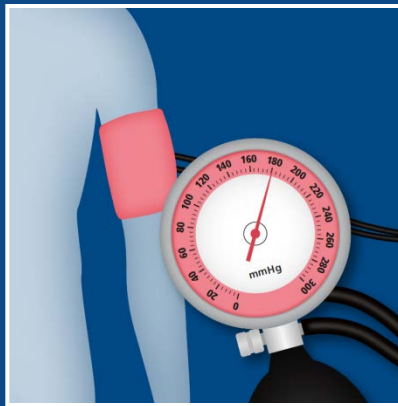


# Nephro Update Europe 2018

5-6 October, Budapest

## Hypertension



**Ton Rabelink, Netherlands**

# State of the Art

## Global Impact of an Elevated Blood Pressure



**In 2015, elevated systolic BP was the leading preventable cause of premature death globally**



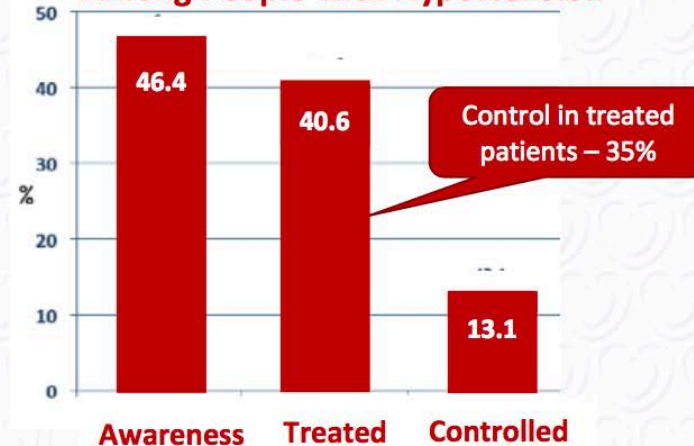
**10 million deaths**  
**Over 200 million adjusted life years disability**



**Ischemic Heart Disease: 4.9m**  
**Hemorrhagic Stroke: 2.0m**  
**Ischemic Stroke: 1.5m**

*Forouzanfar MH, et al JAMA 2017*

### Among People with Hypertension



*Chow C, et al JAMA 2013*

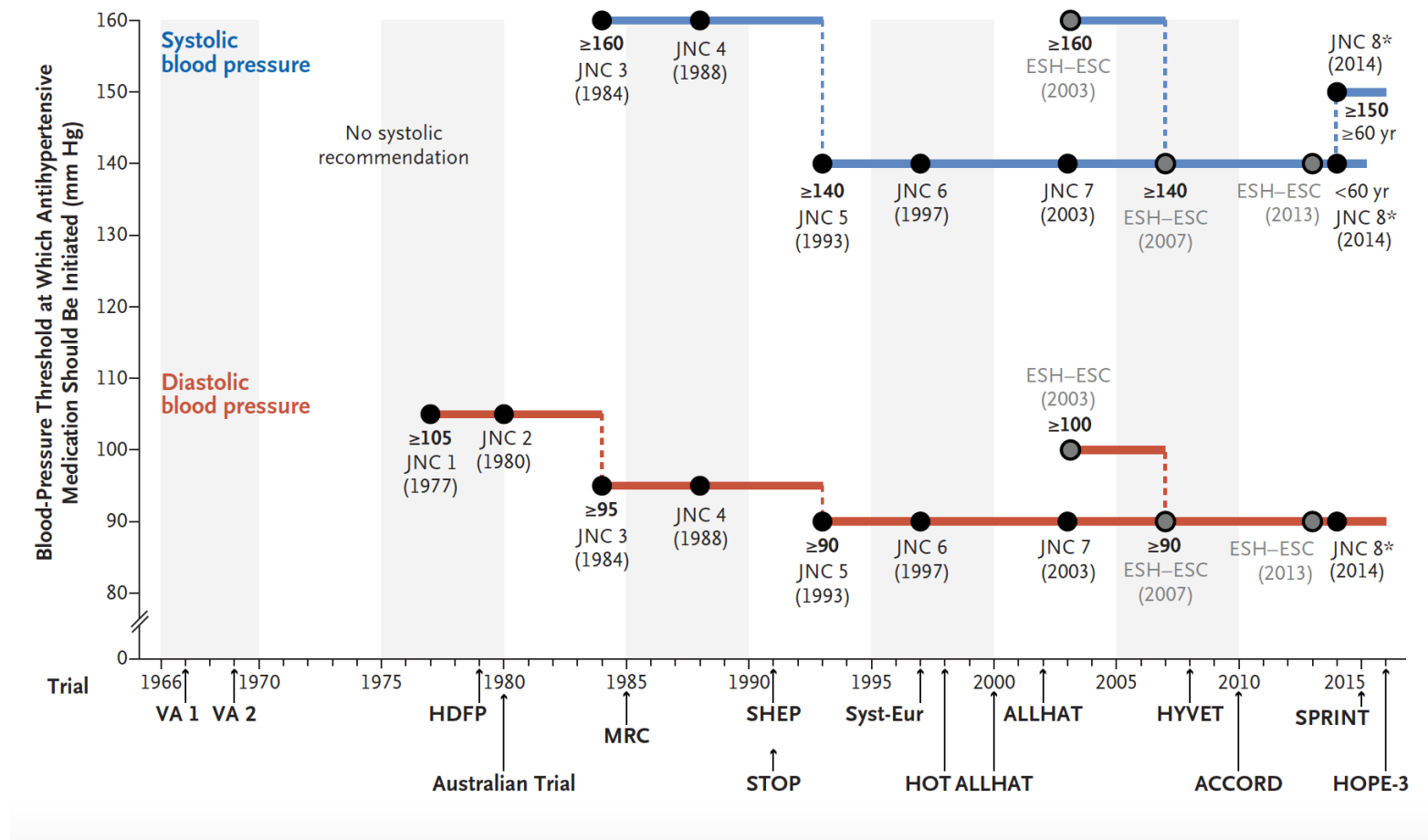
[www.escardio.org/guidelines](http://www.escardio.org/guidelines)

Williams B, Mancia G et al. Eur Heart J (2018); doi:10.1093/eurheartj/ehy339  
Williams B, Mancia G et al. J Hypertens (2018); doi:10.1097/HJH0000000000001940

**Do you believe that the papers published on hypertension in 2017/2018 will change the way you treat hypertension when you go back home ?**

- 1] yes, there will be new insights**
- 2] no, I am already doing the right thing**
- 3] I will be confused after this talk**

# State of the Art

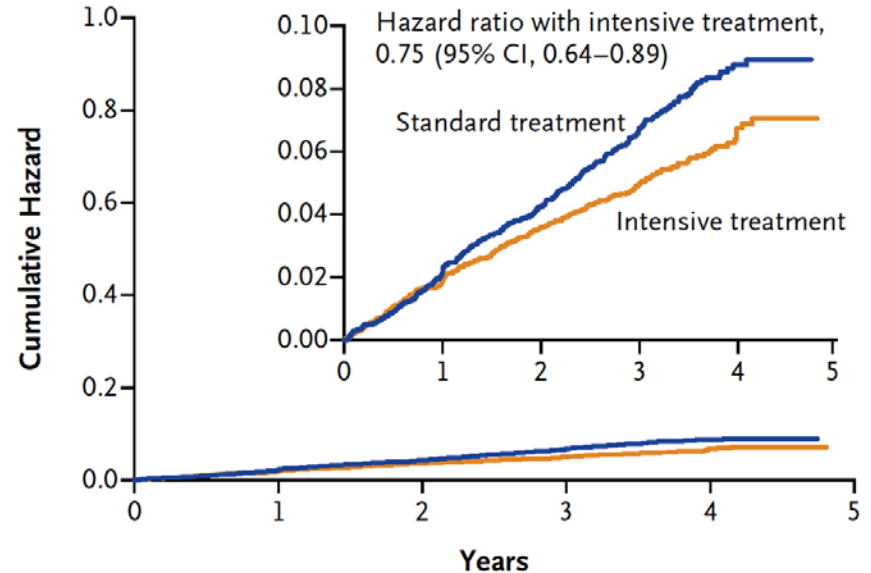
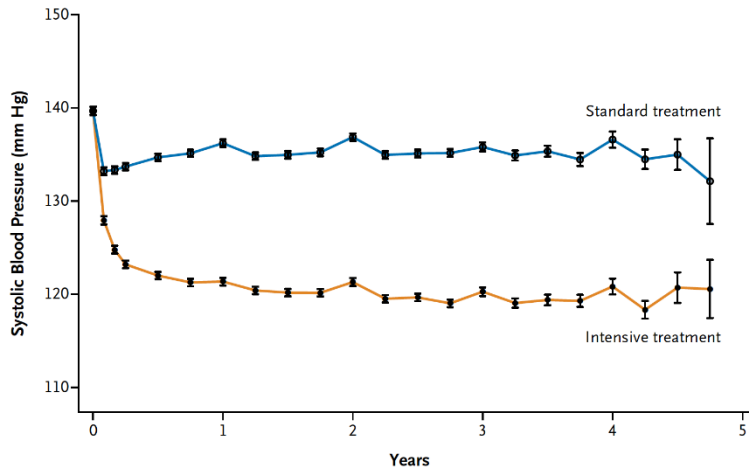


**\* JNC VIII: SBP goal to less than 150 mm Hg for patients aged 60 years or older**

*M Pfeffer, N Engl J Med 2016;375:1756-66.*

# The SPRINT study

A Primary Outcome



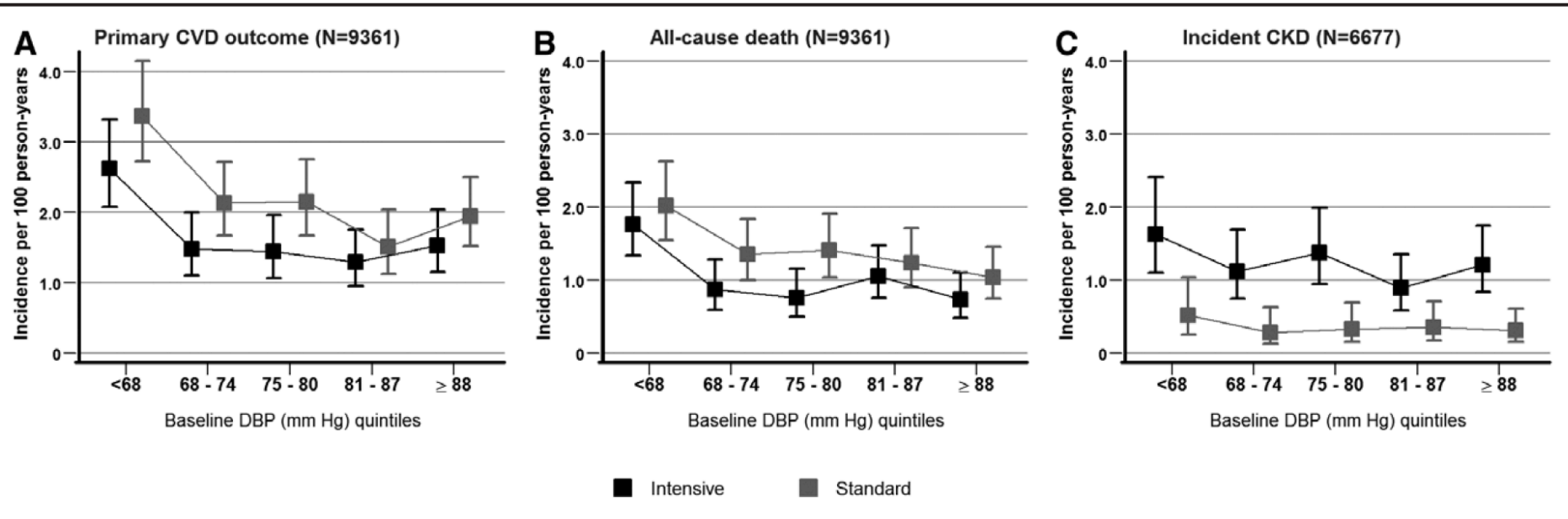
- Pts with high risk for cardiovascular events but without diabetes ( n =9361, mean age 68 yrs), targeting a systolic blood pressure of less than 120 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause

*The SPRINT study group N Engl J Med 373;22 2015*

## Take-Home Message from SPRINT

- Targeting a systolic blood pressure < 120 mmHg reduces CV death and all cause mortality
- - is cost effective and does not reduce QoL
- - is safe in (frail) elderly and mild CKD
- The mean diastolic blood pressure achieved in the intensive group was 62 mm Hg, or 5 mm Hg less than in the standard group.

# Effects of intensive BP lowering also sustained with low baseline diastolic BP ?



Beddhu et al; Circulation. 2018;137:134–143.

## Effects of intensive BP lowering also sustained with low baseline diastolic BP ?

	Intensive vs. Standard in Lowest DBP Quintile, HR (95% CI)	Intensive vs. Standard in Top 4 DBP Quintiles, HR (95% CI)	Interaction <i>p</i> *
Primary CVD outcome (n=9361)	0.78 (0.57–1.07)	0.74 (0.61–0.90)	0.78
All-cause death (n=9361)	0.88 (0.60–1.29)	0.68 (0.53–0.87)	0.29
Composite kidney outcome in CKD subgroup (n=2646)	1.17 (0.36–3.84)	0.79 (0.31–2.00)	0.61

Beddhu et al; Circulation. 2018;137:134–143.



# Implementation of SPRINT in new ACC/AHA guidelines

Table. Key Differences Between the ACC/AHA High Blood Pressure (BP) Guideline and Prior Guidelines

Variable	ACC/AHA	ACP/AAFP <sup>a</sup>	JNC7
Year published	2017	2017	2003
Hypertension diagnostic threshold	130/80 mm Hg	NA	140/80 mm Hg
Drug treatment threshold for hypertensive individuals at "high risk" <sup>b</sup>	130/80 mm Hg	NA	140/90 mm Hg 130/80 mm Hg (diabetes, chronic kidney disease)
Drug treatment threshold for hypertensive individuals not at "high risk" <sup>b</sup>	140/90 mm Hg	150 mm Hg systolic BP <sup>c</sup>	140/90 mm Hg

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACP/AAFP, American College of Physicians /American Academy for Family Physicians; JNC7, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NA, not available (the ACP/AAFP guideline did not include diagnostic threshold or treatment thresholds stratified by risk).

<sup>a</sup> Adults 60 years or older.

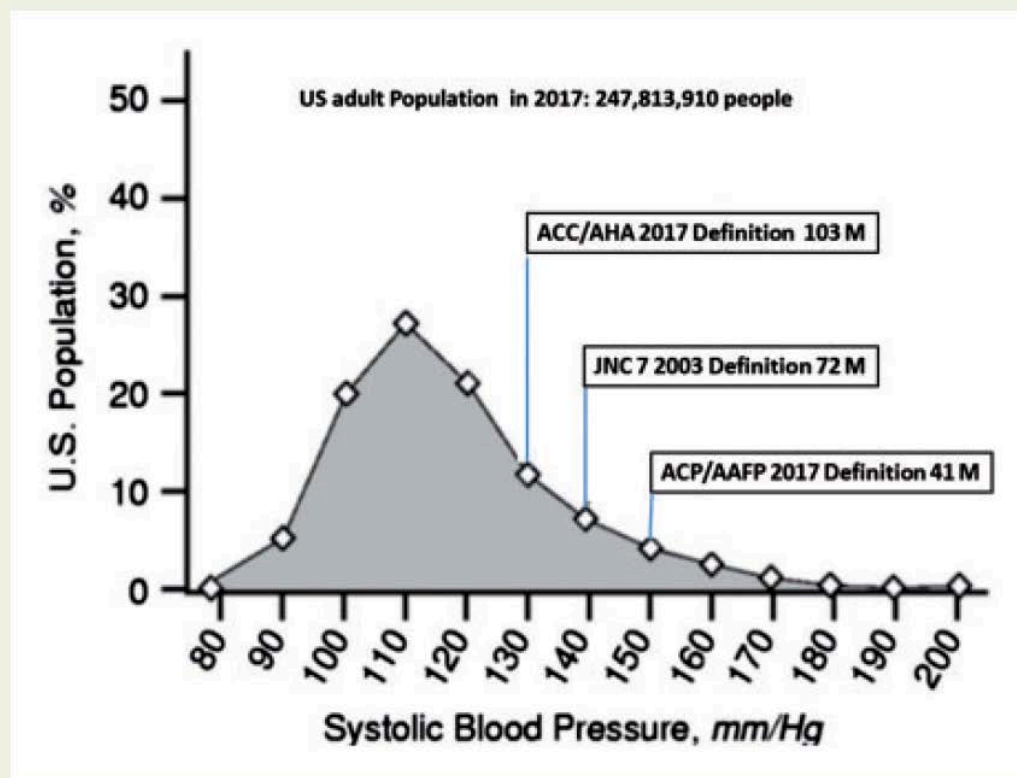
<sup>b</sup> "High risk" indicates people with history of cardiovascular disease, calculated 10-y risk greater than 10%, or with diabetes or chronic kidney disease.<sup>4,5</sup>

<sup>c</sup> No diastolic BP treatment threshold was provided because evidence for this was judged to be insufficient.

Bell et al. JAMA Intern Med. 2018;178(6):755-757

## Changing definition of hypertension in guidelines: how innocent a number game?

Franz H. Messerli<sup>1\*</sup>, Stefano F. Rimoldi<sup>1</sup>, and Sripal Bangalore<sup>2</sup>



**Take home figure** Number of adults in the USA said to have hypertension depending on definition by various guidelines.

Messerli et al. European Heart Journal 2018;39(24):2241-2242

**80% of people with newly diagnosed hypertension according to the ACC/AHA guideline would have **no** expected benefit in terms of CVD risk reduction with BP lowering**

**An additional 11% may expect a modest benefit: absolute CVD risk reduction over 5 years of 1.4%**

## Discussions with respect to BP target

- the SPRINT trial excluded a relevant proportion of the high-risk hypertensive population, in particular patients with diabetes or previous stroke.
- Method of BP measurement used in SPRINT

## Discussion 2

**Method of BP measurement in SPRINT:**

**Unsupervised 3 x Omron measurement in quiet room**

Variable	Bias (95% CI)
Research grade, routine SBP	−12.7 (−14.7 to −10.7)
Research grade, routine DBP	−12.0 (−13.4 to −10.7)
Research grade, day ABPM SBP	−7.9 (−9.4 to −6.4)
Research grade, day ABPM DBP	−11.7 (−12.7 to −10.8)

**BP target 120/80 mmHg in SPRINT is equivalent to  
132/92 mmHg office BP**

*Agarwal, J Am Heart Assoc. 2017;6:e004536*

**Male, 58 years, type II diabetes. No clinically manifest CVD.  
Office blood pressure 150/70 mmHg.**

**Would you set the treatment target for this patient on:**

- 1] 140 mmHg systolic**
- 2] < 130 mmHg systolic**
- 3] accept as is.**

# Implementation of SPRINT in new ACC/AHA guidelines

Variable	ACC/AHA
Year published	2017
Hypertension diagnostic threshold	130/80 mm Hg
Drug treatment threshold for hypertensive individuals at "high risk" <sup>b</sup>	130/80 mm Hg
Drug treatment threshold for hypertensive individuals not at "high risk" <sup>b</sup>	140/90 mm Hg

Bell et al. JAMA Intern Med. 2018;178(6):755-757

## Definition of hypertension according to office\*, ambulatory, and home blood pressure levels

Category	SBP ( mmHg)		DBP ( mmHg)
Office BP*	≥ 140	and/or	≥ 90
Ambulatory BP			
Daytime (or awake) mean	≥ 135	and/or	≥ 85
Night-time (or asleep) mean	≥ 120	and/or	≥ 70
24-h mean	≥ 130	and/or	≥ 80
Home BP mean	≥ 135	and/or	≥ 85

\* Conventional office BP rather than unattended office BP.



## Office BP treatment targets in hypertensive patients - General Recommendations

### Class / Level

- The first objective of treatment should be to lower BP to <140/90 mmHg in all patients IA
- Provided that treatment is well tolerated treated BP should be targeted to 130/80 mmHg or lower in most patients IA

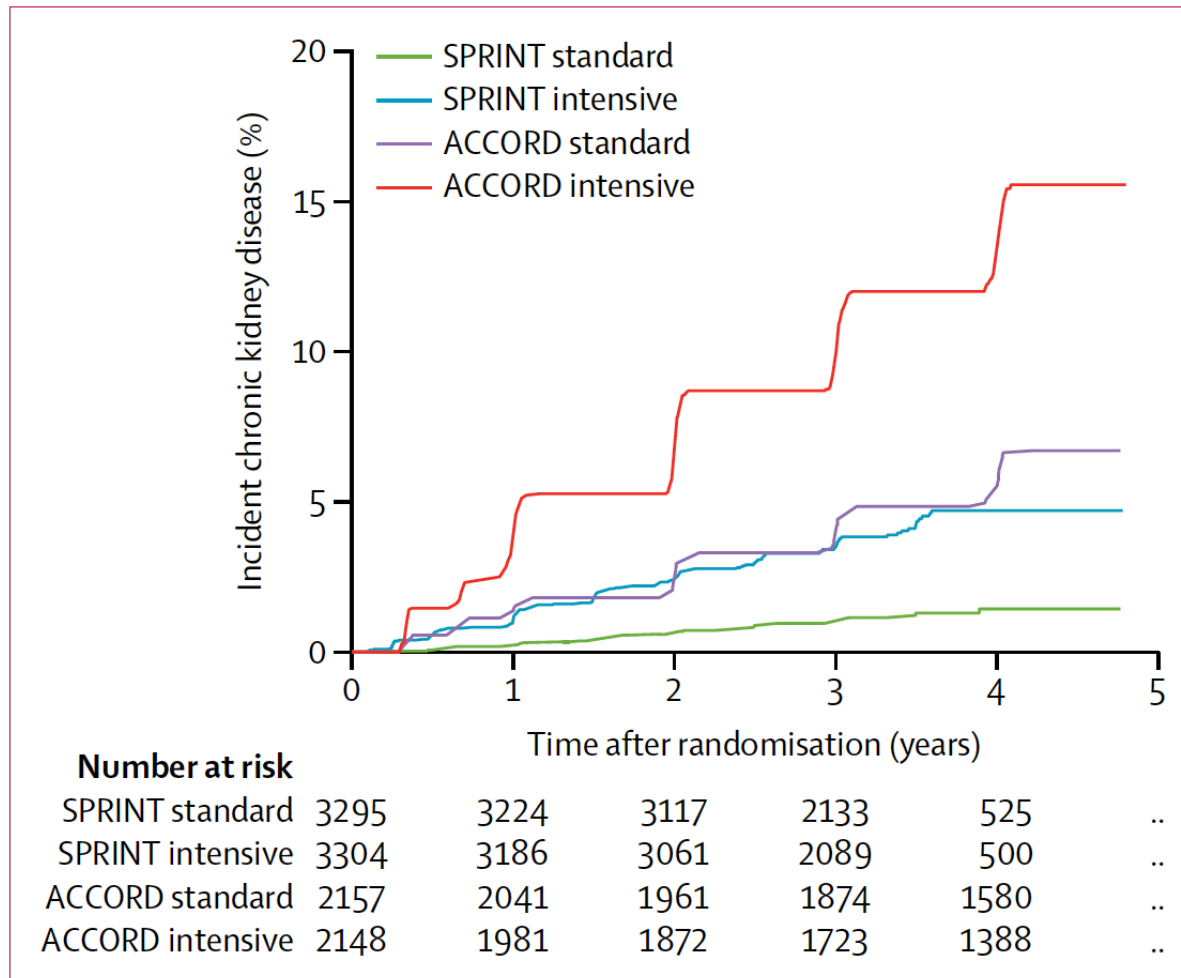
*Williams, Mancia et al., J Hypertens 2018 and Eur Heart J 2018, in press*

**Male, 58 years, type II diabetes. No clinically manifest CVD.  
Office blood pressure 150/70 mmHg.**

**Would you set the treatment target for this patient on:**

- 1] 140 mmHg systolic**
- 2] < 130 mmHg systolic**
- 3] accept as is.**

# Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus



**Figure 2:** Cumulative incidence of chronic kidney disease with intensive and standard systolic blood pressure interventions in SPRINT and the ACCORD trial

## My personal opinion

### Swiss BP rule:

**optimal BP levels should be about 100 plus half of the patient's age.**

**This would correspond to 120mmHg for age of 40, 130mmHg for age of 60, and 140mmHg for 80-year-old patient.**

# What is the optimal dose of BP lowering agents ?

- a systematic review of 354 trials of BP-lowering therapy showed that half-standard-dose achieved almost 80% of BP lowering,
- BP-lowering effect of different classes of drugs was additive.
- Less side effects with half the standard dose

*Chow et al , Lancet 2017; 389: 1035–42*

**Subtopic**

**Renal denervation &  
devices**

# State of the Art

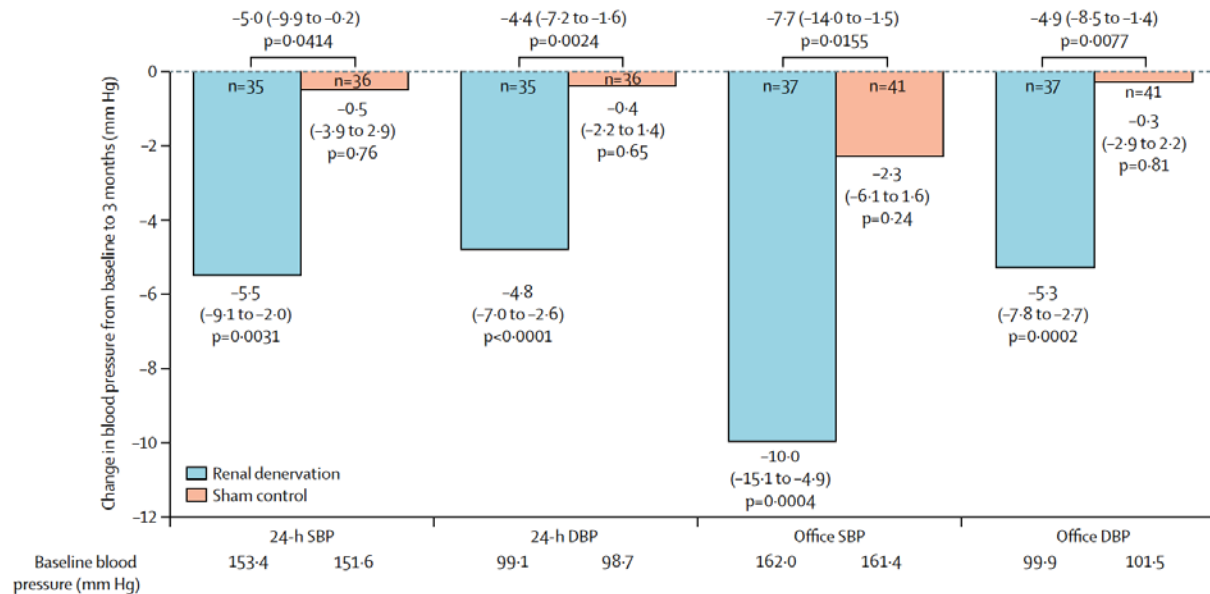
## Renal denervation for therapy resistant hypertension



- Early uncontrolled and unblinded trials reported large reductions in blood pressure following renal denervation in patients with uncontrolled hypertension.
- the randomised, sham-controlled SYMPPLICITY HTN-3 trial showed no significant blood-pressure-lowering benefits
- incomplete ablation of the renal nerves, non-adherence to antihypertensive medications, and patient selection might have influenced these results.

Bhatt et al. N Engl J Med. 2014 Apr 10;370(15):1393-40.

# Renal denervation in uncontrolled hypertension in the absence of antihypertensive medications

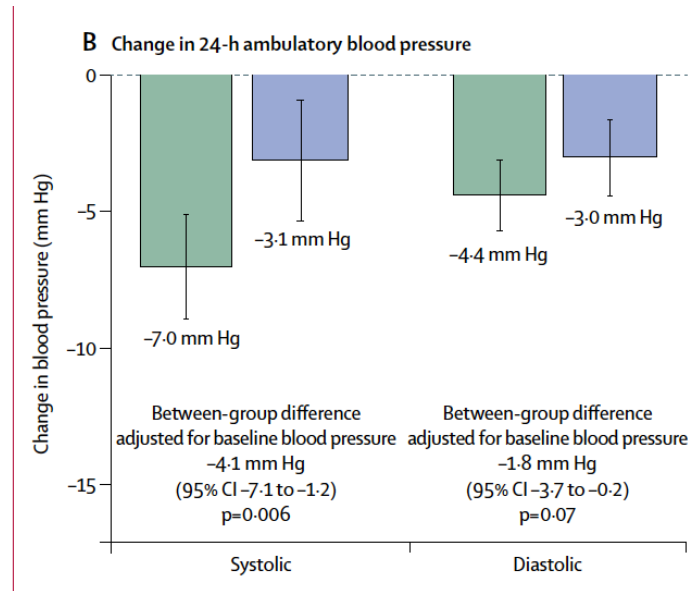


- Sham procedure controlled, new device with reproducible denervation
- N=80, BP systolic 150-180 mmHg; no medication

Townsend et al. Lancet. 2017 Nov 11;390(10108):2160-2170



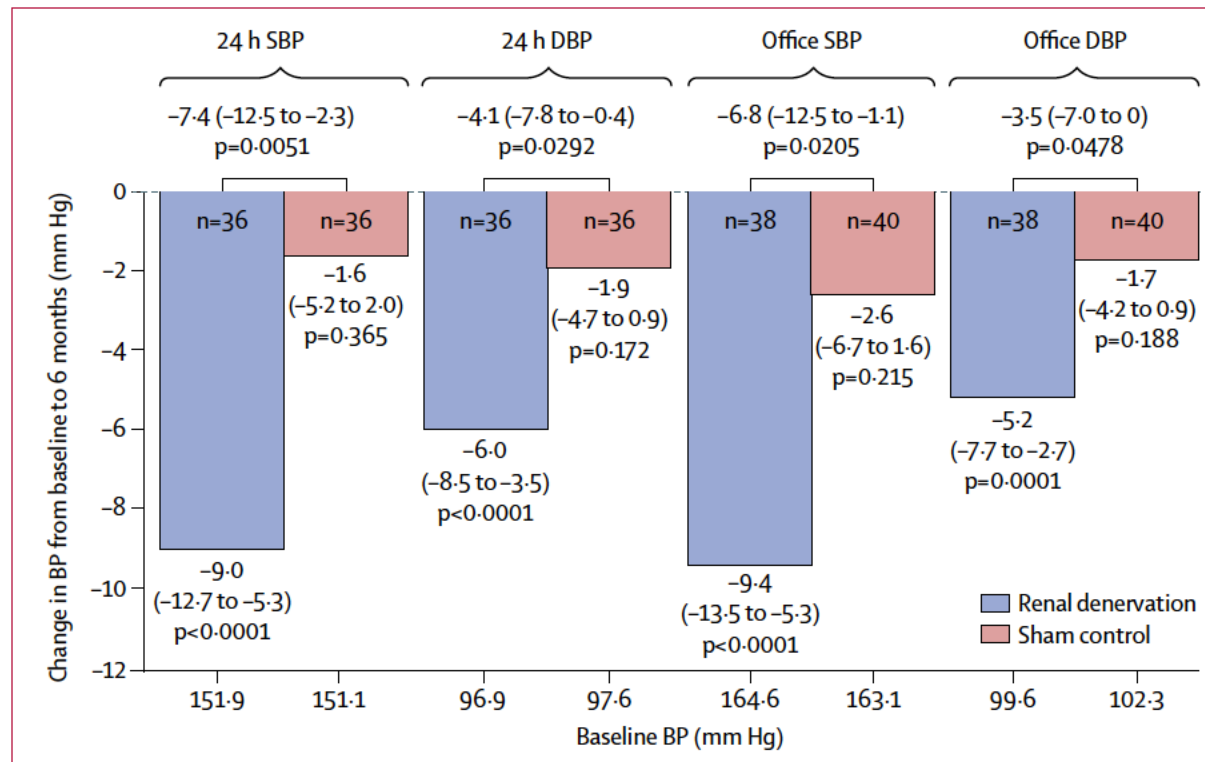
# Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO)



- \* 803 patients were screened for eligibility and 146 were randomised to undergo renal denervation (n=74) or a sham procedure (n=72).
- \* The reduction in daytime ambulatory systolic blood pressure was greater with renal denervation (−8.5 mm Hg, SD 9.3) versus (−2.2 mm Hg,
- \* No major adverse events were reported in either group.

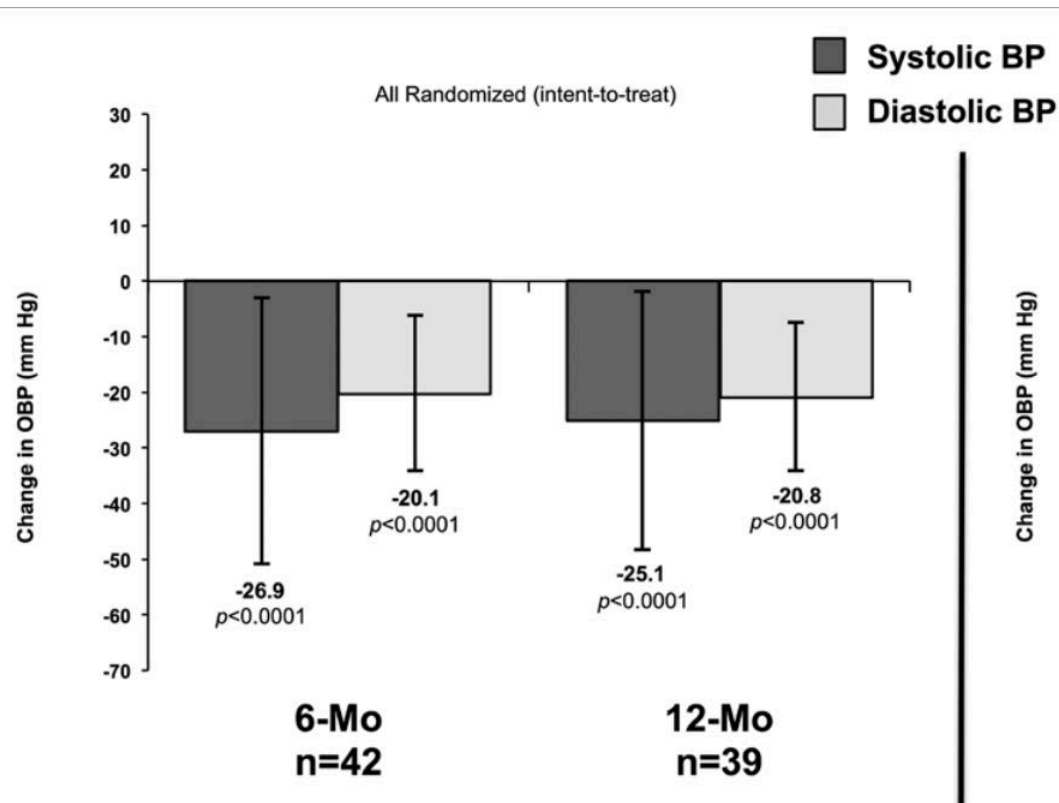
Azizi, Lancet 2018; 391: 2335–45

# Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED



Kandzari Lancet 2018; 391: 2346–55

# Central Iliac Arteriovenous Anastomosis for Uncontrolled Hypertension



included patients with office systolic BP  $\geq 140$  mm Hg, average daytime systolic ABP  $\geq 135$  mm Hg, and diastolic ABP  $\geq 85$  mm Hg despite taking  $\geq 3$  antihypertensive medications.

Lobo, Hypertension 2017;70:1099-1105

# The hypertension drug therapy pipeline

**Table. New Drugs for Hypertension**

Drug	Mechanism of Action	Status
BAY 94–8862 (finerenone)	Mineralocorticoid receptor antagonist	Phase IIb
LCI699	Aldosterone synthase inhibitor	Phase II trials*
C21	AT2 receptor agonist	Preclinical
XNT	ACE2 activator	Preclinical*
DIZE	ACE2 activator	Preclinical*
rhACE2	ACE2 activator	Phase I
HP-β-CD/Ang1-7	Ang1-7 analog	Preclinical
AVE0991	Nonpeptide agonist of MAS	Preclinical
CGEN-856S	Peptide agonist of MAS	Preclinical
Alamandine/HPβCD	Mas-related G-protein coupled receptor, member D agonist	Preclinical
PC18	Aminopeptidase N inhibitor	Preclinical
RB150 (QGC001)	Aminopeptidase A inhibitor	Phase I
LCZ696	Dual-acting angiotensin receptor-neprilysin inhibitor	Phase III
SLV-306 (Daglutril)	Dual acting endothelin-converting enzymes-neprilysin inhibitor	Phase II
PL-3994	Natriuretic peptide A agonist	Phase II
C-ANP <sup>4-23</sup>	ANP analog, selective for NPR-C	Preclinical
AR9281	Soluble epoxide hydrolase inhibitors	Phase II*
Vasomera (PB1046)	Vasoactive intestinal peptide receptor 2 (VPAC2) agonist	Phase II
AZD1722 (Tenapanor)	Intestinal Na <sup>+</sup> /H <sup>+</sup> exchanger 3 inhibitor	Phase I
Etamicastat	Dopamine β-hydroxylase inhibitor	Phase I
<b>Vaccines</b>		
CYT006-AngQβ	Vaccine against angiotensin II	Phase II
AngII-KLH	Vaccine against angiotensin II	Preclinical
pHAV-4AngII	Vaccine against angiotensin II	Preclinical
ATRQβ-001	Vaccine against angiotensin II type 1 receptor	Preclinical
ATR12181	Vaccine against angiotensin II type 1 receptor	Preclinical
<b>Preeclampsia drugs</b>		
DIF	Anti-digoxin antibody fragment	Phase II expedited
ATryn	Recombinant antithrombin	Phase III

ANP indicates atrial natriuretic peptide ATR, Angiotensin II type 1 receptors; DIF, Digoxin-immune Fab; KLH, keyhole limpet hemocyanin; and rhACE2, recombinant human ACE2.

Oparil, Circ Res 2016 . 116:1074-1095

**Male, 38 years,. No clinically manifest CVD.  
Blood pressure 160/100 mmHg. K : 2.8 mmol/l  
No drug treatment**

**What would be your next step ?**

- 1] measure renin-aldosterone ratio**
- 2] do AV aldosterone sampling**
- 3] make a CT scan of the adrenals**

# **Primary Aldosteronism, state-of-the-art**

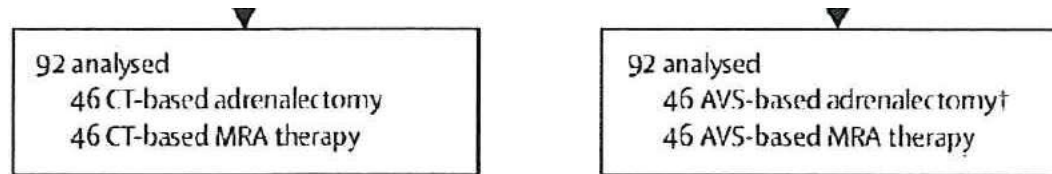
**Upon laparoscopic adrenalectomy, 50 % complete remission without residual hypertension, 50 % still need antihypertensive drugs**

**Adrenal venous sampling is recommended for confirmed PA patients**

**Imaging by computed tomography (CT) is recommended for all patients confirmed to have PA, to exclude the rare cases of adrenal carcinoma**

**Funder JW,. The management of primary aldosteronism:case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:1889–1916**

# Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial (SPARTACUS)



**50% discordance between the diagnostic conclusions derived from the CT and AVS,**

	Total cohort			Adrenalectomy			Mineralocorticoid receptor antagonist		
	CT (n=92)	AVS (n=92)	p value <sup>a</sup>	CT (n=46)	AVS (n=46)	p value <sup>a</sup>	CT (n=46)	AVS (n=46)	p value <sup>a</sup>
Defined daily dose	3.0 (1.0–5.0)	3.0 (1.1–5.9)	0.52	1.2 (0–3.0)	1.2 (0–3.0)	0.42	4.0 (2.3–6.7)	5.7 (3.4–8.7)	0.05
Number of antihypertensive drugs	2 (1–3)	2 (1–3)	0.87	1 (0–2)	1 (0–2)	0.31	2 (2–3)	3 (2–4)	0.39
24 h ambulatory blood pressure									
Systolic, mm Hg	127 (120–138)	128 (121–135)	0.93	129 (121–141)	128 (121–137)	0.53	125 (120–135)	128 (122–133)	0.57
Diastolic, mm Hg	80 (75–86)	81 (76–85)	0.76	82 (76–87)	81 (77–85)	0.98	80 (74–86)	81 (75–85)	0.71

Dekkers et al. Lancet Diabetes Endocrinol. 2016 Sep;4(9):739-746

# Criticism on SPARTACUS

- 4 times higher failure rate of treatment of PA than in earlier studies
- 4 times overrepresentation of male versus female

**Adrenal Vein Sampling Is the Preferred Method to Select Patients With Primary Aldosteronism for Adrenalectomy**

*Pro Side of the Argument*

*Gian Paolo Rossi, John W. Funder*

Rossi et al., Hypertension. 2018 Jan;71(1):5-9



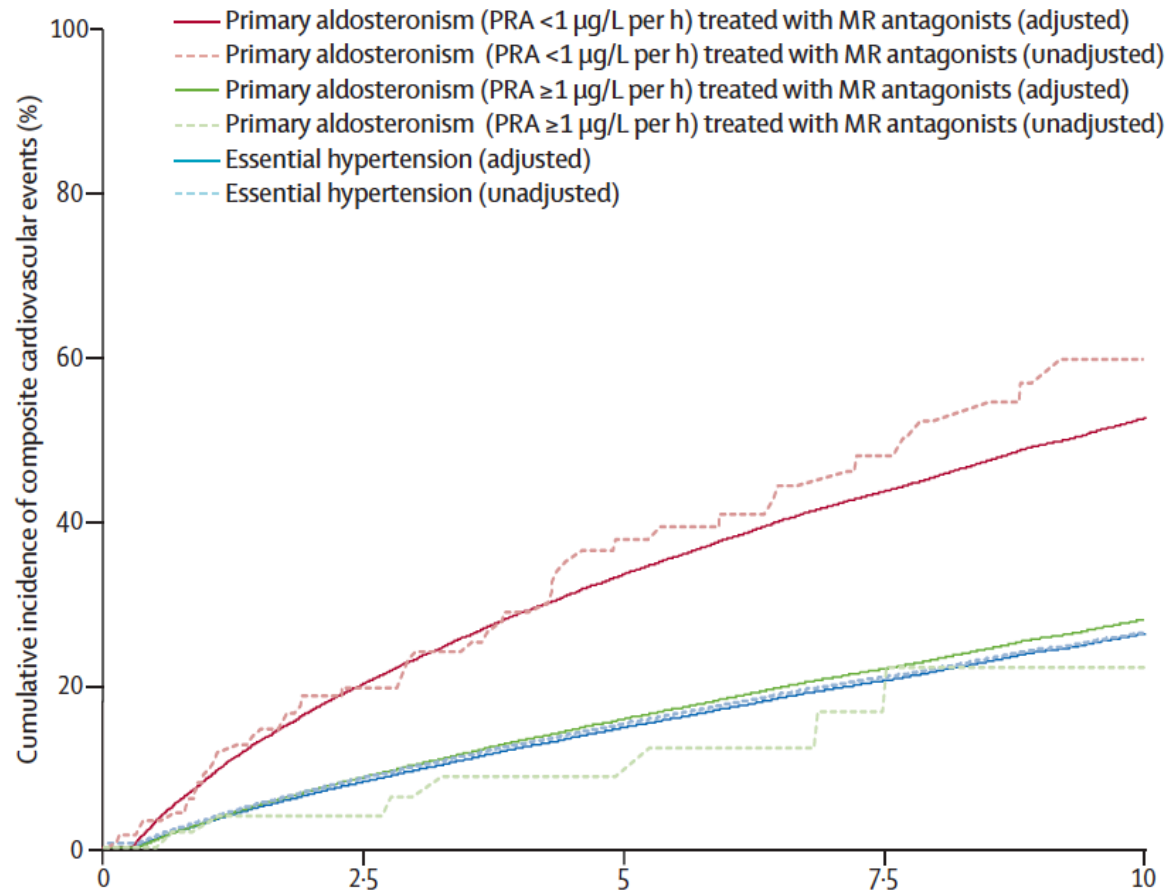
**Male, 38 years,. No clinically manifest CVD.  
Blood pressure 160/100 mmHg. K : 2.8 mmol/l  
No drug treatment**

**Diagnosis of right sided (??) primary hyperaldosteronism  
was confirmed**

**How would you treat this patient ?**

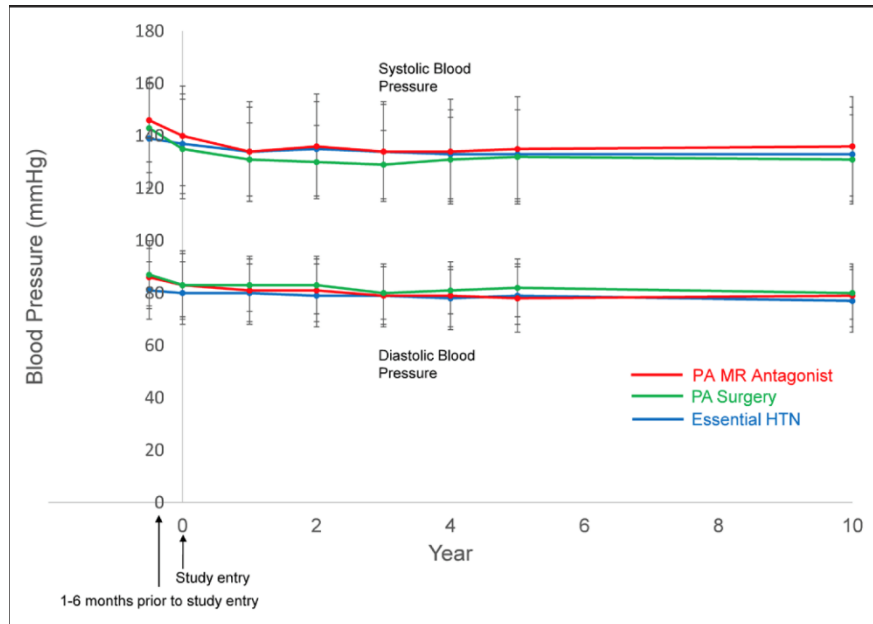
- 1] laparoscopic adrenalectomy**
- 2] Mineralocorticoid receptor antagonism**
- 3] Regular antihypertensive treatment**

# Cardiovascular Outcomes in Medically Primary Aldosteronism



Hundemer, Lancet Diabetes Endocrinol 2018; 6: 51–59

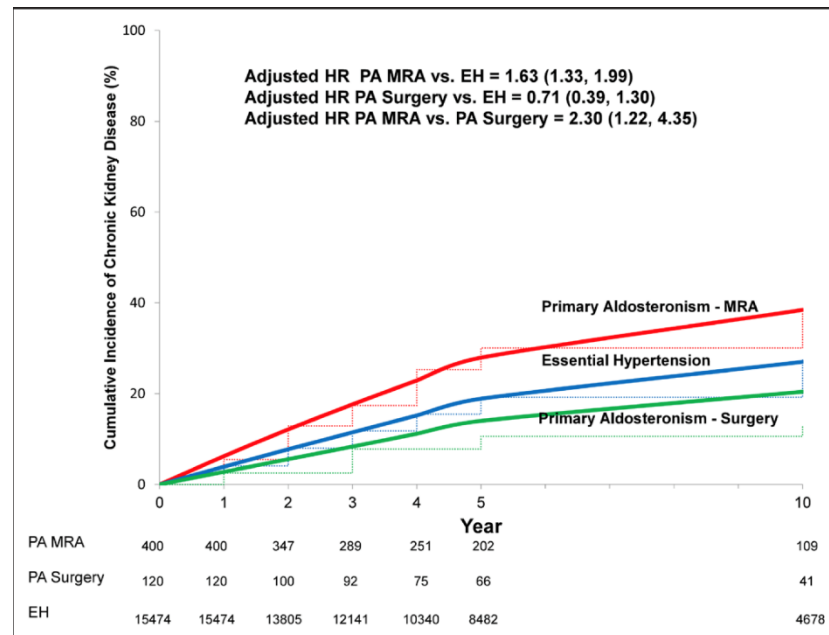
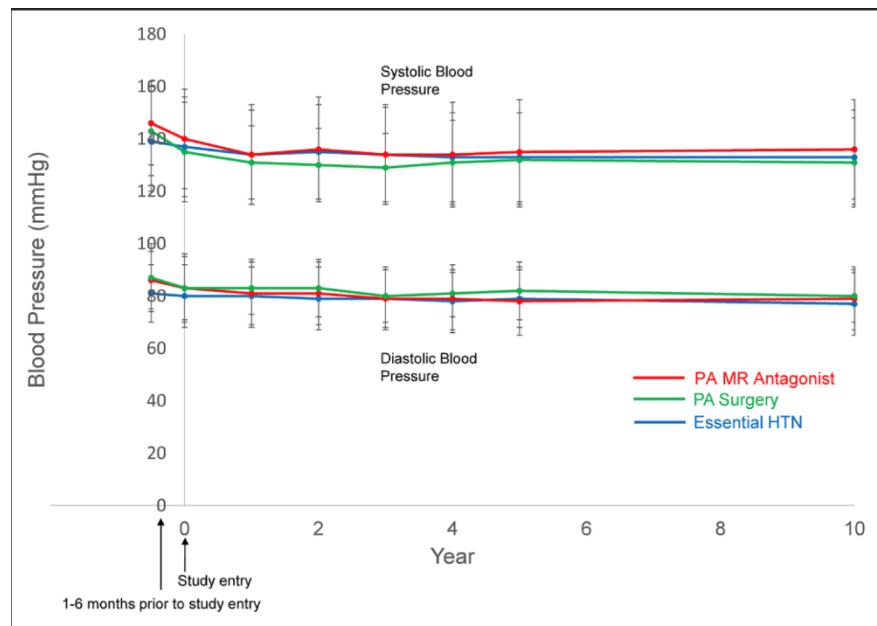
# Renal Outcomes in Medically and Surgically Treated Primary Aldosteronism



a retrospective cohort study of patients with PA treated with MRAs (N=400) or surgical adrenalectomy (N=120) and age- and estimated glomerular filtration rate–matched patients with essential hypertension (N=15 474) to determine risk for chronic kidney disease and longitudinal estimated glomerular filtration rate decline.

Hundemer, Hypertension. 2018;72:658-666.

# Renal Outcomes in Medically and Surgically Treated Primary Aldosteronism



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Hundemer, Hypertension. 2018;72:658-666.

**Female, 36 years, 37 weeks pregnant**  
**Blood pressure 140/100 mmHg. Uric acid in blood is**  
**elevated and blood platelets  $110 \times 10^9/l$ . Albustix 2 +**

**What would be your next step ?**

- 1] start labetalol**
- 2] start nifedipine**
- 3] induction of labor**

# Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy

Parameter	Randomized to Labetalol n=55	Randomized to Nifedipine n=57	Adjusted Mean Difference (95% CI)
Maximum brachial BP, mm Hg			
Systolic	161 (14.7)	163 (19.2)	1.2 (−4.9 to 7.2)
Diastolic	101 (10.2)	105 (11.7)	3.3 (−0.6 to 7.3)

Webster, Hypertension 2017;70:915-922

# Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy

Outcome	Randomized to Labetalol n=55	Randomized to Nifedipine n=57	Adjusted Difference in Mean/Median or Risk Ratio (95% CI)
Time between randomization and delivery,* d	134 (39)	127 (44)	
Superimposed preeclampsia†	8 (15%)	15 (26%)	1.78 (0.84 to 3.77)
Superimposed preeclampsia <34 wk†	6 (11%)	6 (11%)	

Neonatal outcomes	n=51	n=52	
Birthweight,* g	2957 (790)	2732 (883)	−240 (−589 to 109)
Birthweight <10th centile†	16 (31%)	17 (33%)	
Birthweight <3rd centile†	6 (12%)	10 (19%)	
Admitted to neonatal unit†	11 (22%)	15 (29%)	1.3 (0.7 to 2.5)
Adverse perinatal outcome†§	11 (22%)	17 (33%)	

Webster, Hypertension 2017;70:915-922

# Hypertension & pregnancy

**Hypothesis: routine induction of labor at 38 or 39 weeks of gestation in women with chronic hypertension may decrease the risk of superimposed preeclampsia and the associated maternal and perinatal complications**

Ram et al. Obstet Gynecol. 2018 Sep;132(3):669-677



# Hypertension & pregnancy

**Table 2. Pregnancy Outcomes in the Induction and Expectant Management Groups**

Outcome	38 Wk of Gestation			39 Wk of Gestation		
	Induction (n=281)	Expectant Management (n=1,606)	<i>P</i>	Induction (n=259)	Expectant Management (n=801)	<i>P</i>
Superimposed preeclampsia	0 (0.0)*	308 (19.2)	<b>&lt;.001</b>	0 (0.0)*	152 (19.0)	<b>&lt;.001</b>
Eclampsia	0 (0.0)*	10 (0.6)	<b>&lt;.001</b>	0 (0.0)*	6 (0.7)	<b>&lt;.001</b>
Placental abruption	Less than 6 <sup>†</sup>	6 (0.4)	N/A	Less than 6 <sup>†</sup>	Less than 6 <sup>†</sup>	N/A
Labor induction	281 (100)	912 (56.8)	<b>&lt;.001</b>	259 (100)	463 (57.8)	<b>&lt;.001</b>
Epidural	208 (74.0)	1,177 (73.3)	.800	196 (75.7)	596 (74.4)	.683
Cesarean delivery	48 (17.1)	385 (24.0)	<b>.011</b>	52 (20.1)	208 (26.0)	.056

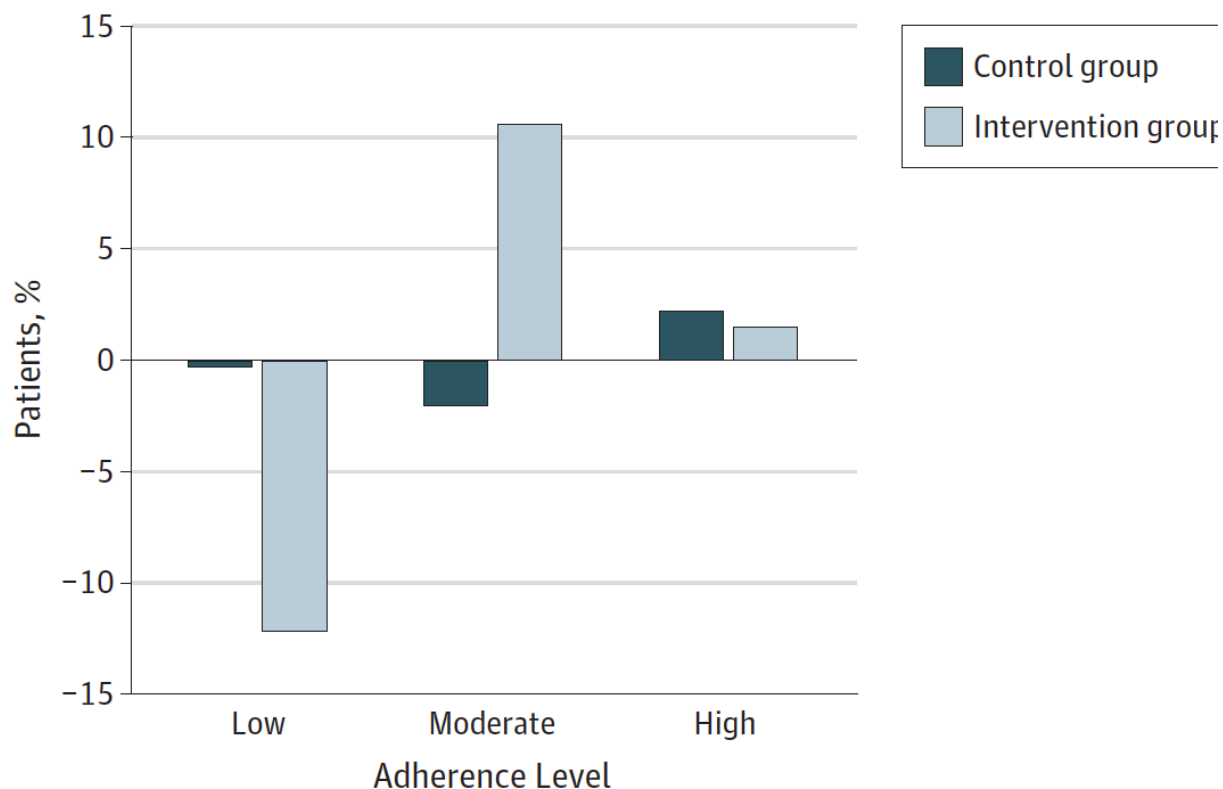
Ram et al. Obstet Gynecol. 2018 Sep;132(3):669-677

**Female African descent, 31 years, 33 weeks pregnant  
with kidney transplant in situ  
Blood pressure 125/85 mmHg.**

**To improve blood pressure control and medication  
adherence you can best advise**

- 1] to use a smartphone app to register BPs**
- 2] to use the smartphone itself to record the BP and  
send it over to your electronic patient record**
- 3] to organize peer support**

# Association of a Smartphone Application With Medication Adherence and Blood Pressure Control: The MedSAFE-BP Randomized Clinical Trial



Morawski et al. JAMA Intern Med. 2018 Jun 1;178(6):802-809

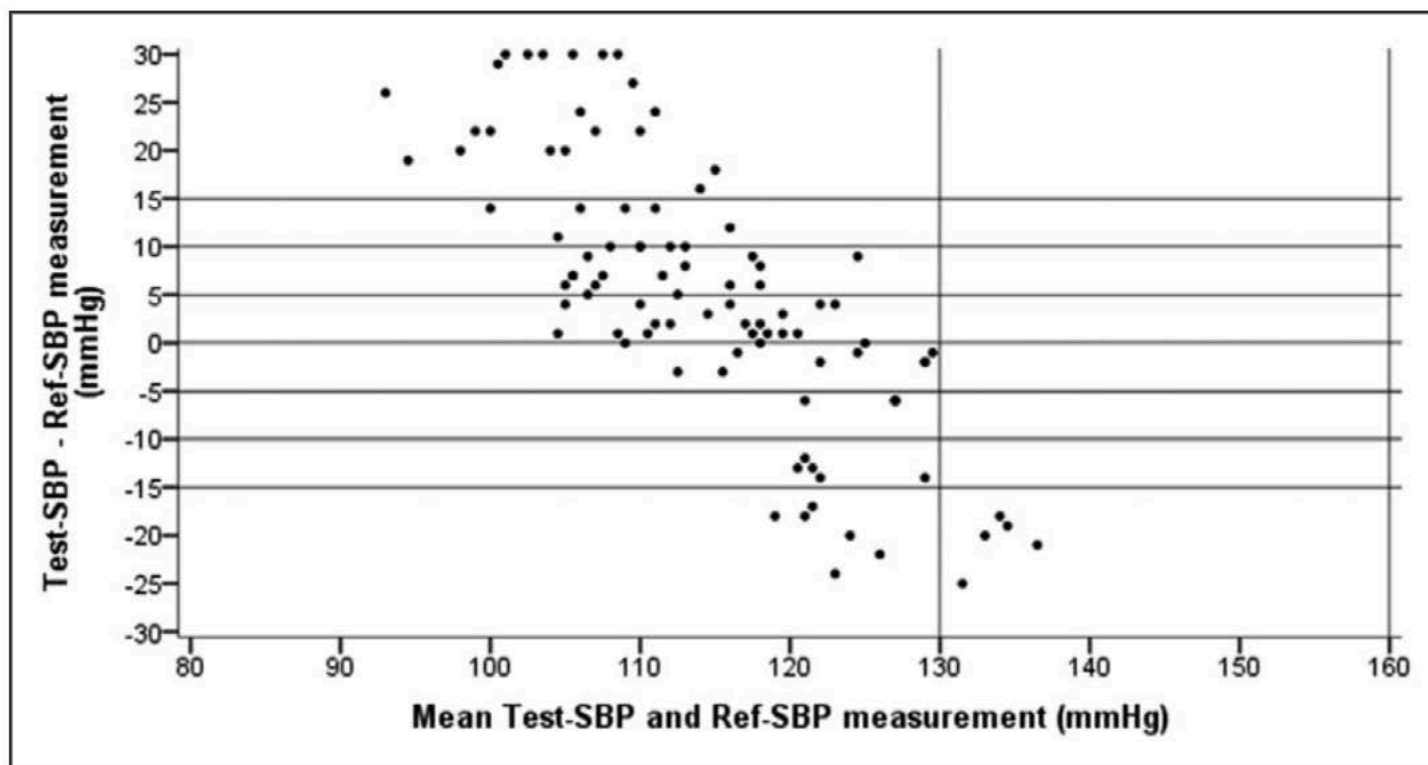
# Association of a Smartphone Application With Medication Adherence and Blood Pressure Control: The MedSAFE-BP Randomized Clinical Trial

Table 2. Primary and Secondary Outcomes<sup>a</sup>

Variable	Intervention Group (n = 209)			Control Group (n = 202)			Unadjusted Effect Estimate		Adjusted Effect Estimate	
	Wk 0	Wk 12	Change	Wk 0	Wk 12	Change	Absolute Difference	P Value	Absolute Difference	P Value
Primary outcomes										
Medication adherence, <sup>b</sup> mean (SD)	6.0 (1.8)	6.3 (1.6)	0.4 (1.5)	5.7 (1.8)	5.7 (1.8)	-0.01 (1.5)	0.4 (0.1 to 0.7)	.01	0.5 (0.2 to 0.7)	.001
Systolic BP, mm Hg, mean (SD)	151.4 (9.0)	140.8 (15.7)	-10.6 (16.0)	151.3 (9.4)	141.2 (17.3)	-10.1 (15.4)	-0.5 (-3.7 to 2.7)	.78	-0.1 (-3.2 to 3.1)	.97
Secondary outcome										
Controlled BP, <sup>c</sup> No. (%)	0	67 (35.8)	35.8	0	69 (37.9)	37.9	OR, 0.9 (95% CI, 0.6 to 1.4)	.68	OR, 0.8 (95% CI, 0.5 to 1.3)	.34

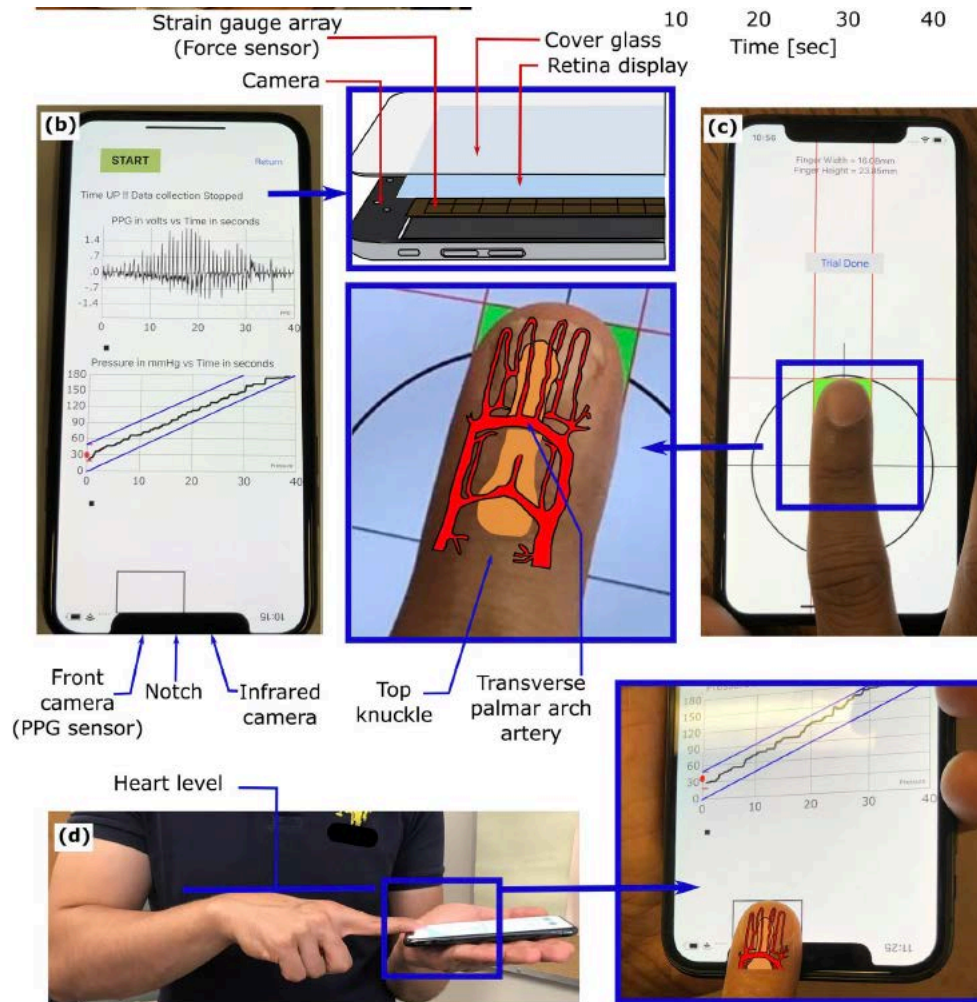
Morawski et al. JAMA Intern Med. 2018 Jun 1;178(6):802-809

## Performance of a Blood Pressure Smartphone App in Pregnant Women



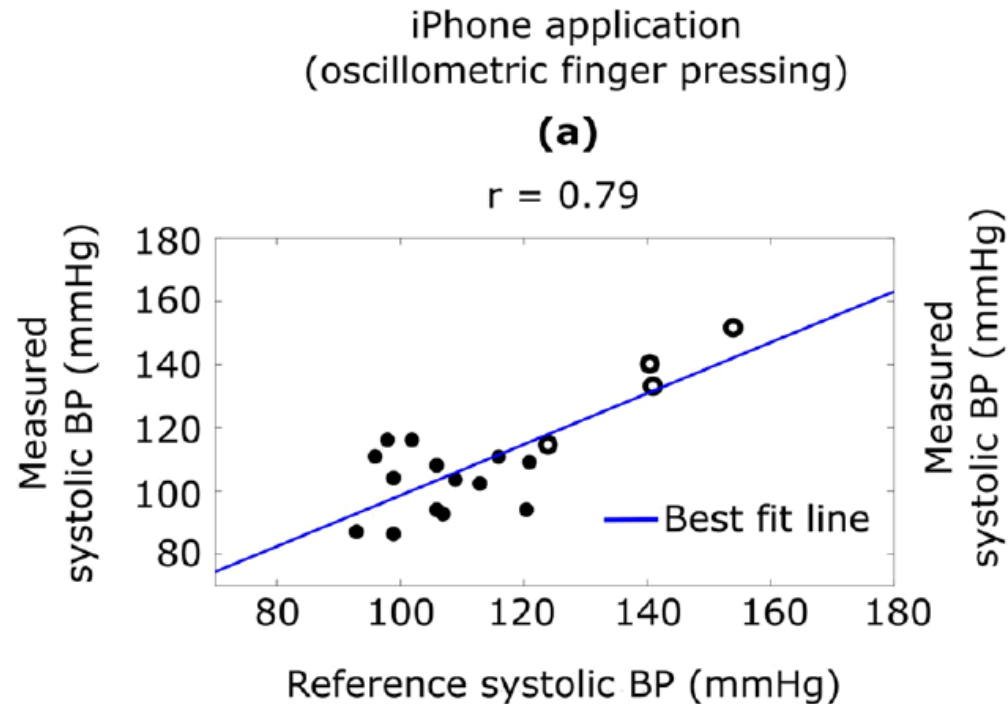
Raichle, Hypertension 2018;71:1164-1169

# An iPhone Application for Blood Pressure Monitoring via the Oscillometric Finger Pressing Method



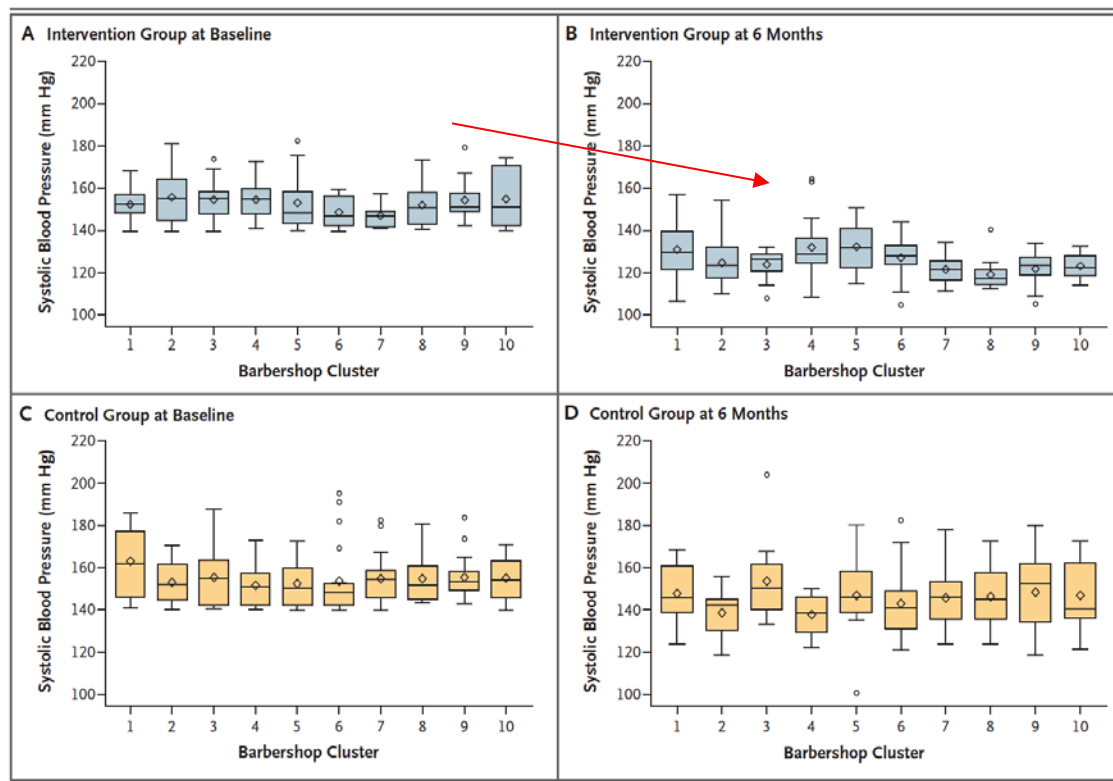
Chandrasekhar, Scientific Reports | (2018) 8:13136 |

# An iPhone Application for Blood Pressure Monitoring via the Oscillometric Finger Pressing Method



Chandrasekhar, Scientific Reports | (2018) 8:13136 |

# A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops



cluster-randomized trial in which barbershops were assigned to a pharmacist-led intervention (in which barbers encouraged meetings in barbershops with specialty-trained pharmacists who prescribed drug therapy or to an active control approach (in which barbers encouraged lifestyle modification and doctor appointments)

Victor et al N Engl J Med 2018;378:1291-301.

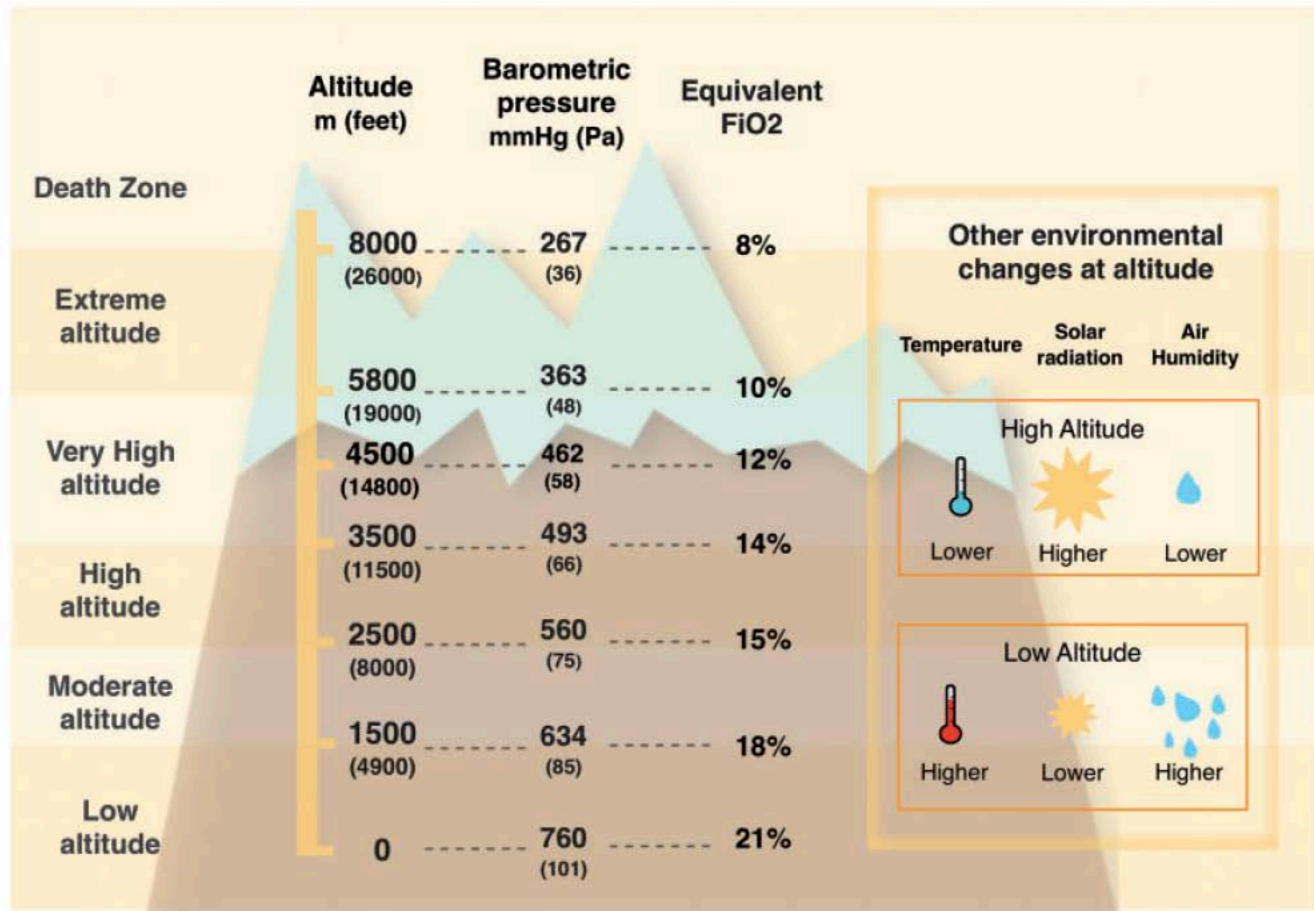


**Male, 60 years old. Office blood pressure 140/95 mmHg with quadruple medication. Experienced once an episode of heart failure, which appeared to be due to HFpEF**

**He wants to book a skiing holiday to the Chamonix area  
And asks you for your advice**

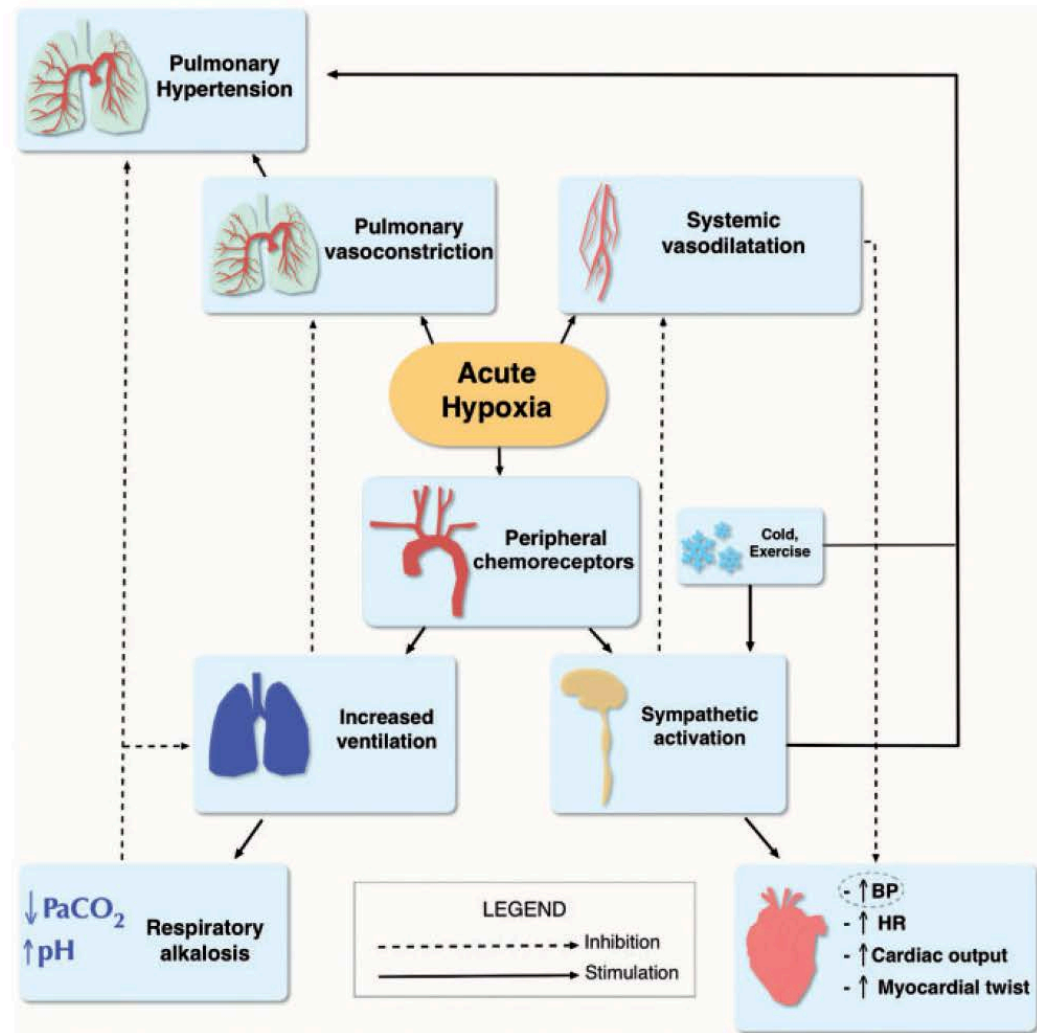
- 1] There is no problem to go up**
- 2] It is okay but he should not go up the Aiguille du midi**
- 3] He should stay down in the village**

# Hypertension & altitude



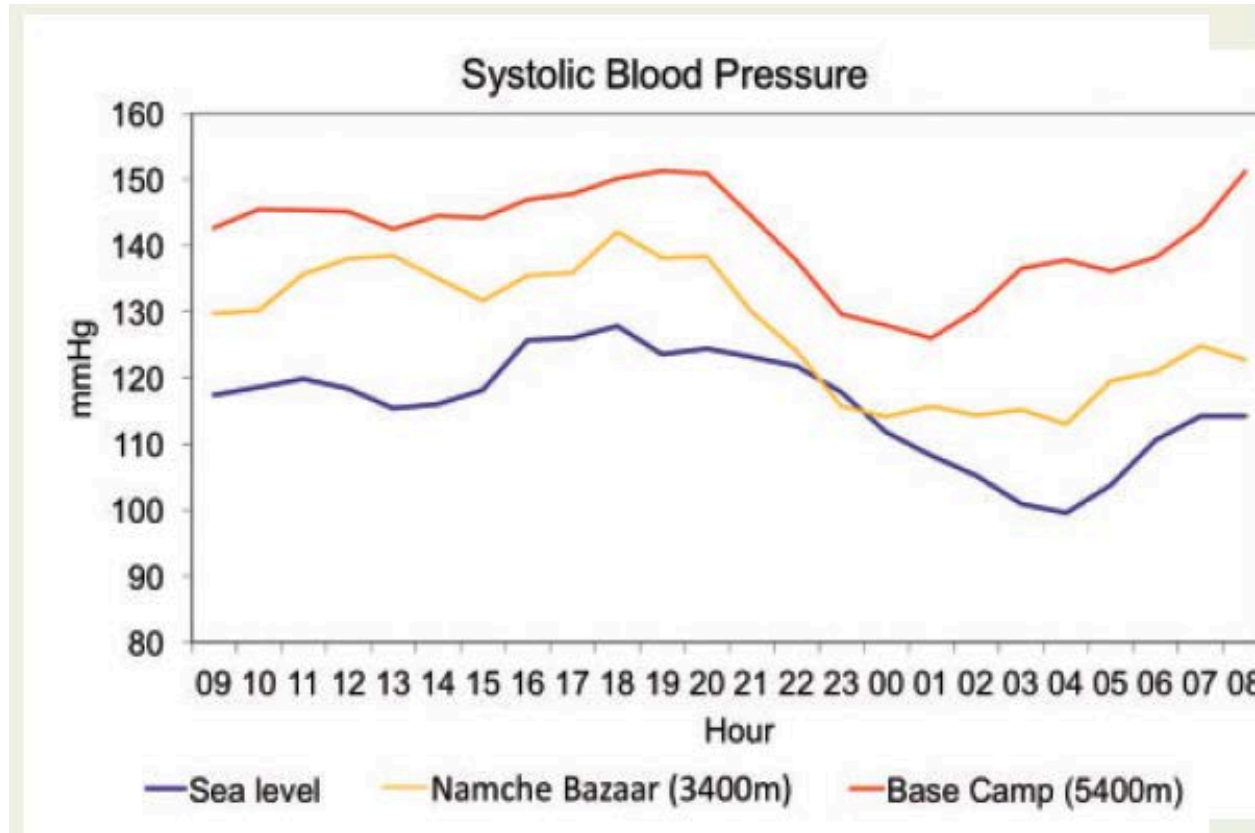
Parati, European Heart Journal (2018) 39, 1546–1554

# Hypertension & altitude



Parati, European Heart Journal (2018) 39, 1546–1554

# Hypertension & altitude



Parati, European Heart Journal (2018) 39, 1546–1554

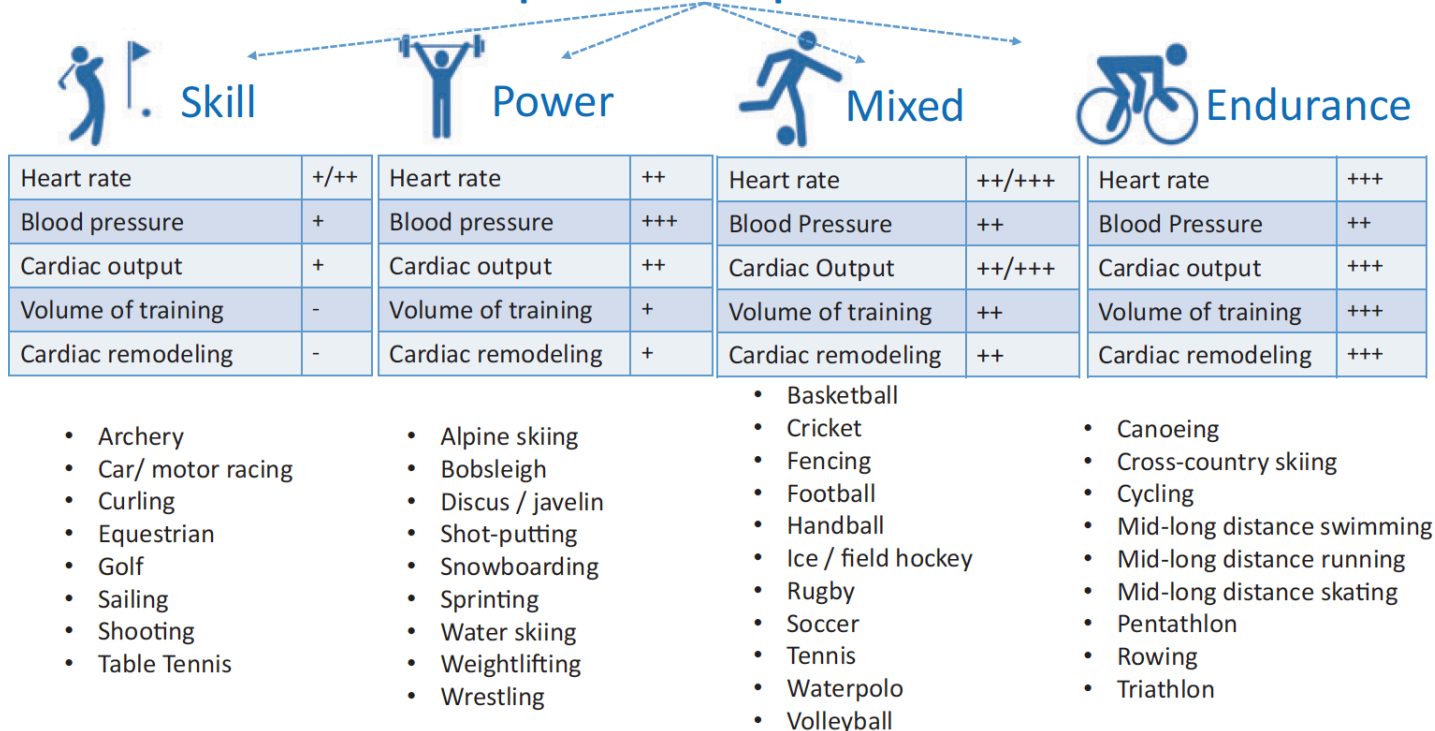
# Hypertension & altitude

**Table 3** Clinical and therapeutic recommendations for hypertensive patients planning to go to high altitude

Patients	Recommendations	Class of evidence	Level of evidence	References
Patients with moderate–severe hypertension and hypertensive patients with moderate–high cardiovascular risk	Check BP values before and during HA sojourn.	IIa	B	7,8,35,36
Well-controlled hypertensive patients/mild hypertensive patients	May reach very HA (>4000 m) with adequate medical therapy.	I	C	8,35,36
Uncontrolled/severe hypertensive patients	Avoid HA exposure in order to prevent risk of organ damage.	I	C	36S

Parati, European Heart Journal (2018) 39, 1546–1554

## Sport Disciplines



Niebauer et al., Eur Heart J. 2018 Oct 21;39(40):3664-3671

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