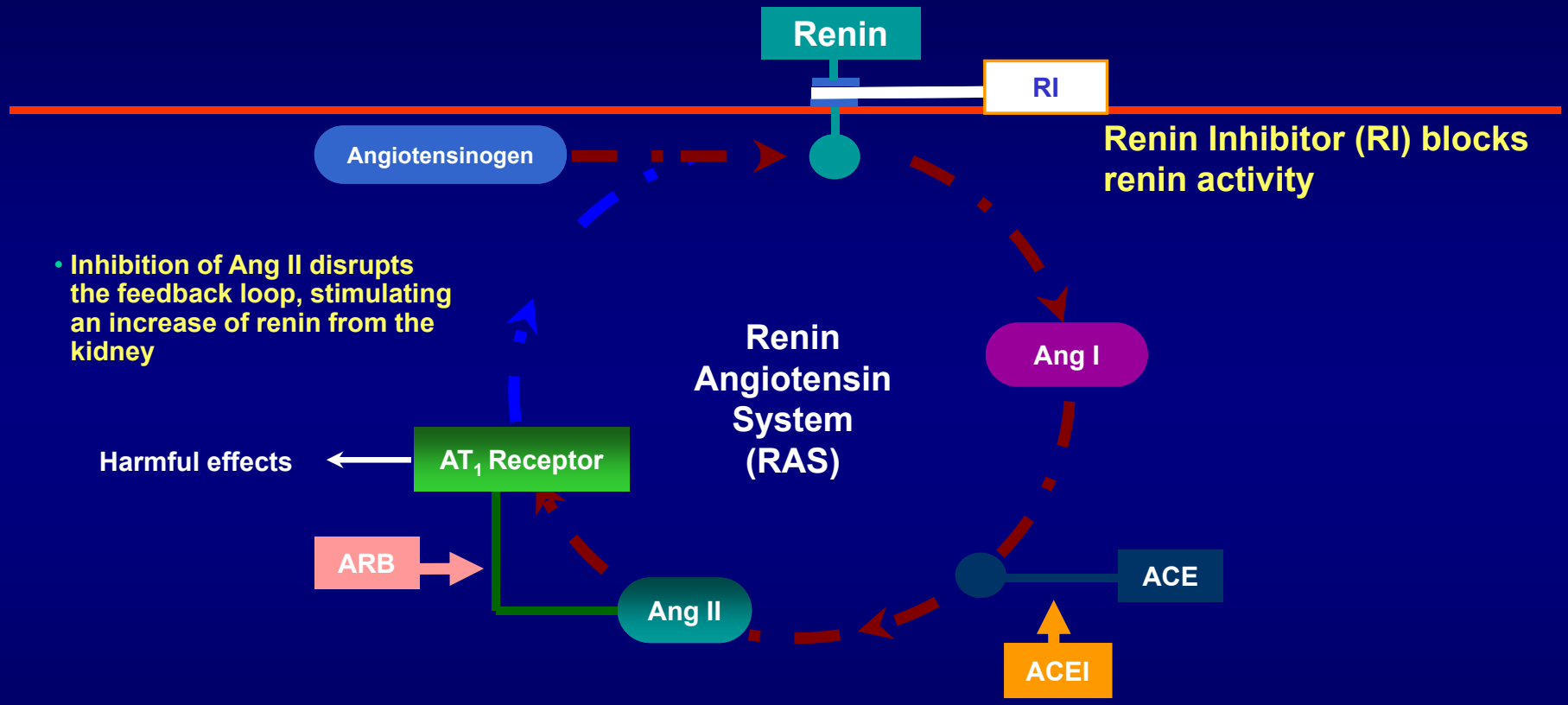
Renin Inhibitors

- MOA: Block activity of renin, and hence no conversion of angiotensinogen to angiotensin I
- No reflex increase in angiotensin II
- Dose: Aliskiren 150 to 300 mg daily

Renin Blockade Inhibits Entire RAS At Its Point Of Activation



ACEI, angiotensin-converting enzyme inhibitor
ACE, angiotensin-converting enzyme
ARB, angiotensin receptor blocker
AT_1, angiotensin II type 1 receptor
Ang, angiotensin

Adapted from:
1. Stanton A. *J Renin Angiotensin Aldosterone Syst*. 2003;4:6-10.
2. Kelly DJ et al. *Hypertension*. 2005;46:471-472.
3. Fisher NDL et al. *J Am Soc Nephrol*. 2005;16:592-599.

Aliskiren: Adverse Reactions

6,460 Patients (1740 for ≥ 6 months)

Treatment discontinued in 2.2% (vs. 3.5% for placebo)

Adverse Effect	Aliskiren	Placebo
GI (diarrhea)	**2.3%**	**1.2%**
Cough	**1.1%**	**0.6%**
Rash	**1.0%**	**0.3%**
Hyperuricemia	**0.4%**	**0.1%**
Gout	**0.2%**	**0.1%**
Kidney stones	**0.2%**	**0%**

Physicians Desk Reference, 61st edition. 2007.

Renin Inhibitors

Advantages:

- Generally well-tolerated
- No dose reduction in elderly, hepatic impairment or mild-moderate renal impairment
- Safe in combination with ARB, CCB, thiazide
- Little hyperkalemia in monotherapy
- Reduced incidence of:
  - Rash, cough, angioedema compared to ACE-I, ARB

Disadvantages:

- Expensive
  - $224 for #30 of 150mg tablets
- Avoid use with ACE-I/ARB in diabetes and renal impairment
- High fat meal reduces absorption
- **Aliskiren is metabolized via CYP3A4 – potential for drug interactions**

Direct Vasodilators

- Cause direct arteriolar smooth muscle relaxation
- Known as afterload reducing agents
  - ↓ systemic pressure in arterial system
  - ↓ impedance to myocardial contractility
- Advantages
  - cheap
  - hydralazine + isosorbide useful in CHF

e.g. hydralazine, minoxidil

Direct Vasodilators

- Disadvantages
  - reflex sympathetic activation - leads to ↑ HR, ↑ CO, renin release
    - effect diminishes over time unless patient is taking sympathetic inhibitor or diuretic
  - ↑ angina in patients with CAD
  - SE: hypertrichosis (minoxidil); lupus-like syndrome (hydralazine); dermatitis, drug fever, peripheral neuropathy, hepatitis, headache

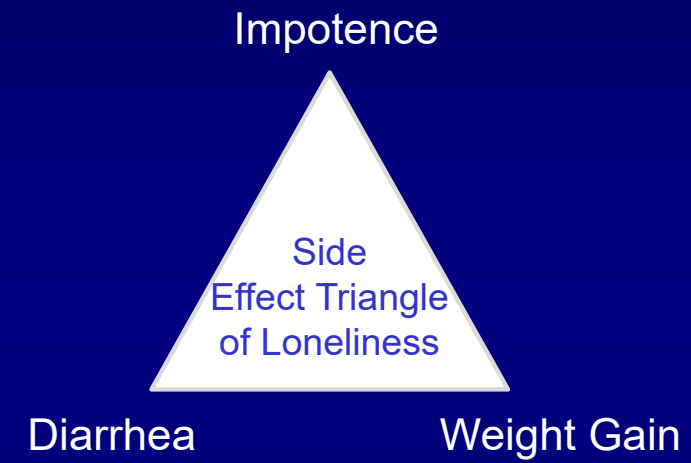
Postganglionic Sympathetic Inhibitors

- MOA: deplete norepinephrine from postganglionic nerve terminals
- inhibit release of norepinephrine in response to sympathetic stimulation
- ↓ CO and PVR
- usually reserved for refractory hypertension

Guanethidine and Guanadrel

Postganglionic Sympathetic Inhibitors

- Advantages
  - Cheap
  - Highly effective
- Disadvantages
  - orthostatic hypotension
  - syncope
  - SE: impotence, diarrhea, weight gain



Reserpine

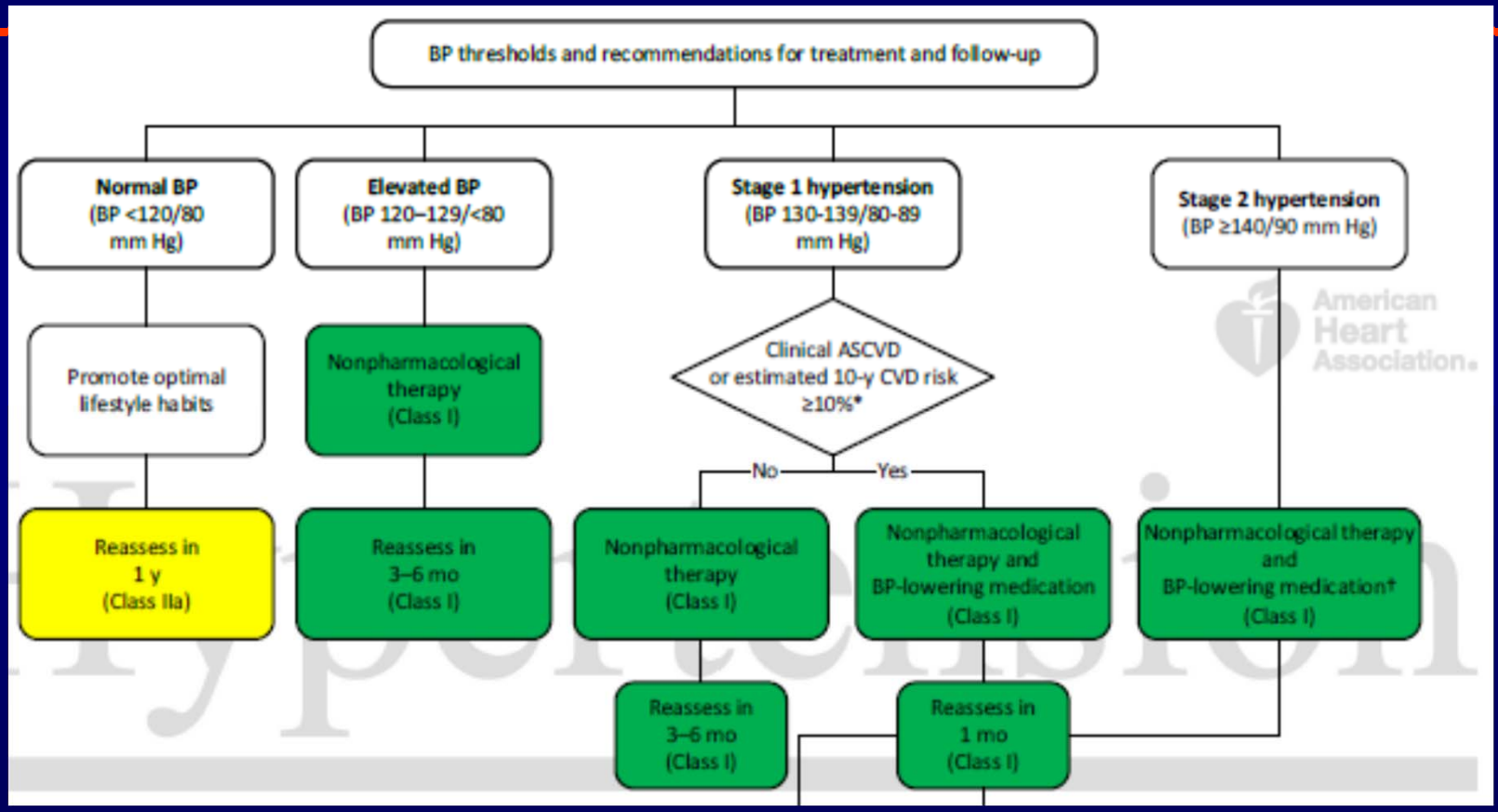
- MOA: depletes NE from sympathetic nerve endings
- blocks transport of NE into storage granules
- ↓ sympathetic tone, depletes catecholamines
- advantages
  - cheap, highly efficacious
- disadvantages
  - sedation, depression, Na/fluid retention, diarrhea, depression

Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	**130–139 mm Hg**	**or**	**80–89 mm Hg**
Stage 2	**≥140 mm Hg**	**or**	**≥90 mm Hg**

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up (continued on next slide)



Recommended Blood Pressure Goals and TREATMENT Thresholds

BP Treatment Threshold	Population
SBP 130 mmHg or DBP 80 mm Hg	Secondary Prevention in patients with clinical CVD
	Primary Prevention in patients with estimated 10-year ASCVD risk ≥10%
	Patients with: - Diabetes Mellitus - Chronic Kidney Disease - Kidney Transplant Recipients
SBP 140 mm Hg or DBP 90 mm Hg	Primary Prevention in patients with estimated 10-year ASCVD risk < 10%

Definitions of Terms for BP Targets

- Clinical CVD
  - CHD
  - Stroke
  - Congestive Heart Failure

- Chronic Kidney Disease
  - Stage 3 or higher CKD (GFR < 60 mL/min/1.73m^2)
  - Stages 1-2 CKD with albuminuria
    - Albuminuria is ≥ 300 mg/day or 300 mg/g albumin:creatinine in first AM void

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

COR	LOE	Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*
I	C-EO	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
IIa	C-EO	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

Choice of Initial Medication

COR	LOE	Recommendation for Choice of Initial Medication
I	A^{SR}	For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

SR indicates systematic review.

Hypertension in Patients With Comorbidities

Chronic Kidney Disease With Albuminuria

- ACE-Inhibitor or ARB

Kidney Transplant Recipients

- Calcium Channel Blocker

Secondary Stroke Prevention

- ACE-Inhibitor or ARB
- Thiazide diuretic

Diabetes Mellitus with Albuminuria

- ACE-Inhibitor or ARB

Hypertension in Patients With Comorbidities

Comorbidity	Preferred Agents
Atrial Fibrillation	ARBs
Chronic Aortic Insufficiency	Avoid Beta-blockers or negative inotropes
Thoracic Aortic Disease	Use Beta-blockers
SIHD	GDMT
HF	GDMT

Pharmacologic Treatment

- Decreases cardiovascular morbidity and mortality based on randomized controlled trials.

- Protects against stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension, and all-cause mortality.

Special Considerations in Selecting Drug Therapy

- Demographics
- Coexisting diseases and therapies
- Quality of life
- Physiological and biochemical measurements
- Drug interactions
- Economic considerations

Follow-Up

- Follow-up within 1 to 2 months after initiating therapy.
- Certain medications may require earlier monitoring (diuretics, ACE-I, ARBs)
- Recognize that high-risk patients often require high dose or combination therapies and shorter intervals between changes in medications.
- Consider reasons for lack of responsiveness if blood pressure is uncontrolled after reaching full dose.

Follow-Up After Initial BP Evaluation

COR	LOE	Recommendations for Follow-Up After Initial BP Elevation
I	B-R	Adults with an elevated BP or stage 1 hypertension who have an estimated 10-year ASCVD risk less than 10% should be managed with nonpharmacological therapy and have a repeat BP evaluation within 3 to 6 months.
I	B-R	Adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of 10% or higher should be managed initially with a combination of nonpharmacological and antihypertensive drug therapy and have a repeat BP evaluation in 1 month.
I	B-R	Adults with stage 2 hypertension should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacological and antihypertensive drug therapy (with 2 agents of different classes) initiated, and have a repeat BP evaluation in 1 month.

Other Medication Considerations

Some antihypertensive drugs may have favorable effects on comorbid conditions:

- **Angina**
  - β-blockers
  - Calcium antagonists
- **Atrial tachycardia and fibrillation**
  - β-blockers
  - Non-dihydropyridine calcium antagonists
  - ACE Inhibitors and ARBs

Other Medication Considerations

Some antihypertensive drugs may have favorable effects on comorbid conditions:

- **Dyslipidemia**
  - α-blockers
- **Prostatism (benign prostatic hyperplasia)**
  - α-blockers

Other Medication Considerations

Some antihypertensive drugs may have favorable effects on comorbid conditions:

- **Essential tremor**
  - Non-cardioselective β-blockers
- **Hyperthyroidism**
  - β-blockers
- **Migraine**
  - Non-cardioselective β-blockers
  - Non-dihydropyridine calcium antagonists
- **Osteoporosis**
  - Thiazides
- **Perioperative hypertension**
  - β-blockers

Treatment Algorithm - Cautions

Some antihypertensive drugs may have UNFAVORABLE effects on comorbid conditions:

- **Bronchospastic disease**
  - β-blockers
- **Depression**
  - β-blockers
- **Dyslipidemia**
  - β-blockers, diuretics
- **Diabetes (I & II)**
  - β-blockers, high-dose diuretics
- **Gout**
  - diuretics
- **Heart Failure**
  - β-blockers (except carvedilol, metoprolol, bisoprolol)
  - CCB (except amlodipine, felodipine)

Current Questions in Hypertension Management

1. Are there differences in the effects from BP lowering with various antihypertensive agents?
   - ALLHAT Study
   - ACCOMPLISH Study
   - LEGEND-HTN

2. What is the optimal approach to achieve BP goals?
   - Protocol approach vs. Guideline approach (STITCH trial)

Current Questions in Hypertension Management

3. What is optimal blood pressure goal?
4. How to evaluate Hypertension studies
4. What is the optimal approach to hypertension management in different types of patients:
   - African Americans
   - Elderly
   - Women
   - Children

Are there differences between medications?

ALLHAT TRIAL

ALLHAT Trial Design

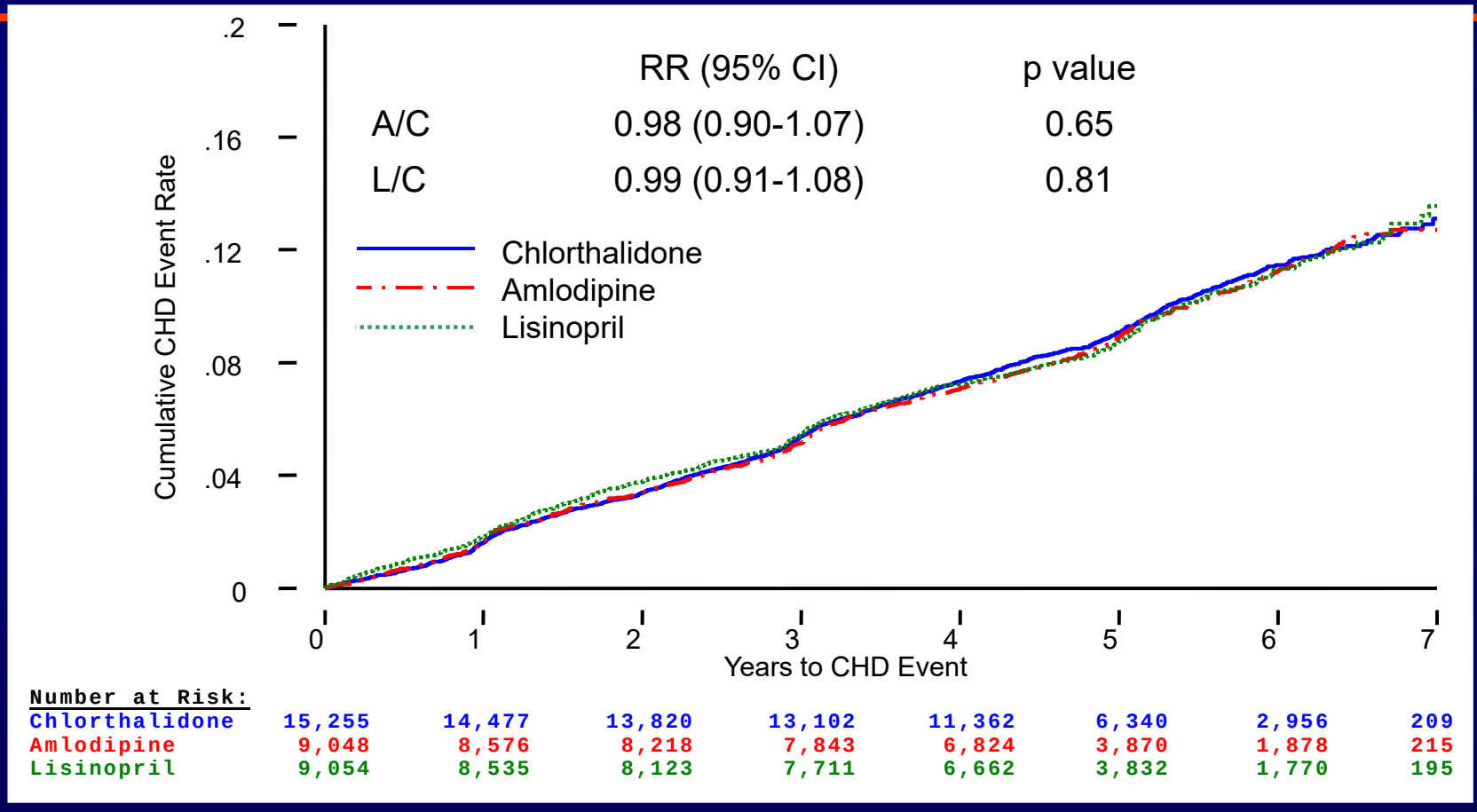
Davis et al. *Am J Hypertens*. 1996;9:342-360.

- ALLHAT is the largest randomized clinical trial undertaken to answer the question whether there are differences among classes of agents
- Randomized, double-blind, multi-center clinical trial
- The combined incidence of fatal CHD and nonfatal MI will be lower in hypertensive patients randomized to

  1. an ACEI (lisinopril), or
  2. a CCB (amlodipine), or
  3. an alpha-adrenergic blocker (doxazosin)

  as first-line therapy than in those randomized to a thiazide-like diuretic (chlorthalidone)
- 42,418 high-risk hypertensive patients ≥ 55 years

Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group



Number at Risk:								
Chlorthalidone	15,255	14,477	13,820	13,102	11,362	6,340	2,956	209
Amlodipine	9,048	8,576	8,218	7,843	6,824	3,870	1,878	215
Lisinopril	9,054	8,535	8,123	7,711	6,662	3,832	1,770	195

ACCOMPLISH study – high risk pts

- what about combination therapy? -

- Hydrochlorothiazide + benazepril vs.
- Amlodipine + benazepril
- Patients were older (mean age 68 years)

Results: Amlodipine and benazepril were better

Implications:

In High Risk patients with stage 2 hypertension – ACE-I and CCB SEEM better than diuretic and ACE-I.

N Engl J Med 2008;359:2417-2428.

ACCOMPLISH: Primary* and secondary end points

End point	Hazard ratio (95% CI)
*Cardiovascular morbidity/mortality	0.80 (0.71–0.90)
Cardiovascular morbidity/mortality (excluding coronary revascularization)	0.79 (0.68–0.92)
Cardiovascular mortality	1.34 (0.98–1.84)
Nonfatal MI	1.09 (0.92–1.45)
Nonfatal stroke	1.22 (0.91–1.63)
Hospitalization for unstable angina	1.36 (0.87–2.13)
Coronary revascularization	1.11 (0.95–1.30)

LEGEND-HTN

- Retrospective cohort study comparing effectiveness and safety amongst BP meds
- 21.6 million previously untreated patients
  - Evaluated monotherapy with first-line agents
- 3 endpoints:
  - MI, Stroke, Hospitalization for heart failure
- Median follow-up 2 years

Lancet 2019;394:1816-26.

LEGEND-HTN

	Comparator	Acute myocardial infarction	Hospitalisation for heart failure	Stroke
THZ	ACEI	0·84 (0·75–0·95), 0·01	0·83 (0·74–0·95), 0·01	0·83 (0·74–0·95), 0·01
THZ	ARB	0·93 (0·81–1·11), 0·41	0·90 (0·79–1·06), 0·19	0·93 (0·80–1·11), 0·41
THZ	dCCB	0·90 (0·81–1·02), 0·14	0·90 (0·80–1·04), 0·18	0·89 (0·79–1·03), 0·14
THZ	ndCCB	0·70 (0·59–0·84), <0·01	0·58 (0·52–0·65), <0·01	0·78 (0·71–0·87) 0·01
ACEI	ARB	1·11 (0·95–1·32), 0·20	1·05 (0·88–1·26), 0·60	1·07 (0·92–1·27), 0·38
ACEI	dCCB	1·08 (0·96–1·22), 0·18	1·08 (0·94–1·25), 0·24	1·05 (0·93–1·21), 0·38
ACEI	ndCCB	0·87 (0·77–1·00), 0·04	0·68 (0·60–0·78), <0·01	0·89 (0·82–0·98), 0·02
ARB	dCCB	0·95 (0·80–1·14), 0·69	1·04 (0·86–1·26), 0·66	0·99 (0·83–1·19), 0·93
ARB	ndCCB	0·78 (0·69–0·91), 0·01	0·71 (0·64–0·80), <0·01	0·84 (0·73–0·97), 0·05
dCCB	ndCCB	0·84 (0·76–0·93), <0·01	0·73 (0·68–0·78), <0·01	0·87 (0·79–0·96), 0·01

Data are HR (95% CI), p value. Estimates were calibrated to reduce residual bias and report the HR for patients in the target cohort relative to comparator cohort. HRs of less than 1 favour target. THZ=thiazide or thiazide-like diuretics. ACEi=angiotensin-converting enzyme inhibitors. ARB=angiotensin receptor blockers. dCCB=dihydropyridine calcium channel blockers. ndCCB=non-dihydropyridine calcium channel blockers. HR=hazard ratio.

Lancet 2019;394:1816-26.

Evaluating HTN studies

- Population studied? (DM, race, etc.)
- Outcome measures?
- If CV events or mortality are endpoints – did they achieve similar BP reduction in comparison groups?
- Are differences clinically significant?
- How do differences in components influence endpoint?
- Duration studied?
- Adverse Events?
- How do findings fit with current literature?
- 24-hour BP or office BP or home BP?

What is the optimal blood pressure goal?

SPRINT Trial

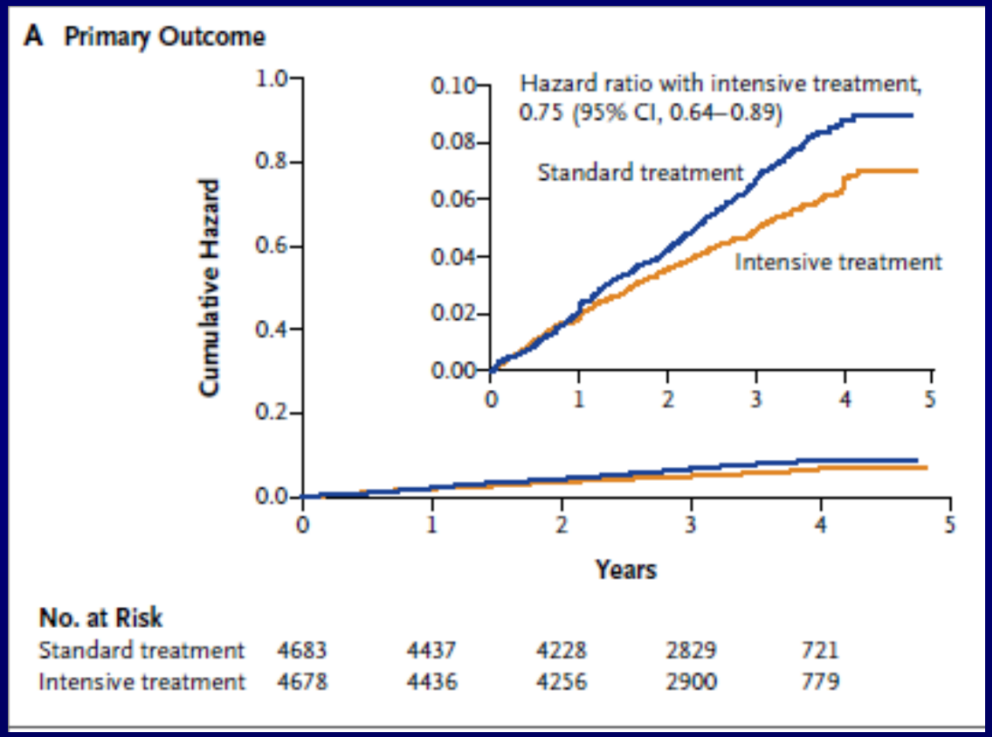
- N Engl J Med 2015;373:2103-2116 -

- N=9261 subjects randomized to:
  - Intensive BP control (< 120/80 mm Hg)
  - Standard BP control (< 140/90 mm Hg)
- Followed up for average 3.26 years (trial stopped early)
- Non-diabetic subjects with SBP > 130 mm Hg
- Composite Endpoint – CV events, CV death

SPRINT Trial

- Average BP:
  - 121.5 mm Hg intensive
  - 134.6 mm Hg standard
- Hazard ratio for endpoint = 0.75 (95% CI 0.64-0.89)

P<0.001



Hypertension in Special Populations

- Elderly
- Children and adolescents
- Women and pregnancy
- African Americans

Elderly

- 16 million Americans > 85 by 2050
- SBP increases with advancing age, DBP decreases with advancing age
  - ↑ prevalence of isolated systolic hypertension (ISH)
- **Recommended therapy:**
  - **Thiazide diuretics**
  - **Calcium channel blockers**

Age-Related Issues

COR	LOE	Recommendations for Treatment of Hypertension in Older Persons
I	A	Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher.
IIa	C-EO	For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs.

Children and Adolescents

- Blood pressure at 95th or higher percentile is Stage 1 HTN, above 99th percentile is stage 2 HTN.
- Lifestyle modifications should be recommended.
- Attempts should be made to determine other causes of high blood pressure and other cardiovascular risk factors.
  - usually associated with increased CO and normal plasma volume and total PVR
  - beta blockers preferred, valsartan now FDA approved also

Children and Adolescents

- Drug therapy started for:
  - stage 2 hypertension,
  - patients with stage 1 HTN who are symptomatic, when left ventricular hypertrophy is present,
  - stage 1 hypertension when blood pressure is unresponsive to lifestyle changes.

95th Percentile of BP for Selected Age/Height

Females

	SBP/DBP (mm Hg)	
Age	50th% height	75th% height
1	104/58	105/59
6	111/74	113/74
12	123/80	124/81
17	129/84	130/85

Males

	SBP/DBP (mm Hg)	
Age	50th% height	75th% height
1	103/56	104/57
6	114/74	115/75
12	123/81	125/82
17	136/87	138/87

Pregnant Women

- Must differentiate between chronic or transient hypertension of pregnancy and preeclampsia
  - Chronic hypertension is high blood pressure present before pregnancy or diagnosed before the 20th week of gestation.
  - Preeclampsia is increased blood pressure (↑ of 30 mmHG systolic or 15 mmHG diastolic) that occurs in pregnancy (generally after the 20th week) and is accompanied by edema, proteinuria, or both.

Antihypertensive Therapy in Women

Am J Cardiol 1996;77:713-722
J Clin Hypertens 2008;10:406-410

- Compared to men, women are MORE likely to experience the following with antihypertensives

Variable	Medication
Hypokalemia	Diuretics
Hyponatremia	Diuretics
Cough	ACE-Inhibitors
Peripheral Edema	Calcium channel blockers

Pregnancy

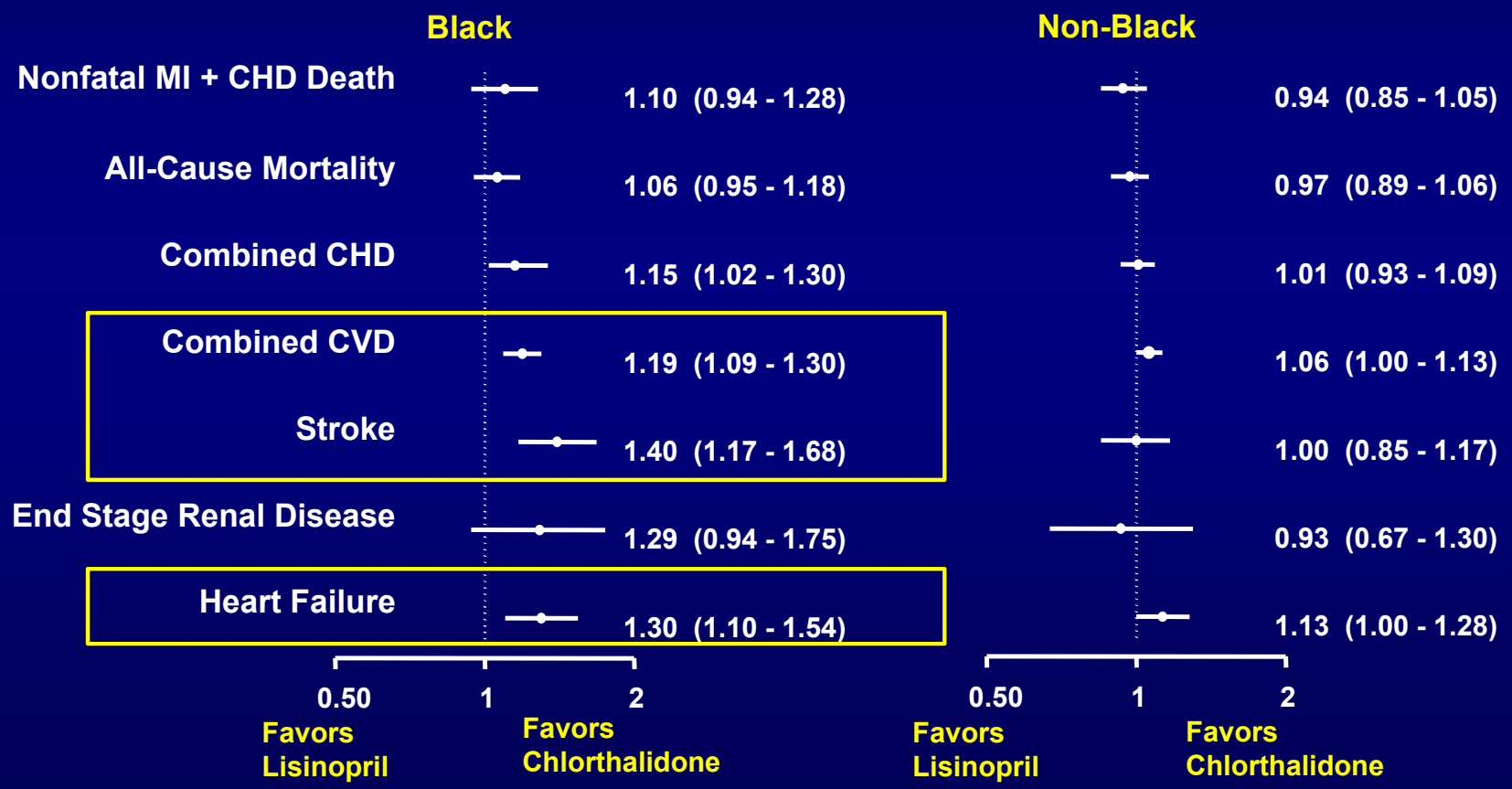
COR	LOE	Recommendations for Treatment of Hypertension in Pregnancy
I	C-LD	Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy.
III: Harm	C-LD	Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.

Hypertension in Special Populations
African-Americans

- Higher prevalence of hypertension, stage 2 hypertension
- 80% higher stroke risk, 50% higher cardiac mortality, 320% greater end-stage renal failure rate
- Blood pressure responsiveness similar to white patients
- High prevalence of cardiovascular risk factors
- Increased response to salt restriction

ALLHAT

Black vs. Non-Black
Lisinopril/Chlorthalidone
Relative Risk and 95% Confidence Intervals



Racial and Ethnic Differences in Treatment

COR	LOE	Recommendations for Race and Ethnicity
I	B-R	In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
I	C-LD	Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.

Why is it Difficult to Achieve Blood Pressure Goals?

And How Can We Improve Blood Pressure Control?

Causes for Inadequate Response to Drug Therapy

- Pseudoresistance
  - white-coat hypertension
  - improper technique
- Non-adherence to therapy
- Volume overload
  - salt intake
  - renal disease
- Drug-related causes
  - dose, antagonist effects of other drugs (e.g. NSAIDs)
- Associated conditions
  - smoking, sleep apnea, insulin resistance, ethanol, chronic pain
- Secondary causes of hypertension

Resistant Hypertension - Strategies

- Use drugs with complimentary MOAs
- Assess the efficacy of each new medication addition
- Discontinue medications if lack of response
- Retry medications in different combinations
- Consider home readings and ambulatory BP monitoring (may be a ‘white-coat’ component)
- Consider further work-up if medication options are exhausted (i.e. renal artery stenosis)

Pearls for Combination Therapy

J Am Soc Hypertens 2010;4:90-98

- Use preferred or acceptable two-drug combinations (see Table)
- Initiate combination therapy routinely in pts who require > 20/10 mm Hg BP reduction to reach BP goal
- Initiate combination therapy in stage 1 pts, especially if 2nd agent improves side effect profile of 1st agent
- Use single pill combinations in circumstances where convenience outweighs other considerations

Recommended Drug Combinations

J Am Soc Hypertens 2010;4:90-98

Preferred	ACE-Inhibitor	Diuretic
	ARB	Diuretic
	ACE-Inhibitor	CCB
	ARB	CCB
Acceptable	Beta-blocker	Diuretic
	CCB (dihydropyridine)	Beta-blocker
	CCB	Diuretic
	Renin inhibitor	Diuretic
	Thiazide Diuretics	K-sparing diuretics
Less Effective	ACE-Inhibitor	ARB
	ACE-Inhibitor	Beta-blocker
	ARB	Beta-blocker
	CCB (nondihydropyridine)	Beta-blocker
	Central alpha agonist	Beta-blocker