Cardiovascular system
Hypertension

Lecture slides: http://semmelweis.hu/pharmacology

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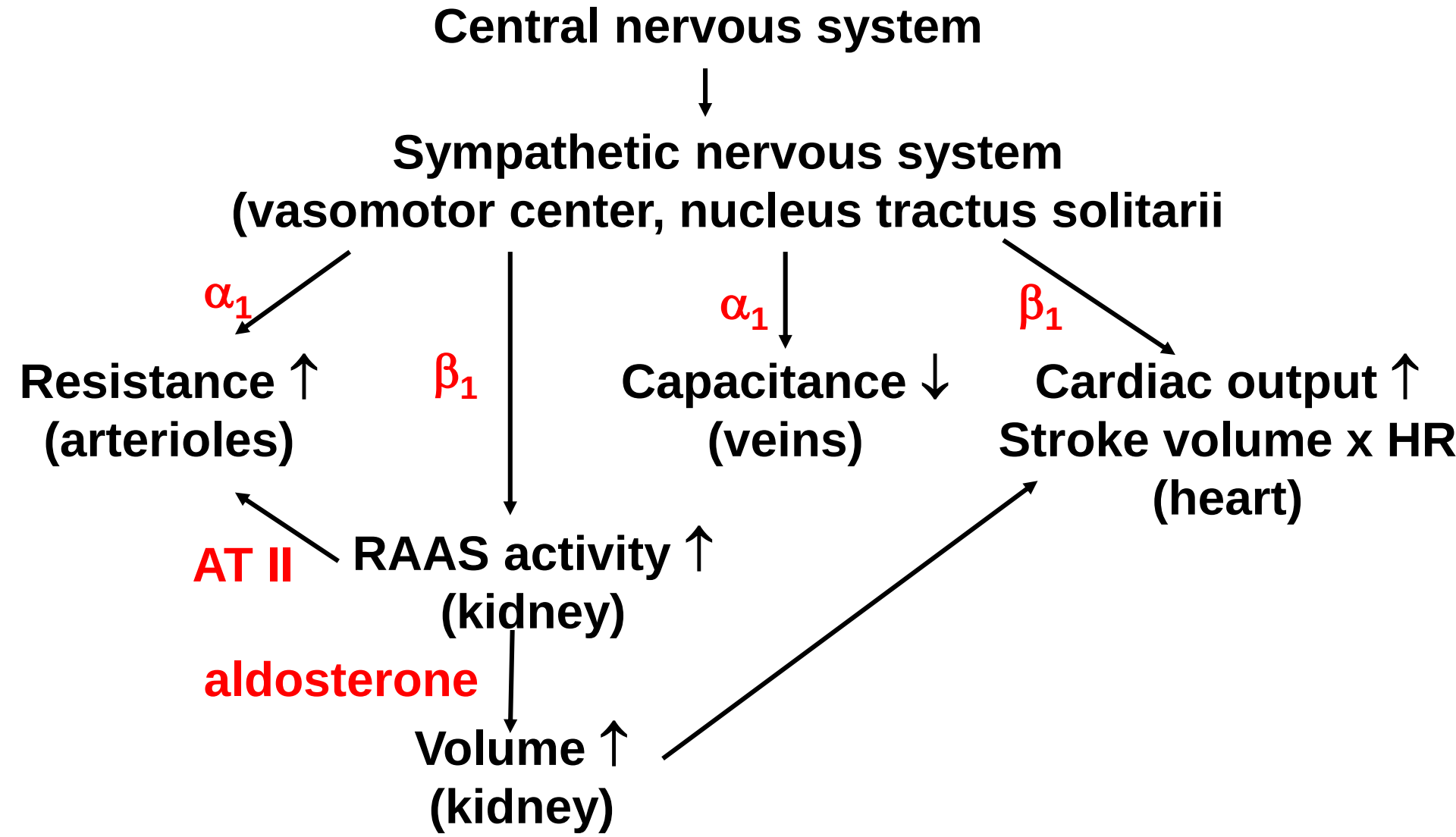
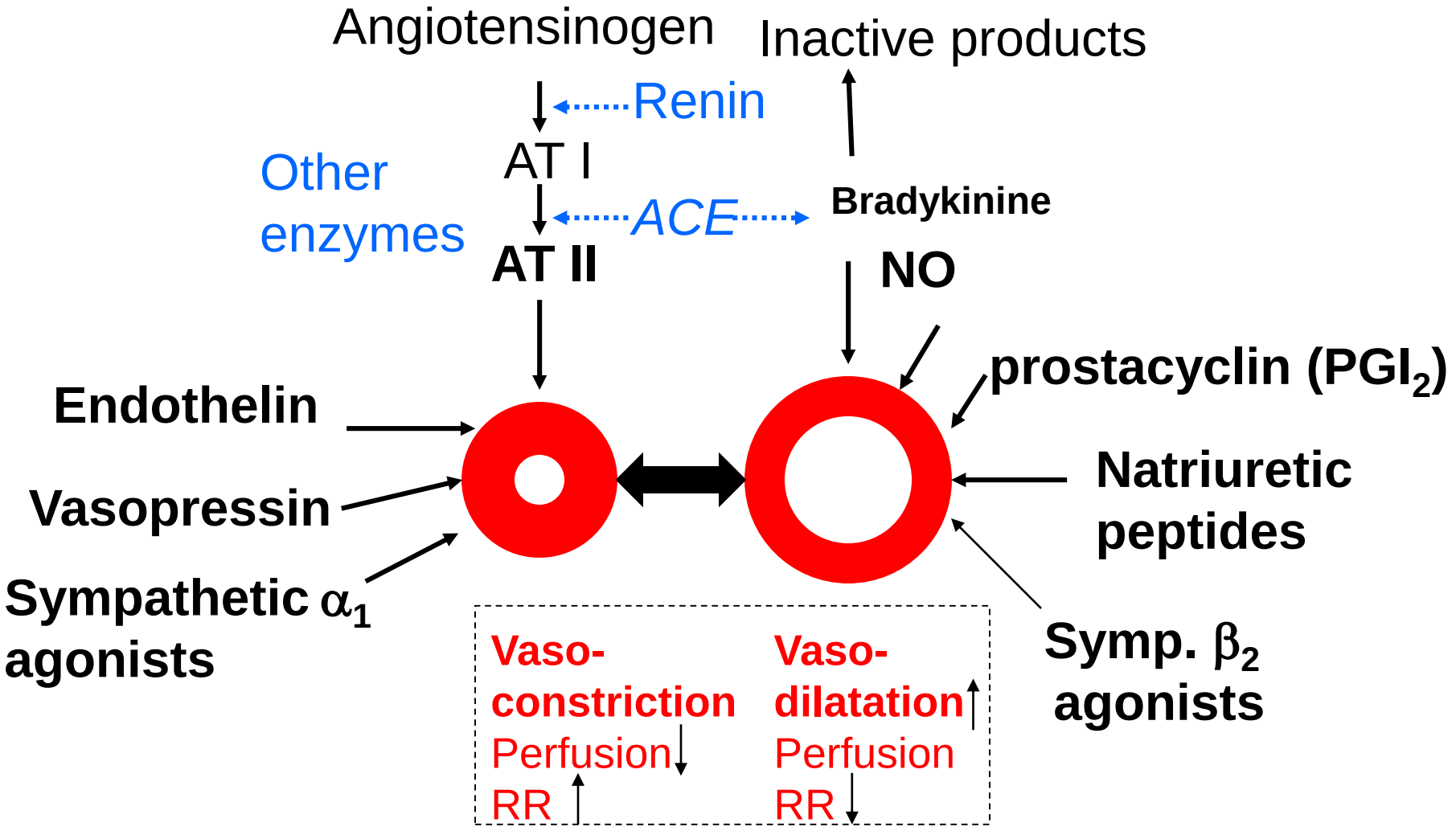
Regulation of blood pressure



Regulation of vascular tone



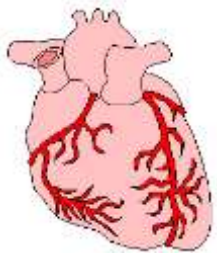
Classification of hypertension

ESH/ESC Guidelines. J.Hypertension, 25:1105-1187, 2007

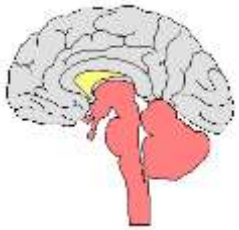
Blood Pressure, mmHg	Systolic	Diastolic
Optimal	< 120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Gr 1 HY (mild)	140-159	90-99
Gr 2 HY (moderate)	160-179	100-109
Gr 3 HY (severe)	≥ 180	≥110
Izolált syst. HY	≥ 140	*< 90**
HY: 24h ambulantory (ABPM), mean	≥ 125-130	≥ 80
Day time mean	≥ 130-135	≥ 85
Night mean	≥ 120	≥70
HY: Home (HBP)	≥ 130-135	≥ 85

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), 2013

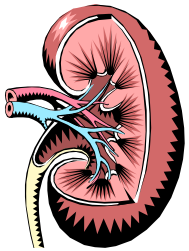
Organic diseases developing as consequences of HY



Left ventricular hypertrophy
Heart failure
Coronary disease
MI
Aortic aneurysm
Peripheral arterial disease

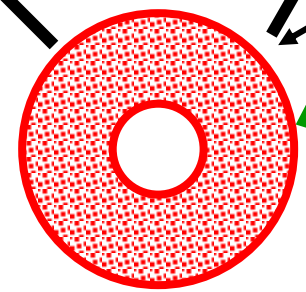


Stroke
(cerebral infarction, hemorrhage)
Hypertonic encephalopathy, retinopathy



Renal disease

Risk factors
Age ↑
M> F (levels off with aging)
Previous cardiovasc. disease
Renal disease
Diabetes
Disturbed lipid metab.: LDL ↑ HDL ↓
Obesity
Elevated fibrinogen level ↑
Socioeconomic status
Smoking ↑
Drinking



Hypertrophic, „remodelled" vascular wall Hypertension

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)

HY: prognostic stratification

ESH/ESC Guidelines. J.Hypertension, 25:1105-1187, 2007

Blood pressure	Normal S: 120-129 D: 80-84	High norm S: 130-139 D: 85-89	Mild HY S: 140-159 D: 90-99	Moder HY S: 160-179 D: 100-109	Sever HY S: ≥ 180 D: ≥ 110
Other risk factors + disease history	*Risk*	*Risk*	*Risk*	*Risk*	*Risk*
No RF	Average	Average	Low	Moderate	High
1-2 RF	Low	Low	Moderate	Moderate	Very high
≥ 3 RF or MS, DM Subclinical organ damage	Moderate	High	High	High	Very high
Proven CV or kidney disease	Very high	Very high	Very high	Very high	Very high

HY: prognostic stratification

ESH AND ESC GUIDELINES, 2013

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	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 RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to Moderate risk	Moderate to high risk	High Risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Therapeutic considerations by risk factors

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	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 risk factors, MS or OD	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

The effect of hypertension on the number of CV events

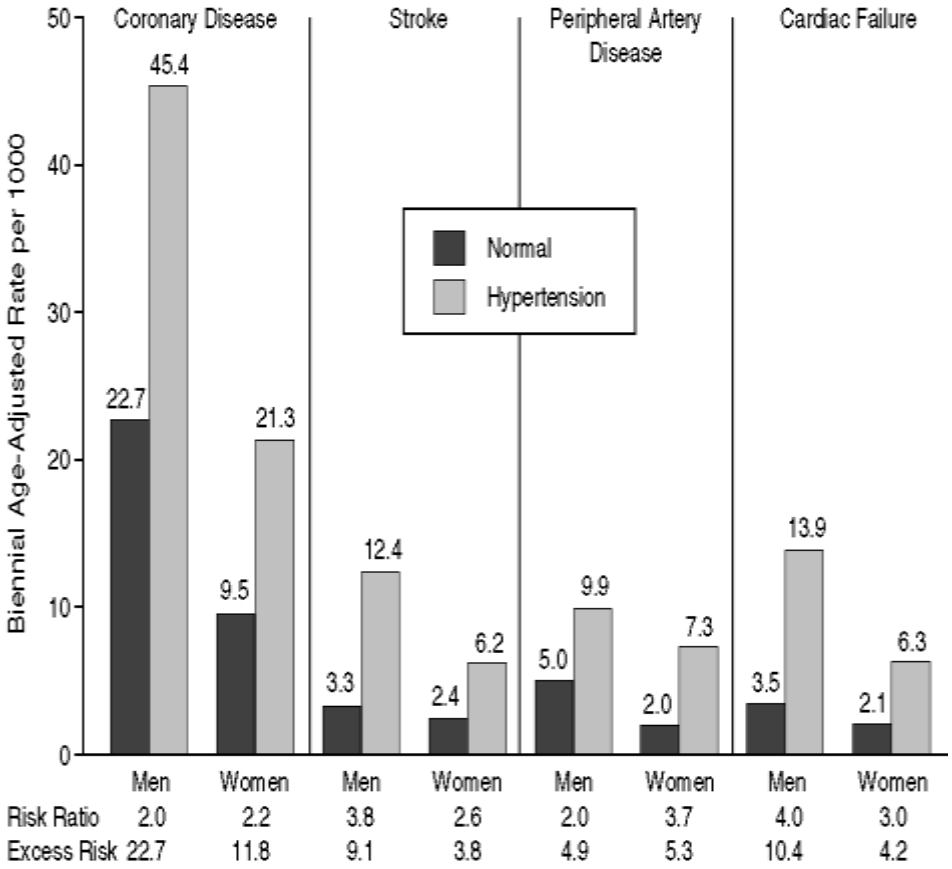
ESH/ESC Guidelines. J.Hypertension, 25:1105-1187, 2007

In the general adult population (40-89 yr) each **20/10 Hgmm** increase of BP, between 115/75-185/115 mmHg, doubles the number of future cardiovascular events

Hypertension as risk factor: Framingham study

Kannel WB: JAMA, 275:1571, 1996

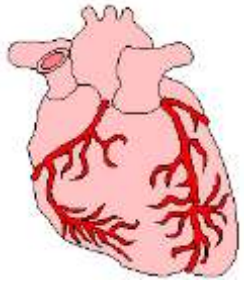
- 5209 male and female (30-62 year) continuous monitoring since 1949
- Goal: detect development of cardiovascular diseases
- Ref ranges of categories:
  - normotension: 140/90;
  - hypertension: 160/95
- 30-65 age – increase in BP 20 Hgmm systolic and 10 Hgmm diastolic
- 65% of cases was isolated systolic hypertension
- Increaed prevalence of hypertension, number of pathological BP values decreased due to treatment



Main goals of antihypertensive therapy

- Decrease mortality
- Increase life span
- Better quality of life
- Decrease occurrence of organ failure

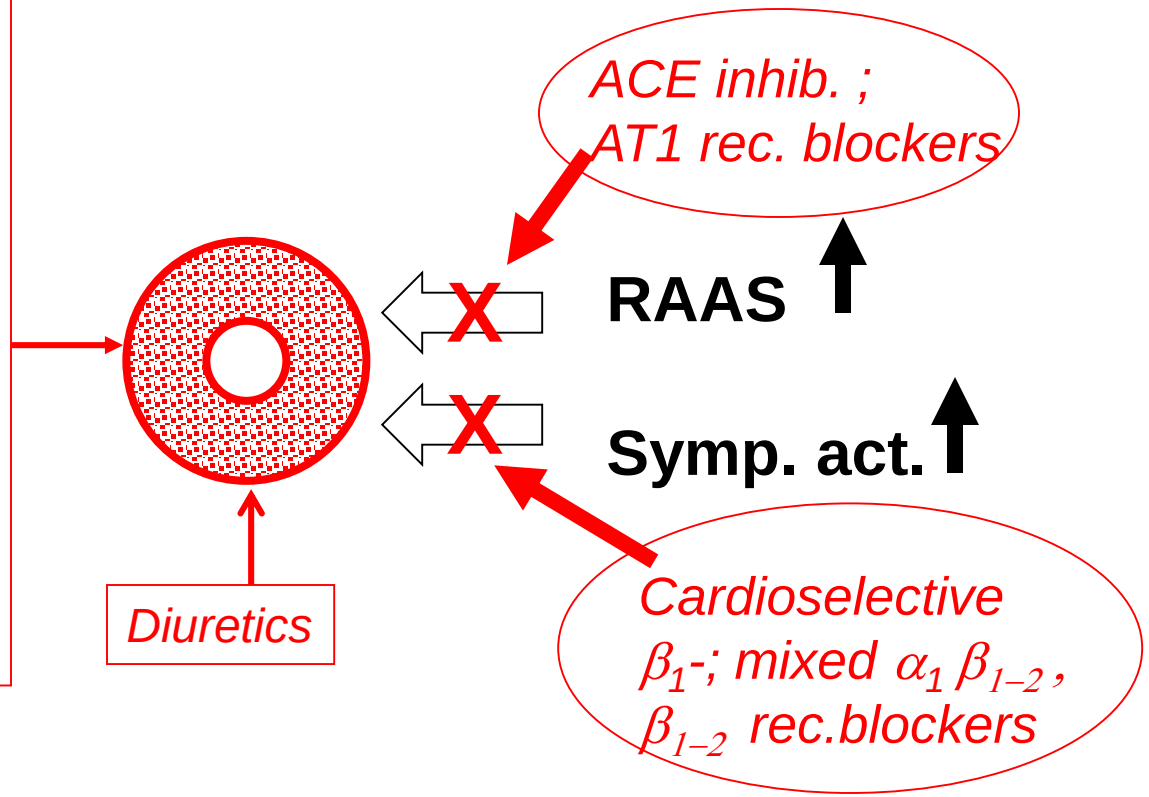
- Persistence
- Adherence



Strategy of the drug treatment of hypertension

Hypertrophy of the walls of resistance vessels
Remodelling: narrow lumen, rigid vasc. wall
Causes: Genetic factors, environmental influences

Vasodilator effect:	***Arterioles***	***Veins***
Nitroprusside	+++	*
Hydralazin	+++	
Minoxidil	+++	
α1-rec. blockers	++	*
ACE inhib.	++	**
Ca - antagonists	++	**
Nitroglycerin	+	***
Isosorbide-di /mononitrate	+	***



Inhibition of overcompensation:
Supportive treatment:

Selection of antihypertensive drugs

WHO-Int. Soc. Of Hypertension. Guidelines. J. Hypertension 17:151, 1999

Drug	Main indication	Second. indic.	*Contraindic.*
Diuretics	HF Elderly patients Syst. HY	Diabetes	*Gout*
β- blockers	Angina Following MI Tachyarrhythmia	HF Pregnancy Diabetes	*Asthma* *COPD* *A-V block (Gr 2-3)*
ACE inhibitors	HF Left vent. dysfunct. Following MI Diab. nephropathy	---	*Pregnancy* *Hyperkalemia* *Bilat. a. ren. sten.*
Ca antagonists	Angina Elderly patients Syst. hypertension	Periph. vasc. disease	*A-V block (Gr 2-3)*
α– blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidemia	----
AT 1 rec. blockers	Cough caused by ACE inhibitors	HF	*Pregnancy* *Hyperkalemia* *Bilat. a. ren. sten.*

Immediate and late results of the antihypertensive treatment

Outcome

Organic damage: heart ↓ brain ↓ kidney ↓ diabetes(?) ↓

RR↓ *Surrogate endpoint*

ACE inhibitors
AT1 rec. blockers

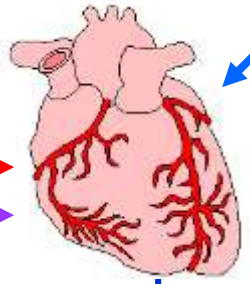
Symp. rec. blockers

α_1

$\beta_{1-(2)}$

Ca anta-gonists

Diuretics



Optimal target BP: HOT study

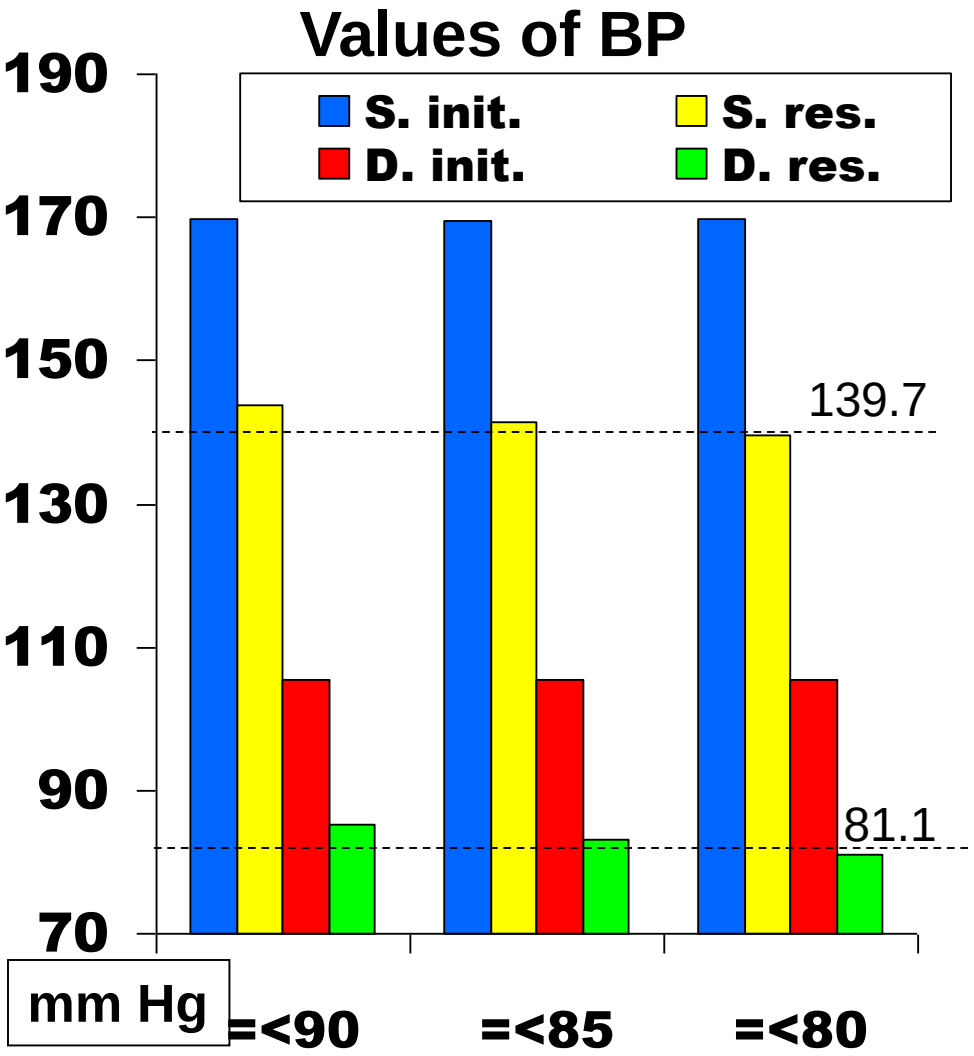
Hansson et al.: Lancet, 351:1755, 1998

Hypertension **O**ptimal **T**reatment Study was a prospective trial conducted in 26 countries. The aims are to (1) evaluate the **relationship between three levels of target office diastolic blood pressure** (BP) (≤80, ≤85, or ≤90 mm Hg) and **cardiovascular morbidity and mortality in hypertensive patients** and (2) examine the **effects on cardiovascular morbidity and mortality** of **75 mg Aspirin** daily **versus placebo**. A total of **19 193** patients between 50 and 80 years of age had been randomized by the end of April 1994.

HY: optimal target BP
HOT study

Hansson et al.: Lancet, 351:1755, 1998

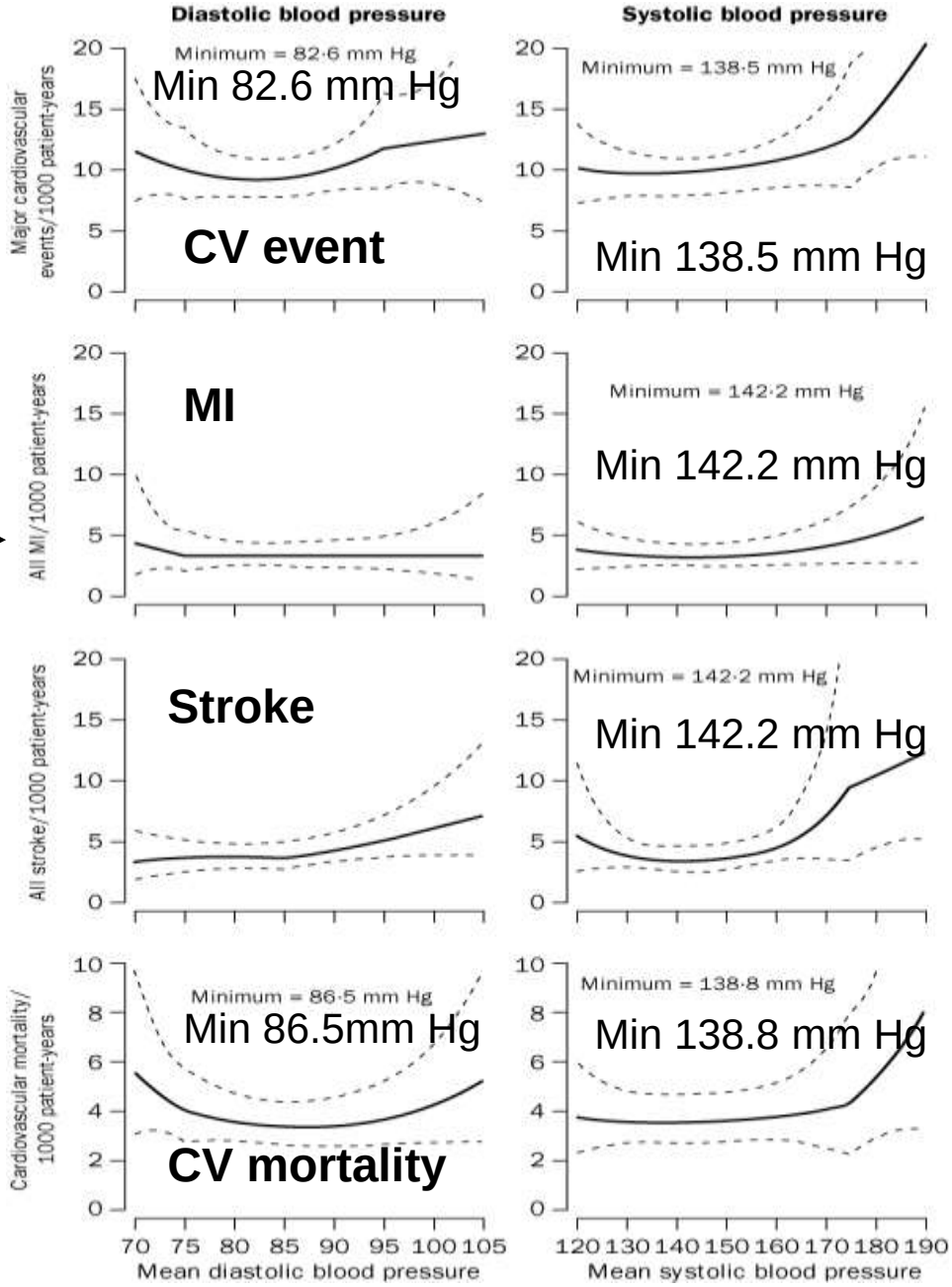
- Aim of study: determination of optimal target BP values of anti-hypertensive therapy at which the occurrences of cardiovasc. events, MI, stroke and death are the lowest
- Prospective, randomized, open study, with blinded evaluation; random selection of target BP
- Patient selection: diast. BP between 100 and 115 mmHg
- Gradual treatment until target BP is reached:
  - 1. Ca blocker: felodipine 5mg/d
  - 2. ACE inhib. or β–blocker
  - 3. Felodipine 10 mg/d
  - 4. ACE inhib. or β -bl. dose 2x
  - 5. Diuretics



HY: Optimal target BP
HOT study

Hansson et al.: Lancet, 351:1755, 1998

Calculated occurrence of cardiovascular events (± 95% CI) according to the BP values reached (Event per 1000 patient-year)

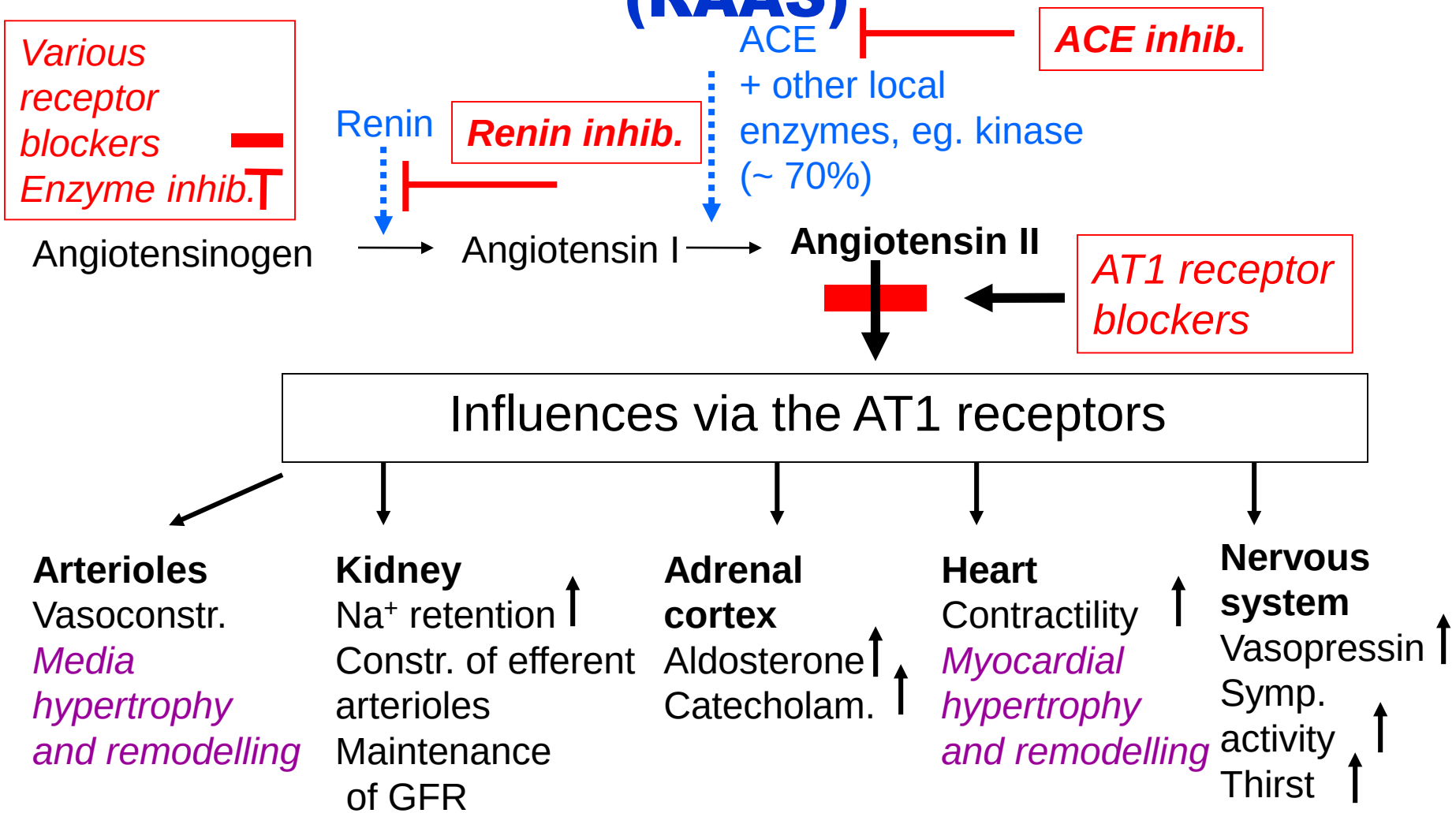


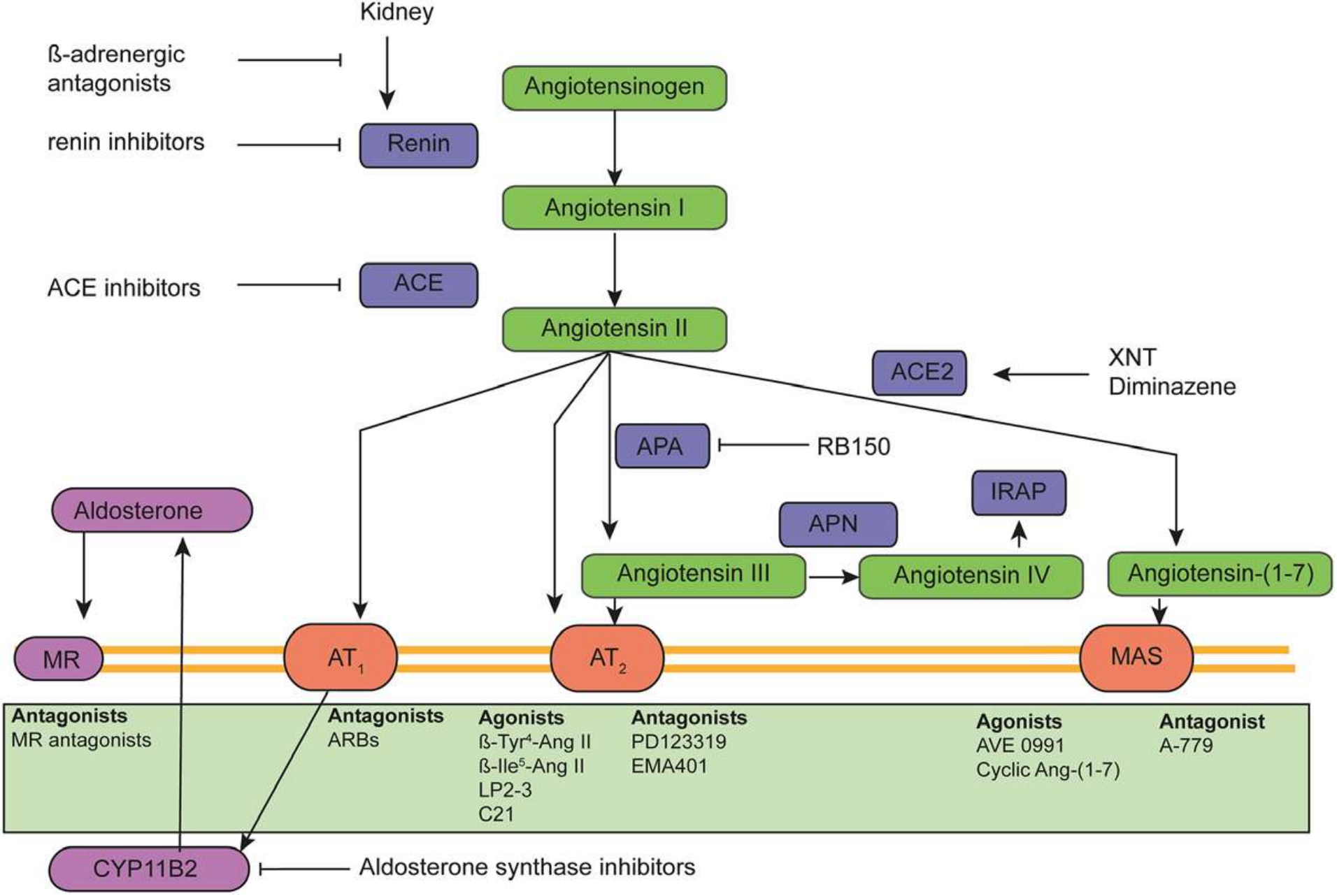
- **Optimal therapeutic end point: 135-140/80-85 mmHg**
- BP may be lowered even below these values but further considerable decrease of cardio-vascular complications may be not expected
- It is especially important to reach the optimal target value in diabetic patients since HY leads to late organic damage in a higher proportion in them

Adoption of lifestyle changes

Recommendations	Class [a]	Level [b,d]	Level [b,e]	Ref. [c]
Salt restriction to 5–6 g per day is recommended.	I	A	B	339, 344–346, 351
Moderation of alcohol consumption to no more than 20–30 g of ethanol per day in men and to no more than 10–20 g of ethanol per day in women is recommended.	I	A	B	339, 354, 355
Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.	I	A	B	339, 356–358
Reduction of weight to BMI of 25 kg/m^2 and of waist circumference to <102 cm in men and <88 cm in women is recommended, unless contraindicated.	I	A	B	339, 363–365
Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week is recommended.	I	A	B	339, 369, 373, 376
It is recommended to give all smokers advice to quit smoking and to offer assistance.	I	A	B	384–386

Pharmacological inhibition of the Renin-Angiotensin-Aldosterone-System (RAAS)




Kidney
ß-adrenergic antagonists
renin inhibitors
ACE inhibitors
Renin
ACE
Angiotensinogen
Angiotensin I
Angiotensin II
ACE2
XNT
Diminazene
APA
RB150
IRAP
APN
Aldosterone
Angiotensin III
Angiotensin IV
Angiotensin-(1-7)
MR
AT1
AT2
MAS
Antagonists
MR antagonists
Antagonists
ARBs
Agonists
ß-Tyr4-Ang II
ß-Ile5-Ang II
LP2-3
C21
Antagonists
PD123319
EMA401
Agonists
AVE 0991
Cyclic Ang-(1-7)
Antagonist
A-779
CYP11B2
Aldosterone synthase inhibitors

RAAS antagonists

- Renin antagonists
  - Aliskiren
- ACE-inhibitors
  - Enalapril
  - Perindopril
  - Ramipril
  - Lisinopril
  - Trandolapril
  - Cilazapril
  - Benazepril
  - Fosinopril
- Angiotensin II antag.
  - Losartan
  - Valsartan
  - Irbesartan
  - Candesartan
  - Telmisartan
  - Olmesartan
- Aldosterone antag.
  - Spironolactone
  - Eplerenone (*HY in the U.S. only*)

Direct clinical pharmacological effects of ACE inhibitors

Cardiovascular system

- Reduction of both the systolic and diastolic blood pressure
- Considerable effect already after 2 weeks of treatment, maximal effect develops in 6-8 weeks, BP remains permanently low during treatment. In sensitive patients the sudden drop of BP may cause fainting
- In normal heart they do not change the LVEF, stroke volume and cardiac output. They lead to a balanced arterial and venous vasodilation. In HF they reduce both the pre-load and the after-load, and decrease the left ventricular hypertrophy

Direct clinical pharmacological effects of ACE inhibitors

Kidney:

- They do not affect glomerular filtration and creatinine clearance, they cause a mild glomerular vasodilatation
- They have a favorable effect on diabetic nephropathy, they decrease the selective albumin clearance

Endocrine system:

- They slightly increase the plasma renin level and slightly decrease the plasma norepinephrine level. Lipid and glucose metabolisms are not affected

Clinical pharmacological characteristics of ACE inhibitors

Name	Bena-zepril	Cap-topril	Ena-lapril	Fosi-nopril	Lisi-nopril	Qui-napril	Ra-mipril	Tran-dolapr.
Prodrug	+	-	+	+	-	+	+	+
Bioavail.%	28	60	40	25	25	<38	44	40-60
T1/2 h	10-20	1,7	11	<12	12,5	2	13-17	16-24
Excretion	R+H	R	R	R=H	R	R	R>H	R>H
Dose reg.	QD	BID/TID	QD/BD	QD	QD	QD/BD	QD/BD	QD

The dose regimen depends rather on the velocity of the dissociation of the enzyme-inhibitor binding than on the plasma half life of the drugs
QD, BID, TID: daily one, two, three administrations

Adverse events, problems or limitations of RAAS antagonists

Adverse events:

- Dry cough (ACE-inhibitors)
- **Hyperkalaemia – all of them !!!**
- Angioneurotic oedema (ACE-inhibitors)
- Acute renal failure
- Hypotension (mostly when combined with diuretics)

Limitations:

- **Pregnancy!!! – all of them are teratonegic**
- Bilateral renal artery or aorta stenosis
- Afroamerican people – low renin level, no effect

HY: ramipril vs. placebo

HOPE study Heart Outcomes Prevention Evaluation

HOPE invest: NEJM, 342: 145, 2000

	Ramip-ril	Placebo		Ramip-ril	Placebo
No. of pat.	4645	4652	**Periph. vasc. disease%**	42.3	44.8
Age	66	66	**Hypertens. %**	47.6	46.1
Syst. mm Hg	139	139	**Diabetes %**	38.9	38
Diast. mmHg	79	79	**β-blocker**	39.2	39.8
Elevated tot. chol. %	65.4	66.4	**Aspirin or antithrom. dr.**	75.3	76.9
Microalbu-minuria %	20.5	21.6	**Lipid reducers**	28.4	28.8
Smoking	13.9	14.5	**Diuretics**	15.3	15.2
Coronary disease %	79.5	81.3	**Ca channel bl.**	46.3	47.9
Stroke %	10.8	11			

Hypertension: ramipril vs. placebo
HOPE study

HOPE invest: NEJM, 342: 145, 2000

- **Composite end point of study:** cardiovascular mortality, MI, stroke
- **Patient inclusion (high risk):** coronary disease, stroke, periph. vasc. disease, diabetes in the case history + at least one cardiovasc. risk factor (hypertension, disturbance of lipid metabolism, microalbuminuria, smoking)
- Double blind, prospective, randomized
- Ramipril: 10 mg/d (2.5; 5; 10)

Relative risk:

Comp. EP: 0.78 (0.70-0.86) p< 0.001

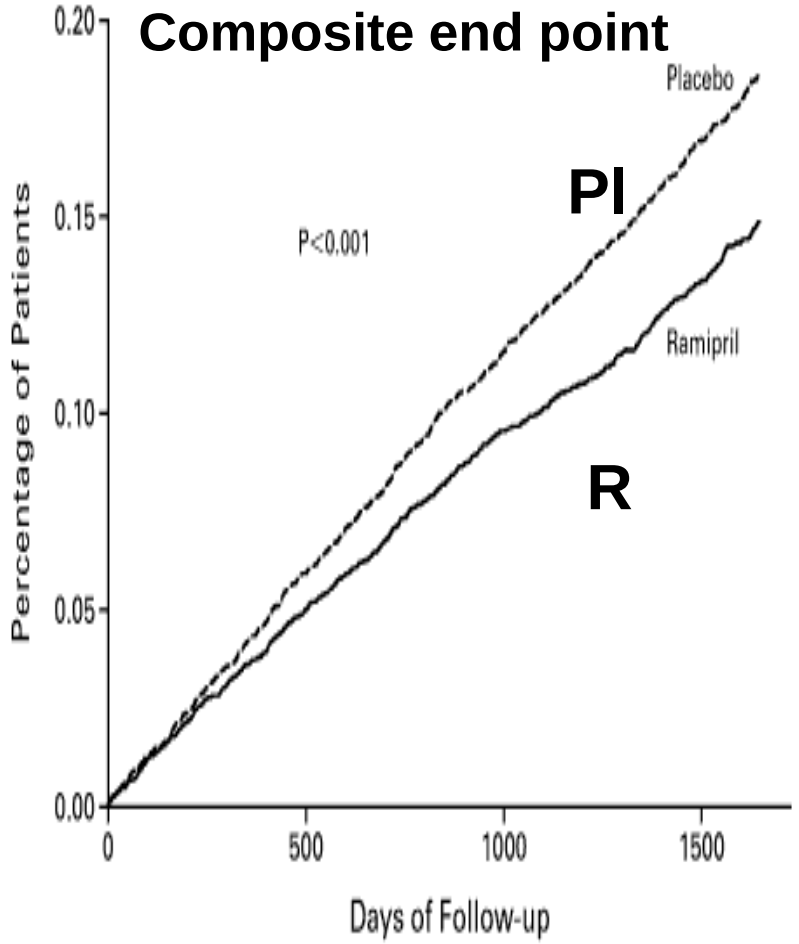
CV mort.: 0.75 (0.64-0.87) p< 0.001

MI: 0.80 (0.71-0.91) p< 0.001

Stroke: 0.69 (0.56-0.84) p< 0.001

Total mort.: 0.84 (0.75-0.95) p< 0.001

New diab. m.:0.68 (0.53-0.87) p< 0.03



The comparison of ACE inhibitor (ACEI) and placebo treatments

Blood Pressure Lowering Treatment Trialsit' Collaboration, Lancet. 356:1955. 2000

No of patients: 6060 / 6064 Outcome	Events % ACEI/ placebo	Relatíve Risk RR (95% CI)	P
Stroke	2.7 / 4.0	0.70 (0.57-0,85)	S
Coronary heart dis.	8.9 / 11.1	0.80 (0.72-0.89)	S
Heart failure	2.5 / 3.0	0.84 (0.68-1.04)	NS
Major CV events	13.5 / 17.2	0.79 (0.73-0.86)	S
CV death	5.1 / 6.7	0.74 (0.64-0.85)	S
Total mortality	8.8 / 10.4	0.84 (0.76-0.94)	S

Dual blockage of the renin-angiotensin system

Makani et al., BMJ 2013; 346:f360 doi: 10.1136/bmj.f360

- Objective: to compare long term efficacy and safety of dual blockage of the RAAS with monotherapy of the components of dual bloockage, ACEI; ARB and reninin inhibitor
- Meta analysis of 68405 pts, follow-up 52 weeks
- **Efficacy**
  - Dual blockage did not improve all cause of mortality and CV mortality
  - Significantly decreased hospitalization due to HF
- **Safety:** the combination significantly increased
  - The occurance of hyperkalemia
  - Renal failure especially in pts with HF
  - Withdrawing of treatment due to side effects
- ***Conclusion: The risk to benfit ratio does not support the application of dual blockage of the RAAS***

Beta adrenergic receptor blockers

- Non-selective $\beta_{1\text{-}2}$
  - Propranolol
  - Pindolol
  - Nadolol
- α_1+β blockers
  - Carvedilol
- Cardioselective
  - Metoprolol
  - Atenolol
  - Bisoprolol
  - Nebivolol
  - Betaxolol

Advantages of the clinical application of selective β_1 blockers

- Favorable hemodynamic effects are due to the blocking of β_1 rec. while side effects mainly to that of β_2 rec.
- β_1 selectivity is not complete, parallel to concentration increase cardio-selectivity decreases
- The hypotensive effect is mainly the consequence of the reduction of cardiac output, i.e. that of the blocking of β_1 receptors
- β_1 selective drugs decrease more the diastolic BP, do not increase peripheral resistance, do not cause disturbances in the peripheral circulation
- Mixed $\alpha_1 - \beta_{1\text{-}2}$ blockers do not cause peripheral vasoconstriction

Advantages of the clinical application of selective β_1 blockers

- Selective β_1 blockers do not affect the carbohydrate metabolism, the blood sugar of diabetic patients usually does not change during the treatment

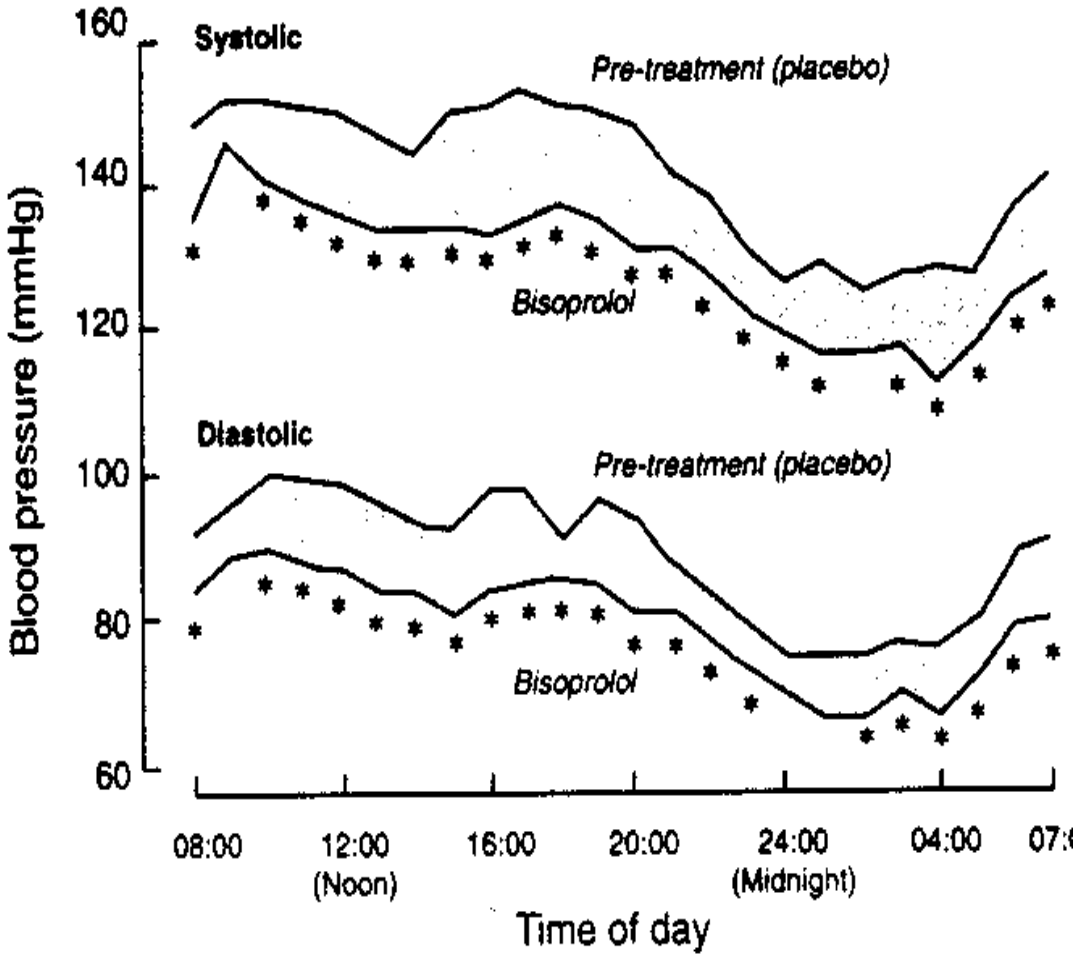
- They do not prolong hypoglycemia following insulin treatment. *Caution:* in hypoglycemia they reduce the reactive tachycardia

- Selective β_1 blockers do not raise the triglyceride level, do not reduce HDL level, their effect on the cholesterol metabolism is negligible

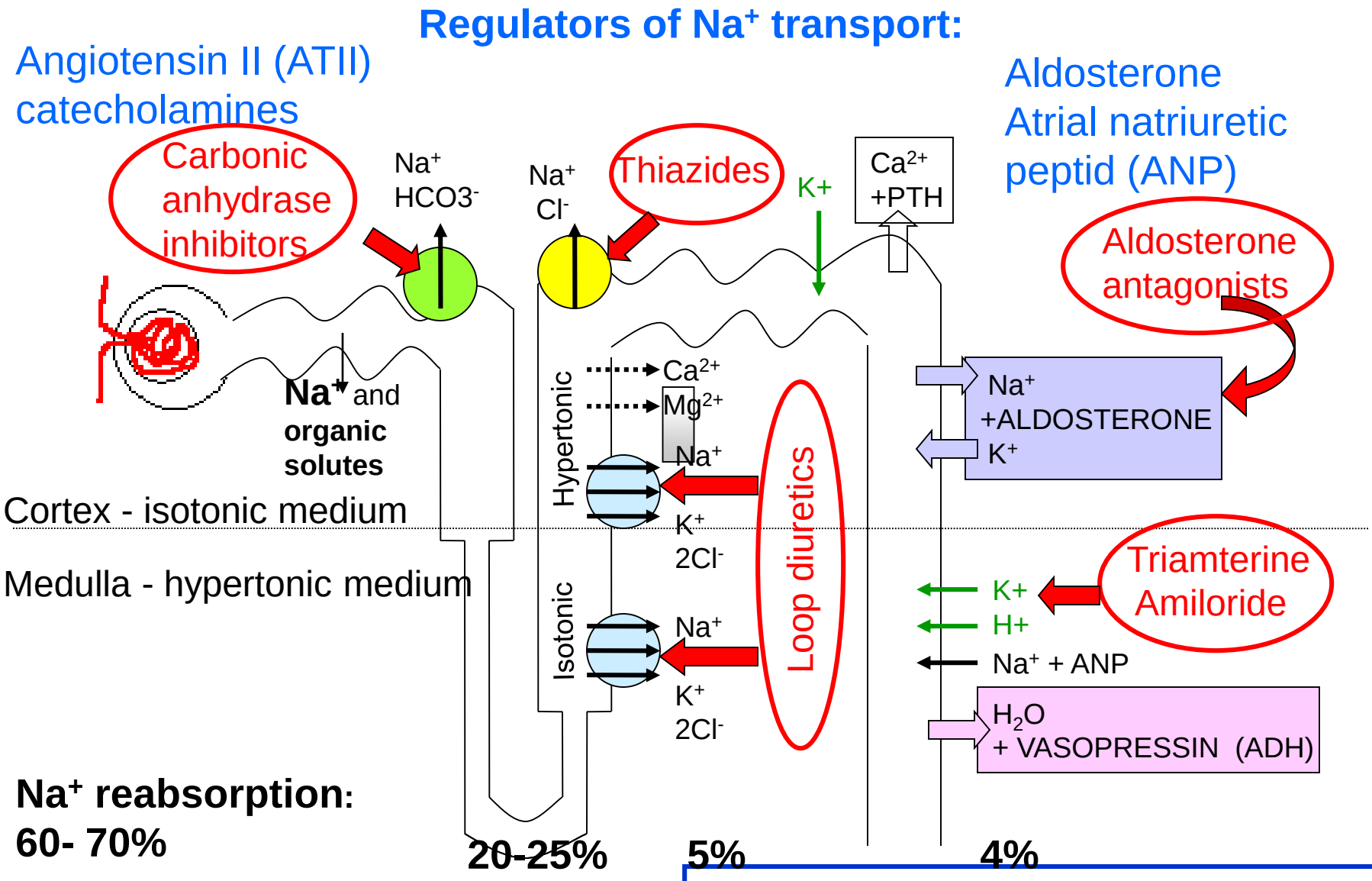
Effect of the selective β_1 receptor blocker bisoprolol on BP

Mengden et al.: Rev. Contemp. Pharmacother., 8: 55, 1997

- Ambulatory 24-h BP monitoring in 23 patients before the beginning of treatment and at the end of the 4-week treatment
- Bisoprolol 10 mg/d, po
- Difference between the values measured in the treatment with placebo and bisoprolol * = p< 0.05
- Diurnal rhythm and the charactaristic BP profile of the patient remain unchanged



Targets of diuretics

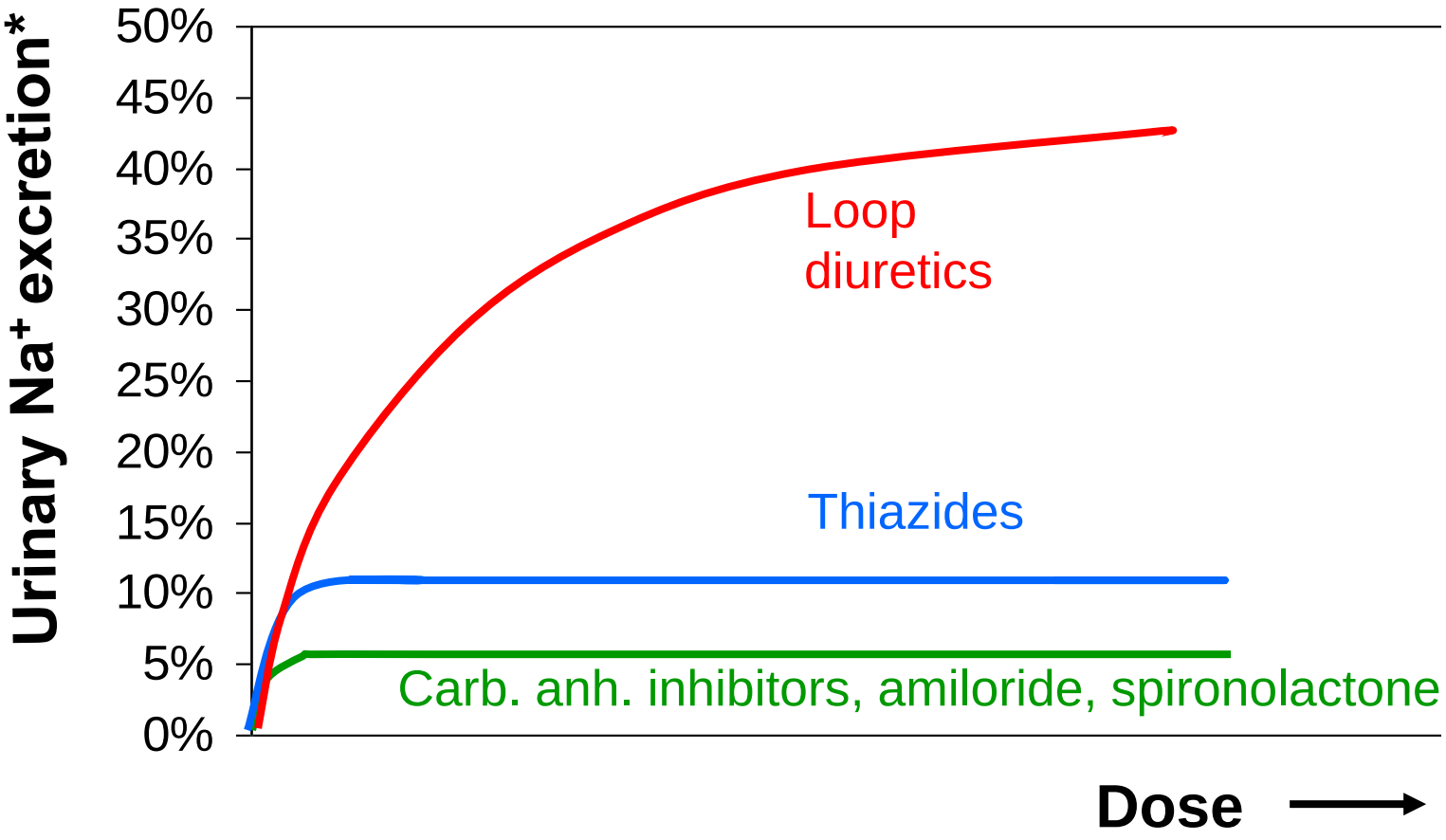


Diuretics used for hypertension

- Thiazides
  - Hydrochlorothiazide
  - Indapamide
  - Chlorthalidone
- Loop diuretics
  - Furosemide (in case of renal insufficiency)
- Potassium-sparing diuretics
  - Spironolactone (add on therapy)
  - Eplerenone (only in the U.S.)
  - Amiloride

Dose-response curve of diuretics

For the elimination of extensive fluid retentions (oedema, ascites) loop diuretics are suitable



(*Urinary Na^+ excretion in % of filtered Na^+)

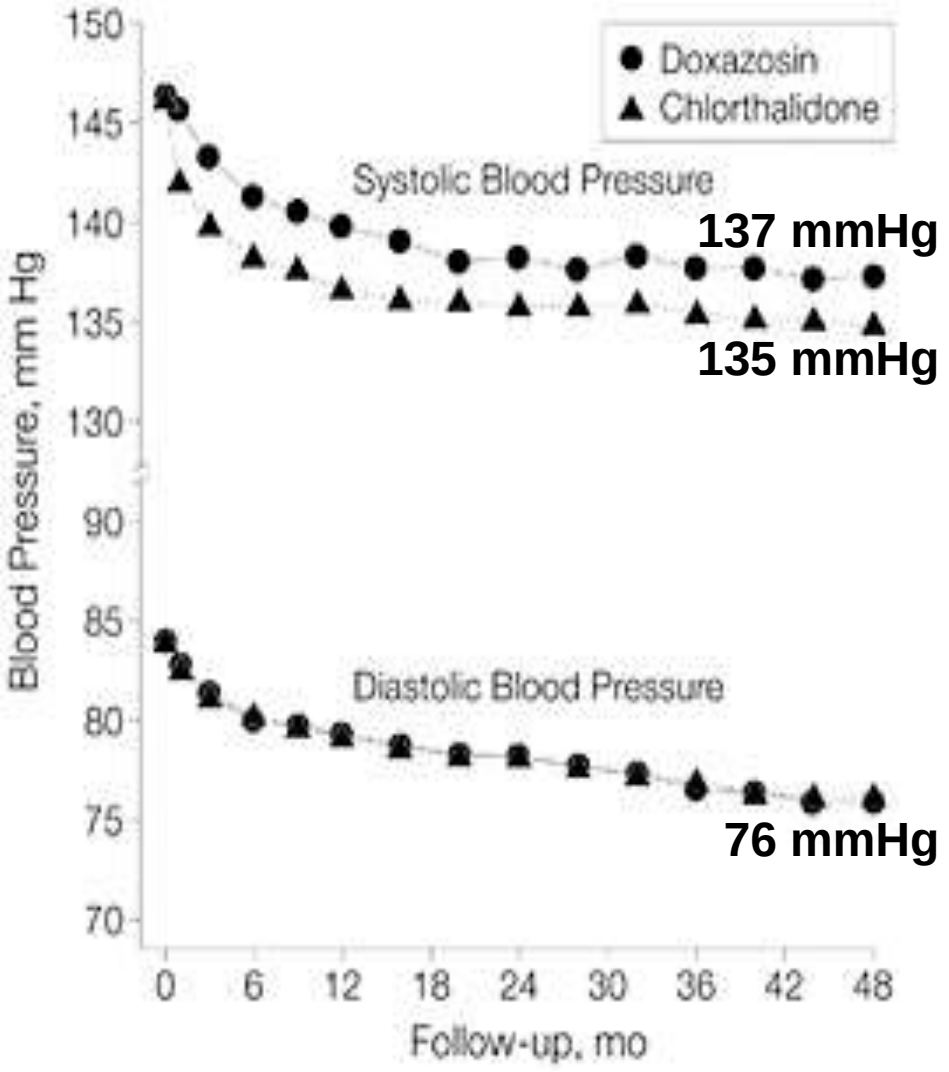
Antihipertensive and diuretic doses of thiazide type diuretics

Diuretics	Half life (h)	Anti-hipertensive dose (mg)	Diuretic dose (mg)
Hydrochloro-thiazide	2.5	6.25-12.5 (25)	25-100
Chlortalidon	44	12.5-25	100-400
Indapamid	10-22	1.25-2.5	2.5-5

Doxazosin vs Chlorthalidone in hypertension

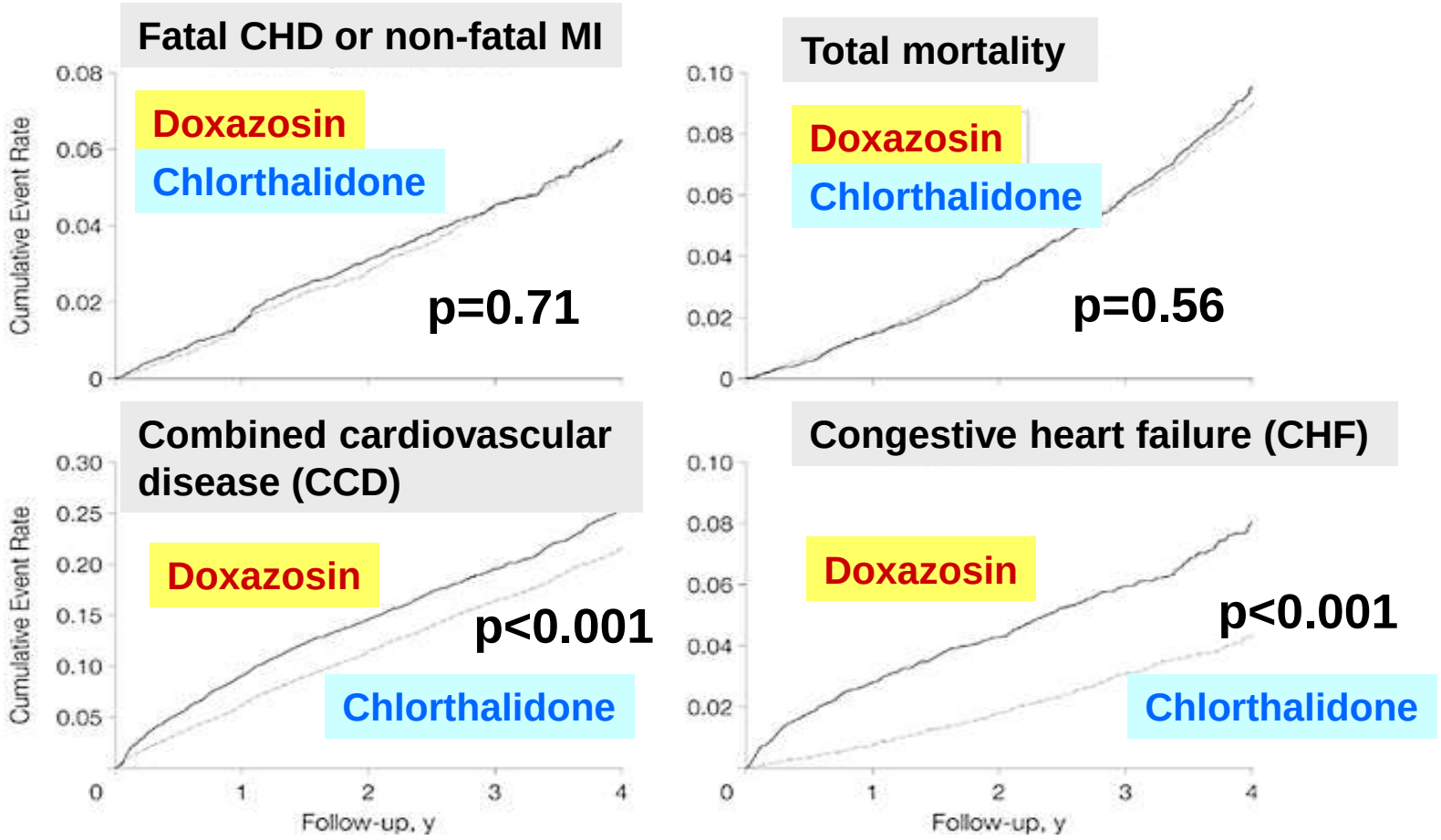
ALLHAT Collaborative Research Group, JAMA, 283:1967, 2000

- Randomized, double blind trial comparing diuretic, chlorthalidone (12.5-25 mg/d); $\alpha_1$antagonist, doxazosin (2-8 mg/d); Ca antagonist, amlodipine and ACE inhibitor, lisinopril (1.7:1:1:1) as primary treatment
- Primary goal: fatal CHD and non-fatal MI
- 24335 pts with high risk hypertension: $\geq$ 55yr, SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg + at least 1 risk factor for CHD
- If BP < 140/90 was not reached with primary therapy then atenolol, reserpine, clonidine or hydralazine could be added
- At 4 yr treatment adherence: 83% diuretic alone + 3% combined with α_1 bl; 62% $\alpha_1$bl alone + 13% $\alpha_1$bl + diuretic



Doxazosin vs Chlorthalidone in hypertension

ALLHAT Collaborative Research Group, JAMA, 283:1967, 2000



- Following the primary therapy with the α_1-blocker total mortality remained the same, but mortality increased due to CCD: CHD death, non-fatal MI, stroke, angina or revascularization procedure and CHF
- Explanation is not clear,

Ca-channel blockers

- Verapamil
- Diltiazem
- Dihidropyridines
  - Nifedipine
  - Amlodipine
  - Felodipine
  - Lacidipine
  - Lercanidipine

Cardiovascular effects of calcium channel blockers

- Calcium antagonists decrease the slow influx of calcium into the smooth muscle cells (L channel), decrease contractility
- They may be applied as primary drugs in hypertension, they are indicated in case of intolerance or contraindication to diuretics and/or β-blockers
- They seem to prevent stroke more effectively than BRBs or diuretics, however, this has to be proven in further trials
- They are especially effective in hypertension with low renin levels and in old age
- Diuretics increase the renin level and decrease the effect of Ca antagonists
- They are well tolerated, may be applied even in diabetes, disturbance of lipid metabolism, COPD, or depression

Cardiovascular effects of calcium channel blockers

- They may be used with precaution in HF, but should not be administered immediately after MI
- **Verapamil** cannot be administered in systolic dysfunction because of its negative inotropic and chronotropic effect, it cannot be combined with β-blockers. Main indication: paroxysmal supraventricular tachycardia (Diltiazem has a similar, but weaker effect)
- **Dihydropyridines** have an extensive vasoselectivity. Reduction of BP results in sympathic compensation and mild tachycardia. The short-acting nifedipin resulted in sudden drops of BP and consequent angina. A slowly developing long-acting effect would be ideal

The comparison of calcium channel blocker (CCB) therapy with placebo treatment

Blood Pressure Lowering Treatment Trialsit' Collaboration, Lancet, 356:1955, 2000

No of patients: 2815 / 2705 Endpoint	Events % CCB / placebo	Relatíve Risk RR (95% CI)	P
Stroke	1.9 / 3.1	0.61 (0.44-0.85)	S
Coronary heart dis.	2.8 / 3.5	0.79 (0.59-1.06)	S
Heart failure	1.5 / 2.1	0.72 (0.48-1.07)	S
Major CV events	5.9 / 8.2	0.72 (0.59-0.87)	S
CV death	2.3 / 3.3	0.72 (0.52-0.98)	S
Total mortality	5.0 / 5.7	0.87 (0.70-1.09)	NS

The most frequent side effects of hypertension treatment in elderly patients

Hanson et al.: Lancet 354:1751, 1999

	DIU-BRB %	ACEI %	CCB %
No of patients	2213	2205	2196
Dyspnoe	***11.8***	7.3	8.5
Palpitation	2.9	5.3	***7.9***
Flushing	1.6	2.2	***9.7***
Headaches	5.7	7.7	***10.0***
Cold extremities	***9.1***	3.3	2.5
Slow pulse	***3.7***	0.8	1.4

The most frequent side effects of hypertension treatment in elderly patients

Hanson et al.: Lancet 354:1751, 1999

(Continued)	DIU-BRB %	ACEI %	CCB %
No of patients	2213	2205	2196
Nightmares	***5.8***	1.4	2.0
Dry mouth	***4.4***	2.0	2.7
Ancle oedema	8.5	8.7	***25.5***
Insomnia	***4.3***	1.8	2.3
Dry cough	3.7	***30.1***	5.7
Diziness	***27.8***	***27.7***	***24.5***

Clinical Trials

Efficacy and Safety of Quarter-Dose Blood Pressure–Lowering Agents

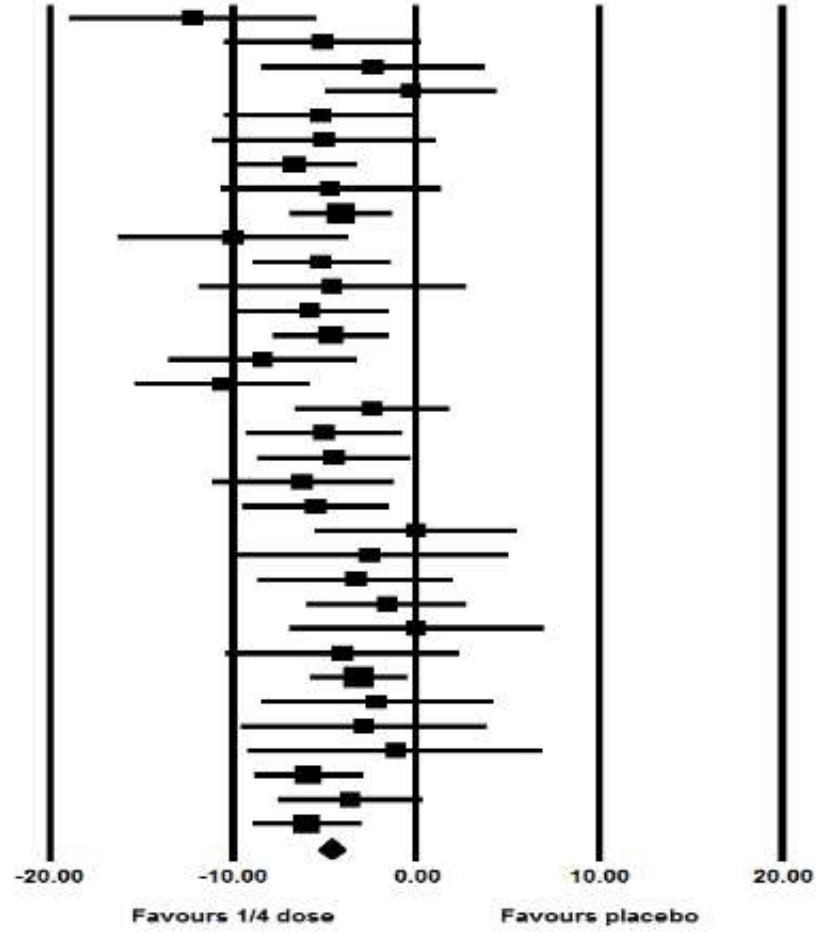
A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Alexander Bennett, Clara K. Chow, Michael Chou, Hakim-Moulay Dehbi, Ruth Webster, Abdul Salam, Anushka Patel, Bruce Neal, David Peiris, Jay Thakkar, John Chalmers, Mark Nelson, Christopher Reid, Graham S. Hillis, Mark Woodward, Sarah Hilmer, Tim Usherwood, Simon Thom, Anthony Rodgers

American Heart Assosiation, 2017

Systolic blood pressure lowering of single quarter dose compared to placebo, of all comparisons

Study name	Comparison	Statistics for each study: Difference in means	Standard error	Lower limit	Upper limit
Bergstrand, 1984	ACEI	-12.2	3.4	-18.9	-5.5
DeQuattro, 1997	ACEI	-5.1	2.7	-10.5	0.2
Gradman, 1997	ACEI	2.4	3.1	-8.4	3.7
Sedman, 1989	ACEI	-0.3	2.4	-5.0	4.4
De Bruijn, 1994	ACEI	-5.2	2.7	-10.5	0.1
Gomez, 1989	ACEI	-5.0	3.1	-11.1	1.1
866-10, 1999	ARB	-6.7	1.7	-10.1	-3.3
Meineke, 1997	ARB	-4.7	3.1	-10.7	1.3
866-09, 2001	ARB	-4.1	1.4	-6.8	-1.4
866-204	ARB	-10.0	3.2	-16.3	-3.7
866-305, 1999	ARB	-5.2	1.9	-8.9	-1.5
EC403, 1996	ARB	-4.6	3.7	-11.9	2.7
Neutel, 1997	ARB	-5.8	2.2	-10.1	-1.5
Oparil, 1996	ARB	-4.7	1.6	-7.8	-1.6
Reif, 1996	ARB	-8.4	2.6	-13.5	-3.3
Study 01-05, 2006	ARB	-10.6	2.4	-15.3	-5.9
Schoenberger, 1989	BB	2.4	2.1	-6.6	1.8
Williams, 1992	BB	-5.0	2.2	-9.2	-0.8
Casadei, 1992	BB	-4.5	2.1	-8.6	-0.4
Frishman, 2006	BB	-6.2	2.5	-11.1	-1.3
NEB - 302, 2003	BB	-5.5	2.0	-9.4	-1.6
Frick, 1988	CCB	0.0	2.8	-5.5	5.5
Mcmahon, 1989	CCB	-2.5	3.8	-10.1	5.0
Mehta, 1993	CCB	-3.3	2.7	-8.6	2.0
Omboni, 1998	CCB	-1.6	2.2	-5.9	2.7
Canter, 1994	DIURETIC	0.0	3.5	-6.9	6.9
Jounela, 1994	DIURETIC	-4.0	3.2	-10.4	2.3
Villamil, 2007	DIURETIC	-3.2	1.3	-5.8	-0.6
McGill, 2001	DIURETIC	-2.2	3.2	-8.5	4.1
Pool, 1997	OTHER	2.9	3.4	-9.5	3.8
Roca-Cusachs, 2001	OTHER	-1.1	4.1	-9.1	6.9
Frishman, 1994	OTHER	-5.9	1.5	-8.8	-3.0
Kochar, 1999	OTHER	-3.6	2.0	-7.5	0.3
Papademetriou, 2006	OTHER	-6.0	1.5	-8.9	-3.1
		-4.7	0.4	-5.4	-3.9

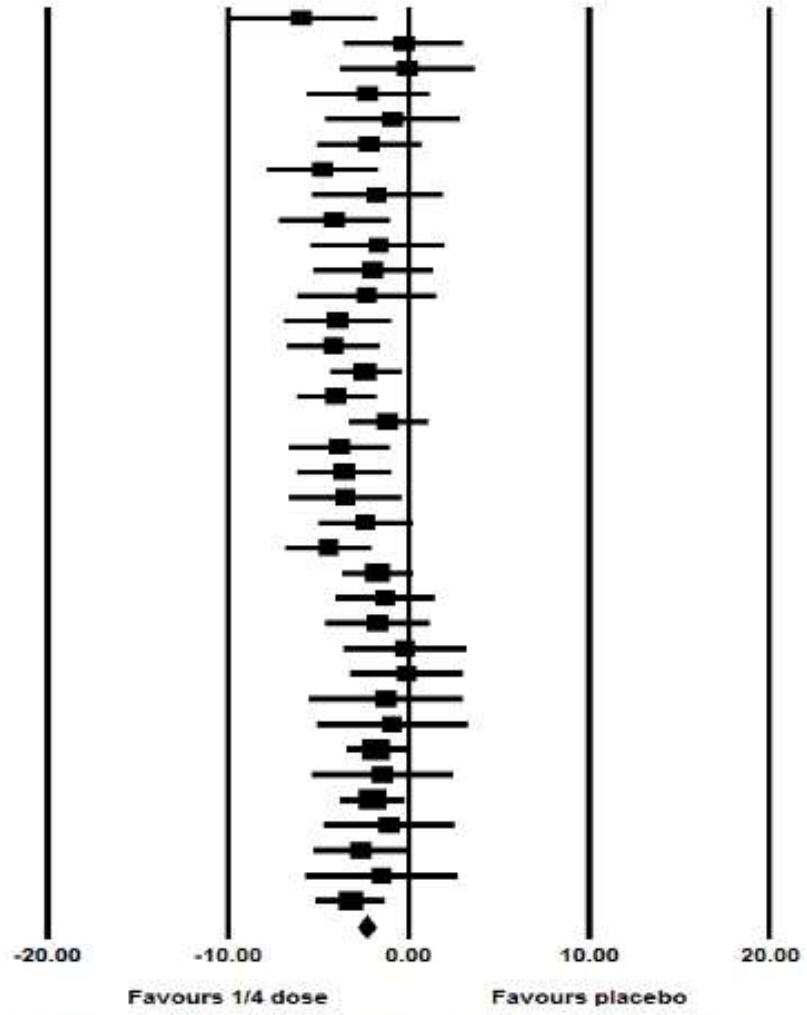


DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Bennett et al, Hypertension AHA, 2017

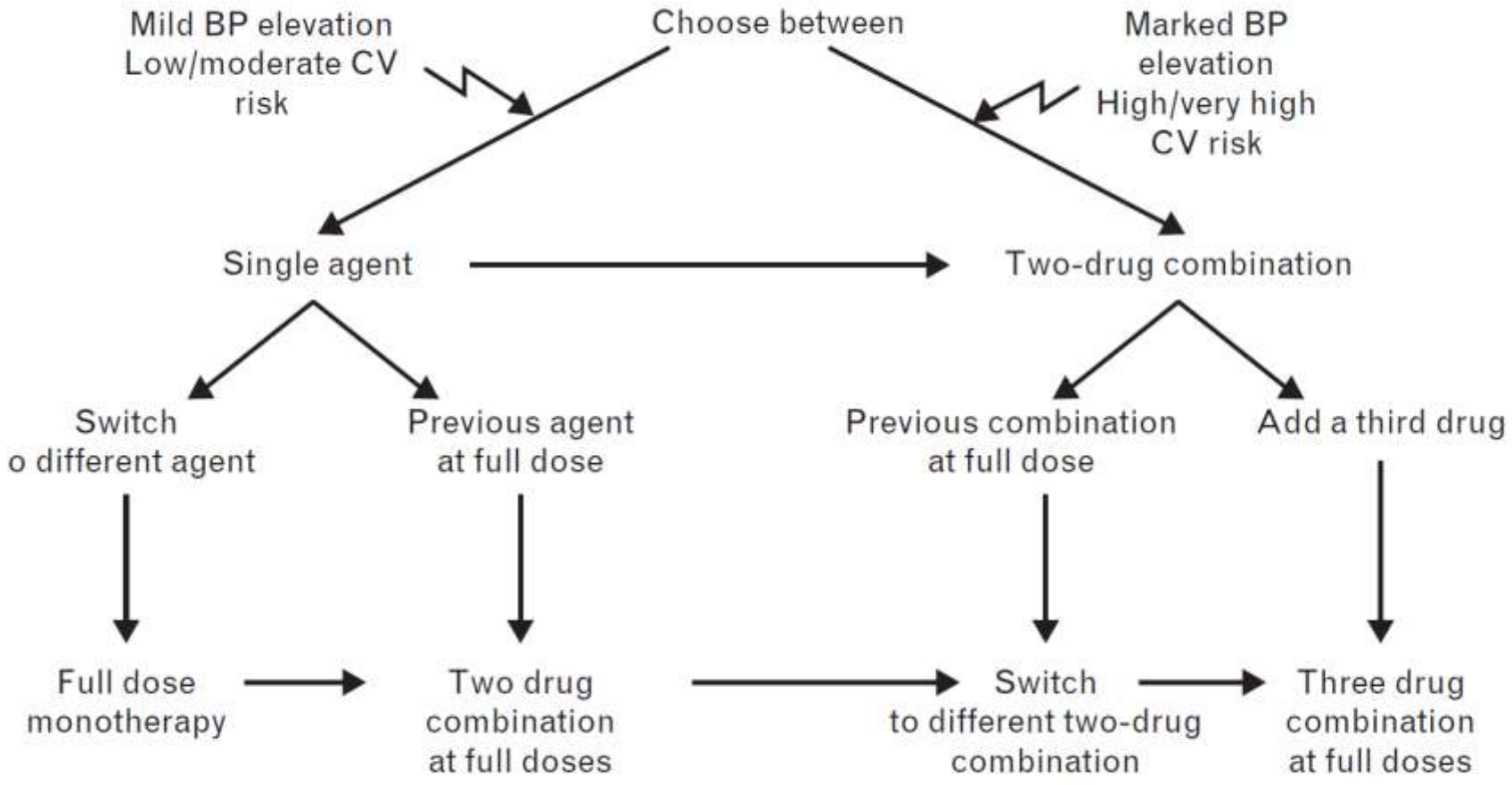
Diastolic blood pressure lowering of single quarter dose compared to placebo of all comparisons

Study name	Subgroup within study	Difference in means	Standard error	Lower limit	Upper limit
Bergstrand, 1984	ACEI	-5.9	2.1	-10.0	-1.8
DeQuattro, 1997	ACEI	-0.2	1.7	-3.5	3.1
Gomez, 1989	ACEI	-0.0	1.9	-3.7	3.6
De Brujin, 1994	ACEI	-2.2	1.7	-5.5	1.1
Gradman, 1997	ACEI	-0.8	1.9	-4.6	2.9
Sedman, 1989	ACEI	-2.1	1.5	-5.0	0.7
Study 01-05, 2006	ACEI	-4.7	1.6	-7.8	-1.7
Moser, 1991	ACEI	-1.7	1.8	-5.3	1.9
Reif, 1996	ARB	-4.1	1.6	-7.1	-1.0
Meineke, 1997	ARB	-1.6	1.9	-5.3	2.0
EC009	ARB	-1.9	1.7	-5.2	1.4
EC403, 1996	ARB	-2.3	1.9	-6.1	1.6
866-204	ARB	-3.9	1.5	-6.8	-0.9
866-305, 1999	ARB	-4.1	1.3	-6.7	-1.6
Oparil, 1996	ARB	-2.3	1.0	-4.3	-0.4
866-10, 1999	ARB	-3.9	1.1	-6.1	-1.8
866-09, 2001	ARB	-1.1	1.1	-3.3	1.0
Neutel, 1997	ARB	-3.8	1.4	-6.5	-1.1
Williams, 1992	BB	-3.5	1.3	-6.1	-0.9
Frishman, 2006	BB	-3.5	1.6	-6.6	-0.4
Schoenberger, 1989	BB	-2.4	1.3	-4.9	0.2
NEB - 302, 2003	BB	-4.4	1.2	-6.7	-2.0
Casadei, 1992	BB	-1.7	1.0	-3.6	0.3
Mehta, 1993	CCB	-1.3	1.4	-4.0	1.5
Omboni, 1998	CCB	-1.7	1.4	-4.5	1.2
Frick, 1988	CCB	-0.1	1.7	-3.5	3.2
Mcmahon, 1989	CCB	-0.0	1.6	-3.1	3.0
Canter, 1994	DIURETIC	-1.2	2.2	-5.4	3.0
Jounela, 1994	DIURETIC	0.9	2.1	-5.0	3.3
Villamil, 2007	DIURETIC	-1.7	0.8	-3.4	-0.1
McGill, 2001	DIURETIC	-1.4	2.0	-5.2	2.5
Frishman, 1994	OTHER	-1.9	0.9	-3.7	-0.2
Pool, 1997	OTHER	-1.0	1.8	-4.6	2.6
Kochar, 1999	OTHER	-2.6	1.3	-5.2	-0.0
Roca-Cusachs, 2001	OTHER	-1.4	2.1	-5.6	2.7
Papademetriou, 2006	OTHER	-3.2	1.0	-5.0	-1.3
		-2.4	0.2	-2.8	-1.9



Legend. DBP- Diastolic Blood Pressure, SBP – Systolic Blood Pressure, CI- Confidence Interval, ACEI – Angiotensin Converting Enzyme Inhibitor, ARB – Angiotensin Receptor Blocker, BB- Beta-blocker, CCB- Calcium Channel Blocker, TZ- Thiazide Diuretic.

Bennett et al, Hypertension AHA, 2017



Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved.

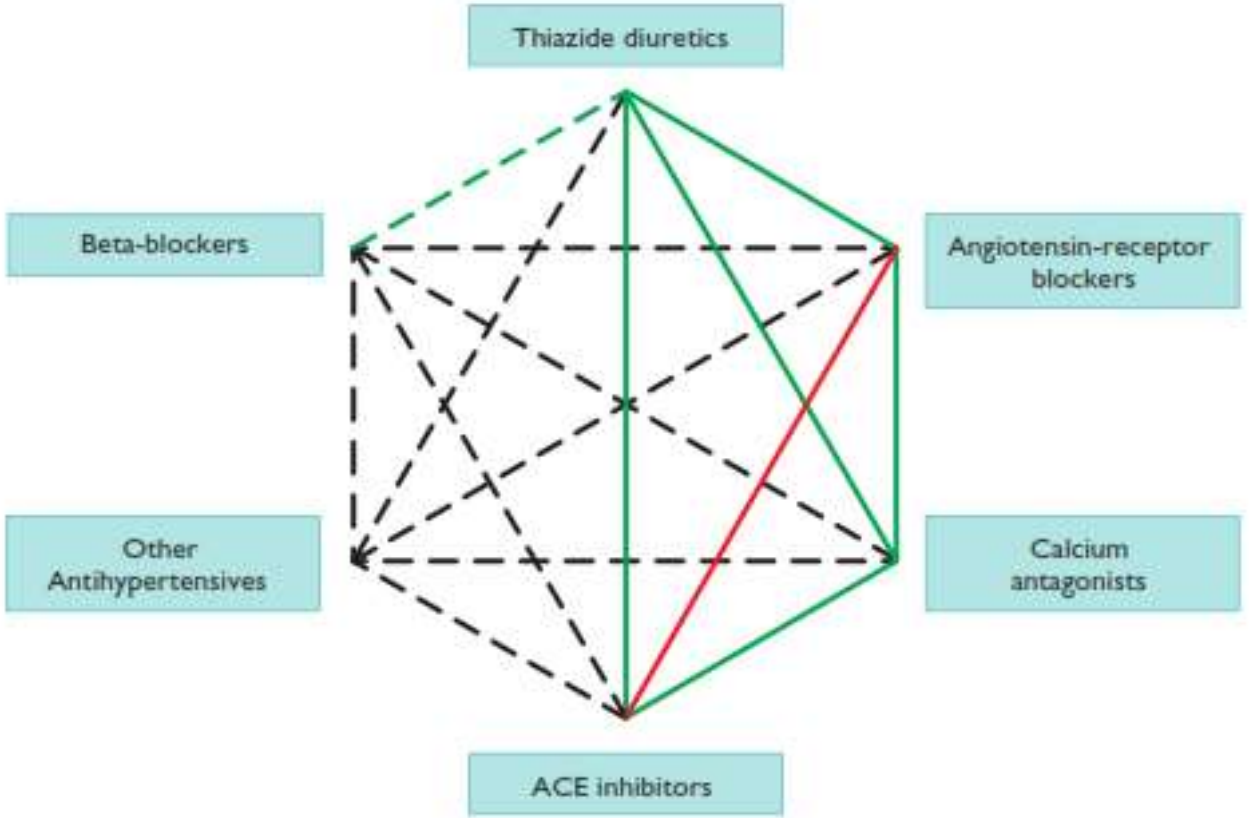
Considerations of start of combined therapy:

- Untreated patient with high risk, if the blood pressure > 200/120 Hgmm
- In case actual BP of the patient is higher with 20/10 Hgmm than the target value
- Metabolic comorbidities, kidney disorder combined with hypertension
- In case of low adherence and persistence of patient

Advantages of combined therapy:

- More effective in comparison to monotherapy
- Shorter duration to reach target value of BP
- More simple tretment
- Better tolarnce because of less side effects – better adherence and persistence
- More balanced effect on BP – less amplitudes in BP
- Fix combinations are cheaper

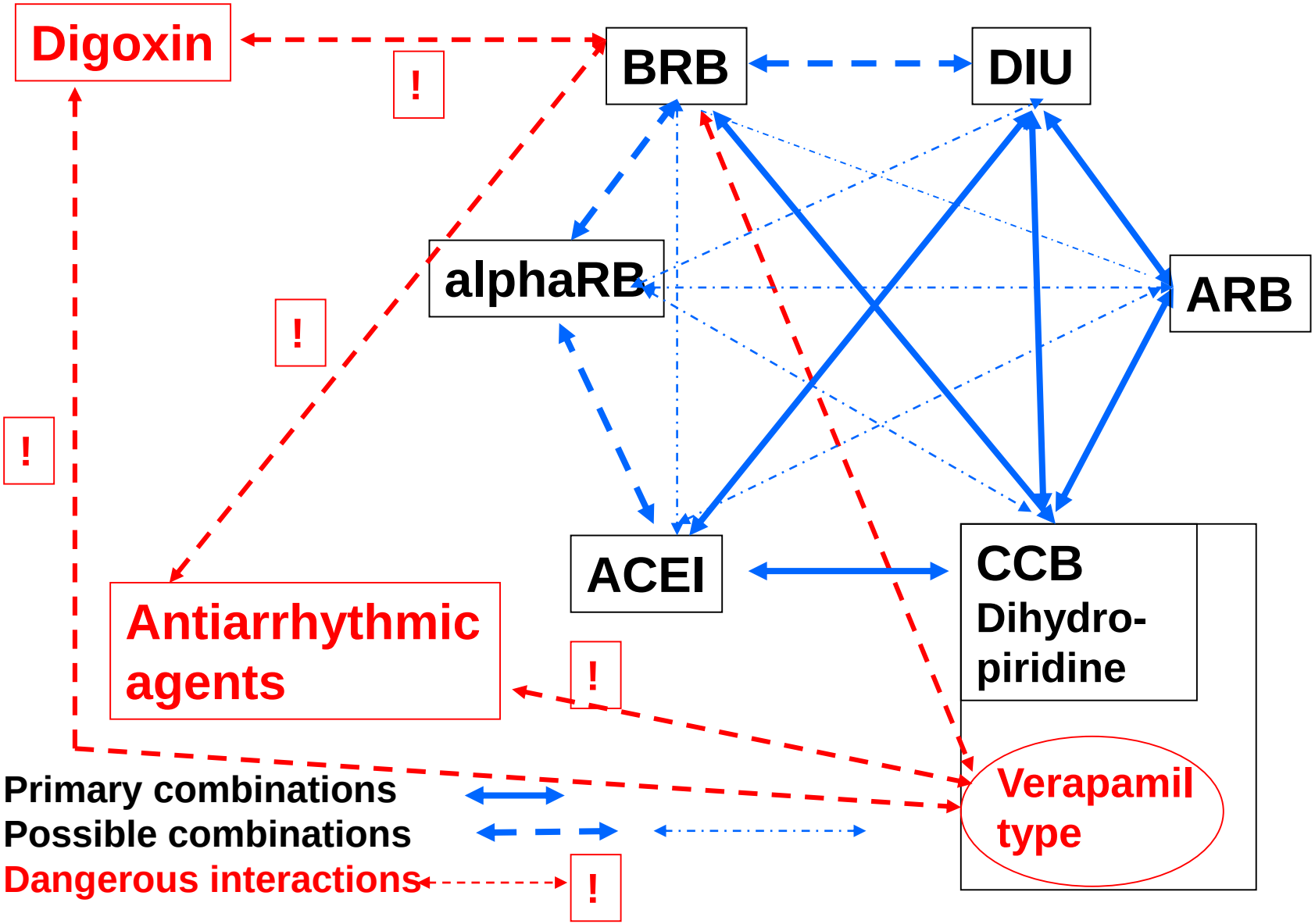
Combination possibilities of antihypertensive drugs

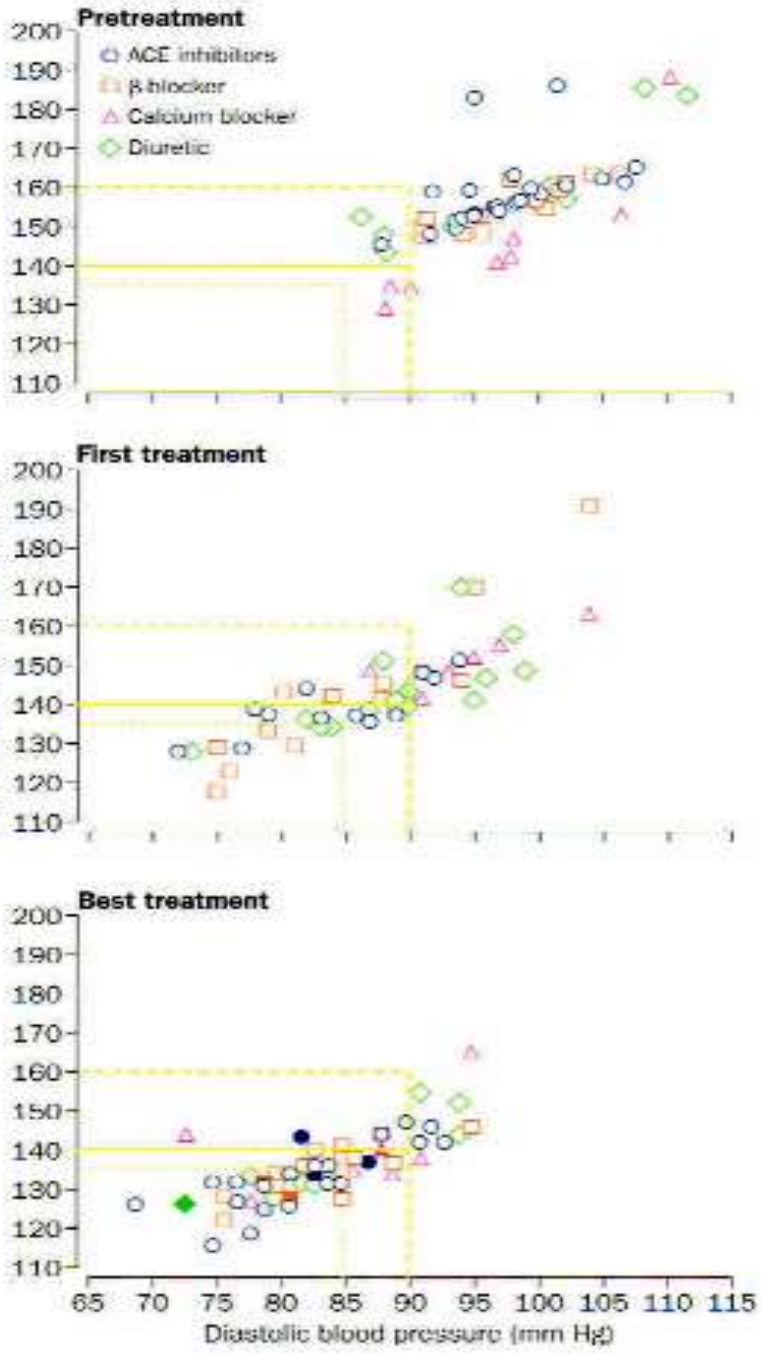


ACE = angiotensin-converting enzyme.

Figure 4 Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

Combination possibilities of cardiovascular drugs





HY: selection of optimal first treatment

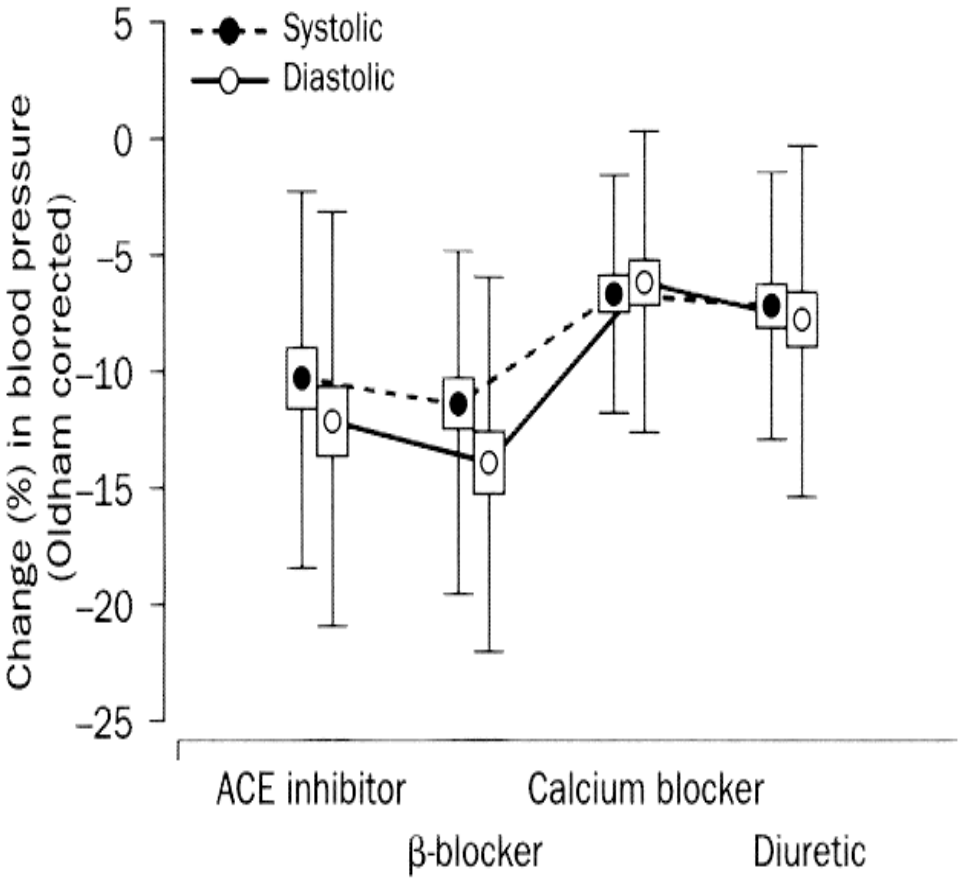
Claire et al.: Lancet: 353, 2008, 1999

- Object: selecting optimal first treatment in an open-label, four-way crossover study. Target BP: ≤ 135/85 Hgmm
- 36 males and 20 females, 22-51 yrs, mean BP 161/98 mm Hg
- 1 month: 1st drug + 1 mo. wash-out + 1 mo. 2nd drug + …, total of 7 months
- If monotherapy was not effective, the dose of the most effective drug was increased, if this was not effective either, 2 (3) drugs were combined:
  - ACE inhibitor (A): Lisinopril 20 mg/d
  - β–blocker (B): bisoprolol 5 mg/d
  - Ca-antagonist (C)t: nifedipine 30 mg/d
  - Diuretics (D): hydrochlorothiazide+ triamterene 25 + 50 mg/d

HY: selection of optimal first treatment

Claire et al.: Lancet: 353, 2008, 1999

- 41/56 patient finished the trial
- ≤ 140/90 mmHg was reached by
  - 1st drug 22/56 (39%)
  - one of the drugs: 41/56 (73%)
  - 50% of patients reached the target value of 135/85 mmHg with monotherapy, a further 40% with combined therapy
- In this young patient group A and B drugs were significantly more effective. Higher levels of renin and catecholamine!
- A close correlation was found between the efficacies of A and B drugs as well as between those of C and D drugs
- For combinations 1drug was taken from each the AB and CD pairs
- Conclusion: Titration is essential! In general practice the treatment is not satisfactory in 50% of the patients, BP > 140/90 mm Hg



(Oldham correction: actual change divided by the average of pre- and post-treatment BPs)

Influencing factors of choosing antihypertensive drugs

ESH/ESC Guidelines. J.Hypertension, 25:1105-1187, 2007

Table 6 Conditions favouring use of some antihypertensive drugs versus others

Thiazide diuretics	Beta-blockers	Calcium antagonists (dihydropyridines)	Calcium antagonists (verapamil/diltiazem)
• Isolated systolic hypertension (elderly) • Heart failure • Hypertension in blacks	• Angina pectoris • Post-myocardial infarction • Heart failure • Tachyarrhythmias • Glaucoma • Pregnancy	• Isolated systolic hypertension (elderly) • Angina pectoris • LV hypertrophy • Carotid/Coronary Atherosclerosis • Pregnancy • Hypertension in blacks	• Angina pectoris • Carotid atherosclerosis • Supraventricular tachycardia
ACE inhibitors	**Angiotensin receptor antagonists**	**Diuretics (antialdosterone)**	**Loop diuretics**
• Heart failure • LV dysfunction • Post-myocardial infarction • Diabetic nephropathy • Non-diabetic nephropathy • LV hypertrophy • Carotid atherosclerosis • Proteinuria/ Microalbuminuria • Atrial fibrillation • Metabolic syndrome	• Heart failure • Post-myocardial infarction • Diabetic nephropathy • Proteinuria/Microalbuminuria • LV hypertrophy • Atrial fibrillation • Metabolic syndrome • ACEI-induced cough	• Heart failure • Post-myocardial infarction	• End stage renal disease • Heart failure

ACEI: ACE inhibitors; LV: Left Ventricle.

Influencing factors of choosing antihypertensive drugs

ESH/ESC Guidelines. J.Hypertension, 25:1105-1187, 2007

Table 7 Compelling and possible contraindications to use of antihypertensive drugs

	Compelling	Possible
Thiazide diuretics	Gout	Metabolic syndrome Glucose intolerance Pregnancy
Beta-blockers	Asthma A-V block (grade 2 or 3)	Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease
Calcium antagonists (dihydropiridines)		Tachyarrhythmias Heart failure
Calcium antagonists (verapamil, diltiazem)	A-V block (grade 2 or 3) Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	
Angiotensin receptor antagonists	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
Diuretics (antialdosterone)	Renal failure Hyperkalaemia	

Table I Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

European Heart Journal (2013) **34**, 2159–2219
doi:10.1093/eurheartj/eht151

Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB

European Heart Journal (2013) **34**, 2159–2219
doi:10.1093/eurheartj/eht151

Drugs to be preferred in specific conditions

Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2013) **34**, 2159–2219
doi:10.1093/eurheartj/eht151

Drugs to be preferred in specific conditions

Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

European Heart Journal (2013) **34**, 2159–2219
doi:10.1093/eurheartj/eht151

European Heart Journal (2013) **34**, 2159–2219
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

Imperial College London

The HYpertension in the Very Elderly Trial

N. Beckett, R. Peters, A. Fletcher, C. Bulpitt on behalf of the HYVET committees and investigators

British Heart Foundation

ClinicalTrials.gov: NCT00122811

http://semmelweis.hu/pharmacology

Baseline data

	Placebo (n= 1912)	Active (n= 1933)
Age (years)	83.5	83.6
Female	60.3%	60.7%
Blood Pressure:		
Sitting SBP (mmHg)	173.0	173.0
Sitting DBP (mmHg)	90.8	90.8
Orthostatic Hypotension‡	8.8%	7.9%
Isolated Systolic Hypertension	32.6%	32.3%

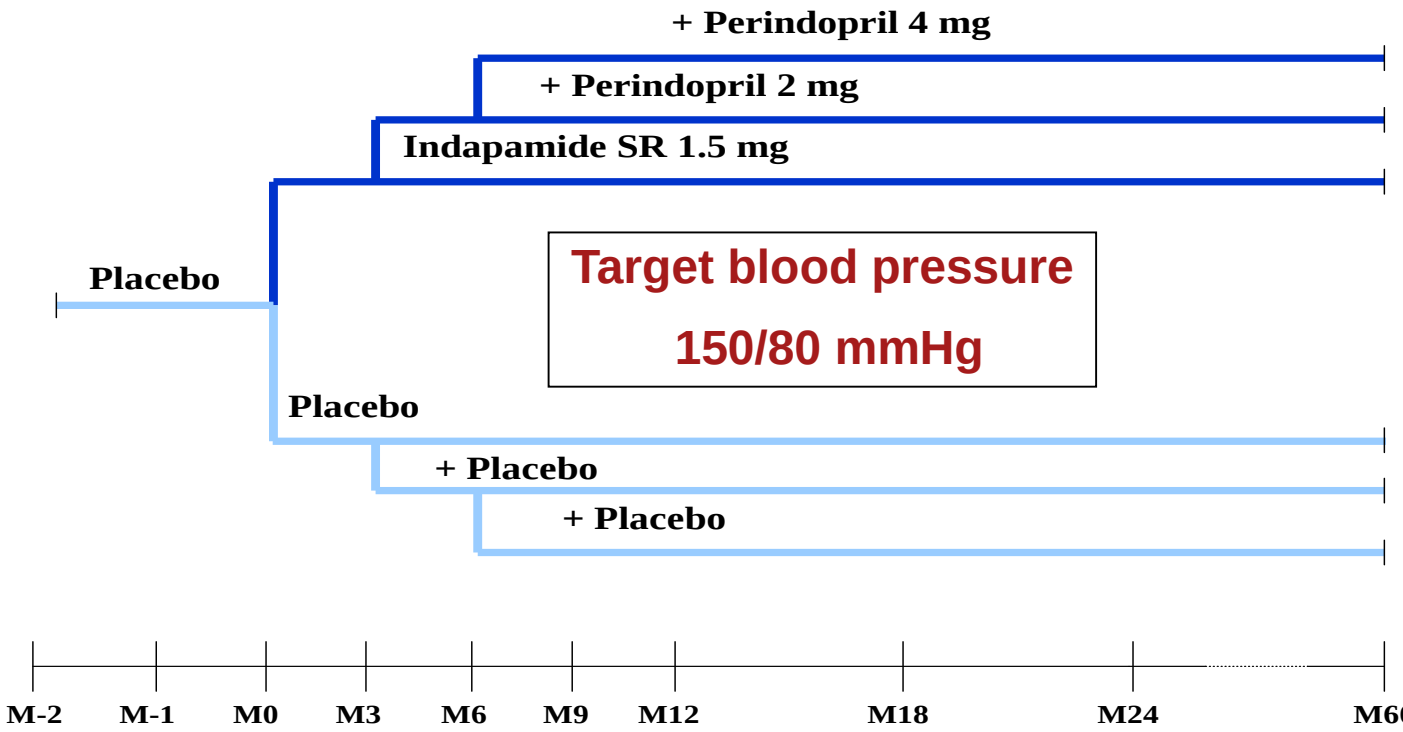
‡ Fall in SBP ≥ 20mmHg and/or fall in DBP ≥ 10mmHg

The Trial:
International, multi-centre, randomised double-blind placebo controlled

Inclusion Criteria:
Aged 80 or more,
Systolic BP; 160 -199mmHg
+ diastolic BP; <110 mmHg,
Informed consent

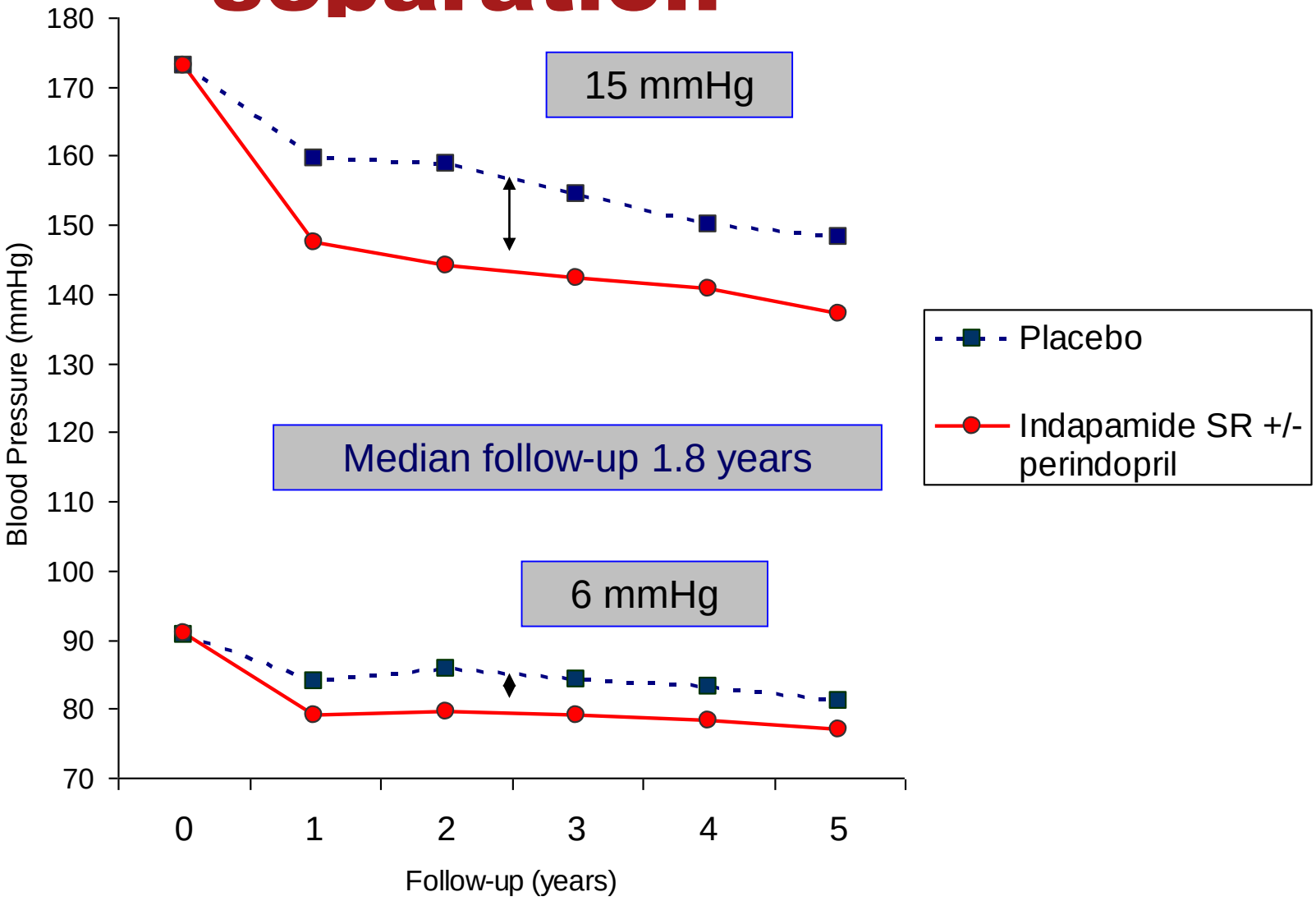
Exclusion Criteria:
Standing SBP < 140mmHg
Stroke in last 6 months
Dementia
Need daily nursing care

Primary Endpoint:
All strokes (fatal and non-fatal)



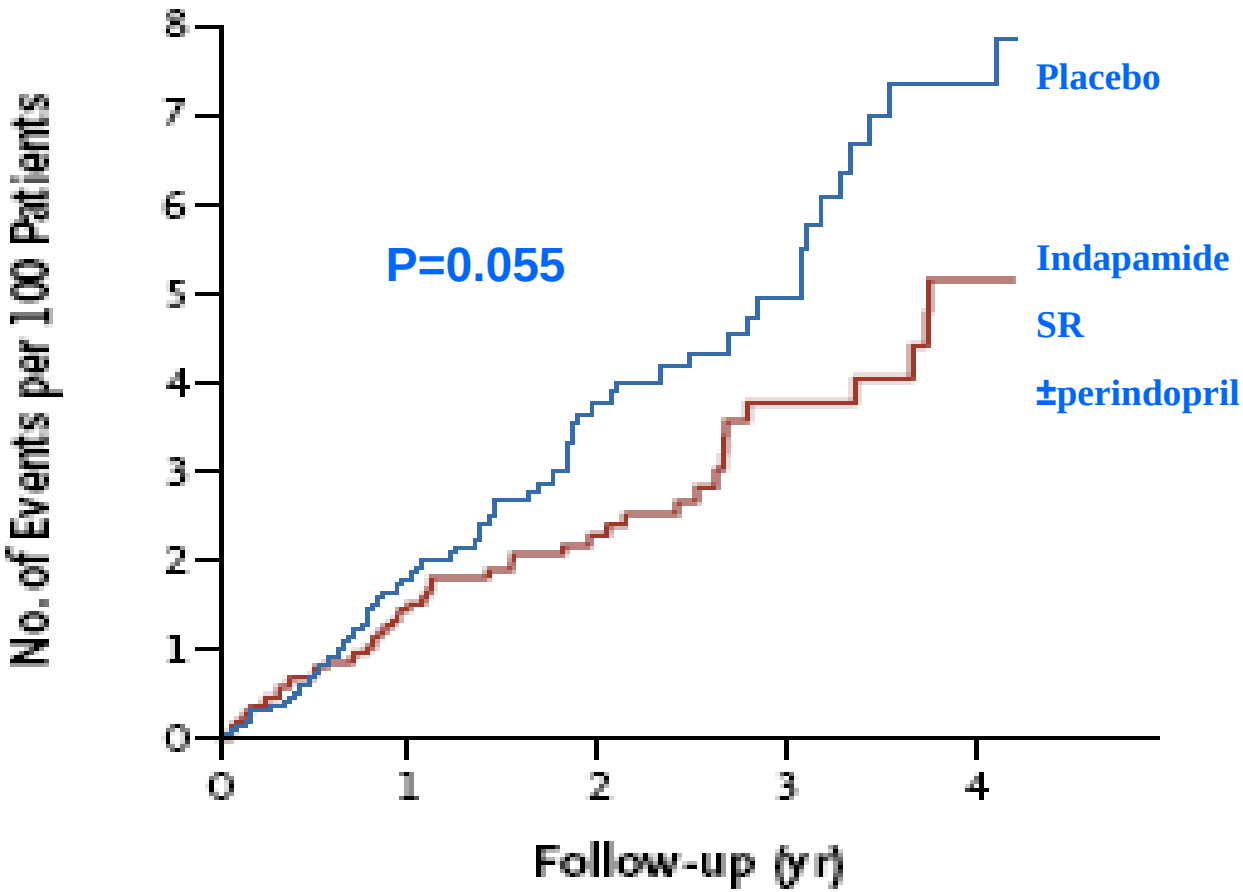
ACE tiaz di

Blood pressure separation



http://semmelweis.hu/pharmacology

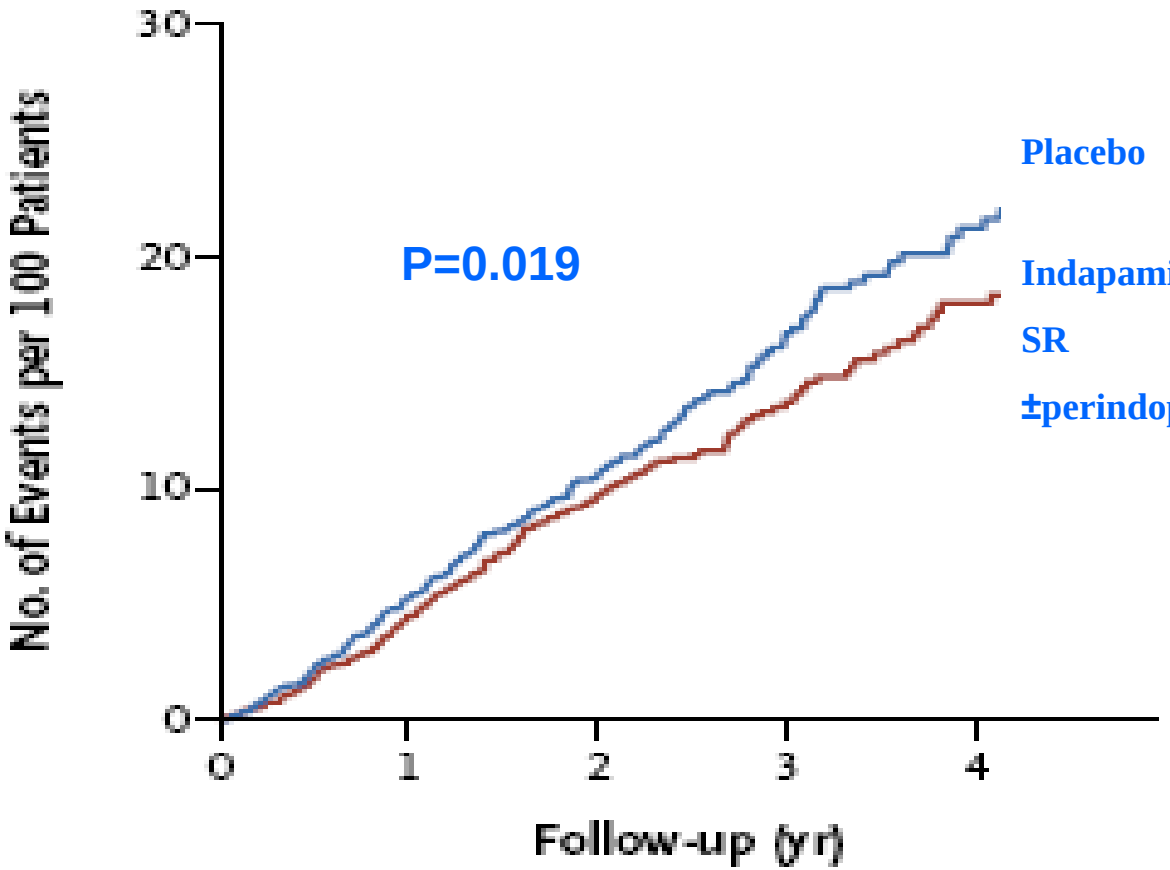
All stroke (30% reduction)



No. at Risk					
Placebo	1912	1484	807	374	194
IndapamideSR ±perindopril	1933	1557	873	417	229

http://semmelweis.hu/pharmacology

Total Mortality (21% reduction)

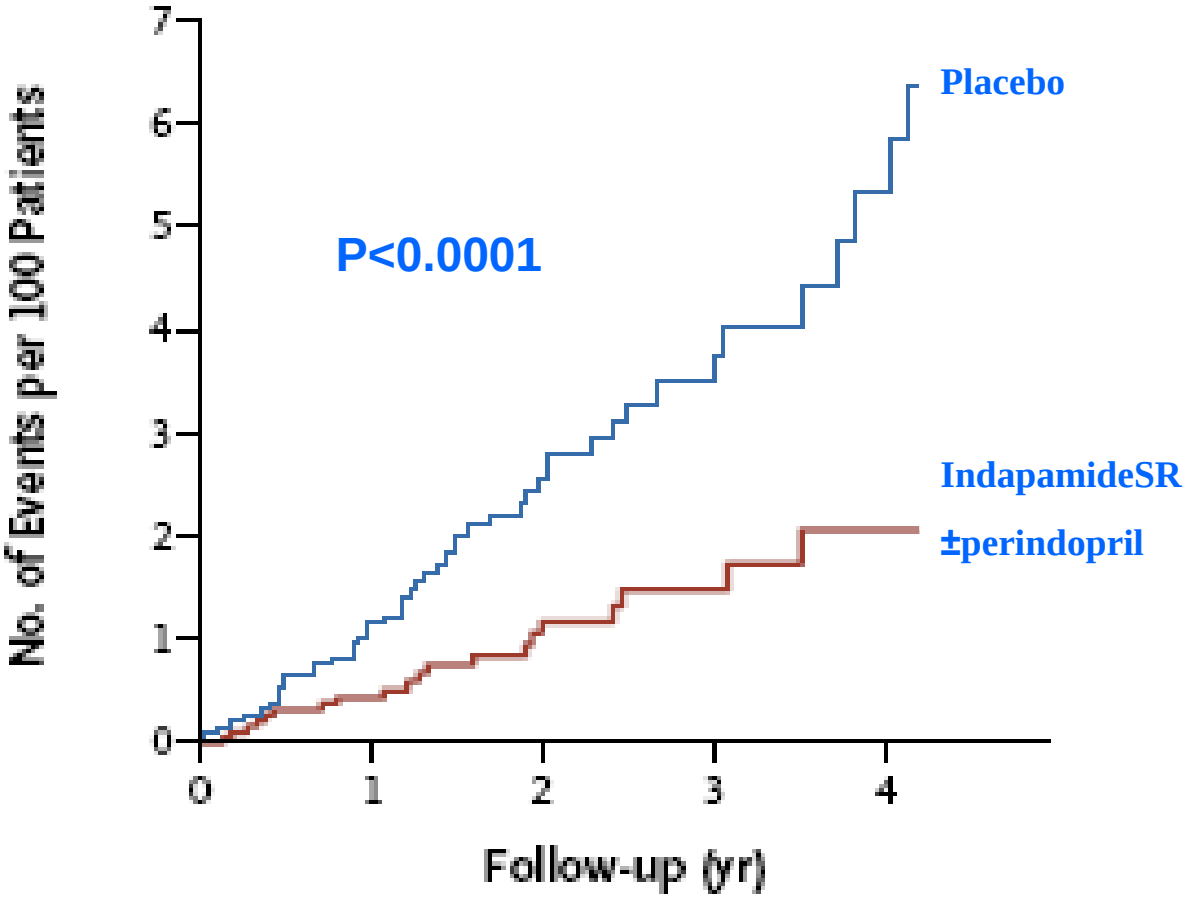


No. at Risk

Placebo	1912	1492	814	379	202
IndapamideSR ±perindopril	1933	1565	877	420	231

http://semmelweis.hu/pharmacology

Heart Failure (64% reduction)



No. at Risk					
Placebo	1912	1480	794	367	188
IndapamideSR ±perindopril	1933	1559	872	416	228