Allopurinol Initiation and Change in Blood Pressure in Older Adults With Hypertension

Catherine J. Beattie, Rachael L. Fulton, Peter Higgins, Sandosh Padmanabhan, Linsay McCallum, Matthew R. Walters, Anna F. Dominiczak, Rhian M. Touyz, Jesse Dawson

Abstract—Hypertension is a key risk factor for cardiovascular disease, and new treatments are needed. Uric acid reduction lowers blood pressure (BP) in adolescents, suggesting a direct pathophysiological role in the development of hypertension. Whether the same relationship is present in older adults is unknown. We explored change in BP 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 pretreatment and during treatment BP readings. Data from comparable controls were extracted. The change in BP in patients with stable BP 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. Three hundred sixty-five patients who received allopurinol and 6678 controls were included. BP fell in the allopurinol group compared with controls (between-group difference in systolic and diastolic BP: 2.1 mm Hg; 95% confidence interval, −0.6 to 4.8; and 1.7 mm Hg; 95% confidence interval, 0.4–3.1, respectively). Allopurinol use was independent of both in systolic and diastolic BP on regression analysis (P<0.001). Results were consistent in the propensity-matched sample. There was a trend toward greater fall in BP in the high-dose allopurinol group, but change in BP was not related to baseline uric acid level. Allopurinol use is associated with a small fall in BP in adults. Further studies of the effect of high-dose allopurinol in adults with hypertension are needed. (Hypertension. 2014;64:00-00.) ● Online Data Supplement

Key Words: allopurinol ◇ hypertension ◇ therapeutics ◇ uric acid ◇ xanthine oxidase

Hyperuricemia is associated with incident hypertension,1 and preclinical studies support a role for hyperuricemia in the development of hypertension. Hyperuricemia has been shown to raise blood pressure (BP) in normotensive rats, and this rise is attenuated by urate-lowering drugs.2 Furthermore, sustained hyperuricemia has been shown to induce a primary renal arteriolopathy and a salt-sensitive rise in BP in experimental models.3 Recently, randomized placebo-controlled and blinded clinical trials have shown that urate-lowering drugs reduce BP in hyperuricemic, hypertensive adolescents and in obese adolescents with prehypertension.4,5 In 1 study, both allopurinol (a xanthine oxidase inhibitor that reduces the 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 that 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 also 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 (3.3 mm Hg; 95% confidence interval [CI], −1.4 to −5.3 mm Hg) for systolic BP.7

We hypothesized 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, formally General Practice Research Database) to test this hypothesis.

Materials and Methods

The CPRD 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 >500 practices giving details of >3.4 million patients, and the

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information contained within the database has been shown to be accurate and representative of the UK population. 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 who were registered with the CPRD on January 1, 1996, with ≥2 years of standard follow-up data before this date. Hypertension was defined as a documented record of hypertension with onset <10 years before cohort entry or at least 2 BP readings of >160/90 mmHg within the same period. Age was derived from date of birth records in the CPRD. It was decided to include patients aged ≥65 years because they are exempt from prescription charges in the United Kingdom, 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 because these could confound antihypertensive and other medication choices.

From this initial cohort of 44,406 patients, 2 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 2 BP measures recorded ≤30 days apart. A preallopurinol treatment serum uric acid level was extracted for allopurinol-treated patients.

**Allopurinol Exposure**

Allopurinol is identified by the British National Formulary (BNF) classification as class 10.1.4. Allopurinol use was defined as ≥3 prescriptions of allopurinol after January 1, 1996. The number of prescriptions, date of prescriptions, and dosages of prescriptions were extracted.

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

**BP Readings**

For both groups, 2 BP readings were extracted: a baseline measurement and a subsequent measurement. For the allopurinol group, the baseline (pretreatment) BP was defined as the BP reading on the day of or closest to and within 1 calendar year of the first allopurinol prescription date. The second measure was ≤30 days after starting (but still during) allopurinol treatment. The difference between these measurements was calculated.

For patients not receiving allopurinol, the baseline BP was the first measurement obtained after January 1, 1996, and the second BP reading was taken ≤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-convert- ing 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), β-blockers (BNF class 2.4), and α-blockers (BNF class 2.5.4).

Based on this study, subjects were organized into 2 groups: those receiving new antihypertensive treatment (if their first prescription above was received ≤30 days before [preallopurinol] baseline BP or between baseline and 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 change in systolic BP (SBP) between baseline and subsequent BP readings. The secondary outcome was change in diastolic BP (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 <0.05 was used to define a statistically significant difference for all analyses. The change in SBP and DBP was compared between allopurinol and control group using a 2-sample t-test (data were normally distributed). One-way ANOVA 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 treatment group (allopurinol versus control) were identified by either correlation analysis for 2 continuous variables or χ² 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.

To further assess the potential for confounding, we used nearest-neighbor propensity matching to refine the control group and repeated the above analyses. Matching was performed on variables that differed between the allopurinol and non-allopurinol groups (age, body mass index, diabetes mellitus, ischemic heart disease, days between BP measurements and for antihypertensive treatment group but not baseline BP because 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 baseline (pretreatment) BP being obtained and patient starting allopurinol.

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

**Results**

From the 44,406 patients included in the CPRD data extract, 1,412 were exposed to allopurinol. Of these, 1,047 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%) patients took allopurinol at a dose of 300 mg daily (no patient took a dose higher than this). Pretreatment serum uric acid levels were available for 202 allopurinol-treated patients.

The median time between baseline BP measurement and commencing allopurinol was 98 days (interquartile range, 21–271 days). Three hundred eight (84.4%) patients began allopurinol ≤6 months and 133 (36.4%) ≤1 month of their BP measurement (these 133 patients were included in the aforementioned sensitivity analysis).

A total of 6,678 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 body mass index, diabetes mellitus, ischemic heart disease, baseline BP, and numbers assigned to the 2 antihypertensive medication groups.

**BP Change During Allopurinol Treatment**

In those receiving no or continued unchanged antihypertensive treatment, SBP fell by 2.60 mm Hg (95% CI, −5.43 to 0.22 mm Hg; \(P=0.071\)) and DBP fell by 2.26 mm Hg (95% CI, −3.81 to −0.71 mm Hg; \(P=0.019\)). In the new antihypertensive treatment group, SBP decreased by 7.82 mm Hg (95% CI, −13.4 to −2.26 mm Hg; \(P=0.006\)) and DBP decreased by 4.26 mm Hg (95% CI, −6.87 to −1.65 mm Hg; \(P=0.002\)).

**Comparison Between Treatment Groups**

Compared with controls, SBP fell by 2.08 mm Hg (95% CI, −0.59 to 4.75 mm Hg; \(P=0.127\)) and DBP fell by 1.72 mm Hg (95% CI, 0.38−3.07 mm Hg; \(P=0.032\)) 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 (−4.81 mm Hg; 95% CI, −10.21 to 0.60 mm Hg; \(P=0.081\)) as did DBP (−2.56 mm Hg; 95% CI, −5.36 to 0.24 mm Hg; \(P=0.073\); Table 2). However, regression analysis showed allopurinol use to be associated with an independent fall in both SBP and DBP in both no or continued and in the new antihypertensive treatment group (Table 3). Age, smoking, body mass index, ischemic 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 ANOVA showed no relationship between change in SBP and receiving no dose, low-dose or high-dose allopurinol (\(P=0.312\)) but did show a significant relationship for 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 mm Hg; 95% CI, −7.58 to 2.40 mm Hg; low dose: −2.61 mm Hg; 95% CI, −6.07 to 0.847 mm Hg; and for DBP high dose: −2.63 mm Hg; 95% CI, −5.49 to 0.227 mm Hg; low dose: −2.06 mm Hg; 95% CI, −3.91 to −0.22 mm Hg).

There was no relationship between baseline serum uric acid and either change in SBP or DBP in either the whole group (\(r=0.01, P=0.84\); and \(r=−0.04, P=0.60\), respectively) or when men (\(r=0.01, P=0.94\); and \(r=−0.00, P=0.97\)) and women (\(r=0.02, P=0.86\); and \(r=−0.00, P=0.99\)) were considered separately.

**Propensity-Matched Data**

Propensity matching yielded 2 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 mm Hg (95% CI, −5.14 to 0.95 mm Hg; \(P=0.177\)) and DBP fell by 2.0 mm Hg (95% CI, −3.69 to −0.30 mm Hg; \(P=0.021\)) in those receiving no or continued unchanged antihypertensive treatment. In those receiving new antihypertensive treatment, SBP fell by 5.67 mm Hg (95% CI, −11.7 to 0.36 mm Hg; \(P=0.065\)) and DBP fell by 3.33 mm Hg (95% CI, −6.08 to −0.59 mm Hg; \(P=0.018\); Table 2).

Comparison of the propensity-matched groups showed SBP to fall by 3.02 mm Hg (95% CI, −1.24 to 7.26 mm Hg; \(P=0.165\)) and DBP by 1.71 mm Hg (95% CI, −0.51 to 3.93 mm Hg; \(P=0.130\)) 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 was greatest in the control group (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 3).

One-way ANOVA showed no relationship between change in SBP or DBP 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 toward fall in both SBP and DBP being greater in patients receiving high-dose allopurinol (see the online-only Data 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. Allopurinol initiation was independently associated with a fall in both SBP and DBP 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 mm Hg 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.
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Epidemiological studies have already shown that uric acid level is associated with incident hypertension, and a role for uric acid in the development of hypertension has been shown in clinical trials in adolescents and obese adolescents. A meta-analysis of small studies that were limited by heterogeneity suggests allopurinol may lower BP in adults, and a recent clinical trial in patients with stroke found a BP-lowering effect. 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. It has been shown to cause hypertension and arteriolopathy in rats through the activation of the renin system and inhibition of nitric oxide synthase. In addition, uric acid stimulates vascular smooth muscle cell proliferation and acts as a proinflammatory mediator. Xanthine oxidase activity also produces reactive oxygen species, namely superoxide, hydrogen peroxide, and the hydroxyl radical. Reactive oxygen species cause tissue damage and inactivate nitric oxide, leading to endothelial dysfunction, a precursor for atherosclerosis and vascular injury. Allopurinol inhibits xanthine oxidase activity, thus lowering reactive oxygen species and improving the bioavailability of nitric oxide. Treatment with allopurinol has been shown to improve endothelial function, measured by forearm blood flow in patients with heart failure and type 2 diabetes mellitus with mild hypertension.

Table 2. Difference in the Change of Blood Pressure Between Allopurinol-Exposed (n=365) and Control Patients (n=6678).

<table>
<thead>
<tr>
<th>Variable</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Whole cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/continued*</td>
<td>2.08</td>
<td>1.4</td>
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<tr>
<td>New antihypertensive treatment</td>
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<tr>
<td>Propensity-matched sample</td>
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<tr>
<td>No/continued*</td>
<td>3.02</td>
<td>2.2</td>
</tr>
<tr>
<td>New antihypertensive treatment</td>
<td>-2.20</td>
<td>4.0</td>
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</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. CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*No or continued antihypertensive treatment.
Table 3. Regression Analysis for the Change in SBP and DBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>95% CI for β</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P Value</th>
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</thead>
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<tr>
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<tr>
<td>Allopurinol use</td>
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<td>−6.719</td>
<td>−4.050</td>
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<td>SBP change in new antihypertensive patients</td>
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<tr>
<td>Allopurinol use</td>
<td>−9.23</td>
<td>−14.880</td>
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<tr>
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<td></td>
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<tr>
<td>Allopurinol use</td>
<td>−6.71</td>
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<tr>
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<td>DBP change in new antihypertensive patients</td>
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<tr>
<td>Allopurinol use</td>
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Regression models included age, smoking, body mass index, diabetes mellitus, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, baseline BP, days between BP measurements, and allopurinol use. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

Thus, there are 2 mechanisms by which allopurinol may lower BP: reduction in uric acid or reduction in reactive oxygen species. This dual action makes it an obvious choice for hypertension trials. The almost identical reductions in BP from allopurinol and probenecid in obese adolescents with prehypertension might suggest that uric acid reduction is responsible for the fall in BP, 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. High-dose allopurinol has been shown to reduce left ventricular hypertrophy in patients with renal disease. In addition, allopurinol has also been shown to improve oxygen consumption in the myocardium and increase the delivery of ATP during heart failure.

The dose used in clinical trials in adolescents was 200 mg twice daily. In this study, patients were prescribed between 100 and 300 mg daily, with 58% being prescribed only 100 mg. Previous studies show a steep dose–response relationship for the action of allopurinol and suggest that higher doses of allopurinol (300 mg twice daily) are needed to exert effects on endothelial function and left ventricular hypertrophy. It may be that these doses are required for a beneficial BP effect. Allopurinol for the treatment of gout can be given ≤900 mg daily in patients without impaired renal function. Although our study did not conclusively show a greater effect of higher doses, we think the totality of evidence supports the use of doses of ≥300 mg daily 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, and our previous analyses support this.

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 that found the prevalence of gout to be 3.1% in patients with hypertension. 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 the 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. To further limit these factors, we included a secondary analysis of a propensity-matched sample that, although smaller, confirmed an independent fall in BP after 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 nonsteroidal anti-inflammatory drug use. As would be expected, nonsteroidal anti-inflammatory drug use was highly prevalent in the allopurinol group. Nonsteroidal anti-inflammatory drug use increases BP, and this would likely bias the results toward 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 hyperuricemic and normouricemic patients warrants further study. We used clinical BP, which is highly variable than the gold standard ambulatory BP monitoring. Furthermore, 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 the use of other xanthine oxidase inhibitors such as Febuxostat. All these areas warrant further study.
Perspectives
Hypertension is a key risk factor for coronary heart disease and stroke, and hyperuricemia 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 limited meta-analysis and our data suggest it may lower BP in older adults. Prospective randomized controlled and blinded studies of allopurinol use in adults with hypertension are needed to clarify whether it has a role in the 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.

Acknowledgments
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Disclosures
None.

References
ON LINE SUPPLEMENT

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

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Short Title - Allopurinol and Blood Pressure

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Figure S1: The mean change in blood pressure for those receiving low dose (<300mg) or high dose (≥300mg) allopurinol. Patients included were those receiving no or continued unchanged antihypertensive treatment from the propensity matched sample (313).