Étude Sprint : nouvelles cibles pour le traitement de l'hypertension artérielle ?

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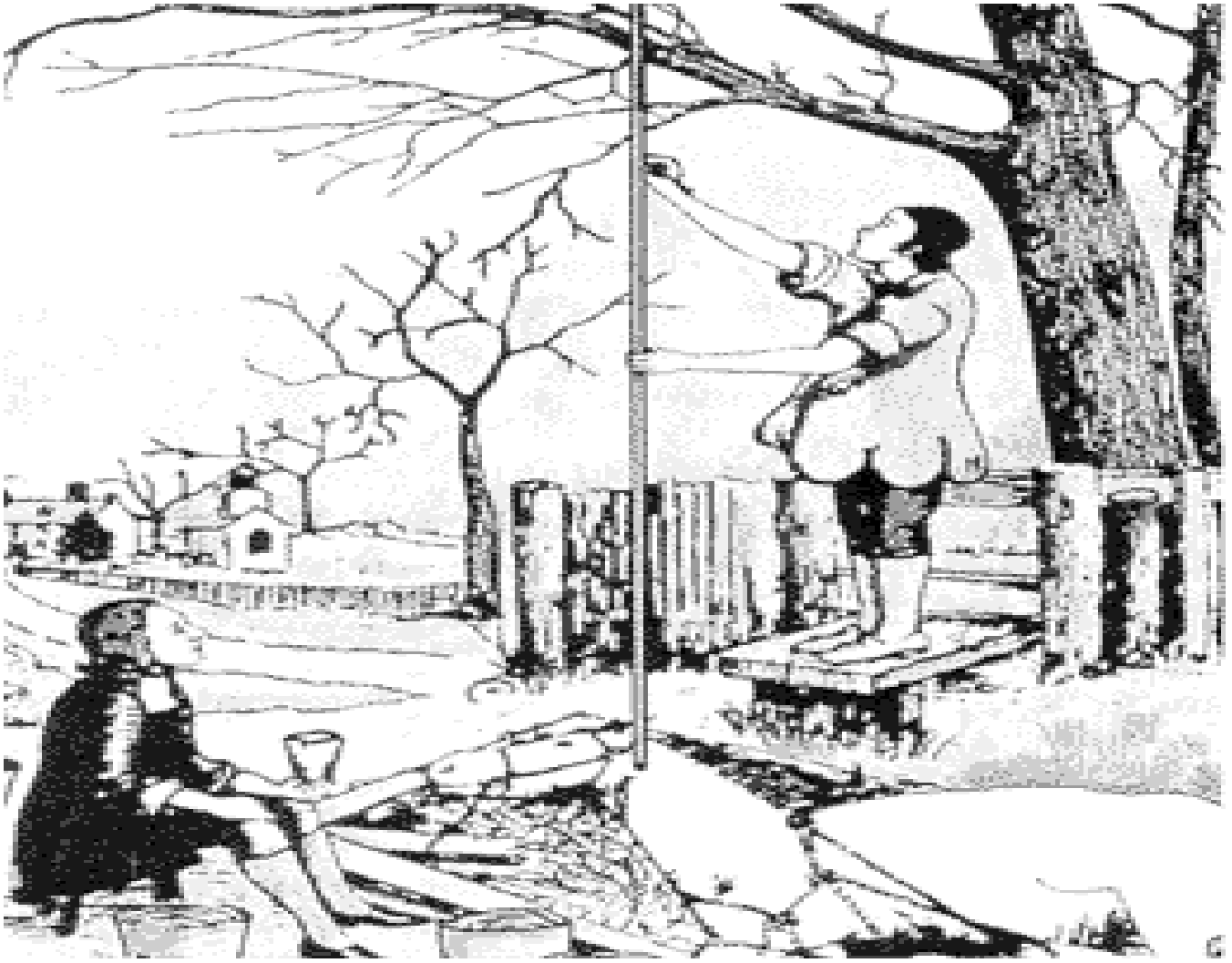
La première mesure de la pression artérielle



1732, Stephen Hales.

Faut-il traiter l’hypertension artérielle ?

Comments about Hypertension

"The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it."

Hay, Brit Med J, 1931

“Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it.”

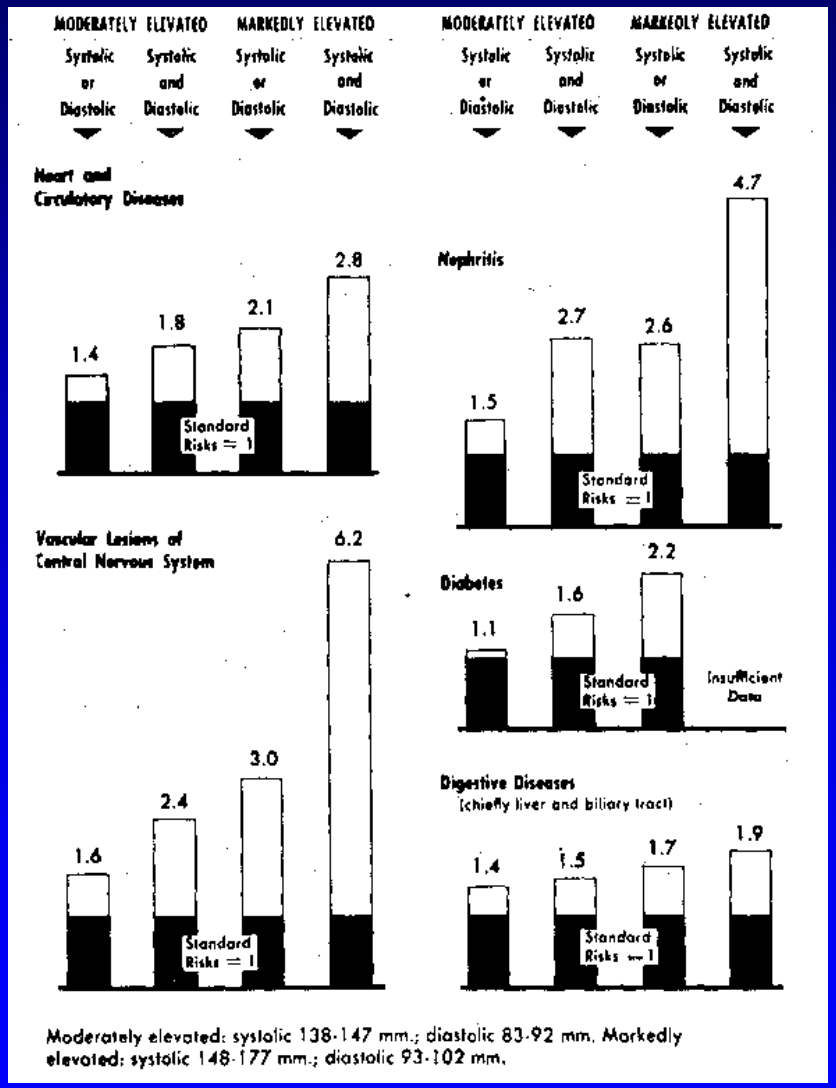
Paul Dudley White, 1931

Treatment of Hypertension

…Remedies suggested - “watermelon and cucumber seeds, mistletoe and garlic” - “red meat and sex were forbidden.”

Page, late 1940s

Actuary Data Relating Blood Pressure to Mortality 1935-1954



Metropolitan Life Insurance Company 1961

The VA Cooperative Study, 1967

Cohort	143 men
Mean age	51 years
Eligibility	Diastolic BP 115-129 mmHg
Design	Double blind; placebo control
Therapy	HCTZ, reserpine, hydralazine
Duration	1.5 years
BP change	-43/30 mmHg

HCTZ=hydrochlorothiazide

VA Cooperative Study Group. JAMA. 1967;202:1028-1034.

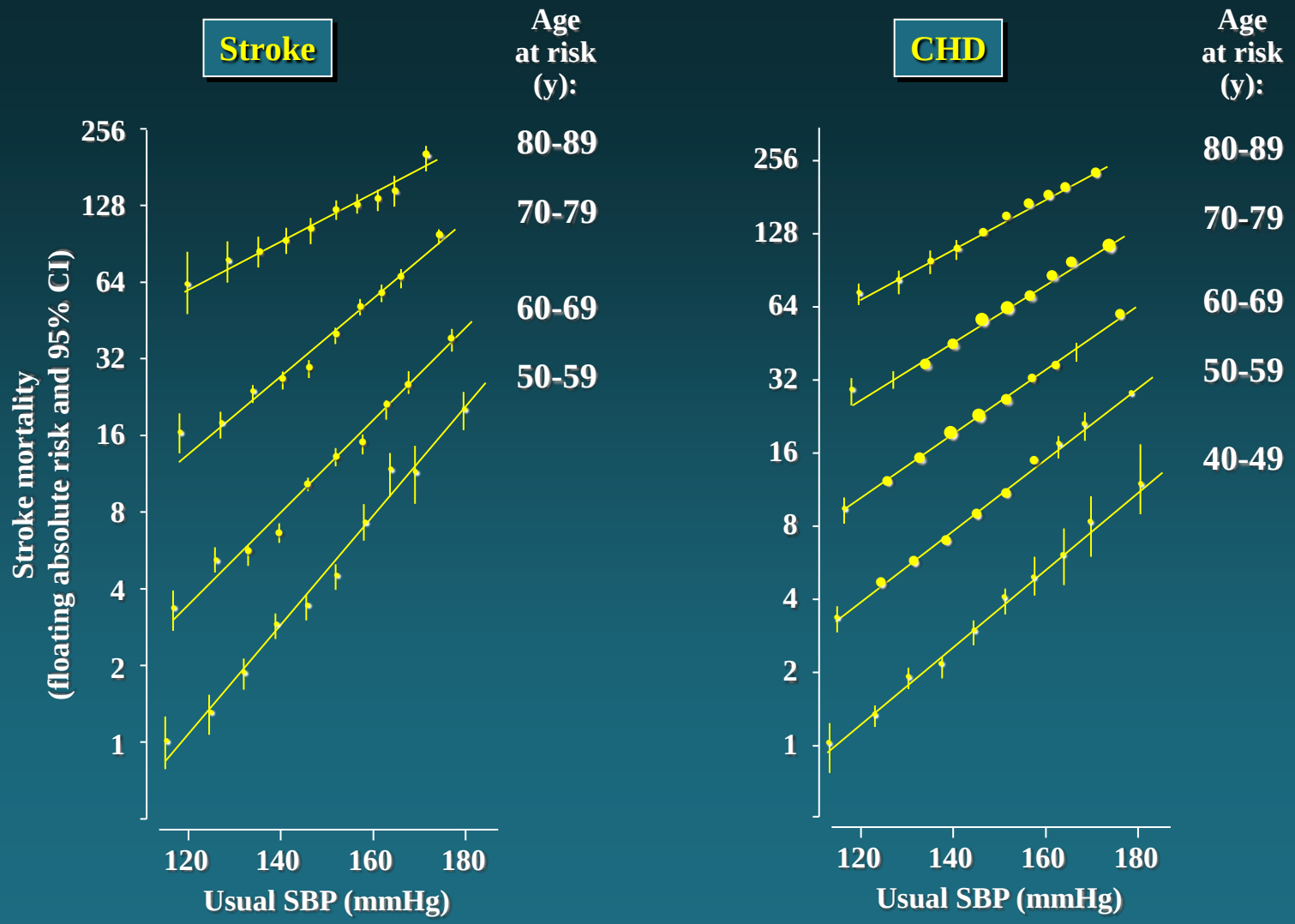
The VA Cooperative Study, 1967: Assessable Morbid/Fatal Events

	Placebo n=70	Active Rx* n=73
Accelerated hypertension	12	0
Stroke	4	1
Coronary event	2	0
CHF	2	0
Renal damage	2	0
Deaths	4	0

*P<0.001 active drug therapy vs placebo

VA Cooperative Study Group. JAMA. 1967;202:1028-1034.

Stroke and CHD Mortality Rate in Each Decade of Age versus Usual Systolic Blood Pressure at the Start of That Decade



Lancet 2002; 360: 1903-1913

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)

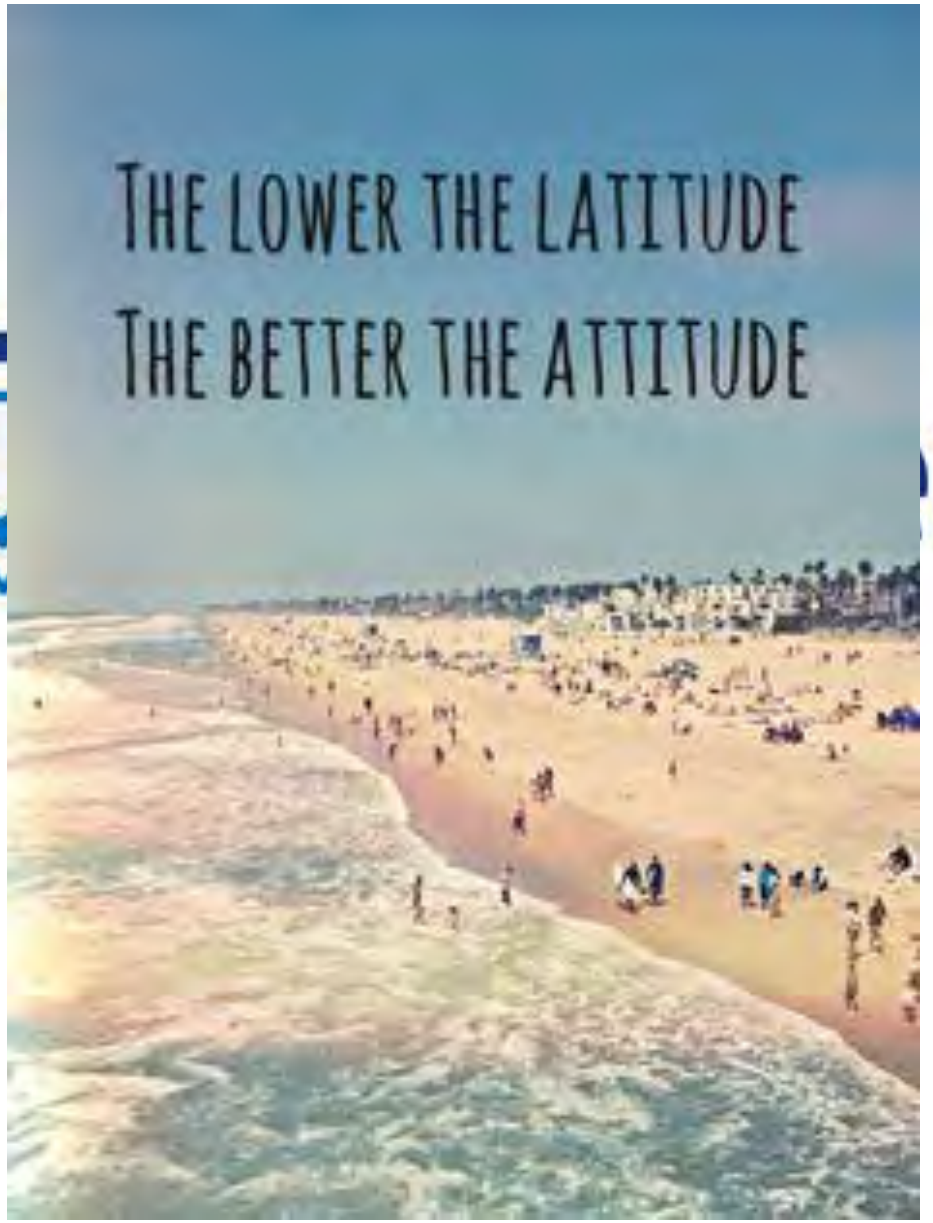
JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

Table 6. Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

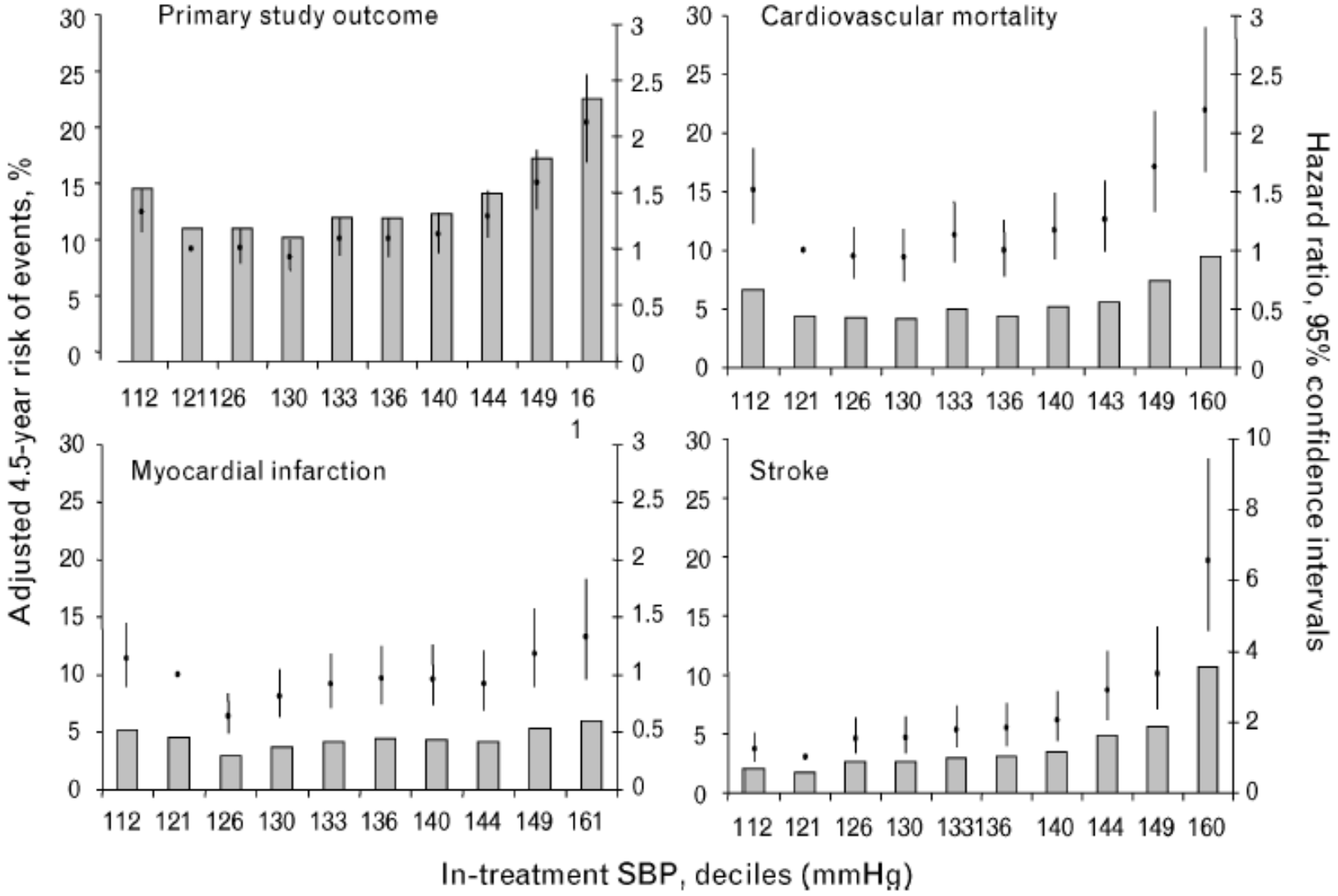
Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013[37]	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
CHEP 2013[38]	General <80 y	<140/90	Thiazide, β-blocker (age <60y), ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
	Diabetes	<130/80	ACEI or ARB with additional CVD risk ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
	CKD	<140/90	ACEI or ARB
ADA 2013[39]	Diabetes	<140/80	ACEI or ARB
KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011[41]	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010[42]	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

La question importante :



Risk of outcome events achieved by SBP in high risk patients: A post-hoc analysis of ONTARGET



Sleight et al , J Hypertens, 27: 1360, 2009

Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

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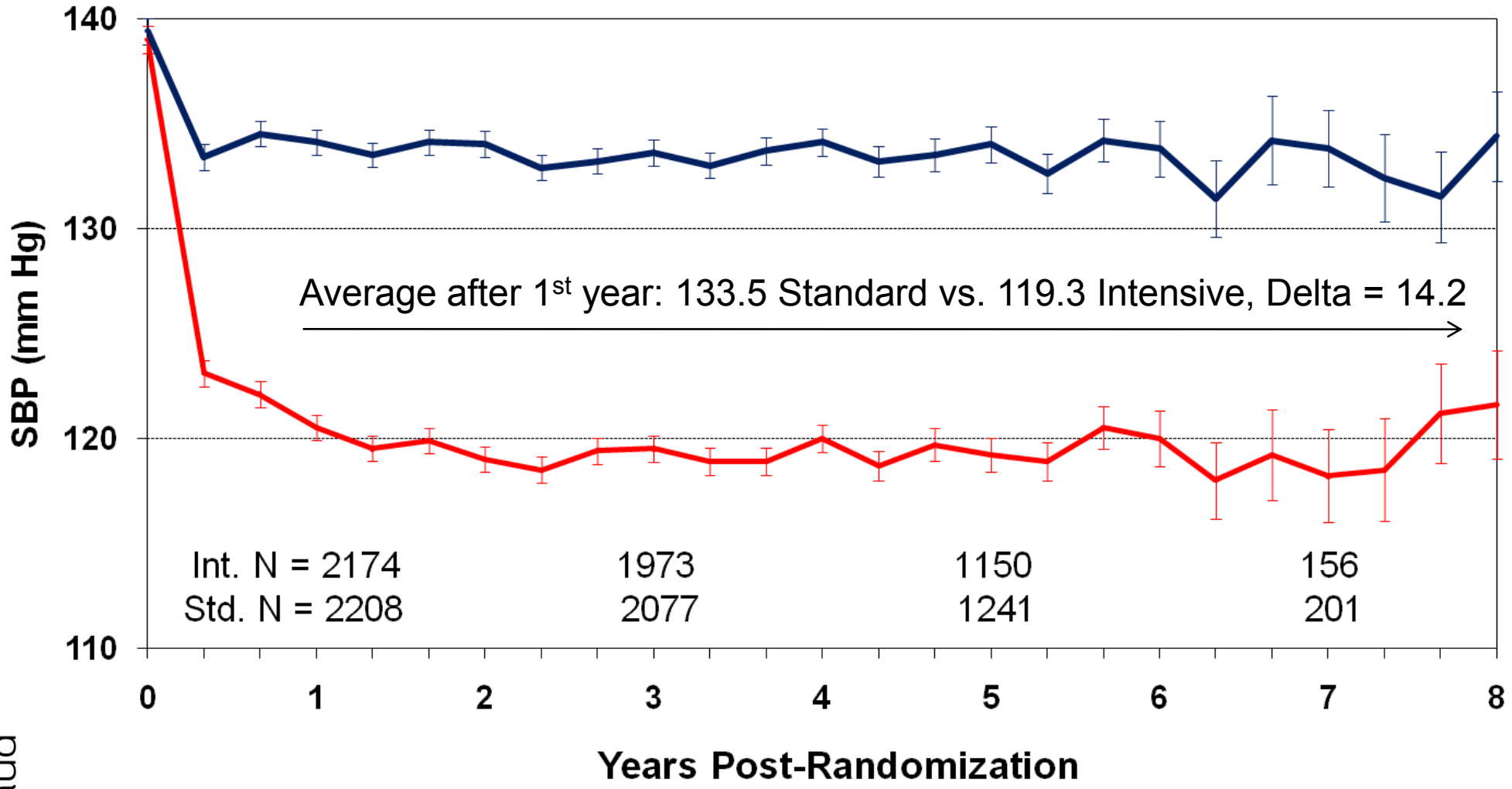
Veterans Affairs Medical Center, Memphis, TN

For The ACCORD Study Group

Changes in Systolic BP in ACCORD



NEJM 362(17):1575-85, 2010

Primary & Secondary Outcomes in ACCORD

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.88 (0.73-1.06)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.96)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

NEJM 362(17):1575-85, 2010

SPRINT Research question

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:

- *ClinicalTrials.gov (NCT01206062)*
- *Ambrosius WT et al. Clin. Trials. 2014;11:532-546.*

SPRINT
Systolic Blood Pressure Intervention Trial

Major Inclusion Criteria

- ≥50 years old
- Systolic blood pressure : 130 – 180 mm Hg (treated or untreated)
- Additional cardiovascular disease (CVD) risk
  - Clinical or subclinical CVD (excluding stroke)
  - Chronic kidney disease (CKD), defined as eGFR 20 – <60 ml/min/1.73m^2
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

At least one

SPRINT Systolic Blood Pressure Intervention Trial

Major Exclusion Criteria

- *Stroke*
- *Diabetes mellitus*
- *Polycystic kidney disease*
- *Congestive heart failure (symptoms or EF < 35%)*
- *Proteinuria >1g/d*
- *CKD with eGFR < 20 mL/min/1.73m^2 (MDRD)*
- *Adherence concerns*

SPRINT
Systolic Blood Pressure Intervention Trial

Primary Outcome and Primary Hypothesis

- **Primary outcome**
  - CVD composite: first occurrence of
    - Myocardial infarction (MI)
    - Acute coronary syndrome (non-MI ACS)
    - Stroke
    - Acute decompensated heart failure (HF)
    - Cardiovascular disease death

- **Primary hypothesis***
  - CVD composite event rate lower in intensive compared to standard treatment

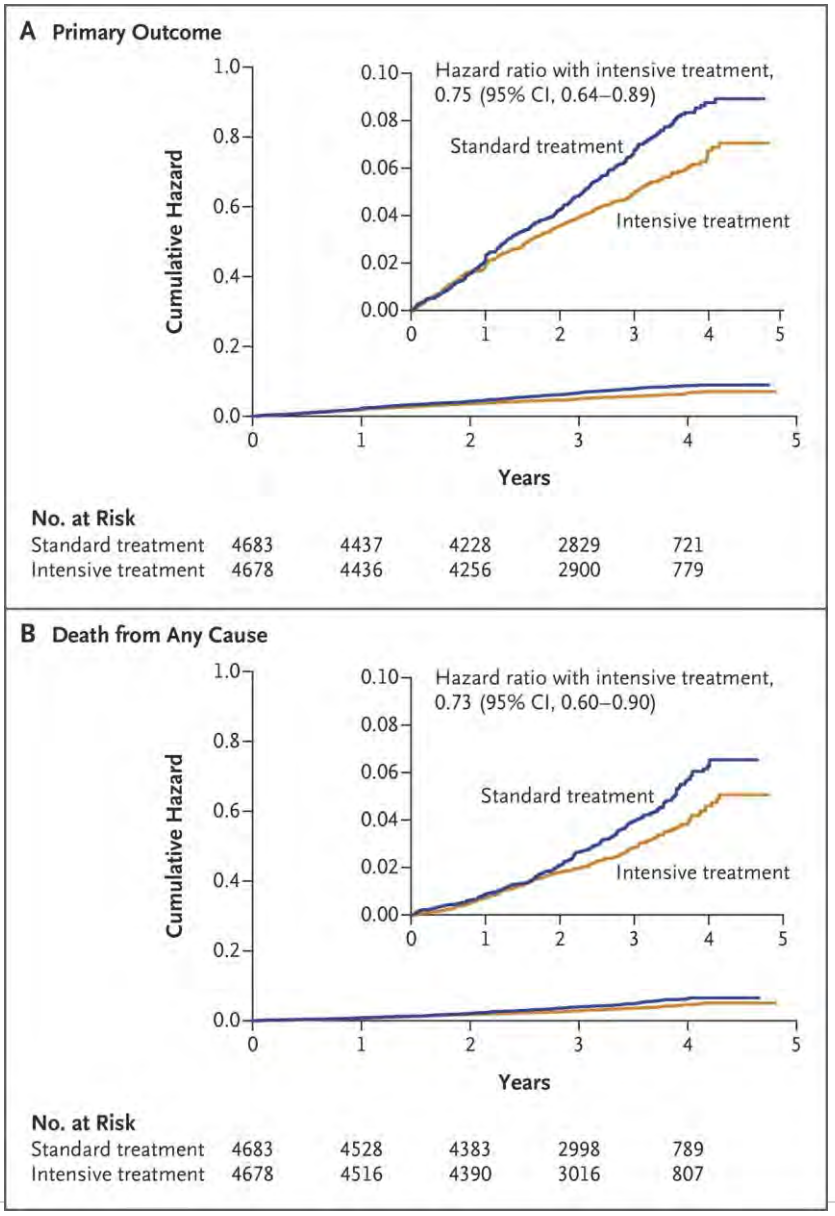
*Estimated power of 88.7% to detect a 20% difference - based on recruitment of 9,250 participants, 4-6 years of follow-up and loss to follow-up of 2%/year.

SPRINT
Systolic Blood Pressure Intervention Trial

Demographic and Baseline Characteristics

	Total N=9361	Intensive N=4678	Standard N=4683
Mean (SD) age, years	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)
% ≥75 years	28.2%	28.2%	28.2%
Female, %	35.6%	36.0%	35.2%
White, %	57.7%	57.7%	57.7%
African-American, %	29.9%	29.5%	30.4%
Hispanic, %	10.5%	10.8%	10.3%
Prior CVD, %	20.1%	20.1%	20.0%
Mean 10-year Framingham CVD risk, %	20.1%	20.1%	20.1%
Taking antihypertensive meds, %	90.6%	90.8%	90.4%
Mean (SD) number of antihypertensive meds	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)
Mean (SD) Baseline BP, mm Hg			
Systolic	139.7 (15.6)	139.7 (15.8)	139.7 (15.4)
Diastolic	78.1 (11.9)	78.2 (11.9)	78.0 (12.0)

Primary Outcome and Death from Any Cause



The SPRINT Research Group. N Engl J Med 2015;373:2103-2116

Primary and Secondary Outcomes and Renal Outcomes

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
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

The SPRINT Research Group. N Engl J Med 2015;373:2103-2116

Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

Variable	Intensive Treatment (N=4678)	Standard Treatment (N=4683)	Hazard Ratio	P Value
	no. of patients (%)			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

Drug prescription in SPRINT

	Intensive (N=4678)	*Standard (N=4683)*
Number of agents		
Average	2.7 (1.2)	1.8 (1.1)
0	125 (2.7)	530 (11.3)
1	493 (10.5)	1455 (31.1)
2	1429 (30.5)	1559 (33.3)
3	1486 (31.8)	807 (17.2)
4+	1137 (24.3)	323 (6.9)
ACE-I or angiotensin II antagonist	3580 (76.7)	2582 (55.2)
ACE inhibitors	1729 (37.0)	1320 (28.2)
Angiotensin II antagonists	1854 (39.7)	1264 (27.0)
Renin inhibitors	1 (0.0)	1 (0.0)
Diuretics	3127 (67.0)	2006 (42.9)
Thiazide-type diuretics	2562 (54.9)	1557 (33.3)
Aldosterone receptor blockers	405 (8.7)	185 (4.0)
Other potassium-sparing diuretics	144 (3.1)	119 (2.5)
Alpha-1 blockers	482 (10.3)	258 (5.5)
Beta blockers	1919 (41.1)	1440 (30.8)
With intrinsic sympathomimetic activity	0 (0.0)	0 (0.0)
Without intrinsic sympathomimetic activity	1919 (41.1)	1440 (30.8)
Central alpha-2 agonists or other centrally acting drugs	107 (2.3)	44 (0.9)
Calcium channel blockers	2667 (57.1)	1654 (35.4)
Dihydropyridines	2465 (52.8)	1463 (31.3)
Non-dihydropyridines	218 (4.7)	199 (4.3)
Direct vasodilators	340 (7.3)	110 (2.4)

Mesure de la TA dans SPRINT

BPs in SPRINT were measured with patients seated in a quiet room without talking and taken as an average of three measurements with an automated device (Omron Healthcare, Lake Forest, IL, USA) that was preset to wait 5 min before measurements without the observer being present. Previous studies in treated hypertensive people have shown that SBP by this automated office technique is comparable to, or even lower than daytime ambulatory SBP, and up to 20 mmHg lower than conventional auscultatory SBP in the office.[19]

Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients

Jan Filipovský[a,b], Jitka Seidlerová[a,b], Zdeněk Kratochvíl[a], Petra Kamosová[a,b], Markéta Hronová[a] and Otto Mayer Jr[a,b]

So 120 mmHg may correspond to 135 mmHg in the GP's office

	Automated BP (mmHg)	Office BP (mmHg)	Δ office BP–automated BP (mmHg)	Automated BP vs office BP *r*
Total sample ($n = 353$)				
SBP	131.2 ± 21.8	146.9 ± 20.8	15.0 ± 13.8	0.79
DBP	77.8 ± 12.1	85.8 ± 12.4	8.0 ± 7.3	0.82

Unanswered questions ?

What are the effects of intensive BP lowering on:

1) Dementia and cognitive function ?
2) Long-term decline in renal function ?
3) Diastolic BP ?

When a study is interrupted prematurely:

The benefits are overestimated

The side effects are underestimated !!

Annals of Internal Medicine

Let's Not SPRINT to Judgment About New Blood Pressure Goals

Eduardo Ortiz, MD, MPH, and Paul A. James, MD

SPRINT (Systolic Blood Pressure Intervention Trial), a randomized, controlled trial that compared aggressive treatment to a target systolic blood pressure (BP) less than 120 mm Hg with a target less than 140 mm Hg in patients at increased cardiovascular risk, was stopped early and its results were promoted widely months before publication (1). Participants were mostly men (64%) with a mean age of 68 years and comorbidities that increased their cardiovascular risk, but patients with diabetes were excluded. With the lower treatment target, the trial found a 25% relative risk reduction in the primary composite outcome. Although a 25% reduction sounds impressive, it corresponds to a decrease in event rates from 6.8% to 5.2% over 3.2 years, or an absolute risk reduction of 1.6%.

On the basis of the SPRINT results, we estimate that for 1000 persons treated over 3.2 years to a systolic BP goal less than 120 mm Hg compared with 140 mm Hg, an average of 16 persons will benefit, 22 persons will be seriously harmed, and 962 will not experience benefits or harms; however, one cannot predict who will benefit or be harmed. Patients may believe that it is worthwhile to aim for lower BPs if they hear that receiving 3 drugs every day for more than 3 years might reduce their risk for cardiovascular events by 25%. However, after learning that their likelihood of absolute benefit is only 1.6%, with a greater likelihood of serious harm, their enthusiasm for more medications may diminish.

cope, electrolyte abnormalities, and acute kidney injury or acute renal failure. Emergency department visits also occurred more often for each of these events, as well as for bradycardia and injurious falls (4). These adverse drug events underscore a concern about potential overtreatment in both groups, given that previous evidence from randomized trials has not demonstrated a benefit in important health outcomes of drug treatment to a BP goal less than 140/90 mm Hg compared with less than 150/90 mm Hg, especially in those without underlying cardiovascular disease (5).

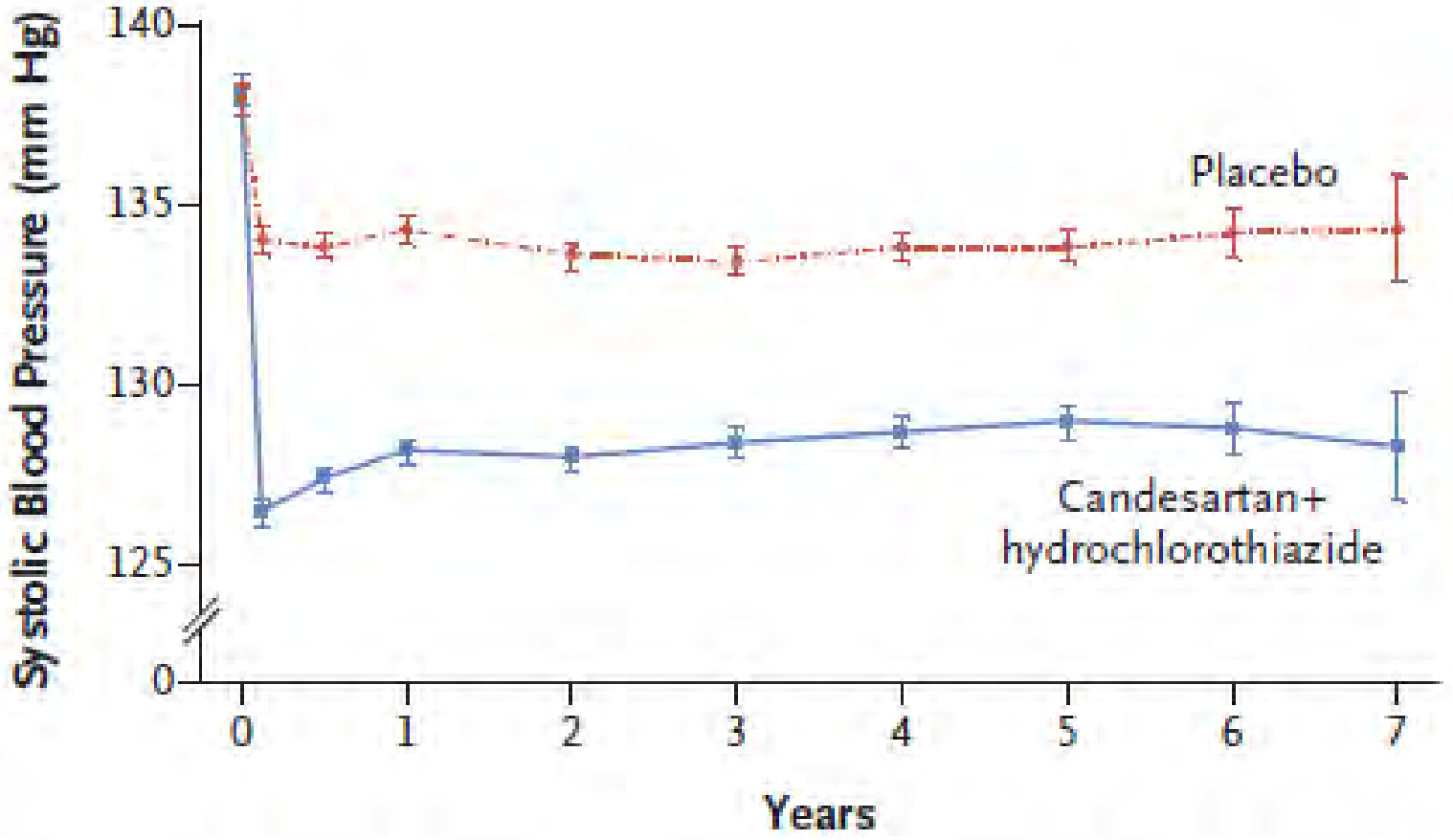
What and how we communicate to patients about the risks and benefits of interventions matters. The prevailing emphasis on relative over absolute risk reduction while ignoring harms of treatment for BP seems intent on labeling more patients with hypertension and pushing for more aggressive drug therapy, especially in older patients (6). However, evidence suggests that patients expect greater treatment benefits than physicians to justify the use of daily antihypertensive medications when presented with similar data on benefits and harms, and specialists are more likely than primary care physicians to believe that more aggressive treatment is beneficial (7).

An evidence-based approach to clinical decision making and guideline development requires the judicious incorporation of new evidence (8). Although patients, providers, and professional organizations should consider the SPRINT results and incorporate them into

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†

BP changes in HOPE-3 in patients with intermediate risk

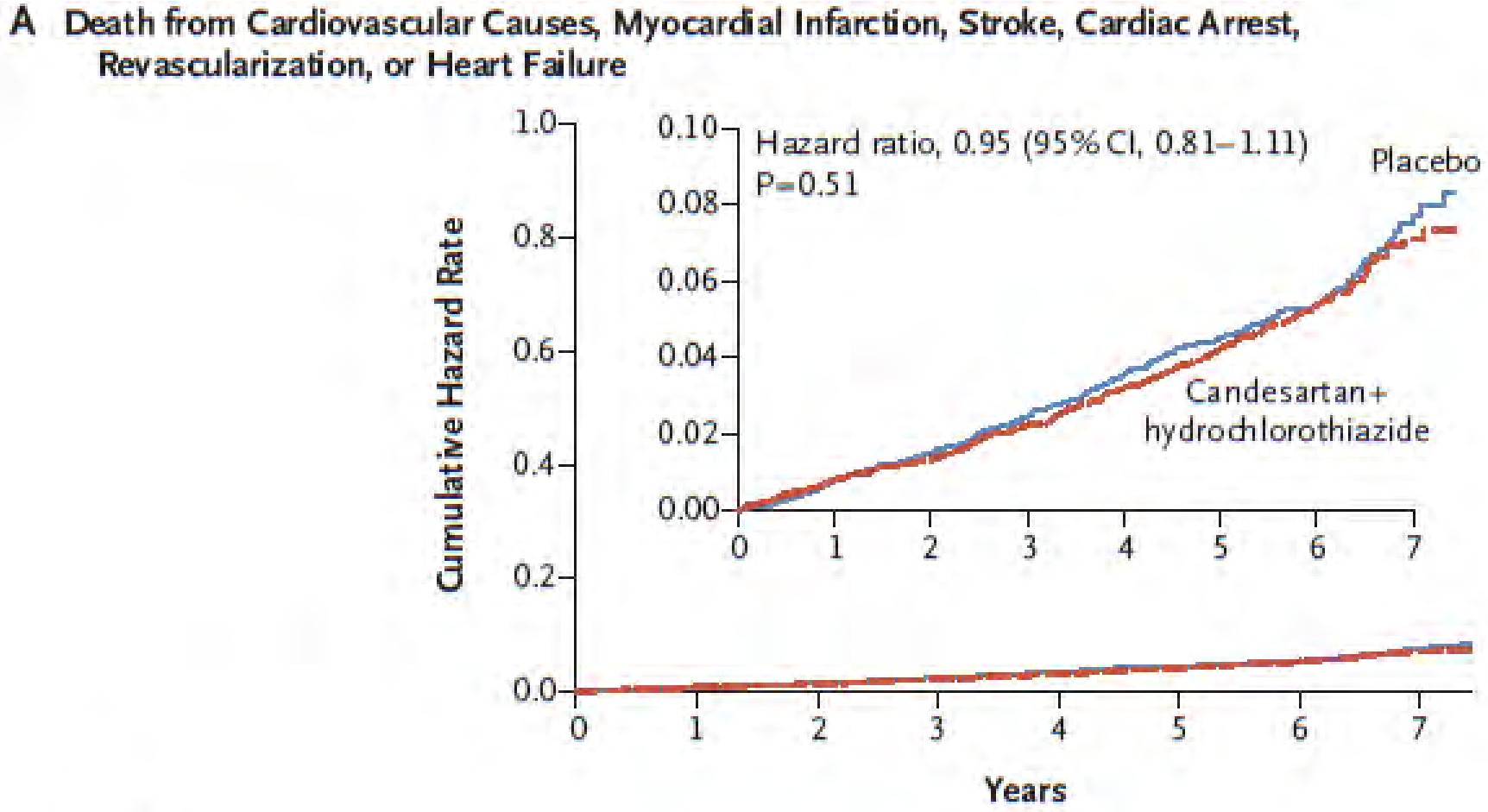


No. at Risk

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

NEJM, April 2016

HOPE-3: effect of the treatment on the primary endpoint

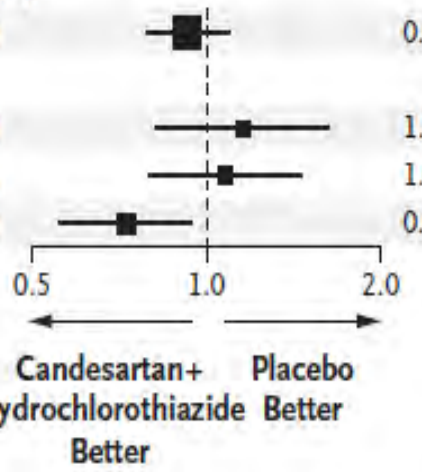


NEJM, April 2016

In HOPE-3, treatment is reducing endpoints only in patients with a systolic BP > 143 mmHg

A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



NEJM, April 2016

Conclusion

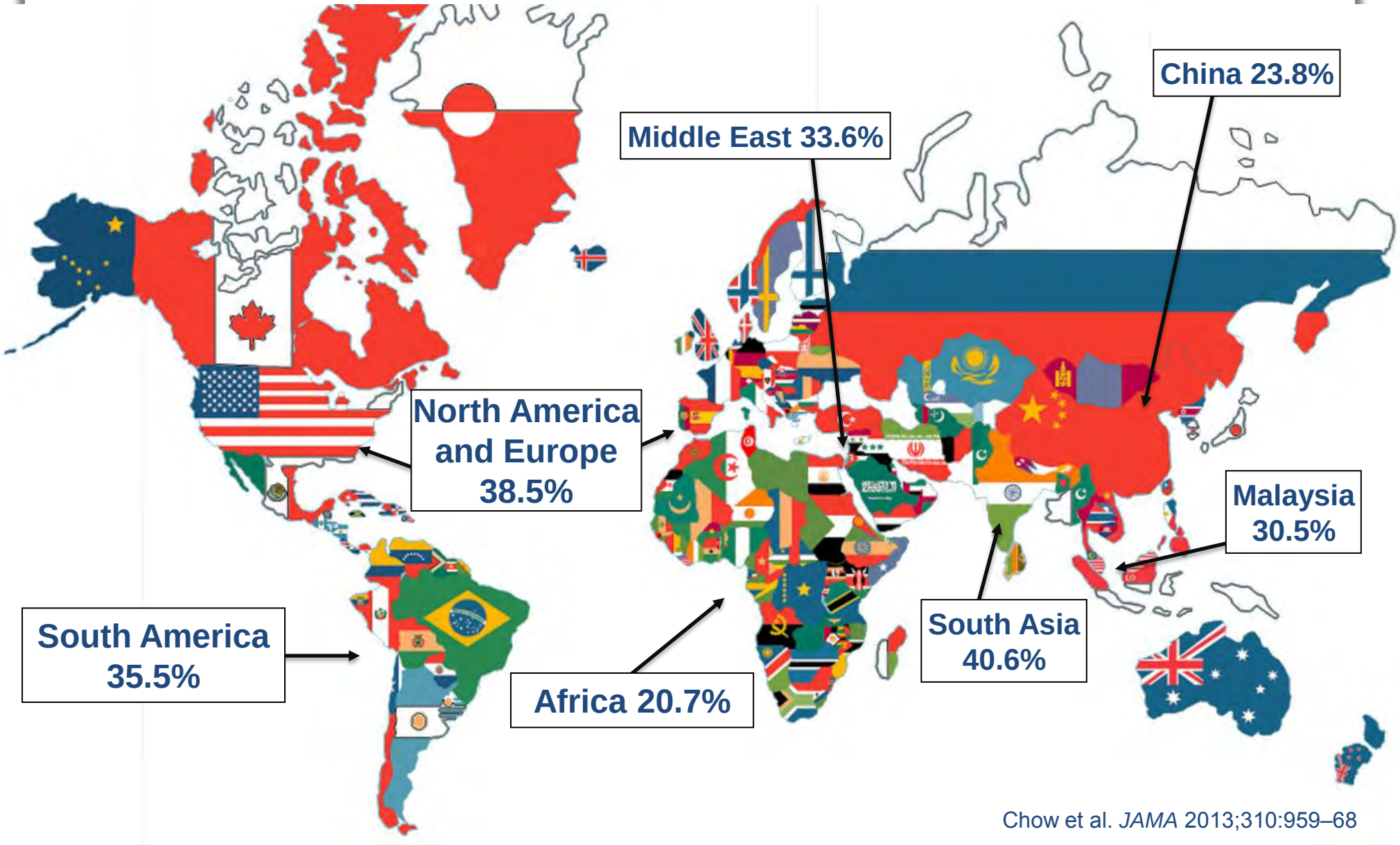
Les résultats de SPRINT suggèrent que les patients à haut risque bénéficient d'un contrôle plus strict de la TA (<120 mmHg).

Cependant, il faut considérer la particularité de SPRINT pour la mesure de la pression artérielle

Il n'y a pas lieu de modifier les recommandations actuelles pour le contrôle de la pression artérielle soit:

< 140/90 mmHg

In real life, BP control is often suboptimal; globally, BP is controlled in only 32.5% of treated hypertensive patients



Chow et al. *JAMA* 2013;310:959–68