OHSU 55th Annual Primary Care Review

Symposia:
Hypertension in 2024: Another guideline and more Debate

February 12th, 2024

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Conflicts of Interest:
None

Objective:

1. Understand the discrepancies between the existing U.S. guideline and the new, 2023 European guideline for hypertension and decide for ourselves what our B.P. goal should be in primary care

ARS (audience response question):

In your current practice, do you prefer a general BP goal of:

1. <140/90 mmHg

2. <130/80 mmHg

3. Other/Find it all very confusing

In case anyone falls asleep in next 30 minutes,

Answer: < 140/90 mmHg is a good, universal goal. Tighter control is controversial

For context and as a reminder, the NIH got out of the guideline business about a decade ago

JAMA 2014;311:507-520

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)

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)

Recommendation 3

In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)

But after JNC 8, (and NCEP IV for cholesterol), NIH handed over guideline writing to professional societies - AHA/ACC for HTN.

But ACC/AHA guidelines had historically taken some criticism.….

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

JAMA 2009;301:831-41

Conclusion: "Recommendations issued in current ACC/AHA clinical practice guidelines are largely developed from lower levels of evidence or expert opinion."

In early-mid 2010's, as ACC/AHA taking over cardiology guidelines, there was mounting criticism to be more strictly evidence-based with less expert opinion…..

And then in 2015, we got the SPRINT trial…..

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

CONCLUSIONS

Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National In-

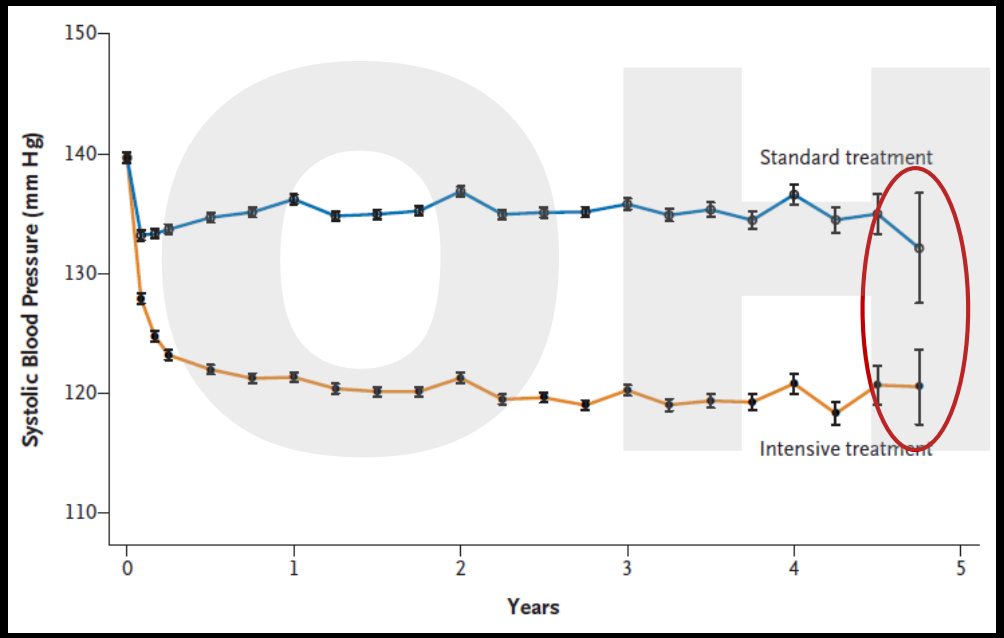
NEJM, Nov 9th, 2015

SPRINT was mostly a very high-risk, primary prevention trial…

Characteristic	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
Criterion for increased cardiovascular risk — no. (%)†		
Age ≥75 yr	1317 (28.2)	1319 (28.2)
Chronic kidney disease‡	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20.0)
Clinical	779 (16.7)	783 (16.7)
Subclinical	247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%	2870 (61.4)	2867 (61.2)

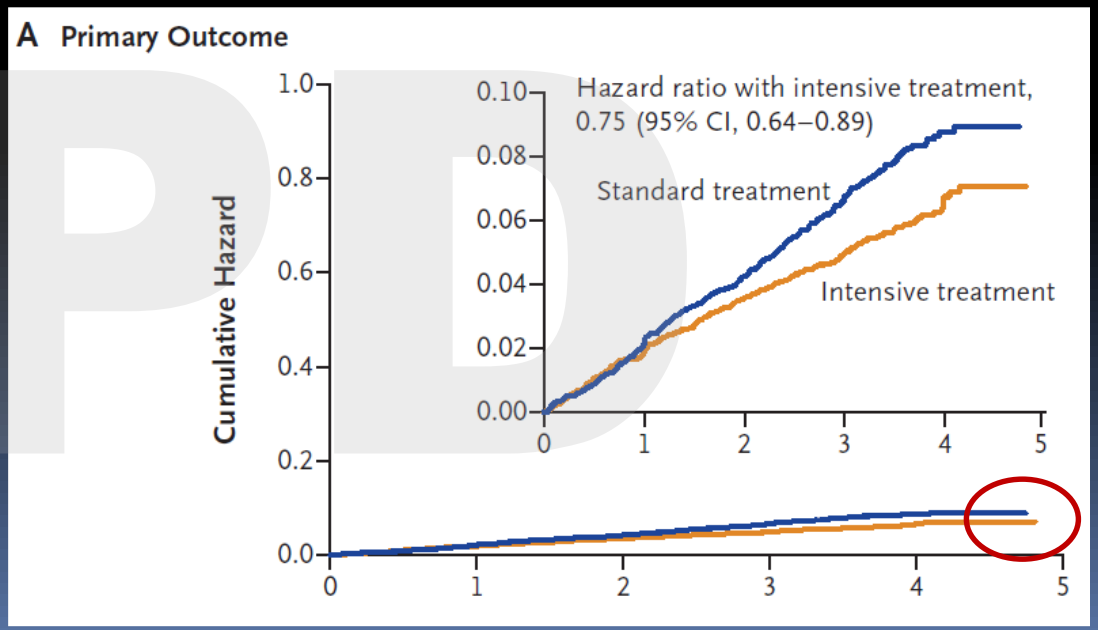
Patients with diabetes were excluded because another, similar trial (ACCORD) was studying ONLY diabetic patients.

BP achieved and what was found…..



Using an average of three medications for intensive treatment, SPRINT achieved a significant SBP reduction from 136 mmHg (control) to 121 mmHg (treatment)

And the benefit on a broad CVD endpoint (CHD death, MI, stroke, CHF) was modest but real (6.8% vs. 5.2%)



At the time SPRINT was published, the ACC/AHA guideline committee had begun its work.

A number of members of the guideline committee were co-authors on SPRINT

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

8.1.5. BP Goal for Patients With Hypertension

Recommendations for BP Goal for Patients With Hypertension

References that support recommendations are summarized in Online Data Supplement 26 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR] DBP: C-EO	1. For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher (see Section 8.1.2), a BP target of less than 130/80 mm Hg is recommended (1-5).

9.1. Stable Ischemic Heart Disease

Recommendations for Treatment of Hypertension in Patients With Stable Ischemic Heart

9.2. Heart Failure

9.6. Diabetes Mellitus

Recommendations for Treatment of Hypertension in Patients With DM

References that support recommendations are summarized in Online Data Supplements 46 and 47 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR] DBP: C-EO	1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (1-8).

of Hypertension in Patients With CKD

summarized in Online Data Supplements 37 and 38

ic Review Report.

Recommendations

n and CKD should be treated to a BP goal of less than

But, the Europeans…

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3021–3104
doi:10.1093/eurheartj/ehy339

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)

Table 3 Classification of office blood pressure[a] and definitions of hypertension grade[b]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

ESC European Society of Cardiology
European Heart Journal (2018) 39, 3021–3104
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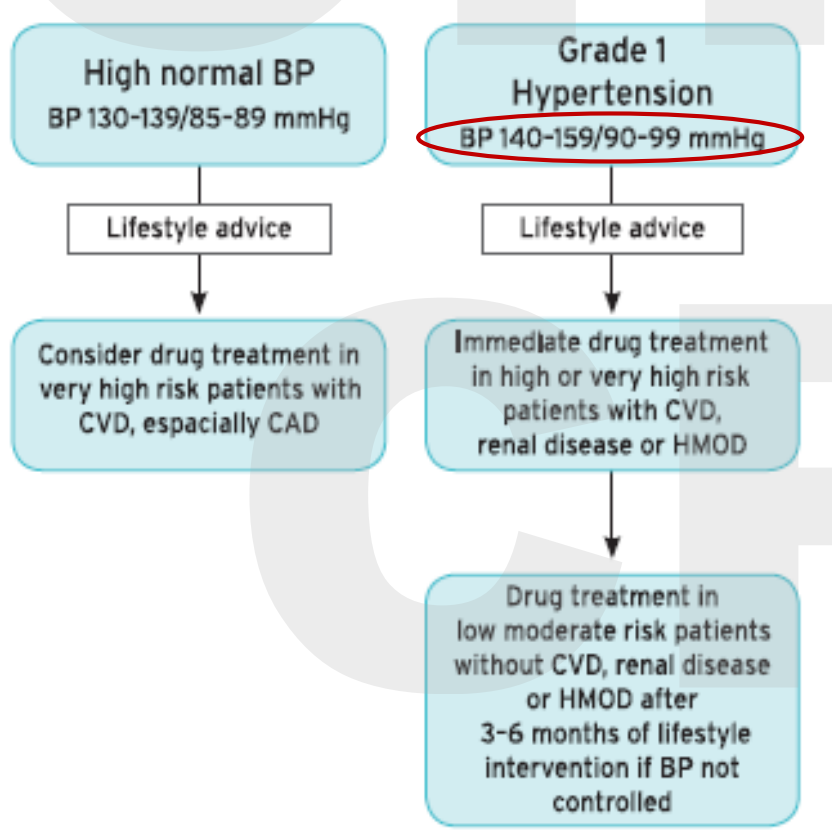

Recommends drug therapy at "Grade 1" HTN, >140/90 mmHg

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH)

Office BP thresholds for drug treatment initiation

Recommendations and statements	CoR	LoE
In patients 18 to 79 years, the recommended office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP.	I	A
In patients ≥80 years, the office SBP threshold for initiation of drug treatment is 160 mmHg.	I	B

2023 ESH Guidelines for the management of arterial hypertension

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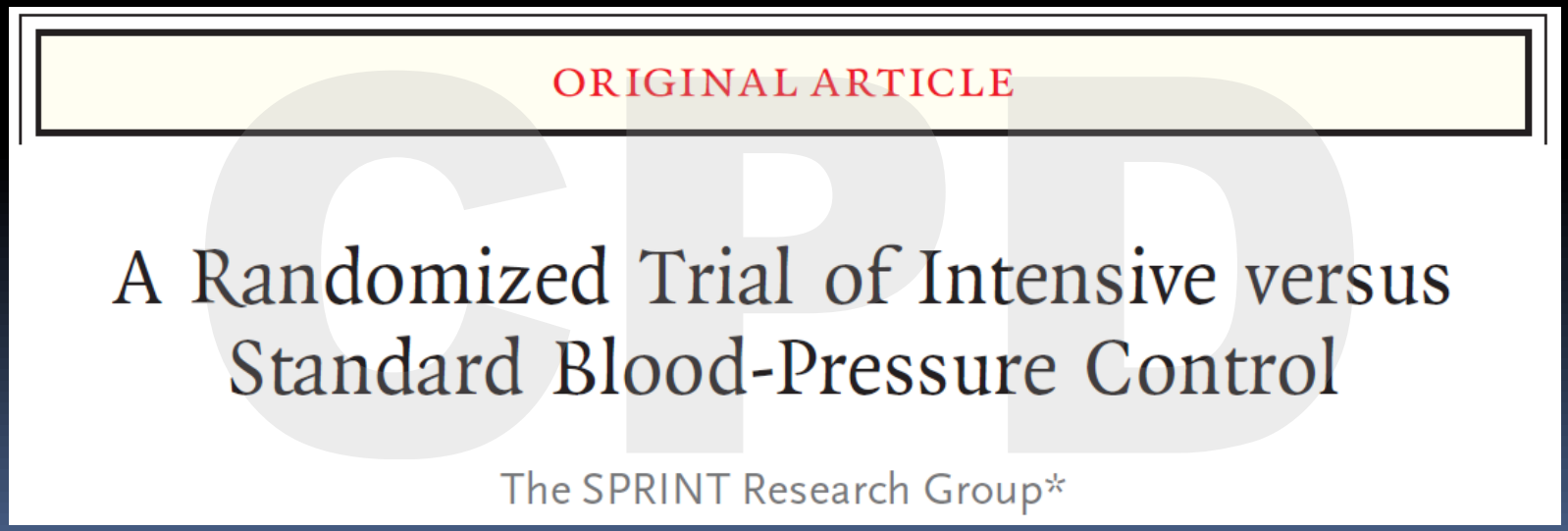
Office BP targets for drug treatment

Recommendations and statements	CoR	LoE
Patients 18 to 64 years old		
The goal is to lower office BP to <130/80mmHg	I	A
Patients 65 to 79 years old		
The primary goal of treatment is to lower BP to <140/80mmHg	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	I	B

What the heck is going on?

Do we really need different goals for a 64-year old vs. a 66-year old vs. an 82-year old? Should patients with diabetes have different goals than patients without diabetes?
And why the specification for office-based measurements


ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

The problem with SPRINT is that it surprised us.

Other studies had failed to find benefits of further BP control once SBP already < 140 mmHg

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

April 2010

ABSTRACT

BACKGROUND

There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120

ACCORD BP: Results (133 mmHg systolic BP vs. 119 mmHg systolic BP)

Table 3. Primary and Secondary Outcomes.

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
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74

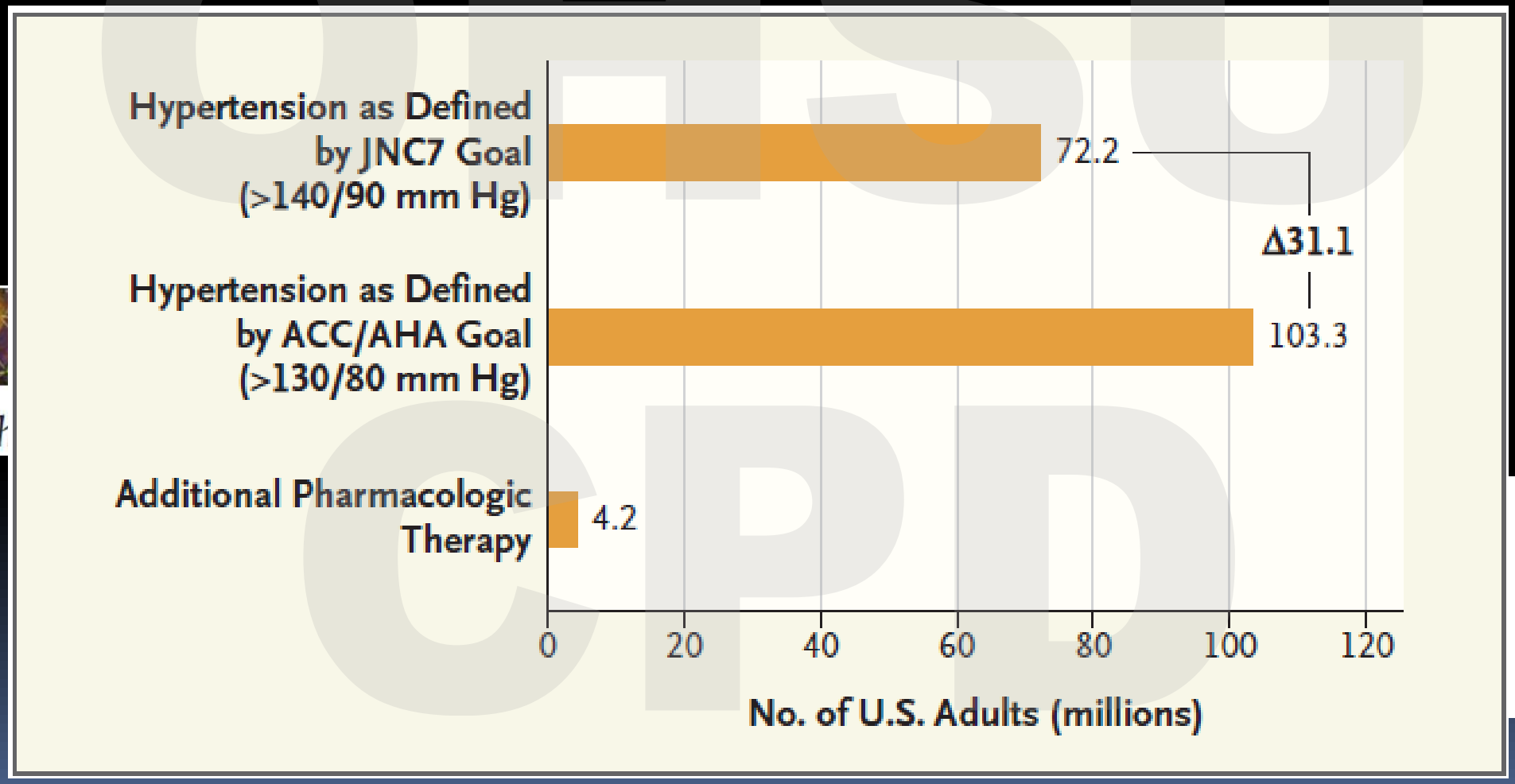
Conclusions: "In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of fatal and nonfatal major CVD events."

So SPRINT was surprising after the ACCORD trial but also, other trials published in the early-mid 2010's did NOT find benefit from tighter control when the control group was already < 140 mmHg

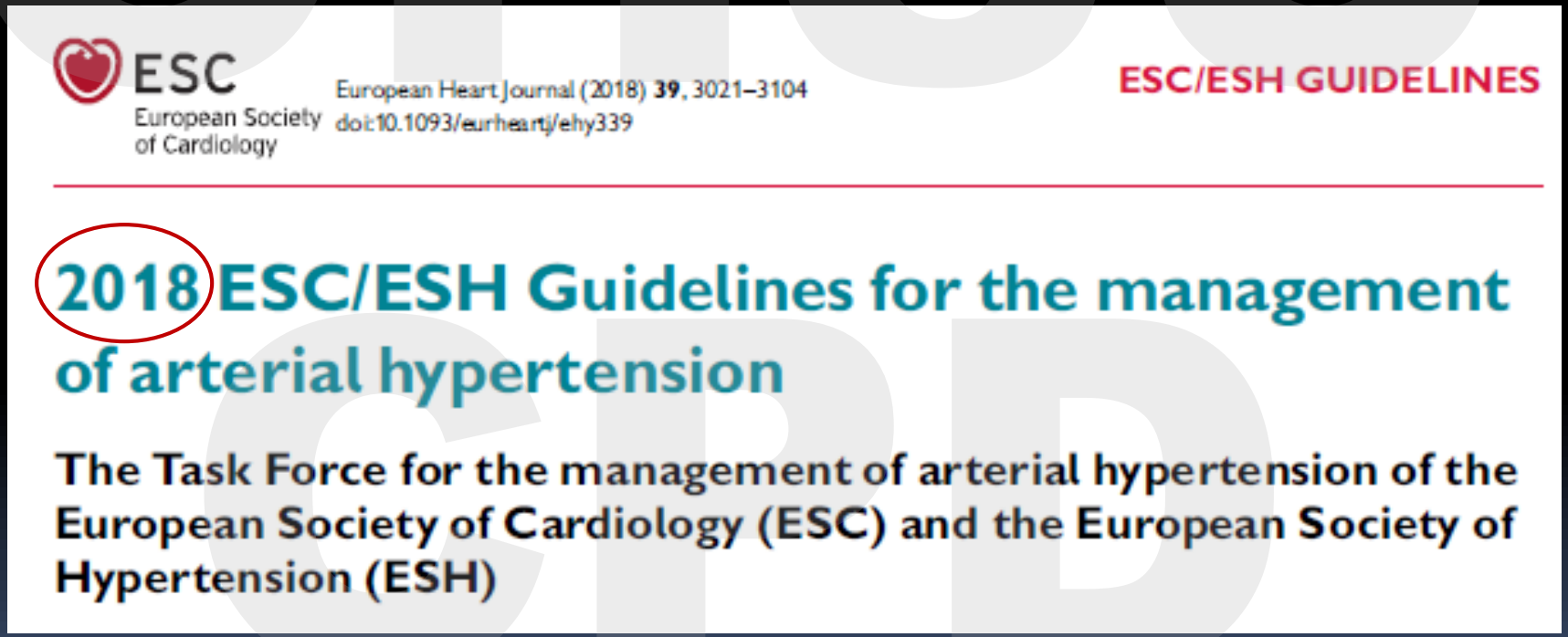
Comparison of significant characteristics of recent, randomized trials of BP control

Characteristic	SPRINT	HOPE-3	SPS-3	ACCORD
Patients, n	9,361	12,705	3,020	4,733
Patients with macrovascular disease, %	17	0	100	33
Patients with DM, %	0	6[b]	36	100
Average f/u (yrs)	3.3[a]	5.6	3.7	4.7
BP (mm Hg) goals	SBP < 120 vs. < 140	Not a trial of BP goals[c]	SBP < 130 vs. 130-139	SBP < 120 vs. < 140
Difference in BP between groups, SBP/DBP (mm Hg)	13.1/NR[d]	6/3[d]	11/NR[d]	14.2/6.1[e]
Annualized rate of CV death, MI, stroke; intense vs. standard BP goals (%)	1.3 vs. 1.7	0.7 vs. 0.8	3.5 vs. 4.1	1.9 vs. 2.1
Number of macrovascular events[d]	562	640	348	445
RRR for macrovascular events %, (95% CI)	25 (11 to 36)	5 (-11 to 19)	16 (-4 to 32)	12 (-6 to 27)

So, while notable that all trials had reductions in major CVD events with tight BP control, SPRINT stood out as different



As the debates continued in the U.S., the joint ESC/ESH guidelines was released in 2018…



2018 ESC guidelines made some important points regarding NOT endorsing <130/80 mmHg as a goal..

7.2.4 Initiation of blood pressure-lowering drug treatment in patients with high–normal blood pressure

The previous (2013) Guidelines[17] recommended not to initiate anti-hypertensive treatment in people with high–normal BP and low–moderate CV risk. This recommendation is further supported by new evidence:

(1) In all RCTs (including SPRINT)[51] and meta-analyses[2] that have reported reduced major outcomes by lowering 'baseline' BP in the high–normal range, the 'baseline' BP was commonly measured on a background of antihypertensive treatment. Therefore, these studies do not provide evidence to support treatment initiation in patients without hypertension.[8]

Why New Blood Pressure Guidelines Could Lead to Harm

By Aaron E. Carroll
Dec. 18, 2017

NYTimes, December 2017

….the fact that those in the intensive therapy group also had more adverse events, like hypotension, syncope and acute kidney injury, got less attention.

….pay attention to the details…..To be eligible for this study, in addition to having a systolic blood pressure from 130 to 180, patients had to be at particularly high risk of disease: subclinical cardiovascular disease, chronic kidney disease or a Framingham 10-year risk of cardiovascular disease of 15 percent or more. Or they had to be 75 years or older.

They also had to have their blood pressure confirmed in three separate readings in which patients were left alone in a room for five minutes.

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

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 (%)			
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

So no free lunch when it comes to intensifying pharmacotherapy. ESC guidelines….

geted to lower BP values.[227] Therefore, advocating more intensive BP-lowering targets for all has to be viewed in the context of an increased risk of treatment discontinuation due to adverse events, which might offset, in part or completely, the limited incremental reduction in CV risk.

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visits. Dose adjustment was based on a mean of three blood-pressure measurements at an office visit while the patient was seated and after 5 minutes of quiet rest; the measurements were made with the use of an automated measurement system (Model 907, Omron Healthcare). Lifestyle

The 2018 ESC guidelines make the point well:

patients. However, this RCT does not clarify the optimal BP target because the method used for office BP measurement in SPRINT (unattended automatic measurement) had not been used in any previous RCTs that provide the evidence base for the treatment of hypertension.[225] This is because unattended automated office BP measurement results in lower BP values, relative to conventional

Using the SPRINT data itself…..

JAMA IM, October 2020

JAMA Internal Medicine | Original Investigation

Concordance Between Blood Pressure in the Systolic Blood Pressure Intervention Trial and in Routine Clinical Practice

Paul E. Drawz, MD, MHS, MS; Anil Agarwal, MD; Jamie P. Dwyer, MD; Edward Horwitz, MD; James Lash, MD;

OBJECTIVES To evaluate the concordance between BPs obtained in routine clinical practice and those obtained using the SPRINT protocol and whether concordance varied by target trial BP.

CONCLUSIONS AND RELEVANCE Outpatient BPs measured in routine clinical practice were generally higher than BP measurements taken in SPRINT, with greater mean SBP differences apparent in the intensive treatment group. There was a consistent high degree of

"…outpatient BPs measure…..were higher than BP measurements taken in SPRINT…"

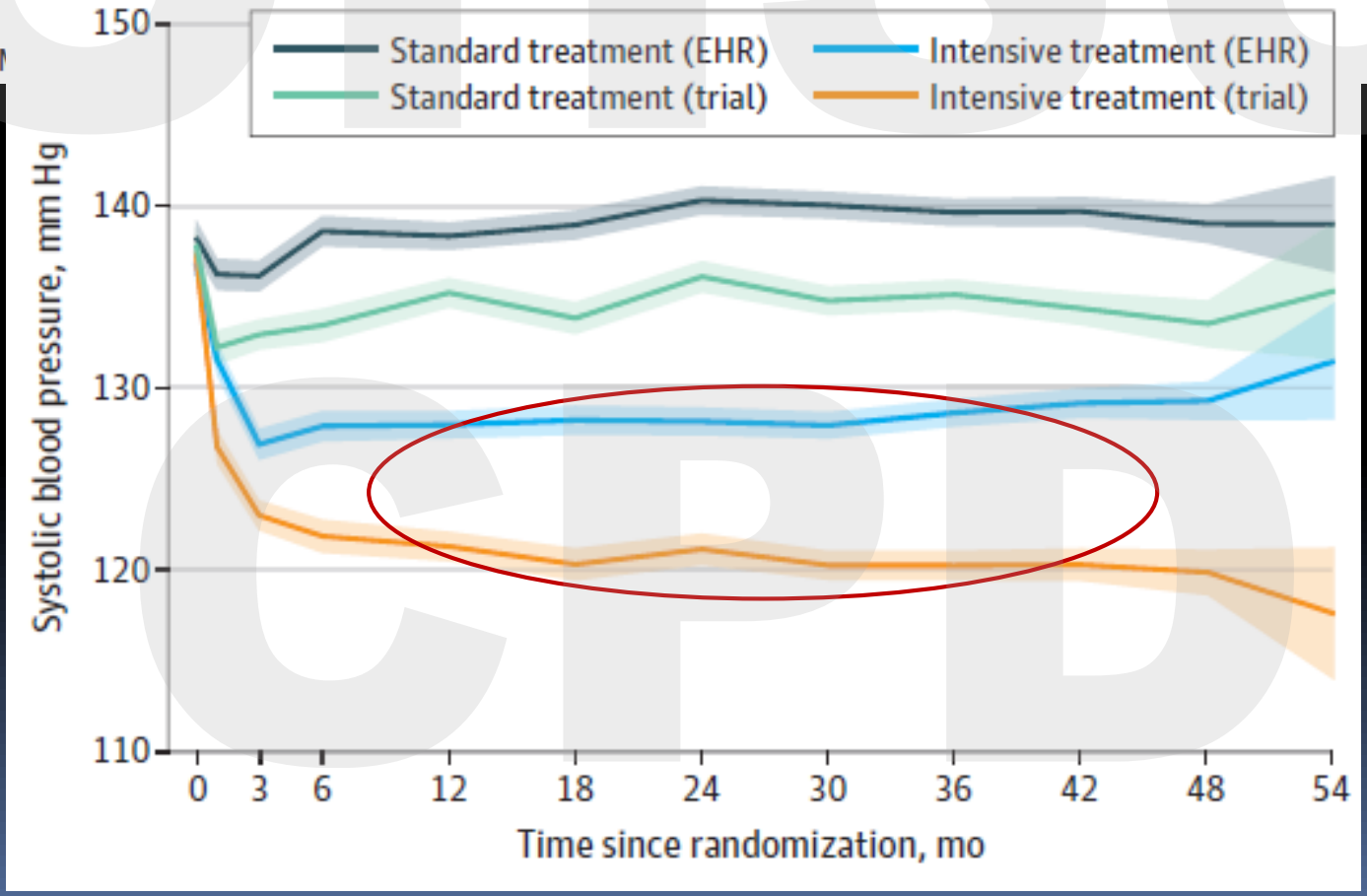
JAMA IM, October 2020

JAMA Internal M

Concorda ressure
Interventi

Paul E. Drawz, MD, M

Figure 2. Systolic Blood Pressure During Follow-up: Trial Measurements vs Outpatient Blood Pressures Extracted From the Electronic Health Record (EHR)



Approaching 10 mmHg different for most of the trial….

J Am Heart Assoc.; 2017

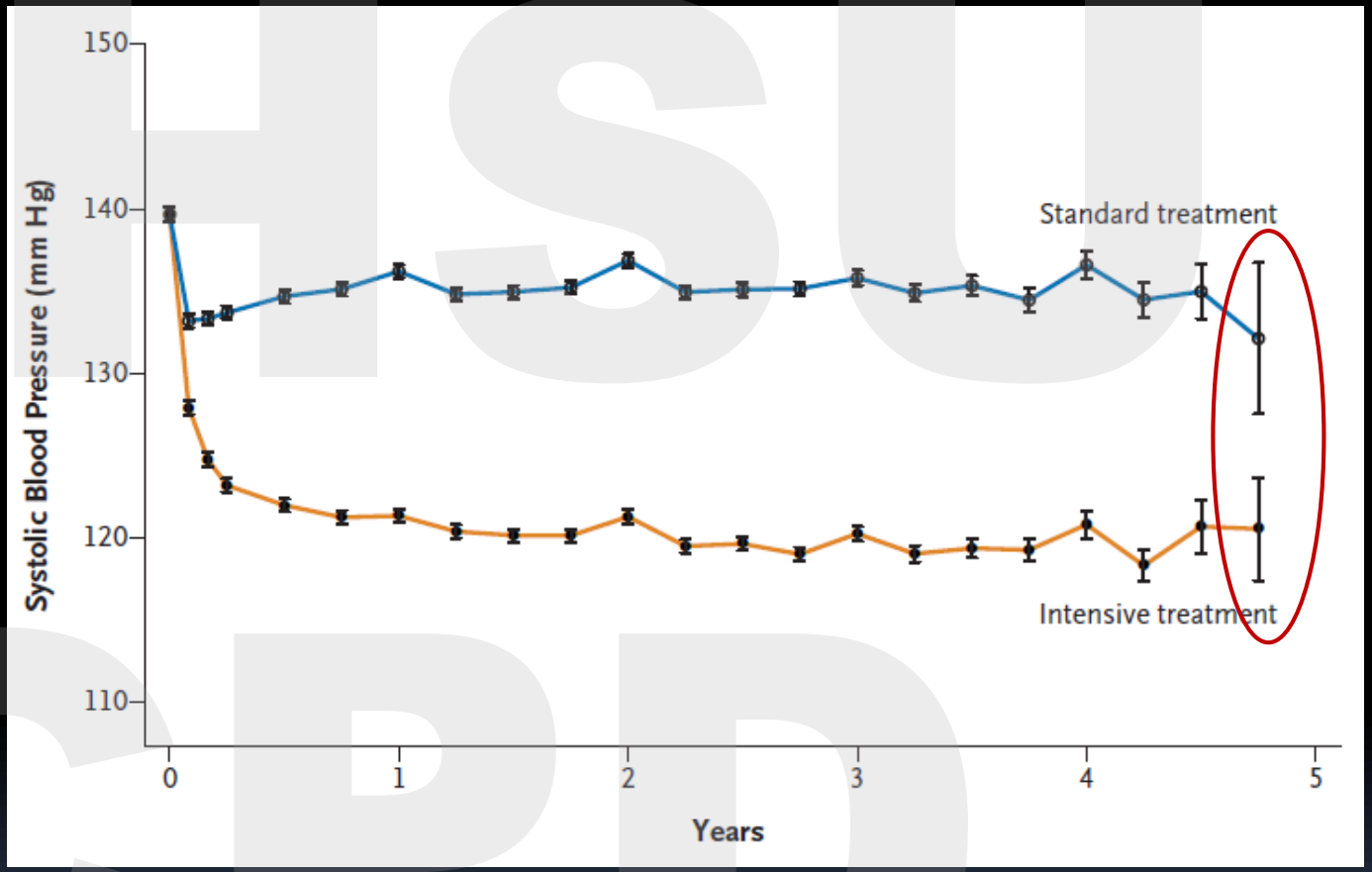
Implications of Blood Pressure Measurement Technique for Implementation of Systolic Blood Pressure Intervention Trial (SPRINT)

Rajiv Agarwal, MD

Methods and Results—Among 275 people with chronic kidney disease who had BP <140/90 mm Hg when they came to the clinic, we measured BP as in SPRINT and recorded BP on the same day without specification of seated rest. Compared with routine measurement, the research-grade systolic BP was 12.7 mm Hg lower with wide limits of agreement (−46.1 to 20.7 mm Hg). Research grade systolic BP was 7.9 mm Hg lower than daytime ambulatory systolic BP and had wide agreement limits (−33.2 to

Among 275 patients enrolled with BP < 140/90 mmHg, the SPRINT method of BP measurement compared to “routine” office measurement produced SBP value 12.7 mmHg lower than routine office measurement and 7.9 mmHg lower than even ambulatory home BP monitoring

As a reminder, the average baseline BP value in SPRINT was 139/78 mmHg and the on-treatment SBP values were 136 and 121 mmHg



So, if SPRINT has used more conventional office-based measurements, SPRINT likely would have been a trial of baseline SBP > 140 mmHg (maybe even closer to 150 mmHg) with control to SBP < 140 mmHg

But lets not let the perfect (or perceived perfect) be the enemy of the good.

Focus attention where there is broad consensus: < 140 mmHg SBP

ESC guideline: Less than half of treated patients with HTN achieve the <140/90 mmHg target

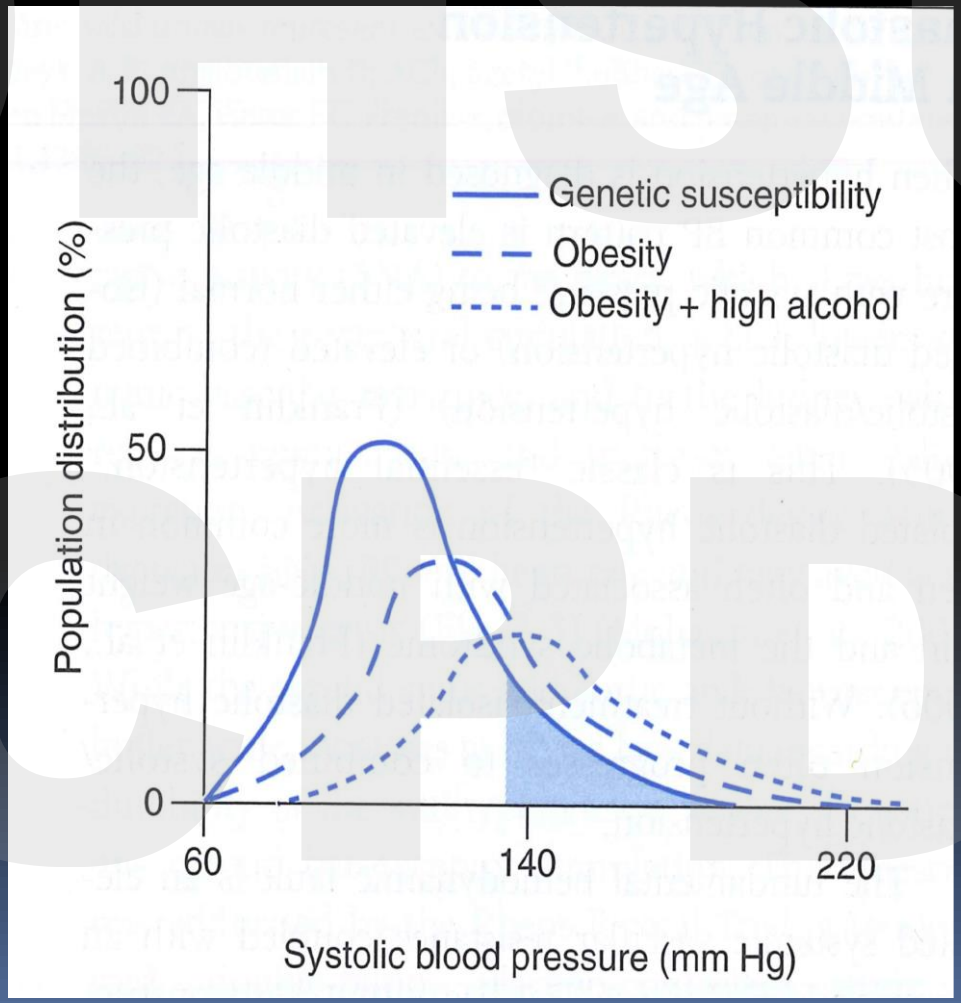
Whilst considering BP targets, it is important to acknowledge that <50% of patients treated for hypertension currently achieve a target office SBP of <140 mmHg.[11,12] This is a major missed opportunity for CVD prevention in millions of people across the world.

This Task Force recommends that when BP-lowering drugs are used, the first objective should be to lower BP to <140/90 mmHg in all patients. Provided that the treatment is well tolerated, treated BP

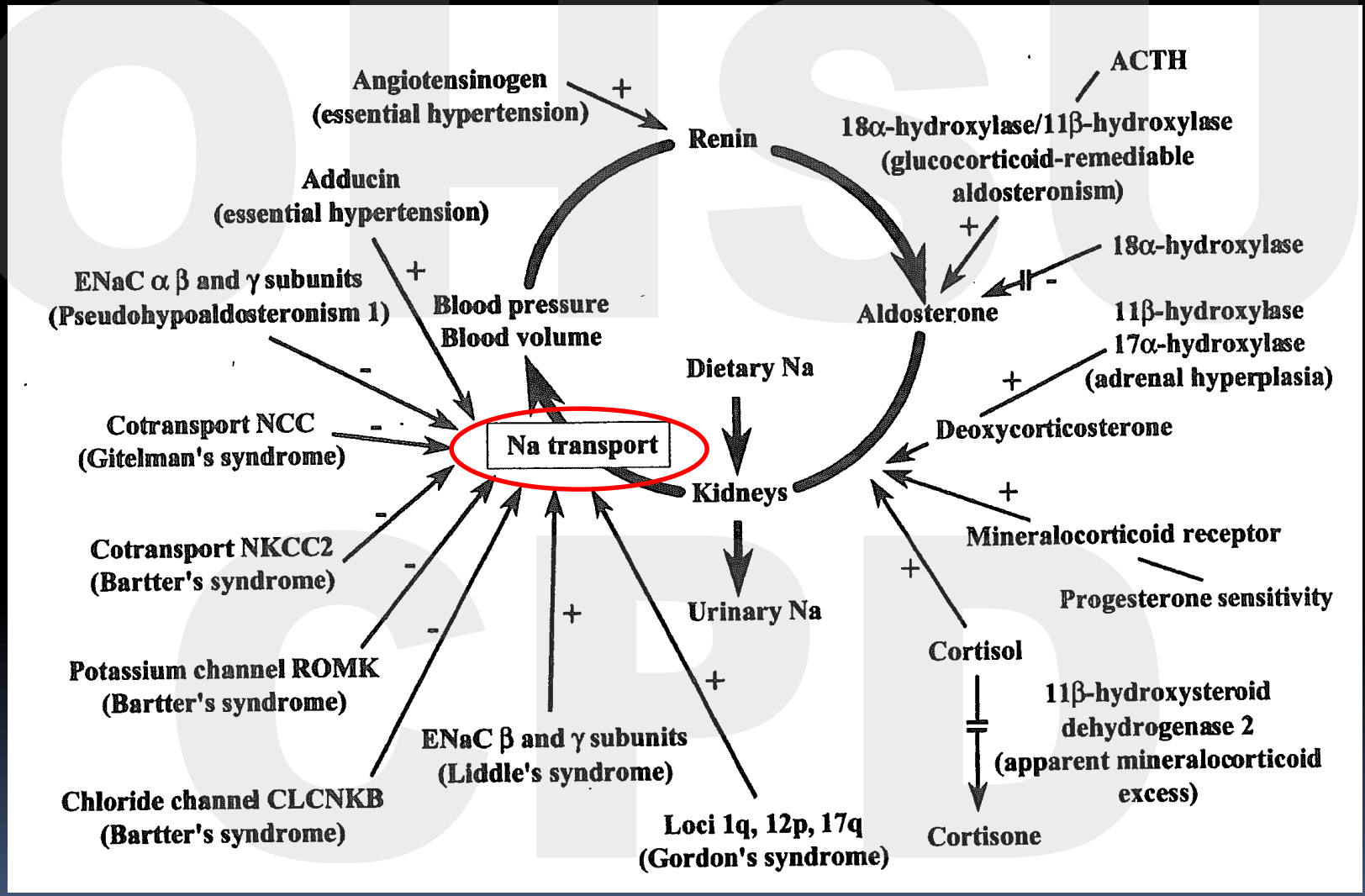
Achieving < 140 mmHg in everyone with HTN is no small charge since the etiology of elevated BP varies and the optimal therapy to achieve BP lowering and minimize ADRs is not always apparent

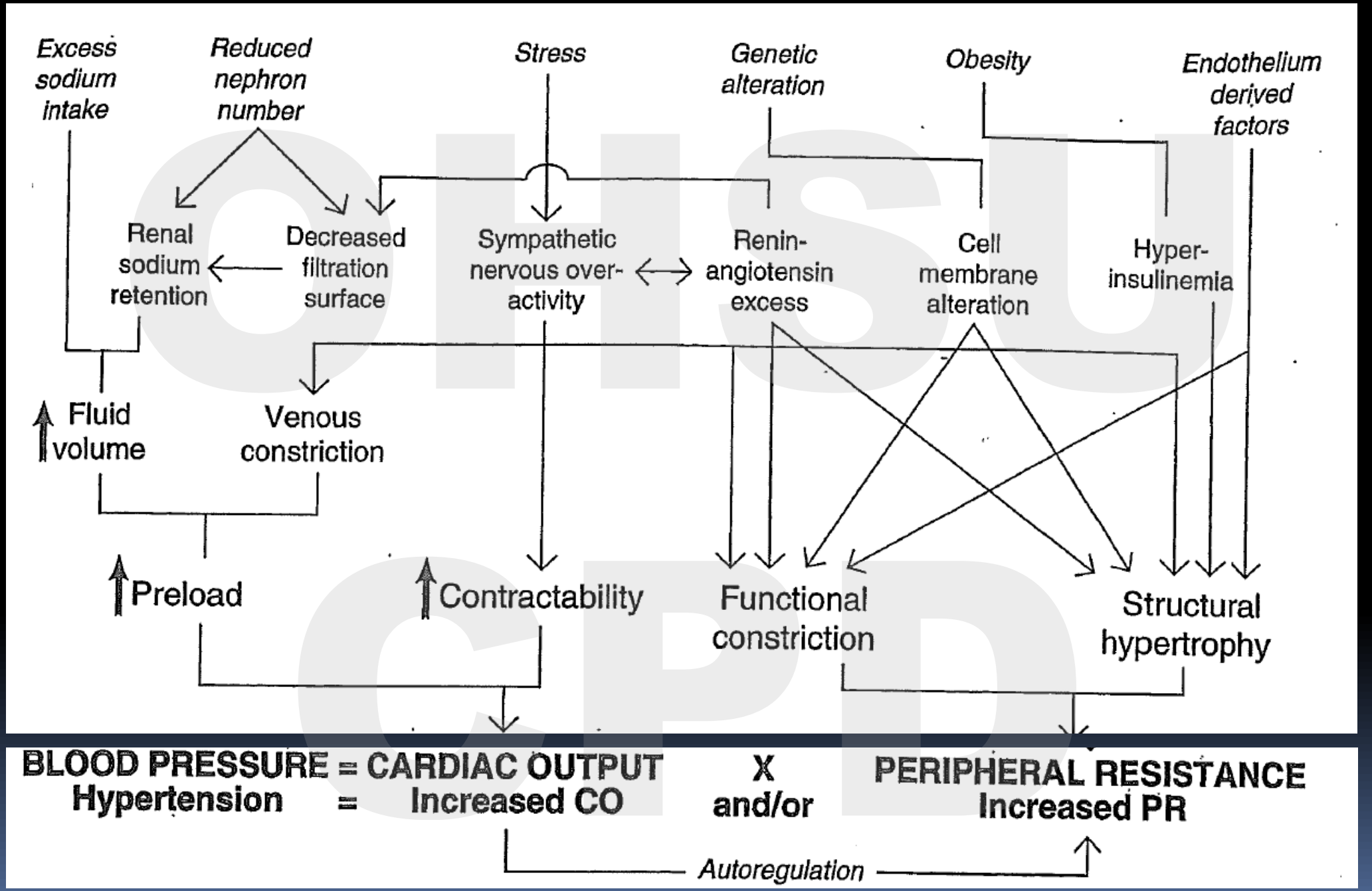
Blood pressure has a bell curve distribution in a healthy population dictated largely by genetics. But nurture matters…

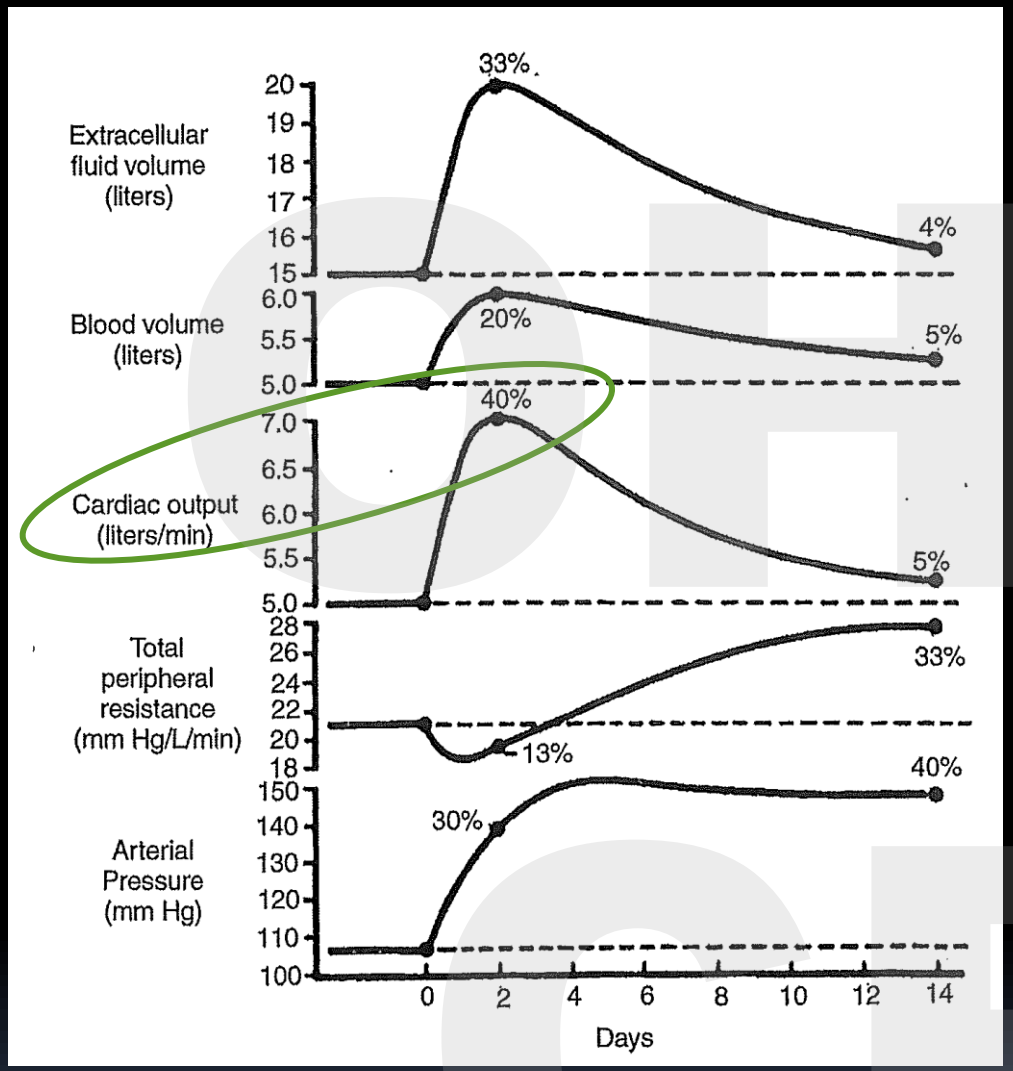
Add some risk factors and the whole curve "shifts to the right"



Nature: most all of the genetic contribution to hypertension involves sodium handling




Excess sodium intake
Reduced nephron number
Stress
Genetic alteration
Obesity
Endothelium derived factors
Renal sodium retention
Decreased filtration surface
Sympathetic nervous over-activity
Renin-angiotensin excess
Cell membrane alteration
Hyper-insulinemia
Fluid volume
Venous constriction
Preload
Contractability
Functional constriction
Structural hypertrophy
BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE
Hypertension = Increased CO and/or Increased PR
Autoregulation

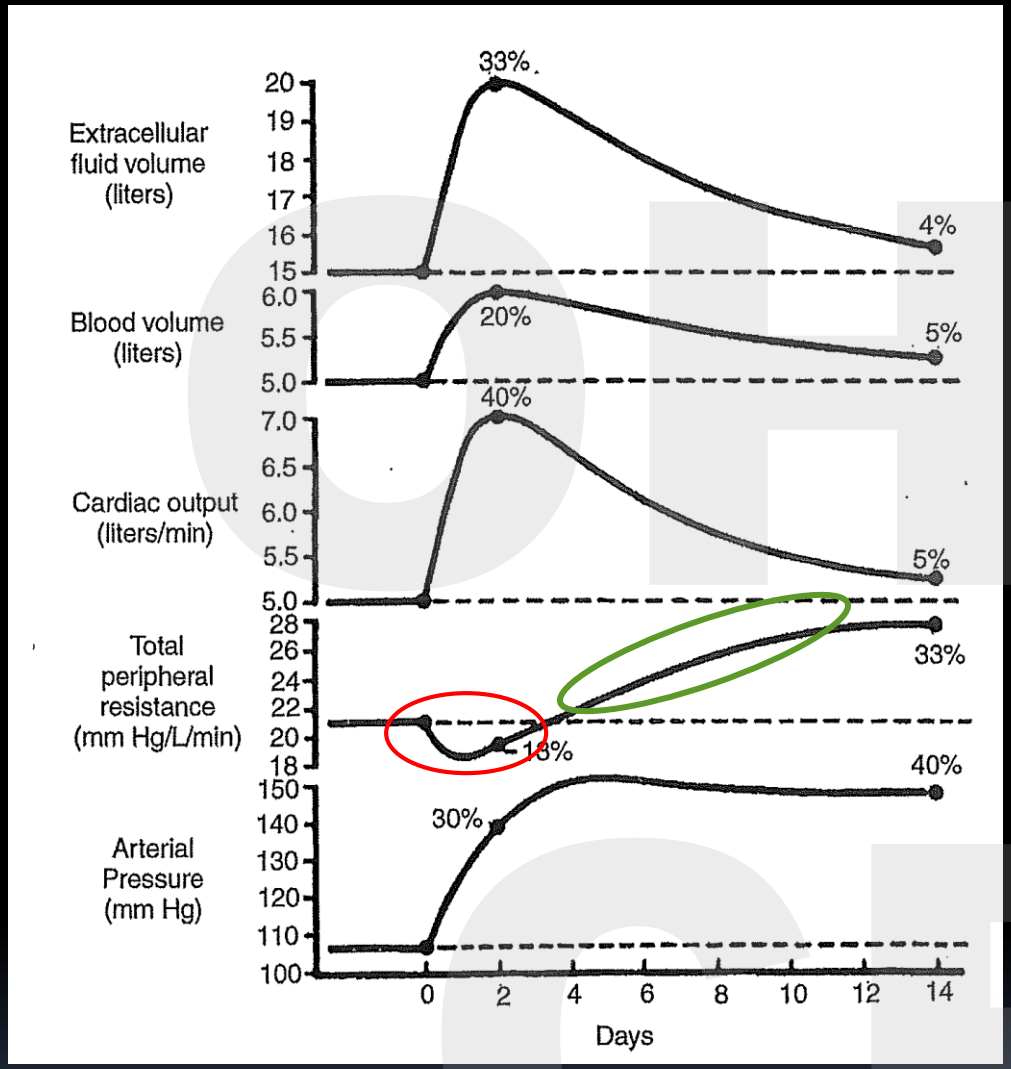


If you volume load individuals and increase C.O.

BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE

Hypertension = Increased CO and/or Increased PR

Autoregulation

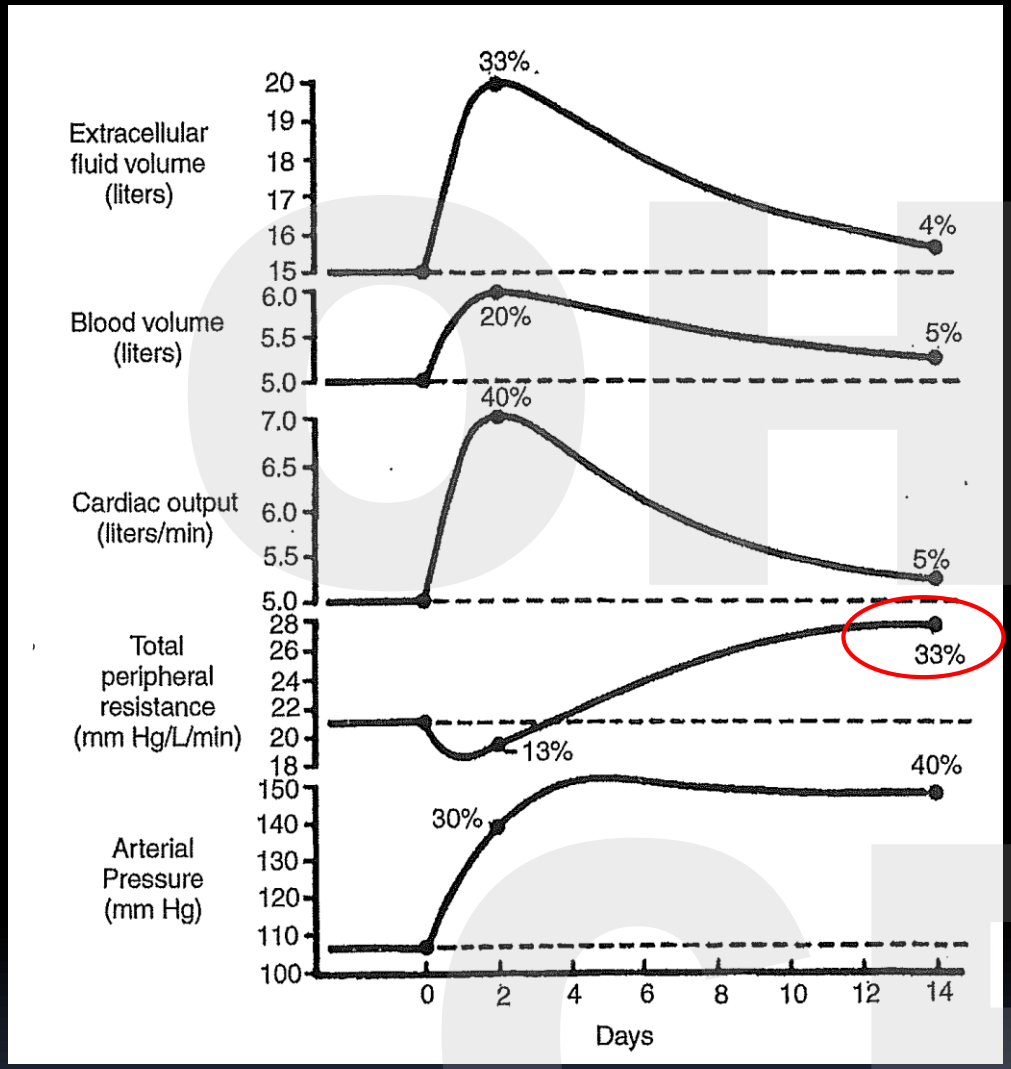


You quickly see a reduction in vascular resistance (red circle) followed by a sustained rise (green oval) that returns C.O. to normal. However the vascular resistance remains elevated and contributes to a sustained rise in B.P.

BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE

Hypertension = Increased CO and/or Increased PR

Autoregulation



We know that what drives long-term HTN is increased PVR resulting from excess vascular volume due to sodium consumption and retention. But the mechanistic pathway to that elevated PVR (high RAAS, low RAAS, autonomic variation, Ca^{++} mediated contraction of vascular smooth muscle, etc.) varies

And so drug response varies….

BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE
Hypertension = Increased CO and/or Increased PR

Autoregulation

JAMA | Original Investigation

Heterogeneity in Blood Pressure Response to 4 Antihypertensive Drugs
A Randomized Clinical Trial

April, 2023

Johan Sundström, MD, PhD; Lars Lind, MD, PhD; Shamim Nowrouzi, MD; Emil Hagström, MD, PhD;

1,468 individuals with BP > 140 mmHg SBP (ave. 150/87 mmHg) and low CVD risk completed a cross-over of four different classes of BP-lowering medications (lisinopril, candesartan, HCTZ, amlodipine)

RESULTS There were 1468 completed treatment periods (median length, 56 days) recorded in 270 of the 280 randomized participants (54% men; mean age, 64 years). The blood pressure response to different treatments varied considerably between individuals ($P < .001$), specifically for the choices of lisinopril vs hydrochlorothiazide, lisinopril vs amlodipine, candesartan vs hydrochlorothiazide, and candesartan vs amlodipine. Large differences were excluded for the choices of lisinopril vs candesartan and hydrochlorothiazide vs amlodipine. On average, personalized treatment had the potential to provide an additional 4.4 mm Hg–lower systolic blood pressure.

Optimizing best drug provided additional 4.4 mmHg lowering

"Personalizing" BP meds is not a new concept. While difficult to operationalize, maybe worth considering with more elevated presenting BP

ARTICLES

Optimisation of antihypertensive treatment by crossover rotation of four major classes

Lancet, 1999

56 patients with baseline BP 161/98 crossed over 4 major drug classes (ACEi, CCB, diuretic, β-blocker)

Target (mm Hg)	Number achieving target on first drug	Number achieving target on any drug
<160/90 (BHS)	36 (64%)	49 (88%)*
<140/90 (JNCVI)	22 (39%)	41 (73%)†
⩽135/85 ("normal")	11 (20%)	28 (50%)†

So, while not practical to rotate patients through multiple BP-lowering drugs classes to find best agent, an unexpectedly poor response to a first agent should maybe be followed by a switch rather than addition

EDITORIAL

JAMA, 2023;329(14):1153-4

Is Personalized Antihypertensive Drug Selection Feasible?

Robert M. Carey, MD

So , where does all this all leave us?

Comparison of significant characteristics of recent, randomized trials of BP control

Characteristic	SPRINT	HOPE-3	SPS-3	ACCORD
Patients, n	9,361	12,705	3,020	4,733
Patients with macrovascular disease, %	17	0	100	33
Number of macrovascular events[d]	562	640	348	445
RRR for macrovascular events %, (95% CI)	25 (11 to 36)	5 (-11 to 19)	16 (-4 to 32)	12 (-6 to 27)

While SPRINT was the only trial that showed statistical significance, all trials showed a trend for benefit with tighter BP control

And a close analysis of SPRINT vs. ACCORD even reveals statistical overlap

The 95% CI for benefit actually overlap in the trials but the larger size of SPRINT (9,361) allowed greater statistical power compared to ACCORD (4,733)

	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20

12% RRR in ACCORD

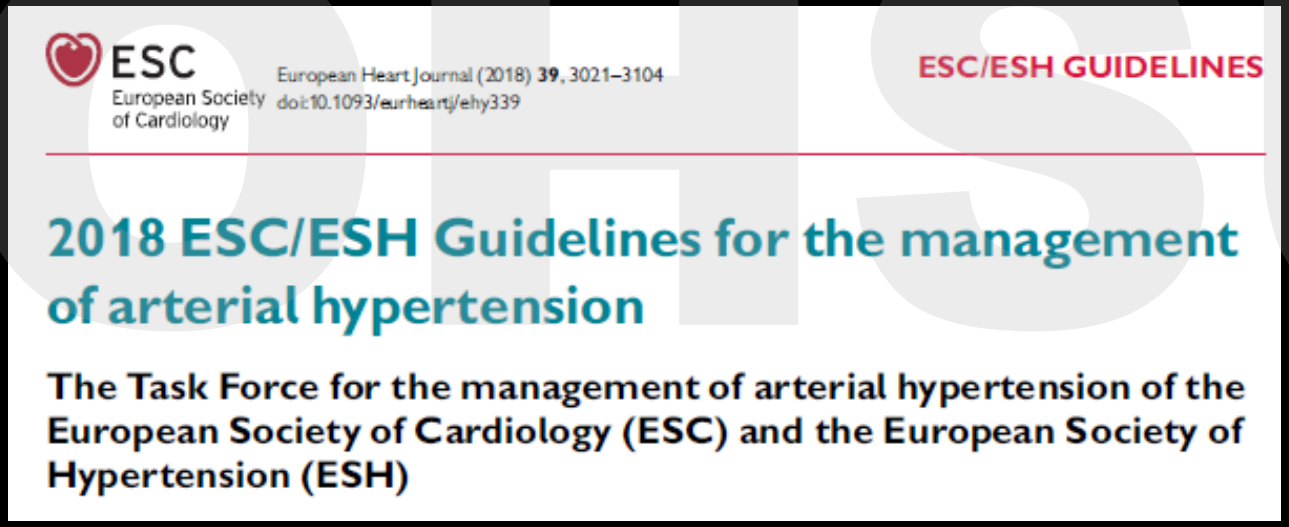
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001

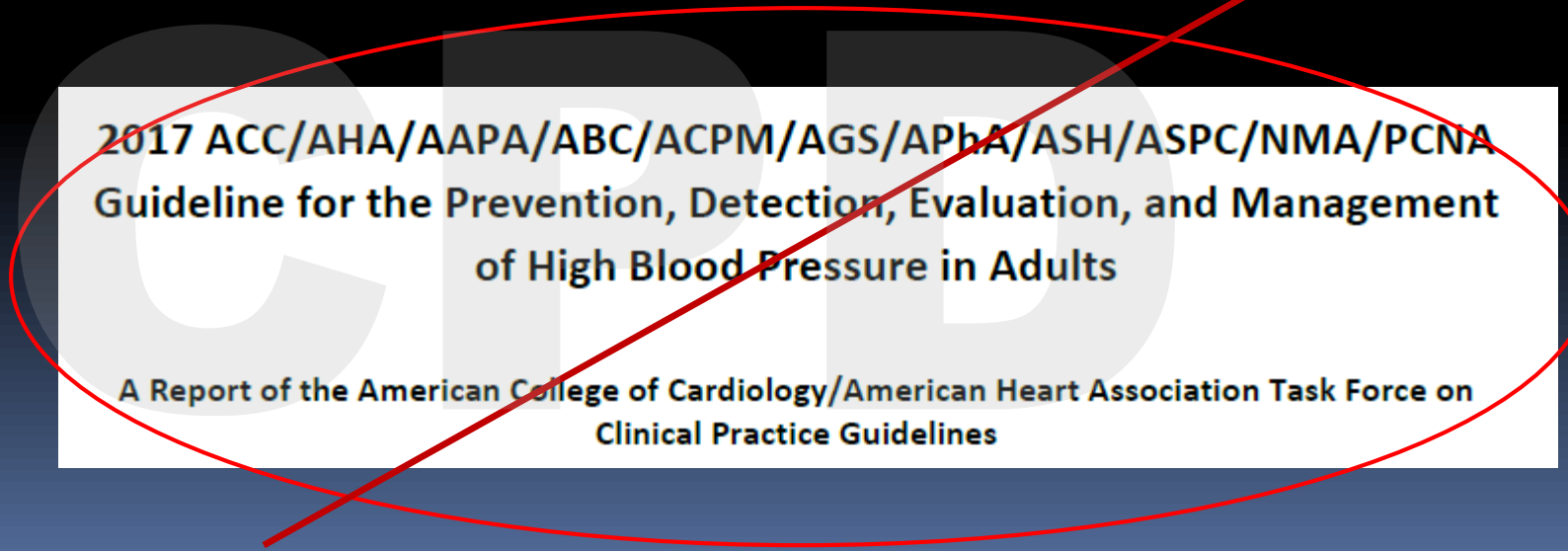
25% RRR in SPRINT

So, we should admit that “tight” control of BP to < 130 mmHg likely does have small benefits in high risk patients….but < 130 mmHg is NOT an appropriate universal goal and is even questionable in high risk patients because:

1. Lack of statistical benefit in ACCORD in a population of high risk diabetic patients as well as multiple other, randomized trials and….
2. Method of BP measurement in SPRINT really does make that trial of questionable relevance to routine, primary practice

Bottom line: For our Primary Practices, Europe wins the HTN Ryder Cup (golf reference)





Conclusions:

- Guidelines are now hyper evidence-based which makes careful interpretation of clinical trials critical
- One trial, SPRINT, weighed too heavy on the ACC/AHA guidelines and used a method of BP-measurement that probably falsely lowered the entry and on-treatment BPs that were studied
- While increased peripheral resistance is a shared mechanism of most HTN, individual mechanisms vary and individual response is meaningfully different across the major classes of BP-lowering agents.
- <140/90 mmHg can be agreed on as a universal target. Additional lowering to < 130/80 may have small additional benefits but comes with increased ADRs and should not be generally recommended at this time