HYPERTENSION GUIDELINES: WHERE ARE WE NOW?

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DISCLOSURES

- I have no relevant relationships to disclose
- Other relationships:
- Advisor to the Centers for Disease Prevention and Control
- Advisor to the Pan American Health Organization

HYPERTENSION GUIDELINES: Questions to consider

- What are the major changes in the new guidelines?
- What is the evidence behind the guidelines?
- What are the major implications of the new guidelines?
- Should the new guidelines be adopted? All, in part, not at all?

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WHERE ARE WE NOW AND HOW DID WE GET HERE?

OR

You can see a lot by just looking! (Yogi Berra)

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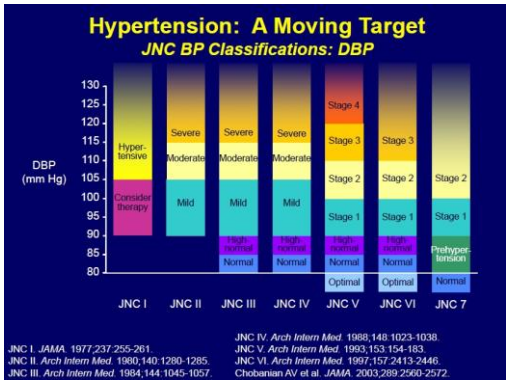
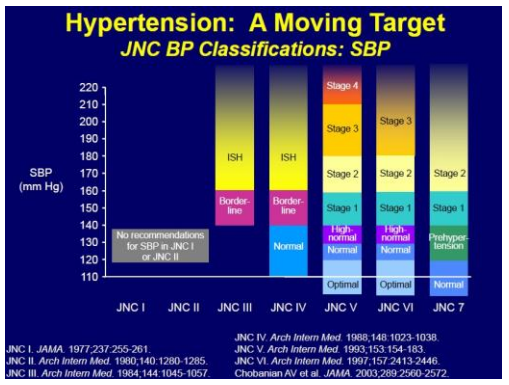
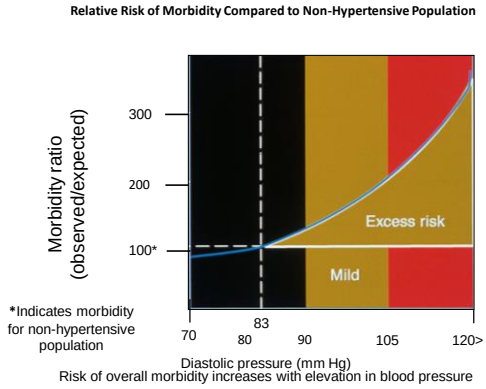




Question: What is the appropriate BP treatment threshold and target goal?

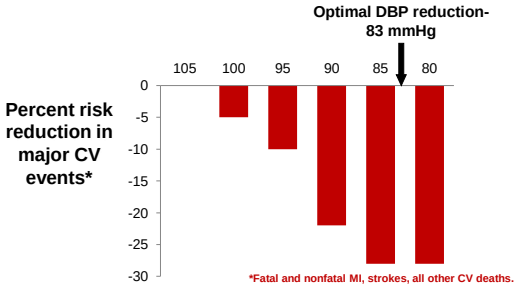
It is important to consider **two groups**:

- The general population younger than 60-65 years of age.
- Those 60-65 years and older, at high cardiovascular risk, or with diabetes, or with chronic kidney disease.



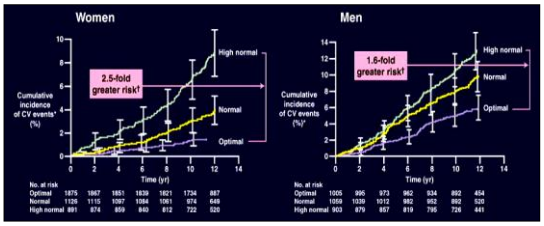
Risk of overall morbidity increases with elevation in blood pressure

HOT Study: Risk of a Major CV Event Reduced by 30% (DBP)



Hansson L et al. *Lancet.* 1998;351:1755-1762

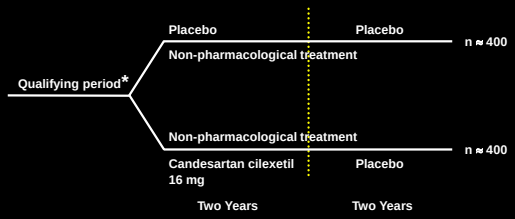
Framingham Heart Study "High-normal" BP Is Not Benign



*CV death, MI, stroke, CHF
†Adjusted for concomitant CV risk factors
Optimal = <120/<80 mmHg
Normal = 120–129/80–84 mmHg
High normal = 130–139/84–89 mmHg

Vasan RS et al. *N Engl J Med.* 2001;345:1291–1297.

TROPHY – study design



*Clinic BP reading of 130-139/≤ 89 mm Hg or ≤ 139/85-89 mm Hg

Julius et al, Hypertension 2004

TROPHY: Risk of hypertension after two years with candesartan vs placebo, followed by two years of placebo vs placebo

Time point	Candesartan, n	Placebo, n	Relative risk (95% CI)	p
At two 2 years	53	154	66.3	<0.001
At four 4 years	208	240	15.6	<0.007

Julius S et al. *N Engl J Med* 2006;available at http://www.nejm.org

Treatment of Mild Hypertension Study (TOMHS): JAMA 1993

- 6 groups of patients with baseline DBP <100 mmHg were studied for five years:
- 1 group: placebo plus intensive life-style modification (sodium reduction, smoking cessation, and exercise)
- 5 groups: intensive life-style modification plus either
  - Chlorthalidone: thiazide diuretic
  - Acebutolol: beta blocker with intrinsic sympathomimetic activity
  - Doxazosin: alpha blocker
  - Amlodipine: calcium channel blocker
  - Enalapril: angiotensin converting enzyme inhibitor

Treatment of Mild Hypertension Study: Results

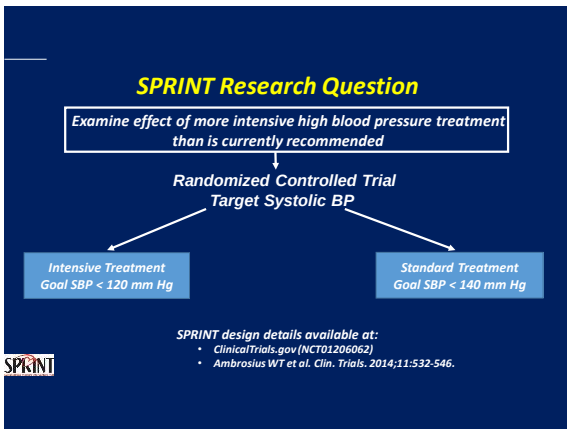
- SBP: significantly less in drug treatment groups vs placebo group (-15.9 vs -9.1 mmHg)
- DBP: significantly less in drug treatment groups vs placebo group (-12.3 vs -8.6 mmHg)
- No difference in either SBP or DBP reduction between drug treatment groups
- Clinical events: significantly less in drug treatment groups vs placebo group (-11.1 vs 16.2 %; p=0.03

JNC-7 Report (2003): BP treatment threshold and target goal?

- In the general population at any age, the treatment threshold is 140/90 mmHg and the target is <140/90 mmHg.
- In those with diabetes or chronic kidney disease, the treatment threshold is 140/90 mmHg and the target is <130/80 mmHg.
- **Cardiovascular risk was not specifically addressed.**

JNC-8 Committee (2013): BP treatment threshold and target goal?

- In the general population younger than 60 years of age, and those with diabetes or chronic kidney disease, the treatment threshold is 140/90 mmHg and the target is <140/90 mmHg.
- In those 60 years of age or older, the treatment threshold is 150/90 mmHg and the target is <150/90 mmHg. **Cardiovascular risk not specifically addressed.**
- What happened between **JNC-7** and the **JNC-8** report? **Greater use of evidence-based medicine**.



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/1.73m²
  - Framingham Risk Score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years

At least one

SPRINT

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/1.73m² (MDRD)
- Adherence concerns

SPRINT

Demographic and Baseline Characteristics

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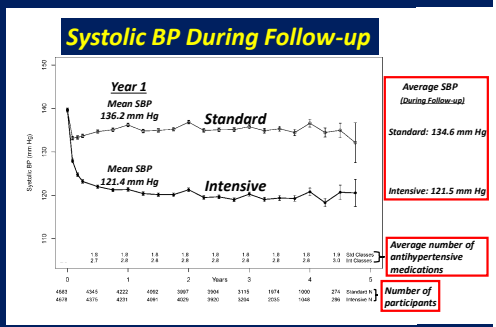
	Total N=9361	Intensive N=4678	Standard N=4683
Mean (SD) age, years	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)
% ≥75 years	28.2%	28.2%	28.2%
Female, %	35.6%	36.0%	35.2%
White, %	57.7%	57.7%	57.7%
African-American, %	29.9%	29.5%	30.4%
Hispanic, %	10.5%	10.8%	10.3%
Prior CVD, %	20.1%	20.1%	20.0%
Mean 10-year Framingham 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)

Systolic BP During Follow-up



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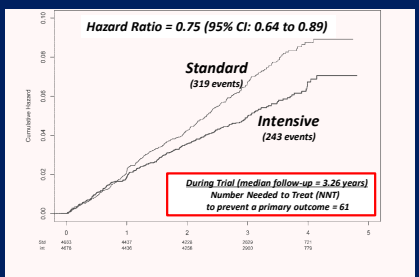
SPRINT Primary Outcome Cumulative Hazard



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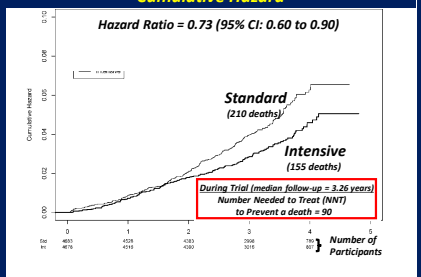
All-cause Mortality Cumulative Hazard



SPRINT

SPRINT Primary Outcome and its Components
Event Rates and Hazard Ratios

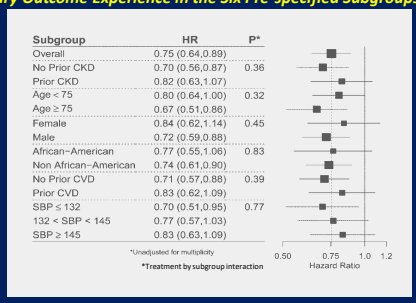
	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	HR (95% CI)	P value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38, 0.85)	0.005

Serious Adverse Events* (SAE) During Follow-up

	Number (%) of Participants		
	Intensive	Standard	HR (P Value)
All SAE reports	1793 (38.3)	1736 (37.1)	1.04 (0.25)
SAEs associated with Specific Conditions of Interest			
Hypotension	110 (2.4)	66 (1.4)	1.67 (0.001)
Syncope	107 (2.3)	80 (1.7)	1.33 (0.05)
Injurious fall	105 (2.2)	110 (2.3)	0.95 (0.71)
Bradycardia	87 (1.9)	73 (1.6)	1.19 (0.28)
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35 (0.020)
Acute kidney injury or acute renal failure	193 (4.1)	117 (2.5)	1.66 (<0.001)

*Fatal or life threatening event, resulting in significant or persistent disability, requiring or prolonging hospitalization, or judged important medical event.

Primary Outcome Experience in the Six Pre-specified Subgroups of Interest



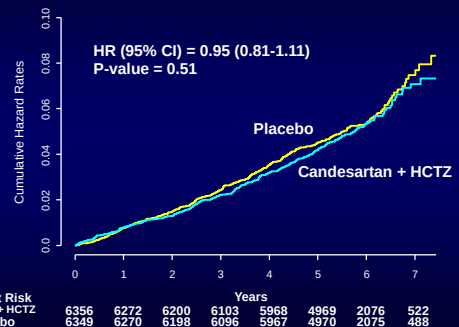
SPRINT: Clinically Important Caveats

- Intensive clinical research setting with close monitoring.
- Adherent, already under treatment (90%-2 drugs), older (68 years), high cardiovascular risk patient population (20%).
- Intensive BP group: 3 agents and greater use of diuretics and RAAS inhibitors (event reduction largely heart failure).
- Relative risk reduction was only 0.5%.
- BPs determined by an automated device, mostly non-observed in a quiet room after 5 minutes of rest
- This methodology **COULD** result in a SBP 10-12 mmHg **LOWER** than BP measurements in clinical practice and previous landmark hypertension trials.

Unique Aspects of HOPE-3

- Intermediate CV risk individuals without CVD
- Placebo controlled
- BP lowering trial with wide range of BP entry criteria
- Cholesterol lowering treatment based on risk opposed to baseline LDL or HDL measurement
- Diverse population

CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure



Prespecified Subgroups: By Thirds of SBP

CV Death, MI, Stroke, Cardiac Arrest, Revasc, HF

Cutoffs	SBP Mean	Diff	Placebo Event Rate%	HR (95% CI)	P Trend
≤131.5	122	6.1	3.5	1.25 (0.92-1.70)	0.009
131.6-143.5	138	5.6	4.6	1.02 (0.77-1.34)	
>143.5	154	5.8	7.5	0.76 (0.60-0.96)	

0.5 1.0 2.0

Candesartan + HCTZ Better Placebo Better

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BP Lowering Arm: Conclusions

- Fixed dose combination of Candesartan 16 mg + HCTZ 12.5 mg/day reduced BP by 6.0/3.0 mmHg, but did not reduce CV events
- CV events were significantly reduced in the highest third of SBP >143.5 mmHg
- Results were neutral in the middle third, and trended towards harm in the lowest third of SBP
- Results differ from recent meta-analysis showing continuous decrease in CV risk and total mortality to SBP 120-124 (Bundy JAMA Cardiology 2017)

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PATIENTS WITH HYPERTENSION AND DIABETES

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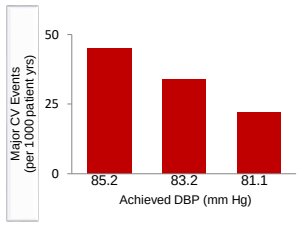
Benefits of BP Reduction in HOT: Diabetic Cohort

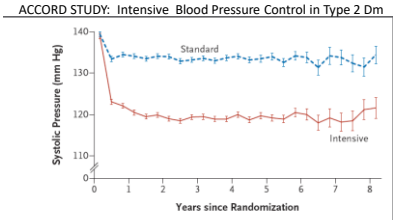
Target DBP (mm Hg)	Achieved SBP (mm Hg)	Achieved DBP (mm Hg)
≤90	143.7	85.2
≤85	141.4	83.2
≤80	139.7	81.1

Achieved = mean of all BPs from 6 months of follow-up to end of study



P = 0.05 for trend
Hansson L et al. *Lancet. 1998;351:1755-1762.*

ACCORD STUDY: Intensive Blood Pressure Control in Type 2 Dm



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.
I bars indicate 95% confidence intervals.

NEJM 2010; 362 (17); 1575

ACCORD STUDY: Intensive Blood Pressure Control in Type 2 Dm

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
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.
† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

NEJM 2010; 362 (17); 1575

ACCORDIAN Trial (2015): Follow-up to ACCORD

- ACCORD ended in 2009. About 4000 pts were still followed (87% of the total pts alive)
- Main result: Intensive BP reduction did not lower primary CV endpoints (similar to ACCORD) but **decrease in stroke now not seen**
- However, there was a **significant interaction between BP and glycemic control**
- In pts with standard BS control, intensive BP reduction **decreased CV events** (21%, p<0.08)

Interpreting the 2017 ACC/AHA Hypertension Guidelines for Clinical Practice

Goals of the Guidelines

- Evaluate potential benefit to home or ambulatory blood pressure monitoring
- **Identify the optimal target for blood pressure lowering among patients being treated for hypertension**
- Identify if differences in benefit and harm exist between different antihypertensive classes
- Identify if differences in benefit and harm exist between initiating treatment with monotherapy vs. dual-therapy

Whelton et al. *Hypertens.* 13 Nov 2017

Classification of Hypertension

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	**130–139 mm Hg**	or	**80–89 mm Hg**
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Whelton et al. *Hypertens.* 13 Nov 2017

Treatment of High Blood Pressure

- **Recommendation Stage 1 HTN:**
- Use **BP-lowering medications at** an average BP ≥130/80 mmHg in patients with CVD or in those with a 10-year ASCVD risk of ≥10%, with a BP target of <130/80 mmHg
- Use **life-style modification** in those without CVD and a 10-year ASCVD risk of <10%, with a BP target of <130/80 mmHg
  - *Strong recommendation (benefit >>> risk) based on randomized-control trial evidence for SBP and expert opinion for DBP*

Whelton et al. *Hypertens.* 13 Nov 2017

Treatment of High Blood Pressure

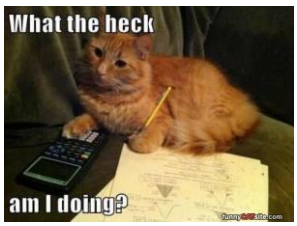
- **Recommendation Stage 2 HTN:**
- Use BP-lowering medications at a BP ≥140/90 mmHg
  - *Strong recommendation (benefit >>> risk) based on observational evidence*
- For these patients, a BP target of <130/80 mmHg may be reasonable
  - *Moderate recommendation (benefit > risk) based on observational evidence for SBP and expert opinion for DBP*

Whelton et al. *Hypertens.* 13 Nov 2017

Special Patient Groups: Older Patients

- **Recommendations:**
- In non-institutionalized ambulatory community-dwelling adults (≥65 years of age), initiate treatment for an SBP ≥ 130 mmHg with a treatment goal <130 mmHg
  - *Strong recommendation (benefit >>> risk) based on RCT evidence*
- For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, it is reasonable to use clinical judgement and patient preference
  - *Moderate recommendation (risk >> benefit) based on expert opinion*

Whelton et al. *Hypertens.* 13 Nov 2017



ACC/AHA 2017 guidelines: Broad U. S. implications (Bundy et al. JAMA Cardiology 2018)

- Compared to the 2014 guidelines, using 2016 NHANES data adopting the 2017 ACC/AHA guidelines will:
- **Increase** the prevalence of HTN (32% to 45.4%)
- **Increase** the number on drug Rx (31.1% to 35.9%)
- **Increase** hypotensive episodes by 62,000
- **Increase** AKI episodes by 79,000 **BUT**
- **Decrease** CV events by 340,000
- **Decrease** total deaths by 156,000
- **Mostly from those >60 years old, high CV risk, Dm, CKD**

ACC/AHA 2017 guidelines: Rapid Response

- **Multiple commentaries and editorials questioning mainly the new HTN classification, treatment thresholds, and targets**
- **American Academy of Family Physicians, American College of Physicians, the Latin American Societies, and the European Societies of Cardiology and Hypertension did not endorse the guidelines**

ECS/ESH Hypertension Guidelines 2018: Hypertension Classification and Treatment

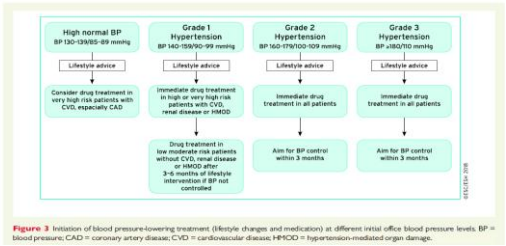


Figure 3 Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.

ACC/AHA Hypertension Guidelines: Population, Health System, and Practice Implications

- HTN prevalence increases and life-style modification (LSM) becomes a primary therapeutic modality.
- Given the difficulty with adherence to LSM and the lower treatment targets, an increase in the use of pharmacologic agents will likely occur.
- Significant changes in "in-office" BP measurement will be needed (SPRINT methodology).
- Out-of-office BPs (home and/or AMBP) required .

ACC/AHA Hypertension Guidelines Patient Implications

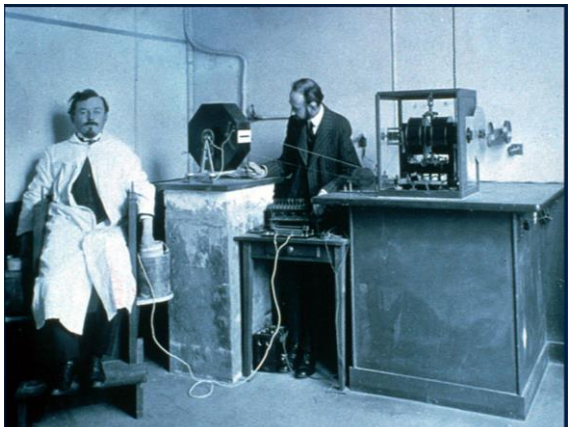
- Increase in provider and patient education.
- Life-style modification (LSM) is difficult and expensive.
- While fixed-dose combination may help, significant increase in medications and polypharmacy is likely.
- Patient adverse events are likely to increase.
- Added complexity of home and/or ambulatory blood pressure measurements.

ACC/AHA Hypertension Guidelines: Moving forward?

- ACC/AHA guidelines are highly dependent on the **SPRINT** results and observational evidence
- Perhaps we should **WALK** before we **SPRINT**
- Follow the debate or better yet, call for new clinical trial driven evidence **but implement what makes sense**

ACC/AHA Hypertension Guidelines: What should we consider to do?

- Continue treatment threshold and control levels at 140/90 mmHg and <140/90 mmHg in all ages.
- Consider <130/80 mmHg especially in those with high CV risk , Dm, or CKD.
- Aggressive life-style modification and proper office and out of office BPs.
- Use a standardized formulary and drug treatment algorithm, fixed-dose combination initial drug therapy, and team-based care.



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Thank You