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Urate-lowering for blood pressure control in adults: another nail in the coffin?

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Short Summary for Pubmed

This editorial discusses the implications of the Serum Urate Reduction to Prevent Hypertension (SURPHER) trial. The findings of SURPHER, together with three previous randomised trials of the effect of urate-lowering therapy on blood pressure in adults, do not support a causal relationship between serum urate and hypertension in adults or provide a clear signal that the beneficial effect of urate-lowering therapy to lower blood pressure seen in adolescents is replicated in adults.

Keywords: allopurinol, urate, blood pressure, gout

Numerous observational studies have reported an association between serum urate and elevated blood pressure in adult populations (1). These observations, together with experimental *in vivo* studies, have generated substantial interest in the role of hyperuricaemia as a mediator of elevated blood pressure, with various postulated mechanisms, including activation of renin-angiotensin system, oxidative stress, reduced endothelial nitric oxide availability, and renal vasoconstriction (2). The potential of urate-lowering therapy for blood pressure lowering was supported by two short-term trials in adolescents with metabolic syndrome and elevated serum urate levels, that reported significant reductions in blood pressure in response to allopurinol or probenecid (3, 4), see **Table 1**.

Despite these promising results in adolescents, more recent studies have not supported the concept that urate-lowering therapy has a blood pressure lowering effect in adults. Mendelian randomization studies have not demonstrated a consistent strong causal relationship between serum urate and blood pressure in adult populations (5, 6). Furthermore, three randomized controlled trials in adults (mean age ranging from 41 to 54 years) have not shown blood pressure lowering effects with urate-lowering therapies (7-9), summarised in **Table 1**.

A key uncertainty has been whether urate-lowering therapy has beneficial effects on blood pressure in young adults who do not have the renal and vascular consequences of long-standing hypertension. In this month's *Arthritis and Rheumatology*, Gaffo and colleagues report the findings of the Serum Urate Reduction to Prevent Hypertension (SURPHER) trial which was designed to address this knowledge gap (10).

SURPHER was a single-centre, double-blind, placebo-controlled cross-over trial, which examined the effect of allopurinol 300mg daily on systolic blood pressure in young adults. The primary outcome was the difference between allopurinol and placebo in the change in 24-hour average systolic blood pressure (SBP) over four weeks, measured by ambulatory blood pressure monitoring. Ninety-nine adults (mean age 28 years, 63% male) were randomised. The mean serum urate at baseline was 5.9mg/dL, and no participants had gout. Mean SBP was 123.6mmHg and 122.6mmHg at the start of the allopurinol and placebo phases, respectively. There was no difference in the primary outcome: 24-hour average SBP reduced over four weeks by 1.39mmHg in the allopurinol phase and 1.06mmHg in the placebo phase. However, serum urate reduced by

1.33mg/dL with allopurinol compared with 0.04mg/dL with placebo. Significant improvement in endothelial function (measured by flow-mediated dilatation) was seen in the allopurinol phase but not in the placebo phase. There were no differences between allopurinol and placebo in other secondary outcomes including diastolic blood pressure, mean arterial pressure and high-sensitivity C-reactive protein.

Strengths of the SURPHER trial include the diversity of the participants recruited, 40% of whom were African-American. Adherence to allopurinol was high during the 4-week treatment phase, with 73% of participants having detectable plasma oxypurinol levels during this period, leading to clinically meaningful reductions in serum urate. The trial included a range of secondary outcomes to explore possible mechanisms through which allopurinol might lower blood pressure, i.e. urate-lowering, endothelial function and inflammation. Retention in the trial was good, with only 17% of participants withdrawn or lost to follow-up. Although trial recruitment fell short of its target of 112 participants, the recruited sample of 99 randomised participants provided 89% power under the assumptions of the original sample size calculation.

An important question about the trial design concerns whether the dose of allopurinol of 300mg daily was sufficient to bring about lowering of blood pressure. This dose is commonly used in clinical practice in the management of hyperuricaemia in gout, and Gaffo et al state that serum urate reduction is usually achieved at this dosage in support of the dose used. However, randomised trials show that allopurinol 300mg is often insufficient to achieve a target serum urate level below 6mg/dL when used to manage hyperuricaemia in gout. Only 21% of participants who received allopurinol 300mg daily achieved a target serum urate level below 6mg/dL in a randomised trial which compared febuxostat with allopurinol for the management of gout (11). In another randomised trial in which 95% of participants who received nurse-led care achieved this target serum urate level, the mean dose of allopurinol required was 460mg per day (12). Larger reductions in serum urate than those observed in the SURPHER trial were reported in other randomised trials of the effect of allopurinol on blood pressure in adolescents or adults in which the doses of allopurinol used were higher (3, 4, 9). Furthermore, a previous trial found that allopurinol produced greater improvements in endothelial function and oxidative stress at a dose of 600mg daily than 300mg daily in patients with heart failure (13). Despite these observations

suggesting that higher doses of allopurinol than 300mg daily might be required to lower serum urate and blood pressure, a dose of 300mg daily led to both clinically meaningful reduction in serum urate (mean baseline urate 5.8mg/dL, reducing by 1.39mg/dL) and an improvement in endothelial function in the SURPHER trial participants. However, this did not result in blood pressure lowering.

A further possible mechanism through which allopurinol could lower blood pressure is through effects on renal function. Outcomes in the SURPHER trial did not include renal function despite considerable interest in the potential beneficial effects of urate-lowering therapy on chronic kidney disease (CKD) progression. However, in the recent CKD-FIX and PERL trials, decline in estimated glomerular filtration rate (eGFR) did not differ between allopurinol and placebo in people with CKD and type 1 diabetes mellitus, respectively (14, 15).

In summary, the findings of the SURPHER trial and the three previous randomised trials of the effect of ULT on blood pressure in adults do not support a causal relationship between serum urate and hypertension in adults or provide a clear signal that the beneficial effect of ULT to lower blood pressure seen in adolescents is replicated in adults. It is likely that the mechanisms leading to hypertension in adults are different from those in children and adolescents. Gaffo et al suggest that young adults may have lost responsiveness to urate-mediated mechanisms proposed to affect blood pressure, consistent with the findings of McMullan et al that allopurinol had no effect on kidney-specific or systemic renin-angiotension system activity despite significant urate-lowering in a population of overweight or obese adults (mean age 41 years) (9).

Whilst the collective findings of these trials do not support the use of urate-lowering therapy to lower blood pressure in young to middle-aged adults, clinicians should not be deterred from prescribing urate-lowering therapies such as allopurinol for people with gout where clinically indicated. Treat-to-target urate-lowering therapy remains a highly effective treatment strategy to reduce the substantial pain, disability, and impairment of quality of life experienced by people with gout (12).

Author contributions

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Table 1. Key characteristics of randomised trials of the effect of urate-lowering therapies on blood pressure in children and adults

Trial	Age/sex/BMI/n	Mean BP at baseline	Mean urate at baseline	Interventions	Change in serum urate	Blood pressure outcomes
Feig 2008 (3) Crossover design, 4-week intervention	Mean age 15 years, 60% male, mean BMI 33, n=30	139/83 mmHg	6.9 mg/dL	Allopurinol 200mg bd, Placebo	Allopurinol: 7.0 to 4.3 mg/dL Placebo: 6.2 to 6.5 mg/dL	Significant reduction in BP with allopurinol; the mean change in systolic BP for allopurinol was −6.9 mmHg vs −2.0 mm Hg with placebo; P=0.009.
Soletsky 2012 (4) RCT, 8-week intervention	Mean age 14 years, 67% male, mean BMI 36, n=60	128/75 mmHg	6.8 mg/dL	Allopurinol 200mg bd, Probenecid 500mg bd, Placebo	Allopurinol: -2.8 mg/dL Probenecid: -2.7mg/dL Placebo: -0.3mg/dL	Reduction in BP with both allopurinol and probenecid; the mean change in systolic BP was −10.1 mmHg with allopurinol, −10.2 mmHg with probenecid, and +0.7 mmHg with placebo; P<0.001.
Segal 2015 (7) RCT, 4-week	Mean age 51, 50% male, mean BMI 35, n=150	118/75 mmHg	6.7 mg/dL	Allopurinol 300mg, Placebo,	Allopurinol:-3.4 mg/dL	No significant difference in BP between allopurinol and placebo groups. The mean change in

intervention				added to chlorthalidone 25mg/day	Placebo: -0.1 mg/dL	systolic BP was -3.4 mmHg with allopurinol and +0.8 mmHg with placebo.
Gunawardhana 2017 (8) RCT, 6-week intervention	Mean age 54 years, 81% male, mean BMI 33, n=121	Not stated (inclusion criteria: systolic BP 130-165 mmHg, diastolic BP 90-105 mmHg)	Not reported (inclusion criterion: ≥7 mg/dL) 28% ≥ 8mg/dL at baseline	Febuxostat 80mg, Placebo	Febuxostat; -3.2 mg/dL Placebo: 0.0 mg/dL	No significant difference in BP between febuxostat and placebo groups (primary endpoint). Significant reduction (-6.7 mmHg) with febuxostat in those with normal renal function in planned subgroup analysis
McMullan 2017 (9) RCT, 8-week intervention	Mean age 41 years, 50% male, mean BMI 34, n=149	119/77 mmHg	6.1 mg/dL	Allopurinol 600mg, Probenecid 1g, Placebo	Allopurinol: 6.1 to 2.9 mg/dL Probenecid; 6.1 to 3.5 mg/dL Placebo: 6.1 to	No effect on BP. The mean change in systolic BP was -0.4 mmHg with allopurinol, -1.6 mmHg with probenecid, and +0.5 mmHg with placebo.

					5.6 mg/dL	
Gaffo, SURPHER 2021 (10) Crossover design, 1-month intervention	Mean age 28 years, 64% male, mean BMI 31, n=99	127/81 mmHg	5.9 mg/dL	Allopurinol 300mg, Placebo	Allopurinol:-1.3 mg/dL Placebo: -0.04 mg/dL	No effect on BP. The mean change in systolic BP was -1.4 mmHg with allopurinol and -1.1 mmHg with placebo.

RCT: randomised controlled trial, BMI: body mass index, BP: blood pressure