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Diabetic Kidney Disease State-of-the-Art Circa 2017

Katherine R. Tuttle, MD, FASN, FACP, FNKF

Executive Director for Research
Providence Health Care

Regional Co-Principal Investigator
Institute of Translational Health Sciences
Professor of Medicine
University of Washington

Disclosures

Consultant on therapeutics for diabetes and kidney disease:

- Eli Lilly and Company
- Boehringer Ingelheim

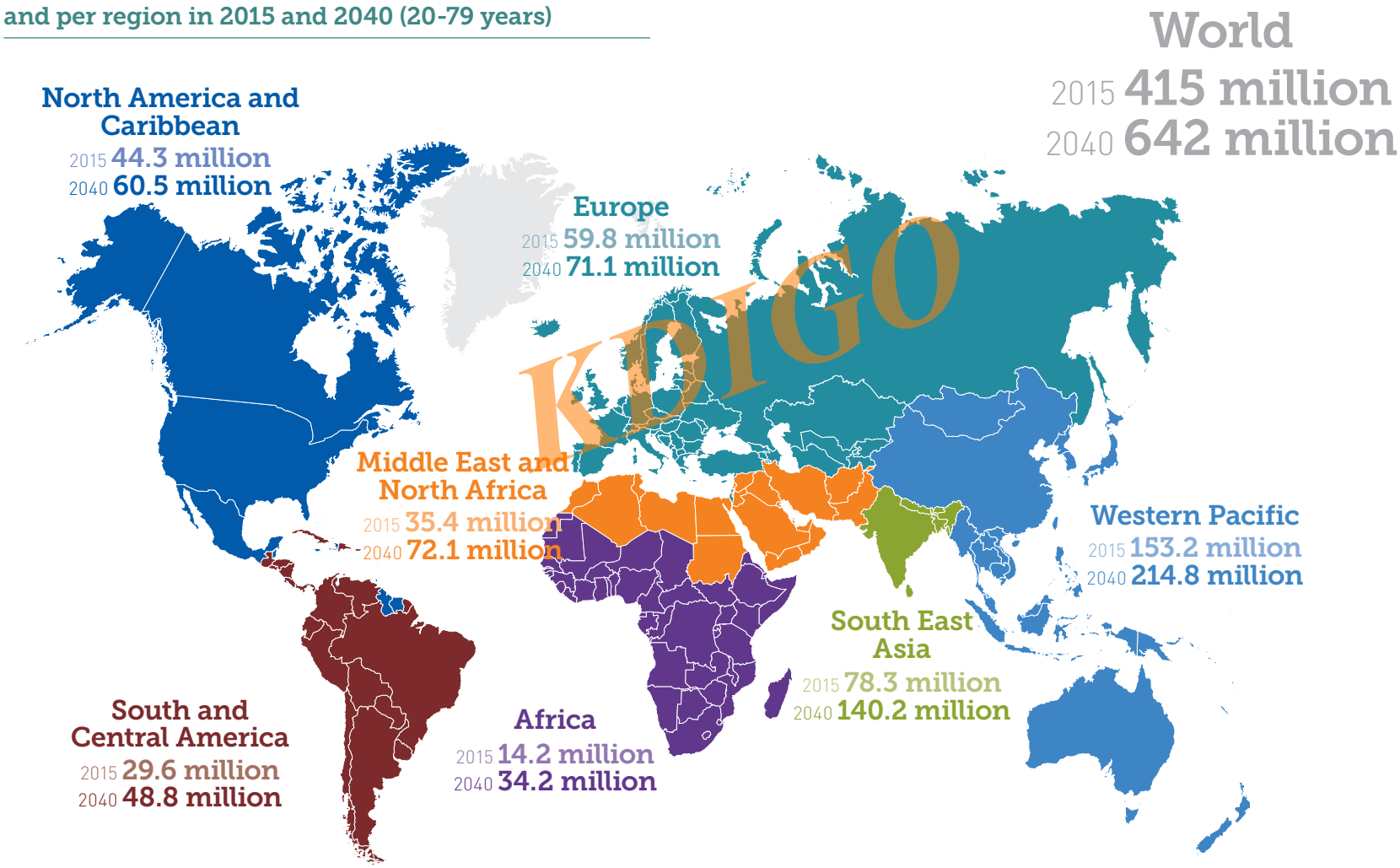
Objectives

- Understand unmet needs in diabetic kidney disease (DKD).
- Review limits and risks of current treatments to prevent or treat DKD.
- Examine effects of new drugs to lower blood glucose on DKD.
- Discuss barriers and facilitators for DKD therapeutic development.

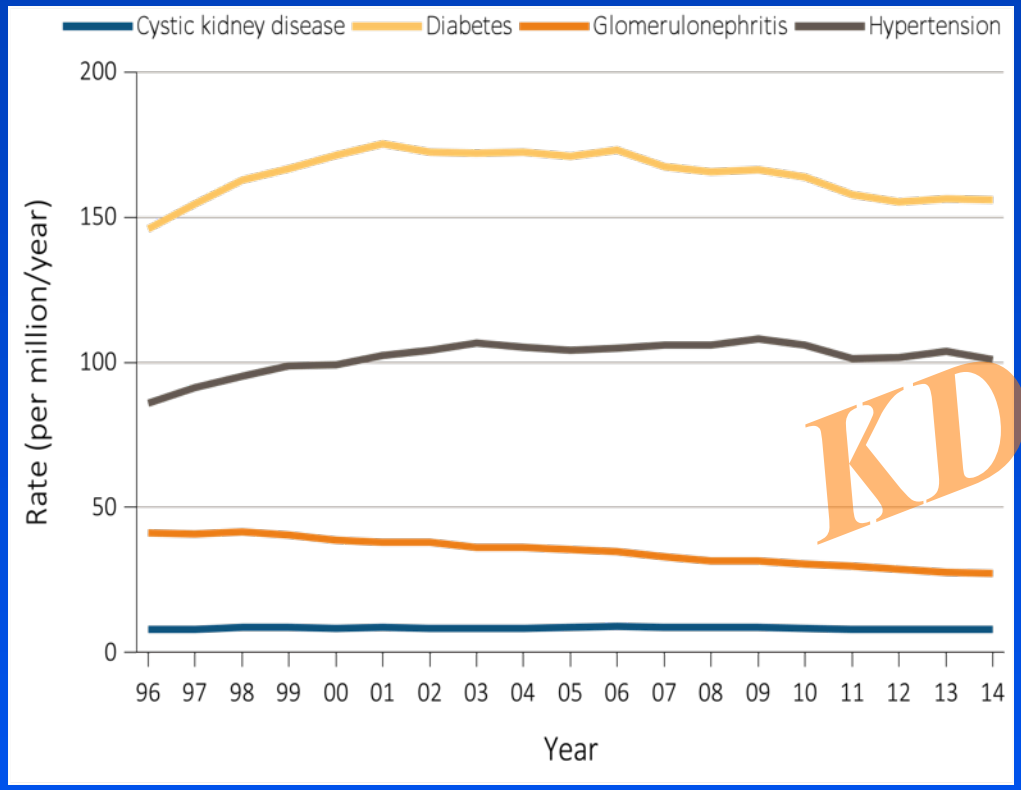
Diabetes: A global emergency

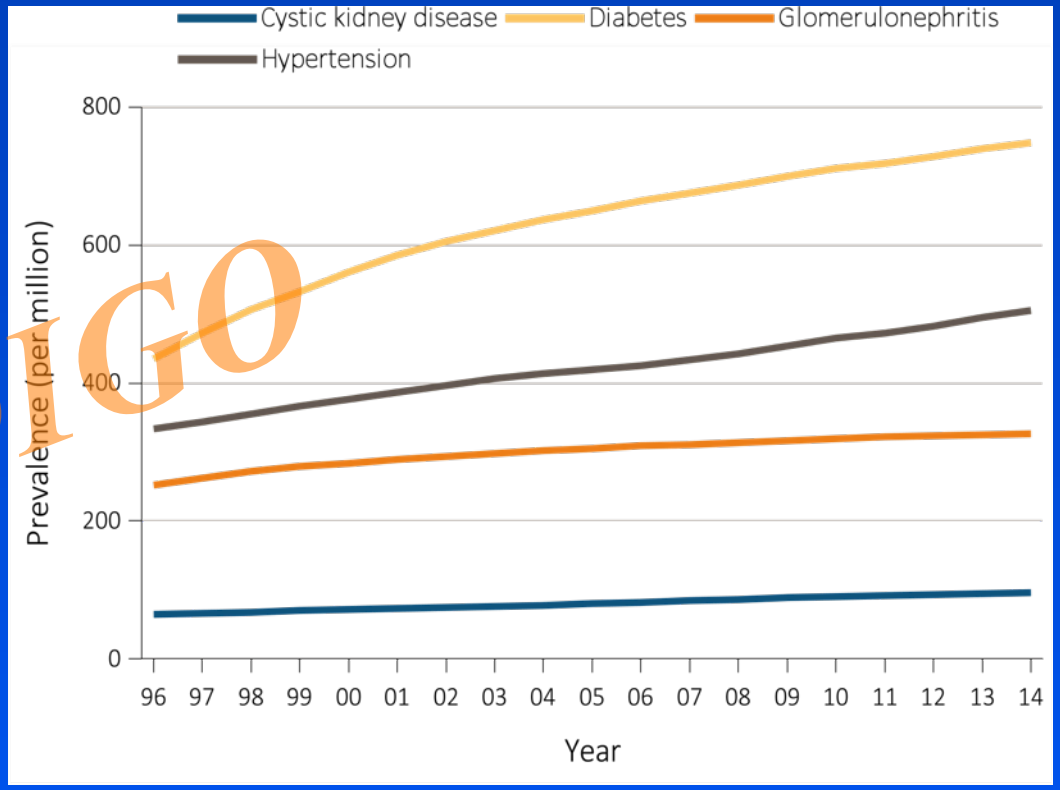
International Diabetes Federation

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



ESRD Incidence and Prevalence Rates by Primary Diagnosis in the USA





Incidence rates of ESRD attributed to diabetes are stable to **decreasing.**

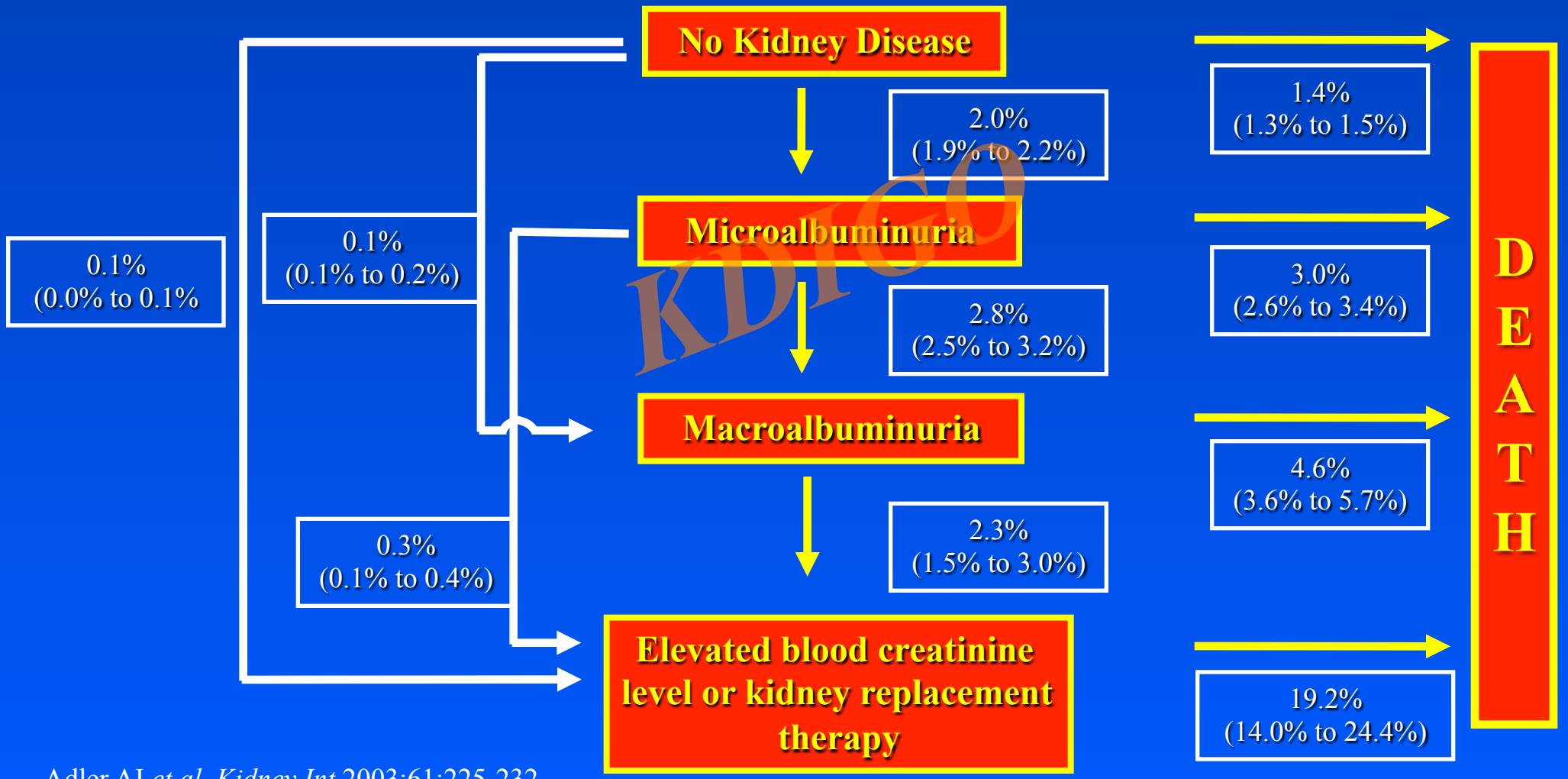
Prevalence rates of ESRD attributed to diabetes are **increasing.**

Rates adjusted for age, gender, & race. *USRDS* 2016

Diabetic Kidney Disease Risks

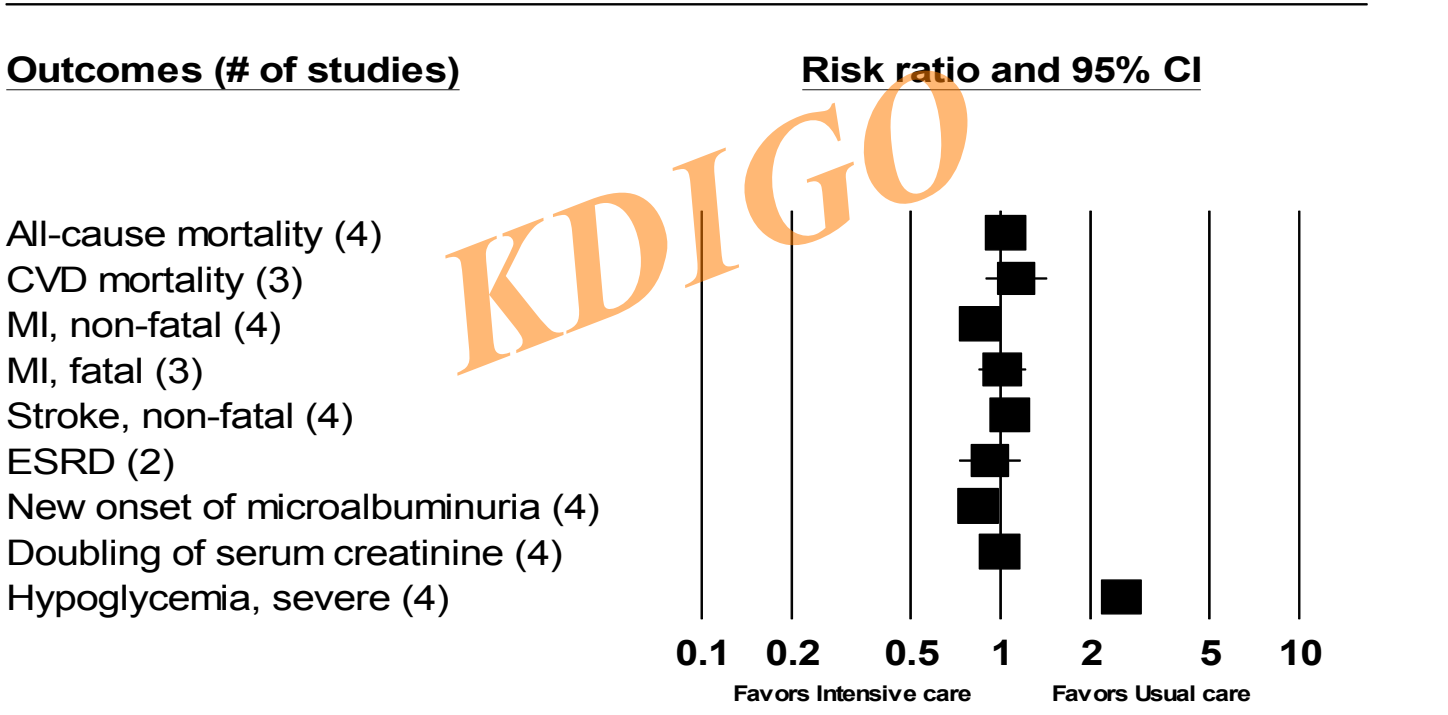
- Progress to ESRD (10 %)
  - Dialysis
  - Kidney transplant
- Die of other causes without reaching ESRD (90 %)
  - CVD
  - Infections

Annual Rates of Kidney Disease Progression and Death in Type 2 Diabetes (UKPDS)



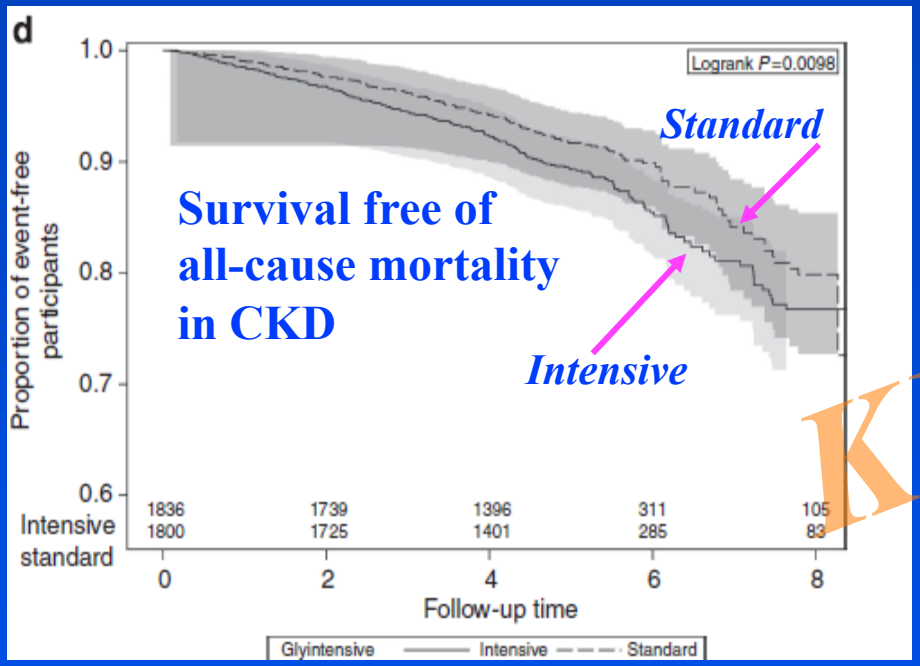
Adler AI *et al. Kidney Int* 2003;61:225-232

Limits and Risks of Current Treatments: Intensive Glycemic Control



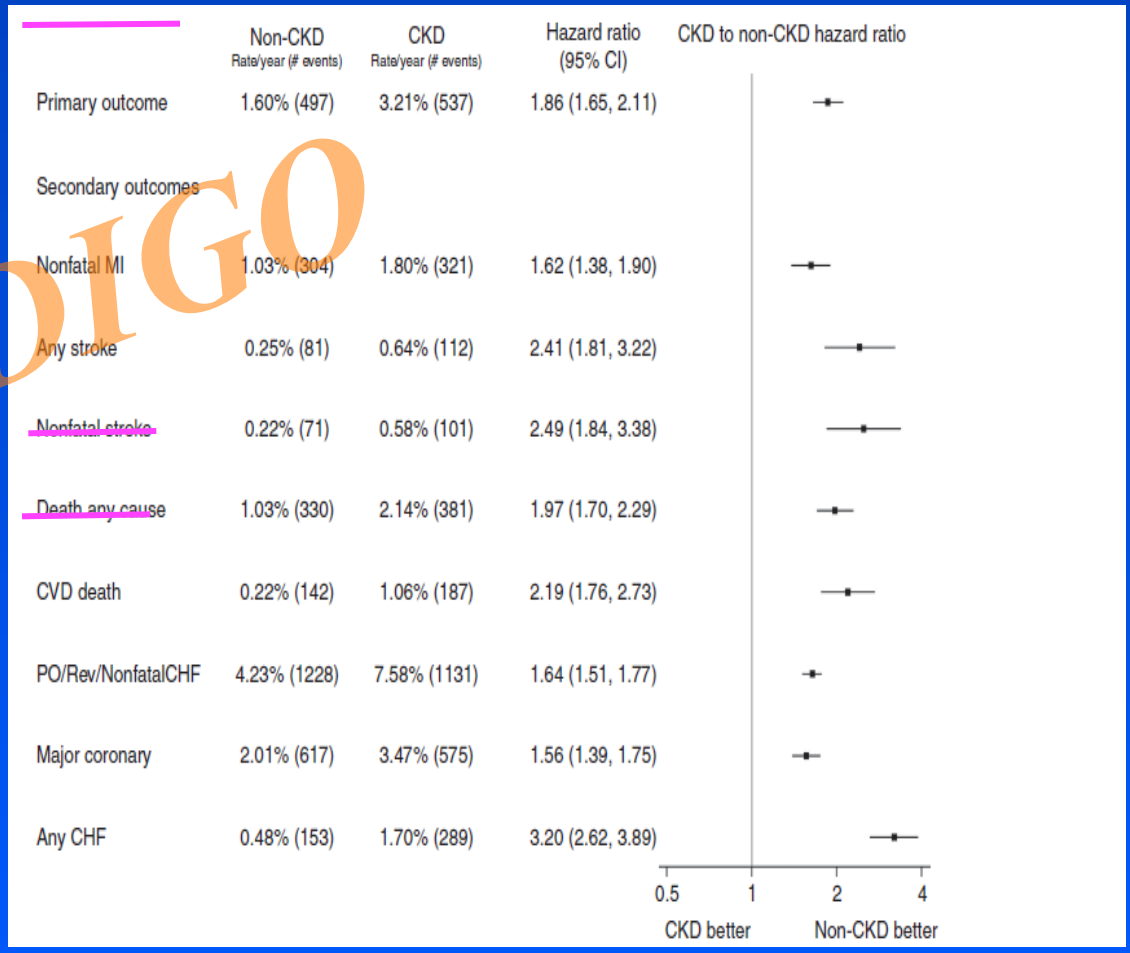
NFK-KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850-886

Mortality, CVD Outcomes, and Severe Hypoglycemia in Diabetes with CKD: ACCORD



Most CKD defined by microalbuminuria: 69 %
eGFR <60 ml/min/1.73m^2: 22 %

CKD at baseline	Glycemia arm	Events	Percent	Annual incidence
Overall percent and annual incidence of hypoglycemia requiring assistance				
Non-CKD	Standard	172	5.2	1.1
Non-CKD	Intensive	500	15.3	3.5
CKD	Standard	165	9.1	2.0
CKD	Intensive	398	21.5	5.3



Papademetriou V *et al. Kidney Int* 2015;87:649-659

ADA Standards of Medical Care in Diabetes Circa 2017

- Recommendations for A1C Goals
  - A reasonable A1C goal for many nonpregnant adults is <7 % (A)
- Exceptions
  - ***Less stringent A1C goals (<8 %)*** may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive co-morbid conditions. (B)
  - ***More stringent A1C goals (<6.5 %)*** for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects… Might include those with short duration of diabetes, type 2 diabetes treated only with lifestyle or metformin, long life expectancy, no significant CVD. (C)

CKD

KDIGO

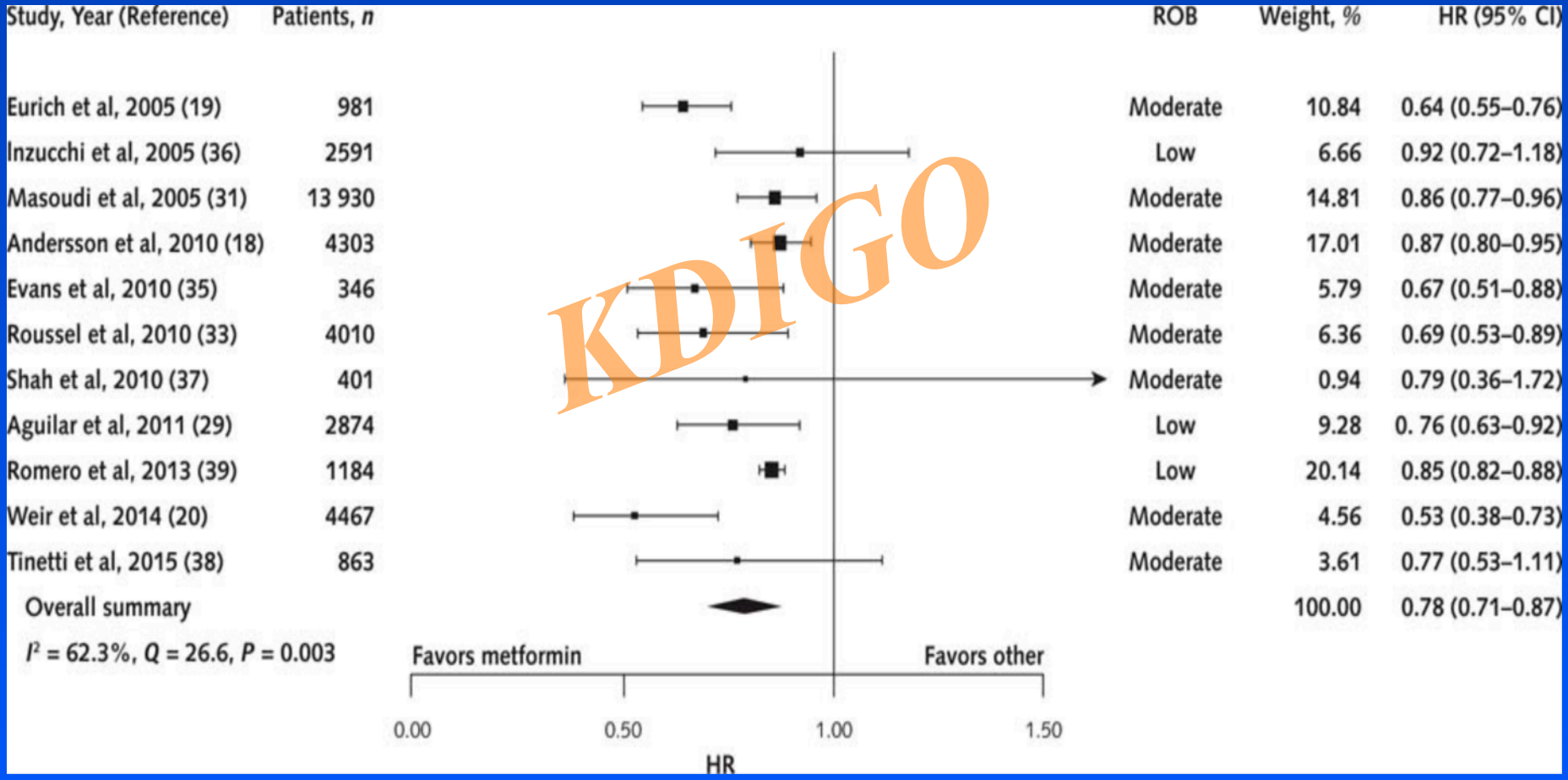
ADA. Standards of Medical Care in Diabetes. *Diabetes Care* 2017;40:S50

US FDA Label Change for Metformin in Diabetes and CKD: April 2016

- **Assess eGFR**
  - Before starting metformin and at least annually.
  - Consider more frequent monitoring in patients at high-risk of eGFR decline.
- **CKD stage 3a:** If eGFR <60 and ≥45 mL/min/1.73m^2
  - Stop metformin with iodinated contrast administration, CHF, liver disease, alcoholism. (*volume depletion, acute illness – KRT comment on FDA guidance*)
  - Reassess eGFR at 48 hours after contrast administration.
- **CKD stage 3b:** If eGFR <45 and ≥30 mL/min/1.73m^2
  - Do not initiate metformin.
  - Metformin may be continued, but reassess benefits versus risks of treatment.
  - Follow same precautions as above.
- **CKD stage 4:** If eGFR <30 mL/min/1.73m^2
  - Do not use metformin.

US FDA website
Accessed April 21. 2016

Meta-analysis of All-Cause Mortality in Moderate-to-Severe CKD by Metformin Usage



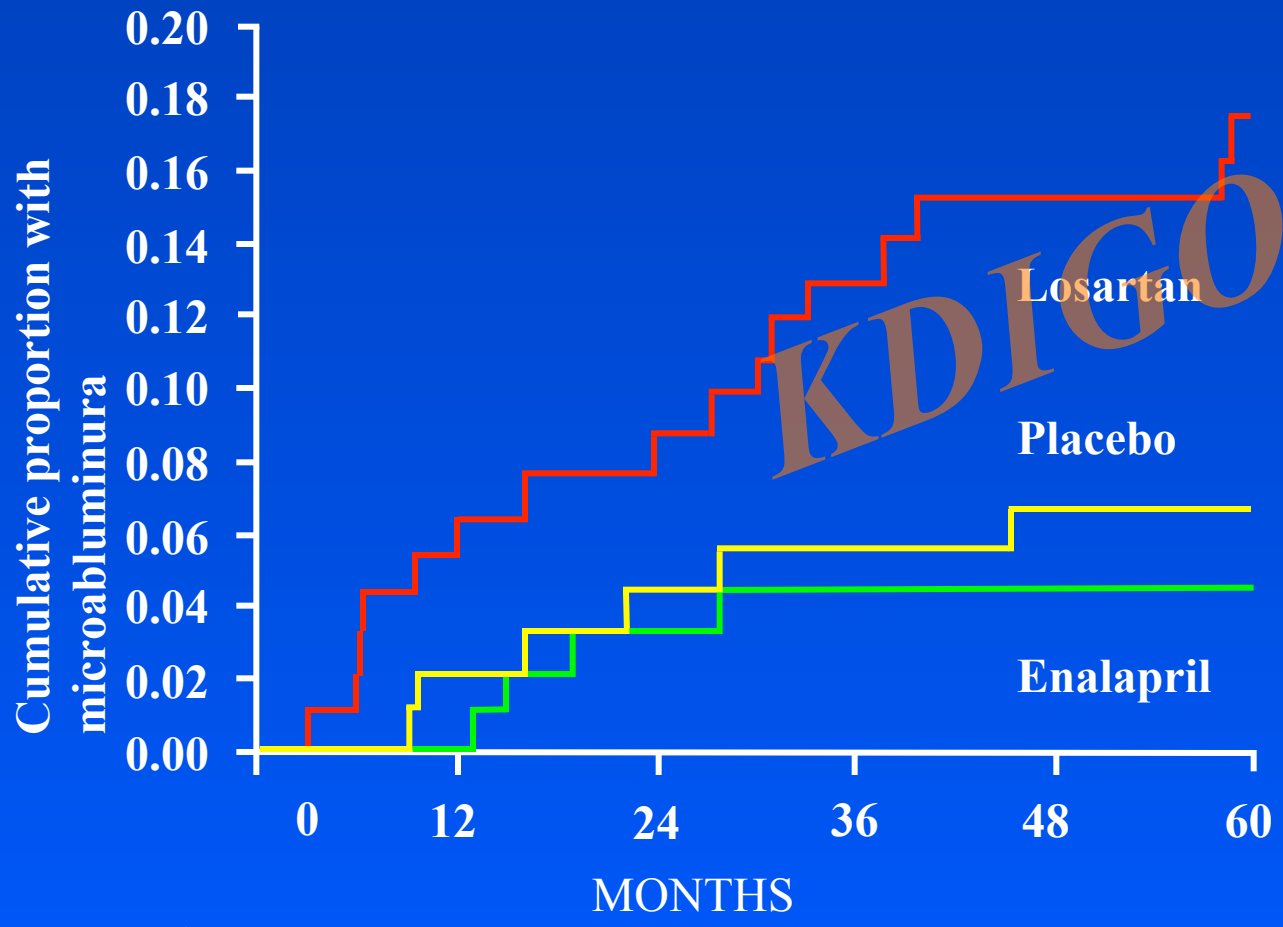
Crowley MJ *et al. Ann Intern Med* 2017;166:191-200.

Limits and Risks of Current Treatments: Anti-Hypertensive Agents

Myths Dispelled

- An ounce of prevention… Put ACE inhibitors/ARBs in the drinking water.
- More is better… Use dual RAS inhibition.

Primary Prevention of Diabetic Kidney Disease: RAS Blockade with ACE Inhibitor or ARB



- RASS (n=285): Normotensive, normoalbuminuric, type 1 diabetes with biopsy
- No benefit of RAS blockade
  - Renal structure
  - Measured GFR

Similar results obtained in Europeans and American Indians with type 2 diabetes.

Mauer M *et al. NEJM* 2009;361:40-51
Bilous R et *al. Ann Intern Med* 2009;151:11-20
Tanamas SK *et al. Diabetes Care* 2016;39:2004-201

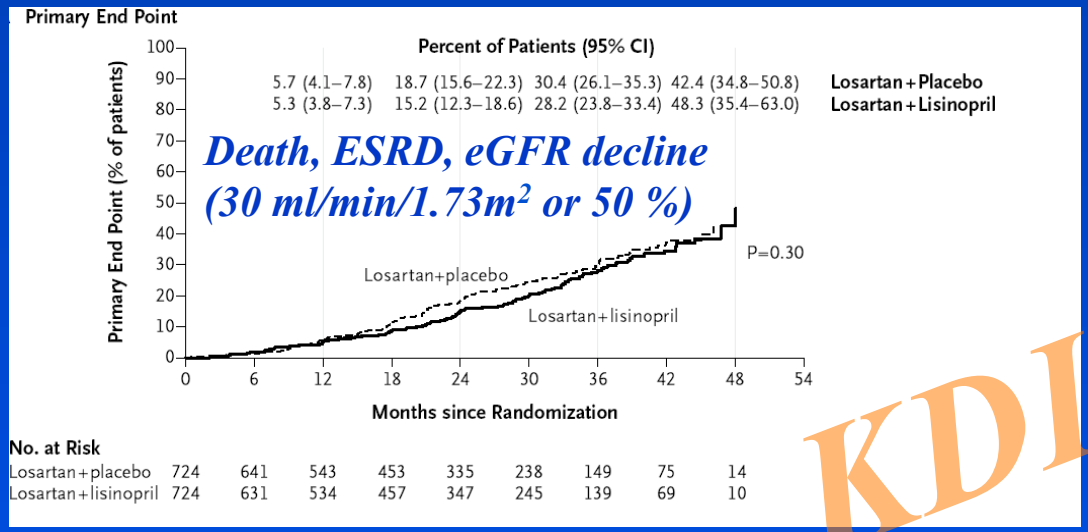
Dual RAS Blockade (losartan plus lisinopril): VA-NEPHRON-D Stopped for Safety

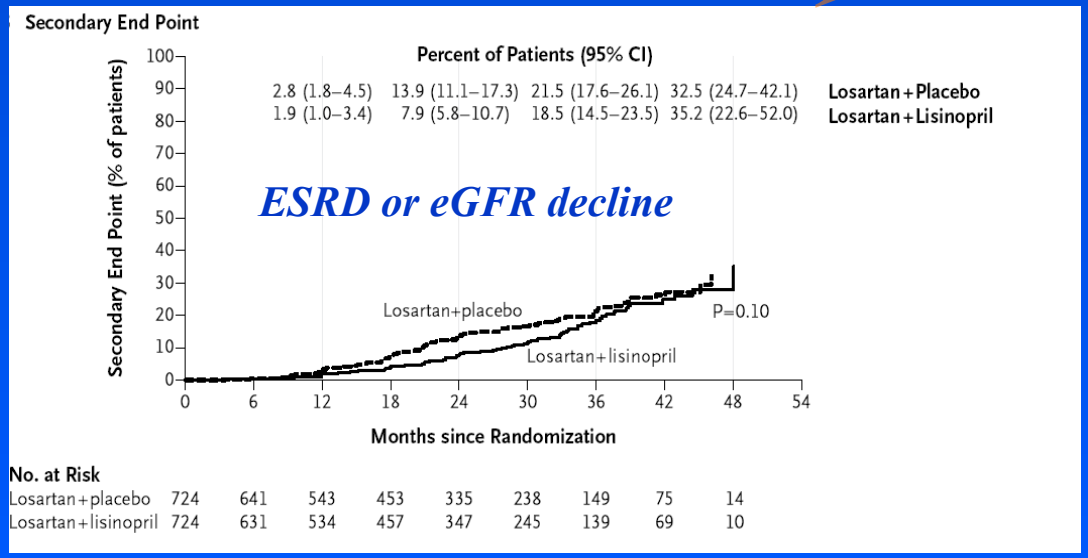
Type 2 diabetic US veterans with macroalbuminuria (n=1448)

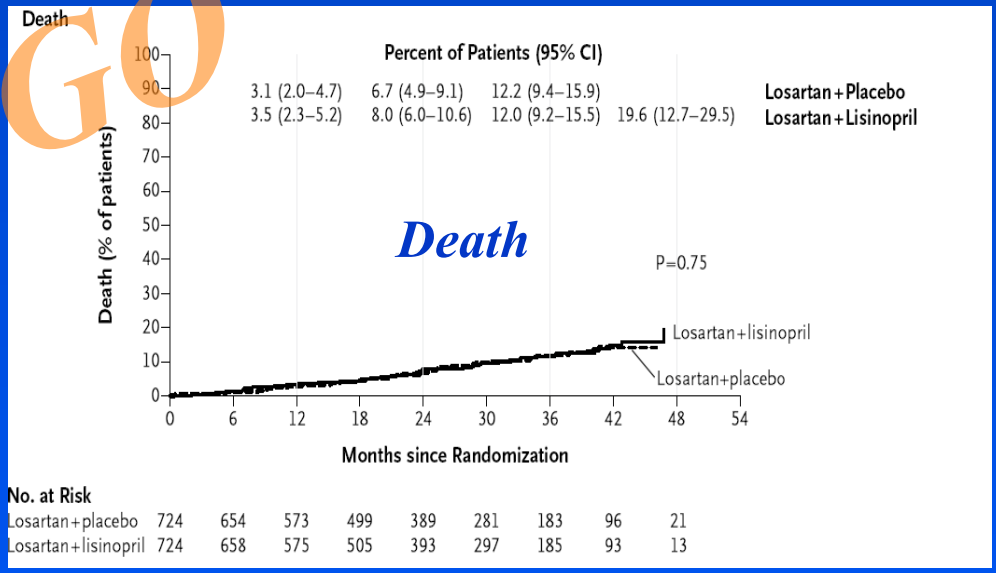
- **Median baseline ACR ≃ 850 mg/g**
  - Decreased to 517 mg/g vs 701 mg/g in combination and losartan groups after 1 year, p<0.001
- **Mean baseline eGFR = 54 ml/min/1.73^2**
  - Decreased 2.7 vs 2.9 ml/min/1.73^2 in combination and losartan after 1 year, p=0.17
- **AEs more frequent in combination group**
  - Hyperkalemia 9.9 % vs 4.4 %, HR 2.8 (1.8-4.3), p<0.001
  - Acute kidney injury 18 % vs 11 %, HR 1.7 (1.3-2.2), p<0.001

Fried LF *et al. N Engl J Med* 2013;369:1892-1903

VA-NEPHRON-D
Stopped for Futility, Too…







Fried LF *et al. N Engl J Med* 2013;369:1892-1903

Novel Therapies in Clinical Trials for Diabetic Kidney Disease

PKC inhibition

Ruboxistaurin - Regulatory/business hold

Anti-AGE treatments

Sevelamer – under study
Pyridoxamine – business termination
Aminoguanidine – safety termination
Alagebrium – business termination

RAS inhibition

Epleronone – under study
Spironolactone – under study
Finerenone – under study
Aliskiren – safety termination
Dual blockade– safety termination

Anti-fibrotic treatments

Perfenidone – under study
Anti-TGF Ab – futility termination
Anti-CTGF Ab – business termination

Uric acid and gout treatments

Allopurinol – under study
Colchicine – under study
Febuxostat – under study

Antioxidants and anti-inflammatories

Bardoxolone - safety termination
Baricitinib – under study
N-acetylcysteine under study
Alpha lipoic acid – under study
CCL2 (MCP-1) receptor antagonists – under study
Pentoxiphylline– under study
Athcar gel – under study

Endothelin antagonists

Atrasentan – under study
Avosentan – safety termination

Supplements, diet, weight loss

Vitamin D- under study
Thiamine – under study
Green tea – under study
Magnesium oxide – under study
Bariatric surgery – under study
Vey low calorie diet – under study

Newer anti-hyperglycemic treatments

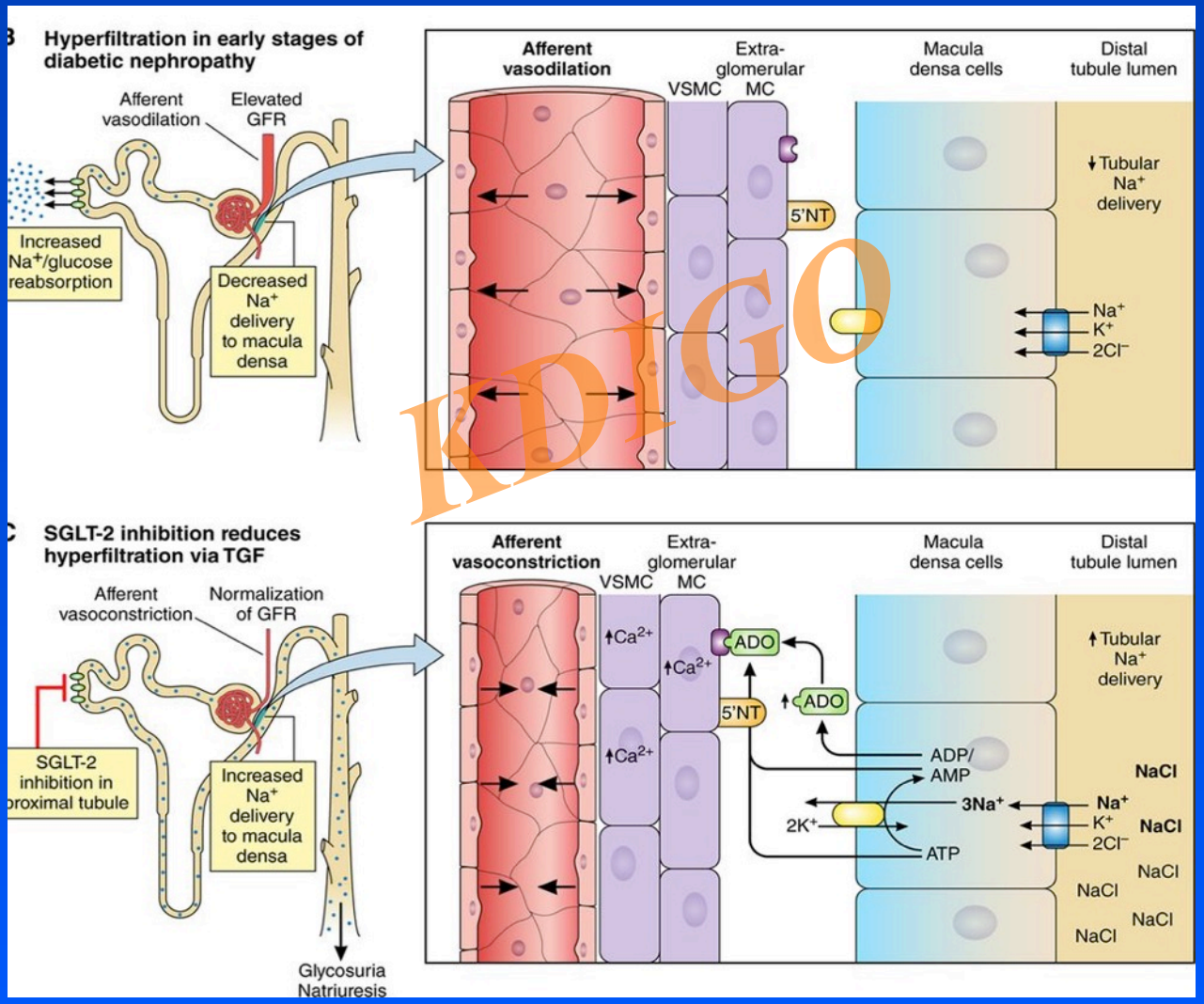
SGLT-2 inhibition – under study
GLP-1 agonists – under study
DPP-4 inhibitors – under study

ClinicalTrials.gov web site accessed October 19, 2016

Anti-Hyperglycemic Treatments Secondary Effects on the Kidney

- Improvement in hyperglycemia
- Loss of body weight
- Natriuresis
- Lower blood pressure

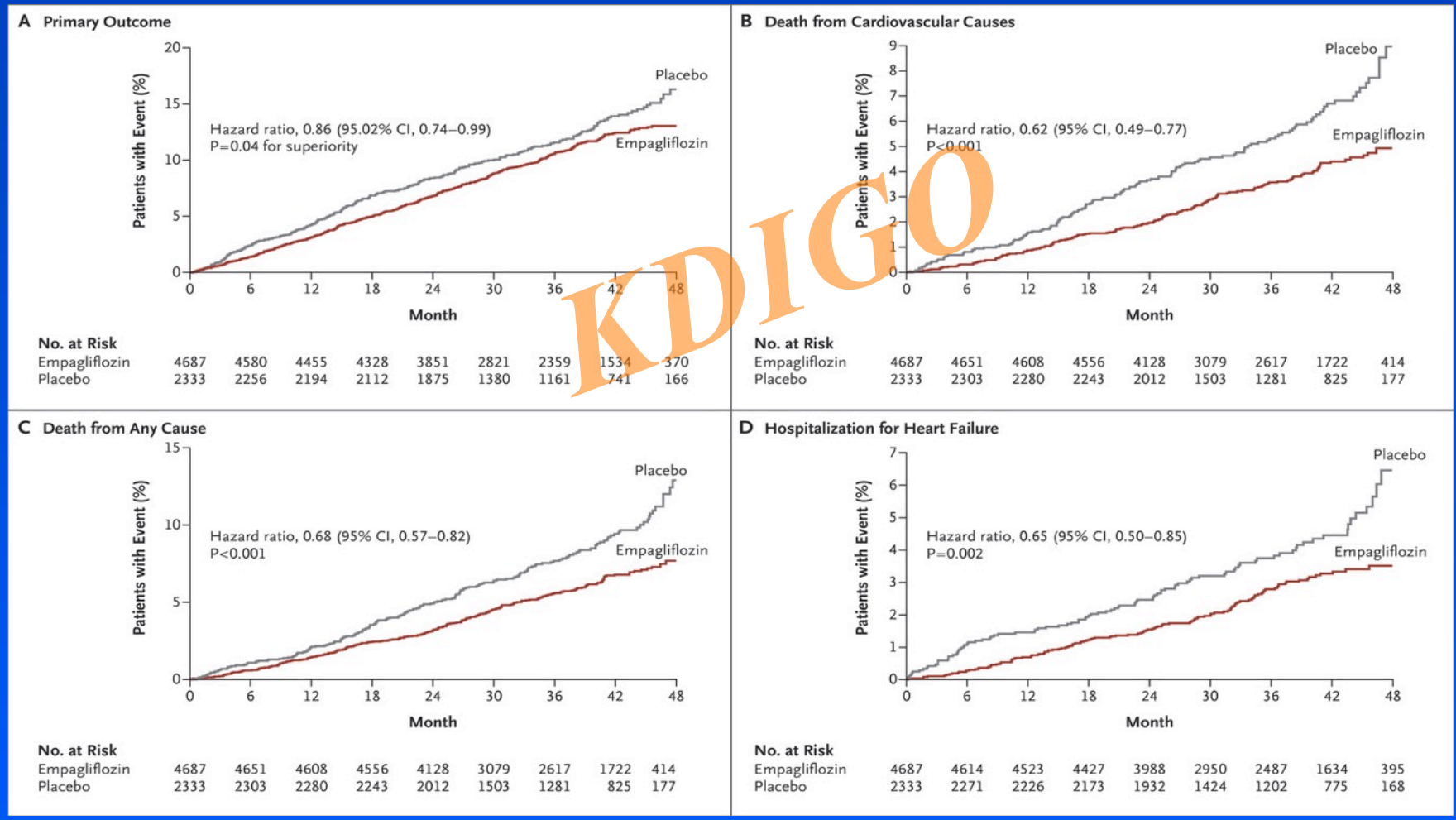
SGLT-2 Inhibition and Glomerular Hyperfiltration in Diabetes



Hiddo J.L. Heerspink *et al. Circulation* 2016;134:752-772

American Heart Association

EmpaReg: Empagliflozin in High-CVD-Risk Type 2 Diabetes



Zinman B *et al. N Engl J Med* 2015;373:2117-2128

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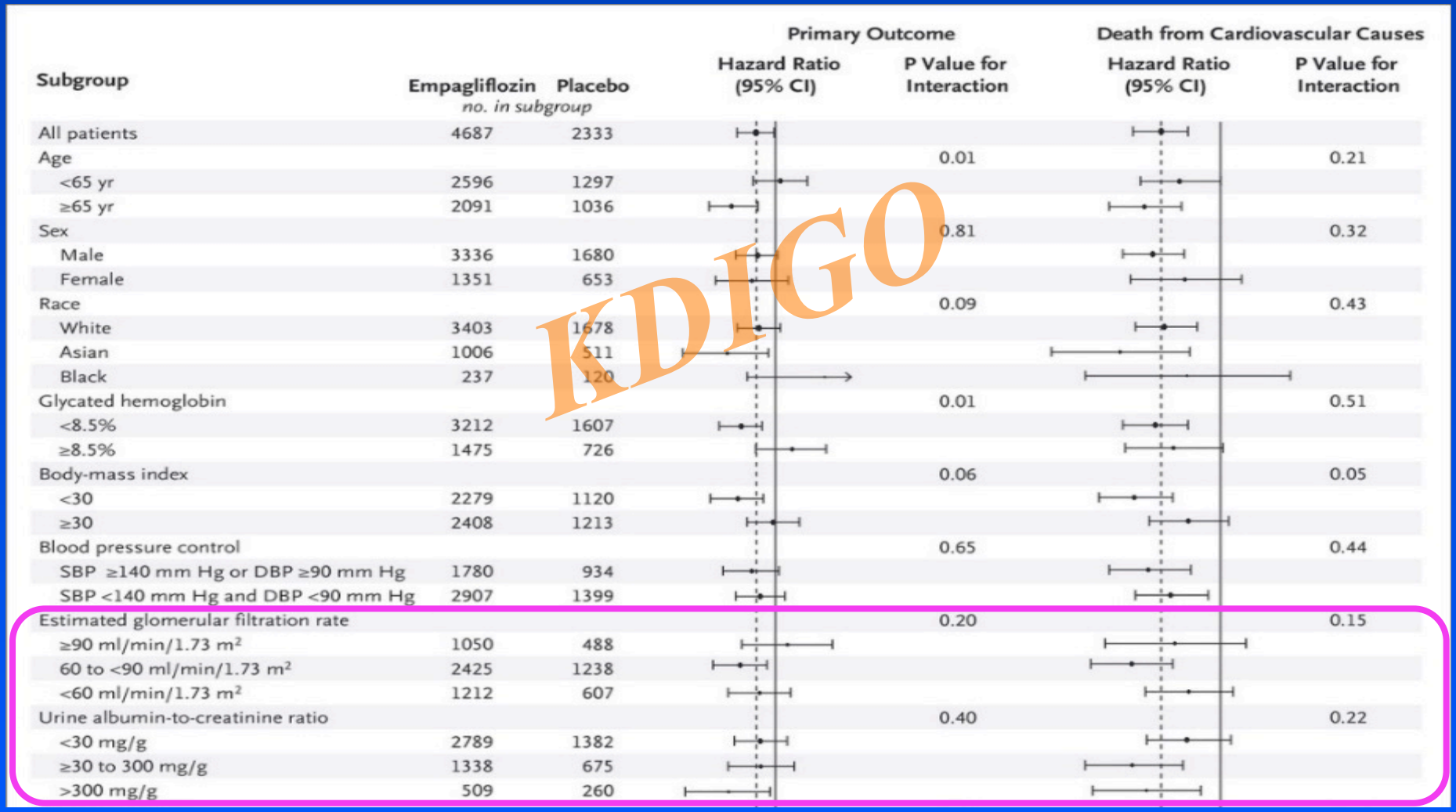
Subgroup Analyses for Primary Outcome and Death from Cardiovascular Causes



Subgroup	Empagliflozin	Placebo	Primary Outcome: Hazard Ratio (95% CI)	Primary Outcome: P Value for Interaction	Death from Cardiovascular Causes: Hazard Ratio (95% CI)	Death from Cardiovascular Causes: P Value for Interaction
	no. in subgroup					
All patients	4687	2333				
Age				0.01		0.21
<65 yr	2596	1297				
≥65 yr	2091	1036				
Sex				0.81		0.32
Male	3336	1680				
Female	1351	653				
Race				0.09		0.43
White	3403	1678				
Asian	1006	511				
Black	237	120				
Glycated hemoglobin				0.01		0.51
<8.5%	3212	1607				
≥8.5%	1475	726				
Body-mass index				0.06		0.05
<30	2279	1120				
≥30	2408	1213				
Blood pressure control				0.65		0.44
SBP ≥140 mm Hg or DBP ≥90 mm Hg	1780	934				
SBP <140 mm Hg and DBP <90 mm Hg	2907	1399				
Estimated glomerular filtration rate				0.20		0.15
≥90 ml/min/1.73 m^2	1050	488				
60 to <90 ml/min/1.73 m^2	2425	1238				
<60 ml/min/1.73 m^2	1212	607				
Urine albumin-to-creatinine ratio				0.40		0.22
<30 mg/g	2789	1382				
≥30 to 300 mg/g	1338	675				
>300 mg/g	509	260				

Zinman B *et al. N Engl J Med* 2015;373:2117-2128

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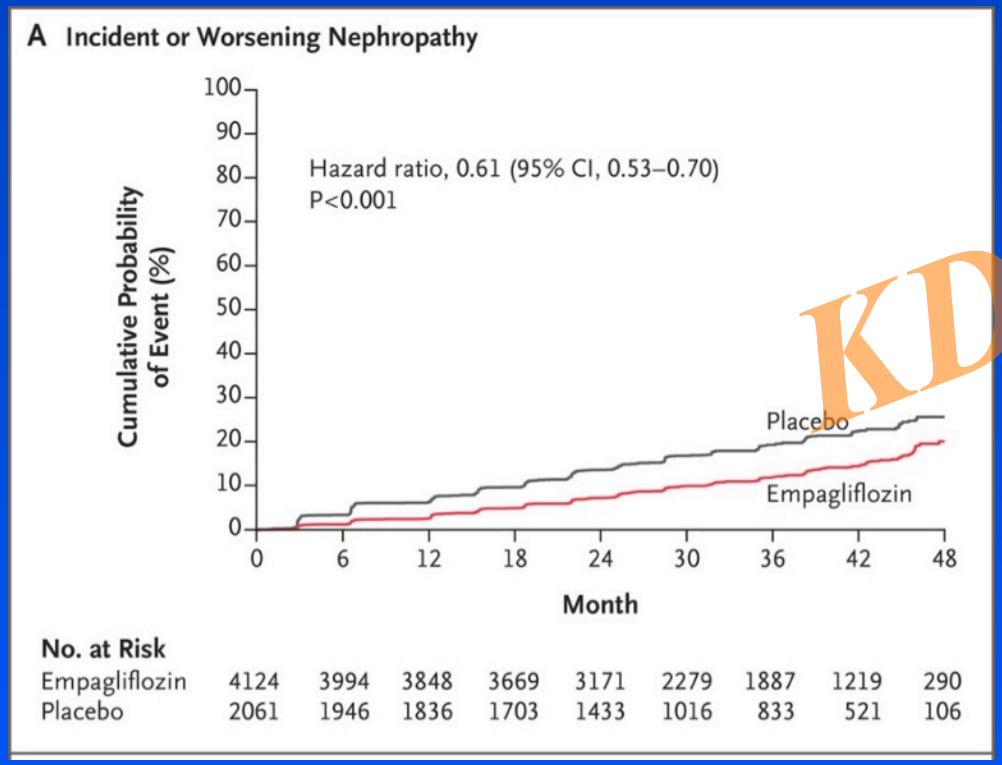
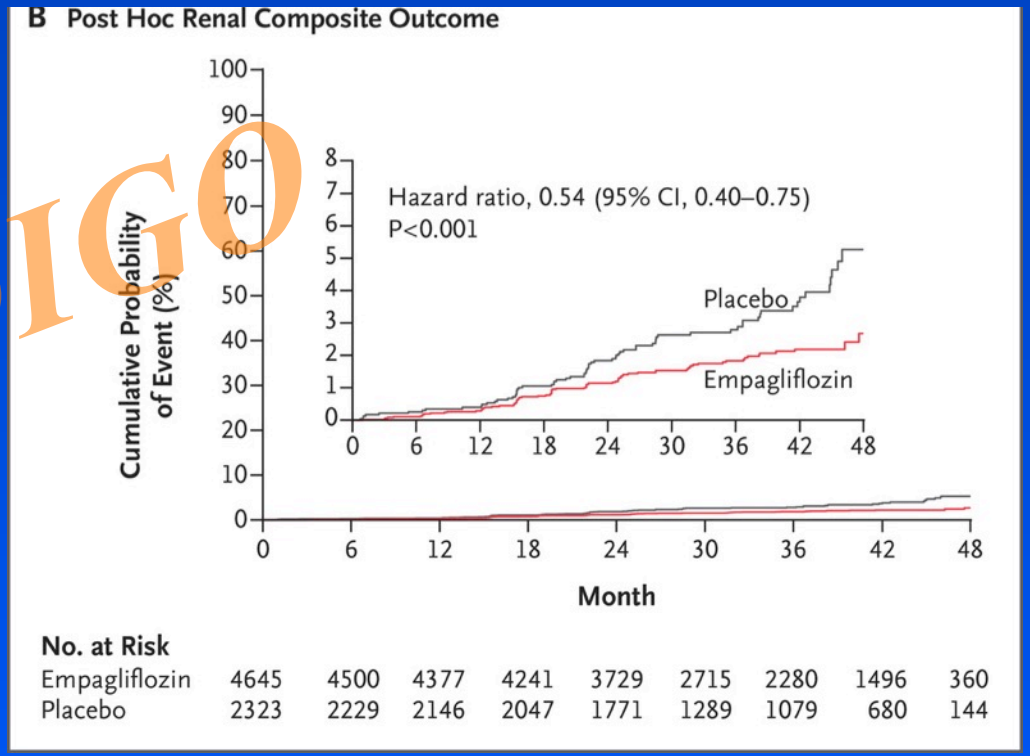
EmpaReg CKD Outcomes in High-CVD-Risk Type 2 Diabetes

- Decreased development of macroalbuminuria.
- Reduced slope of eGFR decline.
- Prevented serum creatinine doubling and ESRD.
- Benefit of empagliflozin occurred in sub-groups with and without pre-existing CKD.

Empagliflozin and CKD Events EmpaReg





Wanner C *et al. N Engl J Med* 2016;375:323-334

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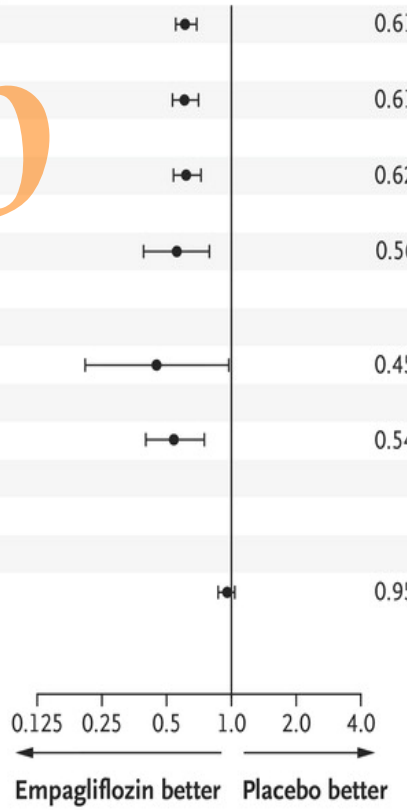
Risk Comparison for CKD Outcomes EmpaReg

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



Wanner C *et al. N Engl J Med* 2016;375:323-334

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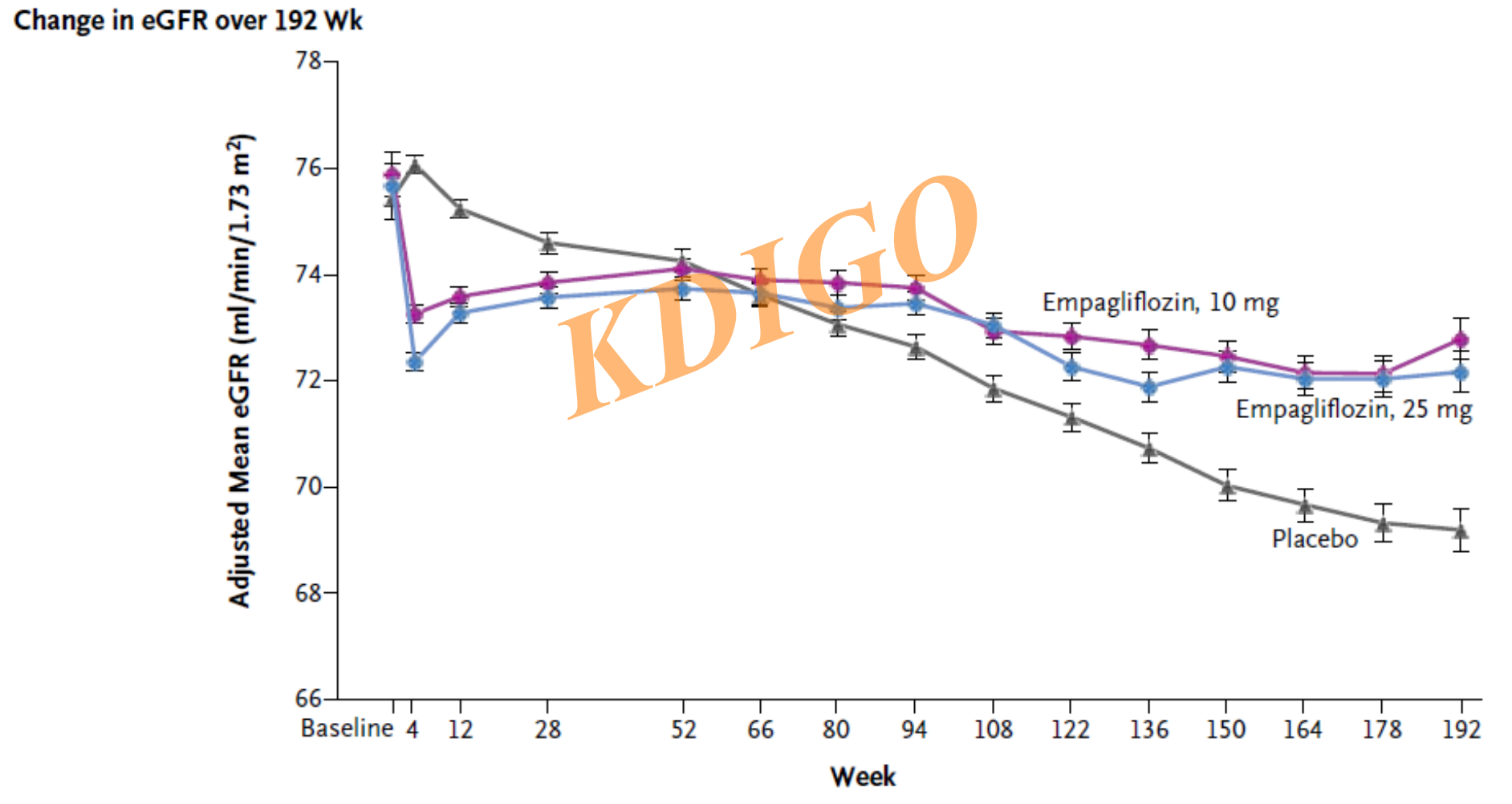
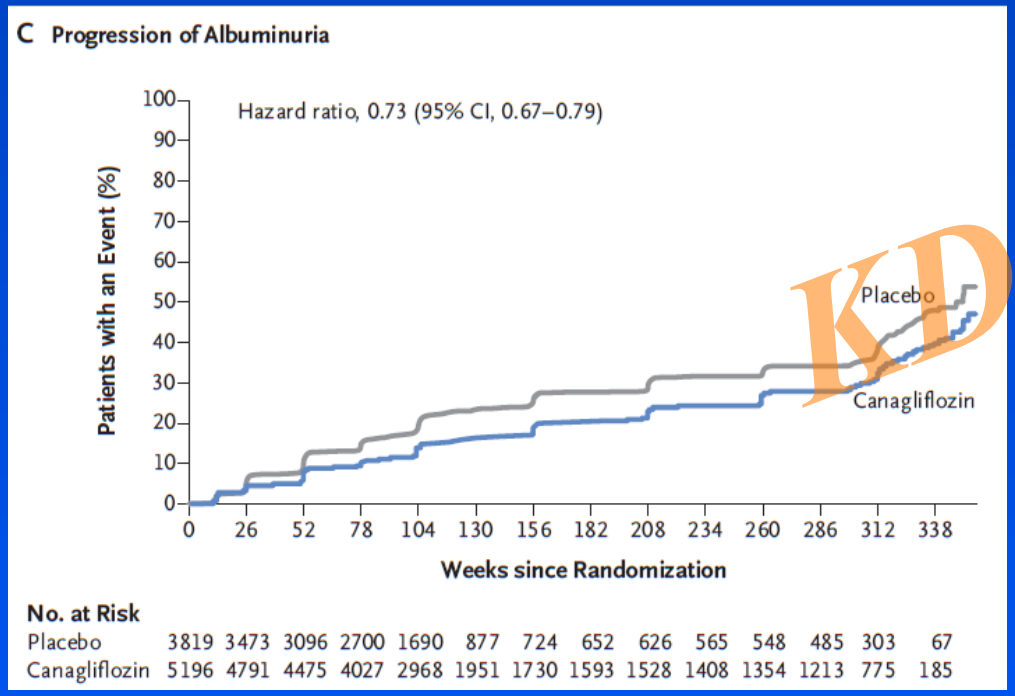
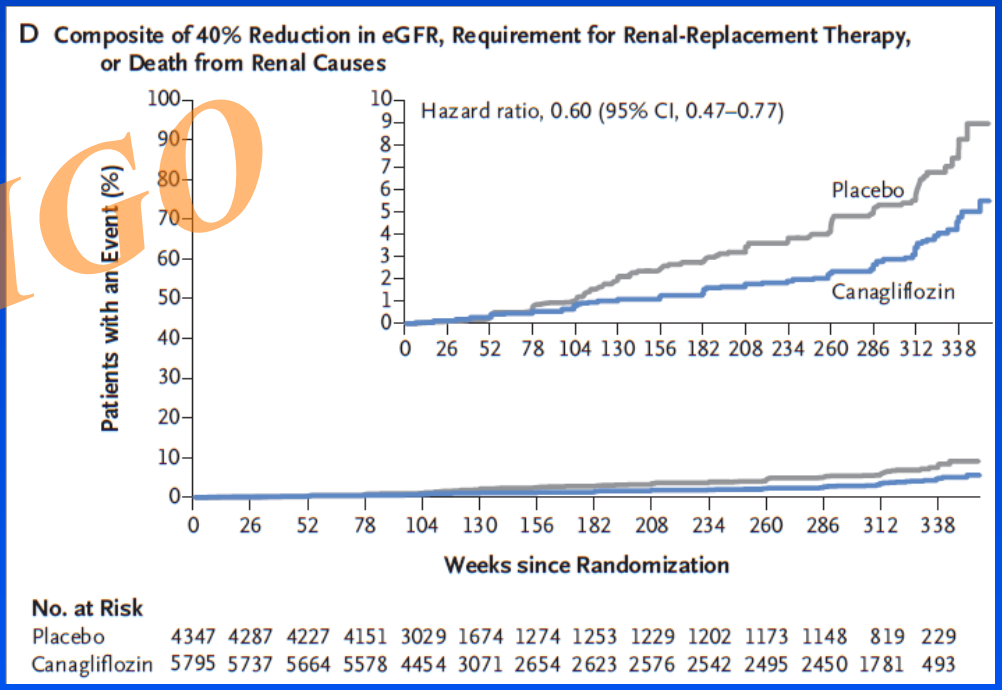
Kidney Function Over Time
EmpaReg



Wanner C *et al. N Engl J Med* 2016;375:323-334

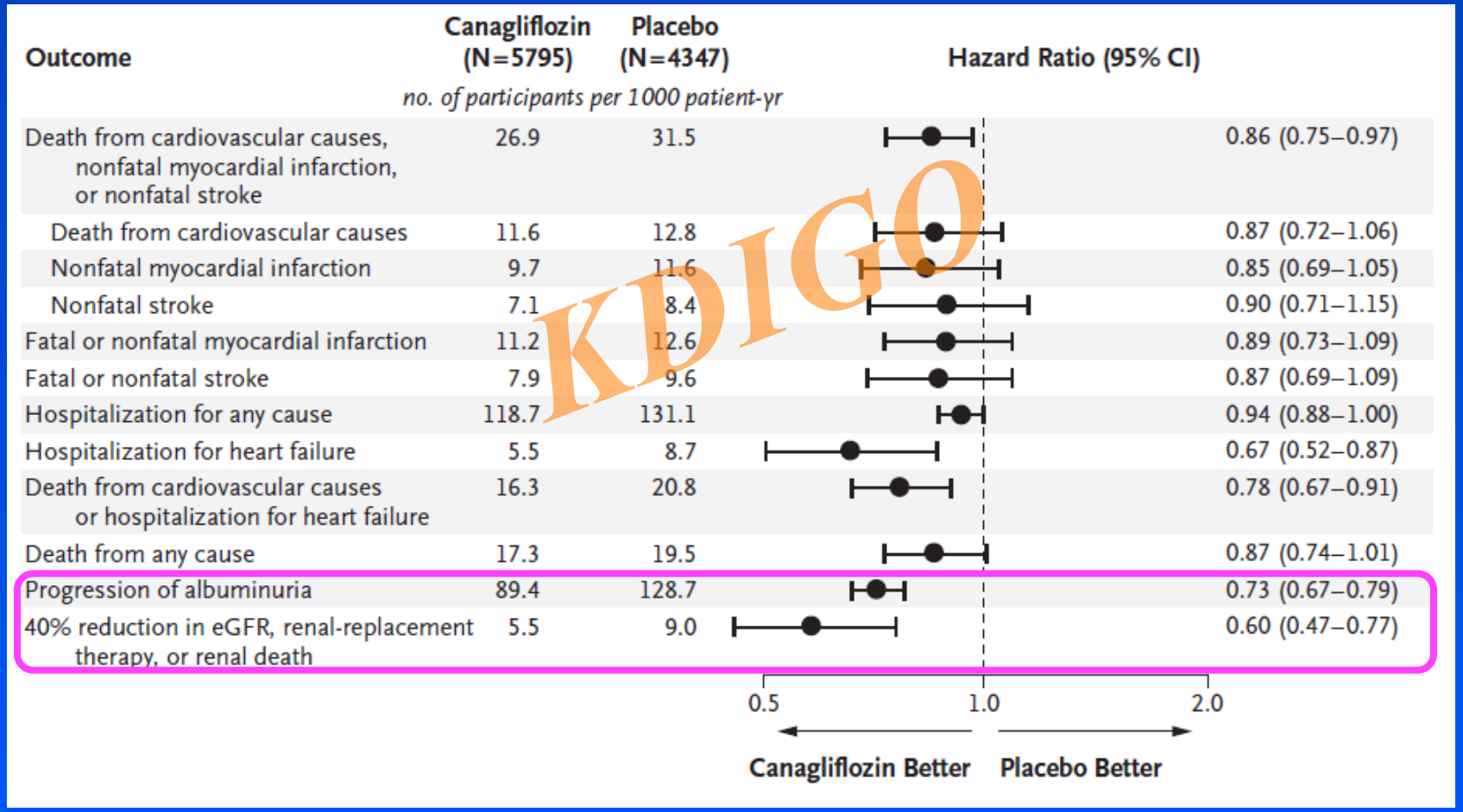
CANVAS: Canagliflozin in High-CVD-Risk Type 2 Diabetes





Neal B *et al. N Engl J Med* 2017; 377:644-657

Subgroup Analyses for Primary and Secondary Outcomes



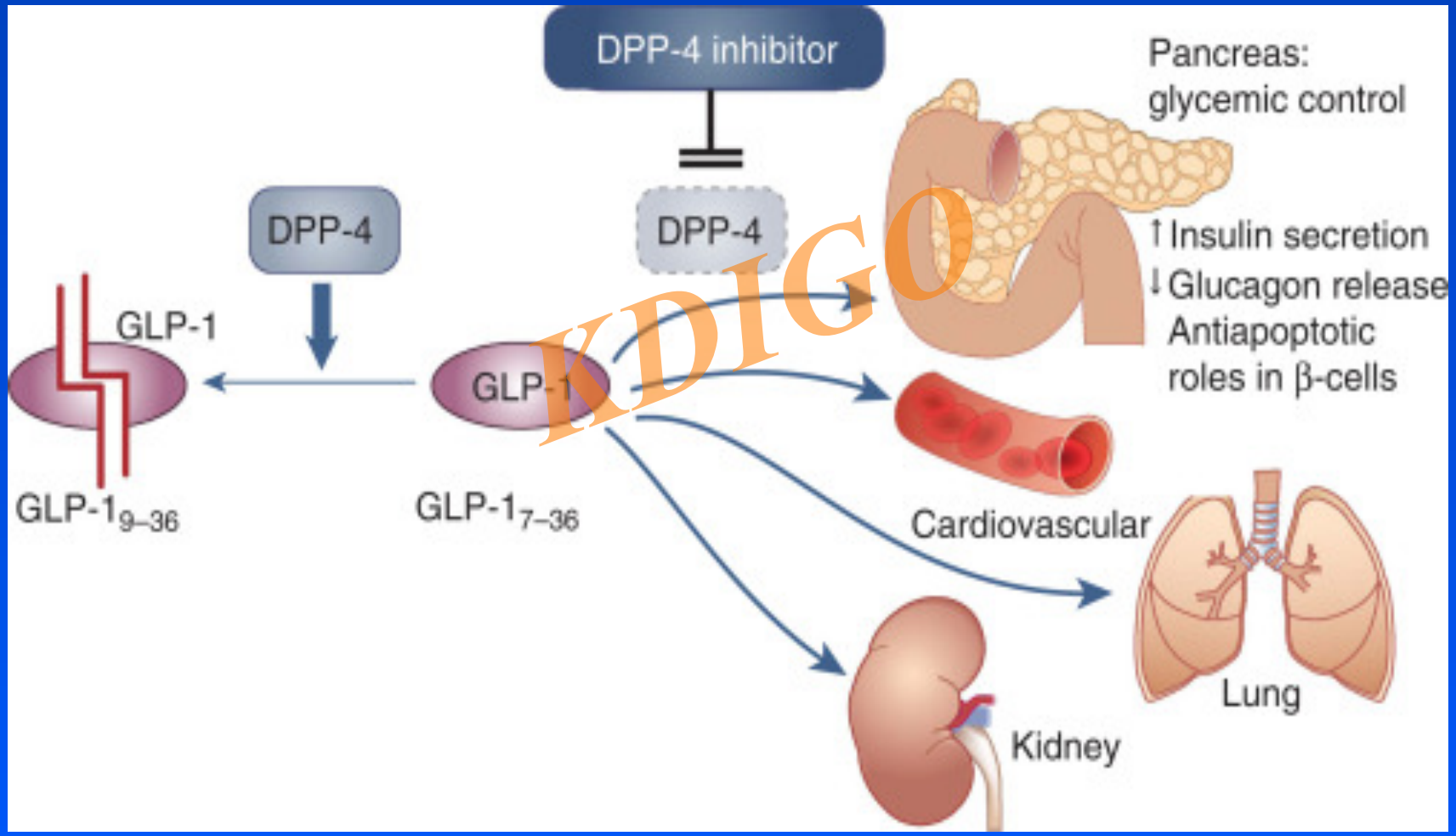
Neal B *et al. N Engl J Med* 2017; 377:644-657

Serious Adverse Events and Adverse Events
CANVAS

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neal B *et al. N Engl J Med* 2017; 377:644-657

Extra Pancreatic Effects of GLP-1 and DPP-4



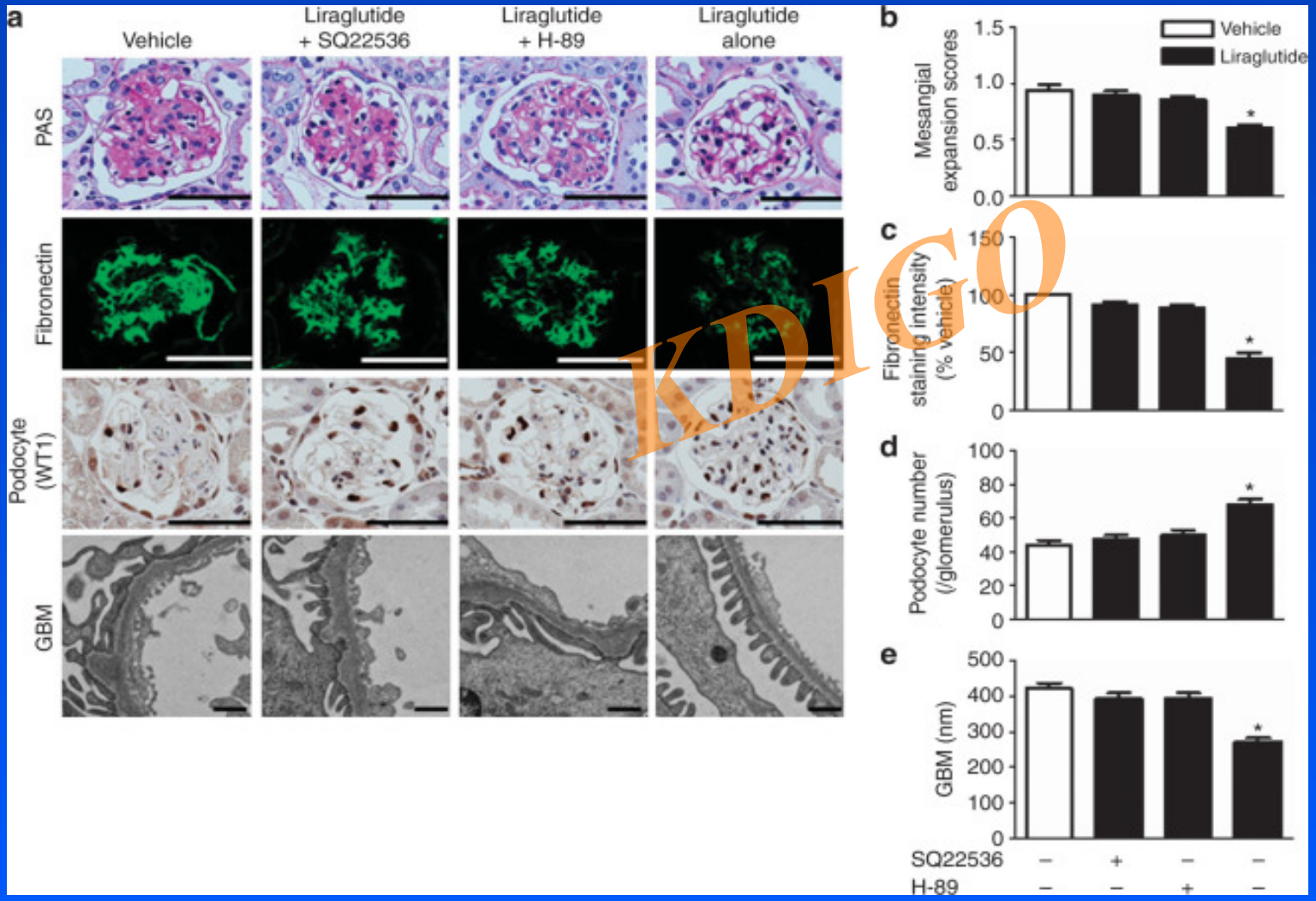
Tanaka T *et al. Kidney Int* 2014;86:701–711,2014

Mechanisms of GLP-1 Receptor Agonists in the Kidney - Primary

- Location of GLP-1 receptors
  - Glomerular endothelial cells, mesangial cells, and macrophages
  - Proximal tubular cells
- Effects of GLP-1 receptor agonists in animal studies
  - Reduce albuminuria
  - Decrease mesangial expansion and GBM thickness
  - Endothelial protection
  - Restore podocytes
- Mechanisms for GLP-1 receptor agonists
  - Signaling – PKC beta inhibition
  - Oxidative Stress – NAD(P)H oxidase inhibition, increased cAMP and PKA
  - Inflammation – inhibition of ICAM-1 expression, macrophage infiltration

Tanaka T *et al. Kidney Int* 2014;86:701–711,2014

Kidney Histopathology in Liraglutide-Treated KK/Ta-Akita Mice



SQ22536: adenylate cyclase inhibitor

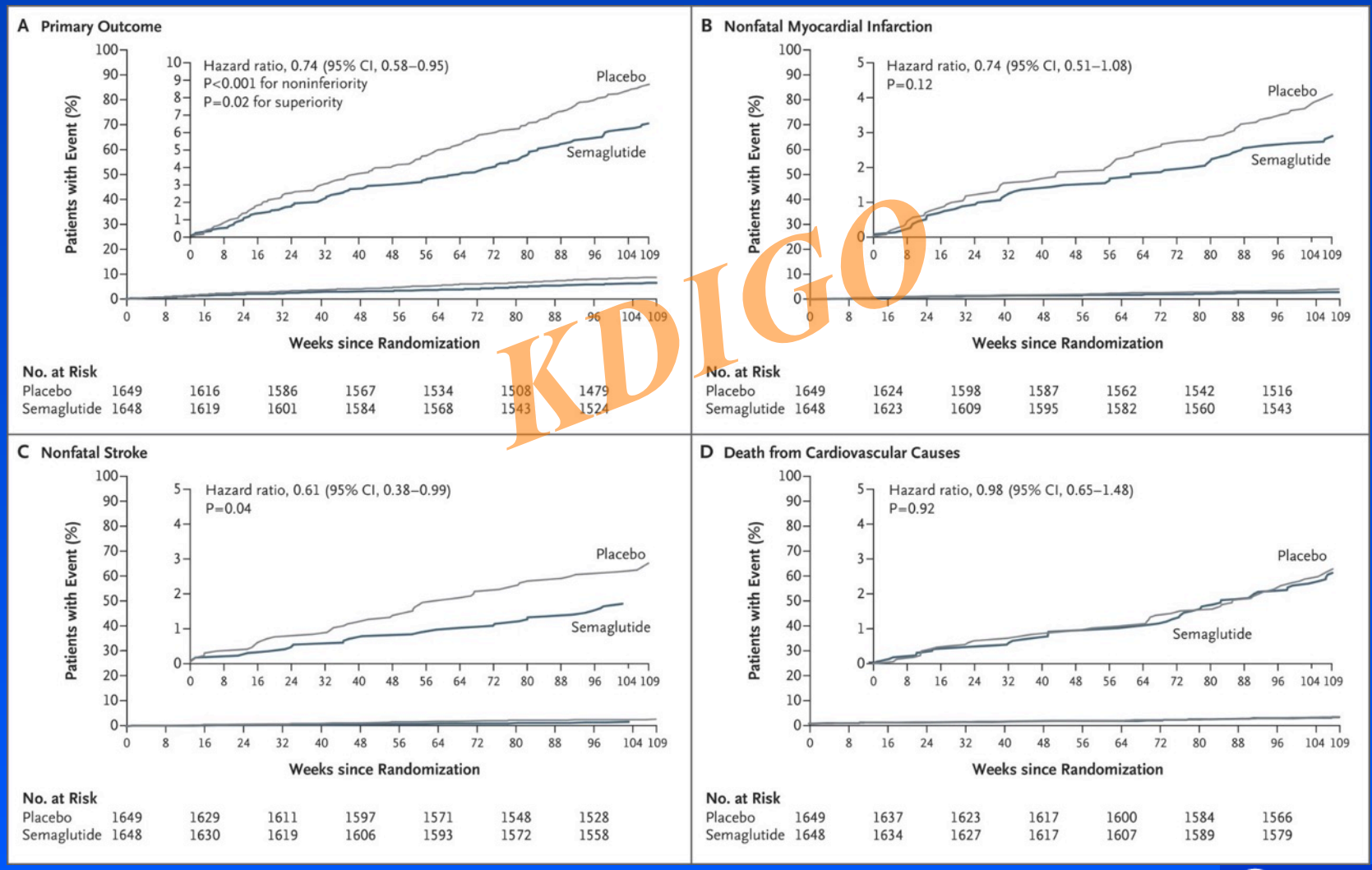
H-89: PKA inhibitor

Fujita H *et al. Kidney Int* 2014;85:579–589

Effects of GLP-1 Receptor Agonists Clinical Trials

- Reduce risk of albuminuria onset and progression across GLP-1 agonists (lira-, sema-, dula- *glutides*).
- Reduce eGFR decline in moderate-to-severe CKD (liraglutide, dulaglutide).
- CVD safety holds up in groups with eGFR <60 ml/min/ 1.73m^2.
- Kidney safety holds up in clinical trials of patients with moderate-to-severe CKD.

Effects of New Drugs to Lower Blood Glucose: Semaglutide in High-CVD-Risk Type 2 Diabetes



Marso SP *et al. N Engl J Med* 2016;375:1834-1844

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Semaglutide in High-CVD-Risk Type 2 Diabetes: CVD and Microvascular Outcomes

SUSTAIN-6

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 composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	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

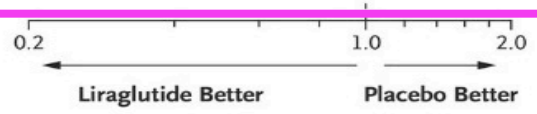
Marso SP *et al. N Engl J Med* 2016;375:1834-1844

The NEW ENGLAND JOURNAL of MEDICINE

Liraglutide in High-CVD-Risk Type 2 Diabetes: Primary Outcome (Death and CVD) in Subgroups

LEADER

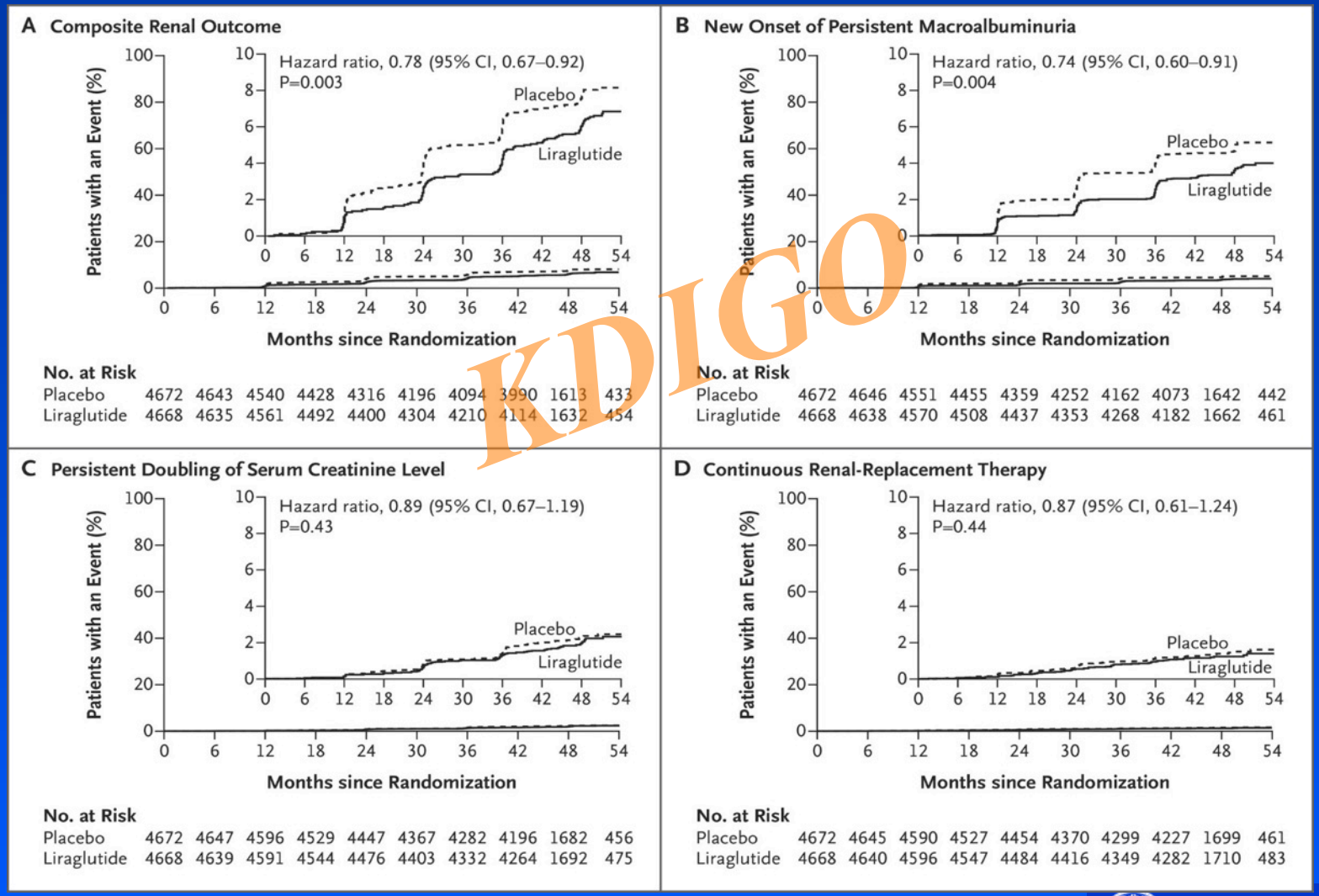
Body-mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	
Duration of diabetes					0.42
≤11 yr	4429	265/2216 (12.0)	316/2213 (14.3)	0.82 (0.70–0.97)	
>11 yr	4892	340/2441 (13.9)	376/2451 (15.3)	0.90 (0.78–1.04)	
Risk of CVD					0.04
≥50 yr of age and established CVD	7598	536/3831 (14.0)	629/3767 (16.7)	0.83 (0.74–0.93)	
≥60 yr of age and risk factors for CVD	1742	72/837 (8.6)	65/905 (7.2)	1.20 (0.86–1.67)	
Chronic heart failure					0.53
Yes	1305	112/653 (17.2)	119/652 (18.3)	0.94 (0.72–1.21)	
No	8035	496/4015 (12.4)	575/4020 (14.3)	0.85 (0.76–0.96)	
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	



Marso SP *et al. N Engl J Med* 2016;375:311-322

The NEW ENGLAND JOURNAL of MEDICINE

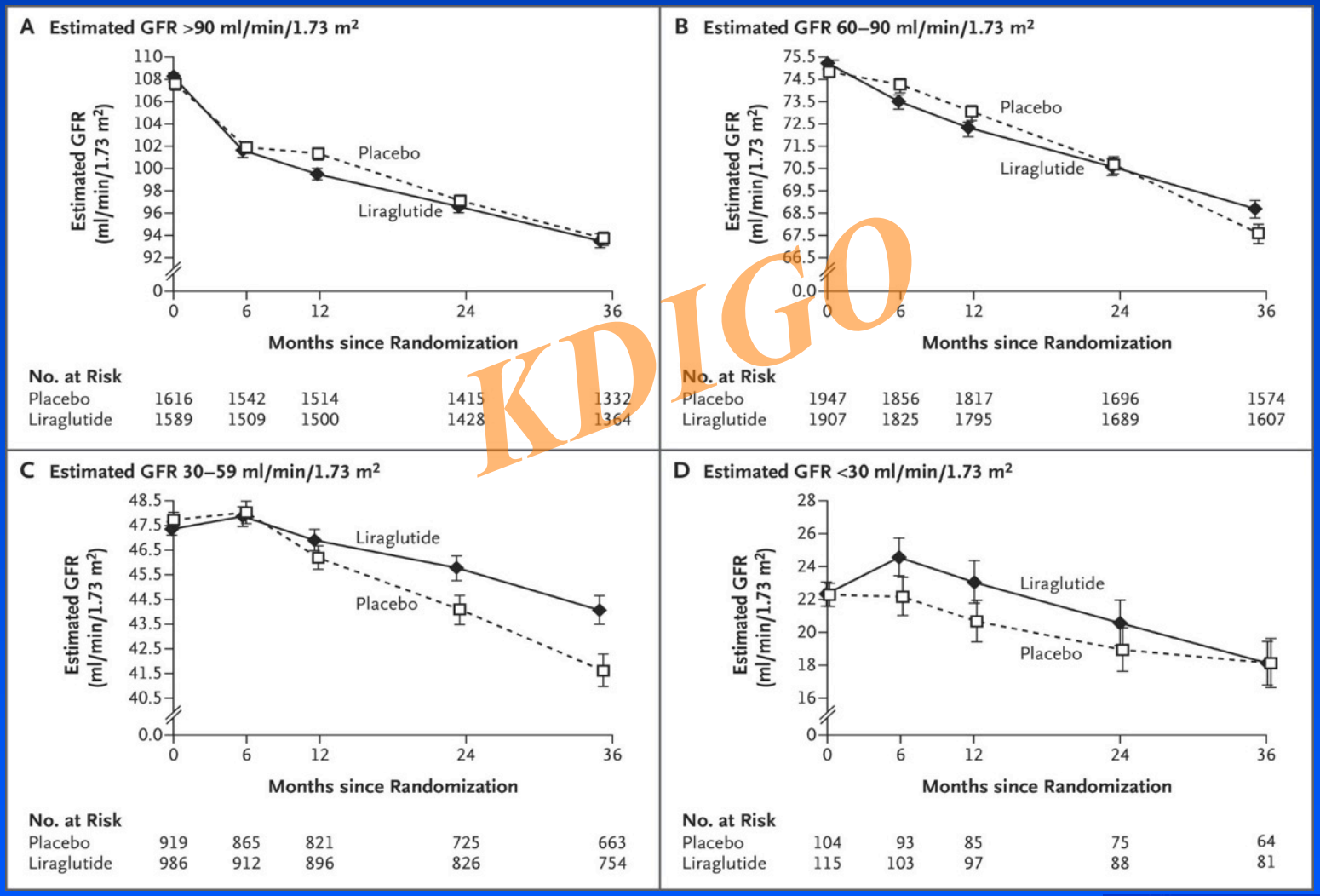
LEADER: Composite Kidney Outcome and Component Outcomes



Mann JFE *et al*. *N Engl J Med* 2017;377:839-848

The NEW ENGLAND JOURNAL of MEDICINE

LEADER: eGFR in Subgroups Stratified According to Baseline eGFR



Mann JFE *et al*. *N Engl J Med* 2017;377:839-848

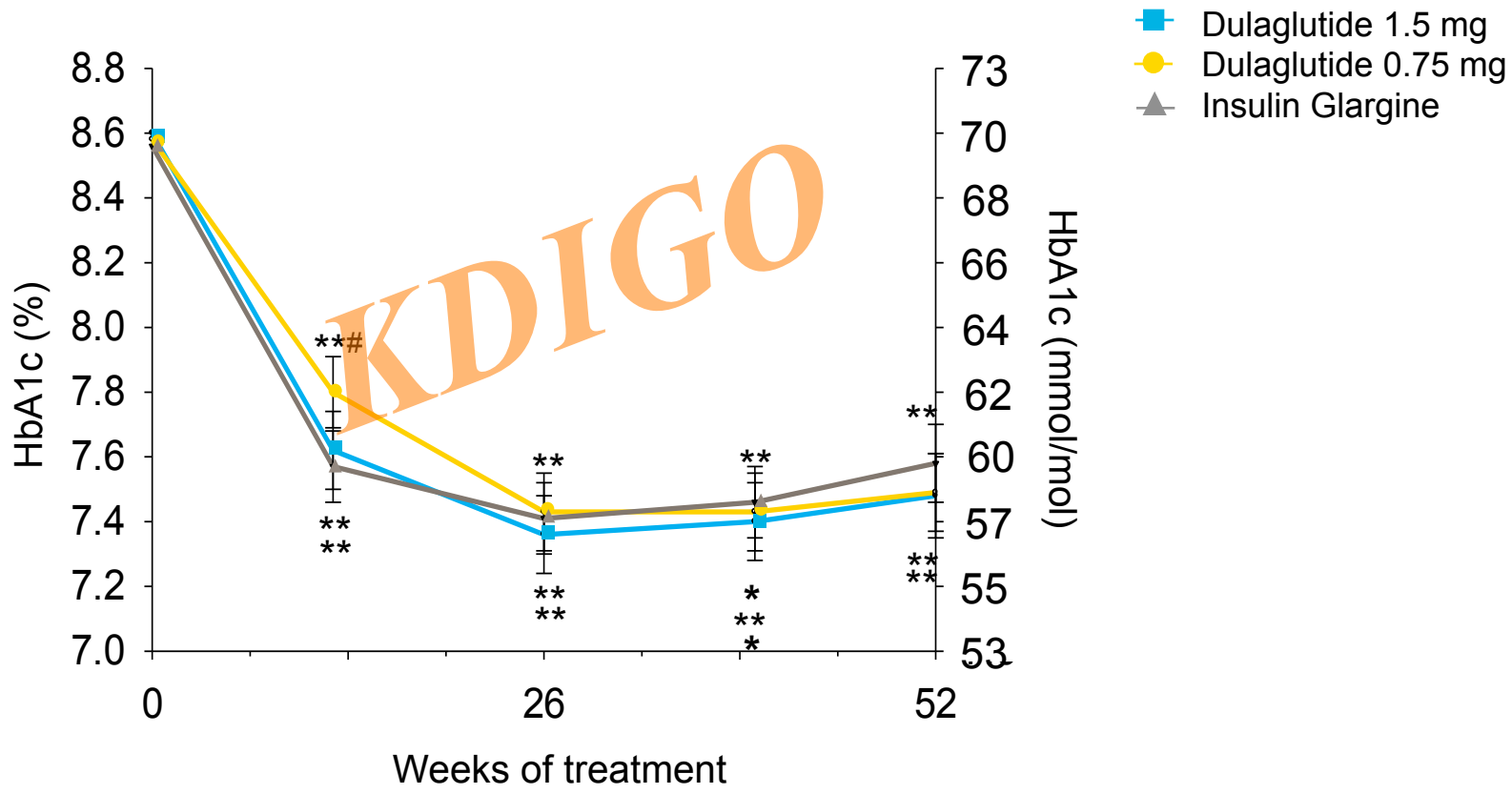
The NEW ENGLAND JOURNAL of MEDICINE

AWARD-7:
Baseline Characteristics Related to Kidney Disease

	DU 1.5 mg (N=192)	DU 0.75 mg (N=190)	Glargine (N=194)
Duration of CKD stage ≥3, years	4.2 ± 5.6	4.0 ± 4.9	3.5 ± 4.0
eGFR, mL/min/1.73m^2	38.0 ± 13.3	38.4 ± 12.3	38.5 ± 13.0
60 ≤ Baseline eGFR <90	9 (4.7)	7 (3.7)	14 (7.2)
45 ≤ Baseline eGFR <60	53 (27.6)	53 (27.9)	51 (26.3)
30 ≤ Baseline eGFR <45	73 (38.0)	75 (39.5)	67 (34.5)
15 ≤ Baseline eGFR <30	55 (28.6)	55 (28.9)	61 (31.4)
Baseline eGFR <15	2 (1.0)	0 (0.0)	1 (0.5)
UACR, mg/g, mean (median)	779 (214)	842 (234)	920 (196)
Normal albuminuria (UACR <30)	34 (17.7)	44 (23.3)	48 (24.7)
Microalbuminuria (30 ≤ UACR ≤ 300)	74 (38.5)	61 (32.3)	56 (28.9)
Macroalbuminuria (UACR >300)	84 (43.8)	84 (44.4)	90 (46.4)

Data are mean ± SD or n (%) unless otherwise noted; safety population; CKD=chronic kidney disease; UACR=urinary albumin to creatinine ratio; baseline eGFR and UACR were determined by mean of values from 2 visits.

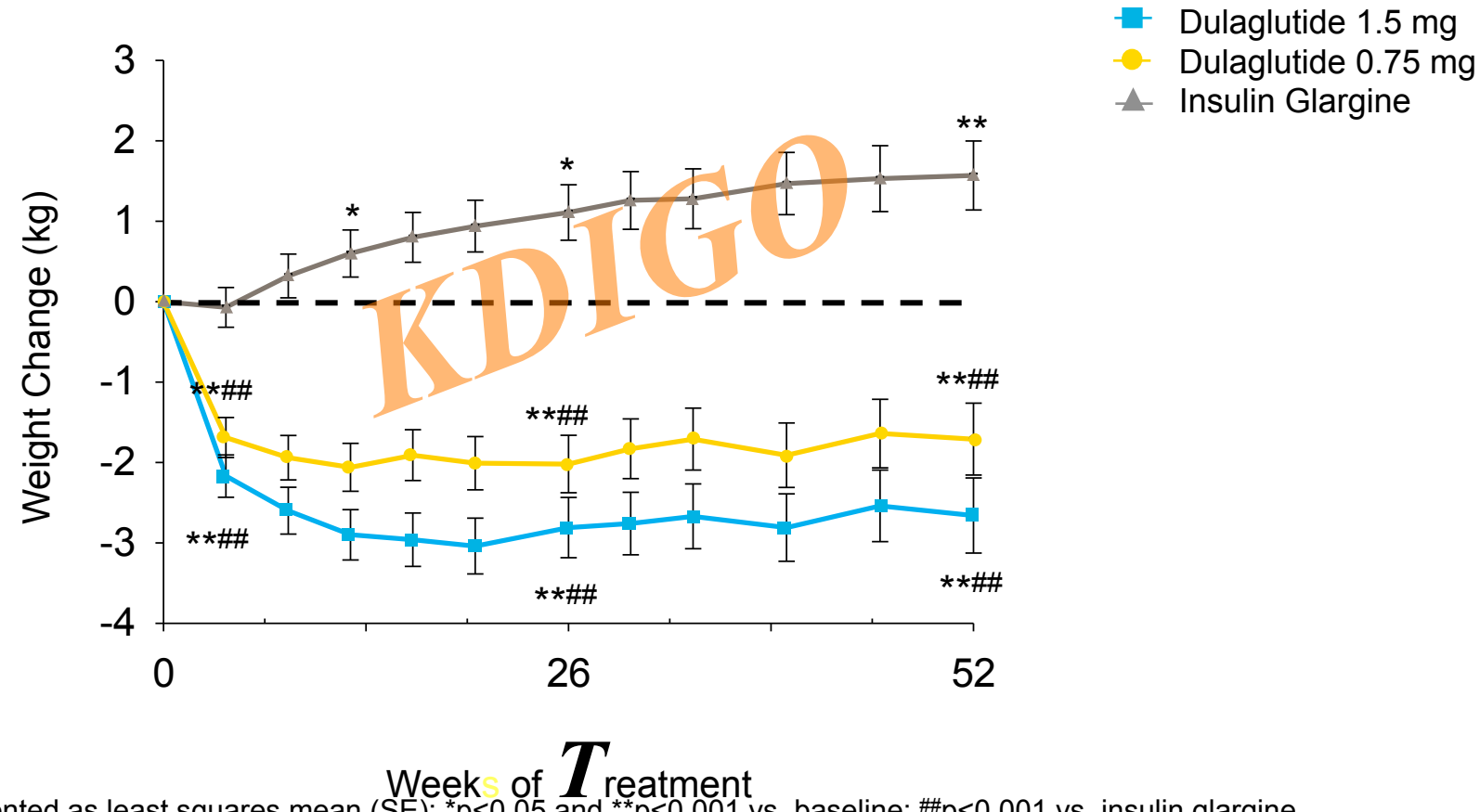
AWARD-7:
HbA1c Over Time to 52 Weeks



Baseline data presented as mean; other time points are least squares mean (SE); mITT without post-rescue values; MMRM analysis. *p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. insulin glargine.

AWARD-7:
Weight Change Over Time

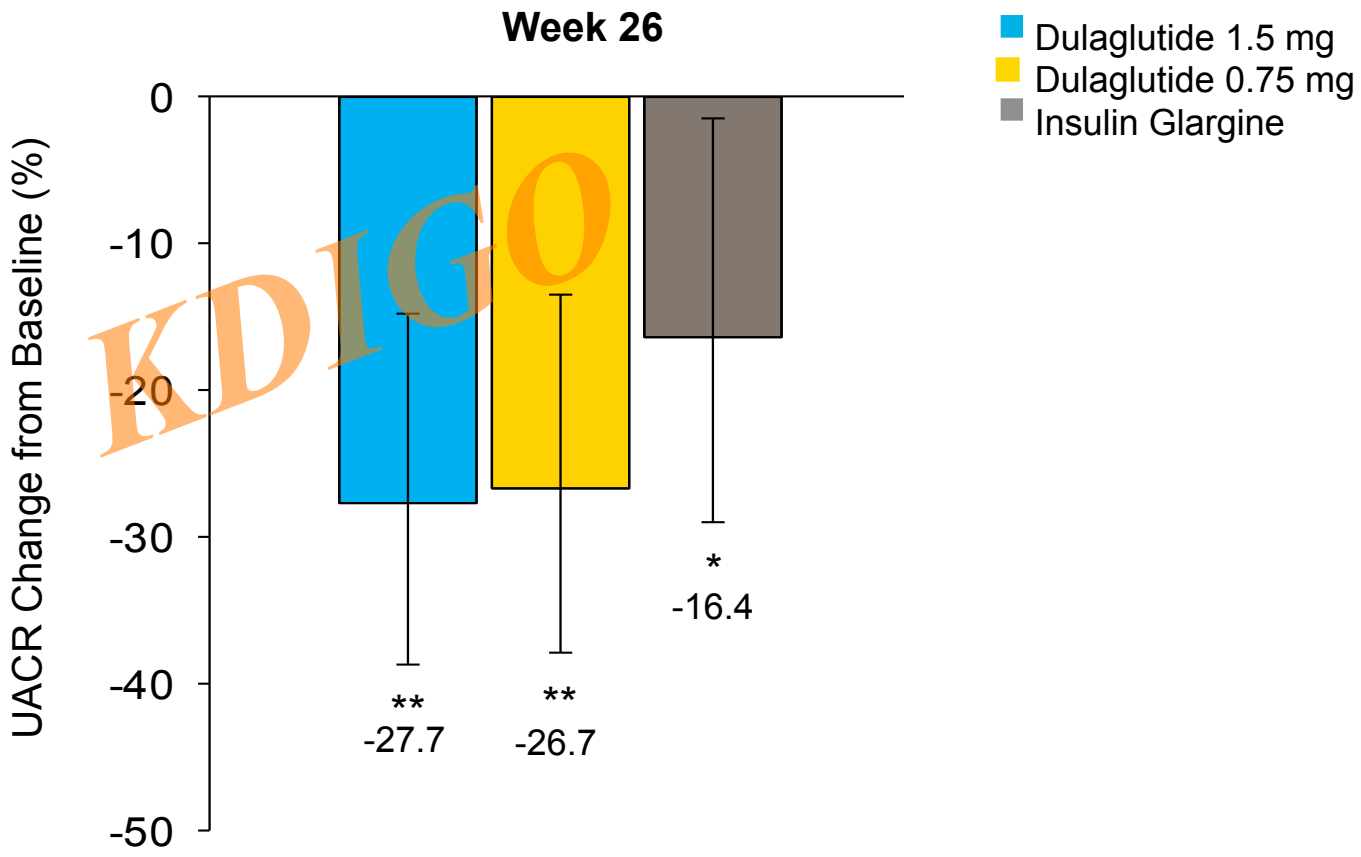
Baseline mean weight = 88.9 kg



Data presented as least squares mean (SE); *p<0.05 and **p<0.001 vs. baseline; ##p<0.001 vs. insulin glargine.
Note, significance indicated only for first time point when significance was seen, week 26, and week 52.

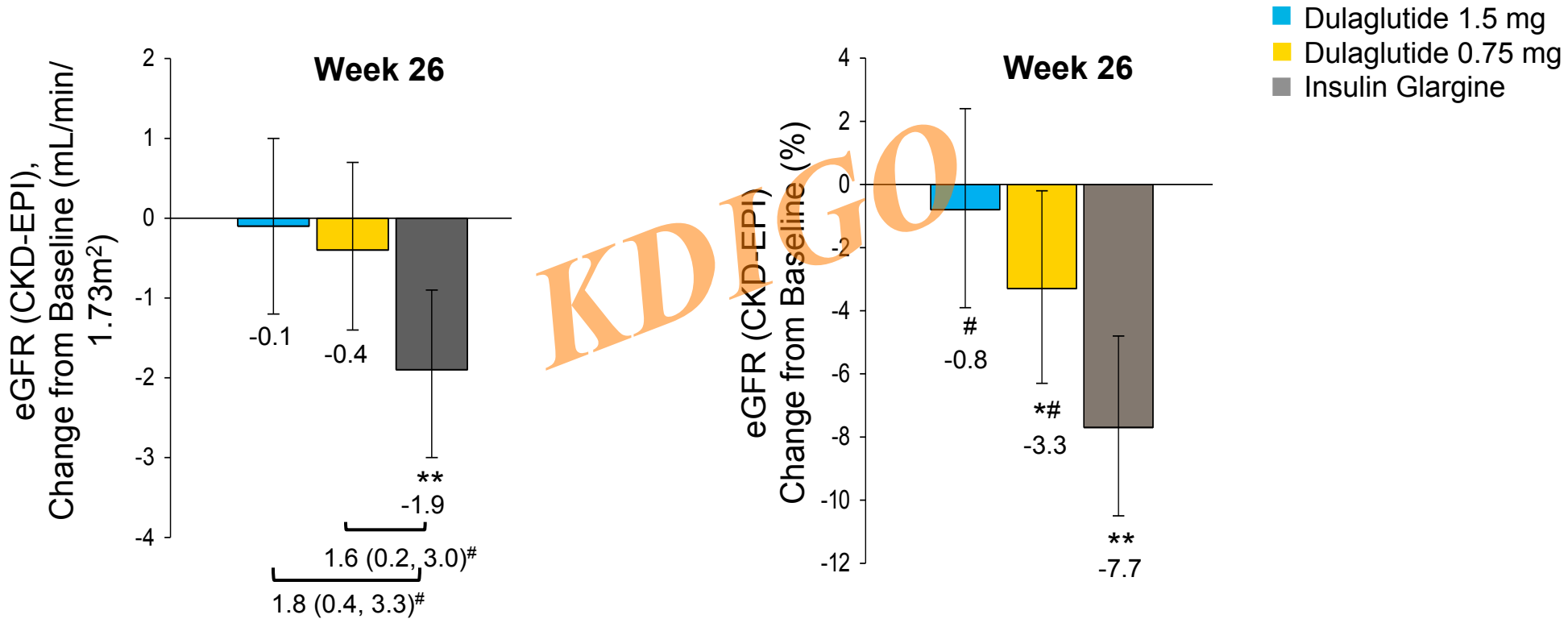
AWARD-7:
Albuminuria Reduction

Baseline UACR, mg/g		
Group	**n**	**Mean/Median**
DU 1.5	192	779/214
DU 0.75	189	842/234
Glargine	194	920/196



Data presented as % change from baseline [least squares mean (95% CI)]; safety population, MMRM analysis; *p<0.05 and **p<0.001 vs. baseline.

AWARD-7:
eGFR Decline at 26 Weeks



Data are least squares mean (LSM) and LSM difference (95% CI); safety population; MMRM analysis; *p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. insulin glargine.

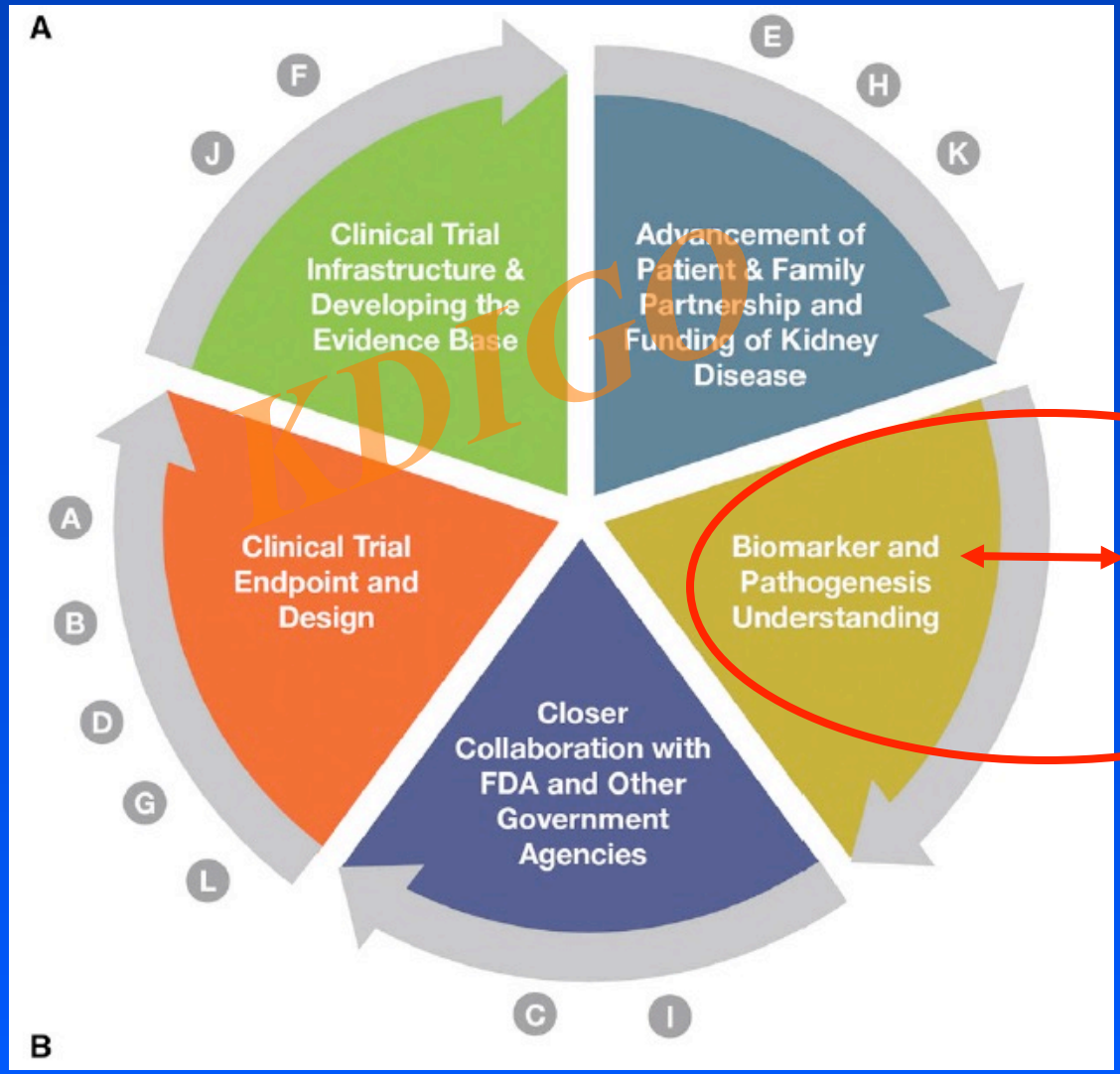
Diabetic Kidney Disease Lost in Translation…

- **Lack of biomarkers for diagnosis, prognosis and actions.**
- Inadequate pre-clinical testing of targets.
- Low study enrollment rates.
- Adverse safety events.
- Regulatory hurdles in clinical trial design.
- Under-appreciation of unmet health need as business opportunity.

Novel Drugs for Diabetic Kidney Disease: "Convergence"

Jackson Pollock Circa 1952

Major Barriers to Therapeutic Innovation and Kidney Health Initiative Facilitators



Where is the action?

Linde P *et al. J Am Soc Nephrol* 2016;27:1902-1910.

Biomarkers and Pathogenesis Understanding: What is Needed in Diabetic Kidney Disease?

- Prognosis
  - Forecasts clinically-meaningful outcome
- Prediction
  - Identifies therapeutic response
  - Efficacy or safety
- Action
  - Target for therapy
  - Monitoring of clinical response

Diabetic Kidney Disease
Systems Biology and Therapeutic Opportunity

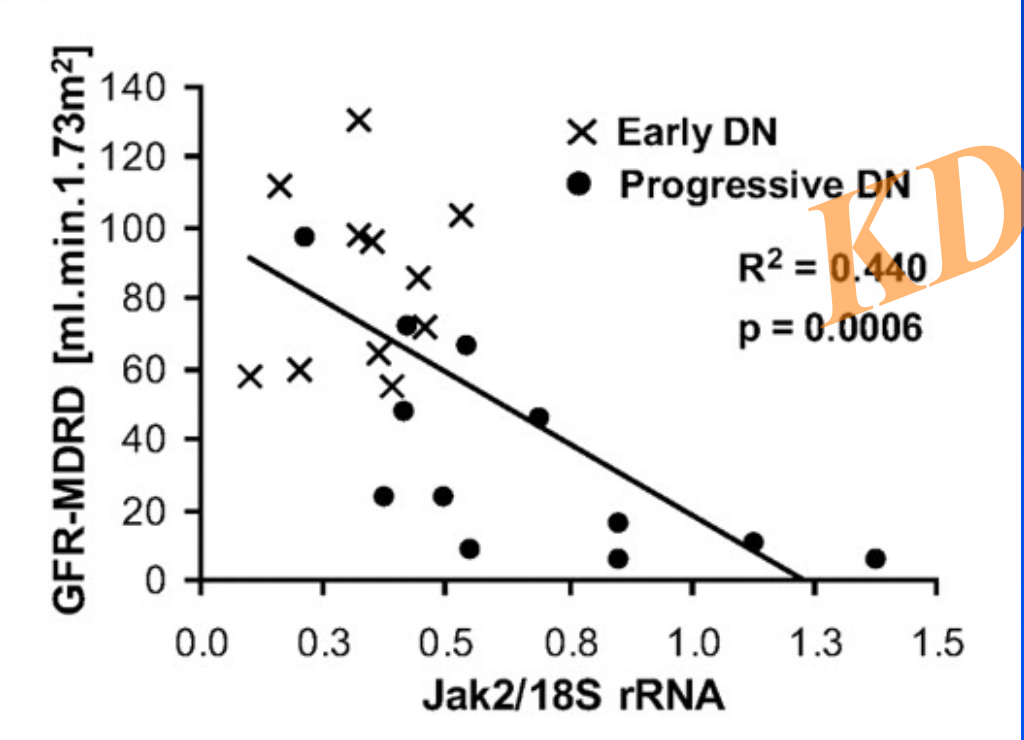
- Many JAK/STAT mRNAs are over-expressed in both human and mouse DKD.
- These changes correlate closely with DKD severity.
- Over-expression of JAK2 appears to "humanize" mouse models

  by producing a phenotype akin to DKD.

. . .so lets see how a JAK1/2 inhibitor might work in DKD…

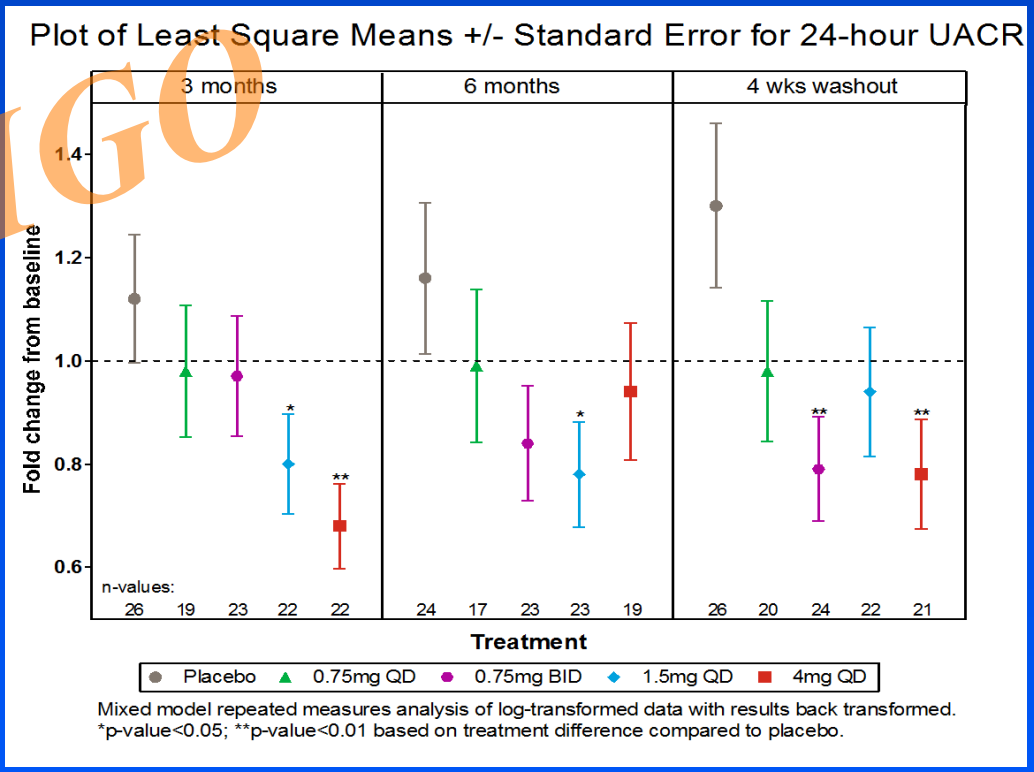
From Gene Expression to Repurposing a Drug to Prevent Progression of DKD

Gene expression in human kidney tissue points to JAK2 inflammatory pathway



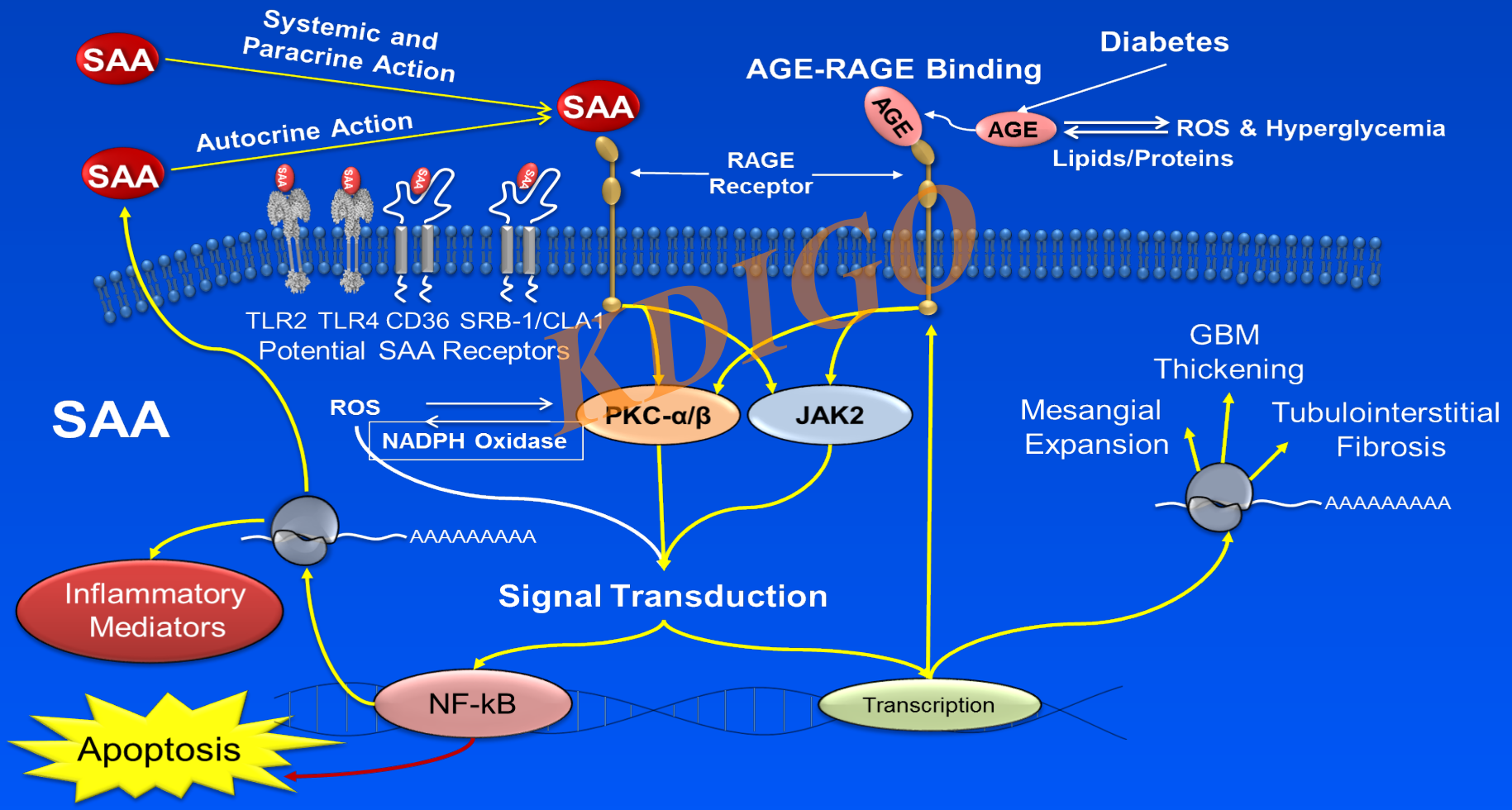
Berthier CC: Diabetes 2009

Baricitinib (JAK 1/2 inhibitor) effect on albuminuria in DKD (n=129)



Tuttle KR: Presented at *ADA* 2015; late-breaking abstract

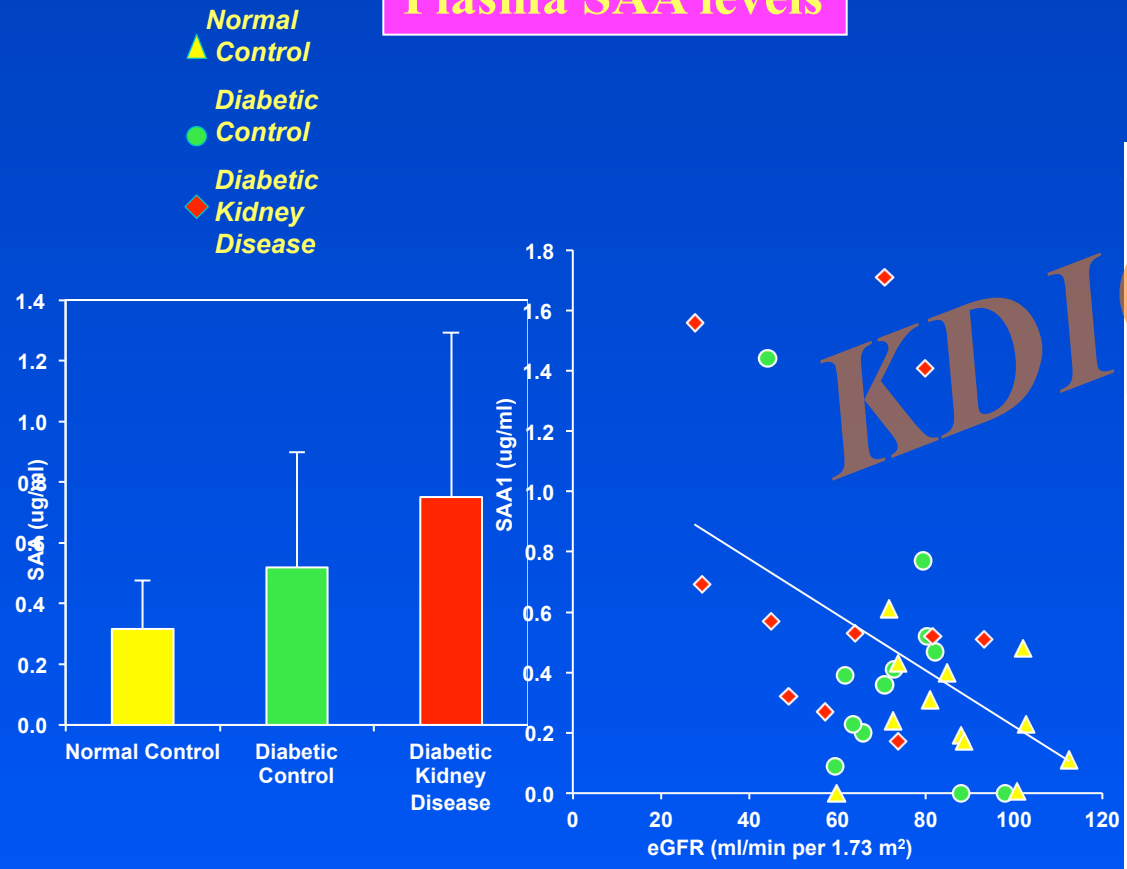
Inflammatory Signals and Serum Amyloid A (SAA) in Diabetic Kidney Disease



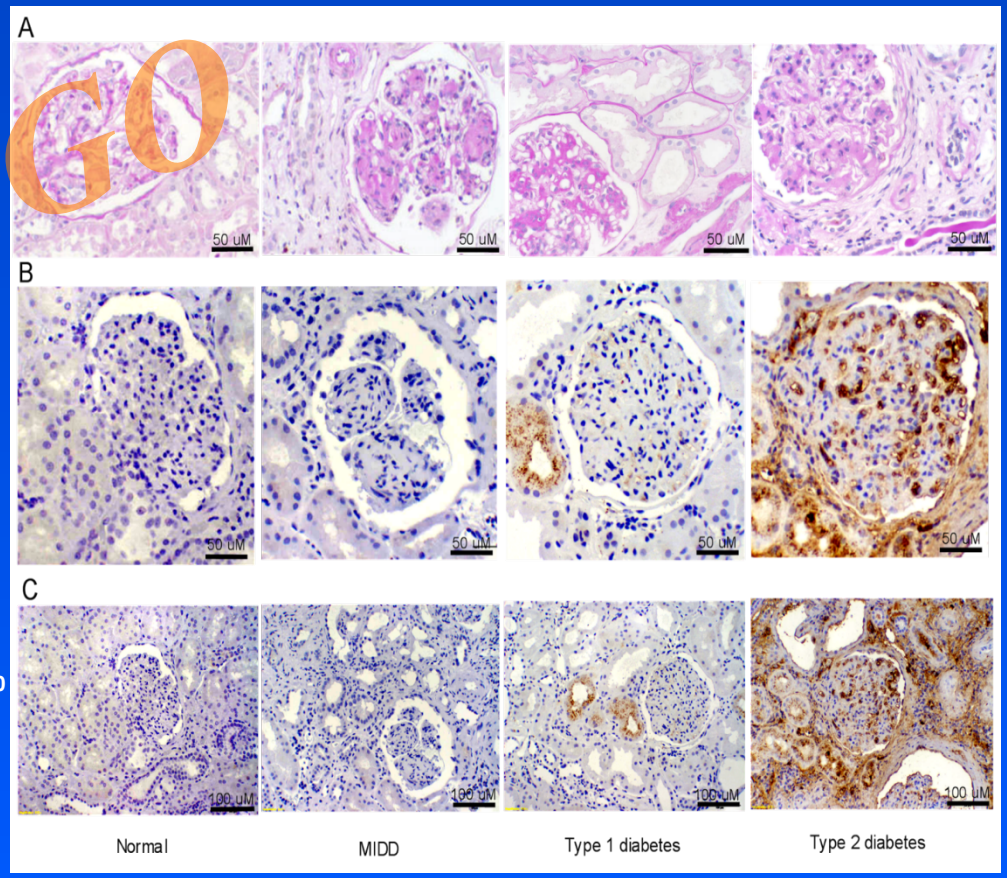
Pichler R, Afkarian M, Dieter BP, Tuttle KR. *Am J Physiol Renal Physiol* Epub:2016 Aug24:ajprenal.00314.2016

SAA in Humans with Diabetic Kidney Disease

Plasma SAA levels

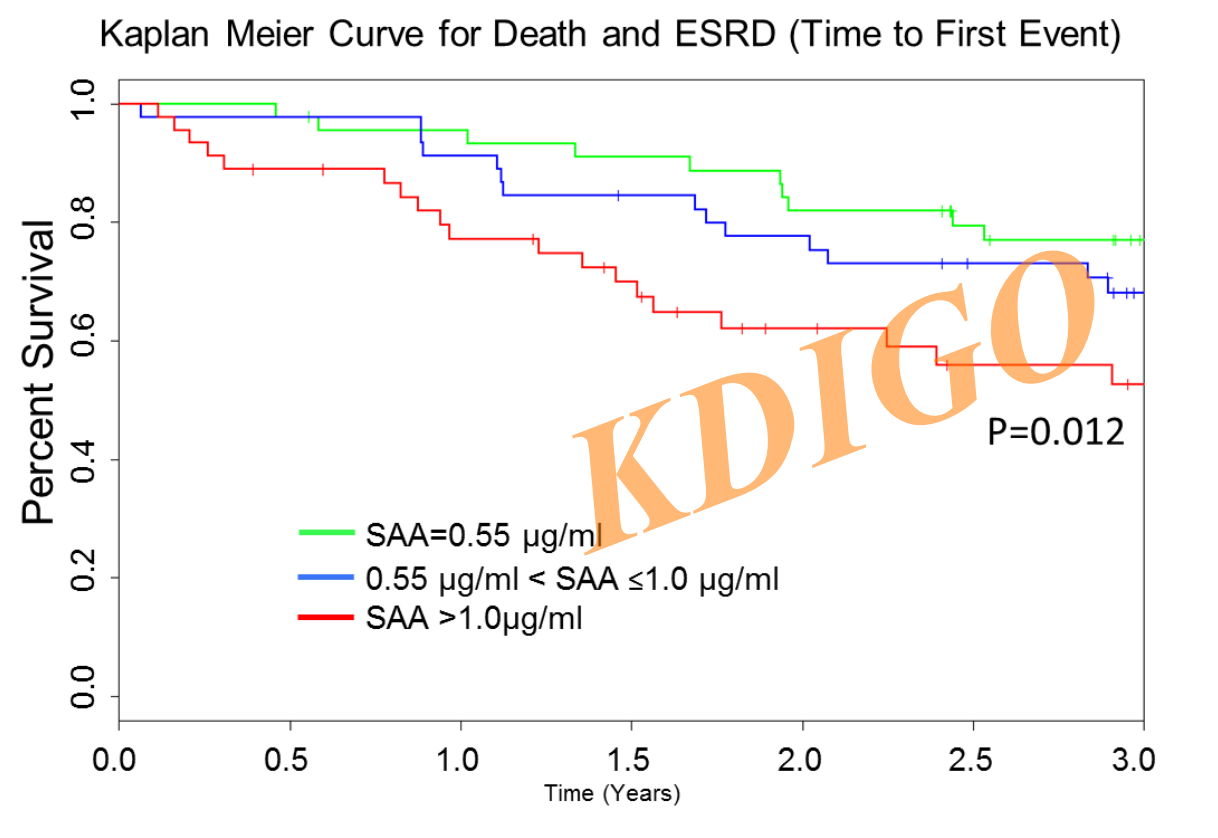


Tissue SAA deposition



Anderberg R *et al. Lab Invest* 2015;95:250-262

Serum Amyloid A and Risk of Death and ESRD in Diabetic Kidney Disease



SAA tertile 3 versus 1:
HR 3.03
95% CI 1.43-6.40
P=0.003
Adjusted for age, sex, race, UACR, eGFR

Model C statistic:
Δ c=0.017

Over a median duration of follow-up of 3.5 years, 30% (40/135) of participants progressed to ESRD and 24% (32/135) died.

Dieter BP, McPherson SM, Afkarian M, de Boer IH, Mehrotra R, Short R, Barbosa-Leiker C, Alicic RZ, Meek RL, Tuttle KR. *J Diabetes Complications* 2016;30:1467-1472.

KDIGO Guideline for Diabetes and CKD: New since NKF-KDOQI 2012 (and others)

- Co-Chairs: Ian de Boer and Peter Rossing

www.kidney-international.org meeting report

KDIGO

Management of patients with diabetes and CKD: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Vlado Perkovic[1,2], Rajiv Agarwal[3], Paola Fioretto[6], Brenda R. Hemmelgarn[7,8,9,10], Adeera Levin[11,12,13], Merlin C. Thomas[4,5], Christoph Wanner[14], Bertram L. Kasiske[15], David C. Wheeler[16] and Per-Henrik Groop[4,17,18,19]; for Conference Participants[20]

OPEN

Kidney International (2016) **90,** 1175–1183

XIX CONGRESSO PAULISTA DE NEFROLOGIA
INOVAÇÃO SUSTENTÁVEL
4-7 OUT 2017

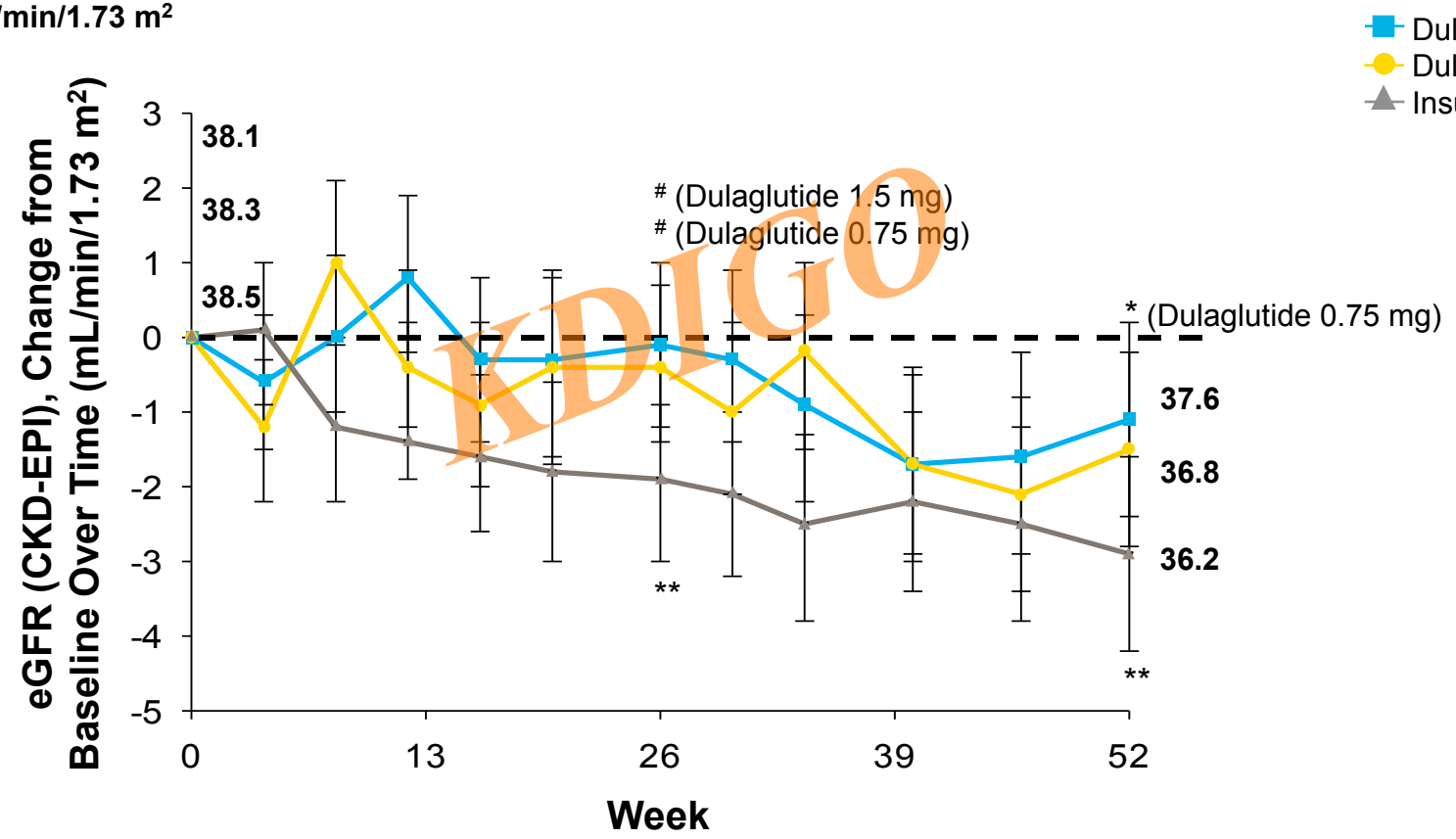
Diabetic Kidney Disease Take Home Points

- Although DKD is the most common cause of ESRD worldwide, most (90%) will die of CVD or infection before reaching ESRD.
- Intensive glycemic control early in the course of type 1 or type 2 diabetes is a proven strategy for DKD prevention, but not for DKD treatment.
- ACE inhibitors or ARBs are approved treatment for DKD, but do not prevent DKD in type 1 or type 2 diabetes with normotension or controlled hypertension.
- SGLT-2 inhibition reduces progression to macroalbuminuria, slope of eGFR decline, serum creatinine doubling, and ESRD.
- GLP-1 receptor agonists lower risk of albuminuria onset and progression as well as reduce eGFR decline.
- New mechanistic-based biomarkers and treatments are urgently needed to more effectively mitigate the global impact of DKD.
- Stay tuned for a KDIGO update!

Mouse Urine
Which One Had Diabetes?

AWARD-7:
Lesser eGFR Decline Over Time with Dulaglutide

Baseline eGFR = 38.3 mL/min/1.73 m²



Data presented as actual value LSM (95% CI); Safety population, MMRM analysis. *p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. insulin glargine. Note, only showing significance for weeks 26 and 52

Liraglutide in High-CVD-Risk Type 2 Diabetes: Primary and Secondary Outcomes

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

Marso SP *et al. N Engl J Med* 2016;375:311-322

The NEW ENGLAND JOURNAL of MEDICINE

Audience Response Question

- For the newer glucose-lowering drugs, SGLT-2 inhibitors and GLP-1 receptor agonists, risk of CVD events was reduced in patients with type 2 diabetes at high CVD risk.
- Which statement is true about subgroups with UACR >300 mg/g or eGFR <60 ml/min/1.73m^2?
  1. There was no effect of SGLT-2 inhibitors or GLP-1 receptor agonists on CVD risk.
  2. SGLT-2 inhibitors or GLP-1 receptor agonists increased CVD risk.
  3. SGLT-2 inhibitors or GLP-1 receptor agonists reduced CVD risk.
  4. SGLT-2 inhibitors or GLP-1 receptor agonists accelerated eGFR decline.