

'CAME OUT OF CLEAR SKY,' SAYS PRESIDENT'S PHYSICIAN

Adm. Ross T. McIntire
Asserts There Was No
Indication of Immi-
nent Danger.

By CHARLES G. ROSS

DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

WASHINGTON, April 13 (AP).
PRESIDENT ROOSEVELT
died from what doctors call
a cerebral hemorrhage,
which means a sudden exten-

Figure 1. Headlines of the *St. Louis Post-Dispatch*,
April 13, 1945.
Reprinted with the permission of the *St. Louis Post-Dispatch*.

Messerli *N Engl J Med* 1995;332:1038.

Severe hypertension is relatively common

Patient and visit characteristics	Number of visits in thousands	Total	Percent distribution					
			Low	Normal	Mildly high	Moderately high	Severely high	Blank
All visits 18 years and over ^a	92,895	100.0	6.0	14.6	33.5	25.8	16.2	3.9
Age								
18-24 years	22,558	100.0	5.2	15.8	31.6	24.9	17.9	4.6
25-44 years	1,800	100.0	8.5	14.7	31.6	23.6	18.4	3.2
45-64 years	1,354	100.0	6.7	14.8	33.3	30.0	12.5	*
65-74 years								
75 years and over								
Sex								
Female	67,183	100.0	6.2	14.1	34.2	26.1	15.6	3.7
Male	22,558	100.0	5.2	15.8	31.6	24.9	17.9	4.6
Race ^b								
White	1,800	100.0	8.5	14.7	31.6	23.6	18.4	3.2
Black	1,354	100.0	6.7	14.8	33.3	30.0	12.5	*
Asian								
Other								
Ethnicity								
Hispanic or Latino	10,696	100.0	5.9	18.0	34.4	24.4	12.6	4.7
Not Hispanic or Latino	82,199	100.0	6.0	14.1	33.4	26.0	16.6	3.8

There are
~100,000 ER
visits each year
for hypertension

~15,000 of those
visits are for
severely high BP

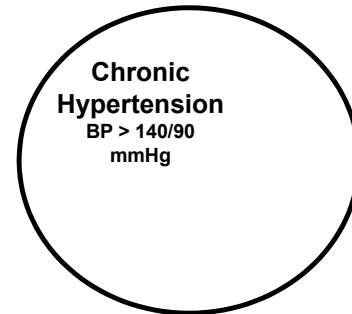
Pitts et al. Natl Health Stat Report 2008;7:1-38.

Current State of Hypertensive Crisis Management

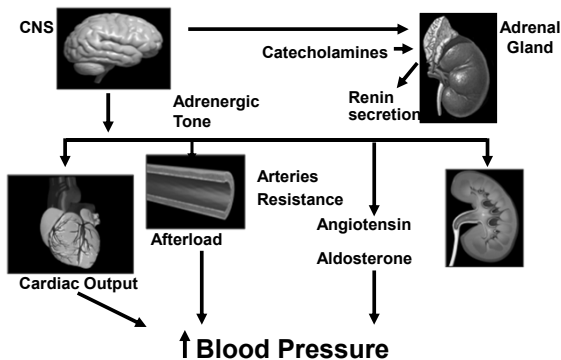
- Hypertensive crises are among the most misunderstood acute medical conditions
- Delays in initiating therapy can cause severe complications
- Overzealous therapy can be equally damaging
- Understanding the pathophysiology involved in hypertensive crises helps in deciding optimal treatment strategies

Varon J, Marik PE. *Chest*. 2000;118:214-227.
Epstein M. *Clin Cornerstone*. 1999;2:41-54.

Hypertension Emergencies in context

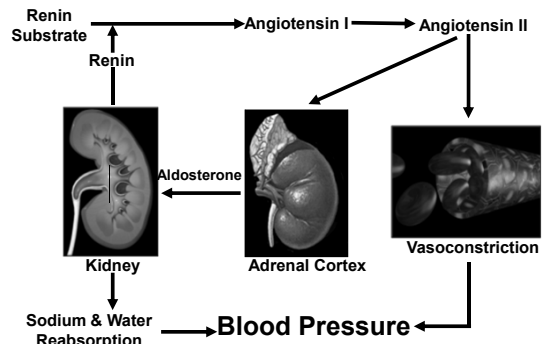


Sympathetic Nervous System Regulation of Blood Pressure



<http://vasoactivetherapy.com/files/CORLOPAM.PPT>

Renin-Angiotensin-Aldosterone Regulation of Blood Pressure



Almost all cases of Hypertension can be explained by:

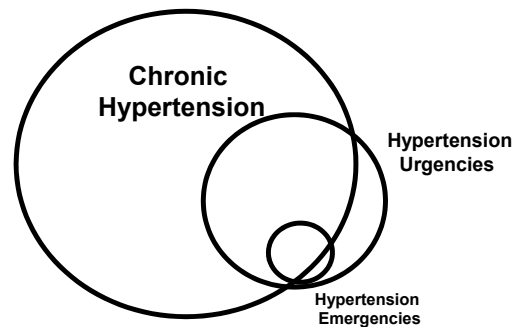
- Sodium excess
- Extracellular volume expansion
- Sympathetic overactivation

Too Much Sodium (Salt)

Too Much Water

Too Much Sympathetic Activity

Hypertension Emergencies in context



Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Follow up

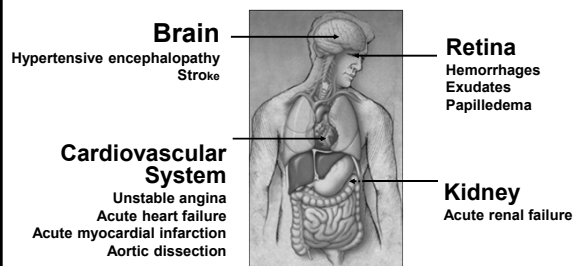
Terminology and Definitions (JNC 7)

Urgency

Emergency

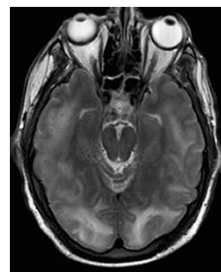
The diagnosis of hypertensive emergencies depends on the clinical manifestations rather than only on the absolute level of the blood pressure.

End-Organ Damage Characterizes Hypertensive Emergencies



Adapted from Varon J, Marik PE. *Chest*. 2000;118:214-227.

Hypertensive Encephalopathy



PRES:
Posterior reversible encephalopathy syndrome

Typically symmetrical white matter edema in the posterior cerebral hemispheres

**What the primary care clinician
needs to know**

**How do you differentiate a
hypertensive *URGENCY* from a
hypertensive *EMERGENCY*?**

How would you classify this patient?

- 81 year old man presents for his regular scheduled clinic visit. He feels well and has no complaints but his entrance BP is 220/110 mm Hg. Physical exam reveals S4 cardiac gallop but no other abnormalities

How would you classify this patient?

- 63 year old man who presents to the emergency room with severe, tearing chest pain. On CT angiogram he is found to have an aortic dissection. His BP is 165/98 mm Hg

How would you classify this patient?

- 51 year old woman with atrial fibrillation is found to have a cardioembolic stroke. Her BP on hospital day #2 is 190/110 mm Hg

Hypertensive crisis

- You will almost certainly see a hypertensive urgency in your career
- You will also likely see a hypertensive emergency
 - Only occur in 1-2% of the hypertensive population
 - But, there are 50 million hypertensive Americans
 - 500,000 hypertensive emergencies/year
- Higher in the elderly and African Americans
- Incidence is twice as high in men as compared to women

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Follow up

**What the primary care clinician
needs to know**

**How do patients with hypertensive
URGENCIES present?**

Signs and Symptoms

Signs and Symptoms	HTN Urgency (%)	HTN Emergency (%)
Headache	22	3
Epistaxis	17	0
Chest Pain	9	27
Dyspnea	9	22
Faintness	10	10
Agitation	10	2
Neurologic Deficit	3	21
Vomiting	2	3
Arrhythmia	6	0

Zampaglione B, et al. Hypertension 1996;27:144-147.

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Outcomes

**Goals of evaluation
are to determine
etiology, and rapidly
assess for end
organ damage**

Initial Evaluation

- Symptoms
- Medical History
 - Episodic palpitations and perspiration?
- Medications
 - MAO inhibitors
 - Clonidine
- Social History
 - Recreational Drugs
 - Amphetamines
 - Cocaine
 - Phencyclidine

Physical Exam

- Blood pressures must be taken in both arms
 - If the cuff is too small, the BP will be falsely elevated
 - If the cuff is too low (below the level of the heart), the BP will be falsely elevated
- Pulses should be checked in upper and lower extremities
- Neuro exam
- Cardiac exam
- Pulmonary exam
- **Ocular exam:** only happens in 13% of pts

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
- Evaluation
- Management
- Outcomes

Management of Hypertensive Urgencies

Reminder:
Have a sense of urgency!

Severely Increased Blood Pressure in the Emergency Department

Philip H. Shayne, MD
Stephen R. Pitts, MD, MPH

See commentary, p. 530.

From the Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA.

Editor's note: This article continues a series of special tributes addressing state-of-the-art techniques, or concepts. State-of-the-art articles will be featured in *Annals* on a regular basis in the next several volumes.

Patients with severely increased blood pressure often present to the emergency department. Emergency physicians evaluate and treat hypertension in various contexts, ranging from the compliant patient with well-controlled blood pressure to the asymptomatic patient with increased blood pressure to the critically ill patient with increased blood pressure and acute target-organ deterioration. Despite extensive

"There is no clear consensus on the acute management"

spectrum of disease, from the asymptomatic to critically ill patient, and the dilemma it creates for the emergency physician in deciding how and when in the process to intervene.

Shayne and Pitts. *Ann Emerg Med.* 2003;41:513-29.

Pharmacological interventions for hypertensive emergencies

Marco I Perez¹, Vijaya M Musini¹, James M Wright¹



Does anti-hypertensive drug therapy as compared to placebo or no treatment affect mortality and morbidity in patients with a hypertensive emergency?

Does one first-line antihypertensive drug class offer a therapeutic advantage, in terms of mortality and morbidity, over another in patients with a hypertensive emergency?

Main results

Fifteen randomized controlled trials (representing 869 patients) met the inclusion criteria. Two trials included a placebo arm. All studies (except one) were open-label trials. Seven drug classes were evaluated in these trials: nitrates (9 trials), ACE-inhibitors (7), diuretics (3), calcium channel blockers (6), alpha-1 adrenergic antagonists (4), direct vasodilators (2) and dopamine agonists (1).

Authors' conclusions

There is no RCT evidence to determine which drug or drug class is most effective in reducing mortality and morbidity in patients with a hypertensive emergency.

"There is insufficient RCT evidence to determine which drug or drug class is most effective in reducing mortality and morbidity."

Perez et al. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD003653.

What the primary care clinician needs to know

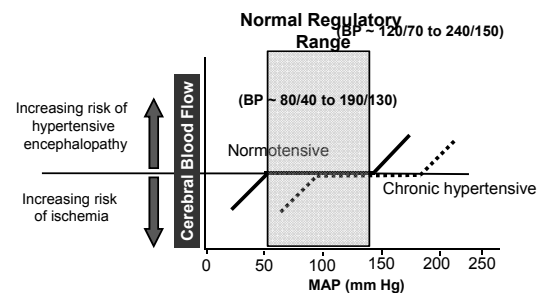
What are appropriate therapies to manage a hypertensive URGENCY?

Management of Hypertensive URGENCY

- Hypertensive urgencies can generally be managed with oral medications as an outpatient. Can lower BP over days (not hours)
 - Important to prevent too-rapid lowering

JNC 7, *JAMA* 2003; 289:2560-2572

Cerebral Autoregulation Is Central to Treatment of Hypertensive Crises



Adapted from Varon J, Marik PE. *Chest*. 2000;118:214-227.

All blood pressure sensitive organs have some degree of autoregulation

CLINICAL PEARL # 1

If BP is lowered too rapidly, ischemic injury can result
(ischemic stroke, acute Kidney injury, or ischemic retinopathy)

For treatment of hypertension urgencies you want:

1. Oral medication
2. Long acting
3. Lowers blood pressure effectively
4. Has few side effects
5. NO rebound
6. Improves outcomes

Oral medication choices for hypertensive urgency

- Appropriate choices
 - ACE-inhibitors
 - Angiotensin receptor blockers (ARBs)
 - Calcium channel blockers
 - Thiazide-type diuretics
- **LESS APPROPRIATE** choices
 - Labetalol (very effective but requires multiple daily doses)
 - Hydralazine (reflex tachycardia, multiple daily doses)
 - Beta blockers (less BP lowering and clinical benefit)
 - Alpha blockers (less clinical benefit)
 - Clonidine (overshoot, rebound hypertension, outcomes)

Clonidine

- MOA is suppression of sympathetic outflow from CNS
- If clonidine is abruptly d/c'd, rebound HTN can occur
 - This happens because of abrupt return of sympathetic outflow (mimics a sympathetic crisis)
- Clonidine withdrawal is often more severe in patients who are also taking a β -blocker
 - β -blockers inhibit beta-mediated vasodilation and leave unopposed α -mediated vasoconstriction
- So stop β -blockers before Clonidine
- Clonidine weaning should occur over WEEKS
- If rebound hypertension occurs, treatment is to re-start clonidine and wean more slowly

Clonidine can “overshoot”

- A 1983 paper reported:
- “In 20 patients with severe hypertension, rapid oral clonidine titration was employed...”
- “Baseline BP was 212 ± 7 / 134 ± 3 mm Hg and decreased to 151 ± 5 / 104 ± 3 mm Hg.”
- “The mean dose was 0.32 ± 0.02 mg, and mean response time 1.8 ± 0.2 hours...”
- “Side effects were minimal, except for **one patient who died of a cerebral infarct, which developed after the blood pressure was lowered with clonidine.**”

Use of Oral Clonidine for Rapid Titration of Blood Pressure in Severe Hypertension, Samuel Spitalerwitz, Jerome G. Porush, Chika Oguagha. Chest, Volume 83, Issue 2, February 1983, Pages 404-407



What the primary care clinician needs to know

What is the appropriate follow up for a patient with a hypertensive URGENCY?

Patients with hypertensive urgency respond to “rest” and meds

- 549 patients admitted to an ED for HTN (avg BP 192/106)
- All patients given a 30-minute rest period
 - A satisfactory BP response to rest was seen in 31.9% of population (BP < 180/105 mmHg)
- Patients who **did not** respond to rest were assigned to: perindopril, amlodipine, or lisinopril
- 79.1% had a satisfactory BP response to treatment
 - At 2 hours, NO difference in BP response by drug
- **AUTHORS CONCLUSIONS:** Rest as an initial step can be effective and safe for hypertensive urgencies

EARLY FOLLOW UP IS ESSENTIAL!

Grassi et al. J Clin Hypertens 2008;10:662-7.

CLINICAL PEARL # 2

Approximately 30% of patients with hypertensive urgency will have an adequate **short-term** BP response to REST alone

Patients with hypertensive urgency have low short term event rates

- Retrospective review of all patients seen at a Cleveland Clinic outpatient facility from 2008-2013.
- 4.6% of visits had hypertensive urgency.
- Mean age - 63.1; 57.7% women; 76.0% white. Mean BMI - 31.3; Mean BP - 183/96 mm Hg
- 0.7% were sent to the hospital; the others sent home.
- 0.9% had a major adverse cardiovascular event in the next 6 months. Rates were not different for those referred to the hospital vs. those sent home

Patel KK et. al. JAMA Intern Med. published on line June 13, 2016

Patients with hypertensive urgency have higher LONG - term event rates

- 206,147 ED visits for HTN in Ontario, Canada, from 2002 to 2012.
- Median age 64 years, 81.4% had known hypertension.
- ED visits for HTN increased from 15,793 per year in 2002 to 25,950 per year in 2012 (a 64.3% increase)
- The most frequent causes for hospital admission were stroke (5.3%), renal failure (5.2%) and CHF (3.1%).
- Mortality was 0.17% at 7 days, 0.43% at 30 days, 0.85% at 90 days, 2.5% at 1 year at 4.4% at 2 years

Masood S, et al. Ann Emerg Med. 2016;doi:10.1016/j.annemergmed.2016.04.060.

Elderly woman with hypertension

- 78 year old woman with HTN
- During a routine visit BP = 205 / 75
- No complaints except “not feeling right”; fundi could not be seen due to cataracts but otherwise normal exam
- Admits to running out of her BP meds
- We placed her in a quiet room and administered her usual BP medications
- 2 hours later BP 165/70; she felt well
- Sent home on usual meds with home health and follow up visit in 1 week

66 year old man with HTN prior NSTEMI

- 66 year old male who is s/p NSTEMI
- Cardiac risk factors include hypertension, obesity and smoking
- Went to urgent care when he "felt ill"
- BP 200/110 but decreased to 170/90
- Ruled out for MI then sent home and told to speak to PCP at next visit
- PCP and cardiologist never notified
- 2 months later wife called cardiologist when patient was 'dragging his left leg'
- Sent to ER where acute stroke was found

Management of Hypertensive Emergencies

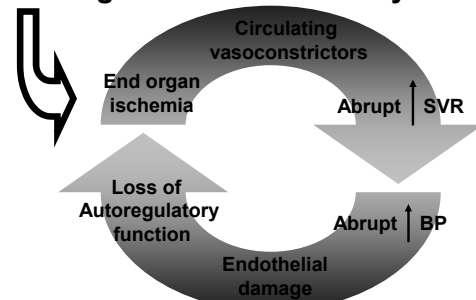


Almost all cases of Hypertension can be explained by:

- Sodium excess
- Extracellular volume expansion
- Sympathetic overactivation

Too Much Sodium (Salt)
Too Much Water
Too Much Sympathetic Activity

Pathophysiology of Hypertensive Emergencies: a Vicious Cycle



Ault NJ, et al. *Am J Emerg Med*. 1985;3(6 suppl):10-15. 2. Wallach R, et al. *Am J Cardiol*. 1980;46:559-565.
Varon J, et al. *Chest*. 2000;118:214-227. 4. Kincaid-Smith P. *J Hypertens*. 1991;9:893-899.

What the primary care clinician needs to know

How do patients with hypertensive **EMERGENCIES** present?

Signs and Symptoms

Signs and Symptoms	HTN Urgency (%)	HTN Emergency (%)
Headache	22	3
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Chest Pain	9	27
Dyspnea	9	22
Faintness	10	10
Agitation	10	2
Neurologic Deficit	3	21
Vomiting	2	3
Arrhythmia	6	0

Zampaglione B, et al. *Hypertension* 1996;27:144-147.

Which end organ damages are most commonly diagnosed in a hypertensive emergency?

End-organ damage type	Cases (%)
Cerebral infarction	24.5
Intracerebral or subarachnoid bleed	4.5
Hypertensive encephalopathy	16.3
Acute pulmonary edema	22.5
Acute congestive heart failure	14.3
Acute myocardial infarction or unstable angina	12.0
Aortic dissection	2.0
Eclampsia	2.0

Zampaglione et al. Hypertension 1996;27:144-7.

39 year old man with chest pain and shortness of breath

Causes of hypertensive emergencies:

1. Too much sodium
2. Too much water (missed HD)
3. Too much sympathetic activity (Methamphetamine use)

What the primary care clinician needs to know

What is the appropriate management for a patient with a hypertensive *EMERGENCY*?

**EMERGENCY DEPARTMENT
EMERGENCY DEPARTMENT
EMERGENCY DEPARTMENT**

How Low Should You Go?

- Simple answer
 - 20-25% reduction in MAP within 1st hour
- Better answer
 - It really depends on clinical condition
 - Less aggressive with ischemic stroke
 - More aggressive with hemorrhagic stroke, acute HF and aortic dissection

Marik and Varon. Critical Care 2003, 7:374-84.

**Intensive Care Unit
Intensive Care Unit
Intensive Care Unit**

Appropriate Therapies for Hypertension Emergencies: IV



- **Adrenergic blockers**
 - Esmolol (β_1)
 - Labetalol (α_1 and β)
 - Phentolamine (α_1)
 - Urapidil (α_1)
- **Nitric Oxide (NO) donors**
 - Nitroprusside
 - Nitroglycerin
- **Dopamine agonist**
 - Fenoldopam
- **Direct vasodilator**
 - Hydralazine
- **Ca^{2+} channel blockers**
 - Nicardipine
 - Clevidipine
- **ACE inhibitors**
 - Enalaprilat

Hypertensive Urgencies / Emergencies:

- Classification / Definition
- Etiology / Pathophysiology
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- Outcomes

STAT Registry Study Population



Patients	1,588
Age - median	58 (49 - 70)
Female sex	49%
Black race	56%
White race	34%
Qualifying BP	
Systolic	200 mm Hg (186 - 220)
Diastolic	110 mm Hg (93 - 123)
Length of stay	5 days (range 2 - 9)

Am Heart J Volume 158, Issue 4, October 2009, Pages 599-606.e1

Medical History



Condition	%
Hypertension	89
Tobacco or alcohol use	38
Diabetes	35
Chronic kidney disease	31
End stage renal disease	11
Previous hospitalization for HTN	27
Neurological event	23
Drug abuse	15

Am Heart J Volume 158, Issue 4, October 2009, Pages 599-606.e1

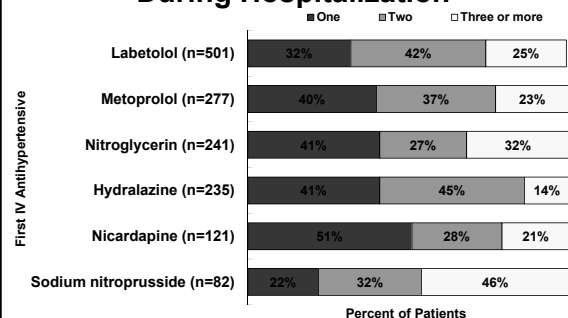
What got them into trouble



Factors	%
Medication non-adherence	25
Chronic	16
Current	10
Missed or incomplete dialysis	3
Anxiety/psychosocial reaction	2
Drug abuse	11

Am Heart J Volume 158, Issue 4, October 2009, Pages 599-606.e1

Number of IV Antihypertensives During Hospitalization



Am Heart J Volume 158, Issue 4, October 2009, Pages 599-606.e1

CLINICAL PEARL # 3

Almost all patients with HTN will require combination therapy (IV or po)



Short-Term (2 to 6 month) Outcomes

Acute Condition	Death	Rehospitalization
ACS ^{1,2,3}	5-7%	30%
CHF ⁴	8.5%	26%
Severe Hypertension ⁵	7-9%	37%

1. OASIS-5 *NEJM* 2006
2. GUSTO IIb *NEJM* 1996
3. GRACE *JAMA* 2007
4. IMPACT-HF *J Cardiac Failure* 2004
5. STAT Registry results

Am Heart J Volume 158, Issue 4, October 2009, Pages 599-606.e1

Summary

- Acute severe hypertension is
 - Associated with medical NONadherence
 - If a hypertensive EMERGENCY, requires ICU admission, IV drugs
 - Alarming low rates of follow-up
 - High mortality and morbidity, especially with new or worsening end-organ damage
- Major need to improve prevention and treatment of this important clinical condition

Areas of Consensus in Hypertension management

- Optimal BP goal is generally < 140/90
 - For higher risk patients may be < 120/80 (SPRINT Trial)
- The main medications for hypertension are:
 - Thiazide-type diuretics
 - ACE inhibitors or ARBs
 - Calcium channel blockers

Diuretics and BP Control

- In states of sodium (and water) excess, diuretics are essential
- Most classes of antihypertensive agents lead to sodium retention, as compensation for lower BP
- JNC 8 recommends a thiazide-type diuretic, as one of four initial antihypertensive choices in the general population
- JNC 8 recommends a thiazide-type diuretic, as one of two initial antihypertensive choices in the Black patients

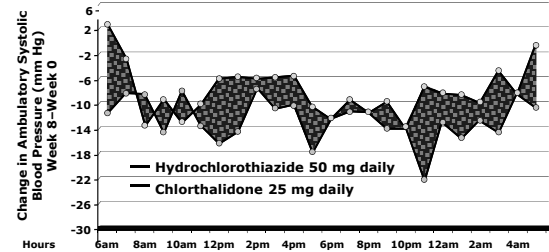
CLINICAL PEARL # 4

In many patients with HTN, adequate diuresis is ESSENTIAL for BP control

Which “Thiazide”?

- Thiazide
 - Hydrochlorothiazide
 - Chlorthiazide (Diuril®)
 - Bendroflumethiazide (Naturetin®)
 - [Bendroflumethiazide / Nadolol (Corzide®)]
- Thiazide-like
 - Metolazone
 - Indapamide (Lozol®)
 - Chlorthalidone (Thalitone®, Hygroton®)

Thiazide Diuretics Differ in Their Antihypertensive Effects



Ernst ME, et al. Hypertension. 2006;47:352-358.

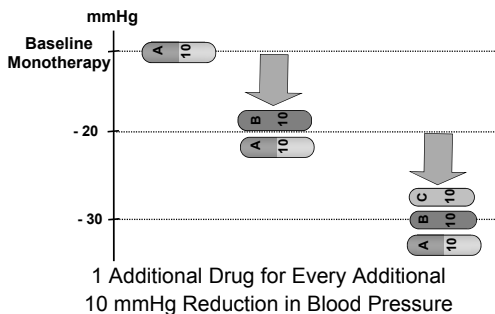
Chlorthalidone vs. HCTZ

- For patients with resistant or difficult-to-control HTN, chlorthalidone appears to lower BP more effectively than hydrochlorothiazide.
- If Chlorthalidone is initiated, serum K⁺ must be monitored after 1 and 4 weeks to avoid hypokalemia. Serum Na⁺ must be monitored periodically to avoid hyponatremia.

CLINICAL PEARL # 5

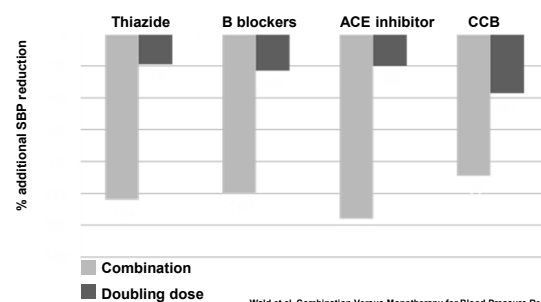
In patients with difficult to control hypertension, switching the diuretic from HCTZ to Chlorthalidone may improve BP control

“Rule of TENS for SBP”



Cushman W and Basile J. J. of Clinical Hypertension

BP lowering effect of “doubling dose” of 1 agent or “combination” of lower doses of 2 agents



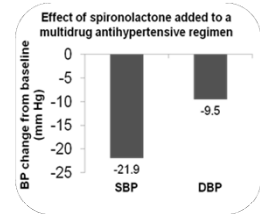
Wald et al. Combination Versus Monotherapy for Blood Pressure Reduction. The American Journal of Medicine, Vol 122, No 3, March 2009

CLINICAL PEARL # 6

Combining lower doses of antihypertensive agents improves BP control and limits side effects

Spironolactone

- **Population:** 1411 patients in the ASCOT Trial whose BP was NOT controlled on their trial assigned 3 drug regimen
- Spironolactone 25 mg daily added to their regimens
- **Results:** With the addition of spironolactone, mean BP fell by 21.9 / 9.5 mm Hg ($p < 0.001$).
- **Adverse events:** Gynecomastia occurred in 6% of patients and biochemical abnormalities (mainly hyperkalemia) occurred in 2% of patients



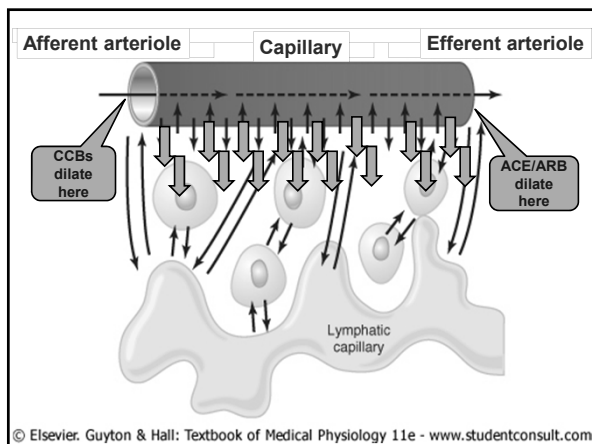
Chapman N, et al. *Hypertension*. 2007;49:839-845.

CLINICAL PEARL # 7

Addition of spironolactone to patients with resistant hypertension, improves BP control

Calcium Channel Blockers and Edema

- Palpable swelling produced by expansion of the interstitial fluid volume



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CLINICAL PEARL # 8

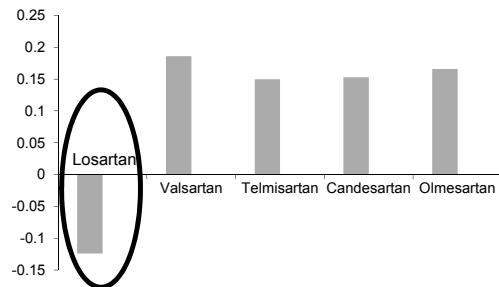
Adding an ACE inhibitor or an ARB to a CCB can decrease lower extremity edema

Risk of Gout with antihypertensive therapy

	Adjusted relative risk* (95% CI)	
Diuretics	2.36 (2.21 to 2.52) 0.03	236% ↑
β blockers	1.48 (1.40 to 1.57) 0.04	148% ↑
ACE inhibitors	1.24 (1.17 to 1.32) 0.04	124% ↑
ARBs OTHER THAN LOSARTAN	1.29 (1.16 to 1.43) 0.72	
Calcium channel blockers	0.87 (0.82 to 0.93) 0.17	
Losartan	0.81 (0.70 to 0.94) 0.20	19% ↓

*Adjusted for sex, age, calendar year, number of visits to a general practitioner, body mass index, alcohol intake, ischaemic heart disease, hyperlipidaemia, diabetes, chronic renal failure and heart failure, and simultaneously for the other antihypertensive drug classes.

Change in serum uric acid levels with treatment



Cardiovascular Diabetology. 2013 12:159

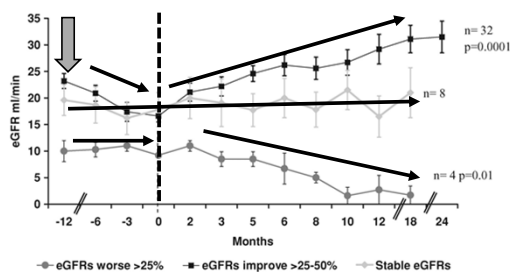
CLINICAL PEARL # 9

Addition of Losartan to a thiazide diuretic can decrease uric acid levels and incidence of gout

Serum Creatinine increase with ACE inhibitors and ARBs

- Starting an ACE inhibitor or ARB can result in a small and nonprogressive increase in serum creatinine (Cr)
- The cause is reduced intraglomerular pressure, which is beneficial, but leads to a decrease in GFR
- A 30% increase in serum Cr is generally acceptable
- The Cr will usually peak within a week of starting therapy, then stabilize
- Electrolytes and Cr should be checked within the first few weeks of therapy.
- If > 30% increase in creatinine occurs, stop the drug

Changes in GFR after stopping ACE-I or ARB in patients with advanced CKD



Aimun K, Ahmed et al. Nephrol. Dial. Transplant. 2010;25:3977-3982

CLINICAL PEARL # 10

A 30% increase in serum Cr after addition of an ACE inhibitor or ARB is acceptable.