

# **KDIGO conference on high CV risk associated with CKD**

## **The role of BP in CKD stage 1-4**

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# **KDIGO conference on high CV risk associated with CKD**

## **The role of BP in CKD stage 1-4**

**What evidence is available if and to what degree BP contributes to high CV risk in CKD?**

- Little epidemiological evidence to our knowledge
- 3 RCT's in CKD with different BP goals and reports of CV outcomes (but powered for renal outcomes)
- Several RCT's in CKD with different BP-drugs and slightly different BP and reports of CV outcomes (but powered for renal outcomes)
- Few RCT's in hypertension and reports of CV outcomes in CKD subgroups (HOPE, ONTARGET, TRANSCEND)

# Relationship Between Blood Pressure Category and Incidence of Stroke and Myocardial Infarction in an Urban Japanese Population With and Without Chronic Kidney Disease

## The Suita Study

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Akira Okayama, MD, PhD; Yuhei Kawano, MD, PhD

**Background and Purpose**—Chronic kidney disease (CKD) is increasingly recognized as an independent risk factor for stroke and myocardial infarction (MI). Few studies, however, have examined the relationship between blood pressure (BP) category and these diseases in subjects with and without CKD.

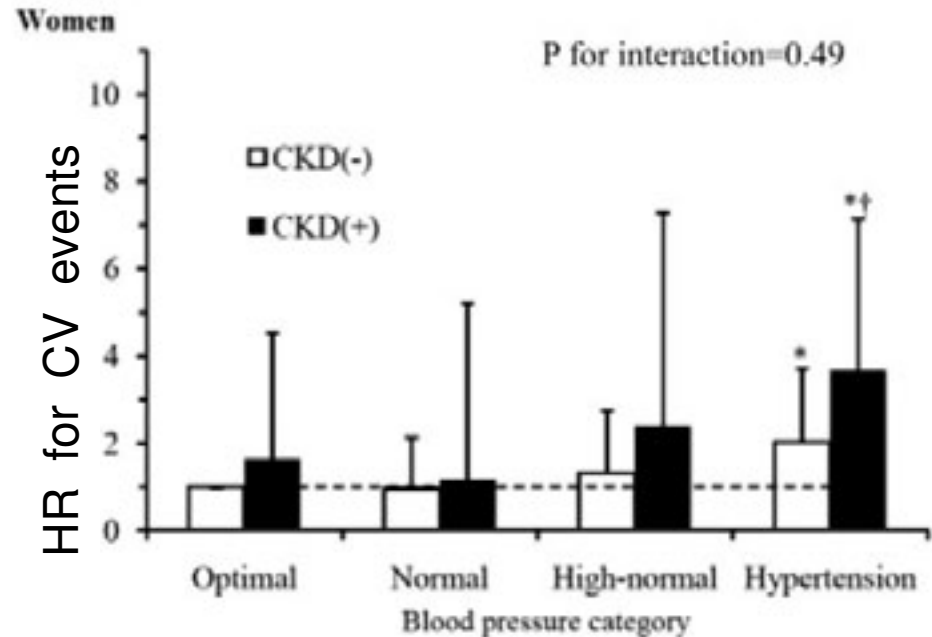
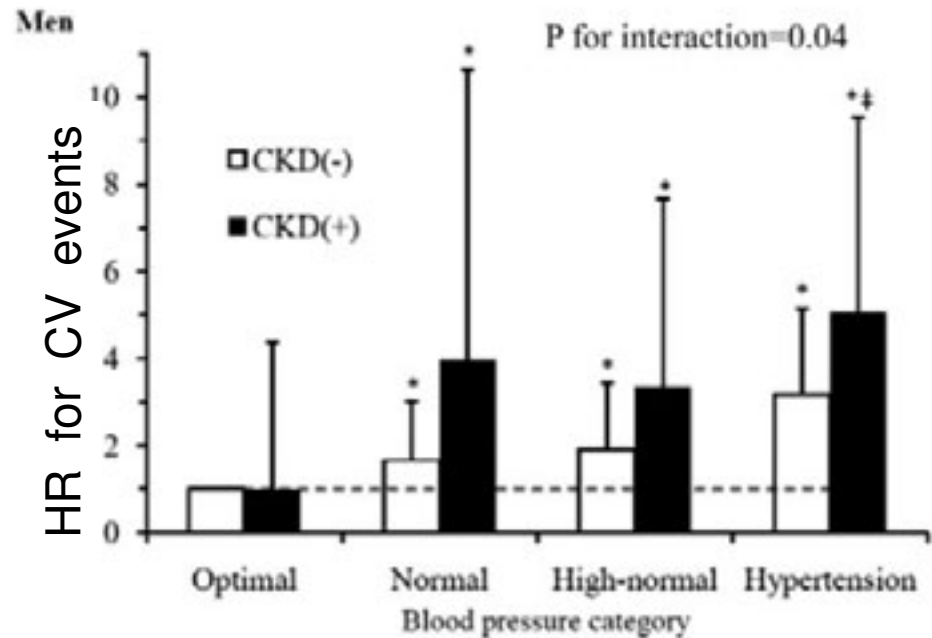
**Methods**—We studied 5494 Japanese individuals (ages 30 to 79, without stroke or MI at baseline) who completed a baseline survey and received follow-up through December 2005. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation modified by the Japanese coefficient. CKD was defined as an estimated GFR  $<60$  mL/min/1.73m<sup>2</sup>. BP categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

**Results**—In 64 395 person-years of follow-up, we documented 346 incidences of cardiovascular diseases (CVD; 213 strokes and 133 MI events). Compared with the GFR ( $\geq 90$  mL/min/1.73m<sup>2</sup>) group, the hazard ratios (95% confidential intervals) for stroke were 1.9 (1.3 to 3.0) in the GFR 50 to 59 mL/min/1.73m<sup>2</sup> group and 2.2 (1.2 to 4.1) in the GFR  $<50$  mL/min/1.73m<sup>2</sup> group. Results for cerebral infarction were similar. Compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD and stroke; however the impact of each BP category on CVD (*P* for interaction: 0.04 in men, 0.49 in women) and stroke (0.03 in men, 0.90 in women) was more evident in men with CKD.

**Conclusions**—CKD may increase the association of BP and CVD in a Japanese urban population. (*Stroke*. 2009;40:2674-2679.)

## Suita study

- Screening 1989-94, evaluation 2005
- 64,300 person-years
- 5-25% with CKD3 (eGFR), depending on age and gender
- 346 CV events: 213 strokes, 133 MI
- Population attributable risk of CKD for CV events: 9% in men, 17% in women



# **AASK: African American Study of Kidney disease and hypertension (N = 1,098)**

GFR 20-65 ml/min (**mean 46**), U<sub>protV</sub> < 3g/d, 3 – 6.4 y F/U

Comparison of two **goal BP's**

102-107 vs  $\leq 92$  MAP (mmHg)

• **Achieved BP** 141/85 vs 128/78 mmHg :

No difference in events rates (death, dialysis, doubling of serum creatinine) for BP groups

# AASK trial: Effects of BP on CV outcomes and mortality

**Table 5.** Rates of Adverse Events or Symptoms During Follow-up\*

	Blood Pressure Goal Intervention, %	
	Lower	Usual
Adverse event		
All-cause mortality	1.6	1.9
Cardiovascular mortality	0.6	0.7
Cardiovascular event†	2.3	2.7

HR for CV event +	0.84, CI 0.61-1.16
HR for stroke (n=55)	0.92 0.55-1.54
HR for CHF (n=50)	1.20 0.70-2.07
HR for CAD (n=42)	0.85 0.47-1.54
HR for all above	1.06 0.76-1.4

+CV event = first CV hospitalization or CV death; events as % / patient-year

Wright et al, JAMA 2002, 288:2421-31

## REIN 2 study (N = 338)

GFR 20-65 ml/min (mean 34), UprotV 1-10 g/d,

3 year F/U

Comparison of two goal BP's

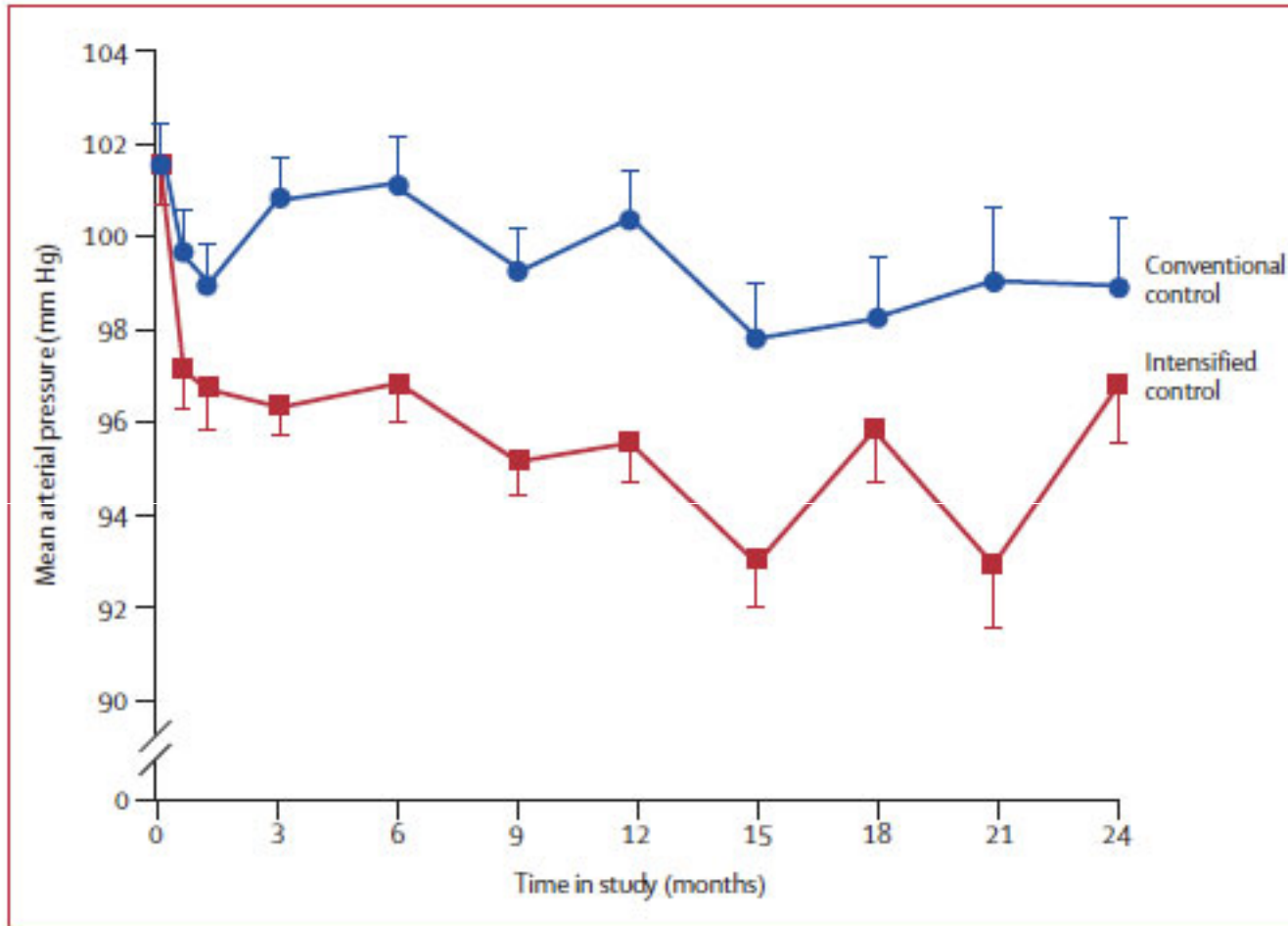
< 90 diastolic vs < 130 / < 80 (mmHg).

• **Achieved BP** 134/82 vs 130/80 mmHg.

No difference in events rates (dialysis, doubling of serum creatinine) for BP groups, independent of UprotV

All patients on ramipril, lower goal on felodipine

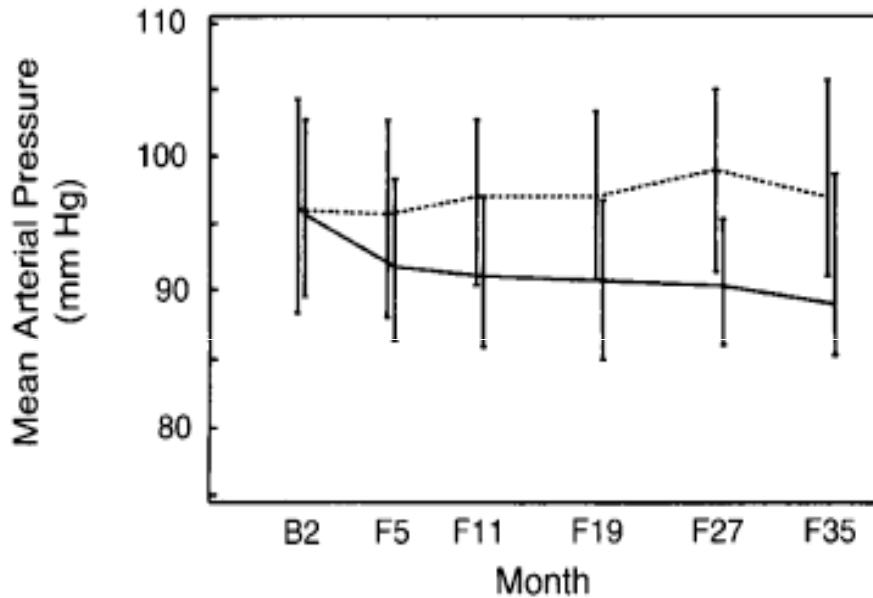
# REIN-2 trial: Effects on BP



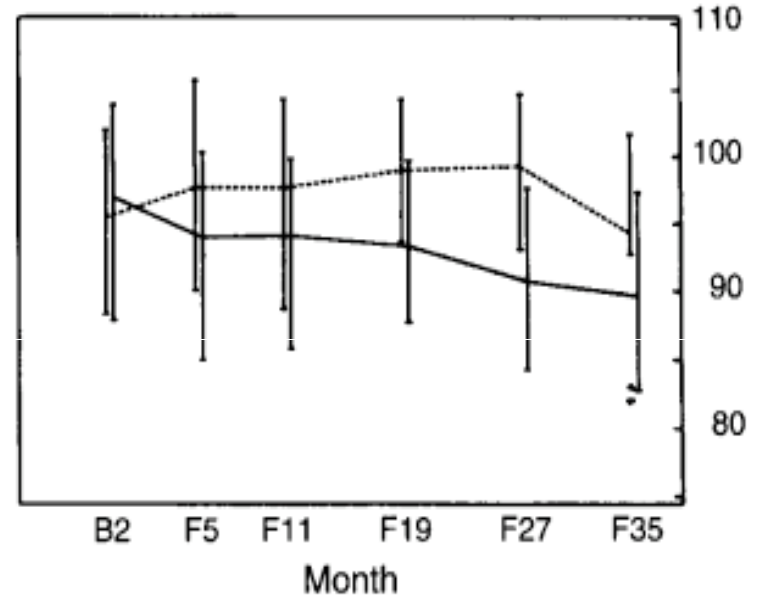
CV events and death: 30 vs 39,  
conventional vs intensified, NS Ruggenenti, Lancet 2005; 365:939



# MDRD trial: Effects on BP



Usual pressure: 283 249 242 203 119 54  
 Low pressure: 300 277 260 209 139 67



Usual pressure: 122 113 103 76 55 29  
 Low pressure: 132 119 116 77 55 28

30 death, 18/30 CV death, no difference reported between BP groups

Klahr S et al, NEJM 1994;330:877

# **Trials with different Meds but identical BP goals, diabetes + hypertension, CKD II-IV**

<b><u>STUDY</u></b>	<b><u>BP (mmHg)</u></b>	<b><u>outcome (n)</u></b>	<b><u>stats</u></b>
RENAAL	142/74 vs 140/74	death (313)	-2% p=0.88
IDNT	144/80 vs 140/77	death (180)	-6% p=0.69
CSG	140/86 vs 137/85	death (22)	-45% p>0.5

# **Trials with different Meds but identical BP goals, diabetes + hypertension, CKD II-IV**

<b><u>STUDY</u></b>	<b><u>BP (mmHg)</u></b>	<b><u>outcome (n)</u></b>	<b><u>stats</u></b>
RENAAL	142/74 vs 140/74	CVdeath (113)	-10% p=0.26
IDNT	144/80 vs 140/77	CVdeath (83)	-21% p>0.2

# **Trials with different Meds but identical BP goals, diabetes + hypertension, CKD II-IV**

<b>STUDY</b>	<b>BP (mmHg)</b>	<b>outcome (n)</b>	<b>stats</b>
RENAAL	142/74 vs 140/74	CHF (216)	-32% p=0.005
IDNT	144/80 vs 140/77	CHF (193)	-28% p=0.048

# **Trials with different Meds but identical BP goals, diabetes + hypertension, CKD II-IV**

<b><u>STUDY</u></b>	<b><u>BP (mmHg)</u></b>	<b><u>outcome (n)</u></b>	<b><u>stats</u></b>
RENAAL	142/74 vs 140/74	MI (118)	-28% p=0.08
IDNT	144/80 vs 140/77	MI (99)	-10% p>0.2

# **Trials with different Meds but identical BP goals, **no** diabetes but hypertension, CKD II-IV**

<b><u>STUDY</u></b>	<b><u>BP (mmHg)</u></b>	<b><u>outcome (n)</u></b>	<b><u>stats</u></b>
AIPRI	142/87 vs 137/85	death (9)	+49% p=0.04
HOU	126/75 vs 126/75	death (1)	
REIN-1	144/88 vs 145/90	death (3)	

For other CV outcomes too few events (<10)

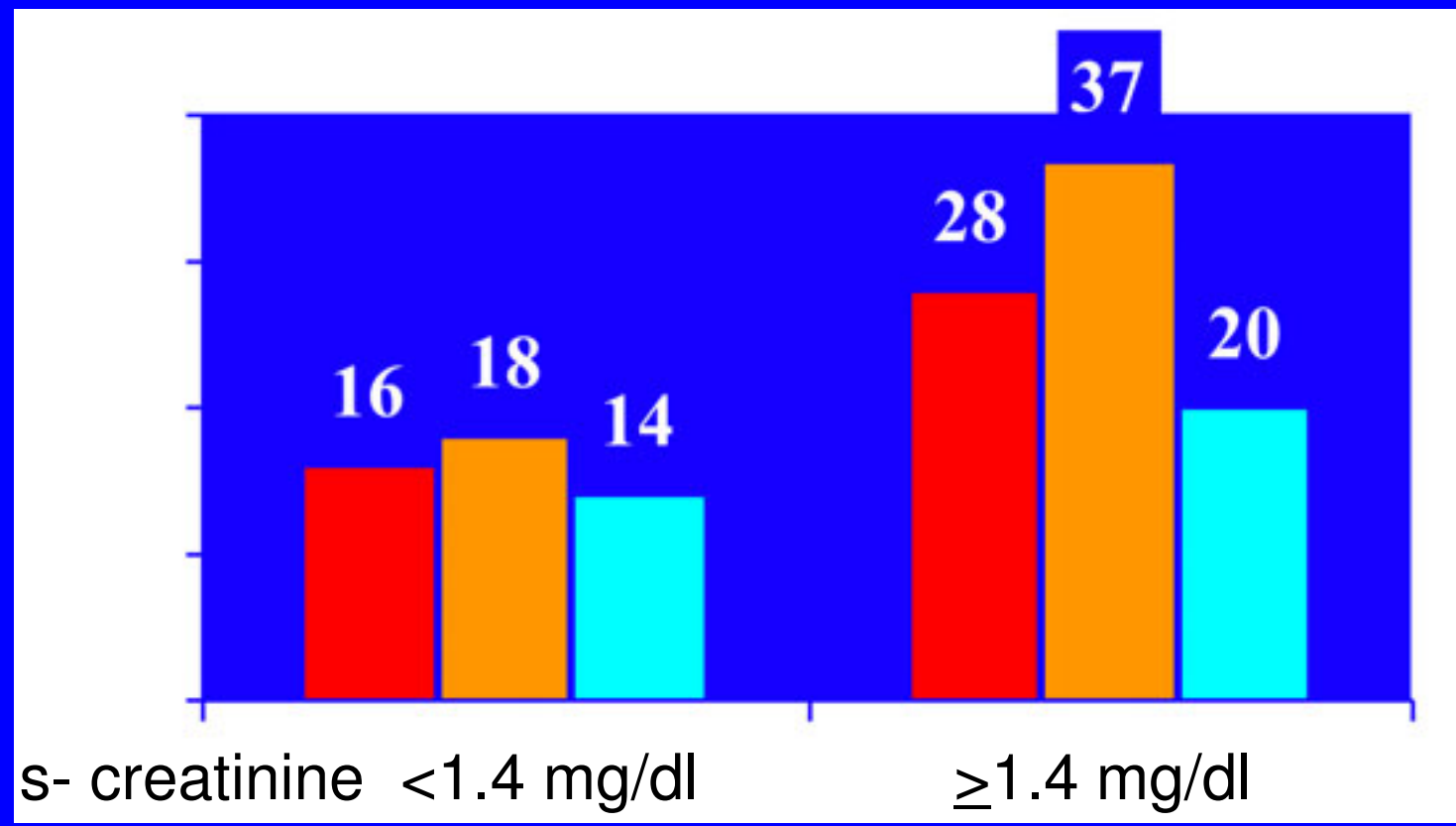
*Hope*

# Main outcomes in patients with CKD

**Difference in BP plac/rami: 4/2 mmHg**

## CV Death

Events (per 1000 pt-yrs)



■ all      ■ Placebo      ■ Ramipril 10 gm/d

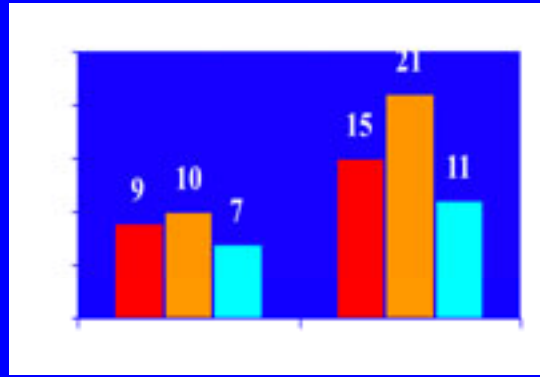
*Hope*

# Main outcomes in patients with CKD (serum creatinine $\geq 1.4$ mg/dl)

Mann, Gerstein & Yusuf, Ann Int Med 2001

Events (per 1000 pt-yrs)

Heart Fail. Hosp.

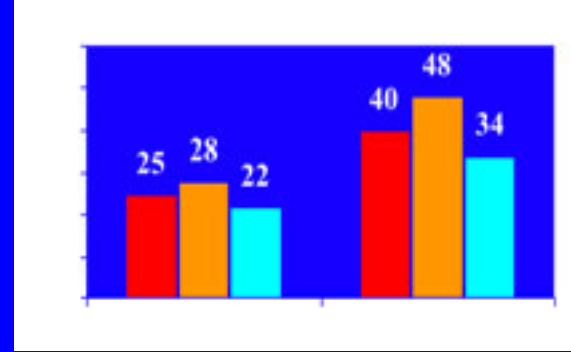


< 1.4

$\geq 1.4$

- All
- Placebo
- Ramipril

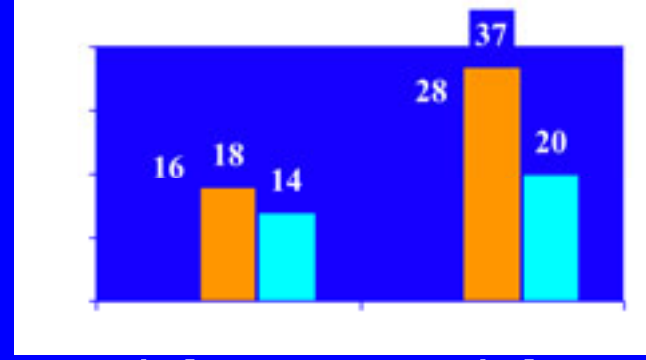
MI



< 1.4

$\geq 1.4$

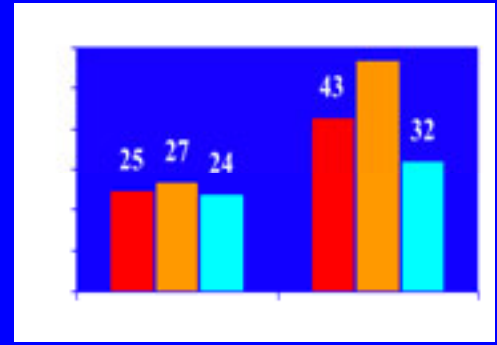
CV Death



< 1.4

$\geq 1.4$

All Death



< 1.4

$\geq 1.4$



# ONTARGET and TRANSCEND trials

6 CKD subgroups, based on normo- micro- macroalb  
AND on eGFR  $\leq$ 60 ml/min

## **BP difference:**

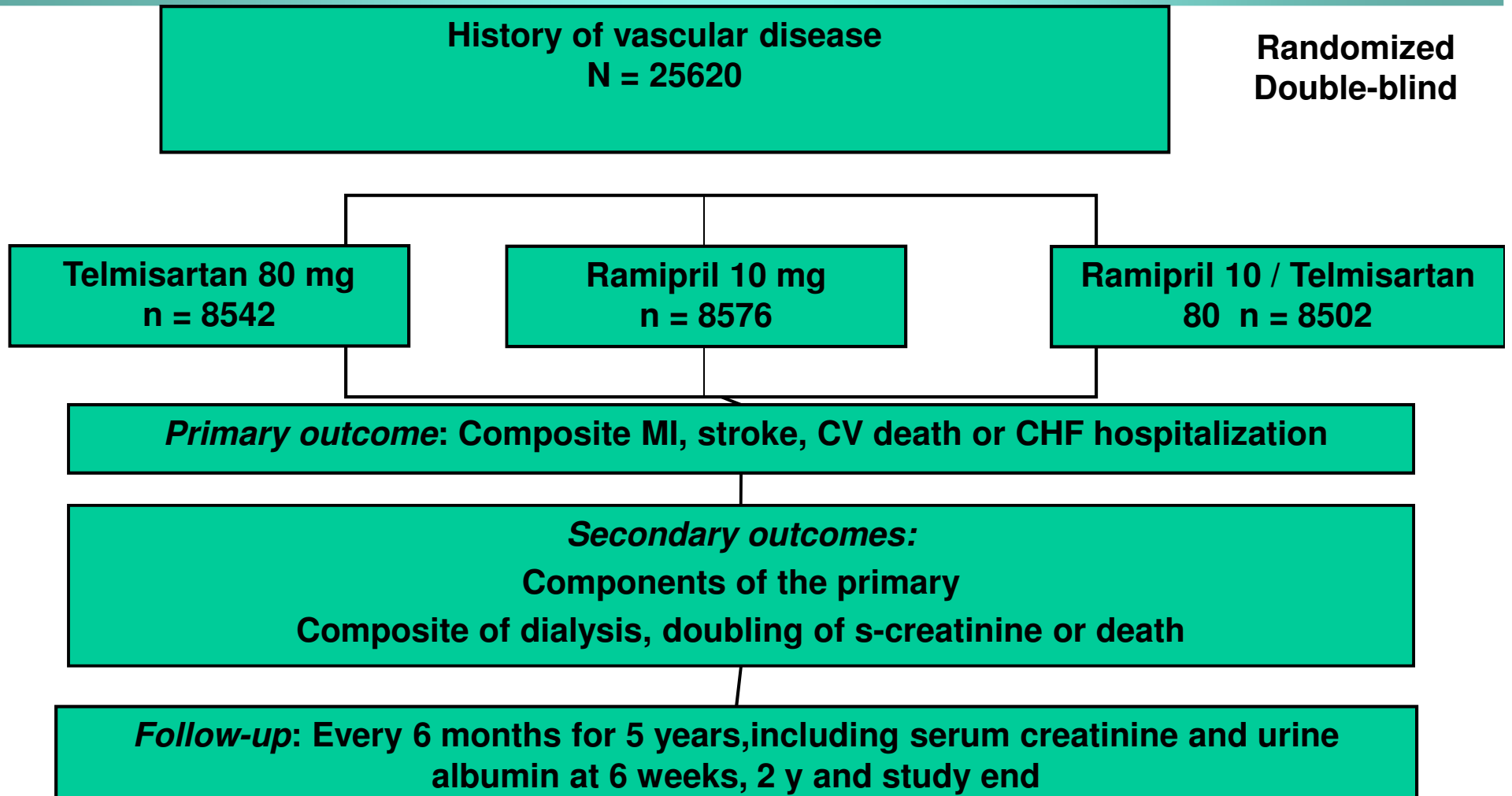
**OT** -3.5 / -2.0 mmHg (dual vs mono),

**TR** -4.0 / -2.5 mmHg (telmisartan vs placebo)

**OT:** No difference in CV outcomes between ramipril, telmisartan or both in any renal subgroup

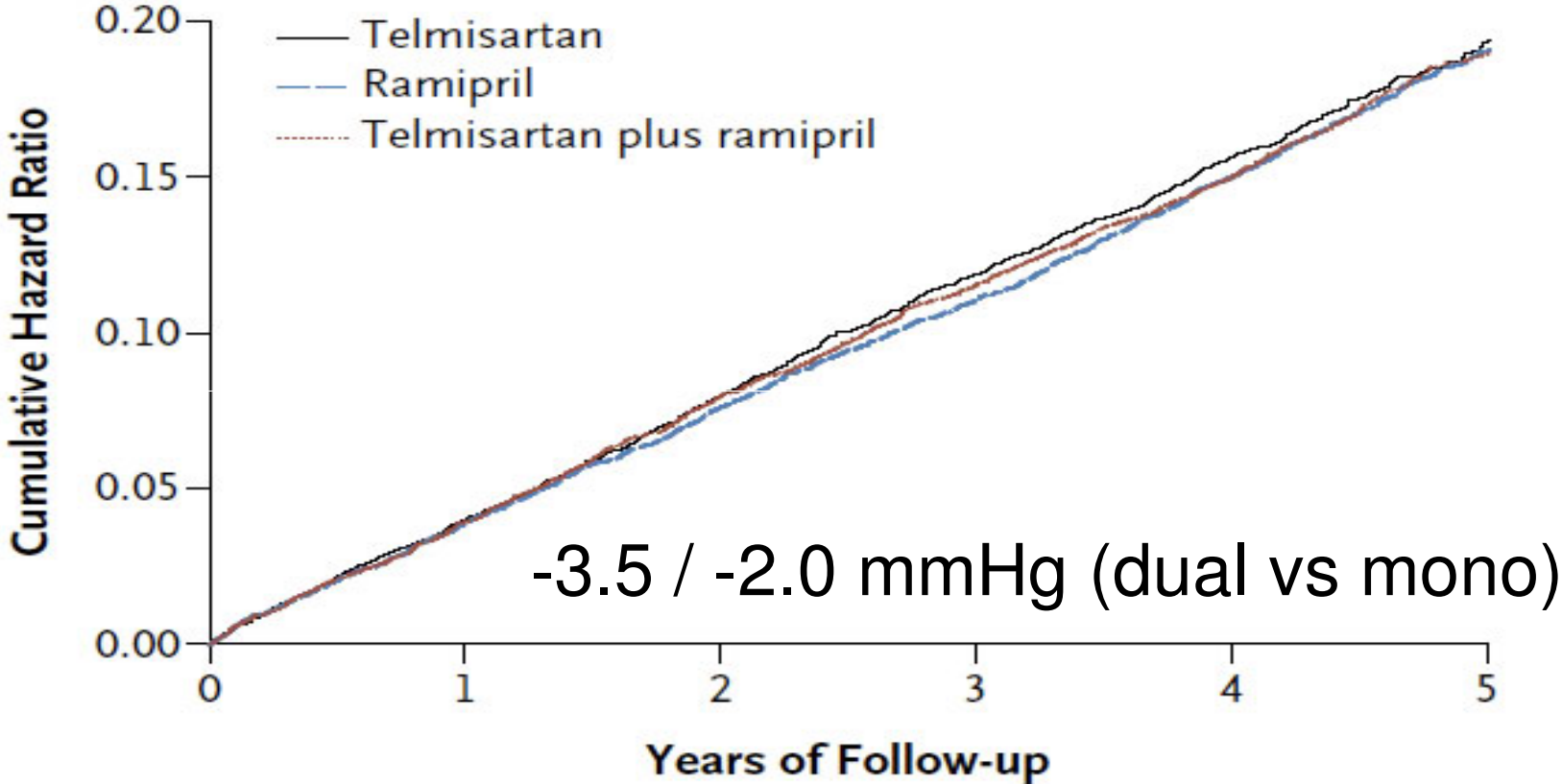
**TR:** Benefit on CV events of temisartan vs placebo in all subgroups

# ONTARGET: Design



Ontarget Investigators *NEJM* 2008;358: 1547; Mann et al., *Lancet* 2008;372:547

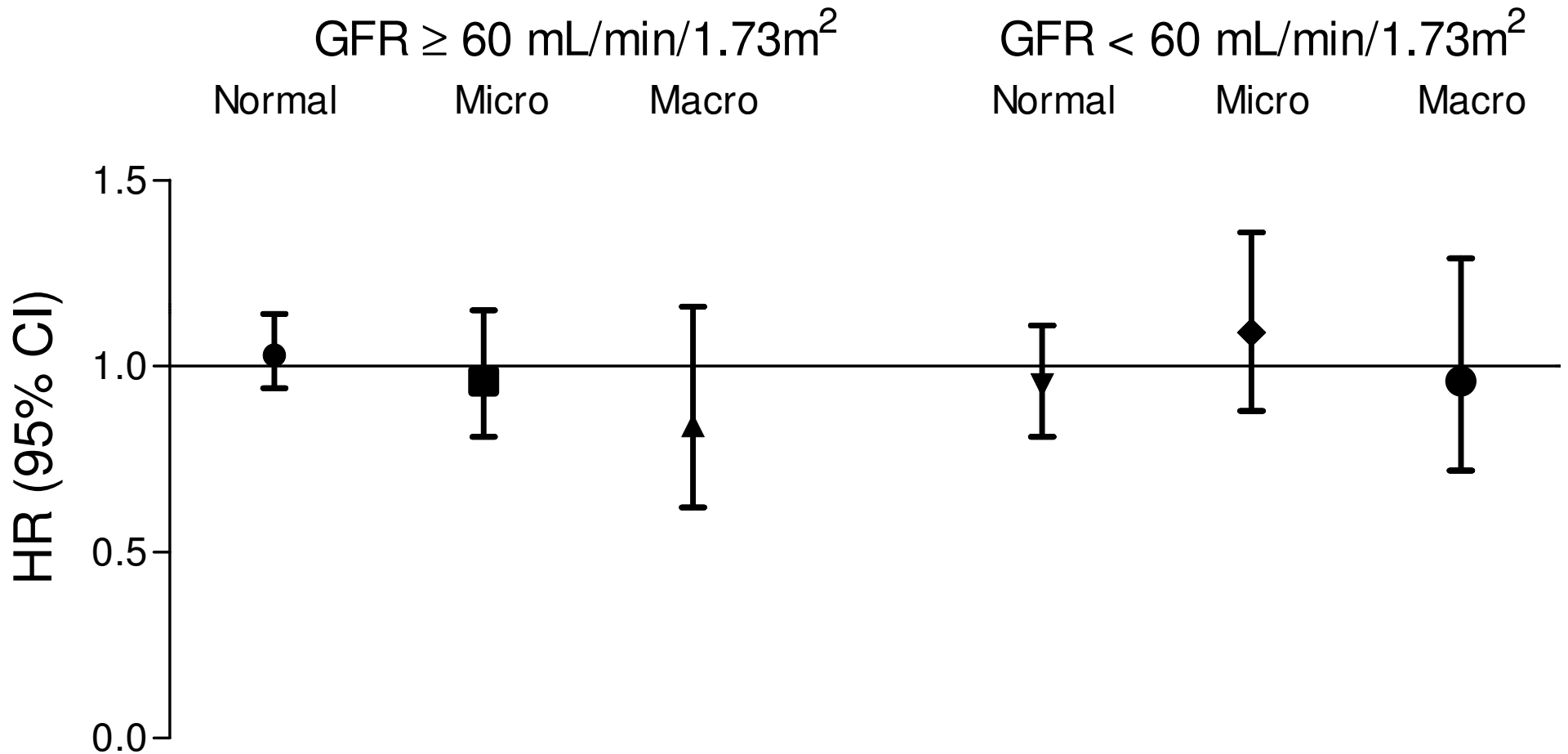
# ONTARGET: primary CV outcome (MI, stroke, CV death, heart failure hospitalization)



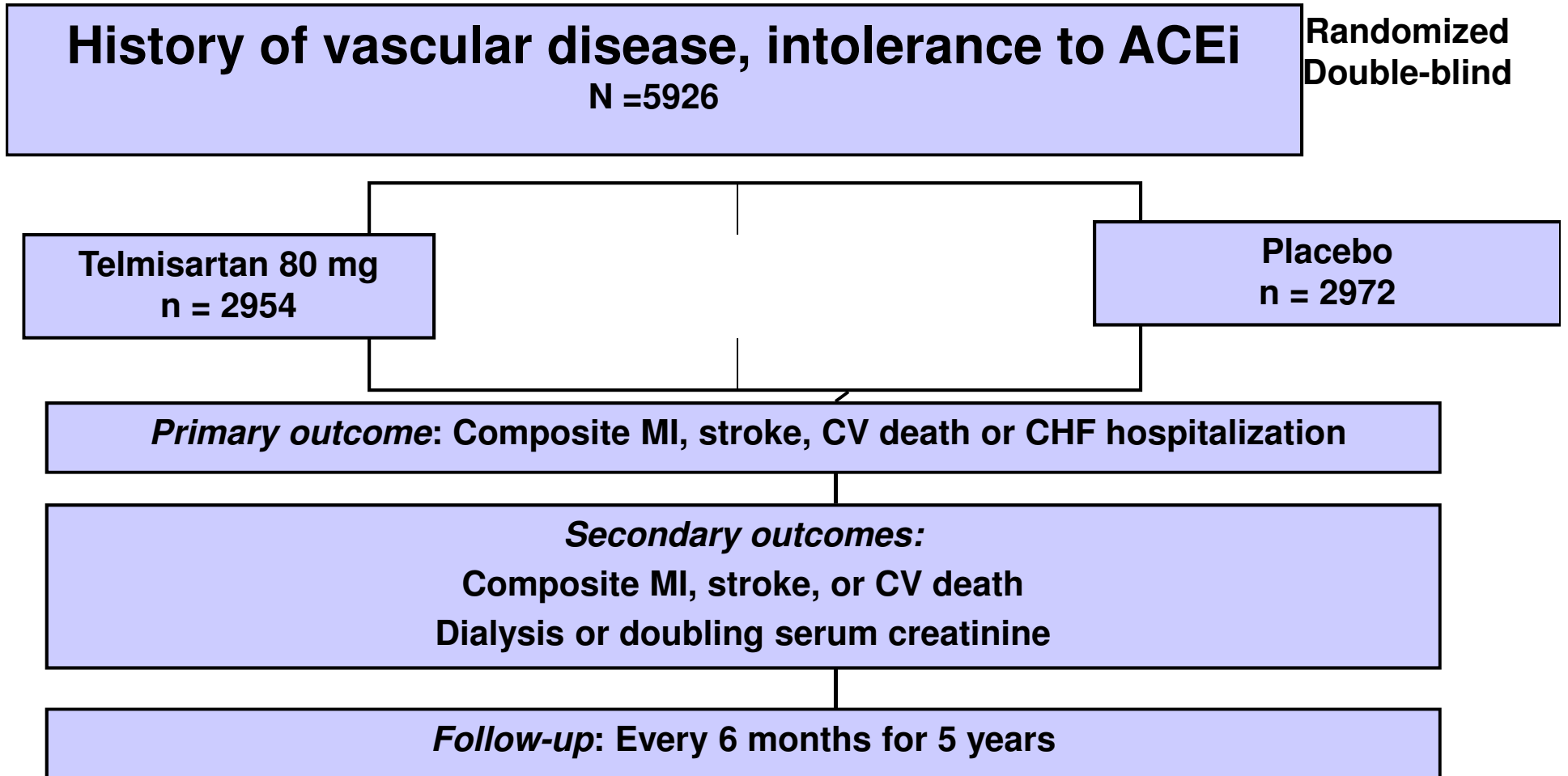
No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Ontarget Investigators *NEJM* 2008;358: 1547

# Primary cardiovascular outcome ONTARGET



# Transcend: design



Yusuf et al, Lancet 2008 and Mann et al, Ann Int Med 2009

# Transcend, composite of MI, stroke or CV death

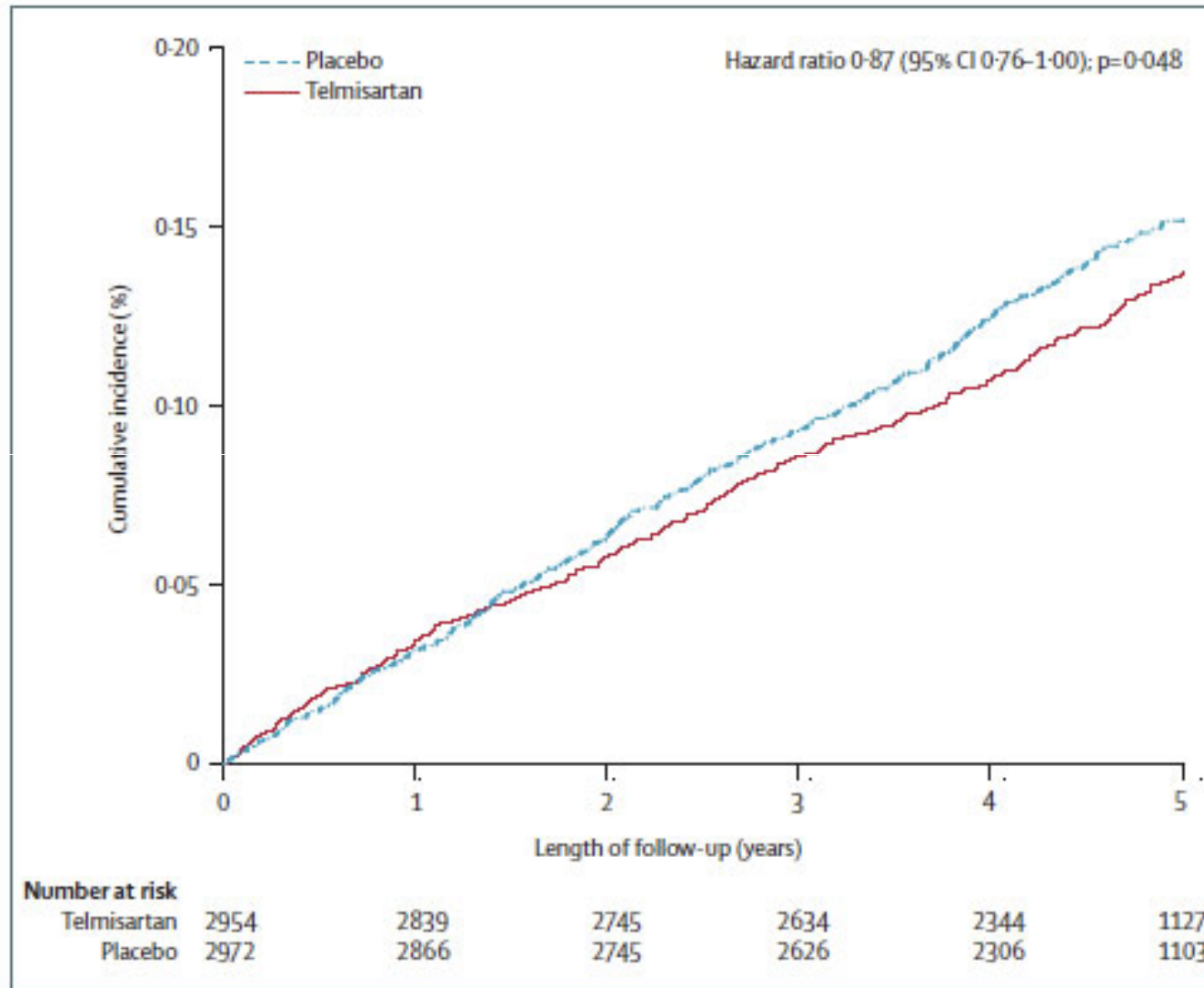
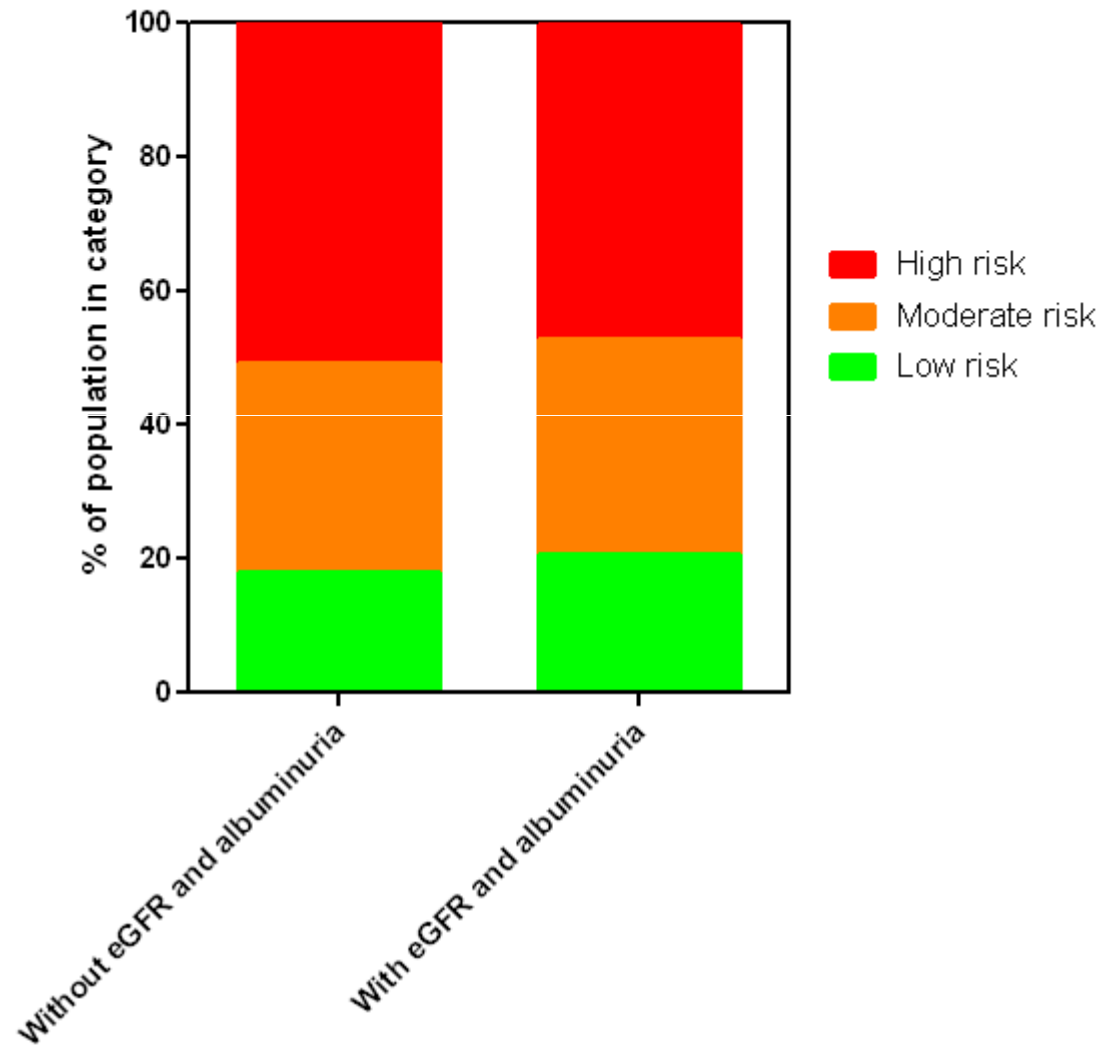


Figure 3: Kaplan-Meier curves for the secondary outcome of cardiovascular death, myocardial infarction, or stroke (HOPE Study outcome)

Is renal risk an important modifier of cardiovascular risk when other risks are known?

# Categories of CV risk in the ONTARGET & TRANSCEND studies based on classical RF





		From Model with EGFR and UACR				
From Model without EGFR and UACR		Low risk (< 10% in 5 years)	Moderate risk (10 - 15% in 5 years)	High risk (> 15% in 5 years)	Total	Percentage in Category
<b>Low risk (&lt; 10% in 5 years)</b>	Patients, n	4226	636	78	4940	17.9%
	Events, n	270	71	14	355	
	Non-events, n	3956	565	64	4585	
	Percentage with events <sup>†</sup>	6.8	12	19.8	7.7	
<b>Moderate risk (10 - 15% in 5 years)</b>	Patients, n	1503	5841	1324	8668	31.4%
	Events, n	124	634	250	1008	
	Non-events, n	1379	5207	1074	7660	
	Percentage with events <sup>†</sup>	9.1	11.7	19.9	12.5	
<b>High risk (&gt;15% in 5 years)</b>	Patients, n	-*	2399	11613	14012	50.7%
	Events, n	-	303	2739	3042	
	Non-events, n	-	2096	8874	10970	
	Percentage with events <sup>†</sup>	.	13.7	25.4	23.4	
<b>Total</b>	Patients, n	5729	8876	13015	27620	
	Events, n	394	1008	3003	4405	
	Non-events, n	5335	7868	10012	23215	
	Percentage with events <sup>†</sup>	7.4	12.3	24.8	17.1	
<b>Percentage Patients in Category</b>		20.7%	32.1%	47.1%		

\* there were no patients in this category.

# Summary on high CV risk in CKD

## The role of BP in CKD stage 1-4

Consistent data of innumerable observational studies: BP is higher in CKD compared to controls (data not reiterated here)

- No consistent data that lowering BP reduces CV risk in CKD
- No consistent data that a change of BP (↑↓) affects CV risk differently in people with/without CKD

# **Summary on high CV risk in CKD**

## **The role of BP in CKD stage 1-4**

What evidence would we like to analyze ?

- RCT's in CKD with different BP goals and powered for CV outcomes
- Metaanalysis of CKD subgroups from published RCT's in hypertension with data of CV outcomes in CKD subgroups

**E N D**

# **KDIGO conference on high CV risk associated with CKD**

## **The role of BP in CKD stage 1-4**

What evidence would we like to analyze ?

- RCT's in CKD with different BP goals and powered for CV outcomes
- Metaanalysis of CKD subgroups from published RCT's in hypertension with data of CV outcomes in CKD subgroups

# To be provocative/for the future:

- Should we individualize blood pressure management by patient groups?
- Should we treat blood pressure only in people with hypertension but instead according to cardiovascular risks?
- Should we measure blood pressure as a method of assessing effectiveness?

**Hazard Ratio by EGFR Category, mL/min/1.73 m<sup>2</sup> (95% Confidence Intervals)**

<b>Primary cardiovascular outcome</b>		<b>≥ 60</b>	<b>45 - &lt; 60</b>	<b>30 - &lt; 45</b>	<b>&lt; 30</b>	<b>Total*</b>
<b>Normoalbuminuria</b>	Unadjusted	1.0	1.39 (1.27, 1.51)	2.12 (1.83, 2.45)	2.44 (1.55, 3.83)	
	Adjusted†	1.0	1.19 (1.09, 1.30)	1.57 (1.35, 1.82)	1.71 (1.08, 2.69)	
<b>Microalbuminuria</b>	Unadjusted	1.73 (1.58, 1.90)	2.52 (2.23, 2.86)	2.79 (2.29, 3.38)	5.66 (3.82, 8.40)	1.82 (1.70, 1.96)
	Adjusted†	1.51 (1.38, 1.65)	1.90 (1.67, 2.16)	1.90 (1.56, 2.31)	3.90 (2.62, 5.80)	1.55 (1.44, 1.67)
<b>Macroalbuminuria</b>	Unadjusted	2.41 (2.08, 2.79)	2.68 (2.21, 3.26)	4.11 (3.34, 5.06)	4.00 (2.54, 6.28)	2.52(2.28, 2.80)
	Adjusted†	1.91 (1.64, 2.23)	1.97 (1.61, 2.40)	2.82 (2.28, 3.48)	2.53 (1.61, 3.99)	1.97 (1.77, 2.20)
<b>Total</b>	Unadjusted		1.46(1.36, 1.57)	2.26(2.04, 2.51)	3.25(2.53, 4.18)	
	Adjusted†		1.24 (1.16, 1.34)	1.64 (1.47, 1.83)	2.23 (1.73, 2.87)	

Hazard Ratio by EGFR Category, mL/min/1.73 m<sup>2</sup> (95% Confidence Intervals)

Cardiovascular death		≥ 60	45 - < 60	30 - < 45	< 30	Total*
Normoalbuminuria	Unadjusted	1.0	1.66 (1.46, 1.90)	3.12 (2.56, 3.81)	4.46 (2.58, 7.71)	
	Adjusted†	1.0	1.36 (1.18, 1.55)	2.11 (1.72, 2.59)	2.81 (1.62, 4.90)	
Microalbuminuria	Unadjusted	1.90 (1.65, 2.18)	3.00 (2.49, 3.61)	4.06 (3.13, 5.27)	8.66 (5.28, 14.20)	1.98(1.78, 2.20)
	Adjusted†	1.64 (1.42, 1.89)	2.13 (1.76, 2.57)	2.49 (1.91, 3.25)	5.74 (3.48, 9.47)	1.66 (1.49, 1.85)
Macroalbuminuria	Unadjusted	3.14 (2.55, 3.88)	4.34 (3.38, 5.57)	6.62 (5.08, 8.63)	8.28 (4.97, 13.81)	3.48(3.03, 4.00)
	Adjusted†	2.47 (1.99, 3.07)	3.11 (2.41, 4.02)	4.50 (3.43, 5.91)	4.84 (2.88, 8.11)	2.71 (2.34, 3.14)
Total	Unadjusted		1.74(1.57, 1.94)	3.26(2.83, 3.76)	5.62(4.16, 7.60)	
	Adjusted†		1.42 (1.27, 1.58)	2.19 (1.89, 2.53)	3.56 (2.62, 4.84)	



Is hypertension a risk for cardiovascular disease in people with CKD?

Yes

What are the effects on CV events of treating lowering blood pressure in general?

Remarkably consistent across:

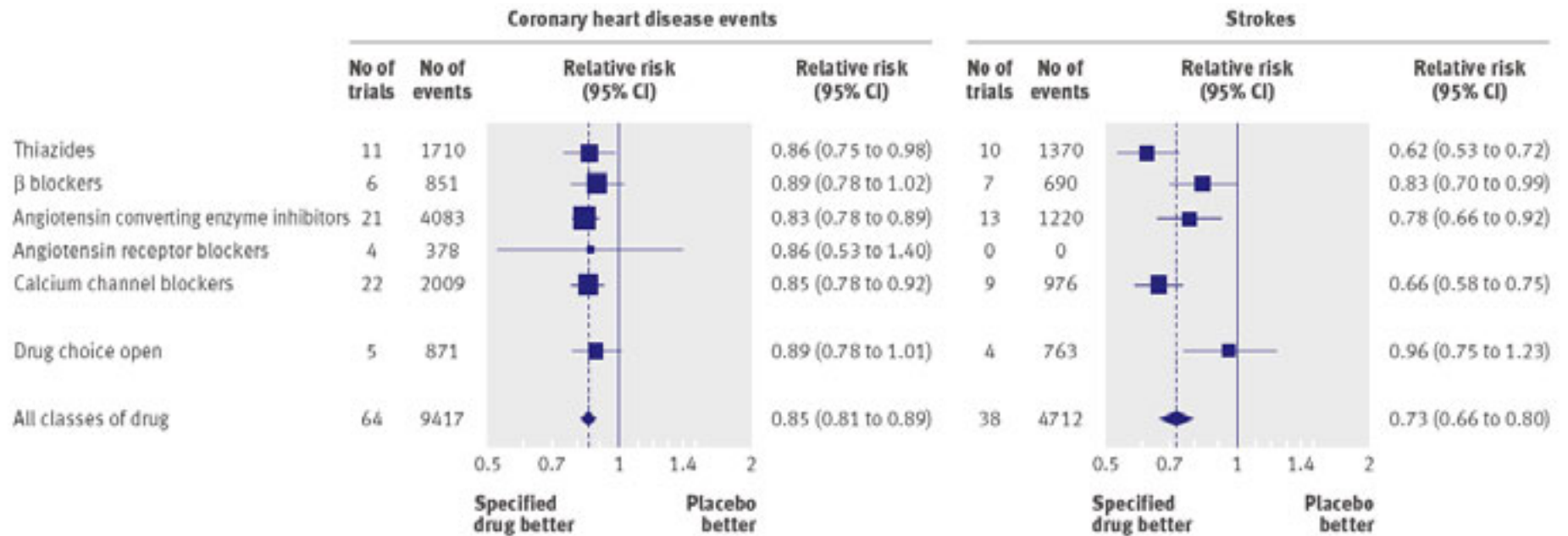
Drug class (RCTs)

Primary and secondary prevention (RCTs)

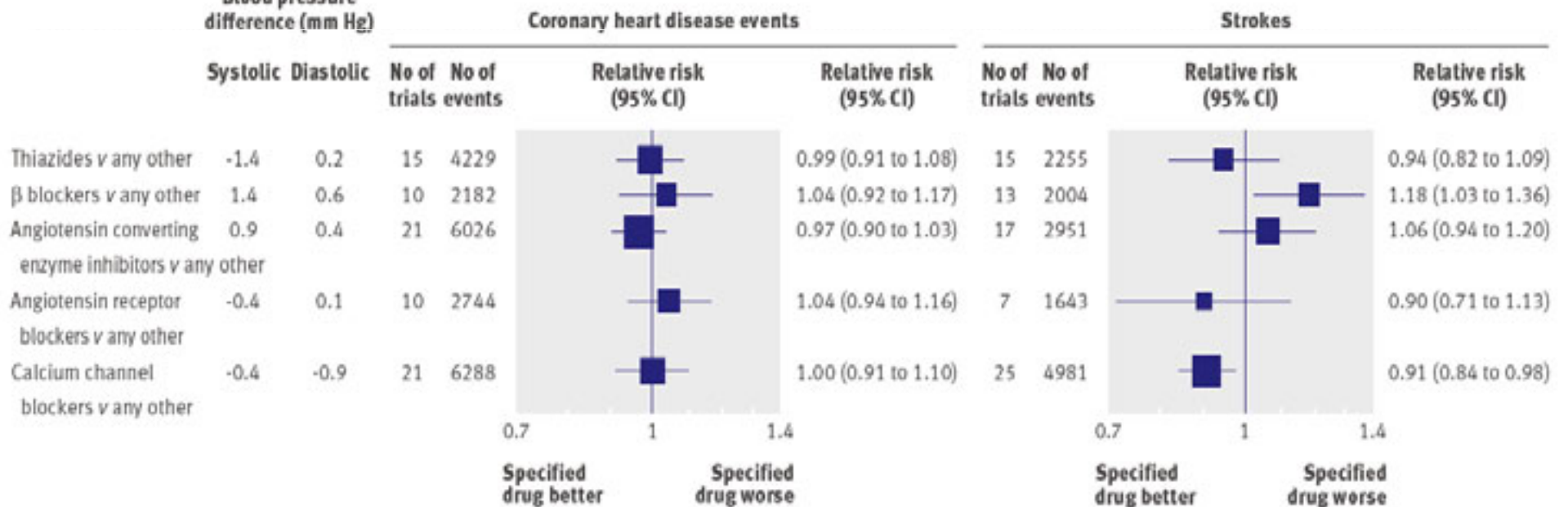
Initial blood pressure (RCTs)

Age (Observational)

Drug class



**Blood pressure difference (mm Hg)**



Primary or secondary prevention

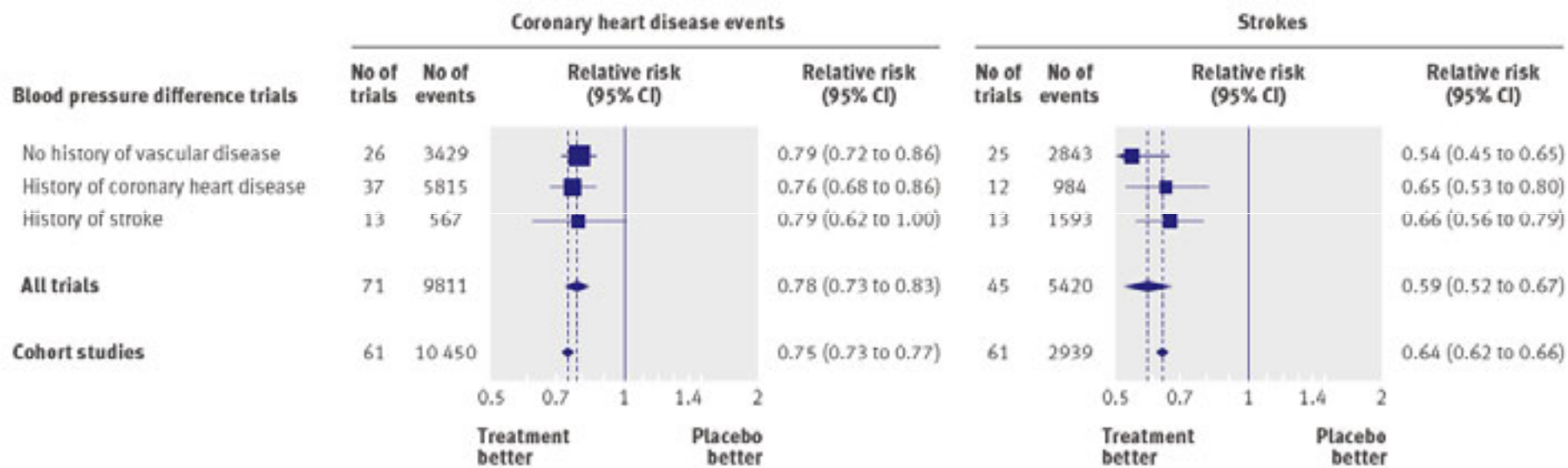
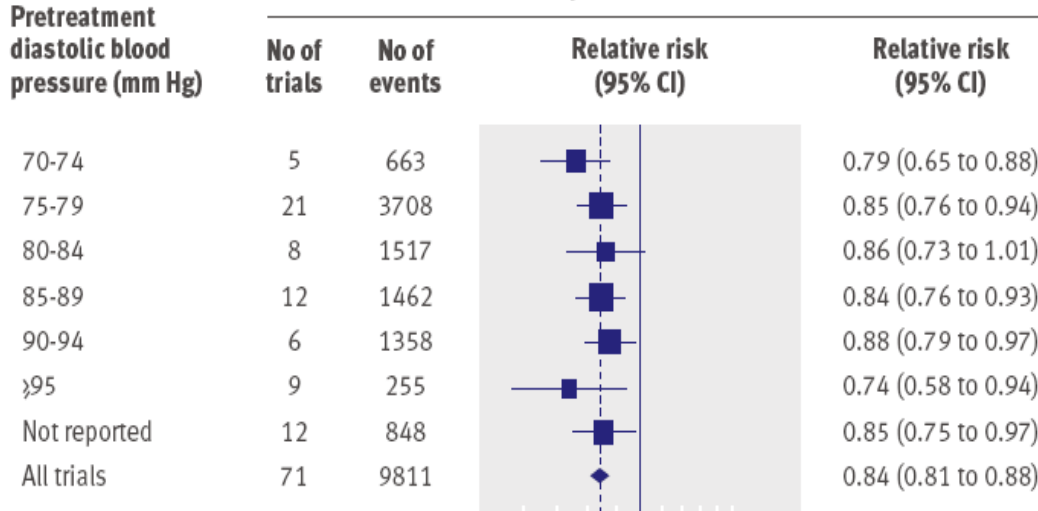


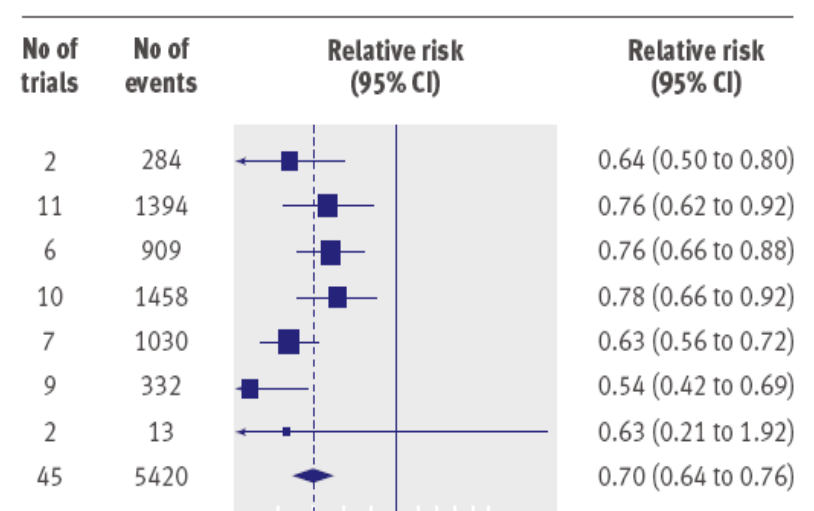
Fig 2 | Relative risk estimates of coronary heart disease events and stroke for a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic in the blood pressure difference trials and in epidemiological cohort studies. (Total number of trials is fewer than the sum of the three categories as five included participants with and without vascular disease; see web extra figures 2a-f for individual trial results and summary estimates)

Initial blood pressure

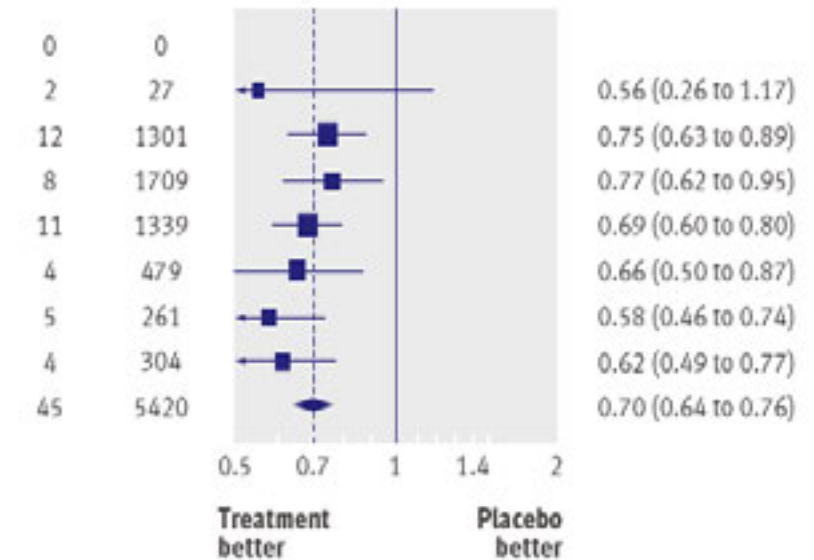
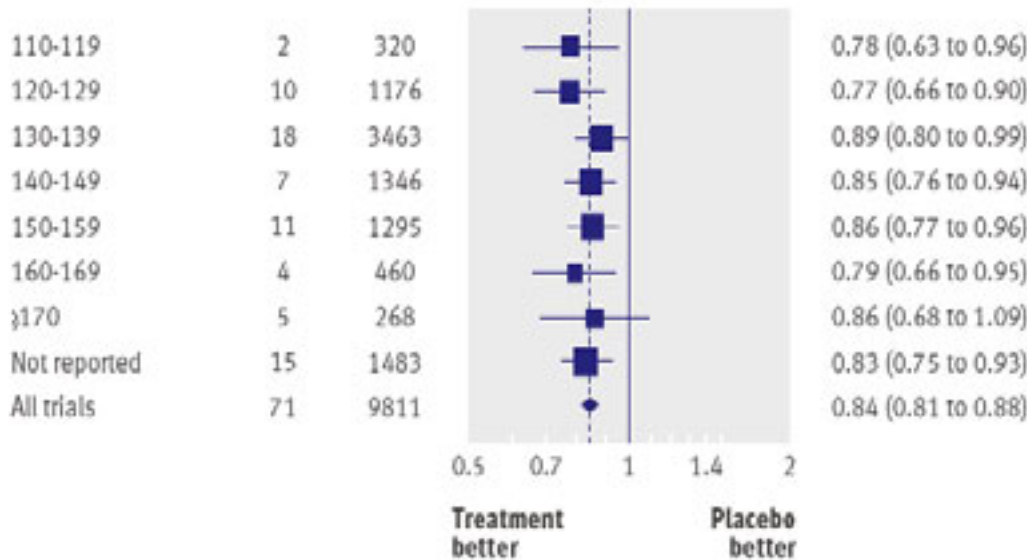
**Coronary heart disease events**



**Strokes**

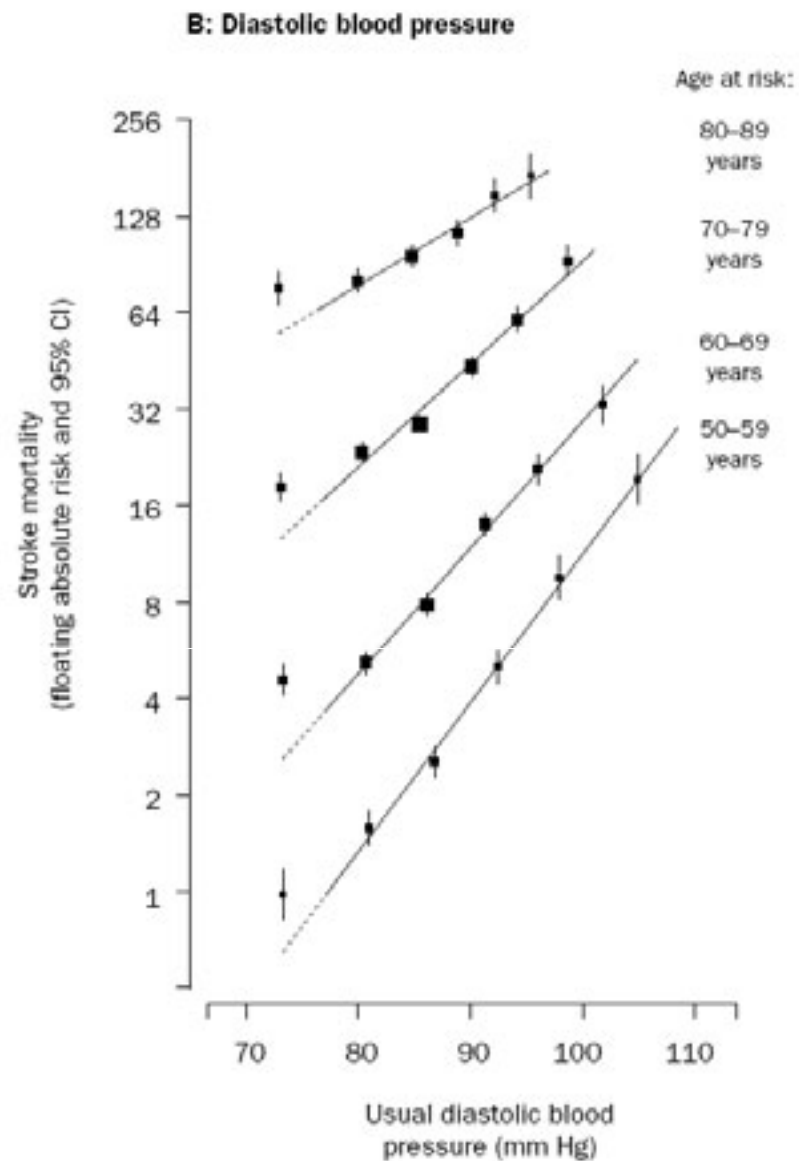
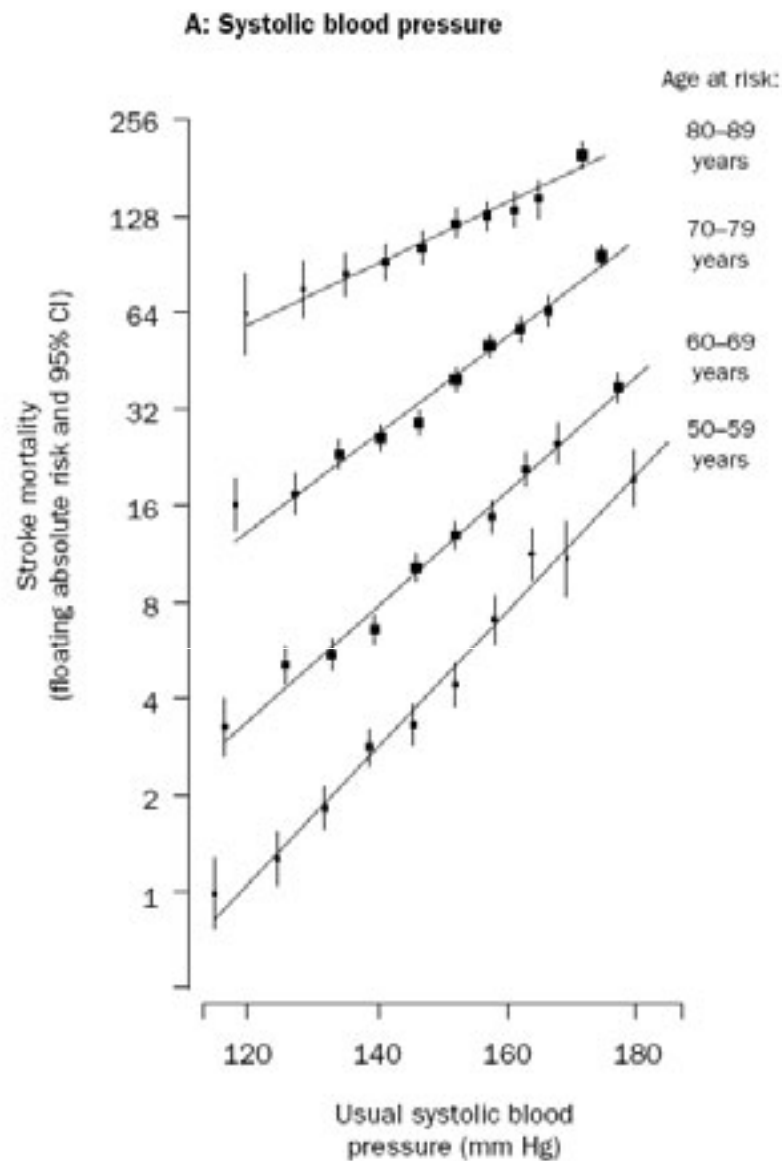


**Pretreatment systolic blood pressure (mm Hg)**





Age



Prospective studies collaboration Lancet 2002

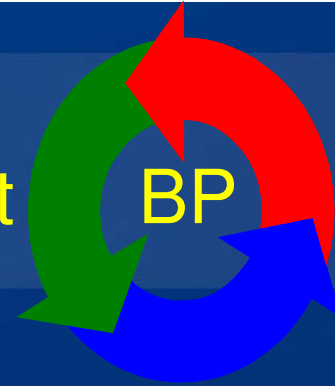
What are we measuring when we measure blood pressure?

**Table 4 | Estimated number of true positive and false positive measurements of systolic blood pressure over threshold of 140 mm Hg from on treatment baseline “true” measurement of 120 mm Hg or 130 mm Hg**

True baseline measurement and time interval between on treatment baseline and follow-up measurements (months)	% of all measurements truly $\geq 140$ mm Hg	“Observed” positive* test as % of all measurements (true positive+false positive)	Ratio of false positive tests to true positive tests
<b>120 mm Hg</b>			
3	0.0000008	2.3 (0.0000008+2.3)	>1 000 000
6	0.02	3.4 (0.01+3.4)	>200
9	1.2	6.0 (0.7+5.3)	7.2
15	1.6	6.6 (1.0+5.5)	5.3
21	2.6	7.5 (1.7+5.8)	3.4
27	3.2	8.0 (2.1+6.0)	2.9
33	3.8	8.6 (2.5+6.1)	2.4
<b>130 mm Hg</b>			
3	0.3	16.8 (0.2+16.6)	93
6	4.6	19.0 (2.7+16.3)	6.0
9	13.8	22.7 (9.3+13.5)	1.5
15	15.3	23.4 (10.4+13.0)	1.3
21	17.5	24.5 (12.2+12.2)	1.0
27	18.6	25.0 (13.1+11.9)	0.9
33	19.7	25.6 (14.1+11.5)	0.8

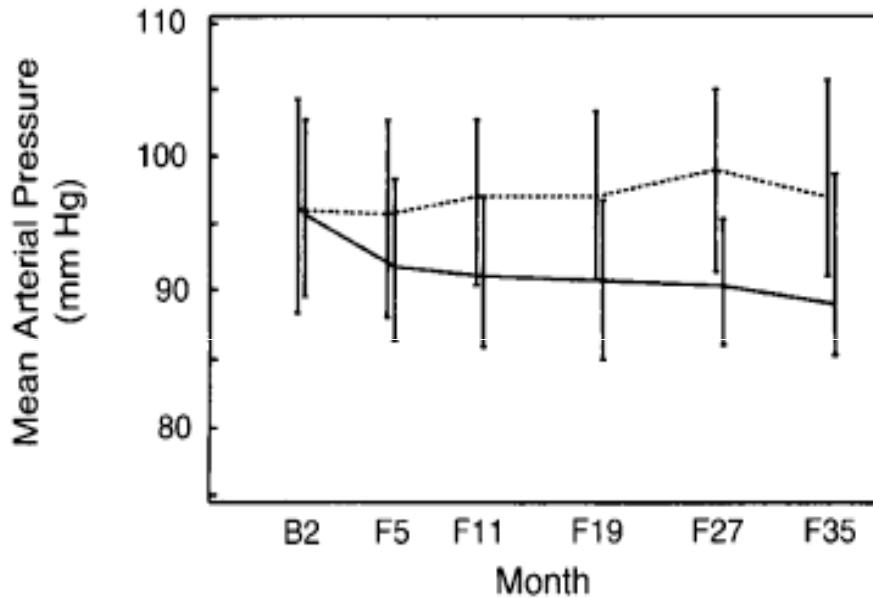
\*Positive\* test is increase in blood pressure above threshold.

Heart BP Kidney

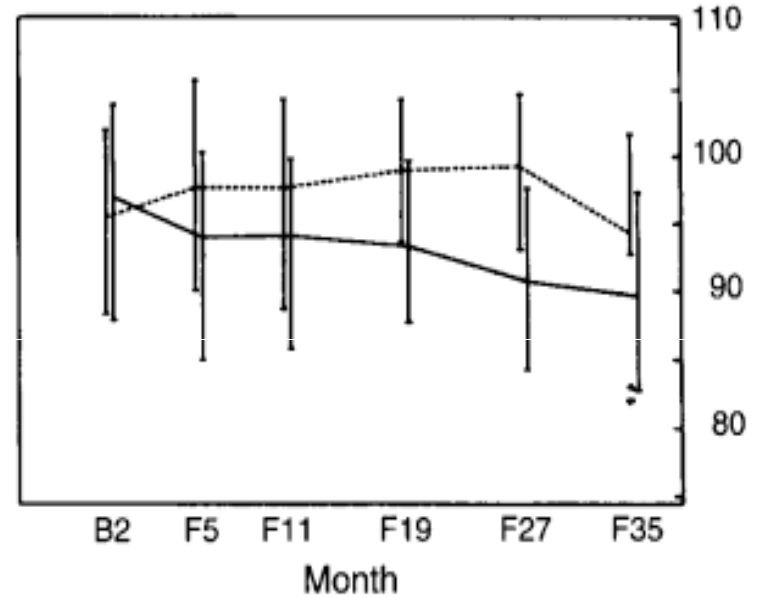


END

# MDRD trial: Effects on BP



Usual pressure: 283 249 242 203 119 54  
 Low pressure: 300 277 260 209 139 67



Usual pressure: 122 113 103 76 55 29  
 Low pressure: 132 119 116 77 55 28

30 death, 18/30 CV death, no difference reported between BP groups

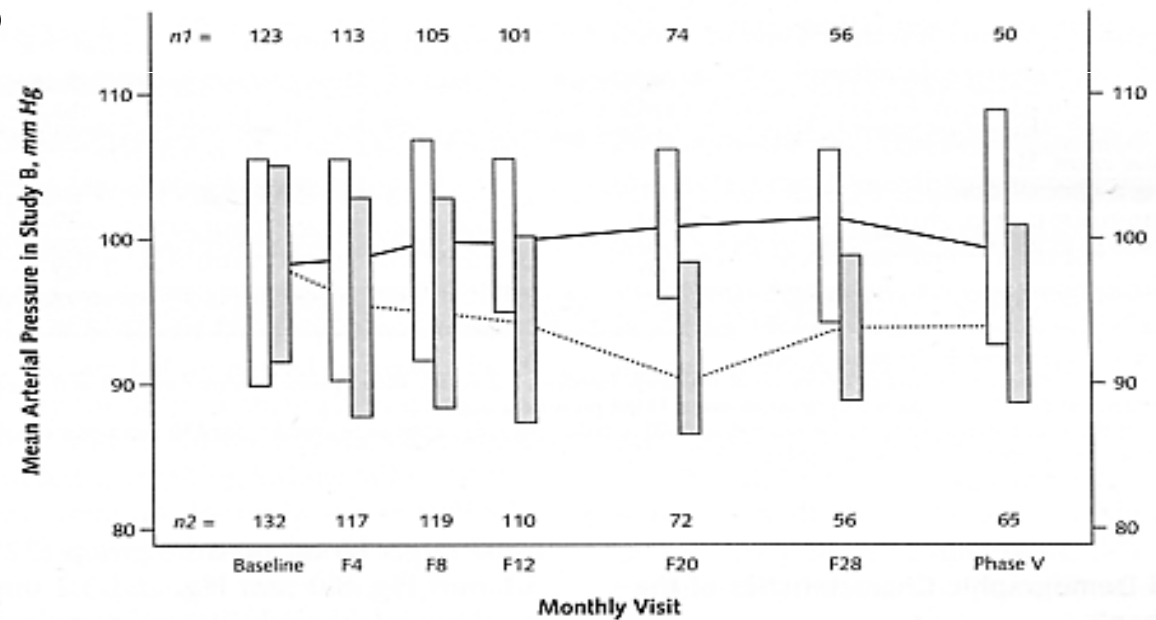
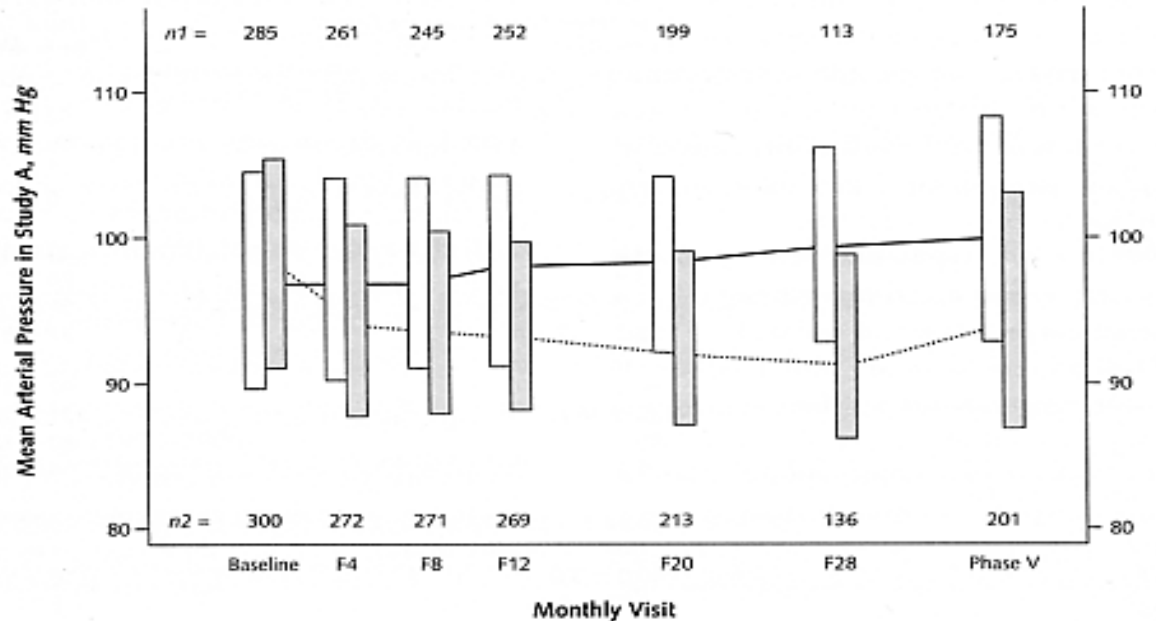
Klahr S et al, NEJM 1994;330:877



# MDRD study (1989 – 1993)

Long-term follow-up  
until 2000:

Study A: CRD stage 3-4  
Study B: CRD stage 4-5

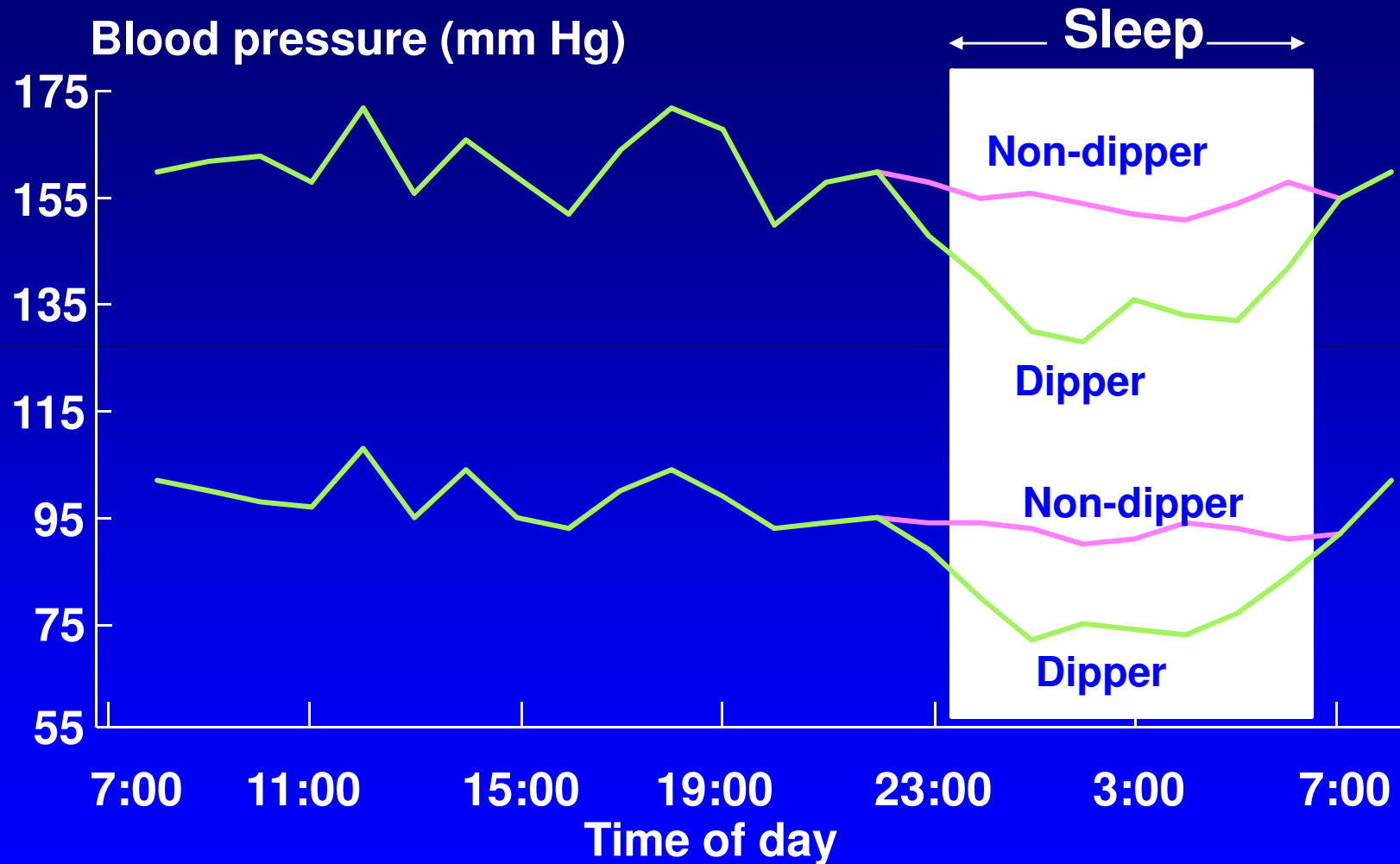
GFR 25 - 55 and  
13 - 24 ml/min



 Usual target blood pressure  
 Low target blood pressure

Phase V = 1994

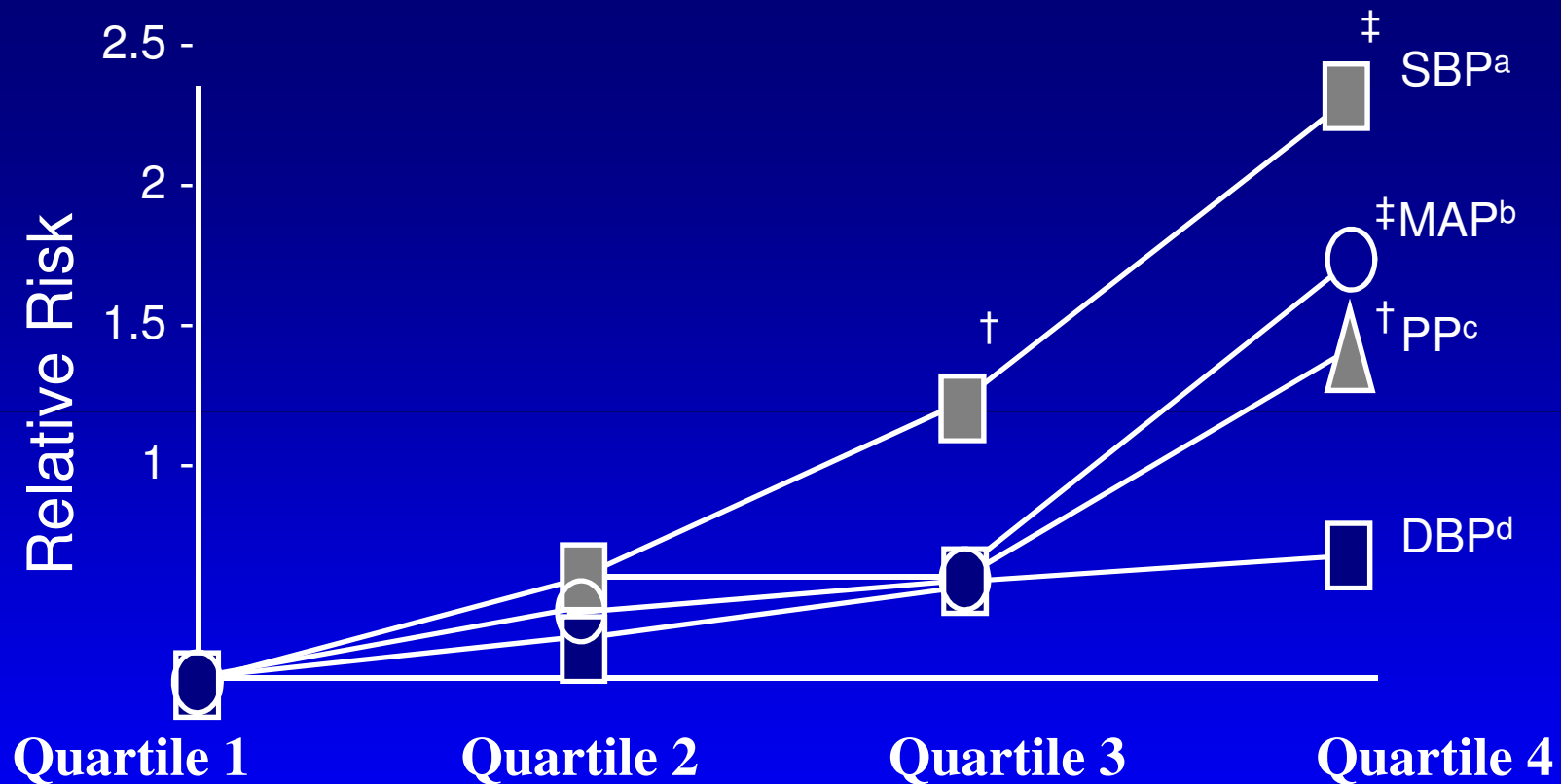
# 24-h blood pressure profile in two patients with hypertension (dipper and non-dipper)



Redman et al, 1976; Mancia et al, 1983; Kobrin et al, 1984; Baumgart et al, 1989;  
Imai et al, 1990; Portaluppi et al, 1991



# Adjusted\* risk of renal function loss in the SHEP study (n =2181)



\*adjusted for age, gender, race, diabetes, CV diseases, smoking