BP and reduce associated risk. Allopurinol is an appealing drug for further study. It lowers BP in adolescents and a small (albeit limited meta-analysis) and our data suggests it may lower BP in older adults. Prospective randomised controlled and blinded studies of allopurinol use in adults with hypertension are needed to clarify whether it has a role in treatment of hypertension. Further studies are also needed to elucidate whether any effect of allopurinol in adults with hypertension are mediated via uric acid reduction or through its other effects.
Acknowledgements

Access to the data was provided by the CPRD under the previous MRC license scheme.

Source of Funding

Access to the data was provided by the GPRD under the MRC license scheme.

Conflicts of Interest

No conflicts of interest.
REFERENCES


Novelty and Significance

What is New?
Allopurinol initiation is associated with a fall in blood pressure in older adults with hypertension.

What is Relevant?
Allopurinol is an attractive drug for further study in patients with hypertension.

Summary
After adjustment for potential confounding factors, allopurinol initiation was associated with an independent fall in blood pressure.

Figure Legends

Figure 1: Flow chart of study participants. CPRD: Clinical Practice Research Datalink.
Table 1: Baseline Characteristics for patients in the allopurinol-exposed and control groups, before and after propensity matching.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Allopurinol Exposed Patients (6678)</th>
<th>Control Exposed Patients (6678)</th>
<th>P-Value</th>
<th>Allopurinol Matched Patients (313)</th>
<th>Control Matched Patients (313)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [mean(SD)]</td>
<td>72.9 (5.3)</td>
<td>72.6 (5.8)</td>
<td>0.34</td>
<td>72.6 (5.33)</td>
<td>72.4 (5.64)</td>
<td>0.60</td>
</tr>
<tr>
<td>Female Sex*</td>
<td>192 (52.6%)</td>
<td>3511 (52.6%)</td>
<td>0.67</td>
<td>161 (49.8%)</td>
<td>162 (51.8%)</td>
<td>0.93</td>
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<tr>
<td>Smoking Status*</td>
<td>31 (8.2%)</td>
<td>760 (11.4%)</td>
<td>0.05</td>
<td>26 (8.3%)</td>
<td>32 (10.2%)</td>
<td>0.43</td>
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<tr>
<td>BMI (kg/m²) [mean(SD)]</td>
<td>28.2 (4.1)</td>
<td>26.1 (4.0)</td>
<td>0.00</td>
<td>28.22 (4.05)</td>
<td>28.51 (5.58)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>127 (34.8%)</td>
<td>1453 (21.8%)</td>
<td>0.00</td>
<td>112 (35.8%)</td>
<td>112 (35.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ischaemic heart disease*</td>
<td>106 (29%)</td>
<td>1214 (18.2%)</td>
<td>0.00</td>
<td>91 (29.1%)</td>
<td>82 (26.3%)</td>
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<tr>
<td>Peripheral vascular</td>
<td>4 (1.1%)</td>
<td>91 (1.4%)</td>
<td>0.66</td>
<td>4 (1.3%)</td>
<td>4 (1.3%)</td>
<td>1.00</td>
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<tr>
<td></td>
<td>Disease*</td>
<td>Cerebrovascular disease*</td>
<td>SBP (mmHg) [mean(SD)]</td>
<td>DBP (mmHg) [mean(SD)]</td>
<td>Time between baseline BP and allopurinol exposure (days) [median (IQR)]</td>
<td>Allopurinol prescriptions [median (IQR)]</td>
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<td></td>
<td></td>
<td>25 (6.8%)</td>
<td>148.7 (21.2)</td>
<td>79.8 (10.9)</td>
<td>52.0 (12-123)</td>
<td>13 (4-36)</td>
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<td></td>
<td></td>
<td>615 (9.2%)</td>
<td>161.1 (21.9)</td>
<td>87.5 (10.8)</td>
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<td></td>
<td></td>
<td>0.12</td>
<td>0.00</td>
<td>0.00</td>
<td>0</td>
<td>7 (3-18)</td>
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<td></td>
<td></td>
<td>20 (6.4%)</td>
<td>148.3 (21.2)</td>
<td>79.6 (11.07)</td>
<td>53.0 (10-126)</td>
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<td>21 (6.7%)</td>
<td>161.8 (21.3)</td>
<td>87.46</td>
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<td></td>
<td>0.87</td>
<td>0.00</td>
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antihypertensive

* Denotes Chi-Squared test used for categorical variables. †Denotes Mann Whitney test used as data was non-parametric. All other continuous variables were analysed using Independent T-tests.
Table 2: The difference in the change of blood pressure between allopurinol exposed (365) and control patients (6678).

<table>
<thead>
<tr>
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<th>SBP (mmHg)</th>
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<th>DBP (mmHg)</th>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>95%CI</td>
<td>Mean</td>
</tr>
<tr>
<td>Whole Cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No / continued *</td>
<td>2.08</td>
<td>1.4</td>
<td>-0.59 to 4.75</td>
<td>0.127</td>
</tr>
<tr>
<td>New antihypertensive</td>
<td>-4.81</td>
<td>2.8</td>
<td>-10.21 to 0.60</td>
<td>0.081</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Propensity Matched Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No / continued *</td>
<td>3.02</td>
<td>2.2</td>
<td>-1.24 to 7.26</td>
<td>0.165</td>
</tr>
<tr>
<td>New antihypertensive</td>
<td>-2.20</td>
<td>4.0</td>
<td>-10.09 to 5.69</td>
<td>0.583</td>
</tr>
</tbody>
</table>

Differences are expressed as control – allopurinol-exposed, positive values show blood pressure to have fallen to a greater extent in allopurinol exposed patients. P-value based on independent sample T-test. * = no or continued antihypertensive treatment.
Table 3: Regression analysis for the change in systolic and diastolic BP.

A- Whole group data (365/6678)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>95% CI for Beta</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
<td></td>
</tr>
<tr>
<td>SBP change in ‘no or continued unchanged’ antihypertensive patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>-7.42</td>
<td>-10.104</td>
<td>-4.744</td>
</tr>
<tr>
<td>DBP change in ‘no or continued unchanged’ antihypertensive patients</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>-5.39</td>
<td>-6.719</td>
<td>-4.050</td>
</tr>
<tr>
<td>SBP change in new antihypertensive patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>-9.23</td>
<td>-14.880</td>
<td>-3.582</td>
</tr>
<tr>
<td>DBP change in new antihypertensive patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>-6.71</td>
<td>-9.423</td>
<td>-3.994</td>
</tr>
</tbody>
</table>

B- Propensity matched data (313/313)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>95% CI for Beta</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
<td></td>
</tr>
<tr>
<td>SBP change in ‘no or continued unchanged’ antihypertensive patients</td>
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<td></td>
<td></td>
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<tr>
<td>Allopurinol use</td>
<td>-6.83</td>
<td>-10.89</td>
<td>-2.761</td>
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<tr>
<td>DBP change in ‘no or continued unchanged’ antihypertensive patients</td>
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<tr>
<td>Allopurinol use</td>
<td>-4.45</td>
<td>-6.649</td>
<td>-2.258</td>
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<tr>
<td>SBP change in new antihypertensive patients</td>
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<tr>
<td>Allopurinol use</td>
<td>-11.35</td>
<td>-19.61</td>
<td>-3.081</td>
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<tr>
<td>DBP change in new antihypertensive patients</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>-8.11</td>
<td>-12.07</td>
<td>-4.147</td>
</tr>
</tbody>
</table>
Regression models included age, smoking, BMI, diabetes, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, baseline BP, days between BP measurements and allopurinol use.