Impact of diabetes drugs on cardiovascular and renal disease in type 2 diabetes

NH Roma Villa Carpegna, Via Pio IV, 6

2-3 Febbraio 2018

EFFETTO DEI NUOVI FARMACI SUL RENE GLP-1 RA

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Dipartimento di Scienze Mediche

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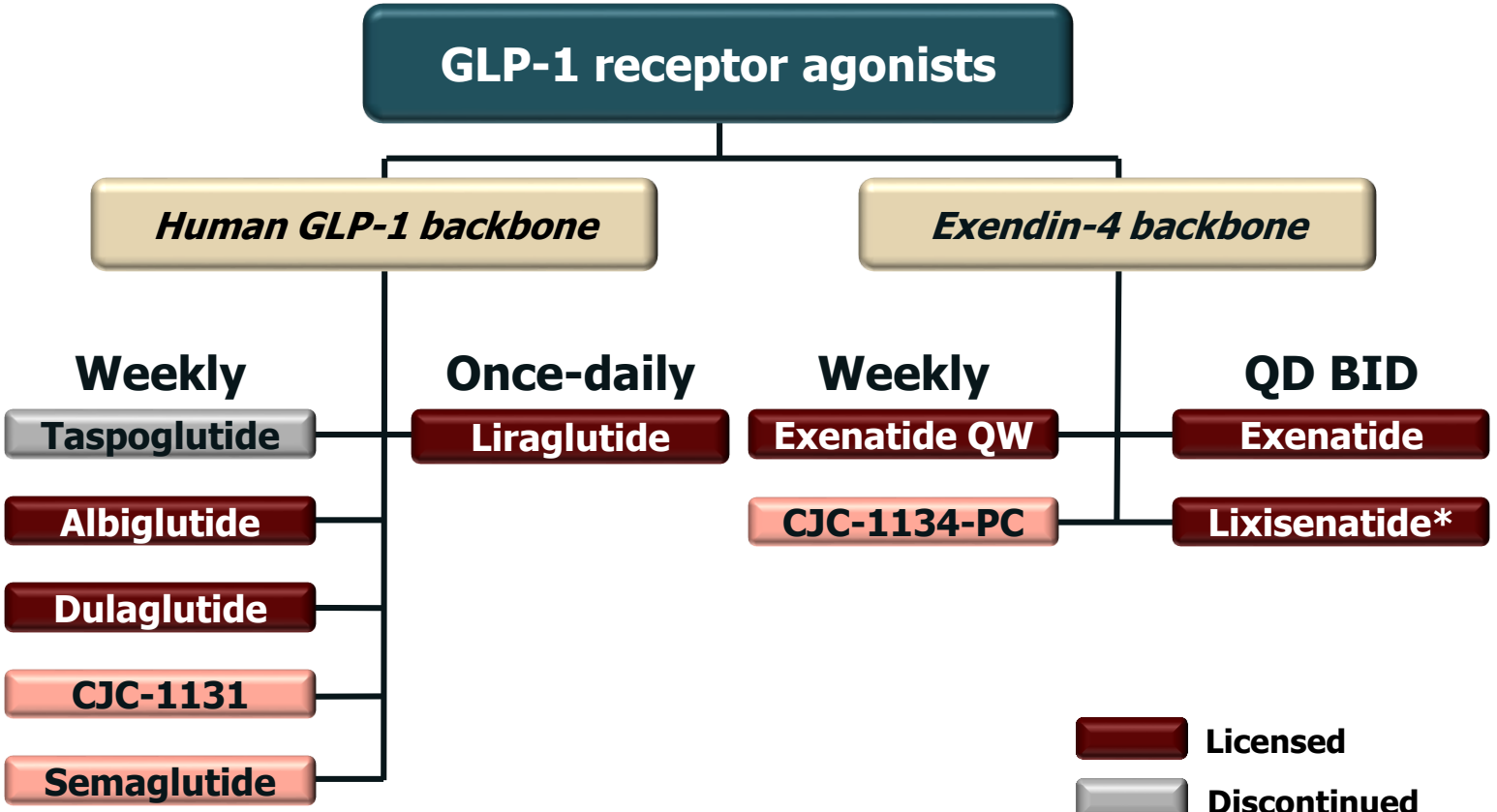
IRCCS "CSS", San Giovanni Rotondo (FG)



I GLP1 agonisti si differenziano per grado di omologia strutturale con il GLP1 nativo, strategie per prolungarne l'azione farmacologica e durata d'azione

*Not licensed in the US.

GLP-1, glucagon-like peptide 1; QD, once daily; BID, twice daily

Modified from: Madsbad S et al. Diabetes Obes Metab 2011;13:394-407

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

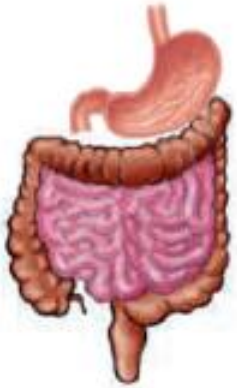
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

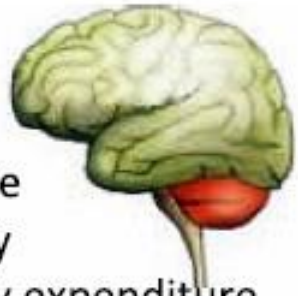
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Diabetes Care 2017;40(Suppl. 1):S64–S74



GIT
↓Gastric emptying
↑Acid secretion
↓GI motility



Brain
↓Apetite
↑Satiety
↑Energy expenditure

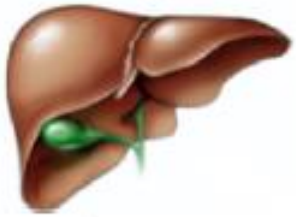
Heart
↓Blood pressure
↑Heart rate
↑Myocardial contractility
↑Cardioprotection

GLP-1
or
GLP-1R AGONISTS

Pancreas
↑Insulin secretion
↓Glucagon secretion
↑Insulin biosynthesis
↑ß-cell survival
↑ß-cell proliferation

↑Insulin sensitivity

Kidney
↑Natriuresis



Liver
↓Hepatic glucose production

Adipose tissue
↑Lyposis
↑FFA synthesis
↑Glucose uptake

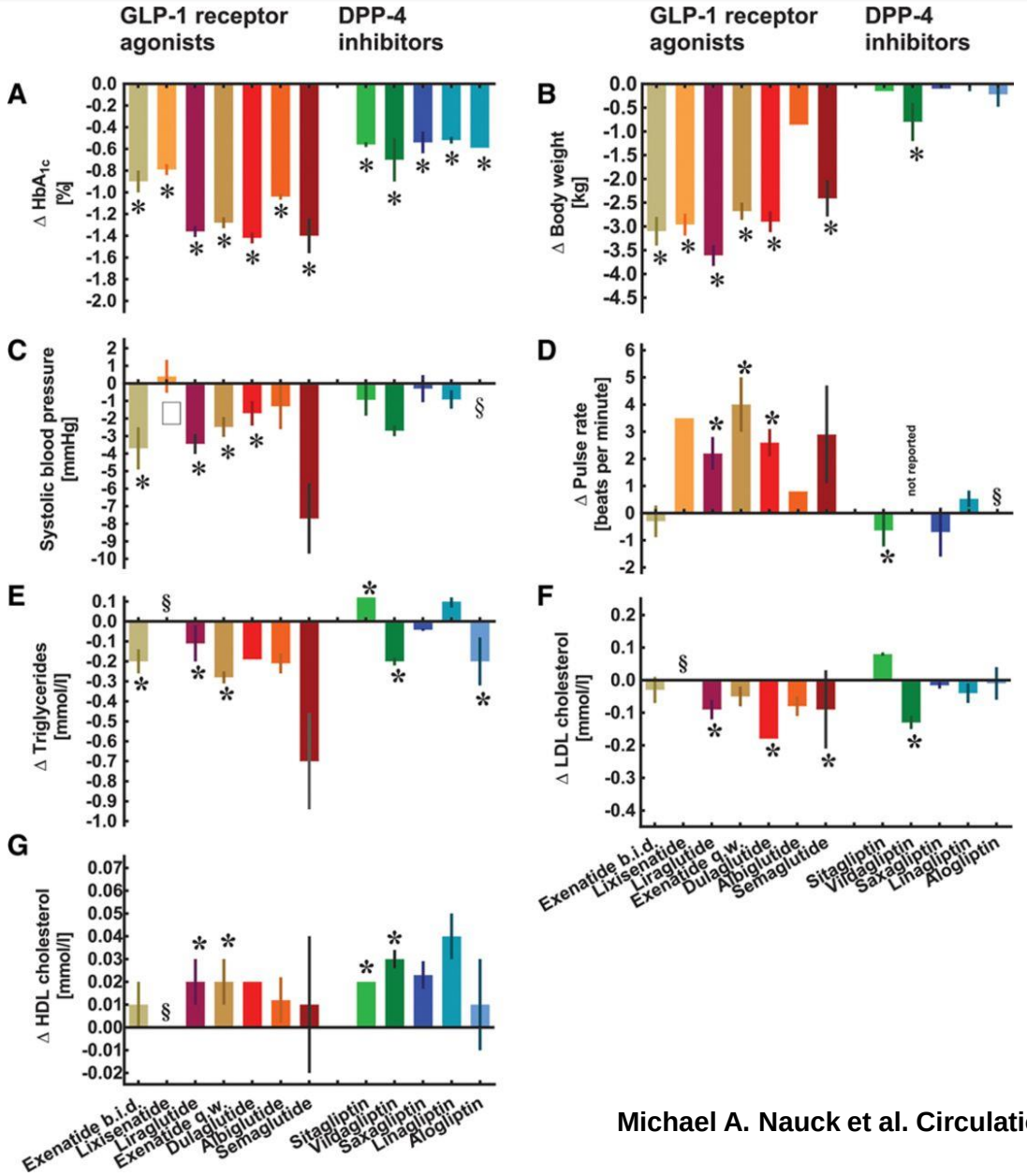
Muscle
↑Glycogen synthesis
↑Glucose oxidation

Baseline clinical characteristics by renal outcomes in 27,029 patients with T2DM

	Overall	Alb-/eGFR-	Alb-/eGFR+	Alb+/eGFR-	Alb+/eGFR+	
	n=27,029	n=18,056	n=2,788	n=4,978	n=1,207	p
Male gender (n,%)	15,249 (56.4%)	10,146 (56.2%)	1,296 (46.5%)	3,156 (63.4%)	651 (53.9%)	<.001
Age (years)	64±10	63±10	69±8	64±10	69±8	<.001
Duration of diabetes (years)	10±8	10±8	12±9	10±8	12±9	<.001
BMI (Kg/m^2)	29.2±5	28.9±4.9	29.6±4.8	29.5±5.1	29.9±5	<.001
eGFR (mL/min/1.73 m2)	85±13	87±13	74±10	87±13	74±10	<.001
HbA1c (%)	7.2±1.3	7.2±1.2	7.3±1.3	7.3±1.3	7.6±1.4	<.001
Total cholesterol (mg/dL)	188±36	189±36	188±37	186±37	185±37	<.001
Triglycerides (mg/dL)	133±88	129±84	139±94	140±96	148±91	<.001
Triglycerides ≥150 mg/dl (n, %)	7,484 (29.2%)	4,727 (27.7%)	821 (31.2%)	1,510 (31.8%)	426 (37.1%)	<.001
HDL-c (mg/dL)	52±15	53±15	52±15	51±15	50±15	<.001
LDL-c (mg/dL)	111±32	112±32	110±33	109±33	107±34	<.001
LDL-c ≥100 mg/dL (n, %)	15,523 (61.9%)	10,585 (63.3%)	1,547 (60.2%)	2,759 (59.3%)	632 (56.8%)	<.001
Systolic BP (mmHg)	139±18	138±18	142±18	139±18	143±18	<.001
Diastolic BP (mmHg)	80±9	80±9	80±9	80±9	80±9	.91
	2,510 (9.3%)	1,499 (8.3%)	318 (11.4%)	541 (10.9%)	152 (12.6%)	<.001

modified form S. De Cosmo et al. for AMD-Annals Study Group, *Medicine,* 2016

Effects of treatment with glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors on cardiovascular risk factors as described in placebo-controlled clinical trials using incretin-based medications as monotherapy.



Michael A. Nauck et al. Circulation. 2017;136:849-870

Putative renal distribution of GLP-1R

Location	Species	mRNA or protein	Detection method
GLP-1R			
Preglomerular* vascular smooth muscle cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1 agonist) and exendin 9–39 (GLP-1R antagonist)
Hilar and intralobular arteries	Human	Protein	Autoradiography of ^{125}I-labelled GLP-1
Glomerular capillary and vascular walls	Mouse	mRNA	*In situ* hybridization; RT-PCR
Glomerular endothelial cells and macrophages	Rat	Protein	Immunofluorescence
Glomerulus (not specified)	Rat	mRNA	RT-PCR
Juxtaglomerular cells	Monkey; human	Protein	Immunohistochemistry
	Rat	Protein	Immunohistochemistry
Proximal tubule	Rat	mRNA	RT-PCR
	Pig; human	mRNA, protein	RT-PCR, immunocytochemistry, immunohistochemistry, Western blotting
	Rat	Protein	Autoradiography of ^{125}I-labelled GLP-1, exendin 4 (GLP-1R agonist) and exendin 9–39 (GLP-1R antagonist)

Muskiet, M. H. A. *et al.* (2017) GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes
Nat. Rev. Nephrol. doi:10.1038/nrneph.2017.123

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1015-8987/12/0303-0749$38.00/0

Original Paper

Inhibition of the Expression of TGF-β1 and CTGF in Human Mesangial Cells by Exendin-4, a Glucagon-like Peptide-1 Receptor Agonist

Wenbin Li Meiyu Cui Yong Wei Xianglei Kong Lijun Tang Dongmei Xu

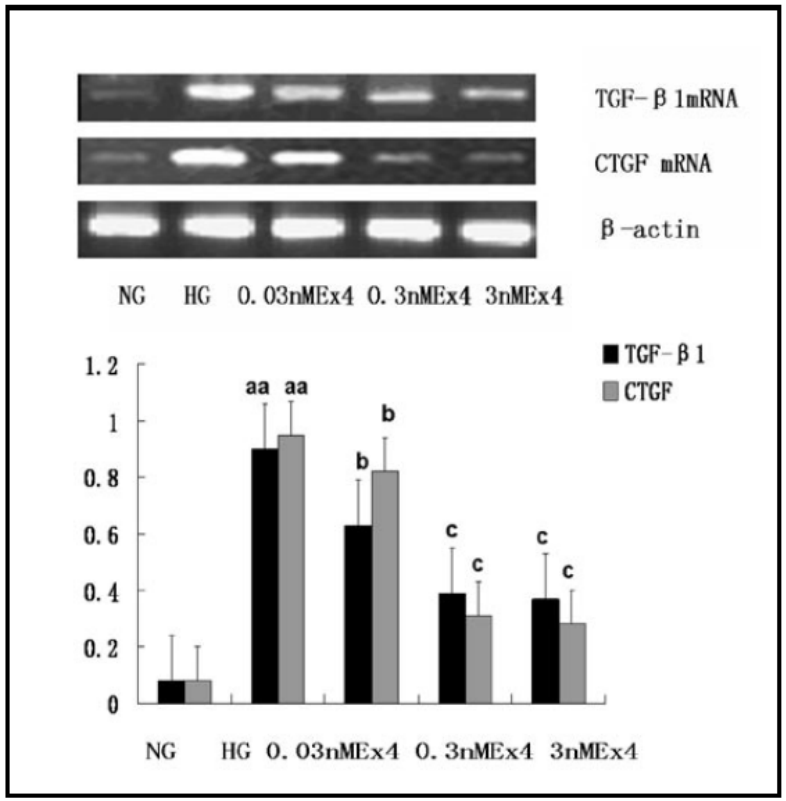
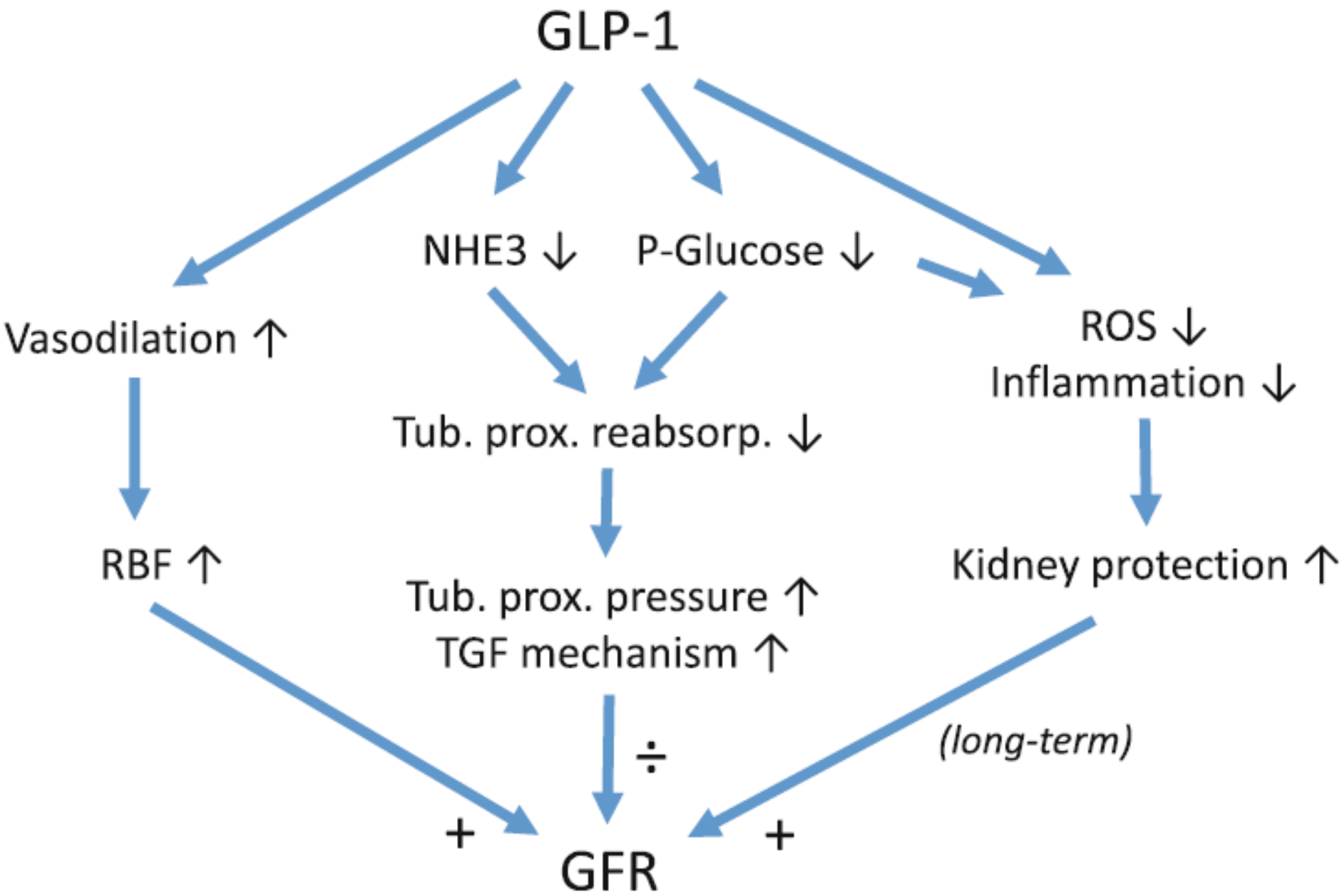
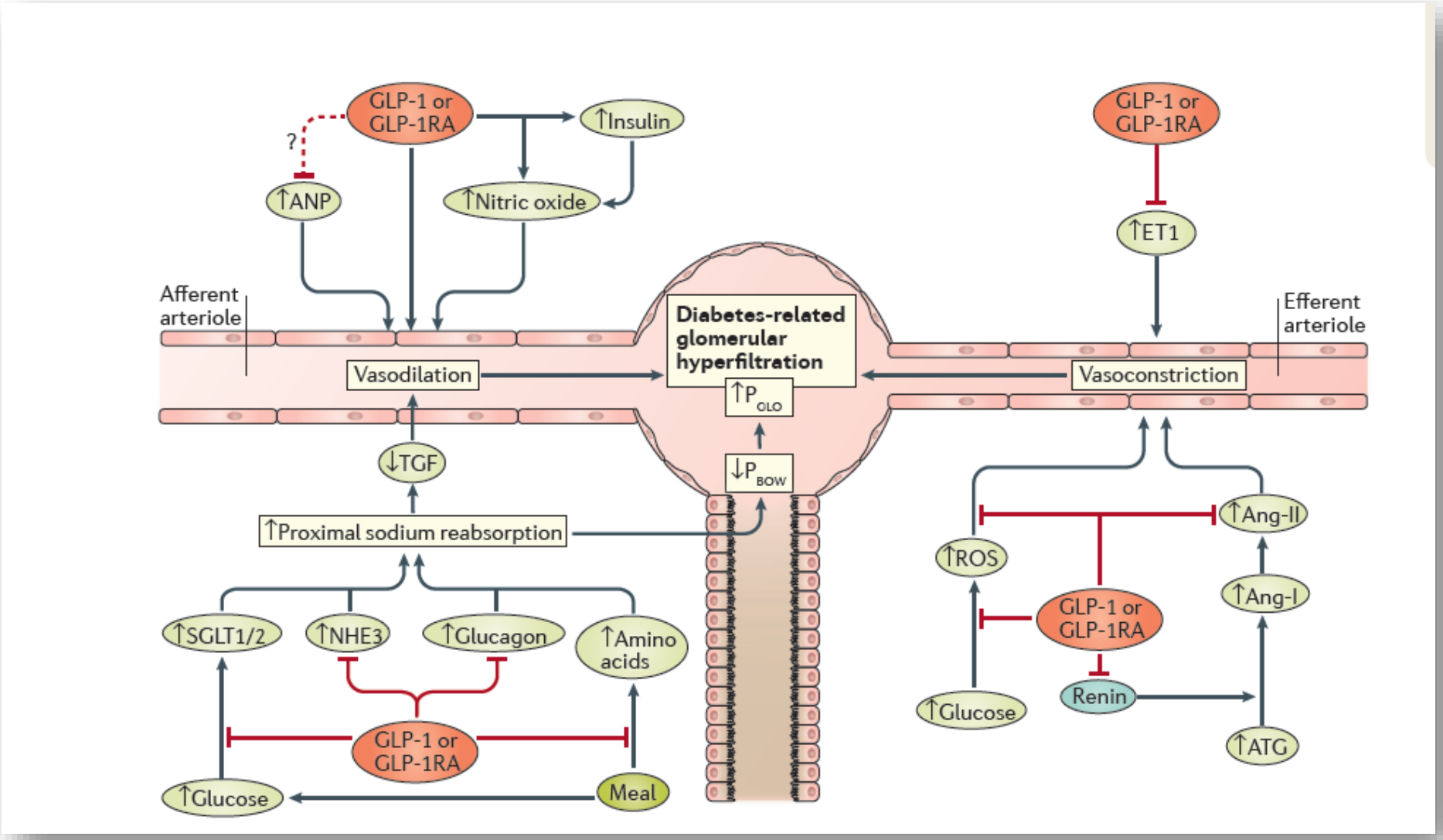


Fig. 2. Ex-4 inhibits the upregulated mRNA levels of HG treated TGF-β_1 and CTGF. Representative RT-PCR results show HG upregulated mRNA levels of TGF-β_1 and CTGF in HMCs and Ex4 inhibits the upregulated mRNA levels of TGF-β_1 and CTGF induced by high glucose. $^{aa}p < 0.01$ versus the control group; $^{b}p < 0.05$ versus HG group; $^{c}p < 0.05$ versus HG + 0.03 nM Ex4 group.

Diagram showing potential GLP-1 regulatory pathways of GFR.
Depending on the setting, GLP-1 may either increase or decrease GFR



Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus



Muskiet, M. H. A. *et al.* (2017) GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2017.123

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,
Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D.,
Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators*

N Engl J Med 2017;377:839-48.

Definition of composite nephropathy outcome (all event adjudicated)

- New onset of persistent macroalbuminuria
- Persistent doubling of serum creatinine
- End stage renal disease (ESRD)
- Death due to renal disease

LEADER

Baseline characteristics

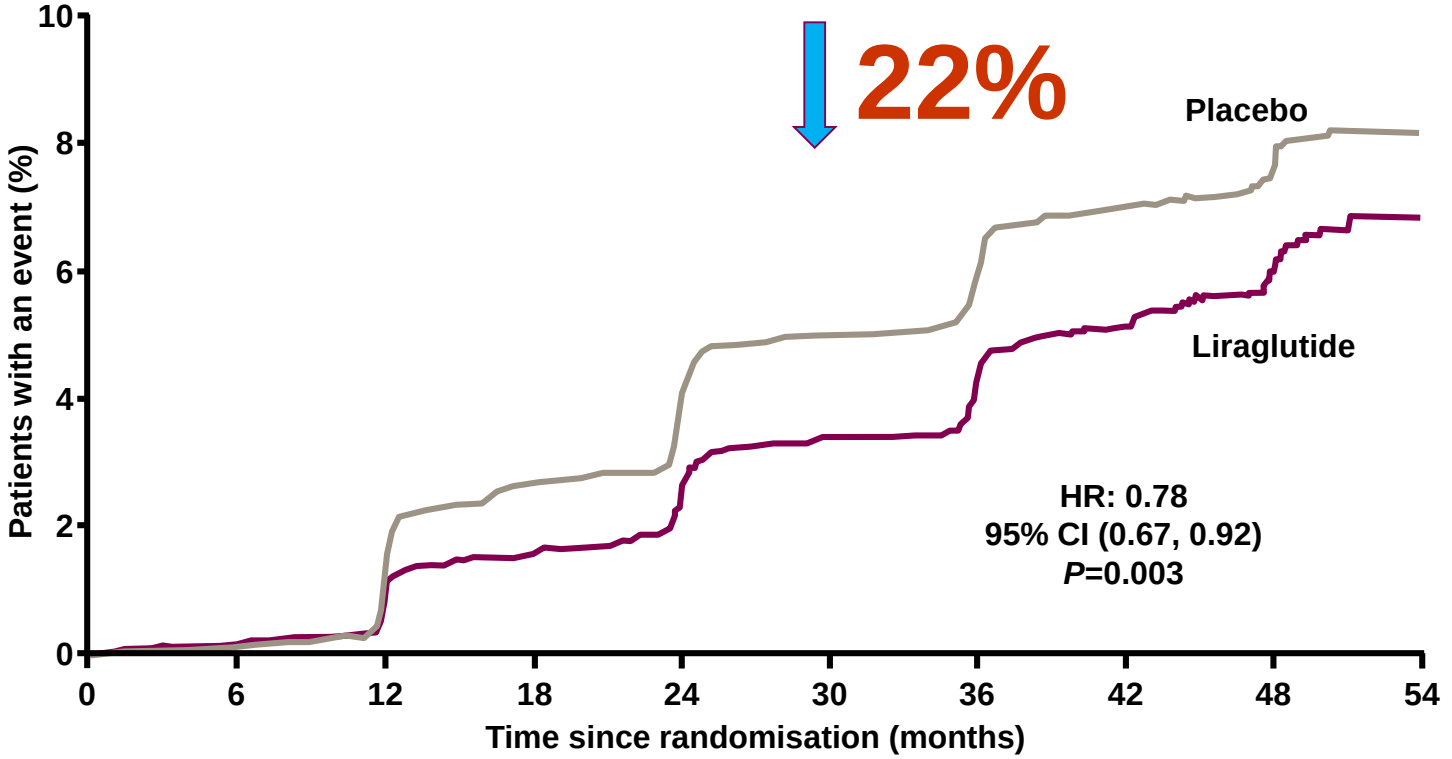
	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic regi		
Europe		(35.5)
North America		(31.0)
Asia		1 (7.5)
Rest of the wo		(26.1)
HbA_{1c}, %		± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

	Liraglutide	Placebo
Microalbuminuria	26.4%	26.6%
Macroalbuminuria	10.0%	11.0%
eGFR <60 mL/min/1.73 m^2	23.9%	22.3%

Full analysis set. Data are means ± standard deviations or number of patients (percentage of either liraglutide-treated or placebo-treated group). Percentage data refer to proportion of patients. *Heart failure includes NYHA class I, II and III. BMI: body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}: glycated hemoglobin; NYHA: New York Heart Association.
Marso S et al. *New Engl J Med* 2016;375:311–322.

N Engl J Med 2017;377:839-48.

LEADER: Time to first renal event Macroalbuminuria, doubling of serum creatinine, ESRD, renal death.

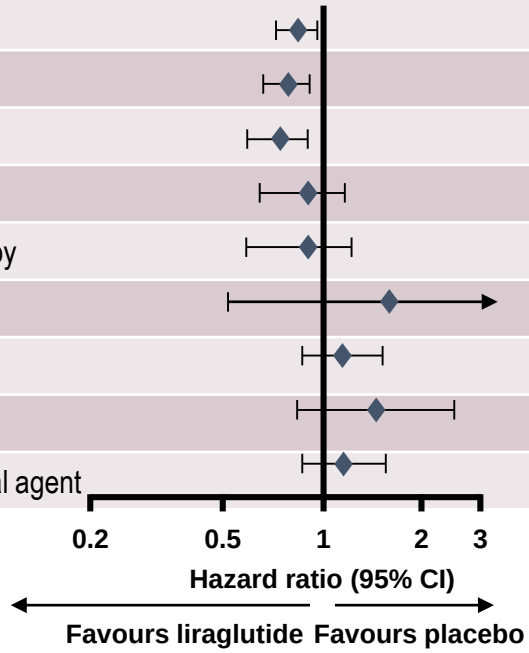


Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

N Engl J Med 2017;377:839-48.

LEADER: Time to first microvascular endpoints

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Number of patients		**4668**	**100**	**4672**	**100**
Microvascular endpoint	**0.84 (0.73–0.97)**	**355**	**7.6**	**416**	**8.9**
Renal event	**0.78 (0.67–0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria*	0.74 (0.60–0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine†	0.88 (0.66–1.18)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61–1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52–4.87)	8	0.2	5	0.1
Eye event	**1.15 (0.87–1.52)**	**106**	**2.3**	**92**	**2.0**
Vitreous haemorrhage	1.45 (0.84–2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87–1.55)	100	2.1	86	1.8



N Engl J Med 2017;377:839-48.

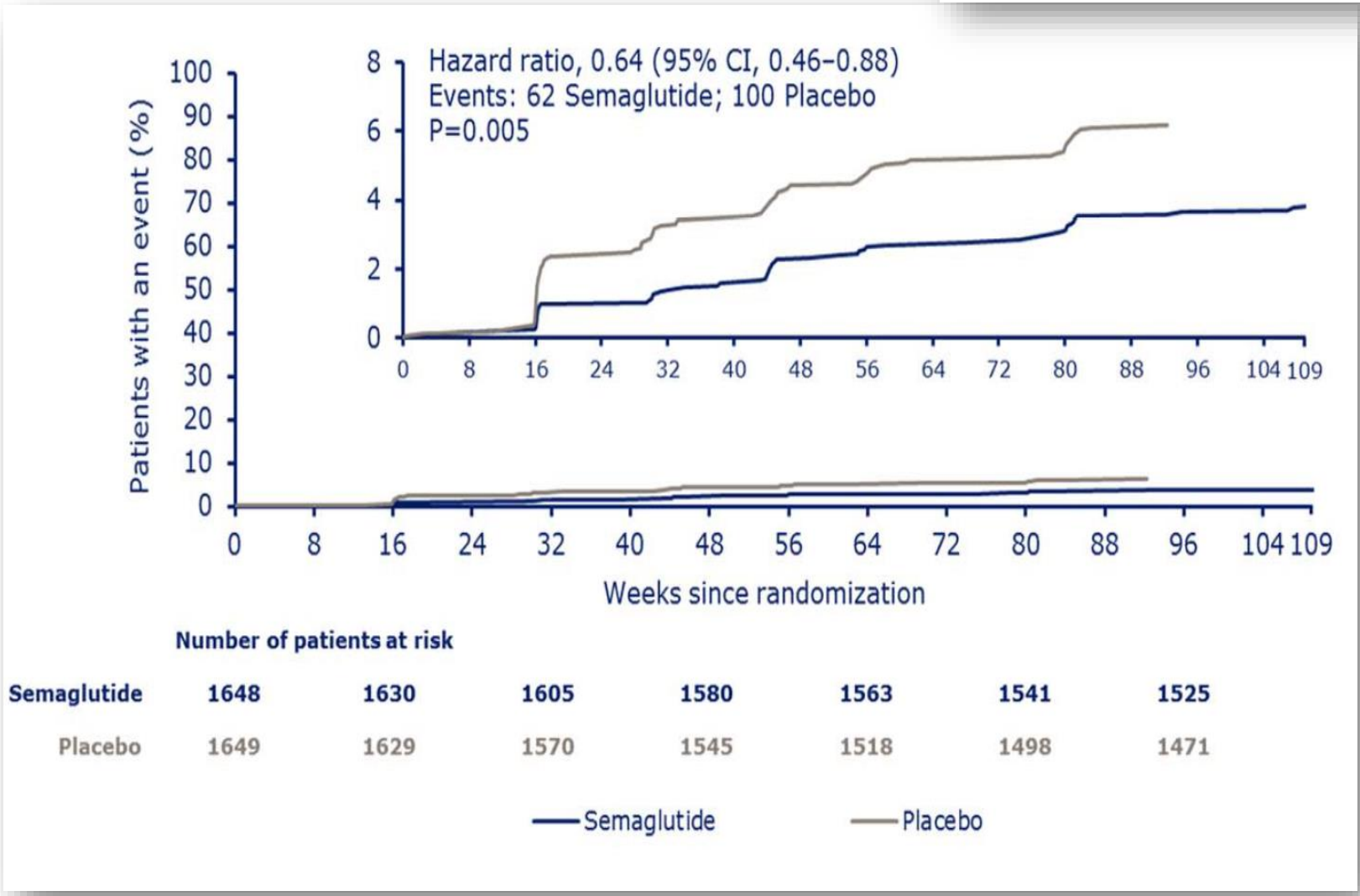
SUSTAIN-6: New or worsening nephropathy

September 16, 2016

ORIGINAL ARTICLE

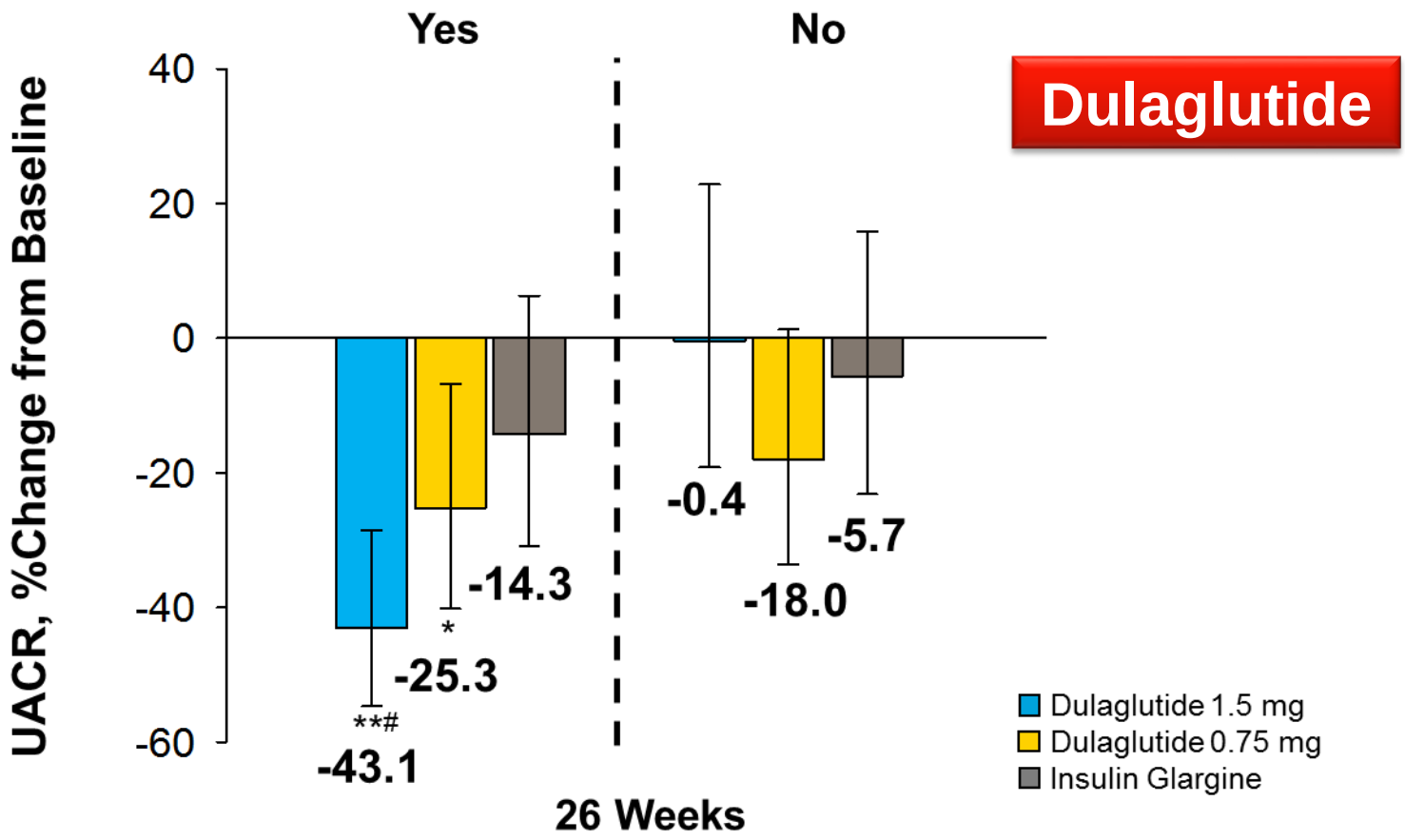
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*



AWARD 7 -UACR by macroalbuminuria

UACR significantly decreased with DU 1.5 mg vs. insulin glargine at 26 weeks in participants with macroalbuminuria



Data presented as LSM (95% CI); Safety population, MMRM analysis; *,**p<0.05 or p<0.001 vs. BL, #p<0.05 vs. insulin glargine

The evaluation of Lixisenatide in acute coronary syndrome: the ELIXA trial

Numbers of patients with events:	Lixisenatide n=3034	Placebo n=3034
Primary composite CV Outcome	13.4%	13.2%
	ITT HR=1.02 (0.89-1.17)	
Individual components		
CV death	5.1%	5.2%
MI (fatal/non-fatal)	8.9%	8.6%
Stroke (fatal/non-fatal)	2.2%	2.0%
Unstable angina	0.4%	0.3%
Hospitalization for heart failure	4.0%	4.2%
Urinary A/C ratio, change from baseline to Month 24	+24%	+34%
	p<0.01	

Pfeffer MA, New Engl J Med 2015

THE LANCET

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Articles

Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial

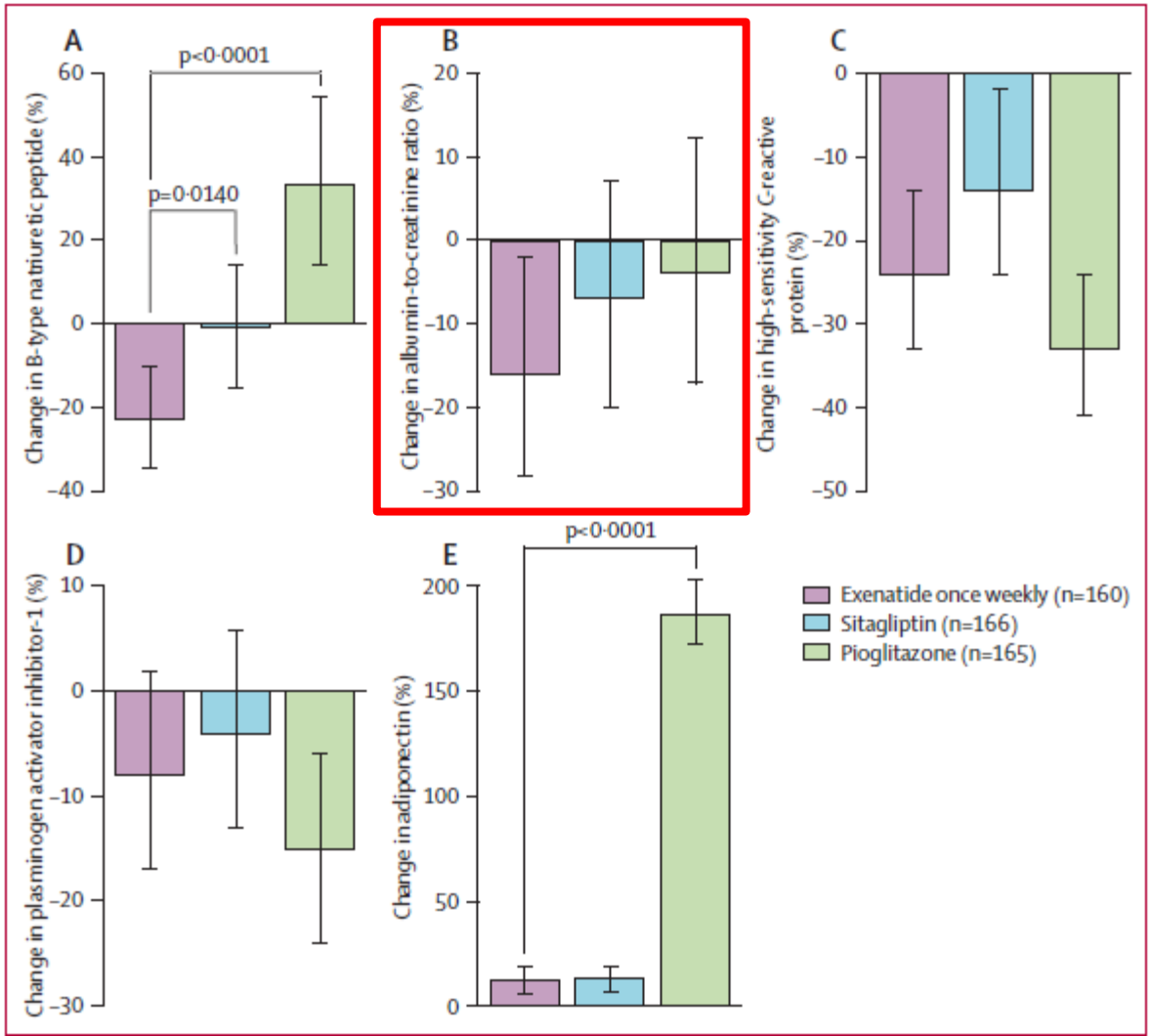
Dr Richard M Bergenstal, MD, Carol Wysham, MD, Leigh MacConell, PhD, Jaret Malloy, PhD, Brandon Walsh, PhD, Ping Yan, PhD, Ken Wilhelm, MD, Jim Malone, MD, Lisa E Porter, MD, for the DURATION-2 Study Group‡

‡ Members listed at end of paper

Published: 26 June 2010

PlumX Metrics

DOI: http://dx.doi.org/10.1016/S0140-6736(10)60590-9



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Changes in Albuminuria Predict Mortality and Morbidity in Patients with Vascular Disease

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This Article

Published online before print June 30, 2011, doi: 10.1681/ASN.2010091001
JASN July 1, 2011 vol. 22 no. 7 1353-1364

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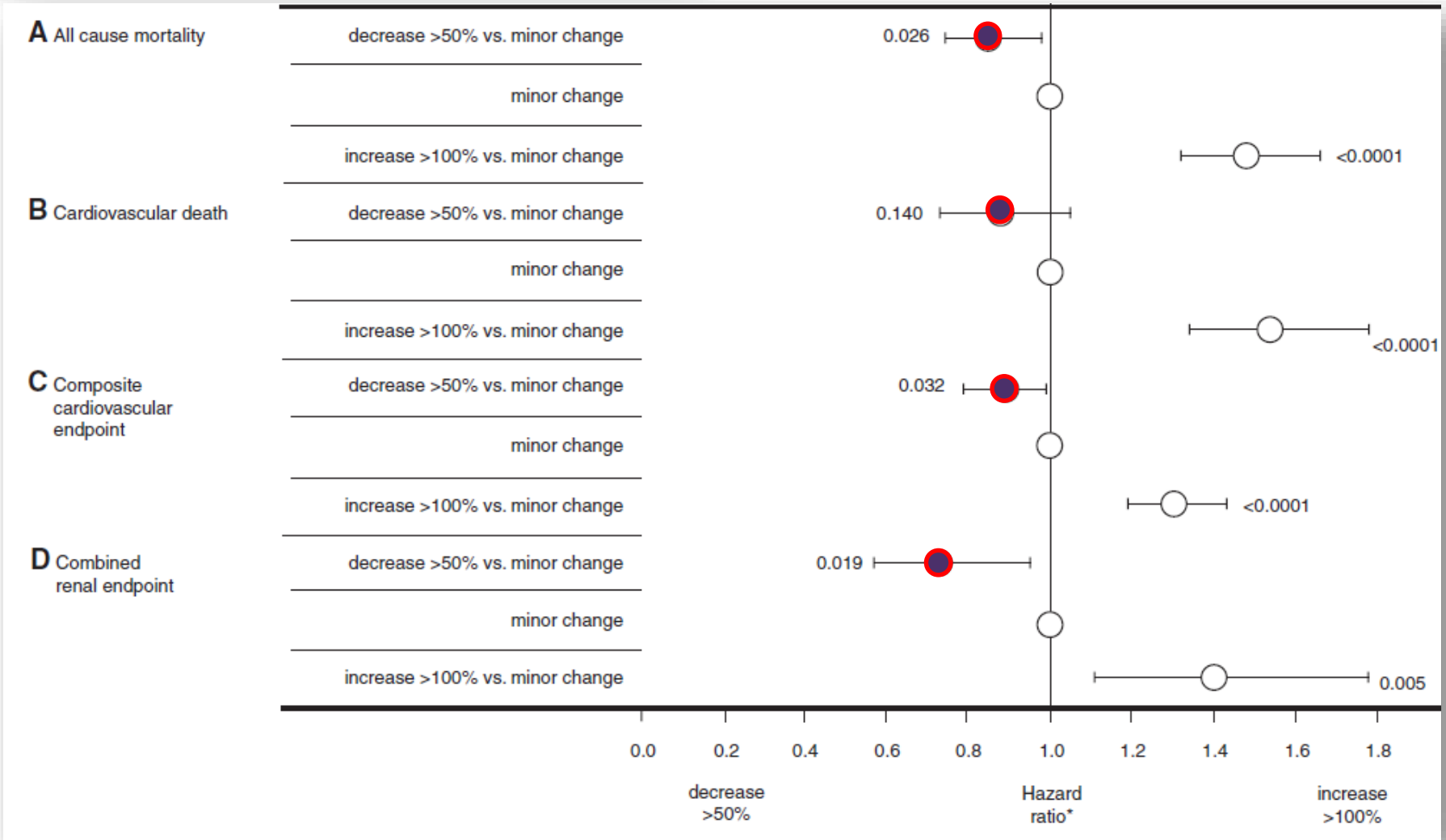
Current Issue

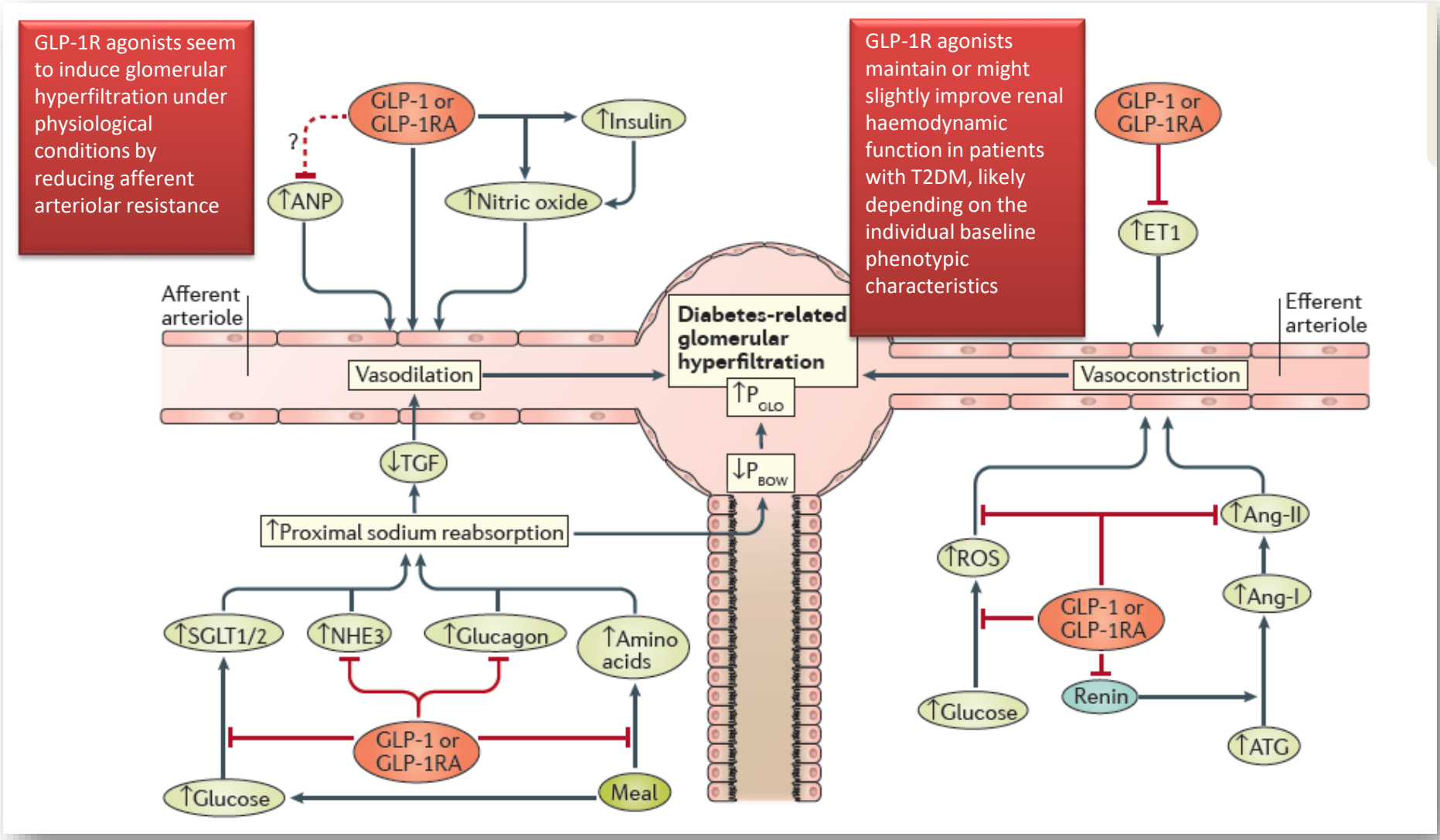
November 2017, 28 (11)

Alert me to new issues of JASN

Roland E. Schmieder*, Johannes F. E. Mann†, Helmut Schumacher‡, Peggy Gao§, Giuseppe Mancia‖, Michael A. Weber¶, Matthew McQueen**, Teo Koon**, Salim Yusuf** and on behalf of the ONTARGET Investigators

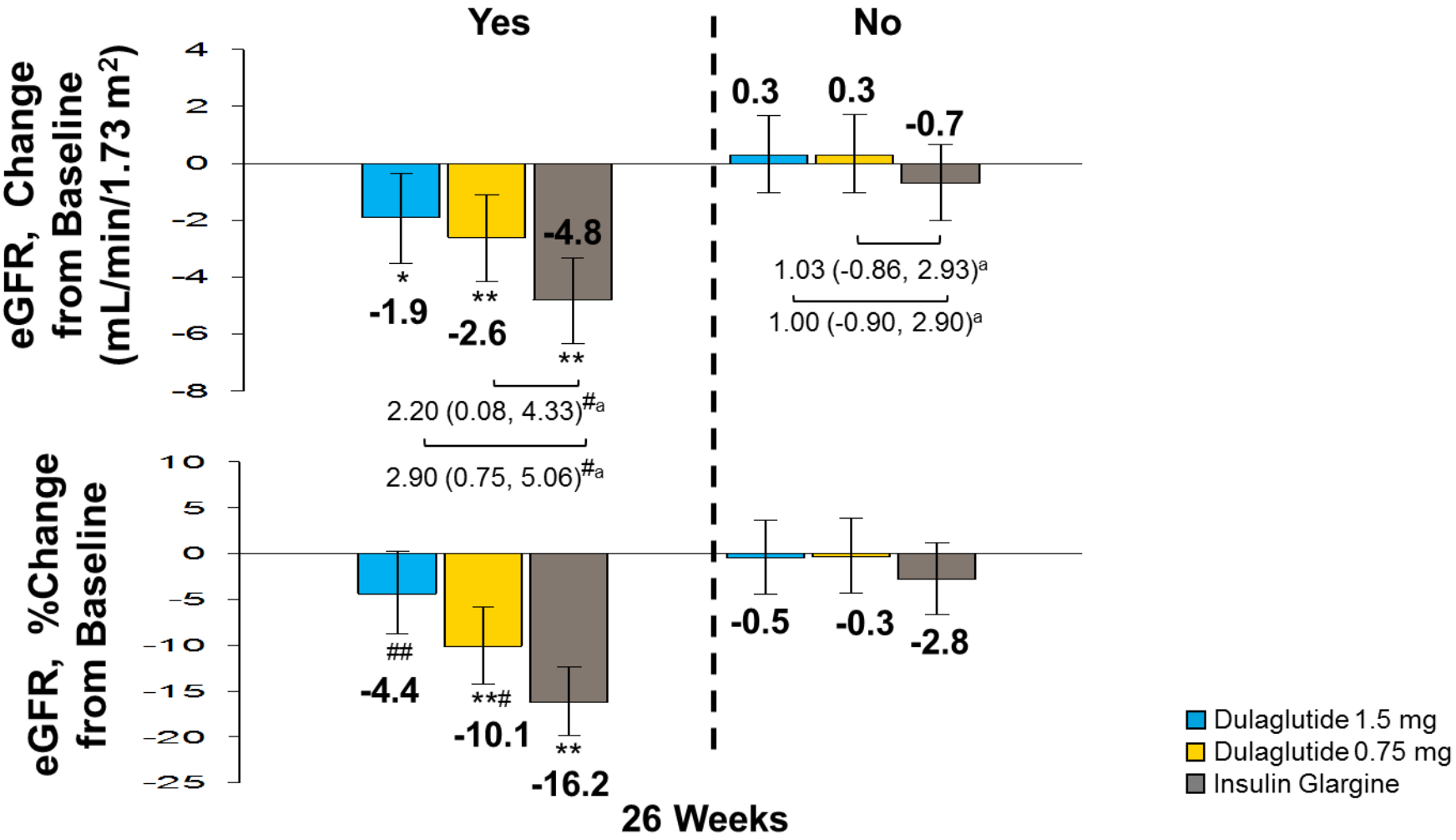


Effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal haemodynamics in diabetes mellitus



Muskiet, M. H. A. *et al.* (2017) GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes
Nat. Rev. Nephrol. doi:10.1038/nrneph.2017.123

AWARD 7- eGFR (CKD-EPI-creatinine) by macroalbuminuria



Data presented as LSM (95% CI); Safety population, MMRM analysis; *,**p<0.05 or p<0.001 vs. BL, #p<0.05 vs. insulin glargine; [a]Treatment difference [LSM difference (nominal 95% CI)]

Table 1 | GLP-1R and DPP-4 expression in the kidney (for details, see main text)

Cells	Species	mRNA/protein
GLP-1R		
Glomerulus (not specified)	Rats (microdissected rat nephron segments)	mRNA
Proximal convoluted tubules		
Proximal tubular cells	Pigs	mRNA/protein
	Humans	Protein
Glomerular capillary walls and vascular walls	Mice	mRNA
Glomerular endothelial cells and macrophages	Rats	Protein
DPP-4		
Preglomerular vascular smooth muscle cells	SHR	mRNA
Mesangial cells	WKY	Protein
Podocytes	Rats	Protein
Proximal tubular cells	Pigs	Protein
	Humans	

Tanaka T. et al. Kidney Internat. 2014