"On Monday, September 26, 1955, Wall Street panicked. The Dow Jones plunged 6.5%, 32 points, to 455. The total paper loss for the day was $14 billion, the largest ever, while volume was 7,720,000 shares, the highest since July 1933."

Messerli FH, et al. New Engl.J.Med. September 2005


PrintsAndPhotos.com

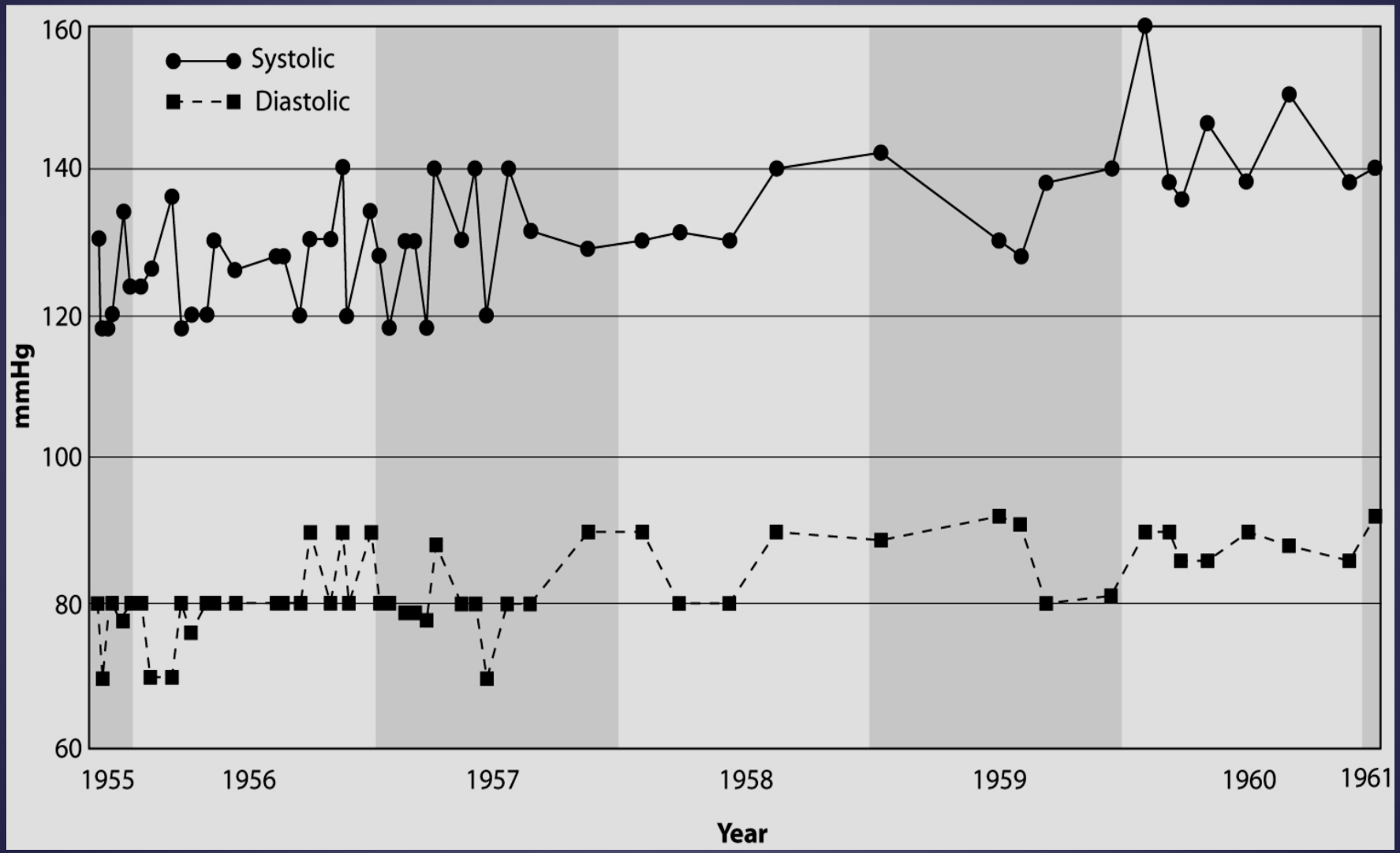
" Ikes heart attack began at 2:00 pm while playing golf at Cherry Hills Country Club on September 23, 1955, when he complained of what he thought was indigestion."

Lasby C.G.
Eisenhower's Heart Attack
1997

“ His wife, Mamie, called Dr. Snyder back to the house about 2:00 a.m.. He mis-diagnosed the heart attack as a GI problem and waited 10 hours before sending Eisenhower to the hospital.”

New York Times, Sept. 26,1955

Blood Pressure Determinations – Dwight D. Eisenhower Nov. 13 ,1955 to Jan. 21, 1961



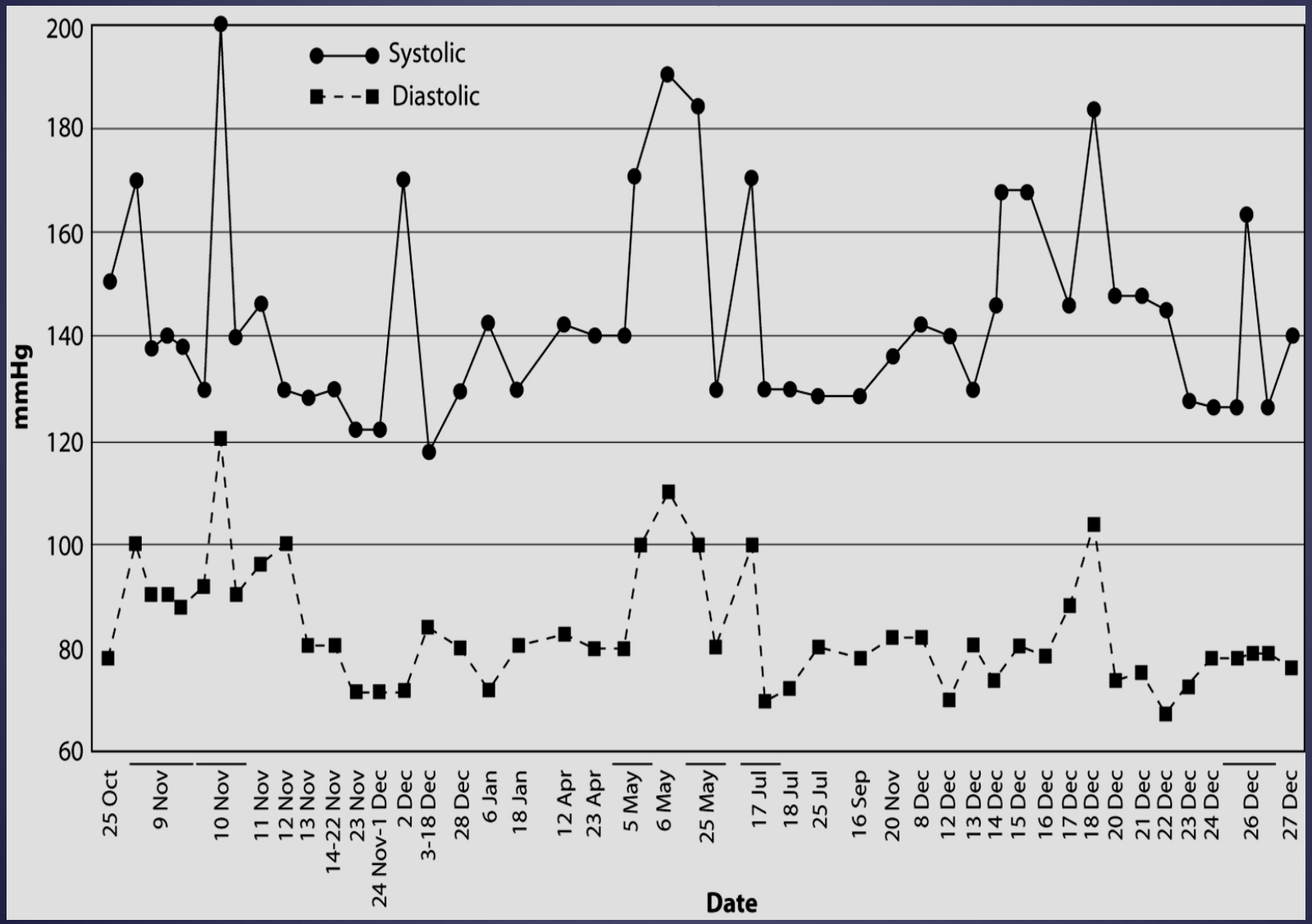
From his first infarction in 1955 until his death in 1969, Eisenhower had at least 7 myocardial infarctions and 14 cardiac arrests. He died from heart failure on March 28, 1969, at the age of 78 years, nearly 14 years after his first heart attack.

New England Journal of Medicine 353:1205-1207
2005

Eisenhower's Billion-Dollar Heart Attack — 50 Years Later

Franz H. Messerli, M.D., Adrian W. Messerli, M.D., and Thomas F. Lüscher, M.D.

Blood Pressure Determinations – Dwight D. Eisenhower 1965-66 at Age 75-76

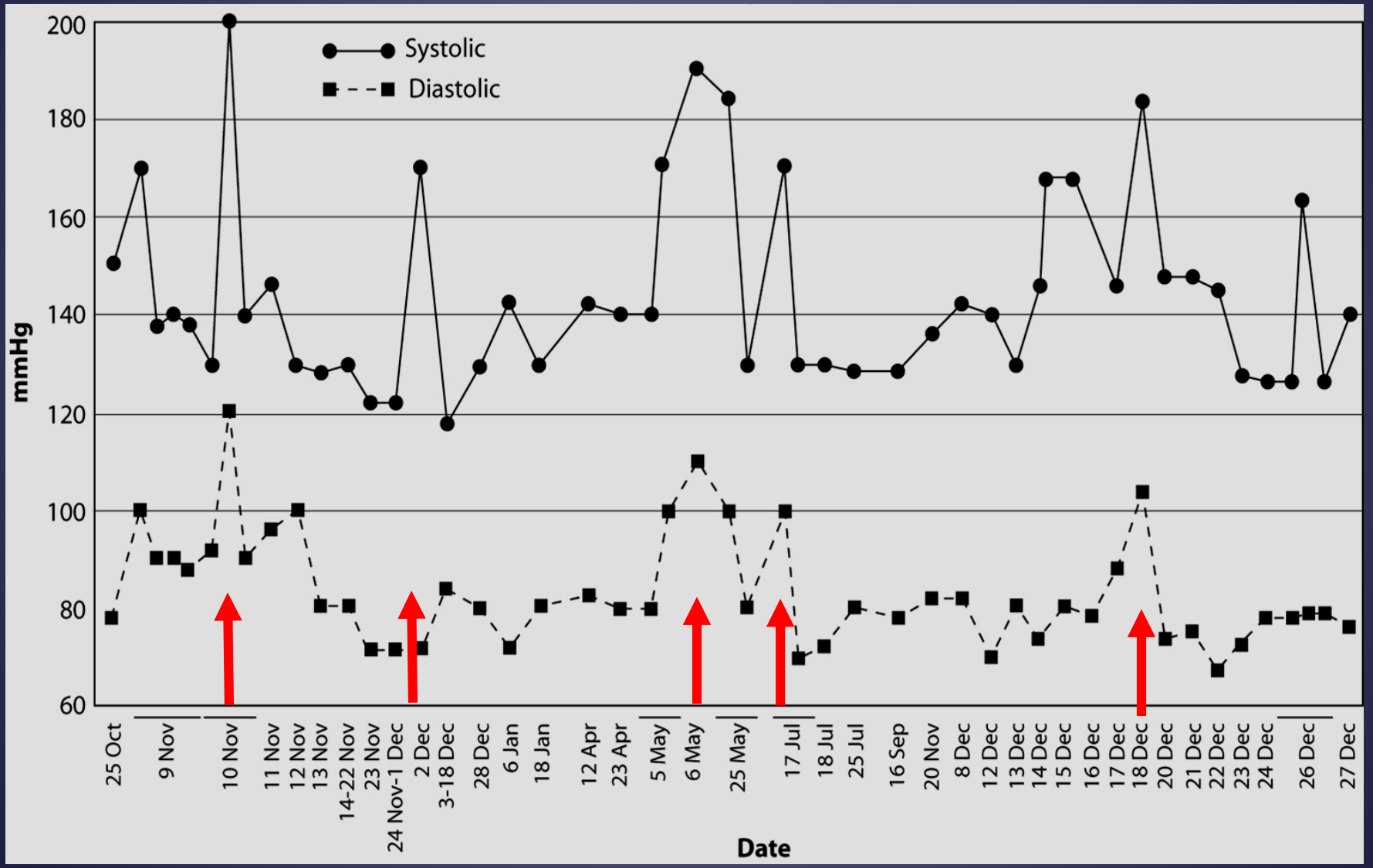


“Unexpectedly, the autopsy at Walter Reed Army Hospital revealed the hitherto unreported finding that Dwight David Eisenhower, 34th President of the United States, had a 1.5 cm tumor of the left adrenal gland…that had histologic features consistent with a pheochromocytoma …

Messerli FH et al. Am J Cardiol. 2007 May 1;99(9):1325-9.

Blood Pressure Determinations – Dwight D. Eisenhower 1965-66 at Age 75-76

Pheochromocytoma



“In the past 100 years, only during the 1918 flu pandemic was cardiovascular disease *not* the number-one cause of death”.

AHA Year End Statistics 2008

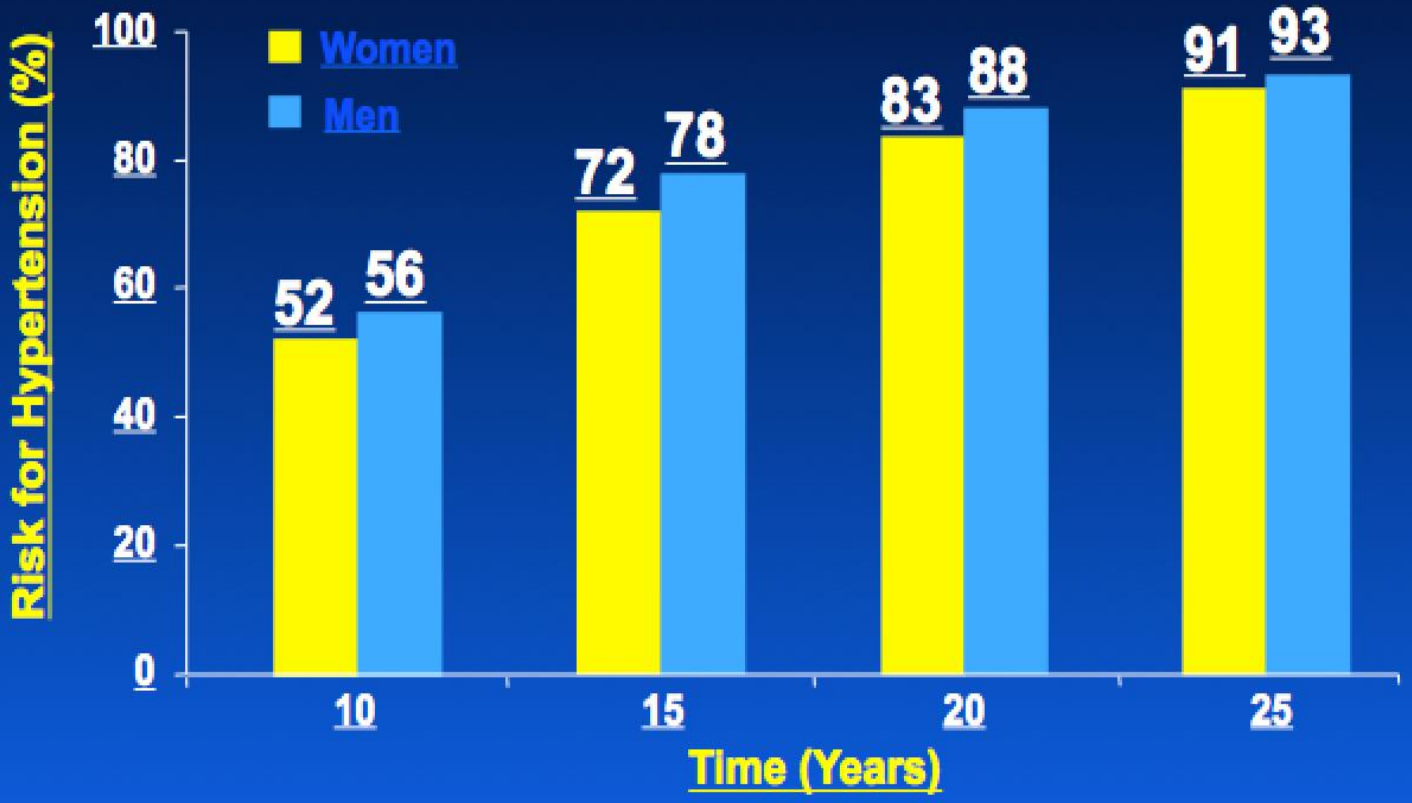

CBS
ONE IN THREE
PEOPLE IN LOUISIANA
WILL DIE FROM HEART DISEASE
Get the facts at heart.org
My Heart. My Life.
POWER TO END STROKE
Go Red
CBS OUTDOOR


CBS
ONE IN THREE
PEOPLE IN LOUISIANA
WILL DIE FROM HEART DISEASE
Get the facts at heart.org
POWER TO END STROKE
Go Red
CBS OUTDOOR
CBS
2 FOR $3
CROISSAN'WICH
Mornings are twice as delicious.
BURGER KING

What is the residual lifetime risk of becoming hypertensive in a normotensive person at age 55?

- 10 – 30 %
- 30 – 50 %
- 50 – 70 %
- 70 – 90 %
- >90 %

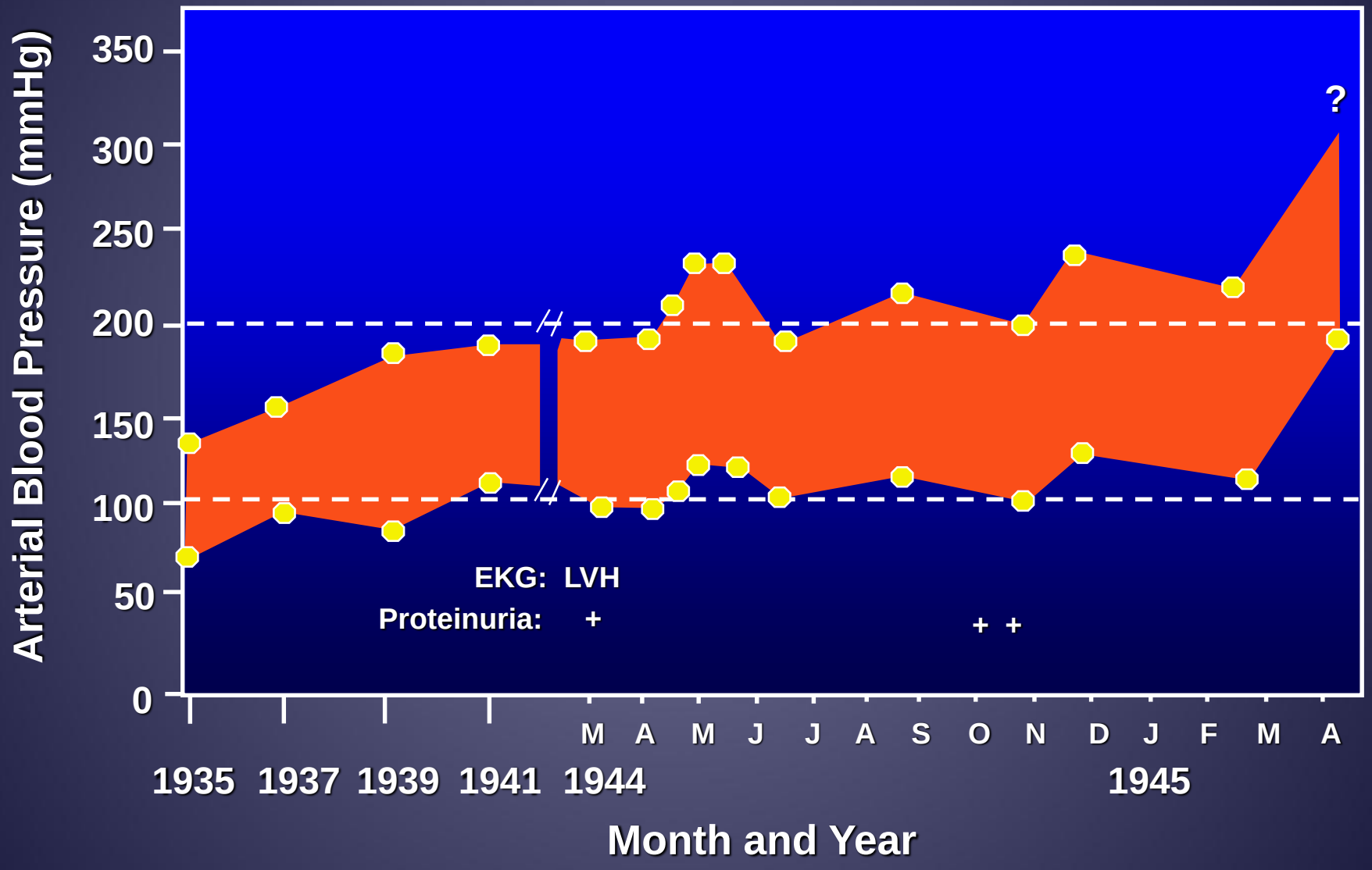
Residual Lifetime Risk for Hypertension From Age 55



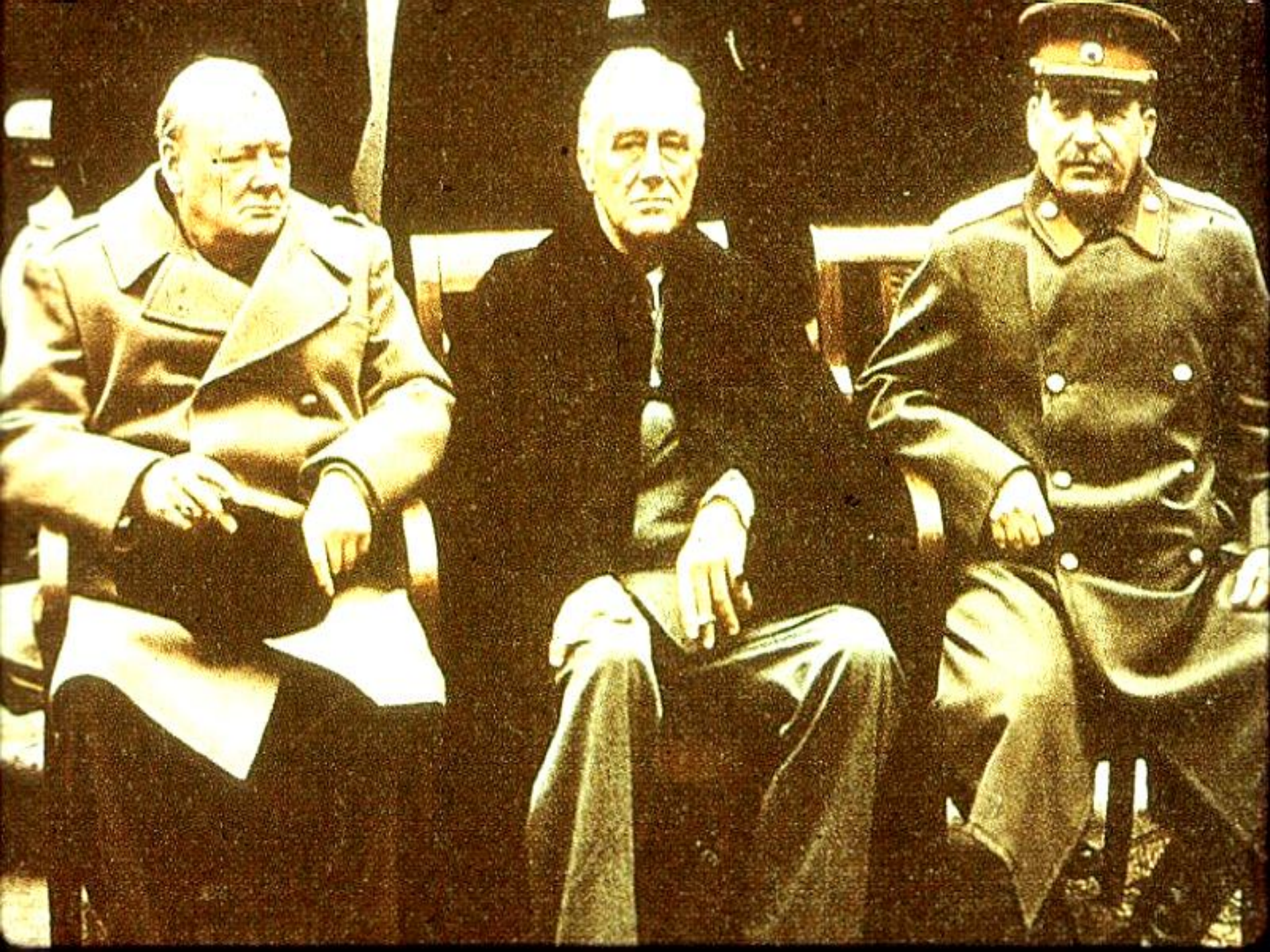
Individuals who are normotensive at age 55 have a > 90% lifetime risk of developing hypertension

Vasan RS et al. *JAMA*. 2002;287:1003-1010 **Framingham.**

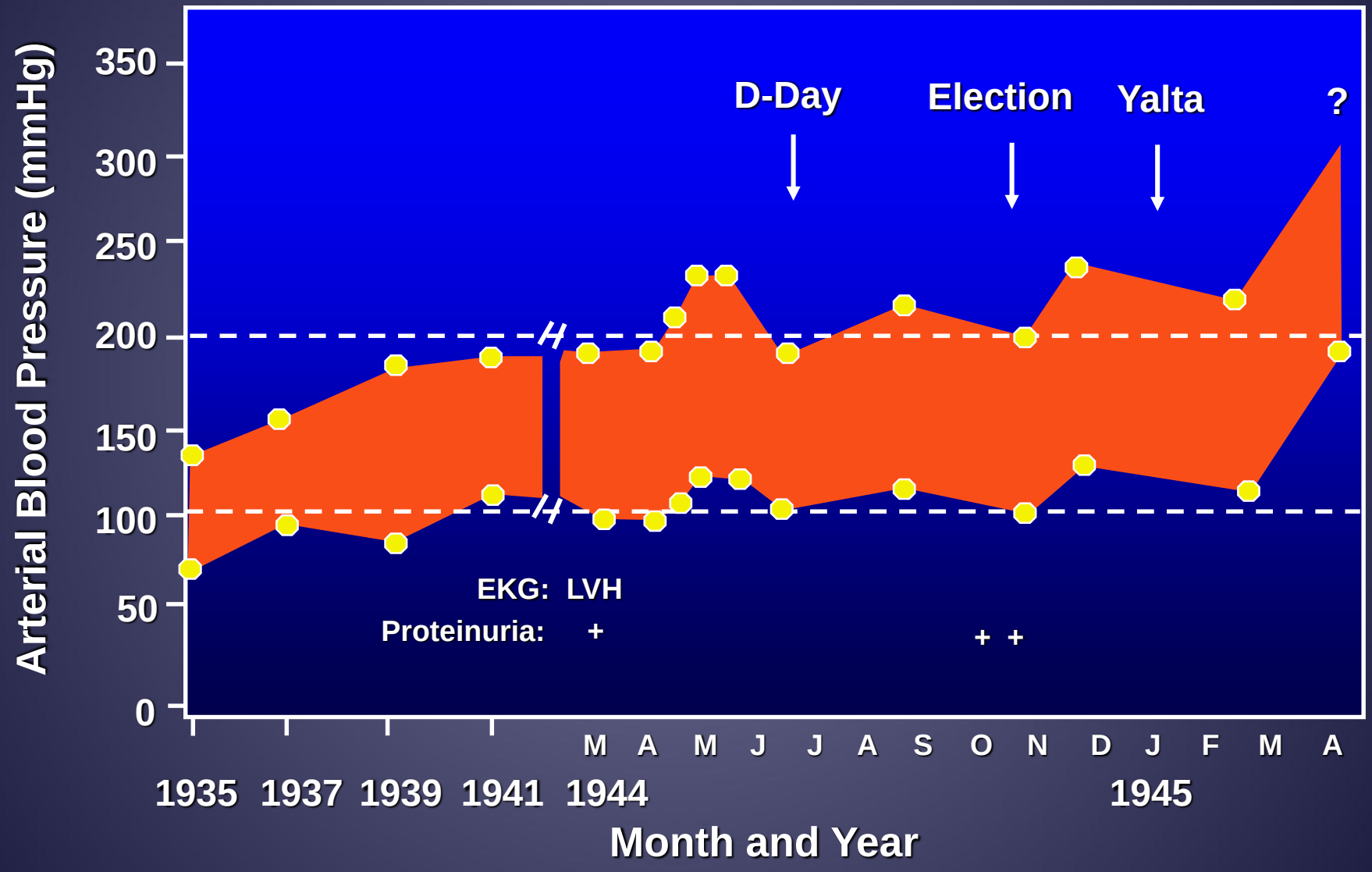
Natural History of “Essential Hypertension”



Messerli FH, NEJM, 332:1038-1039, 1995



Arterial Pressure of Franklin D. Roosevelt from 1935 until his death on April 12, 1945



Messerli FH, NEJM, 332:1038-1039, 1995

'I HAVE TERRIFIC HEADACHE,' LAST WORDS OF F. D. R.

WARM SPRINGS, Ga., April 13 (AP).—President Roosevelt's last words were: "I have a terrific headache."

They were uttered when N. Robbins, a New York artist, was sketching the President. The Chief Executive lost consciousness and never recovered.

'CAME OUT OF CLEAR SKY,' SAYS PRESIDENT'S PHYSICIAN

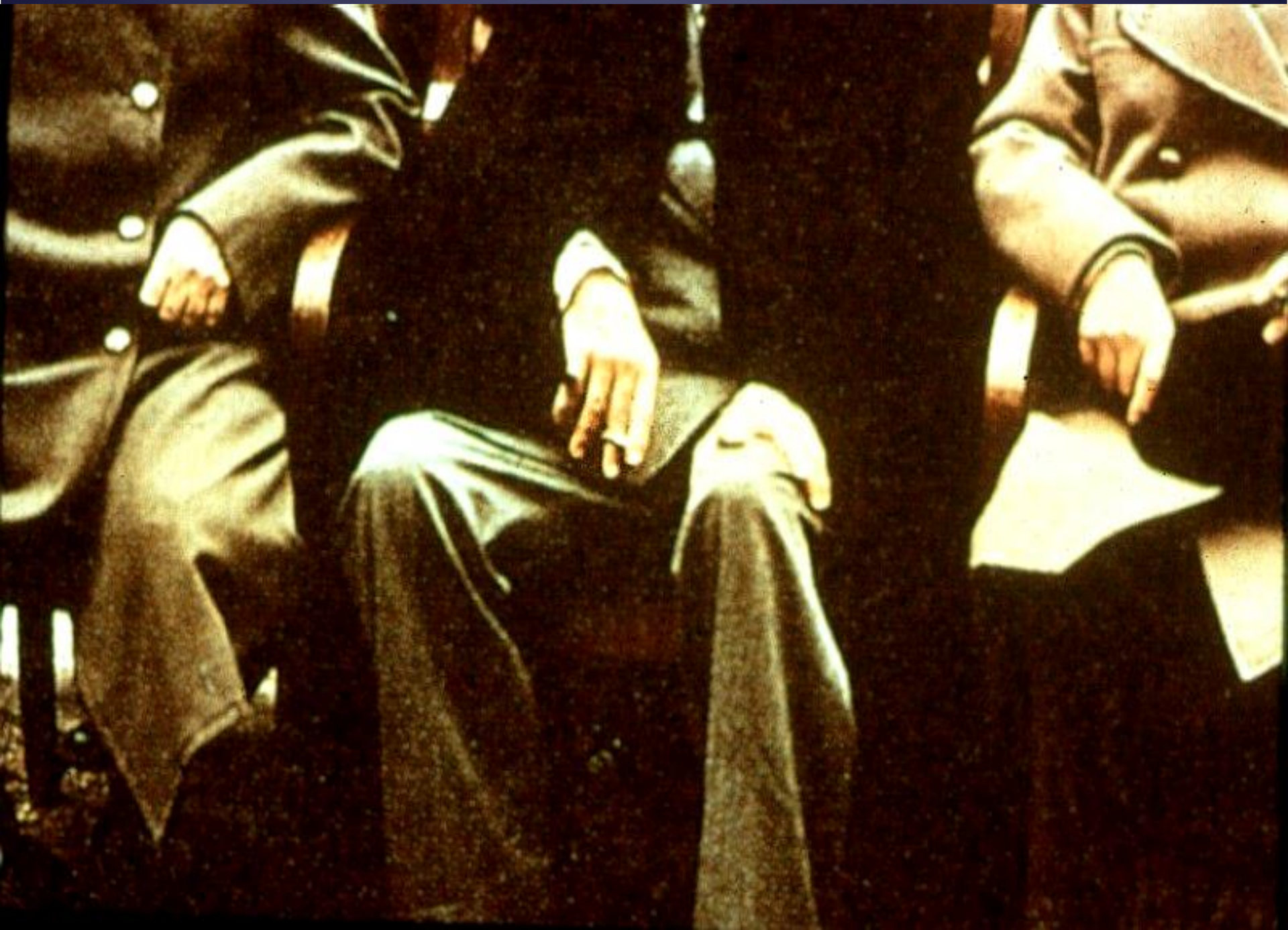
Adm. Ross T. McIntire Asserts There Was No Indication of Imminent Danger.

By CHARLES G. ROSS
Contributing Editor of the

DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

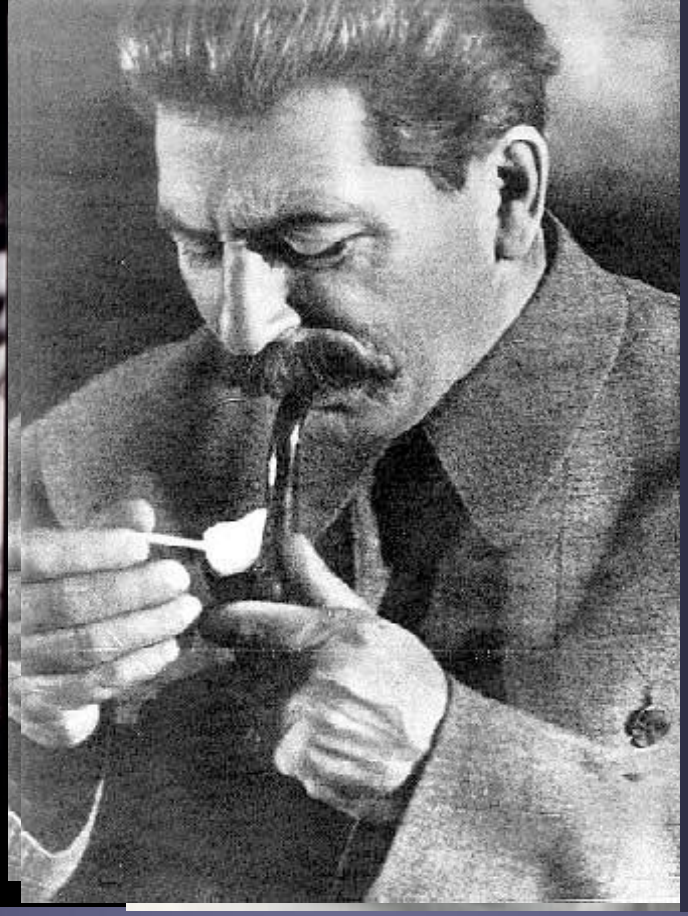
WASHINGTON, April 13 (AP). PRESIDENT ROOSEVELT died from what doctors call a cerebral hemorrhage, which means a sudden extensive bleeding in the brain due

Early said that just before the trip the President was given a thorough examination by seven or eight physicians, including some of the most eminent in the country, and was pronounced organically sound in every way.



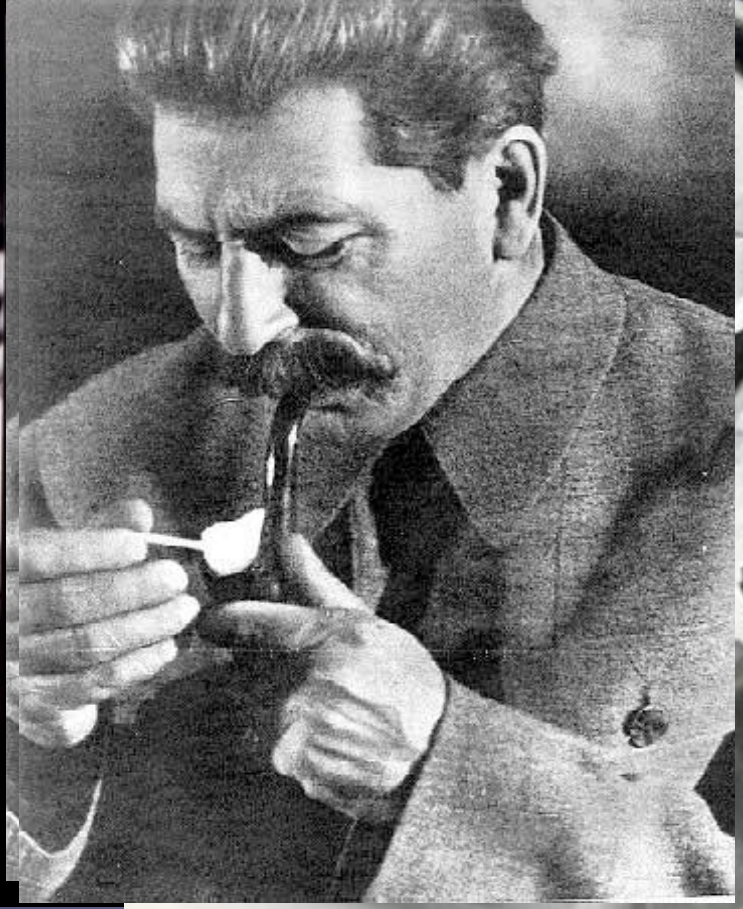
Hypertension,
Died age 63
of CVA

Hypertension,
Died age 63
of CVA



Hypertension,
Died age 75
of CVA

Hypertension,
Died age 63
of CVA



Hypertension,
Died age 75
of CVA

Hypertension,
Died age 81
of CVA

“Stroke, regardless whether ischemic or hemorrhagic, is the most devastating complication of hypertensive cardiovascular disease”.

Sir George Pickering
“The Nature of Essential Hypertension”
London; Churchill; 1961


Elderly
people

"Antihypertensive agents produce no obvious benefit in patients over 65."

J. Fry. *Lancet*. 1974.

"Systolic hypertension in the presence of a normal or reduced diastolic pressure is rarely considered responsible for target organ damage."

Engelman K, Braunwald E. Ch.37, "Elevation of Arterial Blood Pressure," *Harrison's Principles of Internal Medicine*. 6th Ed. 1970.

10 Heart Med Facts Your Doctor Doesn't Know About

- "It's normal for the top number of blood pressure (systolic) to be 100 plus your age. If you're 50, then your systolic should be 150. Taking drugs to bring it down to 115 makes about as much sense as trying to fit into the same shoe you wore when you were 10 years old…"

January 21, 2014

From: **Effect of Treating Isolated Systolic Hypertension on the Risk of Developing Various Types and Subtypes of Stroke: The Systolic Hypertension in the Elderly Program (SHEP)**

JAMA. 2000;284(4):465-471. doi:10.1001/jama.284.4.465

SHEP:

"antihypertensive drug treatment reduced the incidence of both hemorrhagic and ischemic (including lacunar) strokes"

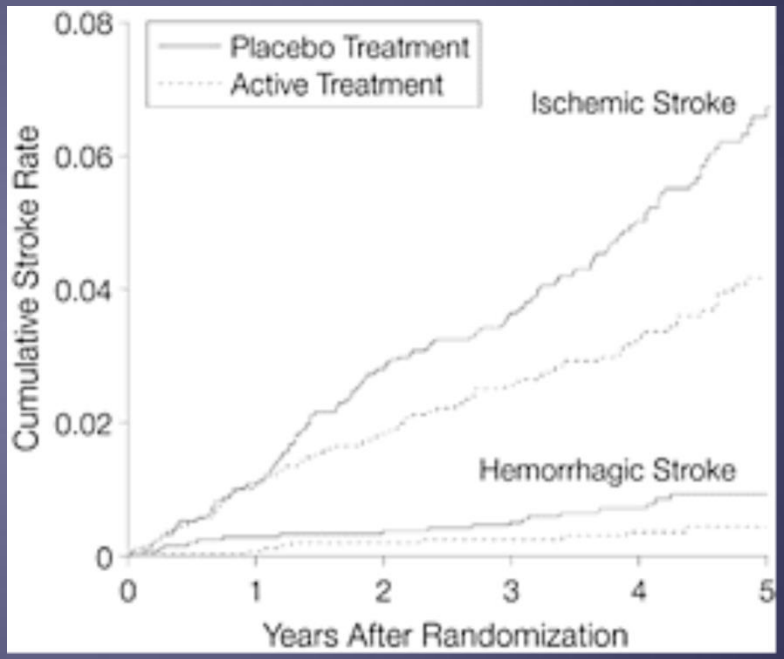
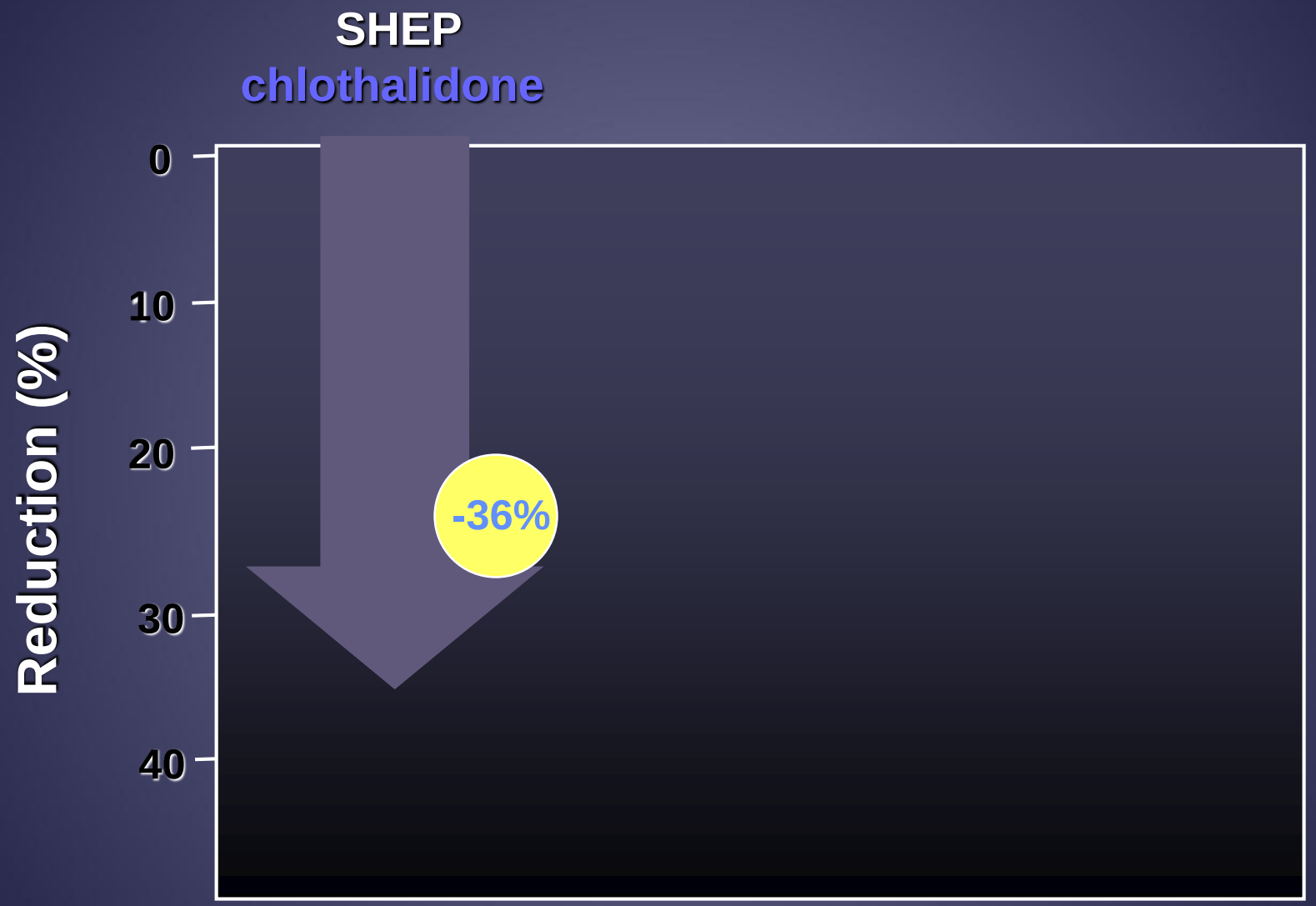


Figure Legend:

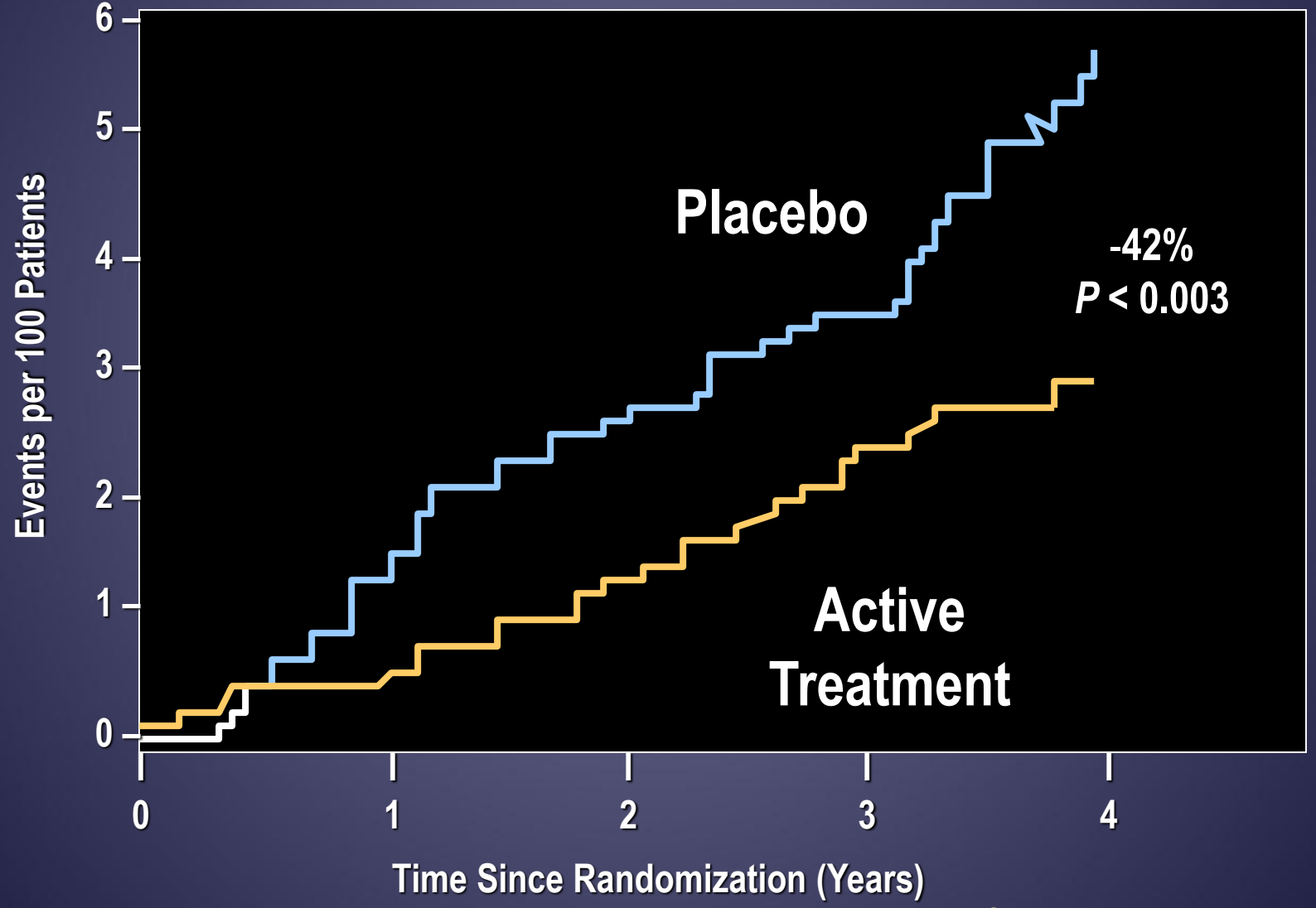
Seventeen strokes of unknown type are omitted. Three additional strokeswere also omitted (1 for a participant in the active treatment group and 2participants in the placebo group). These 3 strokes occurred after the participantshad completed 5 years in the trial.

Reduction of Stroke in Elderly



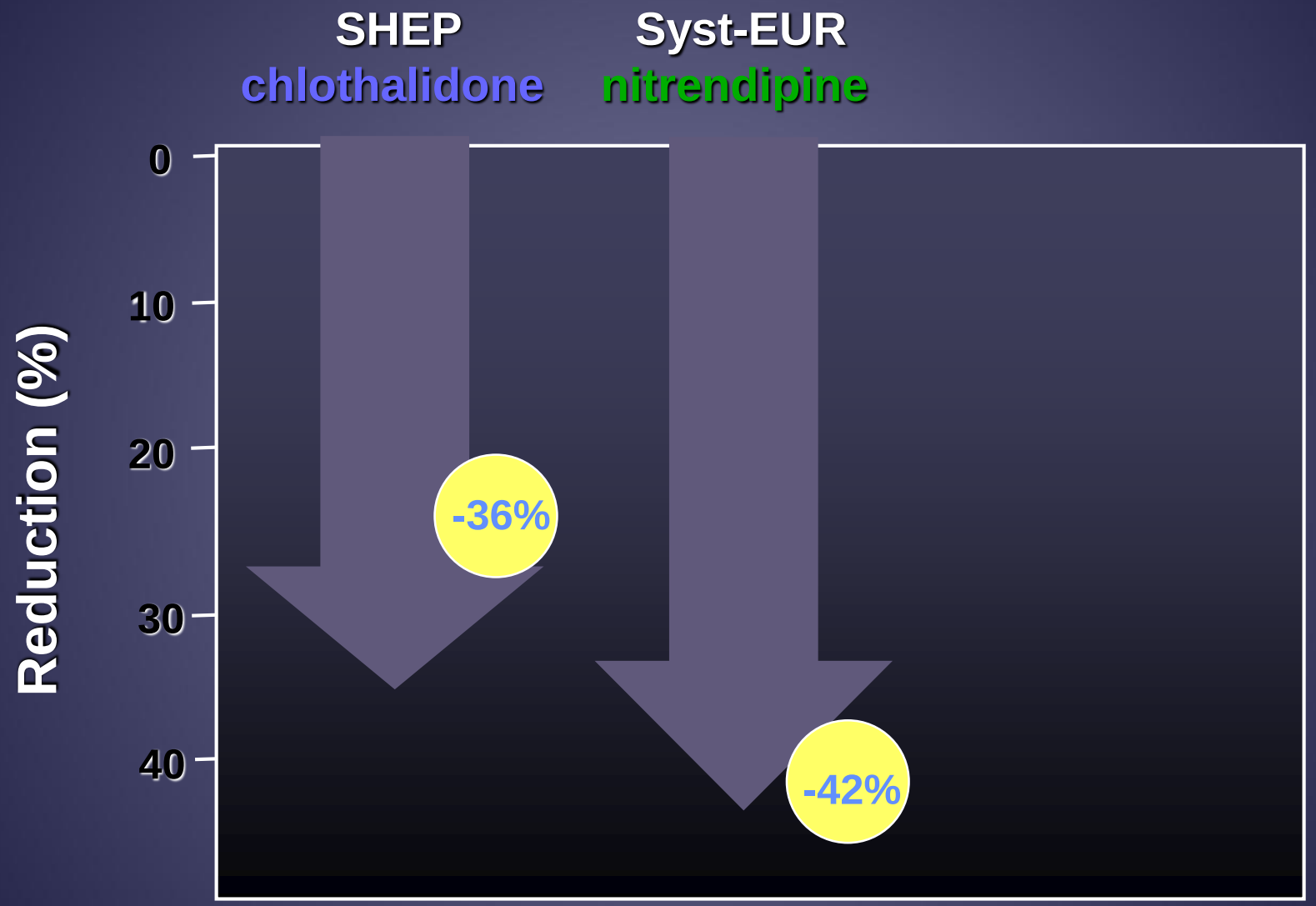
JAMA 1991, Lancet 1997, NEJM 2008

Syst-Eur: Fatal and Nonfatal Stroke (in 4695 Randomized Patients)



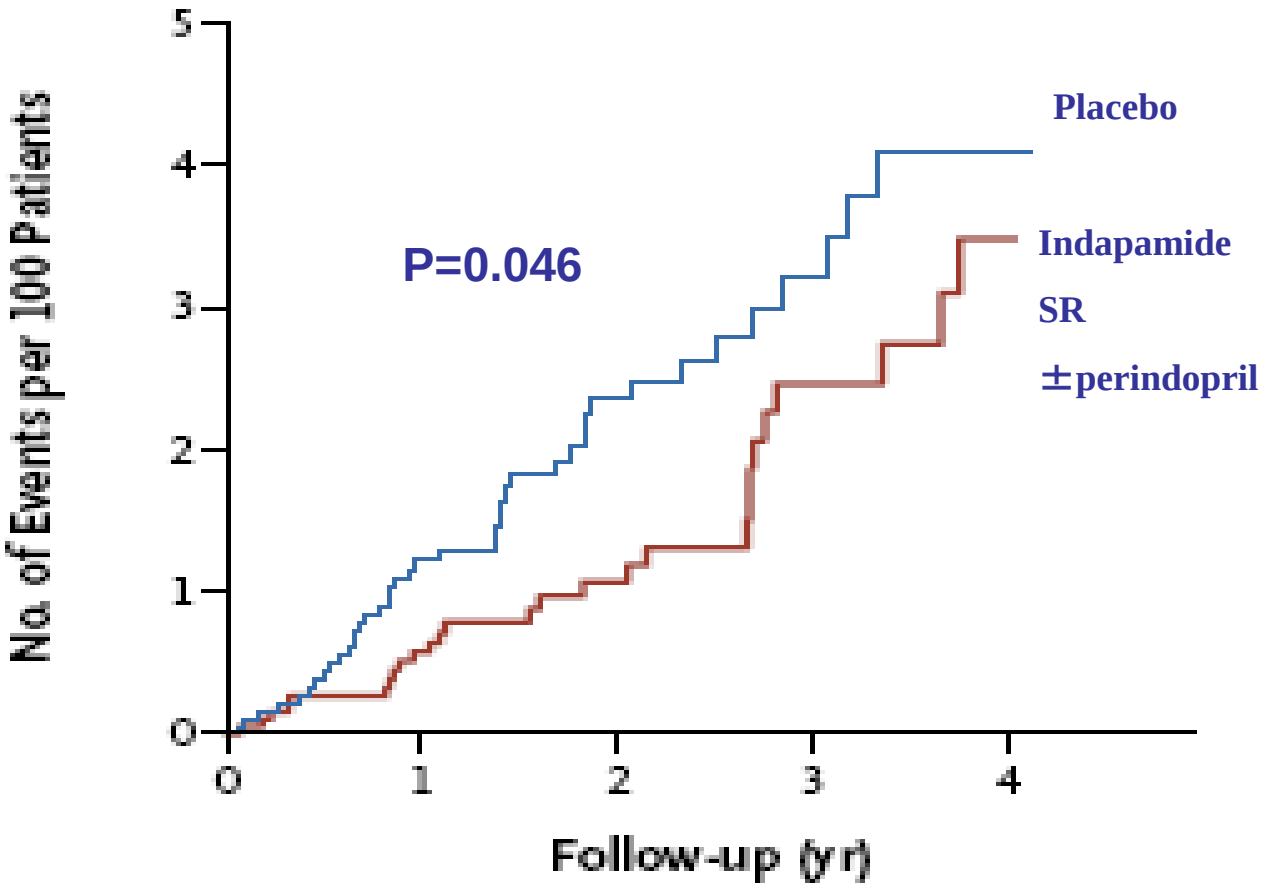
Staessen J et al. Lancet, in press 1997

Reduction of Stroke in Elderly



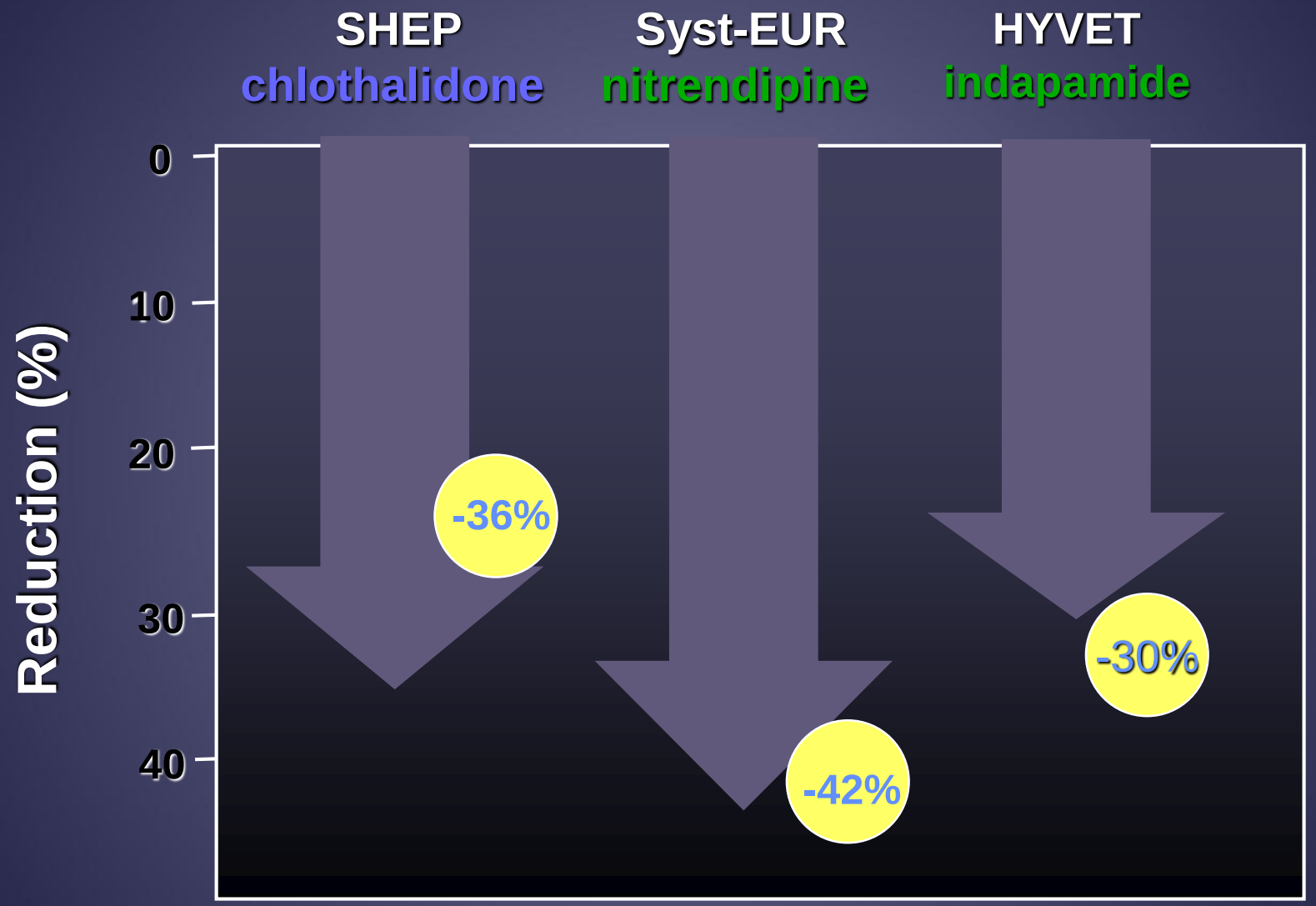
JAMA 1991, Lancet 1997, NEJM 2008

Fatal Stroke (39% reduction)



No. at Risk					
Placebo	1912	1492	814	379	202
IndapamideSR ±perindopril	1933	1565	877	420	231

Reduction of Stroke in Elderly



JAMA 1991, Lancet 1997, NEJM 2008

Antihypertensive Rx: Only millimeters matter….

“Any drug that lowers blood pressure will reduce strokes!”

Bakris G, personal communication 1995

Stroke Vol 24, No. 4, April 1993

Trial of Secondary Prevention With Atenolol After Transient Ischemic Attack or Nondisabling Ischemic Stroke

The Dutch TIA Trial Study Group

Background and Purpose: β-Blockers prevent vascular events in patients after myocardial infarction and lower blood pressure, the main risk factor for stroke. Hence, we assessed the effects of atenolol on the occurrence of death from vascular causes, stroke, or myocardial infarction and on blood pressure in patients after a transient ischemic attack or nondisabling ischemic stroke.

Methods: In a double-blind, placebo-controlled randomized clinical trial we studied the occurrence of the outcome event death from vascular causes, nonfatal stroke, or nonfatal myocardial infarction and the outcome event fatal or nonfatal stroke as well as blood pressure on follow-up. A total of 1,473 aspirin-treated patients with transient ischemic attack or nondisabling ischemic stroke were randomized to 50 mg atenolol daily or placebo. The mean follow-up was 2.6 years.

Results: Patients on atenolol had a risk of 97/732 (13.3%) for the combined outcome event versus a risk of 95/741 (12.8%) for those on placebo (adjusted hazard ratio, 1.00; 95% confidence interval, 0.76–1.33). The adjusted hazard ratio for fatal or nonfatal stroke was 0.82 (95% confidence interval, 0.57–1.19). More patients on β-blocker (153) reported adverse effects than on placebo (103). At the first follow-up visit after randomization (median at 4 months) systolic blood pressure in the atenolol group had dropped by 8.0

Background and Purpose

“ß-blockers prevent vascular events in patients after myocardial infarction and lower blood pressure, the main risk factor for stroke.”

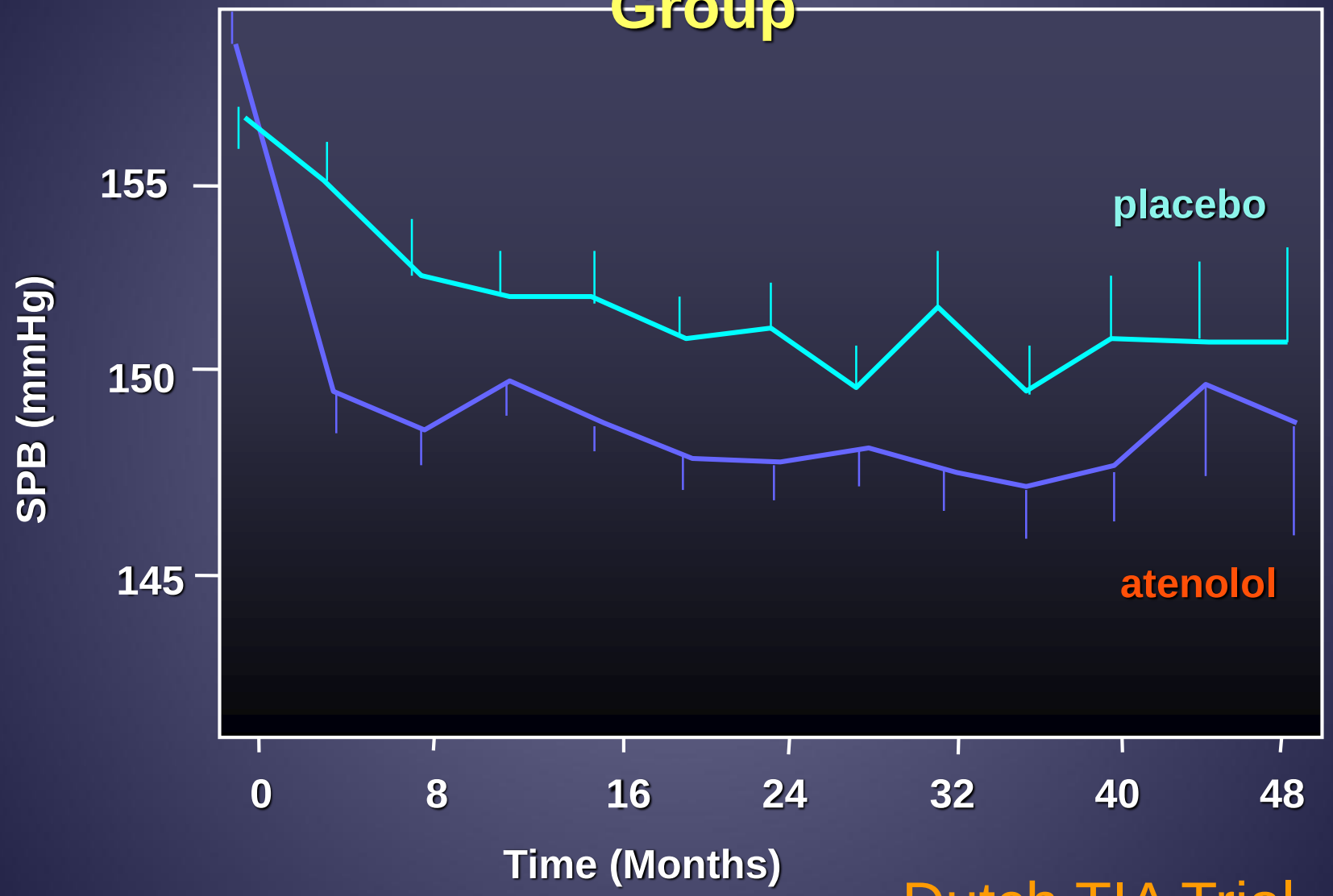
Dutch TIA Trial

Methods

A total of 1,473 aspirin-treated patients with transient ischemic attack or ischemic stroke were randomized to 50 mg atenolol daily or placebo, and followed for 2.6 years.

Dutch TIA Trial

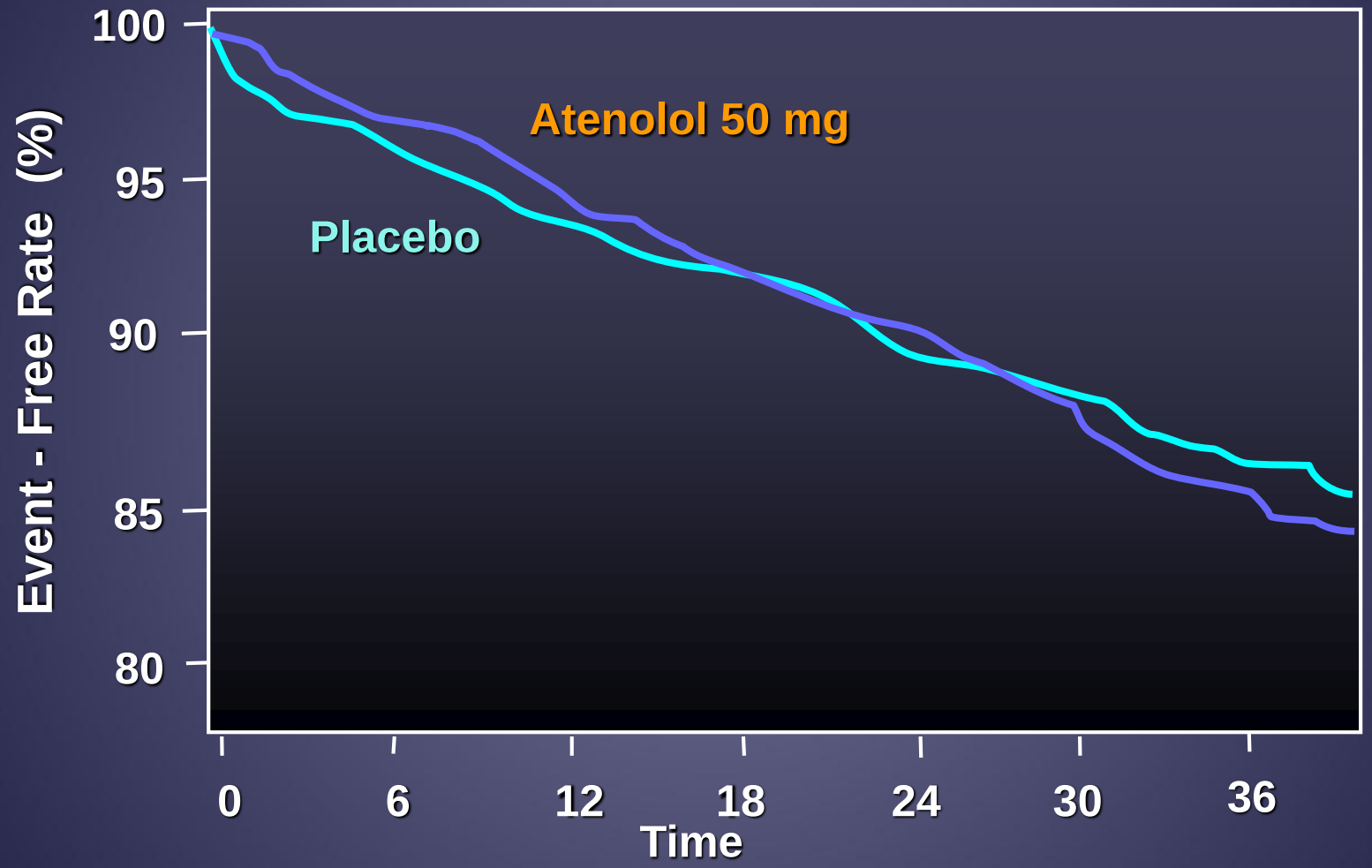
Blood Pressure in the Dutch TIA Trial Study Group



Dutch TIA Trial

Dutch TIA Trial Study Group, Stroke Vol 24, No 4., April 1993

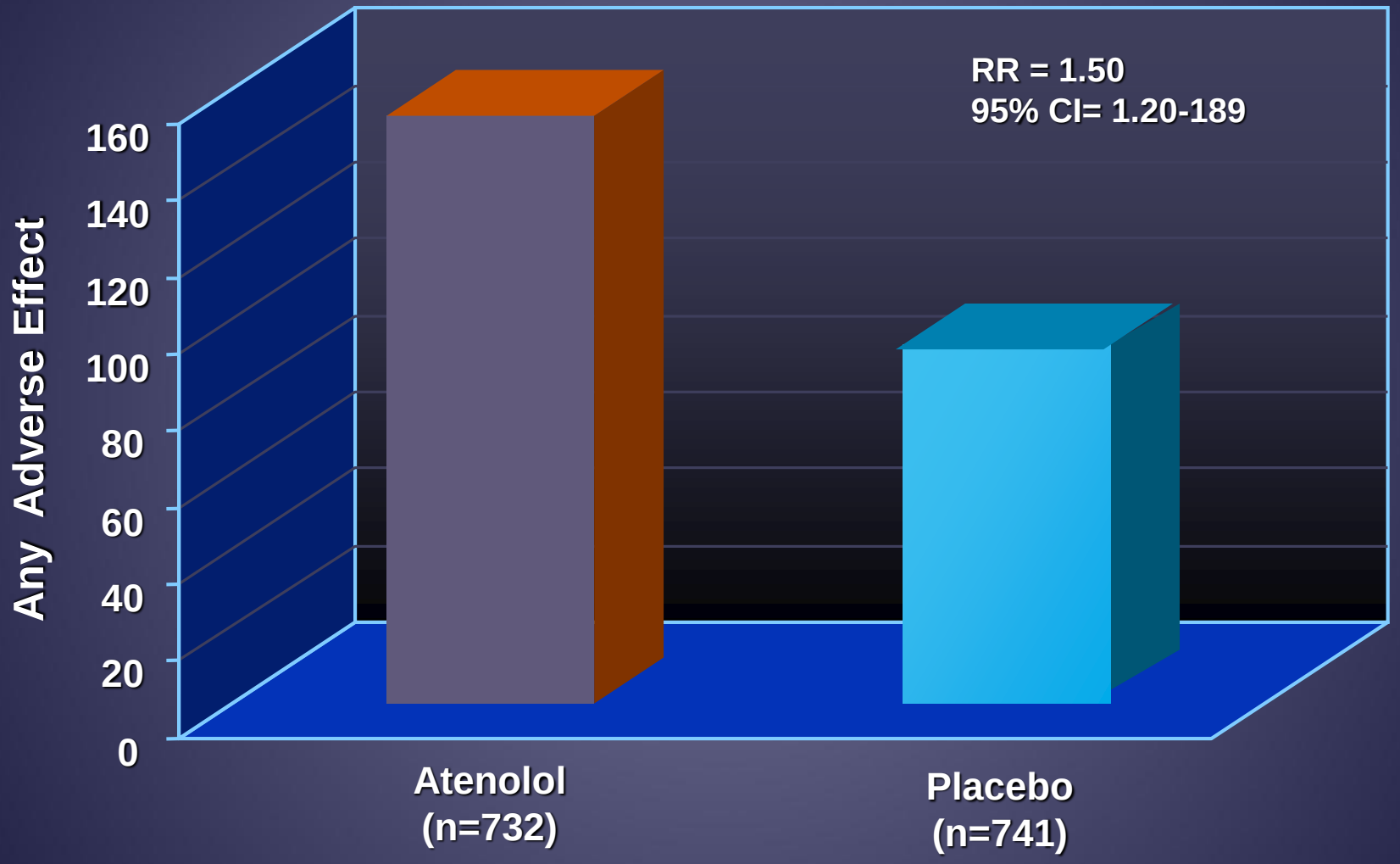
Combined Outcome* Dutch TIA Trial Study Group



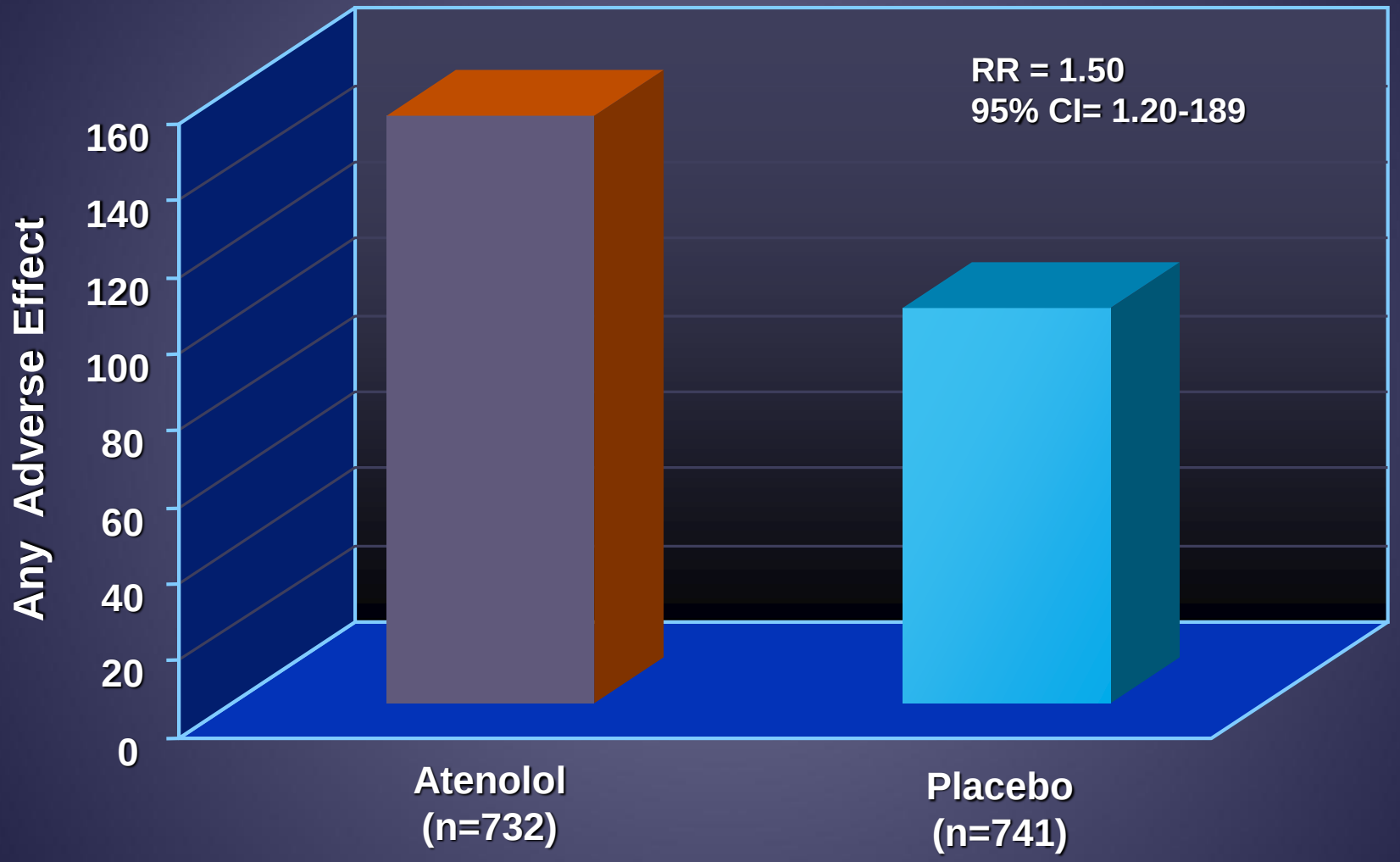
*Death Rate from Vascular Causes, Non-fatal Stroke or Myocardial Infarction

Dutch TIA Trial

Patients with Any Adverse Effect* According to Treatment Group



Patients with Any Adverse Effect* According to Treatment Group



Hypotension, Bradycardia, Impotence, Shortness of Breath, Fatigue, Dizziness, Cold Extremities,

Several independent studies document:

…despite lowering blood pressure, beta blockers (atenolol) do not reduce the risk of stroke!

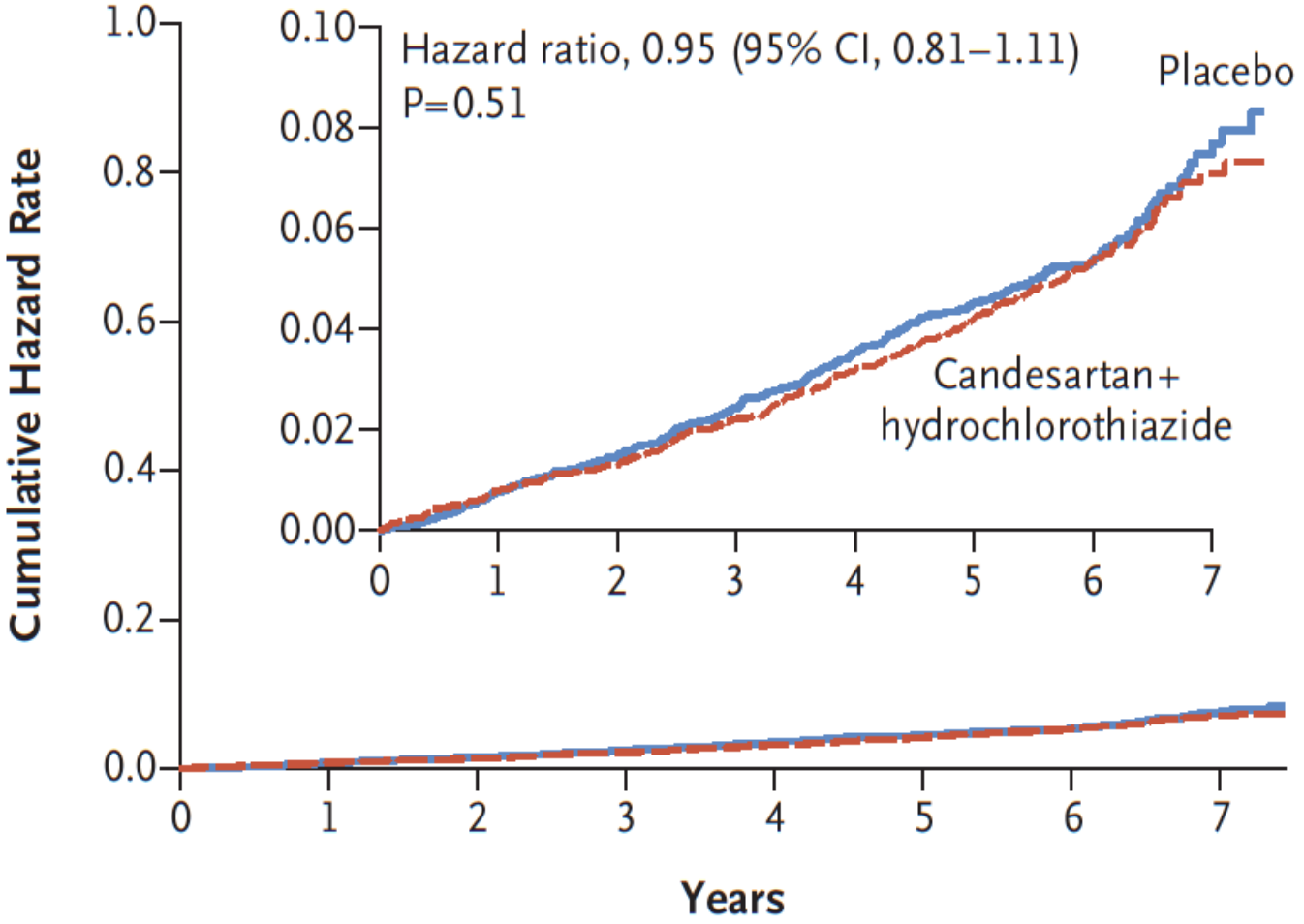
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

A **Death from Cardiovascular Causes, Myocardial Infarction, Stroke, Cardiac Arrest, Revascularization, or Heart Failure**

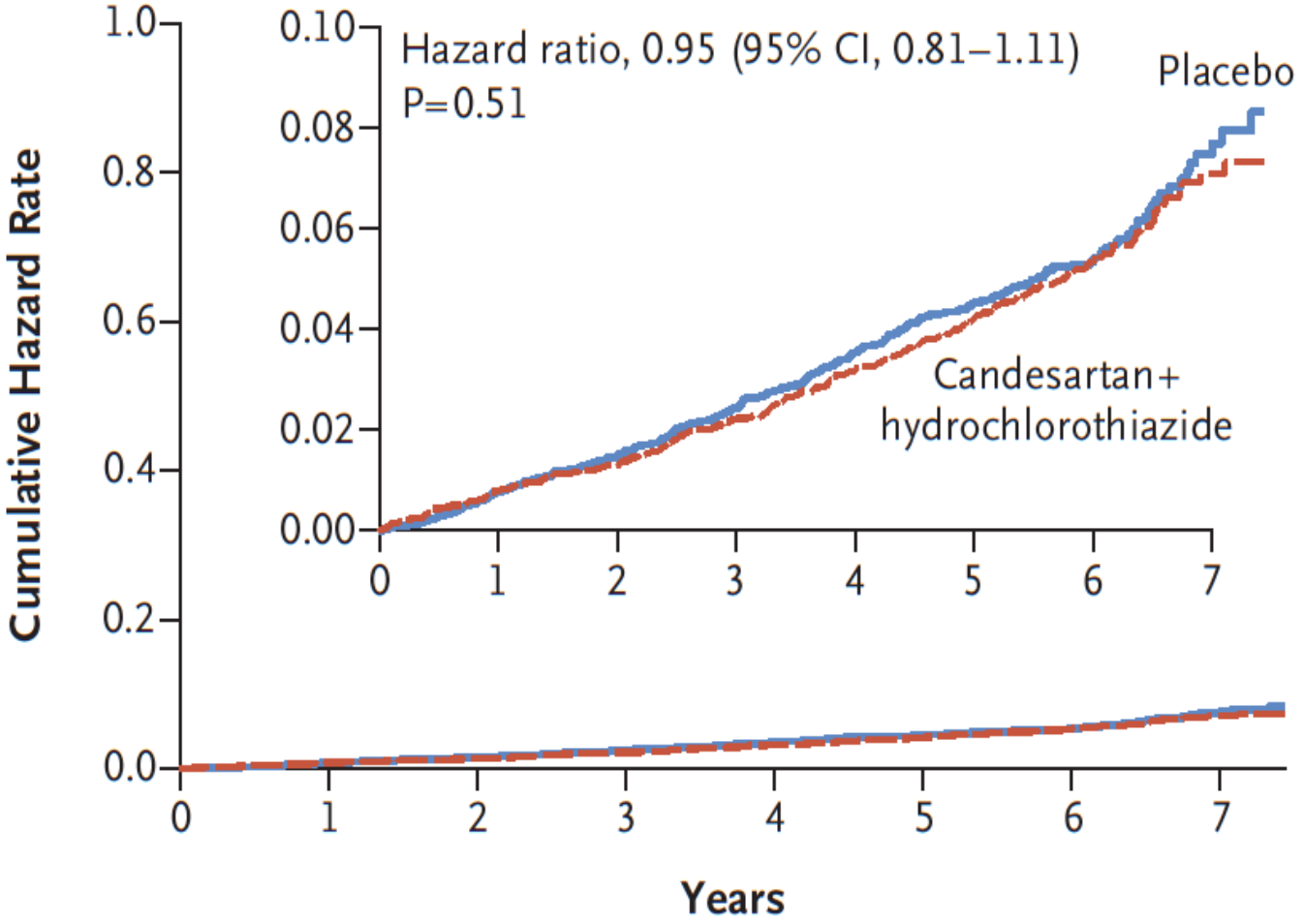


No. at Risk

Candesartan+hydrochlorothiazide	6356	6272	6200	6103	5968	4969	2076	522
Placebo	6349	6270	6198	6096	5967	4970	2075	488

A Death from Cardiovascular Causes, Myocardial Infarction, Stroke, Cardiac Arrest, Revascularization, or Heart Failure

Baseline BP
138/82 mmHg



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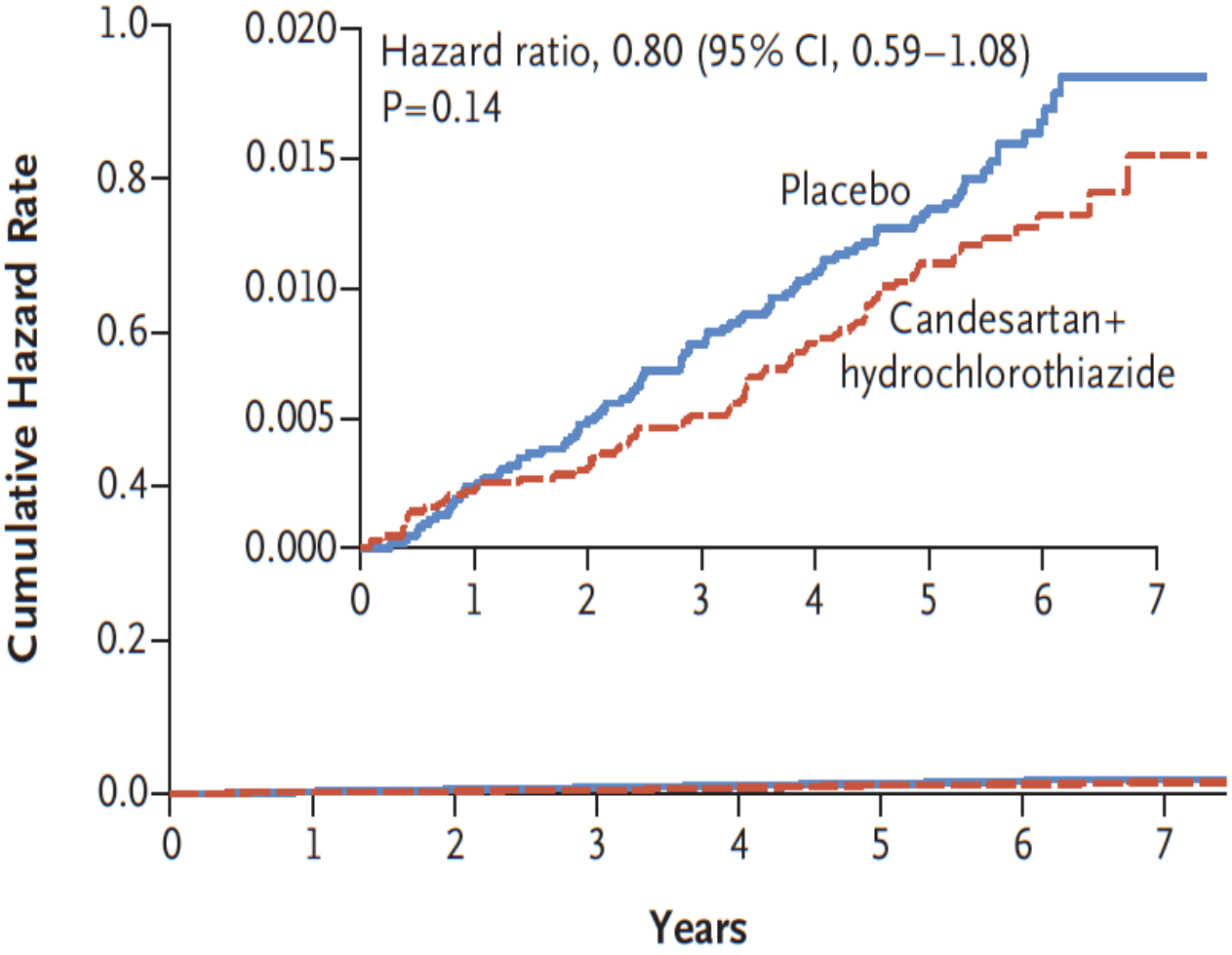
Placebo	6349	6270	6198	6096	5967	4970	2075	488

Lonn et al. NEJM, April 2, 2016,

B Stroke



No. at Risk

Candesartan+hydrochlorothiazide	6356	6292	6235	6155	6038	5042	2111	534
Placebo	6349	6291	6234	6147	6041	5045	2115	505

Lonn et al. NEJM, April 2, 2016,

Salim's Lesson # 1

- Lowering BP in normotensive patients has no effect.

Lowering BP in «normotensive» Patients

Table. Comparison of Characteristics and Results of 5 Recent Trials of BP Lowering[a]

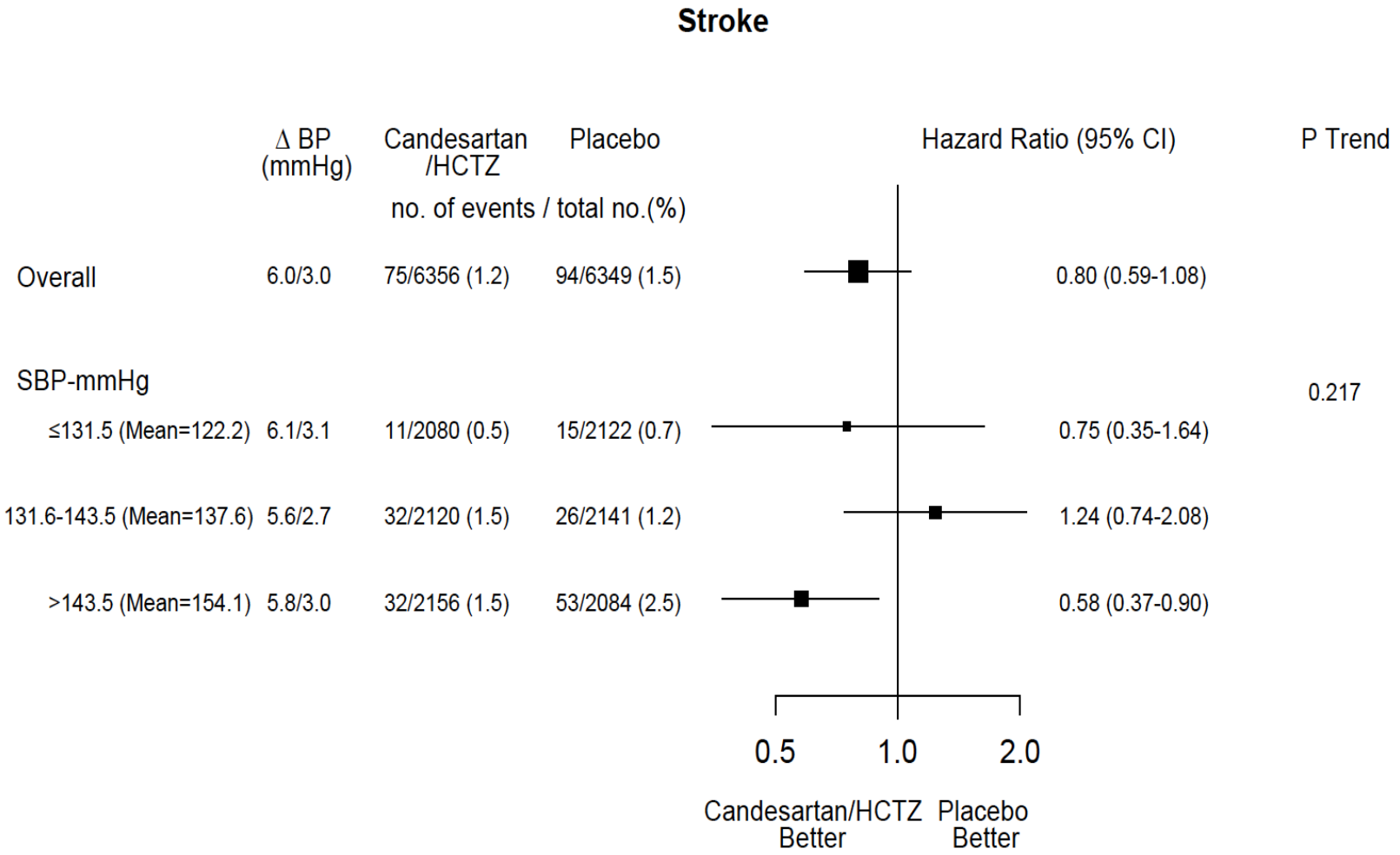
Characteristic	ADVANCE Trial	ACCORD Trial	SPS3 Trial	SPRINT	HOPE-3 Trial
Intervention/ randomization	Perindopril plus indapamide vs placebo	Intensive vs usual BP lowering	Intensive vs usual BP lowering	Intensive vs usual BP lowering	Candesartan plus thiazide vs placebo
Population	High-risk participants with diabetes	High-risk participants with diabetes	High-risk participants with lacunar stroke	High-risk participants with hypertension despite treatment	Older intermediate-risk participants with risk factors
Participants, No.	11 140	4733	3020	9361	12 705
Macrovascular disease, % of participants	32	33	100	20	0
BP, mm Hg	145/81	139/76	143/79	140/78	138/82
BP difference, mm Hg	5.6/2.2	14.2/6.1	11/NA	14.8/7.6	6.0/3.0
Macrovascular events, No.	1000	445	344	562	539
RRR of macrovascular events, % (95% CI)	8 (−4 to 19)	12 (−6 to 27)	16 (−4 to 32)	25 (−11 to 36)	7 (−10 to 21)[b]
P value	.16	.20	.10	.001	.40

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; BP, blood pressure; HOPE-3, Heart Outcomes Prevention Evaluation-3; NA, not available; OR, odds ratio; RRR, relative risk reduction; SPRINT, Systolic Blood Pressure Intervention Trial;

of 14 111 participants (7.7%) in active group vs 1264 of 14 144 participants (8.9%) in control group (OR, 0.85 [95% CI, 0.78-0.93]; *P* = .002). Pooled results of all trials except SPRINT: 1108 of 15 789 participants (7.0%) in active group vs 1224 of 15 810 participants (7.7%) in control group (OR, 0.90 [95% CI, 0.83-0.98]; *P* = .01).

Yusuf and Lonn, Jama Cardiology, September 7, 20

Figure S11B: Secondary Outcome 2 by Tertiles of Baseline Systolic Blood Pressure for the Candesartan/HCTZ versus Placebo Comparison



Lonn et al. NEJM, April 2, 2016,

Salim's Lesson # 2

- Lowering BP in normotensive patients has no effect.
- **Lowering BP in hypertensive patients decreases the risk of stroke.**

Is Blood Pressure Control for Stroke Prevention the Correct Goal?

The Lost Opportunity of Preventing Hypertension

George Howard, DrPH; Maciej Banach, MD, PhD; Mary Cushman, MD;
David C. Goff, MD, PhD; Virginia J. Howard, PhD; Daniel T. Lackland, DrPH;
Jim McVay, DrPA; James F. Meschia, MD; Paul Muntner, PhD; Suzanne Oparil, MD;
Melanie Rightmyer, DNP; Herman A. Taylor, MD

Background and Purpose—Although pharmacological treatment of hypertension has important health benefits, it does not capture the benefit of maintenance of ideal health through the prevention or delay of hypertension.

Methods—A total of 26875 black and white participants aged 45+ years were assessed and followed for incident stroke events. The association was assessed between incident stroke and: (1) systolic blood pressure (SBP)categorized as normal (<120 mm Hg), prehypertension (120–139 mm Hg), stage 1 hypertension (140–159 mm Hg), and stage 2 hypertension (160 mm Hg+), and (2) number of classes of antihypertensive medications, classified as none, 1, 2, or 3 or more.

Results—During 6.3 years of follow-up, 823 stroke events occurred. Nearly half (46%) of the population were successfully treated (SBP<140 mm Hg) hypertensives. Within blood pressure strata, the risk of stroke increased with each additional class of required antihypertensive medication, with hazard ratio [HR], 1.33; 95% confidence interval, 1.16 to 1.52 for normotensive, HR, 1.15; 95% confidence interval, 1.05 to 1.26 for prehypertension, and HR, 1.22; 95% confidence interval, 1.06 to 1.39 for stage 1 hypertension. A successfully treated (SBP<120 mm Hg) hypertensive person on 3+ antihypertensive medication classes was at marginally higher stroke risk than a person with untreated stage 1 hypertension (HR, 2.48 versus HR=2.19; relative to those with SBP <120 on no antihypertensive medications).

Conclusions—Maintaining the normotensive status solely through pharmacological treatment has a profound impact, as

Howard et al. Stroke, 2015;46:1595-1600.

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-R Deviation From the Mean SBP Level for the Category

	Normotensive (<120 mm Hg)	Prehypertension (120 mm Hg–139 mm Hg)	Stage 1 Hypertension (140 mm Hg–159 mm Hg)	Stage 2 Hypertension (160+ mm Hg)
No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication				
2 Antihypertensive medications				
3+ Antihypertensive medications				

Howard et al. Stroke, 2015;46:1595-1600.

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No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication	1.42 (0.94–2.15)			
2 Antihypertensive medications	1.60 (1.06–2.42)			
3+ Antihypertensive medications	2.48 (1.63–3.77)			

Howard et al. Stroke2015;46:1595-1600.

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-R Deviation From the Mean SBP Level for the Category

	Normotensive (<120 mm Hg)	Prehypertension (120 mm Hg–139 mm Hg)	Stage 1 Hypertension (140 mm Hg–159 mm Hg)	Stage 2 Hypertension (160+ mm Hg)
No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication	1.42 (0.94–2.15)	2.00 (1.44–2.77)	1.67 (1.09–2.54)	3.00 (1.71–5.26)
2 Antihypertensive medications	1.60 (1.06–2.42)	1.88 (1.35–2.62)	2.84 (1.95–4.13)	1.42 (0.67–2.99)
3+ Antihypertensive medications	2.48 (1.63–3.77)	2.34 (1.66–3.32)	3.35 (2.28–4.92)	4.62 (2.84–7.51)

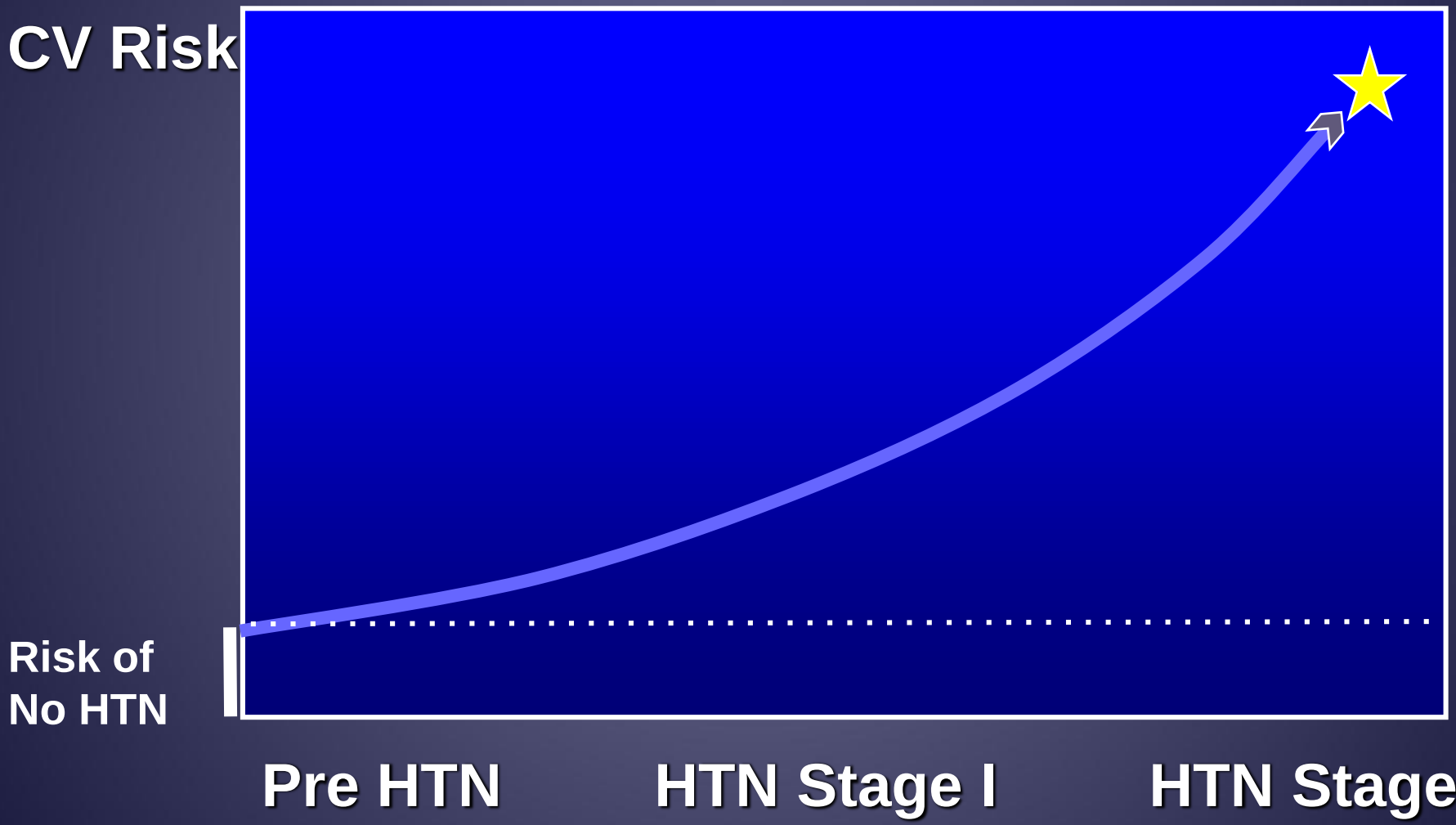
Howard et al. Stroke2015;46:1595-1600.

Conclusions

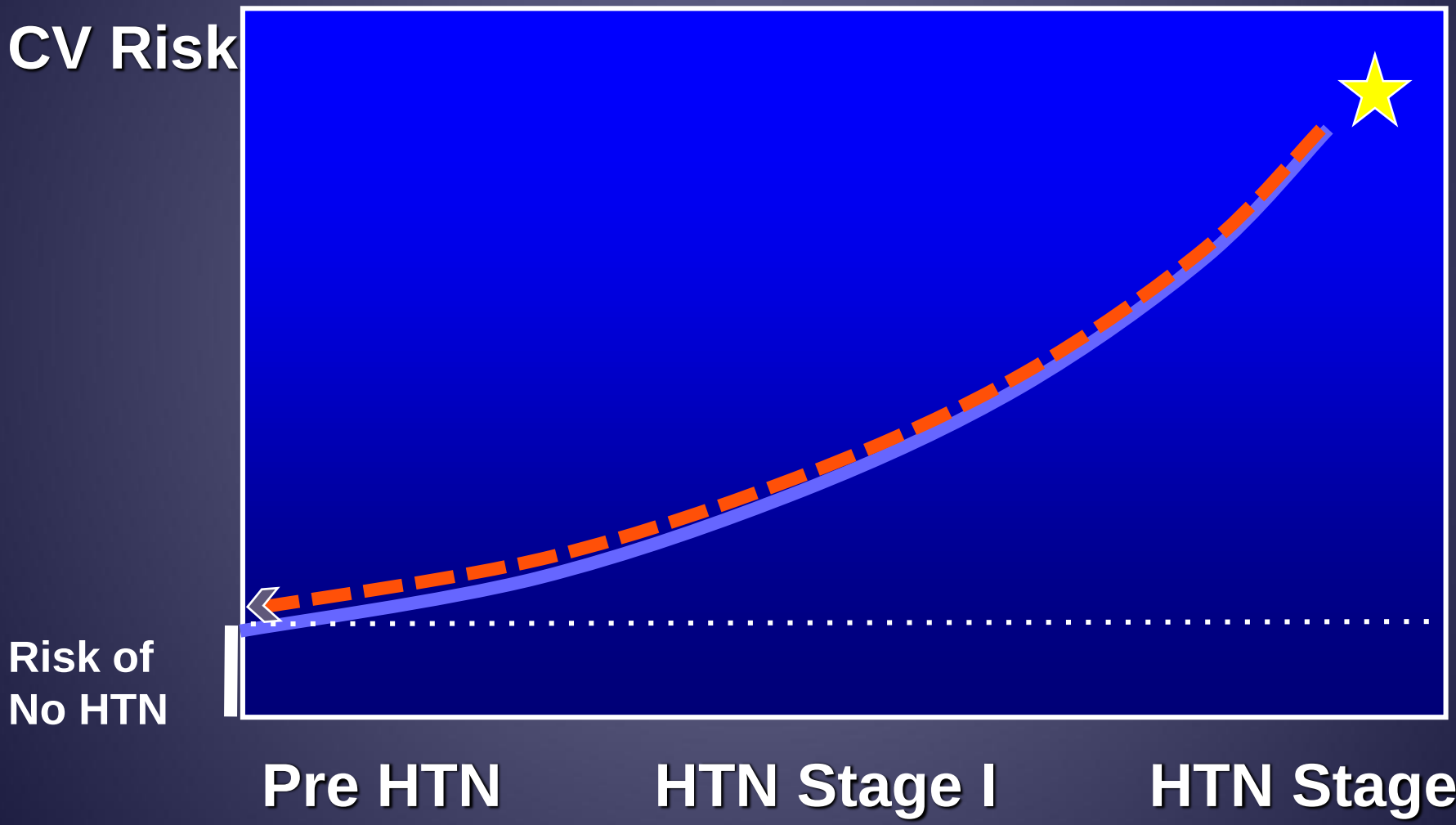
"Maintaining the normotensive status solely through pharmacological treatment…. failed to return to risk levels similar to normotensive individuals. Even with successful treatment, there is a substantial residual risk."

Howard et al. Stroke2015;46:1595-1600.

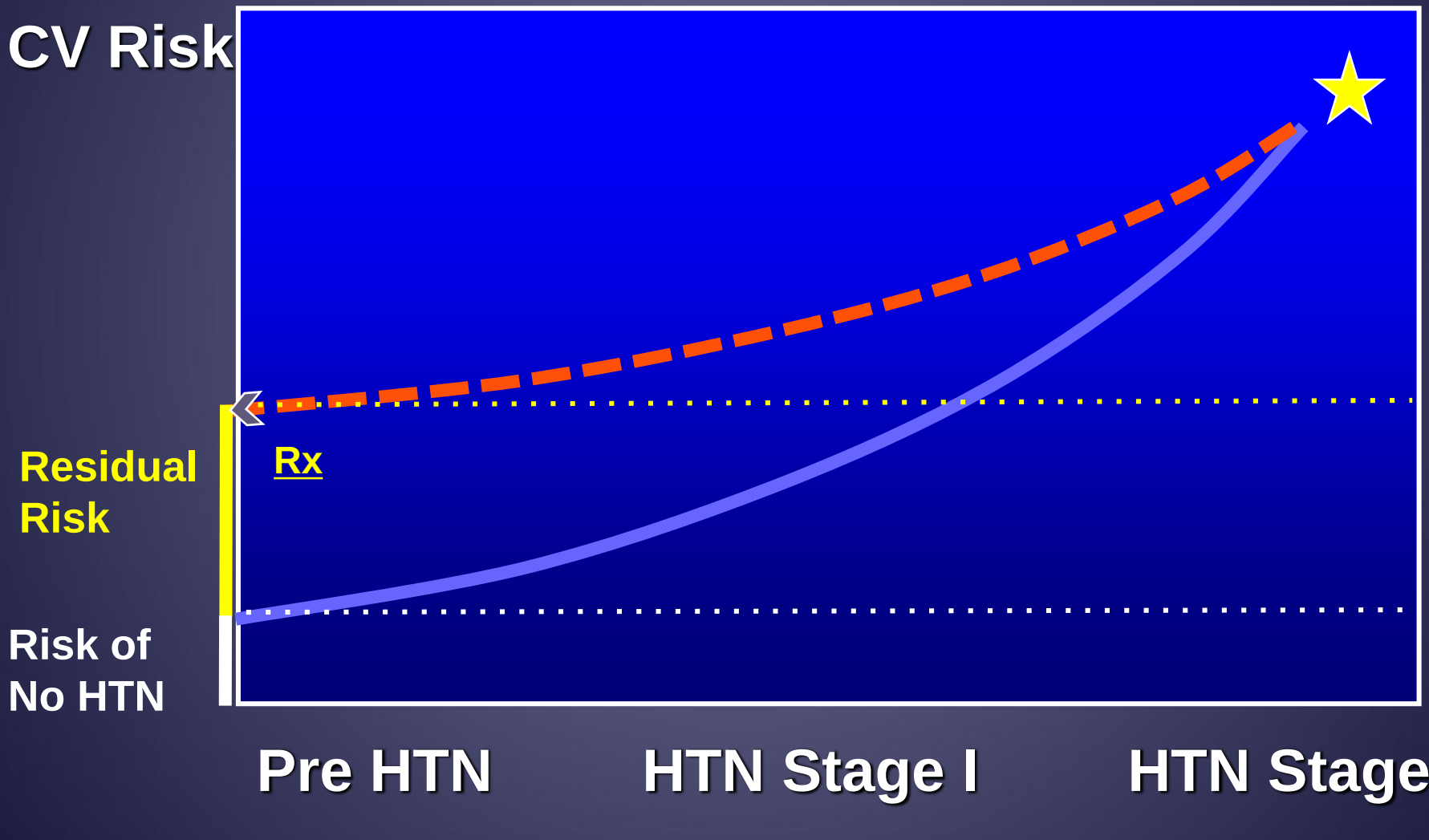
Risk of Hypertension and its Reduction by Antihypertensive Therapy



Risk of Hypertension and its Reduction by Antihypertensive Therapy



Risk of Hypertension and its Reduction by Antihypertensive Therapy



Point of No Return

What is the the underlying Mechanism of the residual risk?

Why is there a

Several independent studies document:

…despite lowering blood pressure, **beta blockers** (atenolol) do not reduce the risk of stroke!

Beta-Blocker –BP/Stroke Paradox

- As long as we use traditional beta-blockers for the treatment of hypertension we will not reduce the risk of stroke.
- We merely create a sense of false security: yes, BP is controlled, but no, the risk of stroke is not!

There Underlying Mechanism of Residual Risk

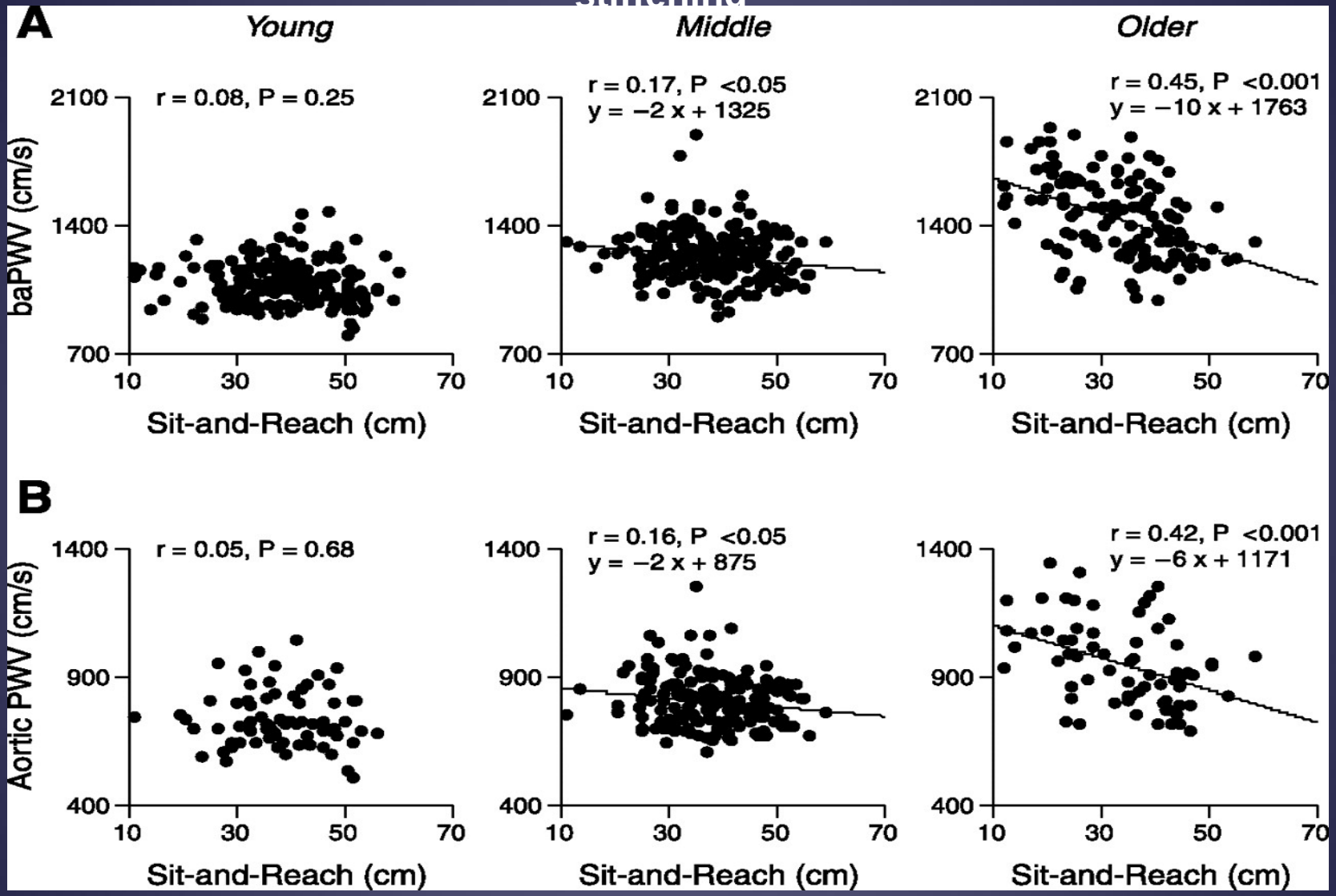
1. **Beta Blockers** lower BP but do not reduce outcome, particularly CVA.

Poor trunk flexibility is associated with arterial stiffening

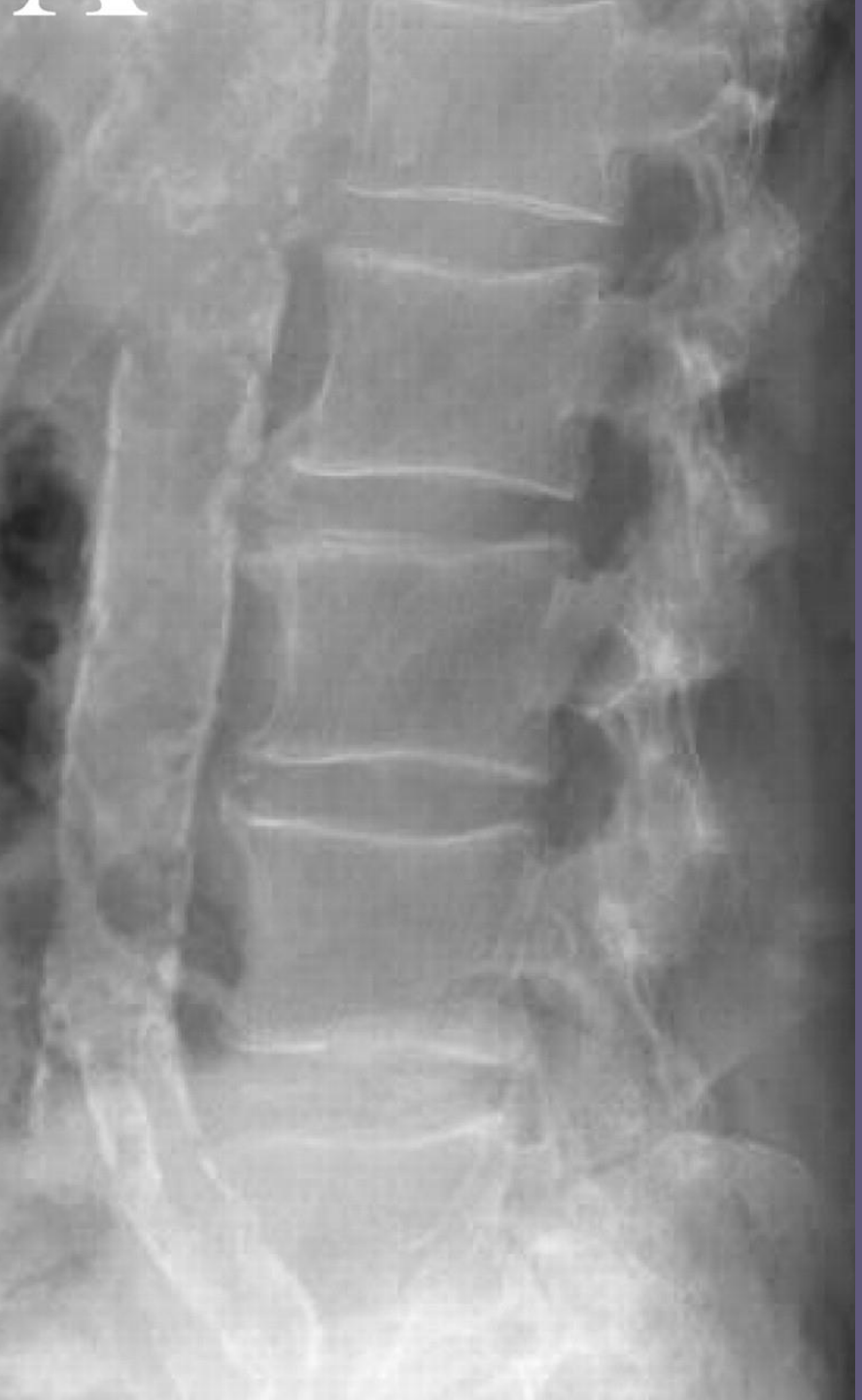
- A stepwise multiple-regression analysis (n = 316) revealed that among the components of fitness (cardiorespiratory fitness, muscular strength, and flexibility) and age, all components and age were independent correlates of baPWV. These findings suggest that **flexibility may be a predictor of arterial stiffening, independent of other components of fitness**.

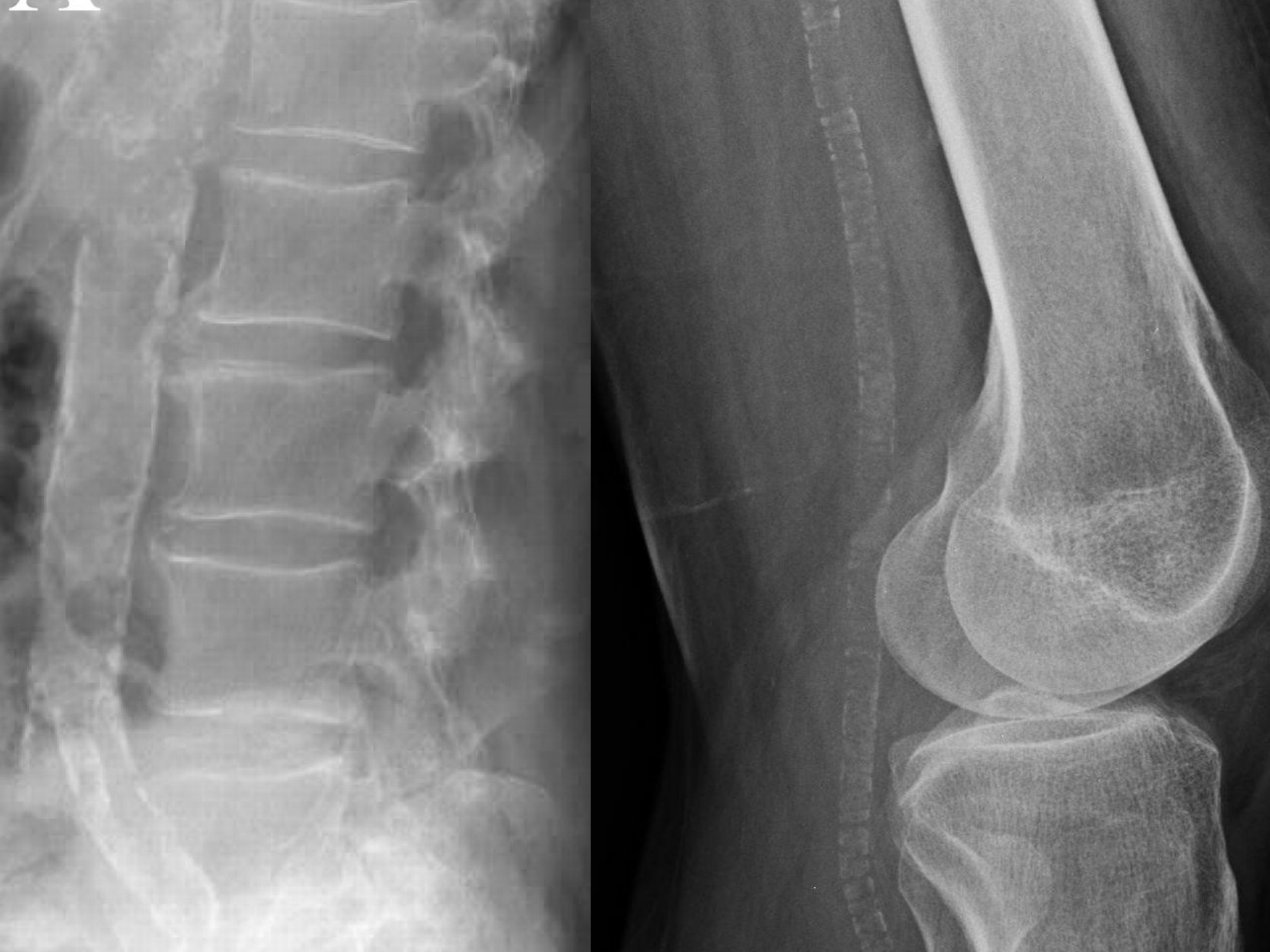
Yamamoto et al. Am J Physiol Heart Circ Physiol. 2009 Oct;297(4):H1314-8

Poor trunk flexibility is associated with arterial stiffening



Yamamoto et al. Am J Physiol Heart Circ Physiol. 2009 Oct;297(4):H1314-8





There Underlying Mechanism of Residual Risk

1. Beta Blockers lower BP but do not reduce outcome, particularly CVA.

2. Longstanding hypertension may have caused irreversible damage in target organs and vascular tree.

31	8:38	154	85	84 R			148	82 98 L
		156	88	94 L		18:38	135	94 96 R
	20:23	170	94	122 R			138	97 97 L
		175	86	128 L		22:41	149	84 98 R
	23:00	157	99	100 R			156	81 80 L
		155	84	104 L		2/5 10:16	137	93 88 R
	6:03	183	101	100 R			174	92 94 L
		166	97	104 L		6:57	119	85 86 R
	20:48	146	103	105 R			121	79 87 L
		171	93	106 L		2/4 9:17	135	84 93 R
		174	102	98 R			126	83 77 L
	22:25	166	89	98 L		10:15	136	82 96 R
		186	101	112 R			139	97 88 L
	9:48	189	93	114 L		2/7 6:01	160	100 98 R
		143	89	88 R		6:01	151	93 112 L

THE LANCET

The Lancet, Volume 375, Issue 9718, Pages 895 - 905, 13 March 2010
doi:10.1016/S0140-6736(10)60308-X Cite or Link Using DOI

< Previous Article | Next Article >

Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

Prof Peter M Rothwell FMedSci [a], Sally C Howard DPhil [a], Eamon Dolan MRCP [b], Prof Eoin O'Brien FRCP [c], Joanna E Dobson MSc [d], Prof Bjorn Dahlöf MD [e], Prof Peter S Sever FRCP [d], Neil R Poulter FMedSci [d]

Summary

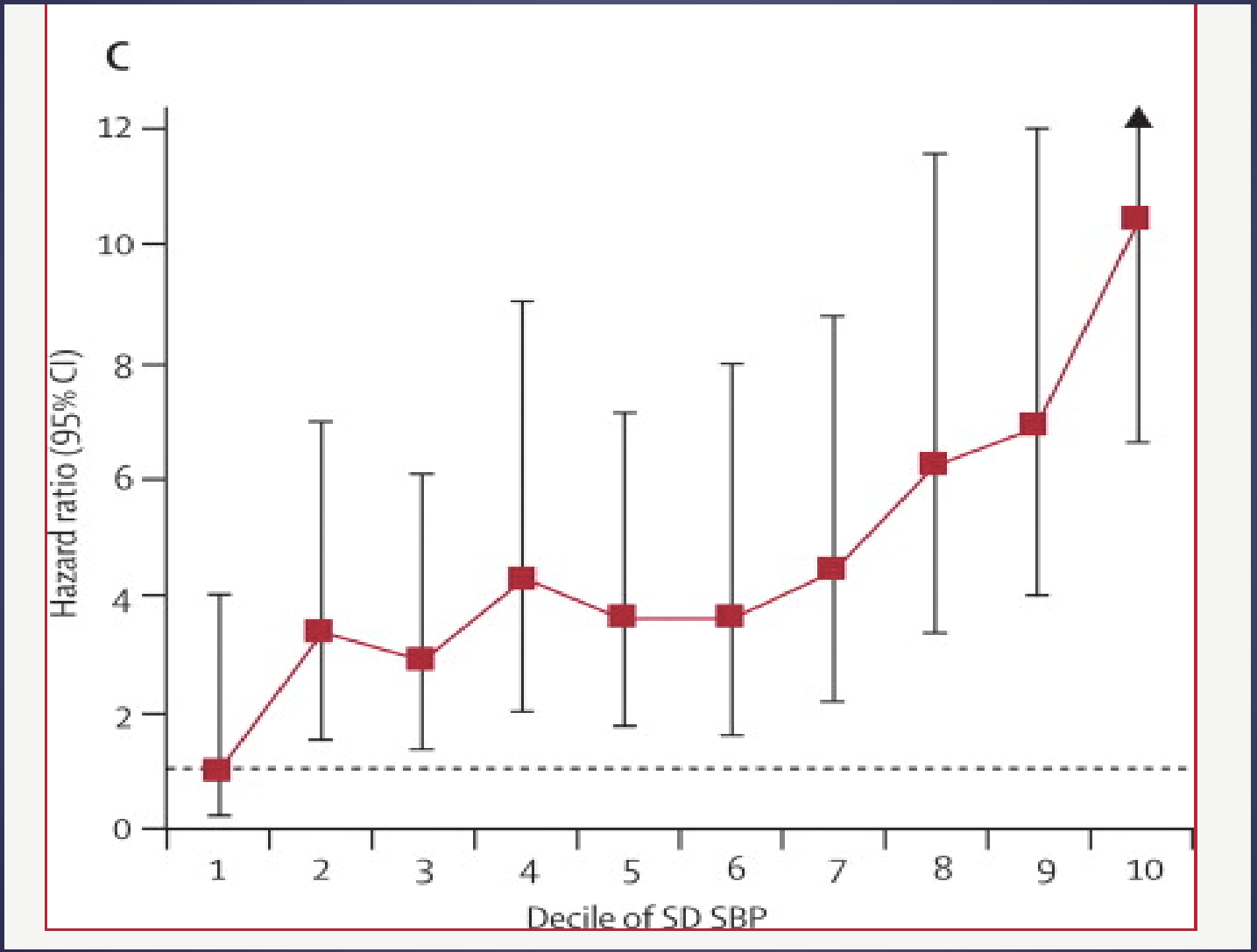
Background

The mechanisms by which hypertension causes vascular events are unclear. Guidelines for diagnosis and treatment focus only on underlying mean blood pressure. We aimed to reliably establish the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, untreated episodic hypertension, and residual variability in treated patients.

Methods

We determined the risk of stroke in relation to visit-to-visit variability in blood pressure (expressed as standard deviation [SD] and parameters independent of mean blood pressure) and maximum blood pressure in patients with previous transient ischaemic

Hazard ratios for risk of any stroke by deciles of SD SBP based on the first seven measurements



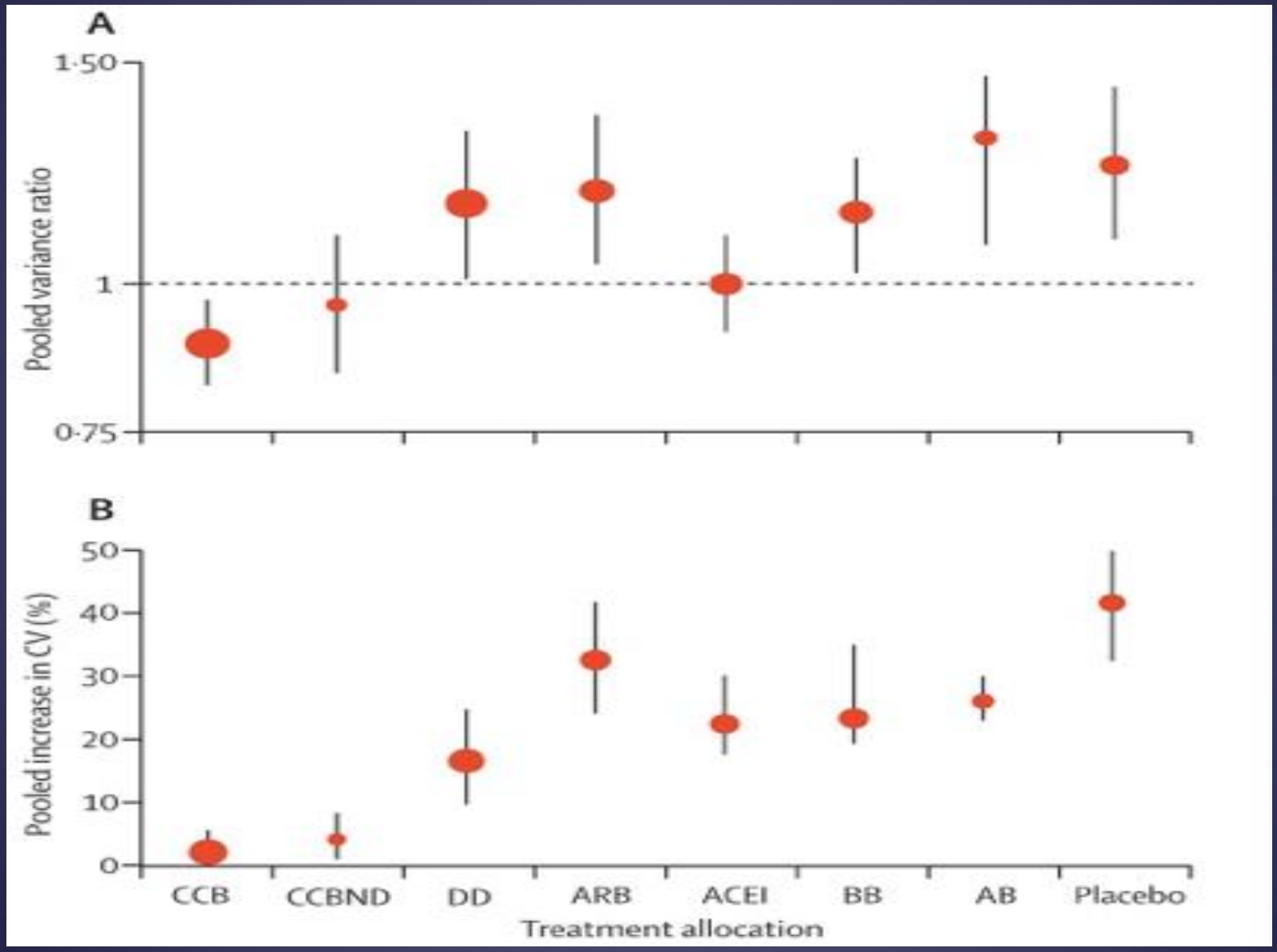
The Lancet, Volume 375, Issue 9718, Pages 895 - 905, 13 March 2010

Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

- Visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke, independent of mean SBP. Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events.

Rothwell et al. Lancet Neurology 2010

Change in group variation in SBP at follow-up compared with baseline as variance ratio (A) and percentage increase in coefficient of variation (B)



Webb et al. The Lancet, Volume 375, Issue 9718, Pages 906 - 915, 13 March 2010

6/9	10:13	117	64	61	7/8	12:09	103	64	93
6/10	13:05	116	70	94	7/9	5:39	98	60	79
6/11	10:39	118	72	77	7/10	10:23	117	69	91
6/12	9:42	112	78	81	7/11	923	115	78	75
6/13	5:36	120	70	87	7/12	10:02	115	69	101
6/14	10:10	115	61	77	7/13	17:25	86	59	61
6/15	20:17	92	61	74	7/14	10:59	130	76	114
6/16	11:04	108	64	76	7/15	936	94	59	75
6/17	7:28	110	46	65	7/16	10:13	112	72	86
6/18	9:15	112	68	70	7/17	8:34	95	45	75
6/19	12:50	115	70	98	7/18	10:10	107	70	88
6/20	6:25	76	55	75	7/19	16:12	97	41	68
		86	73	80					
		R							

Winnie Langley died August 12, 2010, age 103 after having smoked for more than 95 years, HTN since her 40ties…lung cancer at 87.


Smoking
kills


100
Celebrate

ALLHAT

Annals of Internal Medicine

ORIGINAL RESEARCH

Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality

A Cohort Study

Paul Muntner, PhD; Jeff Whittle, MD; Amy I. Lynch, PhD; Lisandro D. Colantonio, MD; Lara M. Simpson, PhD; Paula T. Einhorn, MD; Emily B. Levitan, PhD; Paul K. Whelton, MD; William C. Cushman, MD; Gail T. Louis, RN; Barry R. Davis, MD, PhD; and Suzanne Oparil, MD

Background: Variability of blood pressure (BP) across outpatient visits is frequently dismissed as random fluctuation around a patient's underlying BP.

Objective: To examine the association of visit-to-visit variability (VVV) of systolic BP (SBP) and diastolic BP with cardiovascular disease (CVD) and mortality outcomes.

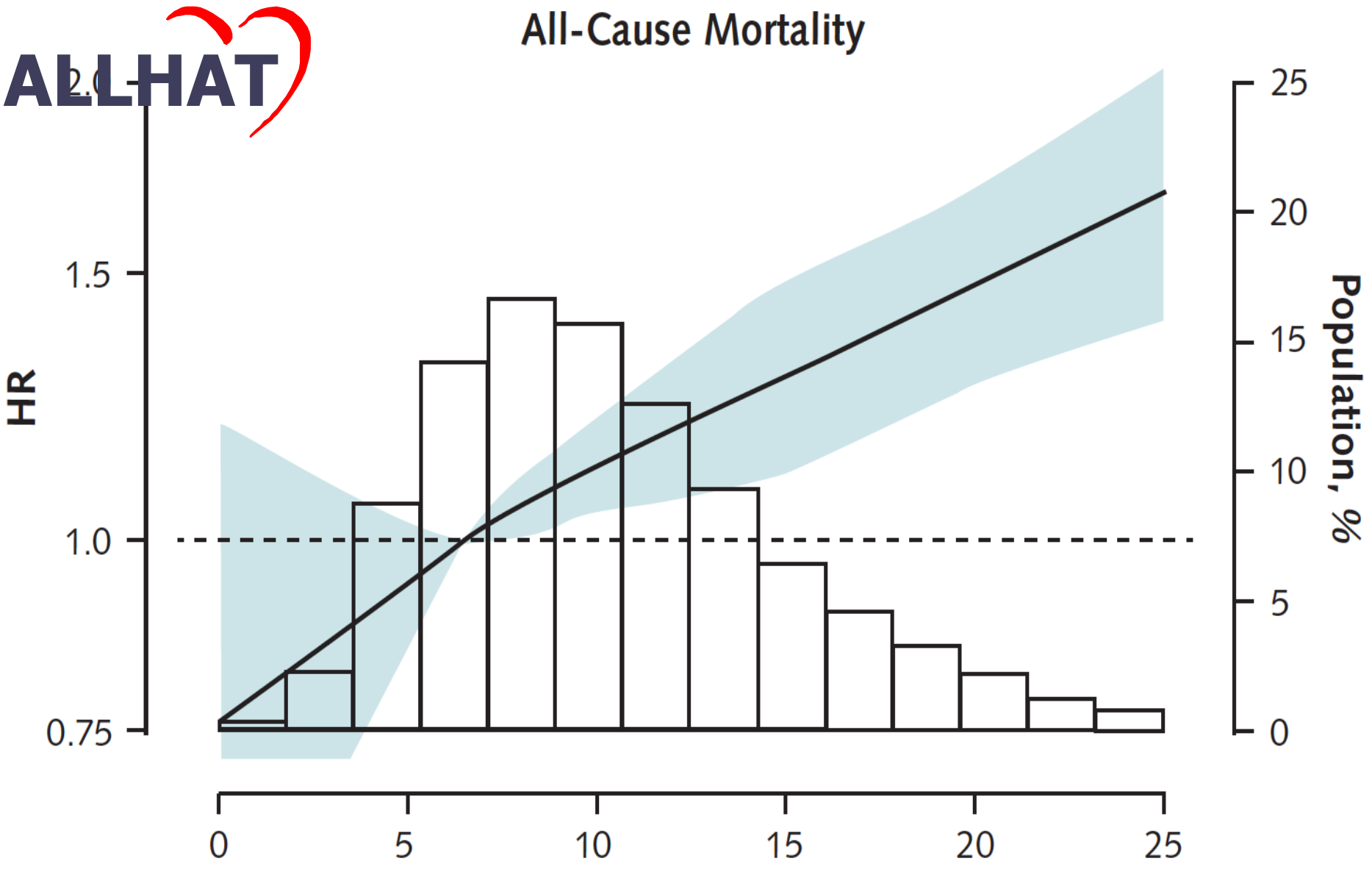
Design: Prospective cohort study.

Setting: Post hoc analysis of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).

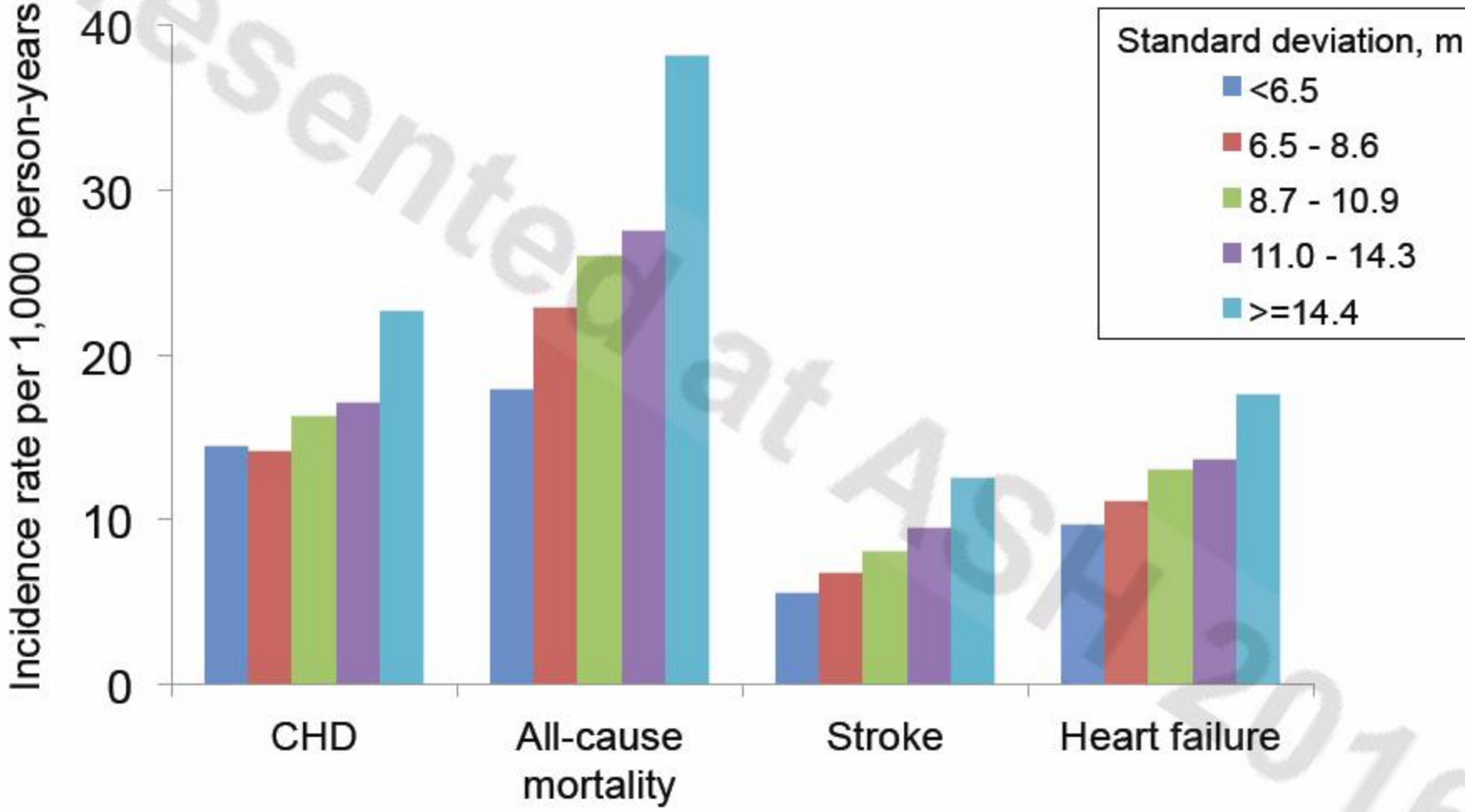
Results: During follow-up, 1194 fatal CHD or nonfatal MI events, 1948 deaths, 606 strokes, and 921 heart failure events occurred. After multivariable adjustment, including for mean SBP, the hazard ratio comparing participants in the highest versus lowest quintile of SD of SBP (≥14.4 mm Hg vs. <6.5 mm Hg) was 1.30 (95% CI, 1.06 to 1.59) for fatal CHD or nonfatal MI, 1.58 (CI, 1.32 to 1.90) for all-cause mortality, 1.46 (CI, 1.06 to 2.01) for stroke, and 1.25 (CI, 0.97 to 1.61) for heart failure. Higher VVV of diastolic BP was also associated with CVD events and mortality.

Limitation: Long-term outcomes were not available.

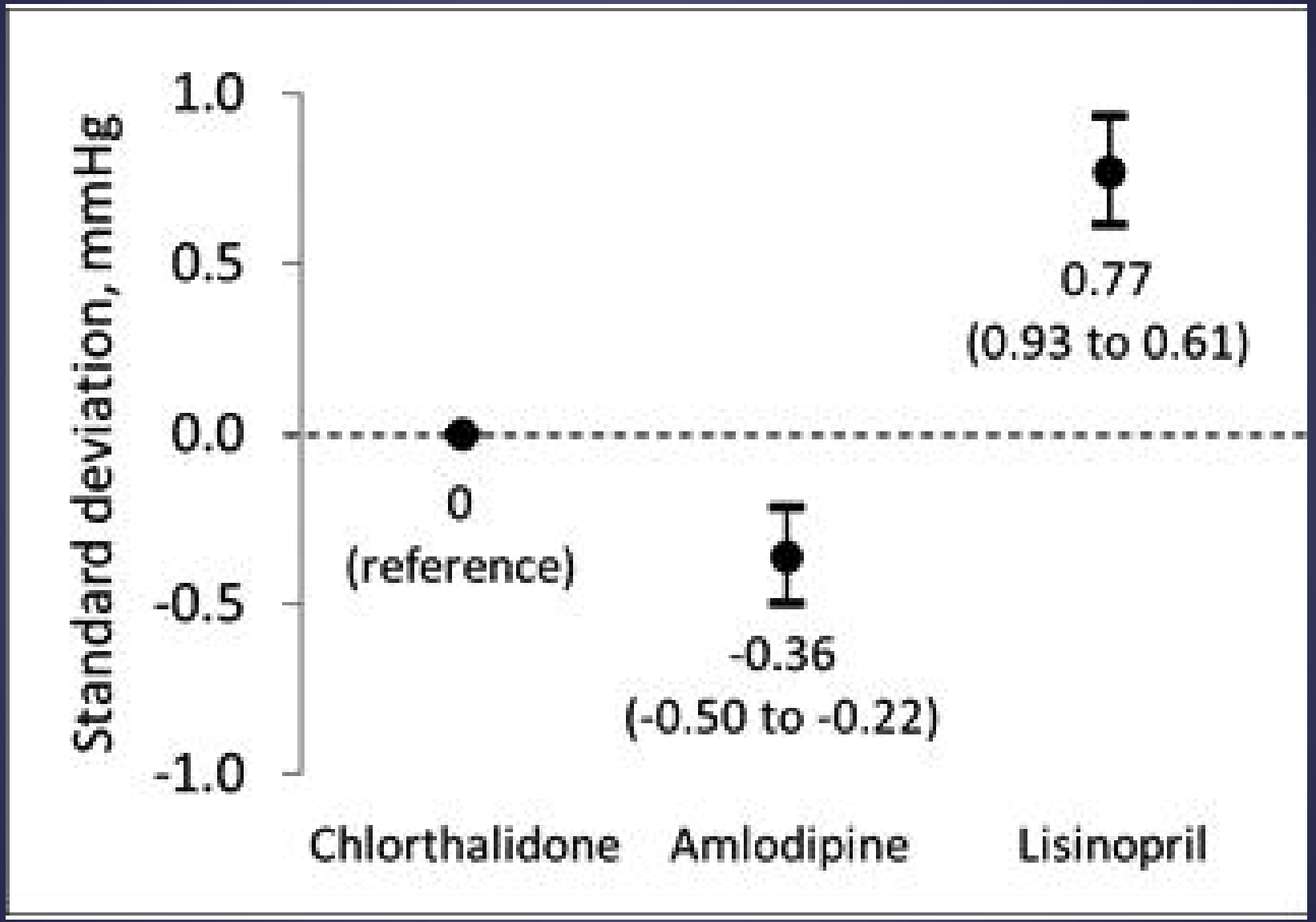
ALLHAT


All-Cause Mortality
HR
1.5
1.0
0.75
Population, %
25
20
15
10
5
0
0
5
10
15
20
25
Standard Deviation of SBP

ALLHAT Results: VVV of BP and CVD events



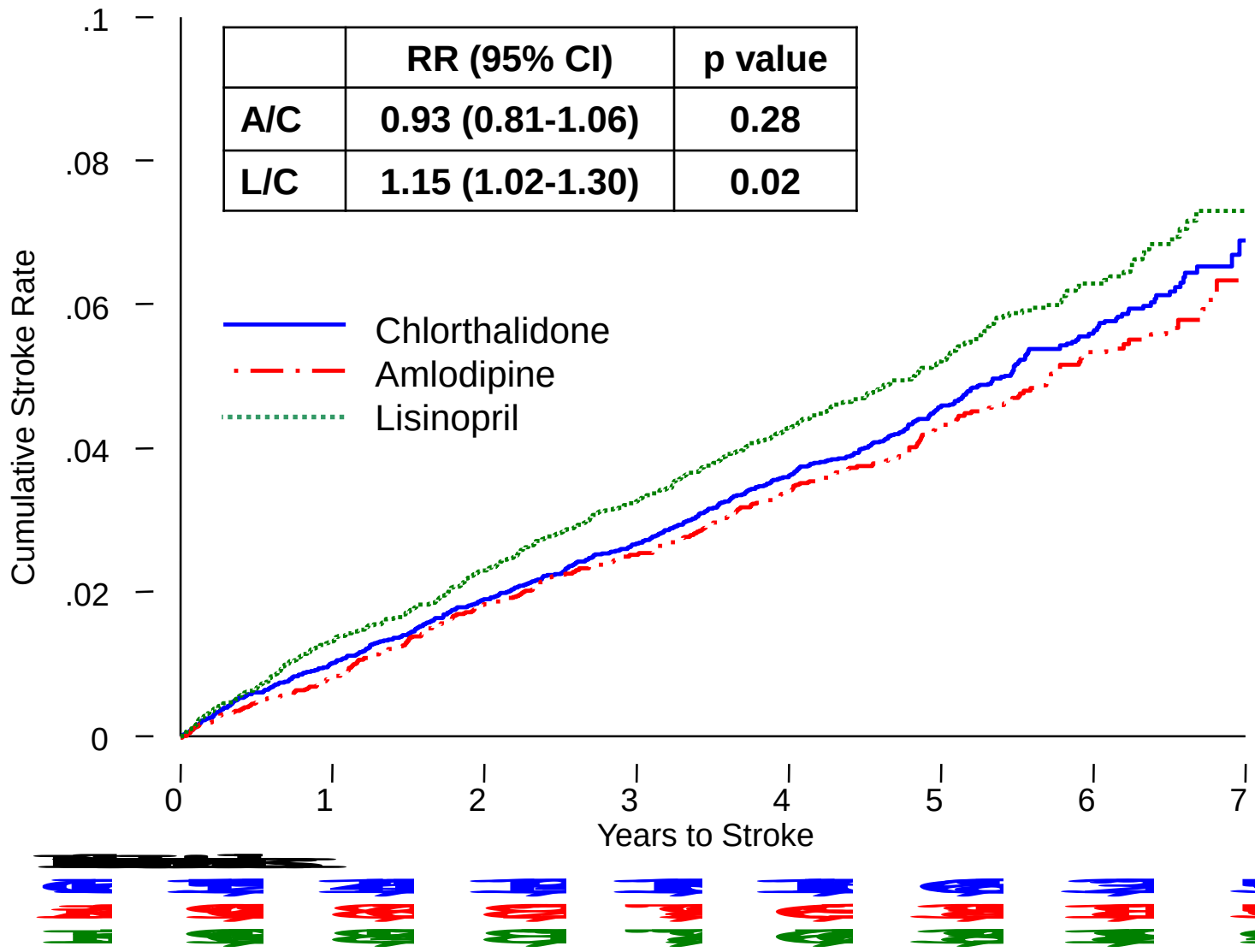
Visit-to-Visit BP Variability in ALLHAT



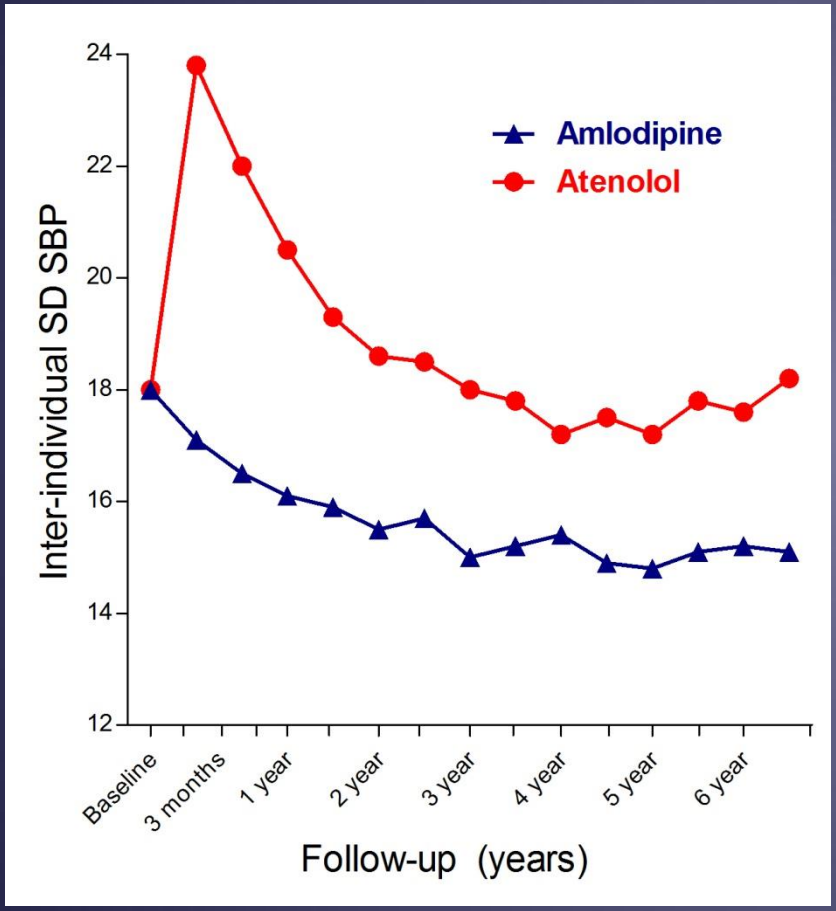
Muntner et al. J. Clin. Hypertension 2014

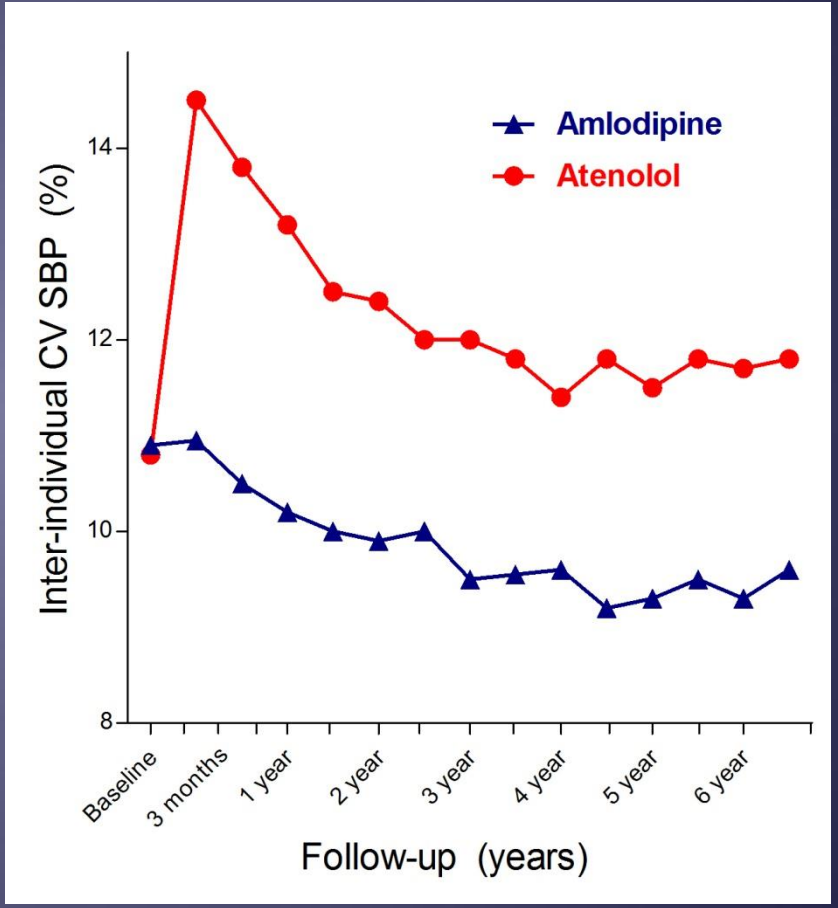
Cumulative Event Rates for Stroke by ALLHAT Treatment Group

	RR (95% CI)	p value
A/C	0.93 (0.81-1.06)	0.28
L/C	1.15 (1.02-1.30)	0.02



Group distribution (SD and CV) of measures of SBP at baseline and at each follow-up visit in the two treatment groups





ascot

Summary

- **"Amlodipine reduces variability compared with atenolol**
- **Variability increased with age, diabetes, smoking, and in those with established vascular disease**
- **Adjusting for BP variability completely explains differences in stroke and CHD outcomes between amlodipine-based and atenolol-based treatment in ASCOT"**

Table 2. HR for Incident Stroke (95% Confidence Interval) After Adjustment for Age, Race, Age-By-F Deviation From the Mean SBP Level for the Category

	Normotensive (<120 mm Hg)	Prehypertension (120 mm Hg–139 mm Hg)	Stage 1 Hypertension (140 mm Hg–159 mm Hg)	Stage 2 Hypertension (160+ mm Hg)
No antihypertensive medications	1.0 (Ref)	1.44 (1.04–2.01)	2.19 (1.45–3.31)	3.35 (1.78–6.28)
1 Antihypertensive medication	1.42 (0.94–2.15)	2.00 (1.44–2.77)	1.67 (1.09–2.54)	3.00 (1.71–5.26)
2 Antihypertensive medications	1.60 (1.06–2.42)	1.88 (1.35–2.62)	2.84 (1.95–4.13)	1.42 (0.67–2.99)
3+ Antihypertensive medications	2.48 (1.63–3.77)	2.34 (1.66–3.32)	3.35 (2.28–4.92)	4.62 (2.84–7.51)

Howard et al. Stroke2015;46:1595-1600.

Journal of the American College of Cardiology

Volume 65, Issue 15, 21 April 2015, Pages 1539–1548

Original Investigation

Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability and Risk of Cardiovascular Outcomes : Insights From the TNT Trial

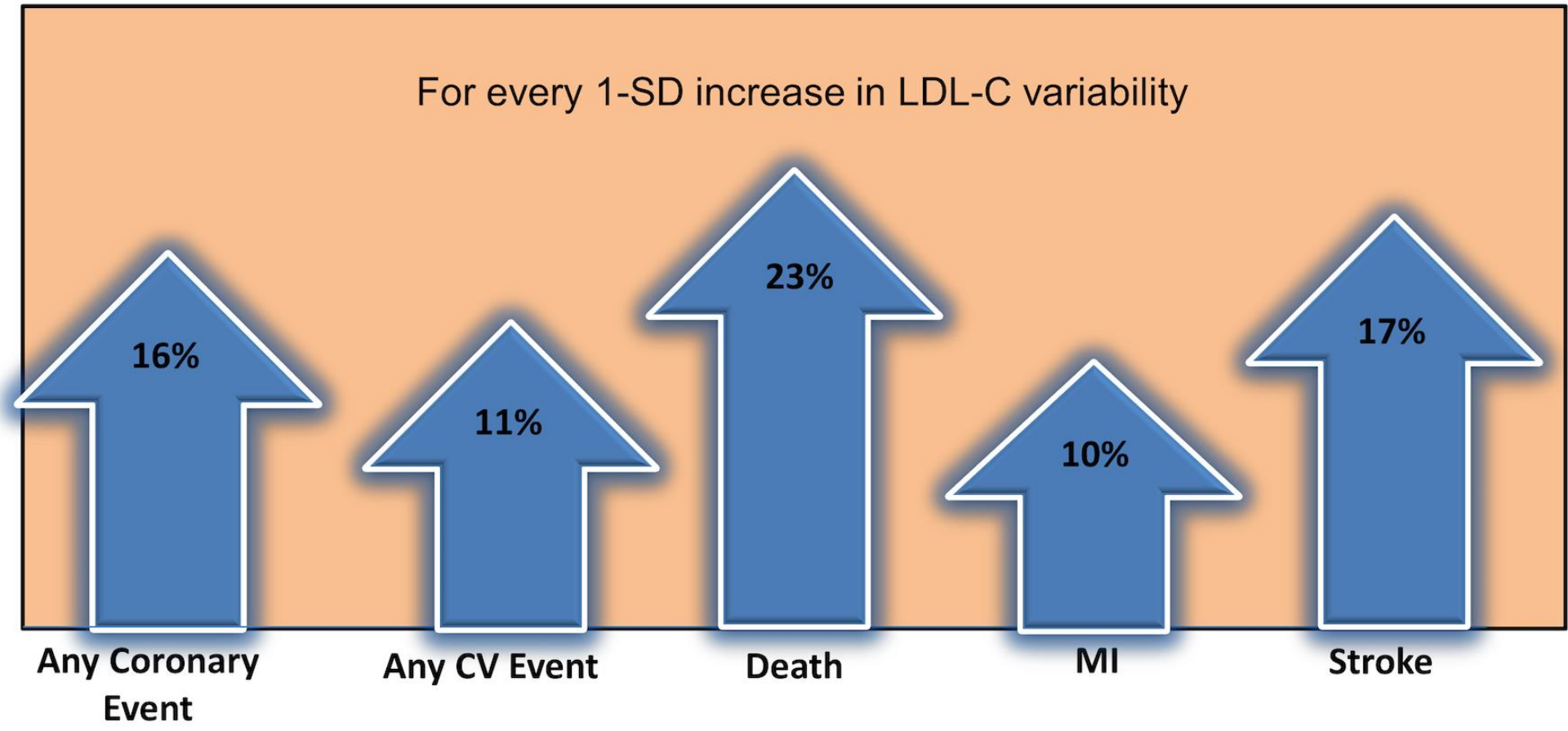
This work was presented in part at the 2012 Annual Scientific Session of the European Society of Cardiology, Munich, Germany.

Sripal Bangalore, MD, MHA*, Andrei Breazna, PhD†, David A. DeMicco, PhamD†, Chuan-Chuan Wun, PhD†, Franz H. Messerli, MD‡, on behalf of the TNT Steering Committee and Investigators

Show more

Visit-to-Visit LDL-C Variability and Outcomes

- Visit-to-visit LDL-C variability* was defined as variability in LDL-C values between visits
- 9572 patients from the TNT trial

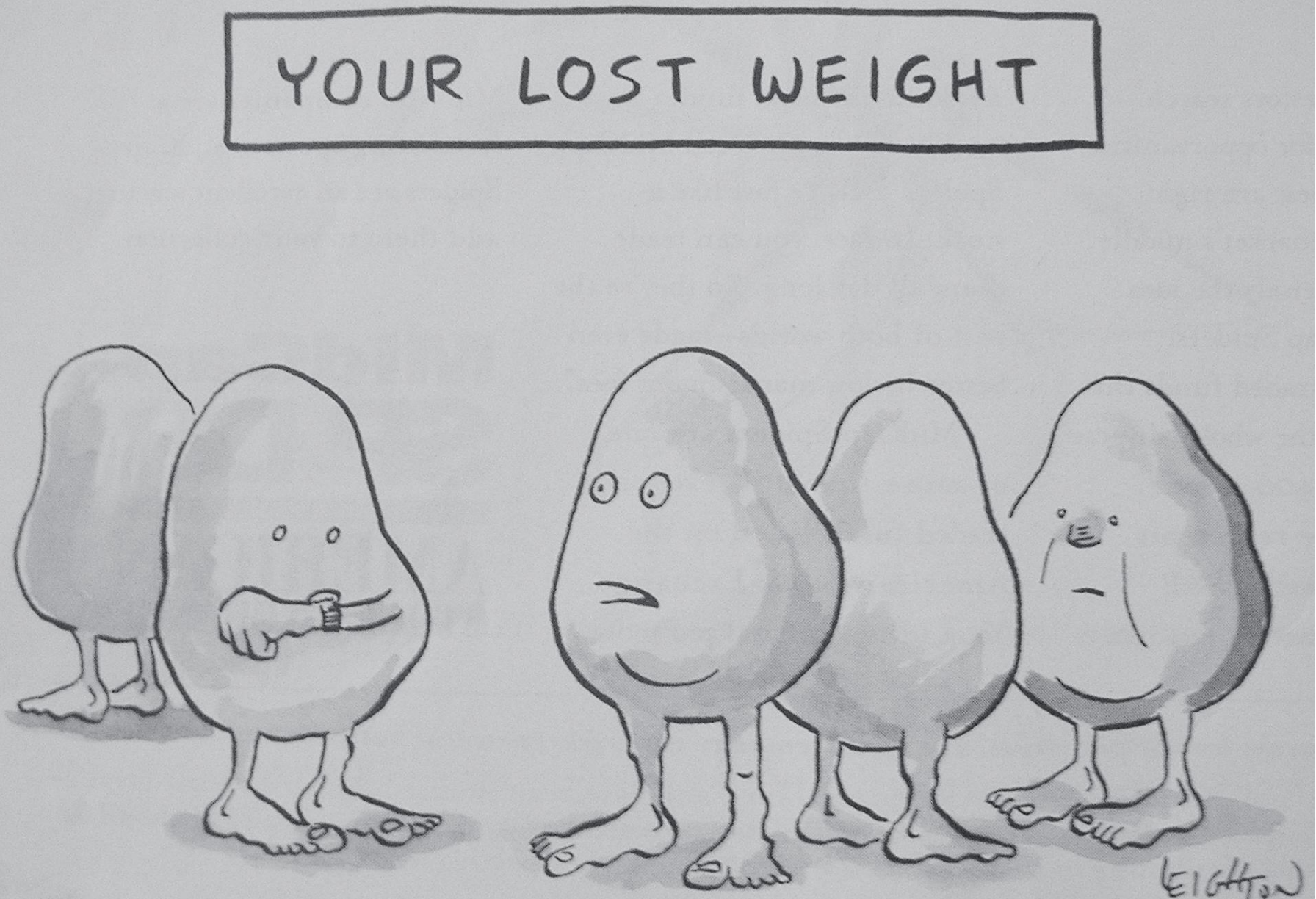


* LDL-C variability measured from 3 months onwards into randomization, as this was the relatively steady phase in LDL-C, after the initial decrease

ch for a Perfect Diet

- **"With more than 60% of adults and 13% of children classified as overweight or obese, the USA has become the fattest nation on earth."**

The Lancet. June 8, 2002.



"Ready to head back?"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Body-Weight Fluctuations and Outcomes in Coronary Disease

Sripal Bangalore, M.D., M.H.A., Rana Fayyad, Ph.D., Rachel Laskey, Ph.D., David A. DeMicco, Pharm.D., Franz H. Messerli, M.D., and David D. Waters, M.D.

ABSTRACT

BACKGROUND

Body-weight fluctuation is a risk factor for death and coronary events in patients without cardiovascular disease. It is not known whether variability in body weight affects outcomes in patients with coronary artery disease.

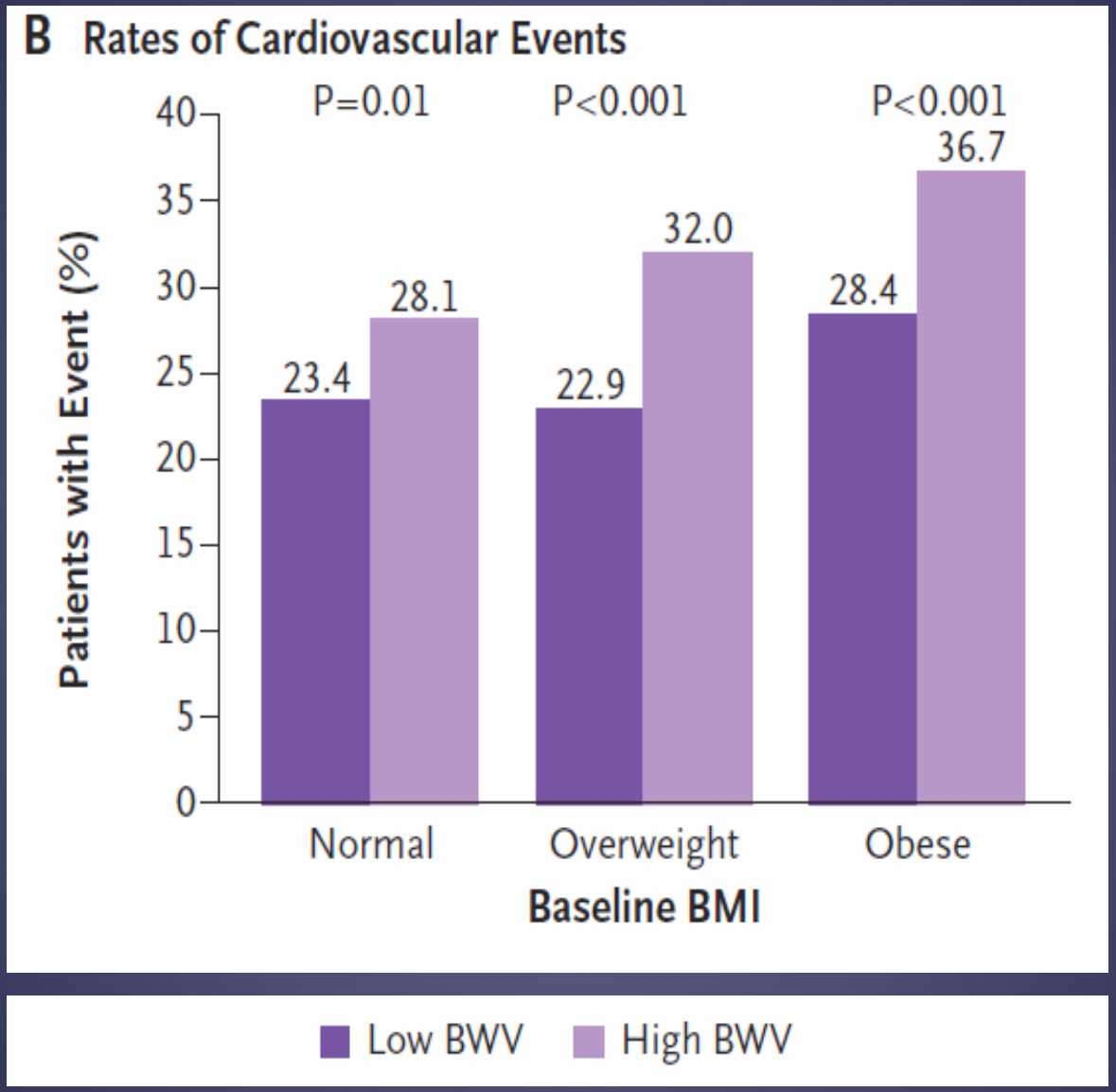
Visit-to-visit Variability in Body Weight and Outcome

Table 3. Multivariable Models and Risk of Outcomes in the Highest versus the Lowest Quintile of Variability in Body Weight.

Outcome	Adjusted Hazard Ratio (95% CI)*	P Value
Any coronary event	1.64 (1.41–1.90)	<0.001
Any cardiovascular event	1.85 (1.62–2.11)	<0.001
Death	2.24 (1.74–2.89)	<0.001
Myocardial infarction	2.17 (1.59–2.97)	<0.001
Stroke	2.36 (1.56–3.58)	<0.001
New-onset diabetes	1.78 (1.32–2.40)	<0.001

Bangalore et al. N Engl J Med. 2017 Apr 6;376:1332

Visit-to-visit Variability in Body Weight and Outcome



Bangalore et al. N Engl J Med. 2017 Apr 6;376:1332

Conclusions

“…fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events independent of traditional cardiovascular risk factors.”

Bangalore et al. N Engl J Med. 2017 Apr 6;376:1332

Blood Pressure
LDL Cholesterol
Glycemia
Body Weight

Mr. Framingham

Once you are fat, you better stay fat!

William Kannel MD, conclusion on weight cycling data in the Framingham cohort

There Underlying Mechanism of Residual Risk

1. Beta Blockers lower BP but do not reduce outcome, particularly CVA.

2. Longstanding hypertension may have caused irreversible damage in target organs and vascular tree.

3. BP Variability may persist despite BP being at target.

How to tackle

There Underlying Mechanism of Residual Risk

1. Beta Blockers lower BP but do not reduce outcome, particularly CVA.

2. Longstanding hypertension may have caused irreversible damage in target organs and vascular tree.

3. BP Variability may persist despite BP being at target.

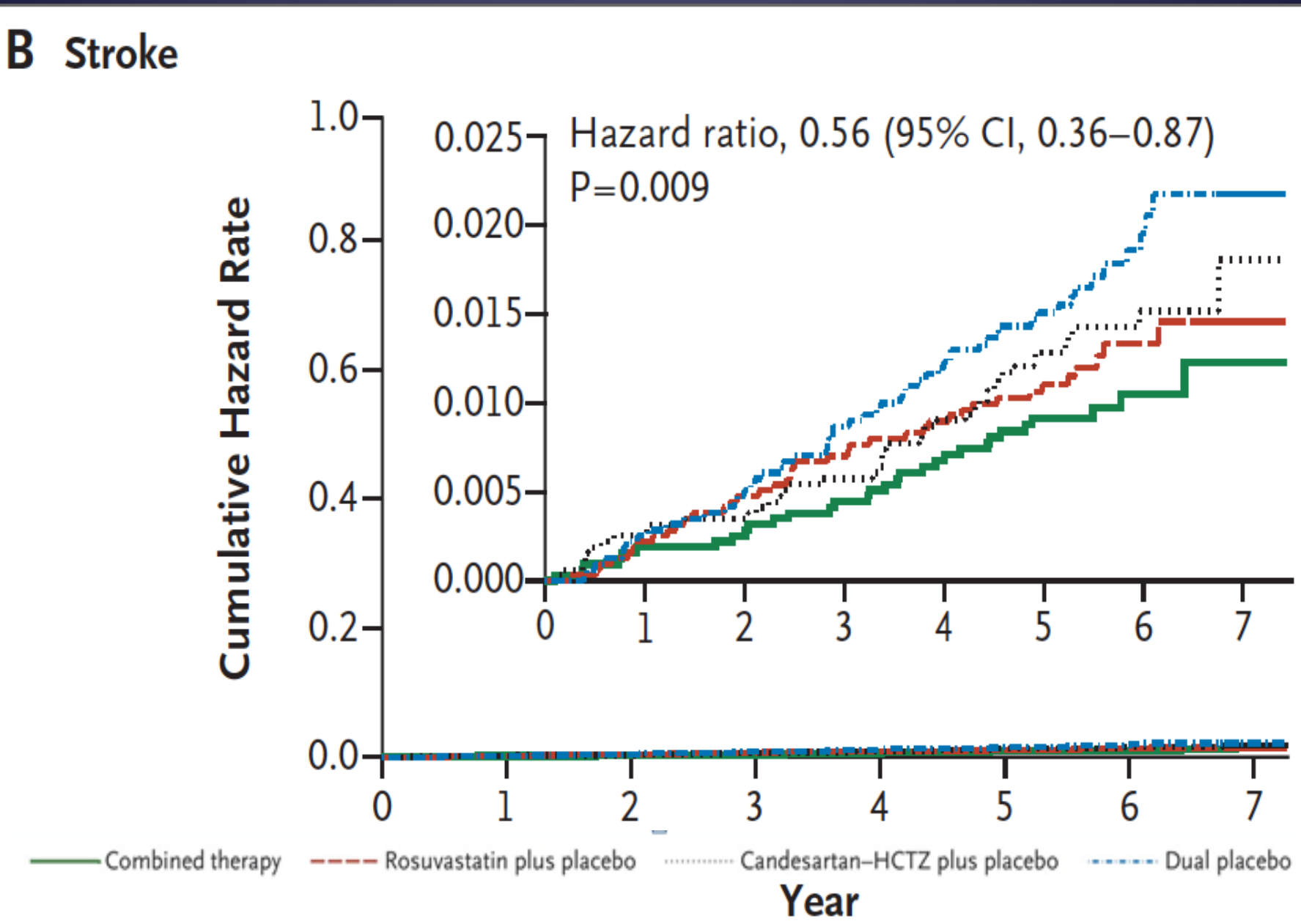
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

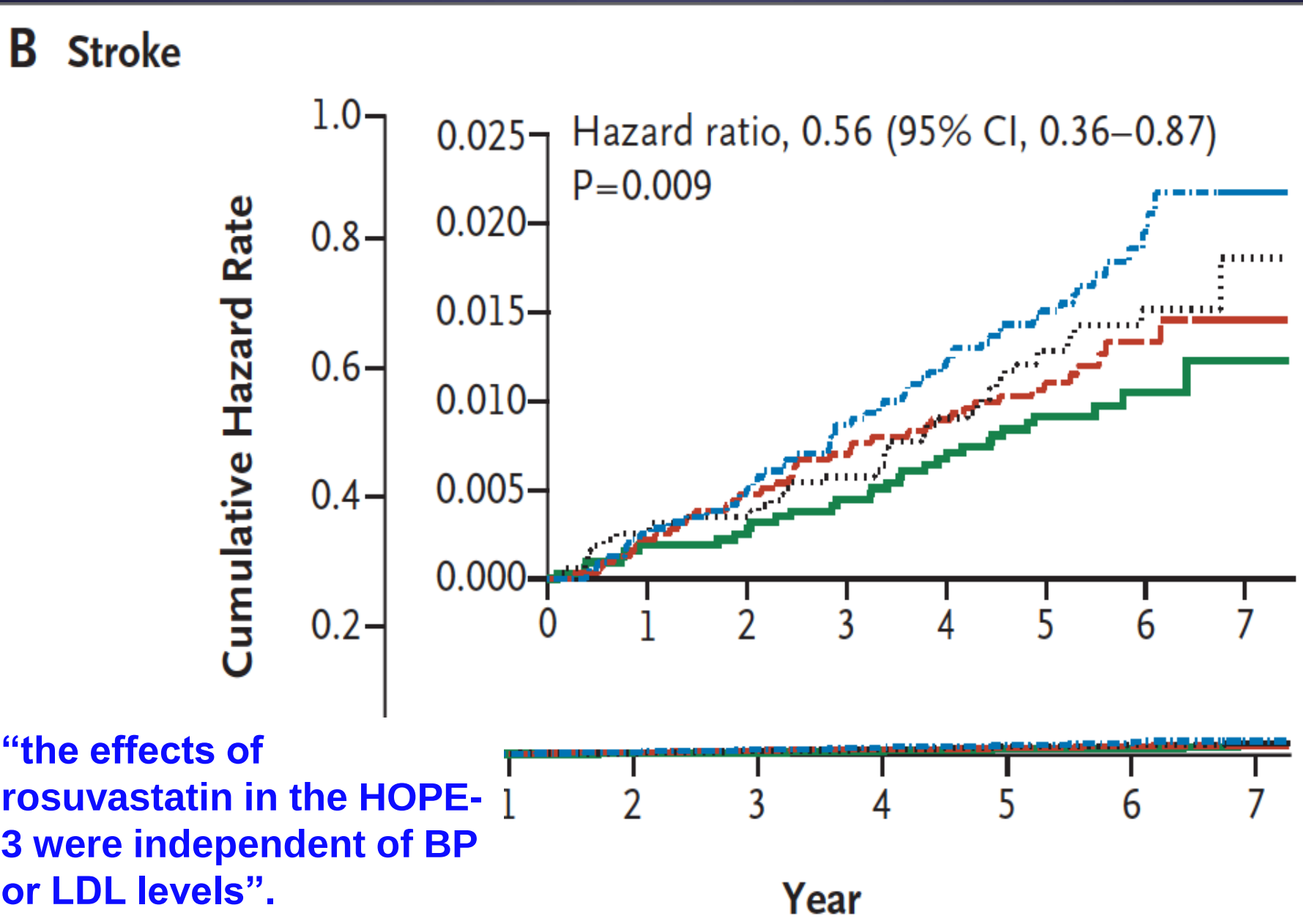
Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf, M.B., B.S., D.Phil., Eva Lonn, M.D., Prem Pais, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Denis Xavier, M.D., Alvaro Avezum, M.D., Ph.D., Lawrence A. Leiter, M.D., Leopoldo S. Piegas, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Karen Sliwa, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Jose L. Accini, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Hyejung Jung, M.Sc., Lisheng Liu, M.D., Rafael Diaz, M.D., Antonio Dans, M.D., and Gilles Dagenais, M.D., for the HOPE-3 Investigators†

Yusuf et al. NEJM, April 2, 2016,



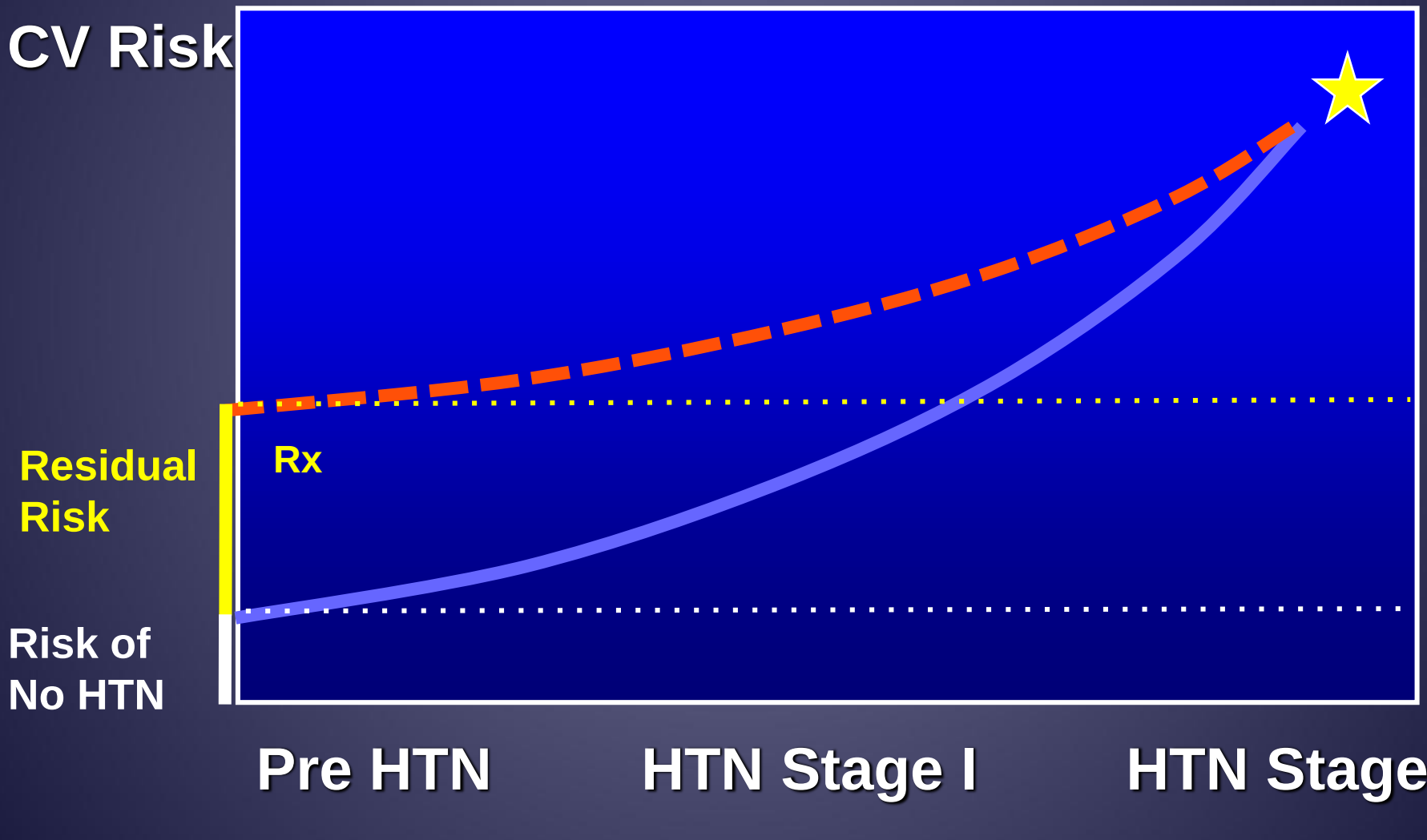
Yusuf et al. NEJM, April 2, 2016,



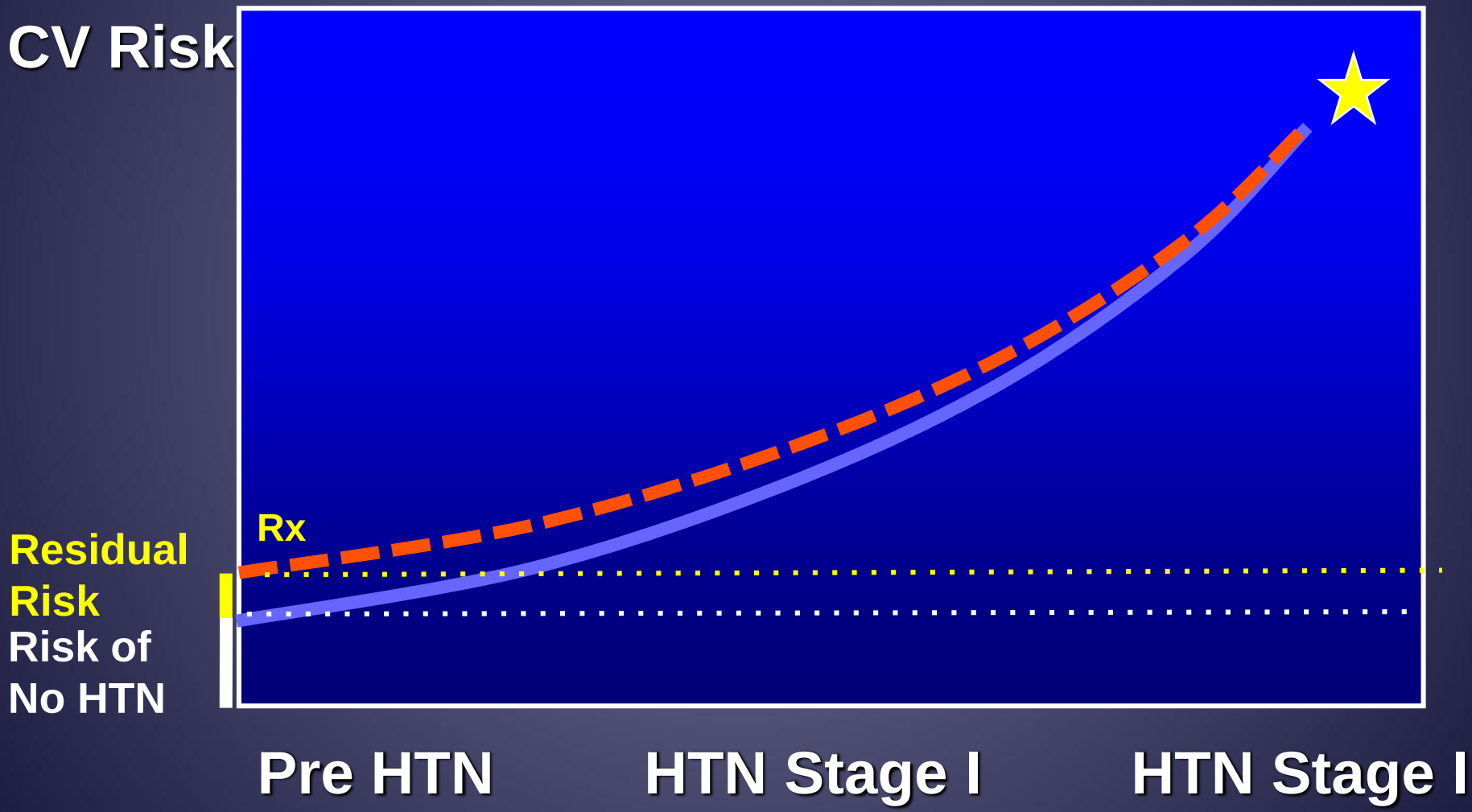
"the effects of rosuvastatin in the HOPE-3 were independent of BP or LDL levels".

Yusuf et al. NEJM, April 2, 2016,

Risk of Hypertension and its Reduction by Antihypertensive Therapy



Risk of Hypertension and its Reduction by Antihypertensive Therapy + Statin



Statins for all hypertensive pts > age 60 ???

Trial Population

The trial included men 55 years of age or older and women 65 years of age or older who had at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of low concentration of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction;

Yusuf et al. NEJM, April 2, 2016,

Characteristics of the 12,705 Participants in the HOPE–3 Trial at Baseline.*

Cholesterol		**mg/dl**
	Total	**201.3**
	LDL	**127.0**
	HDL	**44.7**
Triglycerides		**128.3**

Your hypertensive patient needs a statin!

Yusuf et al. NEJM, April 2, 2016,

Salim's Lesson # 3

- Lowering BP in normotensive patients has no effect.
- Lowering BP in hypertensive patients decreases the risk of stroke.
- **Lowering BP and LDL decreases the risk of stroke by 44 % regardless of baseline BP or LDL levels.**

- “Mr. Milosevic’s systolic blood pressure is about 200, though last week it suddenly rose above 240 and hearings were suspended for two days.”

- “A reading of 140 to 160 would be normal.”

New York Times. July 26, 2003.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

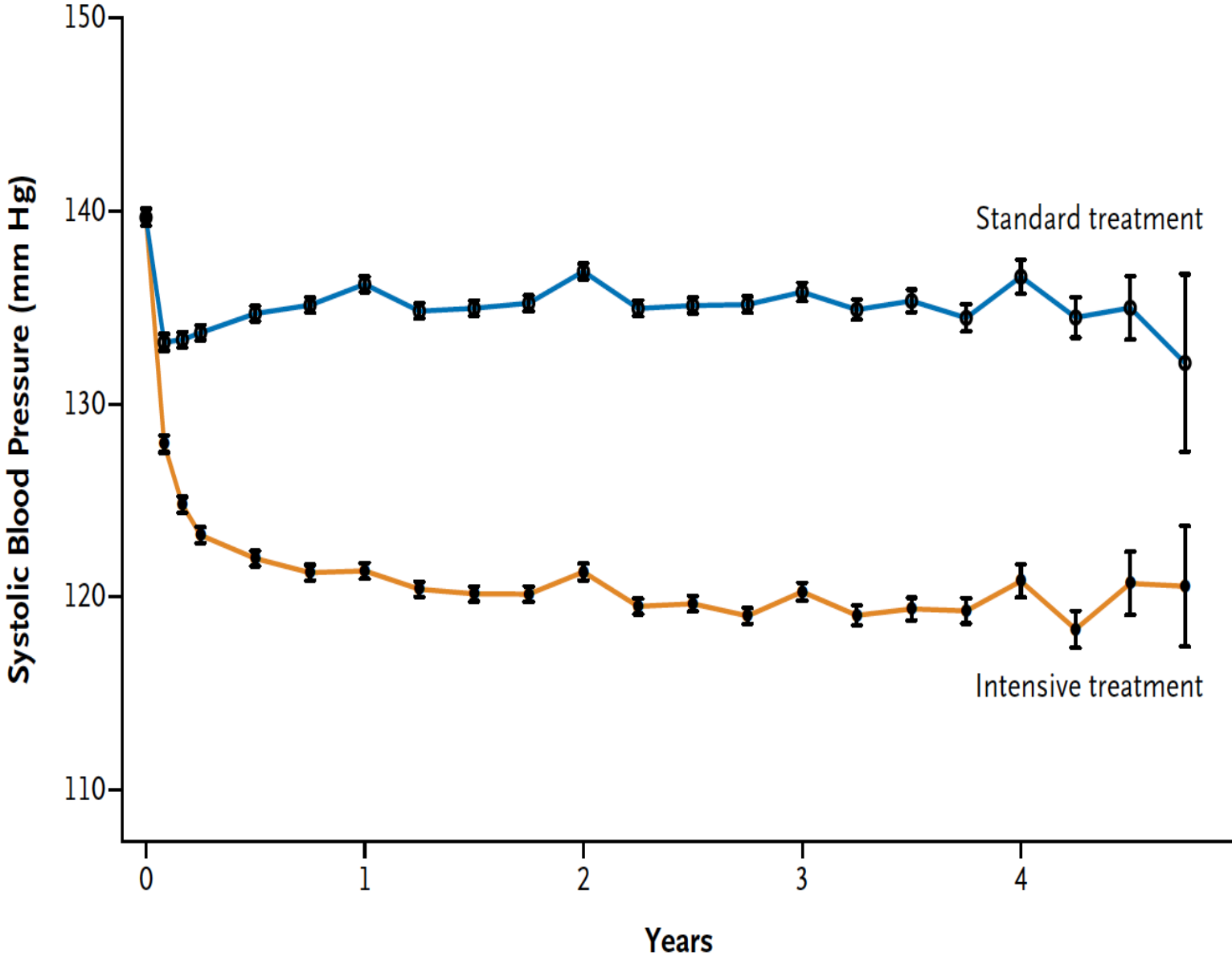
ABSTRACT

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N.

SPRINT



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

?

To SPRINT or not to SPRINT
(toward systolic BP of 120 mmHg)




- you enthusiastically tell your patient that lowering BP to 120 mmHg or below might reduce their risk for cardiovascular events by 25% and increase the risk of adverse events merely from 2.5% to 4.7%.

- Or you gravely frown, mentioning that that lowering BP to 120 mmHg or below will reduce mortality by less than 1% per year, while increasing the risk of hypotension, syncope, and acute kidney injury or acute renal failure by as much as 88%.

SPRINT

Effect of Intensive Blood-Pressure Treatment (less than 120 mmHg)

- "…if patients don't feel miserable on therapy and the therapy is cost-effective, and on top of that, it lowers cardiovascular morbidity and mortality, the argument in favor of intensive treatment becomes very persuasive,"

Dr Dan R Berlowitz,

commentary on

New England Journal of Medicine,

August 23, 2017

SPRINT

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Sure, but exactly how was BP measured in SPRINT?

Dr Dan R Berlowitz,
commentary on
New England Journal of Medicine,
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Increased all-cause mortality with intensive blood-pressure control in patients with a baseline systolic blood pressure of ≥160 mmHg and a Lower Framingham risk score: a cautionary note from SPRINT

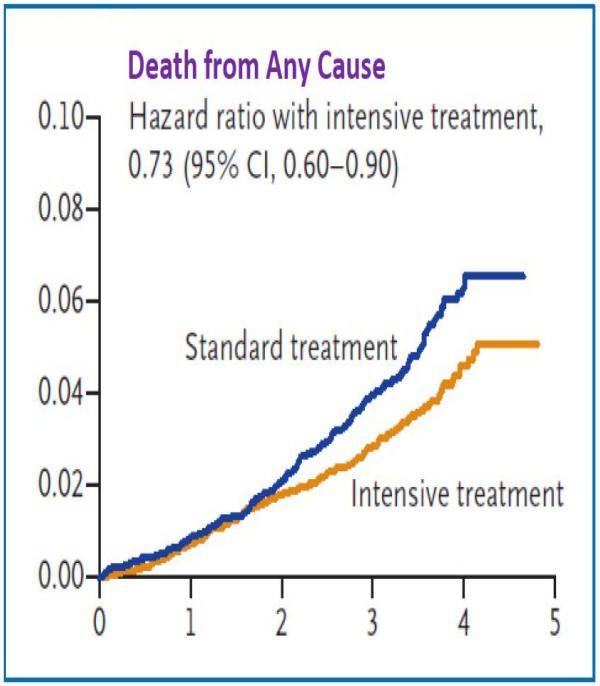
Tzung-Dau Wang[1], FESC, Hung-Ju Lin[1], Wen-Jone Chen[2], FESC, Te-Chang Weng[3], Wen-Yi Shau[3]

*1. Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei City, **Taiwan**; 2. Department of Emergency Medicine, National Taiwan University Hospital, Taipei City, **Taiwan**; 3. Pfizer, Taipei, **Taiwan***

Wang et al. presented at ESC 2017

Results: Step 4, comparing patients with a baseline systolic BP of ≥160 mmHg and a Framingham 10-yr risk score of ≤31.3% to the rest of SPRINT participants

SPRINT-original



† Adjusted for age (treated as quintile) and sex, and assuming common baseline hazard across clinic site due to small sample size

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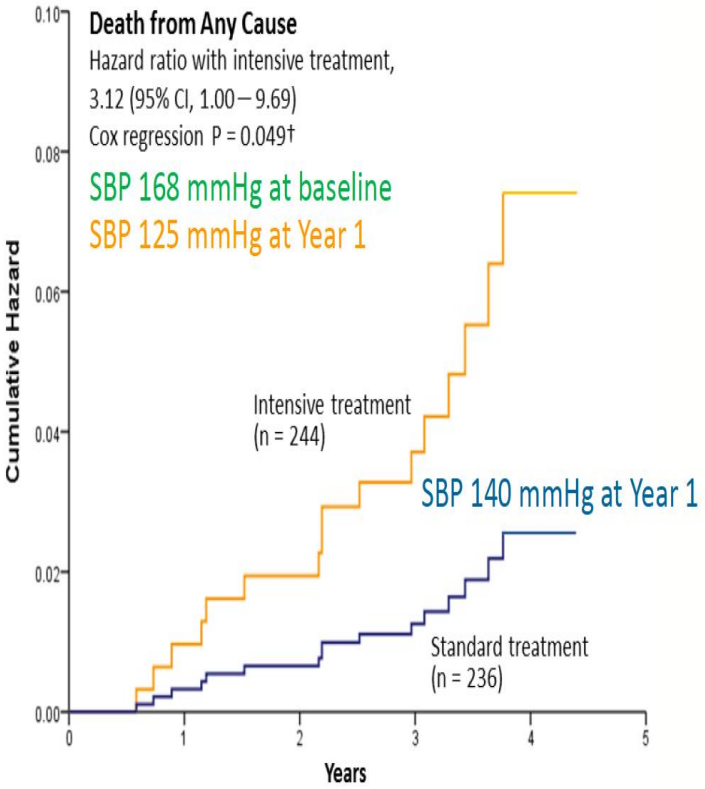
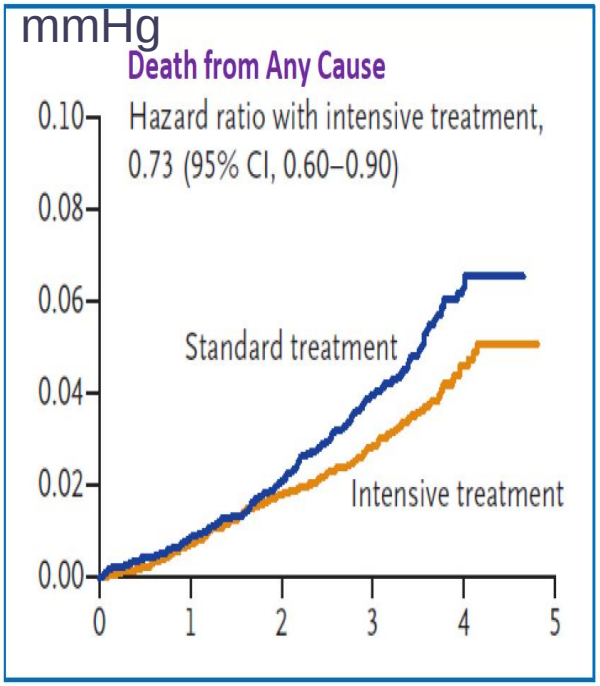
Results: Step 4, comparing patients with a baseline systolic BP of ≥160 mmHg and a Framingham 10-yr risk score of ≤31.3% to the rest of SPRINT participants

Only 5% SPRINT-subgroup: Baseline SBP ≥160 mmHg & 10-yr Framingham risk score ≤31.3%



SPRINT-original

Baseline BP 139.8/78.1 mmHg



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- **Among the SPRINT participants with a baseline systolic BP of ≥160 mmHg and a lower 10-year Framingham risk score (≤31.3%, median), targeting a systolic BP of <120 mmHg compared with <140 mmHg resulted in an approximate 3-fold risk of death from any cause…**

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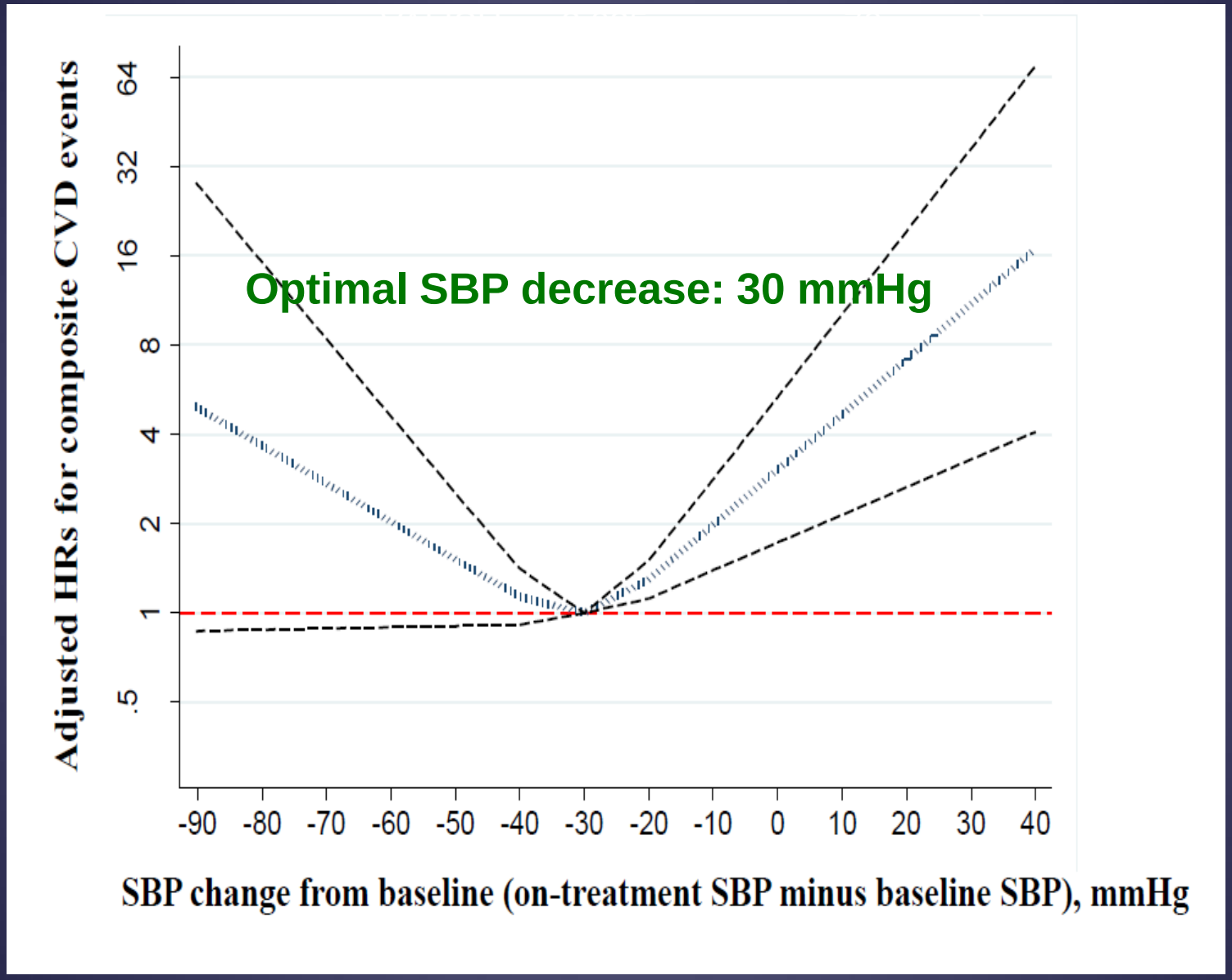
- **Among the SPRINT participants with a baseline systolic BP of ≥160 mmHg and a lower 10-year Framingham risk score (≤31.3%, median), targeting a systolic BP of <120 mmHg compared with <140 mmHg resulted in an approximate 3-fold risk of death from any cause…**

Subgroup is only 5% of whole SPRINT population

Wang et al. presented at ESC 2017

Optimal On-treatment BP in Older Adults with ISH

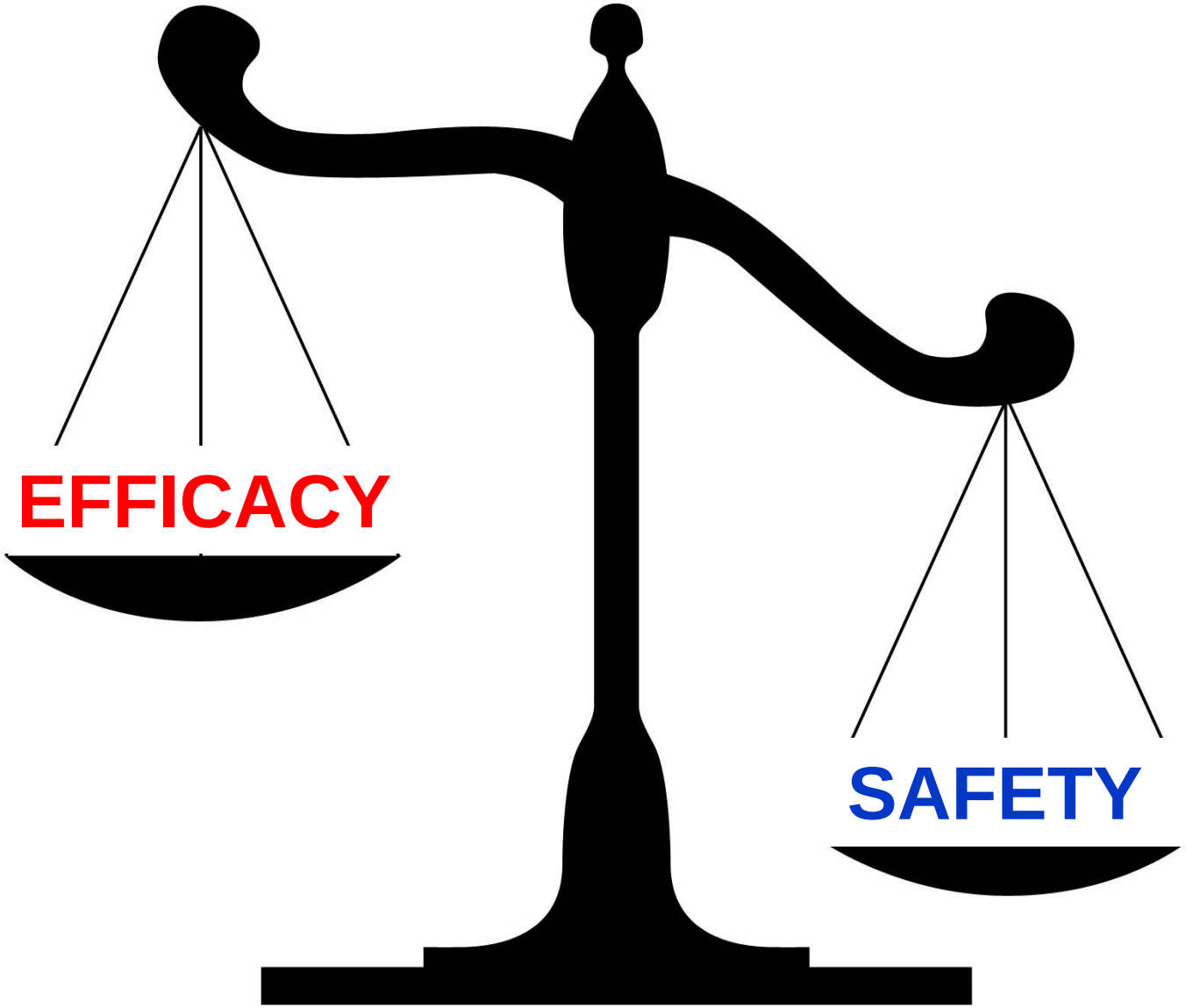


Adjusted for age, sex, treatment strategy, clinical characteristics (smoking, prevalent diabetes, prevalence hyperlipidemia, use of antihypertensive drugs, and prevalent CHD).

Yano Y et al. 2017 in press

- **There was an intricate interaction between each individual's baseline blood pressure, their inherent cardiovascular risk, and their degree of blood pressure reduction.**

Wang et al. presented at ESC 2017



Bangalore, Messerli et al. AJM in press 2

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Optimal Systolic Blood Pressure Target after SPRINT

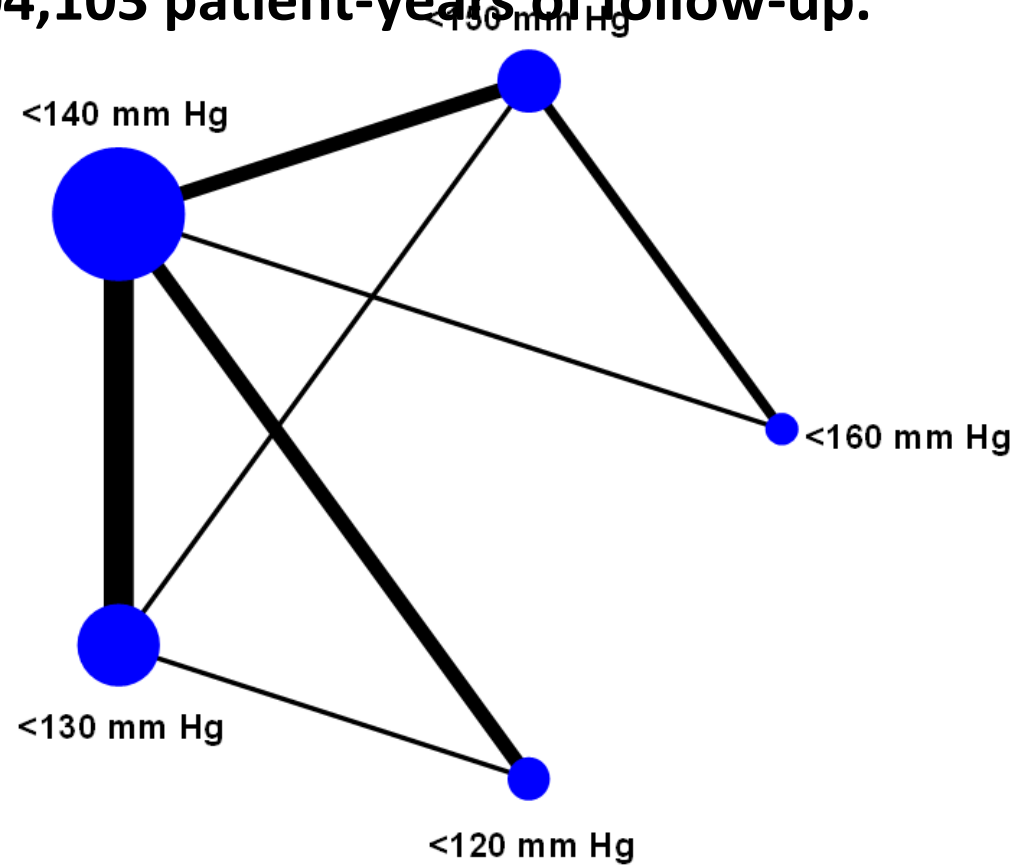
Insights from a Network Meta-Analysis of Randomized Trials

Sripal Bangalore, MD, MHA, Bora Toklu, MD, Eugenia Gianos, MD, Arthur Schwartzbard, MD, Howard Weintraub, MD, Gbenga Ogedegbe, MD, Franz H. Messerli, MD

New York University School of Medicine, New York, NY [SB, EG, AS, GO, HW]
Mount Sinai Beth Israel Medical Center, New York, NY [BT]
University Hospital, Bern, Switzerland and Mount Sinai, Icahn School of Medicine, New York, NY, USA [FHM]

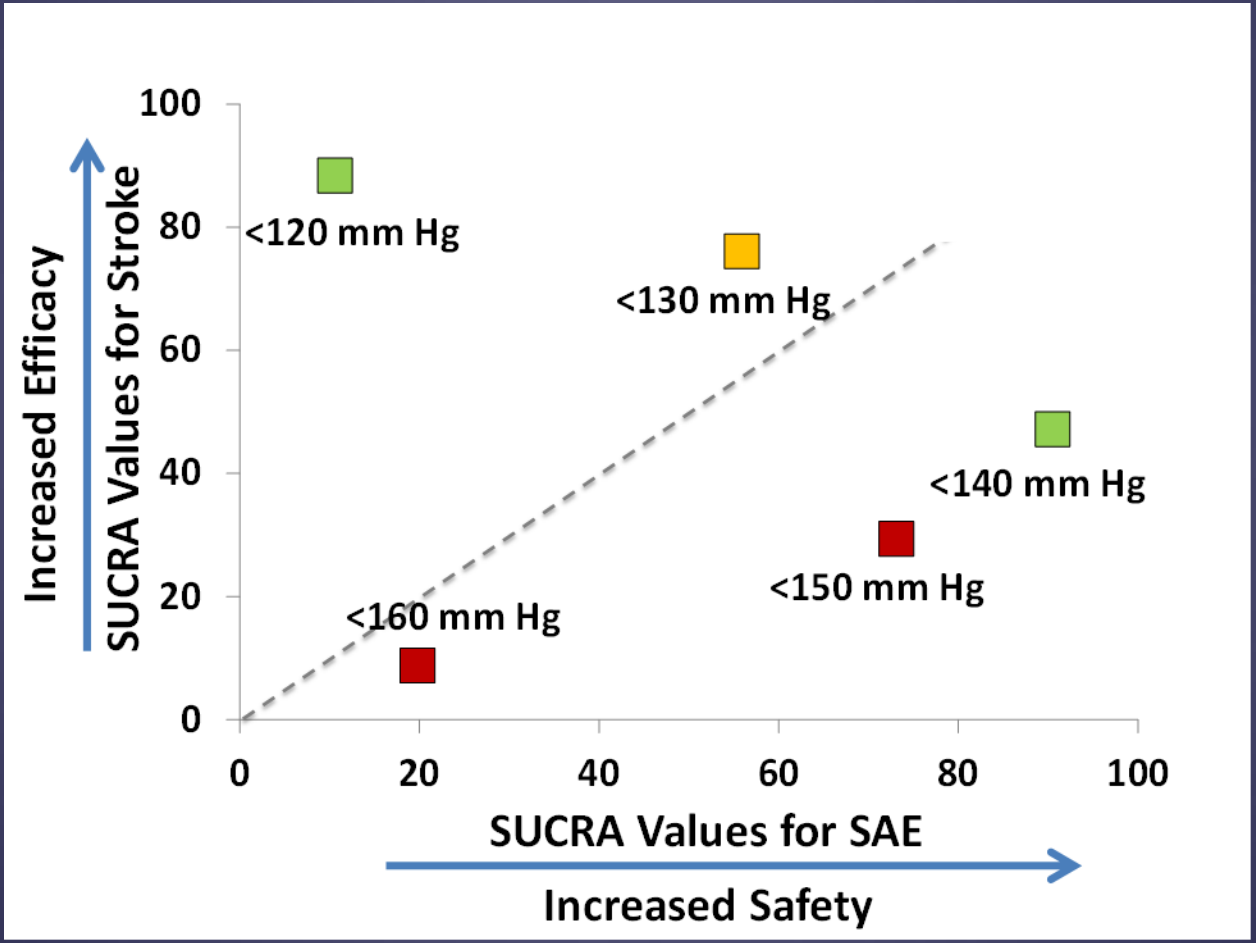
Network of systolic blood pressure target comparisons

Seventeen trials that enrolled 55,163 patients with 204,103 patient-years of follow-up.



Bangalore, Messerli et al. AJM in press 2017

Cluster plot for stroke versus serious adverse effects



Bangalore, Messerli et al. AJM in press 2

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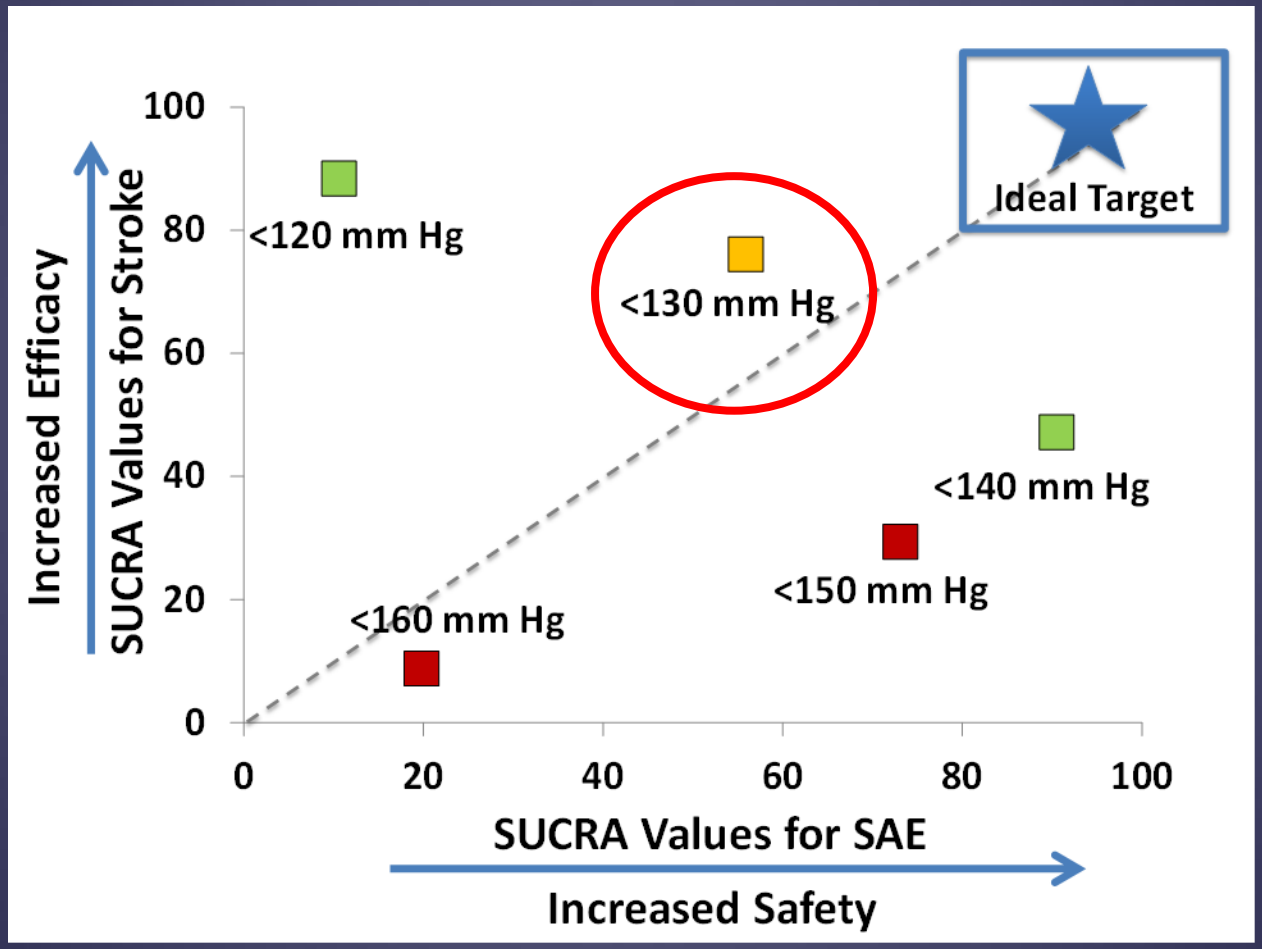
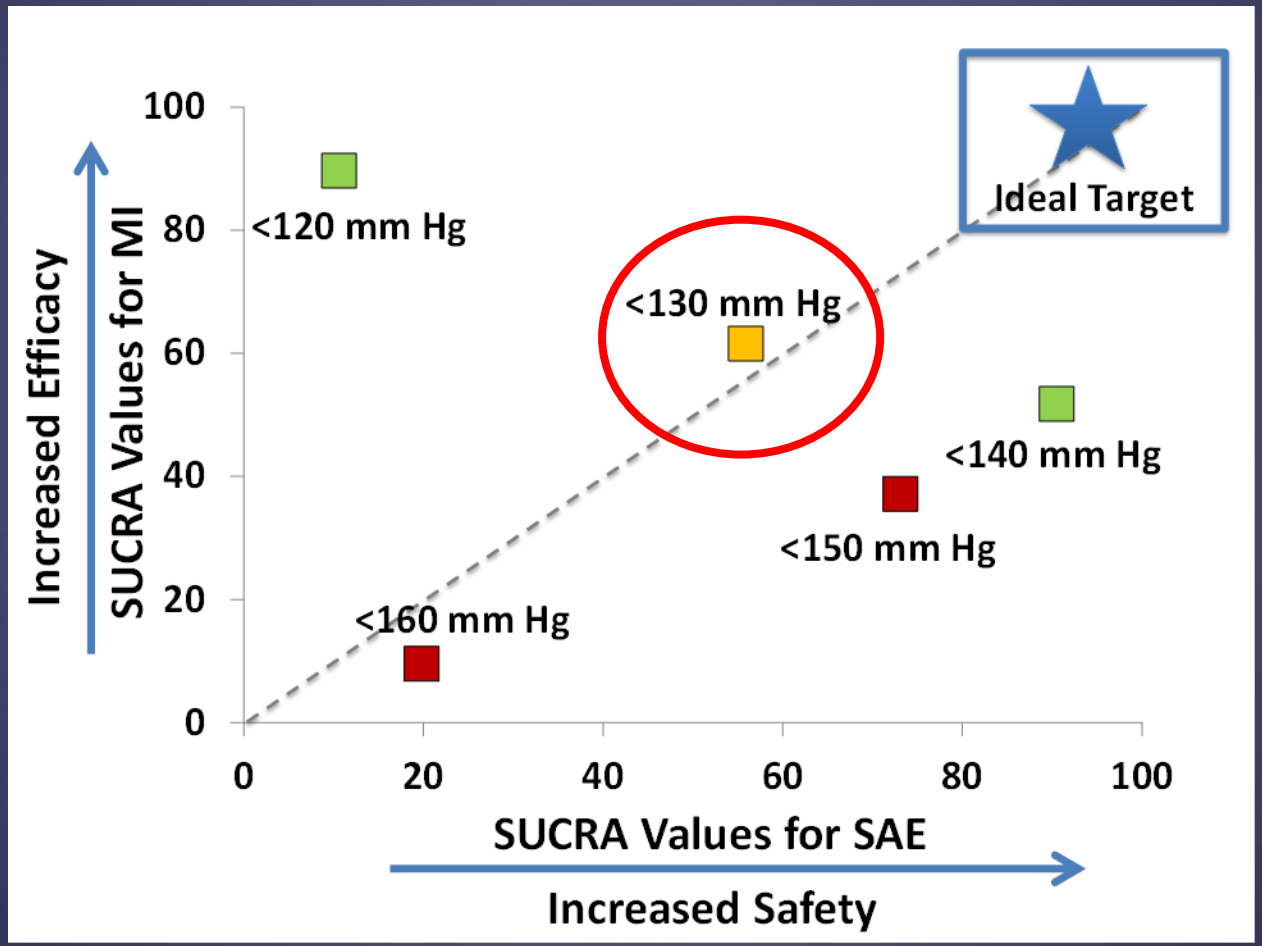


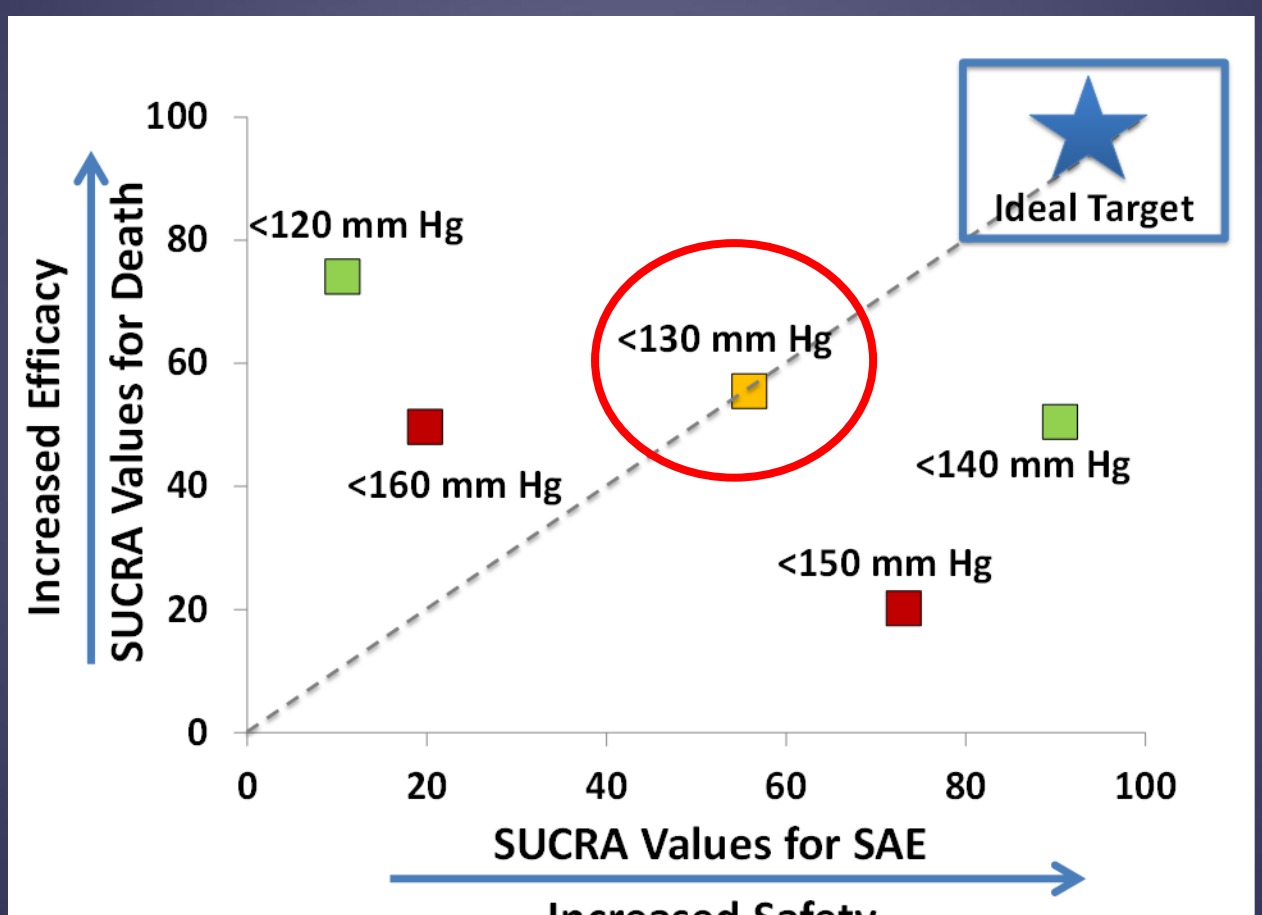
Bangalore, Messerli et al. AJM in press 2

Cluster plot for myocardial infarction versus serious adverse effects



Bangalore, Messerli et al. AJM in press 201

Cluster plot for death versus serious adverse effects.



Bangalore, Messerli et al. AJM in press 201

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Conclusion

- "Cluster plots for combined efficacy and safety showed that a SBP target of <130 mm Hg achieved the optimal balance between efficacy and safety".

Bangalore, Messerli et al. AJM in press 201

- a simple but inescapable truth in medicine is that patients are genetically, physiologically, psychologically, pathologically and culturally different. Accordingly there never will be only one way only to diagnose and treat all medical disorders, including hypertension.

Messerli and Bangalore. Am. J. Med., in press 2016

- To lower systolic pressure of all hypertensive patients uniformly to 120 mmHg or below clearly has to be considered absurd, regardless of the SPRINT results.
- We can only hope that despite (or even because of) SPRINT, physicians will continue to treat patients and not mmHg only.

Messerli and Bangalore. Am. J. Med., in press 2016

H. Daumier, Le malade Imaginaire, Hermitage Museum, St. Petersburg

H. Daumier, Le malade Imaginaire, Hermitage Museum, St. Petersburg

“ Presque tous les hommes meurent de leur remèdes, et non pas de leur maladies. ”

“ Nearly all people die of their remedies, and not of their illnesses. ”

Jean-Baptist Molière,
Le Malade Imaginaire, Act III sc 3, 1673

Wenn ein Arzt hinter dem Sarg seines Patienten geht, folgt manchmal tatsächlich die Ursache der Wirkung.

When a physician walks behind the coffin of his patient, the cause sometimes literally follows the effect.

Robert Koch (1843-1910)

Confidential

- **The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults in the US population.**

To be presented at AHA meeting, Anaheim, November 2017

	Definition of hypertension	
Guideline	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg
2017 ACC/AHA	≥ 130	≥ 80
JNC7	≥ 140	≥ 90
JNC8 panel member report	≥ 140 (≥ 150 for those ≥60 years of age without DM or CKD)	≥ 90

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	Recommended antihypertensive medication	
Guideline	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg
2017 ACC/AHA	≥ 140 or 130 to 139 with high CVD risk†	≥ 90 or 80 to 89 with high CVD risk†
JNC7	≥ 140 or 130 to 139 with DM or CKD	≥ 90 or 80 to 89 with DM or CKD
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	Treatment goal among those taking antihypertensive medication	
Guideline	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg
2017 ACC/AHA	< 130	< 80
JNC7	< 140 (<130 for those with DM or CKD)	< 90 (<80 for those with DM or CKD)
JNC8 panel member report	< 140 (< 150 for those ≥60 years of age without DM or CKD)	< 90

- “A reading of 140 to 160 would be normal.”

New York Times. July 26, 2003.

A rose is
a rose is
a rose..

Data are data are data..

but...

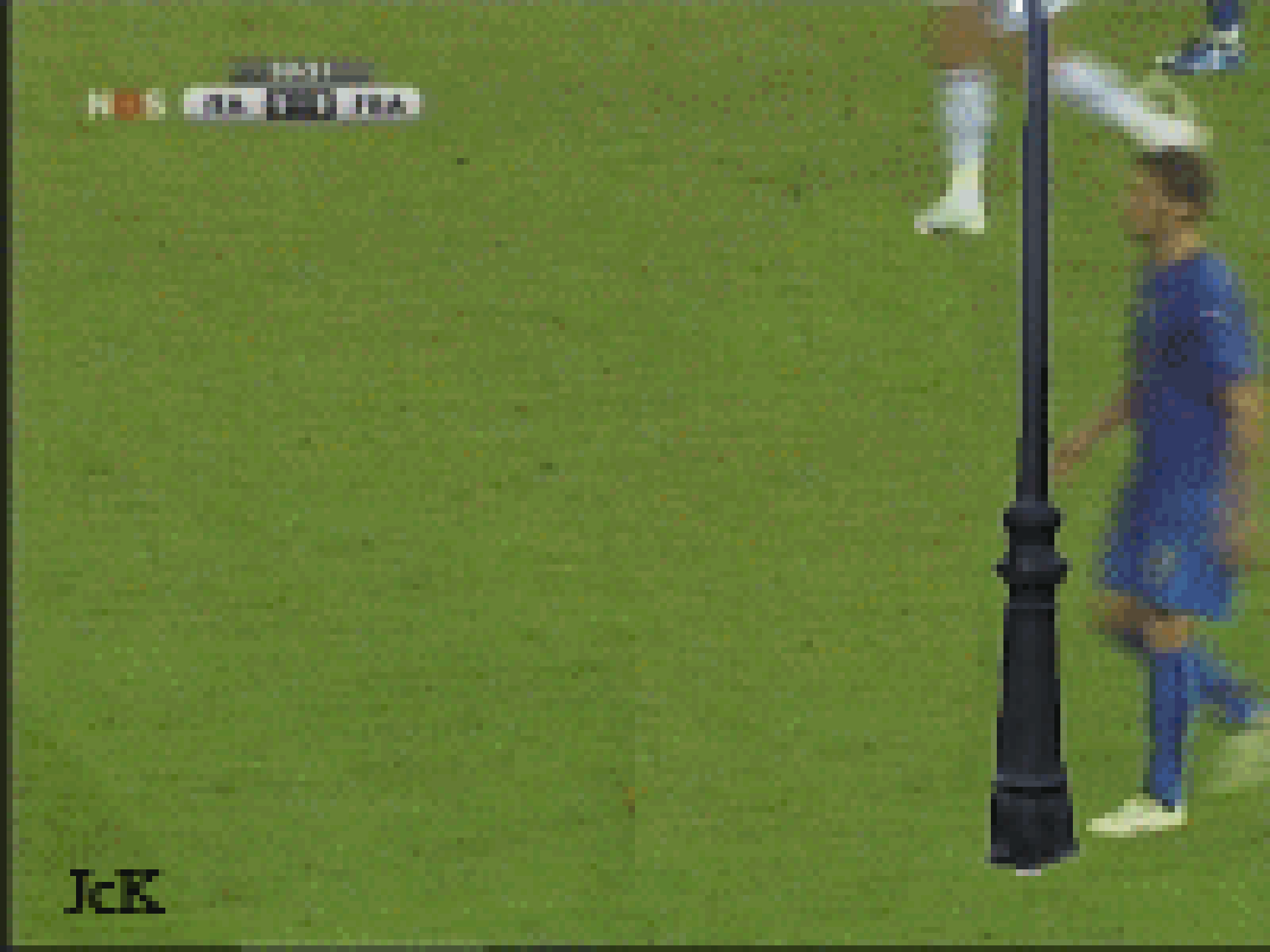
Soccer World Cup 2006

Soccer World Cup 2006

As Seen By Germans

As Reported By Press

As Seen By French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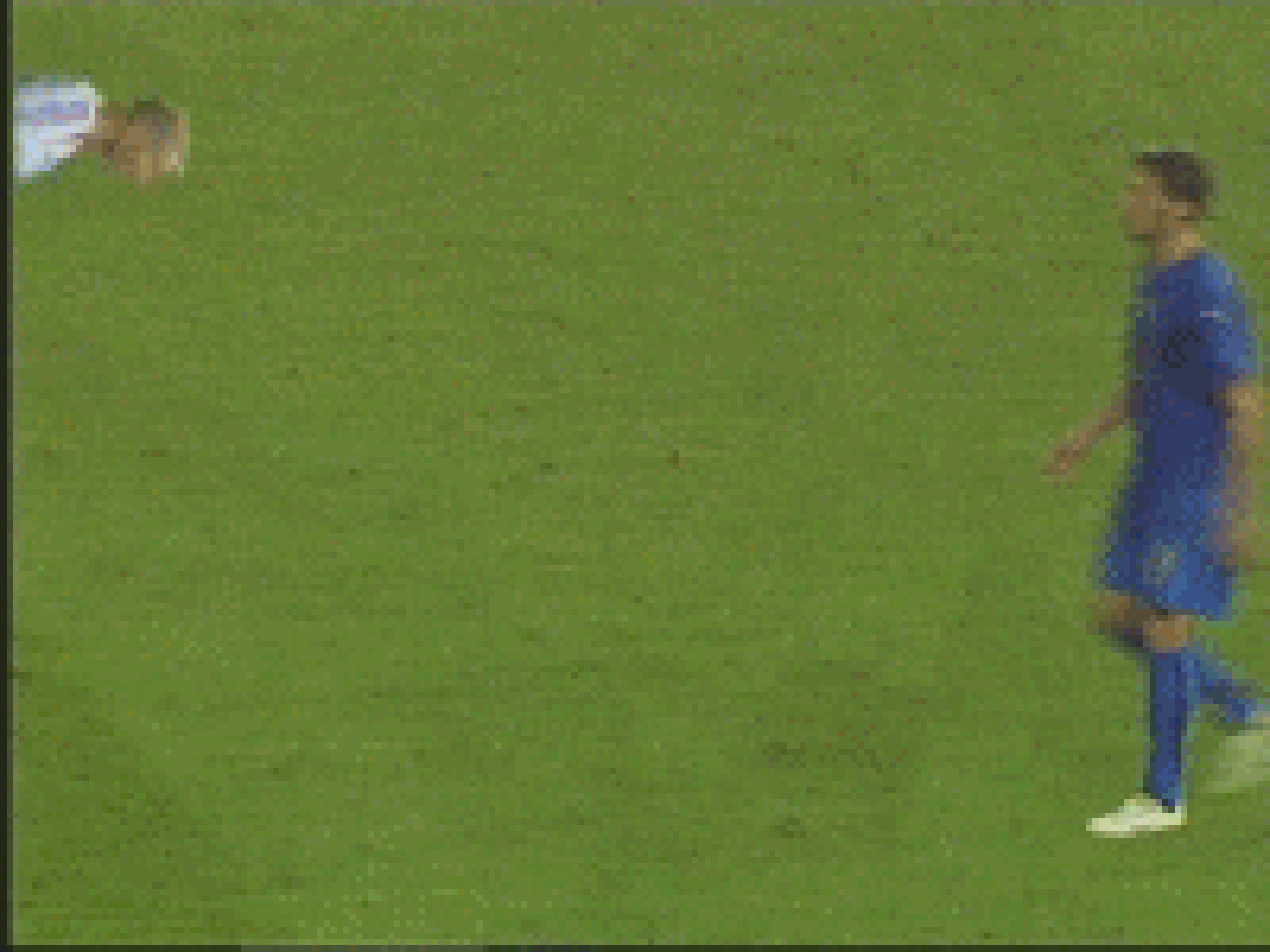
As Seen By Italians



As Seen by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