Role of DPP4i in Diabetic Kidney: Manage Blood Glucose with Renal Protection and Beta Cell Conservation

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107-04-01

Outlines

- New era in the treatment of T2DM
- Diabetic kidney disease(DKD) and CVD
- Intensive Diabetic treatment: focus on both quantity and quality and the efficacy of DPP4i
- Save Kidneys = Save Lives, A nephrologist's perspective
- Pleiotropic effects

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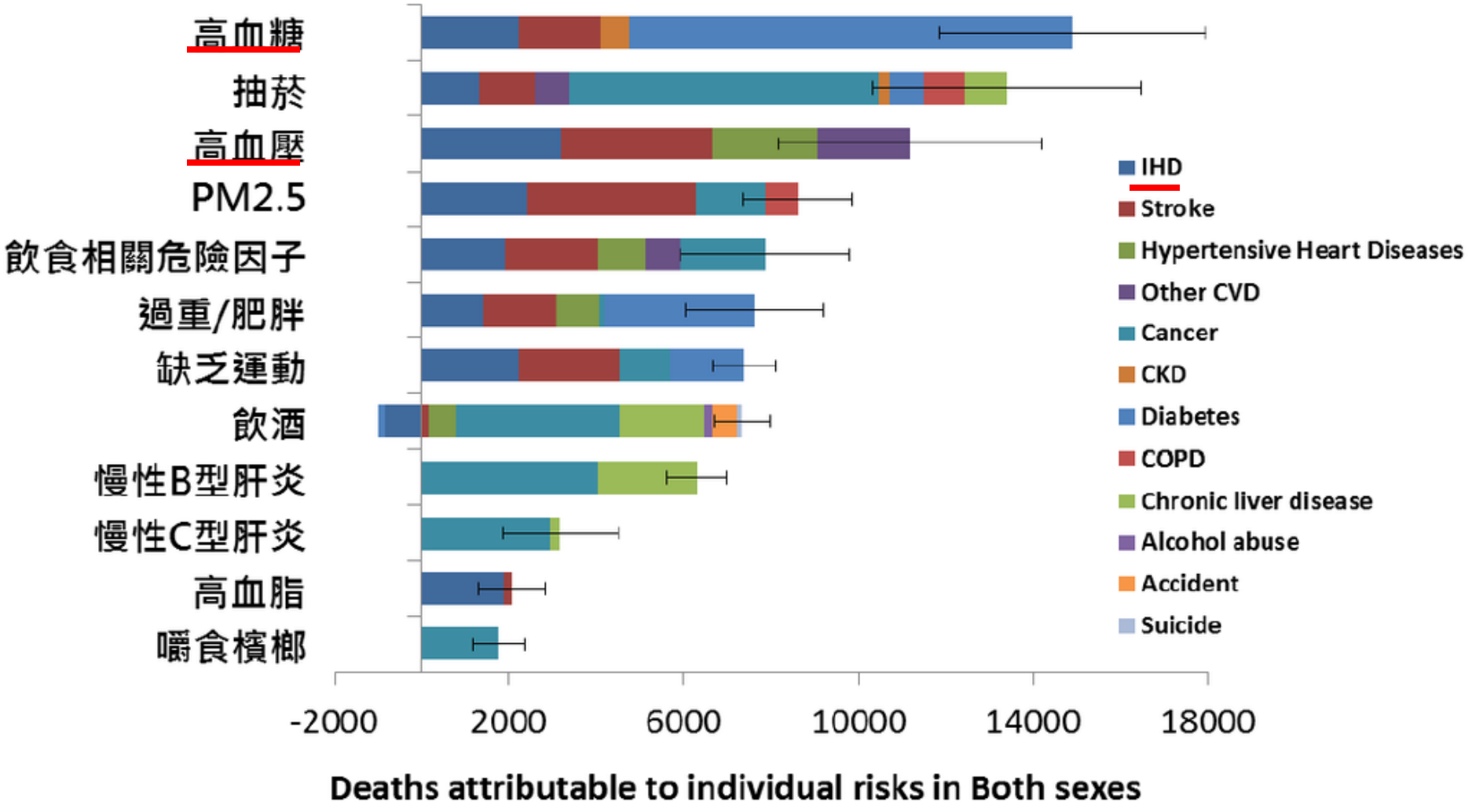
可歸因的死亡人口



Lo et al, PHM 2017

The efficacy of intensive sugar control With SU/insulin therapy

Large Clinical Type 2 Diabetes Trials

	new DM	old DM		
	UKPDS (n=3867)	ADVANCE (n=11,140)	ACCORD (n=10,251)	VADT (n=1,791)
Duration of diabetes	0	8	10	11.5
Mean age (yr)	53	66	62	60
History of CVD	-	32%	34%	40%
Achieved A1c Conventional Intensive	 7.9% 6.2%	 7.3% 6.5%	 7.5% 6.4%	 8.4% 6.9%

Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977. Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545. Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Effects of Intensive Glycemic Control

Study	Microvascular Disease	Macrovascular Disease	Mortality
UKPDS	↓ ↓	↔ ↓	↔ ↓
DCCT/EDIC	↓ ↓	↔ ↓	↔ ↔
ACCORD	? (only retinopathy)	↔	↑
ADVANCE	↓	↔	↔
VADT	↓	↔	↔

↓A1c in 4M:
1.4% in ACCORD
0.6% in ADVANCE

UKPDS. *Lancet* 1998; 352:837-853
UKPDS. *N Engl J Med* 2008; 359:1577-1589
DCCT. *N Engl J Med* 1993; 329: 977-986
DCCT/EDIC. *N Engl J Med* 2005;353:2643-2653
ACCORD. *N Engl J Med* 2008; 358(24):2545-59
ADVANCE. *N Engl J Med* 2008; 358 (24): 2560-72
VADT. *N Engl J Med* 2009;360:129-139

Initial Trial

Long-term Follow-up

Fighting diabetes is a lot like running a marathon: Legacy effect (metabolic memory) matters!!

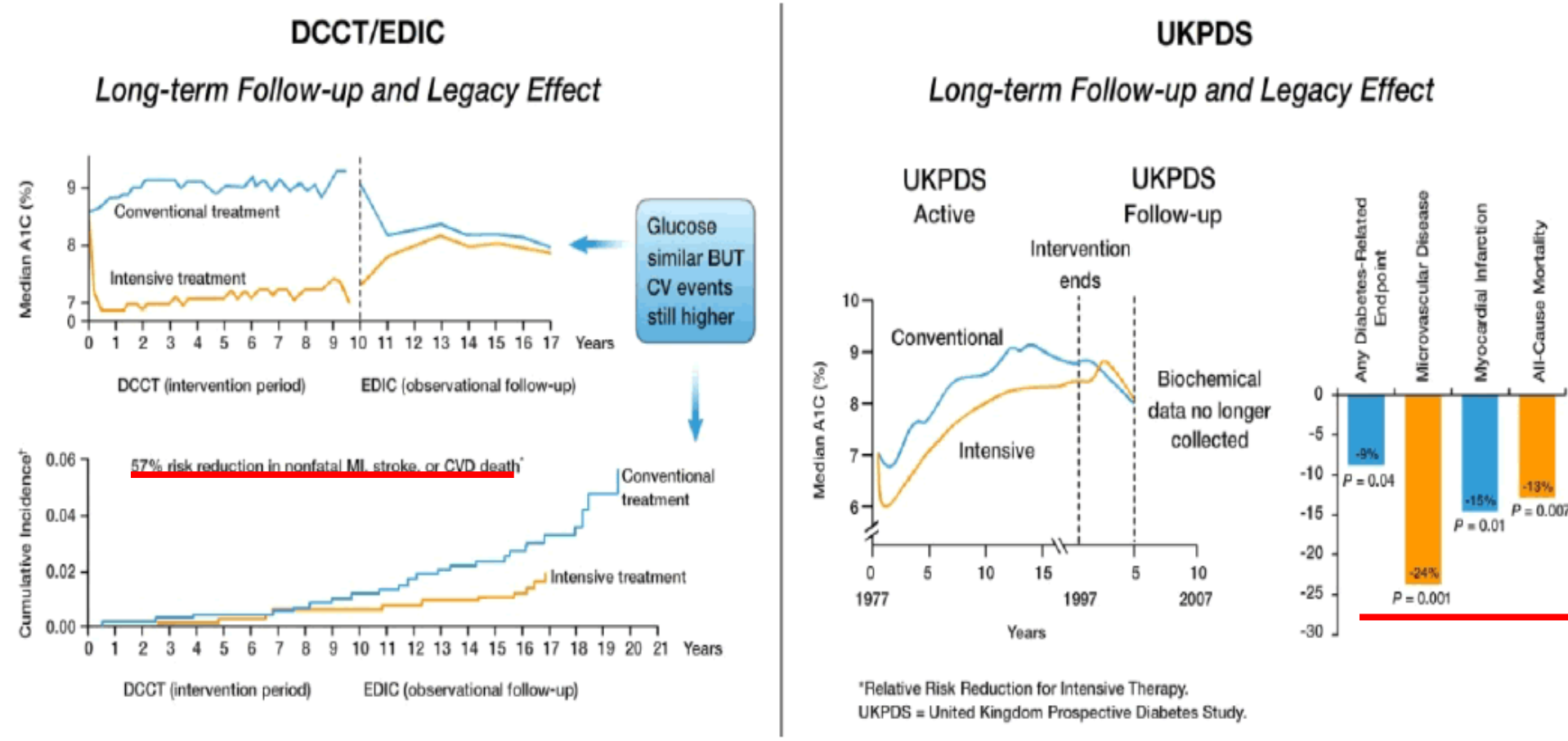
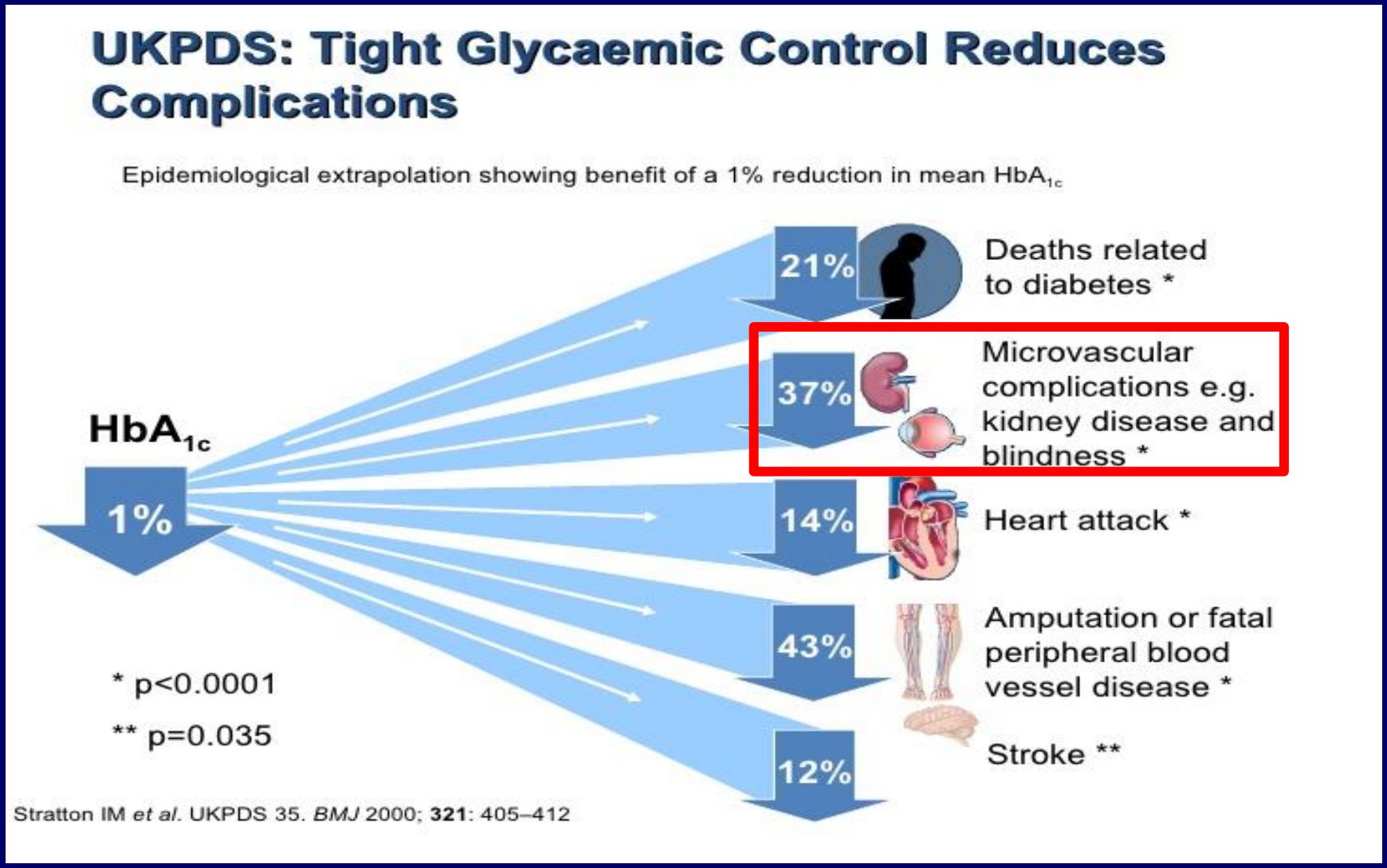


Figure 1: a: DCCT/EDIC Long term follow up and metabolic memory in Type 1 diabetes (T1DM) patients; **b:** UKPDS long term follow up and legacy effect.

N Engl J Med 329: 977-986.

N Engl J Med 353: 2643-2653.

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



Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds ADVANCE trial

Diabetologia (2012) 55:636–643

metabolic memory mattered in old DM !!

Table 2 Unadjusted and adjusted hazards of adverse outcomes associated with a 1% higher mean HbA_{1c} level above and below specified knots

Endpoints	HR (95% CI) per 1% higher mean HbA_{1c} level							
	Knots	Overall population				Intensive glucose control	Standard glucose control	*p* value (intensive vs standard)
		Unadjusted	*p* value	Adjusted[a]	*p* value	Adjusted[a]	Adjusted[a]	
Macrovascular events	Below 7.0	1.07 (0.91, 1.26)	0.4117	1.02 (0.86, 1.21)	0.8310	1.13 (0.89, 1.43)	0.82 (0.65, 1.04)	0.7362
	Above 7.0	1.43 (1.35, 1.51)	<0.0001	1.38 (1.30, 1.47)	<0.0001	1.58 (1.43, 1.75)	1.31 (1.21, 1.42)	0.0974
Microvascular events	Below 6.5	1.06 (0.79, 1.42)	0.7012	1.02 (0.76, 1.39)	0.8744	1.06 (0.69, 1.63)	0.82 (0.54, 1.25)	0.9016
	Above 6.5	1.58 (1.51, 1.65)	<0.0001	1.40 (1.33, 1.47)	<0.0001	1.72 (1.59, 1.87)	1.26 (1.18, 1.35)	<0.0001
All-cause death	Below 7.0	1.04 (0.88, 1.23)	0.6246	1.01 (0.85, 1.21)	0.9158	1.12 (0.87, 1.44)	0.81 (0.64, 1.04)	0.9008
	Above 7.0	1.42 (1.34, 1.51)	<0.0001	1.38 (1.29, 1.48)	<0.0001	1.67 (1.50, 1.86)	1.29 (1.18, 1.41)	0.0080

mean HbA1c of measurements taken at baseline, 6 months and every 12 months for each individual

控制糖尿病像跑馬拉松：一開始就要好好跑。
跑好！ 跑滿！

如果你擁有的是不好的代謝記憶

You definitely need agents more safe and beneficial to control your diabetes.

New era in the treatment of T2DM

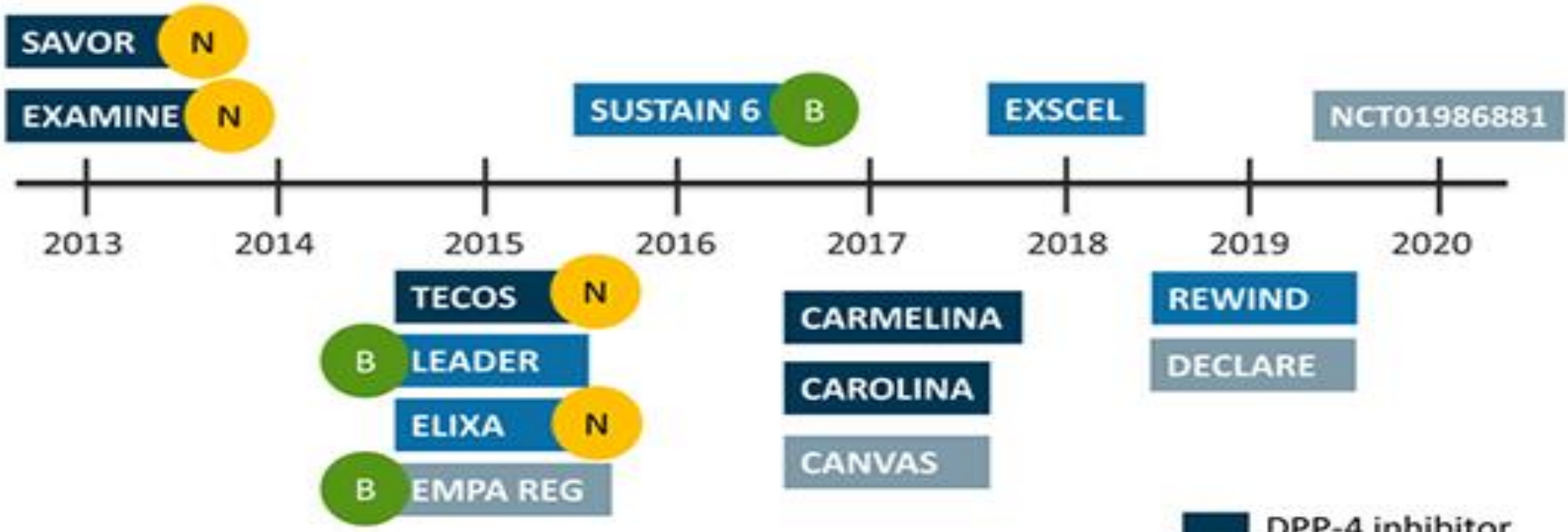
”first, do no harm“

“offer a second chance to improve outcome”

Large CV Outcomes Trials in T2D

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.

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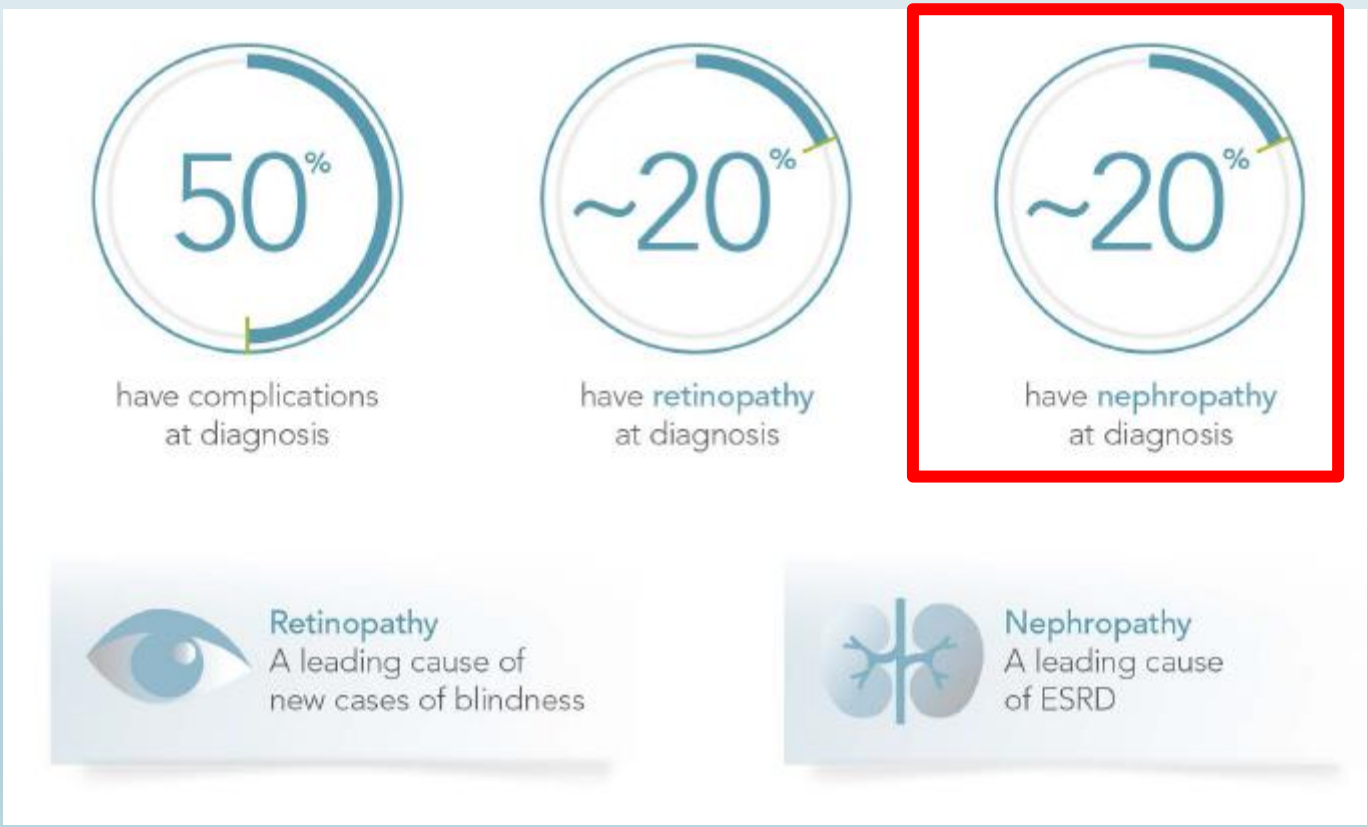
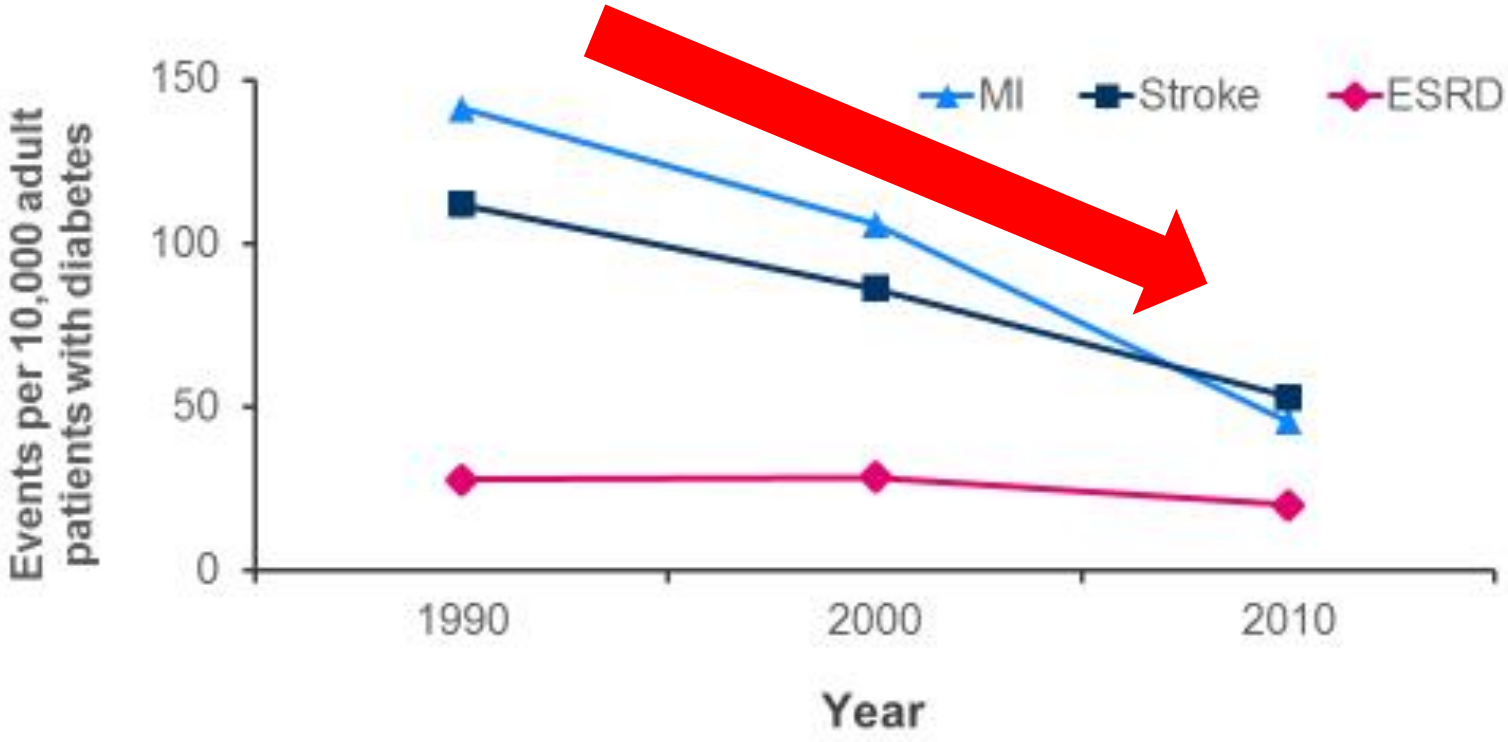
High Percentage of Patients Developed Complications when Diabetes is Diagnosed[BAI05,ALI13]

A high percentage of patients develop micro-vascular complications by the time a diagnosis of type 2 diabetes is made[BAI05,ALI13]



BAI05. Int J Clin Pract, November 2005, 59, 11, 1309–1316.
ALI13. Pak J Med Sci 2013;29(4):899-902.

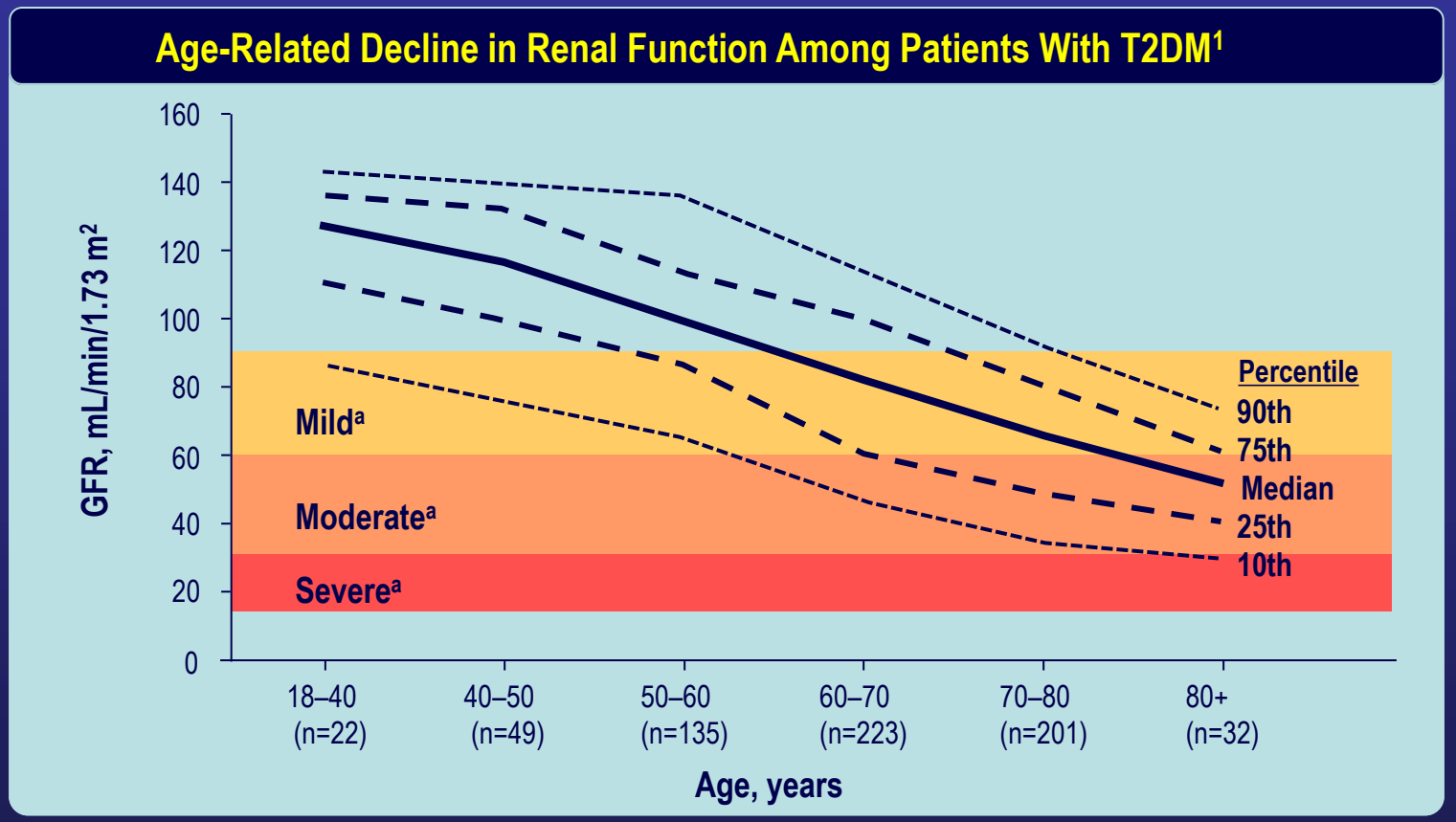
Improved diabetes care has not yet succeeded in reducing renal complications



MI, myocardial infarction

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

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]

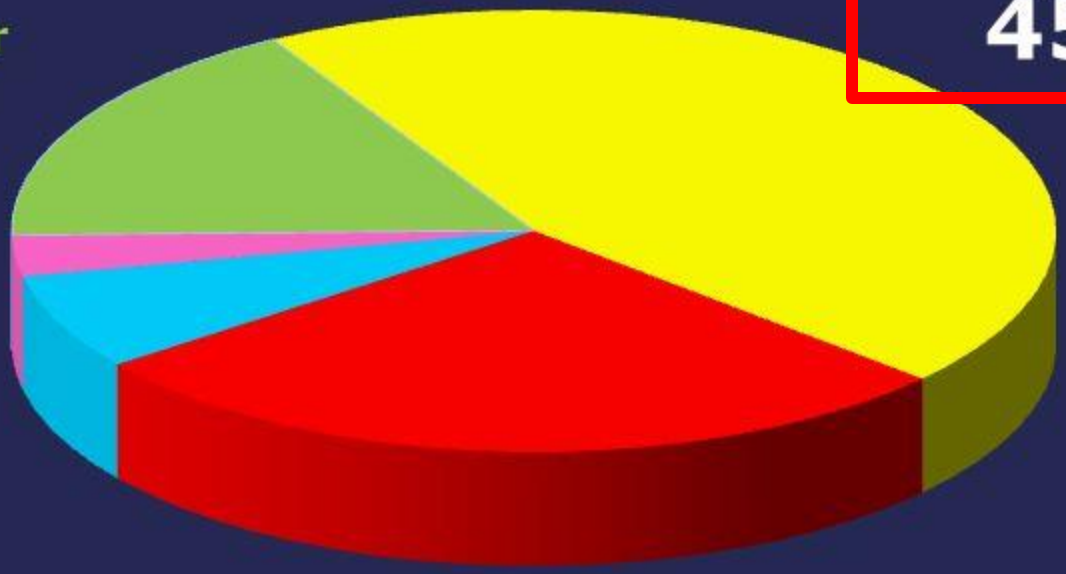
Adapted with permission from Premaratne E et al.[1]

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

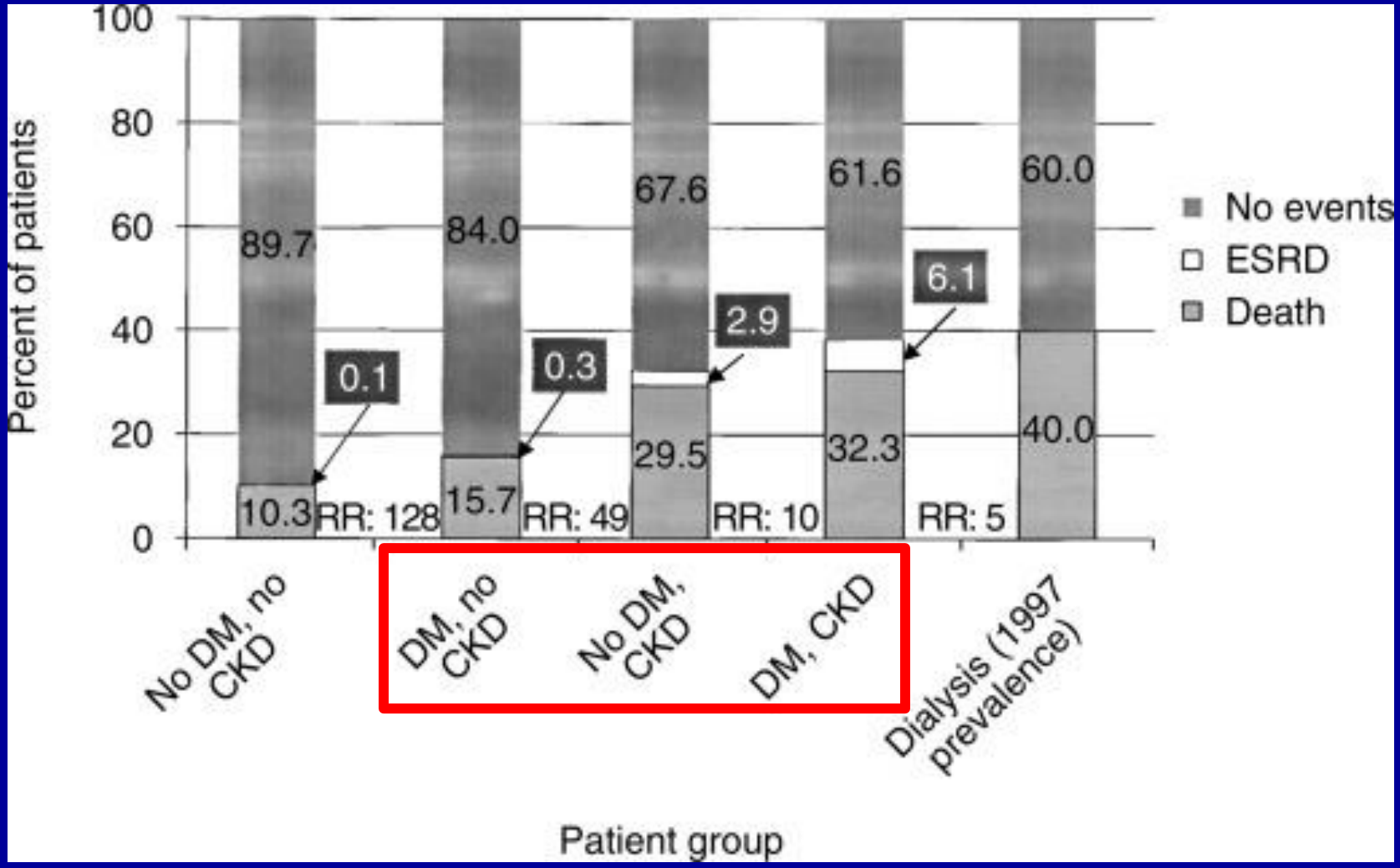
GFR = glomerular filtration rate; T2DM = type 2 diabetes mellitus; eGFR = estimated GFR.

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.

Primary Diagnoses for ALL Patients Who Start Dialysis



USRDS 2010 Annual Data Report



Outcomes during 2-year follow-up(risk of death) ➔ CKD+DM is more risky than DM(~2X for Death and 20X ESRD)

Kidney International, 2003, S24–S31

Patients with CKD should be considered to be in the **highest** risk category, ie, **a CHD risk equivalent**, for risk factor management.

- KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease

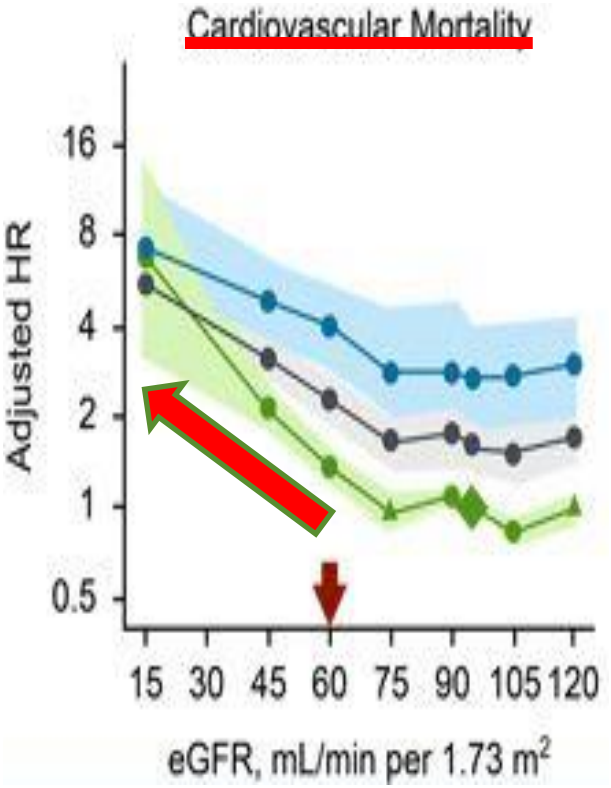
發佈了2017血脂肪控制指引，極高風險族群的LDL竟然要降到…

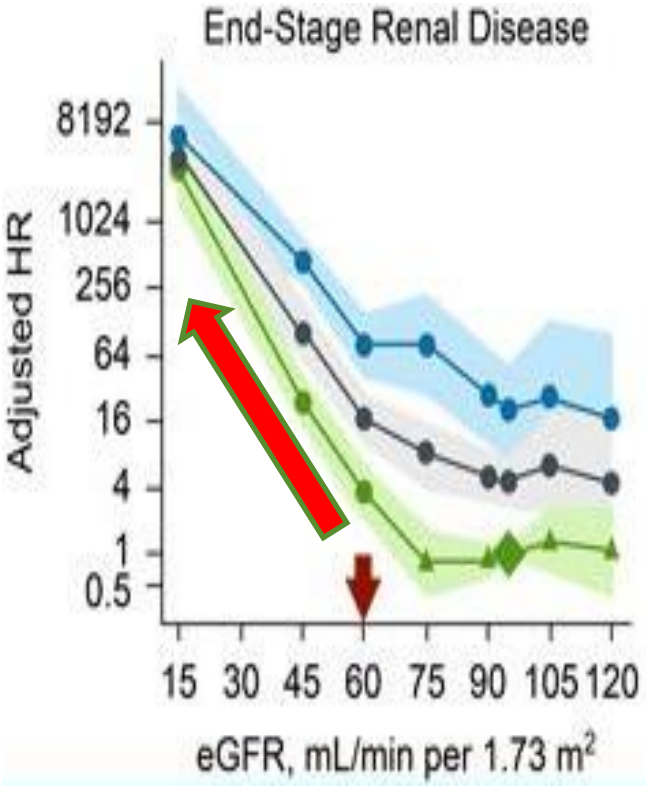
風險	危險因子	LDL	非LDL	Apo B
極高	(1) LDL<70 mg/dL仍發生進展性ASCVD，包括UA (2) DM、第3、4期CKD或家族性高膽固醇＋CVD (3) 早發型ASCVD(♂<55歲 ♀<65歲)	<55	<80	<70
非常高	(1) 確診或最近因ACS、冠狀動脈、頸動脈、或週邊血管疾病住院，10年風險>20% (2) DM、第3、4期CKD合併1個以上危險因子 (3) 家族性高膽固醇	<70	<100	<80

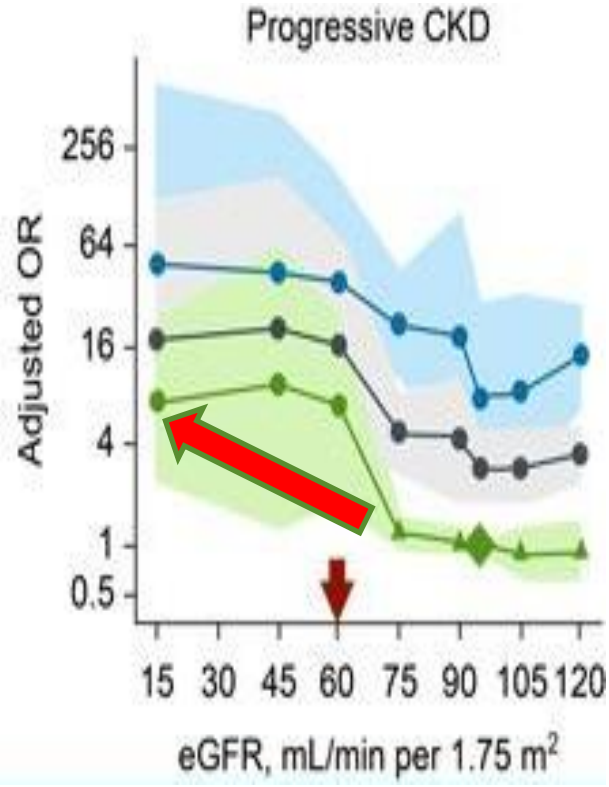
ASCVD = 粥狀動脈心血管疾病、UA = 不穩定性心絞痛、CKD = 慢性腎臟疾病。

資料來源: https://www.aace.com/files/lipid-guidelines.pdf

Accelerated progression of CVD in CKD

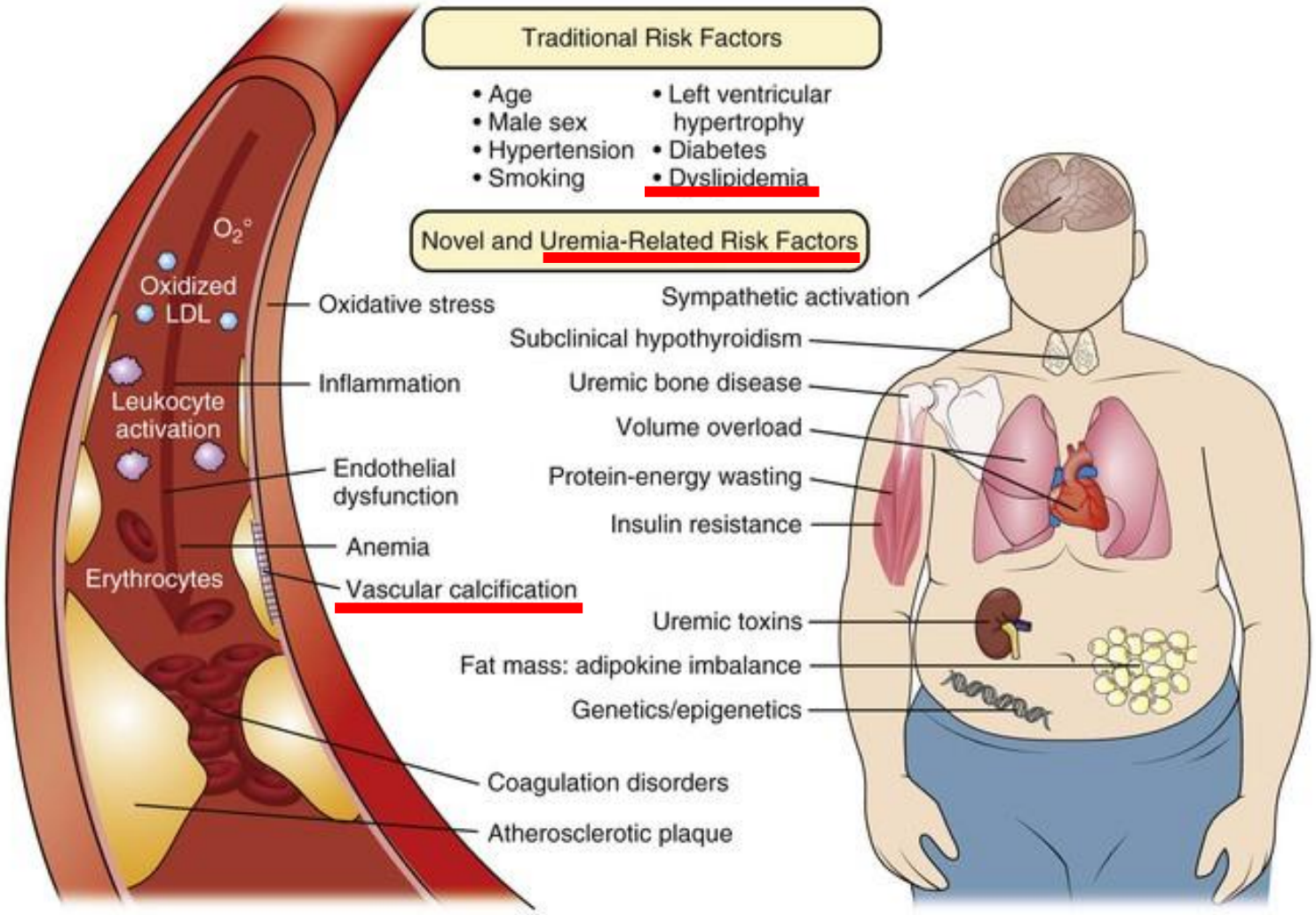






Levey AS, et al. Kidney Int. 2011;80:17-28

Risk Factors for Cardiovascular Disease in Chronic Kidney Disease



Comprehensive Clinical Nephrology

Dyslipidemia in CKD Patients: more atherogenic

Table 1. Effects of renal failure and renal replacement modalities on serum lipids

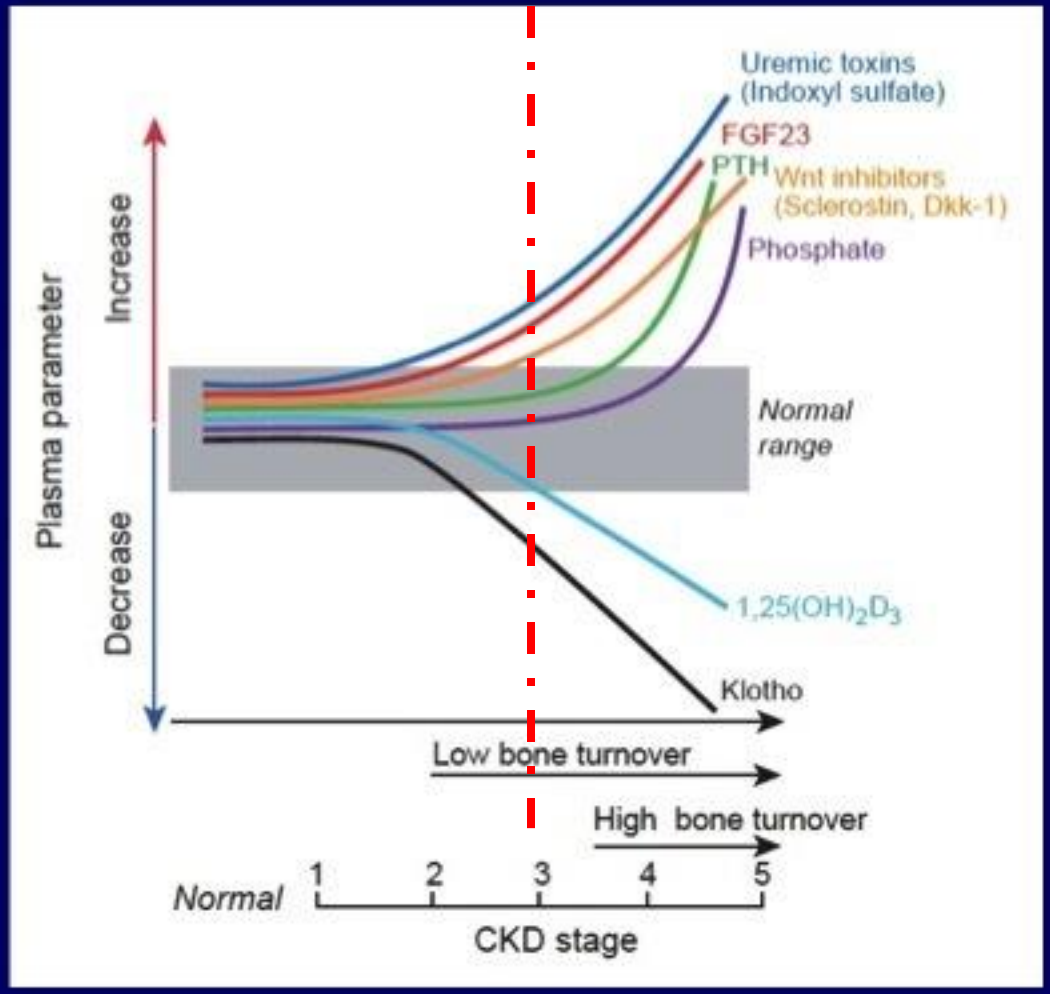
	LDL-C	sdLDL	TRG	HDL-C	Lp(a)
Predialysis CKD	↔ OR ↓	↑	↑	↓	↑[a]
Nephrotic syndrome	↑	↑	↔ OR ↑	↓ OR ↔ OR ↑	↑
Hemodialysis	↔ OR ↓	↑	↑	↓	↑
Peritoneal dialysis	↑	↑	↑	↓	↑
Renal transplantation	↑	↑	↑	↑	↓[a]

CKD = Chronic kidney disease; LDL-C = low-density lipoprotein-cholesterol; sdLDL = small, dense LDL subfractions; TRG = triglycerides; HDL-C = high-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).

↓ = Decrease ; ↑ = increase; ↔ = no change.

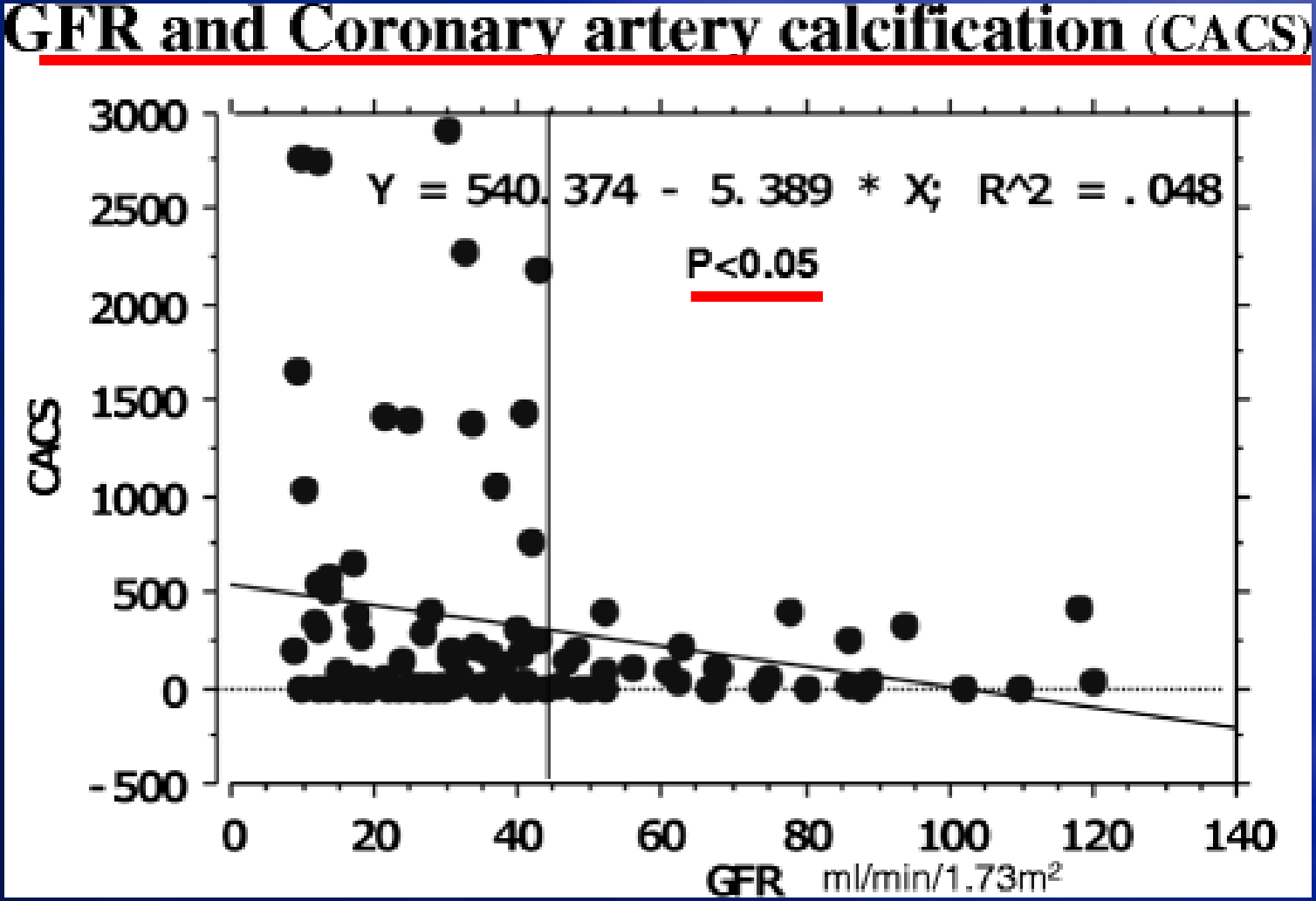
[a] Mainly in individuals with high-molecular-weight apolipoprotein(a) phenotypes.

Time profile of disturbances in mineral hormones and bone turnover with progression of chronic kidney disease

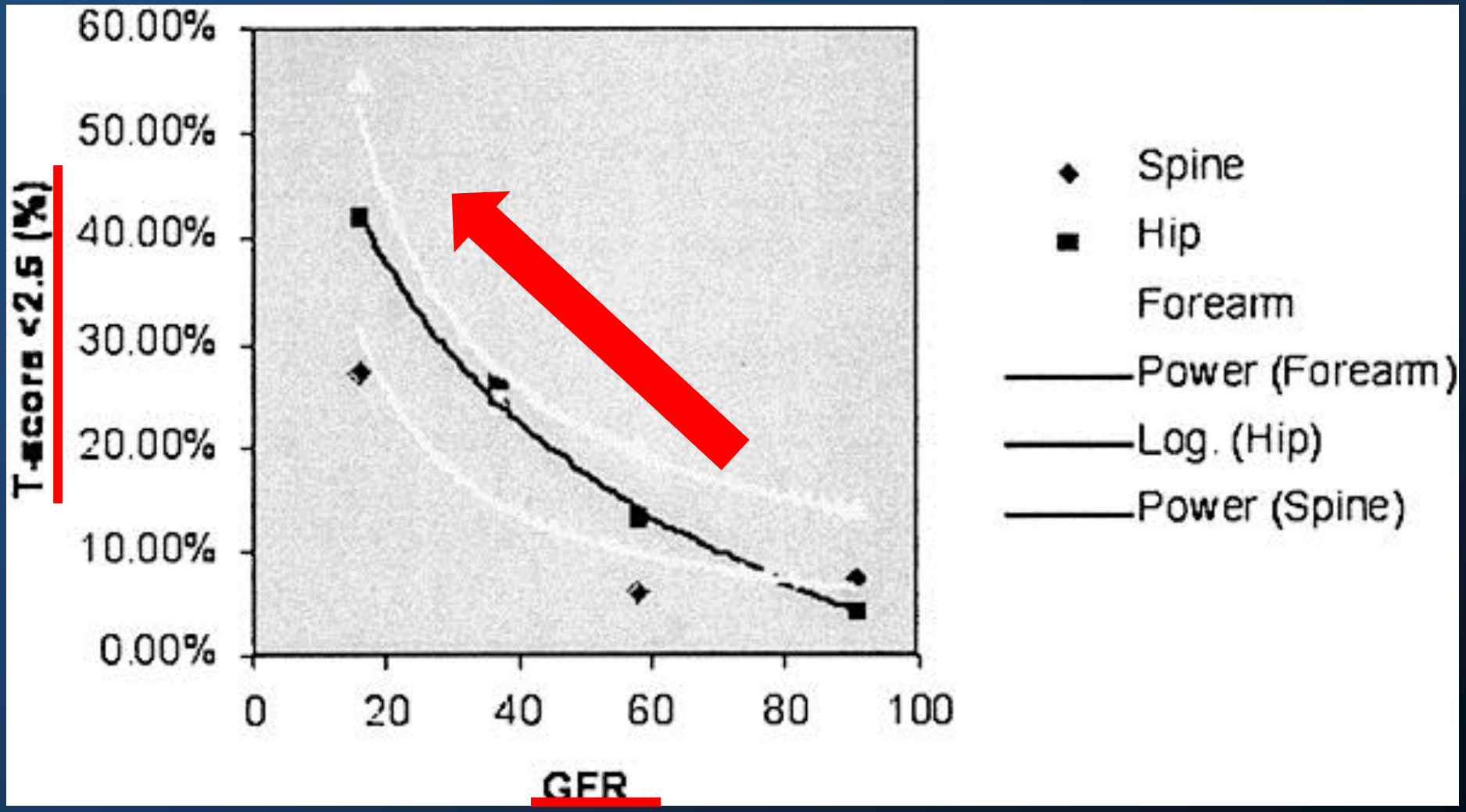


Drüeke TB. Hyperparathyroidism in Chronic Kidney Disease.

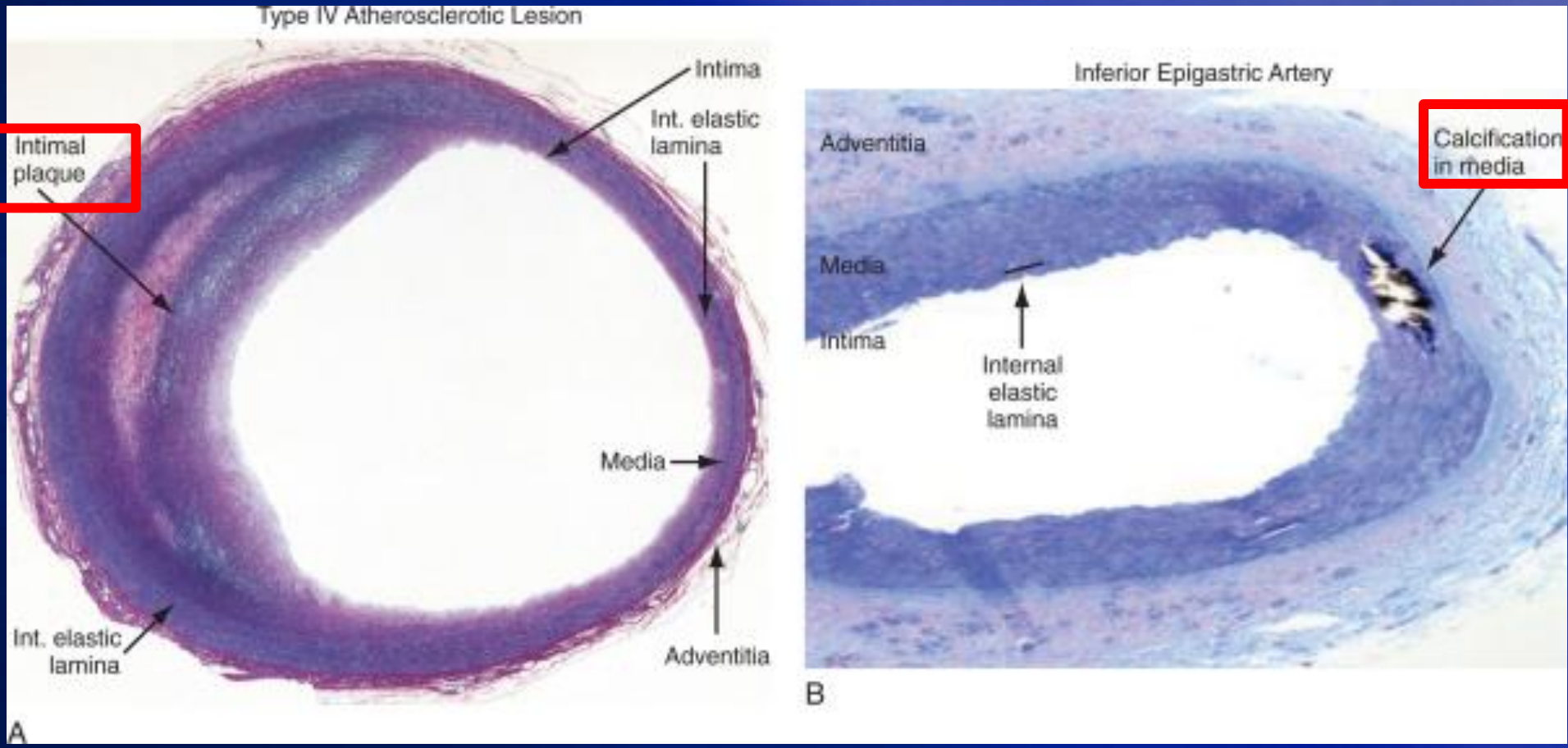
GFR and Coronary artery calcification (CACS)



CJASN. 2008;3:1289–95.



Kidney Int 56:1084-1093, 1999

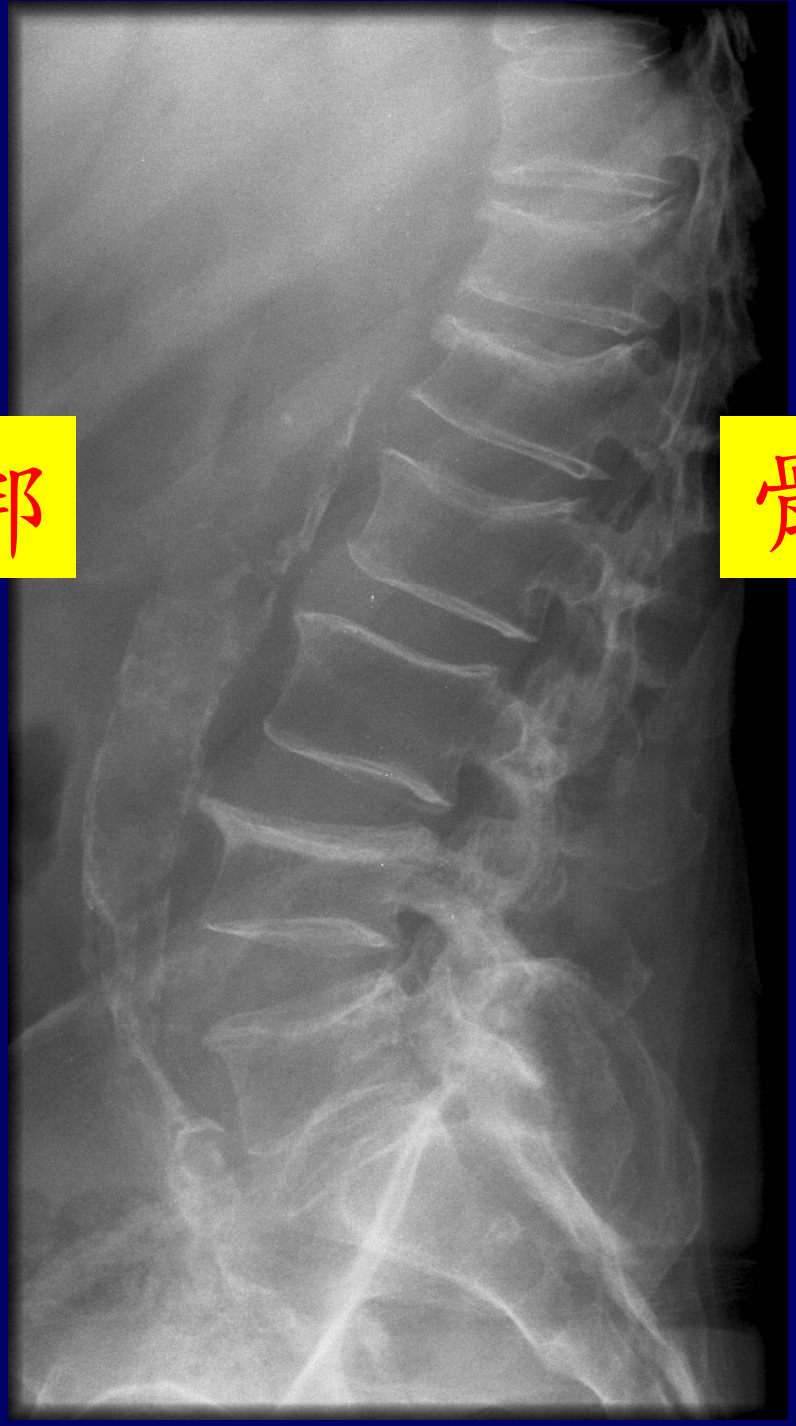


(粥狀動脈硬化)

(動脈硬化/鈣化)

Kidney Int ,2002;61:638–647

血管硬梆梆



骨頭軟趴趴

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Intensive Diabetic treatment should focus on both quantity and quality

Quantity

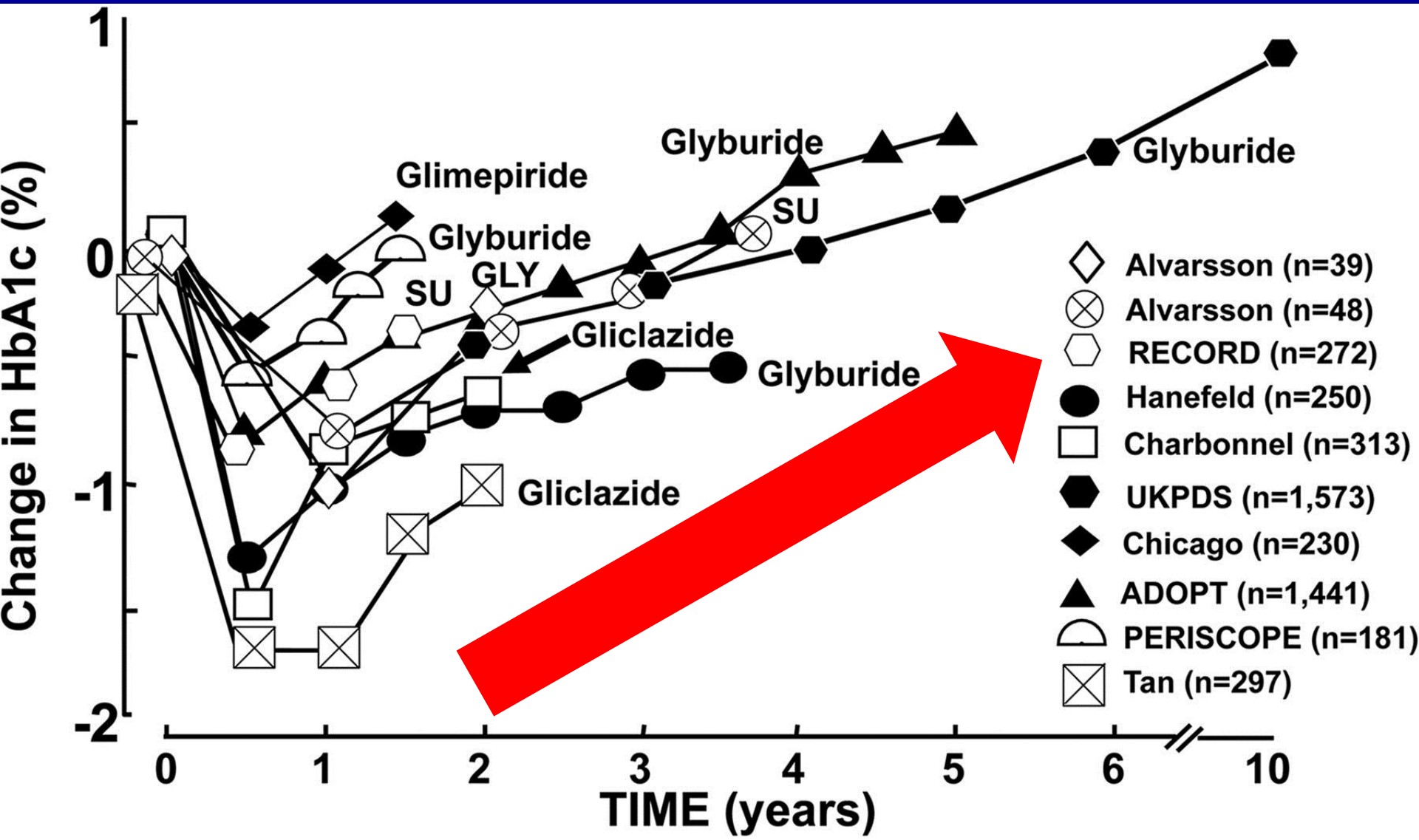
- HbA1c
- FPG
- PPG

Quality

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

Traditional antidiabetic agents:

unsatisfied effects and unmet needs!!

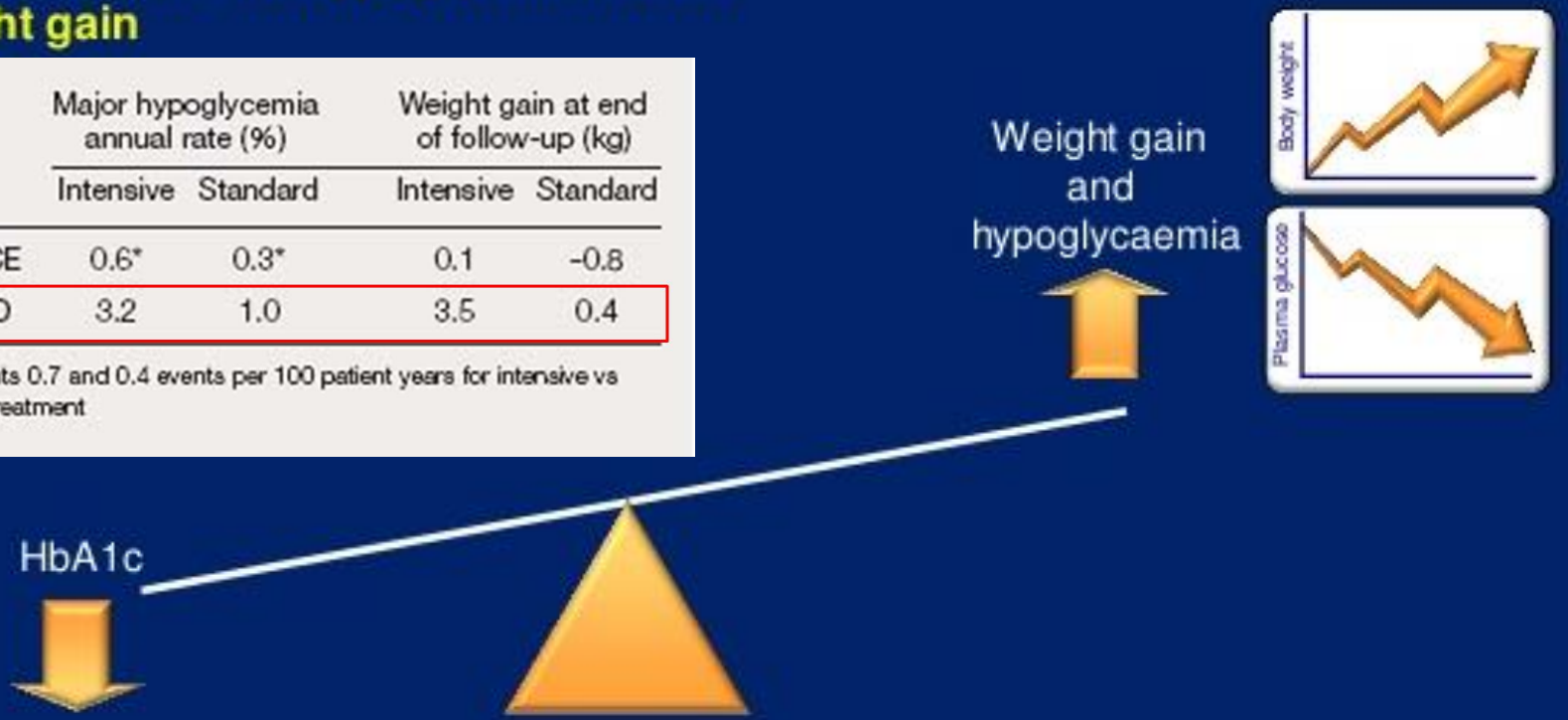


Diabetes 2009 Apr; 58(4): 773-795.

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

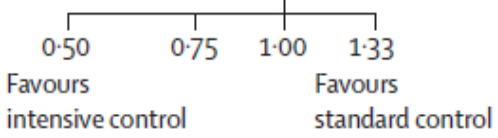


↓A1c in 4M:
1.4% in ACCORD
0.6% in ADVANCE

HbA1c=haemoglobin A1c;
Jacob AN, et al. *Diabetes C*
Kahn SE, et al. *N Engl J Me*
Wright AD, et al. *J Diabetes*

Micro-outcomes in the ACCORD
More renal injury!!

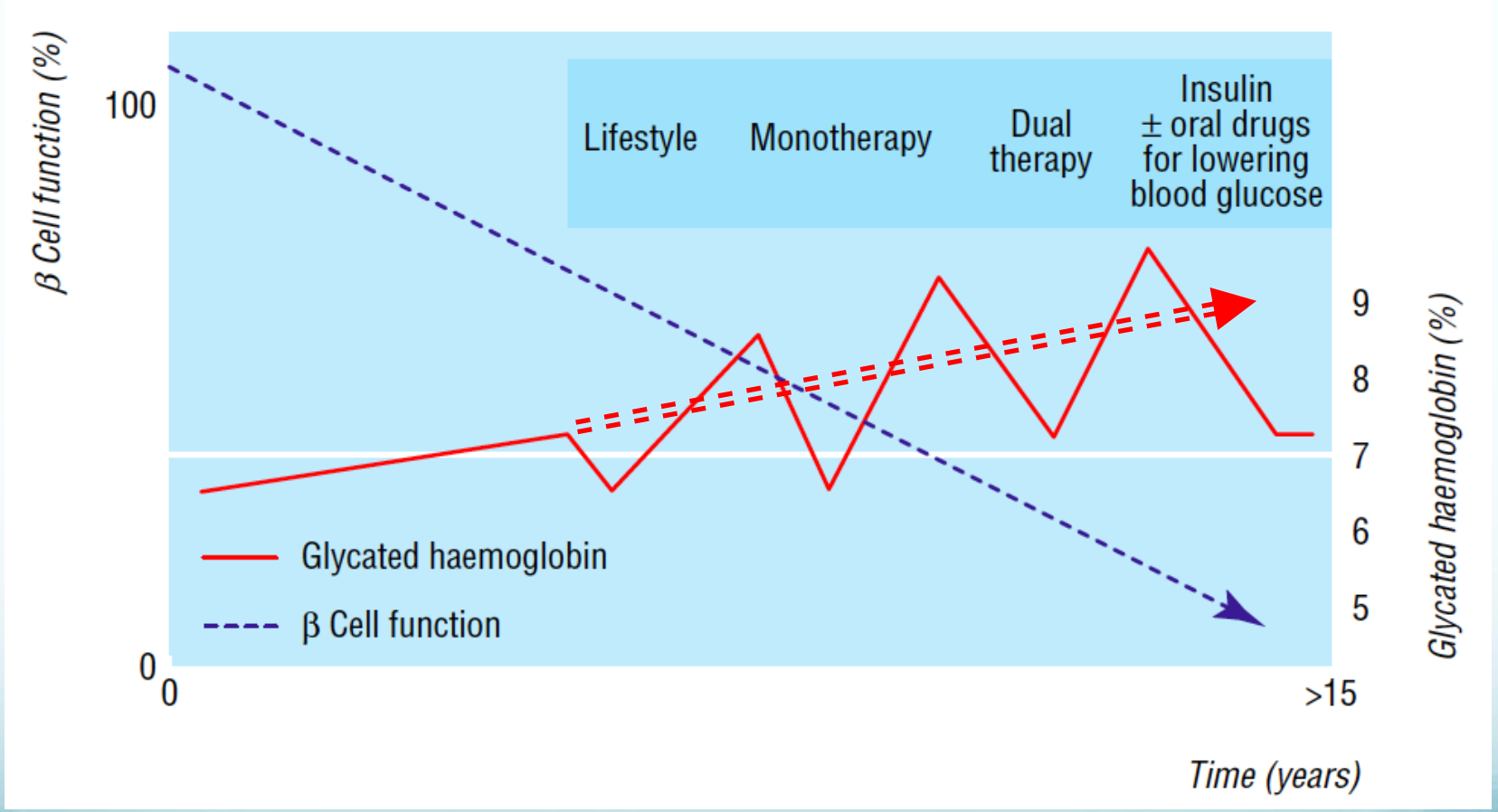
	Glycaemia control				Hazard ratio (95% CI)	p value	NNT
	Intensive		Standard				
	Events/n	%	Events/n	%			
First composite	443/5107	8·7	444/5108	8·7	1·00 (0·88–1·14)	0·9969	
Second composite	1591/5107	31·2	1659/5108	32·5	0·96 (0·89–1·02)	0·1948	
Neph-1: incident microalbuminuria	399/3204	12·5	494/3232	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	447/4886	9·1	495/4910	10·1	0·90 (0·79–1·02)	0·1045	
Eye-3: three-line worsened visual acuity	911/5085	17·9	951/5085	18·7	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



Lancet 2010; 376: 419–30

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

Glycemic variability and mean A1c = Bad metabolic memory!!



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

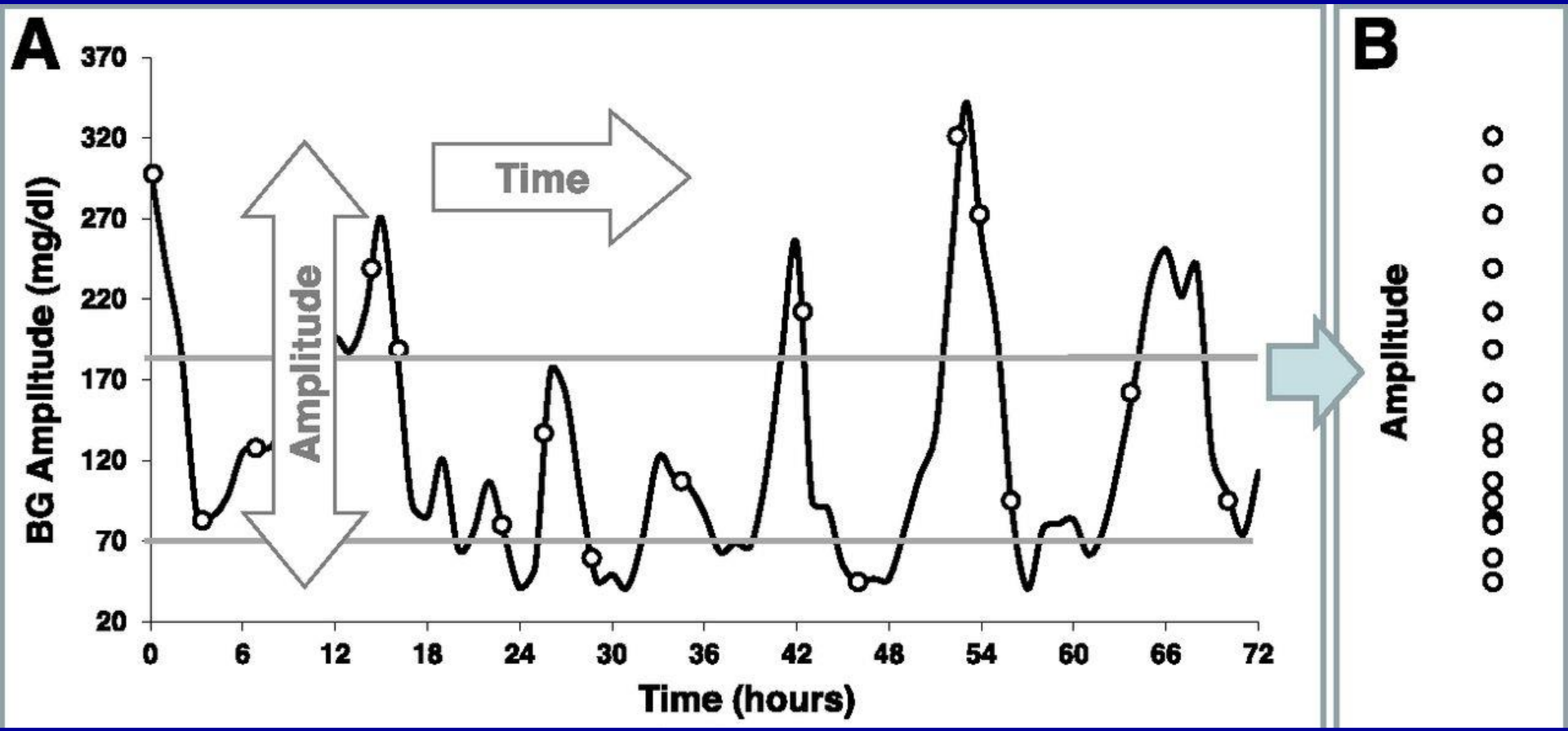
Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis

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.

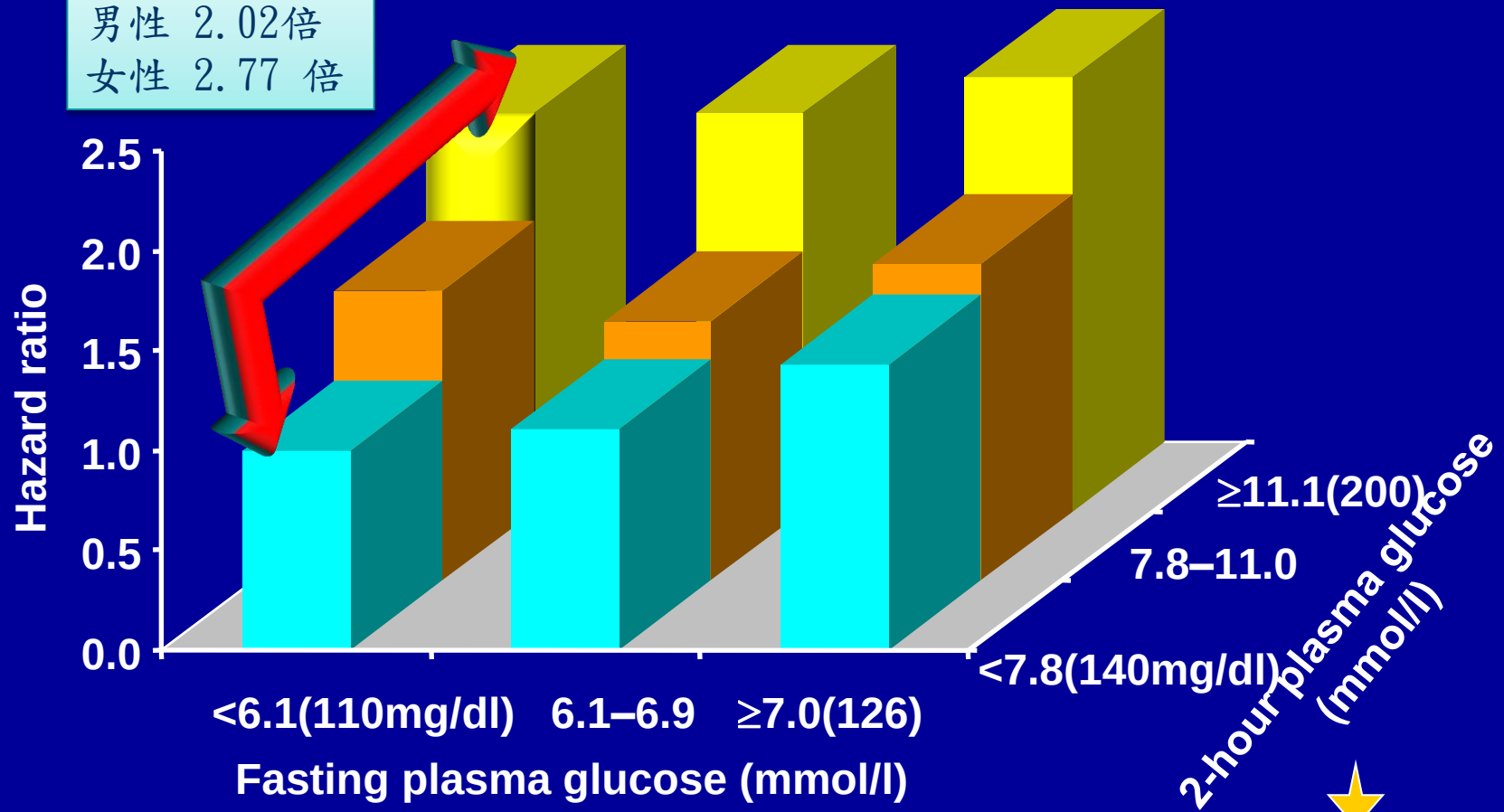
Short term fluctuations in blood glucose concentrations



Relative risk for death increases with 2-hour blood glucose irrespective of the FPG level

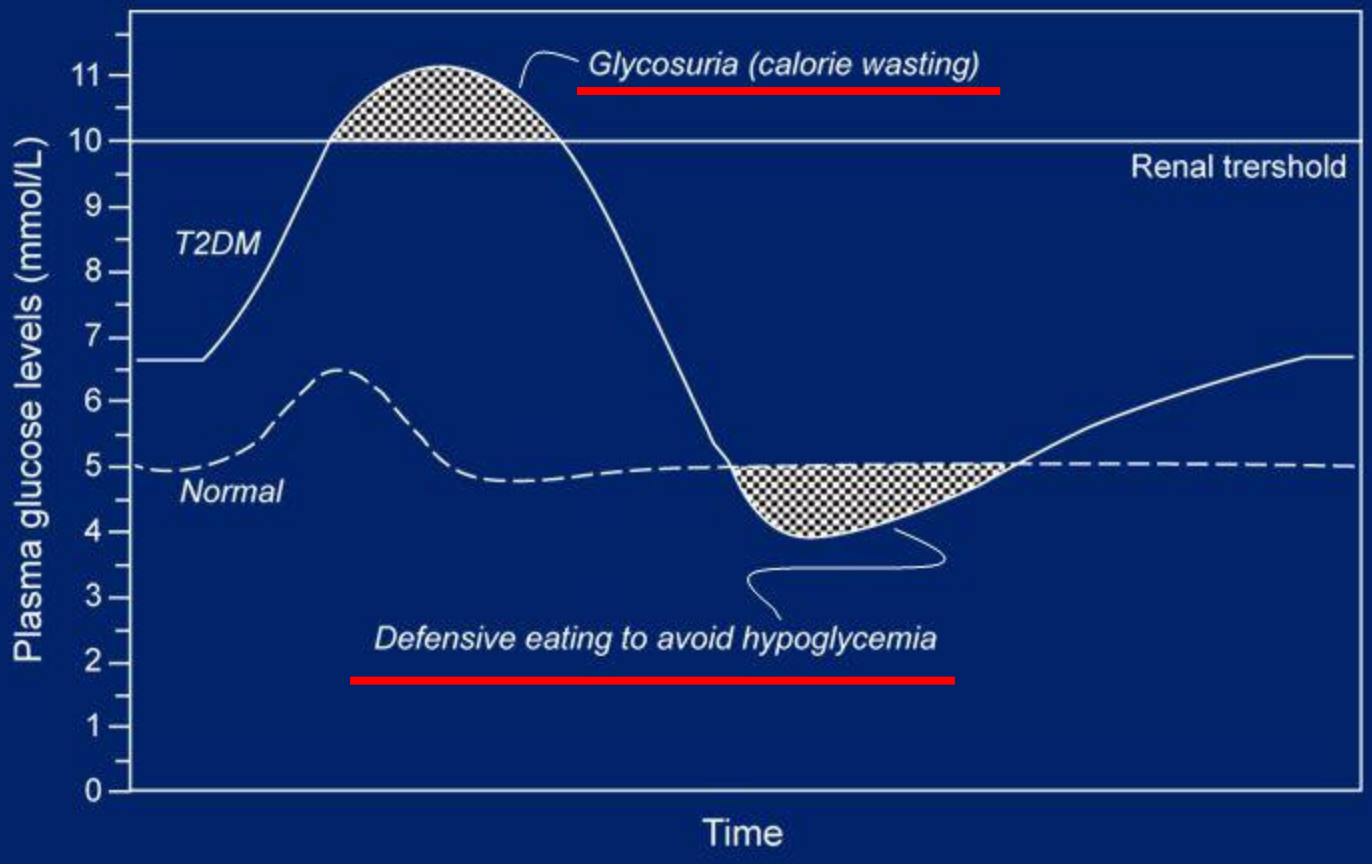
口服 75 克葡萄糖

死亡風險高
男性 2.02倍
女性 2.77 倍



Adjusted for age, center, sex
DECODE Study Group. Lancet 1999;354:617–621

Hypoglycemia and Weight Gain are intertwined



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

Prandial hyperglycemia (glucose fluctuation)

↓

glucosuria (TGF ➔ afferent a. vasodilation)

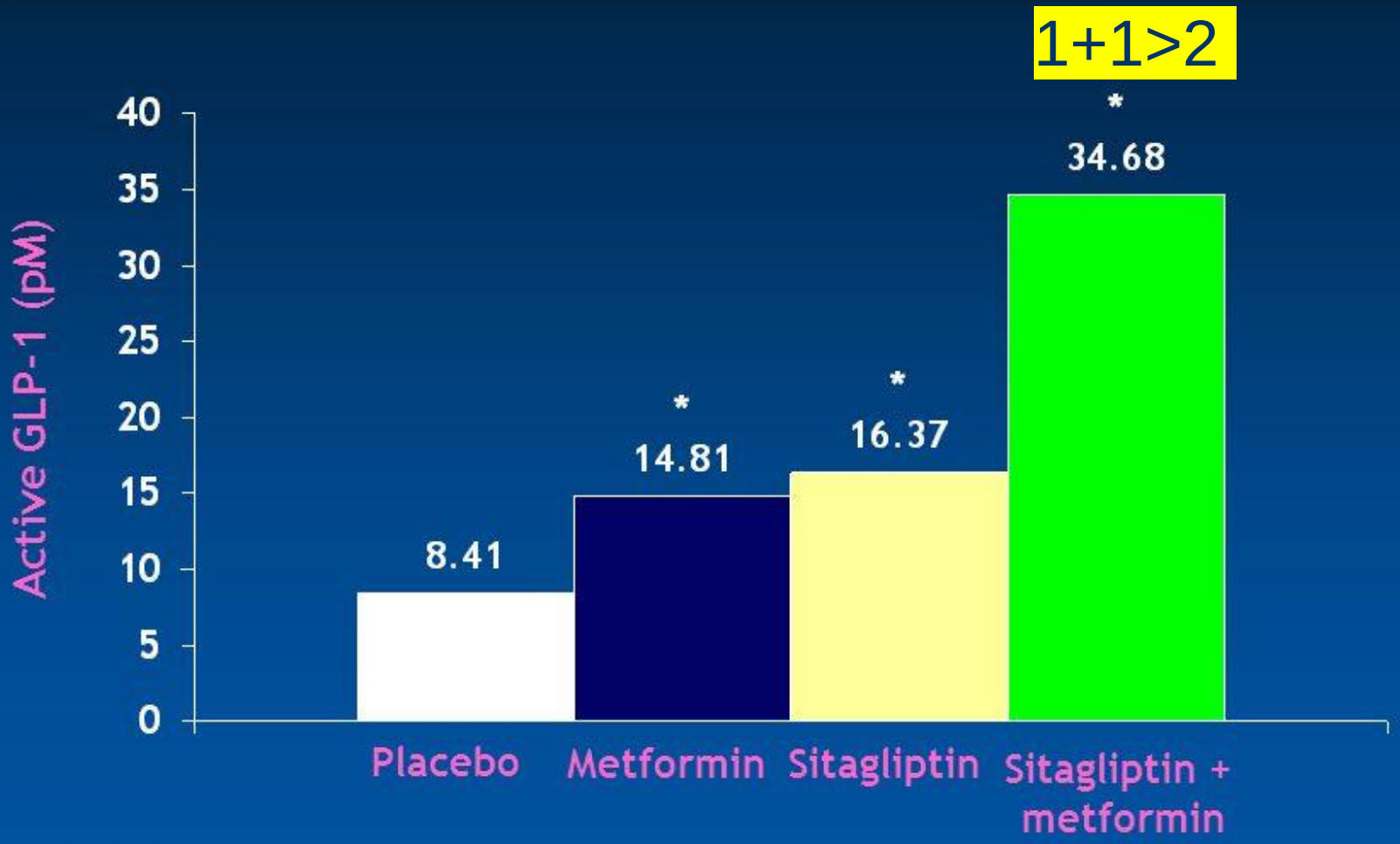
↓

Kidney: Intraglomerular pressure ↑

Outlines

- New era in the treatment of T2DM
- Diabetic kidney disease(DKD) and CVD
- Intensive Diabetic treatment: focus on both quantity and quality
- Efficacy of DPP4i
- Pleiotropic effects of DPP4i on renal protection
- Summary

Complementary Effect of Sitagliptin + Metformin on Active GLP-1



*P<.001 vs placebo.

Migoya EM et al. Presented at 2007 ADA Annual Meeting. Abstract # 286-OR.

The ominous octet

SU
GLP-1Ra

GLP-1Ra

TZD

Existing and Novel Mechanisms to Reduce Hyperglycemia in T2DM[a-d]

Insulin-dependent mechanisms

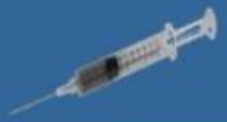
Insulin action
- Thiazolidinediones
- Metformin

Adipose tissue, muscle, and liver

Insulin release
- Sulphonylureas
- GLP-1 RAs*
- DPP-4 inhibitors*
- Meglitinides

Pancreas

Insulin replacement
- Insulin



Insulin-independent mechanism

SGLT2 inhibition

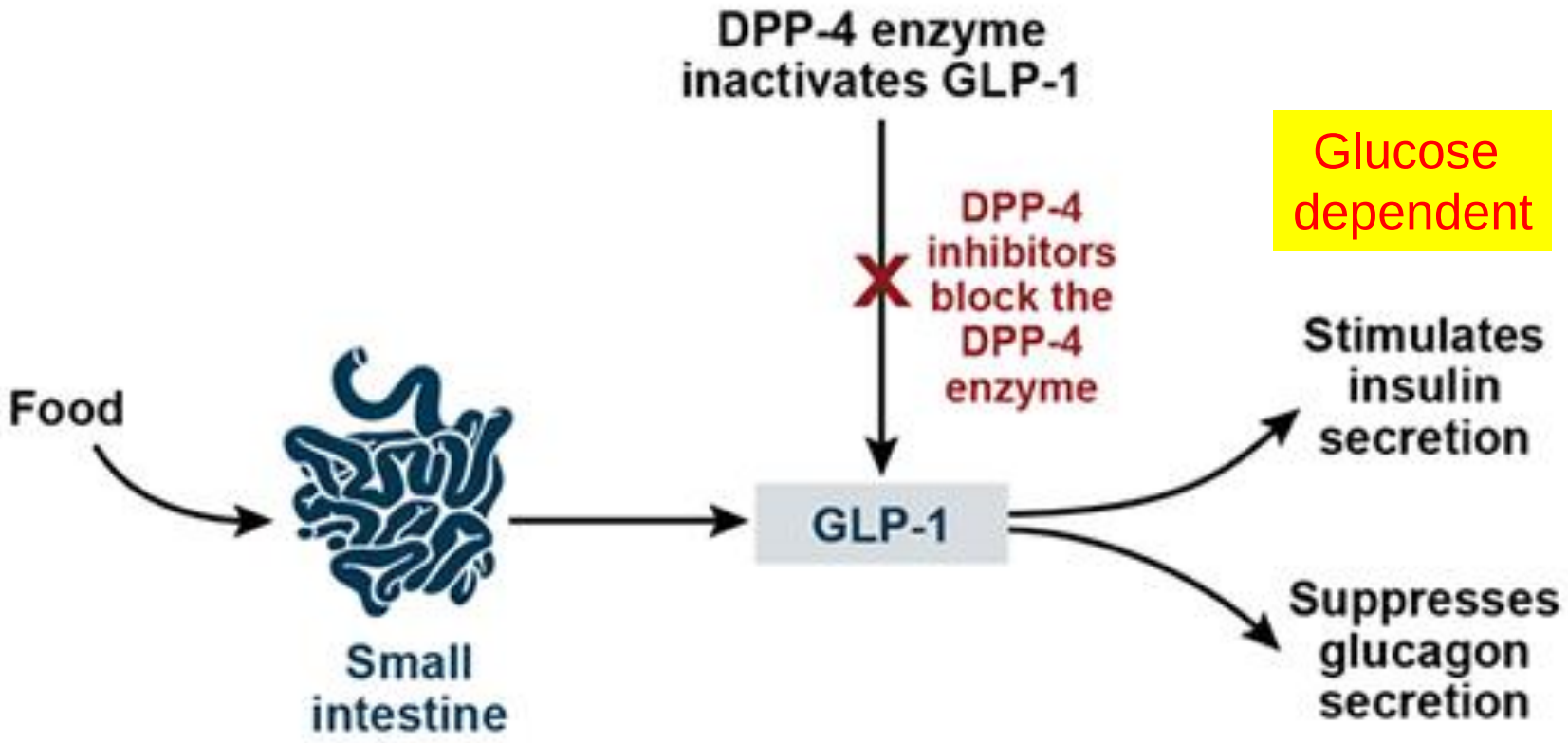
GLP-1Ra
DPP4i

GLP-1Ra

TZD

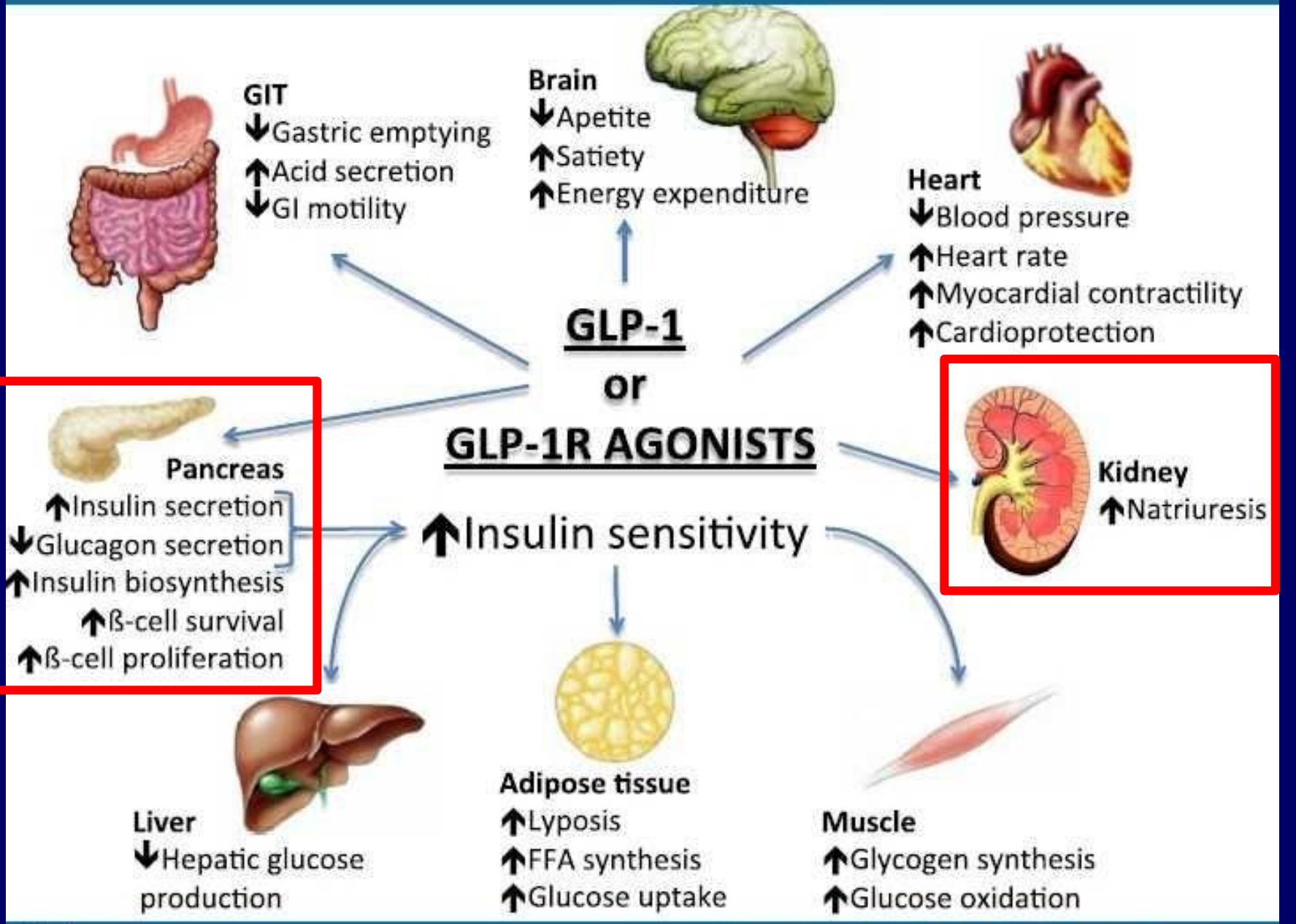
DPP-4-I

Alogliptin, Linagliptin, Saxagliptin, Sitagliptin



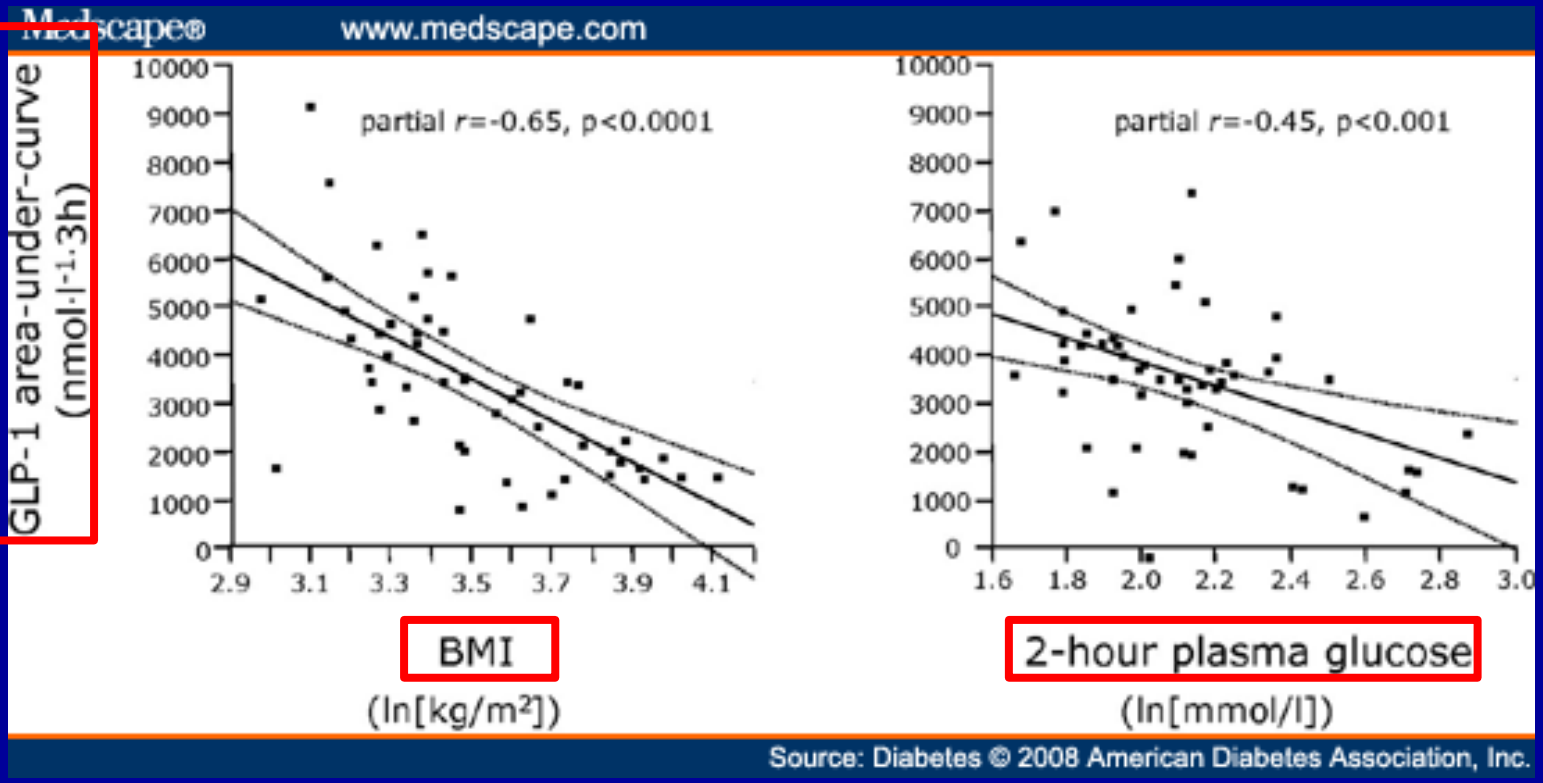
57 Drucker DJ. *Diabetes Care*. 2007;30:1335-1343.

Medscape EDUCATION

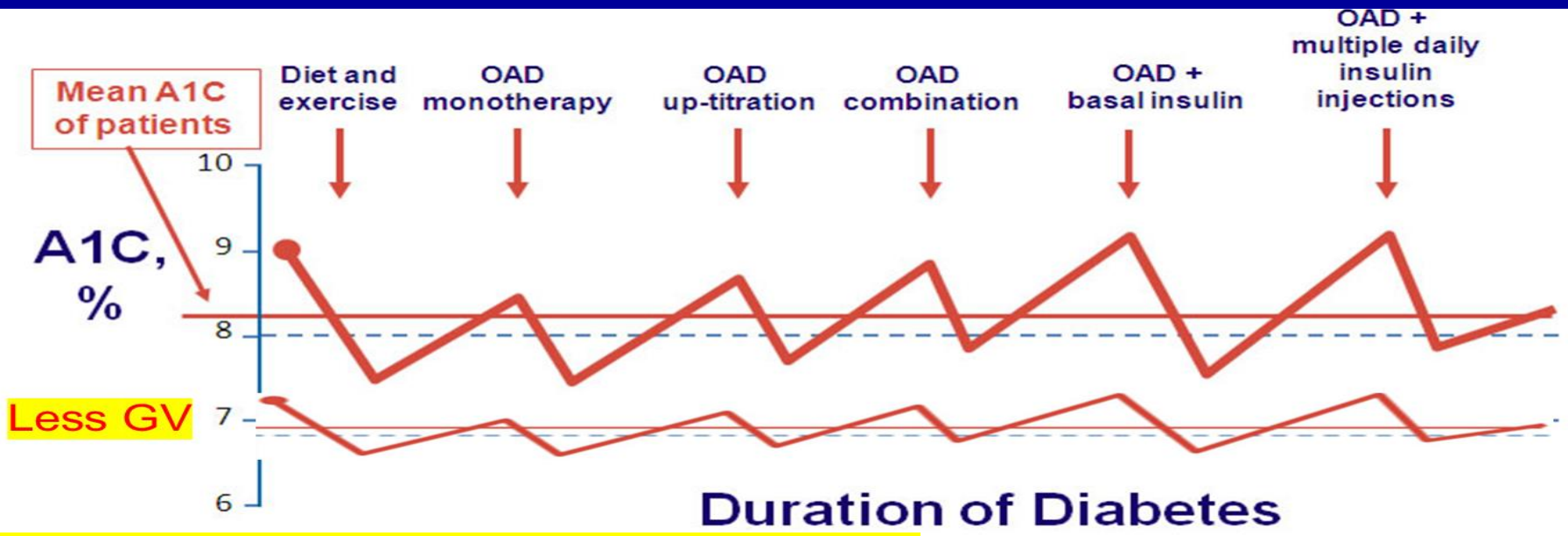


GLP-1

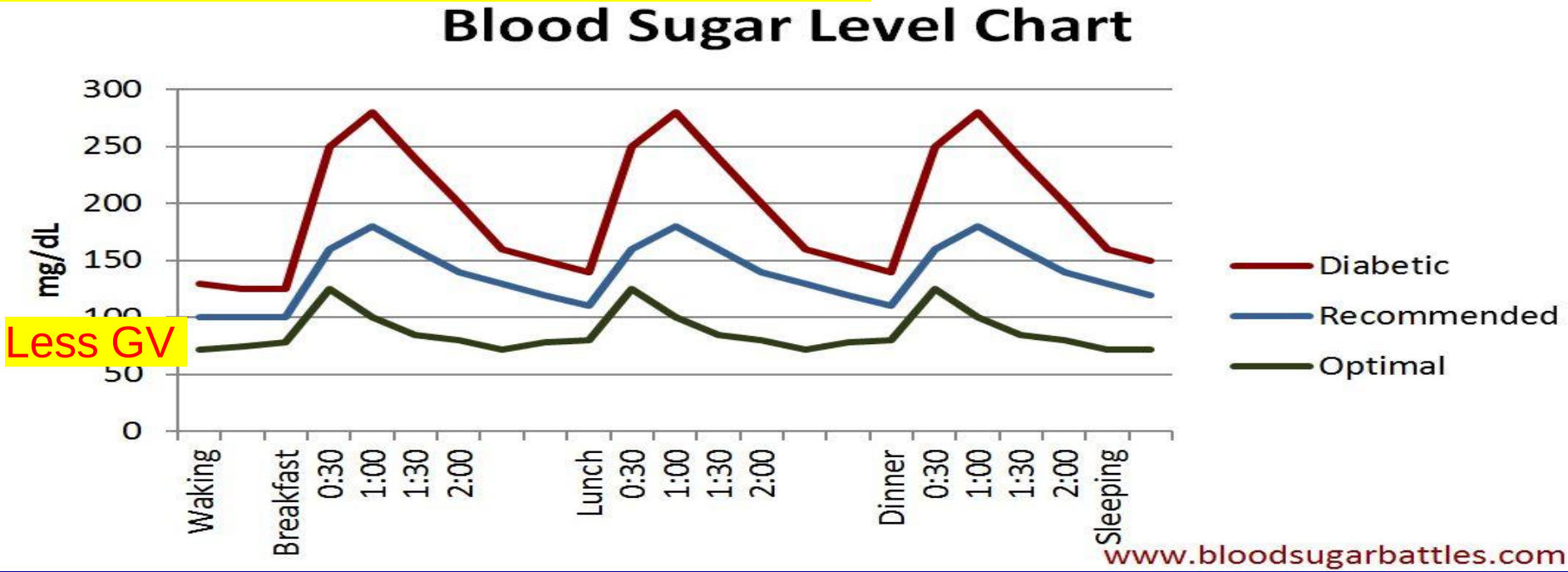
PPG
MAGE
BW



Diabetes. 2008;57(5):1340-1348.

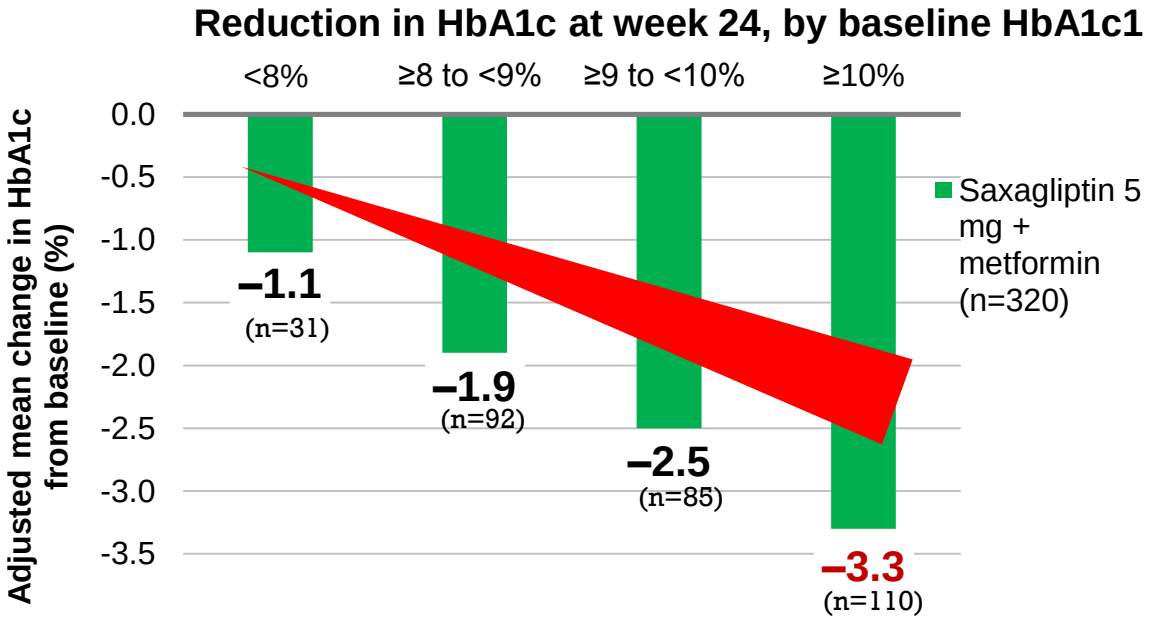


The efficacy of DPP4i in GV?



Onglyza + Metformin Initial Combination: Effective HbA1c Reductions Regardless of Baseline Levels

- Proportion of patients achieving therapeutic glycaemic response (HbA1c <7 or ≤6.5%) significantly greater for saxagliptin + metformin combination versus either monotherapy at 24 weeks
- For all treatment groups, greatest HbA1c reductions in patients with highest baseline HbA1c levels

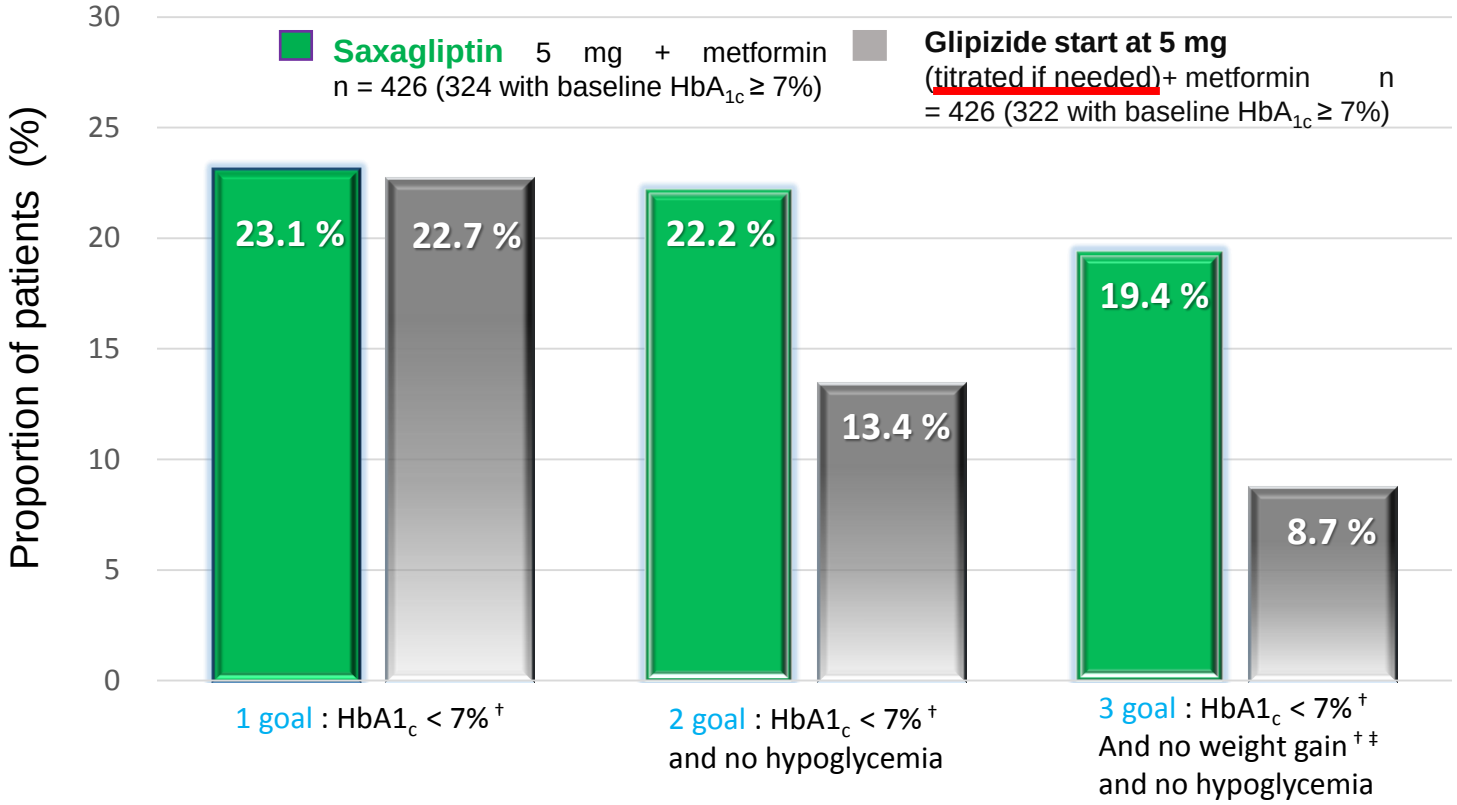


Phase III, 24-week, multicentre, multi-national, randomised, double-blind, active-controlled trial (N=1306) to evaluate the efficacy and safety of saxagliptin plus immediate-release metformin, compared with saxagliptin or metformin monotherapy in treatment-naive adult patients with Type 2 diabetes and high baseline HbA_{1c} (≥8 and ≤12%).[1] Metformin dose was uptitrated from a starting dose of 1000 mg/day to a maximum dose of 2000 mg/day by week 5. Metformin monotherapy HbA_{1c} reduction from baseline in subgroup with HbA_{1c} ≥10%: -2.7%.

1. Jadzinsky M, *et al. Diabetes Obes Metab* 2009;**11**:611–22.

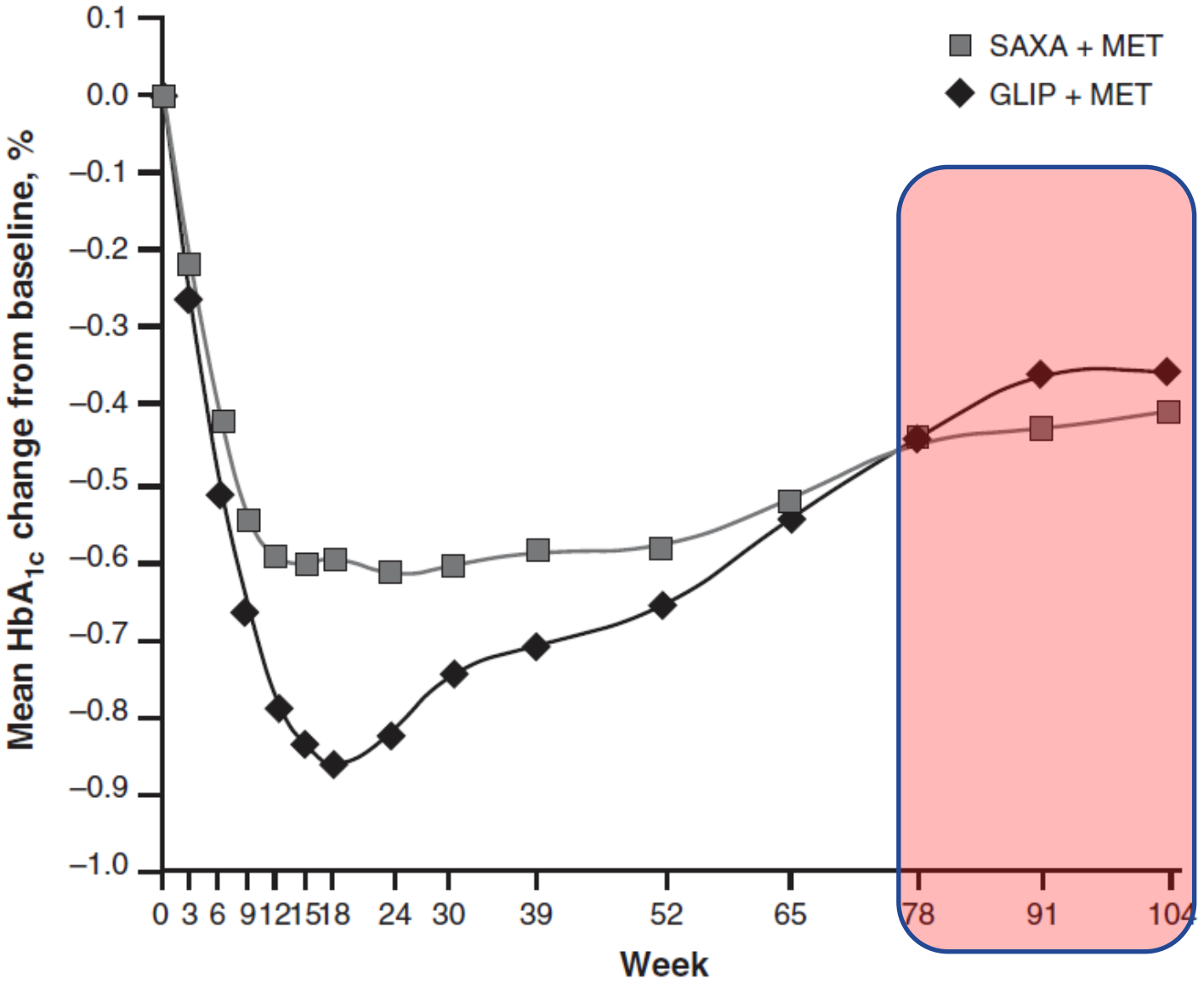
2 years

Baseline HbA1c>7% Achieving HbA1c<7% (Observed) at Week 104 without Hypoglycemia and Weight Gain



*Post-hoc analysis; †Percentage were calculated as n divided by number of patients with baseline HbA_{1c} ≥ 7% included in analysis x 100%;
‡No weight gain was defined as <2% increase from baseline – weight were last observation carried forward.

Adapted from Göke B, *et al. Int J Clin Pract* 2013.[2]



Number of patients with observed data				
SAXA + MET	(*n* = 423)	316	253	184
GLIP + MET	(*n* = 423)	323	251	160

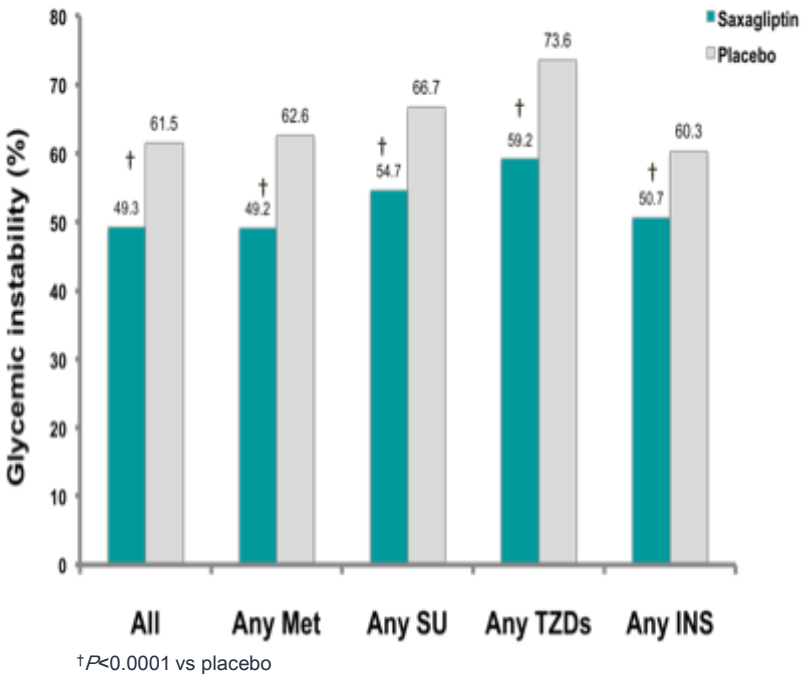
Glycaemic instability was defined by: (i) HbA1c increase of ≥ 0.5%; (ii) add new anti-DM Rx for ≥ 3 months; or (iii) an increase in dose of oral anti-DM or ≥ 25% increase in insulin dose for ≥ 3 months.

Onglyza may Attenuate the Progression of T2D

Reduce ~30% Glycemic Instability

Treatment*	Patients number	Glycemic instability n (%)	HR (95% CI)	p
Any saxagliptin	8280	4081 (49.3)	0.71 (0.68-0.74)	<0.0001
Placebo	8212	5054 (61.5)		
Saxagliptin only	369	175 (47.4)	0.77 (0.63-0.93)	0.0076
Placebo only	414	237 (57.3)		
Any metformin + saxagliptin	5761	2833 (49.2)	0.68 (0.65-0.72)	<0.0001
Any metformin + placebo	5654	3540 (62.6)		
Metformin only + saxagliptin	1659	651 (39.2)	0.59 (0.53-0.65)	<0.0001
Metformin only + placebo	1645	935 (56.8)		
Any SU + saxagliptin	3334	1822 (54.7)	0.72 (0.68-0.77)	<0.0001
Any SU + placebo	3263	2176 (66.7)		
Any TZDs + saxagliptin	510	302 (59.2)	0.66 (0.57-0.77)	<0.0001
Any TZDs + placebo	462	340 (73.6)		
Any insulin + saxagliptin	3423	1734 (50.7)	0.76 (0.72-0.81)	<0.0001
Any insulin + placebo	3363	2028 (60.3)		
Insulin only + saxagliptin	1275	592 (46.4)	0.76 (0.68-0.84)	<0.0001
Insulin only + placebo	1300	732 (56.3)		

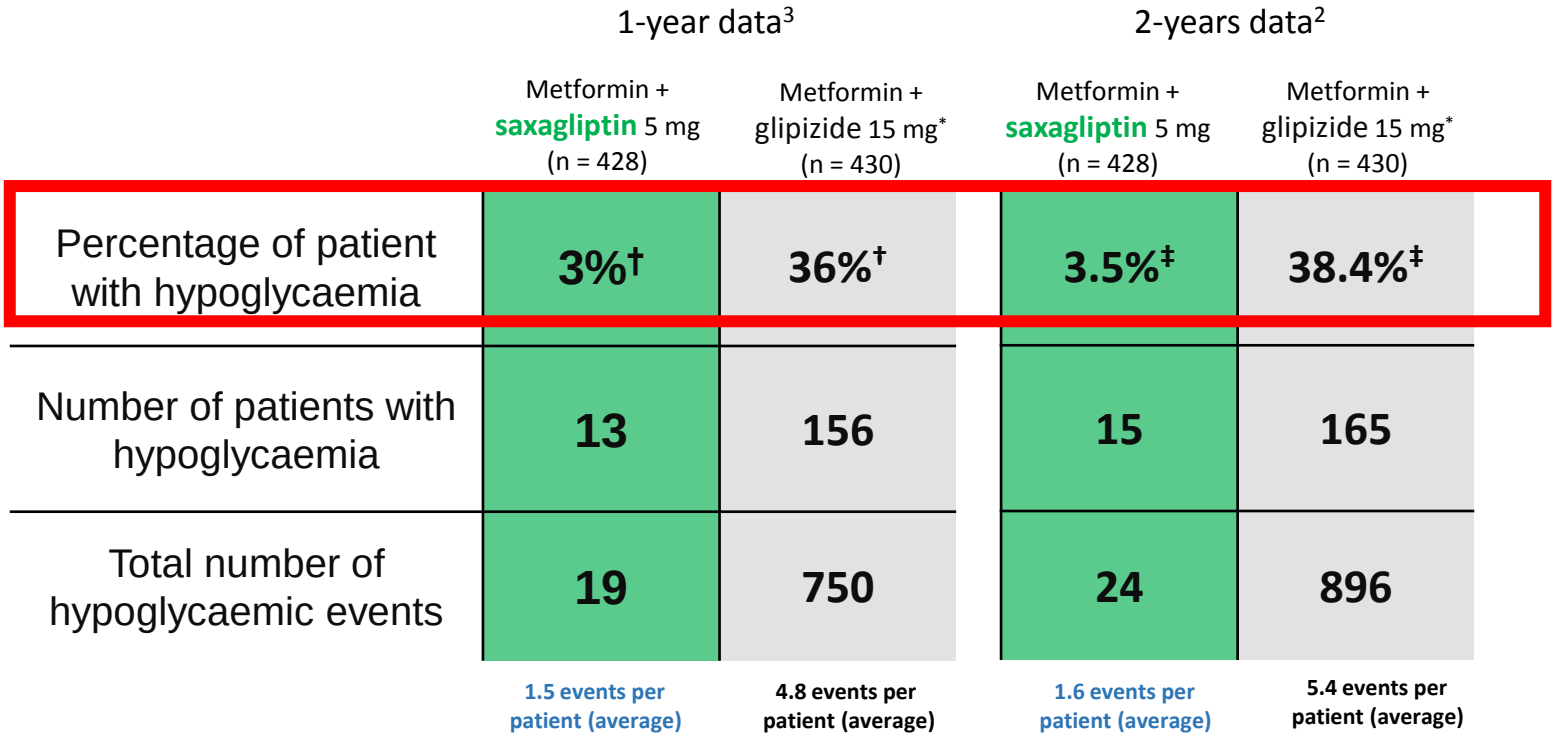
All antidiabetic medications other than saxagliptin are medications at randomization.
CI, confidence interval; HR, hazard ratio; SU, sulphonylurea; TZDs, thiazolidinediones.
*Baseline demographic and biochemical characteristics of the participants treated with saxagliptin and placebo in the different baseline treatment groups were similar (not shown)



†P<0.0001 vs placebo

Diabetes Obes Metab, 2015. doi: 10.1111/dom.12445

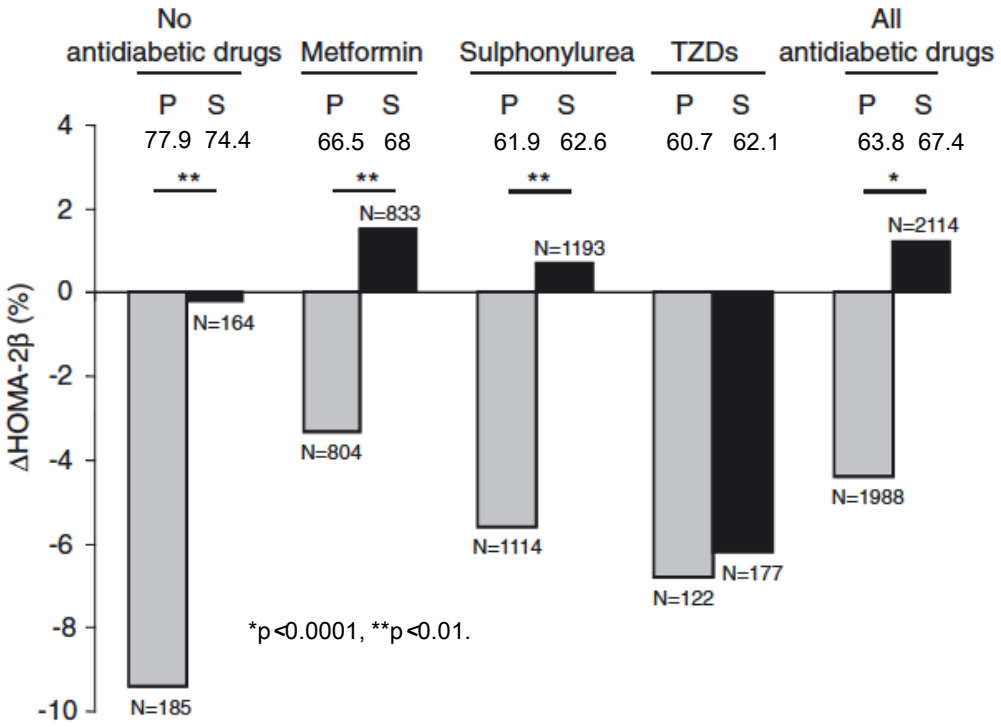
Significantly Less Hypoglycemia at 52 Weeks and 104 Weeks



*Mean dose received. †Difference 33.2%, 95% CI,38.1, -28.5; p< 0.0001, ‡Difference 34.9%, 95% CI, -39.8, -30. In those patients who had a hypoglycaemic event.

Adapted from Göke B, *et al. Int J Clin Pract* 2010;3 and Göke B, *et al. Int J Clin Pract* 2013

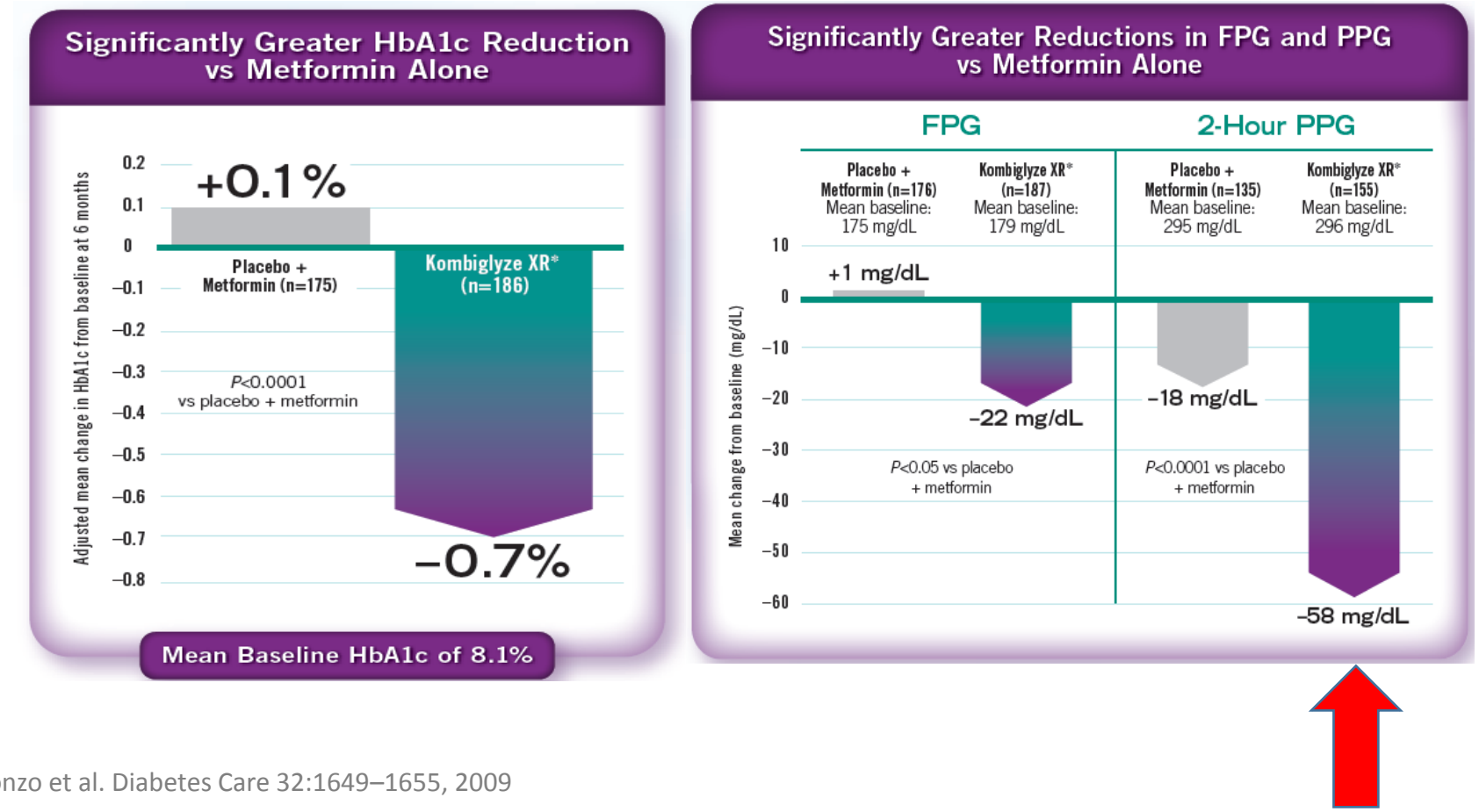
Onglyza can Preserve ß-cell Function



HOMA-2b was not available for patients treated with insulin and therefore were excluded.

Diabetes Obes Metab, 2015. doi: 10.1111/dom.12445

Kombiglyze XR有效降低HbA1c, FPG and PPG



De Fronzo et al. Diabetes Care 32:1649–1655, 2009

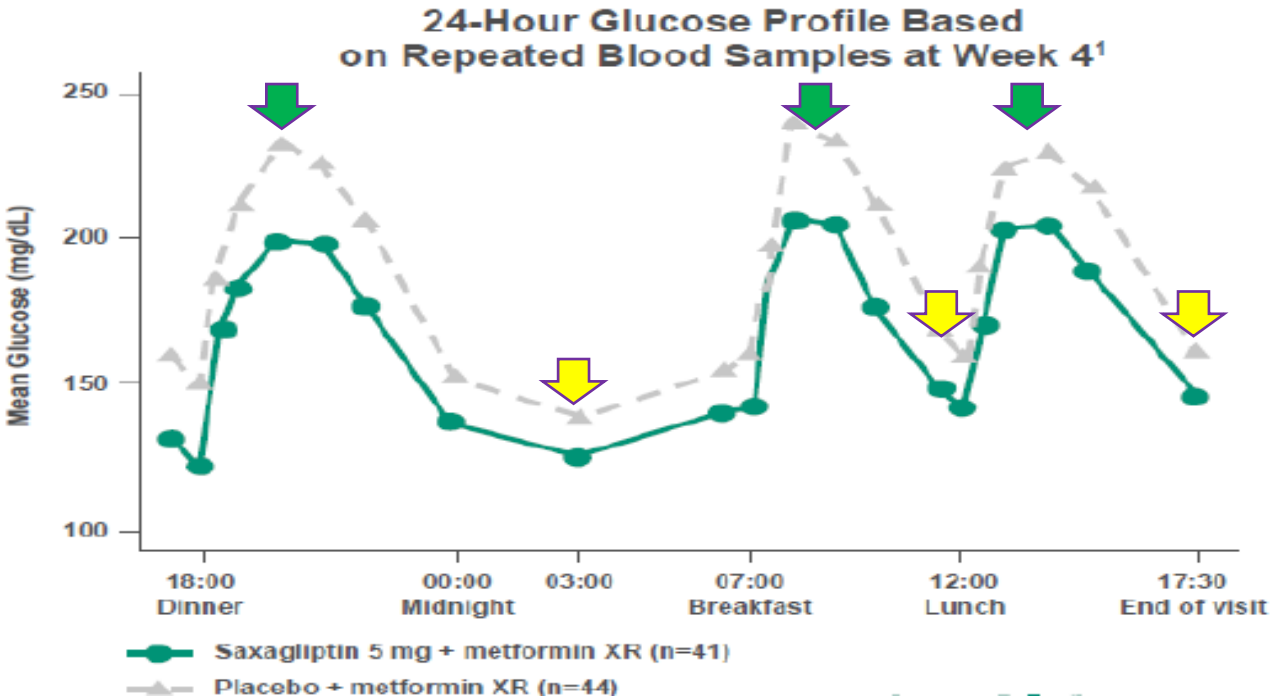
MAGE

Kombiglyze XR 提供良好血糖調控

- Kombiglyze XR produced significant reductions in average blood glucose concentrations over the 24-hour dosing interval

Study Design

- Phase 3, 4-week, multicenter, multinational, randomized, double-blind, placebo-controlled
- Adults (18–77 years) with type 2 diabetes
- Inadequate control for ≥8 weeks with metformin IR 1500–2550 mg/day or metformin XR 2000 mg/day
- A1C 7%–10%
- Saxagliptin 5 mg vs placebo as add-on to OL metformin XR (1500–2000 mg) taken once daily with the evening meal



IR=immediate release, OL=open label

Stenlof K et al. Curr Med Res Opon. 2010;26(10):2355-2363

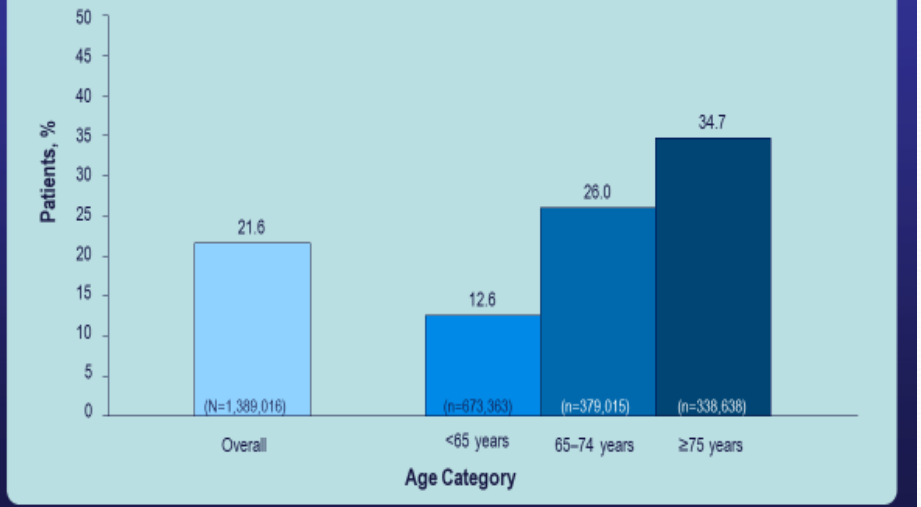
DM + Elderly + CKD = high CVD and mortality

SAVOR, EXAMINE, and TECOS
Baseline Characteristics

	SAVOR[a] n = 16,492	EXAMINE[b] n = 5380	TECOS[c] n = 14,671
	Saxagliptin vs PBO	Alogliptin vs PBO	Sitagliptin vs PBO
Mean age, y	65	61	66
Median duration of T2D, y	10.3	7.3	10.0

Prevalence of Cardiovascular Disease Is Elevated in the Elderly Population With T2DM[1]

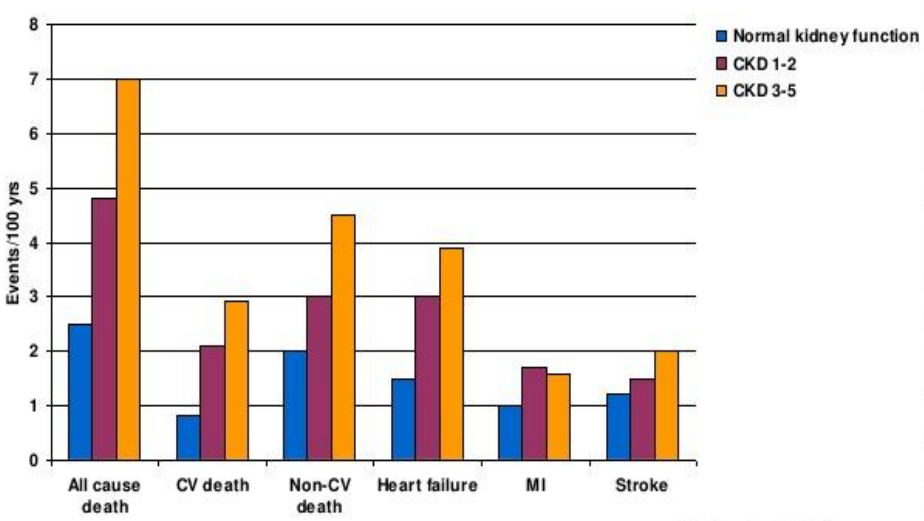
Prevalence of Comorbid Cardiovascular Disease[a] by Age in Patients With T2DM in a Retrospective US Database Study



[a]Diagnosed myocardial infarction, ischemic heart disease, peripheral artery disease, or cerebrovascular disease.
T2DM = type 2 diabetes mellitus.
1. Iglay K et al. *Curr Med Res Opin.* 2016;32:1243-1252.

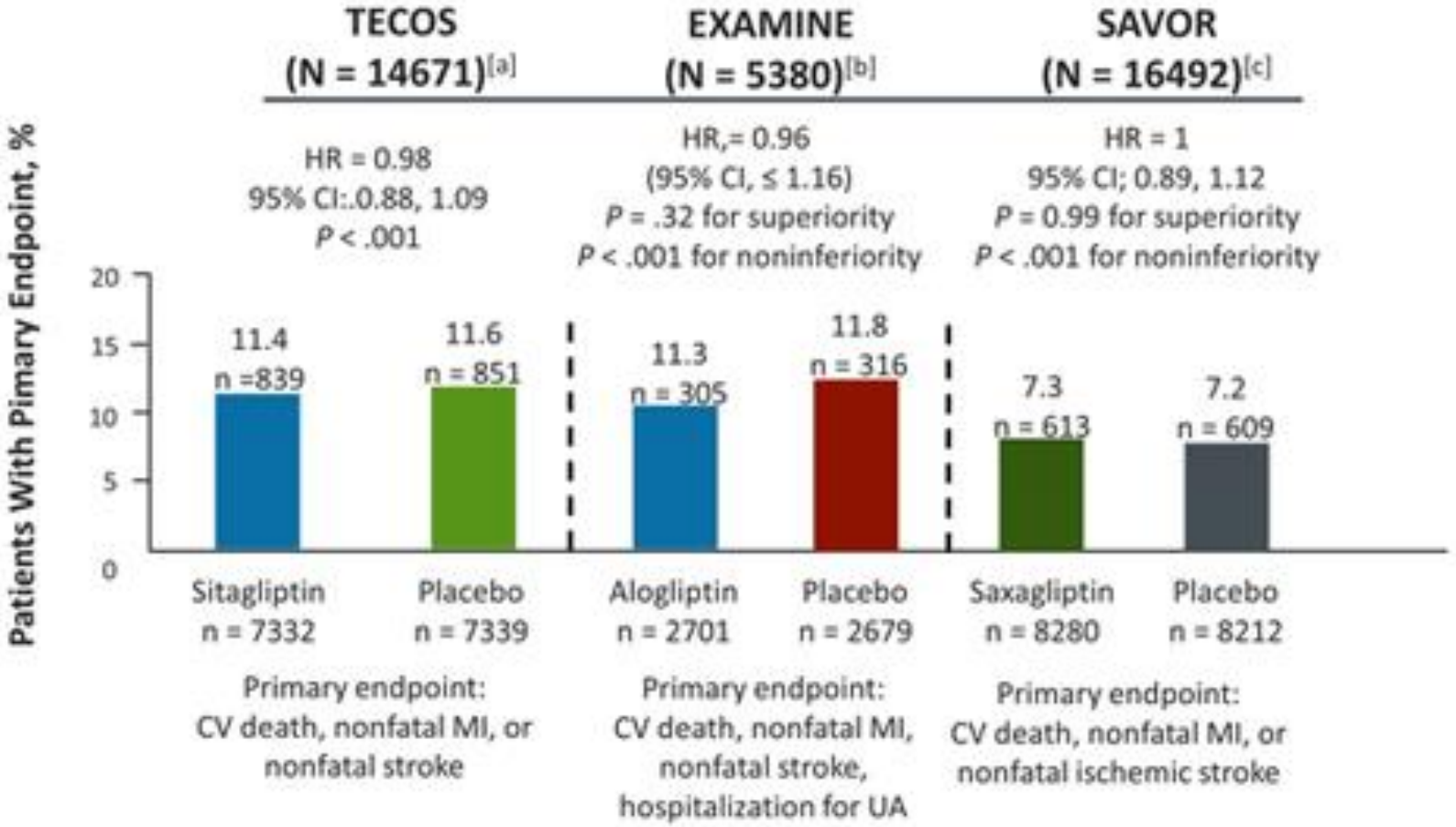
39

Effects of CKD on mortality and cardiovascular disease in the elderly - mean 75yr



Shilpak *et al* Ann Int Med 2006;145:237

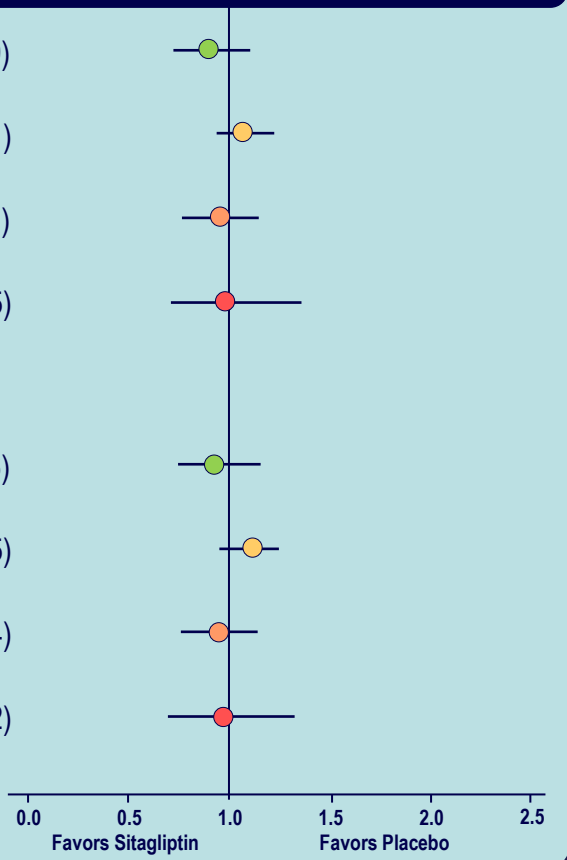
DPP-4 Inhibitors Have Demonstrated Cardiovascular Safety



a. Green JB, et al. *N Engl J Med*. 2015;373:232-242; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

Effect of Sitagliptin on Kidney Function and Respective CV Outcomes in T2DM in TECOS: Selected CV Outcomes by eGFR at Baseline[1]

CV End Point, n (%)		Sitagliptin	Placebo	Interaction *P* Value	HR (95% CI)
4-point MACE	Stage 1	153 (3.30)	177 (3.73)	0.48	0.88 (0.71, 1.09)
	Stage 2	414 (3.63)	385 (3.46)		1.05 (0.92, 1.21)
	Stage 3a	184 (5.44)	209 (6.04)		0.94 (0.77, 1.14)
	Stage 3b	75 (7.22)	70 (7.48)		0.97 (0.70, 1.35)
3-point MACE	Stage 1	133 (2.85)	148 (3.08)	0.46	0.92 (0.73, 1.16)
	Stage 2	363 (3.16)	329 (2.93)		1.08 (0.93, 1.25)
	Stage 3a	167 (4.88)	191 (5.46)		0.93 (0.75, 1.14)
	Stage 3b	72 (6.89)	69 (7.35)		0.95 (0.68, 1.32)



Adapted with permission from Cornel JH et al.[1]

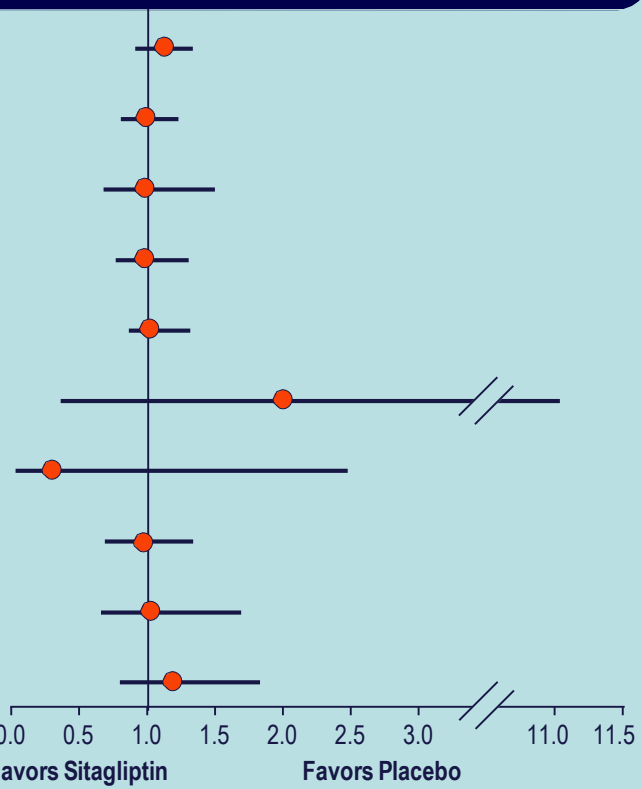
CV = cardiovascular; T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; eGFR = estimated glomerular filtration rate; MACE = major adverse cardiovascular event; HR = hazard ratio; CI = confidence interval.

1. Cornel JH et al. *Diabetes Care.* 2016;39:2304–2310.

Safety of Sitagliptin in Elderly Patients With T2DM in TECOS: Primary and Key Secondary Outcomes in the Elderly Cohort by Treatment Group[1]

Elderly (≥75 Years) Participants (N=2,004) (ITT Population)
Sitagliptin vs Placebo

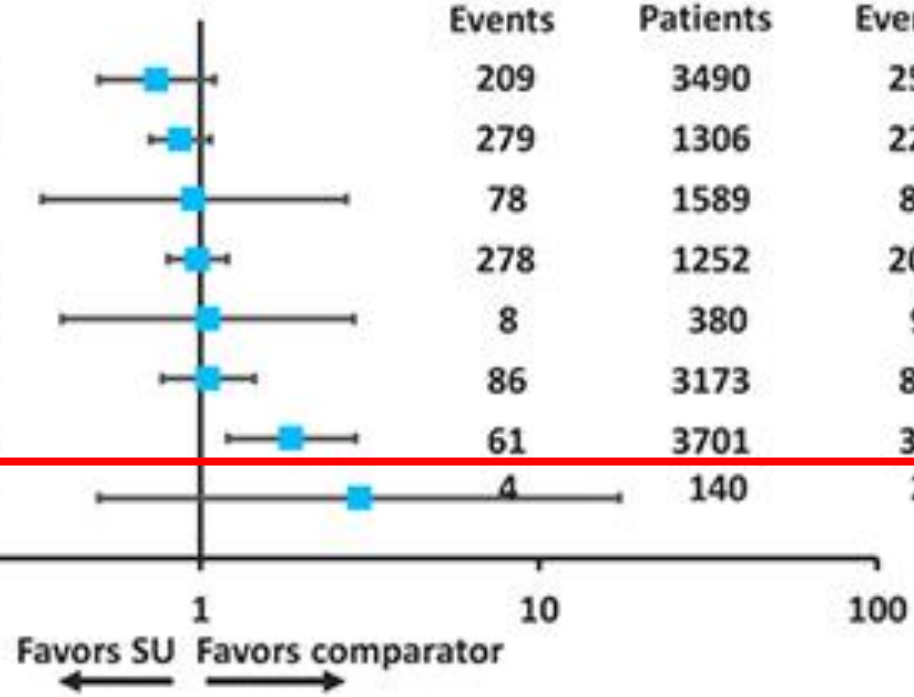
Outcome	HR (95% CI)	*P* Value
4-point MACE	1.10 (0.89, 1.36)	0.40
3-point MACE	1.01 (0.81, 1.26)	0.94
Hospitalization for heart failure	0.99 (0.65, 1.49)	0.94
Hospitalization for heart failure or death	1.00 (0.77, 1.29)	0.99
All-cause mortality	1.05 (0.83, 1.32)	0.71
Acute pancreatitis	2.01 (0.36, 11.04)	0.42
Pancreatic cancer	0.28 (0.03, 2.50)	0.25
Charter defined malignancy	0.95 (0.67, 1.36)	0.78
Severe hypoglycemia	1.03 (0.62, 1.71)	0.92
Bone fracture	1.21 (0.78, 1.85)	0.40



Adapted with permission from Bethel MA et al.[1]
T2DM = type 2 diabetes mellitus; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular events; ITT = Intention-to-treat.

1. Bethel MA et al. *Diabetes Care*. 2017. doi: 10.2337/dc16-1135.

Sulfonylureas and CV Risk



Comparators	Trials	*P*	SU: No. of Events	SU: No. of Patients	Comparator: No. of Events	Comparator: No. of Patients
Rosiglitazone	6	.140	209	3490	251	3714
Placebo/No Therapy	2	.190	279	1306	225	969
Metformin	2	.930	78	1589	85	1610
Insulin	2	.830	278	1252	209	929
GLP-1 RA	2	.920	8	380	9	515
Pioglitazone	8	.740	86	3173	80	3195
DPP-4-I	5	.005	61	3701	32	3704
AGI	2	.230	4	140	2	228

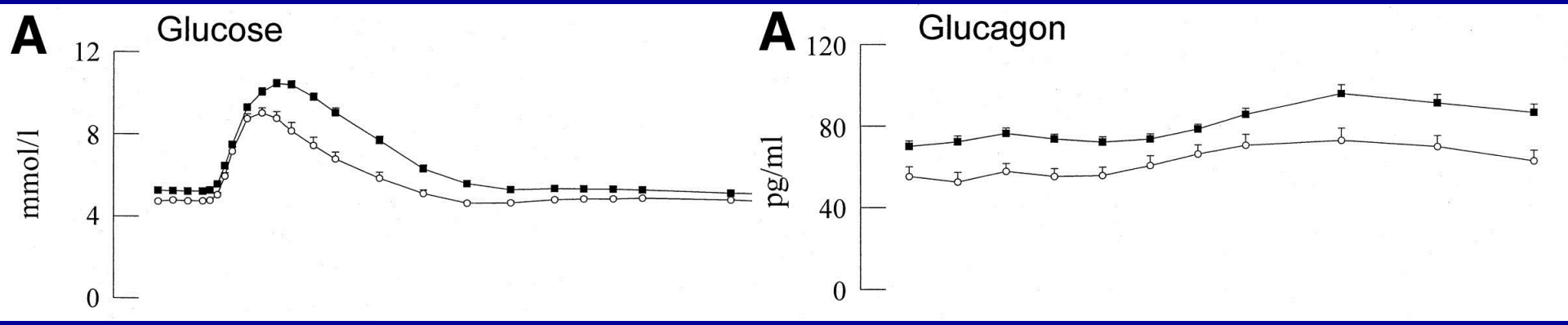
Overall MACE (29 trials) was equivalent for SU vs comparators: MH-OR 1.10 (95% CI: 0.95, 1.28; *P* = .18)
CV mortality (37 trials) was higher for SU vs comparators: MH-OR 1.22 (95% CI: 1.10, 1.49; *P* = .047)

31 Monami M, et al. *Diabetes Obes Metab*. 2013;15:938-953.

Medscape EDUCATION

Islet dysfunction, including hyperglucagonemia and postprandial hyperglycemia, may play a more significant role in elderly with T2D

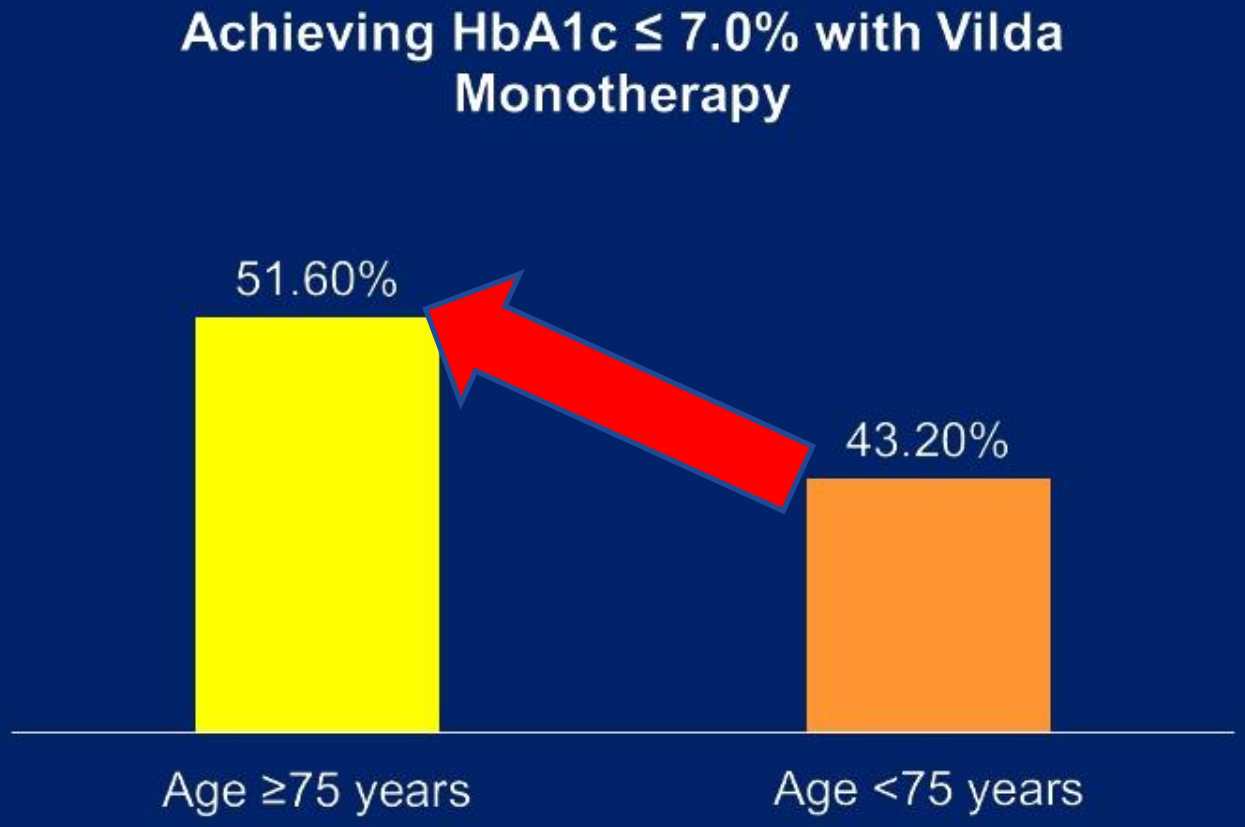
elderly (■) and the young (○)



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

Am J Physiol 284:E7–E12, 2003

≥50% of elderly patients achieving a target HbA1c A1C ≤7% in monotherapy



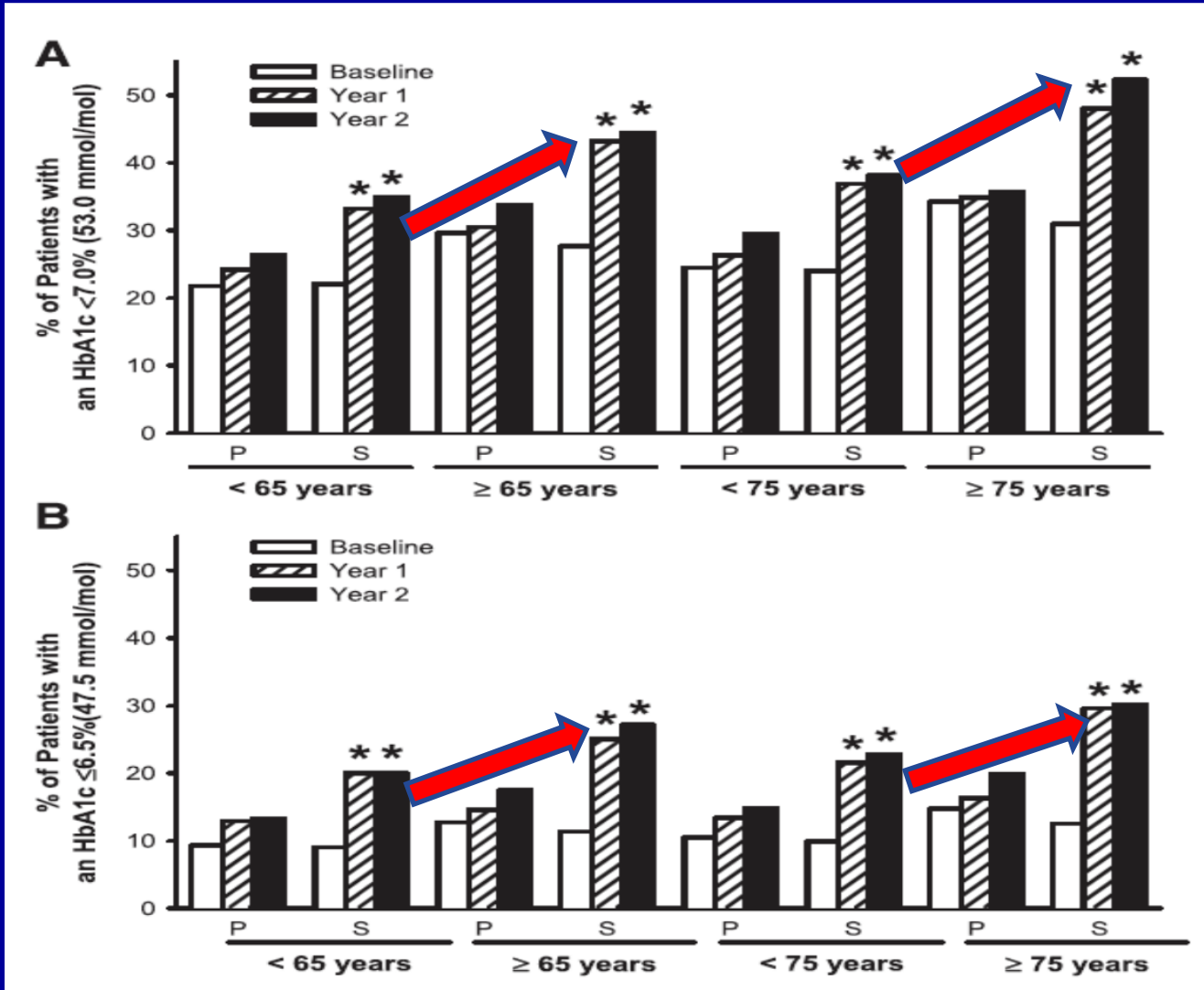
T2DM in older individuals is known to be associated with relative hyperglucagonaemia and elevated postprandial glucose. Vildagliptin treatment appears to address both these defects

Schweizer A et al *Diabetes Obes Metab.* 2011; 13: 55–64.

Efficacy and Safety of Saxagliptin in Older Participants in the SAVOR-TIMI 53 Trial

Diabetes Care 2015;38:1145–1153 | DOI: 10.2337/dc14-2868

Saxa improves reaching A1C goal



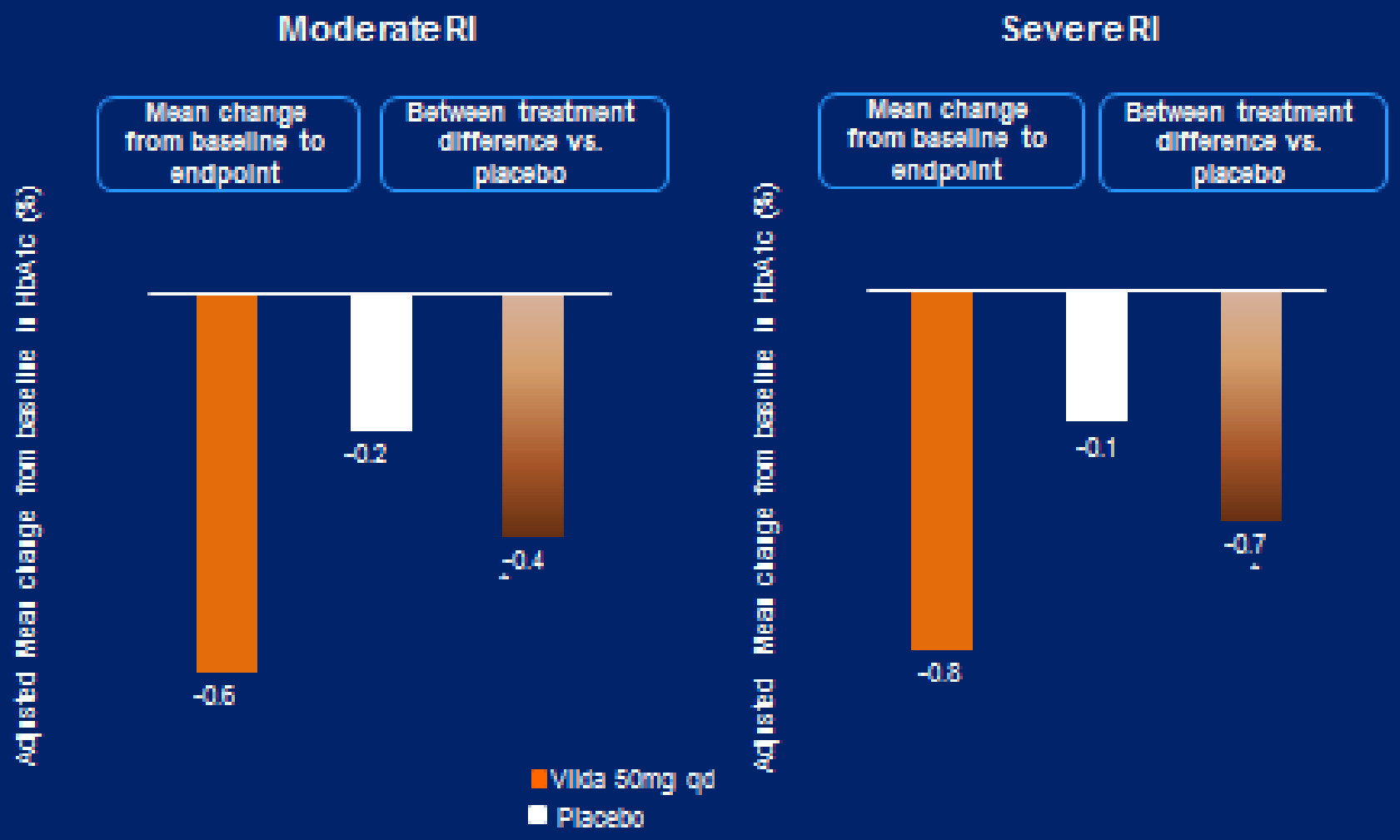
Long-term treatment with saxagliptin in pts with T2DM and renal impairment: a randomised controlled 52-week efficacy and safety study.

Int J Clin Pract. 2011 Dec;65(12):1230-9

SUMMARY

Objective: Therapeutic options are limited for diabetes patients with renal disease. This report presents 52-week results from a study assessing the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. **Design:** Double-blind study in patients stratified by baseline renal impairment (moderate, severe or end-stage renal disease [ESRD] on haemodialysis) randomised to saxagliptin 2.5 mg once daily or placebo added to other antidiabetic drugs in use at baseline, including insulin. **Patients:** A total of 170 adults with glycated haemoglobin (HbA_{1c}) 7–11% and creatinine clearance < 50 ml/min or ESRD were randomised and treated. **Measurements:** Absolute changes in HbA_{1c} and fasting plasma glucose (FPG) from baseline to week 52 were evaluated using analysis of covariance (ANCOVA) with last observation carried forward. Repeated-measures analyses were also performed. **Results:** Adjusted mean decrease in HbA_{1c} was greater with saxagliptin than placebo (difference, −0.73%, $p < 0.001$ [ANCOVA]). Reductions in adjusted mean HbA_{1c} were numerically greater with saxagliptin than placebo in patients with renal impairment rated as moderate (−0.94% vs. 0.19% respectively) or severe (−0.81% vs. −0.49%), but similar to placebo for those with ESRD (−1.13% vs. −0.99%). Reductions in adjusted mean FPG were numerically greater with saxagliptin in patients with moderate or severe renal impairment. Saxagliptin was generally well tolerated; similar proportions of patients in the saxagliptin and placebo groups reported hypoglycaemic events (28% and 29% respectively). **Conclusions:** Saxagliptin 2.5 mg once daily offers sustained efficacy and good tolerability for patients with T2DM and renal impairment.

Vildagliptin provided reduction in HbA1c in T2DM patients with moderate or severe RI (52 wks)



Kothny W, Shao Q, Snoop PH, Lukashevich V.Diabetes Obes Metab. 2012 Jun 13

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)

Treatment with DPP4i has all of these beneficial effects!!

Quantity

- HbA1c
- FPG
- PPG

Quality

- Hypoglycemia
- Body weight
- Glycemic variability
- Safety profile(CV and adverse effects) in all patient populations(CKD and/or elderly, etc.)

Outlines

- New era in the treatment of T2DM
- Diabetic kidney disease(DKD) and CVD
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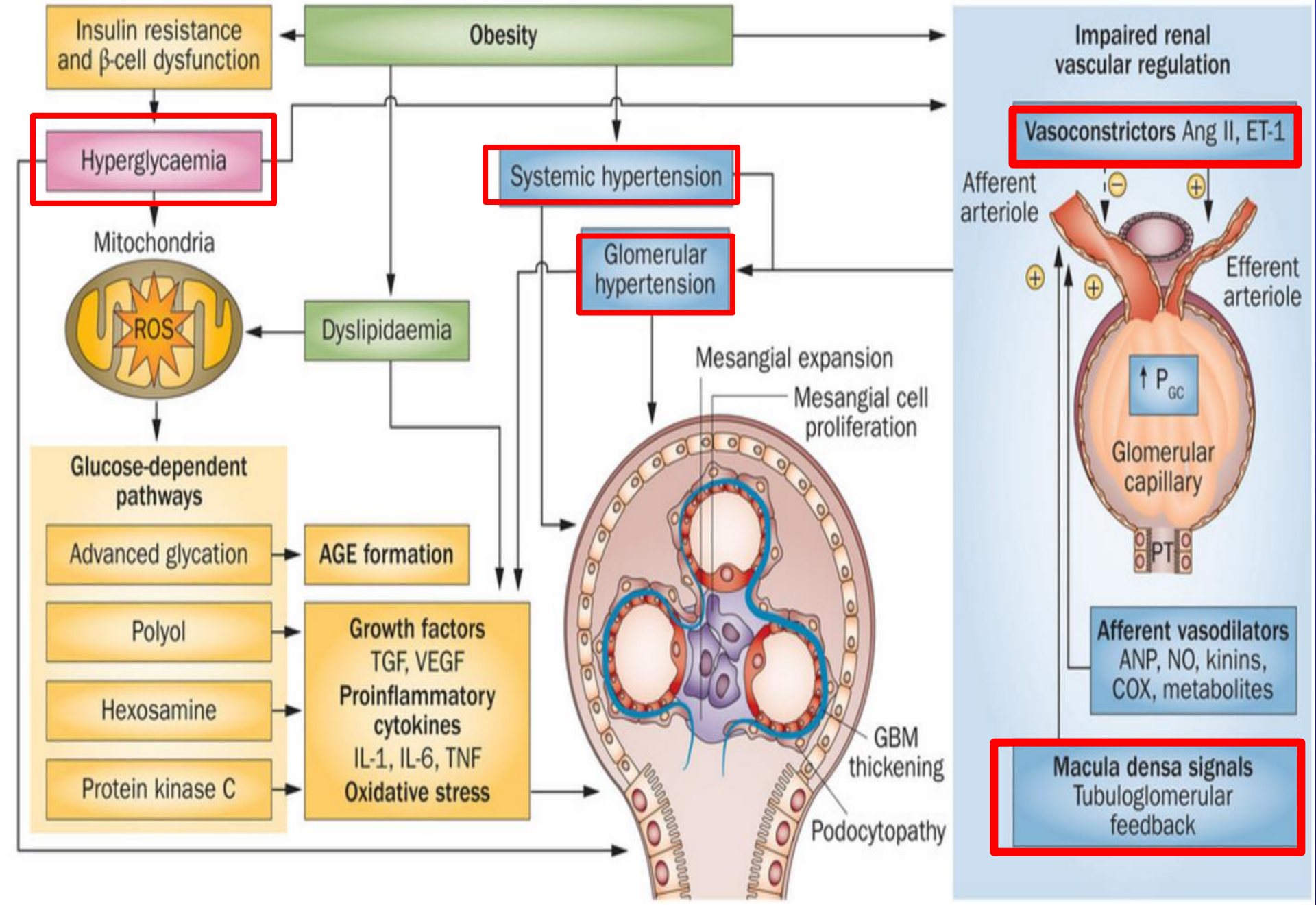
- Save Kidneys = Save Lives, A nephrologist's perspective
- Pleiotropic effects

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



Blood pressure in glomerulus is important for renal protection!!

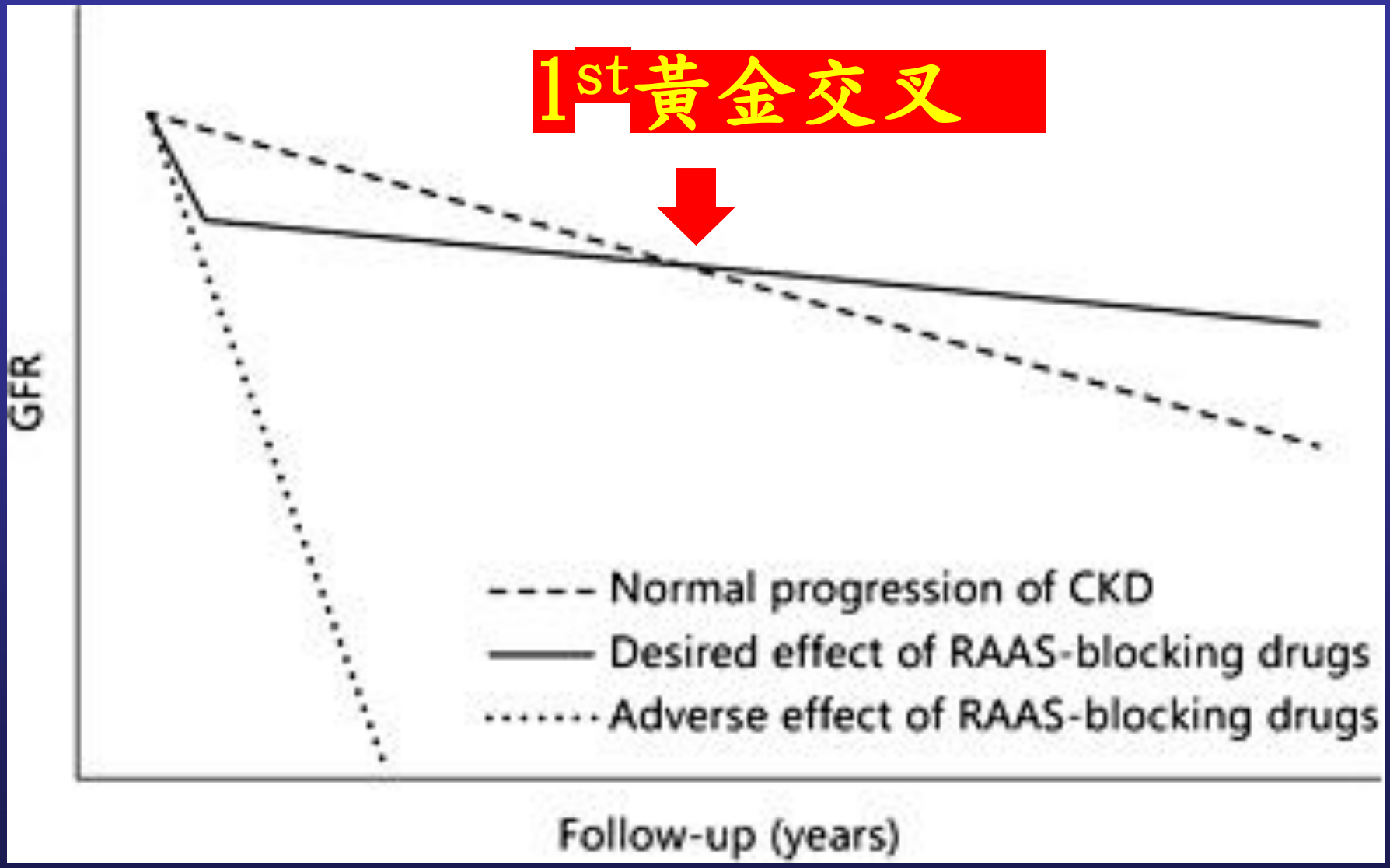
Lessons from ARB/ACEi and SGLT2i

ARBs decrease renal complications in T2DM

	T2DM (N)	Treatment	Primary outcome
IRMA-2	Microalbuminuria (590)	Irbesartan 150/300 mg vs placebo	Time to nephropathy: ↓39% (150 mg, P = 0.08) ↓70% (300 mg, P < 0.001)
IDNT	Nephropathy (1715)	Irbesartan/ amlodipine/ placebo	ESRD/ ↑Cr 2×/mortality: ↓20% vs placebo (P = 0.02) ↓23% vs amlodipine (P = 0.006)
MARVAL	Microalbuminuria (332)	Valsartan/ amlodipine	Δ UAER at 24 weeks: ↓44% valsartan vs ↓8% amlodipine (P < 0.001)
RENAAL	Nephropathy (1513)	Losartan/ placebo	ESRD/Cr 2× /all deaths: 16% vs placebo (P = 0.02)
ROADMAP	normoalbuminuric	40 mg omesartan	出現微量白蛋白尿的危險性減少23%

Cr = creatinine
UAER = urinary albumin excretion rate

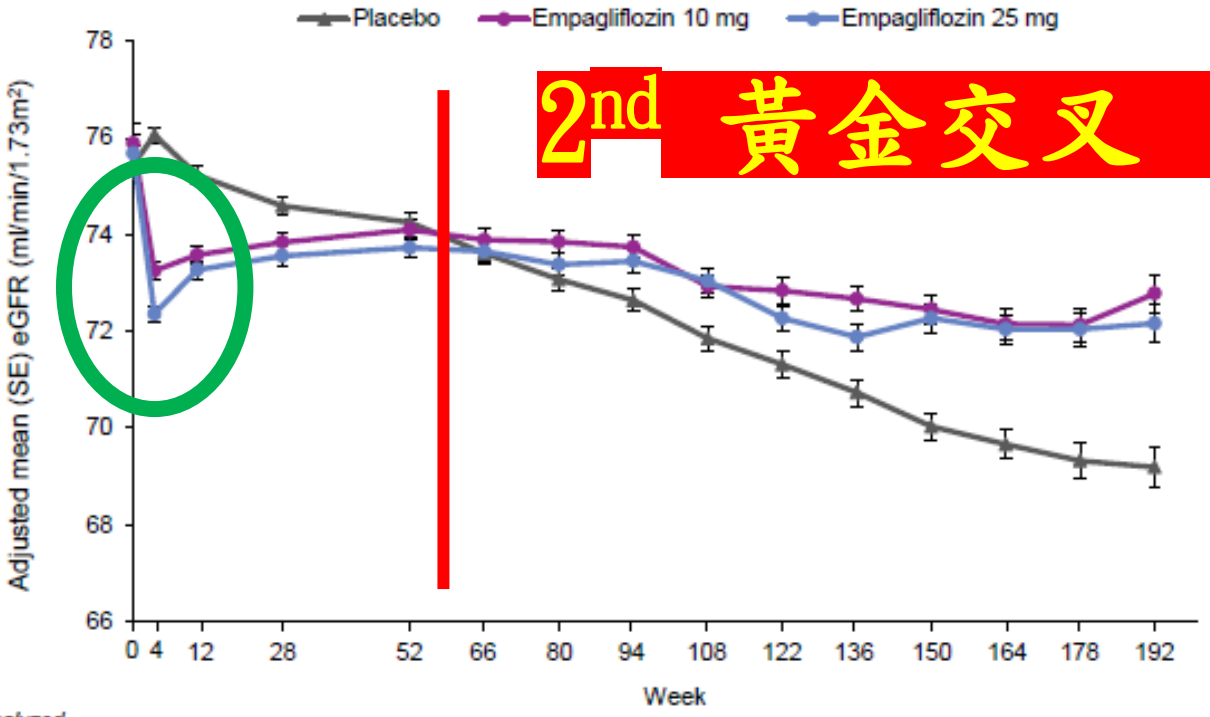
Adapted from Sharma AM. *Hypertension*. 2004;44:12-19.



Cardiology. 2013;126(3):175-86.

80% pts with ACEI/ARB

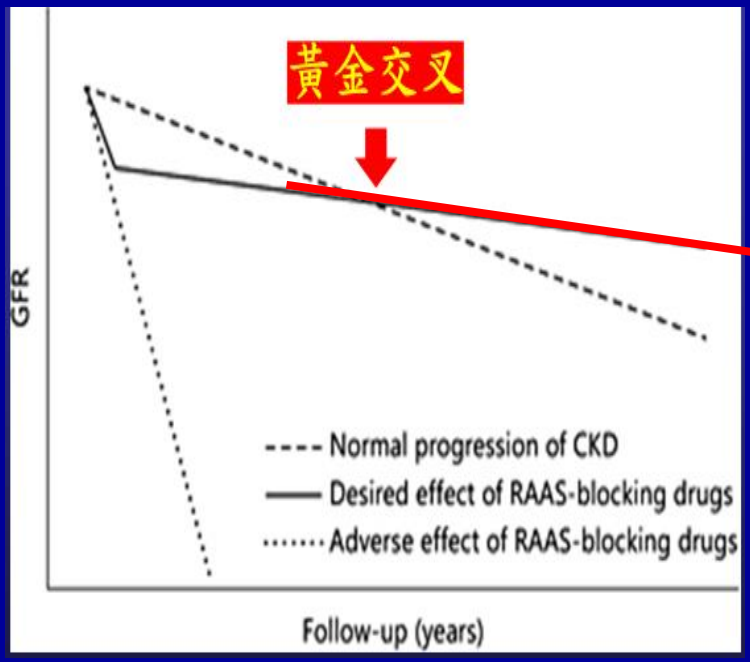
eGFR (CKD-EPI formula) over 192 weeks

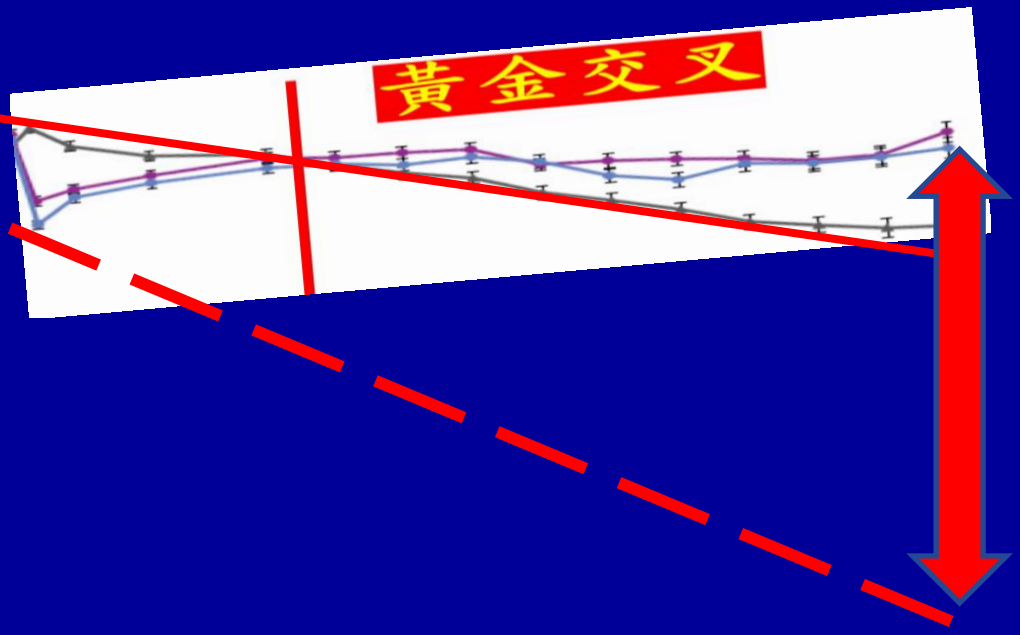


No. analyzed															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in follow-up for adverse/outcome events															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3492	2707	1703

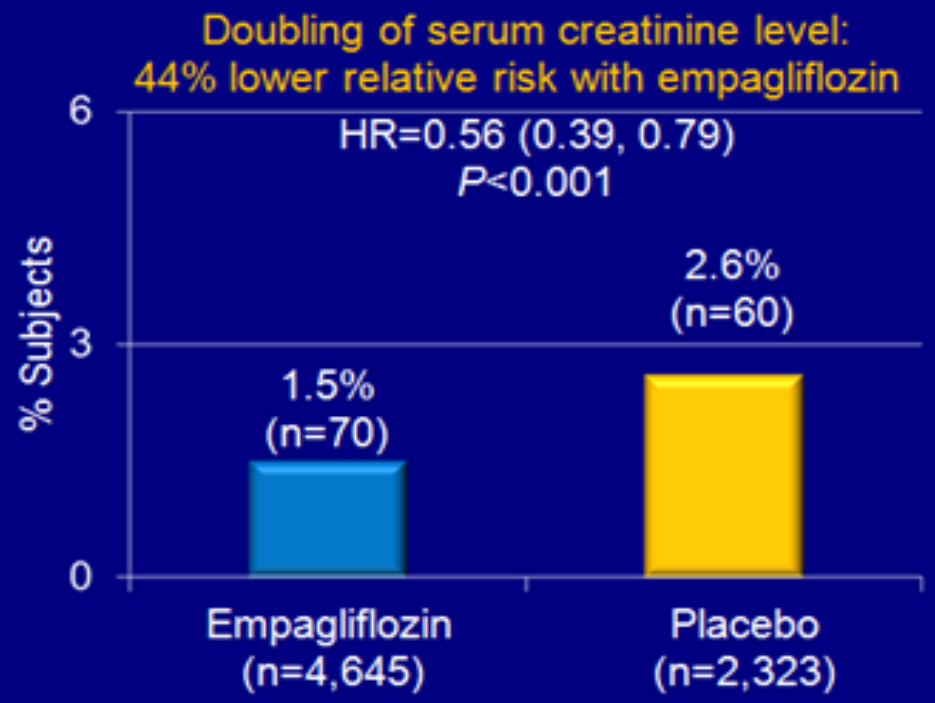
Mixed model repeated measures analysis in all patients treated with ≥1 dose of study drug(OC-AD).
eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

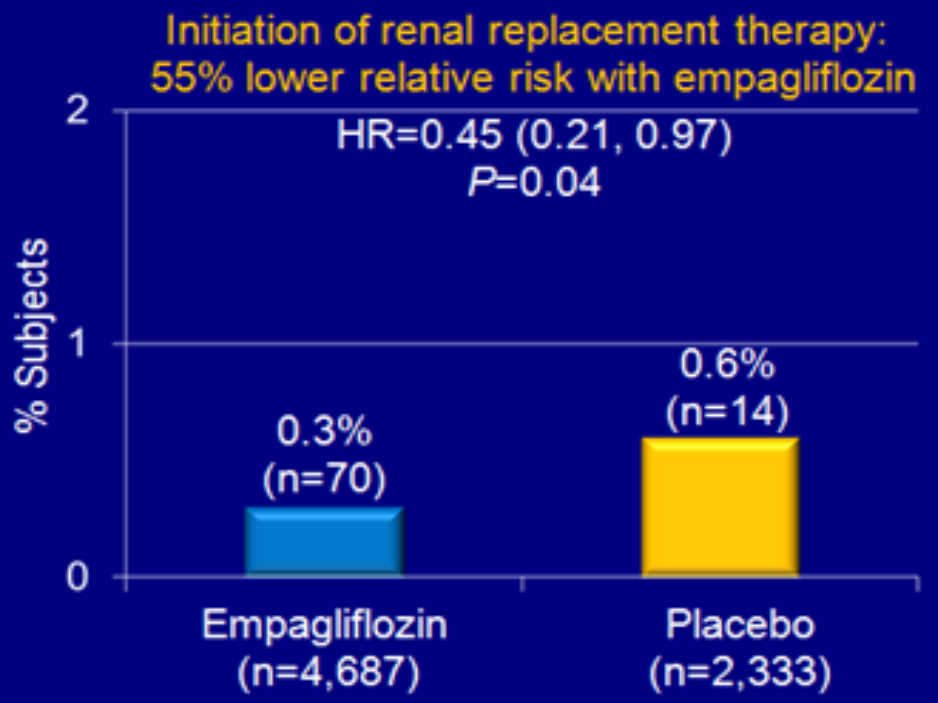
EMPA-REG OUTCOME®


黃金交叉
GFR
Normal progression of CKD
Desired effect of RAAS-blocking drugs
Adverse effect of RAAS-blocking drugs
Follow-up (years)


黃金交叉

Attenuation of glomerular hypertension protects kidneys!!





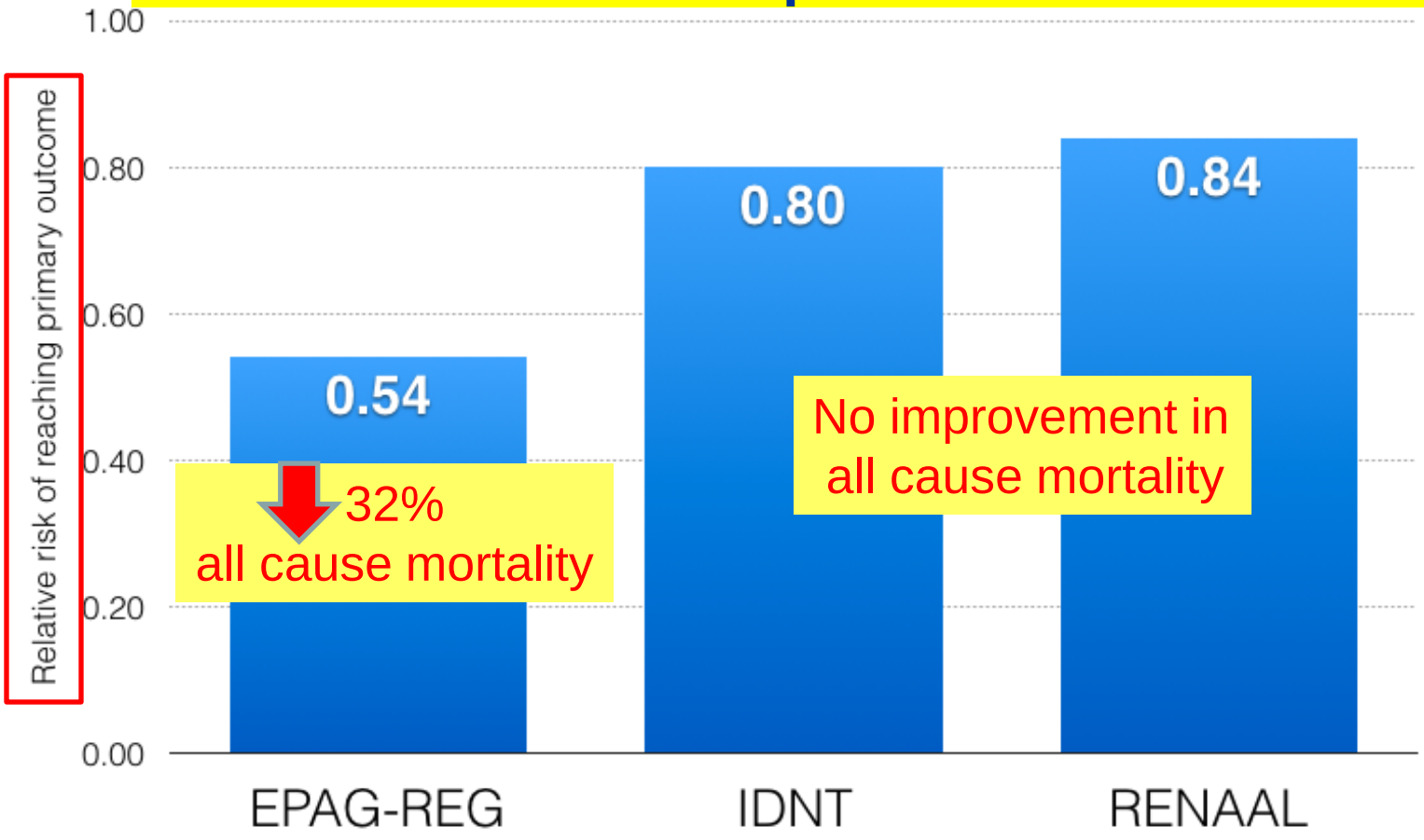
All patients had type 2 diabetes and eGFR ≥30 ml/min/1.73 kg²
Assessment of renal outcomes was a prespecified component of the secondary microvascular outcome in EMPA-REG OUTCOME

EMPA-REG outcome

Wanner C, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med*. 2016. DOI:10.1056NEJMoa1515920.

Save kidneys=Save lives!!

Blood pressure in glomerulus is important for renal protection!!



Outlines

- New era in the treatment of T2DM
- Diabetic kidney disease(DKD) and CVD
- Intensive Diabetic treatment: focus on both quantity and quality and the efficacy of DPP4i
- Save Kidneys = Save Lives, A nephrologist's perspective
- Pleiotropic effects of DPP4i

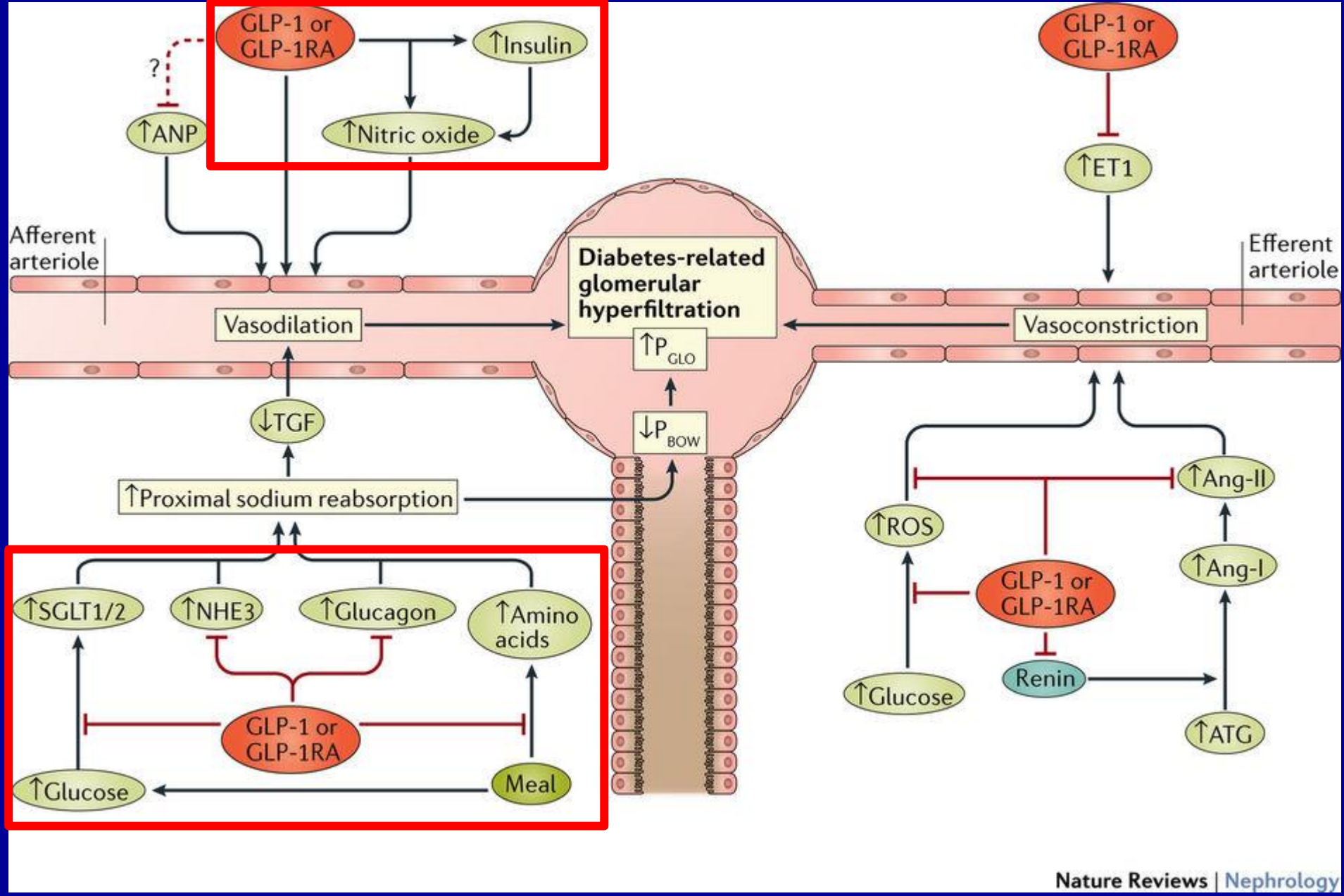
Table 2 | **Glucose-independent effects of incretin-based therapies on renal risk factors in type 2 diabet**

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



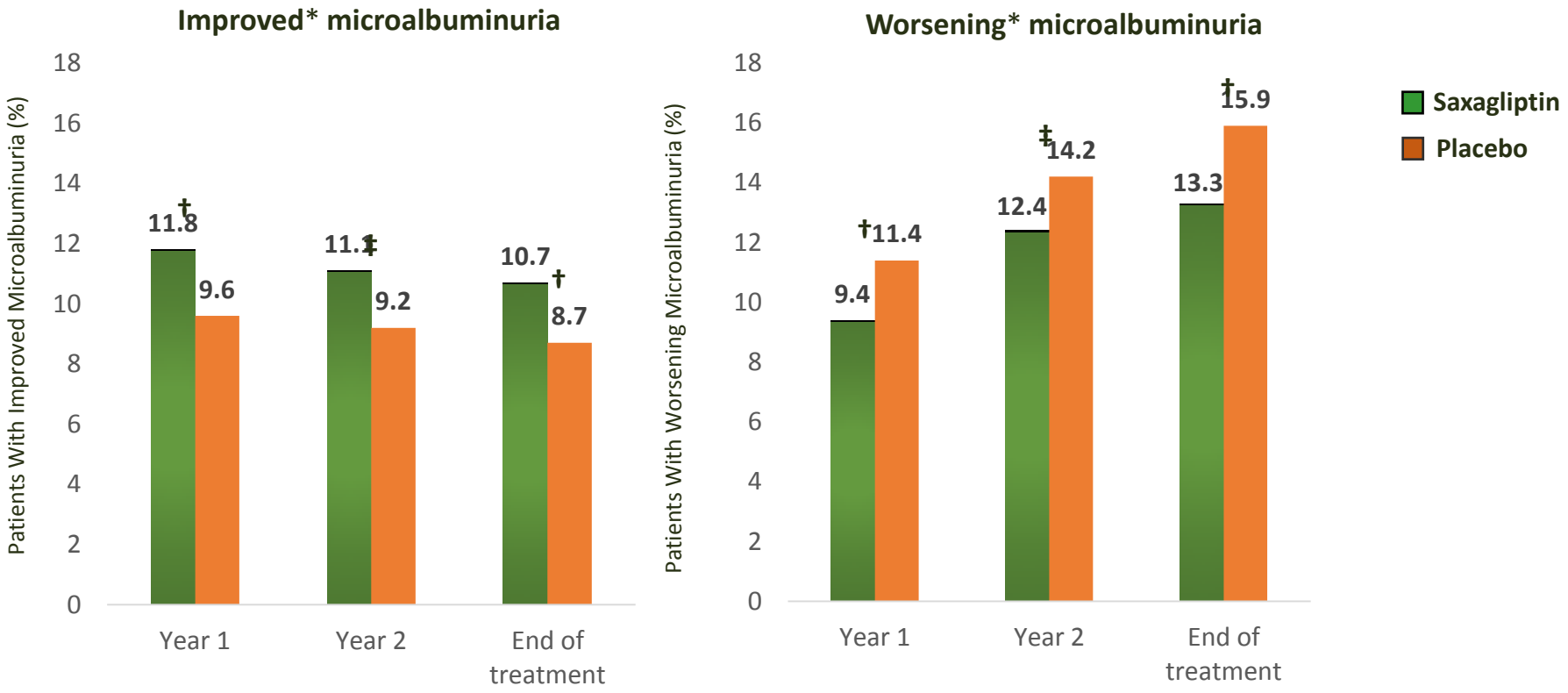
Nature Reviews Nephrology (2017)
doi:10.1038/nrneph.2017.123

Saxa effect on renal outcome

Diabetes Care 2016 Oct; dc160621

There were no meaningful differences in any of the prespecified renal safety outcomes between saxagliptin and placebo treatment arms: doubling of serum creatinine NS rred in 183 (2.02%) versus 166 (1.82%) subjects (hazard ratio [HR] 1.1 [95% CI 0.89–1.36]) and initiation of chronic dialysis, renal transplant, or serum creatinine >6.0 mg/dL o NS ed in 51 (0.61%) versus 55 (0.67%) subjects (HR 0.90 [0.61–1.32]), respectively. The composite end point of death and any of the above occurred in 577 (6.58%) versus 528 (5.86%) subjects (HR 1.08 [0.96–1.22]). The overall change in eGFR during follow-up was similar in the saxagliptin and placebo arms, as well as in the different ACR and eGFR categories (at the EOT, the mean change from baseline was −2.49 vs. −2.37 mL/min in the saxagliptin and placebo groups, respectively; $P = 0.5794$). NS

Onglyza Changes in Microalbuminuria & UACR by Category



*Treatment difference in the number and proportion of patients with albumin/creatinine ratios that worsened, did not change, or improved is defined as a shift from baseline category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol).

†*P*<0.001 vs placebo; ‡*P* = 0.0058 vs placebo.

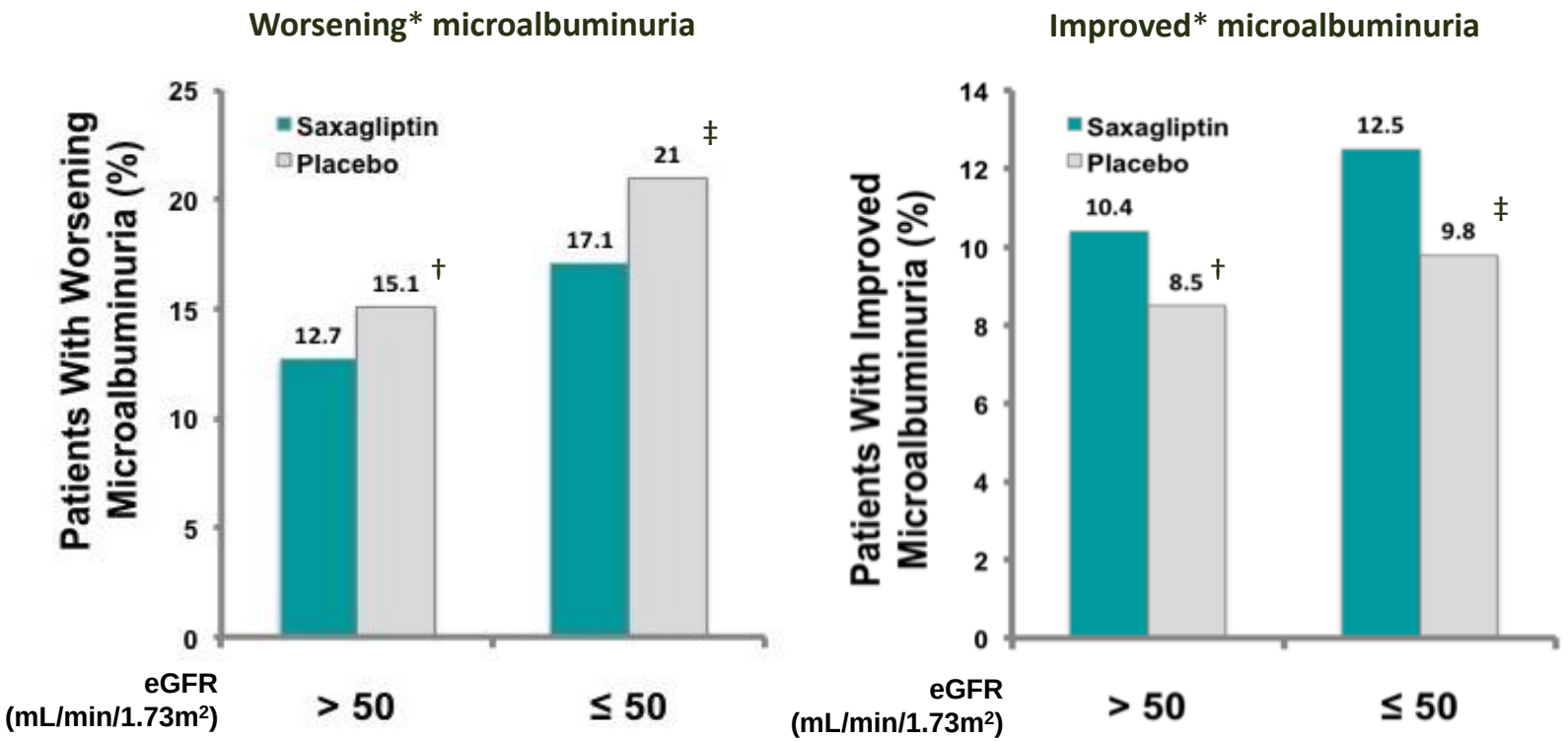
Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684.

Onglyza is not approved for the treatment of albuminuria

Scirica BM, Bhatt DL, Braunwald E, et al…. Raz I. *NEJM* 2013; 369:1317-1326

Onglyza Improved Albuminuria Irrespective of Renal Function

Frequency of Progressive Microalbuminuria by Completion of Follow-up According to Renal Function

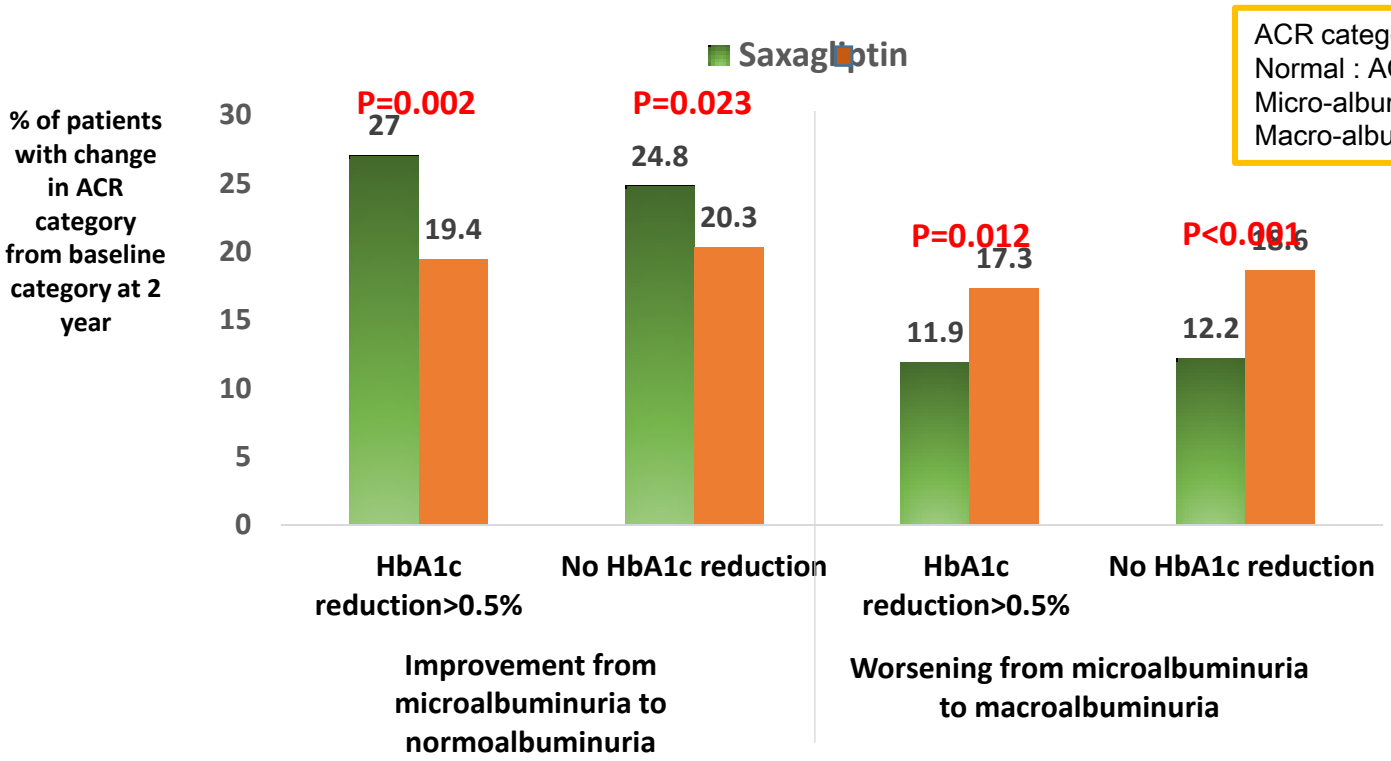


*The risk of progressive microalbuminuria was defined as a treatment difference in the number and proportion of patients with worsening, no change, or improvement in urinary albumin-to-creatinine ratio (ACR), defined as a shift from baseline category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol) over the duration of follow-up among patients with complete data.
†*P*<0.0001 vs placebo; ‡P=0.041 vs placebo. P-values based on chi-square or Fisher's exact test.

Onglyza is not approved for the treatment of albuminuria

Diabetes Care 2015. 10.2337/dc14-1850

Onglyza Improvement and Worsening in ACR Category at 2 years in Patients with and without Improvement in HbA1c



ACR category : albumin/ creatinine ratio
Normal : ACR<30 mg/G,
Micro-albuminuria : ACR 30-300 mg/G
Macro-albuminuria : ACR >300 mg/G

Diabetes Care 2017;40:69–76 | DOI: 10.2337/dc16-0621

Onglyza is not approved for the treatment of albuminuria

Renal outcome from TECOS

Table 3—Estimated mean 4-year eGFR and UACR between-treatment group differences (sitagliptin minus placebo), overall and by baseline eGFR stages

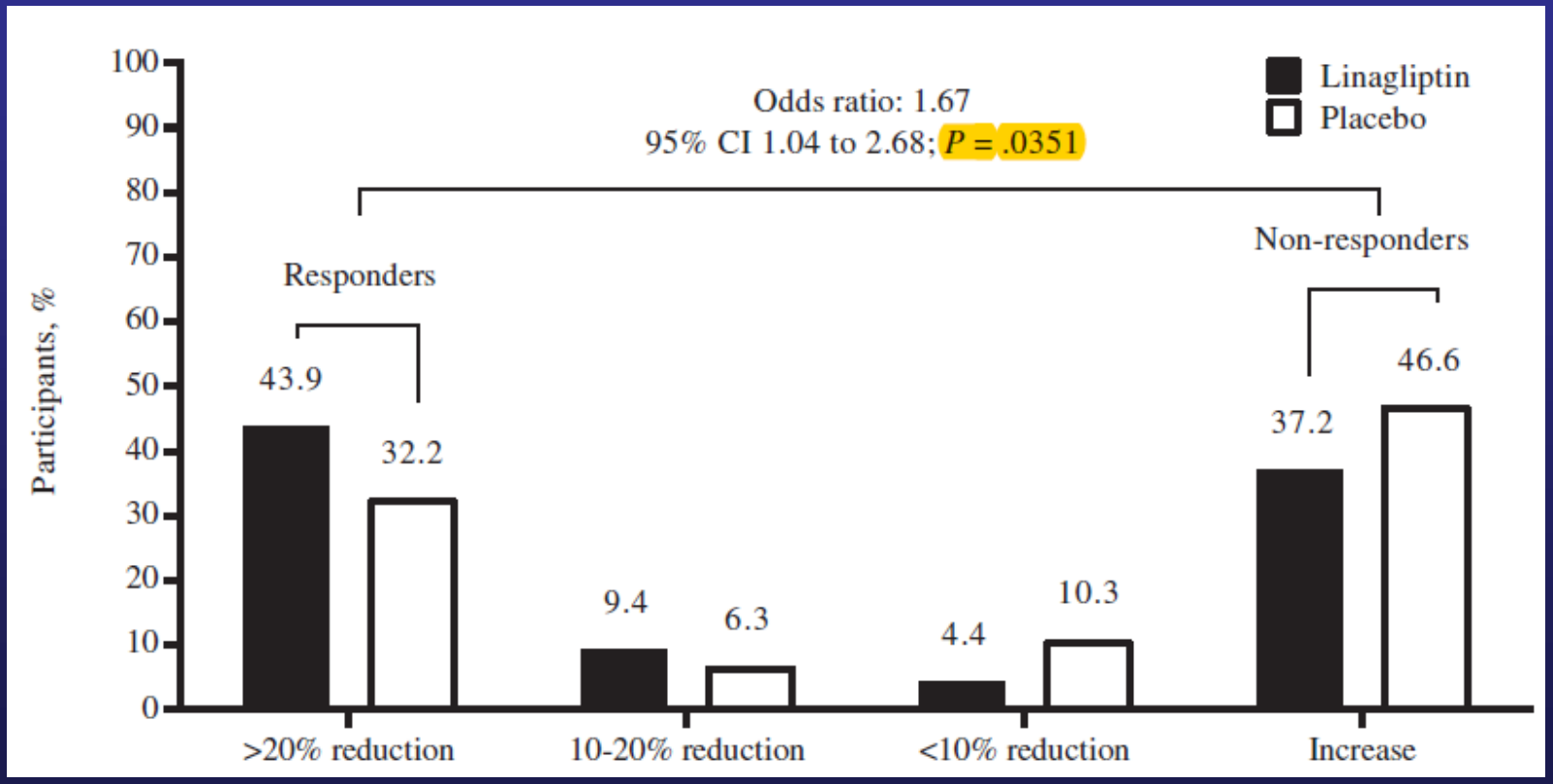
	Baseline value	Mean between-group treatment difference (95% CI)†	*P* value†
eGFR (*N* = 13,604), mL/min/1.73 m^2			
Overall	75.1 ± 21.0	−1.34 (−1.76 to −0.91)	<0.0001
Stage 1 (eGFR ≥90 mL/min/1.73 m^2)	104 ± 14	−0.22 (−1.19 to 0.75)	
Stage 2 (eGFR 60–89 mL/min/1.73 m^2)	73 ± 9	−1.42 (−2.05 to −0.79)	
Stage 3a (eGFR 45–59 mL/min/1.73 m^2)	53 ± 4	−1.33 (−2.45 to −0.21)	Interaction *P* = 0.14
Stage 3b (eGFR 30–44 mL/min/1.73 m^2)	39 ± 4	−2.25 (−4.27 to −0.23)	
UACR (*N* = 3,832), mg/g			
Overall	11.1 (3.9, 35.0)	−0.18 (−0.35 to −0.02)	0.031
Stage 1 (eGFR ≥90 mL/min/1.73 m^2)	11.0 (4.7, 30.2)	−0.18 (−0.53 to 0.16)	
Stage 2 (eGFR 60–89 mL/min/1.73 m^2)	9.7 (3.5, 29.2)	−0.20 (−0.42 to 0.02)	
Stage 3a (eGFR 45–59 mL/min/1.73 m^2)	14.3 (4.1, 55.4)	−0.30 (−0.70 to 0.09)	Interaction *P* = 0.68
Stage 3b (eGFR 30–44 mL/min/1.73 m^2)	27.7 (9.7, 126.6)	0.23 (−0.54 to 1.00)	

Diabetes Care. 2016;39:2304–2310

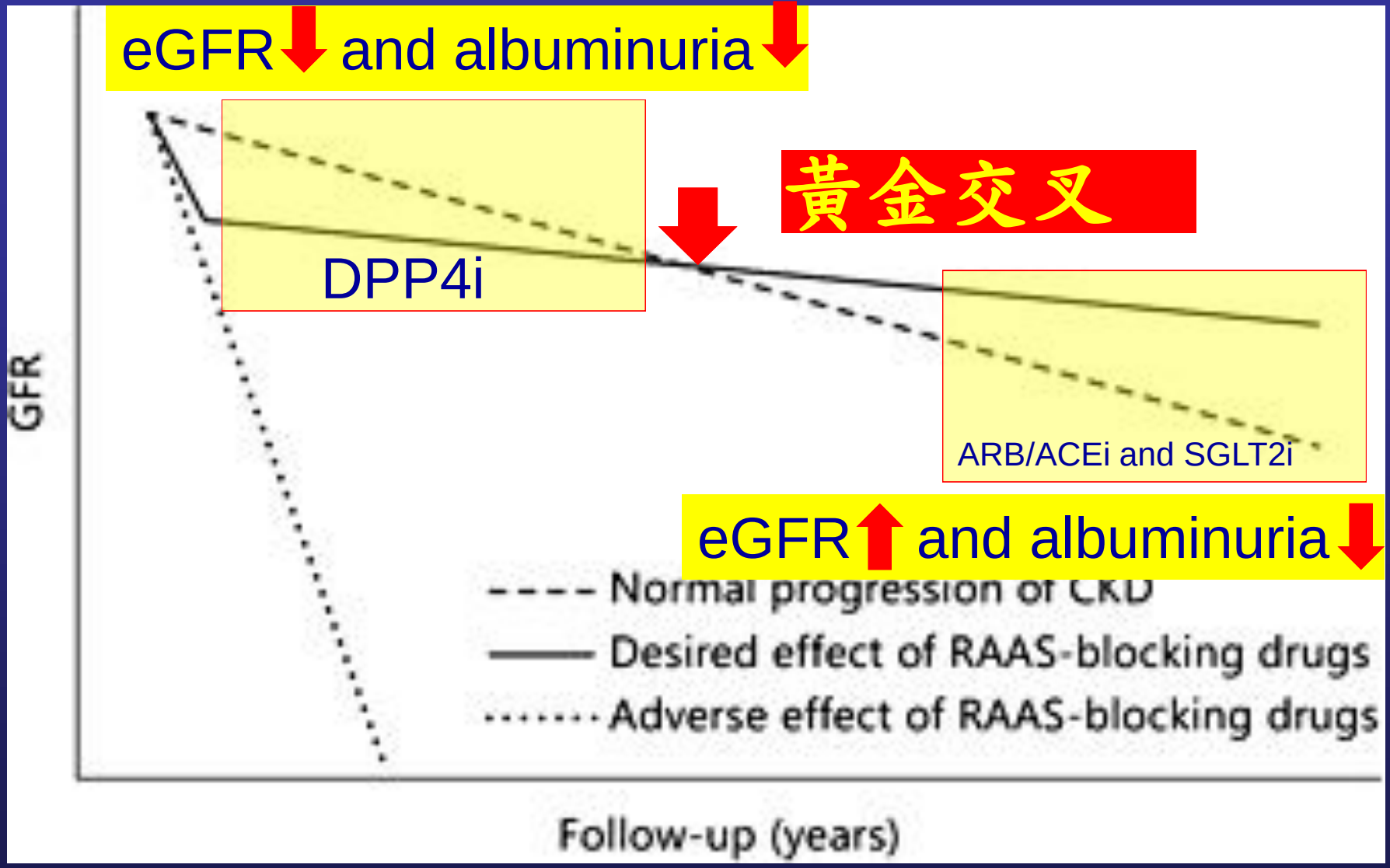
ORIGINAL ARTICLE

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

Diabetes Obes Metab. 2017;1–10.

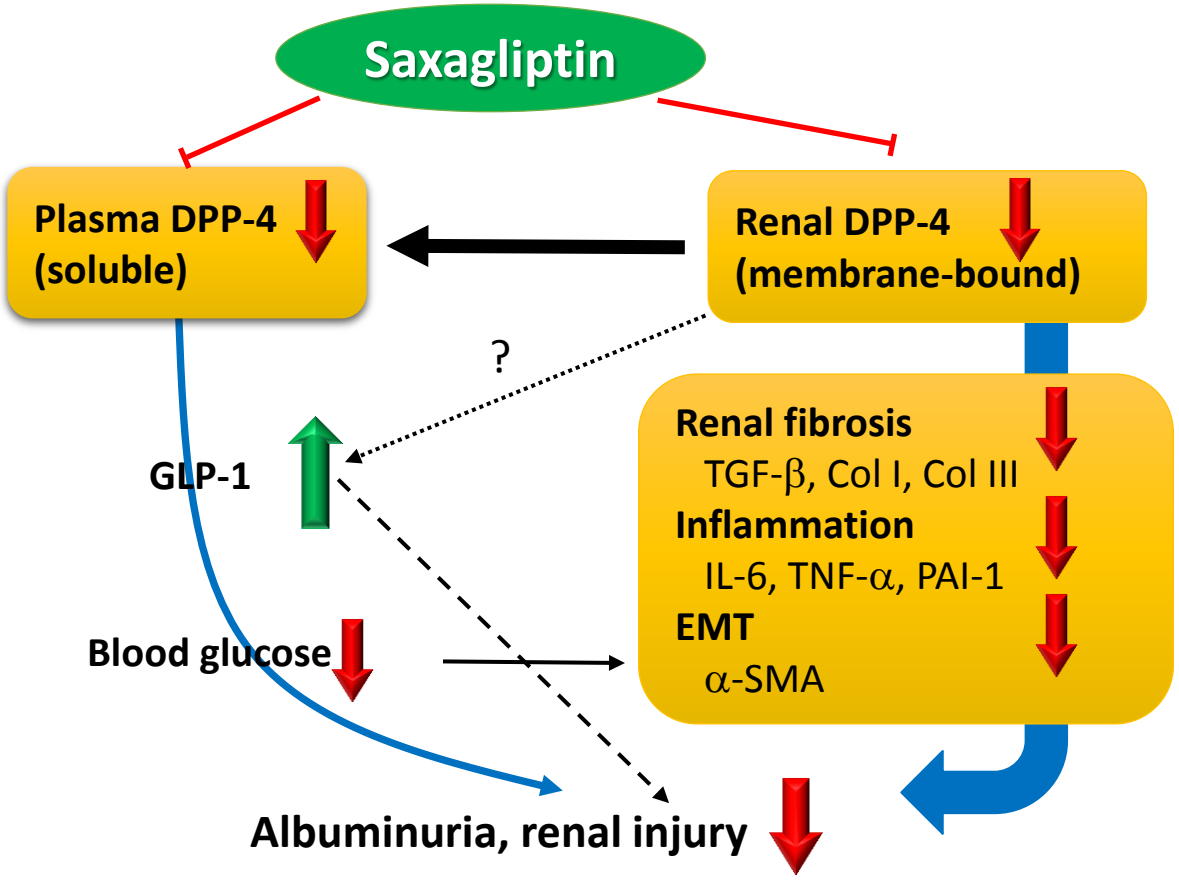


eGFR (CKD-EPI, cystatin C) at week 24 between the linagliptin and placebo groups was −2.63 mL/min (P = .3306).



Cardiology. 2013;126(3):175-86.

Saxagliptin Provide Potential Renoprotective Effect



1. Saxagliptin inhibited the development of renal injury **independent** of its glucose-lowering effect

2. The renoprotective effect of saxagliptin is attributable to **anti-inflammatory** and **anti-fibrotic** action through the strong suppression of renal DPP-4 activity

Eur J Pharmacol. 2016 Apr 7. pii: S0014-2999(16)30209-6. doi: 10.1016/j.ejphar.2016.04.005. [Epub ahead of print]

*Data abstracted from Dahl-S rats
Onglyza is not approved for the treatment of albuminuria

GLP-1 has protective effects on kidney

- Hyperglycaemia causes endothelial dysfunction through several pathways, including reduction of GLP-1R signaling and enhanced angiotensin 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

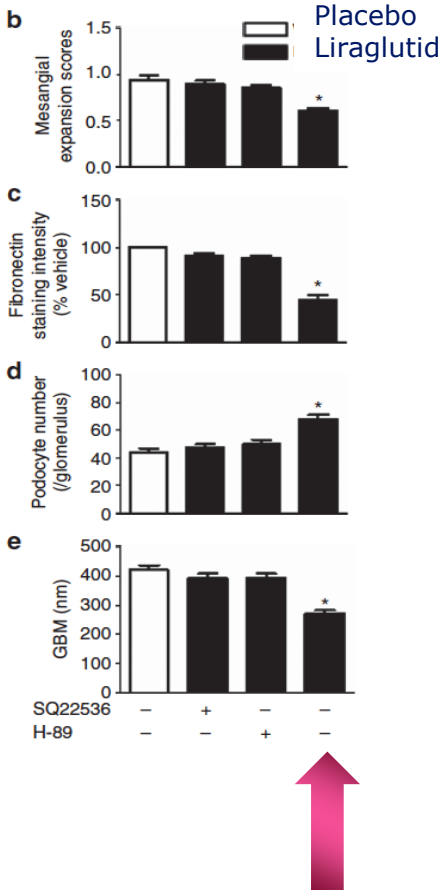
SQ: Inhibitor of cAMP
H-89: Inhibitor of proteinkinase

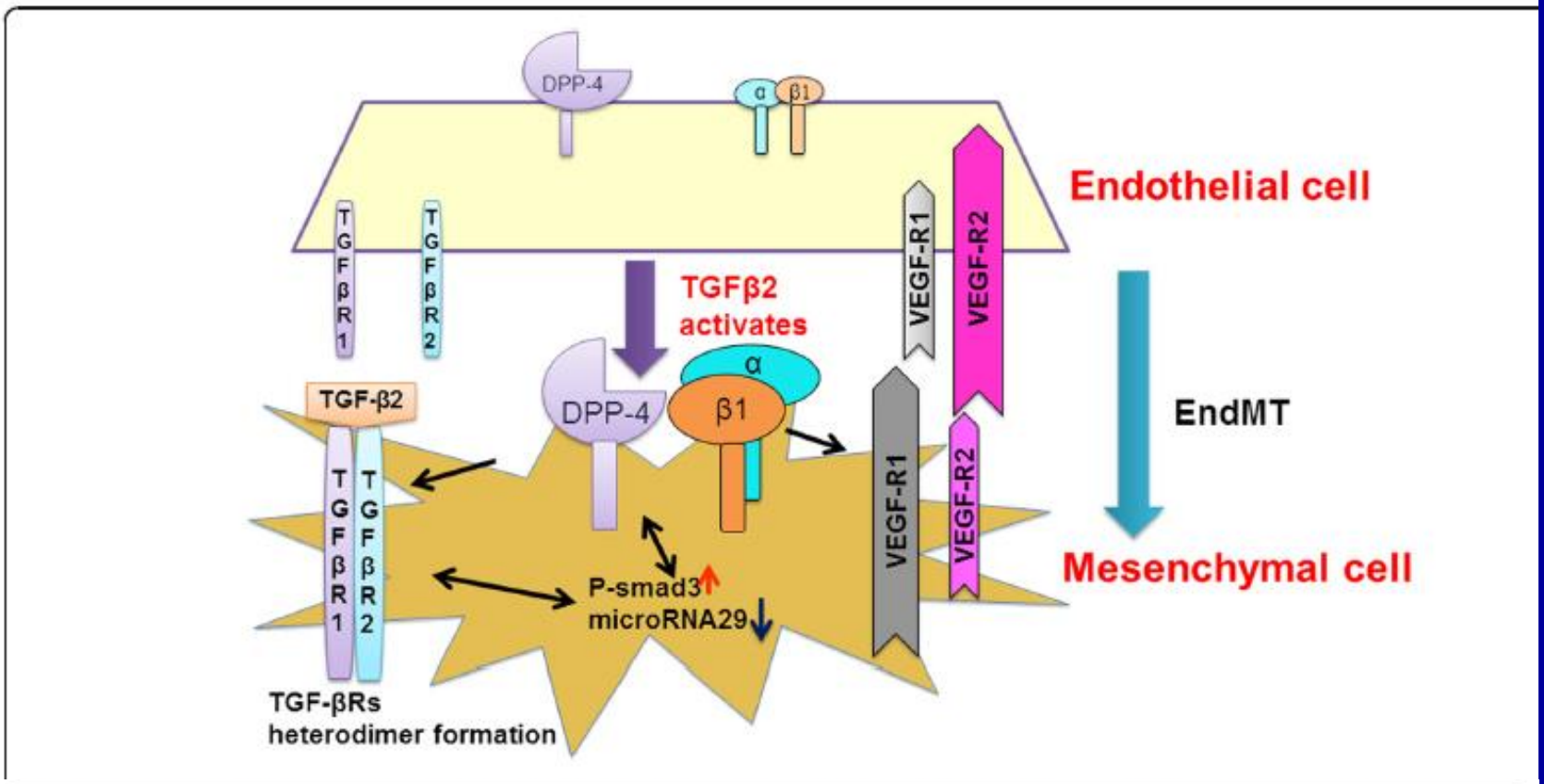
Mesangial Expansion

Fibronectin

Number of podocytes

GBM width





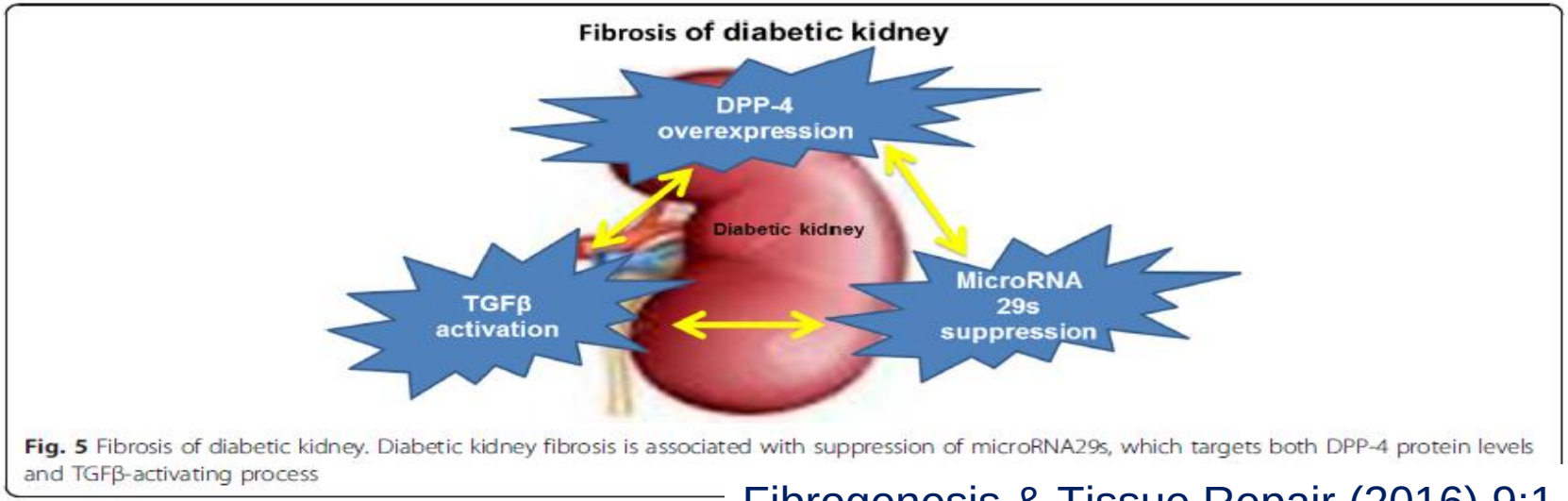
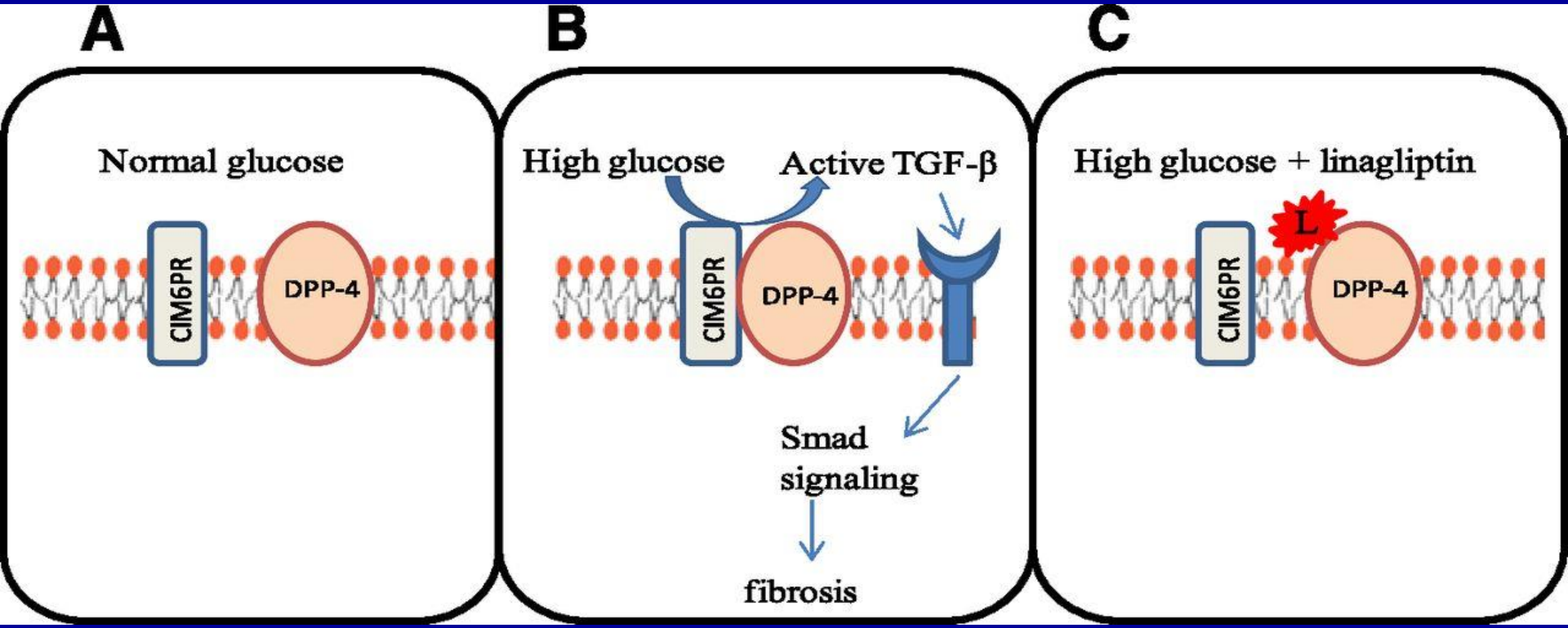


Fig. 5 Fibrosis of diabetic kidney. Diabetic kidney fibrosis is associated with suppression of microRNA29s, which targets both DPP-4 protein levels and TGFβ-activating process

Fibrogenesis & Tissue Repair (2016) 9:1

cation-independent mannose 6-phosphate receptor (CIM6PR) is central to the activation process of TGF- β 1 in human kidney proximal tubular cells exposed to high glucose



Diabetes 2014 Jun; 63(6): 1829-1830

European Journal of Pharmacology 761 (2015) 109–115

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, gastrointestinal and urogenital pharmacology

Critical role of renal dipeptidyl peptidase-4 in ameliorating kidney injury induced by saxagliptin in Dahl salt-sensitive hypertensive rats

Mariko Sakai [a], Masako Uchii [a], Kensuke Myojo [b], Tetsuya Kitayama [a], Shunji Kunori [a,*]

[a] Nephrology Research Laboratories, Nephrology R&D unit, R&D Division, Kyowa Hakko Kirin Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan

[b] Translational Research Unit, R&D Division, Kyowa Hakko Kirin Co., Ltd., 1188 Shimotogari, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8731, Japan

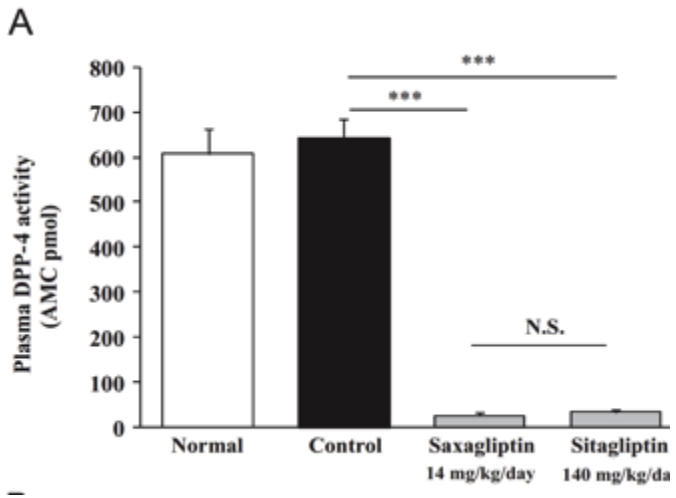
European JournalofPharmacology761(2015)109–115

Sakai, M., Uchii, M., Myojo, K., Kitayama, T. & Kunori, S. Critical role of renal dipeptidyl peptidase-4 in ameliorating kidney injury induced by saxagliptin in Dahl salt-sensitive hypertensive rats. *Eur J Pharmacol* **761,** 109–115 (2015).

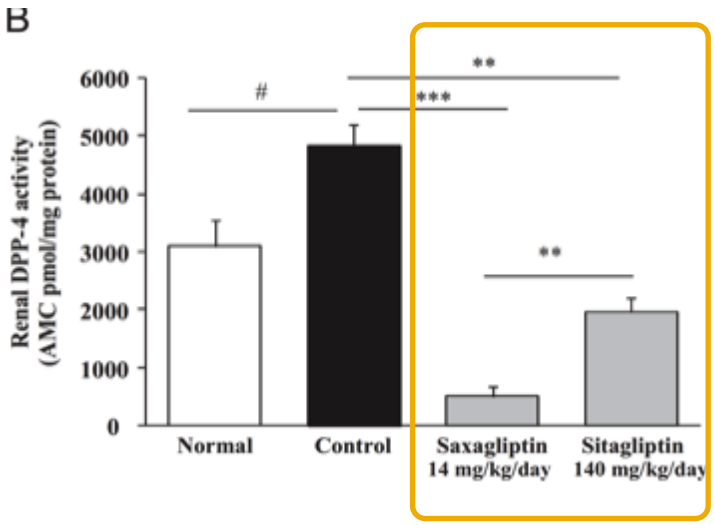
Onglyza is not approved for the treatment of albuminuria

Renal DPP4 Inhibition by Saxagliptin is more potent than Sitagliptin*

Plasma DPP4 activity



Renal DPP4 activity

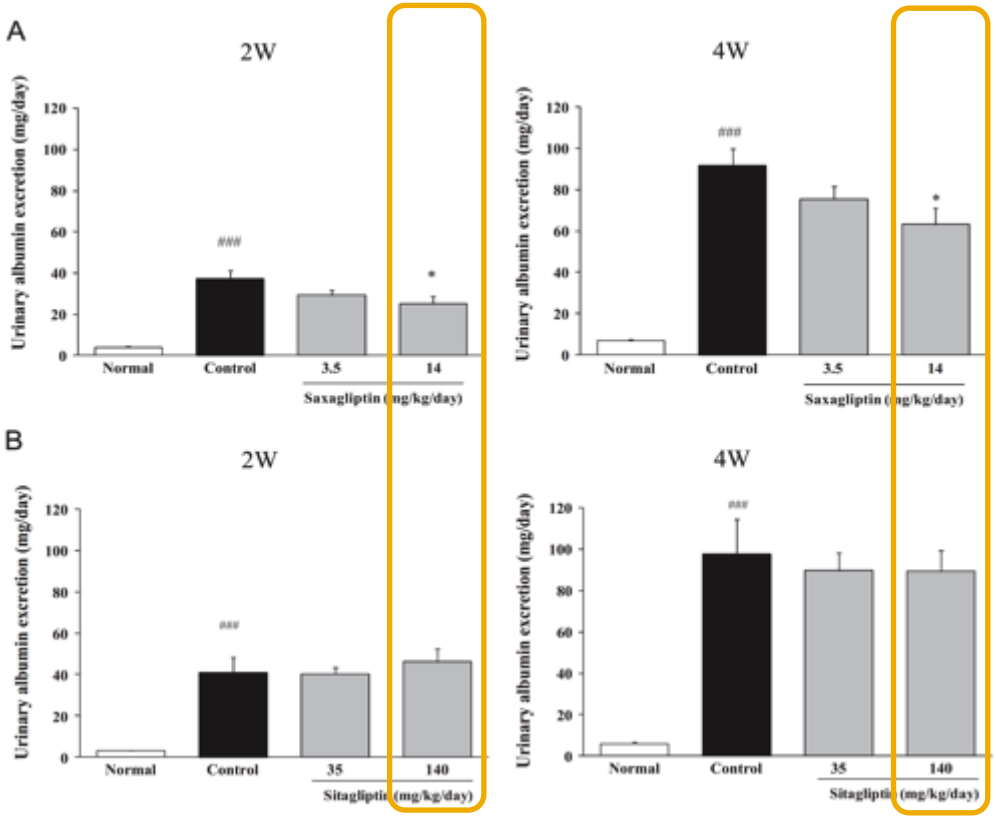


Both saxagliptin and sitagliptin significantly inhibited the plasma DPP-4 activity by 95% or more in the Dahl-S rats; the inhibitory effects on the plasma DPP-4 activity were comparable between saxagliptin and sitaliptin (25+/-5 and 32+/-6 pmol, respectively). In the renal tissues, saxagliptin and sitagliptin also inhibited the increase in the DPP-4 activity, although the inhibitory effect of saxagliptin on DPP-4 was more potent than that of sitagliptin (507+/- 165 and 1971+/-223 pmol /mg protein, respectively; P<0.01)

Sakai, M., Uchii, M., Myojo, K., Kitayama, T. & Kunori, S. Critical role of renal dipeptidyl peptidase-4 in ameliorating kidney injury induced by saxagliptin in Dahl salt-sensitive hypertensive rats. *Eur J Pharmacol* **761,** 109–115 (2015).

*Data abstracted from Dahl-S rats
Onglyza is not approved for the treatment of albuminuria

Onglyza was Associated with Albuminuria Decrease but not Sitagliptin after 2 Weeks and 4 Weeks*



Sakai, M., Uchii, M., Myojo, K., Kitayama, T. & Kunori, S. Critical role of renal dipeptidyl peptidase-4 in ameliorating kidney injury induced by saxagliptin in Dahl salt-sensitive hypertensive rats. *Eur J Pharmacol* **761,** 109–115 (2015).

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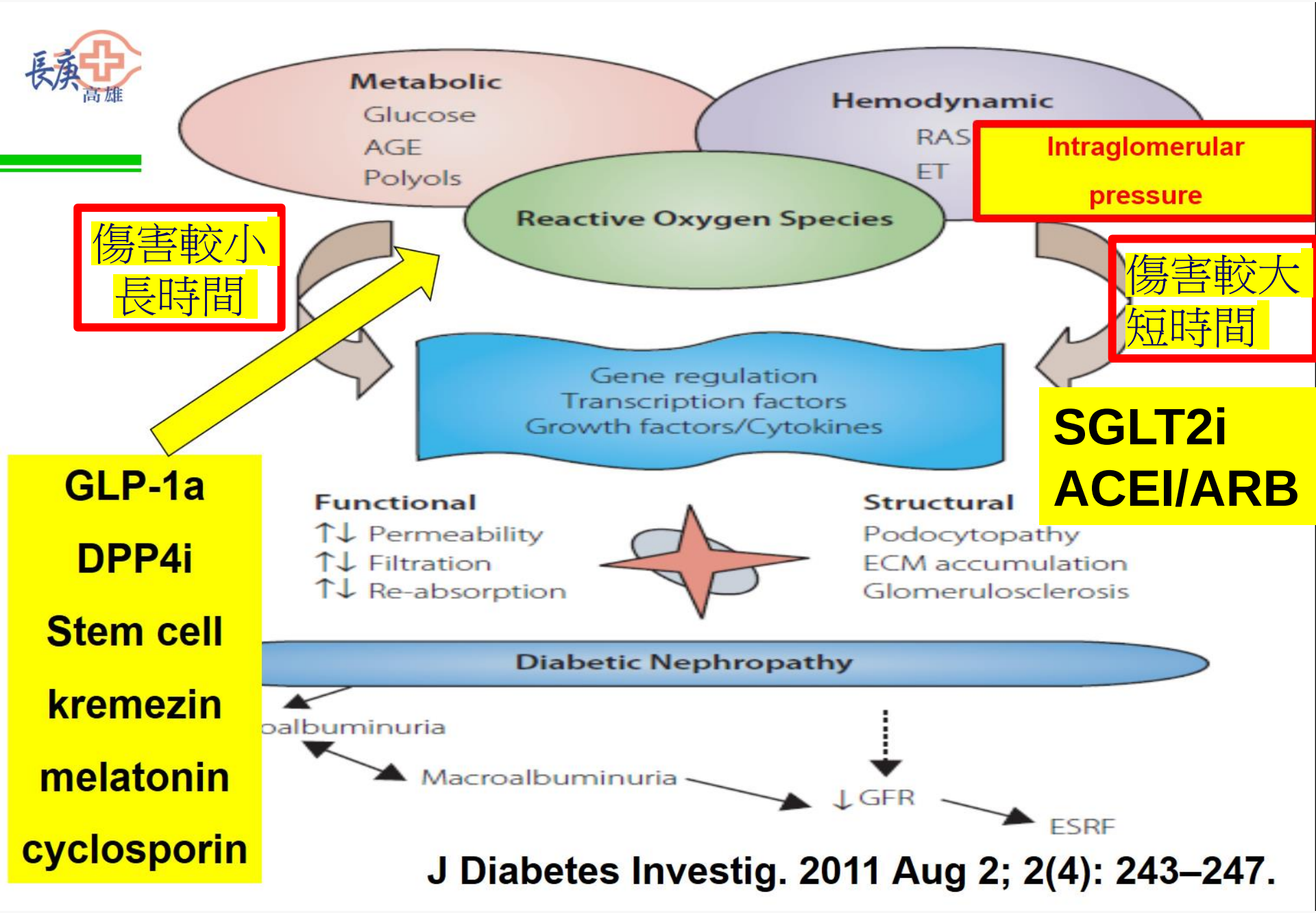
Take home messages



J Diabetes Investig. 2011 Aug 2; 2(4): 243–247.

水管千瘡百孔，一邊把水壓關小一邊來做修補，會得到比較好的效果。

Summary

- Chronic kidney disease is a recognized comorbidity among patients with T2DM
- The presence of renal insufficiency and/or old age is an important consideration for choice of antihyperglycemic therapy
- DPP4is may be an appropriate choice for T2D pts with renal impairment and/or old age in many aspects: glucose fluctuation, hypoglycemia and weight gain
- DPP4i has clinical evidence supporting use: reduce albuminuria and safe CV and renal effects in pts with high CV risk

Thanks!!