Resistant and Refractory Hypertension

Take home message (1)

2 commonest causes of resistant hypertension are

(a) Unrecognised volume excess/ underuse of diuretics

(b) Untreated sympathetic overactivity

Definition of Resistant Hypertension

Blood pressure not at target (<140/90 or < 130/80 in diabetes, CKD or CVD)

Despite

- optimal doses of
- a minumum of three
- complementary drugs
- one of which is a

diuretic

Resistant hypertension ≠ Refractory Hypertension

Definition of Refractory Hypertension

Blood pressure not at target (<140/90 or < 130/80 in diabetes, CKD or CVD)

Despite

- maximal tolerated therapy

Most people with resistant hypertension have the potential to achieve target blood pressure

Take home message (2)

neither hydrochlorothiazide 12.5mg daily…

nor bendrofluazide 2.5mg daily…

have been associated with beneficial cardiovascular outcome in RCT’s

Problem in New Zealand…

Most commonly used combination antihypertensives are

- *Inhibace Plus*
- *Accuretic 10*
- *Accuretic 20*

By definition, hypertension can't be called resistant while a patient is taking one of these daily plus one other drug …

They all contain hydrochlorothiazide 12.5mg, which as a daily dose is *often* ineffective dose

Inhibace Plus (cilazapril 5mg + HCTZ 12.5mg)

combines a probably adequate dose of ACE-inhibitor with and often inadequate dose of thiazide…

And thus can be described as…

"The Work of the Devil"

About 26% of the adult population is hypertensive

Prevalence of resistant hypertension ~13% (NHANES 2003-2008)

Possibly10% of resistant hypertension is truly refractory

Local Experience

358 consecutive new patients seen at the Waitemata Hypertension clinic in 2009 and 2010

Average age 55
59% female
Mean BMI 30
Mean BP at first visit 158/87
Most patients on >= 2 antihypertensive drugs at referral

BP >139+-89 and on a minimum of chlorthalidone 12.5mg, or HCTZ 25mg,or BFZ 5mg, or frusemide 40mg or SPTN 25mg and any 2 other antihypertensive classes

At first visit 32/358 fulfilled criteria for diagnosis of resistant hypertension (9%)

At discharge (or last visit if lost to follow-up) 102 fulfilled criteria for diagnosis of resistant hypertension (28%)

Of these

- 77 achieved blood pressure < 140/90 (Resistant hypertension at target) 21% of total

- 25 did not achieve BP < 140/90 (Refractory) 7% of total

- 93% of all patients referred achieved BP < 140/90

Predictors of Resistant Hypertension**

- Older age
- Obesity
- Female sex
- Chronic kidney disease
- LVH
- Black Race

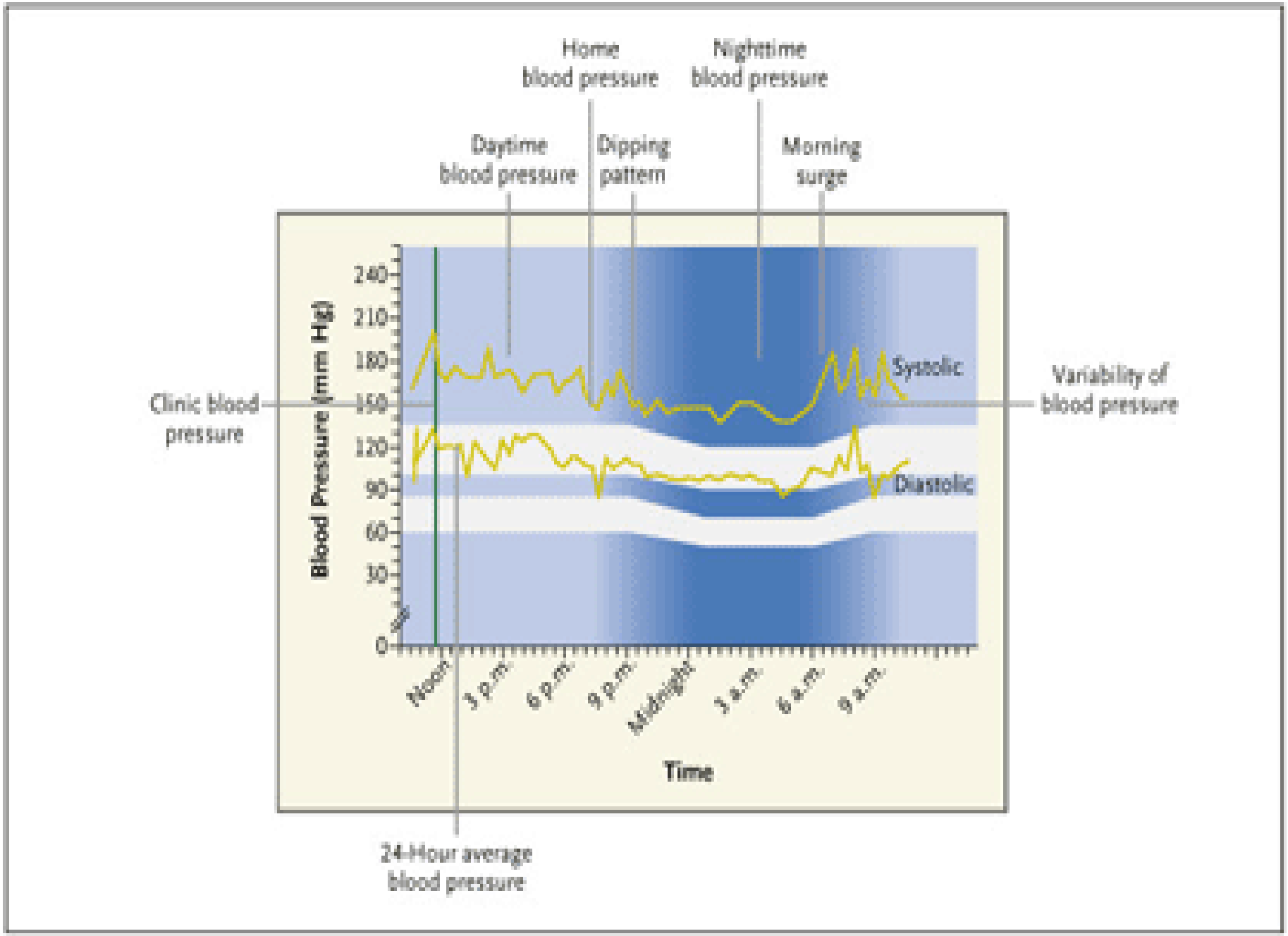
***ALLHAT 2003*

“Pseudoresistance”

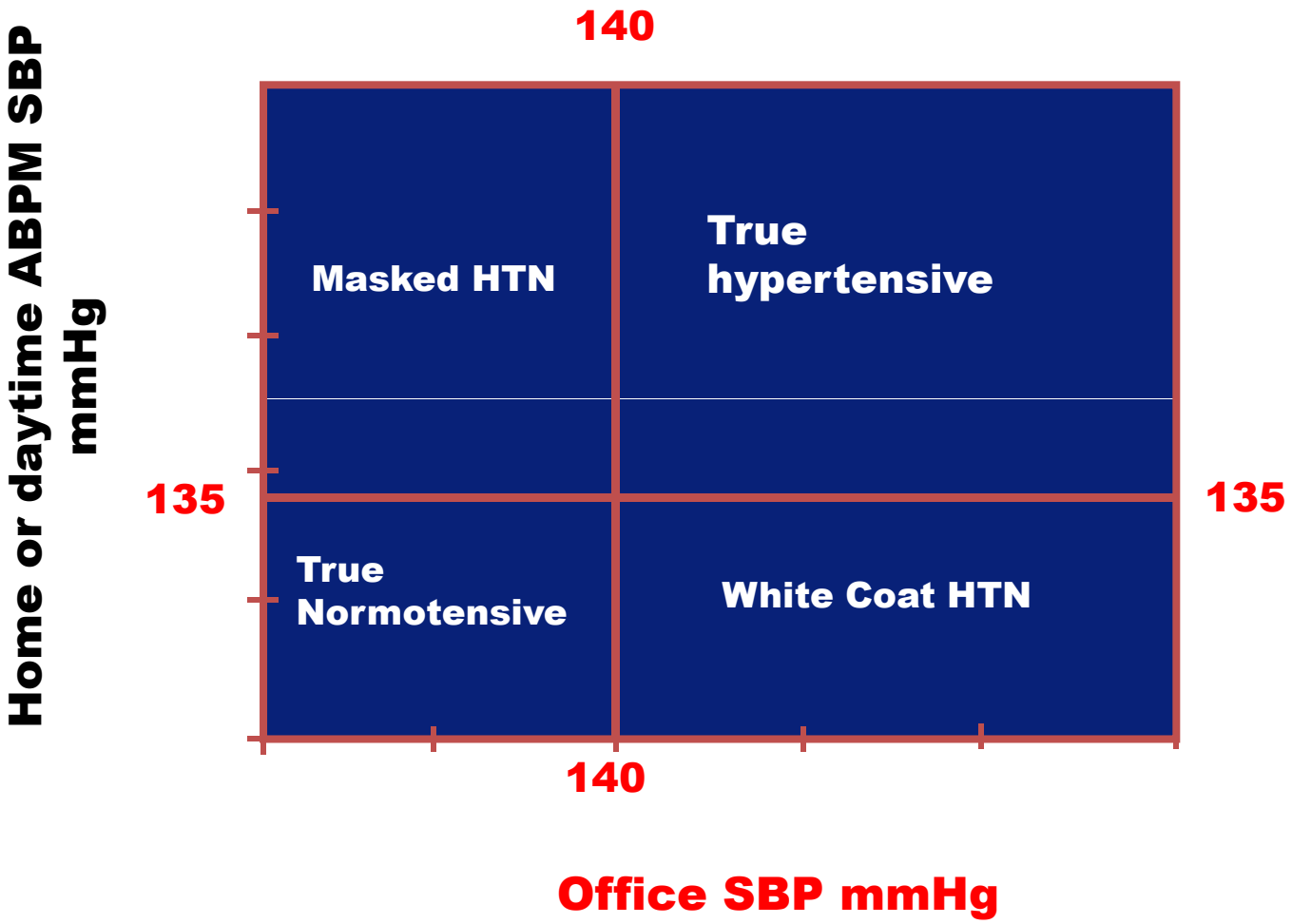
- Poor BP measurement technique
- Poor adherence
- White coat effect

Evaluation

- Confirm true resistance
- Screen for secondary causes
- Document presence of target organ damage


Home blood pressure
Nighttime blood pressure
Daytime blood pressure
Dipping pattern
Morning surge
Clinic blood pressure
Variability of blood pressure
Systolic
Diastolic
Blood Pressure (mm Hg)
240
210
180
150
120
90
60
30
0
Noon
3 p.m.
6 p.m.
9 p.m.
Midnight
3 a.m.
6 a.m.
9 a.m.
Time
24-Hour average blood pressure

The concept of masked hypertension



From Pickering, Hypertension 1992

NHS
National Institute for
Health and Clinical Excellence

Hypertension

Implementing NICE guidance

August 2011

NICE clinical guideline 127

NHS
National Institute for
Health and Clinical Excellence

Diagnosis (1)

If clinic blood pressure is 140/90 or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension

August 2011

NICE clinical guideline 127

Clinical Guideline Implementation Tools

Office BP vs ABPM

General population

- White coat Hypertension 20-25%
- Masked hypertension 10-15%

Subgroups (DM, CKD etc)

- White coat Hypertension 5-15%
- Masked hypertension – up to 40%

Secondary Causes

- Primary aldosteronism up to 20% in some series

Local Experience

635 consecutive patients through Waitemata Hypertension Clinic 2009-2012

Renin and aldosterone not checked – 182

Renin and aldosterone checked – 453

7 confirmed cases of primary aldosteronism

- 4 adenoma
- 3 bilateral adrenal hyperplasia

1.1% of all patients

1.5% of patients in whom renin and aldosterone checked

4% of those meeting strict criteria for resistant hypertension

The 3 most important antihypertensive drug classes (based on outcome data) are:

- ACE-inhibitors (or ARB's)

- thiazide diuretics

- calcium channel blockers.

Balanced Combinations**

PREFERRED	ACCEPTABLE	USE WITH CAUTION
ACE-I/ Thiazide	Beta blocker/ Thiazide	ACE-I/ ARB
ARB/Thiazide	Beta blocker/ CCB	ACE-I/ Beta blocker
ACE-I/ CCB	CCB/ Diuretic	ARB/ Beta blocker
ARB-CCB	Thiazide/ Spironolactone	Non-DHP CCB/ Beta blocker
	(Renin inhibitor/ Thiazide)	Central sympatholytic/ Beta blocker
	(Renin inhibitor/ ARB)	

***AHS**

What is the best 2-drug combination?

ACE-Inhibitor/ thiazide?

or

ACE-Inhibitor/ CCB?

or

CCB/ thiazide?

What is the best 2-drug combination?

ACE-Inhibitor/ thiazide?

or

ACE-Inhibitor/ CCB?

~~or~~

~~CCB/ thiazide?~~

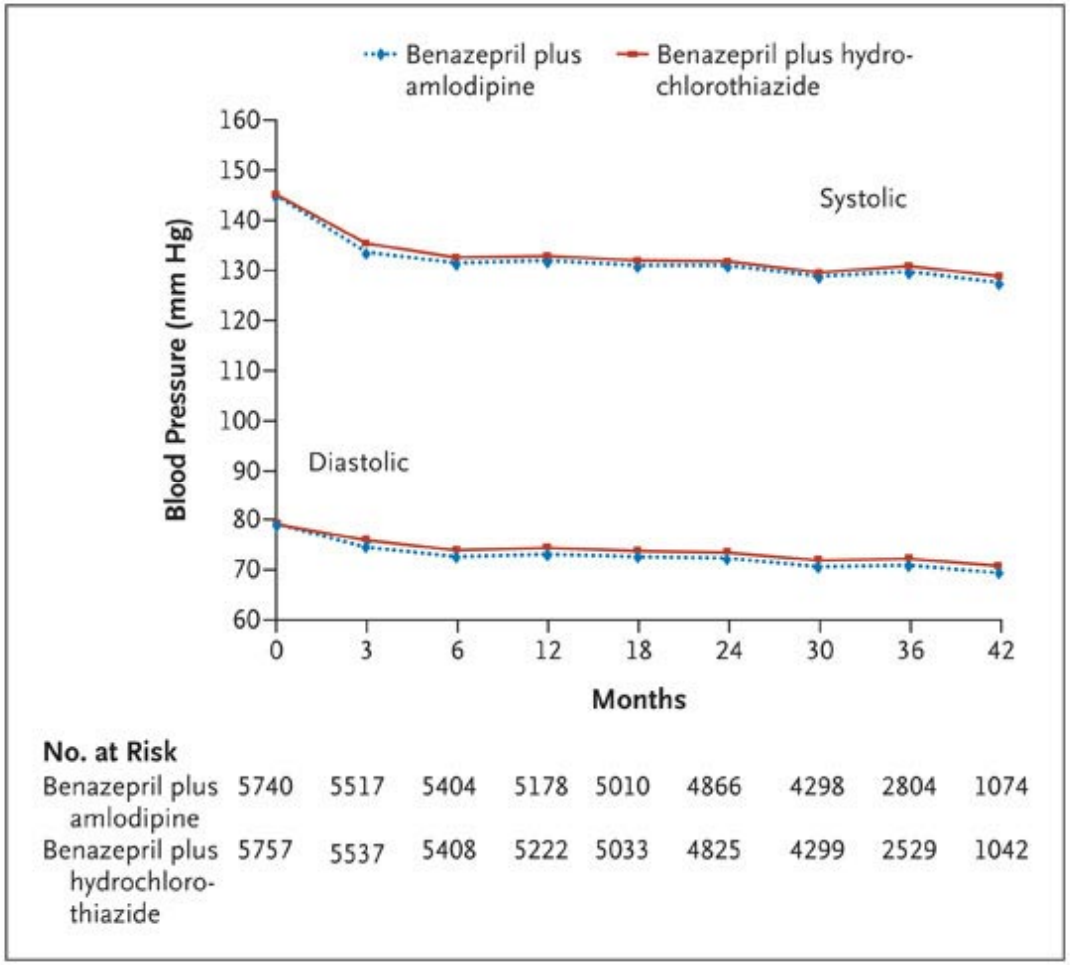
Original Article

Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupte, M.S., Marjorie Gatlin, M.D., Eric J. Velazquez, M.D., for the **ACCOMPLISH Trial** Investigators

N Engl J Med
Volume 359(23):2417-2428
December 4, 2008

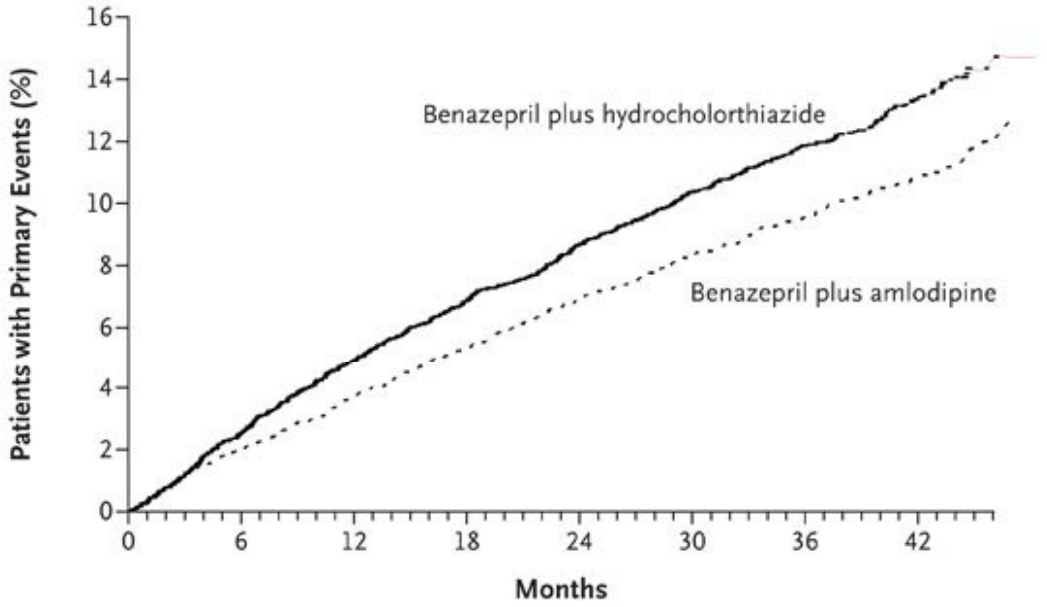
The NEW ENGLAND JOURNAL of MEDICINE



No. at Risk

Benazepril plus amlodipine	5740	5517	5404	5178	5010	4866	4298	2804	1074
Benazepril plus hydrochlorothiazide	5757	5537	5408	5222	5033	4825	4299	2529	1042

The NEW ENGLAND JOURNAL of MEDICINE



No. at Risk

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

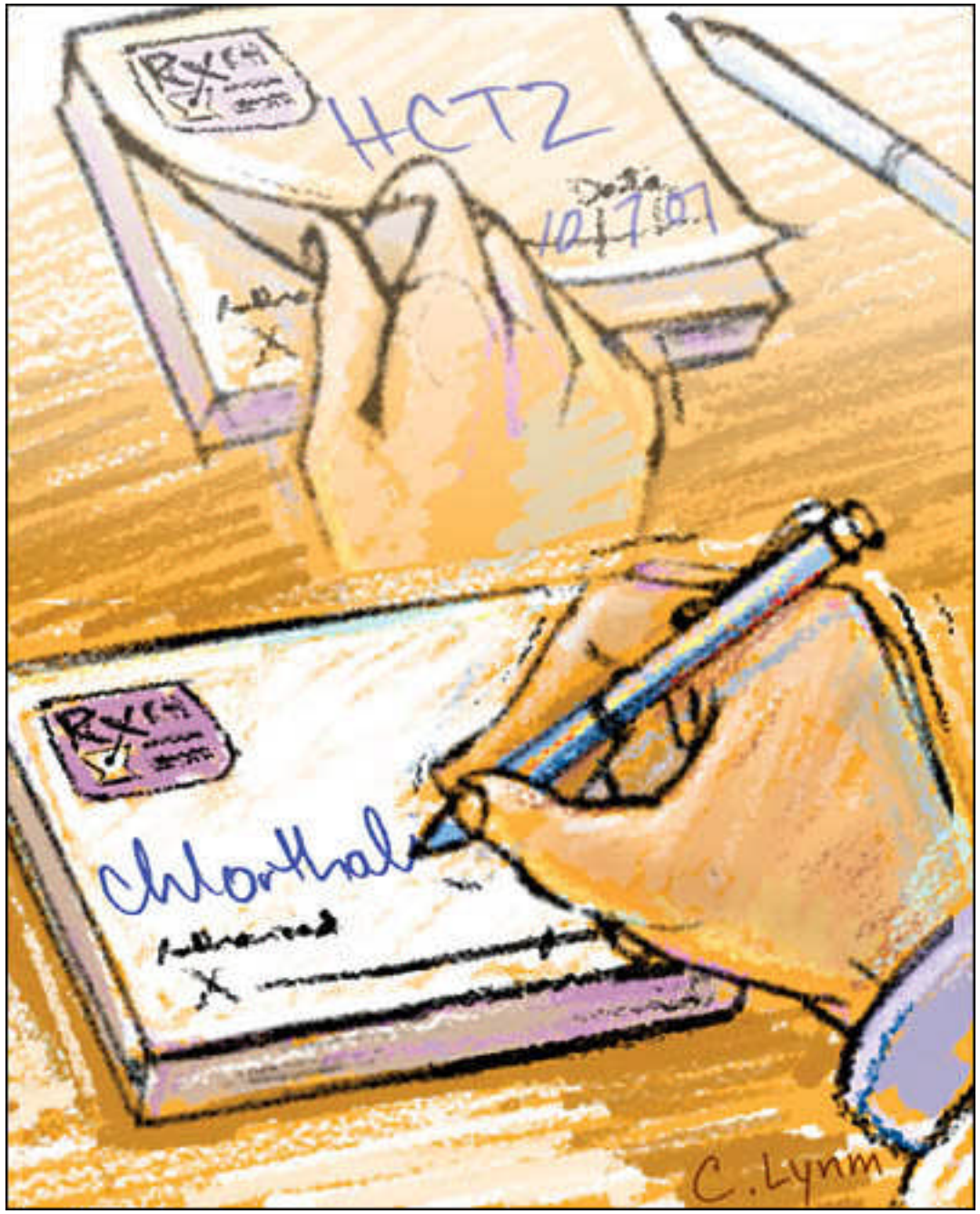
The NEW ENGLAND JOURNAL of MEDICINE

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

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”

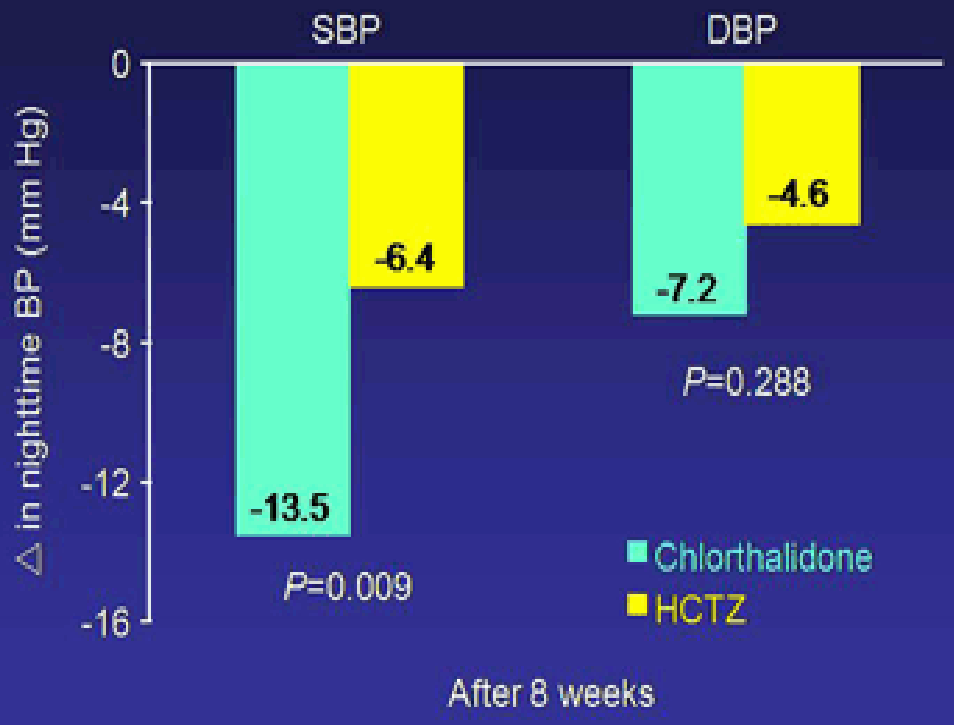
Did they choose the wrong diuretic?


Rx
HCT2
Rx
Chlorthal
C. Lynn

Chlorthalidone

The thiazide(-like) drug shown to be as good as amlodipine and lisinopril in ALLHAT was chlorthalidone. Benefits ascribed to that drug have been (wrongly) extrapolated to hydrochlorothiazide and bendrofluazide

Chlorthalidone 25 mg vs. HCTZ 50 mg Daily



Ernst ME, et al. *Hypertension*. 2006;47(3):352-358.

Chlorthalidone vs Conventional Thiazides

Chlorthalidone

- Unique molecule lacking benzothiadiazine scaffold which defines a thiazide
- 1.5-2 x more potent than HCTZ and BFZ in lowering BP
- Half-life 45-60 hours – better 24-h BP control
- Increases production of nitric oxide
- Decreases platelet aggregation and promotes angiogenesis
- Favourable mortality outcome cf HCTZ in MRFIT Trial
- Better lipid profile
- Bulk of favourable trial outcome data for thiazides with chlorthalidone

Hydrochlorothiazide and Bendrofluazide

- Typical thiazide nucleus
- Short half life (6-9 hours)
- No evidence for beneficial effect on platelets, endothelial function or nitric oxide.
- No trial evidence for outcome benefit in doses commonly used in NZ (HCTZ 12.5mg and BFZ 2.5mg)

ACE-inhibitor or ARB + Calcium channel blocker

↓

optimise doses

↓

add thiazide

↓

optimise dose

↓

minimum CLTD 12.5mg, BFZ 5mg, HCTZ 25mg

↓

where to next?

Three mechanisms known to contribute to blood pressure elevation in essential hypertension

- renin angiotensin system
- volume
- sympathetic nervous system

Clues suggesting need for more potent diuretic regimen

- High sodium intake
- Size of patient
- Presence of oedema
- Low plasma renin
- Absence of GFR drop
- Chronic kidney disease

Three mechanisms known to contribute to blood pressure elevation in essential hypertension

- renin angiotensin system
- volume
- sympathetic nervous system

Clues suggesting SNS potentiating hypertension

- Stroke
- Sleep apnoea
- Alchoholism
- Non-response to effective RAS-blockade and diuretic
- Labile or paroxysmal hypertension
- Sinus tachycardia
- Absence of clinical and biochemical clues of volume excess
- Psychological factors

If BP is not controlled on ACE-I/CCB/thiazide combination – where to go next?

more diuretic

or

spironolactone

alpha/beta blockade

New paradigms for both classes

Aldosterone

- Effects not limited to regulation of sodium and potassium handling in distal nephron
- In all animal models studies aldosterone causes vascular inflammation and myocardial injury and proteinuria independent of blood pressure
- Non-adrenal sites of aldosterone production not regulated by systemic RAAS (**fat cells** and cardiac, vascular)
- Minerallocorticoid receptors in heart and blood vessels

Spironolactone

- Most effective add-on 4th drug in resistant hypertension
- Efficacy not limited to patients with high aldosterone levels
- Beneficial effects on glucose and lipid metabolism
- Antiproteinuric effects
- Particularly effective in hypertension assoc with metabolic syndrome
- Improved outcomes in heart failure
- Counteracts thiazide-induced K+ and Mg++ wasting

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2007;49:839-845

Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension

Neil Chapman, Joanna Dobson, Sarah Wilson, Björn Dahlöf, Peter S. Sever, Hans Wedel and Neil R Poullter

If BP is not controlled on ACE-I/CCB/thiazide combination – where to go next?

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or
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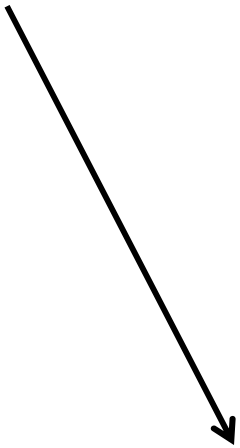

alpha/beta blockade

Why have beta blockers always been such disappointing antihypertensives – particularly when given as monotherapy?

BP reactivity

- *β-receptor–mediated increase in cardiac output and heart rate and by an*

- *α-receptor–mediated increase in peripheral resistance*

often with one or the other predominating.

Beta blockers

•Reduce heart rate and cardiac output
•Unopposed alpha activity increases peripheral vasoconstriction muting the blood pressure lowering effect

Alpha Blockers

•Cause peripheral vasodilatation
•Unopposed beta activity increases heart rate and cardiac output muting the blood pressure lowering effect

Combination of alpha and beta blockers

•Disproportionate blood pressure lowering effect compared with either class alone

The Journal of Clinical Hypertension
Volume 14, Issue 4, pages 191–197, April 2012

Bioavailability

• bioavailability extremely variable and often low due to cytochrome P450–mediated first-pass hepatic metabolism

Propranolol, metoprolol, labetolol and carvedilol

• not subject to this metabolic process

Atenolol, pindolol, bisoprolol

Most reliable way of achieving effective combined alpha and beta blockade is to combine atenolol and doxazosin

BP not at target on optimal doses of 4 drugs?

Already on metoprolol or carvedilol?

HR < 70bpm

↓

Add doxazosin 1-2mg nocte

HR > 70bpm

↓

Swap to atenolol 25mg BD

↓

Not at target

↓

add doxazosin 1-2mg nocte

↓

not at target

↓

HR > 70bpm

↓

increase atenolol to 50mg BD

BP not at target on optimal doses of 4 drugs?

Not yet on a beta blocker?

↓

HR > 70bpm

↓

add doxazosin 1-2mg nocte and atenolol 25mg BD

↓

not at target

↓

HR > 70bpm

↓

increase atenolol to 50mg BD

ACE-I or ARB + CCB

↓

Thiazide

↓

Spironolactone

↓

Alpha and beta blockade

↓

Central sympatholytic

(clonidine, methyldopa, moxonidine)

↓

Direct vasodilator

(minoxidil or hydralazine)

Are some drugs better than others within same class?

RCT evidence is scanty but:

Consider replacing

- HCTZ or bendrofluazide with chlorthalidone
- felodipine with amlodipine
- metoprolol or carvedilol with atenolol
- labetolol with atenolol + doxazosin
- cilazapril 5mg daily or quinapril 20mg daily, with lisinopril 40mg daily
- losartan 100mg daily with candesartan 32mg daily

Combining calcium channel blockers?

Reserve non-DHP CCB's (diltiazem and verapamil) for patients intolerant of amlodipine and beta blocker

Safe to add non-DHP CCB to amlodipine but coexisting beta blocker may preclude this option

Chronic Kidney Disease

At GFR 30-40ml/min thiazides become ineffective

Replace with loop diuretic

Who should be considered for catheter-based renal sympathetic nerve ablation?

Severe refractory hypertension eg > 160/100 on 6-7 drugs?

Refractory hypertension due to multiple drug intolerances?

Unacceptable antihypertensive side effects? (eg hirsutism in women on minoxidil)

Take home messages

1. The 2 commonest causes of resistant hypertension are
   - Unrecognised volume excess/ underuse of diuretics
   - Untreated sympathetic overactivity

2. Neither HTCZ 12.5mg nor BFZ 2.5mg have been associated with beneficial outcome in RCT’s

Thank You

…late breaking news

•All the excess cardiovascular risk in the benazapril-HCTZ arm seen in individuals with normal or low BMI

• Outcomes in HCTZ and amlodipine arms similar for overweight and obese individuals

• Similar results reported on reanalysis of SHEP Trial**

***JAMA 1991*

What do we take from this? (hypothesis)

Overweight and obese patients have important sodium/volume component to their hypertension (due to sympathetic activation and other mechanisms) and benefit from diuretic therapy

Normal weight and thin hypertensives? higher renin, vasoconstricted profile, and diuretics may increase cardiovascular risk.