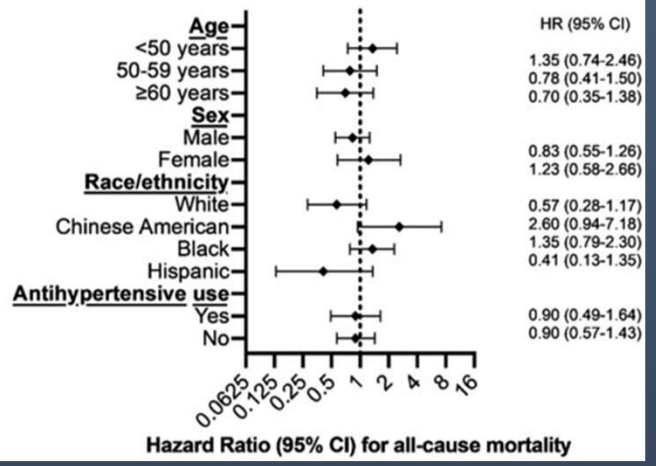
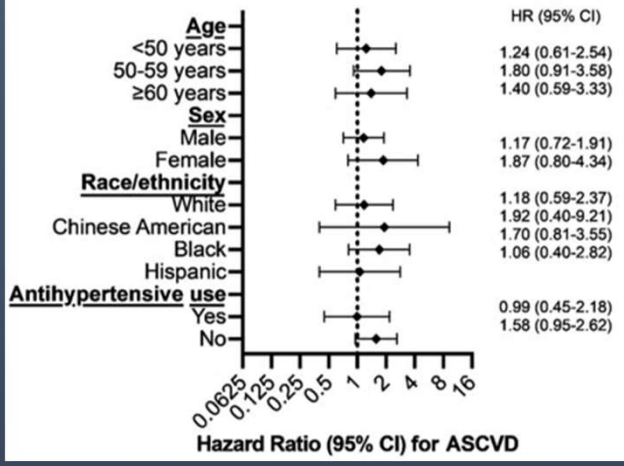
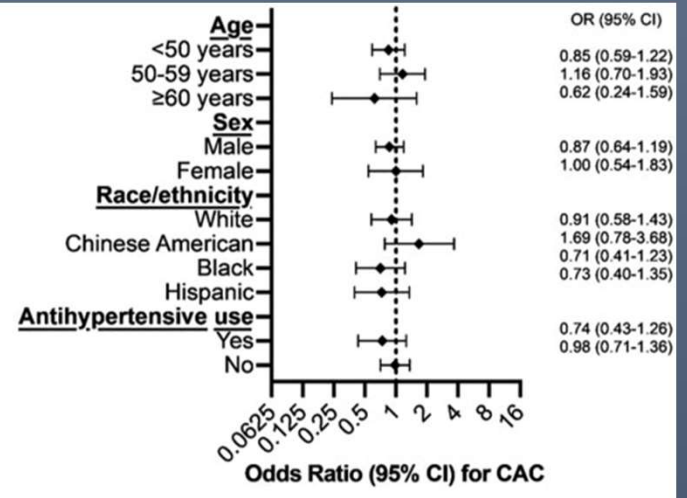
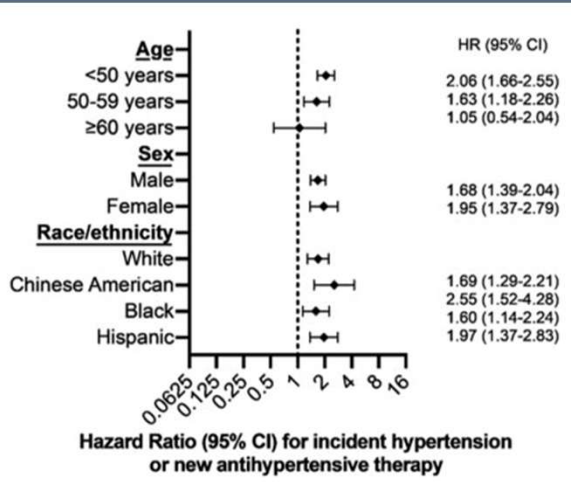
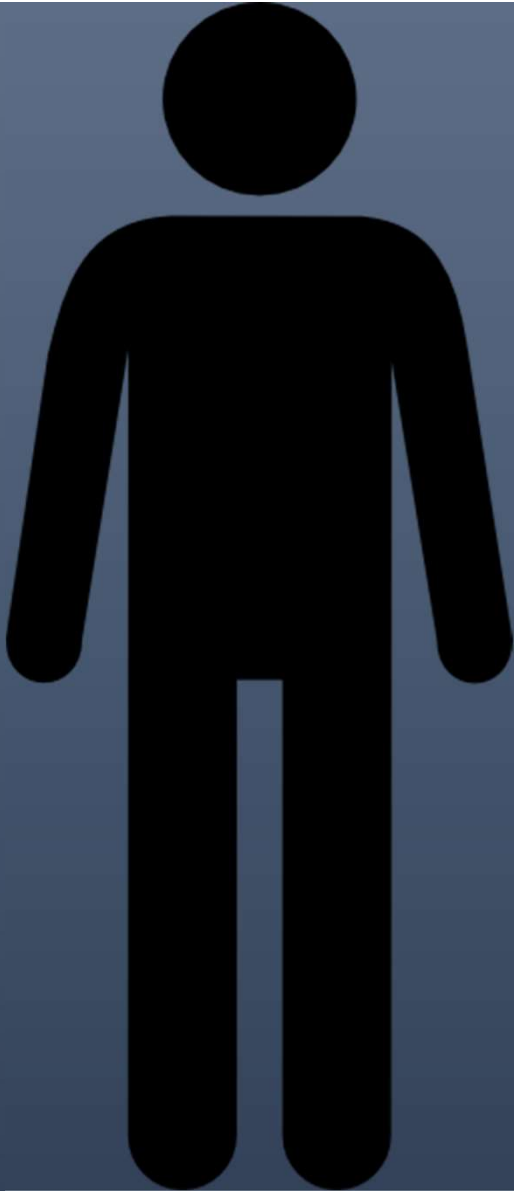


- Absolute CV risk low
- Progressive association between BP subgroups and CV events
- Every 10 mm Hg increment of SBP associated with a 5% increased risk of CV events
- Every 5 mm Hg increment of DBP associated with a 4% increased risk of CV events
- Burden of stroke evident in higher DBP
- All-cause mortality risk rose from SBP 150 – 160 mmHg

Isolated diastolic hypertension (IDH)

- Depending on definition, the estimated US population prevalence is 1.3 – 6.5% (with DBP >90 mmHg and >80 mmHg respectively)
- DBP 80 – 90 mmHg, in the context of well controlled SBP, is not associated with excess risk of CVD risk compared normotensive people
- IDH increases the risk for the development of incident systolic hypertension
- Limitations: Minimum participant age is 45 yo in meta-analyses



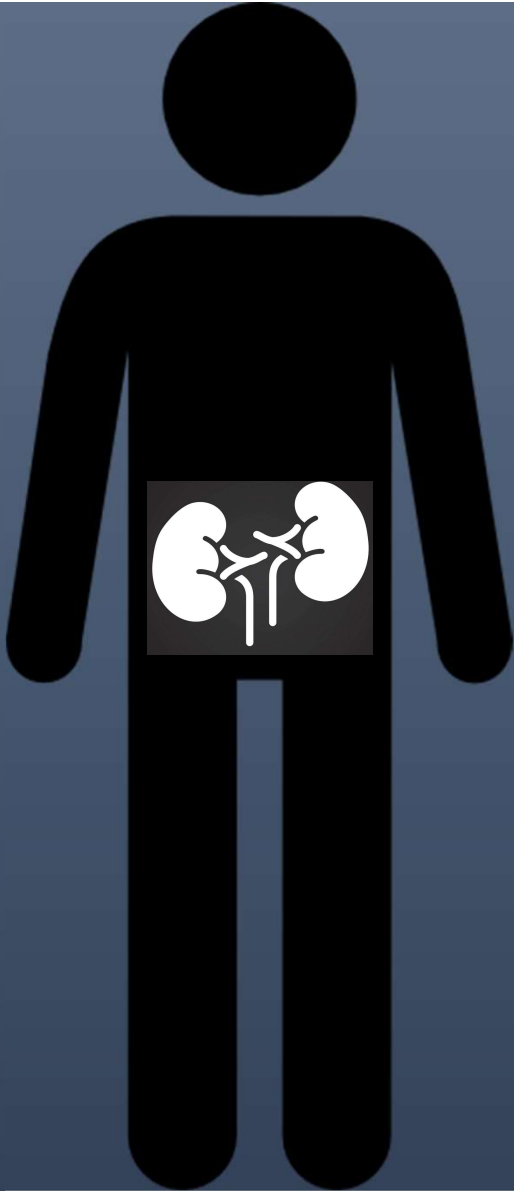


Clinical questions

- A. Does elevated BP in young adults (<40 yo) matter?
- B. What about isolated diastolic hypertension?

- What is the threshold for treatment?

- A. Treatment reasonable in young adults with stage 2 hypertension and those with increased CV risk factors, particularly with targeting stroke risk
- B. No data in young patients. However, important to monitor for the development of systolic hypertension. Consider if increased risk for stroke



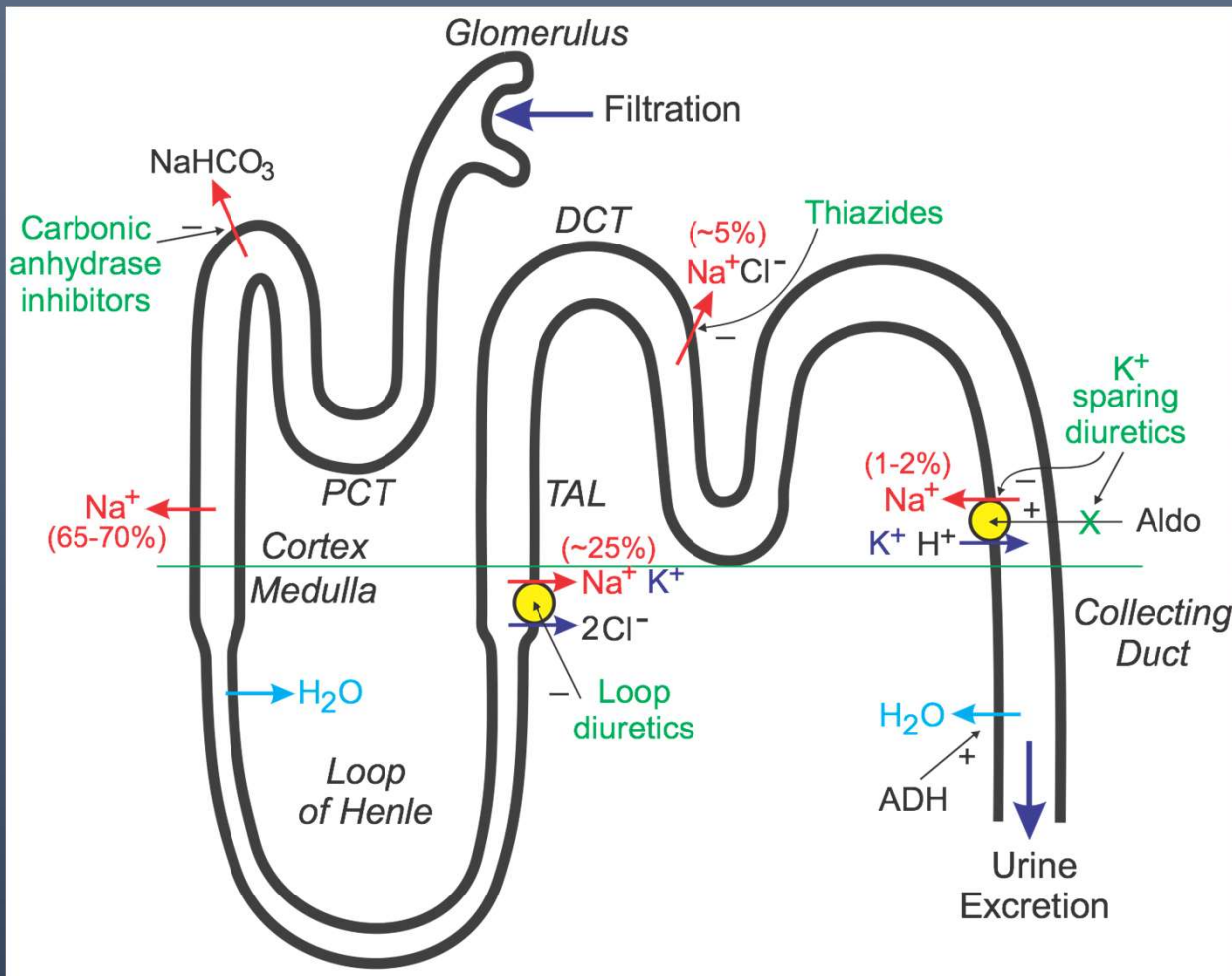
Patient with CKD 4 G2 (eGFR 28 ml/min/1.73m²) has poorly controlled hypertension 150/85 mmHg on optimally dosed Candesartan, Amlodipine and furosemide. His BMI is 35. His aldo/renin ratio is elevated.

Next best step in management?

- A. Salt reduction
- B. Add Spironolactone
- C. Add Chlorthalidone
- D. DASH diet

Renal parenchymal hypertension

- Occur in >90% of patients with CKD (diabetes and hypertension)
- Mechanism driven by RAS upregulation in the setting of ischaemic glomerular injury, and sodium retention and extracellular volume expansion
- BP reduction to <130/80 mmHg primarily to reduce CV risk
- Diuretics cornerstone of the management of hypertension in patients with CKD



- Loop diuretics preferred over thiazides in advanced CKD
- Thiazides thought to be less effective in advanced CKD associated with reduced diuretic delivery to tubular lumen.

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

DECEMBER 30, 2021

VOL. 385 NO. 27

Chlorthalidone for Hypertension in Advanced Chronic
Kidney Disease

Rajiv Agarwal, M.D., Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S.,
Jazmyn H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D.

CLICK study

- Double blind 12 week Phase 2 RCT, N = 160
- Uncontrolled HTN on 24 hour ABPM SBP >130 mmHg or DBP >80 mmHg and on at least 1 antihypertensive agent
- Baseline eGFR 23.2 ± 4.2 ml/min/1.73m²
- 76 % diabetes
- 60 % on loop diuretics
- 3.4 antihypertensive medications at baseline

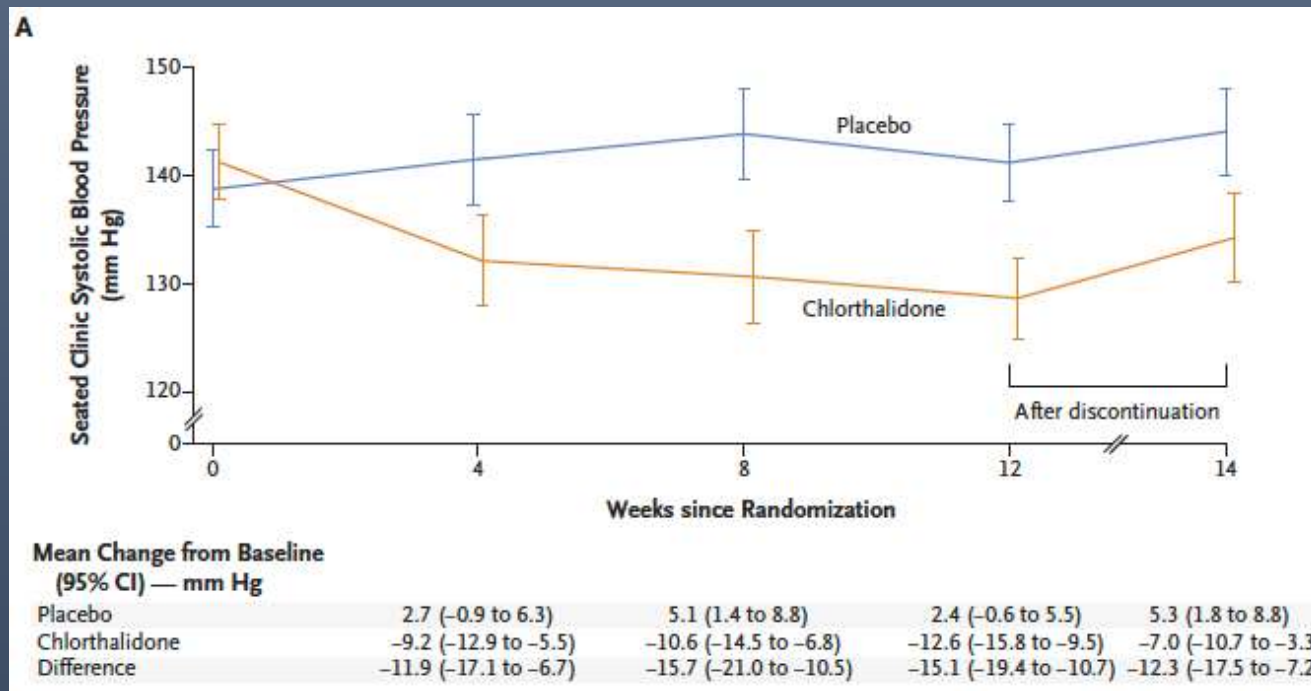
N Engl J Med 2021;385:2507-19.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Chlorthalidone (N=81)	Placebo (N=79)
Age — yr	66.2±10.8	66.7±10.8
Male sex — no. (%)	62 (77)	62 (78)
Race or ethnic group — no. (%)†		
White	46 (57)	47 (59)
Black	32 (40)	32 (41)
Asian	2 (2)	0
Hispanic	1 (1)	0
Medical history — no. (%)		
Diabetes mellitus	60 (74)	61 (77)
Sleep apnea	36 (44)	39 (49)
Coronary artery disease	26 (32)	25 (32)
Hospitalization for heart failure	26 (32)	27 (34)
Gout	20 (25)	24 (30)
Stroke	20 (25)	16 (20)
Myocardial infarction	17 (21)	22 (28)
Percutaneous coronary revascularization	17 (21)	13 (16)
Coronary-artery bypass graft	10 (12)	7 (9)
Peripheral vascular bypass	3 (4)	7 (9)
Cause of chronic kidney disease — no. (%)		
Diabetes	42 (52)	42 (53)
Hypertension	26 (32)	26 (33)
Glomerulonephritis	3 (4)	5 (6)
Obstructive uropathy	3 (4)	2 (3)
Polycystic kidney disease	1 (1)	1 (1)
Other	6 (7)	3 (4)

Characteristic	Chlorthalidone (N=81)	Placebo (N=79)
Estimated GFR — ml/min/1.73 m ²	23.5±4.2	22.8±4.2
Median NT-proBNP (IQR) — pg/ml	545 (189–1342)	636 (274–1601)
Median plasma renin (IQR) — pg/ml	2276 (1160–4702)	2611 (1198–4870)
Median plasma aldosterone (IQR) — pg/ml	313 (181–519)	321 (189–499)
Median urine sodium excretion (IQR) — mmol/24 hr	115 (82–142)	96 (77–129)
Current smoking — no. (%)	21 (26)	19 (24)
Height — cm	171.7±11.3	173.0±8.6
Weight — kg	97.4±23.6	95.8±23.5
Body-mass index‡	33.0±7.0	32.0±7.4
Hip circumference — cm	115.9±14.9	114.6±15.0
Waist circumference — cm	115.3±17.0	115.4±16.6
Waist-to-hip ratio	1.011±0.078	0.998±0.074
Systolic blood pressure — mm Hg	141.2±15.1	138.7±16.0
Diastolic blood pressure — mm Hg	69.2±12.3	67.9±13.9
Pulse rate — beats/min	66.5±11.7	64.3±11.1
Median spot urinary albumin-to-creatinine ratio (IQR)§	862 (187–2274)	812 (128–2022)
Urinary albumin-to-creatinine ratio category — no. (%)§		
<30	5 (6)	9 (11)
30 to <300	19 (23)	19 (24)
≥300	56 (69)	51 (65)

CLICK study: Change in systolic BP



At 12 weeks
SBP – 10.5 mmHg
DBP -3.9 mmHg

Similar reductions in day and night BP

No significant change in proportion of patient with nocturnal dip

Independent effect from the concurrent use of loop diuretics