Essential Hypertension and Treatment

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August 2008

Overview

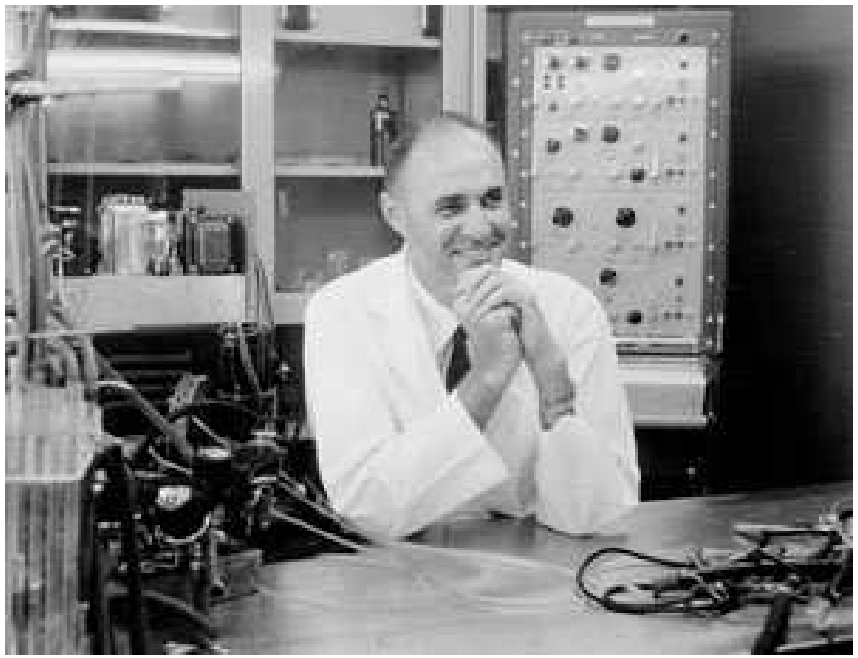
- **Note on the pathogenesis of HTN**
- **Note on home blood pressure measurement**
- **Note on therapy**

Bull. N. Y. Acad. Med. Vol. 45, No. 9, September 1969

PHYSIOLOGIC CONTROL OF ARTERIAL PRESSURE*

ARTHUR C. GUYTON, THOMAS G. COLEMAN, JACQUES C. FOURCADE, AND L. GABRIEL NAVAR

Department of Physiology and Biophysics
University of Mississippi School of Medicine
Jackson, Miss.



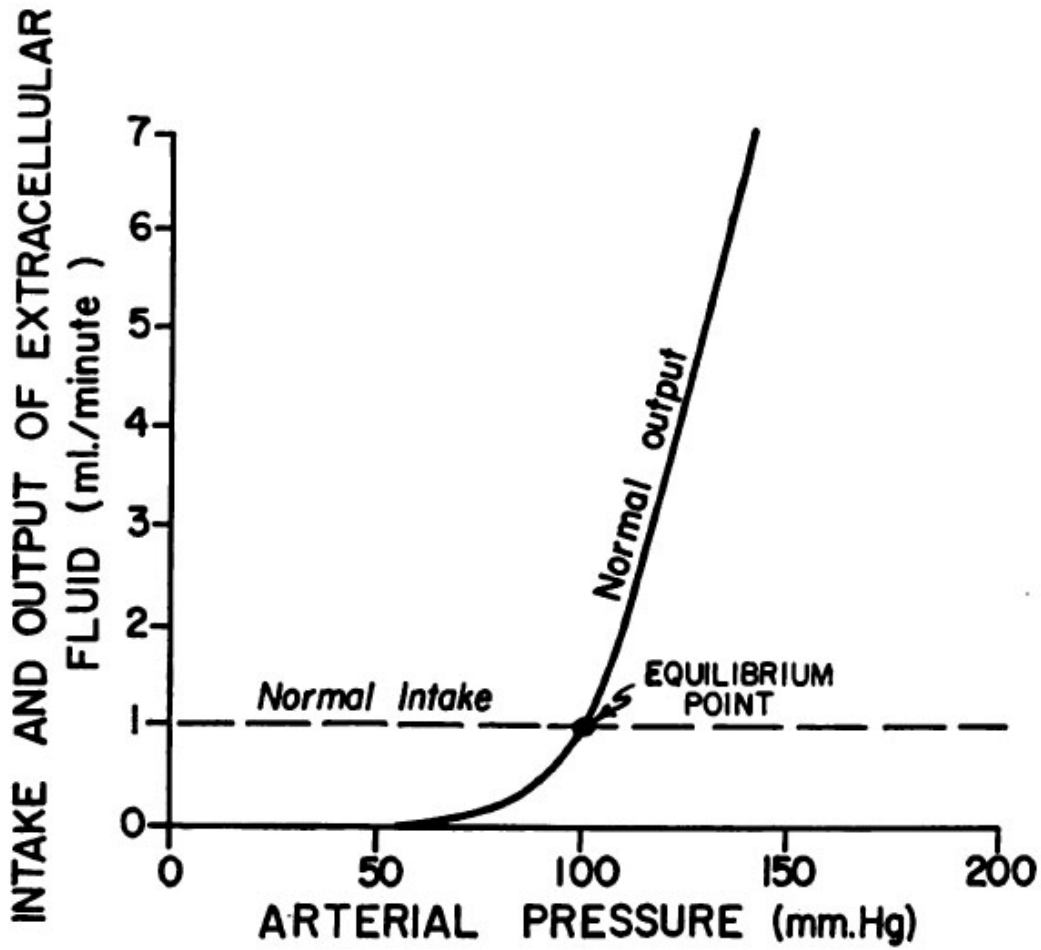


Fig. 2. Equilibration of the normal renal function curve for output of extracellular fluid with the normal curve for intake of extracellular fluid.

Shift of the pressure-natriuresis curve to the right in HTN

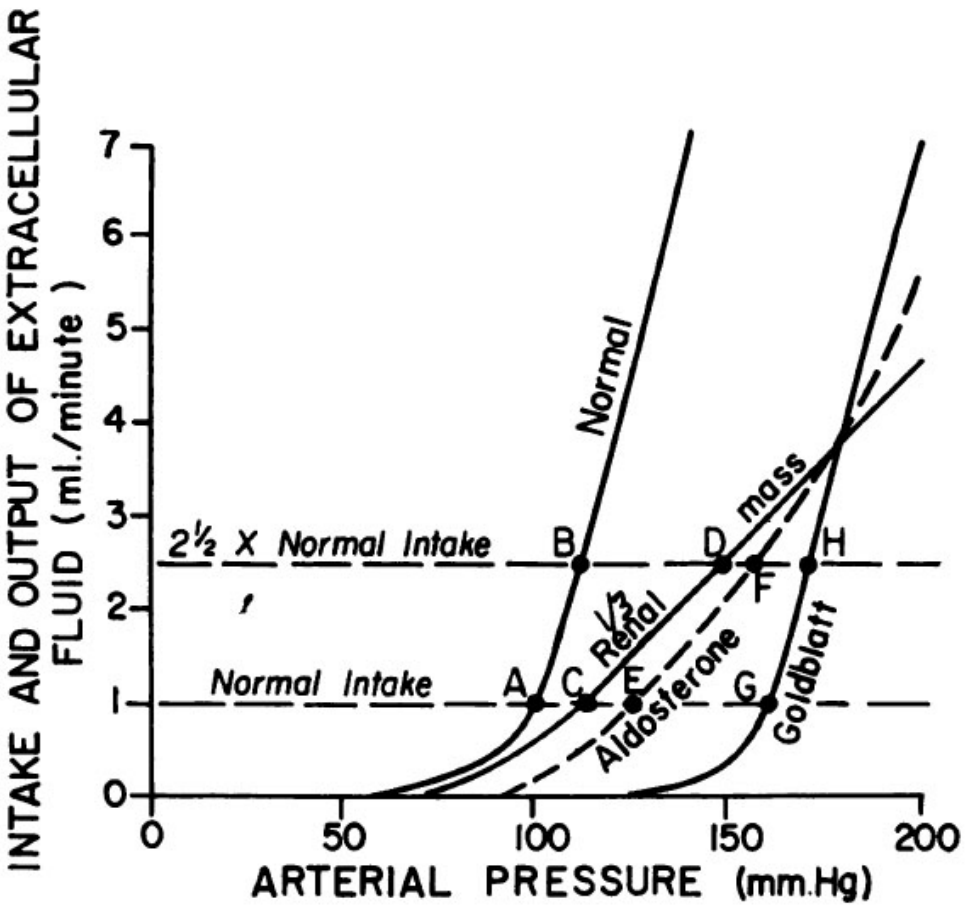


Fig. 3. Equilibration of output and intake of extracellular fluid in a human being with various renal abnormalities.

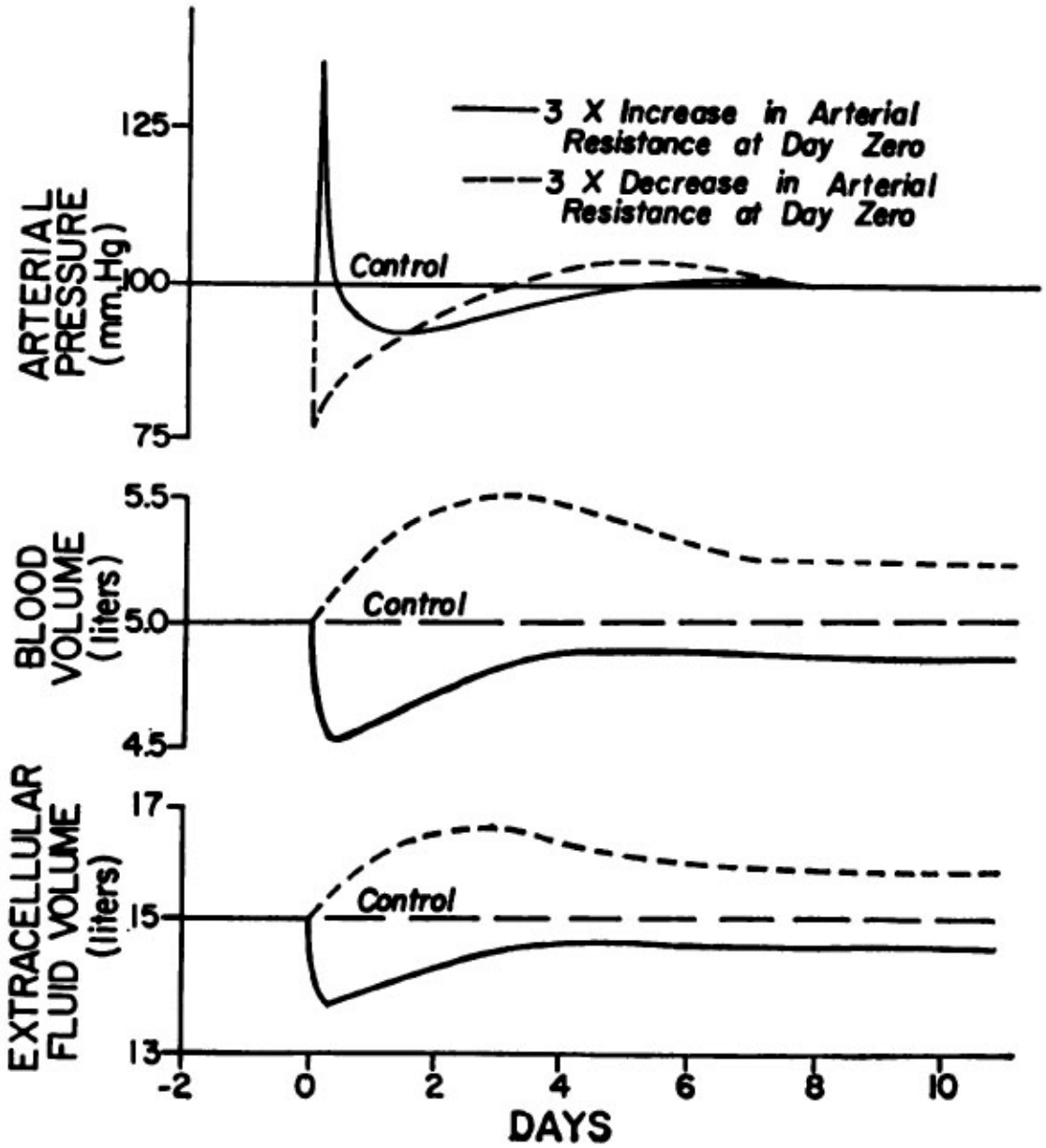
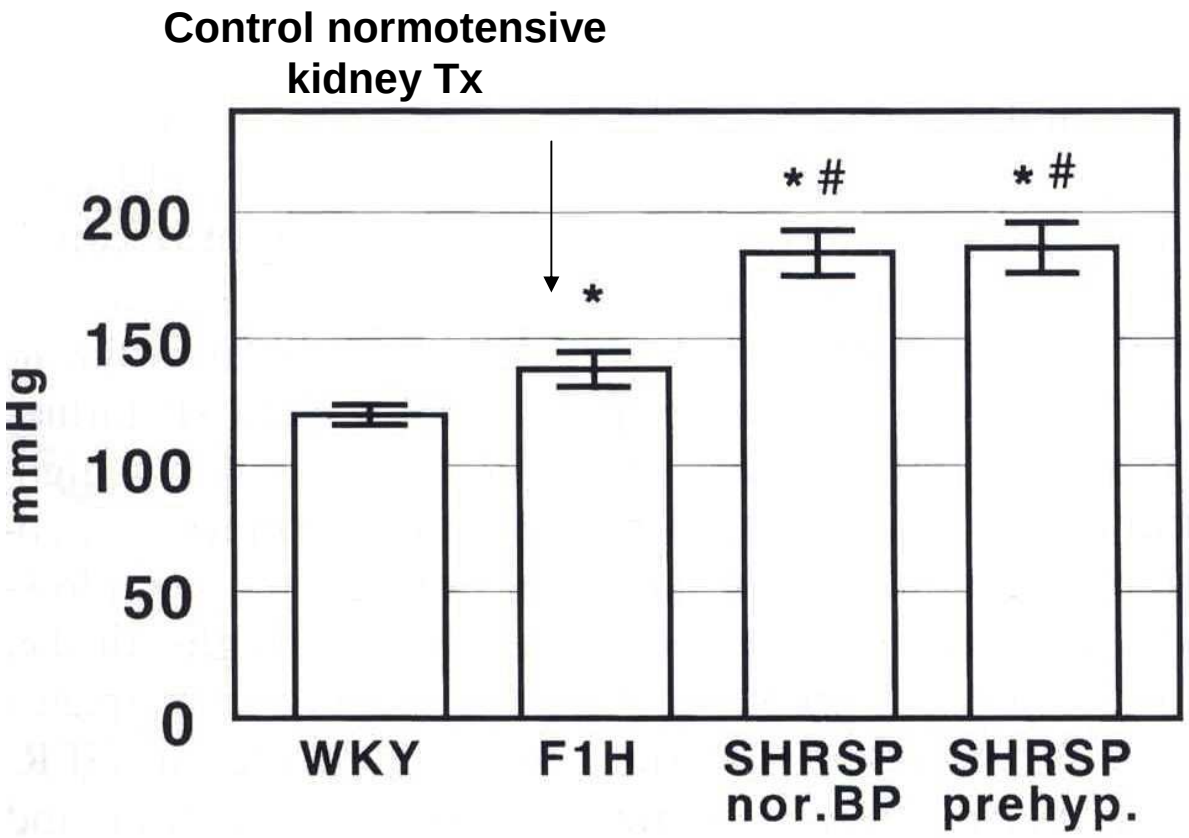


Fig. 4. Computer predictions of changes in circulatory function when total peripheral resistance is suddenly increased threefold or decreased threefold but without altering renal resistances.

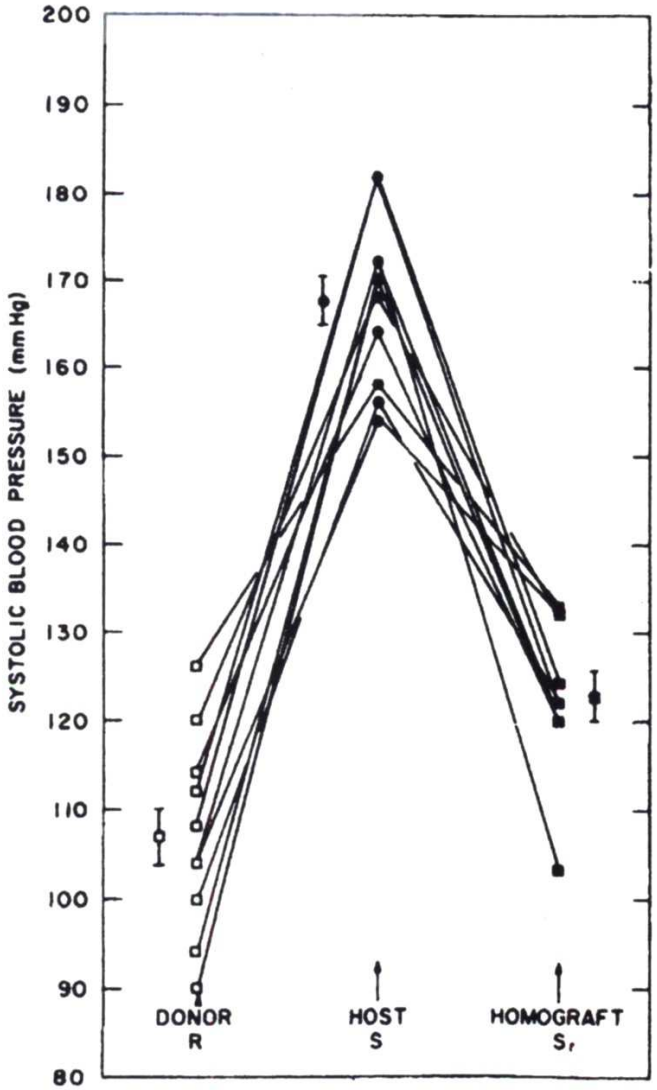
HTN „follows the kidney” after transplantation



Change in blood pressure in genetically normotensive rat (F1H) after transplanting kidney from a genetically hypertensive rat (SHRSP) strain

Am J Physiol 1993;265:F104

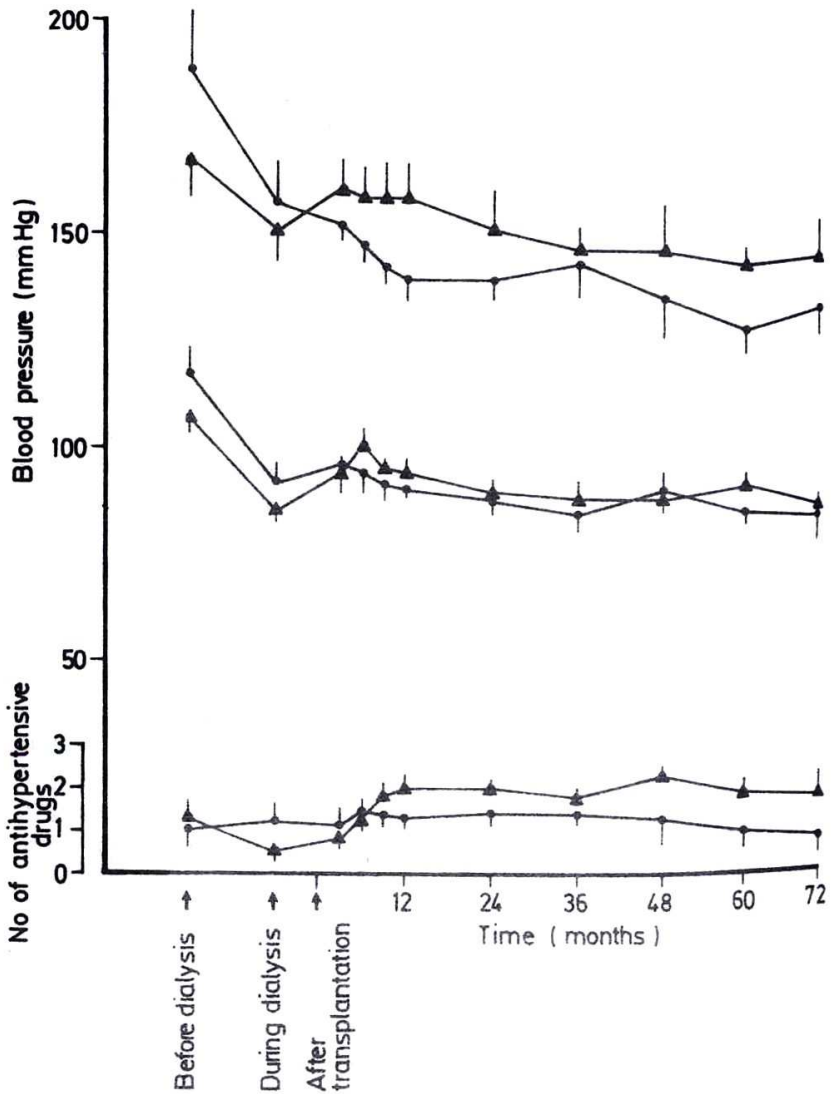
Normotension „follows the kidney” after transplantation



Change in blood pressure after transplanting salt-resistant rat kidney (R) in genetically salt sensitive (S) rat

Circ Res 1975;36:692

Change in blood pressure after transplanting kidneys from hypertensive and non-hypertensive donors in human



● = Kidneys from donors with head injury or cerebral tumor

▲ = Kidneys from donors with subarachnoid hemorrhage

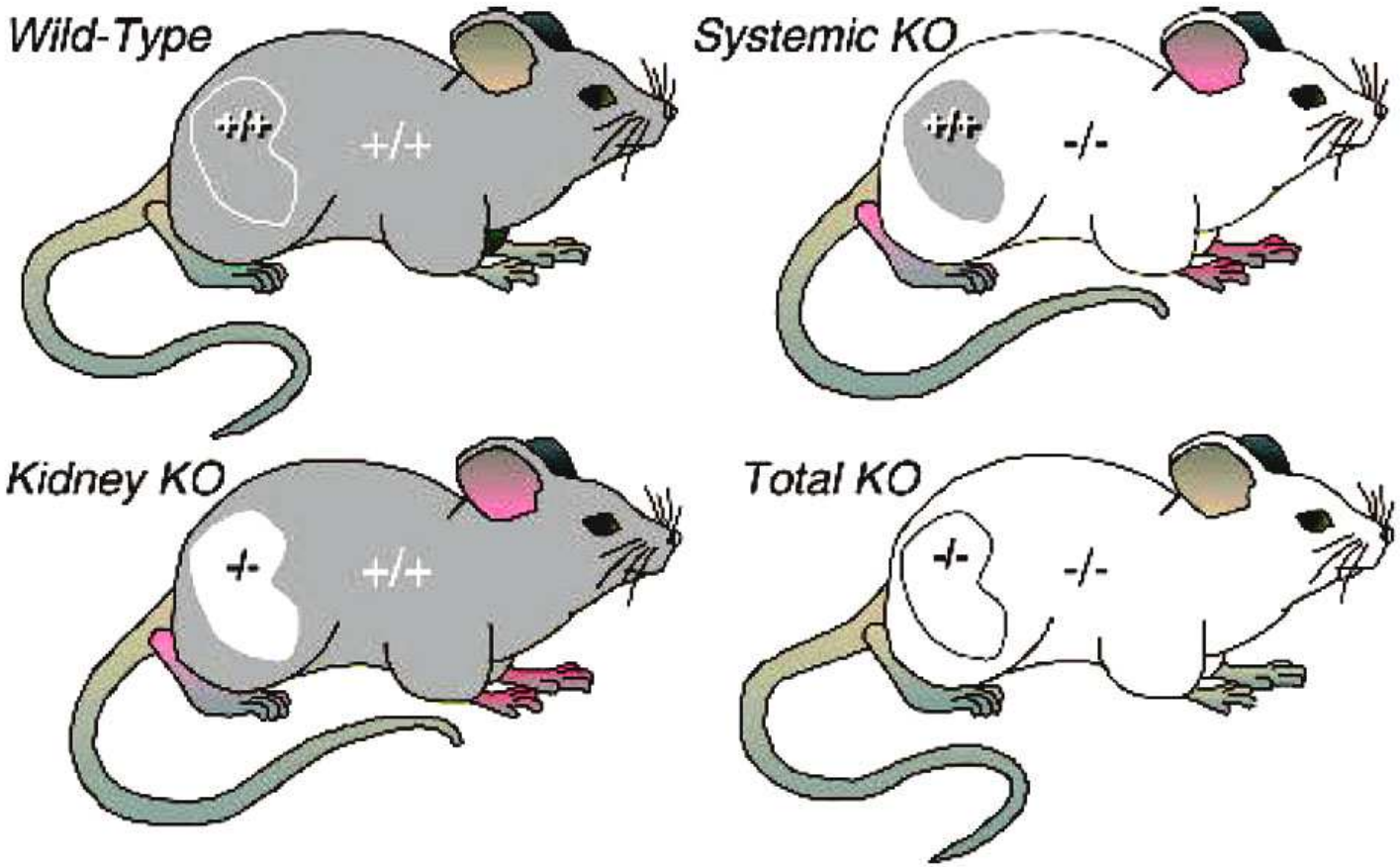
BMJ 1986;292:1041

Distribution and function of AT1 receptors

- **Kidney: vasoconstriction, antinatriuresis**

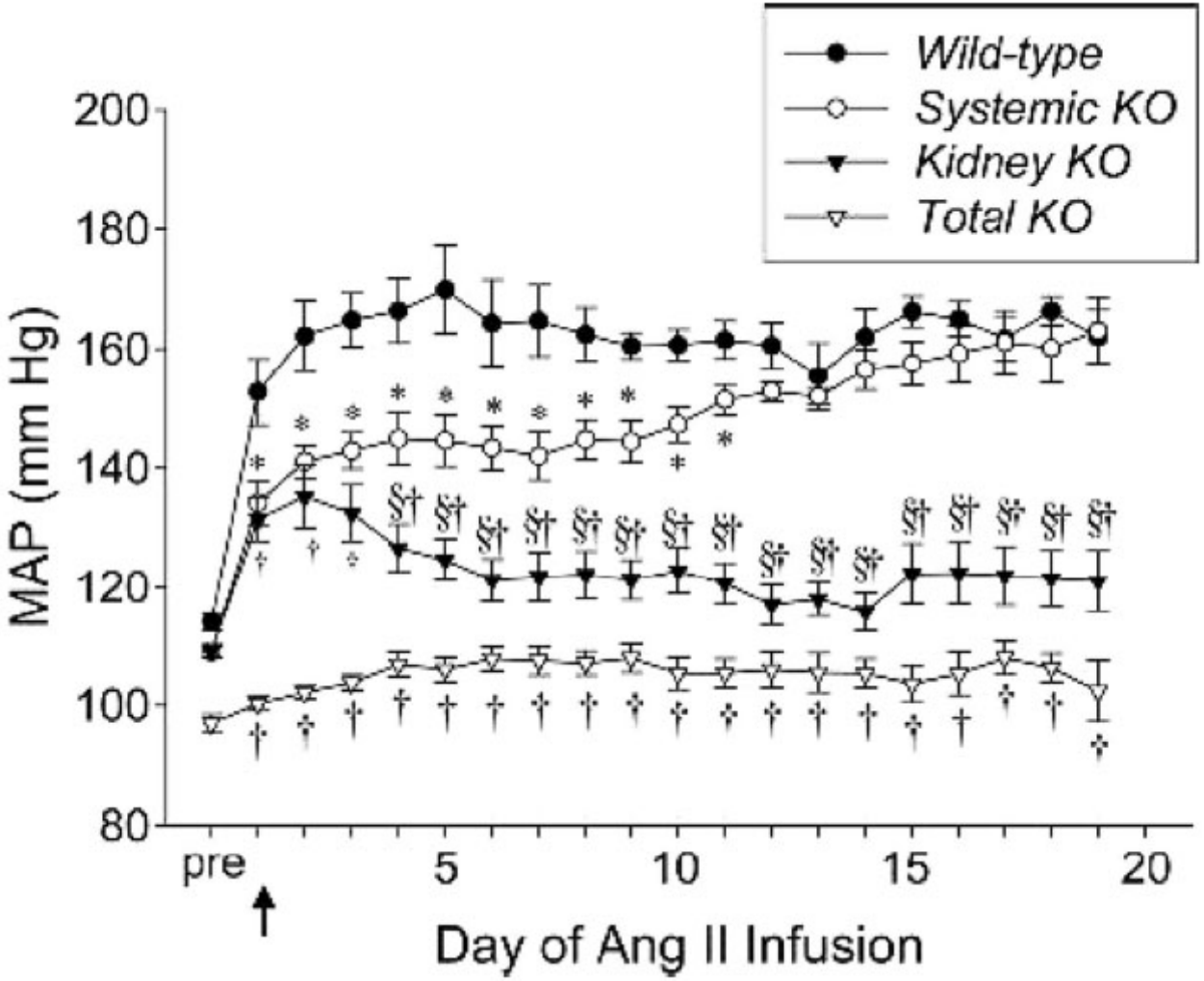
- **Vascular smooth muscle cells: vasoconstriction**
- **Adrenals: aldosterone production**
- **CNS: pressure response**

AT_{1a} receptor knock-out cross-transplantation mice



J Clin Invest 2005;115:1092

Blood pressure response to Ang II infusion



Proc Natl Acad Sci U SA 2006;103:17985

Conclusion

- **Decreased salt excreting ability of the kidneys is sufficient to cause sustained HTN**
- **Vasoconstriction alone, without impairment in salt-excretion, is not sufficient to cause sustained HTN**

Overview

- **Note on the pathogenesis of HTN**
- **Note on home blood pressure measurement (HBPM)**
- **Note on therapy**

Total cardiovascular risk is determined by..

- Level of blood pressure
- Presence of risk factors
- Presence of metabolic syndrome & diabetes
- Presence of organ damage
- Presence of established cardiovascular or renal disease

J Hyp 2007;25:1105

Stratification of total cardiovascular risk into categories

Blood pressure (mmHg)

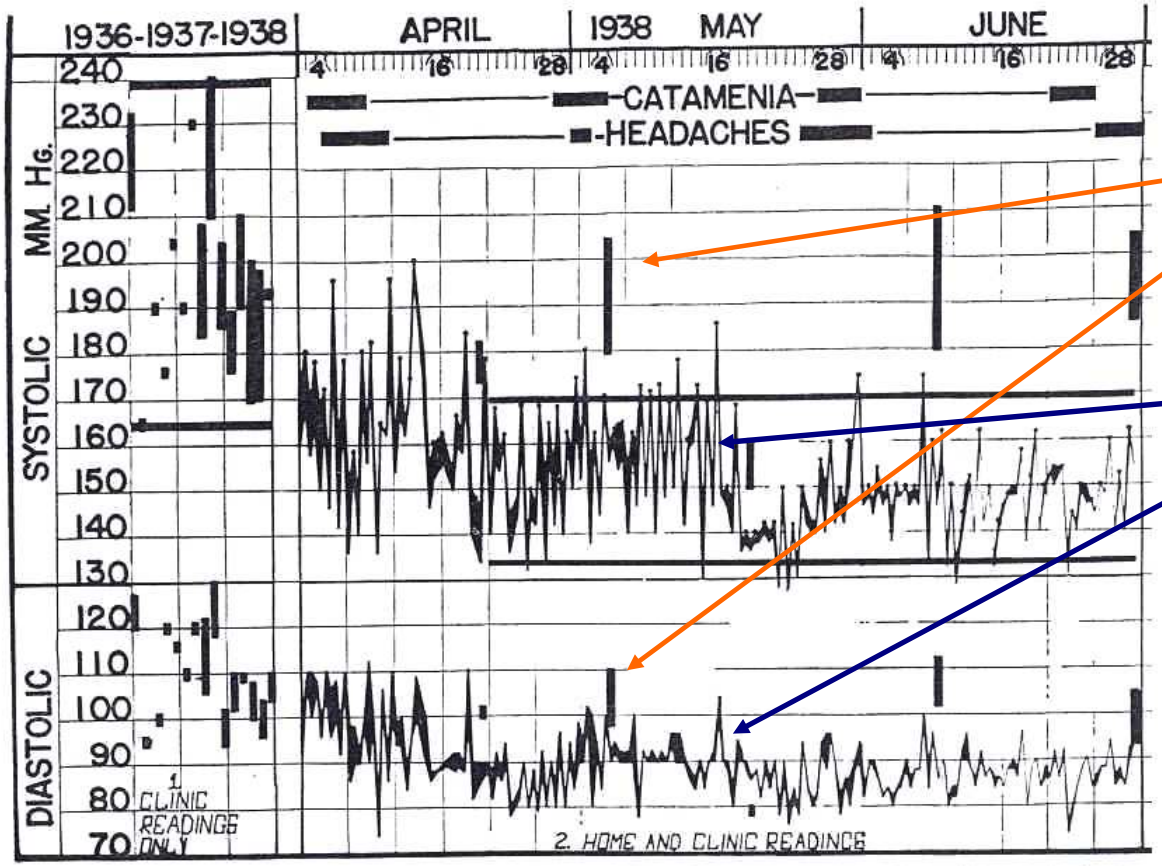
Other risk factors, OD or disease	Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Types of blood pressure measurement

- **Office**
- **Home**
- **Ambulatory**
- **During exercise or laboratory stress**
- **Central**

- **Beat-to beat**

Historical note



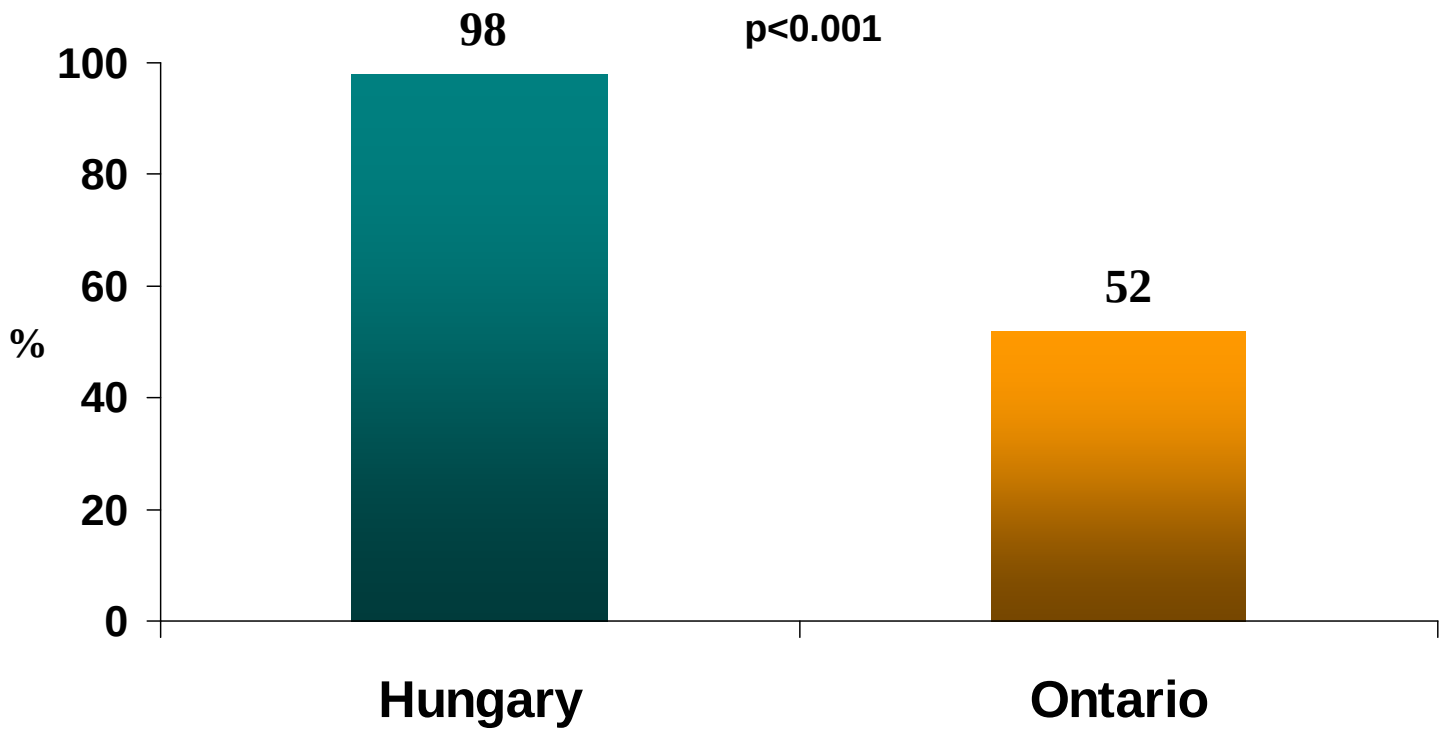
Office BP

Home BP

FIG. 1.—Comparison of clinic and home blood pressure readings in a patient with essential hypertension.

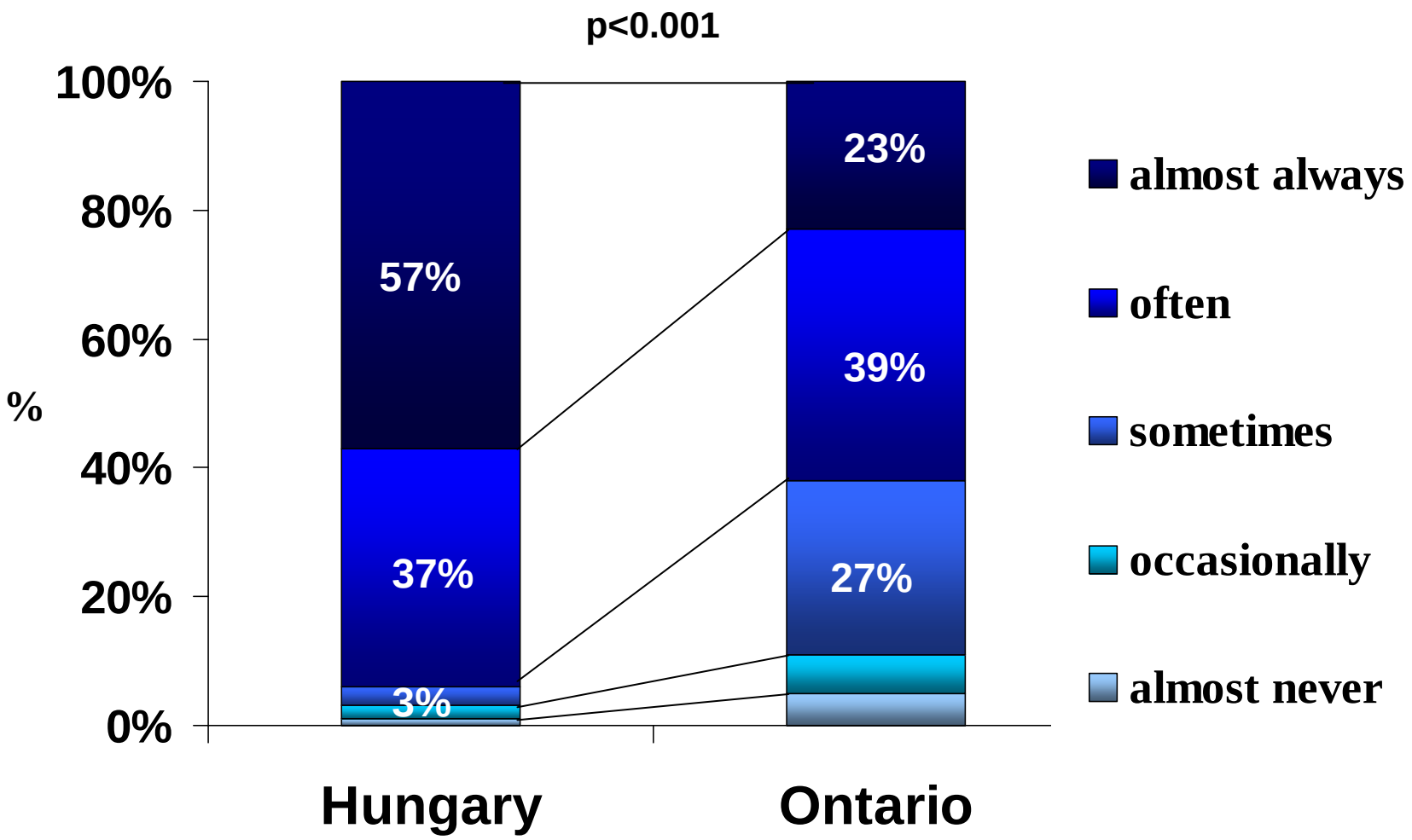
Am J Med Sci, 1940;200:465

Is HBPM considered to be part of standard hypertension patient care ?
„Yes”



J Hypertens 2006;24:1429
J Hypertens 2008;26:446

"How often do you encourage your patient to measure BP at home?"



J Hypertens 2006;24:1429
J Hypertens 2008;26:446

Frequency of use of HBPM

- **US: 38% in 2000, 55% in 2005**
- **Italy: 75% hypertension clinic**

- **MD recommends its use (USA): 35% in 2000, 47% in 2005**

The Gallup Study of the Hypertension Market, 2006
Blood Press 2005;14:251

AHA/ASH/PCNA Scientific Statement

Call to Action on Use and Reimbursement for Home Blood Pressure Monitoring

A Joint Scientific Statement From the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association

Thomas G. Pickering, MD, DPhil, FAHA, Chair; Nancy Houston Miller, RN, BSN, FAHA; Gbenga Ogedegbe, MD, MPH, FAHA; Lawrence R. Krakoff, MD, FAHA; Nancy T. Artinian, PhD, RN, BC, FAHA; David Goff, MD, PhD, FAHA

European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring

Gianfranco Parati[a], George S. Stergiou[b], Roland Asmar[c], Grzegorz Bilo[a], Peter de Leeuw[d], Yutaka Imai[e], Kazuomi Kario[f], Empar Lurbe[g], Athanasios Manolis[h], Thomas Mengden[i], Eoin O'Brien[j], Takayoshi Ohkubo[k], Paul Padfield[l], Paolo Palatini[m], Thomas Pickering[n], Josep Redon[o], Miriam Revera[a], Luis M. Ruilope[p], Andrew Shennan[q], Jan A. Staessen[r], Andras Tisler[s], Bernard Waeber[t], Alberto Zanchetti[u] and Giuseppe Mancia[v], on behalf of the ESH Working Group on Blood Pressure Monitoring

Key issues related to the methodology of HBPM

- **Need of medical supervision and patient training**
- **Need of independent validation**
  - **www.dableducational.com**
  - **www.bhsoc.org/blood_pressure_list.htm**
- **Checking device accuracy in individual patients**

J Hypertens 2008;26:1505

Methods of HBPM: measurement

- **Most frequent errors during HBP measurement**
  - **No rest period prior to measurement (90%)**
  - **No back support or legs crossed (70%)**
  - **incorrect correct cuff placement (50%)**
  - **Talking during measurement (46%)**
  - **Arm not supported at heart level (30%)**
  - **Constrictive clothing (9%)**

Blood Press Monit 2004;9:143

- **Use of cuffs that are inappropriate for the arm**

Devices

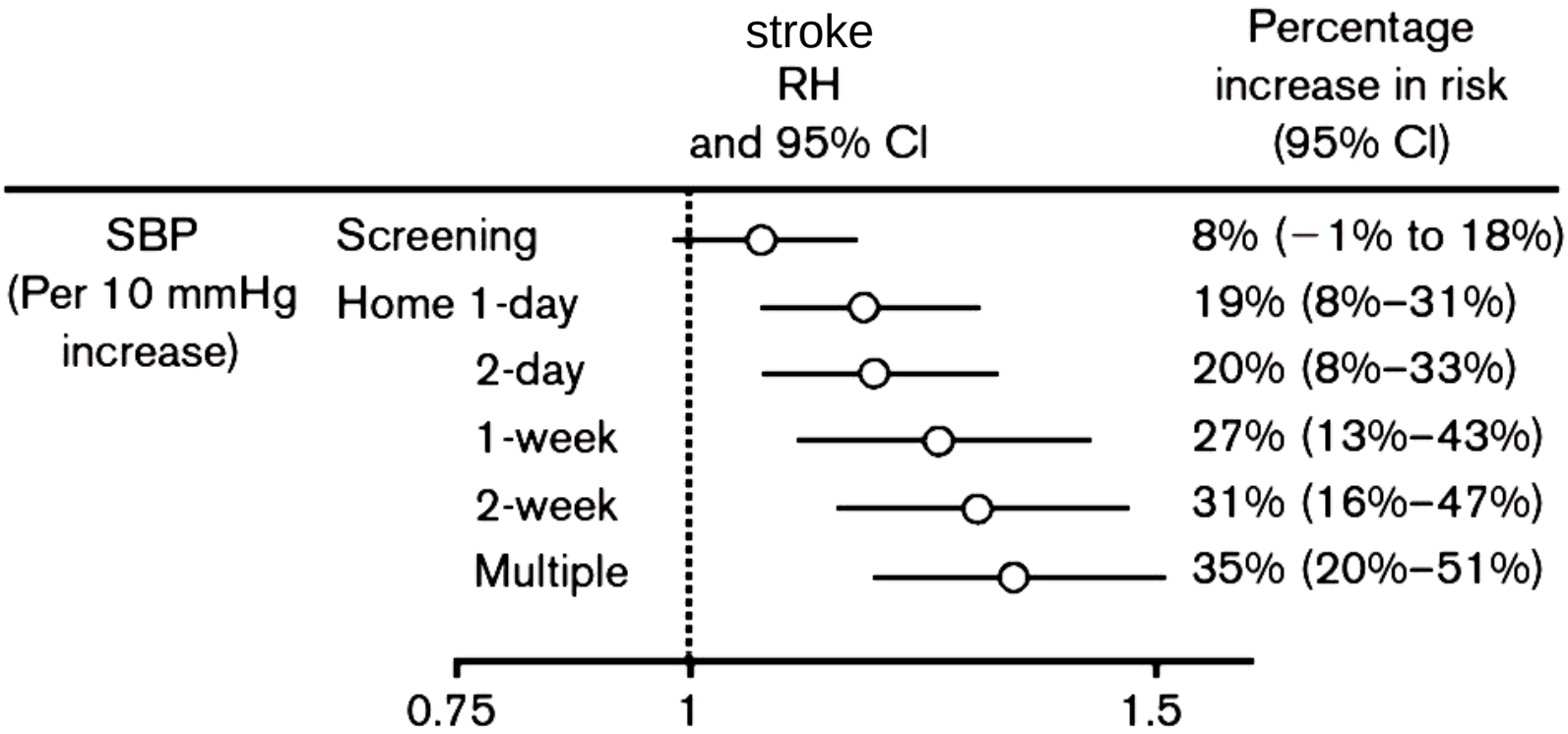
- **Recommended**
  - **Auscultatory, finger cuff, wrist cuff* not recommended**
  - **Small and large adult cuffs should be available**
  - **Semiautomated, preferably automated oscillometric recommended**
  - **Large display, sufficient memory, computation of whole period averages**

- **Optional**
  - **Detection of arm movement, irregular heart beats,**
  - **Separate evening, morning averages**
  - **Automated night time measurement**
  - **Telemonitoring capability may be useful**

*** Under evaluation for special situations**

J Hypertens 2008;26:1505

How many home readings are needed ?



J Hypertens 2004;22:1099

How often and how many times to measure ?

- **At initial assessment, treatment changes, before clinic visits**
  - **7 day measurement**
  - **2 measurement on each session**
  - **2 sessions per day (morning evening)**
  - **Assess average with the first day data discarded**

- **Long term follow-up**
  - **1-2 measurements per week**

J Hypertens 2008;26:1505

Reference values and target home blood pressure

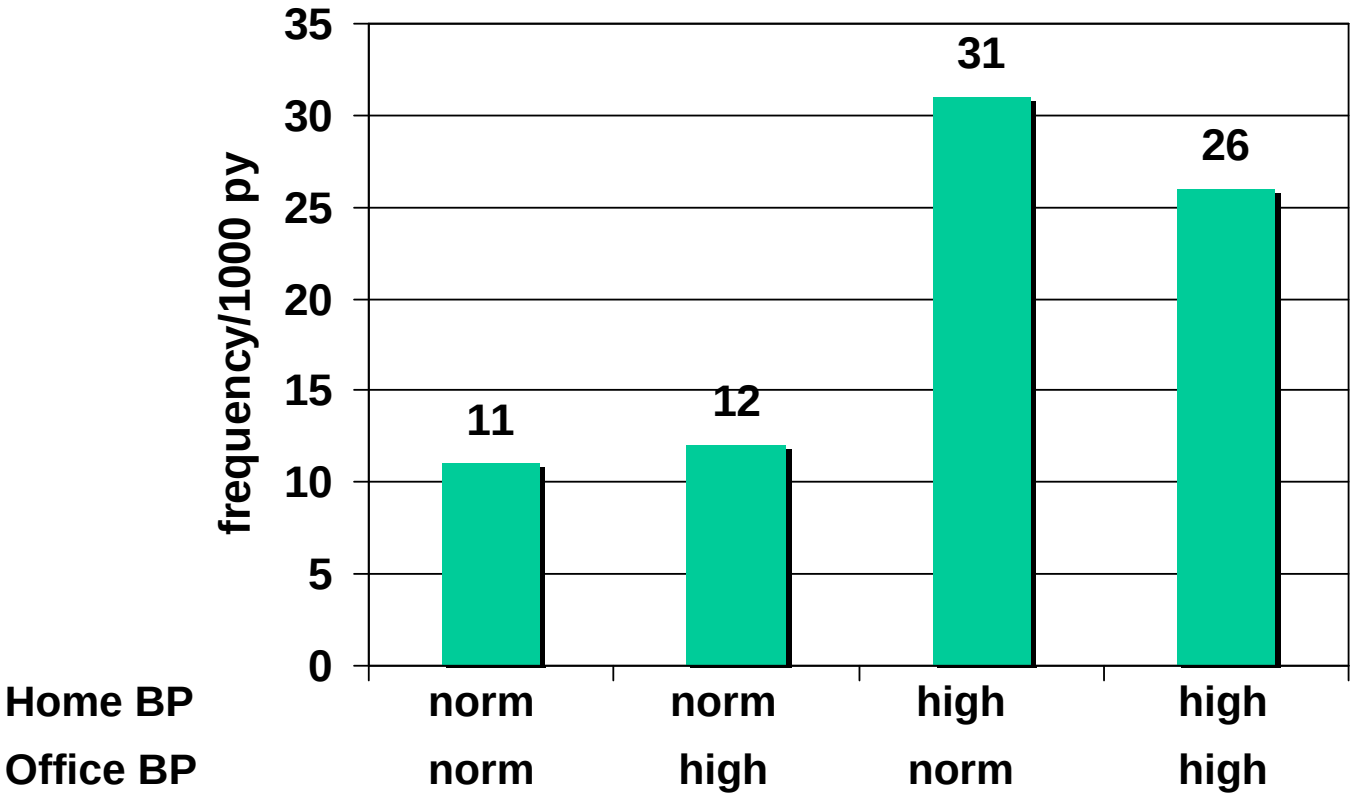
- **Diagnostic threshold**
  - **≥135/85 mmHg**

- **Goal BP**
  - **<135/85 mmHg**
  - **Probably lower in high risk individuals**

    „each mmHg reduction is important"

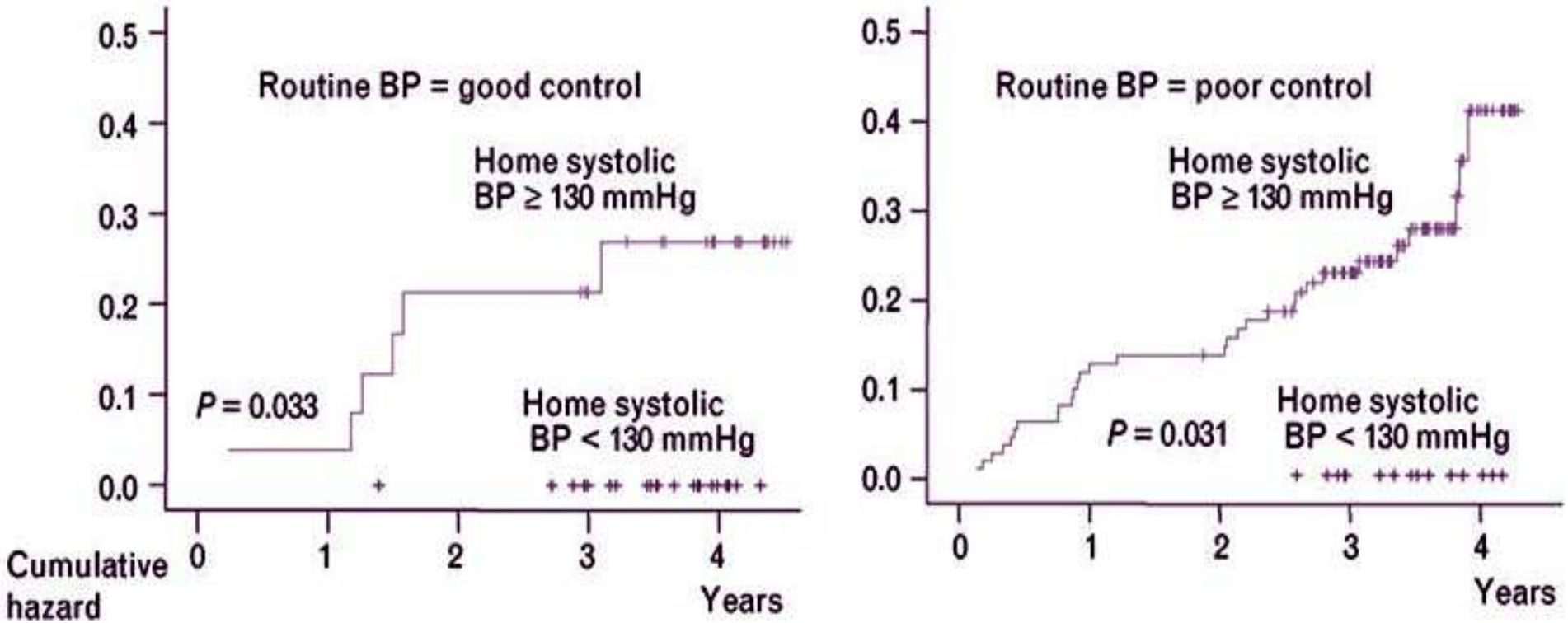
Frequency of cardiovascular events according to office and home blood pressure levels in the SHEAF-study

Normal home BP <135/85 mmHg, normal office BP <140/90 mmHg



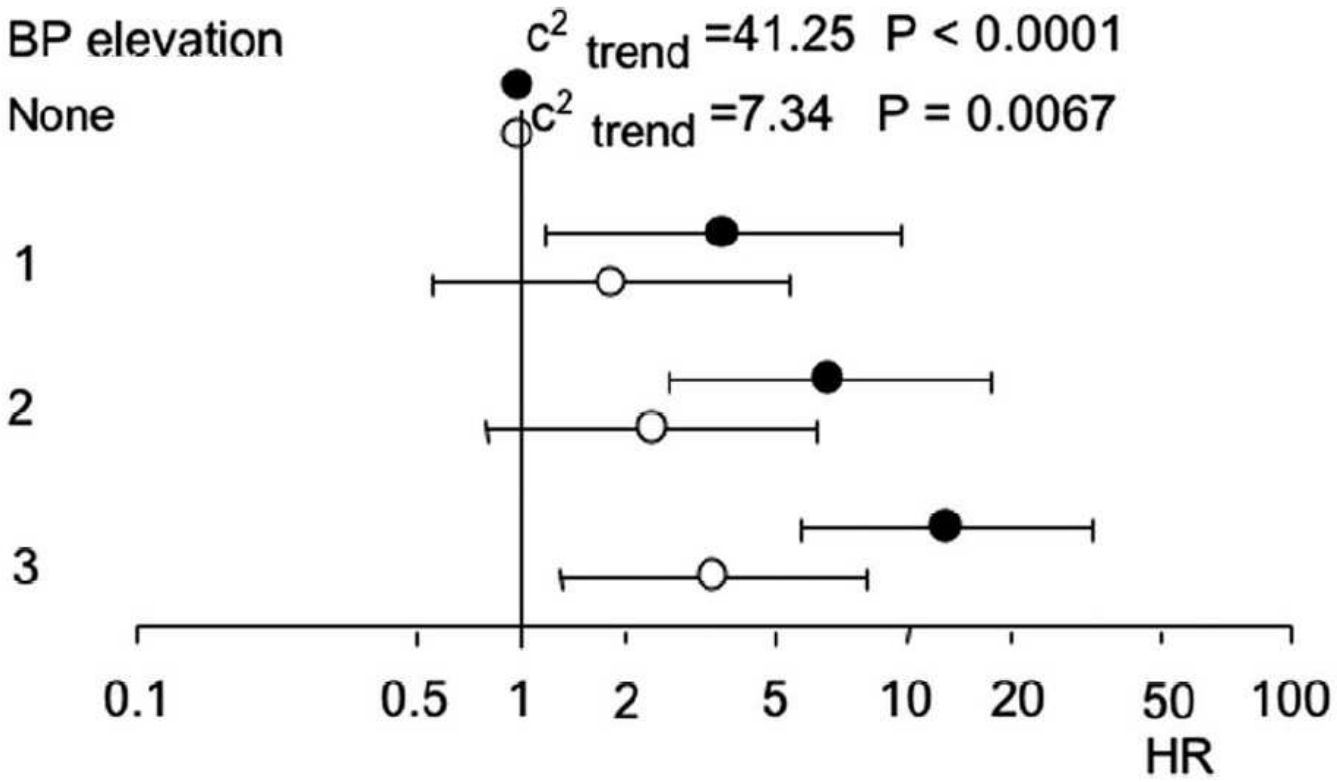
n=4939, 3y f/u JAMA 2004;291:11342

Development of stage 5 CKD according to the level of home and office (routine) BP



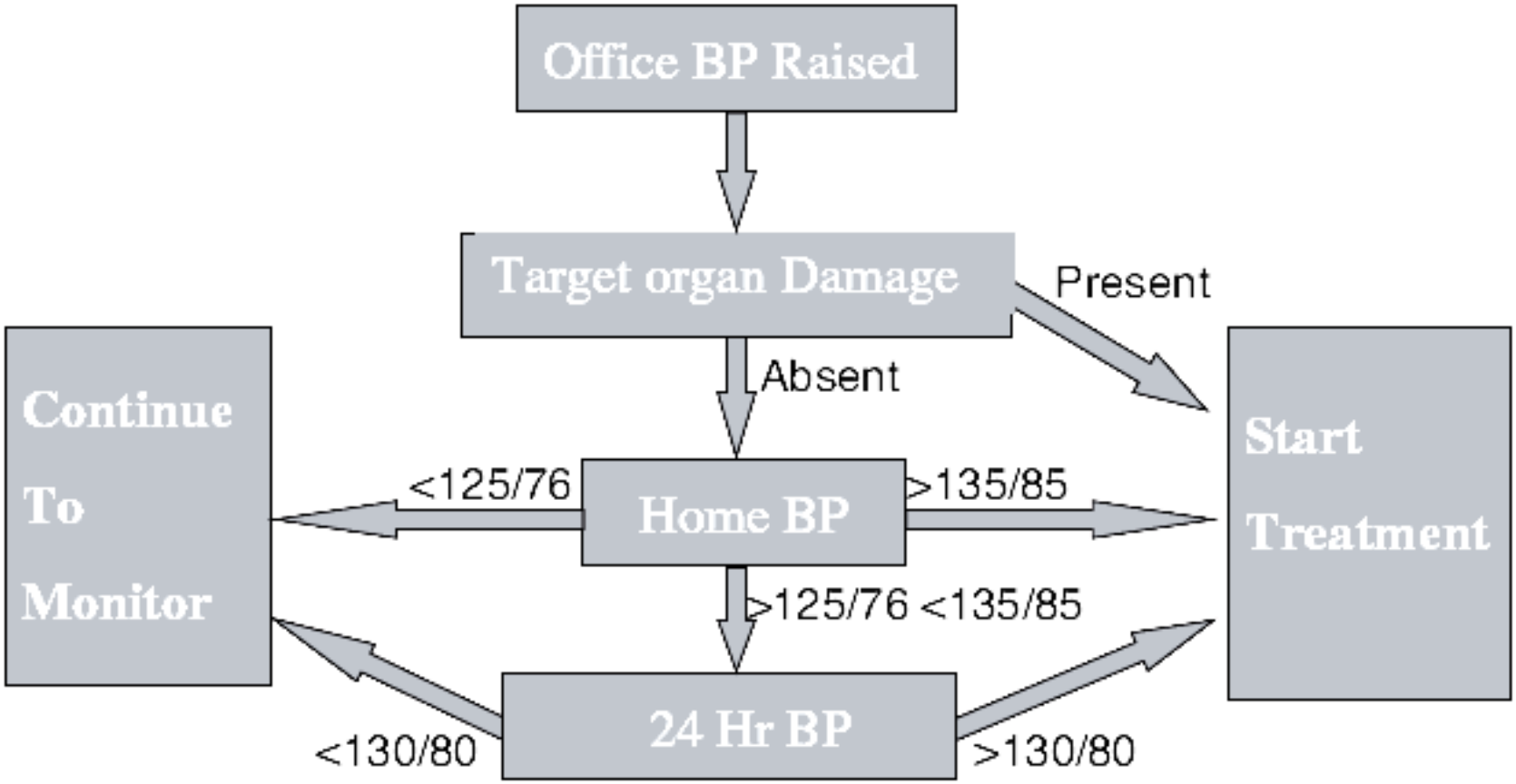
n=217, 3,5 y f/u, Kidney Int 2006;69:406)

Risk of CV mortality according to the number of methods *(office, home, ambulatory)* by which high blood pressure was detected



PAMELA study n=2051, 148 mo f/u, Hypertension 2006;47:846

Flow-sheet for evaluating need for treatment



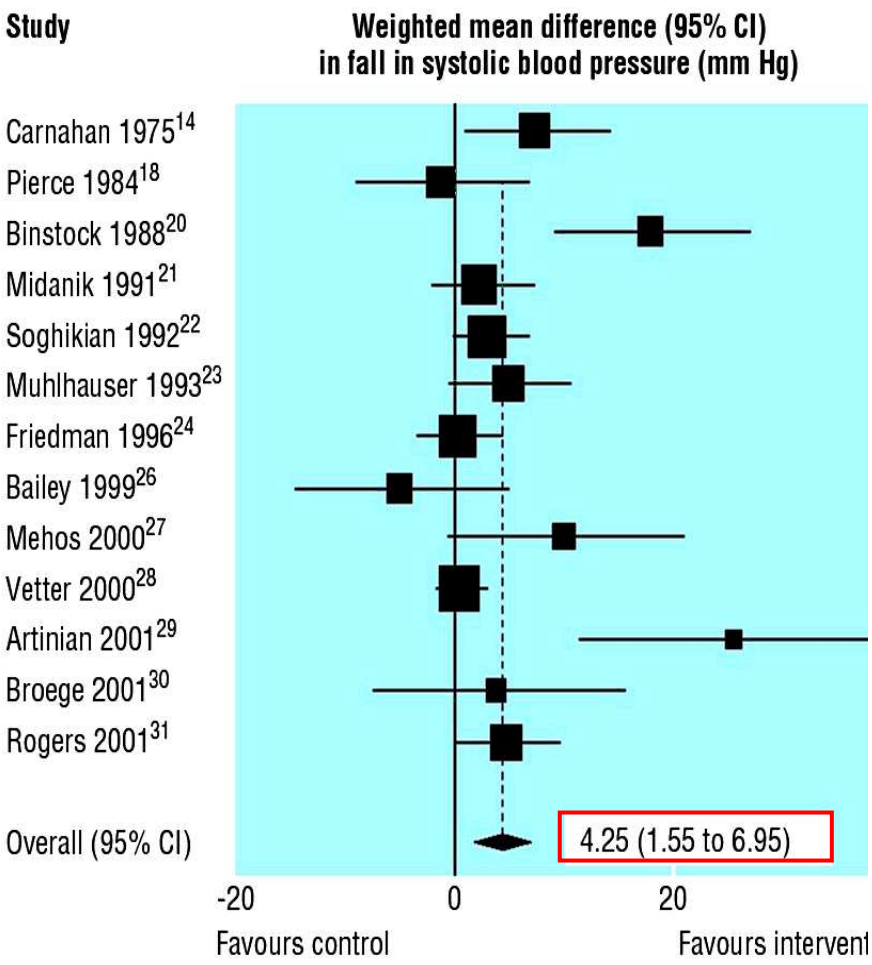
Hypertension 2008;52:10

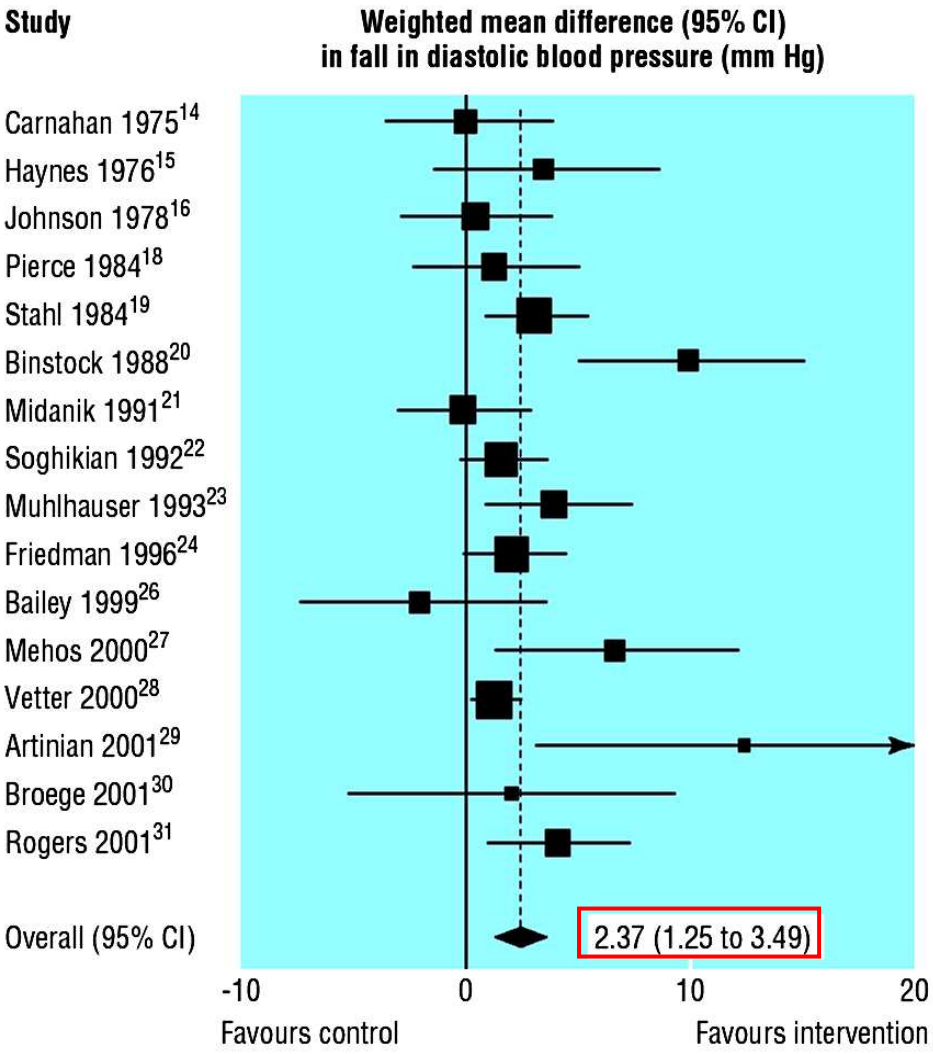
Indications for HBPM in treated patients

- All patients receiving antihypertensive treatment
- Evaluation of white coat HTN
- Evaluation of masked HTN
- Evaluation of resistant HTN
- To improve compliance
- To improve HTN control rates

J Hypertens 2008;26:1505

The effect of HBPM on blood pressure: meta-analysis



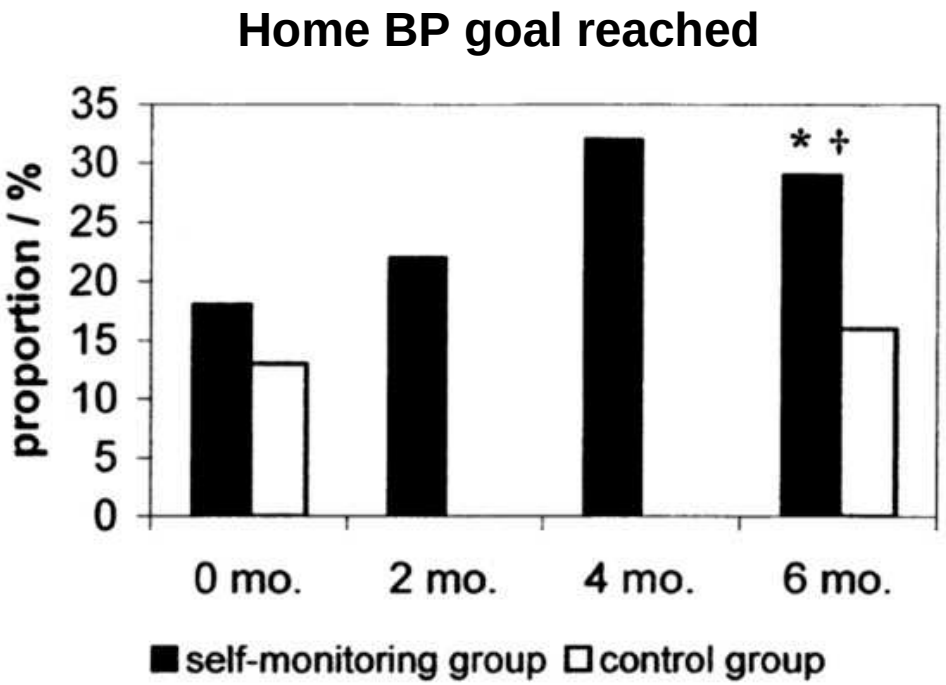


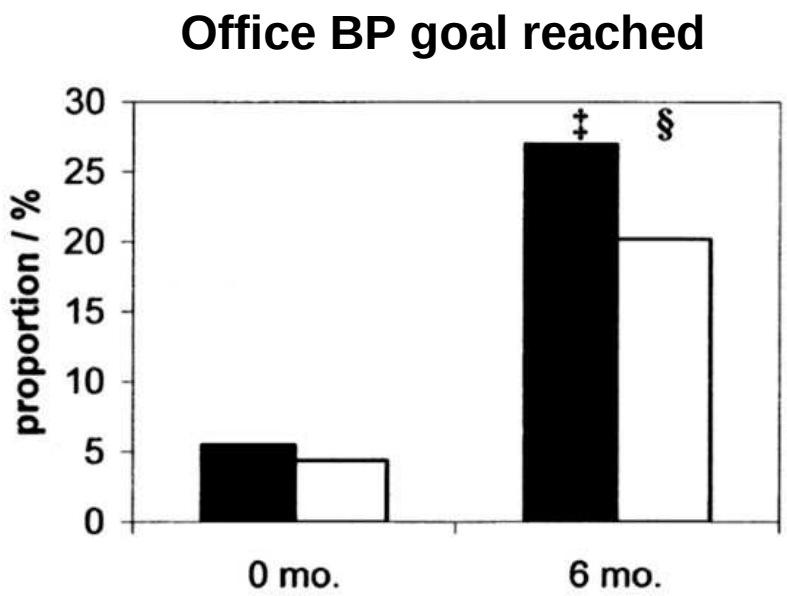
BMJ 2004;329:145

AJH 2005; 18:1415–1420

Self-Monitoring of Blood Pressure Promotes Achievement of Blood Pressure Target in Primary Health Care

Laura Halme, Risto Vesalainen, Mika Kaaja, Ilkka Kantola,
for the HOMER (HOme MEasuRement of blood pressure) study group

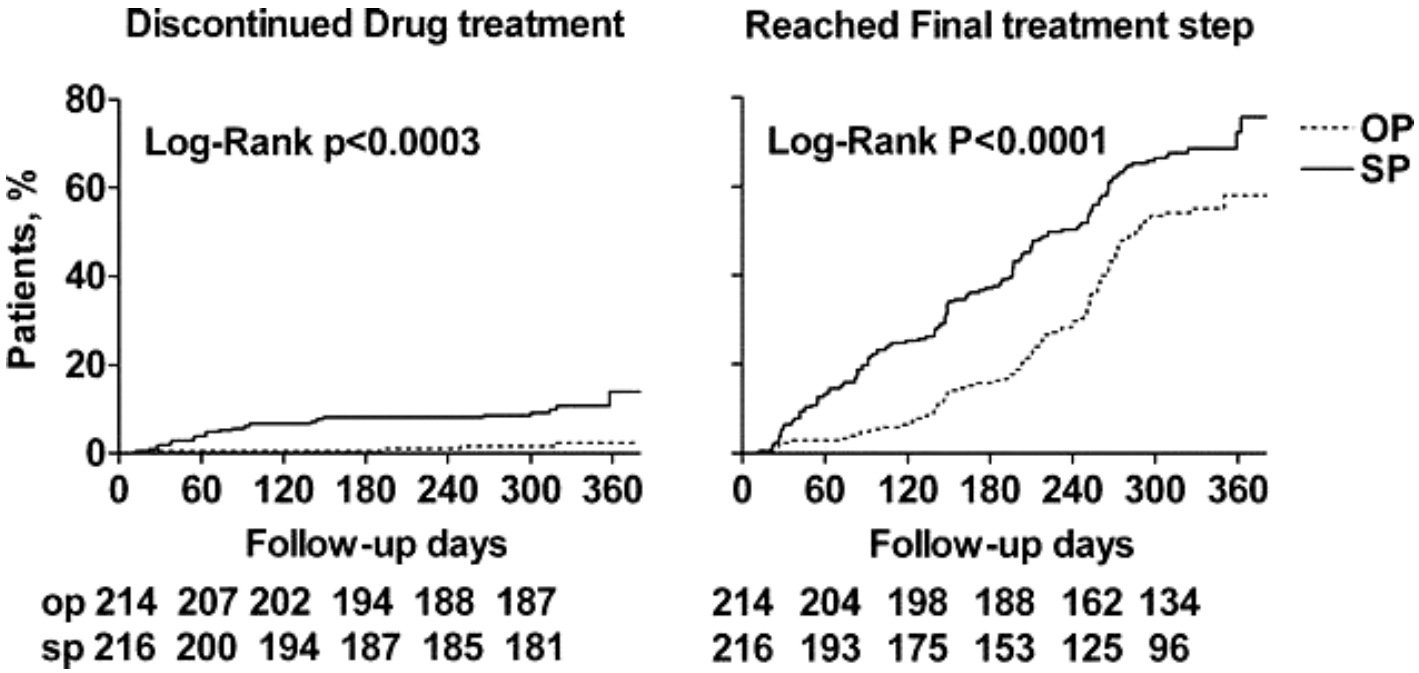




N=269, HBPM vs office BP, office goal <140/85, home goal <135/80 mmHg 6 mo f/u

Self-Measurement of Blood Pressure at Home Reduces the Need for Antihypertensive Drugs

A Randomized, Controlled Trial



HOMERUS trial
N=430 office vs. Home BP guided Rx, goal 120-140/80-90mmHg, 1y f/u

(*Hypertension*. 2007;50:1019-1025.)

Limitations

- **May not work in atrial fibrillation and frequent arrhythmias**
- **In patients where HBPM causes anxiety, preoccupation with BP and self-medication**

Overview

- **Note on the pathogenesis of HTN**
- **Note on home blood pressure measurement**
- **Note on therapy**

Initiation of antihypertensive treatment

Other risk factors, OD or disease	Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	No BP intervention	No BP intervention	Lifestyle changes for several months then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
1-2 risk factors	Lifestyle changes	Lifestyle changes	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes for several weeks then drug treatment if BP uncontrolled	Lifestyle changes + immediate drug treatment
3 or more risk factors, MS, OD or diabetes	Lifestyle changes	Lifestyle changes and consider drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + drug treatment	Lifestyle changes + immediate drug treatment
Diabetes	Lifestyle changes	Lifestyle changes + drug treatment			
Established CV or renal disease	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment	Lifestyle changes + immediate drug treatment

J Hypertens 2007;25:1105

Goals of Treatment

- „the primary goal of treatment is to achieve maximum reduction in total risk of CV disease”
- „This requires treatment of raised BP per se as well as of all associated reversible risk factors”
- „BP should be reduced to at least below 140/90 mmHg (systolic/diastolic) and to lower values, if tolerated, in all hypertensive patients”
- „Target BP should be at least <130/80 mmHg in diabetics and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria)”

J Hypertens 2007;25:1105

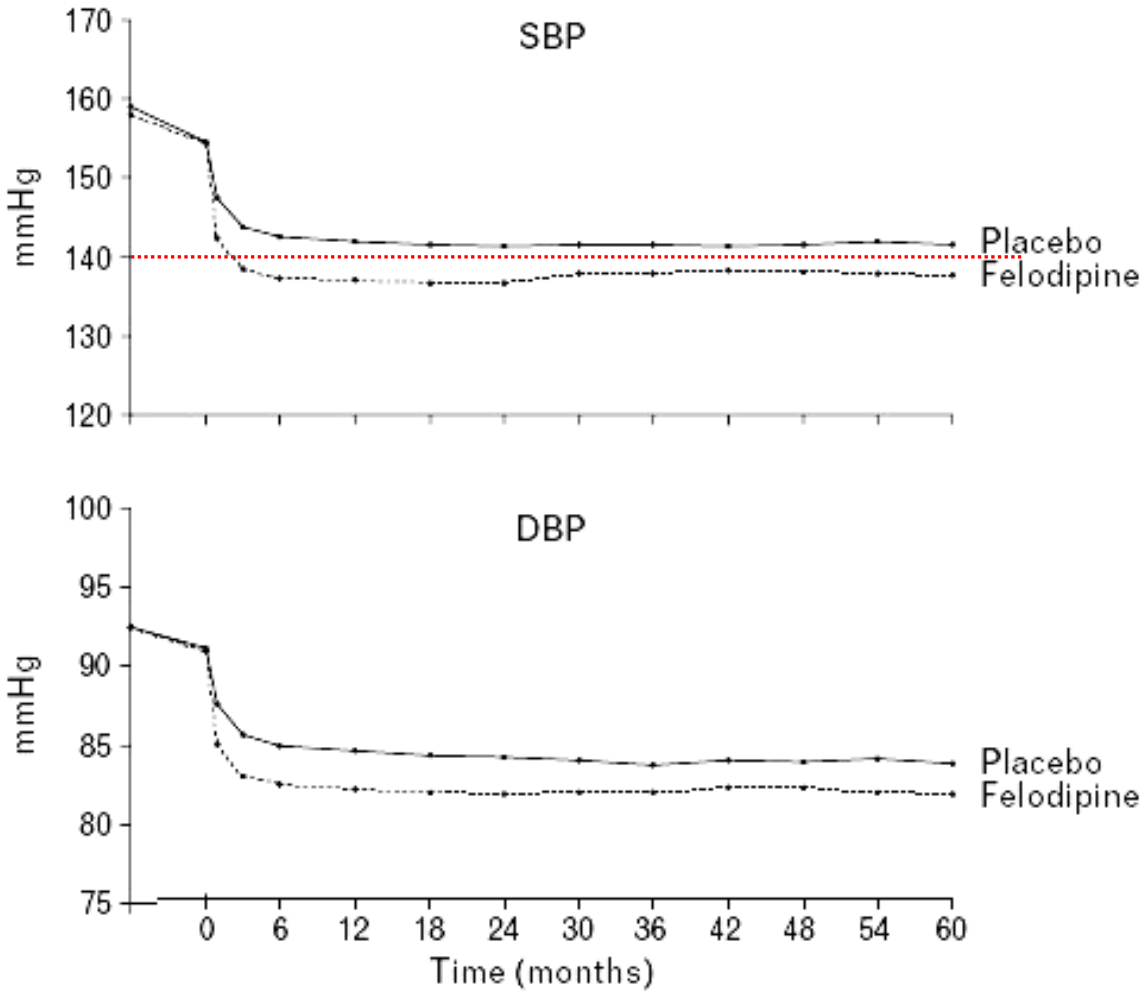
The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients

Lisheng Liu[a,b], Yuqing Zhang[a], Guozhang Liu[a], Wei Li[a], Xuezhong Zhang[b] and Alberto Zanchetti[c] for the FEVER Study Group*

- **Objective**
  - **To compare diuretic/placebo (less intensive) with diuretic/felodipine (more intensive) over 5 years**
- **Patients**
  - **N= 9711, 50-79y, hypertension plus 1CV event or 2 risk factors**
- **Outcome**
  - **Primary: stroke**
  - **Secondary: CV events, all cause mortality**

J Hypertens 2007;23:2157

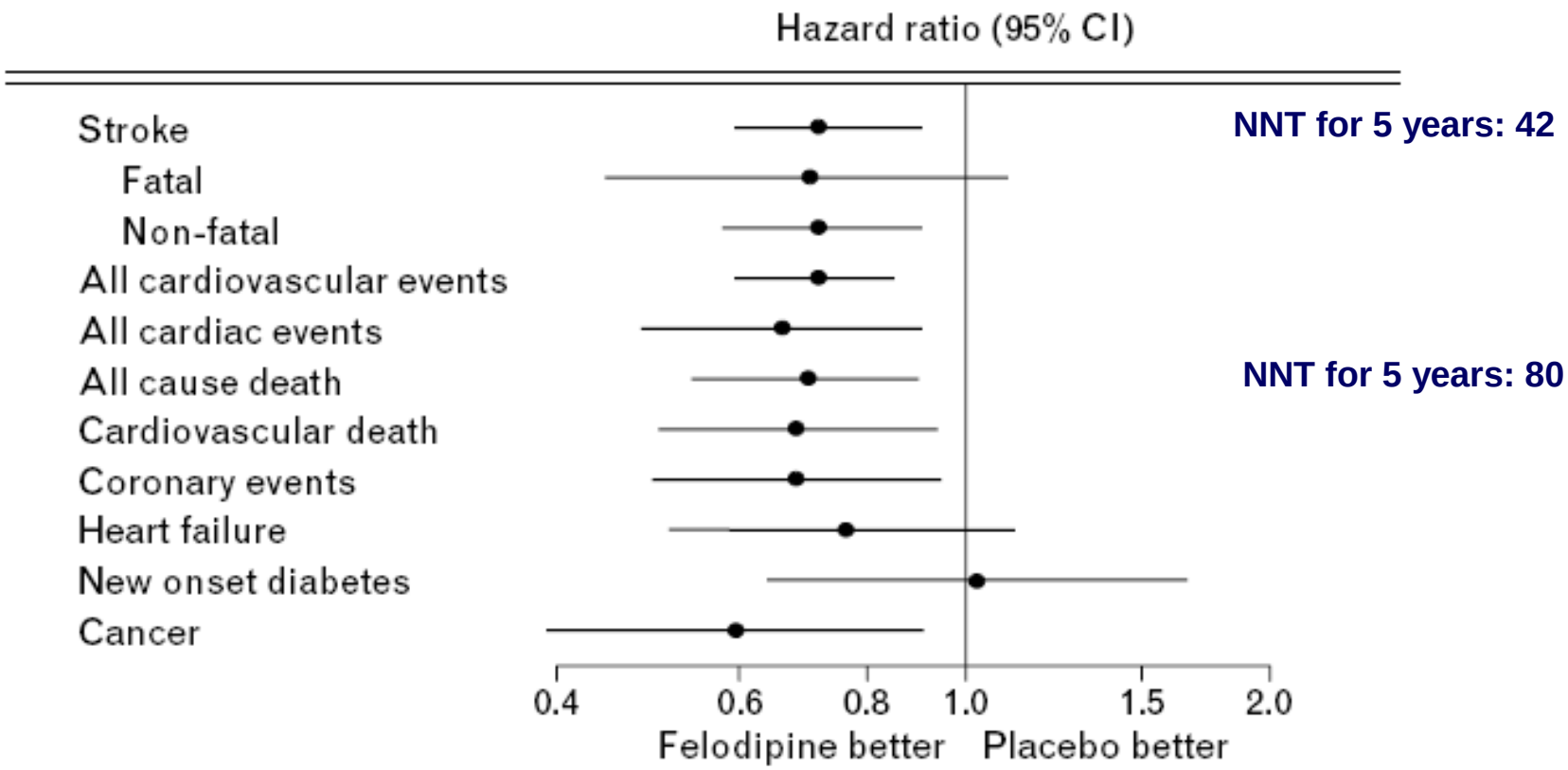
Blood pressure during the FEVER study



Diff:4.2/2.1 mmHg

J Hypertens 2007;23:2157

FEVER study: main outcome



J Hypertens 2007;23:2157

FEVER study conclusion

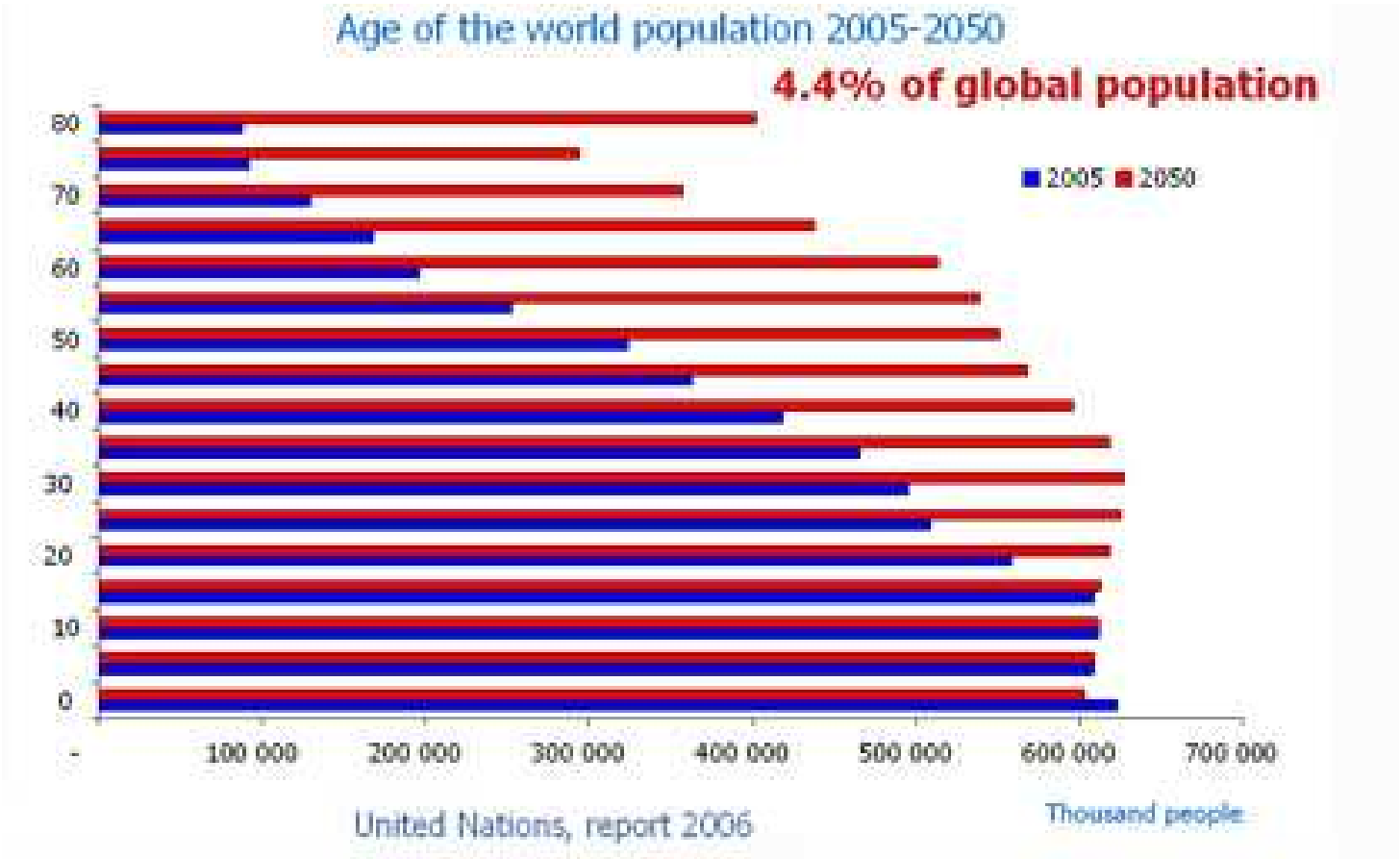
- **The role of small achieved blood pressure difference during treatment is substantial even in low risk patients**

- **First trial to show benefit of lowering blood pressure below the recommended systolic value of 140 mmHg in this population**

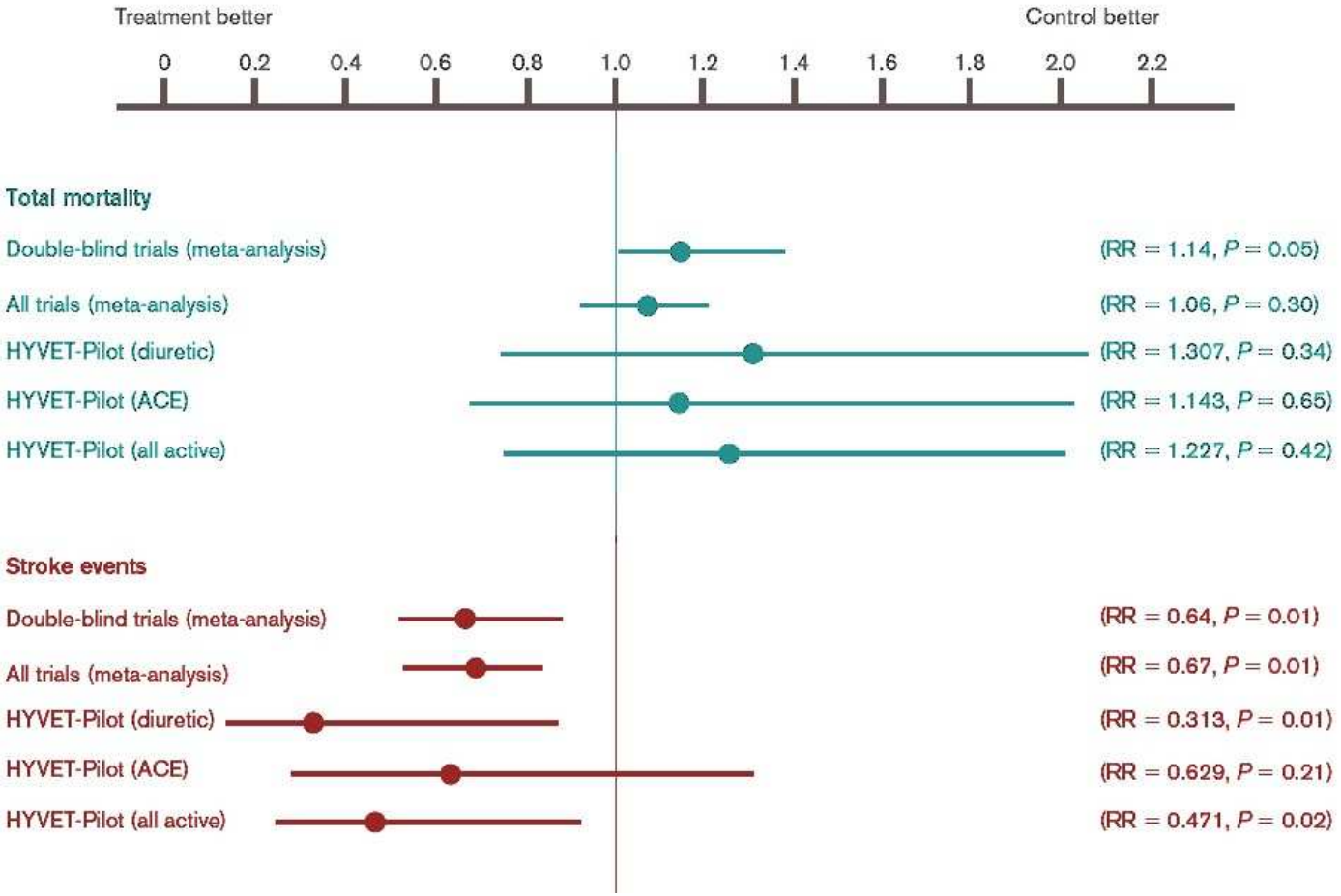
J Hypertens 2007;25:1105

Treatment of Hypertension in Patients 80 Years of Age or Older

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG



HYVET background



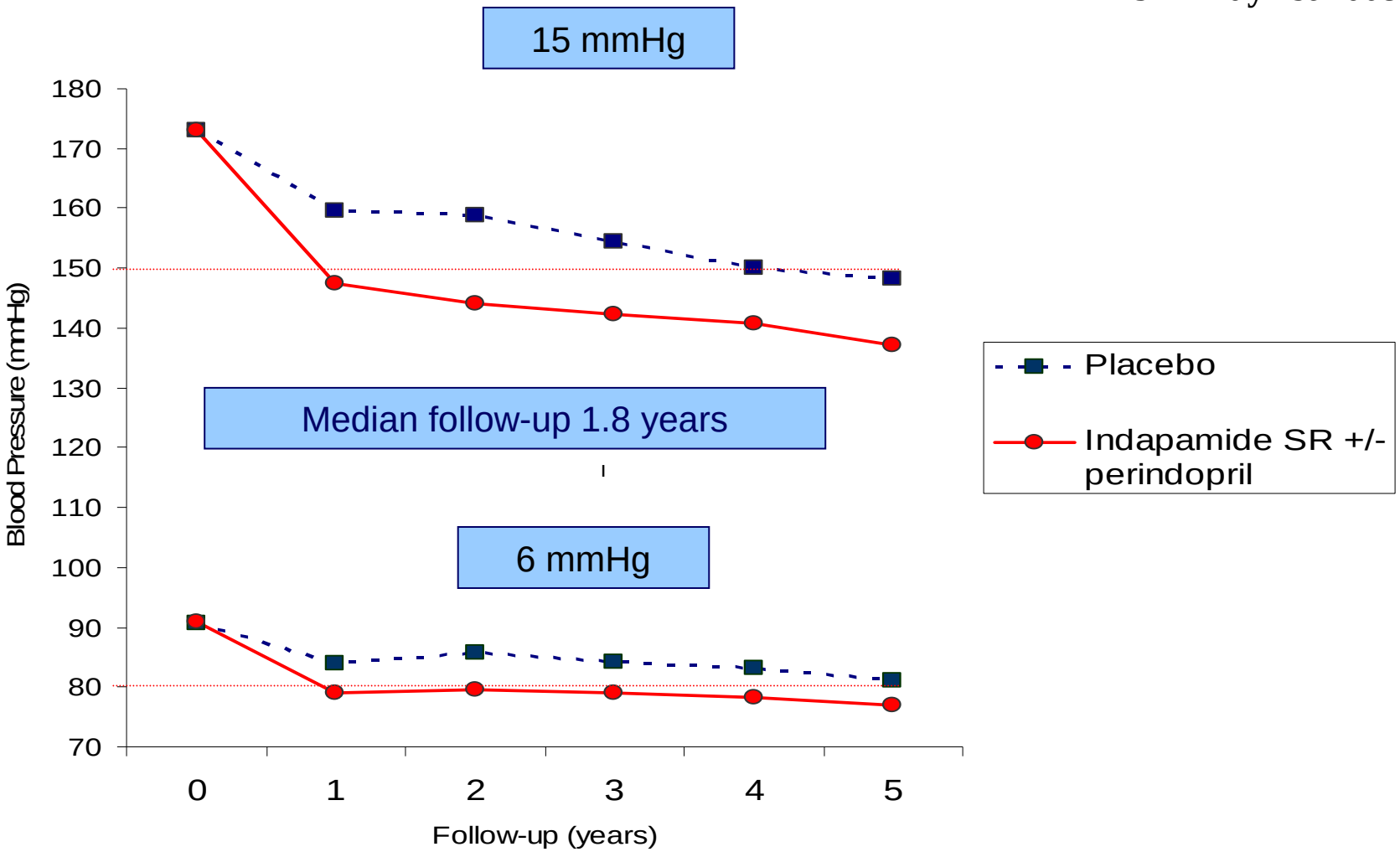
HYVET

- **Objective**
  - **To determine if treatment of HTN in patients ≥ 80 years of age was beneficial**
- **Methods**
  - **n= 3845, ≥160 mmHg, indapamid+perindopril vs. placebo, goal <150/80 mmHg, median f/u 1.8y**
- **Outcome**
  - **Primary: stroke**
  - **Secondary: all cause mortality CV events and mortality**

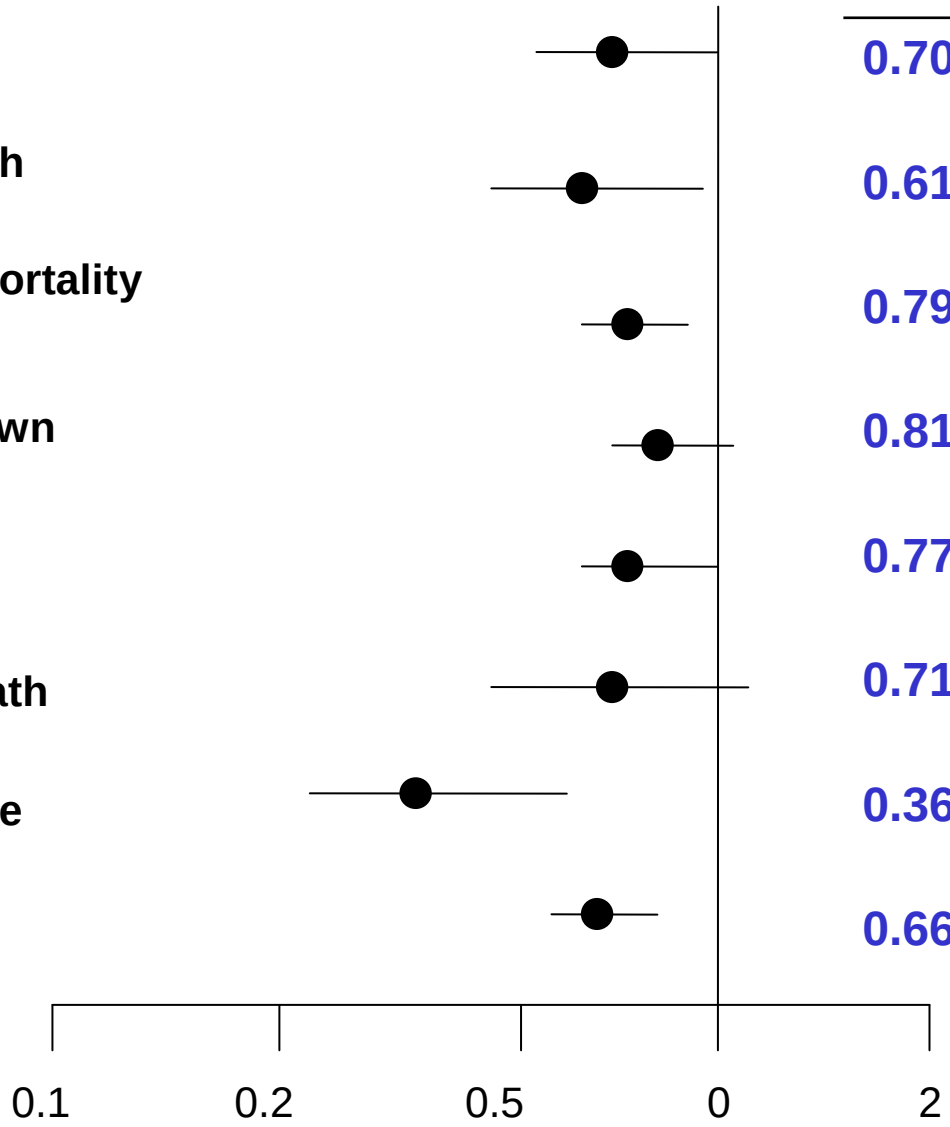
NEJM May 1st 2008

HYVET: change in blood pressure

NEJM May 1st 2008



HYVET: outcome data (intention to treat analysis)



	HR	95% CI	
All Stroke	0.70	(0.49, 1.01)	38 NNT/5y
Stroke Death	0.61	(0.38, 0.99)	
All cause mortality	0.79	(0.65, 0.95)	16 NNT/5y
NCV/Unknown death	0.81	(0.62, 1.06)	
CV Death	0.77	(0.60, 1.01)	
Cardiac Death	0.71	(0.42, 1.19)	
Heart Failure	0.36	(0.22, 0.58)	
CV events	0.66	(0.53, 0.82)	

HYVET: conclusion

- **Treatment of very old hypertensive patients decreases the risk of death from stroke and the risk of any death**

- **Trial evidence to to expand the age range of the treatment of HTN**

Choice of Antihypertensive Drugs

- „The main benefits of antihypertensive therapy are due to lowering of BP *per se*"

- „Five major classes of antihypertensive agents
  - thiazide diuretics
  - calcium antagonists
  - ACE inhibitors
  - angiotensin receptor antagonists
  - β- blockers

  are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination"
- „β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes"

ONTARGET

Objectives

Primary

Is ATII receptor blocking equivalent to ACE inhibition among high risk patients?

Secondary

Is double blockade better than ACE inhibition?

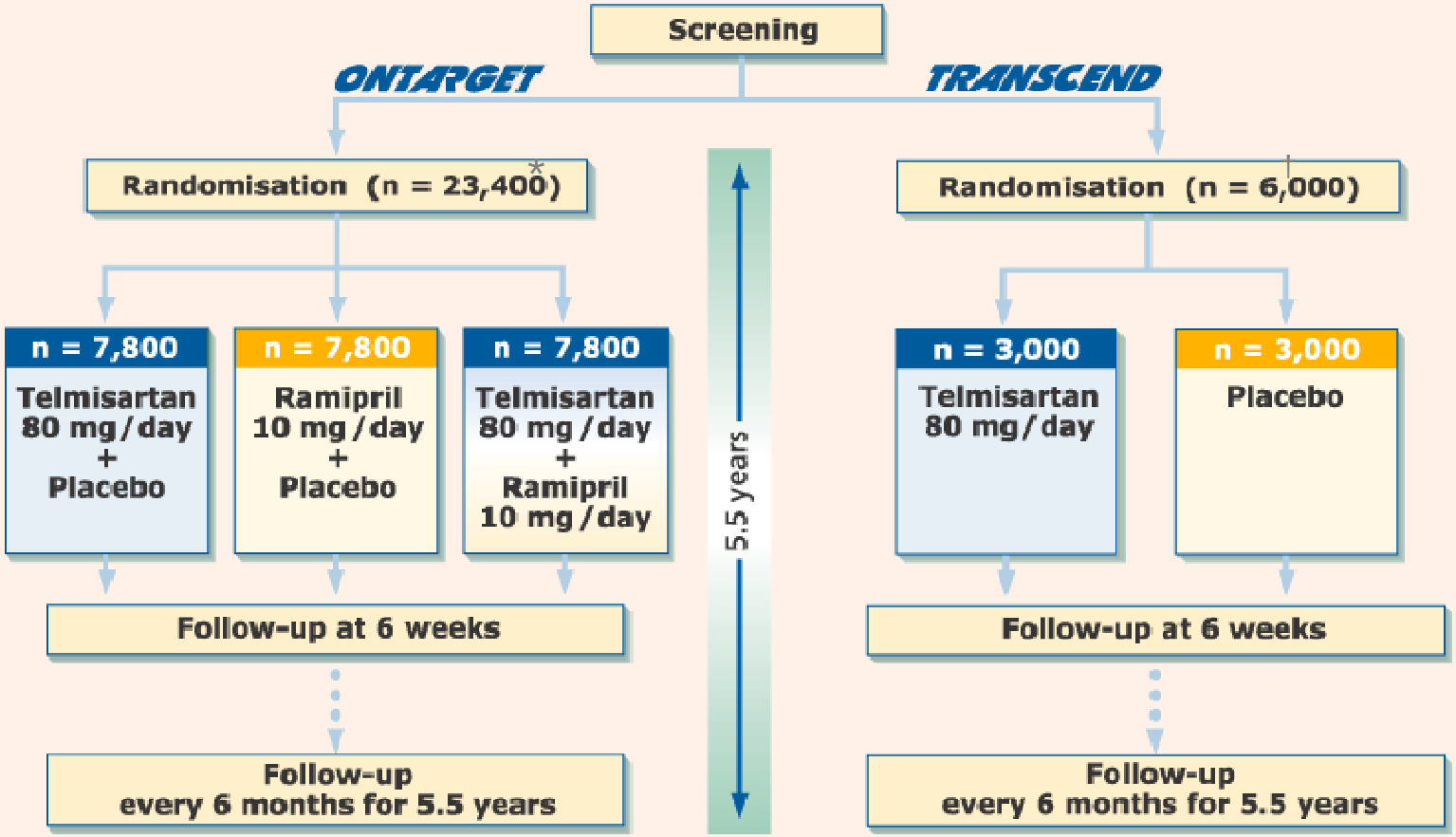
Inclusion Criteria

ONTARGET

- ≥55 y
- High risk
  - CAD
  - PAD
  - Stroke
  - DM + target organ damage

HOPE

- ≥55 y
- High risk
  - CAD
  - PAD
  - Stroke
  - DM + 1 risk factor



* Planned. Actual = 25,620

† Planned. Actual = 5,926

Outcome

ONTARGET

- CV mortality
- AMI
- Stroke
- CHF with admission

HOPE

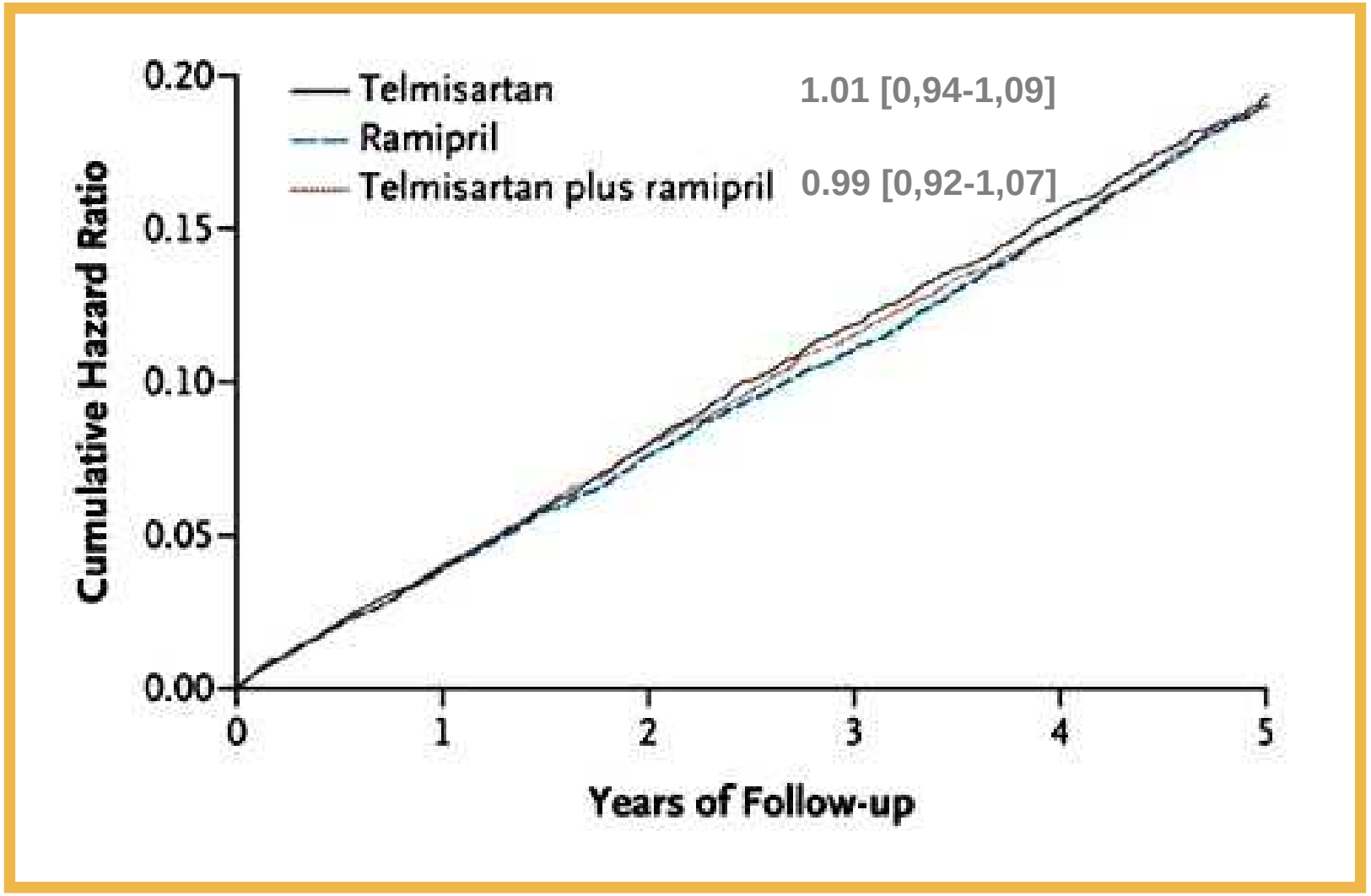
- CV mortality
- AMI
- Stroke

Baseline data

	ONTARGET (n = 25,620)	HOPE (n = 9,541)
Demography		
Age (years)	66.4	65.9
Male (%)	73.3	73.3
Body mass index	28.2	27.7
Waist–hip ratio	0.9	0.9
Medical history		
Hypertension (%)	68.3	46.5
MI (%)	48.7	52.8
Stable angina (%)	34.8	55.8
Stroke/TIA (%)	20.7	10.8
Claudication (%)	11.8	15.9
Diabetes (%)	37.3	38.3
Current smoker (%)	12.5	14.1

Am Heart J 2004;148:52

Occurence of the primary outcome in the three groups of ONTARGET



NEJM;358:1547

Outcome in Ontarget and HOPE

	Ramipril	Telmisartan	Comb.	HOPE
Primary	16,5	16,7	16,3	
CV mort. + AMI+stroke	14,1	13,9	14,1	14,0
MI	4,8	5,2	5,2	9,9
stroke	4,7	4,3	4,4	3,4
CHF hosp.	4,1	4,6	3,9	
CV mort.	7,0	7,0	7,3	6,1

NEJM;358:1547

Discontinuation of study medication and selected reasons

Discontinuation of Study Medications and Selected Reasons

Variable	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
		number (percent)	
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3) *
Reason for permanent discontinuation			
Hypotensive symptoms	149 (1.7)	229 (2.7) *	406 (4.8) *
Syncope	15 (0.2)	19 (0.2)	29 (0.3)
Cough	360 (4.2)	93 (1.1) *	392 (4.6)
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5) *
Angioedema	25 (0.3)	10 (0.1) *	18 (0.2)
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1) *

(29% in HOPE)

* $p<0,01$

ONTARGET: conclusion

- **Telmisartan is similarly effective than ramipril in high risk patients but better tolerated (angioedema, cough)**
- **Double blockade is no more effective than ramipril alone and less tolerated**

Summary

- **Note on the pathogenesis of HTN**
  - **Decreased salt excretiong capacity of the kidneys is necessary for sustained hypertension**

- **Note on home blood pressure measurement**
  - **Inclusion into everyday clinical practice is supported by recent guidelines**

- **Note on therapy**
  - **FEVER: evidence to treat HTN <140 mmHg systolic**
  - **HYVET: evidence to treat HTN in those ≥80 years of age**
  - **ONTARGET: no evidence for difference in efficacy between ramipril and telmisartan among high risk patients**