Drug-induced hyperuricemia and gout present an increasingly prevalent problem in clinical practice. Herein, we review the urate-lowering or urate-raising effects of commonly used agents. We performed a PubMed search using the terms gout, urate, and medication, along with the specific agents/classes described herein. Reports were reviewed until 2022, and original studies were considered if they primarily or secondarily reported the effects of 1 or more drugs on serum urate level. Previous reviews were assessed for references to additional studies that described urate-altering effects of medications. Urate-changing drugs are summarized regarding their magnitude of effect, mechanism of action, and clinical significance. Potentially urate-lowering drugs include angiotensin II receptor blockers, calcium channel blockers, high-dose aspirin and salicylates, some nonsalicylate nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, sodium-glucose cotransporter 2 inhibitors, statins, and fenofibrate. Potentially urate-increasing drugs discussed include diuretics, β-blockers, insulin, pyrazinamide, ethambutol, calcineurin inhibitors, low-dose aspirin, testosterone, and lactate. In patients who have or are at risk for hyperuricemia or gout, an increased awareness of drugs that affect serum urate level may allow for prescribing that effectively treats the indicated problem while minimizing adverse effects on hyperuricemia and gout.

Gout is the most common inflammatory arthritis, and it has significantly increased in worldwide prevalence during the past 50 years.1 With westernized diets, extended life span, and accumulating renal disease, it is unlikely that gout prevalence will decline any time soon.2 Gout is caused by precipitation and deposition of monosodium urate crystals, inducing both acute inflammatory arthritis (gout flares) and chronic low-level inflammation.3 Gout risk correlates with serum urate (sU) level, reflecting total body uric acid (UA) concentration.4 Hyperuricemia is physiologically defined as an sU level greater than 6.8 mg/dL (to convert to mmol/L, multiply by 0.0595), the saturation concentration for urate at pH 7.4; hyperuricemia in the absence of a history of gout is designated as asymptomatic hyperuricemia (AH).5,6 The absolute annual incidence of gout ranges from 0.5% or less for individuals with sU levels between 7.0 and 8.9 mg/dL, and up to 4.9% for individuals with sU levels of 9 mg/dL or greater.4 Because 20% of individuals with AH have sU levels greater than 9 mg/dL, a minority of patients with AH are at highest risk for gout.4

Hyperuricemia affects approximately 38 million adults, or 16.9% of the population in the United States.7 Accumulating evidence links hyperuricemia with various metabolic diseases, including chronic kidney disease (CKD), hypertension, coronary artery disease, type 2 diabetes mellitus (T2DM), and fatty liver disease.6 Whether elevated sU levels play a causative role in any of these entities remains an area of investigation; the 2020 American College of Rheumatology (ACR) gout treatment
Patients with gout may experience elevations or decrements in serum urate (sU) levels due to medications prescribed by physicians. Urate-lowering and urate-increasing capacity is not always a class effect and can be limited to a single drug in the class.

We reviewed the literature to identify the magnitude of the urate-lowering or urate-increasing effects of common medications used in primary care and highlight those that can also serve to reduce sU levels.

Among lipid-lowering therapies, atorvastatin and fenofibrate have greater sU-lowering effects than most other agents.

Among antihypertensives, the angiotensin II receptor blocker losartan most reliably decreases sU levels. Among calcium channel blockers, dihydropyridines have the greatest evidence supporting their ability to lower sU levels. The sU elevation induced by diuretics is dose-dependent. β-Blockers tend to elevate sU levels minimally and less than diuretics.

Among the commonly used drugs in the treatment of diabetes, the sodium-glucose cotransporter 2 inhibitors, especially empagliflozin, seem to have a drug class effect of lowering sU levels, whereas insulin may raise sU levels.

guideline conditionally recommends against urate-lowering therapy for AH, whereas the Japanese Society of Gout and Nucleic Acid Metabolism recommends that high sU levels (≥8 mg/dL) in certain patients with AH should be pharmacologically lowered. Both societies agree that healthful lifestyle changes are warranted to reduce the risk of gout in patients with AH or to enhance treatment in patients with established gout. In this regard, it is worth noting that multiple drugs unrelated to gout treatment may raise sU levels and promote hyperuricemia. Conversely, other drugs have been shown to incidentally reduce sU levels. Prudent selection of nongout drugs has the potential to provide the patient with optimal management for the indicated conditions while reducing the need for escalation of gout therapy.

Herein we review the urate-lowering or urate-raising effects of several commonly used agents. We performed a PubMed search using the terms **gout**, **urate**, and **medication**, along with the specific agents/classes described later herein. Reports were reviewed until 2022, and original studies were considered if they primarily or secondarily reported the effects of 1 or more drugs on sU level. Previous reviews were assessed for references to additional studies that described urate-altering effects of medications. In some cases, urate-changing capacity is a class effect; in others, it is limited to a single drug within the class. In patients with hyperuricemia or gout, selection or avoidance of some of these agents may modify the sU concentration, reduce polypharmacy, and increase medication compliance. We exclude medications that are formally indicated for urate-lowering therapy, that is, xanthine oxidase inhibitors, probenecid, lesinurad, and pegloticase.

**URATE-LOWERING DRUGS**
The mechanisms of some sU-lowering drugs are reviewed in Table 1, and supporting studies are described in Table 2.

**Antihypertensives**

**Angiotensin II Receptor Blockers.** Within the class of angiotensin II receptor blockers (ARBs) there exists significant heterogeneity regarding effect on sU level, which has been attributed to differential effects on uric acid transporter 1 (URAT1), the primary apical membrane transporter for resorption of UA across the renal tubule lumen. Inhibition of URAT1 promotes increased urinary excretion of UA, a feature exploited for sU lowering by drugs such as probenecid and lesinurad. Using URAT1-expressing **Xenopus** oocytes as a model system, Iwanaga et al reported that the ARBs losartan, telmisartan, and pratosartan inhibited URAT1-mediated UA uptake, whereas valsartan, candesartan, and olmesartan did not. These effects may not fully or directly translate into human sU lowering, however. One study of hypertensive patients with T2DM found that only losartan lowered sU levels, whereas valsartan, telmisartan, and candesartan, and
olmesartan had no significant impact. A multicenter randomized controlled trial (RCT) involving 351 hypertensive patients with AH compared losartan and irbesartan. The median sU level declined from 7.09 mg/dL to 6.04 mg/dL (a reduction of 1.05 mg/dL; \( P < .0001 \)) after 8 weeks of losartan therapy compared with a change from 7.04 mg/dL to 6.86 mg/dL (a reduction of 0.18 mg/dL; \( P < .05 \)) with irbesartan. In contrast to effects seen with other ARBs, the amount of sU lowering induced by losartan is potentially clinically important and is comparable with that which can be achieved with rigorous dietary modification. A post hoc analysis of the Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial assessed 1342 patients with CKD and T2DM and found a reduction in sU levels by \(-0.16 \) mg/dL (a smaller change than most other studies) (95% CI, \(-0.30 \) to \(-0.01 \); \( P = .031 \)) in the losartan treatment group compared with the placebo control group. The authors suggested that approximately 20% of losartan’s previously recognized renal protective effects may be due to urate lowering alone and that losartan may be a useful targeted therapy for patients with hyperuricemia and T2DM. Although recent studies are mixed as to whether urate lowering is actually renally protective, evidence suggests that some patient subsets, including those with gout, may be more likely to benefit. Overall, when choosing among multiple antihypertensive agents, the selection of losartan, particularly over other agents that can raise sU levels, can significantly affect a patient’s sU level and may have additional benefits. For this reason, the 2020 ACR gout treatment guideline conditionally recommends “choosing losartan preferentially as an antihypertensive agent for patients with gout.”

**Table 1. Mechanisms of Some Serum Urate–Altering Drugs**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urate-lowering drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Losartan</td>
<td>Increases urinary excretion of urate via inhibiting URAT1</td>
</tr>
<tr>
<td></td>
<td>CCBs</td>
<td>Various</td>
</tr>
<tr>
<td>Anti-inflammatories and immunosuppressives</td>
<td>High-dose aspirin, Leflunomide</td>
<td>Biphasic effect on urate tubular reabsorption</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>Statins</td>
<td>Increases urate excretion</td>
</tr>
<tr>
<td></td>
<td>Fenofibates</td>
<td>Increase urate excretion</td>
</tr>
<tr>
<td>Metabolism modulators</td>
<td>SGLT2 inhibitors</td>
<td>Increase urate excretion due to glucosuria via GLUT9</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Estrogen</td>
<td>Decreases urate reabsorption</td>
</tr>
<tr>
<td>Urate-increasing drugs</td>
<td>Loop diuretics</td>
<td>Decrease secretion via inhibiting MRP4</td>
</tr>
<tr>
<td></td>
<td>Other antihypertensives</td>
<td>Increases uptake via URAT1</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics, ( \beta )-Blockers</td>
<td>Increase reabsorption via OAT4</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Increases urate reabsorption via URAT1</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>Decreases renal clearance of urate</td>
</tr>
<tr>
<td>Anti-inflammatories and immunosuppressives</td>
<td>Low-dose aspirin, Calcineurin inhibitors</td>
<td>Biphasic effect on urate reabsorption</td>
</tr>
<tr>
<td>Metabolism modulators</td>
<td>Lactate</td>
<td>Increases urate reabsorption via URAT1</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Increases urate reabsorption via URAT1 or sodium-dependent anion cotransporter in the proximal tubule</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Testosterone</td>
<td>Increases urate reabsorption via URAT1</td>
</tr>
</tbody>
</table>

CCB = calcium channel blocker; GLUT9 = glucose transporter 9; MRP4 = multidrug resistance protein 4; OAT4 = organic anion transporter 4; SGLT2 = sodium-glucose cotransporter 2; URAT1 = urate transporter 1.

**Angiotensin-Converting Enzyme Inhibitors.** Similar to ARBs, angiotensin-converting enzyme Inhibitors (ACE-Is) are...
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference, year</th>
<th>Study design</th>
<th>Patients (No.)</th>
<th>Dose</th>
<th>Duration</th>
<th>Serum urate effect (mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>Dang et al, 2006</td>
<td>Multicenter RCT</td>
<td>351 with HTN (losartan, n=176; irbesartan, n=175)</td>
<td>50 mg/d for 4 wk, then 50 mg or 100 mg/d to wk 8</td>
<td>8 wk</td>
<td>-1.05</td>
<td>&lt;.0001 vs baseline</td>
</tr>
<tr>
<td>Losartan</td>
<td>Miao et al, 2011</td>
<td>Multinational, randomized, double-blind</td>
<td>1342 with T2DM and nephropathy (losartan, n=678; placebo, n=664)</td>
<td>100 mg</td>
<td>6 mo</td>
<td>-0.16</td>
<td>.031 vs 6 mo of placebo</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Buscemi et al, 2020</td>
<td>Parallel-group, single-blind, single-center RCT</td>
<td>20 normal glucose tolerant, 20 prediabetic, 20 T2DM</td>
<td>2.5-10 mg/d</td>
<td>6 wk</td>
<td>-1.0</td>
<td>&lt;.001 vs 6 wk of hydrochlorothiazide</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Chanard et al, 2003</td>
<td>Randomized, double-blind, parallel group</td>
<td>48 renal transplant recipients with HTN taking cyclosporine (amlodipine, n=24)</td>
<td>5-10 mg/d</td>
<td>60 d</td>
<td>-0.8</td>
<td>&lt;.001 vs baseline</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Weidmann et al, 1989</td>
<td>Placebo controlled, prospective</td>
<td>15 with chronic renal failure and HTN</td>
<td>55 mg/d</td>
<td>6 wk</td>
<td>-1.8</td>
<td>&lt;.001 vs placebo</td>
</tr>
<tr>
<td>Verapamil sustained-release</td>
<td>Schohn et al, 1993</td>
<td>Placebo controlled, prospective</td>
<td>15 with chronic renal failure and HTN</td>
<td>240 mg/d</td>
<td>4 wk</td>
<td>-0.5</td>
<td>&lt;.01 vs baseline</td>
</tr>
<tr>
<td>Aspirin (mid dose)</td>
<td>Yu and Gutman, 1959</td>
<td>Self-controlled, prospective</td>
<td>9</td>
<td>3 g/d</td>
<td>4 d</td>
<td>No decline</td>
<td>&lt;.05 vs control</td>
</tr>
<tr>
<td>Aspirin (high dose)</td>
<td>Yu and Gutman, 1959</td>
<td>Self-controlled, prospective</td>
<td>15</td>
<td>5.2 g/d</td>
<td>4 d</td>
<td>-26% (control range, 5.9-11.7; treatment range, 2.2-10.4)</td>
<td>&lt;.05 (vs control)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Emery et al, 2000</td>
<td>Multicenter, double-blind</td>
<td>999 total active rheumatoid arthritis (n= 501 leflunomide)</td>
<td>100 mg/d x 3 d, then 20 mg/d</td>
<td>1 y</td>
<td>-0.71</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Wu et al, 2016</td>
<td>Multicenter, prospective, double-dummy RCT</td>
<td>360 Primary IgA nephropathy patients total (n=100 for leflunomide only)</td>
<td>20 mg/d</td>
<td>24 wk</td>
<td>-0.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Perez-Ruiz and Nolla, 2003</td>
<td>Prospective</td>
<td>38 total active rheumatoid arthritis</td>
<td>100 mg/d x 3 d, then 20 mg/d</td>
<td>2 mo</td>
<td>-1.47</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Zhao et al, 2018</td>
<td>Meta-analysis of RCTs</td>
<td>34,941 total, 62 trials</td>
<td>NA</td>
<td>NA</td>
<td>MD -0.63 (empagliflozin, MD -0.77)</td>
<td>&lt;.05 vs controls</td>
</tr>
</tbody>
</table>

Continued on next page
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference, year</th>
<th>Study design</th>
<th>Patients (No.)</th>
<th>Dose</th>
<th>Duration</th>
<th>Serum urate effect (mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>Deedwania et al, 2015</td>
<td>RCT</td>
<td>858 total (pravastatin, n=425; atorvastatin, n=433)</td>
<td>40 mg/d</td>
<td>12 mo</td>
<td>−0.09 vs −0.52</td>
<td>&lt;.0001 (change from baseline, atorvastatin vs pravastatin)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Deedwania et al, 2015</td>
<td>RCT</td>
<td>858 (pravastatin, n=425; atorvastatin, n=433)</td>
<td>80 mg/d</td>
<td>12 mo</td>
<td>−0.52 vs −0.09</td>
<td>&lt;.0001 (change from baseline, atorvastatin vs pravastatin)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Saku et al, 2011</td>
<td>Prospective, randomized, controlled, parallel, multicenter</td>
<td>302 (atorvastatin, n=101; rosvastatin, n=100; pivtavastatin, n=101)</td>
<td>10 mg/d</td>
<td>16 wk</td>
<td>−0.2</td>
<td>&lt;.05 vs baseline</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Derosa et al, 2016</td>
<td>Meta-analysis of RCTs</td>
<td>9 trials</td>
<td>NA</td>
<td>NA</td>
<td>MD −0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Takagi and Umemoto, 2012</td>
<td>Meta-analysis of RCTs</td>
<td>2774 total, 8 trials</td>
<td>NA</td>
<td>NA</td>
<td>MD −0.57</td>
<td>&lt;.00001 vs pooled rosvastatin, simvastatin, pravastatin, amlodipine</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Saku et al, 2011</td>
<td>Prospective, randomized, controlled, parallel, multicenter</td>
<td>302 (atorvastatin, n=101; rosvastatin, n=100; pivtavastatin, n=101)</td>
<td>2.5 mg/d</td>
<td>16 wk</td>
<td>−0.18</td>
<td>&lt;.05 vs baseline</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Derosa et al, 2016</td>
<td>Meta-analysis of RCTs</td>
<td>9 trials</td>
<td>NA</td>
<td>NA</td>
<td>MD −0.1</td>
<td>.013</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Takagi and Umemoto, 2012</td>
<td>Meta-analysis of RCTs</td>
<td>2774 total, 8 trials</td>
<td>NA</td>
<td>NA</td>
<td>MD −1.48</td>
<td>&lt;.00001 vs atorvastatin</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Elisaf et al, 1999</td>
<td>Prospective</td>
<td>64</td>
<td>200 mg/d</td>
<td>NA</td>
<td>−1.9</td>
<td>&lt;.001 vs baseline</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Yahyaoui et al, 2008</td>
<td>Prospective</td>
<td>69 total (n= 47 female-to-male, n=22 male-to-female)</td>
<td>Low/medium/high doses</td>
<td>1y</td>
<td>−1.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Nicholls et al, 1973</td>
<td>Prospective</td>
<td>22 total</td>
<td>5-40 mg/d</td>
<td>10 mo</td>
<td>−0.7</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

HTN = hypertension; IM = intramuscular; NA = not applicable; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter 2; T2DM = type 2 diabetes mellitus.
antihypertensives with renoprotective properties. Also, ACE-Is provide afterload reduction in congestive heart failure. However, the class effect of ACE-Is on sU levels is unclear.

A uricosuric property of enalapril and captopril has been ascribed to effects on the proximal convoluted tubule, with resultant increases in renal fractional excretion of UA in healthy volunteers. However, larger studies have revealed nonsignificant results. One multicenter study looking at a subgroup of 69 hypertensive patients treated with captopril revealed a nonsignificant decline in sU level from 5.55 mg/dL to 5.38 mg/dL. Conversely, the Captopril Research Group of Japan performed a multicenter double-blind RCT in which 133 patients received captopril and found a nonsignificant increase in mean ± SD sU levels from 5.8±1.7 mg/dL to 6.0±1.5 mg/dL. Meanwhile, perindopril seemed to promote UA excretion in a dose-dependent manner, but the effects of even maximal doses were not found to be statistically significant.

Schmidt et al performed a prospective randomized 2-way crossover trial comparing enalapril and losartan in 13 hypertensive patients with renal transplants and found that losartan lowered the mean ± SD sU level (from 7.8±2.4 mg/dL to 7.3±1.8 mg/dL; P=.6) and enalapril raised it (from 7.8±1.9 mg/dL to 8.2±1.8 mg/dL; P=.5), although the results were not significant due to the small sample size. Tikkanen et al performed a multicenter double-dummy, double-blind RCT also comparing losartan and enalapril in patients with essential hypertension over 12 weeks, finding that losartan significantly reduced UA levels (from 5.6 mg/dL to 5.41 mg/dL; P<.01) and enalapril non–statistically significantly increased it from 5.83 mg/dL to 5.95 mg/dL. Taken together, the evidence does not currently support a clinically meaningful urate-modulating effect by ACE-Is.

**Calcium Channel Blockers.** Several clinical studies indicate that different subclasses of calcium channel blockers (CCBs) may have urate-lowering effects. The most frequently studied CCBs are the dihydropyridines. In one study, amlodipine decreased sU levels by 1.1 mg/dL (from a mean ± SD of 6.1±1.1 mg/dL to 5.0±1.4 mg/dL) after 6 weeks of treatment, and in another study, from 8.1 mg/dL to 7.3 mg/dL after 9 weeks (60 days) of treatment (P<.001). Nitrendipine treatment for 6 weeks decreased sU levels from 7.6 to 5.8 mg/dL (vs placebo; P<.001). These degrees of urate lowering are similar to that of losartan and represent a potentially clinically significant effect. The mechanism of urate lowering by dihydropyridines is likely through inhibition of renal tubular UA resorption. A preclinical study compared the effect of dihydropyridines on the renal tubule UA-resorbing transporter URAT1 and on xanthine oxidase, the rate-limiting enzyme for urate production, and found that nifedipine, nilvadipine, and nitrendipine strongly inhibited URAT1-mediated UA reuptake but did not inhibit xanthine oxidase–mediated urate production. The uricosuric effects of CCBs may additionally relate to their capacity to increase renal blood flow and glomerular filtration rate (GFR) by dilating renal afferent arterioles. For example, amlodipine was reported to increase fluid output from proximal tubules, demonstrated by decreased fractional proximal reabsorption of sodium.

The effects of nondihydropyridine CCBs on sU levels are less well studied. Treatment with verapamil for 4 weeks decreased the mean sU level by 0.5 mg/dL, from a mean ± SD of 7.1±0.9 mg/dL to 6.6±0.5 mg/dL in a study of 15 patients with hypertension and CKD (P<.01). A preclinical study in rats found that nicardipine-induced uricosuria was accompanied by increased GFR and renal blood flow, whereas diltiazem (nondihydropyridine) induced uricosuria without increasing GFR. Diltiazem increased excreted UA without an increase in urine volume, as evidenced by a significantly increased UA-to-inulin clearance ratio. These findings suggest that dihydropyridines and nondihydropyridines both have uricosuric effects but potentially through different mechanisms, perhaps due to pharmacophore
differences between the classes. More studies need to be performed on the effect of nondihydropyridines on URAT1.

Finally, studies have found that cilnidipine, a novel non-Food and Drug Administration-approved CCB that blocks both L- and N-type calcium channels, also has uricosuric effects. In one human study, cilnidipine induced significant reduction in blood pressure and sU level from a mean \( \pm \) SD at baseline of 5.6\( \pm \)0.3 mg/dL to 5.1\( \pm \)0.2 mg/dL (\( P \)< .01).49 Perhaps consistent with a urate-lowering effect, studies also indicate that CCBs may decrease the risk of gout. Compared with no use of CCBs, CCB use was found to be associated with a 0.87 (95% CI, 0.82 to 0.93) relative risk for incident gout in patients with hypertension after adjusting for age, sex, and use of other antihypertensive drugs. The multivariate relative risks (95% CIs) for individual CCBs were 0.79 (0.73 to 0.86) for amlopidine, 0.86 (0.75 to 0.99) for diltiazem, and 0.87 (0.78 to 0.97) for nifedipine.

**Anti-inflammatories and Immunosuppressives**

**High-Dose Aspirin and Salicylates.** Aspirin has been shown to have a biphasic effect on sU lowering, wherein low doses (\(<\) 2 g/d) raise the sU level16,52 but high doses (\(>\) 3 g/d) decrease it.15 These effects may be explained by 2 modes of salicylate interaction with URAT1: at low doses salicylate acts as an exchange substrate to facilitate UA reabsorption, but at high doses it inhibits tubular reabsorption. In a study by Yu and Gutman et al,16 1 g of aspirin daily resulted in a mean increase in sU level of 6%. In contrast, 3 g daily led to no decline in sU level and 5 g daily led to a mean decrease of 26%. Because such high doses of salicylates are no longer routinely used in clinical practice, their urate-lowering effects currently have little clinical implication.

**Nonsalicylate Nonsteroidal Anti-inflammatory Drugs.** Nonsalicylate nonsteroidal anti-inflammatory drugs (NSAIDs) are standard anti-inflammatory therapy for acute gout flares and for flare prophylaxis during the administration of urate-lowering therapy, but it remains unclear whether they have uricosuric or UA-retaining effects themselves. Some investigators have reported decreases in sU levels in patients with gout treated with NSAIDs. One study of 29 patients found that piroxicam (40 mg/d for 5 days) relieved acute gout flare with a concomitant decreased sU level (\( P \)< .05). However, sU level often falls during a gout flare, even without uricosuric treatment, so the causal role of piroxicam remained uncertain. In contrast, Tiitinen et al reported that piroxicam resulted in decreased UA excretion in 8 of 11 patients (\( P \)< .05) seen 2 to 3 hours after ingestion of the drug, suggesting that piroxicam increases the sU level. Among other NSAIDs in that study, only indomethacin significantly increased UA excretion. In 2011, a study using canine kidney cells expressing URAT1 found that multiple NSAIDs (indomethacin, phenylbutazone, and salicylate) dose-dependently inhibited UA cellular reuptake, suggesting a uricosuric class effect of NSAIDs that might promote sU lowering, potentially through the ability of planar anionic NSAIDs, when protonated, to intercalate into lipid bilayers. On the other hand, NSAIDs decrease the GFR via prostaglandin inhibition at renal afferent and efferent arterioles, potentially reducing urate filtration and promoting sU elevation. Overall, more research needs to be conducted on the effects of NSAIDs on sU level.

**Leflunomide.** Leflunomide is a disease-modifying therapy used to treat rheumatoid arthritis and other autoimmune conditions. After 1 year of treatment with leflunomide, the level of sU decreased significantly by 0.71 mg/dL in a cohort of patients with rheumatoid arthritis. No further changes were noted at year 2 of treatment. The effects of leflunomide on sU levels in that study are consistent with those of other studies in patients with IgA nephropathy and rheumatoid arthritis, where sU levels decreased by 0.78 mg/dL and 1.47 mg/dL, respectively. Because creatinine level was not significantly changed in patients with
rheumatoid arthritis in the previously mentioned studies, the decreased sU level is more likely to be due to increased renal UA excretion than to changes in estimated GFR.

**Metabolism Modulators: Sodium-Glucose Cotransporter 2 Inhibitors**

Among the commonly used drugs in the treatment of DM, the sodium-glucose cotransporter 2 (SGLT2) inhibitors seem to have a drug class effect of hypouricemia. In a meta-analysis of 62 RCTs involving 34,941 patients with T2DM, SGLT2 inhibitors were found to have significant sU-lowering effects compared with controls, ranging from $-0.29$ to $-0.77$ mg/dL, with a total weighted mean of $-0.63$ mg/dL. The SGLT2 inhibitors included empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin. Treatment with empagliflozin resulted in superior reduction in sU level of 0.77 mg/dL. The underlying mechanism for the sU-lowering effect of SGLT2 inhibitors is likely glucosuria increasing urinary UA excretion. Chino et al found that an increase in urinary excretion of UA correlates with an increase in glucose excretion. No direct interaction between SGLT2 inhibitors and major UA transporters was found. The efflux of UA in a Xenopus oocyte model expressing glucose transporter–like protein-9 isoform 2 was trans-stimulated by glucose, and the uptake of UA by oocytes was cis-inhibited by glucose. Thus, it is likely that UA urinary excretion is increased by SGLT2-induced glucosuria. In patients with T1DM, after induction of glucosuria with SGLT2 inhibition while maintaining euglycemia, sU level decreased ($P<.0001$) and urinary excretion of UA increased ($P<.0001$), suggesting again that glucosuria, not hyperglycemia, increases uricosuria in patients with diabetes. Although the effect is modest, it may be worth considering when selecting treatments for diabetes in patients with gout.

**Lipid-Lowering Drugs: Statins and Fenofibrates**

Atorvastatin has been reported to decrease sU level and increase GFR in a retrospective study of patients with CKD stage 3, in contrast to rosuvastatin, which had no effect. In an RCT of 893 individuals followed for 12 months comparing pravastatin 40 mg/d with atorvastatin 80 mg/d, modest sU reductions occurred in both treatment arms, but a greater decline was observed with atorvastatin than with pravastatin ($-0.52$ mg/dL vs $-0.09$ mg/dL; $P<.0001$). In another study, sU levels decreased after atorvastatin or rosuvastatin treatment but increased after pitavastatin use. In the ATOROS (ATORvastatin and ROSuvastatin) study, only atorvastatin was found to lower sU levels. Finally, in the PATROL (Pitavastatin, Atorvastatin, Rosuvastatin for Safety and Efficacy) trial, the mean ± SD sU level was decreased in the atorvastatin and rosuvastatin groups (from 5.19±1.23 mg/dL to 4.99±1.12 mg/dL and from 5.42±1.48 mg/dL to 5.24±1.54 mg/dL, respectively; $P<.05$) but not in the pitavastatin group. A systematic review and meta-analysis by Derosa et al incorporated 9 RCTs and found significant reductions in sU levels with use of atorvastatin (MD (mean difference) $-39.62$ μmol/L; 95% CI, $-60.78$ to $-18.46$ μmol/L; $P<.001$) and simvastatin (MD $-5.95$ μmol/L; 95% CI, $-10.62$ to $-1.28$ μmol/L; $P=.013$) but not with use of pravastatin, rosuvastatin, or lovastatin. Thus, across multiple studies, a consistent signal for limited urate lowering is seen with atorvastatin, with mixed data on a possible benefit of rosuvastatin and simvastatin and no beneficial effect with other statins. On the other hand, colchicine is used by many patients with gout, and because of interactions at the CYP3A4 hepatic enzyme, atorvastatin but not some other statins must be used with caution when administered with colchicine.

Fenofibrate has also been reported to significantly decrease sU levels. In one study, fenofibrate (200 mg daily administered to 64 dyslipidemic patients) significantly reduced sU levels by 1.9 mg/dL (from 6.8 mg/dL to 4.9 mg/dL; $P<.001$) via increased renal fractional excretion of UA (from 8%±3% to 13%±4%; $P<.01$). The fenofibrate-induced decrease in sU levels was
### Table 3. Serum Urate—Increasing Drugs: Supporting Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference, year</th>
<th>Study design</th>
<th>Patients (No.)</th>
<th>Dose (mg/dL)</th>
<th>Duration</th>
<th>Serum urate effect (mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>Carlsen et al., 1990</td>
<td>Double-blind, parallel group</td>
<td>257</td>
<td>1.25, 2.5, 5.0, or 10.0</td>
<td>10 wk</td>
<td>+0.3-1.1</td>
<td>&lt;.01 vs baseline</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Buscemi et al., 2020</td>
<td>Parallel-group, single-blind, single-center RCT</td>
<td>20 normal glucose tolerant, 20 prediabetic, 20 T2DM</td>
<td>12.5-25</td>
<td>6 wk</td>
<td>+0.1 vs baseline; +1.0 vs 6 wk of amlodipine</td>
<td>&lt;.001 vs 6 wk of amlodipine</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Reyes, 2003</td>
<td>Randomized, crossover, double-blind</td>
<td>11</td>
<td>25 mg/d</td>
<td>4 d</td>
<td>+0.76</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>MacKay et al., 1996</td>
<td>Double-blind, placebo controlled</td>
<td>703 hypertensive (n=118, hydrochlorothiazide 12.5 mg)</td>
<td>12.5</td>
<td>12 wk</td>
<td>+0.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>Pollavini, 1984</td>
<td>Multicenter, randomized, crossover, double-blind</td>
<td>298 hypertensive</td>
<td>25</td>
<td>4 wk</td>
<td>+0.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Torsemide</td>
<td>Reyes, 2003</td>
<td>Randomized, crossover, double-blind</td>
<td>16</td>
<td>10 mg/d</td>
<td>7 d</td>
<td>+1.18</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Andersen, 1985</td>
<td>Randomized prospective</td>
<td>136 (atenolol, n=67; bendroflumethiazide, n=69)</td>
<td>50-100</td>
<td>12 wk</td>
<td>+0.5</td>
<td>&lt;.001 vs baseline</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Juraschek et al., 2017</td>
<td>Randomized prospective</td>
<td>630 (metoprolol, n=249; ramipril, n=265; amlodipine, n=116)</td>
<td>NA</td>
<td>12 mo</td>
<td>+0.3</td>
<td>.03 vs baseline</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Captoptil Research Group of Japan, 1985</td>
<td>Multicenter, randomized, double-blind</td>
<td>270 (propranolol, n=137; captopril, n=133; both on diuretic)</td>
<td>60-120</td>
<td>12 wk</td>
<td>+0.3</td>
<td>&lt;.01 vs baseline</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Inayat et al., 2016</td>
<td>Prospective, case-control</td>
<td>46</td>
<td>NA</td>
<td>8 wk</td>
<td>Between weeks 2-6: +4.6</td>
<td>&lt;.05 vs baseline</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Postlethwaite et al., 1972</td>
<td>Retrospective</td>
<td>7</td>
<td>12-19 mg/kg per day</td>
<td>30 d</td>
<td>+3.2</td>
<td>NA</td>
</tr>
<tr>
<td>Aspirin (low dose)</td>
<td>Yu and Gutman, 1959</td>
<td>Self-controlled, prospective</td>
<td>4</td>
<td>1 g/d</td>
<td>4 d</td>
<td>−6% (control range, 10.8-11.4 vs treatment range, 11.2-12.2)</td>
<td>&lt;.05 vs control</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Kanbay et al., 2005</td>
<td>Retrospective</td>
<td>73</td>
<td>NA</td>
<td>24 mo</td>
<td>+1.6</td>
<td>&lt;.001 vs baseline</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Kanbay et al., 2005</td>
<td>Retrospective</td>
<td>47</td>
<td>NA</td>
<td>24 mo</td>
<td>+1.5</td>
<td>&lt;.001 vs baseline</td>
</tr>
<tr>
<td>Insulin</td>
<td>MacFarlane et al., 2015</td>
<td>Retrospective</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
<td>+1.25</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Continued on next page**
independent of changes in serum triglyceride levels or other lipid parameters, confirming the direct hypouricemic action of the drug. A meta-analysis of 8 prospective clinical trials including 2774 patients compared atorvastatin with fenofibates and other drugs, including rosvastatin, simvastatin, pitavastatin, and amlodipine. Pooled analysis found significantly lower final sU levels by 0.57 mg/dL in the atorvastatin group compared with other nonfenofibrate agents (MD −0.57 mg/dL; 95% CI, −0.81 to −0.34 mg/dL; P < .00001). On the other hand, compared with fenofibrate use, atorvastatin therapy was associated with significantly higher final sU levels (ie, less sU lowering) (MD 1.48 mg/dL; 95% CI, 0.88 to 2.08 mg/dL; P < .00001).

In summary, atorvastatin has consistently been found to result in modestly decreased sU concentrations and greater sU-decreasing effects than most statins, although some other statins may have weak sU-lowering effects. Fenofibates also decrease sU levels, probably more so than atorvastatin, although further study is needed. Moreover, statins are generally preferred to fenofibates for lipid lowering, and the ACR, therefore, conditionally recommends against choosing fenofibrate over other lipid-lowering agents for patients with gout.

**Sex Hormones: Estrogen**

Estrogen has been associated with reduced levels of sU. In a prospective study of 69 healthy transsexual persons, after 1 year of hormone therapy, sU levels increased in female-to-male transitions (from 3.91 mg/dL to 5.07 mg/dL, testosterone therapy) and decreased in male-to-female transitions (from 4.87 mg/dL to 3.67 mg/dL, estrogen therapy). Levels of sU were lower (P = .03) and fractional excretion of UA was higher (P = .04) in those who had received higher doses of estrogen (P = .03). Studies have also found that tubular urate level after secretory reabsorption was significantly lower and resulted in higher urinary urate excretion and lower sU levels in women of fertility age than in men (P < .01).
URATE-INCREASING DRUGS

In contrast to drugs that incidentally lower sU levels, several drugs incidentally raise sU levels as an adverse effect (Tables 1 and 3). In patients with gout or hyperuricemia, substituting equally efficacious alternatives for some of these agents may facilitate sU management.

Antihypertensives

Loop and Thiazide Diuretics. Loop and thiazide diuretics are well-known to cause iatrogenic hyperuricemia and increase the risk of gout. Diuretics increase sU concentration in a dose-dependent manner, and increases in the sU level can be seen as early as 24 hours after initiating treatment. Effects have ranged from a 6% to 21% sU increase (0.3-1.1 mg/dL) above baseline after 10 weeks of treatment. Diuretic effects on sU levels are reversible and in one study returned from a mean of 7.5 mg/dL to 6.5 mg/dL 3 weeks after discontinuation (P<.0005). Diuretics raise sU levels through effects on renal UA transporters. Loop and thiazide diuretics enter proximal tubular cells through organic anion transporters and then are transported into the lumen in exchange for UA by organic anion transporter 4, resulting in UA retention. Diuretics also increase UA reabsorption via intravascular volume contraction. More recently, diuretics were found to inhibit multidrug resistance protein 4 and the human voltage-driven drug efflux transporter NPT4 at the proximal tubule.

In patients treated for 7 days with torsemide 10 mg daily, sU levels were elevated by 1.18 mg/dL vs patients treated with placebo for 7 days. Hydrochlorothiazide 12.5 mg at week 12 increased the sU level by 0.3 mg/dL. Reyes found that 4 days of treatment with hydrochlorothiazide 25 mg increased the sU level by 0.76 mg/dL. Chlorothalidone 25 mg at week 4 was associated with a 0.7 mg/dL increase in sU level. Overall, it is difficult to directly compare the effects of the various thiazides on sU level, but all seem to have a potentially significant impact.

Given the availability of other antihypertensives (including those that lower the sU concentration), altering hypertension therapy in patients with gout or AH seems reasonable. Accordingly, the 2020 ACR gout treatment guideline conditionally recommends “switching hydrochlorothiazide to an alternate hypertensive when feasible … for patients with gout.” In contrast, diuretics are the mainstay for treatment of fluid retention and/or congestive heart failure, with no reasonable alternatives. In such patients, or in those for whom diuretics are essential for blood pressure management, using the lowest effective dose diminishes hyperuricemic effects.

β-Blockers. The β-blockers propranolol, atenolol, metoprolol, and sotalol have all been found to modestly increase sU levels. In a trial of hypertensive patients treated with atenolol (50-100 mg once daily; n=67) for 12 weeks, the mean sU level increased from 5.2 mg/dL to 5.7 mg/dL. The addition of propranolol to the antihypertensive regimen of 137 patients increased the mean sU level by 0.3 mg/dL after 12 weeks. β-Blockers overall were found to have less hyperuricemic effect than were diuretics. The mechanism of β-blockers on sU concentration is unknown, but in one study β-blockers were found to modify neither renal clearance nor 24-hour urinary excretion of UA.

Antibiotics: Antitubercular Drugs

Multidrug treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol was reported to result in marked hyperuricemia, increasing the sU level by a mean ± SD of 9.78±3.21 mg/dL (P<.001) after 2 weeks of treatment and beginning as early as 24 hours after a single dose. Most hyperuricemic effects from the treatment are likely from pyrazinamide and ethambutol. Pyrazinamide, a synthetic analogue of nicotinamide with potent mycobactericidal activity, was first reported by Cullen et al to result in hyperuricemia. It was later discovered to be a strong UA retention agent, causing a more than 80% reduction in renal clearance of UA at a 300-
mg therapeutic daily dose.\textsuperscript{94,95} Pyrazinamide reversibly increased the sU level by 4.6 mg/dL between weeks 2 and 6 of treatment, generally remaining stable thereafter, and returning to baseline 2 weeks after discontinuation.\textsuperscript{71} Pyrazinamide promotes UA reabsorption via URAT1, which has the highest affinity for aromatic organic anions such as nicotinate and pyrazinoic acid.\textsuperscript{96–98} Patients with homozygous loss-of-function mutations in the gene for URAT1 lack a full response to pyrazinamide, providing further evidence for its mechanism through URAT1. Similar to pyrazinamide, ethambutol was reported to reversibly increase sU by a mean of 3.2 mg/dL after 1 month of therapy\textsuperscript{72} and can precipitate gout flares,\textsuperscript{99} with sU level returning to baseline after withdrawal of ethambutol. Overall, antitubercular treatment particularly results in increased risk of gout attacks in patients at higher risk for hyperuricemia, including those with higher body mass index, CKD, and higher baseline hyperuricemia,\textsuperscript{100} and the effect on sU level can be dramatic, particularly when pyrazinamide and ethambutol are used together. In one group of high-risk patients, the mean ± SD sU level was increased to 8.4±3.1 mg/dL (P<.001) at 2 months from pretreatment levels of 5.5±1.9 mg/dL.\textsuperscript{100} Mean ± SD time from treatment initiation to gouty attack was 4.13±4 months, and half of the attacks occurred during the first 2 months of treatment.\textsuperscript{100}

**Calcineurin Inhibitors.** Hyperuricemia is more common in transplant recipients than in healthy persons, in part due to the immunosuppressants required after transplant.\textsuperscript{102,103} Cyclosporine, a calcineurin inhibitor, can promote hyperuricemia through decreased renal urate clearance,\textsuperscript{104,105} and gout develops in 4% to 10% of all cyclosporine-treated patients. Compared with patients who develop AH, those with gout induced by cyclosporine are mostly men, are also taking diuretics, and have more advanced CKD. In one study, the onset of gout occurred after a mean of less than 1.5 years of AH, with progression to polyarticular tophaceous gout in nearly half the patients within 3 years.\textsuperscript{106} Tacrolimus is another calcineurin inhibitor that causes hyperuricemia. In one study, mean ± SD sU levels in patients starting cyclosporine or tacrolimus therapy rose from 6.3±1.6 mg/dL to 7.9±1.9 mg/dL (cyclosporine) and from 6.5±1.8 mg/dL to 8.0±1.8 mg/dL (tacrolimus) from pretreatment to 24 months (P<.001 for each). Changing between the 2 inhibitors resulted in no alteration in sU levels (P>.05), indicating that tacrolimus offers no advantage over cyclosporine for minimizing sU elevations in renal transplant recipients.\textsuperscript{73}

Other studies have investigated substitutions for calcineurin inhibitors. One found that when switching from a calcineurin inhibitor to the mTOR inhibitor sirolimus after cardiac transplant,\textsuperscript{107} the mean ± SD sU level decreased from 7.6±2.4 mg/dL to 6.2±1.9 mg/dL (P=.0007), with no difference in cardiac rejection or cardiac allograft function. In contrast, the use of mycophenolate mofetil,
although improving renal function and lowering sU concentration compared with calcineurin inhibitors, increased risk of rejection in liver transplant recipients.103 Compared with renal transplant patients receiving cyclosporine (80%), there was decreased incidence of hyperuricemia with the use of azathioprine (55%; P < .002),108,109 which provides an alternative to cyclosporine without significant differences in live donor kidney transplant rejection rates.110 However, in patients with gout taking allopurinol, azathioprine should be used with caution because their interaction may result in bone marrow suppression. One case report of 4 patients showed that mycophenolate mofetil, when substituted for azathioprine, enabled safe use of allopurinol in kidney transplant patients.111 Alternatively, the uricosuric agent probenecid may be substituted for allopurinol, but probenecid is ineffective in patients with marked CKD (typically, estimated GFR < 50 mL/min). The alternative uricosuric benzbromarone (not approved for use in the United States) can be used to lower sU levels in those with creatinine clearance greater than 25 mL/min/1.73 m² (to convert to mL/s/m², multiply by 0.0167) but requires hepatic function monitoring.112–114

Metabolism Modulators

Lactate. Lactate infusion, used in resuscitation of critically ill patients, increases sU levels. URAT1 is a urate-lactate exchanger, where UA is reabsorbed in exchange for lactate, and thus a high lactate level stimulates UA uptake, promoting hyperuricemia.113,116 Similarly, sU levels rise in lactic acidosis or ketoacidosis, as organic anions compete with UA for proximal secretion.

Insulin. Insulin decreases the urinary excretion of UA and significantly increases the sU level (mean, 1.25 mg/dL; P = .02).74 The effect of insulin is likely due to increased UA reabsorption via URAT1 or through the sodium-dependent anion cotransporter in the proximal tubule.117 This suggests that insulin’s increase of the sU level by 1.25 mg/dL may confer an increased gout risk118,119 that could potentially be avoided by selecting alternative therapies, where possible, for treatment of T2DM.

Sex Hormones: Testosterone

Often used in patients with female-to-male gender identity disorder, and occasionally in older men, testosterone can increase the sU level in a dose-dependent manner. In one study, 3 months of intramuscular testosterone use increased the sU level by 29% and 43% at dosages of 125 and 250 mg every 2 weeks, respectively.75 Testosterone reduces renal excretion of UA by upregulating a sodium-dependent anion cotransporter in the proximal tubule that collaborates with URAT1 to increase UA reabsorption.120 Another mechanism for sU elevation may relate to increased muscle mass—and, therefore, purine turnover—after testosterone treatment.75 This is consistent with findings that men have higher baseline sU levels than age-matched women27 and that sU levels increase in men after puberty.121 Women with polycystic ovary syndrome also have been found to have higher sU levels, likely as a result of testosterone,122 and postmenopausal women have increased sU levels, likely due to decreased estrogen levels.123 Mean ± SD differences in mean sU levels among males, females of child-bearing age, and postmenopausal women were 5.22 ± 1.1 mg/dL, 3.45 ± 1.1 mg/dL, and 4.2 ± 0.9 mg/dL, respectively,124 consistent with a recent study in which postmenopausal women had higher sU levels than premenopausal women by 0.34 mg/dL (95% CI, 0.19 to 0.49 mg/dL) and 0.36 mg/dL (95% CI, 0.14 to 0.57 mg/dL), respectively.125

CONCLUSION

Drugs increase or decrease the sU level largely by affecting renal proximal tubule transporters to increase UA reabsorption or decrease secretion. There are no published guidelines on the prevention of drug-induced hyperuricemia. Yet, lowering the sU level is an essential part of gout treatment and may have a role in reducing associated metabolic comorbidities.
associated with AH, including hypertension, T2DM, CKD, and hyperlipidemia. By selecting agents with inherent sU-decreasing rather than sU-increasing properties, one can potentially increase medication compliance and reduce polypharmacy while treating multiple indications simultaneously. Ultimately, withdrawal or substitution of any drug should be based on benefit-risk ratio. In patients with hyperlipidemia and/or requiring statins for primary prevention, atorvastatin and fenofibrates have been shown to have greater sU-lowering effects than most other agents. In patients with hypertension, specific ARBs (losartan) and CCBs (dihydropyridines) may have consistent sU-lowering effects that could affect the risk of gout. If thiazide or loop diuretics are necessary to control blood pressure, using the lowest effective dose can be considered because drug-induced hyperuricemia by diuretics is dose-dependent. β-Blockers tend to elevate sU levels minimally, but their cardiovascular benefits likely outweigh their adverse effects on sU levels, a consideration that also applies to cardiac aspirin. Among diabetic agents, SGLT2 inhibitors (especially empagliflozin) decrease the sU concentration, whereas insulin raises it. In posttransplant patients who develop cyclosporine- or tacrolimus-induced hyperuricemia or gouty arthritis with tophi, allopurinol or a uricosuric agent can be added to control the sU level. Alternatively, non−u-rate-raising immunosuppressants such as sirolimus, mycophenolate, or azathioprine can be considered after accounting for efficacy in suppressing transplant rejection. However, co-administration of allopurinol and azathioprine is relatively contraindicated. In kidney transplant patients requiring allopurinol, mycophenolate mofetil can be considered as an alternative for azathioprine.

**POTENTIAL COMPETING INTERESTS**

Dr Pillinger is on the data safety monitoring board and advisory board of Horizon Therapeutics. He is also a consultant for Sobi and Fortress Bioscience. Dr Toprover is on the advisory board of Horizon Therapeutics. The other authors report no competing interests.

**Abbreviations and Acronyms**: ACE-I, angiotensin-converting enzyme inhibitor; ACR, American College of Rheumatology; AH, asymptomatic hyperuricemia; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; GLUT9, glucose transporter 9; HTN, hypertension; IM, intramuscular; MRP4, multidrug resistance protein 4; NSAID, nonsteroidal anti-inflammatory drug; OAT4, organic anion transporter 4; RCT, randomized controlled trial; sU, serum urate; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; URAT1, uric acid transporter 1; UA, uric acid

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**Correspondence**: Address to Nicole Leung, MD, NYU Grossman School of Medicine, NYU Langone Orthopedic Hospital, 301 E 17th St, Ste 1410, New York, NY 10003 (nicole.leung@nyulangone.org; Twitter: @NicoleLeungMD).

Dr Leung and Dr Yip are co-first authors

Dr. Pillinger and Dr. Toprover are co-last authors

**ORCID**

Nicole Leung: https://orcid.org/0000-0001-7565-1009
Kevin Yip: https://orcid.org/0000-0003-4011-6238
Michael H. Pillinger: https://orcid.org/0000-0003-3168-1542; Michael Toprover: https://orcid.org/0000-0003-4152-0232

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LOWERING AND RAISING SERUM URATE LEVELS


