

Hypertension 2015: Recent Evidence that Will Change Your Practice

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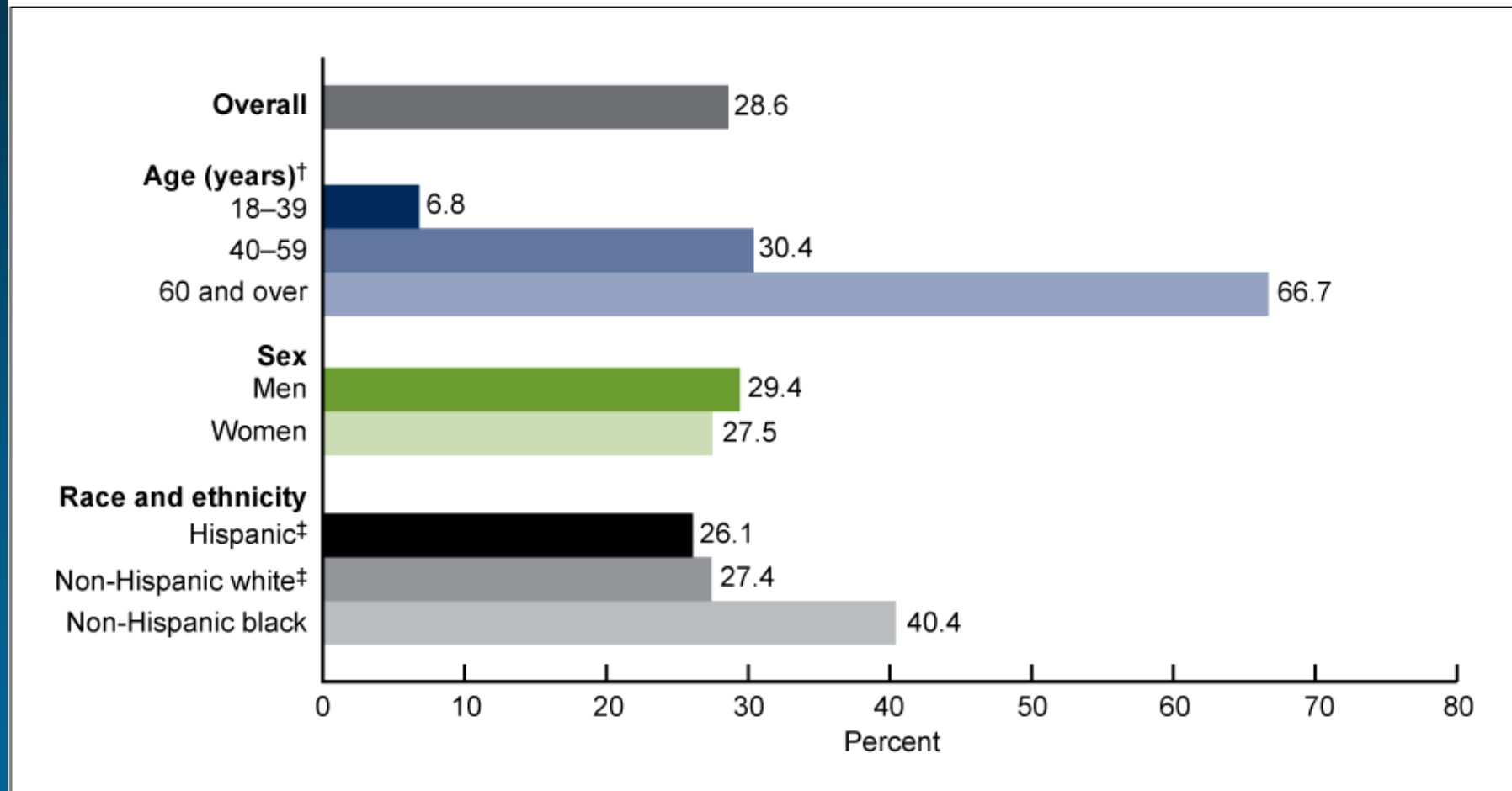
Goals

- JNC-8; new recommendations and controversies
- New blood pressure targets
- How to diagnose hypertension
- Chlorthalidone preferred over HCTZ
- Conflicting data on ARB's
- Risks of alpha-blockers and beta-blockers
- Costs of commonly used medications
- Resistant hypertension
- Expanding role for spironolactone

All Drugs that Lower Blood Pressure Do Not Equally Reduce Cardiovascular Risk

NHANES 2010: Prevalence of Hypertension in U.S.

Figure 1. Age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over: United States, 2009–2010



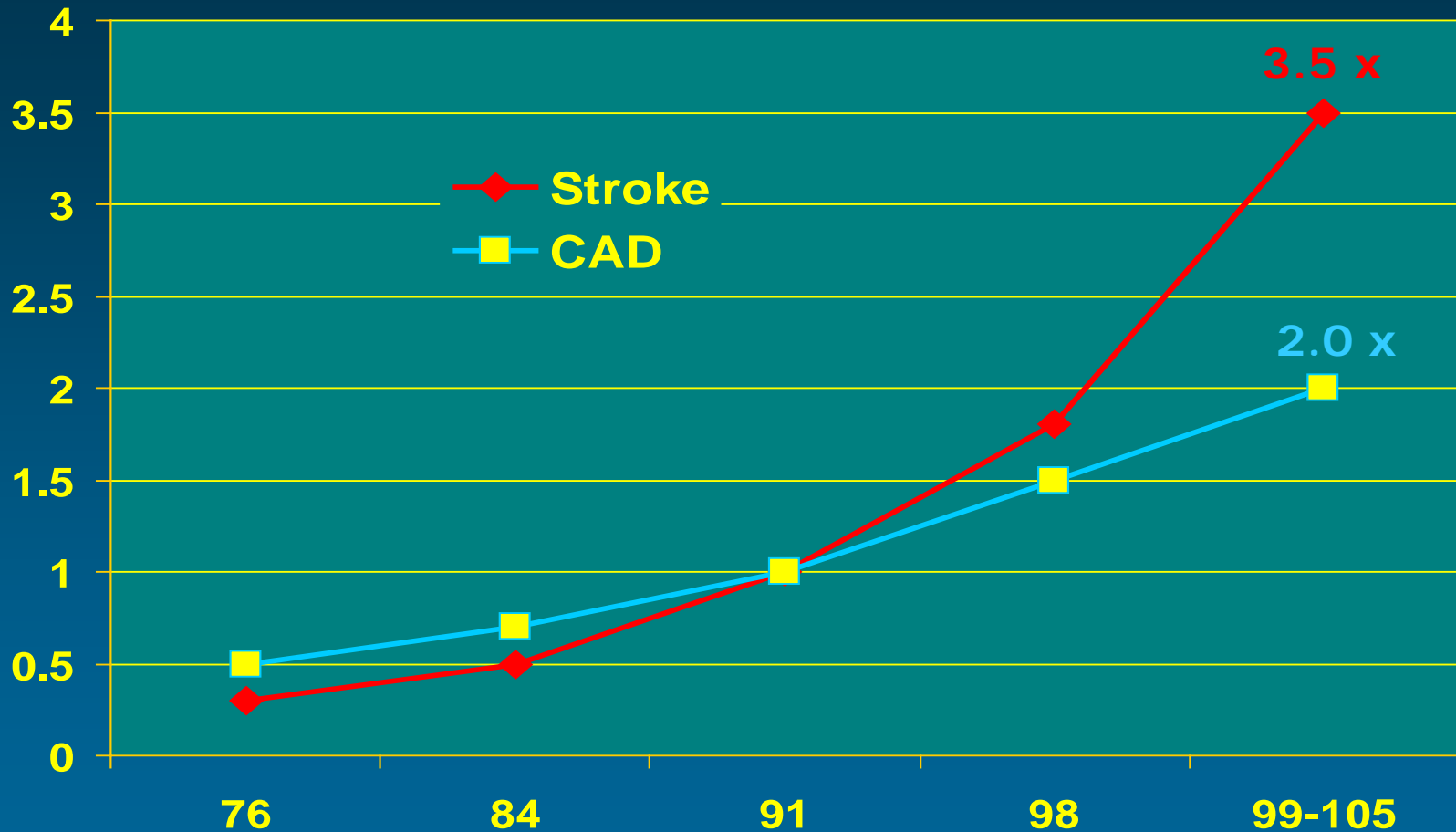
[†] Significant linear trend.

[‡] Significantly different from non-Hispanic black persons.

NOTE: Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db107_tables.pdf#1.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.

Relative Risk of CAD and Stroke by Diastolic Blood Pressure



10 year follow up in 9 studies of untreated patients

Lancet 1990:335:765

JNC-8: Three Core Questions



1. Does initiating anti-hypertensive therapy at specific BP thresholds improve health outcomes?
2. Does treatment with antihypertensive therapy to a specified BP goal lead to improvements in health outcomes?
3. Do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

Does Initiating Therapy at Specific BP Thresholds Improve Health outcomes?

Recommendation #1

GRADE A

- For patients ≥ 60 y.o. initiate Rx if $> 150/90$
- Goal Rx $< 150/90$
- If patient can tolerate $< 140/90$, acceptable to maintain this level of Rx

Recommendations #2-3, GRADE E

- For patients < 60 y.o., initiate Rx bp $> 140/90$
- Goal Rx is $< 140/90$

Recommendations #4-5

GRADE E

- Goal Rx $< 140/90$ if CKD or DM at any age

Do Various Antihypertensive Drug Classes Differ in Benefits and Harms?

Recommendation #6:
Initial Rx for nonblack
patients

GRADE B

- Thiazide
- CCB
- ACEi
- ARB

Recommendation #7: Initial
Rx for black patients,
GRADE C

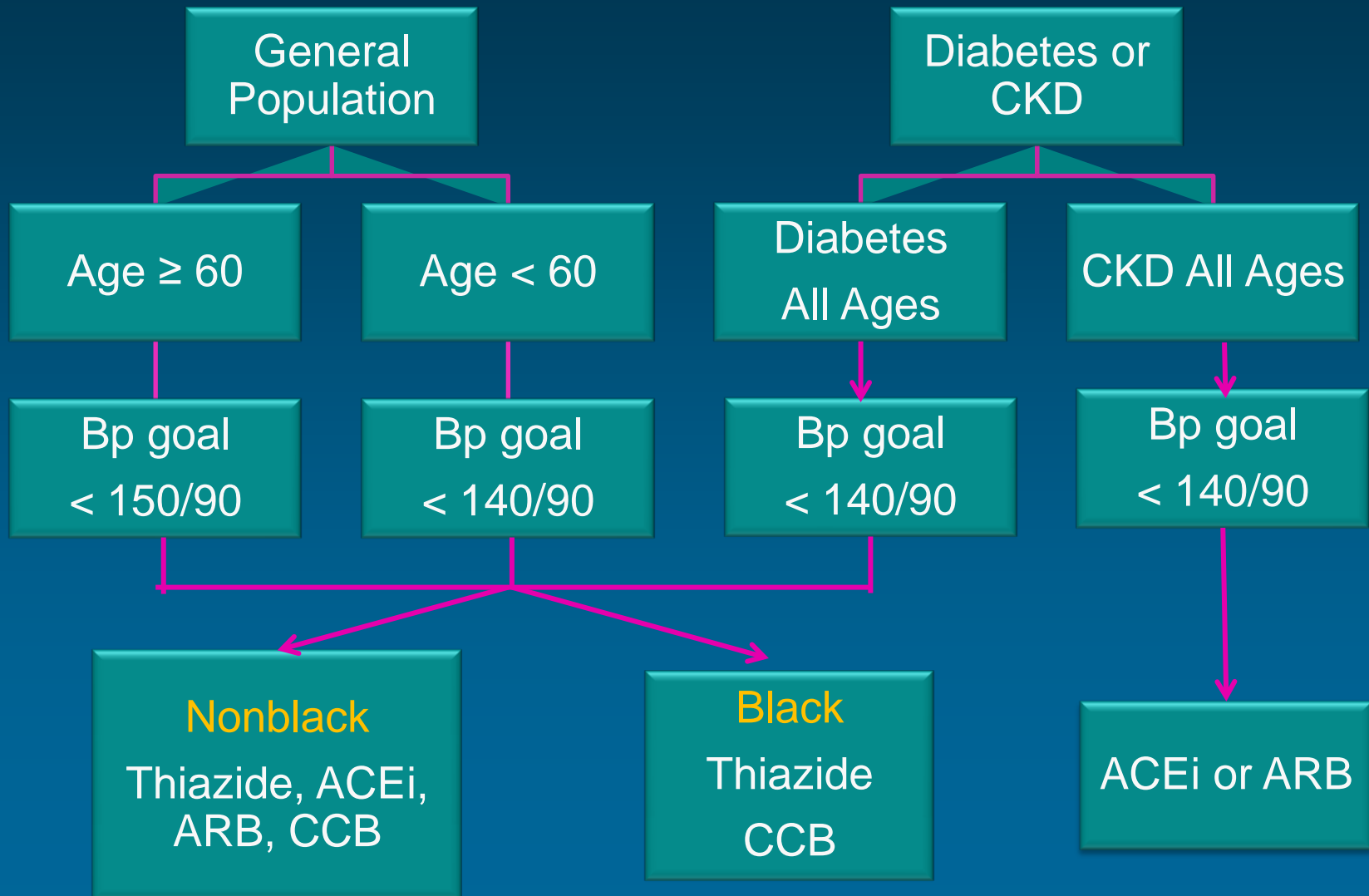
- Thiazide
- CCB

Recommendation #8

Initial or add-on Rx in CKD
should include, GRADE B

- ACEi
- ARB

JNC-8 Flow Chart For Target BP and Drug Selection



JNC-8: Other Recommendations

- For black patients, start with thiazide or CCB even if diabetic
- ACEi or ARB in CKD applies to all patients regardless of race, or diabetes status
- Do not use ACEi and ARB together
- Consider spironolactone for resistant hypertension
- Avoid beta blockers
- No opinion on whether drug doses should be maximized or use two or more drugs at lower doses

JNC-8: Development

- Originally commissioned by NHLBI in 2007
- NHLBI ceased production of guidelines
- Transferred development to AHA/ACC which did not materialize
- 17 members originally appointed to NHLBI panel wrote a limited guideline
- 5 dissenting members wrote article to disagree with bp target of 150/90 in patients > 60 y.o. with no DM or CKD*
- Dissenters favored 140/90 target for this group

Three Comprehensive Guidelines: Issue of Target BP in Older Patients

- 2014 American Society of Hypertension Guidelines
 - Bp target 150/90 only if > 80 y.o.
- 2013 European Society of Hypertension Guidelines
 - Discretion for 150/90 or 140/90 target if 60-80 years old depending on overall fitness
- 2013 Canadian Hypertension Education Program
 - Target bp 150/90 if > 80 y.o.

*J Hypertens 2014;16:14 J Hypertens 2013;31:1281
Can J Cardiol 2013;29:528*

How to Reconcile Competing Guidelines on Target BP if > 60 y.o.?

A reasonable strategy, incorporating all guidelines:

- Goal of at least 150/90 for patients > 60 y.o.
- If generally fit, with minimal or moderate comorbidities, aim for <140/90
- If frail, multiple comorbidities, goal <150/90
- If > 80 y.o., goal < 150/90

What Does JNC-8 Not Address?



- White coat hypertension
- Ambulatory bp monitoring
- Drug selection in advanced CKD
- Identifiable causes of hypertension
- Resistant hypertension
- Influence of cost on drug selection
- Compelling indications
- Comorbidities other than CKD and DM

Secondary (Identifiable) Causes of Hypertension

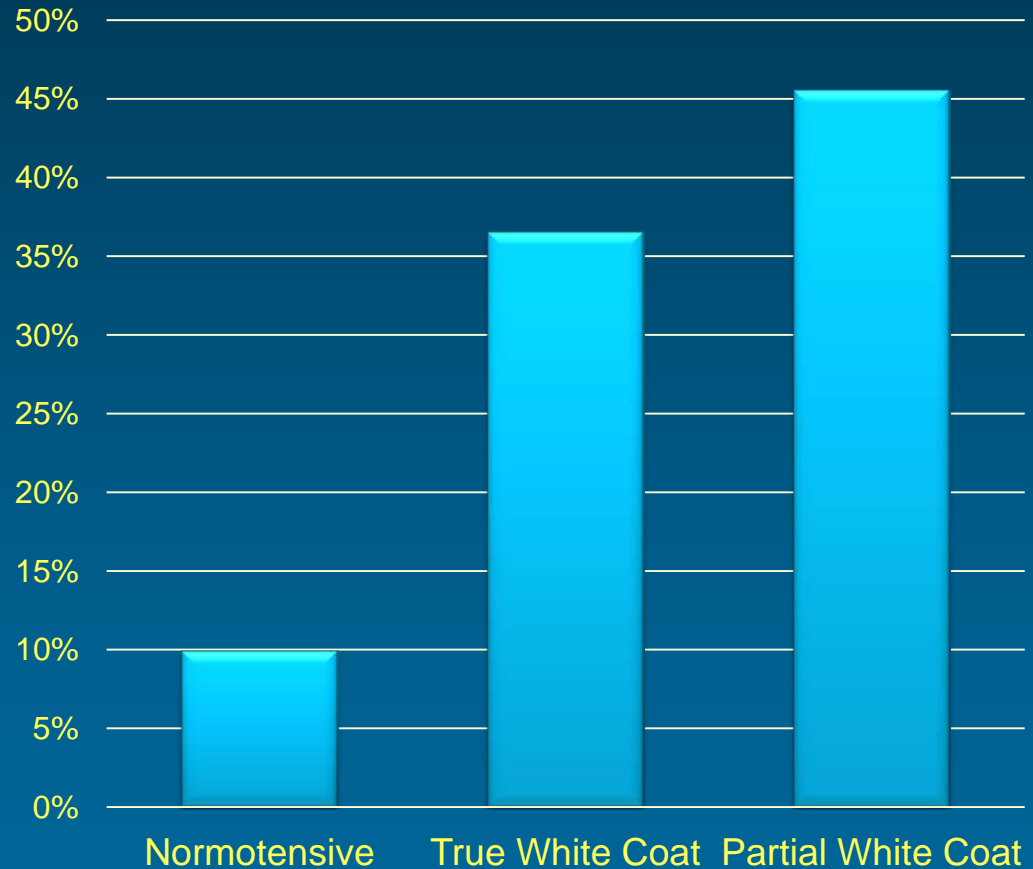
- Cushing's syndrome
- Renal artery stenosis
- Primary aldosteronism
- Pheochromocytoma
- Chronic renal disease
- Coarctation of the aorta
- Thyroid or parathyroid disease
- **Obstructive sleep apnea**



White Coat Hypertension: A Pre-Hypertensive State

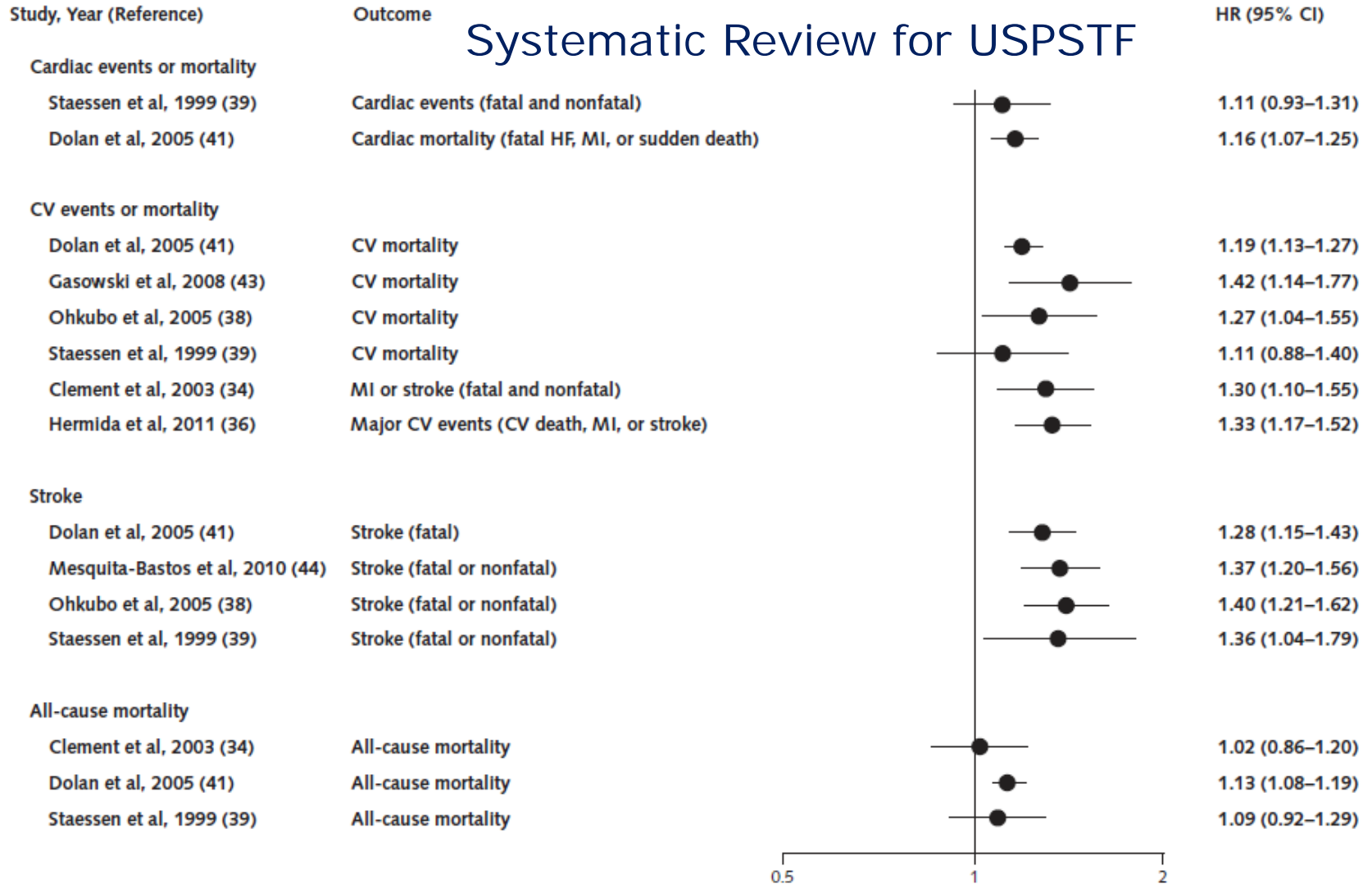
- 2015 persons
- Normotensive (52%)
Hypertensive (23%)
White coat (25%)
- Divided white coat into true (all home reads normal) and partial (at least one home bp elevated)
- 16 years of followup

Incidence of New Onset
Hypertension Over 16 years



Ambulatory Systolic BP Monitoring Predicts CV Events and Mortality Even After Adjustment for Office BP

Systematic Review for USPSTF



Systematic Review: Other Findings

- Ambulatory bp monitoring predicts CV events even after adjustment for office bp values
- HR range from 1.28 to 1.40
- Casual home readings probably equally predictive, but less evidence
- ~55% of initial elevated bp reads are not confirmed by home values
- CV risk of white coat HTN does not differ from normotensive patients

Draft Recommendation Statement from USPSTF on Screening for HTN

Public Comment Completed Jan. 2015, Final Version Pending

The USPSTF recommends screening for high blood pressure in adults ≥ 18 years

Ambulatory blood pressure monitoring is recommended to confirm high blood pressure before the diagnosis of hypertension, except in cases for which immediate initiation of therapy is necessary.

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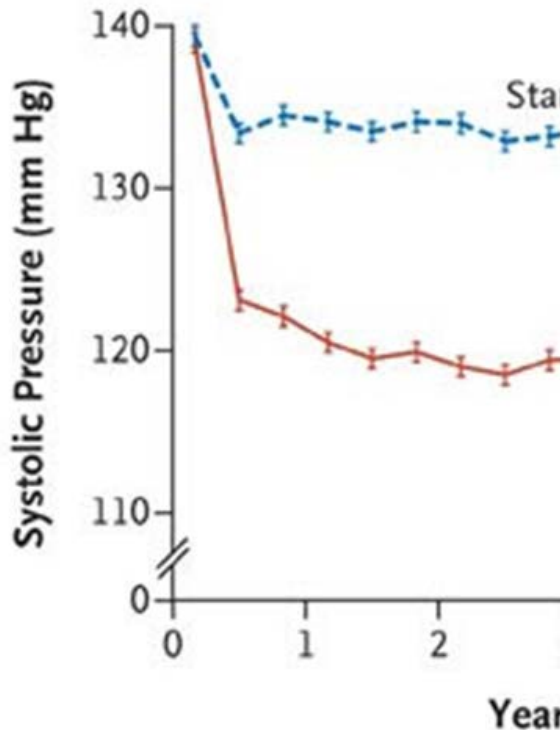
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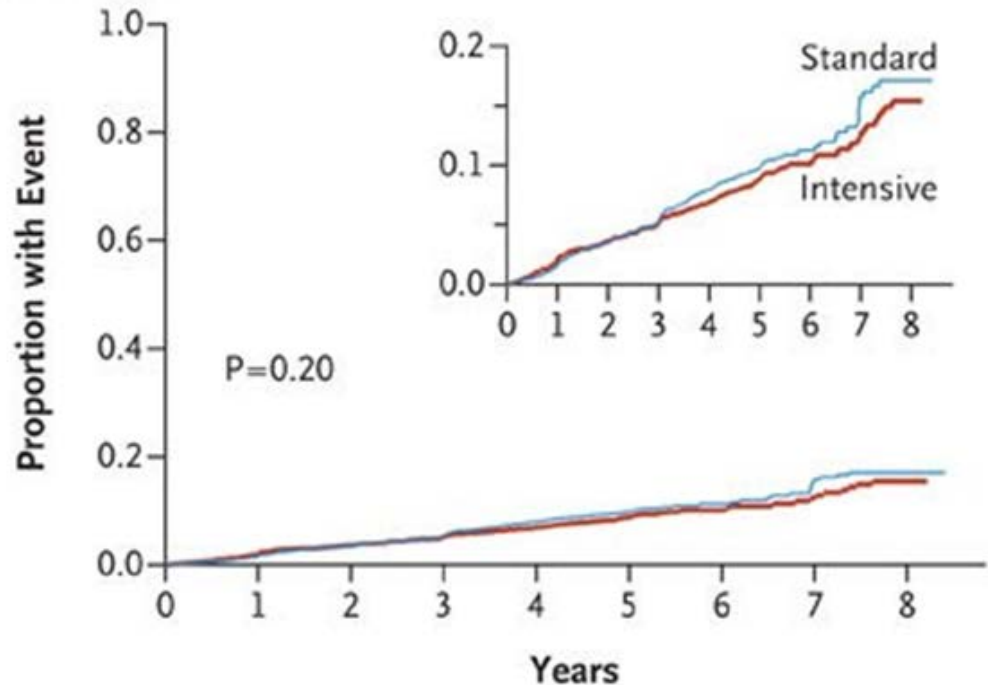
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What is Optimal Target BP? No Benefit from Lower Target BP in Diabetic Patients

N= 4733
Target sbp
120 vs 140



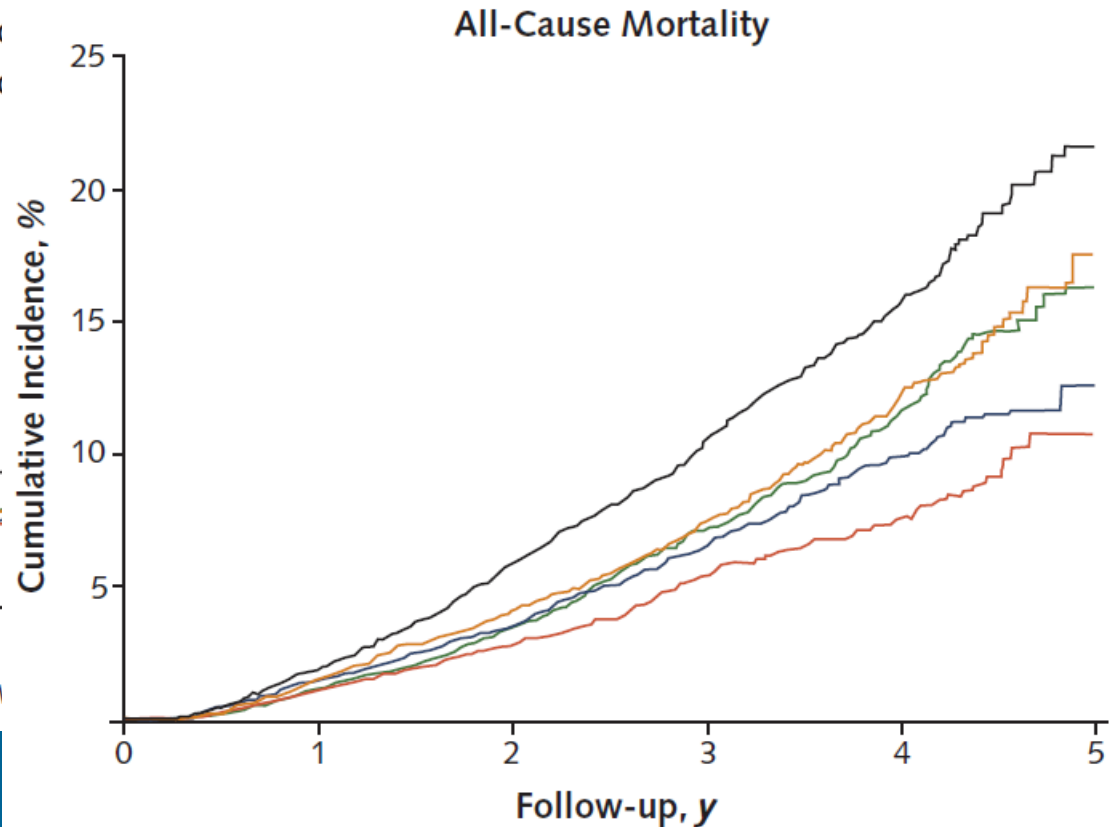
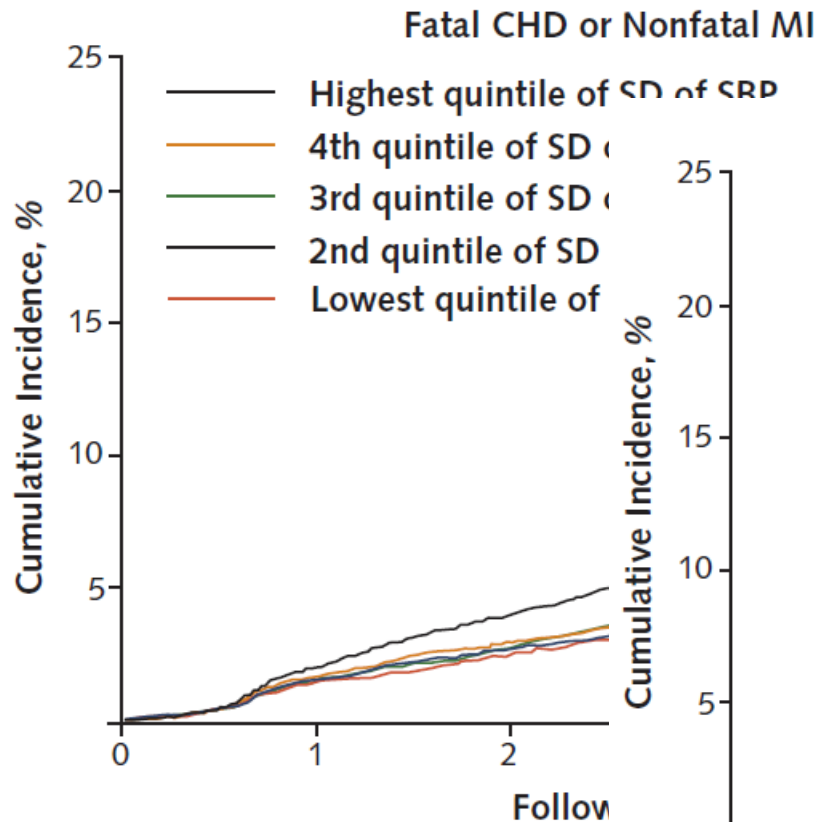
A Primary Outcome



ADA / JNC-8

Target bp <
140/90

Wide Range of Visit to Visit BP Variability Not Benign: Increased CAD Event Risk



ALLHAT Data N=25,814

SD of Bp readings over 7
visits

Muntner P, et al. Ann Intern Med
2015 (epub ahead of press)

ACC/AHA 2013: Lifestyle Modification to Reduce BP and Prevent CV Disease

- DASH/USDA type diet: vegetables, fruits, whole grains, low fat dairy, poultry, fish, legumes, vegetable oils, nuts (Grade A)
- Limit sweets, sugar-sweetened beverages, red meat (Grade A)
- Lower sodium intake: < 2.4 grams per day (Grade A) or less if possible
- Moderate to vigorous aerobic physical activity x 40 minutes, 3-4 times per week (Grade B)



Medications

“Man has an inborn craving for medicine... The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures... Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor’s visit is not thought to be complete without the prescription.”

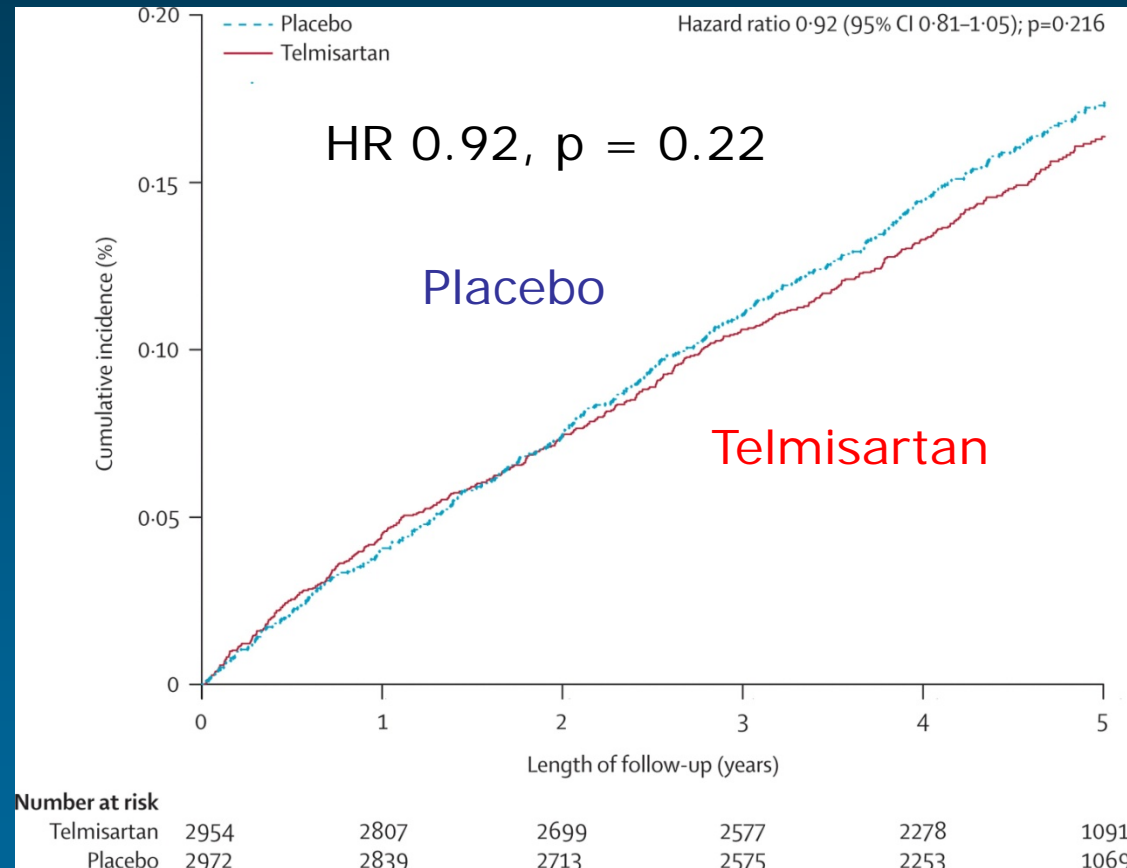


William Osler 1895

TRANSCEND: Telmisartan Does Not Reduce CV Endpoints if Intolerant to ACEi

Endpoint = CV Death + MI + Stroke + CHF Admit

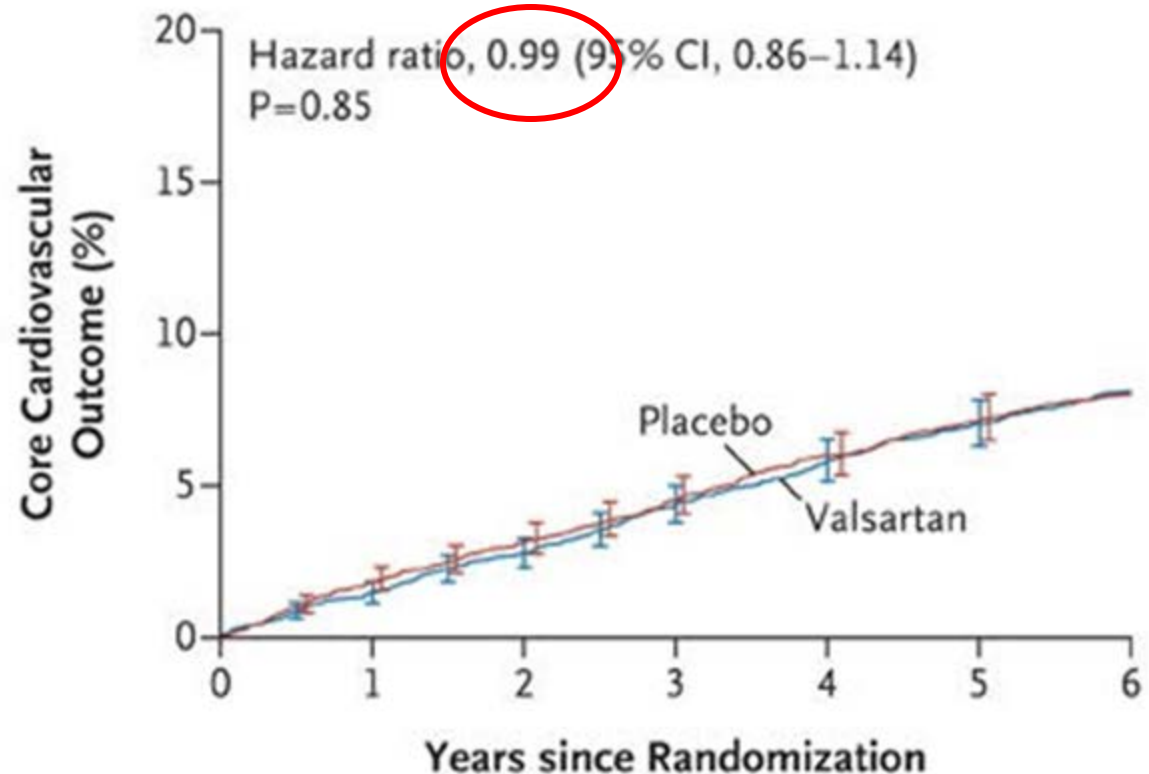
- 5926 high risk patients
- Existing CV disease or diabetes
- End organ disease
- Intolerant to ACEi
- Key exclusions:
 - CHF
 - Sbp > 160
 - CKD
- Randomized to telmisartan 80 mg or placebo



NAVIGATOR: Valsartan Does Not Reduce CV Risk For Patients with Glucose Intolerance

- N=9306
- Impaired fasting glucose
- Established CV disease or CV risk factors
- 77% were hypertensive
- Valsartan 80-160 mg qd vs placebo

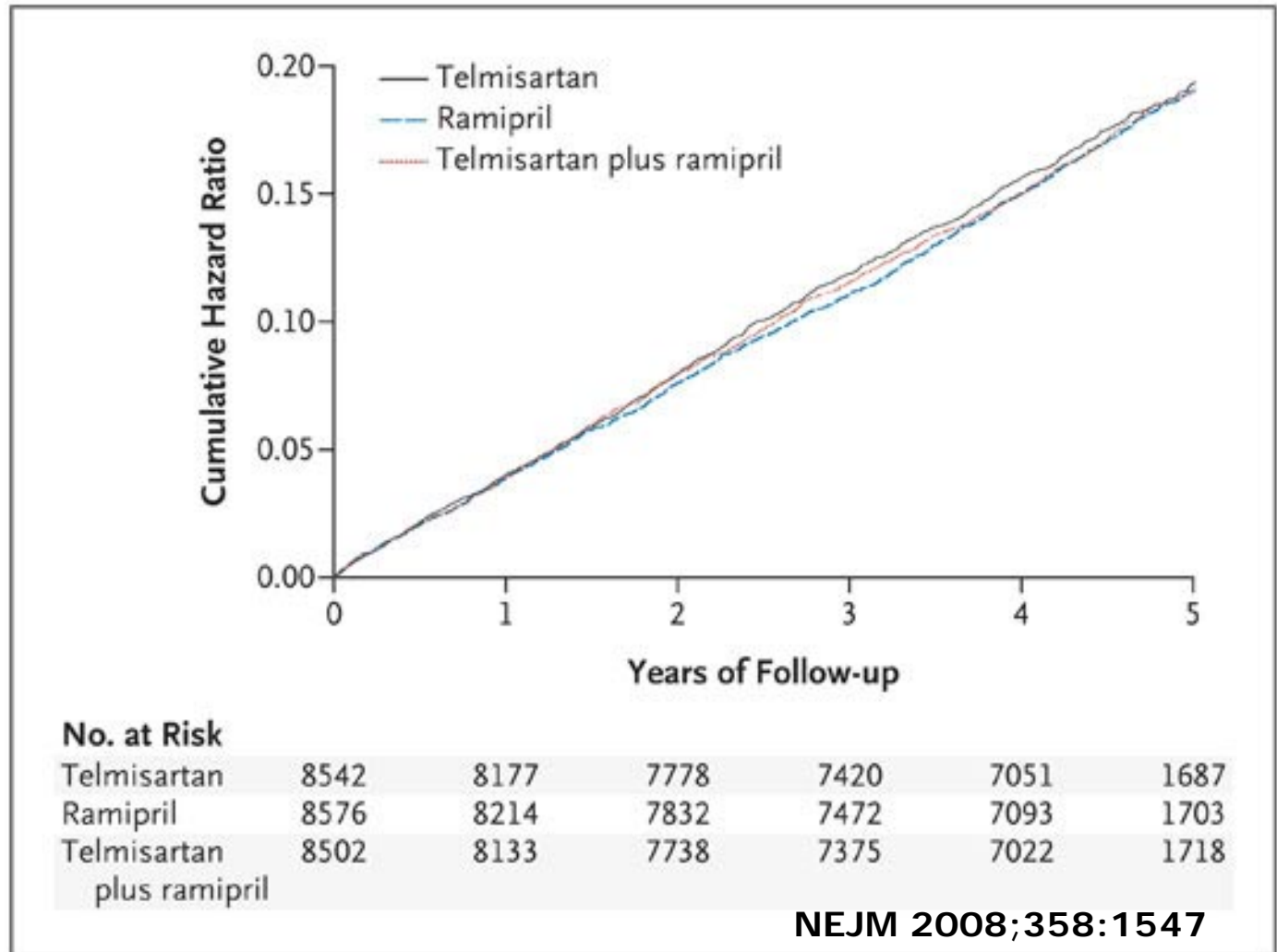
Core Cardiovascular Outcome



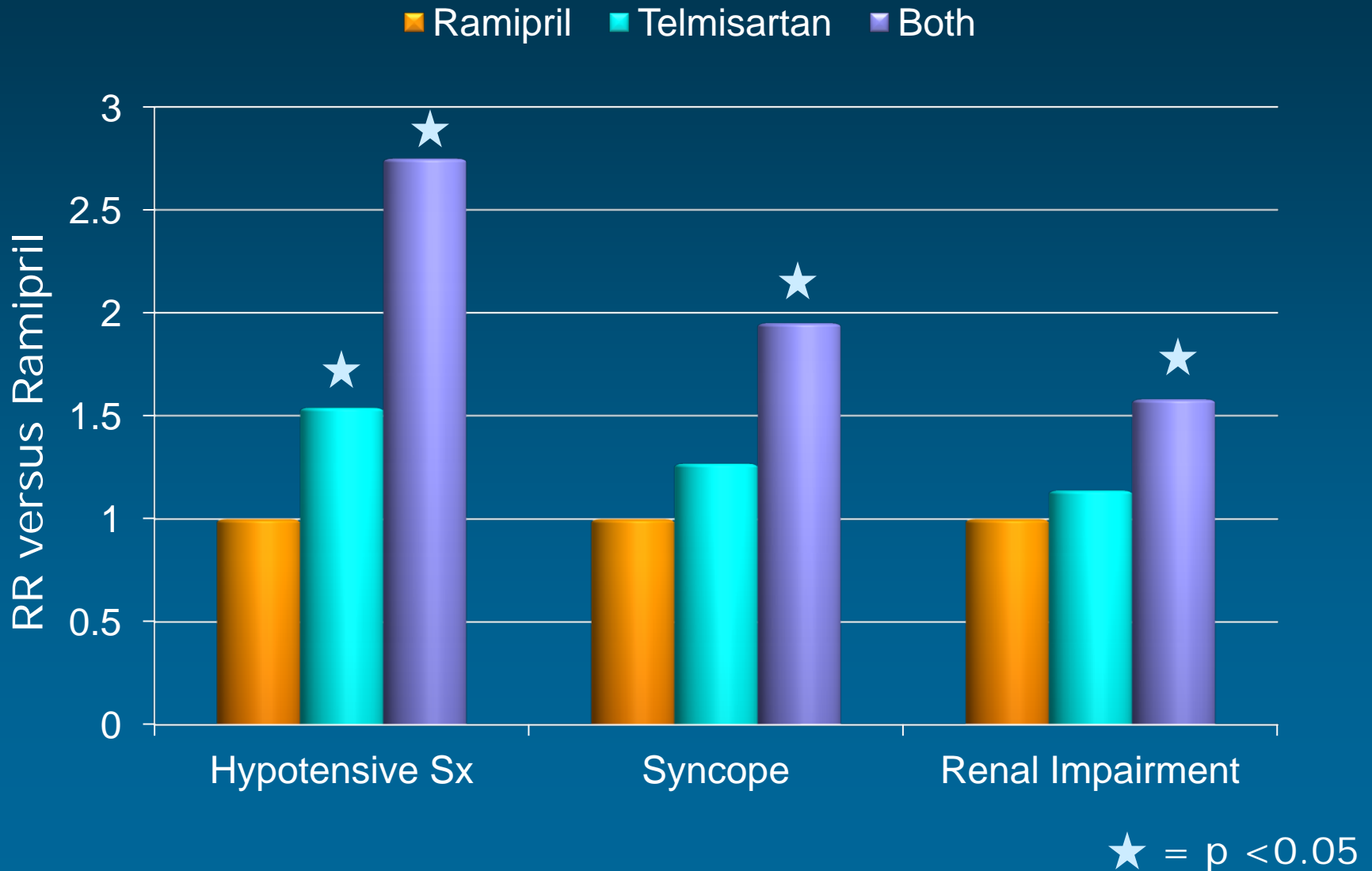
ACEi + ARB. More is Not Always Better: No Difference in Composite CV Endpoint

ONTARGET Trial

- 25,620 patients
- ≥ 55 y.o.
- CAD
- PVD
- CVA or TIA
- DM with end organ damage

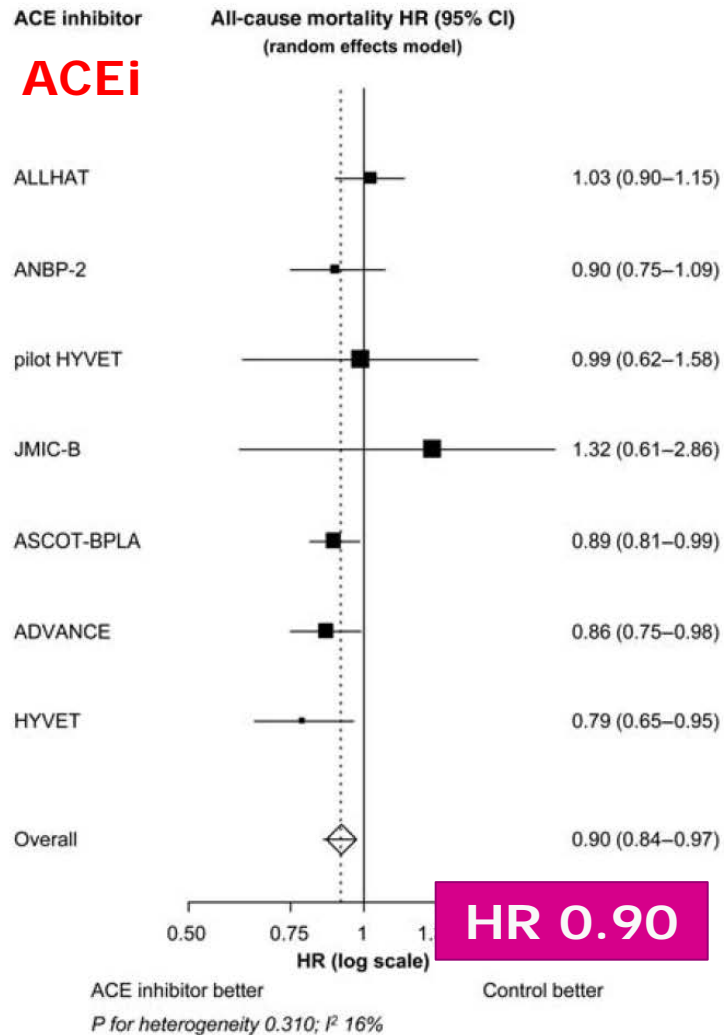


Combination Therapy: More Adverse Events Despite No Additional CV Risk Reduction

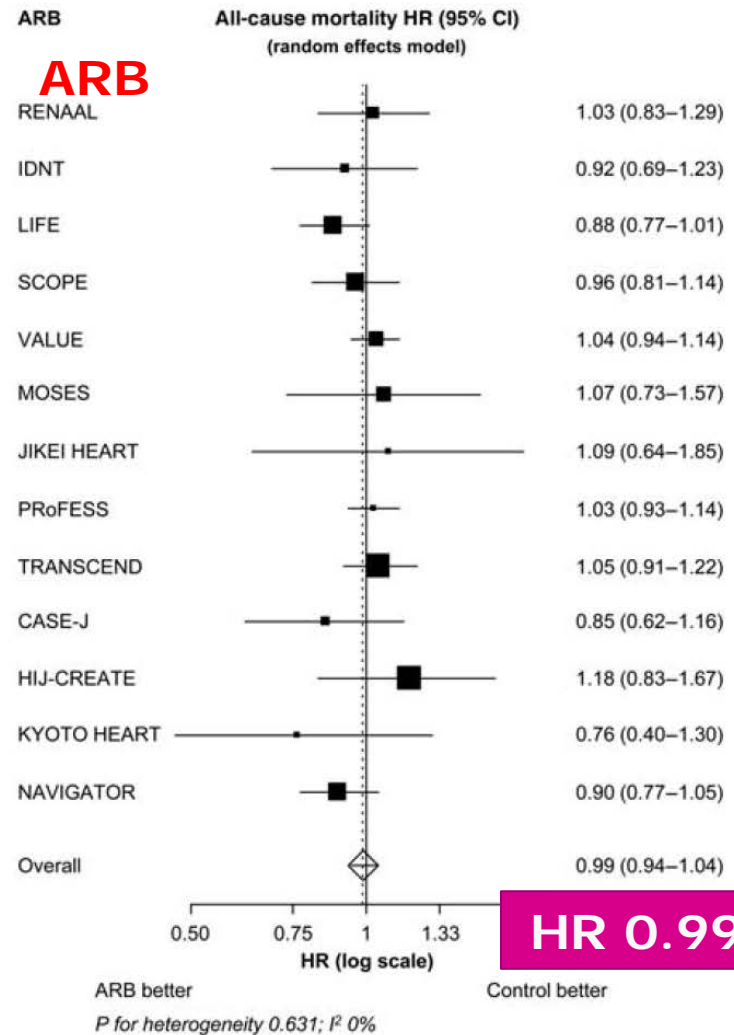


Meta-Analysis: ACEi Reduce Mortality but ARB's Have no Effect

ACE inhibitor ACEi



ARB ARB



Aliskiren Increases Morbidity in Diabetic Patients with Renal Disease

- Direct renin inhibitor
- ALTITUDE Trial: Type 2 diabetes plus renal impairment (proteinuria or CKD)
- All patients on ACEi or ARB
- Randomized to addition of aliskiren or placebo
- Composite outcome of mortality, CV, and renal outcome
- Terminated due to lack of efficacy at 27 months
- Higher rates of renal impairment, hypotension, and hyperkalemia with aliskiren
- Marginal increase in stroke and death
- **FDA: Contraindicated as part of dual Rx with ACEi or ARB**

Renin/Aldosterone Suppression: Conclusions

- ACEi reduce CV risk to same degree as diuretics
- ACEi are appropriate first-line agents
- ARB's comparable to ACEi in ONTARGET
- ARB's are not effective when ACEi intolerant or if glucose intolerance
- Pending further study, would move ARBs to second line status
- This is controversial. JNC-8 endorses ARBs
- Do not use aliskiren (FDA restricts use only in dual Rx)

Hypertensive patients ≥ 55 yrs with at least one other CV risk factor

Consent / Randomize (42,418)

Amlodipine
Chlorthalidone
Doxazosin
Lisinopril

Eligible for lipid-lowering

Not eligible for lipid-lowering

Consent / Randomize (10,355)

Pravastatin

Usual care

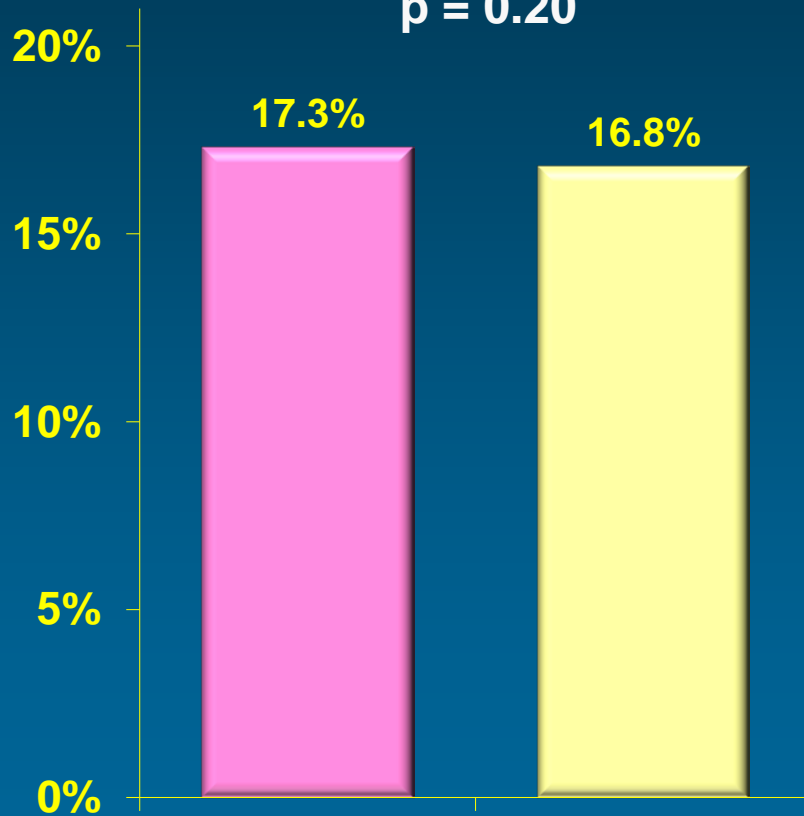
Follow for CHD until death or end of study (mean 4.9 years)

Chlorthalidone vs. Amlodipine: Lower CHF Rates

All Cause Mortality

RR = 0.96

p = 0.20

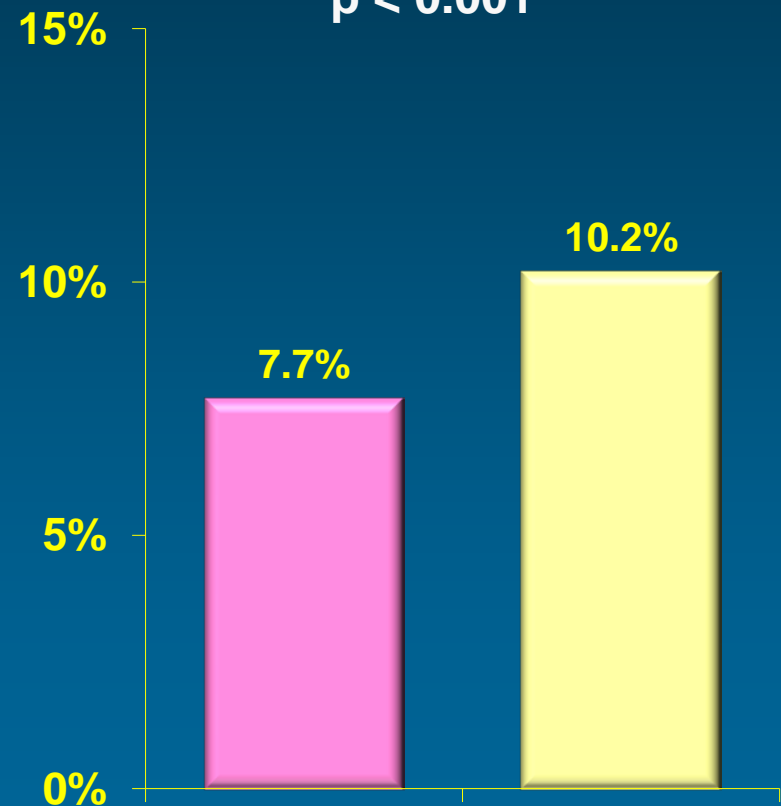


Chlorthalidone Amlodipine

Heart Failure

RR = 1.38

p < 0.001



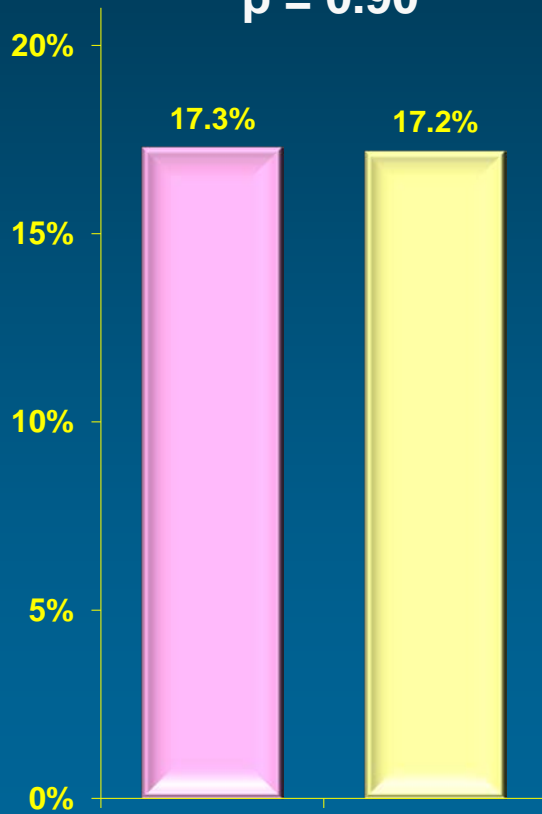
Chlorthalidone Amlodipine

Chlorthalidone vs Lisinopril: Lower CHF and Stroke Rates

All Cause Mortality

RR = 1.00

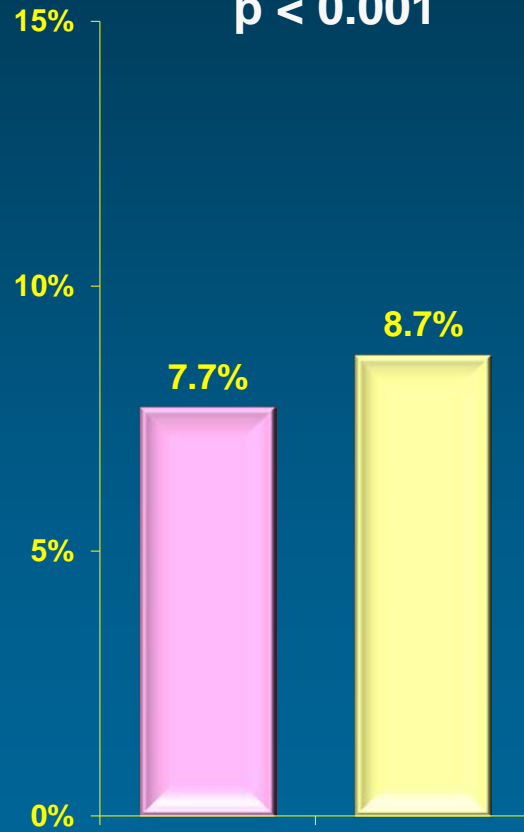
p = 0.90



Heart Failure

RR = 1.19

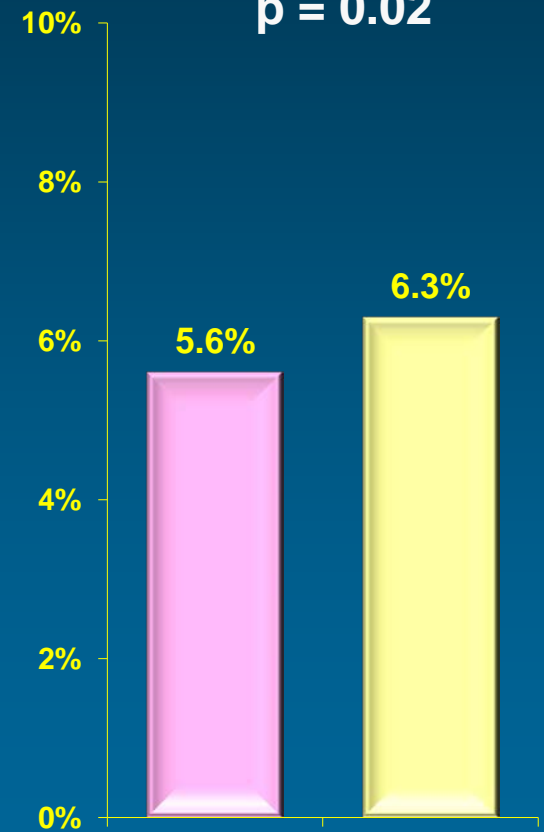
p < 0.001



Stroke

RR = 1.15

p = 0.02

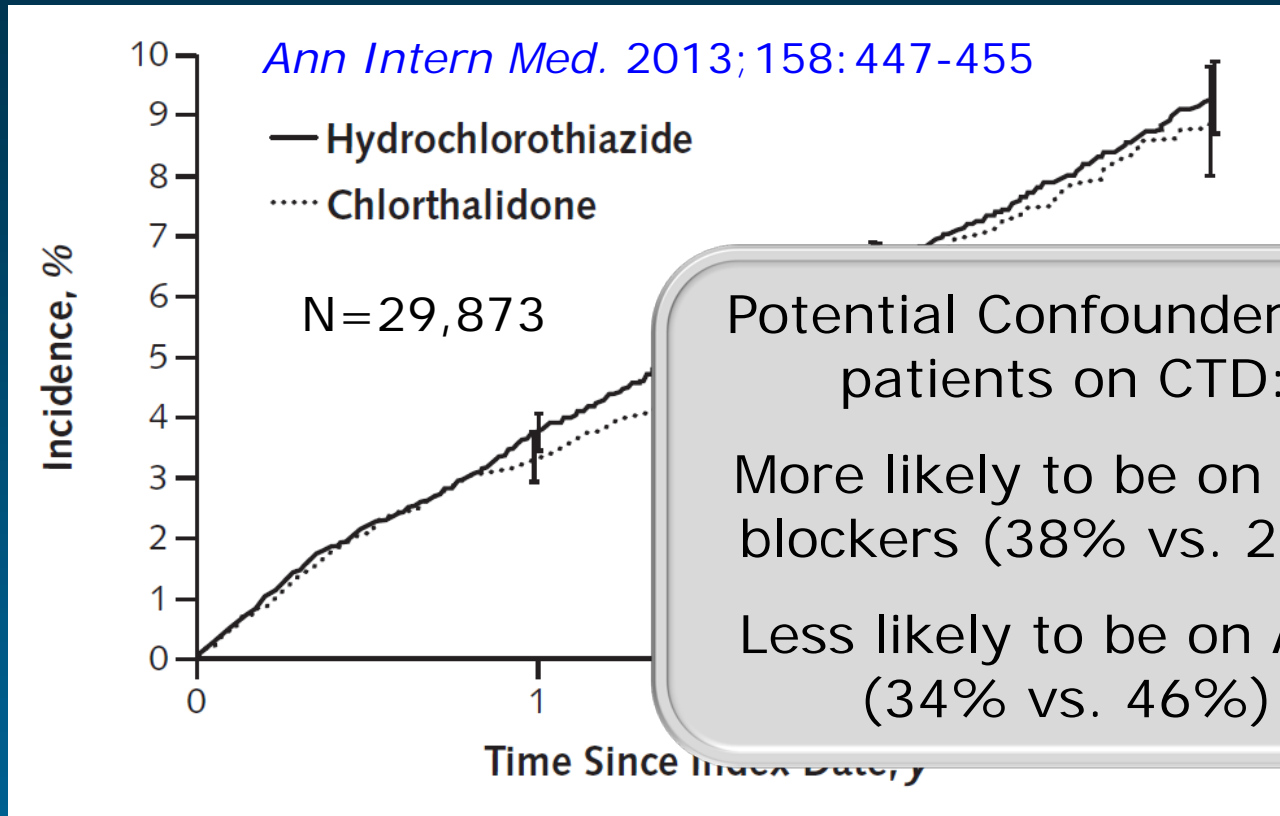


Chlorthalidone Lisinopril

Chlorthalidone Lisinopril

Chlorthalidone Lisinopril

Which Diuretic? Chlorthalidone Comparable to HCTZ in Propensity Matched Cohorts



Potential Confounders for patients on CTD:

More likely to be on beta blockers (38% vs. 22%)

Less likely to be on ACEi (34% vs. 46%)

OR for Chlorthalidone

CV outcome 0.93 Hypokalemia 3.1

Hyponatremia 1.7



Meta-Analysis: Fewer CV Events for Chlorthalidone than HCTZ

- Systematic review
- Studies include chlorthalidone or HCTZ in one arm
- N =9 studies
- Mean bp reduction greater for CTD than HCTZ
- Lower CV rates for CTD even after controlling for bp

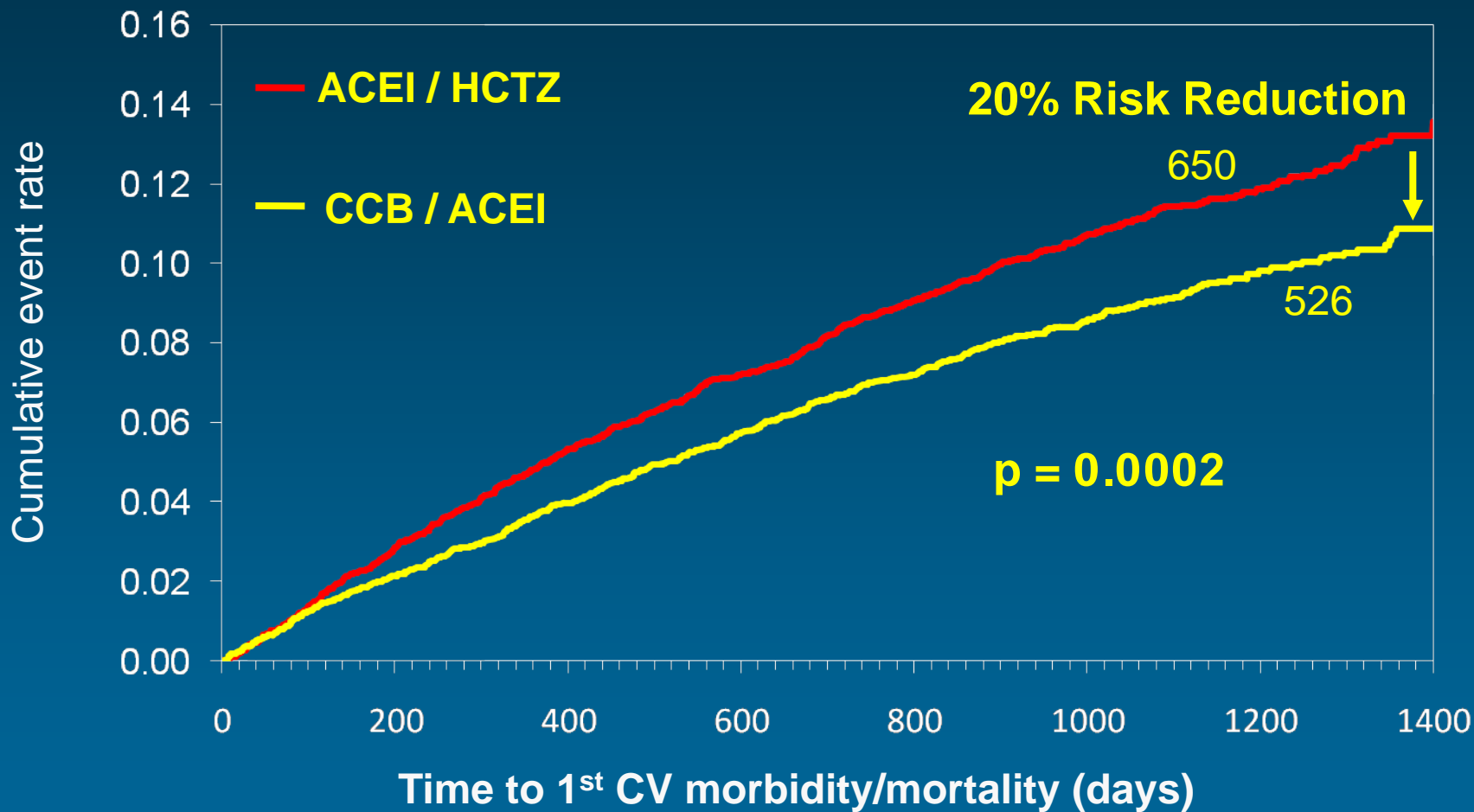
Outcome for Chlorthalidone when Compared to HCTZ		
Outcome	Drug adjusted RR	Bp adjusted RR
Mortality	0.94	
Stroke	0.77	
Total CV events	0.79*	0.82*
CHF	0.77*	

Which Diuretic to Choose?

- JNC-7: Use diuretics as first line therapy unless compelling indication for other agent
- Chlorthalidone is twice as potent as HCTZ
- Longer half life than HCTZ of 24 hours
- More effective at lowering night time bp
- Most positive diuretic trials have used chlorthalidone
- **Chlorthalidone should now become our preferred diuretic for Rx of hypertension**
- **Start at 12.5 mg daily**
- Increased hypokalemia

ACCOMPLISH: ACEi/CCB vs. ACEi/HCTZ

CCB Based Regimen is Superior



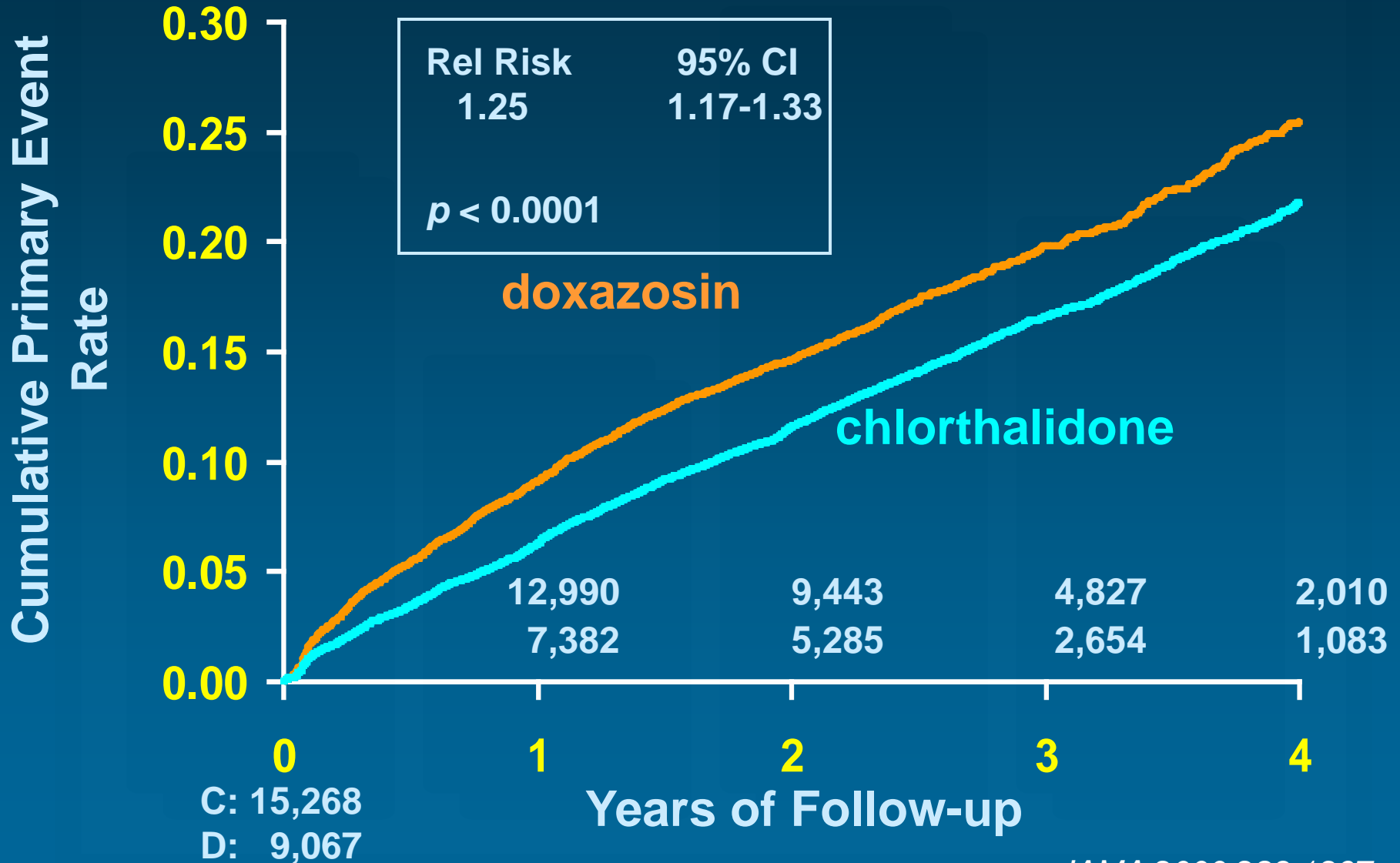
Calcium Channel Blockers: Recommendations

- Some conflicting data
- Higher CHF rates in ALLHAT
- ACCOMPLISH strongest data yet
- May be superior as part of combination Rx
- Good data for systolic HTN in elderly
- I am now moving CCBs up to a 1st line therapy



Doxazosin Inferior to Chlorthalidone

ALLHAT



Cochrane 2012: Comparisons to Placebo β Blockers Do Not Reduce Mortality and Modestly Reduce CV Events

Outcome	# studies	RR Compared to Placebo	95% CI
Total mortality	4	0.99	0.88-1.11
Total CV disease	4	0.88	0.79-0.97
Stroke	3	0.80	0.66-0.96













Beta-Blockers: Recommendations

- Do not use as first line or second line treatment for hypertension
- Consider if three or more drugs required as part of multi-drug regimen for patients with drug intolerances and limited options
- Probably a class effect but most negative trials are for atenolol
- These recommendations apply only to primary prevention

Cochrane Review: Efficacy of 1st Line Treatments for Hypertension

<i>Class</i>	<i>Mortality</i>	<i>Stroke</i>	<i>CHD</i>	<i>CV Events</i>
Thiazides	0.89	0.63	0.84	0.70
Beta blockers	0.96	0.83	0.90	0.89
CCB	0.86	0.58	0.77	0.71
ACEi	0.83	0.65	0.81	0.76

Significant Benefits: Only Thiazides and ACEi Reduce All CV Endpoints

<i>Class</i>	<i>Mortality</i>	<i>Stroke</i>	<i>CHD</i>	<i>CV Events</i>
Thiazides				
Beta blockers				
CCB				
ACEi				

Average Wholesale Price for One Month Supply

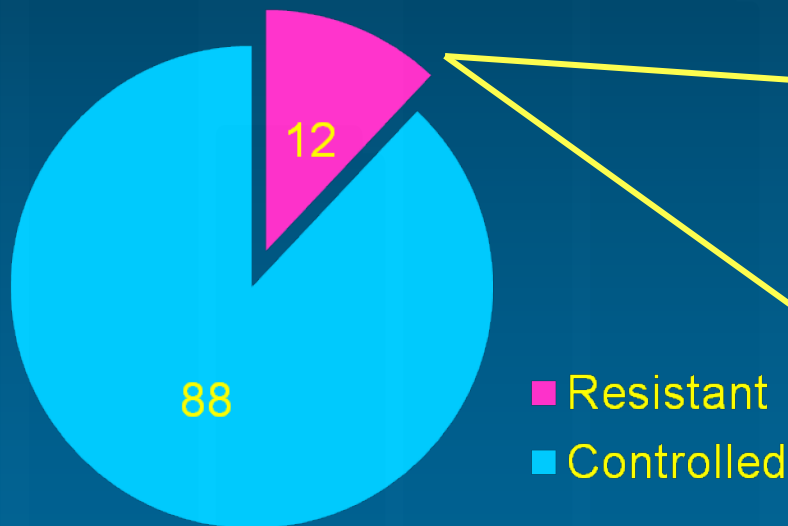


<i>Class</i>	<i>Drug</i>	<i>Monthly Cost</i>	<i>4\$ Option</i>
Diuretics	Chlorthalidone 12.5 mg	\$10	X (HCTZ)
β-blockers	Atenolol 25 mg	\$8	X
CCB	Nifedipine 30 mg	\$27	
	Amlodipine 5 mg	\$8	
ACEi	Lisinopril 10 mg	\$7	X
	Enalapril 10 mg	\$10	X
ARB	Valsartan 80 mg	\$57	
	Losartan 50 mg	\$13	

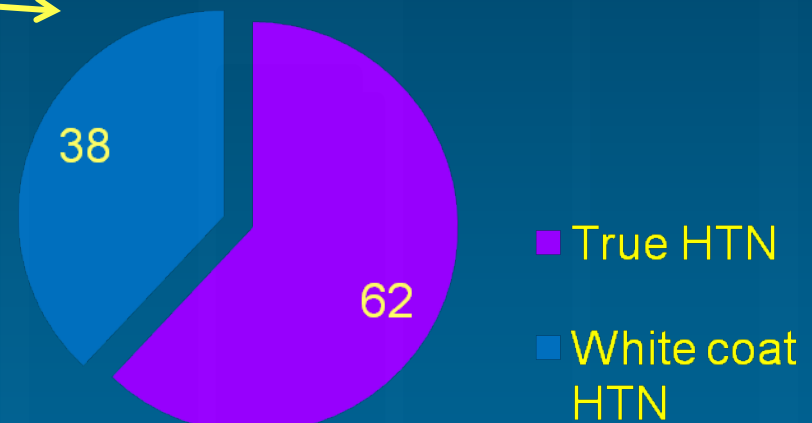
Source: www.rxpricequote.com Aug. 2015

One Third of Patients with Resistant Hypertension Have White Coat Hypertension

All Hypertensive Patients
(n=68,045)



Patients with Resistant Hypertension
(n=8295)



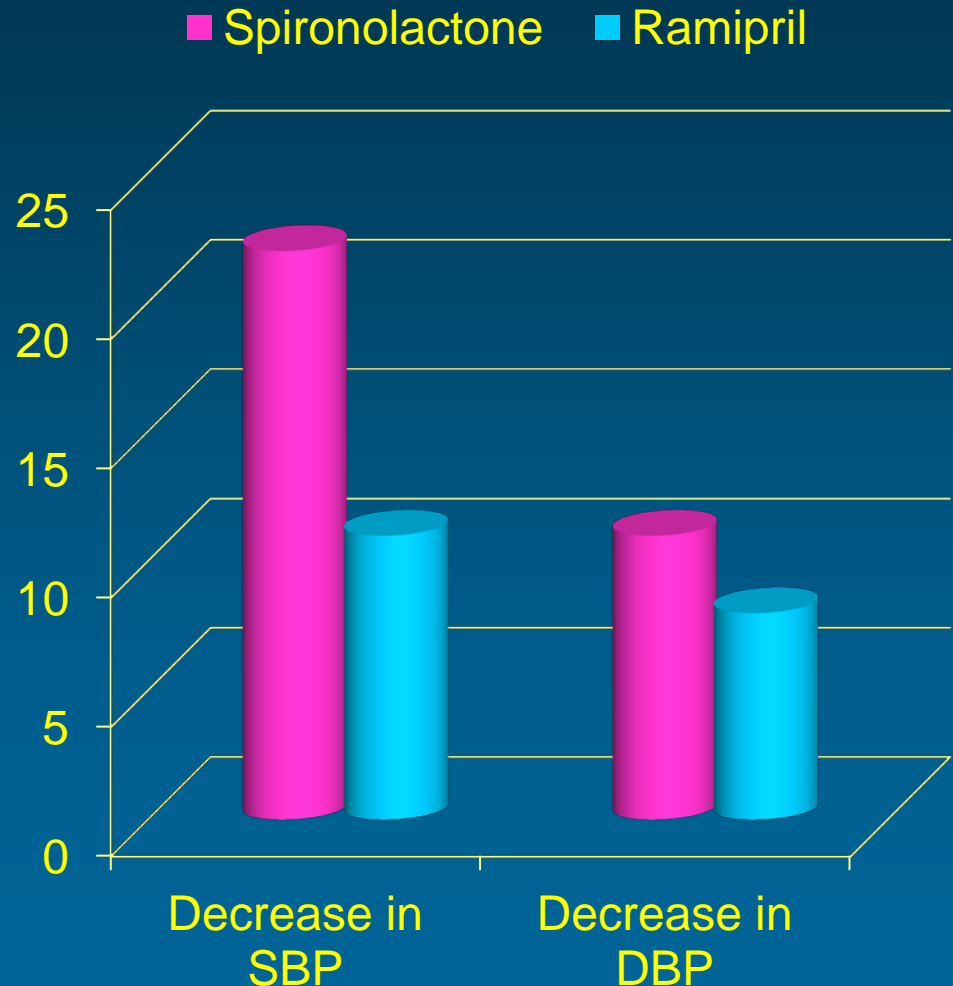
Resistant HTN = Uncontrolled despite
3 drugs including diuretic

Resistant Hypertension: Treatment Strategies

- Effective combinations
 - ACEi/diuretic
 - ACEi/CCB
 - Change HCTZ to chlorthalidone
 - Add spironolactone
- Third line strategies for severe essential hypertension
 - Labetalol
 - Carvedilol
 - Clonidine
 - Dual CCB's
 - Hydralazine
 - Minoxidil

RCT: Spironolactone Superior to Ramipril in Resistant Hypertension

- 167 patients
- Resistant hypertension
- Randomly assigned to addition of spironolactone or ramipril
- Endpoint bp changes at 12 weeks



Renal Sympathetic Denervation RCT: No More Effective than Sham Rx...

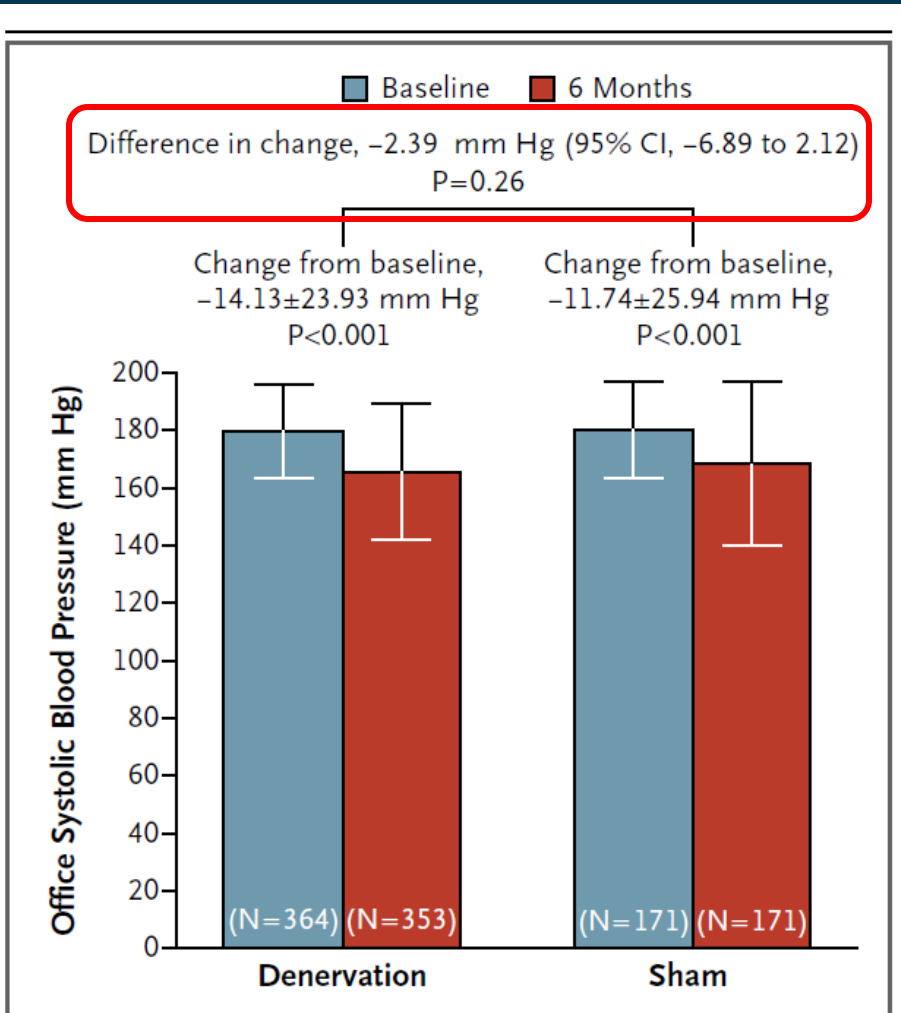


Figure 1. Primary Efficacy End Point.

- 535 patients with resistant HTN
- ≥ 3 drugs including a diuretic
- Randomly assigned to
 - Catheter based RFA renal artery sympathetic denervation or
 - Sham Rx
- End point: systolic bp change at 6 months

Impact of Alternative Approaches to Lower Blood Pressure

Treatment	Class of Recommendation
Transcendental meditation	II B
Biofeedback	II B
Yoga	III
Acupuncture	III
Device guided breathing	II A
Aerobic exercise	I
Resistance exercise	II A
Isometric handgrips	II B

I = Should

IIA = Reasonable

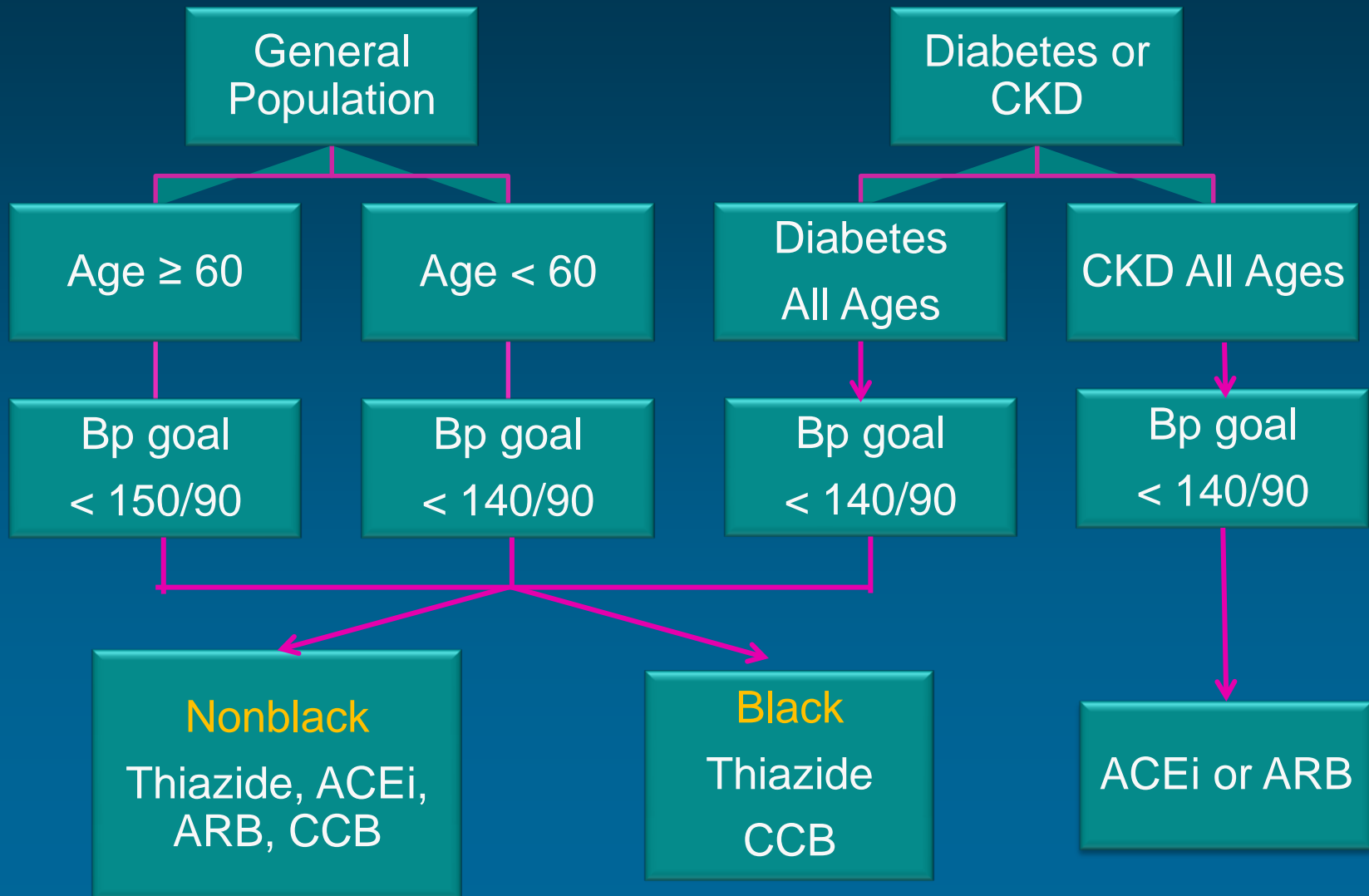
IIB = Consider

III = Do not use

Summary of Evidence

Drug class	Evidence for CV risk reduction	Compelling indications
Diuretics	Yes	Systolic HTN elderly
ACEi	Yes	LV dysfunction Post MI
CCB	Yes	Systolic HTN elderly
ARB	Mixed	LV dysfunction Diabetes
Beta-blockers	Inferior	Post MI LV dysfunction
Alpha blockers	Inferior	None
Renin inhibitor	Inferior	None

JNC-8 Flow Chart For Target BP and Drug Selection



JNC-8: What is New that Should Change Our Practice?

- Consider both systolic and diastolic bp when diagnosing HTN and choosing target bp
- Target bp 150/90 if ≥ 60 y.o.
- Lower target of 140/90 if < 60 y.o.
- Raise target bp for diabetes to 140/90
- Use ACEi or ARB as first line Rx if CKD
- Don't use beta blockers or alpha blockers
- Don't use ACEi and ARB together

What Else to Remember?

- Confirm all elevated office bp values with home measurement before Dx
- Lifestyle modification for all patients
- ARBs may be inferior
- Don't use aliskiren
- Consider white coat HTN if resistant bp
- Spironolactone and labetalol for resistant hypertension
- Consider goal bp < 140/90 if 60-80 y.o. and in good general health

All Drugs that Lower Blood Pressure Do Not Equally Reduce Cardiovascular Risk

