HYPERTENSION UPDATE
What's new in '22……and beyond

Harvey A. Feldman, MD, FACP, FASN
Professor, Physician Assistant Program
Nova Southeastern University, Ft. Lauderdale, FL

1

2022 A BANNER YEAR!

STEP
QUARTET
TRIUMPH
CHAP
SSaSS

PATH-BP
PRECISION
CLICK
BrigHTN
DCP
TIME
PARAGON
SPRINT '22

2

OUTLINE

- Blood pressure targets: Older persons, pregnant women
- Improving BP control: Nonpharmacologic approaches
- Improving BP control: Pharmacologic approaches
- What will we see in 2023?

3

Blood Pressure Targets in Older Persons

	ACC/AHA 2017	ACP/AAFP 2017	ESC/ESH 2018	ISH 2020	AAFP 2022
AGE	All ages	>60 years	≥65 years	≥65 years	All ages
BP target	<130/<80	<150/<90	<140-130/<90	<150/90	<135/<85

4

Background

- ACC/AHA 2017 HTN Guideline BP target: <130/<80
- Systolic Pressure Intervention Trial (SPRINT), 2015
  - Randomized multicenter trial
  - 9361 nondiabetic adults age ≥50 with CVD risk
  - Baseline SBP 130-180 mmHg
  - Intensive arm: Target SBP <120 mmHg
  - Standard arm: Target SBP <140 mmHg
  - **Outcome: Intensive better (at 3.3 years):**
    - **25% reduction in composite of MACE**
    - **23% reduction in all-cause mortality**
    - **43% reduction in cardiovascular death**

STEP Trial
NEJM 2021;
385(14):1268-79

NEJM 2015;373(22):2103-2016

5

Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP Trial)

Study Population	Intervention	Outcomes: SBP	Composite	Stroke	ACS	AHF
China (Han pop.) Randomized multicenter trial N = 8511 Age: 60-80 years Baseline mean BP: 146/83 ± 17/10	Intensive Arm Target SBP 110 to <130	126.7 ↓19	3.5% (1.0%/y)	1.1% (0.3%/y)	1.3% (0.4%/y)	0.1% (0.03%/y)
Follow-up mean 3.3 yrs		Relative Risk Reduction	26%	33%	33%	73%
	Standard Arm Target SBP 130 to <150	135.9 ↓10	4.6% (1.4%/y)	1.7% (0.5%/y)	1.9% (0.6%/y)	0.3% (0.09%/y)

CONCLUSION: Intensive BP control reduced CV events, but not mortality, in 60-80-year-old Chinese patients.

6

The sad footnote to SPRINT

SPRINT Observational Follow-up Study

N = 2944	Mean SBP –Trial Phase (median 3.3 years)	Mean SBP - Observational Phase (10 years post randomization)
Intensive arm	121.5	140.4
Standard arm	134.6	140.2

N = 2944	Hazard Ratio–Trial Phase intensive vs. standard arm	Hazard Ratio - Observational Phase (10 years post randomization)
CV mortality	0.67	NS
All-cause mortality	0.73	NS

Benefit was lost due to increasing SBP levels in the intensive treatment group.

JAMA Cardiol 2022;7(11):1138-46

7

Blood Pressure Targets in Pregnant Women with Chronic HTN

CHAP
Chronic Hypertension and Pregnancy

Is lower also better in pregnancy?

NEJM 2022;386:1781-92

8

Background

- Prior studies have not shown clear benefit of treating mild chronic hypertension in pregnancy
  - Concern over poor fetal growth from ↓ placental perfusion
- CHIPS (2015): Control of Hypertension in Pregnancy Study
  - 987 pregnant women with mild chronic hypertension (DBP 90-105)
  - Tight control (DBP 85) vs. less-tight control (DBP 100)
  - No difference in fetal growth; less progression to severe HTN
  - Underpowered for other treatment benefits or harms
- ACOG Practice Bulletin 203 (2019): Treat for SBP ≥160 or DBP ≥110…."***based on limited or inconsistent evidence"***

N Engl J Med 2015:372:407-17; Obstet Gynecol 2019;133(1):e26-e49

9

Chronic Hypertension and Pregnancy Trial (CHAP)

Study Population	Intervention	1⁰ Composite Outcome	Other Outcomes Fetus	Other Outcomes Mother
Multicenter RCT (US) Singleton pregnancy <23 wks. gestation Mild chronic HTN (BP: 140-160/90-105)	Active Rx Group Goal BP: <140/90 Labetalol or ER nifedipine	30.2%	11.2%	36.1%
	P	<0.001	NS	<0.011
	Control Group Treat to goal BP only if SBP ≥160 or DBP ≥105	37.0%	10.4%	44.3%

N = 2408; assigned 1:1 to active Rx vs. control

1⁰ composite: Preeclampsia with severe features
Indicated preterm birth <35 wks.
Placental abruption
Fetal or neonatal death

Other outcomes:
Fetus: Birth wt. <10th percentile
Mother: Severe hypertension

CONCLUSION: Active Rx to target BP <140/90 yields better pregnancy outcomes without ↑ fetal risk.

10

ACOG | Clinical

Clinical Guidance | Journals & Publications | Patient Education | Topics

Practice Advisory › Clinical Guidance for the Integration of the Findings of the Chronic Hypertension and Pregnancy (CHAP) Study

Clinical Guidance for the Integration of the Findings of the Chronic Hypertension and Pregnancy (CHAP) Study

Practice Advisory | April 2022

"Based on these findings, **ACOG recommends utilizing 140/90 as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy, rather than the previously recommended threshold of 160/110."**

https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/04/clinical-guidance-for-the-integration-of-the-findings-of-the-chronic-hypertension-and-pregnancy-chap-study

11

Nonpharmacologic Improvement in BP control: Take this with a grain of salt

- **S**alt **S**ubstitute **a**nd **S**troke **S**tudy (SSaSS)
- Meta-analysis on effects of salt substitutes
- UK Biobank studies on adding salt to foods

12

The Great Salt Debate

- Short-term trials show a reduction in BP with lower dietary sodium intake
- Effect on reducing CV events and mortality is less certain; J- or U-shaped curves have been found in some studies
- No long-term RCT's with sustained low sodium intake
- Guidelines vary regarding recommended sodium intake
  - USDA and WHO – 2300 mg/d (1 tsp)
  - ACC/AHA – 1500 mg/d is "ideal for most adults"
- Average sodium intake in the U.S. ~ 3400 mg/d (range 2000-5000 mg/d)

13

Salt Substitute & Stroke Study (SSaSS)

Study Population	Intervention	Urine Na⁺	Urine K⁺	Outcomes: Stroke	CV events	Death	↑K⁺
600 rural Chinese villages	100% NaCl	187 mEq/d	36	33.7	56.3	44.6	3.3
				per 1000 patient years			
Open-label, cluster-randomized trial	Follow-up mean 5 yrs	8% ↓	55% ↑	Relative Risk Reduction 14.0 %	13.0%	12.0%	---
N = 20,995	Salt substitute 75% NaCl 25% KCl	172 mEq/d	57	29.1	49.0	39.3	3.4
Age: ≥60 (mean 65)				per 1000 patient years			
H/O stroke or HTN w/o "serious CKD"	BP + 24-h urine Na⁺ and K⁺ to assess compliance	Conclusion: In this high-risk population, partially replacing NaCl with KCl reduced stroke, CV events, and death without increasing risk of hyperkalemia.					

N Engl J Med 2021;385:1067-77

14

Original research

Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis

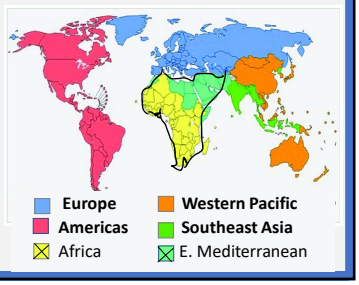
Xuejun Yin,[1] Anthony Rodgers,[1] Adam Perkovic,[2] Liping Huang,[1] Ka-Chun Li,[1] Jie Yu,[1] Yangfeng Wu,[3,4] J H Y Wu,[1] Matti Marklund,[1,5,6] Mark D Huffman,[1,7] J Jaime Miranda,[1,8,9] Gian Luca Di Tanna,[1] Darwin Labarthe,[10] Paul Elliott,[11] Maoyi Tian,[1,12] Bruce Neal[1,11]

Heart 2022;108:1608-1615

15

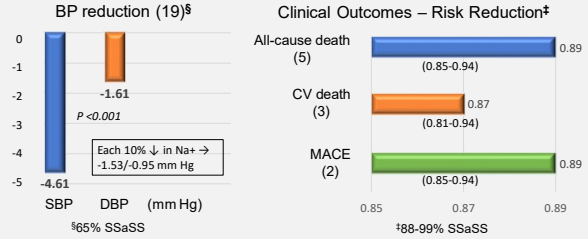
Effects of salt substitute on clinical outcomes: a systematic review and meta-analysis

- 19 trials; 29,528 participants
  - 19 reported effects on BP
  - 5 reported effects on clinical outcomes
  - Diverse populations
    - Europe (5)
    - Western Pacific (11)
    - The Americas (4)
    - Southeast Asia (1)
- Na⁺ 33%-75%; K⁺ 25%-65%



16

Effects of salt substitute on clinical outcomes: a systematic review and meta-analysis



Conclusion: Potassium-enriched salt produces a dose-dependent reduction in BP in diverse populations world-wide. It may also improve cardiovascular and mortality outcomes, though the data are less solid.

17

Adding salt to foods and hazard of premature mortality

Hao Ma[1], Qiaochu Xue[1], Xuan Wang[1], Xiang Li[1], Oscar H. Franco[2], Yanping Li[1,3], Yoriko Heianza[1], JoAnn E. Manson[1,4,5], and Lu Qi[1,4,6]

Eur Heart J 2022 (Aug);43:2878-88

Adding Salt to Foods and Risk of Cardiovascular Disease

Hao Ma, MD, PhD,[a] Xuan Wang, MD, PhD,[a] Xiang Li, MD, PhD,[a] Yoriko Heianza, RD, PhD,[a] Lu Qi, MD, PhD[a,b]

J Am Coll Cardiol 2022 (Dec);2157-67

Large population-based prospective studies using the UK Biobank cohort

Frequency of adding salt to foods

501,379 participants, 9 years follow-up

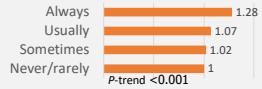
176,570 participants, 11.8 years follow-up

18

Association of long-term added salt consumption with mortality and CVD

Eur Heart J 2022 (Aug);43:2878-88

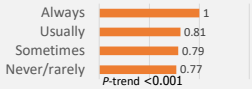
HR of premature mortality



- Frequency of adding salt correlated with 24-h urine sodium excretion
- High intake of fruits and vegetables attenuated risk of high salt intake

J Am Coll Cardiol 2022 (Dec);2157-67

HR of cardiovascular events



- Strongest associations of added salt intake were heart failure and ischemic heart disease (*P*-trend <0.001 for both)
- Lowest added salt intake + DASH diet yielded lowest CVD risk

19

My overall conclusion on what's new in 2022 about salt

- Confirmation of the causal relationship between high salt intake and hypertension
- Added evidence that high salt intake probably directly affects cardiovascular disease and mortality
- Added evidence of the importance of potassium in modifying the adverse effects of sodium
- BUT….we still do not know what the sweet spot is for salt consumption

20

Novel antihypertensive combination strategies

QUARTET[1] and QUARTET-USA[2]

TRIUMPH[3]

1. Lancet 2021;398:1043-52
2. Presented at AHA 2022 Scientific Sessions; Curr Atheroscler Rep 2023;25(1):31-41
3. JAMA Cardiol 2022;7:645-50

21

Background

Initial Treatment of Hypertension

ACC/AHA 2017

- Monotherapy 1 pill – **1 drug**
  Stage 1 hypertension with 10-yr ASCVD risk of ≥10%
- Combination therapy 1 pill – **2 drugs**
  Stage 2 hypertension: ACEi or ARB + CCB or ACEi or ARB + diuretic

ESC/ESH 2018

- Monotherapy 1 pill – **1 drug**
  Stage I hypertension with low ASCVD risk or very elderly or frail
- Combination therapy 1 pill – **2 drugs**
  Stage 1 or 2: ACEi or ARB + CCB or ACEi or ARB + diuretic

22

QUARTET (Australia)

Multicenter double-blind RCT (Australia)

591 adults, mean age 59 ±12 years

Baseline office BP: 140-179/90-109 ½ untreated

Assigned to 1/4-dose quad pill vs. std. dose monotherapy

Target BPs: <140/90 and <120/80

Intervention		12 weeks Quad	12 weeks Control	52 weeks Quad	52 weeks Control
Quad pill (N = 300) **esartan 37.5 mg, lodipine 1.25 mg dapamide 0.625 mg soprolol 2.5 mg**	Need for more meds	15%	40%	19%	58%
	Blood pressure	120/71	127/78	121/71	128/76
	% <140/90	76	58	81	62
Follow-up 12-wk and 52-wk (N = 417)	% <120/80	46	26	53	25
Control Grp (N = 291) Irbesartan 150 mg	hypotension	1%	0.3%	0	1%
	dizziness	1%	0	3%	1%
	bradycardia	1%	0	2%	0

CONCLUSION: ¼-dose combination therapy is superior to monotherapy with good safety profile

23

QUARTET-USA

- RCT – Chicago
- 62 treatment naive patients; 90% Hispanic or Black; >½ low-income
- Mini-dose quad pill vs. standard-dose monotherapy
- 12-week follow-up
- Similar outcomes to QUARTET, but not all statistically significant

TRIUMPH (Sri Lanka)

- Post-hoc analysis of open-label RCT
- 700 patients; mean age 56
- Triple ½-dose combination (ARB, CCB, thiazide) vs. usual care
- Greater time at target BP over 6 months follow-up with triple ½-dose combination

24

Background: Why hypertension experts favor Chlorthalidone (CTD)

- **CTD is more potent and longer-lasting → better 24h BP control due to lower nocturnal BPs**
- **CTD was used in the seminal outcomes trials of hypertension**
- **CTD inhibits platelet aggregation and vascular permeability, improves endothelial function, and promotes angiogenesis**

BUT….No large RCTs have compared head-to-head CTD with HCTZ for cardiovascular outcomes…..until NOW

25

Diuretic Comparison Project (DCP)

Study Design

Pragmatic randomized open-label trial within the VA system

547 primary care centers
4178 providers

13,523 hypertensive adults ≥65 (mean age 72 years); 97% men
Taking HCTZ 25 mg daily (95%) or 50 mg daily (5%)

Randomized to continue same dose of HCTZ or switched to CTD = ½ of their HCTZ dose

Follow-up 2.4 years

Outcome Measures

Primary Outcome
Composite of nonfatal MI, stroke, hospitalization for heart failure, urgent revascularization for unstable angina, and non-cancer death

Secondary Outcomes
Components of primary outcome
Difference in systolic BP

Adverse Events
Hypokalemia

Results

	CTD	HCTZ
Primary composite	10.4%	10.0%
	NS	
Primary components	NS	NS
Systolic BP	139	139
Hypokalemia*	6.0%	4.4%
K+ <3.1 mEq/l*	5.0%	3.6%

Limitations

Male population, already on HCTZ
Primary outcome % less than expected
Only 13% on HCTZ monotherapy
No data on HCTZ >25mg, CTD >12.5mg

NEJM 2022 (Dec 14): DOI: 10.1056/NEJMoa2212270

Conclusion: CTD and HCTZ produce equivalent CVD outcomes.

26

CLICK Trial

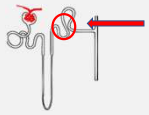
Chlorthalidone in Chronic Kidney Disease

N Engl J Med 2021(Dec 30);385:2507-19

27

Do Thiazides Lower Blood Pressure in Advanced Chronic Kidney Disease?

- Prevailing dogma based on small early studies:
  Thiazides are ineffective with GFR <30 ml/min (Stage 4 CKD)



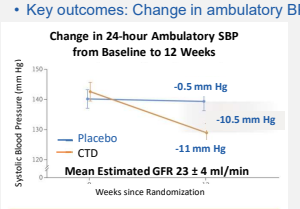
- Only 5% of filtered sodium is reabsorbed here
- Thiazides act on the luminal side of the tubule
- With reduced tubular mass, less drug is secreted into the tubular lumen.

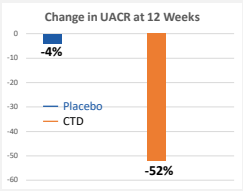
- More recent small studies suggest:
  Thiazides w/wo a loop diuretic have some efficacy for HTN in advanced CKD

28

Chlorthalidone in Chronic Kidney Disease (CLICK)

- Double-Blind RCT in an Indianapolis academic health system
- 160 patients with stage 4 CKD and uncontrolled HTN by ABPM (130-159/80-99)
- CTD 12.5 mg/d titrated prn q4 weeks to 50 mg/d vs. placebo x 12 weeks
  (mean CTD dose at 12 weeks = 23.1 mg/d)
- Key outcomes: Change in ambulatory BP + UACR at 12 weeks





29

Is nocturnal dosing of antihypertensive medications superior to daytime dosing?

Does chronotherapy for hypertension make sense?

HYGIA[1]
vs.
TIME[2]

1. Eur Heart J 2020;41:4565-76
2. Lancet 2022;400:1417-25

30

Rationale for Nocturnal Dosing

- Loss of the normal nocturnal dip in BP is the strongest predictor of adverse cardiovascular events
- Cardiovascular events are associated with the morning surge in blood pressure
- Evening dosing of antihypertensive medication may better normalize the diurnal rhythm of blood pressure and prevent long-term adverse sequelae of hypertension

31

ESC European Society of Cardiology
European Heart Journal (2020) 41, 4565–4576
doi:10.1093/eurheartj/ehz754

CLINICAL RESEARCH
Hypertension

Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial

Ramón C. Hermida [1]*, Juan J. Crespo[1,2], Manuel Domínguez-Sardiña[2], Alfonso Otero[3], Ana Moyá[4], María T. Ríos[1,2], Elvira Sineiro[1,4], María C. Castiñeira[1,5], Pedro A. Callejas [1,2], Lorenzo Pousa[1,2], José L. Salgado[1,2], Carmen Durán[2], Juan J. Sánchez[1,6], José R. Fernández[1], Artemio Mojón[1], and Diana E. Ayala[1]; for the Hygia Project Investigators[‡]

32

Hygia Chronotherapy Trial

- Hazard Ratios: Bedtime vs. Awakening time dosing
  - Primary composite outcome: 0.55
    (CVD death, MI, coronary revascularization, heart failure, stroke)
  - CVD death: 0.44
  - Myocardial infarction: 0.66
  - Coronary artery revascularization: 0.60
  - Heart failure: 0.58
  - Stroke: 0.51
  - Peripheral vascular disease: 0.52

40 to >50% reductions!

33

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

*Isla S Mackenzie, Amy Rogers, Neil R Poulter, Bryan Williams, Morris J Brown, David J Webb, Ian Ford, David A Rorie, Greg Guthrie, J W Kerr Grieve, Filippo Pigazzani, Peter M Rothwell, Robin Young, Alex McConnachie, Allan D Struthers, Chim C Lang, Thomas M MacDonald, on behalf of the TIME Study Group**

Summary

Background Studies have suggested that evening dosing with antihypertensive therapy might have better outcomes than morning dosing. The Treatment in Morning versus Evening (TIME) study aimed to investigate whether evening dosing of usual antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension.

Methods The TIME study is a prospective, pragmatic, decentralised, parallel-group study in the UK, that recruited adults (aged ≥18 years) with hypertension and taking at least one antihypertensive medication. Eligible participants were randomly assigned (1:1), without restriction, stratification, or minimisation, to take all of their usual antihypertensive medications in either the morning (0600–1000 h) or in the evening (2000–0000 h). Participants were

Lancet 2022; 400: 1417–25
Published Online October 11, 2022
https://doi.org/10.1016/S0140-6736(22)01786-X
See Comment page 1383
*Other members of the TIME Study Group and contributors are listed in the appendix (p 17)
MEMO Research

34

Treatment in Morning vs. Evening (TIME)

- Hazard Ratios: Evening vs. Morning dosing
  - Primary composite outcome: NS
    (CVD death, nonfatal myocardial infarction, nonfatal stroke)
  - Myocardial infarction: NS
  - Nonfatal stroke: NS
  - Vascular death: NS
  - Coronary artery revascularization: NS
  - Heart failure: NS
  - All-cause morality: NS

Conclusion: Timing of BP medication makes no difference.

35

A glimpse into the future

Two Cuffless Blood Pressure Measuring Devices

Two New Classes of Antihypertensive Drugs for Resistant Hypertension

36

Cuffless BP Measuring Devices

- Cuffless devices have considerable potential to improve awareness and treatment of hypertension
- Many cuffless devices are currently marketed……
  But their accuracy and performance have been questioned
- Validation protocols for cuff BP devices are inadequate for cuffless devices*……
  But they are in development.

*validatebp.org
stridebp.org
dableducational.org

37

Wristband Cuffless BP Monitor

- Tested and available in Europe; under FDA review
- Uses photoplethysmography signals from optical sensors at the wrist to continuously monitor BP
- BP measurements are displayed on a smartphone app
- Tested……
  - Different body positions
  - Against intra-arterial line BPs
  - Across age, gender, BMI, and skin color
  - Lowered BP in a 6-month clinical trial (AHA meeting 2022)

38

Electronic Tattoos

- Thin, sticker-like tattoos placed over the radial and ulnar arteries
- Grapheen, a lattice of carbon atoms, one atom thick
- Grapheen is conductive and uses bioelectrical impedance technology to capture data that is converted into BP values through a machine learning algorithm
- In development; availability predicted to be in the next five years

39

New Classes of Antihypertensive Drugs for Resistant Hypertension

Resistant hypertension:
BP that is uncontrolled on at least three antihypertensive medications of different classes

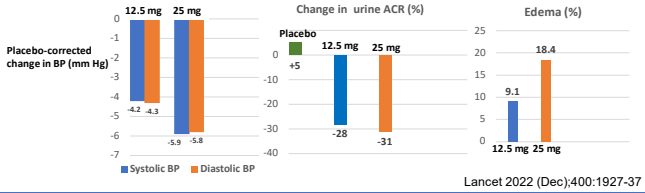
Two new classes:

- Endothelin receptor antagonist
  - Aprocitentan
- Aldosterone synthase inhibitor
  - Baxdrostat

40

Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial

Markus P Schlaich, Marc Bellet, Michael A Weber, Parisa Danaietash, George L Bakris, John M Flack, Roland F Dreier, Mouna Sassi-Sayadi, Lloyd P Haskell, Krzysztof Narkiewicz, Ji-Guang Wang, on behalf of the PRECISION investigators*



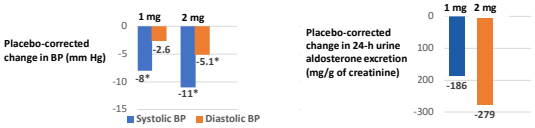
Lancet 2022 (Dec);400:1927-37

41

ORIGINAL ARTICLE

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators*



N Engl J Med 2023;388:395-405

42