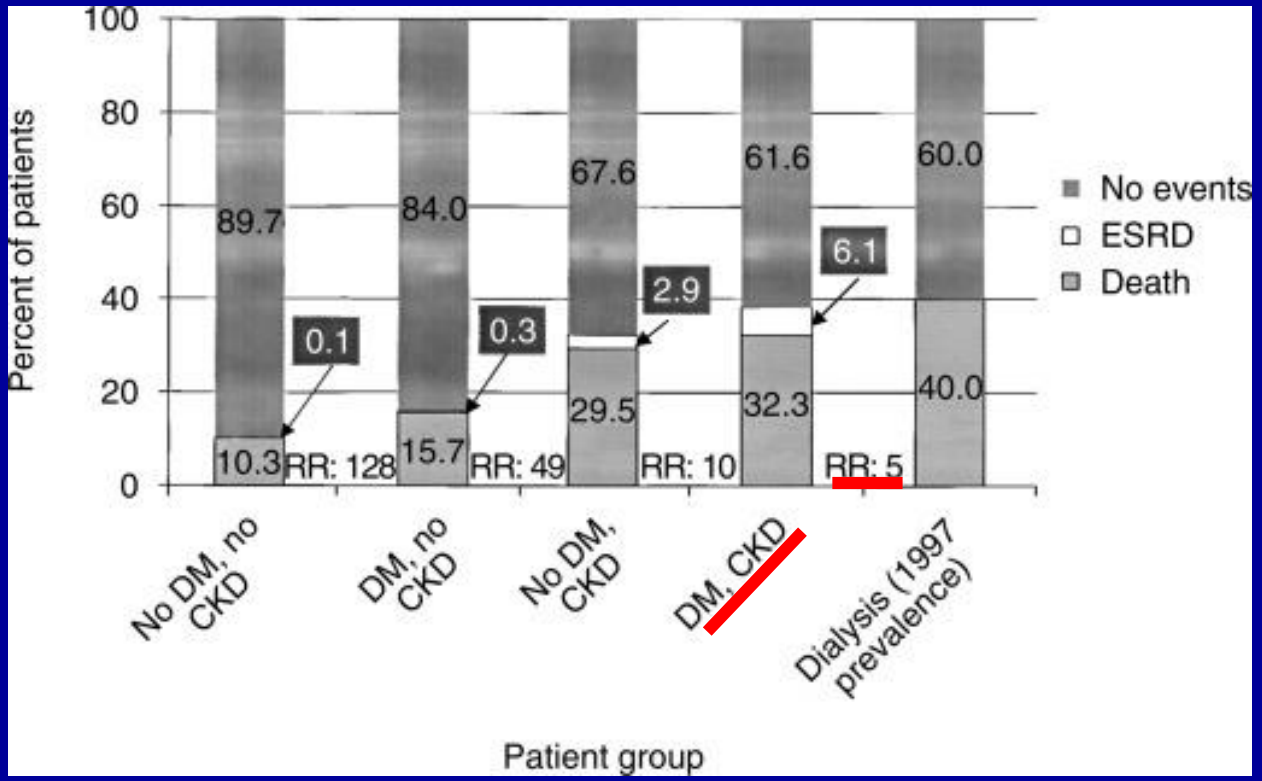
Effects of GLP-RA's on the kidney

高雄長庚醫院腎臟科
楊智超
109-01-11

The burden and progress of DKD in T2DM: focus on aging kidneys



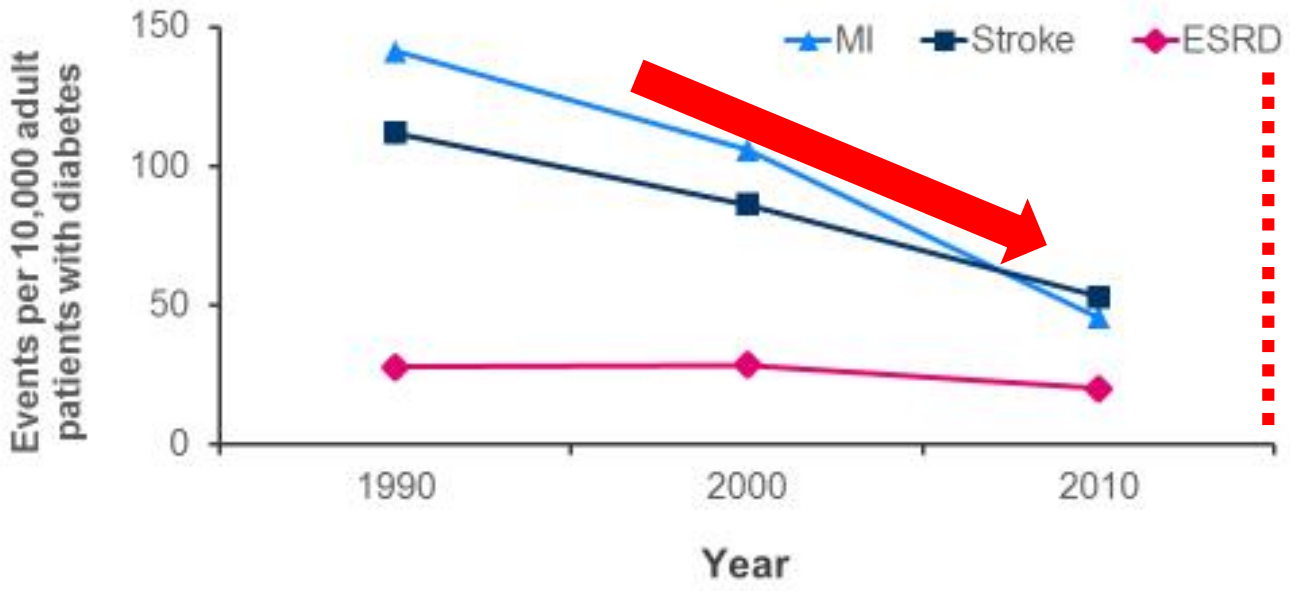
Outcomes during 2-year follow-up(risk of death) ➔

CKD+DM is more likely to die than enter dialysis

Kidney International, 2003, S24–S31

Increased **life** expectancy and aging kidneys!!

Improved diabetes care has not yet succeeded in reducing renal complications



SGLT2i
GLP1a

?

Adapted from Gregg EW *et al. N Engl J Med* 2014;370:1514

Global Burden of Chronic Kidney Disease 1990–2013[a]

CKD Etiology	No. of Cases (x1,000)		Change in No. of Cases	Prevalence per 100,000 Adults		Change in Prevalence
	1990	2013	1990-2013	1990	2013	1990-2013
CKD-diabetes mellitus	43,339	88,711	+82.5%	1230	1355	+11.85%
CKD-hypertension	79,945	101,253	+26.8%	1634	1453	-10.7%
CKD-glomerulonephritis	82,920	108,861	+32.7%	1866	1590	-13.5%
CKD-other causes	112,461	173,091	+53.9%	2507	2575	+3.1%
CKD-all cases	318,665	471,916	+48.1%	7237	6973	-3.6%

- Although the overall age-standardized prevalence rate of all-cause generic CKD declined by 3.6%, the prevalence of CKD associated with diabetes mellitus increased by almost 12% from 1990 to 2013

CKD=chronic kidney disease. [a]Number of cases and adjusted prevalence rates. Note: Prevalence values are age-standardized.
Data are adapted from Global Burden of Disease Study 2013 Collaborators[2]

1. Glassock et al. Nat Rev Nephrol. 2017;13(2):104-114
2. Global Burden of Disease Study 2013 Collaborators. Lancet. 386, 743–800 (2015)

9萬人洗腎創新高...年花健保近450億

2019-09-02

腎病醫療費513億 蟬聯10大疾病首位

〔記者林惠琴／台北報導〕健保支出腎病最花錢！衛福部健保署統計，慢性腎臟病再度蟬聯去年使用醫療費用最多的十大疾病首位，共計三十六．四萬人就醫，花費約五一三．七八億元，且國內洗腎更已增達九萬人，創下歷年新高。

衛福部健保署統計，慢性腎臟病再度蟬聯去年使用醫療費用最多的十大疾病首位，共計三十六．四萬人就醫，花費約五一三．七八億元。（資料照）

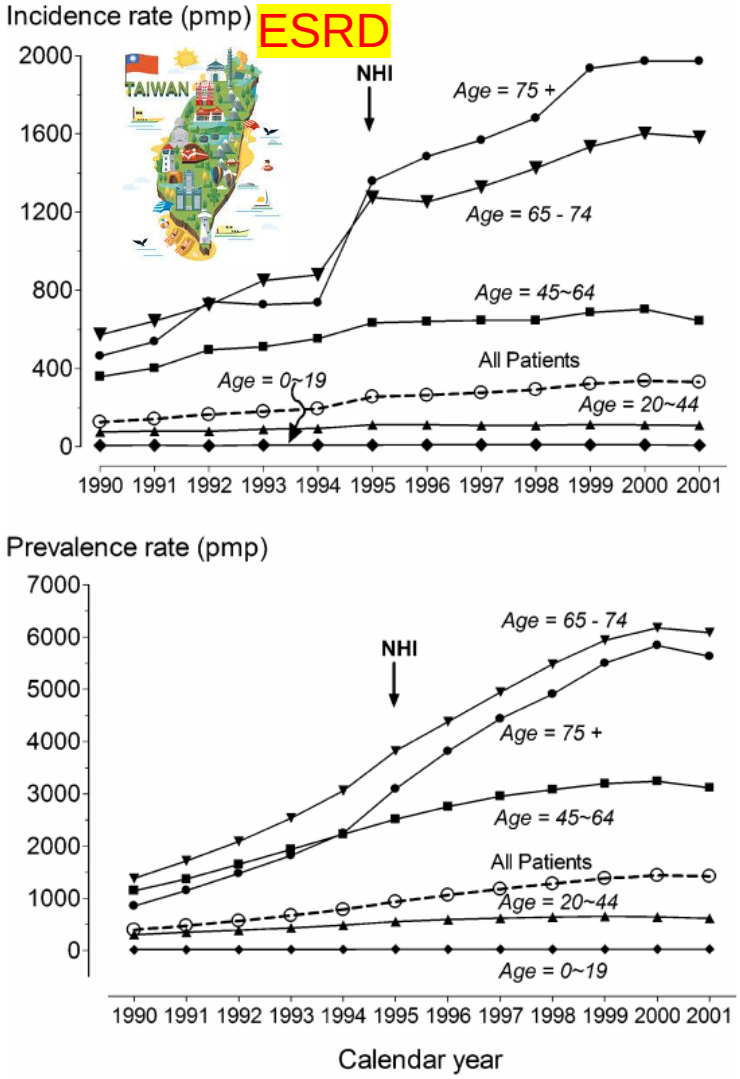
健保署統計，去年給付慢性腎臟病高達五一三．七八億，占健保總額近七%，為所有單一疾病花費之首，且洗腎達到九萬人，一年花費四四九．四六億，包含血液透析八．二萬人、腹膜透析六四九○人，平均每名洗腎患者年花健保近五十萬元。

6成因三高控制不佳 邁入洗腎人生

台灣腎臟醫學會理事長盧國城指出，不少患者是糖尿病、高血壓、高血脂等三高控制不佳，進而邁入洗腎人生，估計洗腎病人中，近五十%有糖尿病、約十五%至二十%有高血壓或心臟病，若三高病況能良好控制，推估可減少六十%洗腎人數。

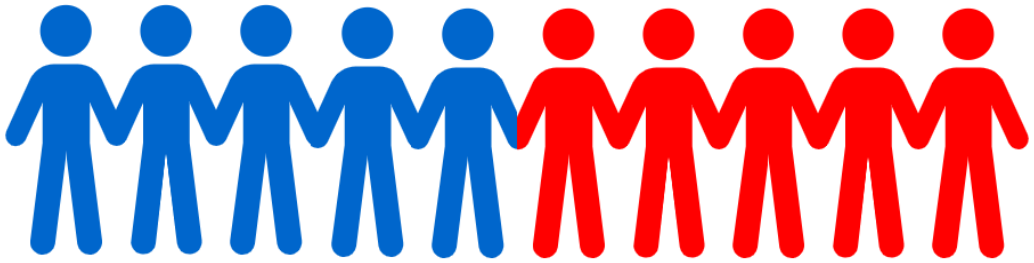
盧國城也提到，洗腎人數高不僅發生在台灣，而是全球現象，可能就與老化、三高病人增加有關，而台灣洗腎較歐美品質佳，病人存活率更長，加上持續新增病人，也因此國內洗腎人數總是居高不下。

除了慢性腎臟病，其次花費健保最多是糖尿病二九一．六八億元、二億元、齲齒一六七．○九億元、高血壓一三九．二億元。



~78,000 hemodialysis patients in Taiwan in 2017

49.3% are diabetic patients



Year	2001	2005	2009	2013
Population	0.16%	0.21%	0.25%	0.30%
Cost	7.2%	7.3%	8.2%	8.3%
	45X	35X	33X	28X

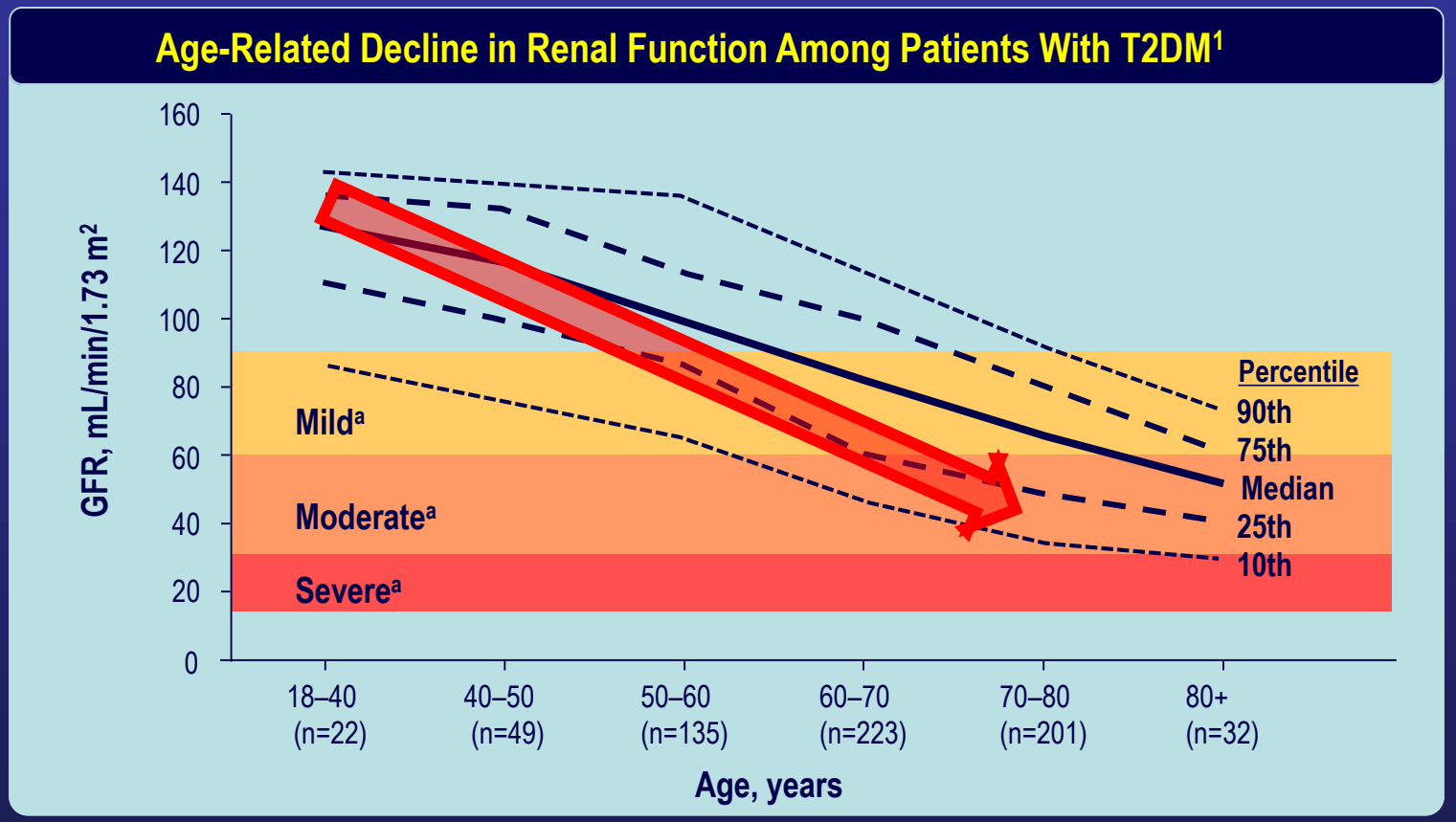
Fig. 7 Growth rate of percentage of dialysis to the general population and percentage of dialysis to the overall healthcare cost in Taiwan 2001–2013.

2017 Annual Report on Kidney Disease in Taiwan.

Nephrology 22, Suppl. 4 (2017) 3–8

Nephrol Dial Transplant (2008) 23: 3977–3982

Increased Age Is Associated With a Lower eGFR Among Patients With T2DM



Additional observational studies have demonstrated an age-related decline in eGFR in the range of 1.5–5.2 mL/min/1.73 m² in patients with T2DM[2–4]

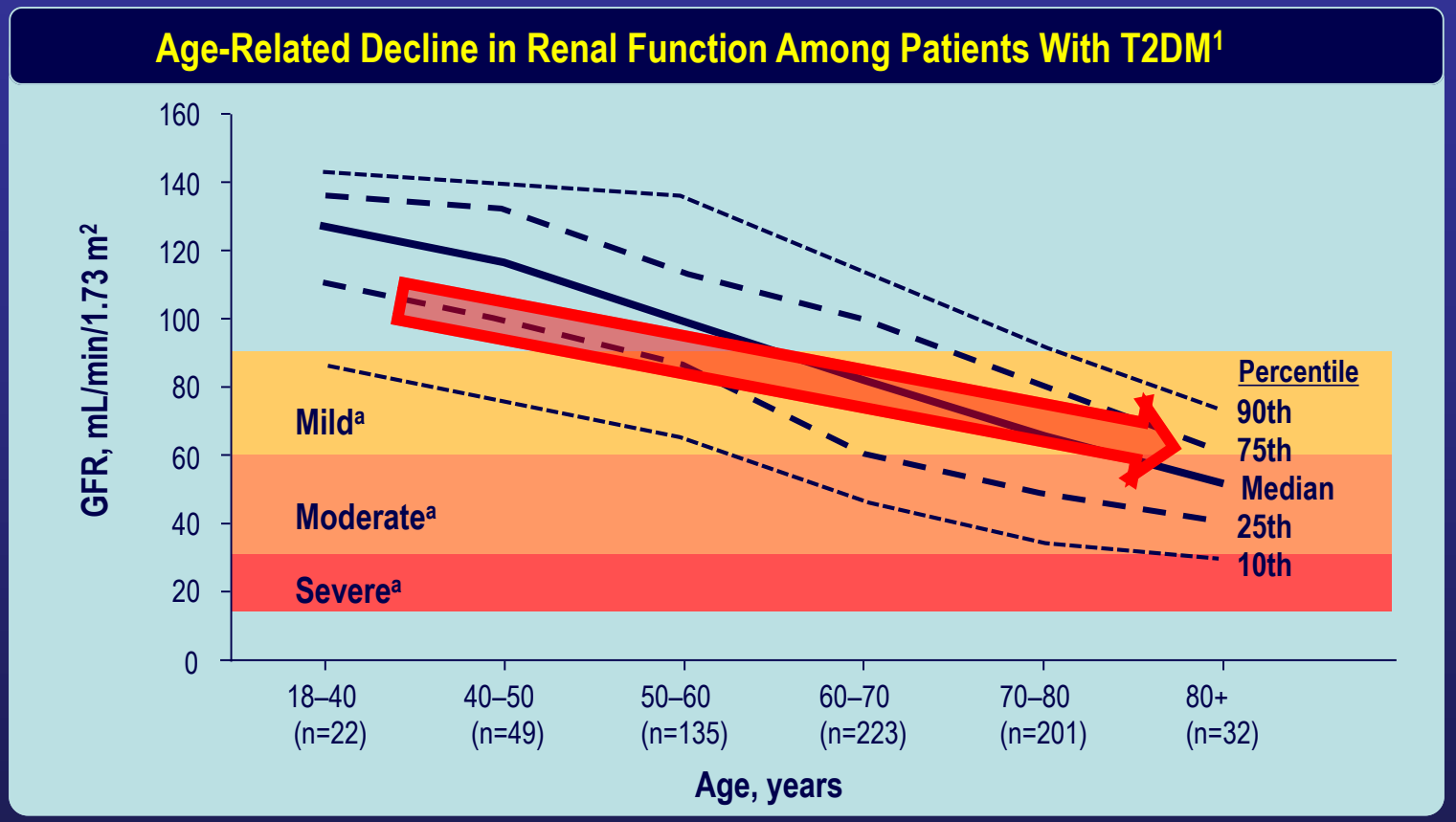
Adapted with permission from Premaratne E et al.[1]

[a]National Kidney Foundation severity scale of renal impairment.

GFR = glomerular filtration rate; T2DM = type 2 diabetes mellitus; eGFR = estimated GFR.

1. Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. **2.** Altemtam N et al. *Nephrol Dial Transplant*. 2012;27:1847–1854. **3**. Ali O et al. *BMJ Open*. 2013;3:e001855. **4**. Rossing K et al. *Kidney Int*. 2004;66:1596–1605.

Increased Age Is Associated With a Lower eGFR Among Patients With T2DM



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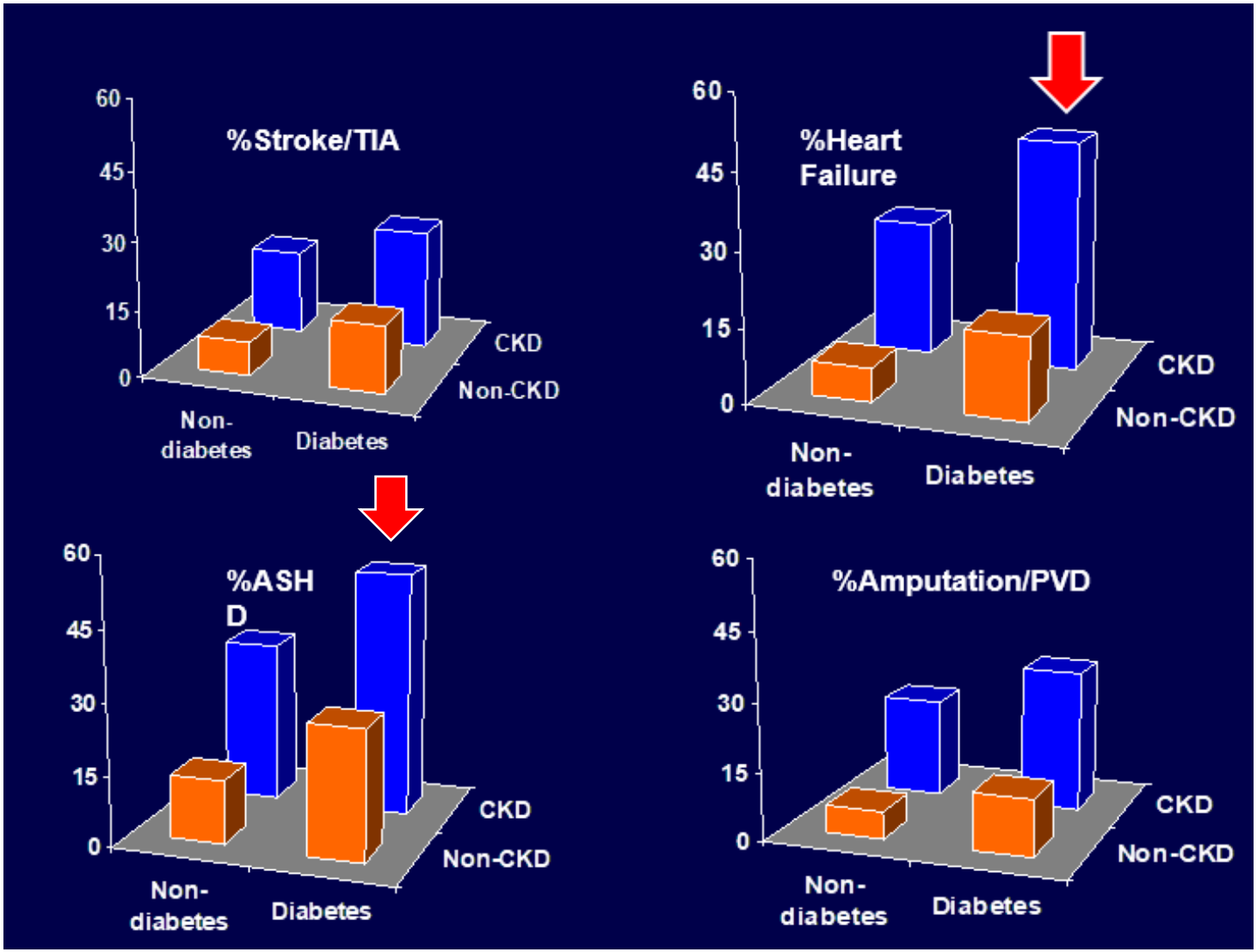
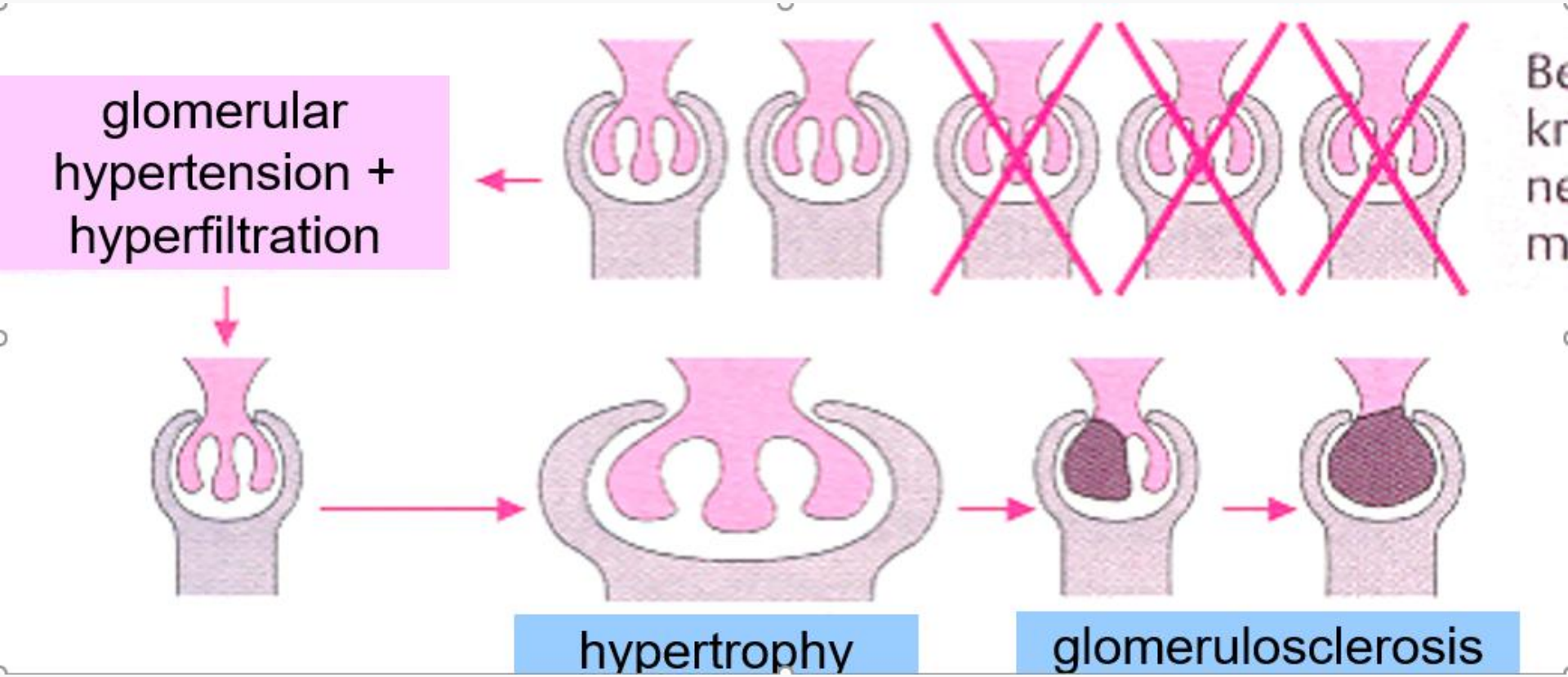
1. Premaratne E et al. *Diabetologia*. 2005;48:2486–2493. **2.** Altemtam N et al. *Nephrol Dial Transplant*. 2012;27:1847–1854. **3**. Ali O et al. *BMJ Open*. 2013;3:e001855. **4**. Rossing K et al. *Kidney Int*. 2004;66:1596–1605.

Cardiovascular Comorbidities,
5% Medicare sample, by Diabetes and CKD status, 1999-2000



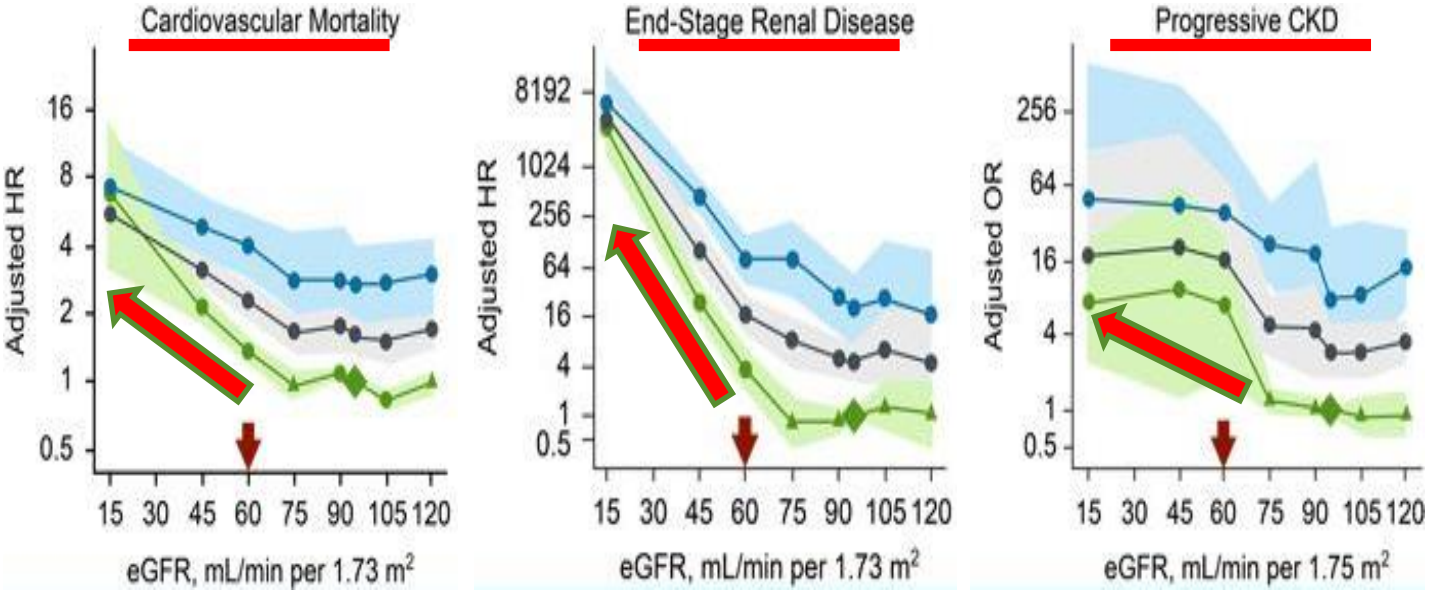
Kidney International, Vol. 64,
Supplement 87 (2003), pp. S24–S31

Acclerated Progression of CKD



Accelerated progression of CVD in CKD

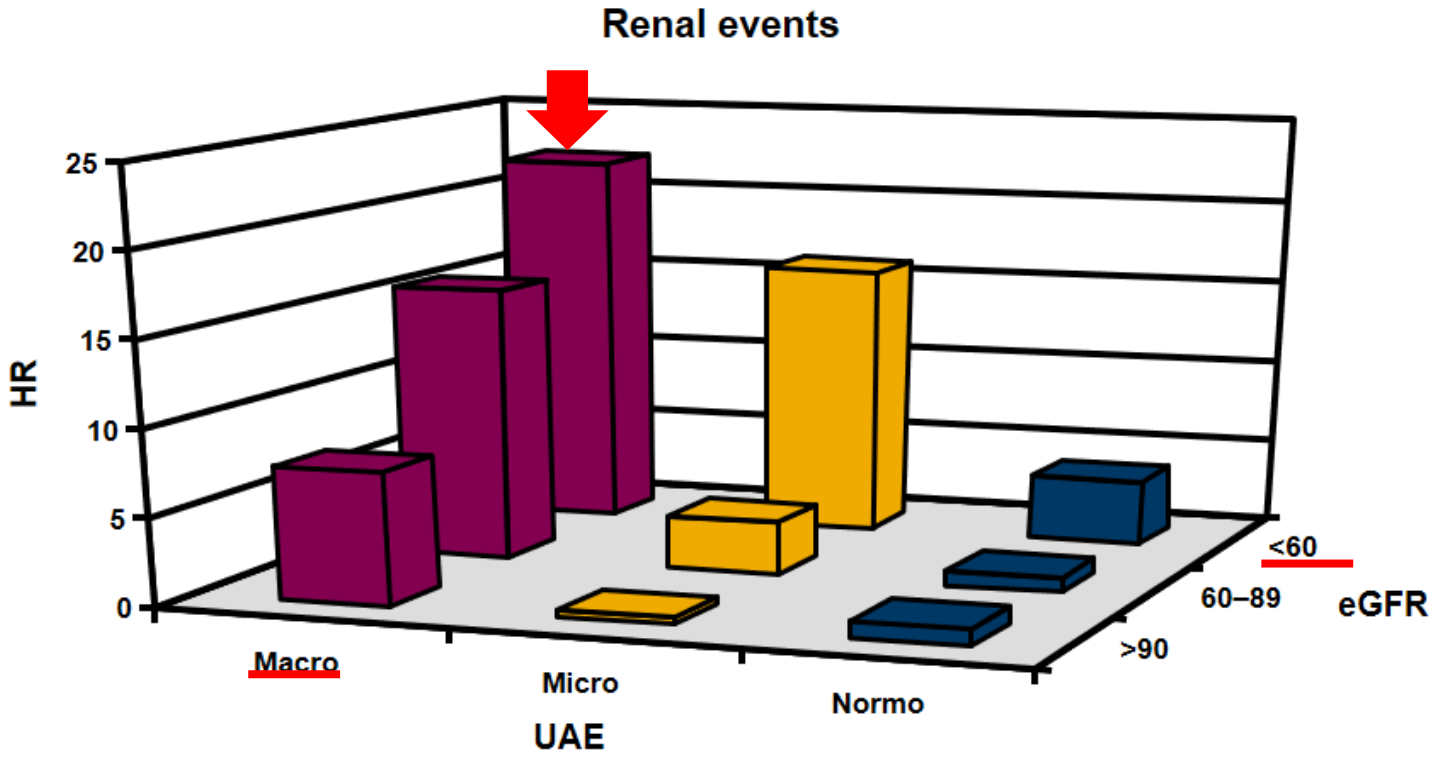
eGFR and albuminuria predict outcome!!



Levey AS, et al. Kidney Int. 2011;80:17-28

Renal Events by eGFR and Albuminuria : ADVANCE Study

Renal events: death as a result of kidney disease, requirement for dialysis or transplantation, or doubling of serum creatinine to >2.26 mg/dL (200 µmol/L)



10,640 patients with T2DM; median follow-up of 4.3 years
eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2DM, Type 2 diabetes mellitus; UAE, urinary albumin excretion
Ninomiya T, et al. *J Am Soc Nephrol* 2009;20:1813–1821

Table 1—Association of CV end points with baseline eGFR stages

End point	Total number of events (events/100 patient-years)				Adjusted hazard ratio (95% CI) vs. eGFR ≥90 mL/min/1.73 m²			
	Stage 1 eGFR ≥90 mL/min/1.73 m²	Stage 2 eGFR 60–89 mL/min/1.73 m²	Stage 3a eGFR 45–59 mL/min/1.73 m²	Stage 3b eGFR 30–44 mL/min/1.73 m²	Stage 2 eGFR 60–89 mL/min/1.73 m²	Stage 3a eGFR 45–59 mL/min/1.73 m²	Stage 3b eGFR 30–44 mL/min/1.73 m²	*P* value
CV death, MI, stroke, or hospitalization for UA	330 (3.52)	799 (3.55)	393 (5.74)	145 (7.34)	0.93 (0.82–1.06)	1.28 (1.10–1.49)	1.39 (1.13–1.72)	<0.0001
CV death, MI, or stroke	281 (2.97)	692 (3.05)	358 (5.17)	141 (7.11)	0.94 (0.82–1.09)	1.36 (1.15–1.61)	1.60 (1.29–1.99)	<0.0001
CV death	136 (1.37)	333 (1.39)	188 (2.52)	79 (3.65)	0.89 (0.73–1.09)	1.31 (1.04–1.65)	1.65 (1.22–2.23)	<0.0001
Hospitalization for UA	57 (0.59)	135 (0.58)	42 (0.59)	7 (0.33)	0.95 (0.69–1.31)	0.85 (0.56–1.30)	0.40 (0.18–0.91)	0.17
MI	130 (1.36)	281 (1.22)	141 (2.00)	57 (2.81)	0.86 (0.69–1.06)	1.26 (0.98–1.63)	1.50 (1.07–2.11)	0.0001
Stroke	53 (0.55)	185 (0.80)	92 (1.29)	27 (1.30)	1.37 (1.00–1.86)	1.96 (1.37–2.79)	1.79 (1.10–2.93)	0.0016
All-cause death	186 (1.87)	489 (2.04)	267 (3.57)	130 (6.01)	0.94 (0.79–1.12)	1.35 (1.11–1.64)	1.97 (1.55–2.52)	<0.0001
Hospitalization for heart failure *	62 (0.64)	214 (0.92)	107 (1.50)	68 (3.36)	1.17 (0.88–1.56)	1.50 (1.08–2.08)	2.64X	<0.0001

UA, unstable angina.

Post hoc analysis of TECOS

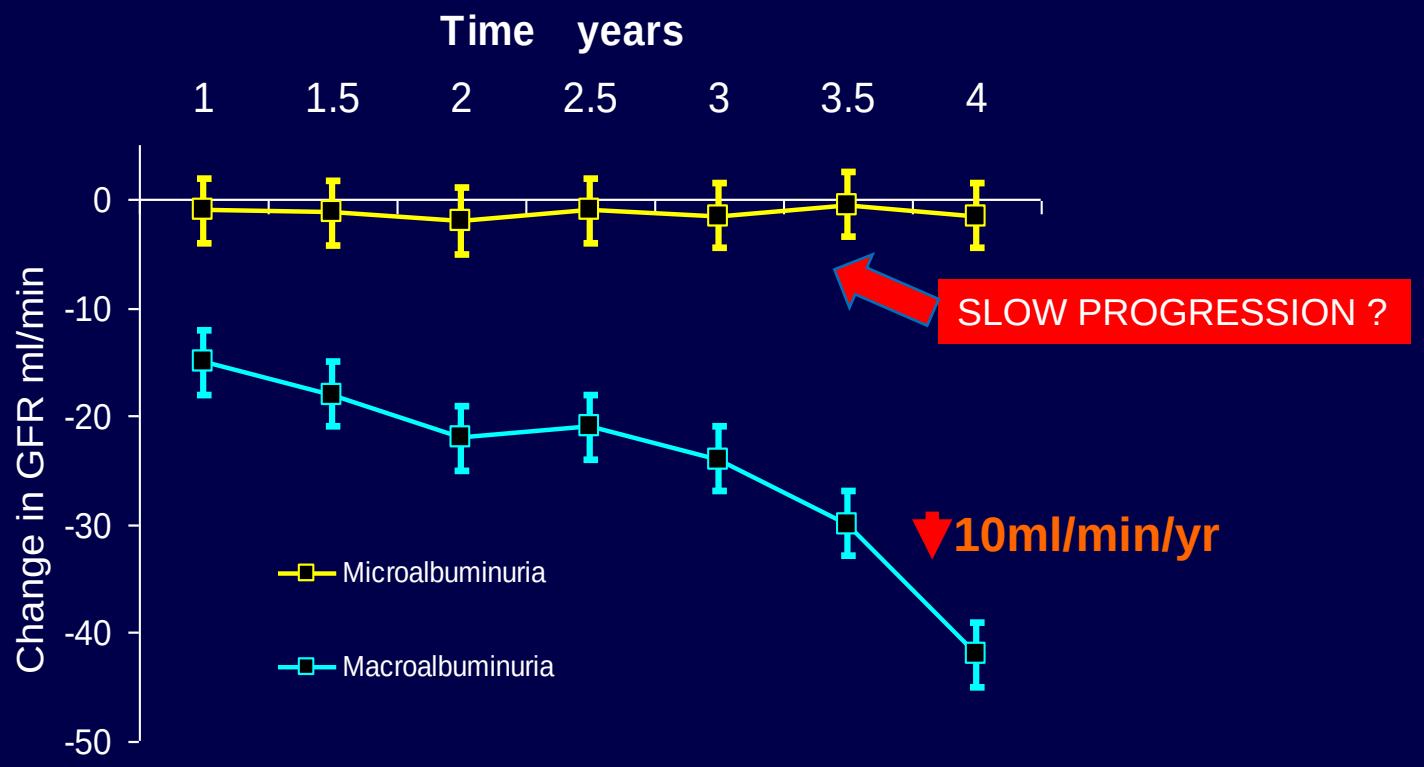
Table 2—Association of CV end points with baseline UACR categories

End point	Total number of events (events/100 patient-yea			Adjusted hazard ratio (95% CI) vs. UACR <30 mg/g		*P* value
	Normoalbuminuria UACR <30 mg/g	Microalbuminuria UACR 30–300 mg/g	Macroalbuminuria UACR >300 mg/g	UACR 30–300 mg/g	UACR >300 mg/g *	
CV death, MI, stroke, or hospitalization for UA	381 (3.54)	165 (5.03)	46 (7.13)	1.19 (0.99–1.43)	1.33 (0.96–1.83)	0.0797
CV death, MI, or stroke	331 (3.05)	155 (4.71)	46 (7.13)	1.28 (1.05–1.56)	1.52 (1.10–2.11)	0.0066
CV death	119 (1.03)	79 (2.26)	24 (3.41)	1.86 (1.39–2.49)	2.27 (1.43–3.60)	<0.0001
Hospitalization for UA	65 (0.58)	12 (0.35)	0 (0)	0.56 (0.30–1.06)		0.2018
MI	174 (1.58)	63 (1.88)	22 (3.36)	1.04 (0.77–1.40)	1.52 (0.95–2.42)	0.2172
Stroke	79 (0.71)	35 (1.03)	12 (1.78)	1.16 (0.77–1.75)	1.75 (0.92–3.32)	0.2179
All-cause death	203 (1.76)	105 (3)	34 (4.83)	1.45 (1.14–1.84)	1.82 (1.25–2.66)	0.0006
Hospitalization for heart failure *	94 (0.84)	53 (1.57)	20 (3.07)	1.63 (1.15–2.29)	2.78X	<0.0001

UA, unstable angina.

Diabetes Care. 2016;39:2304–2310

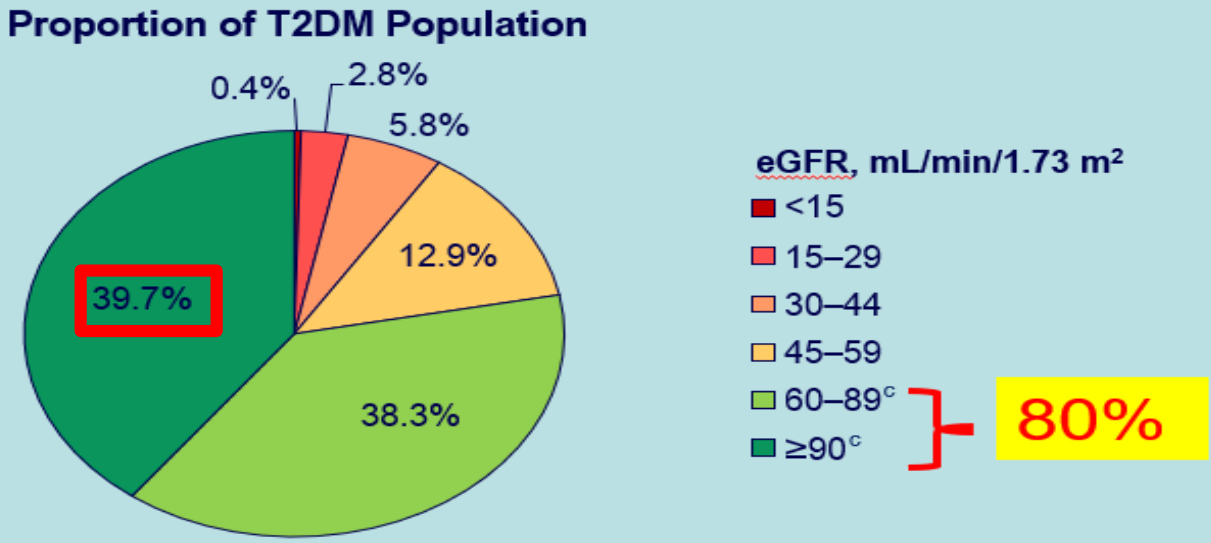
Development of Macroalbuminuria Heralds Rapid Decline in Glomerular Filtration in Type II Diabetes



Nelson RG. et al *NEJM*, 1996

Renal Insufficiency Is a Recognized Comorbidity Among Patients With T2DM[1]

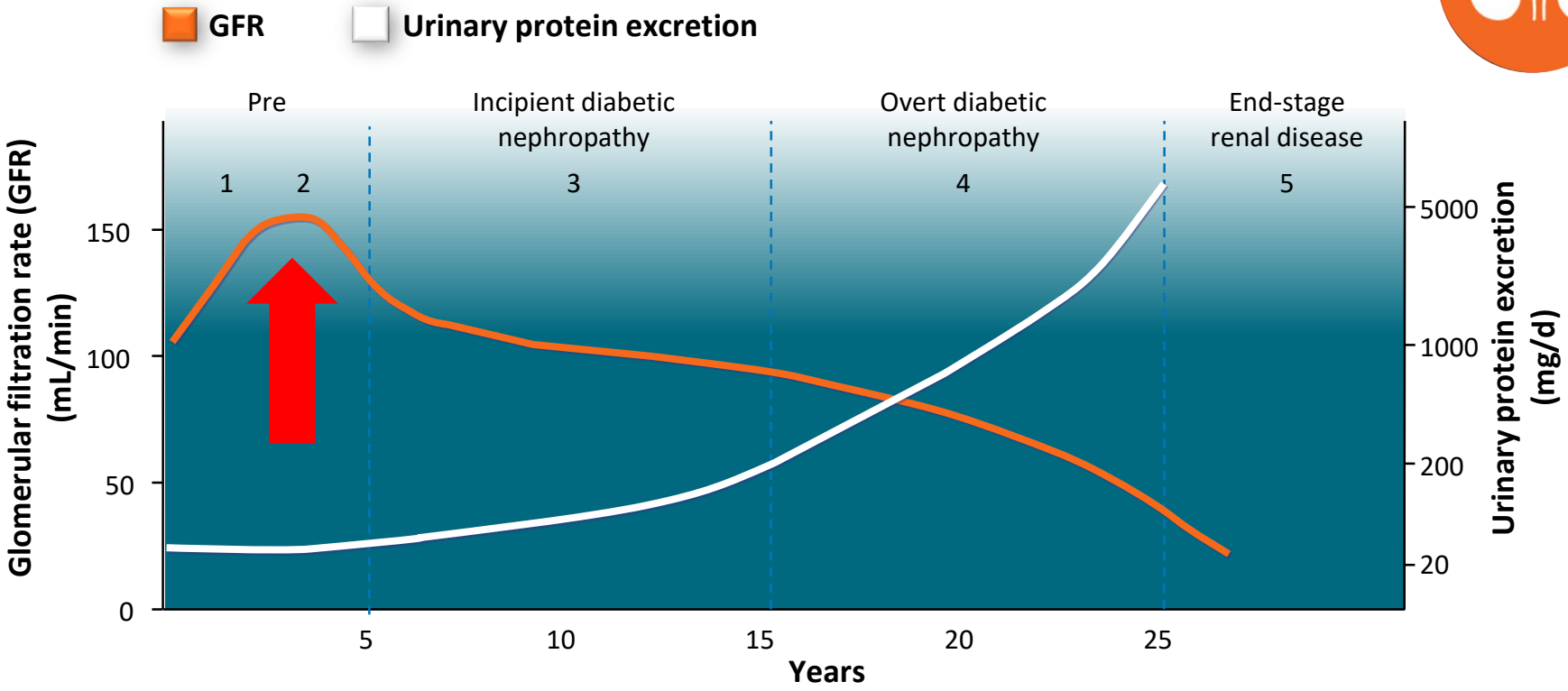
Based on US NHANES Database 1999–2012 Data (N=2,915), Patients With Renal Insufficiency[a] Comprise an Estimated Proportion of Patients With T2DM[b]



[a]Based on eGFR, which was calculated using the CKD-EPI equation.
[b]Age adjusted to 2012 NHIS diabetes population.
[c]Proportion of patients did not meet CKD criteria based on eGFR or albuminuria.
T2DM = type 2 diabetes mellitus; NHANES = National Health and Nutrition Examination Survey; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; NHIS = National Health Interview Survey.

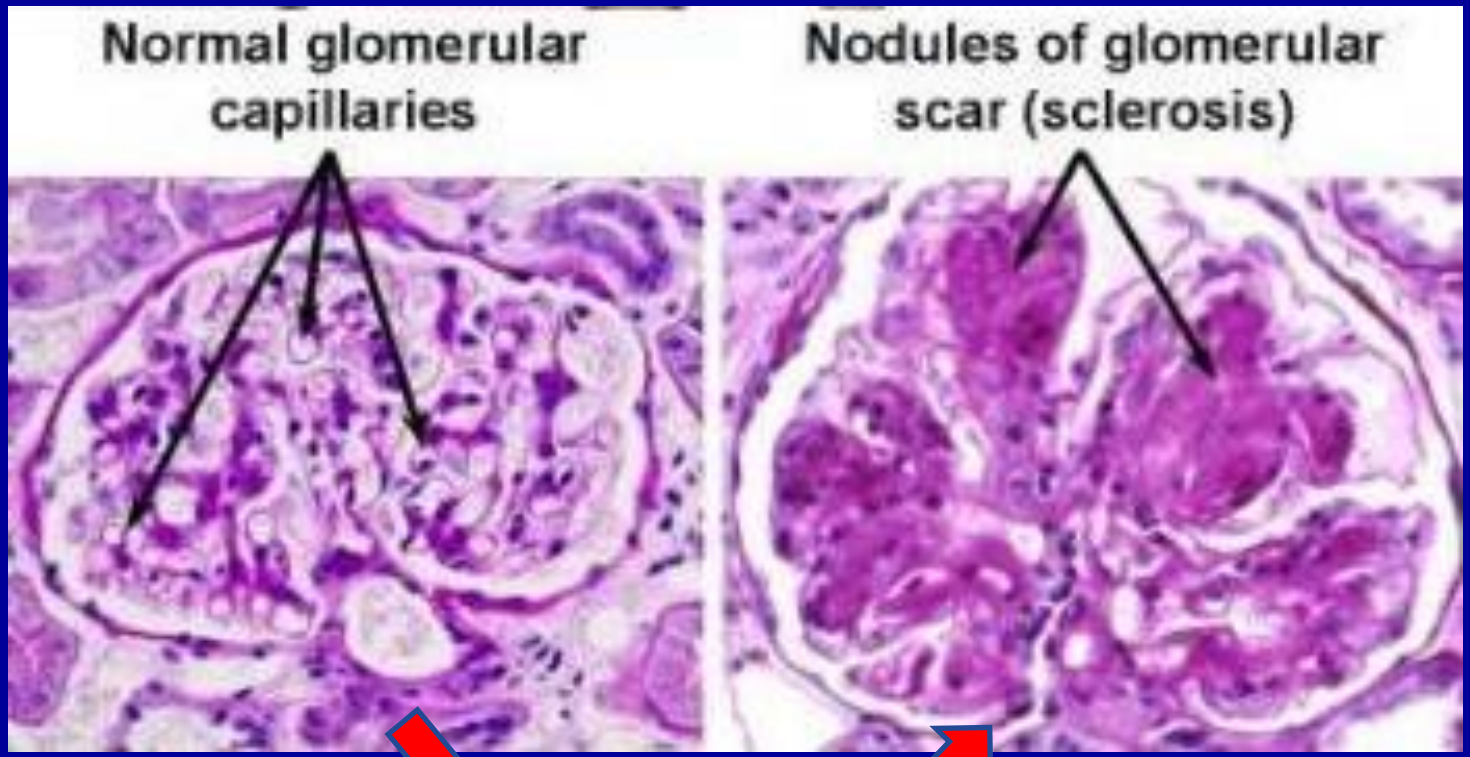
1. Bailey RA et al. *BMC Research Notes*. 2014;7:415.

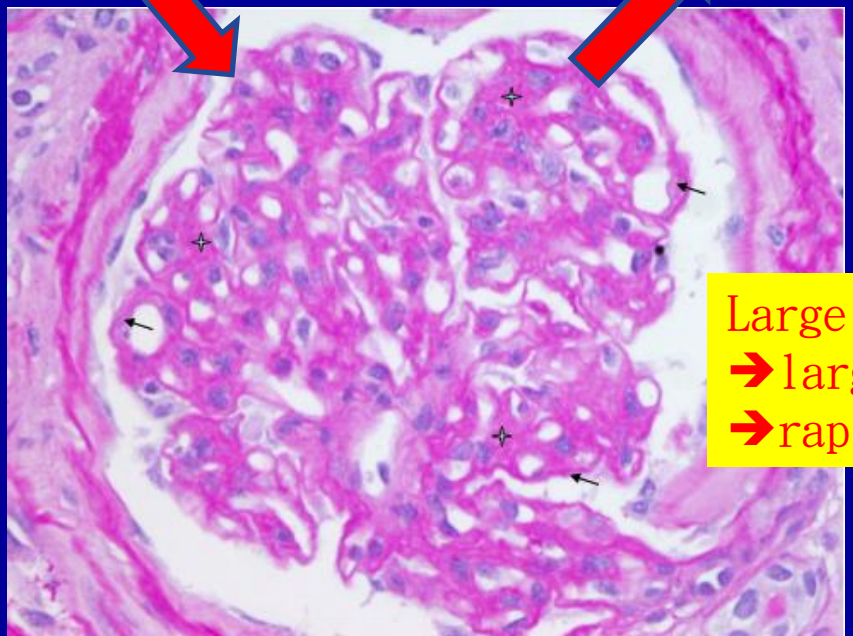
Natural history of diabetic nephropathy



Functional	Hyperfiltration	Microalbuminuria, hypertension	Albuminuira, declining GFR

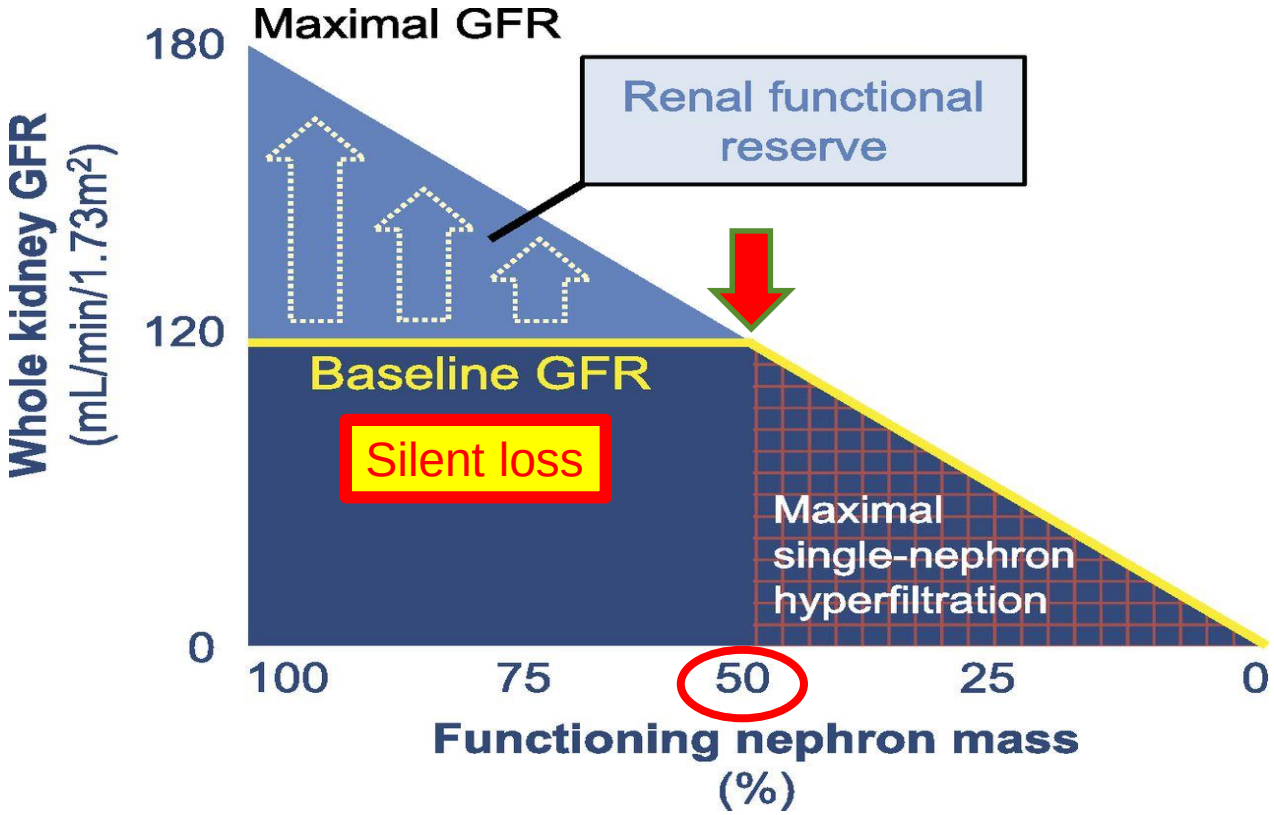
Vora JP, et al. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. New York: Mosby; 2000.





Large glomerulus
➔large filtration surface
➔rapid sclerosis

Save diabetic kidneys: The earlier, the better!!

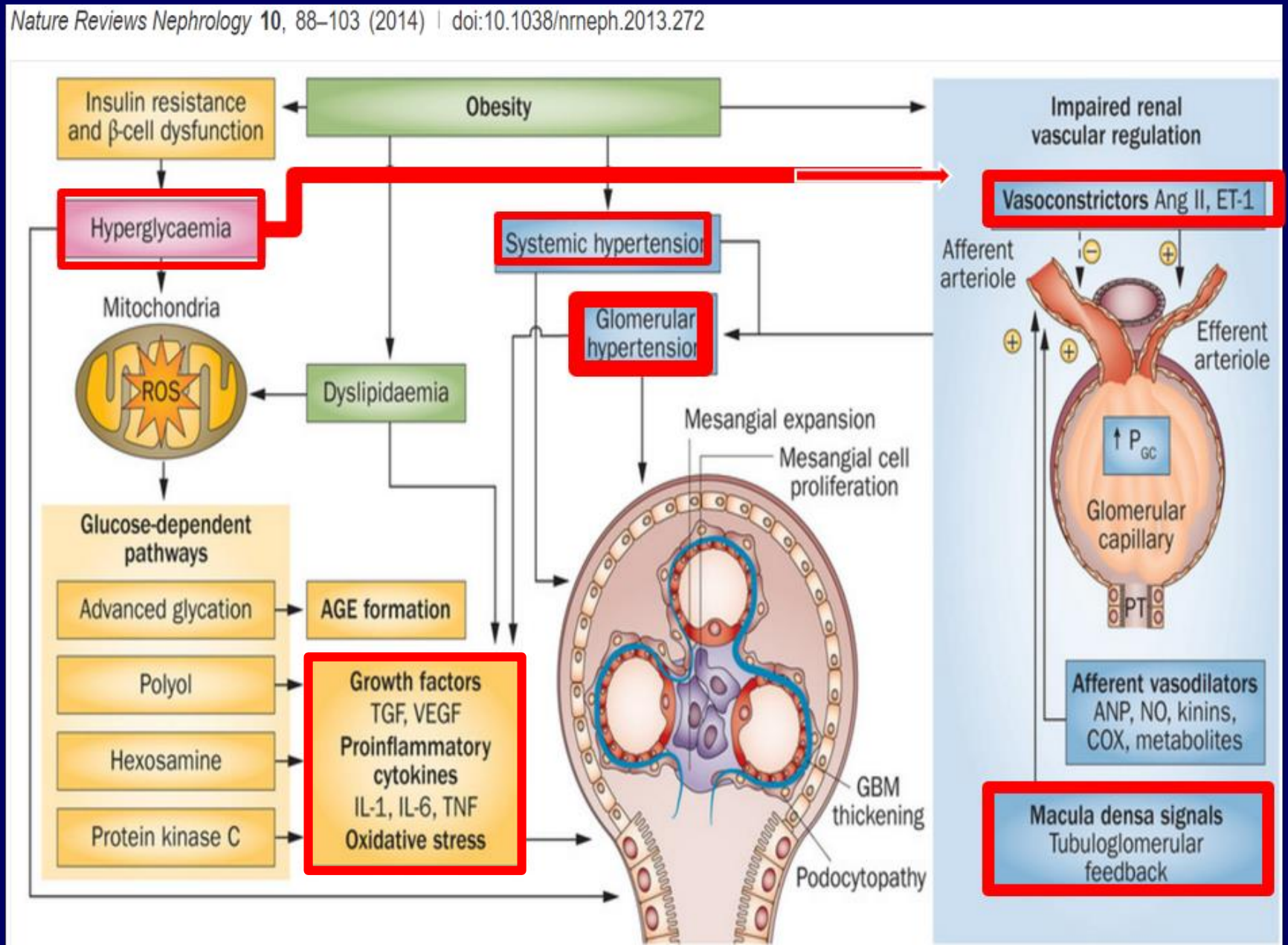


JASN April 2017, 28 (4) 1023-1039

Metabolic

Hemodynamic

Nature Reviews Nephrology **10**, 88–103 (2014) | doi:10.1038/nrneph.2013.272



Diabetic treatment with GLP-1RA: focus on both quantity and quality

Diabetic treatment should focus on both quantity and quality

Quantity

- HbA1c
- FPG
- PPG

Quality

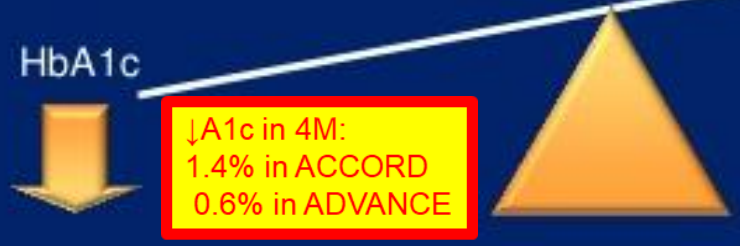
- Hypoglycemia
- Body weight
- Glycemic variability
- CV safety
- Beneficial effects beyond sugar lowering

Weight gain and hypoglycemia ➔ Bad metabolic memory!!

Decreasing HbA1c is associated with increased risks of hypoglycaemia and weight gain

Trial	Major hypoglycemia annual rate (%)		Weight gain at end of follow-up (kg)	
	Intensive	Standard	Intensive	Standard
ADVANCE	0.6*	0.3*	0.1	-0.8
ACCORD	3.2	1.0	3.5	0.4

* Represents 0.7 and 0.4 events per 100 patient years for intensive vs standard treatment

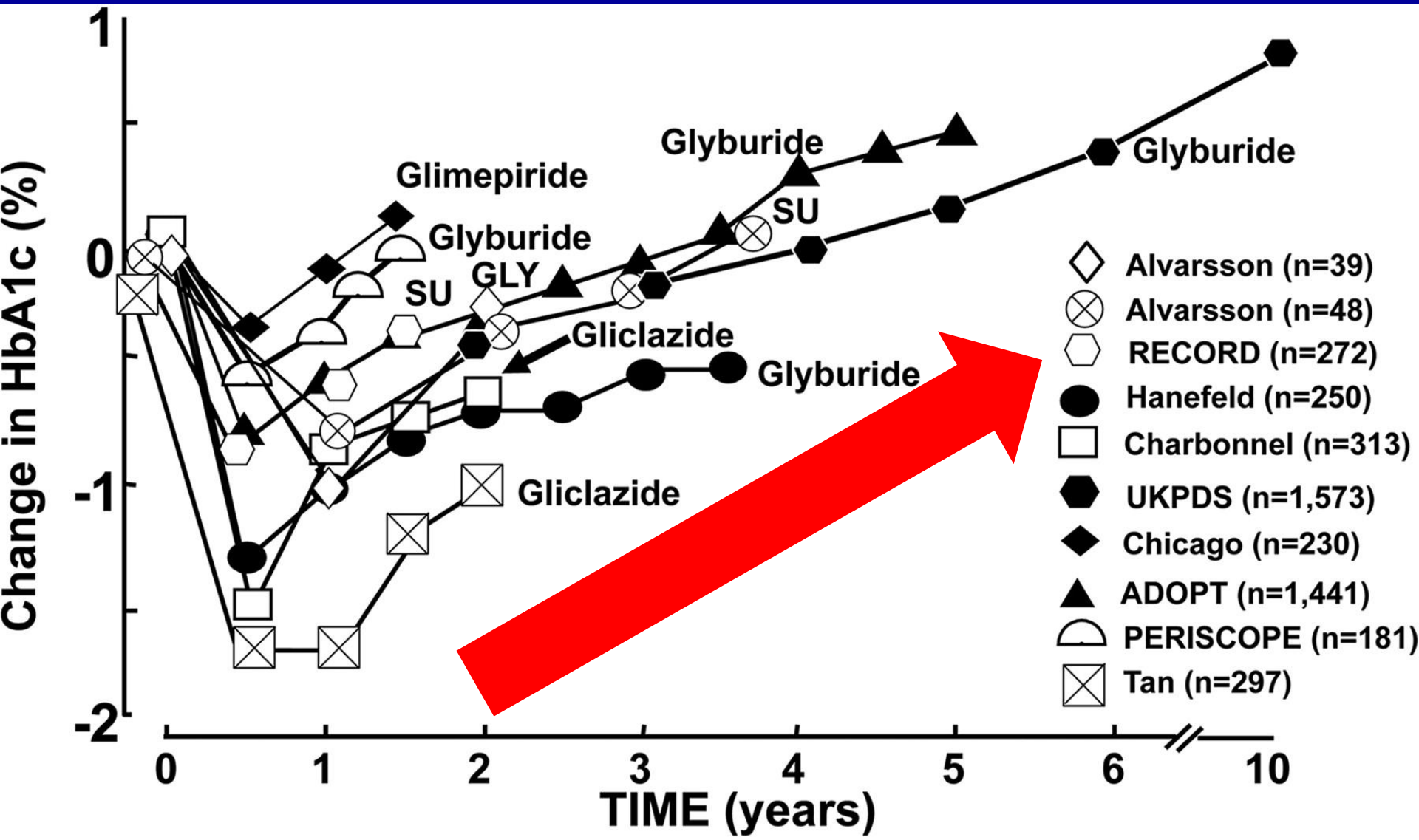


HbA1c=haemoglobin A1c; OAD, oral antidiabetic drugs.
Jacob AN, et al. *Diabetes Obes Metab.* 2007; 9:386–393;
Kahn SE, et al. *N Engl J Med.* 2006; 355: 2427–2443;
Wright AD, et al. *J Diabetes Complications.* 2006; 20: 395–401.

24

Traditional antidiabetic agents:

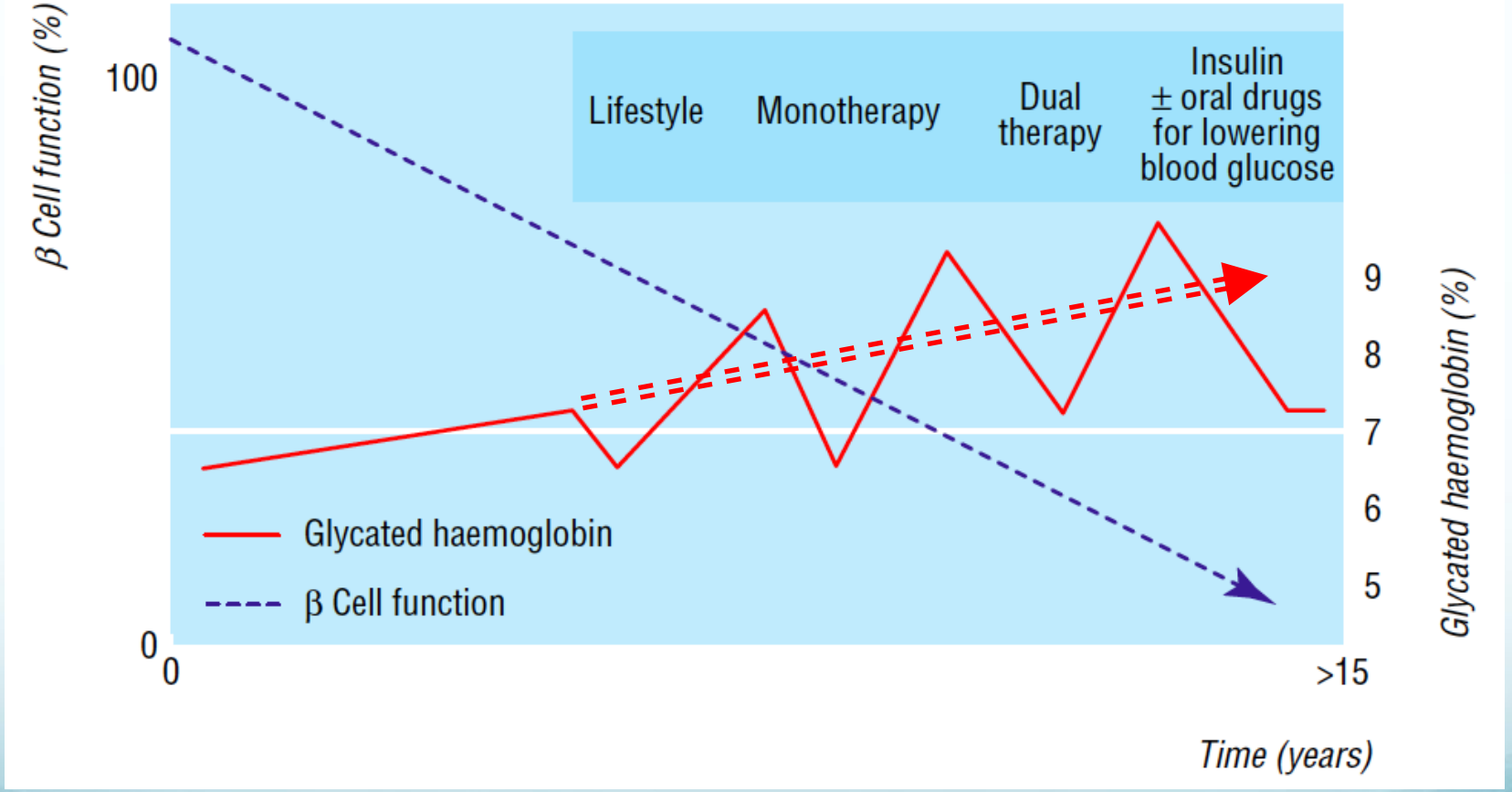
Bad durability=unsatisfied effects and unmet needs!!



Diabetes 2009 Apr; 58(4): 773-795.

Unmet medical need: progressively declining b-cell function in type 2 diabetes patients

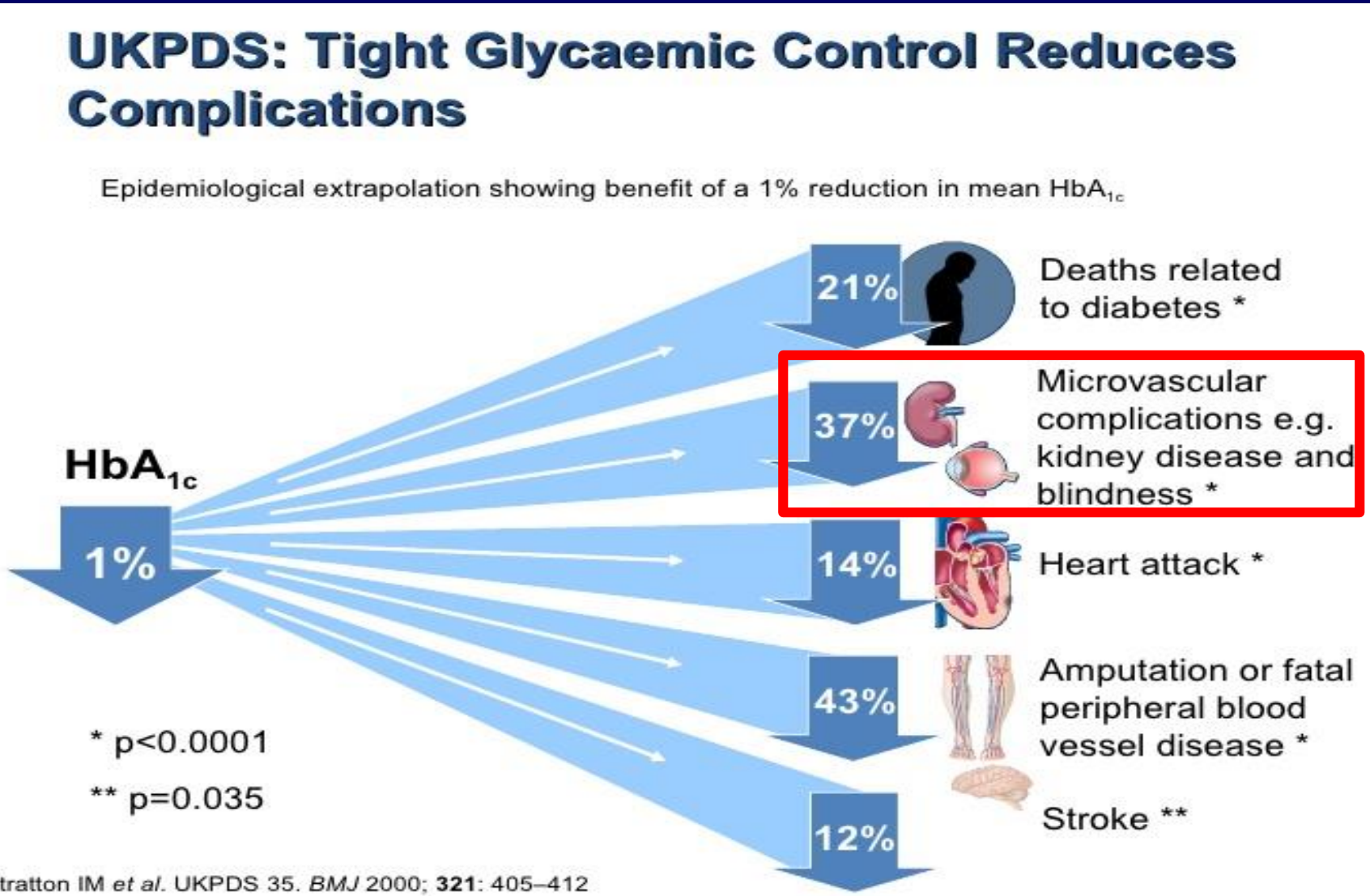
Glycemic variability and mean A1c = Bad durability= Bad memory!!



BMJ (Clinical Research Ed),2006. *333*(7580), 1200–1204.

Quantity

Updated mean A1c and the complications of T2DM (Glucose exposure: metabolic memory !!)



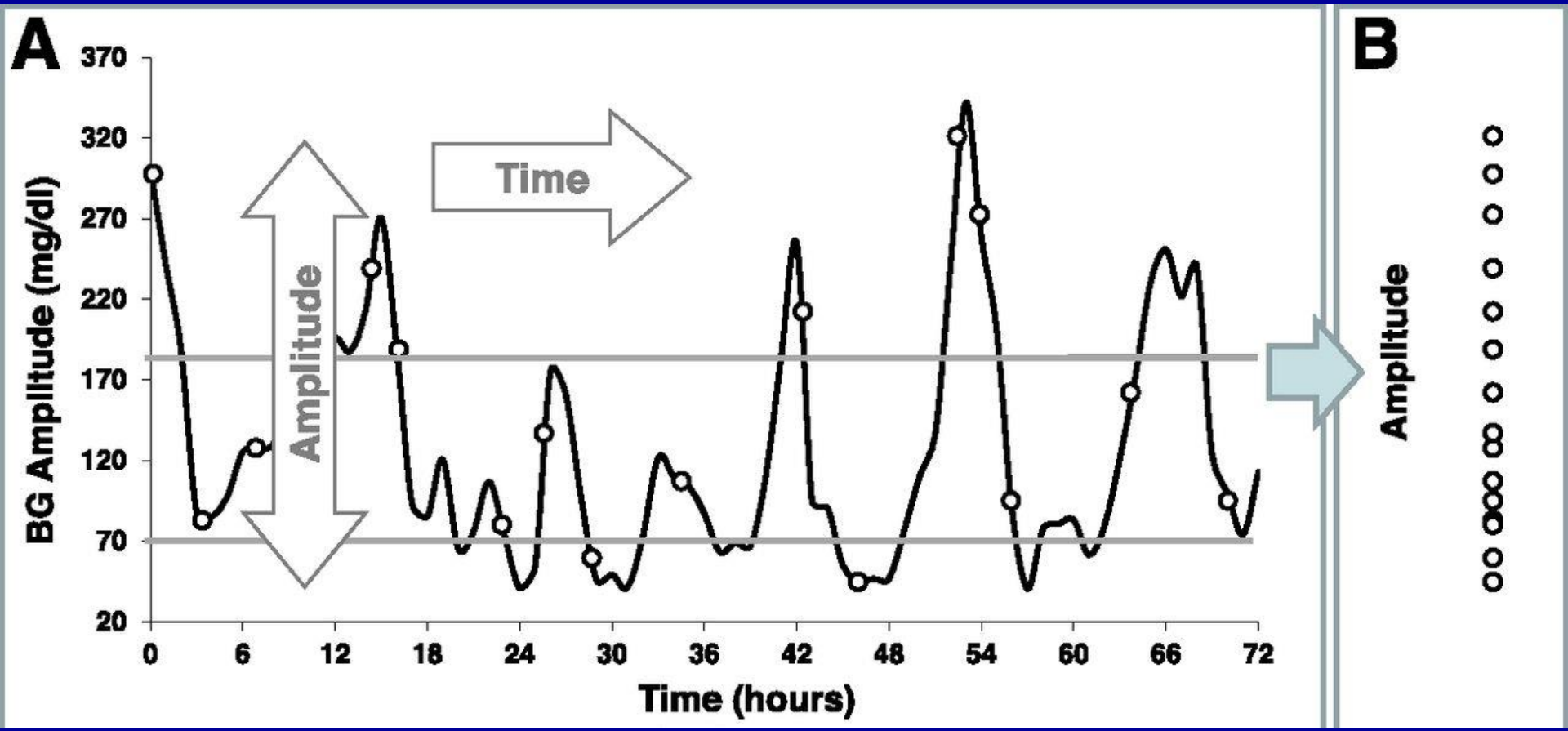
Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis

Diabetes Care 2015;38:2354–2369 | DOI: 10.2337/dc15-1188

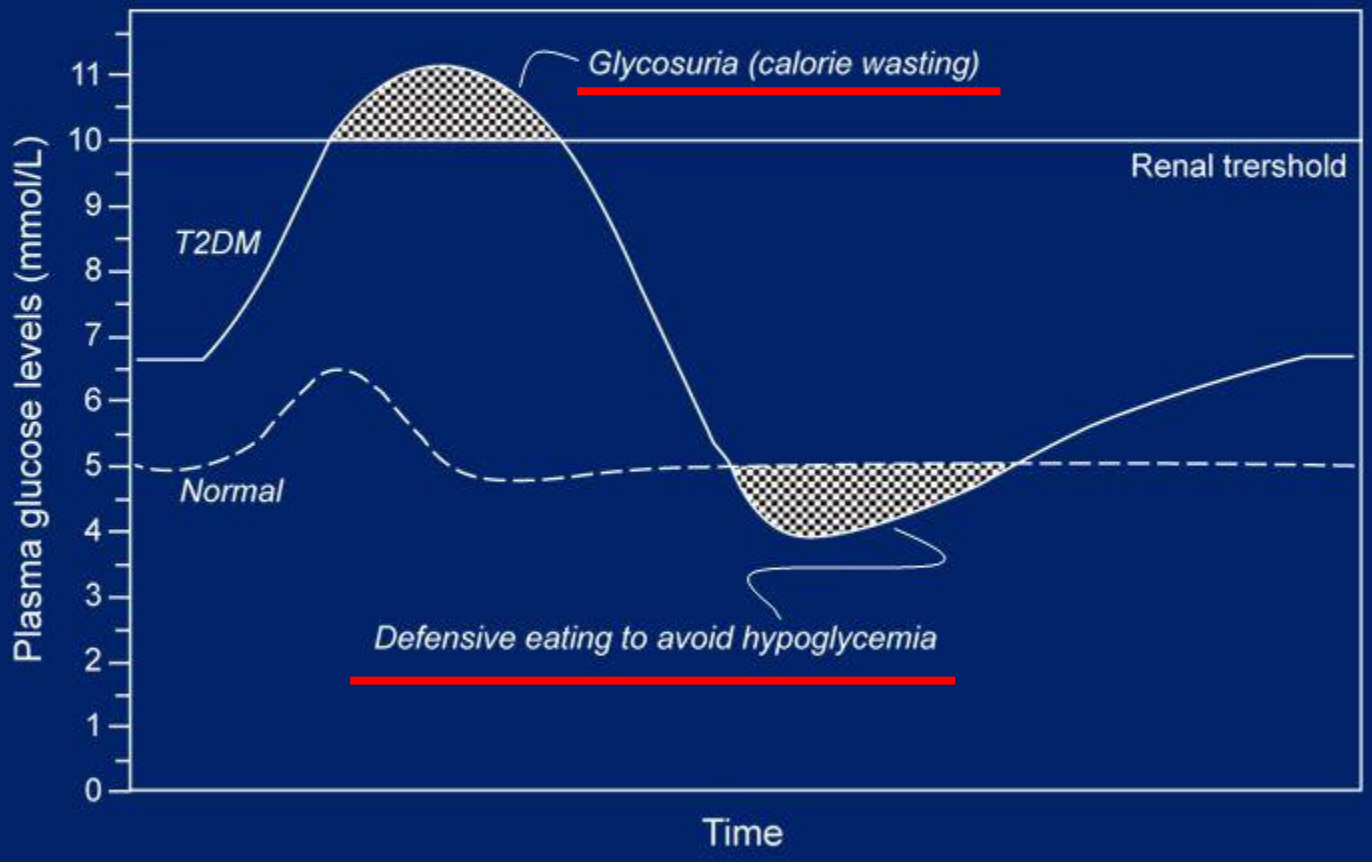
RESULTS

Seven studies evaluated HbA_{1c} variability among patients with type 1 diabetes and showed an association of HbA_{1c} variability with renal disease (risk ratio 1.56 [95% CI 1.08–2.25], two studies), cardiovascular events (1.98 [1.39–2.82]), and retinopathy (2.11 [1.54–2.89]). Thirteen studies evaluated HbA_{1c} variability among patients with type 2 diabetes. Higher HbA_{1c} variability was associated with higher risk of renal disease (1.34 [1.15–1.57], two studies), macrovascular events (1.21 [1.06–1.38]), ulceration/gangrene (1.50 [1.06–2.12]), cardiovascular disease (1.27 [1.15–1.40]), and mortality (1.34 [1.18–1.53]). Most studies were retrospective with lack of adjustment for potential confounders, and inconsistency existed in the definition of HbA_{1c} variability.

Short term fluctuations in blood glucose concentrations



Hypoglycemia and Weight Gain are intertwined



Foley J, et al. Vasc Health Risk Manag. 2010:6 541–548

OPEN

Association of Hypoglycemia With Incident Chronic Kidney Disease in Patients With Type 2 Diabetes

A Nationwide Population-Based Study Medicine 94(16):e771

Abstract: This article aims to investigate the long-term risk of incident chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) patients with hypoglycemia.

This nationwide, population-based, propensity score (PS)-matched cohort study involved 2 cohorts: a hypoglycemic cohort and a matched cohort without hypoglycemia. Data from 1.3 million patients with newly diagnosed T2DM between 2000 and 2010 were extracted from Taiwan's National Health Insurance Research Database. Hypoglycemic events were collected using inpatient, outpatient, and emergency department diagnoses. Patients aged <20 years and those with previous histories of CKD were excluded. The association between hypoglycemia and subsequent CKD risk in patients with T2DM was examined using Cox regression analysis after PS matching.

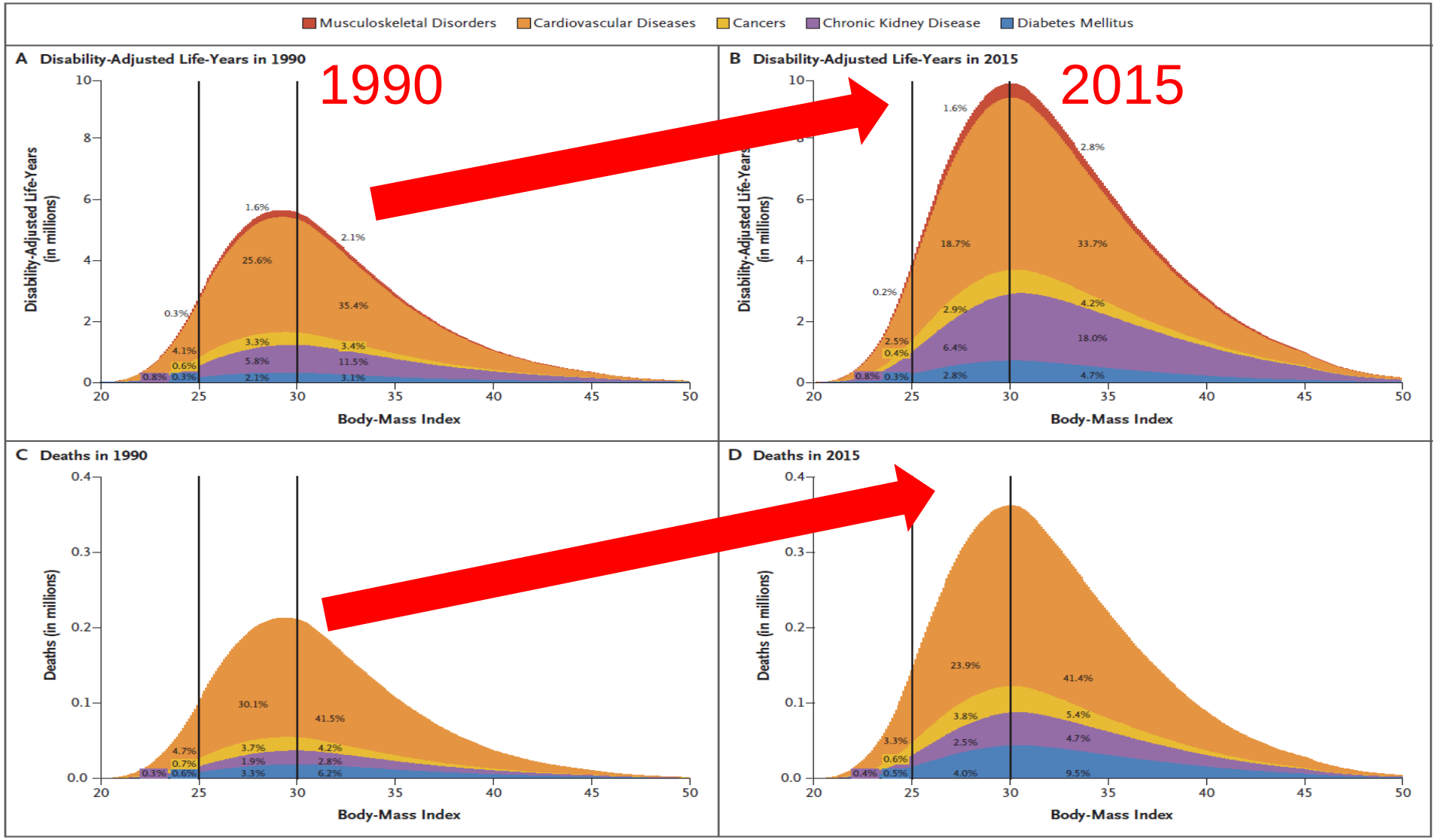
During the mean follow-up period of 4.2 years, a total of 15,036 (1.7 %) patients experienced at least 1 episode of hypoglycemia and 15,036 matched controls without hypoglycemia were identified among 906,368 eligible patients. The incidence rates of subsequent CKD were 26.1 and 14.8 events per 1000 person-years in the hypoglycemic and matched cohorts, respectively. The hazard ratio (HR) of hypoglycemia for incident CKD was 1.77 (95% confidence interval [CI], 1.63–1.92; $P < 0.001$). Compared with those without hypoglycemia, HRs for 1 to 3 and >4 episodes of hypoglycemia for CKD were 1.65 (95% CI, 1.50–1.81) and 1.75 (95% CI, 1.34–2.29), respectively (P for trend <0.001).

Obesity-Related Deaths Hit New High Worldwide

BMI-related mortality: CVD>DM>**CKD**

BMI-related disability-adjusted life-years: CVD>**CKD**>DM

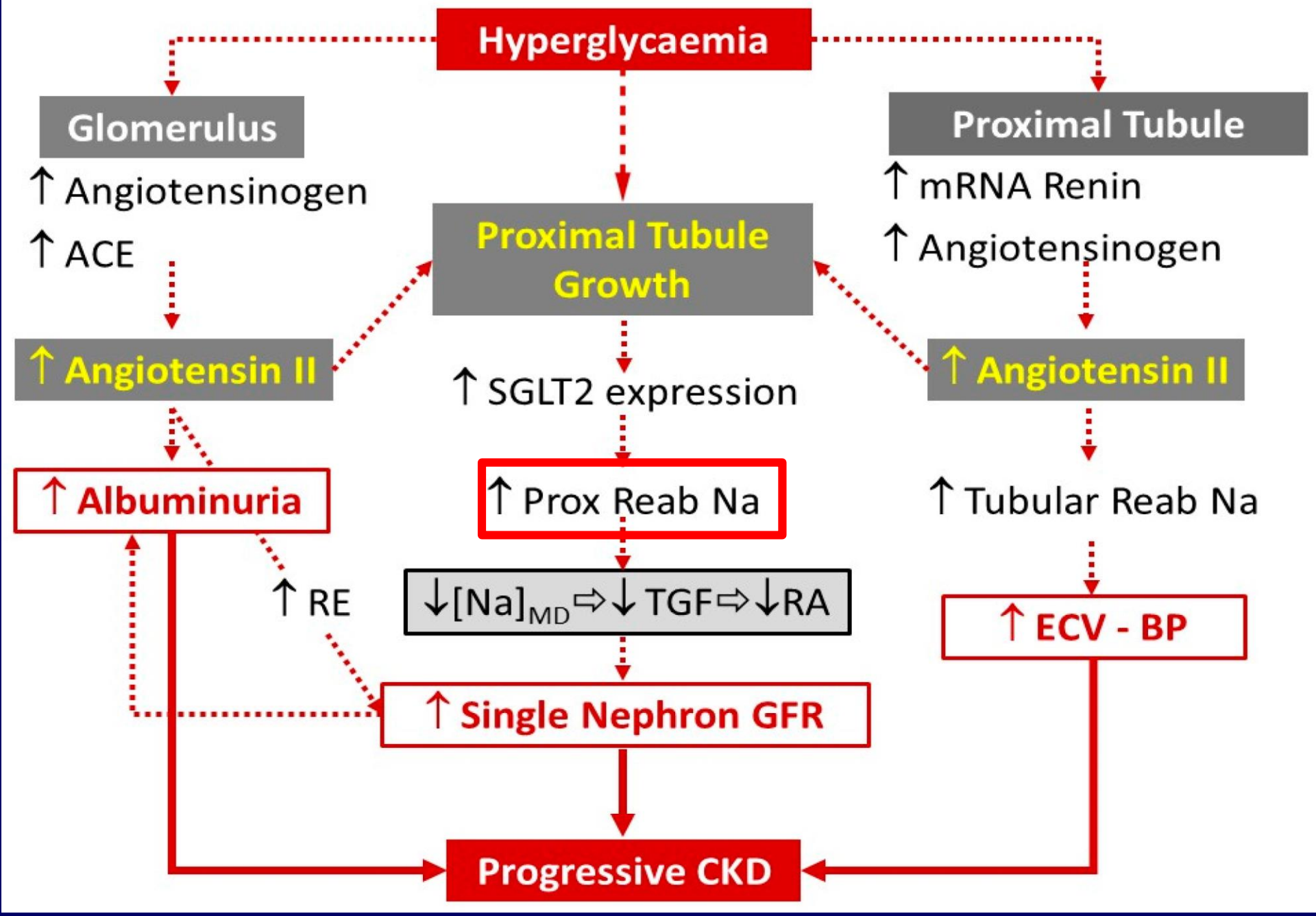
N Engl J Med 2017; 377:13-27



Prandial hyperglycemia (glucose fluctuation)

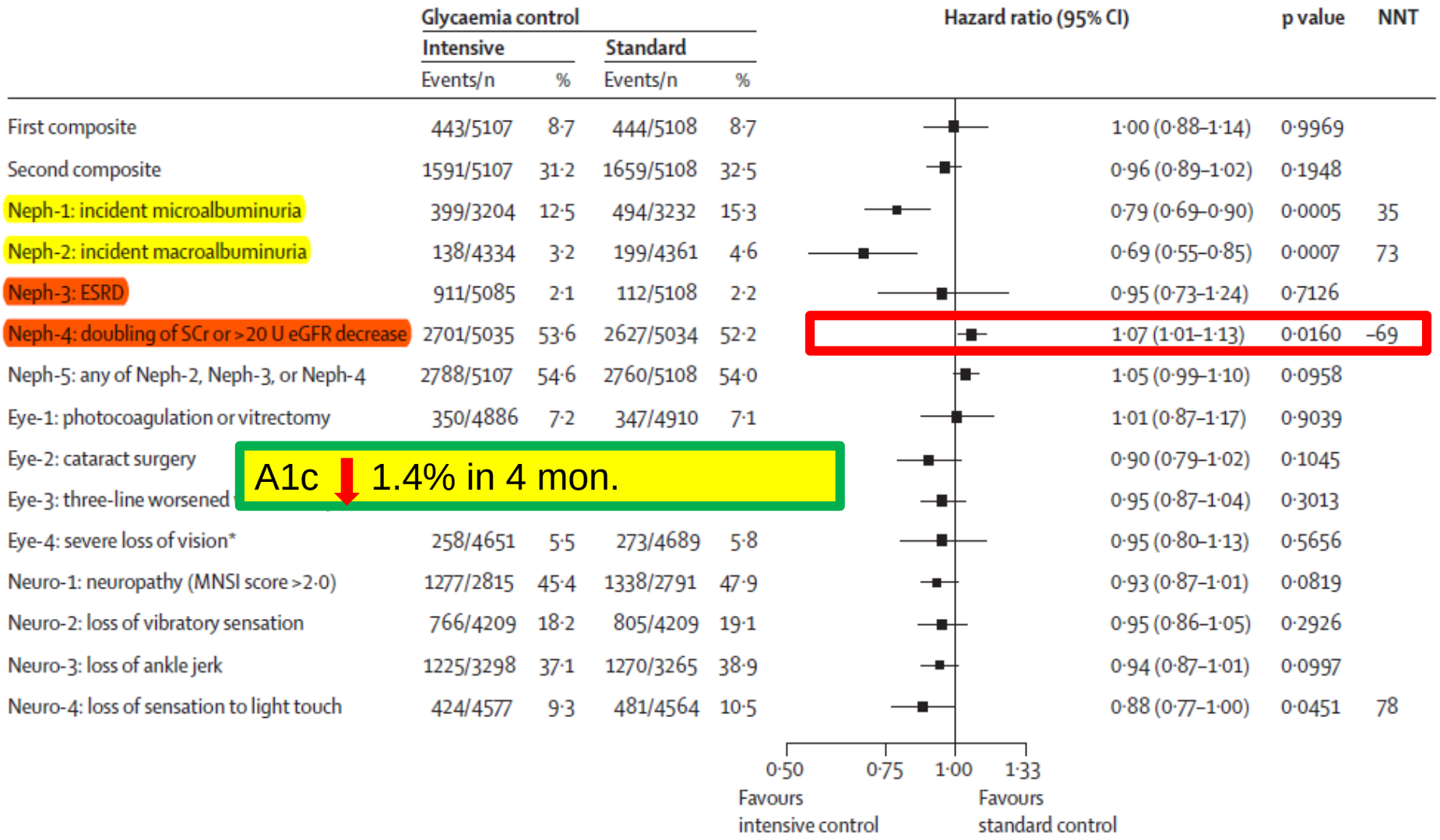
glucosuria (Natriuresis ↓ → TGF → afferent a. vasodilation)

Kidney: Intraglomerular pressure ↑



Medicina 2019, 55(6), 268

Micro-outcomes in the ACCORD
More renal injury!!



	Glycaemia control				Hazard ratio (95% CI)	p value	NNT
	Intensive		Standard				
	Events/n	%	Events/n	%			
First composite	443/5107	8·7	444/5108	8·7	1·00 (0·88–1·14)	0·9969	
Second composite	1591/5107	31·2	1659/5108	32·5	0·96 (0·89–1·02)	0·1948	
Neph-1: incident microalbuminuria	399/3204	12·5	494/3232	15·3	0·79 (0·69–0·90)	0·0005	35
Neph-2: incident macroalbuminuria	138/4334	3·2	199/4361	4·6	0·69 (0·55–0·85)	0·0007	73
Neph-3: ESRD	911/5085	2·1	112/5108	2·2	0·95 (0·73–1·24)	0·7126	
Neph-4: doubling of SCr or >20 U eGFR decrease	2701/5035	53·6	2627/5034	52·2	1·07 (1·01–1·13)	0·0160	–69
Neph-5: any of Neph-2, Neph-3, or Neph-4	2788/5107	54·6	2760/5108	54·0	1·05 (0·99–1·10)	0·0958	
Eye-1: photocoagulation or vitrectomy	350/4886	7·2	347/4910	7·1	1·01 (0·87–1·17)	0·9039	
Eye-2: cataract surgery					0·90 (0·79–1·02)	0·1045	
Eye-3: three-line worsened					0·95 (0·87–1·04)	0·3013	
Eye-4: severe loss of vision*	258/4651	5·5	273/4689	5·8	0·95 (0·80–1·13)	0·5656	
Neuro-1: neuropathy (MNSI score >2·0)	1277/2815	45·4	1338/2791	47·9	0·93 (0·87–1·01)	0·0819	
Neuro-2: loss of vibratory sensation	766/4209	18·2	805/4209	19·1	0·95 (0·86–1·05)	0·2926	
Neuro-3: loss of ankle jerk	1225/3298	37·1	1270/3265	38·9	0·94 (0·87–1·01)	0·0997	
Neuro-4: loss of sensation to light touch	424/4577	9·3	481/4564	10·5	0·88 (0·77–1·00)	0·0451	78

A1c ↓ 1.4% in 4 mon.

0·50 0·75 1·00 1·33

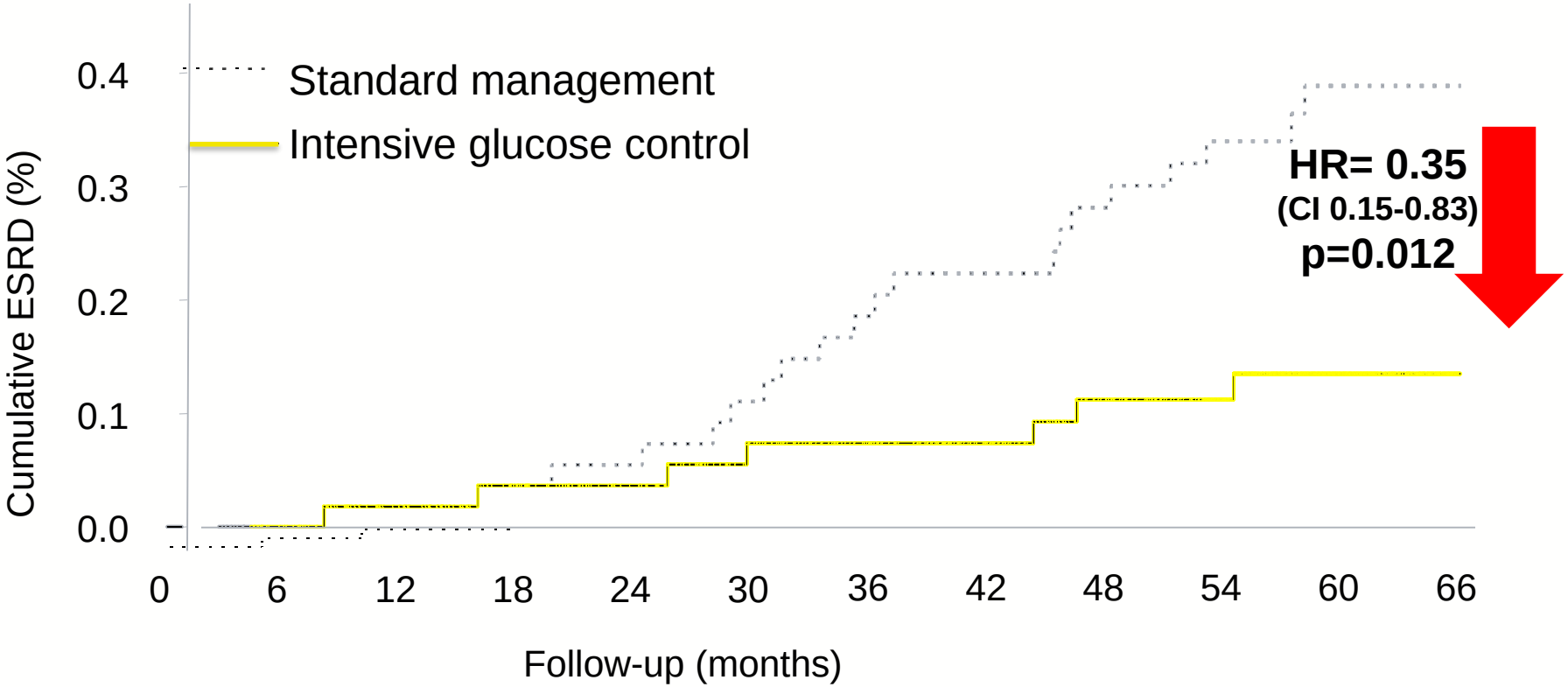
Favours intensive control

Favours standard control

Lancet 2010; 376: 419–30

Intensive glucose lowering and ESRD - The ADVANCE trial

A1c ↓ 0.6% in 4 mon.



Zoungas et al. Kidney International 2012

New era in the treatment of T2DM

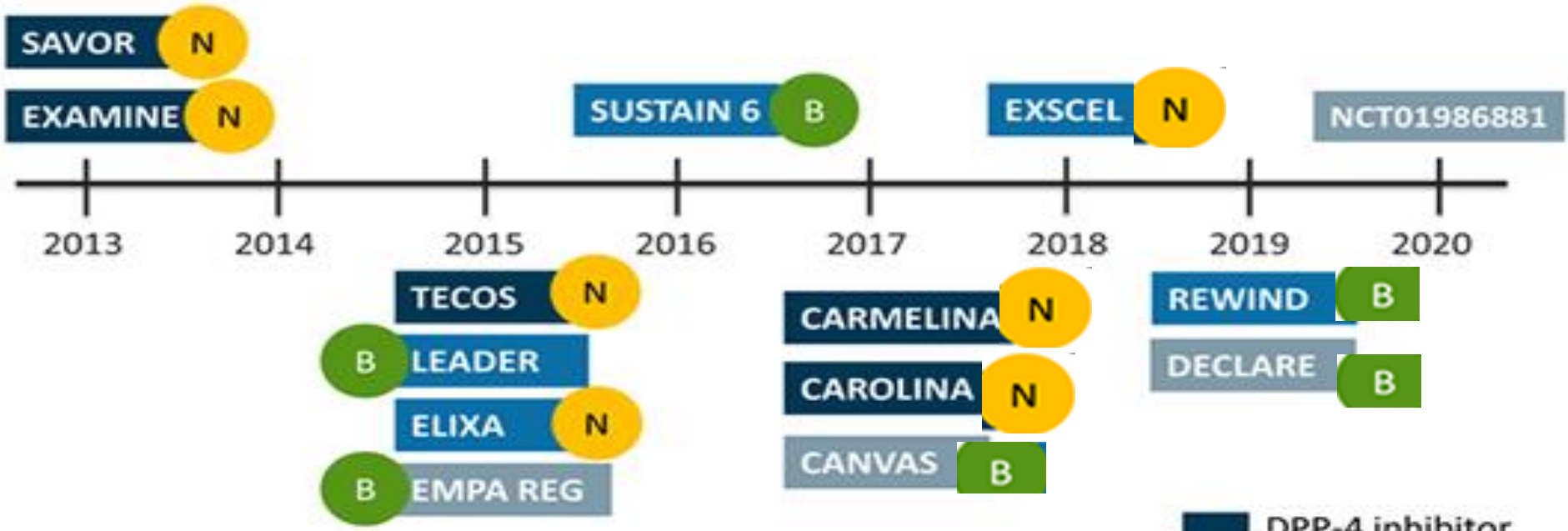
”First, do no harm“

“Better metabolic memory”

“Offer a second chance to improve outcome”

Game changer: shows CV safety/benefits in old DM

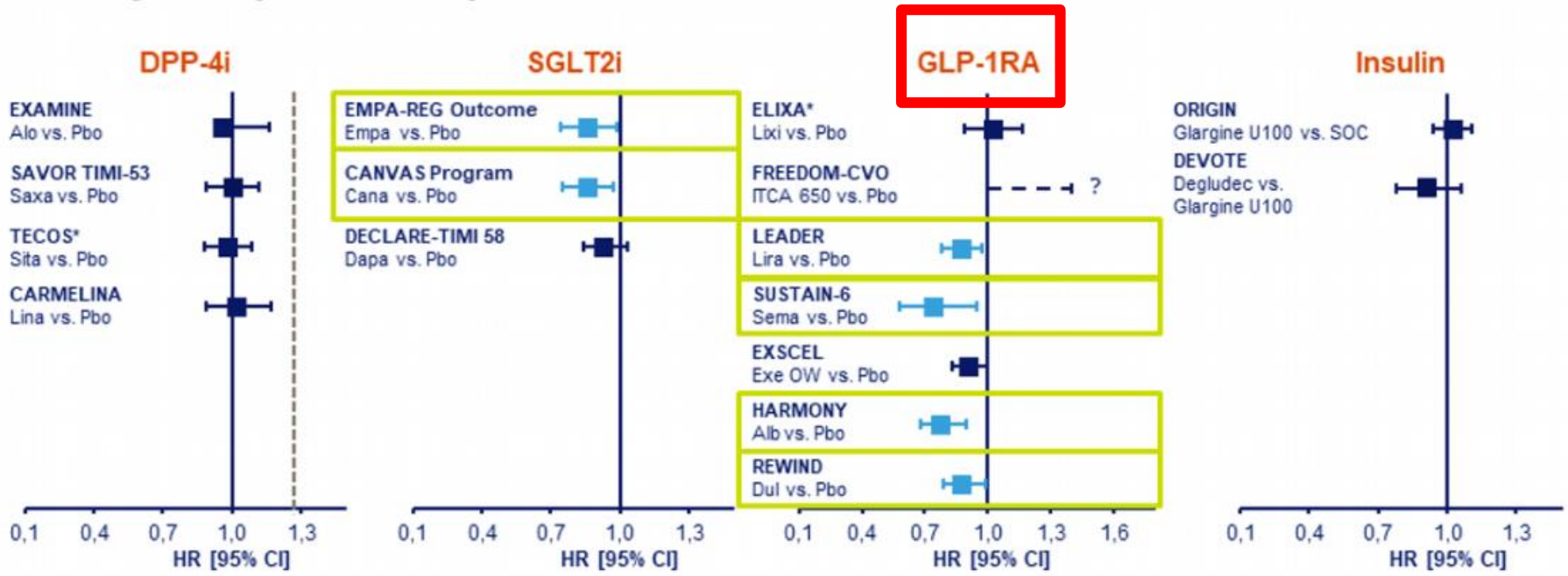
Savor : 10.3 yrs; Examine: 7.3 yrs; Tecos: 11.6 yrs; EMPA-REG: 50%>10 yrs; LEADER: 13 yrs



Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; White WB, et al. *N Engl J Med*. 2013;369:1327-1335; Green JB, et al. *N Engl J Med*. 2015;373:232-242; Marx N, et al. *Diab Vasc Dis Res*. 2015;12:164-174; ClinicalTrials.gov. NCT01897532; Marso SP, et al. *Am J Heart*. 2013;166:823-830.e5; Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257; ClinicalTrials.gov. NCT01144338; ClinicalTrials.gov. NCT01720446; Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; Neal B, et al. *Am Heart J*. 2013;166:217-223.e11; ClinicalTrials.gov. NCT01730534.

Recent CVOTs with antidiabetic agents

Primary composite endpoint: MACE

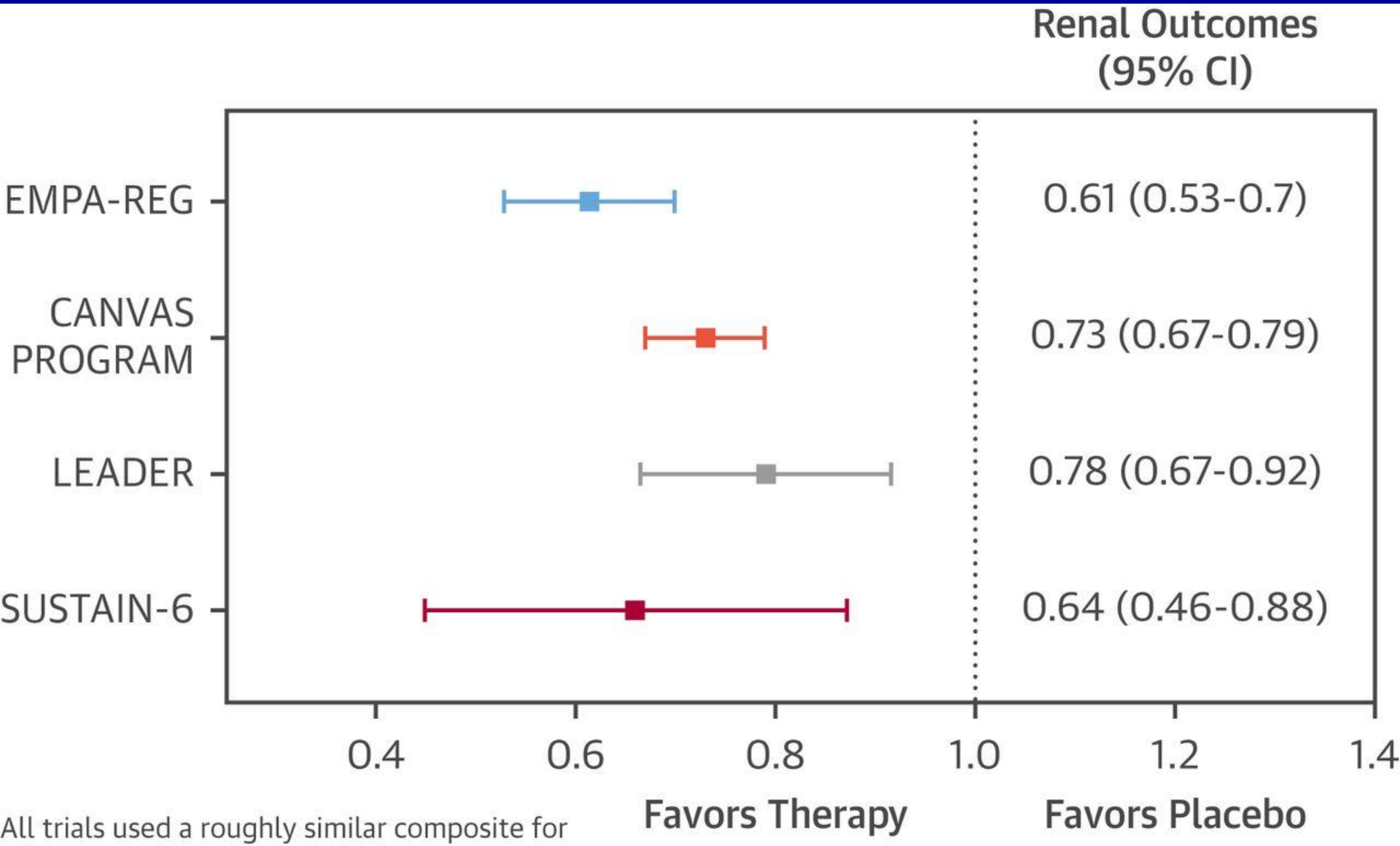


*MACE+
White *et al. N Engl J Med* 2013; 369:1327–35; Scirica *et al. N Engl J Med* 2013;369:1317–26; Green *et al. N Engl J Med* 2015;373:232–42; McGuire *et al. JAMA*. 2019 Jan 1;321(1):69-79.

Zinman *et al. N Engl J Med* 2015; 373:2117-28; Neal *et al. N Engl J Med* 2017;377:644–57; Wiviott *et al. N Engl J Med*. 2019 Jan 24;380(4):347-357.

*MACE+
Pfeffer *et al. N Engl J Med* 2015;373:2247–57; Intarcia press release 06 May 2016; Marso *et al. N Engl J Med* 2016;375:311–22; Marso *et al. N Engl J Med* 2016;375:1834–44; Holman *et al. N Engl J Med* 2017;377:1228–39; Hernandez *et al. Lancet. 2018 Oct 27;392(10157):1519-1529.*; Gerstein et al. *Lancet*. 2019 Jun 10. http://dx.doi.org/10.1016/S0140-6736(19)31149-3

Gerstein *et al. N Engl J Med* 2012;367: 319–28; Marso *et al. N Engl J Med* 2017;377:723–32



All trials used a roughly similar composite for adverse renal outcomes including progression of albuminuria.

J Am Coll Cardiol 2018;72:1856–69

Blood sugar control is more complex in elderly and/or DKD

1. CDA. *Can J Diabetes* 2008; 32:S29–S31. 2. Workgroup on Hypoglycemia, American Diabetes Association. *Diabetes Care*. 2005;28(5):1245-1249; 3. Frier BM. *Diabetes Metab Res Rev*. 2008;24(2):87-92; 4. Cryer PE. *Diabetes*. 2008;57(12):3169-3176.

Recognize Risk Factors for Severe Hypoglycemia

Risk factors in Type 2 DM patients
Elderly
Poor health literacy, Food insecurity
Increased A1C
Duration of insulin therapy
Severe cognitive impairment
Renal impairment
Neuropathy

TABLE 96-2 Glucose and insulin metabolism in patients with chronic kidney disease

Usually normal fasting blood glucose, but tendency to spontaneous hypoglycemia

Fasting hyperinsulinemia with prolonged insulin half-life and elevated blood levels of proinsulin and C peptide

Decreased requirement for insulin by diabetic patients

Usually decreased early, but exaggerated late-insulin reponse to hyperglycemia induced by oral or intravenous glucose administration

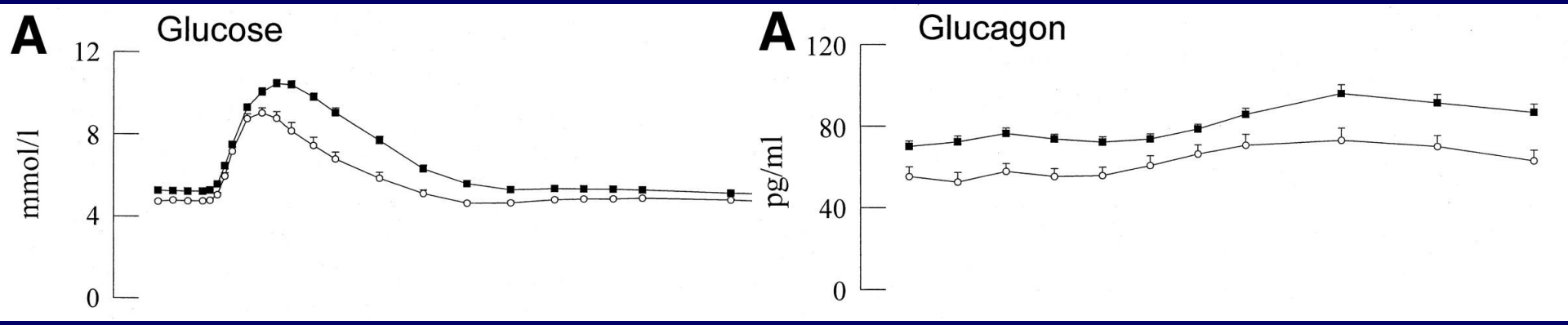
Elevated plasma immunoreactive glucagon concentration

Impaired glucose tolerance (decreased peripheral sensitivity to insulin action, but normal suppression of hepatic glucose production by insulin)

Diseases of the Kidney & Urinary Tract 2007

hyperglucagonemia and postprandial hyperglycemia, play a more significant role in elderly with T2DM

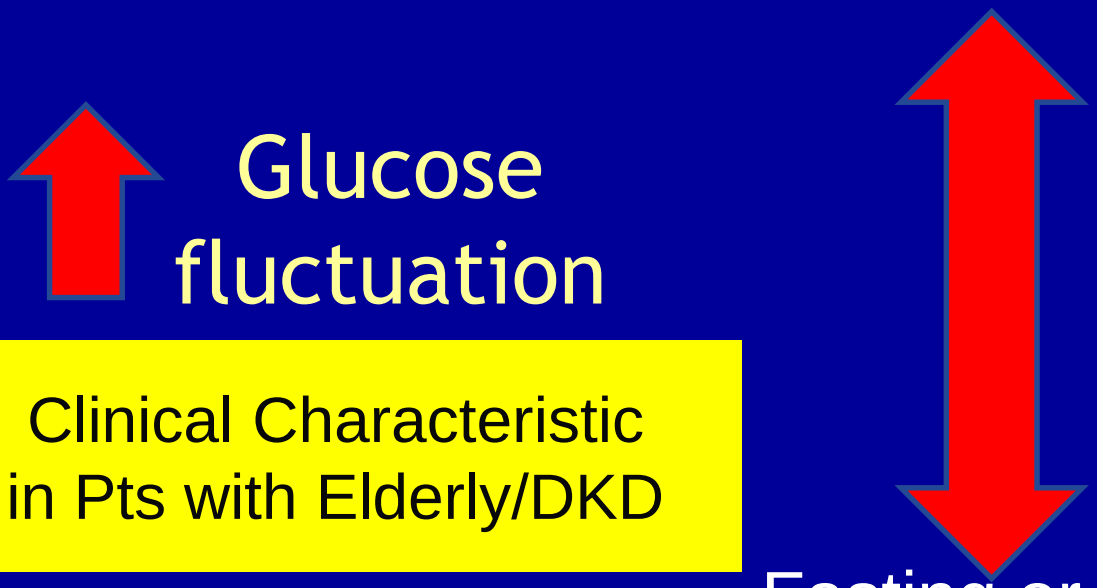
elderly (■) and the young (○)



Diabetes 2003 Jul; 52(7): 1738-1748.

Am J Physiol 284:E7–E12, 2003

Prandial hyperglycemia



Glucose fluctuation

Clinical Characteristic in Pts with Elderly/DKD

Fasting or spontaneous hypoglycemia

Rx with Quality Quantity

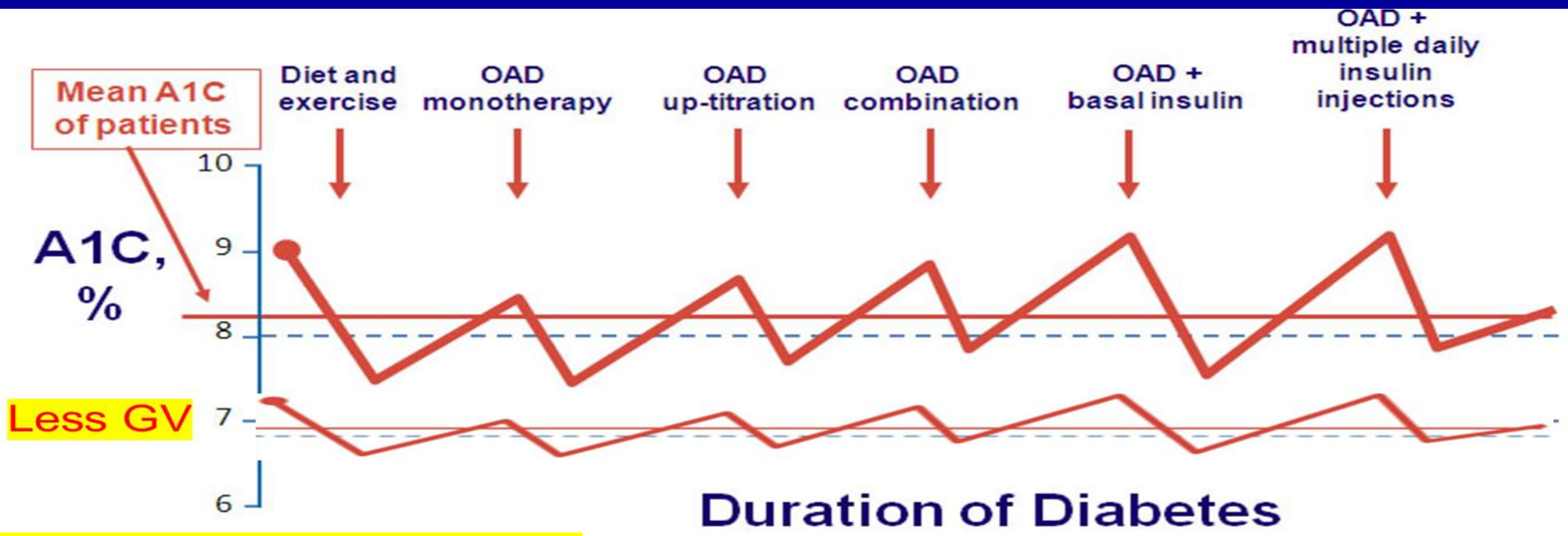
Rx with Quality Quantity?

International Guidelines, year	HbA1c goal for most healthy older adults with intact cognitive and functional status	HbA1c goal for most frail older adults, with multiple comorbidities and limited life expectancy
ADA, 2019	<7.5%	<8–8.5%
AGA, 2013	7–7.5%	7.5–9%
AACE, 2018	≤6.5%	>6.5%
ACP, 2018	7–8%	No specific target but minimizing symptoms related to hyperglycemia

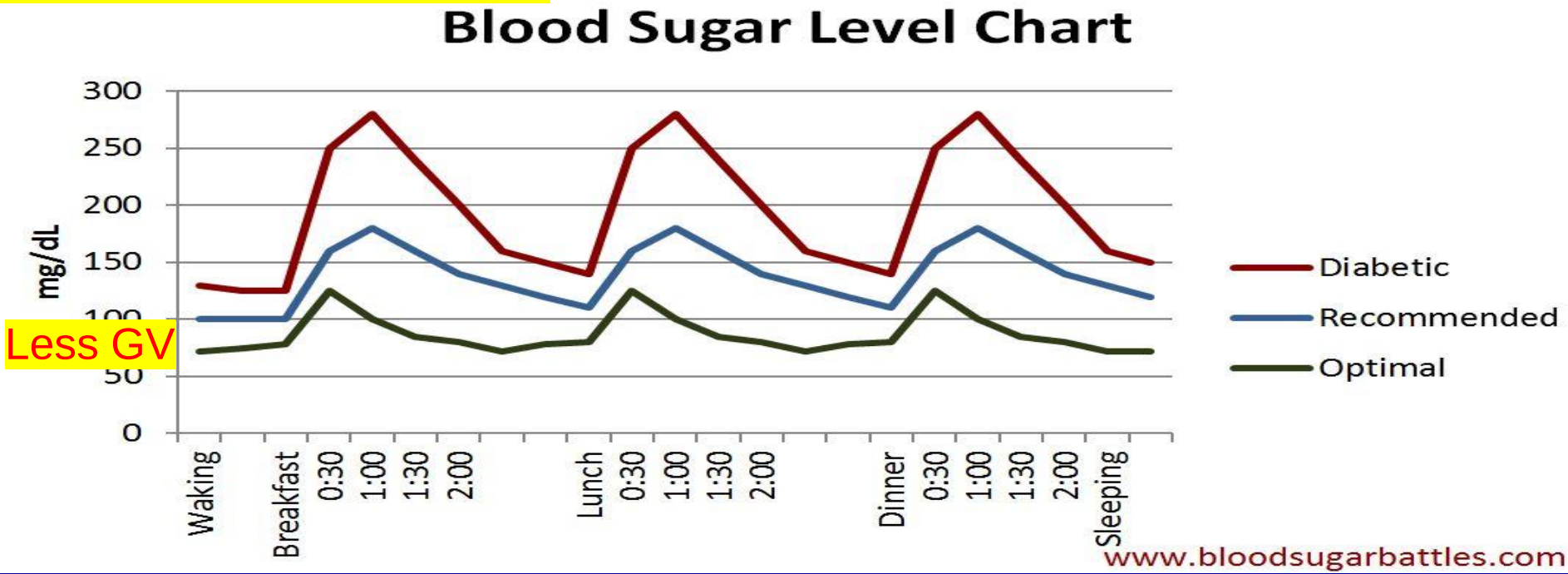
? GLP-1RA

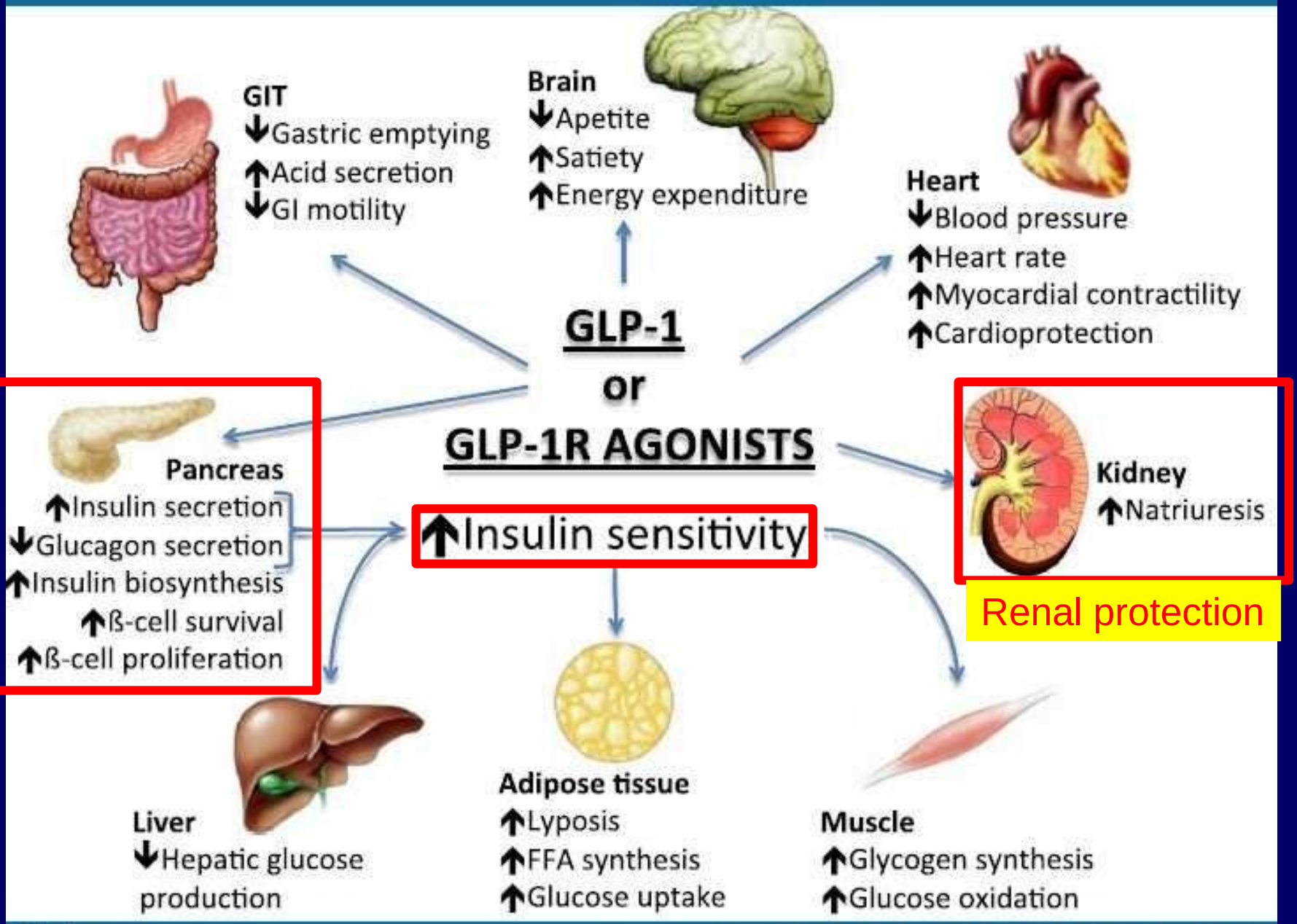
ADA, American Diabetes Association; AGA, American Geriatrics Association; AACE, American Association of Clinical Endocrinologists; ACP, American College of Physician.

The beneficial roles of GLP-1 RA in CKD patients

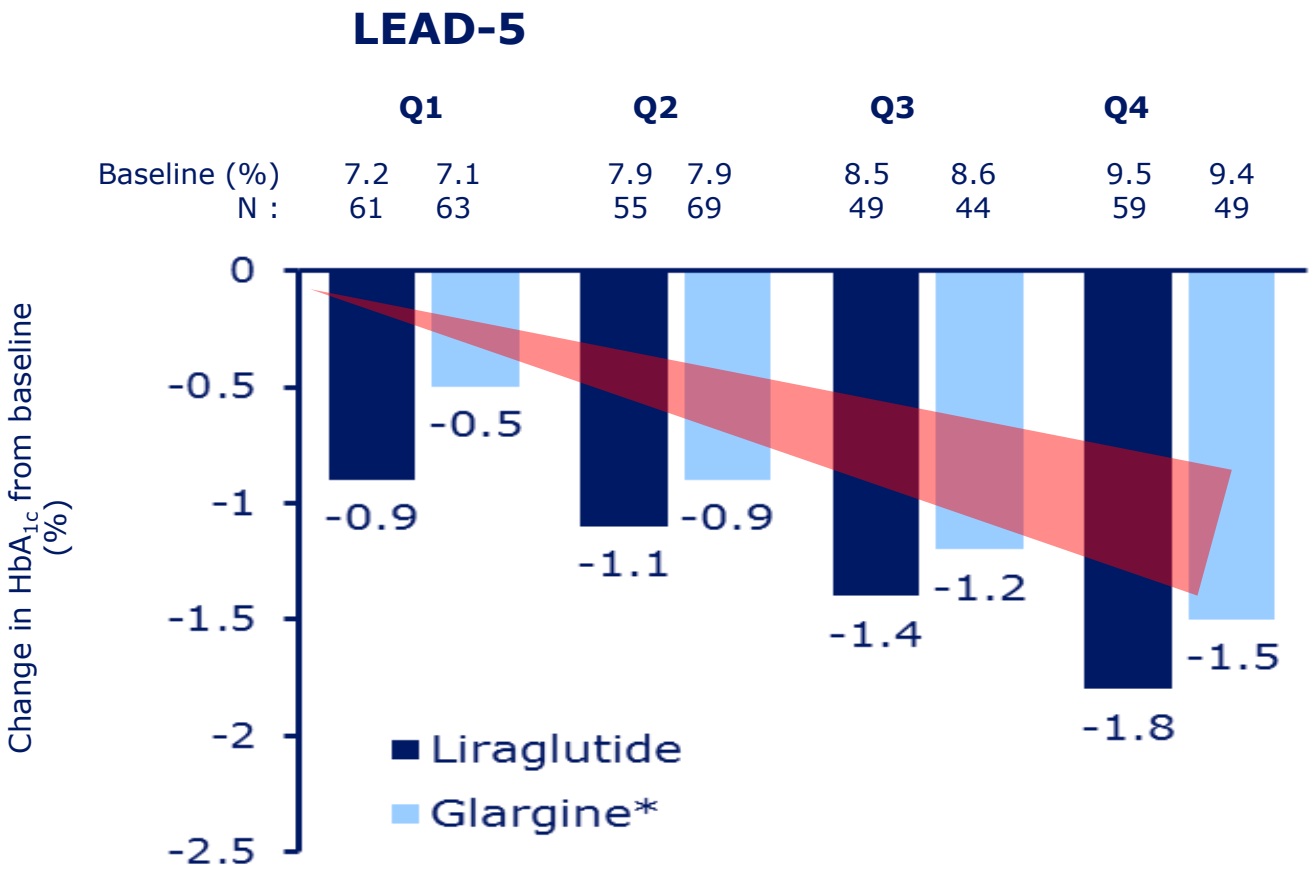


The effect on GV?





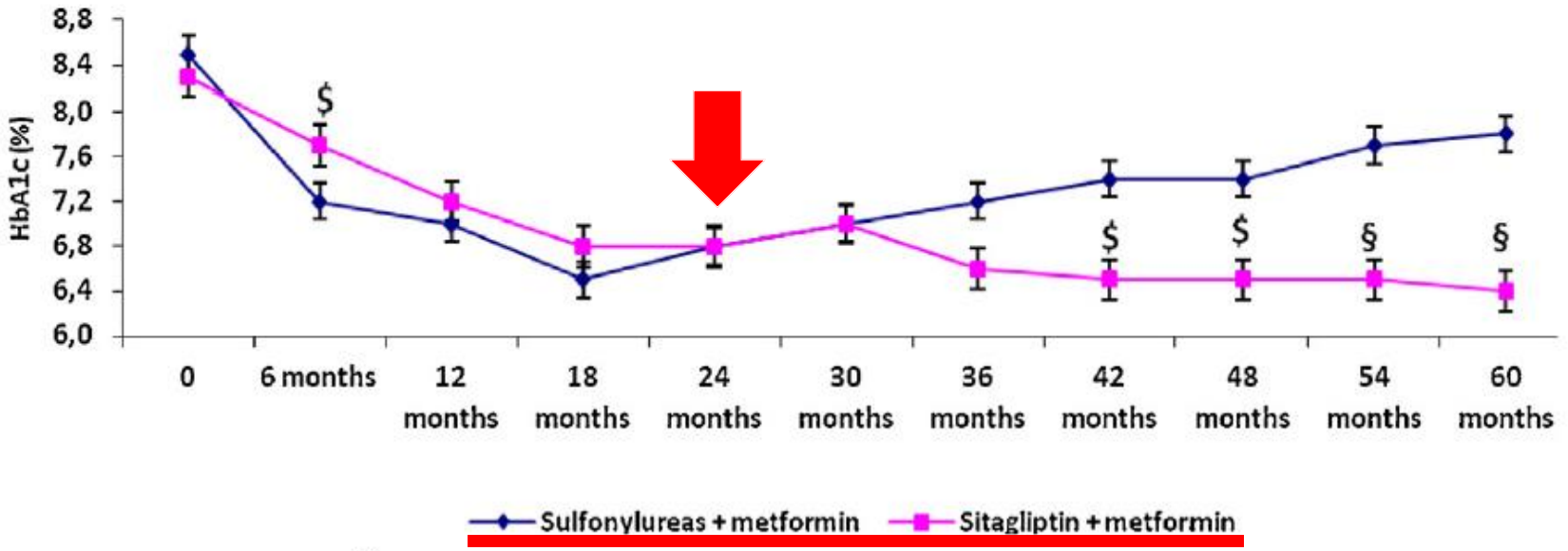
HbA_{1c} reduction by baseline HbA_{1c} quartiles



*Glargine dose increased from Q1 to Q4
HbA_{1c}, glycosylated haemoglobin; OW, once weekly; Q, baseline quartile
Buse JB et al. *Diabetes Obes Metab* 2015;17(2):145–151

Sitagliptin +Metformin can provide longer treatment duration than SU + Metoformin for 5 years

- Observational 5 yrs italian study.
- T2DM patients not well controlled by metformin (n=216)
- Add Sitagliptin 100mg to metformin for combination therapy
- No additional AHA drug allowed; only with dosage adjustment with current drug
- Compared with patients using metformin + SU (matched for age, sex, diabetes duration.)



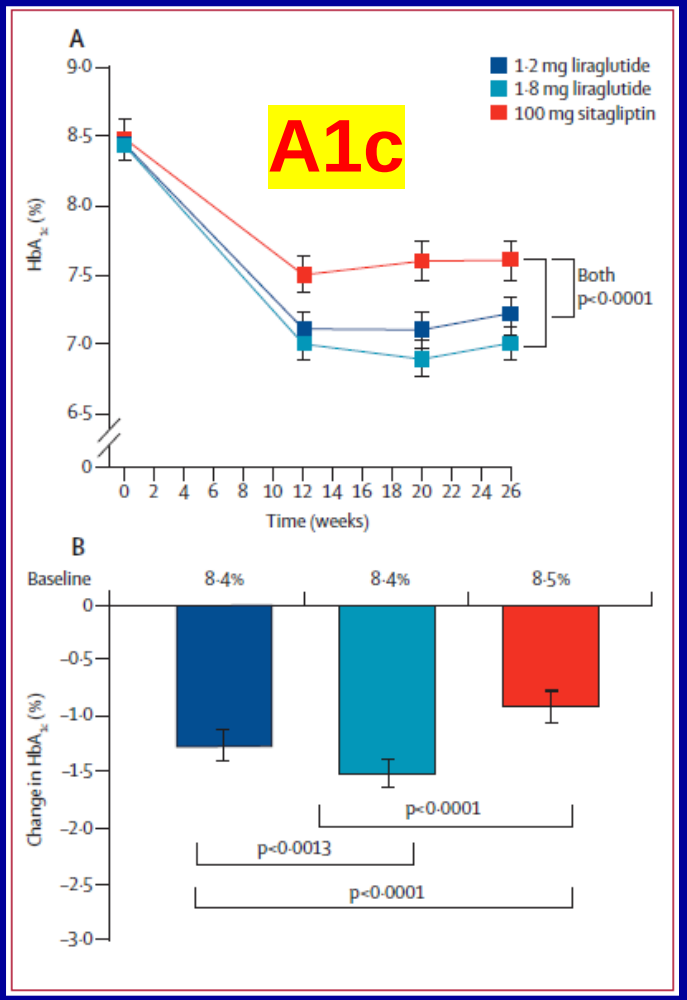
$ p< 0.05 vs competitor; § p< 0.01 vs competitor

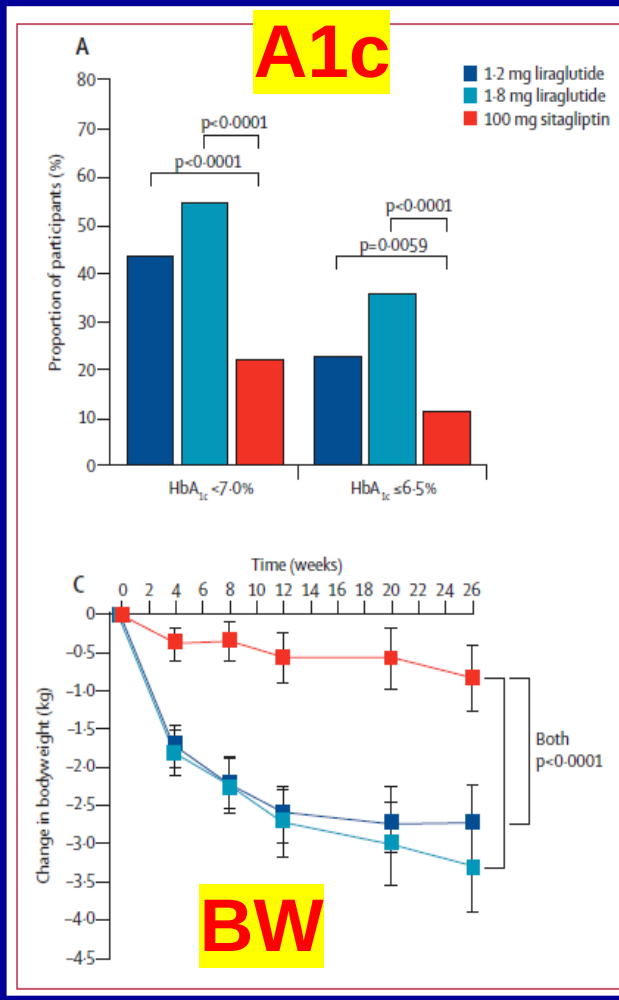
Giuseppe Derosa, et al. Pharmacological Research 100 (2015) 127–134

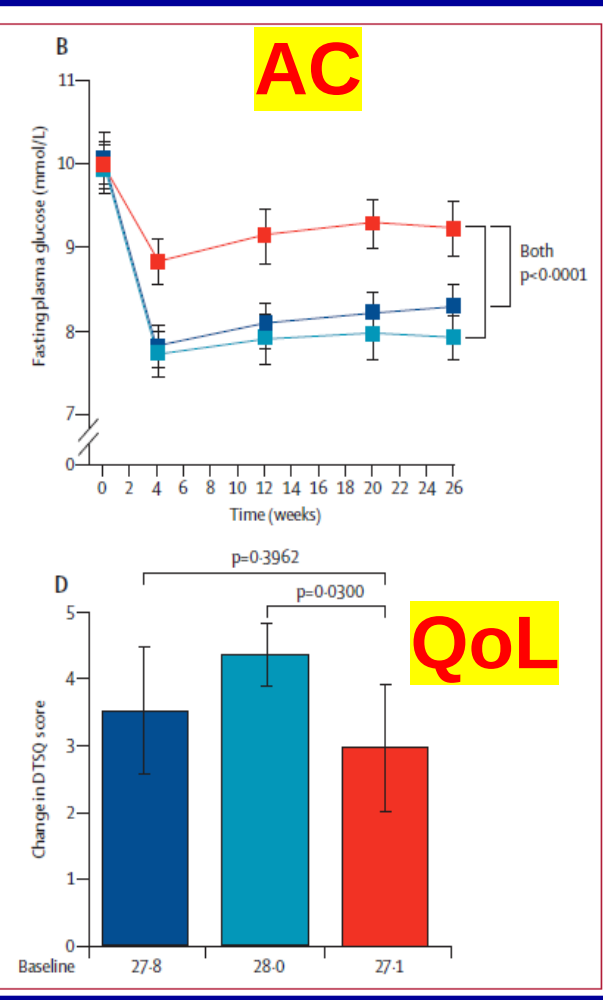
LIRA-DPP-4

Minor hypoglycaemia was recorded in about 5% in each group.

Lancet. 2010 Apr 24;375(9724):1447-56.







Lowest Glucose Variability and Hypoglycemia Are Observed With the Combination of a GLP-1 Receptor Agonist and Basal Insulin (VARIATION Study)

DOI: 10.2337/dc16-1582

GLP-1a: liraglutide for 39 cases
exenatide twice daily for 1 case

stable A1C value <7.5%

BO= Basal insulin + Oral anti-diabetic agents
BGLP= Basal insulin + GLP-1 RA
PM= Pre-mixed insulin
BB= Basal-Bolus insulin

Table 2—ANCOVA and direct cohort comparisons for primary and secondary outcomes from 6-day CGM data

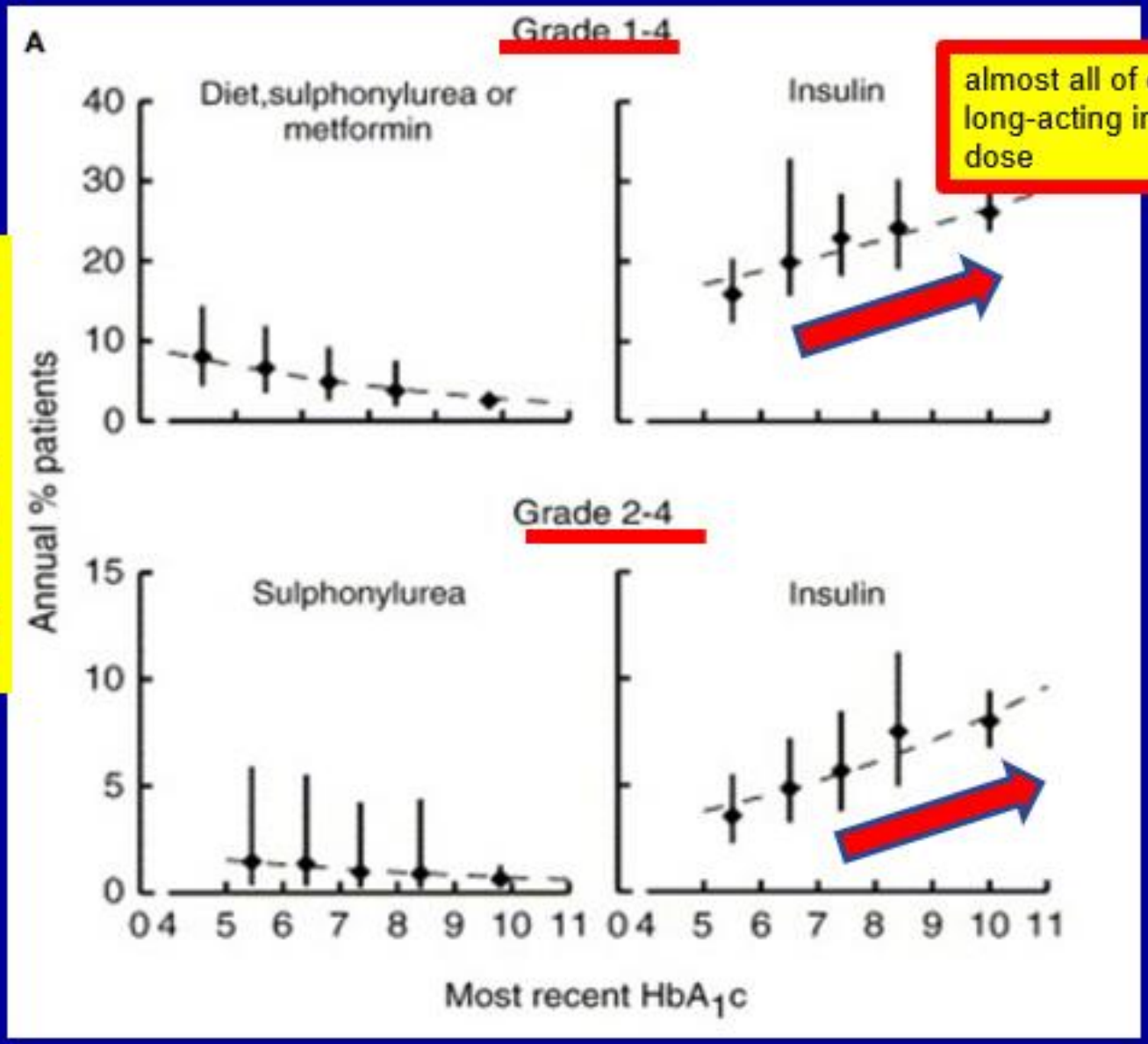
	Cohorts					Between-cohort comparisons		
	BO	BGLP	PM	BB	*P* value^			
Glucose (mg/dL)								
Daily SD (primary outcome)*	34.2 (9)	30.6 (9)	36.0 (10.8)	37.8 (9)	0.01	BO vs. BGLP ($P = 0.03$)	BGLP vs. PM ($P = 0.01$)	BGLP vs. BB ($P < 0.01$)
Total SD*	39.6 (10.8)	34.2 (10.8)	41.4 (10.8)	43.2 (10.8)	0.01	BO vs. BGLP ($P = 0.04$)	BGLP vs. PM ($P = 0.01$)	BGLP vs. BB ($P < 0.01$)
Daily average*	136.8 (19.8)	138.6 (21.6)	144 (19.8)	142.2 (23.4)	0.74			
Daily SD by average*	19.8 (10.8)	16.2 (7.2)	19.8 (9)	19.8 (10.8)	0.20	BO vs. BGLP ($P = 0.07$)	BGLP vs. PM ($P = 0.06$)	BGLP vs. BB ($P = 0.05$)
Hypoglycemia								
Daily frequency**	0.1 (0.4)	0.1 (0.4)	0.4 (0.7)	0.3 (0.4)	0.02		BGLP vs. PM ($P = 0.02$)	BGLP vs. BB ($P = 0.01$)
Daily percentage of time (%)**	0.6 (3.6)	0.1 (2.1)	1.9 (3.9)	2.5 (4.5)	0.02		BGLP vs. PM ($P = 0.02$)	BGLP vs. BB ($P < 0.01$)
Daily duration (minutes)**	7.3 (35.0)	2.9 (25.7)	23.6 (35.7)	31.1 (67.0)	0.01		BGLP vs. PM ($P = 0.03$)	BGLP vs. BB ($P < 0.01$)
Hyperglycemia								
Daily frequency*	1.8 (0.9)	1.7 (1.0)	1.8 (0.8)	1.8 (0.8)	0.85			
Daily percentage of time (%)*	16.4 (12.9)	14.5 (13.7)	20.2 (13.1)	20.4 (12.9)	0.26			
AUC**	0.2 (0.5)	0.1 (0.3)	0.3 (0.4)	0.3 (0.4)	0.04		BGLP vs. PM ($P = 0.01$)	BGLP vs. BB ($P < 0.01$)

^Adjusted for age, BMI, diabetes duration. and baseline A1C; *Data are presented as mean (standard deviation); **Data are presented as median (IQR). All *P* values <0.1 (considered close to significance) are presented.

Diabetes Care 2016 Dec; dc161582

UKPDS (Hemmingsen et al., 2011)

hypoglycemia



只控制空腹血糖可能造成的影響-
減少飯後血糖波動的重要性

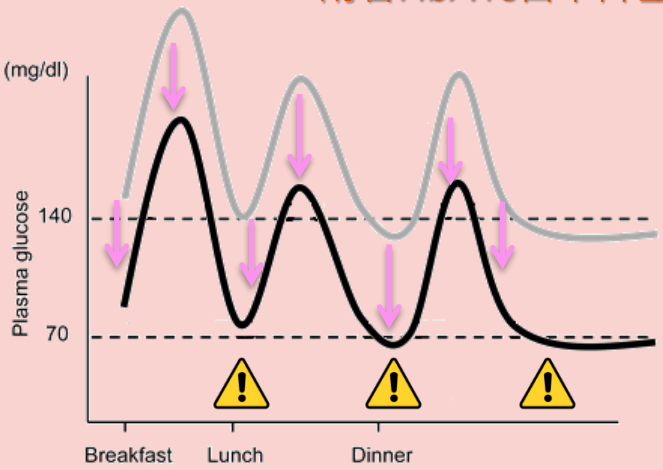
A

1.餐間與夜間有較高的
低血糖風險
2.可調整劑量的空間較小

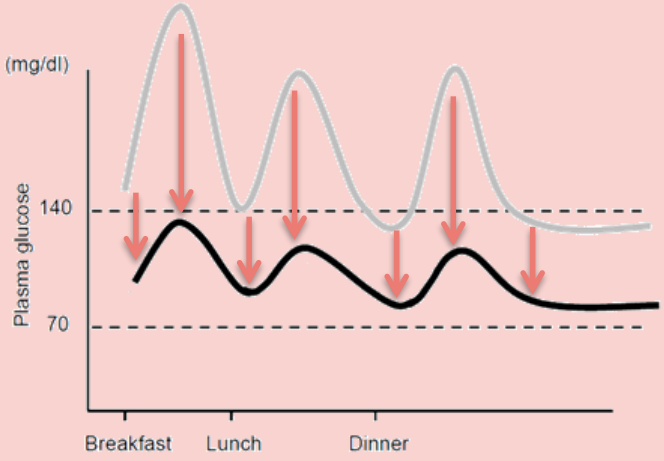
B

1. 較低的低血糖風險
2. 下降至同樣的HbA1c後
仍有調整劑量的空間

兩者HbA1c皆下降至一樣後，接下來？



Treated with basal insulin
(Control Fasting glucose)

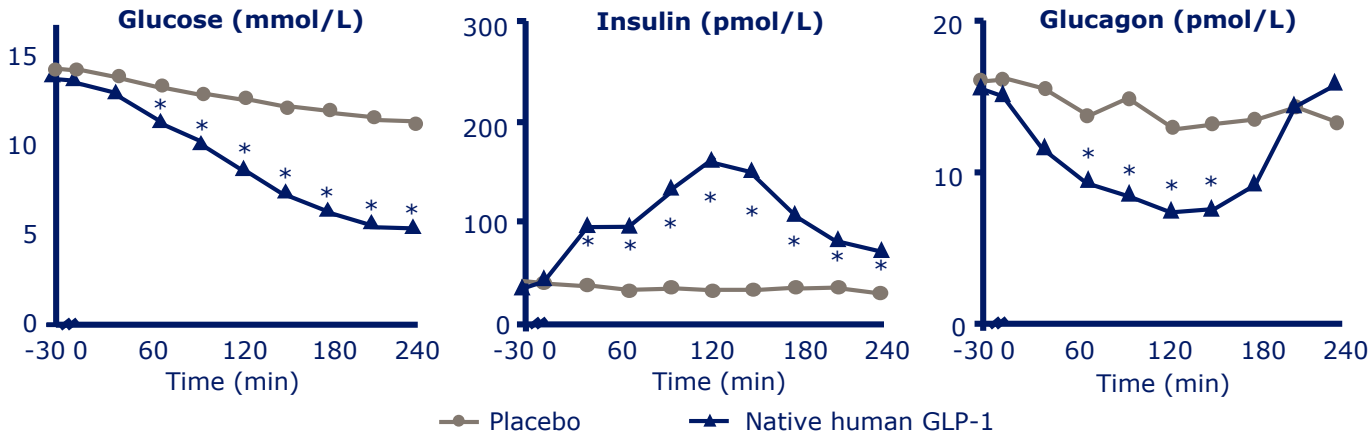


Treated with mealtime insulin
(Control prandial glucose)

Importance of Beta Cell Function for the Treatment of Type 2 Diabetes. *J. Clin. Med.* **2014**, *3*(3), 923-943

*HbA1c = mean plasma glucose level

Effect of GLP-1 is glucose-dependent



- Effects of 4-hour GLP-1 infusion (1.2 pmol/kg/min) in 10 patients with type 2 diabetes

Mean (SE); n=10
*$p<0.05$
GLP-1, glucagon-like peptide-1; SE, standard error
Nauck M et al. *Diabetologia* 1993;36:741–744

INTENSIFYING TO INJECTABLE THERAPIES

ADA&EASD 2018

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

If HbA_{1c} above target despite dual/triple therapy

Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA_{1c} >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target

Consider GLP-1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION

INITIATION FOR GLP-1 RA
- Initiate starting dose (varies across class)

TITRATION FOR GLP-1 RA
- Gradual titration to maintenance dose (varies across class)

Consider insulin as first injectable if
- HbA_{1c} very high >97 mmol/mol (11%)
- Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia, which suggest insulin deficiency
- If type 1 diabetes is a possibility

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred

If above HbA_{1c} target

INITIATION FOR BASAL
- Start 10 IU a day **OR** 0.1–0.2 IU/kg a day

TITRATION FOR BASAL
- Patient self titration is more effective
- Set FBG target that correlates to HbA_{1c} target
- Choose evidence-based titration algorithm, i.e., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10–20%

Add basal insulin
Consider: • INITIATION • TITRATION

For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs

INITIATION
- If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)

TITRATION
- Titrate to FPG target and tolerability

If above HbA_{1c} target
Despite adequately titrated basal insulin **OR** once basal dose > 0.7–1.0 IU/kg **OR** FPG at target

If above HbA_{1c} target
Additional basal insulin or additional prandial insulin

INITIATION FOR PRANDIAL
- 4 IU a day or 10% of basal dose
- If HbA_{1c} <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose

TITRATION FOR PRANDIAL
- Increase dose by 1–2 IU or 10–15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%

Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION

INITIATION
- In insulin-naive patients 10–12 IU or 0.3 IU/kg
- If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs

Consider twice or three times daily premix insulin regimen
Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION

TITRATION
- Individual dose adjustment depends on type of biphasic insulin
- More complex if on three times daily regimen

If above HbA_{1c} target

INITIATION OF STEPWISE PRANDIAL
- Stepwise addition of prandial insulin every 3 months if HbA_{1c} > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION

TITRATION FOR PRANDIAL

If above HbA_{1c} target

INITIATION FOR PRANDIAL

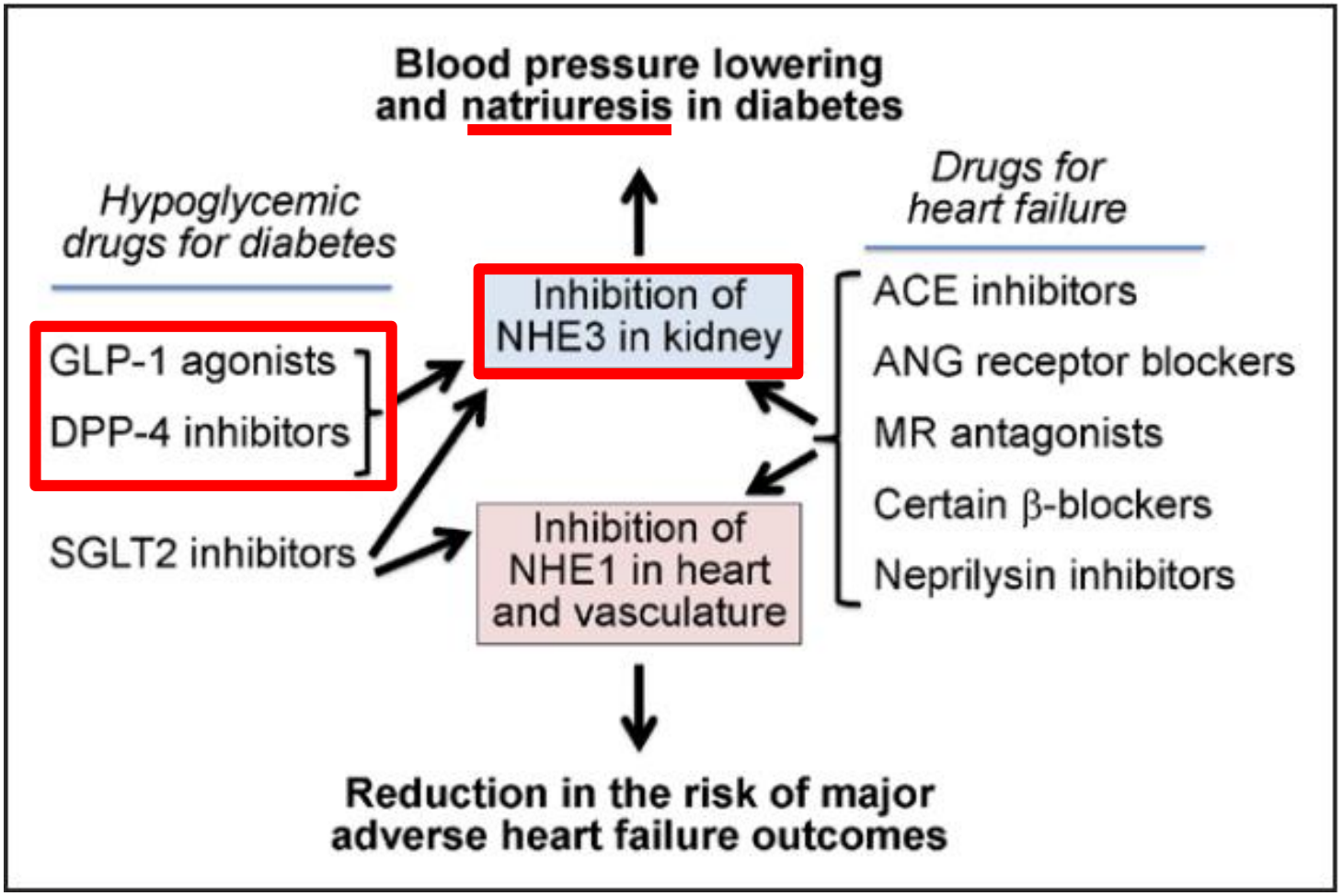
TITRATION FOR PRANDIAL

Proceed to FULL basal-bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION

IF HbA_{1c} DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES

Davies, M.J. et al. Diabetologia (2018) 61: 2461.

GLP-1 has protective effects on kidney



Circulation. 2017;136:1548–1559.

Table 2 | **Glucose-independent effects of incretin-based therapies on renal risk factors in type 2 diabet**

Renal risk factor	GLP-1RA	DPP-4 inhibitor	Putative GLP-1-mediated mechanisms
Inflammation and fibrosis	Decrease	Decrease	↓Renal ROS production (cAMP and PKA)[102,179] ↓AGE–RAGE-mediated renal ROS production (cAMP)[181,265,266] ↓Angiotensin II-induced renal ROS production (PKC)[182,183] ↑Adiponectin (reduces podocyte inflammation; PKA in adipocytes)[267]
Glomerular hyperfiltration	Decrease or neutral effect	Neutral effect	↑Tubuloglomerular feedback (by ↓NHE3 activity) ↓Postprandial glucagon (particularly short-acting GLP-1RA)[70,71,90]? ↓Body weight[90]? ↓GEE* (postprandial hyperfiltration)[90]? ↓RAAS activity[87,127]?

Metabolic

Hemodynamic

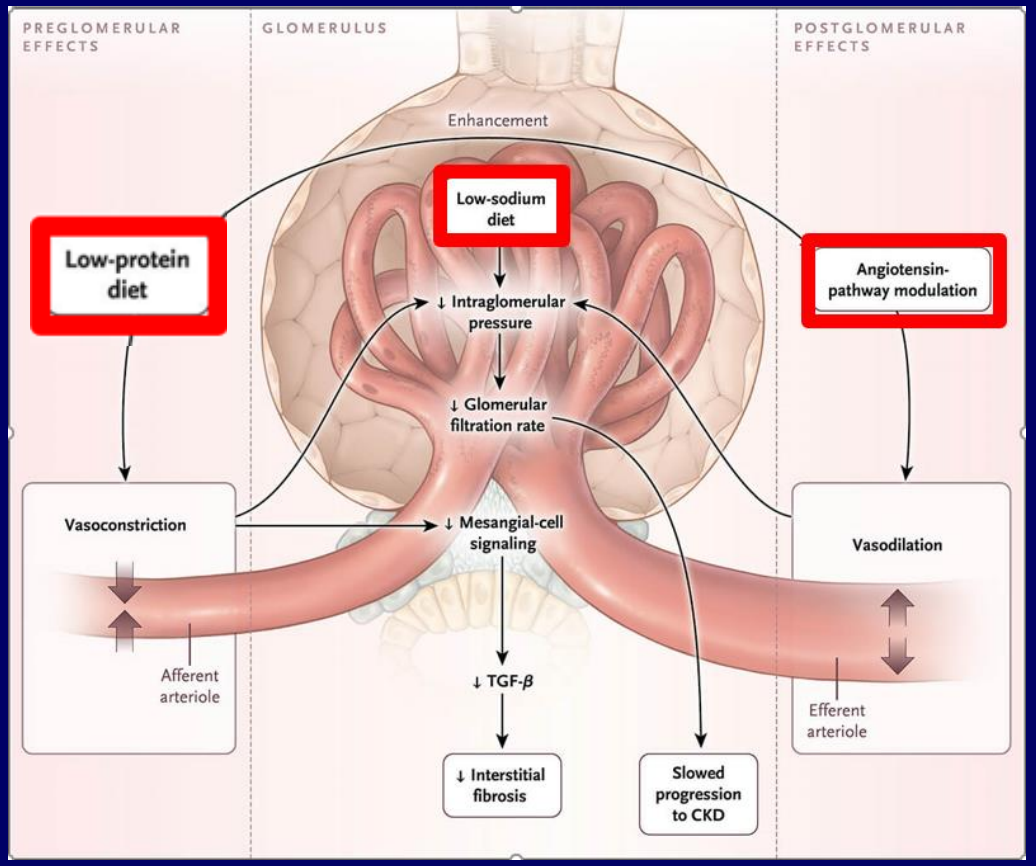
Nature Reviews Nephrology (2017)
doi:10.1038/nrneph.2017.123

Intraglomerular blood pressure is derived from

Systemic blood pressure ↓

Afferent arteriole tone ↑

Efferent arteriole tone ↓

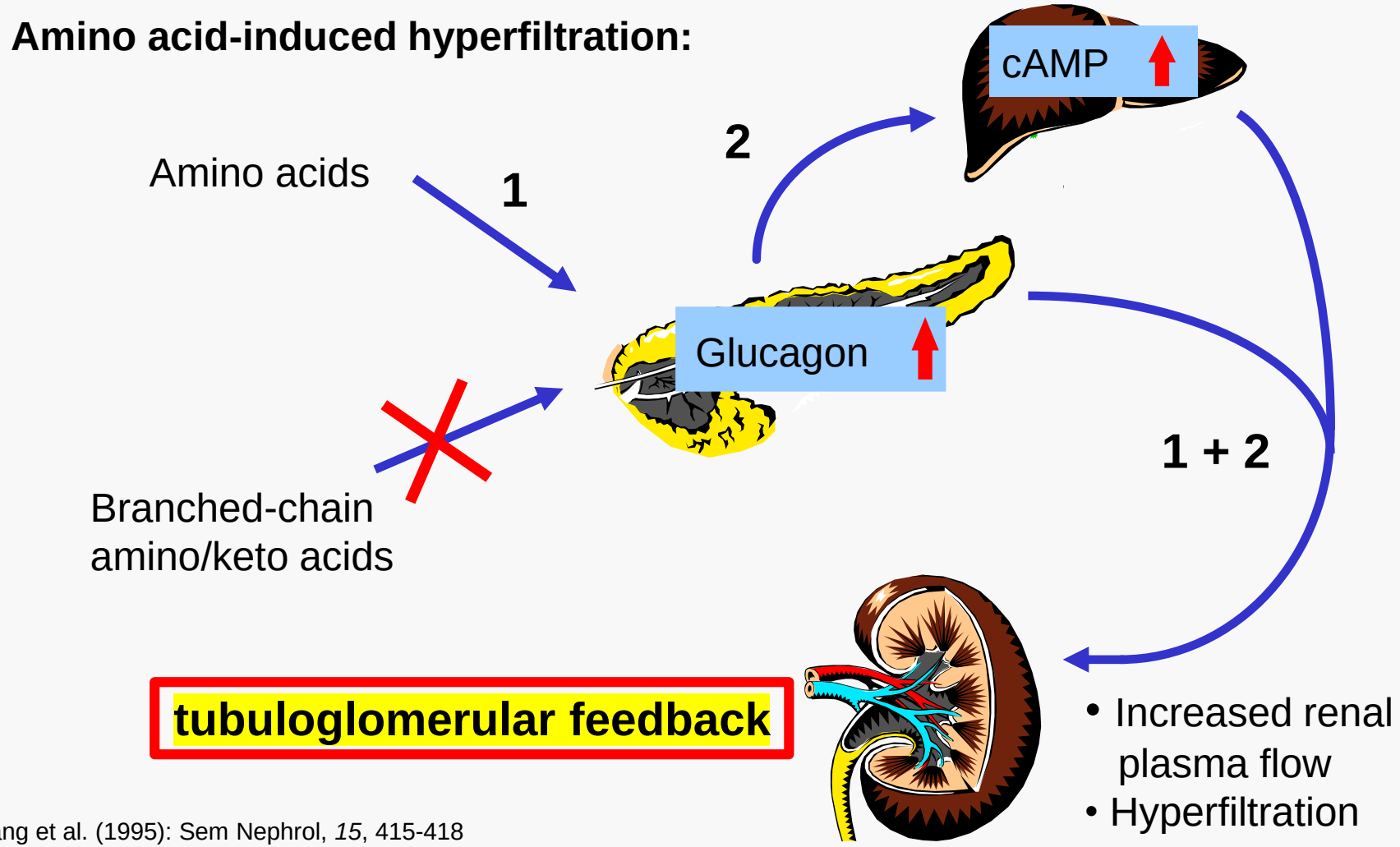


N Engl J Med 2017; 377:1765-1776

Progression of CKD Hyperfiltration

Among the proteinogenic amino acids, there are three BCAAs: leucine, isoleucine and valine

Amino acid-induced hyperfiltration:



Lang et al. (1995): Sem Nephrol, *15*, 415-418

Review

Am J Physiol Renal Physiol 309: F2–F23, 2015.
First published April 29, 2015; doi:10.1152/ajprenal.00614.2014.

Protein- and diabetes-induced glomerular hyperfiltration: role of glucagon, vasopressin, and urea

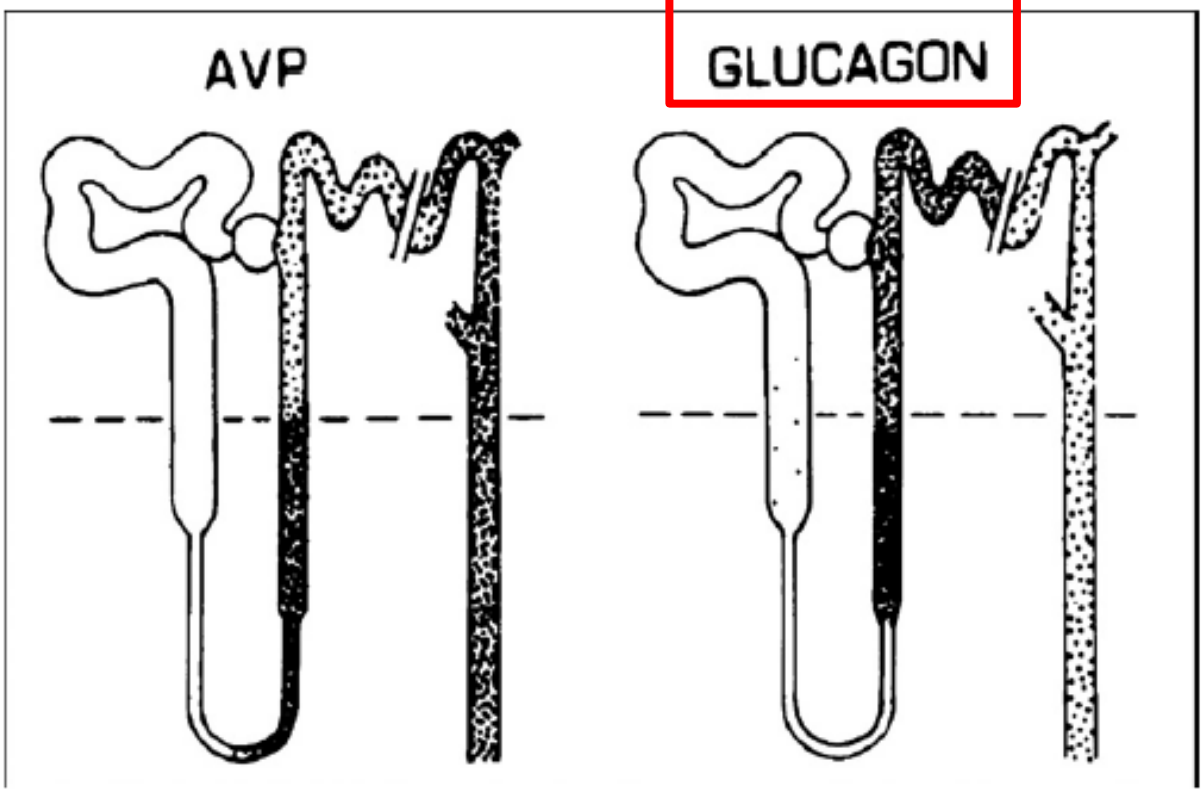
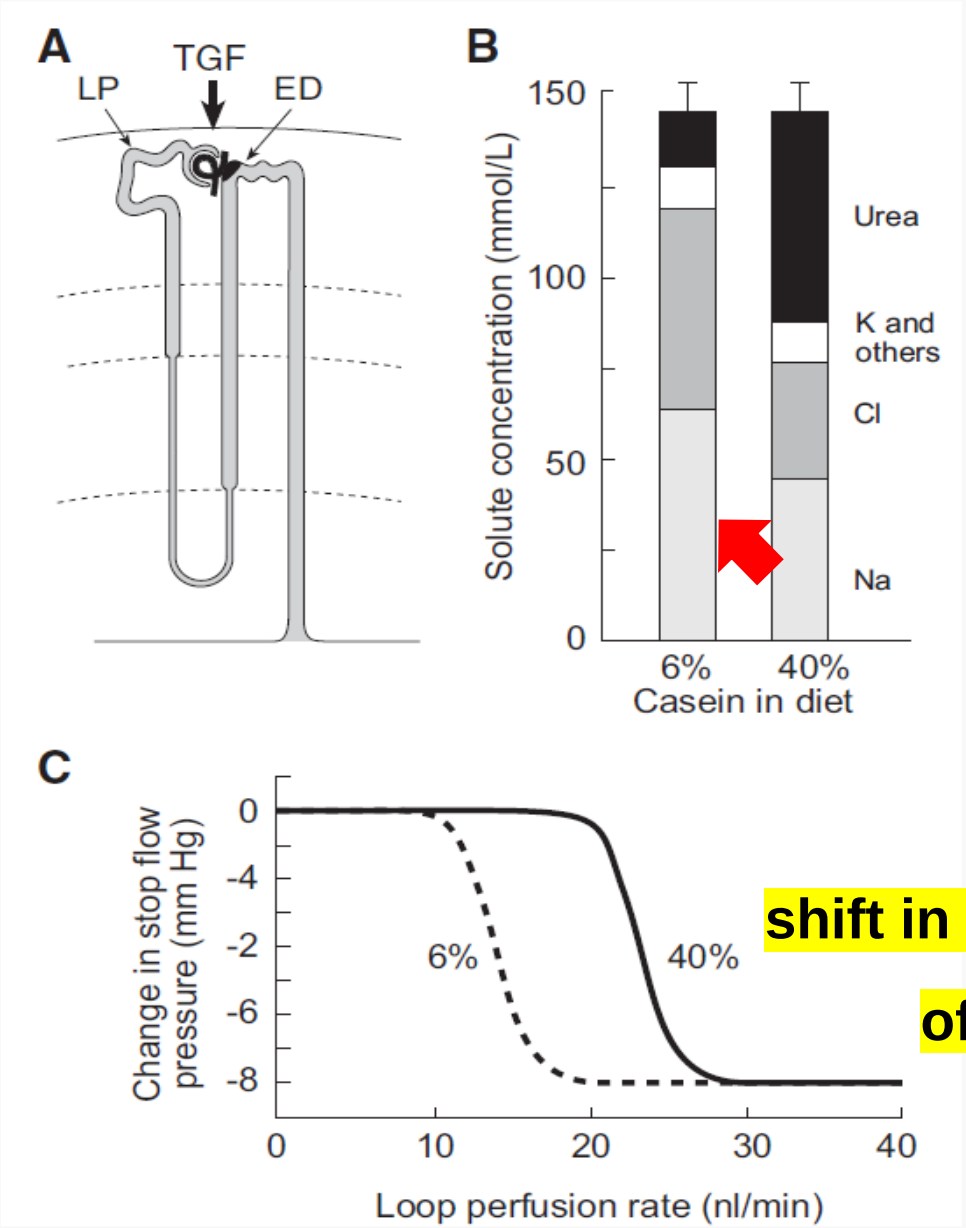


Fig. 1. Localization of vasopressin- and glucagon-sensitive adenylate cyclase along the rat nephron. Dot density in the tubules is proportional to increase in adenylate cyclase activity induced by the corresponding hormone. Reproduced from Ref. 175.



shift in the sensitivity of the TGF

Am J Physiol Renal Physiol 309: F2–F23, 2015.

GLP-1 has protective effects on kidney

- Hyperglycaemia causes endothelial dysfunction through several pathways, including reduction of GLP-1R signaling and enhanced Ang II signaling
- GLP-1 has protective effects on glomerular endothelial cells through inhibition of angiotensin II signaling and inhibition of pro-inflammatory action
- GLP-1 partly mediates its protective action via the GLP-1 receptor
  - Expressed in the renal endothelium

GLP-1, glucagon-like peptide 1
Mima A et al. *Diabetes* 2012;61:2967–2979.

GLP1-R agonist: effects on the kidney

Fujita et al., Kidney Int 2014;85:579

Liraglutid reduces renal damage in diabetic mice

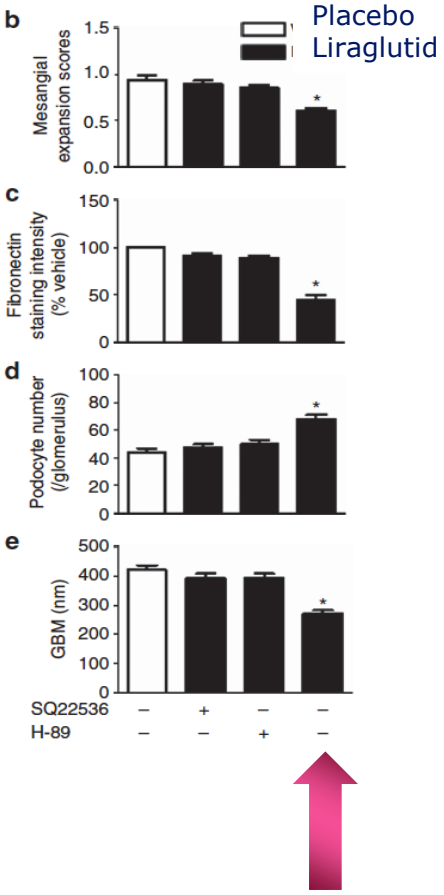
SQ: Inhibitor of cAMP
H-89: Inhibitor of proteinkinase

Mesangial Expansion

Fibronectin

Number of podocytes

GBM width



GLP1-R agonist: effects on the kidney

Fujita et al., Kidney Int 2014;85:579

Knock-out of the GLP-1 Receptor enhances renal damage in diabetic mice

Mice without diabetes
GLP1-Receptor + or -

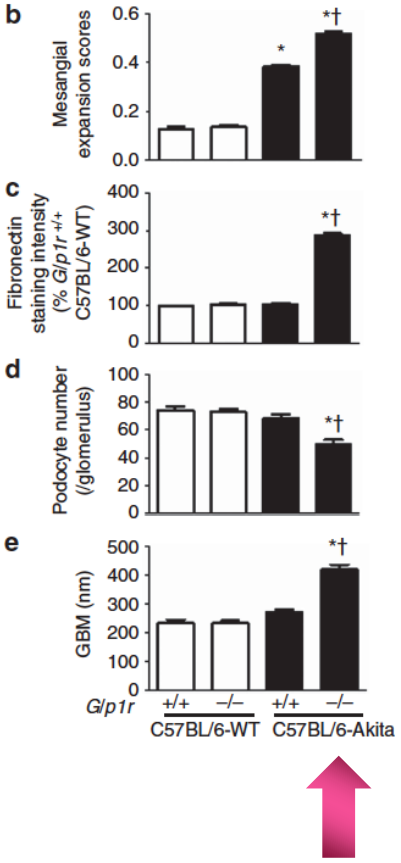
Mice with diabetes
GLP1-Receptor + or -

Mesangiale Expansion

Fibronectin

Number of podocytes

GBM width



Dosing in DKD pts

- FDA: No dose adjustment is recommended in pts with renal impairment including (ESRD).
- Monitor renal function in pts with severe adverse gastrointestinal reactions.

Renal Impairment and GLP-1 Receptor Agonist Use

GLP-1 Receptor Agonists	Use in Renal Impairment
Albiglutide[a]	• No dose adjustment needed for mild, moderate, or severe renal impairment (eGFR 15-89 mL/min/1.73m^2)
Exenatide Extended Release[b]	• Not recommended with eGFR<30 mL/min/1.73m^2 • Use with caution with eGFR 30-50 mL/min/1.73m^2
Exenatide Twice Daily[c]	• Not recommended with eGFR<30 mL/min/1.73m^2 • Use with caution with eGFR 30-50 mL/min/1.73m^2
Liraglutide[d]	• No dose adjustment needed for mild, moderate, or severe renal impairment (eGFR 15-89 mL/min/1.73m^2)
Dulaglutide[e]	• No dose adjustment needed for mild, moderate, or severe renal impairment (eGFR 15-89 mL/min/1.73m^2)

a. Tanzeum® PI 2014[15]; b. Bydureon® PI 2014[13]; c. Byetta® PI 2013[16]; d. Victoza® PI 2013[14]; e. Trulicity®PI 2014.[17]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Table S2. Baseline characteristics according to trial group

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2	64.4
Diabetes duration, years	12.8	12.9
HbA_{1c}, %	8.7	8.7
BMI, kg/m^2	32.5	32.5
Systolic blood pressure, mmHg	135.9	135.9
Diastolic blood pressure, mmHg	77.2	77.0
eGFR (ml/min/1.73 m^2)	80.2	80.6
Renal function (eGFR, ml/min/1.73 m^2)		
Normal (eGFR ≥90)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30)	117 (2.5)	107 (2.3)
Microalbuminuria	1223 (26.2)	1233 (26.4)
Macroalbuminuria	461 (9.9)	505 (10.8)
ACE inhibitors and ARB	3905 (83.7)	3836 (82.1)

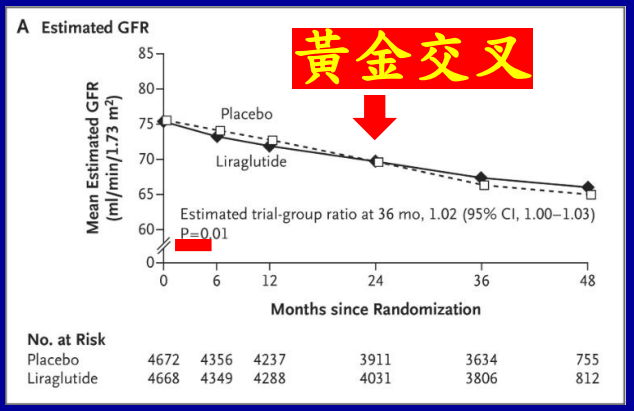
24%

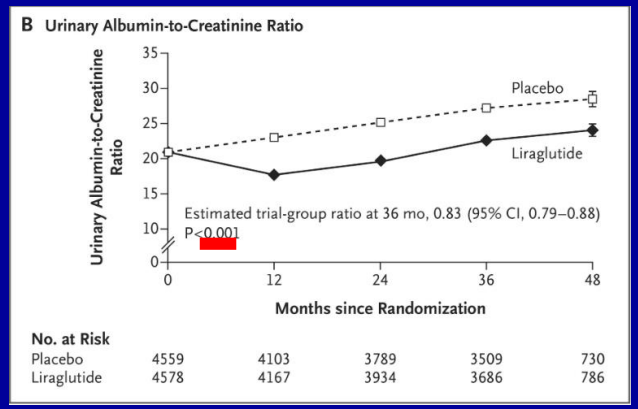
10%

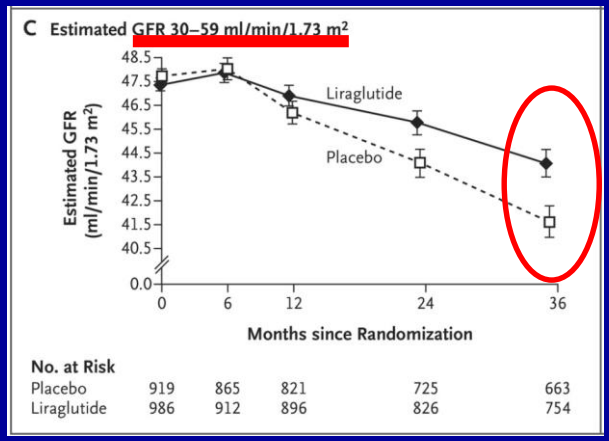
N Engl J Med 2017; 377:839-848

Table 1. Composite Renal Outcome and Individual Components of the Composite Outcome.*

Outcome	Liraglutide (N=4668)	Placebo (N=4672)	Total (N=9340)	Hazard Ratio (95% CI)	P Value
	no. of patients (rate per 1000 patient-yr of observation)				
Composite renal outcome	268 (15.0)	337 (19.0)	605 (17.0)	0.78 (0.67–0.92)	0.003
Components of composite renal outcome†					
New-onset persistent macroalbuminuria	161 (9.0)	215 (12.1)	376 (10.6)	0.74 (0.60–0.91)	0.004
Persistent doubling of serum creatinine level	87 (4.9)	97 (5.5)	184 (5.2)	0.89 (0.67–1.19)	0.43
Renal-replacement therapy	56 (3.1)	64 (3.6)	120 (3.4)	0.87 (0.61–1.24)	0.44
Death due to renal disease	8 (0.4)	5 (0.3)	13 (0.4)	1.59 (0.52–4.87)	0.41





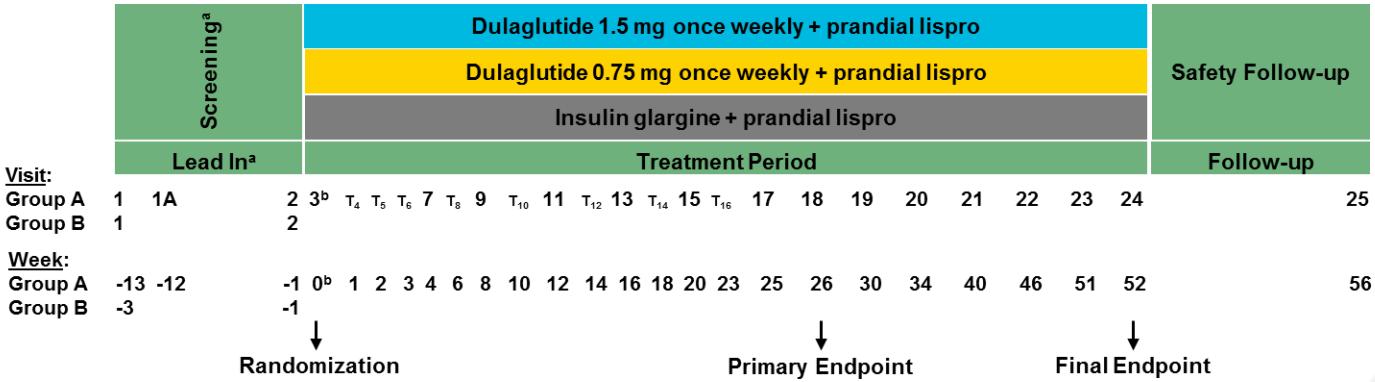


Leader trial

N Engl J Med 2017; 377:839-848

AWARD-7
Study Design

A multicenter, parallel-arm, randomized, 52-week clinical trial that assessed the efficacy and safety of dulaglutide (1.5 mg, N=192; 0.75 mg, N=190) vs insulin glargine (N=194) in people with T2D and moderate-to-severe CKD



- **Primary Objective**: to demonstrate dulaglutide noninferiority for HbA1c change after 26 weeks vs insulin glargine
- **Key inclusion criteria**: adults with T2D, eGFR of <60 to ≥15 mL/min/1.73 m^2, BMI 23-45 kg/m^2, HbA1c ≥7.5% and ≤10.5% for patients receiving insulin + OAM(s) and/or pramlintide or only insulin prior to screening

BMI=body mass index; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; HbA1c=glycated hemoglobin; OAM=oral antihyperglycemic medication; T=telephone visit; T2D=type 2 diabetes. [a]Group A: patients taking OAM(s) ± pramlintide + insulin at Screening had a 13-week Screening/Lead-in Period; Group B: patients taking only insulin at Screening had a 3-week Screening/Lead-In Period; [b]Once randomized, no distinction between Groups A and B. Insulin glargine dose adjusted to target fasting PG values between 100-150 mg/dL; insulin lispro doses adjusted to target pre-prandial PG values between 120-180 mg/dL.. Tuttle et al. Poster presented at: American Diabetes Association 74th Scientific Sessions; June 13-17, 2014, San Francisco, California. Poster 138-LB.

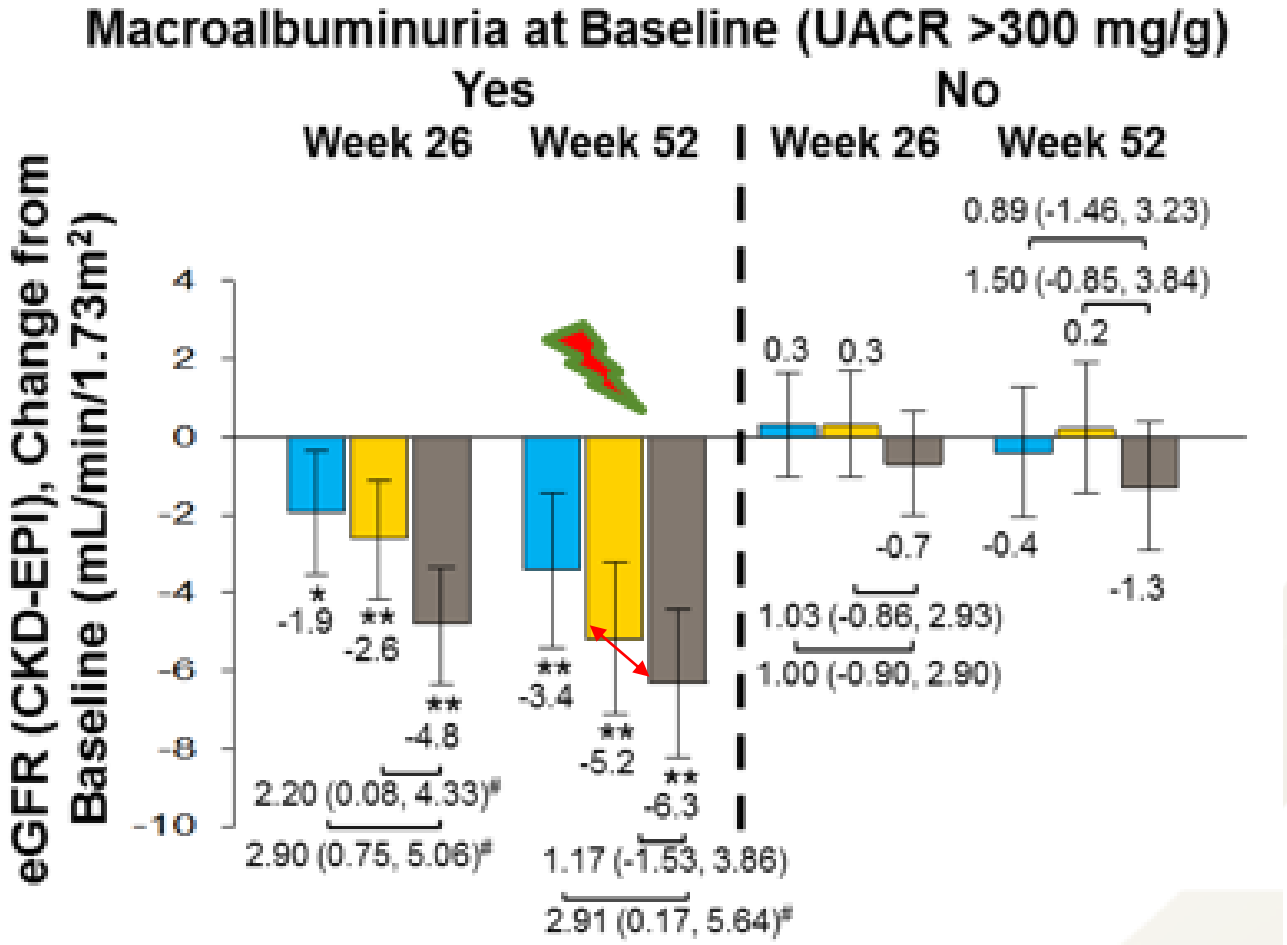
AWARD-7
Baseline Characteristics

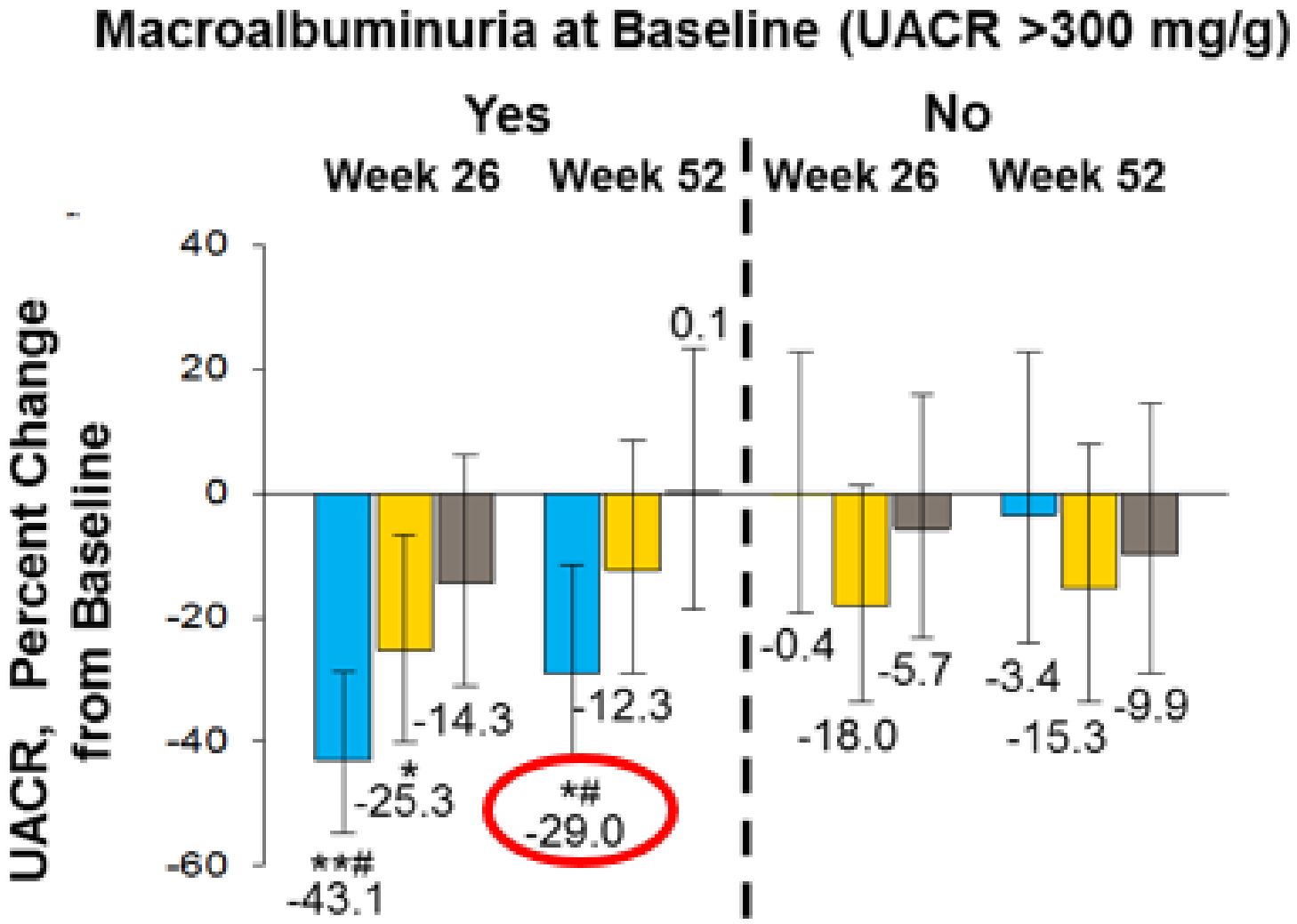
Demographics (safety population, except FBG [mITT population])	Dulaglutide 1.5 mg N=192	Dulaglutide 0.75 mg N=190	Insulin Glargine N=194
Sex, women	88 (45.8)	86 (45.3)	101 (52.1)
Age, years	64.7 ± 8.8	64.7 ± 8.6	64.3 ± 8.4
Duration of diabetes, years	17.6 ± 8.7	18.0 ± 8.8	18.7 ± 8.7
HbA1c, %	8.6 ± 0.9	8.6 ± 1.1	8.6 ± 1.0
FBG, mg/dL	161.5 ± 55.6	166.6 ± 70.6	170.7 ± 72.2
Weight, kg	88.1 ± 16.0	90.9 ± 18.3	88.2 ± 18.5
BMI, kg/m^2	32.1 ± 4.8	33.0 ± 5.5	32.4 ± 5.3
Daily total insulin dose, U	58.8 ± 30.1	56.6 ± 31.2	59.3 ± 34.2
Daily total insulin dose, U/kg	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3
[a]Duration of CKD Stage 3 or higher, years	4.2 ± 5.6	4.0 ± 4.9	3.5 ± 4.0
eGFR-EPI-creatinine[1], mL/min/1.73m^2	38.1 ± 13.2	38.3 ± 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, g/kg (mean [median])	779.1 (213.7)	842.2 (233.6)	919.5 (195.6)
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)

~95%

~45%

BL=baseline; BMI=body mass index; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FBG=fasting blood glucose; HbA1c=glycated hemoglobin; mITT=modified intention to treat; UACR=urine albumin:creatinine ratio. Data presented as mean ± SD or n (%) unless otherwise noted. [a]Stage 3 or higher at BL. 1. Levey et al. Ann Intern Med. 2009;150(9):604-612.


Macroalbuminuria at Baseline (UACR >300 mg/g)
Yes
No
Week 26
Week 52
Week 26
Week 52
eGFR (CKD-EPI), Change from Baseline (mL/min/1.73m²)
4
2
0
-2
-4
-6
-8
-10
*
-1.9
**
-2.6
**
-4.8
**
-3.4
**
-5.2
**
-6.3
0.3
0.3
-0.7
-0.4
0.2
-1.3
2.20 (0.08, 4.33)#
2.90 (0.75, 5.06)#
1.17 (-1.53, 3.86)
2.91 (0.17, 5.64)#
1.03 (-0.86, 2.93)
1.00 (-0.90, 2.90)
0.89 (-1.46, 3.23)
1.50 (-0.85, 3.84)


Macroalbuminuria at Baseline (UACR >300 mg/g)
Yes
No
Week 26
Week 52
Week 26
Week 52
UACR, Percent Change from Baseline
40
20
0
-20
-40
-60
0.1
-14.3
-12.3
-0.4
-5.7
-3.4
-9.9
-18.0
-15.3
*
-25.3
*#
-29.0
**#
-43.1

REWIND
Dulaglutide CV Outcomes Trial

Diabetes-related Characteristics

	All Participants N=9901	Dulaglutide N=4949	Placebo N=4952
HbA1c (%)	**7.3**	7.3	7.4
DM Duration (y)	**10.5**	10.5	10.6
Retinopathy (%)	**9.0**	9.1	8.9
eGFR <60 ml/min/1.73m^2 (%)	**22.2**	21.8	22.6
Albuminuria (%)*	**35.0**	34.5	35.5
Metformin (%)	**81.2**	81.3	81.1
Sulfonylurea (%)	**46.0**	45.9	46.1
Insulin (%)	**23.9**	24.0	23.7
DPP4i (%)	**5.7**	5.4	6.0
Thiazolidinedione (%)	**1.7**	2.0	1.4
Other incl. SGLT2i (%)	**0.3**	0.3	0.4

**** ACR ≥ 3.39 mg/mmol or 30 mg/g***

REWIND
Dulaglutide CV Outcomes Trial

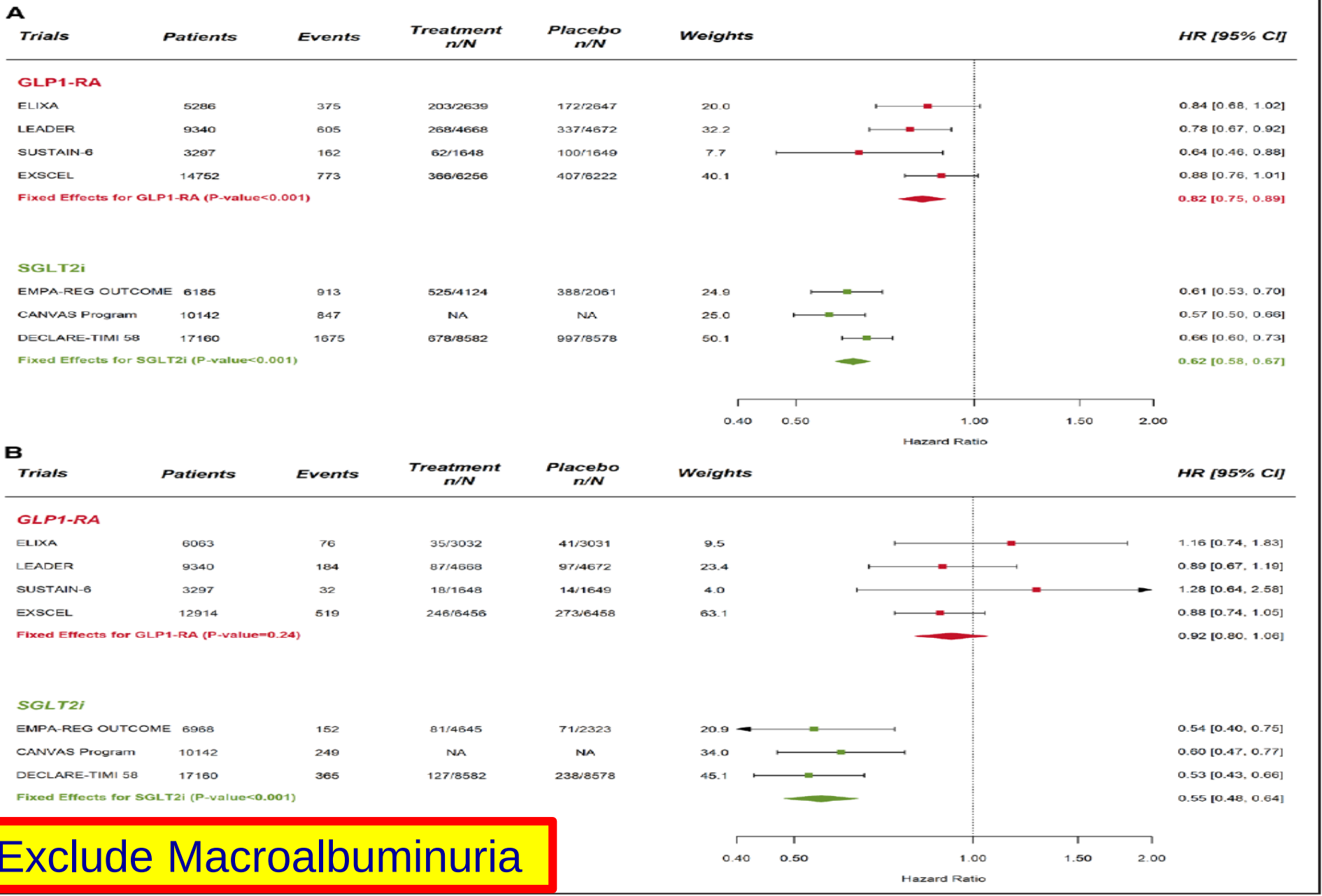
Summary: Dulaglutide & Renal Outcomes

	Dulaglutide (N/100 py)	Placebo (N/100 py)	HR (95%CI)	P
Renal Composite Outcome	3.47	4.07	0.85 (0.77, 0.93)	0.0004
Components of Composite				
First Macroalbuminuria[a]	1.76	2.29	0.77 (0.68, 0.87)	<0.0001
Sustained Decline in eGFR of ≥ 30%	1.79	2.00	0.89 (0.78, 1.01)	0.066
Chronic Renal Replacement	0.06	0.08	0.75 (0.39, 1.44)	0.39
Serious Renal Adverse Event[b]	0.32	0.36	0.90 (0.67, 1.20)	0.46
Sensitivity Analyses				
a) Sustained eGFR Decline ≥ 40%	0.66	0.93	0.70 (0.57, 0.85)	0.0004
Renal composite with this decline	2.36	3.10	0.76 (0.68, 0.84)	<0.0001
b) Sustained eGFR Decline ≥ 50%	0.24	0.42	0.56 (0.41, 0.76)	0.0002
Renal composite with this decline	1.99	2.66	0.74 (0.66, 0.84)	<0.0001

[a]ACR > 33.9 mg/mmol (300 mg/g); [b]any reported AE linked to acute renal failure

Meta-analysis of GLP1-RA and SGLT2i trials on renal end points

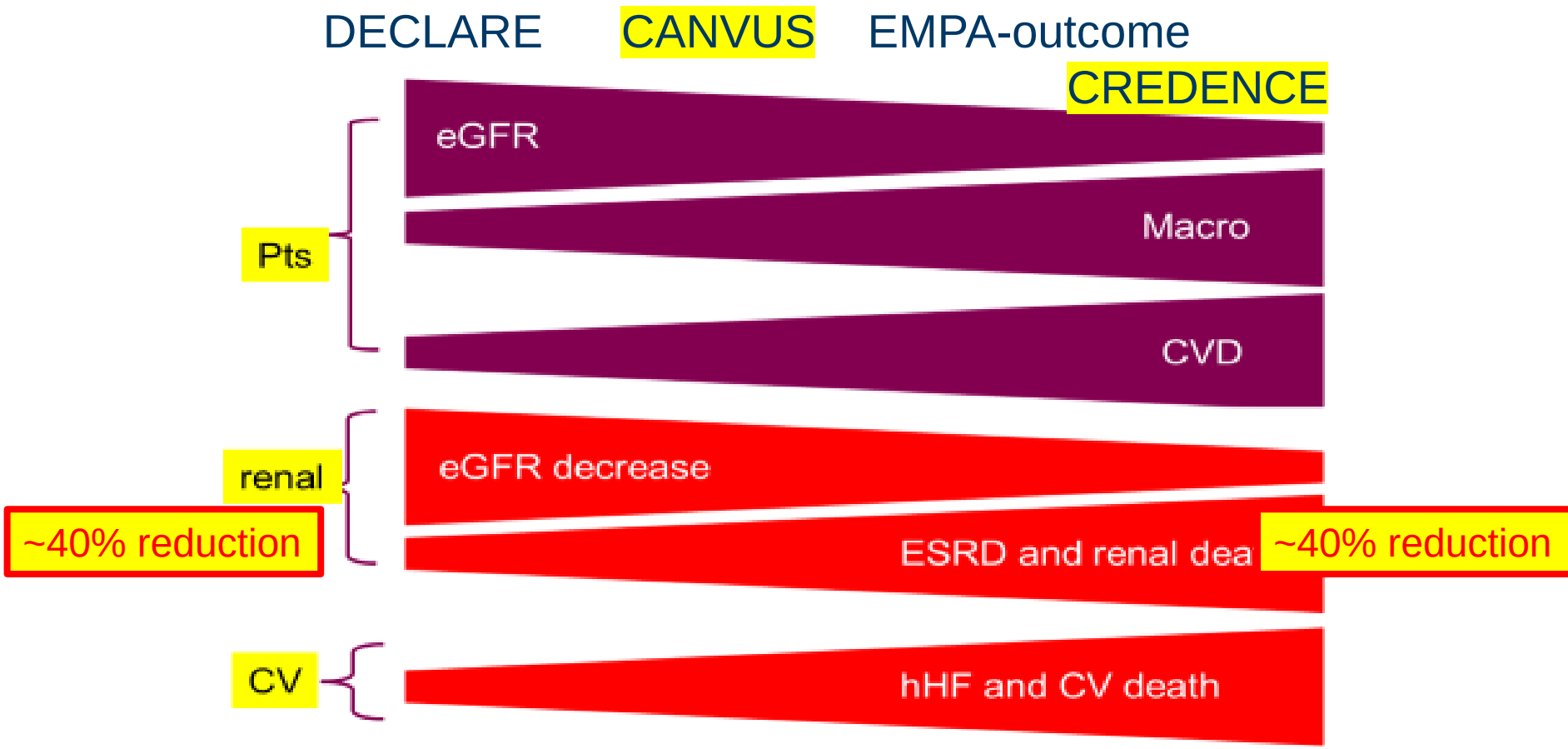
Circulation. 2019;139:2022–2031



Exclude Macroalbuminuria

Patients' CV-renal profile and SGLT2i effects on end-points

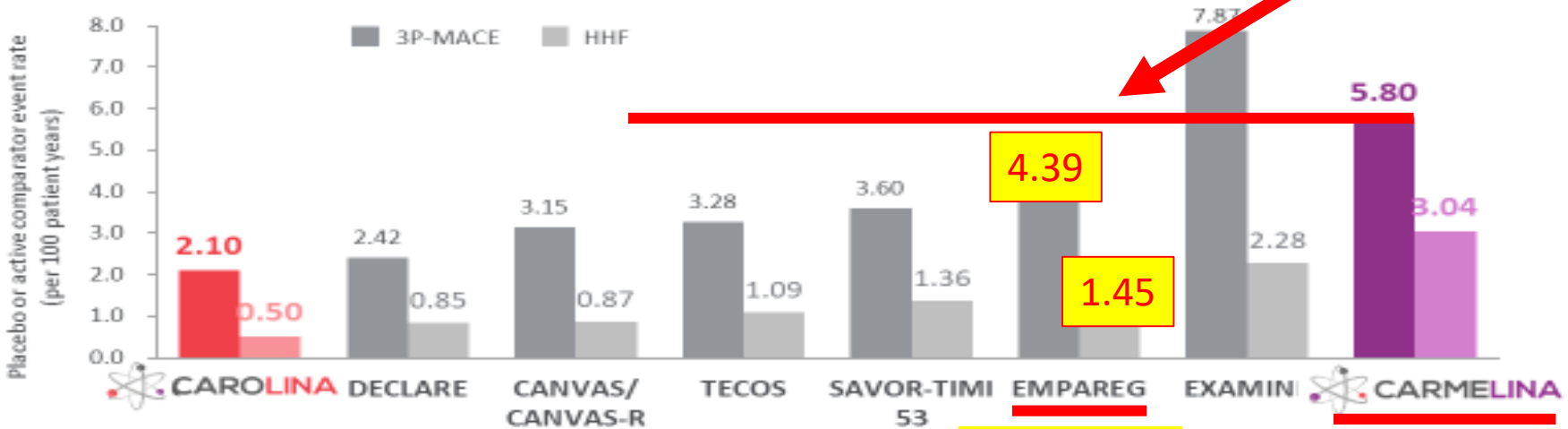
Baseline SBP~ 135-140 mmHg, 80%-100% pts with ACEI/ARB



CREDENCE: 50% CVD
eGfr<60 60%
Macroalbu 100%
3P MACE 4.87
HHF 2.53

CAROLINA® and CARMELINA® provided an opportunity to robustly establish cardiovascular safety in the broader population

3P-MACE and HHF event rates of placebo in DPP-4 and SGLT-2 inhibitor CVOTs



Direct comparison of trials should be interpreted with caution due to differences in study design, populations and methodolo
HHF, hospitalization for heart failure.
1. Scirica B M et al. N Engl J Med 2013;369:1317; 2. White W B et al. N Engl J Med 2013;369:1327; 3. Zannad F et al. Lancet 201
4. Green J B et al. N Engl J Med 2015;373:232; 5. Rosenstock J et al. JAMA 2018; doi: 10.1001/jama.2018.182696. Rosenstock J
doi:10.1001/jama.2019.13772; 7. Wiviott S D et al. N Engl J Med 2018;380:347; 8. Neal B et al. N Engl J Med 2017;377:644; 9. Zinman B et al. N Engl J Med 2015;373:2117

100% CVD

57% CVD
eGfr<60 62%
Macroalbu 38%

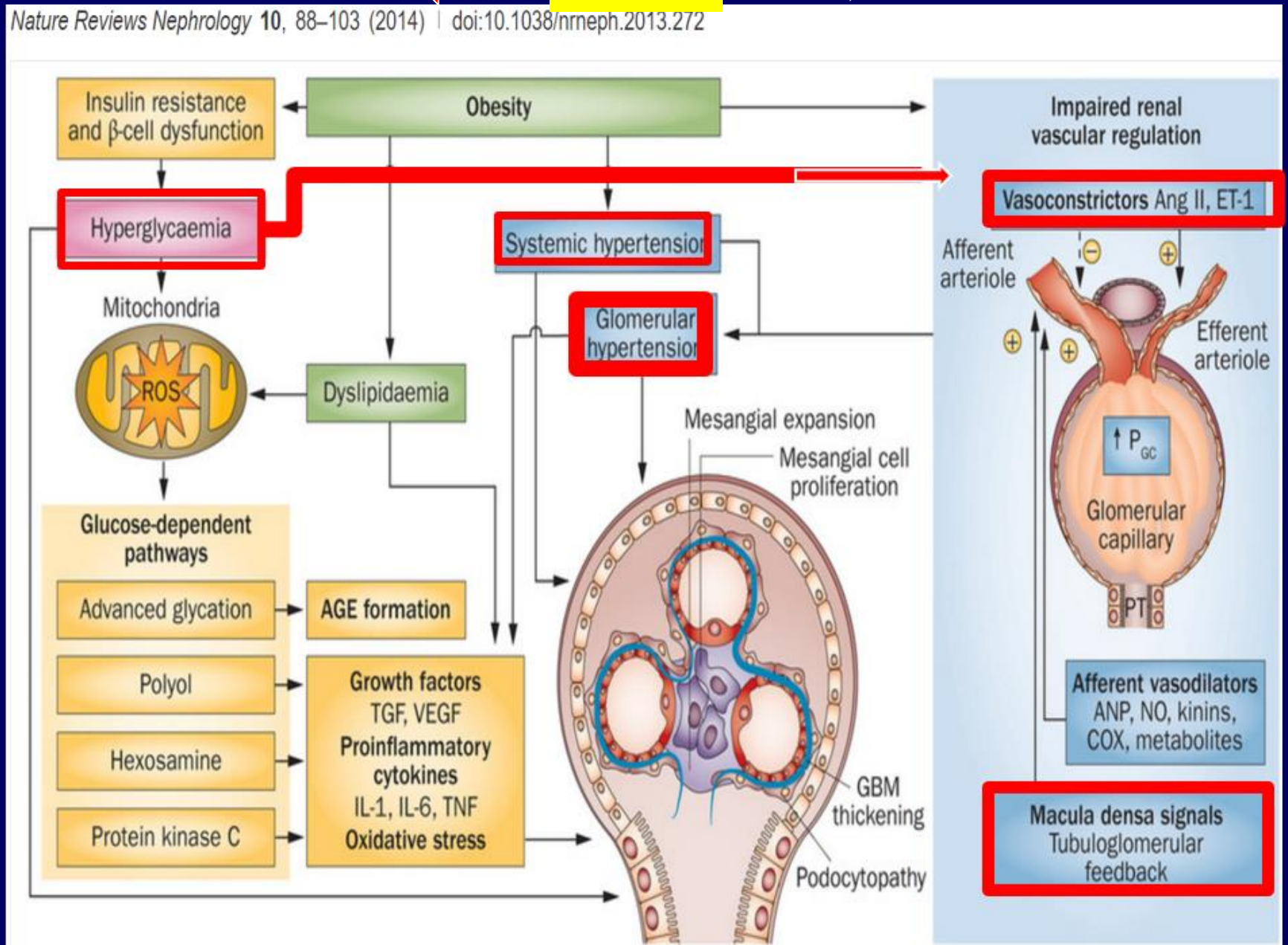
Metabolic

SGLT2i

GLP1a

Hemodynamic

Nature Reviews Nephrology **10**, 88–103 (2014) | doi:10.1038/nrneph.2013.272



ISN WCN'19
APRIL 12-15 - MELBOURNE, AUSTRALIA

Although much has been speculated about the potential advantages of combining an SGLT2 inhibitor with an incretin mimetic, **DELIGHT** is the **first study** to do so in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

THE LANCET
Diabetes & Endocrinology

DELIGHT

Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial

Carol Pollock, Bergur Stefánsson, Daniel Reyner, Peter Rossing, C David Sjöström, David C Wheeler, Anna Maria Langkilde, Hiddo J L Heerspink

Lancet Diabetes Endocrinol. 2019 Apr 12. pii: S2213-8587(19)30086-5.

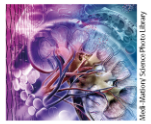
THE LANCET
Diabetes & Endocrinology

Comment

SGLT2 inhibitor and incretin mimetic therapy for type 2 diabetes and chronic kidney disease

The pandemic of diabetes has become a global emergency. Despite increasing knowledge about diabetes prevention, this knowledge has not translated into action that effectively reduces diabetes prevalence in communities. The global picture projects an increase in people living with diabetes, from 425 million in 2017 to nearly 630 million by 2045,[1] and such an increase also means more people with diabetes complications. Chronic kidney disease develops in almost half of people with type 2 diabetes and is the leading cause of end-stage kidney disease worldwide.[2] Chronic kidney disease greatly magnifies the risk of cardiovascular diseases

blocker therapy. Compared with placebo, reductions in albuminuria (UACR) relative to baseline were greater in both the dapagliflozin group (mean difference −21·0% [95% CI −34·1 to −5·2; p=0·011]) and the dapagliflozin–saxagliptin group (−38·0% [−48·2 to −25·8; p<0·0001]) at 24 weeks. Combination treatment produced the numerically greatest decline in albuminuria. Because SGLT2 inhibitors have nominal glycaemic efficacy at lower eGFR, only combination treatment with a DPP-4 inhibitor produced a significant decrease in HbA_{1c} at week 24 versus placebo (mean difference −0·58% [−0·80 to −0·37; p<0·0001]). DELIGHT was



Lancet Diabetes Endocrinol 2019
Published Online
April 13, 2019
http://dx.doi.org/10.1016/S2213-8587(19)30116-0
See Online/Articles
http://dx.doi.org/10.1016/S2213-8587(19)30086-5

Lancet Diabetes Endocrinol. 2019 Apr 12. pii: S2213-8587(19)30116-0.

DELIGHT

ISN WCN'19
APRIL 12-15 - MELBOURNE, AUSTRALIA

Population

- ≥18 years old
- History of Type 2 diabetes for >12 months
- HbA_{1c} ≥7.0% and ≤11.0%
- Stable antidiabetic treatment
- eGFR 25–75 mL/minute/1.73 m^2*
- Micro or macroalbuminuria (UACR 30–3500 mg/g)
- Treatment with ACEi or ARB for ≥3 months
- BMI 20–45 kg/m^2

Randomization 1:1:1

- Placebo (n=148)
- Dapagliflozin 10 mg (n=145)
- Dapagliflozin 10 mg + Saxagliptin 2.5 mg (n=155)

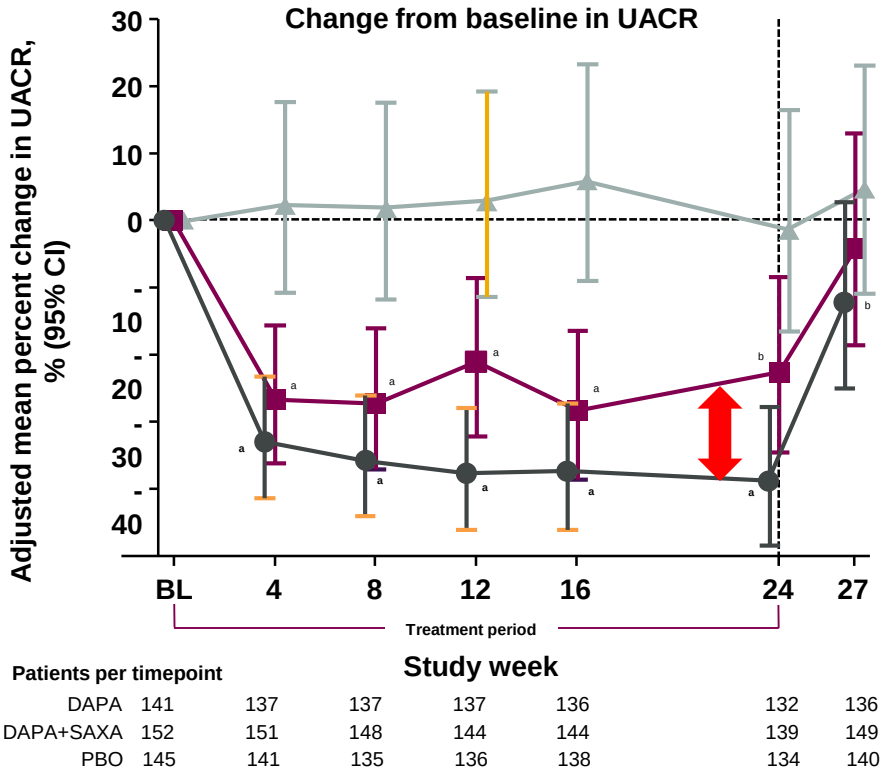
Primary Endpoints

- Change in HbA_{1c}
- Percent change in UACR†

*Dapagliflozin is not recommended for use in patients with eGFR <60 mL/minute/1.73 m^2. The efficacy of dapagliflozin is dependent on renal function.[2]
†Dapagliflozin is not indicated for the management of weight loss, blood pressure reduction or to reduce albuminuria. Weight loss was a secondary endpoint in clinical trials.[2] Dapagliflozin is not indicated for prevention of CV events. Please consult your local prescribing information for the approved use of dapagliflozin. Saxagliptin is not indicated for the management of weight loss, blood pressure or albuminuria. Please consult your local prescribing information for the approved use of saxagliptin.
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; UACR, urine albumin:creatinine ratio.

1. https://clinicaltrials.gov/ct2/show/NCT02547935 Last accessed July 2018; 2. Dapagliflozin. Summary of Product Characteristics.

DELIGHT Primary Endpoint: Adjusted Mean Change in UACR

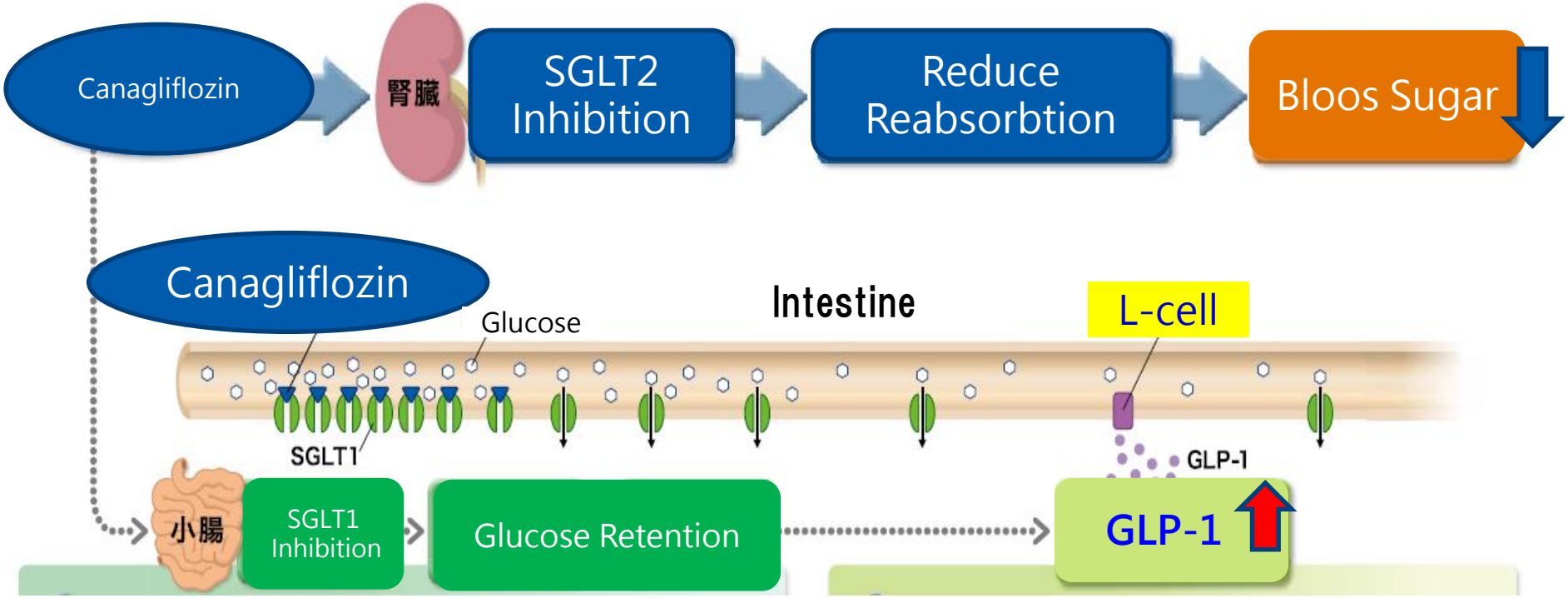


Difference vs. placebo at Week 24		
DAPA	**-21.0%** (95% CI, -34.1 to -5.2)	p=0.011
DAPA+SAXA	**-38.0%** (95% CI, -48.2 to -25.8)	p<0.0001

Proportion of patients that achieved ≥30% reduction in UACR at Week 24		
PBO	**31.3%**	
DAPA	**45.0%**	Odds ratio vs. PBO, 1.9 (95% CI, 1.1-3.0; p=0.013)
DAPA+SAXA	**57.0%**	Odds ratio vs. PBO, 3.0 (1.8-4.8; nominal p<0.0001)

[a]p value: <0.001; [b]p value: <0.05. BL = baseline; DAPA = dapagliflozin; PBO = placebo; SAXA = saxagliptin; UACR = urinary albumin-to-creatinine ratio.
Pollock C et al. Online ahead of print. *Lancet Diabetes Endocrinol*. 2019.

Canagliflozin increase aGLP-1 through SGLT1 inhibition



Canagliflozin Lowers Postprandial Glucose and Insulin by DelayingIntestinal Glucose Absorption in Addition to Increasing UrinaryGlucose Excretion

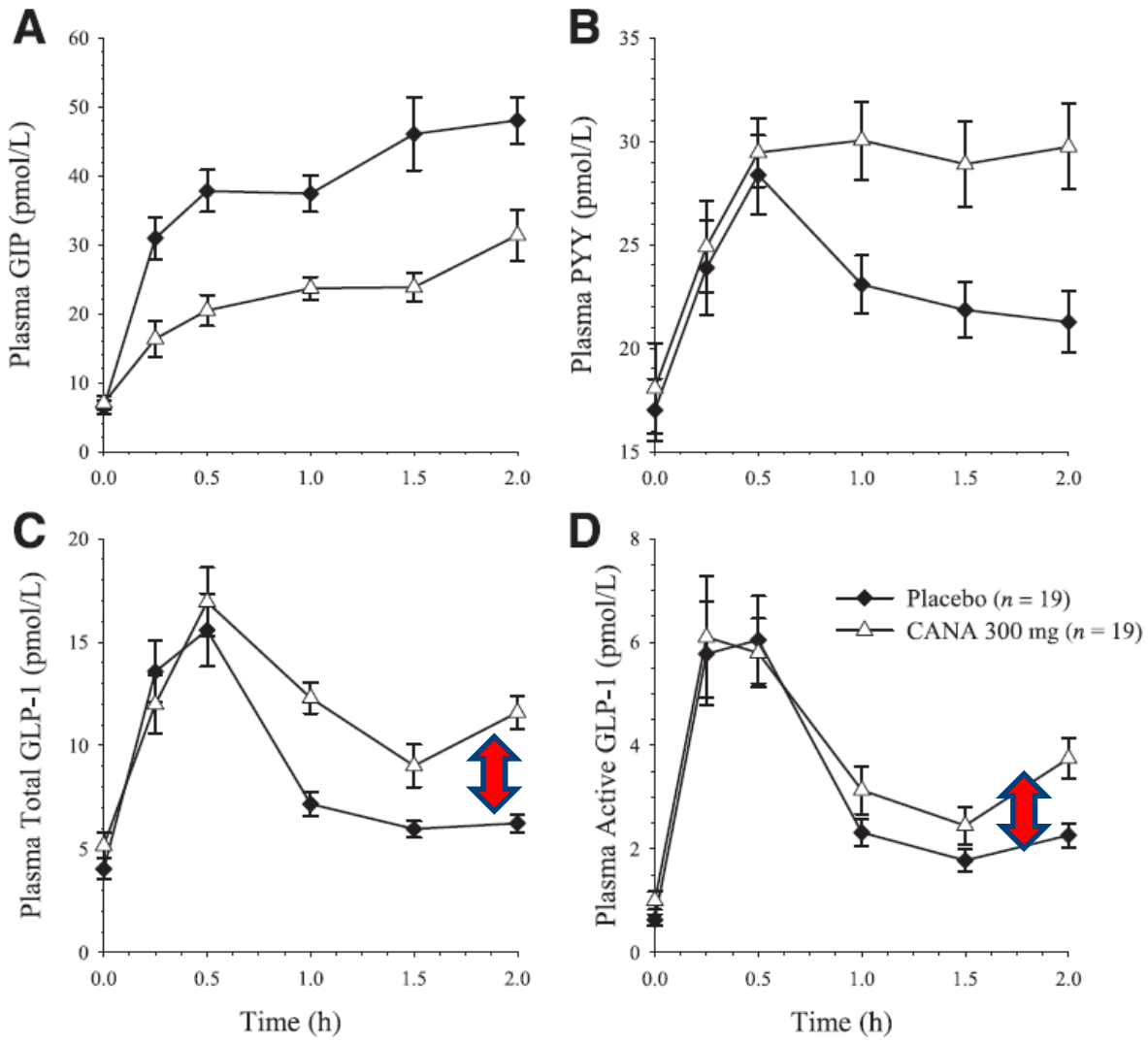
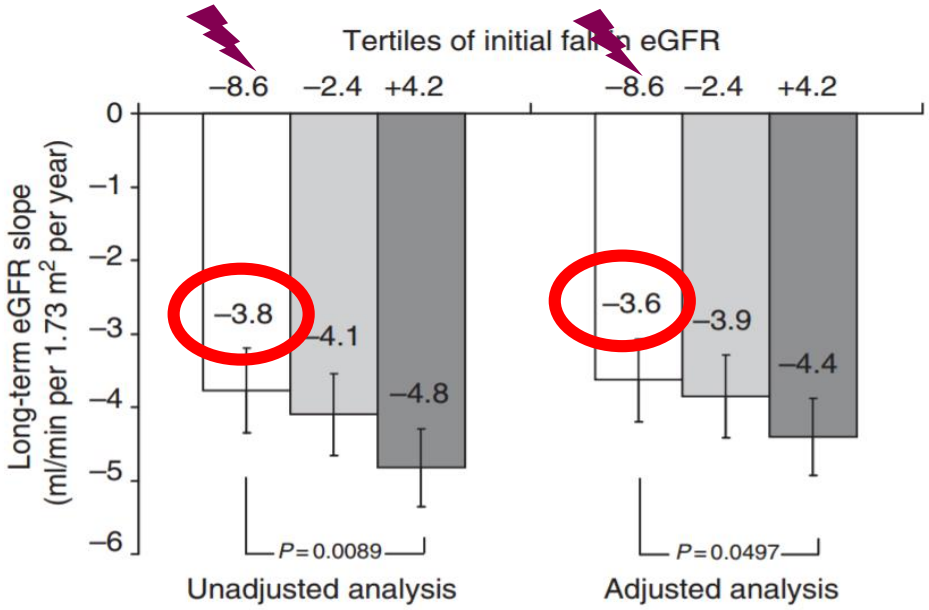


Figure 3—*Mean ± SEM plasma concentration-time profiles of GIP* (A), *PYY* (B), *total GLP-1* (C), *and active GLP-1* (D). *CANA, canagliflozin.*

Endocrine Journal 2017, **64** (9), 923-931

The Greater Changes in eGFR; the Better Protection from ARB

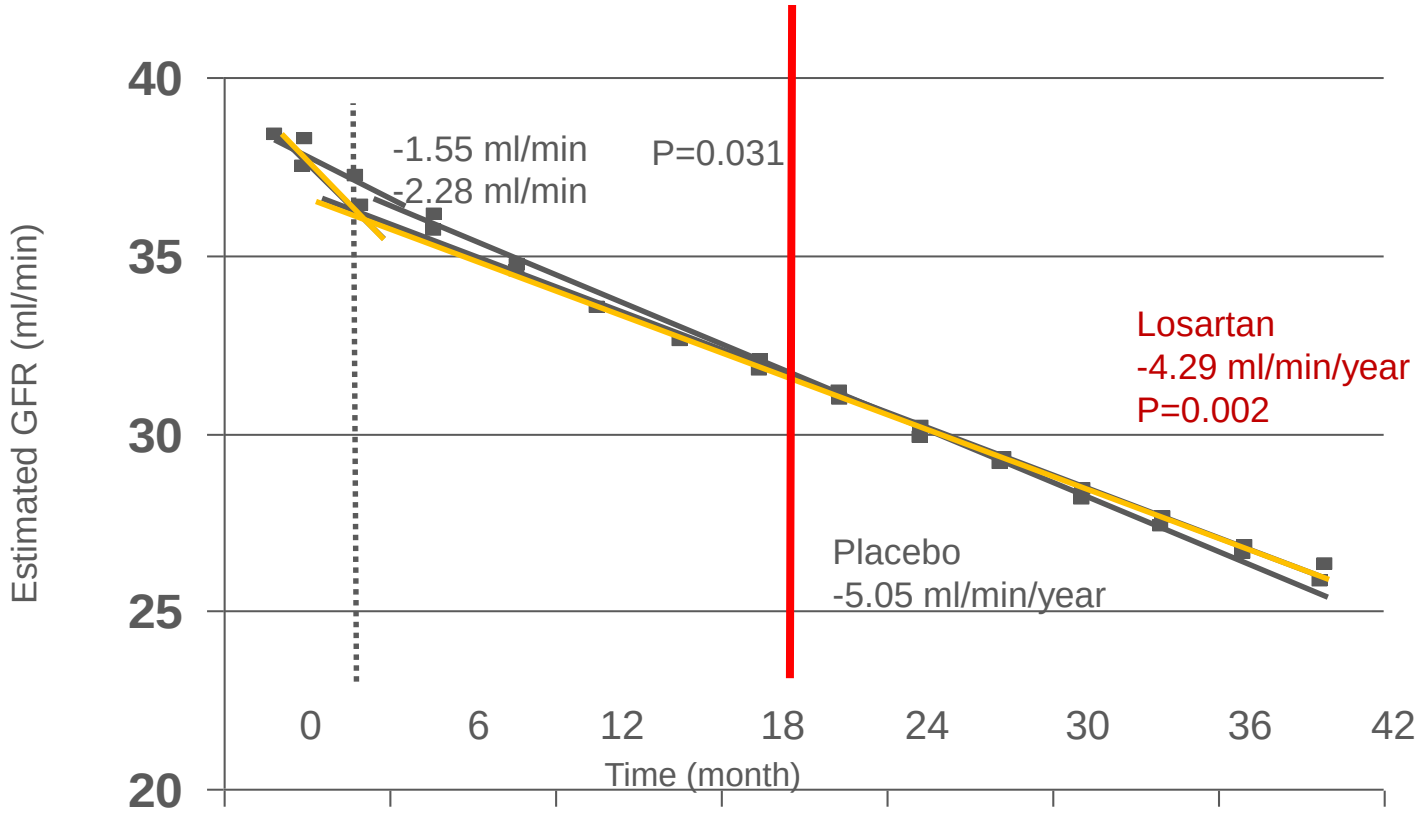


RENAAL trial

Figure 3 | Long-term estimated glomerular filtration rate (eGFR) slope stratified by acute fall in eGFR in losartan-assigned patients. Adjustment for covariates in the multivariable mixed effects model included gender, eGFR, diastolic blood pressure, hemoglobin, urinary albumin/creatinine ratio (UACR) and month 3 change in UACR. The numbers in each bar reflect the annual mean long-term eGFR slope.

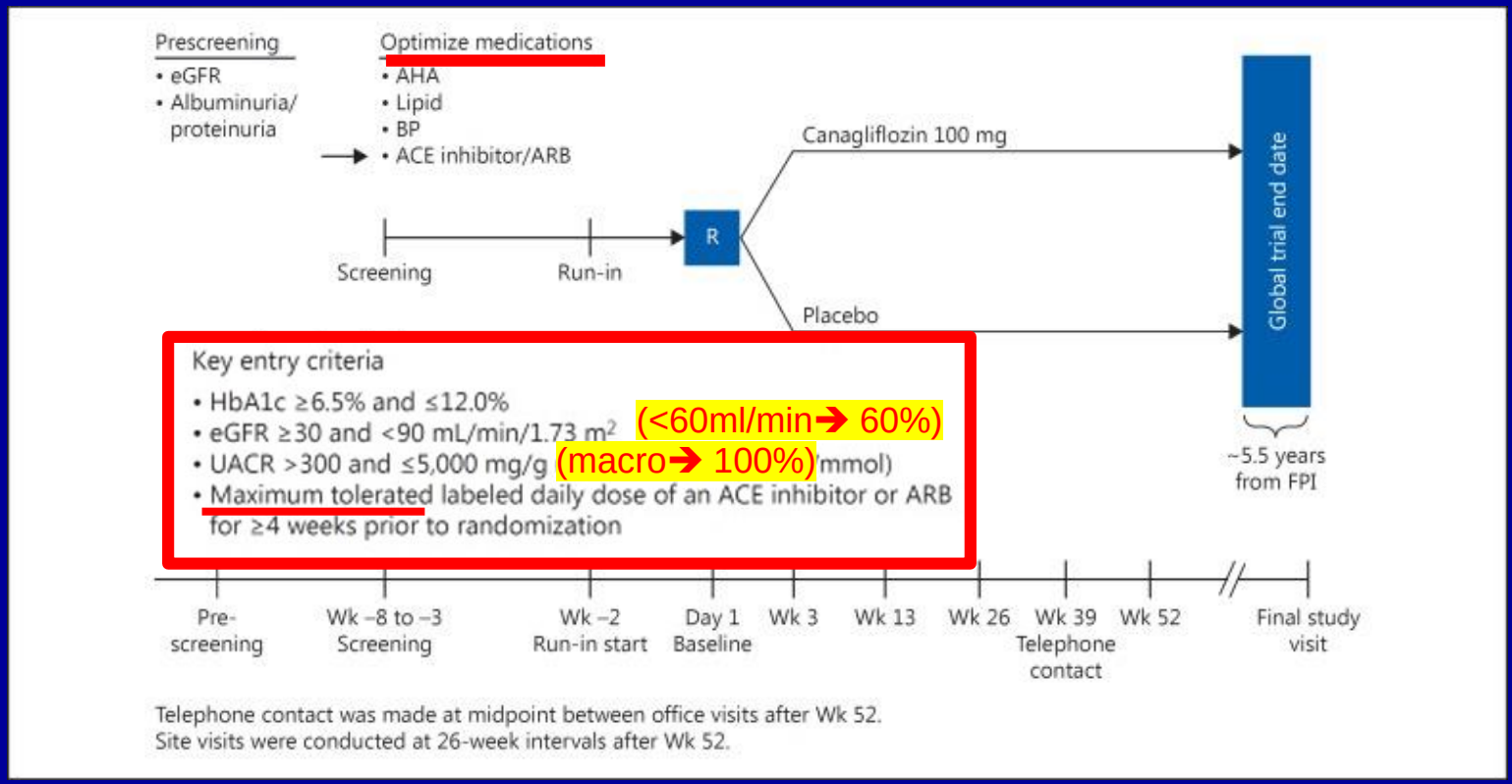
Kidney Int. 2011 Aug;80(3):282-7

RENAAL: Relationship between initial eGFR change and subsequent long-term renal function decline



Holtkamp et al. Kid Int 2011

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics

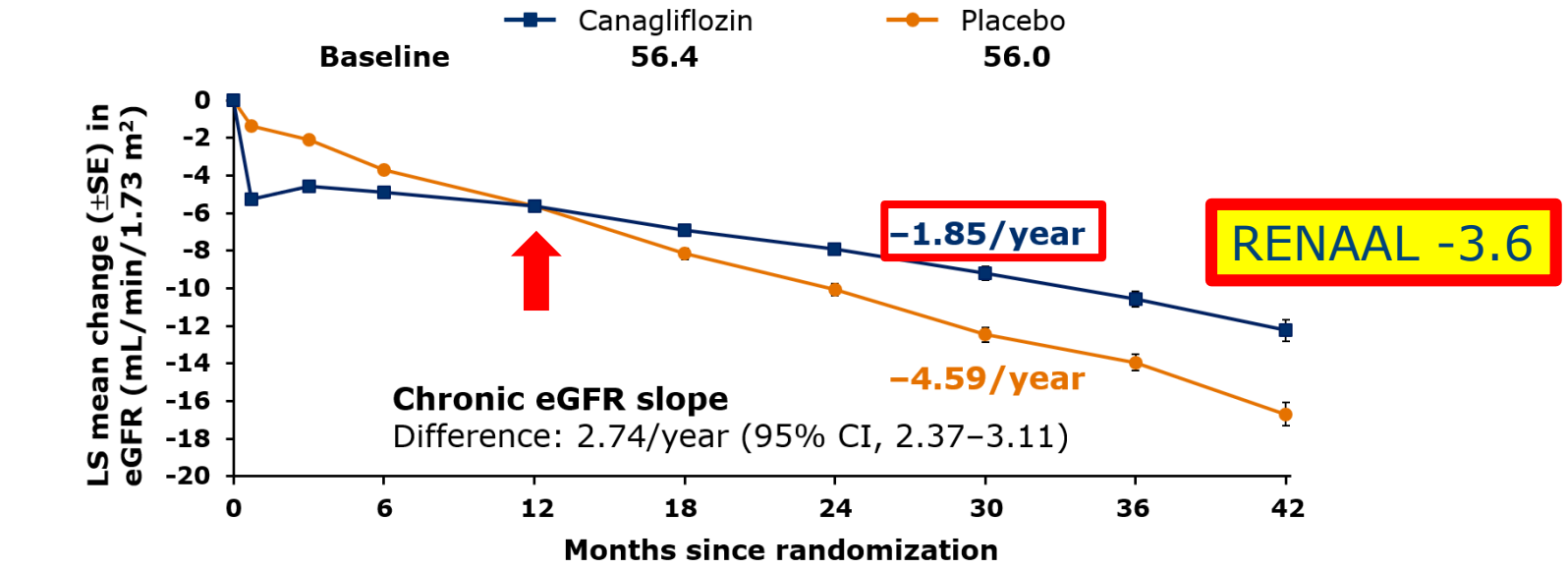


Am J Nephrol. 2018 Jan; 46(6): 462–472.

April 14, 2019 DOI: 10.1056/NEJMoa1811744

Effects on eGFR

60% decline rate



No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

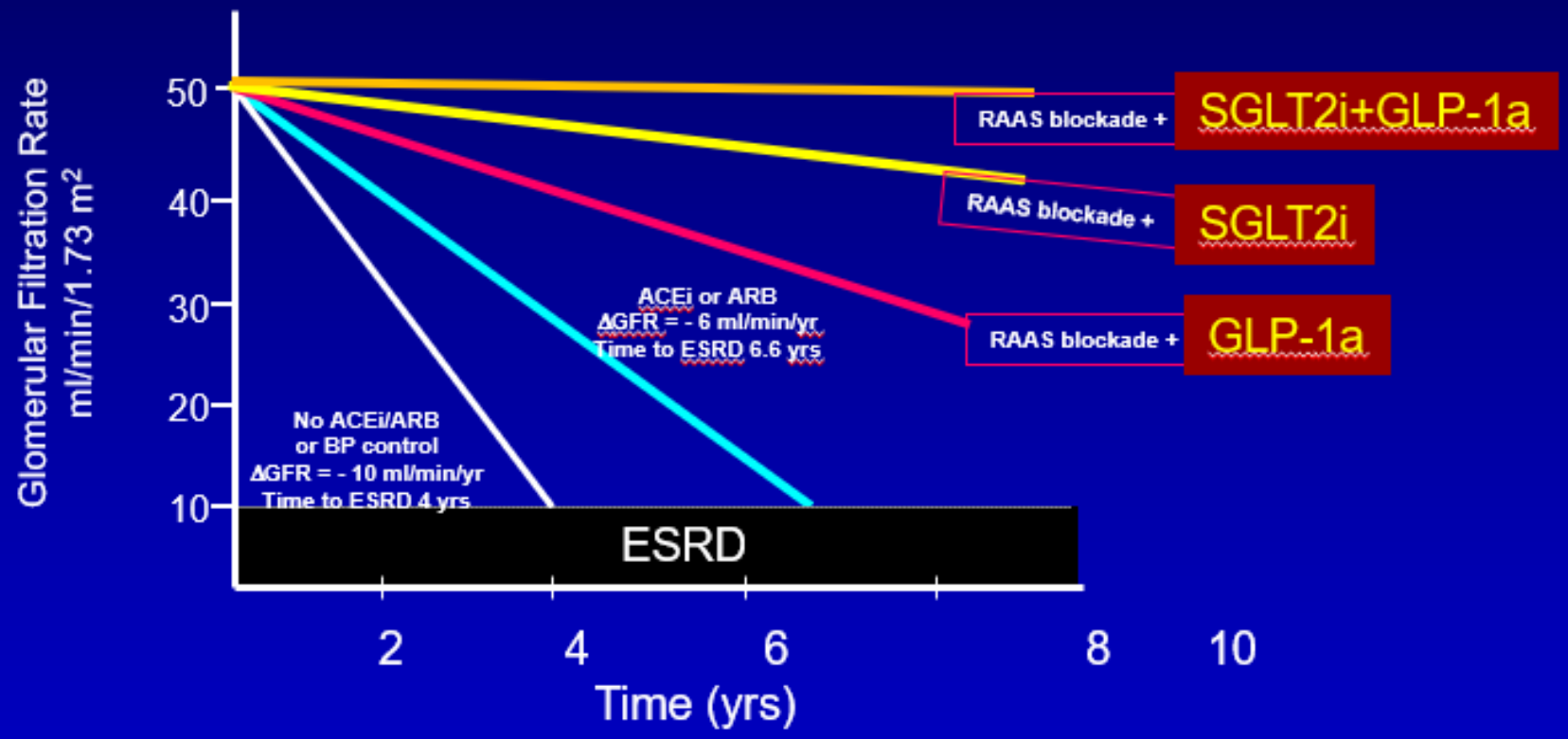
On treatment

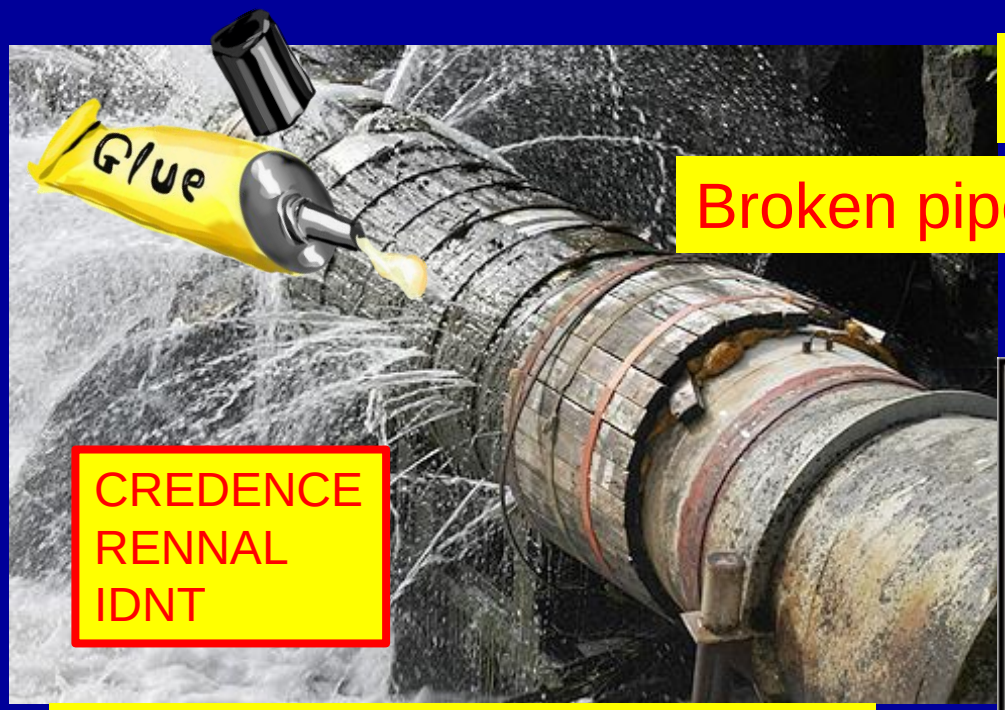
CREDENCE

CREDENCE

TAKE HOME MESSAGES

ACEi- or ARB-Based Regimens for Diabetic Nephropathy Do Not Go Far Enough!





CREDENCE
RENNAL
IDNT

In macroalbuminuria

Broken pipe needs wrench and seal glue!

GLP-1a/DPP4i: seal glue

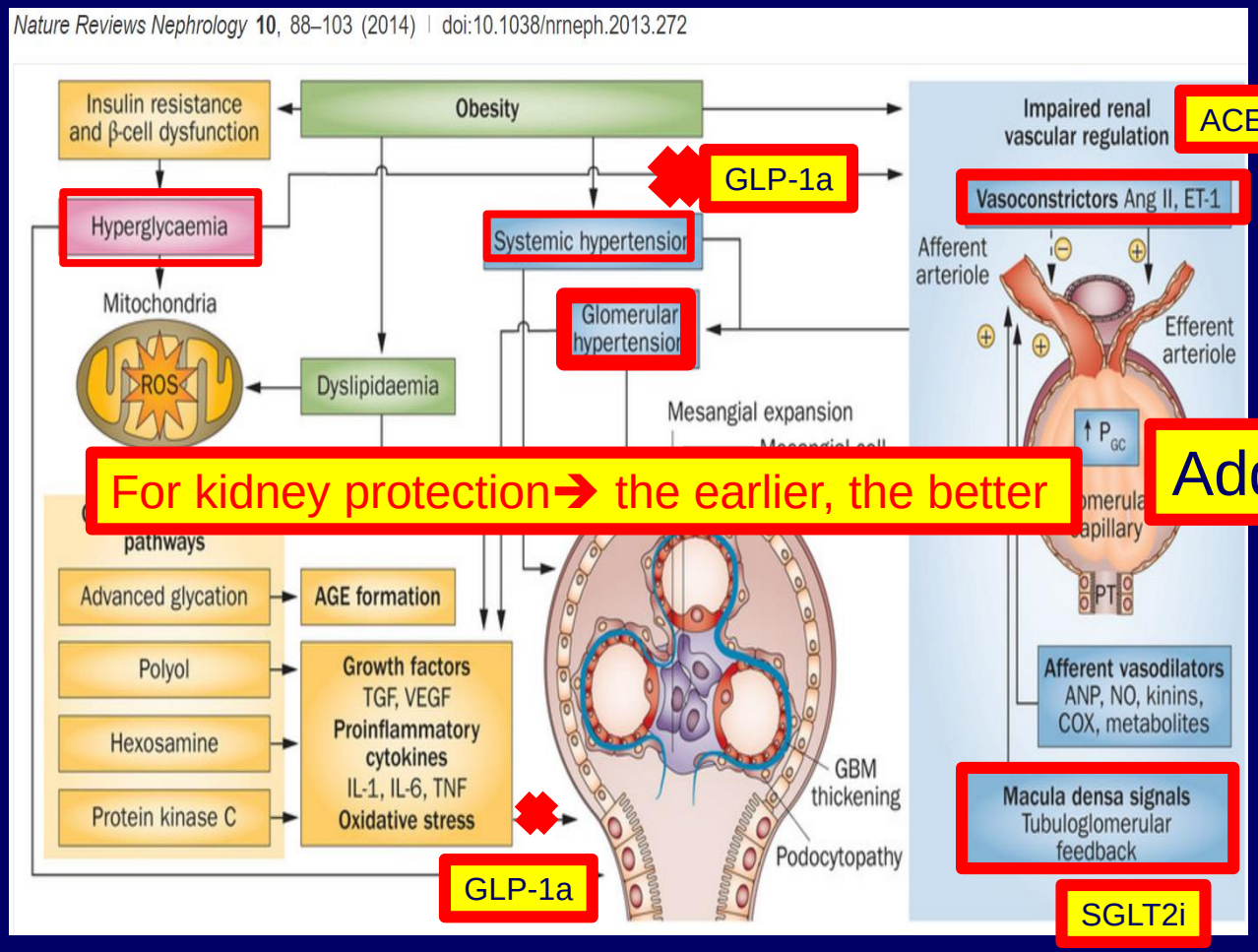
+

SGLT2i+ARB/ACEi: wrench to decrease the flow and pressure

Complementary effect!!

metabolic

Hemodynamic



For kidney protection➔ the earlier, the better

Add GLP-1a??

Thanks!!