Common Side Effects of Algorithm BP Meds
Slides courtesy of Joel Handler, MD, KP SCAL

- Thiazide-related hyponatremia
- Gout occurring on thiazide
- Erectile dysfunction
- ACE inhibitor cough and angioedema
- Calcium blocker related edema

Thiazide Hyponatremia Case

A 74 year old female with controlled hypertension on lisinopril/HCTZ 20/25 mg daily has a serum sodium of 129 on routine surveillance screening. You should advise her to:

A. Change to lisinopril 20 mg daily
B. Maintain lisinopril/HCTZ 20/25 mg daily
C. Reduce lisinopril/HCTZ to 10/12.5 mg daily
D. Stop lisinopril/HCTZ
E. Take salt tablets

Thiazide-Related Hyponatremia

- Most common electrolyte abnormality in the SHEP trial with chlorthalidone (CTD) 25mg, age ≥ 60, was hyponatremia

  1 year rate of K < 3.2 was 1.0%

  1 year rate of Na ≤ 130 was 1.8%
- Highest risk group: frail elderly women
- Not dose related

Management of Hyponatremia

- Asymptomatic Na 125 ± 5 associated with falling
- Preexisting asymptomatic hyponatremia risks symptomatic hyponatremia
- Consider differential diagnosis of hyponatremia: dehydration, fluid overload, NSAIDs, SSRIs, CNS and pulmonary disease
- **Avoid excessive water drinking**
- **Stop thiazide for associated Na less than 130**

Frequency (%) of Adverse Effects

Adverse Effect	Placebo	HCTZ
	N=168	N=173
Abnormal Urination	3	3
Asthenia	4.9	2.3
Dizziness	1.2-11.8	1-5.9
Fatigue	6	3
Headache	7-17.6	5.9-10.3
Rash	1	1
Stress Reaction	1	3

Weir et al. Am J Med 1996; 101: 835-925

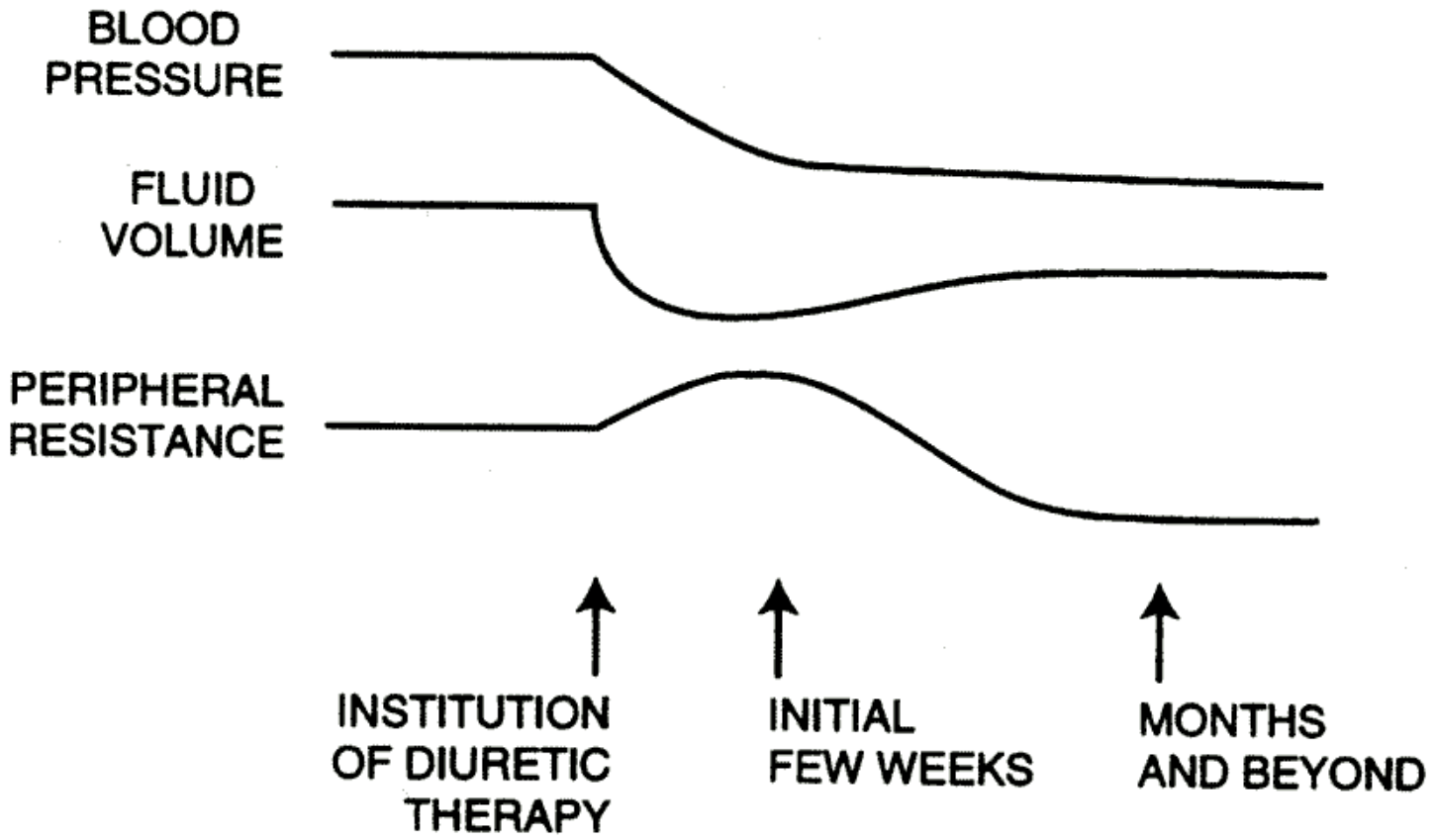


FIG. 7-3. Scheme of the hemodynamic changes responsible for the antihypertensive effects of diuretic therapy.

Thiazide Myths Exposed

- Significant cross reactivity with sulfa antibiotics has not been demonstrated; sulfa allergic patients have the same mildly increased reactivity to penicillin and thiazide (NEJM 2003;349:1628-35)
- Thiazide is first line treatment for calcium kidney stones due to idiopathic hypercalciuria and also treats idiopathic calcium lithiasis; avoid thiazide with hyperparathyroidism (raises serum Ca)

For Mild HCTZ intolerance……

Such as dizziness, mild rash or phototoxicity, switch to thiazide-like….

- Chlorthalidone 12.5 – 25 mg
- Indapamide 1.25 – 2.5 mg

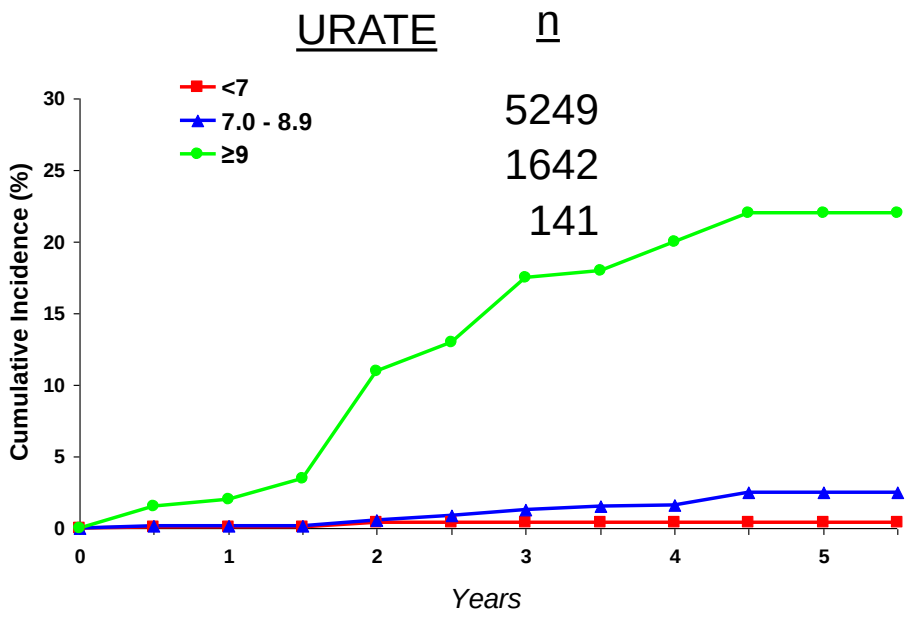
For hyponatremia (sodium < 130) or GFR < 30 cc/min, consider furosemide BID

Agenda

- Thiazide- related hyponatremia
- **Gout occurring on thiazide**
- Erectile dysfunction
- ACE inhibitor cough
- ACE inhibitor angioedema
- Calcium blocker related edema

Thiazide and Gout

- Prospective Normative Aging Study, >30,000 human years: rate of gout was 7%/year in 1.8% who had urate levels ≥ 9 mg/dl
- HDFP study on chlorthalidone 25mg: 18 dropouts out of 3693 patients over 5 years, 0.5%
- Hypertension, weight gain, and furosemide are more strongly related to gout than thiazide
- Hyperuricemia with HCTZ is dose related
- Intercritical gout more than 1 year in 40%; 7% had no recurrence in >10 years



Cumulative incidence of gouty arthritis by prior urate levels.
The numbers refer to the number of examination intervals for each group.

Campion, et al.Am J Med 1987; 82:421-426

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Management Options for Hypertensive Patients With Acute Gout Taking Thiazide Based on Clinical Context

Hypertension controlled on 1 or 2 medications:

Attack of gout, 0 or 1 prior attacks in past year

- Lifestyle measures
- Consider alternative hypertensive drug if serum uric acid > 6mg/dL (not taken during attack)

Attack of gout, ≥ 2 prior attacks in past year

- Lifestyle measures
- Change to alternative antihypertensive drug

Management Options for Hypertensive Patients With Acute Gout Taking Thiazide Based on Clinical Context

Hypertension controlled on ≥ 3 medications

Attack of gout, 0 or 1 prior attacks in past year

- Lifestyle measures
- Thiazide continuation with consideration of dose reduction
- Consider pharmacologic antihyperuricemic therapy, ie, allopurinol, if serum uric acid > 6mg/dl (not taken during attack)

Management Options for Hypertensive Patients With Acute Gout Taking Thiazide Based on Clinical Context

Hypertension controlled on ≥ 3 medications

Attack of gout, ≥ 2 prior attack in past year

- Lifestyle measures
- Consider alternative antihypertensive drug if serum uric acid > 6 mg/dl (not during attack)
- Consider pharmacologic antihyperuricemic therapy, ie, allopurinol and thiazide continuation

Case of Thiazide and Gout

A 74 year old male with controlled hypertension on prinzide 20/25mg x 2, amlodipine 10mg, and terazosin 10mg HS has a second episode of acute podagra. You should advise:

- Stop prinzide and switch to lisinopril 40mg plus furosemide 20mg bid
- Reduce prinzide to 20/25g x 1 and consider adding spironolactone 12.5g if follow-up blood pressures are elevated
- Add allopurinol following gout attack
- Stop prinzide, increase terazosin to 20mg hs, and consider adding atenolol

Agenda

- Thiazide-related hyponatremia
- Gout occurring on thiazide
- Nocebo effects
- **Erectile dysfunction**
- ACE inhibitor cough
- ACE inhibitor angioedema
- Calcium blocker related edema

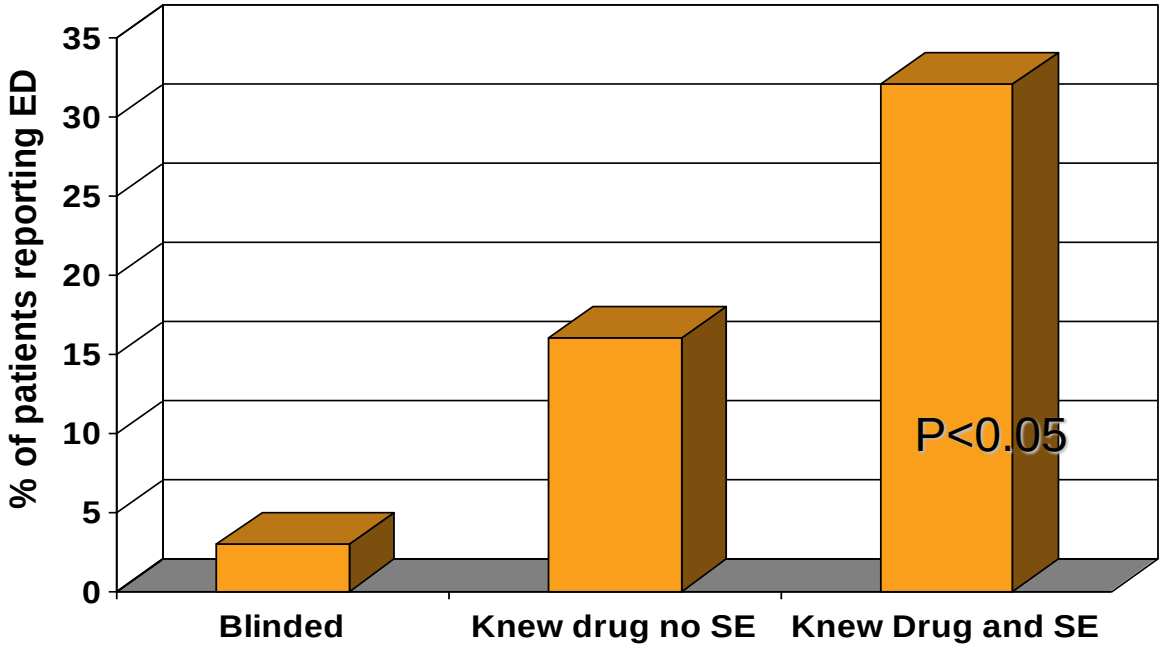
Erectile Dysfunction

- Primary determinants are age and comorbidities
- Weight loss and exercise improve sexual function: TAIM, JAMA study, JCH study
- TOMHS: E.D. proportional to age and systolic pressure
- TOMHS: no change in E.D., CTD 15 mg vs placebo at 4 years
- SHEP: no change in sexual function CTD 25mg vs placebo

Thiazide and Quality of Life

- TOMHS: 8 QOL domains; chlorthalidone 15mg = placebo
- ALPINE: no difference in sexual satisfaction thiazide vs candesartan
- SHEP: sexual problems, thirst, nocturia chlorthalidone 25mg = placebo

Beta-blockers and Report of ED



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Agenda

- Thiazide- related hyponatremia
- Gout occurring on thiazide
- Erectile dysfunction
- **ACE inhibitor cough and angioedema**
- Calcium blocker related edema

Case of Lisinopril and Cough

A 52 year old female with controlled hypertension on prinzide 20/25mg develops persistent dry cough, bothersome to family. There is no history of post nasal drip, GERD, or asthma. You should advise:

A. Reduce prinzide to 10/12.5mg daily

B. Try cromolyn inhaler and iron 325 mg daily

C. Change prinzide to HCTZ 50mg, then consider adding losartan

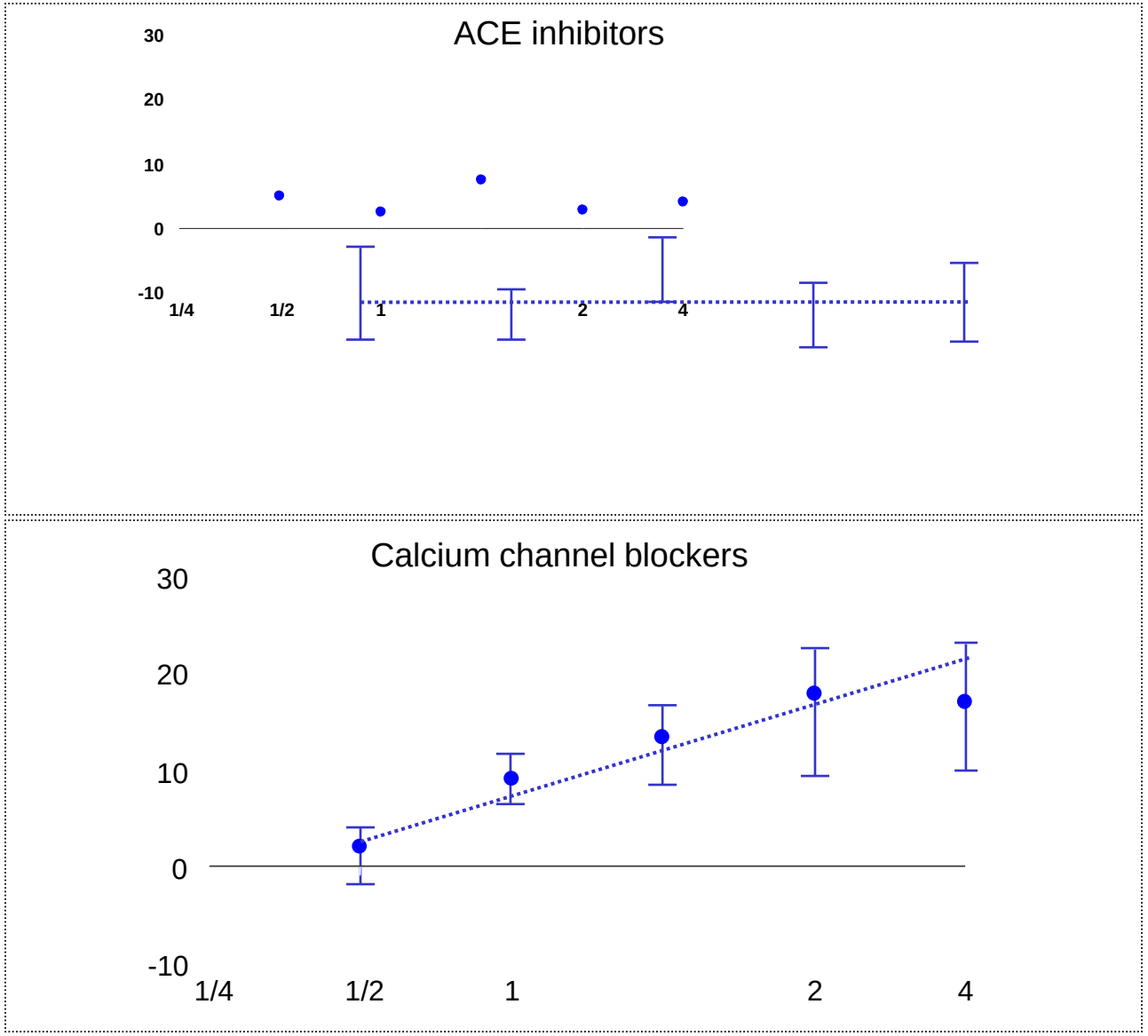
D. Empiric trials of nasarel, chlortrimeton, then omeprazole

ACE Inhibitor Cough

- Incidence 5-40%; higher rate in females, African Americans, Asians
- Cough characteristics not helpful in diagnosis (may be productive)
- Timing: within a week to up to 6 months
- Resolution: 1-4 days, up to 4 weeks
- Pathophysiology: Bradykinin accumulation; no pulmonary dysfunction
- Things that don't work: iron, NSAIDs, cromolyn
- Consider re-challenge

ACE Inhibitor Cough

- Not dose related
- Consider other cough etiologies: post nasal drip, GERD, asthma, heart failure, seasonal viral disease
- ACE inhibitors are preferred over ARBs (losartan) for patients with CAD and high CVD risk (ALL study)



Proportions of people reporting one or more symptoms attributable to treatment (treatment minus placebo, with 95% confidence interval) according to category of drug and dose as a proportion of standard

Law et al. BMJ 2003;326:1427-34

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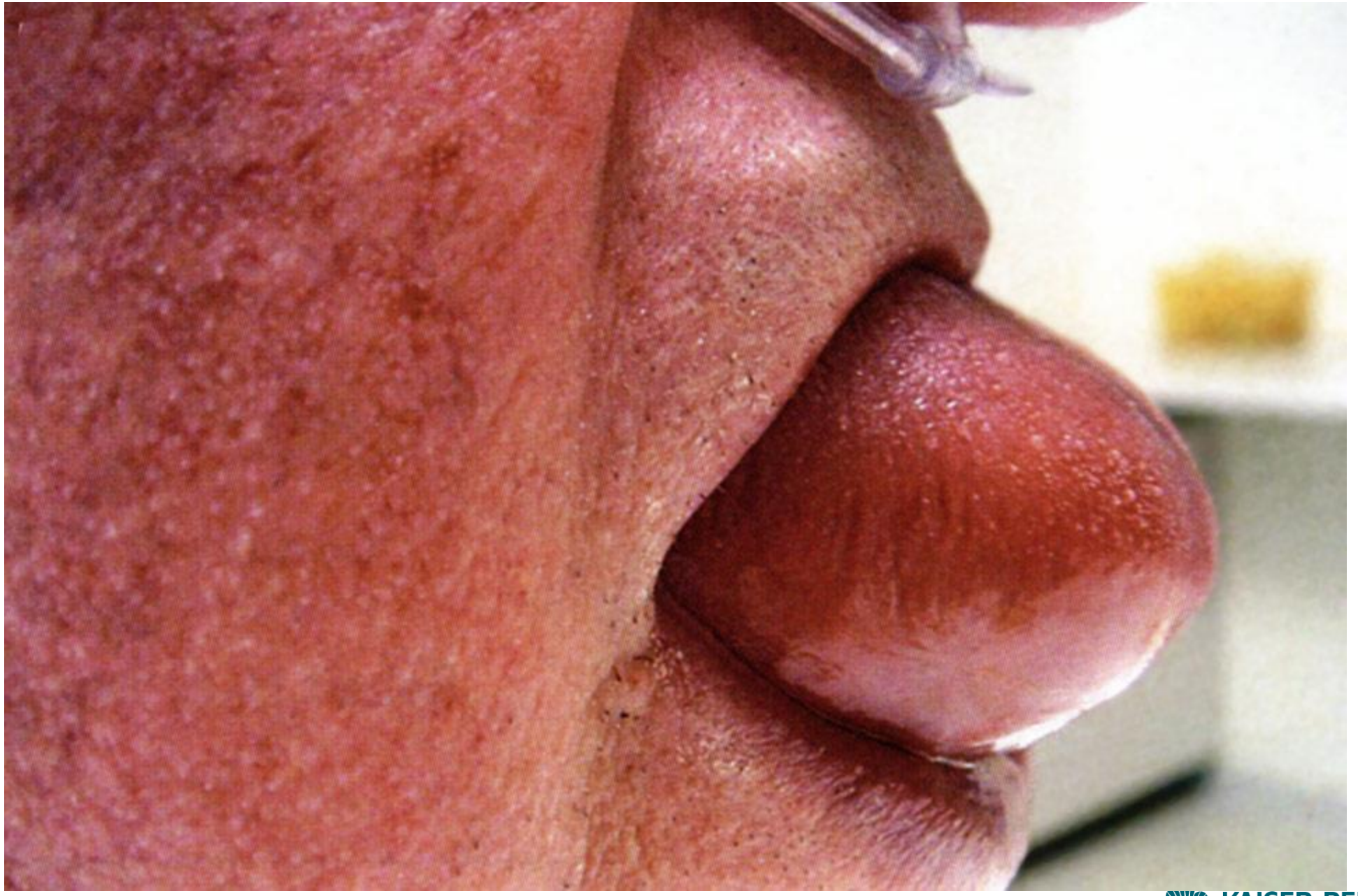
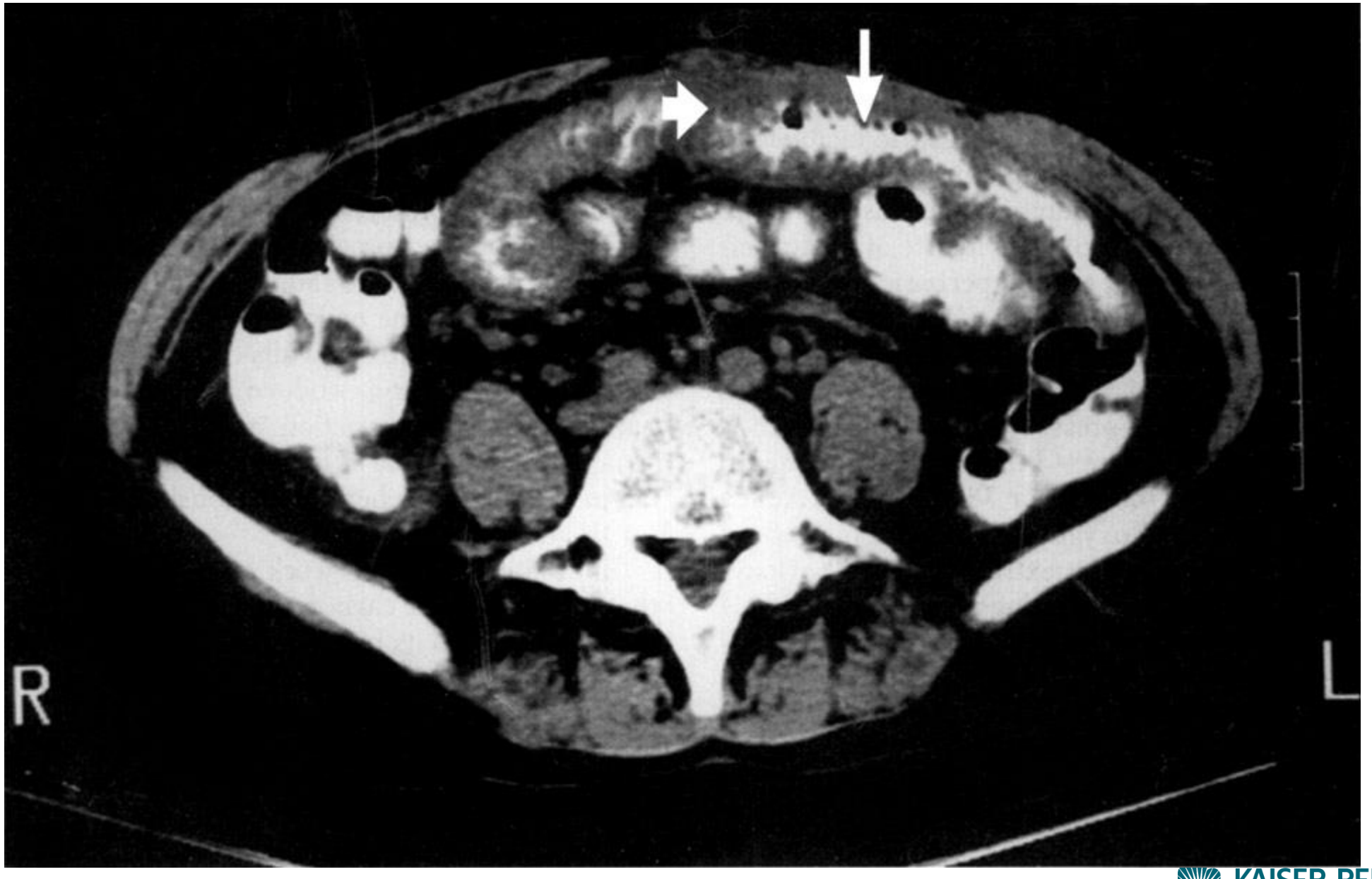


ACE Inhibitor Angioedema

- 0.3% in Caucasian patients, 0.7% in African Americans: ALLHAT
- **Idiopathic angioedema is an ACE inhibitor contraindication**
- Rarely can cause upper airway obstruction and abdominal pain
- Can change to an ARB: losartan



Agenda

- Thiazide-related hyponatremia
- Gout occurring on thiazide
- Erectile dysfunction
- ACE inhibitor cough
- ACE inhibitor angioedema
- **Calcium blocker related edema**

Calcium Blocker Edema Case

A 67 year old female with controlled hypertension on prinzide 20/25mg x 2, amlodipine 10mg, and atenolol 25 mg develops mildly bothersome 1+ bilateral pedal edema. You should advise her to:

A. Change prinzide to lisinopril 40mg plus furosemide 20mg daily

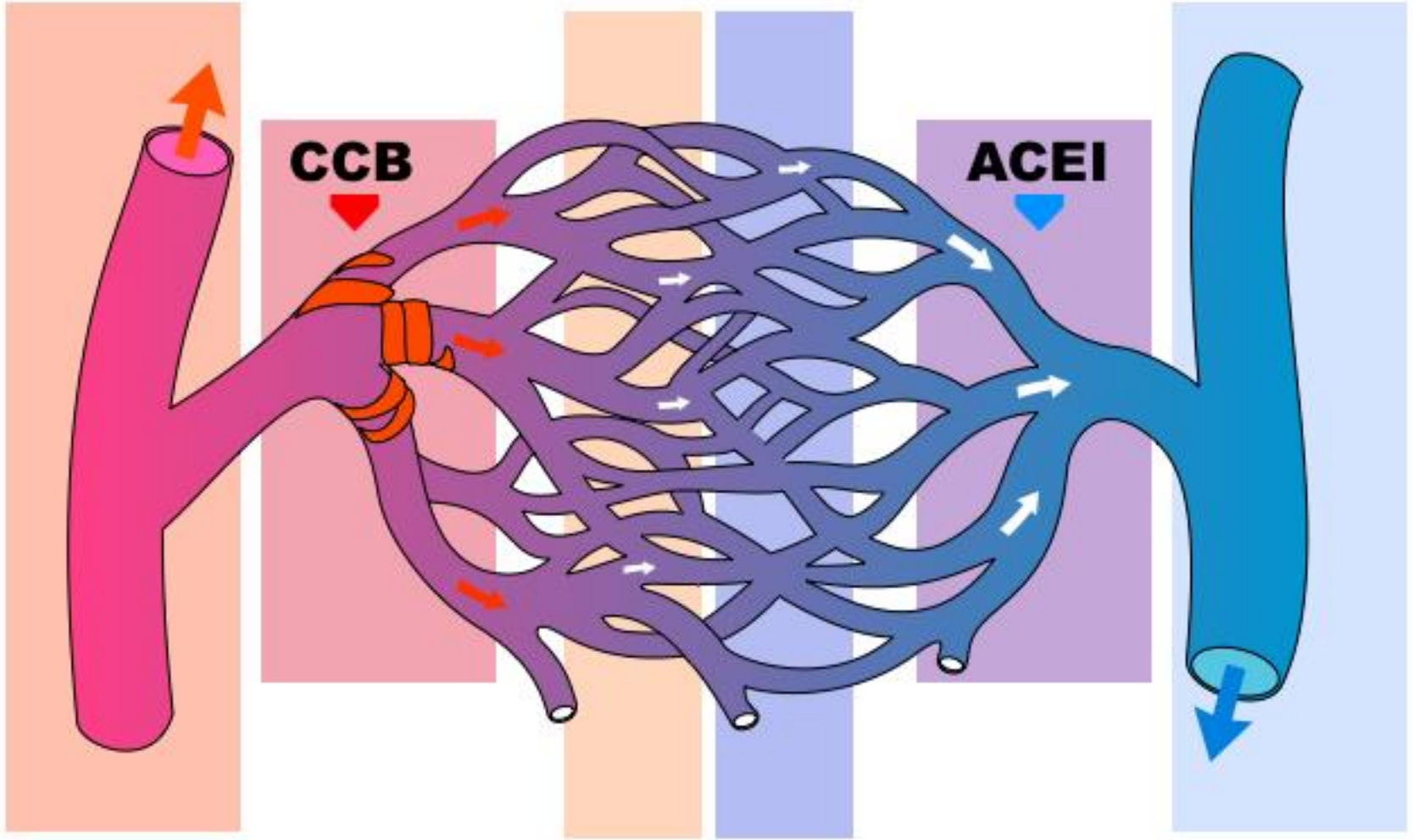
B. Switch amlodipine to long acting diltiazem 120mg daily

C. Advise sodium reduction to control edema

D. Maintain amlodipine 10mg and advise daytime compression stockings as needed, emphasizing reassurance

Pathophysiology of Calcium Channel Blocker Related Edema

- Not caused by fluid overload
- Not responsive to furosemide
- CCBs target precapillary arterioles to increase intracapillary pressure
- Intracapillary hypertension leads to fluid transudation into soft tissue and edema
- Edema is dependent, worse later in day and better in morning



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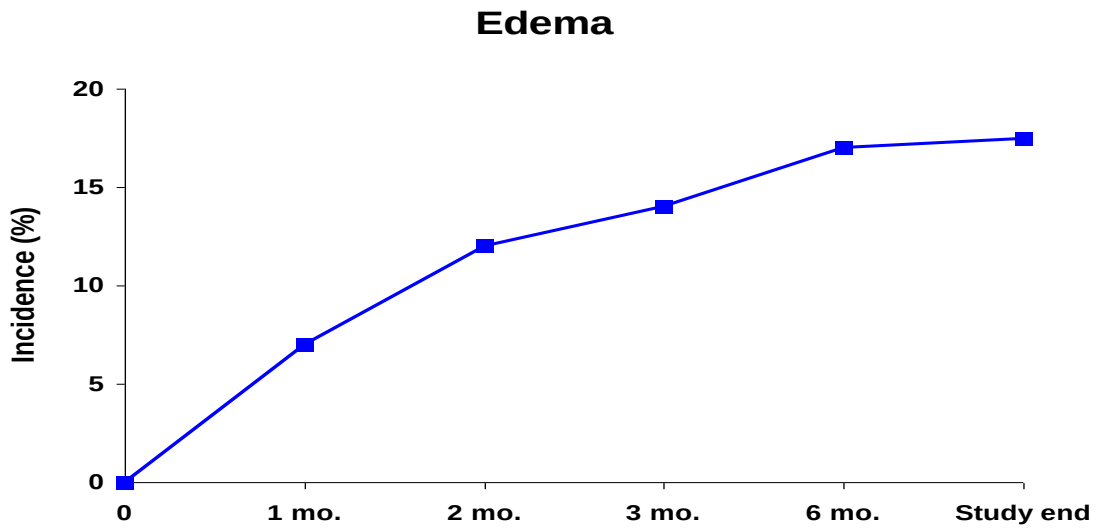

Edema rate over time for amlodipine

AJH 2002;15:932-940

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Managing Calcium Channel Blocker Related Edema

1. Always consider other etiologies of edema, ie right heart failure due to sleep apnea, steroids, anegrilide, NSAIDs; heart, kidney, and liver failure
2. Lisinopril and losartan act on venular side of capillary circuit to reduce intracapillary pressure
3. Additional antihypertensive agents permit reduction of dose of CCB
4. Daytime compression stockings, leg elevation
5. Switch to another calcium blocker
6. Reassurance

Spironolactone:

For Eligible Patients, the Best 4th Antihypertensive Drug

Approximately 20 to 30% of patients with hypertension will not be controlled after taking two tablets of lisinopril/hydrochlorothiazide (Prinzide®) 20/25 mg, plus amlodipine 10 mg. The preferred fourth drug for eligible patients is spironolactone. When used by 1,411 patients as a fourth drug in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the mean decrease in blood pressure was 22/10 mmHg.

Eligibility for spironolactone, as defined by the Care Management Institute (CMI), to promote maximal safety when prescribed by primary care providers, has three requirements for patients:

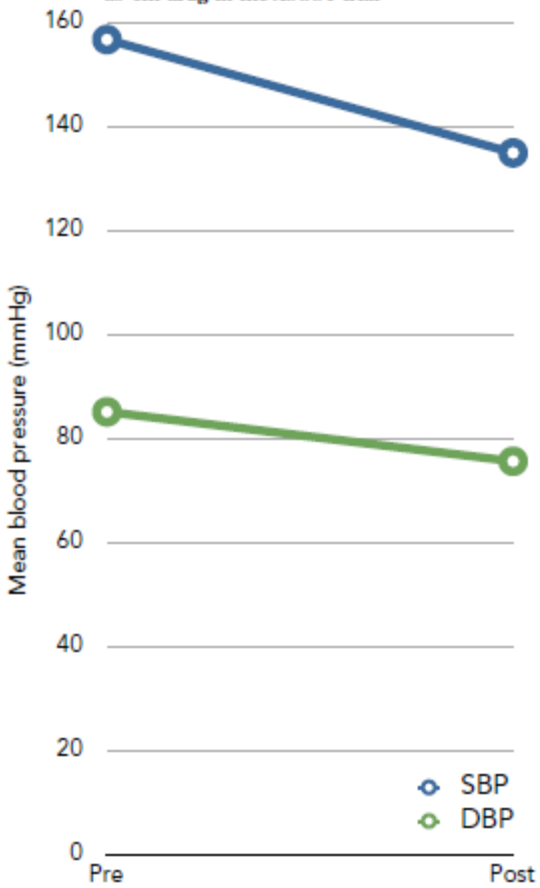
1. Estimated glomerular filtration rate (eGFR) of at least 60 ml/min,
2. Last potassium (K) less than 4.5 mmol/L, and
3. On thiazide, if already on an angiotension converting enzyme (ACE) inhibitor such as lisinopril, or an angiotensin receptor blocker (ARB) such as losartan.

Prescribing spironolactone as the fourth drug

Kaiser Permanente Southern California analyses of patients with uncontrolled hypertension who are taking more than three drugs show that only 3% have been prescribed spironolactone. Underutilization appears due to a lack of familiarity with this medication.

Though the spironolactone dosing range for resistant hypertension is 12.5 to 50 mg daily, the usual primary care dosing range is 12.5 to 25 mg. continues on page 2

Systolic and diastolic blood pressure reductions with spironolactone used as 4th drug in the ASCOT trial*



*Chapman N, et al. Hypertens 2007; 49: 839-845.

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Common questions that arise are: 1) After starting spironolactone, when is it best to check a follow-up potassium, and how is it best to avoid hyperkalemia? 2) How common is gynecomastia? 3) Should aldosterone levels be obtained prior to starting spironolactone? 4) How does one transition patients taking potassium replacement to spironolactone? 5) Are there patient populations who may be more responsive to spironolactone?

When to check follow-up potassiums and how to avoid hyperkalemia?

Onset of spironolactone action is about 48 hours, and potassium homeostasis occurs at 2 to 4 weeks. Checking follow-up electrolytes about 2 weeks after drug initiation, and 2 weeks again after dose increase, is recommended. The CMI eligibility criteria spell out the safety boundaries. Patients whose baseline potassium is 4.5 mmol/L or higher are potentially in trouble with potassium homeostasis, and patients with an eGFR < 60 ml/min are less likely to handle increased potassium within a normal serum range.

In similar fashion, patients on two medications that may cause hyperkalemia, such as an ACE inhibitor or ARB, taken together with spironolactone, have been shown to have an increased incidence of severely high levels of potassium, unless there's also a thiazide or loop diuretic on board.

Even though patients have achieved potassium homeostasis in the normal range on spironolactone, they are still at risk for acute hyperkalemia when there is acute volume loss, which may occur with an acute gastrointestinal illness, poor glycemic control if diabetic, or on certain medications that increase serum potassium levels. These medications include triamterene (sometimes given as triamterene/hydrochlorothiazide, brand name Maxzide®), amiloride, trimethoprim (contained in Bactrim™, which is trimethoprim/sulfamethoxazole) and non-steroidal anti-inflammatory drugs.

In addition to a potassium check 2 weeks after initiating and uptitrating spironolactone, a serum sodium is also indicated. It is uncommon, but hyponatremia may occur. Modest hyponatremia with sodium 130 to 134 mmol/L is well tolerated. Once the level of sodium level stabilizes, it can be followed at 3 to 4 month intervals. When electrolytes and renal function are normal, patients taking spironolactone should have follow-up electrolytes and creatinine at 6 to 12 month intervals.

How common is gynecomastia?

Gynecomastia and breast or nipple tenderness are the most common reasons for discontinuing spironolactone. However, these symptoms are related to dose and pre-disposing conditions. In usual primary care practice, gynecomastia might be expected in less than 5% of men taking 12.5 to 25 mg of spironolactone.

Cirrhosis and heart failure are conditions that may independently cause gynecomastia. Doses of spironolactone up to 200 mg twice daily, which may be prescribed for cirrhosis or primary hyperaldosteronism, have been associated with up to a 50% incidence of gynecomastia.

In the ASCOT trial, when a dose of 12.5 to 50 mg of spironolactone was prescribed for resistant hypertension, 6% of patients withdrew because of gynecomastia or breast tenderness, and 2% withdrew due to hyperkalemia. The 50 mg dose increases the chance of gynecomastia without offering significant additional reduction in blood pressure.

When gynecomastia occurs, it is reversible after spironolactone is discontinued. In patients who have experienced excellent blood pressure reduction with spironolactone, but gynecomastia occurs, eplerenone is a good option.

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Should aldosterone levels be checked prior to starting spironolactone as fourth drug treatment?

No, it is not generally necessary. In large populations, it has been shown that aldosterone levels do not predict responsiveness to spironolactone in patients who have resistant hypertension. Lack of predictability may be due to the fact that serum levels of aldosterone are not usually representative of the levels found in the tissues of critical organs, such as the vasculature, heart, and kidneys.

Additionally, chasing elevated aldosterone/peripheral renin activity ratios for all patients who are resistant to three drugs prior to starting spironolactone is counterproductive, because it carries a high probability of unnecessary downstream testing due to false positive test results.

To illustrate excessive downstream testing, about 20% of patients with resistant hypertension—or about 5% of the entire hypertensive population—would be expected to have an elevated aldosterone/peripheral renin activity ratio. Approximately half of that number would not have true hyperaldosteronism; therefore, there would be a large number of unnecessary and potentially false positive saline administration tests and false positive adrenal imaging (adrenal incidentalomas).

In addition, half of primary hyperaldosteronism patients will have diffuse adrenal hyperplasia, which is medically responsive to spironolactone.

Considering that there are just a few percent of primary hyperaldosteronism patients in the resistant population, it is more appropriate to cull them out later. In these cases, it is necessary for patients to be off spironolactone for at least 4 weeks before performing diagnostic aldosterone measurements, because the drug suppresses this hormone.

A small group of patients who are both spontaneously hypokalemic and hypertensive should have aldosterone and renin levels tested while taking potassium replacement to rule out hyperaldosteronism prior to taking spironolactone. Serum potassium needs to be normalized, because hypokalemia may cause reactive aldosterone secretion and a false positive result.

How does one transition patients taking potassium replacement to spironolactone?

The few comparison studies performed on potassium sparing suggest that spironolactone 25 mg is roughly comparable to 20 to 30 mEq potassium chloride in patients with normal renal function.

One scenario would be a patient taking potassium chloride 40 mEq/day whom you wish to start on spironolactone. The patient should be instructed to start spironolactone 25 mg and to continue taking potassium chloride 40 mEq/day for 2 days. On the third day, the patient should be instructed to reduce potassium chloride to 10 mEq/day and continue to take spironolactone. Two weeks after starting spironolactone, electrolytes should be checked.

Potassium replacement with spironolactone should be avoided whenever possible. If the follow-up potassium level is marginally low, dietary potassium would be safer than pharmacologic.

Hypokalemia induced by diuretics is less common when patients are taking lisinopril/hydrochlorothiazide (Prinzide), because of the counterbalancing effect of the potassium-sparing ACE inhibitor. Spironolactone taken with Prinzide is acceptable, because of the presence of hydrochlorothiazide.

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Are there patient populations who may be more responsive to spironolactone?

Yes. Certain sub-groups of patients may be more responsive. Individuals who are obese or have obstructive sleep apnea are more likely to have higher aldosterone levels. Blacks with hypertension have higher aldosterone levels and may be more responsive to treatment. In addition, some patients with stage 3 and 4 chronic kidney disease may have a beneficial reduction in blood pressure with 6.25 mg spironolactone, with follow-up electrolytes in 1 to 2 weeks to catch any hyperkalemia early.

Adverse effects of aldosterone and benefits of spironolactone

Elevated aldosterone levels are associated with sodium and fluid retention. They are also associated with endothelial dysfunction, inflammation of pancreatic islet cells, myocardial fibrosis, diastolic dysfunction, chronic kidney disease, and heart failure.

Because it is a direct antagonist of aldosterone, spironolactone reduces heart failure mortality in patients with systolic dysfunction,* promotes cardiac diastolic relaxation, reverses left ventricular hypertrophy, reduces proteinuria, and may decrease the severity of obstructive sleep apnea.

Used in the primary care dose range 12.5 mg to 25 mg for eligible patients, as defined by CMI, spironolactone is a well-tolerated and effective fourth antihypertensive drug.

For more information, see SCPMG's **Clinical Practice Guideline for Adult Hypertension**.

*Randomized Aldactone Evaluation Study (RALES)