The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 2, 2023 VOL. 388 NO. 9

Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Nasser A. Dhayat, M.D., Olivier Bonny, M.D., Ph.D., Beat Roth, M.D., Andreas Christe, M.D., Alexander Ritter, M.D., Nilufar Mohebbi, M.D., Nicolas Faller, M.D., Ph.D., Lisa Pellegrini, M.D., Giulia Bedino, M.D., Reto M. Venzin, M.D., Philipp Grosse, M.D., Carina Hüsler, M.D., Irene Koneth, M.D., Christian Bucher, M.D., Rosaria Del Giorno, M.D., Luca Gabutti, M.D., Michael Mayr, M.D., Urs Odermatt, M.D., Florian Buchkremer, M.D., Thomas Ernandez, M.D., Catherine Stoermann-Chopard, M.D., Daniel Teta, M.D., Bruno Vogt, M.D., Marie Roumet, Ph.D., Luca Tamò, Ph.D., Grazia M. Cereghetti, Ph.D., Sven Trelle, M.D., and Daniel G. Fuster, M.D.

ABSTRACT

BACKGROUND

Nephrolithiasis is one of the most common conditions affecting the kidney and is characterized by a high risk of recurrence. Thiazide diuretic agents are widely used for prevention of the recurrence of kidney stones, but data regarding the efficacy of such agents as compared with placebo are limited. Furthermore, dose–response data are also limited.

METHODS

In this double-blind trial, we randomly assigned patients with recurrent calcium-containing kidney stones to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily. The main objective was to investigate the dose–response effect for the primary end point, a composite of symptomatic or radiologic recurrence of kidney stones. Radiologic recurrence was defined as the appearance of new stones on imaging or the enlargement of preexisting stones that had been observed on the baseline image. Safety was also assessed.

RESULTS

In all, 416 patients underwent randomization and were followed for a median of 2.9 years. A primary end-point event occurred in 60 of 102 patients (59%) in the placebo group, in 62 of 105 patients (59%) in the 12.5-mg hydrochlorothiazide group (rate ratio vs. placebo, 1.33; 95% confidence interval [CI], 0.92 to 1.93), in 61 of 108 patients (56%) in the 25-mg group (rate ratio, 1.24; 95% CI, 0.86 to 1.79), and in 49 of 101 patients (49%) in the 50-mg group (rate ratio, 0.92; 95% CI, 0.63 to 1.36). There was no relation between the hydrochlorothiazide dose and the occurrence of a primary end-point event (P=0.66). Hypokalemia, gout, new-onset diabetes mellitus, skin allergy, and a plasma creatinine level exceeding 150% of the baseline level were more common among patients who received hydrochlorothiazide than among those who received placebo.

CONCLUSIONS

Among patients with recurrent kidney stones, the incidence of recurrence did not appear to differ substantially among patients receiving hydrochlorothiazide once daily at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily. (Funded by the Swiss National Science Foundation and Inselspital; NOSTONE ClinicalTrials.gov number, NCT03057431.)

The authors' affiliations are listed in the Appendix. Dr. Fuster can be contacted at daniel.fuster@insel.ch or at the Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Freiburgstr. 15, 3010 Bern, Switzerland.

A complete list of collaborators in the NOSTONE trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2023;388:781-91.
DOI: 10.1056/NEJMoa2209275

A Quick Take is available at NEJM.org

Kidney stones are common, and both the prevalence and incidence have increased worldwide in recent decades.[1,2] Kidney stones recur frequently, and they cause enormous health care expenditures, excess illness, and reduced quality of life.[3-5] Most kidney stones are composed of calcium oxalate, calcium phosphate, or a mixture of these components; indeed, hypercalciuria is the most common metabolic abnormality among patients with kidney stones.[6] Thiazide and thiazide-like diuretic agents (collectively referred to as thiazides) have been the cornerstone of pharmacologic prevention of recurrence for more than 50 years.[7-9] Previous studies have suggested that thiazides effectively prevent the recurrence of stones.[10-20] For the most widely prescribed and best studied thiazide, hydrochlorothiazide, daily doses of 50 or 100 mg have been investigated, and once-daily and twice-daily dose regimens have been found to be equally effective.[12,15,17,19,20]

However, previous studies have had methodologic limitations such as inadequate concealment of treatment assignment, a lack of double-blinding, a lack of an intention-to-treat analysis, the use of outdated dietary recommendations, and the use of imaging methods with low sensitivity and specificity.[21,22] Furthermore, only high doses of thiazides were studied; such dose levels are known to increase the risk of adverse effects.[23,24] Thus, both the efficacy of thiazides in the prevention of the recurrence of kidney stones and the dose–response effect remain unclear. We now report the results of the NOSTONE trial, a double-blind, randomized, placebo-controlled trial that was conducted to evaluate a range of hydrochlorothiazide doses for the prevention of the recurrence of kidney stones.

Methods

Trial Oversight and Design

Details of the trial design have been reported previously[22] and are described briefly here. The trial protocol, available with the full text of this article at NEJM.org, was approved by the appropriate regulatory authorities (Swissmedic and the ethics committee at each participating trial center) before the enrollment of any patients. The trial was conducted in accordance with all applicable regulations. All the patients provided written informed consent before participation. Patients were enrolled at 12 centers in Switzerland. The statistical analysis was performed at CTU Bern by a statistician who was unaware of the treatment assignments; subsequently, the analysis was independently checked by a second statistician who was aware of the treatment assignments. The last two authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Key eligibility criteria included an age of 18 years or older, at least two episodes of kidney stones in the past 10 years, and any previous kidney stone that contained at least 50% calcium oxalate, calcium phosphate, or a mixture of both. The trial excluded patients with secondary causes of kidney stones, as well as those who were receiving drugs that could interfere with the formation of kidney stones. Full eligibility criteria are provided in the protocol. During the course of the trial, patients received dietary recommendations for the prevention of kidney stones that were based on current guidelines.[8,9]

Randomization, Treatment, and Follow-up

Patients were randomly assigned in a 1:1:1:1 ratio to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily. The planned duration of treatment was 3 years, except for patients enrolled during the last year of the trial, for whom treatment was planned to last for 2 to 3 years. Randomization was stratified according to the number of episodes of kidney stones each patient had during the 10 years before enrollment in the trial. Randomization lists were generated by an independent statistician at CTU Bern and implemented during the manufacturing of hydrochlorothiazide and placebo to ensure that randomization was concealed and that the investigators, treating physicians, patients, and outcome assessors were unaware of the treatment assignments. Patients received drug packs that appeared identical across all groups, and each pack contained 90 capsules that appeared identical; patients were advised to take one capsule by mouth daily in the morning.

At the time of randomization, patients underwent a low-dose computed tomographic (CT) study, performed without the administration of intravenous contrast material, that was limited

to the kidneys. All the patients had a clinical follow-up visit 3 months after randomization and yearly thereafter, as well as a telephone visit every 3 months. The maximum planned follow-up was 3 years. Symptomatic recurrence of kidney stones was assessed at both the in-person follow-up visits and during the telephone visits. Radiologic recurrence (as defined below) was assessed at the end of treatment with the use of a second low-dose CT study of the kidneys that was performed without the administration of intravenous contrast material.

END POINTS

The main trial objective was to investigate the dose–response effect for the primary end point, a composite of symptomatic or radiologic recurrence of kidney stones. Symptomatic recurrence was defined as the visible passage of a stone with or without accompanying typical symptoms (such as flank or loin pain and hematuria) or as the presence of a symptomatic or asymptomatic stone that was determined to require surgical removal. If a patient had symptoms during the trial that were suggestive of a possible stone passage but no visible stone had been observed, local investigators evaluated the symptoms of the patient and judged whether a stone passage had occurred. Radiologic recurrence was defined as the appearance of new stones on CT or the enlargement of preexisting stones that had been observed on the baseline CT; details are provided in the protocol.

Secondary end points were the individual end points of symptomatic recurrence and radiologic recurrence, as well as changes in laboratory variables. Urine relative supersaturation ratios, which indicate the degree by which the concentration of calcium oxalate or calcium phosphate in urine exceeds the equilibrium solubility, were calculated with the use of EQUIL2 software.[25] Safety assessments included monitoring of adverse events and clinical laboratory testing, as specified in the protocol.

STATISTICAL ANALYSIS

The null hypothesis was that there would be no relation (i.e., no significant linear trend) between the hydrochlorothiazide dose and the symptomatic or radiologic recurrence of kidney stones. We estimated that a sample of 416 patients (104 patients in each group) would provide the trial with at least 80% power, at a two-sided alpha level of 0.05, using an unweighted log-rank test for trend, on the basis of the following assumptions: uniform enrollment over a period of 2 years, follow-up of 2 to 3 years, a cumulative dropout rate of 10%, and a risk of symptomatic or radiologic recurrence in the placebo group of 0.20 at 12 months and 0.45 at 36 months, with rate ratios of 0.90, 0.65, and 0.50 for the 12.5-mg, 25-mg, and 50-mg hydrochlorothiazide doses, respectively.[12,15,17,19]

Efficacy was evaluated in the intention-to-treat population, which comprised all patients who underwent randomization. Analyses were stratified according to the number of episodes of kidney stones within 10 years before randomization. For the primary end point, we also performed a per-protocol analysis, in which patients were considered to continue receiving their assigned doses until discontinuation of the therapy became medically indicated. The analysis was based on inverse probability of censoring weighting to recreate an unbiased scenario.[26,27] To analyze the dose–response effect between the hydrochlorothiazide dose and the primary end point, we used a log-rank test for dose effect. For this test, the null hypothesis was that there was no dose effect, and the alternative hypothesis was that the dose effect followed a rank ordering, in which the ranks were 0, 1, 2, and 3, corresponding to doses of 0 (i.e., placebo), 12.5, 25, and 50 mg, respectively. Rate ratios in each dose group as compared with placebo were calculated with the use of the Mantel–Cox method. Subgroup analyses were used to investigate whether characteristics of the patients at baseline modified the treatment effect. Symptomatic recurrence was analyzed in a manner similar to that used for the primary end point. Radiologic recurrence was analyzed as a binary end point with the use of logistic regression, and it incorporated the timing of CT assessment. Changes in laboratory measurements during the trial were analyzed as repeated measurements with the use of a mixed-effects model. Adverse events and safety laboratory variables were assessed in the safety population, which included all patients who underwent randomization and received at least one dose of hydrochlorothiazide or placebo.

Confidence intervals reflected uncertainty in the group-specific estimates and were not adjusted for multiplicity; therefore, they should not

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=416)	Placebo (N=102)	12.5-mg Hydrochlorothiazide (N=105)	25-mg Hydrochlorothiazide (N=108)	50-mg Hydrochlorothiazide (N=101)
Median age (IQR) — yr	49 (39–55)	47 (35–55)	49 (40–57)	48 (39–56)	50 (42–55)
Female sex — no. (%)	85 (20)	26 (25)	16 (15)	22 (20)	21 (21)
Race — no. (%)†					
White	411 (99)	100 (98)	105 (100)	106 (98)	100 (99)
Black	2 (<1)	0	0	1 (1)	1 (1)
Asian	2 (<1)	1 (1)	0	1 (1)	0
Other	1 (<1)	1 (1)	0	0	0
No. of stone events in the past 10 yr — no. (%)‡					
2 or 3	277 (67)	70 (69)	68 (65)	73 (68)	66 (65)
≥4	139 (33)	32 (31)	37 (35)	35 (32)	35 (35)
Median urinary calcium excretion (IQR) — mg/24 hr§¶	244 (165–340)	257 (157–339)	239 (164–317)	256 (167–369)	238 (168–338)
Hypercalciuria — no./total no. (%)‖	258/408 (63)	60/101 (59)	63/103 (61)	69/104 (66)	66/100 (66)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race was determined by the investigators.
‡ The median number of stone events in the past 10 years in all four groups was 3 (IQR, 2 to 4).
§ To convert the values for urinary calcium excretion from milligrams per 24 hours to millimoles per 24 hours, divide by 40.
¶ Data were missing for eight patients (for one in the placebo group, for two in the 12.5-mg hydrochlorothiazide group, for four in the 25-mg hydrochlorothiazide group, and for one in the 50-mg hydrochlorothiazide group).
‖ Hypercalciuria was defined as a urinary calcium excretion of more than 200 mg per 24 hours.

be interpreted as hypothesis tests that are applied to each group separately. Full details regarding the statistical analyses are provided in the statistical analysis plan (which is available with the protocol) and in the Supplementary Appendix (available at NEJM.org), which also provides additional results of the trial.

RESULTS

PATIENTS

Between March 30, 2017, and October 31, 2019, a total of 1335 patients underwent screening (Fig. S1 in the Supplementary Appendix); of these, 416 met eligibility criteria, provided written informed consent, and were randomly assigned to receive 12.5-mg (105 patients), 25-mg (108 patients), or 50-mg (101 patients) doses of hydrochlorothiazide once daily or placebo once daily (102 patients). The demographic and clinical characteristics of the patients were well balanced across the trial groups at baseline (Table 1 and Table S1). The median age of the patients was 49 years (interquartile range, 39 to 55), and 85 patients (20%) were women. The median number of events of kidney stones during the 10 years before randomization was 3 (interquartile range, 2 to 4), and 139 patients (33%) had had 4 or more stone events during the 10 years before randomization. Baseline laboratory test results in blood and urine are shown in Tables 1 and 2. At baseline, 258 patients (63%) had hypercalciuria, which was defined as a urinary calcium excretion rate of more than 200 mg in 24 hours.

ADHERENCE AND FOLLOW-UP

The median duration of follow-up was 2.9 years (interquartile range, 2.0 to 3.0), and 387 patients (93%) completed follow-up as planned. Nonadherence, which was defined as missing more than 20% of the daily doses of hydrochlorothiazide or placebo on the basis of patient report, was 26% (27 patients, of whom 12 did not ad-

Table 2. Laboratory Test Results in Urine at Baseline and during Follow-up.*

Variable	Baseline		Follow-up		Effect vs. Placebo (95% CI)
	No. of Patients	Mean	No. of Assessments	Mean	
Total urine volume — liters/24 hr					
Placebo	101	1.74±0.80	252	2.06±0.74	Reference
12.5-mg Hydrochlorothiazide	103	1.90±0.74	267	2.12±0.75	−0.01 (−0.16 to 0.13)
25-mg Hydrochlorothiazide	104	1.93±0.82	277	2.15±0.80	0.07 (−0.09 to 0.22)
50-mg Hydrochlorothiazide	100	1.68±0.66	245	2.06±0.68	0.05 (−0.10 to 0.19)
Urinary sodium excretion — mmol/24 hr					
Placebo	101	170.82±76.95	252	183.16±81.91	Reference
12.5-mg Hydrochlorothiazide	103	179.65±85.04	267	181.89±79.69	−4.32 (−19.81 to 11.18)
25-mg Hydrochlorothiazide	104	197.06±85.65	277	191.80±83.87	−0.37 (−16.87 to 16.13)
50-mg Hydrochlorothiazide	100	168.93±71.63	245	198.58±81.34	15.67 (−0.72 to 32.07)
Urinary calcium excretion — mg/24 hr					
Placebo	101	256.90±124.66	252	277.46±137.07	Reference
12.5-mg Hydrochlorothiazide	103	256.15±132.02	267	231.96±119.53	−42.01 (−68.05 to −15.97)
25-mg Hydrochlorothiazide	104	280.69±159.96	277	232.52±156.80	−40.54 (−67.88 to −13.21)
50-mg Hydrochlorothiazide	100	274.39±154.14	245	236.82±139.19	−51.13 (−78.87 to −23.39)
Urinary citrate excretion — mg/24 hr					
Placebo	101	575.28±326.39	252	588.74±314.08	Reference
12.5-mg Hydrochlorothiazide	103	530.00±267.89	267	588.38±328.68	32.20 (−20.26 to 84.66)
25-mg Hydrochlorothiazide	104	522.16±246.10	276	520.57±292.50	−8.47 (−58.75 to 41.81)
50-mg Hydrochlorothiazide	100	554.09±288.86	245	536.51±309.71	−36.28 (−85.48 to 12.92)
Urinary oxalate excretion — mg/24 hr					
Placebo	101	30.02±18.41	252	34.98±20.60	Reference
12.5-mg Hydrochlorothiazide	103	29.92±17.33	267	37.24±19.63	2.62 (−1.47 to 6.71)
25-mg Hydrochlorothiazide	104	29.90±18.55	276	39.58±24.08	4.68 (0.25 to 9.11)
50-mg Hydrochlorothiazide	100	28.39±13.52	245	34.98±20.52	0.12 (−4.09 to 4.34)
Urine relative supersaturation ratio, calcium oxalate†					
Placebo	100	7.92±5.25	244	7.93±6.19	Reference
12.5-mg Hydrochlorothiazide	102	6.96±4.10	256	6.65±4.19	−0.7 (−1.67 to 0.26)
25-mg Hydrochlorothiazide	104	6.74±3.80	266	7.18±6.05	−0.28 (−1.42 to 0.86)
50-mg Hydrochlorothiazide	98	8.12±4.40	236	6.80±6.86	−1.23 (−2.49 to 0.02)
Urine relative supersaturation ratio, calcium phosphate†					
Placebo	100	2.70±2.76	244	2.52±2.55	Reference
12.5-mg Hydrochlorothiazide	102	2.42±2.58	256	1.83±2.19	−0.54 (−1.04 to −0.04)
25-mg Hydrochlorothiazide	104	2.27±1.70	266	2.00±2.16	−0.38 (−0.85 to 0.10)
50-mg Hydrochlorothiazide	98	2.80±2.62	236	2.21±2.39	−0.38 (−0.85 to 0.10)

* Plus–minus values are means ±SD. To convert the values for urinary calcium excretion from milligrams per 24 hours to millimoles per 24 hours, divide by 40. To convert the values for urinary citrate excretion from milligrams per 24 hours to millimoles per 24 hours, divide by 192. To convert the values for urinary oxalate excretion from milligrams per 24 hours to micromoles per 24 hours, multiply by 11.36. CI denotes confidence interval.

† Urine relative supersaturation ratios indicate the degree by which the concentration of calcium oxalate or calcium phosphate in urine exceeds the equilibrium solubility.

here to the regimen for nonmedical reasons) in the placebo group, 15% (16 patients, of whom 3 had nonmedical reasons) in the 12.5-mg hydrochlorothiazide group, 24% (26 patients, of whom 13 had nonmedical reasons) in the 25-mg hydrochlorothiazide group, and 26% (26 patients, of whom 10 had nonmedical reasons) in the 50-mg hydrochlorothiazide group.

PRIMARY END POINT

In the placebo group, 60 of 102 patients (59%) had symptomatic or radiologic recurrence of kidney stones. A primary end-point event occurred in 62 of 105 patients (59%) in the 12.5-mg hydrochlorothiazide group (rate ratio vs. placebo, 1.33; 95% confidence interval [CI], 0.92 to 1.93), in 61 of 108 patients (56%) in the 25-mg hydrochlorothiazide group (rate ratio, 1.24; 95% CI, 0.86 to 1.79), and in 49 of 101 patients (49%) in the 50-mg hydrochlorothiazide group (rate ratio, 0.92; 95% CI, 0.63 to 1.36) (Fig. 1A and Table S2). We found no evidence of a relation between the hydrochlorothiazide dose and the occurrence of a primary end-point event (rate ratio for trend, 0.98; 95% CI, 0.87 to 1.09; test for trend, P=0.66). These results were confirmed by sensitivity analyses (Tables S3 through S6 and Fig. S2). Subgroup analyses showed no evidence of heterogeneity of the dose–response effect (Fig. 2). In the per-protocol analysis, we observed no evidence of a relation between the hydrochlorothiazide dose and the occurrence of a primary end-point event (rate ratio for trend, 0.98; 95% CI, 0.88 to 1.09) (Table S7).

SECONDARY END POINTS

Symptomatic recurrence of kidney stones occurred in 35 of 102 patients (34%) in the placebo group, in 40 of 105 patients (38%) in the 12.5-mg hydrochlorothiazide group (rate ratio vs. placebo, 1.23; 95% CI, 0.78 to 1.95), in 43 of 108 patients (40%) in the 25-mg hydrochlorothiazide group (rate ratio, 1.26; 95% CI, 0.81 to 1.97), and in 28 of 101 patients (28%) in the 50-mg hydrochlorothiazide group (rate ratio, 0.84; 95% CI, 0.51 to 1.38) (Fig. 1B and Table S9). These findings were confirmed by a sensitivity analysis (Table S10).

Radiologic recurrence of kidney stones (the binary secondary end point) occurred in 46 of 94 patients (49%) in the placebo group, in 44 of 98 patients (45%) in the 12.5-mg hydrochlorothiazide group (odds ratio vs. placebo, 0.85; 95% CI, 0.48 to 1.50), in 32 of 101 patients (32%) in the 25-mg hydrochlorothiazide group (odds ratio, 0.49; 95% CI, 0.27 to 0.87), and in 31 of 90 patients (34%) in the 50-mg hydrochlorothiazide group (odds ratio, 0.54; 95% CI, 0.29 to 0.98) (Fig. 1C and Table S12). Among patients who had radiologic recurrence, 67 new stones were detected on CT in 94 patients in the placebo group, 59 new stones in 98 patients in the 12.5-mg hydrochlorothiazide group (rate ratio vs. placebo, 0.84; 95% CI, 0.48 to 1.47), 45 new stones in 101 patients in the 25-mg hydrochlorothiazide group (rate ratio, 0.61; 95% CI, 0.34 to 1.09), and 46 new stones in 90 patients in the 50-mg hydrochlorothiazide group (rate ratio, 0.72; 95% CI, 0.40 to 1.29) (Table S13).

Treatment effects on laboratory measurements in urine and blood are shown in Table 2 and Tables S14 and S15. Patients who had been assigned to receive hydrochlorothiazide had lower urinary calcium excretion than those who had been assigned to receive placebo; however, the urine relative supersaturation ratios for calcium oxalate and calcium phosphate in the hydrochlorothiazide groups were not consistently lower than those in the placebo group.

SAFETY

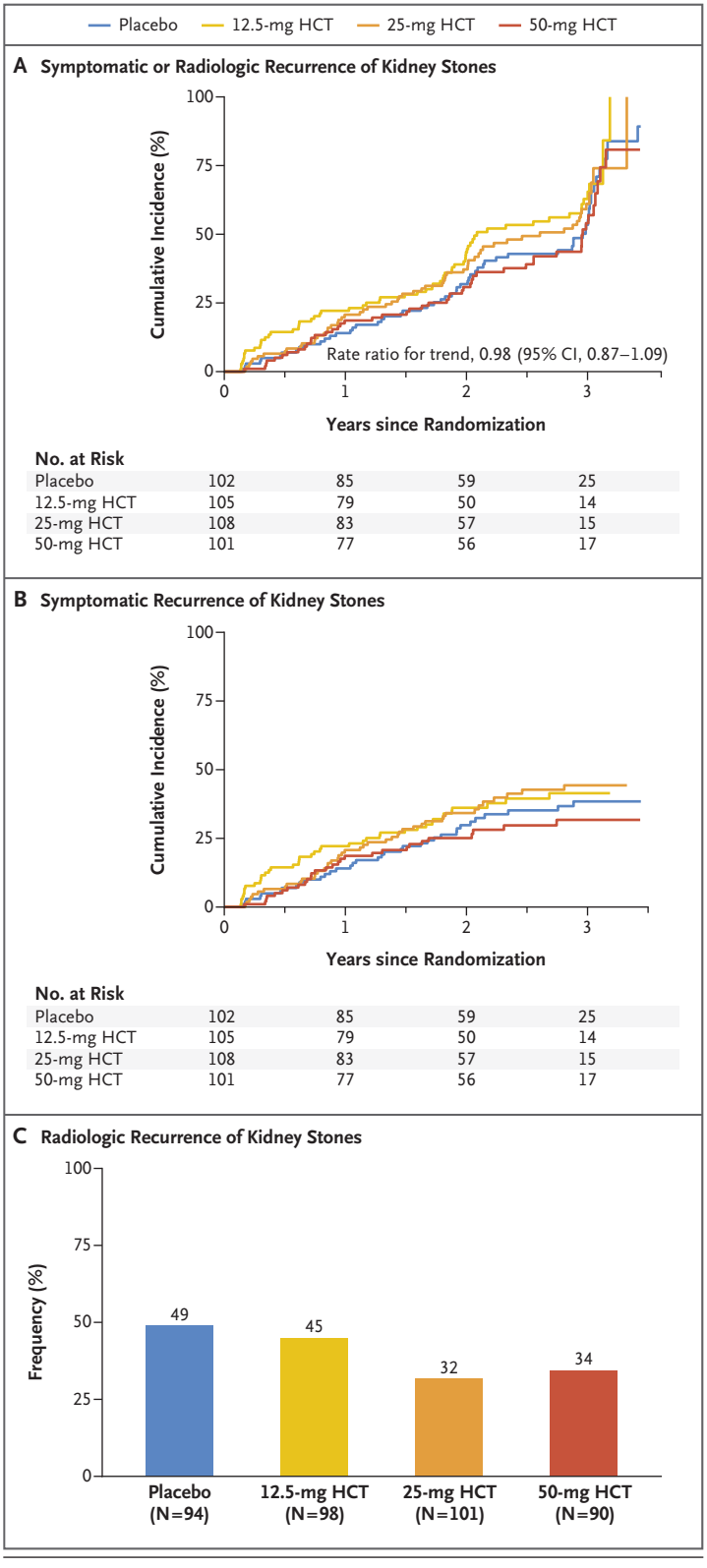
New-onset diabetes mellitus, hypokalemia, gout, skin allergy, and a plasma creatinine level exceeding 150% of the baseline level were more common among patients in the hydrochlorothiazide groups than among those in the placebo group (Table 3 and Table S16). The incidence of serious adverse events was not higher among patients receiving hydrochlorothiazide than among those receiving placebo.

DISCUSSION

In this double-blind trial, 416 patients with recurrent calcium-containing kidney stones were randomly assigned to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily and were followed for a median of 2.9 years. We were not able to confirm our hypothesis; we observed no relation between the hydrochlorothiazide dose and the

Figure 1. Primary End Point and Key Secondary End Points.

The primary end point was a composite of symptomatic or radiologic recurrence of kidney stones. Radiologic recurrence was defined as the appearance of new stones on computed tomography (CT) or the enlargement of preexisting stones that had been observed on the baseline CT. Panel A shows the cumulative incidence of primary end-point events. The rate ratio for trend and associated confidence interval were calculated with the use of the Mantel–Cox method. The P value, which was calculated with the use of a log-rank test for trend, was 0.66. Key secondary end points were symptomatic recurrence and radiologic recurrence of kidney stones; the latter end point was analyzed as a binary end point, a composite of the appearance of new stones on CT or the enlargement of preexisting stones. Panel B shows the cumulative incidence of symptomatic recurrence of kidney stones. In Panels A and B, events that occurred during the first 6 weeks after randomization were excluded, and curves were truncated at the maximum follow-up time. Panel C shows the observed frequencies of radiologic recurrence of kidney stones. HCT denotes hydrochlorothiazide.



primary end point, a composite of symptomatic or radiologic recurrence of kidney stones. The incidence of recurrence was similar across the 12.5-mg, 25-mg, and 50-mg hydrochlorothiazide groups and the placebo group. The trial was adequately powered; the enrollment target of 416 patients was met. Furthermore, the dropout rate was lower than expected (10% expected vs. 7% observed), and the percentage of patients with a primary end-point event in the placebo group was higher than expected (45% expected vs. 59% observed).

Symptomatic recurrence was similar across all four groups. These results were confirmed by several sensitivity analyses, including an analysis that was restricted to patients who had not had kidney stones at baseline and analyses in which symptomatic events that had occurred within the first 6 or 12 months after randomization were excluded to allow for a washout period for preexisting stones. The incidence of radiologic recurrence, a composite of stone growth or new stone formation, was lowest among patients receiving the 25-mg or 50-mg dose of hydrochlorothiazide.

Thiazides reduce urinary calcium excretion, and their purported efficiency in the prevention

Subgroup	No. of Events/Total No.	Rate Ratio (95% CI)	Rate Ratio for Trend
No. of stone events in the past 10 yr			
2 or 3			
Placebo	38/70		0.92 (0.80–1.07)
12.5-mg HCT	37/68	1.34 (0.84–2.14)	
25-mg HCT	37/73	1.05 (0.66–1.66)	
50-mg HCT	26/66	0.78 (0.47–1.30)	
≥4			
Placebo	22/32		1.05 (0.88–1.25)
12.5-mg HCT	25/37	1.33 (0.73–2.41)	
25-mg HCT	24/35	1.68 (0.91–3.09)	
50-mg HCT	23/35	1.18 (0.64–2.16)	
Hypercalciuria			
No			
Placebo	23/41		0.95 (0.78–1.14)
12.5-mg HCT	24/40	1.46 (0.79–2.71)	
25-mg HCT	21/35	1.68 (0.88–3.19)	
50-mg HCT	13/34	0.68 (0.32–1.43)	
Yes			
Placebo	37/60		0.99 (0.84–1.07)
12.5-mg HCT	36/63	1.19 (0.74–1.93)	
25-mg HCT	38/69	1.13 (0.71–1.79)	
50-mg HCT	35/66	1.01 (0.63–1.48)	
Stone composition			
>50% Calcium oxalate			
Placebo	53/89		0.95 (0.84–1.07)
12.5-mg HCT	56/94	1.47 (0.99–2.18)	
25-mg HCT	56/100	1.30 (0.88–1.93)	
50-mg HCT	38/87	0.84 (0.55–1.28)	
>50% Calcium phosphate			
Placebo	7/12		1.23 (0.83–1.82)
12.5-mg HCT	5/10	0.35 (0.07–1.75)	
25-mg HCT	3/5	0.95 (0.21–4.31)	
50-mg HCT	8/11	1.96 (0.73–5.52)	
Any stone at baseline			
No			
Placebo	13/26		0.99 (0.77–1.27)
12.5-mg HCT	14/29	1.33 (0.59–2.97)	
25-mg HCT	15/39	1.05 (0.49–2.25)	
50-mg HCT	13/33	1.00 (0.44–2.23)	
Yes			
Placebo	46/71		1.00 (0.87–1.14)
12.5-mg HCT	44/69	1.27 (0.83–1.96)	
25-mg HCT	44/64	1.40 (0.91–2.17)	
50-mg HCT	34/57	0.93 (0.59–1.47)	

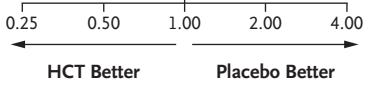


Figure 2. Subgroup Analyses of Symptomatic or Radiologic Recurrence of Kidney Stones.

Subgroup analyses were used to investigate whether disease severity, the presence of hypercalciuria, and the composition of stones at baseline may modify the expected treatment effect. The analysis was performed in each subgroup as it was performed in the primary analysis. The rate ratio for trend is a ratio of rate ratios. It indicates the difference (on a multiplicative scale) in treatment effect for a one-unit increase of one dose group (e.g., a ratio of 0.92 indicates that an increase in dose by one group results in a treatment effect [rate ratio] that is 0.92 times the effect of the lower dose group). At randomization, eight patients had stones that were composed of 50% calcium oxalate and 50% calcium phosphate. Because these patients could not be unequivocally classified and a subgroup comprising these patients would be too small for analysis, the patients were excluded from the subgroup analysis of stone composition. Arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale.

Table 3. Adverse Events during the Treatment Period.

Event	Placebo (N=102)		12.5-mg Hydrochlorothiazide (N=105)		25-mg Hydrochlorothiazide (N=108)		50-mg Hydrochlorothiazide (N=101)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*
Selected adverse events of special interest*								
Total	8 (8)	8	11 (10)	12	18 (17)	21	16 (16)	20
Hypokalemia	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
Gout	0	0	1 (1)	1	1 (1)	2	0	0
New-onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
Serious adverse event	30 (29)	34	17 (16)	18	24 (22)	27	14 (14)	16

* Adverse events of special interest included hypokalemia (defined as a potassium level of <3 mmol per liter), hyponatremia (defined as a sodium level of <125 mmol per liter), hypomagnesemia (defined as a magnesium level of <0.5 mmol per liter), a plasma creatinine level of more than 150% of the baseline level, gout (defined as >3 episodes per year or the receipt of uric acid–lowering therapy), new-onset diabetes mellitus, and skin allergy.

of stone recurrence has been attributed mainly to this unique property. The findings in our trial were consistent with this concept; patients receiving hydrochlorothiazide had decreased urinary calcium excretion. However, urine relative supersaturation ratios for calcium oxalate and calcium phosphate — values that are used as established proxies for the risk of formation of calcium-containing stones and incorporate the key stone promoters and inhibitors that are measured in clinical routine — were not lower among patients receiving hydrochlorothiazide than among those receiving placebo. Urinary citrate excretion tended to be lower among patients receiving hydrochlorothiazide than among those receiving placebo, and there was an increase from baseline in urinary oxalate excretion in all four groups. The differences in citrate and oxalate excretion between the hydrochlorothiazide groups and the placebo group may have counteracted the observed lower urinary calcium excretion that was induced by hydrochlorothiazide, thus resulting in no evident differences among patients receiving hydrochlorothiazide and those receiving placebo with respect to relative supersaturation ratios.

The overall frequency of adverse events was similar in the four groups, but hypokalemia, gout, new-onset diabetes mellitus, skin allergy, and a plasma creatinine level exceeding 150% of the baseline level were more common among patients receiving hydrochlorothiazide than among patients receiving placebo. These results arouse concerns about the long-term use of hydrochlorothiazide for the prevention of kidney stones.

Strengths of our trial include the prospective, double-blind, multicenter design; the large sample size; and the yearly in-person follow-up visits, supplemented by telephone visits. Common biases in clinical trials (e.g., selection and attrition bias or performance bias) and underreporting of symptomatic recurrences are therefore very unlikely. We used highly sensitive and specific imaging, which adds an additional diagnostic layer that nearly eliminates the possibility of underdetection of primary end-point events. The end points that were chosen include the most clinically meaningful one (symptomatic recurrence) and the most sensitive one (radiologic recurrence); together, they provide a comprehensive view of any potentially relevant effects. Finally, the investigated drug therapy was accompanied by dietary counseling according to current guidelines.[8,9]

Our trial has limitations of importance for translating the results into clinical practice (Table S17). The trial had an underrepresentation of women, and most of the patients were White. Still, the prevalence of kidney stones is by far the

highest among White men.[28] The trial therefore directly informs treatment decisions for the most affected population. The median duration of the trial was close to 3 years, but we cannot rule out the possibility that hydrochlorothiazide has an effect on stone formation only after a longer treatment period. Indeed, the analysis of radiologic recurrence showed that patients receiving the 25-mg and 50-mg doses of hydrochlorothiazide had the lowest occurrence of the composite of stone growth or new stone formation. To investigate this finding further, we tested the effect of the dose of hydrochlorothiazide on the primary end point in two sensitivity analyses: the first analysis included only patients who had not had kidney stones at baseline, and the second included only events that had occurred after 6 or 12 months of treatment. Similar to the main analysis, these additional analyses did not reveal any marked effect. Given the observed lack of effect on symptomatic recurrence, any effect of hydrochlorothiazide treatment after 3 years of follow-up would need to be dramatic to be able to show a significant difference between the hydrochlorothiazide groups and the placebo group with respect to the primary end point if the duration of the trial would have been extended by 1 or 2 years — an unlikely scenario for a pharmacologic treatment. This notion is supported by the lack of effect of hydrochlorothiazide treatment on symptomatic recurrence in patients who had not had kidney stones at baseline and on the formation of new stones that were identified on imaging during follow-up.

We performed a per-protocol analysis to investigate whether there was a dose effect among patients who adhered to the protocol. The similarity of the results of the intention-to-treat analysis and the per-protocol analysis provides evidence that treatment discontinuations that were not medically indicated cannot explain the results. Nevertheless, the high incidence of nonadherence may have biased the treatment effects in favor of the null hypothesis. Similarly, the high fluid and sodium intake during follow-up, as well as the increase from baseline in urinary oxalate excretion, may have diminished a potential beneficial treatment effect. Whether our results also apply to longer-acting thiazides remains to be determined.

The results of our trial show that treatment with hydrochlorothiazide did not appear to differ substantially from placebo in preventing the recurrence of kidney stones in patients at high risk for recurrence.

Supported by the Swiss National Science Foundation (grant 33IC30_166785) and Inselspital, Bern University Hospital, University of Bern.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participating patients and their families, the NOSTONE trial team for their contributions, and advisory committee members Rudolf Wüthrich, Bernhard Hess, and Dominik Uehlinger for their input.

APPENDIX

The authors' affiliations are as follows: the Departments of Nephrology and Hypertension (N.A.D., N.F., B.V., L.T., G.M.C., D.G.F.), Urology (B.R.), and Radiology (A.C.), Inselspital, Bern University Hospital, and CTU Bern (M.R., S.T.), University of Bern, Bern, Service of Nephrology, Lausanne University Hospital, University of Lausanne, Lausanne (O.B.), the Department of Nephrology, University Hospital Zurich, Zurich (A.R., N.M.), the Department of Nephrology, Regional Hospital Lugano (L.P., G.B.), and Università della Svizzera Italiana (R.D.G., L.G.), Lugano, the Department of Nephrology, Cantonal Hospital Graubünden, Chur (R.M.V., P.G.), the Department of Nephrology and Transplantation Medicine, Cantonal Hospital St. Gallen, St. Gallen (C.H., I.K., C.B.), the Department of Internal Medicine, Regional Hospital of Bellinzona, Bellinzona (R.D.G., L.G.), the Medical Outpatient Department, University Hospital Basel, University of Basel, Basel (M.M.), the Department of Nephrology, Luzerner Kantonsspital LUKS, Lucerne (U.O.), the Division of Nephrology, Dialysis, and Transplantation, Cantonal Hospital Aarau, Aarau (F.B.), the Department of Nephrology, University Hospital Geneva, University of Geneva, Geneva (T.E., C.S.-C.), and the Nephrology Service, Centre Hospitalier du Valais Romand, Sion (D.T.) — all in Switzerland.

REFERENCES

1. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol 2010;12(2-3):e86-e96.
2. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol 2012;62:160-5.
3. Ferraro PM, Curhan GC, D'Addessi A, Gambaro G. Risk of recurrence of idiopathic calcium kidney stones: analysis of data from the literature. J Nephrol 2017;30:227-33.
4. New F, Somani BK. A complete world literature review of quality of life (QOL) in patients with kidney stone disease (KSD). Curr Urol Rep 2016;17:88.
5. Saigal CS, Joyce G, Timilsina AR, Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int 2005;68:1808-14.
6. Gambaro G, Croppi E, Coe F, et al. Metabolic diagnosis and medical prevention of calcium nephrolithiasis and its systemic manifestations: a consensus statement. J Nephrol 2016;29:715-34.
7. Yendt ER, Guay GF, Garcia DA. The use of thiazides in the prevention of re-

nal calculi. Can Med Assoc J 1970;102:614-20.
8. Türk C, Petřík A, Sarica K, et al. EAU guidelines on interventional treatment for urolithiasis. Eur Urol 2016;69:475-82.
9. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.
10. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol 1993;22:Suppl 6:S78-S86.
11. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol 1988;139:679-84.
12. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis: a double-blind study in general practice. Acta Med Scand 1984;215:383-9.
13. Mortensen JT, Schultz A, Ostergaard AH. Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. Int Urol Nephrol 1986;18:265-9.
14. Ohkawa M, Tokunaga S, Nakashima T, Orito M, Hisazumi H. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. Br J Urol 1992;69:571-6.
15. Wilson DR, Strauss AL, Manuel MA. Comparison of medical treatments for the prevention of recurrent calcium nephrolithiasis. Urol Res 1984;12:39-40.
16. Robertson WG, Peacock M, Selby PL, et al. A multicentre trial to evaluate three treatments for recurrent idiopathic calcium stone disease — a preliminary report. In: Schwille PO, Smith LW, Robertson WG, Vahlensieck W, eds. Urolithiasis and related clinical research. New York: Springer, 1985:545-8.
17. Fernández-Rodríguez A, Arrabal-Martín M, García-Ruiz MJ, Arrabal-Polo MA, Pichardo-Pichardo S, Zuluaga-Gómez A. Papel de las tiazidas en la profilaxis de la litiasis cálcica recidivante. Actas Urol Esp 2006;30:305-9.
18. Brocks P, Dahl C, Wolf H, Transbøl I. Do thiazides prevent recurrent idiopathic renal calcium stones? Lancet 1981;2:124-5.
19. Ahlstrand C, Sandvall K, Tiselius HG. Prophylactic treatment of calcium stone formers with hydrochlorothiazide and magnesium. Edsbruk, Sweden: Akademitryck, 1996.
20. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. J Urol 1982;128:903-7.
21. Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians clinical guideline. Ann Intern Med 2013;158:535-43.
22. Dhayat NA, Faller N, Bonny O, et al. Efficacy of standard and low dose hydrochlorothiazide in the recurrence prevention of calcium nephrolithiasis (NOSTONE trial): protocol for a randomized double-blind placebo-controlled trial. BMC Nephrol 2018;19:349.
23. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. Hypertension 2012;59:1104-9.
24. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2004;43:4-9.
25. Werness PG, Brown CM, Smith LH, Finlayson B. EQUIL2: a BASIC computer program for the calculation of urinary saturation. J Urol 1985;134:1242-4.
26. Grafféo N, Latouche A, Le Tourneau C, Chevret S. ipcwswitch: an R package for inverse probability of censoring weighting with an application to switches in clinical trials. Comput Biol Med 2019;111:103339.
27. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.
28. Chewcharat A, Curhan G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. Urolithiasis 2021;49:27-39.