Hypertension

John M. Dopp, Pharm.D.
Associate Professor (CHS)

4125 Rennebohm Hall
265-9352
JOHN.DOPP@WISC.EDU

Lecture Outline

- Part 1: Hypertension Overview/General Information on Treatment
- Part 2: Drug Therapy
- Part 3: Hypertension Treatment Guidelines
- Part III: Current Questions in HTN management
- Part VI: Hypertensive Crisis

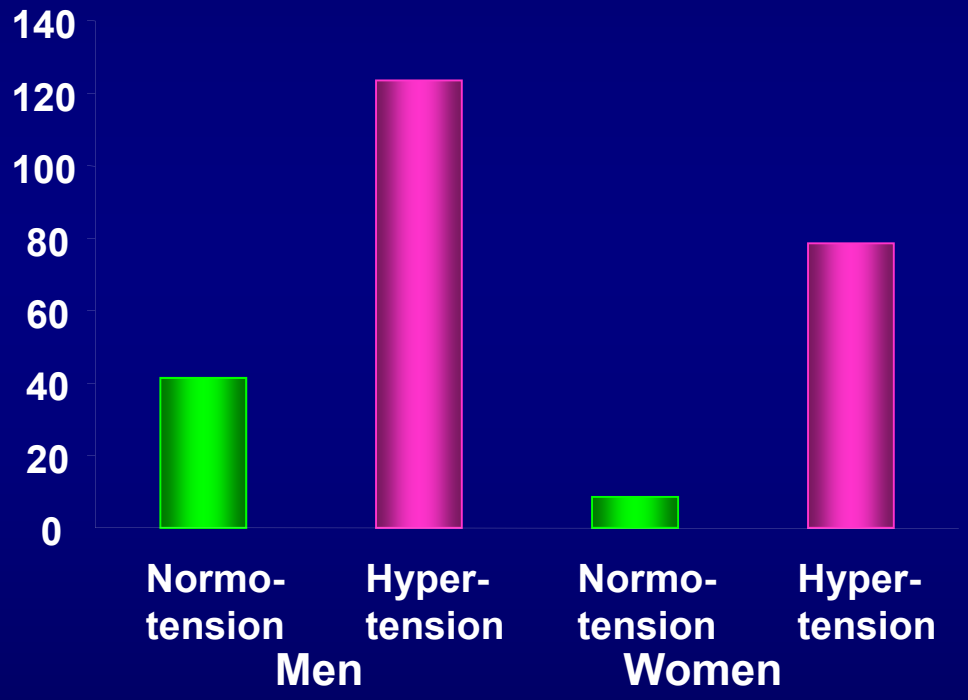
Historical Notes on Hypertension

"The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it."

Brit Med J 1931;2:43-7.

Key Historic Milestones in Hypertension

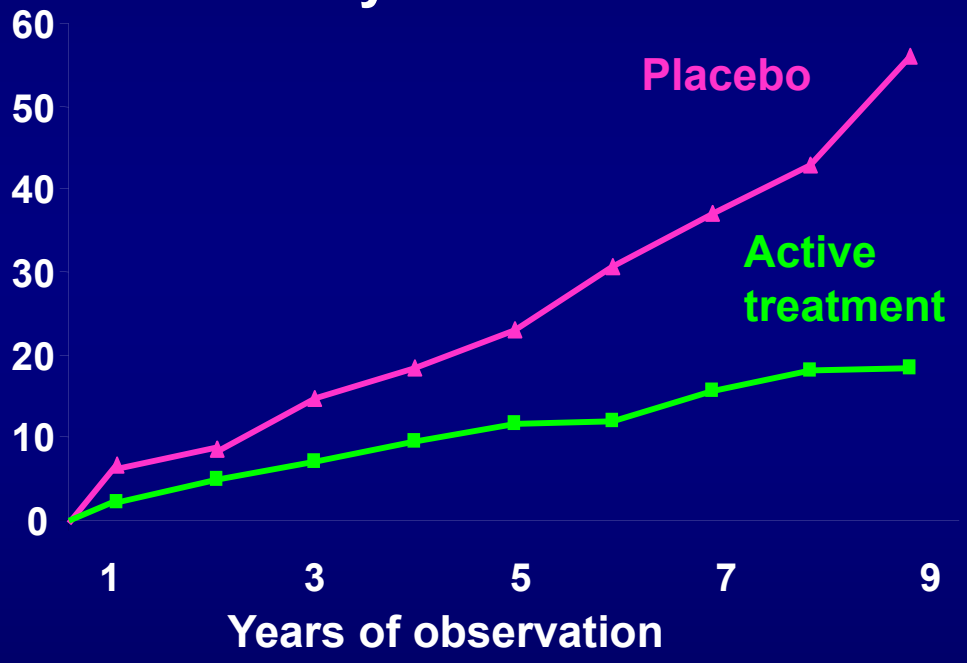
Hypertension:
Increased mortality and morbidity



CHD incidence rate/1000

The Framingham Study
Ann Intern Med 1961;55:33-50

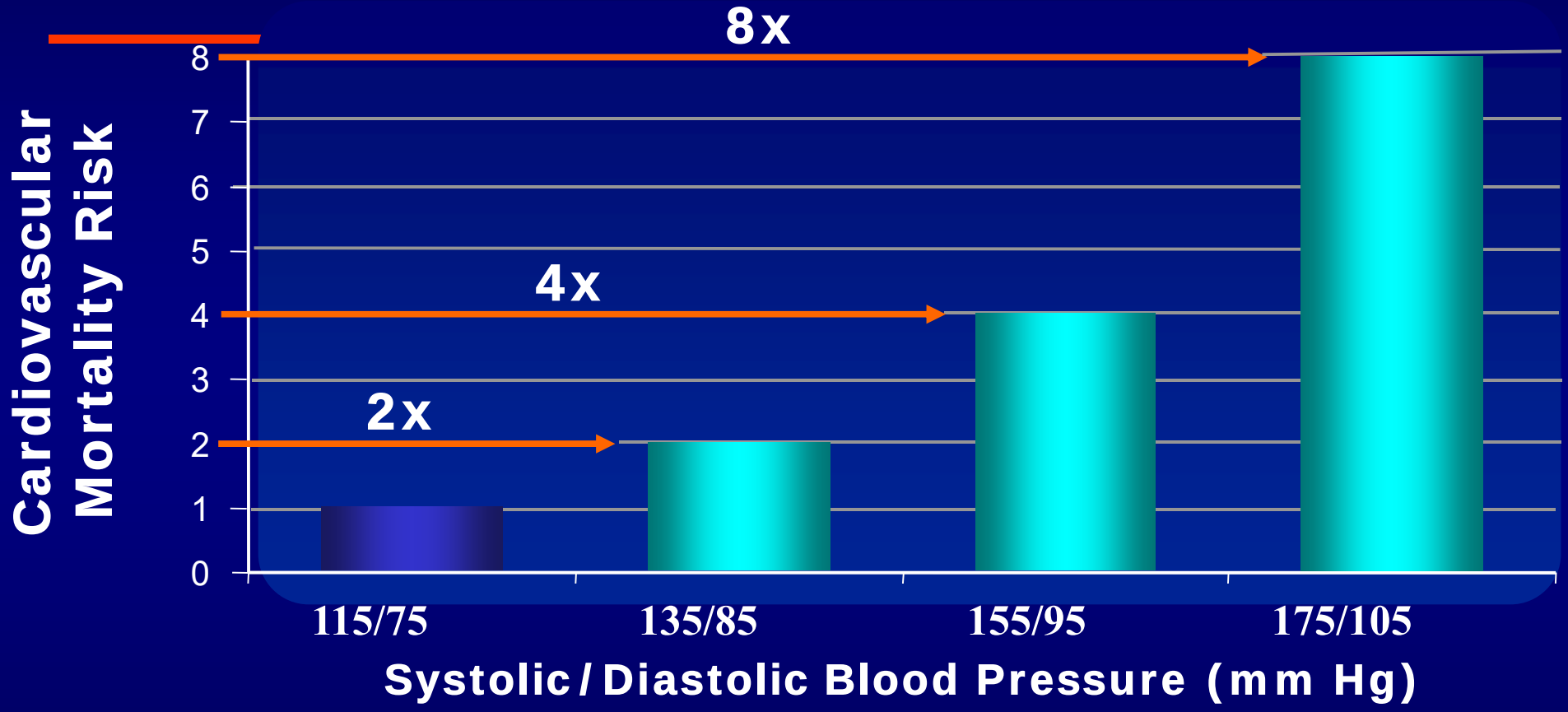
Treatment of hypertension:
Significant reduction of mortality and morbidity



Cumulative incidence of all fatal and non/fatal endpoints

Veterans Administration Study II
JAMA 1970;213:1143-52

Cardiovascular Mortality Risk Increases as Blood Pressure Rises*

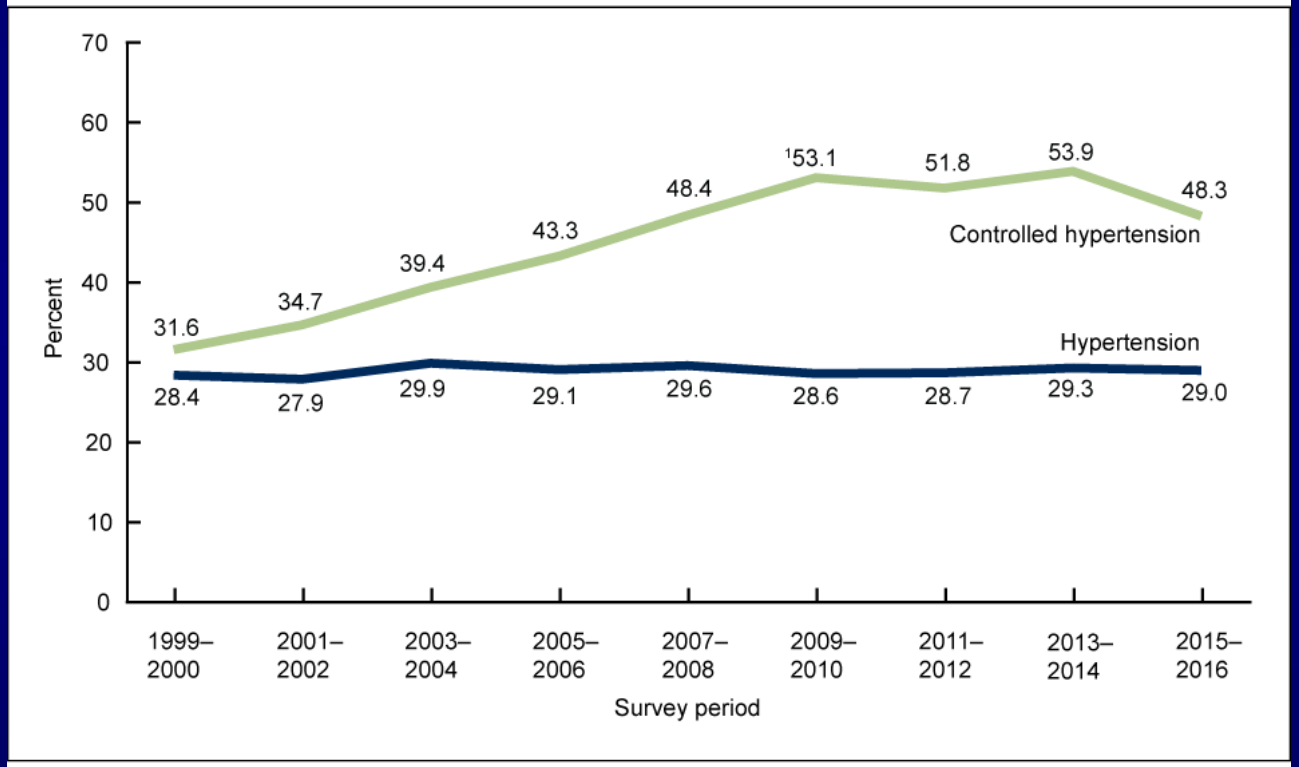


*Measurements taken in individuals aged 40–69 years, beginning with a blood pressure of 115/75 mm Hg.

Lewington S, et al. *Lancet*. 2002;360:1903-1913;
Chobanian AV, et al. *JAMA*. 2003;289:2560-2572.

Hypertension Control Rates (NHANES Data)

Figure 5. Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 and over: United States, 1999–2016



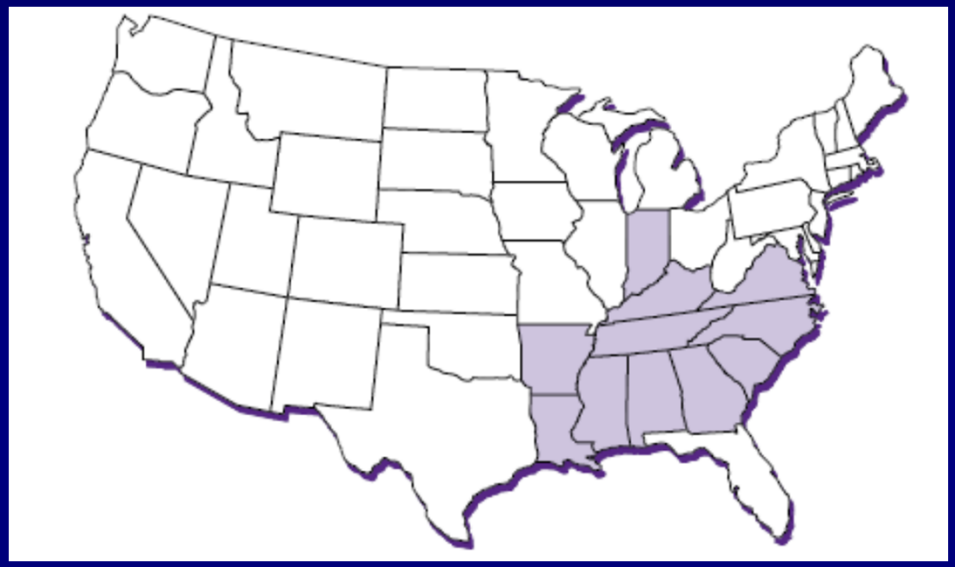
[1]Significant increasing trend for 1999–2010, $p < 0.001$.
NOTES: Hypertension estimates are age adjusted by the direct method to the 2000 U.S. Census population using age groups 18–39, 40–59, and 60 and over. Estimates of controlled hypertension are age adjusted by the direct method using computed weights based on the subpopulation of persons with hypertension in the 2007–2008 National Health and Nutrition Examination Survey, using age groups 18–39, 40–59, and 60 and over. Access data table for Figure 5 at: https://www.cdc.gov/nchs/data/databriefs/db289_table.pdf#5.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

** prior to BP reclassification in 2017 ACC/AHA guidelines

Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015–2016. NCHS data brief, no 289. Hyattsville, MD: National Center for Health Statistics. 2017.

Prevalence of Hypertension
- based on 130/80 cutoff -

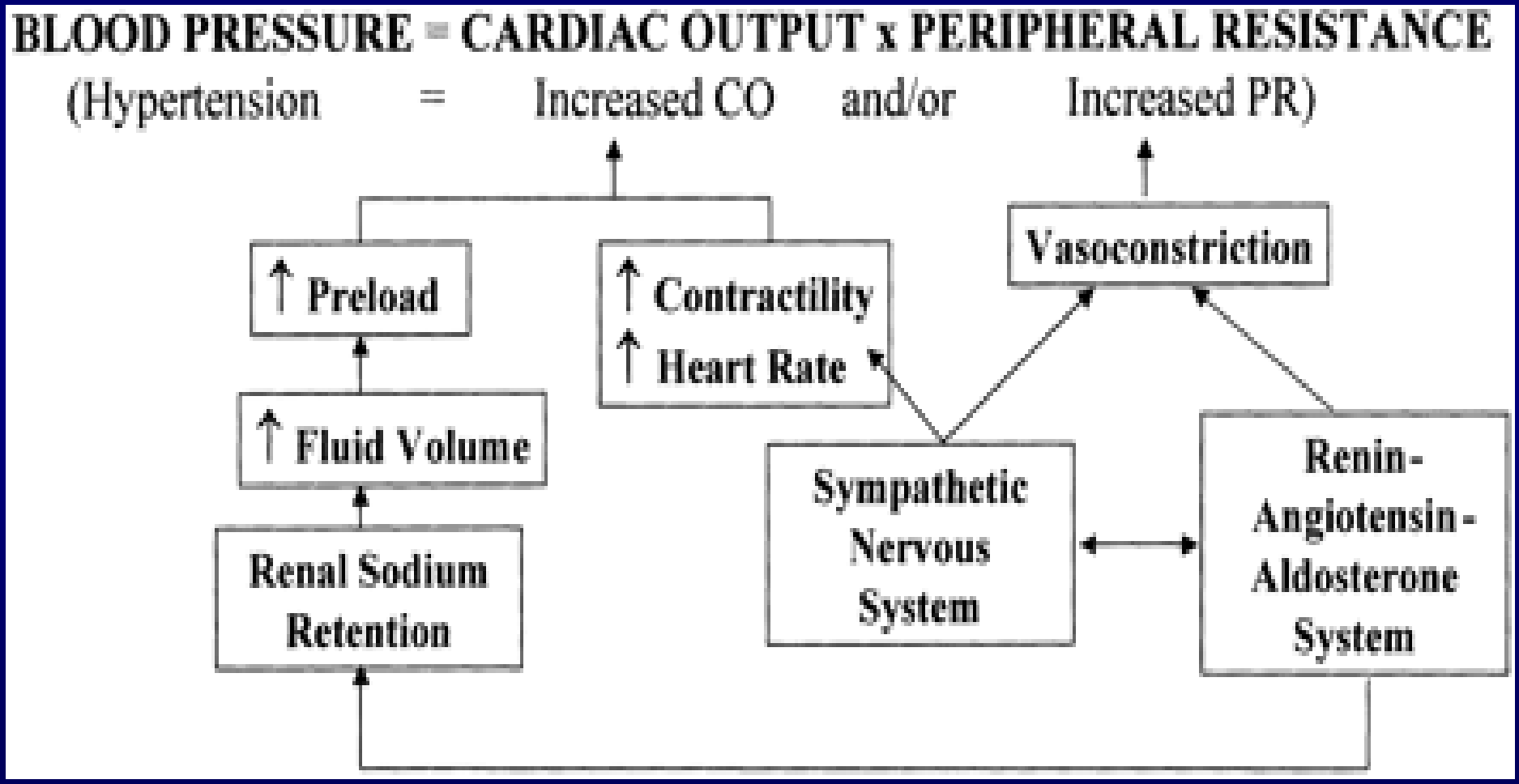
- Affects approx. 108 million Americans
  - increases with age
  - > African Americans
  - > less educated
  - > lower socioeconomic groups
  - > men (young adulthood-middle age)
  - > women (middle age-elderly)
  - > southeast USA (“stroke belt”)



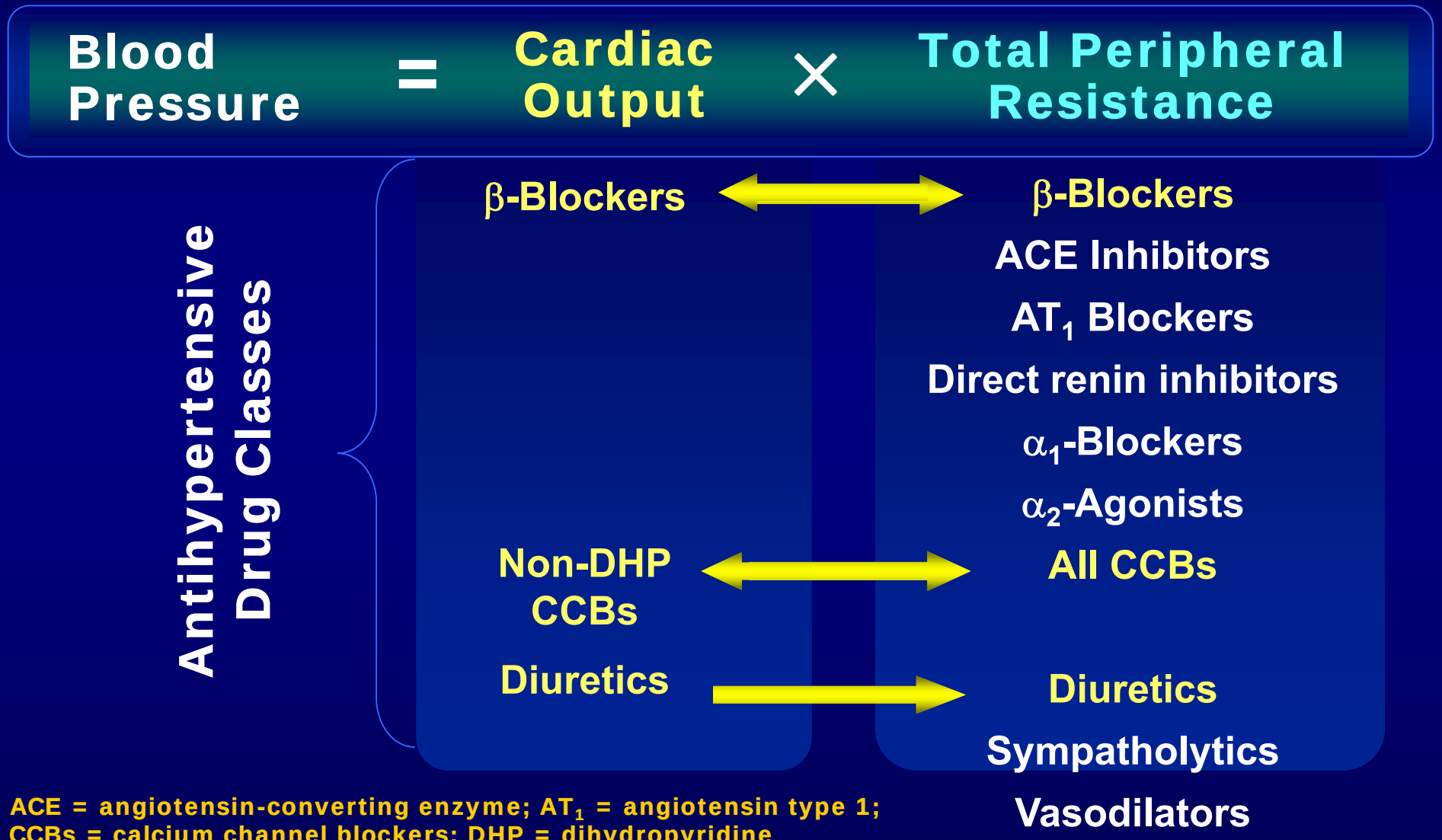
NHLBI stroke belt initiative
http://www.nhlbi.nih.gov/health/prof/heart/other/sb_spec.pdf

- Affects 40% of world population (PURE study)

Pathophysiology



Antihypertensive Drug Classes: Action Sites

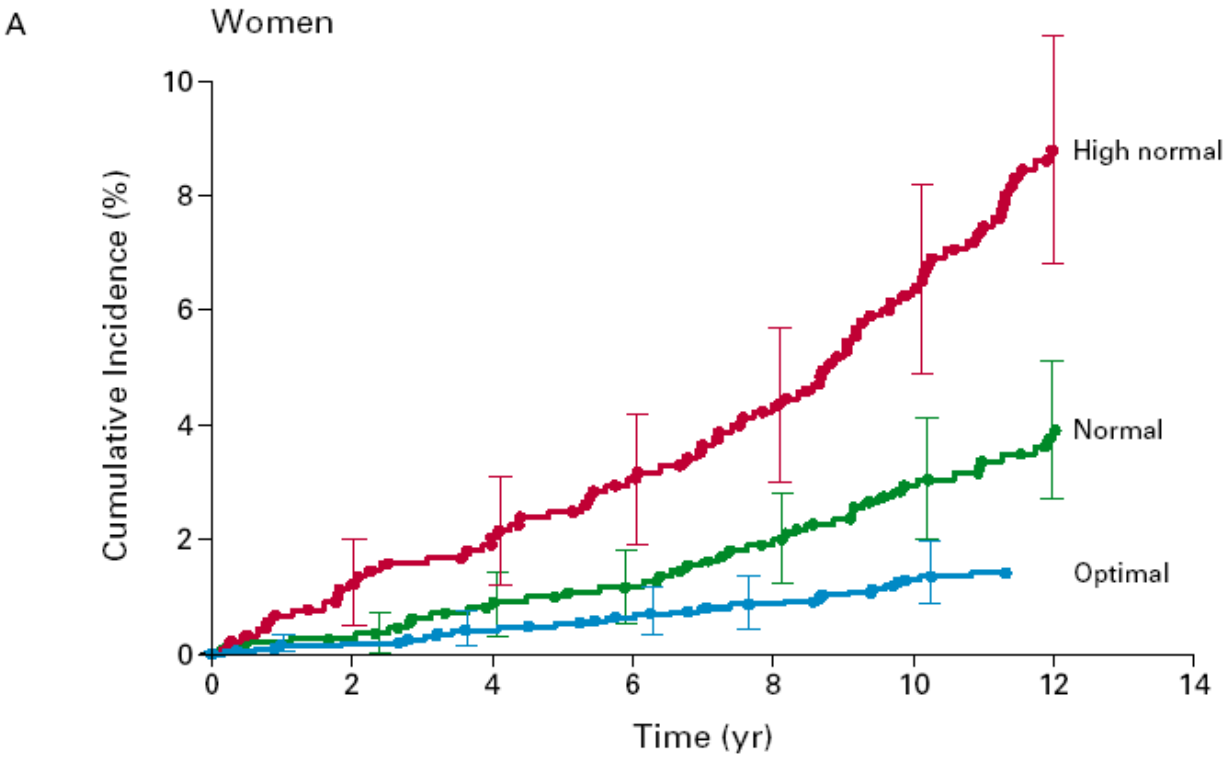


ACE = angiotensin-converting enzyme; AT_1 = angiotensin type 1; CCBs = calcium channel blockers; DHP = dihydropyridine

Definition of Terms

- SBP: peak pressure during ventricular systole (systole=contraction)
- DBP: trough pressure in vasculature at end of diastole (diastole=filling)
- pulse pressure = SBP – DBP
- Mean arterial pressure = $\frac{[(2 \times \text{diastolic}) + \text{systolic}]}{3}$
- BP load: percent of time BP is elevated above a pre-specified value

Risk exists along BP continuum



No. at Risk

Optimal	1875	1867	1851	1839	1821	1734	887
Normal	1126	1115	1097	1084	1061	974	649
High normal	891	874	859	840	812	722	520

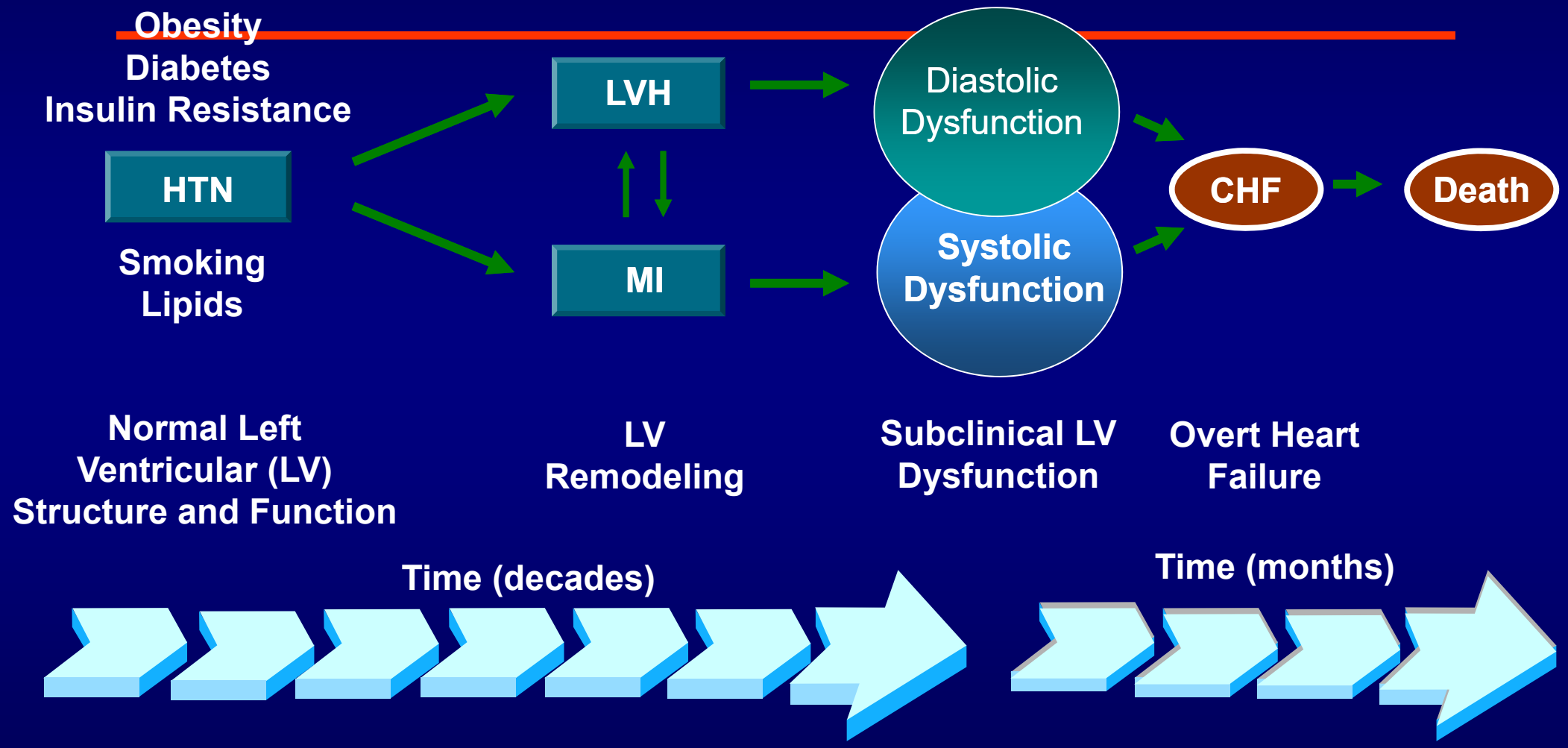
High normal: 130-139 / 85-89 mm Hg

Normal: 120-129 / 80-84 mm Hg

Optimal: < 120/80 mm Hg

N Engl J Med 2001;345:1291–1297

Hypertensive Disease Occurs Along A Continuum



HTN=hypertension; MI=myocardial infarction; CHF=congestive heart failure; LVH=left ventricular hypertrophy

Adapted from Vasan RS, Levy D. *Arch Intern Med*. 1996;156:1790

Measurement

- BP varies with:
  - temperature
  - time of day
  - meals
  - activity
  - posture
  - emotions
  - stressors - e.g. “white coat”

BMJ 2001 Apr 14;322(7291):908-11

ACTIVITY	SBP (mmHg)	DBP (mmHg)
Attending a Meeting	↑ 20	↑ 15
Commuting to Work	↑ 16	↑13
Dressing	↑ 12	↑ 10
Walking	↑ 12	↑ 6
Talking on telephone	↑ 10	↑ 7
Eating	↑ 9	↑ 10
Doing Desk Work	↑ 6	↑ 5
Reading	↑ 2	↑ 2
Watching TV	↑ 0.3	↑ 1
Dopp lectures	No change	No change

Measurement

Method	Brief Description
In-office	Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.
Automated Office BP	New approach where serial measurements (every 5 minutes) are taken over 30 minutes in physician office to detect “white-coat” HTN. Ann Fam Med 2011;9:128-135.
Ambulatory BP monitoring	Indicated for evaluation of “white-coat” HTN. Absence of 10–20% BP decrease during sleep may indicate increased CVD risk.
Self-measurement	Provides information on response and adherence to therapy. May help improve adherence to therapy and evaluate “white-coat” HTN.

Benefit of Home Measurement

- Office measurements correlate poorly with blood pressure measured elsewhere
  - May lead to misclassification of pts as hypertensive
  - May fail to diagnose hypertension in pts with variation in BP
- Should be supplemented with self-measurements with validated devices at home
- Home readings predict CV events, identify white coat HTN
- Home readings increase numbers of BP's taken, to represent true average.

AHA Statement: *Hypertension*. 2005;45:142-161.

BP measurement using Smart Phones

- BP measurements with mobile apps not recommended due to inaccuracies
- Phone tracking may help patients be involved in care and support self-monitoring
- Photoplethysmographic pulse wave recording is available in some APPs
- Mixed results regarding its accuracy
  - This technique was found to not meet accuracy requirements and validation criteria
  - Am Heart J 2020;233:102-108.

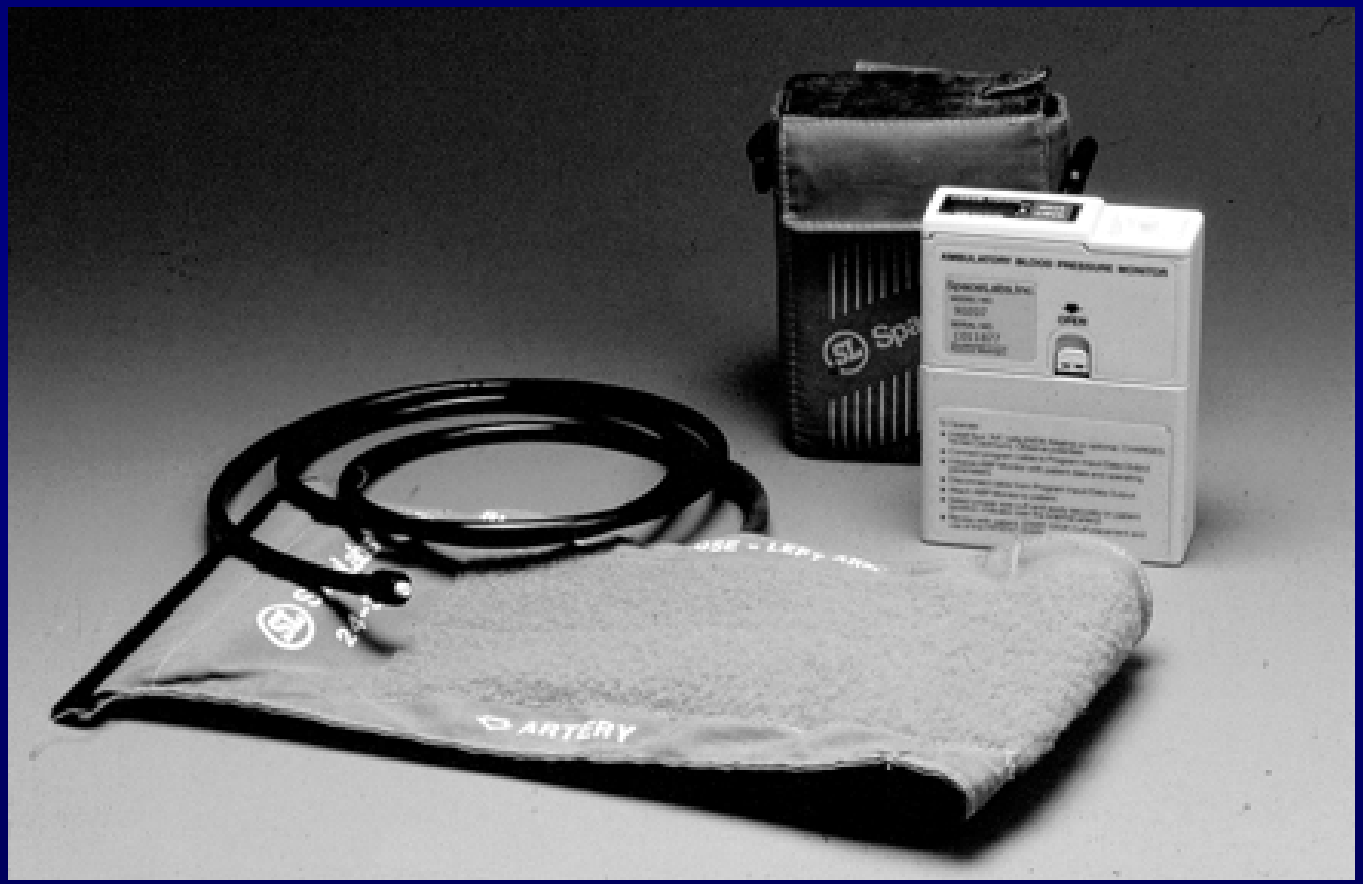
  - In another trial, it was largely accurate (enough)
  - Circulation: Cardiovascular Imaging;2019;12:doi.org/10.1161/CIRCIMAGING.119.008857

Ambulatory Blood Pressure Monitoring (ABPM)

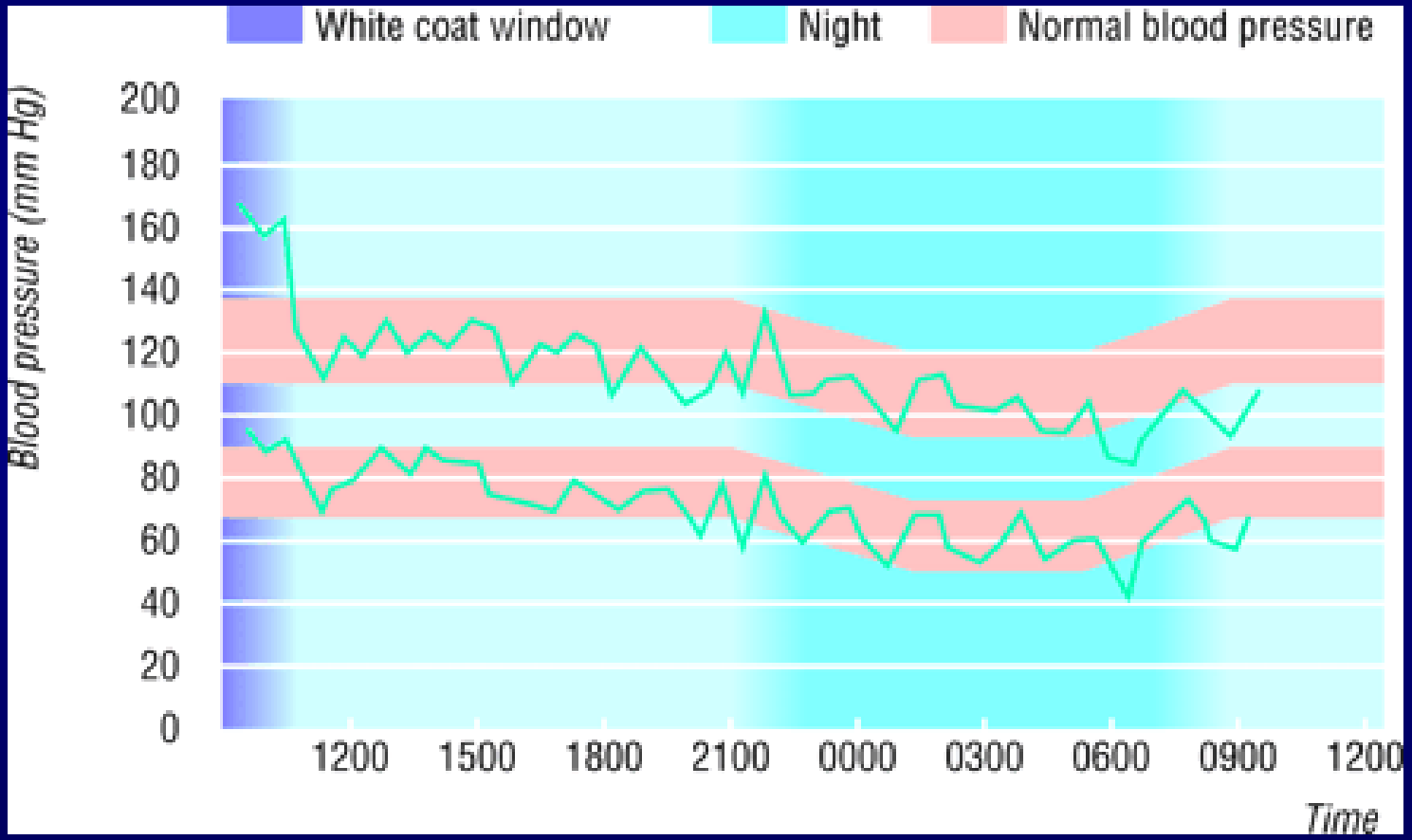
- ABPM can provide:
  - Readings throughout the day during usual activities.
  - Readings during sleep to assess nocturnal changes.
  - SBP and DBP load.
  - correlation with target organ damage
- ABPM readings are usually lower than in clinic.

- Indications for ABPM:
  - office or white-coat HTN
  - borderline or episodic HTN
  - drug resistance
  - drug SE or duration of effect
  - nocturnal HTN

ABPM



ABPM Data



BMJ 2001;322:1110-4

Follow up Recommendations

(adults without acute end organ damage)

Initial Blood Pressure	Recommended Follow-up
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 year
Stage 1 Hypertension	Confirm within 2 months
Stage 2 Hypertension	Evaluate or refer to source of care within one month. If >180/110 mmHg, evaluate/treat immediately

Hypertension Evaluation Components

- Medical history
- Physical examination
- Routine laboratory tests
- Optional tests

- Determine if primary or 2ndary HTN
  - Primary (essential) (~90%)

- Assess for presence or absence of target-organ disease (TOD)
  - cardiac, peripheral, renal, retinal

- Assess for presence or absence of cardiovascular risk factors

Medical History

- Duration and classification of hypertension.
- Patient history of cardiovascular disease.
- Family history.
- Symptoms suggesting causes of hypertension.
- Lifestyle factors.
- Current and previous medications.

Physical Examination

- Blood pressure readings (two or more).
- Verification in contralateral arm.
- Height, weight, and waist circumference.
- Funduscopic (eye) examination.
- Examination of the neck, heart, lungs, abdomen, and extremities.
- Neurological assessment.

Basic and Optional Laboratory Tests for Primary Hypertension

Basic testing	Fasting blood glucose*
	Complete blood count
	Lipid profile
	Serum creatinine with eGFR*
	Serum sodium, potassium, calcium*
	Thyroid-stimulating hormone
	Urinalysis
	Electrocardiogram
Optional testing	Echocardiogram
	Uric acid
	Urinary albumin to creatinine ratio

*May be included in a comprehensive metabolic panel.
eGFR indicates estimated glomerular filtration rate.

Target-Organ Disease (TOD)

Organ	Manifestation
Heart	CAD, LVH, CHF
Cerebrovascular	TIA, Stroke
Peripheral	Claudication, aneurysm
Renal	Serum Cr > 1.5 mg/dL, proteinuria (1+ or greater)
Retinopathy	Exudates, papilledema

Causes of Secondary Hypertension

Common Causes

- Sleep apnea
- Drug-induced or related causes
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Renal Parenchymal Disease

Less Common Causes

- Chronic steroid therapy and Cushing's syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease
- Congenital Adrenal Hyperplasia
- Acromegaly

Medication Effects on Blood Pressure

Agent	Possible Management
Alcohol	Limit to 1 drink daily women, 2 drinks for men
Stimulants	Decrease dose or discontinue
Antidepressants (MAOIs, SNRIs, TCAs)	Consider alternative agent (SSRI) Avoid Tyramine-containing foods with MAO-I
Atypical Antipsychotics (clozapine, olanzapine)	D/C or limit use when possible
Caffeine	Limit intake to < 300 mg/day Avoid use in uncontrolled hypertension Coffee use in controlled hypertension acutely but not long-term increases BP
Decongestants	Use shortest duration possible, avoid in severe and/or uncontrolled hypertension
NSAIDs	Avoid systemic NSAIDs when possible Consider alternatives (acetaminophen, tramadol, topical NSAIDS)

Medication Effects on Blood Pressure

Agent	Possible Management
Herbal Supplements (Ma Huang, St. John's Wort (with MAO-I))	Avoid Use
Immunosuppressants (cyclosporine)	Consider switching to tacrolimus
Oral contraceptives	Use low-dose estrogen agents or progestin only formulations Use alternative form of birth control Avoid use n uncontrolled hypertension
Recreational Drugs	Avoid Use
Systemic corticosteroids	Avoid or limit use when possible
Angiogenesis inhibitor (bevacizumab)	Initiate or intensify antihypertensive therapy
Tyrosine kinase inhibitors (sunitinib, sorafenif)	Initiate or intensify antihypertensive therapy

Lifestyle Modifications

Table 15 – ACC/AHA Guidelines

Modification	Approximate SBP reduction (range)
Weight reduction	1 mm Hg for each 1kg reduction
Adopt DASH eating plan	8–14 mmHg
Dietary sodium reduction (< 1500 mg sodium/day)	2–6 mmHg
Physical activity	4–8 mmHg
Moderation of alcohol consumption	3–4 mmHg
Dietary potassium increase	2-5 mm Hg

Goal of Hypertension Prevention and Management

- To reduce morbidity and mortality by the least intrusive means possible. This may be accomplished by:
  - Achieving and maintaining blood pressures to recommended goals:
  - Controlling other cardiovascular risk factors.
  - Preserve QOL
    - Cost-effective
    - Least intrusive means possible

Drug Therapy

diuretics

beta-blockers

ACE inhibitors (ACE-I)

calcium channel blockers

alpha$_1$ antagonists

alpha $_2$ agonists

angiotensin II receptor blockers (ARBs)

peripheral adrenergic blockers

direct vasodilators

renin inhibitors

Diuretics

- 4 classes:
  - carbonic anhydrase inhibitors (e.g. acetazolamide)
  - Thiazides (e.g. hydrochlorothiazide, chlorthalidone)
  - Loop (e.g. furosemide, bumetanide)
  - K+ sparing (e.g. triamterene)
- thiazides – more potent BP lowering than loop diuretics
- MOA: Decrease BP, fluid volume, PVR
- Synergistic effects with other medications

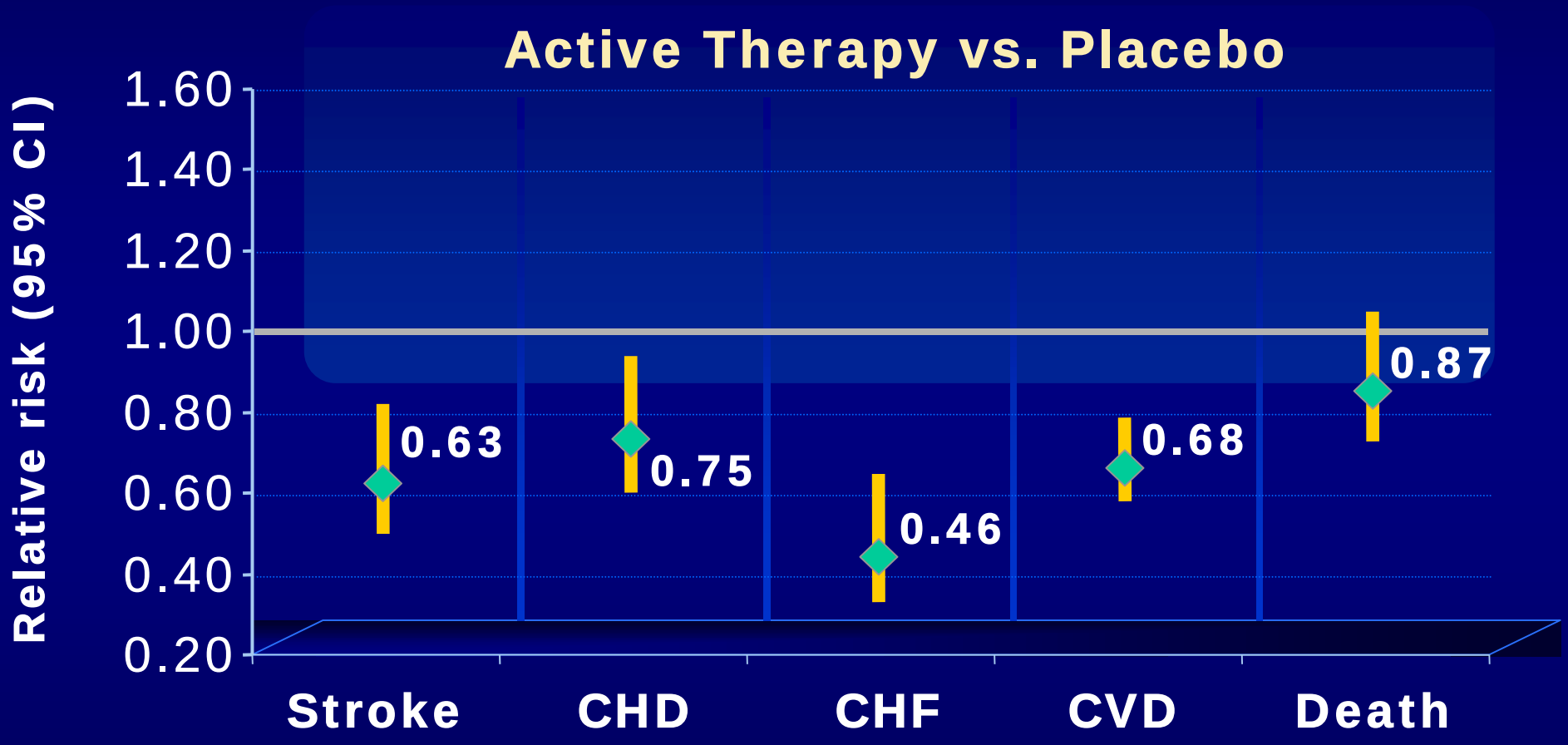
Diuretics

- Pharmacotherapy issues
  - thiazides most effective; loops, K^+ sparing weakly effective when used alone
  - high dietary Na^+ can reverse benefits
  - NSAIDs can antagonize effects
  - Less effective in lean patients?
  - Diuretic effect on electrolytes, cholesterol, glucose
    - Monitor K+, creatinine:
      - baseline,
      - approx. 2-4 weeks later,
      - then periodically thereafter

Diuretic Tx in ISH - SHEP Study

- SHEP (Systolic Hypertension in the Elderly Program)
  - 4736 patients; ≥60 yrs; SBP 160-219 and DBP <90; free of major CV events; f/u 4.5 yrs
  - chlorthalidone 12.5 mg/d, titrated to 25 mg/d vs. placebo
    - goal SBP ≤ 160 if initial pressure > 180; otherwise, ↓ 20 mm Hg for SBP 160-179
- Results
  - goal BP reached by 65-72% of active tx group vs 32-40% of placebo group

SHEP CV Disease Endpoints



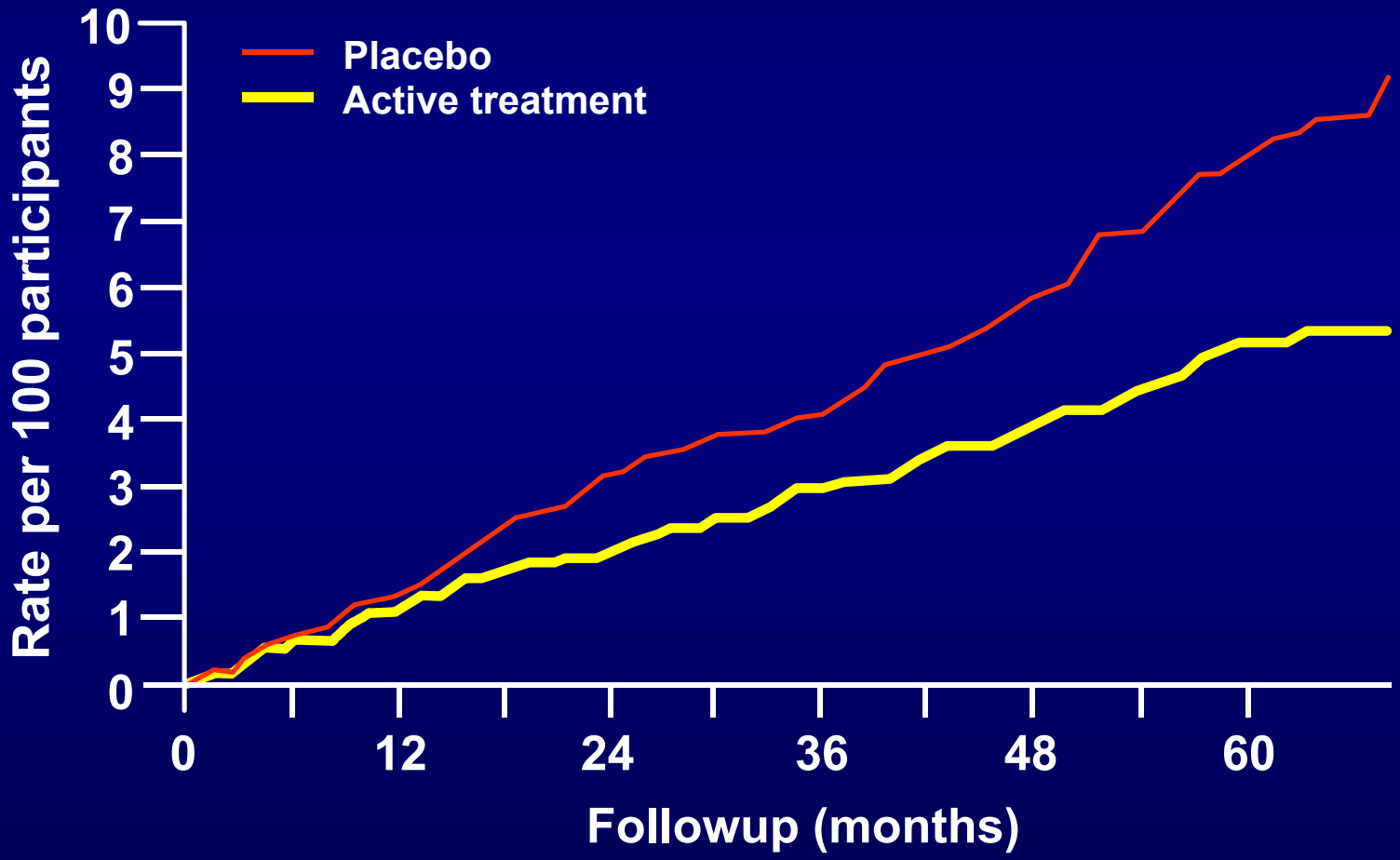
CHD=coronary heart disease; CHF=congestive heart failure; CVD=cardiovascular disease

SHEP=Systolic Hypertension in the Elderly Program

SHEP Research Group. JAMA. 1991;265:3255-3264.

www.hypertensiononline.org

Cumulative Stroke Rate in SHEP Trial



Diuretics

Advantages

- cheap
- Can be dosed once daily
- 30 years of data to support decrease in mortality & morbidity
  - SHEP, SYST-EUR, SYST-CHINA, ALLHAT study
- > response in African Americans and elderly
- ~ 20 % reduction in hip fractures with long term use

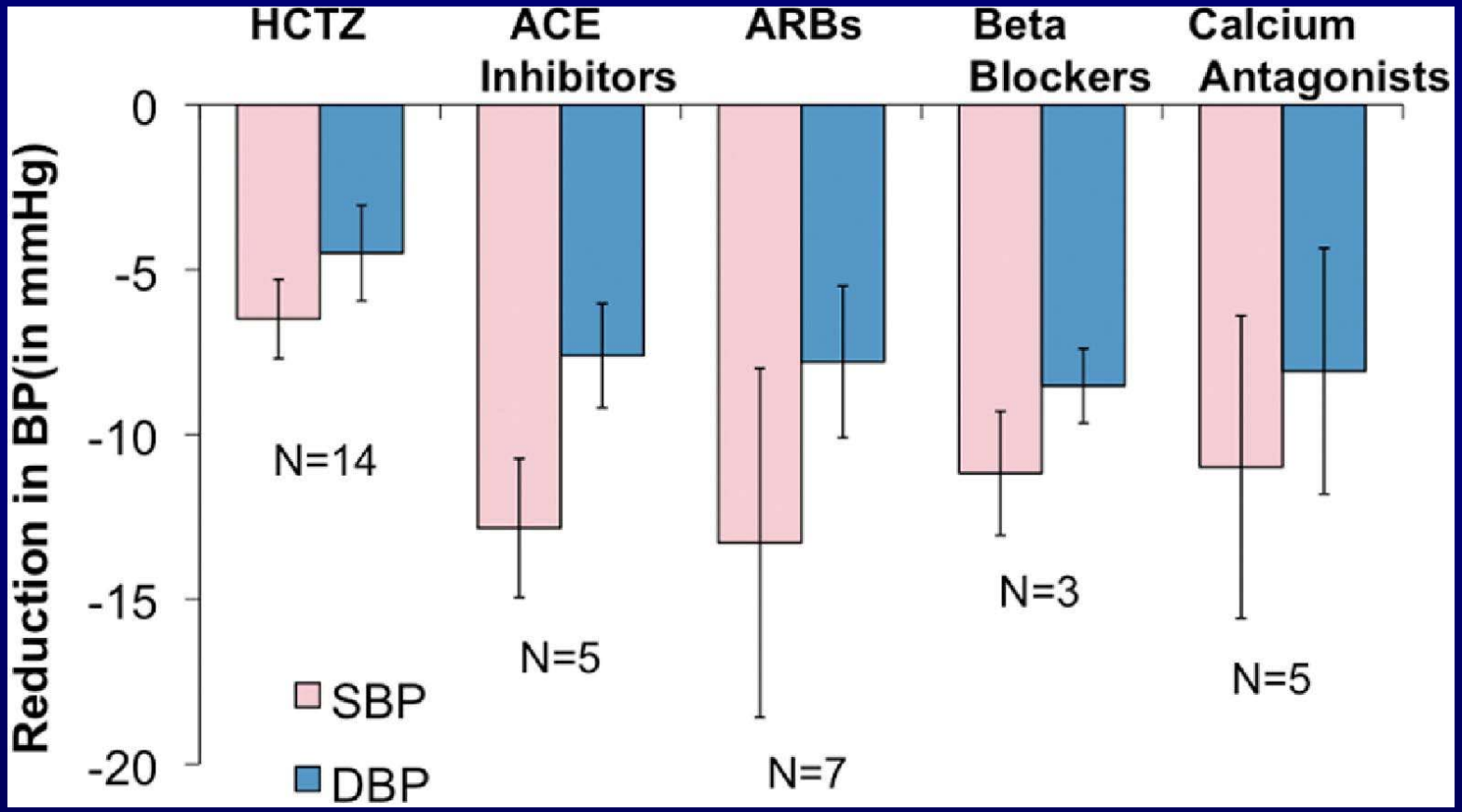
Diuretics

- Disadvantages
  - electrolyte disturbances - ↓ K, Na, Mg; ↑ Ca, uric acid
    - start HCTZ 12.5 mg; use doses ≤ 25 mg
  - diabetes - use low dose
  - gout - use low dose
  - hyperlipidemia - use low dose
  - Thiazides lose efficacy as kidney function decreases
    - not effective when GFR < 30 ml/min
  - Make sure to check for orthostasis, espec. in elderly!

Value of HCTZ Questioned

- meta analysis of its efficacy -

Reductions in mean ambulatory BP with HCTZ and other drug classes



Messerli FH et al. J Am Coll Cardiol 2011;57:590-600

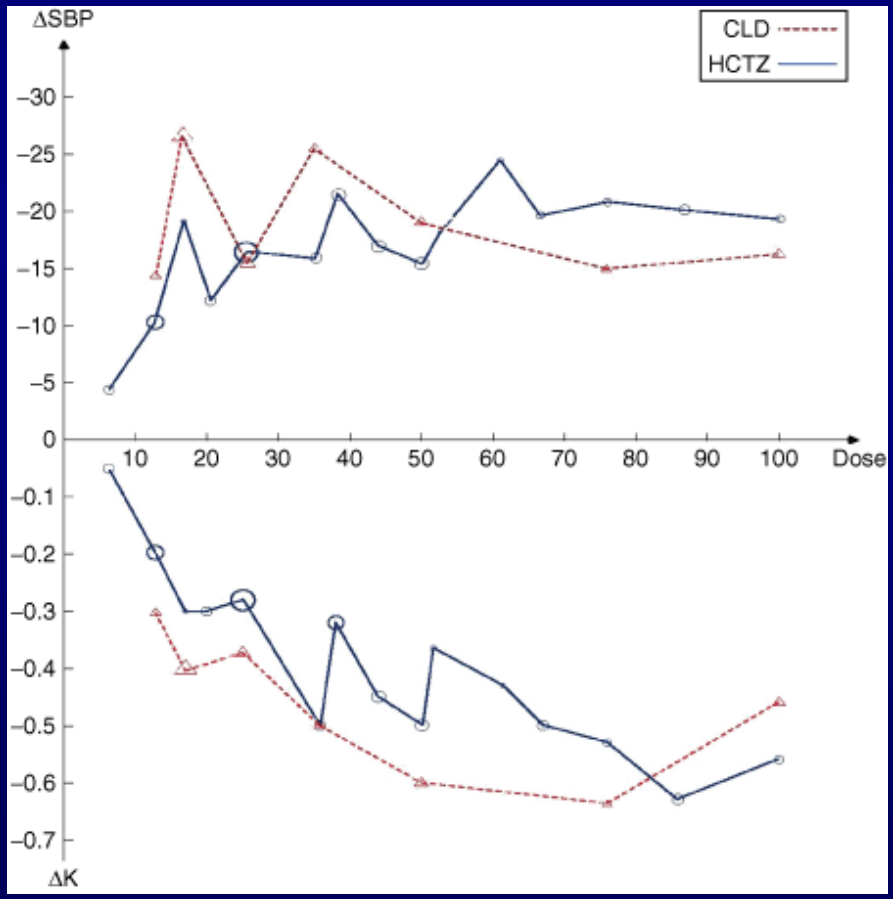
Drug Interactions - Diuretics

Medication	Interaction
Cholestyramine	Reduced HCTZ absorption
Lithium	Increased lithium serum concentration
NSAIDS**	Reduced diuresis
Digoxin	Increased risk of digoxin toxicity
Sulfonylureas	Reduced sulfonylurea efficacy
Cyclophosphamide Fluorouracil Methotrexate	Myelosuppression

** thiazide diuretic + ACE-inhibitor + NSAID increases risk of acute renal injury

Hydrochlorothiazide vs Chlorthalidone

- Meta analysis – using pooled analysis
- mg-per-mg, chlorthalidone produces slightly greater reductions in SBP and potassium than HCTZ.
- In range of 12.5–25 mg, reductions in SBP are not equivalent between the two drugs



Am J Hypertens 2010;23:440-446

Spironolactone and Eplerenone - mineralocorticoid receptor antagonist -

- Spironolactone - Dose: 50-100mg/day (max 400mg/day)
- Eplerenone: Dose: 50mg daily – 50 mg BID
  - Do not use CLcr < 50 mL/min/1.73m^2
- Do not use if acute renal failure, hyperkalemia, or Addison's disease
- Do not combine with potassium supplements/other K+ sparing diuretics

Spironolactone and Eplerenone

- SE:
  - Hyperkalemia
  - Gynecomastia (1% eplerenone)
  - Gynecomastia (10% spironolactone + dose-related)

  - Monitoring – K and Scr baseline and at 2-4 weeks

- Best use as 3rd line agent– especially in patients with resistant hypertension