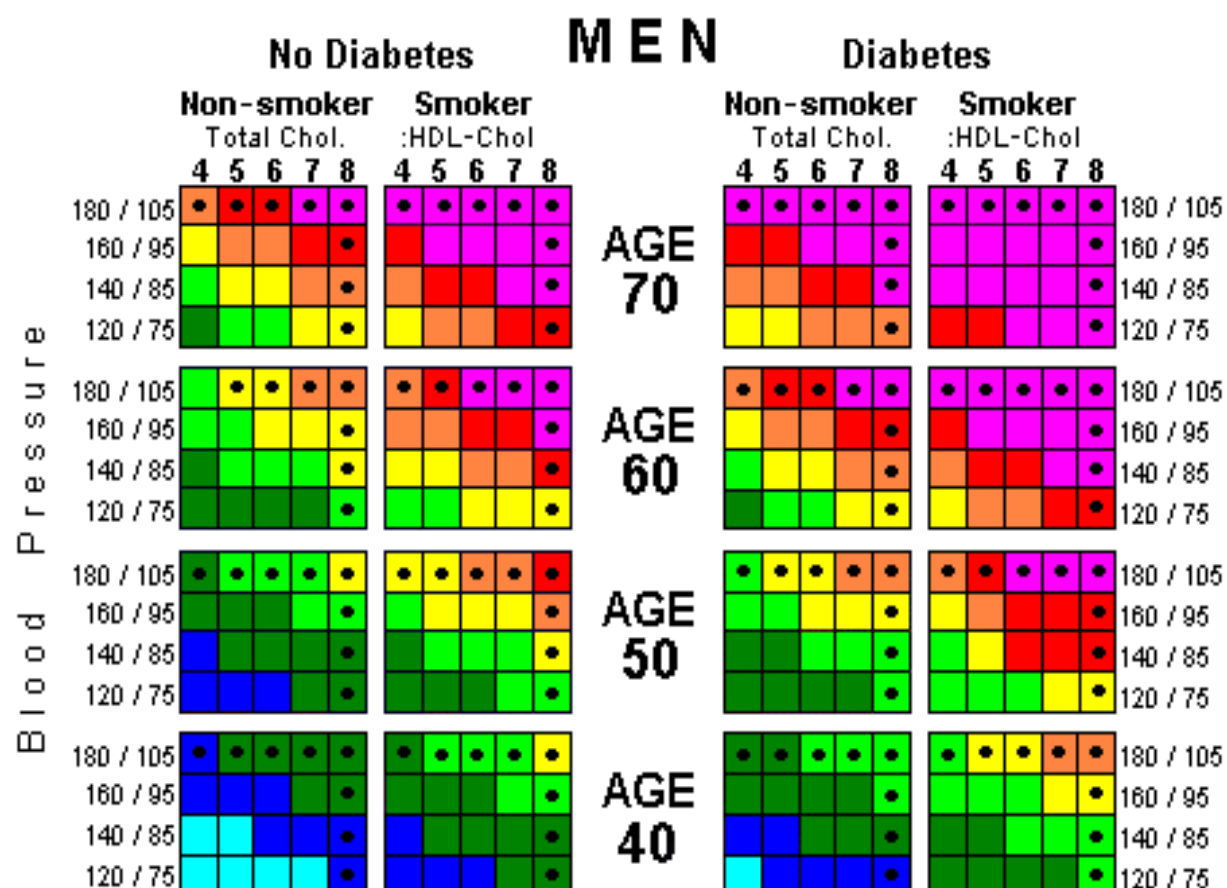


Management of Difficult or Resistant Hypertension in General Practice

JNC 7 Guidelines (2003)

Classification of Blood Pressure

<u>Category</u>	<u>SBP</u>		<u>DBP</u>
Normal	< 120	or	< 80
Prehypertension	120-139	or	80-89
Stage 1	140-159	or	90-99
Stage 2	> 160	or	> 100



EVIDENCE-BASED
BEST PRACTICE
GUIDELINE

THE ASSESSMENT
AND MANAGEMENT OF
CARDIOVASCULAR
RISK



DECEMBER 2003

High blood pressure affects about 26% of adult population

26% of (say) 3.8 million = 988 000

Up to 1/3 of these are undiagnosed or untreated (329 000)

Of the 2/3 who are treated, up to 1/3 are not at target BP (219 600)

Thus – nearly 550 000 untreated or undertreated

- Continuum of increasing CV risk from SBP 115mmHg
- CV mortality doubles for every 10/5 increase in BP > 120/70mmHg
- High BP causes
 - 35% of all cardiovascular deaths
 - 50% of all stroke deaths
 - 25% of all CAD deaths
 - 50% of all congestive heart failure
 - 25% of all premature deaths
 - commonest cause of CKD overall and commonest cause of ESRD in older individuals

Assessment and Management of Global Cardiovascular Risk is Important, but don't forget about the blood pressure!

Irrespective of 5-year CV risk, and allowing for a period of lifestyle modification in lower risk individuals, with stage 1 hypertension, eventually all individuals, irrespective of age should receive antihypertensive drug therapy if blood pressure

➤ **140 +/- 90**

or

➤ **130 +/- 80** in diabetes, CKD, or history of vascular disease (IHD, stroke, PVD et)

Initial choice of drug/s

If there is a compelling indication – use the appropriate drug for that compelling indication

If not - achieving target blood pressure is less important than the choice of drugs you use to get there (“end justifies the means”)

But in general initial choice of drugs and combinations should be from

ACE-inhibitors (or ARB's)

Thiazide diuretics

Calcium channel blockers

And in general for initial monotherapy individuals < 55-60 years ACE-inhibitor (or ARB) is probably preferred choice and > 55-60 years thiazide diuretic or calcium channel blocker

Compelling indications for individual drug classes

- | | |
|--------------------------------|----------------------------------|
| • <u>Compelling Indication</u> | • <u>Initial therapy options</u> |
| • Heart failure | • Thiaz/BB/ACEI/ARB/Aldo Ant |
| • Post myocardial infarction | • BB/ACEI/Aldo Ant |
| • High CVD Risk | • Thiaz/BB/ACEI/ARB/CCB |
| • Diabetes | • Thiaz/BB/ACEI/ARB/CCB |
| • CKD | • ACEI/ARB |
| • Recurrent Stroke Prevention | • Thiazide/ACEI |

If initial BP $> 160 \pm 100$
Start first 2 drugs
simultaneously

Practical Approach to combination therapy (over 55-60 years)

(allow minimum of 2 weeks between dose adjustments)

Thiazide ½ dose (eg chlorthalidone 12.5mg)



Not at target

add ACE-inhibitor ½ dose (eg cilazapril 2.5mg)



Not at target

Up thiazide to full dose (chlorthalidone 25mg)



Not at target

Up ACE-inhibitor to full dose (cilazapril 5mg)



Not at target

Add CCB ½ dose (eg amlodipine 5mg)



Not at target

Up CCB to full dose (eg amlodipine 10mg)

Practical Approach to combination therapy (under 55-60 years)

(allow minimum of 2 weeks between dose adjustments)

ACE-inhibitor ½ dose (eg cilazapril 2.5mg)



Not at target

Up ACE-inhibitor to full dose (cilazapril 5mg)



Not at target

Thiazide ½ dose (eg chlorthalidone 12.5mg)



Not at target

Add CCB ½ dose (eg amlodipine 5mg)



Not at target

Up thiazide to full dose (chlorthalidone 25mg)



Not at target

Up CCB to full dose (eg amlodipine 10mg)

Reasons GP's have difficulty controlling blood pressure in some patients (Take home messages)

- Misconceptions and misinformation about diuretic use and dosing
- Reluctance to optimise drug doses
- Non-complementary drug combinations
- Reluctance to use multi-drug combinations



C. Lynn

“Thiazide diuretics have a flat dose-response curve so there is no point in pushing up the dose in patients who don't have a satisfactory response to low doses...”

Right or wrong?

Right and Wrong – Difficulty is in the understanding of the meaning of “low dose”

	Often subtherapeutic	Low	Medium
Hydrochlorothiazide	12.5mg	25mg	50mg
Bendrofluazide	2.5mg	5mg	10mg
Chlorthalidone		12.5mg	25mg

Definition of Resistant Hypertension

BP **Not at Target** (<140/90 or 130/80 in DM, CKD or TOD)

despite

Optimal Doses of

a **Minimum** of **3**

Complementary Drugs

one of which is a **Diuretic**

COMPLEMENTARY DRUGS

“Good” Combinations

Thiazide + ACE inhibitor

Calcium channel blocker + ACE inhibitor

Beta blocker + alpha blocker

Thiazide + Calcium Channel Blocker

“Bad” Combinations

Beta blocker + ACE-inhibitor

Beta blocker + ARB

ACE inhibitor + ARB

Complementary Drugs

R

(RAAS +/- SNS blockade)

- Beta blockers
- ACE inhibitors
- ARB's
- Clonidine
- Methyldopa

V

(Natriuretic +/- direct vasodilatation)

- Diuretics
 - Thiazide, loop, AA, K-sparing
- CCB's
- Alpha blockers
- Minoxidil

How many drugs required to control blood pressure?

Stage 1 (<160/100) only 30% at target on 1 drug – 70% require 2-3

Stage 2 (>160/100) Minimum 2 drugs – most need 3-4

CKD, DM, CVD (target < 130/80) – add additional (min) 1 drug to above

“Rule of 10/5”

For each drug added, seldom get > 10 (systolic)/5 (diastolic) fall in BP

Causes of Resistant Hypertension

- Suboptimal drug therapy
- White coat hypertension (20%)
- Coexisting conditions – esp. obesity/metabolic syndrome/OSA
- Antagonising substances (usually sodium)
- Non-compliance
- Coexisting medications – eg NSAID's, OCA
- Unrecognised secondary causes of hypertension

Important Secondary (identifiable) Causes of Hypertension

- Sleep apnoea
- Drug induced/ related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing's Syndrome or steroid therapy
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid/ parathyroid disease

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27 13:54

Ethnic Specific Values for Waist Circumference[†]

Ethnic group	Waist circumference (as measure of central obesity)
Europids*	
Men	≥94 cm
Women	≥80 cm
South Asians	
Men	≥90 cm
Women	≥80 cm
Chinese	
Men	≥90 cm
Women	≥80 cm
Japanese	
Men	≥85 cm
Women	≥90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and middle east (Arab) populations	Use European data until more specific data are available

- 80-85% of the hypertensive population is overweight or obese
- A substantial minority of these individuals meet the criteria for “Metabolic Syndrome”
- Abdominal obesity carries the greatest risk
- Many obese hypertensives have coexisting OSA

Metabolic Syndrome Definitions

WHO

FPG > 6.1 or 2hr
GTT > 11.1

Plus at least 2 of:

- Abdo obesity (W/H ratio > 0.9, BMI > 30, or waist girth > 94cm)
- TG > 1.7 or HDL < 0.9
- BP > 140/90 or on antihypertensives

2001 NCEP

3 out of 5 of:

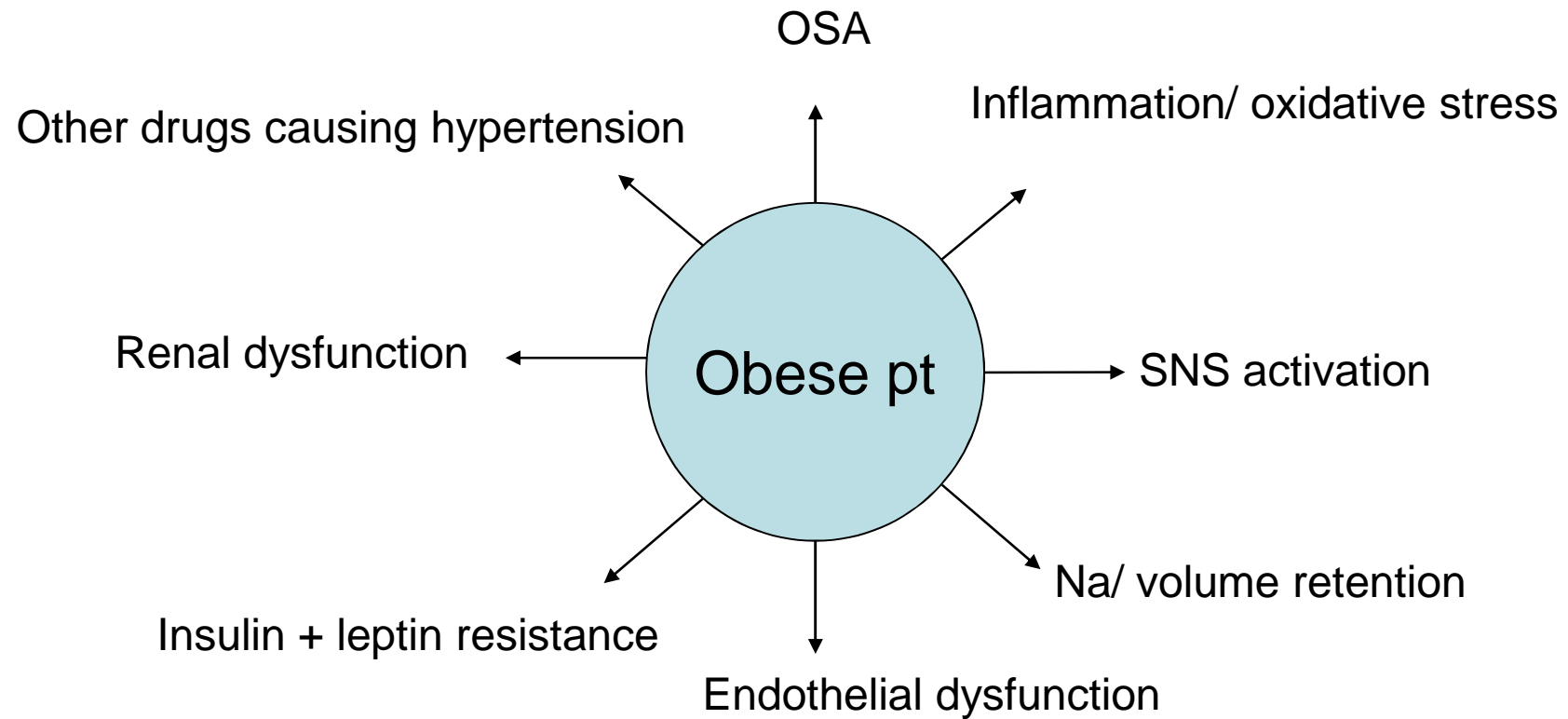
- Waist circ > 102cm (men) 88cm (women)
- TG > 1.7
- HDL < 1
- BP > 130/85
- FPG > 6.1

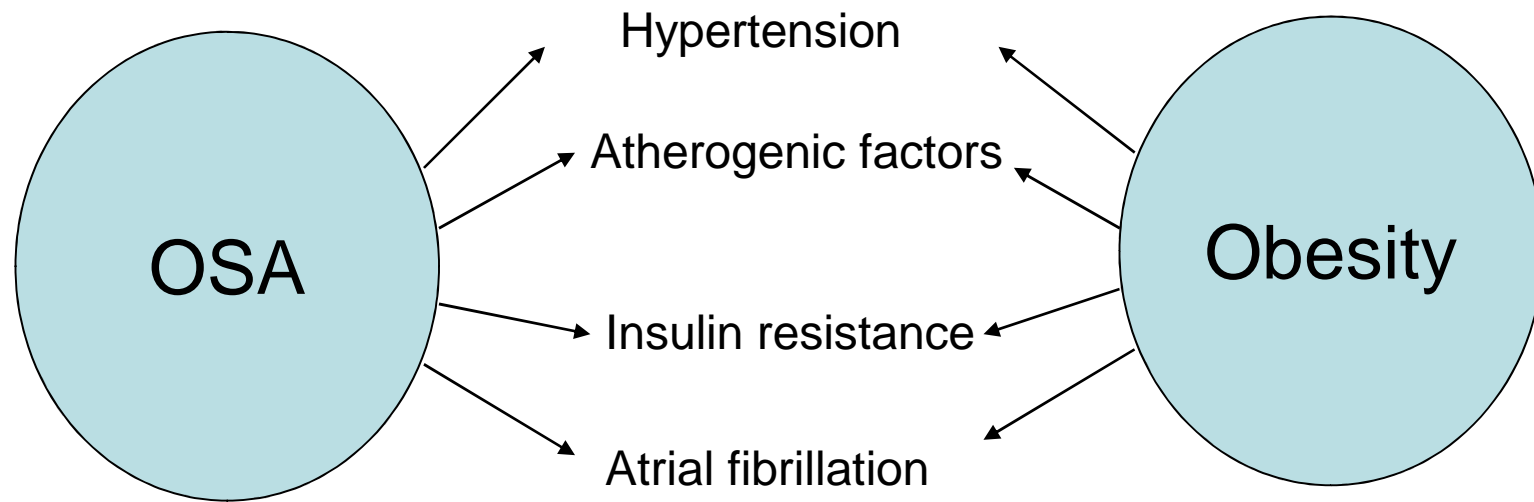
IDF

Increased waist circumference

Plus at least 2 of:

- TG > 1.7
- HDL < 1.03 (men) or 1.25 (women)
- BP > 130/85
- FPG > 5.6





Take home message

Hypertension in the metabolic syndrome is mediated through multiple mechanisms and often requires several drugs for control

Hyperinsulinaemia increases proximal tubular sodium reabsorption and these individuals often require diuretics as part of an effective regimen, sometimes in higher doses and sometimes > 1 diuretic (eg thiazide + spironolactone)

Aldosterone – New Paradigm

Aldosterone is elaborated at many sites apart from the adrenal, including the heart, vascular smooth muscle and kidney where it interacts directly with mineralocorticoid receptors to promote endothelial dysfunction and reduce vascular compliance. It is increasingly recognised as a direct mediator of vascular damage (separate from A2)

Apart from causing sodium and water retention, Aldosterone

- Reduces A and V compliance
- Increases peripheral vascular resistance
- Promotes myocardial hypertrophy + fibrosis
- Increases baroreflex dysfunction

All of these effects are potentially reversed by Spironolactone

(Aldosterone is an important mediator of resistant hypertension in the metabolic syndrome)

Spironolactone is an effective antihypertensive, but has not been used much as a sole agent (except in France)

Recently shown to be very effective as an add-on in resistant hypertension. Usually require 12.5-50mg daily - no antihypertensive benefit beyond 100mg daily

Calhoun et al Hypertension 2002 40:892-6

Black and white subjects with R/H on ave. 4 agents treated with SPTN 25-50mg daily – Ave. BP fell from 156/92 – 130/86

Ouzam et al AJH 2002

ASCOT Resistant Hypertension Substudy Hypertension. 2007;49:839.)

In patients with R/H successfully treated with SPTN – possible to wean off some of their other drugs

Alternative is Eplerenone (no anti-androgenic side-effects)

37.5mg Eplerenone ~ 25mg Spironolactone

Long-term control of BP in patients on an ACE-inhibitor or ARB is highly dependent of the dose of diuretic

Drugs which block the RAAS or SNS convert the patient into a salt-sensitive individual who will respond in a dose-dependent fashion to a diuretic

“All” regimens containing > 2 drugs should “always” include a diuretic (and a diuretic is often the 2nd drug, even in individuals < 55 years)

Are Beta Blockers Appropriate as Initial Therapy in Hypertension?

Beta blockers are effective anti-anginals and are clearly indicated post-MI where there is strong clinical trial evidence for their use in preventing reinfarction. Also improve outcomes in heart failure. Unclear however whether in the absence of these indications (in hypertension) they offer much cardioprotective effect. Cardioprotection was suggested by some early studies, but this has not been borne out in later studies, some even suggesting worse outcomes on beta blockers (including ASCOT, LIFE, and HOPE)

Recent Meta-analysis (Lancet 2005;366:895)

13 RCT's, 106 000 pts - adverse outcomes associated with atenolol, but not other beta blockers. All beta blockers are associated with increased risk of stroke, but non-atenolol beta blockers (alone or in combination with diuretics) are not associated with increased risk of MI or all-cause death.

Current Place of Beta Blockers in Hypertension

- Presence of compelling indication/s (IHD, post MI, AF, heart failure)
- In absence of compelling indication add in as 3rd or 4th agent (after diuretic, ACE/ARB +/- CCB)
- (Possibly) as first-line agent in whites < 55 years if ACE-I/ARB-intolerant (or if resting tachycardia)

Important Considerations in diabetes and hypertension

- (1) More than 50% of individuals with 2 diabetes have elevated blood pressure (IN US NHANES database 58.9% of white type 2 diabetics have hypertension and 78.1% of blacks)
- (2) Individuals with high blood pressure are 2-3x more likely than those with normal blood pressure to have diabetes
- (3) Individuals with type 2 diabetes alone are at risk of premature macrovascular (heart attack, stroke, peripheral macrovascular disease) and microvascular complications (retinopathy, nephropathy, peripheral gangrene)
- (4) Individuals with high blood pressure alone are at risk of premature macrovascular (heart attack, stroke) and microvascular (nephrosclerosis) complications

(5) Patients with diabetes and hypertension and twice as likely to experience a cardiovascular event than those with diabetes only or hypertension only, and 5-6 times more likely to develop end stage renal disease

(6) An estimated 35-75% of cardiovascular and renal complications can be attributed to high blood pressure

Target Blood Pressure in individuals with diabetes is
< 130/80

(same for CKD and secondary prevention of cardiovascular disease + there is extensive overlap of these conditions with diabetes)

Achievement of this target is very uncommon

For example NHANES 3 survey showed that only 11% of people with diabetes treated for high BP achieved 130/80 target

What am I getting at?

- High blood pressure is very common in people with type 2 diabetes and almost universal in those with established diabetic nephropathy
- Evidence is unequivocal that tight BP control is effective at primary and secondary prevention of microvascular and macrovascular complications in type 2 diabetes is unequivocally more beneficial than tight glycaemic control
- Despite this, achievement of BP target is very uncommon in type 2 diabetics with raised blood pressure

Why are BP control rates poor in type 2 diabetes?

- (1) Diabetologists and diabetes nurse specialist focus more on glucose control than blood pressure targets (personal observation)
- (2) Diabetes nurses able to adjust diabetes medications autonomously, but not BP medications
- (3) Many doctors seem to feel that provided the patient is on a ACE-inhibitor their obligation to the patient's BP is discharged (when the focus should be principally on achieving target BP not just prescription of a particular class of drug)

- (4) Apparent reluctance of doctors to use multi-drug regimens to control BP
- (5) Because BP target is 10/10 lower the general BP target of 140/90 it is harder to achieve
- (6) Resistant hypertension is commoner in diabetics and particularly in those with established diabetic nephropathy
- (7) “Clinician Inertia” (possibly most important factor)

Pharmacological considerations in treating blood in patients with type 2 diabetes (including those with established nephropathy)

- (1) ACE-inhibitor or ARB should be part of the antihypertensive regimen but monotherapy with one of these drugs will seldom get the patient to target on its own
- (2) Because target is $< 130/80$, usually minimum of 1 extra drug required to get to target (cf target of $140/90$ in general hypertensive population
- “10/5 rule” – each drug added unlikely to reduce BP by $> 10/5$
- (3) Only 30% of patients with diabetes and elevated BP will achieve BP target on ≤ 2 drugs
- (4) When starting treatment, initiate with 2 drugs when BP $> 150/90$

- (5) Only a minority of patient with established diabetic nephropathy will achieve blood pressure target on ≤ 3 drugs
- (6) Drugs need to be given in full doses
- (7) All regimens containing > 2 drugs should include a diuretic
- (8) “All” patients with chronic kidney disease (reduced GFR) should have a diuretic included in their regimen
 - high blood pressure in CKD is “never” controllable without a diuretic
 - the lower the GFR, the more the diuretic dose required to control BP

Treatment of Hypertension in Patients 80 years of Age or Older (HYVET Study)

N.Engl.J.Med.2008;358:1887-98

- In this study, patients 80 years of age or older with sustained systolic hypertension were randomly assigned to receive either the diuretic indapamide, with or without the angiotensin-converting-enzyme inhibitor perindopril, or matching placebos, for a target blood pressure of 150/80 mm Hg

Table 1. Baseline Characteristics of the Patients.*		
Characteristic	Active Treatment (N=1933)	Placebo (N=1912)
Age — yr	83.6±3.2	83.5±3.1
Female sex — no. (%)	1174 (60.7)	1152 (60.3)
Blood pressure — mm Hg		
While sitting	173.0±8.4/90.8±8.5	173.0±8.6/90.8±8.5
While standing	168.0±11.0/88.7±9.3	167.9±11.1/88.6±9.3
Orthostatic hypotension — no. (%)†	152 (7.9)	169 (8.8)
Isolated systolic hypertension — no. (%)	625 (32.3)	623 (32.6)
Heart rate — beats/min	74.5±9.1	74.5±9.3
Cardiovascular history		
Cardiovascular disease — no. (%)	223 (11.5)	229 (12.0)
Hypertension — no. (%)	1737 (89.9)	1718 (89.9)
Antihypertensive treatment — no. (%)	1241 (64.2)	1245 (65.1)
Stroke — no. (%)	130 (6.7)	131 (6.9)
Myocardial infarction — no. (%)	59 (3.1)	62 (3.2)
Heart failure — no. (%)	56 (2.9)	55 (2.9)
Cardiovascular risk factors		
Current smoker — no. (%)	123 (6.4)	127 (6.6)
Diabetes — no. (%)‡	132 (6.8)	131 (6.9)
Total cholesterol — mmol/liter	5.3±1.1	5.3±1.1
High-density lipoprotein cholesterol — mmol/liter	1.35±0.38	1.35±0.37
Serum creatinine — μmol/liter	88.6±20.5	89.2±20.5
Uric acid — μmol/liter	280.4±79.3	279.0±81.3
Body-mass index§	24.7±3.8	24.7±3.5

* Plus-minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586; to convert values for uric acid to milligrams per deciliter, divide by 59.48; and to convert values for serum creatinine to milligrams per deciliter, divide by 88.4.

† Orthostatic hypotension is defined as a drop in systolic blood pressure of more than 20 mm Hg or a reduction in diastolic blood pressure of more than 10 mm Hg while standing.

‡ Diabetes is defined as reported diabetes, the receipt of antidiabetes treatment, or a random blood glucose measurement of more than 11.1 mmol per liter (200 mg per deciliter).

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

1933 patients on active treatment and 1912 placebo

Mean age 83.6 years (both groups)

Mean seated BP 173/90 (both groups)

Mean BP reduction in treatment group 15/6.1

Followed for mean 4 years

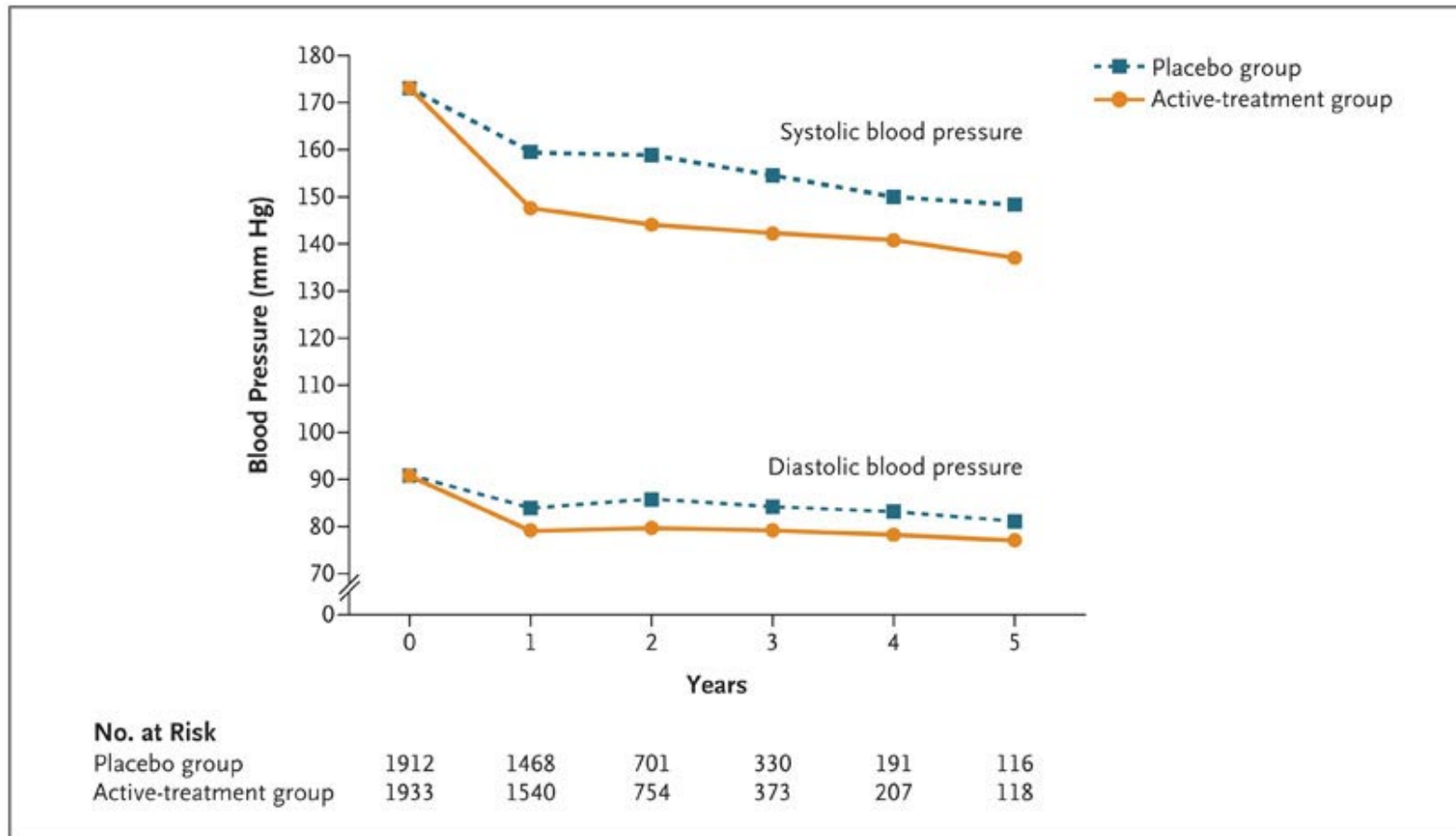


Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

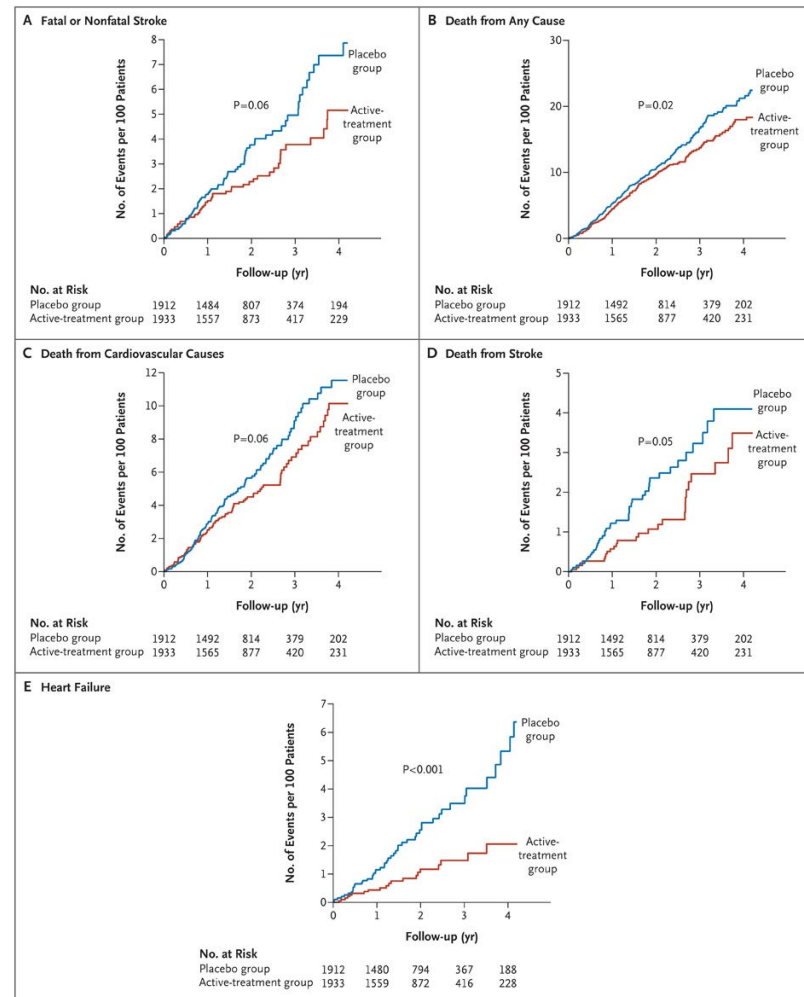
End Point	Rate per 1000 Patient-Yr (No. of Events)		Unadjusted Hazard Ratio (95% CI)	P Value
	Active	Placebo		
	no. (%)			
Stroke				
Fatal or nonfatal	12.4 (51)	17.7 (69)	0.70 (0.49–1.01)	0.06
Death from stroke	6.5 (27)	10.7 (42)	0.61 (0.38–0.99)	0.046
Death				
From any cause	47.2 (196)	59.6 (235)	0.79 (0.65–0.95)	0.02
From noncardiovascular or un- known causes	23.4 (97)	28.9 (114)	0.81 (0.62–1.06)	0.12
From cardiovascular cause	23.9 (99)	30.7 (121)	0.77 (0.60–1.01)	0.06
From cardiac cause*	6.0 (25)	8.4 (33)	0.71 (0.42–1.19)	0.19
From heart failure	1.5 (6)	3.0 (12)	0.48 (0.18–1.28)	0.14
Fatal or nonfatal				
Any myocardial infarction	2.2 (9)	3.1 (12)	0.72 (0.30–1.70)	0.45
Any heart failure	5.3 (22)	14.8 (57)	0.36 (0.22–0.58)	<0.001
Any cardiovascular event†	33.7 (138)	50.6 (193)	0.66 (0.53–0.82)	<0.001

* Death from cardiac causes was defined as fatal myocardial infarction, fatal heart failure, and sudden death.

† Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction, or heart failure.

Treatment Group had:

- 30% reduction in in rate of fatal or non-fatal stroke
- 39% reduction in rate of death from stroke
- 21% reduction in rate of death from any cause
- 23% reduction in rate of death from cardiovascular causes
- 64% reduction in rate of heart failure



ACCOMPLISH Trial (**A**voiding **C**ardiovascular Events in **C**ombination
Therapy in **P**atients **L**iving with **S**ystolic **H**ypertension)
N.Engl.J.Med.2008;359:2417-2428

Summarising 100's of outcome studies the consensus remains that degree of BP lowering is more important than how it is achieved.

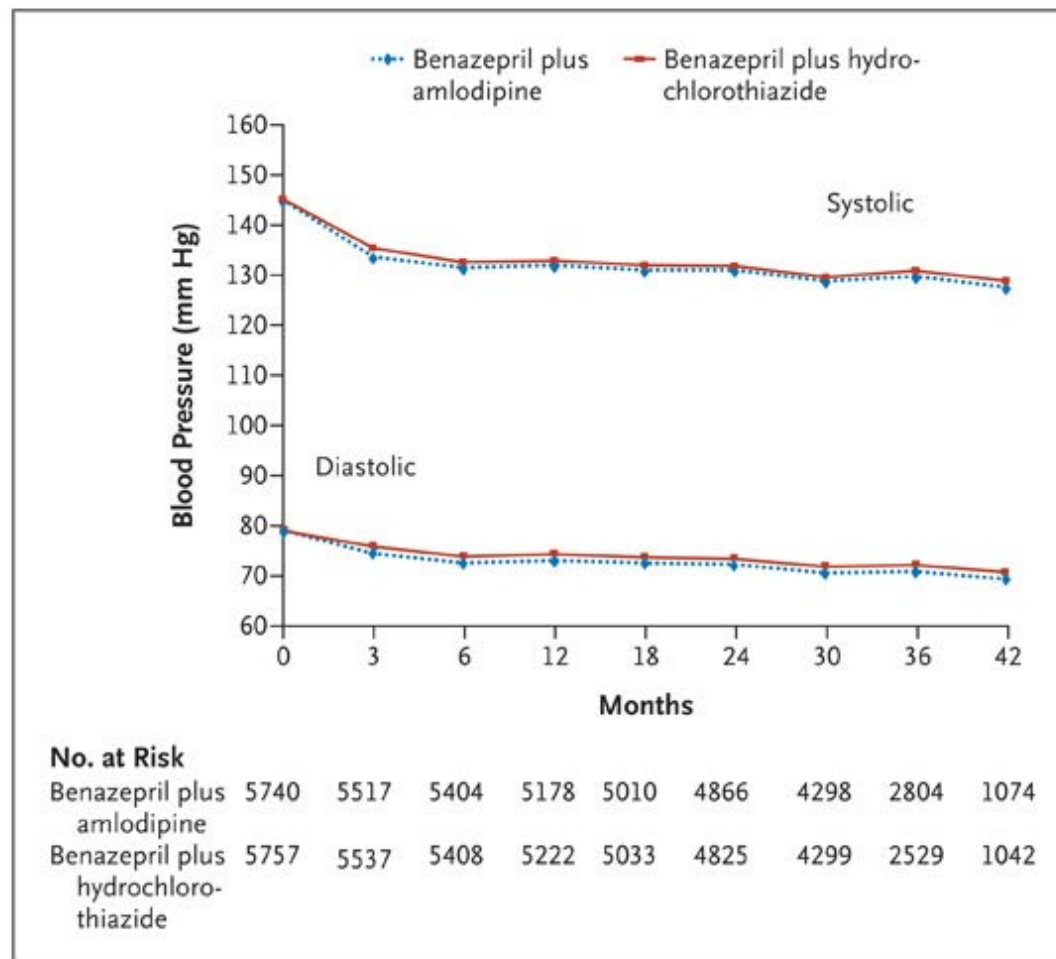
Choice of initial agent determined by age and race of pt as well as compelling indications and contraindications.

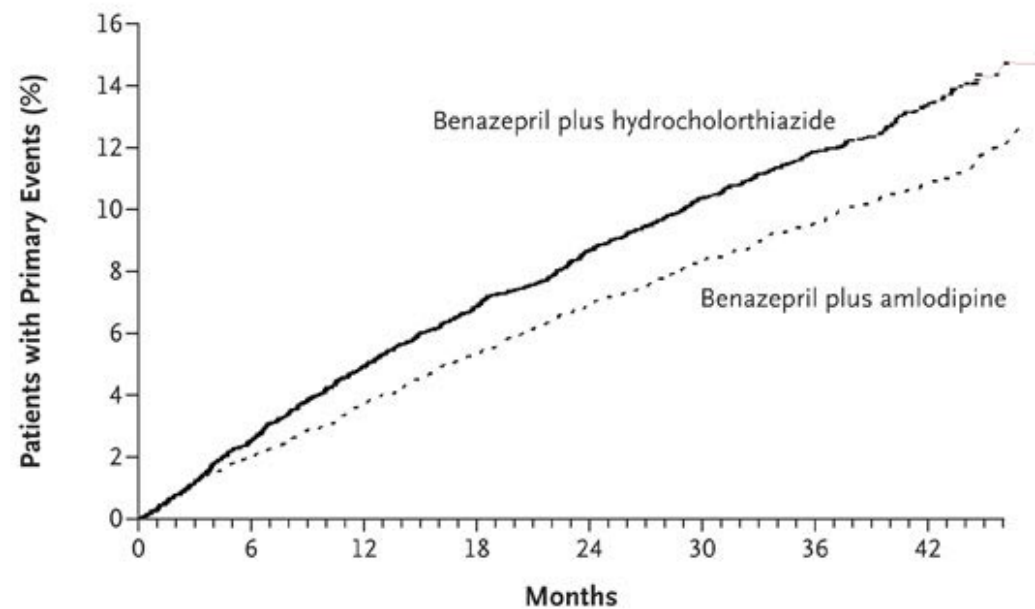
Most patients will require > 1 drug to achieve target BP and JNC 7 suggests that Stage 2 hypertension be treated with combination therapy from the start.

Currently commonest combination is (highly effective) RAAS blocker (ACE-I or ARB) + thiazide with long-acting CCB usually 3rd drug. Because of concern about possible metabolic (+ ? proinflammatory – *Valmarc study*) side effects of thiazides, particularly diabetes, there is interest in whether RAAS blocker/CCB would be an effective first-line combination.

ACCOMPLISH was a large (11 400) outcome study of high risk hypertensives > 55 yrs and SBP > 160 . Many obese and 60% diabetic. Pts randomised to Benazepril/HCTZ or Benazepril/Amlodipine combinations. Excellent BP control with 76% having BP at target at 18 months and few dropouts for side effects. 50% obese 60% diabetes mellitus

Pts randomised from 2003.



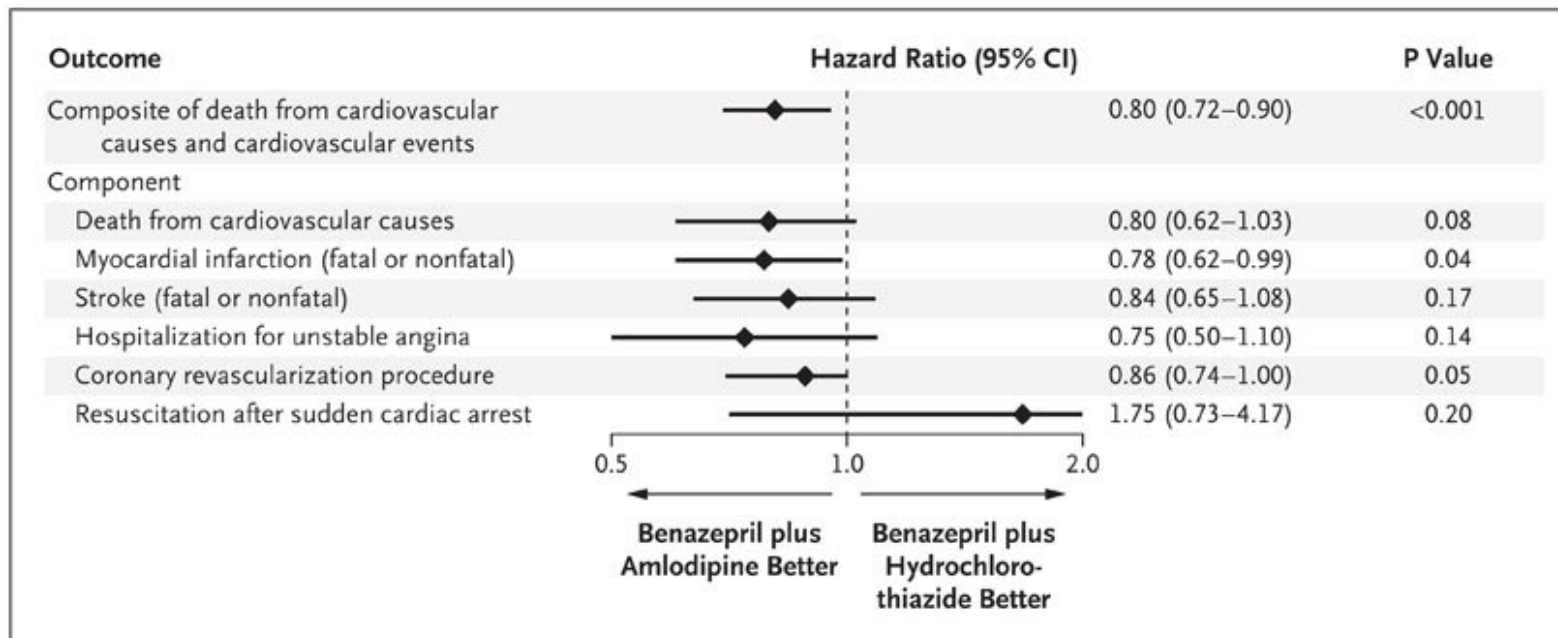


No. at Risk

Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390



The NEW ENGLAND
JOURNAL of MEDICINE



Pts randomised from 2003. Trial stopped early in October 2007 by data safety and monitoring committee following interim analysis of 60% of expected information from the trial.

ACEI/CCB – 81.7% BP < 140/90 ACE/HCTZ 78.5%/ Mean SBP difference 0.7

Over a mean f/u of 39 months, cardiovascular morbidity/mortality was reduced by 20% with the ACEI/CCB compared with the ACEI/HCTZ

The benazepril-amlodipine combination was superior to the benazepril-hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events

- The optimal combination drug therapy for treatment of hypertension is not established, although current U.S. guidelines recommend inclusion of a diuretic
- This double-blind trial, in which high-risk patients with hypertension were randomly assigned to treatment with benazepril plus either amlodipine or hydrochlorothiazide, showed that benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular events in this population

Check out my website

www.hypertensionclinic.co.nz