# Building the pillars of renal protection

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Consultant Nephrologist
Nottingham University Hospitals

# Declarations of interest

| | |
|---|---|
| Speaker fees | Astellas, Astrazeneca |
| Travel/conference | Medice |
| Consultancy | Astellas, CSL Vifor Pharma |
| Research support | Nottingham Hospitals Charity, Kidney Research UK, Sienco |

AKI

CKD


Trans
-plant

HD
PD

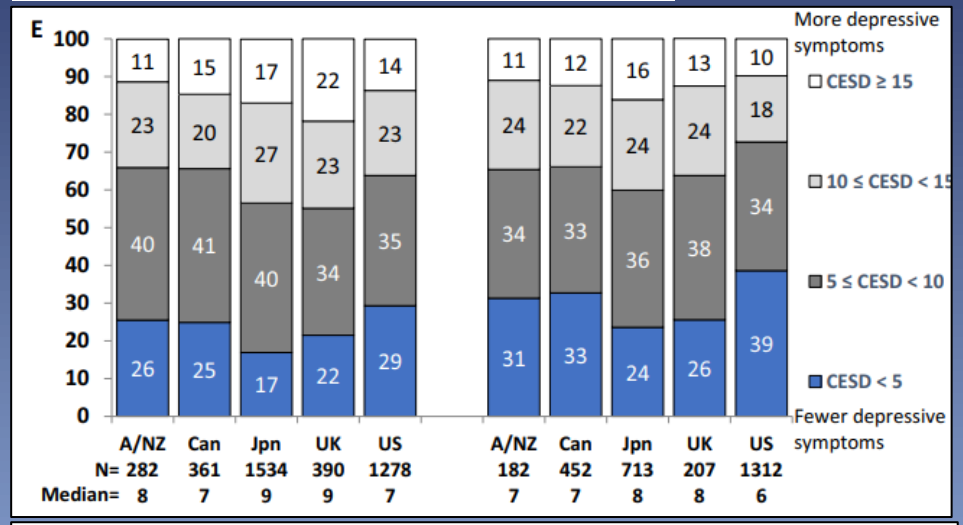

Images: iStock, Fresenius Medical Care

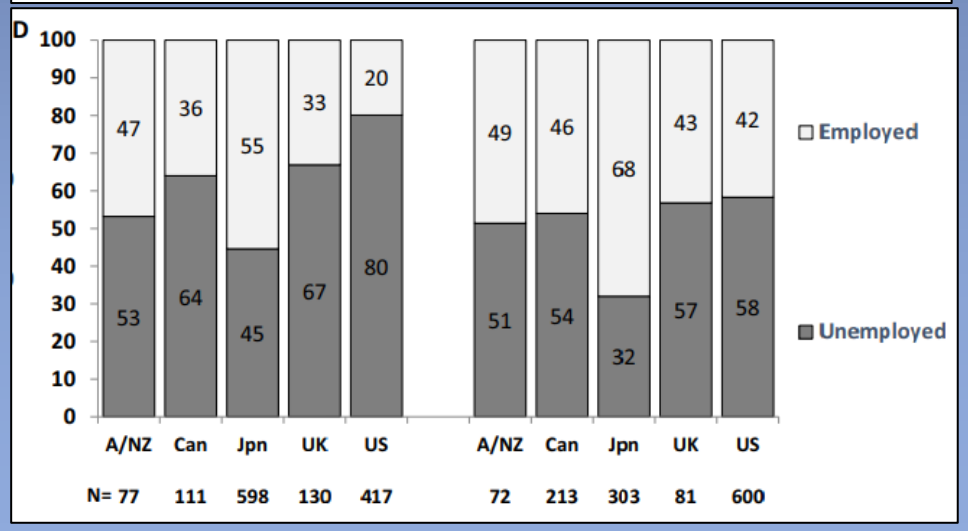
# What is the problem?

Am J Kid Disease 1998:32(5) Suppl 3;S112
Am J Kid Disease 2021:78(4);459

**Burden of Kidney Disease, Health-Related Quality of Life, and Employment Among Patients Receiving Peritoneal Dialysis and In-Center Hemodialysis: Findings From the DOPPS Program**

*Edwina A. Brown, Junhui Zhao, Keith McCullough, Douglas S. Fuller, Ana E. Figueiredo, Brian Bieber, Frederic O. Finkelstein, Jenny Shen, Talerngsak Kanjanabuch, Hideki Kawanishi, Ronald L. Pisoni, and Jeffrey Perl, on behalf of the PDOPPS Patient Support Working Group*

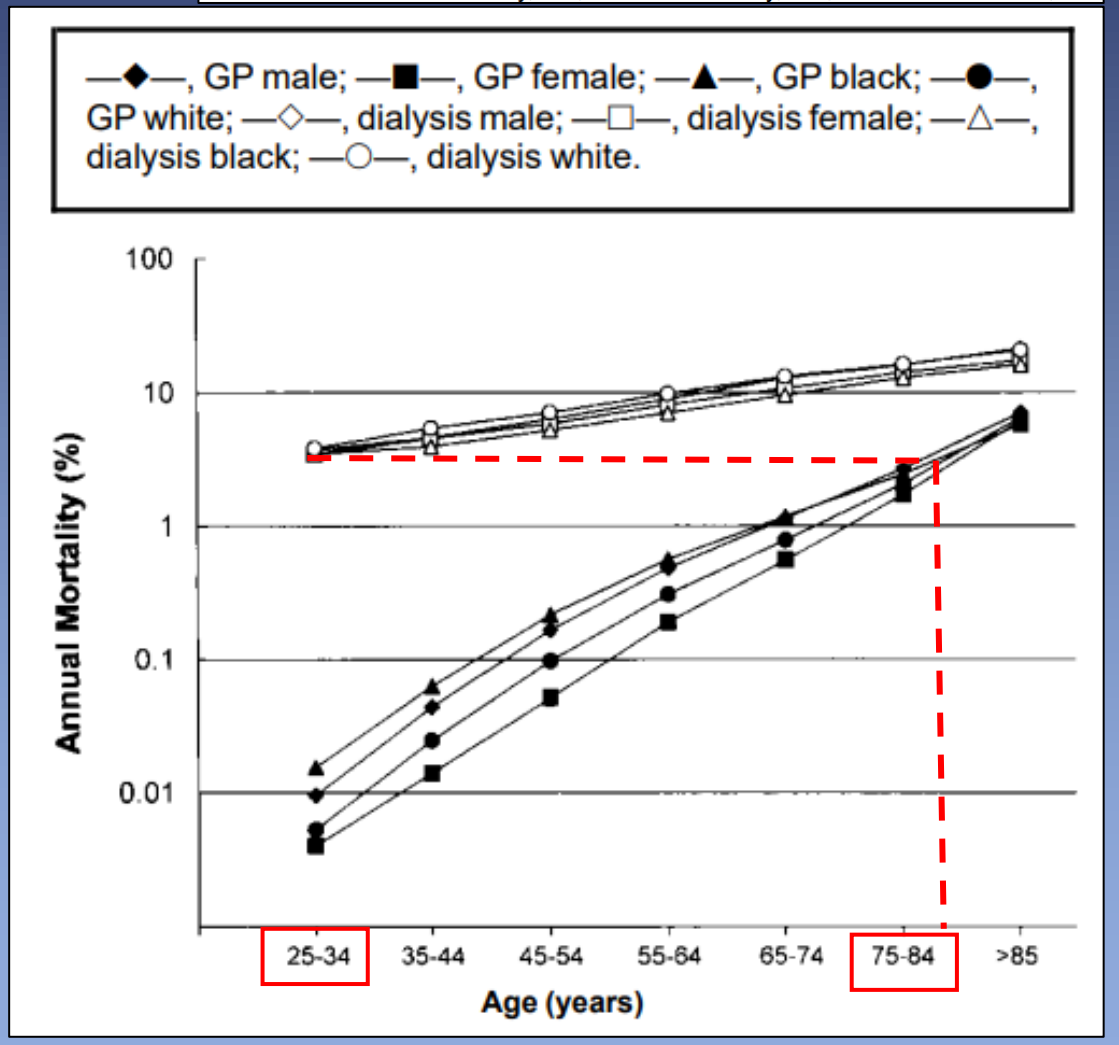


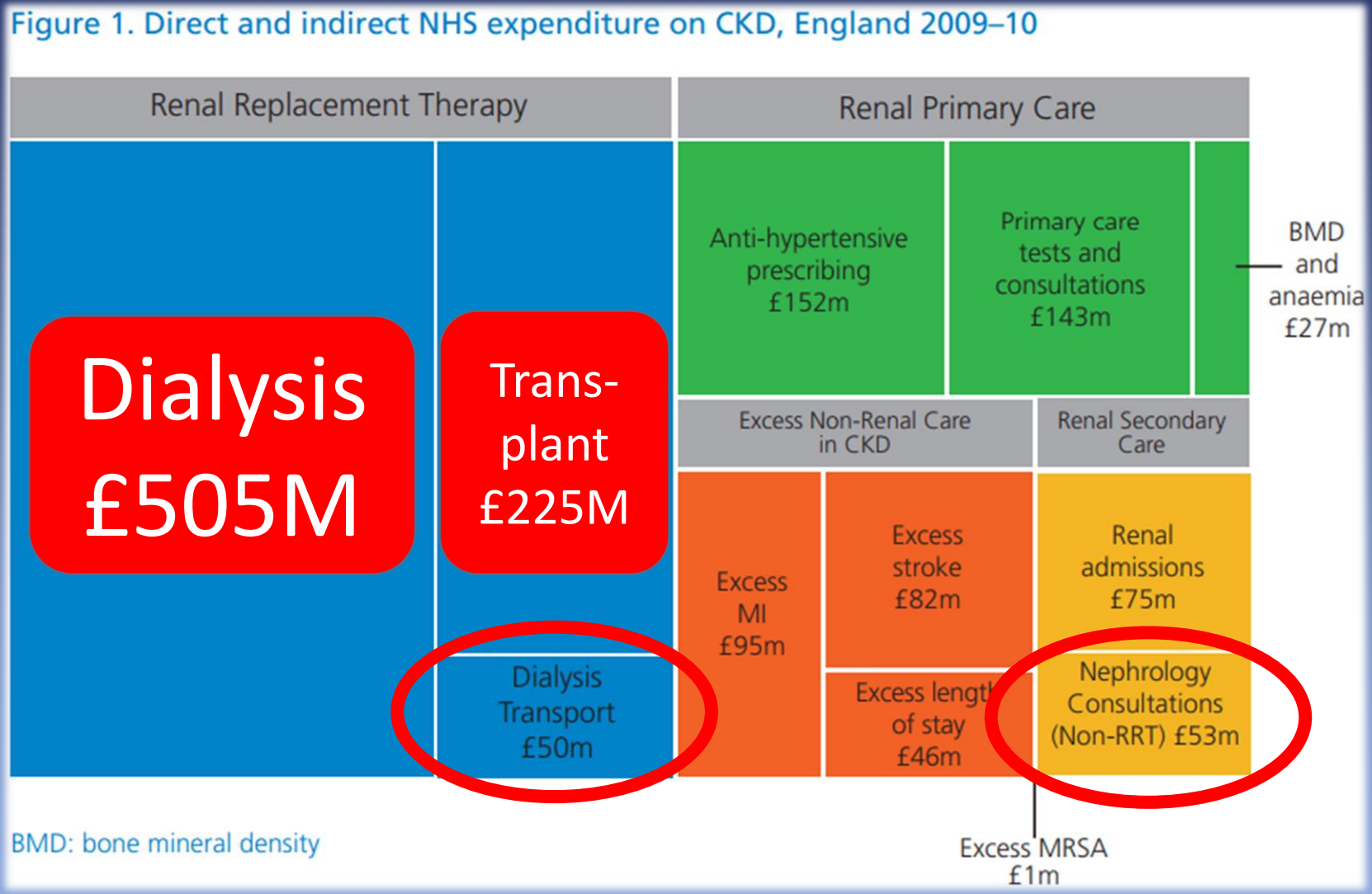

**CARDIOVASCULAR DISEASE IN CHRONIC RENAL DISEASE**

## Clinical Epidemiology of Cardiovascular Disease in Chronic Renal Disease

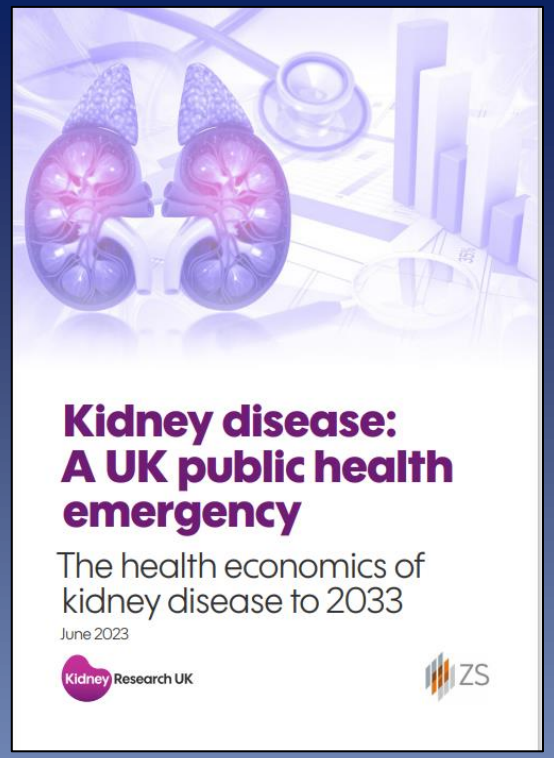
Robert N. Foley, MB, Patrick S. Parfrey, MD, and Mark J. Sarnak, MD

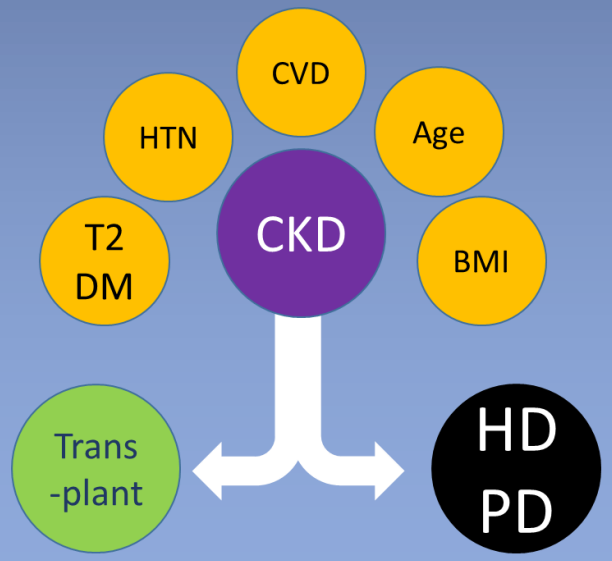


# What is the problem?




Chronic Kidney Disease in England: The Human and Financial Cost.https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf


Kidney disease:
A UK public health emergency
The health economics of kidney disease to 2033
June 2023
Kidney Research UK
ZS


CVD
HTN
Age
T2 DM
CKD
BMI
Trans -plant
HD
PD

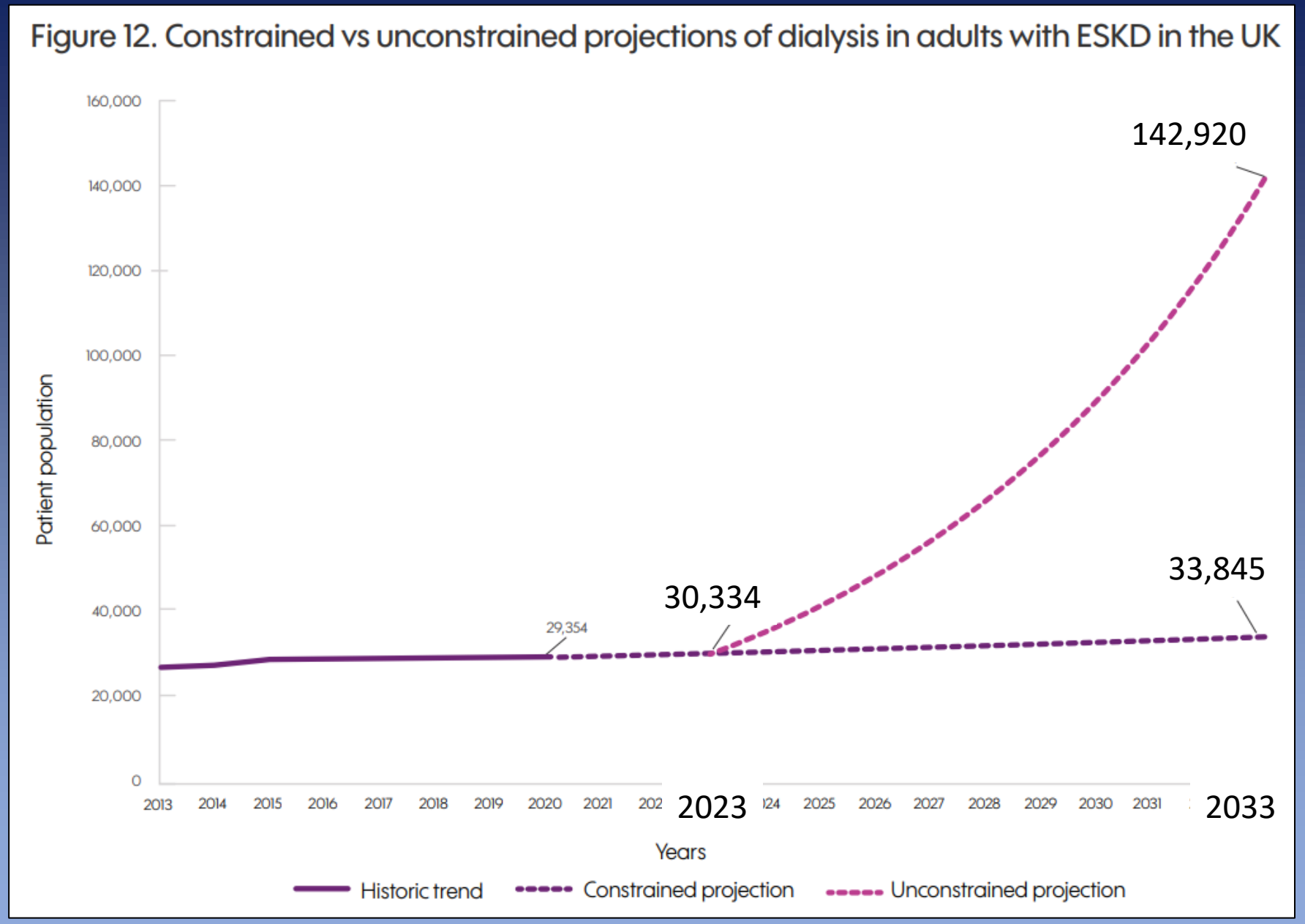
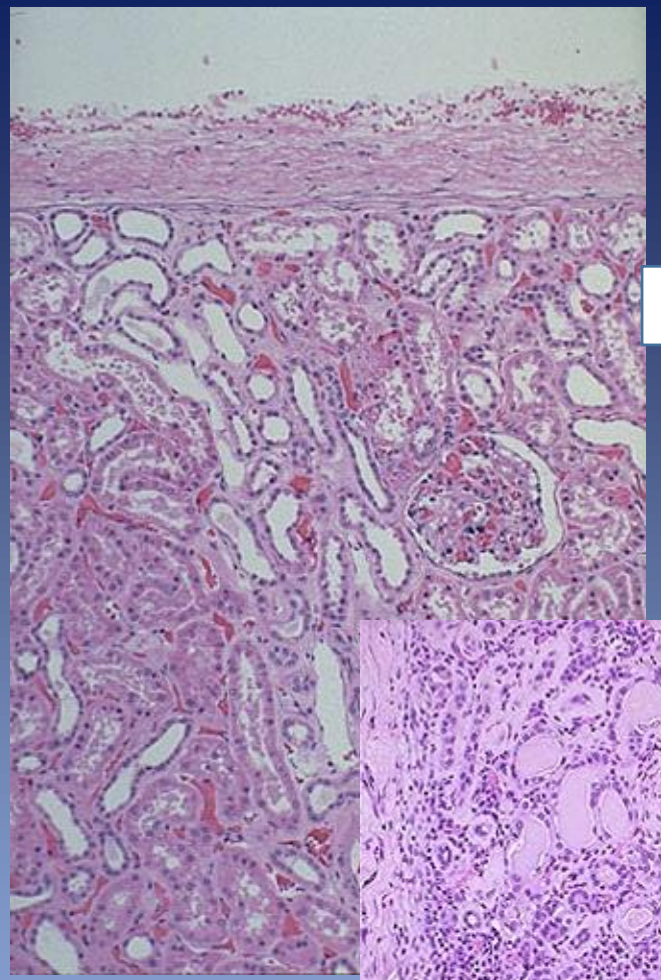


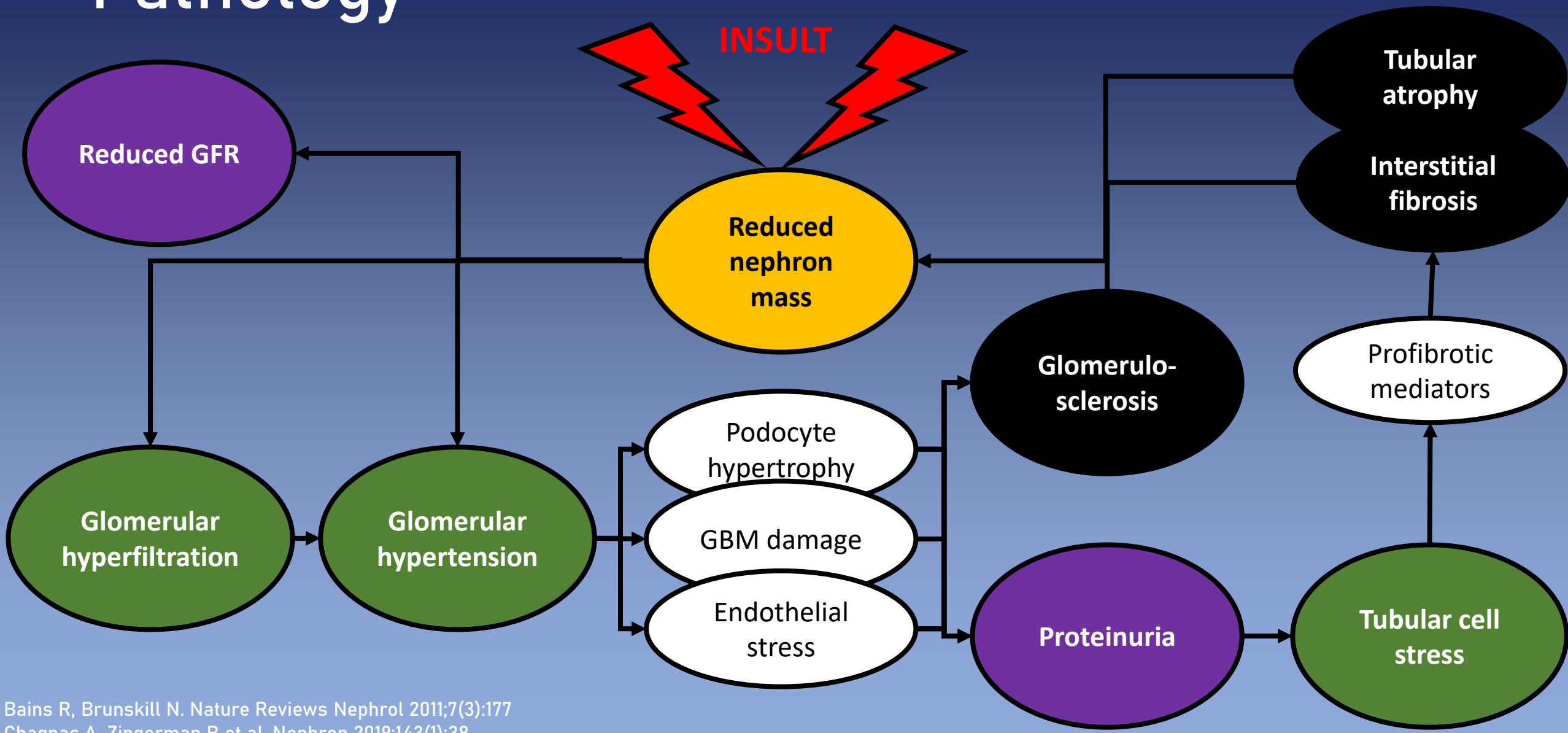
Figure 12. Constrained vs unconstrained projections of dialysis in adults with ESKD in the UK
Patient population
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
142,920
33,845
30,334
29,354
2013
2014
2015
2016
2017
2018
2019
2020
2021
2023
2025
2026
2027
2028
2029
2030
2031
2033
Years
Historic trend
Constrained projection
Unconstrained projection

TIN
GN
PKD
Uro-
logic
CVD
Rx
toxic
-ity
HTN
Age
T2
DM
CKD
BMI
Trans
-plant
HD
PD




Images: webpath.med.utah.edu

# Pathology





Bains R, Brunskill N. Nature Reviews Nephrol 2011;7(3):177
Chagnac A, Zingerman B et al. Nephron 2019;143(1):38
Cortivonis M, Perico N et al. Nature Reviews Nephol 2022;18:435


# What is their risk of end stage renal failure in the next 4-5 years?


45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78

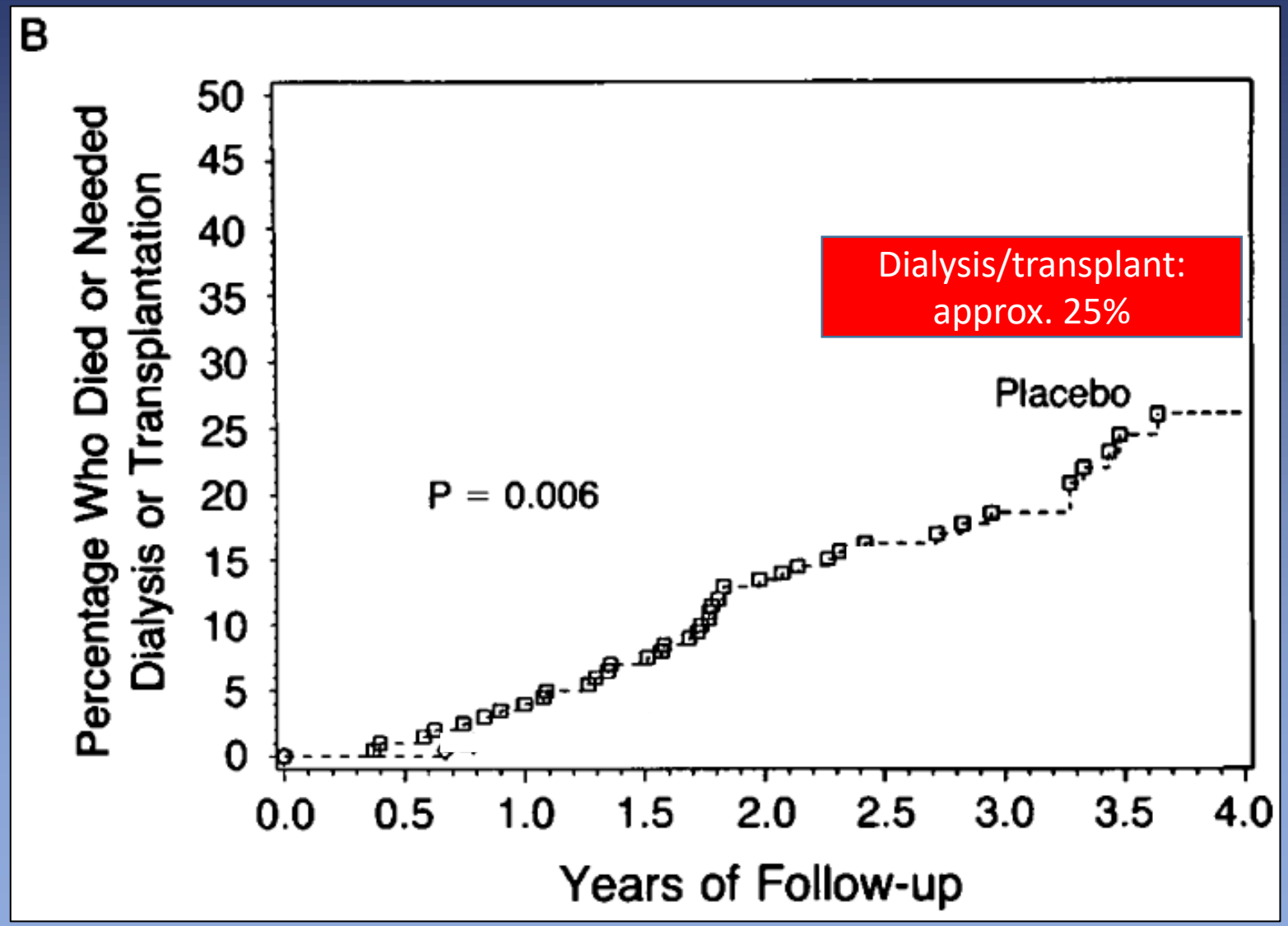
45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78

Images: shutterstock.com, istockphoto.com

# THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D., AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*

Recruitment:
1987-1990




Entry criteria
- 18-49 years
- "Insulin-dependent" diabetes ≥ 7 years
- DM retinopathy
- Proteinuria >500mg per 24 h
- Serum creatinine <221 µmol/l

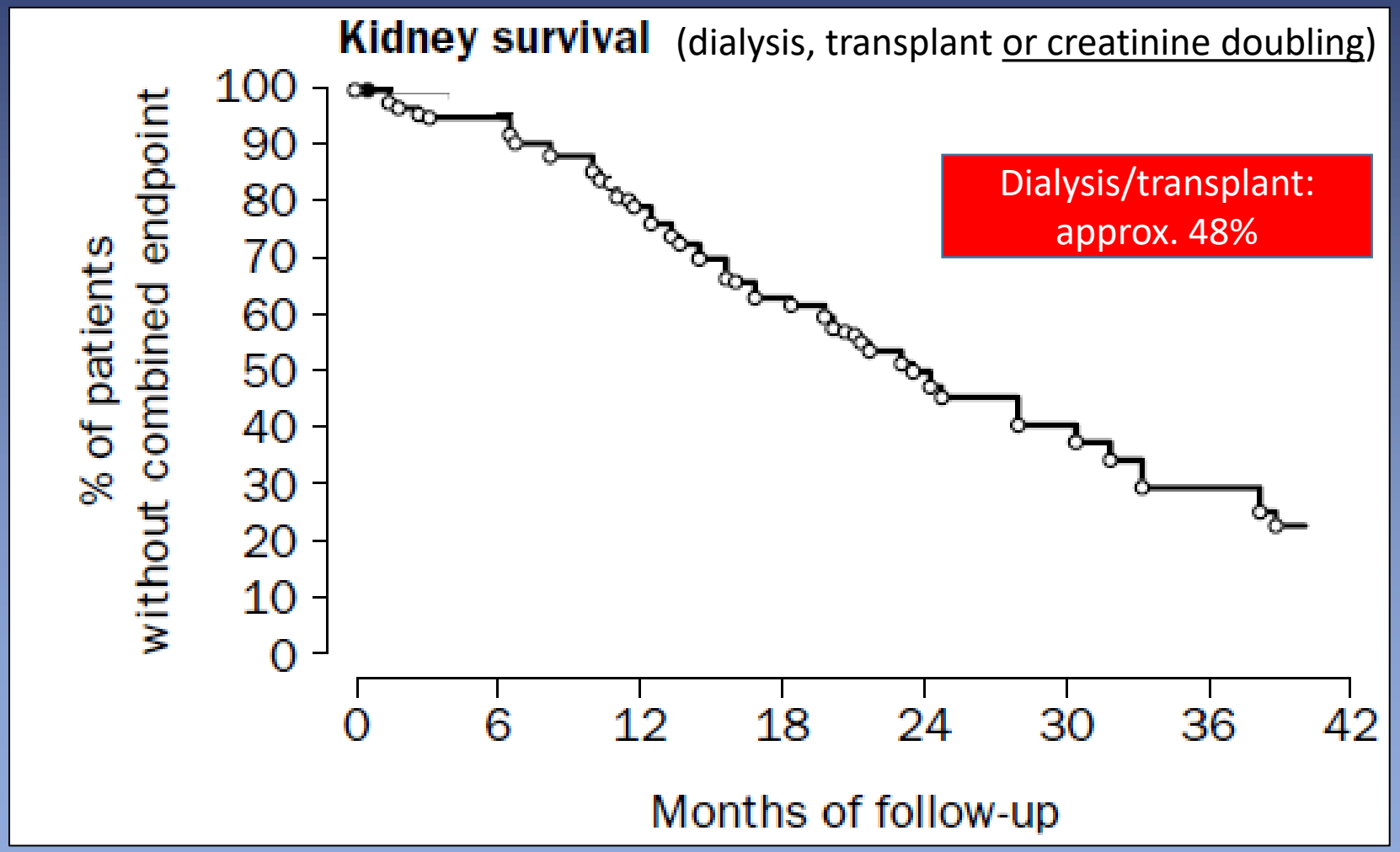
Baseline
- 35±7 years
- Mean BP 137/85
- Proteinuria 2750±2550 mg per 24 h
- Serum creatinine 115±35.3 µmol/l
- HbA1c 11.8 ± 2.8 %

NEJM 1993;329:1456-62

**Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy**

*The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia)**

Published: 1997




Entry criteria
- 18-70 years
- No diabetes
- BP < 140/90
- Proteinuria >3000mg per 24h
- Creatinine clearance 20-70ml/min

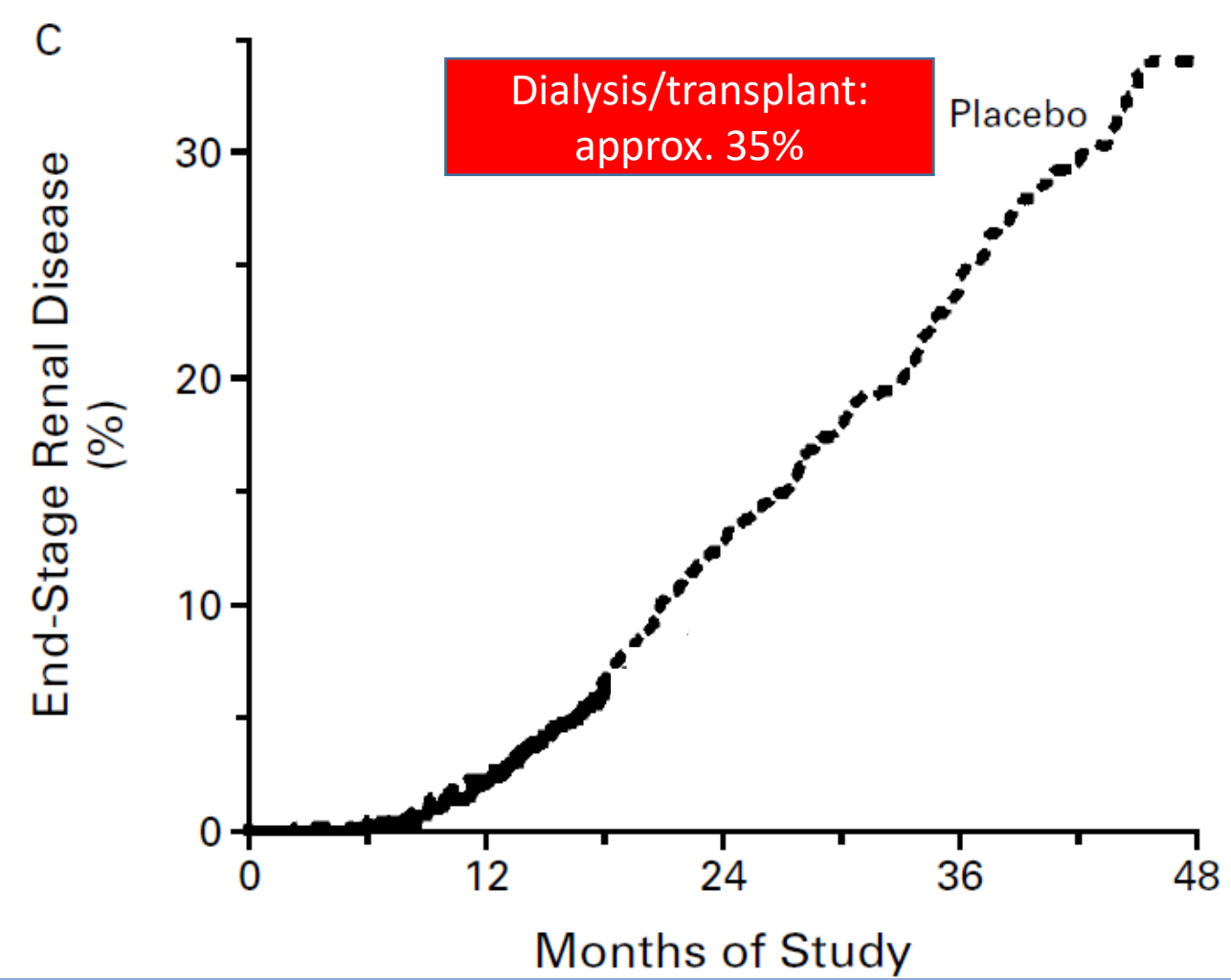
Baseline
- 49 ± 13 years
- Mean BP 149/92 (±17/11) mmHg
- Proteinuria 5350±2400 mg per 24h
- Creatinine clearance 45±20ml/min

Lancet 1997;349:1857

# EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

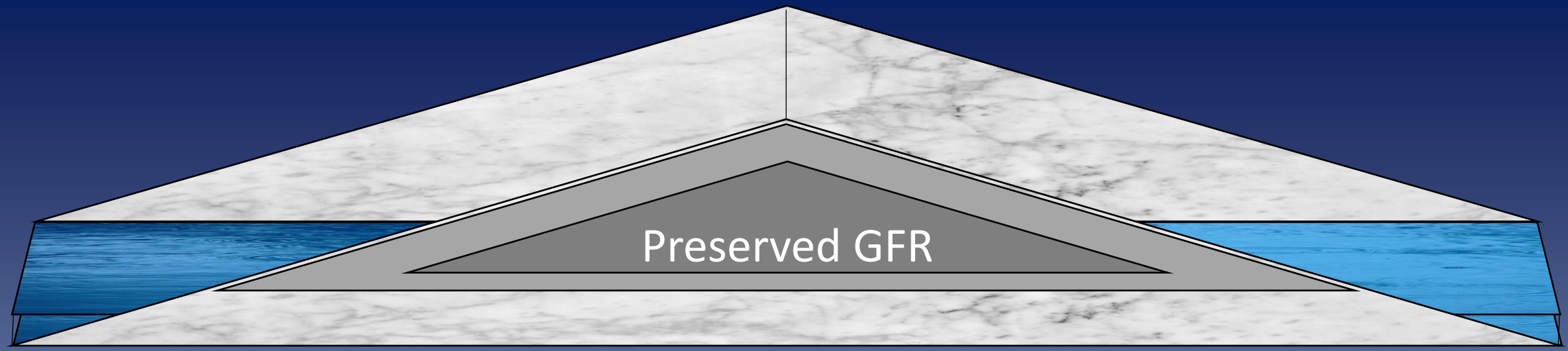
Published: 2001




Entry criteria
- 31–70 years
- Type 2 diabetes
- BP < 140/90
- Urine ACR >34 mg/mmol
- Creatinine 115–265µmol/l

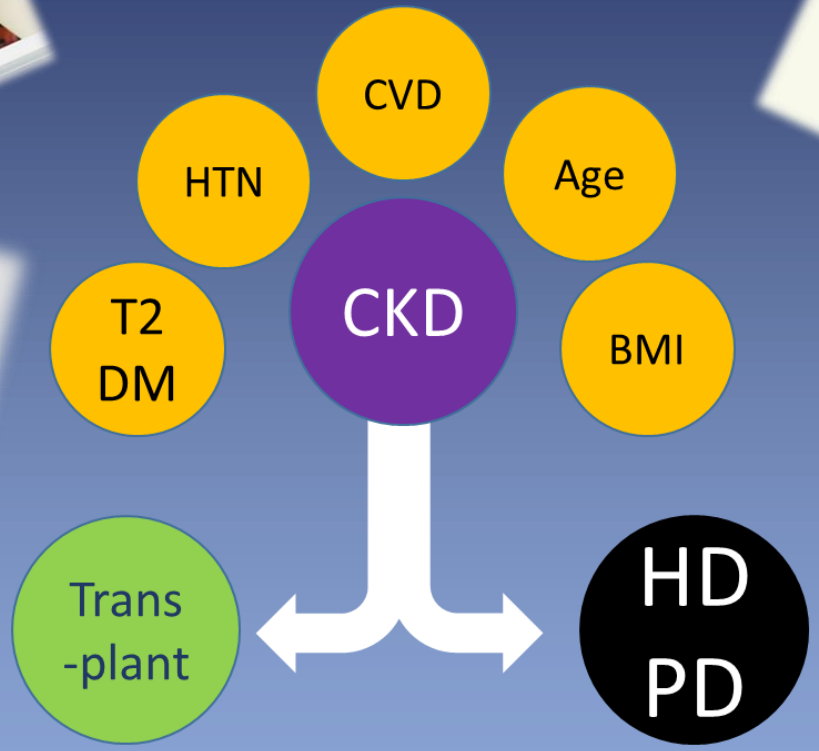
Baseline
- 60 ± 7 years
- Mean BP 152/82 (±20/11) mmHg
- Urine ACR 141 mg/mmol
- Creatinine 168±44 µmol/l

NEJM 2001;345:861




Established kidney failure

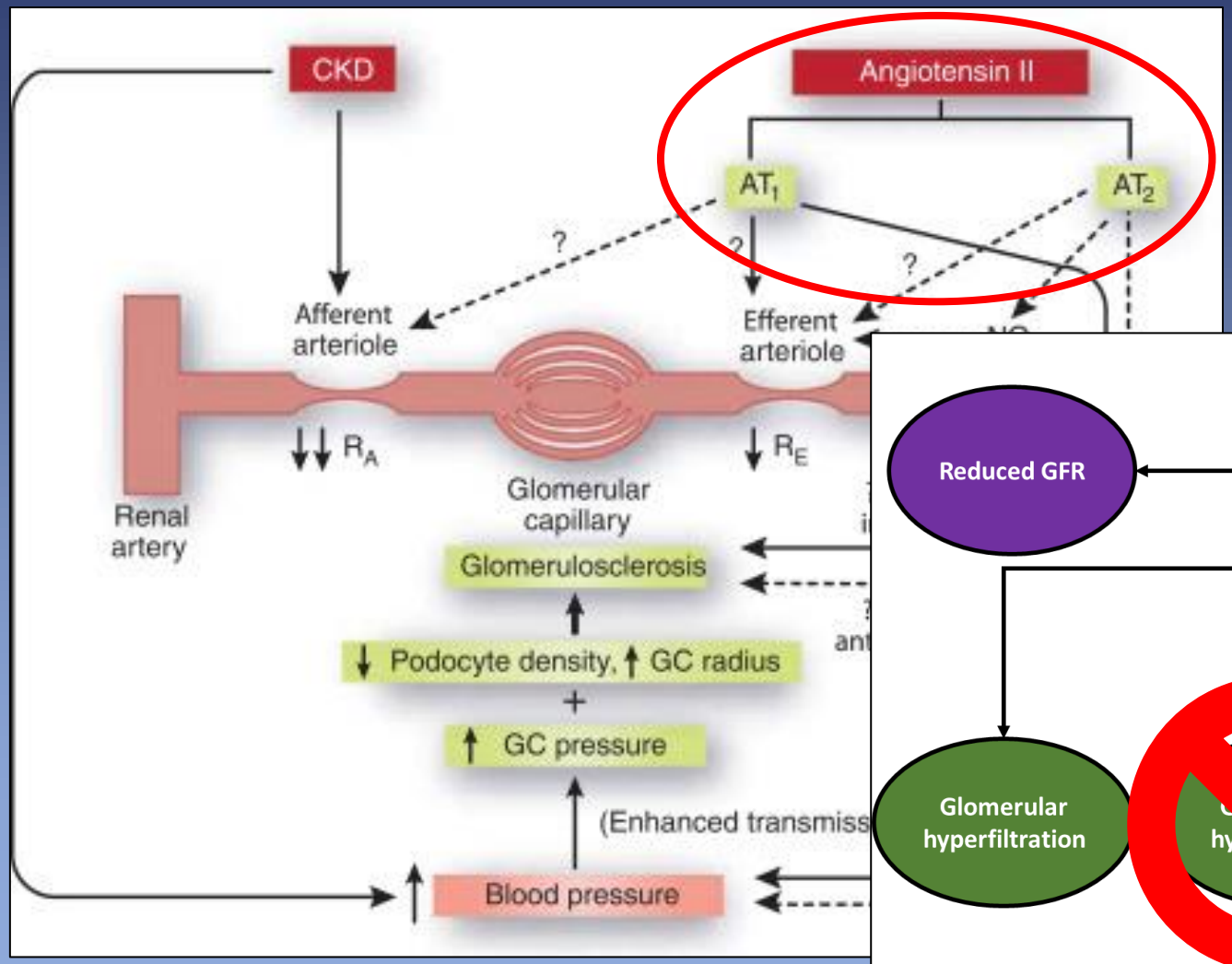


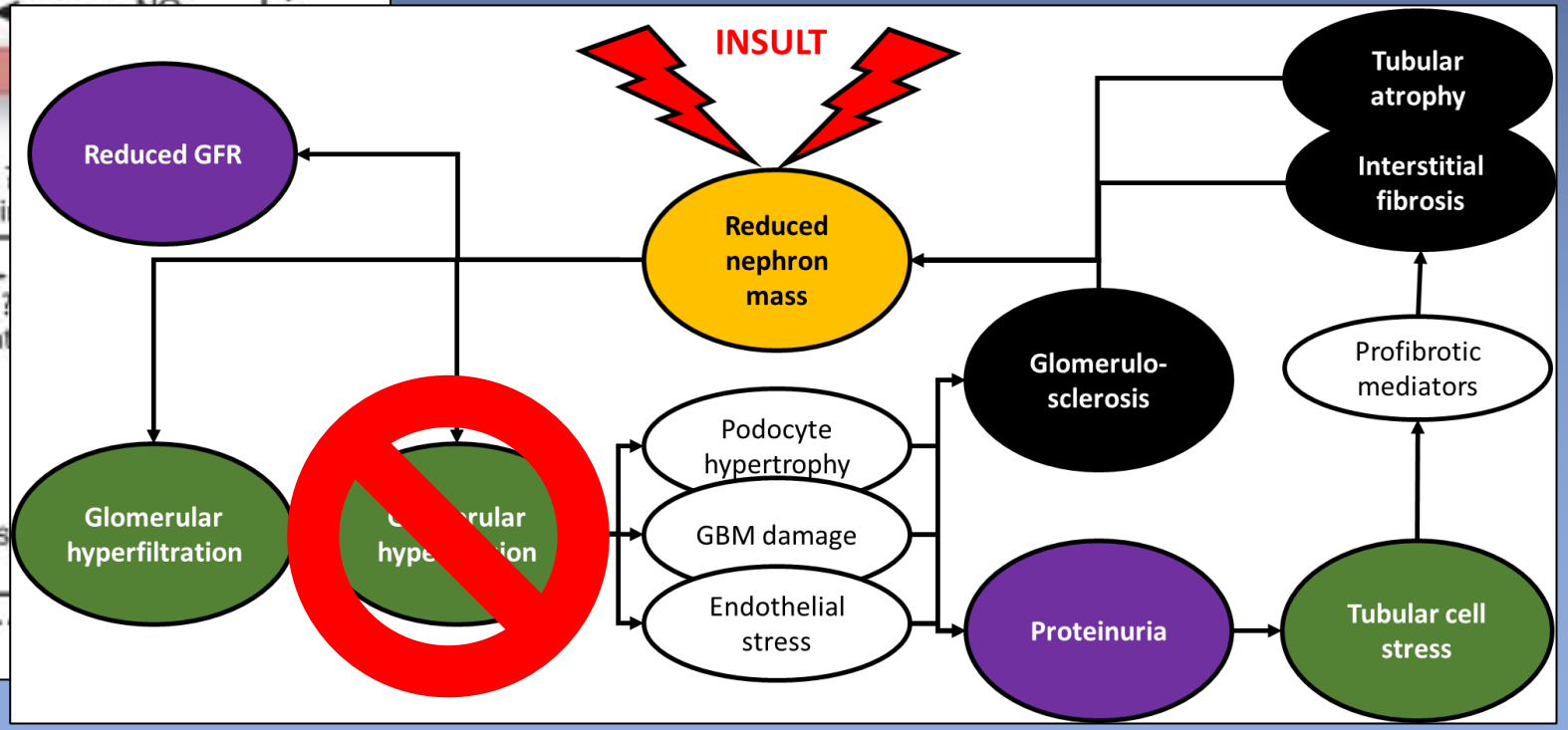




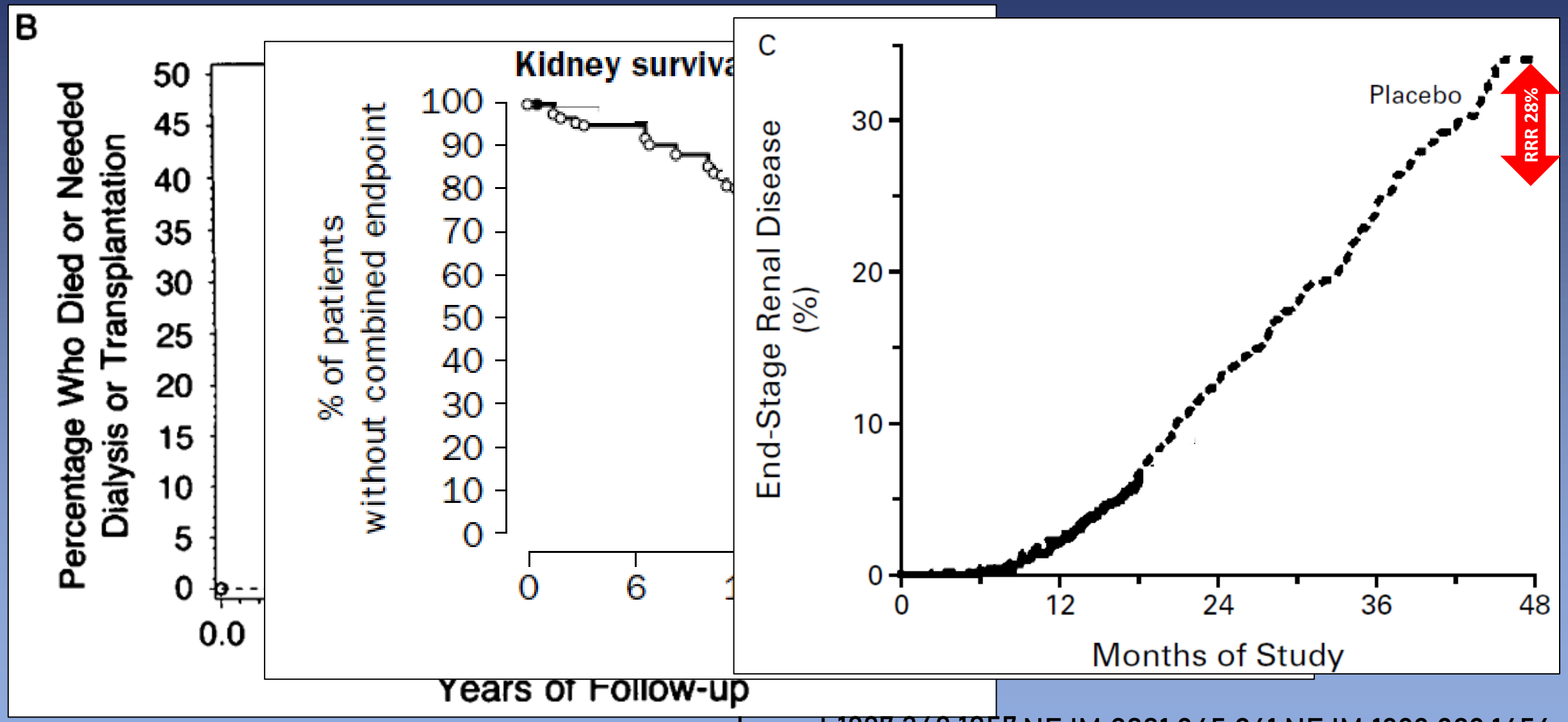
Images: newfoodmagazine.com; qmul.ac.uk; gov.uk; nhs.uk

# ACEi and ARB

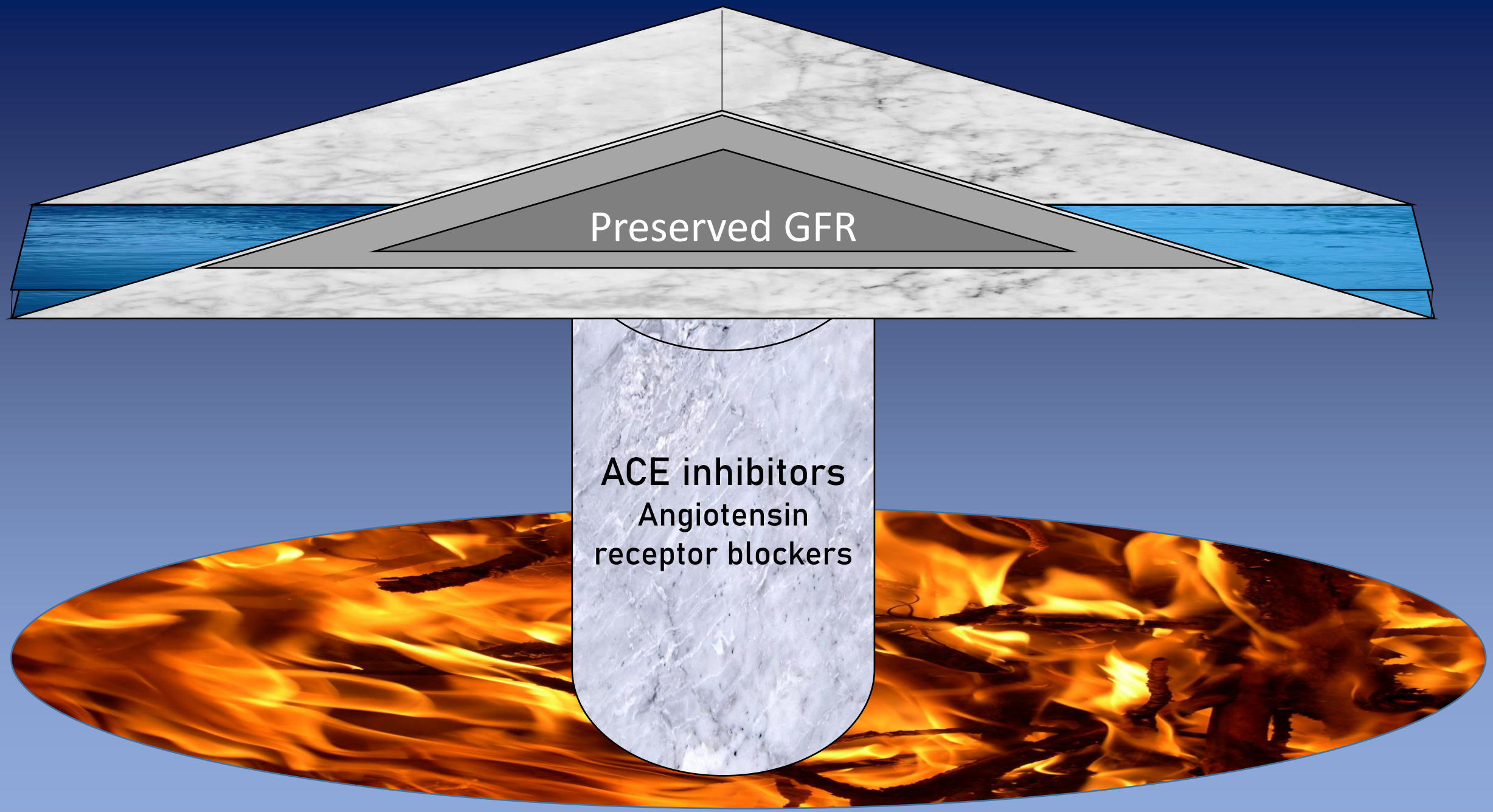

CKD
Angiotensin II
AT1
AT2
?
?
?
Afferent arteriole
Efferent arteriole
RA
RE
Renal artery
Glomerular capillary
Glomerulosclerosis
Podocyte density, GC radius
+
GC pressure
(Enhanced transmiss
Blood pressure

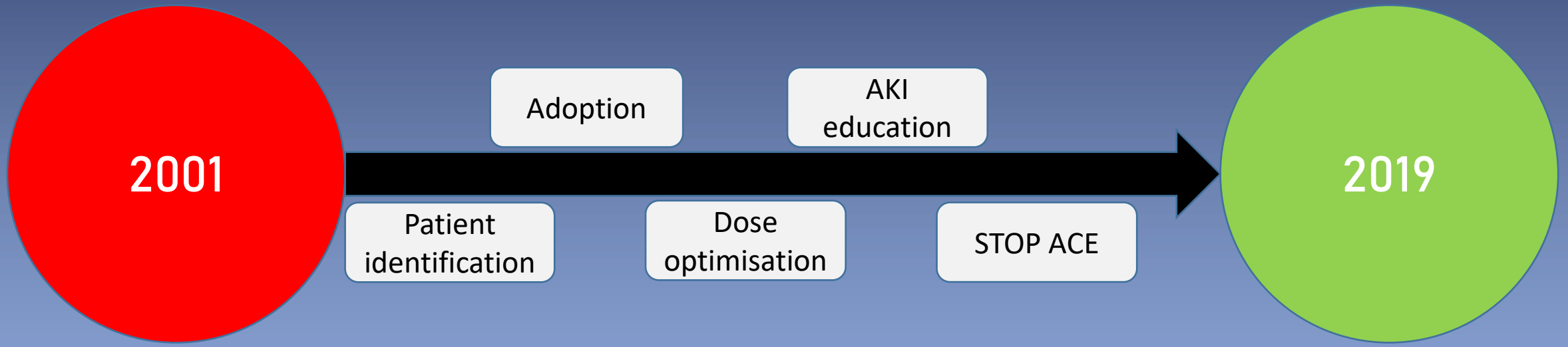

INSULT
Reduced GFR
Reduced nephron mass
Tubular atrophy
Interstitial fibrosis
Glomerulo-sclerosis
Profibrotic mediators
Podocyte hypertrophy
GBM damage
Endothelial stress
Glomerular hyperfiltration
Proteinuria
Tubular cell stress

# ACEi and ARB reduce progression in patients with proteinuria

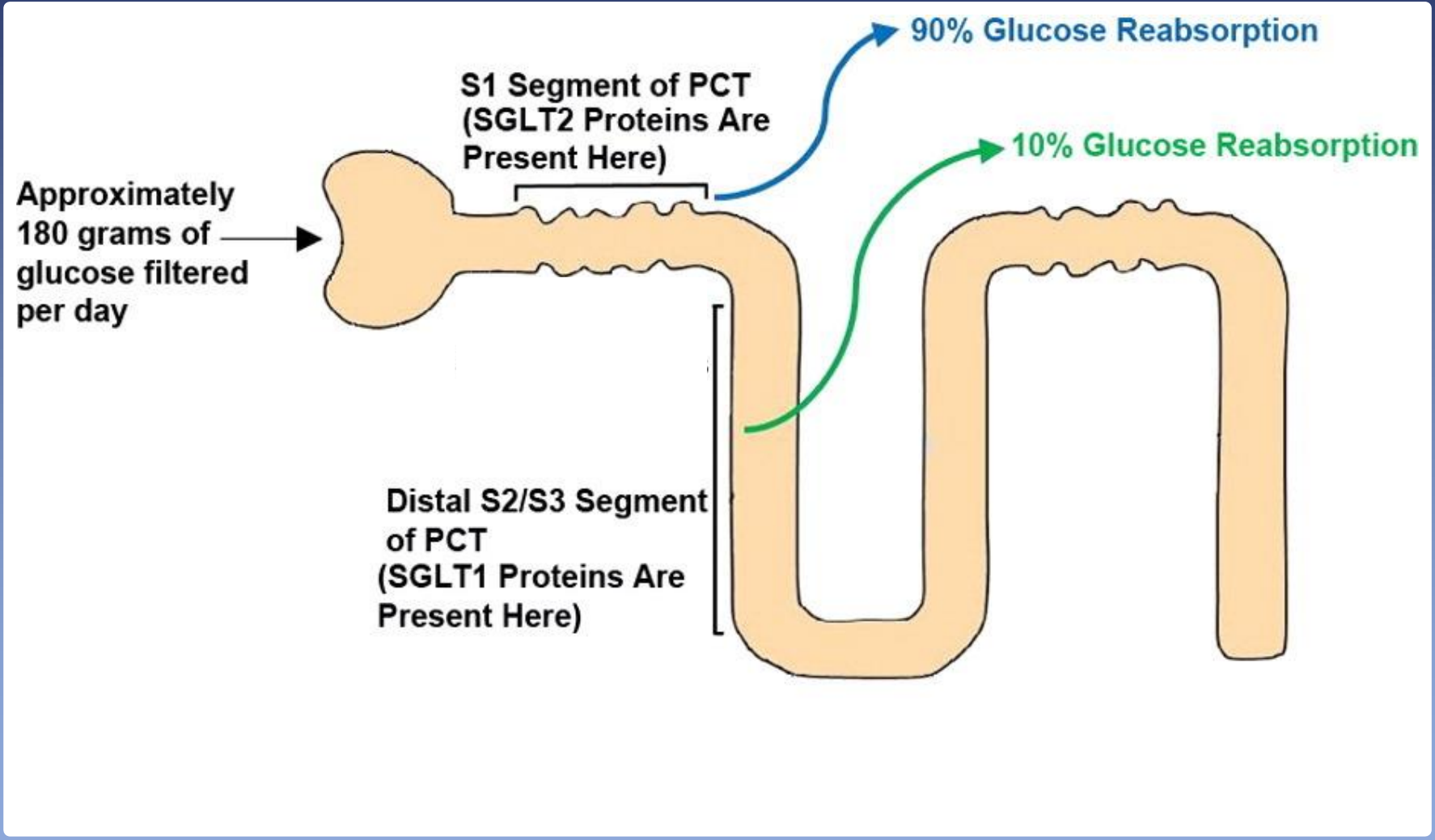



Lancet 1997;349:1857 NEJM 2001;345:861 NEJM 1993;329:1456-62


Preserved GFR
ACE inhibitors
Angiotensin
receptor blockers
Established kidney failure


2001
Adoption
AKI education
Patient identification
Dose optimisation
STOP ACE
2019

# Sodium-glucose cotransporter 2 inhibitors

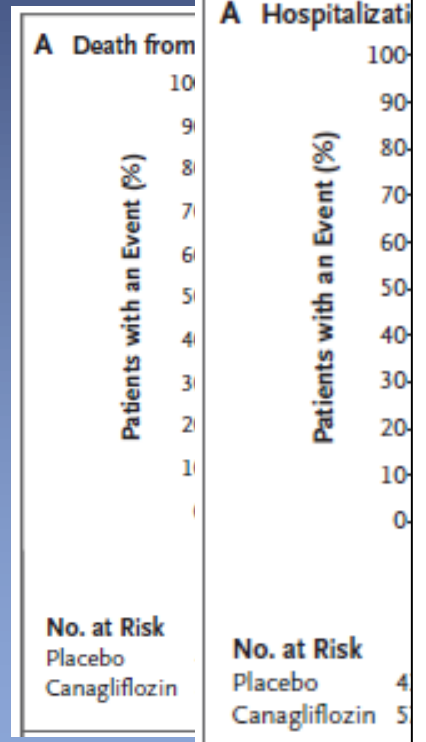



Europ J Pharmaceut Sci 2016;93:244

# Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

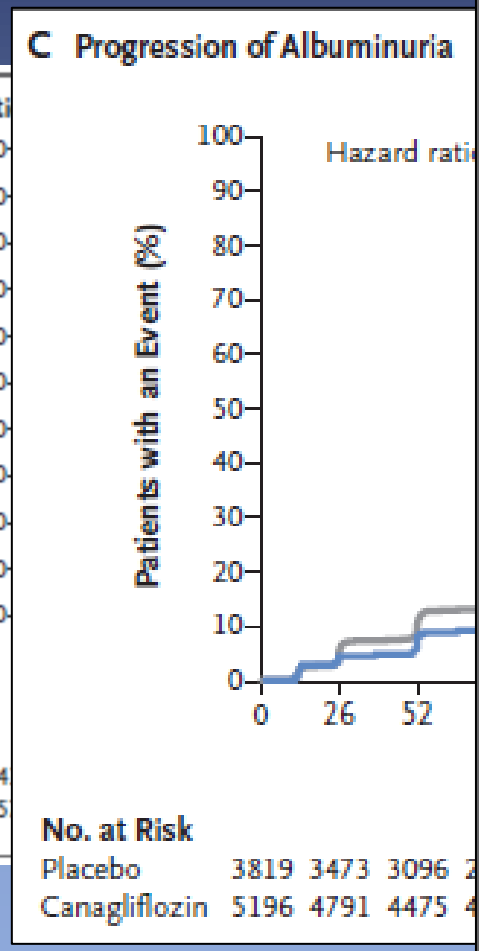
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

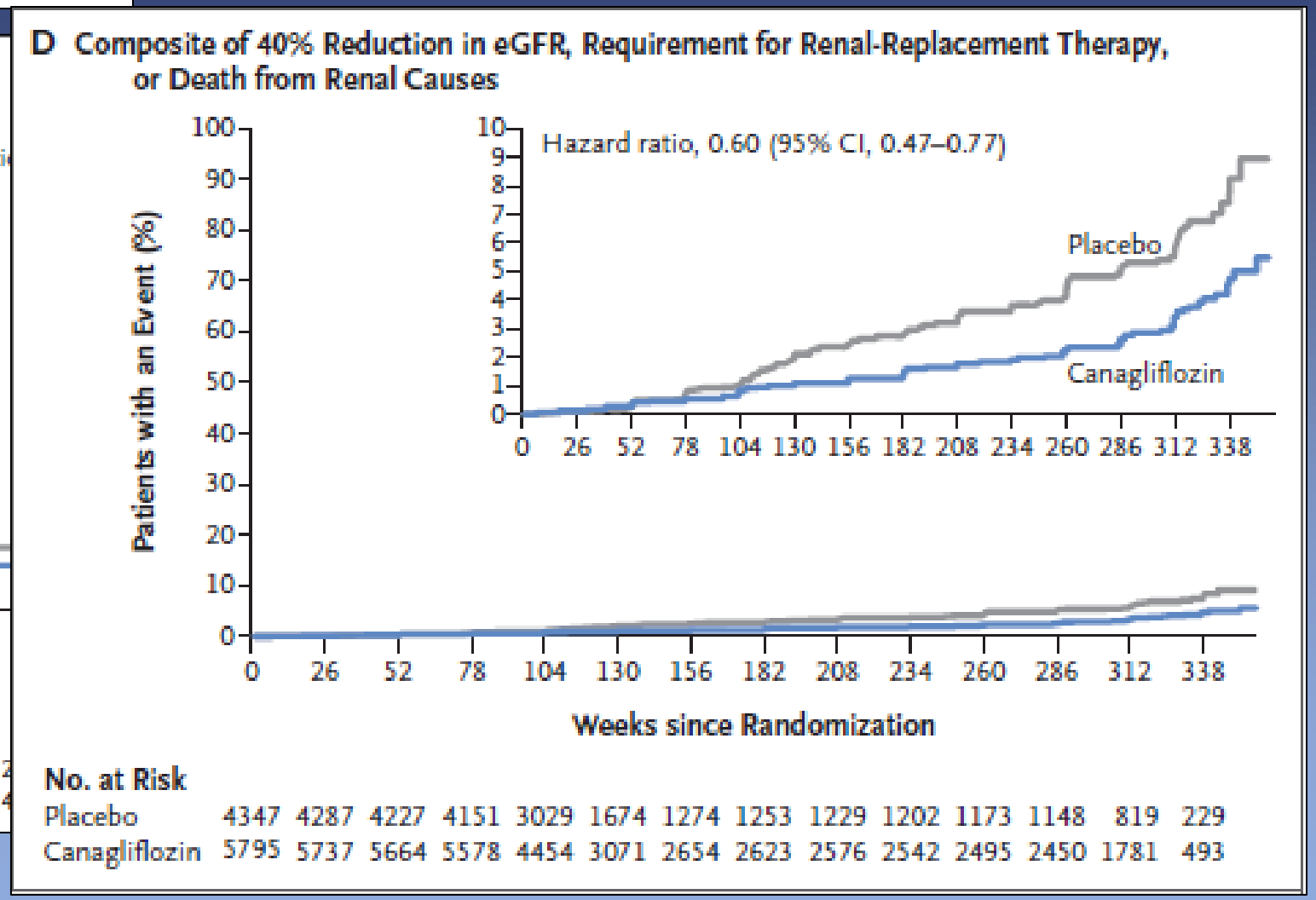
NEJM 2017;377:644



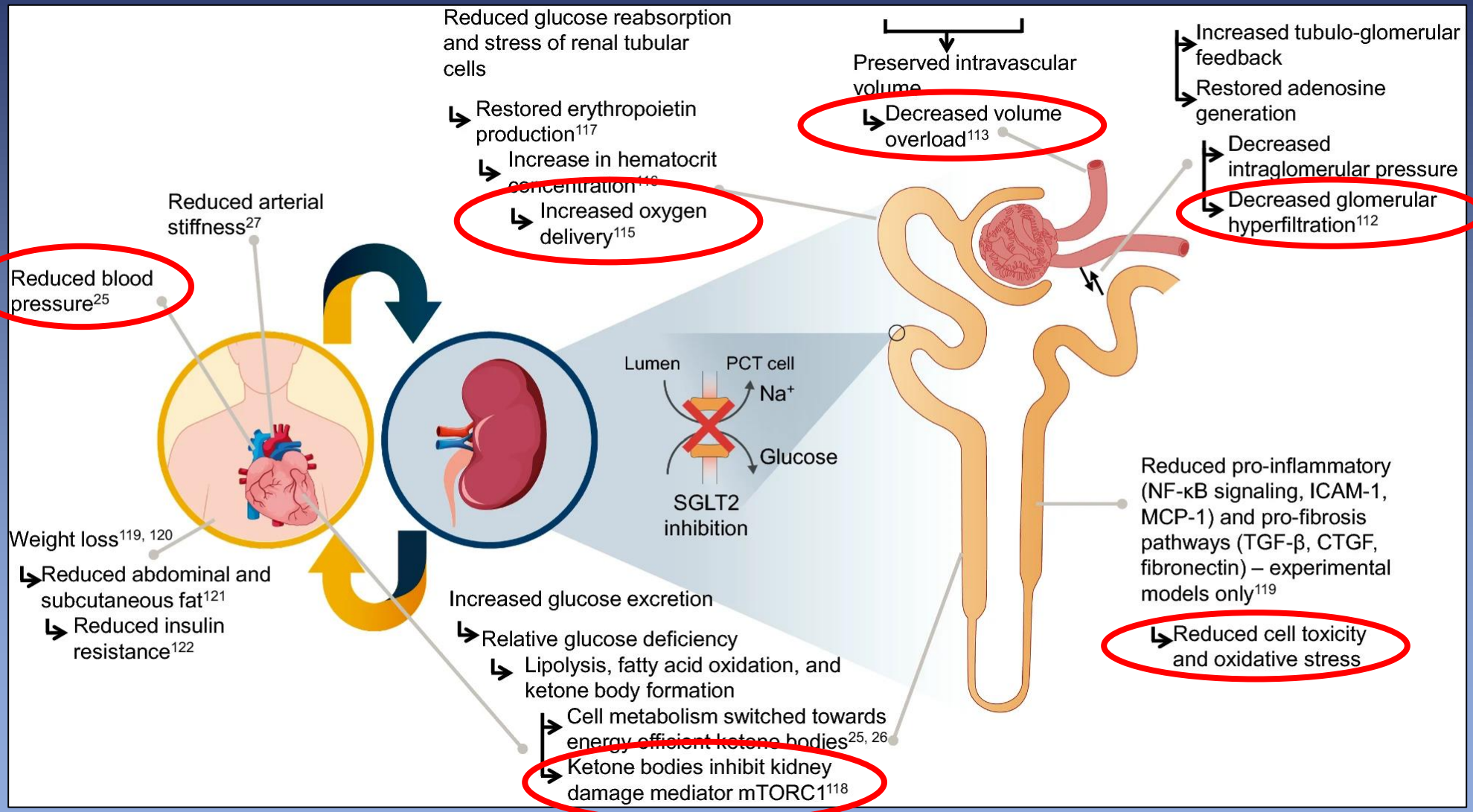






# Sodium-glucose cotransporter 2 inhibitors

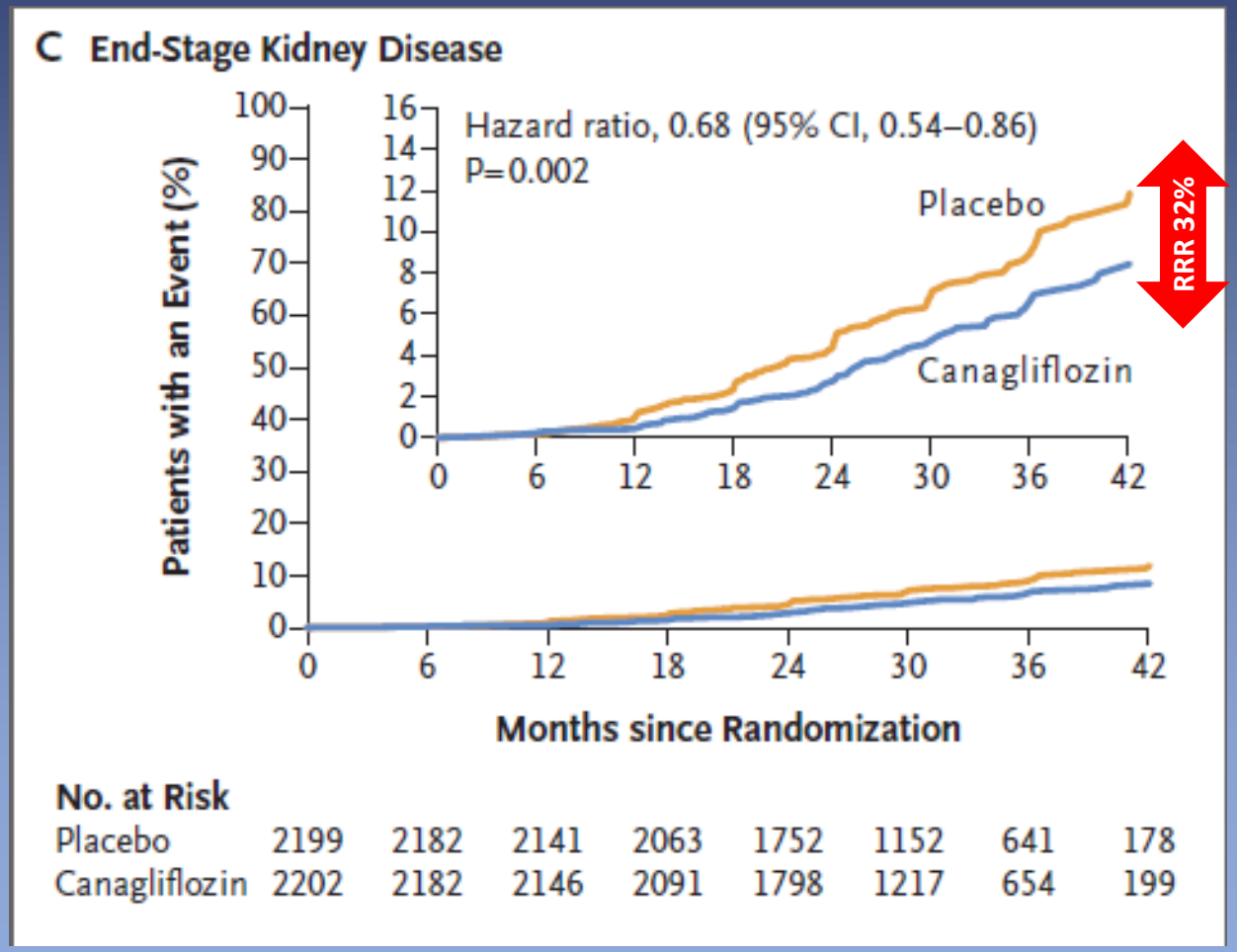



Cardiovasc Diabetol 2020;19:196

# Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

NEJM 2019;380:2295
Recruitment 2014-2017



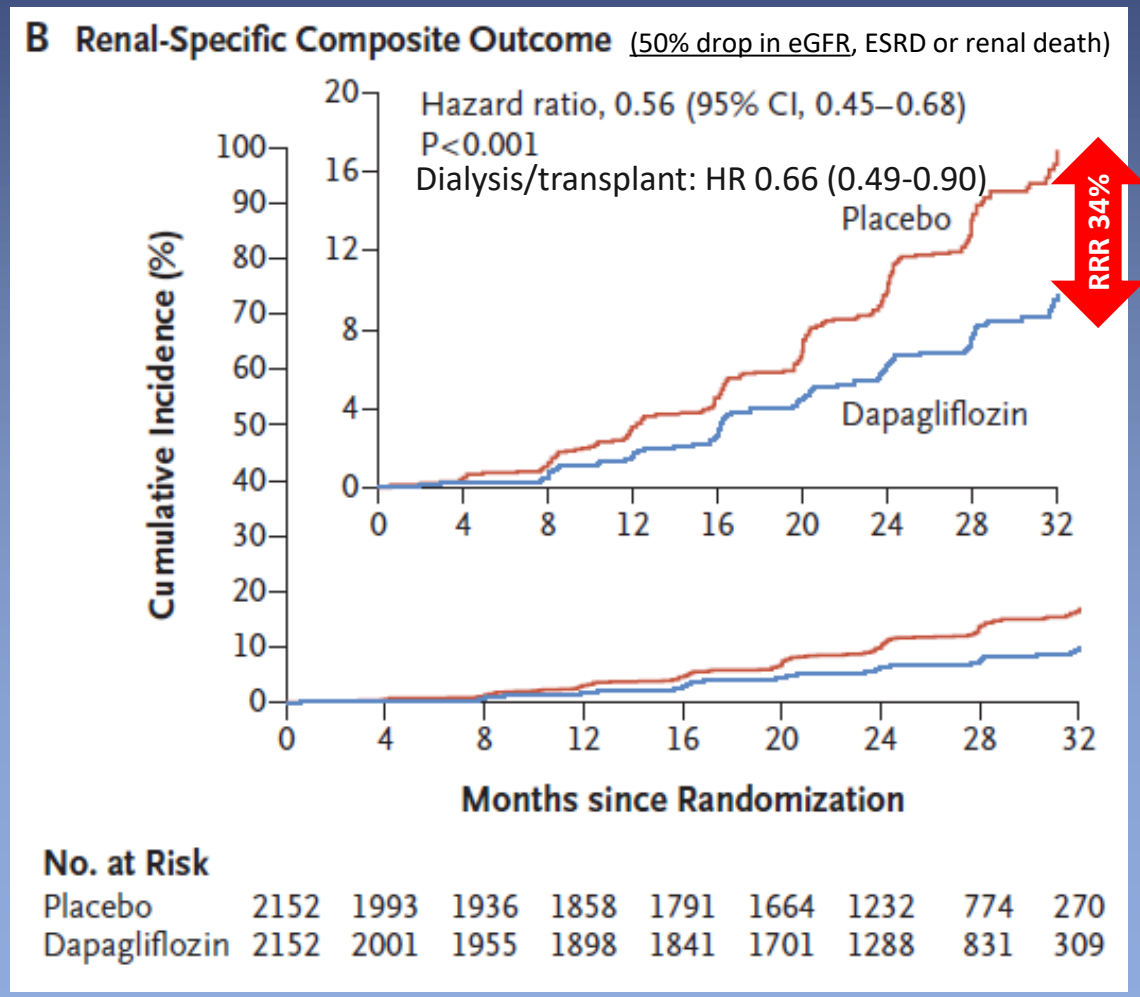

Entry criteria
- ≥30 years
- Type 2 DM
- HbA1c 6.5-12.0%
- uACR 34 – 565 mg/mmol
- eGFR 30-90ml/min
- Maximum tolerated ACEi/ARB dose

Baseline
- 63±9 years
- Mean BP 140/78
- Urine ACR 105 (52-207) mg/mmol
- Estimated GFR 56 ± 18 ml/min
- HbA1c 8.3 ± 1.3 %

# Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

NEJM 2020;383:1436
Recruitment 2017-2020




## Entry criteria

- ≥18 years
- With or without type 2 DM
- uACR 22.6 – 565 mg/mmol
- eGFR 25-75ml/min
- Maximum tolerated ACEi/ARB dose

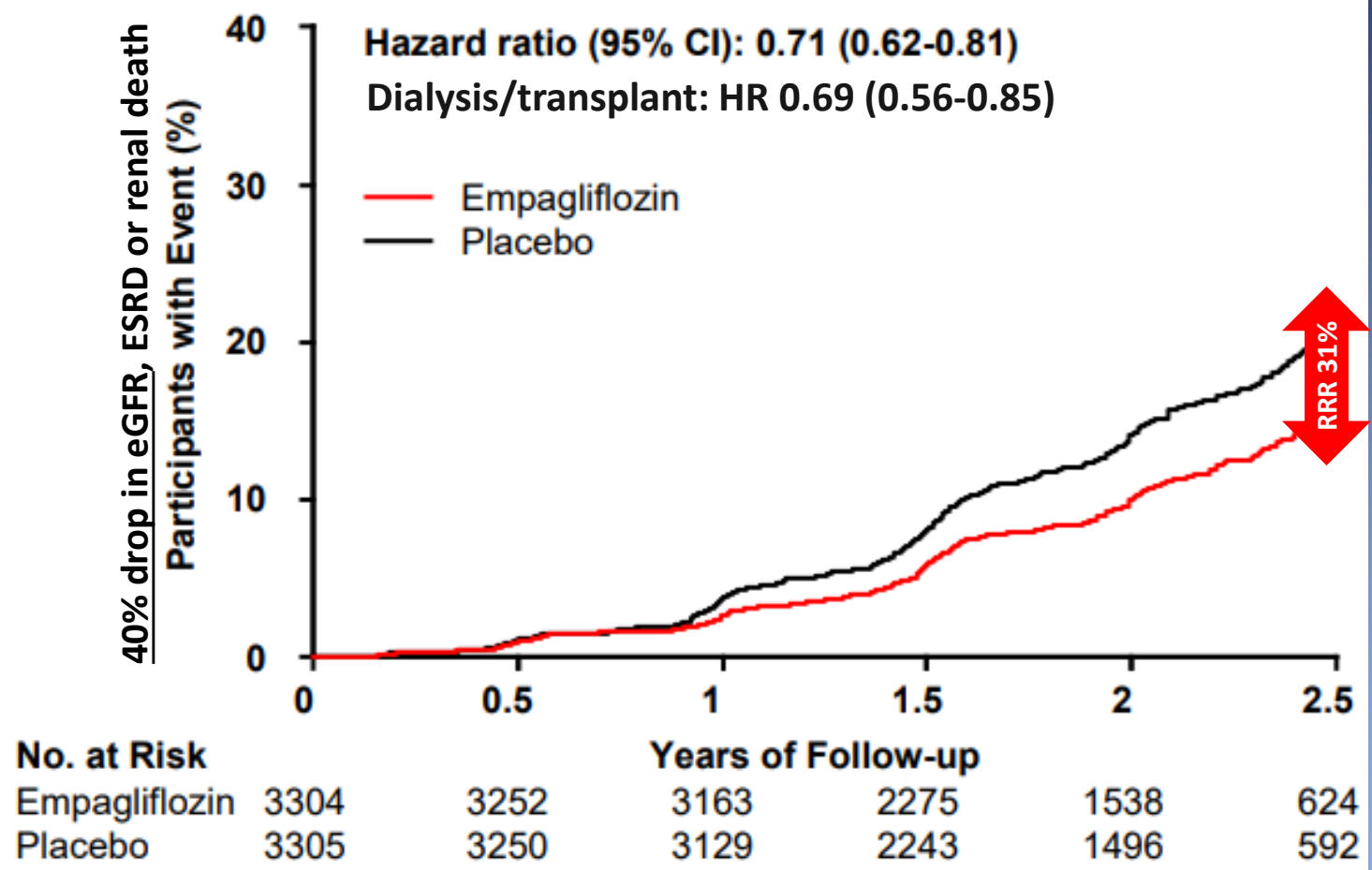
## Baseline

- 62±12 years
- Mean BP 137/78
- Urine ACR 105 (54-213) mg/mmol
- Estimated GFR 43 ± 12 ml/min
- Type 2 DM: 67%

# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

NEJM 2023;388:117
Recruitment 2019-2021




Entry criteria
- ≥18 years
- With or without type 2 DM
- eGFR: 20-45ml/min AND any uACR, OR 45-90ml/min AND uACR>22.6mg/mmol
- Maximum tolerated ACEi/ARB dose

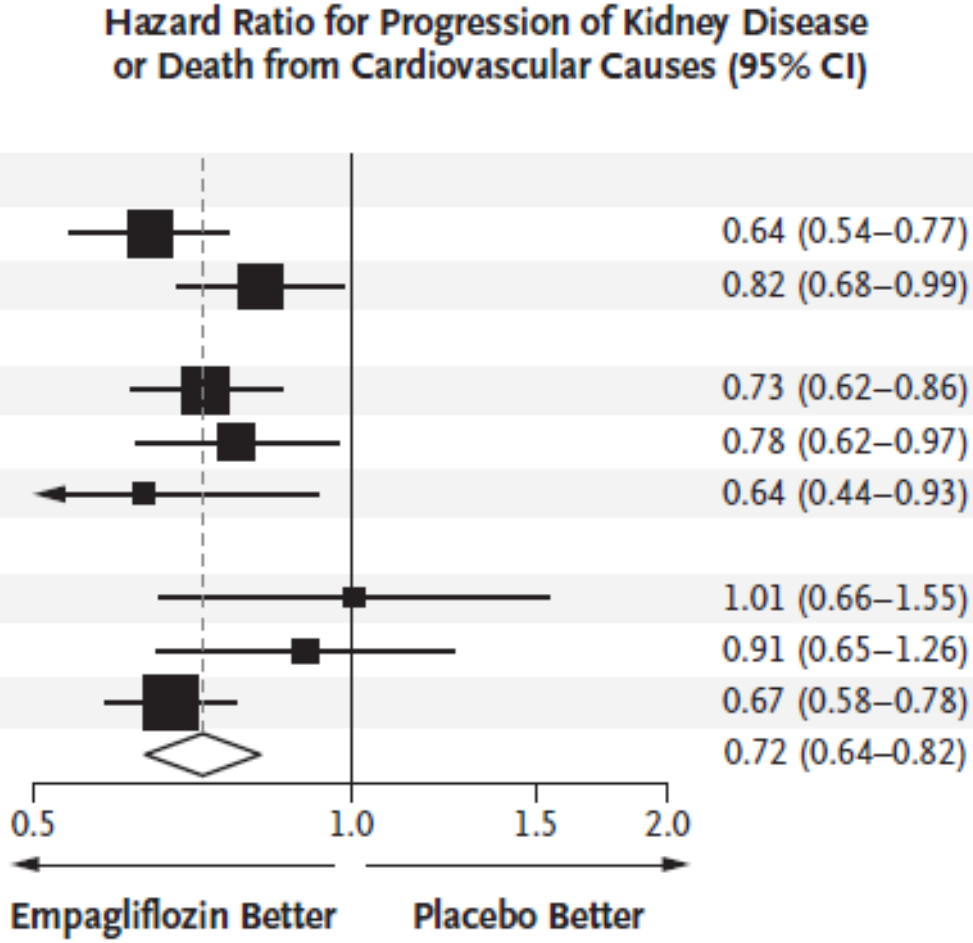
Baseline
- 64±14 years
- Mean BP 136/78
- Urine ACR 37.4 (5.6-121) mg/mmol
  - Urine ACR <3.3mg/mmol: 20%
- Estimated GFR 37 ± 14 ml/min
- Type 2 DM: 46%

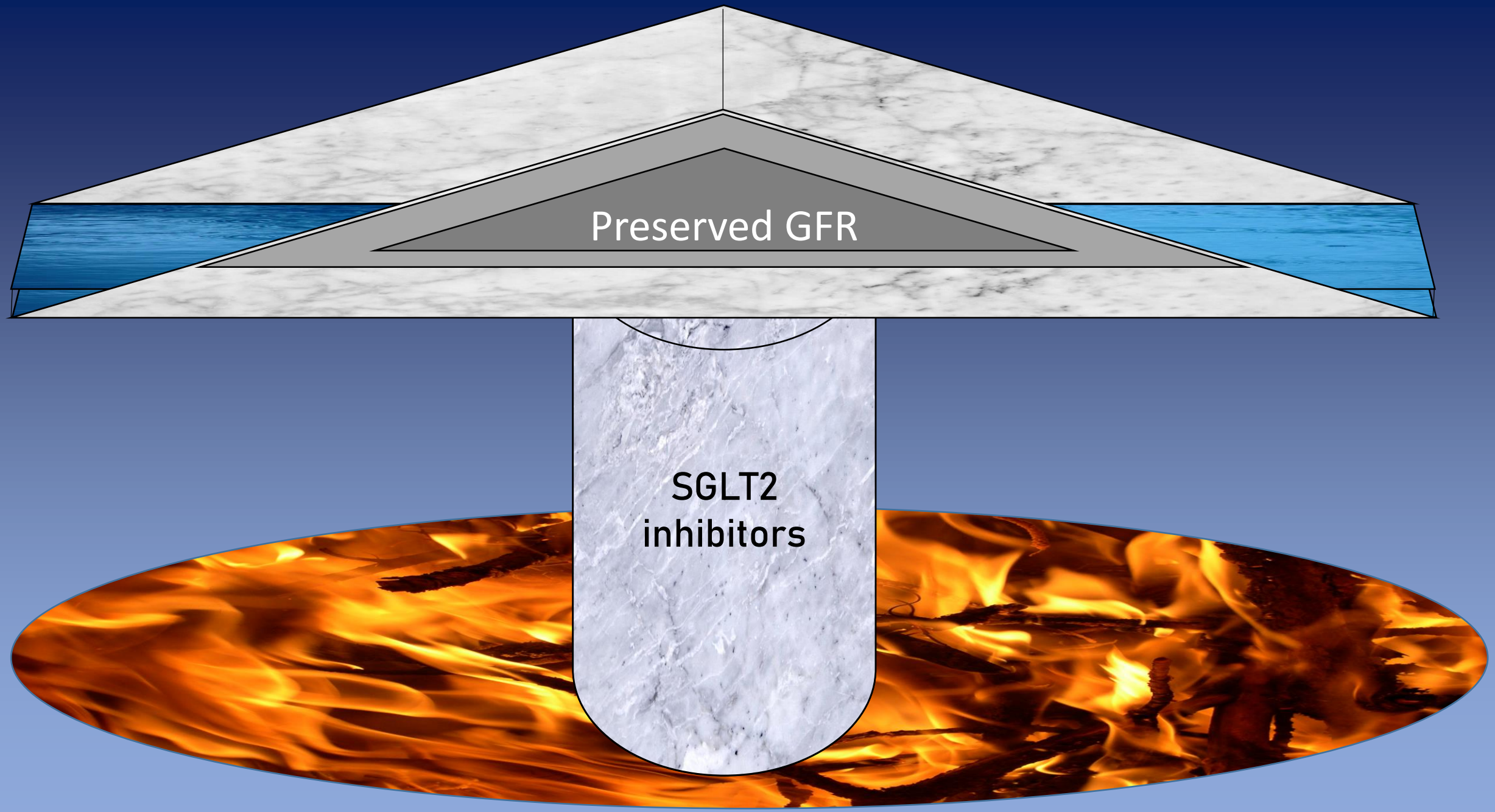
# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

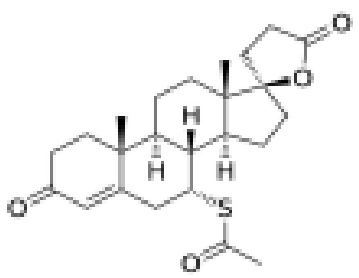
NEJM 2023;388:117
Recruitment 2019-2021

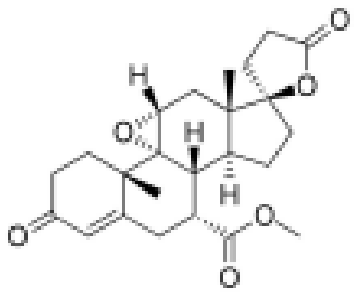
| Subgroup | Empagliflozin | Placebo |
|---|---|---|
| | *no. of patients with event/total no.* | |
| Diabetes mellitus | | |
| Present | 218/1525 | 306/1515 |
| Absent | 214/1779 | 252/1790 |
| Estimated GFR | | |
| <30 ml/min/1.73 $m^2$ | 247/1131 | 317/1151 |
| ≥30 to <45 ml/min/1.73 $m^2$ | 140/1467 | 175/1461 |
| ≥45 ml/min/1.73 $m^2$ | 45/706 | 66/693 |
| Urinary albumin-to-creatinine ratio | | |
| <30 | 42/665 | 42/663 |
| ≥30 to ≤300 | 67/927 | 78/937 |
| >300 | 323/1712 | 438/1705 |
| All patients | 432/3304 | 558/3305 |



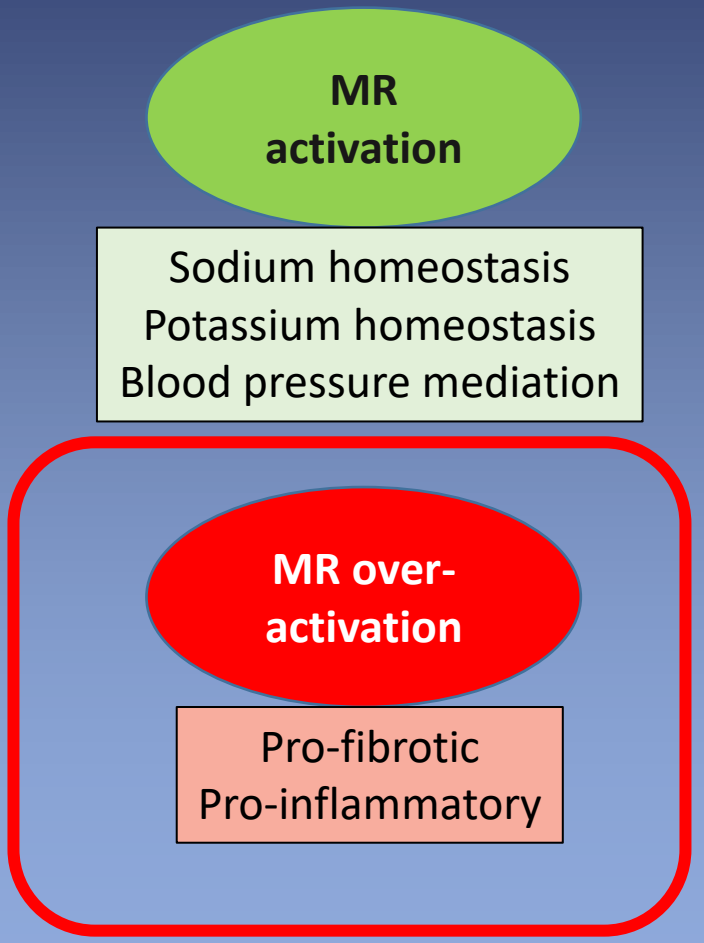

Preserved GFR
SGLT2
inhibitors
Established kidney failure

# Mineralocorticoid receptor antagonists





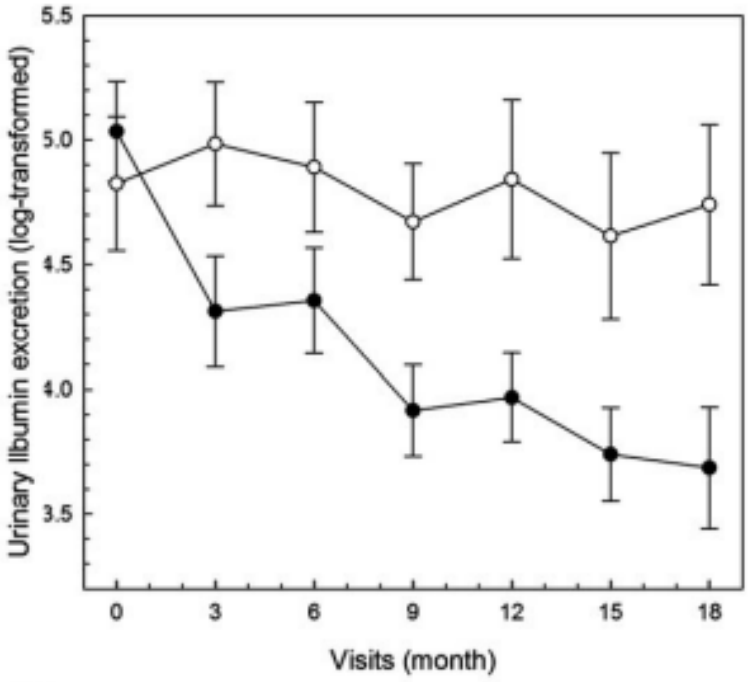
| | Spironolactone | Eplerenone |
|---|---|---|
| **Structure** | Flat (steroidal) | Flat (steroidal) |
| **Potency to MR** | +++ | + |
| **Selectivity to MR** | + | ++ |
| **Tissue distribution** | Kidney > heart | Kidney > heart |
| **Active metabolites** | +++ | - |
| **Half-life** | Long* | 4-6 hours |
| **Sexual side-effects** | ++ | + |

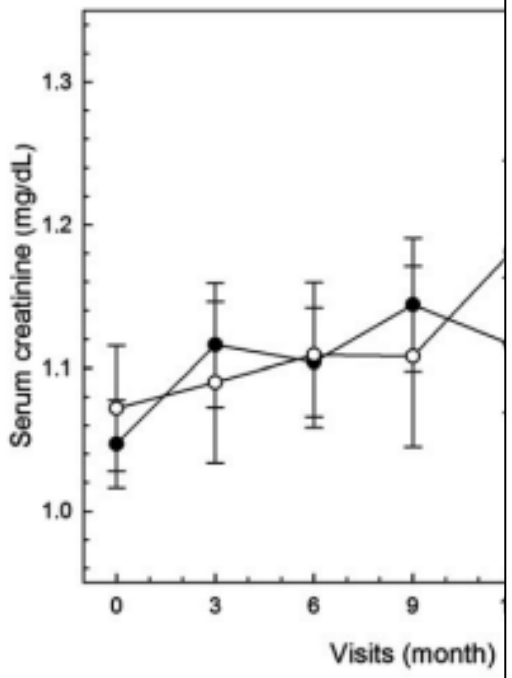



Am J Hypertension 2023;36:135

# Spironolactone/eplerenone

Long-term effects of addition of mineralocorticoid
antagonist to angiotensin II receptor blocker in pat
diabetic nephropathy: a randomized clinical trial



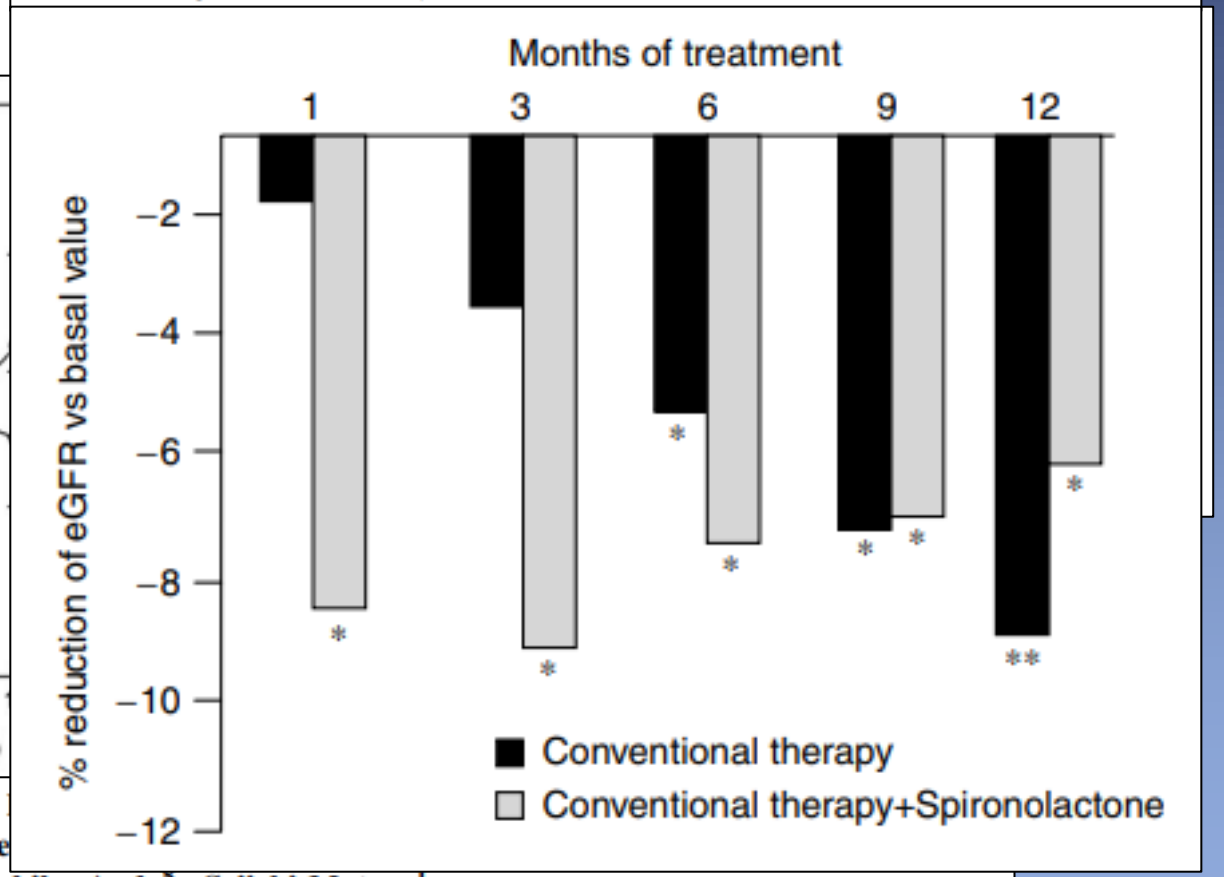




Sawako Kato[1] · Shoichi Maruyama[1] ·
Hisazumi Araki[3] · Daisuke Koya[4] · Ke
ki Kobori[6] · Enyu Imai[7] · Masahiko Ando[8] · Seiichi Matsuo[1]

Nephrol Dial Transplant (2013) 28: 2823–2833

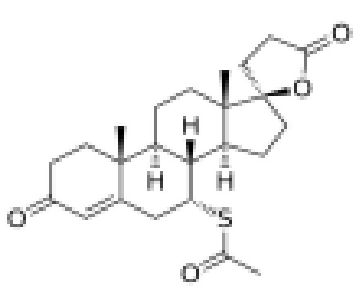
**Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease**

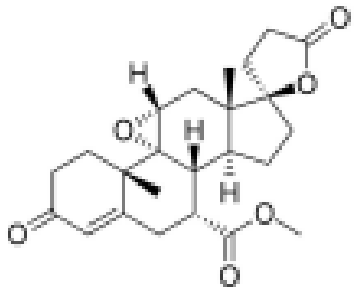
S Bianchi[1], R Bigazzi[1] and VM Campese[2]

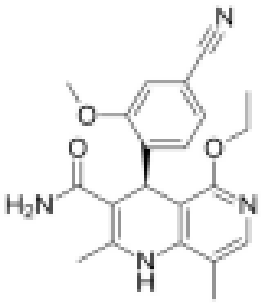



Kidney International (2006) 70, 2116–2123.

# Non-steroidal mineralocorticoid inhibitors







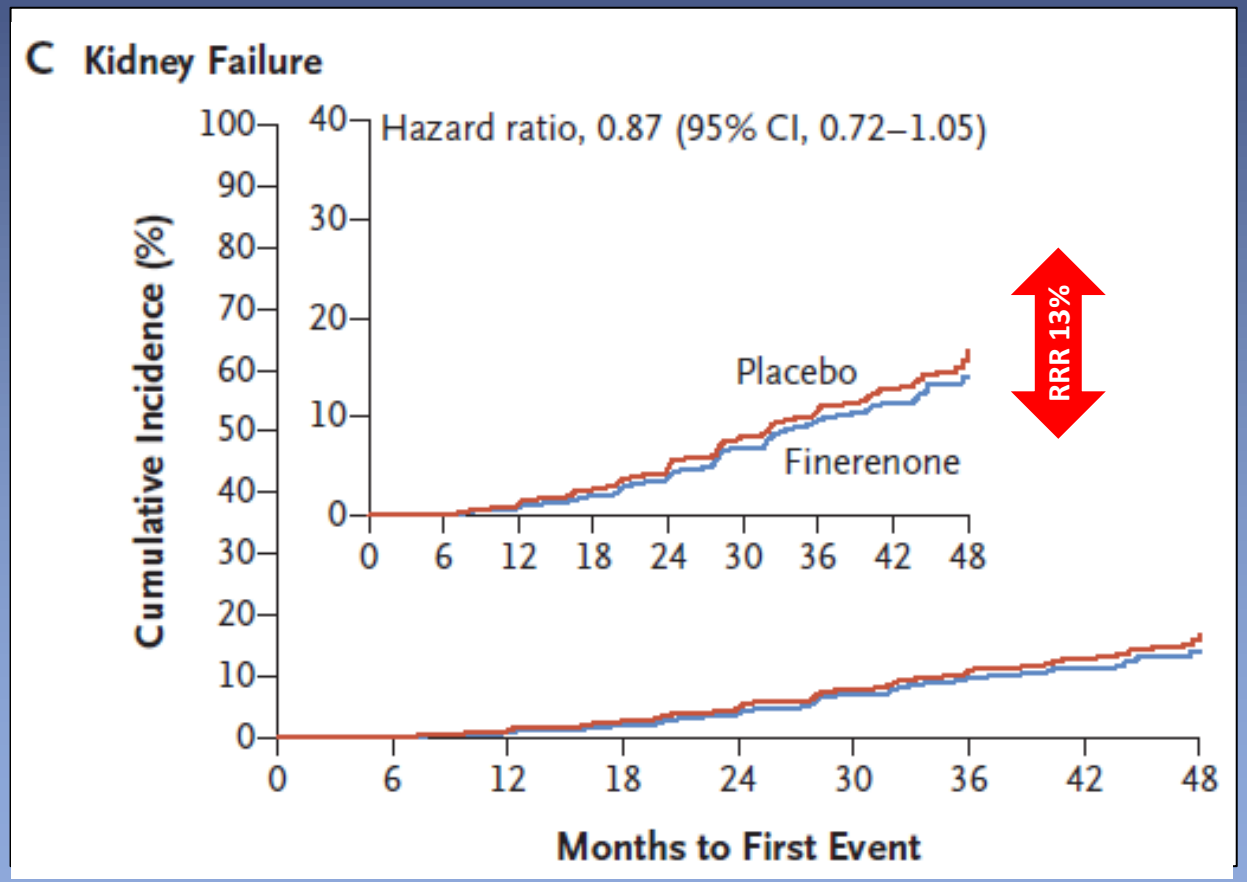
| | Spironolactone | Eplerenone | Finerenone |
|---|---|---|---|
| **Structure** | Flat (steroidal) | Flat (steroidal) | Bulky (non-steroidal) |
| **Potency to MR** | +++ | + | +++ |
| **Selectivity to MR** | + | ++ | +++ |
| **Tissue distribution** | Kidney > heart | Kidney > heart | Balanced kidney-heart |
| **Active metabolites** | +++ | - | - |
| **Half-life** | Long* | 4-6 hours | 2-3 hours |
| **Sexual side-effects** | ++ | + | - |

Am J Hypertension 2023;36:135

# Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

NEJM 2020;383:2219
Recruitment 2015-2018




Entry criteria
- ≥18 years
- With type 2 DM
- eGFR: 25-60ml/min AND uACR 3.3-33 mg/mmol, OR
  eGFR 25-75ml/min AND uACR 33-565 mg/mmol
- Maximum tolerated ACEi/ARB dose
- Potassium <4.8mmol/l

Baseline
- 66±9 years
- Mean SBP 138±14mmHg
- Urine ACR 96 (50-185) mg/mmol
- Estimated GFR 44 ± 12 ml/min
- HbA1c: 7.7±1.3%

Primary outcome (RRT, 40% decrease in eGFR or death from renal causes): HR 0.82 (95% CI 0.73-0.93)

# Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

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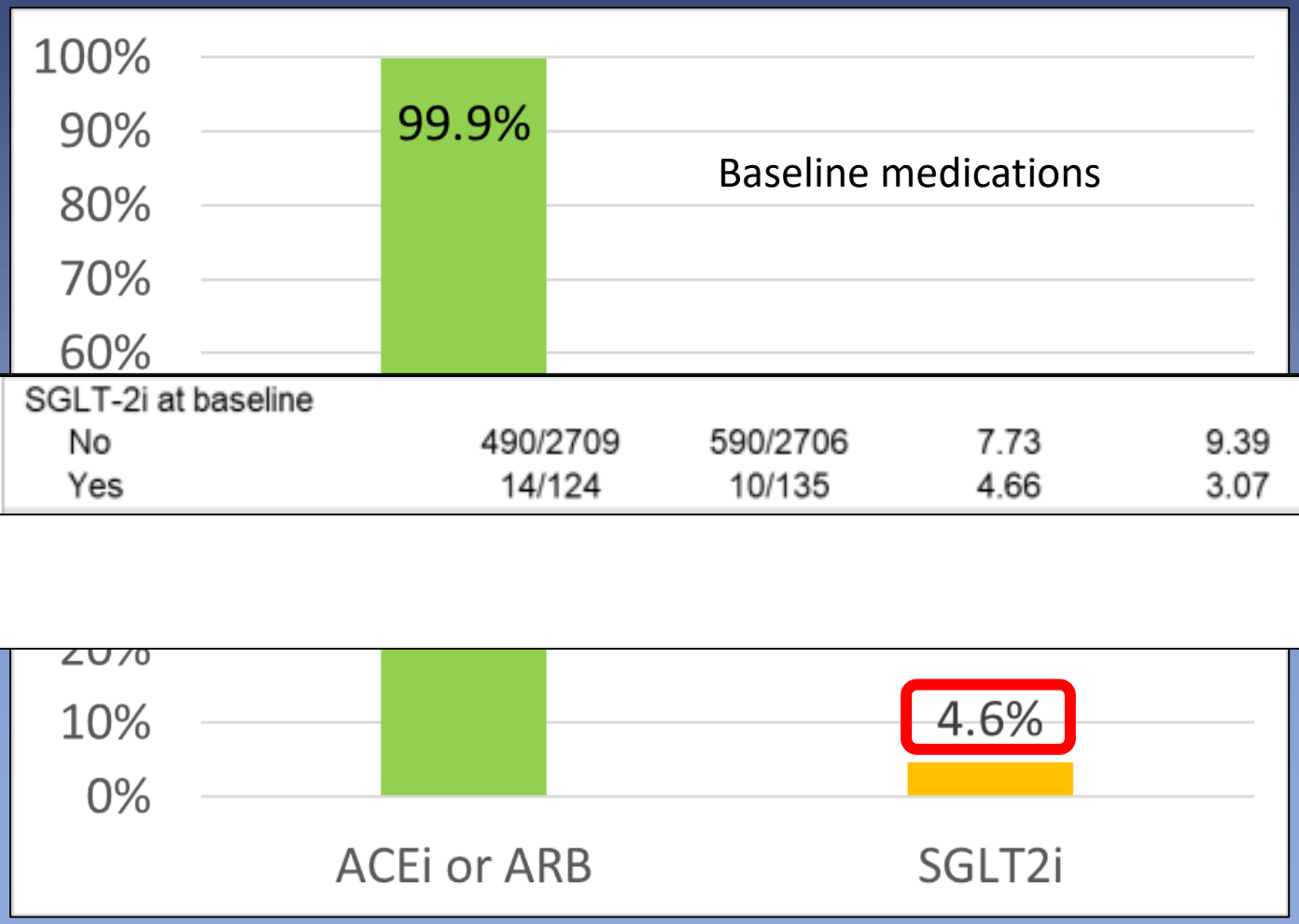

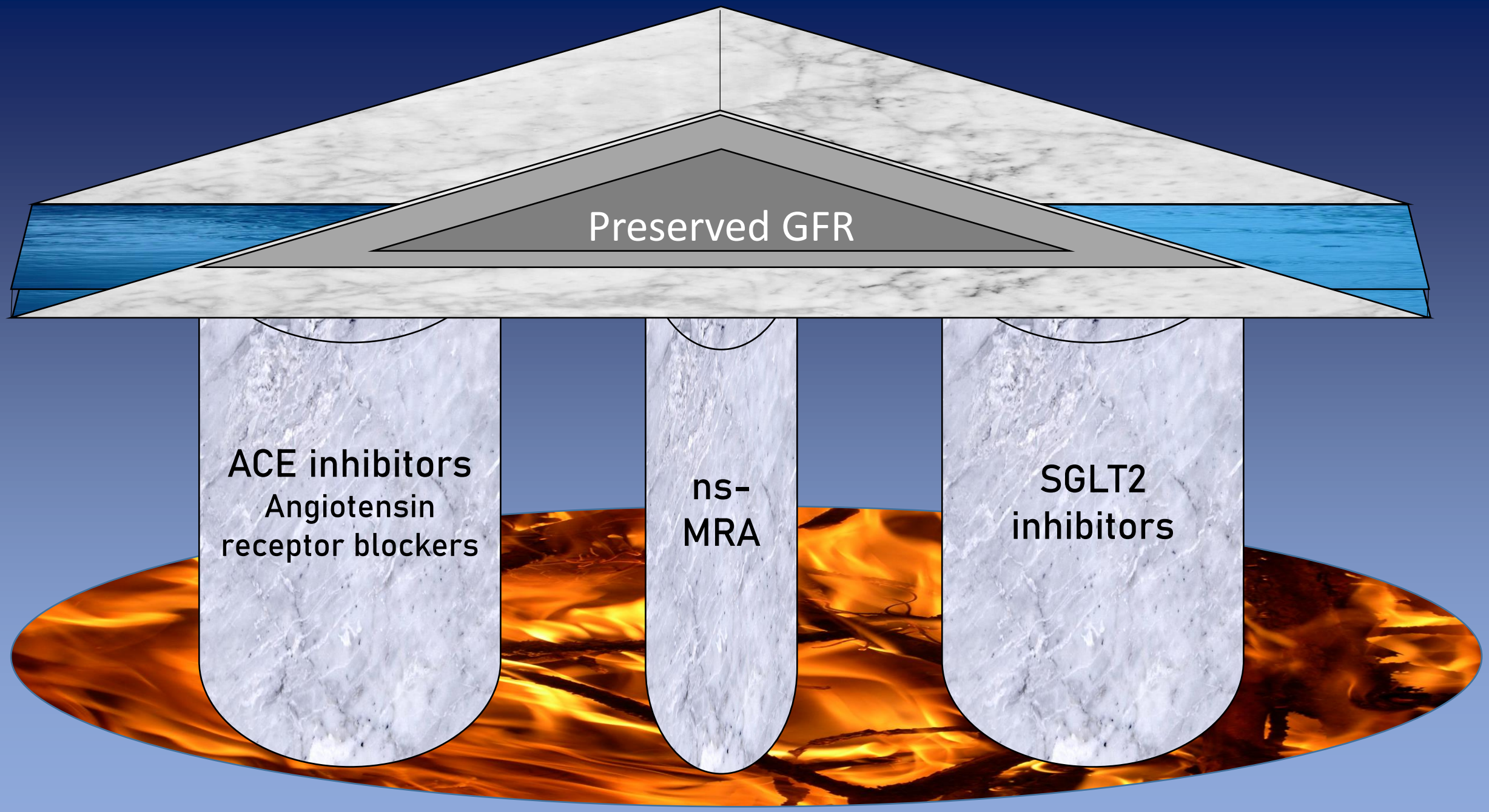
Preserved GFR
ACE inhibitors
Angiotensin receptor blockers
ns-MRA
SGLT2 inhibitors
Established kidney failure

Cardiovasc Diabetol 2021;20:14

# GLP1-RA

ORIGINAL INVESTIGATION Open Access

Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis

Takayuki Yamada[1,2†], Mako Wakabayashi[3†], Abhinav Bhalla[1], Nitin Chopra[1], Hirotaka Miyashita[1], Takahisa Mikami[4], Hiroki Ueyama[1], Tomohiro Fujisaki[5], Yusuke Saigusa[6], Takahiro Yamaji[2], Kengo Azushima[2], Shingo Urate[2], Toru Suzuki[2], Eriko Abe[2], Hiromichi Wakui[2*] and Kouichi Tamura[2]

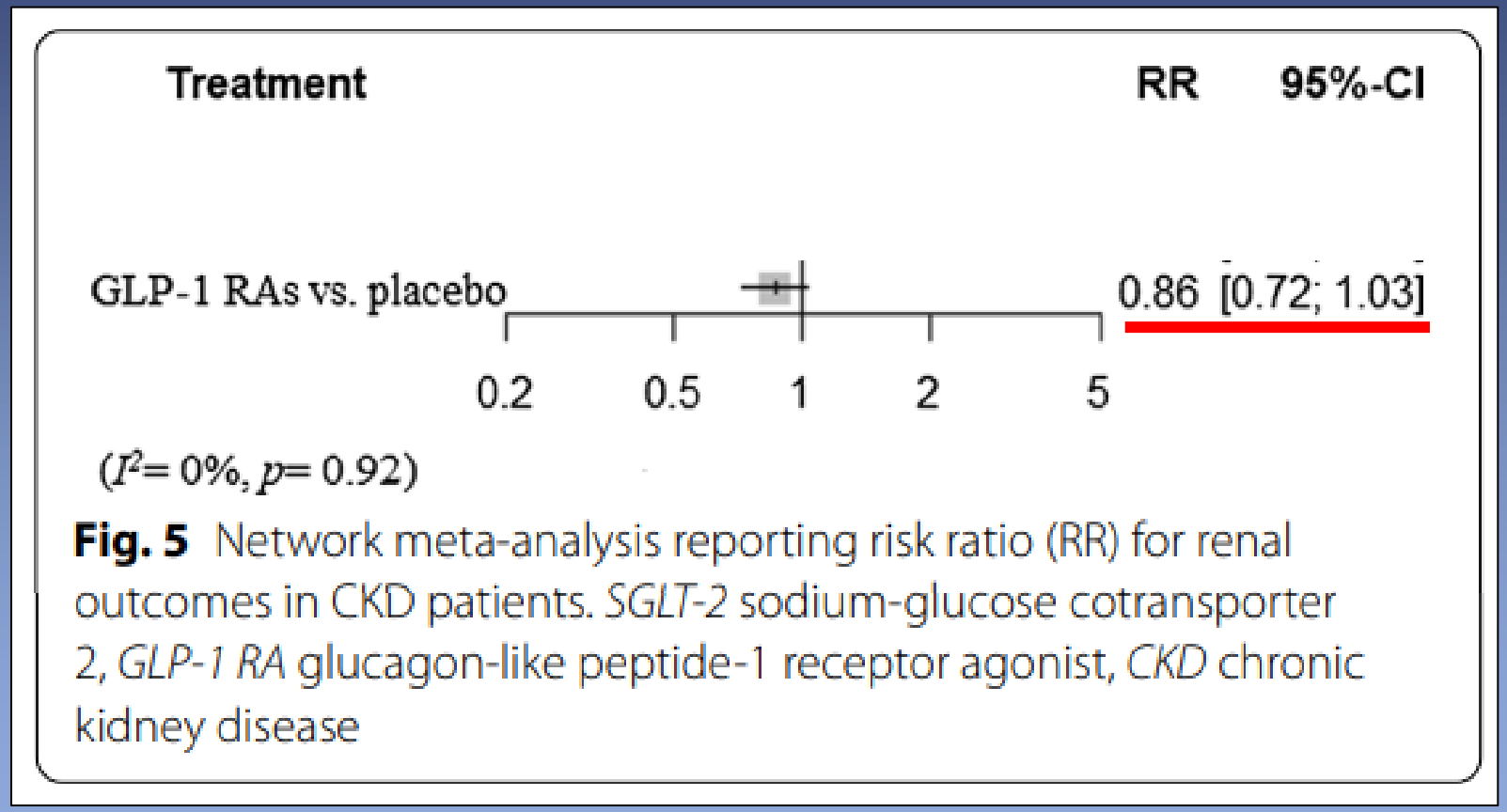


**Fig. 5** Network meta-analysis reporting risk ratio (RR) for renal outcomes in CKD patients. *SGLT-2* sodium-glucose cotransporter 2, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *CKD* chronic kidney disease

# GLP1-RA

State-of-the-Art Review

Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: A review of their kidney and heart protection

Erin D. Michos [a,*], George L. Bakris [b], Helena W. Rodbard [c], Katherine R. Tuttle [d,e]

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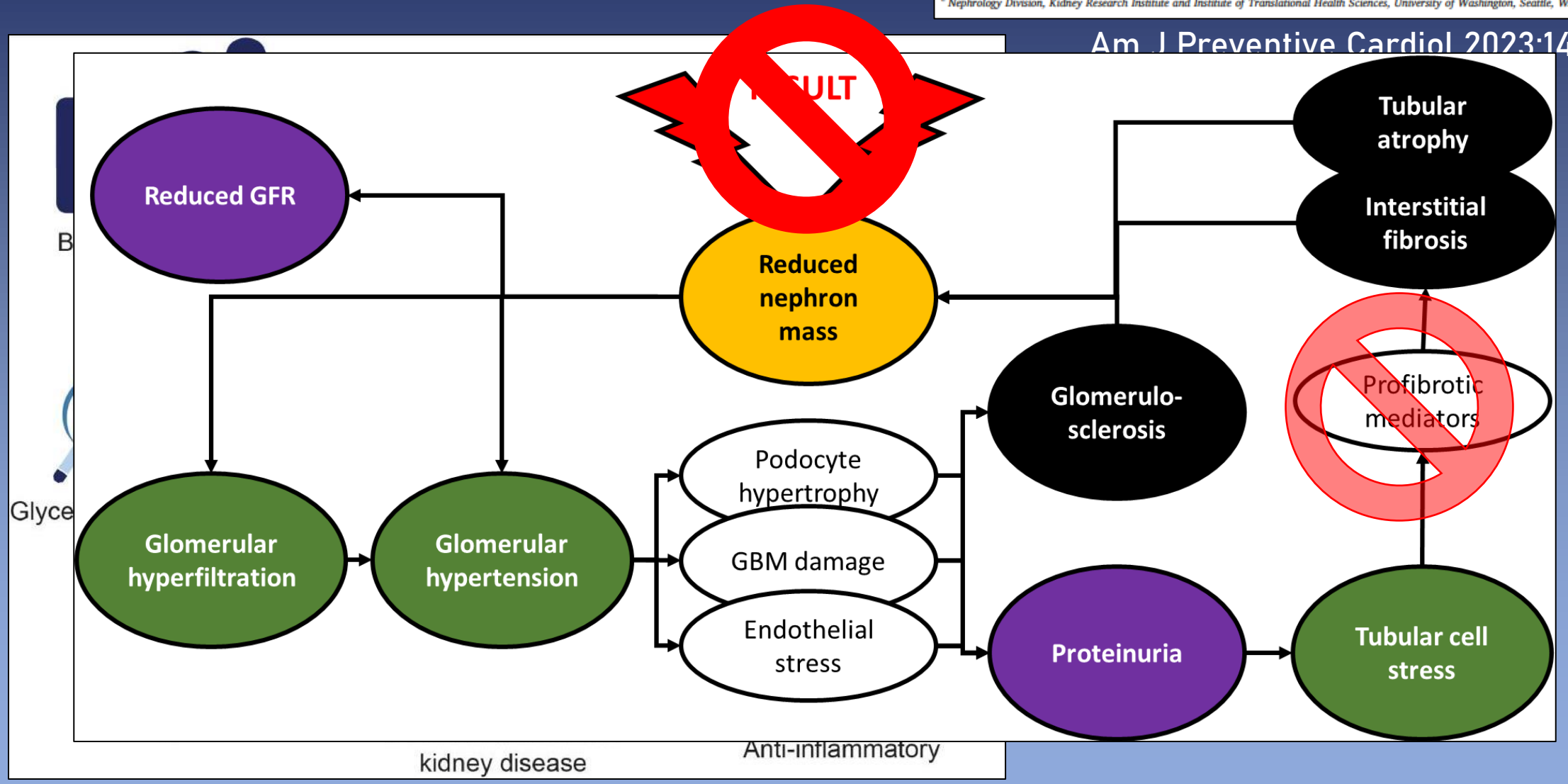
[b] Department of Medicine, University of Chicago Medicine, Chicago, IL, United States
[c] Endocrine and Metabolic Consultants, Rockville, MD, United States
[d] Providence Medical Research Center, Providence Health Care, Spokane, WA, United States
[e] Nephrology Division, Kidney Research Institute and Institute of Translational Health Sciences, University of Washington, Seattle, WA, United States

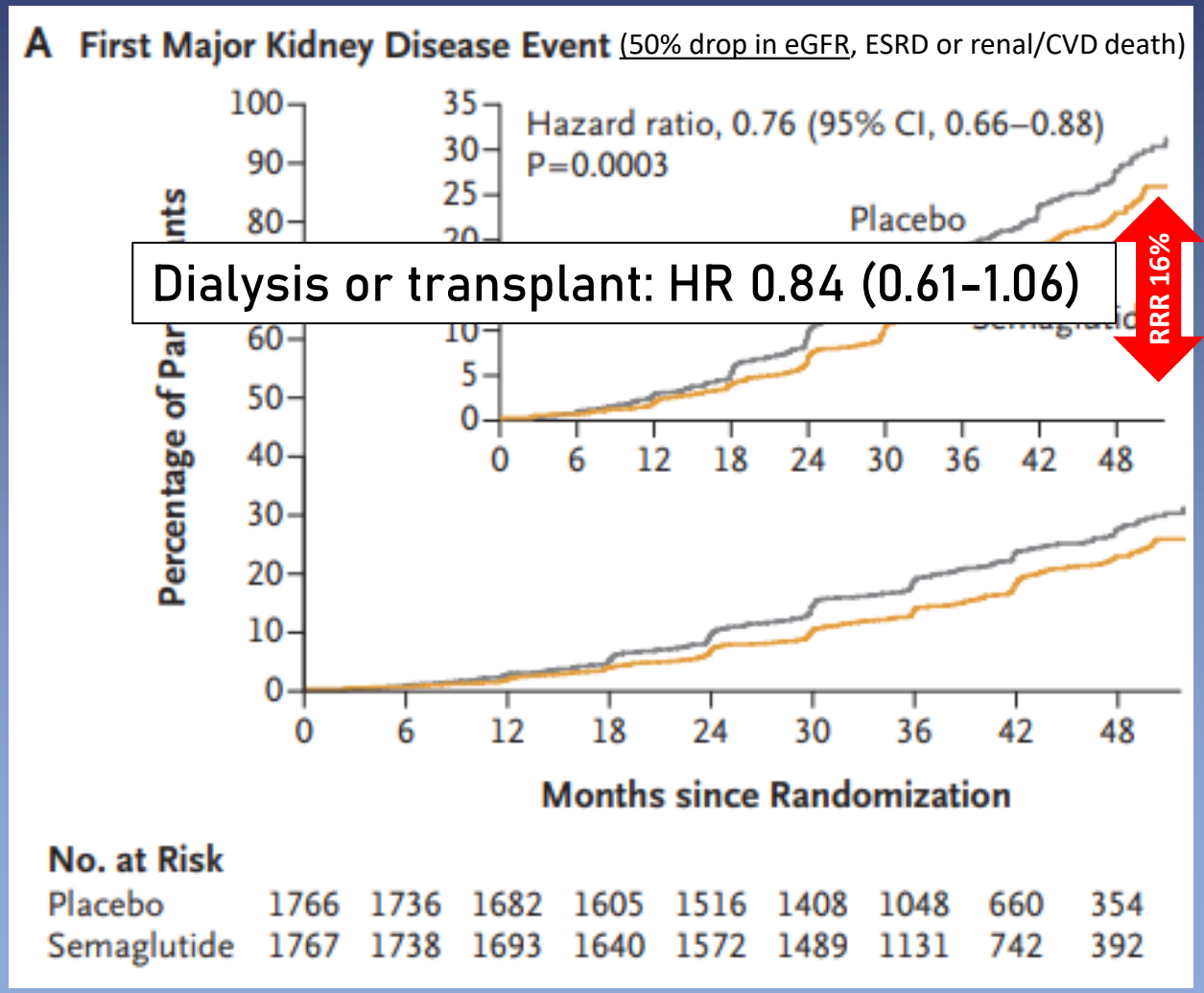
Am J Preventive Cardiol 2023;14:100502



# Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

NEJM 2024;391:109
Recruitment 2019-2021




Entry criteria
- ≥18 years
- With type 2 DM
- eGFR: 25-50ml/min AND uACR 11-565 mg/mmol, OR
  eGFR 25-75ml/min AND uACR 33-565 mg/mmol
- Maximum tolerated ACEi/ARB dose

Baseline
- 67±9 years
- Mean BP 139/76 mmHg
- Median urine ACR 64 mg/mmol
- Estimated GFR 47 ± 15 ml/min
- HbA1c: 7.8±1.3%

# Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

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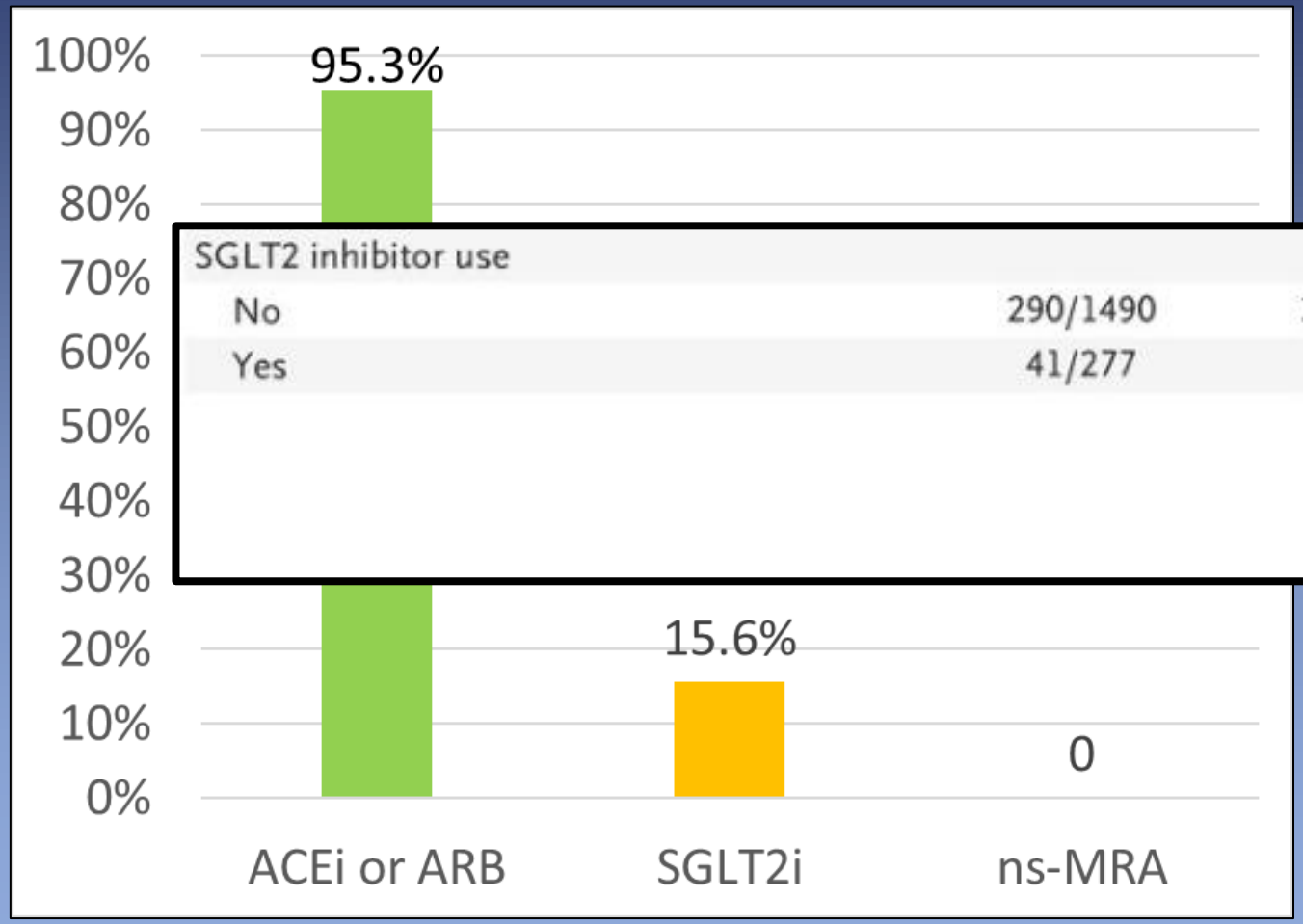
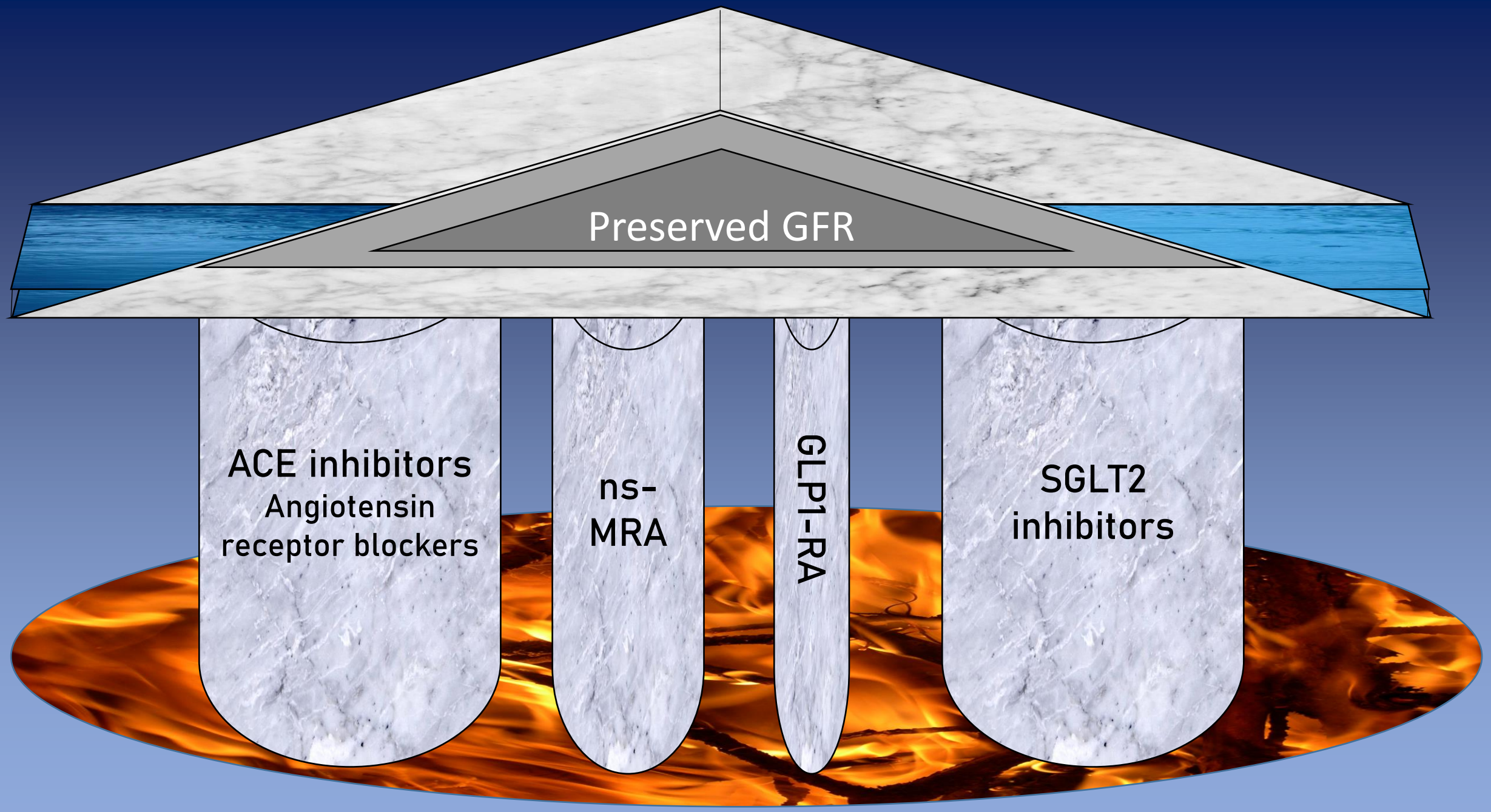



Preserved GFR
ACE inhibitors
Angiotensin receptor blockers
ns-MRA
GLP1-RA
SGLT2 inhibitors
Established kidney failure

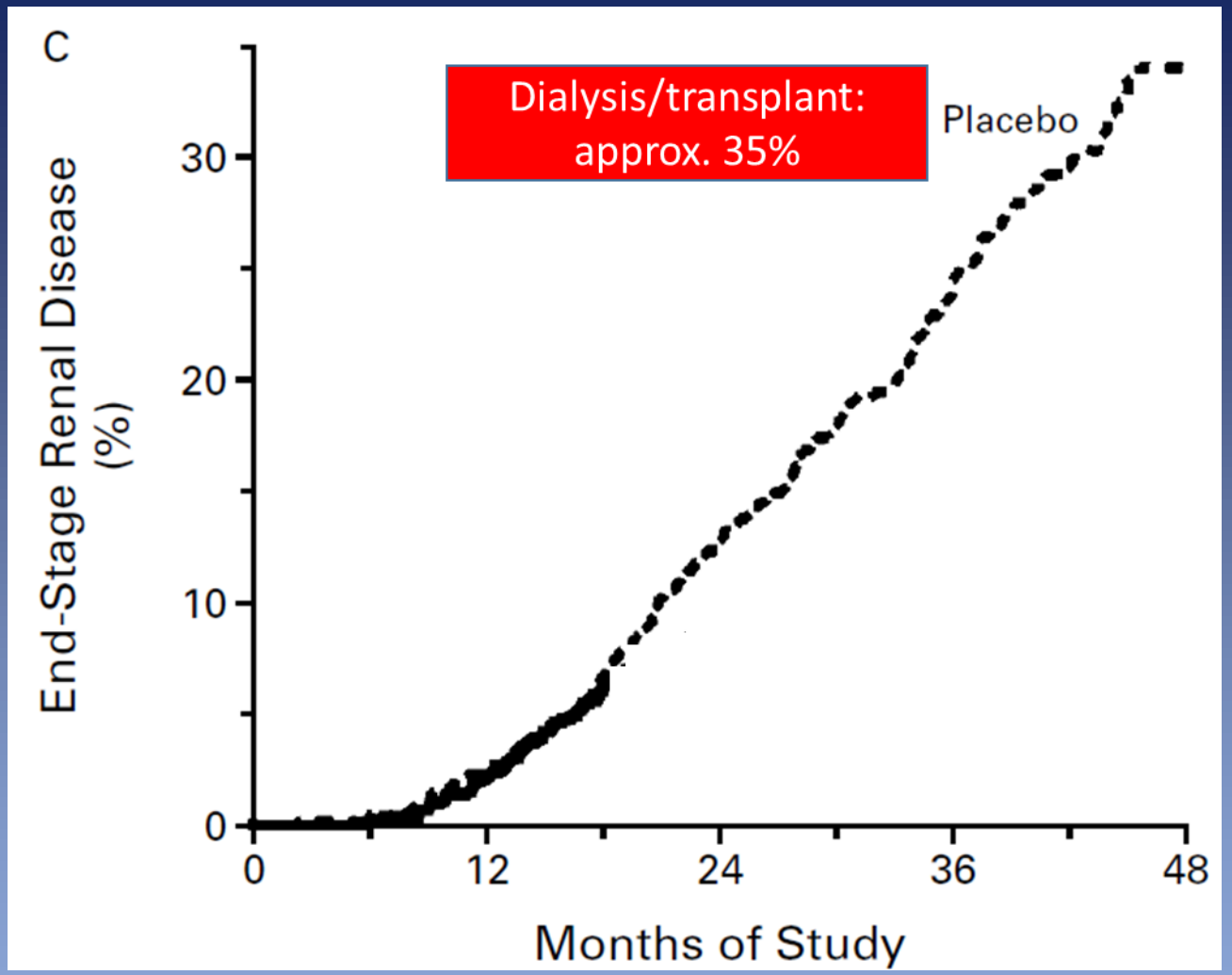

# What is their risk of end stage renal failure in the next 4-5 years?


45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78

45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78

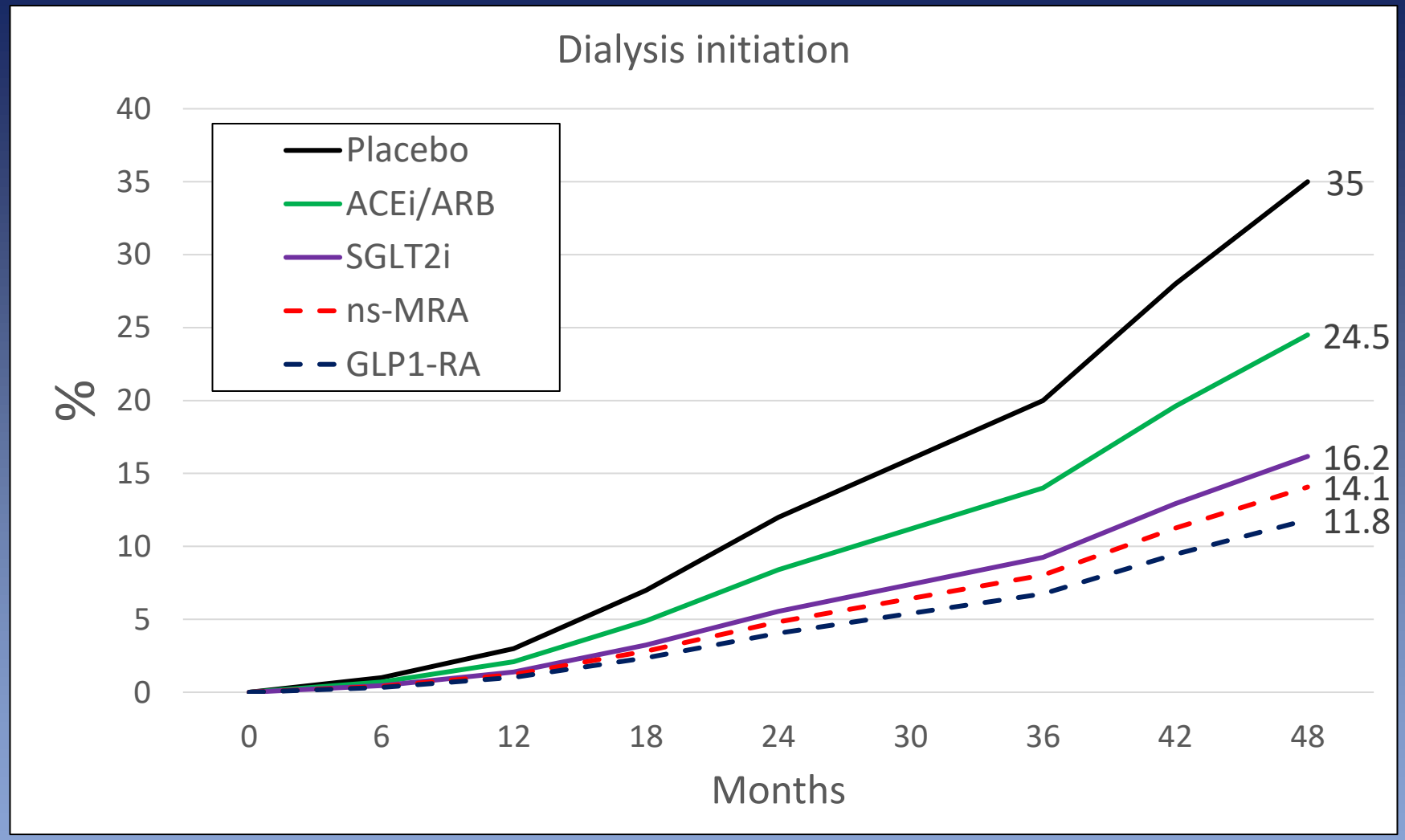
Images: shutterstock.com, istockphoto.com

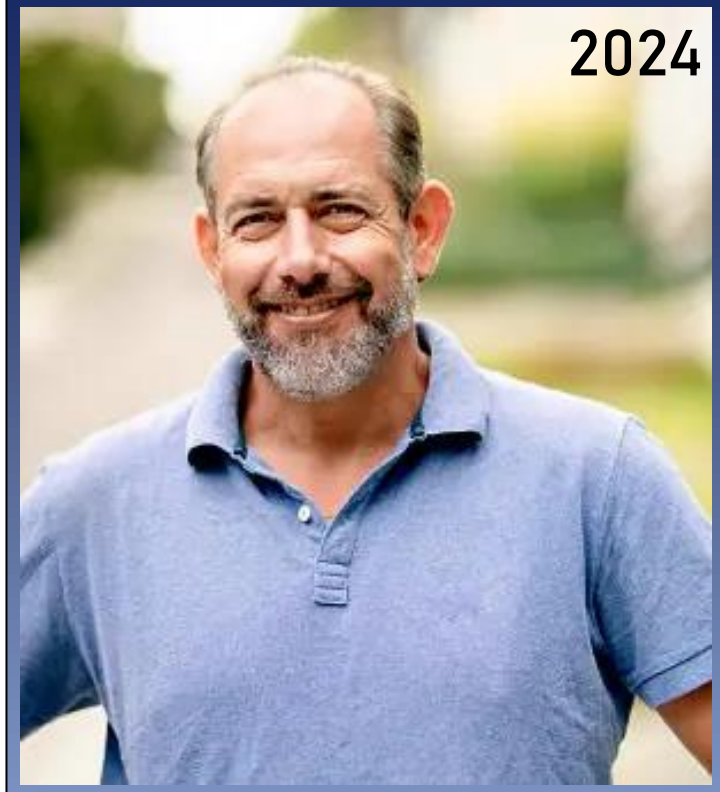

45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78




NEJM 2001;345:861
Image: shutterstock.com

Images: istockphoto.com




45 years old
Diabetes
eGFR 52ml/min
Urine ACR 167mg/mmol
BP 128/78

Limitations and assumptions
30% RRR ACEi/ARB, 34% RRR SGLT2i, 13% RRR ns-MRA, 16% RRR GLP1-RA
Published evidence to support cumulative benefits of ns-MRA or GLP-RA on top of ACEi/ARB+SGLT2i is minimal
Tolerance of each medication limited by cumulative side effect profiles, including hyperkalaemia, AKI episodes, hypotension

NEJM 2001;345:861
NEJM 2020;383:1436
NEJM 2020;383:2219
NEJM 2024;391:109

# Where are we now?

Proteinuric Kidney Disease*
Diabetic Kidney Disease

| | Evidence | License | NICE approval | Guidelines |
|---|---|---|---|---|
| ACEi/ARB | ✓ | ✓ | ✓ | ✓ |
| SGLT2i | ✓ | ✓ | ✓ | ✓ |
| Finerenone | ✓ | ✓ | ✓ | ✓ |
| Semaglutide | ✓ | X | X | X |

*Empagliflozin evidence and license includes eGFR 20-45 without proteinuria

# Where are we heading?

Disease-specific therapies (eg, IgAN, lupus)

Endothelin-receptor antagonists

Aldosterone synthase inhibitors

ns-MRA in non-diabetic kidney disease

Gene therapy for inherited disease (eg Alport, ADPKD)

https://clinicaltrials.gov/search?cond=proteinuria. Accessed Sept 2nd 2024

- **Intervention 1. Early/improved diagnosis:** This intervention targets underserved populations through outreach programmes to improve screening opportunities and increase early diagnosis and is illustrative of the benefits which can be achieved through well-targeted early/improved diagnosis in general.

- **Intervention 2. Improved CKD management:** This intervention targets eligible patients with chronic kidney disease who are either untreat or not receiving standard care according to clinical guidelines (e.g. adequate blood pressure management).

- **Intervention 3. Use of SGLT-2 inhibitors:** This intervention aims to increase uptake of new medications such as sodium-glucose tran protein 2 (SGLT-2) inhibitors to reduce cardiovascular events and progression to end-stage kidney disease.

- **Intervention 4. Increased rates of transplantation:** This interventio models the impact of increased outreach and awareness to increa pre-emptive live donor transplants. It is illustrative of the benefits of improving transplantation rates more generally.

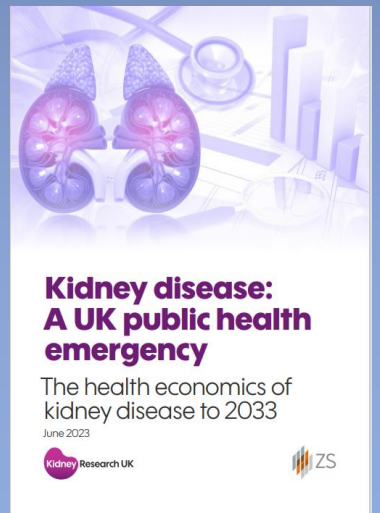
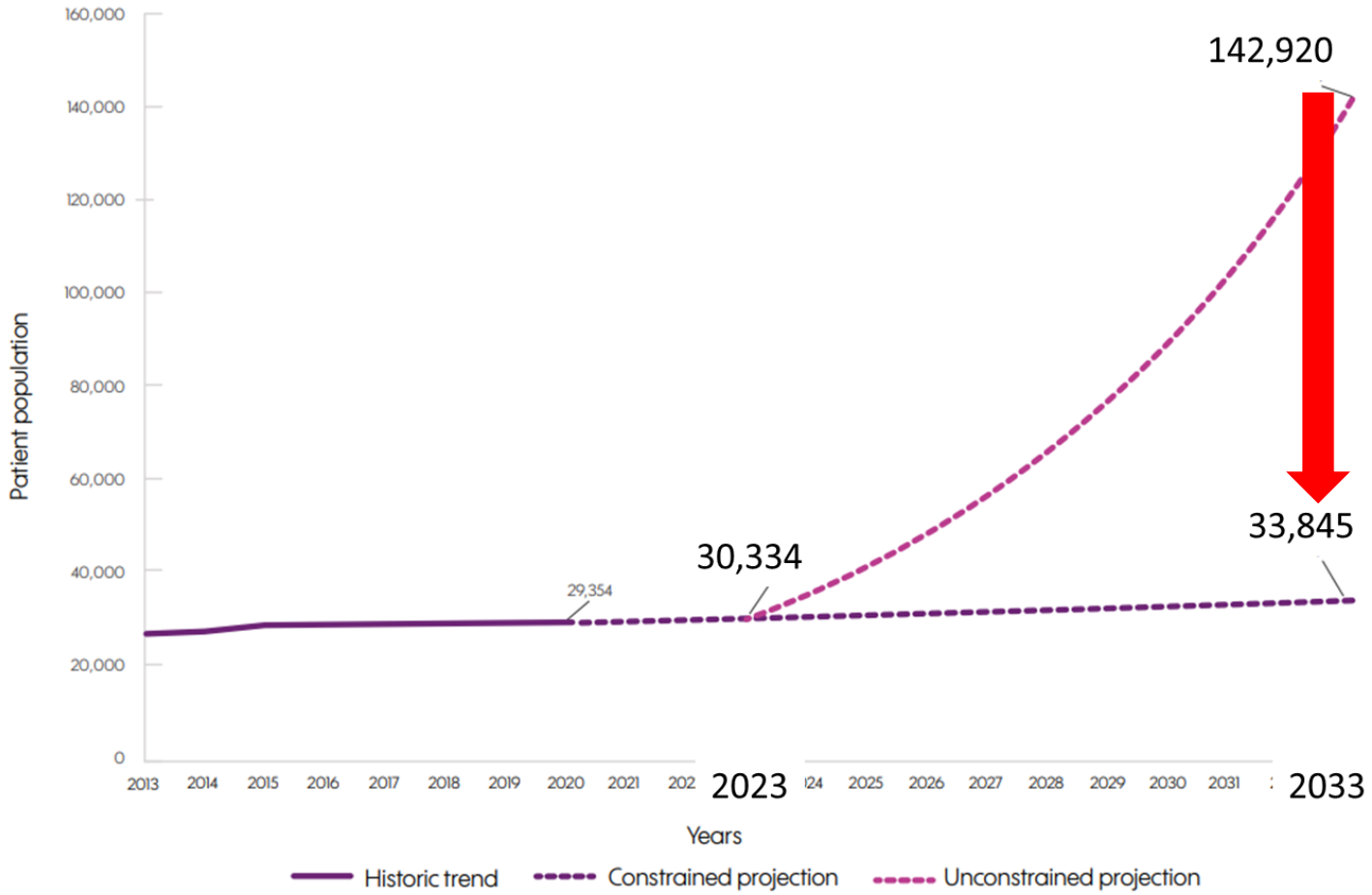



Figure 12. Constrained vs unconstrained projections of dialysis in adults with ESKD in the UK



# Summary

- The incidence and prevalence of patients requiring dialysis are predicted to escalate rapidly
- Earliest recognition of CKD and initiation of protective agents permits the greatest protective effect
- ACEi/ARB and SGLT2i have a major effect on reducing patients' progression to established kidney failure
- ACEi/ARB and SGLT2i should be paused during dehydrating illnesses but instructions to restart them are essential
- Finerenone and semaglutide may offer further renal protection for patients with diabetic kidney disease