# Thiazides and Kidney Disease

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# Outline

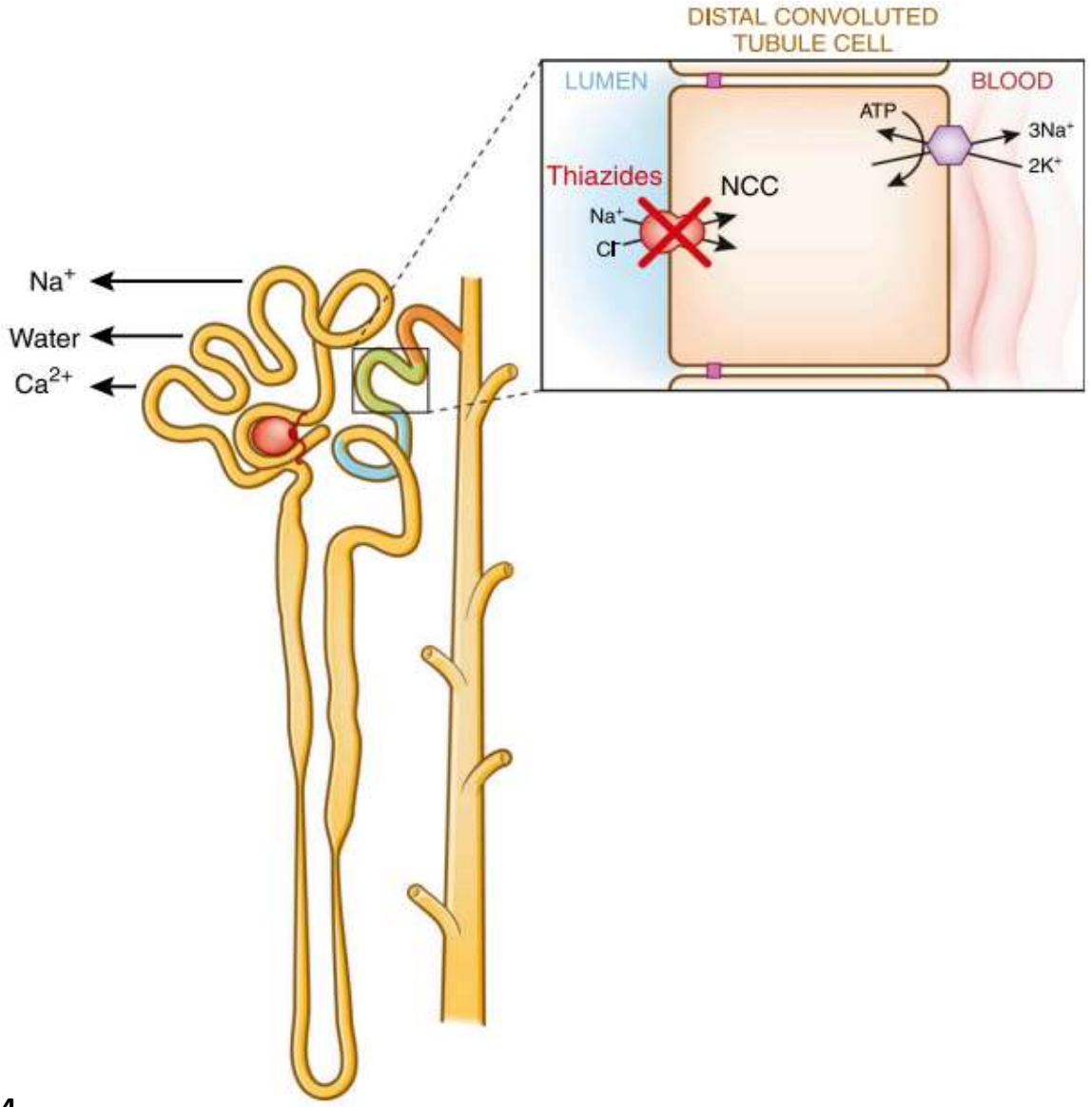
- Introduction
- Renal physiology
- Evidence
- Current guidelines and treatment recommendations
  - Blood pressure/volume
  - Nephrolithiasis/hypercalciuria

# Introduction

- Thiazides induce natriuresis and subsequently increased water excretion by inhibiting the NCC channel in the distal convoluted tubule
- FDA approved indications for Thiazide diuretics include hypertension and edema
- Often prescribed (off-label) for prevention of kidney stones
- Sometimes used (off-label) to increase bone mass/mineralization in patients with hypercalciuria and bone loss

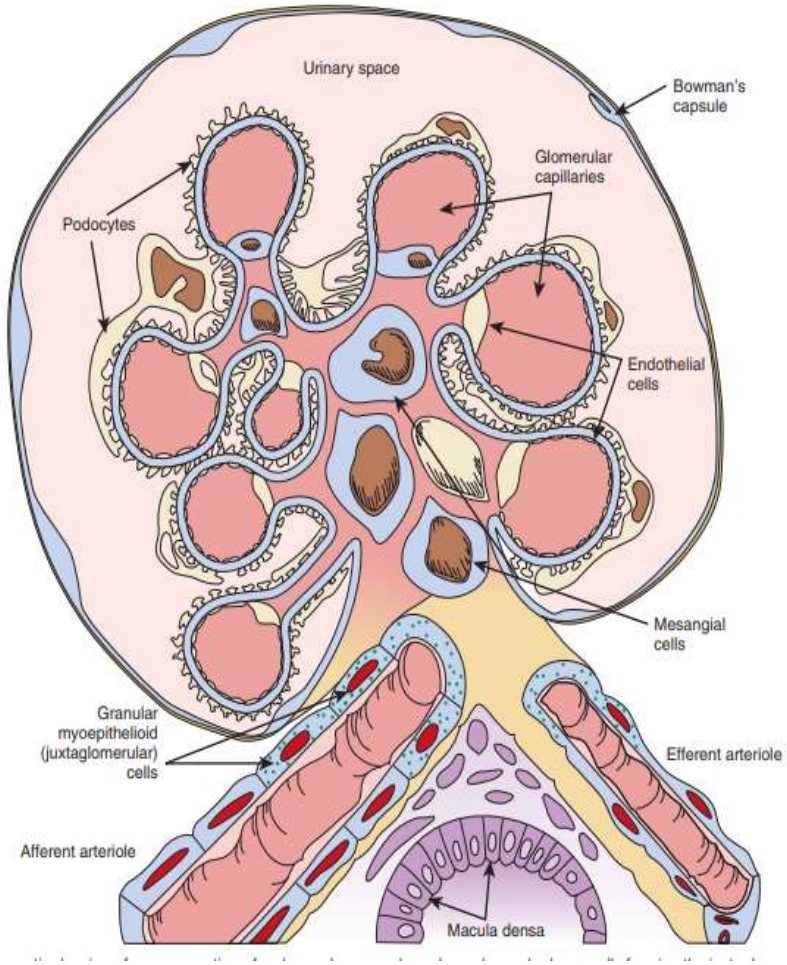
# Renal Physiology

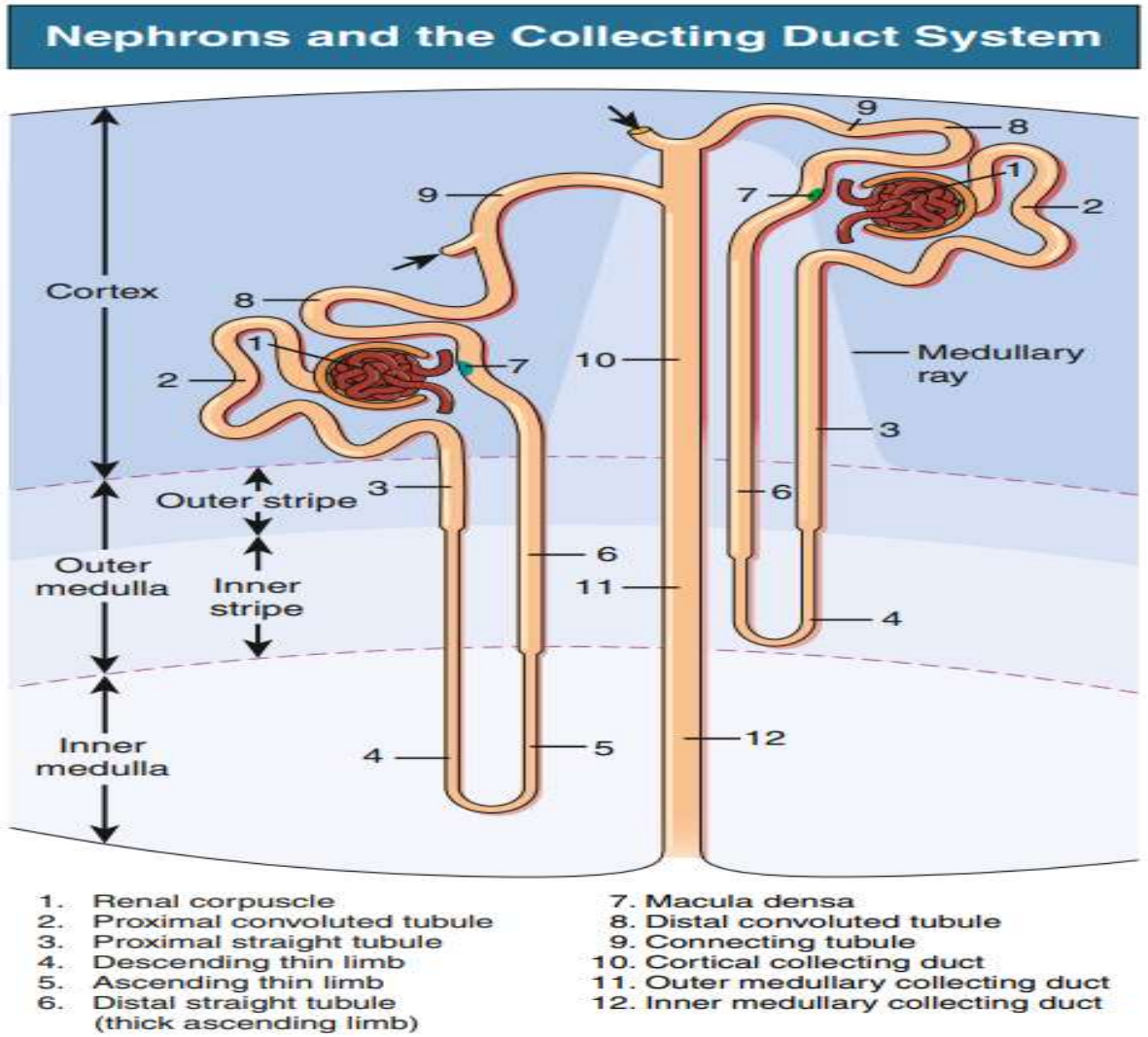
# Renal physiology – mechanism of action




Clin J Am Soc Nephrol 9: 2147–2163, December, 2014

# Renal physiology – hypocalciuria

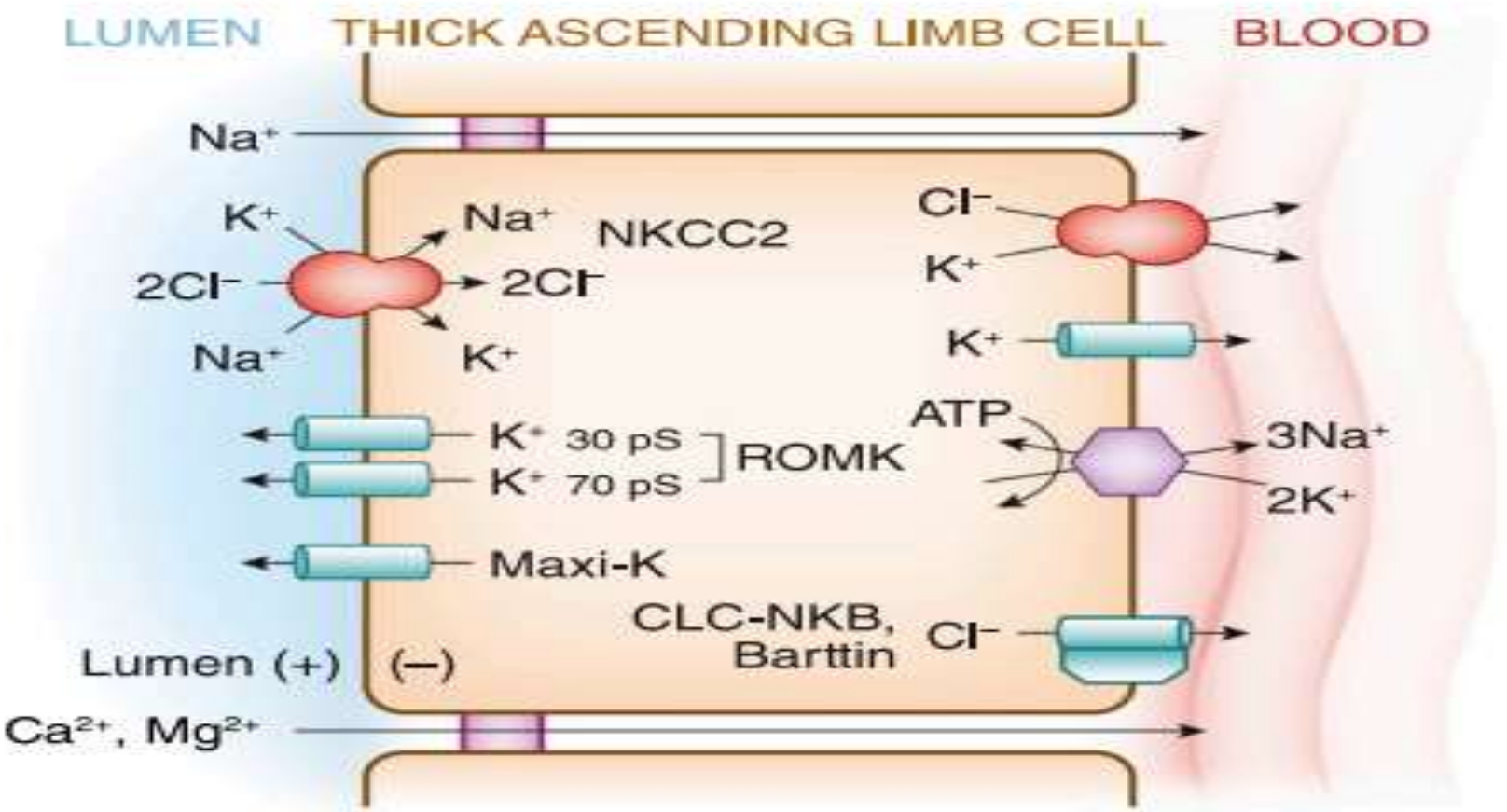



Brenner and Rector's the Kidney, 11th Edition. © 2020 by Elsevier, Inc. Chapter 3, pages: 80-114

Comprehensive Clinical Nephrology, 7th Edition. © 2024 by Elsevier, Inc. Chapter 1, pages: 1-12

# Renal physiology – Loop of Henle

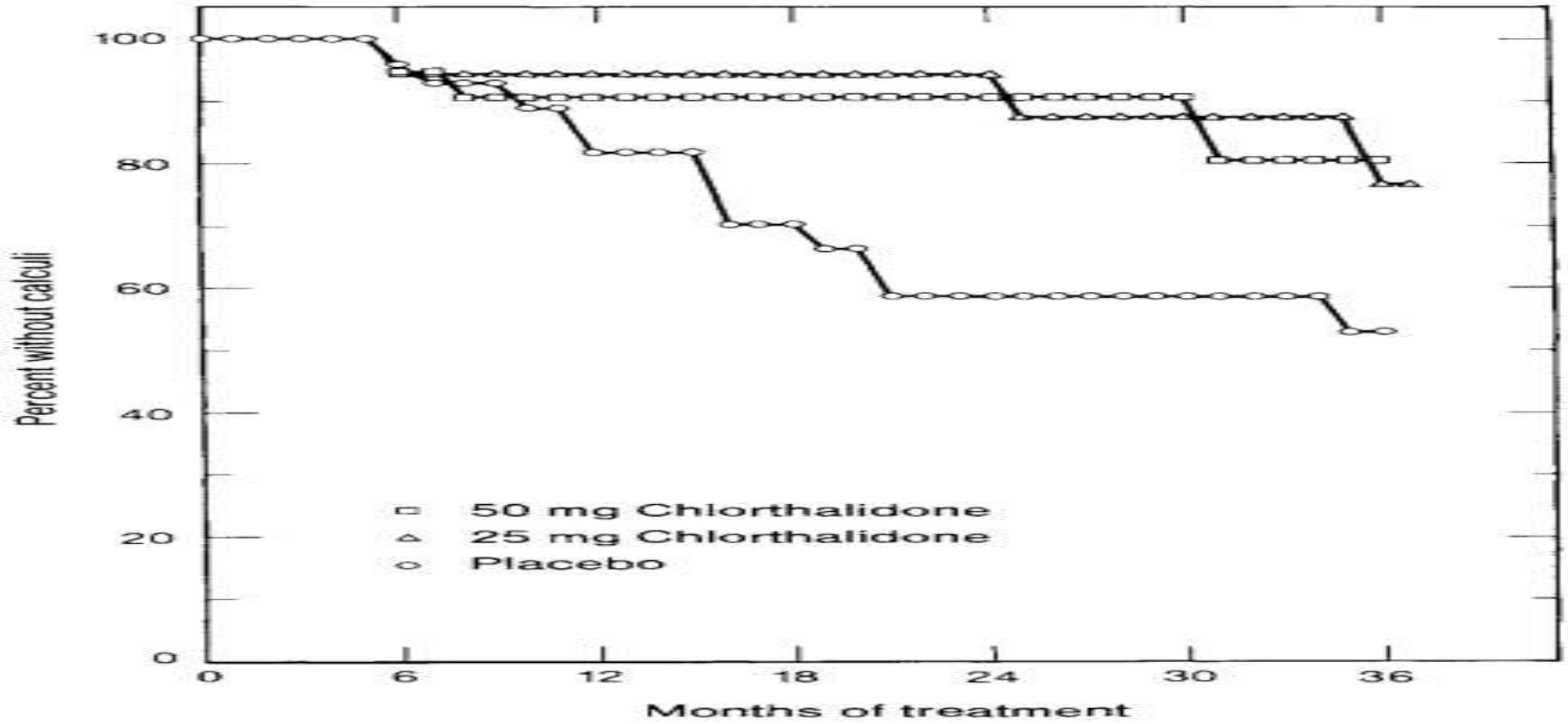



Clin J Am Soc Nephrol 9: 1974–1986, November, 2014

# Nephrolithiasis

# Evidence of benefit – hypercalciuria

- Double-blind randomized trial using Chlorthalidone (42 patients) or Magnesium Hydroxide (51 patients) or Placebo (31 patients)
- All patients had some degree of hypercalciuria




J. Urol., 139: 679-684, 1988

# Evidence of benefit – hypercalciuria

- Double-blind randomized study of 50 stone formers
- 25mg of Hydrochlorothiazide vs placebo

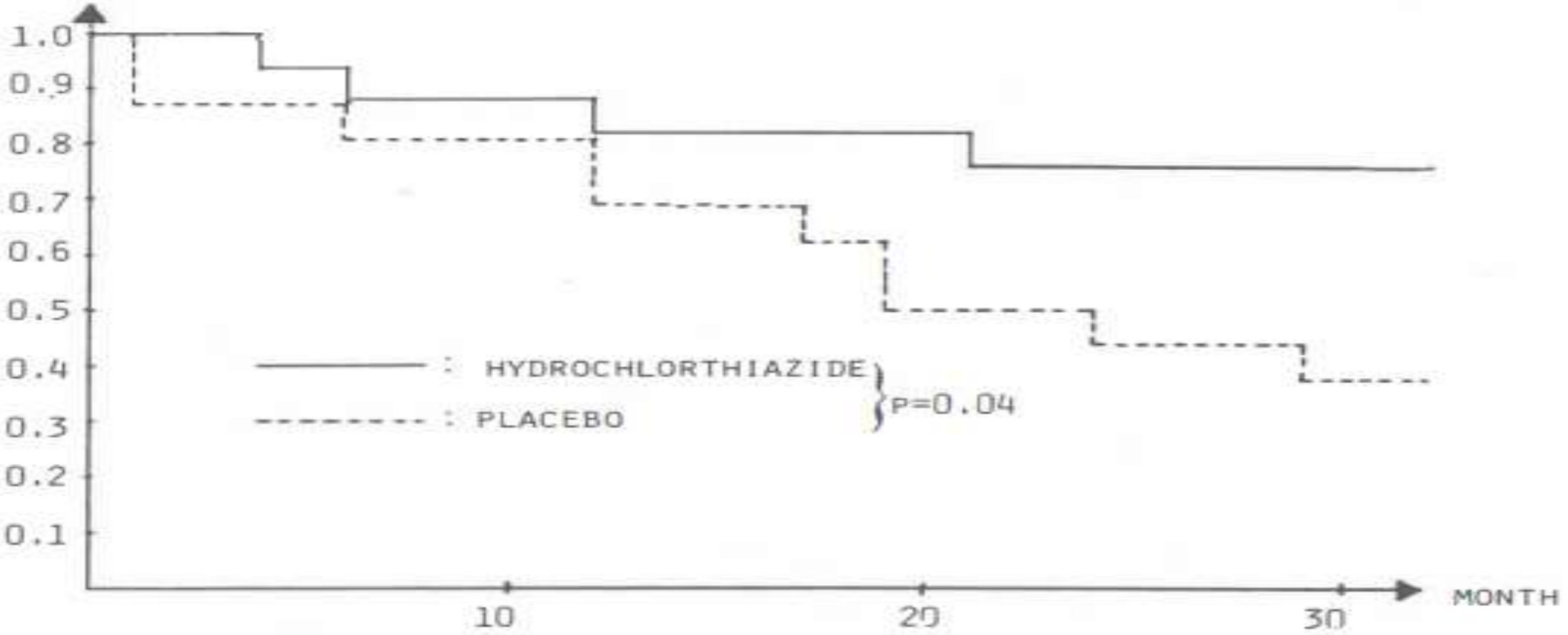



*Fig. 1.* Probability of not forming a new stone during a median treatment period of 3 years with thiazide or placebo (Kaplan and Meier plot).

Acta Med Scand 1984; 215: 383-389

# Evidence of benefit – hypercalciuria

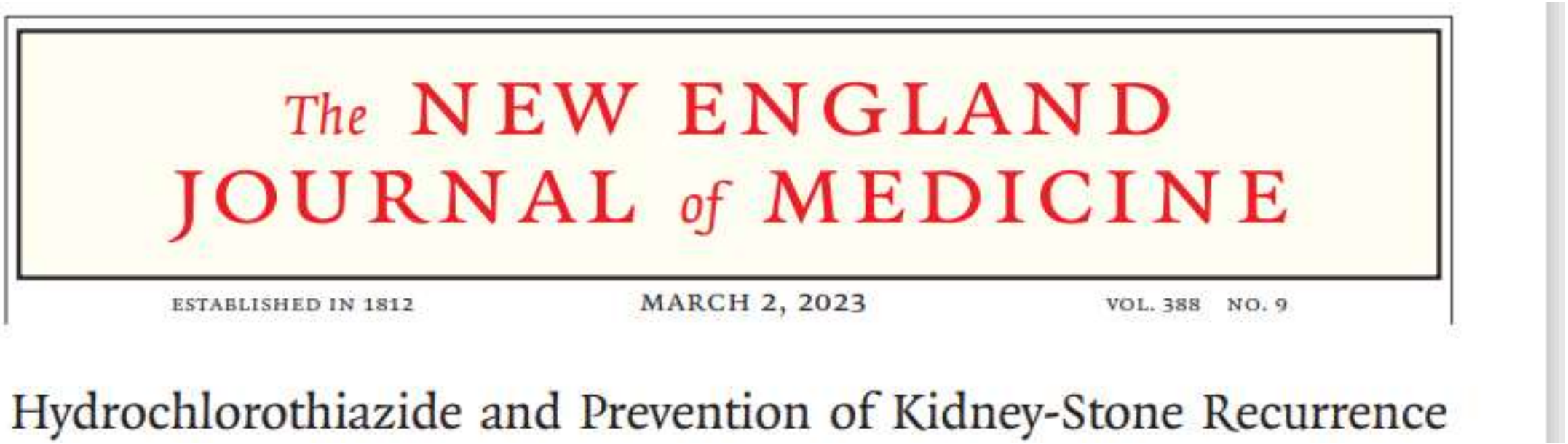
*Table 1.* RCTs of thiazide diuretics in stone prevention

| Author, Year | Treatment | Selection/Percent Hypercalciuria | Follow-Up (years) | *n* Treated/*n* Placebo | RR |
|---|---|---|---|---|---|
| Brocks, 1981 (17) | Bendroflumethiazide 2.5 mg TID | None | 1.6 | 33/29 | NS |
| Scholz, 1982 (18) | HCTZ 25 mg BID | None | 1 | 25/26 | NS |
| Laerum, 1984 (12) | HCTZ 25 mg BID | None/20% | 3 | 25/25 | 0.39 |
| Wilson, 1984 (16) | HCTZ 100 mg daily | None | 2.8 | 23/21 | 0.48 |
| Robertson, 1985 (15) | Bendroflumethazide 2.5 mg TID | None | 3 to 5 | 13/9 | 0.38 |
| Mortensen, 1986 (13) | Bendroflumethazide 2.5 mg + KCl | None | 2 | 12/10 | NS |
| Ettinger, 1988 (10) | Chlorthalidone 25/50 mg | None/13% to 15.8% | 3 | 19/23/31 25 mg/50 mg/placebo | 0.23 |
| Ohkawa, 1992 (14) | Trichlormethiazide 4 mg | Hypercalciuria | 2.1 to 2.2 | 82/93 | 0.42 |
| Borghi, 1993 (9) | Indapamide 2.5 mg daily | Hypercalciuria | 3 | 43/14 | 0.21 |
| Fernandez-Rodriguez, 2006 (11) | HCTZ 50 mg daily | None/52% | 3 | 50/50 | 0.56 |

TID, 3 times a day; BID, twice a day; KCl, potassium chloride; RR, relative risk.

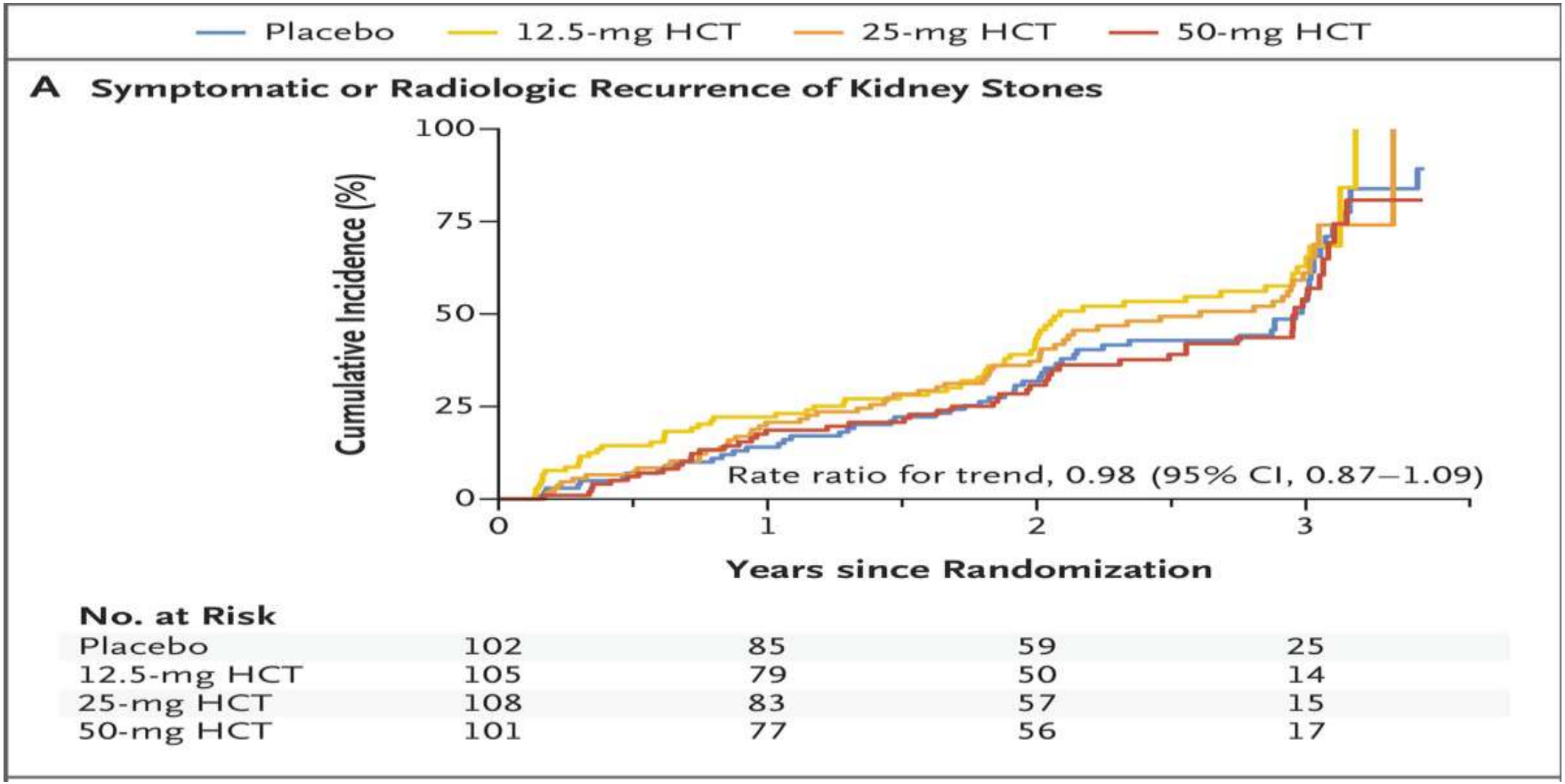
Clin J Am Soc Nephrol 5: 1893–1903, 2010

# Controversial evidence – hypercalciuria




- Randomized placebo controlled trial
- 416 patients with recurrent stone disease
- Placebo vs Hydrochlorothiazide (12.5mg, 25mg and 50mg dose)
- 3 year follow up period
- Primary end point: composite of symptomatic or radiologic stone recurrence

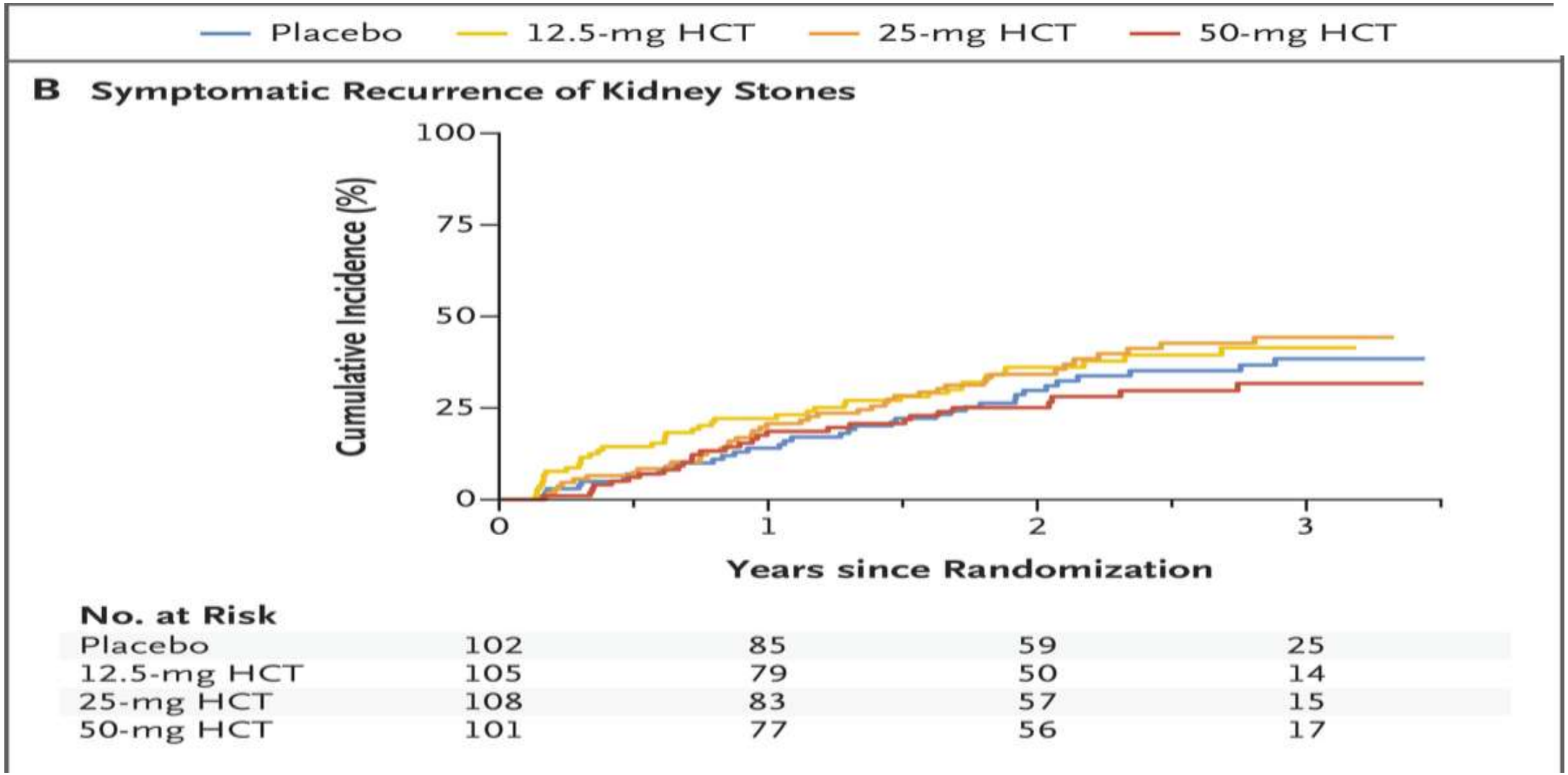
# Controversial evidence – hypercalciuria




| No. at Risk | | | | |
|---|---|---|---|---|
| Placebo | 102 | 85 | 59 | 25 |
| 12.5-mg HCT | 105 | 79 | 50 | 14 |
| 25-mg HCT | 108 | 83 | 57 | 15 |
| 50-mg HCT | 101 | 77 | 56 | 17 |

NA Dhayat et al. N Engl J Med 2023;388:781-791

# Controversial evidence – hypercalciuria

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NA Dhayat et al. N Engl J Med 2023;388:781-791

# Controversial evidence – hypercalciuria

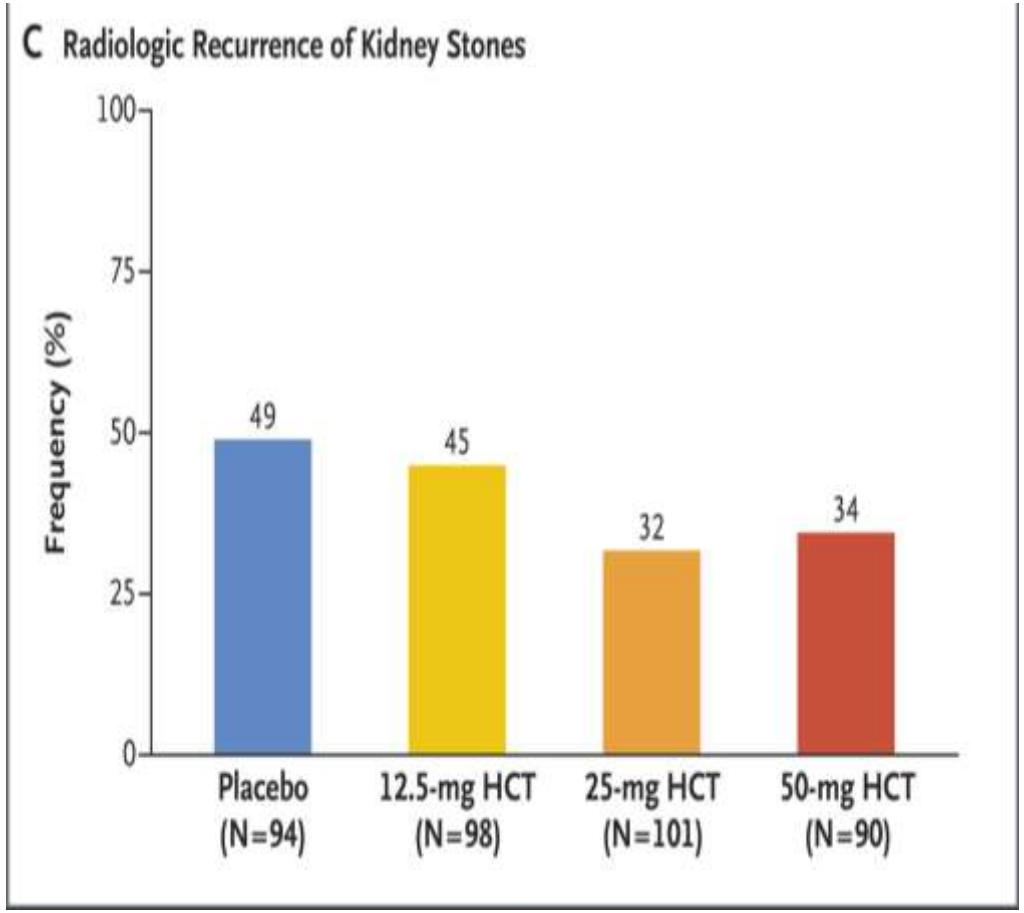


**Table S12: Secondary End Point Analysis: Radiologic Stone Recurrence.**

| Group | Patients | Events | % (No. Events/ No. Patients) | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Placebo | 94 | 46 | 49% | Reference |
| 12.5 mg HCT | 98 | 44 | 45% | 0.85 (0.48-1.50) |
| 25 mg HCT | 101 | 32 | 32% | 0.49 (0.27-0.87) |
| 50 mg HCT | 90 | 31 | 34% | 0.54 (0.29-0.98) |

CI, confidence interval; HCT, hydrochlorothiazide.

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# Controversial evidence – hypercalciuria

**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) |

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# Controversial evidence – hypercalciuria

| | | | | | |
|---|---|---|---|---|---|
| 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) |

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# Controversial evidence – hypercalciuria

| | | | | | |
|---|---|---|---|---|---|
| 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) |

NA Dhayat et al. N Engl J Med 2023;388:781-791

# Summary of the NEJM study

- Hydrochlorothiazide is shorter acting then Chlorthalidone which could have reduced the effectiveness of the drug and hence effected the primary analysis (symptomatic stones or radiographic evidence of stone recurrence)
- The secondary endpoint (radiological stone recurrence) was lower for the thiazide groups compared to placebo
- Symptomatic stones could have been from stones that formed before participants were started on the thiazide
- Urine sodium was very high in the treatment group even after 3 years of treatment which likely reduced the efficacy of the thiazide
- Duration of study was only 3 years, could take longer to show significant benefit

# Hypertension and Kidney Disease

# Evidence – hypertension

The NEW ENGLAND JOURNAL of MEDICINE

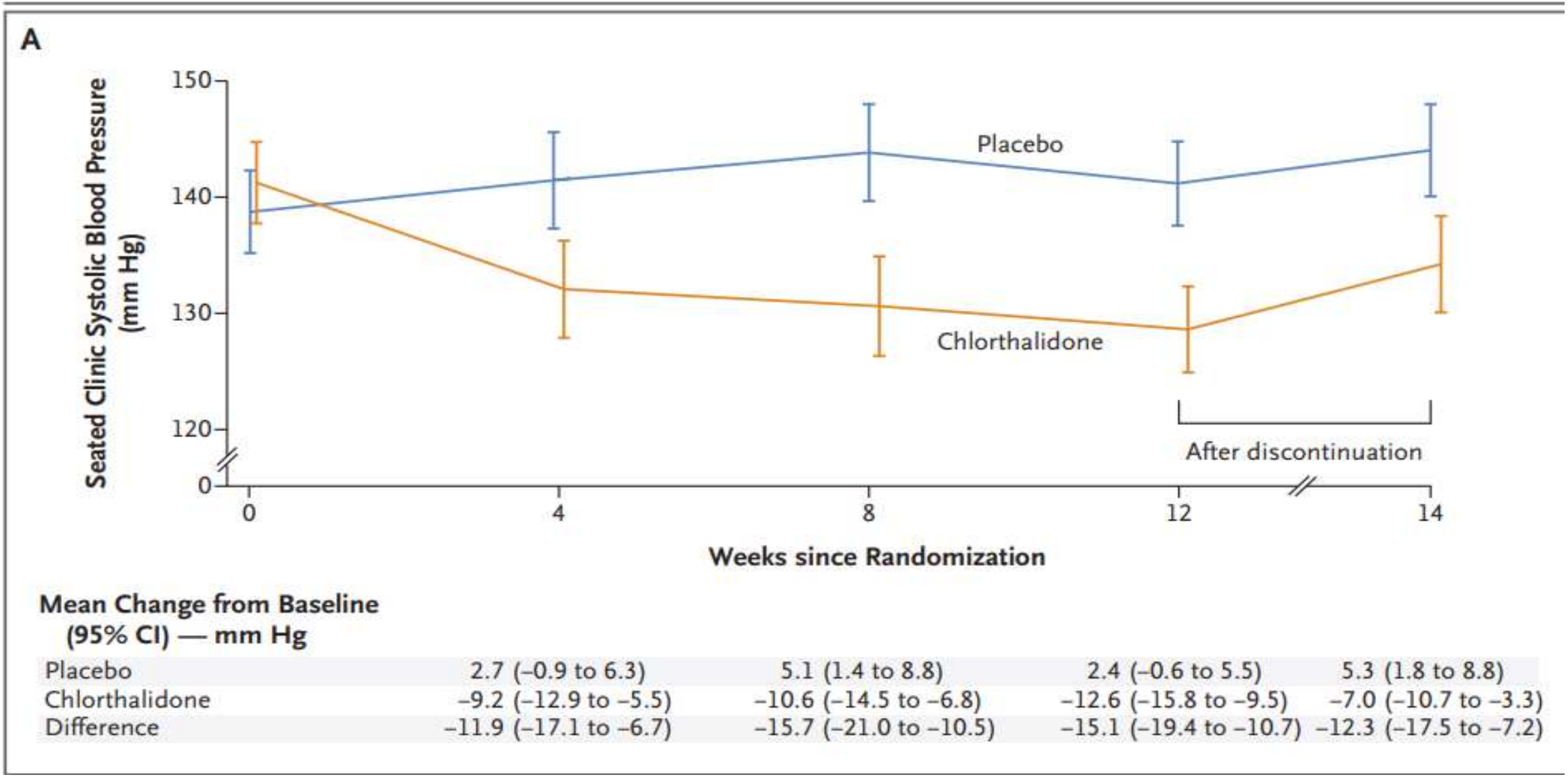
ESTABLISHED IN 1812 DECEMBER 30, 2021 VOL. 385 NO. 27

## Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Rajiv Agarwal, M.D., Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S., Jazmyn H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D.

- Placebo controlled randomized trial
- 160 patients with CKD stage 4 and hypertension
- Chlorthalidone: started at 12.5mg increased every 4 weeks to maximum dose of 50mg daily
- Primary outcome: Change in blood pressure at 12 weeks

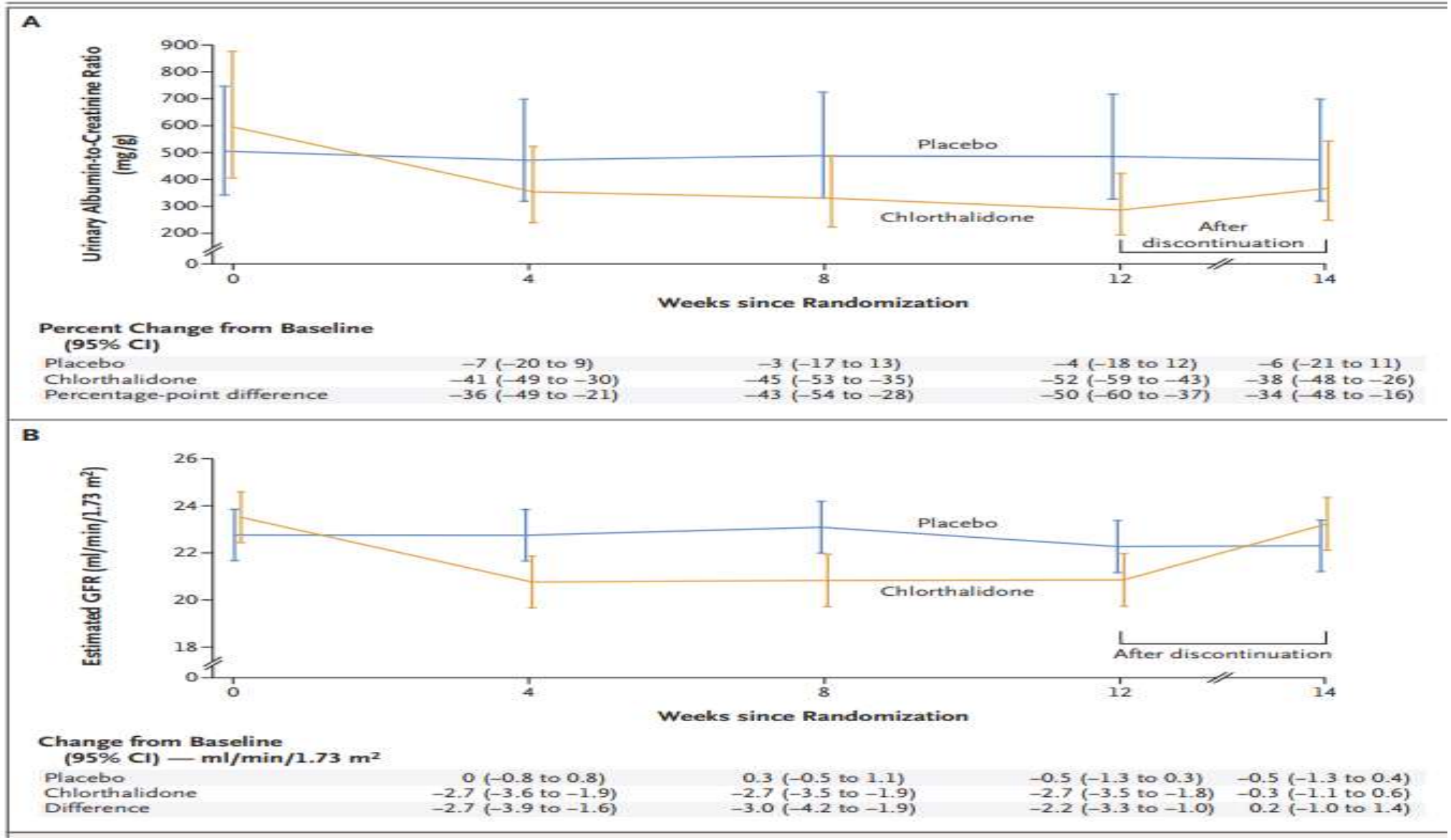
# Evidence – hypertension




| Mean Change from Baseline (95% CI) — mm Hg | | | | |
|---|---|---|---|---|
| Placebo | 2.7 (–0.9 to 6.3) | 5.1 (1.4 to 8.8) | 2.4 (–0.6 to 5.5) | 5.3 (1.8 to 8.8) |
| Chlorthalidone | –9.2 (–12.9 to –5.5) | –10.6 (–14.5 to –6.8) | –12.6 (–15.8 to –9.5) | –7.0 (–10.7 to –3.3) |
| Difference | –11.9 (–17.1 to –6.7) | –15.7 (–21.0 to –10.5) | –15.1 (–19.4 to –10.7) | –12.3 (–17.5 to –7.2) |

Agarwal et al N Engl J Med 2021;385:2507-19

# Evidence – hypertension




Agarwal et al N Engl J Med 2021;385:2507-19

# Evidence – hypertension

*Table 2.* Thiazide diuretic use in large-scale hypertension trials

| Study | Year | *n* | Primary (P)/ Add-On (A) | Control | Agent/Dose (mg) | Diuretic Outcome | Comments |
|---|---|---|---|---|---|---|---|
| VA Cooperative Study (29) | 1970 | 380 | P | Placebo | HCTZ 50 BID in combination with reserpine | Better | 70% less deaths and major CV events |
| Hypertension Detection and Follow-Up Study (HDFP) (33) | 1979 | 10,940 | P | Placebo | Chlorthal 25 to 100 daily | Better | 17% to 20% less all-cause deaths |
| Australian Therapeutic Trial in Mild Hypertension (31) | 1980 | 3427 | P | Placebo | Chlorothiazide 500 daily BID | Better | 30% less all-cause deaths, 58% less CV deaths |
| The Oslo Study (30) | 1980 | 785 | P | Placebo | HCTZ 50 daily | Better | Effect restricted to decreased strokes. All CV events decreased (54%) only in patients with baseline DBP ≥ 100 mmHg |
| European Working Party on High Blood Pressure in the Elderly (34) | 1985 | 840 | P | Placebo | HCTZ/Triamterene 25/50 to 50/100 daily | Better | 27% lower CV mortality, no difference in all-cause deaths |
| Heart Attack Primary Prevention in Hypertension Trial (HAPPHY) (40) | 1987 | 7569 | P | Active (metoprolol) | HCTZ 50 daily or Bendro 5 daily | Same | No differences in any outcomes. Only trend was toward more fatal strokes in the diuretic group (OR = 3.37 [0.96 to 9.53]) |
| Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) (39) | 1988 | 3234 | P | Active (metoprolol) | HCTZ 50 daily or Bendro 5 daily | Worse | 48% less all-cause deaths and 58% less CV deaths in the metoprolol group |
| Multiple Risk Factor Intervention Trial (MRFIT) (36) | 1990 | 8012 | P | Placebo | HCTZ 50 to 100 or chlorthal 50 to 100 daily | Better | Less CV deaths at some points during follow-up, especially if baseline DBP >100 mmHg. No effect during randomized trial phase. Chlor better than HCTZ |
| Swedish Trial of Old Patients with Hypertension (STOP) (37) | 1991 | 1627 | P | Placebo | Co-amilozide 2.5/ 25 daily | Better | 40% less CV events, 43% lower all-cause mortality |

Clin J Am Soc Nephrol 5: 1893–1903, 2010

# Evidence – hypertension

*Table 2.* (Continued)

| Study | Year | *n* | Primary (P)/ Add-On (A) | Control | Agent/Dose (mg) | Diuretic Outcome | Comments |
|---|---|---|---|---|---|---|---|
| Systolic Hypertension in the Elderly Program (SHEP) (32) | 1991 | 4736 | P | Placebo | Chlorthal 12.5 to 25 daily | Better | 36% decrease in stroke (primary endpoint). 20% lower CV mortality and 32% less CV events |
| Medical Research Council Working Party (35) | 1992 | 4396 | P | Placebo | Co-amilozide 25/ 2.5 to 50/5 daily | Better | Diuretics decreased CV events by 35% compared with placebo. β-blockers had no significant effect |
| Treatment of Mild Hypertension Study (TOMHS) (43) | 1993 | 902 | P | Active (placebo, acebutolol, doxazosin, amlodipine, enalapril) | Chlorthal 15 to 30 daily | Same | Active treatment modestly better than placebo. No difference among the five drug classes |
| Shangai Trial of Nifedipine in the Elderly (STONE) (54) | 1996 | 1632 | A | Placebo | HCTZ 25 daily | NA | |
| Systolic Hypertension in Europe (Syst-Eur) (52) | 1997 | 4695 | A | Placebo | HCTZ 12.5 to 25 daily | NA | |
| Verapamil in Hypertension and Atherosclerosis Study (46) | 1998 | 498 | P | Active (verapamil) | Chlorthal 25 daily | Same/ Worse | Trend toward more CV events in Chlor group, who also had greater progression of carotid atherosclerosis |
| Captopril Primary Prevention Project (CAPPP) (42) | 1999 | 10,985 | P | Active (captopril) | HCTZ 25 daily or Bendro 2.5 daily | Same | |
| Swedish Trial of Old Patients with Hypertension 2 (STOP 2) (41) | 1999 | 6614 | P | Active (enalapril or lisinopril, felodipine or isradipine) | Co-amilozide 2.5/ 25 daily | Same | |
| International Nifedipine GITS Study (INSIGHT) (44) | 2000 | 6321 | P | Active (nifedipine GITS) | Co-amilozide 25/ 2.5 daily to 50/5 daily | Same | |
| Chinese Trial on Isolated Systolic Hypertension in the Elderly (Syst-China) (53) | 2000 | 1253 | A | Placebo | HCTZ 1.5 to 25 daily or BID | NA | |

Clin J Am Soc Nephrol 5: 1893–1903, 2010

# Evidence – hypertension

*Table 2.* (Continued)

| Study | Year | *n* | Primary (P)/ Add-On (A) | Control | Agent/Dose (mg) | Diuretic Outcome | Comments |
|---|---|---|---|---|---|---|---|
| Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) (51) | 2002 | 9193 | A | NA | HCTZ 12.5 to 25 daily | NA | |
| Anti-Hypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) (2) | 2002 | 33,357 | P | Active (lisinopril, amlodipine) | Chlorthal 12.5 to 25 daily | Same | |
| Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) (58) | 2003 | 16,602 | P, A | Active (verapamil COER) | HCTZ 12.5 daily | Same | |
| Second Australian National Blood Pressure Study (ANBP2) (47) | 2003 | 6083 | P | Active (enalapril) | HCTZ recommended, no dose specified | Worse | 11% less CV events or deaths with enalapril |
| Valsartan Antihypertensive Long Term Use Evaluation (VALUE) (55) | 2004 | 15,245 | A | NA | HCTZ 12.5 to 25 daily | NA | |
| Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (50) | 2005 | 19,257 | A | NA | Bendro 1.25 to 2.5 daily | NA | [No Title] |
| Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) (48) | 2008 | 11,506 | P | Active | HCTZ 12.5 to 25 daily as fixed combination with benazepril | Worse | 20% less CV events in the benazepril/amlodipine group |
| Hypertension in the Very Elderly Trial (HyVET) (38) | 2008 | 3845 | P | Placebo | Indapamide 1.5 daily | Better | 39% less stroke deaths, 21% lower total mortality, 64% less heart failure |

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# Guidelines

# Guidelines – Hypertension


“For CV disease prevention in those with high BP, unless there is a strong indication for 1 specific class, it seems reasonable to begin with 1 or more drugs among ACEi or ARB, CCB, and thiazide-like diuretic"

Kidney International (2021) 99, S1–S87

# Guidelines – Nephrolithiasis

**Medical Management of Kidney Stones: AUA Guideline**

Margaret S. Pearle, David S. Goldfarb, Dean G. Assimos, Gary Curhan, Cynthia J. Denu-Ciocca, Brian R. Matlaga, Manoj Monga, Kristina L. Penniston, Glenn M. Preminger, Thomas M. T. Turk and James R. White

*From the American Urological Association Education and Research, Inc., Linthicum, Maryland*

"Pharmacologic Therapies 14. Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (Standard; Evidence Strength: Grade B)"

THE JOURNAL OF UROLOGY®
Vol. 192, 316-324, August 2014

# Summary

- Thiazides cause increased urine sodium and water loss
- The loss of sodium and water result in lower blood pressure and treatment of edema
- Thiazides likely induce a state of intravascular volume depletion which causes an increase in proximal tubule calcium uptake and hence reduce urine calcium excretion leading to a reduced risk for recurrent nephrolithiasis

Thank you for your attention