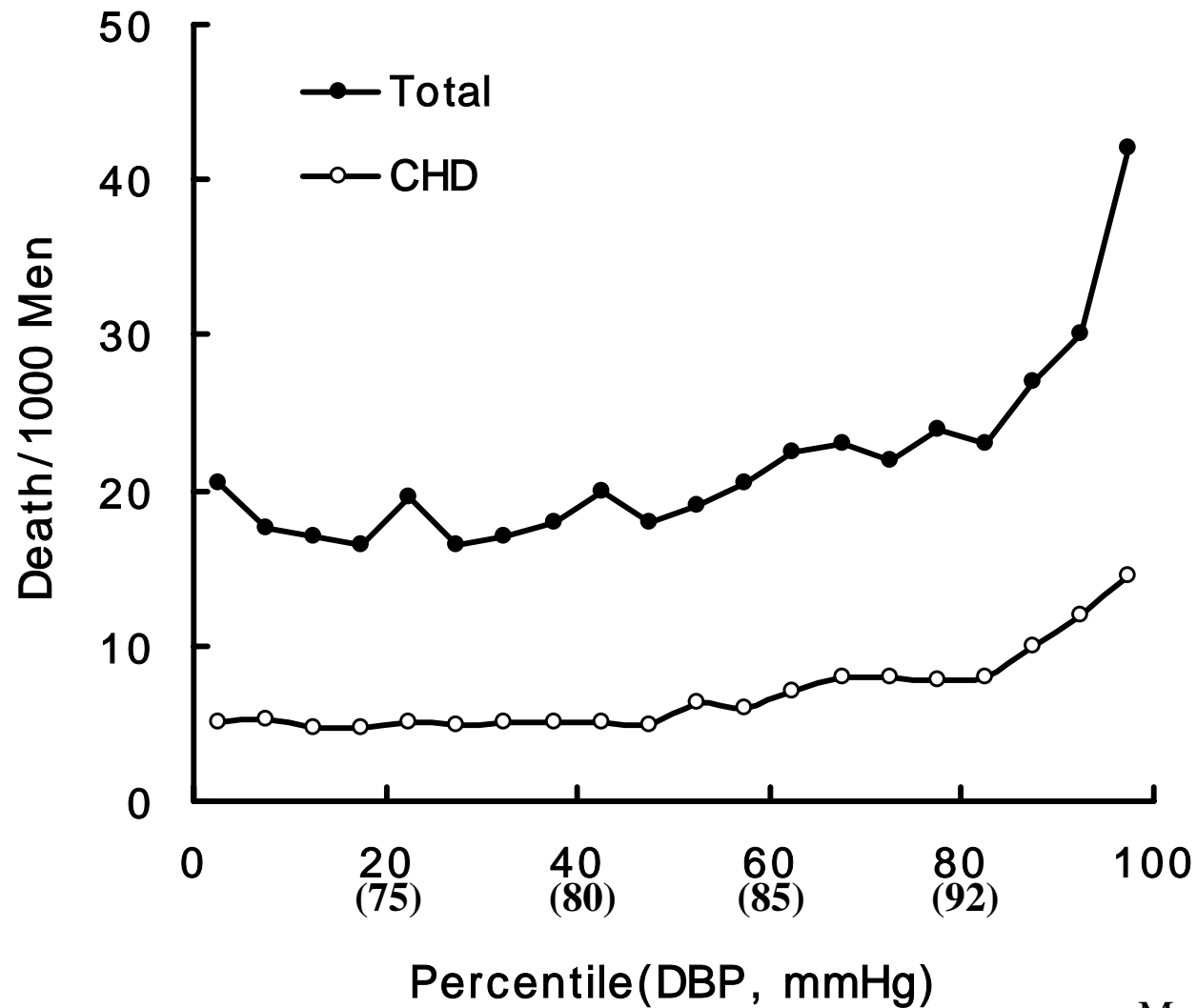


J- Curve in Management of Hypertension Maybe Not Exist

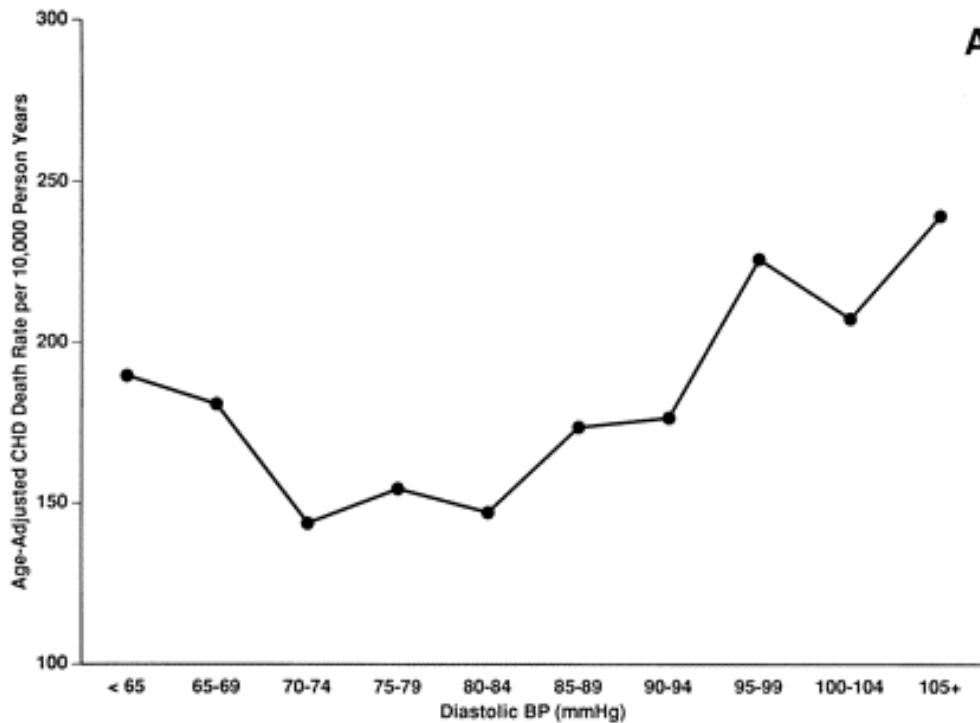
Diastolic Blood Pressure and Mortality

- MRFIT -

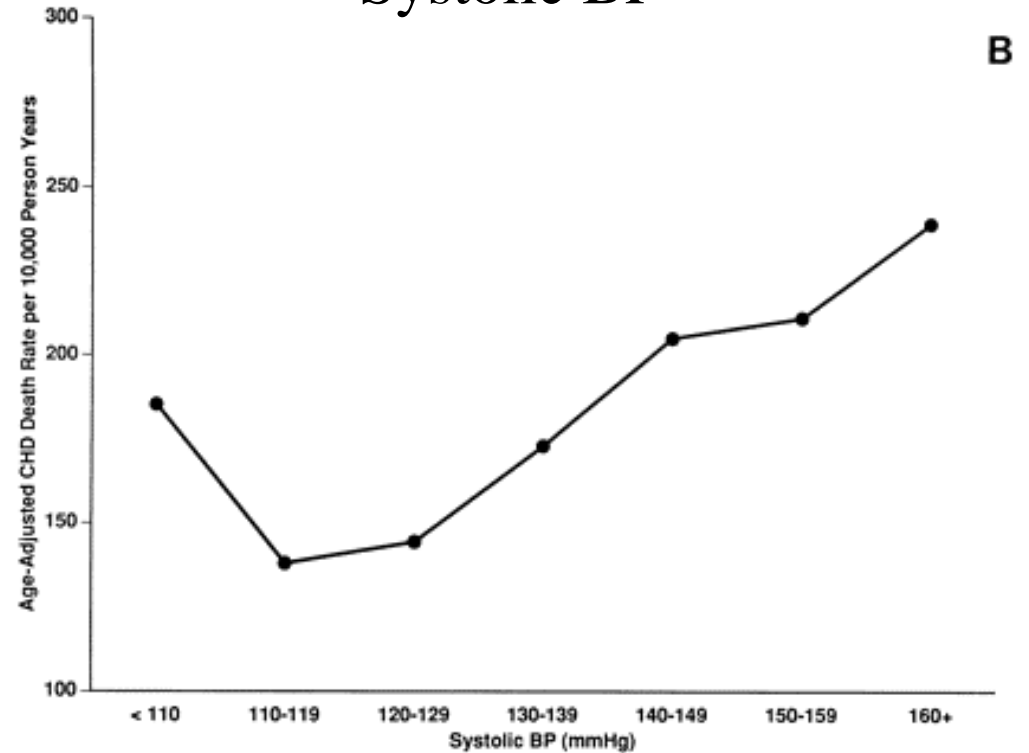


CHD Death Rates according to Initial DBP and SBP level in MRFIT Men with MI.

Diastolic BP



Systolic BP



Meta-analysis of Antihypertensive Medication

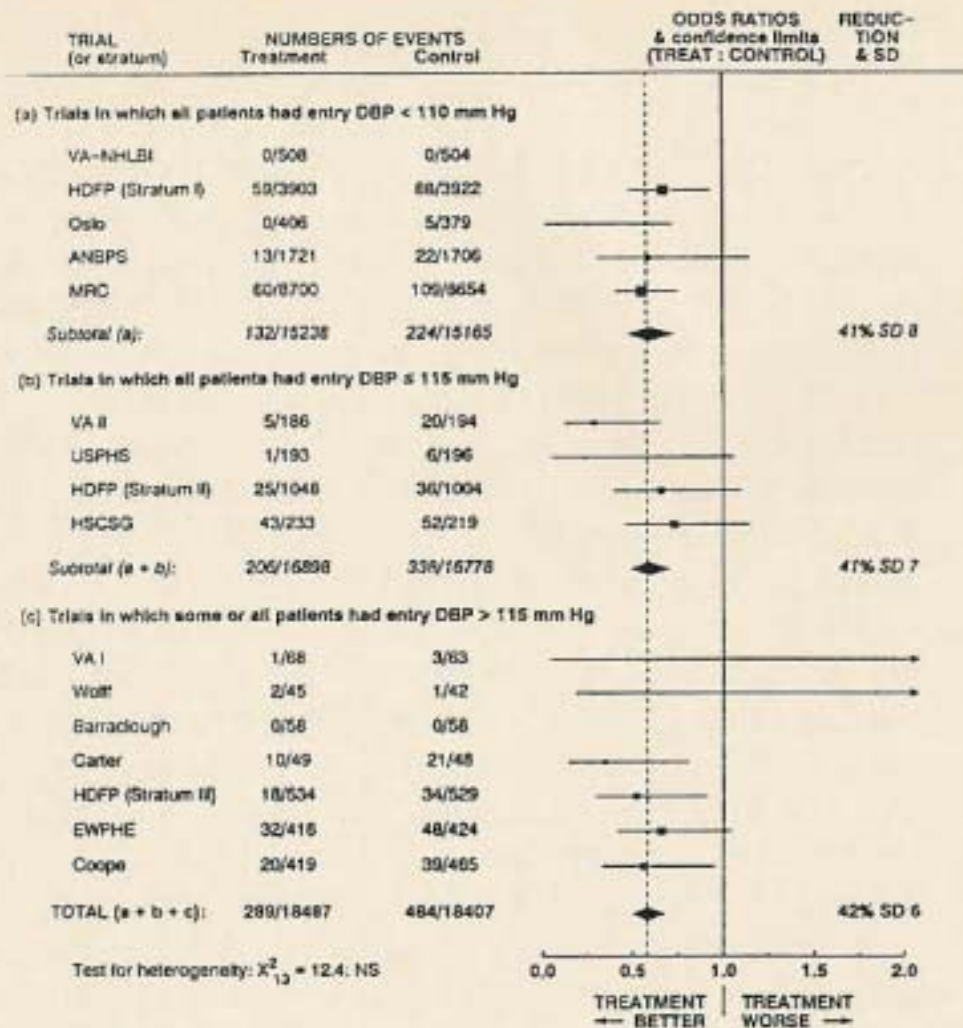
TABLE I—POPULATION AND TRIAL DESIGN IN UNCONFOUNDED RANDOMISED TRIALS OF AT LEAST ONE YEAR OF ANTIHYPERTENSIVE DRUG TREATMENT

Trial or stratum (ref)	No of patients	Entry DBP (mm Hg)	Mean age (yr)	Male (%)	Mean follow-up (yr)	Blinding	Main drugs	Mean DBP difference (mm Hg) in attenders*
<i>Trials in which all patients had entry DBP < 110 mm Hg</i>								
VA-NHLBI (25, 26)	1012	85-105	38	81	1.5	Double	CD	7
HDFP stratum I (27-31)	7825	90-104	51†	55†	5.0	None	CD	5
Oslo (32, 33)	785	90-109‡	45	100	5.5	None	HZ	10
ANBPS (34)	3427	95-109	50	63	4.0	Single	CZ	6
MRC (35)	17 354	90-109	52	52	5.0	Single	BF or PR	6
<i>Trials in which all patients had entry DBP ≤ 115 mm Hg</i>								
VA (10, 37)	380	90-114	51	100	3.3	Double	HZ + RE + HD	19
USPHS (24)	389	90-114	44	80	7.0	Double	CZ + RU	10
HDFP stratum II (27-31)	2052	105-114	51†	55†	5.0	None	CD	7
HSCSG (36)	452	90-115	59	41	2.3	Double	MC + DS	12
<i>Trials in which some or all patients had entry DBP > 115 mm Hg</i>								
VA (10, 37)	143	115-129	51	100	1.5	Double	HZ + RE + HD	27
Wolff (11)	87	100-130	49	32	1.4	Double	RE	20
Barracough (38)	116	100-120	56	43	2.0	Single	BF or MD	13
Carter (41)	99	≥ 110	NR	57	4.0	None	TH	NR
HDFP stratum III (27-31)	1063	≥ 115	51†	55†	5.0	None	CD	6
EWPHE (39)	840	90-119	72	30	4.7	Double	HZ + TT	10
Coope (40)	884	105-120	69	31	4.4	None	AT	11
Mean or total	36 908	99	52	53	5.0	—	—	6*

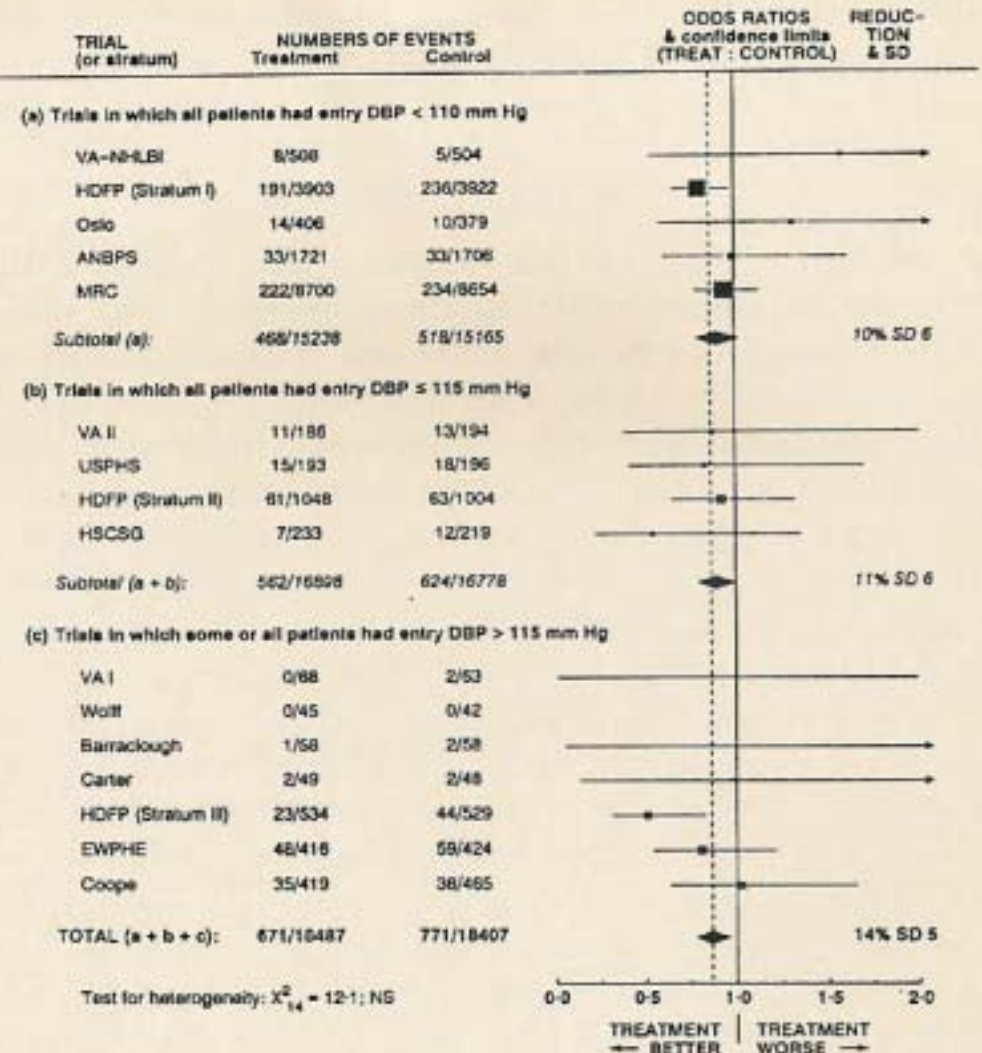
*The difference in mean DBP per person-year of follow-up, based on data from those who attended follow-up for blood pressure measurement, was 6.4 mm Hg. The difference

Meta-analysis of Antihypertensive Medication

(i) STROKE IN ANTIHYPERTENSIVE TRIALS

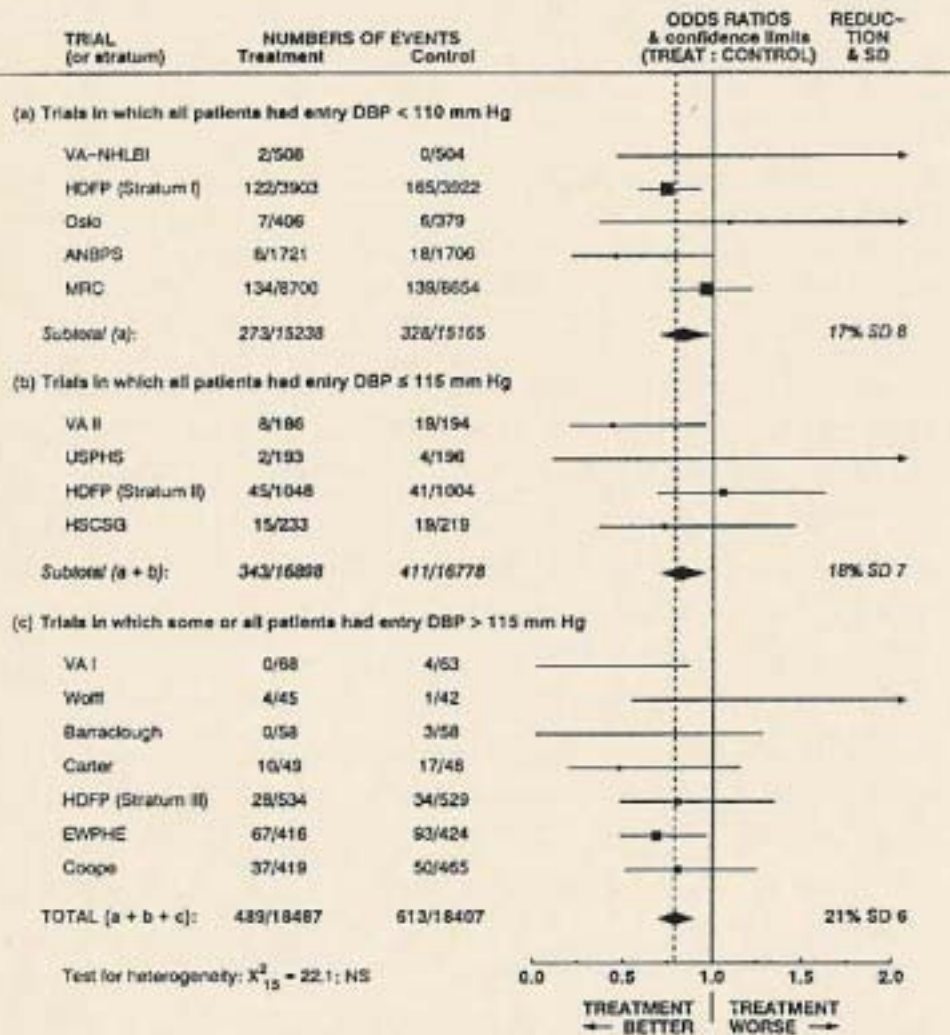


(ii) CHD IN ANTIHYPERTENSIVE TRIALS

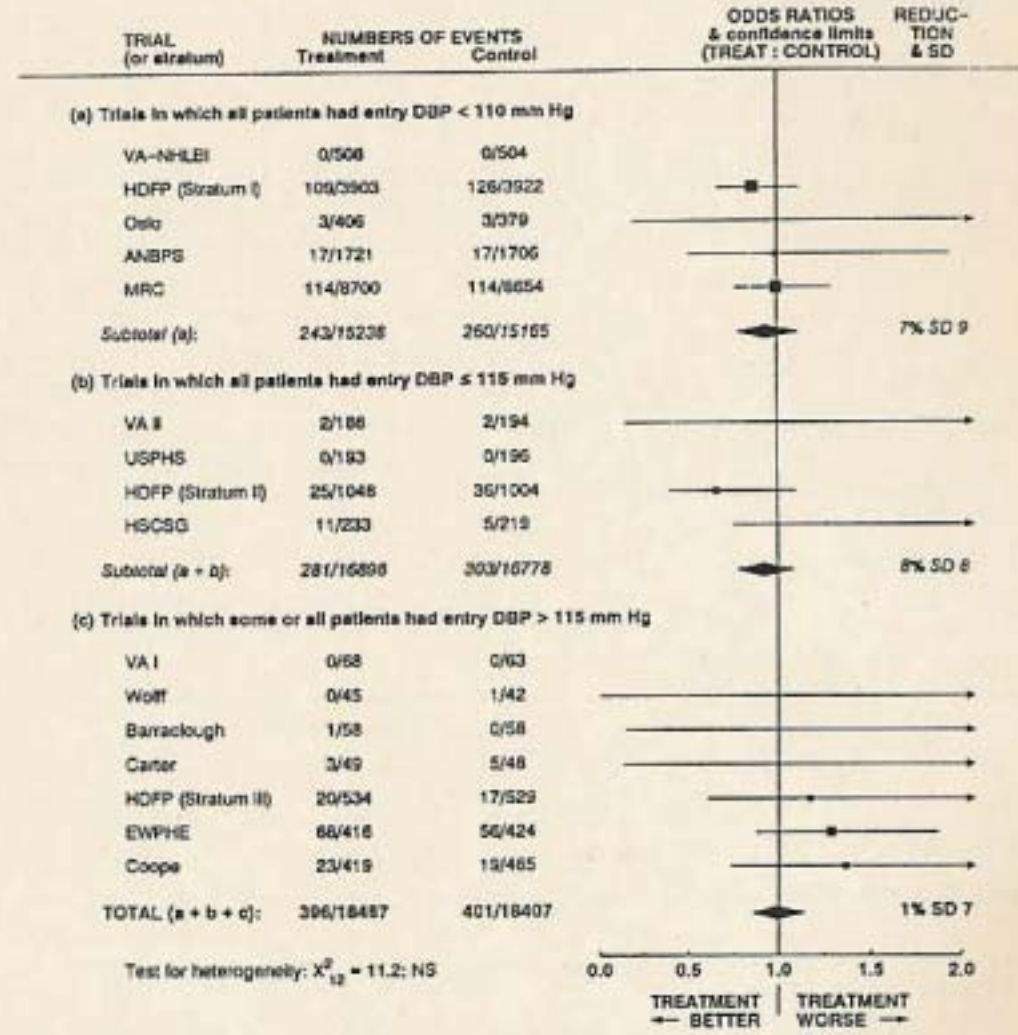


Meta-analysis of Antihypertensive Medication

(iii) VASCULAR DEATHS IN ANTIHYPERTENSIVE TRIALS



(iv) NON-VASCULAR DEATHS IN ANTIHYPERTENSIVE TRIALS



Goals of Therapy for Hypertension

- **JNC VII**

- Treating SBP and DBP to targets that are $<140/90$ mmHg is associated with a decrease in CVD complications.
- In patients with hypertension and diabetes or renal disease, the BP goal is $<130/80$ mmHg.

- **ESH & ESC**

- lowered at least below $140/90$ mmHg and to definitely lower values, if tolerated, in all hypertensive patients
- below $130/80$ mmHg in diabetics.

Three-Year Morbidity in Dalby, Sweden (40-59 year Men)

	Treated Patients (n=66)	Normotensives (n=75)	p value
CVD	21%	1%	<0.001
CHD	20%	1%	<0.001
DM	8%	5%	ns
BP (mmHg)			
Untreated	183/114		
Treated	149/91	133/80	<0.001

J- Curve in Management of Hypertension

Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet*. **1979** Apr 21;1(8121):861-5.

The findings suggest that the blood-pressure in severe middle-aged hypertensives should seldom be reduced by more than 22% or to diastolic levels less than **104-110 mm Hg**.

Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet*. **1987** Mar 14;1(8533):581-4.

There was a J-shaped relation, in those with evidence of **ischaemic heart disease**, the frequency of death from myocardial infarction was lowest at treated DBP of **85-90 mm Hg**.

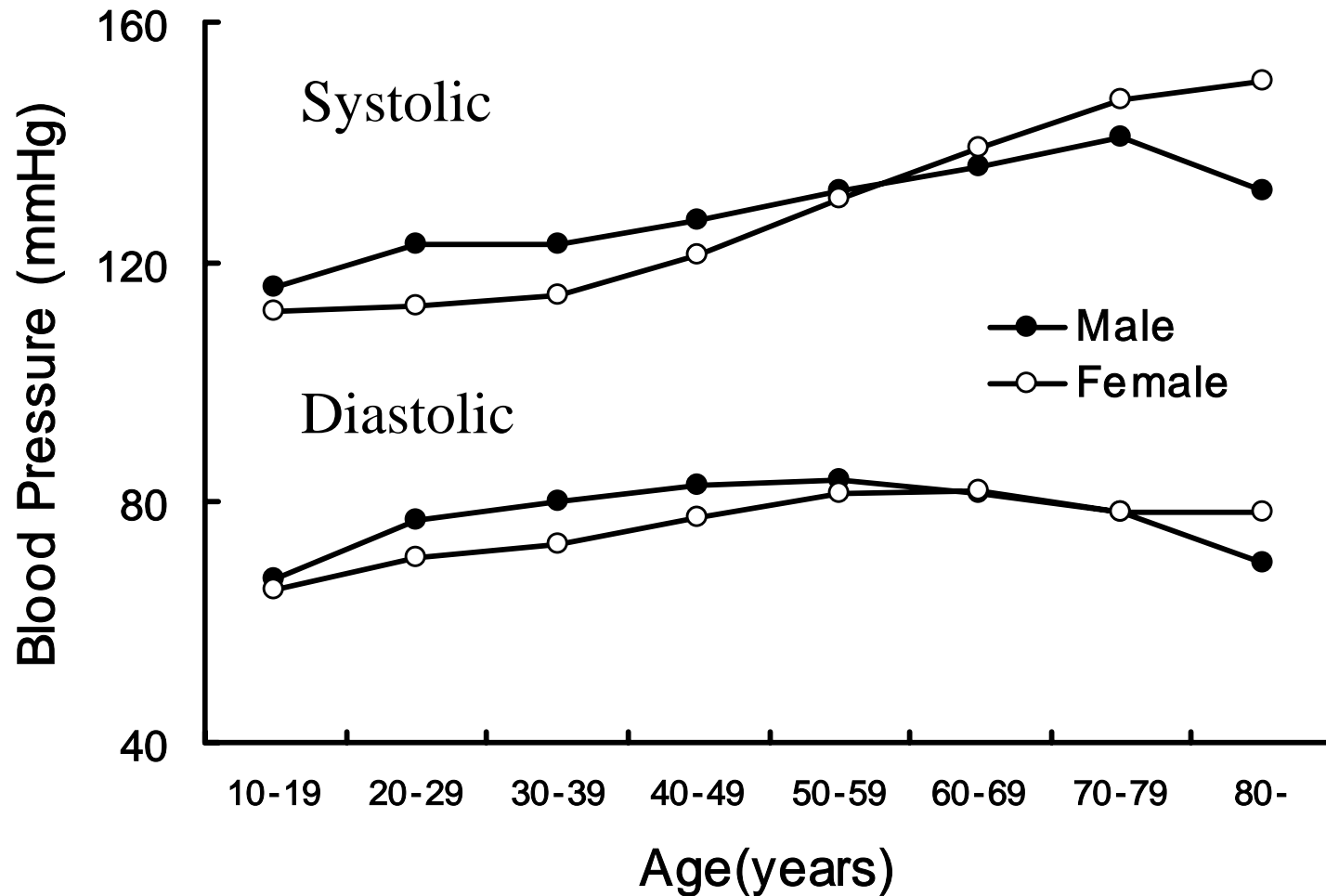
Berglund G. Goals of antihypertensive therapy. Is there a point beyond which pressure reduction is dangerous? *Am J Hypertens*. **1989** Jul;2(7):586-93. Review. (Gothenburg) Caution should be to avoid decreasing diastolic BP below **85 mm Hg**.

Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? *JAMA*. **1991** Jan 23-30;265(4):489-95. Meta-Analysis

Low treated diastolic blood pressure levels, ie, below **85 mm Hg**, are associated with increased risk of cardiac events.

Blood Pressures and Age

First National Health and Nutrition Survey, 1998



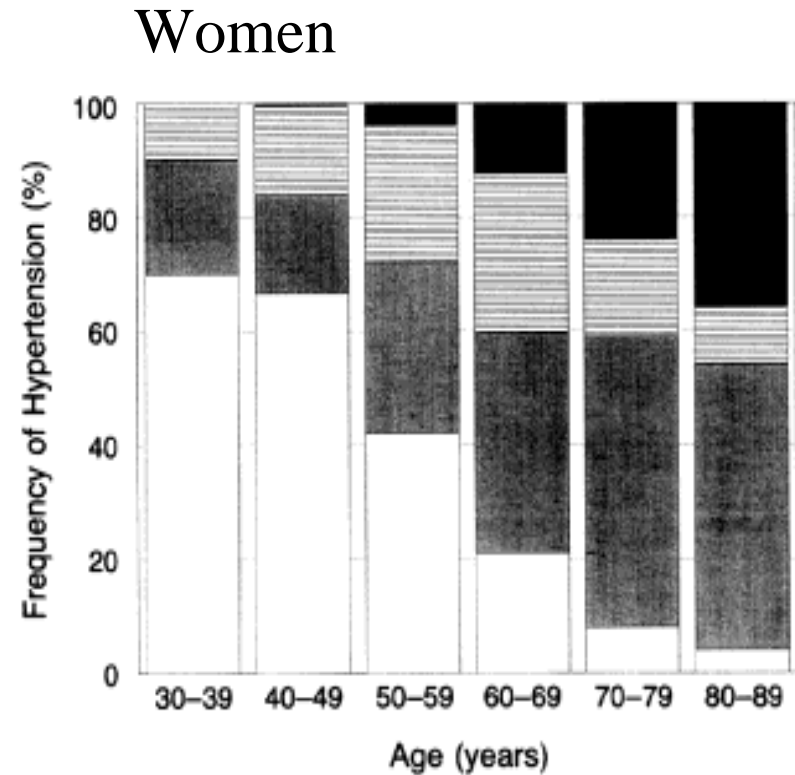
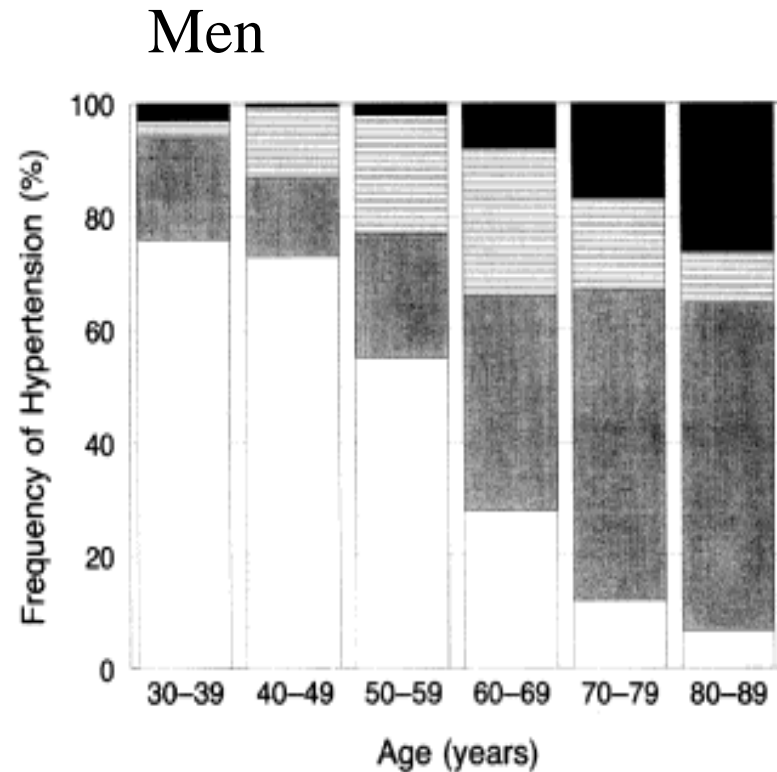
Incidence of CHD and SBP, DBP, and PP by Age Groups

Framingham Study

	β 2	SE2	Wald	HR (95% CI)
Age <50 y				
SBP	0.13	0.04	10.8	1.14 (1.06-1.24)**
DBP	0.29	0.06	21.8	1.34 (1.18-1.51)***
PP	0.02	0.07	0.1	1.02 (0.89-1.17)
Age 50-59 y				
SBP	0.08	0.03	6.3	1.08 (1.02-1.15)*
DBP	0.10	0.06	2.9	1.11 (0.99-1.24)
PP	0.11	0.05	5.4	1.11 (1.02-1.22)*
Age \geq60 y				
SBP	0.16	0.03	30.0	1.17 (1.11-1.24)***
DBP	0.11	0.06	3.2	1.12 (0.99-1.27)
PP	0.21	0.04	36.9	1.24 (1.16-1.33)***

Proportional-Hazard Regression Coefficients. *,p<0.05, **,p<0.01, ***,p<0.001
 HR was associated with a 10 mm Hg increase in BP.

Relative Frequencies of Hypertension Status According to Age. Framingham Study



Prospective RCT for the Effect of Intensified Anti-hypertensive Tx

- Diastolic Hypertension with/without Systolic Hypertension
 - The BBB Study in Sweden
 - Hypertension Optimal Treatment (HOT)
- Isolated Hypertension
 - No Study
 - SHEP, STOP-Hypertension, MRC trial

The BBB Study

- Study Design
 - 2127 treated HT patients with DBP 90-100 mmHg (45-67 years)
 - Further reduction of DBP to 80 mmHg vs unchanged
 - 4 year follow-up
- Results
 - 6-7 mmHg difference of DBP
 - No increase of the number or severity of side effects of drugs
 - No difference in the hard endpoints, stroke and MI

Hypertension Optimal Treatment (HOT)

- 18790 patients from 26 countries, aged 50-80 years (mean 61.5 years) with DBP between 100 mmHg and 115 mmHg
- 3 groups with target DBP \leq 90 mmHg, 85 mmHg, and 80 mmHg
- Felodipine as baseline therapy with the addition of other agents, Aspirin
- Follow-up 3.8 years (3.3-4.9 years)

Events in Relation to Target Diastolic BP

-HOT-

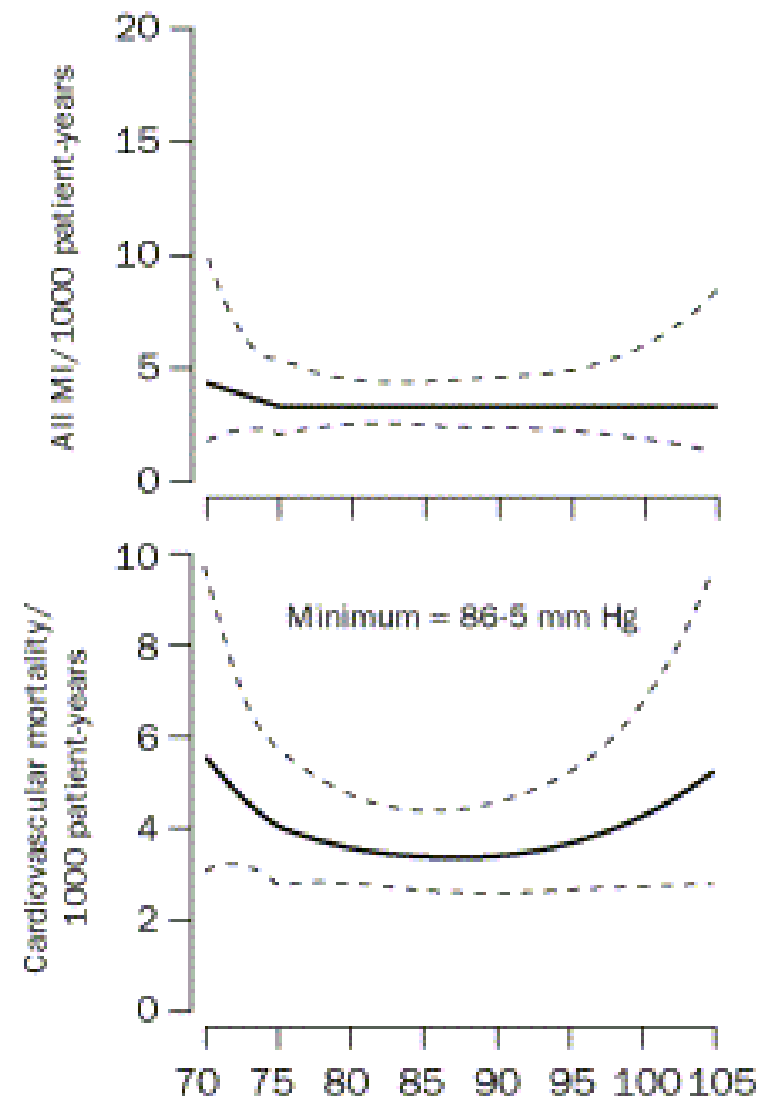
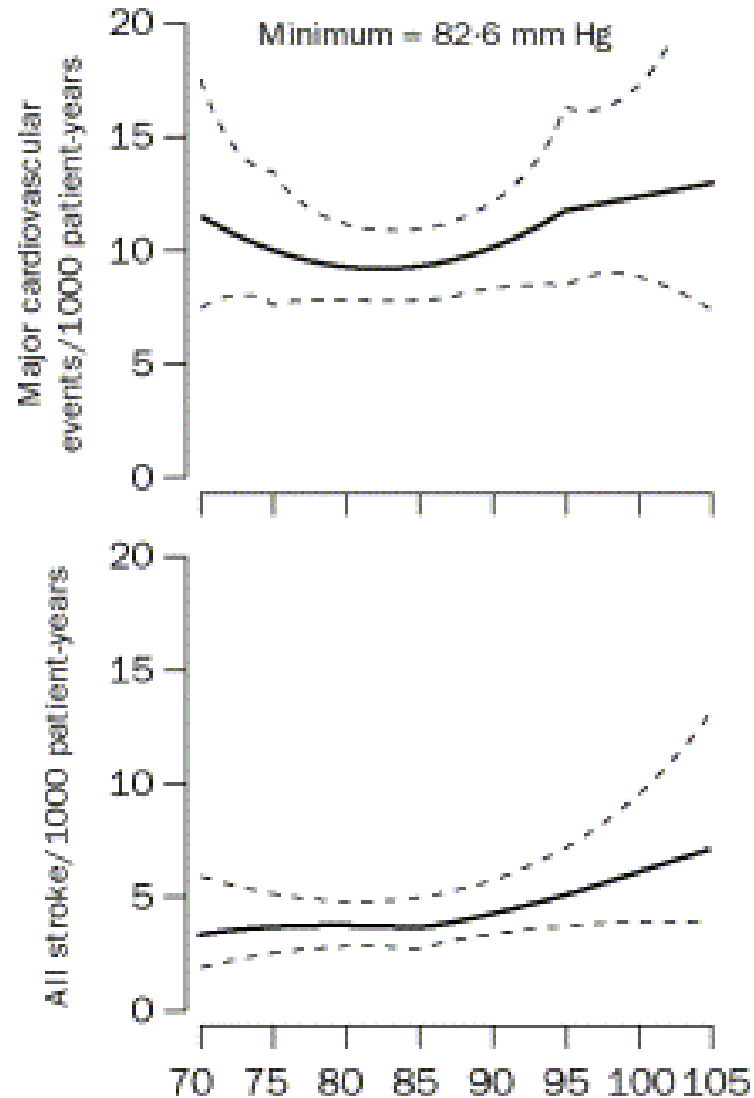
Target BP*	Number of events	Events rate**	p for trend	Target BP*	Number of events	Events rate**	p for trend
Major cardiovascular events				Cardiovascular mortality			
90 mm Hg	232	9.9	0.50	90 mm Hg	87	3.7	0.49
85 mm Hg	234	10.0		85 mm Hg	90	3.8	
80 mm Hg	217	9.3		80 mm Hg	96	4.1	
All myocardial infarction				Total mortality			
90 mm Hg	84	3.6	0.05	90 mm Hg	188	7.9	0.32
85 mm Hg	64	2.7		85 mm Hg	194	8.2	
80 mm Hg	61	2.6		80 mm Hg	207	8.8	
All stroke							
90 mm Hg	94	4.0	0.74				
85 mm Hg	111	4.7					
80 mm Hg	89	3.8					

*: actual BP; 85.2, 83.2, 81.1 mmHg respectively

**; per 1000 patient-year

CV Events in Relation to Achieved DBP

-HOT-



Events in Patients with Diabetes Mellitus

HOT

Target BP*	Number of events	Events rate**	p for trend	Target BP*	Number of events	Events rate**	p for trend
Major cardiovascular events				Cardiovascular mortality			
90 mm Hg	45	24.4	0.005	90 mm Hg	21	11.1	0.016
85 mm Hg	34	18.6		85 mm Hg	21	11.2	
80 mm Hg	22	11.9		80 mm Hg	7	3.7	
All myocardial infarction				Total mortality			
90 mm Hg	14	7.5	0.11	90 mm Hg	30	15.9	0.068
85 mm Hg	8	4.3		85 mm Hg	29	15.5	
80 mm Hg	7	3.7		80 mm Hg	17	9.0	
All stroke							
90 mm Hg	17	9.1	0.34				
85 mm Hg	13	7.0					
80 mm Hg	12	6.4					

*: actual BP; 84.9, 82.9, 81.0 mmHg respectively

**; per 1000 patient-year

Events in 3080 Patients with IHD

-HOT-

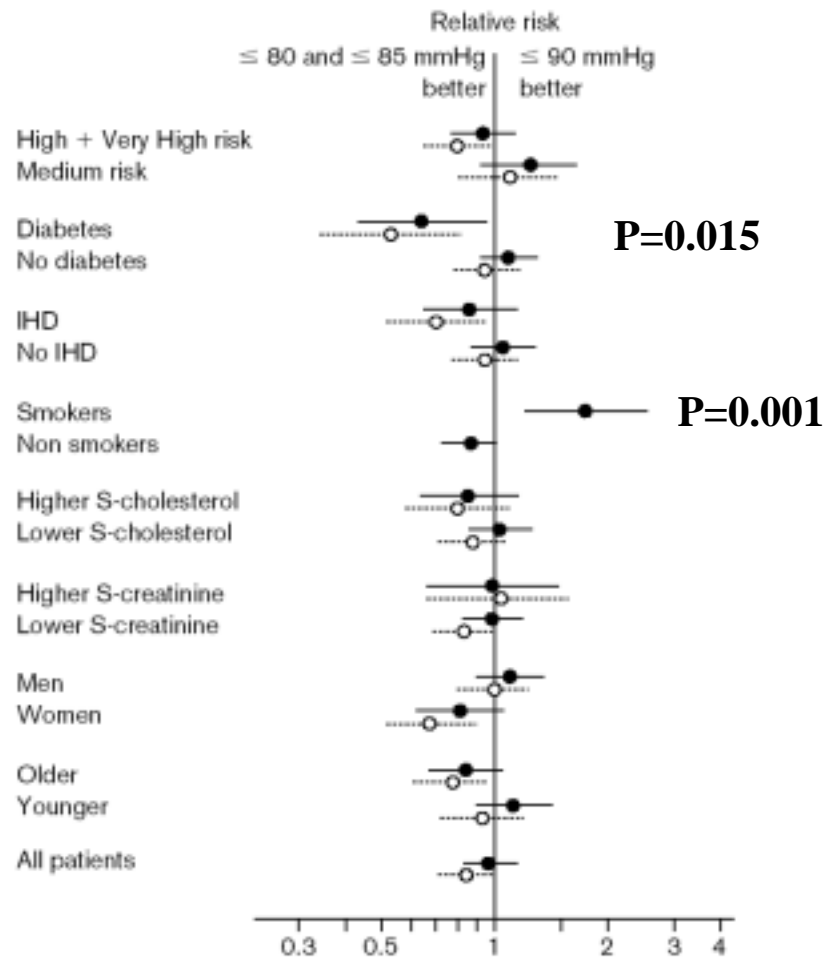
Target BP*	Number of events	Events rate**	p for trend	Target BP*	Number of events	Events rate**	p for trend
Major cardiovascular events				MI mortality			
90 mm Hg	77	20.5		90 mm Hg	4	1.0	
85 mm Hg	68	17.9		85 mm Hg	3	0.8	
80 mm Hg	62	16.4	ns	80 mm Hg	2	0.5	ns
All myocardial infarction				Stroke mortality			
90 mm Hg	35	9.3		90 mm Hg	5	1.3	
85 mm Hg	26	6.8		85 mm Hg	6	1.5	
80 mm Hg	31	8.3	ns	80 mm Hg	5	1.3	ns
All stroke							
90 mm Hg	35	9.3					
85 mm Hg	30	7.9					
80 mm Hg	20	5.3	0.046				

*: actual BP; 85.2, 83.2, 81.1 mmHg respectively

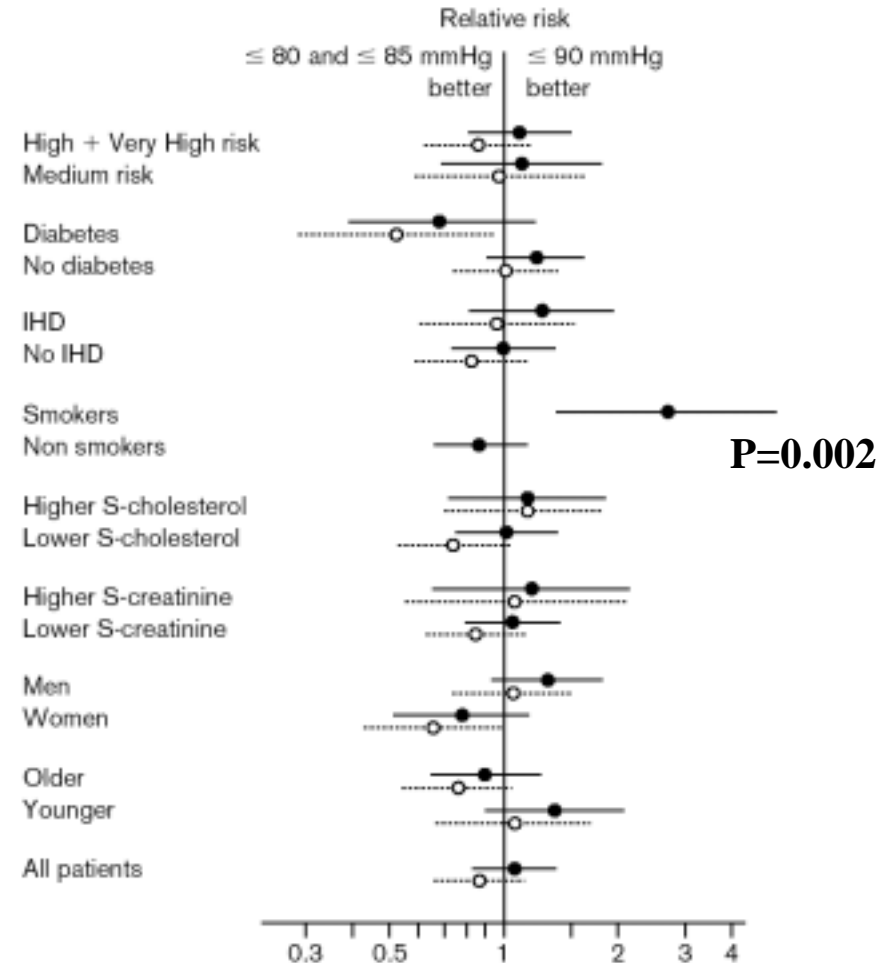
**; per 1000 patient-year

Subgroup Analysis of HOT

CV Event



CV Mortality



Systolic Hypertension in the Elderly Program (SHEP)

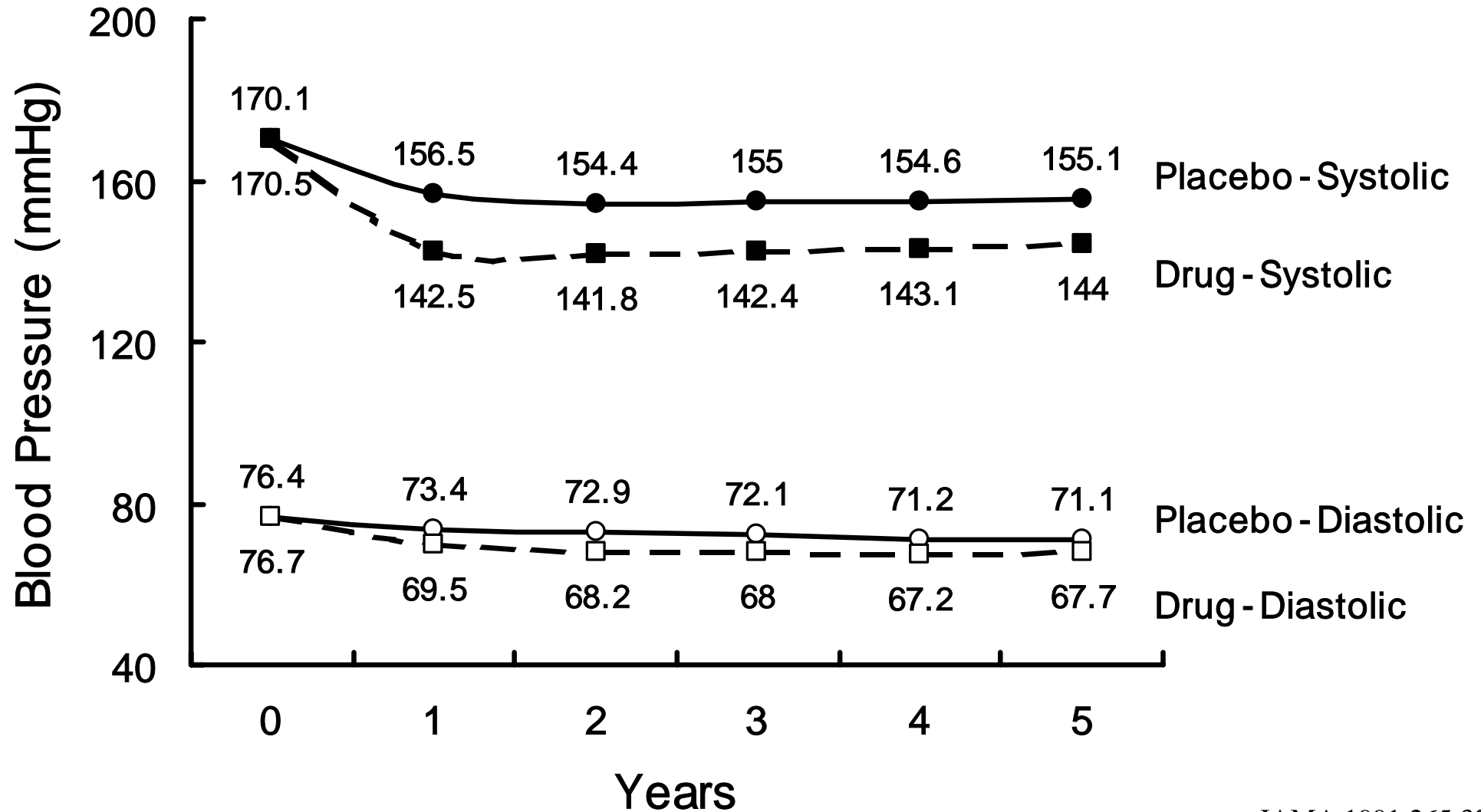
Old age (≥ 60 y), systolic pressure ≥ 160 mmHg and diastolic pressure ≤ 90 mmHg

Placebo vs. chlorthalidone with atenolol

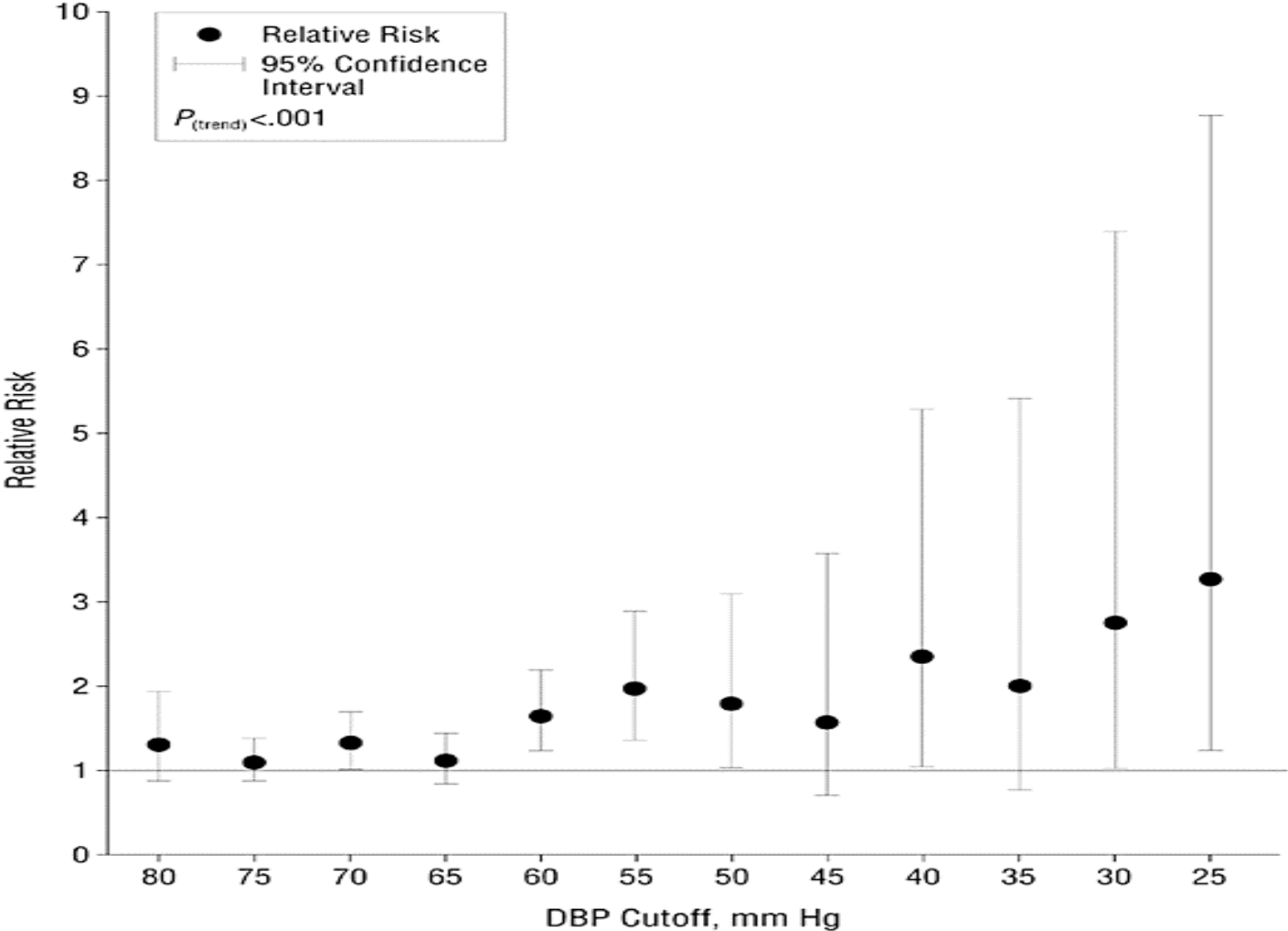
Average 4.5 years follow-up

		Placebo (n=2371)	Active (n=2365)	Relative Risk (95% CI)
Death	Total	242	213	0.87(0.73-1.05)
	Cardiovascular	112	90	0.80(0.60-1.05)
	Other	103	109	1.05(0.80-1.38)
Event	Stroke	149	96	0.63(0.49-0.82)
	MI	74	50	0.67(0.47-0.96)
	LVH	102	48	0.46(0.33-0.65)
Combined	Nonfatal MI+CHD death	141	104	0.73(0.57-0.94)
	CHD	184	140	0.75(0.60-0.94)
	CVD	414	289	0.68(0.58-0.79)

Systolic and Diastolic Pressure during Follow-up in SHEP



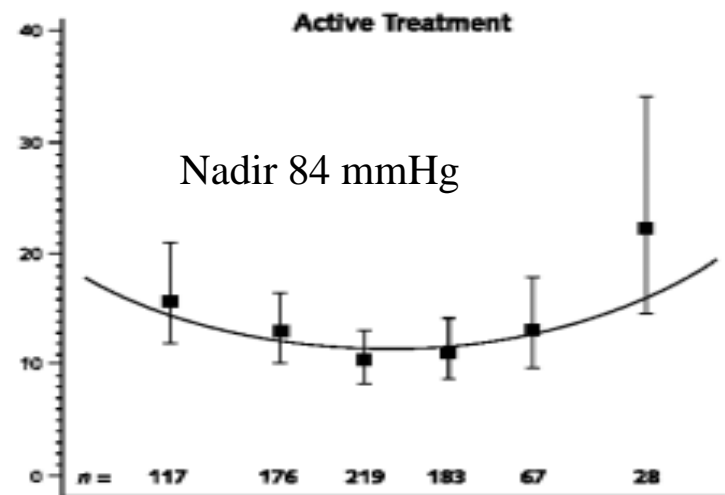
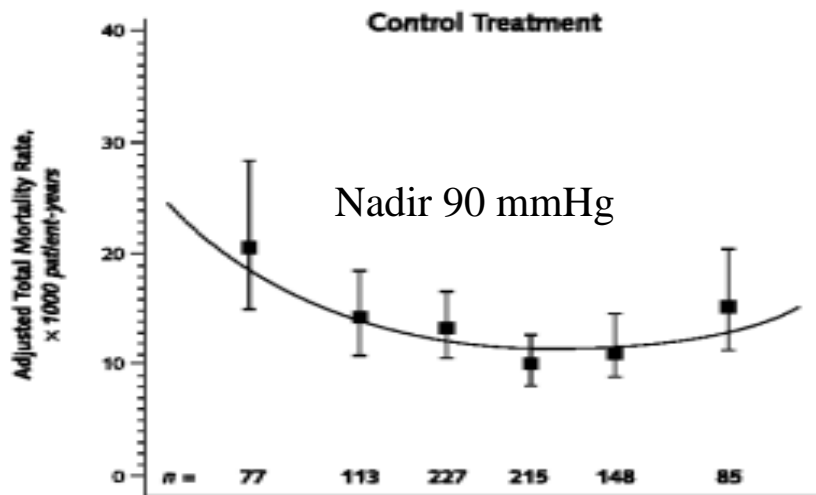
RR for CVD by DBP in Treatment Group -SHEP-



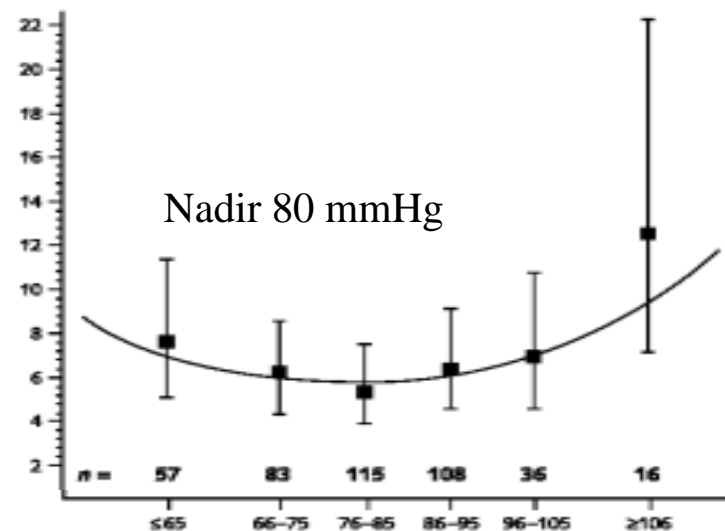
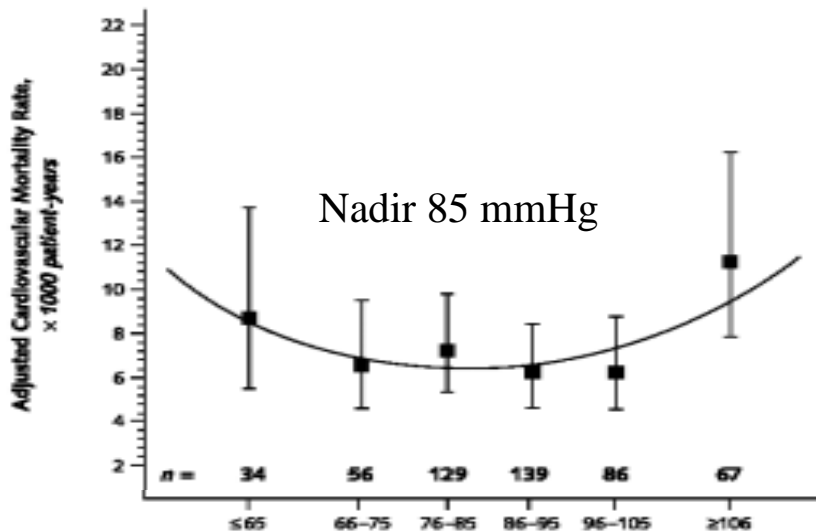
Rates of Events and Diastolic Blood Pressure in Active Treatment and Control Groups

- Meta-Analysis of 7 RCTs -

Total Mortality



CV Mortality



Summary

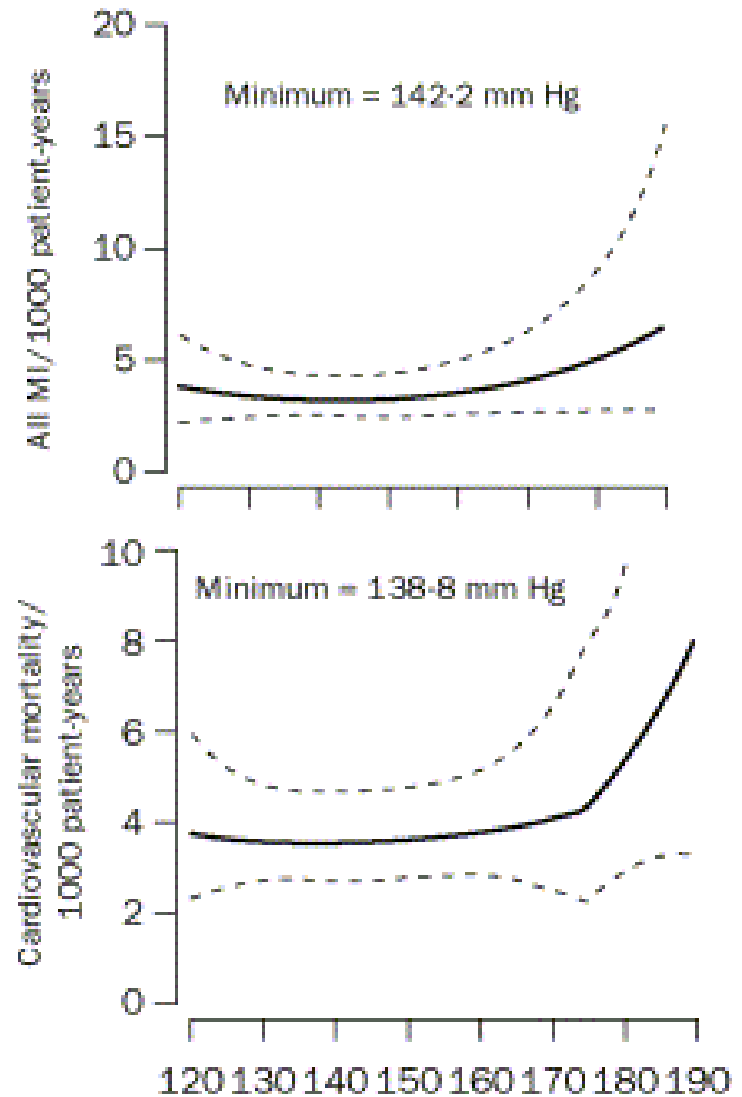
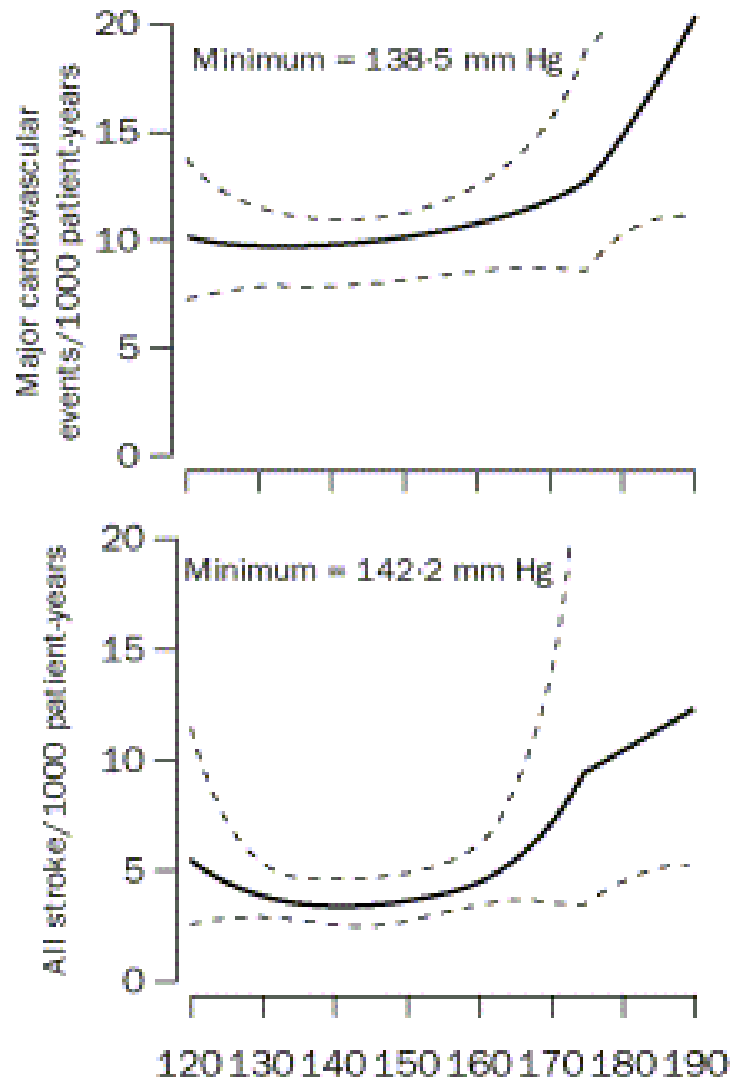
- endpoint J-
curve - 가 가 . ,
- 85 mmHg J curve 가 가 , 가 .

Cruickshank J. The J-curve in hypertension. *Curr Cardiol Rep.* 2003 Nov;5(6):441-52. Review

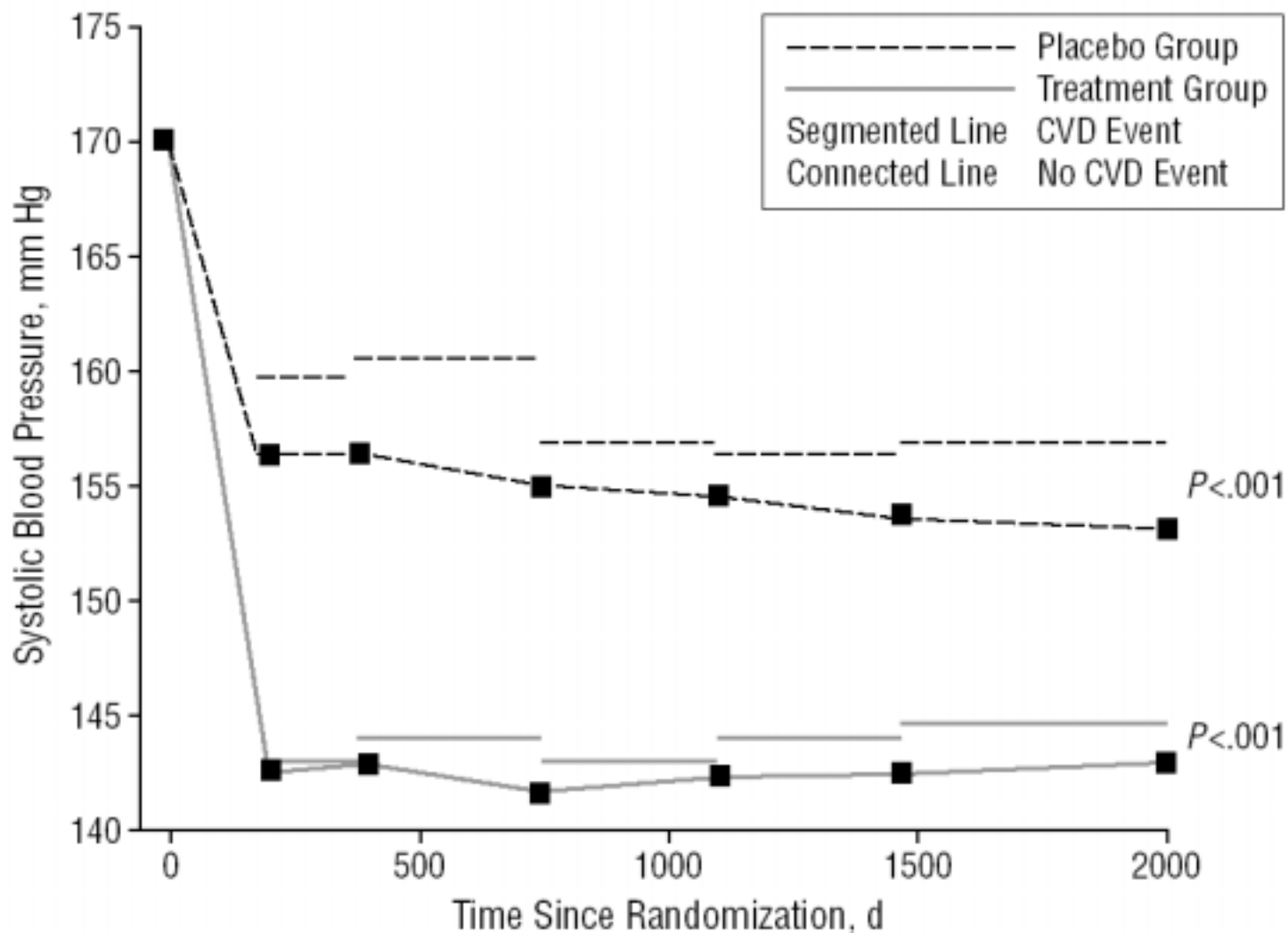
It is now reasonable to conclude that for nonischemic hypertensive subjects the therapeutic lowering of diastolic blood pressure (DBP) to the low 80s mm Hg is beneficial, but it is safe (though unproductive) to go lower.

However, in the presence of coronary artery disease (limited coronary flow reserve) there is a J-curve relationship between treated DBP and myocardial infarction, but not for stroke. In such high-risk (for myocardial infarction) cases it would be prudent to avoid lowering DBP to below the low 80s mm Hg.

CV Events in Relation to Achieved SBP -HOT-

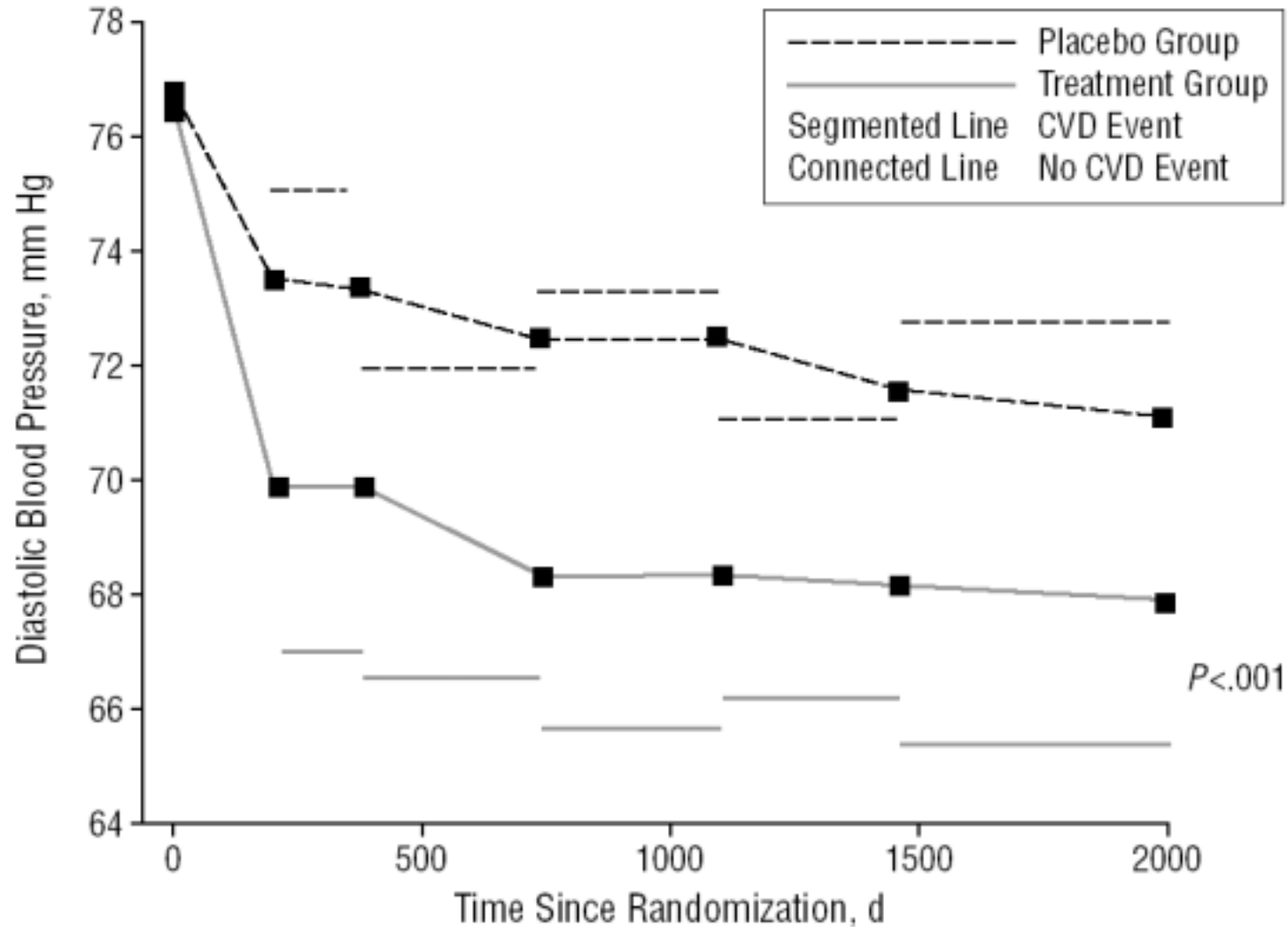


Systolic BP in Patient with/without CVD -SHEP-



Diastolic BP in Patient with/without CVD

-SHEP-



RR of Events for 5 mmHg Decrease of Pressure

-SHEP-

Relative Risk by Type of Event and Treatment Group*

Event	Stroke		CHD		CVD	
	Active Treatment (n = 103)	Placebo (n = 159)	Active Treatment (n = 139)	Placebo (n = 183)	Active Treatment (n = 287)	Placebo (n = 413)
SBP†	0.90‡ (0.85-0.95)	0.96 (0.92-1.01)	0.98 (0.93-1.04)	0.95§ (0.91-1.00)	0.94‡ (0.91-0.97)	0.95‡ (0.93-0.98)
DBP†	1.14‡ (1.05-1.22)	0.92§ (0.85-1.00)	1.08§ (1.00-1.16)	1.00 (0.93-1.08)	1.11‡ (1.05-1.16)	1.00 (0.95-1.05)
Composite variable	2.16‡	1.56§	1.81‡	2.50‡	2.05‡	1.97‡
Age¶	1.13	1.33‡	1.05	1.04	1.09	1.12‡
Sex (men)	1.28	1.27	2.16‡	1.74‡	1.69‡	1.49‡
Race (black)	1.10	1.41	0.56	0.87	0.72	0.99
Medication	1.03	1.30	0.82	1.00	0.93	1.18
Smoker (ever)	1.00	0.99	1.15	1.13	1.13	1.13

*CHD indicates coronary heart disease; CVD, cardiovascular disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

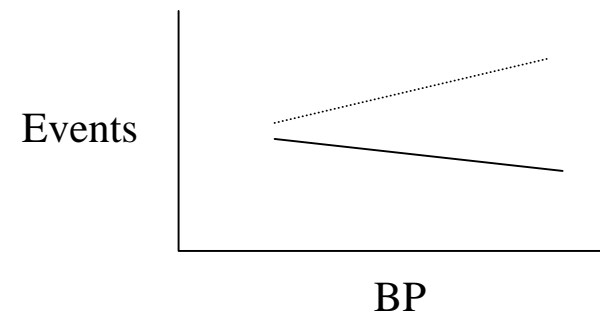
†For 5-mm Hg decrease; values are relative risk (95% confidence interval).

‡P < .01.

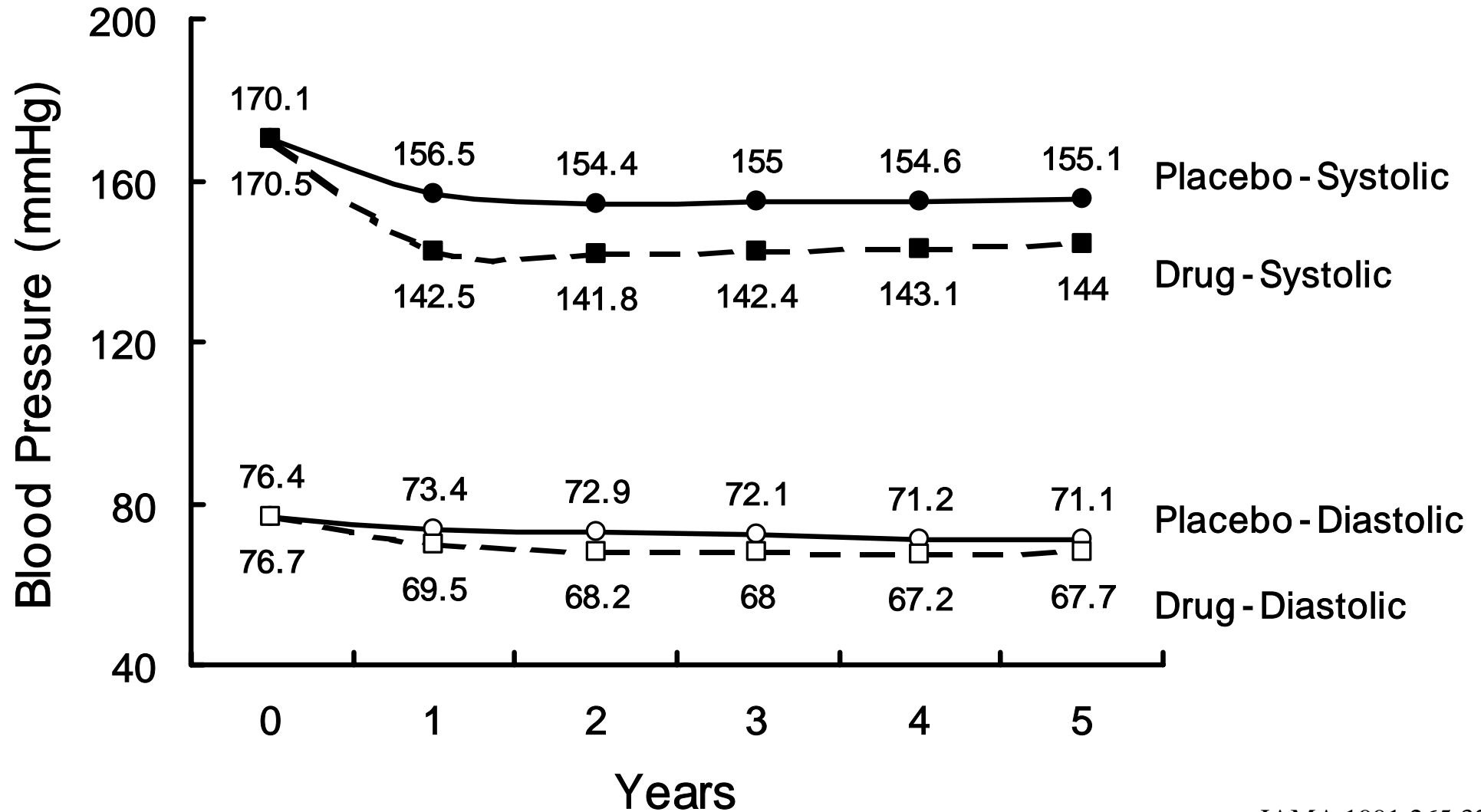
§P < .05.

||Includes diabetes, previous heart attack, or stroke.

¶For 5 years.



Systolic and Diastolic Pressure during Follow-up in SHEP

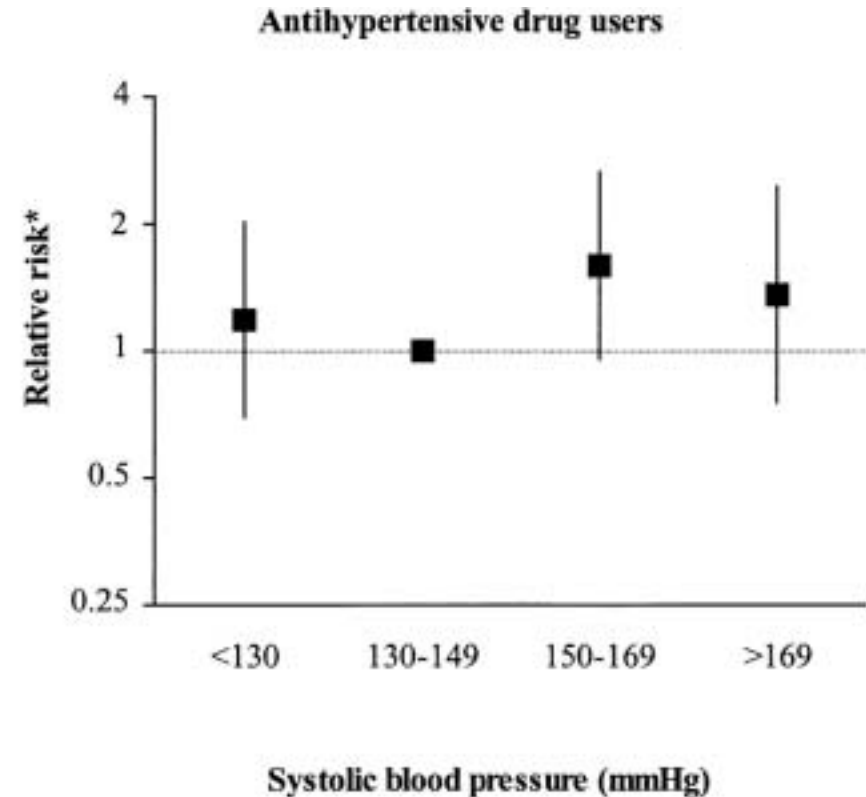
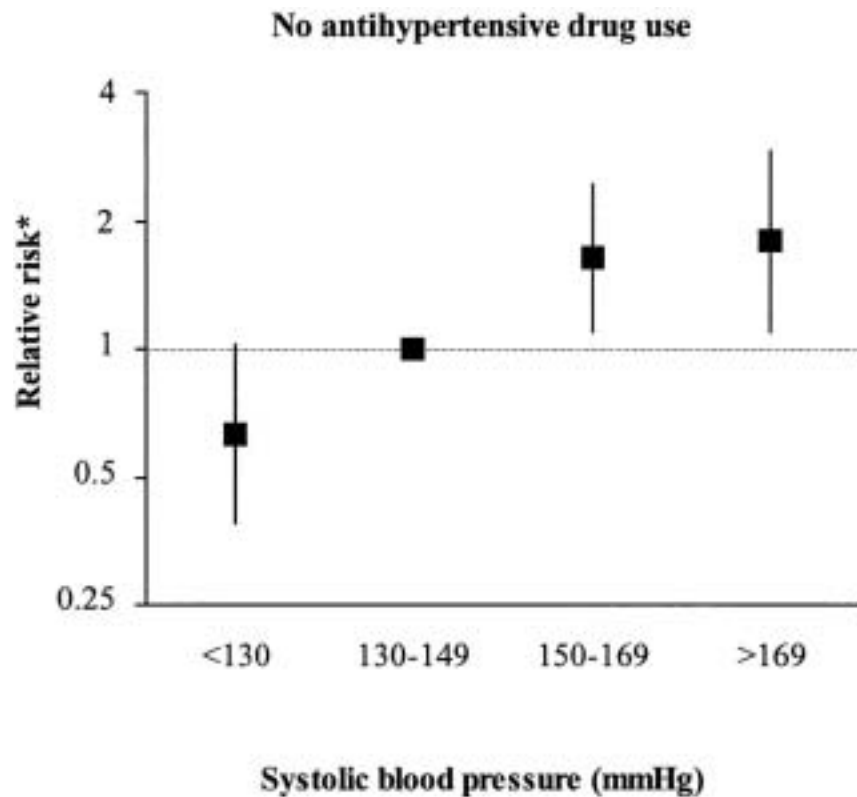


Comparison of Treatment Groups between Old Meta-analysis and HOT

	Collins et al. 1990 (n=18487)	HOT, 1998 (n=18790)
Age (years)	52.0	61.5
Initial DBP (mmHg)	99	105
Achieved DBP (mmHg)	93	83.2
DBP reduction (mmHg)	6	20-24
F/U duration (years)	5	3.8
Events (/1000 person-year)		
MI	7.8	3.0
CV Mortality	6.5	3.8

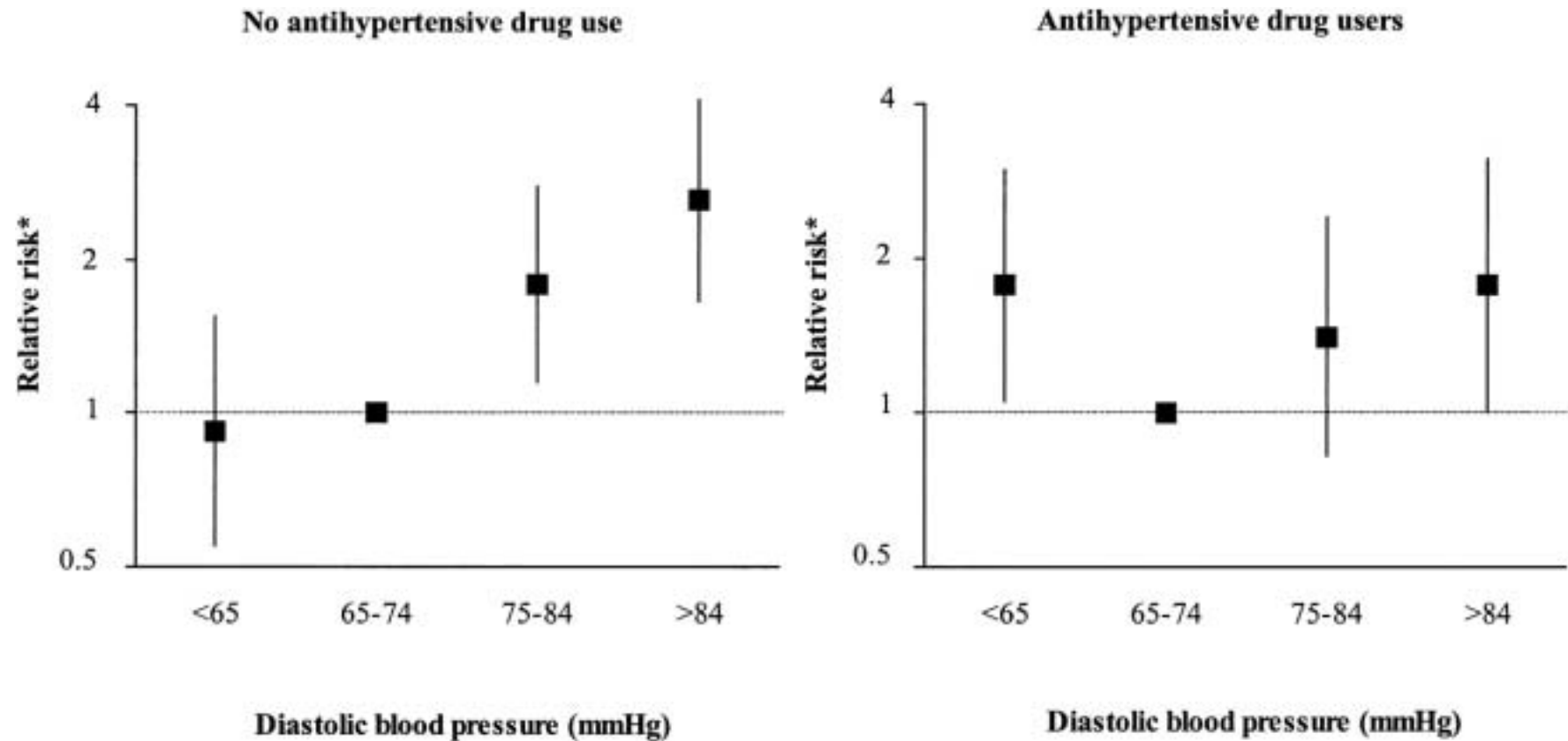
Systolic BP and Risk of Stroke according to Antihypertensive Treatment

-Rotterdam Study-



Diastolic BP and Risk of Stroke according to Antihypertensive Treatment

-Rotterdam Study-



Events in Patients without Diabetes Mellitus

-HOT-

Target BP*	Number of events	Events rate**	p for trend
------------	------------------	---------------	-------------

Major cardiovascular events

90 mm Hg	187		
85 mm Hg	200		
80 mm Hg	195		

All myocardial infarction

90 mm Hg	70		
85 mm Hg	56		
80 mm Hg	54		

All stroke

90 mm Hg	77		
85 mm Hg	97		
80 mm Hg	77		

Target BP*	Number of events	Events rate**	p for trend
------------	------------------	---------------	-------------

Cardiovascular mortality

90 mm Hg	66	3.1	
85 mm Hg	69	3.2	
80 mm Hg	89	4.1	0.061

Total mortality

90 mm Hg	158		
85 mm Hg	165		
80 mm Hg	190		

*: actual BP; 85.2, 83.2, 81.1 mmHg respectively

**; per 1000 patient-year

Report of the European Working Party on High Blood Pressure in the Elderly (EWPHE)

- Patients with low blood pressure had decreased values for body mass index and hemoglobin—two indicators of poor health

CVD vs Systolic and Diastolic BP

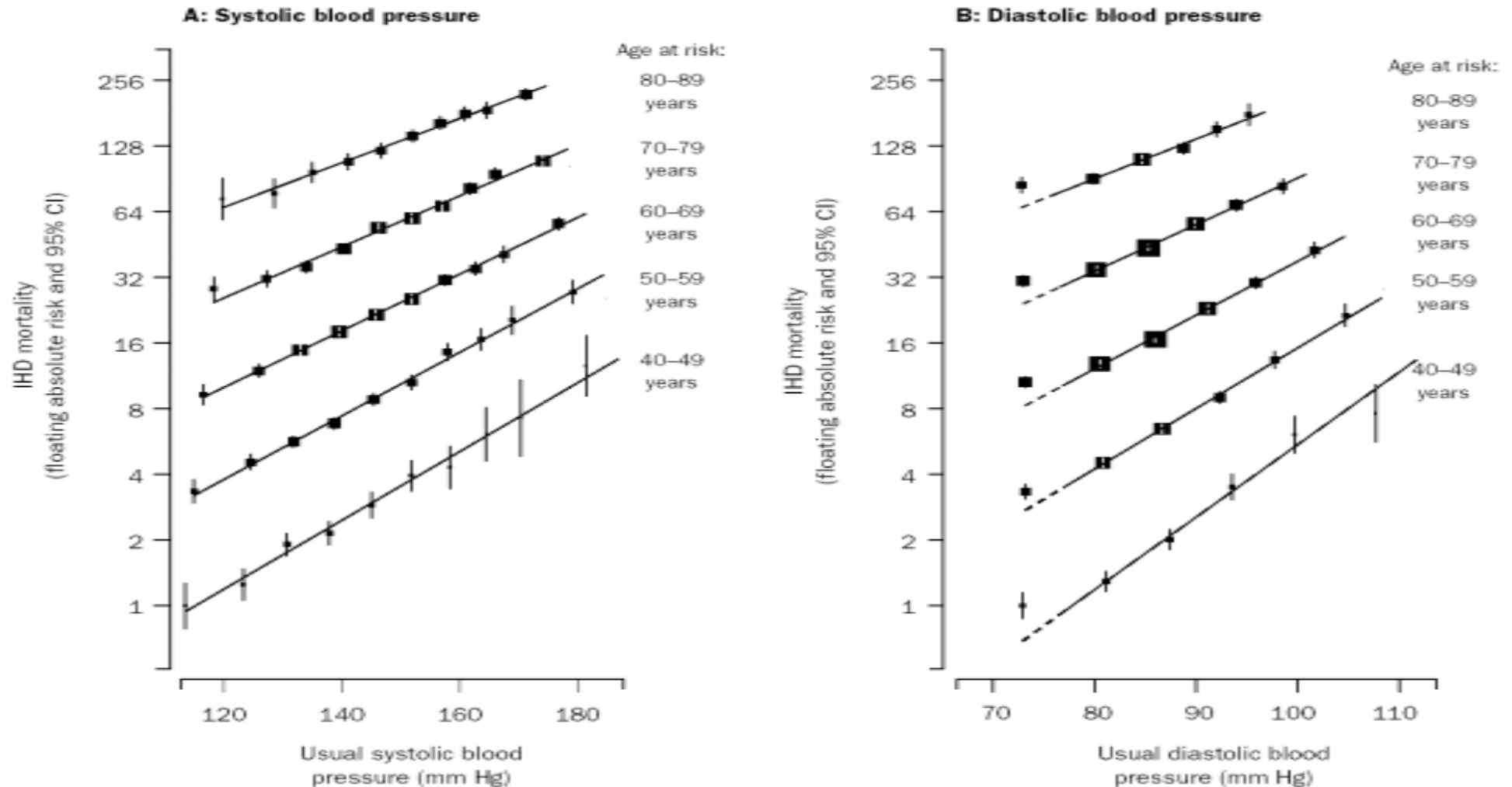
Framingham Study

TABLE 4 Incidence of Nonfatal Cardiovascular Events by Diastolic Pressure at Specified Levels of Systolic Blood Pressure*

Diastolic BP (mm Hg)	10-Yr Incidence Rate (%)								
	Systolic BP (mm Hg): <140			140–159			>160		
	At risk	Events	Rate	At risk	Events	Rate	At risk	Events	Rate
Men									
<80	1,147	129	11.3%	65	29	44.6%	12	6	50.0%
80–90	1,219	139	11.4%	211	44	20.9%	42	19	45.2%
>90	288	56	19.4%	414	79	19.1%	230	76	33.0%
Women									
<80	1,918	92	4.8%	133	30	22.6%	38	12	31.6%
90	1,023	68	6.7%	267	36	13.5%	89	19	21.4%
>90	163	17	10.4%	289	42	14.5%	250	58	23.2%
Both									
<80	3,065	221	7.2%	198	59	29.8%	50	18	36.0%
80–89	2,242	207	9.2%	478	80	16.7%	131	38	29.0%
>90	451	73	16.2%	703	121	17.2%	480	134	27.9%

*Framingham study cohorts, subjects ages 35 to 80 years.
Crude rates unadjusted for age or other risk factors.

Age-Specific Relevance of Usual Blood Pressure to Vascular Mortality: a Meta-Analysis



Randomized Trials of Drug Therapy in AMI (Beta-blocker)

	Agents	No. of Patients	Duration of Study	RR of Death (95% CI)	p
During Infarction					
ISIS-1	Atenolol	16,027	7 days	0.85 (0.73-0.99)	0.04
MIAMI	Metoprolol	5,778	15 days	0.87 (0.67-1.08)	0.29
TIMI IIB	Metoprolol	1,434	6 days	1.00 [‡]	0.98
After Infarction					
Norwegian	Timolol	1,884	33 mo	0.61 (0.46-0.80)	0.001
BHAT	Propranolol	3,837	25 mo	0.72 (0.64-0.80)	0.005

Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs

- 484 men born in 1914 and living in Malmö, Sweden during 1982 and follow up for up to 10 years
- Among men with diastolic blood pressure >90 mm Hg, the risk was increased twofold but disappeared when adjustments were made for other cardiovascular risk factors
- Among those with diastolic blood pressure ≤ 90 mm Hg, the risk associated with taking antihypertensive drugs was four times higher and remained after adjustment for other cardiovascular risk factors

