

Year in review

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August, 2023



SEMMELWEIS
EGYETEM 1769

Sources

- **Medline search (2021-2023)**
 - Kidney diseases, hypertension
 - Major medical journals
 - Focus on RCTs
- **Medline search (2022-2023)**
 - GN, ADPKD, dialysis in
 - Major nephrology journals
 - Focus on RCTs
- **NephJC**
- **Personal preference**

Database: Ovid MEDLINE(R) <1946 to July 17, 2023>

Search Strategy:

- 1 [exp](#) Kidney Diseases/ (573562)
- 2 [exp](#) Polycystic Kidney Diseases/ or [exp](#) Kidney Failure, Chronic/ or [exp](#) Kidney Cortex/ or [exp](#) Kidney/ or [exp](#) Acute Kidney Injury/ or [exp](#) Medullary Sponge Kidney/ or [exp](#) "Chronic Kidney Disease-Mineral and Bone Disorder"/ or [exp](#) Kidney Transplantation/ or [exp](#) Kidney Tubules, Collecting/ or [exp](#) Kidney Cortex Necrosis/ or [exp](#) Kidney Diseases, Cystic/ or [exp](#) Kidney Tubular Necrosis, Acute/ or [exp](#) Kidney Calculi/ or [exp](#) Kidney Glomerulus/ or [exp](#) Polycystic Kidney, Autosomal Recessive/ or [exp](#) Kidney Tubules/ or [exp](#) Kidney Function Tests/ or [exp](#) Kidney Calices/ or [exp](#) "Chronic Kidney Diseases of Uncertain Etiology"/ or [exp](#) Kidney Medulla/ or [exp](#) Polycystic Kidney, Autosomal Dominant/ or [exp](#) Kidney Diseases/ (899179)
- 3 1 or 2 (899179)
- 4 [exp](#) Essential Hypertension/ or [exp](#) Hypertension/ or [exp](#) Hypertension, Renal/ or [exp](#) Intra-Abdominal Hypertension/ (318214)
- 5 3 or 4 (1163682)
- 6 "new england journal of medicine".jn. (83580)
- 7 lancet.jn. (140264)
- 8 jama.jn. (76652)
- 9 british medical journal.jn. (46999)
- 10 "annals of internal medicine".jn. (34751)
- 11 (nature or nature medicine).jn. (119590)
- 12 "journal of the american college of cardiology".jn. (28573)
- 13 european heart journal.jn. (20171)
- 14 circulation.jn. (45897)
- 15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (596477)
- 16 5 and 15 (30523)
- 17 limit 16 to yr="2021 -Current" (913)
- 18 limit 17 to randomized controlled trial (123)

Results (2022-2023)

Glomerular diseases
MCD: anti-nephrin antibodies
APOL1 variants: inaxaplin
IgAN: Testing, budesonid/NeflgArd, sparsentan / PROTECT
LN: anti-CD19 CAR-T cell therapy
CKD/DKD
Finerenone / FIDELITY
STOP-ACEI
Empa Kidney
Hypertension
Morning vs. evening dosing / TIME
Mild hypertension in pregnancy / CHAP
Renal denervation/Radiance II
Chlorthalidone vs HCTZ
Baxdrostat RHT / BrigHTN
Aprocicentan RHT / PRECISION

ADPKD
Venglustat / Staged-PKD
HCTZ/Met for polyuria
Kidney stones
HCTZ/NOSTONE
Dialysis
Anakinra in HD / ACTION
Apixaban for AF/ Renal-AF, Axadia-AFNET8
HD vs. HDF / Convince
AKI
Delayed vs. more delayed / AKIKI2
Transplantation
Two cases of xenotransplantation
Balanced vs. Saline / BEST-Fluids

Results

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Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology

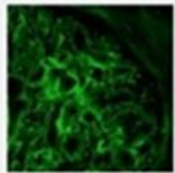
Circulating anti-nephrin antibodies are present in almost 1/3 of patients with MCD, that correlates with disease activity

Two independent patient cohorts
(Bx proven MCD + Active NS)

Nephrotic Syndrome Study Network Patients at our institutions



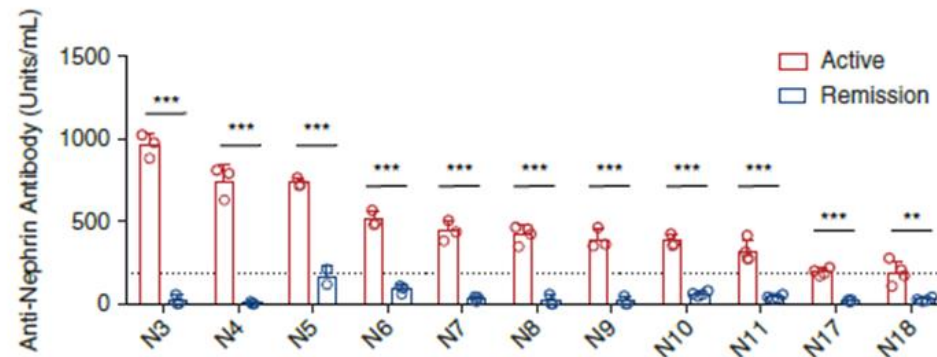
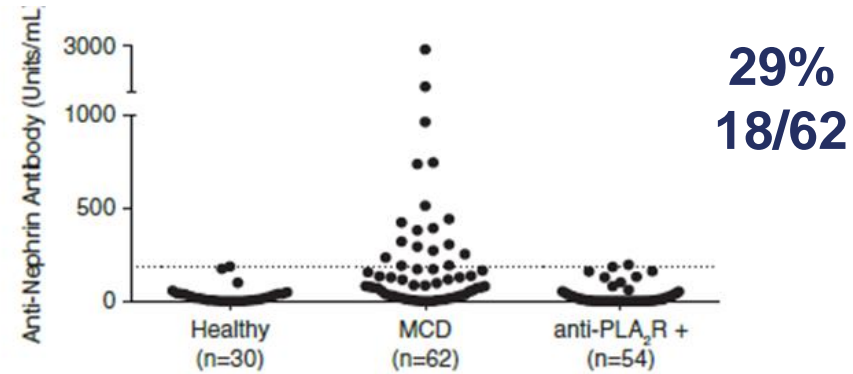
ELISA for anti-nephrin antibodies (both cohorts)



Immunofluorescence evaluation of renal biopsies for punctate IgG (our cohort)

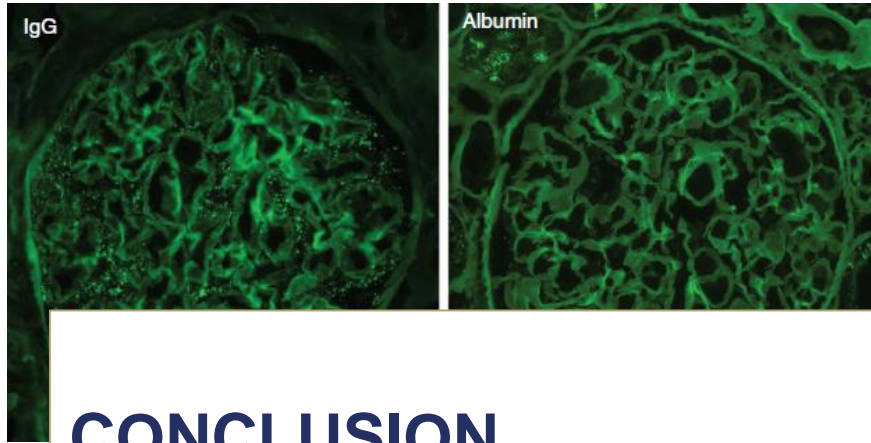


Comparison of circulating nephrin autoantibodies pre and post treatment response (both cohorts)

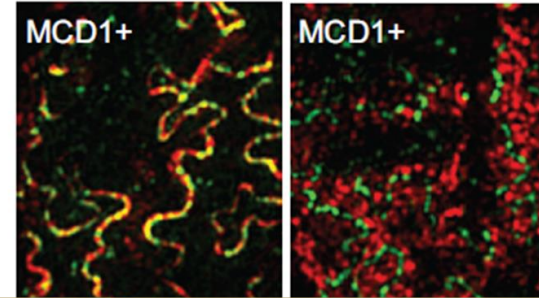


Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology

Diffuse punctate IgG (but not albumin) staining in a patient with MCD

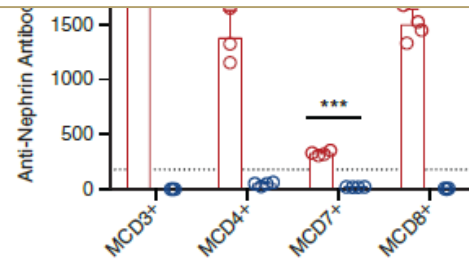
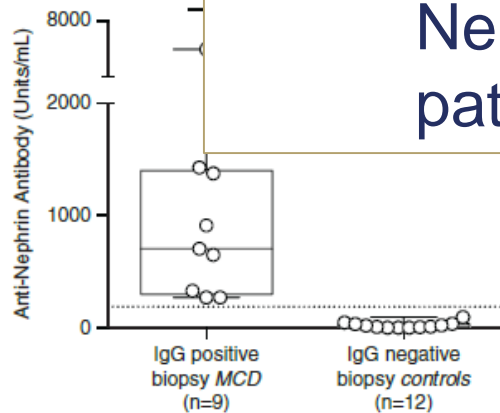


IgG colocalizes with nephrin but not with synaptopodine



CONCLUSION

Nephrin is a target of circulating autoantibodies in a subset of patients with MCD



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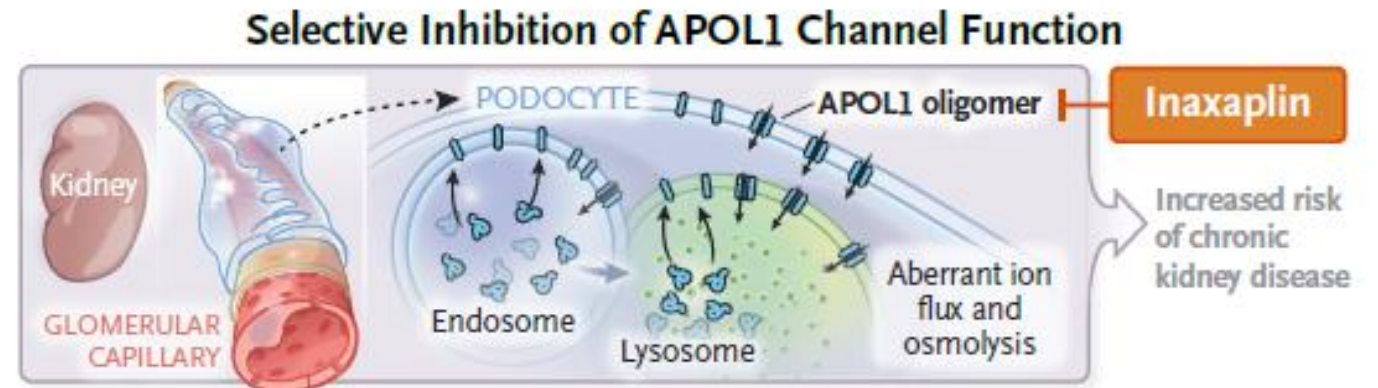
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Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

Egbuna O et al. DOI: 10.1056/NEJMoa2202396

- *APOL1* G1 G2 gain-of-function variants increase *APOL1* channel function, and increase the risk of progressive proteinuric kidney diseases, including FSGS
- Inaxaplin may inhibit *APOL1* channel function and lower proteinuria
- *in vitro* and mouse model followed by a
- open, phase 2A, 13 week study with inaxaplin in 16 patients with two (G1,G2) variants and FSGS
- Outcome: change in protein-to-creatinine ratio

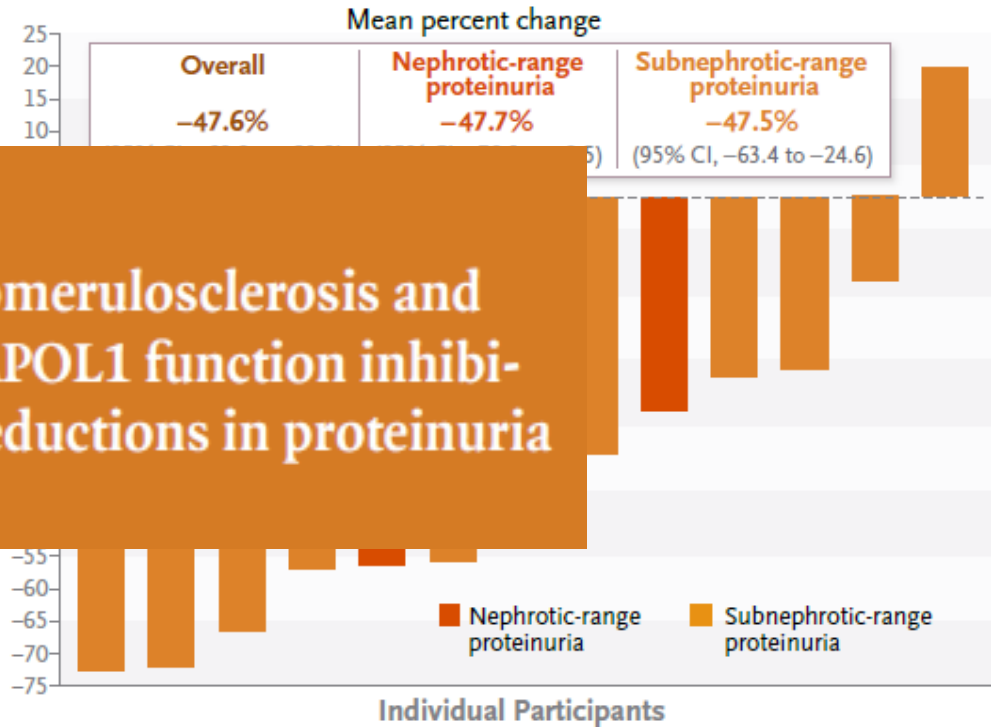


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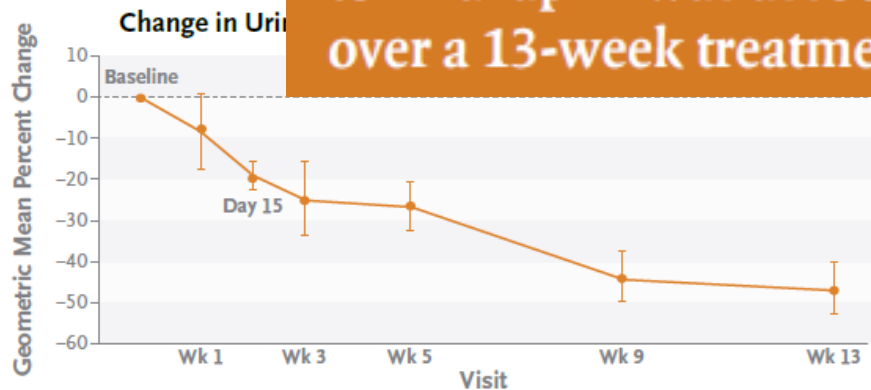
- Inaxaplin inhibited *APOL1* channel function *in vitro* and reduced proteinuria in the mouse model
- 13 evaluable participants had a mean reduction in the urinary protein-to-creatinine ratio; the mean decrease was 47.6%
- No adverse events led to discontinuation of treatment

Change in Urinary Protein-to-Creatinine Ratio in Each Participant at Wk 13



CONCLUSIONS

In persons with focal segmental glomerulosclerosis and two high-risk *APOL1* variants, the *APOL1* function inhibitor inaxaplin was associated with reductions in proteinuria over a 13-week treatment period.





A Step Forward for Precision Equity in Kidney Disease

SCIENCE BEHIND THE STUDY

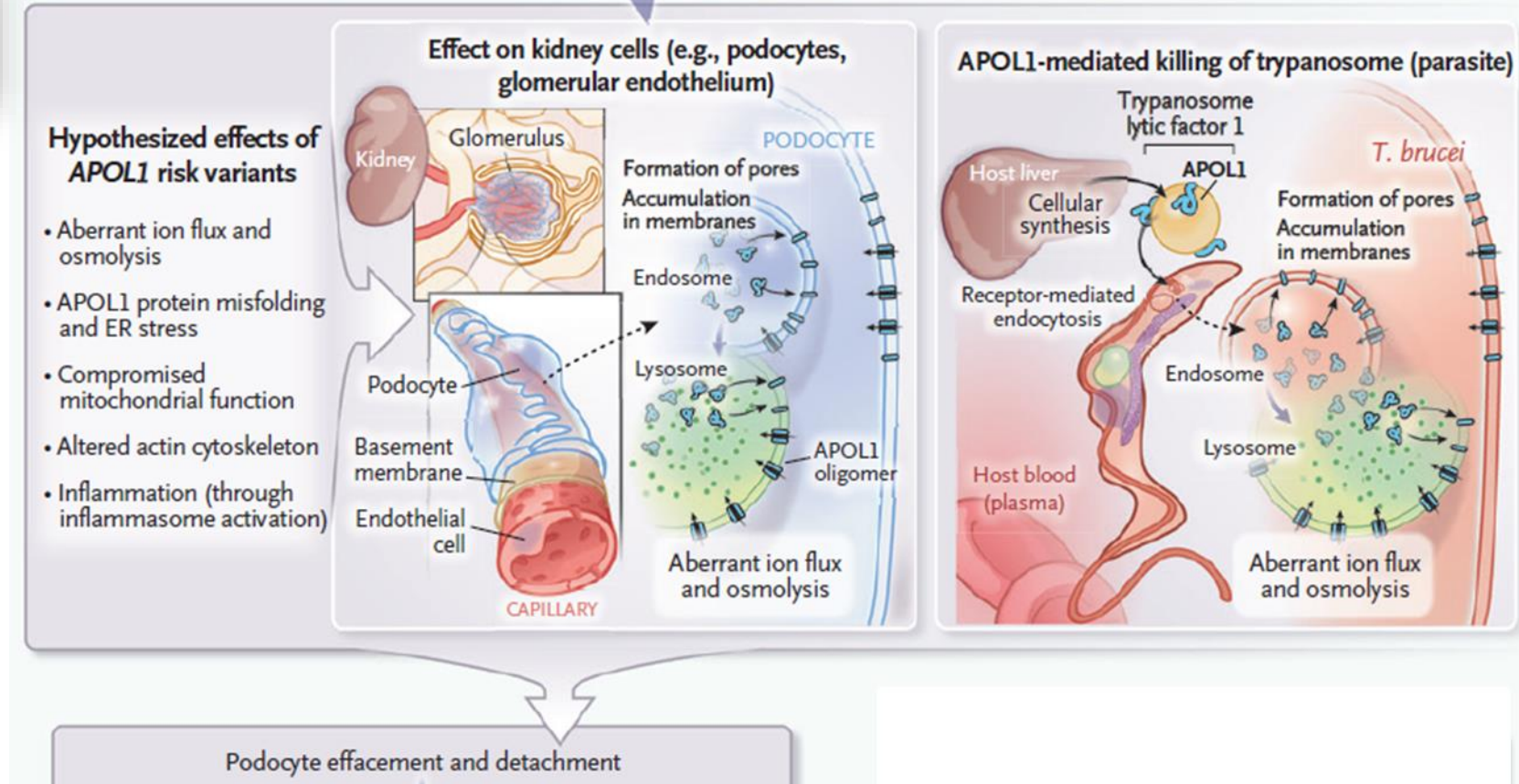
Inhibiting APOL1 to Treat Kidney Disease

- APOL1 expressed in the kidney (among others) confers protection against infection by *Trypanosoma brucei*
- G1 and G2 variants conferred further fitness advantage against the rhodesiense and gambiense variants in sub-Saharan Africa

Allele combinations

High-risk: G1/G1, G2/G2, G1/G2

Baseline risk: G0/G0, G0/G1, G0/G2



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QUESTION What are the effects of oral glucocorticoids, compared with placebo, in patients with IgA nephropathy and proteinuria of 1 g per day or greater receiving optimal supportive therapy?

CONCLUSION Treatment with oral methylprednisolone significantly reduced the risk of the composite of kidney function decline, kidney failure, or death due to kidney disease in patients with IgA nephropathy, but the incidence of serious adverse events was increased.

POPULATION

305 Men
198 Women



Adults with IgA nephropathy and proteinuria ≥ 1 g per day

Mean age: 38 years

LOCATIONS

67
Medical centers
worldwide



INTERVENTION

503 Patients randomized

257

Methylprednisolone

6- to 9-month course of oral methylprednisolone



246

Placebo

Matching oral placebo



PRIMARY OUTCOME

Composite outcome of the first occurrence of a sustained 40% decrease in estimated glomerular filtration rate, kidney failure, or death due to kidney disease

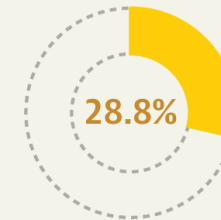
FINDINGS

© AMA

Patients with composite primary outcome

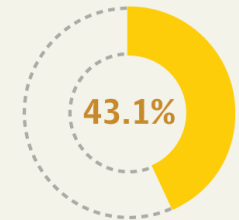
Methylprednisolone

74 of 257 patients



Placebo

106 of 246 patients



The primary outcome occurred significantly less frequently in the methylprednisolone group:

Hazard ratio, **0.53**

(95% CI, 0.39 to 0.72); $P < .001$

Absolute annual event rate difference, **-4.8%**

(95% CI, -8.0% to -1.6%)

Lu J, Wong MG, Hladunewich MA, et al; for the TESTING Study Group. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. Published May 17, 2022. doi:10.1001/jama.2022.5368

Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

Cohort and intervention

Randomised

201 patients with IgAN

Nefecon 16 mg od: n=97

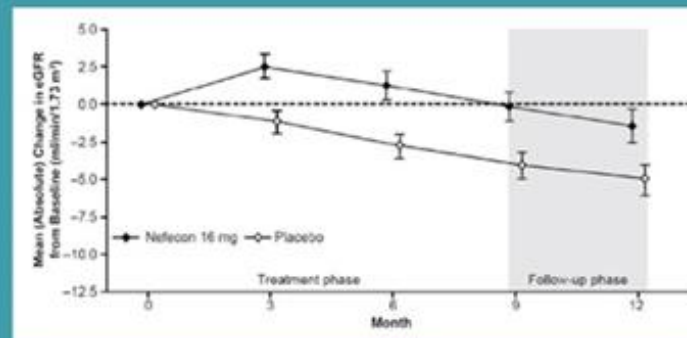
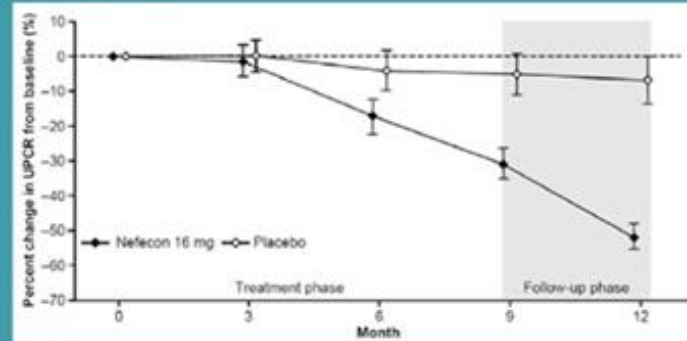
Placebo: n=102

9-month treatment → 3-month follow-up

Key baseline characteristics

- Optimised RAS blockade: ALL
- Median UPCR: 1.26 g/g
- Median proteinuria: 2.26 g/24 h
- ≥2g/24h proteinuria: 58%
- Median eGFR: 55 ml/min/1.73 m²

Outcomes



UPCR:

- At 9 months: **27% reduction** vs placebo ($P = 0.0003$)
- At 12 months: **48% reduction** vs placebo ($P < 0.0001$)

eGFR:

- At 9 months: **3.87 ml/min/1.73 m² treatment benefit** ($P = 0.0014$)
- 1-year eGFR slope **improvement: 3.37 ml/min/1.73 m²** ($P = 0.0111$)

Safety:

- Patients with **TEAEs**: 86.6% with Nefecon vs 73.0% with placebo, mostly mild or moderate
- **No severe infections requiring hospitalisation**

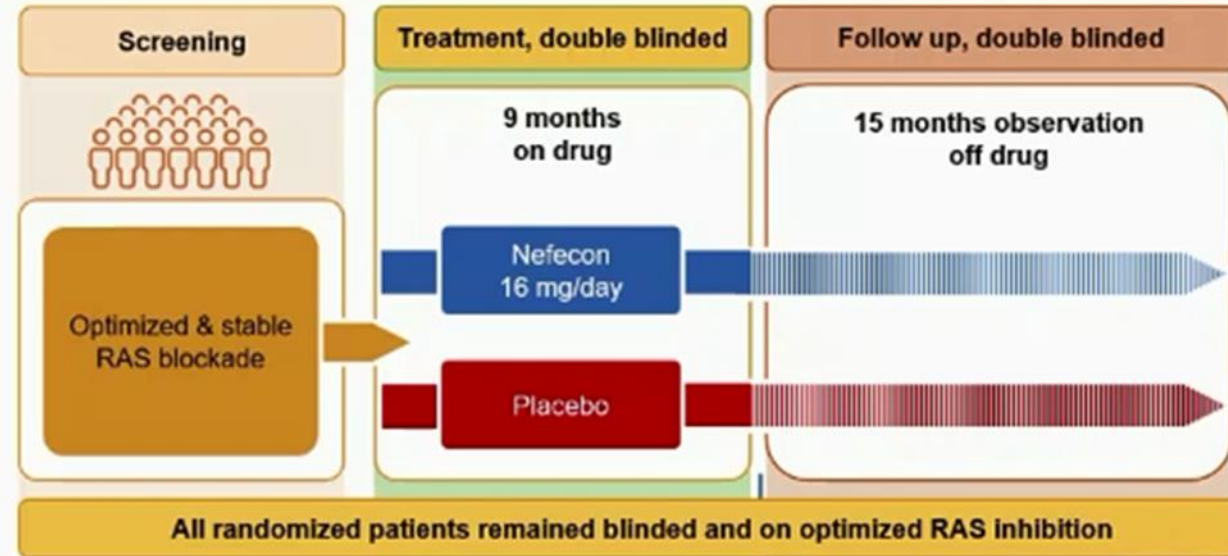
Barratt et al, 2022

CONCLUSION

9 months of treatment with Nefecon, in addition to optimised and stable RAS blockade, was well tolerated and resulted in clinically important improvements in UPCR, UACR, and eGFR compared with optimised supportive care alone

NeflgArd phase B

NeflgArd: A two-part, global, randomized, double-blind, placebo-controlled study



Interim readout 199 patients; primary endpoint proteinuria reduction

Base inclusion/exclusion criteria:

- Study included patients ≥ 18 years old with biopsy-proven IgAN; >1 g of proteinuria; eGFR >35 – <90 mL/min/1.73 m², and well-controlled blood pressure of $<140/90$ mmHg
- Among the exclusion criteria were systemic diseases, having undergone a kidney transplant, and the presence of other glomerulopathies

Primary efficacy endpoint: Time-weighted average change from baseline in eGFR over the 2-year period

Full Phase 3 trial

- Designed to confirm the long-term renal benefit of observed proteinuria reduction
- Primary endpoint eGFR
- Read out positive data in March 2023; global study with 364 patients
- Estimated FDA filing July 2023



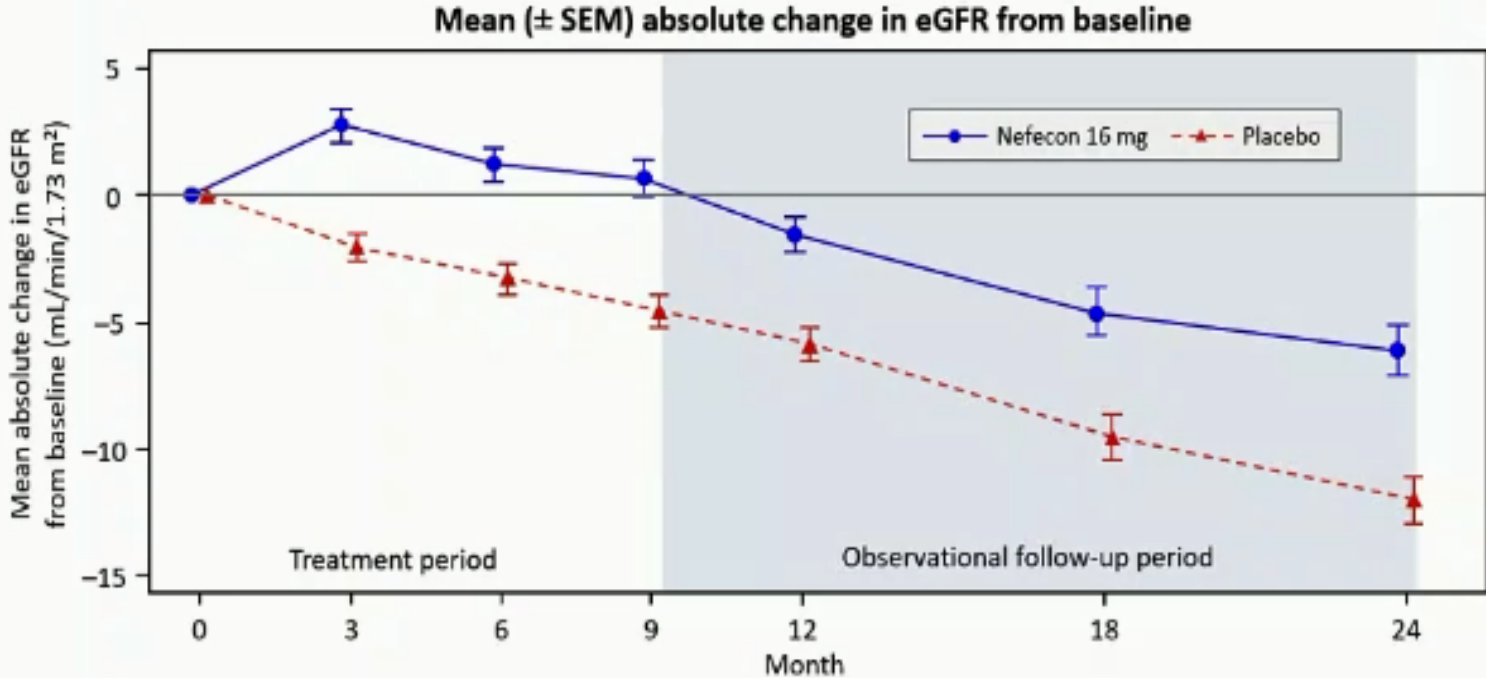
eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; IgAN, immunoglobulin A nephropathy; RAS, renin-angiotensin system.

NeflgArd phase B

Main result

Primary endpoint: time-weighted average change from baseline in eGFR over the 2-year period

- 5.05 mL/min/1.73 m² eGFR treatment benefit in favor of Nefecon vs placebo over 2 years (p<0.0001)
- eGFR benefit at the end of the 9-month treatment period with Nefecon was maintained during the 15-month observational follow-up



Nefecon 16 mg/day, mL/min/1.73 m ²	+0.66	-1.52	-6.11
Placebo, mL/min/1.73 m ²	-4.56	-5.85	-12.00
Absolute difference, mL/min/1.73 m ² (95% CI)	5.21 (3.35–7.58)	4.33 (2.44–6.66)	5.89 (3.35–9.15)

NeflgArd phase B

Conclusion

- 9 month treatment with 16mg of Nefecon, on top of standard of care, provided clinically relevant preservation of eGFR in IgAN
- The size of eGFR benefit was maintained over the 15 month off-drug observation period
- Generally well tolerated



Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

Hiddo J L Heerspink, Jai Radhakrishnan, Charles E Alpers, Jonathan Barratt, Stewart Biedler, Ulysses Diva, Jula Inrig, Radko Komers, Alex Mercer, Irene L Naronha, Michelle N Rheault, William Rote, Brad Rovin, Howard Trachtman, Hernán Trimarchi, Muh Geat Wong, Vlado Perkovic, for the PROTECT Investigators*

- Sparsentan, a dual endothelin A and angiotensin receptor antagonist, being evaluated as non-immune renoprotective therapy in IgAN
- Prespecified interim analysis at 36 weeks
- N=404, PCR 1.3, eGFR 57
- Sparsentan vs. Irbesartan
- Primary outcome: change in PCR

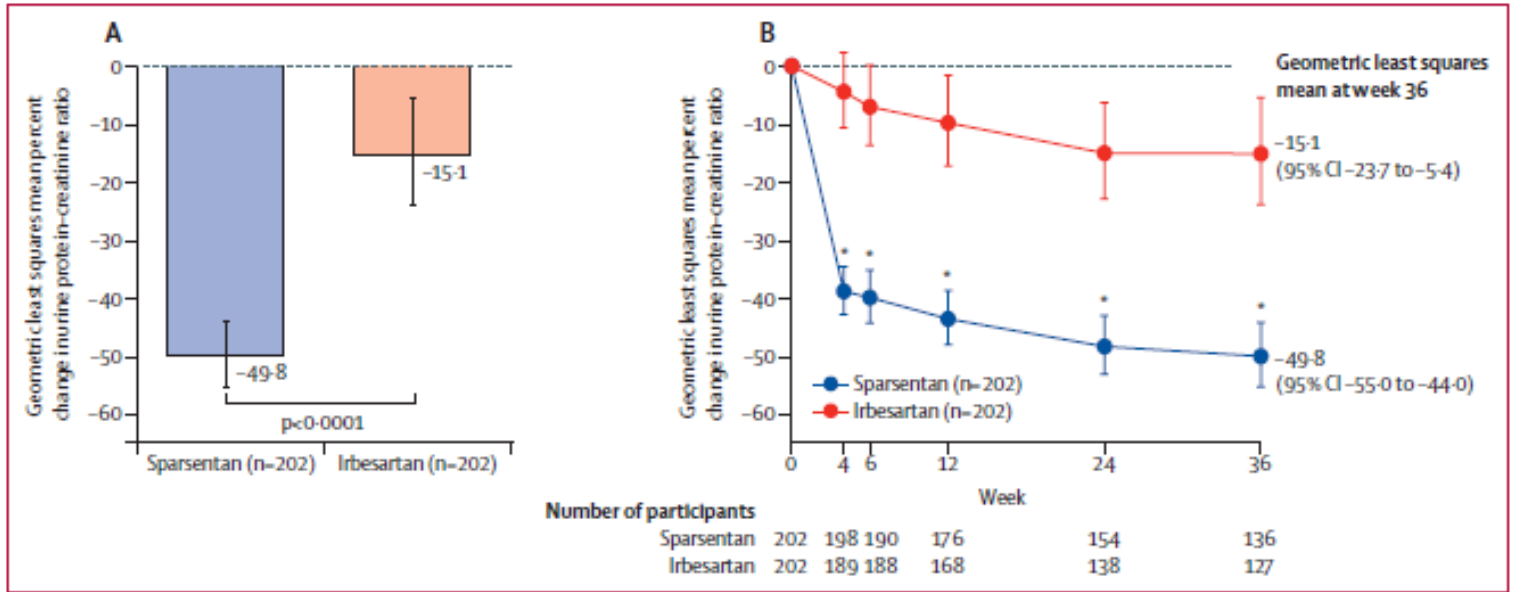


Figure 2: Percent change from baseline in urine protein-creatinine ratio in the sparsentan vs irbesartan treatment groups at week 36 (primary efficacy endpoint) and by visit



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Conclusion

- in patients with high risk IgA nephropathy once-daily sparsentan compared with the active control of maximum labelled or tolerated irbesartan produces a robust and meaningful reduction in proteinuria
- safety of sparsentan was consistent with previous studies in focal segmental glomerulosclerosis and similar to irbesartan

Results

Glomerular diseases

MCD: anti-nephrin antibodies

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Is Anti-CD19 CAR T Cell therapy an efficacious and tolerable treatment for refractory SLE?



Methods



University Hospital
Erlangen, Germany



N = 5 participants
Ages 18 – 24 yrs



Baseline SLEDAI-2K
scores 8-16



Failure to respond to
multiple
immunomodulatory
therapies

Timeline

Day -13

Leukapheresis

Day -5 to -3

Fludarabine
Cyclophosphamide

Day 0

CAR T cell infusion

Day 0 to +10

Inpatient monitoring

Follow-up:

3 months

Long term (5 – 17 m)

Results



SLEDAI-2K
N=4 score 0
N=1 score 2



NO
nephritis
N=5



Drug-free
remission
N=5



DORIS remission
criteria N=5
LLDAS N=5



Anti-DsDNA antibody
seroconversion
N=5

Tolerability (3 months)



Fever (CRS Grade 1)
N=3



Infection
N=0



Neurotoxicity
(ICANS)
N=0

Long-term (5-17 months)



B cell
reconstitution time
 \bar{x} = 110 ± 32 d



New B cells
mostly naïve



SLE relapse
N=0

Conclusion: In patients with treatment resistant SLE, CD19 CAR T cell therapy achieved drug-free remission 3 months after treatment. It was well tolerated, with only mild cytokine release syndrome (CRS) observed.

Reference: Mackensen, A., Müller, F., Mougiakakos, D. et al. Anti-CD19 CART T cell therapy for refractory systemic lupus erythematosus. *Nat Med* 28, 2124–2132 (2022).
<https://doi.org/10.1038/s41591-022-02017-5>



Visual abstract by @thana_susa

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Does the discontinuation of RAS inhibitors improve eGFR in patients with advanced CKD?



		1° Outcome eGFR (by MDRD*)	2° Outcome (ESKD or RRT)	MACE
Open-Label Randomized Control Trial 39 Centers United Kingdom 411 Adults Stage 4 or 5 CKD (eGFR < 30 mL/min/1.73m ²) > 2 mL/min/1.73m ² per year eGFR decline over 2 year RAS inhibitor > 6 months (ACEi or ARB)	Continue RAS inhibitor n=205	 13.3±0.6 mL/min/1.73m ²	 56% (115/205)	 43% (88/205)
	3 years	P = 0.42 (-2.5 to 1.0)	HR = 1.28 (0.99 to 1.65)	Similar
	Discontinue RAS inhibitor n=206	12.6±0.7 mL/min/1.73m ²	62% (128/206)	52% (108/206)

Conclusion: Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of eGFR decline.

*Modification of Diet in Renal Disease

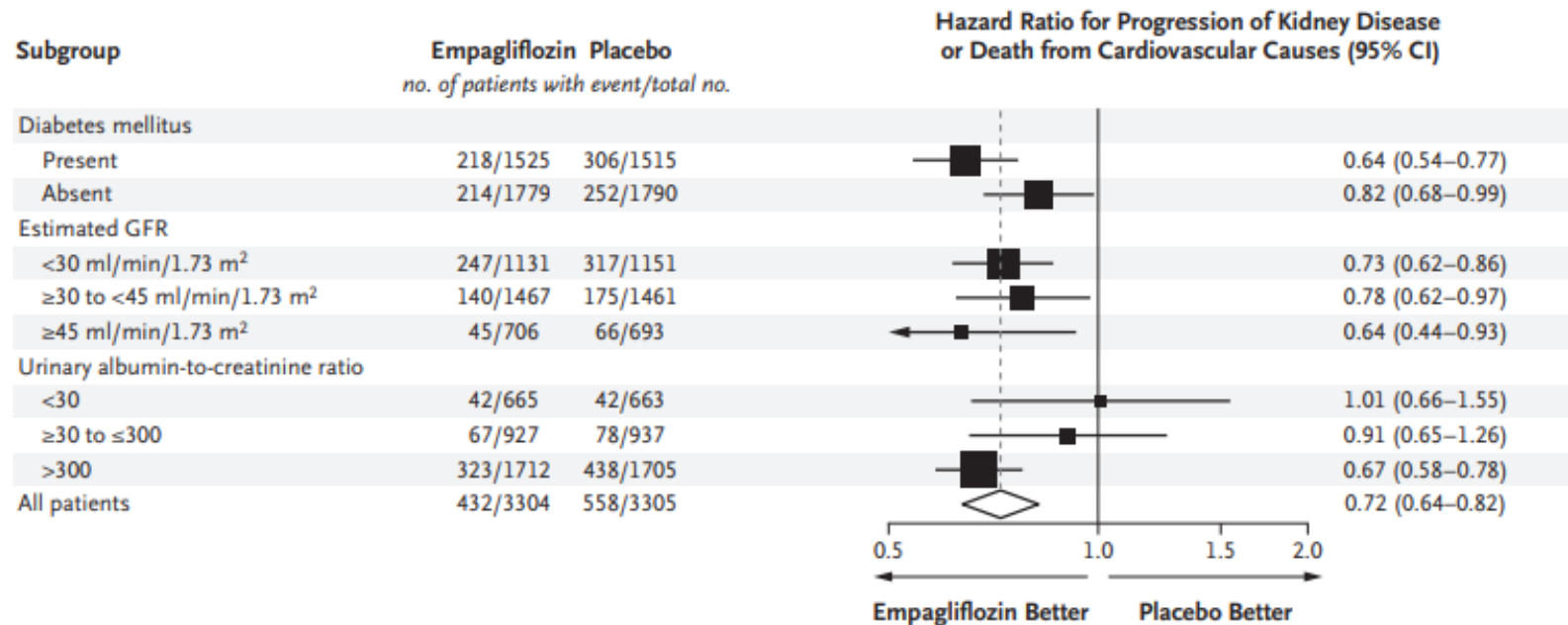
Reference: STOP ACEi trial investigators, Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease.

Visual Abstract by: Dana Larsen, MD [@dana_m_larsen](#)

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

- To evaluate the effects of empagliflozin in patients with a wide range of CKD, independent of diabetic status
- eGFR 20-45 or eGFR 45-90 and ACR>200g/g
- N=6609, 54% no diabetes, 34% <30eGFR , 20% < 30ACR
- 10mg empagliflozin vs. placebo
- Primary outcome: progression of kidney disease or CV death



Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

Conclusion

- Among a wide range of patients with chronic kidney disease who were at risk for progression, empagliflozin therapy was associated with a lower risk of disease progression or death from cardiovascular causes
- Well tolerated
- Further study of patients with a ACR < 300 mg/g may be useful.

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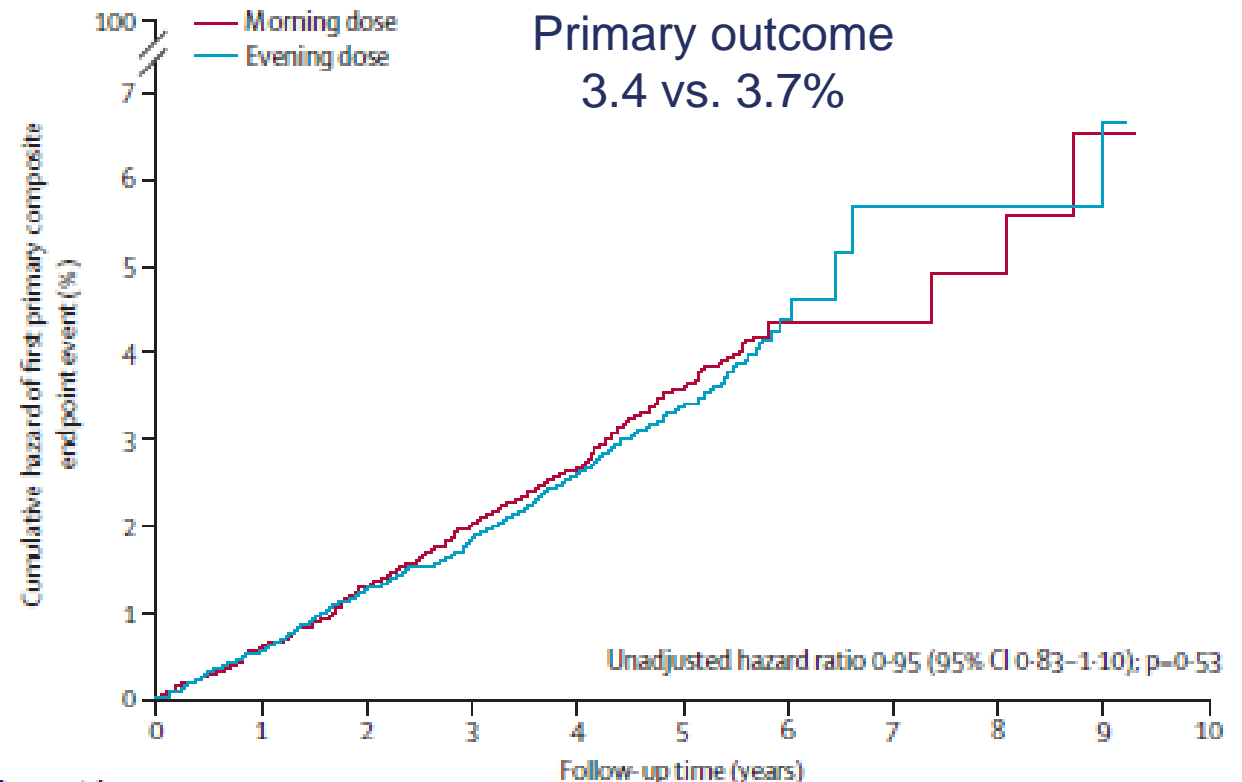
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Two cases of xenotransplantation

Balanced vs. Saline / BEST-Fluids

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

- Studies have suggested that evening dosing with antihypertensive therapy might have better outcomes than morning dosing
- N=21104 HTN-ve patients (UK)
- Randomisation: all antihypertensives in the morning v.s. evening
- Age 65y, 13% previous CVD, 13% diabetes
- Primary outcome: CV death, hospitalisation for stroke, MI (data linkage)



Lancet 2022; 400: 1417-25

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

Conclusion

- Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes.
- Patients can be advised that they can take their regular antihypertensive medications at a convenient time that minimizes any undesirable effects.

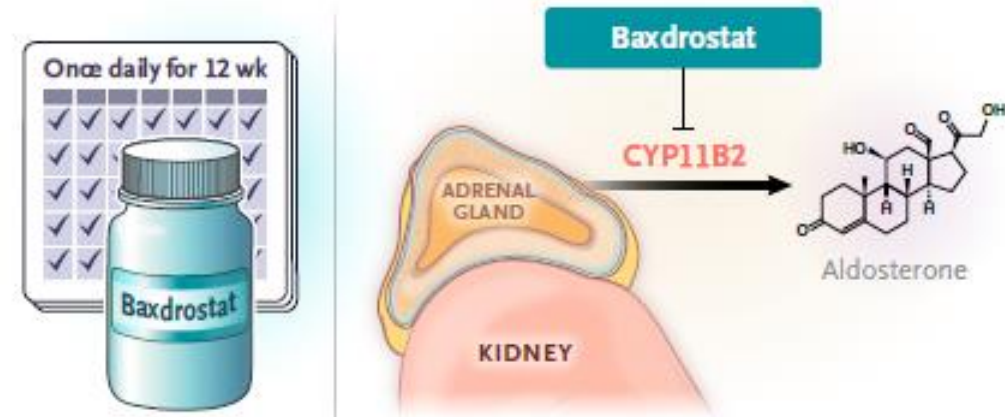
Lancet 2022; 400: 1417–25

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*

- Blocking of aldosterone synthase is difficult as it shares 93% sequence similarity the enzyme required for cortisol synthesis
- Baxdrostat has 100:1 selectivity for aldosterone synthase
- To assess efficacy and safety of baxdrostat in RHT
- N=275 RHT, eGFR >45
- 0.5, 1, 2mg baxdrostat or placebo for 12 weeks
- Outcome: change in seated office SBP

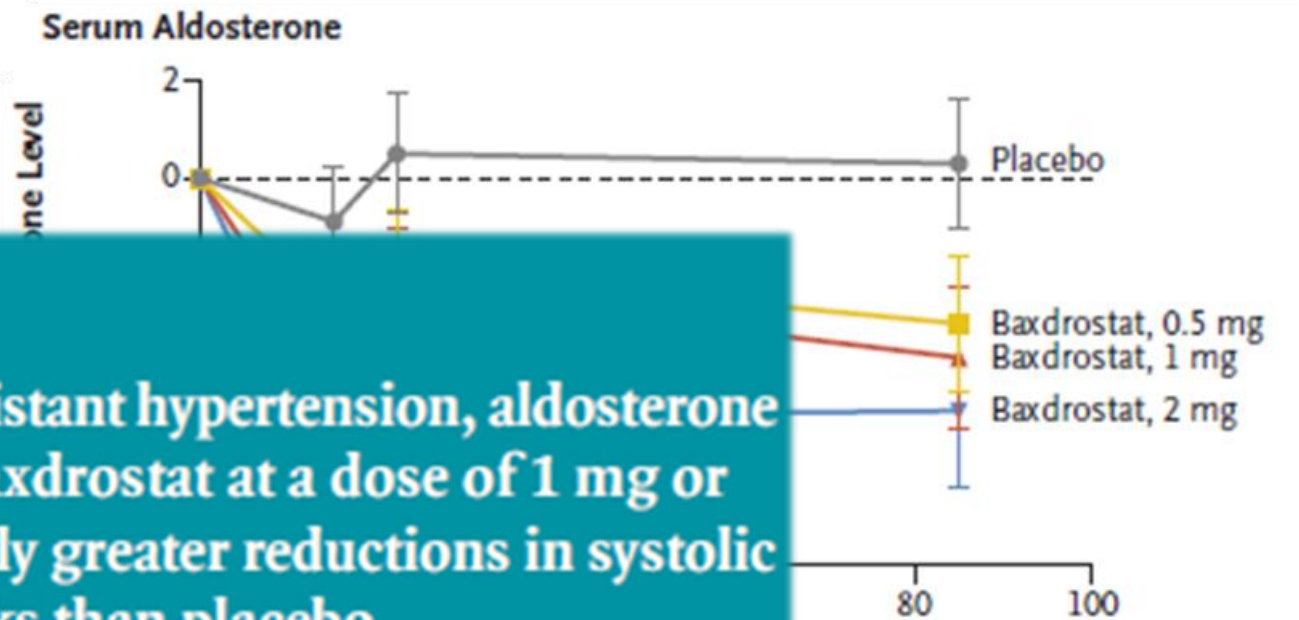
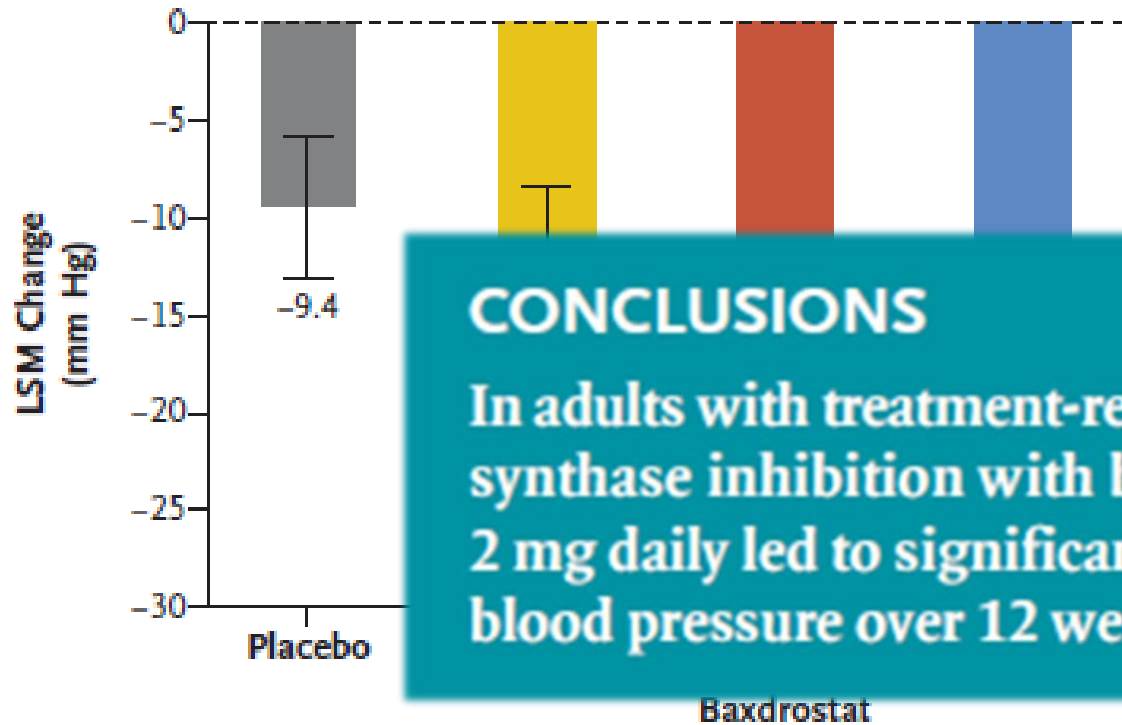
Selective Inhibition of Aldosterone Synthase (CYP11B2)



N Engl J Med 2023;388:395-405.

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Change from Baseline in Systolic Blood Pressure



CONCLUSIONS

In adults with treatment-resistant hypertension, aldosterone synthase inhibition with baxdrostat at a dose of 1 mg or 2 mg daily led to significantly greater reductions in systolic blood pressure over 12 weeks than placebo.

- No change in cortisol levels
- Baxdrostat related $K > 6 \text{ mmol/l}$ in 2 patients

N Engl J Med 2023;388:395-405.

Results

Glomerular diseases

MCD: anti-nephrin antibodies

APOL1 variants: inaxaplin

IgAN: Testing, budesonid/NeflgArd, sparsentan / PROTECT

LN: BLISS-LN ext, CAR-T therapy

CKD/DKD

Finerenone / FIDELITY

STOP-ACEI

Empa Kidney

Hypertension

Morning vs. evening dosing / TIME

Mild hypertension in pregnancy / CHAP

Renal denervation/Radiance II

Chlorthalidone vs HCTZ

Baxdrostat RHT / BrigHTN

Aprocicentan RHT / PRECISION

ADPKD

Venglustat / Staged-PKD

HCTZ/Met for polyuria

Kidney stones

HCTZ/NOSTONE

Dialysis

Anakinra in HD / ACTION

Apixaban for AF/ Renal-AF, Axadia-AFNET8

HD vs. HDF / Convince

AKI

Delayed vs. more delayed / AKIKI2

Transplantation

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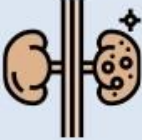






Delayed vs. more delayed / AKIKI2

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Effects of Hydrochlorothiazide and Metformin on Aquaresis and Nephroprotection by a Vasopressin V2 Receptor Antagonist in ADPKD

 45±8 years Age	 Three 2 week periods	Urine Volume (L/ 24 hours) PRIMARY END POINT	Plasma Copeptin (pmol/ L)	Measured GFR (mL/min/1.73 m²)
 54% Female	 Hydrochlorothiazide	5.13±1.46 p<0.001	20±7 p=0.006	51±10 p<0.001
 ADPKD eGFR 55±11 mL/min/1.73 m²	 Metformin	5.4±1.51 p<0.001	28±8 p=0.4	54±11 p=0.2
 Tolvaptan n=13	 Placebo	6.34±1.62 p=0.002	26±7 p=0.9	55±12 p=0.9
 6.9±1.4 Urine Volume at baseline (L/ 24 hours)	 Cystic index p=0.04	Water intake in tolvaptan-hydrochlorothiazide co-treated mice was 35% lower than in mice treated with tolvaptan only		 Kidney weight p=0.003
		Combination treatment was superior to 'no treatment' on markers of disease progression and superior or equal to tolvaptan alone		

Conclusion Both metformin and hydrochlorothiazide reduced tolvaptan-caused polyuria in a short-term study. Hydrochlorothiazide also reduced polyuria in an animal model, without negatively impacting nephroprotection.

Bart J. Kramers, Iris W. Koorevaar, Maatje D.A. van Gastel, et al. *Effects of Hydrochlorothiazide and Metformin on Aquaresis and Nephroprotection by a Vasopressin V2 Receptor Antagonist in ADPKD*. CJASN doi: 10.2215/CJN.11260821 **Visual Abstract by Edgar Lerma, MD FASN**

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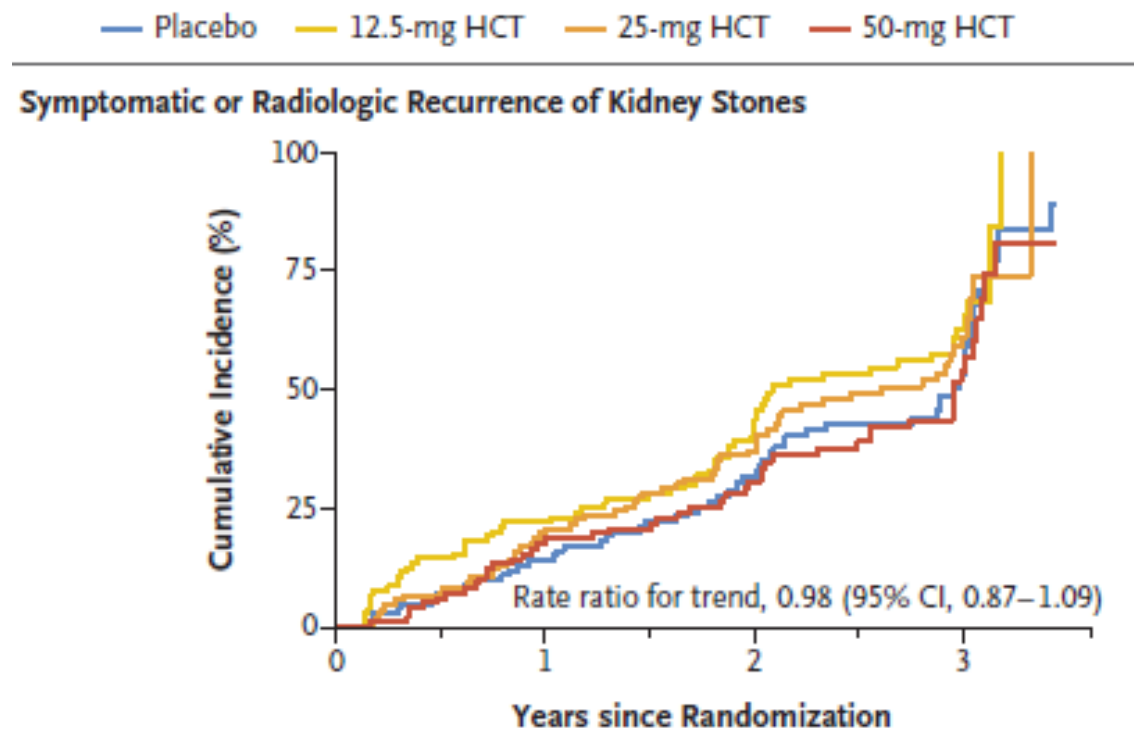
Two cases of xenotransplantation

Balanced vs. Saline / BEST-Fluids

Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Dhayat NA et al. DOI: 10.1056/NEJMoa2209275

- Thiazide diuretics are widely used for the prevention of kidney-stone recurrence, but data regarding their efficacy and dose–response effects are limited.
- To assess three doses of HCT in patients with recurrent calcium-containing kidney stones
- N=416, median 2.9 years
- 12.5, 25, 50 mg HCTZ or placebo
- Primary outcome: symptomatic or radiologic recurrence of kidney stones

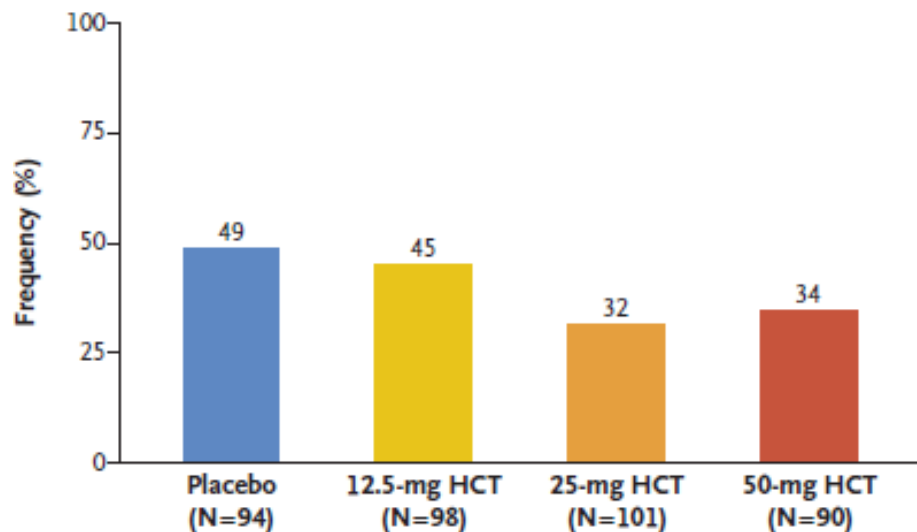


N Engl J Med 2023;388:781-91

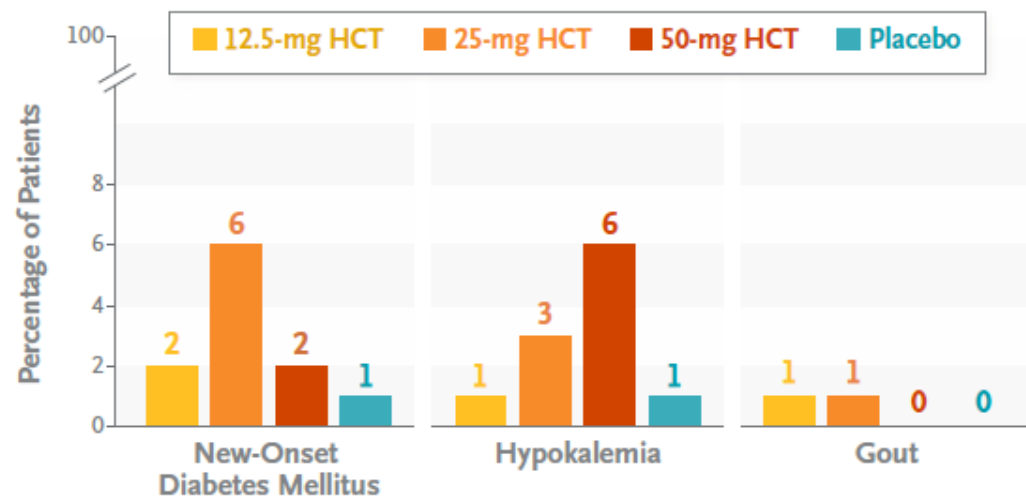
Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Dhayat NA et al. DOI: 10.1056/NEJMoa2209275

Radiologic Recurrence of Kidney Stones



Selected Adverse Events of Special Interest



Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Dhayat NA et al. DOI: 10.1056/NEJMoa2209275

Conclusion

Among patients with recurrent kidney stones, the incidence of recurrence did not appear to differ substantially among patients receiving HCTZ once daily

- Dosing frequency?
- Oxalate excretion increased, citrate excretion decreased
- High Na intake

Results

Glomerular diseases

MCD: anti-nephrin antibodies

APOL1 variants: inaxaplin

IgAN: Testing, budesonid/NeflgArd, sparsentan / PROTECT

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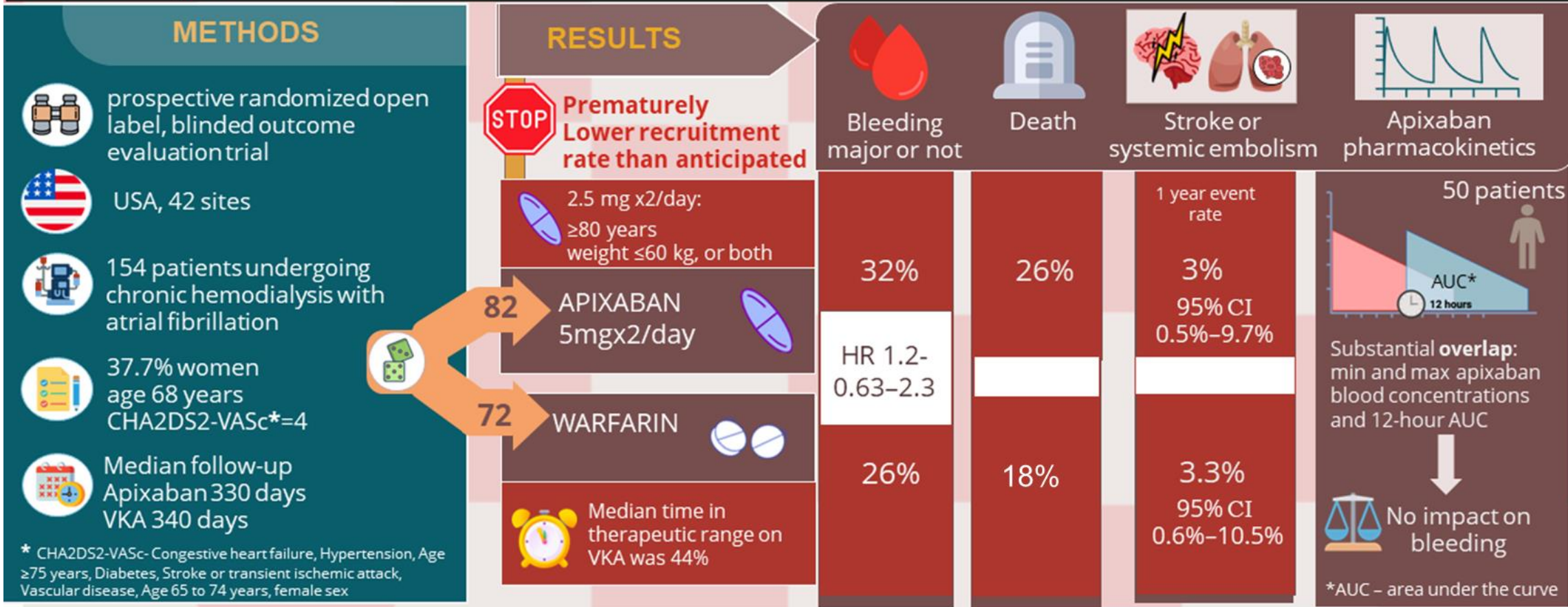
Delayed vs. more delayed / AKIKI2

Transplantation

Two cases of xenotransplantation

Balanced vs. Saline / BEST-Fluids

RENAL AF trial: Is Apixaban a Safe and Effective Anticoagulant compared to Vitamin K Antagonists (VKAs) for Atrial Fibrillation Patients on Hemodialysis?



Conclusion: Clinically relevant bleeding were 10-fold more frequent than stroke or systemic embolism among patients with AF and end-stage kidney disease on anticoagulation. Though there was inadequate power to draw any conclusion regarding rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and end-stage kidney disease on hemodialysis.

Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. Circulation. 2022 Dec

Visual abstract by Cristina Popa MD. @NephroSeeker

Results

Glomerular diseases

MCD: anti-nephrin antibodies

APOL1 variants: inaxaplin

IgAN: Testing, budesonid/NeflgArd, sparsentan / PROTECT

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Balanced vs. Saline / BEST-Fluids

A randomized controlled pilot trial of anakinra for hemodialysis inflammation

Design and Setting

- Pilot trial
- Randomized
- Placebo-controlled



- 4 U.S. academic centers
- In-center hemodialysis
- 80 participants with hsCRP ≥ 2.0 mg/L
- Funded by NIDDK/NIH

Intervention

- Anakinra: recombinant human IL-1 receptor antagonist
- 100 mg 3X/week via hemodialysis circuit
- Treatment: 24 weeks
- Post-treatment safety follow-up: 24 weeks



Findings

Safety: events per pt-yr

	Anakinra (N=38)	Placebo (N=42)	P value
Any SAE	2.71	2.74	0.6
Infection	0.36	1.40	0.02
Neutropenia	0.06	0	0.2
Death	0.12	0.22	0.5

Feasibility & Tolerability

Withdrawal, # (%)	8 (21.1)	8 (19)	0.7
Drug administration % of target, mean (SD)	71.9 (30.7)	75.5 (31.8)	0.6

Efficacy: 24-week change

mean (SD) or median (IQR)			
hsCRP; log(mg/L)	-0.4 (0.9)	-0.2 (0.7)	0.3
IL-6, pg/ml	-0.7 (-2.4 - 0.3)	0.0 (-1.0 - 0.7)	0.02

Dember LM et al, 2022

Kidney International (2022) 102, 1178–1187

CONCLUSION: The promising safety data and signals for potential efficacy of anakinra in reducing CRP and IL-6 levels provide support for conducting definitive trials of IL-1 inhibition to improve outcomes in the hemodialysis population.

Results

Glomerular diseases

MCD: anti-nephrin antibodies

APOL1 variants: inaxaplin

IgAN: Testing, budesonid/NeflgArd, sparsentan / PROTECT

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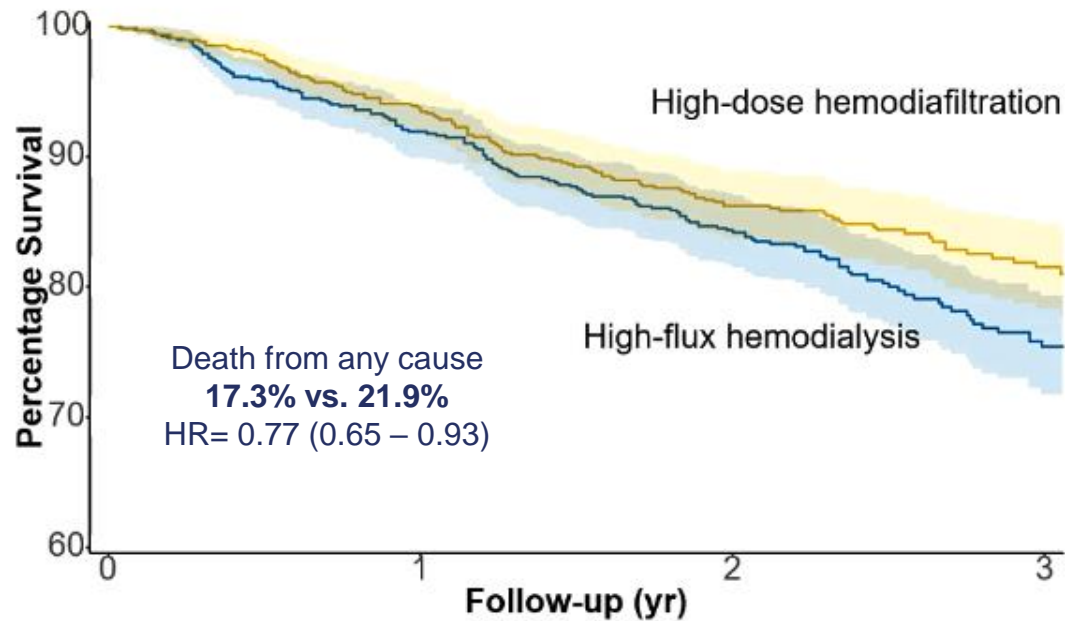
Balanced vs. Saline / BEST-Fluids

Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

- Several studies have suggested that patients with ESKD may benefit from high-dose HDF
- N=1360, 62y, 45%CVD, 35% DM, on >3 months high-flux HD
- Candidates for convection volume >23L/session
- Open label high-dose HDF vs. high-flux HD
- Median 30 months
- Primary outcome: death from any cause



Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure



	HDF (N)	Risk per 100/py	HD (N)	Risk per 100/py	Hazard ratio (95% CI)
Death from any cause	118	7,1	148	9,2	0,77 (0,65-0,93)
Cardiovascular death	31	1,9	37	2,3	0,81 (0,49-1,33)
Non-CV death	87	5,3	111	6,9	0,76 (0,59-0,98)
Infection + COVID	38	2,3	54	3,6	0,69 (0,49-0,96)
Infection - COVID	23	1,4	33	2,1	0,82 (0,42-1,59)
Kidney transplantation	75	4,8	71	4,7	1,01 (0,71-1,44)



Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

Conclusion

Online HDF (>23L volume per session) resulted in a lower risk of death compared to high-flux HD

- Considerable benefit in HD patients
- No reason for safety concern
- Cause specific mortality: interpretation with caution

Results

Glomerular diseases

MCD: anti-nephrin antibodies

APOL1 variants: inaxaplin

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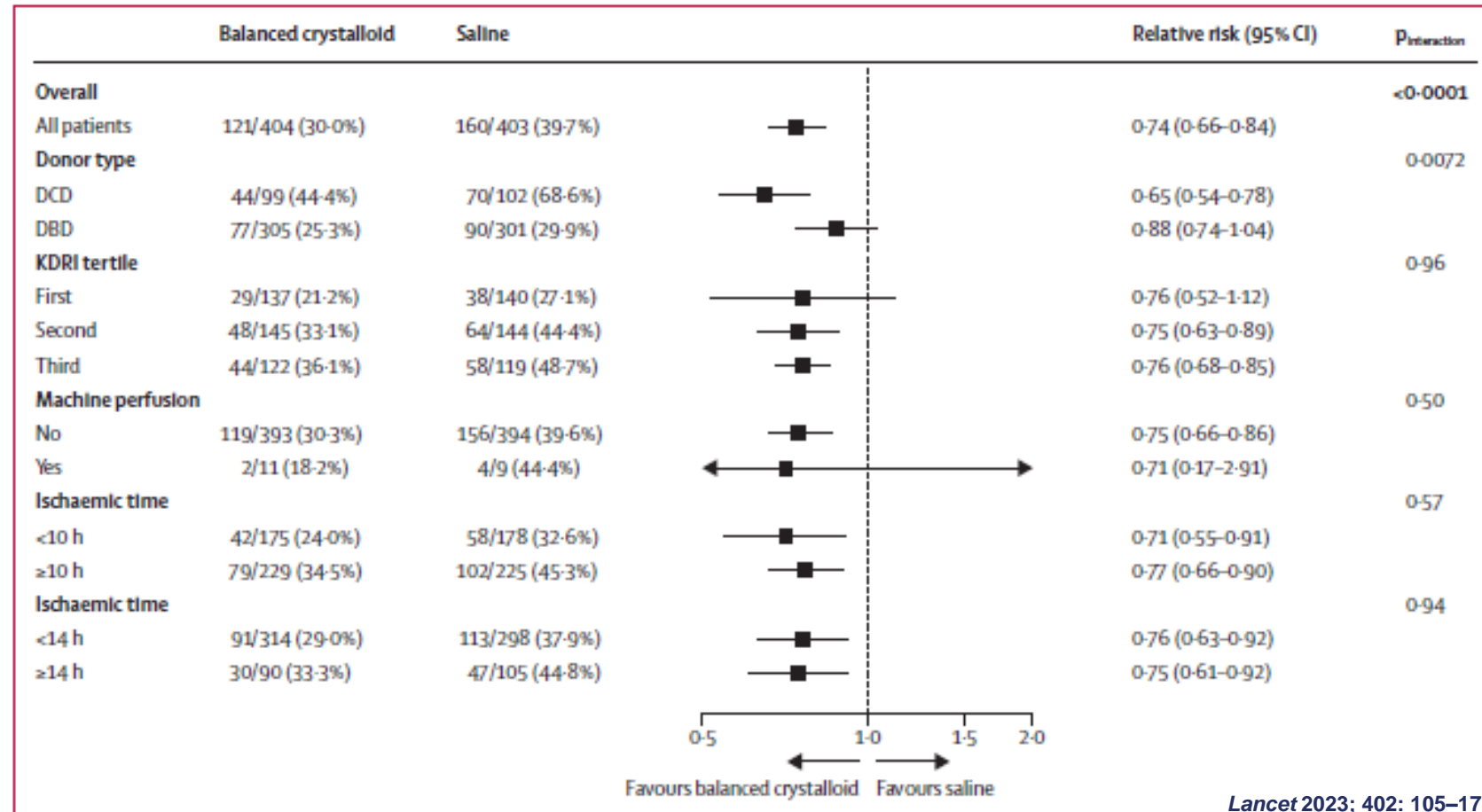
Two cases of xenotransplantation

Balanced vs. Saline / BEST-Fluids

Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial



- 0.9% sodium chloride is widely used during and after Tx surgery but might increase the risk of delayed graft function (DGF) due to its high chloride content
- Balanced solutions might decrease the risk of DGF
- N=808 kidney Tx (55y, 5-6 mismatch 38%, DCD 25%)
- Saline or Plasma-Lyte 148 during surgery and up until 48h
- Outcome: DGF (dialysis within 7 days post Tx)



Lancet 2023; 402: 105–17

Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial



Conclusion

Among patients receiving a deceased donor kidney transplant, intravenous fluid therapy with balanced crystalloid solution reduced the incidence of DGF compared with saline

- Higher pH and HCO_3^- , no difference in K^+
- No difference in long term (52 weeks) kidney and patient outcome

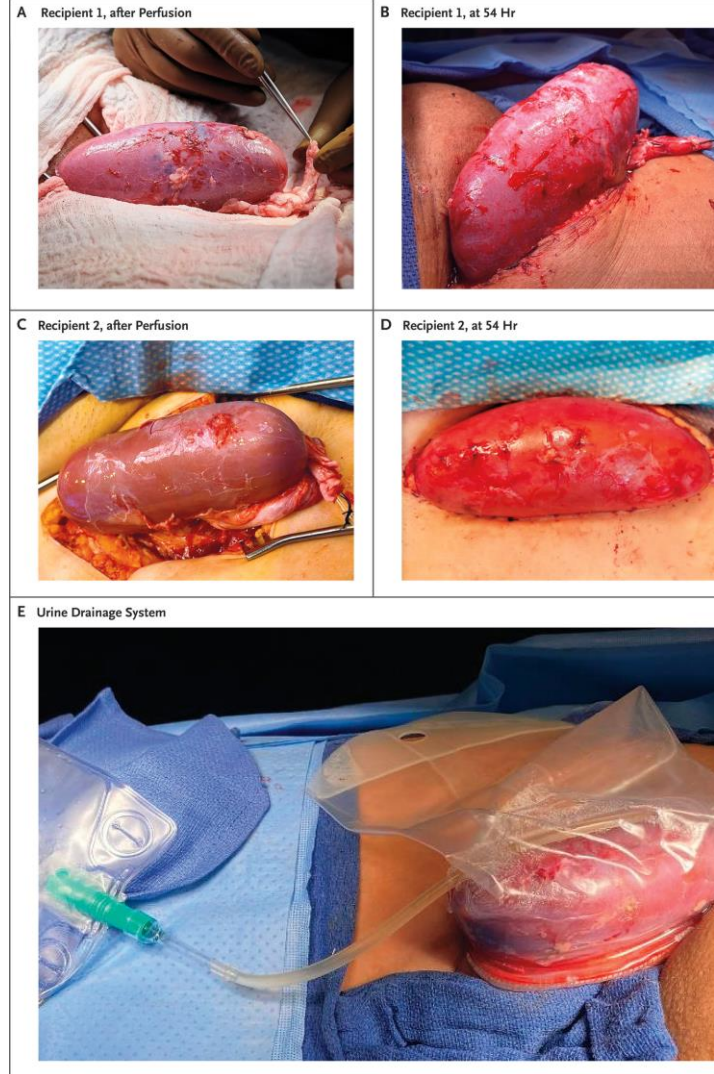
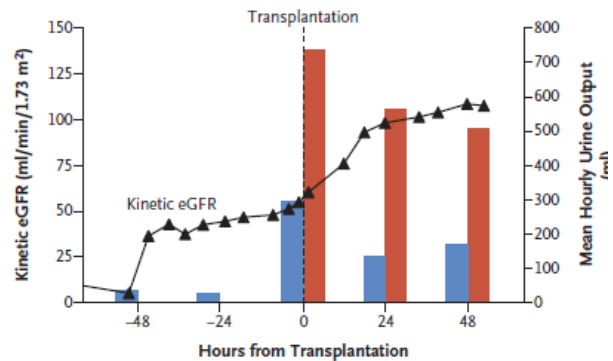
Lancet 2023; 402: 105–17

ORIGINAL ARTICLE

Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

Robert A. Montgomery, M.D., D.Phil., Jeffrey M. Stern, M.D.,
 Bonnie E. Lonze, M.D., Ph.D., Vasishta S. Tatapudi, M.D.,
 Massimo Mangiola, Ph.D., Ming Wu, M.D., Elaina Weldon, M.S.N., A.C.N.P.-B.C.,
 Nikki Lawson, R.N., Cecilia Deterville, M.S., Rebecca A. Dieter, Pharm.D., B.C.P.S.,
 Brigitte Sullivan, M.B.A., Gabriella Boulton, B.A., Brendan Parent, J.D.,
 Greta Piper, M.D., Philip Sommer, M.D., Samantha Cawthon, B.S.,
 Erin Duggan, M.D., David Ayares, Ph.D., Amy Dandro, M.S.,
 Ana Fazio-Kroll, Ph.D., Maria Kokkinaki, Ph.D., Lars Burdorf, M.D., Ph.D.,
 Marc Lorber, M.D., Jef D. Boeke, Ph.D., Harvey Pass, M.D.,
 Brendan Keating, Ph.D., Adam Griesemer, M.D., Nicole M. Ali, M.D.,
 Sapna A. Mehta, M.D., and Zoe A. Stewart, M.D., Ph.D.

B Recipient 2



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