

# HYPERTENSION IN DIABETES



Symposium on Cardiometabolic Risk in Type 2 Diabetes  
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Department of Endocrinology  
June 22, 2019

# Objectives

Epidemiology of Hypertension in Diabetes.

Pathogenesis of Hypertension in Diabetes.

Evolution of hypertension guidelines.

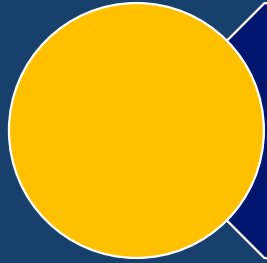
Discuss the evidence leading to different blood pressure targets.

Review the nonpharmacologic and pharmacologic interventions for management of hypertension.

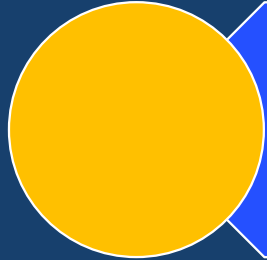
Establish the difference between white coat hypertension and masked hypertension.

# Hypertension and Diabetes

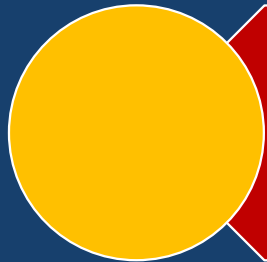
**(Deadly Duo)**



Hypertension is the most common comorbidity in patients with type 2 diabetes.



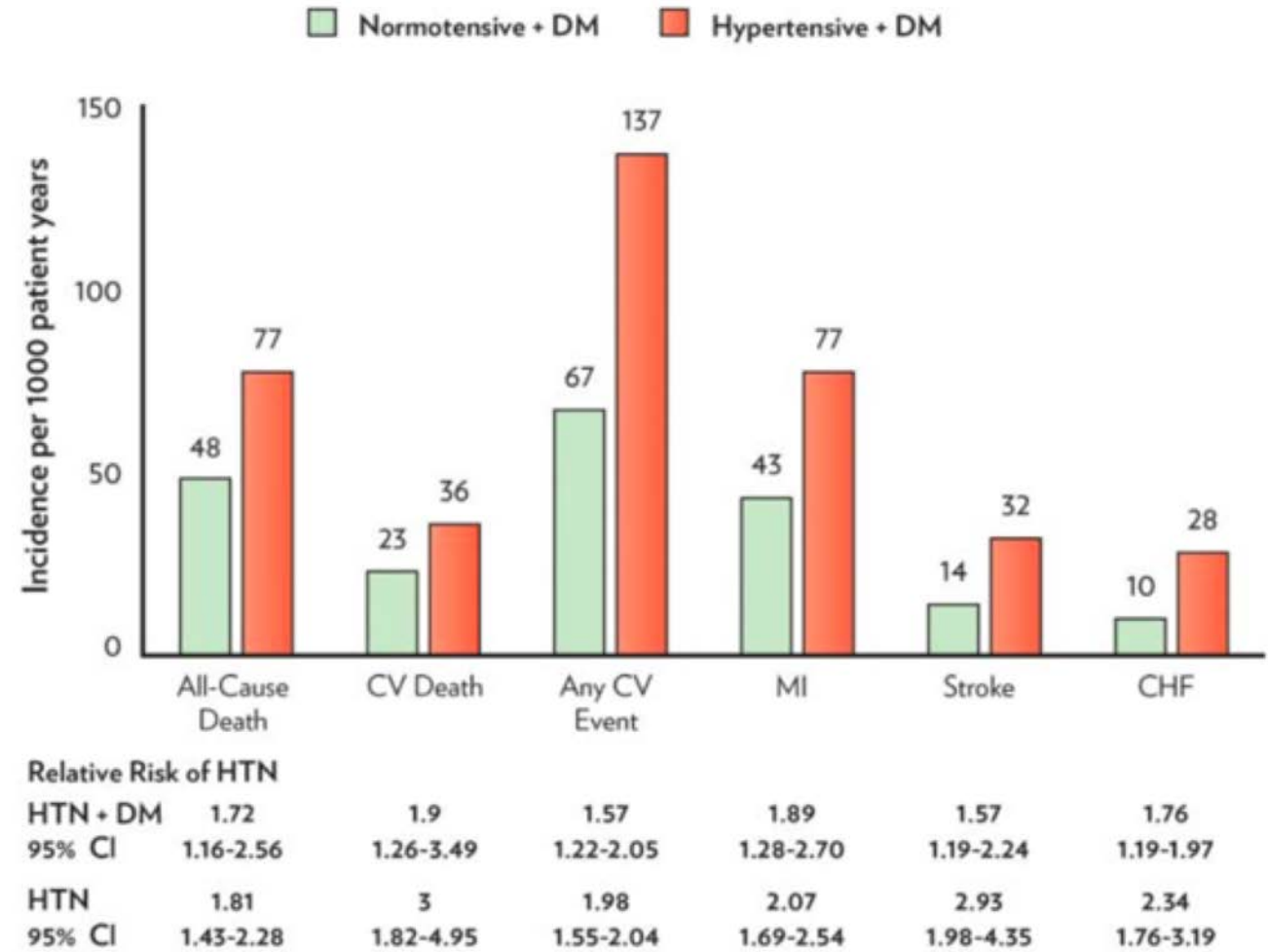
The prevalence of hypertension is higher in patients with diabetes than in the general population.



The coexistence of hypertension and diabetes increases the incidences of CVD and mortality and augments the risks of nephropathy and retinopathy

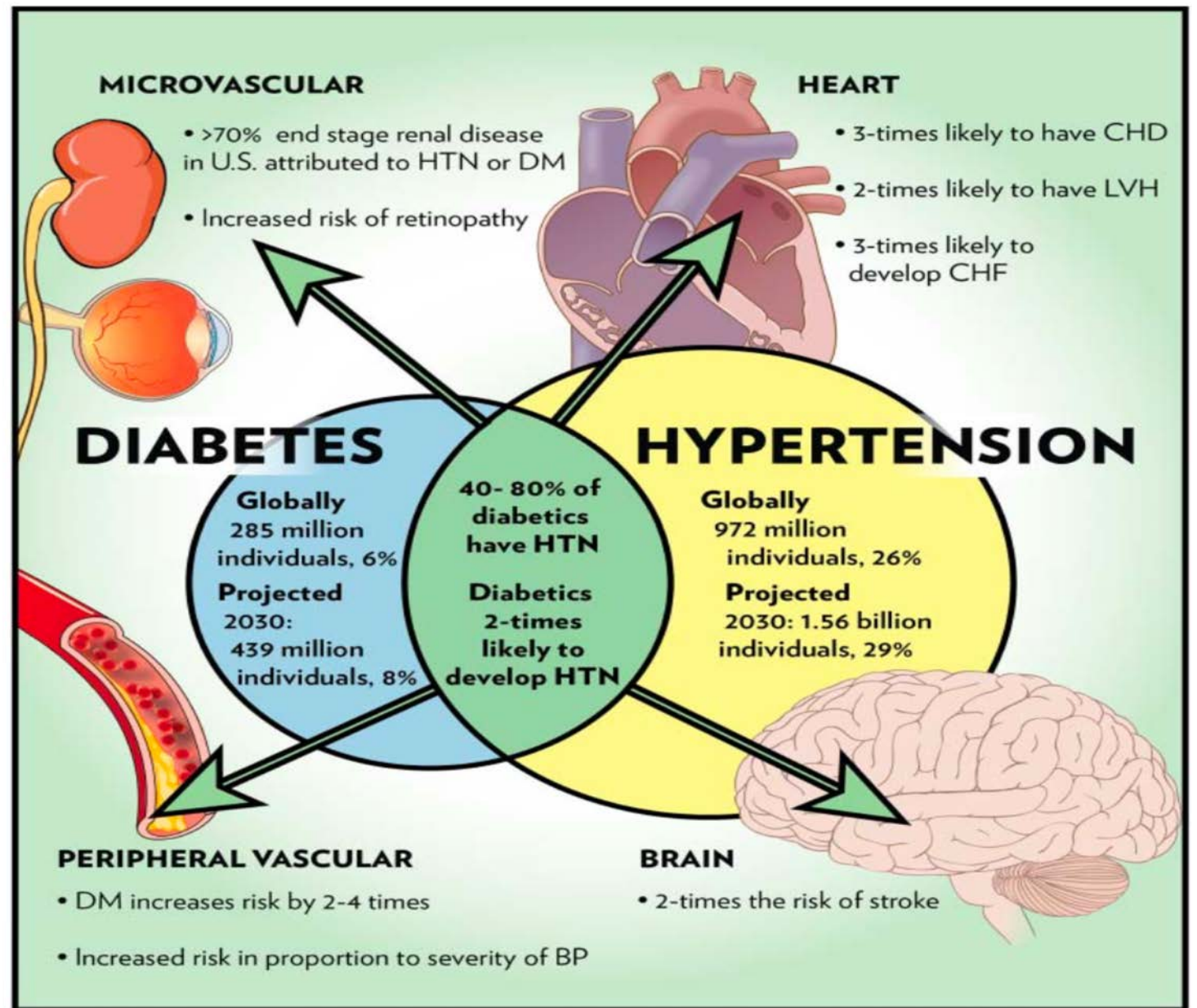
# Impact of Hypertension and Diabetes in CVD

(*Framingham study*)



# Prevalence

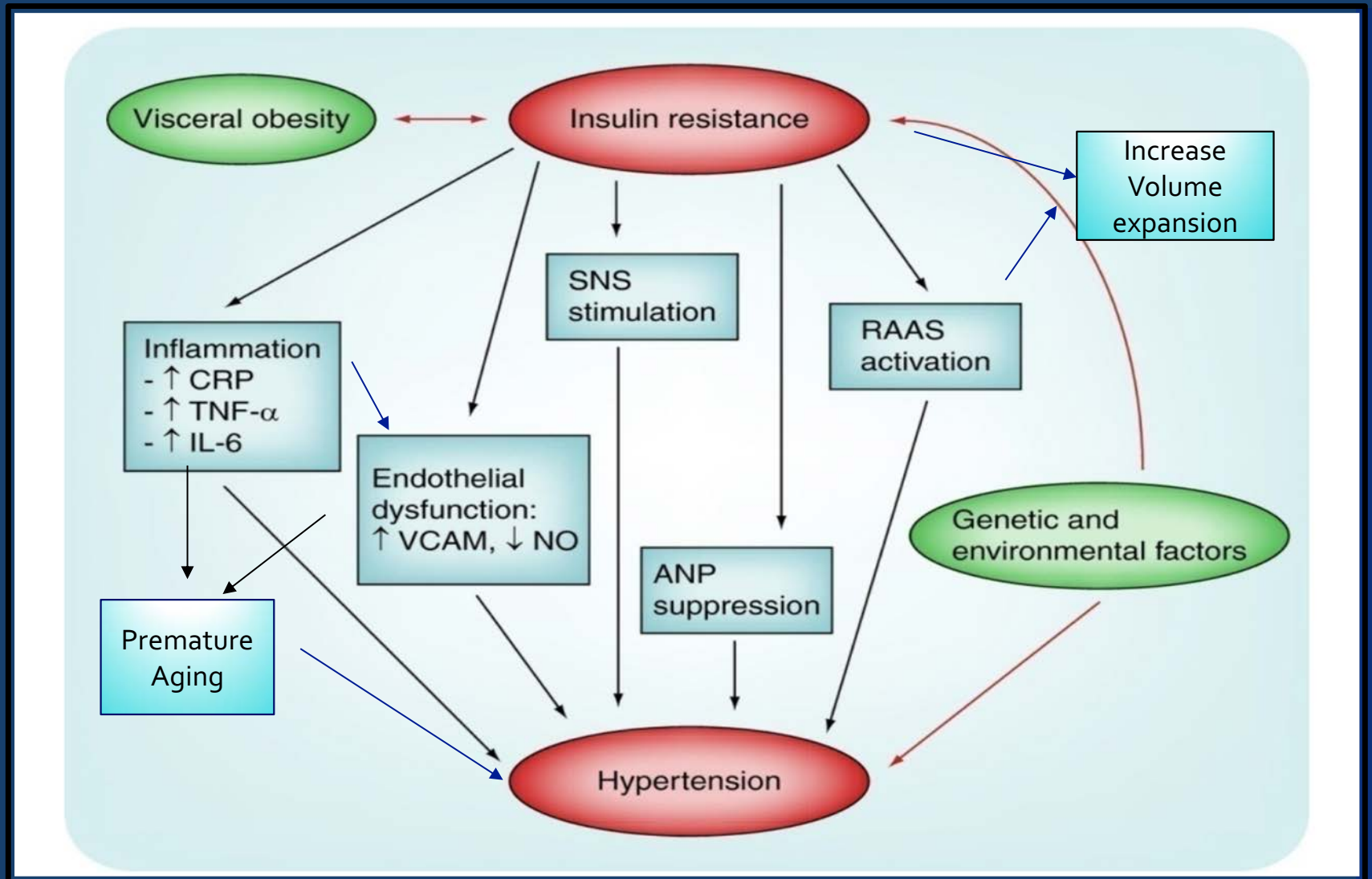
The prevalence depends on **type and duration of diabetes**, age, sex, race/ethnicity, BMI, history of glycemic control, and the presence of kidney disease, among other factors.



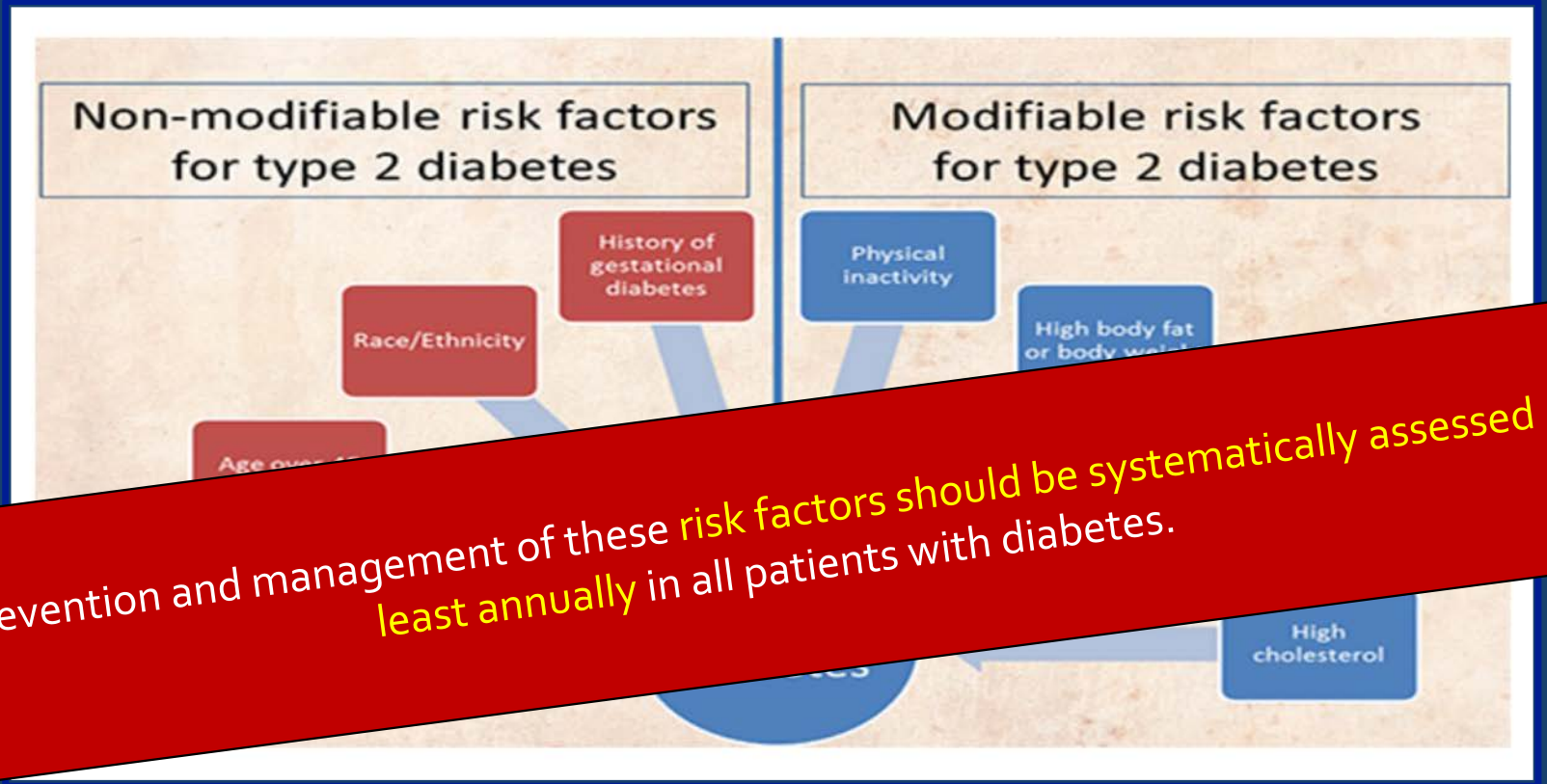


# Pathogenesis

Although the cause of HTN is multifactorial and the insulin resistant state is one factor.



# Diabetes and Hypertension



prevention and management of these risk factors should be systematically assessed at least annually in all patients with diabetes.

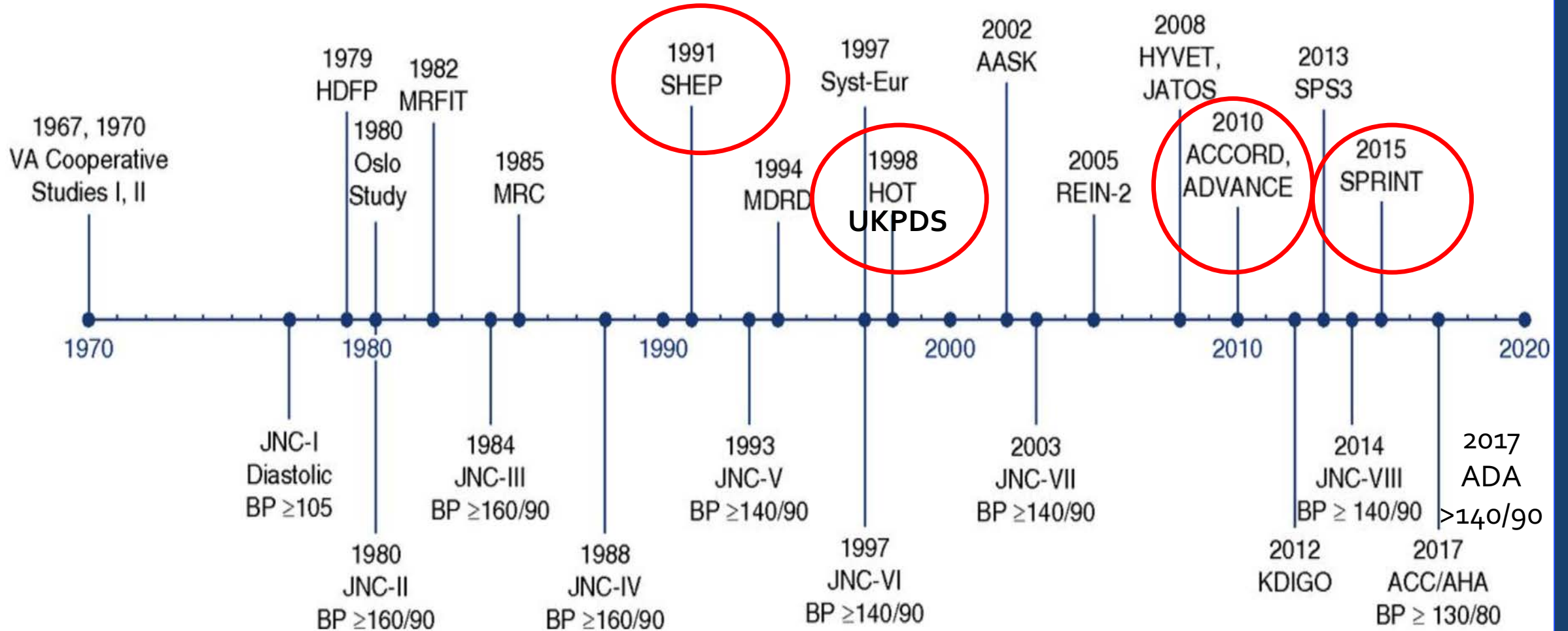
**T2DM:** 40% are hypertensive at the time of diagnosis, and one half of these patient has high BP before the onset of moderately increased albuminuria.

**EVIDENCE**

**BENEFITS OF TREATMENT**



The Definition of Hypertension per United States BP Guidelines has Changed Over Time



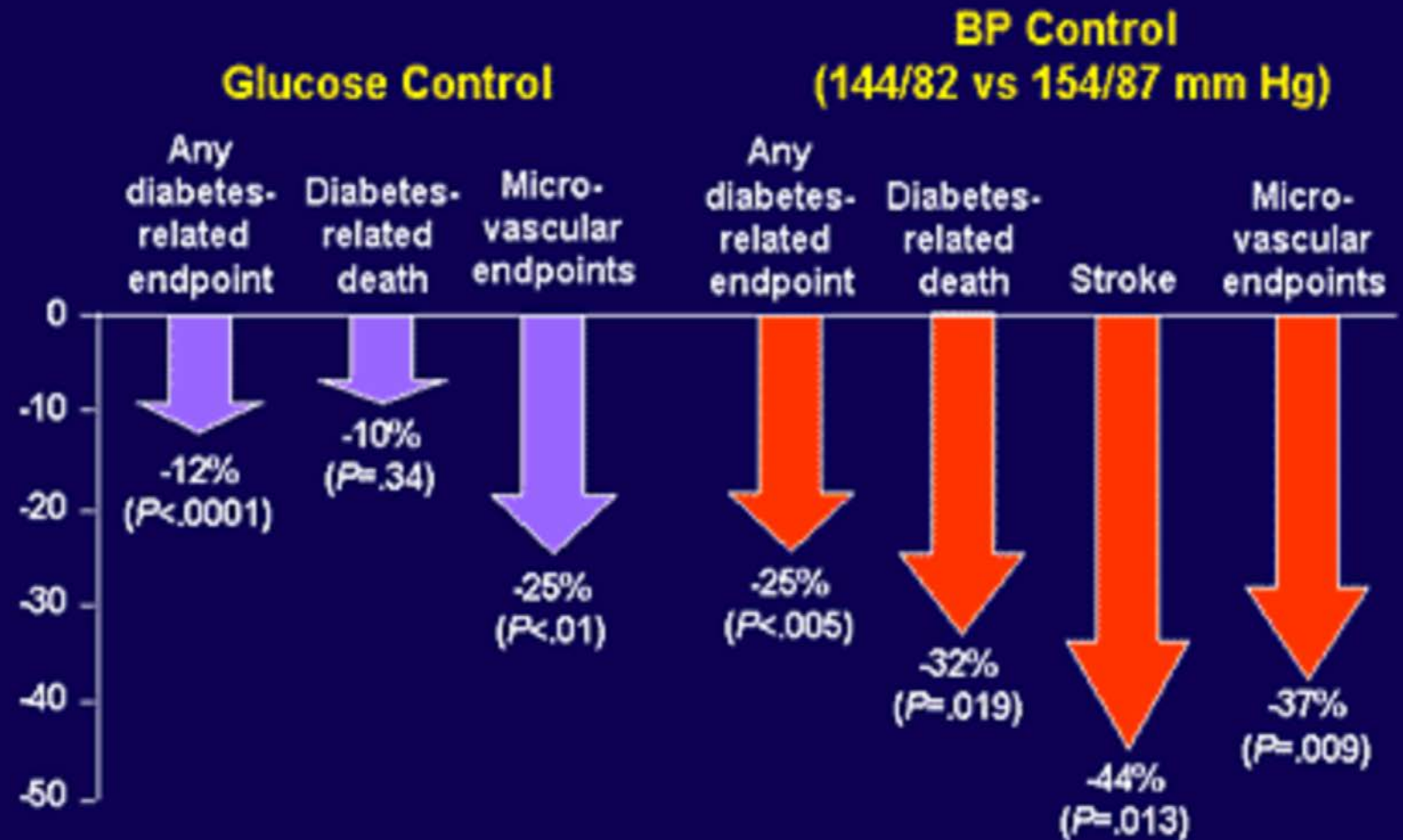
# UKPDS (n=1148)

160/94mmHg

Intensive vs Standard

144/82 vs 154/87

## United Kingdom Prospective Diabetes Study (UKPDS): Results

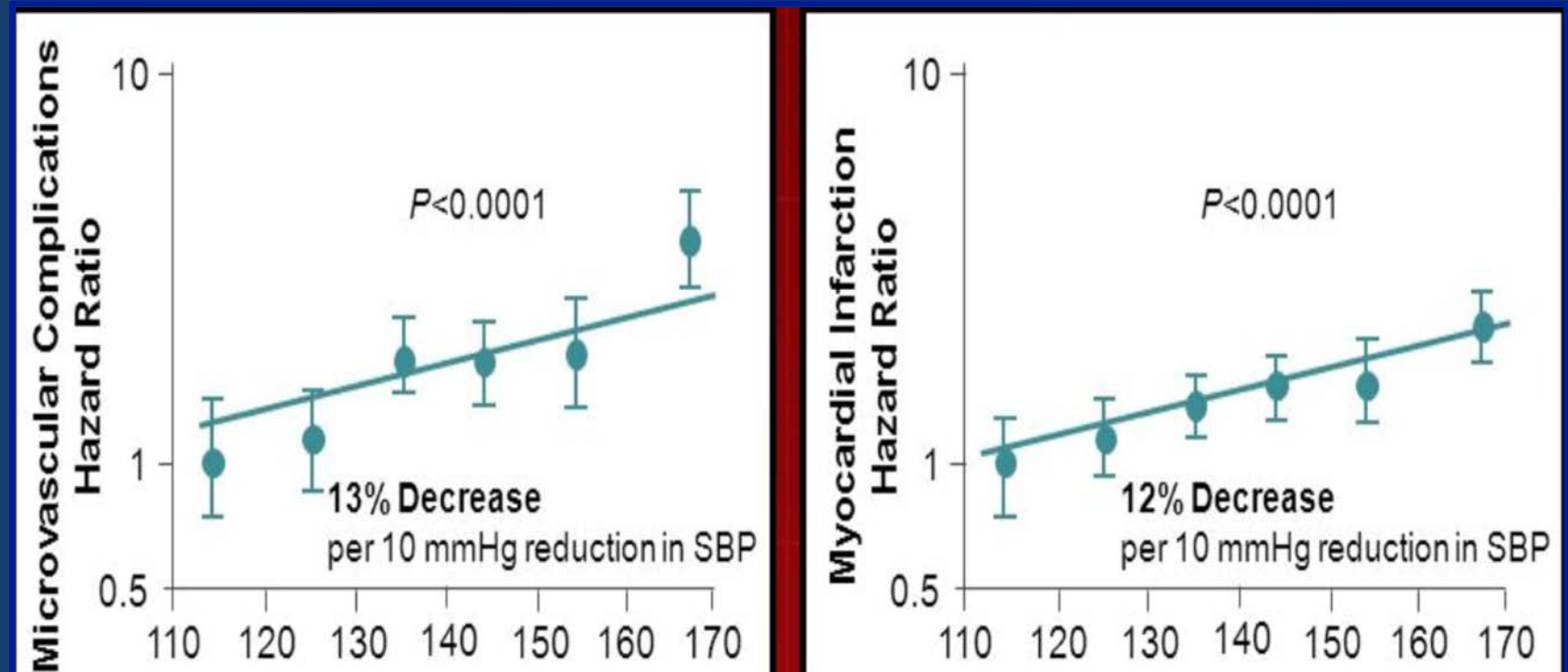


UK Prospective Diabetes Study Group 38. *BMJ*. 1998;317:703-713.  
UK Prospective Diabetes Study Group 33. *Lancet*. 1998;352:837-853.

# Blood Pressure and Diabetic Complications

## United Kingdom Prospective Diabetes Study

UKPDS



# SHEP (n=590)

170/77mmHg

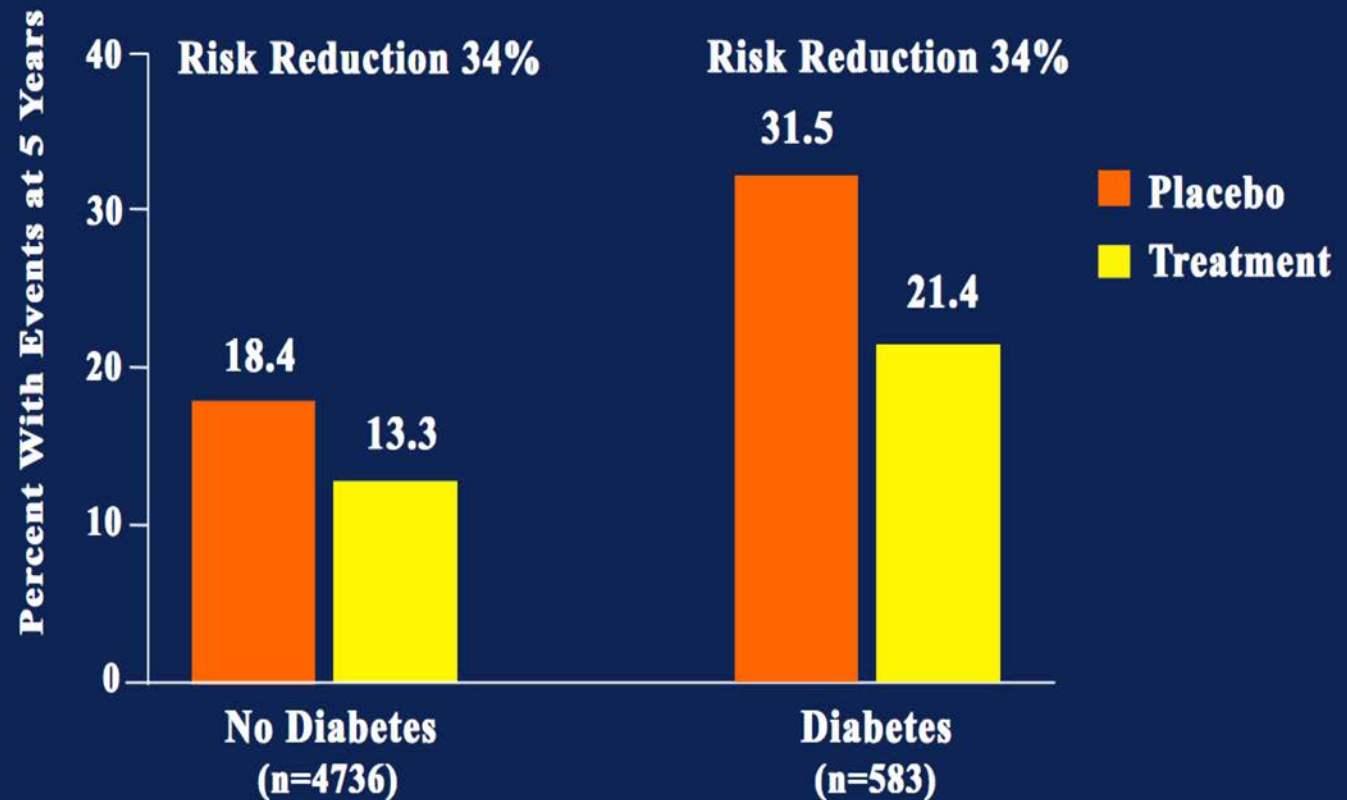
Treatment vs Placebo

143/65 vs 155/72

## SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP)

### Diabetes Subgroup Analysis

#### Effect of Thiazide-Based Treatment on CV Events



Curb JD et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886-92.



# HOT (n=1,501)

170/105 mmHg

Intensive vs  
Conventional

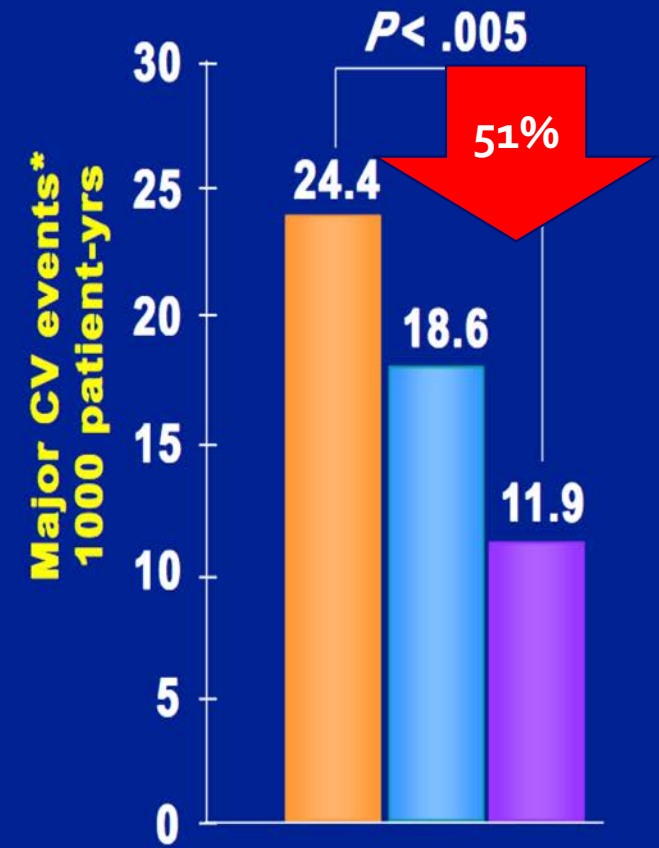
139/81 vs 143/85

## HOT Trial: BP Control Reduces Cardiovascular Events in Diabetics

### Diabetes Subgroup

Target Diastolic BP (mmHg)	Number of Patients	Achieved Systolic BP (mmHg)	Achieved Diastolic BP (mmHg)
■ ≤ 90	501	143.7	85.2
■ ≤ 85	501	141.4	83.2
■ ≤ 80	499	139.7	81.1

† Achieved = Mean of all BPs from 6 months of follow-up to end of study



\*includes all myocardial infarction, all strokes, and all other CV deaths

# ADVANCE BP

(n=11,140)

long standing diabetes

**145/81 mmHg**

Intensive vs Conventional

134/74 vs 140/70

ORIGINAL ARTICLE

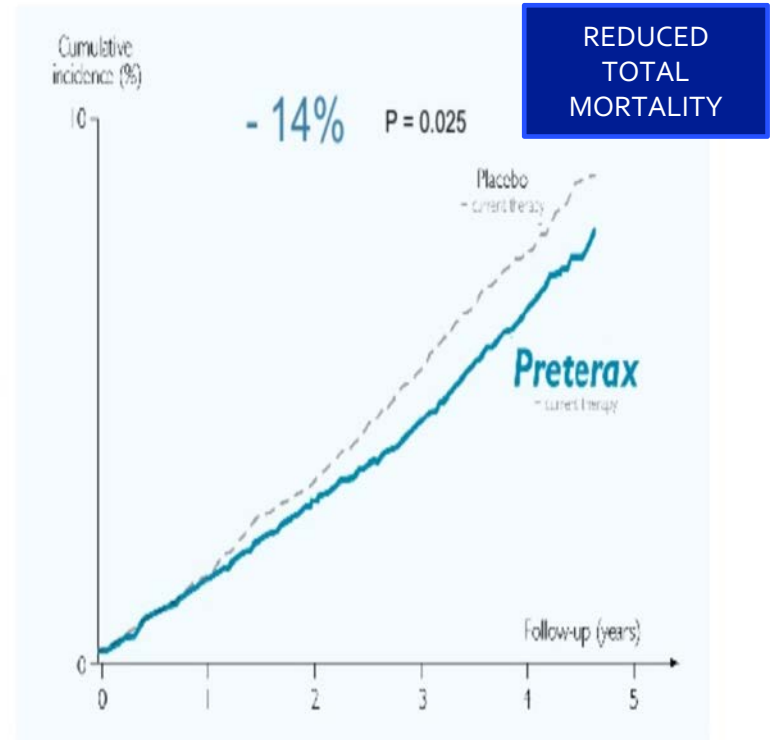
## Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group\*

### Summary

Routine treatment of type 2 diabetic patients with perindopril-indapamide resulted in:

- > 14% reduction in total mortality
- > 18% reduction in cardiovascular death
- > 9% reduction in major vascular events
- > 14% reduction in total coronary events
- > 21% reduction in total renal events





*These observations supported a historical goal blood pressure for diabetic patients of less than 140/90 mmHg*

The treatment of hypertension in diabetic patients was associated with significant clinical benefits

UKPDS (1998)

144/82 versus 154/87 mmHg

HOT (1998)

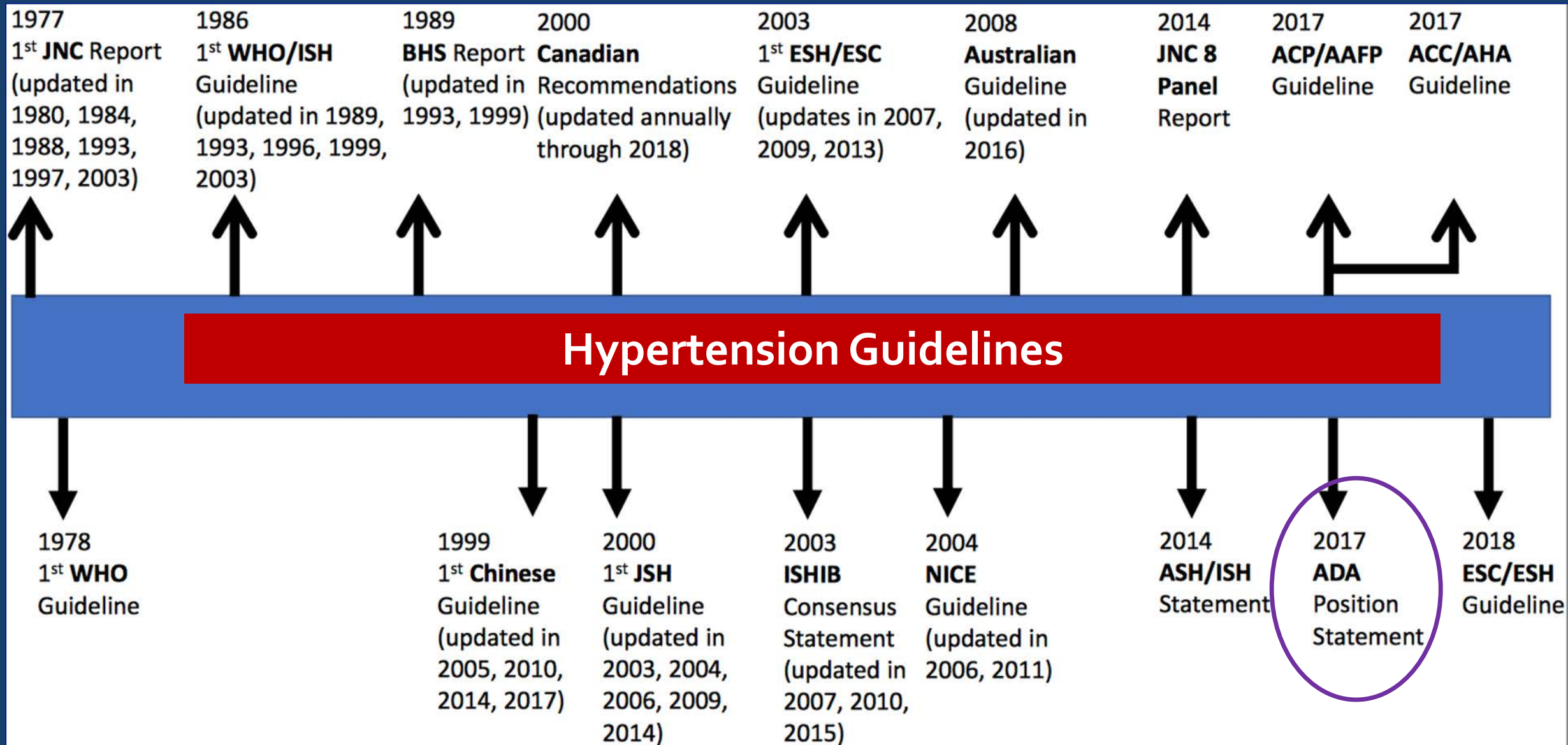
140/81 versus 144/85 mmHg.

ADVANCE BP (2010)

134.5/74 versus 140/76 mmHg

# Timeline of History of Hypertension Guidelines

**EVIDENCE**



A photograph of a flooded urban street. In the foreground, a red car is partially submerged in murky, brown water. In the background, there are trees with bare branches and a multi-story building with several windows. The scene is overcast and appears to be a recent flood event.

# *A Flood of Hypertension Guidelines*

*"Although there is an unequivocal call to treat hypertension in diabetes, professional organizations and experts have different opinions regarding the most optimal blood pressure targets and treatment to lower vascular risks in diabetes population"*

Pasquale Passarella, et al. Diabetes Spectrum Aug 2018, 31 (3) 218-224.

# Blood Pressure Goals DIABETICS

Summary of Blood Pressure Goals and Initial Choice of Antihypertensive Agent for Patients With Diabetes Endorsed by Different Professional Societies or Expert Groups

Recommendation (Year)	Blood Pressure Goals (mmHg)	First-Line Pharmacological Treatment
ADA (2018)	<140/90 (<130/80 <sup>*</sup> )	ACEI/ARB <sup>†</sup> , thiazide-like diuretic, or dihydropyridine CCB
ACC/AHA (2017)	<130/80	No preference
JNC 8 (2014)	<140/90	Non-black: ACEI/ARB, thiazide-like diuretic, or CCB Black: thiazide-like diuretic or CCB
VA/DoD (2014)	<150/85 (140/85 <sup>**</sup> )	Thiazide-like diuretic (chlorthalidone or indapamide)
CDA (2013)	<130/80	ACEI/ARB <sup>‡</sup> , thiazide-like diuretic, or dihydropyridine CCB
ESH/ESC (2013)	<140/85	ACEI/ARB <sup>†</sup> , thiazide-like diuretic, or CCB

↩<sup>\*</sup> May be appropriate for individuals at high risk of CVD.

↩<sup>\*\*</sup> Suggested for patients who can tolerate the antihypertensive medications necessary to reach this goal.

↩<sup>†</sup> Recommended if hypertension is associated with proteinuria and suggested if hypertension is associated with microalbuminuria as the preferred first-line agent.

↩<sup>‡</sup> Recommended in the presence of known kidney disease, including microalbuminuria, or CVD.



**EVIDENCE**

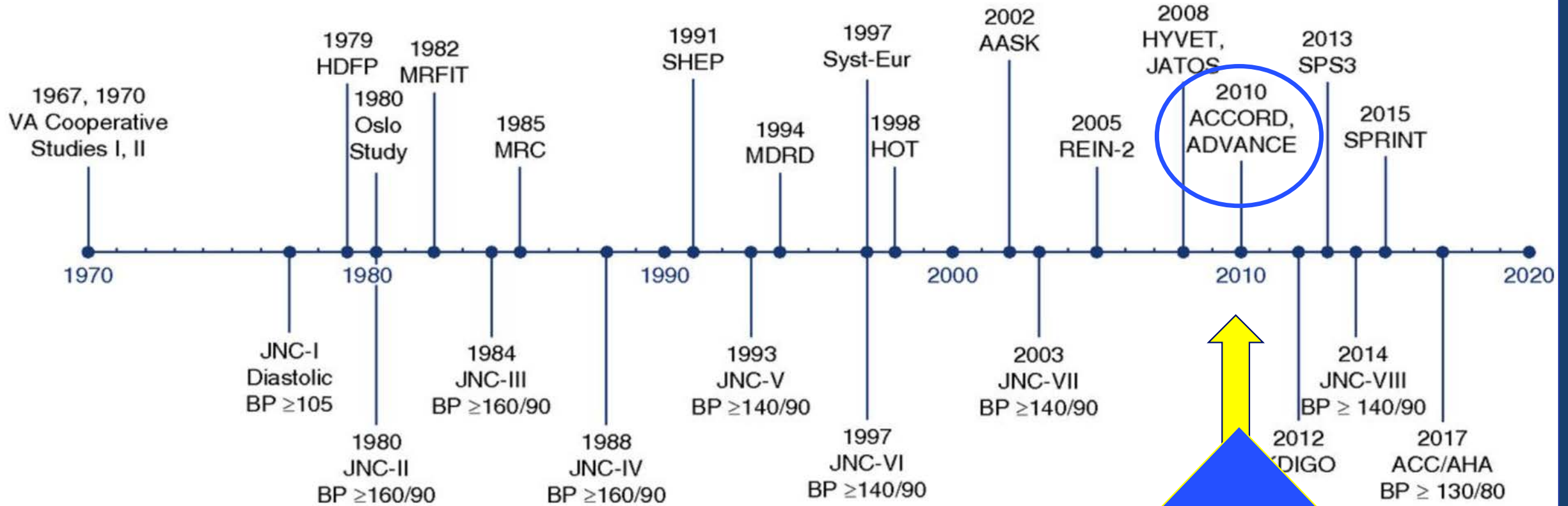
**BLOOD PRESSURE TARGETS**



# Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
<b>HOT</b>	18,790 participants, including 1,501 with diabetes	<b>DBP target: &lt;80 mmHg</b>	<b>DBP target: &lt;90 mmHg</b>	In diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events
<b>ADVANCE BP</b>	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Achieved (mean) <b>136/73 mmHg</b>	Achieved (mean) <b>141.6/75.2 mmHg</b>	reduced risk of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)
<b>ACCORD BP</b>	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Target <120 mmHg  Achieved (mean) <b>119.3/64.4</b>	Target: < 140 mmHg  Achieved (mean) <b>133.5/70.5 mmHg</b>	No benefit in MACE  Stroke risk reduced 41% with intensive control
<b>SPRINT</b>	9,361 participants without diabetes	Target <120 mmHg  Achieved (mean): <b>121.4 mmHg</b>	Target <140 mmHg  Achieved (mean): <b>136.2 mmHg</b>	lowered risk of the primary composite outcome 25%, reduced risk of death 27% increased risks of electrolyte abnormalities and AKI

The Definition of Hypertension per United States BP Guidelines has Changed Over Time



ACCORD  
BP

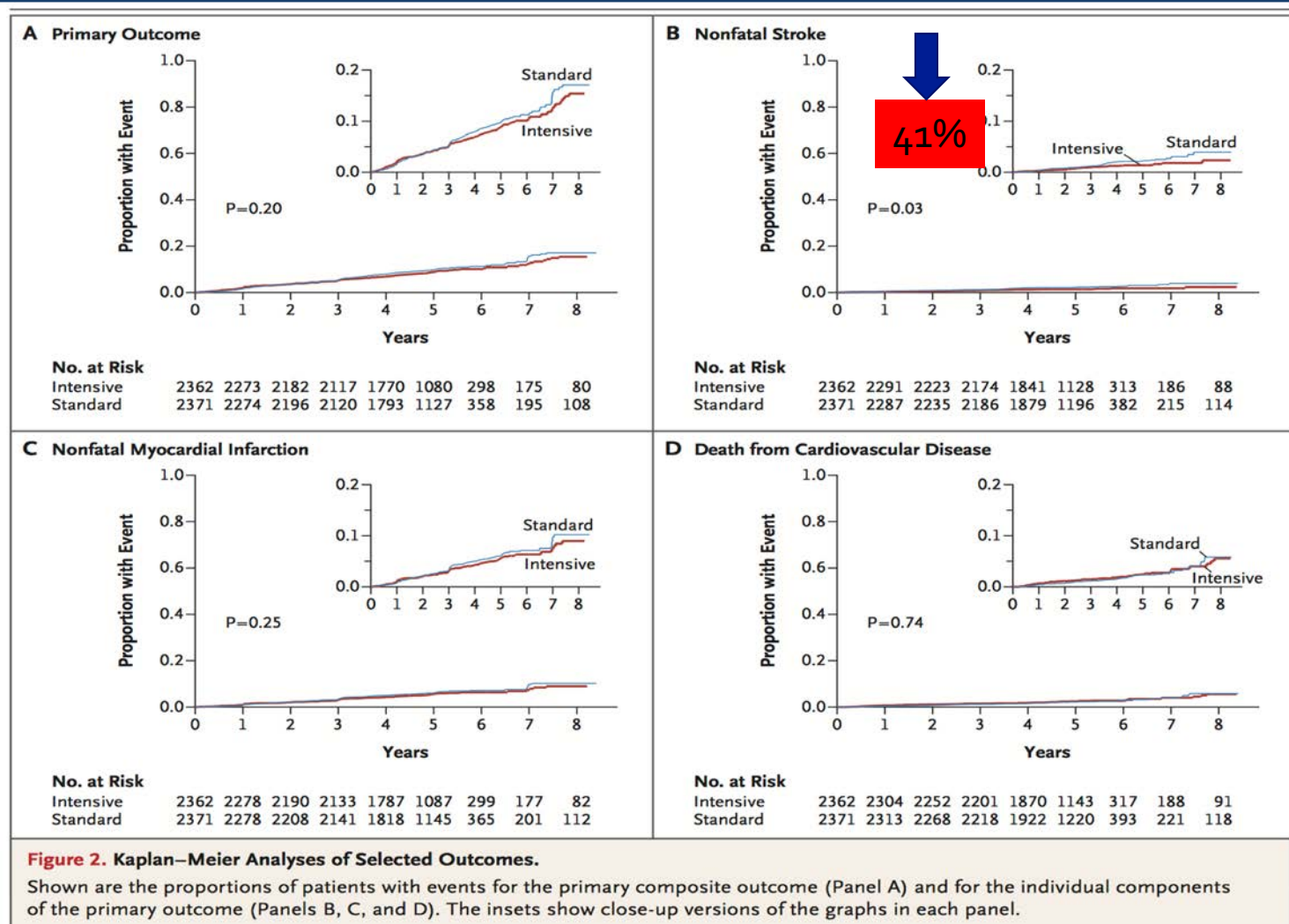
# ACCORD BP (n=4,733)

139/76

Intensive vs Standard

<120 VS <140

119.3 VS 133.5



# SPRINT

(n=9,371)  
(No diabetics)  
High risk

139/78

Intensive vs Standard  
<120 VS <140

121 VS 136



## A Randomized Trial of Intensive versus Standard Blood-Pressure Control

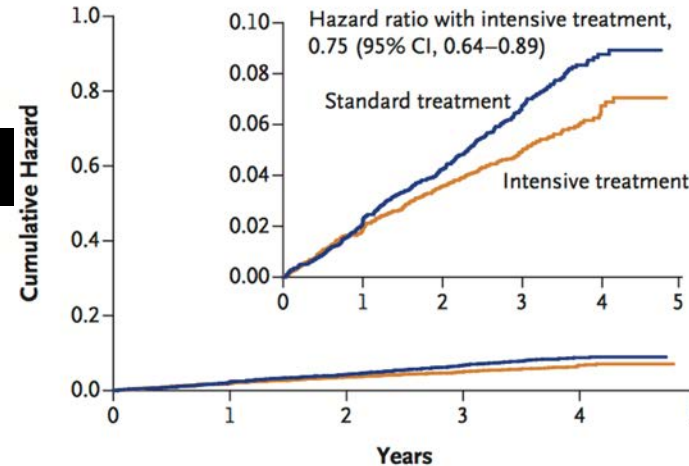
The SPRINT Research Group<sup>1</sup>



### A Primary Outcome



25%



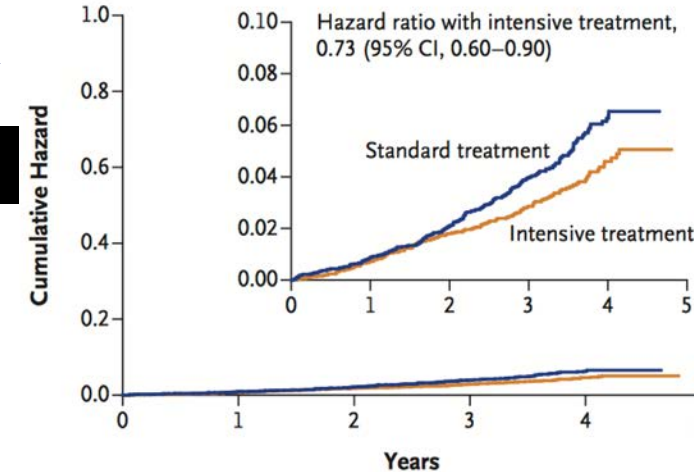
#### No. at Risk

Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

### B Death from Any Cause



27%



#### No. at Risk

Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

# Intensive Versus Standard Blood Pressure Control in SPRINT-Eligible Participants of ACCORD-BP

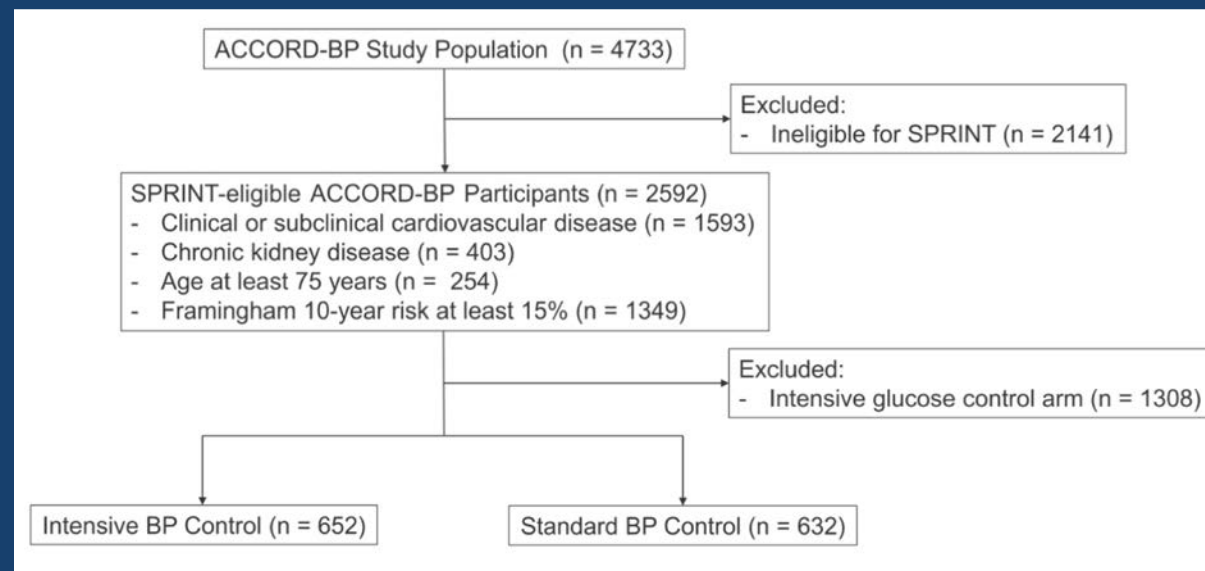
*Diabetes Care* 2017;40:1733–1738 | <https://doi.org/10.2337/dc17-1366>

## Subgroup Analyses from ACCORD BP (n=2592)

139-140/75-76

Intensive vs Standard  
<120 VS <140

120 VS 134

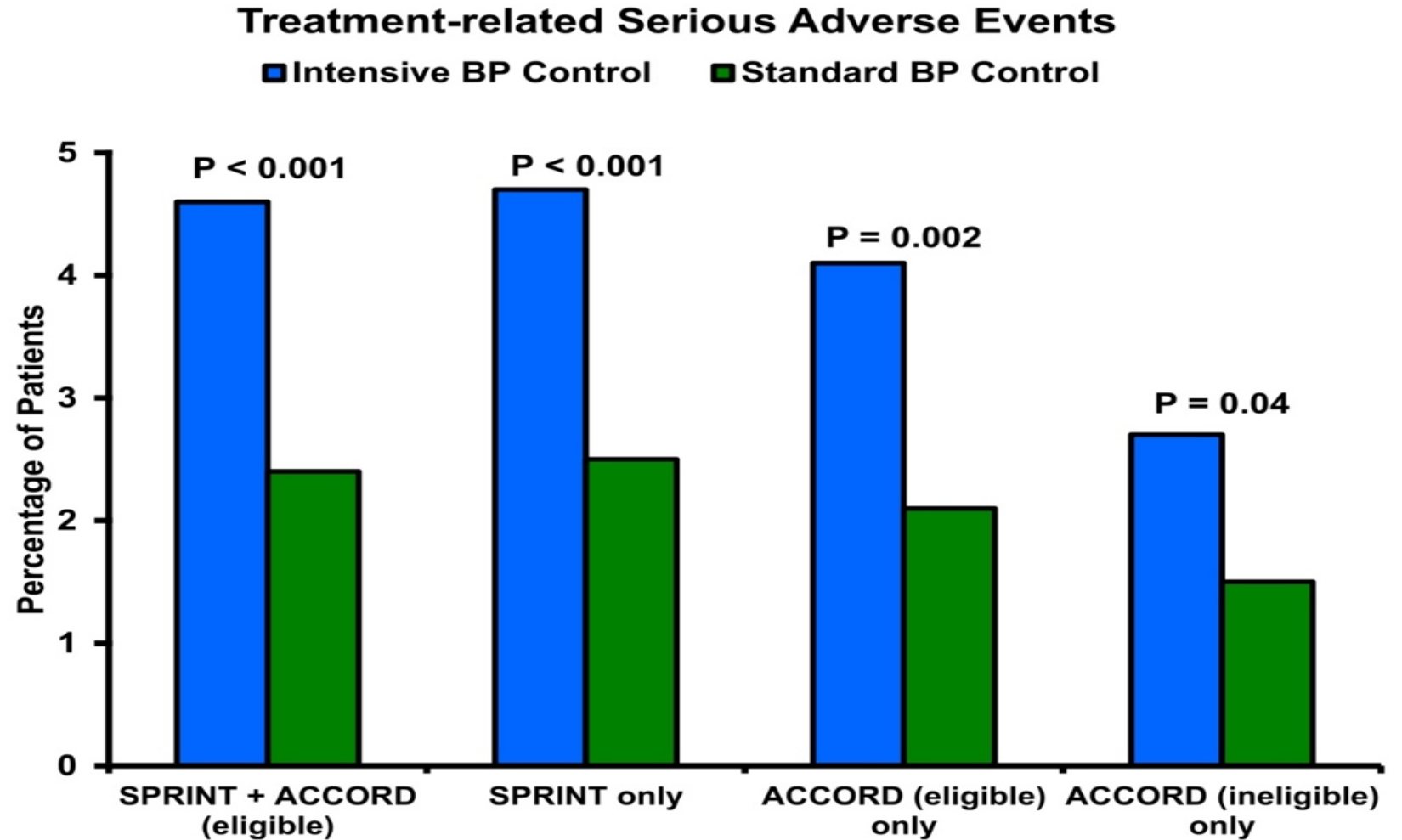


**Table 2—Clinical efficacy outcomes among SPRINT-eligible ACCORD-BP patients**

Outcome	Intensive BP control		BP standard control		Hazard ratio (95% CI)	P value
	Events (n)	% per year	Events (n)	% per year		
Cardiovascular death, nonfatal MI, nonfatal stroke, any revascularization, heart failure	182	6.75	221	8.71	0.79 (0.65–0.96) →	0.02
Cardiovascular death, nonfatal MI, nonfatal stroke	74	2.47	105	3.65	0.69 (0.51–0.93) →	0.01
Coronary death, nonfatal MI, unstable angina	96	3.29	119	4.26	0.77 (0.59–1.01) →	0.06
Any death	49	1.54	61	1.96	0.79 (0.54–1.16)	0.23
Cardiovascular death	18	0.58	26	0.88	0.68 (0.37–1.25)	0.68
Nonfatal MI	48	1.59	67	2.32	0.69 (0.48–1.00)	0.05
Nonfatal stroke	12	0.39	23	0.76	0.54 (0.27–1.10)	0.09
Heart failure	26	0.85	38	1.28	0.63 (0.38–1.04)	0.07



# Serious Adverse Events



**Figure 3**—Treatment-related serious adverse events among SPRINT and ACCORD-BP patients. *P* values reflect the comparison between intensive and standard BP control within each study population.



# BP Target

<140 ?

<130 ?

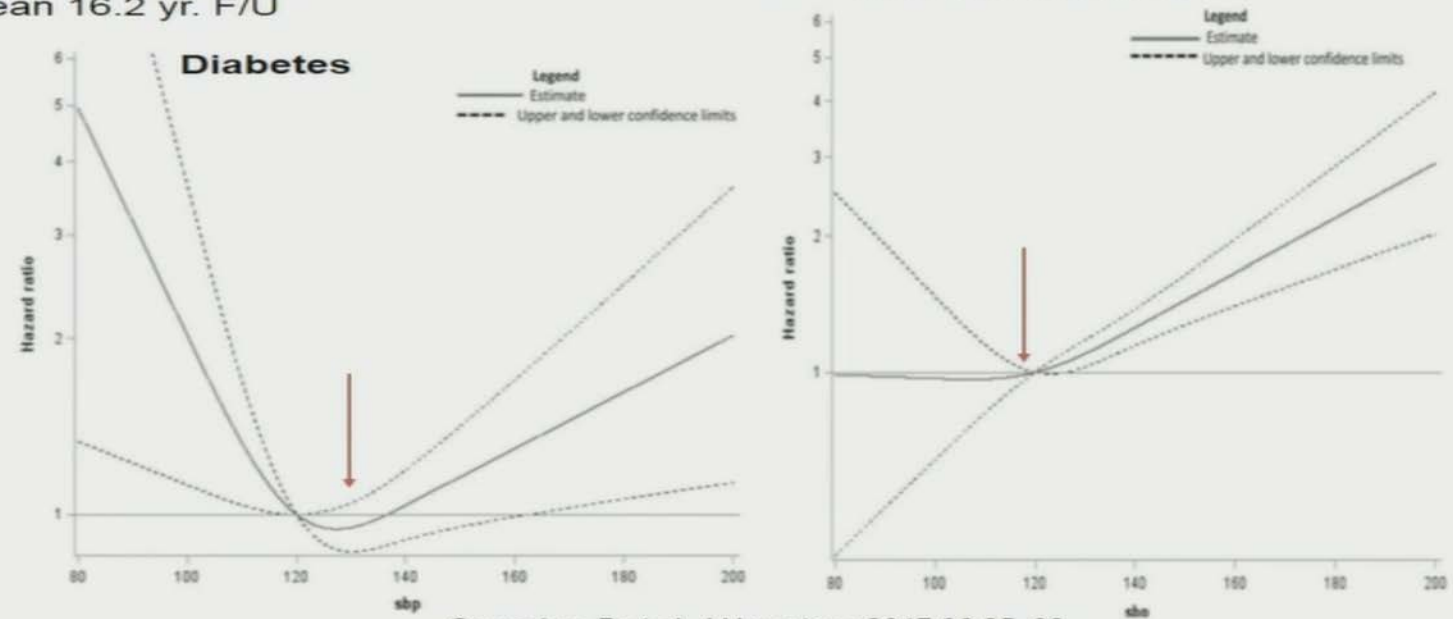
<120 ?

Yes or Not?

## Adjusted cubic spline model of the association between hazard ratio and SBP of persons with and without diabetes mellitus

N=17,650 NHANES III + 1439 DM Heart Study  
Mean 16.2 yr. F/U

### Without Diabetes



Gomadam P et.al. J Hypertens 2017;36:85–92

# ADA

## *Diabetes and Hypertension : Position statement*

Most patient with DM and HTN should be treated to a

**<140/90 mmHg**

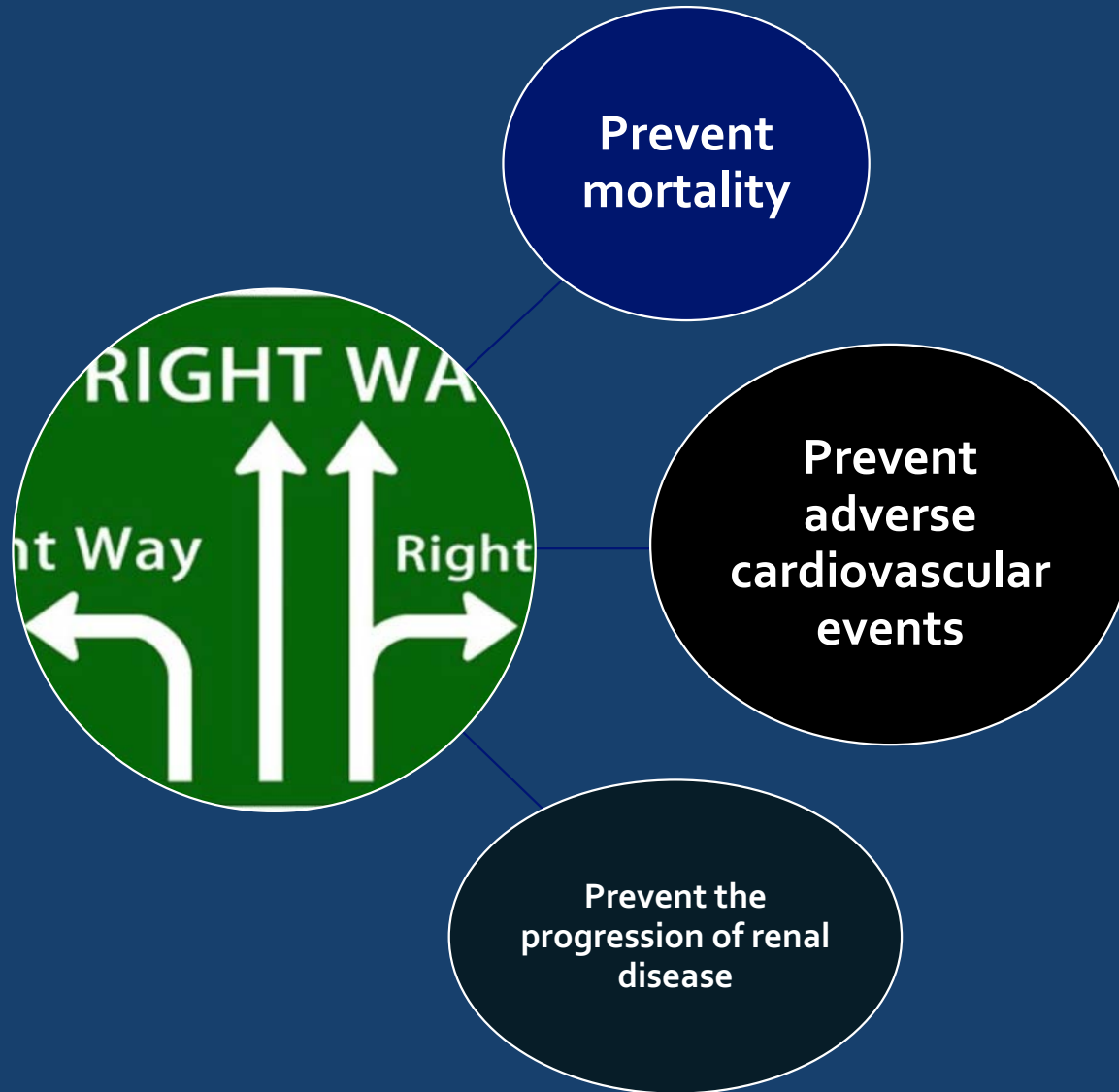
For individuals at high risk of CVD if they can be achieved without undue treatment burden.

**<130/80 mmHg**

**EVIDENCE**

**CHOICE OF ANTIHYPERTENSIVE DRUGS**

# Selecting Therapy



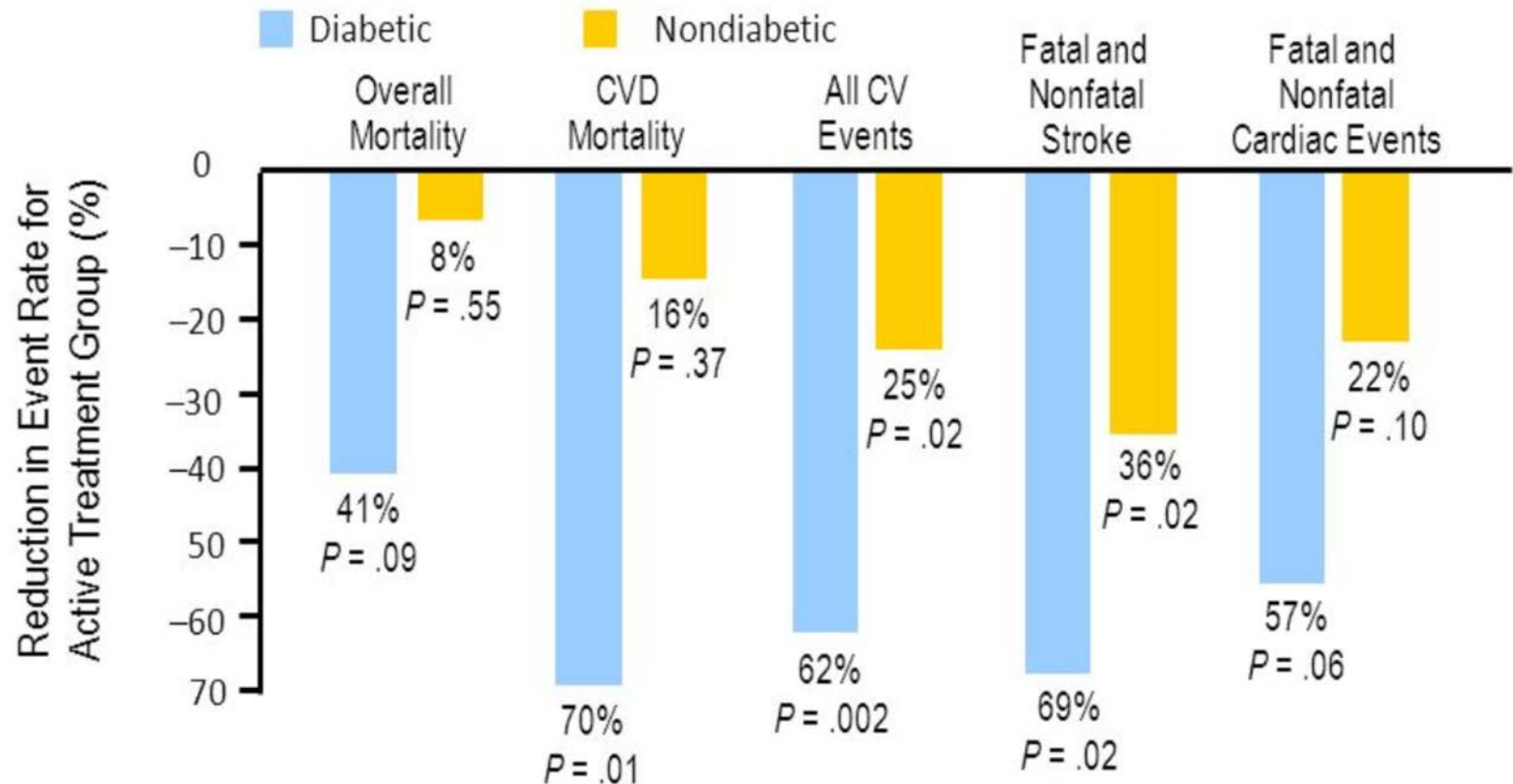
# Systolic Hypertension in Europe Trial

Placebo vs Nitrendipine

160/95

Decrease  
8/4mmHg

## Syst-Eur: CV Protection Resulting From BP Lowering Was Greatest in Patients With Diabetes



hypertension received nitrendipine ± enalapril or HCTZ. N = 4695.  
Diabetes n = 492. Syst-Eur = Systolic Hypertension in Europe; CV = cardiovascular.  
Adapted from Tuomilehto J et al. *N Engl J Med*. 1999;340:677-684.

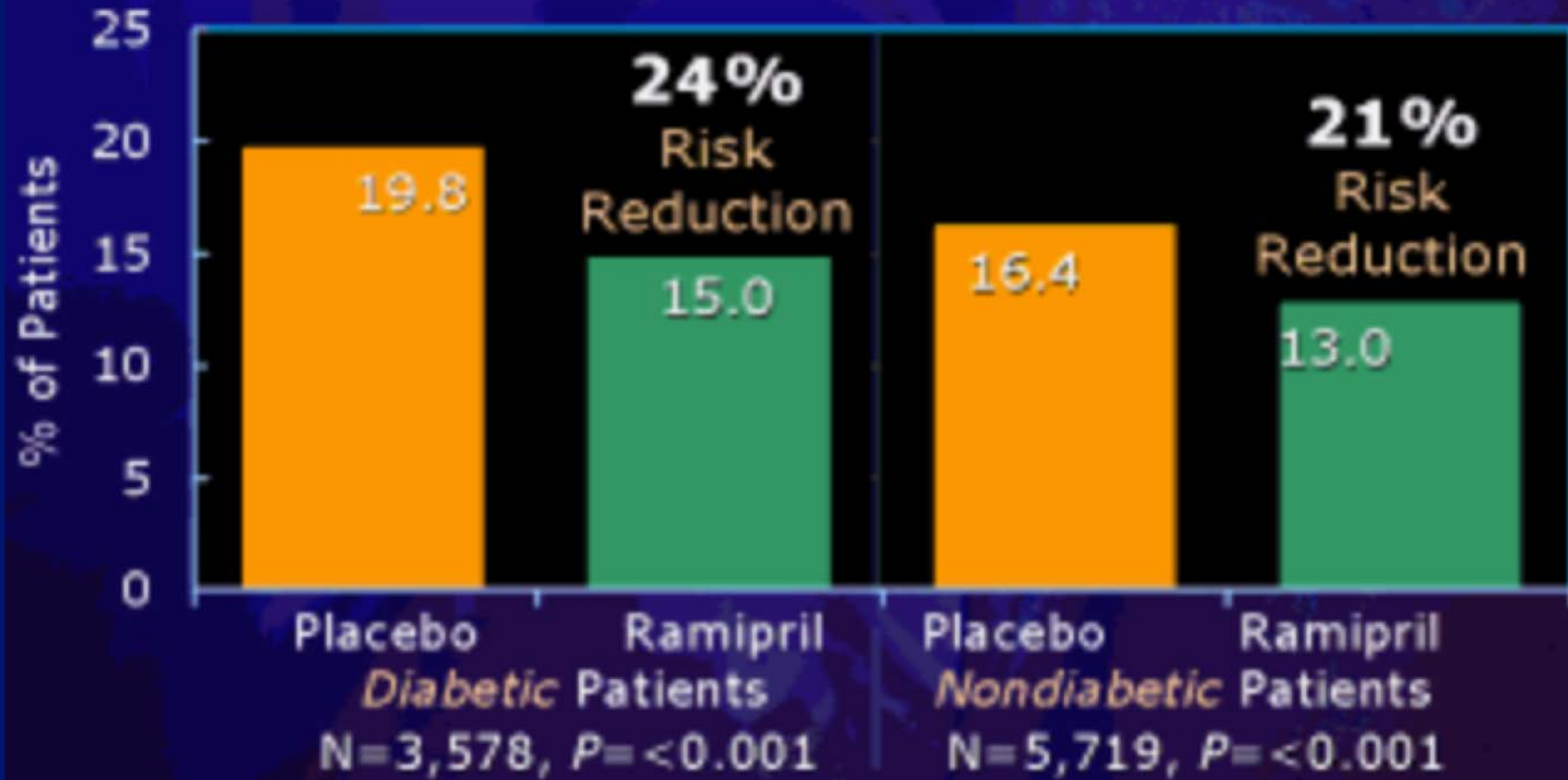
# HOPE Trial (40% DM + risk factors)

Ramipril vs  
Placebo

139/79

Decrease  
3-4/2mmHg

## Heart Outcomes Prevention Evaluation (HOPE) Study Effect of Ramipril on Cardiovascular Events (Myocardial Infarction, Stroke, or CVD Death) ~ 4.5 Yrs



June 27, 2005

19



# ALL HAT trial (36% DM)

Amlodipine  
Chlorthalidone  
Lisinopril  
Doxazosin

146/84mmHg

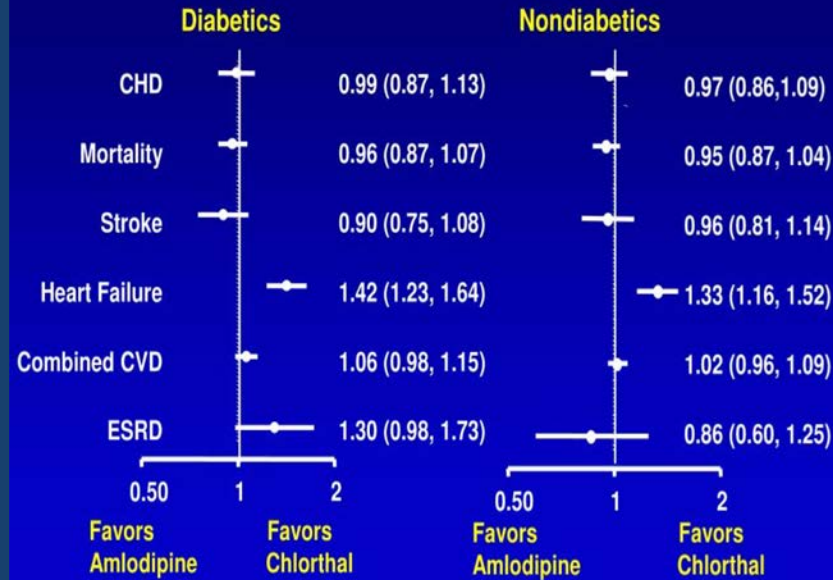
Achieved  
136/75

The Antihypertensive and Lipid lowering to prevent  
heart attack  
Trial .



## Diabetics & Nondiabetics Amlodipine/Chlorthalidone

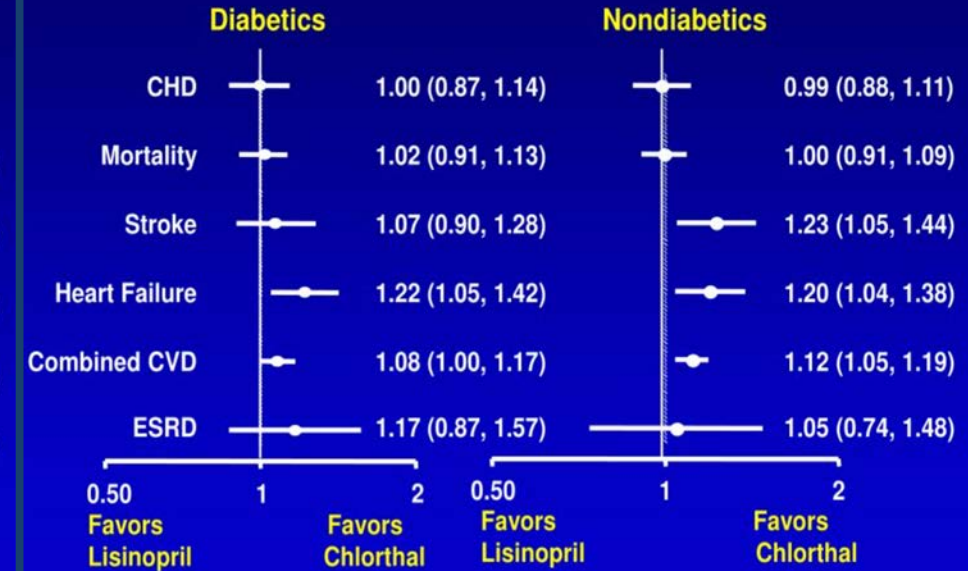
Relative Risk and 95% Confidence Intervals



There is no difference in treatment group effect by baseline history of diabetes.

## Diabetics & Nondiabetics Lisinopril/Chlorthalidone

Relative Risk and 95% Confidence Intervals



There is no difference in treatment group effect by baseline history of diabetes.

## The Irbesartan Diabetic Nephropathy Trial (IDNT)

Irbesartan vs Placebo  
Irbesartan vs Amlodipine  
Amlodipine vs Placebo

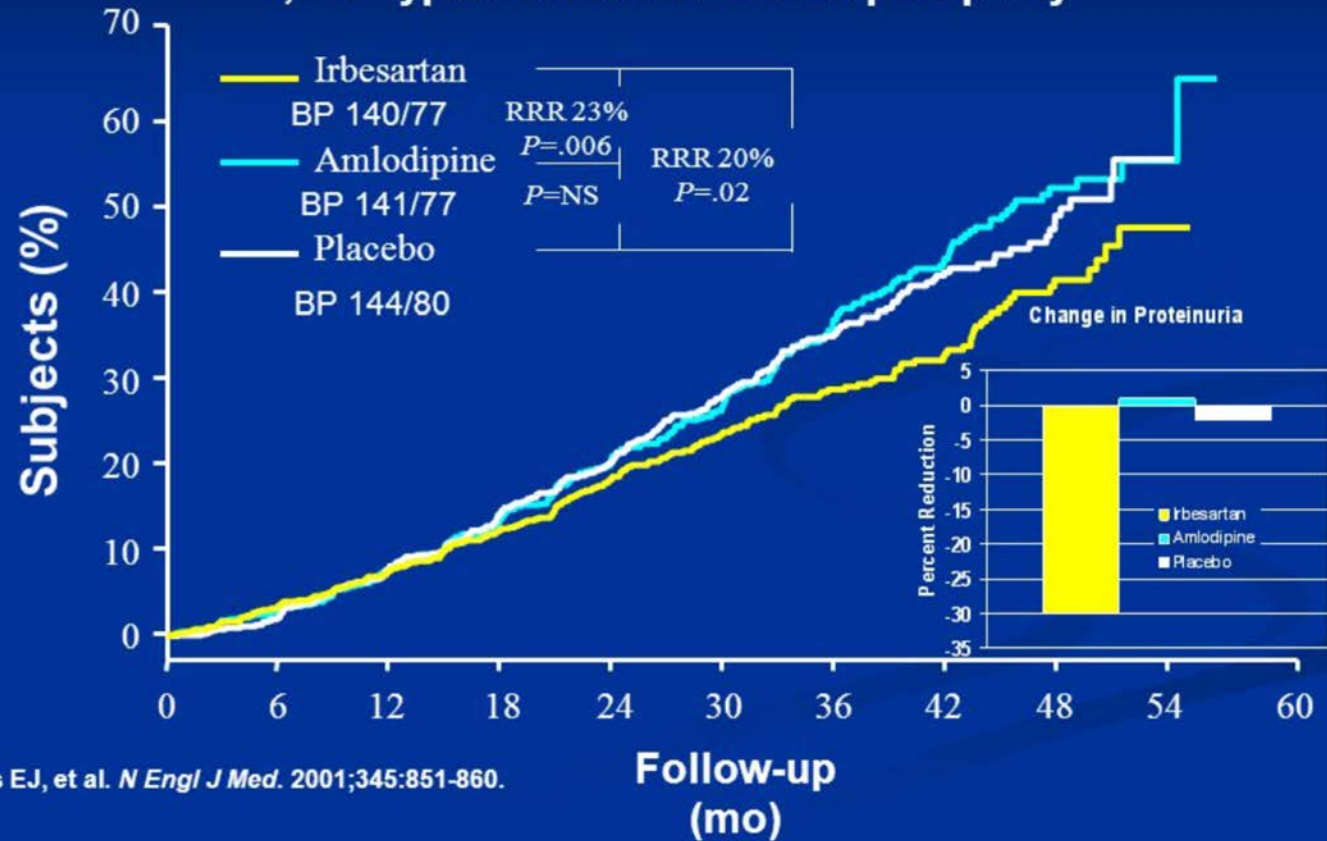
160/87mmHg

Achieved

140-144/77-80

## Irbesartan in Diabetic Nephropathy Trial: Time to Doubling of Serum Creatinine, ESRD, or Death

1,715 Type 2 Diabetics with Nephropathy



# RENAAL trial (1,513 DM)

Losartan vs  
placebo

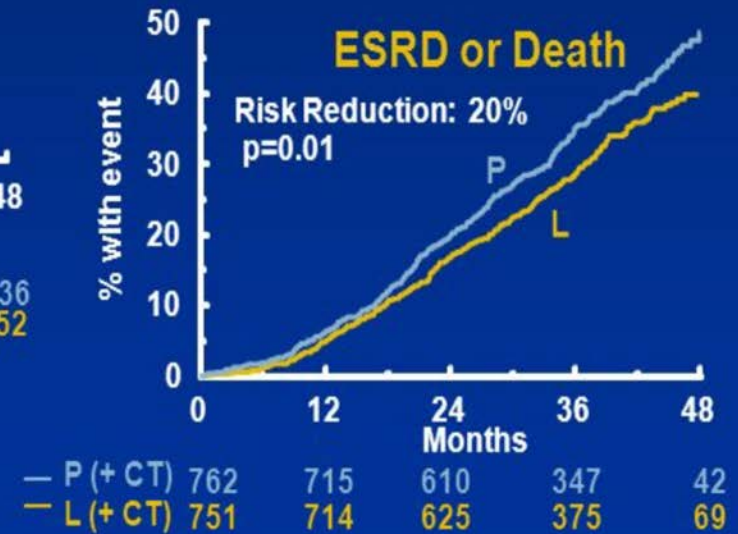
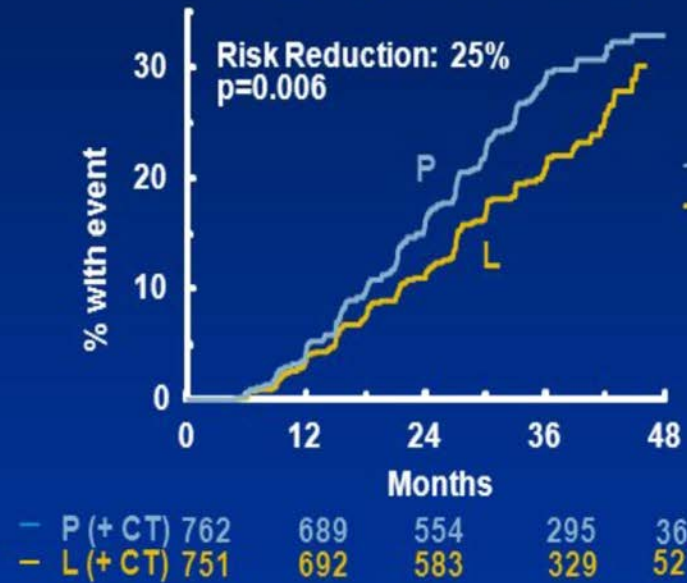
153/82mmHg

Achieved

140/74

## RENAAL Primary Components

### Doubling of Serum Creatinine



Brenner BM et al *New Engl J Med* 2001;345(12):861-869.



## LIFE trial

(13 % DM)

Efficacy of an ARB was compared with a beta blocker

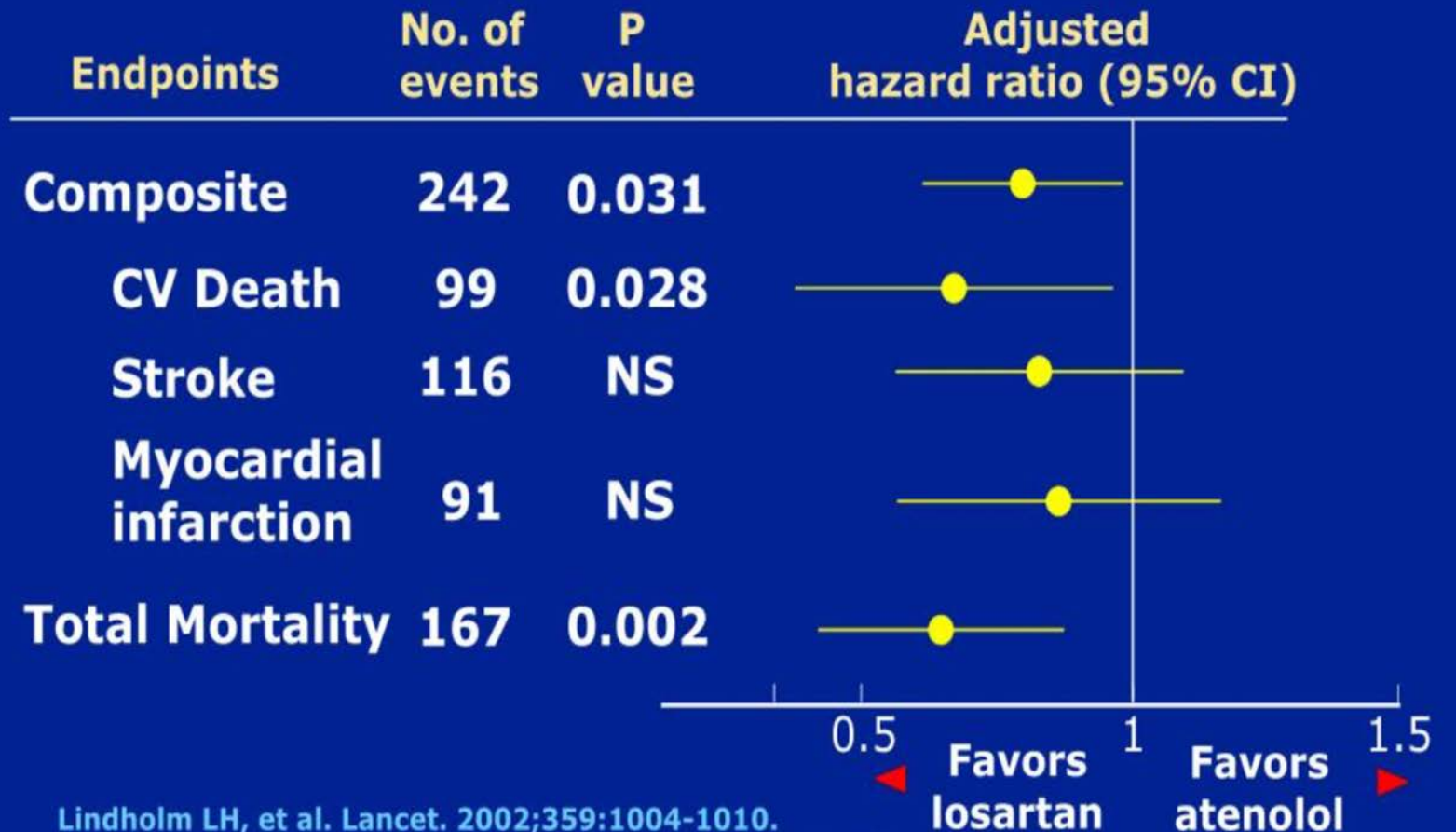
Losartan vs atenolol

174/93mmHg

Achieved

144/81 vs 145/81

## LIFE Study Diabetes Subgroup Primary Composite Endpoint and Components



Lindholm LH, et al. Lancet. 2002;359:1004-1010.

Presented by B Dahlof at the American College of Cardiology Scientific Sessions Late-Breaking Clinical Trials III, 2002.

[www.hypertensiononline.org](http://www.hypertensiononline.org)

# ACCOMPLISH trial (60% DM)

Benazepril +  
Amlodipine  
Vs  
Benazepril+HCTZ

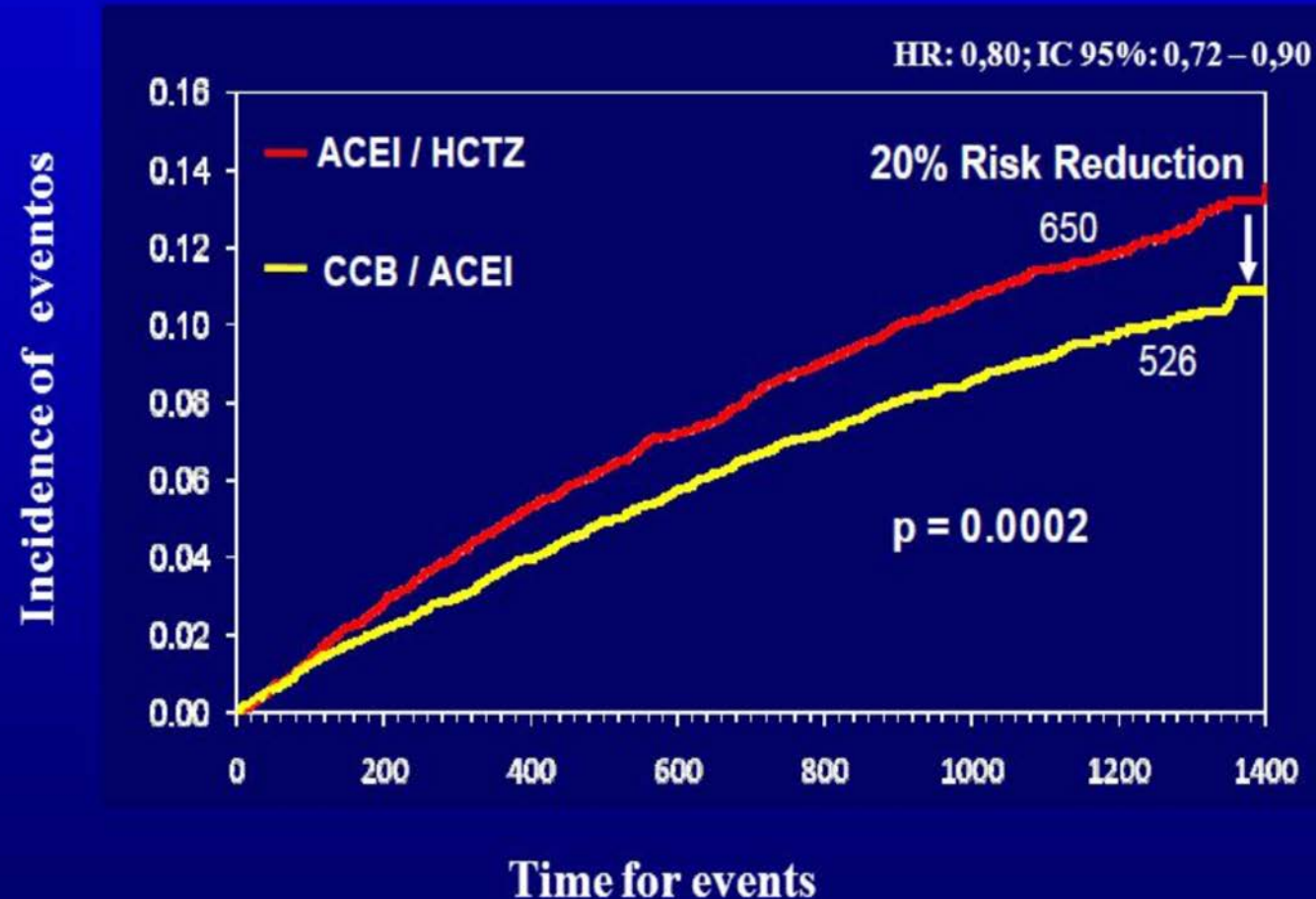
145/80

Achieved

131/73 vs 132/74

## Composed end-point comparing a fixed combination of a CCB +ACEI vs a thiazide+ACEI

ACCOMPLISH Trial



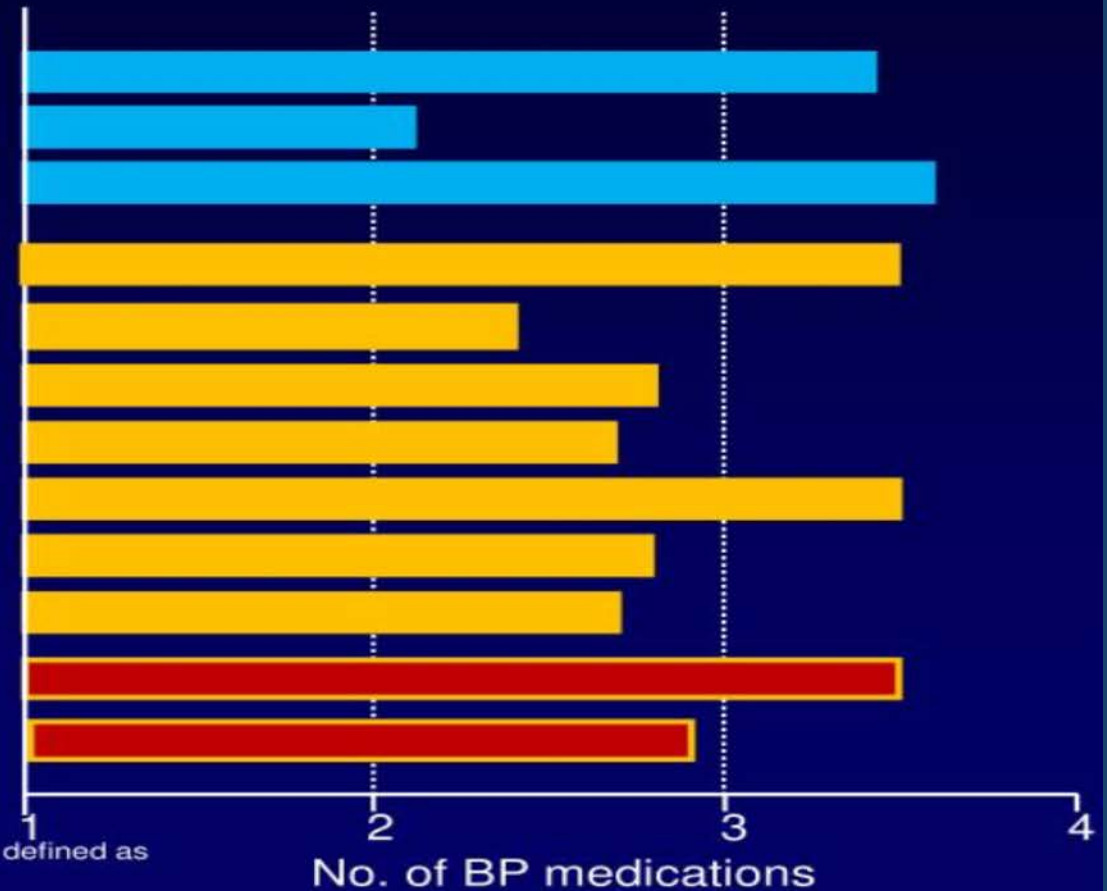


# Pharmacologic Therapy

- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes.
  - **ACE inhibitors**
    - ACE inhibitor or ARB, is the recommended first-line treatment for hypertension in patients with diabetes and urine albumin-to- creatinine ratio >300 mg/g creatinine or 30–299 mg/g creatinine ratio.
  - **Angiotensin receptor blockers (ARBs)**
  - **Thiazide-like diuretics**
  - **Dihydropyridine calcium channel blockers**
- Multiple-drug therapy is generally required to achieve blood pressure targets.

# Multiple Medications Are Required to Achieve BP Control in Clinical Trials

	Trial	SBP achieved (mm Hg)
<b>Hyper-tension</b>	ACCOMPLISH	131
	ALLHAT	138
	HOT	138
<b>Diabetes</b>	ACCORD (intensive)*	119
	ACCORD (standard)*	133
	INVEST	133
	IDNT	138
	RENAAL	141
	ABCD	132
	UKPDS	144
<b>Kidney disease</b>	MDRD	132
	AASK	128



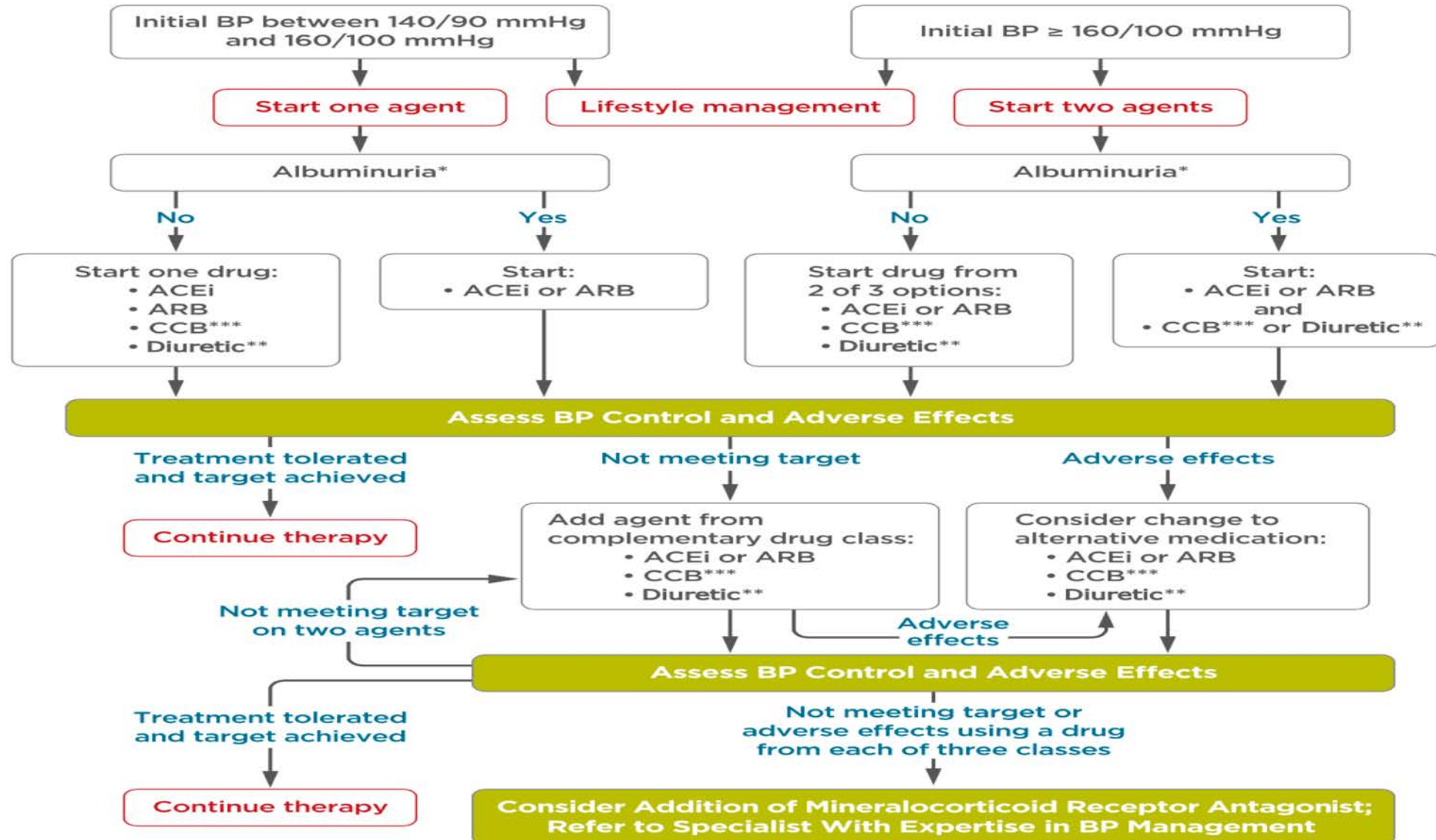
SBP=systolic blood pressure. \*Target blood pressure control groups in ACCORD defined as <120 mm Hg (intensive) and <140 mm Hg (standard).  
 Updated from Bakris G et.al Am J Kidney Dis 2000.  
 The ACCORD Study Group. *N Engl J Med*. 2010 Mar 14. [Epub ahead of print]

# AMERICAN DIABETES ASSOCIATION

## *Recommendations*

*Patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, adverse effects of antihypertensive medications, and patient preferences.*

## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



## Recommendations

**ADA**

Patients found to have an elevated blood pressure ( $>140/90$  mmHg) should have blood pressure confirmed using multiple reading.

All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension.

Orthostatic measurement of blood pressure should be performed during initial evaluation of hypertension and periodically at follow-up.

10-year ASCVD risk  
 $>15\%$

$<130/80$  mmHg

10-year ASCVD  
 $<15\%$

$<140/90$  mmHg



# Lifestyle Management

## Best Proven Nonpharmacologic Interventions for Prevention and Treatment of Hypertension\*

	Nonpharmacologic Intervention	Dose	Approximate Impact on SBP	
			Hypertension	Normotension
<b>Weight loss</b>	Weight/body fat	Ideal body weight is best goal but at least 1 kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1 kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg
<b>Healthy diet</b>	DASH dietary pattern	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and trans fat	-11 mm Hg	-3 mm Hg
<b>Reduced intake of dietary sodium</b>	Dietary sodium	<1,500 mg/d is optimal goal but at least 1,000 mg/d reduction in most adults	-5/6 mm Hg	-2/3 mm Hg
<b>Enhanced intake of dietary potassium</b>	Dietary potassium	3,500–5,000 mg/d, preferably by consumption of a diet rich in potassium	-4/5 mm Hg	-2 mm Hg
<b>Physical activity</b>	Aerobic	<ul style="list-style-type: none"> <li>90–150 min/wk</li> <li>65%–75% heart rate reserve</li> </ul>	-5/8 mm Hg	-2/4 mm Hg
	Dynamic Resistance	<ul style="list-style-type: none"> <li>90–150 min/wk</li> <li>50%–80% 1 rep maximum</li> <li>6 exercises, 3 sets/exercise, 10 repetitions/set</li> </ul>	-4 mm Hg	-2 mm Hg
	Isometric Resistance	<ul style="list-style-type: none"> <li>4 x 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk</li> <li>8–10 wk</li> </ul>	-5 mm Hg	-4 mm Hg
<b>Moderation in alcohol intake</b>	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: <ul style="list-style-type: none"> <li>Men: ≤2 drinks daily</li> <li>Women: ≤1 drink daily</li> </ul>	-4 mm Hg	-3 mm Hg

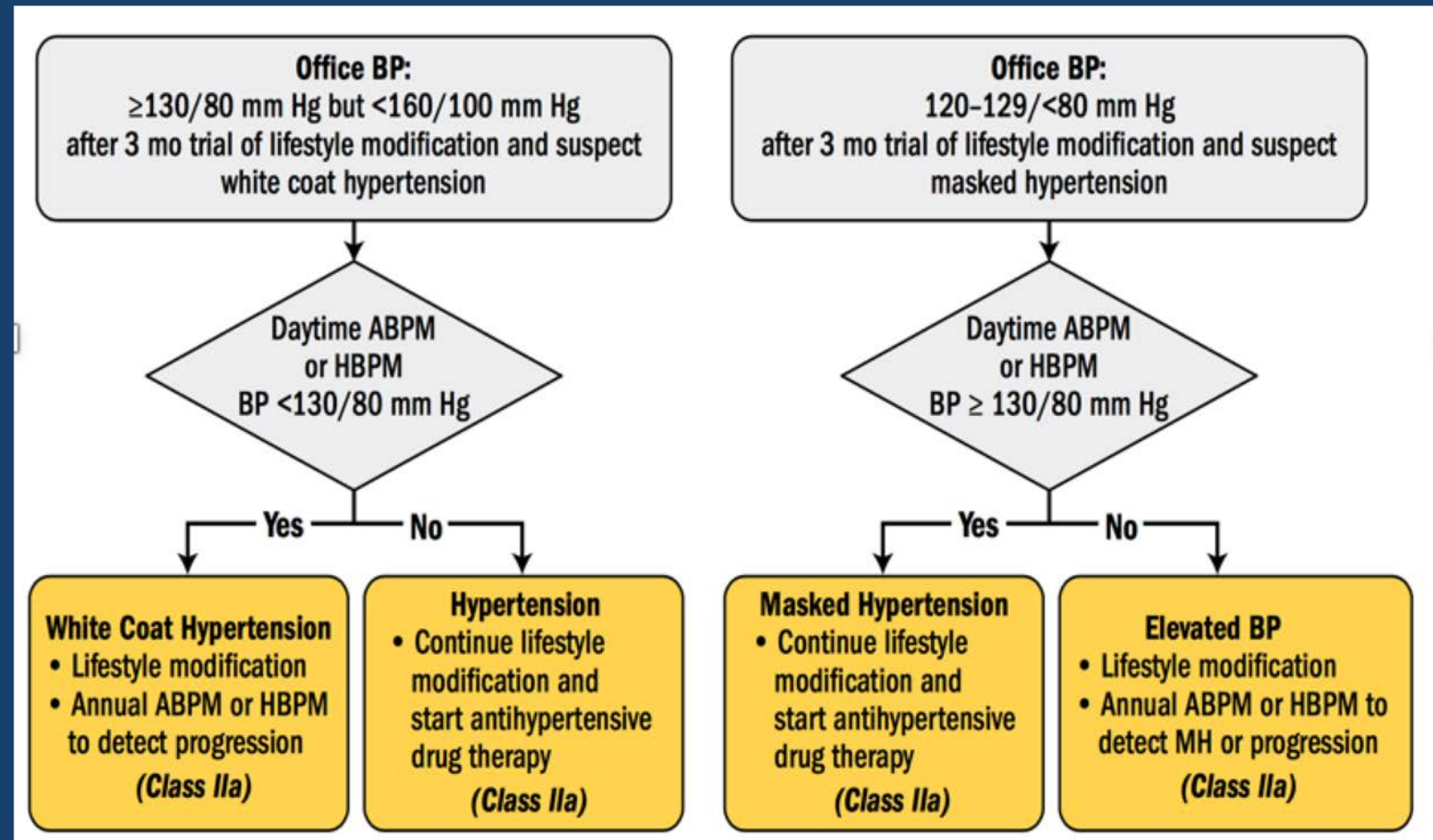
\*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

†In the United States, one “standard” drink contains roughly 14 grams of pure alcohol, which is typically found in 12 ounces of regular beer (usually about 5% alcohol), 5 ounces of wine (usually about 12% alcohol) and 1.5 ounces of distilled spirits (usually about 40% alcohol).

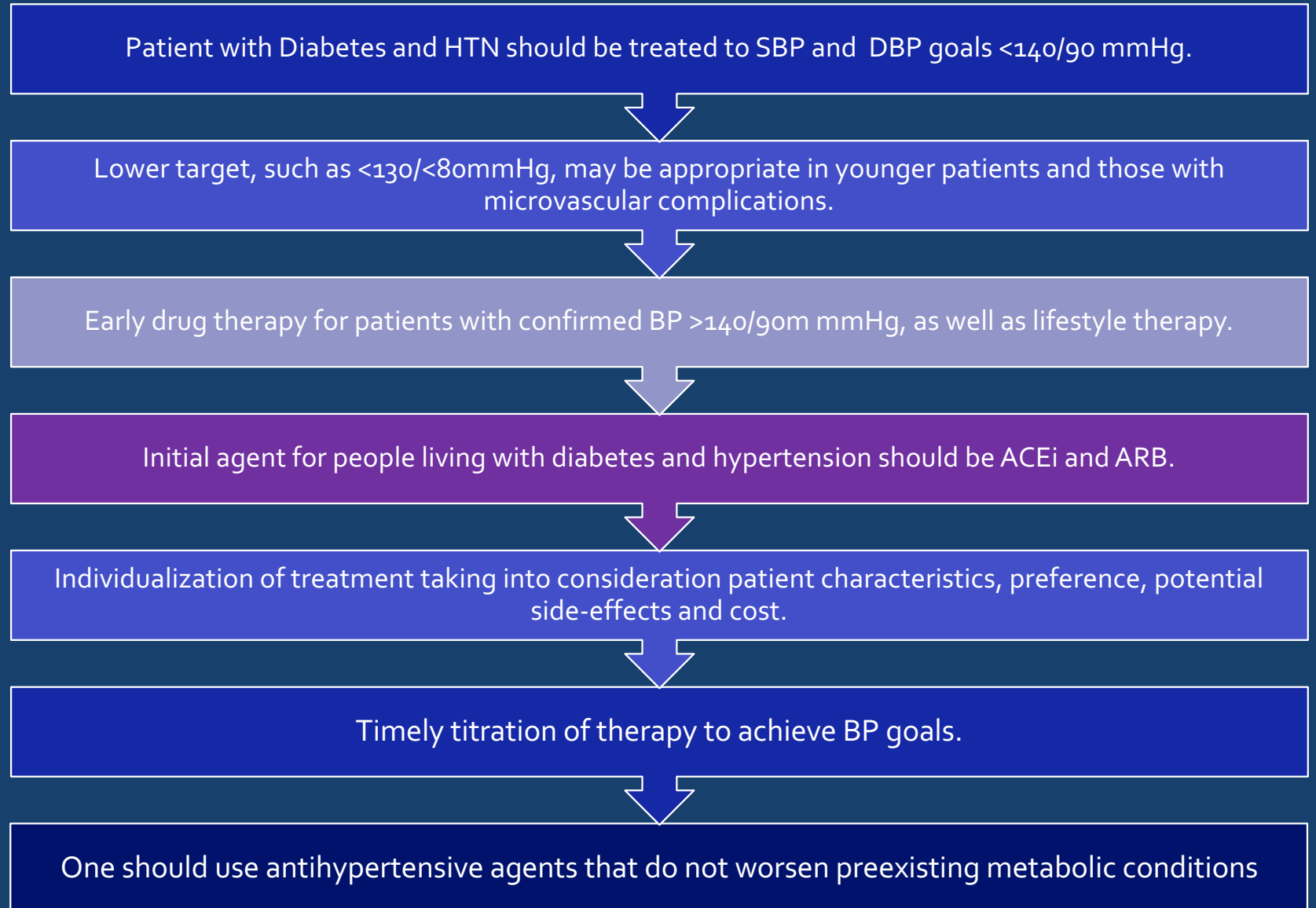
Hypertension diagnosis and management can be complicated by two common conditions:

**Masked Hypertension**

**White-Coat Hypertension**



# Take- Home Messages



# Gracias



THE GOOD PHYSICIAN  
TREATS THE DISEASE; THE  
GREAT PHYSICIAN TREATS  
THE PATIENT WHO HAS THE  
DISEASE

WILLIAM OSLER