Hypertension: Beyond the ACE and ARB in Diabetes and the Time of COVID

Hypertension and Diabetes: The Essentials

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Disclosures

- I have no conflicts of interest

Outline

- Blood Pressure Target
- Standardized Measurement
- Pathogenesis
- Non-pharmacologic therapies
- Ideal medical management
- Resistant Hypertension
- Nocturnal Hypertension/Chronotherapy

- "The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try to reduce it."

-J.H. Hay, 1931

Target BP?

What is your blood pressure target for patients with diabetes?

A. <140/80

B. <130/80

C. <120/80

D. Other

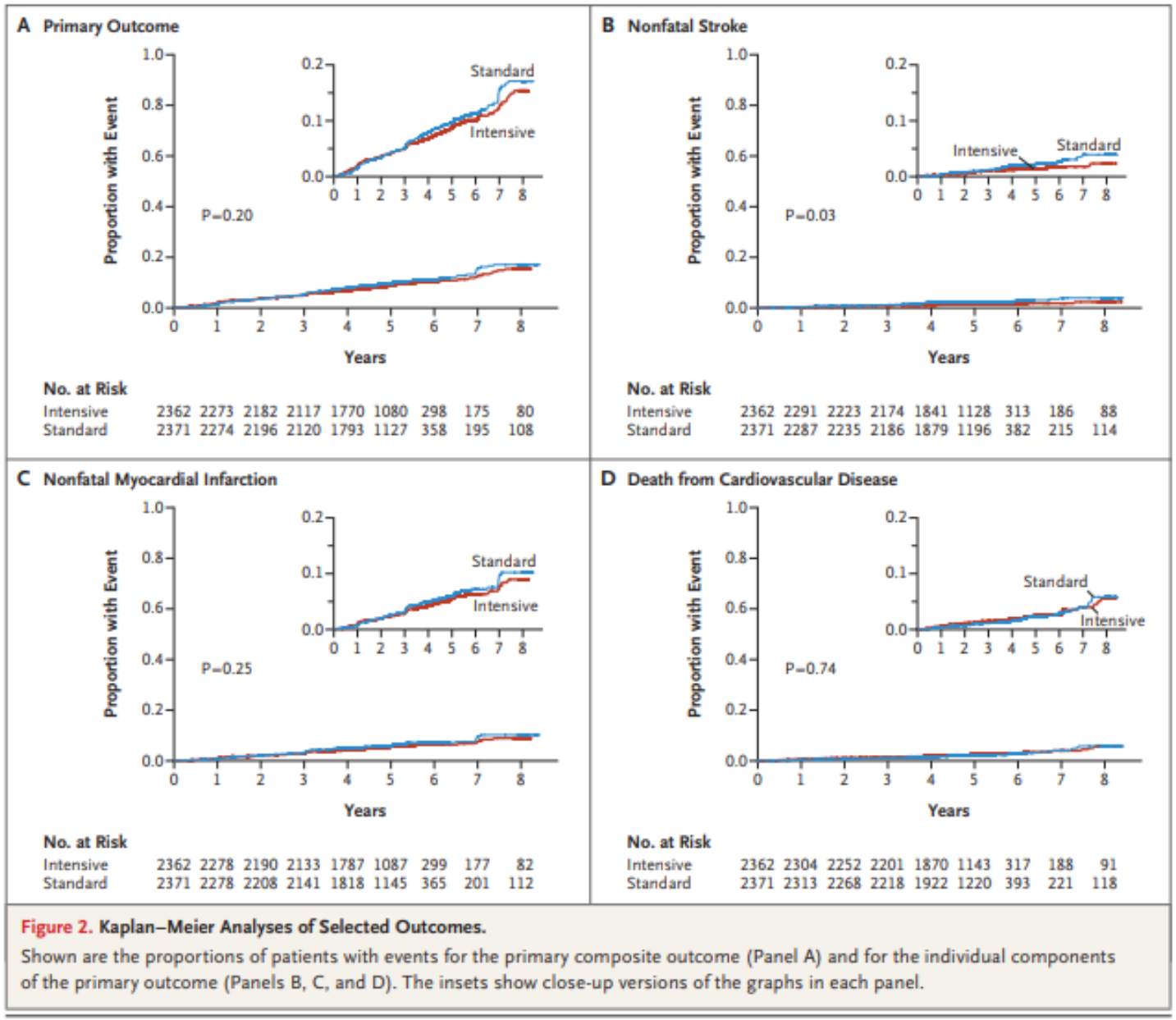
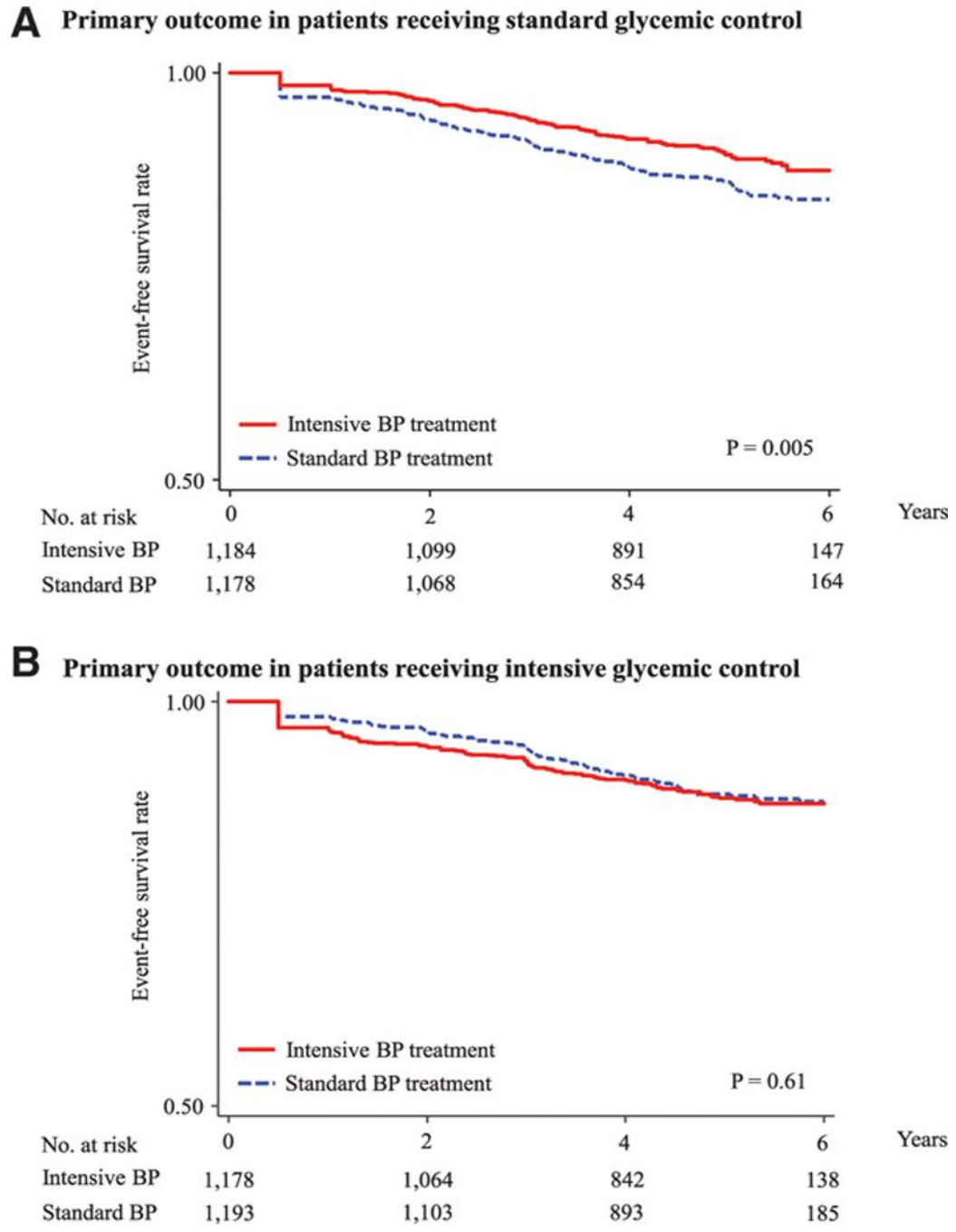


Figure 2. Kaplan–Meier Analyses of Selected Outcomes.
Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.

ACCORD BP. NEJM. 2010



Tsujimoto et al. Hypertension. 2018

What about elderly patients?

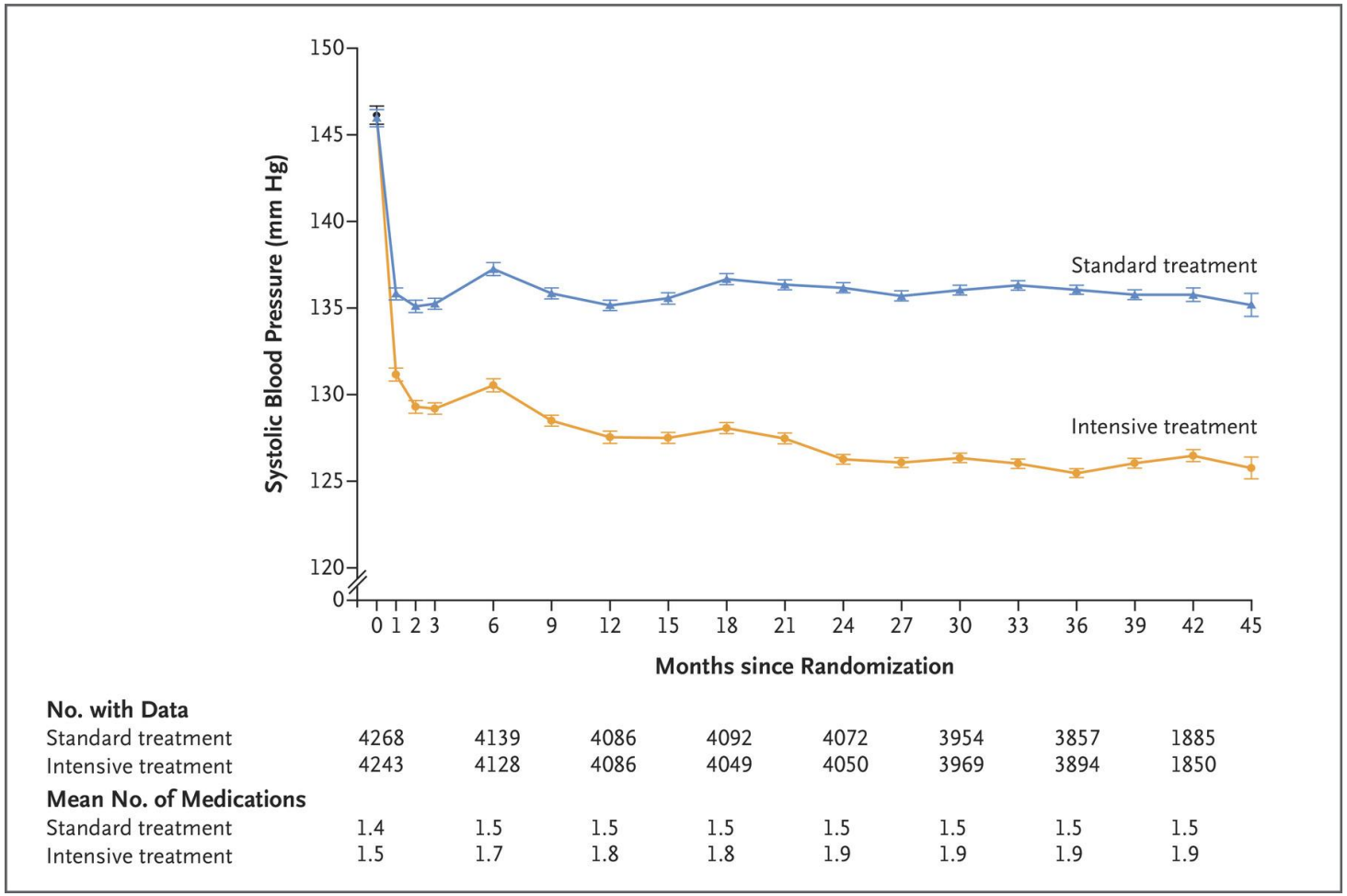
STEP Trial

BP 110-130 v 130-150

Age 60-80

N=8500

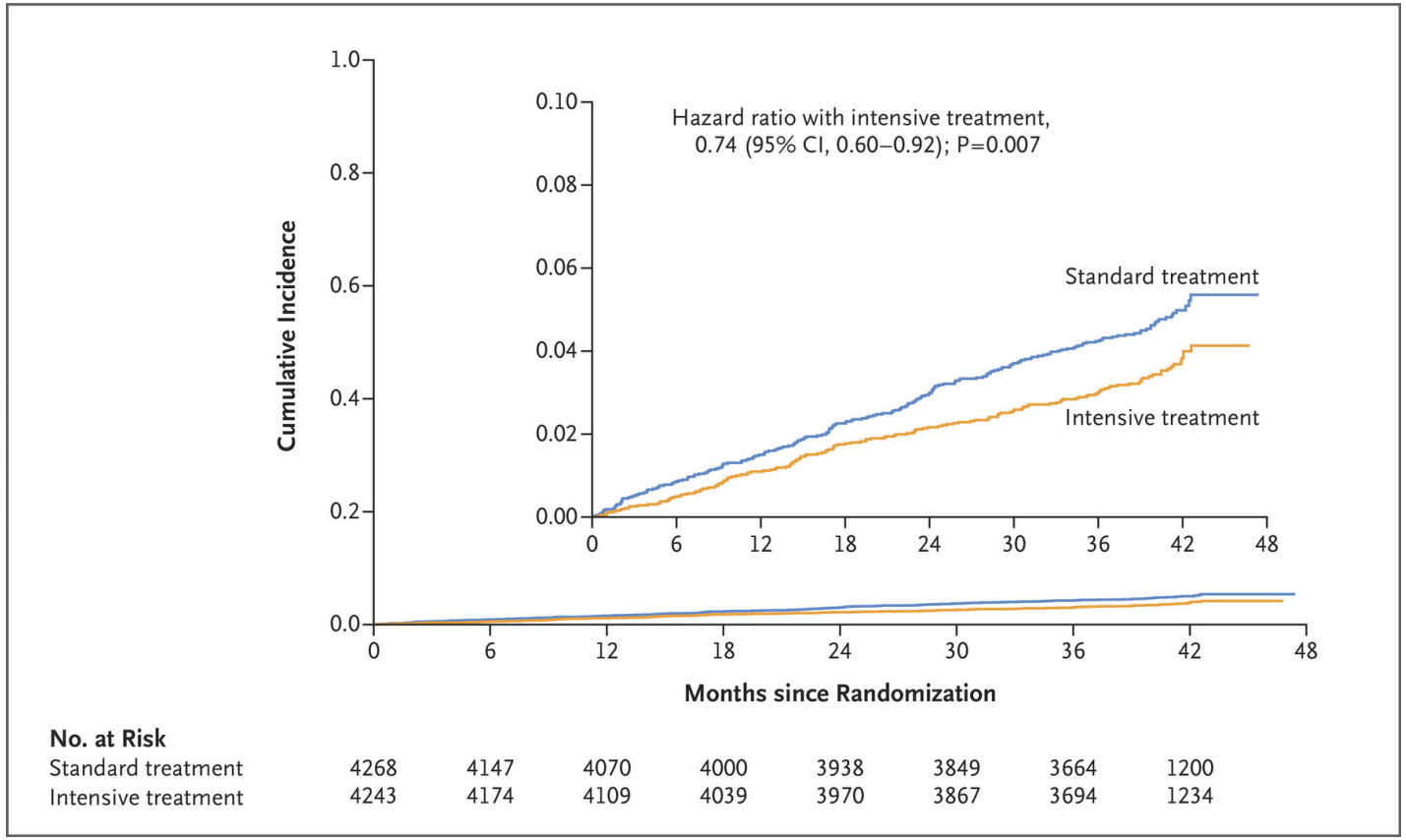
~20% with DM



No. with Data								
Standard treatment	4268	4139	4086	4092	4072	3954	3857	1885
Intensive treatment	4243	4128	4086	4049	4050	3969	3894	1850
Mean No. of Medications								
Standard treatment	1.4	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Intensive treatment	1.5	1.7	1.8	1.8	1.9	1.9	1.9	1.9

Zhang et al. NEJM. 2021

STEP trial

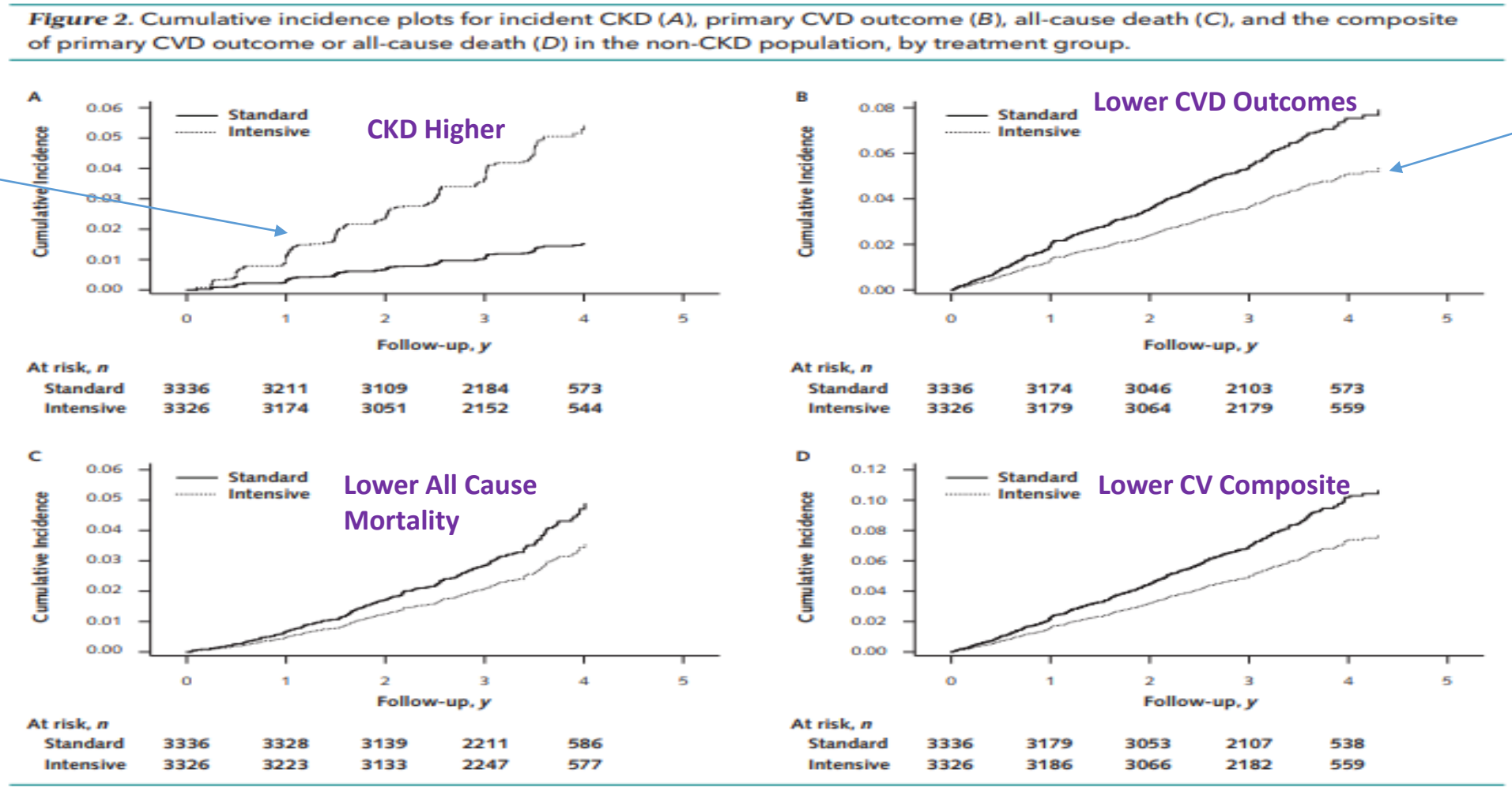


Zhang et al. NEJM. 2021

SPRINT TRIAL

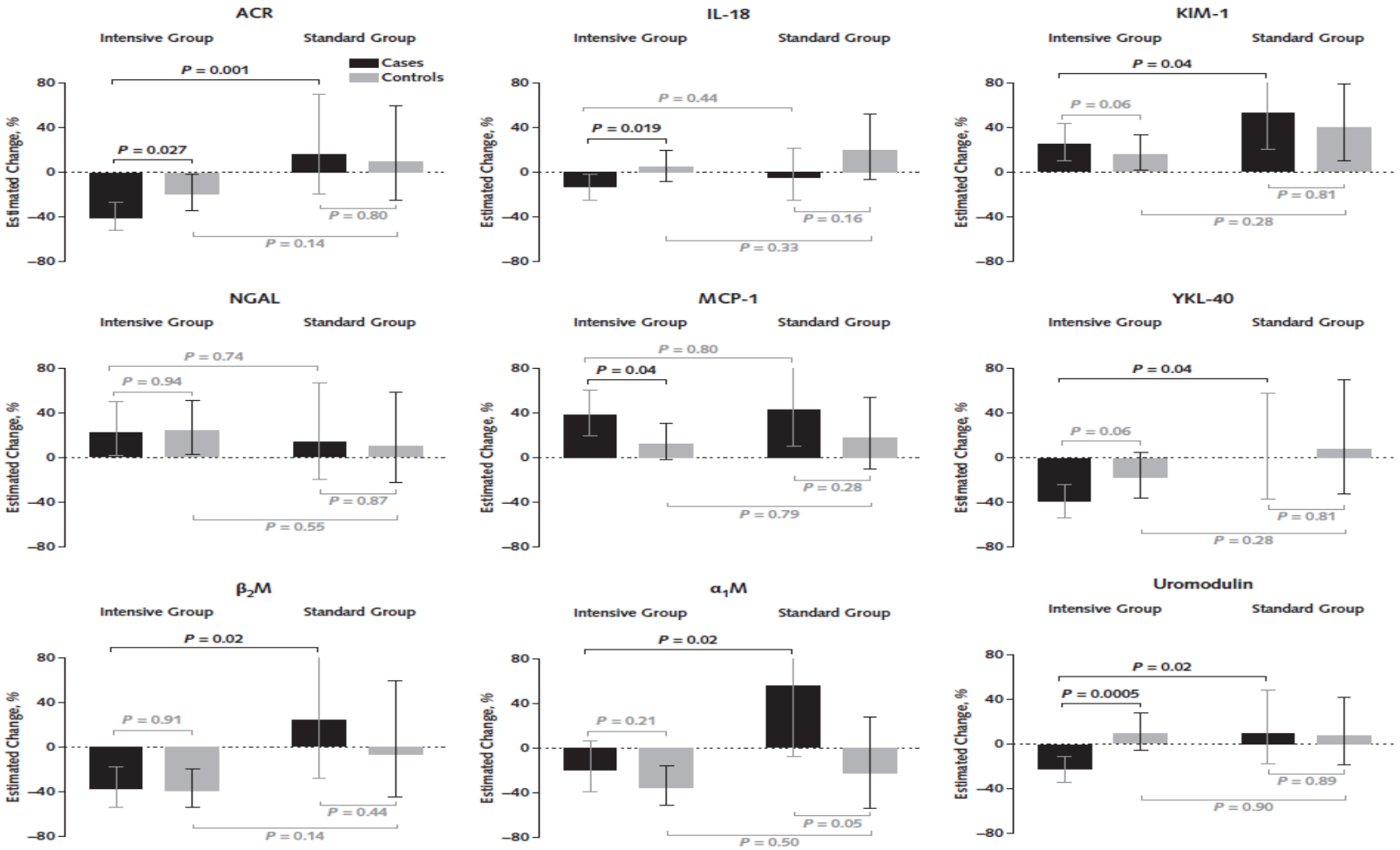
Increased Incidence of CKD

BUT ALL Hard Outcomes Better



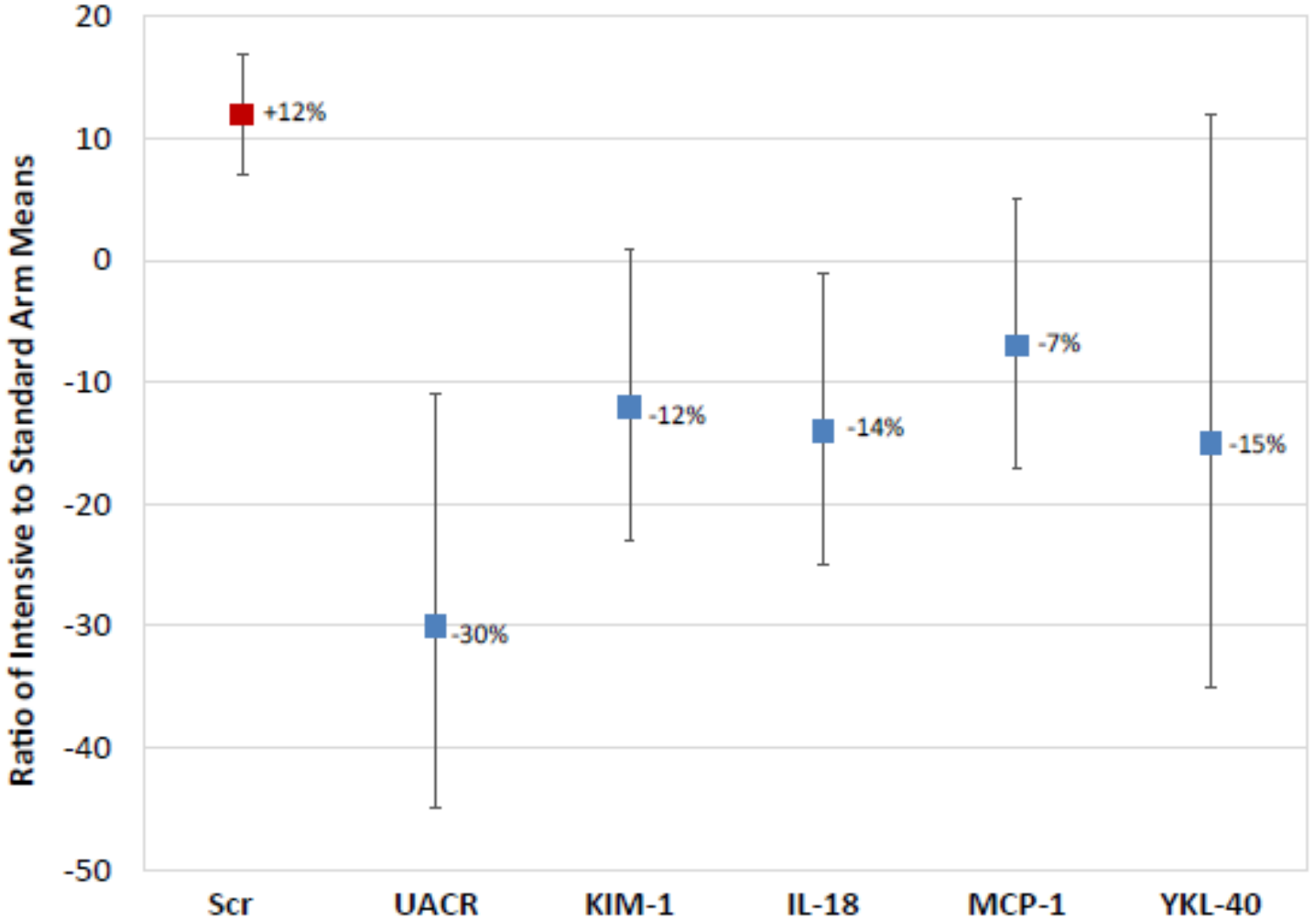
Beddu et al. Ann Intern Med. 2017

Lower urinary biomarkers in SPRINT participants in intensive arm who developed "CKD"



Zhang et al. Ann Intern Med. 2018

Similar Findings in ACCORD

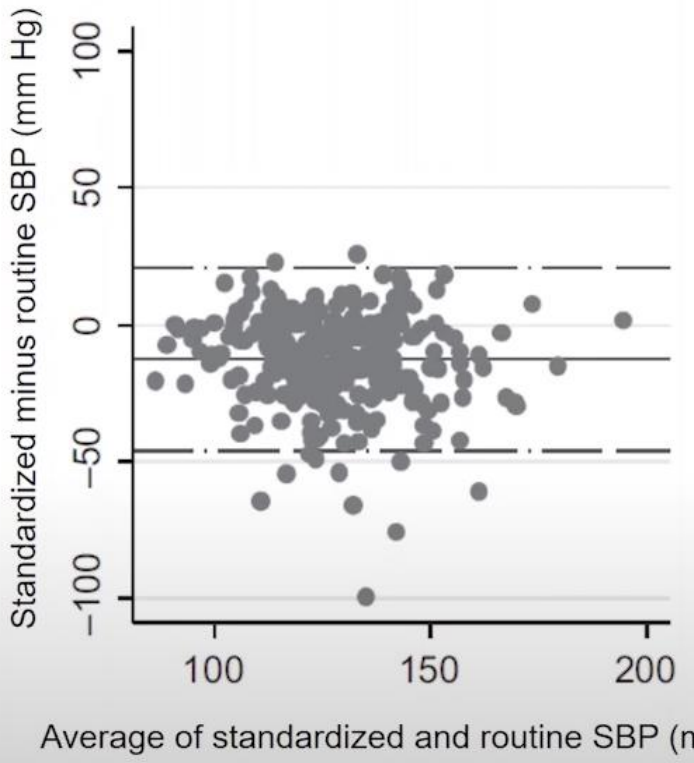


GFR decreased but urinary biomarkers went DOWN!

Nadkarni et al. Am J Kid Dis 2018

The KEY is Standardized Measurements!

Poor Correlation Between Routine and Standardized Office BP



- N = 275 CKD
- eGFR 29±10 ml/min/1.73m^2
- Bland-Altman plot with limits of agreement

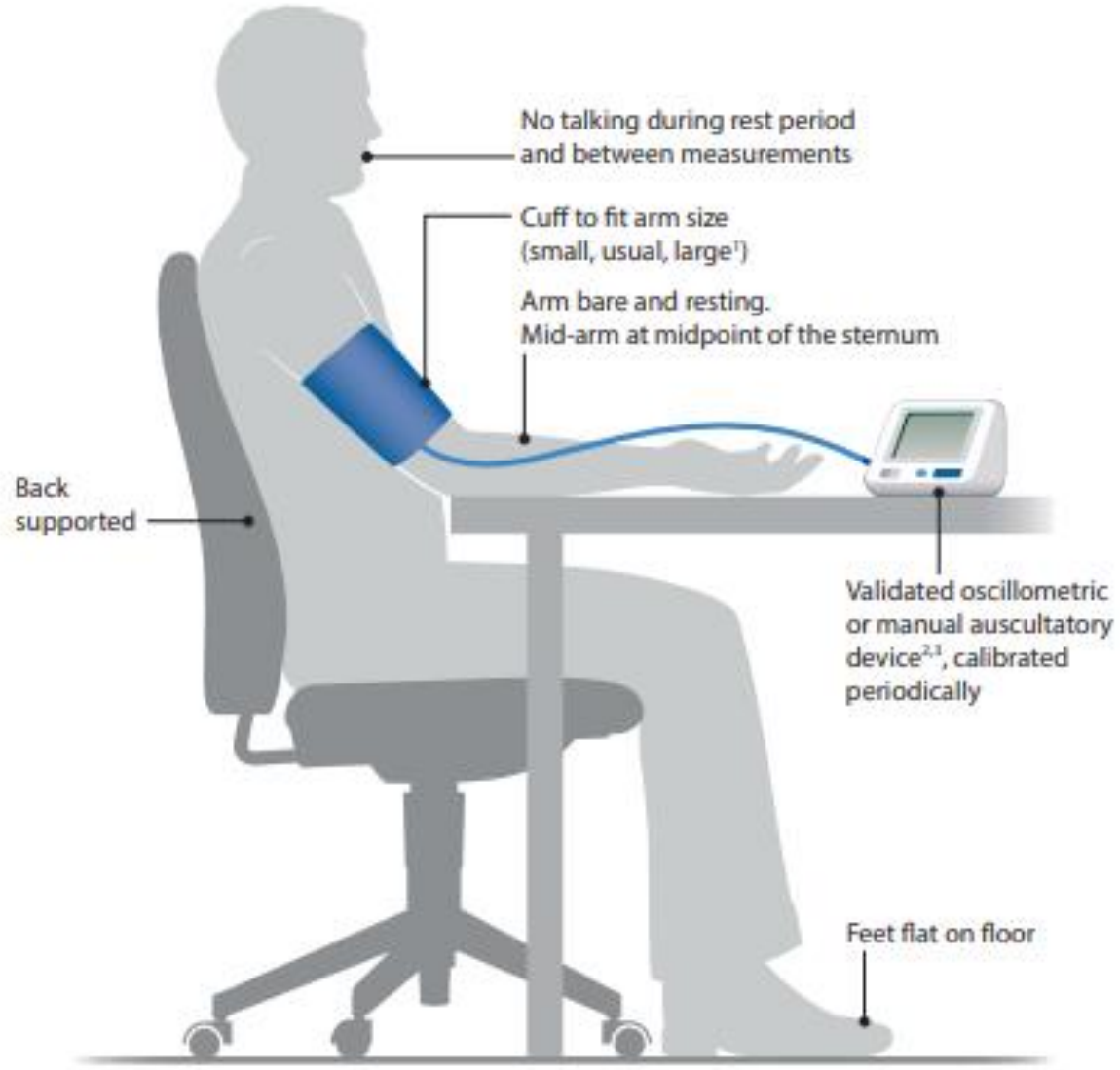
← **+20.7 mm Hg**

← -12.7 mm Hg

← **-46.1 mm Hg**

Agarwal, JAHA, 2017

Standardised BP measurement protocol	Achieved?
Select cuff size - bladder should encircle 80% of upper arm - note if larger or smaller cuff is used	☐ ☐
Positioning - sat in chair, back supported, legs uncrossed, feet flat on floor - cuffed arm must be supported by a table or the observer - middle of cuff on upper arm must be at heart level (at the midpoint of the sternum or 4th intercostal space)	☐ ☐ ☐
Patient preparation - abstain from caffeine, exercise, & smoking for at least 30 mins prior - ensure bladder emptied - remove clothing over arm and place cuff on bare skin (do not roll up shirtsleeves as tourniquet effect) - relax for >5 mins without talking or moving (observer also not speaking), and continue silence during the measurements	☐ ☐ ☐ ☐
Measurement technique - use validated device, which has been calibrated periodically - use arm which gives higher readings (measure BP in both arms at first visit) - separate readings by 1-2 minutes If using auscultatory measurement (bell or diaphragm acceptable) - inflate cuff to 20-30mmHg above obliteration of radial pulse - deflate cuff by 2 mmHg per second while listening for Korotkoff sounds - take 3 readings, and discard the first one	☐ ☐ ☐ ☐ ☐ ☐
Record readings - document SBP and DBP (to nearest even number if auscultatory measurement) - note time of most recent antihypertensive use - provide readings verbally and in writing to patient	☐ ☐ ☐
Estimate individual's BP - use average of ≥2 readings taken on ≥2 visits	☐



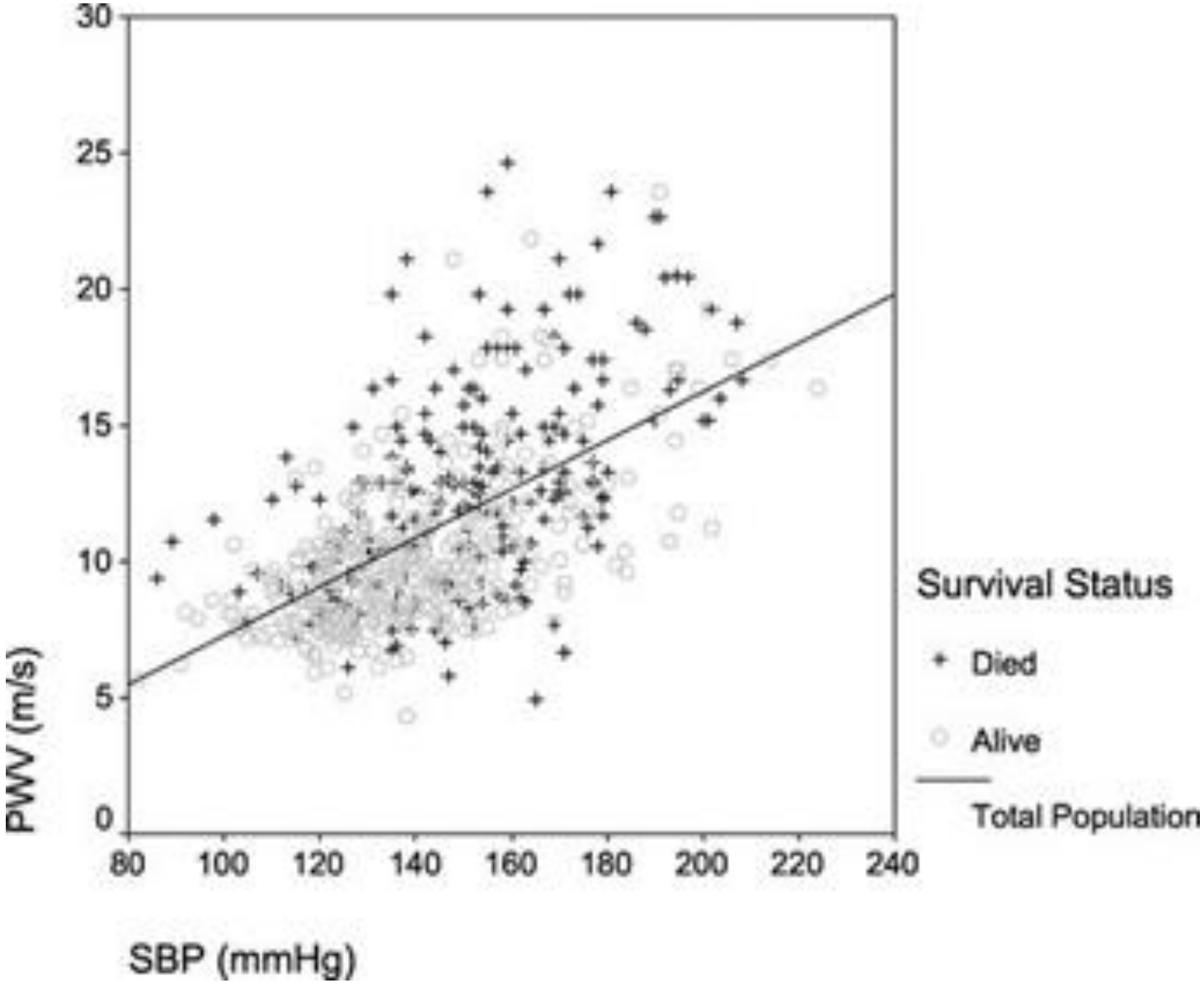
- Quiet room (no talking by patient or observer)
- No smoking, caffeine, or exercise for ≥30 min before measurement
- Empty bladder
- Note the time of most recent BP medication taken before measurements
- Relax for >5 min
- At first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings
- Separate repeated measurements by 1–2 minutes
- Use an average of ≥2 readings obtained on ≥2 occasions
- Provide patients with the SBP/DBP readings verbally and in writing

[1]Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used

[2]See validated electronic devices lists at www.stridebp.org

[3]For auscultatory readings, either the stethoscope diaphragm or bell may be used. Use a palpated radial pulse obliteration pressure to estimate SBP, then inflate the cuff 20–30 mm Hg above this level for auscultatory determination of BP level. Deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds

Pathogenesis



Kennedy Cruickshank. Circulation. Aortic Pulse-Wave Velocity and Its Relationship to Mortality in Diabetes and Glucose Intolerance, Volume: 106, Issue: 16, Pages: 2085-2090, DOI: (10.1161/01.CIR.0000033824.02722.F7)

Pathogenesis – Sodium Retention

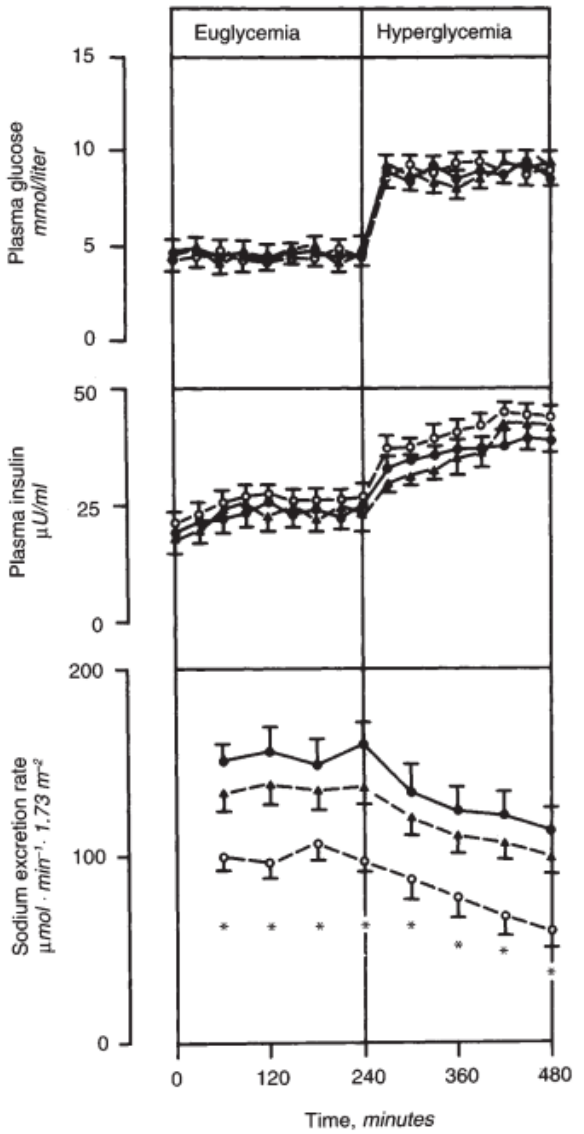
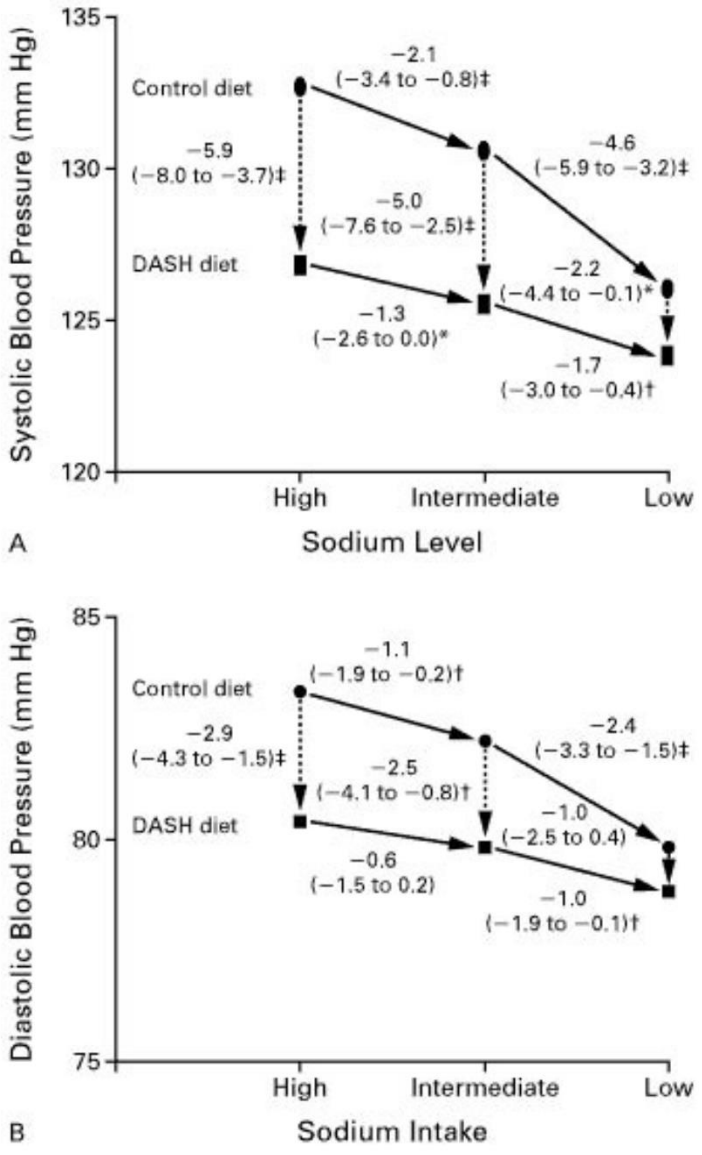


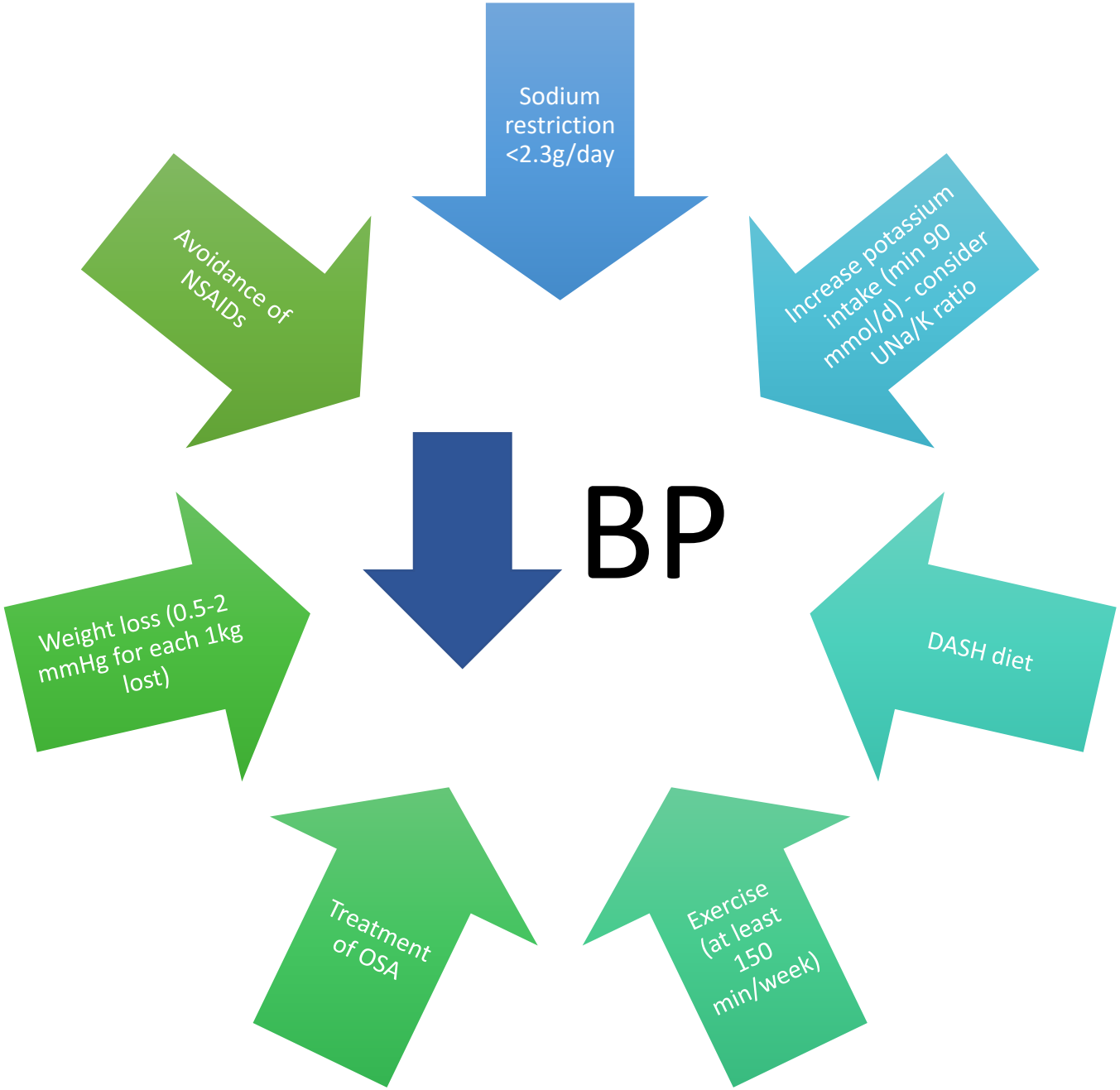
Fig. 3. *Mean ± SE plasma glucose and insulin concentrations and rates of sodium excretion in controls (●), Group 1 NIDDM (△) and Group 2 (○) during euglycemic and hyperglycemic clamp with constant subcutaneous insulin infusion, along with variable glucose administration rates to achieve and maintain either euglycemia or hyperglycemia.*

Rosadini et al. Kidney International. 1993



Sacks et al. NEJM. 2001

Non-Pharmacologic Therapies



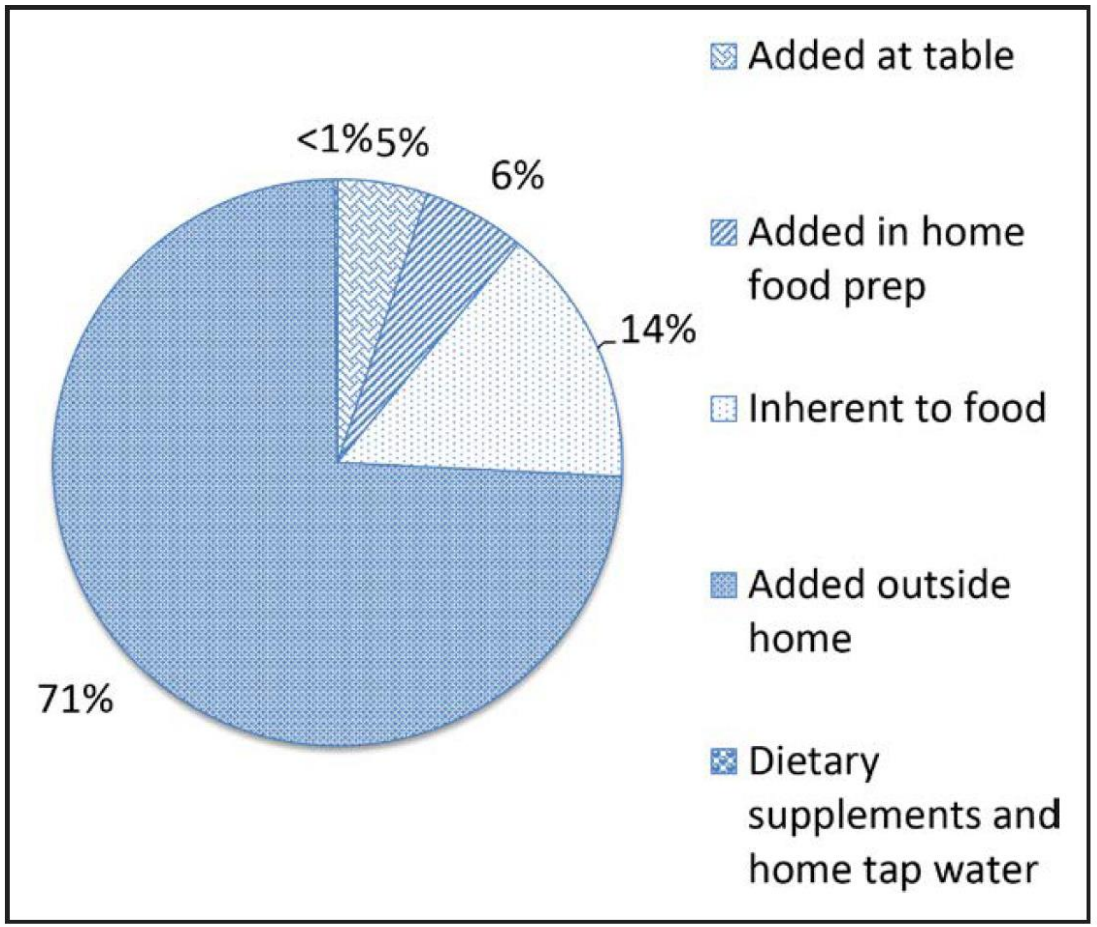
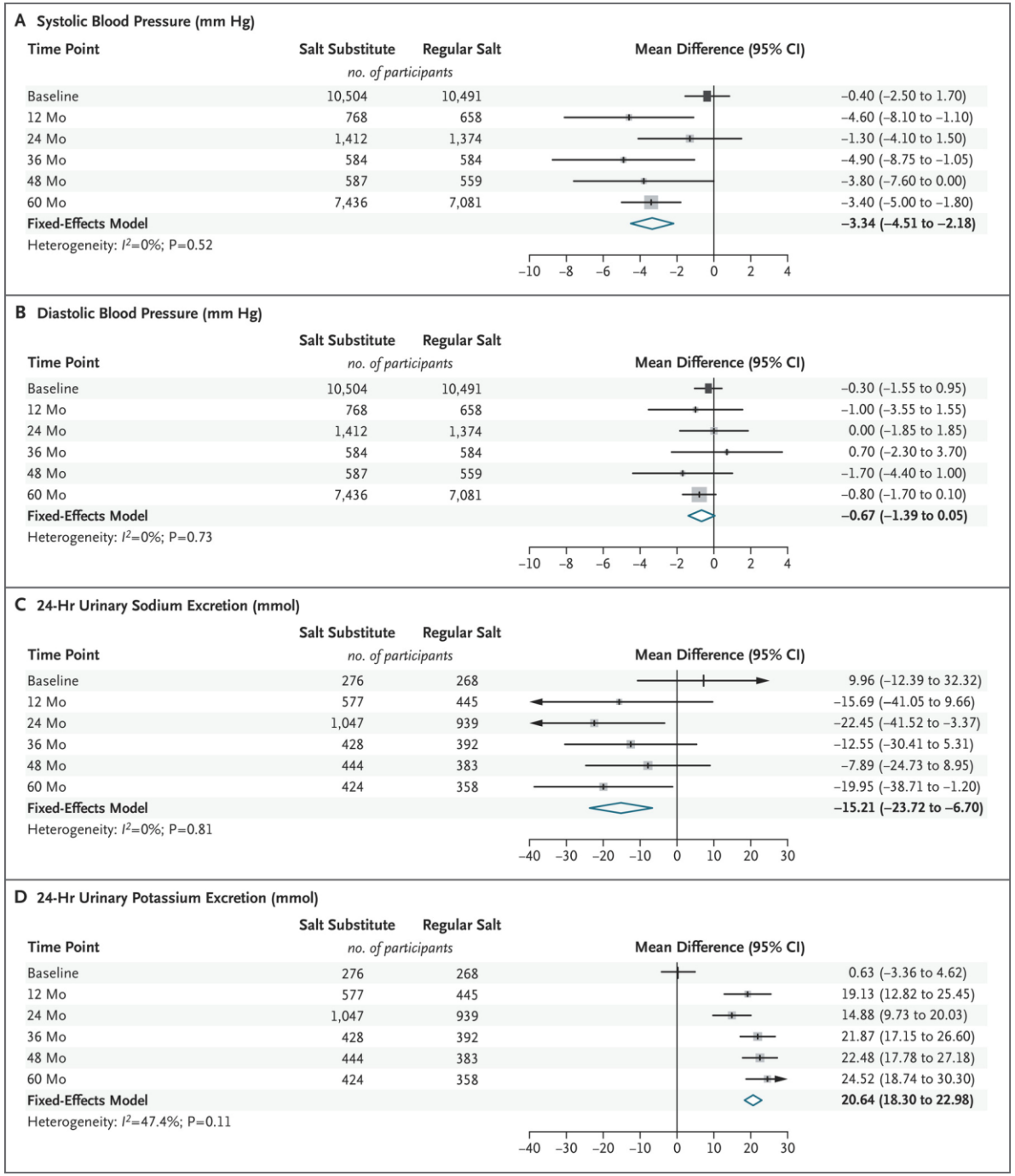


Figure. Proportion of total sodium intake from various sources (n=450).

Don't Blame the Saltshaker

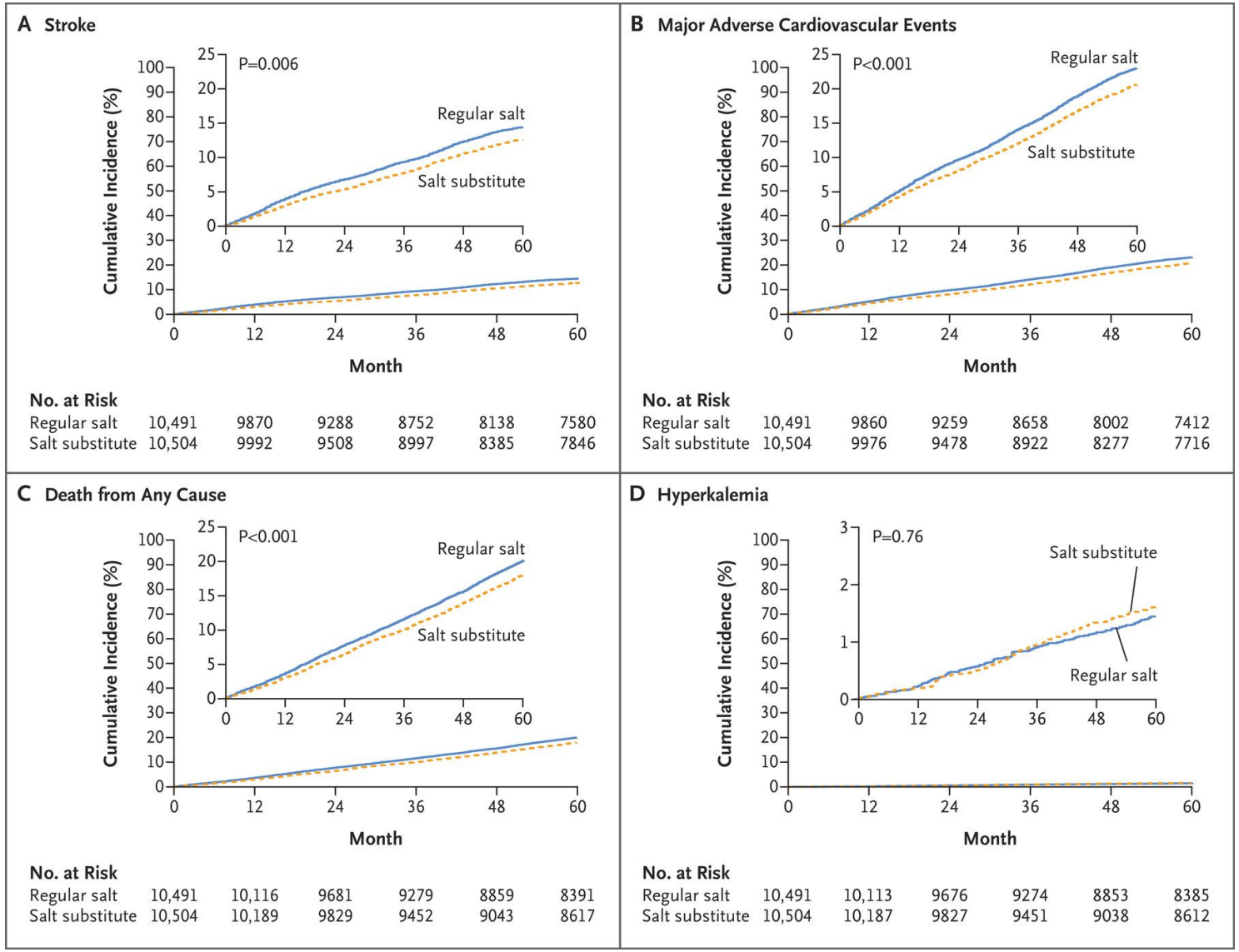
Harnack et al. Circulation. 2017

Substituting potassium for sodium



B Neal et al. NEJM. 2021

Substituting potassium for sodium



B Neal et al. NEJM. 2021

Essential Hypertension

What is your first line agent for essential hypertension?

A. ACEi/ARB

B. Thiazide Diuretic

C. Dihydropyridine calcium channel blocker

D. Beta-Blocker

E. Either A, B or C

Thiazides and Glucose Intolerance

Table 4. Biochemical Changes by Treatment Group*

	Chlorthalidone	Amlodipine	Lisinopril	*P* Value: Amlodipine vs Chlorthalidone	*P* Value: Lisinopril vs Chlorthalidone
Fasting Glucose Among Nondiabetics With Baseline Fasting Glucose <126 mg/dL					
No. of participants (%)					
Baseline	6766 (100)	3954 (100)	4096 (100)		
2 Years	3074 (45.4)	1787 (45.2)	1737 (42.4)		
4 Years	2606 (40.3)	1567 (39.6)	1464 (35.7)		
Mean (SD)					
Baseline	93.1 (11.7)	93.0 (11.4)	93.3 (11.8)	.52	.45
2 Years	102.2 (27.1)	99.0 (22.5)	97.4 (20.0)	<.001	<.001
4 Years	104.4 (28.5)	103.1 (27.7)	100.5 (19.5)	.11	<.001
≥126 mg/dL, No. (%)					
2 Years	295 (9.6)	132 (7.4)	101 (5.8)	.006	<.001
4 Years	302 (11.6)	154 (9.8)	119 (8.1)	.04	<.001

ALLHAT. JAMA. 2002

Thiazides and Glucose Intolerance

Likely related to hypokalemia

Indirect Reduction in Insulin Secretion

Higher Proinsulin to Insulin levels

PATHWAY 3

- PATHWAY 3. Lancet Diabetes Endocrinol. 2016

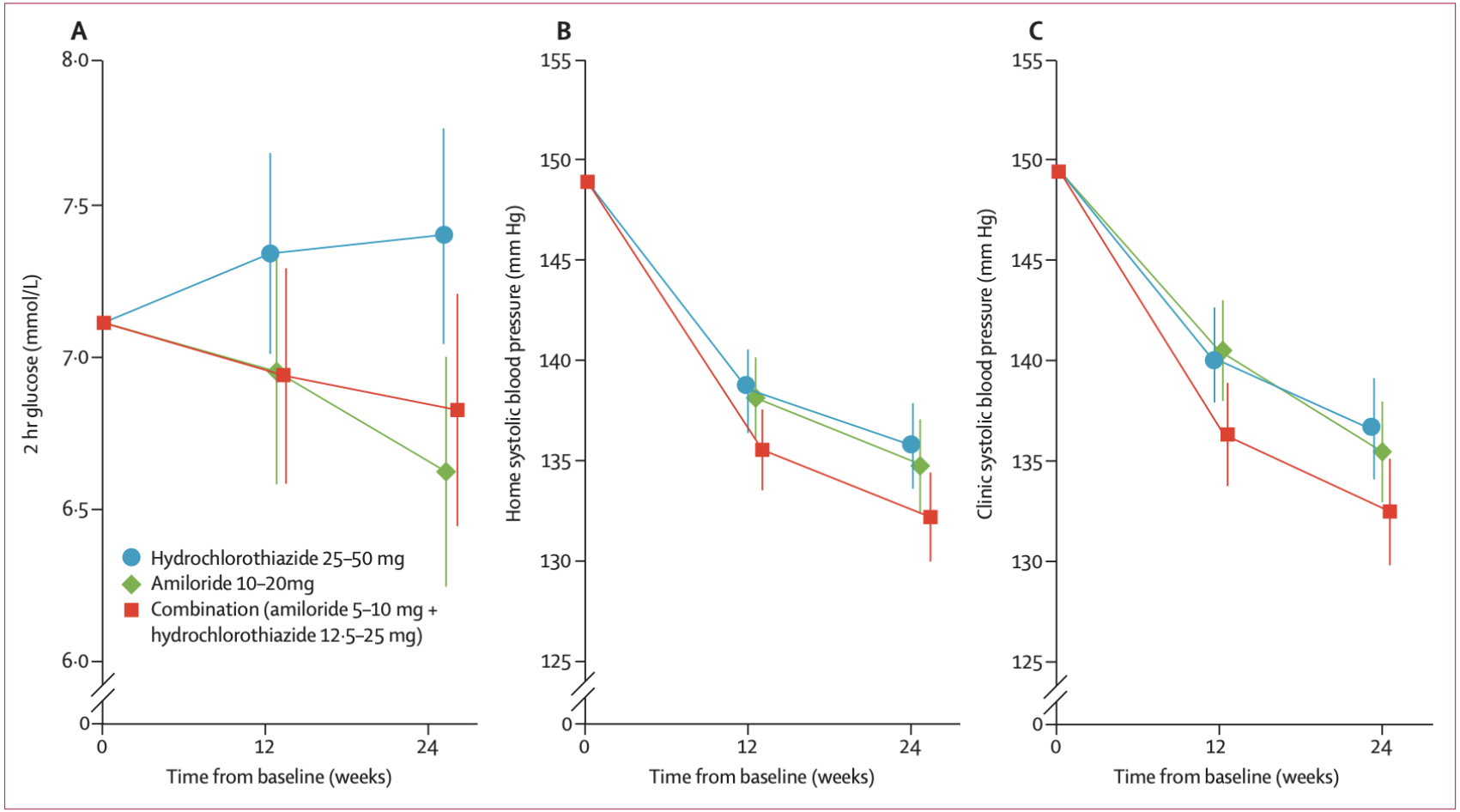


***Figure 2*: Changes in 2 h blood glucose concentrations (A), home systolic blood pressure (B), and clinic systolic blood pressure (C)**
Data are adjusted means; error bars show 95% CIs. For (A), p=0·0026 for the comparison between the amiloride and hydrochlorothiazide groups and 0·039 for comparisons between the combination and hydrochlorothiazide groups at 24 weeks, in a model adjusting for baseline covariates. For (B), averaged across 12 weeks and 24 weeks, the fall in home blood pressure was significantly greater in the combination group than in the hydrochlorothiazide group (p=0·0068). For (C), averaged across 12 weeks and 24 weeks, the fall in clinic blood pressure was significantly greater in the combination group than in the hydrochlorothiazide group (p=0·0064).

Resistant Hypertension

What is your preferred agent for patients with resistant hypertension?

A. Beta blocker

B. Non-dihydropyridine CCB

C. Alpha antagonist

D. Mineralocorticoid Antagonist

Resistant Hypertension: Is there a PATH forward?

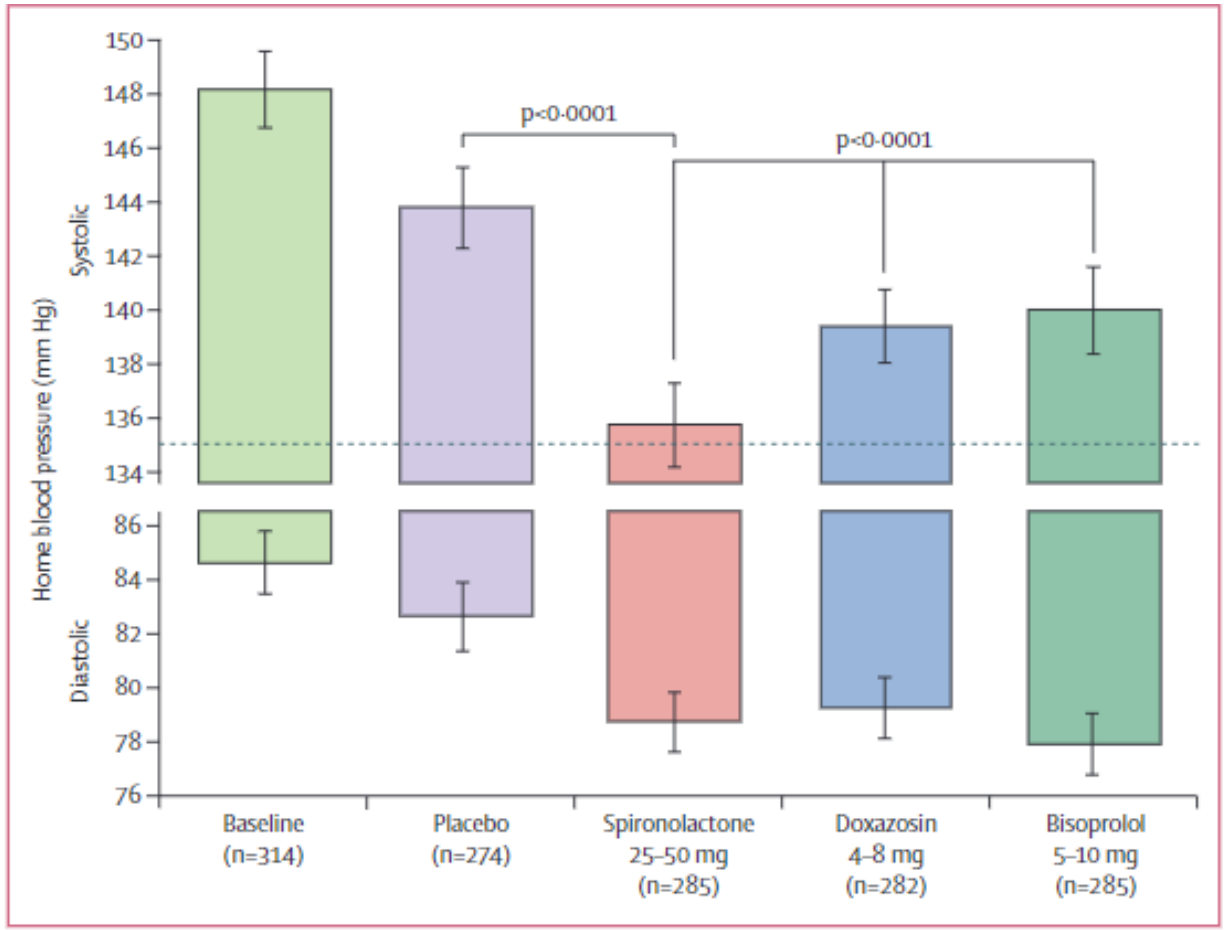
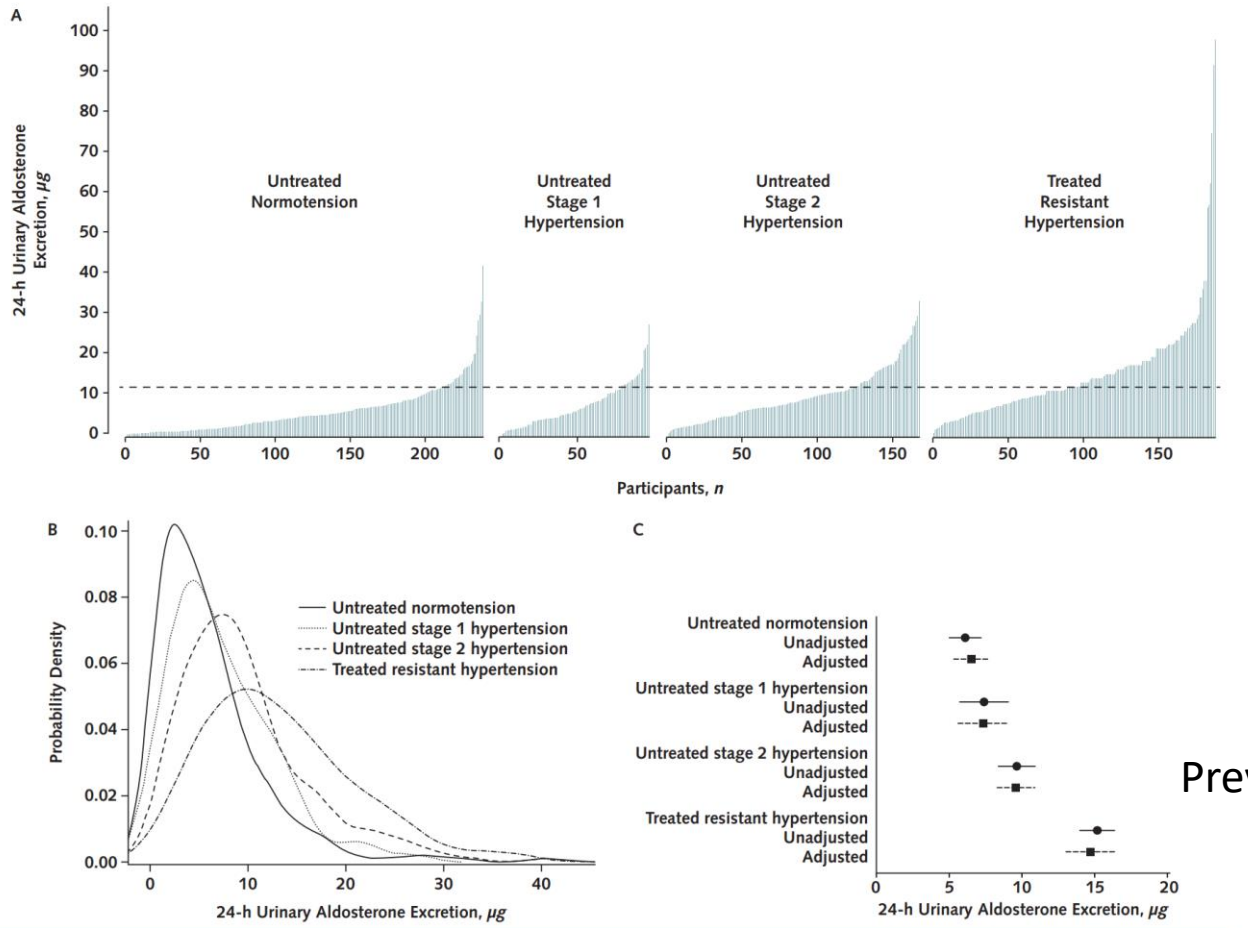


Figure 2: **Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles**

The top and bottom of each column represents the unadjusted home systolic and diastolic blood pressures, respectively, averaged across the mid-cycle (low-dose) and end-of-cycle (high-dose) visits (6 weeks and 12 weeks) in which patients received the drug. Error bars represent 95% CI. Comparisons are as described under methods for the primary endpoint.

Hyperaldosteronism is Underrecognized



A. The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the unadjusted renin-independent aldosterone excretion rate (*y*-axis) for each individual participant, ordered from lowest to highest (*x*-axes). The dashed horizontal line represents the conventional 12 μg/24 h threshold for the diagnosis of biochemically overt primary aldosteronism. B. Unadjusted overlaid density plots depicting the distribution of renin-independent aldosterone production, by blood pressure category (truncated at 45 μg/24 h). The *x*-axis shows the 24-h urinary aldosterone excretion rate. The *y*-axis shows the probability density function (smoothed using a kernel density estimation) per unit on the *x*-axis. C. Mean (95% CI) urinary aldosterone excretion rates for each blood pressure category, unadjusted (*solid lines with circles*) and adjusted (*dotted lines with squares*) for age, body mass index, race, sex, history of diabetes, and 24-h urinary sodium excretion.

Normotensive: 11%

Resistant Hypertension: 22%

Prevalence using 24-urine aldosterone cutoff of 12 μg/24h

Brown et al. Annals of IM. 2020

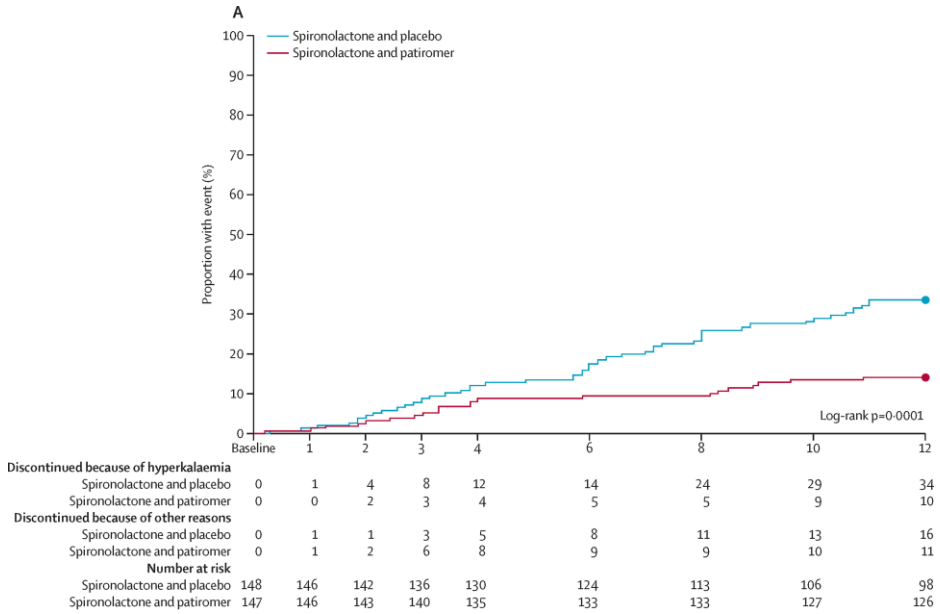
Table 3. Circulating Renin and Aldosterone Measurements and Test Characteristics of the ARR Using a Cutoff of 832 pmol/L per µg/L per hour (30 ng/dL per ng/mL per hour)*

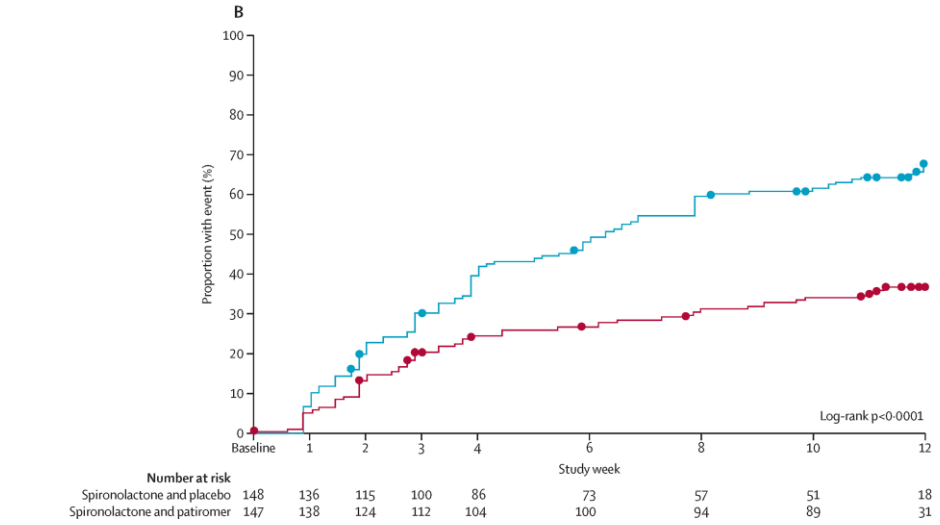
Characteristic	Untreated Normotension	Untreated Stage 1 Hypertension	Untreated Stage 2 Hypertension	Treated Resistant Hypertension
Crude prevalence of biochemically overt primary aldosteronism by oral sodium suppression test with urinary aldosterone excretion ≥12 µg/24 h	9.0 (26/289)	15.7 (18/115)	20.7 (42/203)	24.0 (98/408)
Percentage of total population with ARR >832 pmol/L per µg/L per hour	7.6 (22/289)	9.6 (11/115)	22.2 (45/203)	8.8 (36/408)
Crude prevalence of biochemically overt primary aldosteronism using screening ARR >832 pmol/L per µg/L per hour	2.4 (7/289)	3.5 (4/115)	10.3 (21/203)	6.6 (27/408)
Sensitivity of ARR >832 pmol/L per µg/L per hour	26.9 (7/26)	22.2 (4/18)	50.0 (21/42)	27.6 (27/98)
Specificity of ARR >832 pmol/L per µg/L per hour	94.3 (248/263)	92.8 (90/97)	85.1 (137/161)	97.1 (301/310)
Positive predictive value of ARR >832 pmol/L per µg/L per hour	31.8 (7/22)	36.4 (4/11)	46.7 (21/45)	75.0 (27/36)
Negative predictive value of ARR >832 pmol/L per µg/L per hour	92.9 (248/267)	86.5 (90/104)	86.7 (137/158)	80.9 (301/372)
ARR, *pmol/L per µg/L per hour*				
Mean (SD)	368.7 (317.3)	430.1 (411.7)	658.6 (649.8)	312.9 (355.8)
Median (IQR)	257.0 (138.7–462.3)	289.2 (173.5–694.0)	446.9 (231.3–721.2)	190.8 (65.4–447.0)
Serum aldosterone level, *pmol/L*				
Mean (SD)	136.8 (142.3)	114.6 (82.4)	147.3 (105.5)	304.4 (222.2)
Median (IQR)	83.2 (69.4–149.8)	77.1 (69.4–121.2)	105.4 (69.4–185.9)	249.7 (141.5–388.4)
PRA, *µg/L per hour*				
Mean (SD)	0.56 (0.60)	0.43 (0.34)	0.39 (0.43)	5.11 (13.49)
Median (IQR)	0.50 (0.20–0.60)	0.32 (0.14–0.60)	0.30 (0.10–0.50)	1.10 (0.60–3.10)

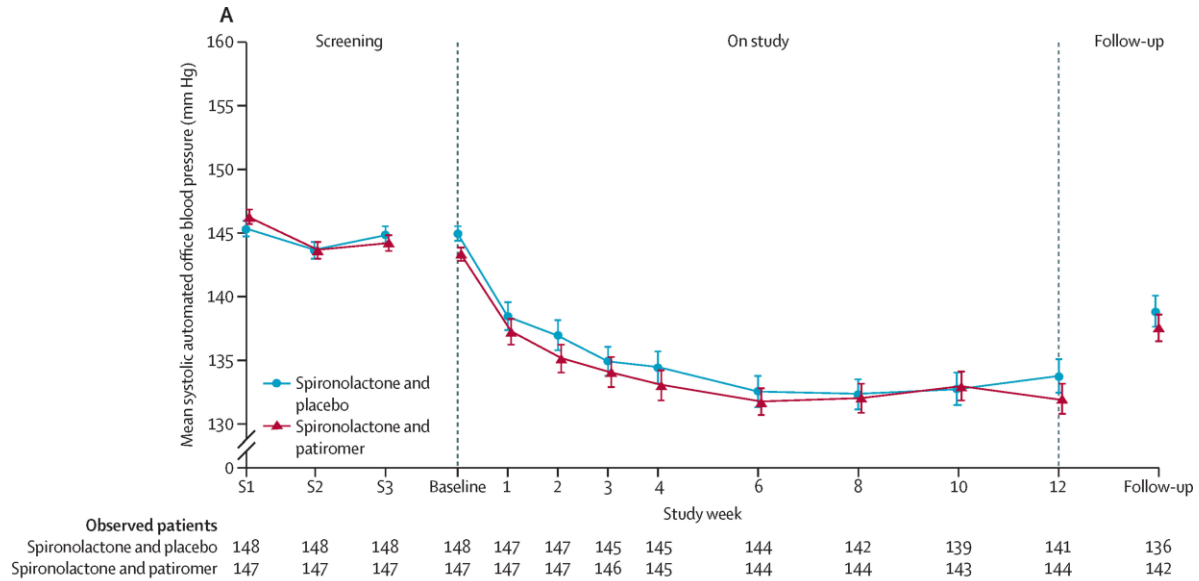
ARR = aldosterone–renin ratio; IQR = interquartile range; PRA = plasma renin activity.
* Values are percentages (n/N) unless otherwise specified. An ARR threshold of 832 pmol/L per µg/L per hour (30 ng/dL per ng/mL per hour) is shown. For the purposes of standardization, supine aldosterone values below the assay limit of <69.4 pmol/L (2.5 ng/dL) were set at 69.4 pmol/L and supine PRA values below the assay limit of <0.1 µg/L per hour were set at 0.1 µg/L per hour; seated aldosterone values below the assay limit of <83.2 pmol/L (3.0 ng/dL) were set at 83.2 pmol/L and seated PRA values below the assay limit of <0.6 µg/L per hour were set at 0.6 µg/L per hour.

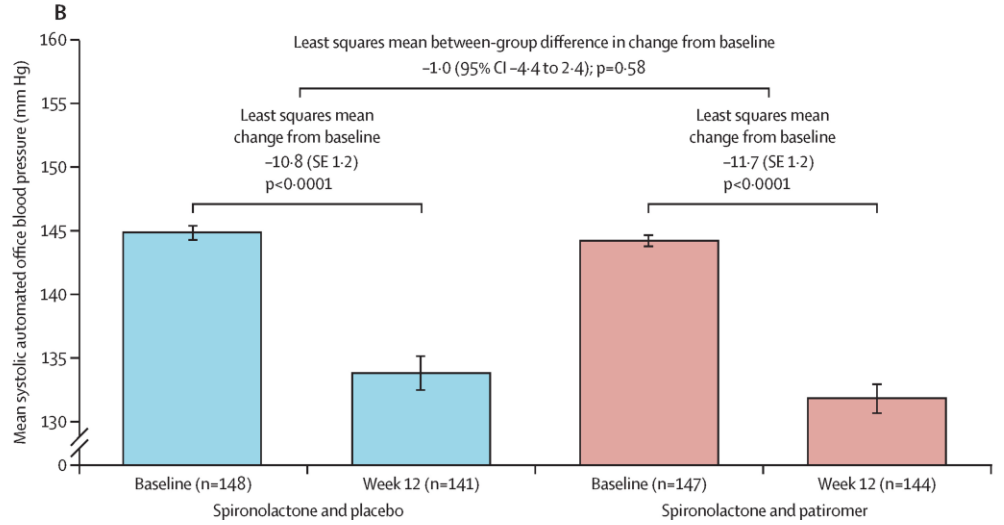
AMBER trial

Agarwal et al. Lancet. 2019









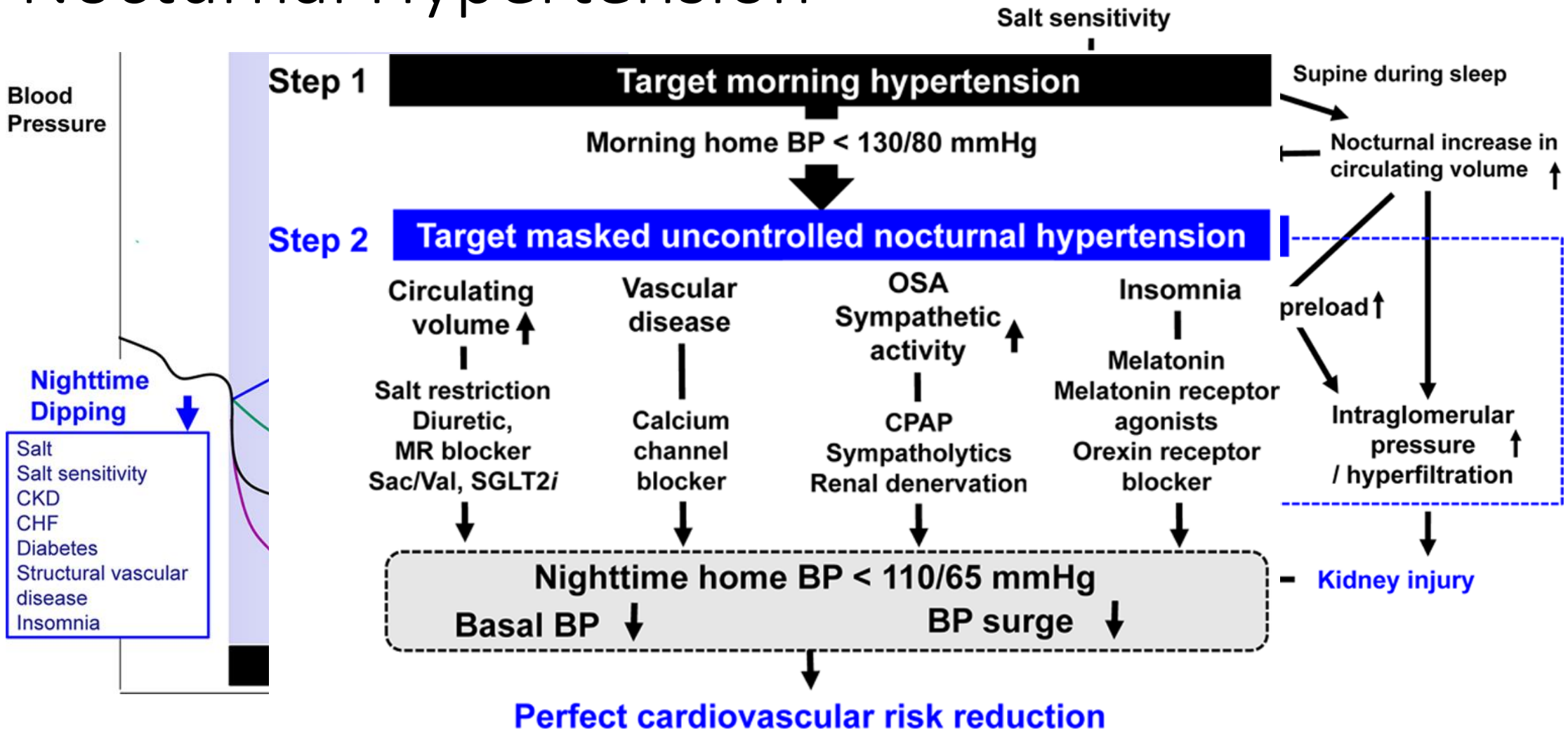
Nocturnal Hypertension

Do you believe in chronotherapy?

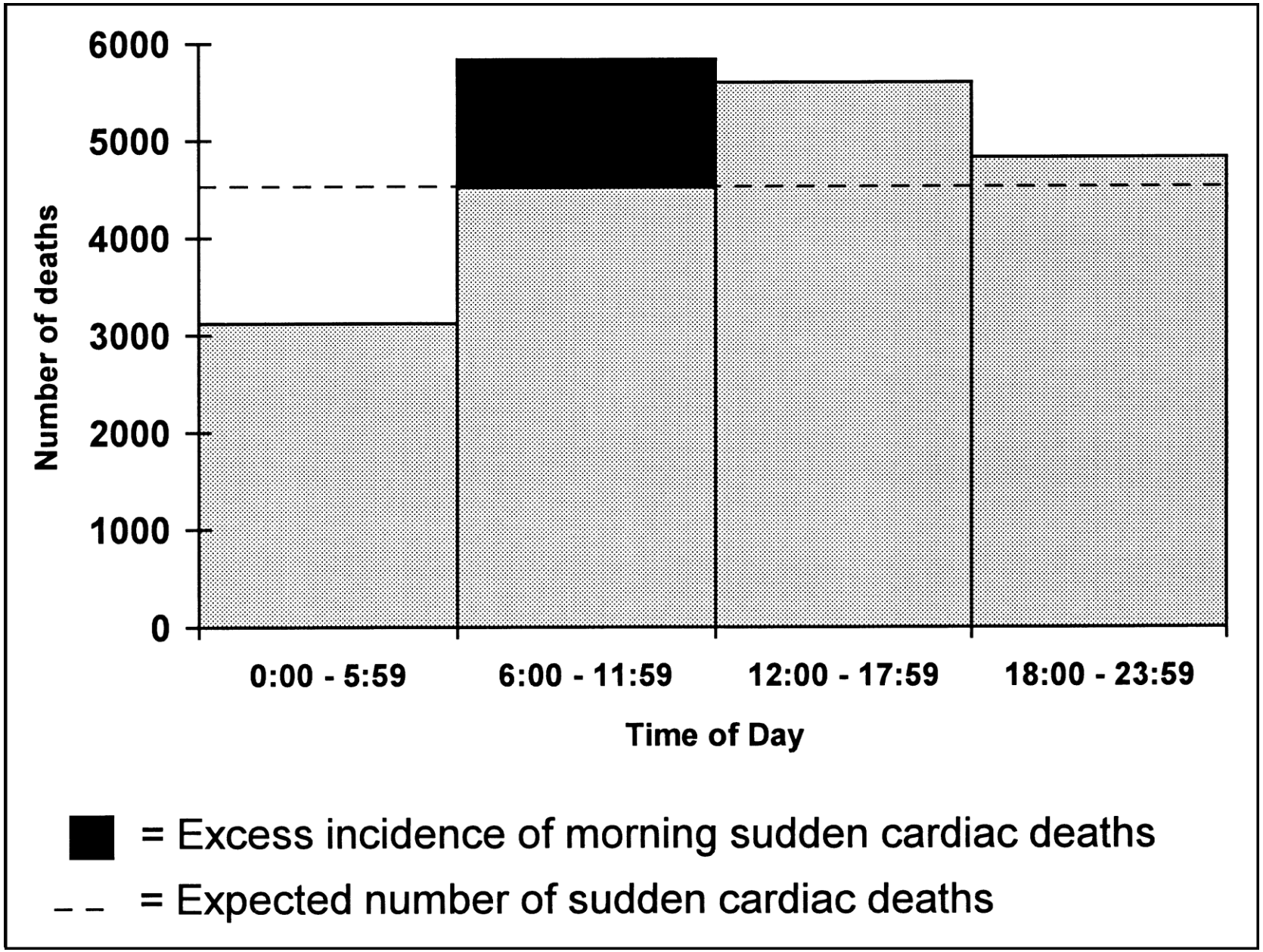
Yes

No

Nocturnal Hypertension

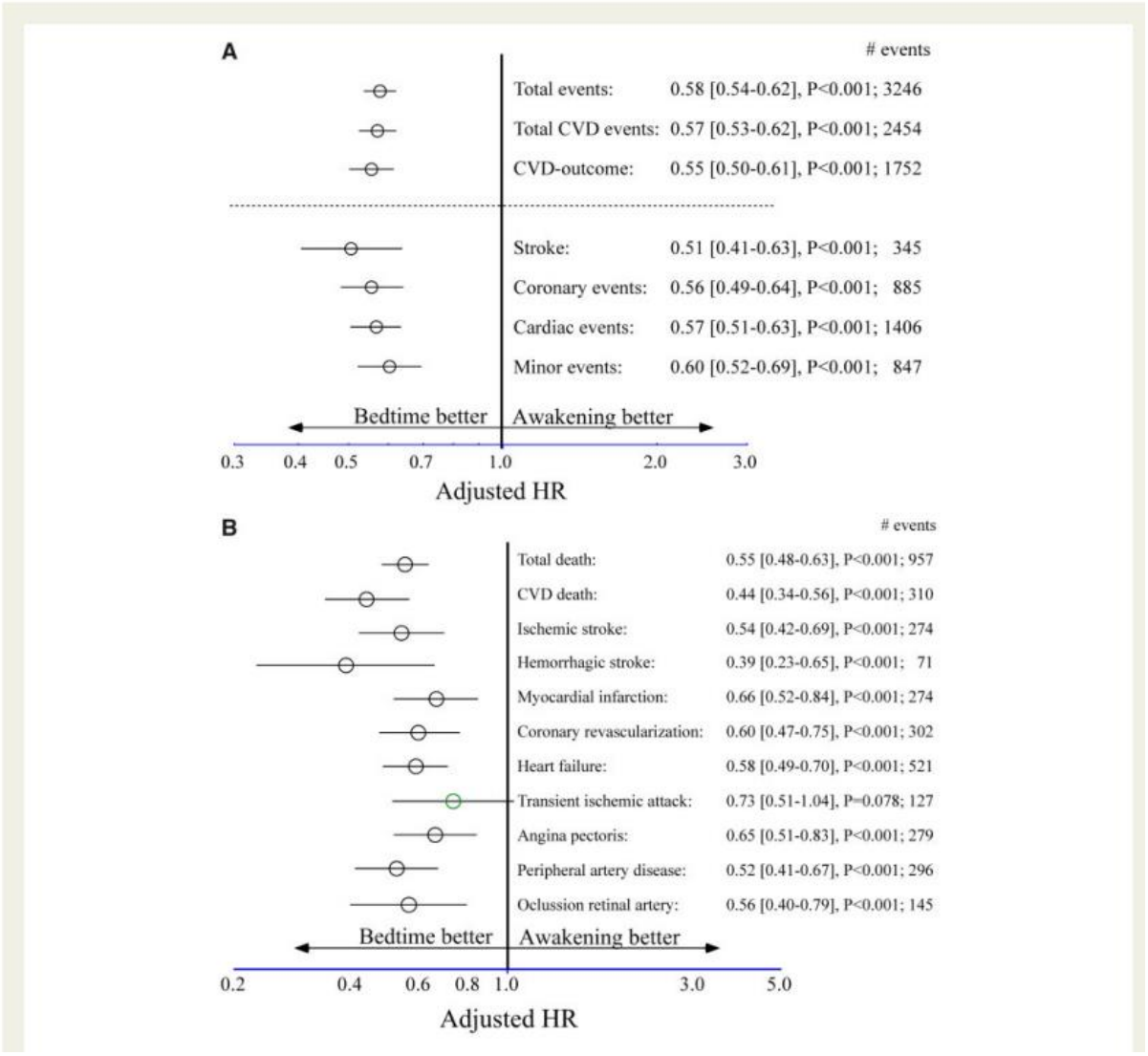


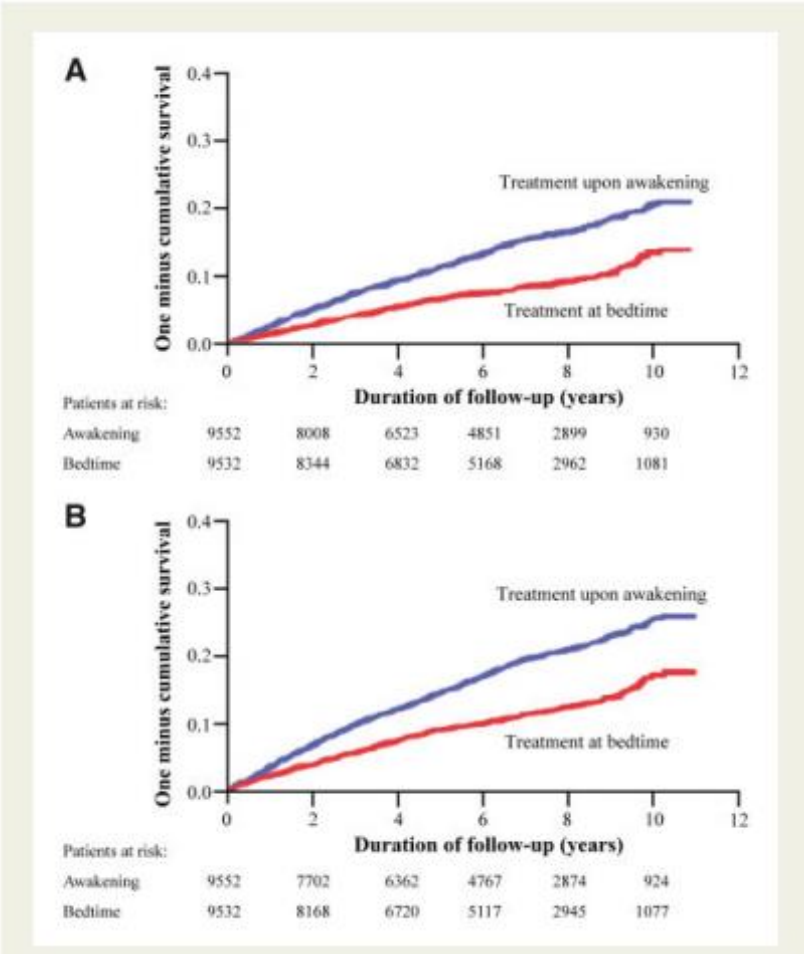
Kario. Hypertension. 2018



Cohen et al. Am J Card. 1997

Nocturnal Hypertension





Hermida et al. The Hygia Chronotherapy Trial. ESC. 2020

HYPERTENSION

Blood-pressure medication timing matters

Bed time is the best time to take blood pressure medication

Largest study finds greater reduction in risk of cardiovascular disease and death from bedtime rather than morning medicatio

23 Oct 2019

NEJM Journal Watch

SPECIALTIES & TOPICS BLOGS CME SPECIAL FEATURES ARCHIVES/PDFs

LETTER TO READERS | GENERAL MEDICINE, CARDIOLOGY, HOSPITAL MEDICINE

INFORMING PRACTICE

March 17, 2020

Taking Antihypertension Medications at Night: Interview

Dr. Allan Brett interviews Dr. Raymond Townsend on the benefits of this practice in hypertensive patients.

NEJM Journal Watch General Medicine recently published a review of a trial from Spain, in which hypertensive patients were randomized to taking their blood pressure medications either first thing in the morning or at bedtime. The results — nearly 50% fewer adverse cardiovascular events at 6 years in the bedtime group — seemed almost too good to be true. To dig more deeply into this trial and its implications for practicing clinicians, *NEJM Journal Watch General Medicine* Editor-in-Chief Dr. Allan Brett interviewed Dr. Raymond Townsend, a well-known hypertension researcher at the University of Pennsylvania. Click for NEJM Journal Watch's coverage of the article, and Dr. Brett's audio interview with Dr. Townsend.

Can We Mend the Broken Clock by Timing Anti

Panagiotis I. Georgianos and Rajiv Agarwal

CJASN October 2020, 15 (10) 1513-1515; DOI: https://doi.org/10.2215/CJN.00360120

Letter

Should clinical practice change to bedtime administration of antihypertensive?

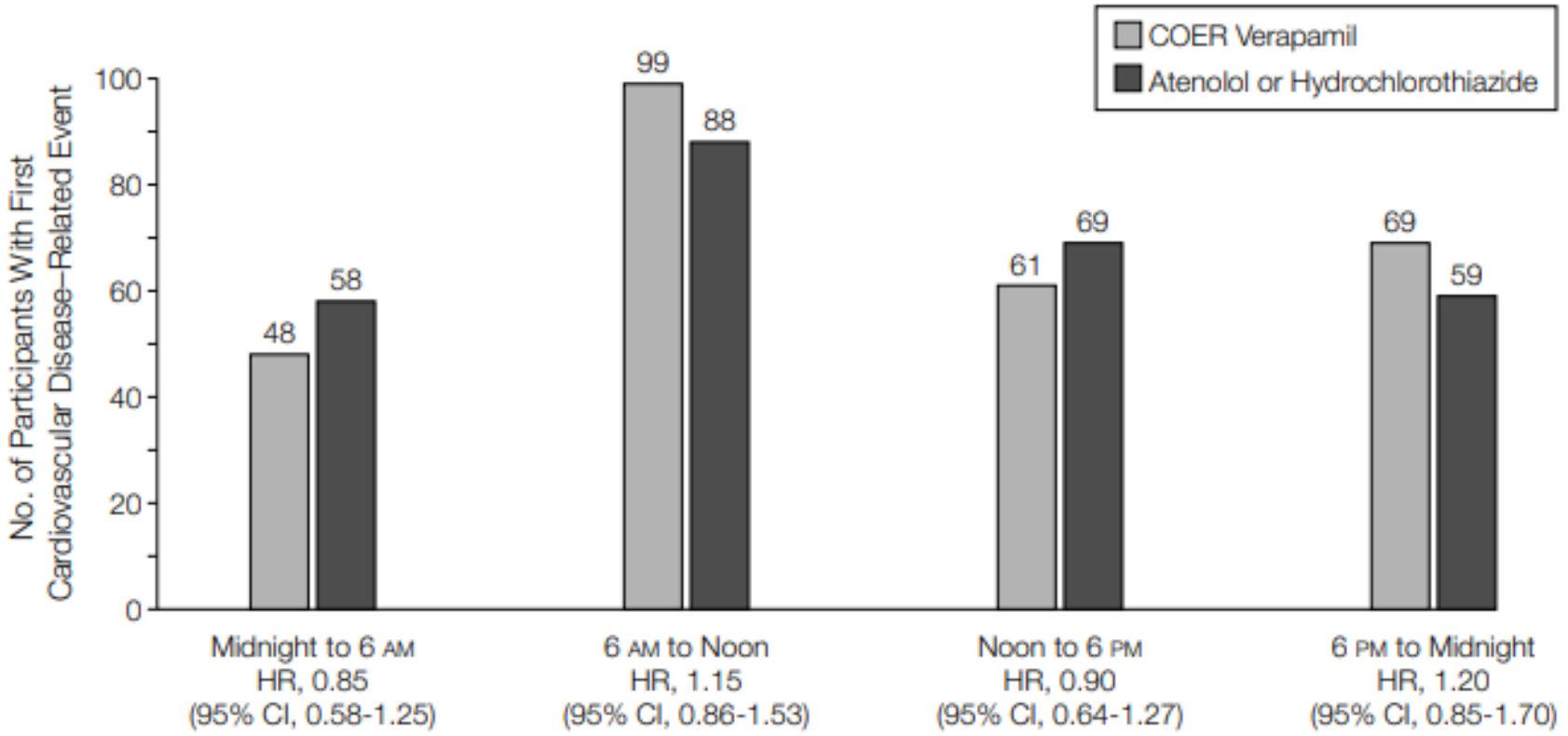
Editorial

Blood pressure medication should not be routinely dosed at bedtime. We must disregard the data from the HYGIA project

Reinhold Kreutz, **Sverre E. Kjeldsen** ✉, Michel Burnier, Krzysztof Narkiewicz, Suzanne Oparil & Giuseppe Mancia

Pages 135-136 | Published online: 27 Apr 2020

Figure 4. Incidence of Primary End Points by Treatment Assignment and Time of Day



Time of onset of first cardiovascular disease–related event was determined for 277 participants in the controlled-onset extended-release (COER) verapamil group and 274 participants in the atenolol or hydrochlorothiazide group. There were 178 (24%) events for which time of onset could not be determined (87 among those randomized to COER verapamil and 91 among those randomized to atenolol or hydrochlorothiazide; hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.73-1.32).

Black et al. CONVINCE. JAMA. 2003

THE END

- Questions?

Orthostatic Hypotension

- Prevalence up to 25% in patients with diabetes

  - Parkinson's
  - Multi-system atrophy
  - Baroreflex dysfunction
  - Antidepressants (TCAs)

Orthostatic Hypotension

Table 3.

Target organ damage markers in patients with and without supine hypertension

	nOH with supine hypertension (n=38)	nOH without supine hypertension (n=19)	P-value
Target organ damage markers			
Creatinine, mg/dl	0.97±0.33	0.82±0.21	0.056
Blood urea nitrogen, mg/dl	22.9±6.2	18.4±4.9	**0.005***
eGFR, ml/min per 1.73 m^2	69.6±24.1	91.6±26.89	**0.008***
Left ventricular hypertrophy, n (%)	9 (24)	0	**0.040***
Cerebral WMH volume, mm^3	11,517±11,771	5,426±3,132	**0.019***
Other test results			
Sodium, mmol/l	140.8±2.9	140.3±2.3	0.73
Potassium, mmol/l	4.4±0.9	4.1±0.4	0.12
Hemoglobin, g/dl	12.6±1.7	13.2±1.1	0.75
Hematocrit, %	38.5±5.5	38±6.9	0.19
QTc, ms	431±47	422±22	0.45

Asterisks denote statistical significance. eGFR: estimated glomerular filtration rate; WMH: white matter hyperintensities. MRI: magnetic resonance imaging. (mean±SD). P-value obtained using appropriate non-parametric (Mann-Whitney test) and parametric (Unpaired t-test) tests for quantitative variables and χ^2 (or Fisher exact test) for qualitative variables.

Palma et al. Parkinsonism Relat Disord. 2020

Orthostatic Hypotension

- Non-pharmacologic therapies
  - Arise slowly
  - Discontinue offending agents
  - Stand with legs crossed
  - Compression stockings or Ab binder
  - Increase fluid intake throughout the day but cease water intake 60-90 min prior to bedtime
  - Avoid NSAIDs at bedtime
  - Alcohol
  - Carb-rich snack at bedtime
  - Raise HOB ~30 degrees
  - Avoid fludrocortisone

Orthostatic Hypotension

- Pharmacologic Therapies
  - Goals: Supine <140mmHg

    Standing: >90 mmHg

    Nitro patch (0.1 mg/h)
    Clonidine/Guanfacine
    Atenolol
    Verapamil
    Captopril
    Hydralazine

    Individualize Treatment!!