MOVE Symposium
Challenges in Hypertension 2017

박 광 열

중앙대학교 신경과

Hypertension and Stroke

J curve in Stroke?

BP Goal

- SPRINT
- HOPE-3

Summary

Pre-requisite quiz

In February 2014, George Cobb, Professor Emeritus of Mathematics and Statistics at Mount Holyoke College, posed these questions to an ASA discussion forum:

Ronald L. Wasserstein & Nicole A. Lazar The American Statistician, 2016, 70:2, 129-133

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Q Why do so many people still use p = 0.05?

A Because that's what they were taught in college or grad school.

Ronald L. Wasserstein & Nicole A. Lazar The American Statistician, 2016, 70:2, 129-133

Pre-requisite quiz

In Null Hypothesis Significance Testing,

Ronald L. Wasserstein & Nicole A. Lazar The American Statistician, 2016, 70:2, 129-133

Pre-requisite quiz

In Null Hypothesis Significance Testing,

- What is the meaning of $p < 0.05$?

Ronald L. Wasserstein & Nicole A. Lazar The American Statistician, 2016, 70:2, 129-133

Pre-requisite quiz

In Null Hypothesis Significance Testing,

- What is the meaning of $p < 0.05$?
- What is the meaning of $p > 0.05$?

Ronald L. Wasserstein & Nicole A. Lazar The American Statistician, 2016, 70:2, 129-133

Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble

Vasilis Kontis, James E Bennett*, Colin D Mathers, Guangquan Li, Kyle Foreman, Majid Ezzati*

Summary

Background Projections of future mortality and life expectancy are needed to plan for health and social services and

Lancet 2017; 389: 1323–35

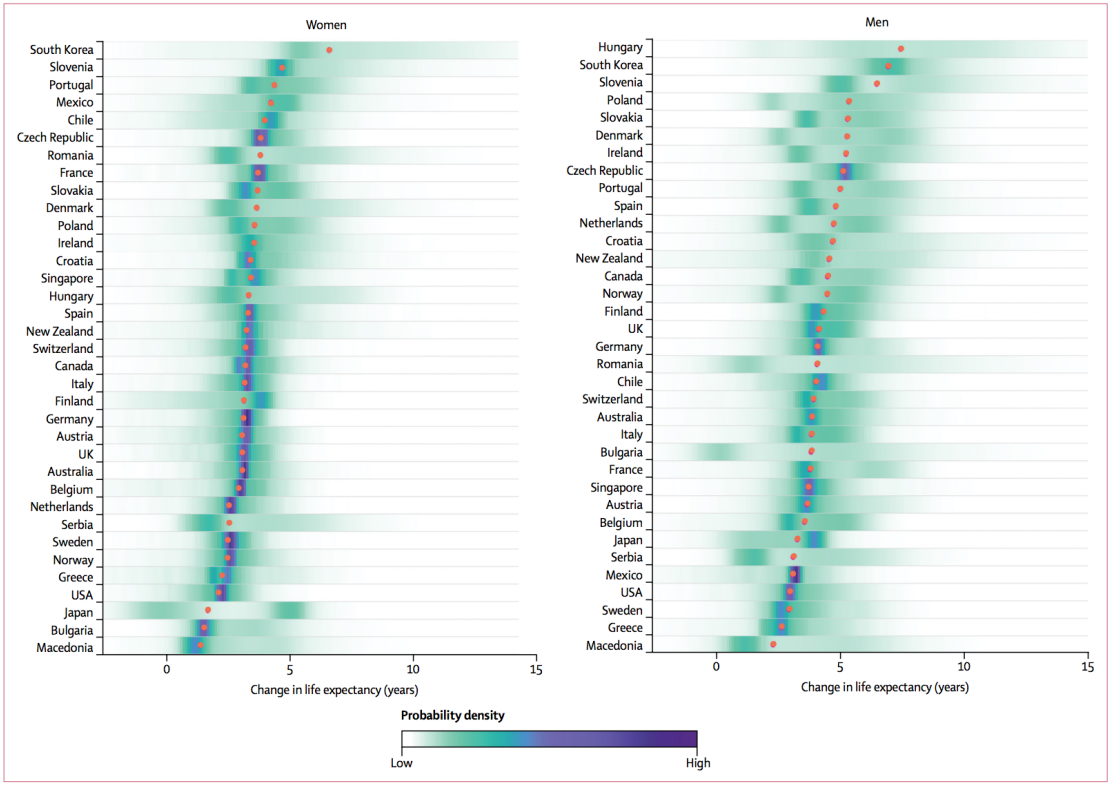
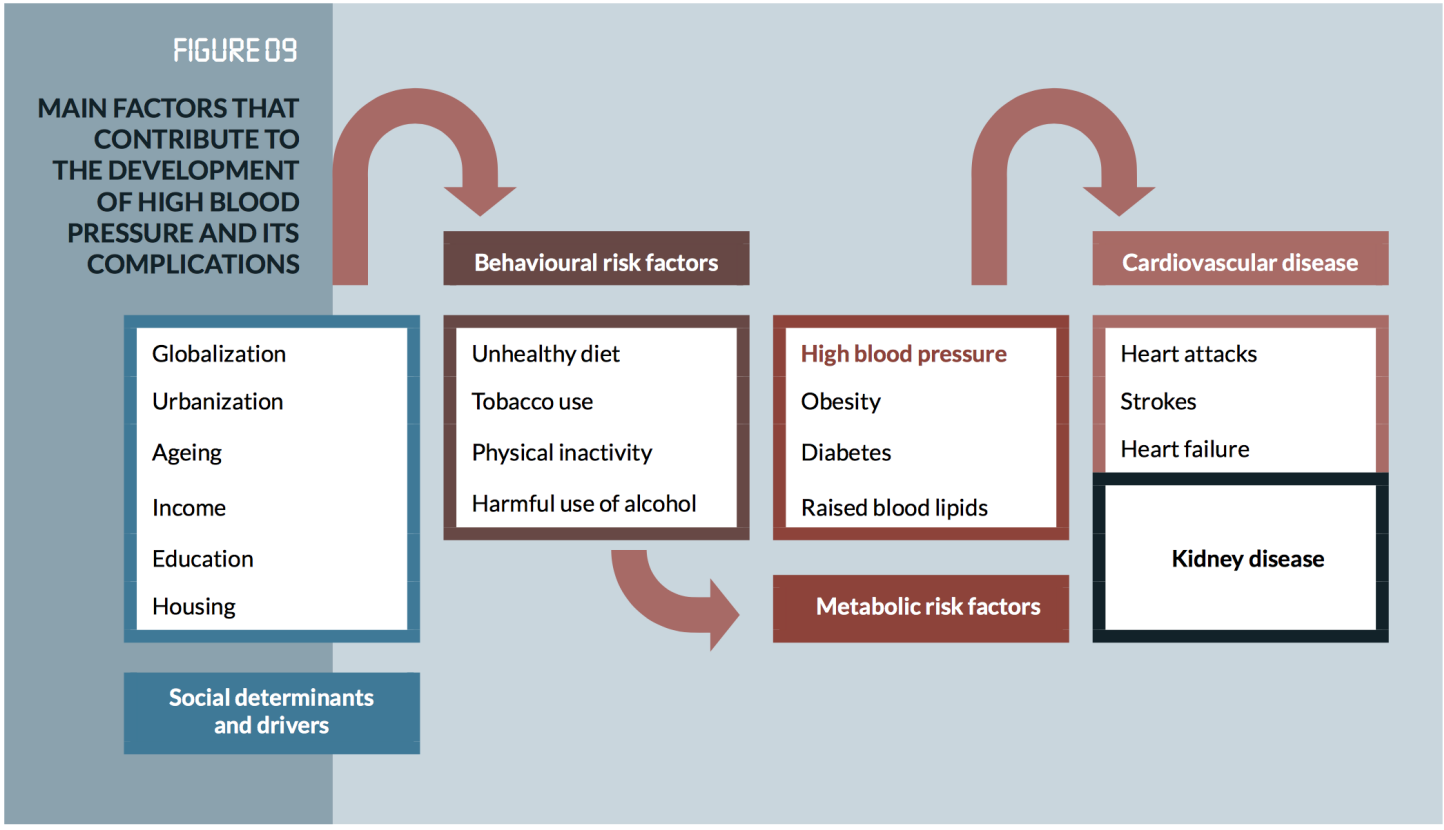


Figure 1: **Posterior distribution of projected change in life expectancy at birth from 2010 to 2030**
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

There is a 90% probability that life expectancy at birth among South Korean women in 2030 will be higher than $86 \cdot 7$ years,and a **57% probability that it will be higher than 90 years**.

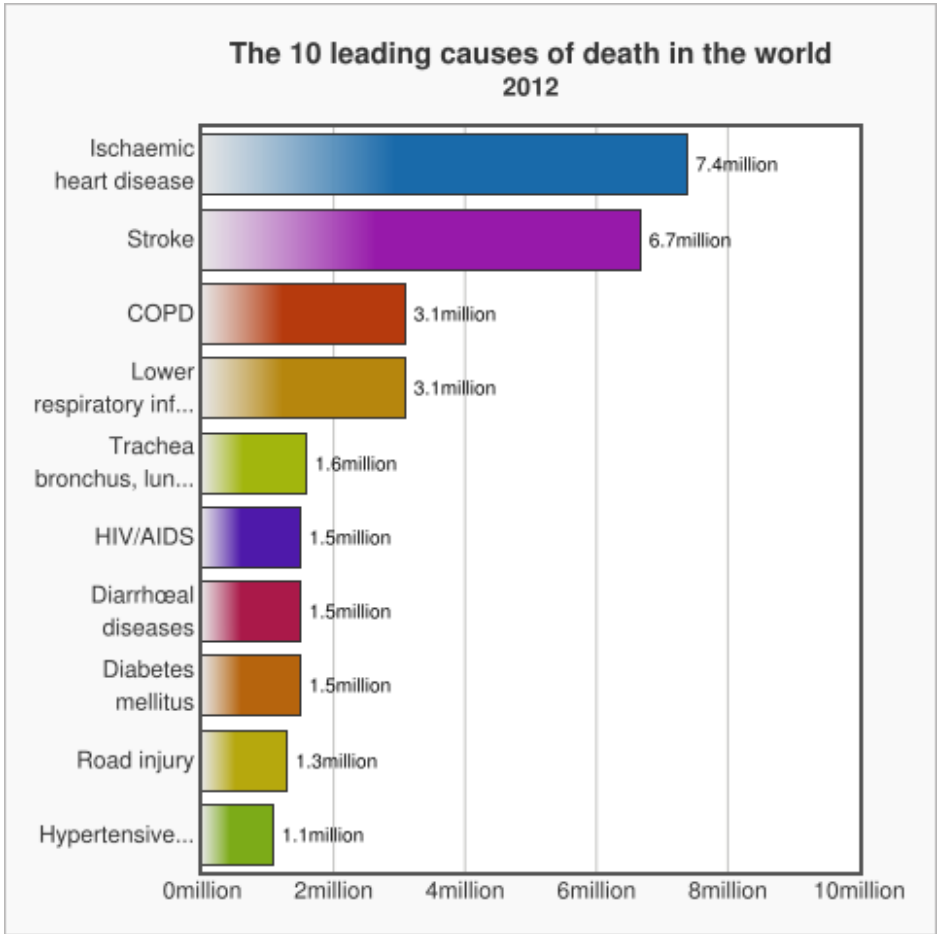
There is a greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.

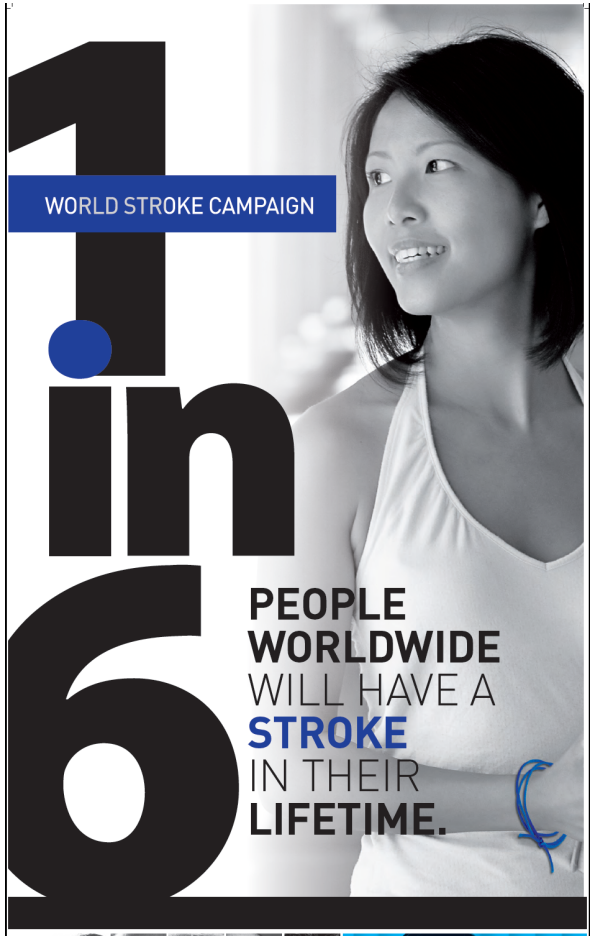
Kontis V et al. Lancet 2017; 389: 1323–35



http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/ accessed on May 07, 2017

Global burden of stroke

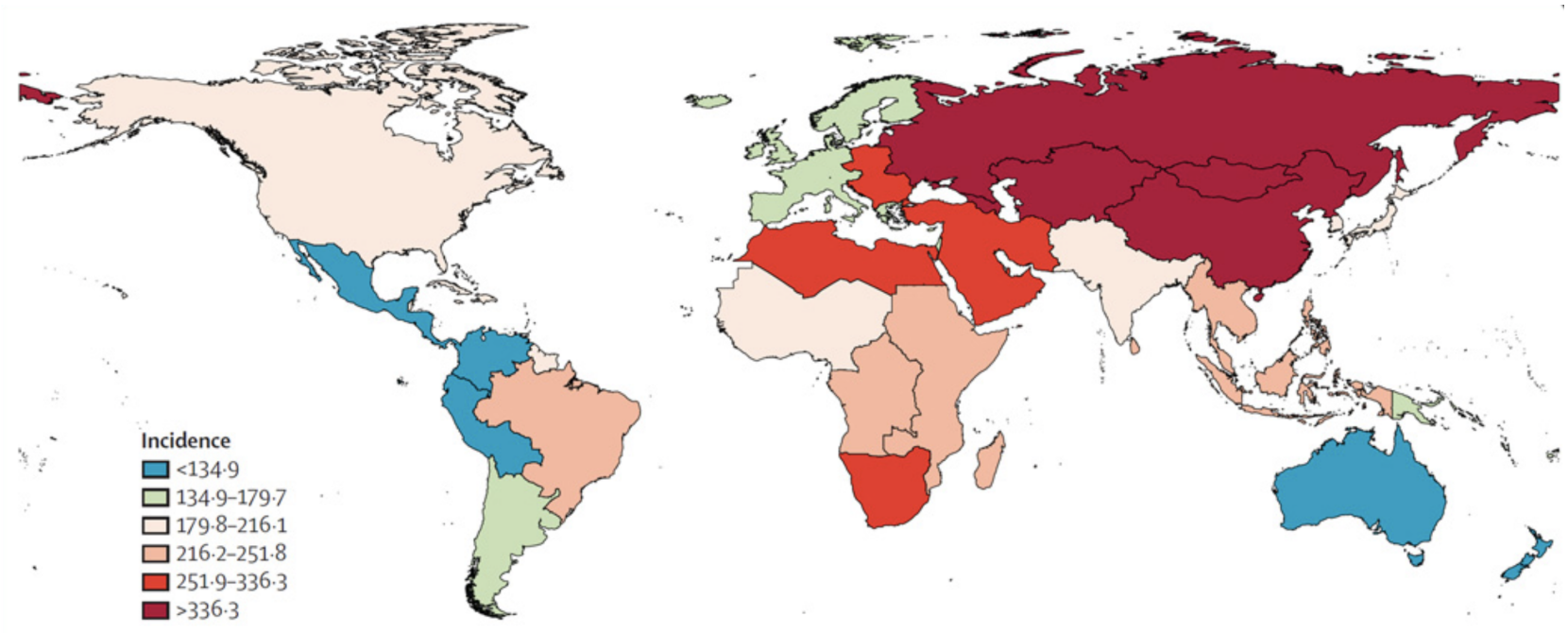




http://www.who.int/mediacentre/factsheets/fs310/en/ accessed on Jan 16, 2016
http://www.worldstrokecampaign.org/get-involved/2015-08-20-01-49-19/campaign-posters.html

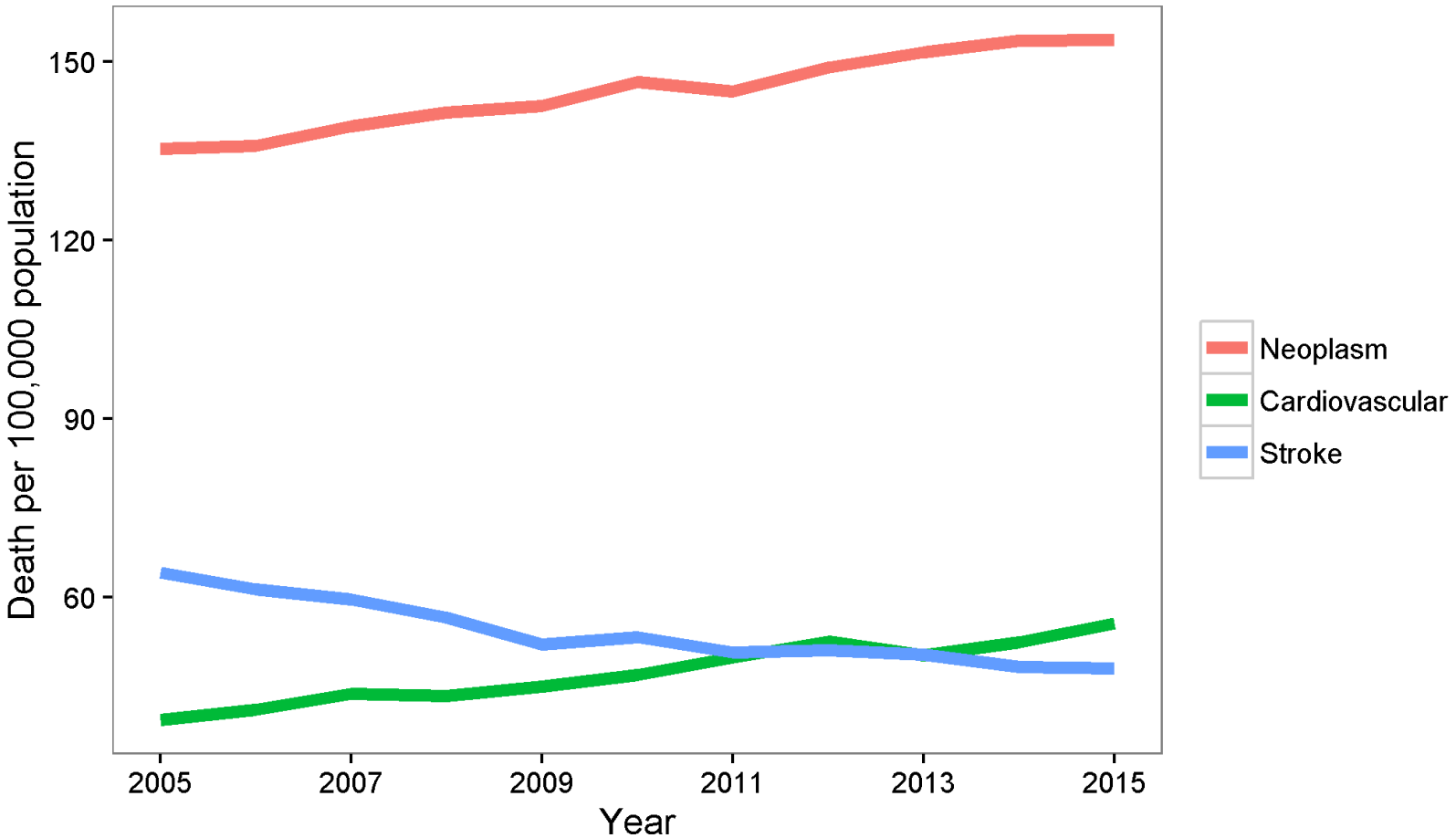
Age-standardised stroke incidence

per 100 000 person-years for 2010



Lancet Neurol. 2014 383(9913): 245–254.

Secular trend of mortality in Korea



http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012 accessed on Nov 03, 2016

Etiologies of stroke

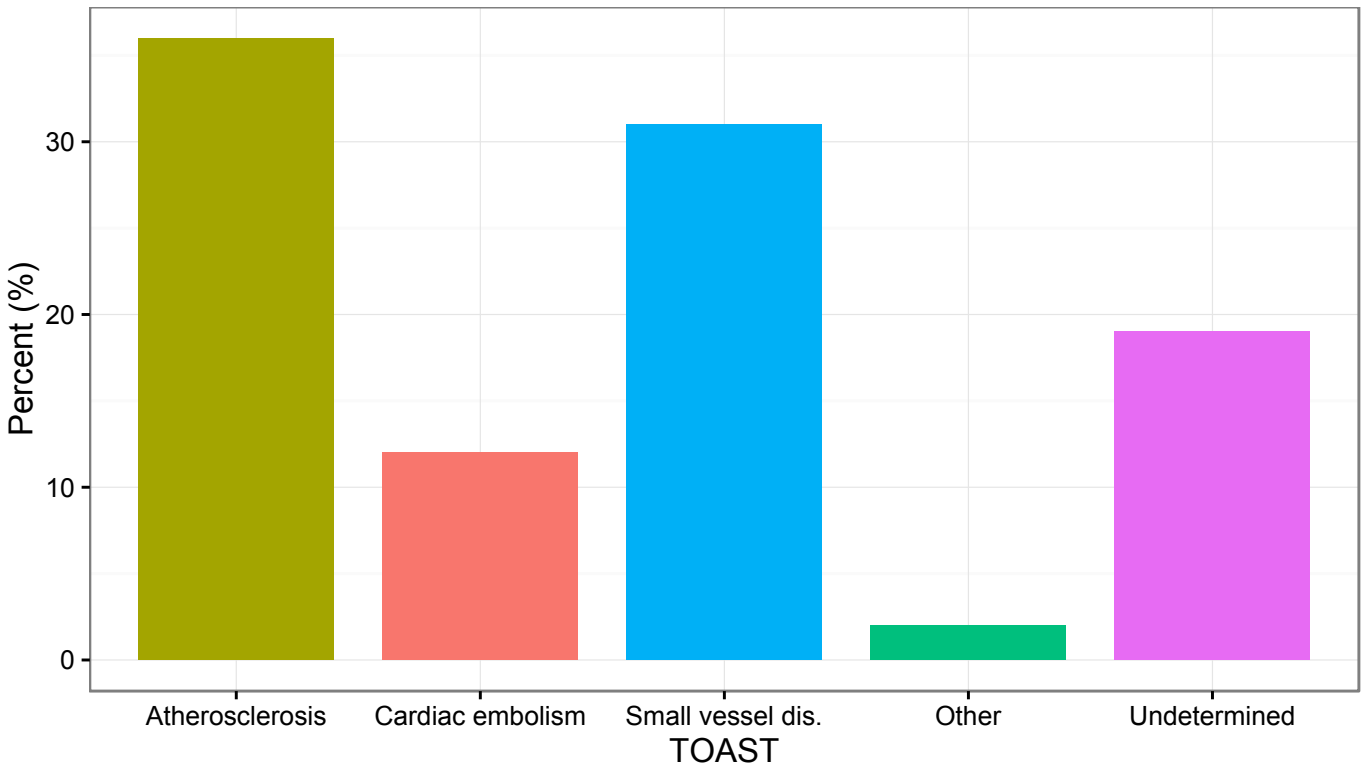
Ischemic Stroke

- Atherosclerosis
- Small artery occlusion
- Cardiac disease causing embolism
- Other causes such as moyamoya disease

Hemorrhagic Stroke

- Hypertensive hemorrhage
- Cerebral amyloid angiopathy
- Arteriovenous malformations
- Subarachnoid hemorrhage

Ischemic stroke in Korea: Analysis of 10,861 cases in Korean Stroke Registry



Yu KH et al. J Korean Neurol Society 2006

Risk factors for Stroke

Non-modifiable factors

1. Age
2. Sex
3. Race
4. Family history

Modifiable factors

1. **Hypertension**
2. Diabetes
3. Dyslipidemia
4. Smoking
5. Carotid disease
6. Cardiac disease such as atrial fibrillation
7. Obesity
8. Inactivity

Stroke and HT

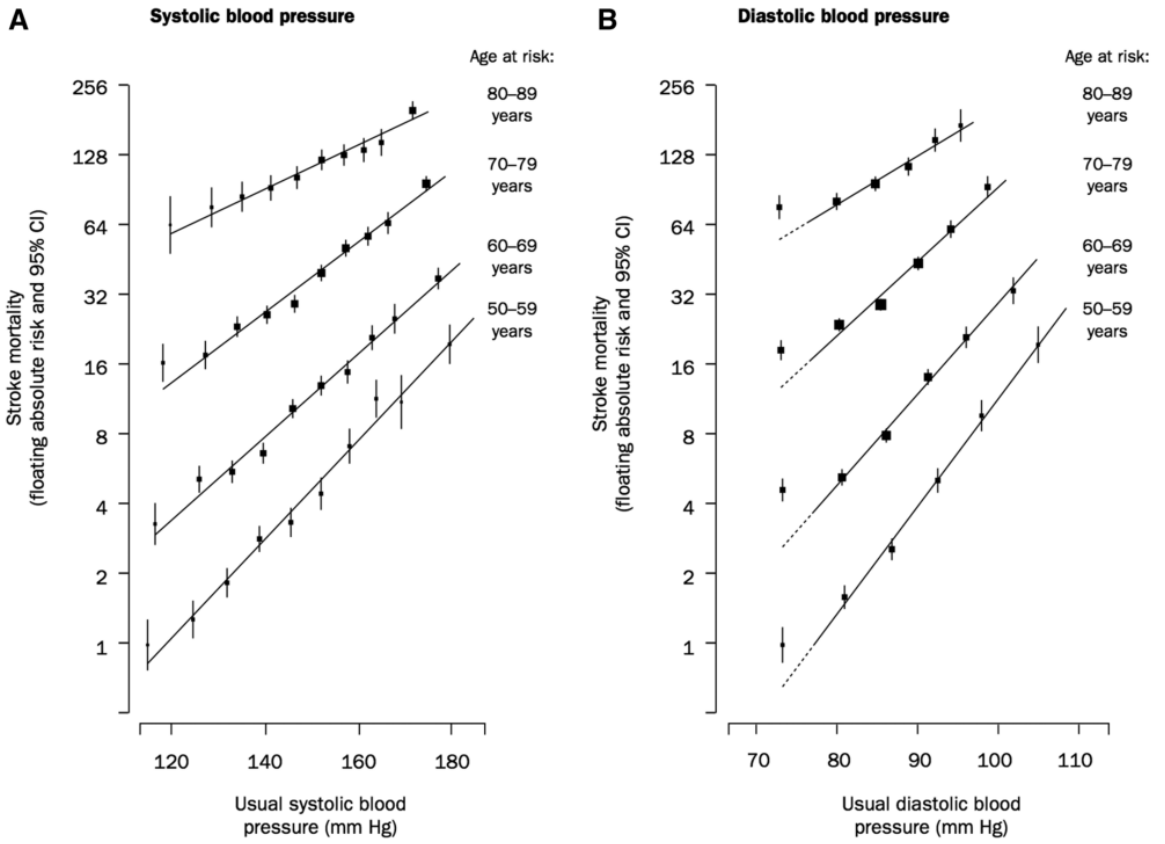


Figure 2. Stroke mortality in each decade of age vs usual blood pressure at the start of the decade. CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al[12]) with permission of the publisher. Copyright ©2002, Elsevier.

Rahimi, K et al. Cir Res 2015

IHD and HT

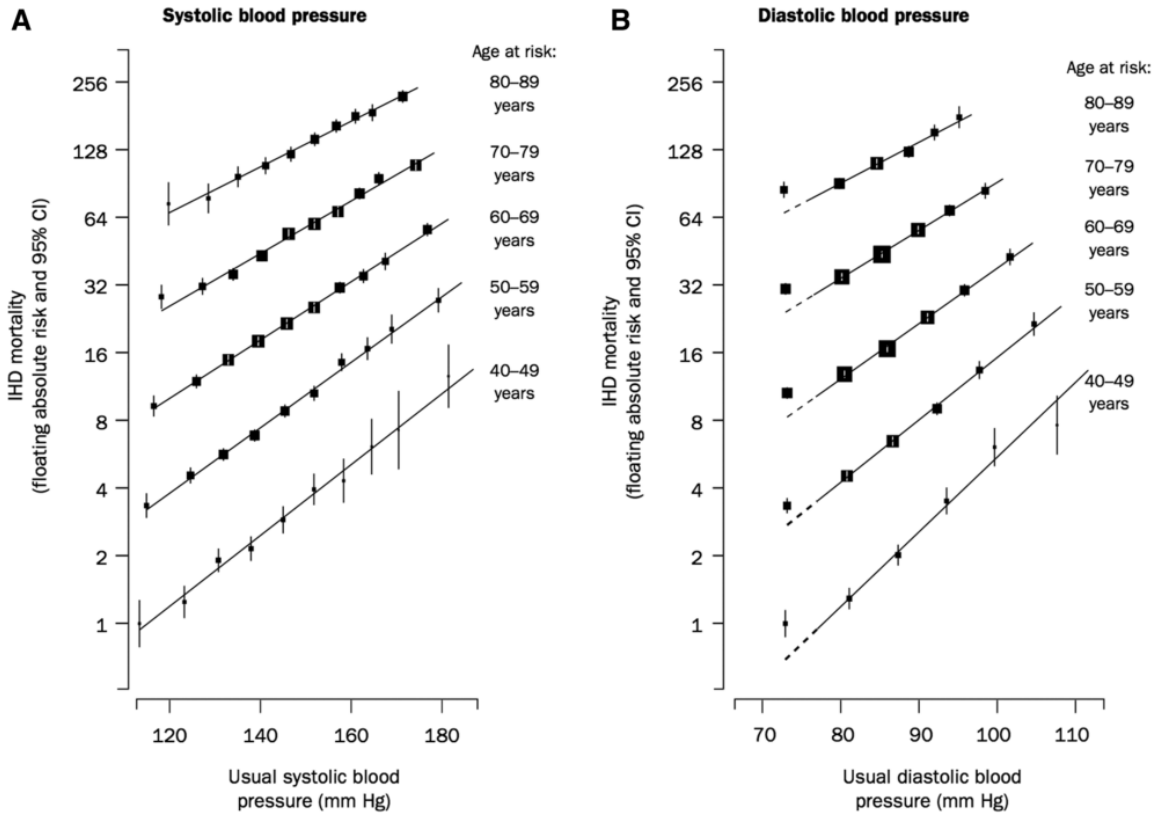


Figure 1. Ischemic heart disease (IHD) mortality in each decade of age vs usual blood pressure at the start of the decade.
CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al[12]) with permission of the publisher.

Rahimi, K et al. Cir Res 2015

IHD vs Stroke and SBP

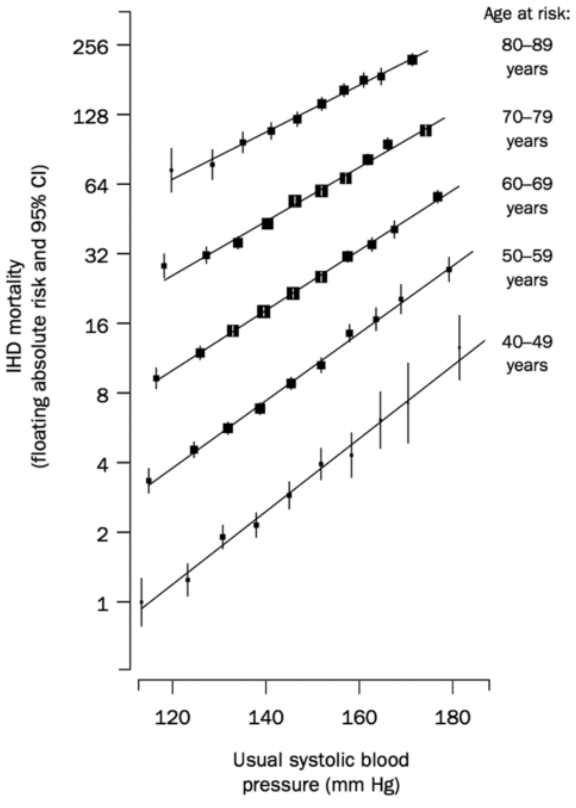


Figure 1. Ischemic heart disease (IHD) mortality

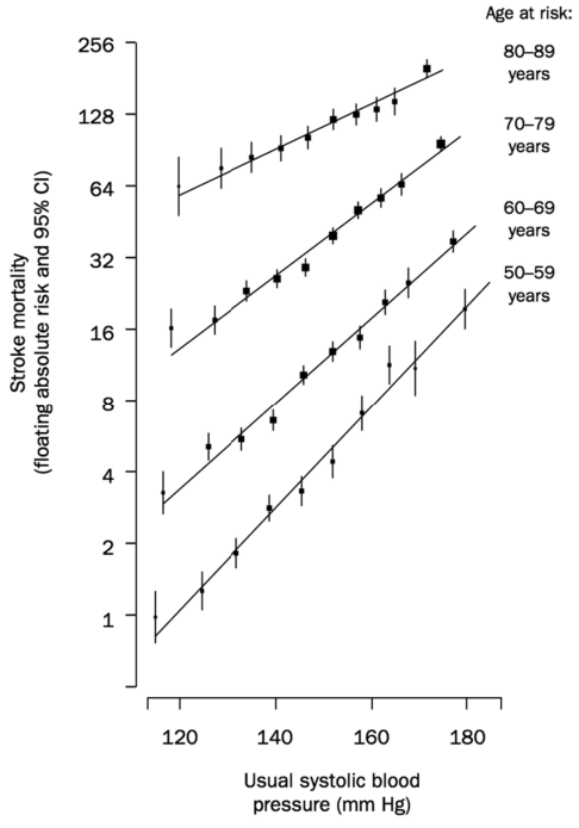
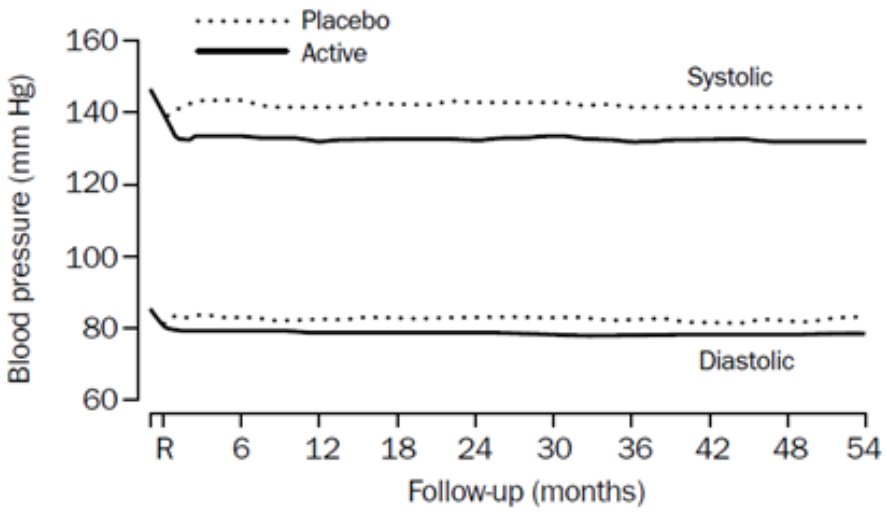


Figure 2. Stroke mortality

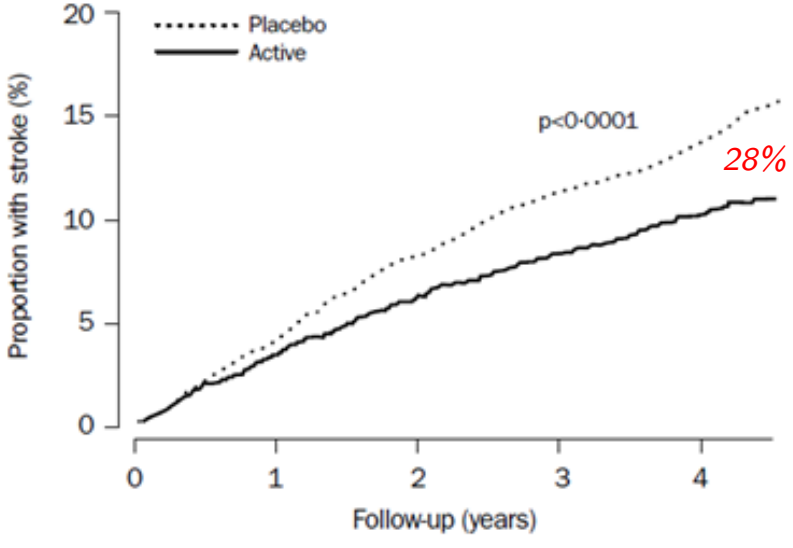
Rahimi, K et al. Cir Res 2015

PROGRESS

Randomizied trial enrolling 6,105 patients with a history of TIA or stroke (ischemic or hemorrhagic) to perindopril+ indapamide or placebo



BP difference: 9/4 mm Hg

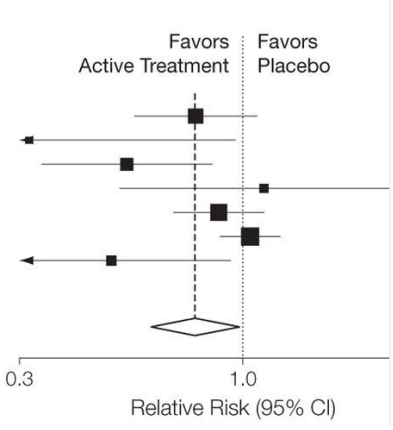


Cumulative incidence of Stroke

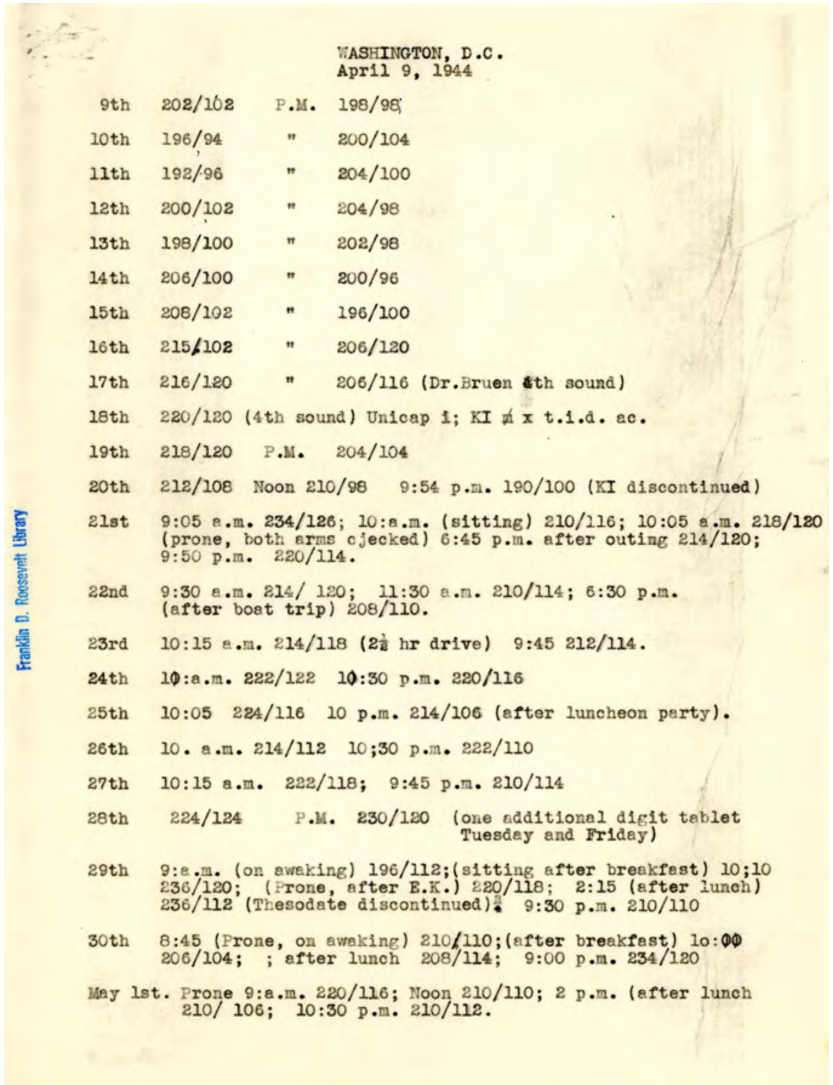
PROGRESS Collaborative Group et al. Lancet 2001;358:1033-41

Anti-HT Tx. and stroke

Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Fatal or nonfatal stroke				
SOLVD,[28] 1995	79/2077	62/2068	0.77 (0.56-1.08)	–8.1 (–19.1 to 3.0)
ABCD,[14] 2002	13/243	4/237	0.32 (0.10-0.95)	–36.6 (–69.3 to –3.9)
PEACE,[52] 2004	52/3071	27/2979	0.54 (0.34-0.85)	–7.9 (–13.6 to –2.2)
SAVE,[54] 2004	22/669	25/656	1.12 (0.51-2.44)	5.2 (–14.7 to 25.2)
PROGRESS,[56] 2006	121/1065	107/1072	0.88 (0.69-1.12)	–13.8 (–40.0 to 12.4)
PRoFESS,[61] 2008	259/3409	270/3413	1.04 (0.88-1.22)	3.1 (–9.6 to 15.8)
PATS,[65] 2009	28/470	13/443	0.49 (0.26-0.94)	–30.2 (–56.8 to –3.7)
Total	574/11 004	508/10 868		
Pooled relative risk			0.77 (0.61-0.98)	–7.7 (–15.2 to –0.3)
Heterogeneity: $P = .02$, $I^2 = 61.9\%$				



Thompson, AM et al. JAMA 2011 305(9): 913-922.



WASHINGTON, D.C.
April 9, 1944

9th 202/102 P.M. 198/98

10th 196/94 " 200/104

11th 192/96 " 204/100

12th 200/102 " 204/98

13th 198/100 " 202/98

14th 206/100 " 200/96

15th 208/102 " 196/100

16th 215/102 " 206/120

17th 216/120 " 206/116 (Dr.Bruen 4th sound)

18th 220/120 (4th sound) Unicap i; KI ℔ x t.i.d. ac.

19th 218/120 P.M. 204/104

20th 212/108 Noon 210/98 9:54 p.m. 190/100 (KI discontinued)

21st 9:05 a.m. 234/126; 10:a.m. (sitting) 210/116; 10:05 a.m. 218/120 (prone, both arms ojecked) 6:45 p.m. after outing 214/120; 9:50 p.m. 220/114.

22nd 9:30 a.m. 214/ 120; 11:30 a.m. 210/114; 6:30 p.m. (after boat trip) 208/110.

23rd 10:15 a.m. 214/118 (2½ hr drive) 9:45 212/114.

24th 10:a.m. 222/122 10:30 p.m. 220/116

25th 10:05 224/116 10 p.m. 214/106 (after luncheon party).

26th 10. a.m. 214/112 10;30 p.m. 222/110

27th 10:15 a.m. 222/118; 9:45 p.m. 210/114

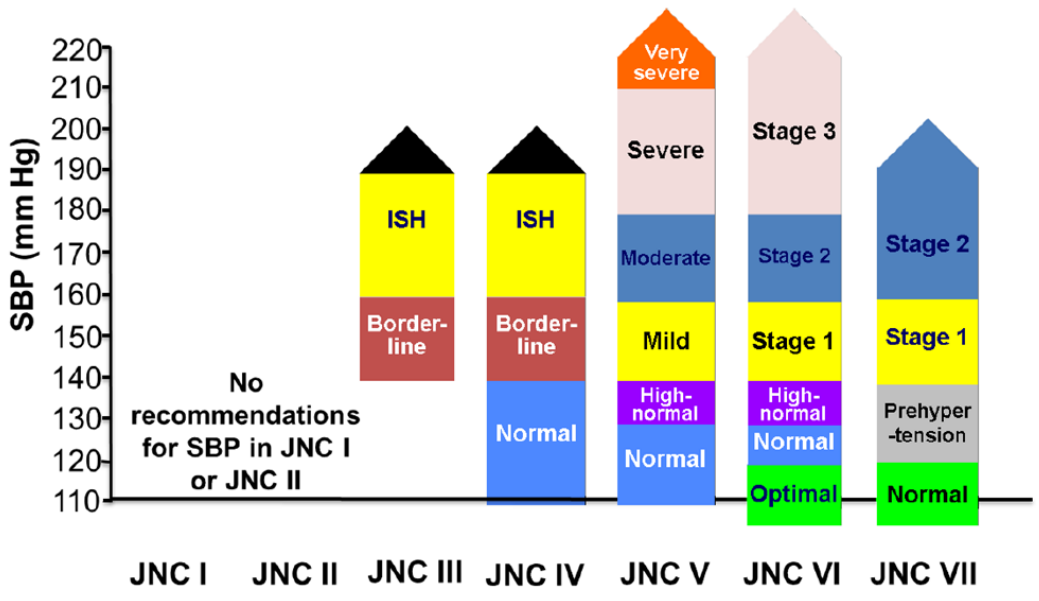
28th 224/124 P.M. 230/120 (one additional digit tablet Tuesday and Friday)

29th 9:a.m. (on awaking) 196/112;(sitting after breakfast) 10;10 236/120; (Prone, after E.K.) 220/118; 2:15 (after lunch) 236/112 (Thesodate discontinued) 9:30 p.m. 210/110

30th 8:45 (Prone, on awaking) 210/110;(after breakfast) 10:00 206/104; ; after lunch 208/114; 9:00 p.m. 234/120

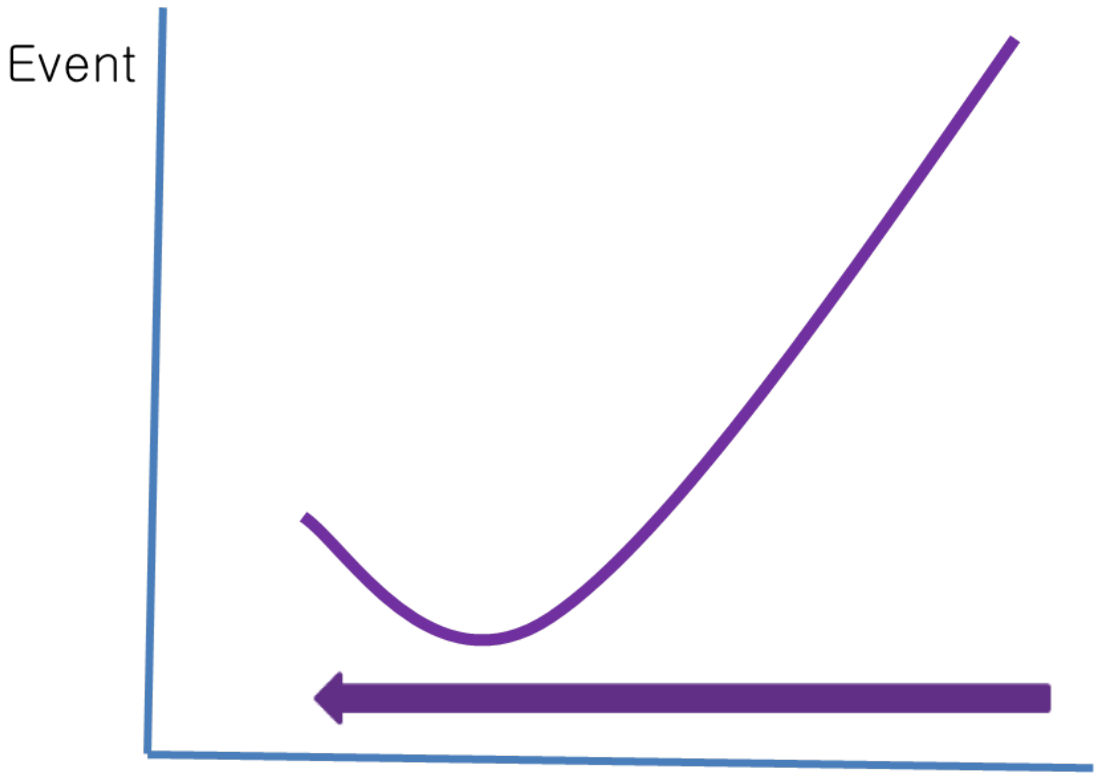
May 1st. Prone 9:a.m. 220/116; Noon 210/110; 2 p.m. (after lunch 210/ 106; 10:30 p.m. 210/112.

http://www.fdrlibraryvirtualtour.org/graphics/07-38/7.5_FDRs_Health.pdf accessed on May 07, 2017

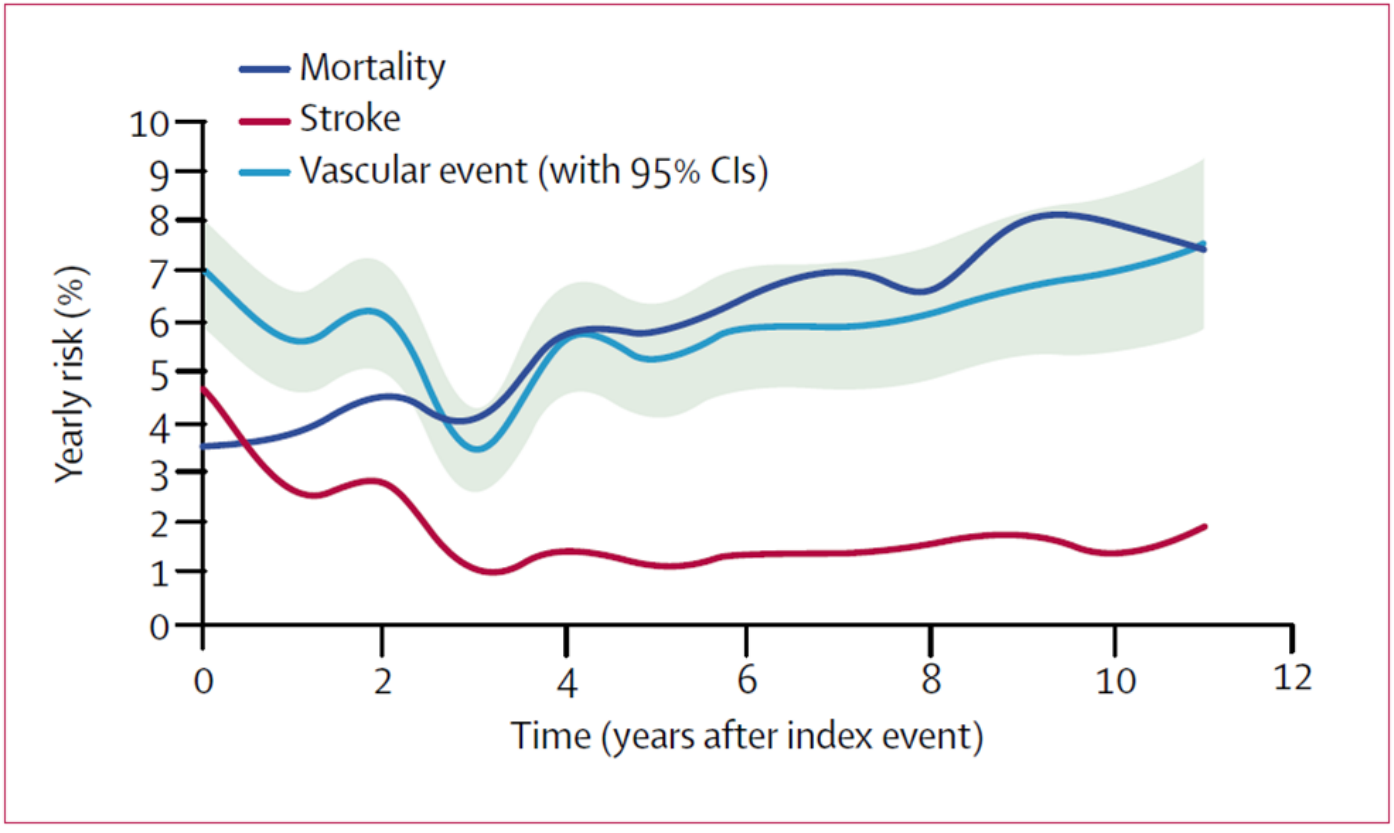


JNC I. JAMA. 1977;JNC II. Arch Intern Med. 1980; JNC III. Arch Intern Med. 1984; JNC IV. Arch Intern Med. 1988; JNC V. Arch Intern Med. 1993;JNC VI. Arch Intern Med. 1997;JNC 7 Express

Hypertension: J curve ?



Yearly Risk over Time in Dutch TIA trial



Lancet. 2005

Vascular events after stroke

Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke

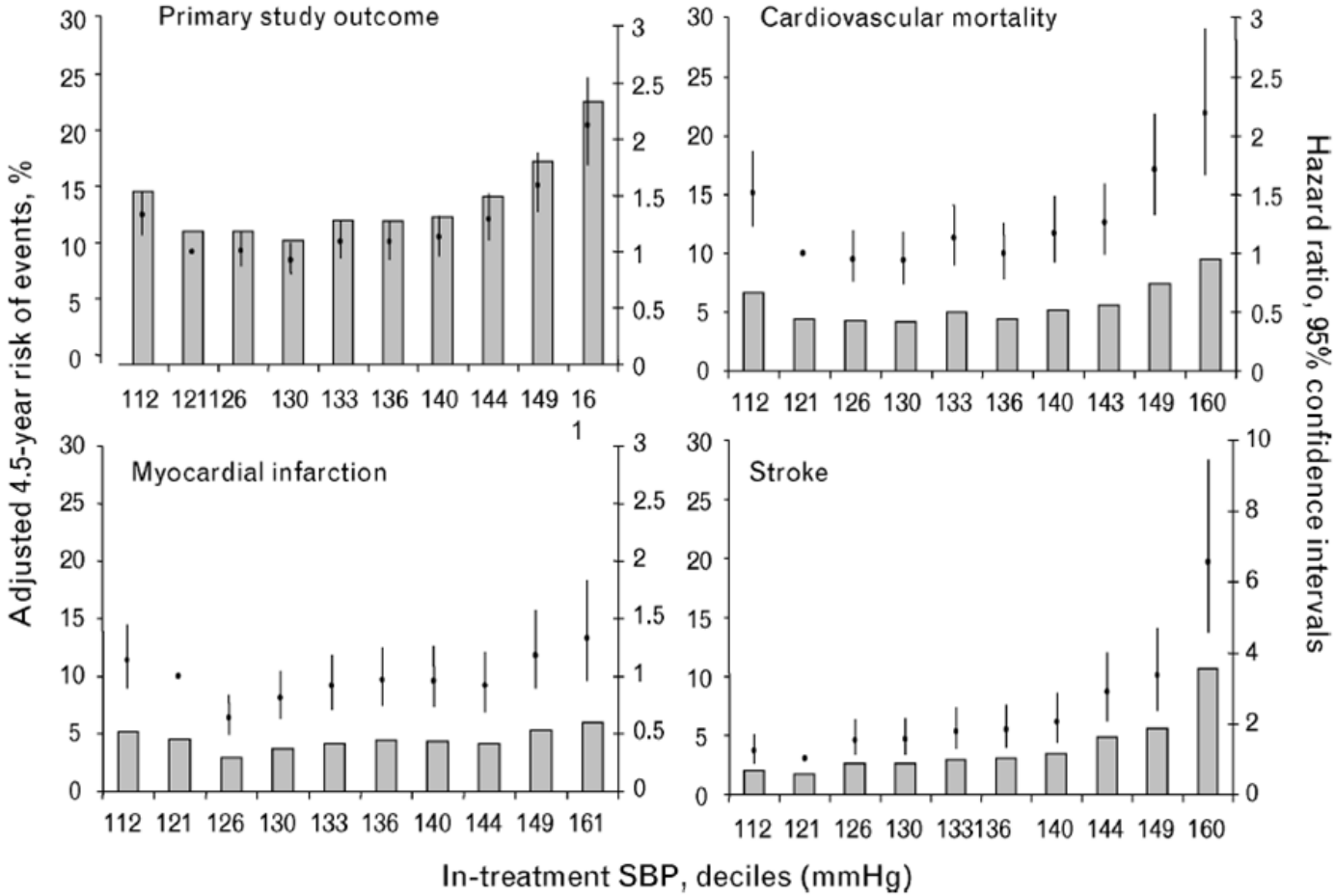
A Systematic Review and Meta-Analysis

Emmanuel Touzé, MD; Olivier Varenne, MD, PhD; Gilles Chatellier, MD, PhD;
Séverine Peyrard, MSc; Peter M. Rothwell, MD, PhD, FRCP; Jean-Louis Mas, MD

	Annual Risk
Nonstroke vascular death	2.1% (1.9 to 2.4)
Total MI	2.2% (1.7 to 2.7)
Nonfatal MI	0.9% (0.7 to 1.2)
Fatal MI	1.1% (0.8 to 1.5)

Touze et al. Stroke. 2005.

Ontarget study

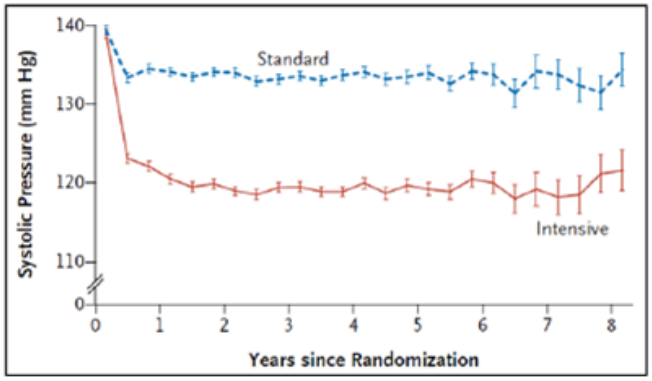


Journal of Hypertension 2009, 27:1360 - 1369

The lower BP looks beneficial in stroke: ACCORD

- 4733 patients with type 2 DM
- SBP

  < 140 mm Hg vs. < 120 mm Hg



Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03

N Engl J Med. 2010 362(17):1575-85

	ACCORD
Population	4733 DM
Intervention	<120 vs. <140
Primary endpoint	MI, Stroke, CV death
SBP at 1yr	119 vs. 134
Outcome/yr	1.87% vs. 2.09%
All cause mortality/yr	1.28% vs. 1.19%
Stroke	0.32% vs. 0.53% *

N Engl J Med. 2010 362(17):1575-85

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

James PA et al. JAMA 2013

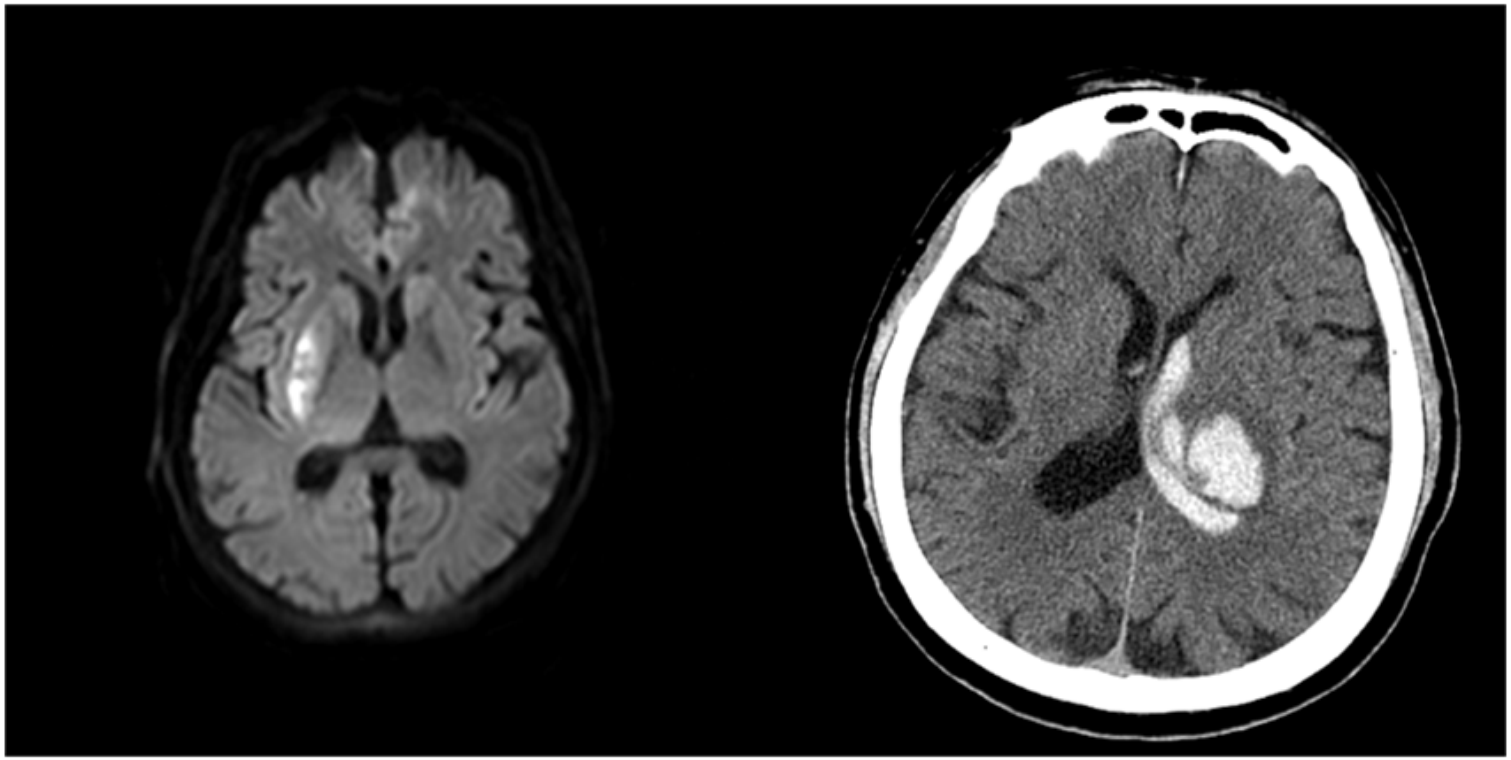
Recommendation 1

In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

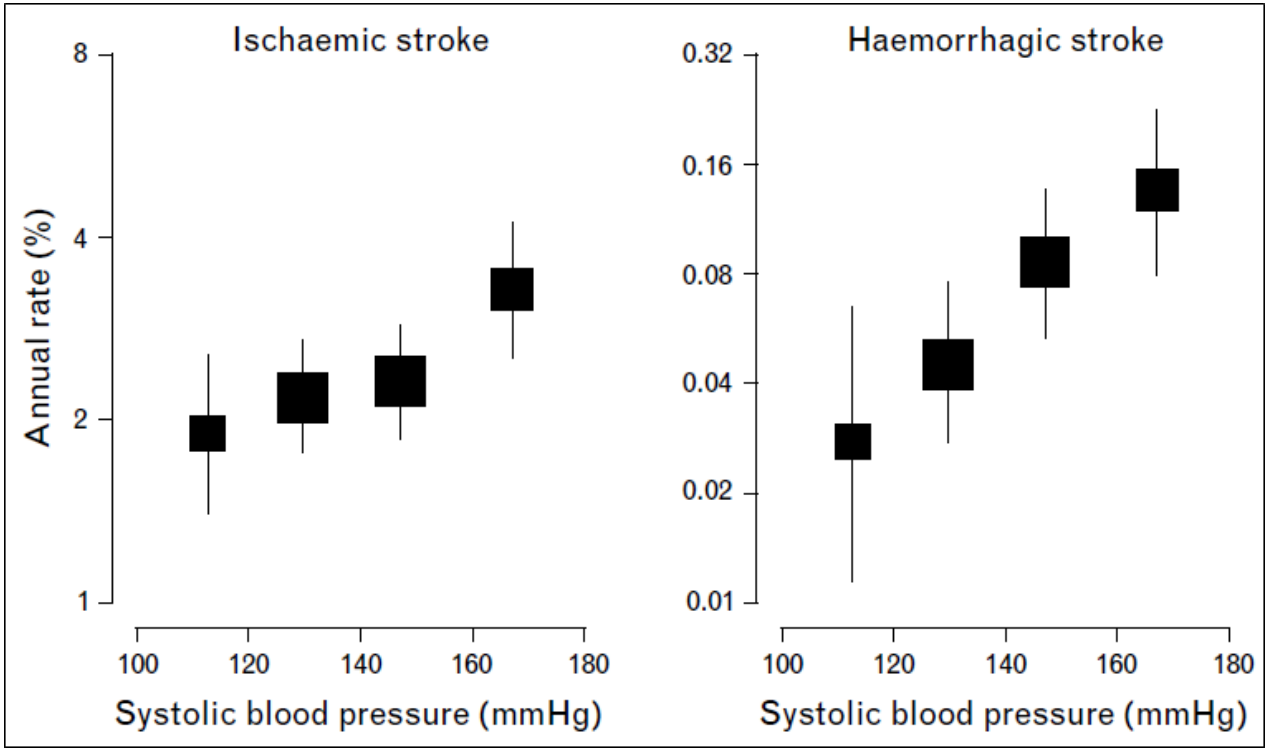
Corollary Recommendation

In the general population aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

James PA et al. JAMA 2013



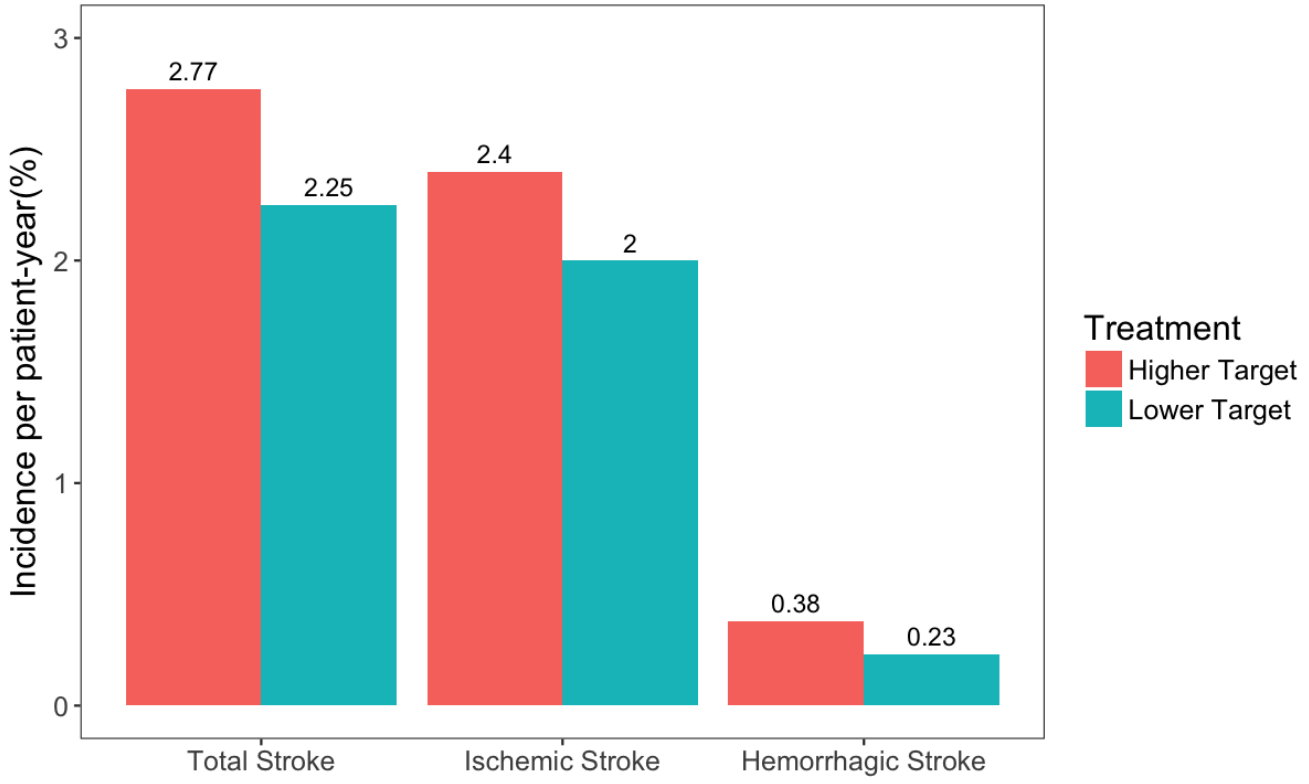
Lower target BP for stroke prevention: PROGRESS



PROGRESS Collaborative Group et al. Lancet 2001;358:1033-41

BP targets in recent lacunar stroke: SPS3

3020 patients assigned to a SBP target of 130–149 or < 130 mm Hg.
After 1 year, mean SBP was 138 mm Hg vs. 127 mm Hg.



The SPS3 Study Group. Lancet 2013;382:507-15

2014 AHA/ASA 2ndary Prevention of Stroke Guideline

For patients with a recent lacunar stroke, it might be reasonable to target an SBP of $<$130 mmHg (Class IIb; Level of Evidence B). (Revised recommendation)

Kernan WN et al. Stroke. 2014;45

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.

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

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., B.S.N., M.A., Kaycee M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cush-

N Engl J Med. 2015 Nov 26;373(22):2103-16

SPRINT: Demographics

	Intensive Tx.	Standard Tx.
Number	4678	4683
Age	67.9 ± 9.4	67.9 ± 9.5
Female	1684 (36.0%)	1648 (35.2%)
CVD	940 (20.1%)	937 (20.0%)
CKD	1330 (28.4%)	1315 (28.1%)
GFR	71.8 ± 20.7	71.7 ± 20.5
Initial BP	139.7/78.2 mm Hg	139.7/78.0 mm Hg
Mean SBP	121.5 mm Hg	134.6 mm Hg

N Engl J Med. 2015 Nov 26;373(22):2103-16

SPRINT: Primary outcome

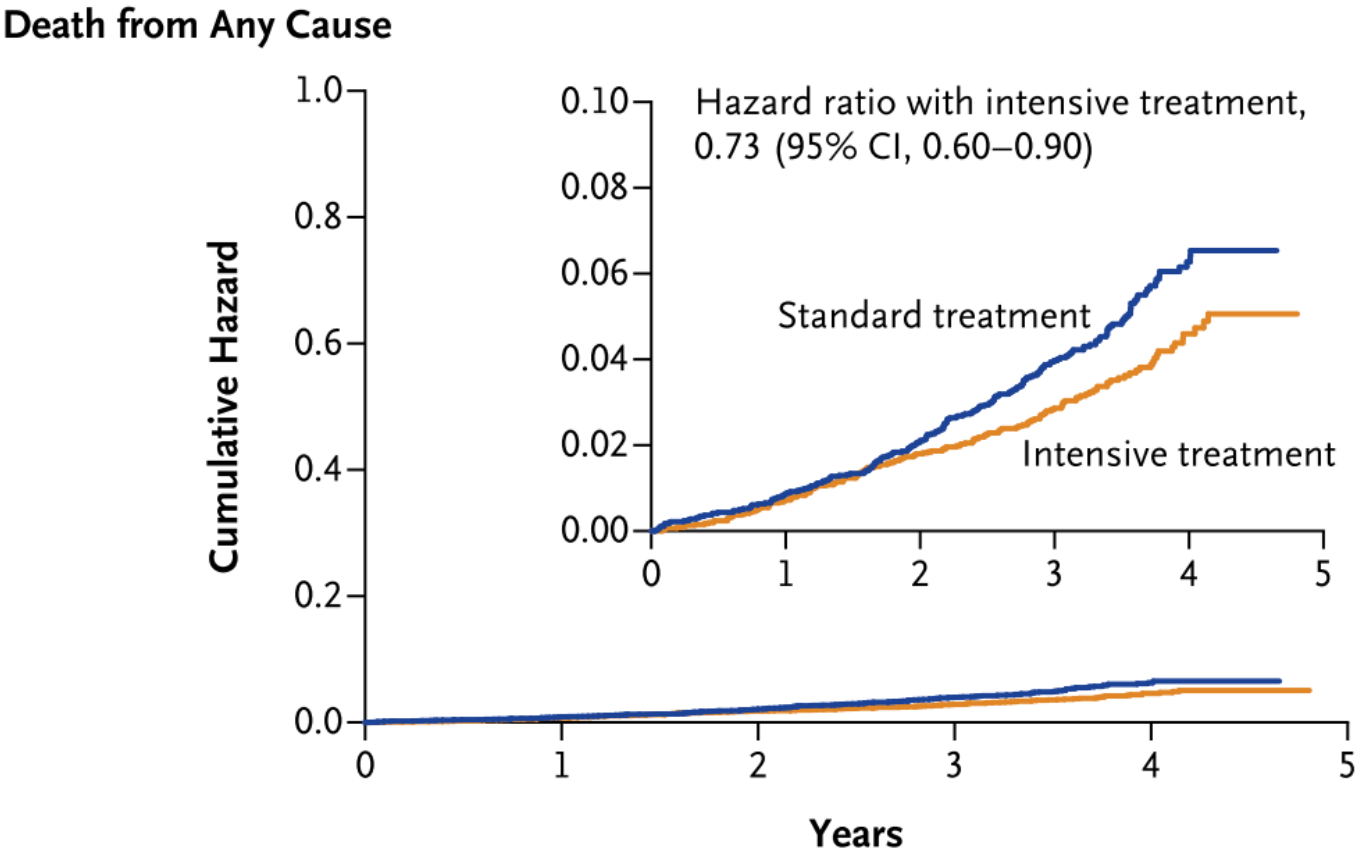
The first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005

N Engl J Med. 2015 Nov 26;373(22):2103-16

SPRINT: All cause mortality



N Engl J Med. 2015 Nov 26;373(22):2103-16

Data sharing and SPRINT

SPRINT and ACCORD

	ACCORD	SPRINT
Population	4733 DM	9631 non-DM
Intervention	<120 vs. <140	<120 vs. <140
Primary endpoint	MI, Stroke, CV death	+ HF, other ACS
SBP at 1yr	119 vs. 134	121 vs. 136
Outcome/yr	1.87% vs. 2.09%	1.65% vs. 2.19% *
All cause mortality/yr	1.28% vs. 1.19%	1.03% vs. 1.40% *
Stroke	0.32% vs. 0.53% *	0.41% vs. 0.47%

N Engl J Med. 2010 362(17):1575-85; N Engl J Med. 2015 Nov 26;373(22)89mm:2103-16

SPRINT and ACCORD

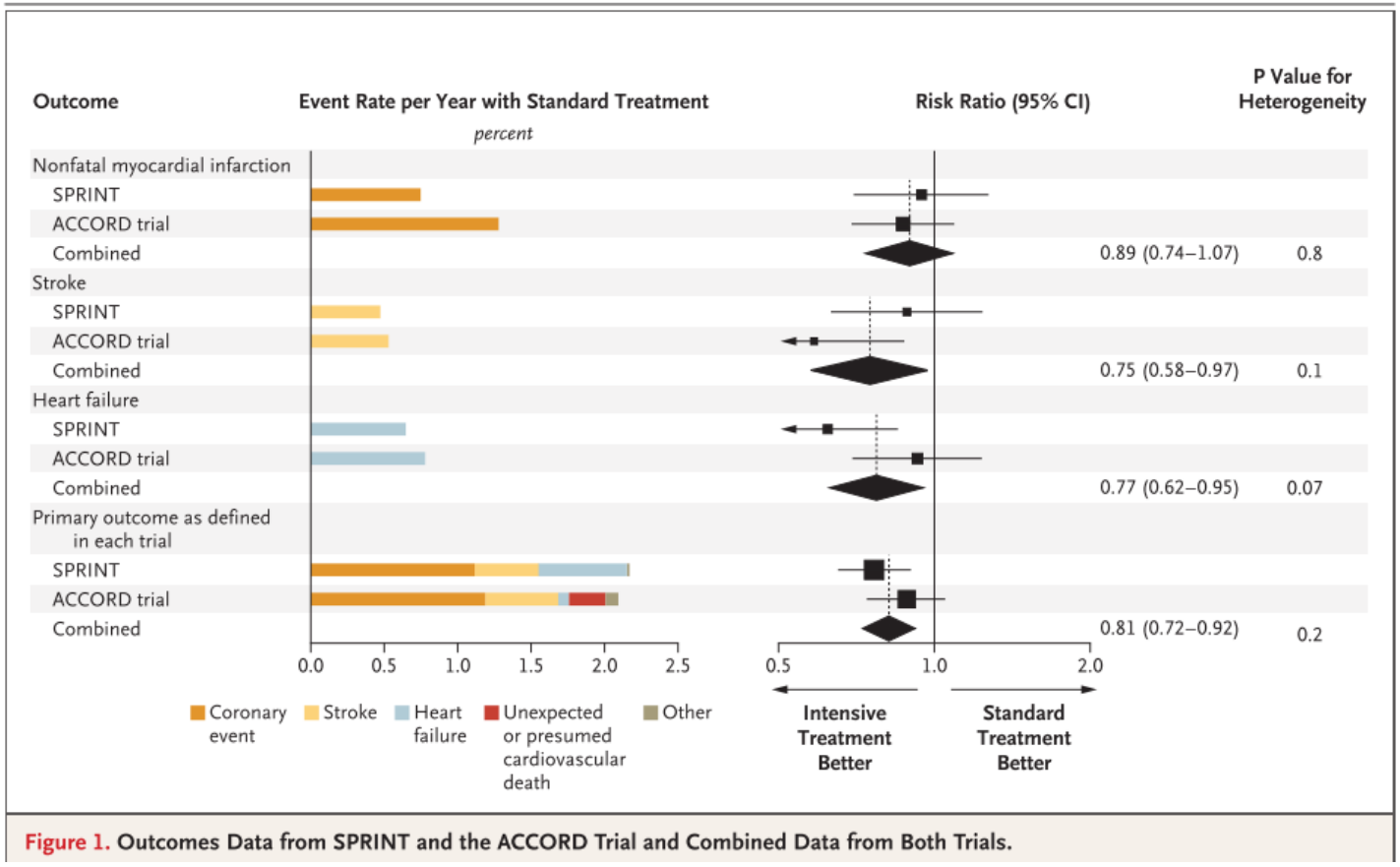
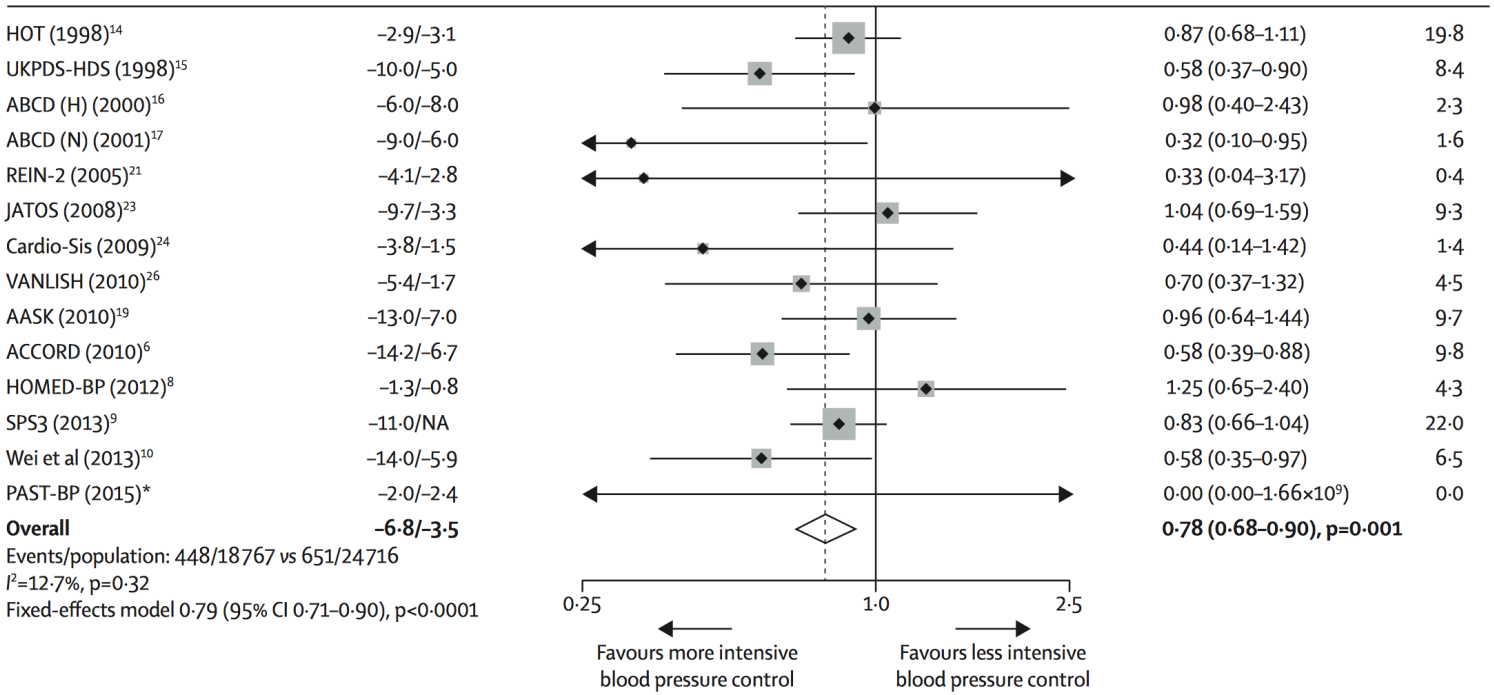


Figure 1. Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials.

Perkovic V, Rodgers A. N Engl J Med. 2015 Nov 26;373(22):2175-8

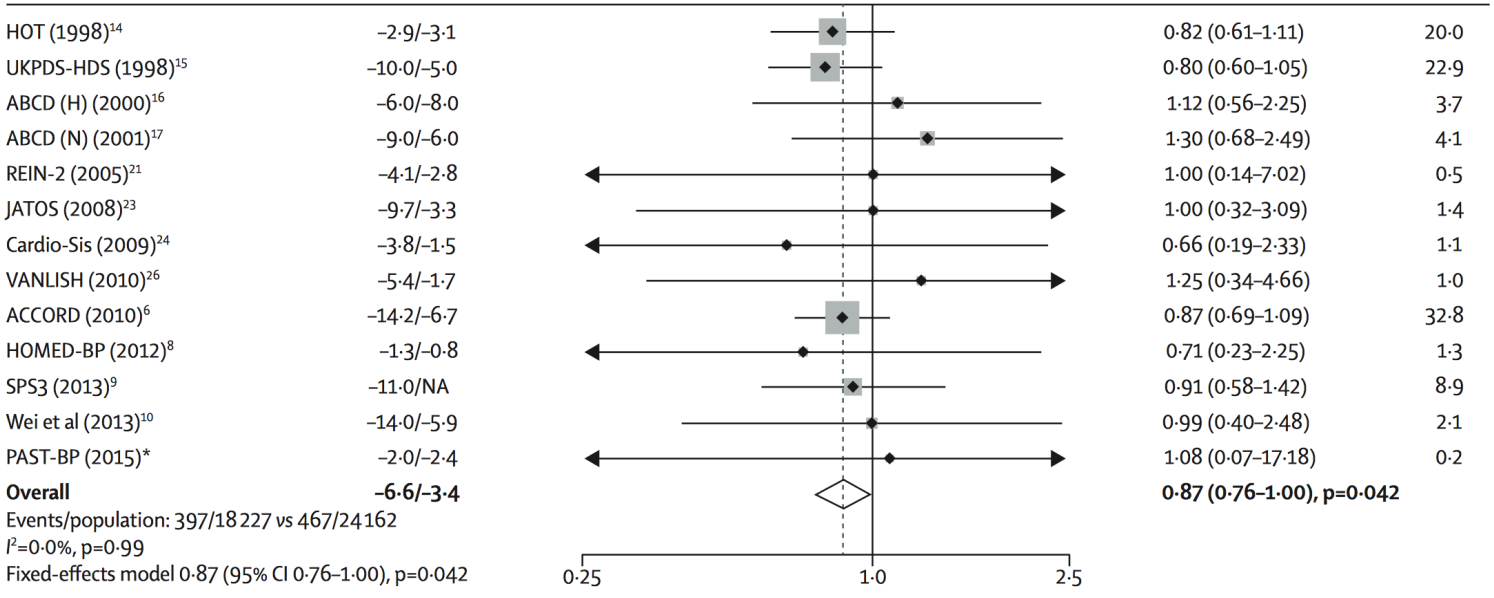
Effect of intensive BP lowering on Stroke



133/76 mm Hg vs. *140/81 mm Hg*

Xie X et al. Lancet 2016; 387: 435–43

Effect of intensive BP lowering on MI



133/76 mm Hg vs. *140/81 mm Hg*

Xie X et al. Lancet 2016; 387: 435–43

HOPE-3

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2016 VOL. 374 NO. 21

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.,

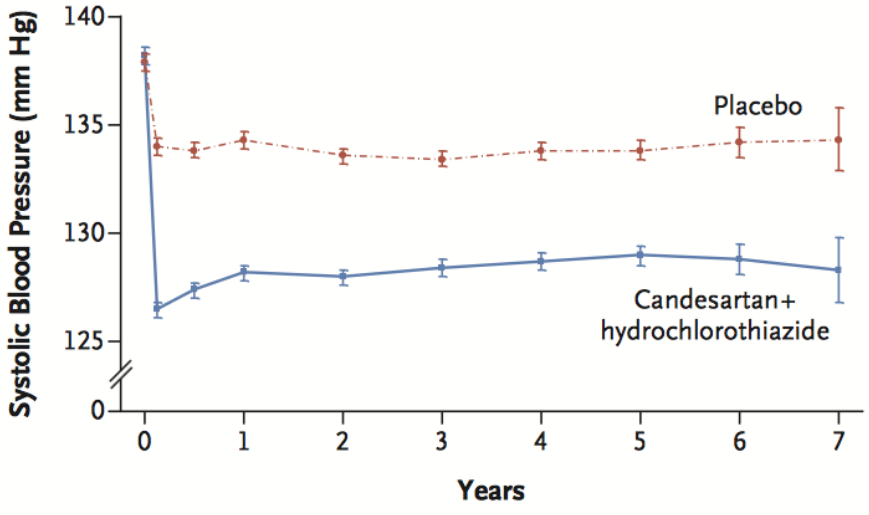
Lonn EM et al. N Engl J Med 2016;374:2009-20

HOPE-3

Characteristic	Candesartan + Hydrochlorothiazide (N = 6356)	Placebo (N = 6349)
Age — yr	65.7±6.4	65.8±6.4
Female sex — no. (%)	2910 (45.8)	2964 (46.7)
Cardiovascular risk factor — no. (%)		
Elevated waist-to-hip ratio	5511 (86.7)	5523 (87.0)
Recent or current smoking	1782 (28.0)	1742 (27.4)
Low concentration of HDL cholesterol	2297 (36.1)	2291 (36.1)
Impaired fasting glucose or impaired glucose tolerance	799 (12.6)	817 (12.9)
Early diabetes mellitus	386 (6.1)	345 (5.4)
Family history of premature coronary heart disease	1668 (26.2)	1667 (26.3)
Early renal dysfunction	184 (2.9)	166 (2.6)
Hypertension	2398 (37.7)	2416 (38.1)
Blood pressure — mm Hg		
Systolic	138.2±14.7	137.9±14.8
Diastolic	82.0±9.4	81.8±9.3

Lonn EM et al. N Engl J Med 2016;374:2009-20

HOPE-3



No. at Risk

Candesartan+hydrochlorothiazide	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

Lonn EM et al. N Engl J Med 2016;374:2009-20

ACCORD, SPRINT, and HOPE-3

	ACCORD	SPRINT	HOPE-3
Population	4733 DM	9631 non-DM	12705
Intervention	<120 vs. <140	<120 vs. <140	drug vs. placebo
Primary outcome	MI, Stroke, CV death	+ HF, other ACS	= ACCORD
SBP at 1yr	119 vs. 134	121 vs. 136	≈ 128 vs. ≈ 134
Outcome/yr	1.87% vs. 2.09%	1.65% vs. 2.19% *	4.1% vs. 4.4%
All cause death/yr	1.28% vs. 1.19%	1.03% vs. 1.40% *	5.4% vs. 5.5%
Stroke	0.32% vs. 0.53% *	0.41% vs. 0.47%	1.2% vs. 1.5%

HOPE-3: event rates during follow-up (median f/u 5.6year)

N Engl J Med. 2010 362(17):1575-85; N Engl J Med. 2015 Nov 26;373(22)89mm:2103-16; N Engl J Med 2016;374:2009-20

Guidelines Debate

Is It Time to Reappraise Blood Pressure Thresholds and Targets?

A Statement From the International Society of Hypertension—A Global Perspective

Michael A. Weber, Neil R. Poulter, Aletta E. Schutte, Louise M. Burrell, Masatsugu Horiuchi, Dorairaj Prabhakaran, Agustin J. Ramirez, Ji-Guang Wang, Ernesto L. Schiffrin, Rhian M. Touyz

Taking into consideration the global target population of interest to the International Society of Hypertension, together with evidence derived from SPRINT and other recent meta-analyses and clinical trials, the practical message from the International Society of Hypertension is to strive for a systolic blood pressure target of 130 mm Hg in most patients with hypertension. This is especially important considering that

Weber MA et al. Hypertension. 2016;68:266-268.

Take-Home Message

- Stroke and Hypertension are big health issues in rapidly aging societies like Korea.
- Therapeutic target of BP in patients with stroke should be individualized.
- The practical therapeutic goal of SBP in patients with hypertension might be **130 mm Hg**.