

# **Hypertension and the Patient with Diabetes**

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# HTN in DM: Facts

- HTN is the leading cause of morbidity and mortality worldwide
- Affecting 20–60% of people with diabetes
- HTN is 1.5 to 3 times more common in people with diabetes than in those without

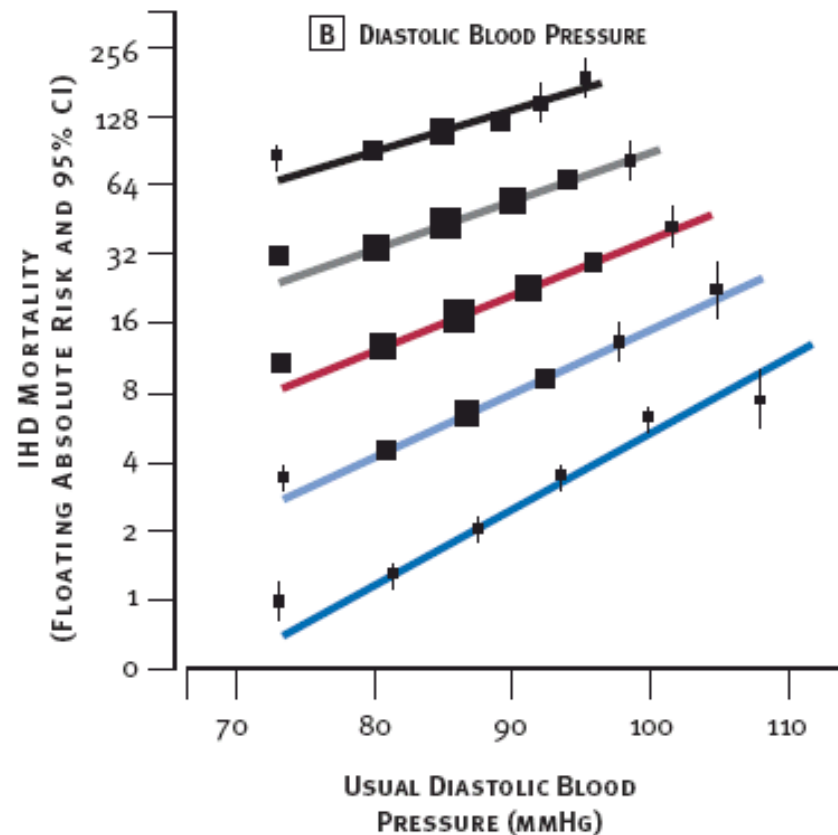
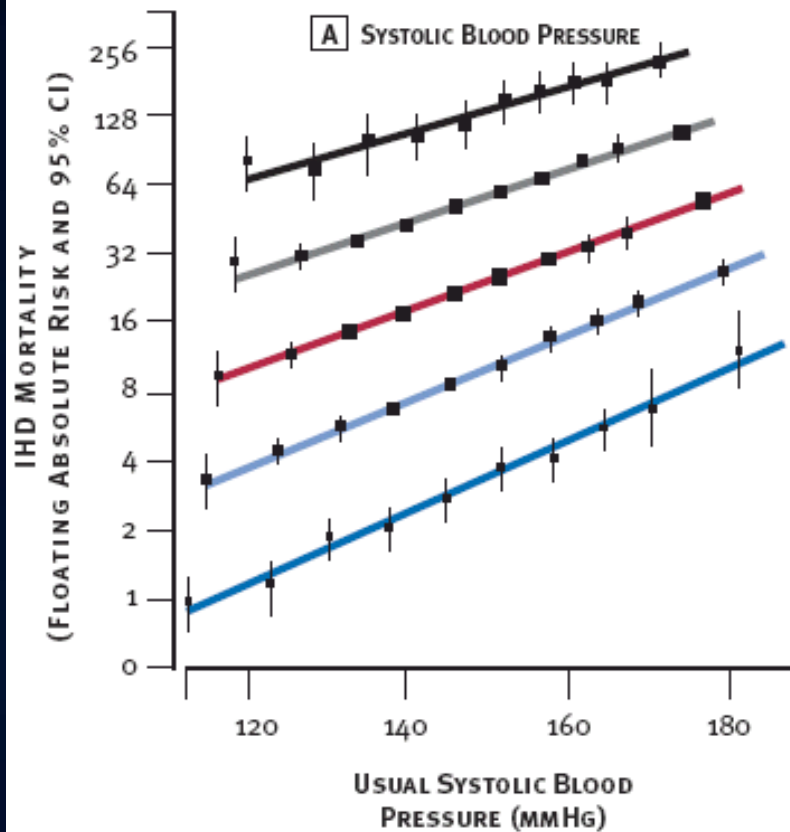
# HTN in DM: Facts

- Hypertensive people with diabetes vs hypertensive people without diabetes: Twice the risk of CVD
- 1 in every 4 individuals in the U.S. has HTN<sup>1</sup>
- The greatest reduction in cardiovascular mortality occurs at achieving a diastolic blood pressure of ~80 mm Hg and systolic blood pressure <130 mm Hg

<sup>1</sup>ADA, 2005.

# HTN in DM: Facts

## IHD Mortality Rate in Each Age Decade vs HTN



Age at risk:

80-89 years    70-79 years    60-69 years    50-59 years    40-49 years

# HTN in DM: Prevalence

## USA

- ~ 60% of people with diabetes have HTN
- 14% of Af. Am. have HTN & DM<sup>1</sup>

## Germany

- 50% of primary care pts have HTN
- 12% of all pts have HTN & DM<sup>2</sup>

WHO Fact Sheet	World		KSA	
	2000	2030	2000	2030
DM	171,000,000	366,000,000	890,000	2,523,000

Estimated DM + HTN	102,600,000	219,600,000	543,000	1,513,800
<b>NOW</b>	133,800,000		801,880	

<sup>1</sup>ADA, 2005.

<sup>2</sup>Lehnert H et al., 2005.

# HTN in DM: Prevalence

## The Third National Health and Nutrition Evaluation Survey (NHANES III)

- 29% of individuals with diabetes who had hypertension were unaware of the HTN diagnosis
- 43% of individuals with diabetes who had hypertension were untreated for the HTN
- 55% of individuals with diabetes on treatment for HTN had a blood pressure  $\geq 140/90$
- 12% of individuals with diabetes on treatment for HTN had a blood pressure  $< 130/85$

# HTN in DM: Prevalence

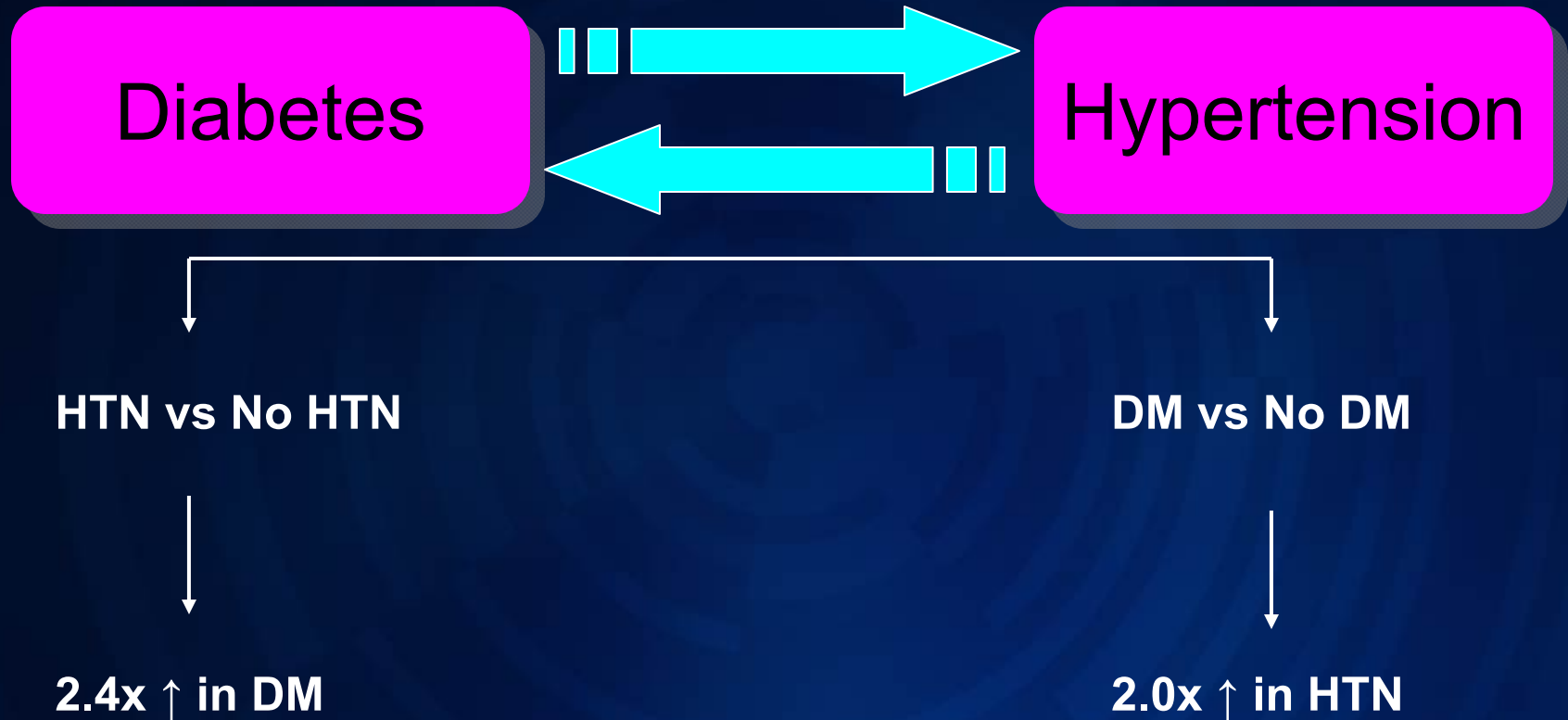
<b>Type 1</b> <b>(1/4 have HTN)</b>	<b>At diagnosis: 20–40%</b>
	<b>With microalbuminuria: 30–50%</b>
	<b>With macroalbuminuria: 65–88%</b>
<b>Type 2</b> <b>(1/2 have HTN)</b>	<b>At diagnosis: 50%</b>
	<b>With microalbuminuria: 80%</b>
	<b>With macroalbuminuria: &gt;90%</b>

*N Engl J Med.* 2000;342:905.

*Diabetes Care.* 2005;28:310

*Am J Kid Dis.* 2007;49(Suppl 2):S74.

# HTN in DM: Partners in Crime



*N Engl J Med.* 2000;342:905.

*Diabetes Care.* 2005;28:310.

# HTN in DM: Partners in Crime

Diabetes



Hypertension

**DM-1**

- Cause: Hypertension is usually renoparenchymal in origin, caused by or pointing to underlying diabetic nephropathy
- Onset: Typically becomes manifest about the time that patients develop microalbuminuria<sup>1</sup>

**DM-2**

- Cause: Mainly due to insulin resistance (as a facet of MS), but may be due to underlying DN or other causes<sup>1</sup>
- Onset: Usually precedes the onset of nephropathy and even the onset of type 2 diabetes by years or decade<sup>2</sup>

<sup>1</sup>American Diabetes Association. *Diabetes Care*, 2004.

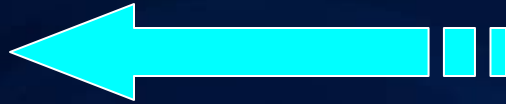
<sup>2</sup>Ritz et al. *J Int Med*. 2001;249:215-223.

# HTN in DM: Partners in Crime

- The RAS itself plays an important role in the development of diabetes
- Over activity of RAS appears to be linked to reduced insulin and glucose delivery to the peripheral skeletal muscle and impaired glucose transport and response to insulin signalling pathways, thus increasing insulin resistance<sup>1</sup>
- Activation of a local pancreatic RAS, in particular within the islets, may represent an independent mechanism for the progression of islet cell damage in diabetes<sup>2</sup>

# HTN in DM: Partners in Crime

Diabetes

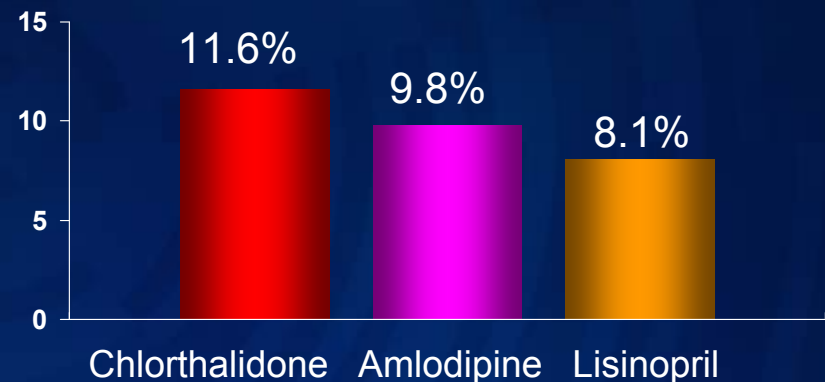


Hypertension

## Role of Antihypertensive Drugs

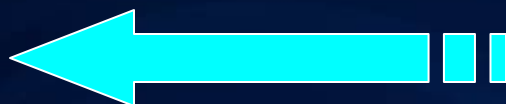
- The risk of diabetes associated with antihypertensive-drug therapy appears to be explained by the presence of hypertension
- Among the subjects who had hypertension, the risk among those not taking medication was similar to that among those taking one or more agents
- Among the subjects who were not taking any antihypertensive medication, the risk of diabetes was much higher among hypertensive subjects than in nonhypertensive subjects

## ALLHAT: Incidence of New-Onset Diabetes at 4 Years



# HTN in DM: Partners in Crime

Diabetes



Hypertension

## Role of Antihypertensive Drugs

- Taking a thiazide diuretic, ACE inhibitor, or CCB carry no greater risk for the subsequent development of DM
- DM was 28% more likely to develop in subjects taking BB than in those taking no medication
- This adverse effect of BB must be weighed against the proven benefits of this drug in reducing the risk of cardiovascular events

**TABLE 3.** RISK OF DIABETES MELLITUS AMONG 3804 SUBJECTS WITH HYPERTENSION, ACCORDING TO CATEGORY OF ANTIHYPERTENSIVE MEDICATION.\*

ANTIHYPERTENSIVE MEDICATION	HAZARD RATIO (95% CONFIDENCE INTERVAL)		
	MODEL 1	MODEL 2	MODEL 3
None	1.0	1.0	1.0
ACE inhibitor	0.99 (0.73–1.35)	0.96 (0.71–1.31)	0.98 (0.72–1.34)
Beta-blocker	1.26 (1.03–1.52)†	1.25 (1.03–1.52)†	1.28 (1.04–1.57)†
Calcium-channel antagonist	1.17 (0.85–1.62)	1.16 (0.84–1.60)	1.17 (0.83–1.66)
Thiazide diuretic	0.95 (0.77–1.17)	0.93 (0.76–1.15)	0.91 (0.73–1.13)

\*Model 1 adjusted for age, sex, race, and use of other antihypertensive medications. Model 2 adjusted for the variables included in model 1, as well as body-mass index, waist-to-hip ratio, level of education, smoking status, alcohol use, and physical-activity level. Model 3 adjusted for the variables included in model 2, as well as systolic blood pressure, diastolic blood pressure, fasting serum insulin concentration, and the presence or absence of hypercholesterolemia, cardiovascular disease, pulmonary disease, renal insufficiency, and a family history of diabetes. ACE denotes angiotensin-converting enzyme.

† $P < 0.05$  for the comparison with subjects taking no antihypertensive medication.

# HTN in DM: Partners in Crime

## Microvascular and Macrovascular Complications of Hypertension in Patients with Diabetes

### Microvascular complications

Renal disease—hypertension contributes to the risk of renal disease in patients with diabetes.

#### Autonomic neuropathy

Sexual dysfunction—hypertension and antihypertensive therapies may independently contribute to autonomic-associated sexual dysfunction in diabetes.

Orthostatic hypotension—supine hypertension with orthostatic hypotension can occur in persons with diabetes because of autonomic dysfunction. Blood pressure should be measured in the supine, sitting, and standing positions.

Eye disease—hypertension increases the risk of eye disease in patients with diabetes, including glaucoma and diabetic retinopathy with potential blindness.

### Macrovascular complications

Cardiac disease—hypertension in patients with diabetes increases the risk of coronary artery disease, congestive heart failure, and cardiomyopathy.

Cerebrovascular disease—hypertension increases the incidence of stroke in patients with diabetes.

Survival rates and recovery from stroke are reduced in patients with diabetes compared with patients without diabetes.

Peripheral vascular disease—hypertension increases the risk of peripheral vascular disease and subsequent foot ulcers and amputations in patients with diabetes.

Diabetes and HTN vs Diabetes	Relative Risk of Complications
CHD	X 3.0
Stroke	X 4.0
Retinopathy	X 2.0
Nephropathy	X 2.0
Neuropathy	X 1.6
Mortality	X 2.0
75% die from CVD	

# HTN in DM: Partners in Crime

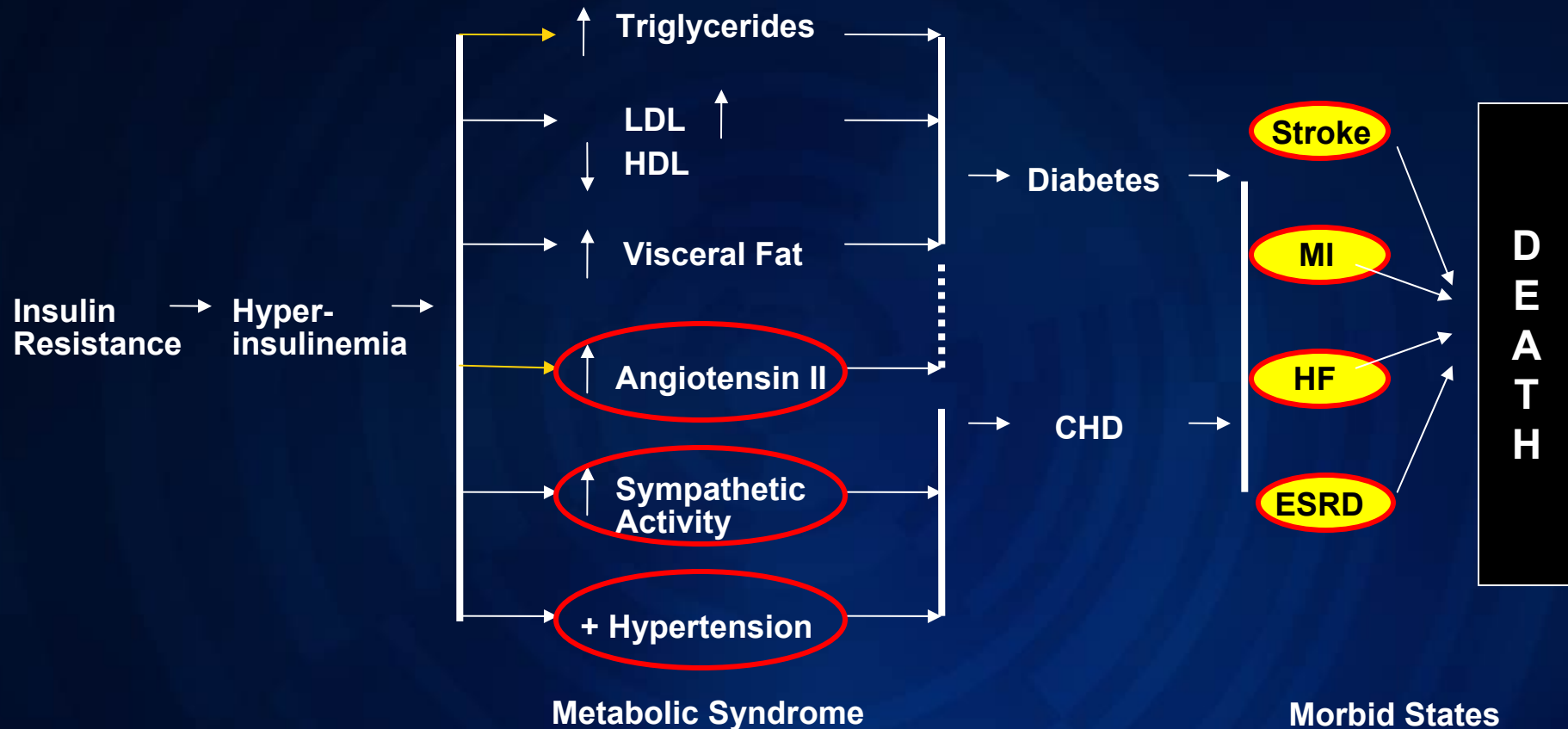
The HIPERFRE study, 2008

1724 hypertensive patients, 35 physicians, 14 primary care units

	Uncontrolled AHT			Refractory HT		
	OR	95% CI	p	OR	95% CI	p
Age (each year)	1.01	0.99-1.02	ns	1.03	1.01-1.05	< 0.01
Male sex	1.30	0.99-1.70	ns	1.62	1.10-2.37	< 0.05
<b>Diabetes</b>	<b>4.39</b>	<b>3.18-6.05</b>	<b>&lt; 0.001</b>	<b>6.34</b>	<b>4.24-9.50</b>	<b>&lt; 0.001</b>
Alcoholism	1.96	1.05-3.66	< 0.05	2.00	0.83-4.81	ns
Obesity	1.22	0.95-1.57	ns	1.51	1.04-2.19	< 0.05
Metabolic synd	2.85	2.17-3.74	< 0.001	4.36	2.95-6.45	< 0.001
Ischemic heart dis	0.58	0.39-0.88	< 0.05	0.40	0.21-0.73	< 0.01
Heart failure	0.26	0.12-0.55	< 0.001	0.78	0.37-1.65	ns
Atrial fibrillation	0.44	0.26-0.75	< 0.01	1.42	0.26-0.75	ns
Valve disease	0.38	0.20-0.72	< 0.01	0.84	0.40-1.78	ns

AHT: arterial hypertension. OR: odds ratio. CI: confidence interval. ns: non statistically significant difference.  
The reference category is controlled arterial hypertension.

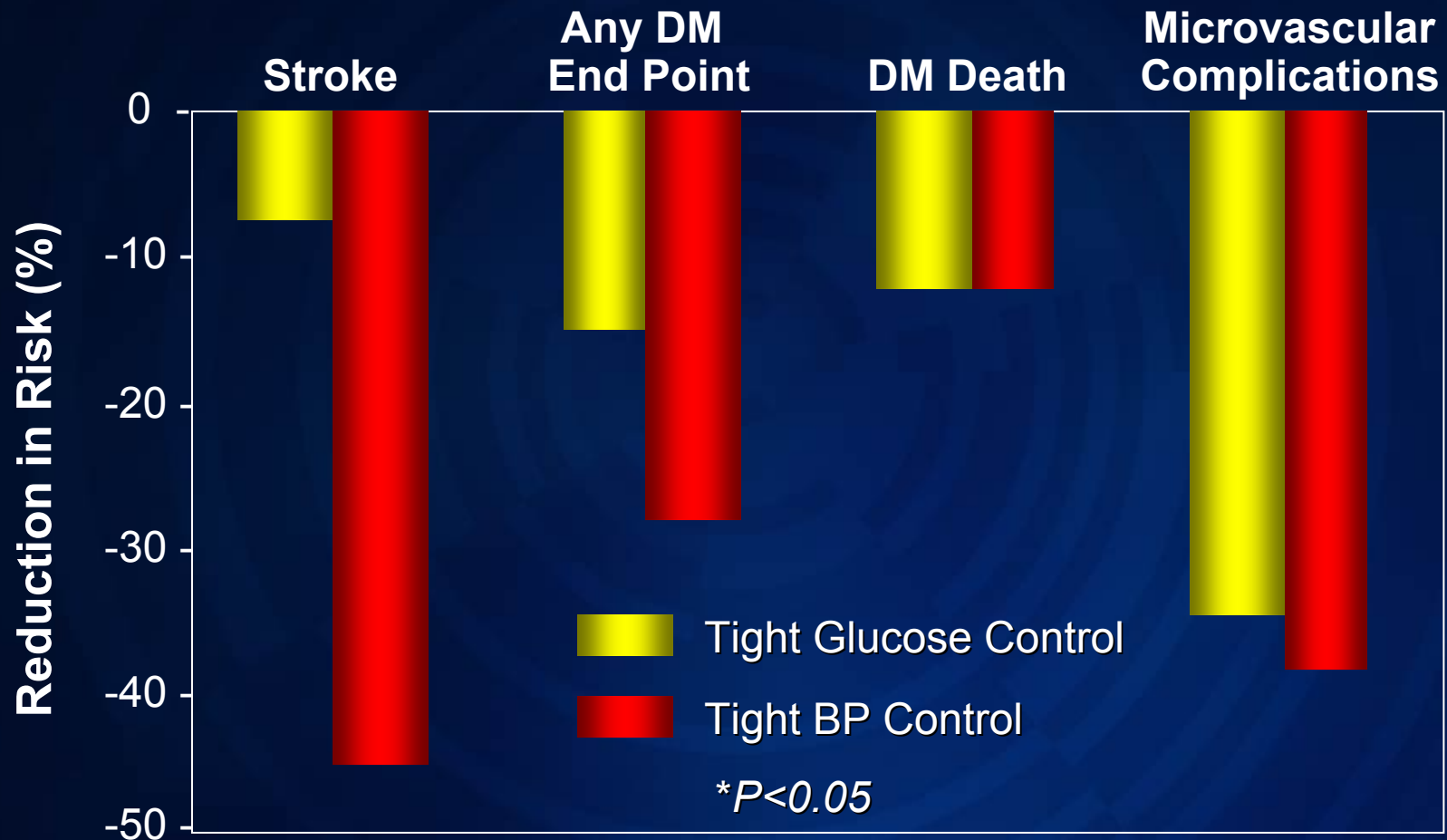
# HTN in DM: Partners in Crime



LDL=low-density lipoprotein; HDL=high-density lipoprotein; MI=myocardial infarction; CHD=congestive heart failure; HF=heart failure; ESRD=end-stage renal disease

# HTN in DM: Effect of BP Control

## Tight BP Control vs Tight Glucose Control



# HTN in DM: Effect of BP Control

## Tight BP Control vs Tight Glucose Control

Table 2. The Effectiveness of Hypertension versus Glucose Control in the United Kingdom Prospective Diabetes Study\*

End Point	Strategy	Tight BP Control			Tight Glucose Control		
		8.4-y Event Rate, n/n	10-y Absolute Risk Reduction	10-y NNT <sub>B</sub>	10-y Event Rate, n/n	10-y Absolute Risk Reduction	10-y NNT <sub>B</sub>
Any diabetes end point	Conventional	170/390	–	–	438/1138	–	–
	Intensive	259/758	0.112 (0.05 to 0.17)§	8.9	963/2729	0.032 (0.00 to 0.07)§	31.2
Diabetes-related death	Conventional	62/390	–	–	129/1138	–	–
	Intensive	82/758	0.061 (0.02 to 0.11)§	16.4	285/2729	0.009 (–0.01 to 0.03)	112.1
All-cause mortality	Conventional	83/390	–	–	213/1138	–	–
	Intensive	134/758	0.043 (–0.01 to 0.10)	23.3	489/2729	0.008 (–0.02 to 0.04)	125.3
Myocardial infarction	Conventional	69/390	–	–	186/1138	–	–
	Intensive	107/758	0.043 (–0.01 to 0.09)	23.3	387/2729	0.022 (0.00 to 0.05)	46.2
Stroke	Conventional	34/390	–	–	55/1138	–	–
	Intensive	38/758	0.044 (0.01 to 0.08)§	22.7	148/2729	–0.006 (–0.02 to 0.01)	169.40
Peripheral vascular death or amputation	Conventional	8/390	–	–	18/1138	–	–
	Intensive	8/758	0.012 (–0.01 to 0.03)	83.3	29/2729	0.005 (0.00 to 0.01)	192.7
Microvascular	Conventional	54/390	–	–	121/1138	–	–
	Intensive	68/758	0.058 (0.02 to 0.10)§	17.2	225/2729	0.024 (0.00 to 0.05)§	41.9

\* Values in parentheses are 95% CIs. NNT<sub>B</sub> = number needed to treat for benefit.

† Achieved mean blood pressure was 154/87 mm Hg in the control group versus 144/82 mm Hg in the tight blood pressure control group; achieved mean hemoglobin A<sub>1c</sub> level was 7.9% in the control group versus 7.0% in the tight glucose control group.

‡ Mean follow-up in the blood pressure trial was 8.4 years; the crude event rate is presented for this 8.4-year follow-up, while the absolute risk reduction and the number needed to treat for benefit are standardized to a 10-year time frame to allow a more direct comparison with intensive blood glucose control (20).

§ Statistically significant relative risk reduction in primary data.

|| For stroke, intensive glucose control led to a trend toward harm rather than benefit. As a result, the presented statistic is number needed to harm.

# HTN in DM: Practical Strategy

1. Measure BP properly
2. Define hypertensive patients
3. Evaluate hypertensive patients
4. Therapy

# HTN in DM: 1. Measure BP Properly

“The measurement of BP is likely the clinical procedure of greatest importance that is performed in the sloppiest manner.”

—Norman Kaplan, MD  
*Lancet*. 2007;370:591.

“Health care professionals should take particular care to ensure that they are using accurate techniques to measure BP in all their patients.”

—International Working Group, 2008  
*J Hum Hypertens*. 2008;22:63.

	<b>Δ BP (mm Hg) if not done</b>
<b>Rest ≥ 5min, quiet</b>	<b>↑ 12/6</b>
<b>Seated, back supported</b>	<b>↑ 6/8</b>
<b>Cuff midsternal level</b>	<b>↑ ↓ 2/inch</b>
<b>Correct cuff size</b>	<b>↑ 6–18/3–14</b>
<b>Bladder center over artery</b>	<b>↑ 3–5/2–3</b>
<b>Deflate 2 mm Hg/sec</b>	<b>↑ SBP/↓ DBP</b>



# HTN in DM: 1. Measure BP Properly

- The patient should be seated for at least 5 minutes, relaxed and not moving or speaking.
- The arm must be supported at the level of the heart. Ensure no tight clothing constricts the arm.
- Place the cuff on neatly with the center of the bladder over the brachial artery. The bladder should encircle at least 80% of the arm (but not more than 100%).
- The column of mercury must be vertical, and at the observer's eye level.
- Estimate the systolic beforehand:
  - Palpate the brachial artery
  - Inflate cuff until pulsation disappears
  - Deflate cuff
  - Estimate systolic pressure
- Then inflate to 30 mm Hg above the estimated systolic level needed to occlude the pulse.
- Place the stethoscope diaphragm over the brachial artery and deflate at a rate of 2–3 mm/sec until you hear regular tapping sounds.
- Measure systolic (first sound) and diastolic (disappearance) to nearest 2 mm Hg.

Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. *JNC-7*

# HTN in DM: 1. Measure BP Properly

## Indications of Ambulatory BP monitoring

- Suspected white-coat hypertension in patients with hypertension and no target organ damage
- Apparent drug resistance (office resistance)
- Hypotensive symptoms with antihypertensive medication
- Episodic hypertension
- Autonomic dysfunction

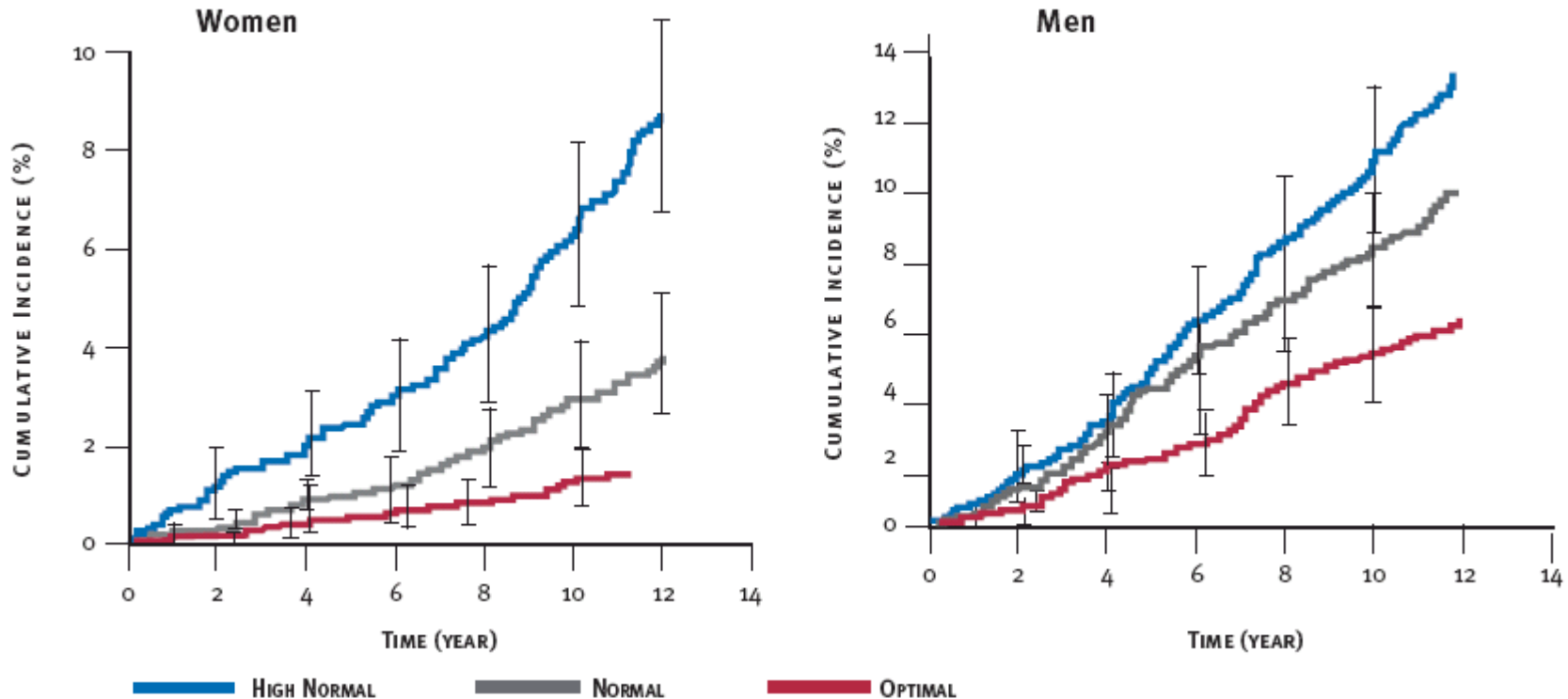
### Self-Measurement

Self-monitoring of BP at home and work is a practical approach to assess differences between office and out-of-office BP prior to consideration of ABPM. For those whose out-of-office BPs are consistently <130/80 mmHg despite an elevated office BP, and who lack evidence of target organ disease, 24-hour monitoring or drug therapy can be avoided.

Self-measurement or ABPM may be particularly helpful in assessing BP in smokers. Smoking raises BP acutely, and the level returns to baseline about 15 minutes after stopping.

# HTN in DM: 2. Define Hypertensive Patients






## High Normal BP and CVD Risk



Cumulative incidence of cardiovascular events in women (panel A) and men (panel B) without hypertension, according to blood pressure category at the base-line examination. Vertical bars indicate 95 percent confidence intervals. Optimal BP is defined here as a systolic pressure of <120 mmHg and a diastolic pressure of <80 mmHg. Normal BP is a systolic pressure of 120–129 mmHg or a diastolic pressure of 80–84 mmHg. High-normal BP is a systolic pressure of 130–139 mmHg or a diastolic pressure of 85–89 mmHg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used.

Joint National Committee 7 (JNC-7)

# HTN in DM: 2. Define Hypertensive Patients

JNC 6 CATEGORY	SBP/DBP	JNC 7 CATEGORY
OPTIMAL	<120/80	 NORMAL
NORMAL	120-129/80-84	 PREHYPERTENSION
BORDERLINE	130-139/85-89	
HYPERTENSION	≥140/90	 HYPERTENSION
STAGE 1	140-159/90-99	 STAGE 1
STAGE 2	160-179/100-109	 STAGE 2
STAGE 3	≥180/110	

Joint National Committee 7 (JNC-7)

# HTN in DM: 2. Define Hypertensive Patients

## Systolic or Diastolic Hypertension?

- **Systolic is stronger predictor of risk than diastolic BP**
  - Cardiovascular disease
  - Diabetic nephropathy
- **65% of DM hypertensives have isolated systolic hypertension**
- **Systolic hypertension more difficult to control**

CV=cardiovascular; SBP=systolic blood pressure.

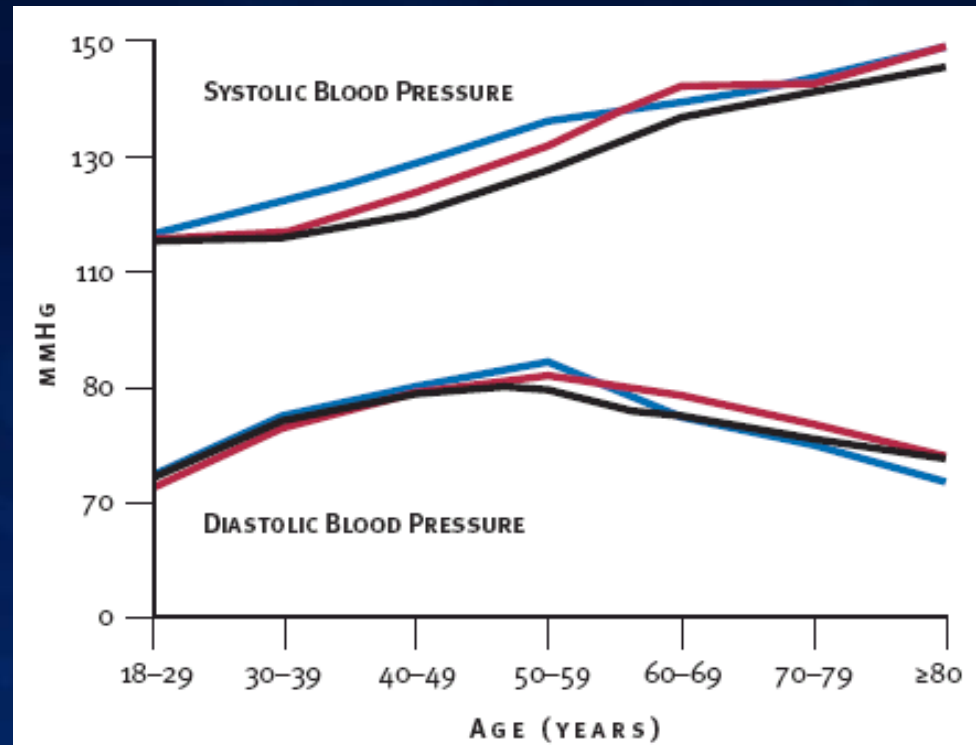
**CV mortality risk doubles with each 20/10 mm Hg BP increment**

*Lancet.* 2002;360:1903. | *Hypertension.* 2003;42:1206. | National Kidney Foundation: Guideline 8. *Am J Kidney Dis.* 2004;43(Suppl. 1):S142-S159. | Sowers JR et al. *Hypertension.* 2001;37:1053-1059. | Stamler J et al. *Diabetes Care.* 1993;16:434-444.

# HTN in DM: 2. Define Hypertensive Patients

## Systolic or Diastolic Hypertension?

- Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation.
- Systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension.
- DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.
- DBP control rates exceeded 90 percent, but SBP control rates were considerably less (60–70 percent)



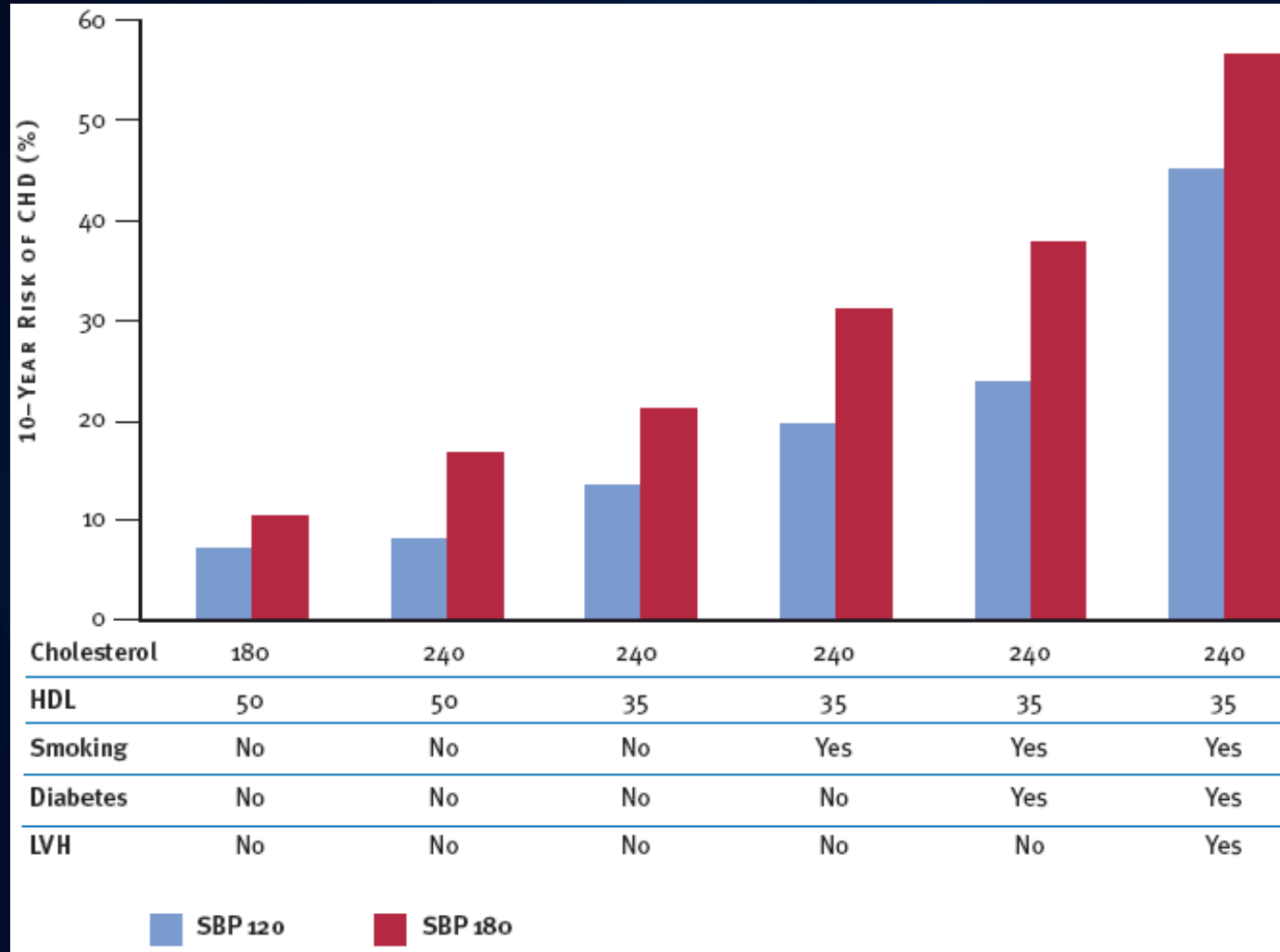
# HTN in DM: 2. Define Hypertensive Patients

## Systolic or Diastolic Hypertension?

- Three-fourths of primary care physicians failed to initiate therapy if SBP 140–159
- Most physicians have been taught that the diastolic pressure is more important than SBP and thus treat accordingly
- Most primary care physicians did not pursue control to <140 mm Hg

# HTN in DM: 2. Define Hypertensive Patients

## Systolic or Diastolic Hypertension?



# HTN in DM: 2. Define Hypertensive Patients

## Follow-up BP Measurements

INITIAL BLOOD PRESSURE (mmHg) <sup>*</sup>	FOLLOWUP RECOMMENDED <sup>†</sup>
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 year <sup>‡</sup>
Stage 1 Hypertension	Confirm within 2 months <sup>‡</sup>
Stage 2 Hypertension	Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g., >180/110 mmHg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.

*\* If systolic and diastolic categories are different, follow recommendations for shorter time followup (e.g., 160/86 mmHg should be evaluated or referred to source of care within 1 month).*

*† Modify the scheduling of followup according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.*

<b>Normal</b>	<b>&lt;120/&lt;80</b>
<b>Prehypertension</b>	<b>120–139 / 80–89</b>
<b>Stage 1</b>	<b>140–159 / 90–99</b>
<b>Stage 2</b>	<b>≥160 / ≥100</b>

# HTN in DM: 3. Evaluate Hypertensive Patients

- Estimate CV risk factors
- Diagnose target organ damage
- Exclude identifiable causes of HTN
- Routine laboratory work up with ECG, lipid profile and urinary albumin

# HTN in DM: 3. Evaluate Hypertensive Patients

## Cardiovascular Risk Factors

- HTN
- Age
  - Older than 55 years for men
  - Older than 65 years for women
- DM
- Abnormal lipid profile
  - Elevated LDL (or total) cholesterol
  - Low HDL cholesterol
- Estimated GFR <60 mL/min
- Family history of premature CVD
  - men <55 years of age
  - women <65 years of age
- Microalbuminuria
- Obesity (BMI >30 kg/m<sup>2</sup>)
- Physical inactivity
- Tobacco usage, particularly cigarettes

$$\frac{(140 - \text{age}) \times \text{weight} \times 1.23 \times (0.85 \text{ if female})}{\text{S Creatinine (micromol/L)}}$$

$$\frac{(140 - \text{age}) \times \text{Weight (Kg)} \times (0.85 \text{ if female})}{72 \times \text{S Creatinine (mg/dL)}}$$

Normoalbuminuria <30 mg/day  
Microalbuminuria 30–300 mg/day  
Macroalbuminuria >300 mg/day  
BMI=Weight (Kg) / (Height in meters)<sup>2</sup>

# HTN in DM: 3. Evaluate Hypertensive Patients

## Target Organ Damage

- **Heart**
  - LVH
  - Angina/prior MI
  - Prior coronary revascularization
  - Heart failure
- **Brain**
  - Stroke or transient ischemic attack
  - Dementia
- **CKD**
- **Peripheral arterial disease**
- **Retinopathy**

# HTN in DM: 3. Evaluate Hypertensive Patients

## Identifiable Causes of HTN

- **ABCD diagnosis of secondary HTN**
  - A. Accuracy, Apnea, Aldosteronism**
  - B. Bruit, Bad Kidney**
  - C. Catecholamines, Coarctation, Cushing S.**
  - D. Drugs, Diet**

## Findings That Suggest Secondary Hypertension

<i>Findings</i>	<i>Disorder suspected</i>	<i>Further diagnostic studies</i>
Snoring, daytime somnolence, obesity	Obstructive sleep apnea	Sleep study
Hypernatremia, hypokalemia	Aldosteronism	Ratio of plasma aldosterone to plasma renin activity, CT scan of adrenal glands
Renal insufficiency, atherosclerotic cardiovascular disease, edema, elevated blood urea nitrogen and creatinine levels, proteinuria	Renal parenchymal disease	Creatinine clearance, renal ultrasonography
Systolic/diastolic abdominal bruit	Renovascular disease	Magnetic resonance angiography, captopril (Capoten)-augmented radioisotopic renography, renal arteriography
Use of sympathomimetics, perioperative setting, acute stress, tachycardia	Excess catecholamines	Confirm patient is normotensive in absence of high catecholamines.
Decreased or delayed femoral pulses, abnormal chest radiograph	Coarctation of aorta	Doppler or CT imaging of aorta
Weight gain, fatigue, weakness, hirsutism, amenorrhea, moon facies, dorsal hump, purple striae, truncal obesity, hypokalemia	Cushing's syndrome	Dexamethasone-suppression test
Use of drug in Table 2	Drug side effect	Trial off drug, if possible

## Findings That Suggest Secondary Hypertension

<i>Findings</i>	<i>Disorder suspected</i>	<i>Further diagnostic studies</i>
High salt intake, excessive alcohol intake, obesity	Diet side effects	Trial of dietary modification
Erythropoietin use in renal disease, polycythemia in COPD	Erythropoietin side effect	Trial off drug, if possible
Paroxysmal hypertension, headaches, diaphoresis, palpitations, tachycardia	Pheochromocytoma	Urinary catecholamine metabolites (vanillylmandelic acid, metanephrines, normetanephrines) Plasma free metanephrines
Fatigue, weight loss, hair loss, diastolic hypertension, muscle weakness	Hypothyroidism	TSH levels
Heat intolerance, weight loss, palpitations, systolic hypertension, exophthalmos tremor, tachycardia	Hyperthyroidism	TSH levels
Kidney stones, osteoporosis, depression, lethargy, muscle weakness	Hyperparathyroidism	Serum calcium, parathyroid hormone levels
Headaches, fatigue, visual problems, enlargement of hands, feet, tongue	Acromegaly	Growth hormone level

## Drugs That Can Raise Blood Pressure

<i>Drug class</i>	<i>Drug examples</i>
Immunosuppressive agents	Cyclosporine (Sandimmune), tacrolimus (Prograf), corticosteroids
Nonsteroidal anti-inflammatory drugs	Ibuprofen (Motrin), naproxen (Naprosyn), piroxicam (Feldene)
COX-2 inhibitors	Celecoxib (Celebrex), rofecoxib (Vioxx), valdecoxib (Bextra)
Estrogens	30- to 35-mcg estrogen oral contraceptives
Weight-loss agents	Sibutramine (Meridia), phentermine (Adipex), ma huang (ephedra)
Stimulants	Nicotine, amphetamines
Mineralocorticoids	Fludrocortisone (Florinef)
Antiparkinsonian	Bromocriptine (Parlodel)
Monoamine oxidase inhibitors	Phenelzine (Nardil)
Anabolic steroids	Testosterone
Sympathomimetics	Pseudoephedrine (Novafed)

# HTN in DM: 4. Therapy

- **Blood pressure goal**
- **Lifestyle modification**
- **Pharmacological therapy**

# HTN in DM: 4. Therapy

## Goal Blood Pressure

**Less Than 130/80**

- HOT (Hypertension Optimal Treatment)
- ABCD-NT (Appropriate Blood Pressure Control in Diabetes)
- UKPDS (UK Prospective Diabetes Study)
- IDNT (Irbesartan in Diabetic Nephropathy Trial)
- INVEST (International Verapamil-Trandolapril)
- ADA (American Diabetes Association)
- ISHIB (International Society of Hypertension in Blacks)
- CHEP (Canadian Hypertension Education Program)
- BHS (British Hypertension Society)
- JNC 7 (Joint National Committee 7)

# HTN in DM: 4. Therapy

## Goal Blood Pressure

**Less Than 130/80**

### Can We Go to a Lower Target?

- National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group<sup>1</sup>
- American Association of Clinical Endocrinologists, 2006
  - Target BP 125/75 if proteinuria > 1 g

**IDNT<sup>2</sup>**

An achieved SBP  $\leq 120$  showed a significantly greater risk of CV mortality compared to those with an achieved SBP  $> 120$  mmHg, RR 4.06 (2.11 to 7.80),  $p < 0.0001$

Those with an achieved SBP  $\leq 120$  had a significantly greater risk of CHF than those with an achieved SBP  $> 120$  mmHg, RR 1.80 (1.17 to 2.86),  $p = 0.008$

<sup>1</sup>Am J Kidney Dis. 2000;36(3):646-661.

<sup>2</sup>JASN. 2005;16(7):2170-2179.

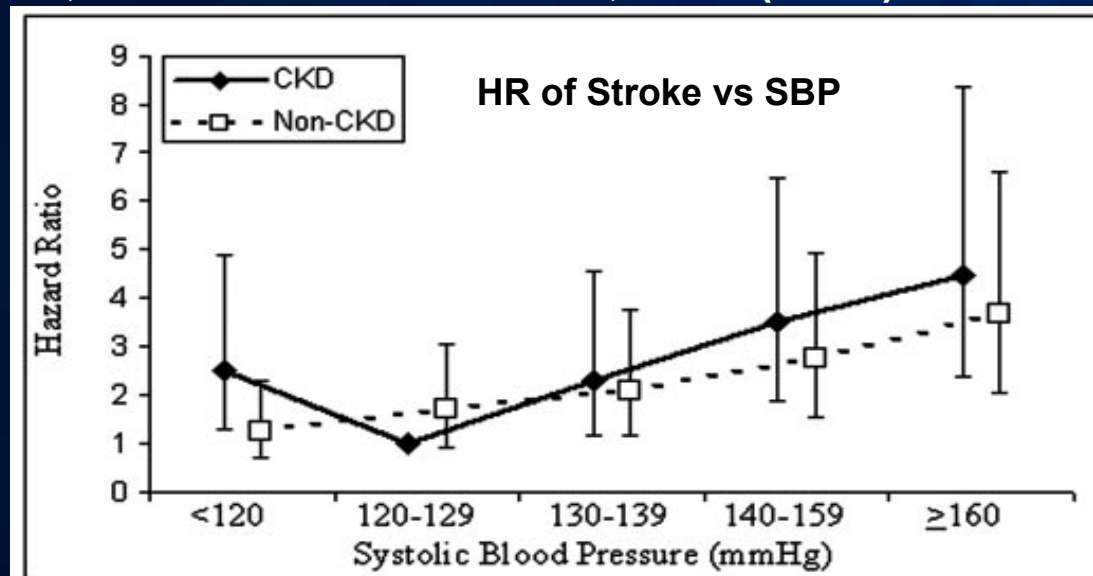
# HTN in DM: 4. Therapy

## Goal Blood Pressure

**Less Than 130/80**

Can We Go to a Lower Target?

20,358 individuals studied; 1549 (7.6%) had CKD



Lowest systolic blood pressure is associated with stroke in stages 3–4 chronic kidney disease

# HTN in DM: 4. Therapy

## Lifestyle Modifications

MODIFICATION	RECOMMENDATION	APPROXIMATE SBP REDUCTION (RANGE) <sup>†</sup>
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m <sup>2</sup> ).	5–20 mmHg/10kg <sup>92,93</sup>
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg <sup>94,95</sup>
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg <sup>94,96</sup>
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg <sup>97,98</sup>
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg <sup>99</sup>

# HTN in DM: 4. Therapy

## Lifestyle Modifications

<b>Intervention</b>	<b>Target</b>								
Reduce foods with added sodium	< 2300 mg /day								
Weight loss	BMI <25 kg/m <sup>2</sup>								
Alcohol restriction	Less or equal to 2 drinks/day								
Physical activity	at least 30 minutes 4 times/week								
Dietary patterns	DASH diet								
Smoking cessation	Smoke-free environment								
Waist circumference <ul style="list-style-type: none"><li>• Euroid, Sub-Saharan African, Middle Eastern</li><li>• South Asian, Chinese</li><li>• Japanese</li></ul>	<table><thead><tr><th>Men</th><th>Women</th></tr></thead><tbody><tr><td>&lt;94 cm</td><td>&lt;80 cm</td></tr><tr><td>&lt;90 cm</td><td>&lt;80 cm</td></tr><tr><td>&lt;85 cm</td><td>&lt;90 cm</td></tr></tbody></table>	Men	Women	<94 cm	<80 cm	<90 cm	<80 cm	<85 cm	<90 cm
Men	Women								
<94 cm	<80 cm								
<90 cm	<80 cm								
<85 cm	<90 cm								

# HTN in DM: 4. Therapy

## Lifestyle Modifications: Dietary

- High in fresh fruits
- High in vegetables
- High in low fat dairy products
- High in dietary and soluble fibre
- High in plant protein
- Low in saturated fat and cholesterol
- Low in sodium

### Dietary Sodium

Less than 2300 mg / day  
(Most of the salt in food is hidden and comes from processed food)

### Dietary Potassium

If required, daily dietary intake  
>80 mmol

### ~~Calcium Supplementation~~

~~No conclusive studies for hypertension~~

### ~~Magnesium Supplementation~~

~~No conclusive studies for hypertension~~

# HTN in DM: 4. Therapy

## Lifestyle Modifications: Daily Sodium

### ➤ Less than:

- 2300 mg sodium (Na)
- 100 mmol sodium (Na)
- 5.8 g of salt (NaCl)
- 1 teaspoon of table salt



**2300 mg sodium = 1 level teaspoon of table salt**

# HTN in DM: 4. Therapy

## Lifestyle Modifications: Physical Activity

Should be prescribed to reduce blood pressure

**F** **Frequency** – Four to seven days per week

**I** **Intensity** – Moderate

**T** **Time** – 30–60 minutes

**T** **Type**

- Cardiorespiratory activity
- Walking, jogging
- Cycling
- Noncompetitive swimming

Exercise should be prescribed as adjunctive to pharmacological therapy

# HTN in DM: 4. Therapy

## Lifestyle Modifications: Weight Loss

**Hypertensive and all patients**

**BMI over 25**

- Encourage weight reduction
- Healthy BMI: 18.5–24.9 kg/m<sup>2</sup>

**Waist Circumference**

- Europid, Sub-Saharan African, Middle Eastern
- South Asian, Chinese
- Japanese

**Men**

- <94 cm
- <90 cm
- <85 cm

**Women**

- <80 cm
- <80 cm
- <90 cm

For patients prescribed pharmacological therapy, weight loss has additional antihypertensive effects. Weight-loss strategies should employ a multidisciplinary approach and include dietary education, increased physical activity, and behavioral modification.

# HTN in DM: 4. Therapy

## Lifestyle Modifications

<b>Intervention</b>	<b>Amount</b>	<b>SBP/DBP</b>
Reduce foods with added sodium	1800 mg sodium hypertensive	-5.1 / -2.7
Weight loss	per kg lost	-1.1 / -0.9
Alcohol intake	3.6 drinks/day	-3.9 / -2.4
Aerobic exercise	120–150 min/week	-4.9 / -3.7
Dietary patterns	DASH diet:	
	Hypertensive	-11.4 / -5.5
	Normotensive	-3.6 / -1.8

# HTN in DM: 4. Therapy

## Important Considerations

- Use caution in initiating therapy with 2 drugs where aggressive blood pressure lowering is more likely or more poorly tolerated (e.g., those with postural hypotension)
- ACE inhibitors and ARBs are contraindicated in pregnancy and caution is required in prescribing to women of childbearing potential
- Diuretic-induced hypokalemia should be avoided through the use of potassium-sparing agent if required

# HTN in DM: 4. Therapy

## Important Considerations

- **Monitor creatinine and potassium when combining K-sparing diuretics, ACE inhibitors, and/or ARBs**
- **If dihydropyridine CCB chosen: Not to be used without ACE-I or ARB agents**
- **If a diuretic is not used as first- or second-line therapy, triple-drug therapy should include a diuretic, when not contraindicated**
- **Short-acting dihydropyridine calcium antagonists should not be used in IHD because of their potential to increase risk of mortality, particularly in the setting of acute myocardial infarction**

# HTN in DM: 4. Therapy

## Important Considerations

### Beta Blockers

- BBs less appealing as first-line agents for treatment of hypertension in patients with either type 2 or type 1 diabetes mellitus (grade A).
- BBs, however, have proved effective in the management of the ischemic and congestive cardiomyopathies that are more common in patients with diabetes than in those without diabetes
- Because the major adverse effects of BBs may be mediated by peripheral vasoconstriction and increasing insulin resistance, the use of the new third-generation BBs (such as nebivolol) or drugs that block both  $\alpha$  and  $\beta$  receptors (such as carvedilol) may prove to be particularly beneficial (grade A)
- These agents cause vasodilatation and an increase in insulin sensitivity
- Beta-adrenergic blockers are not recommended for patients age 60+ without another compelling indication

# HTN in DM: 4. Therapy

## Important Considerations

### Beta Blockers

- Two-drug combinations of beta blockers with ACE inhibitors or ARBs have not been proven to have additive hypotensive effects
- Therefore, these potential two-drug combinations should not be used unless there is a compelling (non blood pressure-lowering) indication such as ischemic heart disease, post myocardial infarction, congestive heart failure, or chronic kidney disease with proteinuria
- Avoid combining a nondihydropyridine CCB and a beta blocker to reduce the risk of bradycardia or heart block

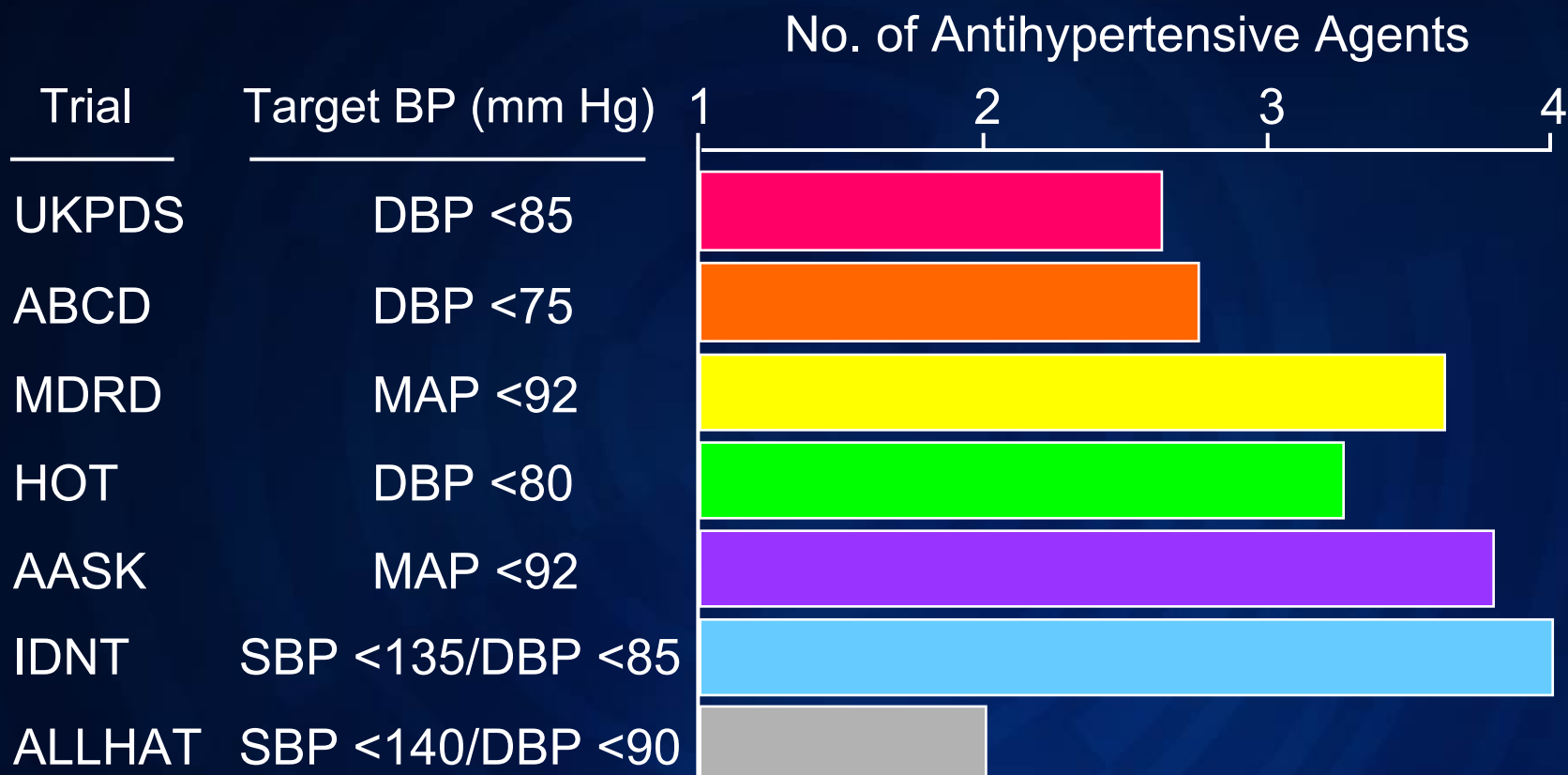
# HTN in DM: 4. Therapy

## Important Considerations

- **If diuretic chosen (preferred if no other compelling indications):**
  - **Creatinine  $<1.8$  mg/dL → thiazide diuretic**
  - **Creatinine  $\geq 1.8$  mg/dL → loop diuretic**
  - **Max. dose 25 mg hydrochlorothiazide (or equivalent)**

# HTN in DM: 4. Therapy

## Most Hypertensive Patients Need Multiple Drugs



DBP=diastolic blood pressure; MAP=mean arterial pressure; SBP=systolic blood pressure.

Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-661.

Lewis EJ et al. *N Engl J Med.* 2001;345:851-860.

Cushman WC et al. *J Clin Hypertens.* 2002;4:393-404.

# HTN in DM: 4. Therapy

## Compelling Indications

Compelling indication	Initial therapy options
<ul style="list-style-type: none"><li>• Heart failure</li></ul>	thiazide diuretic, beta blocker, ACEI, ARB, aldosterone antagonist
<ul style="list-style-type: none"><li>• Post myocardial infarction</li></ul>	beta blocker, ACEI, aldosterone antagonist
<ul style="list-style-type: none"><li>• High CVD risk</li></ul>	thiazide diuretic, beta blocker, ACEI, calcium channel blocker
<ul style="list-style-type: none"><li>• Diabetes</li></ul>	thiazide diuretic, beta blocker, ACEI, ARB, calcium channel blocker
<ul style="list-style-type: none"><li>• Chronic kidney disease</li></ul>	ACEI, ARB
<ul style="list-style-type: none"><li>• Recurrent stroke prevention</li></ul>	thiazide diuretic, ACEI

# HTN in DM: 4. Therapy

## ADA Guidelines

	<u>Systolic</u>	<u>Diastolic</u>
Goal (mm Hg)	<130	<80
Behavioral therapy alone (maximum 3 months) then add pharmacologic treatment	130–139	80–89
Behavioral therapy + pharmacologic treatment	≥140	≥90

# HTN in DM: 4. Therapy

## Practical View

1. Pts. at goal BP < 130/80

2. Pts. with BP 130–139 / 80–89

3. Pts. with BP  $\geq$ 140/90

1

Without  
Compelling  
Indications

- LSM
- Recheck each visit

With  
Compelling  
Indications

- LSM
- Recheck each visit
- Treat CI

2

Without  
Compelling  
Indications

- LSM 3 m
- If high BP  $\rightarrow$  drug therapy

With  
Compelling  
Indications

- LSM
- Drug Th of HTN
- Drug Th of CI

3

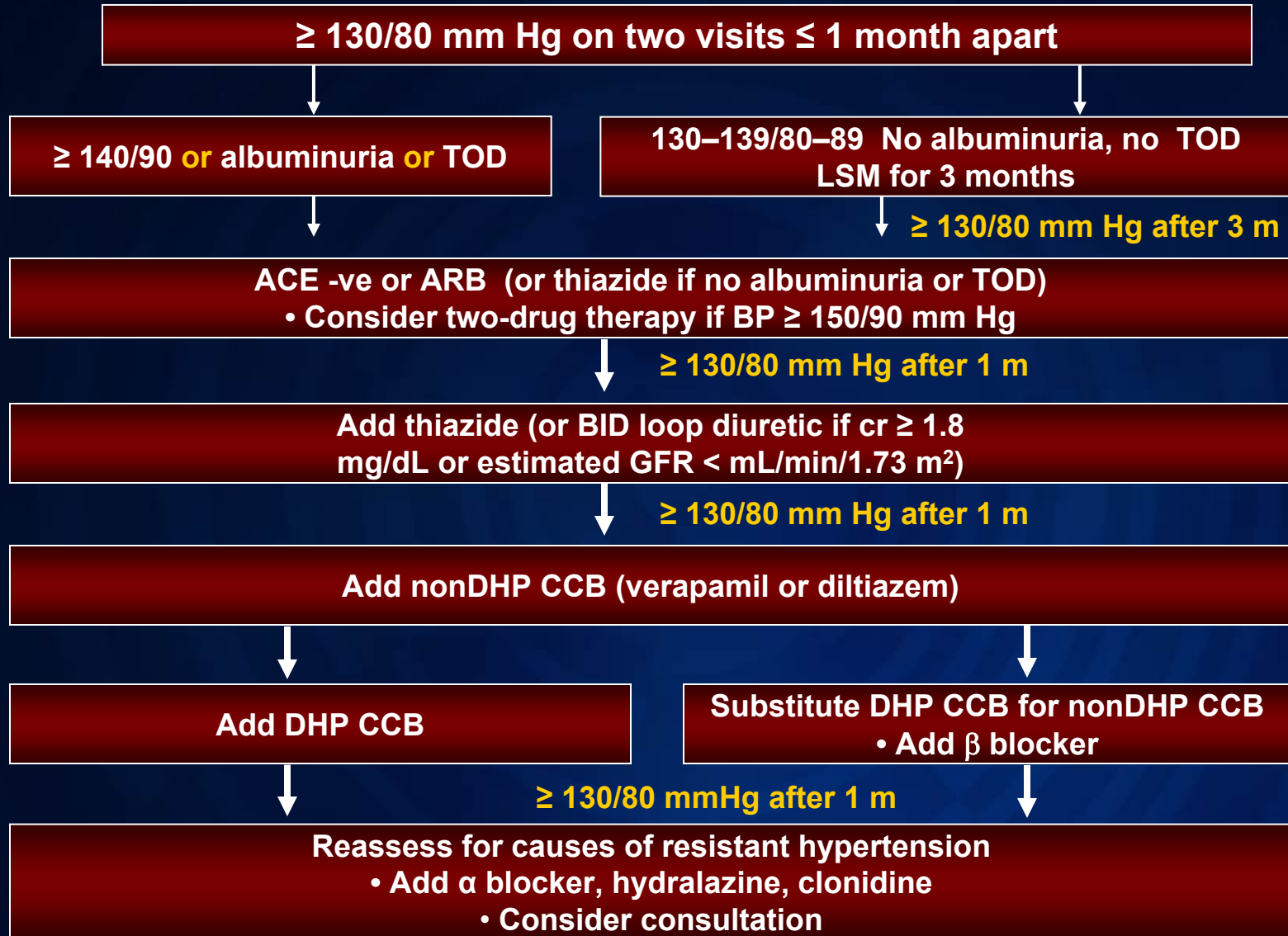
Without  
Compelling  
Indications

- LSM
- Drug Th of HTN

With  
Compelling  
Indications

- LSM
- Drug combined
- Drug of CI

# Algorithm for the Treatment of Hypertension in DM



# HTN in DM: 4. Therapy

For Patients with Microalbuminuria or Proteinuria

- In type 2 patients: ACE-I or ARBs as a first line
- In type 1 patients: ACE-I is recommended to reduce protein excretion
- Consider the use of verapamil or diltiazem in patients with proteinuria unable to tolerate ACE-I or ARBs

# HTN in DM: 4. Therapy

## ACE-I + ARBs: Limited Utility

- Theoretically attractive: More complete RAAS blockade
- Limited BP ↓ and ↓ CVD events vs ACE-I at max dose
  - ONTARGET RCT: 25,620 with CVD ± Stroke ± DM  
Ramipril vs Telmisartan vs R⊕T
    - Minimal BP ↓: 2.4/1.4 mm Hg
    - No ↓ CVD events
    - More side effects
- ↓ Albuminuria 30–40% vs mono Rx with ACE-I or ARB
  - ? Effects on ESRD?
  - NKF, 2007: Consider if albumin/cr > 500 mg/g on mono Rx

# HTN in DM: 4. Therapy

## ACE-I + HCTZ: Excellent First-Line Agent

- Increased HTN control
- Reduced hypokalemia
- Cardioprotective
- Available as a generic medication
- Increased adherence

# HTN in DM: 4. Therapy

## ACE-I Cough

- **Consider continuing the ACE-I**
  - 38–55% likelihood the cough will resolve
  - Consider changing the time of administration or lowering the dose
  - Consider antitussives or lozenges while waiting for symptom to resolve
- **Consider switching to a 2nd ACE-I**
  - Effective for 1 in 10 patients
- **Consider using a different drug class**
  - Diuretic, beta blocker, or calcium channel blocker
  - If an ACE-I is indicated because of comorbid conditions (e.g., DM, HF, CKD), an ARB (i.e., losartan) can be used as an alternative

# HTN in DM: 4. Therapy

## ACE-I or ARBs and Hyperkalemia

- **ACE-I or ARBs may cause hyperkalemia**
  - Avoid other medications that cause hyperkalemia (K suppl, NSAIDs, Cox-2 inhibitors, K-sparing diuretics)
  - Evaluate causes of hyperkalemia
  - Treat hyperkalemia with diuretics
  - Continue ACE-I or ARBs if  $K < 5.5$  mmol/L
- **Monitor GFR**
  - If GFR  $>30\%$  within 4 weeks, evaluate
  - Continue ACE-I or ARBs if GFR  $< 30\%$  from baseline over 4 months

# HTN in DM: 4. Therapy

## Resistant Hypertension

### CAUSES of RESISTANT HYPERTENSION

- Improper BP measurement
- Excessive sodium intake
- Inadequate diuretic therapy
- Excessive alcohol intake
- Identifiable causes of hypertension
- Medication:
  - Inadequate doses
  - Drug actions and interactions (eg, nonsteroidal anti-inflammatory drugs (NSAIDs), illicit drugs, sympathomimetics, oral contraceptives)
  - Over-the-counter drugs and dietary supplements

# JNC-7

BP CLASSIFICATION	SBP* MMHG	DBP* MMHG	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
NORMAL	<120	and <80	Encourage		
PREHYPERTENSION	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
STAGE 1 HYPERTENSION	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
STAGE 2 HYPERTENSION	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

Clinical Features	Prevalence (%)
Type 1 diabetes, microalbuminuria	30-50
Type 1 diabetes, macroalbuminuria	65-88
Type 2 diabetes, microalbuminuria	40-83
Type 2 diabetes, macroalbuminuria	78-96

The prevalence in type 2 diabetes varies among ethnic populations and thus has a wider range.<sup>149-153</sup>

Clinical Assessment	Target Blood Pressure	Preferred Agents for CKD	Other Agents to Reduce CVD Risk and Reach Target Blood Pressure
Blood pressure $\geq 130/80$ mm Hg	$<130/80$ mm Hg	ACE inhibitor or ARB	Diuretic preferred, then $\beta$ -blocker or calcium channel blocker

Note: Letters in shaded areas denote strength of recommendations.