Boca Raton Hospital Annual Conference

Nephrology Update
Publication Year in Review 2023



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Disclosures

Warren Kupin, M.D., faculty for this educational activity, has no relevant financial relationships with ineligible companies to disclose, and has indicated that the presentation or discussion will not include off-label or unapproved product usage.

10 TOP NEPHROLOGY STORIES 2023

1. IGA Nephropathy: Now with the new drugs!
2. Hyponatremia correction: Speed doesn't kill ?
3. Renal Denervation is FDA-approved (Finally)
4. Diuretics: Just a class effect after all (DCP and TRANSFORM HF)
5. The rise of aldosterone synthase inhibitors
6. Hydrochlorothiazide doesn't prevent stones (NOSTONE)
7. Endothelin antagonists advance
8. CONVINCE: HDF is better than HD (or is it?)
9. Balanced fluids : the best saline in transplant
10. Inaxaplin phase 2a trial APOL-1 mediated kidney diseases

HDF: Hemodiafiltration, HD: Hemodialysis

Designed by Dr Priti Meena, M.D, FASN @priti899

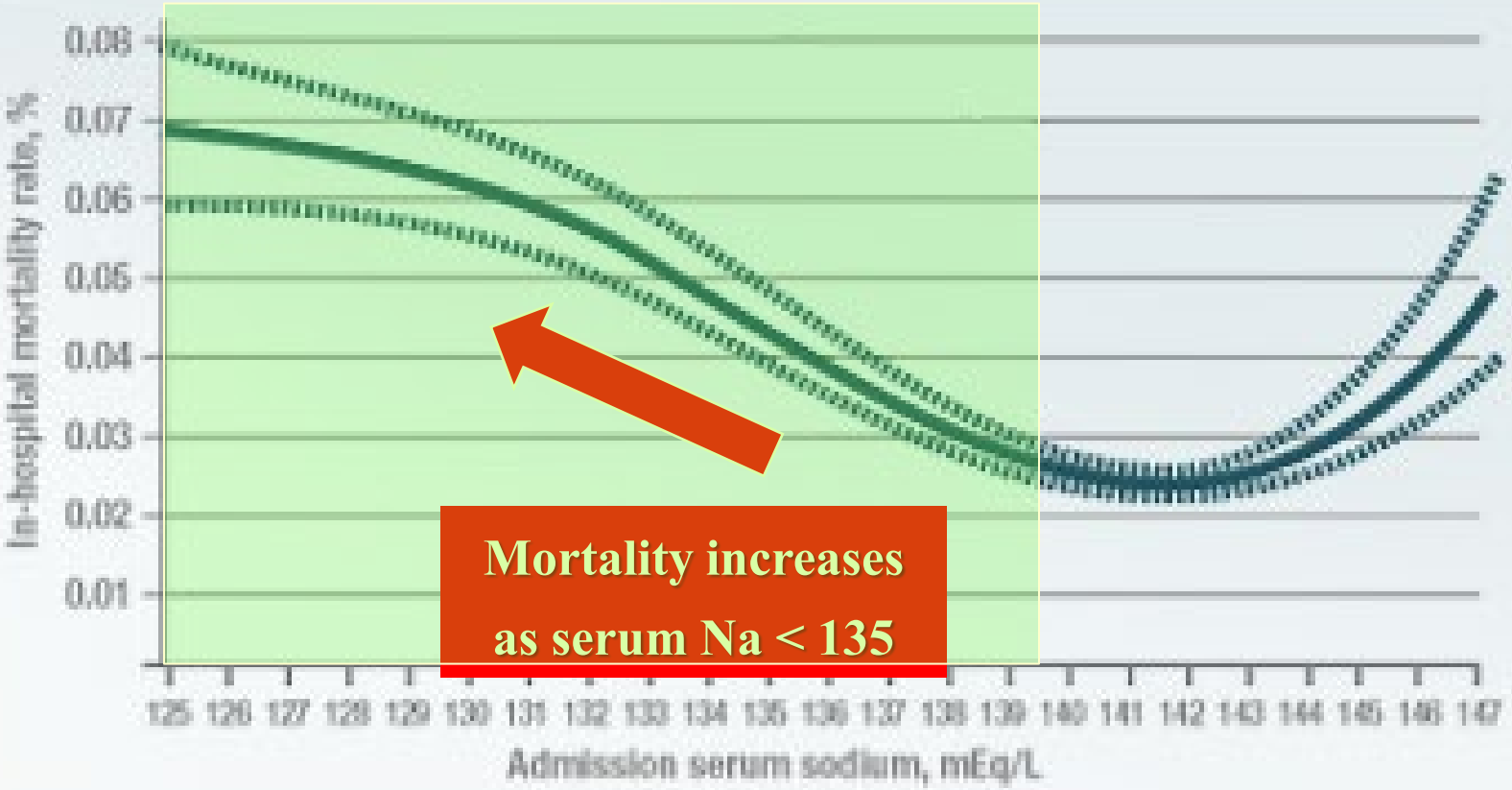
Definitions

- **Hyponatremia is defined as**
  - **Plasma sodium < 135 meq/liter**

- **Mild Hyponatremia is defined as**
  - **Plasma sodium 130 - 134 meq/liter**
- **Moderate Hyponatremia is defined as**
  - **Plasma sodium 121 – 129 meq/liter**
- **Severe hyponatremia is defined as**
  - **Plasma sodium < 120 meq/liter**

Seizures

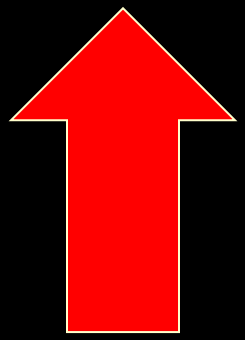
Hospital Mortality and Hyponatremia



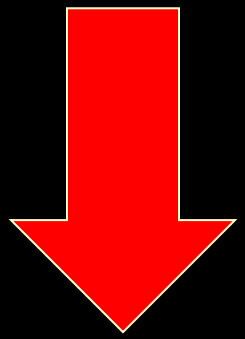
Restrictive cubic spline transformation plot with 95% confidence intervals is shown.
Adapted with permission from Gheorghiade M, et al. *Eur Heart J*. 2007;28(8):980-988.

Prevent Seizures and Brain Herniation

(Hyponatremic Encephalopathy)



Treatment of Hyponatremia



Avoid

Osmotic Demyelinating Syndrome

HYPONATREMIA MANAGEMENT

Cristina Popa
@Nephroseeker

#NephJC

NEPHROLOGY SOCIAL MEDIA COLLECTIVE EST 2015

		Verbalis JG, et al. *Am J Med.* 2013	Spasovski G, et al. *Nephrol Dial Transplant.* 2014
Acute or symptomatic hyponatremia	Severe symptoms	Bolus 3% NaCl (100 ml over 10 minx3 as needed)	Bolus 3% NaCl (150 ml over 20 min x 2-3 as needed)
	Moderate symptoms	Continous infusion 3%NaCl (0.5-2 ml/kg/h)	Bolus 3%NaCl (150 ml over 20 min once)
CHRONIC HYPONATREMIA			
SIADH	1st line	Fluid restriction	Fluid restriction
	2nd line	Demeclocycline, urea or vaptan	Urea/loop diuretics + oral NaCl DOES NOT recommend vaptans Against lithium/ demeclocycline Isotonic saline/ balanced crystalloid
Hypovolemic hypoNa		Isotonic saline	Isotonic saline/ balanced crystalloid
Hypervolemic hypoNa		Fluid restriction Vaptans	Fluid restriction Recommend against vaptans
Correction rate	Minimum	4-8 mmol/L/day 4-6 mmol/L/day **(high risk ODS)**	No minimum
	Limit	10-12 mmol/L/day 8 mmol/L/day **(high risk ODS)**	10 mmol/L/day
Management of overcorrection	Baseline Na	≥120 mmol/L - probably unnecessary <120- start relowering with electrolyte free water/ desmopressin, if correction> 6-8mmol/L/day	Start once limit exceeded Electrolyte free water (10ml/kg) ± 2 µg desmopressin

Risk of Osmotic Demyelination

Common	Rare
Hypokalemia	Hyperosmolar hyperglycemic state
Malnutrition	Hypophosphatemia
Liver disease	Folate deficiency
Alcoholism	Dialysis disequilibrium syndrome
Liver transplantation	Correction of hyperammonemia

Everyone Agreed for Decades with this Rate of Correction !!!

I want Guidelines with a slow rate

I want NA correction with an easy touch

I want a physician who will spend some time

Not correct and go in a demyelinating rush

I want somebody who will understand

When it comes to Hyponatremia , I want a slow rate (of correction)

And then came this article in 2023 !

ORIGINAL ARTICLE

Severe Hyponatremia Correction, Mortality, and Central Pontine Myelinolysis

Authors: Harish Seethapathy, M.D., Sophia Zhao, Ph.D., Tianqi Ouyang, M.P.H., Christie Passos, B.A., Adviti Sarang, B.S.A., Pui W. Cheung, M.D., M.S., Sushrut S. Waikar, M.D., M.P.H., David J.R. Steele, M.D., Sahir Kalim, M.D., M.M.Sc., Andrew S. Allegretti, M.D., M.Sc., Juan Carlos Ayus, M.D., and Sagar U. Nigwekar, M.D., M.M.Sc. Author Info & Affiliations

Published September 26, 2023 | NEJM Evid 2023;2(10) | DOI: 10.1056/EVIDoa2300107 | VOL. 2 NO. 10

Does The Rate of Severe Hyponatremia Correction Impact Mortality, Length of Stay, and Incidence of Central Pontine Myelinolysis?

#NephJC

Cohort and Methods

- Retrospective study
- 2 Centers in Boston, USA
- Jan 1993 to Dec 2018
- **3274** patients
- Mean age 66 ± 16 years
- Mean serum Na 116 ± 4 mEq/L

Results

Correction Rate mEq/L/24 hours		In-hospital Mortality	30-day Mortality	Length of Stay	CPM
< 6 (n=1255)	38%	OR 1.71 (95% CI 1.27 – 2.31)	OR 2.13 (95% CI 1.64 – 2.77)	6 days (IQR 4 – 11 days)	N = 1
6 - 10 Reference	29%				N = 4
>10 (n=1067)	33%	OR 0.64 (95% CI 0.44 - 0.93)	OR 0.69 (95% CI 0.50 – 0.96)	5 days (IQR 3 – 9 days)	N = 2

CPM – Central Pontine Myelinolysis; CI – Confidence Interval; IQR - Interquartile Range

Conclusion: Slower correction of serum sodium in hyponatremia was associated with higher mortality and longer length of stay. Although the correction exceeded the recommended rates, the incidence of CPM was infrequent in this group. Whether correction rates impact the neurological outcome needs further investigation.

Seethapathy H, Zhao S, Ouyang T, et al. Severe Hyponatremia Correction, Mortality, and Central Pontine Myelinolysis. NEJM Evidence 2023;2:EVIDoa2300107.

VA by Arjunmohan Mohan @Arjun_Mohan1

Mean Na 116 meq/L

Severe Hyponatremia Correction, Mortality, and Central Pontine Myelinolysis

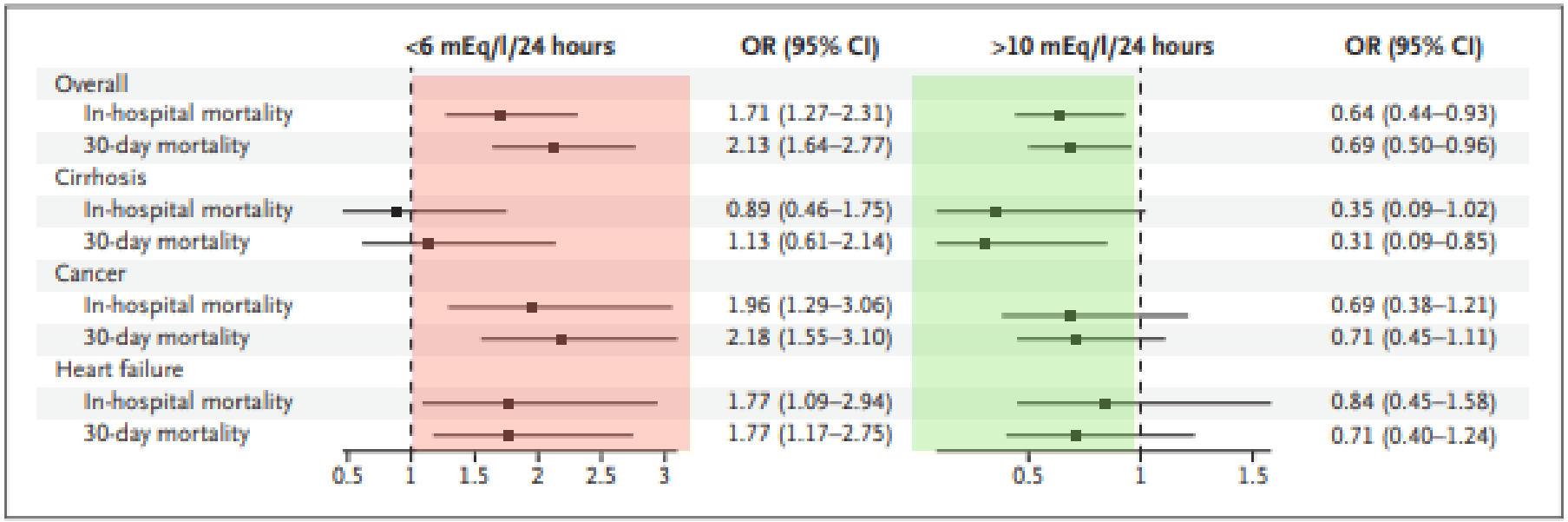


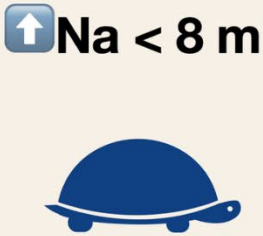
Figure 2. Forest Plot Showing the Association between Sodium Correction Rates and Mortality.

Seethapathy H. NEJM Evid 2023; 2 (10)

Rapid Correction of Hyponatremia Improved Patient Survival in ICU Patients

208 Hospitals

52% women

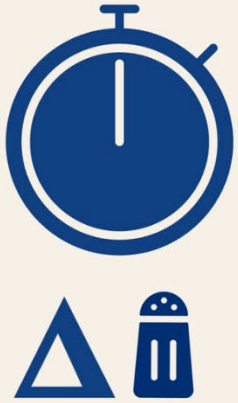


573

56%

1,024 ICU patients

48 years



Na <120 mEq/L

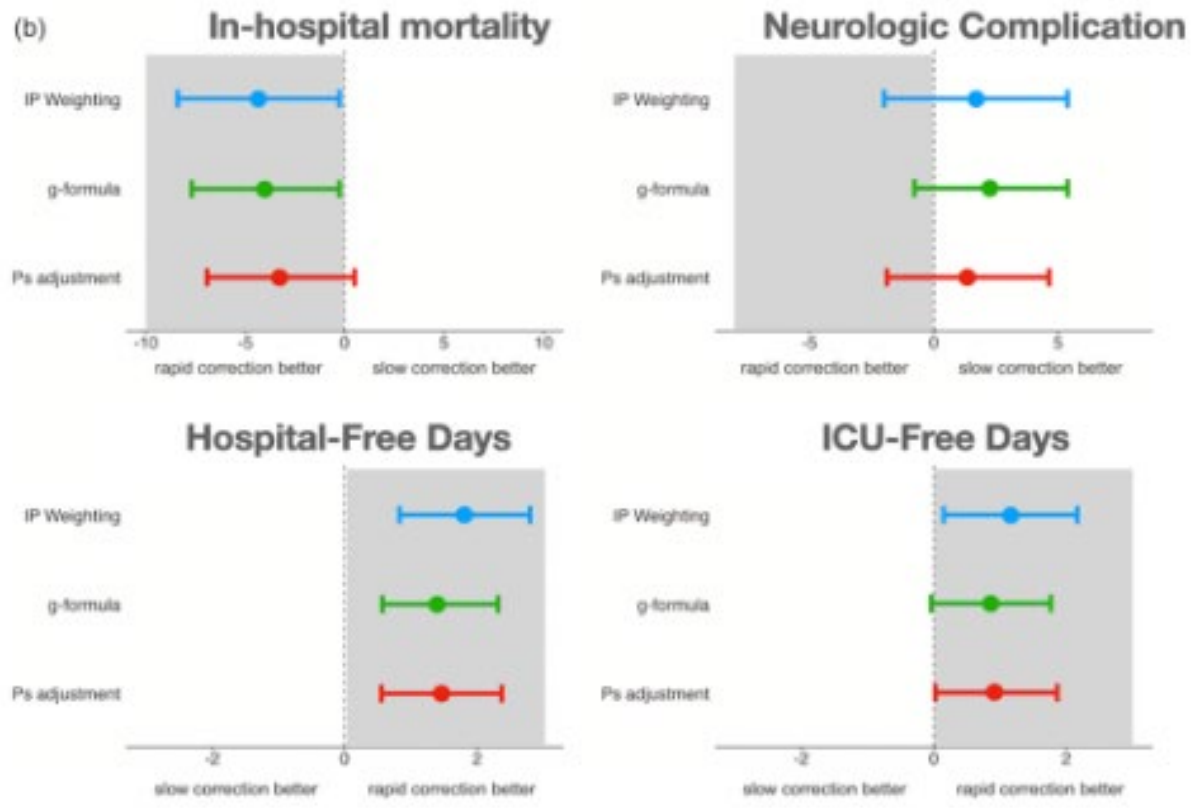
116 mEq/L

451

44%

Kinoshita T, Et. Al. (2023). *J Crit Care*

Rapid vs Slow Correction of Hyponatremia

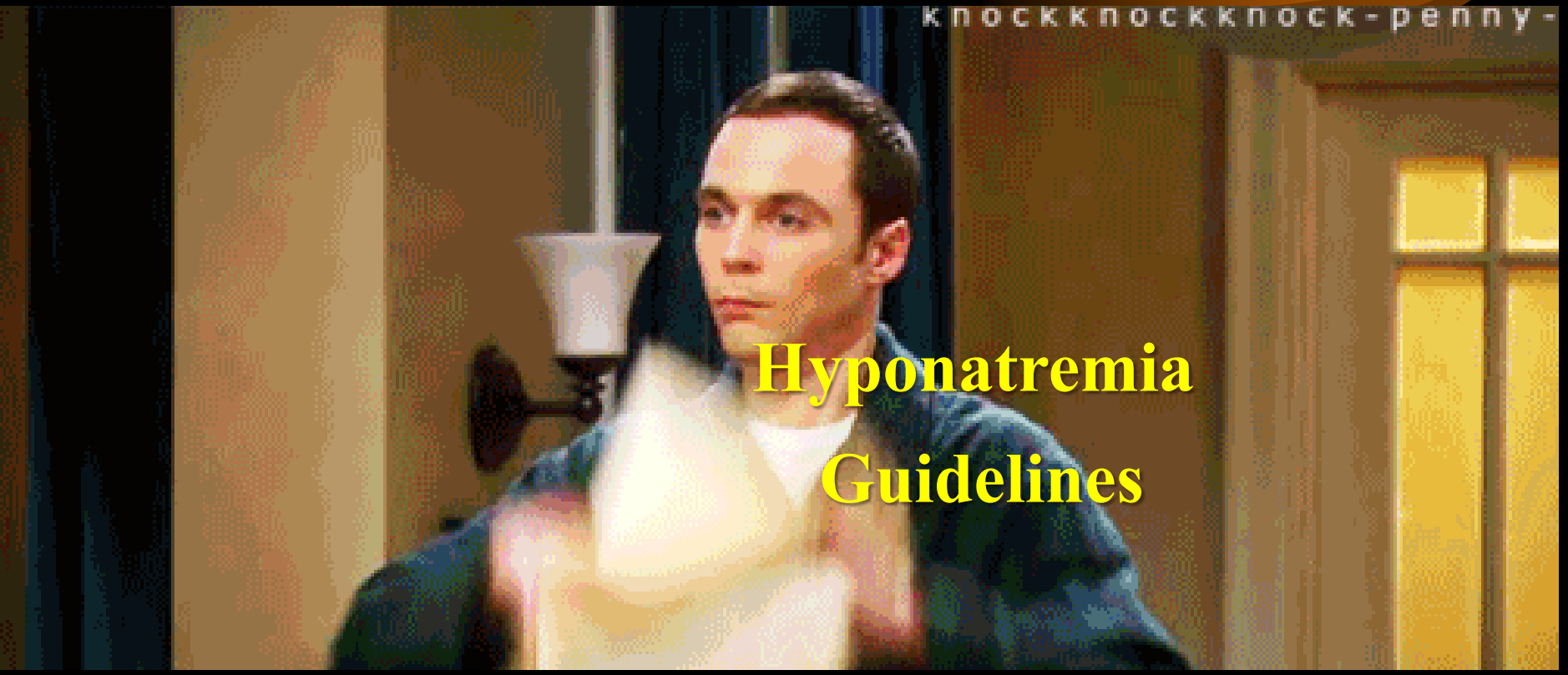


Kinoshita T, Et. Al. (2023). J Crit Care

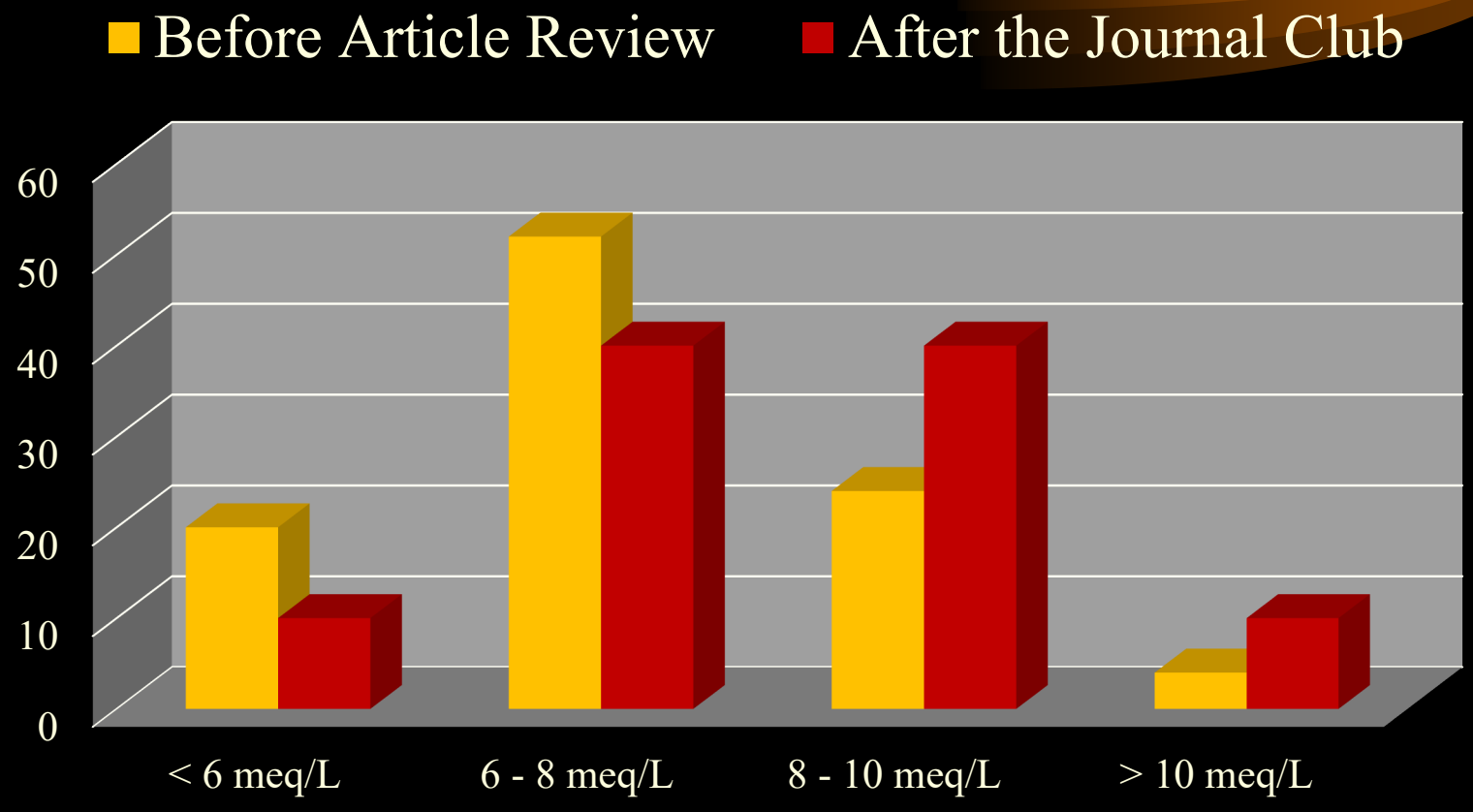
"Blockbuster" Conclusions

- **There was a poor correlation between the rate of Na correction and the development of ODS**
- **A higher mortality was associated with a slow rate of correction < 6 meq/L/24 hours**
- **A lower mortality was associated with a higher rate of correction**

As a Result of this Study ……



Impact of This Article on Practice Pattern in Treating Hyponatremia – Twitter Survey



Rate of Na Correction in the first 24 hours

The Rebuttal !

14 | ASN Kidney News | May 2023 Volume 15: Issue 5

We Do Not Need to Rethink Our Approach to Overcorrection of Hyponatremia

By Helbert Rondon-Berrios and Richard H. Sterns

- **The authors' methodology for defining overcorrection may also have led them to erroneous conclusions. Based on the results of this study, do we need to rethink our current approach to overcorrection of hyponatremia? Do we need to relax our PNa correction limits? Is it safe to rapidly correct all patients with hyponatremia? We believe the answer to these questions is no!**

Dr Kupin's Konclusions

- **ODS is unlikely to develop in patients without pre-existing risk factors of cirrhosis / CHF / malnutrition even with severe Hyponatremia regardless of the rate of correction**
- **Avoid excessively slow rates of correction < 6 meq/L in first 24 hours**
- **Not yet established if rates > 10 meq/L are clearly better than 6 – 10 Meq/L but increasing evidence points to the safety of slightly faster correction rates than previously thought**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 2, 2023 VOL. 388 NO. 9

Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Nasser A. Dhayat, M.D., Olivier Bonny, M.D., Ph.D., Beat Roth, M.D., Andreas Christe, M.D., Alexander Ritter, M.D., Nilufar Mohebbi, M.D., Nicolas Faller, M.D., Ph.D., Lisa Pellegrini, M.D., Giulia Bedino, M.D., Reto M. Venzin, M.D.,

ACP American College of Physicians℠
Leading Internal Medicine, Improving Lives

SUMMARY OF THE AMERICAN COLLEGE OF PHYSICIANS GUIDELINE ON DIETARY AND PHARMACOLOGIC MANAGEMENT TO PREVENT RECURRENT NEPHROLITHIASIS IN ADULTS

Disease/Condition	Recurrent nephrolithiasis
Target Audience	Internists, family physicians, and other clinicians
Target Patient Population	Adults with recurrent nephrolithiasis
Interventions Evaluated	Dietary: increased fluid intake, increased oligomineral water intake, decreased soft drink intake, multicomponent dietary interventions, high fiber intake, and low animal protein intake Pharmacologic: thiazide diuretic, citrate, allopurinol, acetohydroxamic acid, and magnesium
Outcomes Evaluated	Symptomatic stone recurrence, radiographic and composite stone recurrence, pain, urinary tract obstruction with acute renal impairment, infection, procedure-related morbidity, emergency department visits, hospitalizations, quality of life, and ESRD
Benefits	Decreased stone recurrence
Harms	Adverse events associated with dietary interventions: Multicomponent diet: hypertension, gout, and stroke Adverse events associated with pharmacologic interventions: Thiazides: orthostasis, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms Citrates: gastrointestinal symptoms Acetohydroxamic acid: anemia, headache, alopecia, tremor, and deep venous thrombosis Allopurinol: rash, acute gout, and leukopenia Magnesium: diarrhea
Recommendations	*Recommendation 1: ACP recommends management with increased fluid intake spread throughout the day to achieve at least 2 L of urine per day to prevent recurrent nephrolithiasis. (Grade: weak recommendation, low-quality evidence)* *Recommendation 2: ACP recommends pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones. (Grade: weak recommendation, moderate-quality evidence)*
Inconclusive Areas of Evidence	Relationship between pretreatment or in-treatment stone composition and biochemistry (blood and urine) with treatment efficacy to prevent stone recurrence
Clinical Considerations	Evidence is applicable primarily to calcium stones. Evidence showed that patients who decreased intake of soda that was acidified by phosphoric acid had reduced kidney stone recurrence. Clinicians should encourage patients to avoid colas as opposed to fruit-flavored soft drinks, which are often acidified by citric acid.

Benefit of Low Dose Thiazide in Preventing Calcium Stone Disease

Author, Year	Treatment, Dose	Allocation Concealment	Blinding	Intention-to-treat Analysis	Withdrawals described	Selection for Hypercalciuria	Follow-Up (Years)	Treated/ Placebo, n/N	Events/Total, n/N Thiazide	Events/Total, n/N Placebo	RR [c]	Recurrence Outcome
Brocks, 1981 [29]	Bendroflumethiazide, 2.5 mg TID [a]	Unclear	Double-blind	No	No	No	1.6	33/29	5/33	5/29	NS	Composite
Scholz, 1982 [31]	HCTZ, 25 mg BID [b]	Unclear	Double-blind	No	No	No	1	25/26	6/25	6/26	NS	Symptomatic
Laerum, 1984 [23]	HCTZ, 25 mg BID	Unclear	Double-blind	Yes	Yes	No	3	23/25	5/23	12/25	0.45	Composite
Wilson, 1984 [26]	HCTZ, 100 mg daily	Unclear	Open-label	No	No	No	2.8	23/21	0.15 stones/year	0.32 stones/year	0.48	Symptomatic
Robertson, 1985 [27]	Bendroflumethiazide, 2.5 mg TID	Unclear	Open-label	No	No	No	3–5	13/9	0.22 stones/year	0.58 stones/year	0.38	Symptomatic
Mortensen, 1986 [24]	Bendroflumethiazide, 2.5 mg	Unclear	Double-blind	No	No	No	2	12/10	0/12	4/10	–	Composite
Ettinger, 1988 [22]	Chlorthalidone, 25 m /50 mg	Adequate	Double-blind	No	Yes	No	3	19/23/31 (25 mg /50 mg/placebo)	6/42	14/31	0.32	Composite
Ohkawa, 1992 [25]	Trichlormethiazide, 4 mg	Unclear	Open-label	No	No	Yes	2.14–2.21	82/93	24/82	57/93	0.42	Composite
Borghi, 1993 [21]	Indapamide, 2.5 mg daily	Unclear	Open-label	No	Yes	Yes	3	25/25	3/25	9/25	0.33	Composite
Ahlstrand, 1996 [30]	HCTZ, 25 mg BID	Unclear	Open-label	Yes	Yes	Yes	3.6–4.3	17/22	9/17	19/22	0.61	Composite
Fernandez-Rodriguez, 2006 [28]	HCTZ, 50 mg daily	Unclear	None stated	Yes	No withdrawals	No	3	50/50	16/50	28/50	0.57	Composite

[a]TID, three times daily, [b] BID, twice times daily, [c] RR, relative risk

Dhayat N, *BMC Nephrology* volume 19: 349 (2018)

Rationale for the NOSTONE Study

- **A variety of thiazide derivatives were used in the prior studies**
- **Multiple dosing regimens – once daily / twice daily**
- **Few RCT**
- **Few Prospective trials**
- **Lack of double-blinding and intention-to-treat analysis**
- **Absence of adverse event and drop out reporting**

NOSTONE

- Prospective, multicenter, parallel-arm, double-blind and placebo-controlled design with
  - stratification by disease activity
  - clear allocation concealment and intention-to-treat analysis
  - employment of high sensitivity and high specificity imaging
  - use of state-of-the-art dietary recommendations,
  - careful assessment of putative side effects in the stone population
  - exclusive public funding support

NOSTONE Patient Population

- Study Participants:
  - **Age 18 years or older**
  - **Recurrent kidney stone disease (≥ 2 stone events within the 10 years prior to randomization)**
  - **Any past kidney stone containing 50% or more of calcium oxalate, calcium phosphate or a mixture of both**

Did I mention the Study was done in …….???????

NOSTONE Protocol

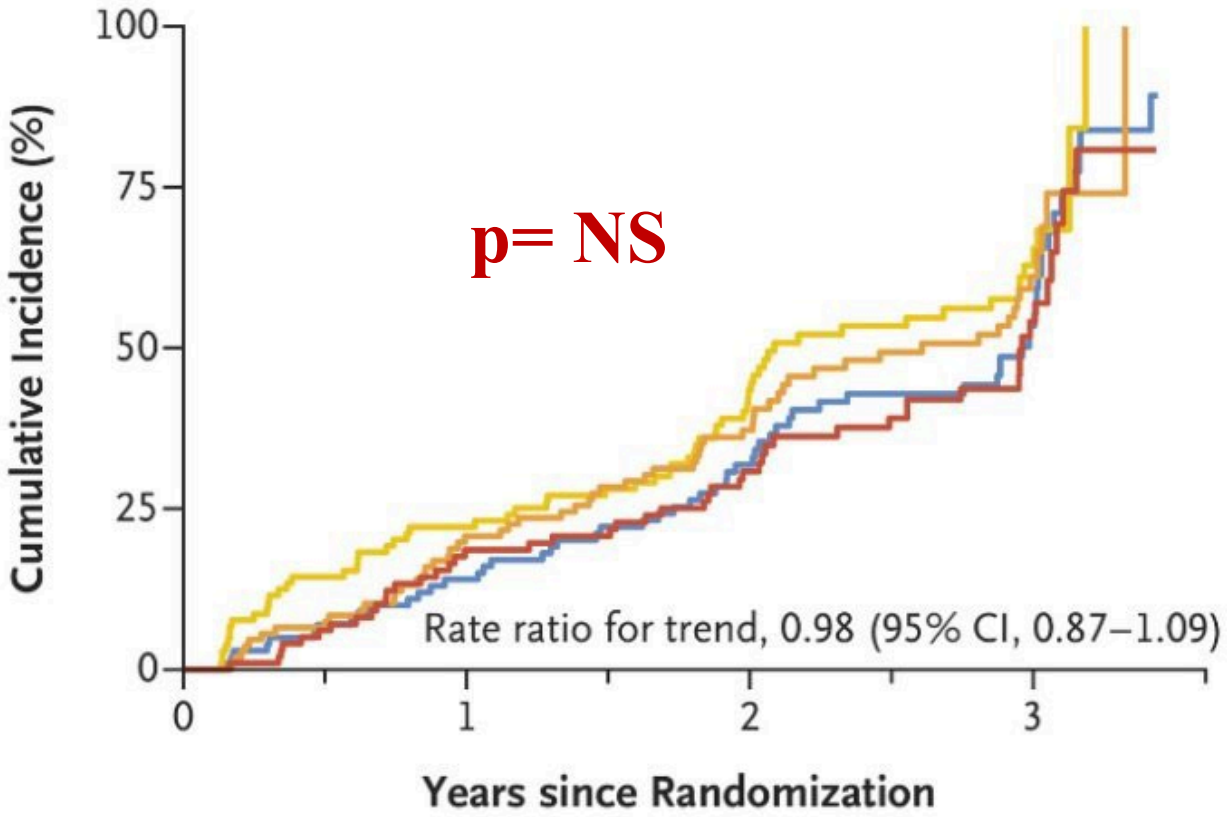
- Participants were randomized into 4 groups:
  - 12.5 mg hydrochlorothiazide daily
  - 25 mg hydrochlorothiazide daily
  - 50 mg hydrochlorothiazide daily
  - Placebo daily
- Participants underwent non-contrast CT scan of kidneys at start of randomization and at the end of 3 years. Follow up visits were at 3 months and then yearly. There were telephone visits every 3 months.

Patient Population

- **100 patients in EACH group !**
- **99.9 % Caucasian**
- **35% had a history of > 4 stones / lifetime**
- **60% had documented Hypercalciuria**

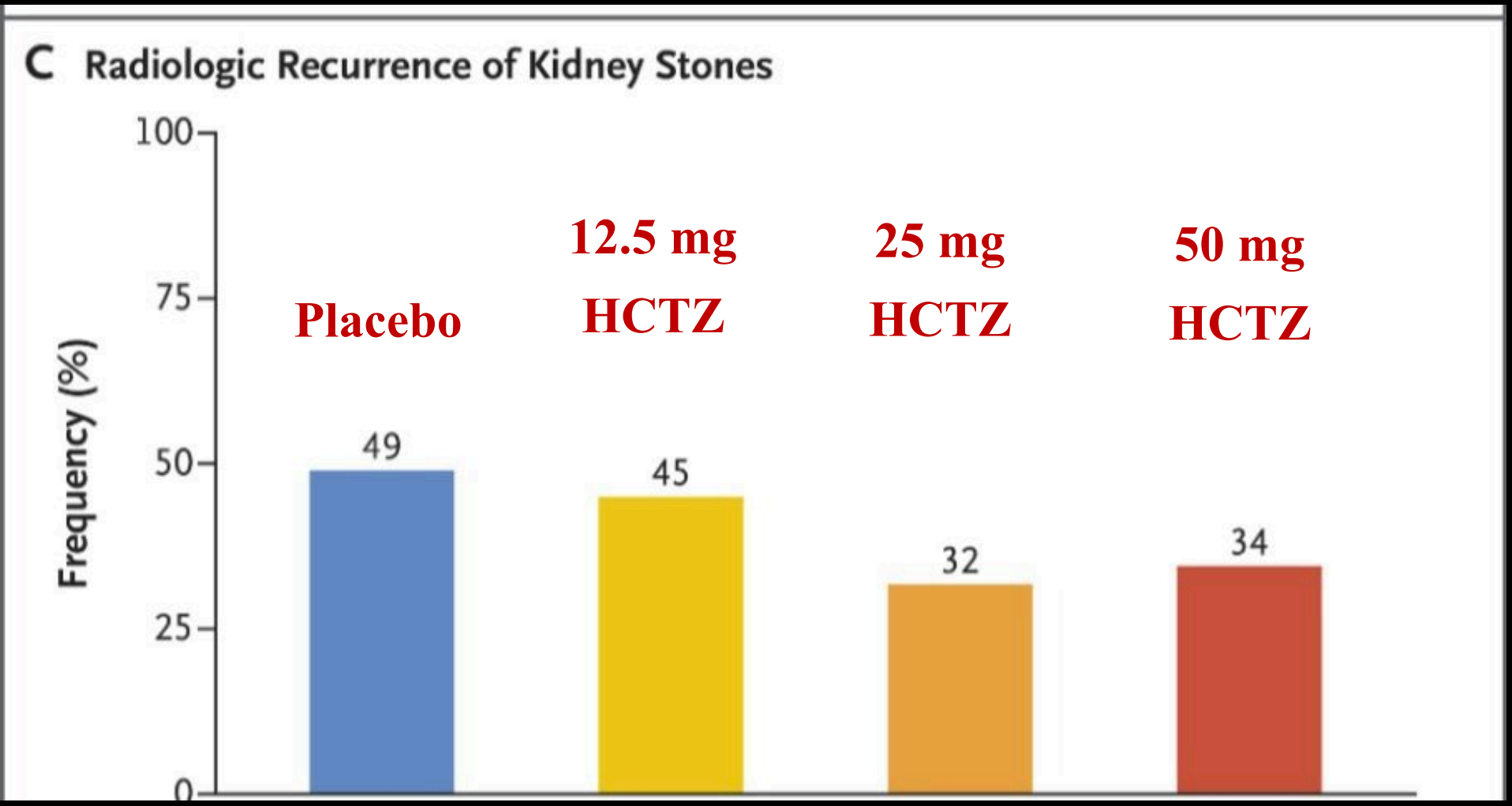
Placebo — 12.5-mg HCT — 25-mg HCT — 50-mg HCT

A Symptomatic or Radiologic Recurrence of Kidney Stones

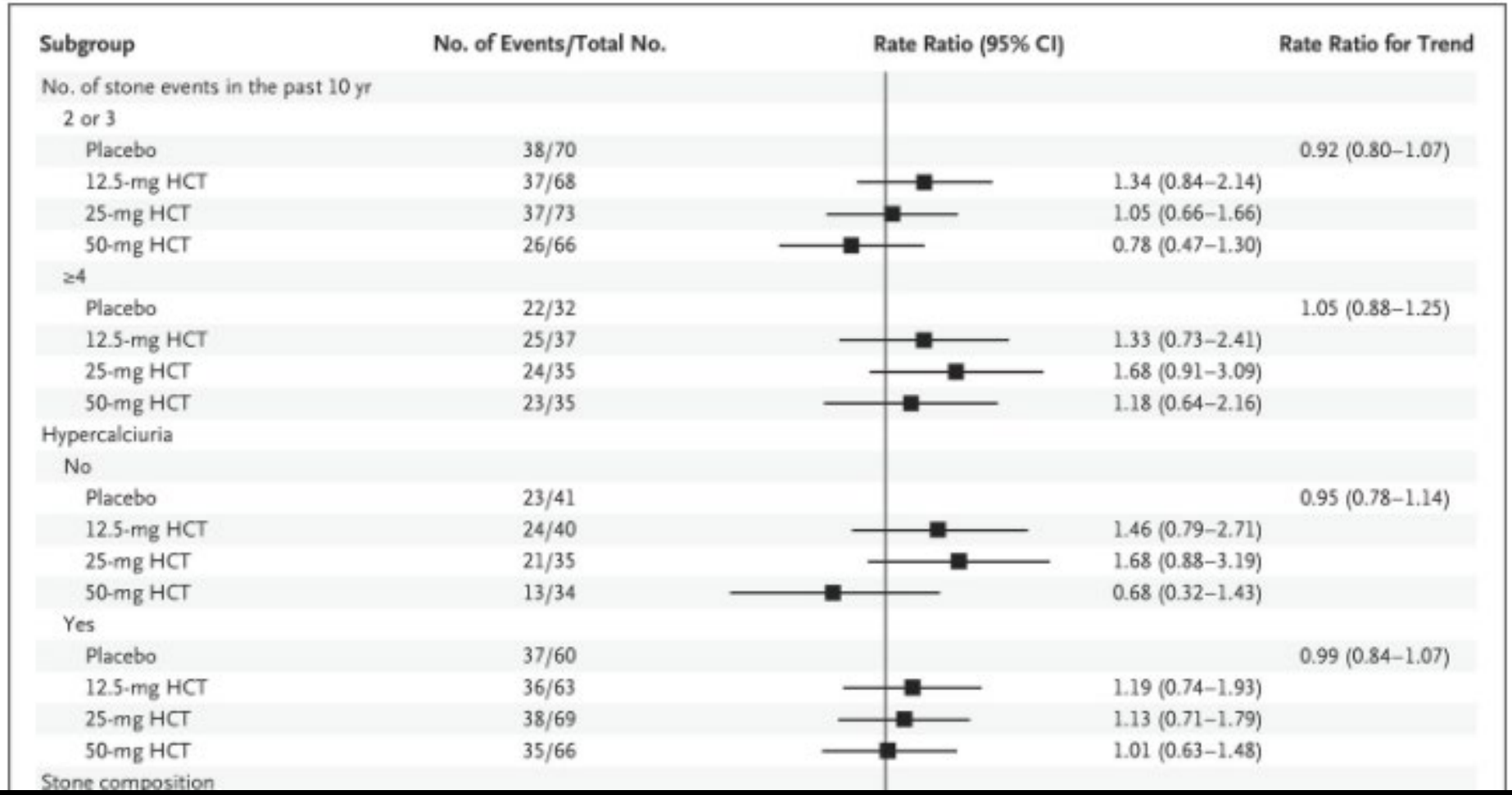


No. at Risk				
Placebo	102	85	59	25
12.5-mg HCT	105	79	50	14
25-mg HCT	108	83	57	15
50-mg HCT	101	77	56	17

Dhayat et al. N Engl J Med 2023 Mar 2;388(9):781-791



Dhayat et al. N Engl J Med 2023 Mar 2;388(9):781-791



Subgroup	No. of Events/Total No.	Rate Ratio (95% CI)	Rate Ratio for Trend
No. of stone events in the past 10 yr			
2 or 3			
Placebo	38/70		0.92 (0.80–1.07)
12.5-mg HCT	37/68	1.34 (0.84–2.14)	
25-mg HCT	37/73	1.05 (0.66–1.66)	
50-mg HCT	26/66	0.78 (0.47–1.30)	
≥4			
Placebo	22/32		1.05 (0.88–1.25)
12.5-mg HCT	25/37	1.33 (0.73–2.41)	
25-mg HCT	24/35	1.68 (0.91–3.09)	
50-mg HCT	23/35	1.18 (0.64–2.16)	
Hypercalciuria			
No			
Placebo	23/41		0.95 (0.78–1.14)
12.5-mg HCT	24/40	1.46 (0.79–2.71)	
25-mg HCT	21/35	1.68 (0.88–3.19)	
50-mg HCT	13/34	0.68 (0.32–1.43)	
Yes			
Placebo	37/60		0.99 (0.84–1.07)
12.5-mg HCT	36/63	1.19 (0.74–1.93)	
25-mg HCT	38/69	1.13 (0.71–1.79)	
50-mg HCT	35/66	1.01 (0.63–1.48)	
Stone composition			

NO benefit from HCTZ in patients with or without Hypercalciuria

Dhayat et al. N Engl J Med 2023 Mar 2;388(9):781-791

Table 3. Adverse Events during the Treatment Period.

Event	Placebo (N=102)		12.5-mg Hydrochlorothiazide (N=105)		25-mg Hydrochlorothiazide (N=108)		50-mg Hydrochlorothiazide (N=101)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	*no. of events*
Selected adverse events of special interest*								
Total	8 (8)	8	11 (10)	12	18 (17)	21	16 (16)	20
Hypokalemia	1 (1)	1	1 (1)	1	3 (3)	3	6 (6)	8
Gout	0	0	1 (1)	1	1 (1)	2	0	0
New-onset diabetes mellitus	1 (1)	1	2 (2)	2	7 (6)	7	2 (2)	2
Serious adverse event	30 (29)	34	17 (16)	18	24 (22)	27	14 (14)	16

Hypokalemia and new onset Diabetes were more common in the HCTZ groups

Dhayat et al. N Engl J Med 2023 Mar 2;388(9):781-791

Conclusions : NOSTONE TRIAL

- HCTZ did not result in a lower frequency of symptomatic calcium stone recurrence
- HCTZ did not result in an overall lower frequency of radiologic kidney stone recurrence
- HCTZ was not effective in reducing stone recurrence evcn in patients with hypercalciuria
- HCTZ therapy was associated with an increased risk of new onset diabetes and hypokalemia

Limitations : NOSTONE TRIAL

- Study duration was only 3 years while kidney stone recurrence may take a longer duration to occur
- NO control for the use of Kcitrate in any of the groups
- Only HCTZ was used while prior studies used Chlorthalidone and Indapamide

Published Articles Influence Clinical Practice

NOSTONE: Is Hydrochlorothiazide (HCT) Beneficial in Recurrent Kidney Stone Prevention?

#NephJC

METHODS

- Randomized Control Trial (1:1:1:1)
- Double Blind
- 12 Centers in Switzerland
- Age>18 + ≥ 2 episodes of kidney stones
  n = 416
- 2.9 year median follow-up

- Placebo
- HCT 12.5 mg
- HCT 25 mg
- HCT 50 mg

RESULTS

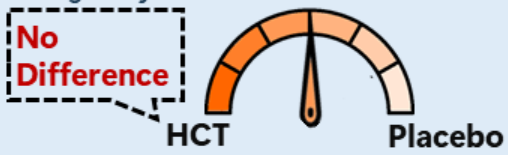
Primary Outcome

Stone Recurrence
(Symptomatic or Radiologic)
HCTZ vs Placebo
No Difference
(Rate ratio 0.98
95% CI, 0.87 to 1.09)

Safety Outcomes

Adverse Events
New-onset Diabetes, Hypokalemia, gout, skin allergy, plasma creatinine elevation

Serious Adverse Events
Cardiac, GI, Kidney, CNS, Kidney, Malignancy



CONCLUSION: Among patients with recurrent kidney stones, the incidence of recurrence did not appear to differ substantially between HCT or placebo.

Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence. *N Engl J Med.* 2023; 388(9):781-791

Visual Abstract by: Renz Pasilan @RenzPasilan

It's Time for Precision Medicine : Hitting the Bullseye of Therapeutic Action

The NEW ENGLAND JOURNAL of MEDICINE

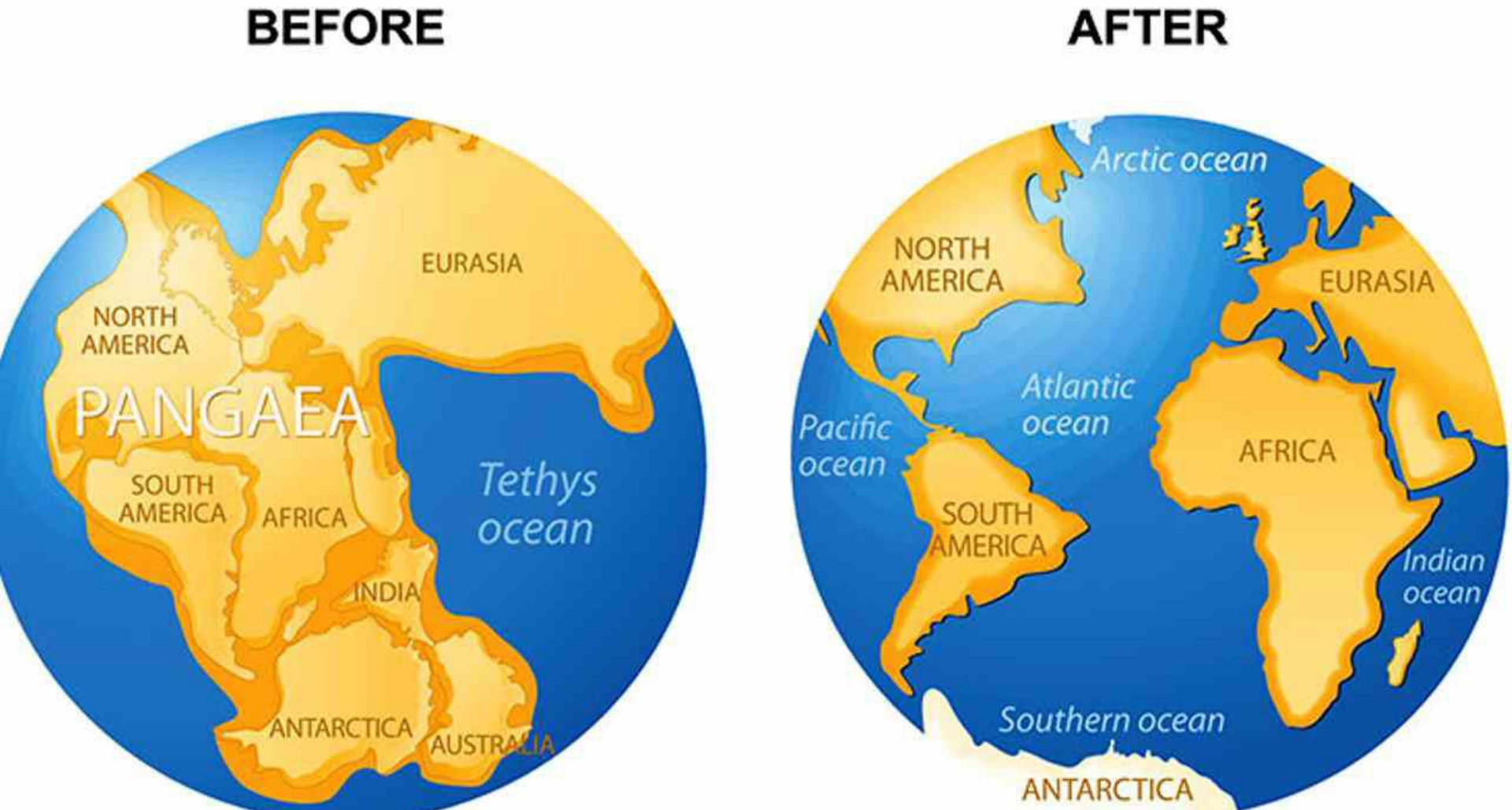
ESTABLISHED IN 1812 MARCH 16, 2023 VOL. 388 NO. 11

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*

- **What are APOL1 variants ?**
- **What is Inaxaplin ?**
- **Why would anyone but a nephrologist be interested in this ?**
- **Dr K -This is an Internal Medicine conference <u>not</u> Renal Grand Rounds ! (and it's Sunday morning!)**

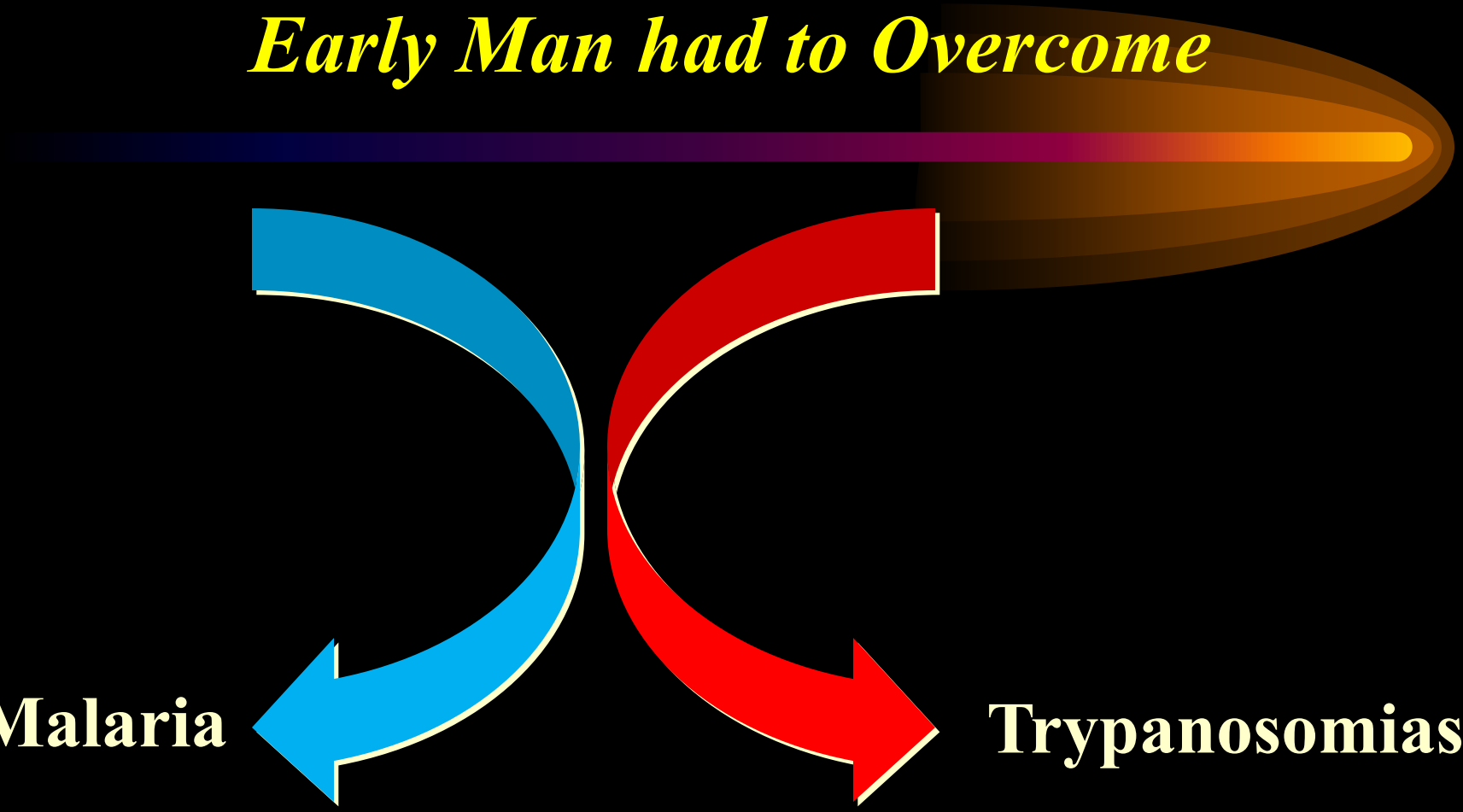
A Supercontinent Splits Apart



Barriers to Survival on the African Continent

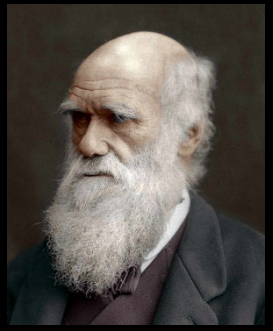
- Food / Water
- Environment
- Shelter
- Hostile Animals
- Microbiologic Diseases

Diseases in Africa Early Man had to Overcome

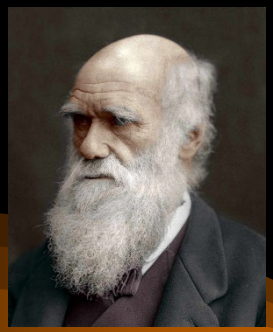


Malaria

Trypanosomiasis (African Sleeping Sickness)



Darwinian Theory of Survival of the Fittest : Genetic Mutations



Malaria **Trypanosomiasis**

Black Race

Sickle cell Mutation

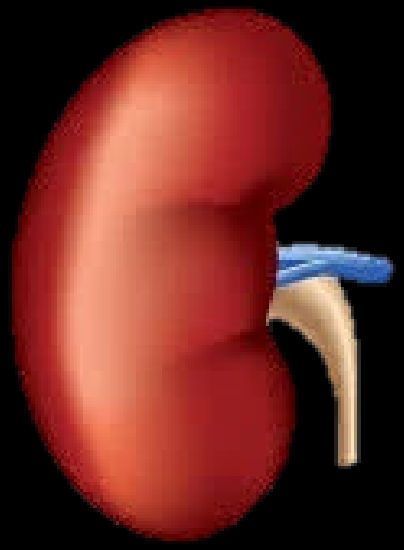
APOL1 Mutations

Su !!

CAUTION

NO GOOD DEED GOES UNPUNISHED

The Verdict is in : Evidence is Clear



Homozygous

APOL1

Variants

CKD / ESRD

DM / ESRD

HTN / ESRD

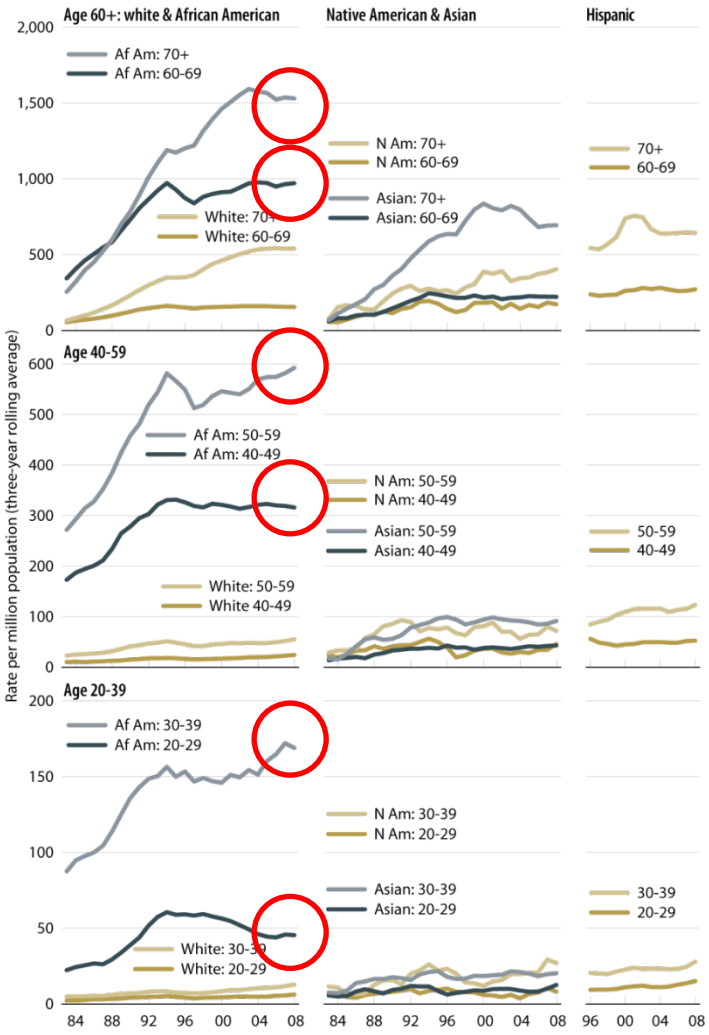
SLE / ESRD

HIV / ESRD

Transplant / ESRD

The Slave Trade Spread APOL1 Variants Across the World

Racial Differences in the Incidence of CKD / ESRD



Black Race 13% of U.S. population but 32% of ESRD population

At every age group, the incidence of CKD and ESRD are significantly higher in people of African black race ancestry

Hereditary APOL1 Variants Account for the Major Risk of Kidney Disease in Black Patients in the U.S.

African-Americans, Kidney Failure and APOL1

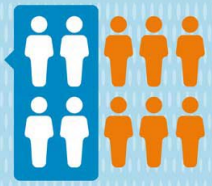
African-Americans are **13%** of the **US** population but account for **32%** of **kidney failure** in the US[1]

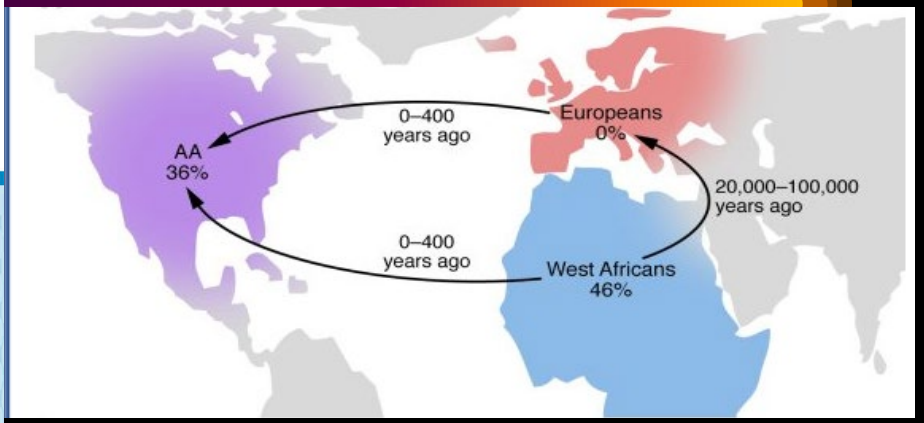
African-Americans are almost **4 times** more likely to develop **kidney failure** than caucasians.[1]

About **1 in 5** people with two copies of **APOL1 renal risk variants** will develop **kidney disease**[2]

These **APOL1 variants** account for **70%** of non-diabetic **kidney failure** in **African-Americans**[2]

About **4 in 10** **African-Americans** on dialysis have **kidney failure** caused by **APOL1**[2]

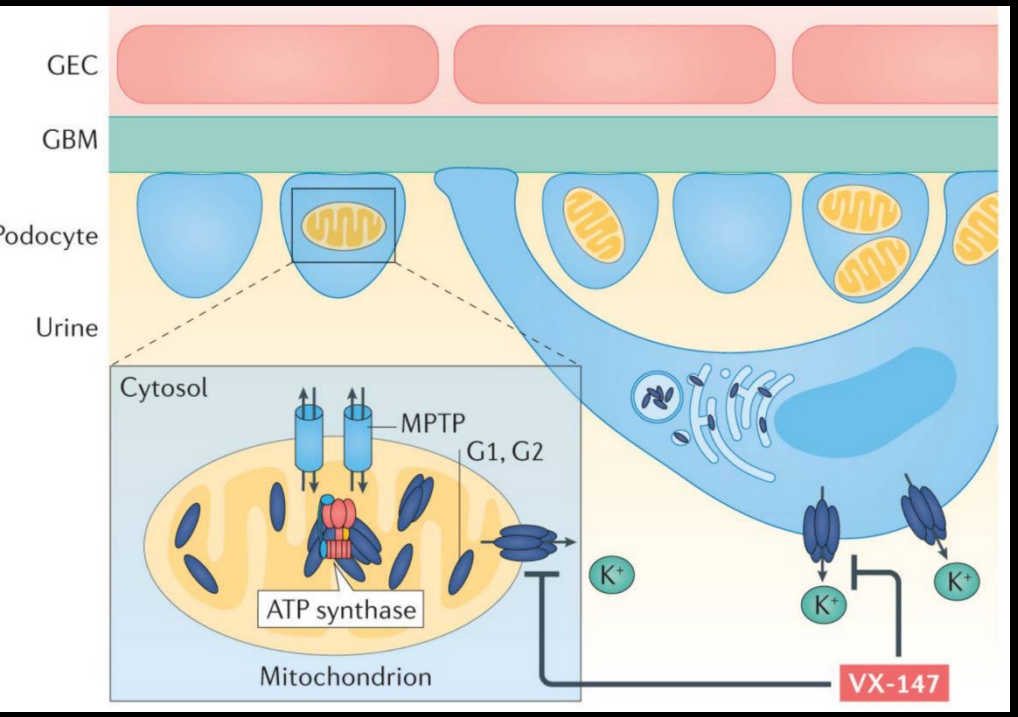




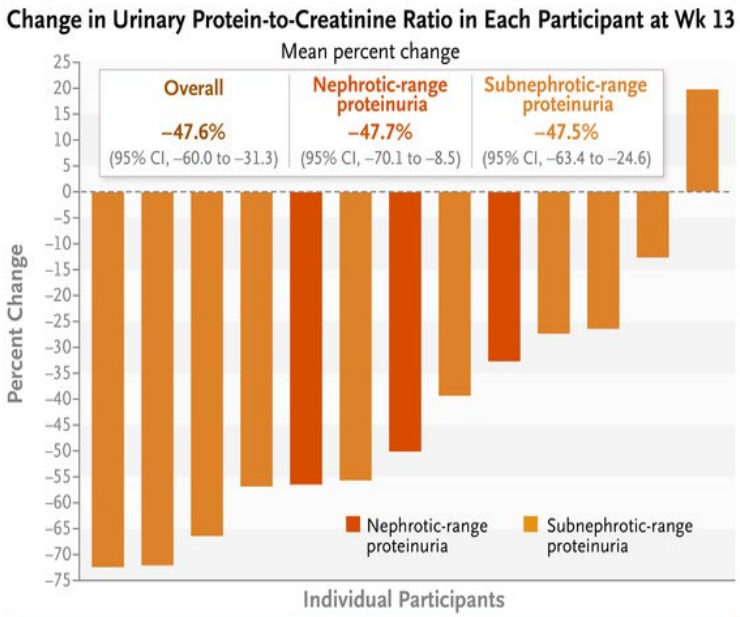
36% of Black race individuals in the U.S. carry a mutation either G1 or G2 of the APOL1 allele

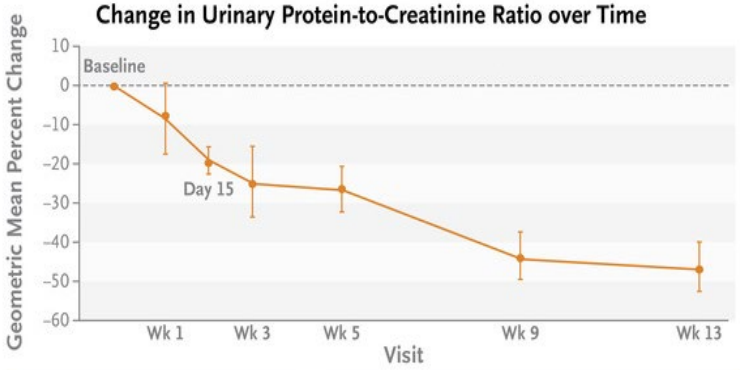
Friedman, D. Clin J Am Soc Nephrol. 2021 Feb 8; 16(2): 294–30

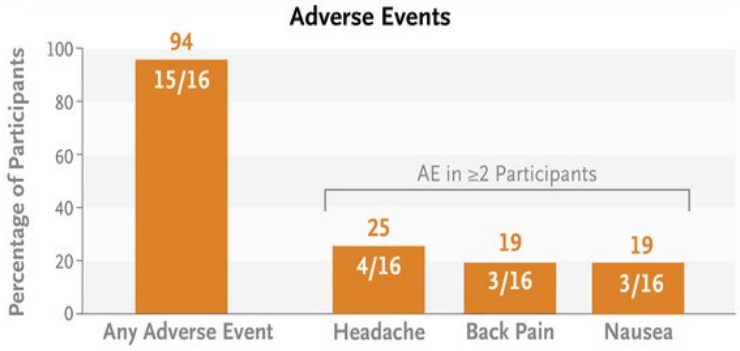
Inaxaplin



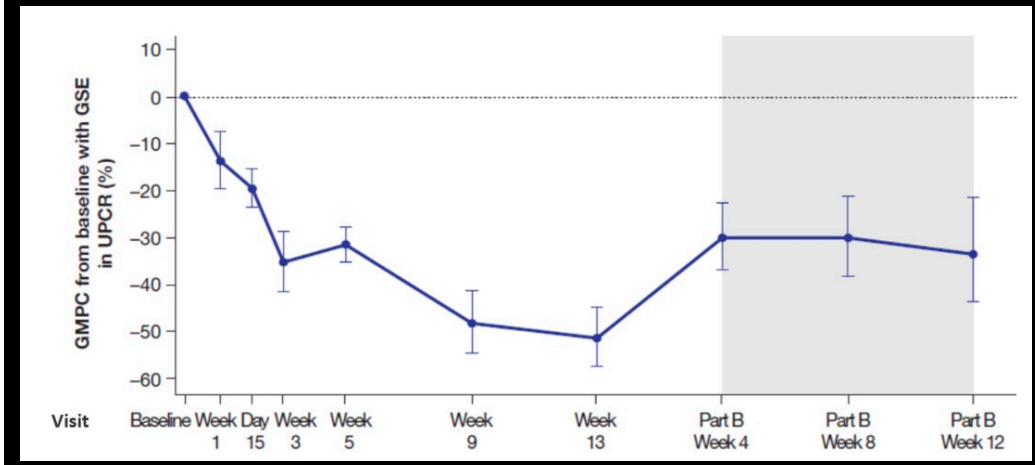
- APOL1 is not only produced in the liver and circulates but is intrinsic to PODOCYTES
- Variants cause a gain of function mutation and the insertion of pores into the cell wall and mitochondria
- Inaxaplin will block these pores from functioning







Significant decrease in proteinuria for all patients after 13 weeks that was sustained 3 months beyond the study period !



O Egbuna et al. N Engl J Med 2023;388:969-979.


WOW!!!

Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

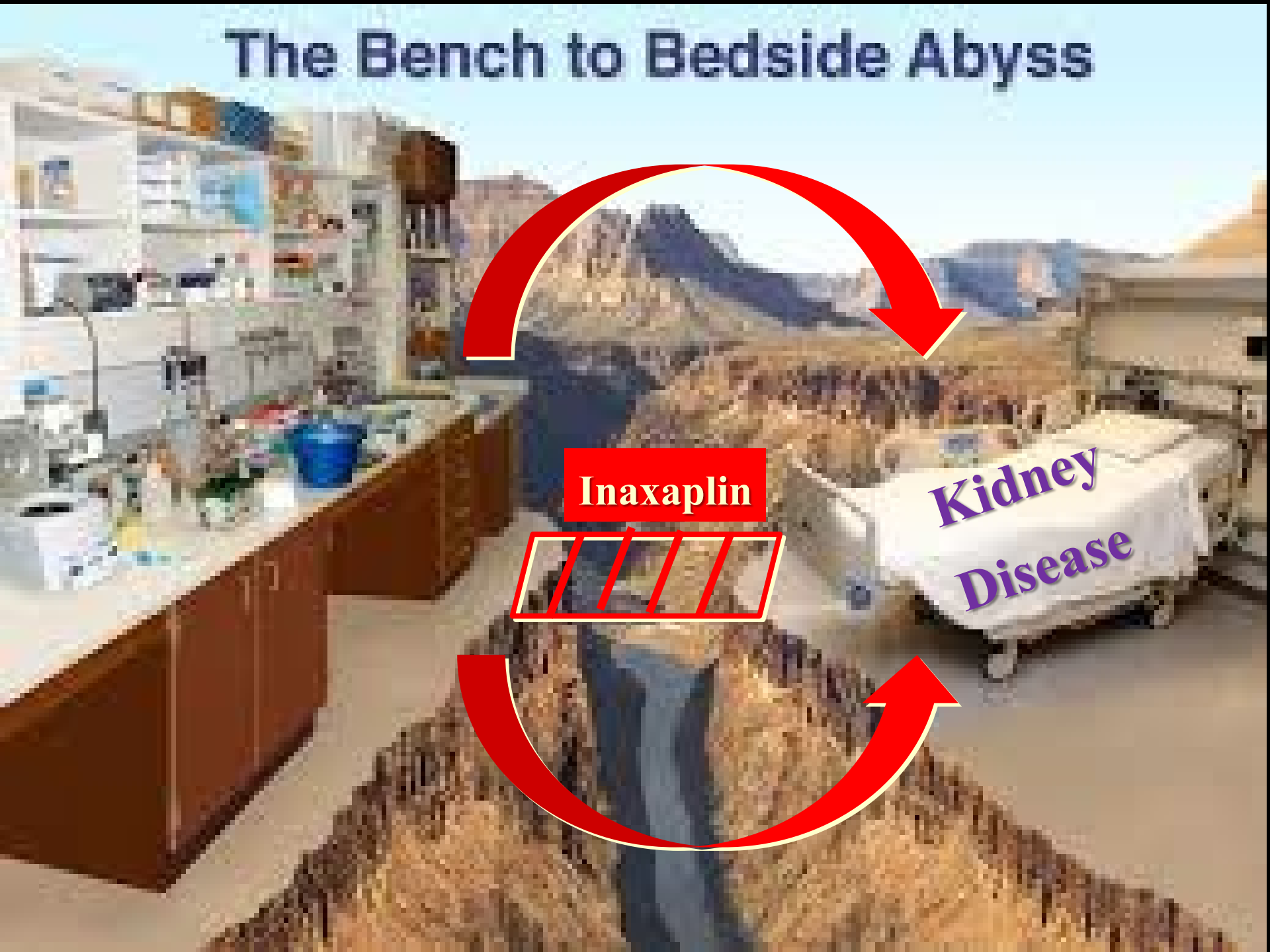
O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group*

APLO1 variants first discovered 10 years ago

First clinical trial (Phase 2a) showing the benefit of an oral agent in blocking the clinical manifestations of renal injury (proteinuria)

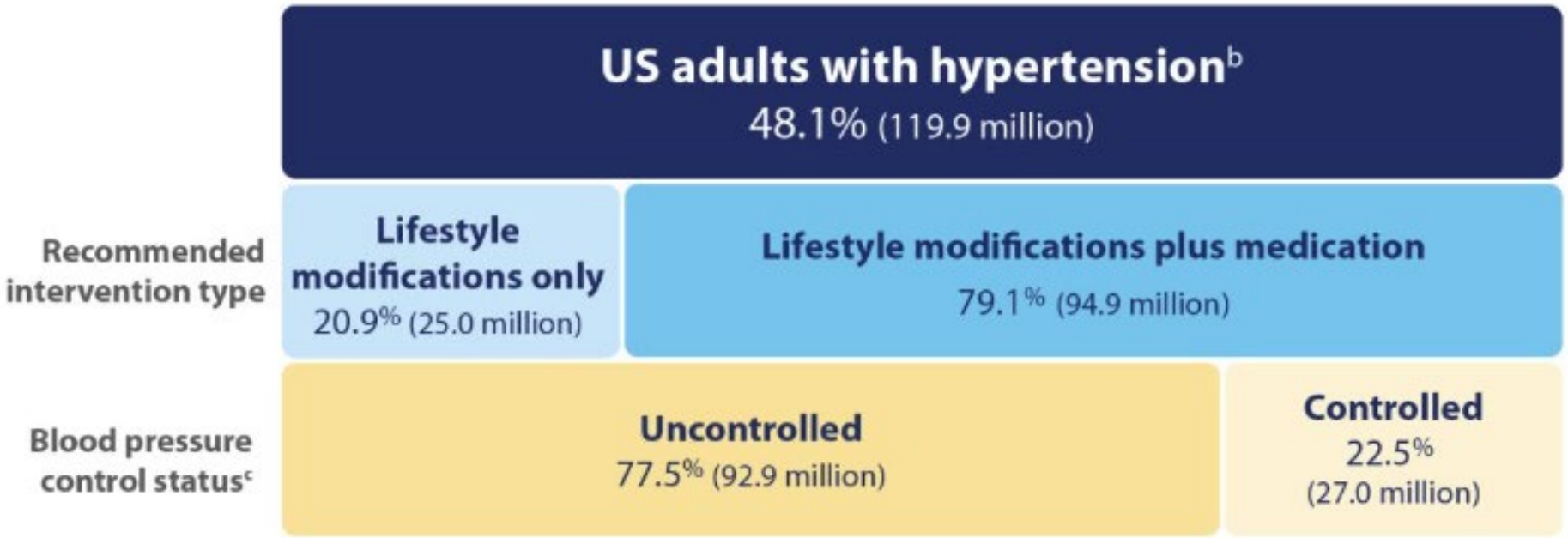
A remarkable achievement and demonstration of the concept ……

The Bench to Bedside Abyss



HTN is Out of Control in the U.S.

Applying the criteria from the American College of Cardiology and American Heart Association's (ACC/AHA) 2017 Hypertension Clinical Practice Guideline - NHANES 2017- March 2020



Data source: National Center for Health Statistics, Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey (NHANES) 2019-March 2020. Definitions: ACC/AHA criteria adapted from Ritchey MD, Gillespie C, Wozniak G, et al. Potential need for expanded pharmacologic treatment and lifestyle modification services under the 2017 ACC/AHA Hypertension Guideline. *J Clin Hypertens*. 2018; 1377-1391. https://doi.org/10.1111/jch.13364

BREAKING NEWS

FDA Approves Renal Denervation Therapy for the Treatment of Hypertension

FDA Approves 2 Devices for Renal Denervation

Recor Medical

- Approved Nov 8 2023
- Symplicity Spyral System
- Ultrasound Ablation
- FDA Advisory panel 10-2 approval

Medtronic

- Approved Nov 20 2023
- Paradise System
- Radiofrequency Ablation
- FDA Advisory panel 6-7 approval

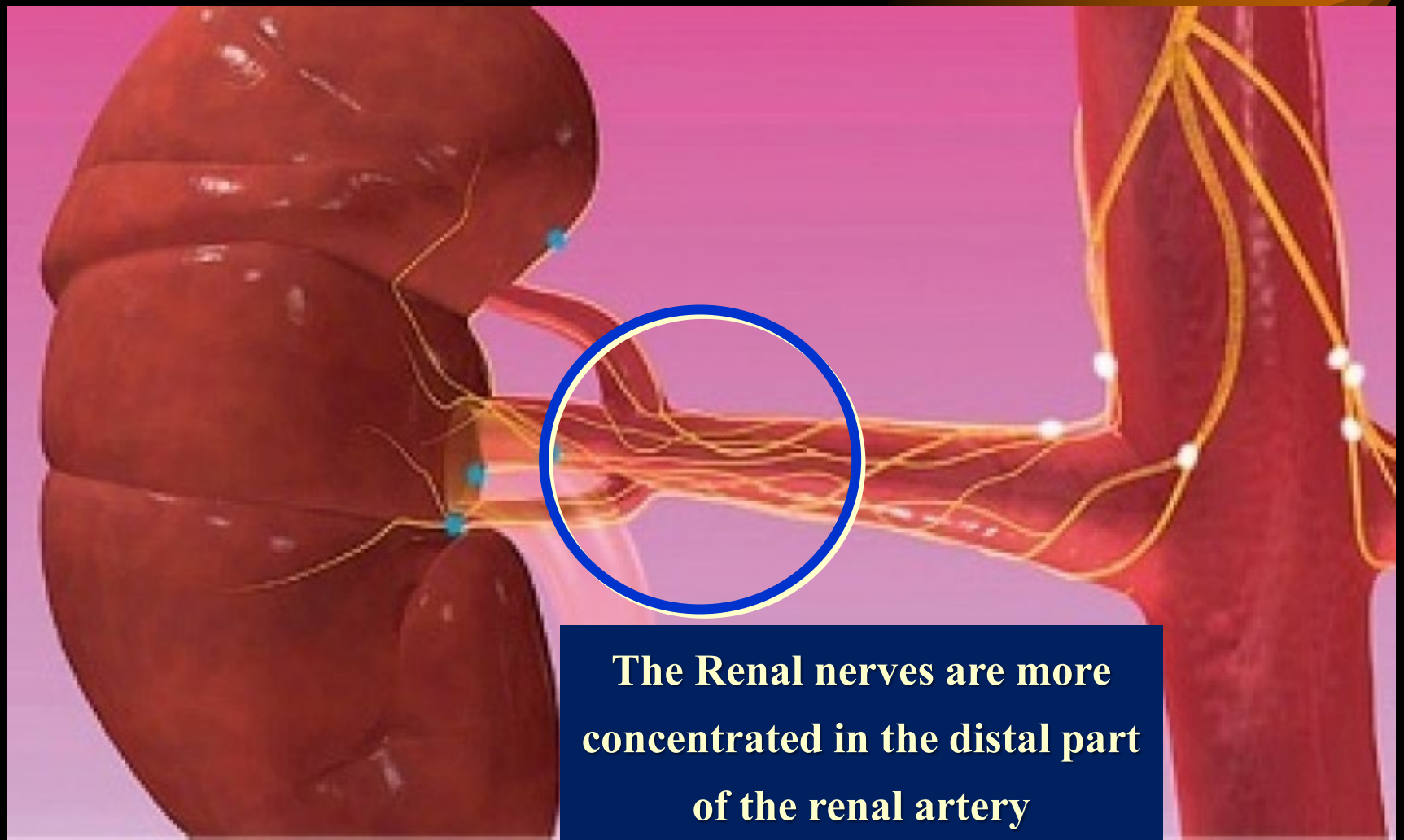
Potential Market for Renal Denervation

500 million (First year)

to 3 Billion Dollars (3 years)

https://healthcare-in-europe.com/media/story/12107/image-1413131225.jpg

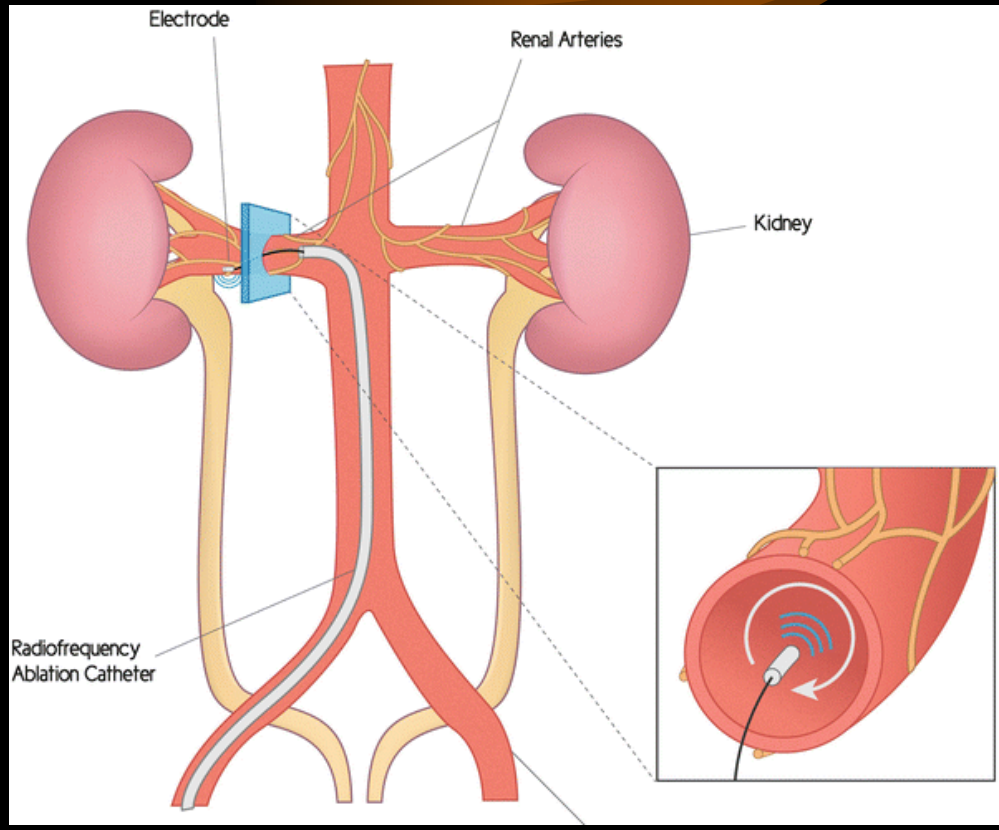
Anatomy of Renal Denervation



https://www.google.com/url?sa=i&url=https%3A%2F%2Fthoracickey.com%2Fdenervation%2F&psig=AOvVaw3gCBMXv08IAm4TKsmUkPTd&ust=1708368932913000&source=images&cd=vfe&opi=89978449&ved=0CBMQjRxqFwoTCJjM06zItYQDFQAAAAAdAAAAABAE

Procedure to Perform Renal Denervation

- Access the femoral artery
- Insert the device up the aorta into the renal artery **using angiography** to guide location
  - Risks
    - Wall dissection
    - Damage to atherosclerotic plaques – emboli
    - Perforation / bleeding
- Apply signals : radiofrequency or ultrasound



Sesa-Ashton G. Hypertension. 2023;80:811–819

Renal Denervation Leads to Sustained Decrease in BP over 9 Years

Catheter-based renal denervation – 9 year follow up data on safety and blood pressure reduction in patients with resistant hypertension

Participants

66 RDN trial participants + 9-years follow-up

Research Questions

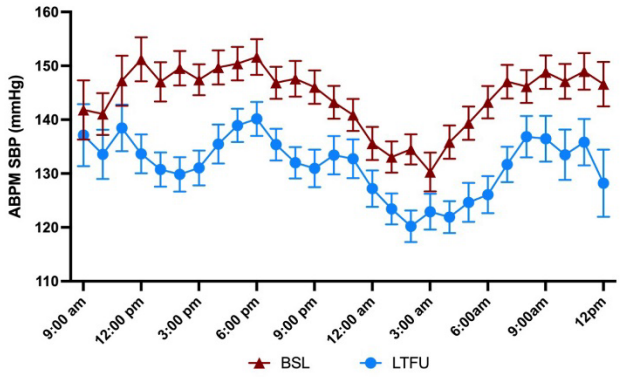
Is BP reduced long-term?

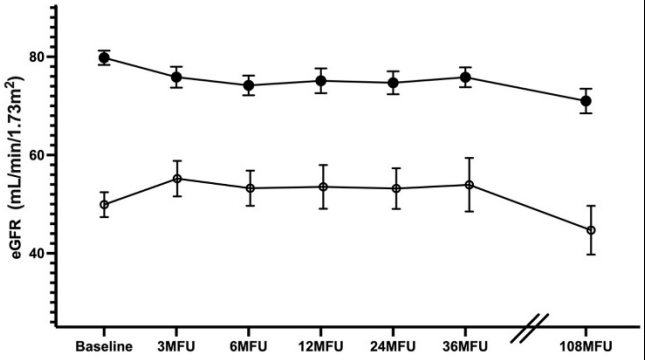
Are there detrimental effects on renal function?

Key Findings

BP significantly reduced by ***-12.1/8.8 mmHg*** on ABPM

No evidence of detrimental effects on eGFR





Conclusions: Blood Pressure is significantly reduced at nine year follow up after renal denervation without adverse renal consequences

Key Facts to Keep in Mind

10 mmHG Reduction in BP

20% Decrease in CV Events

Average Renal Denervation Reduction in BP

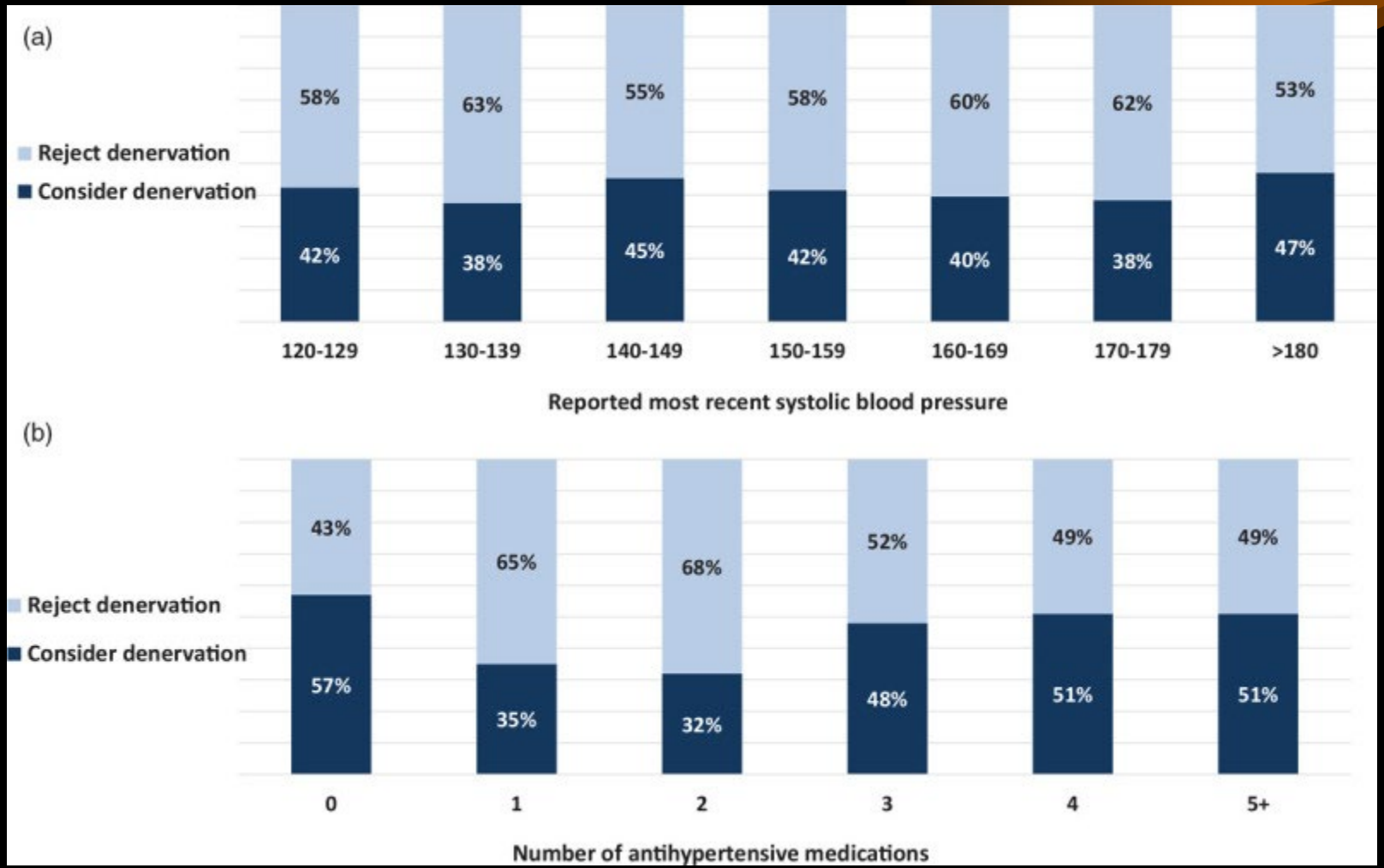
5 - 10 mm Hg Decrease in Systolic BP

Renal Denervation

33% Non-Responder rate

•. 2021 Jan;39(1):162-168
•. 2021 Jan;39(1):162-168

Patients Willing to Undergo Renal Denervation Therapy is Influenced by the Number of Anti-HTN Drugs they Take



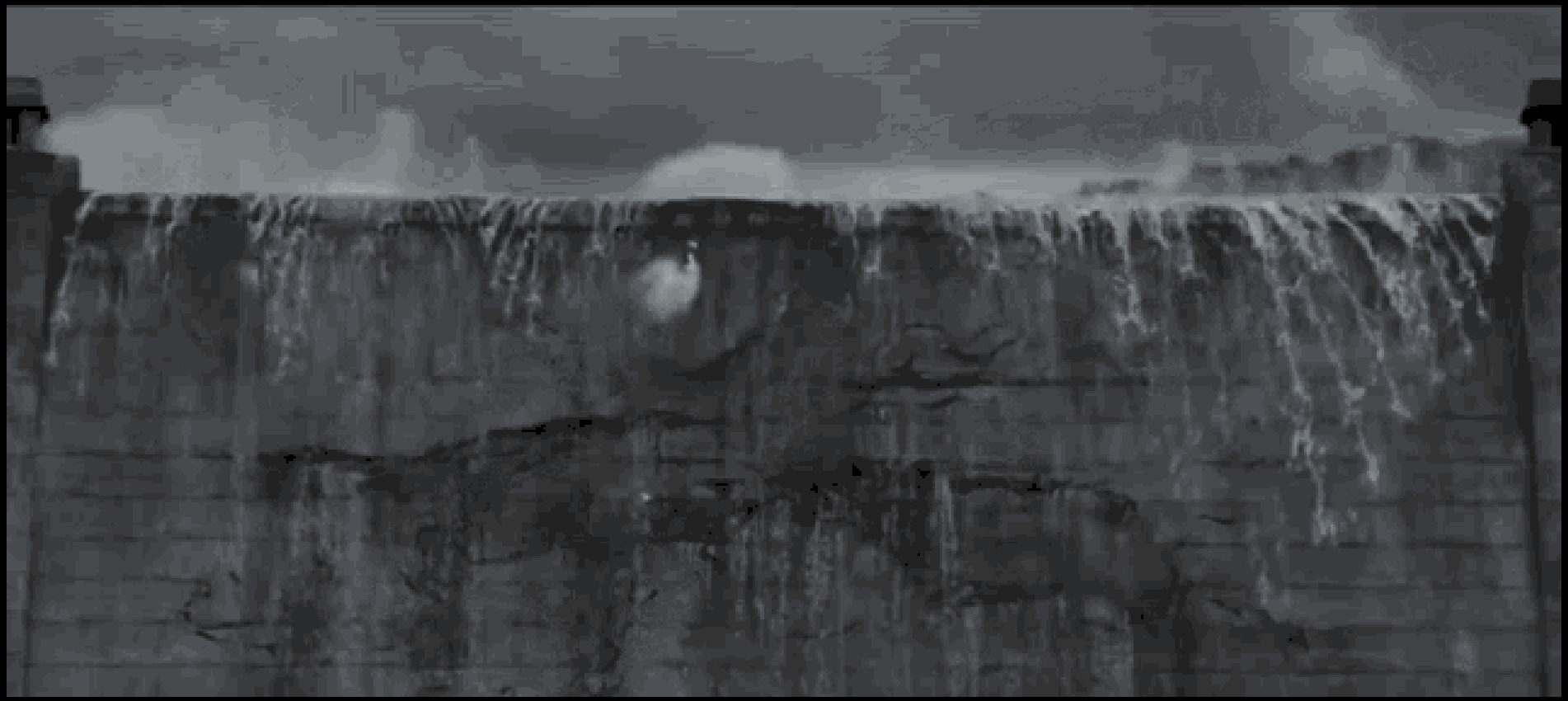
Schmieder R. 2021 Jan;39(1):162-168

Candidates for Renal Denervation Therapy

Patients with resistant hypertension, defined by blood pressure >130/80 mm Hg despite being on 3 medications with maximally tolerated doses incluidnig a diuretic

Patients with uncontrolled hypertension despite attempting lifestyle modification and antihypertensive medication but who are either intolerant of additional medication or do not wish to be on additional medications and who are willing to undergo renal denervation after shared decision-making

The Renal Denervation Tsunami Has Started – Let's See what Happens in 2024 !



10 TOP NEPHROLOGY STORIES 2023

1. IGA Nephropathy: Now with the new drugs!
2. Hyponatremia correction: Speed doesn't kill ?
3. Renal Denervation is FDA-approved (Finally)
4. Diuretics: Just a class effect after all (DCP and TRANSFORM HF)
5. The rise of aldosterone synthase inhibitors
6. Hydrochlorothiazide doesn't prevent stones (NOSTONE)
7. Endothelin antagonists advance
8. CONVINCE: HDF is better than HD (or is it?)
9. Balanced fluids : the best saline in transplant
10. Inaxaplin phase 2a trial APOL-1 mediated kidney diseases

HDF: Hemodiafiltration, HD: Hemodialysis

Designed by Dr Priti Meena, M.D, FASN @priti899

Thank you !!!

- **What new discoveries will come in 2024 ???**
- **Let’s get together next year and find out !!!**

References

- Seethapathy, H., Zhao, S., Ouyang, T., Passos, C., Sarang, A., Cheung, P. W., ... & Nigwekar, S. U. (2023). Severe hyponatremia correction, mortality, and central pontine myelinolysis. NEJM evidence, 2(10), EVIDoa2300107.
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- Dhayat, N. A., Bonny, O., Roth, B., Christe, A., Ritter, A., Mohebbi, N., ... & Fuster, D. G. (2023). Hydrochlorothiazide and prevention of kidney-stone recurrence. New England Journal of Medicine, 388(9), 781-791.
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