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The effect of angiotensin II receptor blockers on hyperuricemia

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***Abstract*:** The objective of this review was to explore the efficacy of angiotensin II receptor blockers (ARBs) for the treatment of hyperuricemia in individuals diagnosed with gout or hyperuricemia defined as ⩾7 mg/dl at baseline. A literature search of MEDLINE (1946 to June 2015) and EMBASE (1947 to June 2015) was conducted. The following search terms were used: 'uric acid', 'urate transporter', 'gout', 'angiotensin II receptor blockers', 'hyperuricemia' and the names for individual ARBs, as well as any combinations of these terms. Studies were excluded that did not explore fractional excretion or serum uric acid as an endpoint, if patients did not have a diagnosis of gout or hyperuricemia at baseline, or if they were non-English language. A total of eight studies met the inclusion criteria. Of the eight studies identified, six explored ARB monotherapy and two studies investigated ARBs as adjunct therapy. Losartan demonstrated statistically significant reductions in serum uric acid levels or increases in fractional excretion of uric acid in all studies, whereas no other ARB reached statistical benefit. The effect of ARBs on the occurrence of gout attacks or other clinical outcomes were not represented. Four studies evaluated safety effects of these agents indicating abnormalities such as minor changes in lab values. In conclusion, losartan is the only ARB that has consistently demonstrated a significant reduction in serum uric acid levels, although the significance of impacting clinical outcomes remains unknown. Losartan appears to be a safe and efficacious agent to lower serum uric acid levels in patients with hyperuricemia.

Keywords: angiotensin receptor antagonists, hyperuricemia, gout, uric acid, losartan

Background

Gout and the presence of elevated uric acid levels, defined as ⩾7 mg/dl, has been linked to multiple chronic comorbidities including hypertension, chronic kidney disease, diabetes, obesity and heart failure [Zhu *et al.* 2011, 2012; Duskin-Bitan *et al.* 2014; Terkeltaub, 2010]. The presence of hyperuricemia has also been associated with poor health-related outcomes including myocardial infarction (MI), stroke and nephrolithiasis [Zhu *et al.* 2012]. In addition, it is estimated that employed individuals diagnosed with gout miss 5 days more per year than their counterparts without the disease. When comparing those diagnosed with gout to those without gout, annual medical costs are in excess of US$3000 more in those with gout [Wertheimer *et al.* 2013]. In the most recent National Health and Nutrition Examination Survey from 2007–2008, the prevalence of gout in the United States was 3.9% of the total population, affecting approximately 8.3 million individuals [Zhu *et al.* 2012]. In a population-based study from the United Kingdom in 2013, results showed that the prevalence of gout has increased by 63.9% since 1997 [Kuo *et al.* 2015]. This information highlights the current and growing number of individuals afflicted with this disease state and underscores the importance of identifying viable options for the treatment of gout.

Gout is an arthritis classified commonly by uric acid crystallization that occurs within joints [Choi *et al.* 2005]. Humans lack the enzyme uricase, which is responsible for breaking down ingested purines from dietary sources (e.g. alcoholic beverages, red meat and seafood) into allantoin, a more soluble form to be excreted or removed. As urate levels increase, individuals are at a greater

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risk for saturation and formation of crystals. However, the true amount of urate in an individual's body depends on several factors including dietary intake, synthesis and individual rates of urate excretion.

There are three urate transporters, URAT1, GLUT9 and ABCG2, which have been studied for their important roles in serum uric acid regulations. URAT1 serves as a urate–anion exchanger in the proximal tubule of the kidney and is a key target for uricosuric agents [Choi *et al.* 2005]. In contrast, genetic mutations in GLUT9 can precipitate individuals to a defect in uric acid absorption leading to hypouricemia [Dinour *et al.* 2010]. Finally, when there is dysfunction of the urate transporter ABCG2, it has been found that there is the potential for both renal underexcretion of uric acid and a blockade of intestinal urate excretion, thereby leading to renal urate overload [Matsuo *et al.* 2014].

Urate underexcretion is responsible for 90% of hyperuricemia, while the other 10% occurs from urate overproduction. One-third of urate elimination occurs in the gastrointestinal tract, while the other two-thirds are eliminated through the kidneys and excreted in the urine [Choi *et al.* 2005]. When excretion is impaired, hyperuricemia and uric acid crystallization can result, which predisposes individuals to gout and potentially painful gout attacks.

The 2012 American College of Rheumatology (ACR) Treatment Guidelines outline the recommended treatments for gout. First-line interventions include dietary modifications such as exercise and consuming a low purine diet [Crittenden and Pillinger, 2013; Khanna *et al.* 2012a]. While the use of nonsteroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids and colchicine are recommended for acute gout attacks, urate-lowering therapy is recommended for individuals with chronic gout consisting of multiple gouty attacks per year and other prespecified conditions as indicated by the treatment guidelines [Khanna *et al.* 2012b]. First-line urate-lowering agents are xanthine oxidase inhibitors such as allopurinol and febuxostat. Probenecid, a uricosuric agent that helps to promote excretion of uric acid, can be utilized second-line if xanthine oxidase inhibitor use is contraindicated. Newer agents such as pegloticase have also emerged in treatment guidelines, but the use of these agents is only recommended in severe gout when oral agents have failed [Khanna *et al.* 2012a]. The 2012 ACR Guidelines endorse the use of additional uricosuric agents such as fenofibrate and losartan in combination with xanthine oxidase inhibitors if target urate levels are not met with first-line agents alone [Khanna *et al.* 2012a]. Asymptomatic hyperuricemia can occur and, treatment with urate-lowering therapy most commonly occurs only in high risk patients such as those with a history of multiple gout attacks [Khanna *et al.* 2012a].

Uricosuric agents increase the urinary excretion of uric acid, thereby decreasing serum uric acid levels. This is thought to occur by inhibition of the URAT1 anion exchanger responsible for the reabsorption of filtered urate, which is located in the proximal tubule of the kidney [Choi *et al.* 2005]. Many medication therapies have secondary uricosuric effects, and although used for alternate primary indications, can assist conventional agents in reducing serum uric acid levels. High-dose salicylate and indomethacin have both been studied for their uricosuric effects [Shin et al. 2011]. Angiotensin II receptor antagonists (ARBs) have also been studied for their URAT1 inhibition potential and residual uricosuric effects [Iwanaga *et al.* 2007].

ARBs inhibit the activity of angiotensin II, a potent vasoconstrictor that is formed through a conversion from angiotensin I by angiotensin-converting enzyme (ACE) [Michel *et al.* 2013]. Angiotensin II is a vital regulator of homeostasis and is a primary component of the renin-angiotensin system. This vasoconstrictor not only plays a role in many tissues in the body, but also has several effects in the cardiac system including increased cardiac contractility and renal reabsorption of sodium. Therefore ARBs play a significant role in the treatment of hypertension and as renoprotective agents [Michel *et al.* 2013]. While utilized for similar indications, the available ARBs differ widely in their chemical structures, which correlate to various differences in their pharmacodynamic and pharmacokinetic effects. Overall, ARBs are well tolerated; however, the most common adverse effects include hypotension, hyperkalemia and increased serum creatinine levels [Taylor *et al.* 2011].

The objective of this review article is to explore the efficacy of ARBs for the treatment of hyperuricemia in individuals diagnosed with gout or hyperuricemia defined as $\geq$7 mg/dl at baseline.

Table 1. Summary of studies using angiotensin II receptor blockers for uricosuric effects.

Study	Design	*n*	Treatment/ comparator	Pertinent endpoints	Results
Rayner *et al.* [2006]	OL, 24 weeks	59	Losartan	Serum uric acid levels	Losartan: ↓ 0.84 mg/dl*$
			Candesartan		Candesartan: ↑ 0.33 mg/dl
Dang *et al.* [2006]	DB, 8 weeks	351	Losartan	Serum uric acid levels	Losartan: ↓ 1.06 mg/dl*
			Irbesartan		Irbesartan: ↓ 0.16 mg/dl
Würzner *et al.* [2001]	DB, CO, 8 weeks	16	Losartan	Serum uric acid levels	Losartan: ↓ 0.88 mg/dl*
			Irbesartan		Irbesartan: ↓ 0.21 mg/dl
Shahinfar *et al.* [1999]	DB, PC, 3 weeks	63	Losartan	Serum uric acid levels	Losartan: NR*
			Losartan/thiazide		Losartan/thiazide: NR
			Thiazide		Thiazide: NR
			Placebo		Placebo: NR
Khan *et al.* [2008]	OL, 12 weeks	60	Losartan	Serum uric acid levels	Losartan: ↓ 2.02 mg/dl*
			Losartan/thiazide		Losartan/thiazide: ↓ 1.11 mg/dl*
			Thiazide		Thiazide: ↑ 0.6 mg/dl*
Khan *et al.* [2011]	OL, 12 weeks	60	Losartan	Urinary uric acid excretion level	Losartan: ↑ 31.75 mg/dl*
			Losartan/thiazide		Losartan/thiazide: ↑ 66.29 mg/dl*
			Thiazide		Thiazide: ↓ 41.28 mg/dl*
Elisaf *et al.* [1999]	OL, 8 weeks	25	Losartan/ fenofibrate	Serum uric acid levels	Losartan/fenofibrate: ↓ 2.7 mg/dl$
			Fenofibrate		Fenofibrate: ↓ 2 mg/dl*
Takahasi *et al.* [2003]	OL, 8 weeks	25	Losartan/ benzbromarone	Serum uric acid levels	Losartan/benzbromarone: ↓ 0.4 mg/dl*
			Losartan/ allopurinol		Losartan/allopurinol: ↓ 0.5 mg/dl*

*Denotes statistical significance of baseline *versus* final results.
$Denotes statistical significance of losartan *versus* comparator agent.
CO, crossover; DB, double-blind; NR, not reported; OL, open-label; PC, placebo-controlled.

Literature search

A literature search of MEDLINE (1946 to June 2015) and EMBASE (1947 to June 2015) was conducted. The following search terms were used: 'uric acid', 'urate transporter', 'gout', 'angiotensin II receptor blockers', 'hyperuricemia' and the drug names for individual ARBs, as well as any combinations of these terms. Studies were excluded if they were published in a language other than English, did not explore either fractional excretion of uric acid or serum uric acid as an endpoint, or if the patients did not have a diagnosis of gout or hyperuricemia as defined as group mean uric acid level ⩾7 mg/dl at baseline. Bibliographies of relevant articles were reviewed for additional citations. Search results using the specified terms yielded a total of 776 citations found in PubMed and 2321 citations found in EMBASE meeting search criteria. Some duplicate citations were included in these results and were removed by comparing each result against the prespecified inclusion and exclusion criteria. From those, eight studies met criteria [Rayner *et al.* 2006; Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011; Elisaf *et al.* 1999; Takahasi *et al.* 2003] and are described in Table 1.

Literature review

ARB monotherapy

Rayner and colleagues conducted an open-label, randomized, controlled, two-parallel group study [Rayner *et al.* 2006]. In the study, 59 patients were enrolled to receive either losartan 50–100 mg daily or candesartan 8–16 mg daily for 24 weeks. Individuals were eligible for the study if they had a uric acid level ⩾7 mg/dl at baseline, were receiving a thiazide, thiazide-like or loop diuretic, and had uncontrolled mild-to-moderate essential hypertension, defined as systolic blood pressure

between 140 and 180 mmHg, and diastolic blood pressure between 90 and 110 mmHg. Individuals had to be maintained on a stable dose of diuretics for at least 12 weeks before study entry. Those with baseline use of steroids, NSAIDs, allopurinol, colchicine or with renal dysfunction were excluded. The study medications could be titrated to losartan 100 mg daily or candesartan 16 mg daily if blood pressure remained elevated >140/90 mmHg at 6 weeks.

As the primary outcome, the uric acid levels of the losartan group decreased from 7.39 mg/dl at baseline to 6.55 mg/dl at week 24; in the candesartan group, uric acid levels increased from 7.73 mg/dl at baseline to 8.06 mg/dl at week 24 ($p = 0.01$). Of note, in the losartan group, the uric acid levels decreased with no effect on serum creatinine, while in the candesartan group, there was no change in uric acid levels but there was a slight increase in serum creatinine. Both drugs were well tolerated; however, there was one serious adverse effect noted in the study that was not described by the authors [Rayner *et al.* 2006].

Dang and colleagues conducted a multicenter study across 20 clinical institutions exploring the effects on serum uric acid levels after administration of losartan or irbesartan [Dang *et al.* 2006]. Individuals were required to have baseline mild-to-moderate hypertension and a uric acid level ⩾7.0 mg/dl. Study participants were excluded if they had a diagnosis of gout or renal lithiasis within the last 2 years. A total of 351 patients were randomized to receive either losartan 50 mg daily or irbesartan 150 mg daily. If diastolic blood pressure was ⩾90 mmHg or systolic blood pressure was ⩾140 mmHg at 4 weeks, the regimen was increased to either losartan 100 mg daily or irbesartan 300 mg daily for the next 4 weeks. Losartan decreased serum uric acid levels from 7.09 mg/dl at baseline to 6.17 mg/dl at week 4 ($p < 0.0001$) and further decreased serum uric acid to 6.03 mg/dl at week 8 ($p < 0.0001$). Irbesartan decreased serum uric acid levels from 7.06 mg/dl to 6.9 mg/dl at week 4 and further to 6.85 mg/dl at week 8; however, these changes were not statistically significant. Potassium and serum creatinine levels were reviewed and both lab values remained within accepted normal ranges throughout the study [Dang *et al.* 2006].

Würzner and colleagues explored the use of both irbesartan and losartan for potential uricosuric effects [Würzner *et al.* 2001]. This study was a prospective, randomized, double-blind, crossover study design. A total of 16 individuals with diagnoses of hypertension and gout defined as hyperuricemia ⩾7.06 mg/dl and documentation of uric acid crystals in the synovial fluid were enrolled. Participants initially received 3 weeks of enalapril therapy as a run-in and were then randomized to receive either losartan 50 mg daily or irbesartan 150 mg daily for 4 weeks. Losartan was then increased to 50 mg twice daily and irbesartan to 150 mg twice daily for 4 additional weeks. The patients then crossed over to receive the alternate therapy. From a baseline serum uric acid level of 9.7 mg/dl, initiation of losartan 50 mg daily significantly decreased uric acid levels to 8.8 mg/dl ($p < 0.01$). There was no difference in uric acid reduction between losartan 50 mg daily and losartan 50 mg twice a day. Compared with the baseline uric acid level of 9.9 mg/dl in the irbesartan group, there was not a significant change in uric acid levels with either irbesartan 150 mg daily or twice daily. Losartan 50 mg daily also had a significant uric acid reduction when compared with irbesartan 150 mg daily ($p < 0.05$). Several gout attacks occurred through each phase of the study. There were 4 gout attacks during the losartan 50 mg daily and 50 mg twice daily regimens, 2 gout attacks during the irbesartan 150 mg daily treatment regimen, and 4 during the irbesartan 150 mg twice daily treatment regimens. Four individuals experienced an acute gouty attack after being switched from losartan back to enalapril therapy. No other safety endpoints were determined to be significant [Würzner *et al.* 2001].

Shahinfar and colleagues conducted a double-blind, placebo-controlled, parallel study with 63 patients to explore the safety and efficacy of losartan in individuals with thiazide-induced hyperuricemia [Shahinfar *et al.* 1999]. All individuals were required to have a history of diastolic blood pressure between 90 and 105 mmHg and asymptomatic hyperuricemia at baseline, defined as serum uric acid between 7 mg/dl and 12 mg/dl. Individuals with secondary hypertension, significant cardiac history including MI within the past year, and transient ischemic attack (TIA) or cerebrovascular attack (CVA) within the past 3 years were excluded. Patients were randomized into one of 4 treatment groups for 3 weeks: losartan 50 mg daily; losartan 50 mg and hydrochlorothiazide 50 mg daily; hydrochlorothiazide 50 mg daily; or placebo. Outcomes included urine uric acid excretion, serum uric acid levels,

urine pH and dihydrogen urate supersaturation. Urine uric acid excretion increased at hours 2, 4 and 6 on day 1. There was a significant change at hours 4 and 6 for losartan *versus* placebo ($p < 0.0021$) and at 6 hours when evaluating hydrochlorothiazide and losartan combination *versus* hydrochlorothiazide alone ($p < 0.0021$). There were no significant serum uric acid level increases at hours 2, 4 and 6 on day 1. Serum uric acid levels fell significantly following subsequent losartan dosing by day 7 ($p < 0.001$) and remained decreased by day 21 ($p < 0.05$), although this reduction was not quantified. There was a significant increase in urine pH at hours 4 and 6 on day 1 ($p < 0.0021$) and decrease in dihydrogen urate supersaturation at hours 4 and 6 on day 1 for losartan *versus* placebo ($p < 0.0021$). Uric acid excretion rate changes following subsequent dosing of losartan therapy were significant at hour 4 ($p < 0.05$) on both days 1 and 7 but not on day 21. Losartan was well tolerated and no participants experienced urate nephropathy [Shahinfar *et al.* 1999].

Khan and colleagues conducted a randomized, open-label, prospective, comparative study in which 60 patients with hyperuricemia (ranging from 7.0 to 12.0 mg/dl) were divided into 3 groups of 20 patients [Khan *et al.* 2008]. Individuals with a history of secondary hypertension, history of gout and renal lithiasis in the last 2 years, history of malignant hypertension, history of CVA within the last 2 years and history of cardiac arrhythmia were all excluded from this study. Patients were split into treatment groups consisting of losartan 50 mg daily, losartan 50 mg daily plus hydrochlorothiazide 50 mg daily, and hydrochlorothiazide 50 mg daily. A total of 57 patients were analyzed at 12 weeks. In the hydrochlorothiazide monotherapy group, uric acid levels increased from 8.41 mg/dl $\pm$ 0.21 at baseline to 9.01 mg/dl $\pm$ 0.20 at day 90 ($p < 0.001$). In the hydrochlorothiazide and losartan group, uric acid levels decreased from 8.70 mg/dl $\pm$ 0.25 at baseline to 7.59 mg/dl $\pm$ 0.22 at day 90 ($p < 0.001$). In the losartan monotherapy group, uric acid levels decreased from 8.21 mg/dl $\pm$ 0.17 at baseline to 6.19 mg/dl $\pm$ 0.11 ($p < 0.001$). There was no safety analysis conducted in this study [Khan *et al.* 2008].

A follow-up study was conducted by the same study investigators which evaluated an additional outcome of urinary acid excretion [Khan *et al.* 2011]. In those treated with losartan 50 mg daily, urinary uric acid excretion increased from 472.75 mg/dl at baseline to 495.75 mg/dl on day 45 and 504.50 mg/dl at day 90 ($p < 0.001$). Individuals who received hydrochlorothiazide 50 mg daily plus losartan 50 mg daily had a urinary acid excretion that increased from a baseline 499.50 mg/dl to 546.25 mg/dl on day 45 and 565.79 mg/dl on day 90 ($p < 0.001$). In those patients receiving thiazide 50 mg daily, urinary uric acid excretion decreased from a baseline 443.50 mg/dl to 419.17 mg/dl at day 45 and 402.22 mg/dl at day 90 ($p < 0.0001$). There was no safety analysis conducted in this follow-up study [Khan *et al.* 2011].

ARB adjunctive therapy

Elisaf and colleagues conducted a small study of 25 patients with stage 1 hypertension defined as blood pressure 140–149/90–99 mmHg [Elisaf *et al.* 1999]. Individuals also had mixed dyslipidemia [total cholesterol >200 mg/dl, low-density lipoprotein (LDL) cholesterol >130 mg/dl, triglycerides >200 mg/dl but ⩽400 mg/dl] and serum uric acid levels ⩾7 mg/dl. At baseline, individuals were treated with micronized fenofibrate 200 mg once daily and, if blood pressure remained above >140/90 mmHg after 4 weeks, they were started on losartan 50 mg daily for another 4 weeks. From baseline, fenofibrate reduced serum uric acid levels from 7.6 mg/dl $\pm$ 0.55 to 5.6 mg/dl $\pm$ 0.5 ($p = 0.0001$). Following combination therapy, the addition of losartan further decreased uric acid levels from 5.6 mg/dl to 4.9 mg/dl $\pm$ 1, which was statistically significant when compared with monotherapy ($p = 0.04$). This represented an additional 12.5% in serum uric acid lowering with addition of losartan. In addition, combination therapy with losartan, increased the fractional excretion of uric acid from 6.8 $\pm$ 1.8% to 14 $\pm$ 5.5% ($p = 0.05$). This study did not complete a safety analysis [Elisaf *et al.* 1999].

Takahasi and colleagues explored the combination therapy of losartan with either benzbromarone (a uricosuric agent and noncompetitive inhibitor of xanthine oxidase) 50 mg daily or allopurinol 200 mg twice a day [Takahasi *et al.* 2003]. Individuals were diagnosed with gout at baseline as well as a systolic blood pressure >140 mm Hg or diastolic blood pressure of >90 mm Hg. A total of 25 patients received losartan 50 mg daily plus benzbromarone or allopurinol for 8 weeks. Losartan plus benzbromarone significantly decreased serum uric acid from 4.8 to 4.4 mg/dl ($p < 0.05$) and increased uric acid clearance from

7.9 ml/min to 9.8 ml/min ($p < 0.01$) and 24-hour urinary uric acid excretion from 2.13 mmol/m^2/day to 2.31 mmol/m^2/day, ($p < 0.05$). Losartan plus allopurinol significantly decreased serum uric acid from 6.0 mg/dl to 5.49 mg/dl ($p < 0.01$) and increased uric acid clearance from 4.2 ml/min to 5.4 ml/min ($p < 0.01$) and 24-hour urinary acid excretion from 1.45 mmol/m^2/day to 1.68 mmol/m^2/day ($p < 0.05$). This study did not conduct a safety analysis [Takahasi *et al.* 2003].

Discussion

This review explored the available literature for the urate-lowering effects of ARBs. Losartan was the only ARB which was found to reduce serum uric acid levels and to increase the excretion of uric acid in all the studies discussed in this review [Rayner *et al.* 2006; Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011; Elisaf *et al.* 1999; Takahasi *et al.* 2003]. The most common dosage utilized was 50 mg daily. In studies that explored the higher doses of losartan, there was no added benefit with administering the losartan 50 mg twice a day or 100 mg once daily [Dang *et al.* 2006; Würzner *et al.* 2001].

Candesartan and irbesartan were the other ARBs found in the literature that were compared to losartan for their potential uricosuric effects. Upon review of the three studies which looked at the uricosuric effects of candesartan and irbesartan, there was no significant benefit with use of these agents [Dang *et al.* 2006; Würzner *et al.* 2001; Rayner *et al.* 2006]. In two of the studies, serum uric acid levels were not reduced with the use of candesartan or irbesartan and, in the final study, serum uric acid levels decreased with irbesartan, but this result was not found to be statistically significant [Dang *et al.* 2006; Würzner *et al.* 2001; Rayner *et al.* 2006]. There are multiple explanations as to why candesartan and irbesartan do not have the same effects as losartan. There are differences in the chemical structures of the ARBs, there is potential for the ARB to be *cis*-inhibitory or *trans*-stimulating or both, and there is variability amongst ARBs to have inhibitory effects on the uptake of uric acid by the URAT1 receptor [Iwanaga *et al.* 2007]. Further studies with additional ARBs could be beneficial in determining if any of the other agents within this class are able to exert similar effects to losartan. The presence of an active metabolite has not been shown to be the cause for differences between the ARBs in their uricosuric effects; however, many have postulated that it is the position in which the ARB binds to the URAT1 transporter [Iwanaga *et al.* 2007]. It is unclear whether alternative ARBs other than those studied in this review have the same binding potential as losartan. Future studies would be needed to determine if this is the case.

Despite the reduction in serum uric acid levels and increased excretion of uric acid from losartan therapy as evidenced by the studies reviewed, it would be beneficial to explore more clinically meaningful endpoints in the future, such as reduction in the number of gout attacks or hospitalizations associated with gout. Furthermore, evaluating quality of life and gout attack free intervals would help quantify the relevance of incorporating losartan with xanthine oxidase inhibitors for gout management. One study in this review did demonstrate an increase in gouty attacks as an unexpected adverse effect upon switching from ARBs back to enalapril [Würzner *et al.* 2001]. It may also be necessary to conduct additional studies for longer periods of time to capture this clinical outcome. Although beyond the scope of this review, other clinically meaningful results unrelated to gout manifestations have been reported. Losartan has demonstrated renoprotective effects directly related to the degree of serum uric acid lowering; however, these endpoints were not explored in the included studies that enrolled patients with baseline hyperuricemia or a gout diagnosis [Ito *et al.* 2012; Miao *et al.* 2011].

In addition, hyperuricemia has been linked to an increase in cardiovascular events such as stroke, hypertension and heart failure [Zhu *et al.* 2012]. Many individuals with hypertension are treated with thiazide diuretics, which can cause hyperuricemia. In three of the studies incorporated in this review, the addition of losartan was beneficial in offsetting the rise of uric acid levels in the setting of hydrochlorothiazide use [Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011]. However, only two of the studies evaluated the use of losartan in combination with hydrochlorothiazide in those with elevated blood pressure at baseline, and it was found to have a beneficial effect on blood pressure lowering in these patients [Shahinfar *et al.* 1999; Khan *et al.* 2008]. These findings highlight a niche for the incorporation of losartan into therapeutic regimens for individuals with thiazide diuretic-induced hyperuricemia.

A major limitation of the available literature is that only four of the studies reviewed explored potential adverse effects or safety concerns with ARB therapy [Rayner *et al.* 2006; Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999]. Changes in lab values such as elevations in serum creatinine and potassium were noted; however, these results were deemed clinically insignificant as they remained within normal limits [Dang *et al.* 2006]. In one trial, five gout attacks occurred and individuals had to be treated with colchicine or NSAIDs when switching from ARB therapy back to enalapril therapy [Würzner *et al.* 2001]. This adverse effect was not expected, although this raises an important concern with chronically elevated serum uric acid levels precipitating gout attacks. In addition, it is hard to discern if this occurred due to losartan discontinuation or if it was due to the patient's underlying risk factors. Finally, one study in this review explored the safety of losartan on urate nephropathy and determined that losartan did not increase flank pain, hematuria or crystalluria [Shahinfar *et al.* 1999]. It is important to continue to monitor for the side effects that were found within the studies, as well as the common adverse effects associated with ARB use.

Several of the studies were conducted within a short time frame lasting only for several weeks [Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008]. This makes it difficult to extrapolate the longer potential effects on serum uric acid with losartan use. In addition, with several of the studies enrolling such small groups of patients and excluding those with a gout diagnosis at baseline, it is difficult to generalize the data from such a small group into a larger patient population [Rayner *et al.* 2006; Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011; Elisaf *et al.* 1999; Takahasi *et al.* 2003]. However, most studies included comorbid hypertension at baseline, indicating potential for ARB use to be beneficial in this patient population. It is important to note that their use would be limited by potential for hypotension [Rayner *et al.* 2006; Dang *et al.* 2006; Shahinfar *et al.* 1999; Elisaf *et al.* 1999; Takahasi *et al.* 2003].

Furthermore, all of the studies looked only at surrogate endpoints including serum uric acid levels and fractional excretion of uric acid and did not further explore clinical outcomes. While losartan demonstrated statistical significance in improving these surrogate endpoints, it is hard to correlate this to clinical significance. No studies reviewed the incidence of gout attacks during the prespecified time [Rayner *et al.* 2006; Dang *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011; Elisaf et al.1999; Takahasi *et al.* 2003]. Many of the studies also lacked a control group [Rayner *et al.* 2006; Würzner *et al.* 2001; Shahinfar *et al.* 1999; Khan *et al.* 2008, 2011; Elisaf *et al.* 1999; Takahasi *et al.* 2003]. Future prospective, randomized, placebo-controlled studies should include larger patient populations, and should explore more relatable and generalizable endpoints such as gout attack free periods or incidence of gout attacks.

Conclusion

This review explored evidence for ARBs and the reduction of serum uric acid levels and increased fractional excretion of uric acid. All patients had to have a diagnosis of gout or hyperuricemia (group mean uric acid level $\geqslant$7 mg/dl) at baseline. Of the ARBs included in the studies, losartan was the only ARB to significantly lower uric acid levels, although the significance of impacting clinical outcomes such as gout attacks is unknown. The literature regarding the potential uricosuric effects of other ARBs is either inconclusive or nonexistent. As hyperuricemia is a risk factor for gout attacks and individuals may not be able to reach an adequate reduction in uric acid levels with a xanthine oxidase inhibitor alone, the addition of a uricosuric agent such as losartan may be beneficial. Future studies are needed with additional ARBs and with losartan evaluating endpoints such as prevention of gout attacks or gout-related hospitalizations.

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