



# Hypertension and CKD



- The terms nephrosclerosis or hypertensive nephropathy are usually applied to CKD associated with HTN
- Nephrosclerosis is described in patients with chronic kidney disease and essential hypertension with no other cause of kidney disease



- Even though considered the second most common cause of ESRD, hypertensive nephrosclerosis has been histologically confirmed in very few cases
- The causal relationship with hypertension is still a subject for debate



- The most characteristic microscopic lesion is hyalinosis of afferent arterioles
- The vascular changes cause glomerular ischemia (retraction of the glomerular tuft with focal or global sclerosis), and in some areas, interstitial fibrosis and tubular atrophy



- In other cases the hyalinization of afferent arterioles initially causes glomerular hypertrophy and, in the long term glomerulosclerosis lesions that would favor the development of proteinuria and disease progression
- These abnormalities are more frequent in black patients



- Hypertensive nephropathy is more frequent in African Americans
- Pharmacologic treatment of mild-to-moderate hypertension in African Americans has little impact on the incidence of CKD, whereas it significantly reduces the progression in Caucasians



Those differences persist despite controlling for:

- Age
- Sex
- Initial serum creatinine concentration
- Initial and treated blood pressures
- Number of missed office visits
- Antihypertensive medications prescribed



- Kopp et al initially identified excess African ancestry on chromosome 22p in African Americans with idiopathic FSGS and HIV-associated collapsing FSGS
- MYH9 was eventually identified as the associated gene
- MYH9 was associated with clinically diagnosed ‘hypertensive ESRD’ in African Americans as well
- The Family Investigation in Nephropathy and Diabetes (FIND) study rapidly replicated association in several nondiabetic forms of ESRD in African Americans, including idiopathic FSGS, HIVAN and clinically diagnosed ‘hypertensive-ESRD’



- Genovese and colleagues examined large chromosomal regions adjacent to MYH9
- Statistically stronger associations were detected between two independent sequence variants in the *APO1* and nondiabetic nephropathy in African Americans, with odds ratios of 10.5 in idiopathic FSGS and 7.3 in hypertension-attributed ESRD
- The genetic risk that was previously attributed to MYH9 may reside, in part or in whole, in *APO1*, although more complex models of risk cannot be excluded

# Effect of kidney disease on blood pressure




- Sodium retention is generally of primary importance, even if the degree of extracellular volume expansion is insufficient to induce edema
- Increased activity of the renin-angiotensin system (probably due to regional ischemia induced by scarring) is often responsible for at least part of the hypertension that persists even after the restoration of normovolemia
- Enhanced activity of the sympathetic nervous system has been demonstrated in patients with chronic kidney disease
- Secondary hyperparathyroidism raises the intracellular calcium concentration, which can lead to vasoconstriction and hypertension
- Hypertension may occur or be exacerbated in patients with advanced chronic kidney disease treated with epo
- Impaired NO synthesis and endothelium-mediated vasodilatation has been demonstrated in patients with uremia



**Goal blood pressure**

# Goal BP in people with kidney disease or diabetes from various consensus committees around the world

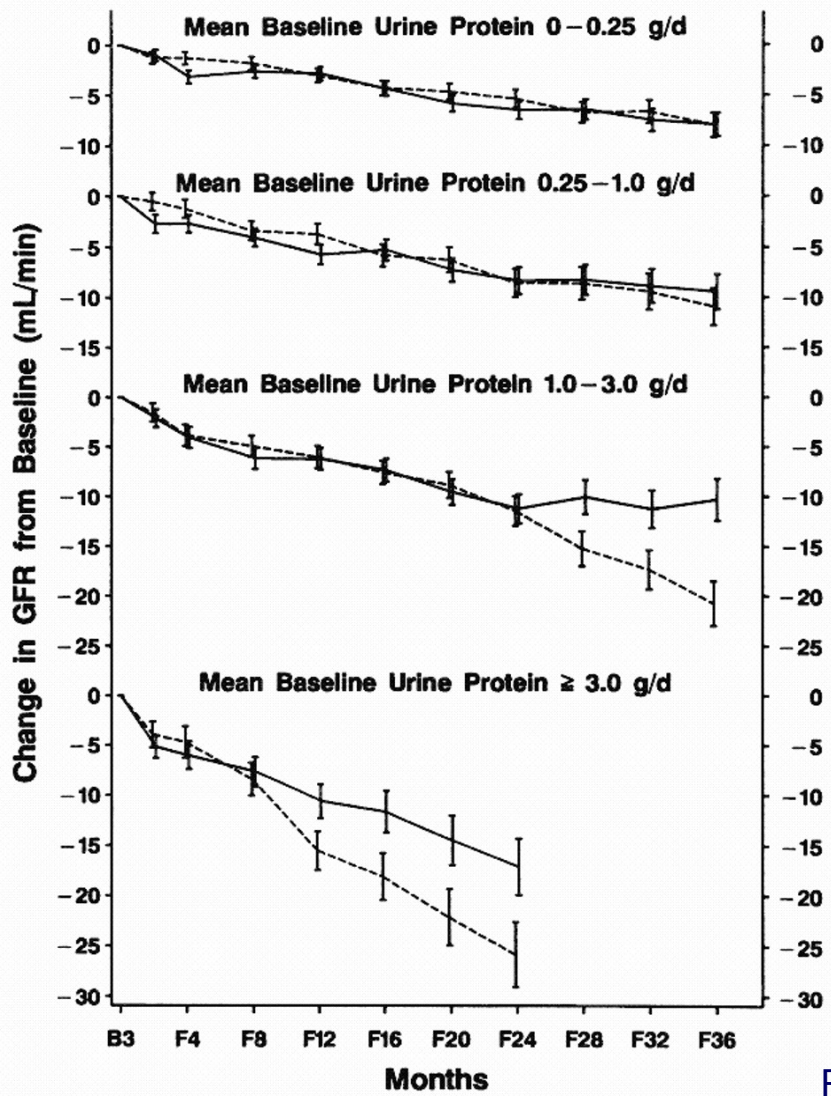


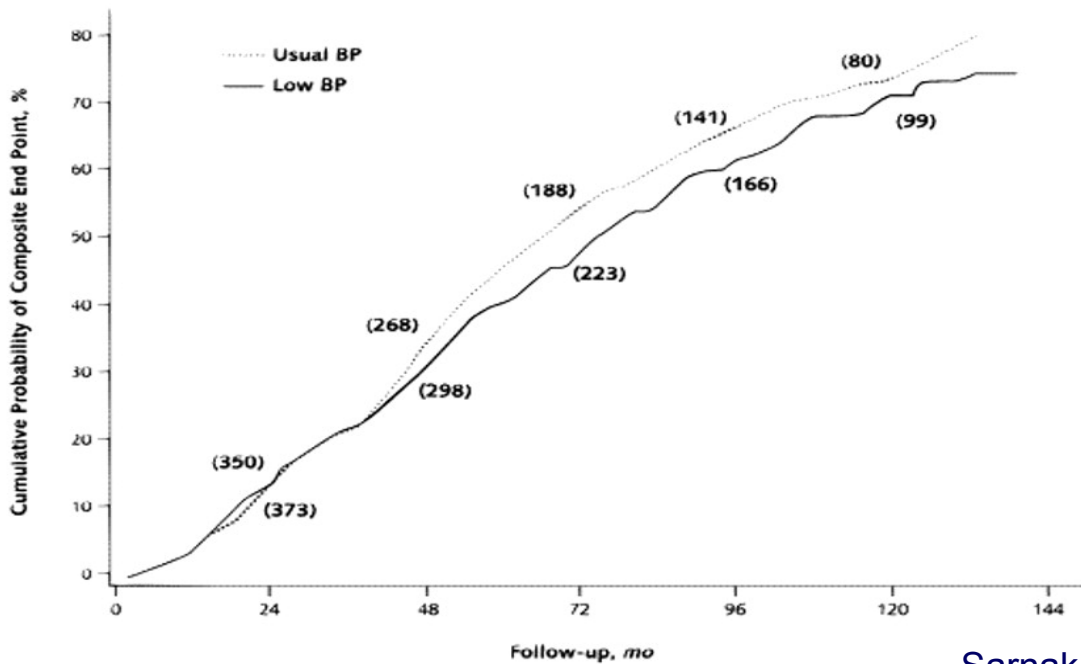
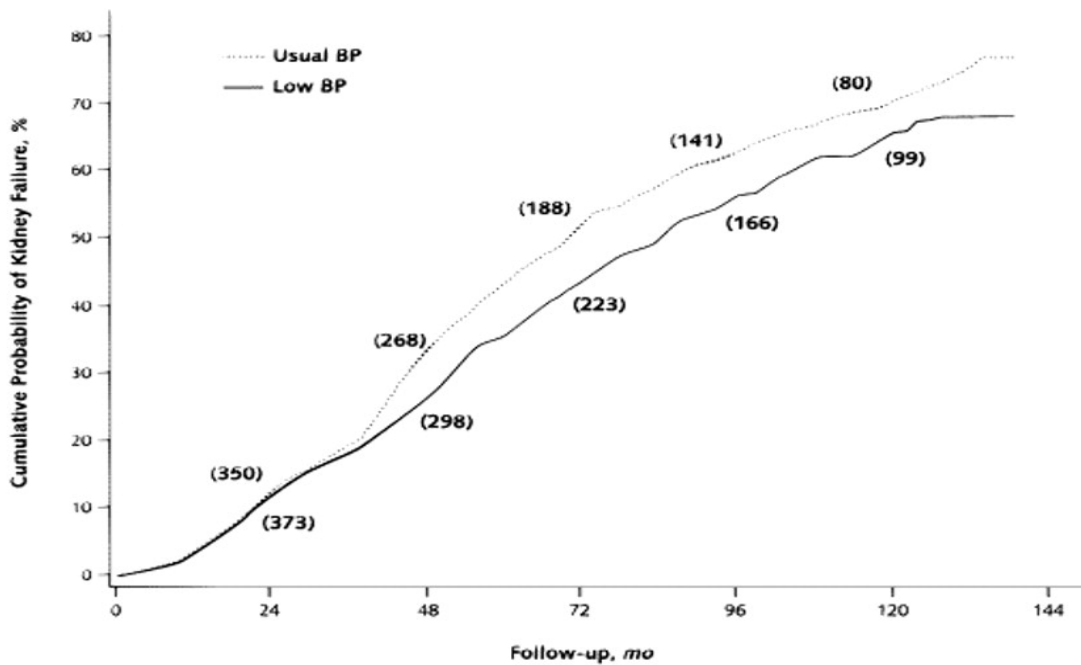
<b>Group</b>	<b>Goal BP (mm Hg)</b>	<b>Initial Therapy</b>
Am. Society of HTN (2008)	<130/80	ACE inhibitor/ARB
Canadian HTN Society (2007)	≤130/80	ACE inhibitor/ARB
Am. Diabetes Assoc. (2005)	<130/80	ACE inhibitor/ARB
Japanese HTN Society (2006)	≤130/80	ARB
National Kidney Foundation (2004)	<130/80	ACE inhibitor/ARB
British HTN Society (2004)	≤130/80	ACE inhibitor/ARB
JNC 7 (2003)	<130/80	ACE inhibitor/ARB
ISH/ESC (2003)	<130/80	ACE inhibitor/ARB
Australia-New Zealand (2002)	<130/85	ACE inhibitor
WHO/ISH (1999)	<130/85	ACE inhibitor

**Table 3. Mean Rate of Decline in the Glomerular Filtration Rate in Study 1, According to Diet and Blood-Pressure Group.\***

STUDY PERIOD AND DIET	DECLINE IN GLOMERULAR FILTRATION RATE		
	USUAL PRESSURE	LOW PRESSURE	BOTH
<i>milliliters per minute per 4 months</i>			
<b>Base line to 4 months</b>			
Usual protein	1.2 (0.1–2.3)	2.4 (1.4–3.5)	1.8 (1.1–2.6)
Low protein	2.6 (1.5–3.7)	4.3 (3.2–5.3)	3.4 (2.7–4.2)
Both	1.9 (1.1–2.7)	3.4 (2.6–4.1)	2.6 (2.1–3.2)
<i>milliliters per minute per year</i>			
<b>4 Months to end</b>			
Usual protein	4.5 (3.7–5.3)	3.3 (2.5–4.1)	3.9 (3.3–4.4)
Low protein	3.3 (2.5–4.2)	2.3 (1.5–3.0)	2.8 (2.2–3.4)
Both	3.9 (3.3–4.5)	2.8 (2.2–3.3)	3.3 (2.9–3.7)
<i>milliliters per minute per 3 years</i>			
<b>Base line to 3 years</b>			
Usual protein	13.1 (10.8–15.4)	11.2 (8.8–13.5)	12.1 (10.5–13.8)
Low protein	11.5 (9.1–13.9)	10.3 (8.0–12.6)	10.9 (9.2–12.5)
Both	12.3 (10.6–14.0)	10.7 (9.1–12.4)	11.5 (10.3–12.7)

\*The means were estimated with the maximum-likelihood method for the two-slope model (with separate slopes from the final base-line visit to the fourth month of follow-up and from the fourth month of follow-up to the end of follow-up) and for the projected decline in the glomerular filtration rate from base line to three years. There were no significant interactions between the diet and blood-pressure interventions. There were significant effects of dietary and blood-pressure interventions from the final base-line visit to the fourth month of follow-up ( $P = 0.004$  and  $P = 0.010$ , respectively) and from the fourth month to the end of follow-up ( $P = 0.009$  and  $P = 0.006$ , respectively). The estimated decline in the glomerular filtration rate over three years did not differ significantly between the diet groups or between the blood-pressure groups. Values in parentheses indicate 95 percent confidence intervals.





Cumulative probability of kidney failure (top) and cumulative probability of the composite of kidney failure or all-cause mortality before kidney failure (bottom)

# Antihypertensive Therapy and Blood Pressure During Follow-up



**Table 2. Antihypertensive Therapy and Blood Pressure During Follow-up\***

	Blood Pressure Goal Intervention		Drug Intervention		
	Lower	Usual	Ramipril	Amlodipine	Metoprolol
Mean arterial pressure, mean (SE), mm Hg†	95 (8)	104 (7)	100 (9)	99 (8)	100 (9)
Systolic blood pressure, mean (SE), mm Hg†	128 (12)	141 (12)	135 (14)	133 (12)	135 (13)
Diastolic blood pressure, mean (SE), mm Hg†	78 (8)	85 (7)	82 (9)	81 (8)	81 (9)
Visits with mean arterial pressure in goal, %‡	51.6	39.2	44.1	48.9	44.7
Visits with mean arterial pressure of <107 mm Hg, %‡	81.3	64.3	71.5	76.5	72.0
Visits with systolic/diastolic blood pressure of <140/90, %‡	68.6	35.5	51.2	54.9	50.8
Visits with systolic/diastolic blood pressure of <125/75, %‡	24.7	6.2	16.2	14.4	14.9
Visits with assigned primary drug, %‡	81.7	80.1	76.8	83.4	83.6
Visits with high dose, %‡	62.8	45.0	53.5	54.6	53.6
Visits with crossover to 1 of other 2 classes, %‡	9.3	8.1	10.9	6.4	7.6
Total No. of drug classes, mean (SE)‡	3.04 (1.14)	2.39 (1.18)	2.66 (1.23)	2.65 (1.24)	2.79 (1.15)
Visits with level 2 (furosemide), %‡	82.2	66.6	74.0	70.8	76.4
Visits with level 3 (doxazosin), %‡	55.2	34.4	42.0	46.3	46.6
Visits with level 4 (clonidine), %‡	40.5	27.3	34.4	34.4	33.1
Visits with level 5 (minoxidil), %‡	34.9	22.7	27.5	24.1	32.3
Protocol visits held, %	90.3	87.5	88.0	88.7	89.8
GFRs performed, %	83.2	80.0	80.9	81.9	82.0

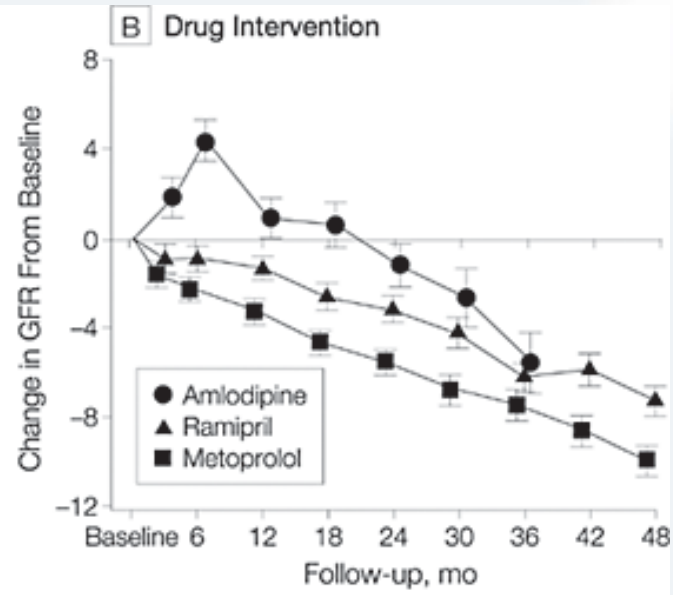
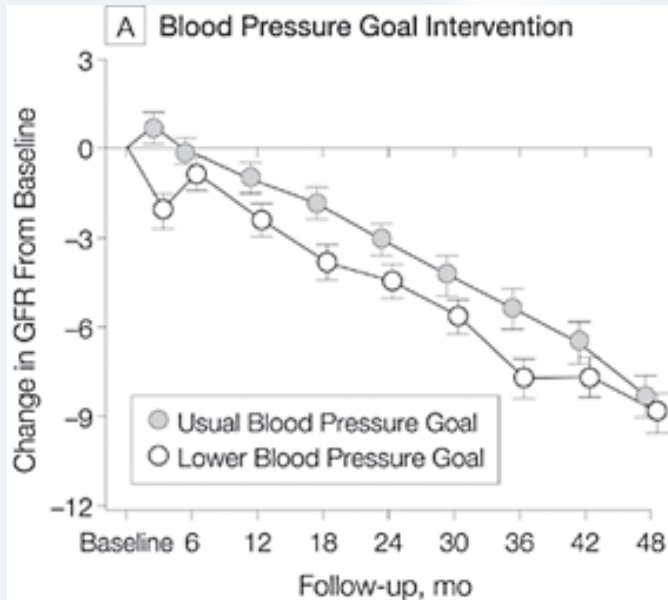
\*GFR indicates glomerular filtration rate.

†Blood pressure summaries include visits after 3 months and exclude GFR visits.

‡Medication summaries include all visits starting at month 1 and are censored on September 22, 2000, for the calcium channel blocker (amlodipine) group only.

Wright et al. AASK JAMA 2002

# Mean Change in Glomerular Filtration Rate by Randomized Group





- 1094 black patients with hypertensive chronic kidney disease were randomized to receive either intensive or standard blood-pressure control
- After completing the trial phase, patients were invited to enroll in a cohort phase in which the blood-pressure target was less than 130/80 mm Hg
- The primary clinical outcome in the cohort phase was the progression of chronic kidney disease, which was defined as a doubling of the serum creatinine level, a diagnosis of ESRD, or death
- Follow-up ranged from 8.8 to 12.2 years



Baseline Characteristics of 1094 Patients Assigned to Receive Intensive or Standard Blood-Pressure Control, According to the Level of Urinary Protein Excretion.

**Table 1.** Baseline Characteristics of 1094 Patients Assigned to Receive Intensive or Standard Blood-Pressure Control, According to the Level of Urinary Protein Excretion.\*

Variable	All Patients		Urinary Protein-to-Creatinine Ratio, $\leq 0.22$		Urinary Protein-to-Creatinine Ratio, $> 0.22$	
	Intensive Control (N=540)	Standard Control (N=554)	Intensive Control (N=357)	Standard Control (N=376)	Intensive Control (N=181)	Standard Control (N=176)
Age — yr	54.5±10.9	54.7±10.4	56.6±10.1	55.8±9.67	50.4±11.3	52.1±11.4
Female sex — no. (%)	206 (38.1)	219 (39.5)	147 (41.2)	149 (39.6)	59 (32.6)	70 (39.8)
Current smoker — no. (%)	182 (33.7)	139 (25.1)	117 (32.8)	87 (23.1)	64 (35.4)	51 (29.0)
Did not complete high school — no. (%)†	218 (40.4)	226 (40.9)	158 (44.3)	168 (44.8)	60 (33.3)	57 (32.4)
Weight — kg	89.5±20.9	89.4±20.5	87.4±19.7	88.0±20.1	93.7±22.6	92.4±21.1
Body-mass index‡	30.5±6.71	30.6±6.47	30.0±6.22	30.3±6.44	31.7±7.47	31.3±6.52
Estimated GFR (ml/min/1.73 m <sup>2</sup> )	48.1±13.9	46.8±14.0	51.5±13.2	50.7±12.3	41.4±12.7	38.5±13.6
Serum creatinine — mg/dl	1.98±0.70	2.02±0.70	1.79±0.58	1.80±0.50	2.35±0.77	2.48±0.83
Median urinary protein — g/day (interquartile range)	0.12 (0.04–0.55)	0.11 (0.04–0.59)	0.06 (0.03–0.12)	0.06 (0.04–0.12)	0.96 (0.54–1.99)	1.06 (0.63–2.08)
Median urinary protein-to-creatinine ratio (interquartile range)	0.08 (0.03–0.36)	0.08 (0.03–0.37)	0.04 (0.02–0.08)	0.04 (0.02–0.09)	0.58 (0.35–1.08)	0.73 (0.42–1.37)

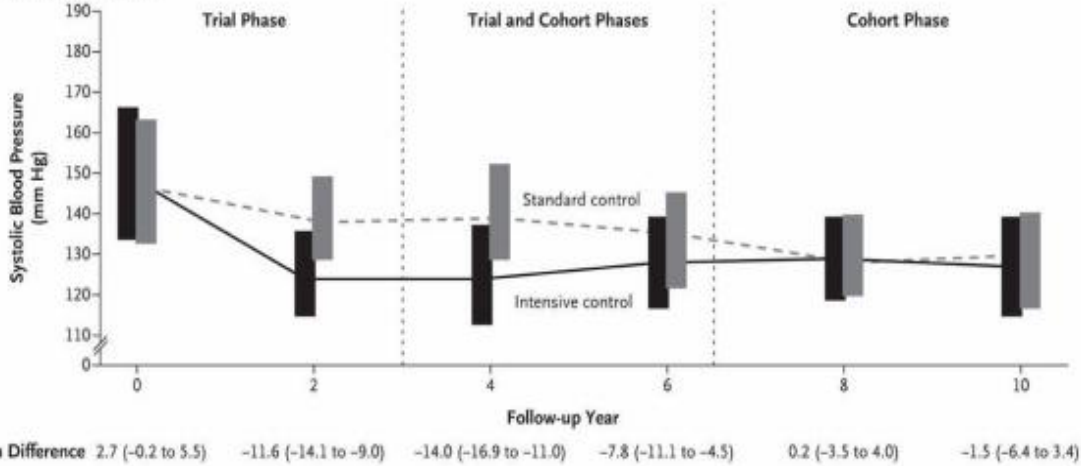
\* Plus-minus values are means ±SD. Four patients did not undergo baseline measurement of the urinary protein-to-creatinine ratio. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GFR denotes glomerular filtration rate.

† Data were missing for one patient in the intensive-control group and one in the standard-control group.

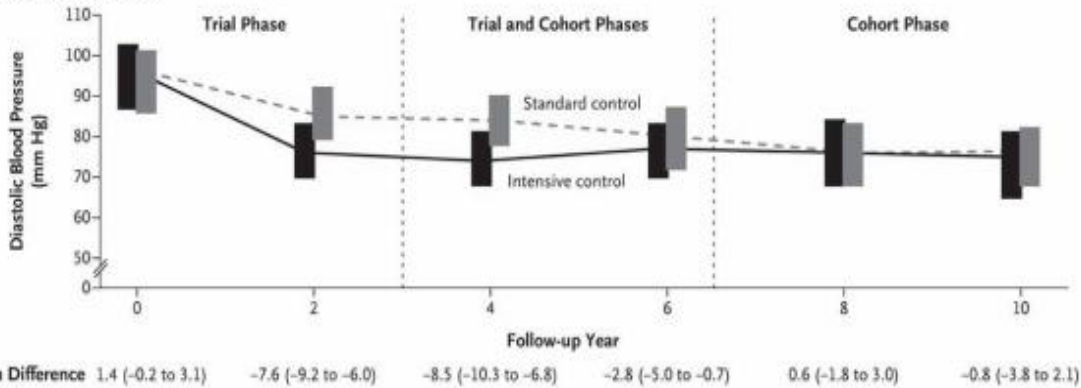
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.



**A Systolic Blood Pressure**



**B Diastolic Blood Pressure**



During the trial phase, the mean blood pressure was 130/78 mm Hg in the intensive-control group and 141/86 mm Hg in the standard-control group. During the cohort phase, corresponding mean blood pressures were 131/78 mm Hg and 134/78 mm Hg

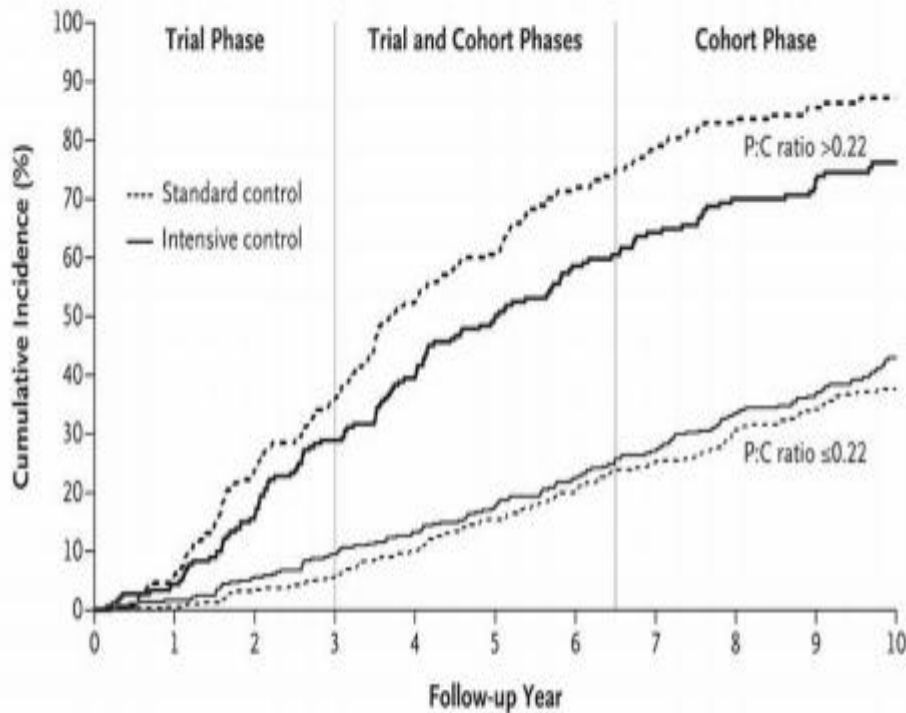
**Table 3. Event Rates for Primary and Secondary Outcomes, According to Study Phase and Proteinuria Status at Baseline.<sup>a</sup>**

Variable	Intensive Control		Standard Control		Hazard Ratio (95% CI)	P Value
	no./total no.	rate per 100 person-yr	no./total no.	rate per 100 person-yr		
<b>All patients</b>						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	159/540	7.0	169/554	7.3	0.88 (0.71–1.09)	0.24
Cohort phase	123/377	7.9	116/382	7.7	0.95 (0.74–1.23)	0.70
Both phases	282/540	7.3	285/554	7.5	0.91 (0.77–1.08)	0.27
Doubling of serum creatinine level or ESRD						
Trial phase	121/540	5.3	125/554	5.4	0.91 (0.71–1.18)	0.49
Cohort phase	92/377	5.9	84/382	5.5	0.99 (0.73–1.33)	0.95
Both phases	213/540	5.5	209/554	5.5	0.95 (0.78–1.15)	0.59
ESRD or death						
Trial phase	124/540	5.3	140/554	5.9	0.84 (0.66–1.07)	0.16
Cohort phase	114/412	6.4	116/411	6.9	0.86 (0.67–1.12)	0.27
Both phases	238/540	5.8	256/554	6.3	0.85 (0.71–1.02)	0.08
<b>Patients with baseline urinary protein-to-creatinine ratio ≤0.22</b>						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	64/357	4.0	61/376	3.6	1.14 (0.80–1.63)	0.46
Cohort phase	81/290	6.5	74/312	5.6	1.21 (0.88–1.66)	0.24
Both phases	145/357	5.1	135/376	4.5	1.18 (0.93–1.50)	0.16
Doubling of serum creatinine level or ESRD						
Trial phase	42/357	2.6	34/376	2.0	1.44 (0.91–2.26)	0.12
Cohort phase	56/290	4.5	49/312	3.7	1.36 (0.92–2.00)	0.12
Both phases	98/357	3.4	83/376	2.7	1.39 (1.04–1.87)	0.03
ESRD or death						
Trial phase	47/357	2.9	50/376	2.9	0.98 (0.66–1.47)	0.94
Cohort phase	72/307	5.2	62/323	4.3	1.22 (0.87–1.72)	0.25
Both phases	119/357	3.9	112/376	3.6	1.12 (0.87–1.45)	0.39
<b>Patients with baseline urinary protein-to-creatinine ratio &gt;0.22</b>						
Doubling of serum creatinine level, ESRD, or death						
Trial phase	94/181	13.9	108/176	18.3	0.74 (0.56–0.99)	0.04
Cohort phase	42/86	13.7	41/68	21.1	0.66 (0.43–1.03)	0.07
Both phases	136/181	13.8	149/176	19.0	0.73 (0.58–0.93)	0.01
Doubling of serum creatinine level or ESRD						
Trial phase	78/181	11.5	91/176	15.4	0.76 (0.55–1.04)	0.08
Cohort phase	36/86	11.8	35/68	18.0	0.68 (0.43–1.09)	0.11
Both phases	114/181	11.6	126/176	16.1	0.76 (0.58–0.99)	0.04
ESRD or death						
Trial phase	76/181	10.6	90/176	14.3	0.76 (0.56–1.04)	0.09
Cohort phase	42/104	11.0	53/86	20.3	0.55 (0.37–0.84)	0.005
Both phases	118/181	10.8	143/176	16.1	0.67 (0.52–0.87)	0.002

<sup>a</sup> Hazard ratios and P values are for the comparison between the intensive-control group and the standard-control group. Hazard ratios have been adjusted for five prespecified baseline factors (log-transformed urinary protein excretion, age, sex, presence or absence of a history of heart disease, and baseline mean arterial pressure), along with a linear interaction term between the log-transformed baseline urinary protein-to-creatinine ratio and follow-up time. ESRD denotes end-stage renal disease.



Event Rates for Primary and Secondary Outcomes, According to Study Phase and Proteinuria Status at Baseline.



**P:C Ratio >0.22**

Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25

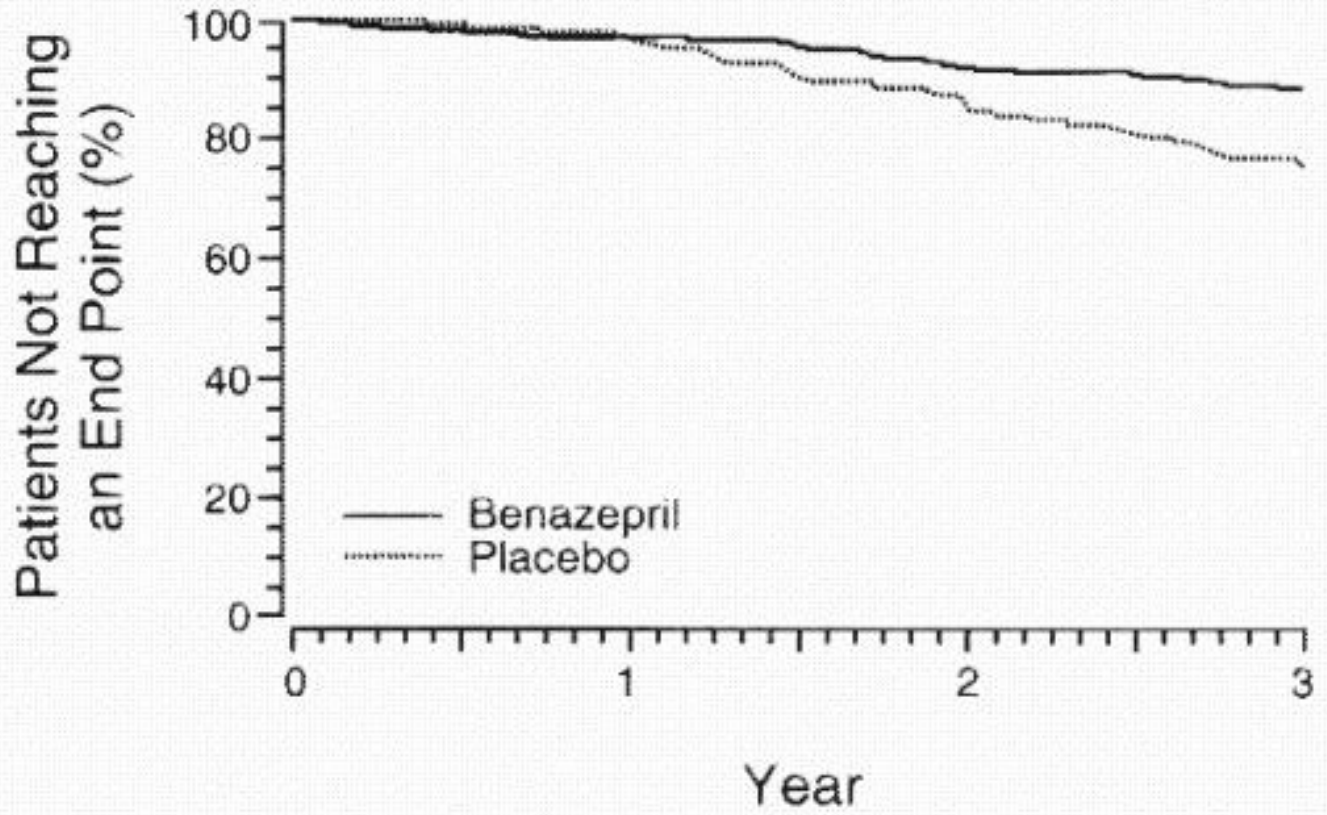
**P:C Ratio ≤0.22**

Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

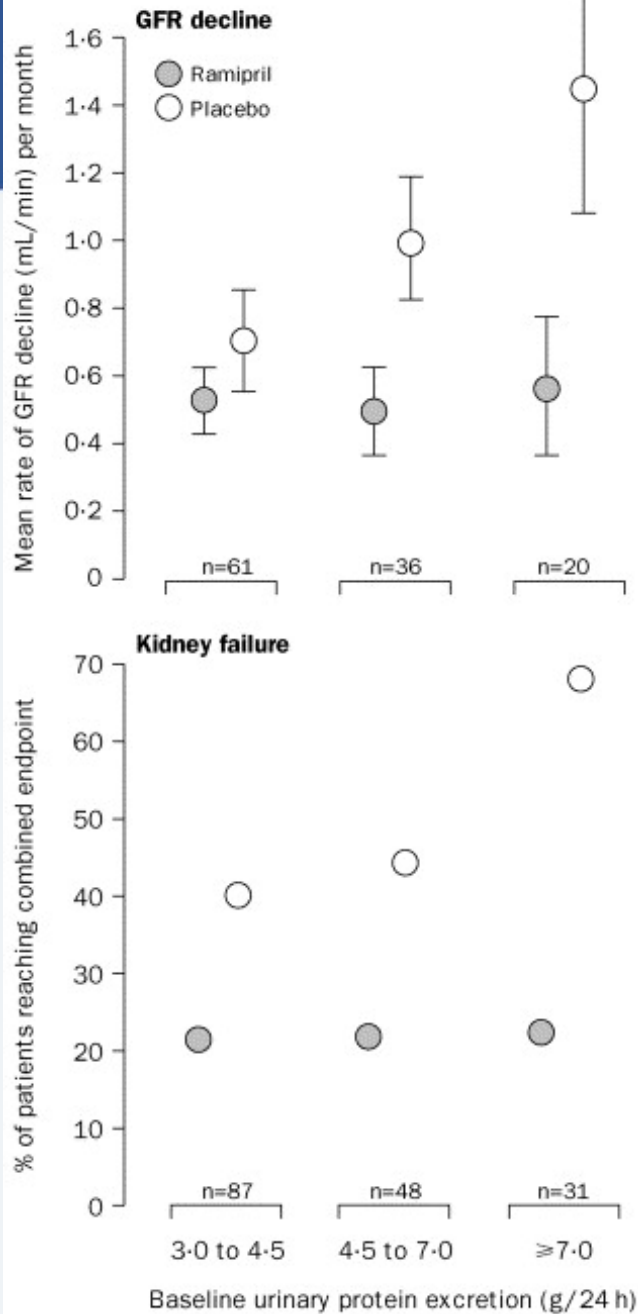
Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status. Among patients with baseline proteinuria, which was defined as a urinary protein-to-creatinine ratio (P:C) of more than 0.22, those who received intensive blood-pressure control had a significantly lower cumulative incidence of the composite primary outcome (a doubling of the serum creatinine level, end-stage renal disease, or death) than those who received standard blood-pressure control (hazard ratio in the intensive-control group, 0.73; 95% confidence interval [CI], 0.58 to 0.93; P=0.01). However, the between-group difference was not significant among patients with a P:C of 0.22 or less (hazard ratio, 1.18; 95% CI, 0.93 to 1.50; P=0.16). The values at the bottom of the graph are numbers of patients.



# Evidence for RAAS blockade in kidney disease



NO. OF PATIENTS							
Benazepril	300	275	259	252	230	219	82
Placebo	283	252	236	217	198	179	53



Rate of decline in GFR and percentage risk of progression of nephropathy (combined endpoint=doubling of baseline serum creatinine or endstage renal failure) in two treatment groups according to baseline urinary protein excretion



**Table 4. Analyses of Clinical Event Composite Outcomes\***

Outcome§	Lower vs Usual Blood Pressure Goal Intervention		Drug Intervention					
			Ramipril vs Metoprolol		Metoprolol vs Amlodipine		Ramipril vs Amlodipine†	
	% Risk Reduction (95% Confidence Interval)‡	P Value	% Risk Reduction (95% Confidence Interval)‡	P Value	% Risk Reduction (95% Confidence Interval)‡	P Value	% Risk Reduction (95% Confidence Interval)‡	P Value
GFR event, ESRD, or death	2 (-22 to 21)	.85	22 (1 to 38)	.04	20 (-10 to 41)	.17	38 (14 to 56)	.004
GFR event or ESRD	-2 (-31 to 20)	.87	22 (-2 to 41)	.07	24 (-9 to 47)	.13	40 (14 to 59)	.006
ESRD or death	12 (-13 to 32)	.31	21 (-5 to 40)	.11	42 (17 to 60)	.003	49 (26 to 65)	<.001
ESRD alone	6 (-29 to 31)	.72	22 (-10 to 45)	.16	59 (36 to 74)	<.001	59 (36 to 74)	<.001

\*GFR indicates glomerular filtration rate; ESRD, end-stage renal disease.

†Secondary comparison described in previous publication.<sup>25</sup>

‡All risk reductions adjusted for prespecified covariates: baseline proteinuria, mean arterial pressure, sex, history of heart disease, and age. Risk difference for ESRD or death composite and ESRD alone also adjusted for baseline GFR.

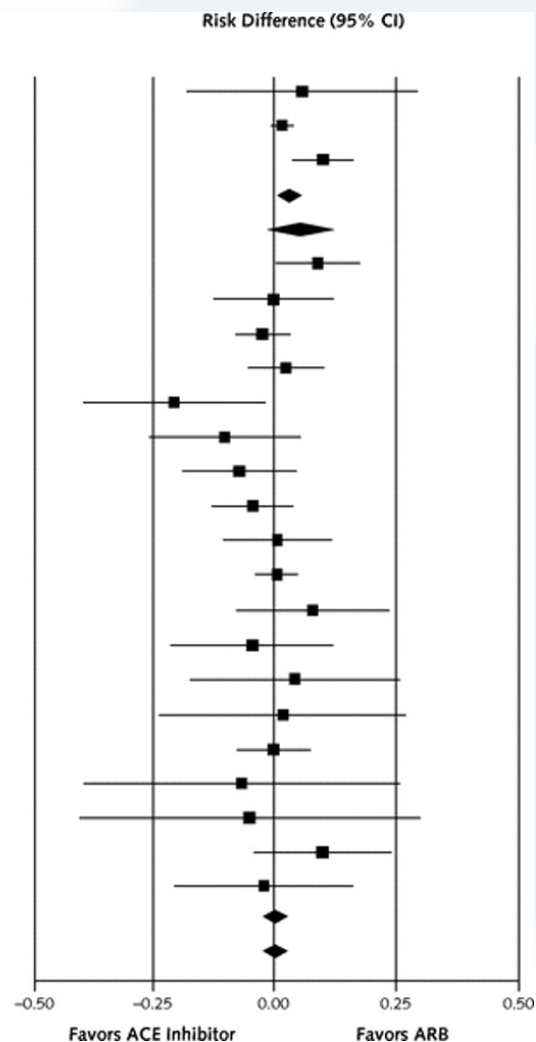
§GFR event, ESRD, or death: main secondary composite clinical outcome with 340 events, including 179 declining GFR events, 84 additional participants with ESRD events, and 77 deaths; GFR event or ESRD: composite end point with 263 events, including 179 declining GFR events and 84 additional participants with ESRD events; ESRD or death: composite end point with 251 events, including 171 ESRD events and 80 deaths; and ESRD alone: end point with 171 events and deaths censored in this analysis.



ACE inh, ARB or both?

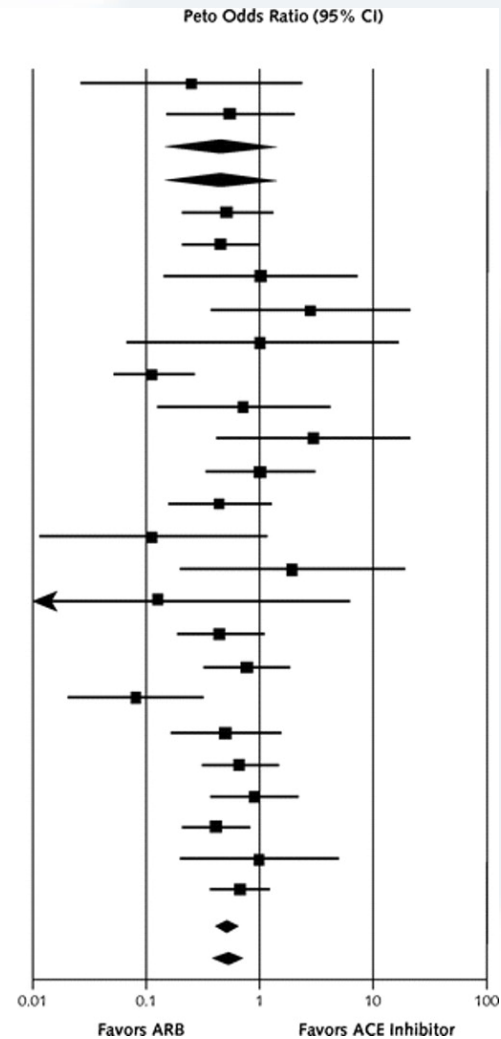
# Successful monotherapy: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs). The first group is observational studies and the second group is randomized, controlled trials

Study, Year (Reference)	Time Point, wk	Events/Total, n/n	
		ARB	ACE inhibitor
Verdecchia et al., 2000 (68)	172	12/22	32/66
Mazzaglia et al., 2005 (83)	52	348/1382	1072/4602
Hasford et al., 2002 (80)	52	394/754	140/333
Fixed			
Random			
Saito et al., 2004 (60)	26	66/200	51/214
Cuspidi et al., 2002 (34)	48	53/115	57/124
Ruilope et al., 2001 (59)	12	153/168	152/163
Larochelle et al., 1997 (47)	12	11/121	4/61
Lacourcière et al., 2000 (46)	52	20/52	30/51
Ruff et al., 1996 (69)	12	3/50	4/25
Townsend et al., 1995 (66)	12	62/132	72/136
Neutel et al., 1999 (55)	48	169/385	93/193
Karlberg et al., 1999 (43)	26	89/139	88/139
Malacco et al., 2004 (49)	16	479/604	479/609
Fogari et al., 2004 (73)	16	45/75	39/75
Rosei et al., 2005 (58)	24	39/66	40/63
Ghiadoni et al., 2003 (42)	26	23/29	21/28
Uchiyama-Tanaka et al., 2005 (67)	52	14/18	19/25
Argenziano and Trimarco, 1999 (27)	26	182/264	182/264
Robles et al., 2004 (82)	12	10/15	11/15
Kavgaci et al., 2002 (44)	26	13/20	7/10
Mogensen et al., 2000 (53)	24	54/66	46/64
Eguchi et al., 2003 (37)	12	29/37	29/36
Fixed			
Random			

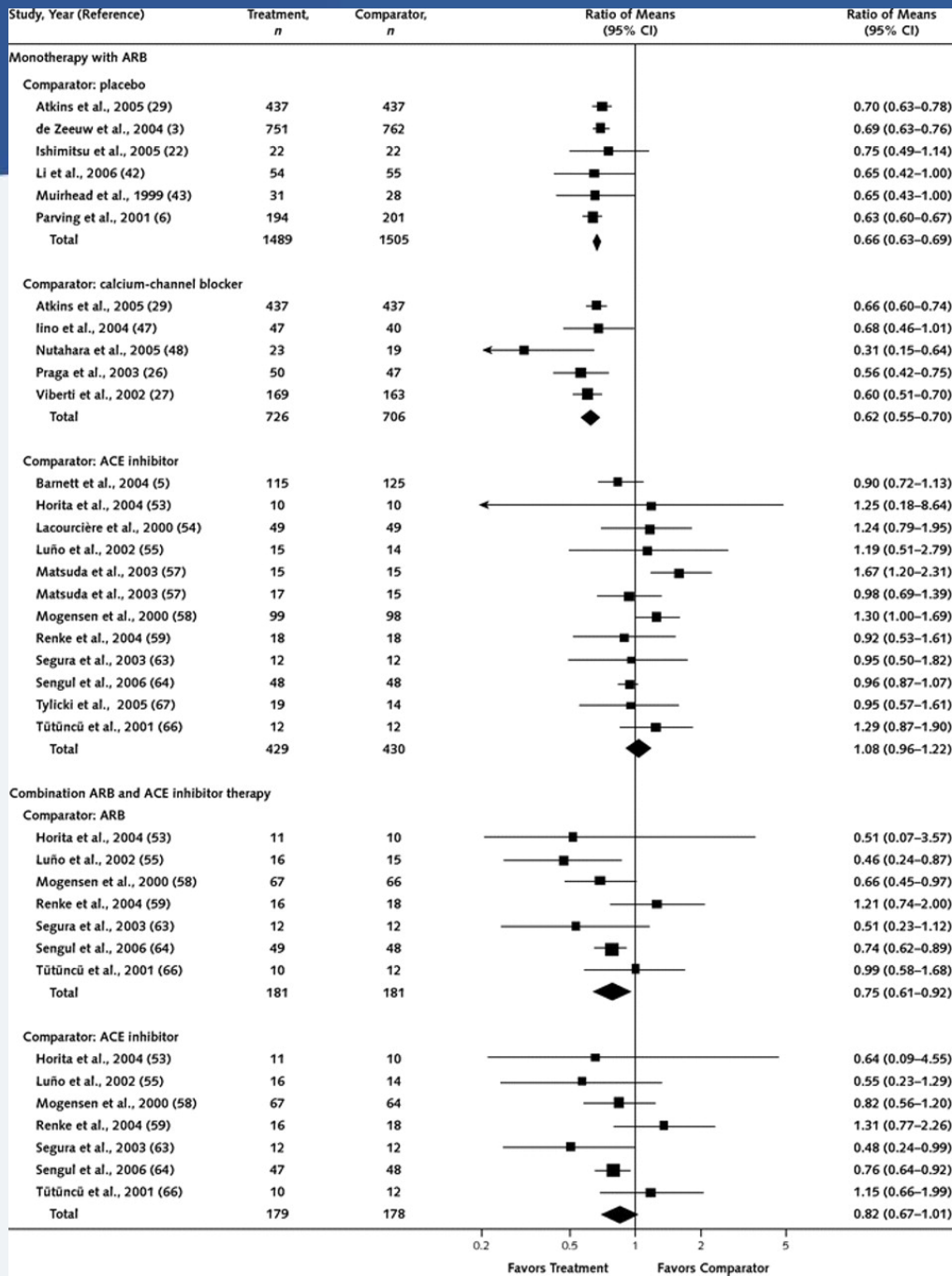


# Withdrawals due to adverse events: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs). The first group is observational studies and the second group is randomized, controlled trials.

Study, Year (Reference)	Events/Total, n/n	
	ARB	ACE inhibitor
Avanza et al., 2000 (28)	0/17	4/45
Verdecchia et al., 2000 (68)	2/22	12/66
Fixed		
Random		
Cuspidi et al., 2002 (34)	6/115	13/124
McInnes et al., 2000 (51)	14/237	14/116
Mogensen et al., 2000 (53)	2/66	2/64
Schram et al., 2005 (62)	3/24	1/22
Elliott, 1999 (38)	1/264	1/264
Koylan et al., 2005 (45)	0/337	23/298
Coca et al., 2002 (33)	2/111	3/115
Mimran et al., 1998 (52)	3/98	1/102
Mallion et al., 1995 (75)	10/109	5/54
Roca-Cusachs et al., 1997 (78)	4/192	10/204
De Rosa et al., 2002 (35)	0/26	3/24
Lacourcière et al., 2000 (46)	2/52	1/51
Shand, 2000 (63)	0/15	1/14
Tikkanen et al., 1995 (70)	6/202	14/205
Townsend et al., 1995 (66)	9/132	12/136
Neutel et al., 1999 (55)	1/385	8/193
Amerena et al., 2002 (72)	4/264	8/258
Karlberg et al., 1999 (43)	11/139	16/139
Black et al., 1997 (30)	14/364	8/187
Malacco et al., 2004 (49)	9/604	23/609
Naidoo et al., 1999 (54)	3/176	3/173
Barnett et al., 2004 (29)	20/120	30/130
Fixed		
Random		



# Reduction in proteinuria at 5 to 12 months



# ON TARGET

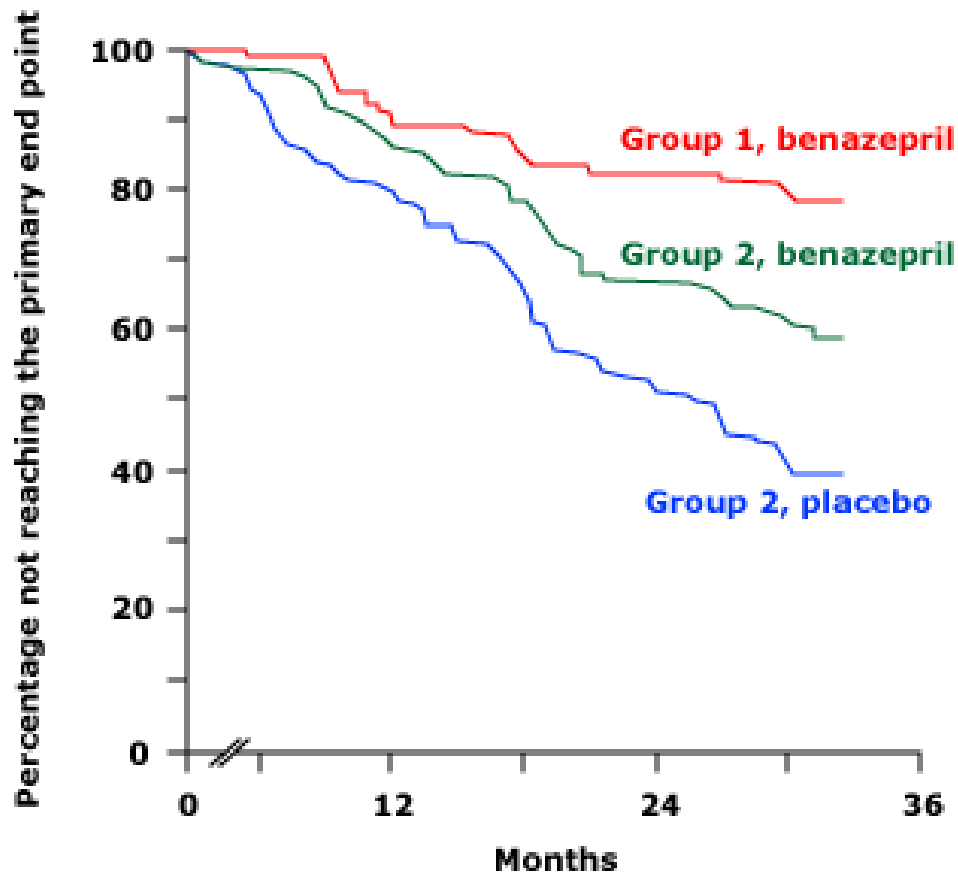
- **After a 3-week run-in period, 25 620 participants were randomly assigned to ramipril 10 mg a day, telmisartan 80 mg a day, or to a combination of both drugs**
- **The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death**



- **The number of events for the composite primary outcome was similar for telmisartan and ramipril hazard ratio but was increased with combination therapy (HR 1.09, 1.01–1.18,  $p=0.037$ )**
- **And authors concluded that even though combination therapy reduces proteinuria to a greater extent than monotherapy, it worsens major renal outcomes**



Use in advanced kidney disease



Group 1 had a serum creatinine level of 1.5 to 3.0 mg/dL (141 patients), and group 2 had a serum creatinine level of 3.1 to 5.0 mg/dL (281 patients) at baseline. Significantly fewer group 2 patients treated with benazepril reached the primary end point (41 versus 60 percent with placebo), resulting in a overall risk reduction of 43 percent with active therapy. Fewer patients in group 1 (who were all treated with benazepril) reached the primary end point (22 percent).

# ACCOMPLISH trial



- **11 506 patients with hypertension who were at high risk for cardiovascular events were randomly to receive benazepril (20 mg) plus amlodipine (5 mg) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg), orally once daily**
- **Progression of chronic kidney disease, a prespecified endpoint, was defined as doubling of serum creatinine concentration or end-stage renal disease**



- **The trial was terminated early (mean follow-up 2.9 years) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide**
- **There were 113 (2%) events of chronic kidney disease progression in the benazepril plus amlodipine group compared with 215 (3.7%) in the benazepril plus hydrochlorothiazide group (HR 0.52, 0.41–0.65,  $p < 0.0001$ )**



# HTN management in dialysis patients



- The blood pressure targets for hemodialysis patients are not currently clear
- Routine peri-dialytic BP recordings performed by a dialysis unit staff shortly before and after the HD session are highly variable and poorly reproducible
- Achieving KDOQI-recommended peri-dialytic BP targets of  $<140/90$  mmHg pre-dialytic and  $<130/80$  mmHg post-dialytic is associated with increased frequency of intra-dialytic hypotension
- UK Renal Registry indicates that in 2008, only 43.1% and 46.8% of HD patients achieved those goals of pre-dialytic and post-dialytic BP respectively



- Observational studies in HD patients have shown an increase in mortality with low or even normal pre-dialytic BP levels
- Chang et al. conducted a secondary analysis of data from the HEMO Study, a randomized trial in prevalent HD patients
- In this study, a pre-dialysis systolic BP  $<120$  mmHg was associated with a higher risk of mortality compared with the reference group with a pre-dialysis systolic BP between 140 and 159 mmHg
- Interestingly, even higher pre-dialysis systolic BP was not associated with higher risk of mortality



- Goal pre-dialysis systolic BP between 140 and 160 mmHg and a pre-dialysis diastolic BP between 70 and 90 mmHg were recommended
- For postdialysis, goal systolic BP at 135–154 mmHg, and diastolic BP was still at 70–90 mmHg



- The reproducibility of BP measurements follows the following order: home BP monitoring > ABPM >> pre-dialysis BP > post-dialysis BP
- However measurement of BP during each third of the inter-dialytic interval gives the best precision in predicting ambulatory BP



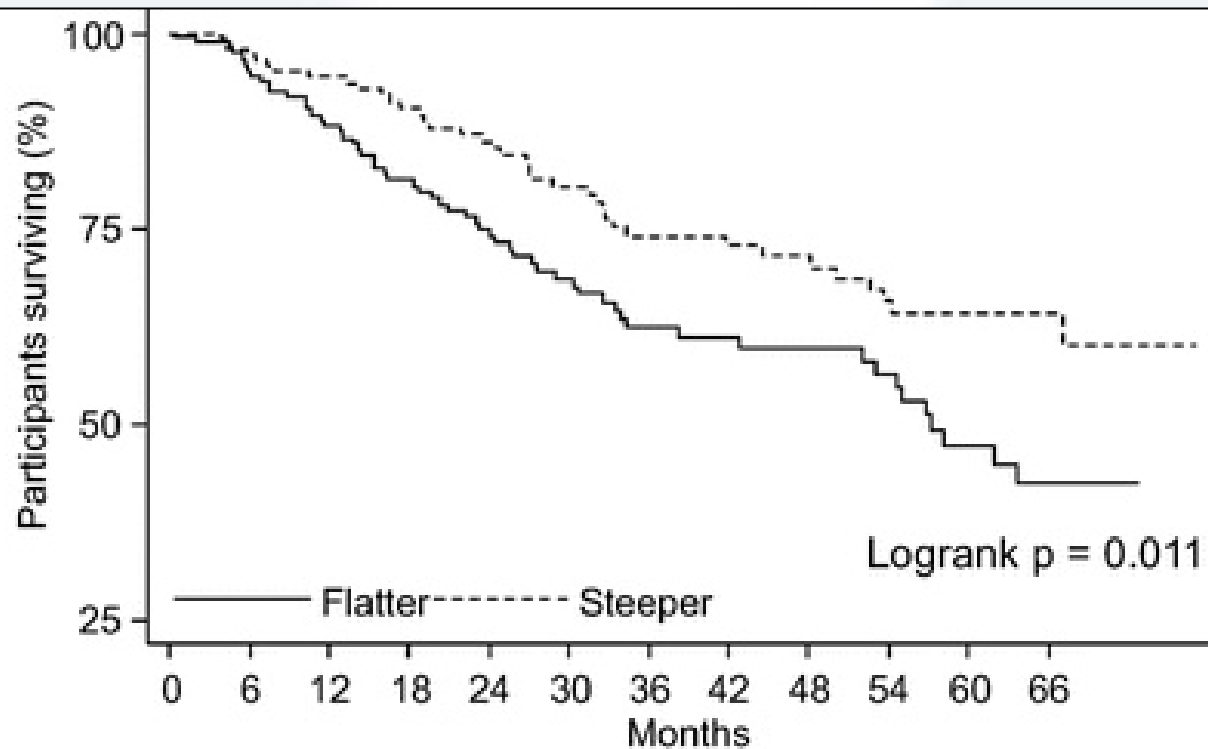
- A meta-analysis of eight relevant trials, which provided data for 1679 patients and 495 cardiovascular events, was performed
- In actively treated patients, reduction of blood pressure was associated with lower risks of cardiovascular events, all-cause mortality, and cardiovascular mortality than control regimens



- In patients with ESRD treated with dialysis, a direct relationship between volume status and BP has long been recognized
- Dry-weight reduction by additional ultrafiltration combined with obsessive daily dietary salt restriction should be recommended to hypertensive HD patients even in the absence of clinical signs of volume overload



- Restricting dialysate sodium can also reduce thirst, limit inter-dialytic weight gain and assist the achievement of dry-weight
- Strict volume control makes antihypertensive drug treatment often unnecessary and even dangerous



Number at risk

Flatter slope	155	136	121	103	87	73	52	44	39	34	22	15
Steeper slope	154	138	123	111	97	80	66	55	51	43	29	18

Kaplan-Meier survival curves for RPV slope and mortality. The log-rank test demonstrated a significant difference in survival between medians of RPV slopes. Multivariable adjustments did not remove the statistical significance

# Conclusions

- HTN is a questionable cause of kidney disease especially in African Americans
- BP goal should not be lower than 140/80 in pts with CKD unless they have more than 1 g of proteinuria
- ACE inh or ARB are considered first line agents but evidence supports their use only in proteinuric kidney disease
- Ace inh continues to affect outcomes even if used in advanced CKD
- Combination ACE inh and ARB is not supported by evidence
- Volume and dry weight should be the focus of BP control in dialysis patients

