Novel therapies in DKD

Rajiv Agarwal MD

Professor of Medicine

Indiana University

KDIGO

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Overview of therapeutic area

- Approved drugs
  - Captopril for Type 1 diabetes mellitus and CKD
  - Losartan and Irbesartan for Type 2 DN
- Kidney neutral drugs
  - Ezetemibe-Simvastatin (SHARP)
  - Near normal hemoglobin with Darbepoeitin (TREAT)
- Drug trials that were terminated early
  - Bardoxolone (NRF2 activator)
  - Combination ACE inhibitor – ARB (VA-Nephron D)
  - Sulodexide
- Abandoned (kidney) drug
  - Aleglitazaar

The Big 3 phase III trials

- Endothelin: Atrasentan
- SGLT2: Canagliflozin
- DPP4: Linagliptin

The Big 3 phase III trials

- Endothelin: Atrasentan
- SGLT2: Canagliflozin
- DPP4: Linagliptin

Direct Action of Endothelin-1 on Podocytes Promotes Diabetic Glomerulosclerosis

Olivia Lenoir,*† Marine Milon,*† Anne Virsolvy,‡ Carole Hénique,*† Alain Schmitt,†§‖ Jean-Marc Massé,†§‖ Yuri Kotelevtsev,¶** Masashi Yanagisawa,†† David J. Webb,¶ Sylvain Richard,‡ and Pierre-Louis Tharaux*†‡‡

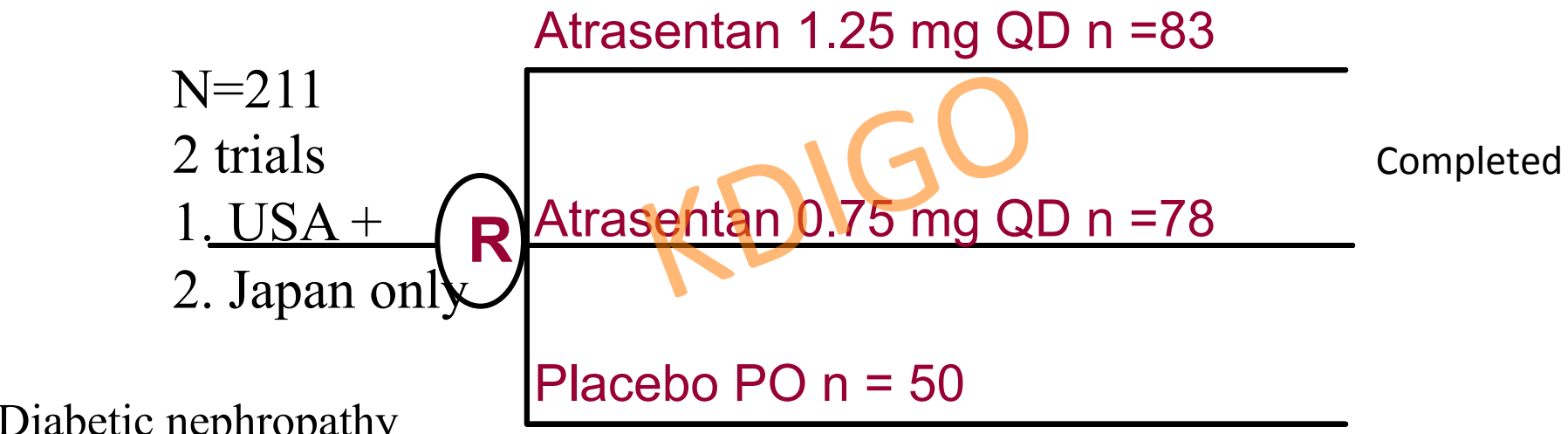
*Paris Cardiovascular Research Centre, Institut National de la Santé et de la Recherche Médicale, Paris, France; †Université Paris Descartes, Sorbonne Paris Cité, Paris, France; ‡Physiologie et Médecine expérimentale du Cœur et des Muscles, Institut National de la Santé et de la Recherche Médicale U1046, Université Montpellier 1, Université Montpellier 2, Montpellier, France; §Transmission Electron Microscopy Platform, Institut National de la Santé et de la Recherche Médicale U1016, Cochin Institut, Paris, France; ‖Centre National de la Recherche Scientifique UMR81044, Paris, France; ¶The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; **Pushchino State Institute for Natural Sciences, Pushchino, Moscow Region, Russian Federation; ††University of Texas Southwestern Medical Center, Dallas, Texas; and ‡‡Nephrology Service, Georges Pompidou European Hospital, Assistance Publique Hopitaux de Paris, Paris, France

ABSTRACT

The endothelin system has emerged as a novel target for the treatment of diabetic nephropathy. Endothelin-1 promotes mesangial cell proliferation and sclerosis. However, no direct pathogenic effect of endothelin-1 on podocytes has been shown *in vivo* and endothelin-1 signaling in podocytes has not been investigated. This study investigated endothelin effects in podocytes during experimental diabetic nephropathy. Stimulation of primary mouse podocytes with endothelin-1 elicited rapid calcium transients mediated by endothelin type A receptors (ETARs) and endothelin type B receptors (ETBRs). We then generated mice with a podocyte-specific double deletion of ETAR and ETBR (NPHS2-Cre×*Ednra*$^{lox/lox}$×Ednrb$^{lox/lox}$ [Pod-ETRKO]). *In vitro*, treatment with endothelin-1 increased total β-catenin and phospho-NF-κB expression in wild-type glomeruli, but this effect was attenuated in Pod-ETRKO glomeruli. After streptozotocin injection to induce diabetes, wild-type mice developed mild diabetic nephropathy with microalbuminuria, mesangial matrix expansion, glomerular basement membrane thickening, and podocyte loss, whereas Pod-ETRKO mice presented less albuminuria and were completely protected from glomerulosclerosis and podocyte loss, even when uninephrectomized. Moreover, glomeruli from normal and diabetic Pod-ETRKO mice expressed substantially less total β-catenin and phospho-NF-κB compared with glomeruli from counterpart wild-type mice. This evidence suggests that endothelin-1 drives development of glomerulosclerosis and podocyte loss through direct activation of endothelin receptors and NF-κB and β-catenin pathways in podocytes. Notably, both the expression and function of the ETBR subtype were found to be important. Furthermore, these results indicate that activation of the endothelin-1 pathways selectively in podocytes mediates pathophysiologic crosstalk that influences mesangial architecture and sclerosis.

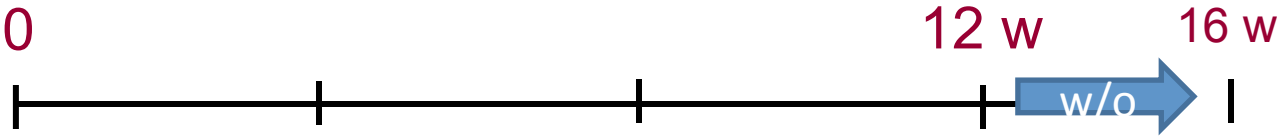
J Am Soc Nephrol 25: 1050–1062, 2014. doi: 10.1681/ASN.2013020195

Phase II study of Atrasentan in Diabetic nephropathy (RADAR)



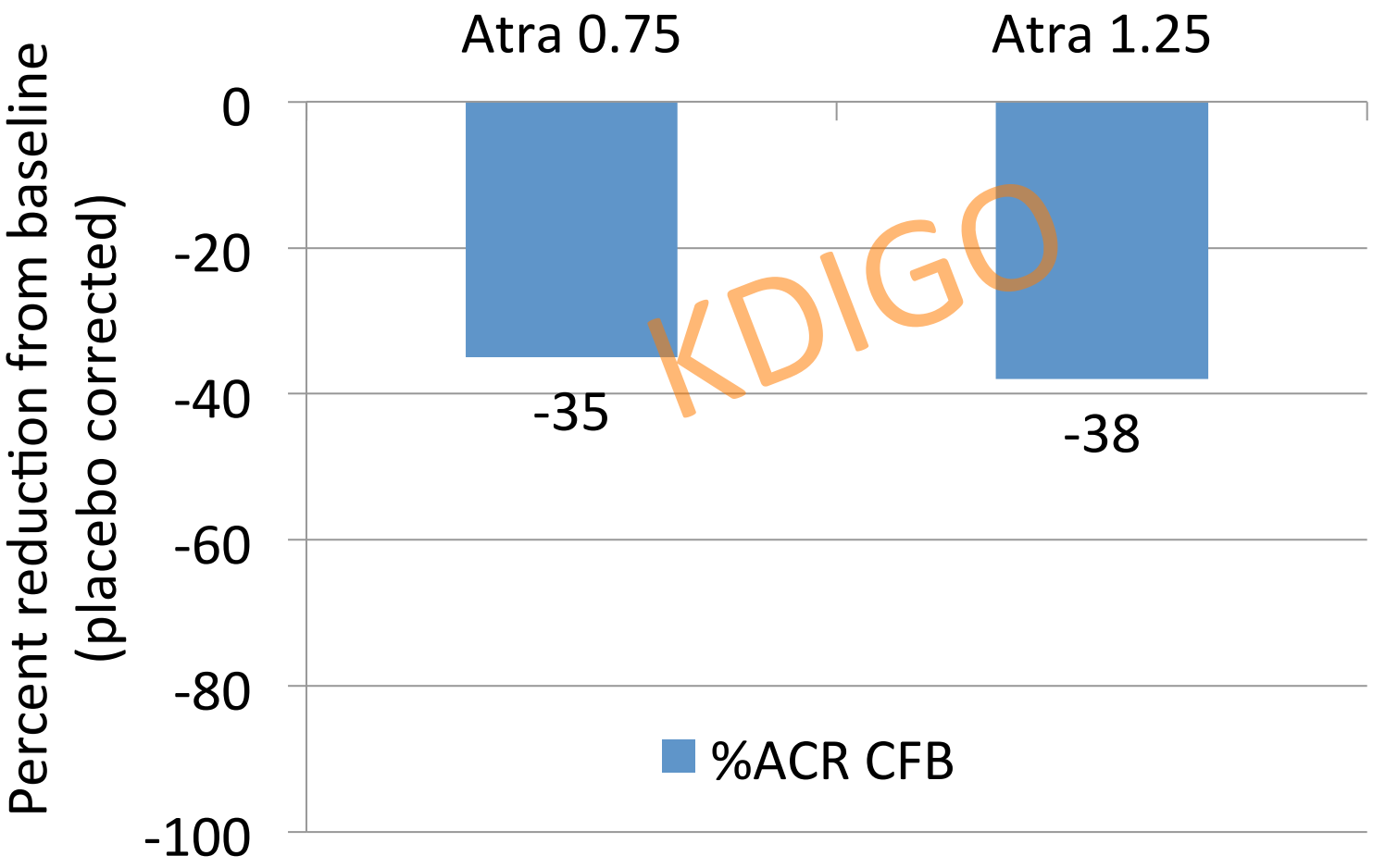
Diabetic nephropathy
- UACR: 300-3500 mg/d
- eGFR 30-75
- BNP <200
- no heart failure.
- Max ACEi

Primary end-point: %CFB ACR at 12w

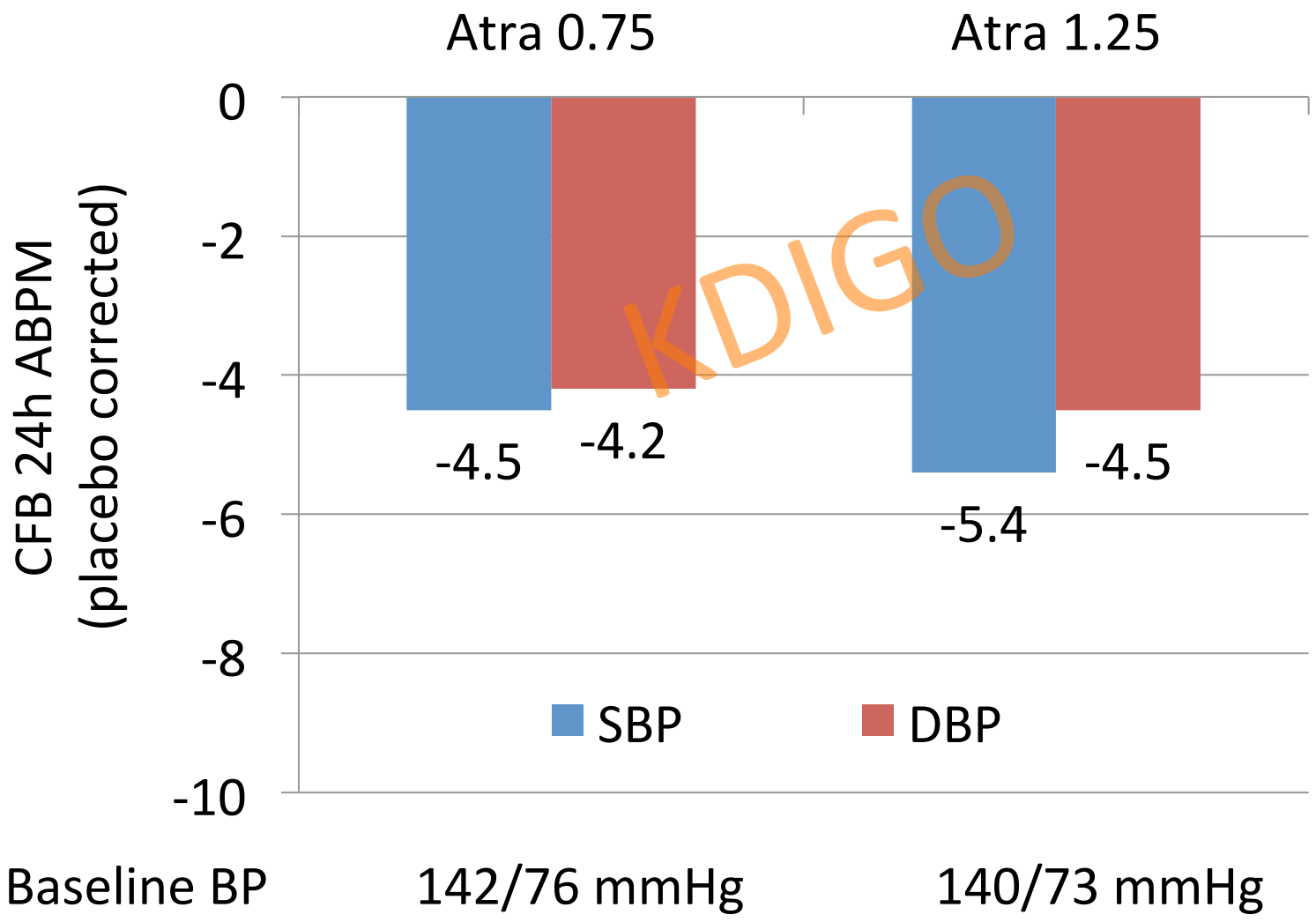


De Zeeuw D et al, JASN 2014

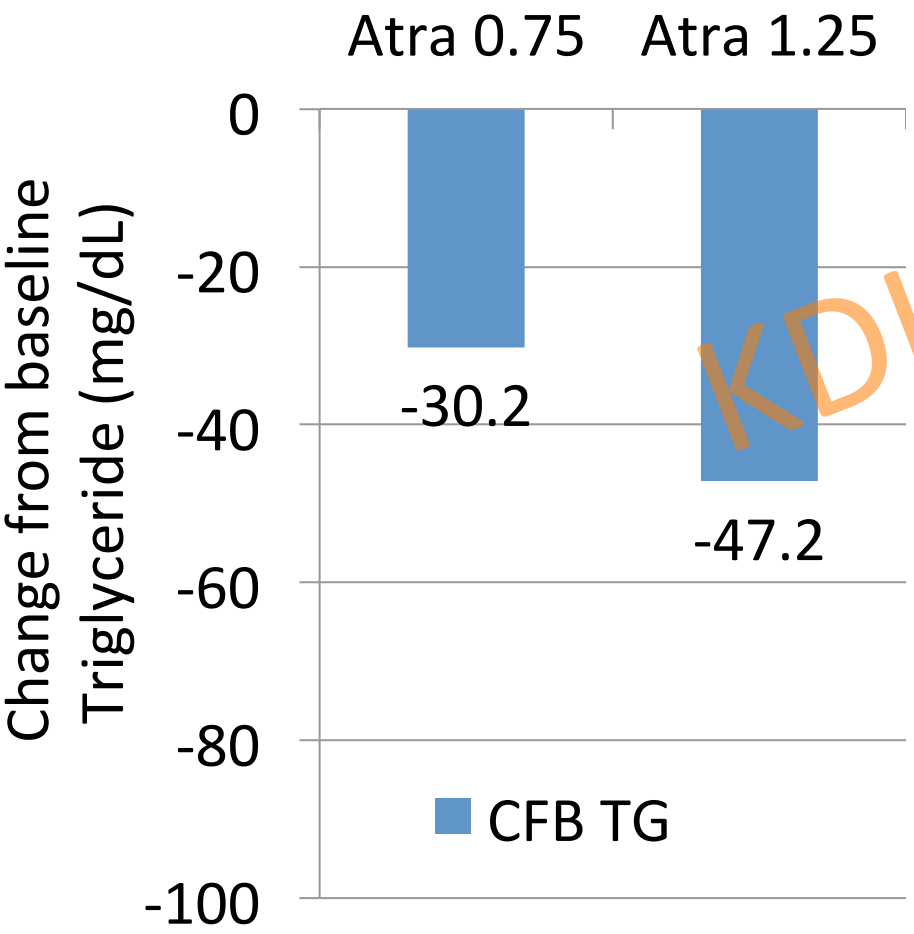
Atrasentan elicited a large reduction in albuminuria at 12 weeks



Significant reduction in systolic and diastolic ABPM at 12 weeks



Improvement in TG at 12 weeks

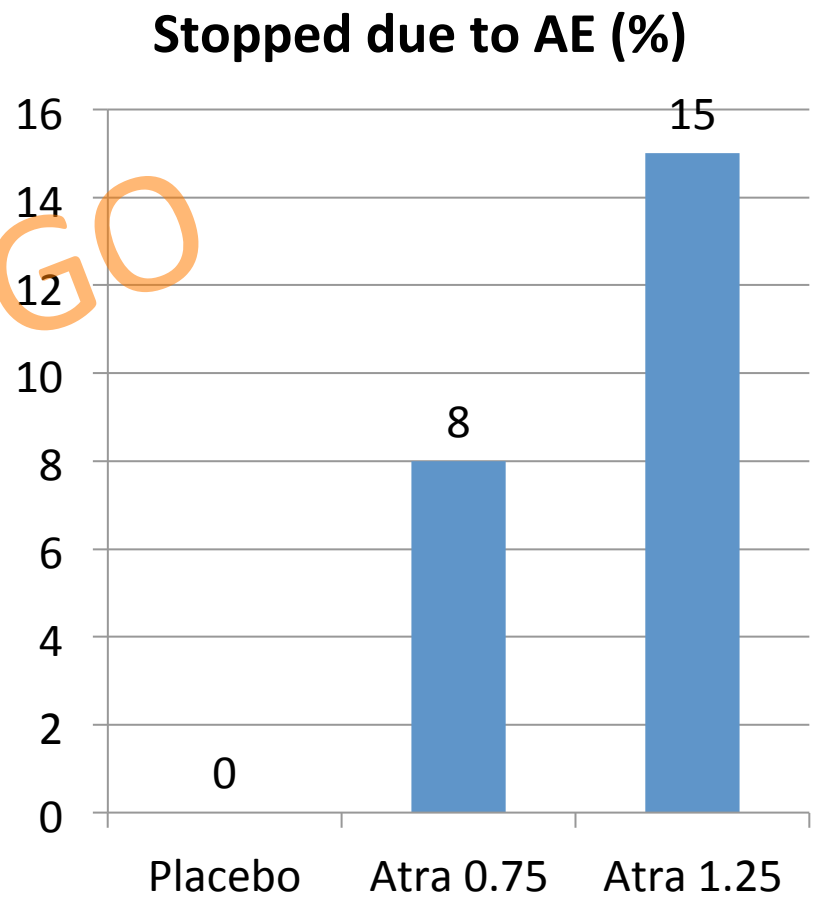


- Reduction in LDL-cholesterol 14.6 mg/dL (from BL of 88 mg/dL)
- HDL cholesterol did not change.

Stopping the drug for 4 weeks restored pretreatment levels.

Atrasentan side effects

- Weight gain seen in a dose-dependent and time-dependent manner.
- Drop in Hgb seen as an AE.
- 1 heart failure each in placebo and drug groups.



ASCEND trial

- Phase 3 trial in diabetic nephropathy type 2
- Drug: Avosentan, n=1392
- Outcomes: Doubling of SCR, ESRD, Death
- Premature termination
  - More heart failure in treated group

Mann JF JASN 21: 523-535, 2010

Study Of Diabetic Nephropathy With Atrasentan (SONAR)

- N=4148, sites=590
- Inclusion
  - eGFR 25-75 (eGFR 60-75 = 10% total)
  - UACR 300-5000 mg/g
  - BNP ≤ 200 pg/mL
  - SBP 110-160 mmHg
  - Diuretic use
- Exclusion
  - documented diagnosis of heart failure
  - previous hospitalization for heart failure
  - Symptoms of heart failure
- For double-blind treatment after enrichment
  - Weight change <3 kg
  - Absolute BNP <300 pg/mL
  - No AKI

Primary end point: 2XCr, ESRD, Renal/CV death

Clinicaltrials.gov NCT01858532

Likelihood of success

PROS

- *Promising* results in Phase 2 study
  - Large reduction in UACR.
  - Benefits on BP and lipids.
- More *selective* ETA inhibitor than prior drug. ETB blockade may be important for Na retention.
- *Enrichment* design may reduce the number of participants needed to be randomized.

CONS

- Narrow therapeutic window
  - Heart failure with avosentan
- May not be broadly applicable to patients with DN (excludes elevated BNP)
- Uninhibited ETB, animal studies suggest that this may be important.

The Big 3 phase III trials

- Endothelin: Atrasentan
- SGLT2: Canagliflozin
- DPP4: Linagliptin

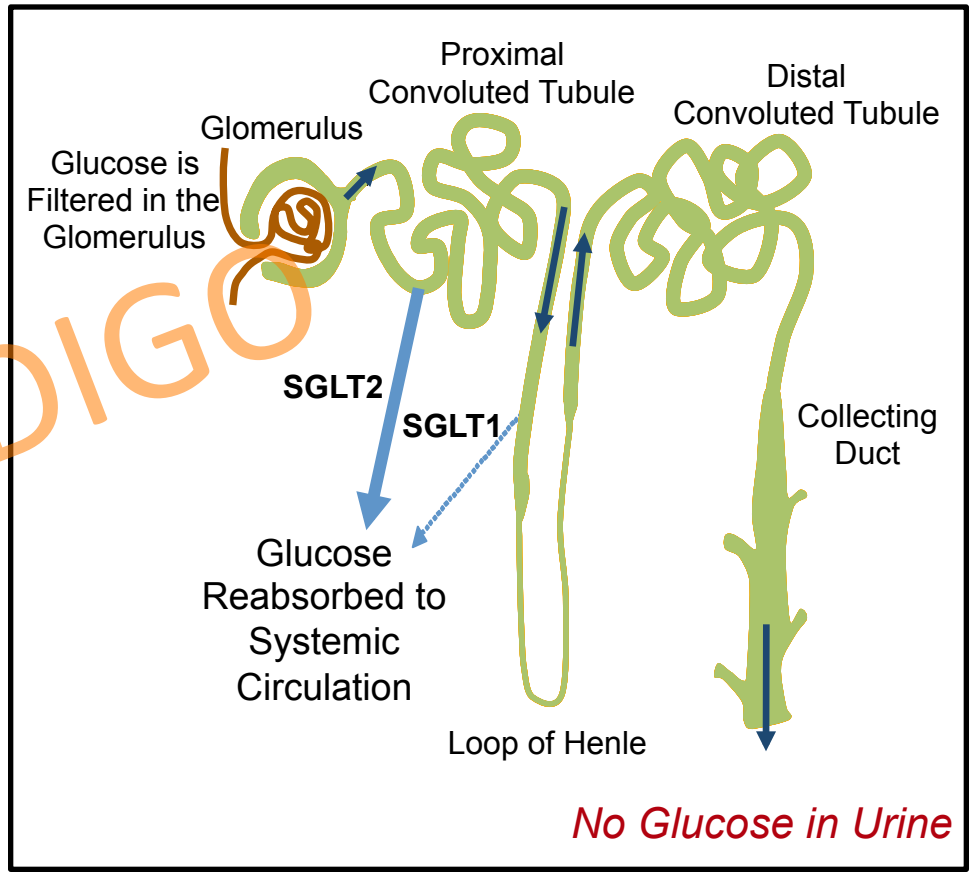
SGLT2 inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin

Sodium glucose-linked transporter-2 (SGLT2)

Key Renal Transporter Reabsorbing Filtered Glucose Back into Systemic Circulation

- SGLT2
  - Mostly kidney
  - 97% of renal glucose reabsorption
- SGLT1
  - Mostly gut
  - 3% of renal glucose reabsorption

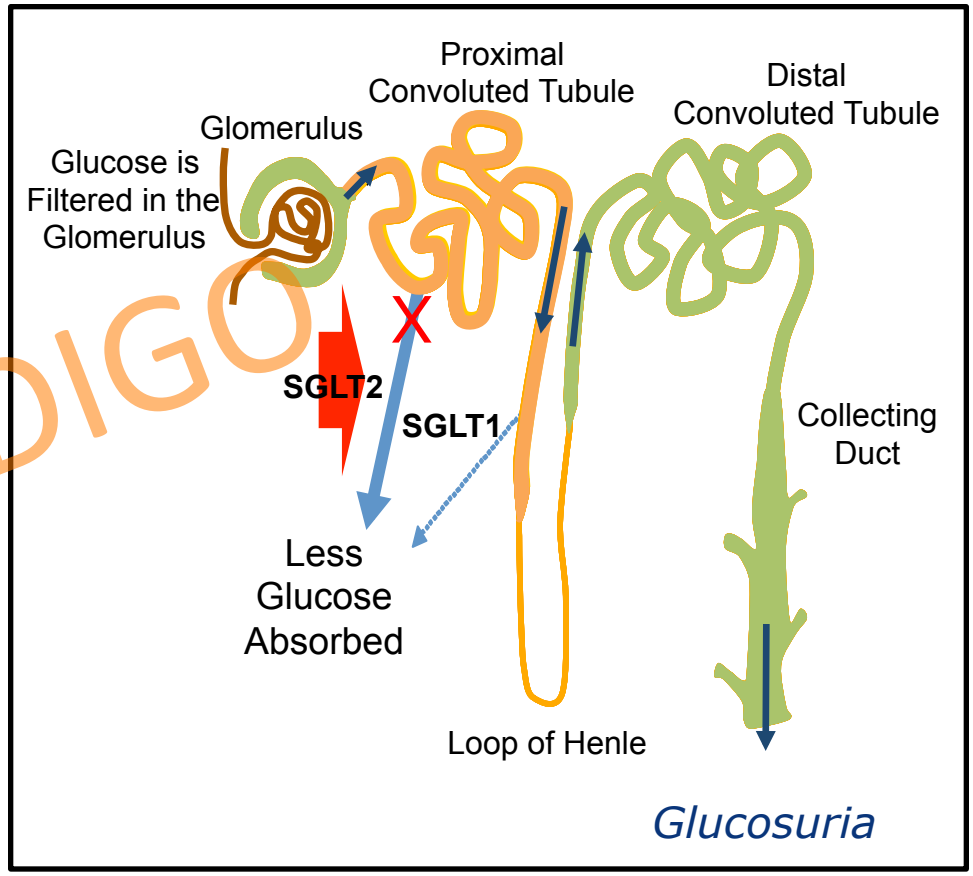


SGLT2 inhibition wastes 50-60% of the filtered glucose load.
This is due to increase in SGLT1 expression in the more distal nephron

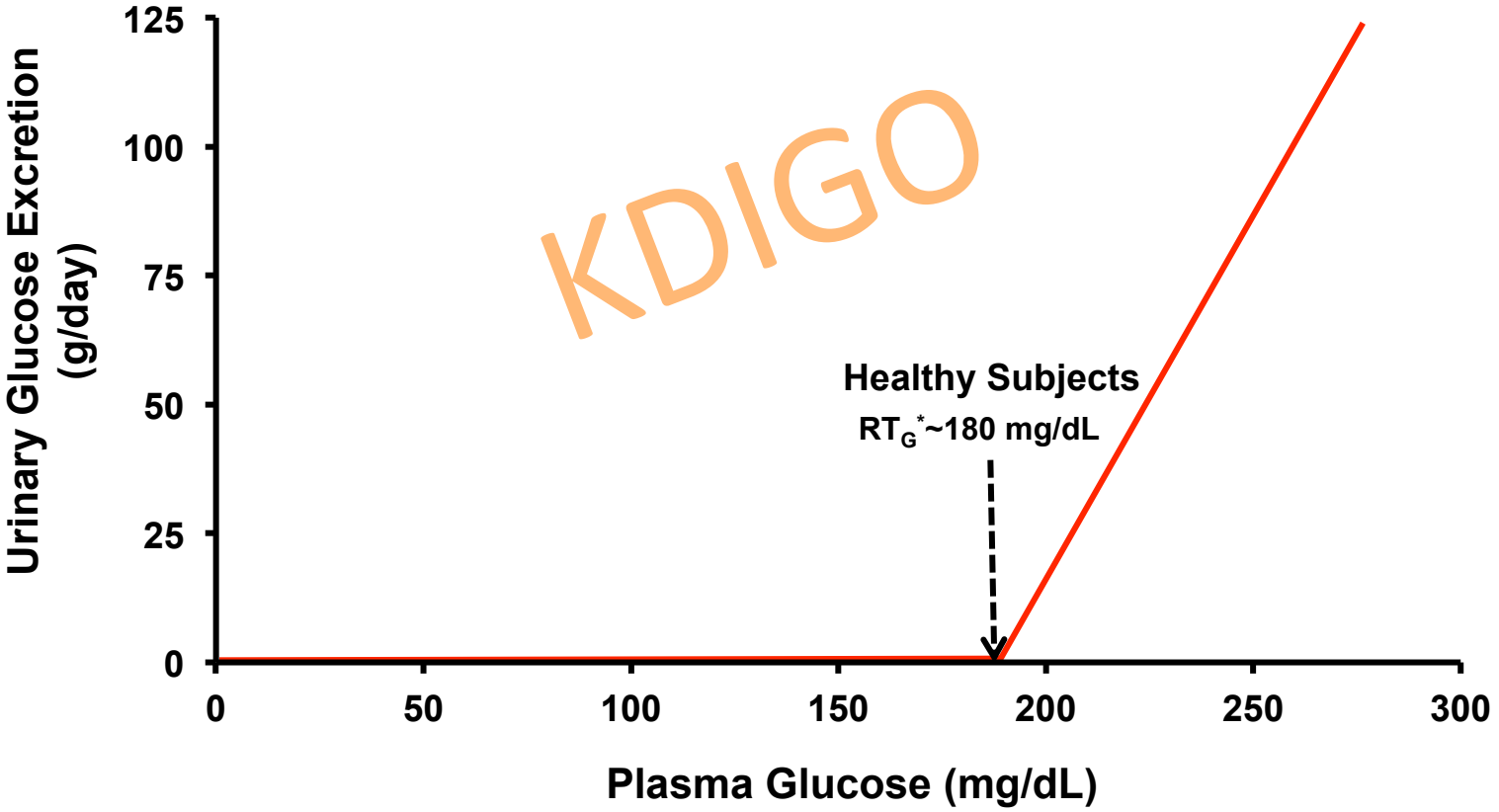
Vallon V AJP Renal 306: F194, 2814

SGLT2 Inhibition improves glycemic control in T2DM

- Canagliflozin is a selective inhibitor of SGLT2
- Causes glycosuria: 24h $U_{glucose}$ 100 ± 20 grams
- Also reduction in body weight due to ~400 kcal/day loss to UGE
- Glycemic lowering expected to decline with decreasing eGFR and renal function: diuretic with "brakes"

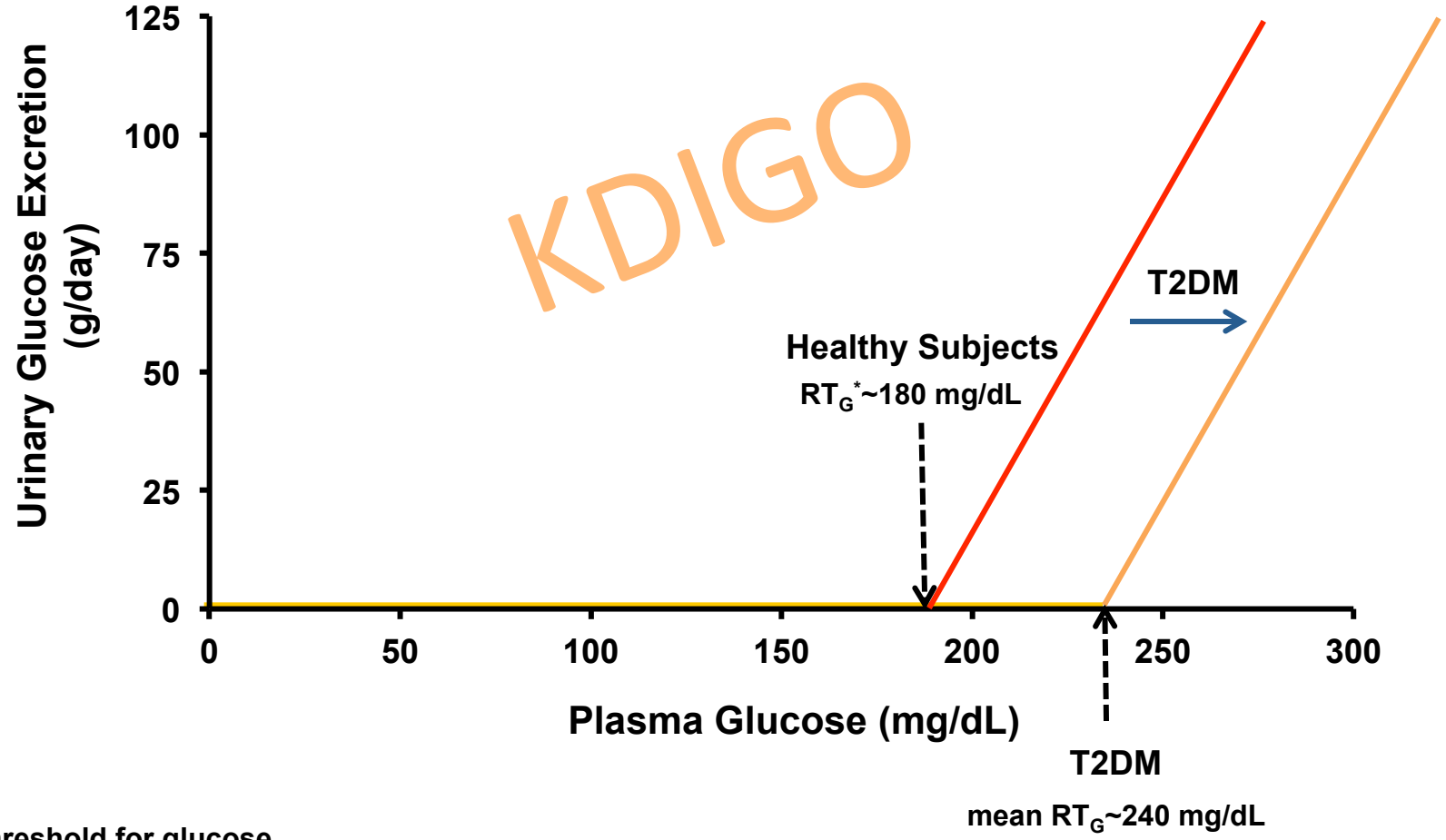


There is a Threshold Relationship Between Plasma Glucose and UGE



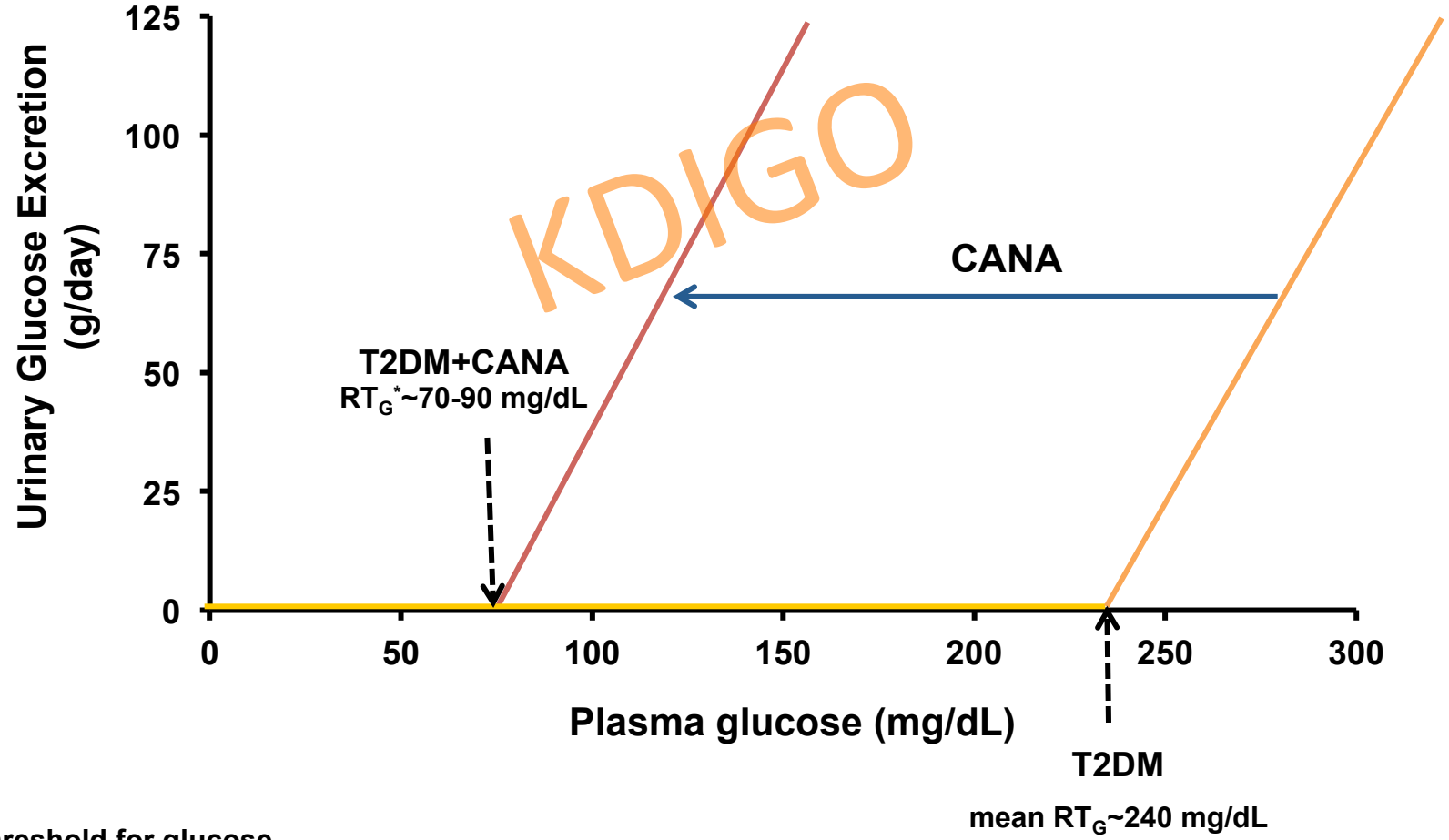
*Renal threshold for glucose

Renal Glucose Reabsorption and RT_G are Elevated in T2DM



*Renal threshold for glucose

Canagliflozin Lowers RT_G



*Renal threshold for glucose

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

David Z.I. Cherney, Bruce A. Perkins, Nima Soleymanlou, Maria Maione, Vesta Lai, Alana Lee, Nora M. Fagan, Hans J. Woerle, Odd Erik Johansen, Uli C. Broedl and Maximilian von Eynatten

Circulation. 2014;129:587-597; originally published online December 13, 2013;
doi: 10.1161/CIRCULATIONAHA.113.005081
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SGLT2 Inhibition and ACEi/ARB Reduce Intraglomerular Pressure

Possible Mechanism for Renal Protection

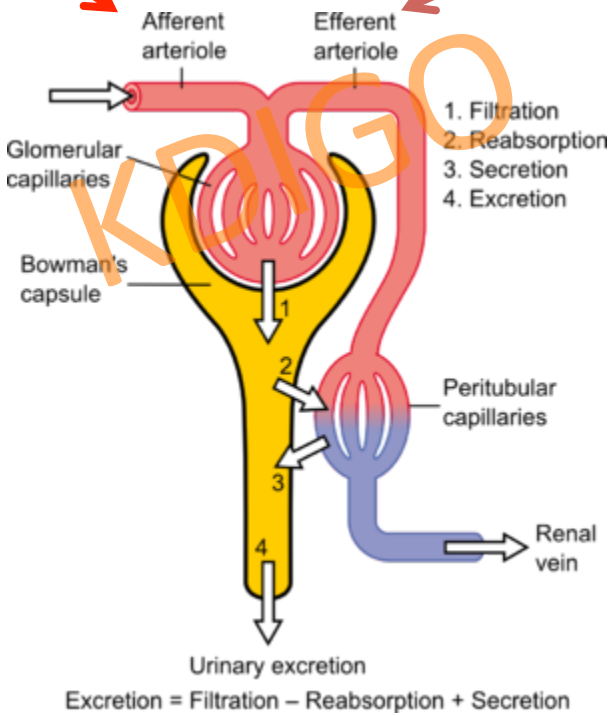
SGLT2i ↑ tubuloglomerular feedback, ↑ afferent arteriole tone and ↓intraglomerular pressure

↓

GFR ↓between 10-15% by iohexol clearance.
↓ albuminuria

↓

Renal Protection (to be determined)



ACEi and ARB ↓ efferent arteriole tone and ↓ intraglomerular pressure

↓

Initial ↓ in eGFR followed by stabilization

↓ albuminuria

↓

Renal Protection

Increased intraglomerular pressure and hyperfiltration are key steps in the development and progression of diabetic nephropathy

Cherney D et al, Circulation 129: 587, 2014

Post-hoc analysis of Canagliflozin trials show benefits of renal surrogates

- Reduction in albuminuria:
  - ~30-35% in both micro and macro groups
- Reduction in systolic BP
  - about 3-5 mmHg dose dependent
- Lipid changes
  - 5-10% increase in HDL
  - 2-6% increase in LDL
  - No change in TG
- Drop in body weight 3-4%

Source: FDA documents

CREDENCE

- Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy
- N = 3627, ? sites, 66 months (5.5 years), estimated end: Feb 2019
- Inclusion
  - albuminuria (UACR 300-5000 mg/g)
  - eGFR 30-90
- Outcomes:
  - Primary outcome: time to first of end-stage kidney disease (ESKD), doubling of serum creatinine, renal or cardiovascular (CV) death.
  - Secondary outcome:
    - CV composite: CV death, MI, stroke, hosp-CHF, hosp-USAP
    - Individual components of renal composite: ESKD, doubling of serum creatinine, or renal death.
    - All cause mortality

NCT02065791

Likelihood of success

PROS

- Strong pathophysiological basis
  - Reduction in intraglomerular pressure
- Promising results in Phase 2 study
  - Large reduction in UACR.
  - Benefits on BP and lipids.
- Safety profile excellent
- Diuretic effect with “brakes”

CONS

- May not work in later stages of kidney disease.
- Increased risk of infections, may be more pronounced in CKD due to immunosuppressed state.

The Big 3 phase III trials

- Endothelin: Atrasentan
- SGLT2: Canagliflozin
- DPP4: Linagliptin

Joo et al. BMC Nephrology 2013, 14:98
http://www.biomedcentral.com/1471-2369/14/98

BMC Nephrology

RESEARCH ARTICLE Open Access

Dipeptidyl peptidase IV inhibitor attenuates kidney injury in rat remnant kidney

Kwon Wook Joo[1,2†], Sejoong Kim[3†], Shin-young Ahn[3], Ho Jun Chin[2,3], Dong-Wan Chae[2,3], Jeonghwan Lee[1], Jin Suk Han[1,2] and Ki Young Na[2,3*]

In this study, sitagliptin, anti-diabetic drug, did not reduce blood glucose levels in the nephrectomized rats. Therefore, the renoprotective effect of sitagliptin is irrelevant to the reduction of glycemia. DPP IV

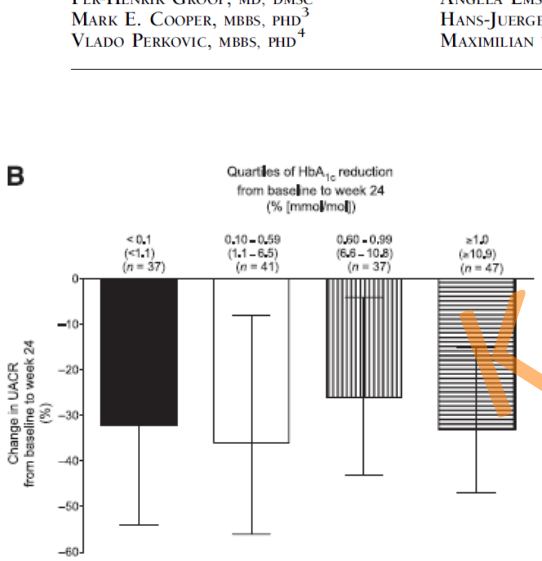
activity and increased the renal expression of glucagon-like peptide-1 receptor (GLP-1R). The subtotal nephrectomy led to the activation of phosphatidylinositol 3-kinase (PI3K)-Akt and FoxO3a phosphorylation, whereas sitagliptin treatment reversed these changes, resulting in PI3K-Akt pathway inactivation and FoxO3a dephosphorylation. The renal expression of catalase was increased and the phosphorylation of c-Jun N-terminal kinase (JNK) was decreased by sitagliptin. Sitagliptin treatment reduced apoptosis by decreasing cleaved caspase-3 and –9 and Bax levels and decreased macrophage infiltration.

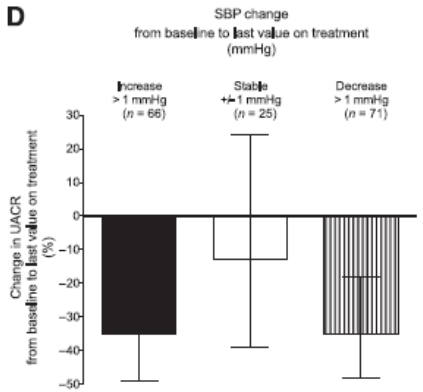
Conclusions: In rat remnant kidneys, DPP IV inhibitor attenuated renal dysfunction and structural damage. A reduction of apoptosis, inflammation and an increase of antioxidant could be suggested as a renoprotective mechanism together with the activation of FoxO3a signaling. Therefore, DPP IV inhibitors might provide a promising approach for treating CKD, but their application in clinical practice remains to be investigated.

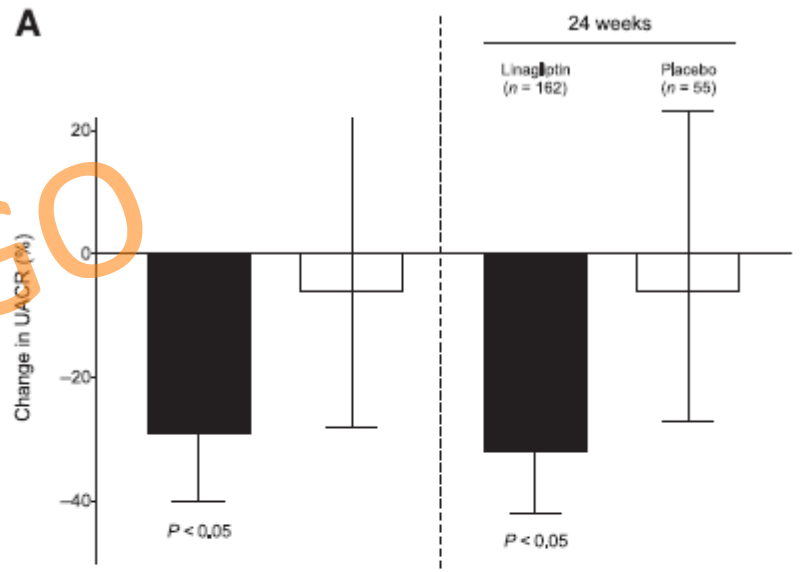
Keywords: Dipeptidyl peptidase IV, Glucagon-like peptide-1 receptor, FoxO3a, Sitagliptin, Kidney injury

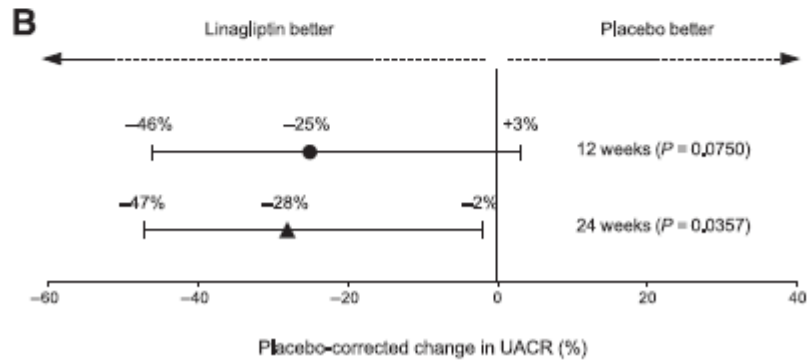
Linagliptin Lowers Albuminuria on Top of Recommended Standard Treatment in Patients With Type 2 Diabetes and Renal Dysfunction

Per-Henrik Groop, MD, DMSC[1,2,3]
Mark E. Cooper, MBBS, PHD[3]
Vlado Perkovic, MBBS, PHD[4]
Angela Emser, PHD[5]
Hans-Juergen Woerle, MD[5]
Maximilian von Eynatten, MD[5]



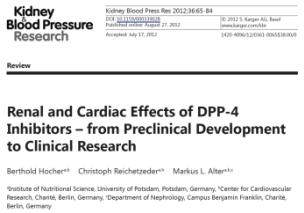






How might DPP4 inhibitors benefit the kidney?

- By reducing albuminuria.
- By reducing inflammation
  - Directly by increased GLP-1
  - Indirectly by inhibition of TNF-alpha
  - Increased protein kinase A-mediated inhibition of renal NADPH oxidase.
- By reducing oxidative stress
  - GLP-1 receptor stimulation (eg with exendin-4 or liraglutide) reduce oxidative stress.
- By increasing Stromal Derived Factor 1α (due to its reduced breakdown)
  - Increased stem cell (CD34+ CXCR4+) mobilization and repair.
  - Direct anti-apoptotic effect



CARMELINA (Phase 4)

- Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk
- N = 8300, 459 sites, 48 months (4 years), estimated end: Jan 2018
- Inclusion includes high risk of CV events defined by:
  - 1) albuminuria (micro or macro) and previous macrovascular disease
    AND/OR
  - 2) impaired renal function with predefined UACR
- Outcomes:
  - Primary outcome: CV death, MI, stroke, hosp-USAP
  - Secondary outcome:
    - Components of primary
    - Renal death, end stage renal disease and a sustained decrease of 50% or more in eGFR

NCT01897532

Likelihood of success

PROS

- Strong biological basis:
  - Reduction in inflammation, oxidative stress
  - Increase in SDF 1α
- Promising results in post-hoc analyses
  - Large reduction in UACR independent of glucose or BP.
- Safety profile reasonable.

CONS

- DPP4-ACE inhibitor interaction: ?risk of angioedema. Many patients with diabetes mellitus on ACE inhibitors.(PMID : 19581505)
- Renal end-point secondary outcome.
- Little effect on BP and lipids.

http://www.ncbi.nlm.nih.gov/pubmed/19581505

CLINICAL RESEARCH www.jasn.org

Pyridorin in Type 2 Diabetic Nephropathy

Edmund J. Lewis,* Tom Greene,† Samuel Spitalewiz,‡ Samuel Blumenthal,§ Tomas Berl,‖ Lawrence G. Hunsicker,¶ Marc A. Pohl,** Richard D. Rohde,†† Itamar Raz,‡‡ Yair Yerushalmy,§§ Yoram Yagil,‖‖ Tommy Herskovits,¶¶ Robert C. Atkins,*** Anne T. Reutens,*** David K. Packham,††† and Julia B. Lewis,‡‡‡ for the Collaborative Study Group

Regarding the primary end point, a statistically significant change in serum creatinine from baseline to 52 weeks was not evident in either Pyridorin group compared with placebo.

- However, analysis of covariance suggested that the magnitude of the treatment effect differed by baseline renal function.
- Among patients in the lowest tertile of baseline serum creatinine concentration, treatment with Pyridorin associated with a lower average change in serum creatinine concentration at 52 weeks
  - Placebo 0.28
  - Pryidorine 150 mg 0.07
  - Pyridorine 300 mg 0.14 mg/dl
- there was no evidence of a significant treatment effect in the middle or upper tertiles (the interaction effect was not significant).

PIONEER Phase 3 Program

PYR-311: Pyridorin in Patients with Diabetic Nephropathy

Pivotal program uses new FDA-approvable endpoint

The Phase 3 PIONEER program includes two identical double-blind, placebo-controlled Phase 3 trials. Each is designed to evaluate the safety and efficacy of PYRIDORIN® (pyridoxamine dihydrochloride) at 300 mg twice a day compared to placebo in reducing the rate of renal disease progression in Type 2 diabetic patients.

Both studies will enroll approximately 600 patients randomized in a 1:1 ratio to receive either Pyridorin or placebo. Patients will have baseline serum creatinine (SCr) levels of 1.3 to 3.0 mg/dL and protein/creatinine ratio (PCR) levels greater than 1200 mg/g. Patients must also be on an established and stable regimen of ACE inhibitors (ACEIs) or Angiotensin II Receptor Blockers
(ARBs)—the standard of care treatments for diabetic nephropathy—for 6 months prior to randomization. About 100 centers will participate worldwide, with the majority located in the U.S.

Importantly, this pivotal trial will utilize a new endpoint, as established under a Special Protocol Assessment (SPA) with the FDA. Primary efficacy endpoints are time to a 50% increase in SCr levels, or end stage renal disease (ESRD). Pyridorin has also received Fast Track designation from the FDA for this indication.

Ruilope et al. BMC Nephrology 2014, 15:180
http://www.biomedcentral.com/1471-2369/15/180

BMC Nephrology

RESEARCH ARTICLE Open Access

Effects of the dual peroxisome proliferator-activated receptor-α/γ agonist aleglitazar on renal function in patients with stage 3 chronic kidney disease and type 2 diabetes: a Phase IIb, randomized study

Luis Ruilope[1*], Markolf Hanefeld[2], A Michael Lincoff[3], Giancarlo Viberti[4], Sylvie Meyer-Reigner[5], Nadejda Mudie[5], Dominika Wieczorek Kirk[5], Klas Malmberg[5,6] and Matthias Herz[5]

Reversible decline in eGFR (52 w study)

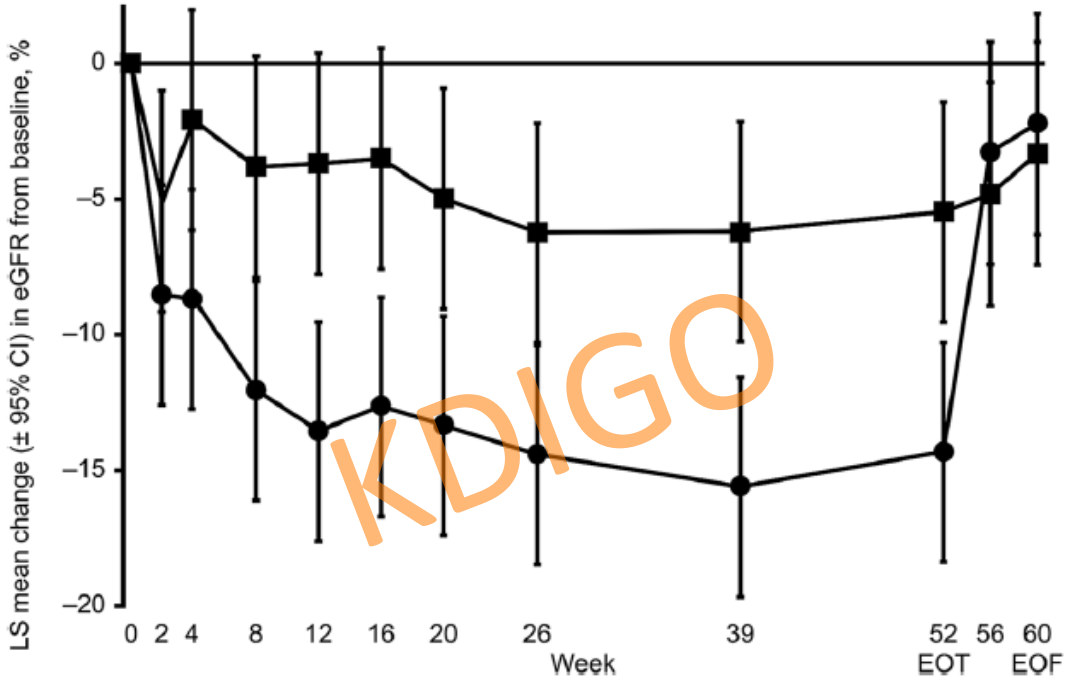


Figure 3 LS mean percentage change in eGFR from baseline at end of follow-up by analysis population. Circles = aleglitazar; squares = pioglitazone. LS mean change from baseline and ± 95% CI. Analysis of covariance of percentage change from baseline. Missing data imputed using last-observation-carried-forward principle applied only to follow-up measurements of serum creatinine ≥ 21 days after last treatment intake. CI = confidence interval; eGFR = estimated glomerular filtration rate; EOF = end of follow-up; EOT = end of treatment; LS = least squares. *Numbers reflect patients included in the full analysis population who had at least one follow-up measurement of serum creatinine ≥ 21 days after last treatment intake.

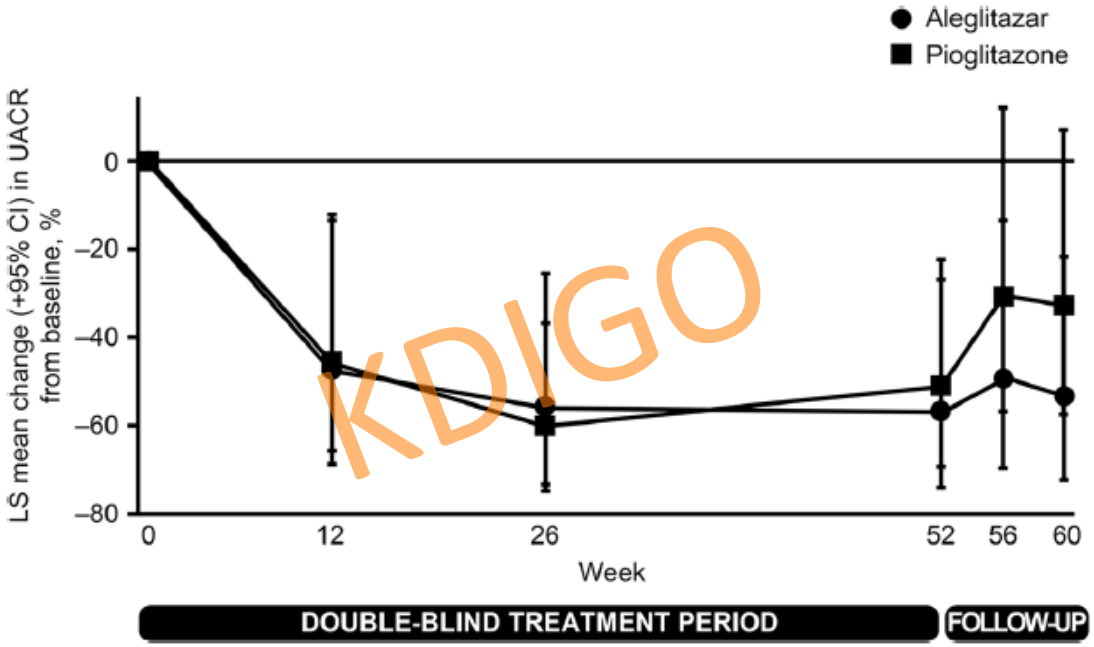


Figure 4 LS mean percentage change in UACR from baseline over time (patients with macroalbuminuria at baseline). Median baseline UACR values (interquartile range) were 75.4 mg/mmol (55.7–133.8) for aleglitazar (n = 21) and 89.6 mg/mmol (43.3–116.0) for pioglitazone (n = 27). Analysis on log-transformed scale, geometric means ratio expressed as percentage change. Patients analyzed at end of treatment (using last-observation-carried-forward principle): n = 20 for aleglitazar and 26 for pioglitazone, and at end of follow-up: n = 19 for aleglitazar and 25 for pioglitazone. LS = least squares; UACR = urine albumin-to-creatinine ratio.

Phase II clinical trials

- Inflammation pathway
  - CCR2 or CCR2/CCR5 chemokine receptor antagonists
  - CCL2 antagonists
  - JAK1/JAK2 inhibitors
- Fibrosis pathway
  - TGF beta antagonists
- Oxidative stress pathway
  - NADPH Oxidase inhibitors
- Salt and water regulation
  - Mineralocorticoid receptor antagonists
  - Tenapanor
- Others

How may the landscape change?

- Multiple trials, multiple targets
- Cautious optimism that important therapies will be developed in this area.
- Hopefully, some of abandoned therapies (eg aliglitazaar) will be resurrected in the hopes of slowing the relentless march of diabetic nephropathy to dialysis or death.