Möglichkeiten der medikamentösen Prävention bei Hypertonie

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125 Jahre
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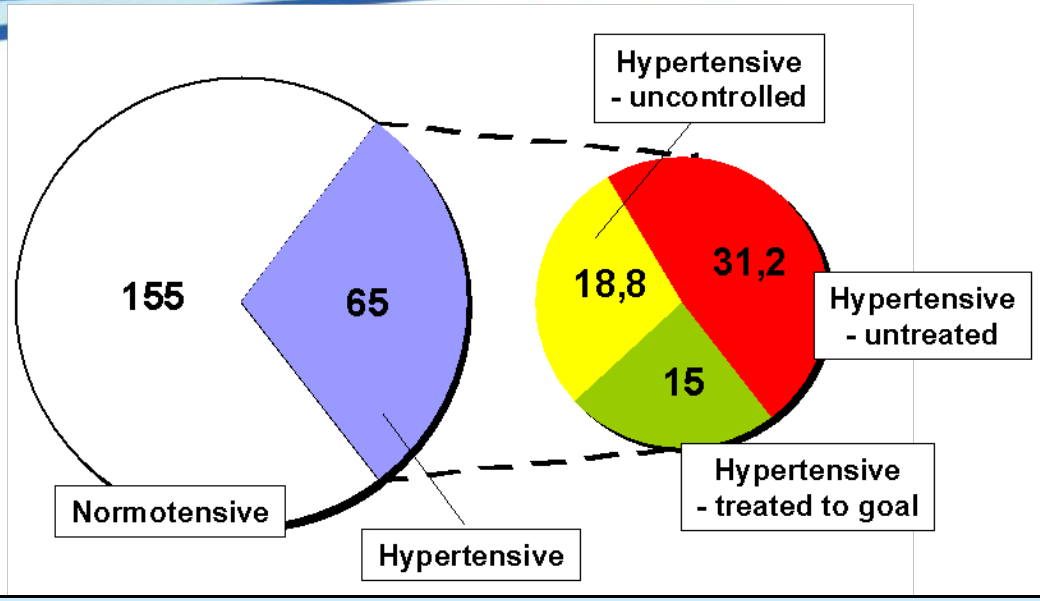
Hypertension – Definition/Epidemiology



Numbers of patients in the US
(in millions)
Data from NHANES-III and IV
Hypertension 2001 and 2004

2006 — **Blood Pressure (BP) Classification for Adults ≥ 18 year**

		Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal		< 120	and	< 80
Pre-hypertension		120-139	or	80-89
Isolated systolic hypertension		> 140	and	< 90
Hypertension**	**Stage 1**	**140-159**	**or**	**90-99**
	Stage 2	**≥ 160**	**or**	**≥ 100**
Complicated Hypertension	**Diabetes/ Nephropathy**	**> 130**	**or**	**> 80**

**Based on the average of two or more readings at each of two or more visits after an initial screening.

Hypertension - Prevalence

Prevalence in Hypertension is still growing

- **In 2000, 26.4% of the adult worldwide population had hypertension.**
- **In 2025, the number of adults with hypertension will be 1.56 billion (+60%).**
- **Although effective anti-hypertensive treatment options exist there is unmet medical need.**

Lancet 2005, 365:217.

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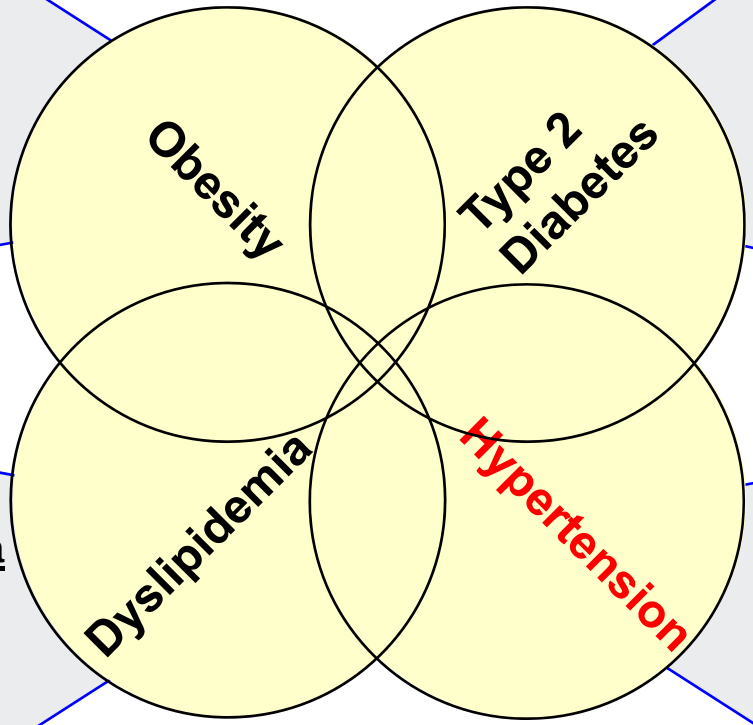
Hypertension as part of the Metabolic Syndrome

Patients with Obesity

- 50% have hypertension
- 28% have dyslipidemia
- 19% T2D

Patients with Type 2 Diabetes

- 71%have obesity
- 60%have dyslipidemia
- 76%have cardiovascular family history
- 60% have hypertension



Patients with dyslipidemia

- 48% have hypertension
- 33% have obesity
- 14% T2D

Patients with hypertension

- 65% have dyslipidemia
- 16% have T2D
- 35% are obese

Source: ADA Meeting with Pharmaceutical Industry, June 2001, Philadelphia

Aims in management of ‘hypertension’

- Improving diagnosis of hypertension
- Decreasing prevalence of hypertension
- Increasing effectivity of hypertension therapy
  - Non-drug (life style)
  - Drug
- Increasing patient compliance
- Reduction of total cardiovascular risk
- Lower target blood pressure goal (<130/80 mmHg) in sub populations with high CV risk

Requirements on an effective anti-hypertensive drug

- Efficient reduction of blood pressure
- Once a day treatment
- Safe and well tolerated
- End-organ protection demonstrated
- Reduction in hypertension-induced moratality demonstrated

- Anti-hypertensive drugs recommended today based on large outcome studies:
  - Diuretics
  - Calcium channel blocker
  - β-blocker
  - ACE-inhibitors
  - Angiotensin-II receptor blocker

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- **What is the value of an ‚old‘ diuretic in the management of hypertension today?**

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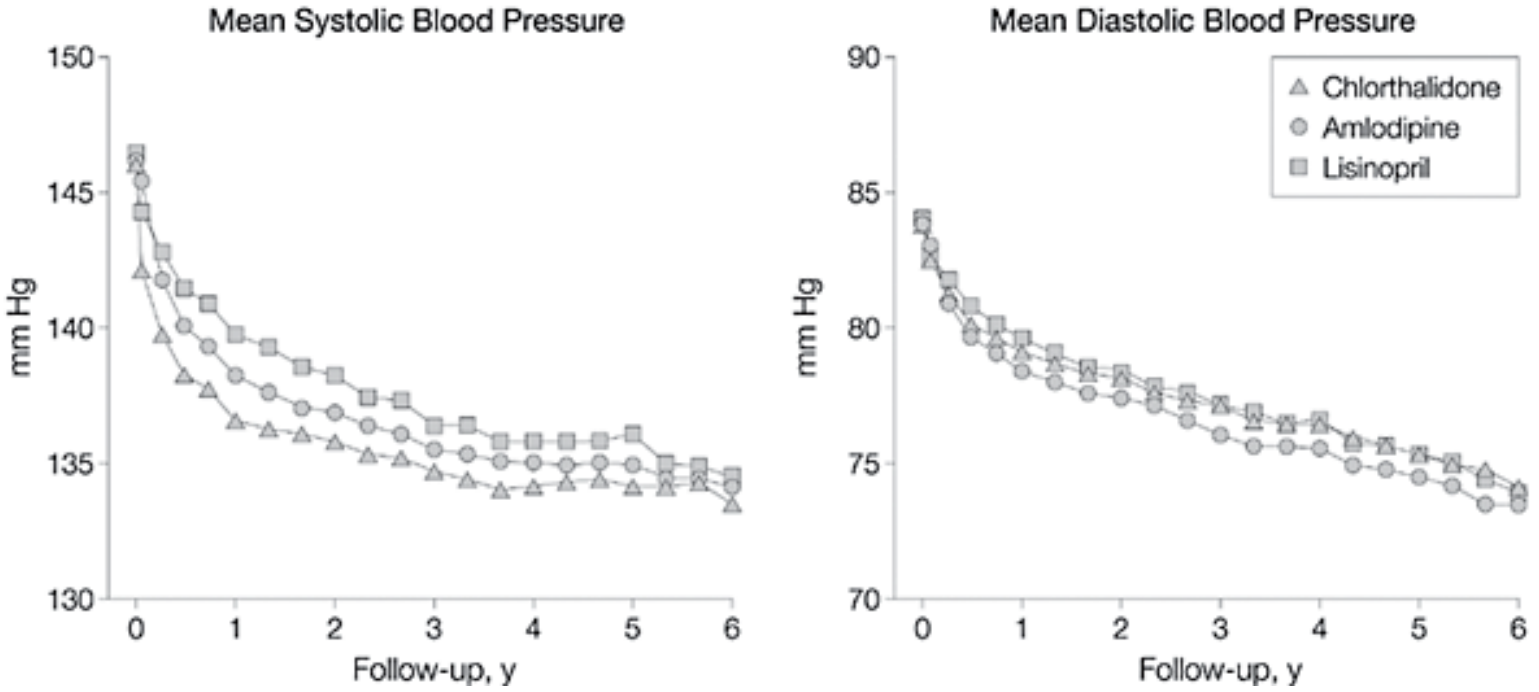
Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic (ALLHAT)

Mean Systolic and Diastolic Blood Pressure by Year During Follow-up



5-year systolic blood pressure was significantly lower in the chlorthalidone vs. amlodipine and lisinopril groups. Diastolic blood pressure was lowest in the amlodipine group.

JAMA, 2002;288:2981-2997

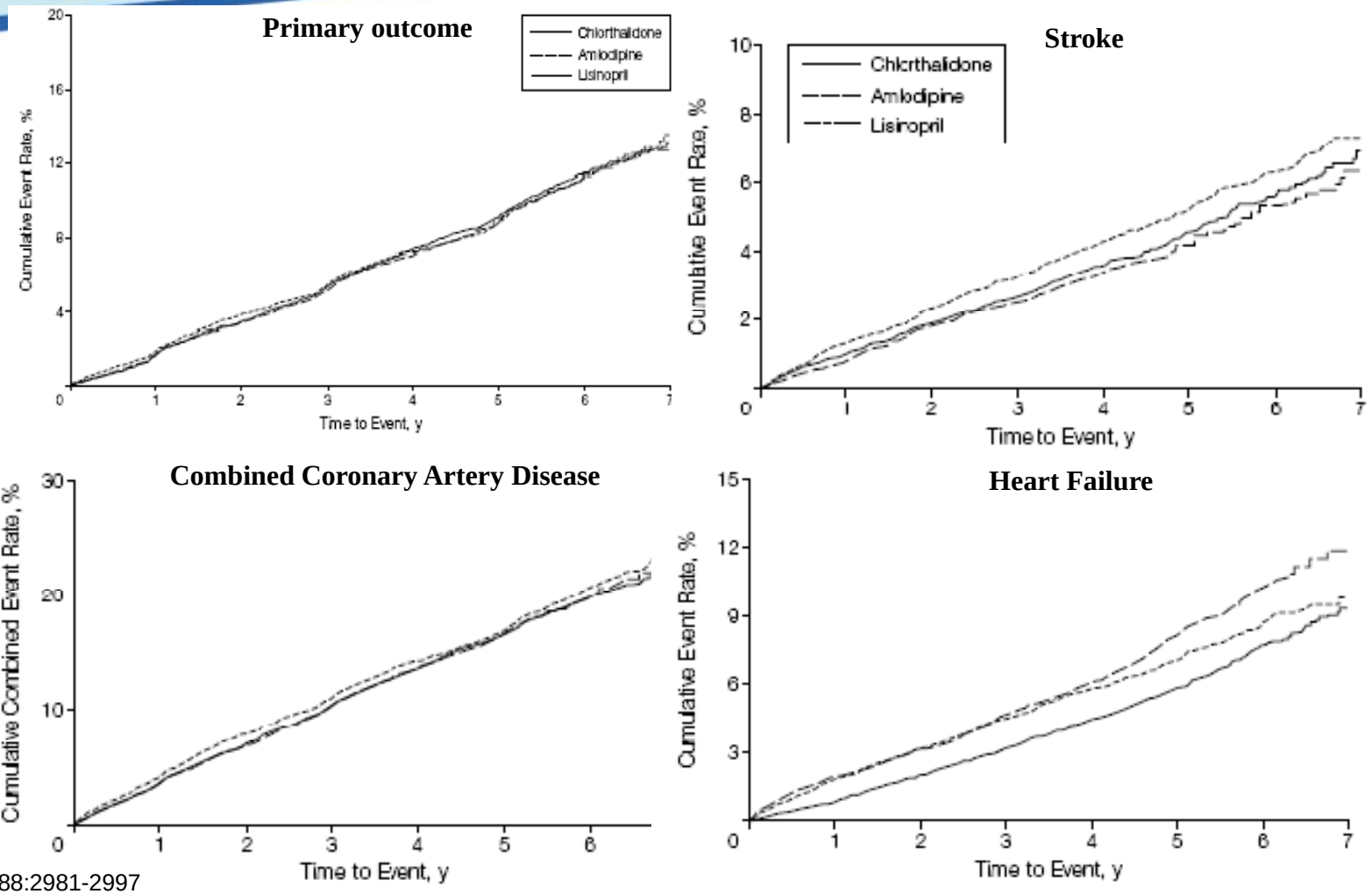
Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic (ALLHAT)

	Chlorthalidone	Amlodipine	Lisinopril	*P* Value: Amlodipine vs Chlorthalidone	*P* Value: Lisinopril vs Chlorthalidone
Systolic Blood Pressure, Mean (SD), mm Hg					
Baseline	146.2 (15.7)	146.2 (15.7)	146.4 (15.7)	.98	.39
1 Year	136.9 (15.8)	138.5 (14.9)	140.0 (18.5)	<.001	<.001
2 Years	135.9 (15.9)	137.1 (15.0)	138.4 (17.9)	<.001	<.001
3 Years	134.8 (15.4)	135.6 (15.2)	136.7 (17.3)	.001	<.001
4 Years	133.9 (15.7)	134.8 (15.0)	135.5 (17.2)	.002	<.001
5 Years	133.9 (15.2)	134.7 (14.9)	135.9 (17.9)	.03	<.001
Diastolic Blood Pressure, Mean (SD), mm Hg					
Baseline	84.0 (10.1)	83.9 (10.2)	84.1 (10.0)	.52	.49
1 Year	79.3 (9.9)	78.7 (9.5)	79.9 (10.5)	<.001	<.001
2 Years	78.3 (9.6)	77.7 (9.6)	78.6 (10.3)	<.001	.03
3 Years	77.2 (9.5)	76.4 (9.6)	77.3 (10.3)	<.001	.42
4 Years	76.5 (9.7)	75.7 (9.6)	76.6 (10.4)	<.001	.48
5 Years	75.4 (9.8)	74.6 (9.9)	75.4 (10.7)	<.001	.94
Achieved Blood Pressure Goal of <140/90 mm Hg, No. (%)					
Baseline	4149 (27.2)	2497 (27.6)	2381 (26.3)	.56	.12
1 Year	7434 (57.8)	4200 (55.2)	3806 (50.6)	<.001	<.001
2 Years	7161 (61.0)	3951 (57.4)	3625 (54.1)	<.001	<.001
3 Years	6836 (63.9)	4046 (63.4)	3597 (59.2)	.54	<.001
4 Years	6293 (67.1)	3709 (65.8)	3360 (63.1)	.15	<.001
5 Years	3615 (68.2)	2118 (66.3)	1813 (61.2)	.09	<.001

JAMA, 2002;288:2981-2997

Achieved blood pressure goal (<140/90 mmHg) was best in chlorthalidone group. ACE-inhibitors have only moderate blood pressure lowering effects

Cumulative Event Rates for All-Cause Mortality, Stroke, Combined Coronary Heart Disease, and Heart Failure by Treatment Group



JAMA, 2002;288:2981-2997

Primary outcome (fatal coronary heart disease or non-fatal MI) were not different between groups.

- **Are diuretics assoiated with a higher risk for type II diabetes?**

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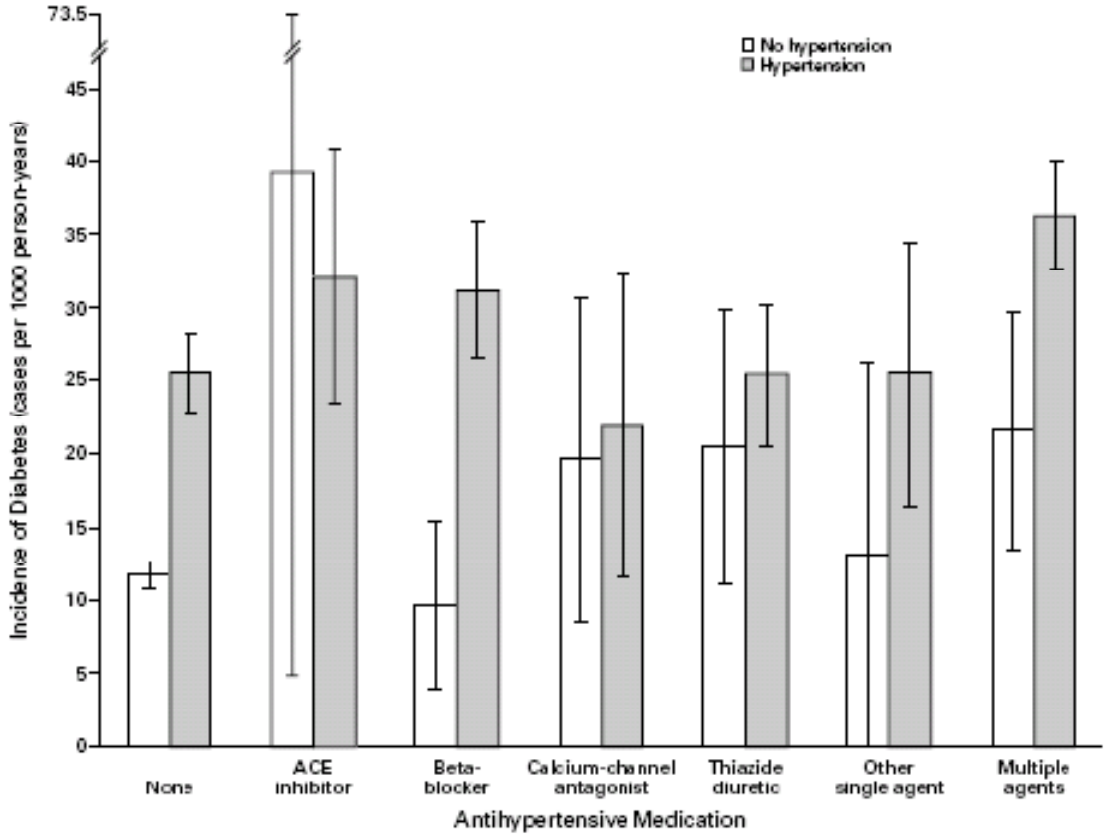
Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus (ARIC)



Atherosclerosis risk in community study (ARIC):

- Prospective study in 12.550 patients (US)
- 8.500 no hypertension
- 4.000 hypertension
- Extensive health evaluation (medication use, blood pressure measurment)
- Incidence of type II diabetes after 6 years

N Engl J Med, 2000;342:905-912

Beta-blocker, but not diuretics are associated with a higher risk of developing type II diabetes

- **Are ACE-inhibitors particular effective in type II diabetic patients?**

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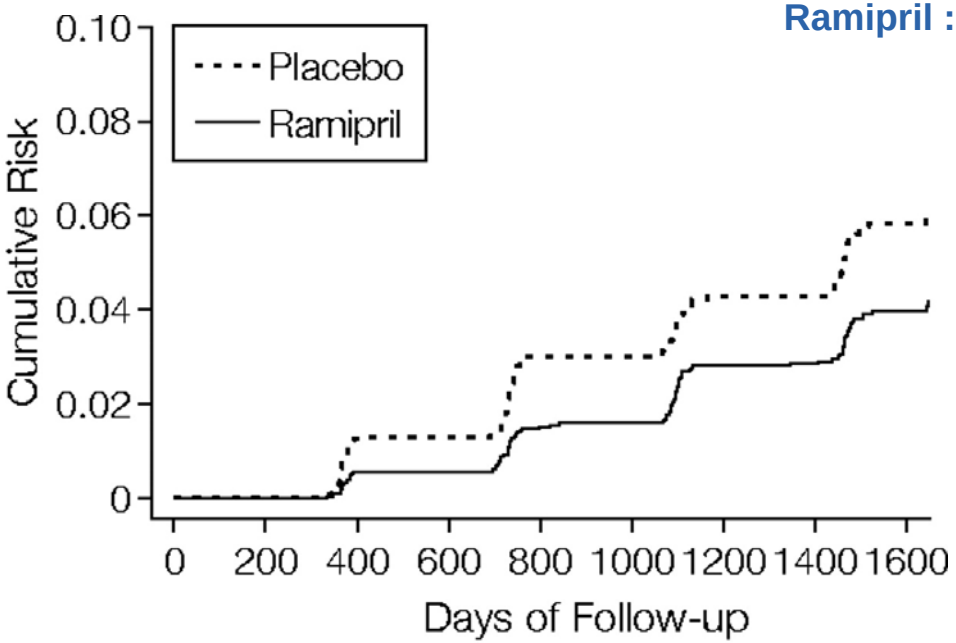
Heart Outcome Prevention Evaluation (HOPE) trial - Development of Diabetes in individuals with high CV risk : Ramipril vs Placebo

Blood pressure at baseline:
Placebo : 137/79 mmHg
Ramipril : 136/78 mmHg



No. at Risk

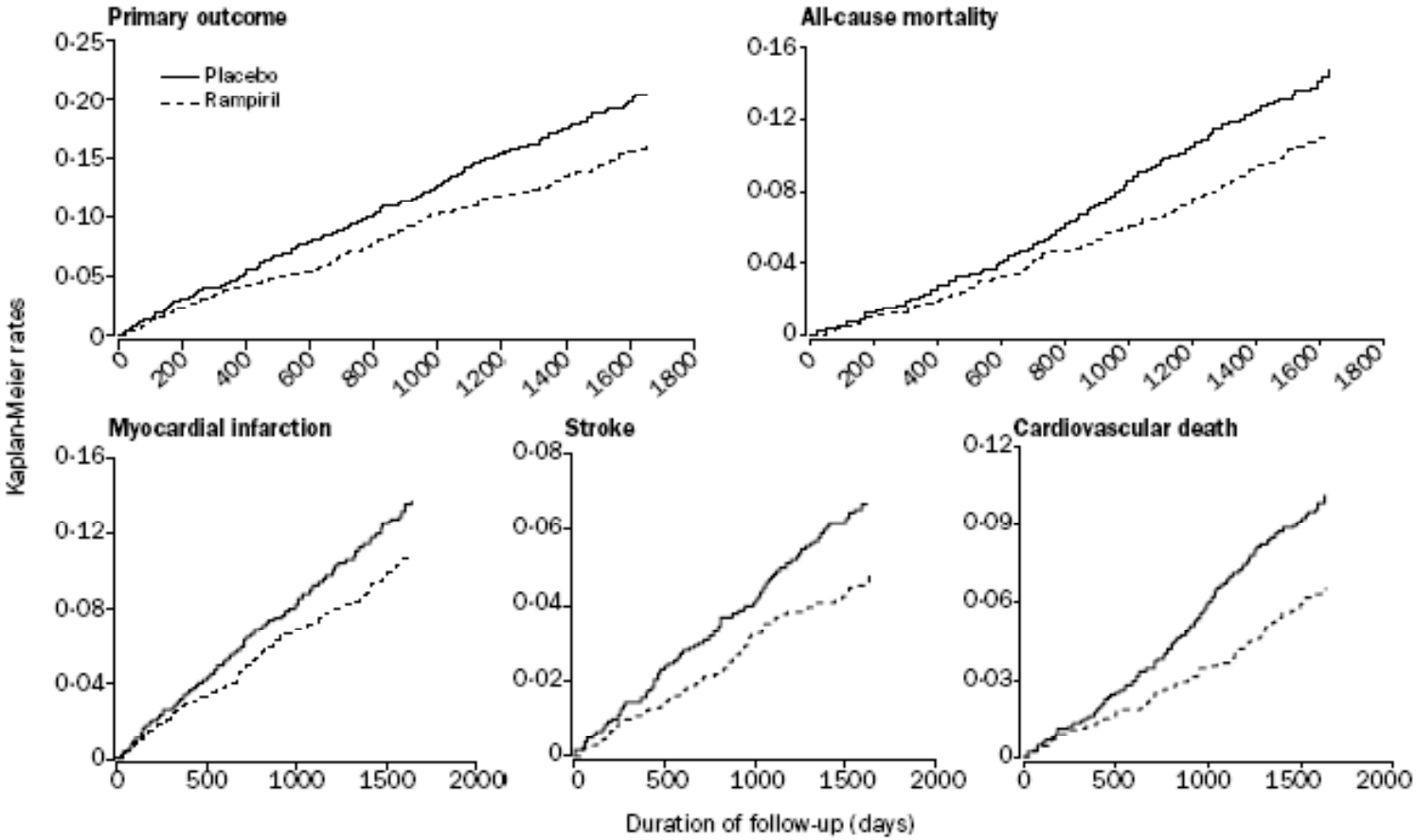
Placebo	2883	2867	2800	2765	2682	2645	2571	2497	1279
Ramipril	2837	2807	2772	2725	2672	2635	2571	2528	1317

JAMA 2001;286:1882-1885.

Ramipril is associated with lower rates of new diagnosis of diabetesin high risk individuals

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy

Kaplan-Meier survival curves for participants with diabetes



Ramipril reduced CV events and overt nephropathy in people with diabetes. The CV benefit was greater than attributable to decrease in blood pressure.

Lancet 2000;355:253-259.

- **For the same blood pressure control, is an ARB better renoprotective in type II diabetic patients with nephropathy?**

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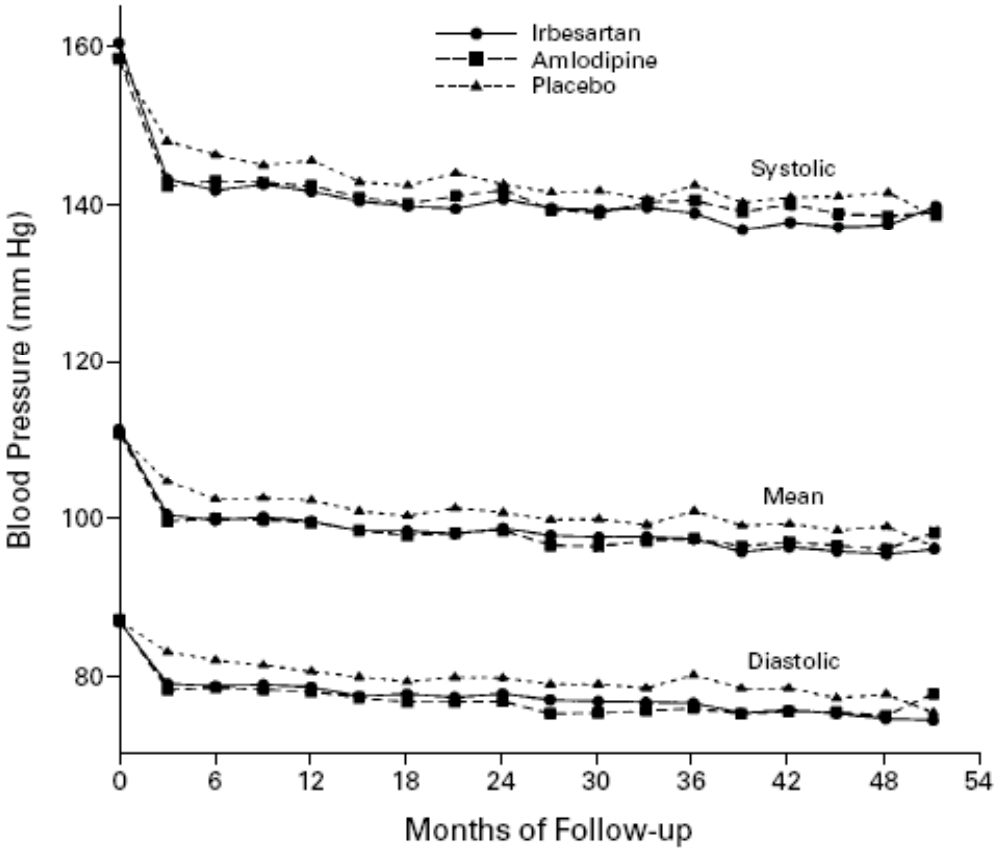
RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES (IDNT trial)

Blood pressure effect



Outcomes

Variable	Irbesartan Group (N=579)	Amlodipine Group (N=567)
Primary composite outcome — no. (%)	189 (32.6)	233 (41.1)
Doubling of serum creatinine concentration	98 (16.9)	144 (25.4)
End-stage renal disease	82 (14.2)	104 (18.3)
Death from any cause	87 (15.0)	83 (14.6)
Secondary composite outcome — no. (%)	138 (23.8)	128 (22.6)
Never received study medication — no. (%)†	2 (0.3)	8 (1.4)
Lost to follow-up — no. (%)‡	5 (0.9)	2 (0.4)
Completed study without primary outcome — no. (%)	385 (66.5)	332 (58.6)
Mean duration of follow-up — days§	952	924

The AT-II–receptor blocker irbesartan protected against the progression of nephropathy in type 2 diabetes independent of ist blood pressure lowering effect

N Engl J Med 2001;345:851-860.

- **For the same blood pressure control, does an ARB reduce better cardiac morbidity and mortality than amlodipine in hypertensive patients at high risk?**

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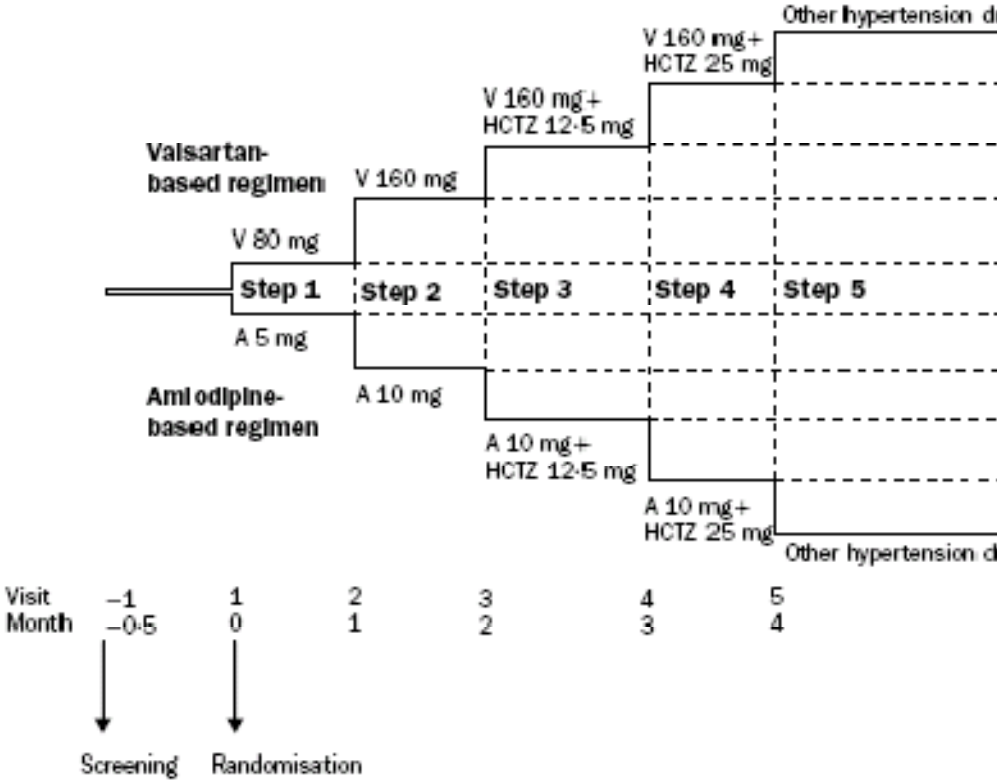
The Valsartan Anti-hypertensive Long-term Use Evaluation (VALUE) trial

Patients with treated or untreated hypertension and high risk for cardiac events

Study Design

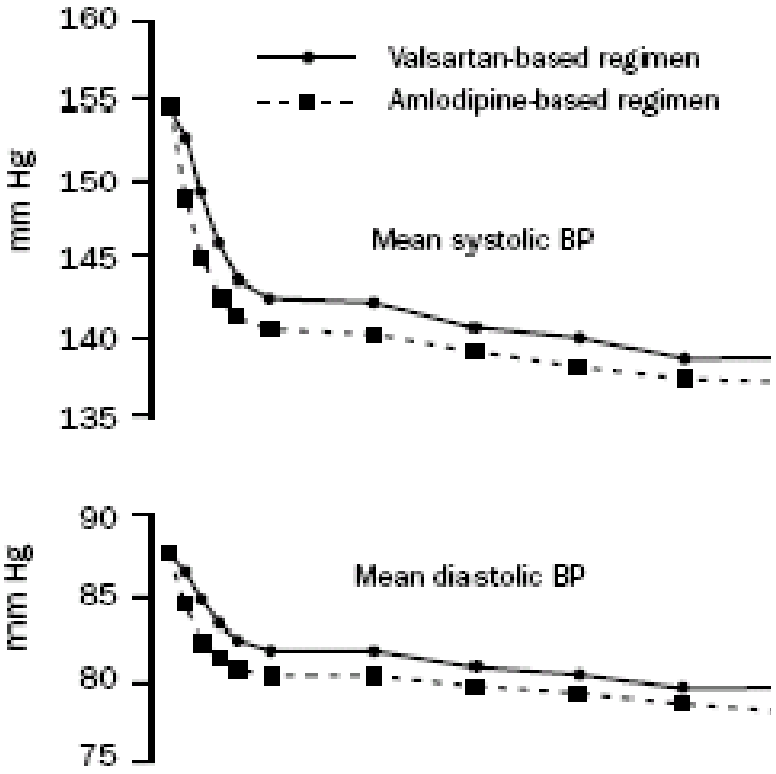


	Valsartan	Amlodipine
Patients on study medication at primary endpoint including stroke or at final visit for patients without event (ITT population)	n=7649	n=7596
Valsartan 80 mg or amlodipine 5 mg	1213 (15·9%)	1583 (20·8%)
Valsartan 160 mg or amlodipine 10 mg	852 (11·1%)	1105 (14·5%)
Valsartan 80 mg or amlodipine 5 mg plus HCTZ	159 (2·1%)	329 (4·3%)
Valsartan 160 mg or amlodipine 10 mg plus HCTZ	1719 (22·5%)	1481 (19·5%)
Other combinations or drugs	1758 (23·0%)	1279 (16·8%)
No study therapy*	1948 (25·5%)	1819 (23·9%)
Patients on concomitant therapy (safety population)	n=7622	n=7576
ACE inhibitors	1574 (20·7%)	1461 (19·3%)
α blockers	1856 (24·4%)	1385 (18·3%)
β blockers	3656 (48·0%)	3295 (43·5%)
Diuretics as monotherapy	1023 (13·4%)	1137 (15·0%)
Diuretics as part of combination therapy	318 (4·2%)	319 (4·2%)
Statins	3553 (46·6%)	3516 (46·4%)
Aspirin	5570 (73·1%)	5505 (72·7%)

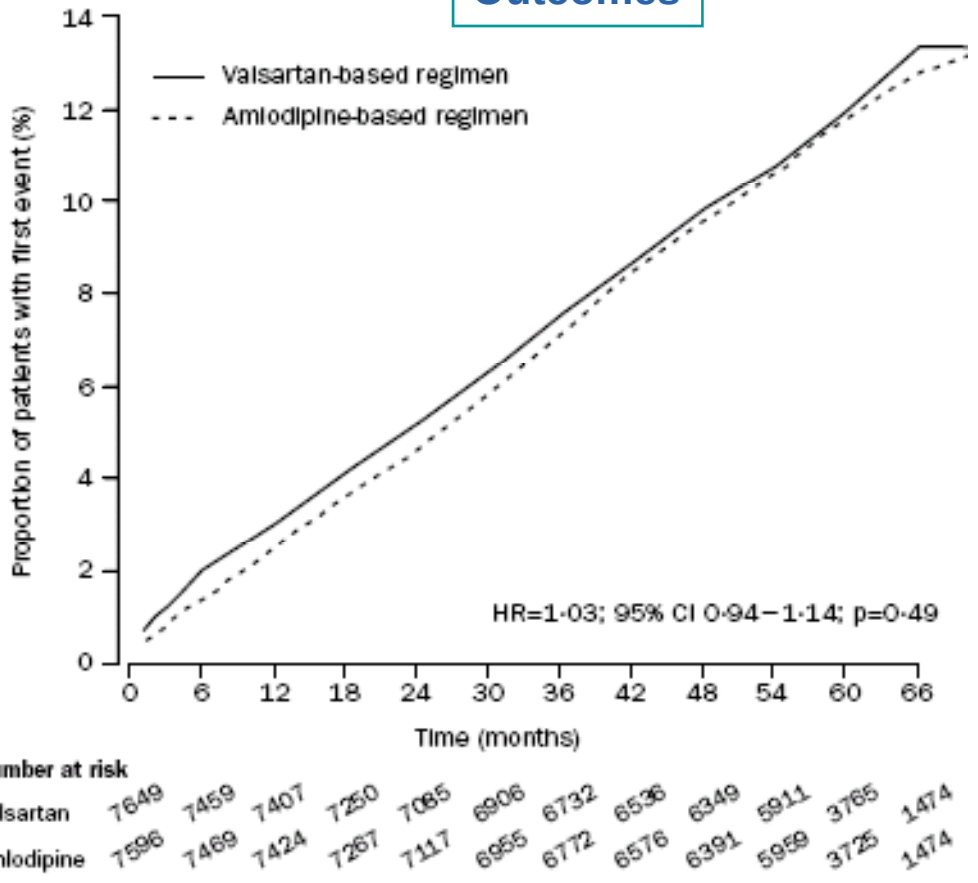
Lancet. 2004;363:2022-2031

The Valsartan Anti-hypertensive Long-term Use Evaluation (VALUE) trial

Blood pressure effect



Outcomes



Lancet. 2004;363:2022-2031

Valsartan was inferior in lowering blood pressure compared to amlodipine. Cardiac disease did not differ between the treatment groups.

- **Is the combination of an ACE inhibitor and an ARB more effective than the single drugs in high CV risk patients?**

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Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events (ONTARGET)

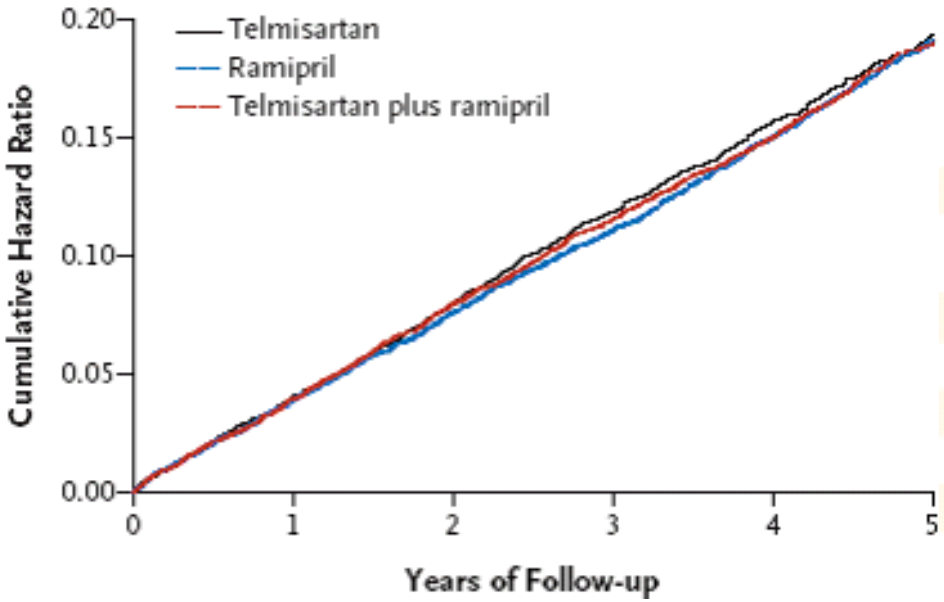
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
Age — yr	66.4±7.2	66.4±7.1	66.5±7.3
Blood pressure — mm Hg†	141.8±17.4/82.1±10.4	141.7±17.2/82.1±10.4	141.9±17.6/82.1±10.4
Heart rate — beats/min	67.9±12.2	68.0±12.3	67.7±12.2
Body-mass index‡	28.1±4.5	28.1±4.6	28.0±4.5
Cholesterol — mmol/liter			
Total	4.9±1.1	4.9±1.1	5.0±1.2
Coronary artery disease	6382 (74.4)	6367 (74.5)	6353 (74.7)
Myocardial infarction	4146 (48.3)	4214 (49.3)	4189 (49.3)
Angina pectoris			
Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)
Stroke or transient ischemic attacks	1805 (21.0)	1758 (20.6)	1779 (20.9)
Peripheral artery disease	1136 (13.2)	1161 (13.6)	1171 (13.8)
Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
Left ventricular hypertrophy	1085 (12.7)	1120 (13.1)	1082 (12.7)
Microalbuminuria¶	929 (13.1)	923 (13.2)	929 (13.3)

N Engl J Med 2008;358:1547-59.

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events (ONTARGET)

Composite endpoint*



* death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

Discontinuation of study medication

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)

Telmisartan and Ramipril or their combination are equally effective in reducing cardiovascular events in high risk patients. However, the combination of both is associated with more adverse events.

Is the lower the better?

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Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes (SANDS trial)

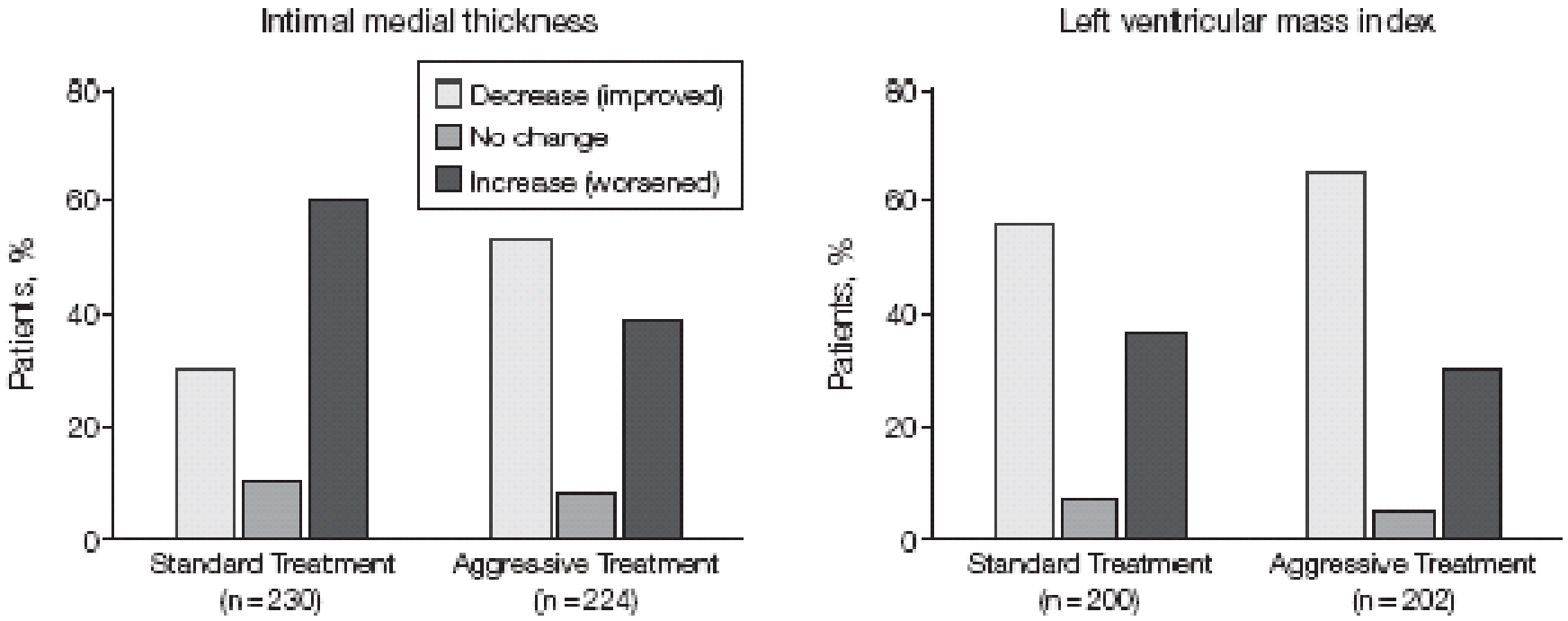
Differences in mean changes from baseline to 36 months

	Baseline		36 mo[b]	
	Aggressive	Standard	Aggressive	Standard
Weight, kg	90 (88 to 93)	90 (88 to 92)	91 (89 to 94)	91 (88 to 93)
BMI[c]	34 (33 to 34)	33 (32 to 34)	34 (33 to 35)	34 (33 to 34.4)
Waist, cm	110 (108 to 112)	110 (108 to 112)	111 (109 to 113)	110 (108 to 112)
CRP mg/L[d]	2.7 (2.3 to 3.1)	2.8 (2.4 to 3.3)	2.2 (1.9 to 2.7)	3.3 (2.8 to 3.8)
DBP, mm Hg	74 (73 to 76)	76 (75 to 78)	67 (66 to 68)	73 (72 to 74)
SBP, mm Hg	128 (126 to 130)[g]	133 (131 to 135)[g]	117 (115 to 118)	129 (128 to 130)
Glucose, mg/dL	159 (151 to 168)	156 (147 to 166)	169 (158 to 179)	169 (158 to 180)
HDL-C, mg/dL	46 (44 to 48)	46 (44 to 47)	48 (47 to 50)	48 (47 to 50)
LDL-C, mg/dL	104 (100 to 108)	104 (100 to 108)	72 (69 to 75)	104 (101 to 106)
Non-HDL-C, mg/dL	138 (134 to 142)	140 (136 to 144)	102 (98 to 106)	138 (135 to 141)
TC, mg/dL	184 (180 to 188)	185 (181 to 190)	150 (146 to 154)	187 (183 to 190)
TC/HDL-C, mg/dL	4.2 (4.1 to 4.4)	4.2 (4.1 to 4.4)	3.3 (3.1 to 3.4)	4.0 (3.9 to 4.2)
Triglycerides, mg/dL[d]	158 (149 to 167)	168 (159 to 177)	137 (130 to 144)	160 (153 to 168)
Hemoglobin A_{1c}	8.2 (7.9 to 8.4)	7.9 (7.6 to 8.1)	8.3 (8.0 to 8.6)	8.2 (7.8 to 8.5)

JAMA. 2008;299:1678-1689

Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes (SANDS trial)

Changes in Left Ventricular Mass Index and Intimal Medial Thickness



JAMA. 2008;299:1678-1689

Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes.

- **Is their any upcoming innovation in the treatment of hypertension?**

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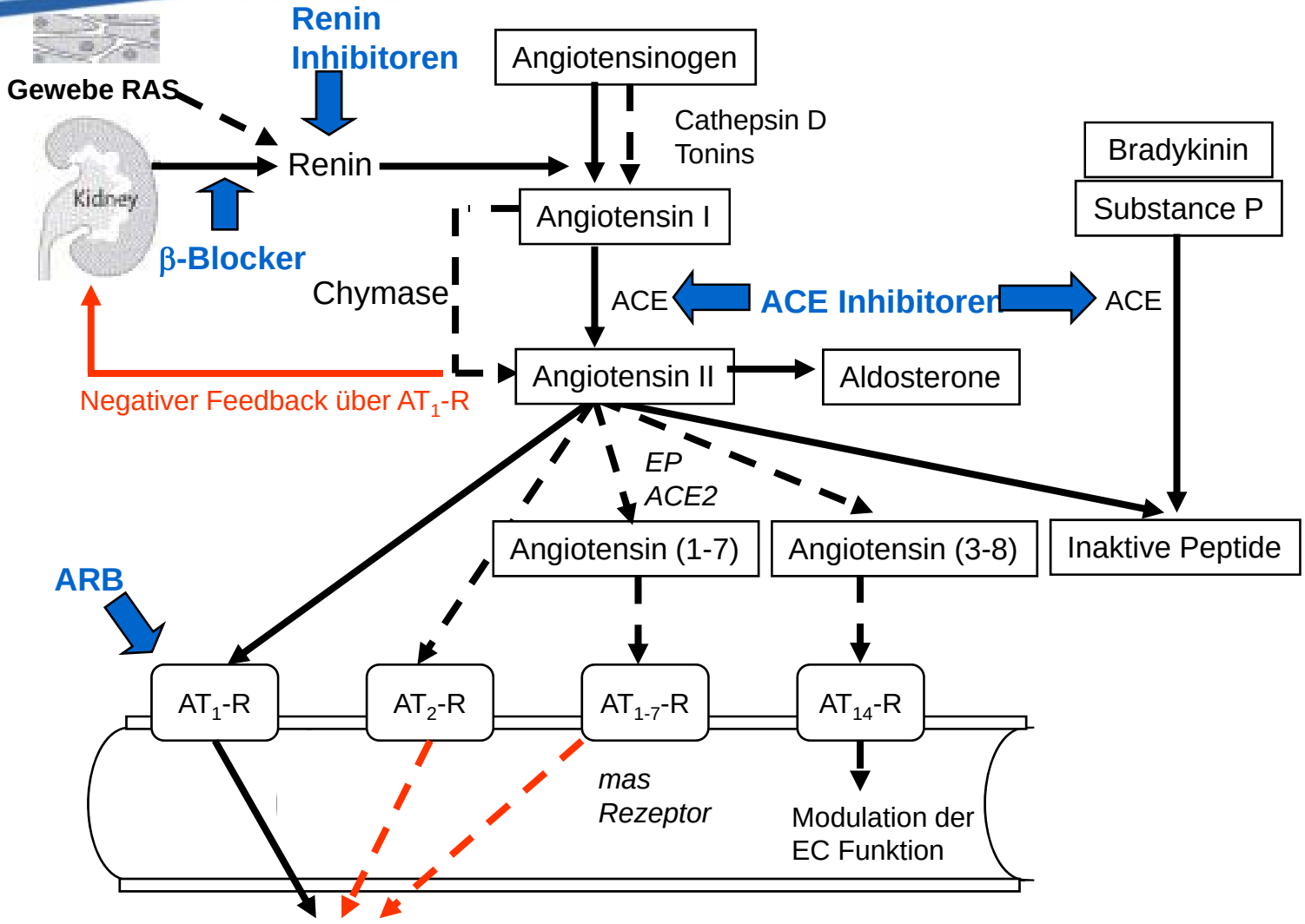
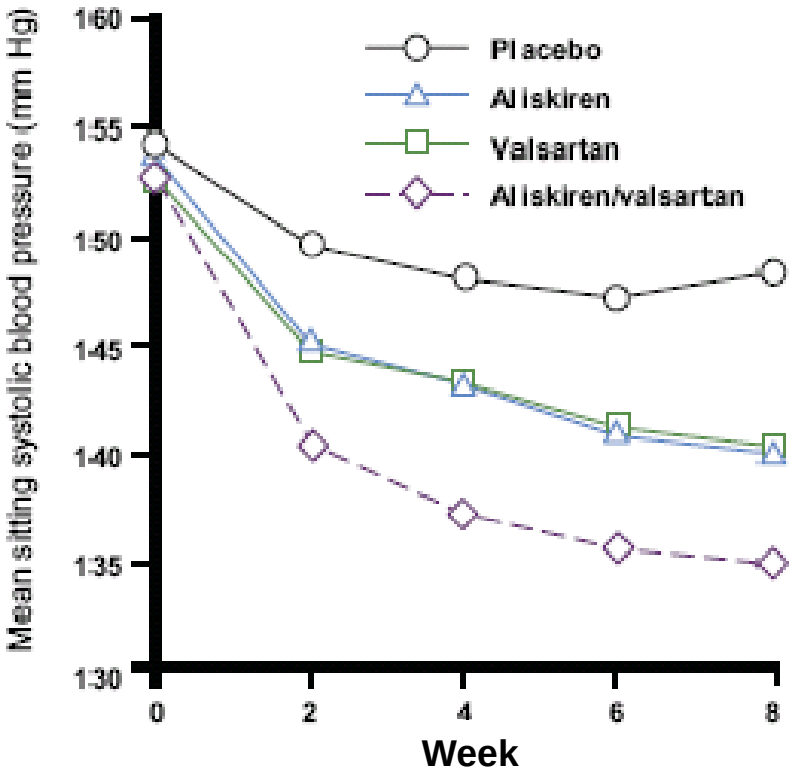
Das Renin-Angiotensin-Aldosterone-System

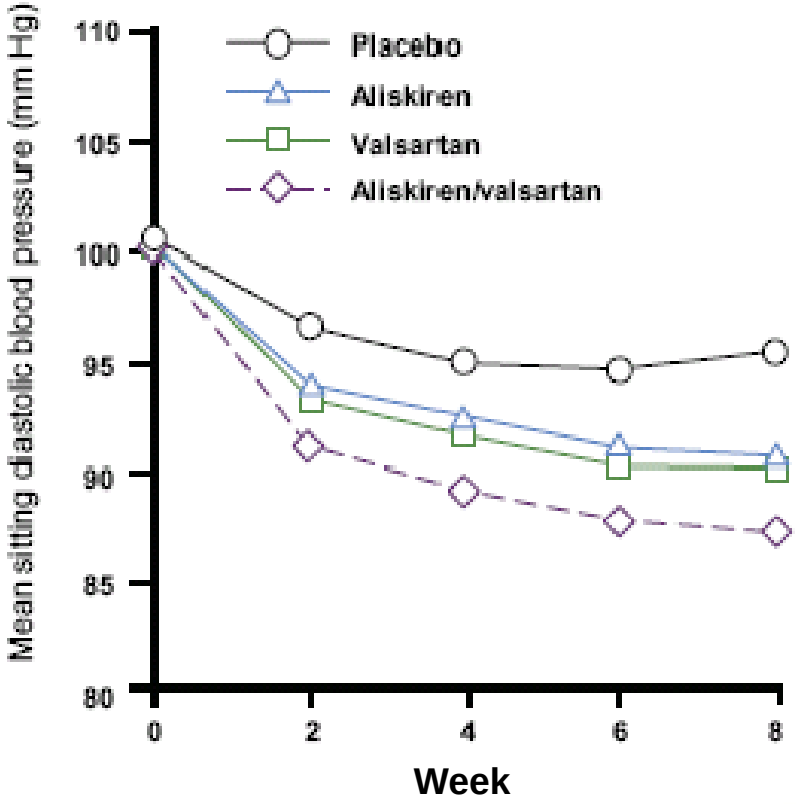


Straessen, JA et al. Lancet, 2006;368:1449-1456

Blood pressure lowering activity of the renin inhibitor Aliskiren in hypertensive patients

Lancet, 2007;370:221-229





Aliskiren is as effective as the Valsartan in reducing blood pressure. The combination is even more effective. However, outcome data will determine whether Aliskiren will add additional benefit over current standard treatment

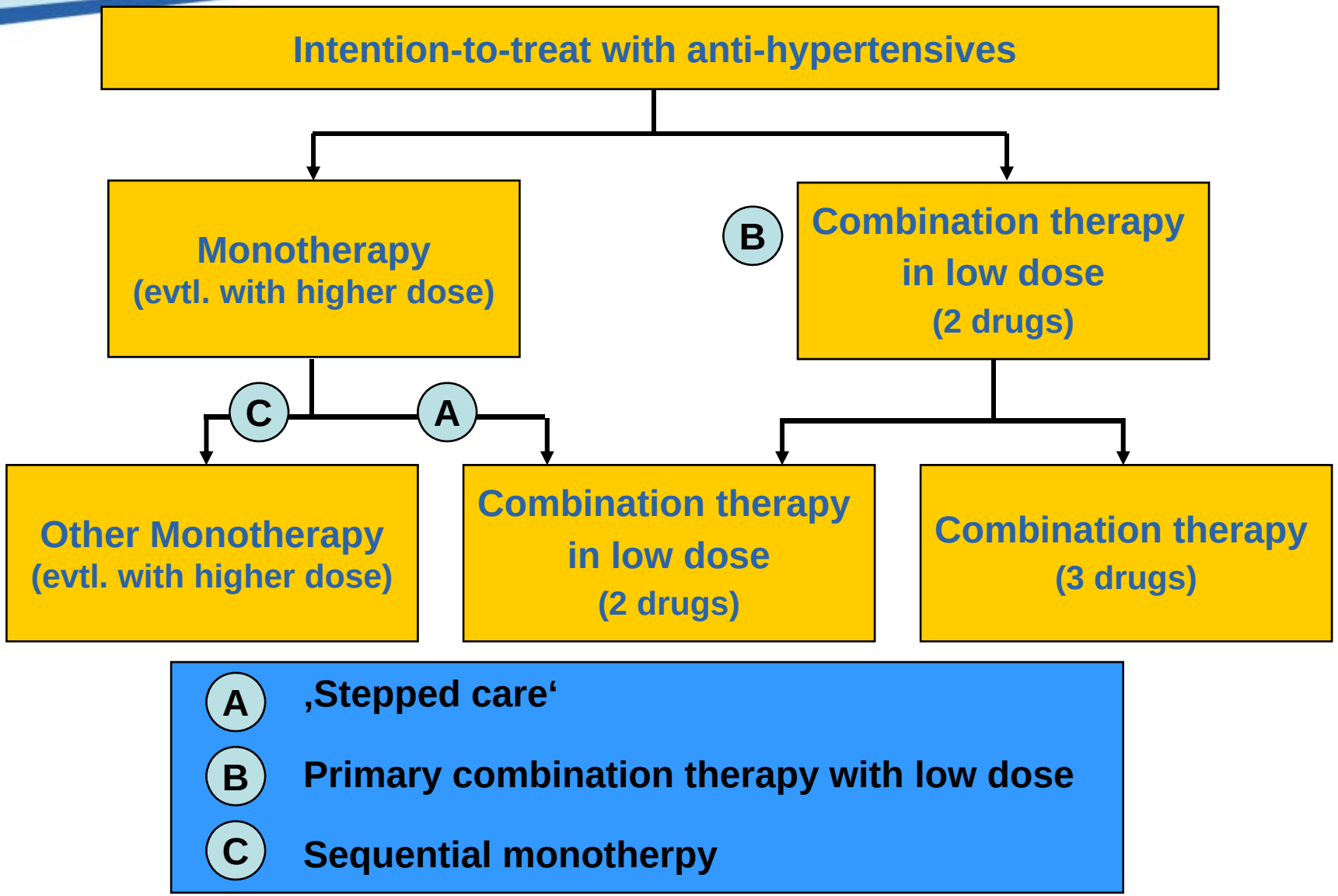
Anti-hypertensives recommended in sub-populations

Prompt blood-pressure control in hypertensive patients at high CV risk is of major importance !

- **Elderly (age >65)**
  - Diuretics, Calcium channel blockers
- **Patients with Cardiac Diseases**
  - **Left ventriculat hypertrophy**
    - ACE-inhibitors, Calcium channel blockers
  - **Coronary Heart Disease**
    - β-blocker
  - **Post-myocardial infarction**
    - β-blocker, ACE-inhibitors
  - **Heart Failure**
    - ACE-inhibitors, diuretics, carvedilol, bisoprolol
- **Renal insufficiency**
  - ACE-inhibitors, Angiotensin-II receptor blockers
- **Diabetes mellitus (diabetic nephropathy)**
  - ACE-inhibitors, Angiotensin-II receptor blockers

Backup

Strategies in drug treatment of hypertension

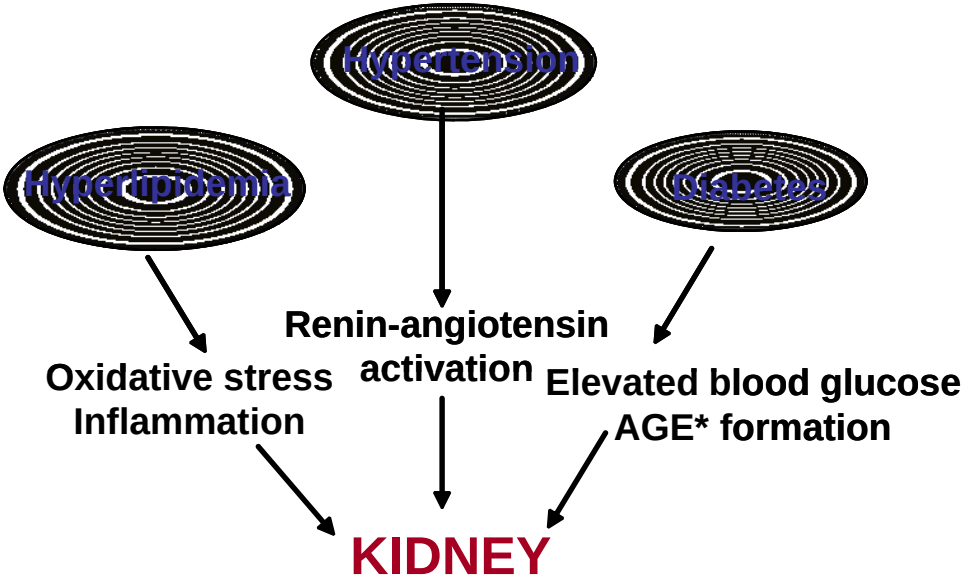


ALLHAT

	Chlorthalidone	Amlodipine	Lisinopril	*P* Value: Amlodipine vs Chlorthalidone	*P* Value: Lisinopril vs Chlorthalidone
No. of participants (%)					
Baseline	11 273 (73.9)	6648 (73.5)	6752 (74.6)		
2 Years	5980 (39.2)	3506 (38.7)	3333 (36.8)		
4 Years	4972 (32.6)	2954 (32.6)	2731 (30.2)		
Mean (SD)					
Baseline	123.5 (58.3)	123.1 (57.0)	122.9 (56.1)	.71	.54
2 Years	127.6 (59.2)	122.4 (54.2)	120.8 (54.0)	<.001	<.001
4 Years	126.3 (55.6)	123.7 (52.0)	121.5 (51.3)	.20	.002
≥126 mg/dL, No. (%)					
Baseline	3258 (28.9)	1941 (29.2)	1985 (29.4)	.68	.55
2 Years	1967 (32.9)	1048 (29.9)	947 (28.4)	<.001	<.001
4 Years	1626 (32.7)	901 (30.5)	784 (28.7)	.11	<.001
Fasting Glucose Among Nondiabetics With Baseline Fasting Glucose <126 mg/dL					
No. of participants (%)					
Baseline	6766 (100)	3954 (100)	4096 (100)		
2 Years	3074 (45.4)	1787 (45.2)	1737 (42.4)		
4 Years	2606 (40.3)	1567 (39.6)	1464 (35.7)		
Mean (SD)					
Baseline	93.1 (11.7)	93.0 (11.4)	93.3 (11.8)	.52	.45
2 Years	102.2 (27.1)	99.0 (22.5)	97.4 (20.0)	<.001	<.001
4 Years	104.4 (28.5)	103.1 (27.7)	100.5 (19.5)	.11	<.001
≥126 mg/dL, No. (%)					
2 Years	295 (9.6)	132 (7.4)	101 (5.8)	.006	<.001
4 Years	302 (11.6)	154 (9.8)	119 (8.1)	.04	<.001

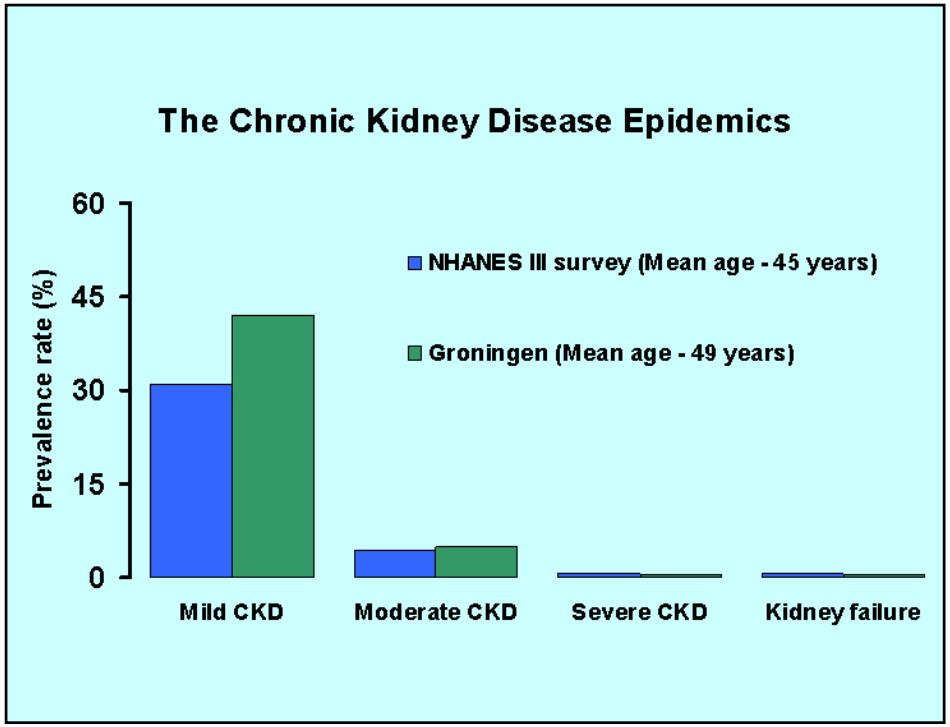
JAMA, 2002;288:2981-2997

Chronic Kidney Disease – Multiple Pathologies

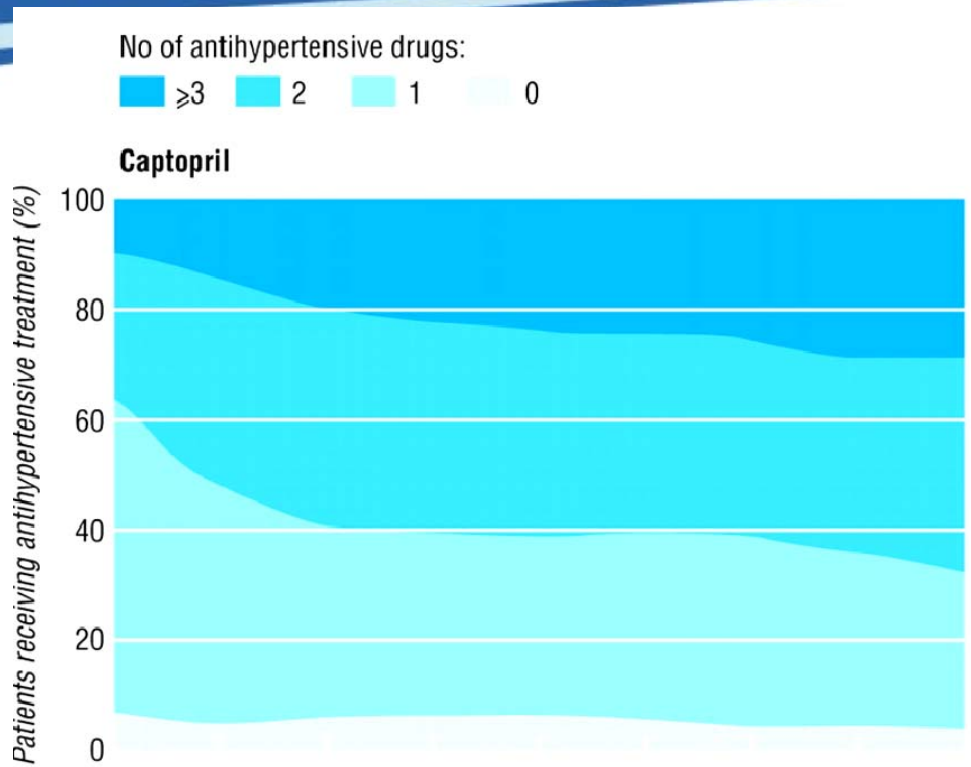


- Abnormal glomerular permeability
- Glomerular hypertrophy
- Fibrosis
- Tubular necrosis

CHRONIC KIDNEY DISEASE



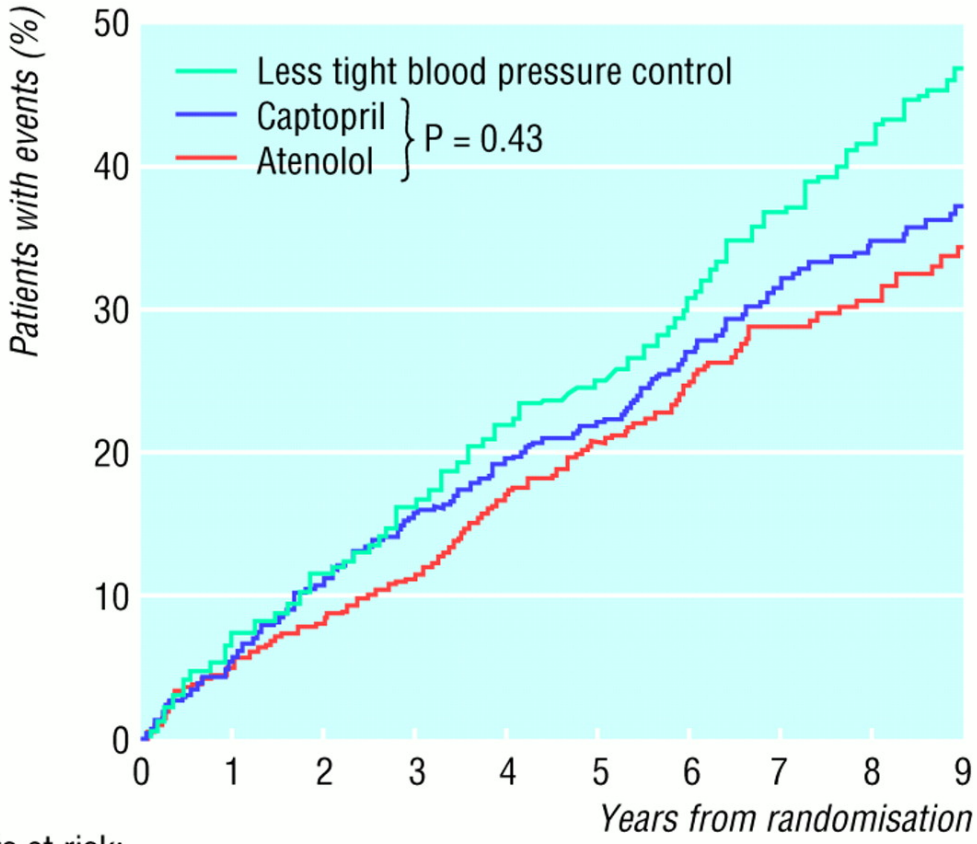
UKPDS



UK Prospective Diabetes Study Group, BMJ 1998;317:713-720

sanofi aventis
Because health matters

UKPDS



No of patients at risk:

Captopril	400	327	257	124
Atenolol	358	314	237	112

UK Prospective Diabetes Study Group, BMJ 1998;317:713-720

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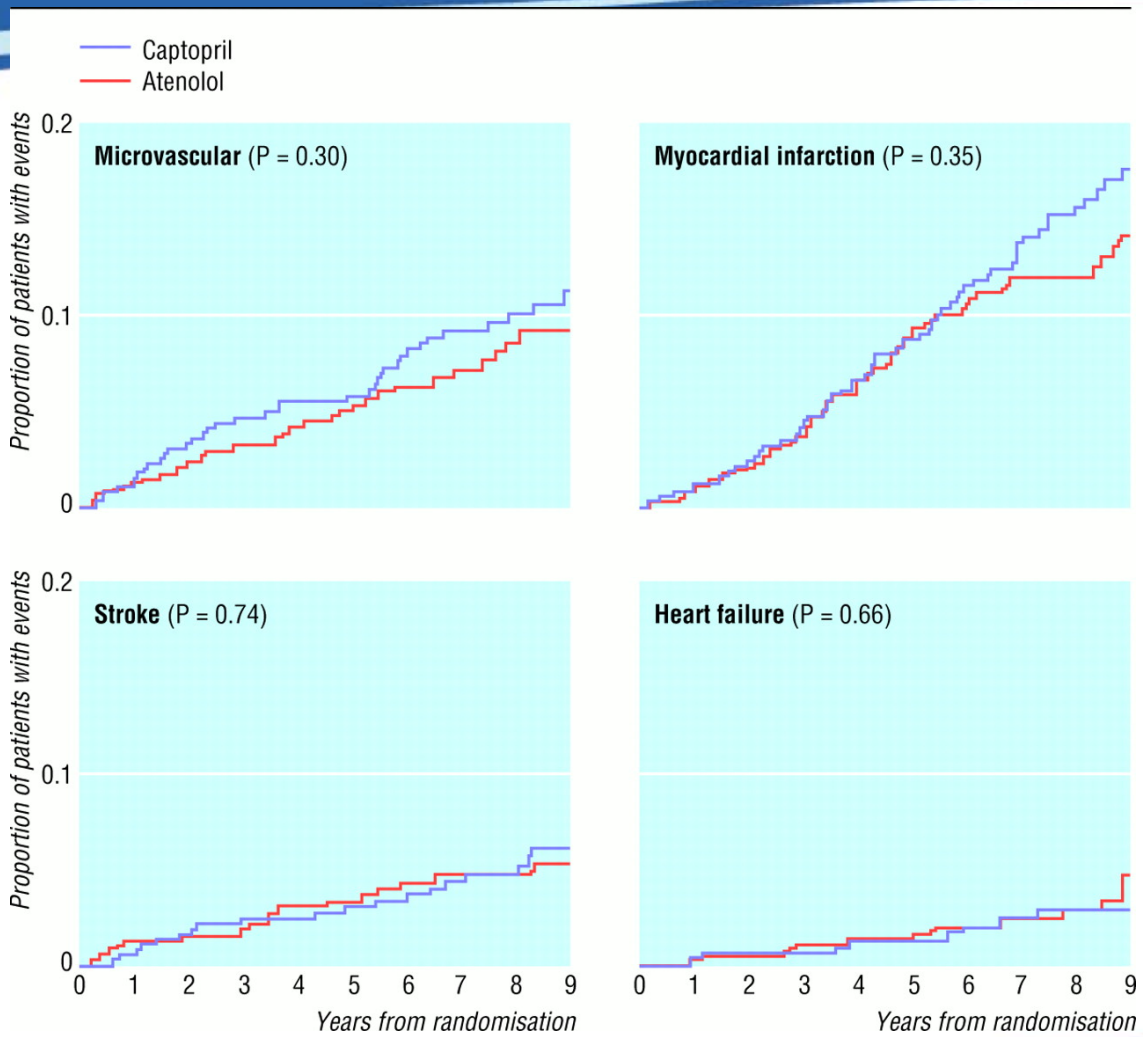
UKPDS



UK Prospective Diabetes Study Group, BMJ 1998;317:713-720

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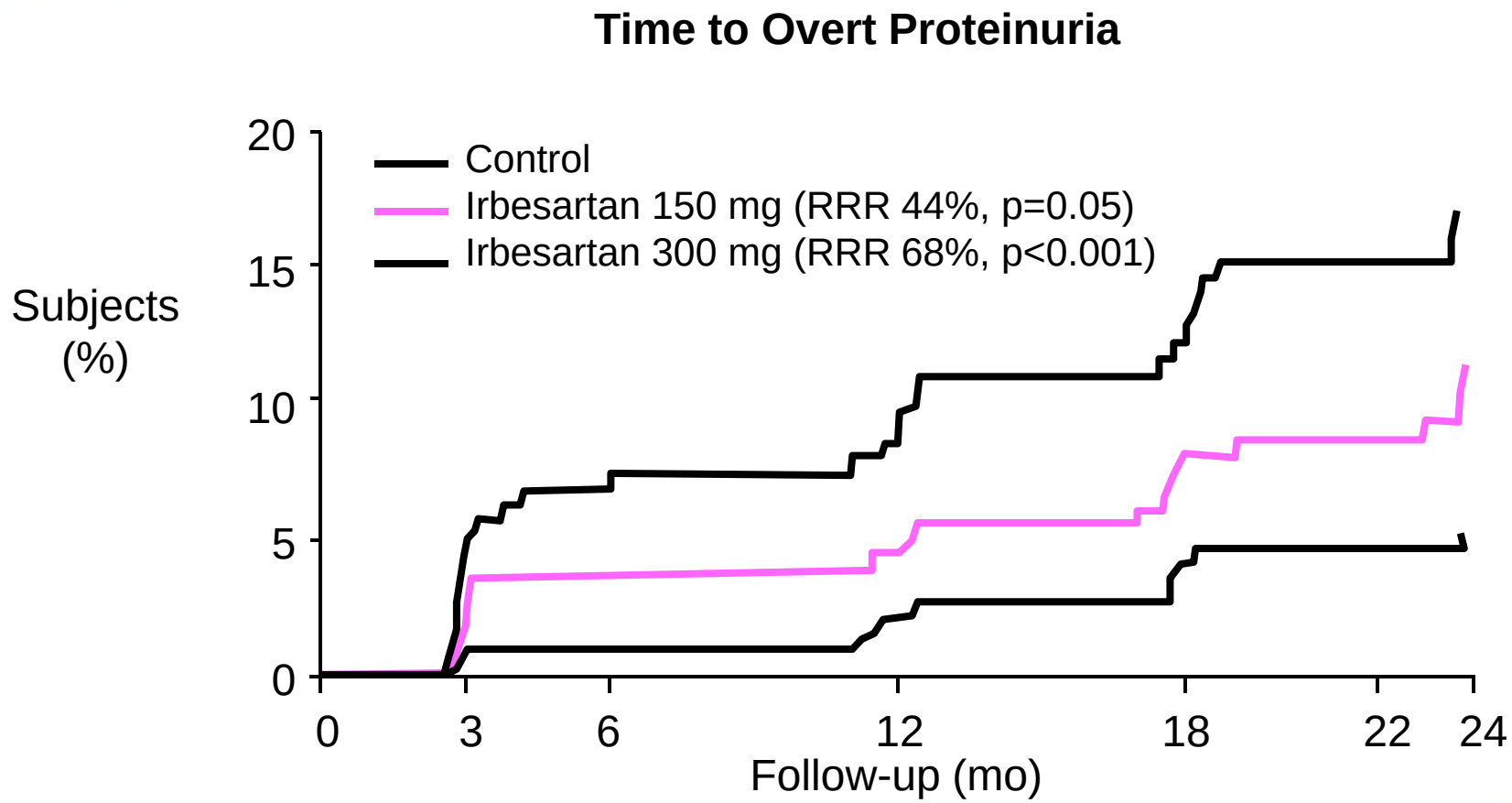
IRMA 2 : Primary Endpoint



Parving H-H, et al. *N Engl J Med* 2001;345:870-878.

PRIME
IRBESARTAN MORTALITY/MORBIDITY EVALUATION
Because health matters