Comparison of New-Onset Gout in Adults Prescribed Chlorthalidone vs Hydrochlorothiazide for Hypertension

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This study assessed the risk of new-onset gout following prescribing of hydrochlorothiazide (HCTZ) compared with chlorthalidone (CTD). This retrospective cohort analysis used administrative claims from 2000 to 2012 to identify patients aged 18 to 89 years with hypertension who were prescribed CTD or HCTZ. Patients were excluded if they had a prior diagnosis of gout, conditions or prescription claims for medications that alter risk of gout, or if they switched between these two diuretics. A total of 1011 patients prescribed CTD were matched with 2022 patients prescribed HCTZ based on age, sex, and Chronic Condition Indicator. New-onset gout occurred in 17 of 1011 (1.68%) patients in the CTD group and in 26 of 2022 (1.29%) patients in the HCTZ group (P=.27). The number of days to first occurrence of gout was 183.6 days and 152.7 days in the CTD and HCTZ groups, respectively (P=.39). The mean daily dose was 22.7 mg for CTD and 24.3 mg for HCTZ, and the median dose of both CTD and HCTZ was 25 mg at the time of new-onset gout. Patients prescribed CTD for hypertension have a similar risk of developing new-onset gout compared with patients prescribed similar doses of HCTZ. *J Clin Hypertens (Greenwich).* 2014;16:864–868. © 2014 Wiley Periodicals, Inc.

Gout is one of the most common rheumatic diseases and is the most common cause of inflammatory arthritis among adults in the United States.[1,2] An analysis of the National Health and Nutrition Examination Survey estimates that approximately 8 million Americans are affected by gout.[3] Gout prevalence continues to rise, particularly in the United States. In addition to poor dietary patterns, likely contributing factors are an increase in comorbidities that are associated with hyperuricemia such as obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease (CKD). Importantly, hypertension is independently associated with increased gout risk in middle-aged African American and white adults.[4] Another factor that can increase the incidence of gout is use of medications that are known to increase serum urate concentrations.

Acute gouty arthritis is a painful and bothersome condition for patients. Additionally, costs associated with frequent episodes of gout, defined as ≥3 gouty arthritis attacks per year, are a burden to the healthcare system. Patients with frequent gout episodes have been shown to experience more comorbidities and have significantly higher gout-related healthcare costs when compared with patients with infrequent gout. Patients with frequent gout have also been shown to have more absolute or relative contraindications to gouty arthritis medications compared with patients with infrequent gout. Importantly, patients with frequent gout are more often prescribed a diuretic, a medication class known to cause or worsen gout, than patients with infrequent gout.[5]

Contributing factors for gout such as comorbidities and contraindications can be difficult or impossible to eliminate and use of medications known to increase serum urate should be avoided in patients with a history of gout.

Several medications are known to increase serum urate concentrations and may potentially increase the occurrence of gout and gouty attacks. These include loop and thiazide diuretics, calcineurin inhibitors, niacin, levodopa, teriperatide, low-dose salicylates, ethambutol, and pyrazinamide.[6] Of these medications, thiazide diuretics are the most widely prescribed in the United States and, of the diuretic subclasses, have a more pronounced increase in serum urate elevations because of their marked decrease in urate renal excretion.[7,8]

Hydrochlorothiazide (HCTZ) and chlorthalidone (CTD) are commonly used diuretics. Major landmark hypertension clinical trials that have consistently demonstrated reduced cardiovascular events with diuretic-based therapy have used CTD as their primary diuretic therapy, not HCTZ.[9–12] Practice guidelines consistently recommend thiazide diuretics as initial therapy for most patients with hypertension and have been the foundation of hypertension therapy for decades.[13]

No specific type of thiazide diuretic is recommended over another for the routine treatment of hypertension. However, the fact that CTD is 1.5 to 2 times more

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potent in lowering blood pressure than HCTZ and has a longer duration of action has led to CTD being recommended ahead of HCTZ in patients with resistant hypertension.[14–16] Nonetheless, most providers prescribe HCTZ as their thiazide diuretic of choice for hypertension instead of CTD. Reasons for this phenomenon are unclear but could be due to the numerous available combination products with HCTZ and perhaps perceived fear of more pronounced electrolyte and other metabolic disturbances with CTD. There are limited data directly comparing HCTZ with CTD in relation to the incidence of new-onset gout. Further evaluations describing the incidence of gout and diuretic use could potentially guide future prescribing patterns of these agents in patients at risk for gout. The primary objective of this study was to assess the risk of new-onset gout following the use of CTD compared with HCTZ. The secondary objective was to evaluate the dose characteristics and duration of therapy of both CTD and HCTZ for new-onset gout.

METHODS

Study Population

The IMS LifeLink database (IMS Health, Alexandria, VA), which contains medical and pharmacy claims for insured patients across the United States, was used to identify patients eligible for this retrospective cohort database analysis. This total database represents approximately 70 million members, and we utilized a 10% sample (approximately 7 million patients). Patients aged 18 to 89 years with a prescription claim for either HCTZ or CTD from 2000 to 2012 were identified for inclusion into the study. The first prescription claim for either diuretic was considered the study index date.

Inclusion criteria were a diagnosis of hypertension (*International Classification of Diseases, 9th Revision* [*ICD-9*] 401.XX) prior to the index date, with continuous medical and prescription eligibility throughout a 36-month period (24 months prior and 12 months after the index date). Exclusion criteria were a prescription claim for any medication known to increase (loop diuretics, niacin, calcineurin inhibitors, levodopa, teriparatide, ethambutol, pyrazinamide) or decrease (losartan, fenofibrates) serum urate concentrations, a medical claim for a condition that can affect serum urate concentrations (hyperuricemia of malignancy, tumor lysis syndrome, lymphoma, leukemia, myeloma, stages IV and V CKD, heart failure), a prior history of gout, or switching between HCTZ and CTD after the index date.

Based on the first thiazide prescription at the index date, patients were identified for either the CTD or HCTZ group. Patients prescribed CTD who met study criteria were matched to patients prescribed HCTZ who met study criteria in a ratio of 1:2. This matching was based on age, sex, and the Chronic Condition Indicator (CCI) score.[17]

Outcome Analyses

The primary outcome was the incidence of new-onset gout. A claims-based algorithm was developed to define new-onset gout, which was defined by presence of a medical claim for gout using *ICD-9* codes (274.XX) or a prescription claim for a gout-specific medication using National Drug Codes for allopurinol, febuxostat, colchicine, and probenecid occurring 14 days to 12 months following the index date for CTD or HCTZ. The purpose of the 14-day time lapse from the index date to new-onset gout evaluation was to allow time for adequate diuretic exposure. This timeframe also more accurately captured new-onset gout related to diuretic use rather than gout related to other causes.

Secondary outcomes included the duration of diuretic exposure prior to new-onset gout and the following diuretic dose evaluations: (1) dose prescribed at index, (2) mean daily dose throughout study duration, and (3) dose prescribed immediately prior to new-onset gout.

Statistical Analysis

Descriptive statistics with logistic regression were used to evaluate the incidence of new-onset gout and dose evaluations between the CTD and HCTZ groups. For categorical variables, χ^2 tests were used. A time-to-event analysis was used to measure the duration of diuretic therapy prior to new-onset gout. All study analyses were conducted using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

From our database population, 1025 patients met inclusion criteria for the CTD group and 39,296 for the HCTZ group. However, 14 patients prescribed CTD could not be matched to an HCTZ equivalent, resulting in a total CTD group of 1011 who were matched to 2022 patients to create the HCTZ group. Baseline demographic characteristics among the CTD and HCTZ groups were similar (Table I). Mean patient age was 55 years, 52% were women, 84% were covered by commercial health plans, and 42% were from the Midwest region of the United States. The mean CCI score was 3.5.

The primary outcome of new-onset gout occurred in 17 of 1011 (1.68%) patients in the CTD group and in 26 of 2022 (1.29%) patients in the HCTZ group (P=.27). Patient characteristics of those who developed new-onset gout were similar between groups. There were no significant differences in these characteristics from baseline with the exception of sex, with more men (12 and 18 patients for CTD and HCTZ, respectively) developing new-onset gout than women (5 and 8 patients for CTD and HCTZ, respectively). The mean age of all patients who developed new-onset gout was 57 years (58.3 and 56.4 years for CTD and HCTZ, respectively; P=.67) and the mean CCI score was 4.0 (3.8 and 4.2 for CTD and HCTZ, respectively; P=.52), both slightly higher than baseline. The majority of patients that developed gout in both

TABLE I. Demographic Characteristics of Matched Patients

Characteristic	CTD, No. (%)	HCTZ, No. (%)	*P* Value
Patients in cohort, No.	1011	2022	N/A
Women	528 (52.23)	1056 (52.23)	N/A[a]
Men	483 (47.77)	966 (47.77)	
Chronic disease			
CKD	4 (0.40)	10 (0.49)	.706
Diabetes	144 (14.24)	316 (15.63)	.316
Hyperlipidemia	482 (47.68)	996 (49.26)	.411
Obesity	82 (8.11)	159 (7.86)	.812
Urolithiasis	26 (2.57)	77 (3.81)	.078
Geographical region			
East	194 (19.19)	369 (18.25)	.53
Midwest	480 (47.48)	802 (39.66)	<.001
South	288 (28.49)	721 (35.66)	<.001
West	49 (4.85)	130 (6.43)	.082
Insurance			
Commercial plan	823 (81.40)	1,730 (85.56)	.003
Medicaid	2 (0.20)	3 (0.15)	.752
Medicare cost	25 (2.47)	29 (1.43)	.044
Medicare risk	60 (5.93)	85 (4.20)	.035
S-CHIP	1 (0.10)	0 (0.00)	.951
Self-insured	98 (9.69)	172 (8.51)	.280
Unknown	2 (0.20)	3 (0.15)	.752

Abbreviations: CCI, Chronic Condition Indicator; CKD, chronic kidney disease; CTD, chlorthalidone; HCTZ, hydrochlorothiazide; N/A, not applicable; S-CHIP, State Children's Health Insurance Program.
[a]Patients were matched based on these characteristics.

TABLE II. Diuretic Duration and Dose Characteristics in Matched Patients With New-Onset Gout

	Mean	SD	Minimum	Maximum	*P* Value
Days until first occurrence of gout					
CTD	183.6	105.44	21	362	.39
HCTZ	152.7	107.60	22	345	
Dose prescribed at index date, mg					
CTD	22.1	5.47	12.5	25	.45
HCTZ	23.6	21.60	12.5	25	
Last prescribed dose, mg					
CTD	22.8	4.91	12.5	25	.37
HCTZ	25.0	21.21	12.5	25	
Daily dose, mg					
CTD	22.7	4.88	12.5	25	.78
HCTZ	24.3	21.31	12.5	25	

Abbreviations: CTD, chlorthalidone; HCTZ, hydrochlorothiazide; SD, standard deviation.

groups were from the Midwest and South regions of the United States.

New-onset gout manifested later in the CTD group (183.6 days) compared with the HCTZ group (152.7 days), but this difference was not significant (*P*=.39). In addition, there were no significant differences in dose characteristics (Table II). The median diuretic dose prescribed in both groups across all parameters (dose at index date, daily dose, and prior to new-onset gout) was 25 mg.

DISCUSSION

Using the IMS Lifelink database, we compared the incidence of new-onset gout associated with prescribing of CTD vs HCTZ. Overall, there was a very low incidence of new-onset gout associated with prescribing of these two diuretics within our population. The most common prescribed dose throughout the study was 25 mg for both CTD and HCTZ. Although 25 mg of CTD is equivalent to a higher dose (approximately 37.5–50 mg) of HCTZ in terms of antihypertensive effects, there was no significant difference in new-onset gout. The time course of new-onset gout was similar between CTD and HCTZ and occurred approximately 5 to 6 months after initial prescribing. Our population of patients who developed new-onset gout represents a large portion of the US population in regard to average age at onset, male sex, presence of multiple comorbidities, and prominence in the Midwest and South regions.

Long-term morbidity and impairment of quality of life in patients with gout are well defined.[1] Poorly controlled gout is linked to a high utilization of the healthcare system, including emergency department, urgent care, hospital, and outpatient visits.[18–20] In addition, studies have consistently demonstrated a lower quality of life and higher comorbidity burden in patients with poorly controlled gout.[21] It is clinically reasonable and worthwhile to identify patients at risk for gout, or at risk for worsening gout, to target interventions to mitigate the burden of gout. Even though the prevalence of CTD or HCTZ associated with new-onset gout may be low, the overall burden incurred by patients who develop gout is concerning.

Hypertension is an independent comorbidity of gout.[22,23] Treating patients with hypertension who are potentially at risk for gout is further complicated because thiazide diuretics are one of the preferred medication classes for the treatment of hypertension, and yet they have repeatedly been associated with an increased risk of new-onset and worsening gout. However, most studies have observed the increased risk of gout with diuretic use as a broad class effect rather than one that is more of an issue within certain subclasses.[24] The studies that have evaluated differences between diuretic subclasses or differences between individual diuretic agents were based on small sample sizes.[15,25,26] Furthermore, these studies have not commonly adjusted for or excluded factors known to increase or decrease risk of gout, including disease states, comorbidities, and medications.[24]

A prospective population-based cohort from the Atherosclerosis Risk in Communities (ARIC) trial quantified the role of diuretic use in gout development among adults with hypertension.[27] The ARIC cohort trial included patients from four US communities

studied over a 9-year period. Patients were included in the gout analysis if they responded to a series of questions about diuretic use and gout over the course of four office visits, had no history of gout, and had a diagnosis of hypertension. This cohort trial included 2169 patients exposed to a diuretic, which included a thiazide diuretic (n=1212).[27] Thiazide-like diuretics were included in the thiazide group; results did not differentiate the two groups. Among patients exposed to diuretics, 63 (5%) in the thiazide group developed incident gout. Compared with patients not using any diuretic, thiazide diuretic use resulted in an independent increased risk of incident gout in patients with hypertension (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.0–2.1).[28]

Furthermore, Bruderer and colleagues[28] investigated the association between different classes of diuretics, including thiazide and thiazide-like diuretics, and the risk of developing incident gout and also adjusted for confounders using a retrospective case-control database analysis. Patients with an episode of new gout (n=91,530) between 1990 and 2010 were matched with the same number of control patients who did not have a new gout diagnosis. Diuretic exposure was classified as "current users" (last prescription issued 1–180 days prior to gout diagnosis), "past users" (last prescription issued >180 days prior to gout diagnosis), or "nonusers" (no prescription issued throughout study duration). When compared with nonusers, incident gout was significantly increased with current use of thiazide diuretics (OR, 1.7; 95% CI, 1.6–1.8) and thiazide-like diuretics (OR, 2.3; 95% CI, 2.0–2.7).[28]

The ARIC cohort and the investigation by Bruderer and colleagues are well-designed studies that confirmed the risk of gout relative to thiazide diuretics. Similar to our results, Bruderer and colleagues found that risk increased as the duration of diuretic use increased. However, these studies differ from ours in that they did not directly compare new-onset gout incidence between particular agents within a diuretic class. To our knowledge, our study is the first to directly compare gout risk between CTD and HCTZ. The comparison between these two agents is important considering the increasing prevalence of both uncontrolled hypertension and gout.[1,28]

The perceived increase in adverse events with CTD compared with HCTZ may be a likely reason that HCTZ is prescribed at least 20-fold more often than CTD.[29] Results of our initial eligible population prior to matching would suggest that this number is even closer to 40-fold, since we identified 1025 patients who were prescribed CTD vs 39,296 who were prescribed HCTZ. Many patients with uncontrolled hypertension typically also possess risk factors for developing gout including poor lifestyle and multiple comorbidities, particularly CKD. According to our results, as prescribers pursue methods to maximize antihypertensive therapy, the use of CTD as the more potent and superior blood pressure–lowering agent when compared with HCTZ should be considered in eligible patients, even in the presence of gout risk factors. The management of hypertensive patients who also have gout who are prescribed a thiazide diuretic should be guided by clinician judgment that considers patient-specific factors, primarily blood pressure control compared with frequency of acute gouty arthritis.

STUDY LIMITATIONS AND STRENGTHS

There are important limitations to consider when interpreting our results. Many variables were unavailable for study inclusion, including patient racial/ethnic background, body mass index, and lifestyle factors. Reasons for discontinuation of HCTZ or CTD could not be captured. Theoretically, a patient may have experienced an adverse effect unrelated to gout and discontinued the diuretic. If the patient, by chance, later developed gout within the year, they would still be included in the gout cohort. Laboratory values were not available in our database so we could not capture baseline serum urate concentrations or changes associated with CTD or HCTZ prescribing. Some of the comorbidities that we controlled for are typically undercoded or coded incorrectly in healthcare databases, particularly obesity and CKD. We assumed that allopurinol, febuxostat, probenecid, and colchicine were prescribed for gout, which cannot account for the infrequent, yet potential use of these agents for other conditions (eg, colchicine for familial Mediterranean fever). Our study included patients with medical and pharmacy benefit coverage and, therefore, may not be representative of the uninsured population. These limitations are typical of database analyses, which also have strengths including real-world findings in a large, diverse patient population across the United States.

Because of unknown baseline serum concentrations and lifestyle factors, it is possible that our population was at low risk for the development of new-onset gout. This may have limited the number of patients who developed gout in either cohort and, in turn, impeded our ability to detect a difference between CTD and HCTZ. It is also possible that the incidence of gout would increase if the study period were extended beyond 1 year. Still, we believe that our population was representative of the general antihypertensive population and that the baseline demographics align with gout epidemiologic data related to age and the presence of comorbidities.[30] Future studies are needed to further compare the effects of thiazide diuretics in a population stratified by gout risk including patients with an established gout diagnosis and concomitant HCTZ or CTD use.

CONCLUSIONS

Patients prescribed typical doses of CTD for hypertension have a similar risk of developing new-onset gout compared with patients prescribed similar doses of HCTZ. Overall, there was a low incidence of new-onset gout, which was noted after a similar duration of use

with both CTD and HCTZ. These results support more widespread use of CTD for the management of hypertension and suggest that the use of thiazide diuretics in the presence of gout should be based on patient-specific factors and comorbid disease state management.

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