

Bone Density Disorders More Likely for Patients Prescribed Multiple Blood Pressure Medications Compared to Those on One Medication

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Key Findings:

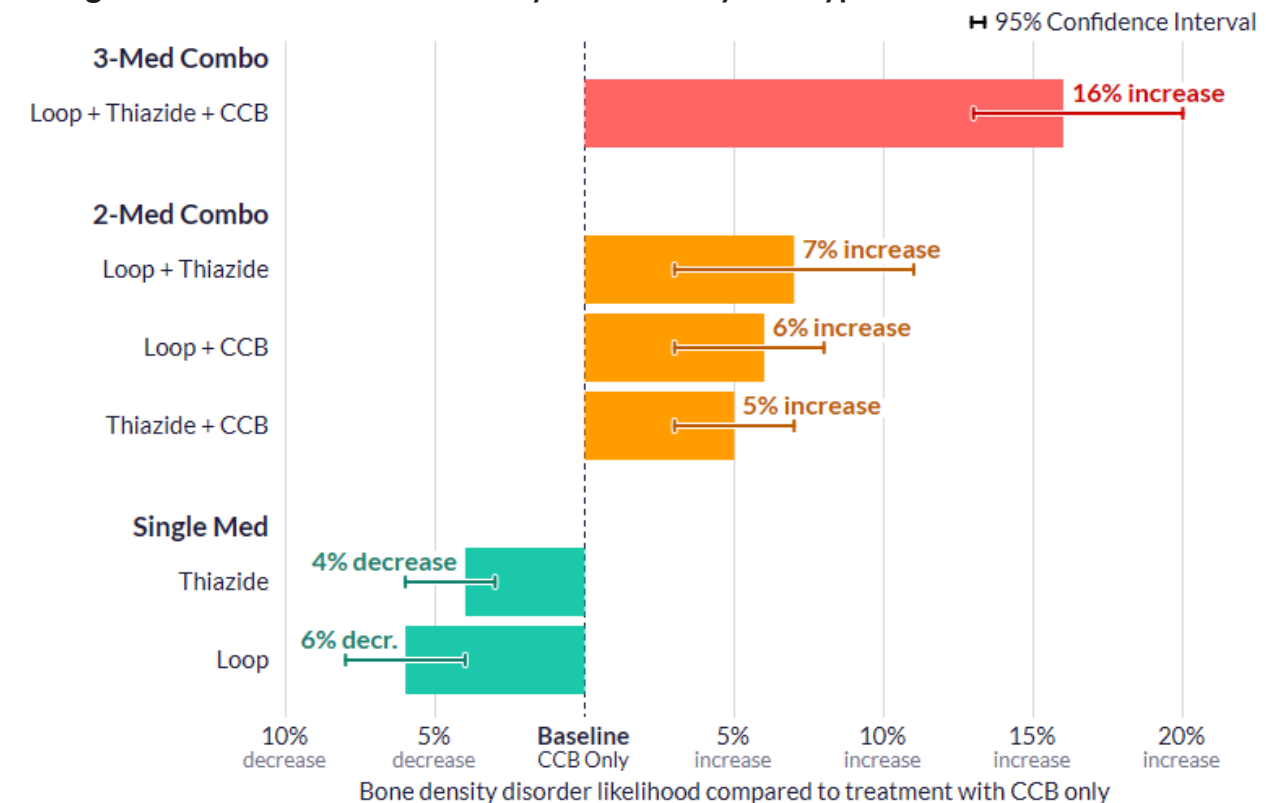
- Patients with hypertension who are treated with loop and thiazide diuretics in addition to a calcium channel blocker are 16% more likely to be diagnosed with a bone density condition within three years compared to those treated with just a calcium channel blocker.
- Patients with hypertension who are treated with only a thiazide or loop diuretic have a reduced likelihood of developing a bone density disorder within three years compared to those on a calcium channel blocker.

Osteoporosis is a condition in which bones are weakened and are more likely to break. There are several known risk factors for developing osteoporosis such as sex, age, medical conditions, and some medications.¹ Specifically, there have been reports of a correlation between diuretics and bone density concerns, including osteoporosis, though findings have been inconsistent.²

To understand the relationship between diuretics and bone density conditions, we studied 2,002,769 patients who were diagnosed with hypertension between January 1, 2017, and August 1, 2021, were treated with a diuretic, a calcium channel blocker, or both, and who had three years of follow-up care. Calcium channel blockers (CCBs) were selected as a subclass of medications that have been previously found to have no effect on bone density.² We adjusted for age, sex, race, ethnicity, BMI, height, comorbidities, and Social Vulnerability Index score.

We found that the likelihood of being diagnosed with a bone density condition within three years of starting an antihypertensive medication varied greatly by which combination and number of medications a patient received, as seen in Figure 1. Those who were prescribed a thiazide and loop diuretic in addition to a CCB were 16% more likely to be diagnosed with a bone density condition compared to patients only on a CCB. Conversely, those on only a thiazide diuretic had a 4% reduced likelihood of developing a bone density condition compared to those on a CCB, while those on only a loop diuretic had a 6% reduced likelihood.

Change in Likelihood of Bone Density Disorders by Antihypertensive Medication



N=2,002,769 patients

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Figure 1. The likelihood of a patient with hypertension being diagnosed with a bone density disorder by antihypertensive medication.

A sensitivity analysis assessing patients prescribed another blood pressure management medication, beta blockers, in place of calcium channel blockers as a control, showed similar results.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 277 million patient records from 1,500 hospitals and more than 36,000 clinics from all 50 states, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

1. Osteoporosis. Mayo Clinic. Published February 24, 2024. <https://www.mayoclinic.org/diseases-conditions/osteoporosis/symptoms-causes/syc-20351968>. Accessed August 26, 2024.
2. Zhang R, Yin H, Yang M, Lei X, Zhen D, Zhang Z. Advanced Progress of the Relationship Between Antihypertensive Drugs and Bone Metabolism. Hypertension. 2023;80(11):2255-2264. doi:10.1161/HYPERTENSIONAHA.123.21648

Data Definitions

Term	Definition
Study period	01/01/2017 to 08/01/2024
Study population	Patients diagnosed with hypertension between January 1, 2017, and 8/1/2021

	• Index date is the date of first medication receipt after hypertension diagnosis • At least one face-to-face encounter in the following three calendar years from the index date • At least three months of time between medication starting and outcome diagnosis Patients were excluded if they were diagnosed with hyperparathyroidism or prescribed: • A simple generic name of Medroxyprogesterone Acetate • A pharmaceutical class of Antineoplastic - Aromatase Inhibitors • A pharmaceutical class of Insulin Response Enhancers – Thiazolidinediones (PPAR-gamma agonists) • A pharmaceutical class of Immunosuppressive - Calcineurin Inhibitors • A chemotherapy treatment
Hypertension	A diagnosis with ICD-10-CM code I10*, I11*, I12*, I13*, or I15*
Hyperparathyroidism	A diagnosis with ICD-10-CM code E21*
Exposures	Diuretic orders with the following pharmaceutical classes: • Thiazide and thiazide-like: Diuretics – Thiazide and Related • Loop: Diuretic – Loop Calcium channel blockers with the following RxNorm codes: • Amlodipine: 17767 • Diltiazem: 3443 • Verapamil: 11170 • Nifedipine: 7417 • Felodipine: 4316 • Nisoldipine: 7435 • Nimodipine: 7426 • Isradipine: 33910 • Nicardipine: 7396 • Levamlodipine: 2376944 • Clevidipine: 233603
Outcomes	Osteoporosis: A diagnosis with ICD-10-CM code M80* or M81* Osteomalacia: A diagnosis with ICD-10-CM code M83* Other disorders of bone density and structure: A diagnosis with ICD-10-CM code M85*
Confounders	Age Social Vulnerability Index quartile Legal sex: male or female Race and ethnicity BMI • A patient's average BMI in the year before through the year after the index date

	• Categorize as underweight, normal weight, overweight, obese, class 1 obesity, class 2 obesity, class 3 obesity
	Height • Most recent height
	Cancer: A diagnosis with ICD-10-CM code C*
	Type 2 diabetes: A diagnosis with ICD-10-CM code E11*
	Kidney disease: A diagnosis with ICD-10-CM code I12*-I13*, N15*, N18*-N19*, E08.22, E09.22, E10.22, E11.22, or E13.22
	Family history of osteoporosis: A diagnosis with ICD-10-CM code Z82.62
	An order with a pharmaceutical class of 'ANTIHYPERTENSIVE-HMGCOA REDUCTASE INHIB(STATINS)'
	An order with a pharmaceutical class of 'ANTICOAGULANTS'
	An order with a pharmaceutical class of 'Antidepressant - Selective Serotonin Reuptake Inhibitors (SSRIs)'
	An order with a pharmaceutical class of 'PROTON-PUMP INHIBITORS'
	An order with a pharmaceutical class of 'GLUCOCORTICOIDS' or 'MINERALCORTICOIDS' for over 30 days
	Other diuretics: • Potassium Sparring: 'Diuretic – Potassium Sparring' • Other: 'Diuretic – Aldosterone Receptor Antagonist, Non-Selective,' 'Diuretic – Aldosterone Receptor Antagonist, Selective,' 'Diuretic – Carbonic Anhydrase Inhibitors,' 'Diuretic – Osmotic,' 'Diuretic-Selective Arginine Vasopressin V2 Receptor Antagonists,' or 'Polycystic Kidney Disease – Vasopressin V2 Receptor Antagonist'
Social Vulnerability Index	The social vulnerability quartile for the ZIP Code of the patient's most recent address
Race and ethnicity	Patients were classified as Hispanic, Non-Hispanic Black, Non-Hispanic White, and Non-Hispanic Other

Table 1: Change in Likelihood of Bone Density Disorders by Antihypertensive Medication

Medication Combination	Odds Ratio	Lower CI	Upper CI	% Increase
Loop + Thiazide + CCB	1.16	1.13	1.20	16% increase
Loop + Thiazide	1.07	1.03	1.11	7% increase

Loop + CCB	1.06	1.03	1.08	6% increase
Thiazide + CCB	1.05	1.03	1.07	5% increase
Thiazide	0.96	0.94	0.97	4% decrease
Loop	0.94	0.92	0.96	6% decrease