Prevention of Chronic Kidney Disease in Patients with Hypertension

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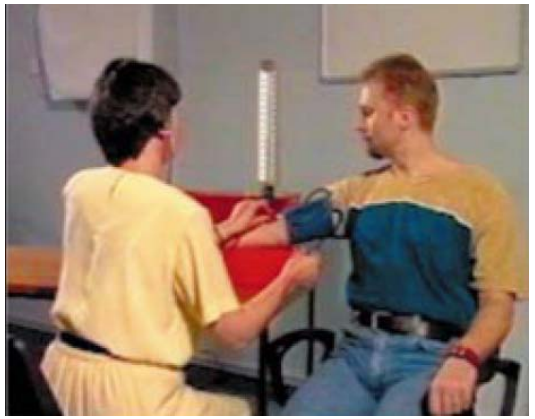
What will I cover?

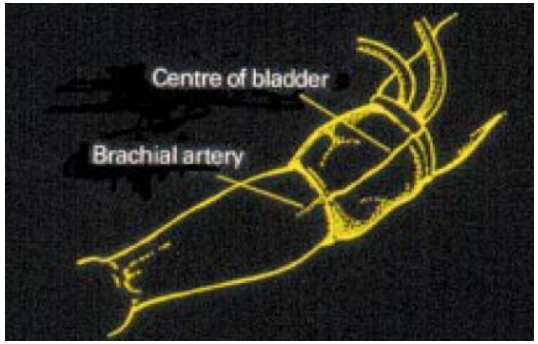
- Definition of hypertension
- Complication of hypertension
- Treatments in hypertensive patients
  - -Lifestyle modification
  - -Antihypertensive drugs

*** J curve phenomenon***

Blood pressure measurement

- Patients should be seated with back supported and arm bared and supported.
- Avoid smoking or ingesting caffeine for 30 minutes before measurement.
- Measurement should begin after at least 5 minutes of rest.
- Appropriate cuff size.
- Two or more readings should be averaged.





Definition of hypertension

Table 1. Classification and management of blood pressure for adults*

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).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

Definition of hypertension

- The average of diastolic BP ≥ **90** mmHg

  or

  the average of systolic BP ≥ **140** mmHg

  on at least 2 subsequent visits.

- Isolated systolic hypertension is defined as systolic BP ≥ 140 mmHg and diastolic BP < 90 mmHg.

Patient evaluation

(1) Identifiable causes of high BP
(2) Assess lifestyle and identify other cardiovascular risk factors
(3) Assess the presence or absence of target organ damage.

***The data needed are acquired through medical history, physical examination, routine laboratory tests, and other diagnostic procedures.

Table 4. Identifiable causes of hypertension

Sleep apnea
Drug-induced or related causes (see table 9)
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing's syndrome
Pheochromocytoma
Coarctation of the aorta
Thyroid or parathyroid disease

Table 3. Cardiovascular risk factors

Major Risk Factors
Hypertension*
Cigarette smoking
Obesity* (body mass index ≥30 kg/m^2)
Physical inactivity
Dyslipidemia*
Diabetes mellitus*
Microalbuminuria or estimated GFR <60 mL/min
Age (older than 55 for men, 65 for women)
Family history of premature cardiovascular disease (men under age 55 or women under age 65)

Complication of hypertension

Target Organ Damage
Heart • Left ventricular hypertrophy • Angina or prior myocardial infarction • Prior coronary revascularization • Heart failure
Brain • Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

GFR, glomerular filtration rate.

* Components of the metabolic syndrome.

Treatments in hypertensive patients

- **Lifestyle modification**
- **Antihypertensive drugs**

Lifestyle modification

Long-Term Effects of Weight Loss and Dietary Sodium Reduction on Incidence of Hypertension

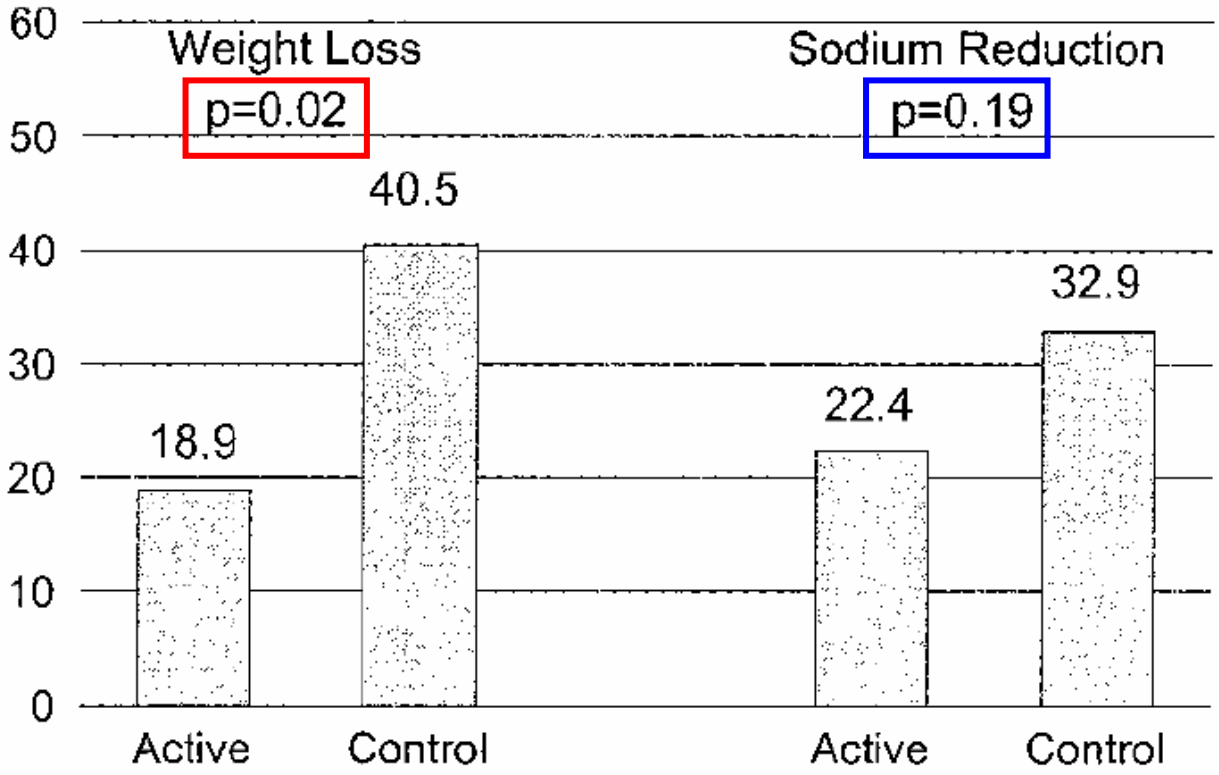
Jiang He, Paul K. Whelton, Lawrence J. Appel, Jeanne Charleston, Michael J. Klag

Abstract—To examine the long-term effects of weight loss and dietary sodium reduction on the incidence of hypertension, we studied 181 men and women who participated in the Trials of Hypertension Prevention, phase 1, in Baltimore, Md. At baseline (1987 to 1988), subjects were 30 to 54 years old and had a diastolic blood pressure (BP) of 80 to 89 mm Hg and systolic BP <160 mm Hg. They were randomly assigned to one of two 18-month lifestyle modification interventions aimed at either weight loss or dietary sodium reduction or to a usual care control group. At the posttrial follow-up (1994 to 1995), BP was measured by blinded observers who used a random-zero sphygmomanometer. Incident hypertension was defined as systolic BP ≥160 mm Hg and/or diastolic BP ≥90 mm Hg and/or treatment with antihypertensive medication during follow-up. Body weight and urinary sodium were not significantly different among the groups at the posttrial follow-up. After 7 years of follow-up, the incidence of hypertension was 18.9% in the weight loss group and 40.5% in its control group and 22.4% in the sodium reduction group and 32.9% in its control group. In logistic regression analysis adjusted for baseline age, gender, race, physical activity, alcohol consumption, education, body weight, systolic BP, and urinary sodium excretion, the odds of hypertension was reduced by 77% (odds ratio 0.23; 95% confidence interval 0.07 to 0.76; $P=0.02$) in the weight loss group and by 35% (odds ratio 0.65; 95% confidence interval 0.25 to 1.69; $P=0.37$) in the sodium reduction group compared with their control groups. These results indicate that lifestyle modification such as weight loss may be effective in long-term primary prevention of hypertension. (***Hypertension*. 2000;35:544-549.**)

Key Words: diet, sodium-restricted ■ blood pressure ■ hypertension, incidence ■ weight loss

TABLE 2. Change From Baseline in Body Weight, Urinary Sodium Excretion, and Blood Pressure During the 18-Month Intervention in 181 Trials of Hypertension Prevention, Phase I, Participants at the Baltimore Clinical Center

	Active		Control		Active-Control	
	n	Mean±SD	n	Mean±SD	Mean	*P*
Weight loss						
Change in weight, kg	53	−2.4±5.0	42	1.1±3.5	−3.5	<0.001
Change in sodium excretion, mmol/24 h	49	−21.0±72.1	36	−26.3±67.5	−5.2	0.74
Change in SBP, mm Hg	53	−6.9±6.4	42	−1.2±7.6	−5.8	<0.001
Change in DBP, mm Hg	53	−8.6±4.7	42	−5.5±5.9	−3.2	0.005
Sodium reduction						
Change in weight, kg	58	0.6±2.9	70	0.5±3.2	0.2	0.78
Change in sodium excretion, mmol/24 h	49	−53.5±63.3	63	−20.2±65.1	−33.3	0.008
Change in SBP, mm Hg	58	−5.7±6.5	70	−2.4±8.5	−3.3	0.01
Change in DBP, mm Hg	58	−7.2±4.6	70	−5.6±5.9	−1.7	0.08



Comparison of the 7-year cumulative incidence of hypertension between active intervention and control groups for weight loss and sodium reduction interventions.

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EFFECTS ON BLOOD PRESSURE OF REDUCED DIETARY SODIUM AND THE DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET

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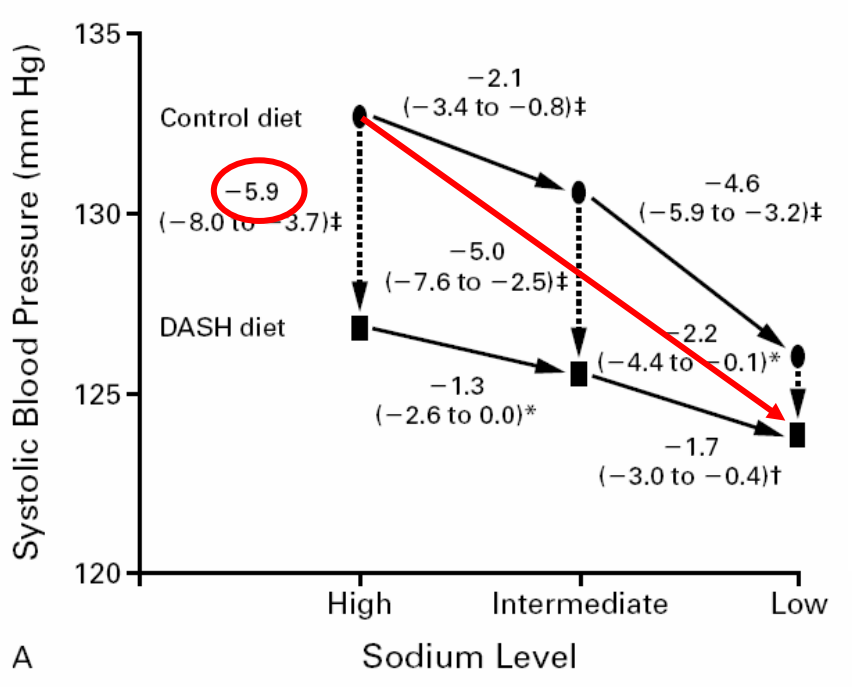
ABSTRACT

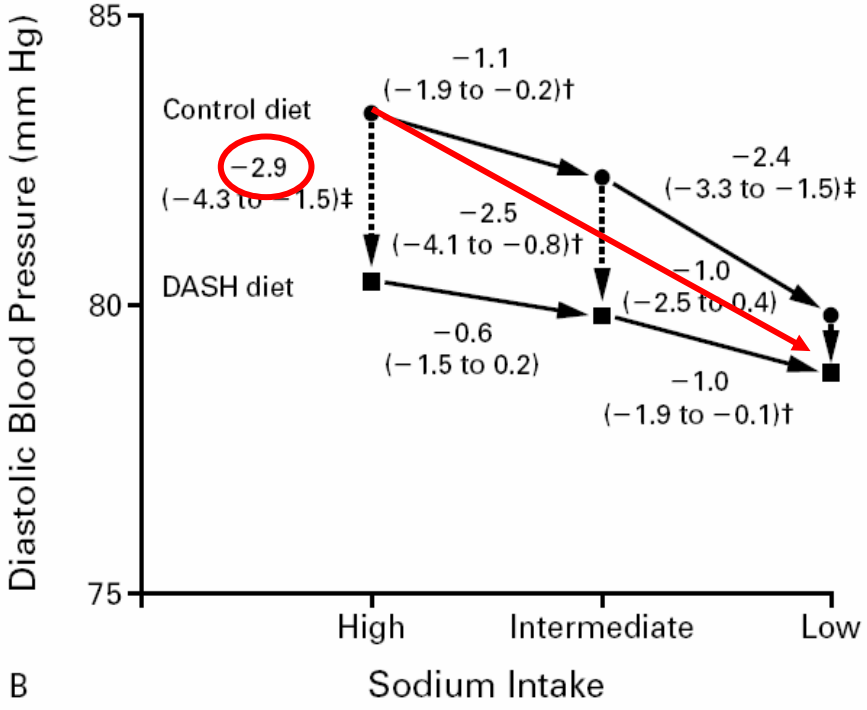
Background The effect of dietary composition on blood pressure is a subject of public health importance. We studied the effect of different levels of dietary sodium, in conjunction with the Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in vegetables, fruits, and low-fat dairy products, in persons with and in those without hypertension.

Methods A total of 412 participants were randomly assigned to eat either a control diet typical of intake in the United States or the DASH diet. Within the assigned diet, participants ate foods with high, intermediate, and low levels of sodium for 30 consecutive days each, in random order.

Results Reducing the sodium intake from the high to the intermediate level reduced the systolic blood pressure by 2.1 mm Hg ($P<0.001$) during the control diet and by 1.3 mm Hg ($P=0.03$) during the DASH diet. Reducing the sodium intake from the intermediate to the low level caused additional reductions of 4.6 mm Hg during the control diet ($P<0.001$) and 1.7 mm Hg during the DASH diet ($P<0.01$). The effects of sodium were observed in participants with and in those without hypertension, blacks and those of other races, and women and men. The DASH diet was associated with a significantly lower systolic blood pressure at each sodium level; and the difference was greater with high sodium levels than with low ones. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mm Hg lower in participants without hypertension, and 11.5 mm Hg lower in participants with hypertension.

Conclusions The reduction of sodium intake to levels below the current recommendation of 100 mmol per day and the DASH diet both lower blood pressure substantially, with greater effects in combination than singly. Long-term health benefits will depend on the ability of people to make long-lasting dietary changes and the increased availability of lower-sodium foods. (N Engl J Med 2001;344:3-10.)


Systolic Blood Pressure (mm Hg)
135
130
125
120
Control diet
−5.9
(−8.0 to −3.7)‡
−2.1
(−3.4 to −0.8)‡
−4.6
(−5.9 to −3.2)‡
−5.0
(−7.6 to −2.5)‡
DASH diet
−2.2
(−4.4 to −0.1)*
−1.3
(−2.6 to 0.0)*
−1.7
(−3.0 to −0.4)†
High
Intermediate
Low
Sodium Level
A


Diastolic Blood Pressure (mm Hg)
85
80
75
Control diet
−2.9
(−4.3 to −1.5)‡
−1.1
(−1.9 to −0.2)†
−2.4
(−3.3 to −1.5)‡
−2.5
(−4.1 to −0.8)†
DASH diet
−1.0
(−2.5 to 0.4)
−0.6
(−1.5 to 0.2)
−1.0
(−1.9 to −0.1)†
High
Intermediate
Low
Sodium Intake
B

Progressive Resistance Exercise and Resting Blood Pressure

A Meta-Analysis of Randomized Controlled Trials

George A. Kelley, Kristi Sharpe Kelley

Abstract—Hypertension is a major public health problem affecting an estimated 43 million civilian, noninstitutionalized adults in the United States (24% of this population). The purpose of this study was to use the meta-analytic approach to examine the effects of progressive resistance exercise on resting systolic and diastolic blood pressure in adult humans. Studies were retrieved via (1) computerized literature searches, (2) cross-referencing from original and review articles, and (3) review of the reference list by 2 experts on exercise and blood pressure. Inclusion criteria were as follows: (1) trials that included a randomized nonexercise control group; (2) progressive resistance exercise as the only intervention; (3) adult humans; (4) journal articles, dissertations, and masters theses published in the English-language literature; (5) studies published and indexed between January 1966 and December 1998; (6) resting systolic and/or diastolic blood pressure assessed; and (7) training studies lasting a minimum of 4 weeks. Across all designs and categories, fixed-effects modeling yielded decreases of ≈2% and 4% for resting systolic and diastolic blood pressure, respectively (mean±SD systolic, −3±3 mm Hg; 95% bootstrap CI, −4 to −1 mm Hg; mean±SD diastolic, −3±2 mm Hg; 95% bootstrap CI, −4 to −1 mm Hg). It was concluded that progressive resistance exercise is efficacious for reducing resting systolic and diastolic blood pressure in adults. However, a need exists for additional studies that limit enrollment to hypertensive subjects as well as analysis of data with an intention-to-treat approach before the effectiveness of progressive resistance exercise as a nonpharmacological intervention can be determined. (***Hypertension*. 2000;35:838-843.**)

Key Words: exercise ■ blood pressure ■ meta-analysis

Effects of Alcohol Reduction on Blood Pressure

A Meta-Analysis of Randomized Controlled Trials

Xue Xin, Jiang He, Maria G. Frontini, Lorraine G. Ogden, Oaitse I. Motsamai, Paul K. Whelton

Abstract—Alcohol drinking has been associated with increased blood pressure in epidemiological studies. We conducted a meta-analysis of randomized controlled trials to assess the effects of alcohol reduction on blood pressure. We included 15 randomized control trials (total of 2234 participants) published before June 1999 in which alcohol reduction was the only intervention difference between active and control treatment groups. Using a standard protocol, information on sample size, participant characteristics, study design, intervention methods, duration, and treatment results was abstracted independently by 3 investigators. By means of a fixed-effects model, findings from individual trials were pooled after results for each trial were weighted by the inverse of its variance. Overall, alcohol reduction was associated with a significant reduction in mean (95% confidence interval) systolic and diastolic blood pressures of −3.31 mm Hg (−2.52 to −4.10 mm Hg) and −2.04 mm Hg (−1.49 to −2.58 mm Hg), respectively. A dose-response relationship was observed between mean percentage of alcohol reduction and mean blood pressure reduction. Effects of intervention were enhanced in those with higher baseline blood pressure. Our study suggests that alcohol reduction should be recommended as an important component of lifestyle modification for the prevention and treatment of hypertension among heavy drinkers. (***Hypertension***. **2001;38:1112-1117.**)

Key Words: alcohol ■ blood pressure ■ meta-analysis ■ clinical trials

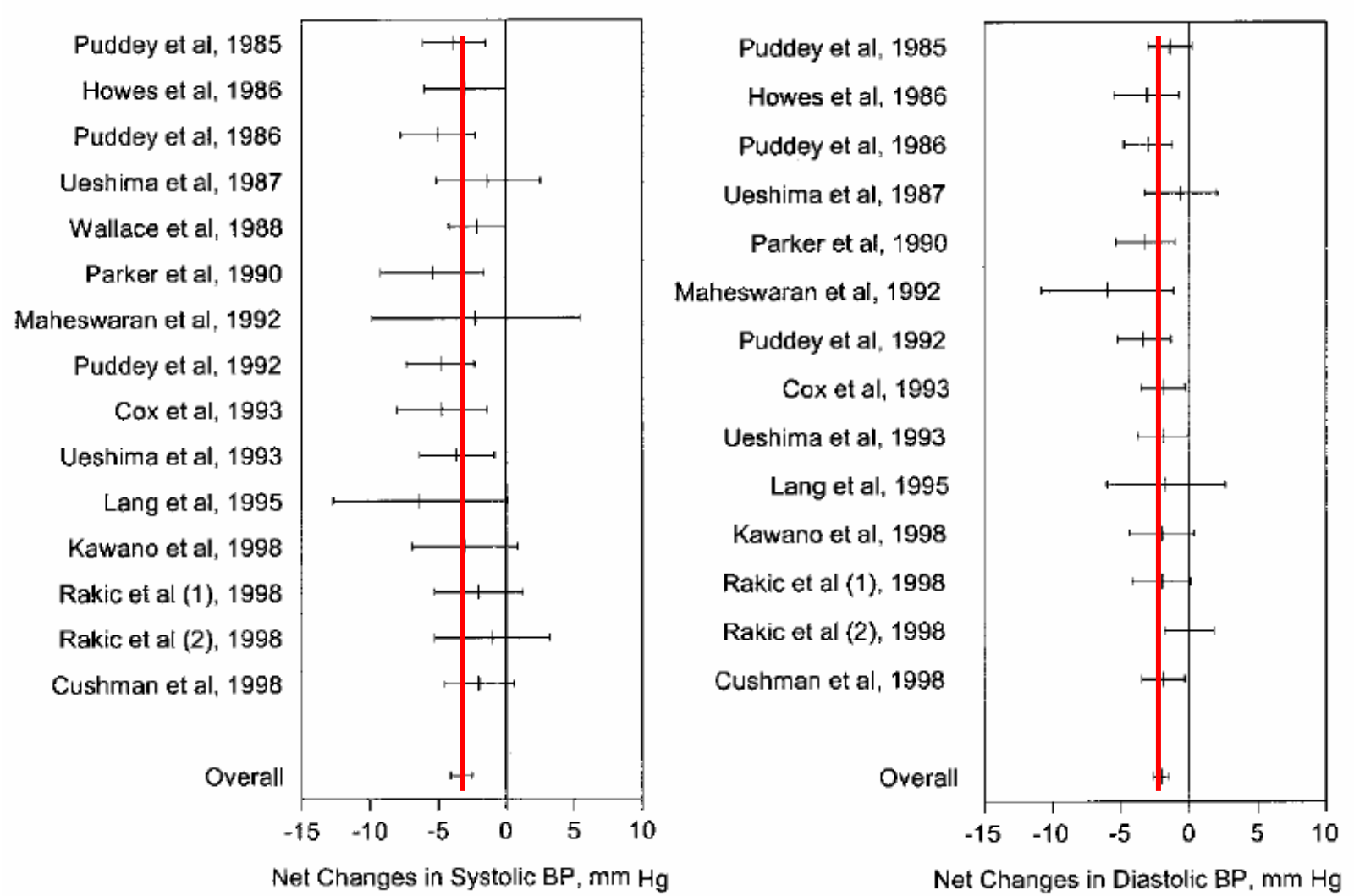


Figure 1. Average net change in systolic BP (left) and diastolic BP (right) and corresponding 95% CIs related to **alcohol reduction** intervention in 15 randomized controlled trials. Net change was calculated as the difference of the baseline minus follow-up levels of BP for the intervention and control groups (parallel trials) or the difference in BP levels at the end of the intervention and control treatment periods (crossover trials). The overall effect represents a pooled estimate obtained by summing the average net change for each trial, weighted by the inverse of its variance. Data on diastolic BP were not available in 1 trial.1

Lifestyle modification

Table 5. Lifestyle modifications to manage hypertension*†

Modification	Recommendation	Approximate SBP Reduction (Range)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2).	5–20 mmHg/10 kg weight loss[23,24]
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[25,26]
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[25–27]
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[28,29]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; 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[30]

DASH, Dietary Approaches to Stop Hypertension.

* For overall cardiovascular risk reduction, stop smoking.

† The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

Antihypertensive drugs

Antihypertensive drugs

A

Table 6. Oral antihypertensive drugs* (CONTINUED)

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
ACE inhibitors	benazepril (Lotensin†)	10–40 (1–2)
	captopril (Capoten†)	25–100 (2)
	enalapril (Vasotec†)	2.5–40 (1–2)
	fosinopril (Monopril)	10–40 (1)
	lisinopril (Prinivil, Zestril†)	10–40 (1)
	moexipril (Univasc)	7.5–30 (1)
	perindopril (Aceon)	4–8 (1–2)
	quinapril (Accupril)	10–40 (1)
	ramipril (Altace)	2.5–20 (1)
	trandolapril (Mavik)	1–4 (1)
Angiotensin II antagonists	candesartan (Atacand)	8–32 (1)
	eprosartan (Tevetan)	400–800 (1–2)
	irbesartan (Avapro)	150–300 (1)
	losartan (Cozaar)	25–100 (1–2)
	olmesartan (Benicar)	20–40 (1)
	telmisartan (Micardis)	20–80 (1)
	valsartan (Diovan)	80–320 (1)

Antihypertensive drugs

B

Table 6. Oral antihypertensive drugs*

Class	Drug (Trade Name)	Usual dose range in mg/day (Daily Frequency)
Beta-blockers	atenolol (Tenormin†)	25–100 (1)
	betaxolol (Kerlone†)	5–20 (1)
	bisoprolol (Zebeta†)	2.5–10 (1)
	metoprolol (Lopressor†)	50–100 (1–2)
	metoprolol extended release (Toprol XL)	50–100 (1)
	nadolol (Corgard†)	40–120 (1)
	propranolol (Inderal†)	40–160 (2)
	propranolol long-acting (Inderal LA†)	60–180 (1)
	timolol (Blocadren†)	20–40 (2)
Beta-blockers with intrinsic sympathomimetic activity	acebutolol (Sectral†)	200–800 (2)
	penbutolol (Levatol)	10–40 (1)
	pindolol (generic)	10–40 (2)
Combined alpha- and beta-blockers	carvedilol (Coreg)	12.5–50 (2)
	labetalol (Normodyne, Trandate†)	200–800 (2)

Antihypertensive drugs

C

Table 6. Oral antihypertensive drugs*

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
Calcium channel blockers—non-Dihydropyridines	diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac†)	180–420 (1)
	diltiazem extended release (Cardizem LA)	120–540 (1)
	verapamil immediate release (Calan, Isoptin†)	80–320 (2)
	verapamil long acting (Calan SR, Isoptin SR†)	120–360 (1–2)
	verapamil—Coer (Covera HS, Verelan PM)	120–360 (1)
Calcium channel blockers—Dihydropyridines	amlodipine (Norvasc)	2.5–10 (1)
	felodipine (Plendil)	2.5–20 (1)
	isradipine (Dynacirc CR)	2.5–10 (2)
	nicardipine sustained release (Cardene SR)	60–120 (2)
	nifedipine long-acting (Adalat CC, Procardia XL)	30–60 (1)
	nisoldipine (Sular)	10–40 (1)

Antihypertensive drugs

D

Table 6. Oral antihypertensive drugs*

Class	Drug (Trade Name)	Usual dose range in mg/day (Daily Frequency)
Thiazide diuretics	chlorothiazide (Diuril)	125–500 (1)
	chlorthalidone (generic)	12.5–25 (1)
	hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5–50 (1)
	polythiazide (Renese)	2–4 (1)
	indapamide (Lozol†)	1.25–2.5 (1)
	metolazone (Mykrox)	0.5–1.0 (1)
	metolazone (Zaroxolyn)	2.5–5 (1)
Loop diuretics	bumetanide (Bumex†)	0.5–2 (2)
	furosemide (Lasix†)	20–80 (2)
	torsemide (Demadex†)	2.5–10 (1)
Potassium-sparing diuretics	amiloride (Midamor†)	5–10 (1–2)
	triamterene (Dyrenium)	50–100 (1–2)
Aldosterone receptor blockers	eplerenone (Inspra)	50–100 (1–2)
	spironolactone (Aldactone†)	25–50 (1–2)

Antihypertensive drugs

Table 6. Oral antihypertensive drugs* (CONTINUED)

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
Alpha$_1$-blockers	doxazosin (Cardura)	1–16 (1)
	prazosin (Minipress†)	2–20 (2–3)
	terazosin (Hytrin)	1–20 (1–2)
Central alpha$_2$-agonists and other centrally acting drugs	clonidine (Catapres†)	0.1–0.8 (2)
	clonidine patch (Catapres-TTS)	0.1–0.3 (1wkly)
	methyldopa (Aldomet†)	250–1,000 (2)
	reserpine (generic)	0.05‡–0.25 (1)
	guanfacine (generic)	0.5–2 (1)
Direct vasodilators	hydralazine (Apresoline†)	25–100 (2)
	minoxidil (Loniten†)	2.5–80 (1–2)

* These dosages may vary from those listed in the "Physicians' Desk Reference."[38]

† Are now or will soon become available in generic preparations.

‡ A 0.1 mg dose may be given every other day to achieve this dosage.

Antihypertensive drugs

Table 7. Combination drugs for hypertension

Combination Type*	Fixed-Dose Combination, mg†	Trade Name
ACEIs and CCBs	Amlodipine/benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20) Enalapril maleate/felodipine (5/5) Trandolapril/verapamil (2/180, 1/240, 2/240, 4/240)	Lotrel Lexxel Tarka
ACEIs and diuretics	Benazepril/hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25) Captopril/hydrochlorothiazide (25/15, 25/25, 50/15, 50/25) Enalapril maleate/hydrochlorothiazide (5/12.5, 10/25) Lisinopril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25) Moexipril HCl/hydrochlorothiazide (7.5/12.5, 15/25) Quinapril HCl/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Lotensin HCT Capozide Vaseretic Prinzide Uniretic Accuretic
ARBs and diuretics	Candesartan cilexetil/hydrochlorothiazide (16/12.5, 32/12.5) Eprosartan mesylate/hydrochlorothiazide (600/12.5, 600/25) Irbesartan/hydrochlorothiazide (150/12.5, 300/12.5) Losartan potassium/hydrochlorothiazide (50/12.5, 100/25) Telmisartan/hydrochlorothiazide (40/12.5, 80/12.5) Valsartan/hydrochlorothiazide (80/12.5, 160/12.5)	Atacand HCT Teveten/HCT Avalide Hyzaar Micardis/HCT Diovan/HCT
BBs and diuretics	Atenolol/chlorthalidone (50/25, 100/25) Bisoprolol fumarate/hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25) Propranolol LA/hydrochlorothiazide (40/25, 80/25) Metoprolol tartrate/hydrochlorothiazide (50/25, 100/25) Nadolol/bendrofluthiazide (40/5, 80/5) Timolol maleate/hydrochlorothiazide (10/25)	Tenoretic Ziac Inderide Lopressor HCT Corzide Timolide
Centrally acting drug and diuretic	Methyldopa/hydrochlorothiazide (250/15, 250/25, 500/30, 500/50) Reserpine/chlorothiazide (0.125/250, 0.25/500) Reserpine/hydrochlorothiazide (0.125/25, 0.125/50)	Aldoril Diupres Hydropres
Diuretic and diuretic	Amiloride HCl/hydrochlorothiazide (5/50) Spironolactone/hydrochlorothiazide (25/25, 50/50) Triamterene/hydrochlorothiazide (37.5/25, 50/25, 75/50)	Moduretic Aldactone Dyazide, Maxzide

* Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

† Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

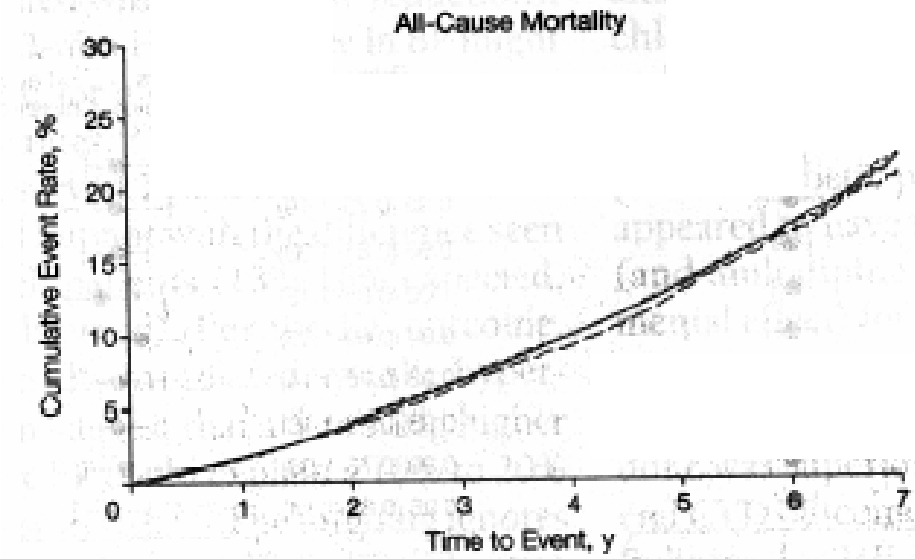
OBJECTIVE: To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic.

DESIGN: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002. SETTING AND PARTICIPANTS: A total of **33 357 participants** aged 55 years or older with hypertension and at least 1 other CHD risk factor from 623 North American centers.

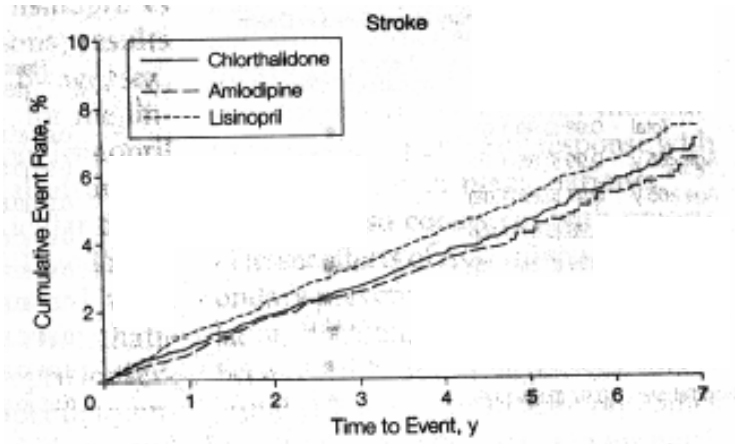
INTERVENTIONS: Participants were randomly assigned to receive **chlorthalidone**, 12.5 to 25 mg/d (n = 15 255); **amlodipine**, 2.5 to 10 mg/d (n = 9048); or **lisinopril**, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 years. MAIN OUTCOME MEASURES: The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure [HF], and peripheral arterial disease).

RESULTS: Mean follow-up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI, 0.91-1.08) for lisinopril (6-year rate, 11.4%). Likewise, all-cause mortality did not differ between groups. Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, P =.03) and lisinopril (2 mm Hg, P<.001) groups compared with chlorthalidone, and 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, P<.001). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30); and HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31).

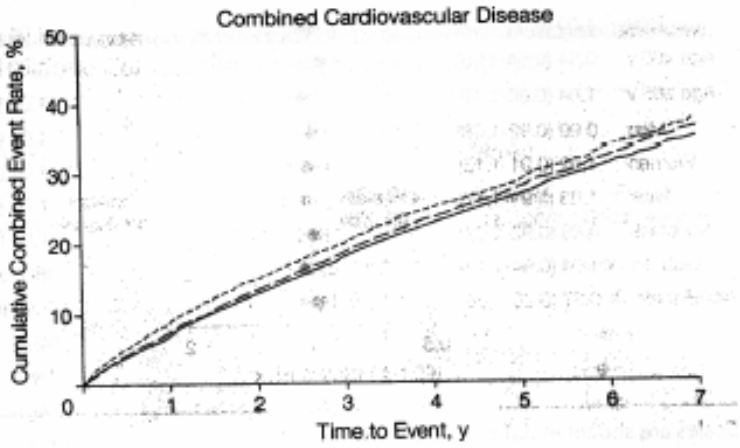
CONCLUSION: Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.



No. at Risk								
Chlorthalidone	15255	14933	14564	14077	12480	7185	3523	426
Amlodipine	9048	8847	8654	8391	7442	4312	2101	217
Lisinopril	9054	8853	8612	8318	7382	4304	2121	144

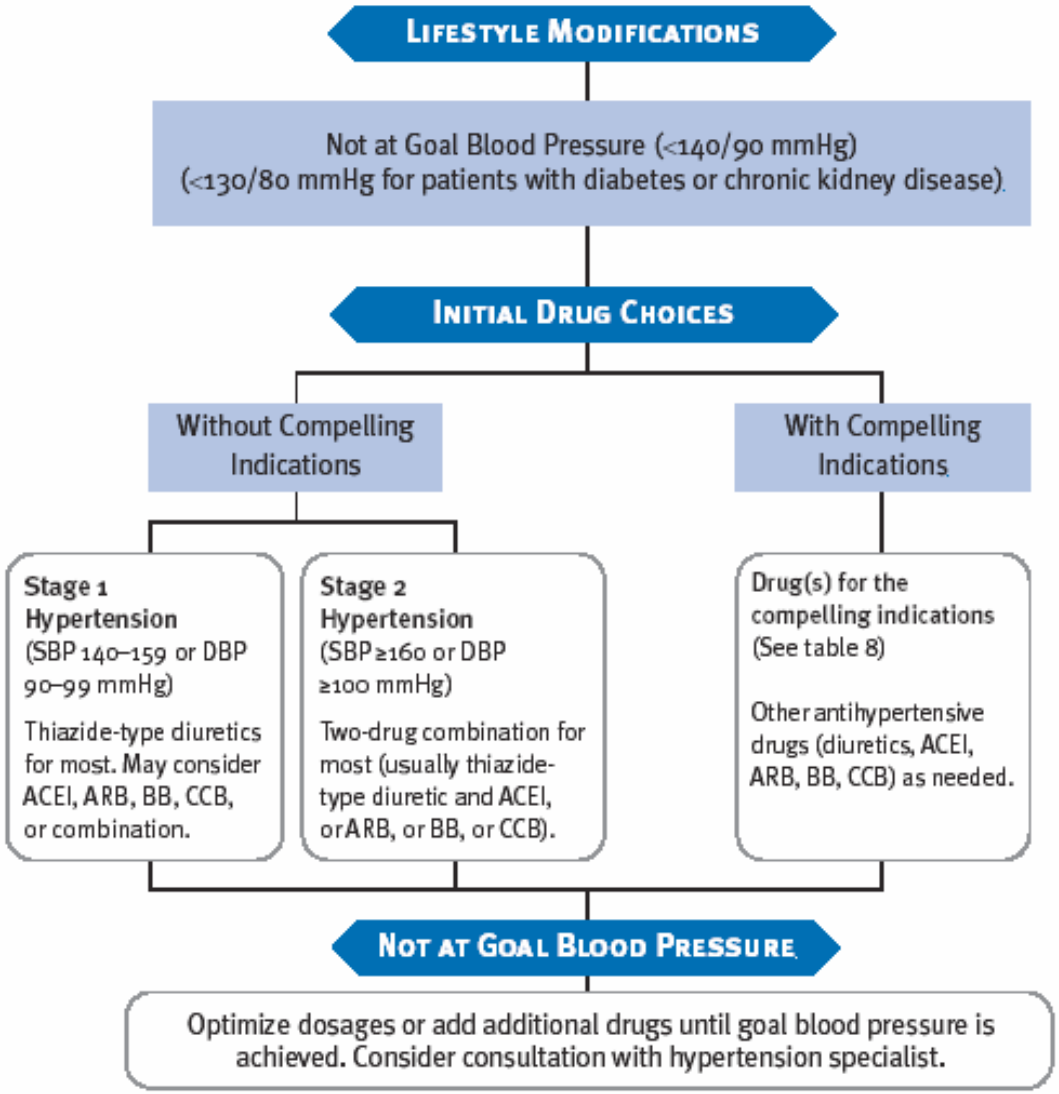


15255	14515	13934	13309	11570	6385	3217	567
9048	8617	8271	7949	6937	3845	1813	506
9054	8543	8172	7784	6765	3891	1828	949



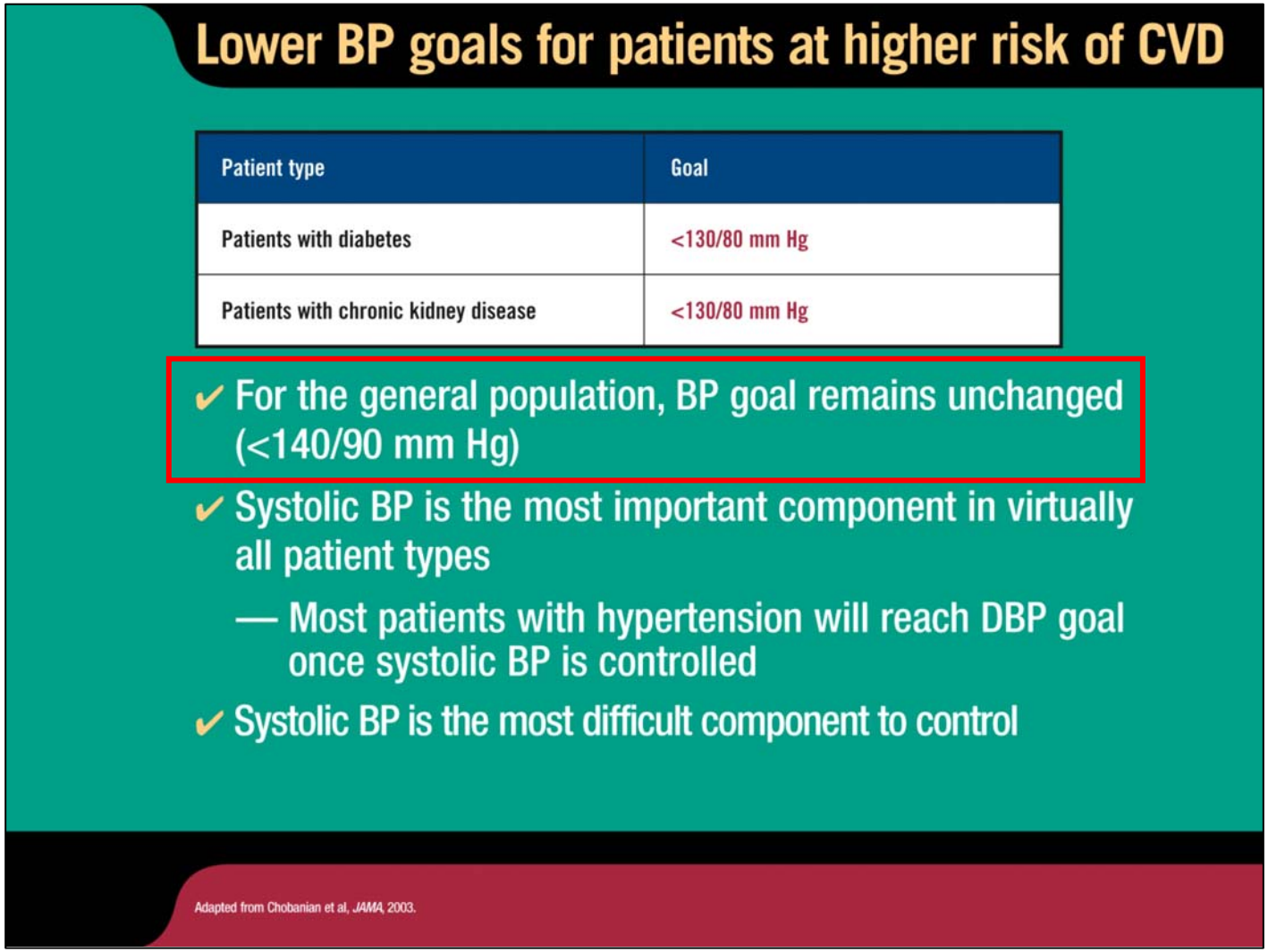
15255	13752	12594	11517	9643	5167	2362	288
9048	8118	7451	6837	5724	3049	1411	153
9054	7962	7259	6631	5560	3011	1375	139

Figure 1. Algorithm for treatment of hypertension

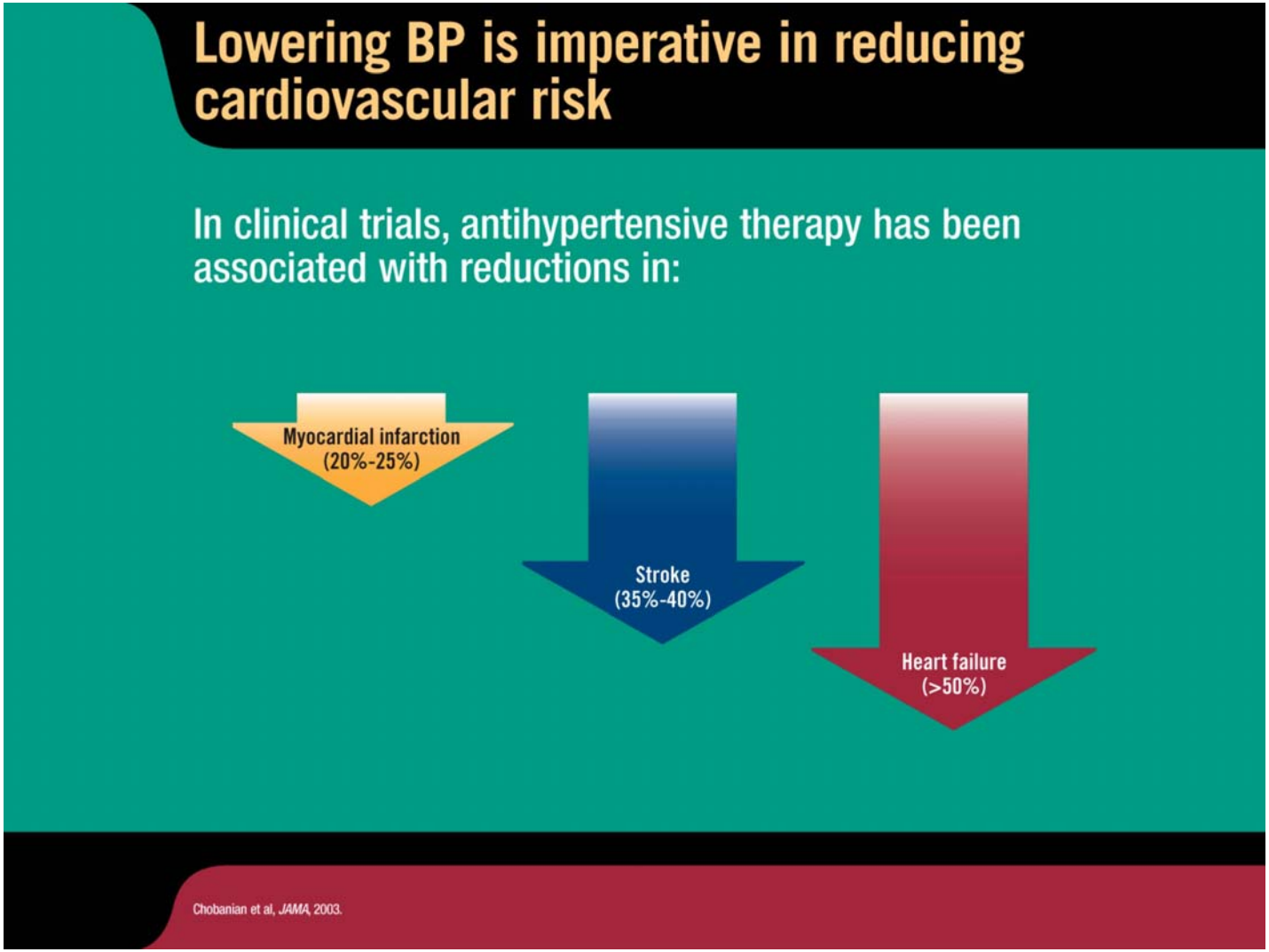


DBP, diastolic blood pressure; SBP, systolic blood pressure.
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

Goal of blood pressure control



Benefit of blood pressure control



BLOOD PRESSURE AND END-STAGE RENAL DISEASE IN MEN

MICHAEL J. KLAG, M.D., M.P.H., PAUL K. WHELTON, M.D., BRYAN L. RANDALL, M.S., JAMES D. NEATON, PH.D., FREDERICK L. BRANCATI, M.D., M.H.S., CHARLES E. FORD, PH.D., NEIL B. SHULMAN, M.D., AND JEREMIAH STAMLER, M.D.

Abstract *Background.* End-stage renal disease in the United States creates a large burden for both individuals and society as a whole. Efforts to prevent the condition require an understanding of modifiable risk factors.

Methods. We assessed the development of end-stage renal disease through 1990 in 332,544 men, 35 to 57 years of age, who were screened between 1973 and 1975 for entry into the Multiple Risk Factor Intervention Trial (MRFIT). We used data from the national registry for treated end-stage renal disease of the Health Care Financing Administration and from records on death from renal disease from the National Death Index and the Social Security Administration.

Results. During an average of 16 years of follow-up, 814 subjects either died of end-stage renal disease or were treated for that condition (15.6 cases per 100,000 person-years of observation). A strong, graded relation between both systolic and diastolic blood pressure and end-stage renal disease was identified, independent of associations between the disease and age, race, income, use of medication for diabetes mellitus, history of myocardial infarction, serum cholesterol concentration, and cigarette smoking. As compared with men with an optimal level of blood pressure (systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg), the relative risk of end-stage renal disease for those with stage 4 hypertension (systolic pressure ≥210 mm Hg or diastolic pressure ≥120 mm Hg) was 22.1 ($P<0.001$). These relations were not due to end-stage renal disease that occurred soon after screening and, in the 12,866 screened men who entered the MRFIT study, were not changed by taking into account the base-line serum creatinine concentration and urinary protein excretion. The estimated risk of end-stage renal disease associated with elevations of systolic pressure was greater than that linked with elevations of diastolic pressure when both variables were considered together.

Conclusions. Elevations of blood pressure are a strong independent risk factor for end-stage renal disease; interventions to prevent the disease need to emphasize the prevention and control of both high-normal and high blood pressure. (N Engl J Med 1996;334:13-8.)

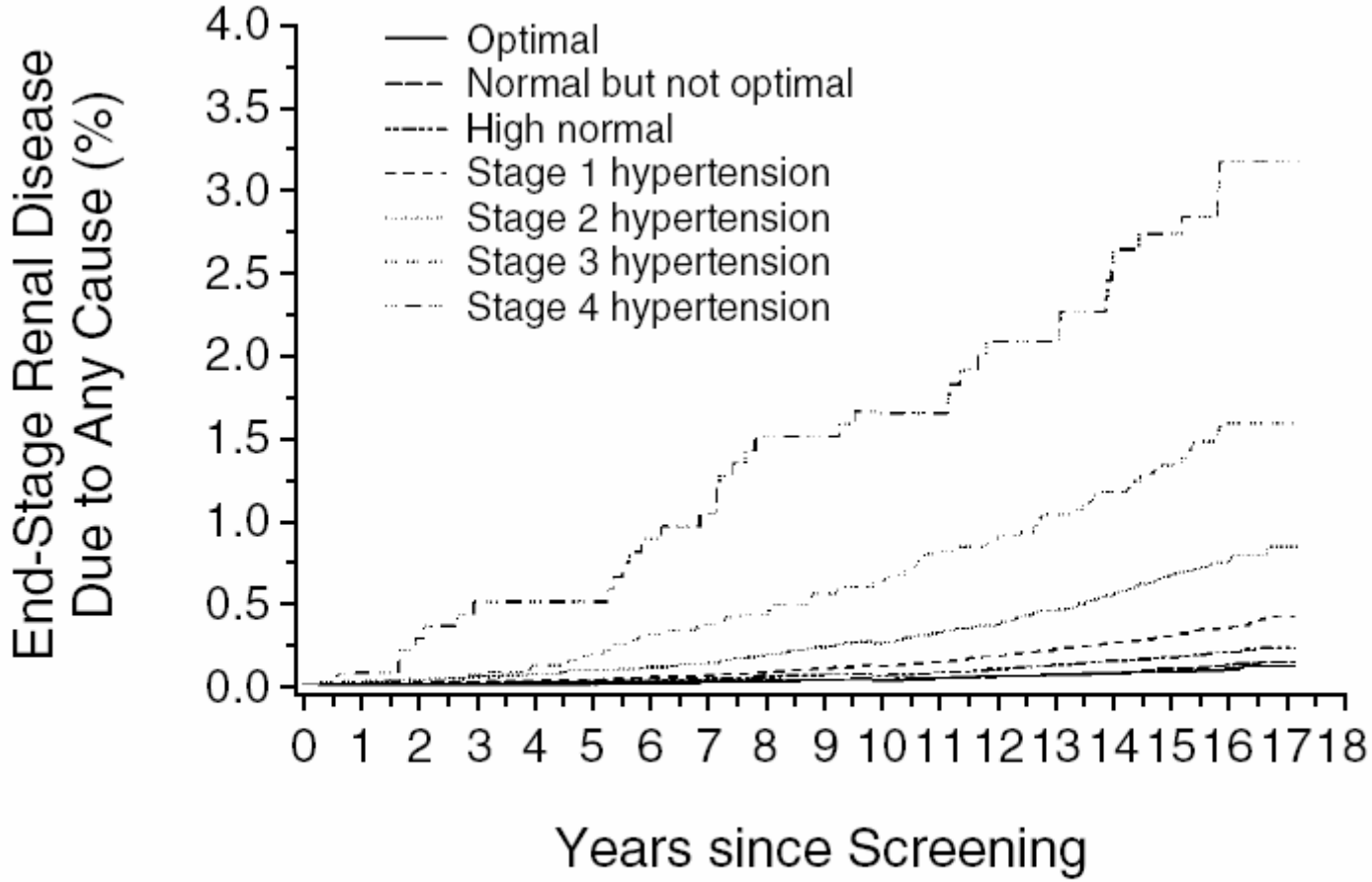


Figure 1. Cumulative Incidence of End-Stage Renal Disease Due to Any Cause, According to Blood-Pressure Category in 332,544 Men Screened for MRFIT.

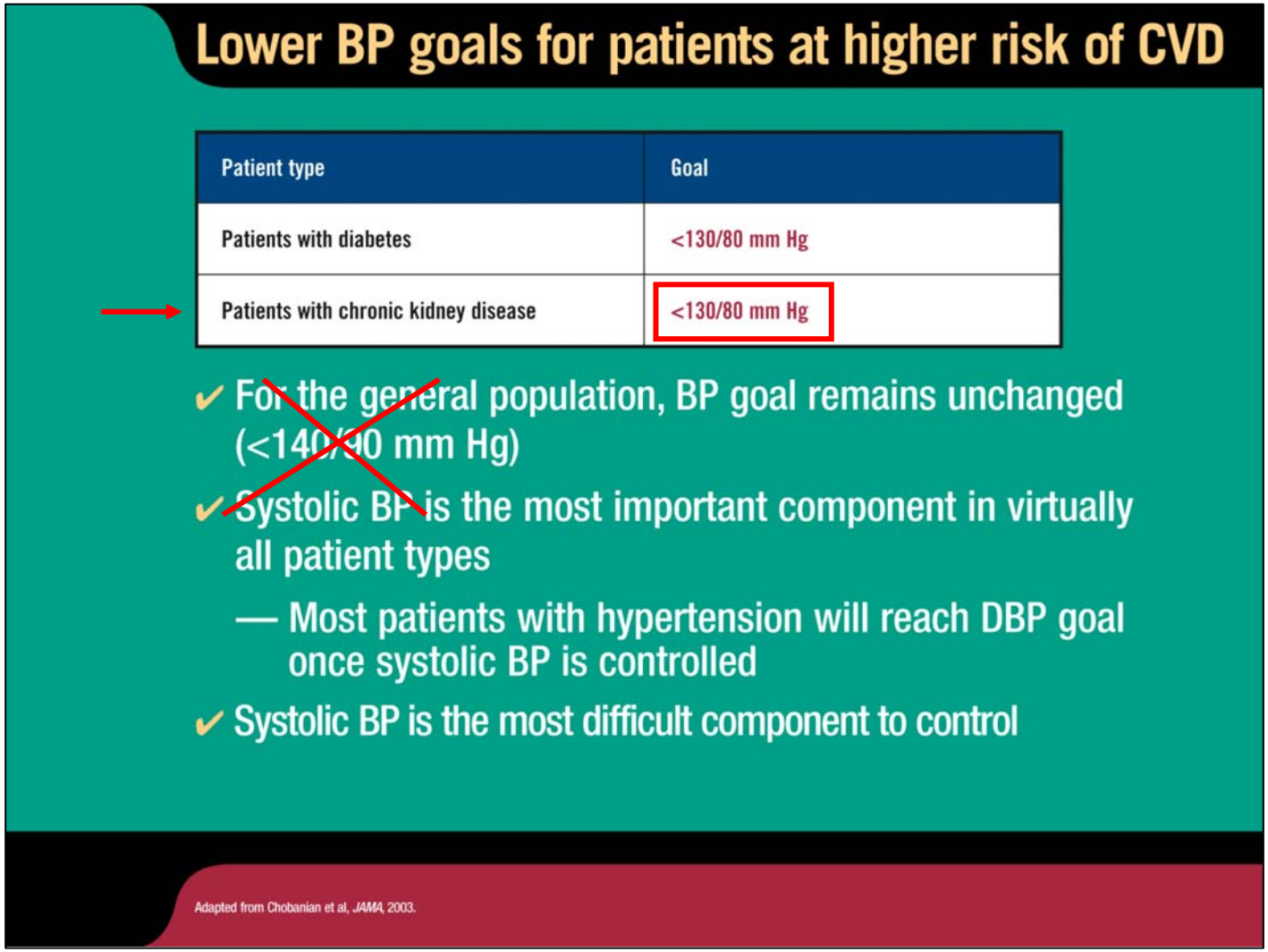
Principle problems of CKD patients

- **UREMIC SYMPTOMS CAUSED BY THE ACCUMULATION OF UNEXCRETED METABOLIC PRODUCTS**
- **PROGRESSIVE LOSS OF KIDNEY FUNCTION**
- **PROGRESSIVE CARDIOVASCULAR DISEASE**

Secondary causes of progression in CKD patients

- **SYSTEMIC HYPERTENSION**
- **INTRAGLOMERULAR HYPERFILTRATION AND HYPERTROPHY**
- **PROTEINUREA**
- **METABOLIC ACIDOSIS**
- **PHOSPHATE RETENTION INDUCE SECONDARY HYPERPARATHYROIDISM**
- **DYSLIPIDEMIA**
- **UREMIC TOXINS**

Goal of blood pressure control



Annals of Internal Medicine | ARTICLE

Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease

A Meta-Analysis of Patient-Level Data

Tazeen H. Jafar, MD, MPH; Christopher H. Schmid, PhD; Marcia Landa, MA; Ioannis Giatras, MD; Robert Toto, MD; Giuseppe Remuzzi, MD; Giuseppe Maschio, MD; Barry M. Brenner, MD; Annelise Kamper, MD; Pietro Zucchelli, MD; Gavin Becker, MD; Andres Himmelmann, MD; Kym Bannister, MD; Paul Landais, MD; Shahnaz Shahinfar, MD; Paul E. de Jong, MD, PhD; Dick de Zeeuw, MD; Joseph Lau, MD; and Andrew S. Levey, MD, for the ACE Inhibition in Progressive Renal Disease Study Group*

Purpose: To examine the efficacy of ACE inhibitors for treatment of nondiabetic renal disease.

Data Sources: 11 randomized, controlled trials comparing the efficacy of antihypertensive regimens including ACE inhibitors to the efficacy of regimens without ACE inhibitors in predominantly nondiabetic renal disease.

Study Selection: Studies were identified by searching the MEDLINE database for English-language studies evaluating the effects of ACE inhibitors on renal disease in humans between May 1977 (when ACE inhibitors were approved for trials in humans) and September 1997.

Data Extraction: Data on 1860 nondiabetic patients were analyzed.

Data Synthesis: Mean duration of follow-up was 2.2 years. Patients in the ACE inhibitor group had a greater mean decrease in systolic and diastolic blood pressure (4.5 mm Hg [95% CI, 3.0 to 6.1 mm Hg]) and 2.3 mm Hg [CI, 1.4 to 3.2 mm Hg], respectively) and urinary protein excretion (0.46 g/d [CI, 0.33 to 0.59 g/d]). After adjustment for patient and study characteristics at baseline and changes in systolic blood pressure and urinary protein excretion during follow-up, relative risks in the ACE inhibitor group were 0.69 (CI, 0.51 to 0.94) for end-stage renal disease and 0.70 (CI, 0.55 to 0.88) for the combined outcome of doubling of the baseline serum creatinine concentration or end-stage renal disease. Patients with greater urinary protein excretion at baseline benefited more from ACE inhibitor therapy ($P = 0.03$ and $P = 0.001$, respectively), but the data were inconclusive as to whether the benefit extended to patients with baseline urinary protein excretion less than 0.5 g/d.

Conclusion: Antihypertensive regimens that include ACE inhibitors are more effective than regimens without ACE inhibitors in slowing the progression of nondiabetic renal disease. The beneficial effect of ACE inhibitors is mediated by factors in addition to decreasing blood pressure and urinary protein excretion and is greater in patients with proteinuria. Angiotensin-converting inhibitors are indicated for treatment of nondiabetic patients with chronic renal disease and proteinuria and, possibly, those without proteinuria.

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For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 138-139.

*For other members of the ACE Inhibition in Progressive Renal Disease Study Group, see Appendix 1.

Table 2. Comparison of Randomized Groups in the Pooled Analysis*

Variable	All Patients	ACE Inhibitor Group	Control Group	*P* Value†
Patients, *n*	1860	941	919	
Baseline characteristics				
Men, *n* (%)	1215 (65)	615 (65)	600 (65)	>0.2
Nonblack ethnicity, *n* (%)	1746 (94)	881 (94)	865 (94)	>0.2
Cause of renal disease, *n* (%)				>0.2
Glomerular disease	611 (33)	310 (33)	301 (33)	
Polycystic kidney disease	142 (8)	68 (7)	74 (8)	
Hypertensive nephrosclerosis	614 (33)	305 (32)	309 (34)	
Tubulointerstitial disease	219 (12)	113 (12)	106 (12)	
Other	274 (15)	145 (15)	129 (14)	
Hypertension, *n* (%)	1708 (92)	862 (92)	846 (92)	>0.2
Age, *y*	52 ± 13	52 ± 13	52 ± 13	>0.2
Serum creatinine concentration, *μmol/L (mg/dL)*	203 ± 106 (2.3 ± 1.2)	203 ± 106 (2.3 ± 1.2)	203 ± 106 (2.3 ± 1.2)	>0.2
Systolic blood pressure, *mm Hg*	148 ± 22	148 ± 21	149 ± 22	>0.2
Diastolic blood pressure, *mm Hg*	91 ± 11	90 ± 11	91 ± 11	>0.2
Urinary protein excretion, *g/d*	1.8 ± 2.3	1.8 ± 2.5	1.8 ± 2.1	>0.2
Follow-up characteristics				
Systolic blood pressure, *mm Hg*	142 ± 17	139 ± 16	144 ± 16	<0.001
Diastolic blood pressure, *mm Hg*	86 ± 8	86 ± 7	87 ± 8	<0.001
Urine protein excretion, *g/d*	1.6 ± 1.8	1.4 ± 1.8	1.7 ± 2.0	<0.001
Outcomes, *n* (%)				
ESRD	176 (9.5)	70 (7.4)	106 (11.6)	0.002
Doubling of baseline serum creatinine concentration	223 (12.1)	89 (9.5)	134 (14.7)	0.001
Doubling of baseline serum creatinine concentration or ESRD	311 (16.8)	124 (13.2)	187 (20.5)	0.001
Death	31 (1.6)	20 (2.1)	11 (1.2)	0.12
Death or ESRD	207 (11.1)	90 (9.6)	117 (12.8)	0.03
Withdrawals, *n* (%)	387 (20.8)	207 (22.0)	180 (19.6)	0.2
ACE inhibitor side effects‡	55 (3.0)	40 (4.3)	15 (1.6)	0.001
Nonfatal cardiovascular disease§	36 (1.9)	18 (1.9)	18 (2.0)	>0.2
Other nonfatal event‖	90 (4.8)	55 (5.8)	35 (3.8)	0.04
Lost to follow-up or unknown	206 (11.1)	94 (10.0)	112 (12.2)	0.13
Completed study, *n* (%)	1131 (60.8)	590 (62.7)	541 (58.9)	0.15
Duration of follow-up, *y*	2.2 ± 1.1	2.2 ± 1.1	2.2 ± 1.1	>0.2

* Values are given as the number (percentage) of patients or the mean ± SD. ACE = angiotension-converting enzyme inhibitor; ESRD = end-stage renal disease.
† Comparison of variables between randomized groups was done by using the *t*-test for continuous variables and chi-square test for discrete variables.
‡ Nonfatal angioedema, hyperkalemia, cough, acute renal failure, and hypotension.
§ Myocardial infarction, congestive heart failure, stroke, transient ischemic attacks, and claudication.
‖ Malignant disease, pneumonia, cellulitis, headache, gastrointestinal disturbances, and other events.

Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial

Naoyuki Nakao, Ashio Yoshimura, Hiroyuki Morita, Masyuki Takada, Tsuguo Kayano, Terukuni Ideura

Summary

Background Present angiotensin-converting-enzyme inhibitor treatment fails to prevent progression of non-diabetic renal disease. We aimed to assess the efficacy and safety of combined treatment of angiotensin-converting-enzyme inhibitor and angiotensin-II receptor blocker, and monotherapy of each drug at its maximum dose, in patients with non-diabetic renal disease.

Methods 336 patients with non-diabetic renal disease were enrolled from one renal outpatient department in Japan. After screening and an 18-week run-in period, 263 patients were randomly assigned angiotensin-II receptor blocker (losartan, 100 mg daily), angiotensin-converting-enzyme inhibitor (trandolapril, 3 mg daily), or a combination of both drugs at equivalent doses. Survival analysis was done to compare the effects of each regimen on the combined primary endpoint of time to doubling of serum creatinine concentration or end-stage renal disease. Analysis was by intention to treat.

Findings Seven patients discontinued or were otherwise lost to follow-up. Ten (11%) of 85 patients on combination treatment reached the combined primary endpoint compared with 20 (23%) of 85 on trandolapril alone (hazard ratio 0·38, 95% CI 0·18–0·63, p=0·018) and 20 (23%) of 86 on losartan alone (0·40, 0·17–0·69, p=0·016). Covariates affecting renal survival were combination treatment (hazard ratio 0·38, 95% CI 0·18–0·63, p=0·011), age (1·30, 1·03–2·29, p=0·009), baseline renal function (1·80, 1·02–2·99, p=0·021), change in daily urinary protein excretion rate (0·58, 0·24–0·88, p=0·022), use of diuretics (0·80, 0·30–0·94, p=0·043), and antiproteinuric response to trandolapril (0·81, 0·21–0·91, p=0·039). Frequency of side-effects with combination treatment was the same as with trandolapril alone.

Interpretation Combination treatment safely retards progression of non-diabetic renal disease compared with monotherapy. However, since some patients reached the combined primary endpoint on combined treatment, further strategies for complete management of progressive non-diabetic renal disease need to be researched.

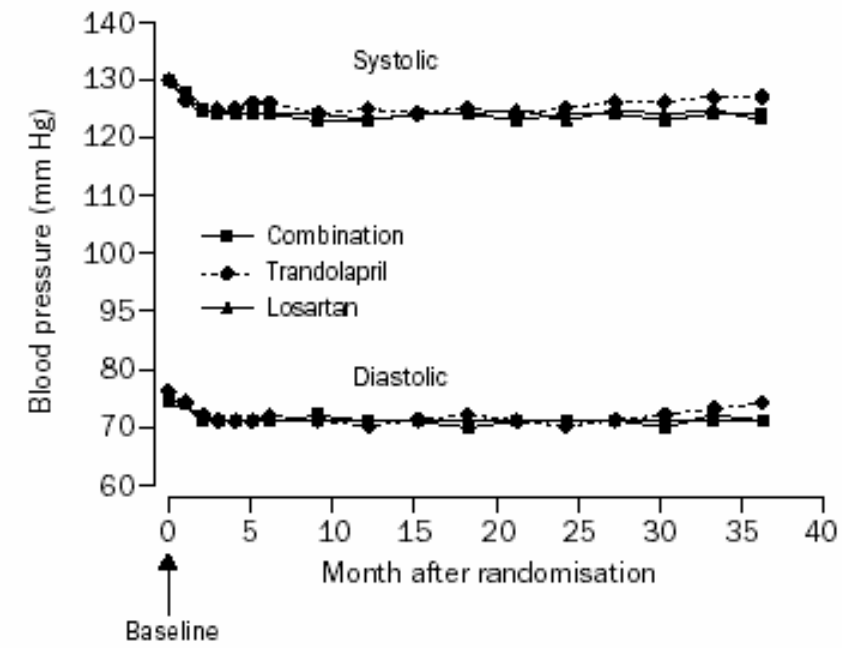


Figure 3: **Blood pressure by treatment group**

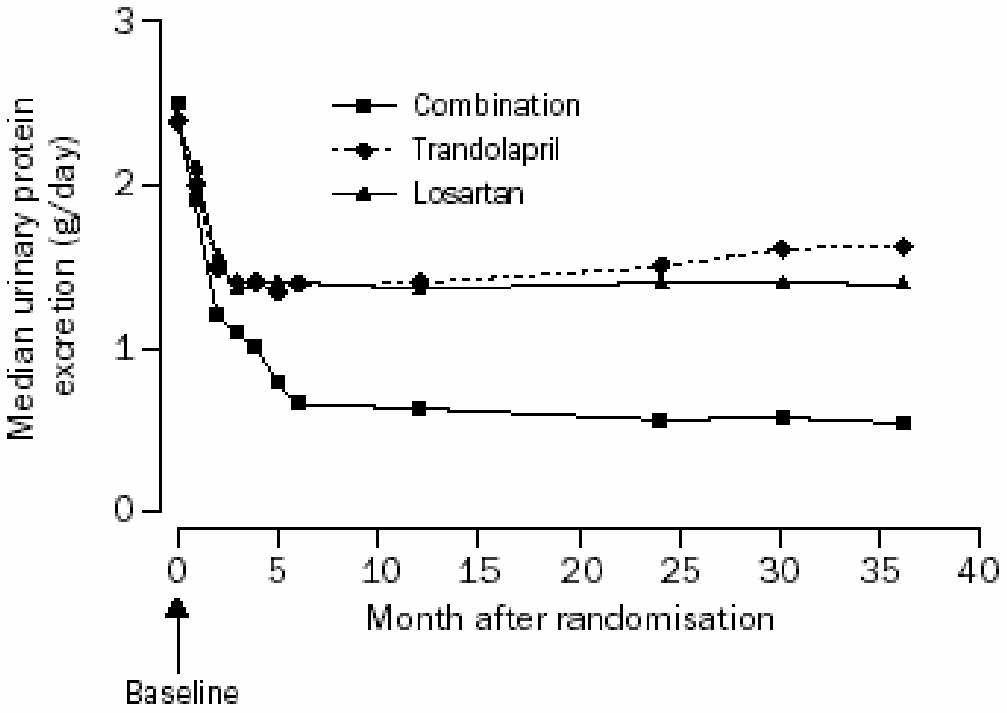


Figure 4: **Median urinary protein excretion by treatment group**

A Five-year Comparison of the Renal Protective Effects of Angiotensin- Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients with Non-Diabetic Nephropathy

Junko Shoda, Yoshihiko Kanno and Hiromichi Suzuki

Abstract

Objective Evidence suggests that the effectiveness of angiotensin-converting enzyme (ACE) inhibition diminishes with time, resulting in increasing angiotensin II levels, the action of which can be inhibited by the addition of an angiotensin receptor blocker (ARB). In the present study, the renal protective effects of ACE inhibitors and ARBs were compared over a five-year period in a prospective, randomized, open-blind study in 68 non-diabetic Japanese patients with elevated serum creatinine levels.

Patients and Methods Japanese patients with renal insufficiency were randomly assigned to receive either an ACE inhibitor (benazepril 1.25 to 5 mg daily or trandolapril 0.5 to 4 mg daily) or ARB (candesartan 2 to 8 mg daily or losartan 25 to 100 mg daily) at the Kidney Disease Center at Saitama Medical School Hospital. The primary study endpoint was a change in glomerular filtration rate (GFR) between the baseline value and the last available value obtained during the five-year treatment period, as estimated by the Cockcraft-Gault equation. Secondary endpoints included the annual changes in GFR, serum creatinine level, urinary protein excretion, and blood pressure, as well as the rate of development of end-stage renal disease.

Results There were no significant differences in the primary endpoint between the two groups. However, after 4 years, the decline in GFR in patients treated with ARBs was significantly greater than that seen in patients treated with an ACE inhibitor ($p<0.05$). Furthermore, the rate of introduction of dialysis therapy was also significantly greater in the ARB-treated patients (52.7% in ACE inhibitor and 81.2% in ARB group at year 5. $p<0.01$).

Conclusion While our data suggested that ARB, like ACE, treatment might slow the progression of renal dysfunction, it also pointed to the necessity to be alerted to the progression to end-stage renal disease with long-term medication.

Key words: angiotensin-converting enzyme (ACE) inhibitors, angiotensin type 1 receptor blocker (ARB), glomerular filtration rate (GFR), non-diabetic renal disease

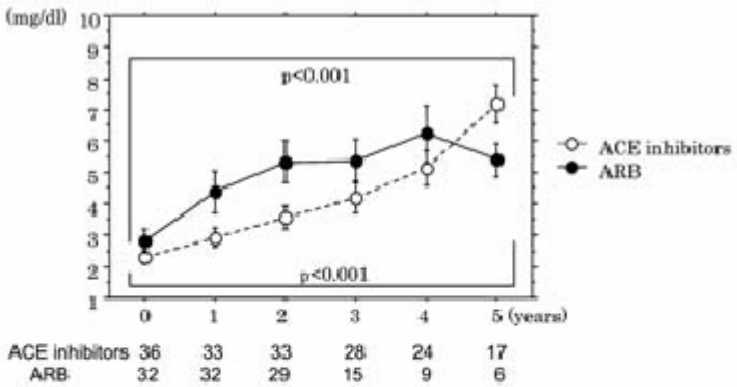


Figure 1. **Changes in serum creatinine. Serum creatinine, which was used as a criterion for the initiation of dialysis therapy, showed a gradual tendency to increase in both groups; there were no significant differences between groups. Numbers under the time course express the number of surviving patients in each group.**

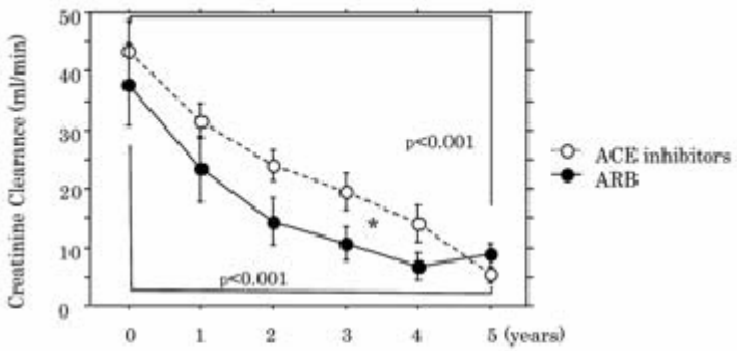


Figure 2. **Changes in creatinine clearance. Creatinine clearance, another criterion for the determination of a patient's entry into dialysis treatment, similarly showed a gradual tendency to increase. * p<0.05 versus the ACE inhibitor group**

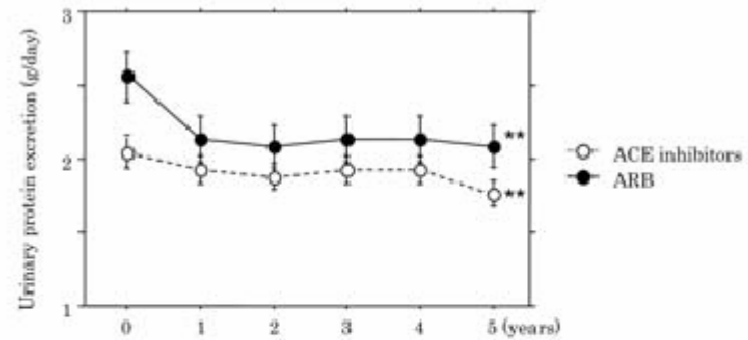


Figure 5. **Changes in urinary protein excretion. Patients in the ARB group excreted more protein than those in the ACE inhibitor group from the very beginning of the study. In both groups, urinary protein excretion was significantly decreased. ** denotes p<0.01 vs. each basal value.**

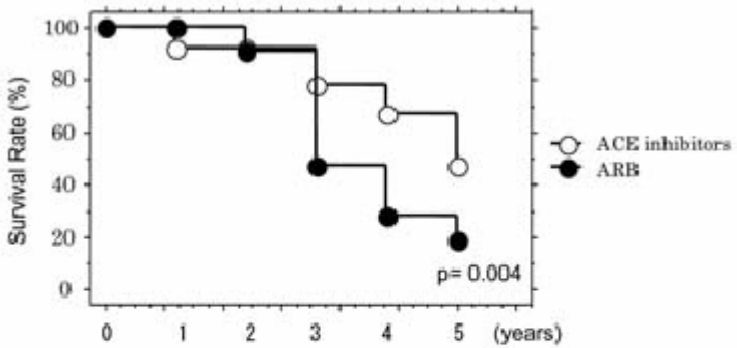


Figure 6. **Kaplan-Meier survival curves for patients treated with an ACE inhibitor or ARB. At year 3, there were no significant differences in the rate of introduction into dialysis therapy between the two groups. However, during the last 2 years, there was a significant increase in the rate of introduction of dialysis therapy in ARB patients.**

Antihypertensive drugs with compelling indications

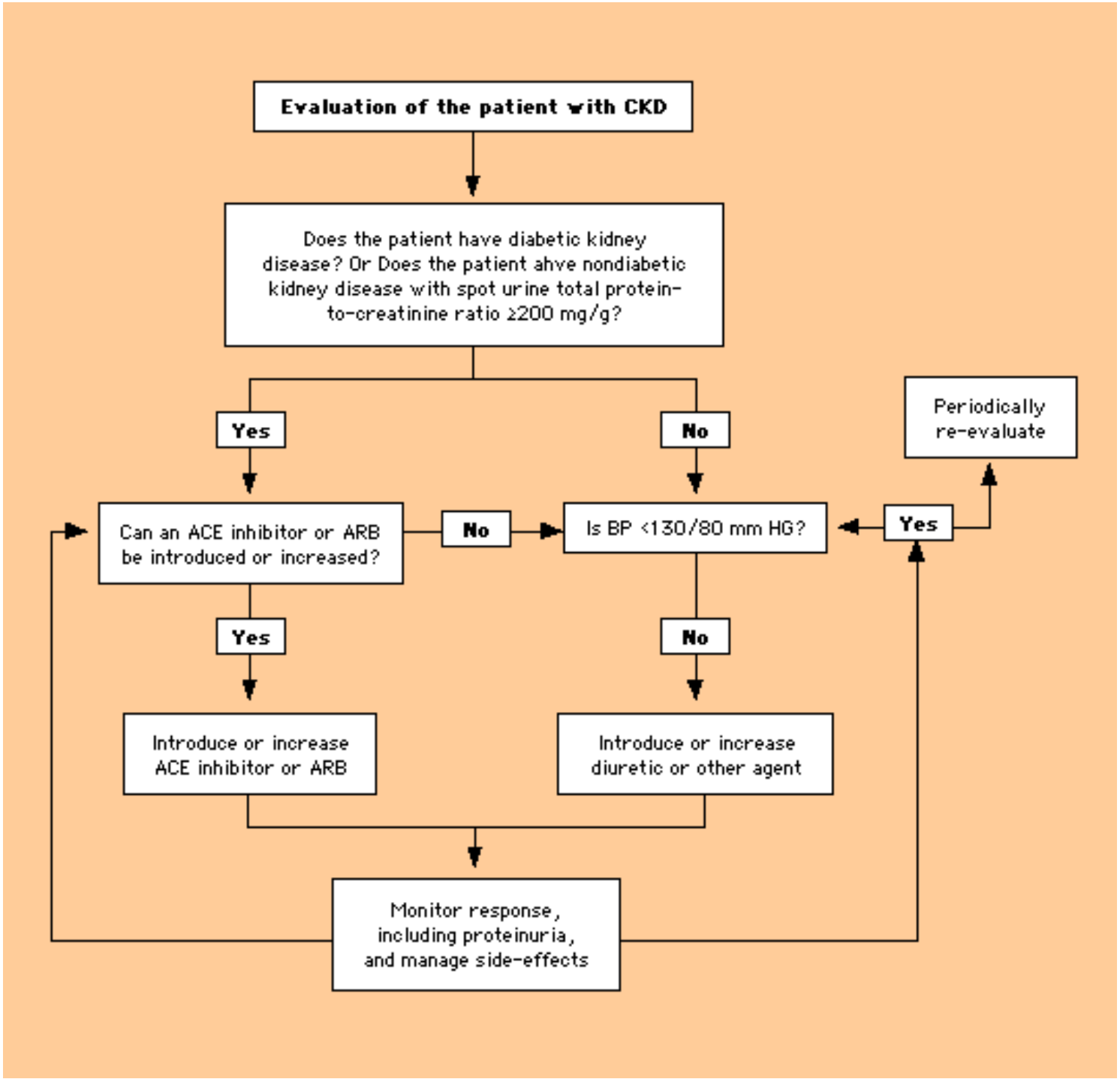
Table 8. Clinical trial and guideline basis for compelling indications for individual drug classes

Compelling Indication*	Recommended Drugs†						Clinical Trial Basis‡
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline,[40] MERIT-HF,[41] COPERNICUS,[42] CIBIS,[43] SOLVD,[44] AIRE,[45] TRACE,[46] ValHEFT,[47] RALES[48]
Postmyocardial infarction		•	•			•	ACC/AHA Post-MI Guideline,[49] BHAT,[50] SAVE,[51] Capricorn,[52] EPHESUS[53]
High coronary disease risk	•	•	•		•		ALLHAT,[33] HOPE,[54] ANBP2,[55] LIFE,[32] CONVINCE[31]
Diabetes	•	•	•	•	•		NKF-ADA Guideline,[21,22] UKPDS,[56] ALLHAT[33]
Chronic kidney disease			●	●			NKF Guideline,[22] Captopril Trial,[55] RENAAL,[56] IDNT,[57] REIN,[58] AASK[59]
Recurrent stroke prevention	•		•				PROGRESS[35]

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Aldo ANT, aldosterone antagonist; BB, beta-blocker; CCB, calcium channel blocker.

‡ Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.


Evaluation of the patient with CKD
Does the patient have diabetic kidney disease? Or Does the patient ahve nondiabetic kidney disease with spot urine total protein-to-creatinine ratio ≥200 mg/g?
Yes
No
Periodically re-evaluate
Can an ACE inhibitor or ARB be introduced or increased?
No
Is BP <130/80 mm HG?
Yes
Yes
No
Introduce or increase ACE inhibitor or ARB
Introduce or increase diuretic or other agent
Monitor response, including proteinuria, and manage side-effects

J Curve Phenomenon

Progression of Chronic Kidney Disease: The Role of Blood Pressure Control, Proteinuria, and Angiotensin-Converting Enzyme Inhibition

A Patient-Level Meta-Analysis

Tazeen H. Jafar, MD, MPH; Paul C. Stark, ScD; Christopher H. Schmid, PhD; Marcia Landa, MA; Giuseppe Maschio, MD; Paul E. de Jong, MD, PhD; Dick de Zeeuw, MD, PhD; Shahnaz Shahinfar, MD; Robert Toto, MD; and Andrew S. Levey, MD, for the AIPRD Study Group*

Background: Angiotensin-converting enzyme (ACE) inhibitors reduce blood pressure and urine protein excretion and slow the progression of chronic kidney disease.

Purpose: To determine the levels of blood pressure and urine protein excretion associated with the lowest risk for progression of chronic kidney disease during antihypertensive therapy with and without ACE inhibitors.

Data Sources: 11 randomized, controlled trials comparing the efficacy of antihypertensive regimens with or without ACE inhibitors for patients with predominantly nondiabetic kidney disease.

Study Selection: MEDLINE database search for English-language studies published between 1977 and 1999.

Data Extraction: Data on 1860 nondiabetic patients were pooled in a patient-level meta-analysis. Progression of kidney disease was defined as a doubling of baseline serum creatinine level or onset of kidney failure. Multivariable regression analysis was performed to assess the association of systolic and diastolic blood pressure and urine protein excretion with kidney disease progression at 22 610 patient visits.

Data Synthesis: Mean duration of follow-up was 2.2 years. Kidney disease progression was documented in 311 patients. Systolic blood pressure of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression. Angiotensin-converting enzyme inhibitors remained beneficial after adjustment for blood pressure and urine protein excretion (relative risk, 0.67 [95% CI, 0.53 to 0.84]). The increased risk for kidney progression at higher systolic blood pressure levels was greater in patients with urine protein excretion greater than 1.0 g/d ($P < 0.006$).

Conclusion: Although reverse causation cannot be excluded with certainty, a systolic blood pressure goal between 110 and 129 mm Hg may be beneficial in patients with urine protein excretion greater than 1.0 g/d. Systolic blood pressure less than 110 mm Hg may be associated with a higher risk for kidney disease progression.

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For author affiliations, see end of text.

*For members of the AIPRD Study Group, see the Appendix (available at www.annals.org).

See editorial comment on pp 296-298.

Table 2. **Adjusted Relative Risk for Kidney Disease Progression by Systolic Blood Pressure during Follow-up***

Systolic Blood Pressure†	Patients‡	Visits§	Events	Adjusted Relative Risk (95% CI)‖
mm Hg	←	*n*	→	
<110	253	947	10	2.48 (1.07–5.77)
110–119	548	1976	12	1.00
120–129 (JNC normal)	959	3746	32	1.23 (0.63–2.40)
130–139 (JNC high-normal)	1220	4506	59	1.83 (0.97–3.44)
140–159 (JNC stage 1 hypertension)	1501	7369	113	2.08 (1.13–3.86)
≥160 (JNC stage 2 and 3 hypertension)	1088	4066	85	3.14 (1.64–5.99)
Total	5569	22 610	311	

* Kidney disease progression is defined as doubling of baseline serum creatinine concentration or kidney failure. JNC = Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

† JNC stage refers to classification of systolic blood pressure by the JNC (3).

‡ Number of patients with even a single reading of systolic blood pressure in the corresponding range. Each patient may be assigned more than once in the group depending on the systolic blood pressure at each visit.

§ Number of patient visits with blood pressure in the corresponding range.

‖ Factors other than current systolic blood pressure and current urine protein excretion in the multivariable model included assignment to angiotensin-converting enzyme inhibitor group (relative risk, 0.67 [95% CI, 0.53 to 0.84]), female sex (relative risk, 1.35 [CI, 1.05 to 1.73]), younger age (relative risk, 0.84 [CI, 0.78 to 0.90] per 20% higher age), lower reciprocal serum creatinine concentration (relative risk, 0.51 [CI, 0.47 to 0.56] per 0.1 dL/mg higher), higher baseline systolic blood pressure (relative risk, 1.03 [CI, 1.00 to 1.07] per 5 mm Hg), higher baseline urine protein excretion (relative risk, 1.01 [CI, 0.96 to 1.07] per 0.1 g/d), and higher baseline diastolic blood pressure (relative risk, 1.03 [CI, 0.96 to 1.10] per 5 mm Hg higher). Current diastolic blood pressure is not included.

J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives

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Abstract—The objective of this study was to investigate the relationship between hypertension and risk of stroke in the elderly. The study was performed within the framework of the Rotterdam Study, a prospective population-based cohort study. The risk of first-ever stroke was associated with hypertension (relative risk, 1.6; 95% CI, 1.2 to 2.0) and with isolated systolic hypertension (relative risk, 1.7; 95% CI, 1.1 to 2.6). We found a continuous increase in stroke incidence with increasing blood pressure in nontreated subjects. In treated subjects, we found a J-shaped relation between blood pressure and the risk of stroke. In the lowest category of diastolic blood pressure, the increase of stroke risk was statistically significant compared with the reference category. Hypertension and isolated systolic hypertension are strong risk factors for stroke in the elderly. The increased stroke risk in the lowest stratum of blood pressure in treated hypertensive patients may indicate that the therapeutic goal of "the lower the better" is not the optimal strategy in the elderly. (***Hypertension*. 1999;34:1181-1185.)**

Key Words: cerebrovascular disorders ■ stroke ■ blood pressure ■ cohort studies ■ drug therapy

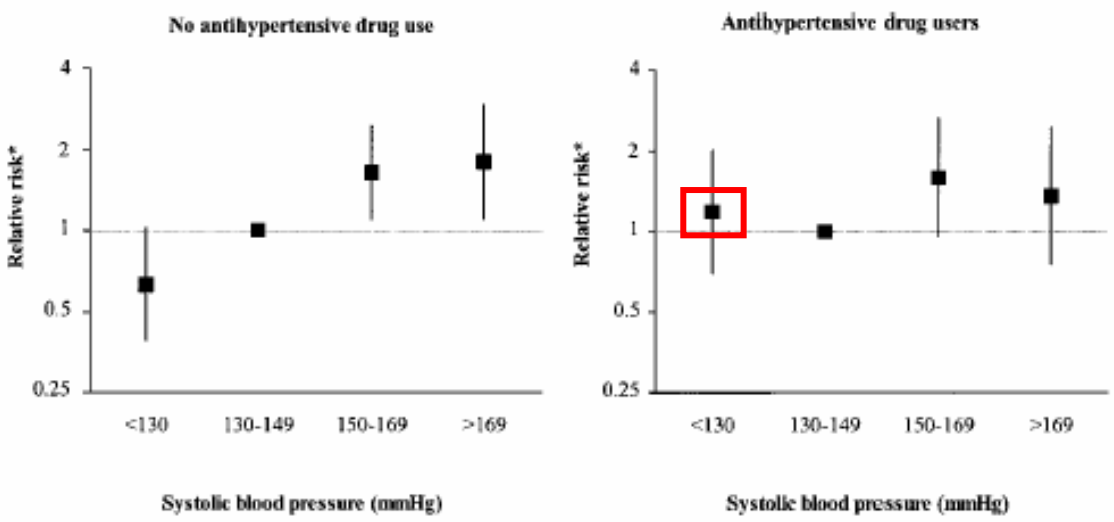

Figure 1. Association between systolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of systolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical TIA.

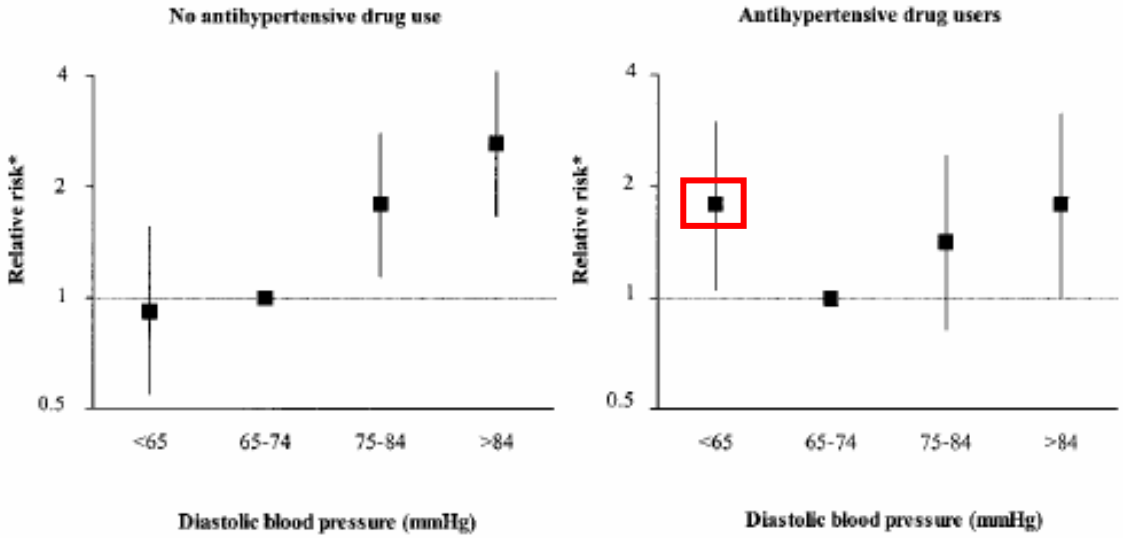

Figure 2. Association between diastolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of diastolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical TIA.

Conclusion

- Treatments in hypertensive patients
  - -Lifestyle modification
  - -Antihypertensive drugs
- Thiazide-type diuretic should be preferred for first-step antihypertensive therapy in patients without compelling indications (ex. CKD).
- Additional of other antihypertensive drugs must be done to keep BP<140/90 mmHg.

Conclusion

- Treatment of patients with CKD, administration of an ACE inhibitor and /or ARB in an attempt to both control blood pressure and slow the rate of progression of the renal disease.
- Target blood pressure is < 130/80 mmHg.
- However, evidence from the Modification of Diet in Renal Disease study, suggest that an even lower BP may be more effective in slowing progressive renal disease in patients with UPCI >1
- Caution is advised about lowering the systolic blood pressure below 110 mmHg.

THANK YOU FOR YOUR ATTENTION