Current concept in diabetic nephropathy

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نفرولوژیست

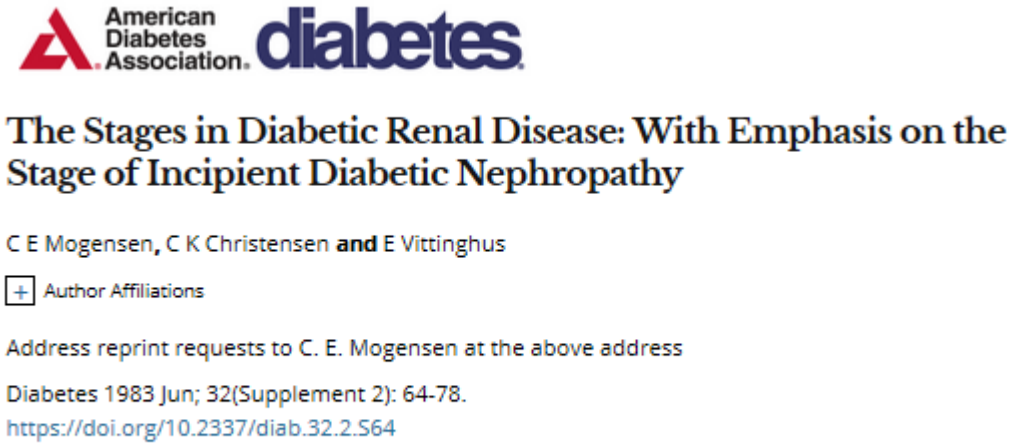
دانشگاه علوم پزشکی اصفهان

مرکز تحقیقات بیماریهای کلیوی

- Diabetic nephropathy about 40% of end-stage renal disease (ESRD).
- Type 1 diabetes, about 40%
- Type 2 diabetes, about 25%

Stages of diabetic nephropathy

1. Glomerular hyperfiltration
2. Silent stage
3. Incipient nephropathy
4. Overt nephropathy
5. End-stage kidney disease



- Proteinuria appears to be both the cause and the effect of DN
- For over two decades, RAAS blockade has played an important role in delaying the progression of DN via anti-hypertensive and anti-proteinuric effects

ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005

Pathogenesis of DN

- Pathogenesis of DN is a complex and multifactorial combination of
  1. Inflammation
  2. oxidative stress
  3. epigenetic factors

frontiers in
ENDOCRINOLOGY

MINI REVIEW ARTICLE
published: 21 December 2012
doi: 10.3389/fendo.2012.00170

Inflammation in the pathogenesis of microvascular complications in diabetes

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Diabetes and hyperglycemia create a proinflammatory microenvironment that progresses to microvascular complications such as nephropathy, retinopathy, and neuropathy. Diet-induced insulin resistance is a potential initiator of this change in type 2 diabetes which can increase adipokines and generate a chronic low-grade inflammatory state. Advanced glycation end-products and its receptor, glycation end-products AGE receptor axis, reactive oxygen species, and hypoxia can also interact to worsen complications. Numerous efforts have gained way to understanding the mechanisms of these modulators and attenuation of the inflammatory response, however, effective treatments have still not emerged. The complexity of inflammatory signaling may suggest a need for multi-targeted therapy. This review presents recent findings aimed at new treatment strategies.

Keywords: inflammation, diabetes mellitus, microvascular complications, oxidative stress, advanced glycation end-products, inflammatory cytokines

hyperfiltration

The role of glomerular hyperfiltration early in the course of diabetes lies at the heart of pathophysiology of DN.

Vallon et al., through their single-nephron GFR studies, showed that the dysregulated tubuloglomerular feedback in diabetic rats leads to a reduced tone in afferent arteriole which causes glomerular hypertension .

Tubuloglomerular Feedback and the Control of Glomerular Filtration Rate

Volker Vallon

Institute of Pharmacology and Toxicology, University of Tübingen, D-72074 Tübingen, Germany

In every nephron the glomerular filtration rate is adapted to changes in the salt concentration of early distal tubular fluid through the mechanism of tubuloglomerular feedback. Recent studies indicate that adenosine and possibly ATP mediate this mechanism and demonstrate its role in glomerular hemodynamic alterations in the early diabetic kidney.

- Through these experiments

1. Juxta glomerular apparatus fine-tunes the glomerular filtration and is an important homeostatic mechanism that regulates glomerular pressures
2. Adenosine is an important mediator of TGF
3. In diabetes, the activity of sodium-glucose transporter (SGLT-2) is increased

salt paradox phenomenon

- Absorbtion most of the sodium in the PT lowered sodium to the distal tubule.

- This decreased local adenosine levels resulting in the dilation of afferent arteriole.

SGLT-2 inhibitors

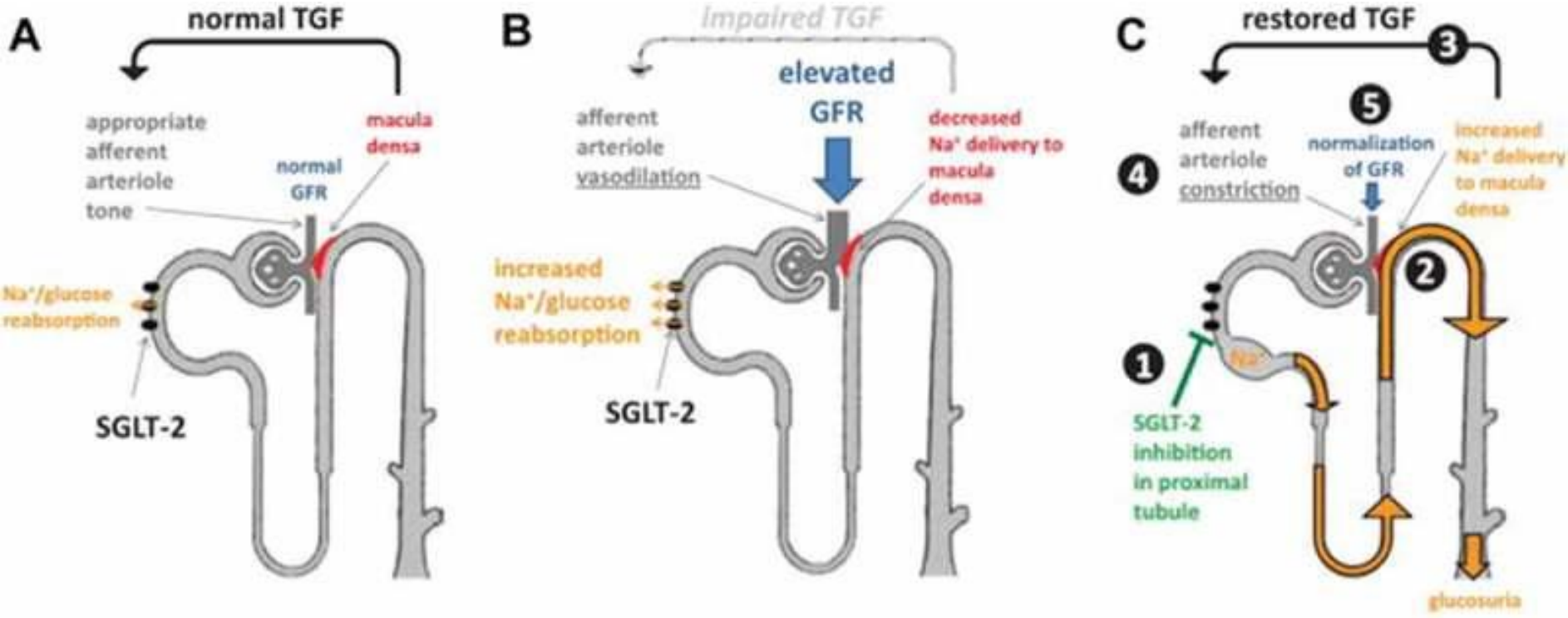
- Sodium glucose co-transporter-2 inhibitors have beneficial effects on

1. Blood pressures
2. Weight
3. Arterial stiffness

FDA Approved agents

- Empagliflozin
- Dapagliflozin
- Canagliflozin

- The renal significance of these drugs comes from their ability to restore a dysregulated TGF.



Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

EMPA-REG OUTCOME

- Empagliflozin cardiovascular event outcome event trial in type 2 diabetes mellitus (T2DM) patients
- Patients were randomized to receive empagliflozin (10 or 25 mg) or placebo along with standard diabetes care.

- At the end of ~164 weeks
- Reduction in cardiovascular death
- All -cause mortality
- Hospitalization
- The risk reduction was similar between patients with and without CKD.

- More importantly, from a renal perspective
  - Renal end points occurred in 12.7% in empagliflozin group versus 18.8% in placebo group
  - Worsening of albuminuria occurred in 11.2% in treatment group compared to 16.2% in the control group.
  - Doubling of creatinine occurred in 1.5% in the treatment group compared to 2.6% in the control group.
- All these outcomes reached statistical significance.

- This study was not designed with renal outcomes as primary end point
  - better renal outcome

- A larger randomized controlled trial (RCT) targeting renal outcomes is still needed.

CANVAS program

- This program in turn consisted of two sister programs
  - CANVAS (canagliflozin cardiovascular)
  - CANVAS-R (CANVAS-renal)
- CANVAS involved 4330 participants and CANVAS-R involved 5812 participants.
- Primarily towards studying cardiac outcomes, and the renal outcomes were secondary.
- The study subjects were followed for 3.6 years.

The NEW ENGLAND
JOURNAL of MEDICINE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

November 23, 2017
N Engl J Med 2017; 377:2097-2099
DOI: 10.1056/NEJMc1712572

This article has no abstract; the first 100 words appear below.

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D. for the EMPA-REG OUTCOME Investigators*

July 28, 2016
N Engl J Med 2016; 375:323-334
DOI: 10.1056/NEJMoa1515920

39 References **1015** Citing Articles Letters

- Progression of albuminuria occurred less frequently in the treatment group with a hazard ratio of 0.64.

- Regression of albuminuria occurred more frequently in the treatment group compared to the control group with a corresponding hazard ratio of 1.7.

- The composite renal outcome (reduction in eGFR <40%, dialysis, death from kidney failure) occurred less frequently in the canagliflozin group.

- In another pooled analysis of 11-phase 3 RCTs involving patients with type 2 diabetes, effects of dapagliflozin was analysed on changes in eGFR and UACRs
- In this analysis, there were 220 patients with eGFR between 12 and 45 ml/min/1.73m^2.
- At the end 102 weeks of the study period, dapagliflozin 5mg and 10 mg daily reduced UACR by 47.1% and 38.4 %, respectively.
- No changes in eGFR were noted at the end of study between the two groups.

- All the above RCTs established the role of potential nephroprotective ability of SGLT-2

- CREDENCE trial (canagliflozin and renal events in diabetes with established nephropathy clinical evaluation) A dedicated RCT to study the effects of SGLT-2 inhibitors on renal outcomes is currently in process

Incretin-related therapies

1. GLP-1 (glucagon-like peptide type 1) analogues
2. DPP-4 (dipeptidyl peptidase type 4) inhibitors.

- GLP-1 is a gastrointestinal hormone that enhances insulin secretion and has a pleotropic effect on glucose metabolism.
- GLP-1 is metabolized and degraded by DPP-4 at proximal convoluted tubules and podocytes

- Experiments have shown that insulin resistance in diabetes results from

1. lower levels of GLP-1
2. Increased expression of DPP-4

GLP-1 agonists

- Available GLP-1 analogues
    1. Exenatide
    2. Liraglutide
    3. Dulaglutide
    4. Albiglutide

SCALE diabetes trial

nature reviews nephrology

Review Article | Published: 04 September 2017

GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes

Marcel H. A. Muskiet ✉, Lennart Tonneijck, Mark M. Smits, Michaël J.B. van Baar, Mark H. H. Kramer, Ewout J. Hoorn, Jaap A. Joles & Daniël H. van Raalte

Nature Reviews Nephrology **13**, 605–628 (2017) | Download Citation ⬇

SCALE diabetes trial

- Liraglutide on weight reduction, noted that the drug caused a dose-dependent reduction in albuminuria
- Dulaglutide lowered UACR by 17% compared to placebo which reduced UACR by only 10%.
- Similarly, dulaglutide reduced UACR by 16.7% compared to glargine, which reduced UACR by only 3.7%.
- Reduction of albuminuria was statistically significant in both cases.
- There were no significant changes in eGFR over the follow-up period

Two RCTs, LEADER and SUSTAIN-6

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., et al., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

July 28, 2016
N Engl J Med 2016; 375:311-322
DOI: 10.1056/NEJMoa1603827

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., et al., for the SUSTAIN-6 Investigators*

November 10, 2016
N Engl J Med 2016; 375:1834-1844
DOI: 10.1056/NEJMoa1607141

Two RCTs, LEADER and SUSTAIN-6

- Study designed liraglutide and semaglutide on cardiac end points in type 2 diabetes.

- They also included microvascular outcomes : Worsening of new-onset proteinuria, doubling of serum creatinine, or need for dialysis.

- However, renal outcomes were secondary again.
- Lower rate of renal outcomes were noted in both LEADER trial and SUSTAIN-6 trial.

In conclusion

Most studies involving GLP-1 analogues show a favourable effect on albuminuria

DPP-4 inhibitors

- Among the available DPP-4 inhibitors
  1. Linagliptin
  2. Saxagliptin
  3. Alogliptin
  4. Sitagliptin

American Diabetes Association. Diabetes Care

Clinical Care/Education/Nutrition/Psychosocial Research

Diabetes Care 2016 Feb; 39(2): 222-230.

Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial

Melanie J. Davies[1], Stephen C. Bain[2], Stephen L. Atkin[3], Peter Rossing[4], David Scott[5], Minara S. Shamkhalova[6], Heidrun Bosch-Traberg[7], Annika Syrén[7] **and** Guillermo E. Umpierrez[8]

- LIRA-RENAL RCT
- Primarily designed : the effect of liraglutide in lowering glycohaemoglobin in patients with moderate renal impairment (eGFR 30–59 ml/min/1.73m^2).

- At the end of 26 weeks, albuminuria in linaliptin group was 17% lower, although it did not attain statistical significance

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

ORIGINAL ARTICLE | Open Access

Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial

Per-Henrik Groop MD, DMSc, Mark E. Cooper MBBS, PhD, Vlado Perkovic MBBS, PhD, Berthold Hocher MD, PhD, Keizo Kanasaki MD, PhD, Masakazu Haneda MD, PhD ... See all authors

First published: 21 June 2017 | https://doi.org/10.1111/dom.13041 | Citations: 45

- MARLINA-T2D trial
  - Investigate linagliptin in patients with T2DM and CKD
  - 360 participants who were followed over 24 weeks
  - Test superiority of linagliptin over placebo in terms of albuminuria.
  - Despite a trend towards reduction in albuminuria, the differences between the study groups were not statistically significant.

In a pooled analysis of 13 RCTs (*Am J Kidney Dis*. 2015)

- Effect of linagliptin was studied on renal end points
- Primary end points
  - New onset of moderate albuminuria
  - Severe elevation in albuminuria
  - Reduction in kidney function

- 5466 participants, 3505 received linagliptin and the rest received placebo.

- In this analysis, linagliptin significantly reduced the hazard of the first occurrence of primary event by 16% (HR: 0.84, *P*=0.02).

- New-onset moderate elevation in albuminuria was reduced by 18% (HR: 0.82, *P*=0.03).

- No difference in decline in eGFR was noted between the two groups.

CARMELINA trial

(composite and renal microvascular outcome study with linagliptin)

7003 participants to study composite renal end points over 54 months

The results are much awaited.

Endothelin receptor antagonists

- ASCEND, a multicentre RCT, was designed to study the effects of avosentan, an endothelin antagonist, on composite renal outcomes including albuminuria

Mineralocorticoid receptor antagonists

- Mineralocorticoid receptor activation is associated with activation of pro-inflammatory, oxidative, and pro-fibrotic pathways in various organ systems

- However, steroidal MRAs such as Eplerenone and Spironolactone, when added to ACE-I or ARB, often result in severe hyperkalemia

Finerenone

- A novel nonsteroidal MRA
  - More selectivity towards mineralocorticoid receptors
  - Lower incidence of hyperkalemia in earlier trials

Original Investigation

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy
A Randomized Clinical Trial

JAMA. 2015;314(9):884-894. doi:10.1001/jama.2015.10081

George L. Bakris, MD; Rajiv Agarwal, MD; Juliana C. Chan, MD; Mark E. Cooper, MD, PhD; Ron T. Gansevoort, MD, PhD; Hermann Haller, MD, PhD; Giuseppe Remuzzi, MD; Peter Rossing, MD; Roland E. Schmieder, MD; Christina Nowack, MD; Peter Kolkhof, PhD; Amer Joseph, MBBS; Alexander Pieper, DiplStat; Nina Kimmeskamp-Kirschbaum, PhD; Luis M. Ruilope, MD, PhD; for the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group

- ARTS-DN was a randomized trial designed to test the efficacy and safety of finerenone in patients with DN and persistent albuminuria
- 820 patients were randomized and followed for 90 days
- Pimary outcome : UACR at 90 days versus baseline.

The Finerenone group had dose-dependent reduction in UACR from the dose of 7.5 mg/day and above.

Phosphodiesterase inhibitors

- Pentoxifylline, a nonspecific phosphodiesterase inhibitor, in experimental models
  - Anti -inflammatory
  - Anti -fibrotic properties

JASN Journal of the American Society of Nephrology

Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease: The PREDIAN Trial

Juan F. Navarro-González, Carmen Mora-Fernández, Mercedes Muros de Fuentes, Jesús Chahin, María L. Méndez, Eduardo Gallego, Manuel Macía, Nieves del Castillo, Antonio Rivero, María A. Getino, Patricia García, Ana Jarque and Javier García

JASN January 2015, 26 (1) 220-229; DOI: https://doi.org/10.1681/ASN.2014010012

- PREDIAN trial
- Test if pentoxifylline would benefit patients with DN
  - Percent change in UACR
  - e GFR
- This study therefore concluded by saying that pentoxifylline could slow the progression of DN in advanced CKD.
- However, there were two major limitation :
  - All the study participants were Caucasian, and the follow-up duration was short.

Drugs targeting AGE-RAGE axis

- Pyridoxamine dihydrochloride
- In a pilot trial (PYR-210), pyridoxamine showed a trend towards improved creatinine in a cohort of patients with DN

A larger RCT, PIONEER-CSG-17, is currently in process.

Antioxidants

- Oxidative stress has been proposed as an important mechanism in progression of renal disease

- reactive oxygen species cause impaired activity of the transcription factor call Nrf-2 (nuclear 1 factor-related factor 2)

- Bardoxolone methyl, is a potent activator of Nrf-2 that was shown to reduce oxidative stress in rat models
- BEAM study, a RCT, was designed to study the effect of Bardoxolone on CKD patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE FREE PREVIEW

Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes

› E. Pergola, M.D., Ph.D., Philip Raskin, M.D., Robert D. Toto, M.D., Colin J. Meyer, M.D., J. Warren Huff, J.D., Eric B. Grossman, M.D., Melissa Krauth, M.B.A., Stacey Ruiz, Ph.D., Paul Audhya, M.D., Heidi Christ-Schmidt, M.S.E., Janet Wittes, Ph.D., and David G. Warnock, M.D. for the BEAM Study

July 28, 2011
N Engl J Med 2011; 365:327-336
DOI: 10.1056/NEJMoa1105351

- 227 patients with CKD (eGFR 20–45 ml/min/1.73m^2)
- 25,75, or 150 mg of Bardoxolone daily versus placebo
- eGFR in the treatment group was significantly higher compared to the placebo group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease

Dick de Zeeuw, M.D., Ph.D., Tadao Akizawa, M.D., Ph.D., Paul Audhya, M.D., M.B.A., George L. Bakris, M.D., Melanie Chin, Ph.D., Heidi Christ-Schmidt, M.S.E., Angie Goldsberry, M.S., Mark Houser, M.D., Melissa Krauth, M.B.A., Hiddo J. Lambers Heerspink, Pharm.D., Ph.D., John J. McMurray, M.D., Colin J. Meyer, M.D., et al., for the BEACON Trial Investigators*

December 26, 2013
N Engl J Med 2013; 369:2492-2503
DOI: 10.1056/NEJMoa1306033

- RCT, BEACON, was designed to test bardoxolone in 2185 patients with type 2 diabetes and stage 4 CKD

Unfortunately, the study was prematurely terminated after 9 months due to higher rate of cardiovascular deaths.

nephron

Clinical Practice: Clinical Trial Protocol

Design of a Phase 2 Clinical Trial of an ASK1 Inhibitor, GS-4997, in Patients with Diabetic Kidney Disease

Lin J.H.[a] · Zhang J.J.[a] · Lin S.-L.[a] · Chertow G.M.[b]

Author affiliations

Corresponding Author

Keywords: Diabetic Kidney Disease › DKD › Phase 2 › ASK1 › GS-4997 › ACEi › ARB › eGFR › Proteinuria › Albuminuria

Nephron 2015;129:29-33

- Apoptotic signal-regulating kinase-1 (ASK-1)
- ASK-1 pathway activation results in downstream activation of terminal kinases, leading to the production of inflammatory chemokines
- The primary outcome being studied is change in eGFR and the secondary outcome is change in albuminuria

Summary of newer and clinically relevant drugs for diabetic nephropathy.

DRUGS WITH FAVOURABLE OUTLOOK IN THE MANAGEMENT OF DIABETIC NEPHROPATHY
SGLT-2 inhibitors
GLP-1 agonists
DPP-4 inhibitors
DRUGS WITH POSSIBLE POTENTIAL IN THE MANAGEMENT OF DIABETIC NEPHROPATHY BUT IN THE NEED OF MORE EVIDENCE
MRA antagonist: Finerenone
Phosphodiesterase inhibitors: Pentoxifylline
ON-GOING CLINICAL TRIALS/DRUGS
CARMELINA trial: Linagliptin (DPP-4 inhibitor)
PERL trial: Allopurinol
PIONEER-CSG-17: Pyridoxamine (AGE-RAGE axis inhibitor)
GS-4997: ASK-1 pathway inhibitor
ABORTED TRIALS/DRUGS, DUE TO EITHER INCREASED ADVERSE EFFECTS OR FUTILITY
Endothelin antagonists: Avosentan, atrasentan
Antioxidants: Bardoxolone

شاد و خرم باشید