

Antihypertensive therapy and incident gout

Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 344, d8190 (2012). A nested case-control study aimed at determining the independent associations of antihypertensive drugs with the risk of incident gout among individuals with hypertension. Calcium channel blockers and losartan were associated with lower risk of incident gout among individuals with hypertension. By contrast, diuretics, β -blockers, angiotensin-converting enzyme inhibitors and nonlosartan angiotensin II receptor blockers were associated with an increased risk of gout. In addition, both duration of treatment and dose influenced the magnitude of the response to both calcium channel blockers and losartan.

KEYWORDS: β -blockers ■ calcium channel blockers ■ diuretics ■ gouty arthritis ■ hypertension ■ hyperuricemia ■ losartan

**Raquel Cuchacovich
& Luis R Espinoza***

LSU Health Sciences Center,
Department of Medicine,
Rheumatology Section, 1542 Tulane
Avenue, New Orleans, LA 70112-2822,
USA

*Author for correspondence:
lespin1@lsuhsc.edu

Gout is an acquired autoinflammatory disorder characterized by severe joint inflammation and deposition of monosodium urate crystals in the joints. Hypertension (HTN), diabetes, chronic renal failure, obesity, insulin resistance, hypercholesterolemia, metabolic syndrome and cardiovascular disease are common comorbid-associated conditions [1–5].

Normotensive individuals with baseline hyperuricemia (HU) have an 80% excess risk for developing HTN compared with those who do not have HU. Approximately 25–40% of adult patients with untreated HTN might develop HU (>6.0 mg/dl). Multiple population-based human studies have established a strong association between increasing levels of serum urate and subsequent development of HTN by determining whether lowering serum urate improves HTN [6,7]. Feig *et al.* showed that in children with newly diagnosed HTN, serum uric acid was highly correlated with both systolic and diastolic blood pressure. Elevated uric acid level (>5.5 mg per deciliter [$330 \mu\text{mol/l}$]) was observed in nearly 90% of adolescents with essential HTN, whereas uric acid levels were significantly lower in controls and teenagers with either white-coat or secondary HTN [8].

On the other hand, many drugs can lead to HU and gout arthropathy, such as low-dose aspirin, cyclosporine, pyrazinamide, β -blockers and diuretics among others. In addition, certain angiotensin II receptors antagonists, such as losartan, have also been shown to increase renal uric acid clearance and therefore lower uric acid levels. However, to date no study has

directly addressed the relationship between various antihypertensive agents and the risk of gout [9,10].

In the January 2012 issue of the *BMJ*, Choi *et al.* [11] studied the association of multiple antihypertensive drug use and risk of new-onset gout in a large population of hypertensive patients in the UK. From January 2000 to December 2007, 24,768 people with newly diagnosed gout and 50,000 matched in age, sex and calendar year controls from the health improvement database (UK general practice database) were followed for an average of 5.2 years. The study population was followed up until one of the following end points was met: detection of gout, 90th birthday, death or end of study period. Gout cases were diagnosed by the general practitioner (first diagnosis or the first antigout treatment, whichever came first). The impact of the antihypertensive drugs was evaluated by class: diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, nonlosartan angiotensin II receptor blockers and losartan. Losartan was analyzed by itself owing to its well-known uricosuric effect. These medications were classified as current use (prescription lasted until index date or ended in the 30 days before that date), recent use (prescription ended between 31 and 365 days before the index date) and past use (ended more than 365 days earlier). In addition, personal data, risk factors such as alcohol use, smoking, BMI, and comorbidities, such as ischemic heart disease, HTN, hyperlipidemia, renal failure and heart failure, were included.

**Future
Medicine**  

A total of 24,768 incidental gout cases were found, which were associated with an increased number of visits to the general practitioner, alcohol use, adiposity, ischemic heart disease, hyperlipidemia and renal failure. Almost 52% of the gout patients had the diagnosis of HTN before the diagnosis of gout; after adjusting for age, sex, calendar year and visits to a general practitioner, the relative risk of gout among those with HTN was 1.99 compared with those without HTN. After adjusting for several covariates (gender, age, BMI, visits to the general practitioner, alcohol consumption, pertinent drugs, associated comorbidities) the multivariate relative risk of incident gout associated with antihypertensive drugs use was 0.87 for calcium channel blockers, 0.81 for losartan, 2.36 for diuretics, 1.48 for β -blockers, 1.24 for angiotensin-converting enzyme inhibitors and 1.29 for nonlosartan angiotensin II receptor blockers. The multivariate relative risk for antihypertensive duration treatment for calcium channel blockers in the HTN group was 1.02 (<1 year), 0.88 (1–1.9 years), 0.75 (2 or more years), and for losartan was 0.98, 0.87 and 0.71, respectively ($p < 0.05$) for trend of treatment duration, except for β -blockers and nonlosartan angiotensin II receptor blockers. In addition, these associations tended to be stronger with higher rather than medium or low doses, except for angiotensin-converting enzyme inhibitors. The inverse association tended to be stronger with high-dose losartan than with medium- or low-dose use. By contrast, current use of diuretics, β -blockers, angiotensin-converting enzyme inhibitors and non-losartan angiotensin II receptor blockers in the hypertensive population were all associated with increased risk of developing gout. In the combination therapy including diuretics, the multivariate relative risk for incidence of gout compared with no use of antihypertensive medication were larger with angiotensin-converting enzyme inhibitors and with β -blockers than with calcium channel blockers. In this study calcium channel blockers and losartan use was associated with a moderately lower risk of new-onset gout among hypertensive patients; these associations were independent of the classic risk factors for gout. This is the first time that an inverse association between longer treatment duration and a higher dose were found to be protective against gout. Diuretics, β -blockers, angiotensin-converting enzyme inhibitors and non-losartan angiotensin II receptor blockers were associated with an increased risk of

incident gout among HTN patients, being the highest for diuretics (six per 1000 person-years) as compared with the other agents (one to two per 1000 person-years).

A recent study by McAdams DeMarco *et al.* has corroborated some of the previously described findings [12]. The objective of their study was to quantify the role of diuretic use in gout development in an adult population with HTN. Participants, who were free of gout at baseline, included in The ARIC study, a prospective population-based cohort from four US communities were included in the analysis. Trained interviewers recorded use of antihypertensive drugs, and incident gout was defined as self-reported onset of gout after baseline. There were 5789 participants with HTN; 37% were treated with a diuretic. Use of any diuretic (hazard ratio [HR]: 1.48 [95% CI: 1.11–1.98]), a thiazide diuretic (HR: 1.44 [95% CI: 1.00–2.10]) or a loop diuretic (HR: 2.31 [95% CI: 1.36–3.91]) was associated with incident gout compared with no diuretic, no thiazide diuretic or no loop diuretic, respectively. After adjusting for serum urate level, the association between diuretic use and gout was null. Use of antihypertensive medication other than diuretic agents was associated with decreased gout risk (adjusted HR: 0.64 [95% CI: 0.49–0.86]) compared with untreated HTN. The longitudinal change in serum urate levels was 0.72 mg/dl (95% CI: 0.57–0.87) higher in those who began treatment with a diuretic than in those who did not ($p < 0.001$). The authors concluded that thiazide and loop diuretics were associated with increased gout risk, an association mediated by a change in serum urate levels.

Notwithstanding the differences between studies, both reached a similar conclusion in regard to use of diuretics and gout, their use is associated with increased gout risk. There are important clinical implications from the reported findings, and as suggested by Choi *et al.* calcium channel blockers or losartan should be the drugs of choice in the hypertensive population at higher risk of developing gout and its comorbidities. In addition, these drugs should also be highly considered in people with HU and at risk of developing HTN, chronic renal disease, Type 2 diabetes mellitus and those with increased cardiovascular risk [13].

Another issue that deserves further study and discussion is whether diuretic agents should be used in patients with gouty arthritis. Hueskes *et al.* recently reviewed the literature

investigating the relationship between use of diuretics and the risk of gouty arthritis. Three cohort studies and four case-control studies found higher risks of gouty arthritis in users compared with nonusers of diuretics. They showed that there was a trend towards a higher risk for acute gouty arthritis attacks in patients on loop and thiazide diuretics, but the magnitude and independence was not consistent. The authors concluded that, based on their findings, discontinuing these useful drugs in patients who develop gouty arthritis is not supported by the results of their review [14].

Losartan also deserves further attention. An angiotensin II receptor antagonist with uricosuric properties, and its principal metabolite E-3174 inhibit the urate anion exchanger URAT1 and diminish urate reabsorption in the brush border of the proximal tubules, and as a result the urate excretion fraction increases by 13–30%. This effect is not associated with an increase in incidence of uric acid stones and is also not observed with other drugs in this class [15,16]. In addition, in the LIFE study, Hoiegggen *et al.* clearly demonstrated that uric acid is an independent cardiovascular risk factor [17]. As shown by Choi *et al.* combination therapy, duration of therapy and dose administered are all associated with a lower risk of incident gout among people with HTN [11]. With this in mind, other agents, such as statins and fenofibrate alone or in combination, with known urate-lowering capacity should also be investigated [18–20].

In summary, the findings of Choi *et al.* and corroborated by those of McAdams DeMarco

et al. clearly established a link between the use of certain antihypertensive agents and risk of incident gout in patients with HTN [12]. The findings may have important clinical and public health implications for choosing the appropriate antihypertensive therapy in patients with HTN.

Future perspective

Data presented clearly establishes a link between the use of certain antihypertensive drugs and an increased risk of gout. In addition, the protective role of calcium channel blockers and losartan against the risk of developing gout among individuals with HTN is also clearly confirmed. A number of questions remain to be clarified, including whether results obtained could be extrapolated to other ethnic groups, other clinical disorders in which antihypertensive drugs are used and also the elucidation of the effects of switching antihypertensive drugs. Other future studies may be directed at defining the role of combination therapy, such as losartan and calcium channel blockers, in reducing the overall burden of comorbidities associated with gout and HTN.

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Executive summary

Findings from the study

- Losartan and calcium channel blockers may protect against the risk of gout in patients with hypertension.
- Both losartan and calcium channel blockers have urate-lowering effects.
- Diuretics, β -blockers, angiotensin-converting enzyme inhibitors and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout.

Impact on the use of antihypertensive drugs in patients with gout

- Use of losartan and calcium channel blockers alone or in combination may be associated with a decrease in the burden of comorbidities associated with gout and hypertension.

Conclusion

- The use of certain antihypertensive drugs may be associated with a decreased risk of developing gout.
- Use of combination therapy, including losartan, statins and calcium channel blockers, may also reduce serum urate level and confer a protective effect against the risk of gout and associated comorbidities.

Future perspective

- The effects of switching antihypertensive drugs in patients with gout needs further investigation.
- The urate-lowering effect of losartan, calcium channel blockers and others need to be investigated in normal people with hyperuricemia and other clinical disorders.

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