# Farmaci in nefroprotezione: a che punto siamo?

**Luca De Nicola**

*UOC Nefrologia e Dialisi*

Università
degli Studi
della Campania
*Luigi Vanvitelli*

# Conflitti di interesse



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

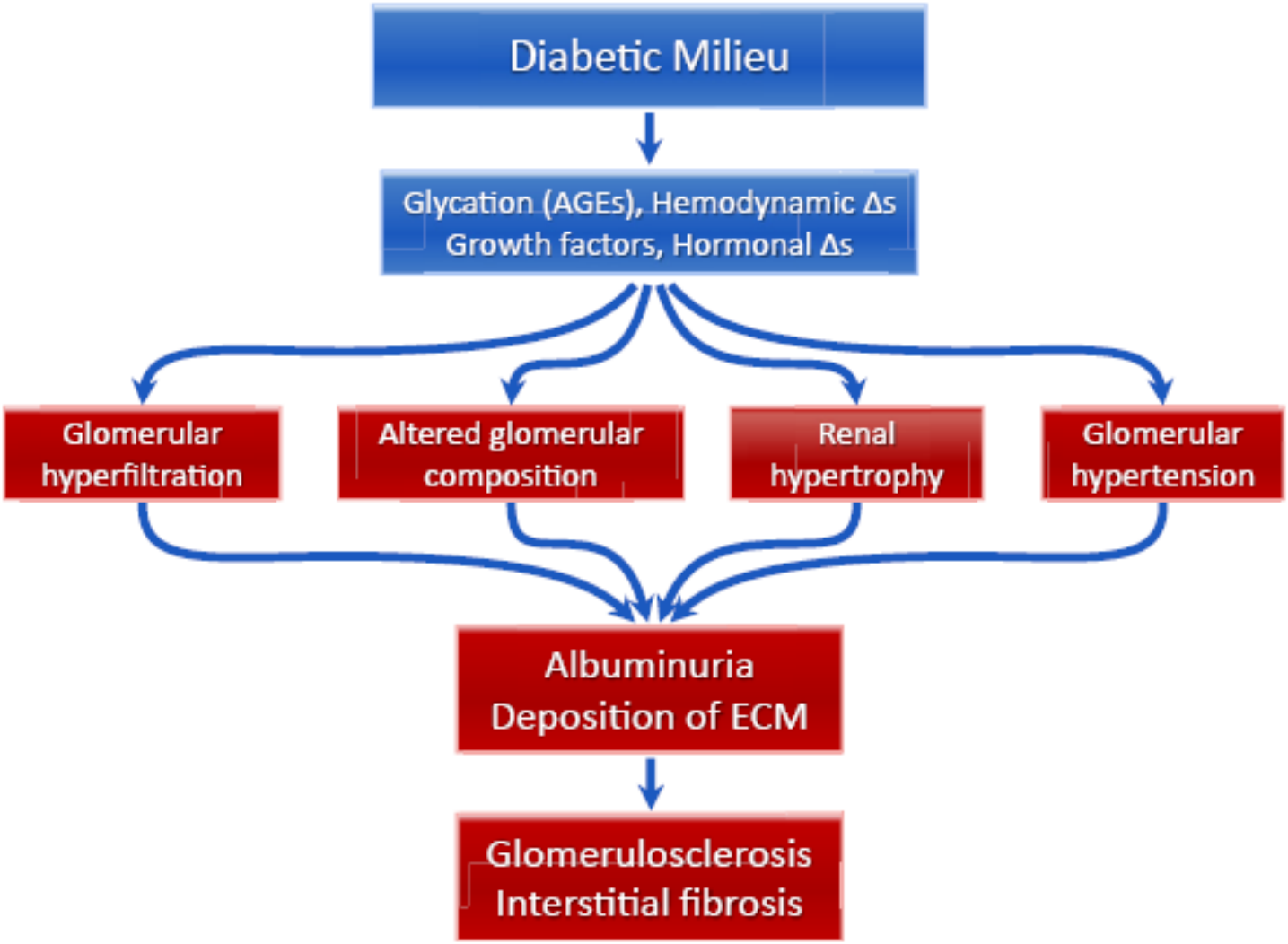
**-Abbvie**

**-Astrazeneca**

**-Janssen**

**-Vifor**

# Proteinuria is the main determinant of CKD-DM progression




K. Umanath and J. B. Lewis, AJKD 2018

Original Investigation

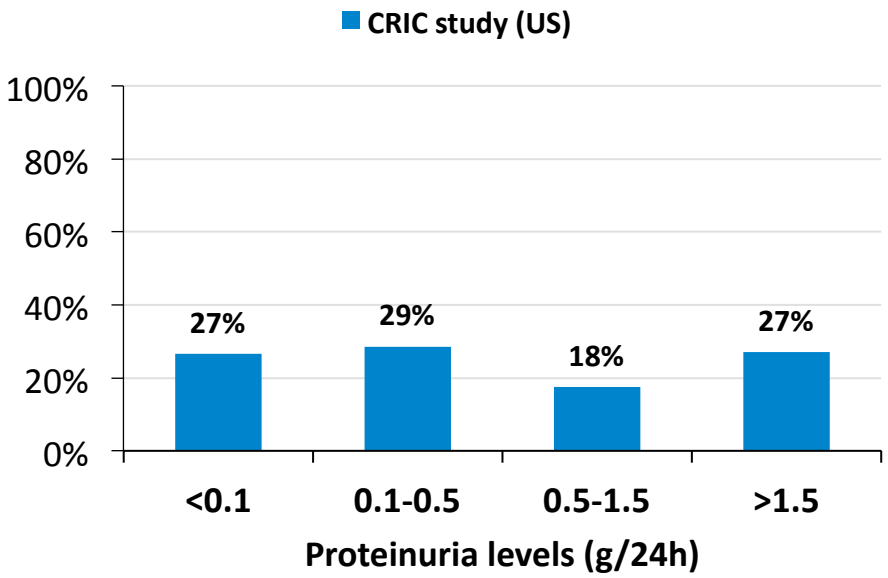
AJKD

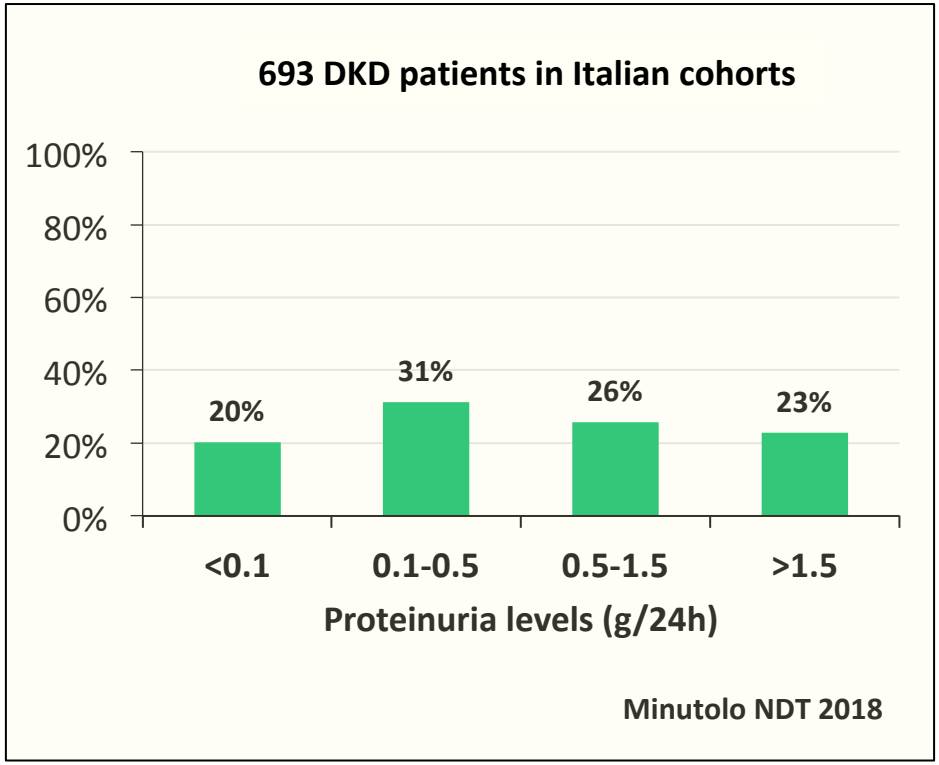
# Risk of Progression of Nonalbuminuric CKD to End-Stage Kidney Disease in People With Diabetes: The CRIC (Chronic Renal Insufficiency Cohort) Study

*Digsu N. Koye, Dianna J. Magliano, Christopher M. Reid, Christopher Jepson, Harold I. Feldman, William H. Herman, and Jonathan E. Shaw*

*AJKD* Vol XX | Iss XX | Month 2018

## CRIC participants with diabetes and reduced GFR (n=1,813) stratified by proteinuria



Original Investigation

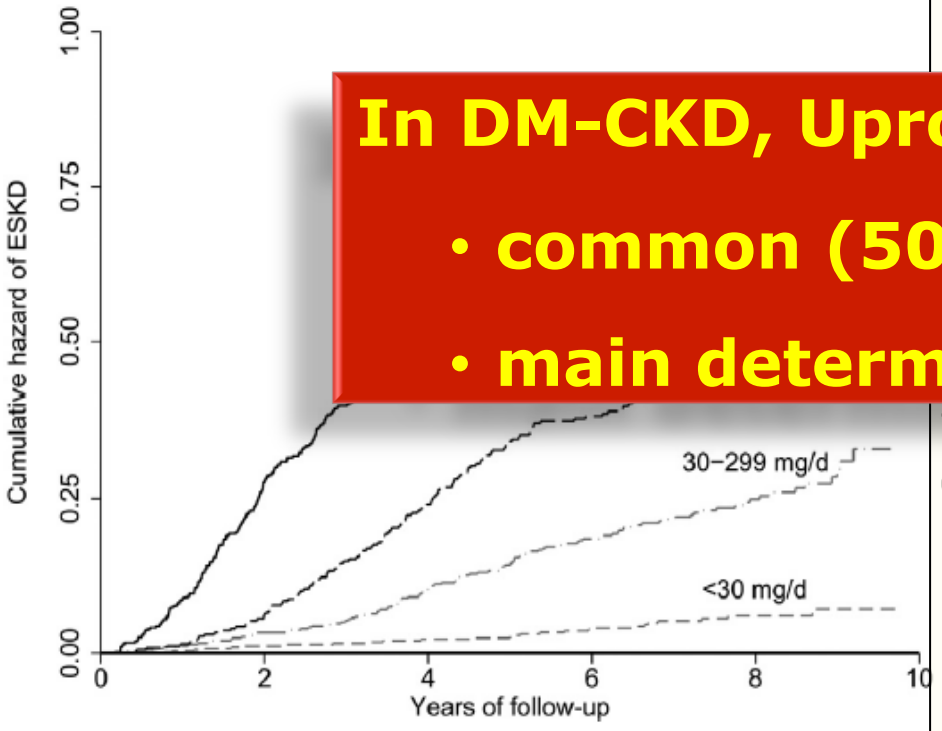
AJKD

# Risk of Progression of Nonalbuminuric CKD to End-Stage Kidney Disease in People With Diabetes: The CRIC (Chronic Renal Insufficiency Cohort) Study

*Digsu N. Koye, Dianna J. Magliano, Christopher M. Reid, Christopher Jepson, Harold I. Feldman, William H. Herman, and Jonathan E. Shaw*

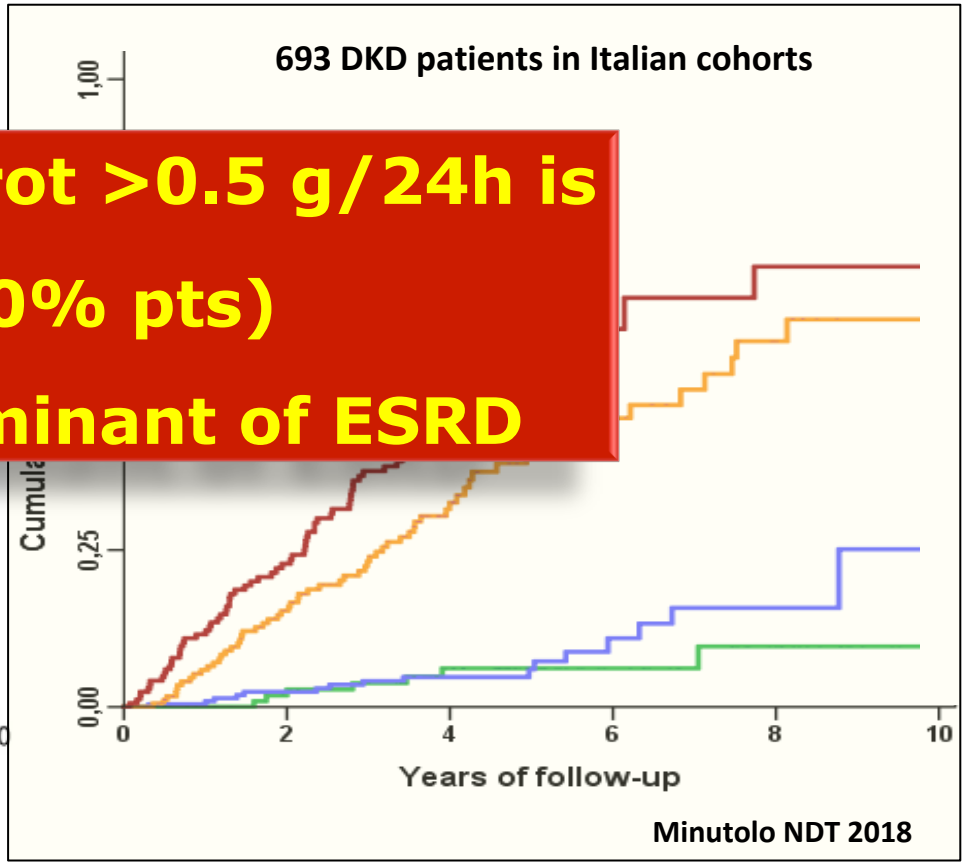
*AJKD* Vol XX | Iss XX | Month 2018

## CRIC participants with diabetes and reduced GFR (n=1,813) stratified by proteinuria




**In DM-CKD, Uprot >0.5 g/24h is**

- **common (50% pts)**
- **main determinant of ESRD**



# REVERSAL OF DIABETIC NEPHROPATHY IN HUMAN CADAVERIC KIDNEYS AFTER TRANSPLANTATION INTO NON-DIABETIC RECIPIENTS

- Kidneys removed from cadaveric donor with 17-year history of DM1
- Donor had ⇧ Uprot but normal sCreat

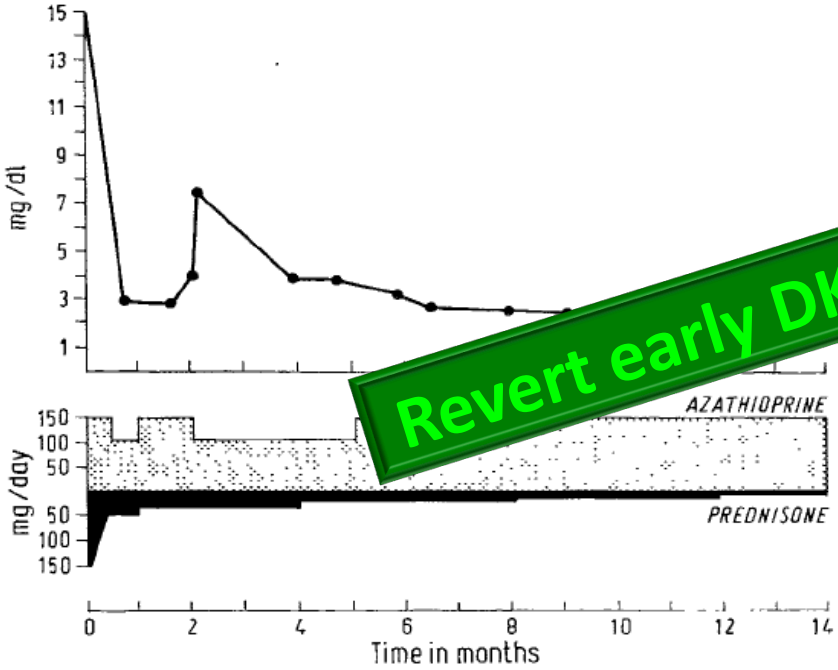



Fig 1—Renal function in the first recipient.

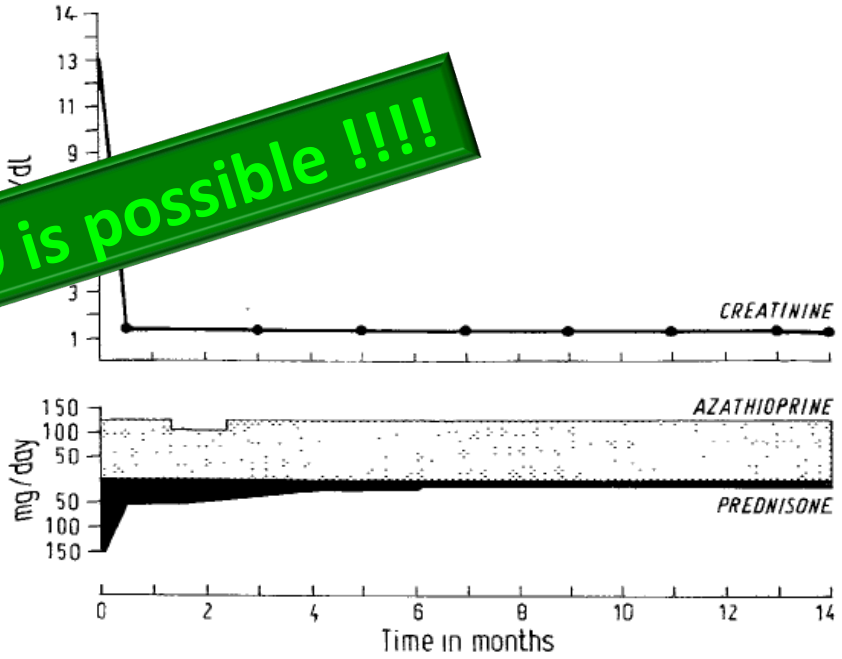



Fig 2—Renal function in the second recipient.

Revert early DKD is possible !!!!

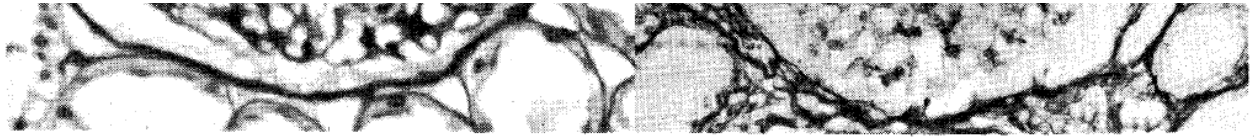


Fig 4—Biopsy specimen seven months after transplantation showing (left) widely open glomerular capillaries with almost normal basemen membrane and mesangium (PAS × 400) and (right) almost normal glomerular architecture (methenamine silver × 400).

THE LANCET, DECEMBER 3, 1983

# Trials in Diabetic CKD

# Residual renal risk in DM-CKD patients under optimal anti-RAS therapy

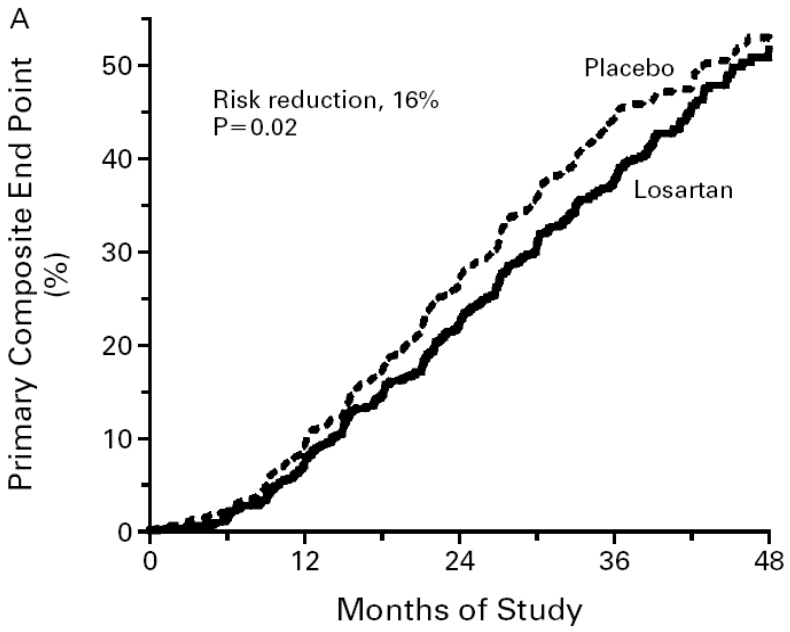
VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

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

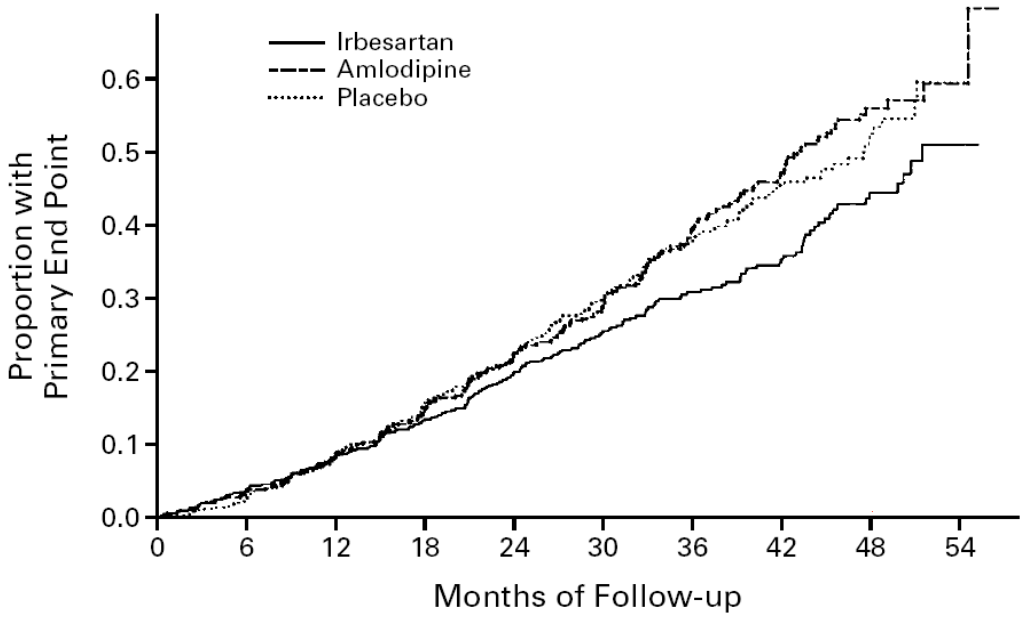
BARRY M. BRENNER, M.D., MARK E. COOPER, M.D., PH.D., DICK DE ZEEUW, M.D., PH.D., WILLIAM F. KEANE, M.D., WILLIAM E. MITCH, M.D., HANS-HENRIK PARVING, M.D., GIUSEPPE REMUZZI, M.D., STEVEN M. SNAPINN, PH.D., ZHONXIN ZHANG, PH.D., AND SHAHNAZ SHAHINFAR, M.D., FOR THE RENAAL STUDY INVESTIGATORS*

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*




**RENAAL Study NEJM 2001**




**IDNT Study NEJM 2001**

# RCTs after RENAAL and IDNT

- Dual RAS block: Altitude & NephronVA-D (CKD progression, **AKI/High sK)**
- Aldosterone-antagonists (Uprot reduction, **NO Hard Endpoint**)
- Erythropoietin (Hb rise; hard endpoint trial; TREAT; CV/renal; **NO Effect**)
- Sulodexide (prot reduction; hard endpoint trial; SUN-Overt**; STOP**)
- Sulodexide (alb reduction; surrogate endpoint; SUN-Micro**; NO Effect**)
- Statins (hard endpoint trial; SHARP; CV/renal; CV but **NO Renal Effect**)
- VDRA-Paracalcitol 1-2 µg/d (prot reduction, VITAL, **NO Hard Endpoint**)
- Nrf2 agonist (rise in eGFR; hard endpoint; BEACON**; STOP for HF risk**)
- Anti-TGF-β1 (rise in eGFR, renal; **STOP for Futility**)
- $ET_A$-RA: SONAR (hard renal endpoint; **STOP for Low Event Rate**)
- **SGLT2-I and GLP1-RA: Beneficial Cardiorenal Effects**

# SGLT-2-I

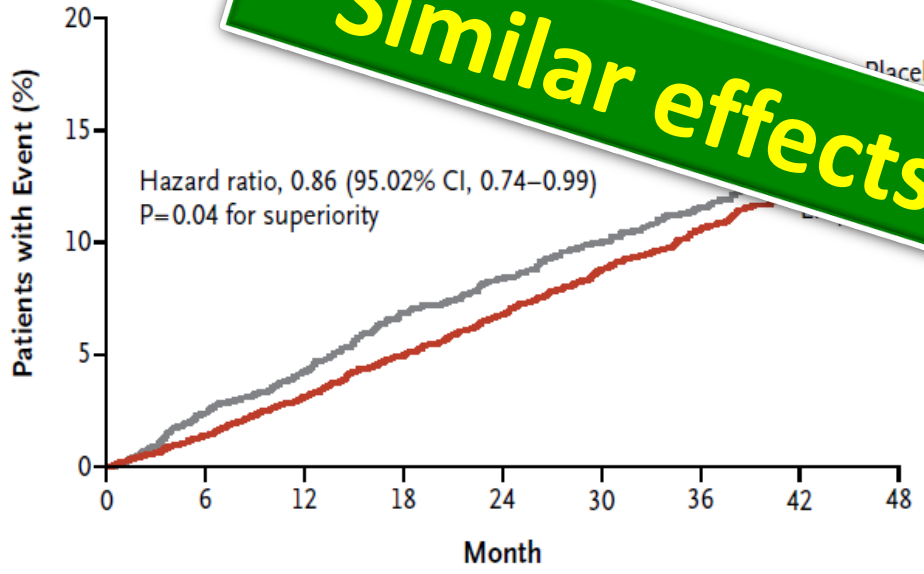
The NEW ENGLAND JOURNAL of MEDICINE

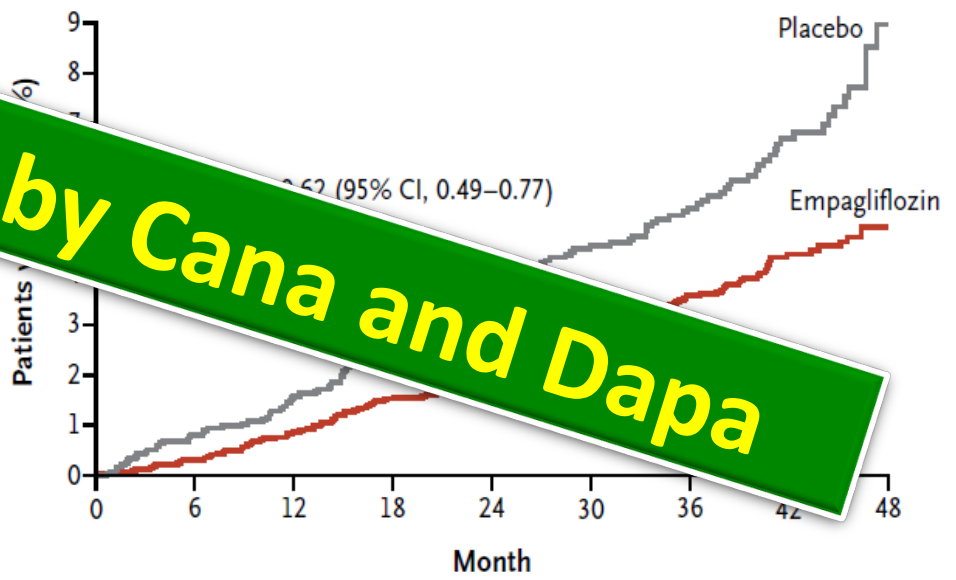
ORIGINAL ARTICLE

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

- N=7,020, High CV risk, Age 63±9 yrs, BMI 30±5; Median FU 3.1 years
- eGFR <60 in 26%, Ualb >30 in 40% (>300 in 27%), 80% under anti-RAS
- Primary composite outcome: CV death, nonfatal MI, or nonfatal stroke

**Similar effects by Cana and Dapa**

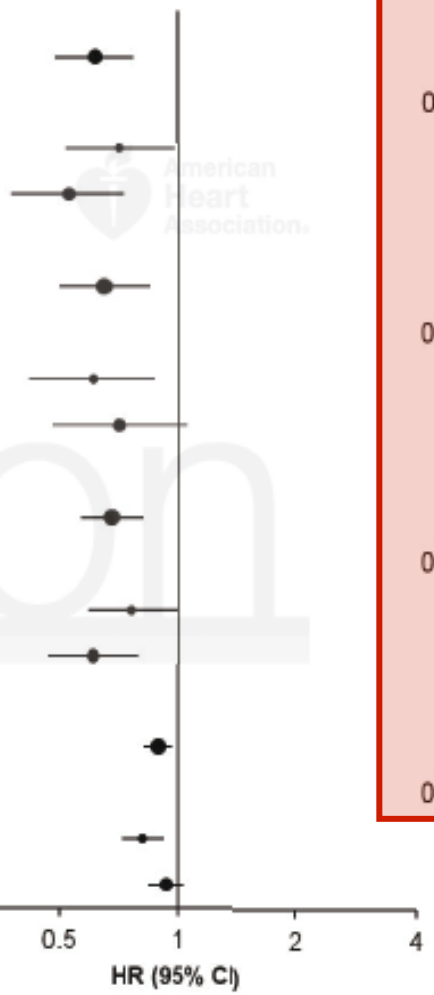



N Engl J Med 2015;373:2117-28.

# Cardiovascular Protection in EMPAREG by CKD status

| | Empagliflozin | | Placebo | | | Interaction p-value |
|---|---|---|---|---|---|---|
| | n with event/N (%) | Rate/ 1000 pt-yr | n with event/N (%) | Rate/ 1000 pt-yr | HR (95% CI) | |
| Cardiovascular death | | | | | | |
| All patients | 172/4687 (3.7) | 12.4 | 137/2333 (5.9) | 20.2 | 0.62 (0.49, 0.77) | |
| Prevalent kidney disease* | | | | | | 0.1926 |
| Yes | 94/1498 (6.3) | 21.4 | 65/752 (8.6) | 30.1 | 0.71 (0.52, 0.98) | |
| No | 77/3149 (2.4) | 8.3 | 72/1569 (4.6) | 15.7 | 0.53 (0.38, 0.73) | |
| Hospitalization for heart failure | | | | | | |
| All patients | 126/4687 (2.7) | 9.4 | 95/2333 (4.1) | 14.5 | 0.65 (0.50, 0.85) | |
| Prevalent kidney disease* | | | | | | 0.5780 |
| Yes | 66/1498 (4.4) | 15.5 | 53/752 (7.0) | 25.9 | 0.61 (0.42, 0.87) | |
| No | 60/3149 (1.9) | 6.6 | 42/1569 (2.7) | 9.4 | 0.71 (0.48, 1.05) | |
| All-cause mortality | | | | | | |
| All patients | 269/4687 (5.7) | 19.4 | 194/2333 (8.3) | 28.6 | 0.68 (0.57, 0.82) | |
| Prevalent kidney disease* | | | | | | 0.2242 |
| Yes | 143/1498 (9.5) | 32.5 | 92/752 (12.2) | 42.5 | 0.76 (0.59, 0.99) | |
| No | 125/3149 (4.0) | 13.4 | 102/1569 (6.5) | 22.2 | 0.61 (0.47, 0.79) | |
| All-cause hospitalization | | | | | | |
| All patients | 1725/4687 (36.8) | 161.9 | 925/2333 (39.6) | 183.3 | 0.89 (0.82, 0.96) | |
| Prevalent kidney disease* | | | | | | 0.1234 |
| Yes | 663/1498 (44.3) | 208.4 | 375/752 (49.9) | 258.9 | 0.81 (0.72, 0.92) | |
| No | 1046/3149 (33.2) | 141.8 | 549/1569 (35.0) | 154.1 | 0.93 (0.84, 1.03) | |

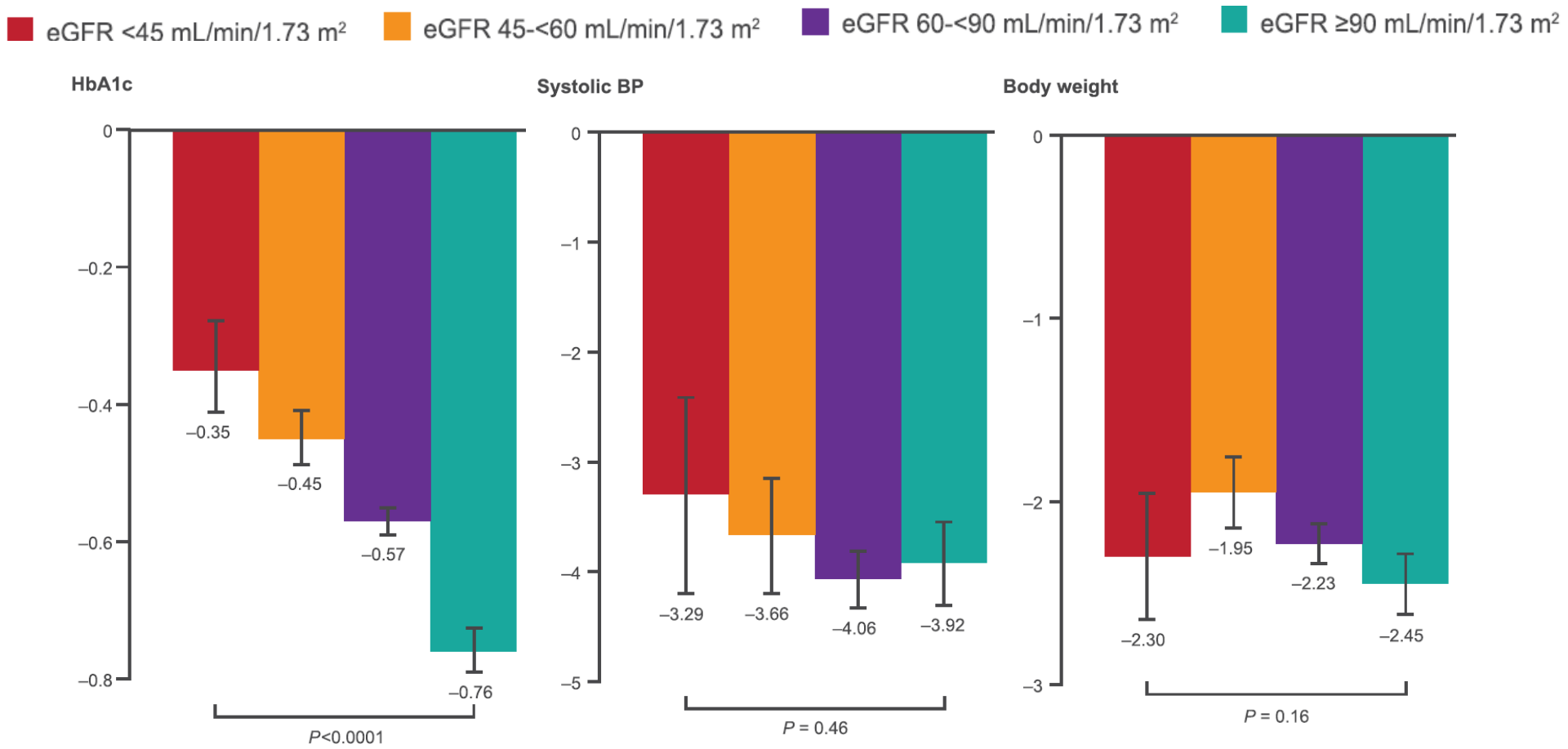



Wanner for EMPAREG group, Circulation 2018

# Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function Data From the CANVAS Program

Circulation
October 9, 2018

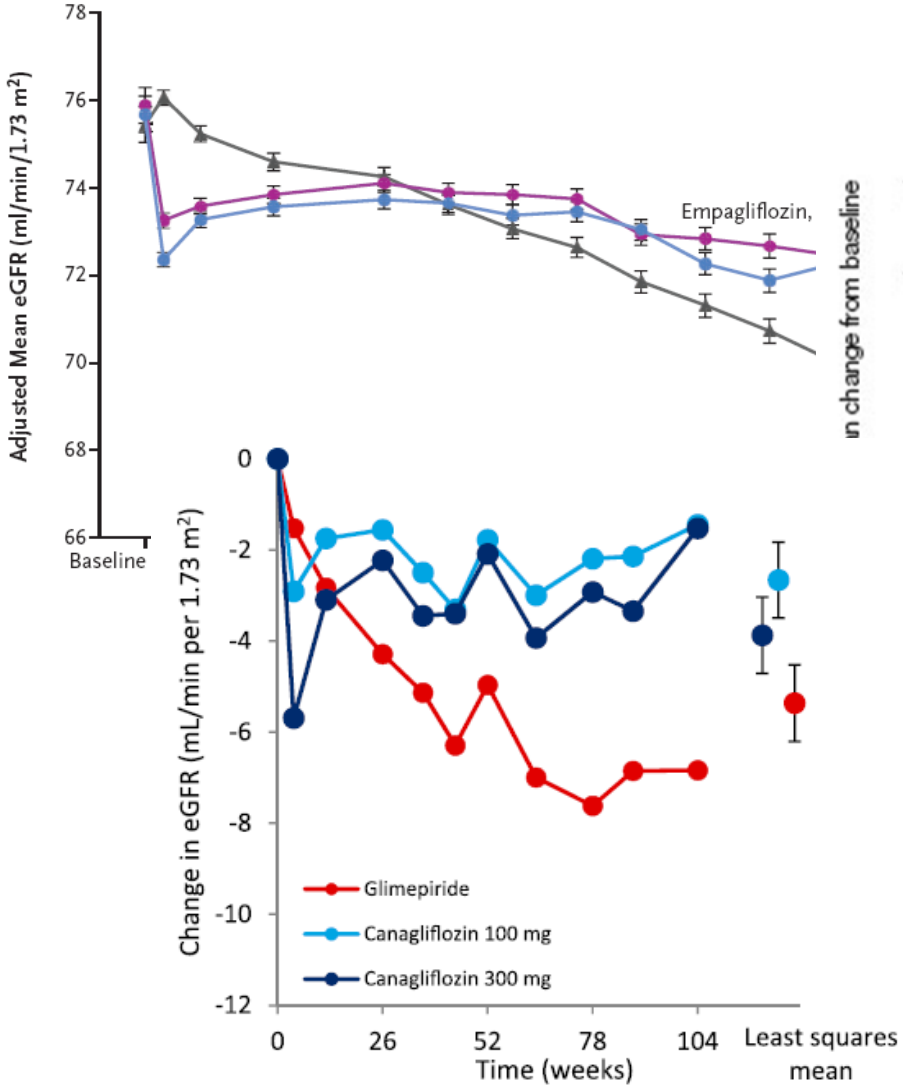
- 10.142 pts with type 2 diabetes and eGFR >30 mL/min/1.73 m2
- 2039 pts -20%- with eGFR <60 mL/min/1.73 m2)

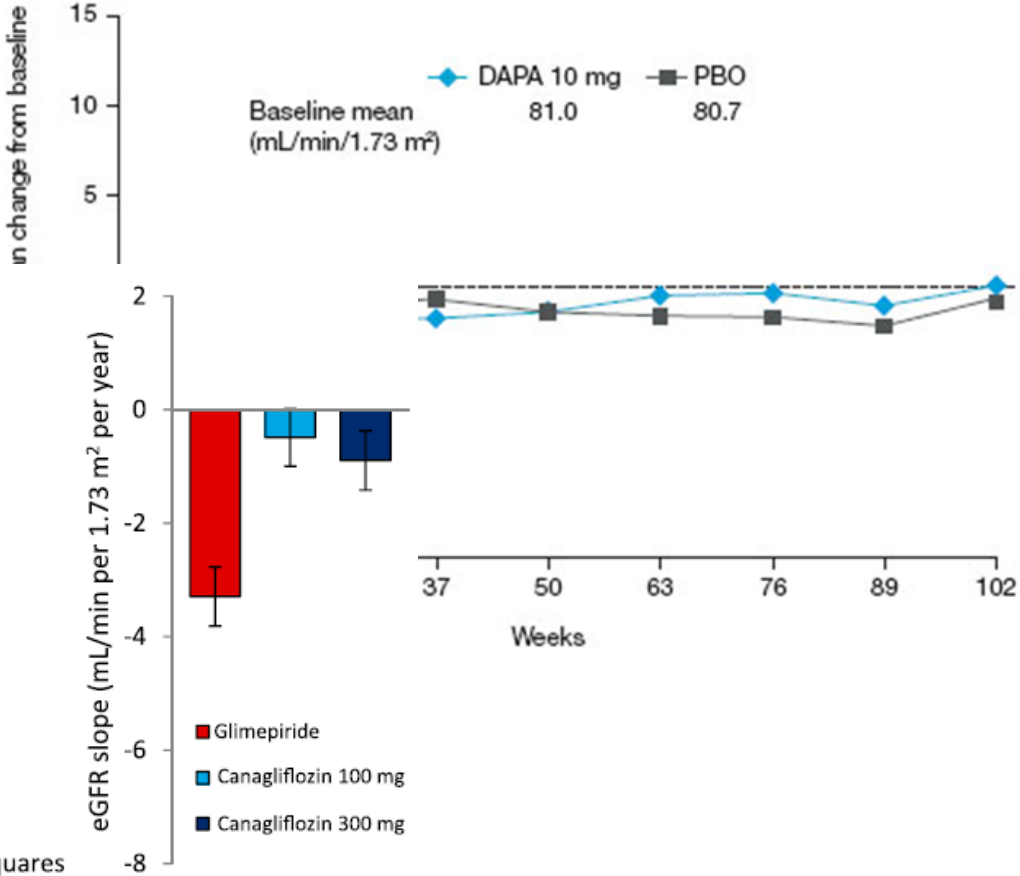


# Nephroprotection by SGLT-2-I

# SGLT-2-I slow progressive GFR decline…

## … *a Class Effect … similar to anti-RAS*

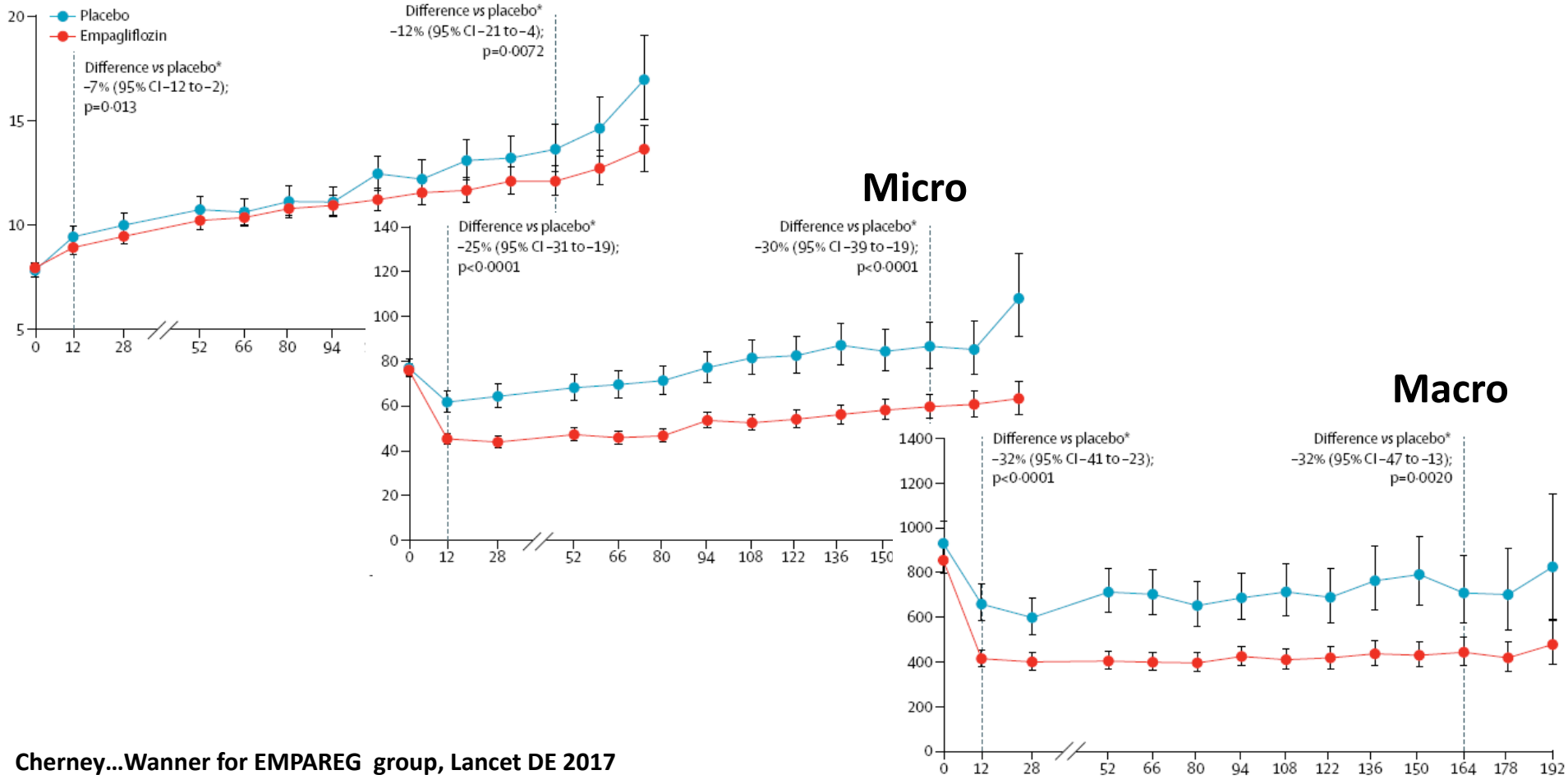



**Wanner, NEJM 2016**
**Ptaszynska, ADA 2014**
**Heerspink, JASN 2016**

# Antialbuminuric effects and Nephroprotection in EMPA by basal level of albuminuria

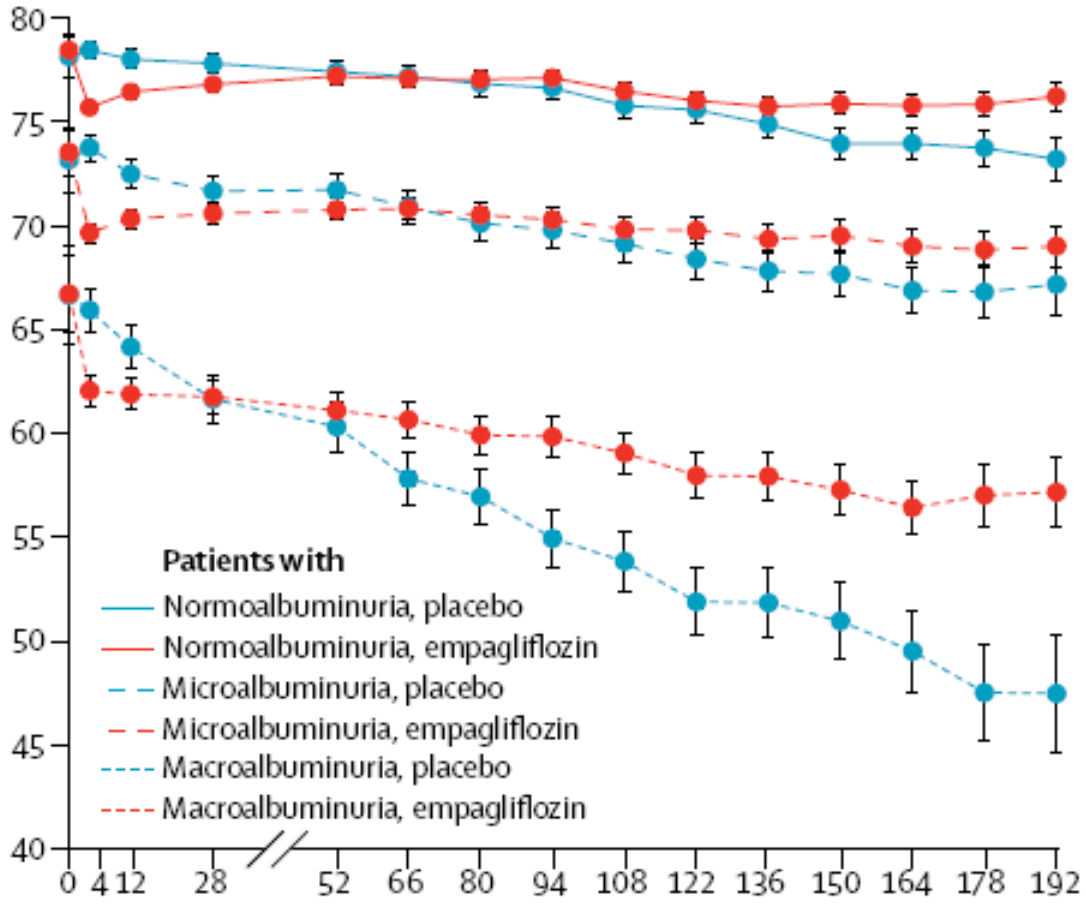
**UACR (mg/g) during FU (weeks)**




Cherney…Wanner for EMPAREG group, Lancet DE 2017

# Antialbuminuric effects and Nephroprotection in EMPA by basal level of albuminuria

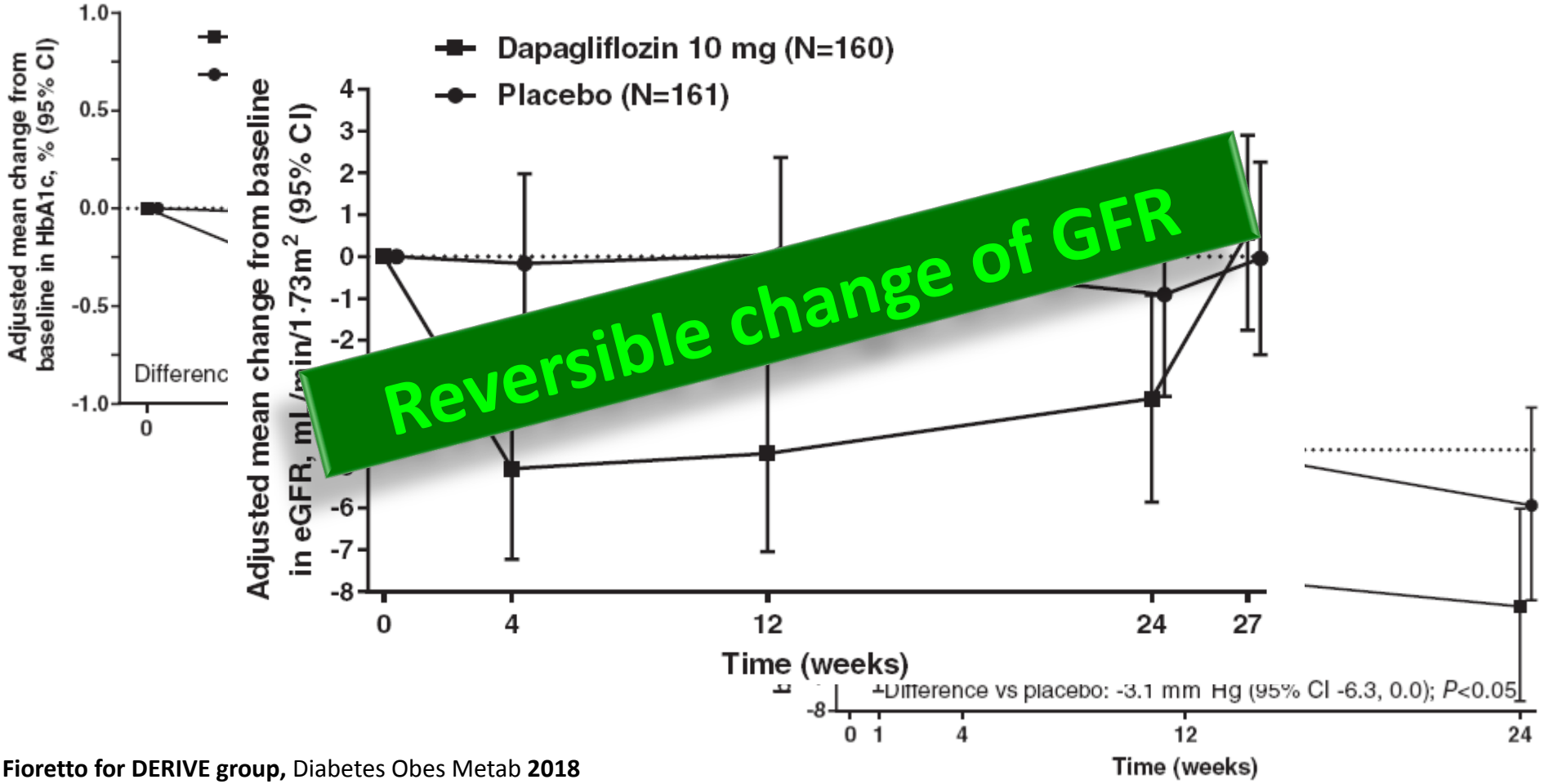
**eGFR (mL/min/1.73m$^2$) during FU**




Cherney…Wanner for EMPAREG group, Lancet DE 2017

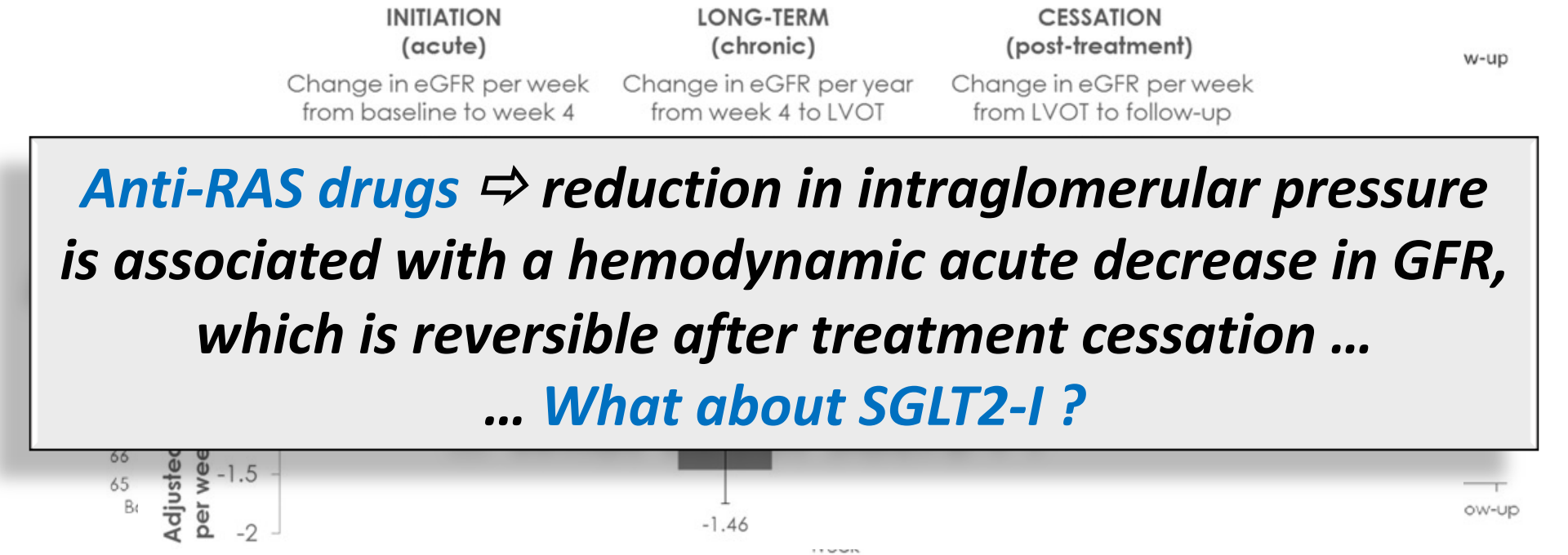
# Efficacy of Dapagliflozin in patients with DM2 and moderate CKD

- **Double-blind, phase 3 RCT, 24 wk-treatment, 321 DM-CKD stage 3A**
- **HbA1c 8.1%; MDRD eGFR: 53 mL/min; UACR: 26 mg/g**




**Fioretto for DERIVE group,** Diabetes Obes Metab **2018**

# Empagliflozin and Kidney Function Decline in Patients with Type 2 Diabetes: A Slope Analysis from the EMPA-REG OUTCOME Trial



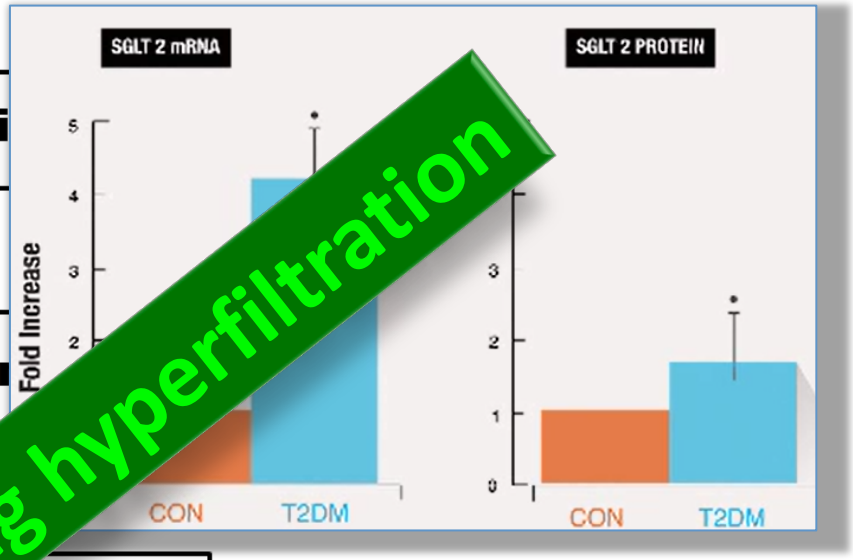

***Anti-RAS drugs ⇨ reduction in intraglomerular pressure is associated with a hemodynamic acute decrease in GFR, which is reversible after treatment cessation …***

***… What about SGLT2-I ?***

**These data support an hemodynamic effect of Empa, which may lead to reductions in intraglomerular pressure. During chronic maintenance treatment, this glomerular response to Empa may translate into long-term preservation of kidney function**

**Wanner, JASN published online 12 Oct 2018**

# The hemodynamic nephroprotective effects of SGLT-2-I




Hyperglycemi

Proximal tubule g

SGLT-2 Inhibition

Proxi sorption

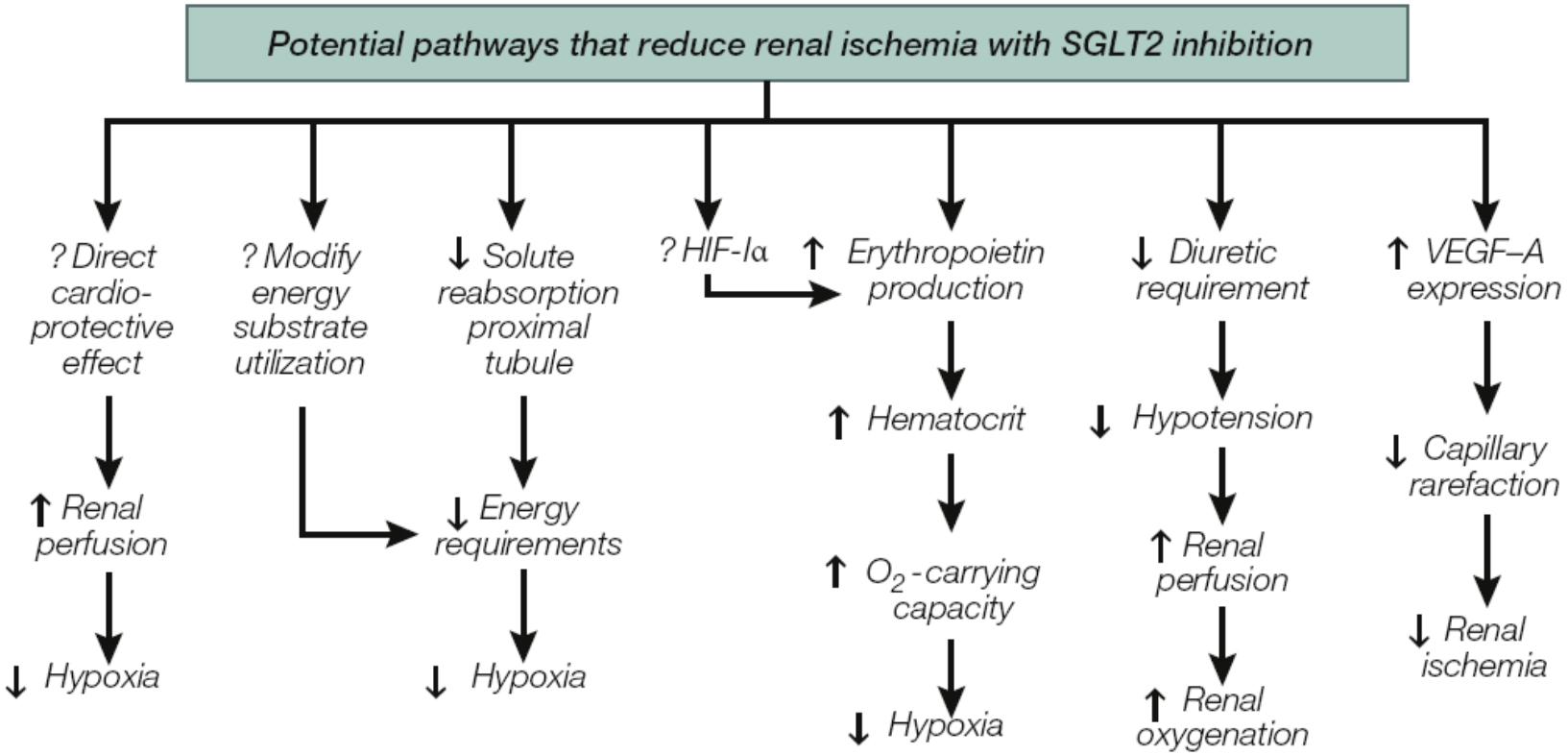
Distal NaCl delivery

SNGFR

Correction of damaging hyperfiltration

Blantz AJP 2004
Rahmoune, Diabetes 2005
De Nicola, AJKD 2014

# SGLT-2 Inhibitors …
# not only anti-hyperfiltration agents



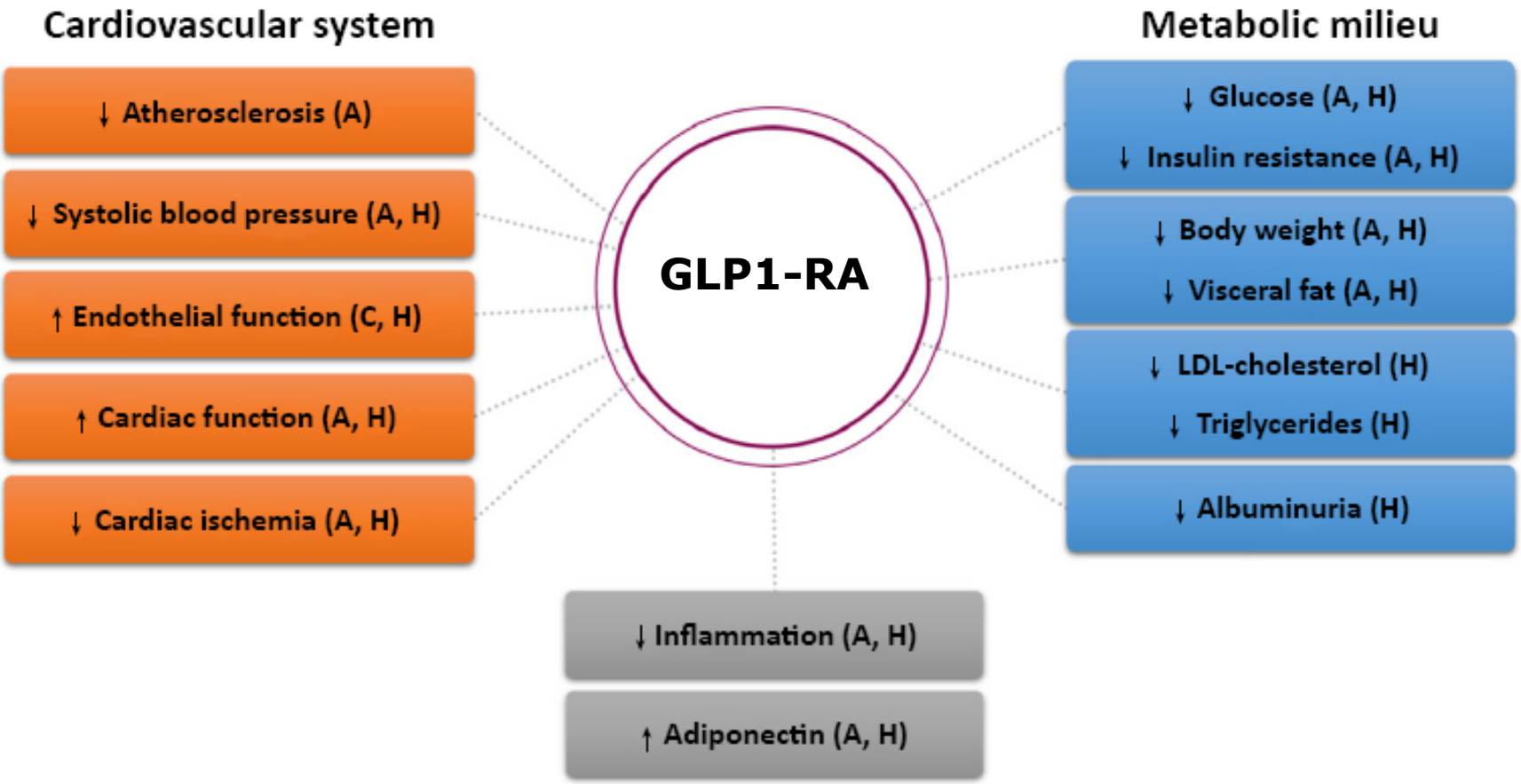

Rahmoune, Diabetes 2005

# More SGLT-2-I trials in CKD are coming

| Agent | Brand Name/Company | Admin/ Route | Half-Life/Dose (sc) | Elimination/Use According to Renal Function (eGFR) |
|---|---|---|---|---|
| Shorter-acting GLP-1RA | | | | |
| Exenatide | Byetta®/ AstraZeneca (Cambridge, England) | Twice daily/sc | ~2.4 hrs/5–10 µg | Glomerular filtration/ contraindicated eGFR <30 mL/min/1.73 $m^2$ |
| Lixisenatide | Lyxumia® (EU) Adlyxin™ (US)/Sanofi (Gentilly, France) | Once daily/ sc | ~2–5 hrs/ 20 µg | Glomerular filtration/ not recommended eGFR <30 mL/min/1.73 $m^2$ |
| Longer-acting GLP-1RA | | | | |
| Liraglutide | Victoza®/ Novo Nordisk (Bagsværd, Denmark) | Once daily/ sc | ~13 hrs/ 1.2–1.8 mg | Endogenous metabolism/ not recommended eGFR <30 mL/min/1.73 $m^2$ |
| Exenatide QW | Bydureon®/ AstraZeneca (Cambridge, England) | Once weekly/ sc | ~2.4 hrs/ 2 mg (prolonged release) | Glomerular filtration/ contraindicated eGFR <30 mL/min/1.73 $m^2$ |
| Dulaglutide | Trulicity®/ Eli Lilly and Co. (Indiana, USA) | Once weekly/ sc | ~4.7 days/ 0.75, 1.5 mg | Endogenous metabolism/ caution eGFR <50 mL/ min/1.73 $m^2$ |
| Albiglutide | Eperzan® (Canada, EU) Tanzeum™ (US)/GSK (London, England) | Once weekly/ sc | ~4–5 days/ 30, 50 mg | Endogenous metabolism/ caution eGFR <50 mL/ min/1.73 $m^2$ |

**COMING SOON: Semaglutide injectable once weekly**

# GLP-1-RA: Potential Mechanisms of Cardiorenal Benefits



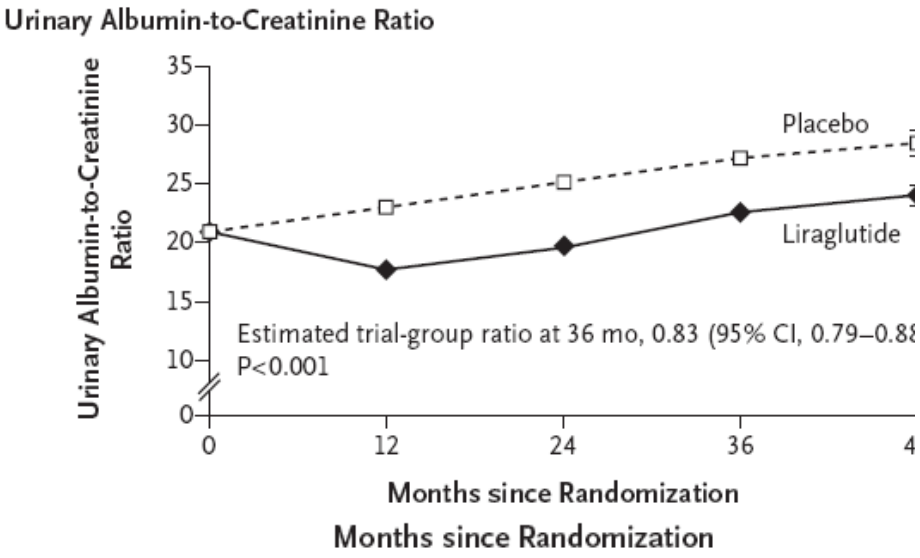
# SGLT-2-I versus GLP-1-RA

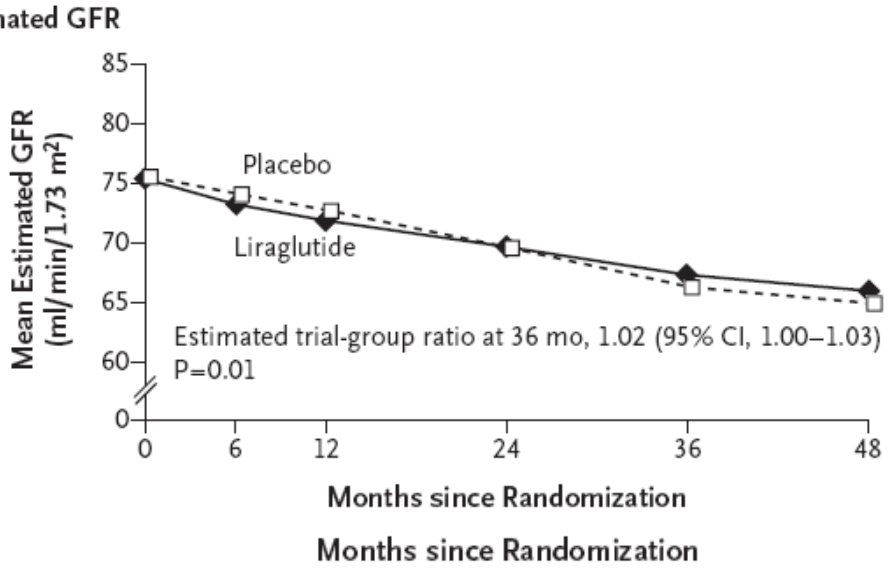
| Properties/effects | SGLT-2 inhibitors | Glucagon-like peptide-1 receptor agonists |
|---|---|---|
| Molecules | Canagliflozin, dapagliflozin, empagliflozin, ertuglifozin | Exenatide, liraglutide, lixisenatide, semaglutide |
| Administration | Oral, once a day | Subcutaneous, once a day to once a week |
| Target organ | Kidney (proximal tubule) | Endocrine pancreas |
| Effect | Forced glucosuria<br>Reduction in glucose toxicity | Enhanced insulin secretion (incretin mimetics) |
| Primary mechanism | Insulin-independent | Glucose-dependent |
| Effect on glucagon | Increased secretion | Decreased secretion |
| Food intake | Increase (compensatory mechanism) | Reduction (central and peripheral effects) |
| Reduction in HbA1c | −0.7 to −1.0% | −1.0 to −1.2% |
| Risk of hypoglycemia | Low (except if added to sulfonylurea or insulin) | Low (except if added to sulfonylurea or insulin) |
| Change in body weight | Diminution | Diminution |
| Arterial blood pressure | Lowering effect | Lowering effect |
| Other effects | Increase in haematocrit<br>Reduction in serum uric acid | Reduced postprandial hypertriglyceridaemia<br>Anti-atherosclerotic effects (?) |
| Fatty liver | Reduced | Reduced |
| Adverse events | Mycotic genital infections<br>Urinary tract infections (rare)<br>Dehydration/hypotension<br>Euglycaemic ketoacidosis<br>Fractures, amputations (canagliflozin) | Nausea, vomiting<br>Pancreatitis (initially suspected but not confirmed) |
| Use in patients with renal impairment | No initiation if eGFR < 60 ml/min/1.73 $m^2$<br>Stop if eGFR < 45 ml/min/1.73 $m^2$ | Use now approved if eGFR > 15 ml/min/1.73 $m^2$ |
| Cardiovascular protection | Superiority versus placebo (EMPA-REG OUTCOME, CANVAS) | Superiority versus placebo (LEADER, SUSTAIN 6) |
| Prevention of heart failure | Less hospitalization for heart failure (EMPA-REG OUTCOME, CANVAS) | No effect demonstrated |
| Renal protection | Proven in EMPA-REG OUTCOME and CANVAS | Proven in LEADER |

The NEW ENGLAND JOURNAL of MEDICINE

# Liraglutide and Renal Outcomes in Type 2 Diabetes

- 9340 patients with type 2 DM and high CV risk
- High Ualb 11%, eGFR<60 22%
- Median follow-up 3.84 years
- Composite renal outcome: new-onset persistent macroUalb, persistent doubling of the sCreat and eGFR <45, need for continuous RRT, death due to renal disease

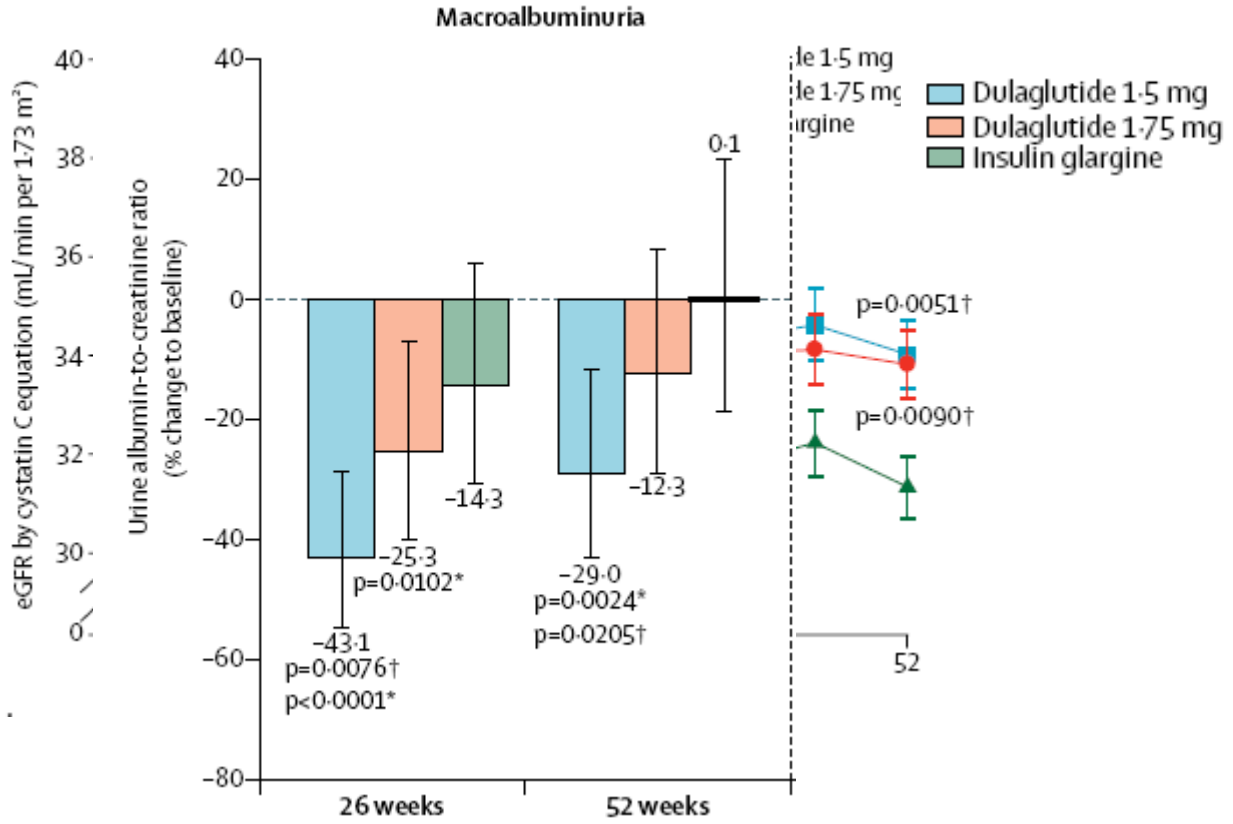



**J Mann, LEADER, NEJM 2017**

# Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

- **577 patients with type 2 DM and CKD stage 3 and 4**
- **High Ualb 78%, eGFR 38**
- **Follow-up 18 months**
- **Secondary outcomes: change in eGFR**



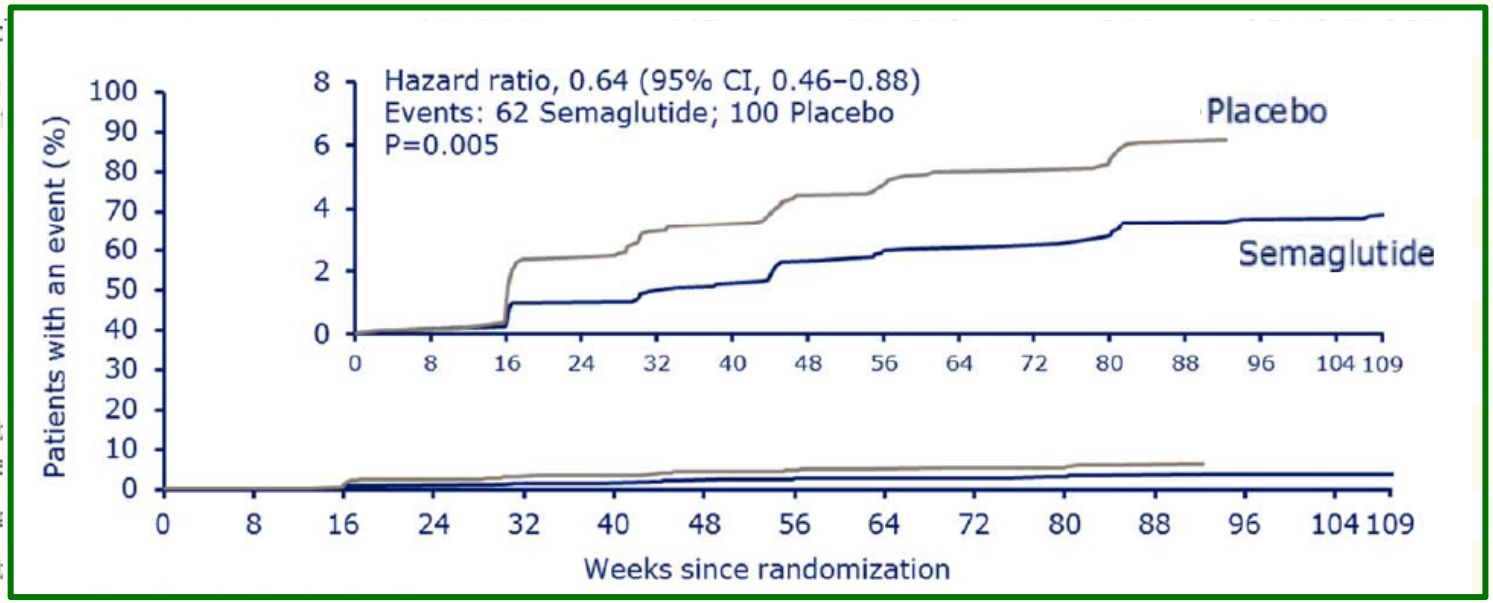

K Tuttle, Lancet DE 2018

# Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

SUSTAIN-6 Investigators

**Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.**

| Outcome | Semaglutide (N=1648) | | Placebo (N=1649) | | Hazard Ratio (95% CI)* | P Value |
|---|---|---|---|---|---|---|
| | *no. (%)* | *no./100 person-yr* | *no. (%)* | *no./100 person-yr* | | |
| Primary composite outcome† | 108 (6.6) | 3.24 | 146 (8.9) | 4.44 | 0.74 (0.58–0.95) | <0.001 for noninferiority; 0.02 for superiority |
| Expanded | | | | | | 0.002 |
| All-cause | | | | | | 0.03 |
| Death | | | | | | |
| From | | | | | | 0.79 |
| From | | | | | | 0.92 |
| Nonfatal | | | | | | 0.12 |
| Nonfatal | | | | | | 0.04 |
| Hospitali | | | | | | 0.49 |
| Revascul | | | | | | 0.003 |
| Hospitali | | | | | | 0.57 |
| Retinopathy complications¶ | 50 (3.0) | 1.49 | 29 (1.8) | 0.86 | 1.76 (1.11–2.78) | 0.02 |
| New or worsening nephropathy¶ | 62 (3.8) | 1.86 | 100 (6.1) | 3.06 | 0.64 (0.46–0.88) | 0.005 |

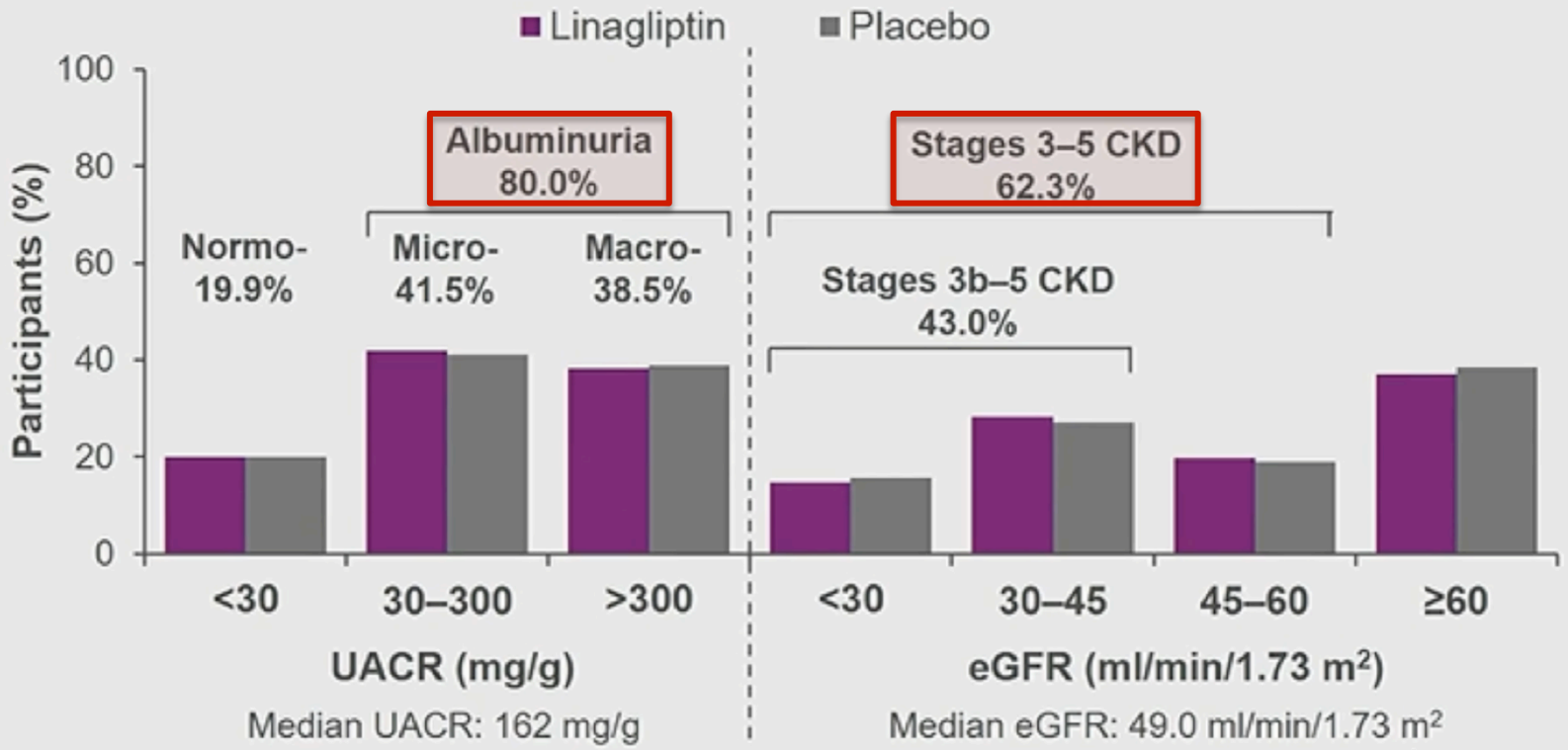


# DPP-4-I

# CARMELINA trial in DM2

## *ASN, 24-28 Oct 2018, San Diego (CA)*

CARMELINA included a large proportion of patients with kidney disease

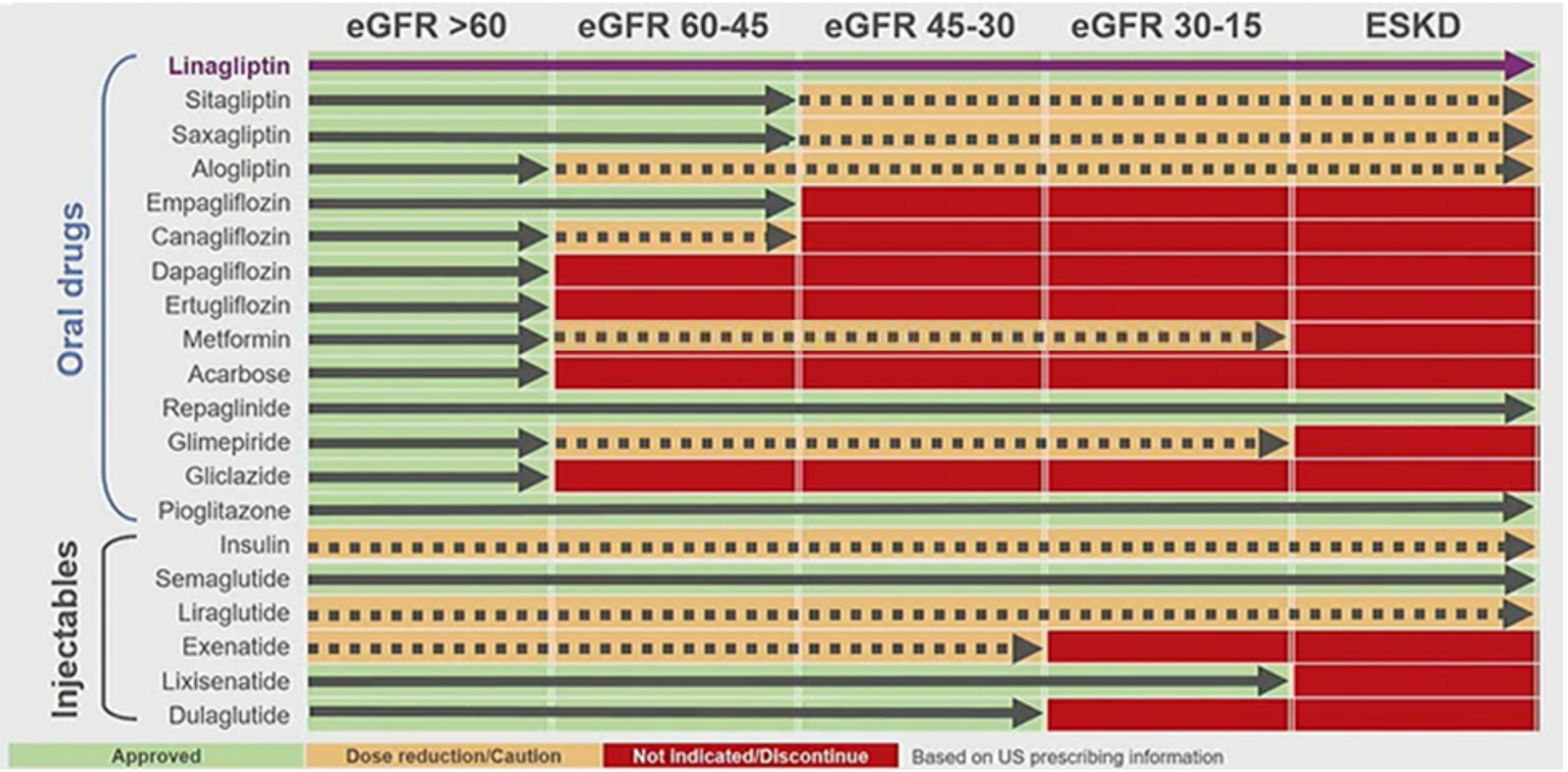



Treated set

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

CARMELINA

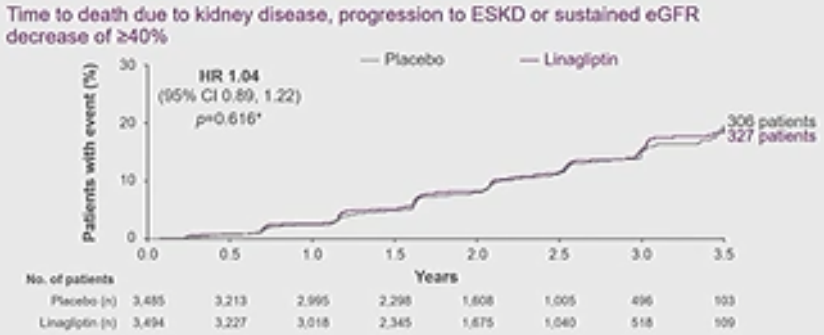
# Patients with type 2 DM and CKD have limited glucose-lowering treatment options

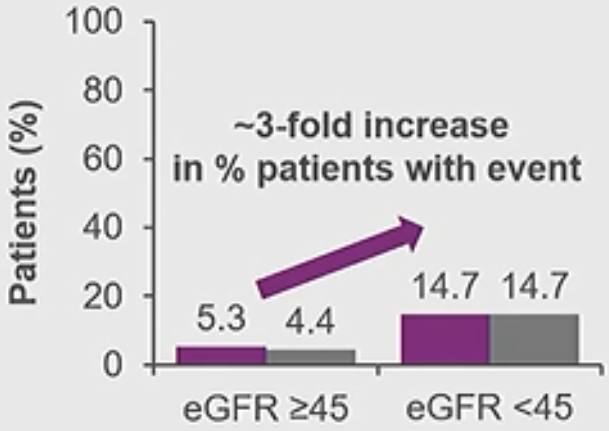


# CARMELINA trial in DM2

## *ASN, 24-28 Oct 2018, San Diego (CA)*

### Effects on key secondary kidney outcome




| | Linagliptin n/N (%) | Placebo n/N (%) | HR (95% CI) | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| All patients | 327/3494 (9.4) | 306/3485 (8.8) | 1.04 (0.89, 1.22) | | |
| eGFR ≥45 | 105/1984 (5.3) | 87/1995 (4.4) | 1.19 (0.89, 1.58) | | |
| eGFR <45 | 222/1510 (14.7) | 219/1490 (14.7) | 0.97 (0.80, 1.17) | | 0.240† |



CARMELINA

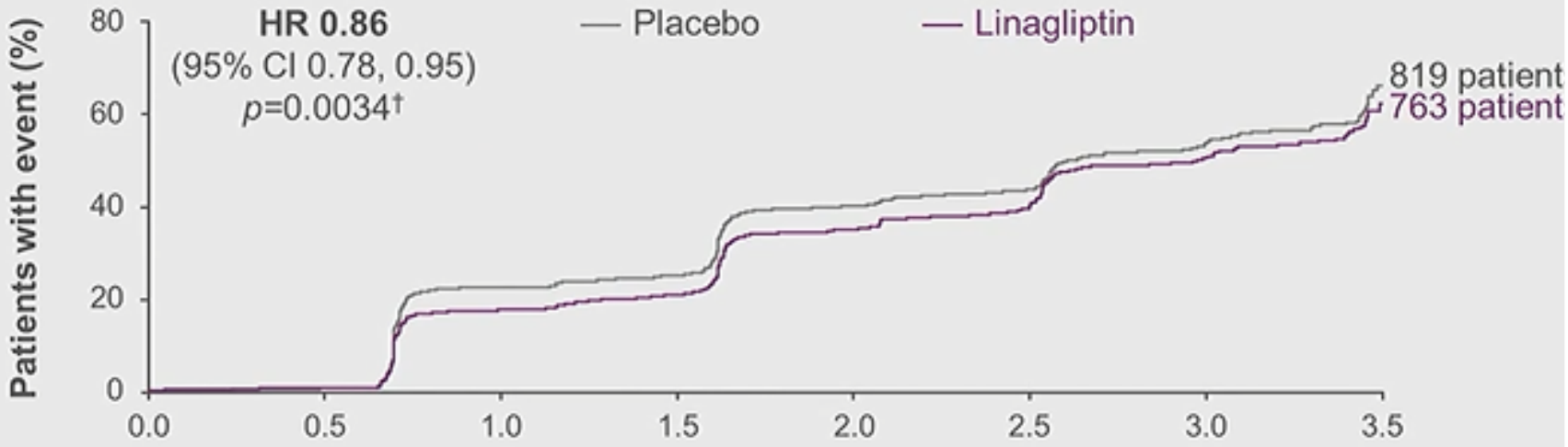
p-value for treatment interaction; eGFR <45 and ≥45 subgroup analysis was post-hoc.

# CARMELINA trial in DM2

## *ASN, 24-28 Oct 2018, San Diego (CA)*

### Lingaliptin significantly reduced the risk of progression of albuminuria

Time to first occurrence of albuminuria progression*



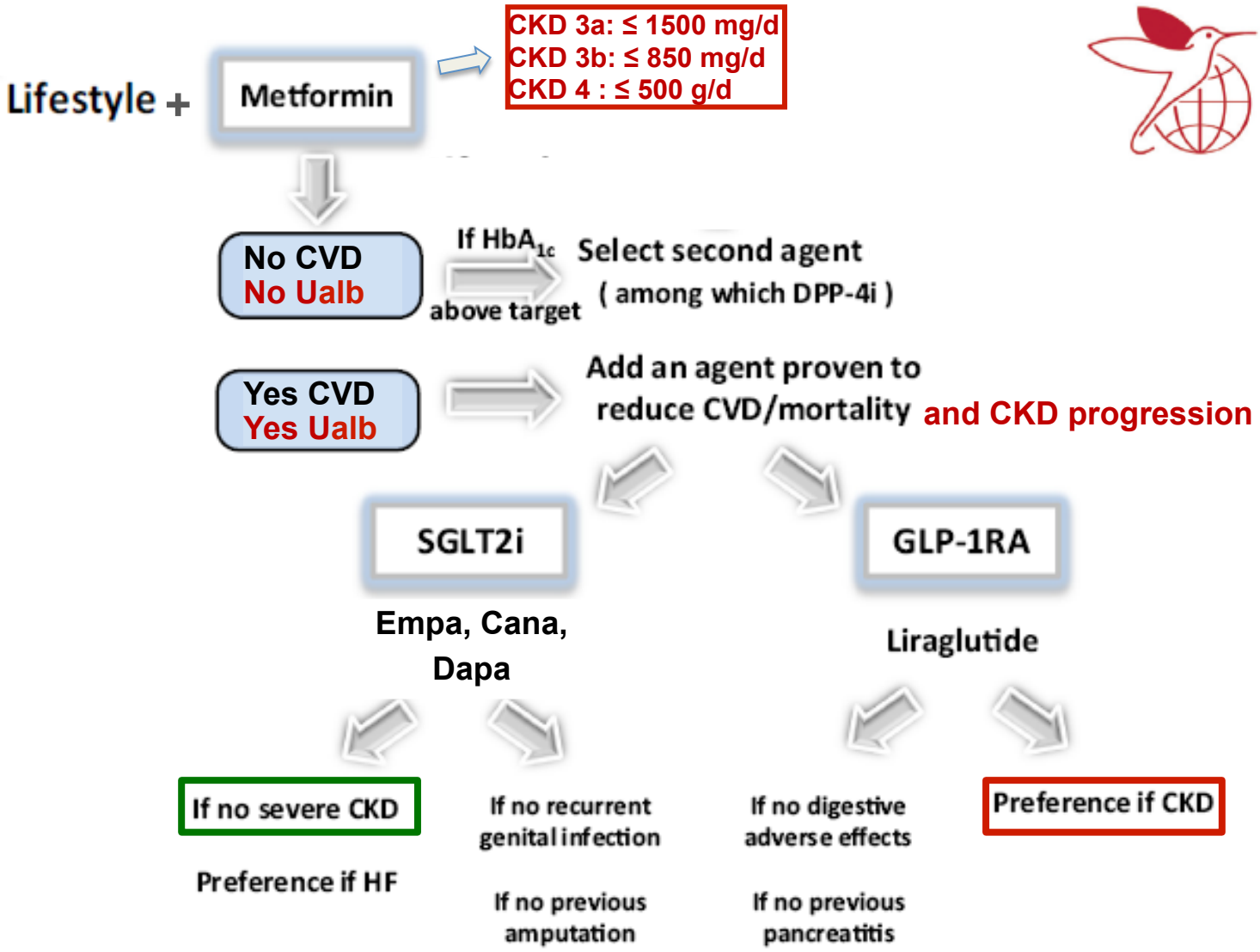

| No. of patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo (n) | 2129 | 1972 | 1434 | 1139 | 667 | 430 | 200 | 35 |
| Linagliptin (n) | 2162 | 2004 | 1554 | 1263 | 756 | 487 | 213 | 39 |

Linagliptin event rate 21.36/100 PY Placebo event rate 2.4.54/100 PY
Treated set, Kaplan-Meier estimate. Hazard ratio and 95% CI based on Cox regression model with terms for treatment group (p=0.0034) and region (p<0.0001)
*change from normo- to micro- or macroalbuminuria, or from micro- to macroalbuminuria; †two-sided

CARMELINA

# Take-Home

# New antidiabetic approach in non-dialysis DM2-CKD




Modified from Scheen for the Int. Diab. Fed., *Diab Res Clin Practice 2018*