

Managing Hypertension: have we ACCOMPLISHED anything at ALL or still drawing drugs out of a HAT?

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Disclosure information

No conflicts of interest to declare

Objectives

- To be familiar with the therapeutic controversy of thiazide diuretic interchangeability
- To be familiar with the differences between HCTZ and chlorthalidone with respect to PK/PD and supporting evidence for these agents
- To be familiar with the signs, symptoms of diuretic induced hyponatremia and predisposing factors

Objectives

- To be familiar with the latest evidence for treatment of hypertension in the elderly
- To be familiar the role of & latest evidence supporting non-drug measures to manage hypertension
- To be familiar with new upcoming agents in hypertension

Case

- 83 year old female admit to ICU with status epilepticus
- HPI: Fell at home, C6/7 #, OR for repair Aug 14th. On Aug 23rd became ↑ confused & ↓ LOC. Stat electrolytes showed serum Na of 100. This was gradually corrected to 123 over 3 days. She thereafter developed status epilepticus and was transferred to ICU.


Case

- PMHx
 - HTN
 - OP
 - Hypothyroidism
- Meds PTA
 - Telmisartan 80 mg daily
 - HCTZ 25 mg daily
 - Felodipine 2.5 mg daily
 - Atenolol 25 mg bid

- ICU decided severe hyponatremia secondary to HCTZ in post operative phase
- ICU attending wrote ...
 - ALLERGY: HCTZ – severe hyponatremia

Points of pontification...

- Did this patient have her drugs pulled out of a hat or was there a method to this cocktail?
- Have we ACCOMPLISHED anything in the literature that can improve the magic of managing her?
- Do we really need 4 drugs at sub-optimal doses?



Canadian Impact

- HTN affects 1 in 5 Canadians
- #1 risk factor for heart disease
- 42% are unaware of the presence of HTN

<http://www.heartandstroke.com/site/c.ikiQLcMWJtE/b.3484023/>
last accessed Dec 13, 2007

Top 10 diagnoses in Canada

All diagnoses	Patient visits***	% Male	% Female	% Patient visits with drug recommendations
1 Hypertension	20,938	48	52	81
2 Health check-up**	10,649	45	55	1
3 Diabetes mellitus w/o complications	9,486	53	47	68
4 Depression	8,529	32	68	82
5 Anxiety	6,292	33	67	57
6 Acute upper respiratory infection	5,780	45	55	40
7 Normal pregnancy supervision	5,445	0	100	15
8 Hyperlipidemia	5,003	60	40	81
9 Unspecified otitis media	3,565	50	50	75
10 Urinary tract infection	3,484	10	90	85

* Based on ICD 9 classifications.
IMS Health, Canada 2009 http://us.imshealth.com/canada/Trends06_En_09.pdf

Top 10 dispensed classes in Canada

Rank 2008	Therapeutic class	Prescriptions dispensed** 2008 (000s)	% Change over 2007
1	Cardiovasculars	70,848	7.8
2	Psychotherapeutics	57,198	7.3
3	Gastrointestinal/Genitourinary	30,531	11.7
4	Cholesterol agents	29,549	11.1
5	Hormones	25,243	2.5
6	Anti-infectives systemic	24,495	1.0
7	Analgesics	22,049	7.5
8	Diabetes therapy	19,707	7.7
9	Neurological disorders	18,085	12.1
10	Diuretics	17,079	4.4
Total prescriptions		453,074	7.1

IMS Health, Canada 2009 http://us.imshealth.com/canada/Trends06_En_09.pdf

Challenges to therapy

- Most patients need ≥ 2 medications
- Multidrug regimens are associated with lower adherence rates
 - Lower adherence = inadequate BP control
- “Therapeutic inertia”

Hypertension 2009;53:646-53; Clin Ther 2001;23:1296-1310; Am Fam Physician 2005;71:2089-90

ORIGINAL CONTRIBUTION JAMA-EXPRESS

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)

JAMA 2002;288:2981-97

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Eligible for BP trial: Hypertension >55 years At least 1 other CVD risk factor

42,418 Eligible Participants Enrolled & Randomized to 5 years of Double-Blind Treatment

Chlorthalidone Amlodipine Lisinopril Doxazosin

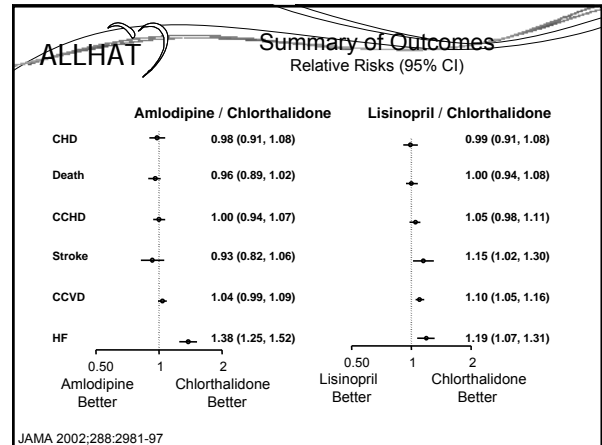
BP Trial Primary End Points: -Fatal CHD & Non-Fatal MI
BP Trial Secondary End Points: -All-cause mortality -Stroke -Combined CHD -Fatal CHD, non-fatal MI, coronary revascularization, hospitalized angina -Combined CVD -combined CHD, stroke, lower extremity revascularization, treated angina, fatal / hospitalized / treated heart failure (HF), hospitalized or outpatient peripheral arterial disease (PAD) -Other -renal (reciprocal serum creatinine, ESRD, estimated GFR) and cancer

Predefined Subgroups: -Age (<65 y; 65+y) -Gender -Race (Black; Non-Black) -Diabetes

Discontinued due to higher relative risk of CVD events in doxazosin compared to chlorthalidone group

Baseline Characteristics (33,357 Participants)

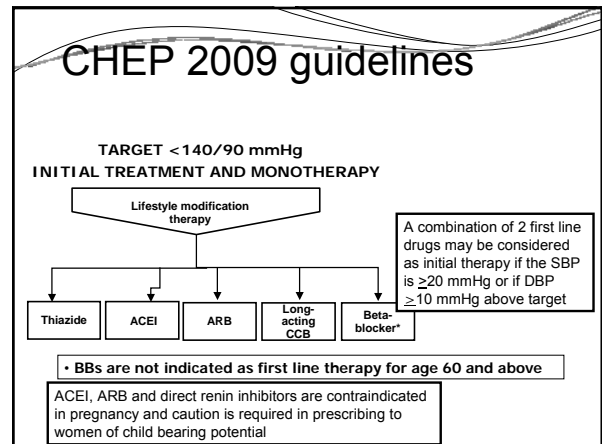
	Chlorthalidone	Amlodipine	Lisinopril
Sample Size	15,255	9,048	9,054
Mean age, years	67	67	67
Mean SBP/DBP	145 / 83	145 / 83	145 / 83
Mean BMI, kg/m ²	30	30	30
Women, %	47	47	46
Black %	35	36	35
Current smoking %	22	22	22
ASCVD, %	47	46	47
History of CHD, %	26	24	25
Type II diabetes, %	36	37	35



JNC 7

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

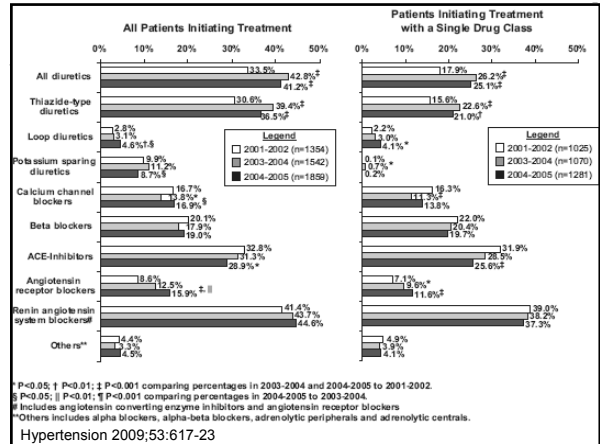
BP CLASSIFICATION	SBP* MMHg	DBP* MMHg	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
NORMAL	<120	and <80	Encourage		
PREHYPERTENSION	120-139	or 80-89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications. [†]
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).	



Antihypertensive Prescriptions for Newly Treated Patients Before and After the Main Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Results and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines

Paul Munter, Marie Krousel-Wood, Amanda D. Hyde, Erin Stanley, William C.ushman, Jeffrey A. Cutler, Linda B. Piller, Gary A. Goforth, Paul K. Whelton

Hypertension 2009;53:617-23



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359, NO. 23

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., Berttram Pitt, M.D., Victor Shi, M.D., Allen Hester, Ph.D., Jitendra Gupta, M.S., Marjorie Gaslin, M.D., and Eric J. Velazquez, M.D., for the ACCOMPLISH trial investigators*

Patients	HTN patients, age > 60, SBP ≥160mmHg on HTN tx, evidence of CVS or CKD or target organ damage and one of the following: previous MI, stroke/TIA, UA hospitalization, coronary revascularization, PAD, DM, LVH or SrCr >133 umol/L OR age 55-59 if evidence of ≥2 CV diseases or target organ damage
N= 11, 506	
Mean follow up: 36 mths	
Excluded:	angina prior 3 mths, HF or LVEF <40%, MI/ACS in prior month, stroke within 3 mths, severe refractory HTN
Intervention	Benazepril 40 mg + amlodipine 10 mg vs.
Comparator	Benazepril 40 mg + HCTZ 25 mg
Outcome	1 ^o EP: CV death, non fatal MI & stroke, hospitalization for angina, resuscitation after sudden cardiac arrest & coronary revascularization

NEJM 2008;359(23):2417-28

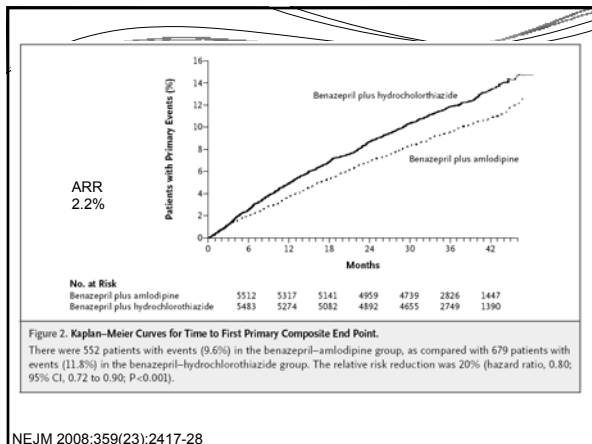


Table 3. Results of Prespecified Safety Analysis.*

Adverse Event	Any		Serious		Drug-Related Serious	
	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazide Group (N=5762)	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazide Group (N=5762)	Benazepril-Amlodipine Group (N=5744)	Benazepril-Hydrochlorothiazide Group (N=5762)
	number (percent)					
Dizziness	1189 (20.7)	1461 (25.4)	18 (0.3)	31 (0.5)	2 (<0.1)	5 (0.1)
Peripheral edema	1792 (31.2)	772 (13.4)	10 (0.2)	8 (0.1)	4 (0.1)	2 (<0.1)
Dry cough	1177 (20.5)	1220 (21.2)	7 (0.1)	7 (0.1)	3 (0.1)	3 (0.1)
Angioedema	53 (0.9)	34 (0.6)	7 (0.1)	13 (0.2)	2 (<0.1)	5 (0.1)
Hyperkalemia	34 (0.6)	33 (0.6)	10 (0.2)	11 (0.2)	6 (0.1)	6 (0.1)
Hypokalemia	3 (0.1)	17 (0.3)	2 (<0.1)	12 (0.2)	1 (<0.1)	0
Hypotension	142 (2.5)	208 (3.6)	22 (0.4)	30 (0.5)	6 (0.1)	9 (0.2)

NEJM 2008;359(23):2417-28

Results summarized

Endpoints	ACEI + Amlodipine % n=5744	ACEI + HCT % n=5762	ARR %	RRR %	NNT/3yrs	p value
CV death, non fatal MI & stroke, hospitalization for angina, revascularization after sudden cardiac arrest & coronary revas.	9.6 (552 events)	11.8 (679 events)	2.2	18.4	46 (95% CI 38-54)	<0.001
CV death, non fatal MI & stroke (ACEI + HCT)	5.0 (283 events)	6.3 (364 events)	1.3	21	77 (95% CI 67-87)	0.002
coronary revascularization	5.8	6.7	0.9	14	113	0.04
fatal & non-fatal MI	2.2	2.8	0.6	21	171	0.04
fatal & non-fatal stroke	1.9	2.3	0.4	17	NS	0.17
hospitalizations for heart failure	1.7	1.7	-	-	NS	0.77
CVD mortality	1.9	2.3	0.4	17	NS	0.08
mortality-all cause	4.1	4.5	0.4	9	NS	0.24
Discontinuation due to adverse events	13.4	14.3	0.9	6.3	NS	0.6

- ### Points to ponder...
- Is the benefit of the CCB + ACE arm secondary to...
 - Synergistic combination of CCB + ACE?
 - ~18% of patients had a GFR < 60 ml/min – impaired diuretic efficacy?
 - Was there a difference in 24 hr blood pressure control between the groups?
 - Inferior diuretic?

heartwire

More of our ESH 2009 coverage »

HYPERTENSION
HCTZ a "paltry" antihypertensive, with no effect on outcomes, new analysis suggests

JUNE 16, 2009 | Lisa Nainggolan

Download slides

“HCTZ, the most commonly employed blood-pressure-lowering drug in the US, is a "paltry" antihypertensive, inferior to all other drug classes, and there is no published evidence that it reduces heart attack or stroke”- Dr. Messerli

<http://www.theheart.org/article/978957.do>

Reductions in mean ambulatory BP with HCTZ and other drug classes

Drug class	Reduction in 24-h ABPM (mm Hg)– systolic	Reduction in 24-h ABPM (mmHg)– diastolic
HCTZ	7.5	4.6
ACE inhibitors	12.9	7.6
ARBs	13.3	7.8
Beta blockers	11.2	8.5
Calcium antagonists	11.0	8.1

<http://www.theheart.org/article/978957.do>

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Hydrochlorothiazide Versus Chlorthalidone: Evidence Supporting Their Interchangeability

Barry L. Carter, Michael E. Ernst and Jerome D. Cohen
Hypertension 2004;43:4-9; originally published online Nov 24, 2003.
DOI: 10.1161/01.HYP.0000103652.19915.0E

Learn and Live™

PK/PD comparisons

TABLE 1. Pharmacokinetic and Pharmacodynamic Comparisons of HCTZ and Chlorthalidone

Drug	Onset, h	Peak, h	Half-Life, h	Duration, h
HCTZ	2	4-6	6-9 (Single dose)	12 (Single dose)
			8-15 (Long-term dosing)	16-24 (Long-term dosing)
Chlorthalidone	2-3	2-6	40 (Single dose)	24-48 (Single dose)
			45-60 (Long-term dosing)	48-72 (Long-term dosing)

Hypertension 2004;43:4-9

TABLE 3. Comparative Trials of HCTZ and Chlorthalidone

Author, y (Sample Size)	Diuretic Doses	BP Reduction, mm Hg
Bowlus et al, 1964 ⁸⁷ (n=19)	HCTZ 100 mg daily	18/8
	Chlorthalidone 50 mg daily	25/10
Clark et al, 1979 ⁹⁰ (n=126)	HCTZ 25 mg+triamterene 50 mg daily	15/8
	HCTZ 50 mg+triamterene 100 mg daily	18/12
Finnerty, 1976 ⁸⁸ (n=55)	Chlorthalidone 50 mg daily	25/16
	HCTZ 50 mg twice daily (100 mg daily)	22/16
	Chlorthalidone 50 mg daily	18/15

Hypertension 2004;43:4-9

Authors' bottom line

- The weight of the evidence suggests clinicians should use one of these two agents as preferred diuretic for treating hypertension. Most patients will respond to 12.5-25 mg of HCTZ, but max doses of 50 mg maybe necessary in some patients. Studies should be conducted that compare these 2 agents in lower doses to help elucidate whether one agent is clearly superior for management of HTN.

Hypertension 2004;43:4-9

Hypertension American Heart Association
JOURNAL OF THE AMERICAN HEART ASSOCIATION *Learn and Live*

Comparative Antihypertensive Effects of Hydrochlorothiazide and Chlorthalidone on Ambulatory and Office Blood Pressure
 Michael E. Ernst, Barry L. Carter, Chris J. Goerdt, Jennifer J.G. Steffensmeier, Beth Bryles Phillips, M. Bridget Zimmerman and George R. Bergus
Hypertension 2006;47:352-358, originally published online Jan 23, 2006.

Patients N=30 patients	Inclusion: age 18-79, pre-hypertension or a new or established diagnosis of stage 1 or 2 HTN, not receiving any antihypertensives, average BP in last 6 mths of 140-179 systolic or 90-109 mmHg diastolic Exclusion: use of antihypertensive in last 3 mths, type 1 or 2 DM, CRI, pregnancy, dementia or other cognitive impairment impairing ability to give consent, history of ischemic stroke/UA/MI within last 6 mth, chronic decongestants or sympathomimetics or NSAIDS, documented ETOH, gout, Afib
Intervention	Randomized, single blind, 8 week, active treatment, cross over trial with 4 week washout of HCTZ 50 mg vs.
Comparator	chlorthalidone 25 mg
Outcome	1 ^o EP: change in 24-hour mean SBP & DBP in ambulatory BP from baseline to week 8 2 ^o EP: change in ambulatory daytime and nighttime mean SBP & DBP from baseline to week 8, rates of hypokalemia

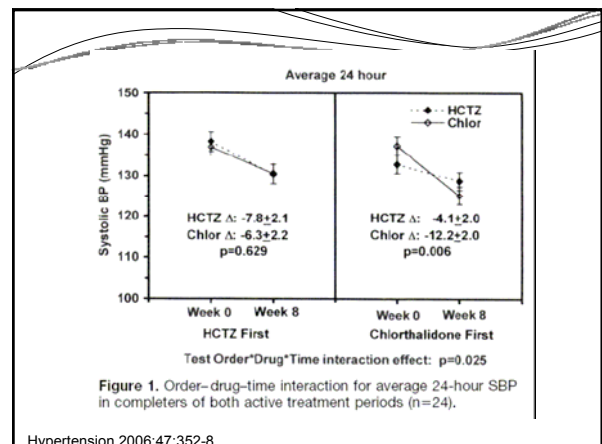
Hypertension 2006;47:352-8

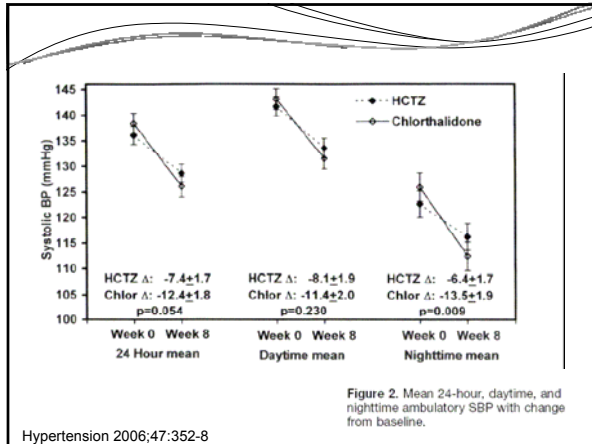
Baseline Demographic Characteristics of Subjects Completing Study Period 1 (n=30)

Variable	HCTZ (n=16)	Chlorthalidone (n=14)	P Value
Sex (male)	9 (56%)	7 (50%)	1.0
Ethnicity (white)	13 (81%)	12 (86%)	1.0
Age	49±11	46±15	0.582
Weight, kg	90.1±17.4	80.0±15.0	0.103
Height, cm	173.6±10.0	173.0±9.4	0.873
Body mass index	29.7±4.0	26.6±3.4	0.029
Glomerular filtration rate, mL/min (MDRD method)	86.4±13.2	87.5±15.4	0.840
Office SBP, mm Hg	140.1±12.7	144.9±9.8	0.255
Office DBP, mm Hg	91.1±11.5	95.6±7.2	0.215
Serum potassium, meq/L	4.2±0.3	4.2±0.2	0.85

Values reported as mean±SD. MDRD indicates Modification of Diet in Renal Disease Study Group.

Hypertension 2006;47:352-8





Rates of hypokalemia

	Chlorthalidone	HCTZ
Serum K < 3.5 mmol/L*	46%	50%
HCTZ first	55%	45%
Chlorthalidone first	38%	54%

*serum K measured every 2 weeks, patients were advised to eat foods high in K during the study

Hypertension 2006;47:352-8

Authors' conclusions

- "...our ABPM findings suggest the intriguing prospect that a difference in cardiovascular outcomes is possible between HCTZ and chlorthalidone..."
- "... affirms that chlorthalidone is approximately twice as potent as HCTZ..."

ASH: Calcium Channel Blocker Benefits in ACCOMPLISH Not Explained by Ambulatory BP

Posted by: UKAdmin in General nephrology on Jun 2, 2009

Tagged in: hypertension , clinical trials

By Crystal Phend, Staff Writer, MedPage Today
 Published: May 12, 2009
 Reviewed by Zalman S. Agus, MD; Emeritus Professor
 University of Pennsylvania School of Medicine.

SAN FRANCISCO, May 12 -- Ambulatory blood pressure monitoring didn't explain the cardiovascular advantage of calcium channel blockade found in the ACCOMPLISH trial, researchers said.

573 patients underwent 24 hr ABPM at 2 years. SBP was 1.6 mmHg lower with benazepril and HCTZ compared to benazepril and amlodipine - NSS

Reductions in mean ambulatory BP with HCTZ and other drug classes

Drug class	Reduction in 24-h ABPM (mm Hg) -- systolic	Reduction in 24-h ABPM (mmHg) -- diastolic
Calcium antagonists	11.0	8.1

"...and then we were curious: what are the data showing HCTZ reduces heart attack and stroke? There are none. No study showing that 12.5 mg to 25 mg of HCTZ reduces morbidity and mortality." Dr. Frank Messerli

<http://www.theheart.org/article/978957.do>

Chlorthalidone		Hydrochlorothiazide	
Study	Endpoint	Study	Results
ALLHAT JAMA 2002	↓ CVD vs. lisinopril, ↓ HF vs. amlodipine	ANBP -2 NEJM 2003 Choice of dose per MD	NSS CVD ↑ MI vs. enalapril
SHELL Blood Press 2003 Chlorthalidone 12.5 mg	NSS vs. lacidipine in CVD	EWPHE 1985 HCTZ 25-50 mg + triamterene	↓ MI vs. placebo NSS dif in strokes
SHEP JAMA 1991 Chlorthalidone 25 mg	↓ CVD vs. placebo	HAPPHY J Hypertens 1987 BFTZ/HCTZ 50 mg	NSS CHD, death, ↑ strokes vs. atenolol
SHEP -- PS Stroke 1989 Chlorthalidone 12.5 mg	NSS vs. placebo	INSIGHT Lancet 2000 HCTZ 25/amlodide 2.5	1° EP: NSS to nifedipine
VHAS J Hypertens 1997 Chlorthalidone 25 mg	NSS vs. verapamil	MAPHY JAMA 1988 HCTZ 50 mg/day	inferior to metoprolol
VA-NHLBI Ann N Y Acad Sci 1978 Chlorthalidone 50 mg	NSS vs. placebo	VA I JAMA 1967 HCTZ 50 mg + reserpine	↓ Total mortality vs. placebo
MR FIT Circulation 1990 chlorthalidone 50-100 mg	↓ CVD vs. placebo	MRC-oid Br Med J 1992 HCTZ 25/amlodide 2.5	Superior vs. atenolol
		OSLO Am J Med 1980 HCTZ 50 mg	NSS vs. placebo
		MIDAS JAMA 1996	IMT- NSS vs. CCB

Tran et al. Thiazide Diuretics as first line treatment for HTN: meta analysis and economic evaluation. www.cadth.ca

Bottom line

- Chlorthalidone is a reasonable choice

Harjinder Parwana: "chlorthalidone for my mom... and HCTZ is good enough for my mother in law..."

Case

- 83 year old female admit to ICU with status epilepticus
- PMHx
 - HTN
 - OP
 - hypothyroidism
- Meds PTA
 - Telmisartan 80 mg
 - HCTZ 25 mg
 - Felodipine 2.5 mg
 - Atenolol 25 mg bid

1. If no hyponatremia, would you consider changing her to chlorthalidone? Or optimize the dose of HCTZ?
2. Is there utility to being so aggressive in an 83 year old?

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2008 VOL. 358 NO. 18

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

Patients	Inclusion: ≥80 y/o with HTN (≥160 mmHg)
N= 3845 Median follow up: 1.8 years	Exclusion: accelerated HTN, secondary HTN, hemorrhagic stroke in last 6 mths, HF requiring treatment with antiHTN meds, SrCr > 150 umol/L, Sr K < 3.5 mmol/l or > 5.5 mmol/L, gout, dementia, requirement of nursing care
Intervention	Indapamide 1.5 mg +/- perindopril 2 or 4 mg for a target BP < 150/80 mmHg
Comparator	Placebo
Outcome	1° EP: fatal or non-fatal stroke (not including TIAs) 2° EP: death from any cause, CVD, death by stroke

NEJM 2008;358(18):1887-98

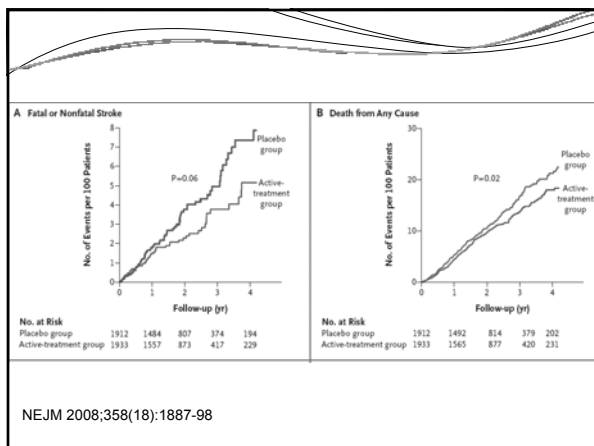


Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

End Point	Rate per 1000 Patient-Yr (No. of Events)		Unadjusted Hazard Ratio (95% CI)	P Value
	Active	Placebo		
Stroke	no. (%)	no. (%)		
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.

NEJM 2008;358(18):1887-98

Points to ponder

- Primarily Eastern European and Chinese centres
 - Higher rate of stroke than North Americans
- Very healthy, elderly patients – does not apply to the frail, elderly

Case

- 83 year old female admit to ICU with status epilepticus
- PMHx
 - HTN
 - OP
 - hypothyroidism
- Meds PTA
 - Telmisartan 80 mg
 - HCTZ 25 mg
 - Felodipine 2.5 mg
 - Atenolol 25 mg bid

We've established need for ongoing treatment – can we use a thiazide diuretic?

Diuretic induced hyponatremia

Diuretic induced hyponatremia
Y Sharabi *et al*

Table 3 Clinical symptoms on admission

Clinical symptom	Prevalence (%)
Weakness	39.4
Vomiting	37.8
Nausea	26.7
Confusion	16.7
Dizziness	15.0
Abdominal pain	12.2
Asymptomatic	17.2

Journal of Human Hypertension 2002;16:631-35

Risk factors for thiazide induced hyponatremia

Table 1 Patients' characteristics

	Mean ± SD	Range
Number of patients	180	–
Gender (M/F)	31/149	–
Age (years)	76.4 ± 9.6	45–95
Patients >65 years	162	–
SBP (mm Hg)	165 ± 33	80–240
DBP (mm Hg)	88 ± 15	50–130
Serum sodium (mmol/L)	120 ± 6	90–134
Serum potassium (mmol/L)	3.8 ± 0.7	2.1–6.2
Serum osmolality	257 ± 14	226–282
Serum creatinine (mg/dL)	1.1 ± 1.0	0.5–12.0
Serum urea (mg/dL)	36 ± 22	6–156

SD = standard deviation; M = male; F = female; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Journal of Human Hypertension 2002;16:631-35

Diuretic induced hyponatremia

- In the SHEP study 4.1% of elderly HTN patients developed hyponatremia (Na < 130mmol/L)
- Retrospective review of patients admitted with hyponatremia
 - Diagnosed within 1 month of treatment in 44% of patients
 - After > 6 mths of treatment in 45% of patients
 - Within first 10 days of treatment in 37%

Journal of Human Hypertension 2002;16:631-35

How to prevent hyponatremia?

- Use low doses
- Monitor serum Na closely
 - If Sr Na decreases more than “a few” mEq/L within one day of beginning therapy – stop diuretic
 - Re-check in 1-2 days to be sure stable
- Counsel patients to avoid excess free water

Am J of Neph;1999(19):447-52

Case

- 83 year old female admit to ICU with status epilepticus
- PMHx
 - HTN
 - OP
 - hypothyroidism
- Meds PTA
 - Telmisartan 80 mg
 - HCTZ 25 mg
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 - Atenolol 25 mg bid

We've established the need for ongoing treatment – can we use a thiazide diuretic? Given her severity of presentation, would not re-challenge

What about the need to have so many other medications at “sub-optimal” doses?

Simplified Treatment Intervention to Control Hypertension (STITCH): Objective & Study Design

To assess if the use of a fixed-dose combination as initial treatment of HTN will improve the proportion of patients reaching goal BP as compared with the use of the Canadian HTN Education Program (CHEP) algorithm

2104 patients from 45 primary care practices in southern Ontario

Guideline-Care Algorithm (27 Practices) STITCH-Care Algorithm (18 Practices)

Primary endpoint: proportion of patients reaching BP target (practice level) at 6 months

HYPERTENSION Feldman RD, et al. Hypertension. 2009;53:646-653. the heart.org

STITCH: Study Design

CHEP Guidelines: Treatment of HTN Without Other Compelling Indications
Target SBP < 140 DBP < 90 mmHg

STITCH – Care Algorithm

Initial therapy with a low-dose ACE-diuretic or ARB/diuretic combination

BP controlled?

- Yes: Continue with current therapy
- No: Uptitrate combination therapy successively to the highest dose

BP controlled? (after uptitration)

- Yes: Continue with current therapy
- No: Add CCB and uptitrate

BP controlled? (after adding CCB)

- Yes: Continue with current therapy
- No: Add alpha blocker, beta-blocker or spironolactone

Lifestyle Modification Therapy

Thiazide Diuretic, ACE-I, ARB, Long-Acting CCB, beta-blocker

Dual Combination, Triple or Quadruple Therapy

Consider: Nonadherence? Secondary HTN? Interfering drugs or lifestyle? White-coat effect?

HYPERTENSION Feldman RD, et al. Hypertension. 2009;53:646-653. the heart.org

STITCH Results: Systolic BP Reductions

	Baseline BP (mmHg)	6-month BP (mmHg)	BP change (mmHg) (95% CI)	P value (6 mo vs baseline)
Guideline-Care	153.4	136.1	-17.2 (-19.8,-15.6)	.03
STITCH-Care	155.2	132.2	-22.6 (-25.6,-20.4)	.002

Change in SBP (mmHg)

Guideline-Care: -17.2 STITCH-Care: -22.6

P < .005 between groups

HYPERTENSION Feldman RD, et al. Hypertension. 2009;53:646-653. the heart.org

STITCH Results: % Patients Reaching Goal BP at 6 Months

Guideline Care: 52.7% STITCH Care: 64.7%

P < .05

HYPERTENSION Feldman RD, et al. Hypertension. 2009;53:646-653. the heart.org


Points to ponder

- Cost of combination pills at half doses vs. up titration of monotherapy
 - System cost of “therapeutic inertia” implications vs. patient cost of combination pill
- Adverse events not reported
- Interactions 2⁰ to polypharmacy
 - especially in elderly patients
- Compliance rates in the long term?

Dietary Salt recommendations

Less than:

- 2,300 mg sodium (Na)
- 100 mmol sodium (Na)
- 5.8 g of salt (NaCl)
- 1 teaspoon of table salt



2,300 mg sodium = 1 level teaspoon of table salt however, 80% of average sodium intake is in processed foods and only 10% is added at the table or in cooking

2009 Canadian Hypertension Education Program Recommendations

Hypertension

American Heart Association
JOURNAL OF THE AMERICAN HEART ASSOCIATION
Learn and Live™

Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension: Results From a Randomized Trial
 Eduardo Piovella, Kriviana K. Guddim, Suzanne Oparil, Inmaculada Aban, Saima Husain, Louis J. Dell’Italia and David A. Calhoun
Hypertension 2009;54:475-481; originally published online Jul 20, 2009;

Patients N= 12	Inclusion: resistant HTN (>140/90 at ≥2 visits while on ≥3 antiHTN meds on “effective doses”; stable drug regimen for at least 4 weeks (including diuretic) Exclusion: history of atherosclerotic disease (MI or stroke in previous 6 mths), CHF, DM on insulin or if BP > 160/100 mmHg
Intervention	4 week randomized, crossover evaluation of low (50 mmol) of Na per day OR
Comparator	High salt diet (>250 mmol/day) for 1 week with a 2 week washout period in between cross over
Outcome	Body weight, office BP, 24 hour ABPM determined before and after randomization and end of each 1 week dietary interval

Hypertension 2006;47:352-8

Table 2. Values During Ingestion of Low- and High-Salt Diets

Characteristics	High-Salt (Mean ±SD)	Low-Salt (Mean ±SD)	Mean Change Between High- and Low-Salt (95% CI)	P
Weight, kg	91.5 ±16.4	90.1 ±15.4	-0.9 (-1.73; 0.04)	0.0421
Serum potassium, mg/dL	3.8 ±0.3	4.1 ±0.5	0.3 (0.02; 0.61)	0.0386
Serum creatinine, mg/dL	1.0 ±0.2	1.0 ±0.2	...	0.1945
Brain natriuretic peptide, pg/mL	37.9 ±31.9	13.4 ±10.8	-23.2 (-37.4; -9.0)	0.0041
Plasma aldosterone, ng/dL	10.8 ±4.9	14.4 ±5.1	...	0.0604
Plasma renin activity, ng/mL/h	0.6 ±0.71	2.7 ±15.2	1.85 (0; 18.8)*	0.042*
Urinary aldosterone, mcg/24 hours	11.7 ±5.1	16.5 ±7.9	5.0 (1.2; 8.9)	0.0149
Urinary sodium, mmol/24 hours	252.2 ±64.6	46.1 ±26.8	-206.6 (-231.5; -181.8)	<0.0001
Urinary potassium, mmol/24 hours	53.2 ±17.8	66.0 ±26.4	11.4 (0.1; 22.7)	0.0487
Creatinine clearance, mL/min	117.5 ±33.5	95.3 ±29.7	-21.4 (-39.0; -3.8)	0.0218
Ab, %	29.7 ±16.5	26.6 ±12.9	...	0.0554
PWV, m/s	10.9 ±2.6	9.2 ±1.8	...	0.1671
Office BP, mm Hg				
Systolic	145.6 ±15.1	122.8 ±14.8	-22.7 (-33.5; -11.9)	0.0008
Diastolic	84.9 ±12.1	74.9 ±12.5	-9.1 (-15.1; -3.1)	0.0065
ABPM, mm Hg				
Daytime systolic	152.3 ±13.3	131.2 ±14.2	-20.7 (-29.1; -12.4)	0.0002
Daytime diastolic	84.5 ±6.5	75.4 ±9.1	-9.6 (-14.0; -5.3)	0.0005
Nighttime systolic	146.8 ±20.2	126.7 ±11.7	-20.3 (-32.3; -8.3)	0.0034
Nighttime diastolic	76.9 ±8.3	67.8 ±4.5	-9.9 (-15.0; -4.8)	0.0013
24-hour systolic	150.3 ±15.1	130.0 ±11.6	-20.1 (-28.1; -12.1)	0.0002
24-hour diastolic	82.1 ±6.7	72.8 ±6.9	-9.3 (-13.6; -5.0)	0.0002

Ab, antihypertensive agent; PWV, pulse wave velocity; BP, blood pressure; ABPM, ambulatory BP monitoring.
 *P value and 95% confidence interval for the median are based on the sign test.
 †Median ± interquartile range are presented because there was 1 outlier; PRA increased up to 120 ng/mL/h in 1 subject during low-salt diet intake.

Hypertension 2009;54:475-81

Authors' conclusions

- "...that in patients with resistant hypertension, a low-salt diet may be more effective than increasing the number of antihypertensive medications.."

Points to ponder

- Degree of BP reduction is much larger than in normotensive or general hypertensive cohorts
 - DASH decreased 24-hr BP by 5/2 mmHg after 5 weeks
- Unblinded administration of salt diets
- Short duration- does the effect last?
- Can this level of dietary sodium restriction be achieved in real life?
 - 75% of daily intake in Western countries is from salt added during commercial processing of foods or food prep in restaurants

Sodium content of foods

Food	Serving	Sodium (mg)
Chicken noodle soup	1 cup	1106
Cheese, cottage	1 cup	851
Cheeseburger with condiments	1 sandwich	616
Plain bagel	4 in bagel	475
Mixed vegetables, drained	1 cup	243
Raw carrots	1 cup	76
Fish, salmon, cooked	½ fillet	102

Lifestyle Recommendations for Hypertension: Physical Activity

Should be prescribed to reduce blood pressure

F Frequency - Four to seven days per week

I Intensity - Moderate

T Time - 30-60 minutes

T Type
 Cardiorespiratory activity
 - Walking, jogging
 - Cycling
 - Non-competitive swimming

Exercise should be prescribed as adjunctive to pharmacological therapy


2009 Canadian Hypertension Education Program Recommendations

Lifestyle Recommendations for Hypertension: Alcohol

Low risk alcohol consumption

- 0-2 standard drinks/day
- Men: maximum of 14 standard drinks/week
- Women: maximum of 9 standard drinks/week

A standard drink is about 142 ml or 5 oz of wine (12% alcohol), 341 mL or 12 oz of beer (5% alcohol) 43 mL or 1.5 oz of spirits (40% alcohol).



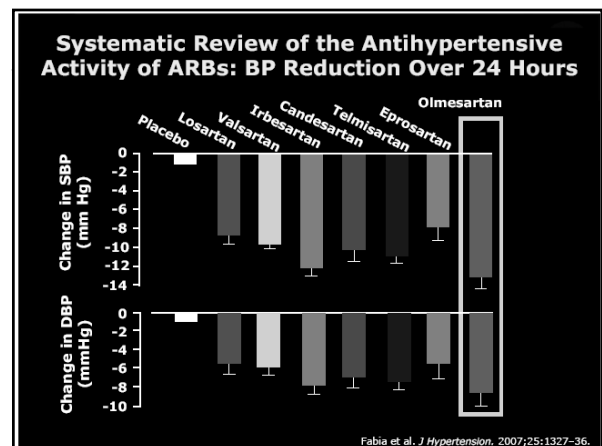
2009 Canadian Hypertension Education Program Recommendations

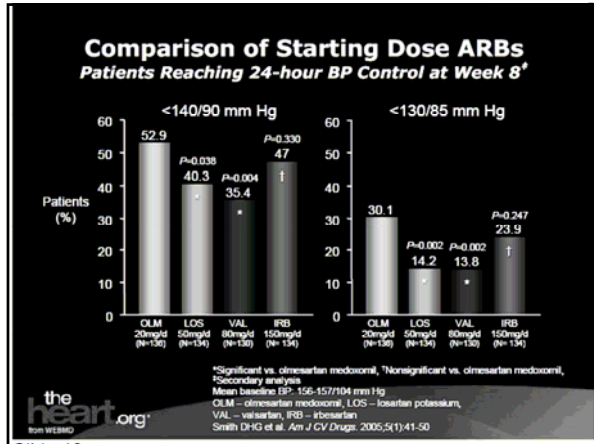
Impact of Lifestyle Therapies on Blood Pressure in Hypertensive Adults

Intervention	Amount	SBP/DBP
Reduce foods with added sodium	1.8g or 78 mmol/d	-5.1 / -2.7
Weight loss	per kg lost	-1.1 / -0.9
Alcohol intake	- 3.6 drinks/day	-3.9 / -2.4
Aerobic exercise	120-150 min/week	-4.9 / -3.7
Dietary patterns	DASH diet	-11.4 / -5.5
	Hypertensive	-3.6 / -1.8
	Normotensive	

2009 Canadian Hypertension Education Program Recommendations

- ### New agents
- Aliskiren— direct renin inhibitor
 - Olmesartan – new angiotensin receptor blocker
 - Darusentan – selective endothelin-receptor antagonist
 - Not yet approved by Health Canada or FDA
 - Being studied in resistant HTN





Case follow up

- 83 year old female admit to ICU with status epilepticus
- PMHx
 - HTN
 - OP
 - hypothyroidism
- Meds PTA
 - Telmisartan 80 mg
 - HCTZ 25 mg
 - Felodipine 2.5 mg
 - Atenolol 25 mg bid

Discontinue thiazide diuretic
 Optimize CCB and ARB for BP control for target < 150/80 mmHg
 Wean off atenolol

Questions

Baseline characteristic	ALLHAT	ACCOMPLISH
Age	66 years	68 years
Women	47%	40%
Black	30%	12.5%
Baseline BP	146/84	145/80
Smokers	20%	11%
Previous MI	23%	23%
DM-2	35%	60%
ASA	35%	65%
Lipid lowering	N/A	67%
Previous antiHTN	90%	~90%

JAMA 2002;288:2981-97
 NEJM 2008;359(23):2417-28

European Heart Journal Advance Access published August 31, 2009

FASTTRACK
 ESC HOT LINE

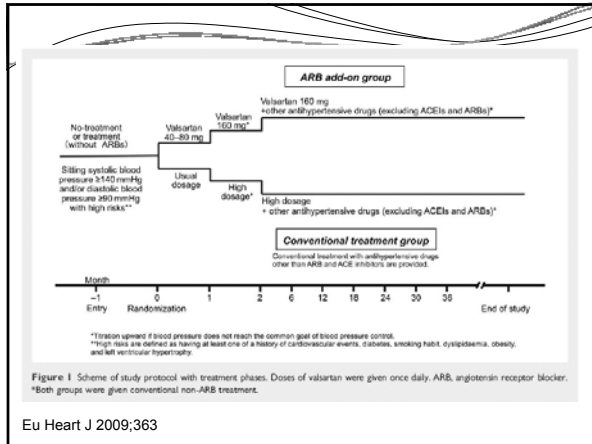
Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study

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 Received 4 August 2009; accepted 13 August 2009

Patients N=	Inclusion: Japanese HTN patients ≥ 20 years old, uncontrolled BP x 4 weeks (despite antiHTN therapy) and at least one of: CAD, CVD, PAD and/or one or more CVD risk factor (DM-2, hyperlipidemia, smoker, obesity, LVH) Exclusion: treated with ARB previously, h/o worsening HF, UA or MI, PCI or CABG within last 6 mths
Intervention	Valsartan 160 mg to target a BP < 140/90 mmHg added to their baseline regimen
Comparator	Placebo
Outcome	¹ EP: cardio- and cerebro-vascular events ² EP: all cause mortality, worsening cardiac function, new arrhythmias, DM, uncontrolled HTN

Eu Heart J 2009;363



Eu Heart J 2009;363

Table 1 Baseline characteristics

	Valartan, n = 1517	Non-ARB, n = 1514
Age	66 (11)	66 (11)
Men/women	861/656 (57/43%)	867/647 (57/43%)
Current smoker	341 (22%)	332 (22%)
Obesity BMI ≥ 25	513 (33%)	506 (33%)
Coronary artery disease	355 (23%)	352 (23%)
Cardiovascular disease	58 (4%)	45 (4%)
Heart failure	86 (6%)	109 (7%)
Diabetes	401 (26%)	406 (27%)
Dyslipidemia	1068 (70%)	1079 (71%)
LMI by electrocardiogram	122 (8%)	129 (9%)
Systolic blood pressure (mmHg)	137 (16)	137 (16)
Diastolic blood pressure (mmHg)	88 (11)	88 (11)
Heart rate (b.p.m.)	70 (18)	70 (16)
EF (%)	63 (10)	63 (9)
HDL cholesterol (mg/dL)	35 (15)	35 (15)
LDL cholesterol (mg/dL)	122 (33)	122 (31)
Triglyceride (mg/dL)	147 (45)	150 (46)
Fasting plasma glucose (mg/dL)	121 (45)	121 (45)
HbA1c (%)	6.1 (2.7)	6.0 (1.3)
Serum creatinine (mg/dL)	0.87 (0.3)	0.84 (0.38)
Sodium (mEq/L)	142 (2.7)	142 (2.3)
Potassium (mEq/L)	4.5 (0.2)	4.3 (0.2)

Data are number (%).

Table 2 Medications at baseline

	Valartan, n = 1517	Non-ARB, n = 1514
Angiotensin converting enzyme inhibitor	289 (19%)	305 (20%)
Calcium channel α -Blocker	825 (54%)	832 (55%)
β -Blocker	45 (3%)	51 (3%)
β -Blocker	264 (17%)	277 (18%)
Anti-aldosterone agents	31 (2%)	26 (2%)
Thiazide	52 (3%)	45 (3%)
Other diuretics	76 (5%)	86 (6%)
Statins	491 (32%)	503 (33%)
Fibrate	35 (2%)	30 (2%)
Oral hypoglycaemic agents	219 (14%)	202 (13%)
Anti-coagulation agents	89 (6%)	106 (7%)
Anti-platelet agents	402 (26%)	427 (28%)

Data are number (%).

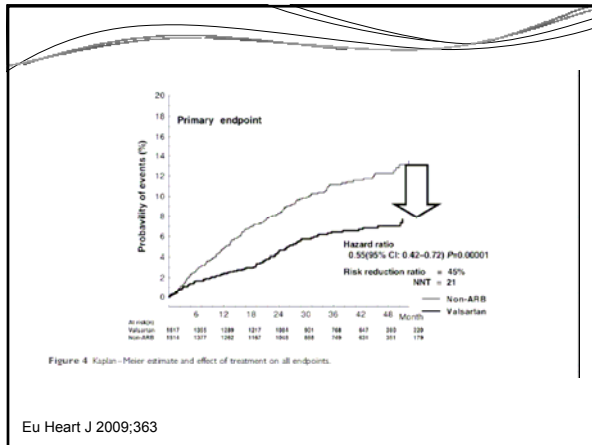
Table 3 Baseline characteristics (continued)

	Valartan, n = 1517	Non-ARB, n = 1514
Diabetes	401 (26%)	406 (27%)
Dyslipidemia	1068 (70%)	1079 (71%)
LMI by electrocardiogram	122 (8%)	129 (9%)
Systolic blood pressure (mmHg)	137 (16)	137 (16)
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HbA1c (%)	6.1 (2.7)	6.0 (1.3)
Serum creatinine (mg/dL)	0.87 (0.3)	0.84 (0.38)
Sodium (mEq/L)	142 (2.7)	142 (2.3)
Potassium (mEq/L)	4.5 (0.2)	4.3 (0.2)

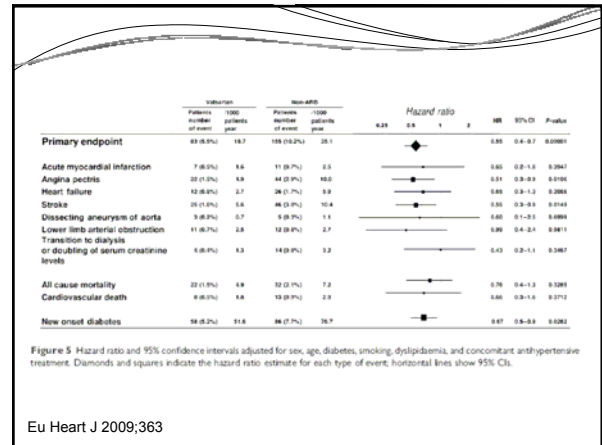
Data are mean (SD) or number (%).

ARB, angiotensin receptor blocker; BMI, body-mass index; HDL, high-density lipoprotein; Hb, haemoglobin; EF, ejection fraction; LMI, left ventricular hypertrophy.

Eu Heart J 2009;363



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Table 1. Demographic and Baseline Characteristics of the Study Patients.*

Characteristic	Benzazepril-Ambidigrine Group (N = 1744)	Benzazepril-Hydrochlorothiazide Group (N = 1742)
Sex — no. (%)		
Male	1448 (83.1)	1411 (81.0)
Female	2296 (131.9)	2244 (128.0)
Age — yr	65.4 (6.5)	65.3 (6.5)
≥ 65 yr — no. (%)	1313 (75.3)	1327 (76.1)
< 65 yr — no. (%)	2363 (136.1)	2340 (134.0)
Race or ethnic group — no. (%)		
Black	607 (34.8)	719 (41.2)
White	4037 (232.0)	4700 (269.2)
Hispanic	300 (17.2)	323 (18.6)
Other	230 (13.2)	247 (14.1)
Region — no. (%)		
United States	4067 (233.8)	4086 (235.0)
Non-US countries	1677 (96.2)	1676 (96.2)
Weight — kg	85.7 (18.0)	85.3 (18.0)
Waist circumference — cm	103.7 (13.2)	103.8 (13.4)
Body mass index†	31.0 (6.2)	31.0 (6.2)
Blood pressure — mmHg		
Systolic	145.1 (19.4)	145.4 (19.3)
Diastolic	80.1 (10.8)	80.0 (10.7)
Pulse — beats/min	70.5 (10.9)	70.3 (11.1)
Estimated glomerular filtration rate — mL/min/1.73 m ² of body surface area†	78.9 (21.2)	79.0 (21.5)
Serum values†		
Creatinine — mg/dL	1.0 (0.3)	1.0 (0.3)
Glucose — mg/dL	127.0 (45.8)	127.0 (45.8)
Potassium — mmol/L	4.3 (0.4)	4.3 (0.4)
Total cholesterol — mg/dL	184.0 (49.5)	184.1 (49.5)
High-density lipoprotein cholesterol — mg/dL	49.0 (14.1)	49.5 (14.1)
Previous antihypertensive treatment — no. (%)		
0	169 (9.7)	153 (8.8)
1	1392 (79.3)	1379 (78.2)
2	2136 (122.8)	2047 (117.5)
3	2147 (122.8)	2283 (131.0)
Lipid-lowering agents	1013 (57.9)	1013 (57.9)
Beta-blockers	2075 (118.9)	2007 (115.2)
Angiotensin agents	1710 (98.0)	1715 (98.4)