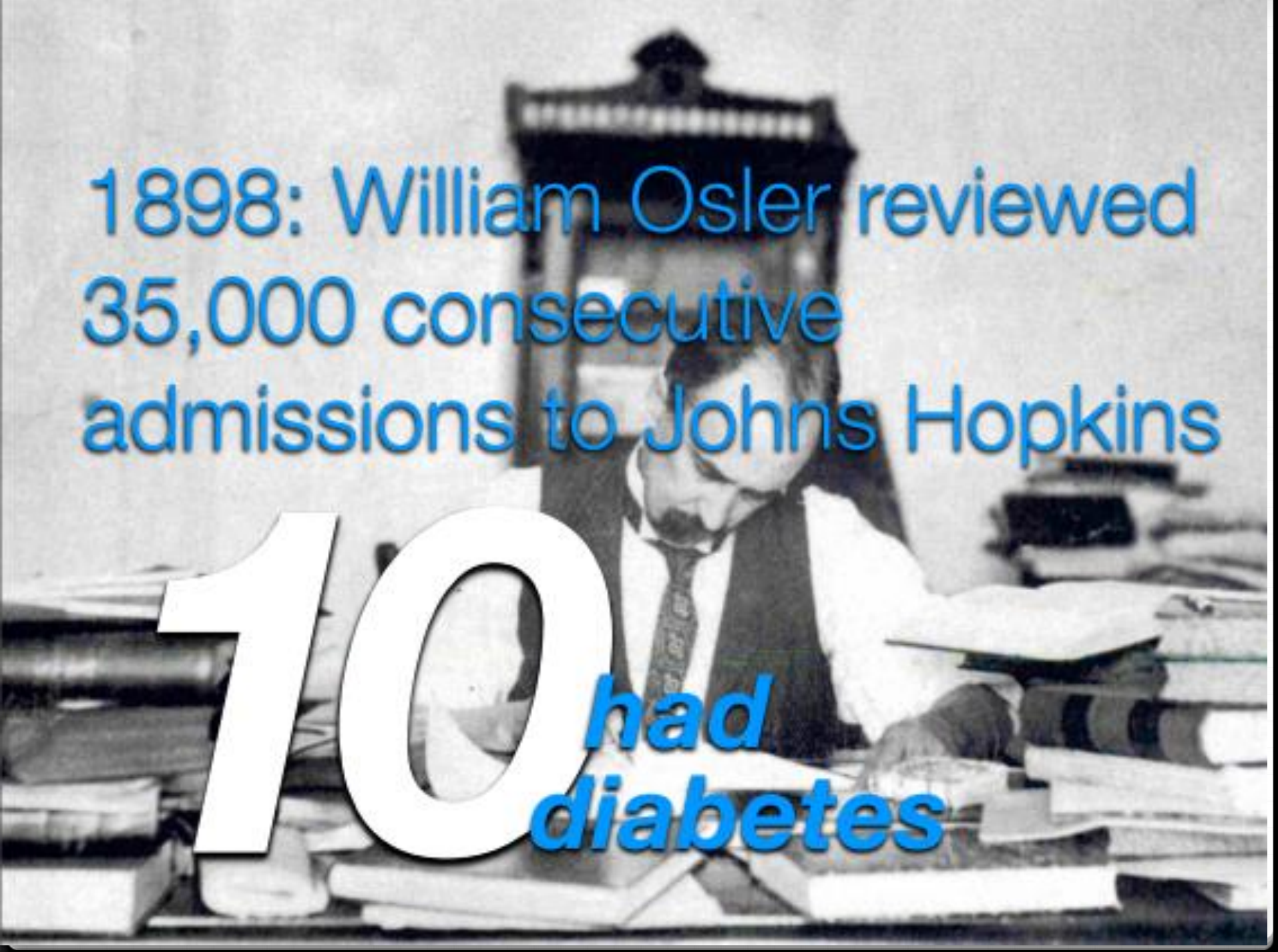
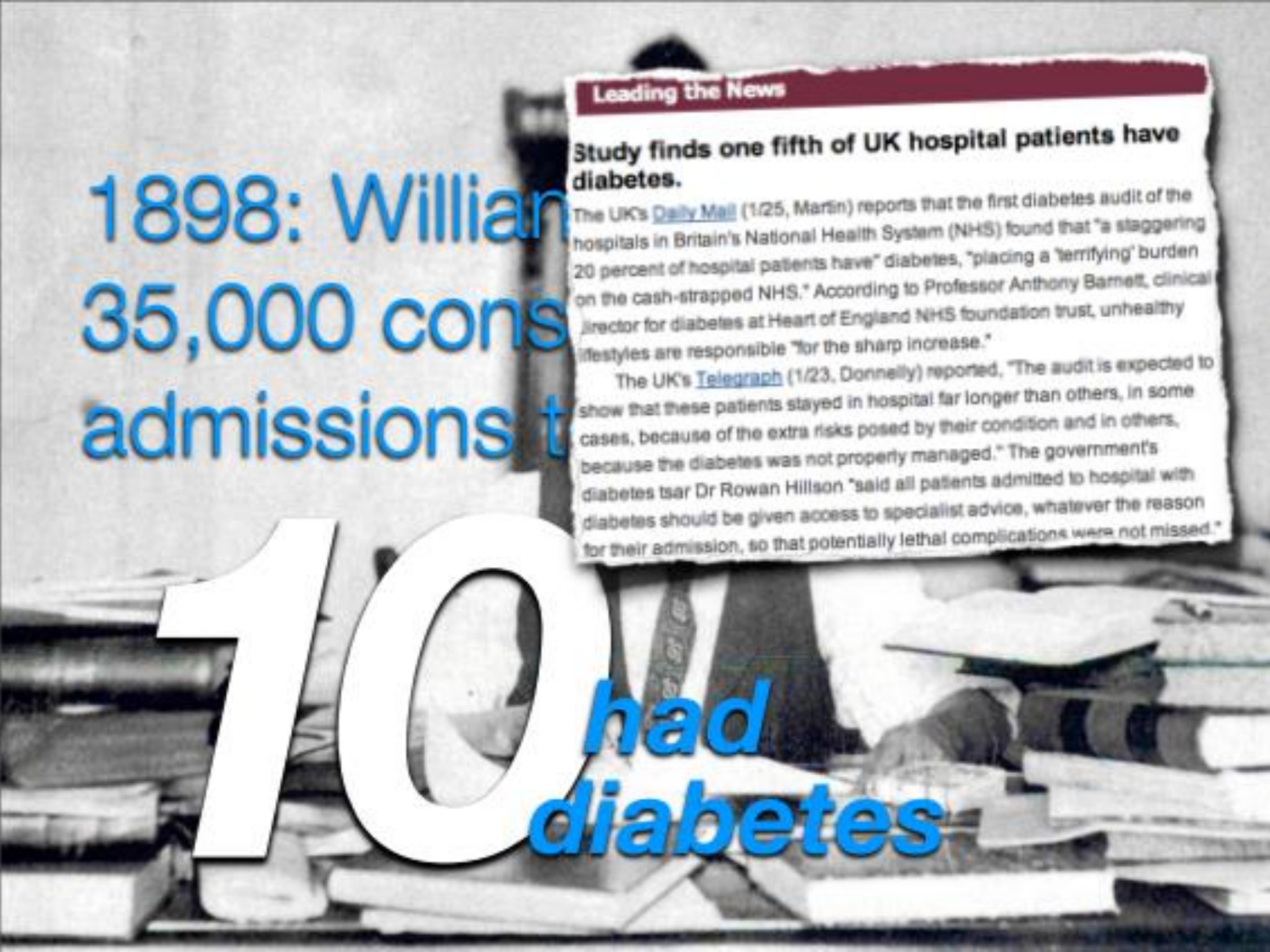
Current challenges in management of morbidity and mortality in T2DM "nephropathy"

治療糖尿病腎病變所面臨的挑戰

台灣大學附設醫院腎臟科
吳允升醫師，Vin-Cent Wu

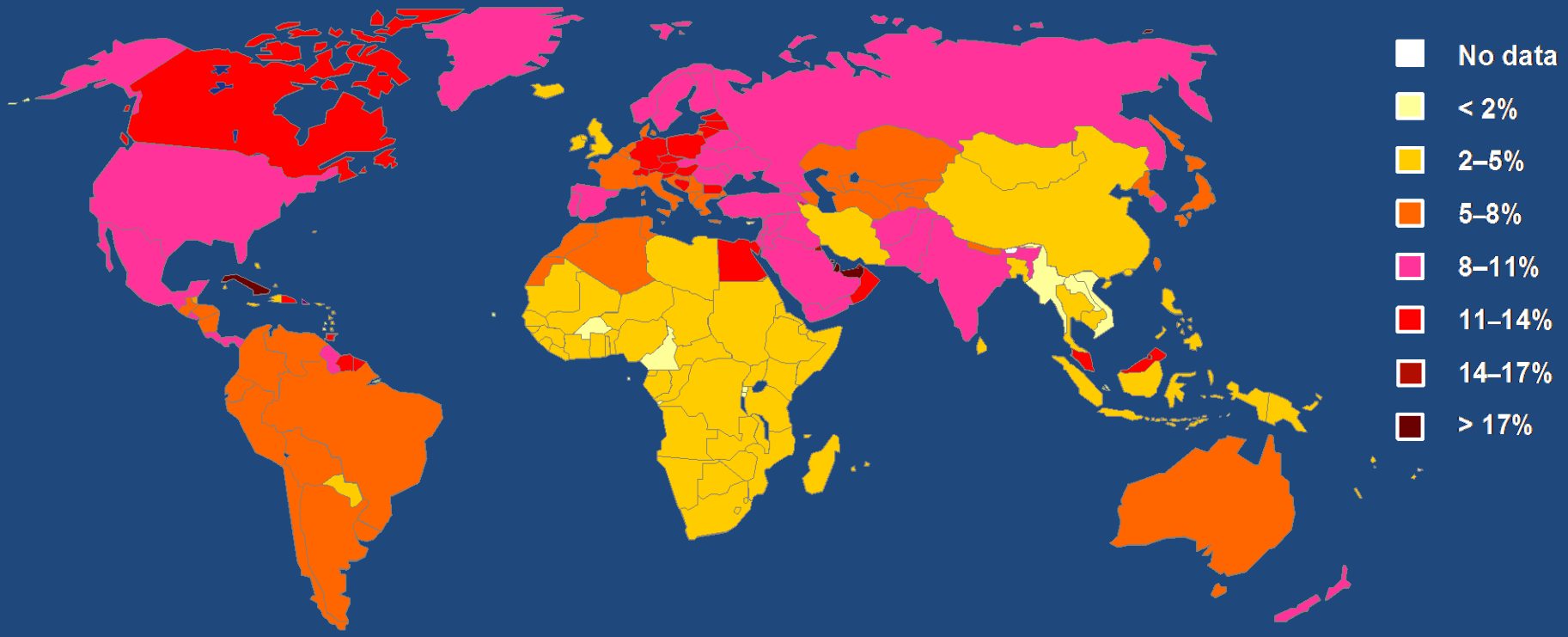

Happy
New
Year


1898: William Osler reviewed
35,000 consecutive
admissions to Johns Hopkins
10
had
diabetes


1898: Willian
35,000 cons
admissions t
10
had
diabetes
Leading the News
Study finds one fifth of UK hospital patients have diabetes.
The UK's Daily Mail (1/25, Martin) reports that the first diabetes audit of the hospitals in Britain's National Health System (NHS) found that "a staggering 20 percent of hospital patients have" diabetes, "placing a 'terrifying' burden on the cash-strapped NHS." According to Professor Anthony Barnett, clinical director for diabetes at Heart of England NHS foundation trust, unhealthy lifestyles are responsible "for the sharp increase."
The UK's Telegraph (1/23, Donnelly) reported, "The audit is expected to show that these patients stayed in hospital far longer than others, in some cases, because of the extra risks posed by their condition and in others, because the diabetes was not properly managed." The government's diabetes tsar Dr Rowan Hillson "said all patients admitted to hospital with diabetes should be given access to specialist advice, whatever the reason for their admission, so that potentially lethal complications were not missed."

Diabetes: the growing global burden

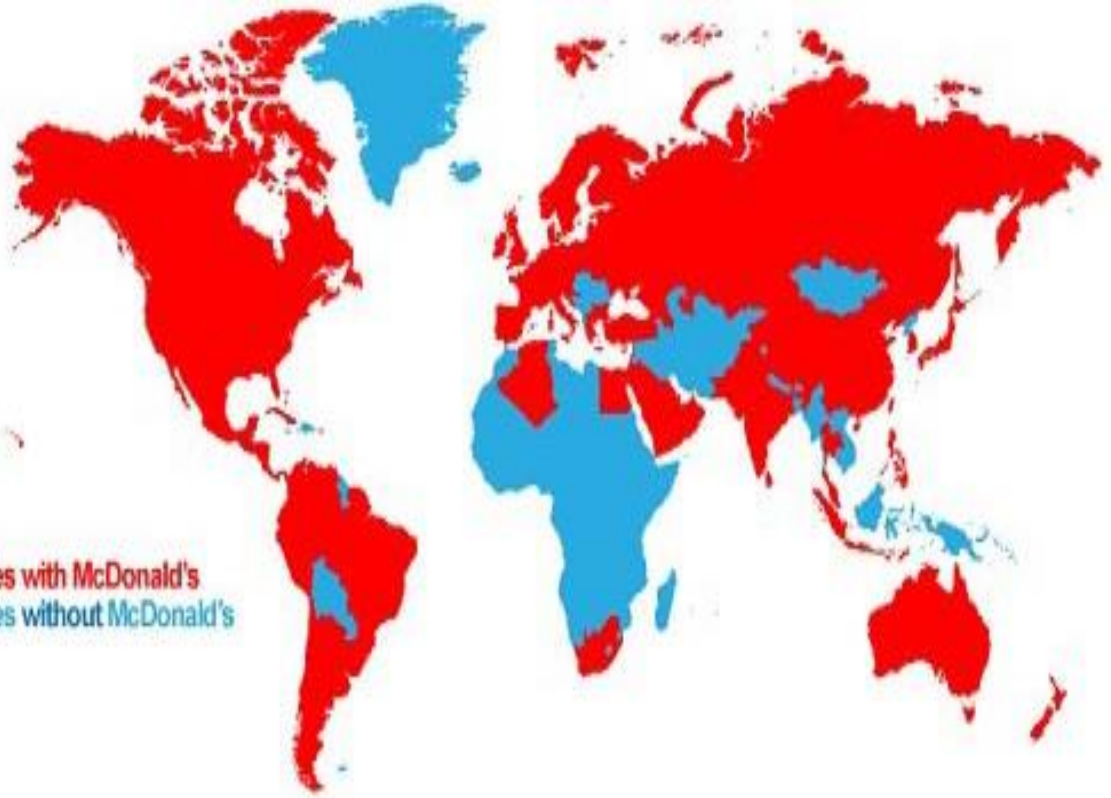
Prevalence estimates of diabetes mellitus 2025



IDF:

- **Diabetes currently affects 246 million people worldwide**
- **It is expected to affect 380 million by 2025**

ACROSS THE WORLD



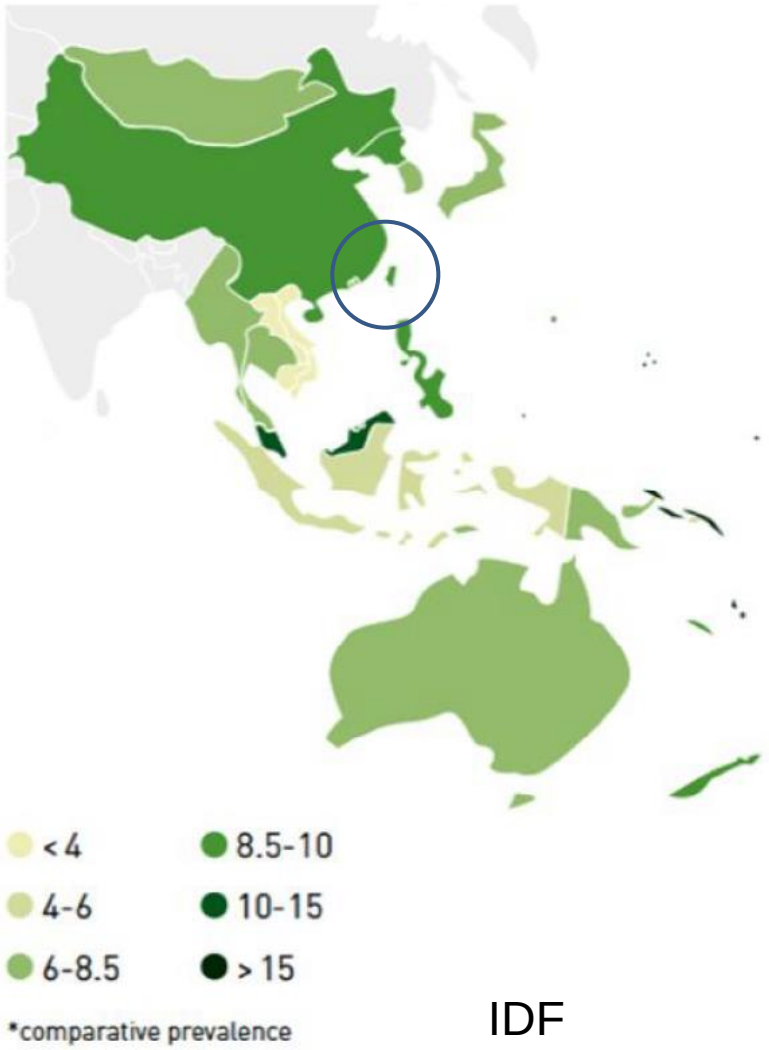
Number of McDonald's outlets of selected countries

US	Japan	Canada	Germany	UK	China
13,381	3,598	1,400	1,276	1,250	660

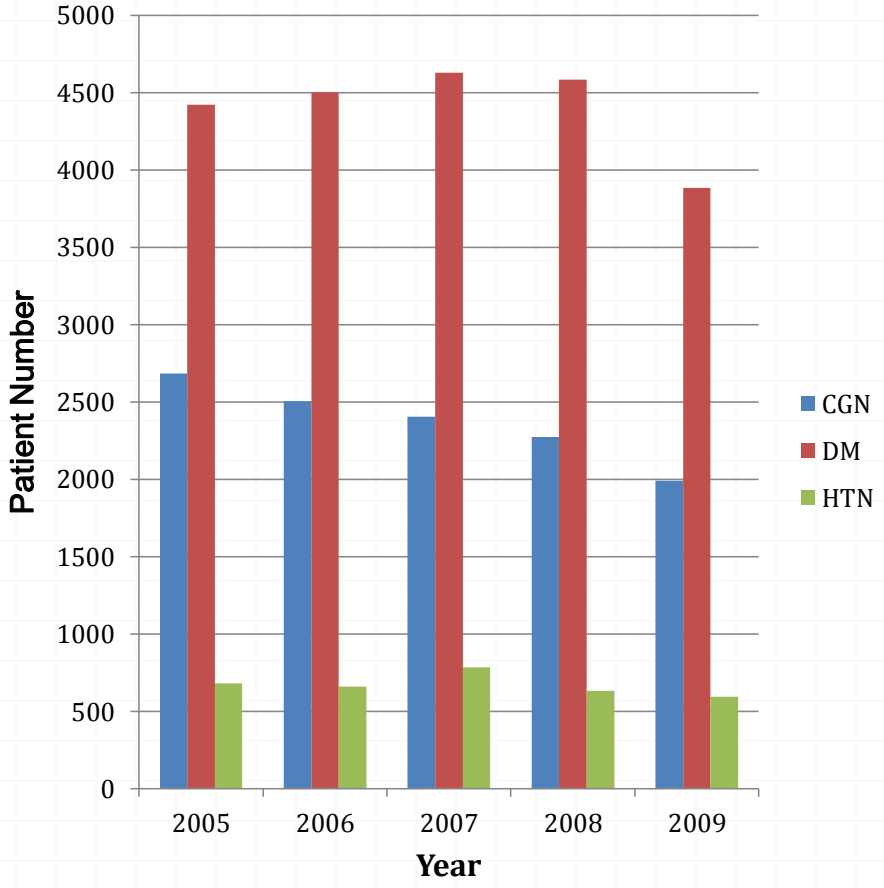
Most expensive McDonald's burger - seleted countires (USD)*

Norway	Demark	Iceland	Eurozone	US
7.18	5.93	5.21	4.96	3.57

Incident rates in the DM, ESRD , TAIWAN

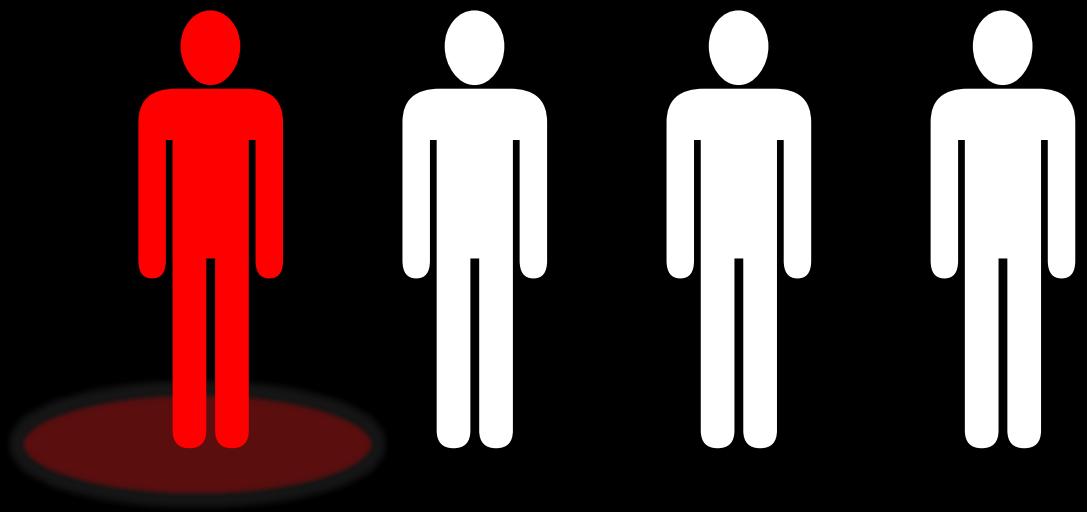


IDF



TSN, Leading incidence for dialysis

When patients with type 2 diabetes see their doctor

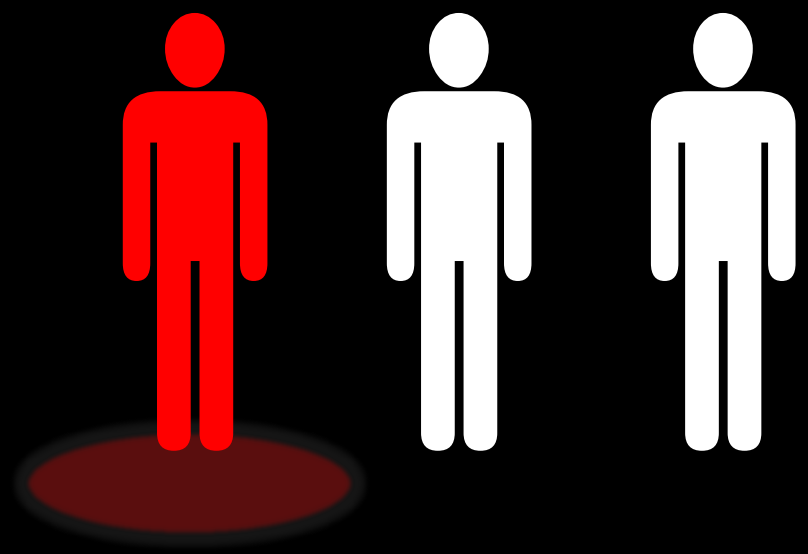


1 in 4 have an eGFR< 60

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

Parving HH, et al. Kidney Int. 2006;69:2057-2063

In diabetic individuals over 65 years old



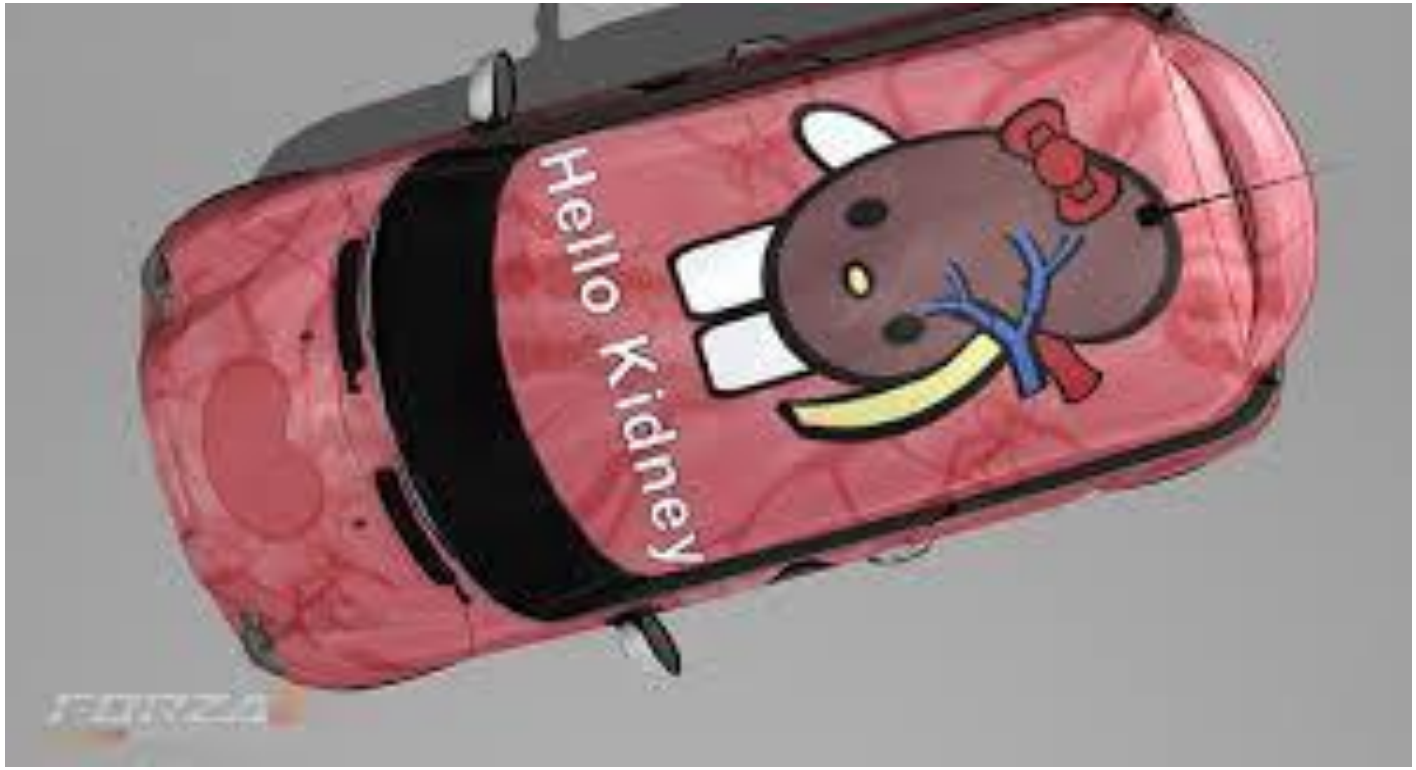
1 in 3 have an eGFR< 60

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

Thomas M, et al. MJA. 2006;185:140–144; Parving HH, et al. Kidney Int. 2006;69:2057-2063

Diabetic kidney disease

Old disease, New perspectives



A Taiwan National Health Survey 2002-2007

Risk factors vs. End organ damages

Relative Risk	Stroke	Kidney diseases	Cardiac diseases
Hypertension*	2.8	1.7	1.9
Hyperglycemia	2.9	2.4	1.5
Hyperlipidemia	2.4	1.6	1.8

*serum glucose level ≧126mg/dL or receiving antidiabetic treatment

摘錄自國民健康局網站. http://www.bhp.doh.gov.tw/bhpnet/portal/PressShow.aspx?No=200907170001

Strategy for DM nephropathy

Case presentation_1

- 45 y/o M with type II DM, CKD (eGFR= 45) who presents with hypoglycemia (glu= 40 mg/dL) , loss of consciousness.
- Hyperglycemia for more than 7 years without well control, his baseline creatinine is 3.7 mg/dL,

How would you manage this?

Medication

Start date	Medication	Dose and frequency
2012/2/1	Acarbose(Glucobay 50mg/tab)	1 tab P bid QD
2012/2/1	Glimepiride (Amaryl, 2 mg/tab)	0.5tab PO QD
2012/2/1	Folic Acid(Folic Acid 5mg/tab)	1 tab PO QD
2012/2/1	Nifedipine(ADALAT OROS 30mg/tab)	1 tab PO QD
2012/2/1	Pentoxifylline(Trenfylline SR FC 400mg/tab)	**1 tab PO QD**

BH:160 cm BW:74.2 kg, BMI= 29

T:37.9 P:105 R:15 BP:116/64 mmHg

- Consciousness E4M3V2
- Head-Eye-ENT

conjunctiva: pale; sclera:non-icteric

- Neck

Jugular vein engorgement(-)

Meningismus: Kernig sign(-); Brudzinski sign(-)

- Chest: Vocal fremitus and expansion: symmetric
- Heart : RHB without murmur
- Abdomen : Flat & soft
- Skin : warm and moisture

Abnormal pigmentation(-)

Petechiae(-) Purpura(-) Ecchymoses(-) Tenlagiectasia(-)

What tests might you order?

Hypoglycemia

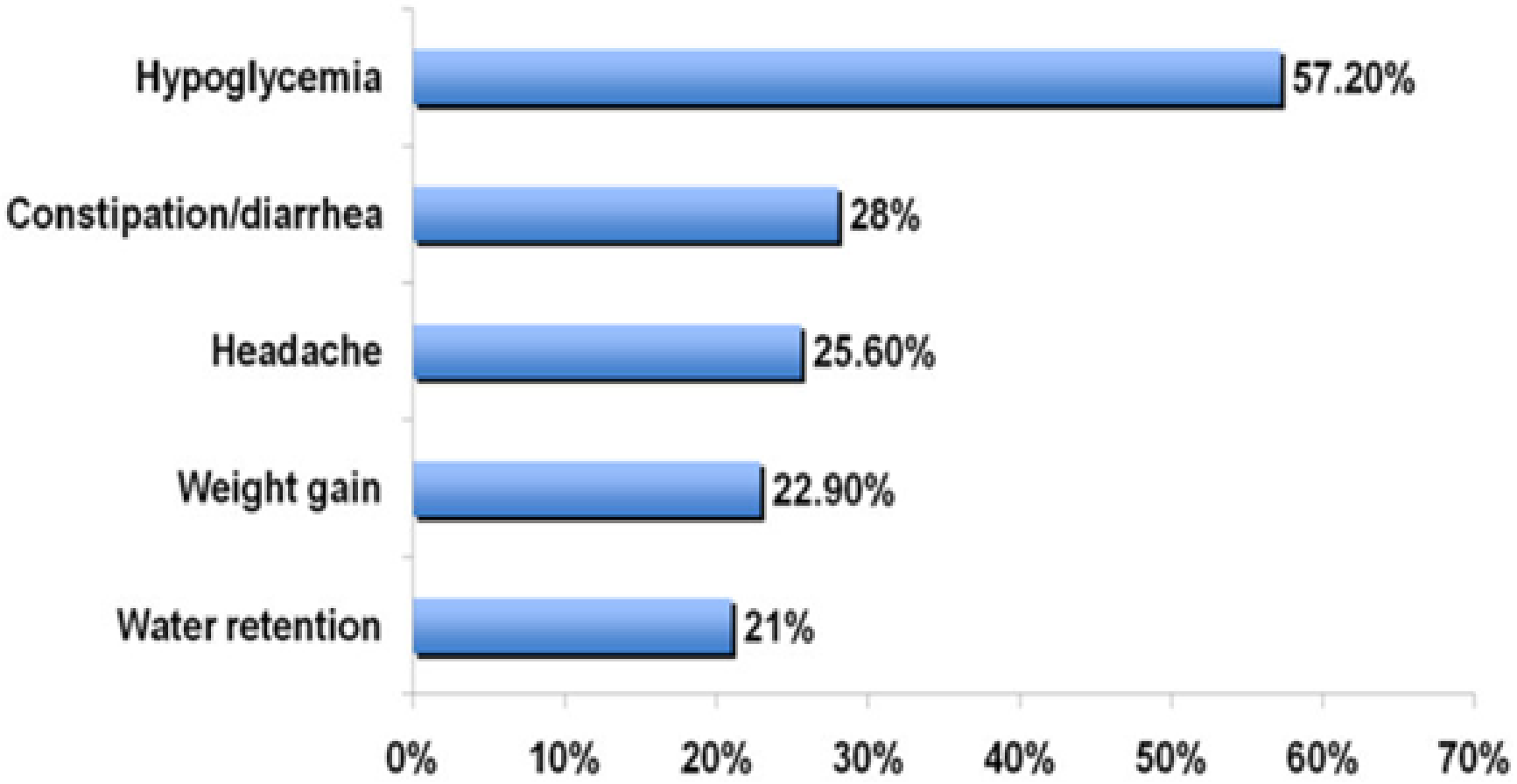
	2012/11/15
UN(mg/dL)	56
CRE(mg/dL)	3.7
K(mmol/L)	5.7
UA(mg/dL)	2.5
P(mg/dL)	5.1
Ca (mmole/L)	1.97
Na(mmol/L)	137
Glu (mg/dL)	40

MULTISTIX	2012/11/15 14:14
Sp. Gr.(C)(*)	1.009
pH(C)(*)	7.0
Protein(C)(mg/dL)	200 (2+)
Glu.(C)(mg/dL)	-
Ketones(C)(mg/dL)	-
O.B.(C)(mg/dL)	-
Urobil.(C)(mg/dL)	NORMAL
Bil.(C)(mg/dL)	-
Nitrite(C)(*)	-
Color(*)	Colorless
Turbidity(*)	Clear

Tentative diagnosis

1. SU related hypoglycemia
2. Type 2 diabetes mellitus, complicated with retinopathy and nephropathy
3. Hypertension

Tolerability Issues Reported by T2D



N = 2074 adults taking > 1 oral antIdiabetic drugs (OAD) but not insulin
Diabetes Res Clin. Pracr. 2010;87(2):204-210

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

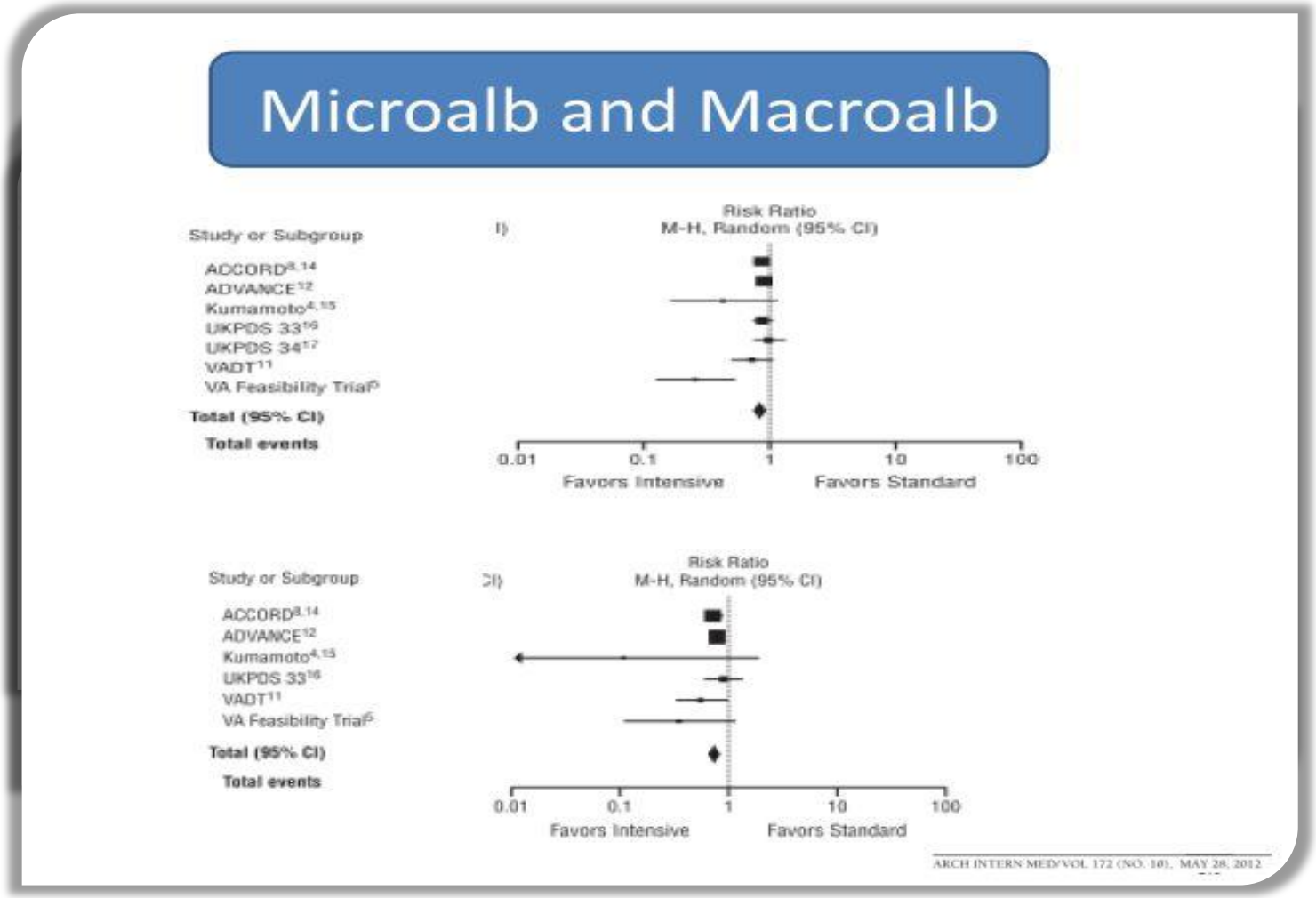
Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Long Term Follow-up

Initial Trial

* in T1DM

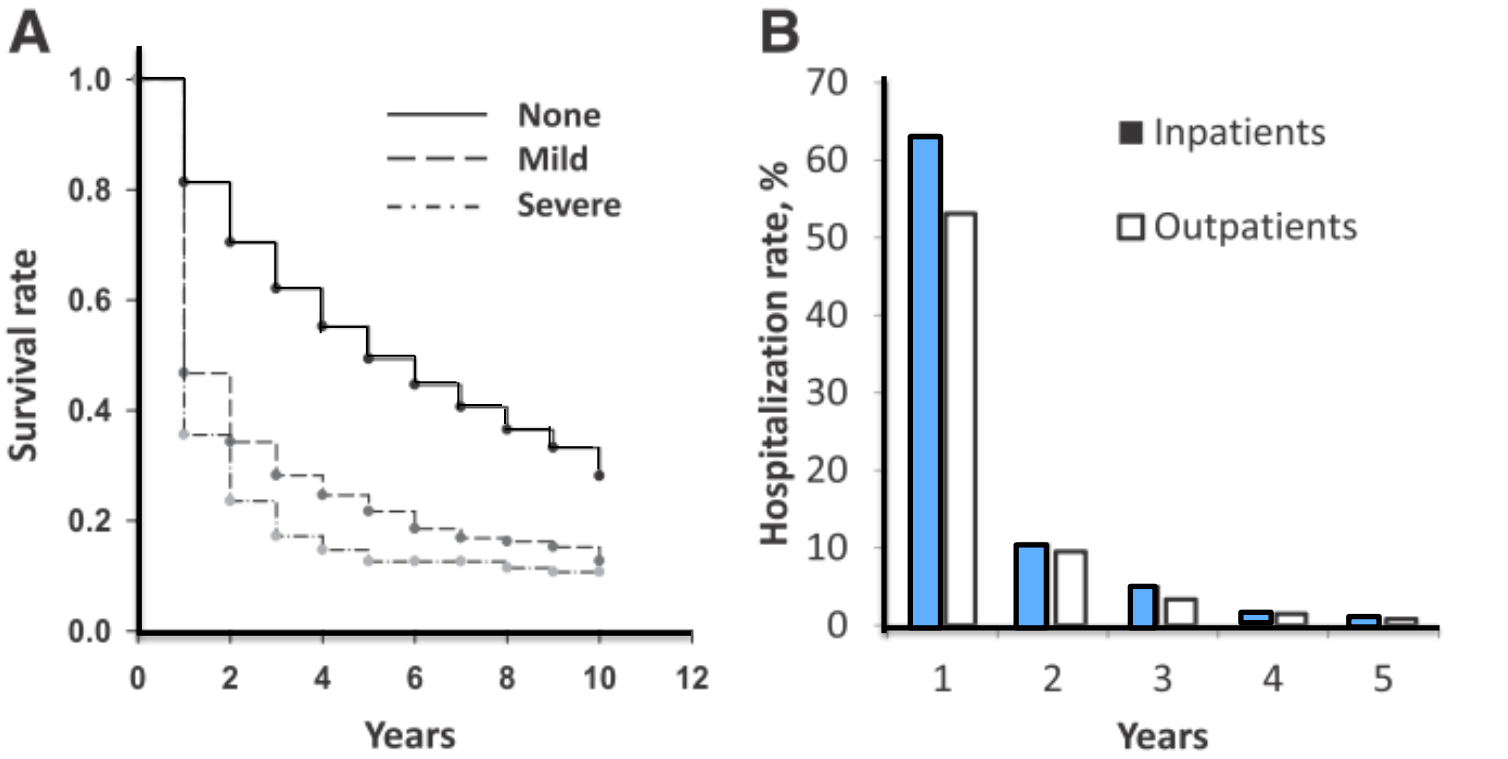
Intensive glucose control, individualization?



江山代有才人出，*各領風騷*數百年

Hypoglycemia and outcome

77,611 new onset type 2 DM, NHIR, 1844 hypoglycemic events, Taiwan

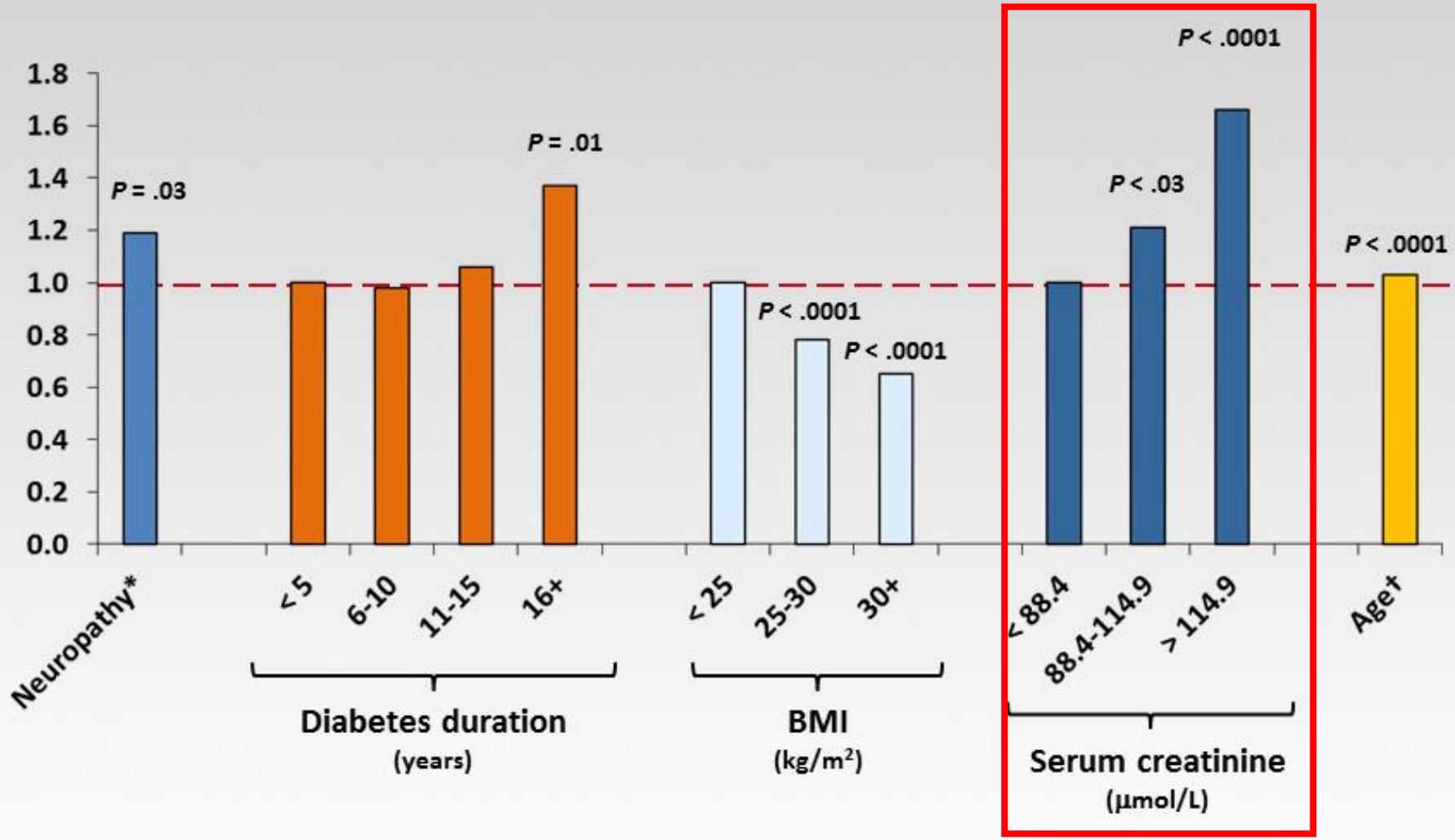


Diabetes Care, volume 36, April 2013

擔心

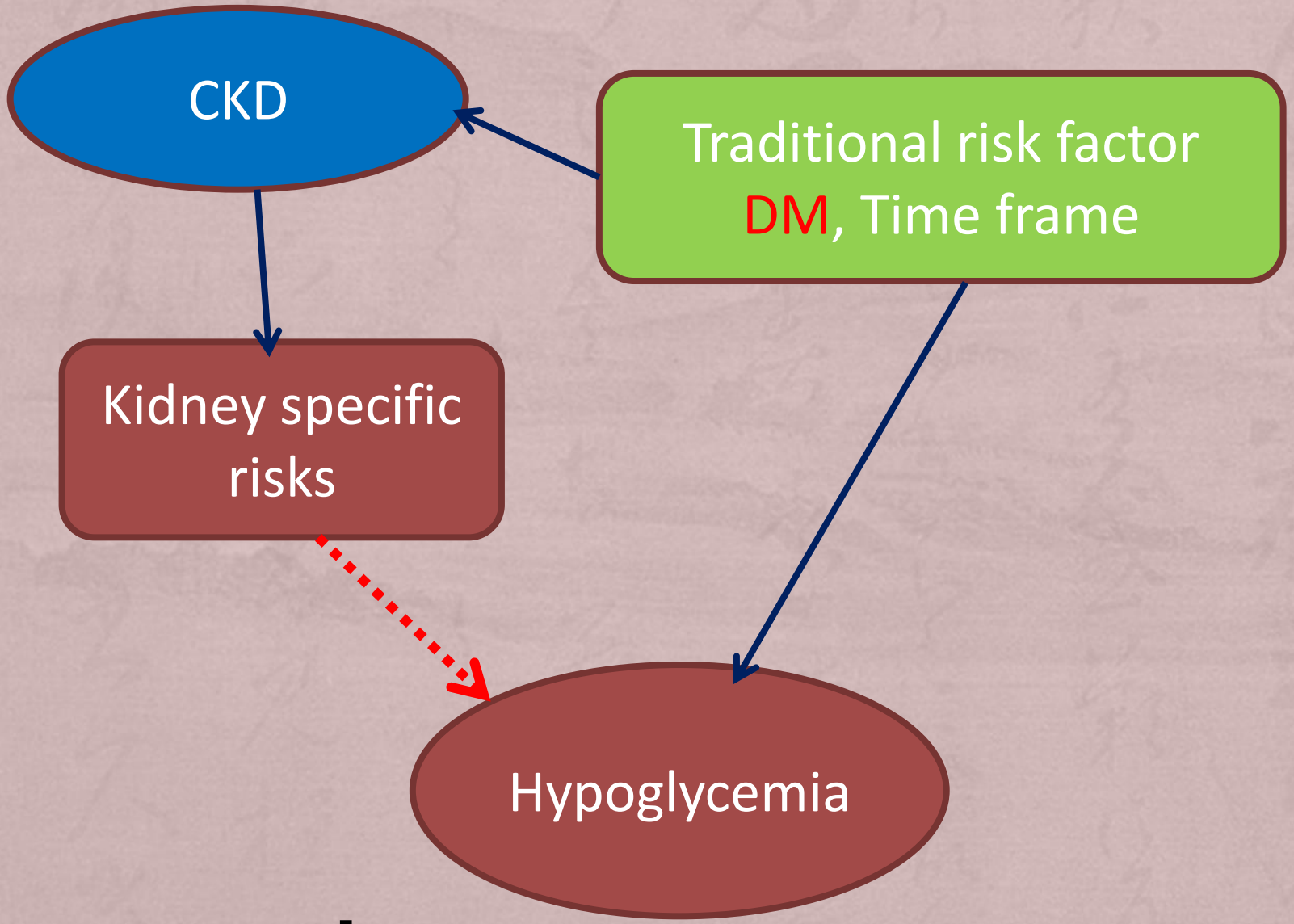
[龍巖好兄弟：象漾女孩變白琴女孩]

The Risk for Severe Hypoglycemia: Post Hoc Epidemiological Analysis of the ACCORD Study



*History of peripheral neuropathy (yes vs no); †per 1-year increase

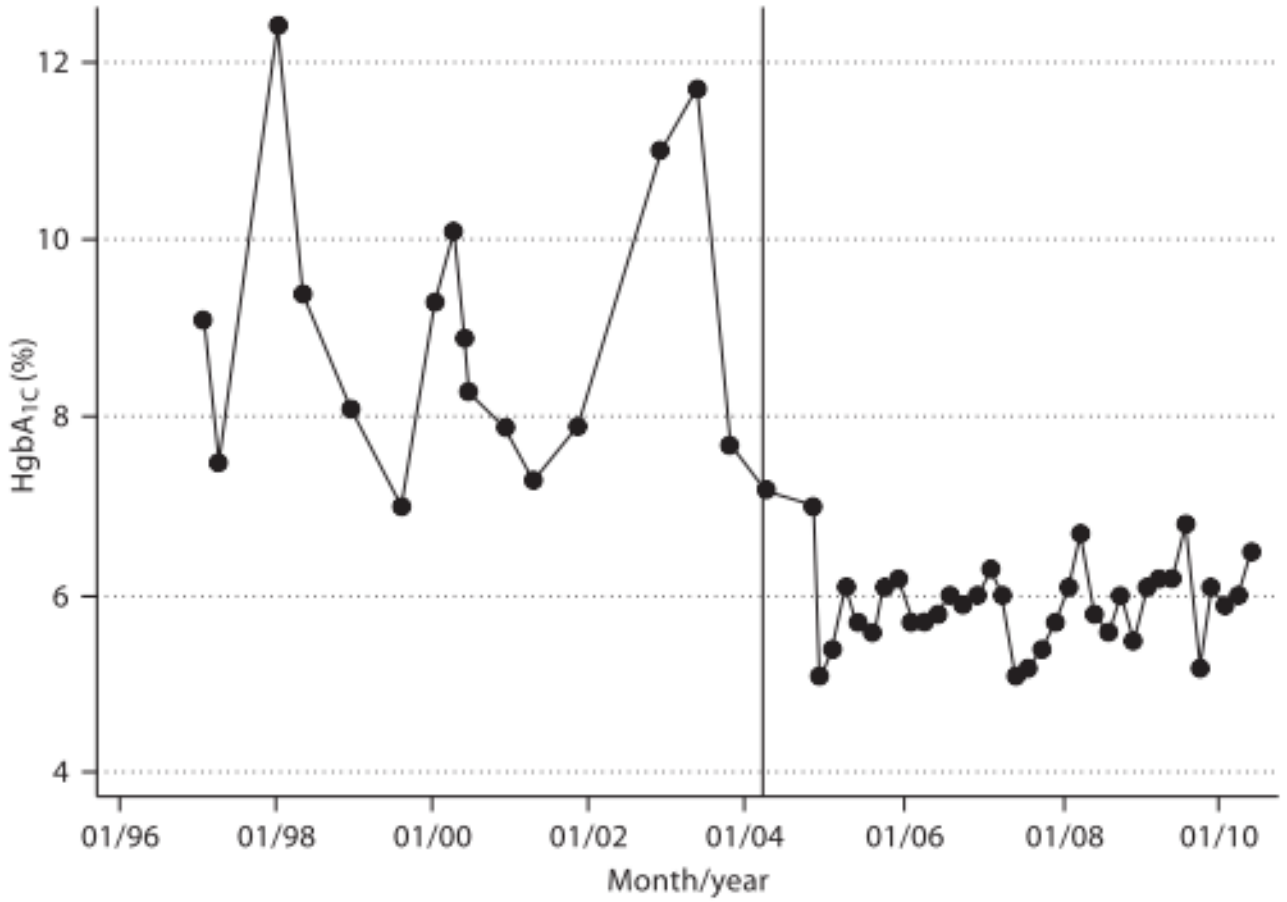
Miller ME, et al. BMJ. 2012;340:b5444.



The scenario

- Insulin degradation, eGFR < less than 20 mL/min
  - Gluconeogenesis
  - Poor calorie intake or occult disease
- Methods used HbA1c

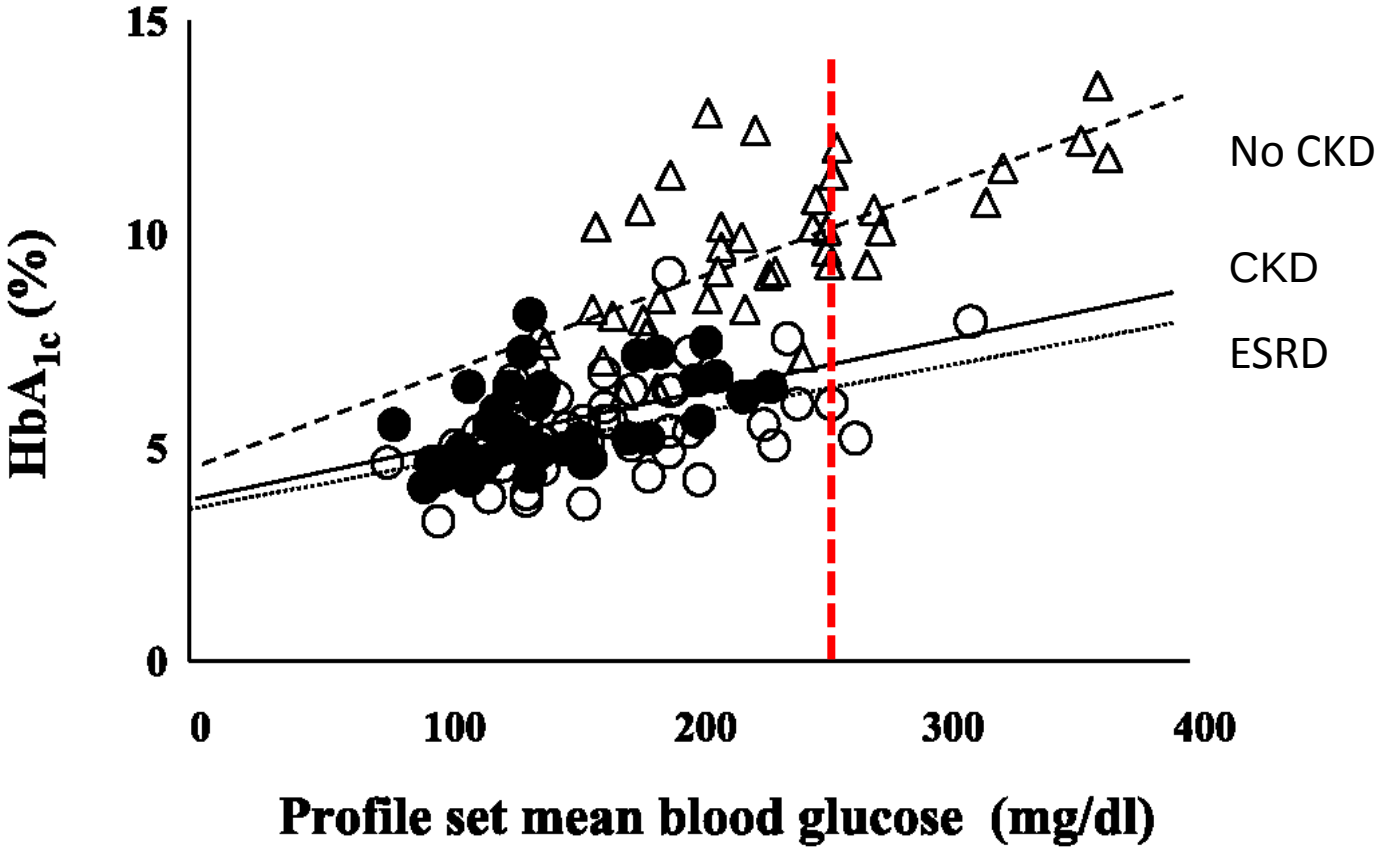
HbA1C change during CKD proceeding



Start dialysis

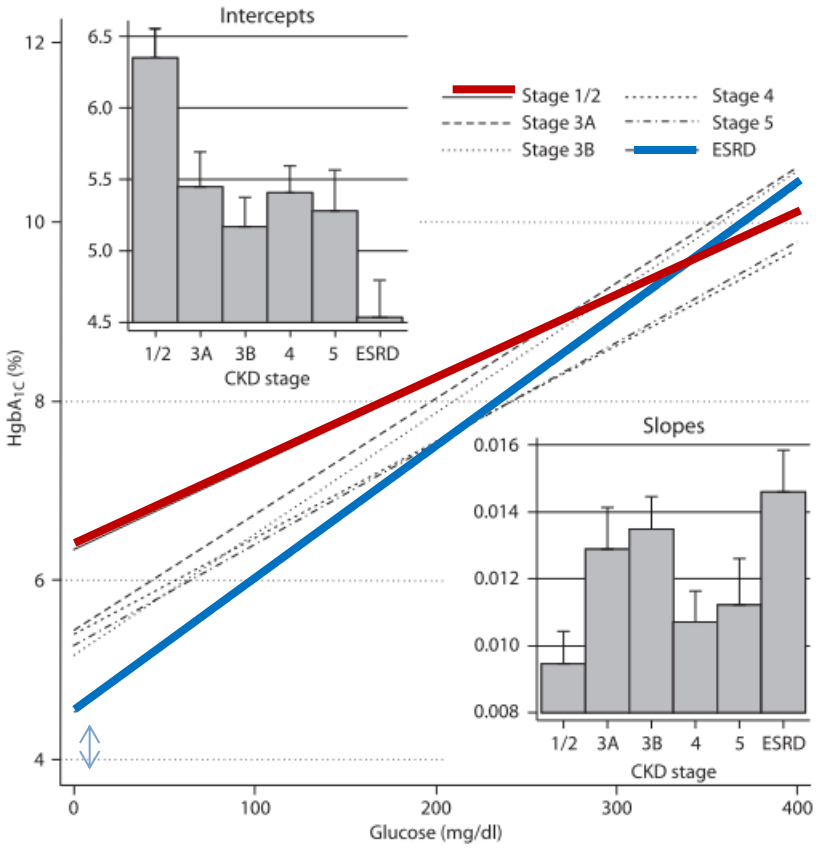
Measuring glycaemic control in CKD

HbA_{1c} is lower in CKD for the same mean glucose control



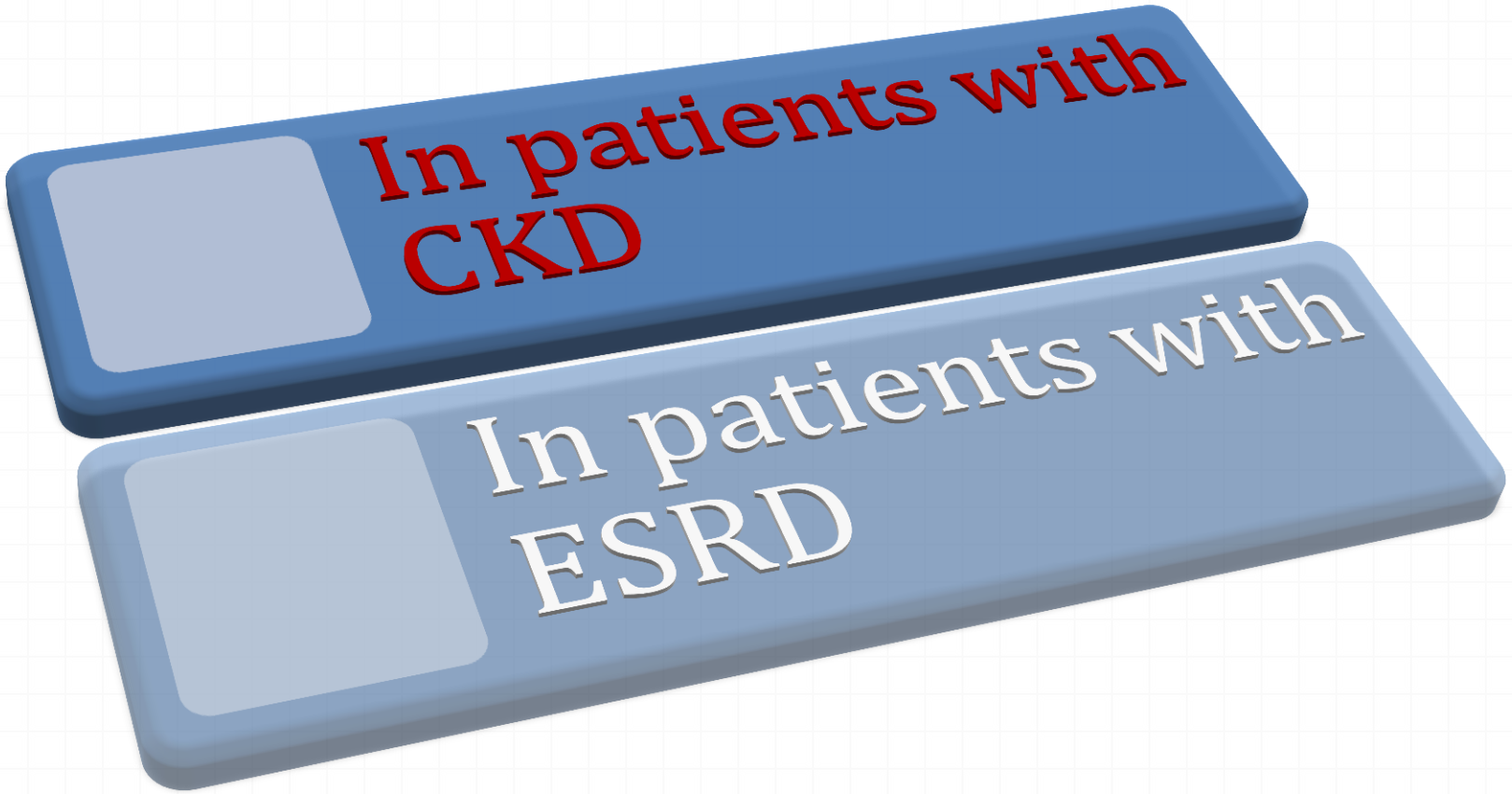
J Med Invest 2006; 53: 223-8

Glucose and HbA1c stratified by CKD



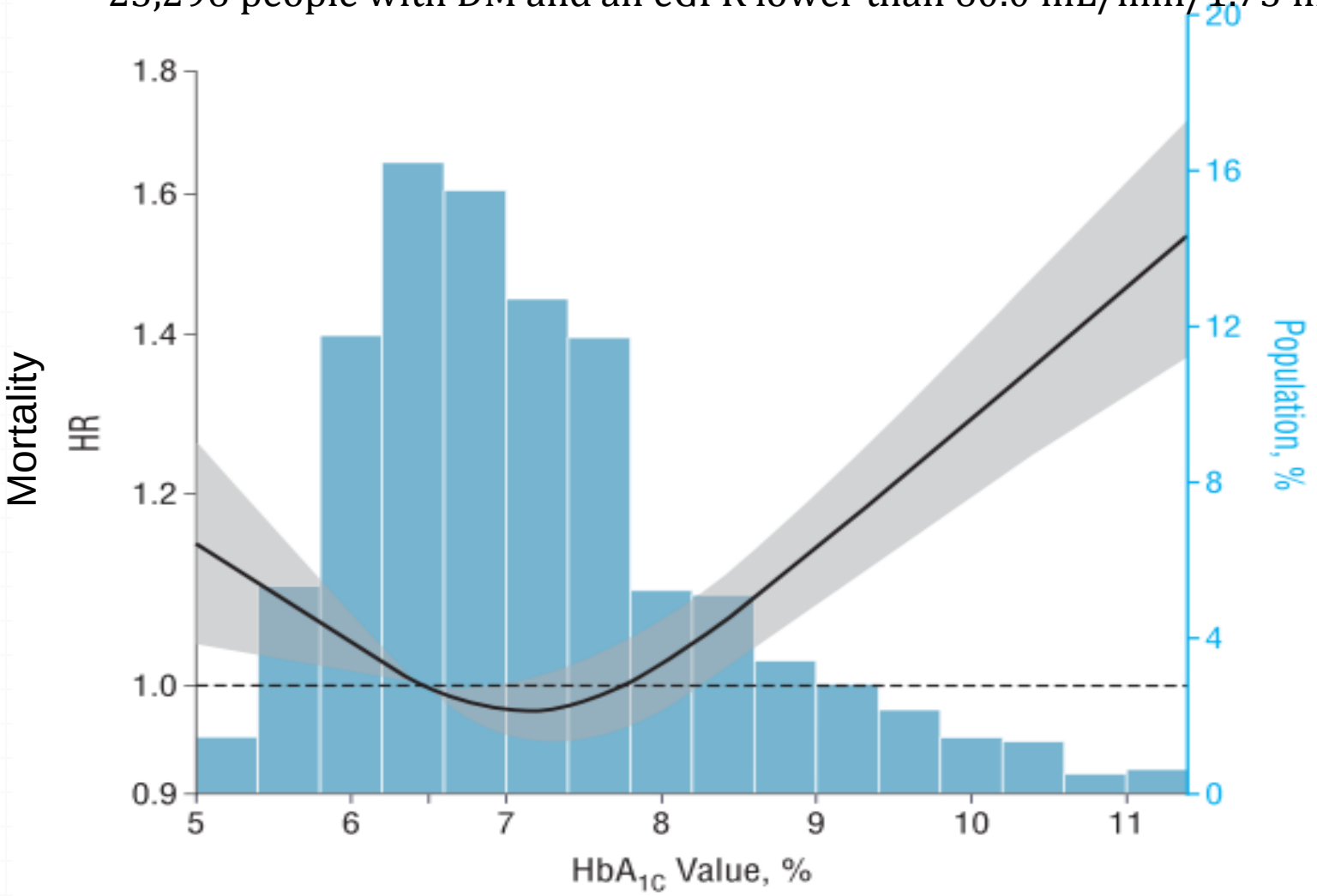
How should we do?

Carbamylation of hemoglobin


In patients with CKD
In patients with ESRD

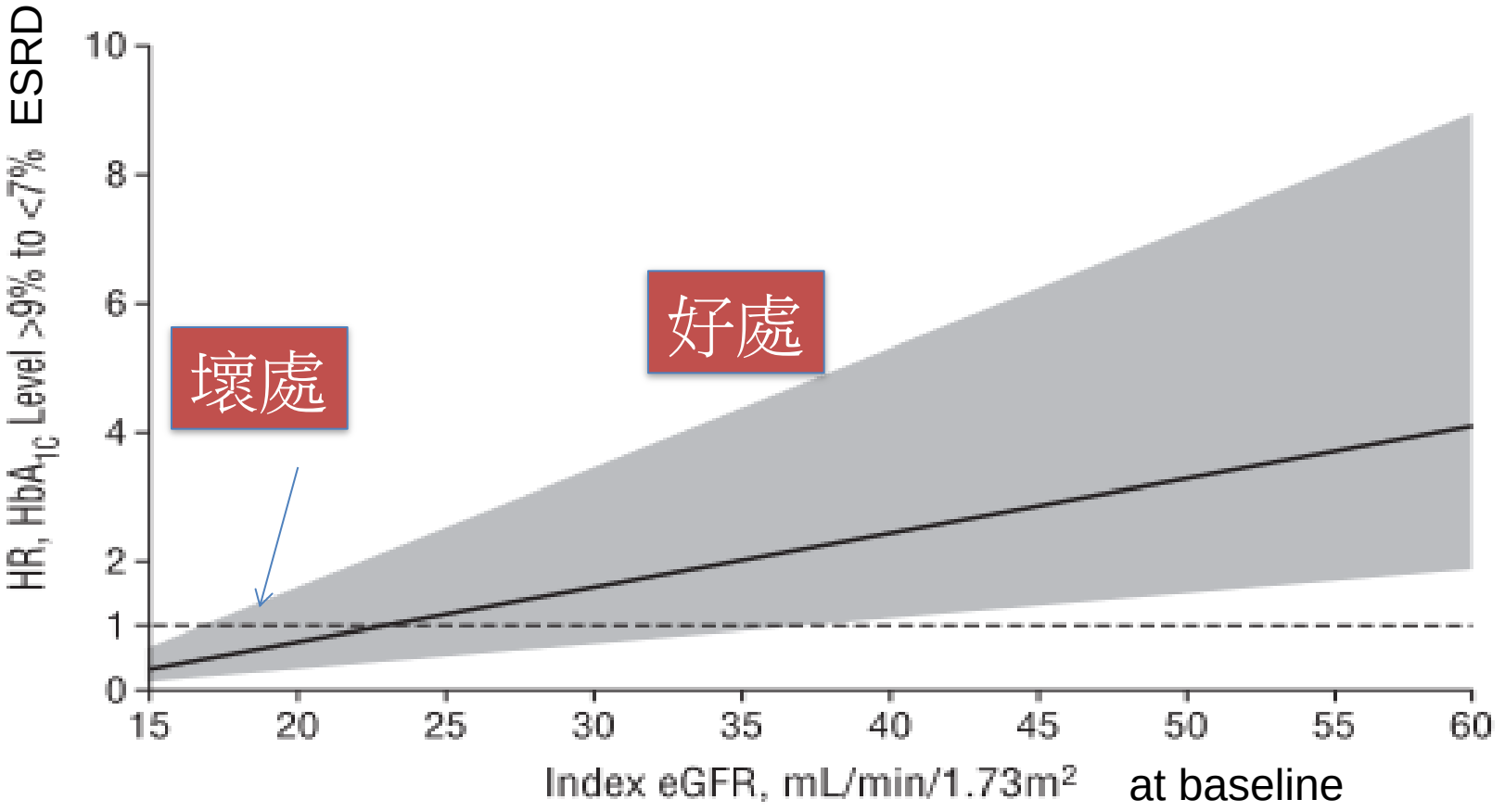
Advanced CKD and HbA1c

23,296 people with DM and an eGFR lower than 60.0 mL/min/1.73 m(2).



Arch Intern Med. 2011;171(21):1920-1927

eGFR and glucose control



Arch Intern Med. 2011;171(21):1920-1927

Yes, that's true different

KDIGO

3.1.15: We recommend a target hemoglobin A1c (HbA1c) of ~7.0% (53mmol/mol) to prevent or delay progression of the microvascular complications of diabete ase. (*1A*)

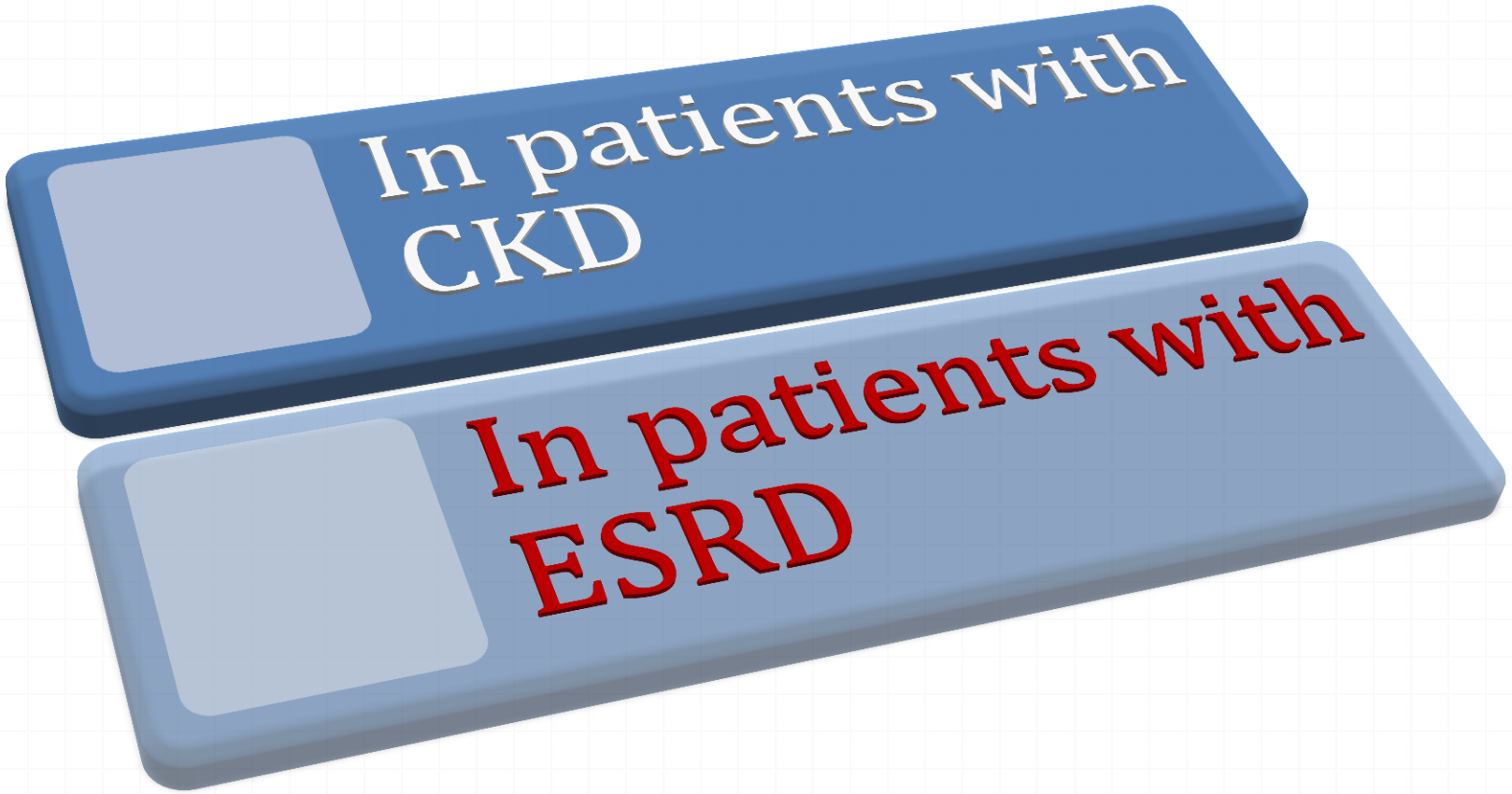
Not treating HbA1c < 7 %

3.1.16: We recommend not treating to an HbA1c target of <7.0% (<53mmol/mol) in patients at risk of hypoglycemia.(*1B*)

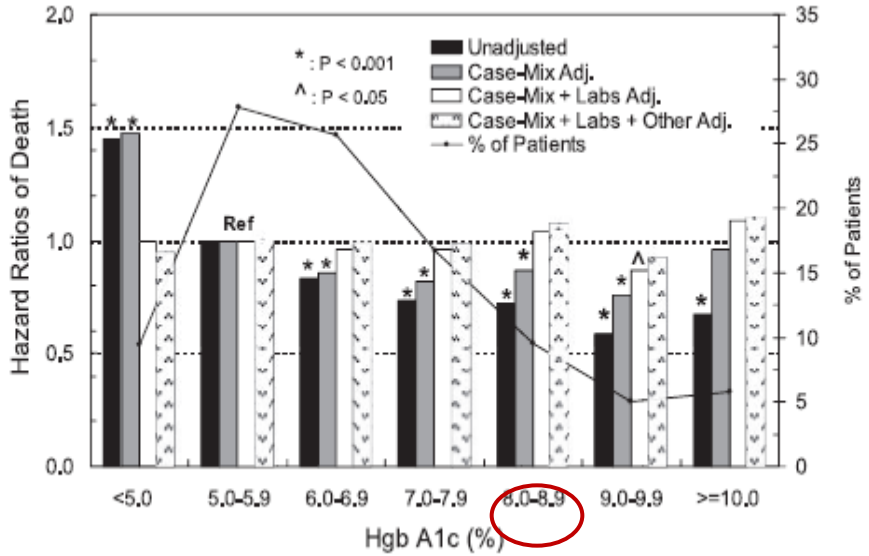
3.1.17: We suggest that target HbA1c be extended above 7.0% (53mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia.(*2C*)

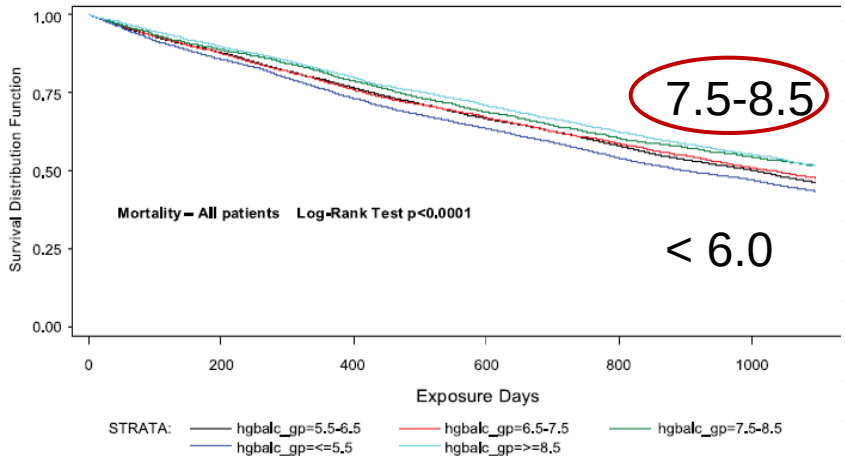
Individualization

Kidney International Supplements (2013) 3, 73–90


In patients with CKD
In patients with ESRD

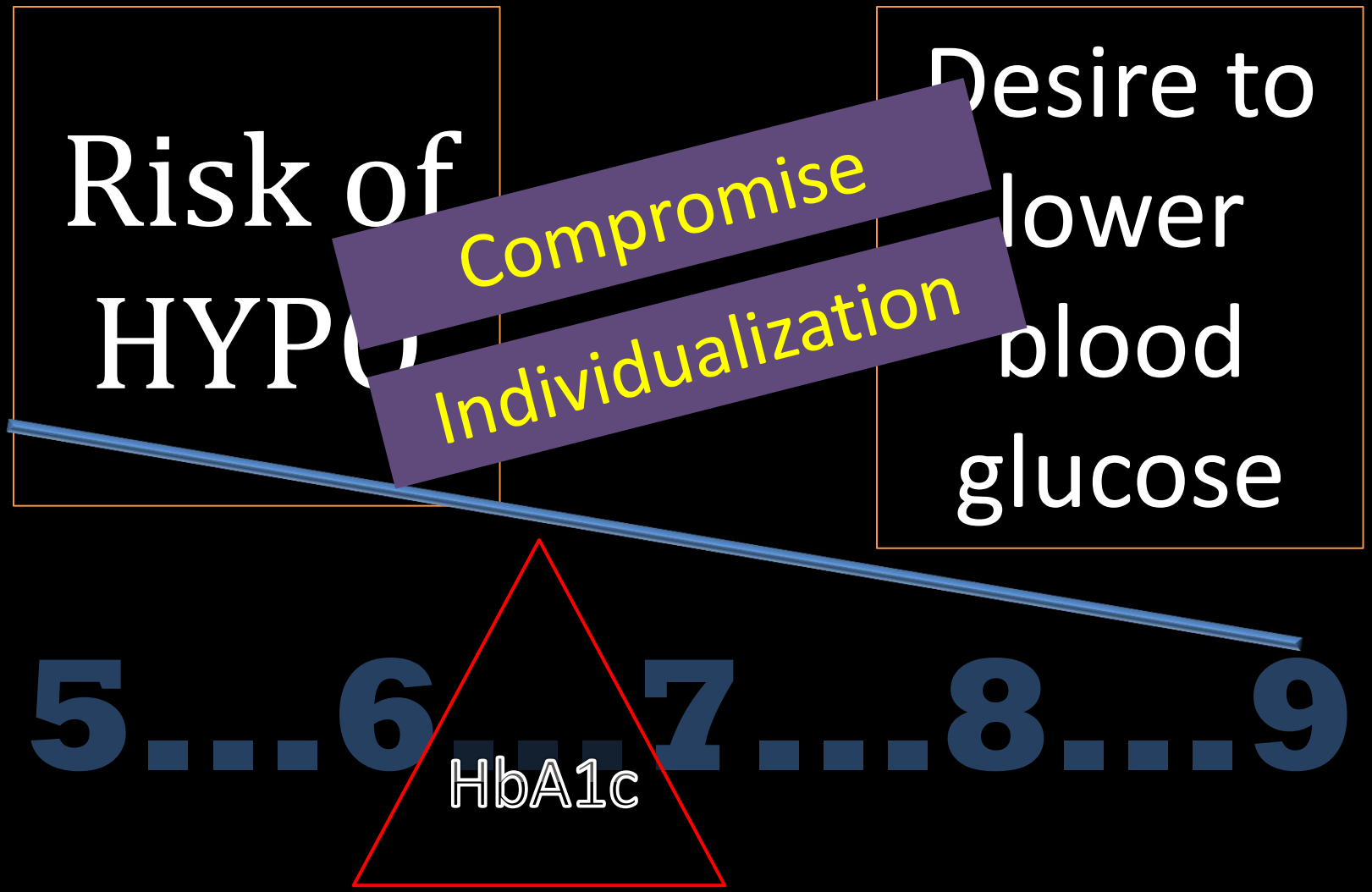
Glycemia control in DM dialysis patients





24,875 DM dialysis patients, follow up 3 years, correlated with repeated HbA1c

Clin J Am Soc Nephrol 5: 1595–1601, 2010.

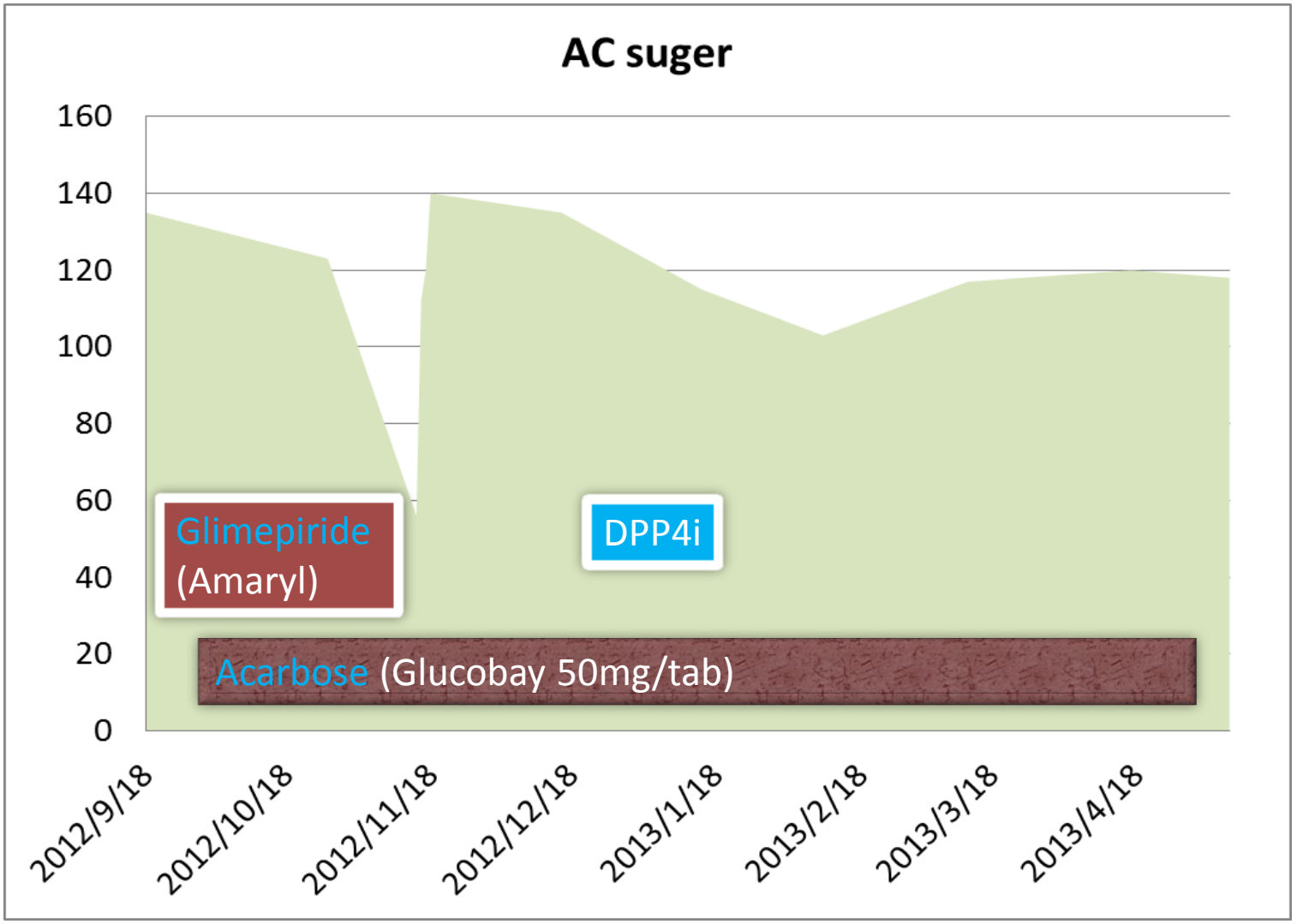

Risk of HYPO
Desire to lower blood glucose
Compromise
Individualization
5...6...7...8...9
HbA1c
CKD

Individualization

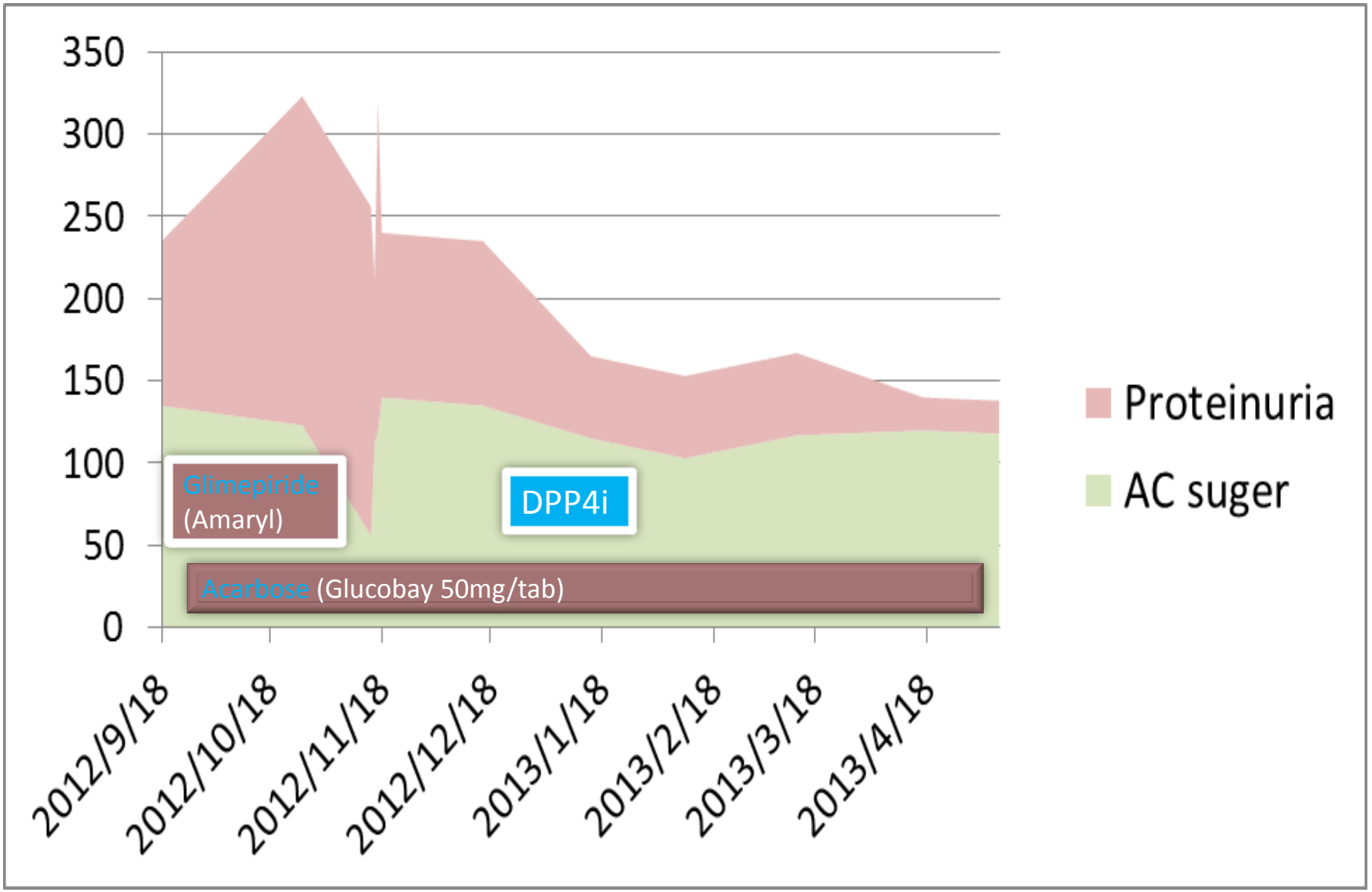
台灣糖尿病醫學會

個人化的血糖控制目標	較嚴格目標 (如HbA1c <6.5%)	較寬鬆目標 (如HbA1c <8%)
糖尿病罹病時間	短(例如<5年)	長
糖尿病大小血管併發症	沒有或少	嚴重
低血糖或其他治療相關副作用的風險	低	高
預期壽命	長	短
認知功能	佳	差
其他重大疾病	無	嚴重
醫療資源與支持系統	佳	有限

Temporal sugar change



Restored of proteinuria



Proteinuria and CKD interaction

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR >105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney Int 2011; 80:

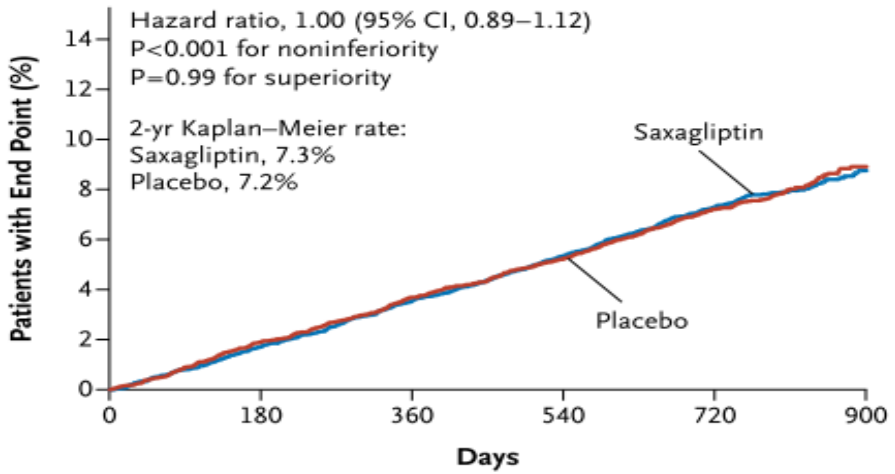
ORIGINAL ARTICLE

NEJM FREE FULL TEXT

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

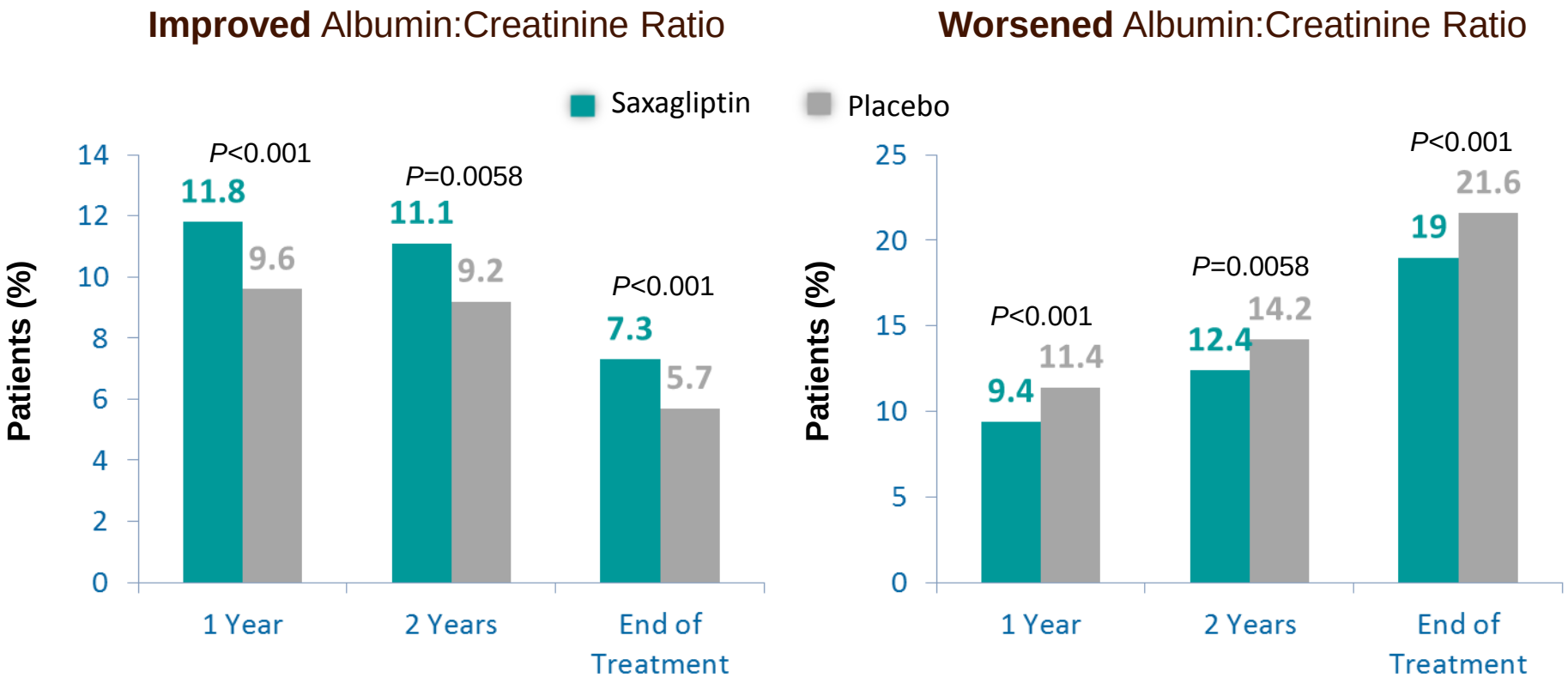
16,492 patients with type 2 diabetes, for 2.1 years, cardiovascular death, myocardial infarction, or ischemic stroke.

A Primary End Point



No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

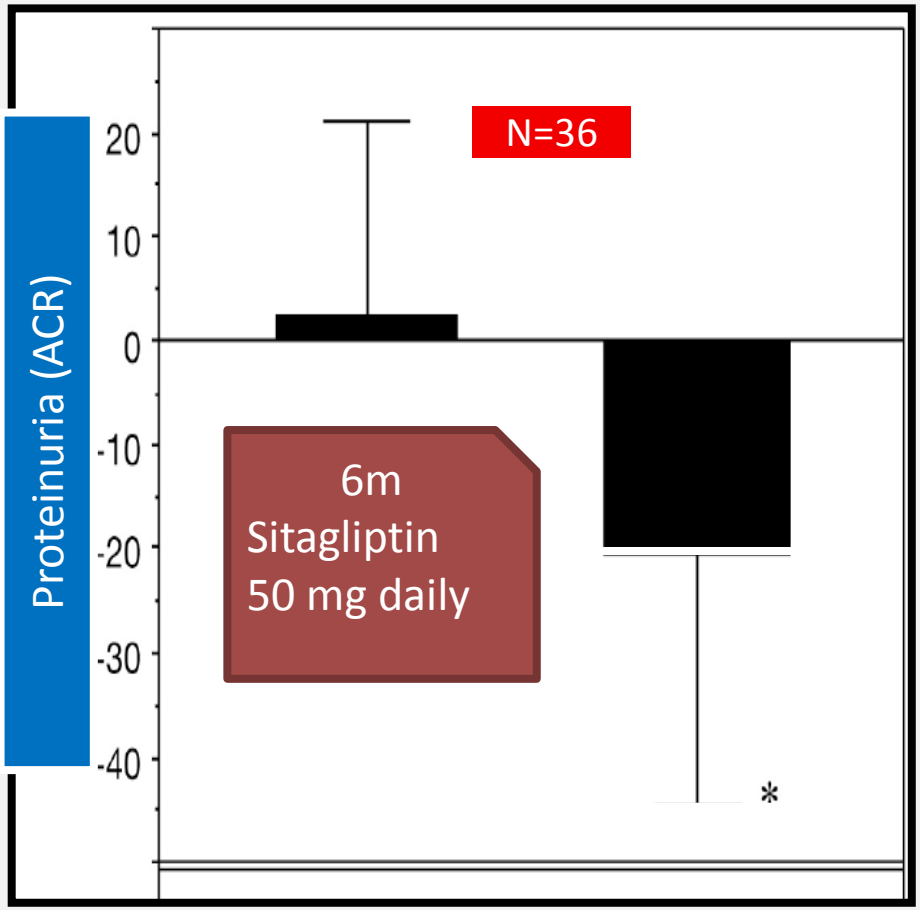
Saxagliptin and CVA



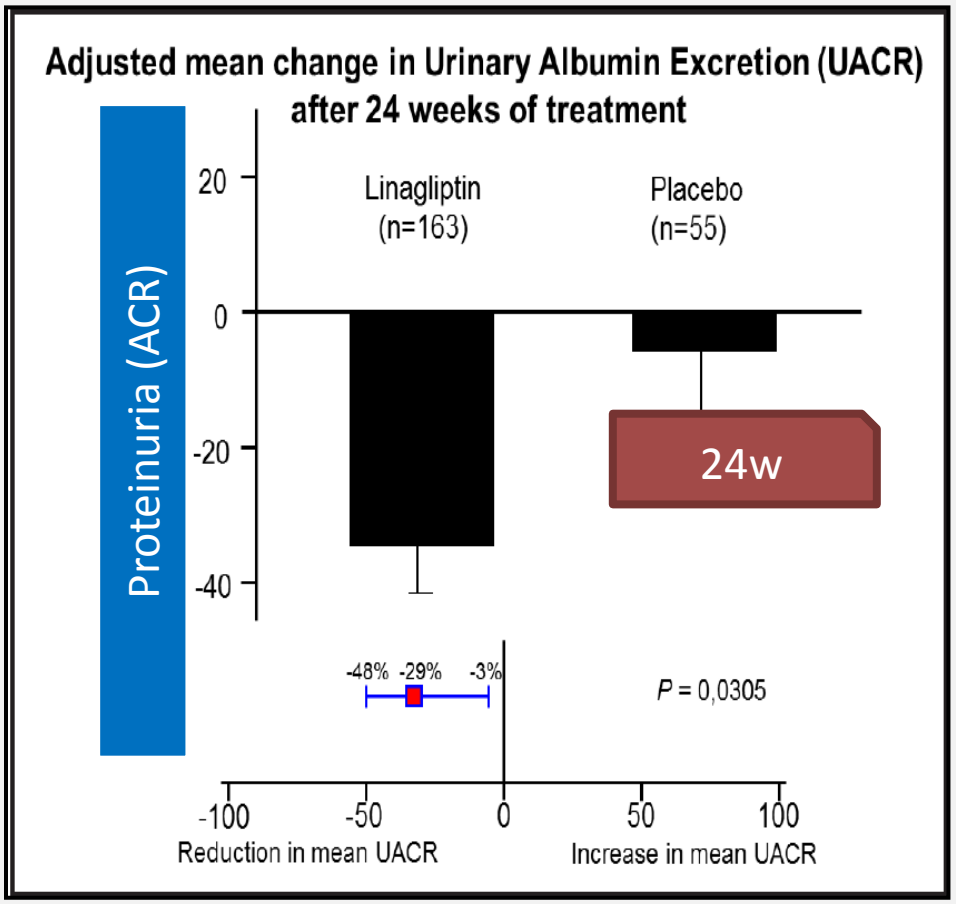
As assessed in an exploratory analysis, saxagliptin reduced the development and progression of microalbuminuria.

Scirica BM, et al. *N Engl J Med.* 2013; doi: 10.1056/NEJMoa1307684.

DPP4i and proteinuria



Before After

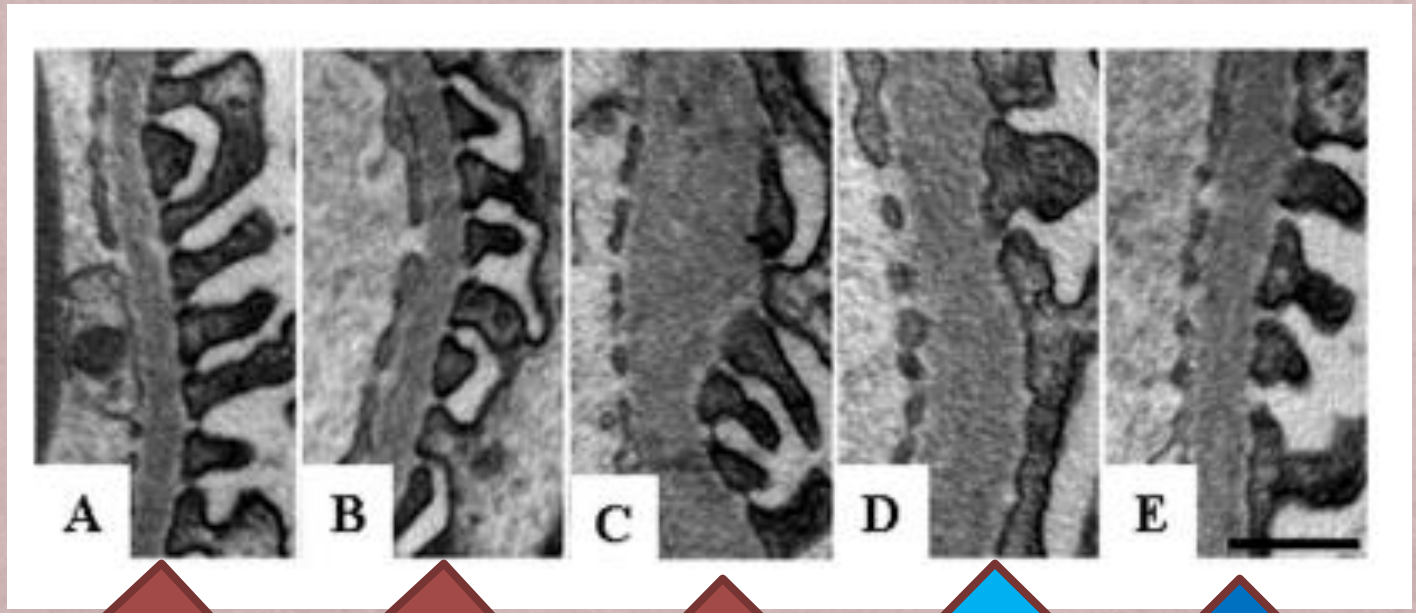


Before After

Hattori S; Endocrine journal 2011, 58(1),69-73

Groop P et al; 72nd Sci Sess of the American Diabetes Association (ADA), 2012, p 953-P.

DPP4i and proteinuria_ rat



Non-DM

DM+8DPP4i

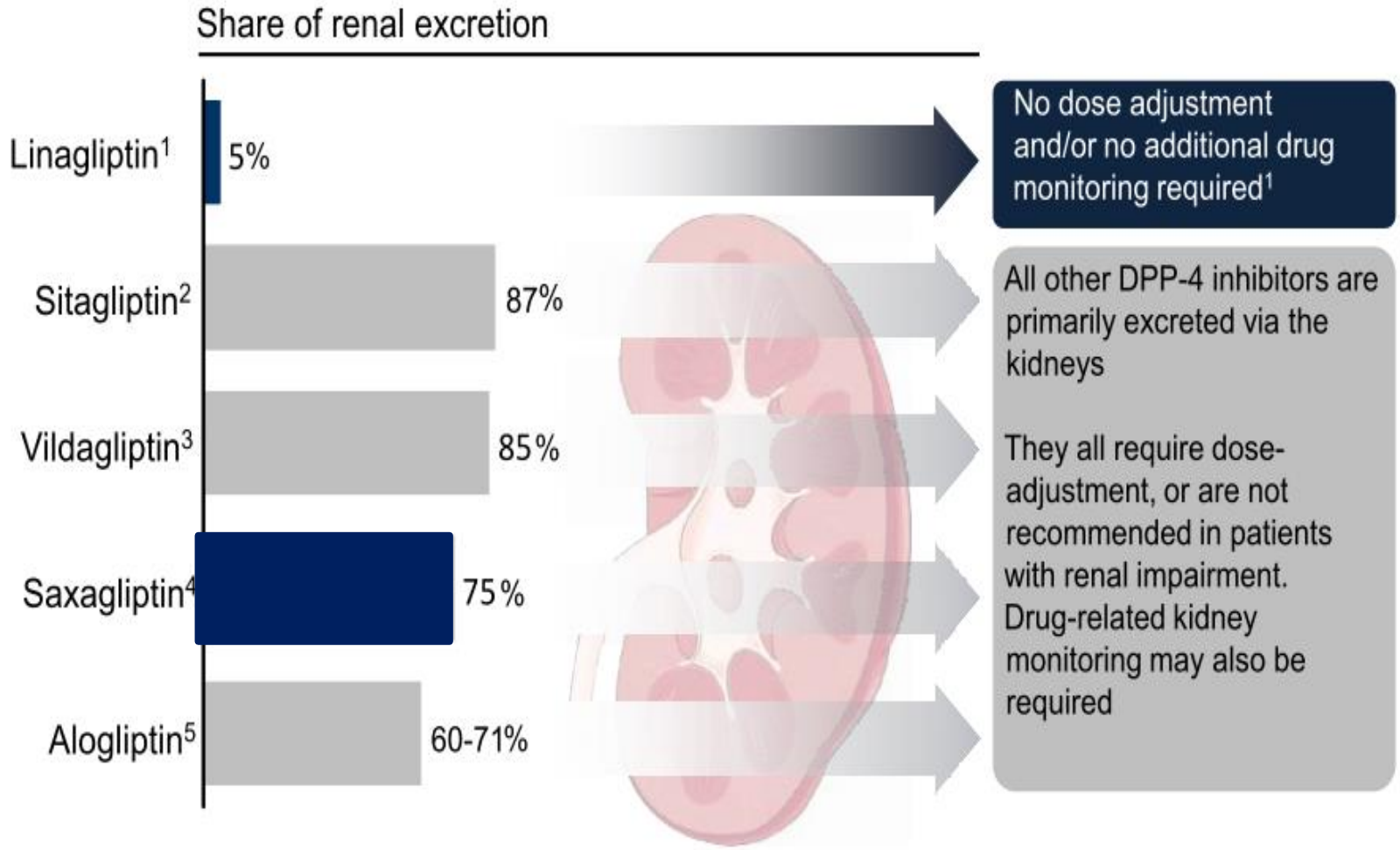
DM

DM+4 DPP4i

DM+8 DPP4i

JPET 340:248–255, 2012

Linagliptin is the only DPP-4 inhibitor which is primarily excreted by bile and gut*

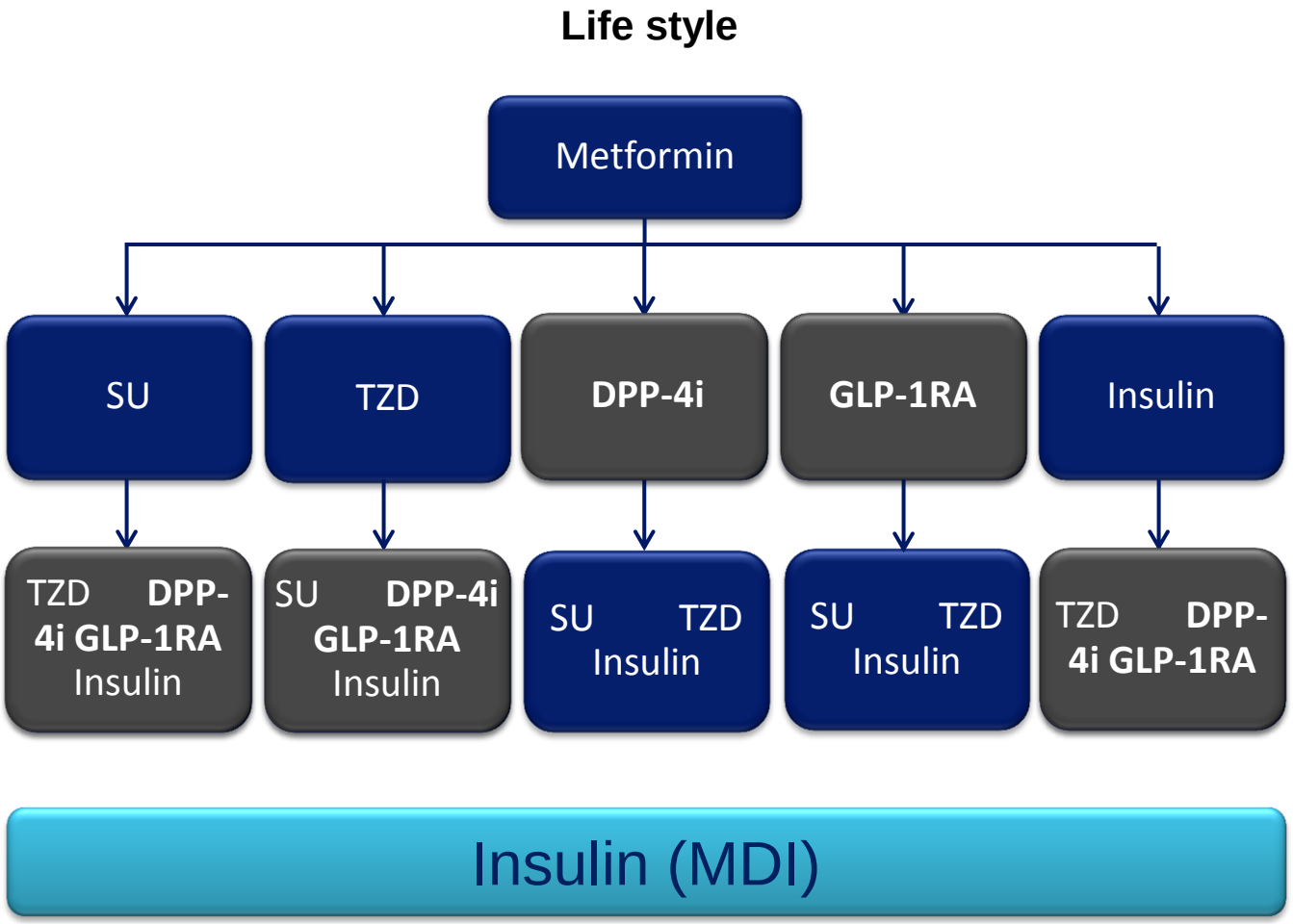


* of currently globally approved DPP-4 inhibitors

Data from multiple trials, includes metabolites and unchanged drug; excretion after single dose administration of [14C] labeled drug

1. Linagliptin US prescribing information

ADA/EASD position statement 2012



Inzucchui SE et al, Diabetes Care (2012), 35 (6), 1364-1379

Johnson et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr (2007) vol. 86 (4) pp. 899-906

Johnson et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr (2007) vol. 86 (4) pp. 899-906

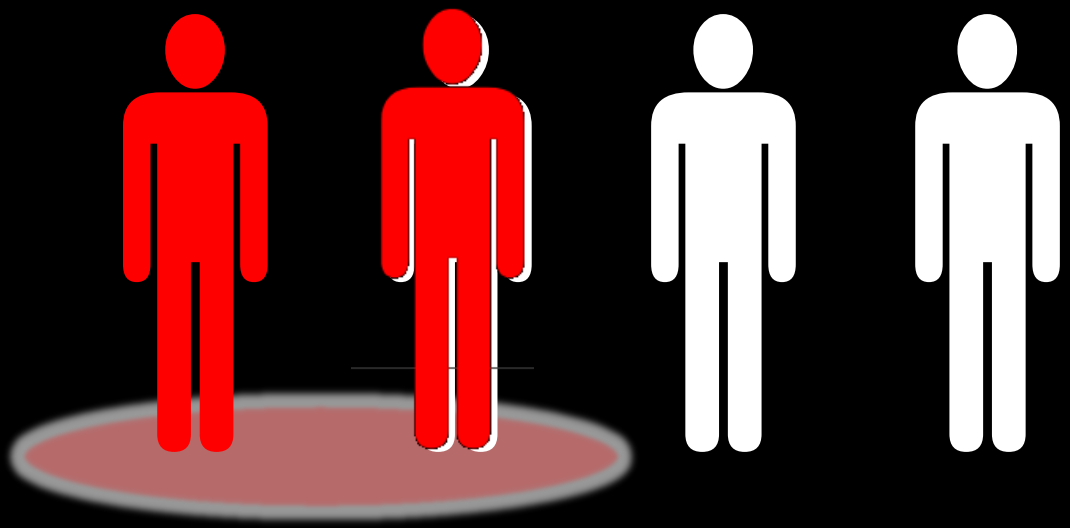
Johnson et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr (2007) vol. 86 (4) pp. 899-906

and hypertension

Complication	GFR category (ml/min/1.73 m^2)					F
	≥90	60-89	45-59	30-44	<30	
Anemia[1]	4.0%	4.7%	12.3%	22.7%	51.5%	
Hypertension[2]	18.3%	41.0%	71.8%	78.3%	82.1%	
25(OH) Vit D deficiency[3]	14.1%	9.1%	10.7%		27.2%	
Acidosis[4]	11.2%	8.4%	9.4%	18.1%	31.5%	
Hyperphosphatemia[5]	7.2%	7.4%	9.2%	9.3%	23.0%	
Hypoalbuminemia[6]	1.0%	1.3%	2.8%	9.0%	7.5%	
Hyperparathyroidism[7]	5.5%	9.4%	23.0%	44.0%	72.5%	

Kidney international , 2013, 73-90

When patients with CKD see their doctor



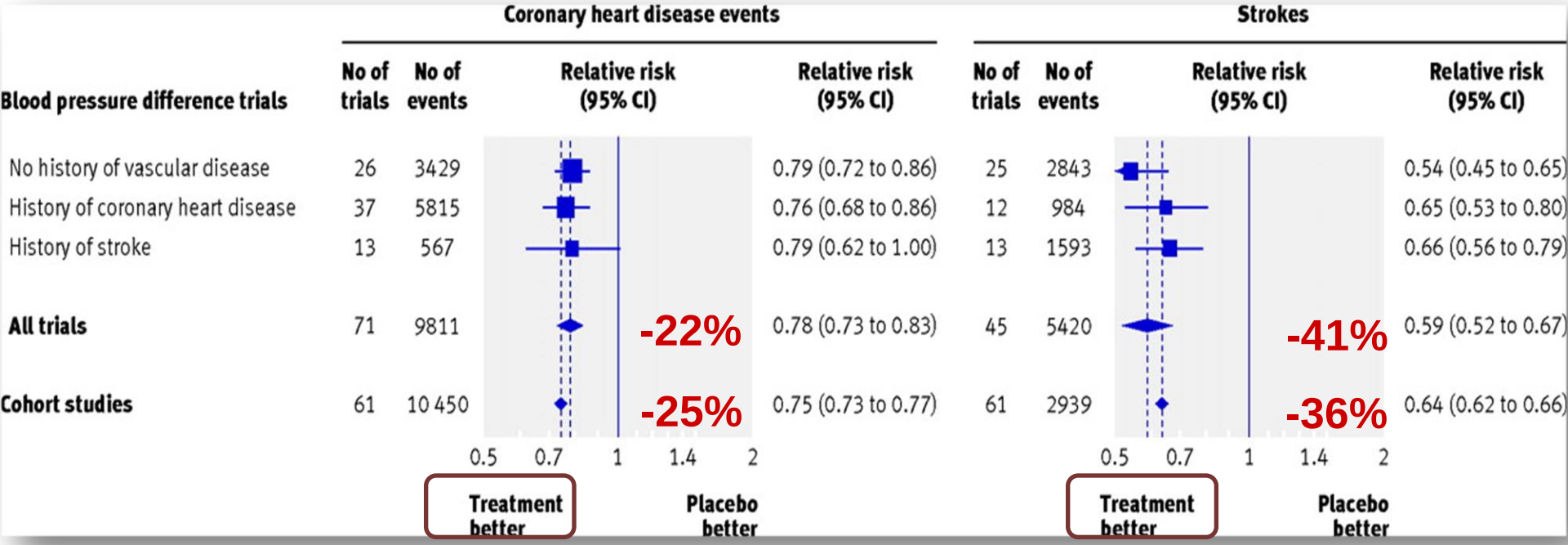
1 in 2 have an **sBP> 140**

Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes (DEMAND)

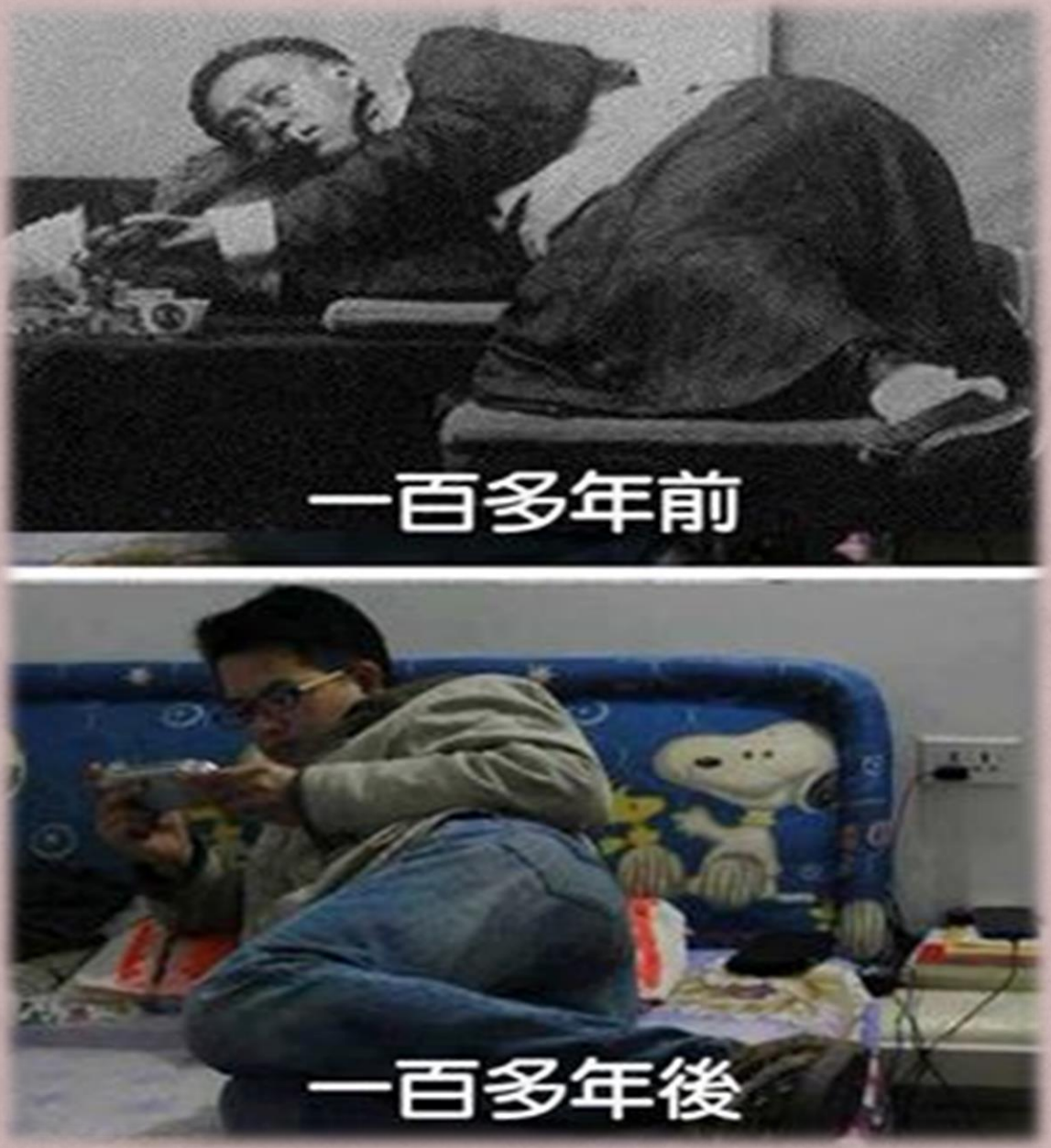
Parving HH, et al. Kidney Int. 2006;69:2057-2063

Relative Risk Reduction of CAD events and stroke for a SBP - 10 mm Hg or DBP - 5 mm Hg at 1 year

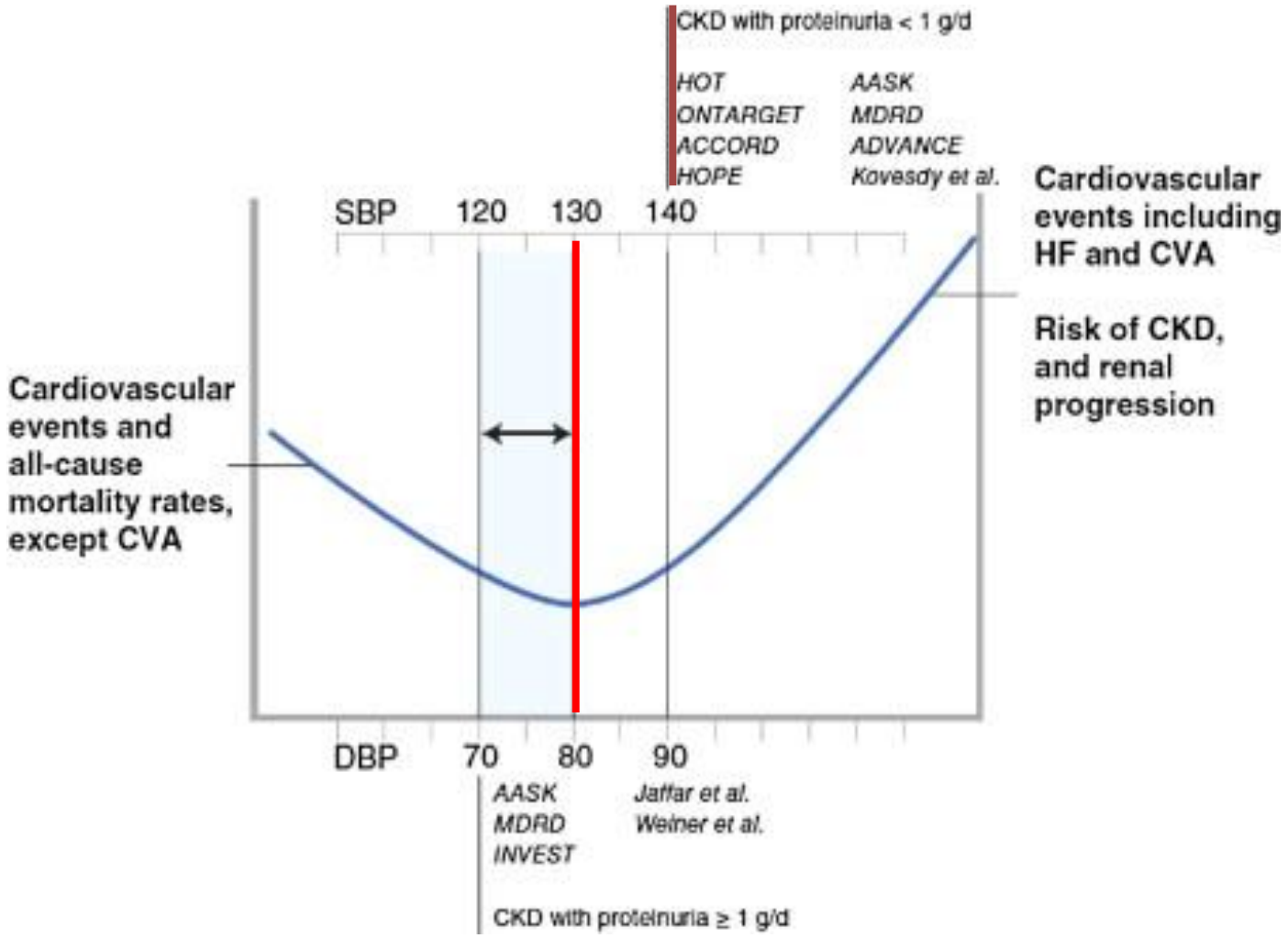
A meta-analysis of 147 randomized trials, 464,000 pts



Law, M R et al. BMJ 2009;338:b1665


一百多年前
一百多年後

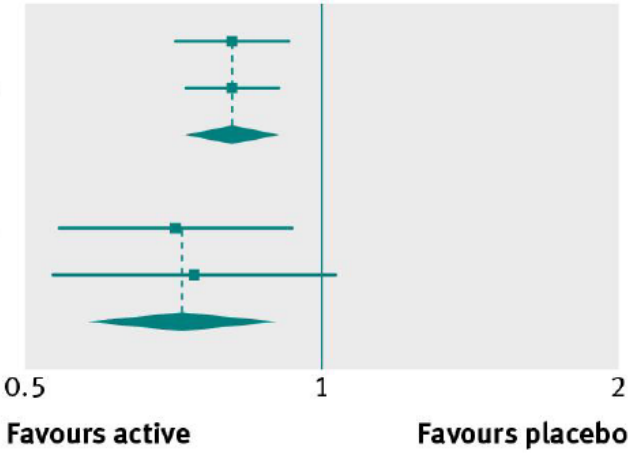
Optimal blood pressure targets for patients with CKD



Curr Probl Cardiol, May 2013

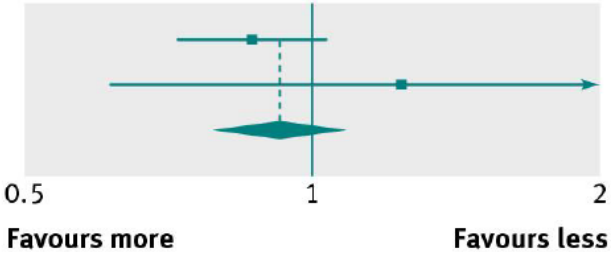
Active treatment vs standard treatment

Study	No of events/patients: Active	Placebo	Difference in systolic/diastolic blood pressure (mm Hg)	Hazard ratio (95% CI)	P for homogeneity
ACE-I *v* placebo					
eGFR ≥60	1712/17 844	2115/18 127	-4.7/-2.1	0.81 (0.72 to 0.91)	0.99
eGFR <60	742/5064	892/4980	-4.6/-2.0	0.81 (0.73 to 0.89)	
Overall				0.81 (0.73 to 0.90)	
Calcium antagonist *v* placebo					
eGFR ≥60	87/2155	118/2097	-7.9/-3.6	0.71 (0.53 to 0.93)	0.85
eGFR <60	64/950	80/905	-9.9/-3.2	0.74 (0.53 to 1.03)	
Overall				0.72 (0.58 to 0.89)	



Intensive vs Less intensive treatment

Study	No of events/patients: More	Less	Difference in systolic/diastolic blood pressure (mm Hg)	Hazard ratio (95% CI)	P for homogeneity
eGFR ≥60	200/5329	399/10 341	-3.0/-3.2	0.87 (0.73 to 1.03)	0.33
eGFR <60	91/1339	147/2537	-3.2/-3.2	1.24 (0.62 to 2.48)	
Overall				0.93 (0.80 to 1.07)	



26 trails with 30295 patients with eGFR< 60

BMJ 2013;347:f5680 doi: 10.1136/bmj.f5680

KDIGO 2012[40]	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
CHEP 2013[38]	Diabetes	<130/80	ACEI or ARE ACEI, ARB, ? tional CVD ?
ESH/ESC 2013[37]	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
2014 Hypertension guideline	CKD	<140/90	ACEI or ARB

(JNC8)

Guidlines 大不同

Lower blood pressure in not always the better!

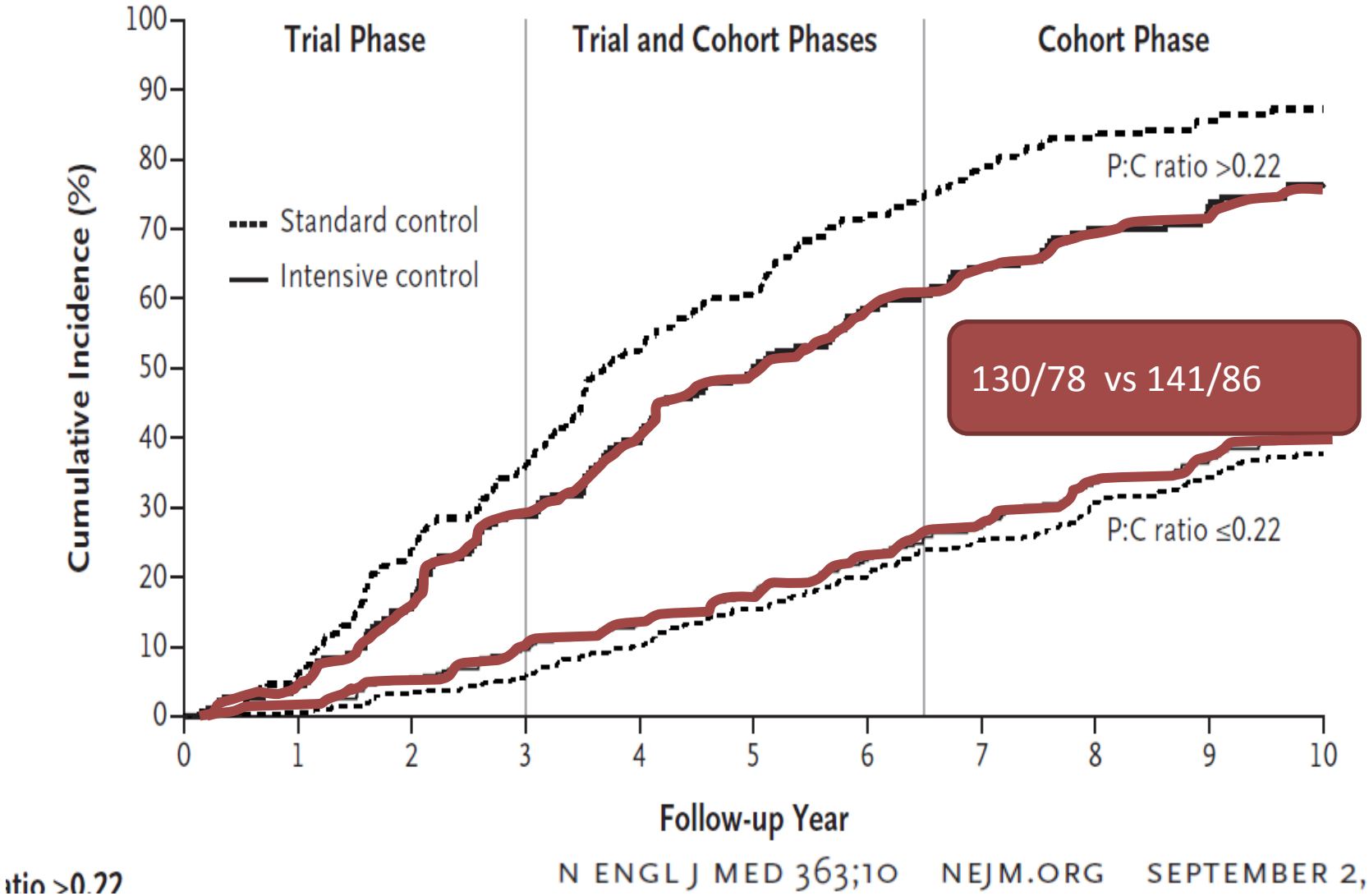
Annals of Internal Medicine | Review

Systematic Review: Blood Pressure Target in Chronic Kidney Disease and Proteinuria as an Effect Modifier

Ashish Upadhyay, MD; Amy Earley, BS; Shana M. Haynes, DHSc; and Katrin Uhlig, MD, MS

Ann Intern Med. 2011;154:541-548.

Intensive control and outcomes



tio >0.22

N ENGL J MED 363;10 NEJM.ORG SEPTEMBER 2, 2010

1094 black patients with hypertensive CKD, 8.8 to 12.2 years.
doubling of the serum creatinine level, a diagnosis of ESRD, or death

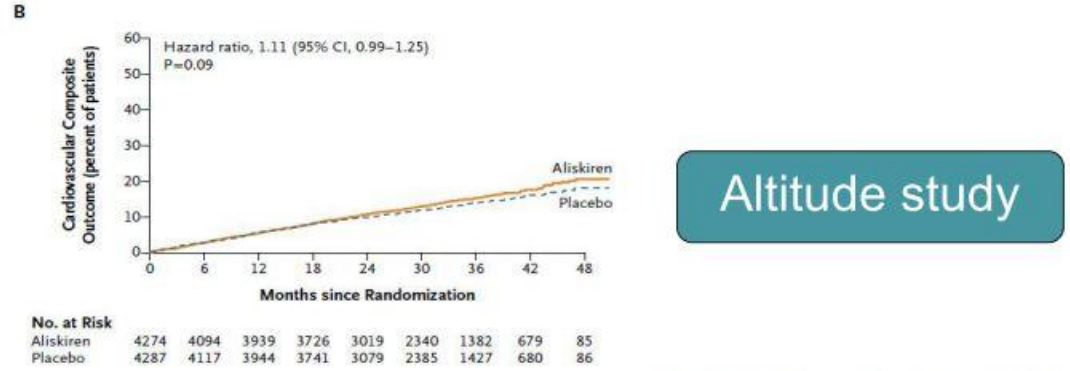
Dual Therapy with RAS System Blockade. The End ?

ORIGINAL ARTICLE

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans-Henrik Parving, M.D., D.M.Sc., Barry M. Brenner, M.D., Ph.D., John J.V. McMurray, M.D., Dick de Zeeuw, M.D., Ph.D., Steven M. Haffner, M.D., Scott D. Solomon, M.D., Nish Chaturvedi, M.D., Frederik Persson, M.D., Akshay S. Desai, M.D., M.P.H., Maria Nicolaides, M.D., Alexia Richard, M.Sc., Zhihua Xiang, Ph.D., Patrick Brunel, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the ALTITUDE Investigators*

Follow-up of 32.9 months,
783 DM2 (18.3%) aliskiren +RASi ; 732 (17.1%) placebo



Altitude study

N ENGL J MED 367;23 NEJM.ORG DECEMBER 6, 2012

滾滾長江東逝水，浪花淘盡英雄

High Dose ARB

	High CV risk	High CV risk without CKD	High CV risk with CKD
Prevention of Cardiovascular death	■ Not favor high dose ARB (ROADMAP N Engl J Med 2011;364:907-17)	■**CCB+ARB~=High dose ARB** (OSCAR CKD study)	■**CCB+ARB>High dose ARB** (OSCAR and OSCAR CKD study)
Prevention of progression to CKD or eGFR decline	■High dose ARB ~=control (ROADMAP N Engl J Med 2011;364:907-17)	■**CCB+ARB>High dose ARB>Low dose ARB** (OSCAR CKD study; IRMA 2)	■**CCB+ARB~=High dose ARB** (OSCAR CKD study)
Reduction of proteinuria	■Favor high dose ARB (ROADMAP N Engl J Med 2011;364:907-17)	■Favor high dose ARB (IRMA 2 N Engl J Med 2001;345:870-8)	■Favor high dose ARB (RENAAL N Engl J Med 2001;345:851-60/ IDNT New Engl J Med 2001; 345:861-9)


馬
鹿
東森新聞雲
ETtoday.net

ARB+ARB

ARB+CCB

ARB+ARB

ARB+CCB

No-CKD

CKD

RENAL
IRMA2

ARB+ARB

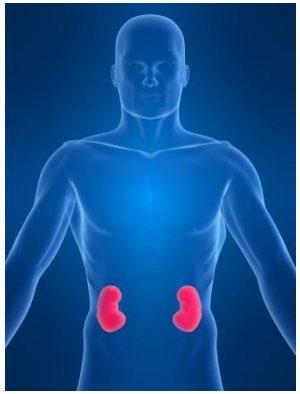
ARB+CCB

ARB+ARB

ARB+CCB

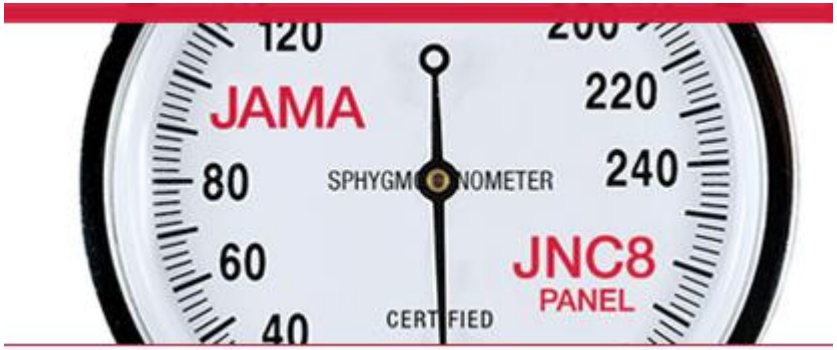
No-CKD

CKD



OSCAR

JNC 8 at Last! Guidelines Ease Up on BP Thresholds



JNC 8

Set blood pressure goal and initiate blood pressure lowering-medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD)

Diabetes or CKD present

Age ≥60 years

Blood pressure goal
SBP <150 mm Hg
DBP <90 mm Hg

Age <60 years

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

All ages
Diabetes present
No CKD

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

All ages
CKD present with or without diabetes

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Nonblack

Initiate thiazide-type diuretic **or** ACEI **or** ARB **or** CCB, alone **or** in combination.[a]

Black

Initiate thiazide-type diuretic **or** CCB, alone **or** in combination.

All races

Initiate ACEI **or** ARB, alone **or** in combination with other drug class.[a]

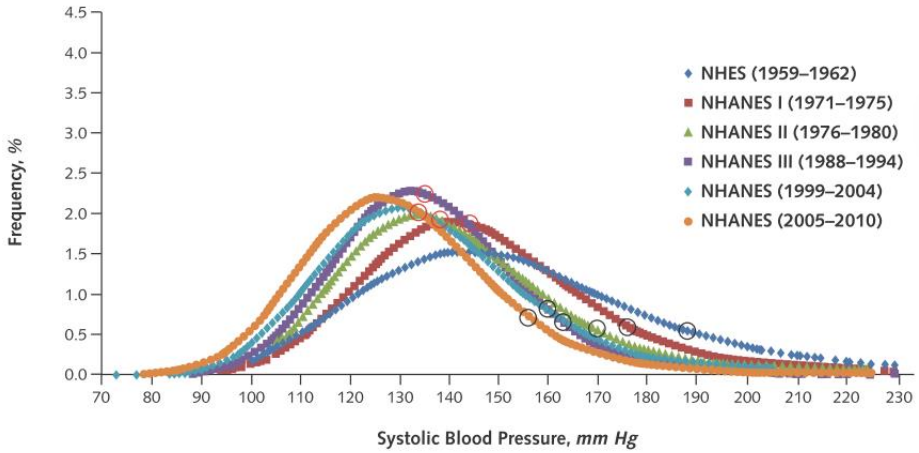
JAMA Published online December 18, 2013

Hypertension guideline, but wait, there is more!

Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

Jackson T. Wright Jr., MD, PhD; Lawrence J. Fine, MD, DrPH; Daniel T. Lackland, PhD; Gbenga Ogedegbe, MD, MPH, MS; and Cheryl R. Dennison Himmelfarb, PhD, RN, ANP

Annals of internal Medicine, 2014



Annals of Internal Medicine

Table 1. **U.S. Cardiovascular Disease Death Rates for Persons Younger and Older Than 65 y**

Condition (Underlying Cause of Death)	Age, y	Annual Average Death Rate, *deaths per 100 000 persons*		Average Annual Change in Age-Adjusted Death Rate, %*	
		1989–1998	1999–2010	1989–1998	1999–2010
Coronary heart disease	<65	36	30	−3.6	−3.4
Coronary heart disease	≥65	1312	1038	−2.7	−5.6
Stroke	<65	9	7	−1.3	−2.3
Stroke	≥65	436	356	−0.9	−5.3

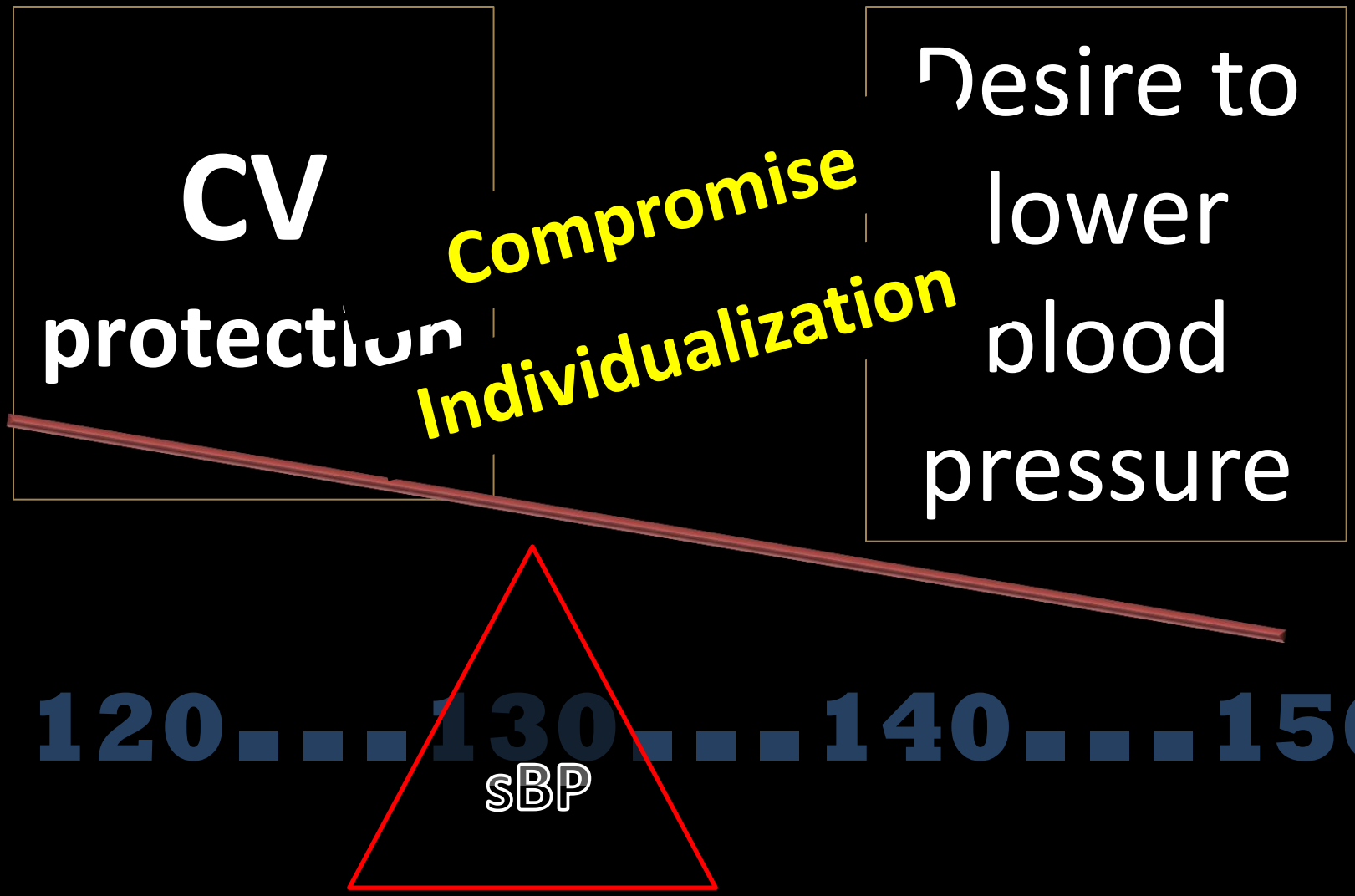
Chapter 3: Management of progression and complications of CKD

Kidney International Supplements (2013) **3,** 73–90; doi:10.1038/kisup.2012.66

the continuous cycle of blood pressure control

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of ≥ 30 mg/24 hours (or equivalent*) whose office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. *(2D)*

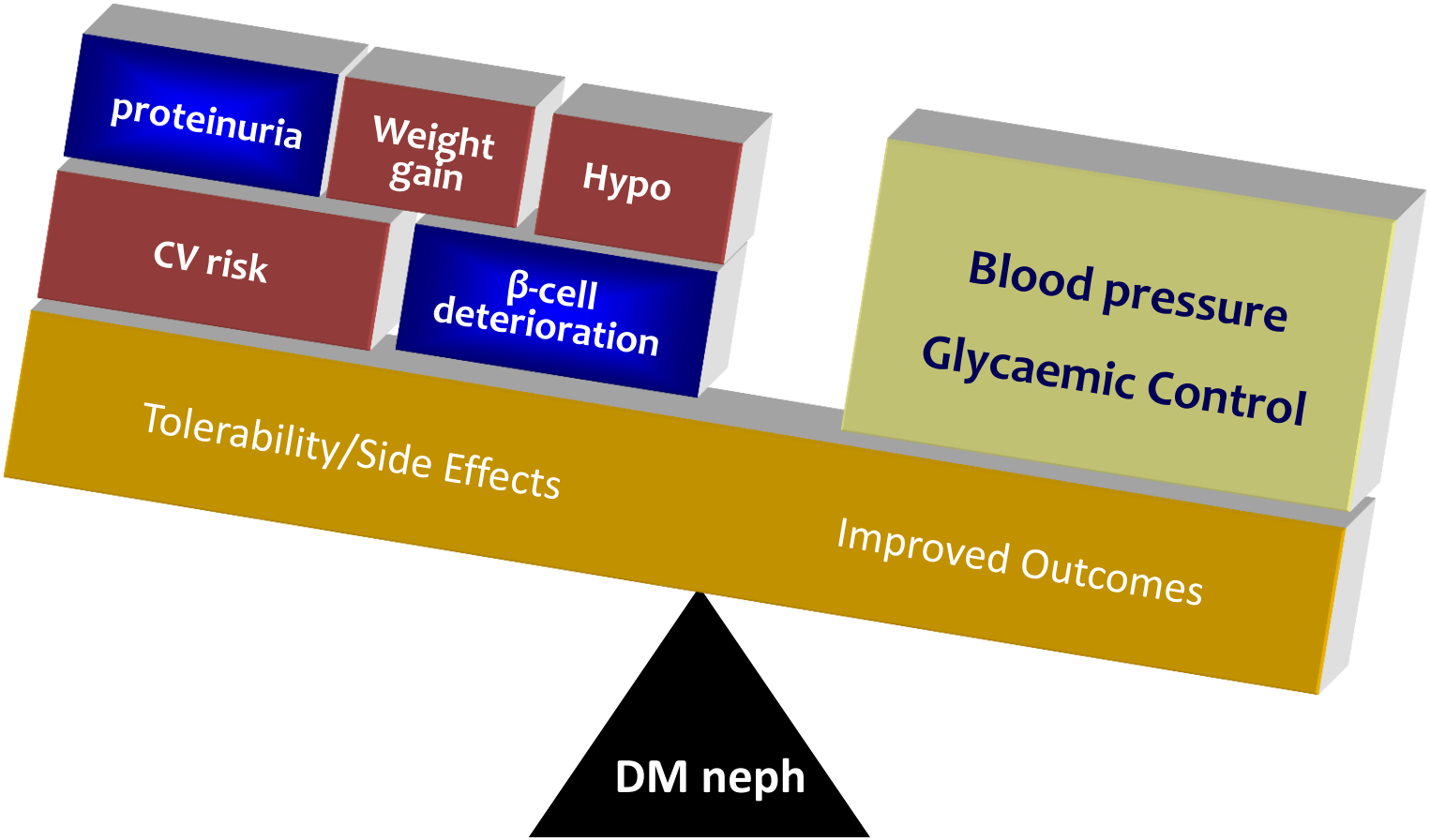
- Urine albumin level of 30 to 300 mg per 24 hours (microalbuminuria) is a risk factor for CVD and CKD progression.
- RCTs suggest that a BP $\leq 130/80$ mm Hg may reduce progression of CKD.


CV protection
Desire to lower blood pressure
Compromise
Individualization
120...130...140...150
sBP
CKD


(貨車展)
恩……
我們的
訴求非常清楚


(跑車展)

Individualization



Keep it simple- DM nephropathy

1. **Individualization to control blood glucose and pressure in DM patients**
2. **Control glucose level avoiding hypoglycemia**
3. **DPP4_GLP1 could improve glucose control and proteinuria.**
4. **BP less than 140/90 mmHg for patients with nonproteinuric CKD, and less than 130/80 mmHg for those with proteinuria.**

Journal of the American Society of Hypertension 4(2) (2010) 90–98

ASH Position Article

謝謝

Why use DPP-4 Inhibitors ?

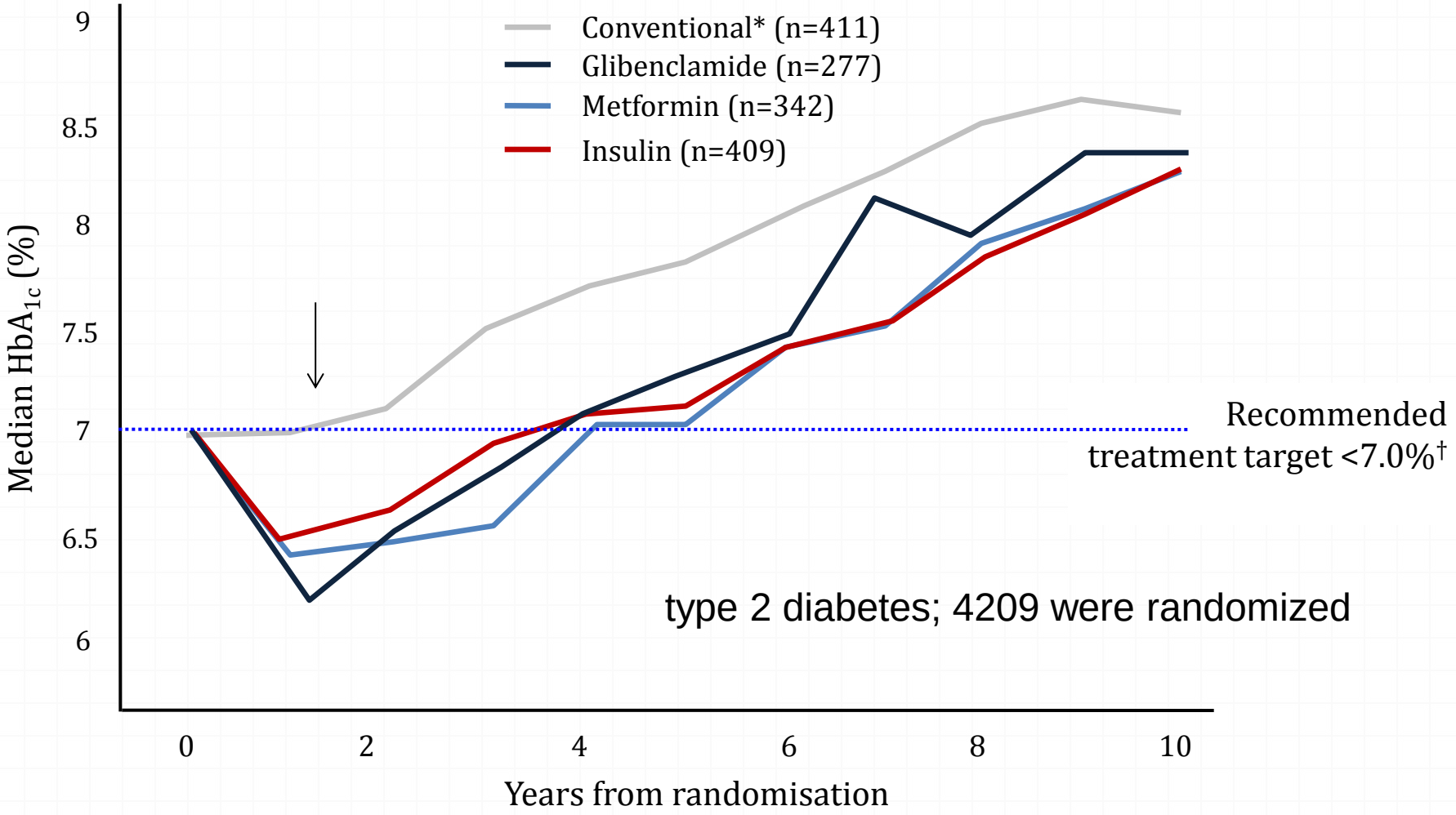
1. HbA_{1c} reduction 0.6-0.8% (and FPG + PPG effects)
2. Immediate activity without hypoglycemia
3. No weight gain
4. No significant edema or GI side effects
5. Saxagliptin could use in renal insufficiency is relative safe.
6. The albuminuria-lowering effects of DPP4i is beyond glucose lowering effect.

GI = gastrointestinal; HbA_{1c} =hemoglobin A_{1c}

Kendall DM, et al. Am J Med. 2009;122:S37-S50.

Type 2 diabetes is a progressive disease and in UKPDS glycaemic control deteriorates over time

UKPDS 34 Study



*Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/L
†ADA clinical practice recommendations. UKPDS 34, n=1704

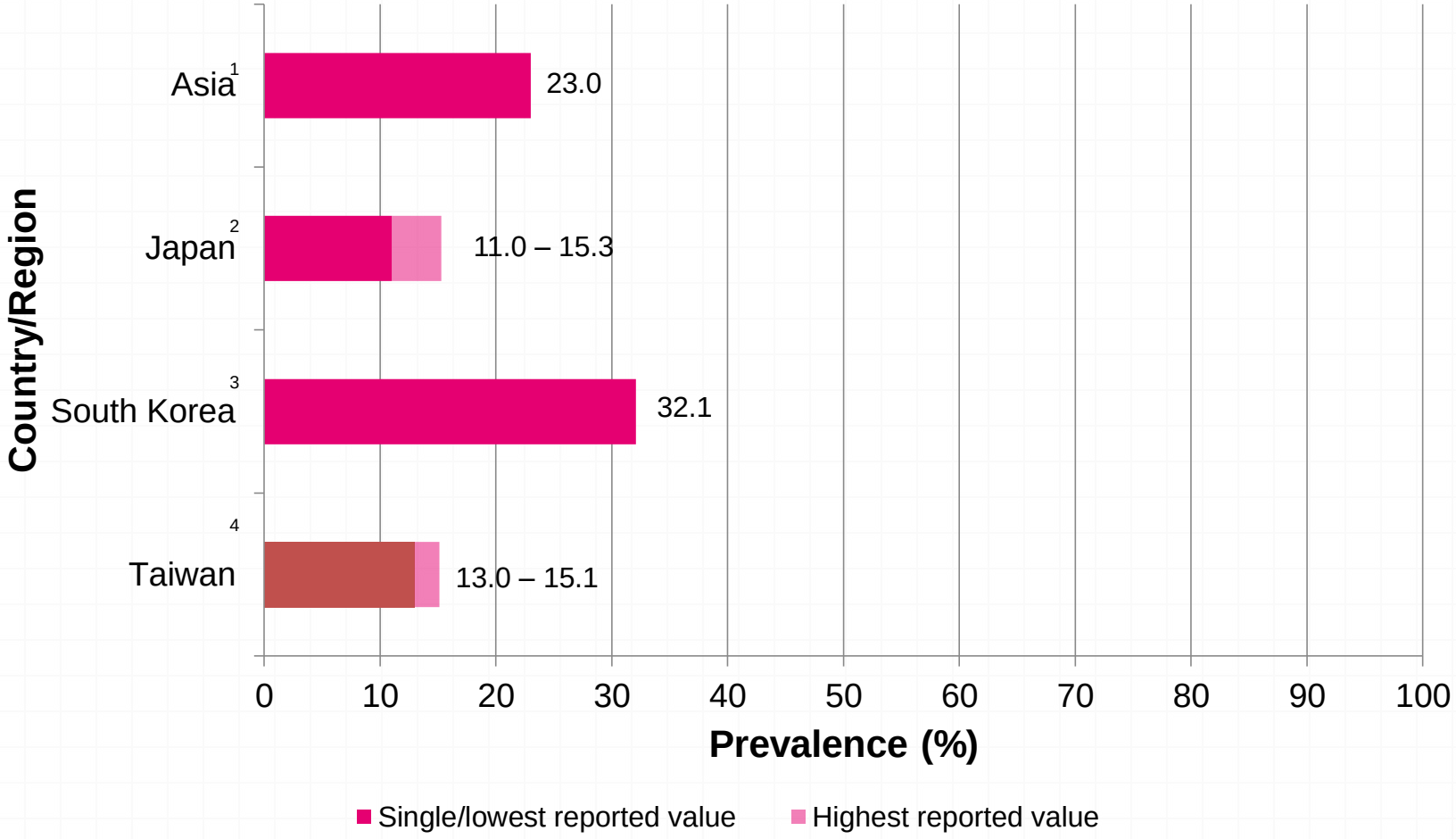
UKPDS 34 Study. Lancet 1998:352:854–65

DPP-4 Inhibitor Use in Type 2 Diabetes

	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin
Usual Dose	100mg QD	50 mg BID Routine LFT required for every 3 month	5mg QD	5mg QD
US FDA Approval	Yes	No	Yes	Yes
Use in Liver Impairment	Yes	Contraindication in pts with LFT >= x3 NL	Yes	Yes
Use in Renal Impairment	Yes Reduce Dose (moderate 50mg, severe/ESRD 25mg)	Yes Moderate/Severe/ESRD Pts. (50mg)	Yes Moderate/Severe/ESRD Pts. (2.5mg)	Yes
Drug-Drug Interaction	No	No	Yes (CYP3A4/5 substrate)	Yes (P-gp & CYP3A4 substrate)

References: Taiwan DOH website accessed 2012/12. Taiwan Package Inserts of Sitagliptin, Vildagliptin, Saxagliptin and Linagliptin

Prevalence of renal impairment* in T2DM patients in Asia



*Renal impairment: eGFR < 60 ml/min/1.73m^2

1 Pan CY, et al. Diabetes Technol Ther. 2008;10(5):397-403; 2 Yokoyama H, et al. Diabetes Care. 2007 Apr;30(4):989-92, Yokoyama H, et al. Nephrol Dial Transplant. 2009 Apr;24(4):1212-9; 3 Yang CW, et al. Nephrol Dial Transplant. 2011;26(10):3249-55; 4 Lin CH, et al. Diabetes Res Clin Pract. 2007 Mar;75(3):306-12

UK Prospective Diabetes Study

20-year Interventional Trial from 1977 to 1997

5,102 patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991

Median follow-up 10.0 years

10-year Post-Trial Monitoring from 1997 to 2007

Annual follow-up of the survivor cohort

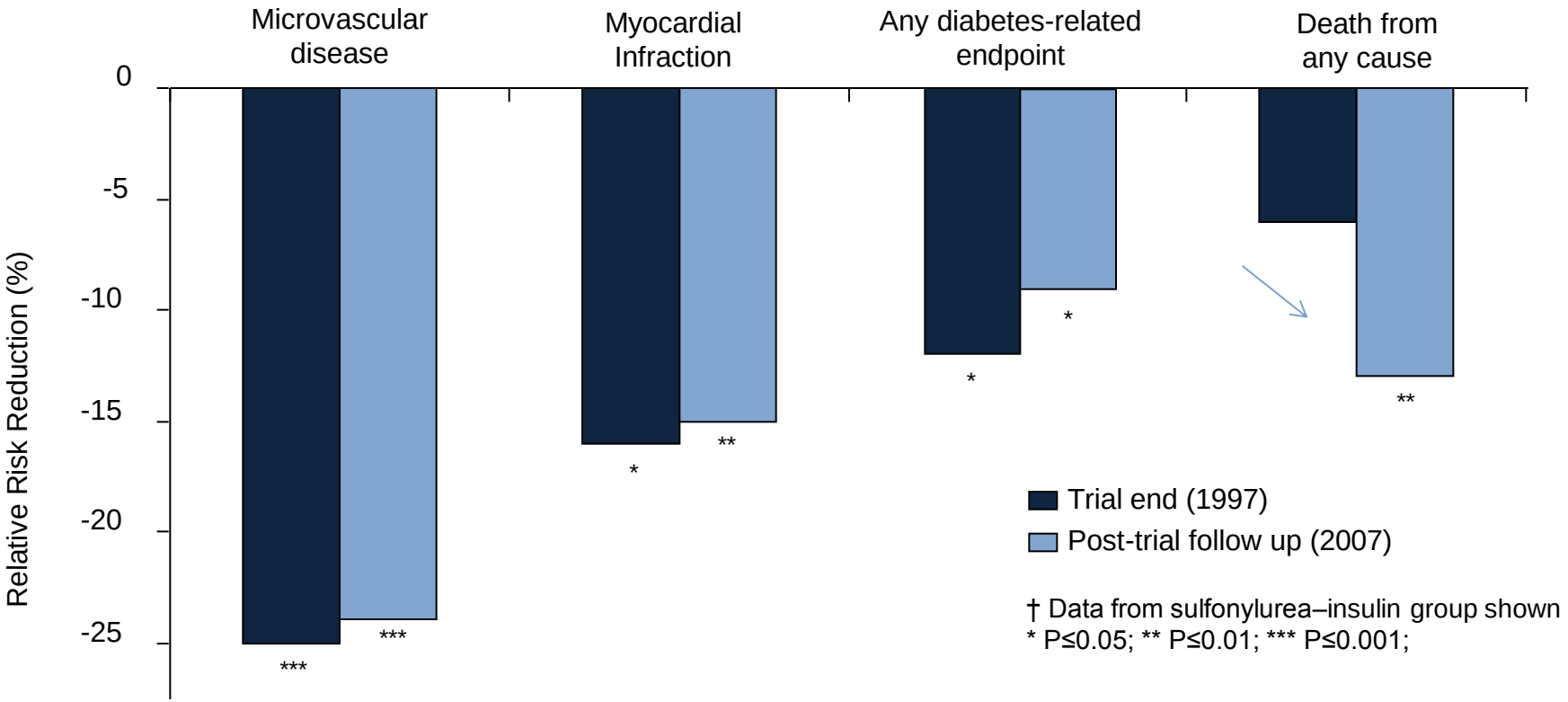
Clinic-based for first five years

Questionnaire-based for last five years

Median overall follow-up 17.0 years, range 16 to 30 years

Early glycemic control provides lasting protection: *The legacy effect*

10-year post-trial monitoring from 1997 to 2007 of UKPDS Study†



- Randomized intervention to achieve either intensive or conventional targets - stopped at the trial end (1997)
- Differences in mean HbA_{1c} between the two groups were lost by year 1 of post-trial follow-up.
- Relative reductions in risk in patients who had been treated to intensive goals, compared with conventional targets, persisted after 10 years

The legacy effect – a reduction in complications persists 10 years after intensive therapy

1. UKPDS 33 Study Group. *Lancet.* 1998;352:837-853; 2. Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589.
3. Chalmers J and Cooper ME. *N Engl J Med*. 2008; 359: 1618–1620.

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		**1997**
Any diabetes related endpoint	*RRR:*	12%
	P:	0.029
Microvascular disease	*RRR:*	25%
	P:	0.0099
Myocardial infarction	*RRR:*	16%
	P:	0.052
All-cause mortality	*RRR:*	6%
	P:	0.44

RRR = Relative Risk Reduction, P = Log Rank

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

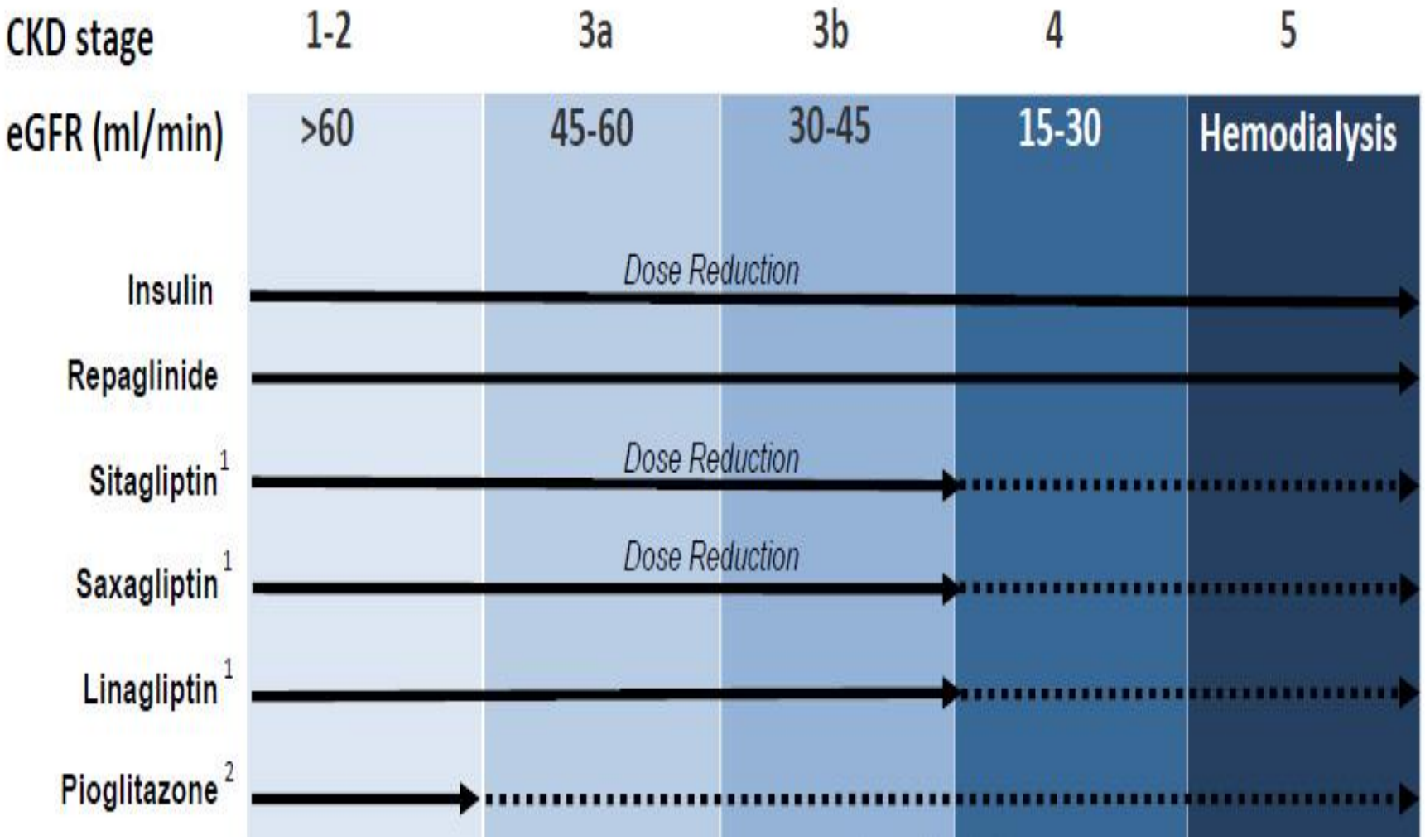
Aggregate Endpoint		**1997**	**2007**
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

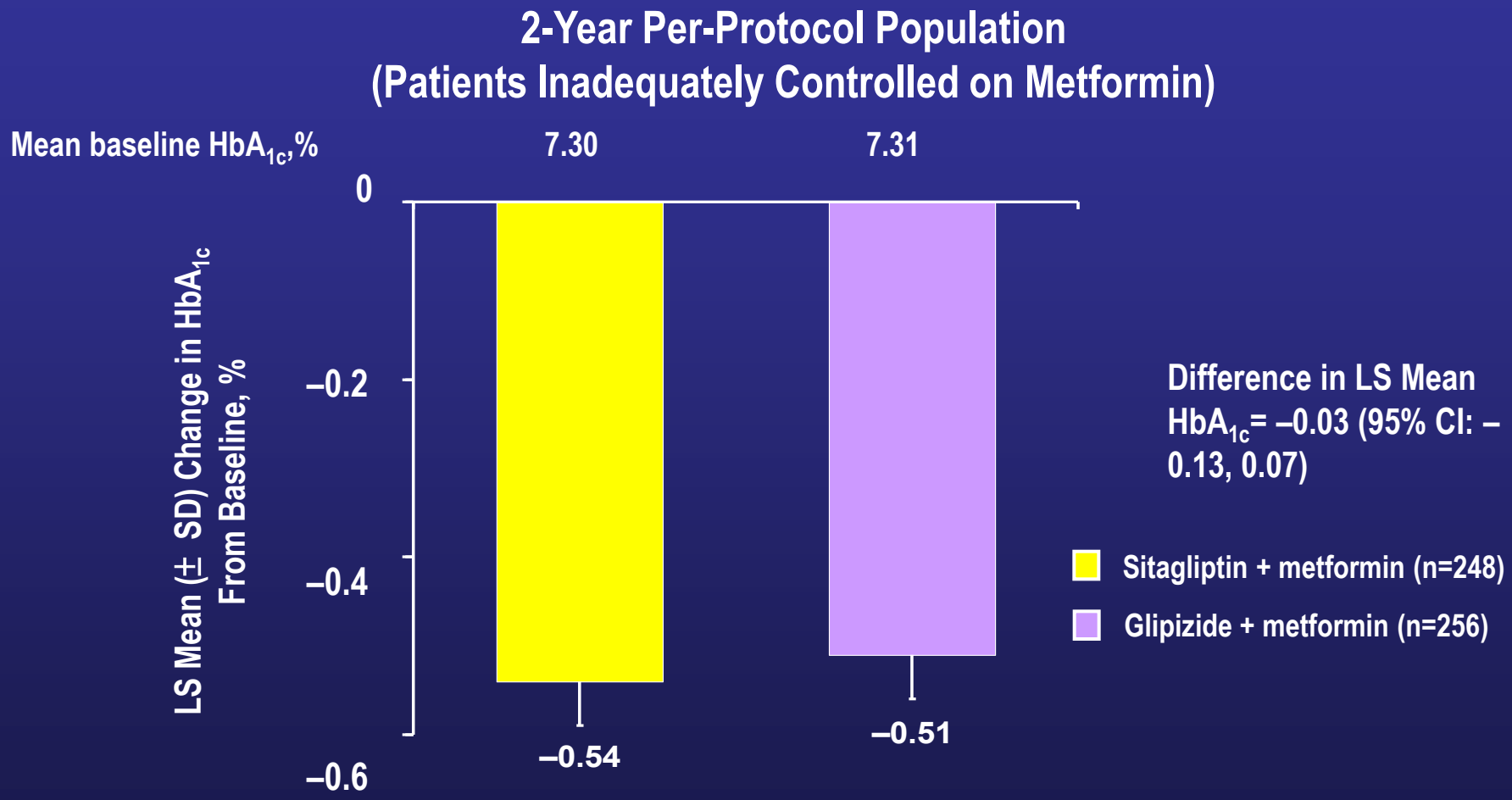
Anti-Hyperglycemic Agents in Type 2 Diabetes

Class	Advantages	Disadvatages
Insulin	Efficacy Titratability	phobia to insulin and needle
Sulfonylureas, particularly glimepiride and glipizide GITS	easy to use (once daily)	Min. hypoglycemia Minimal weight gain
Fast acting insulin secretagogue ("glinides"):	Flexibility Fast on and Fast off	TID
Biguanides (metformin)	No weight gain primary CVD risk reduction	Contraindication of nephropathy
Thiazolidinediones ("glitazones")	secondary CVD risk reduction Preserve β-cell function	Expensive ; Weight gain; Fluid retention; CHF; fracture; CHD risk (rosi ?)
Alpha-glucosidase inhibitors	No weight gain	GI complaints; Low efficacy
Exenatide, pramlintide (amylin)	Weight loss	Injected Expensive

Improve drug compliance -*in CKD*



Sitagliptin Was Noninferior to Glipizide in Reducing HbA_{1c} at Week 104[1]



LS=least-squares; SD=standard deviation.

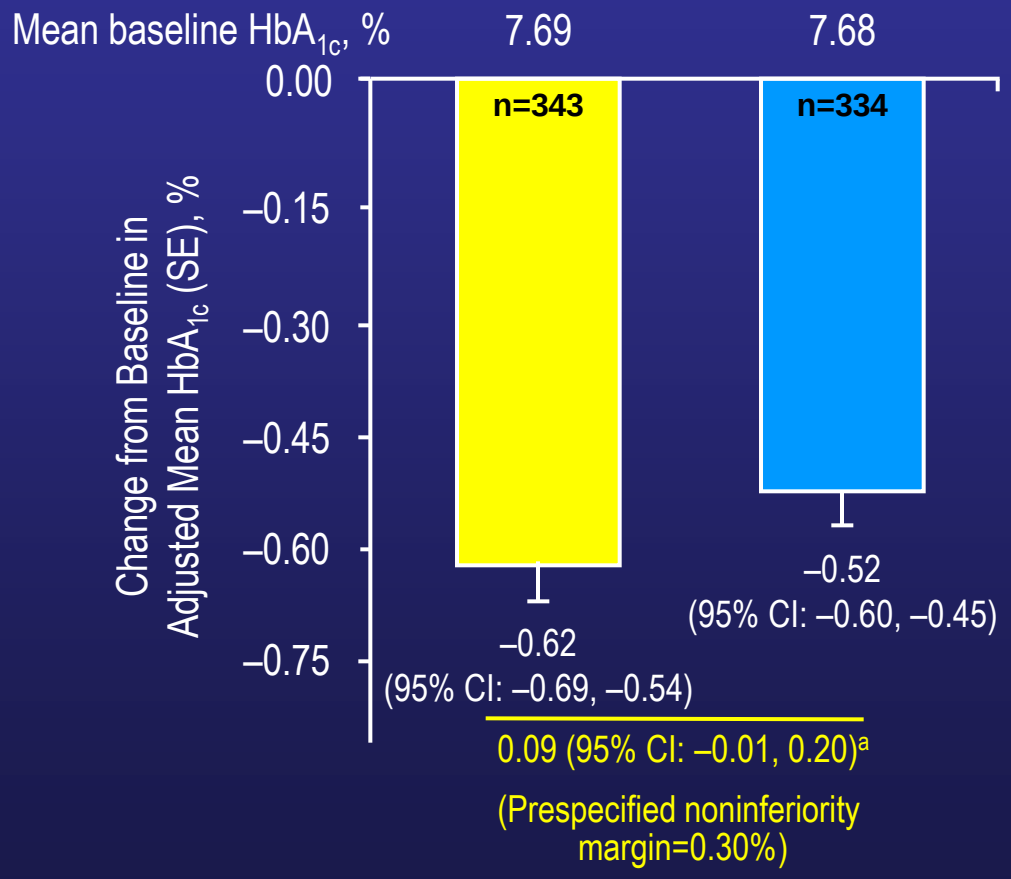
1. Seck T et al. *Int J Clin Pract*. 2010;64(5):562–576.

Saxagliptin vs. Sitagliptin Head-to-Head

Sponsored by BMS

Saxagliptin Was Non-inferior to Sitagliptin in Reducing HbA_{1c} at 18 Weeks

Primary End Point (Per-Protocol Population; on background of metformin therapy)



Sitagliptin 100 mg + metformin

Saxagliptin 5 mg + metformin

In the FAS population, numerically greater HbA_{1c} reductions from baseline were observed for sitagliptin 100 mg compared with saxagliptin 5 mg. Difference between groups: 0.17% (95% CI: 0.06, 0.28).

CI=confidence interval; FAS=full analysis set; SE=standard error.

[a]Difference in adjusted change from baseline vs sitagliptin + metformin.

Scheen AJ et al. *Diabetes Metab Res Rev*. 2010 Sep 7. [Epub ahead of print]

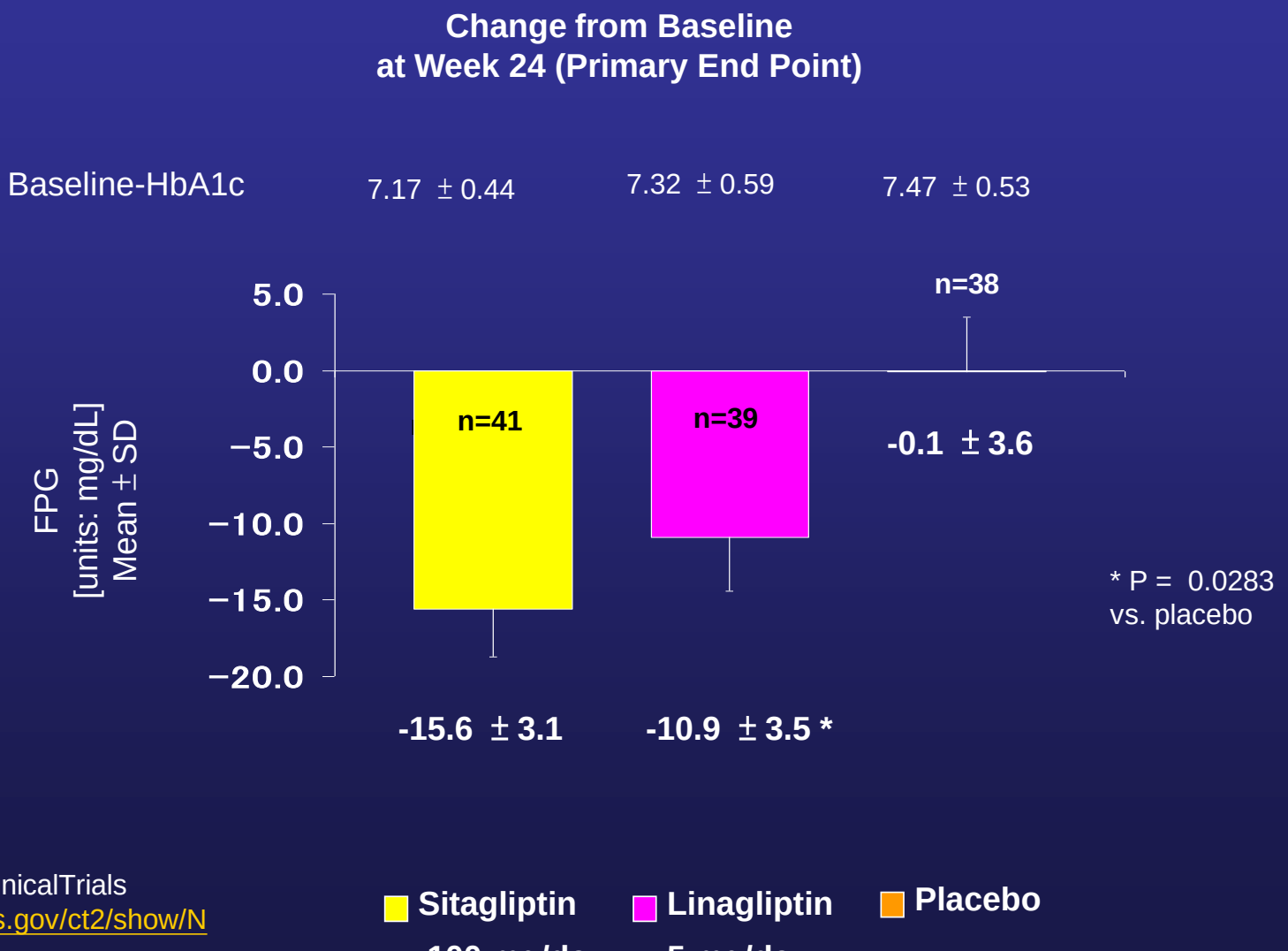
Linagliptin vs. Sitagliptin Head-to-Head

Sponsored by BI

Fasting Plasma Glucose

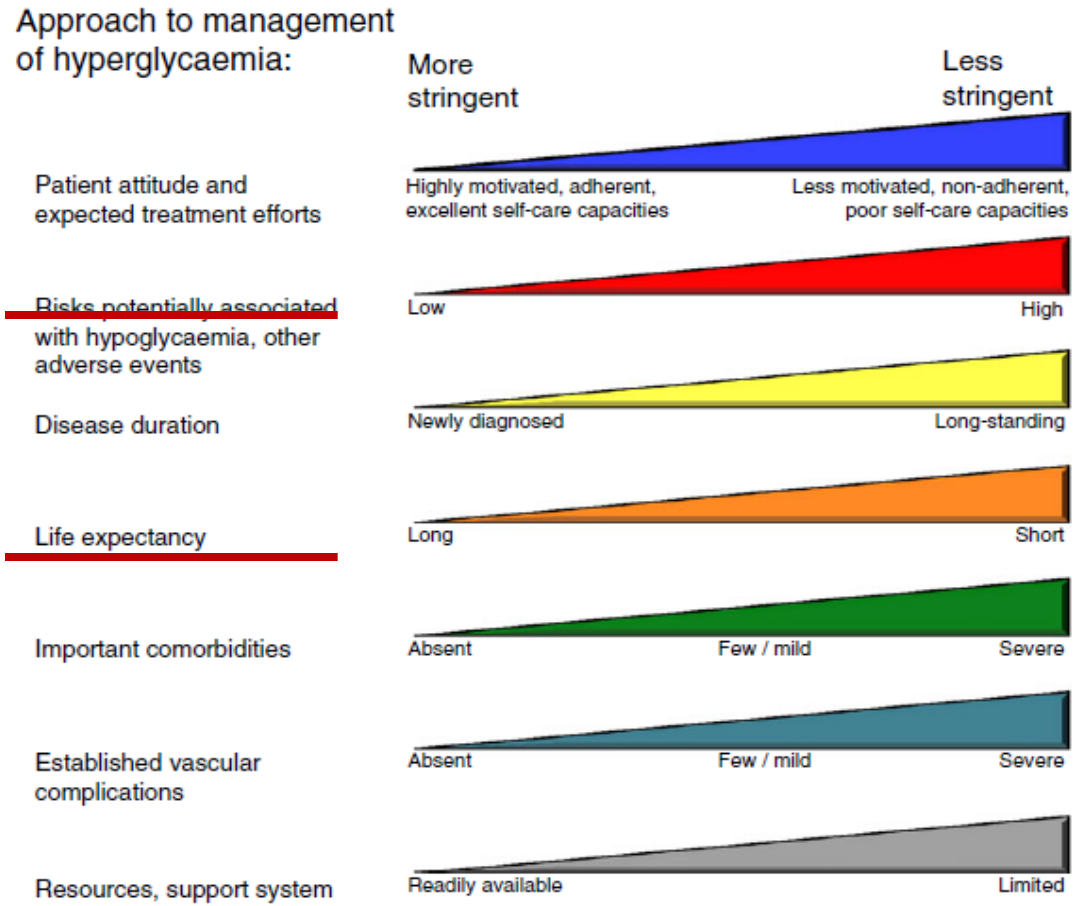
Change From Baseline at Day 28

Sitagliptin, Linagliptin Compared to Placebo



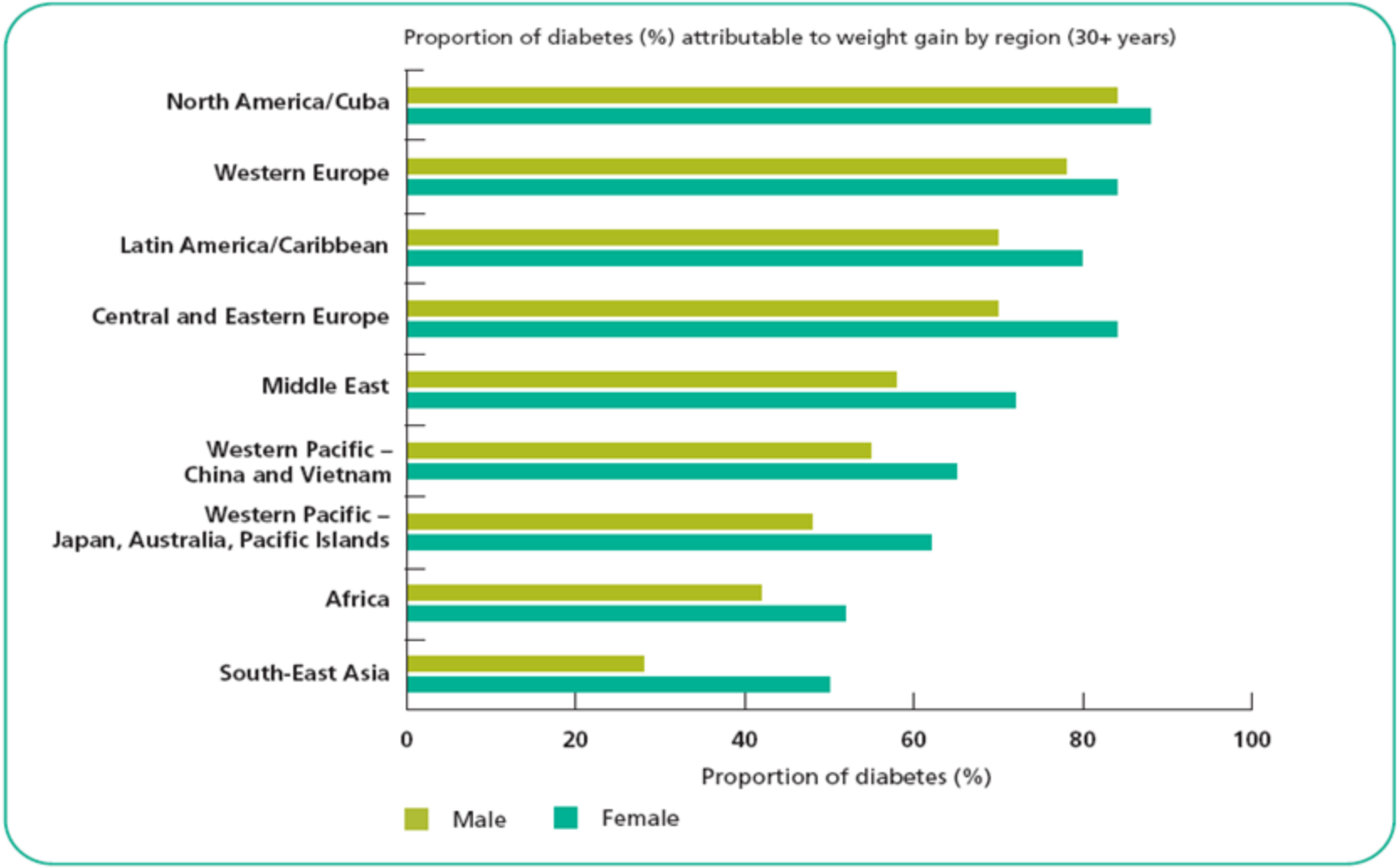
Adapted from ClinicalTrials
http://clinicaltrials.gov/ct2/show/NCT00716092
Access Date: 01/02/2012

New ADA quidline for kidney ..



Diabetologia
Received: 24 February 2012 / Accepted: 24 February 2012

Obesity as a major cause of diabetes

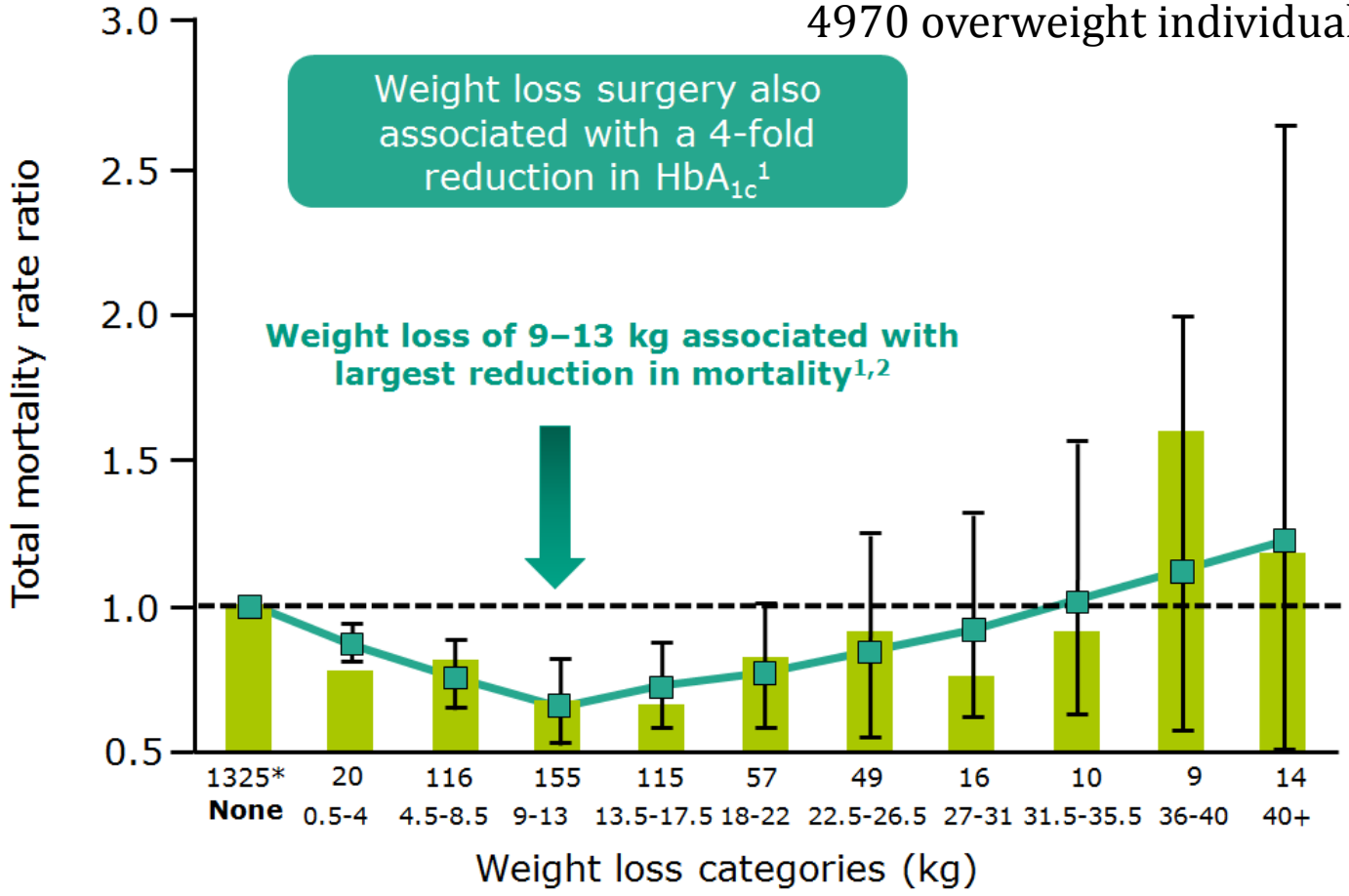


IDF Diabetes Atlas. Second edition 2003

Weight loss reduces mortality

Intentional weight loss associated with 25% reduction in total mortality

4970 overweight individuals with diabetes

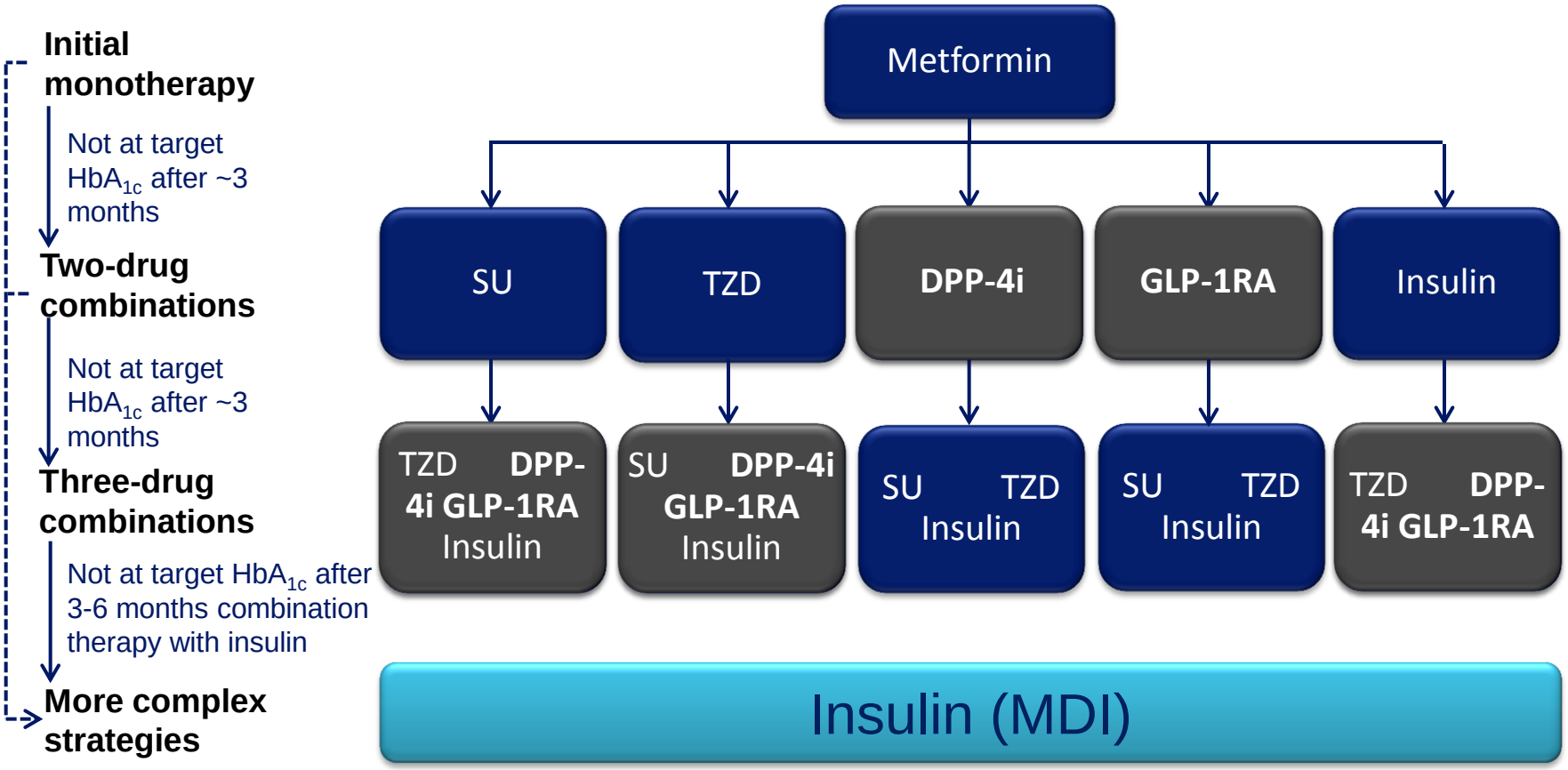


*Number of deaths

1. Dixon *et al*. *JAMA* 2008;299:316–23; 2. Williamson *et al*. *Diabetes Care* 2000;23:1499–504

ADA/EASD position statement 2012

Healthy eating, weight control, increased physical activity



MDI, multiple daily injections; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SU, sulphonylurea; TZD, thiazolidinedione

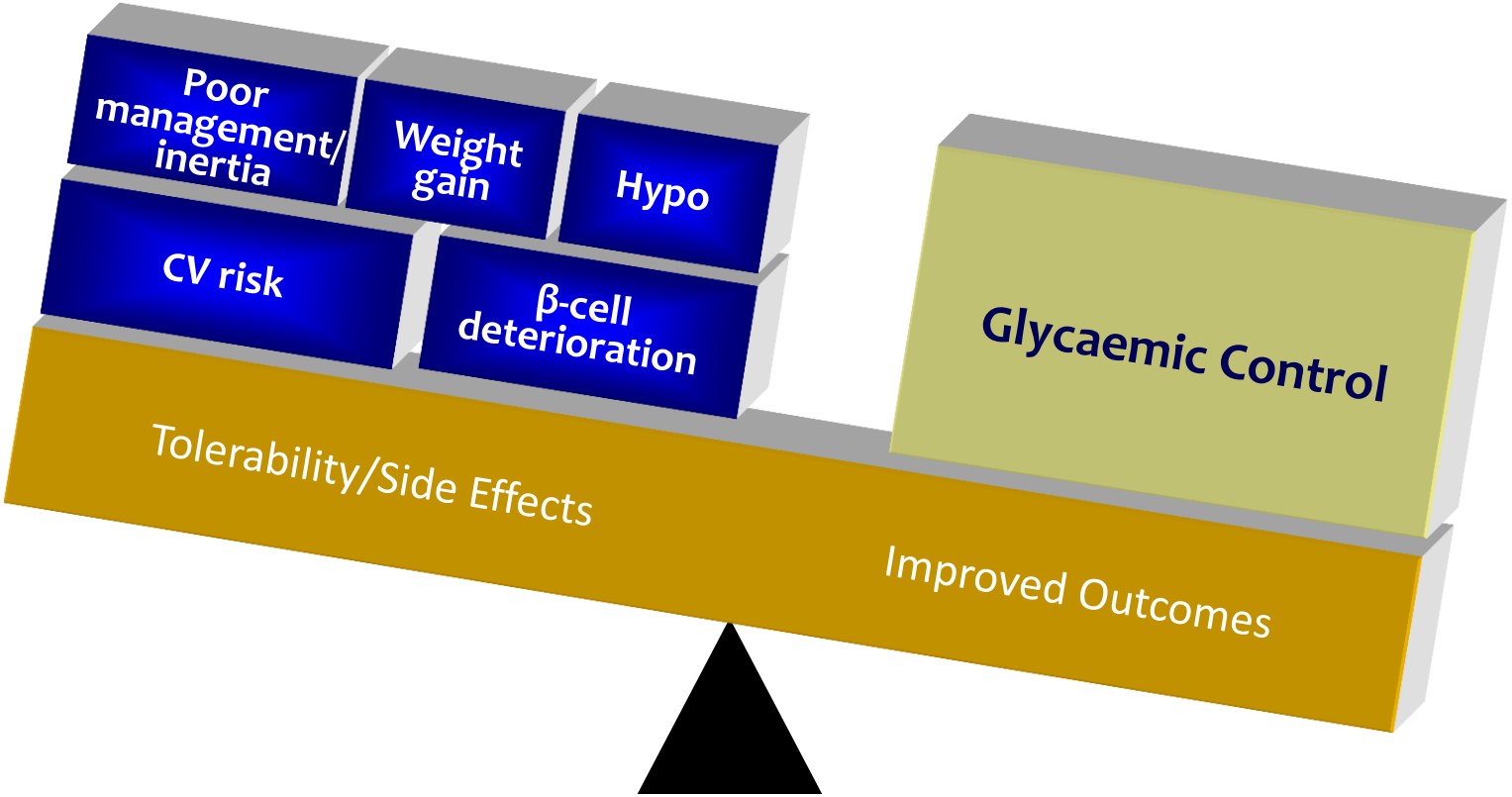
Inzucchui SE et al, Diabetes Care (2012), 35 (6), 1364-1379

KDOQI 2007: Drugs Used for Treating Hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 m^2 Avoid when GFR <50 mL/min/1.73 m^2	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m^2	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m^2 and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m^2	Reduce dose by 75% (25 mg/day)

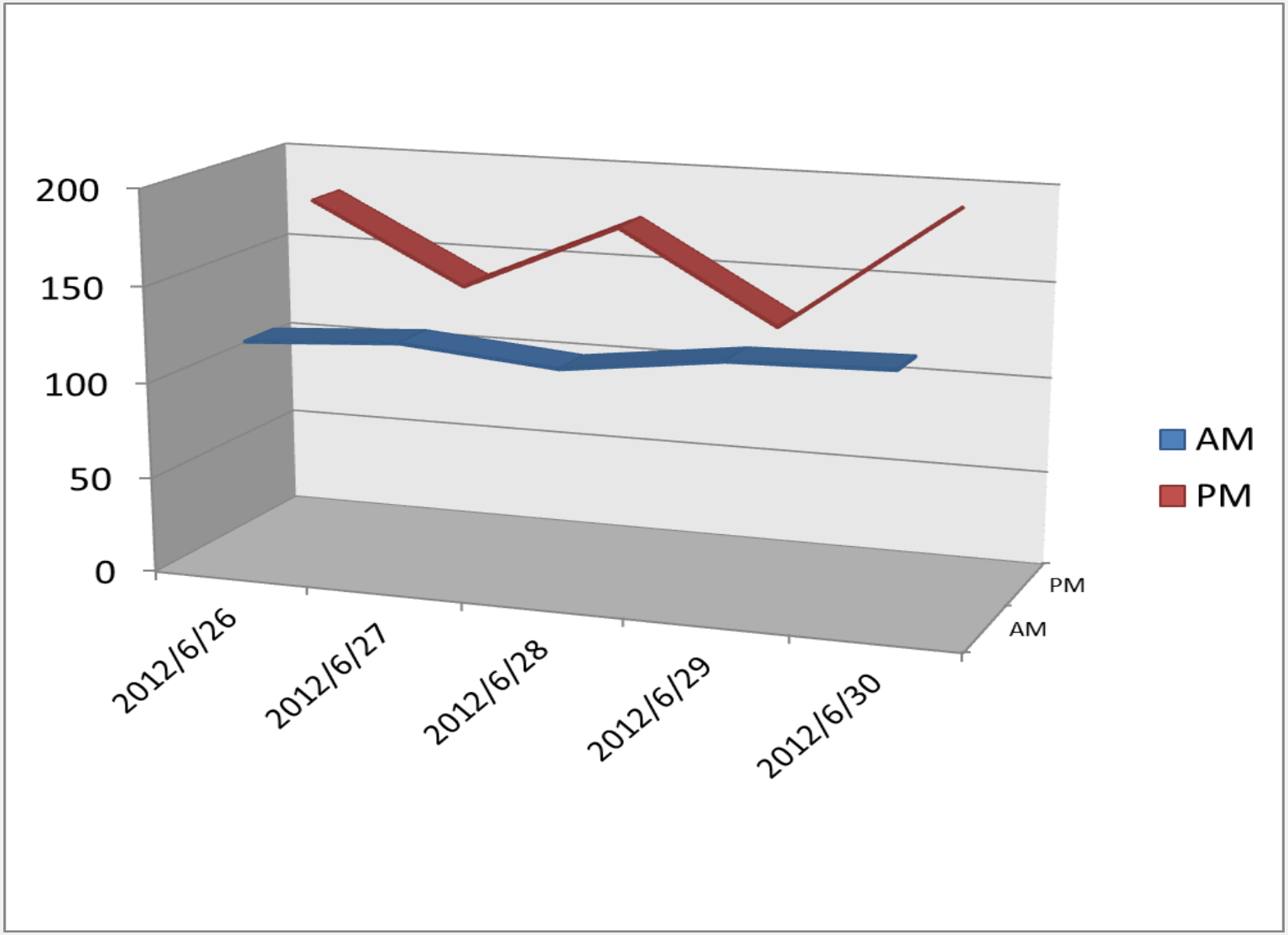
KDOQI Guidelines 2007. AJKD 2007:49;S2:S13-S155

Need for personalized care: the benefits versus risks of diabetes therapy must be assessed for each patient

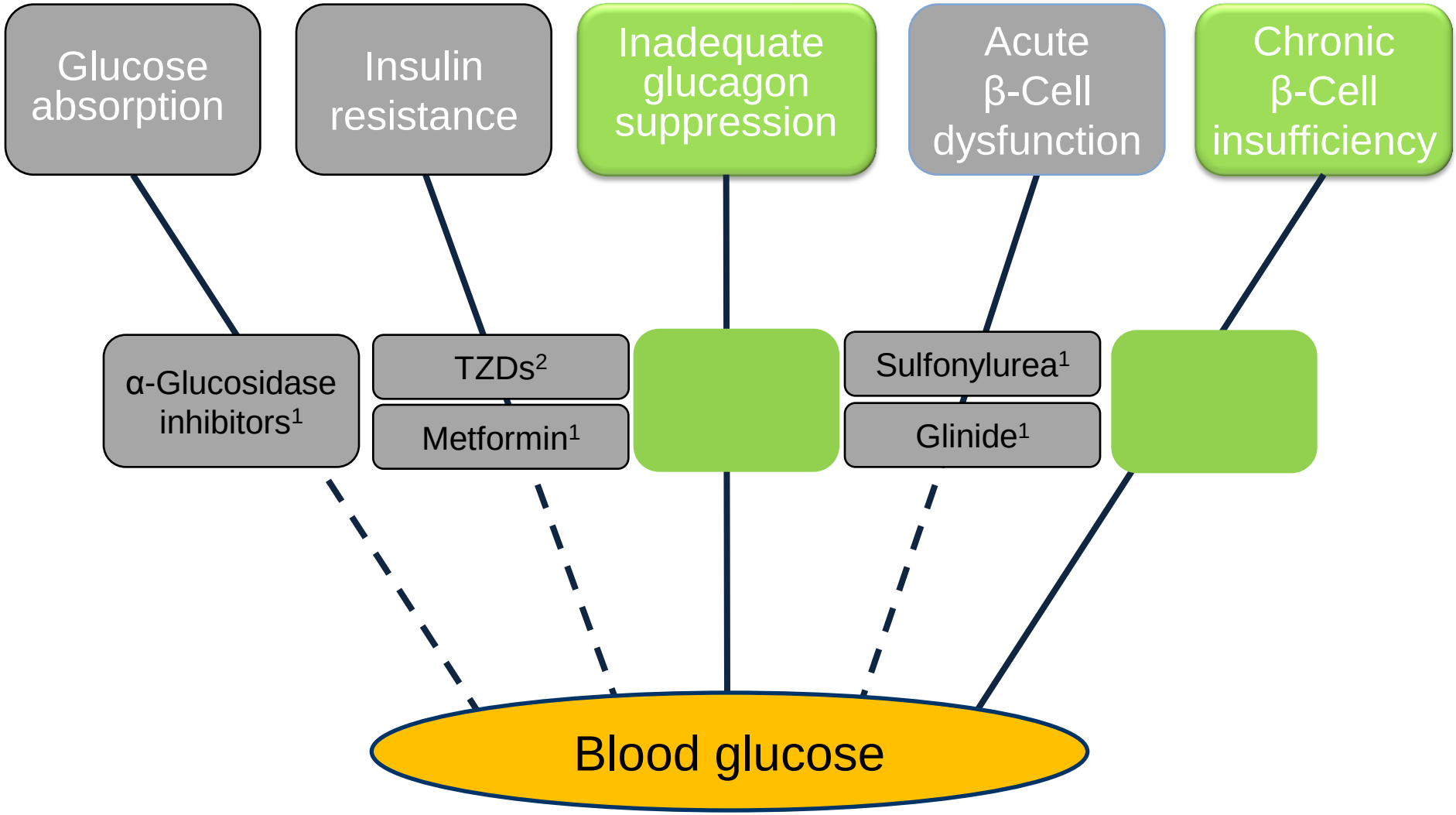


笑傲江湖

Poor glu control at PM

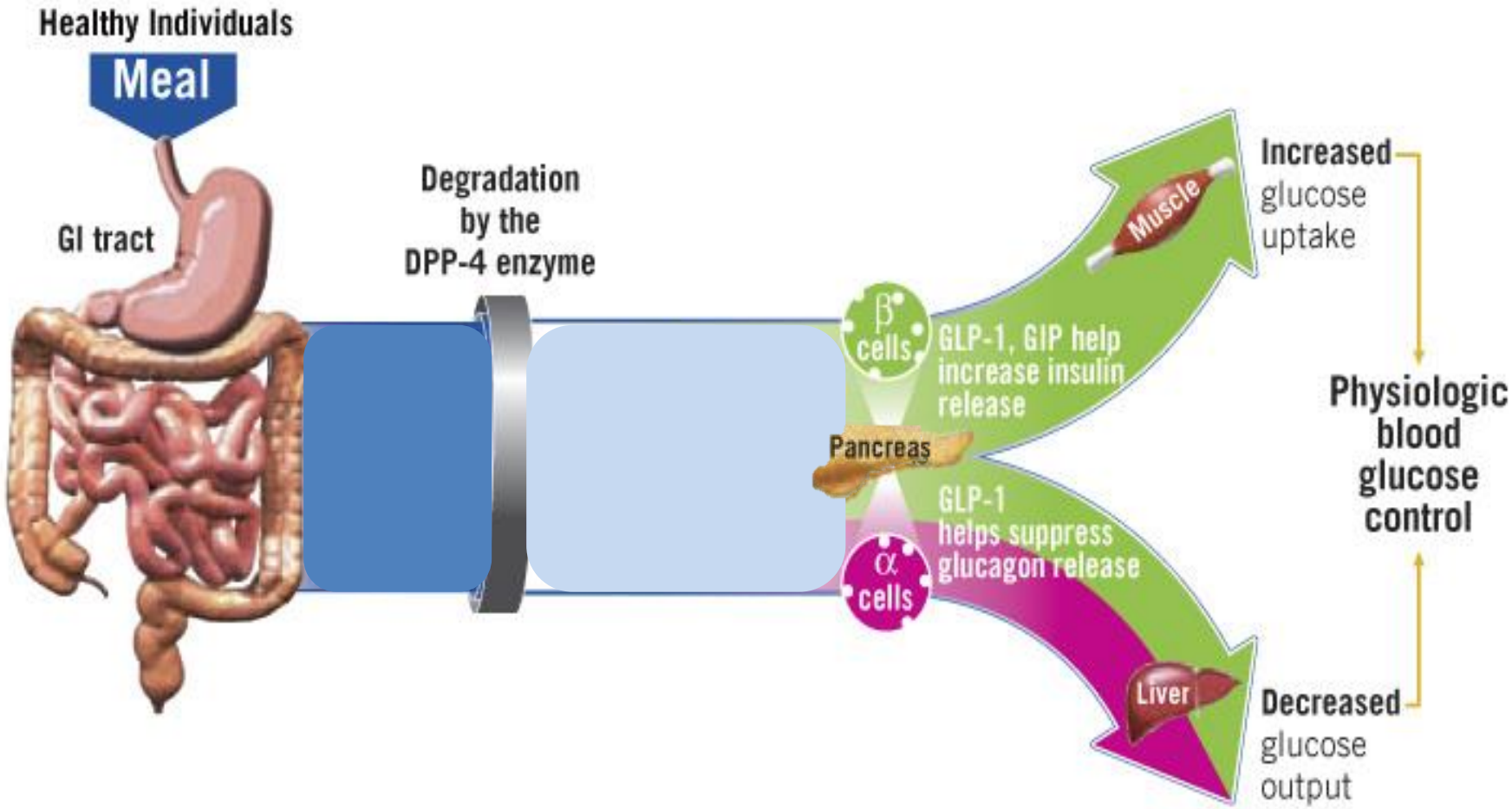


Traditional oral glucose-lowering agents in type 2 diabetes



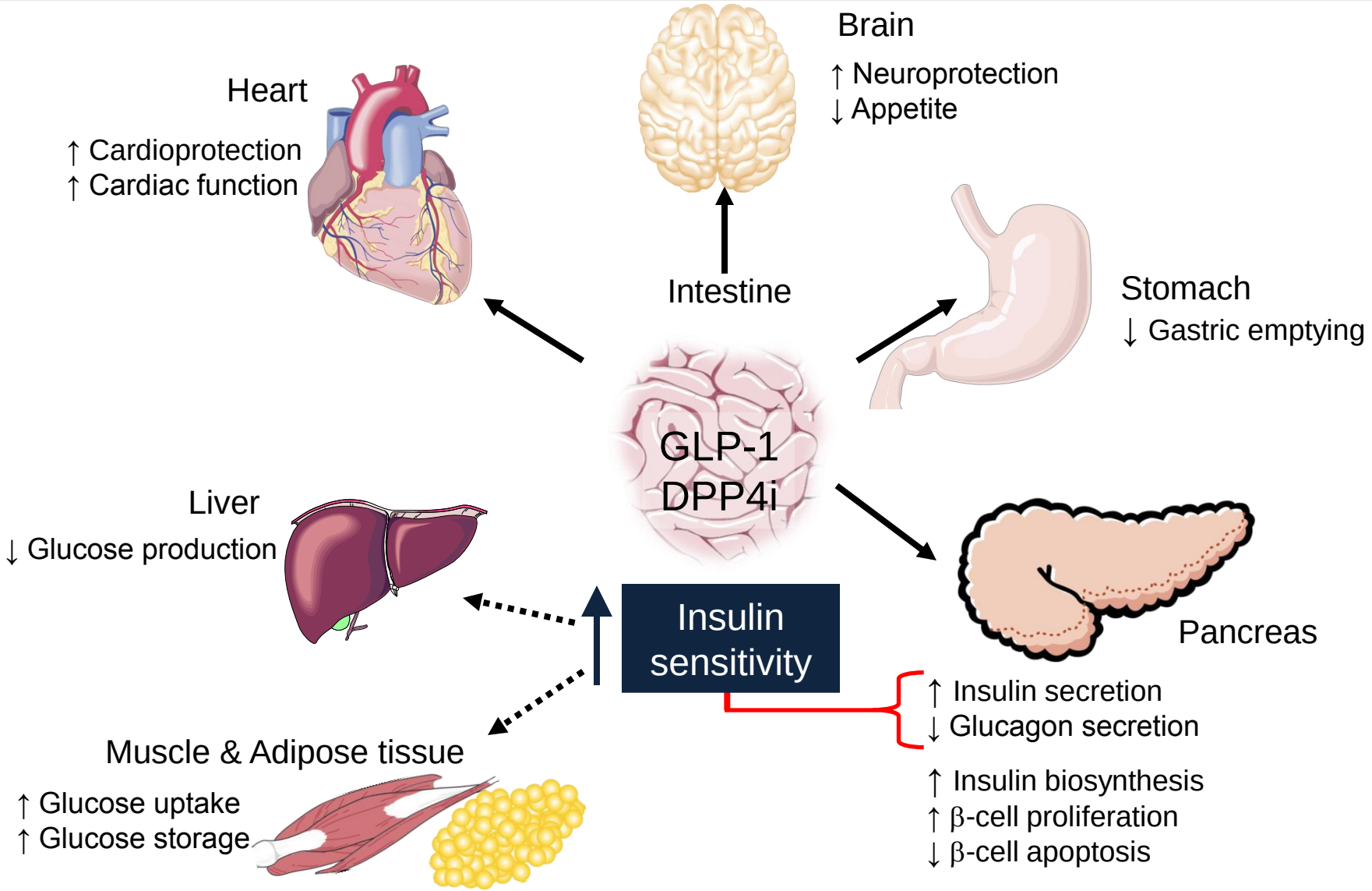
Gila Monster
Heloderma suspectum

DPP4 and incretin



The era of DPP-4

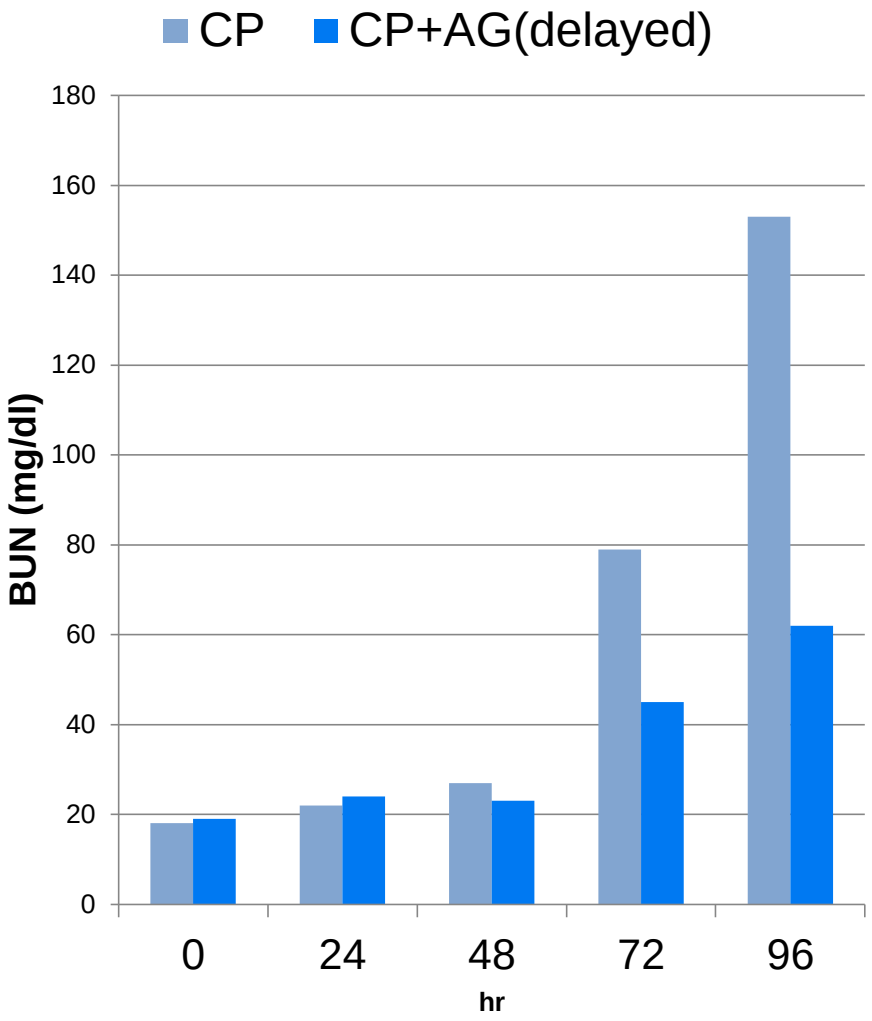
GLP-1/DPP4i has wide-ranging biological activity

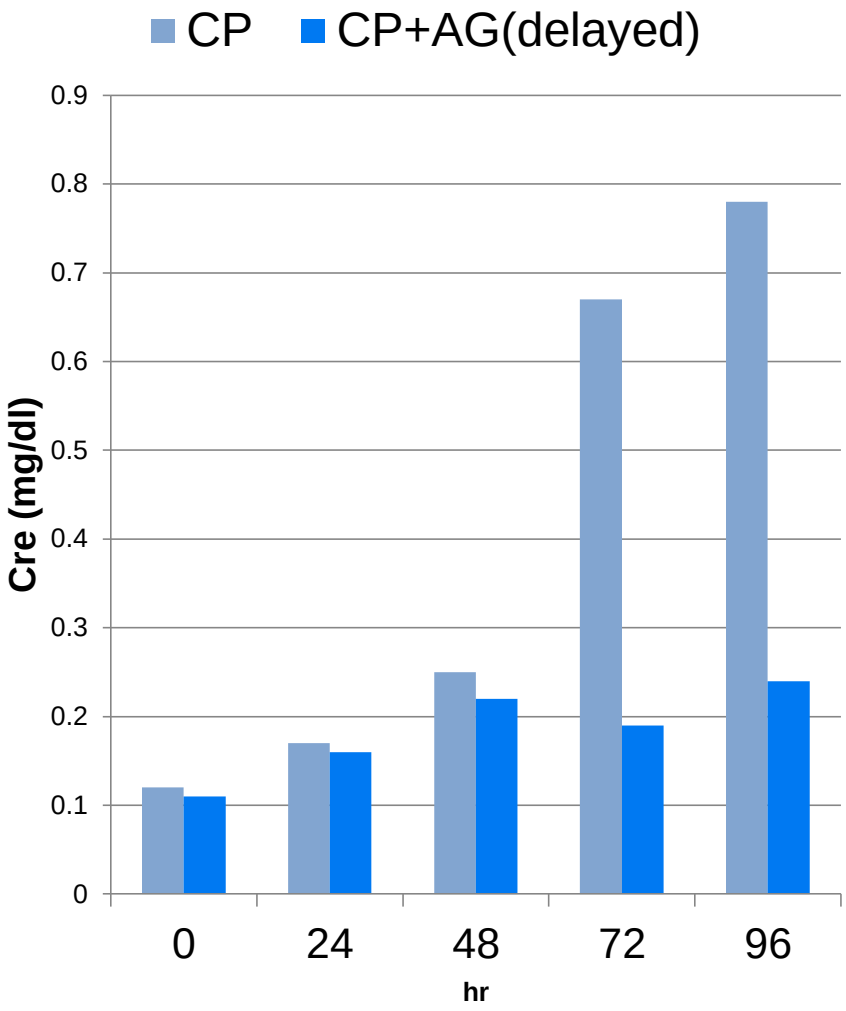


Baggio & Drucker. *Gastroenterol.* 2007;132:2131–57.

GLP-1 /DPP4/ Gut-Kidney Connection

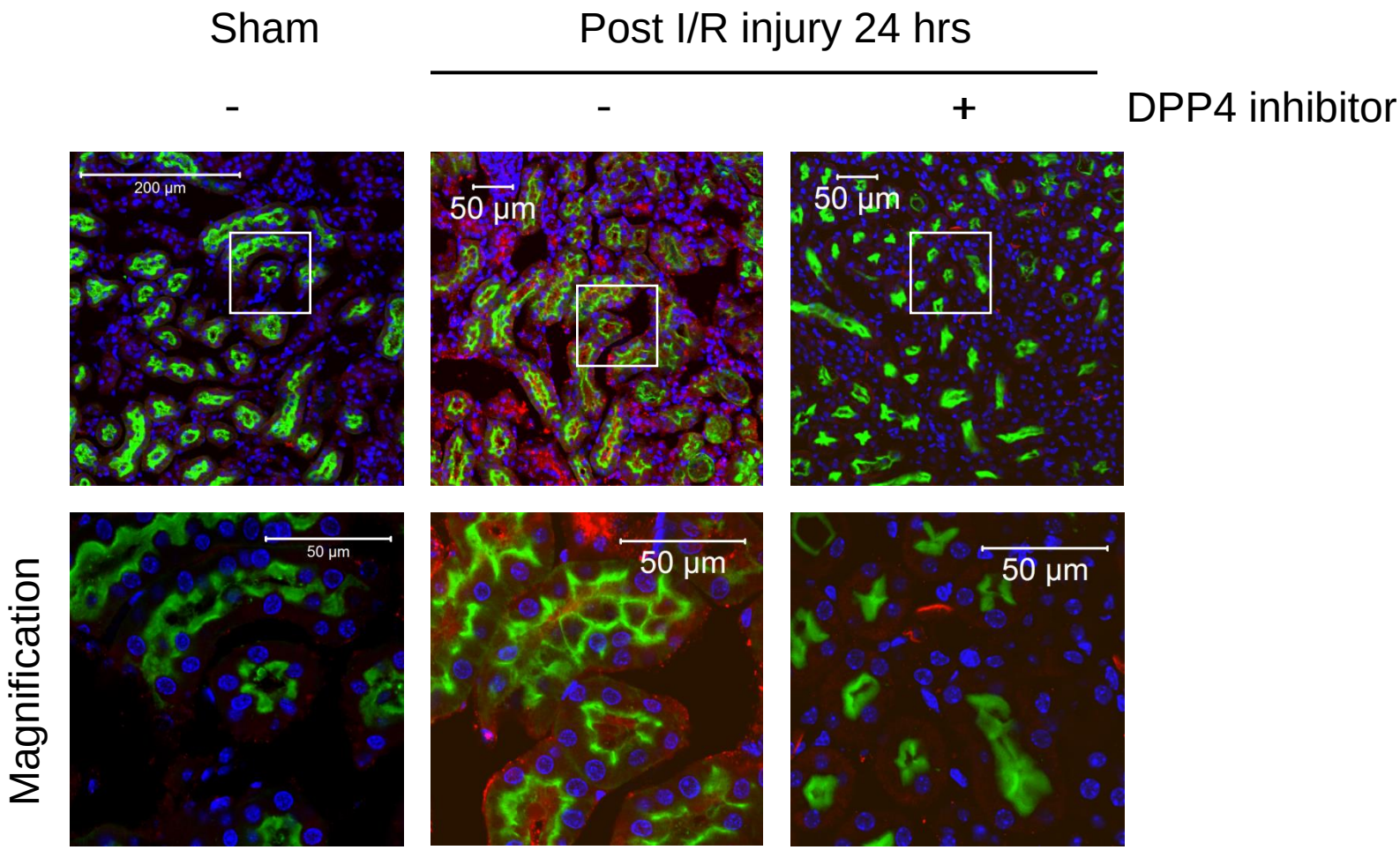
Cisplatin





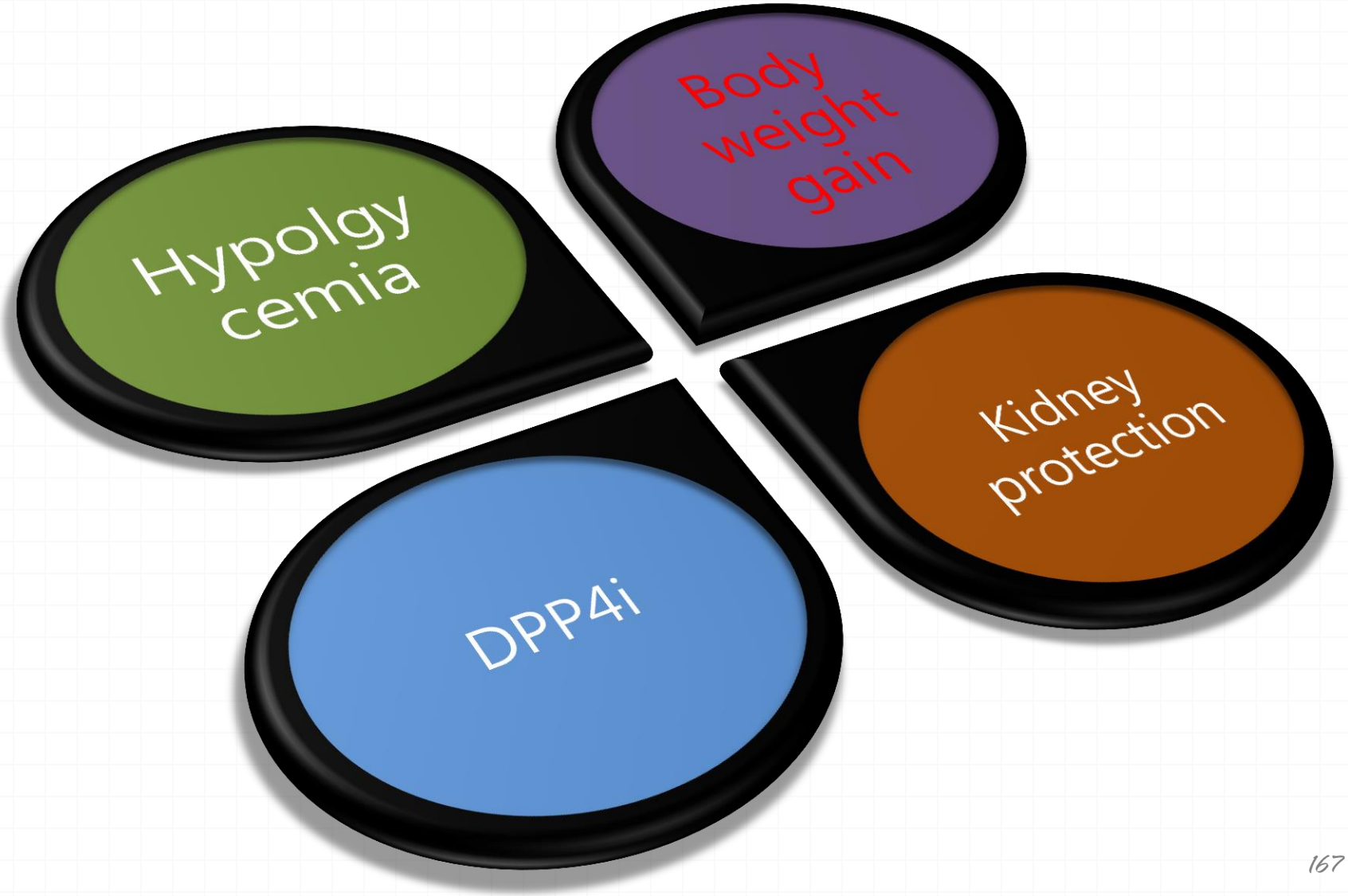
J Am Soc Nephrol 24: 2034–2043, 2013

DPP4i attenuate kidney injury in AKI



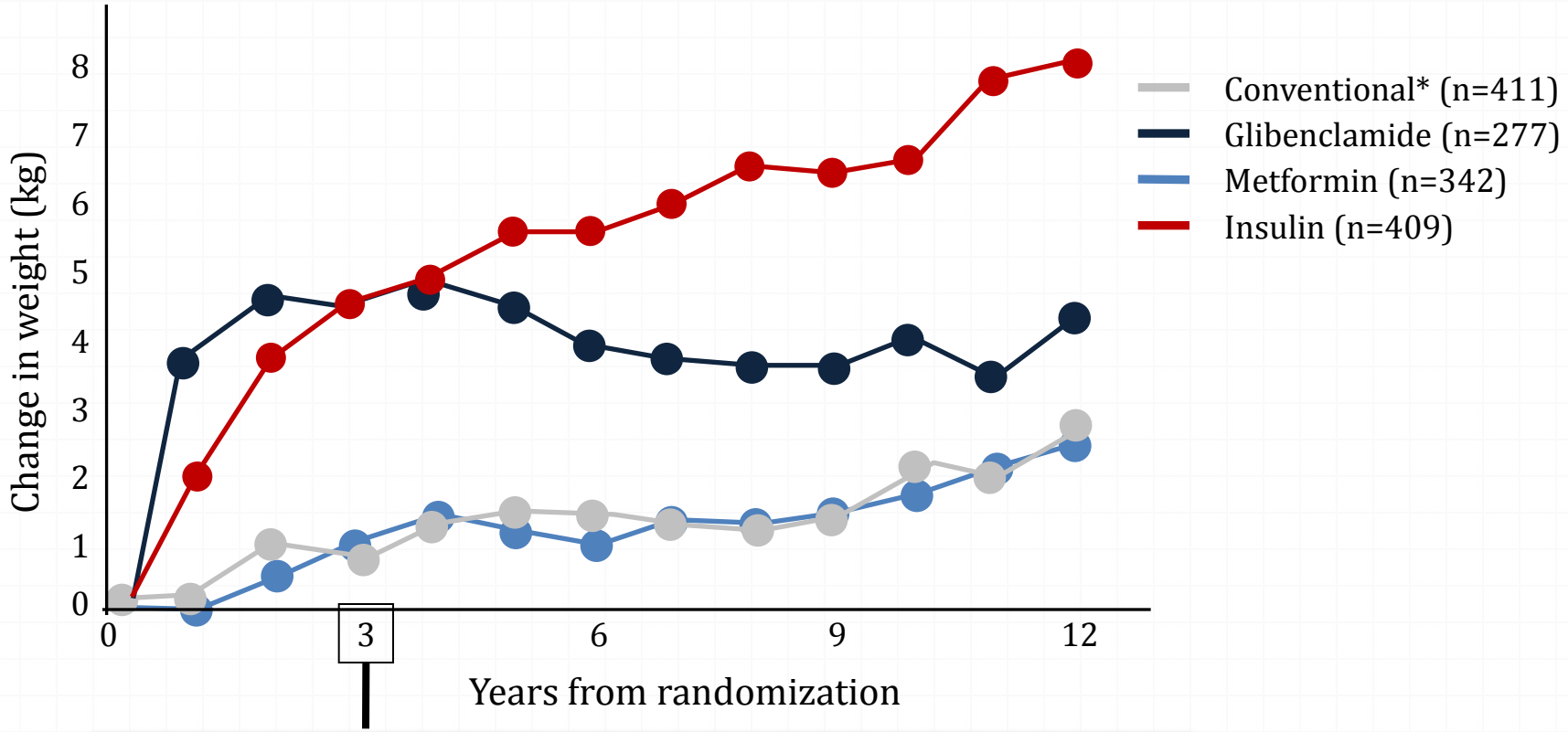
Red: NGAL Green: Proximal tubule Blue: Nuclei

NSARF
NTUH Surgery Intensive Care Unit Acute Renal Failure Group


Body weight gain
Hypolgy cemia
Kidney protection
DPP4i

Weight Gain

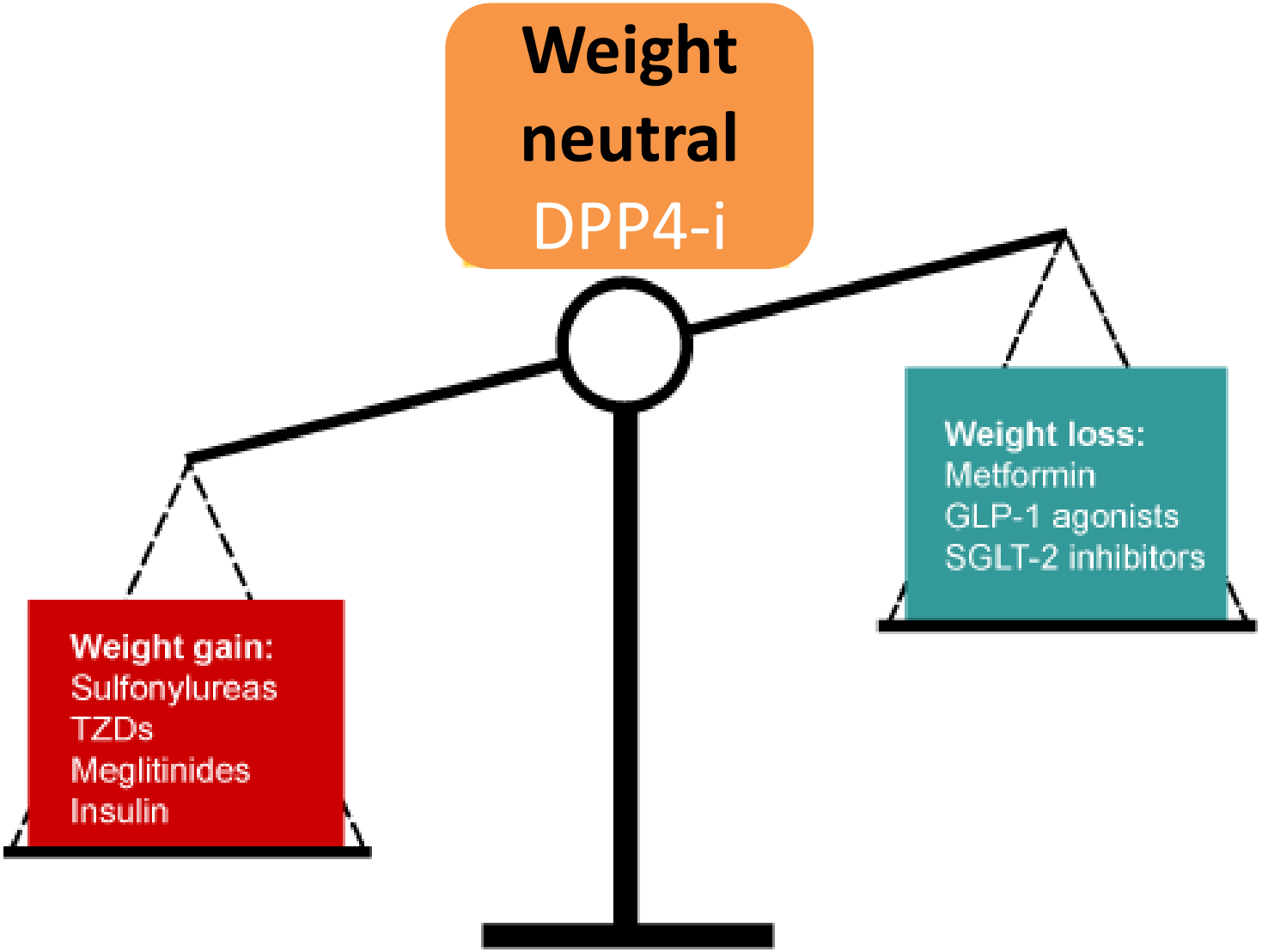
UKPDS 34 Study



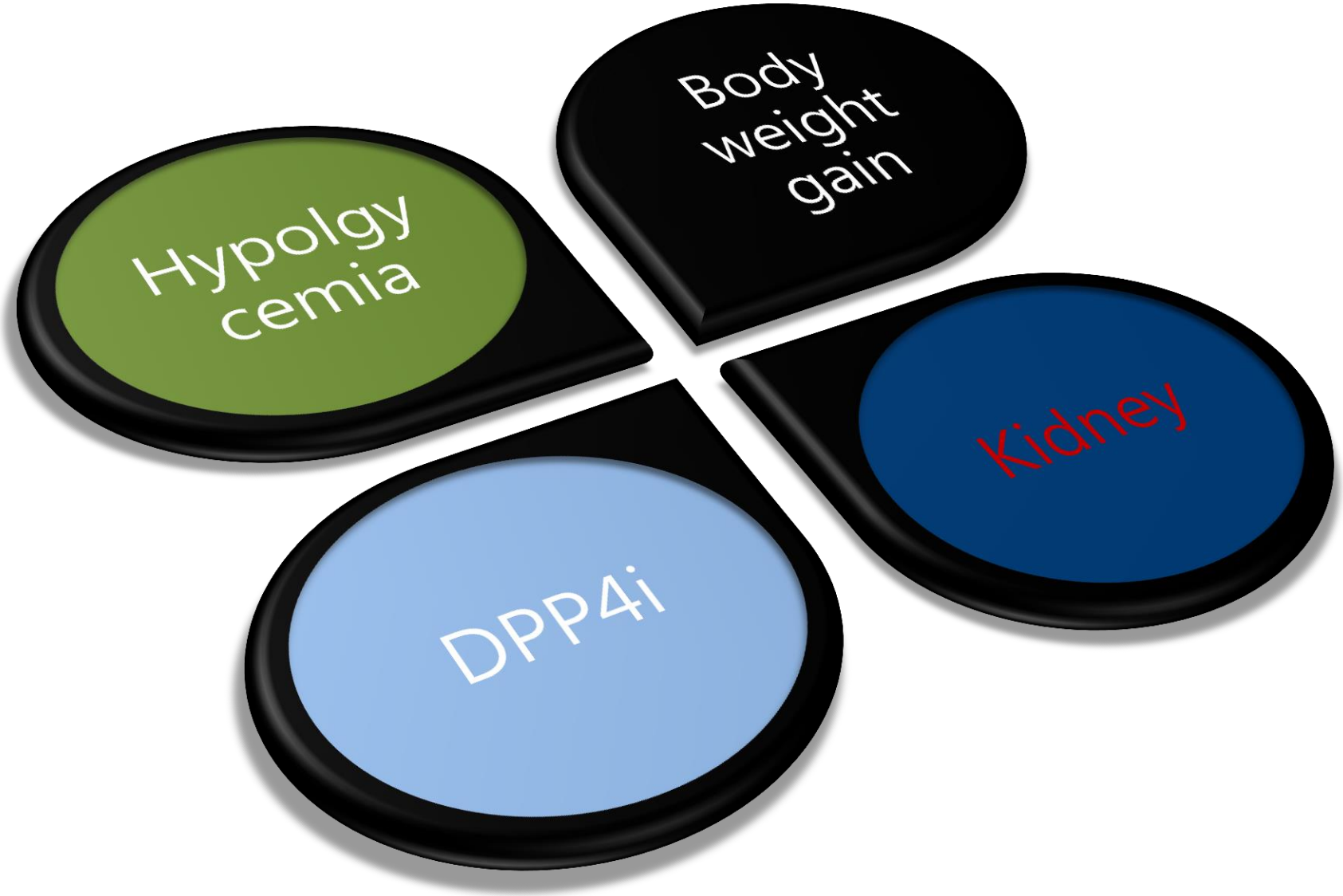
Up to 5 kg is already gained within just 3 years with a sulphonylurea or insulin

Lancet 1998:352:854–65

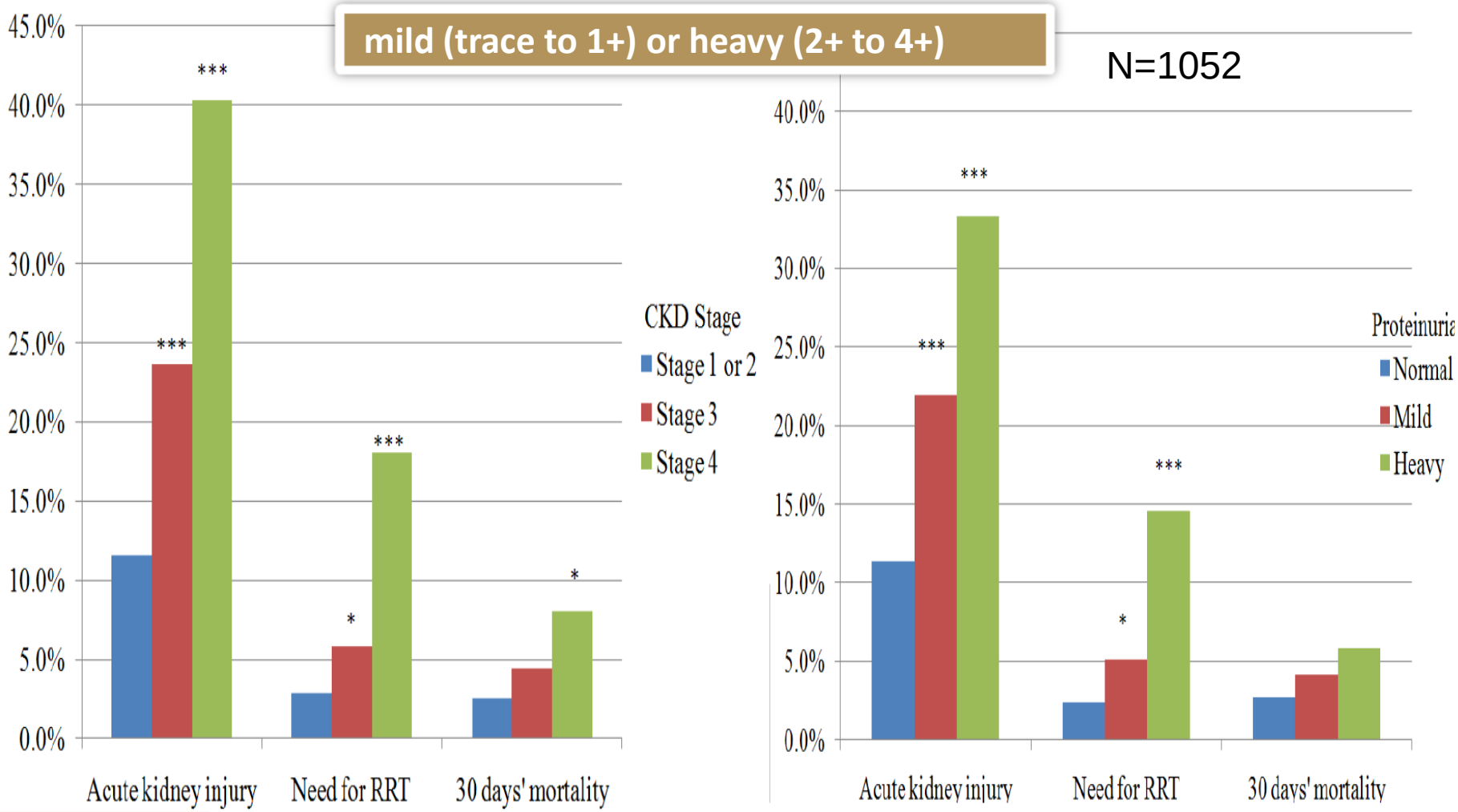
Yes, body weight is big issue



The era of DPP-4i



Post-operative AKI, RRT and 30 day's all cause mortality



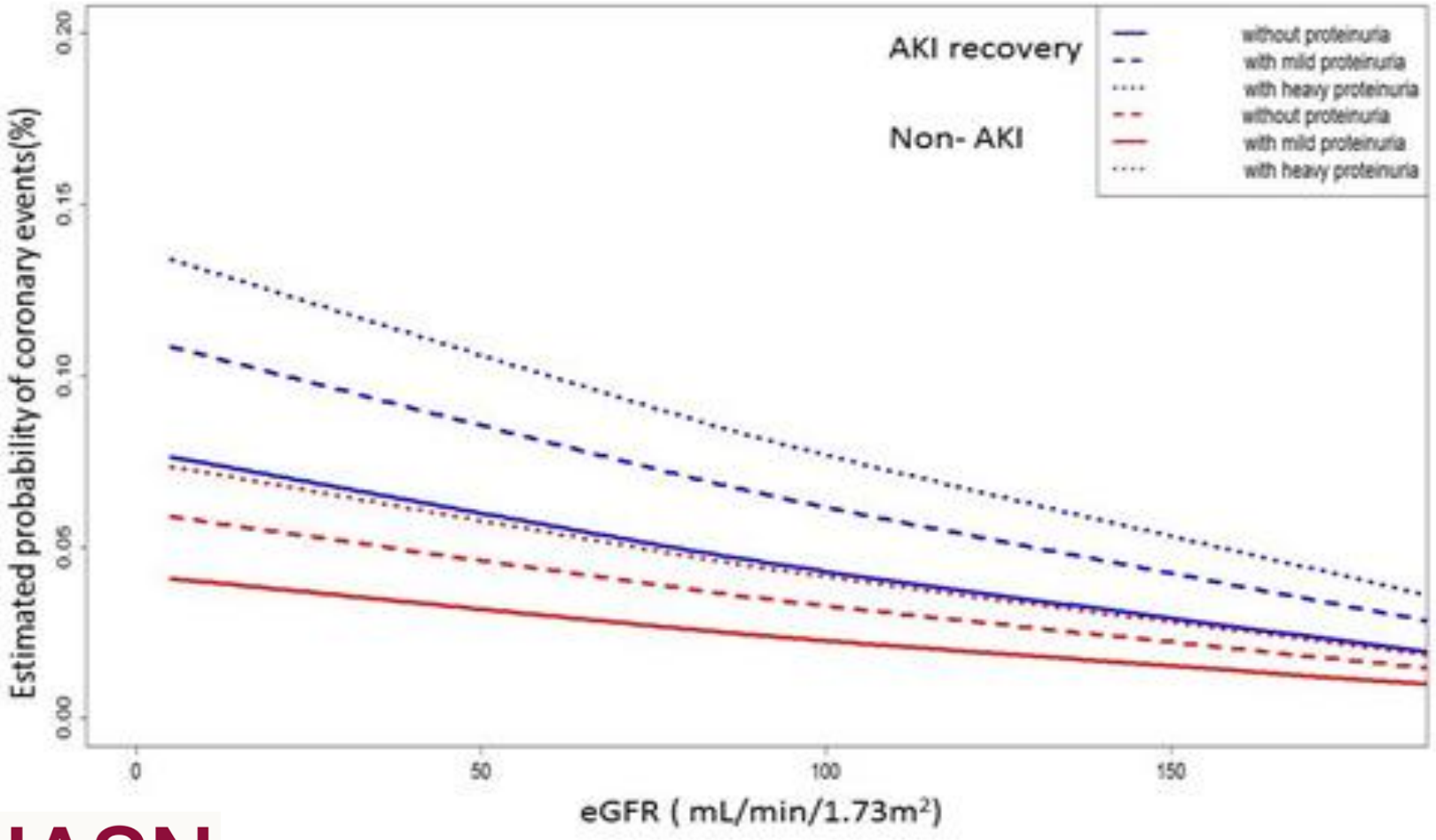
JASN

Huang DM, Wu VC et al, JASN, 2011

Proteinuiria predict coronary events after recovery from AKI

CLINICAL EPIDEMIOLOGY www.jasn.org

NSARF
NTUH Surgery Intensive Care Unit Acute Renal Failure Group



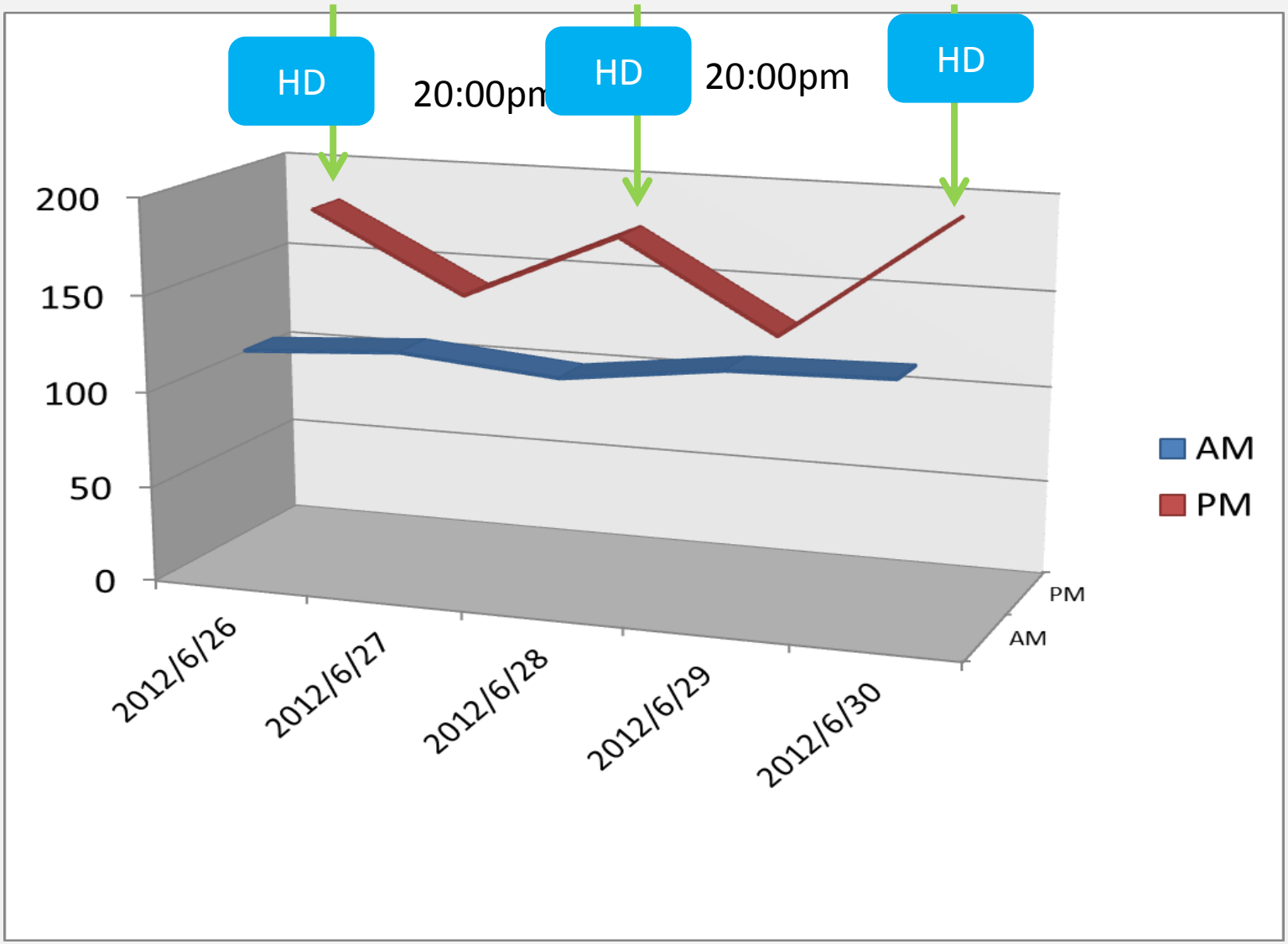
JASN

Wu VC, et al , 2014, JASN

Pt2_Brief history

1. 47 Male, Diabetes mellitus, type 2 for over 10 years with nephropathy, neuropathy, and retinopathy under regular medication control
2. End stage renal disease under HD recently, (AM)
3. Obstructive sleep apnea syndrome
4. Peripheral arterial occlusive disease

Poor glu control at PM

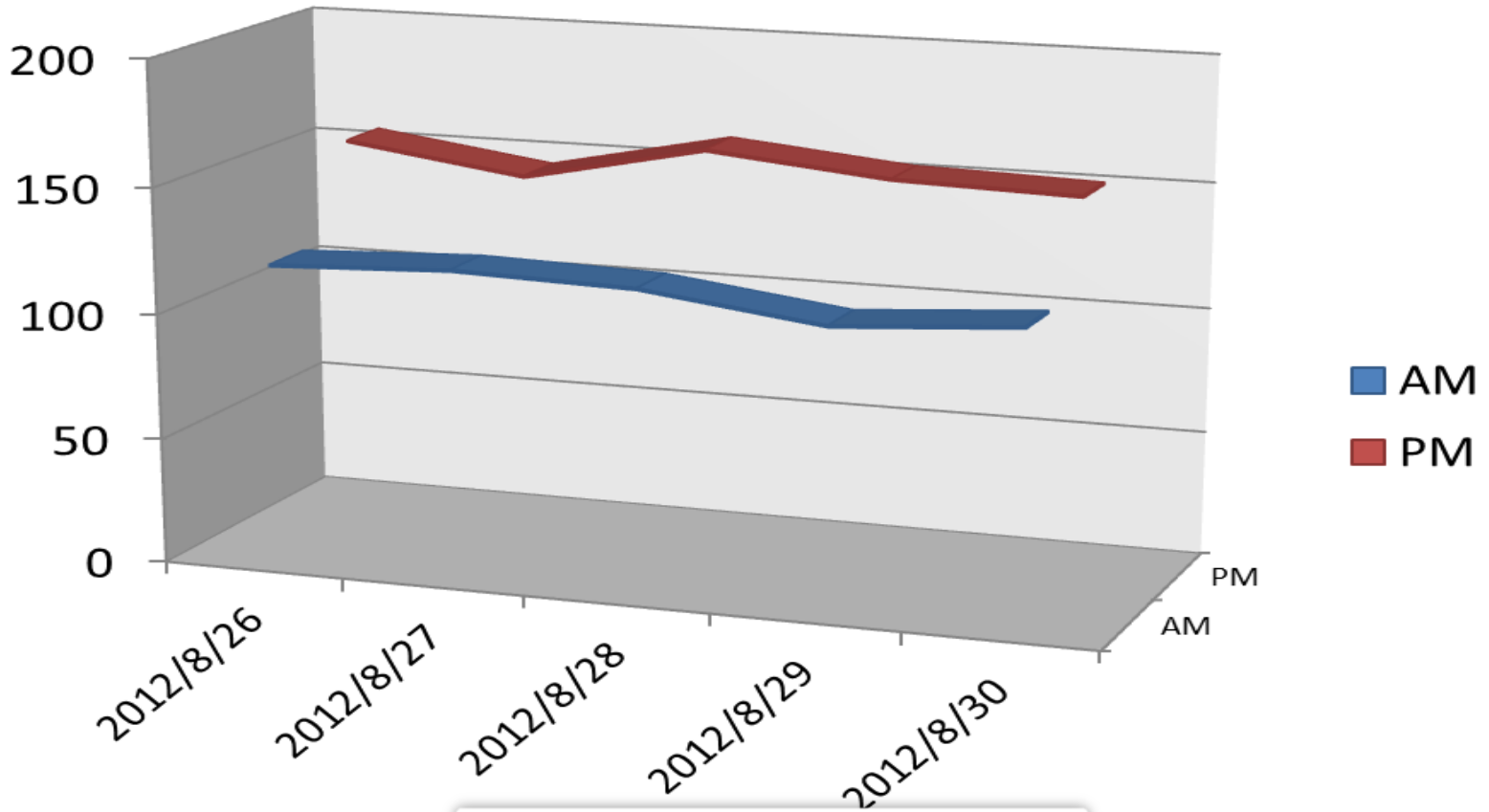


Medication

Start data	Medication	Dose and frequency
2012/6/26	Furosemide(Lasix 40mg/tab)	1 tab PO BID
2012/6/26	Pentoxifylline(Trental SR 400mg/tab)	1 tab PO QD
2012/6/26	非Saxagliptin, DPP4i mg/tab)	1 tab PO QD
2012/7/6	Folic Acid(Folic Acid 5mg/tab)	1 tab PO QD
2012/7/7	Methoxy polyethylene glycol-epoetin beta(Mircera 100mcg/.3mL /syrg)	100 mcg SC STAT
2012/7/7	Nifedipine (ADALAT OROS) 30 mg/tab	**1 tab PO BID**

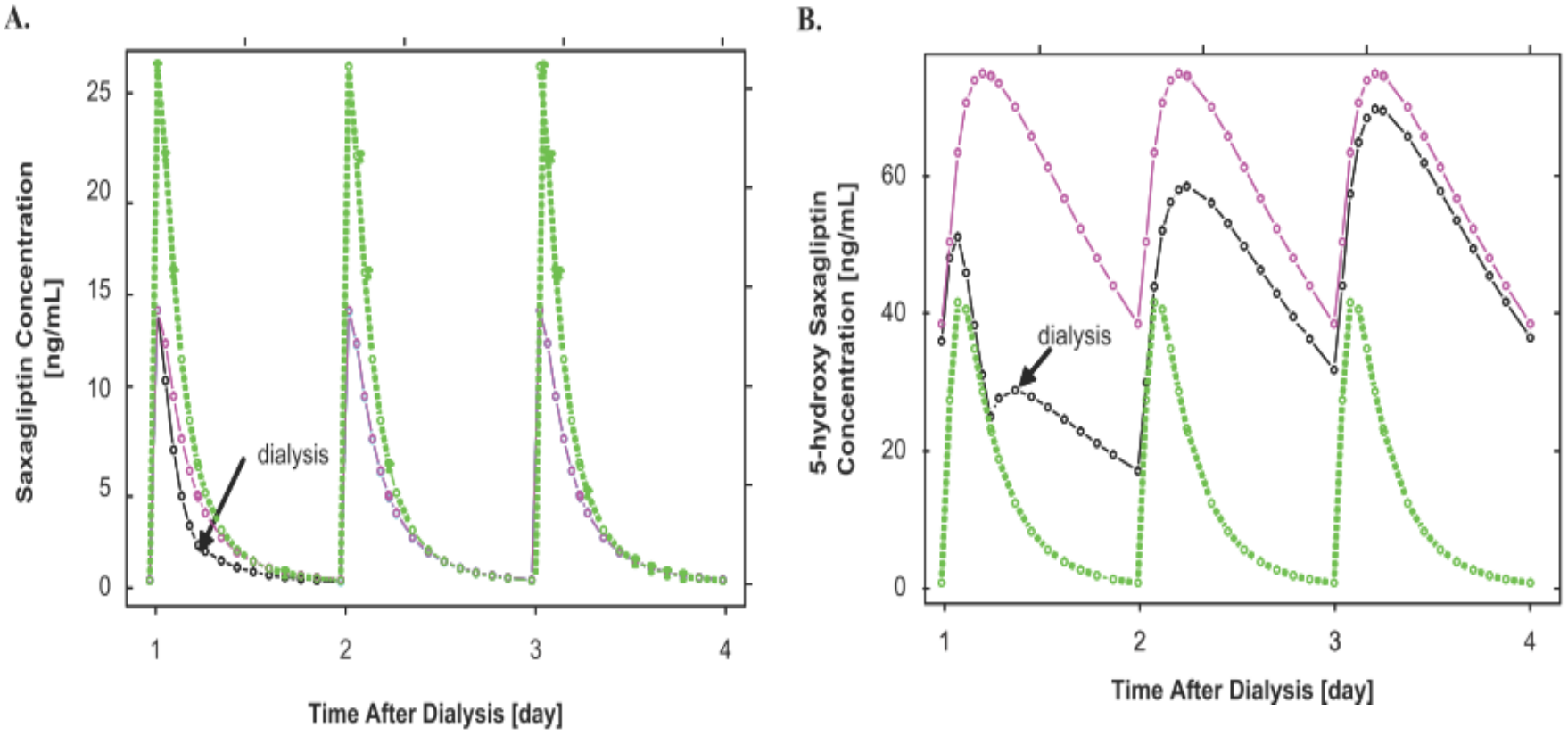
How would you manage this?

47 DM nephropathy, dialysis



Saxagliptin (2.5 mg) post HD

A Pharmacometric Approach



J Clin Pharmacol 2012;52:126S-133S

+

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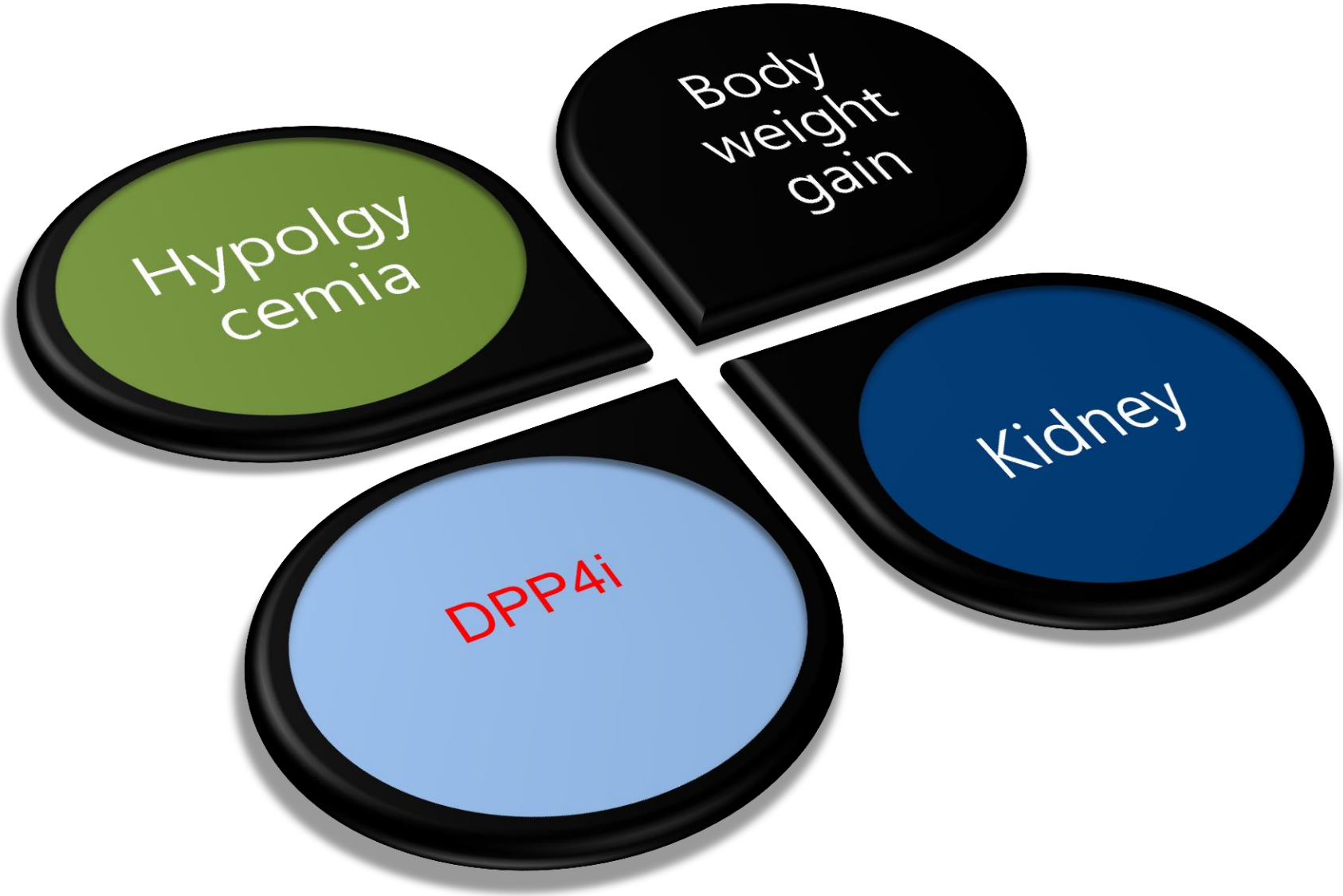
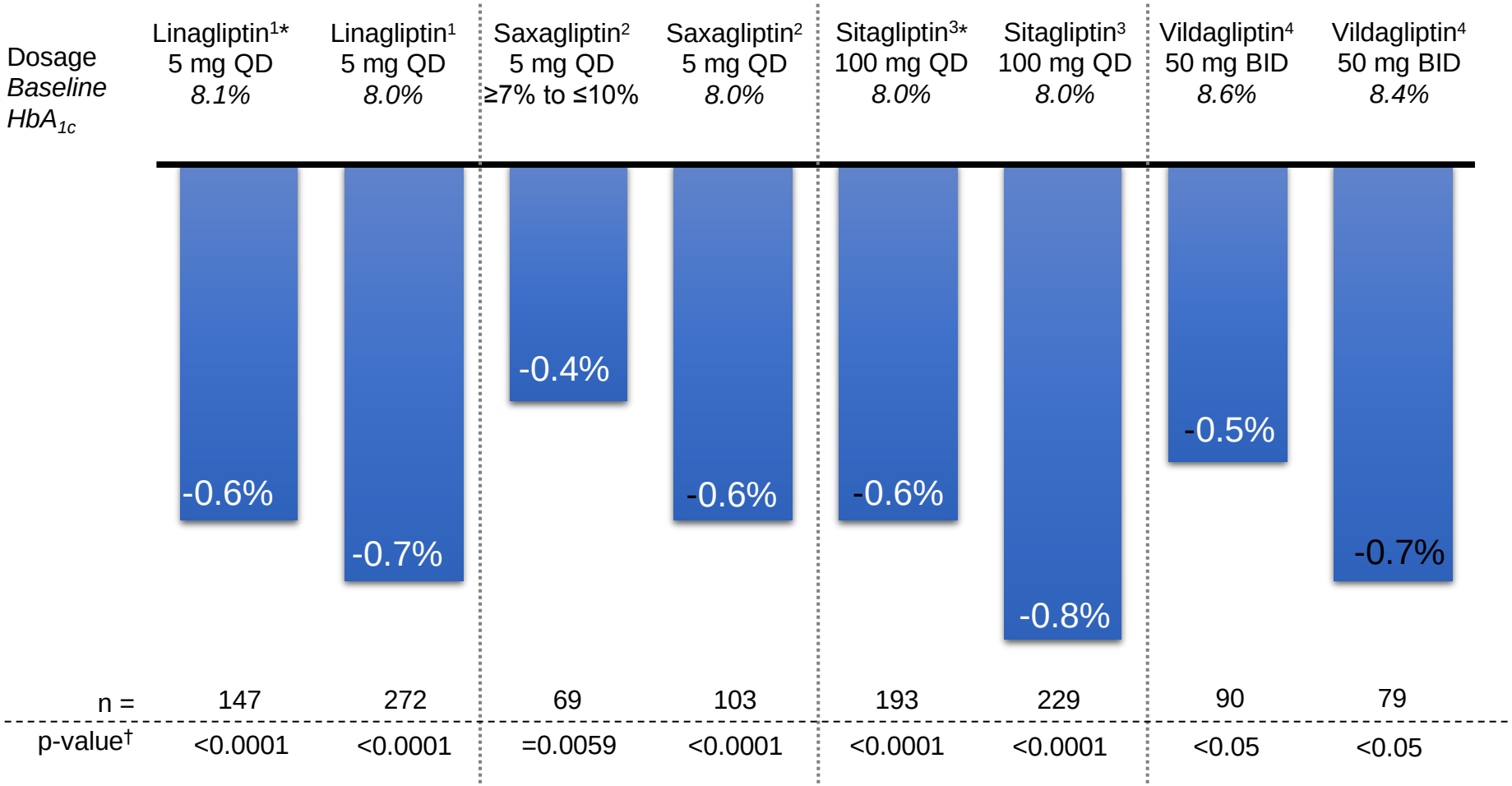
Improve safety -*in CKD*

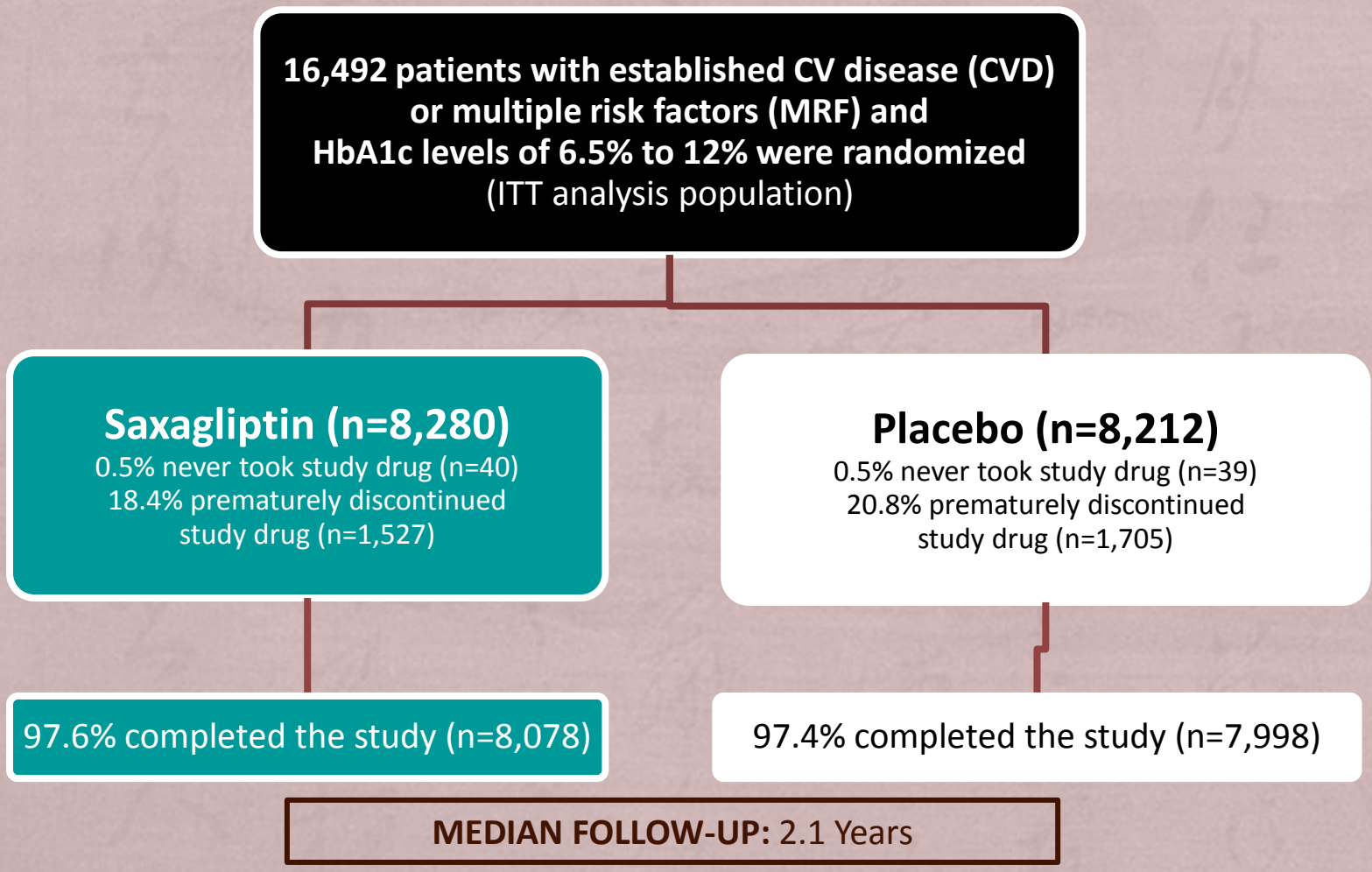

怨天尤人
不如
挺胸做人
Januvia™
(sitagliptin) tablets
100 mg
30 Tablets


Hypolgy
cemia
Body
weight
gain
Kidney
DPP4i

Efficacy of DPP-4 inhibitors in monotherapy trials

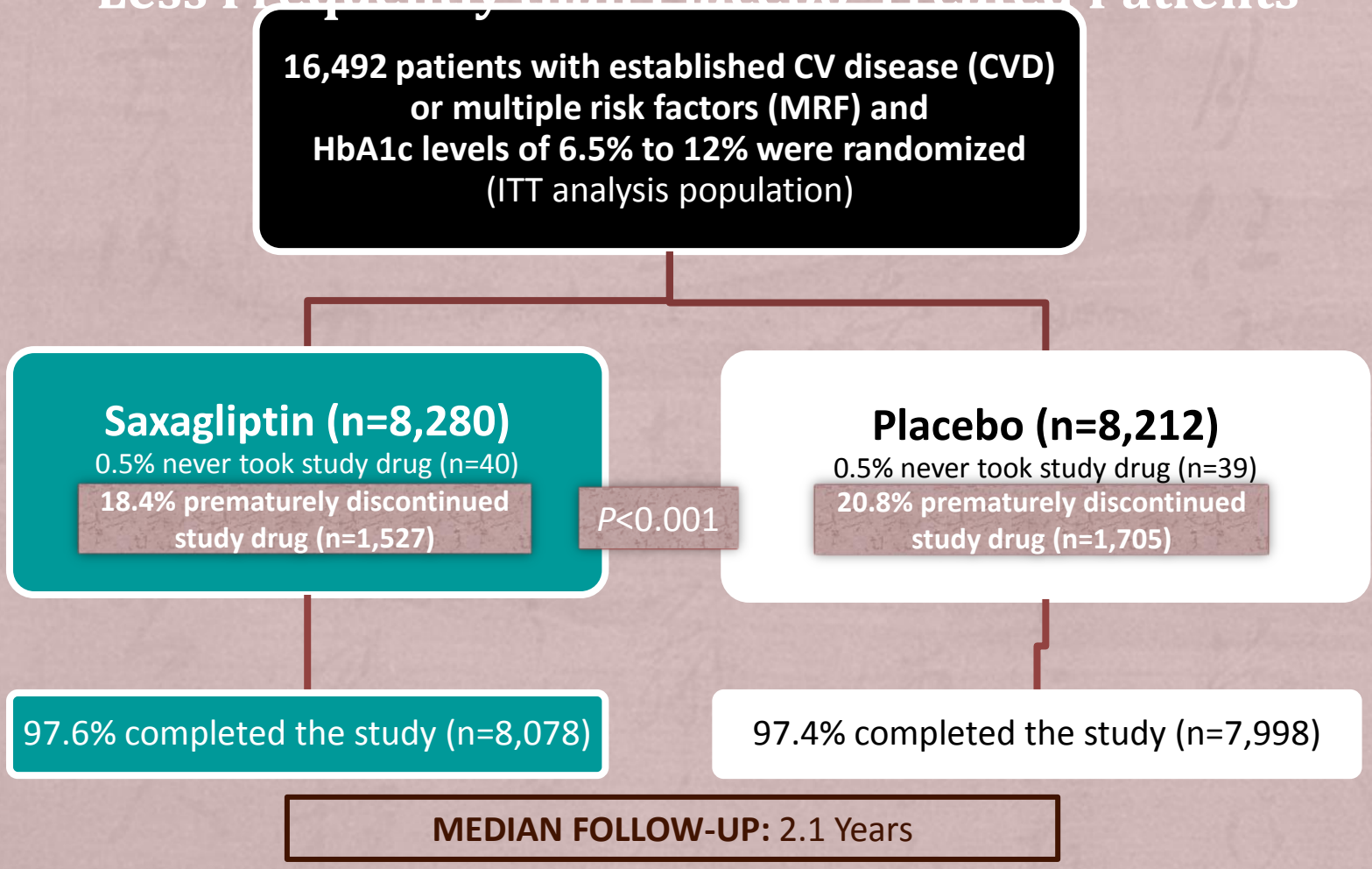


Study Disposition



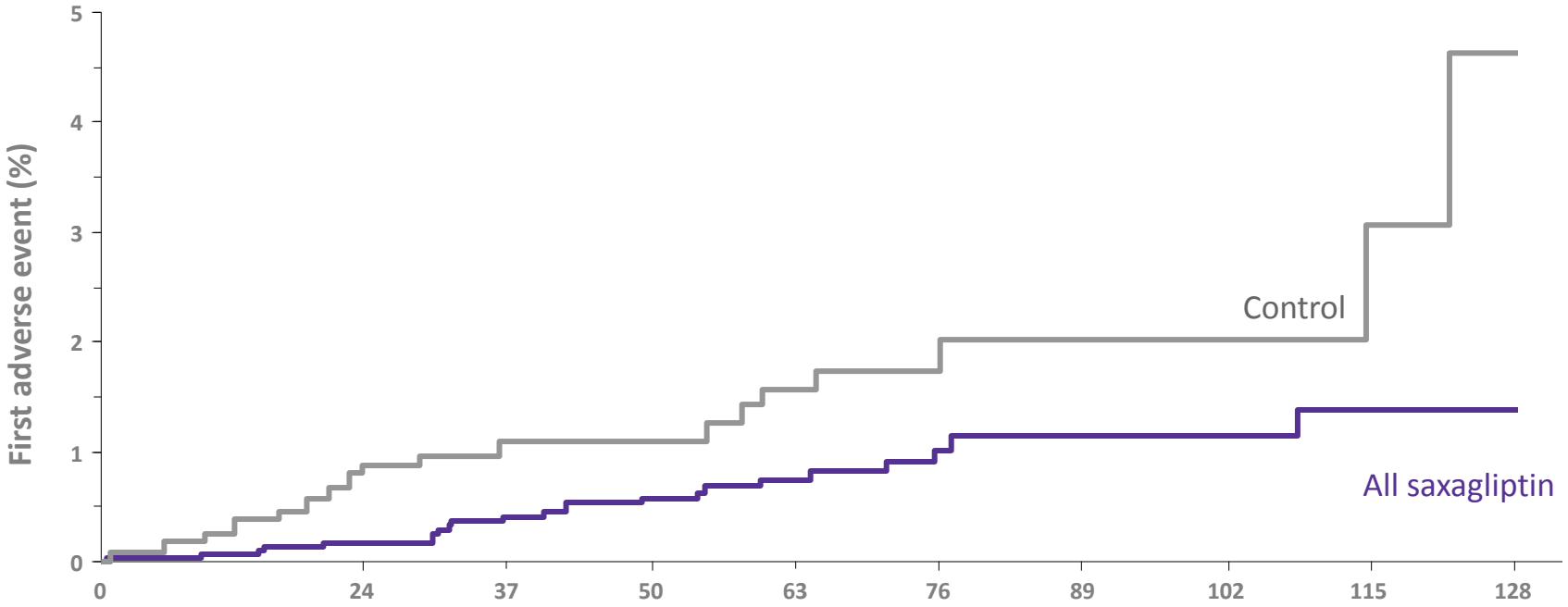
Scirica BM, et al. *N Engl J Med.* 2013; doi: 10.1056/NEJMoa1307684.

Saxagliptin-Treated Patients Discontinued Study Drug Less Frequently than Placebo-Treated Patients



Scirica BM, et al. *N Engl J Med.* 2013; doi: 10.1056/NEJMoa1307684.

Time to onset of first primary Major Adverse Cardiovascular Event (MACE)



Patients at risk										
Control	1,251	935	860	774	545	288	144	123	102	57
All saxagliptin	3,356	2,615	2,419	2,209	1,638	994	498	436	373	197

Pancreatitis and Pancreatic Cancer

Endpoint	Patients (%)		P-value
	Saxagliptin (n=8,280)	Placebo (n=8,212)	
Any pancreatitis*	0.3%	0.3%	0.77
Acute (Definite or possible)	0.3%	0.2%	0.42
Acute (Definite)	0.2%	0.1%	0.17
Acute (Possible)	0.1%	0.1%	0.79
Chronic	<0.1%	0.1%	0.18
Pancreatic cancer	5	12	0.095

The observed rates of pancreatic cancer were lower in the saxagliptin group (5 patients) than in the placebo group (12 patients; P*=0.095).*

*Patients may have had more than one type of event.

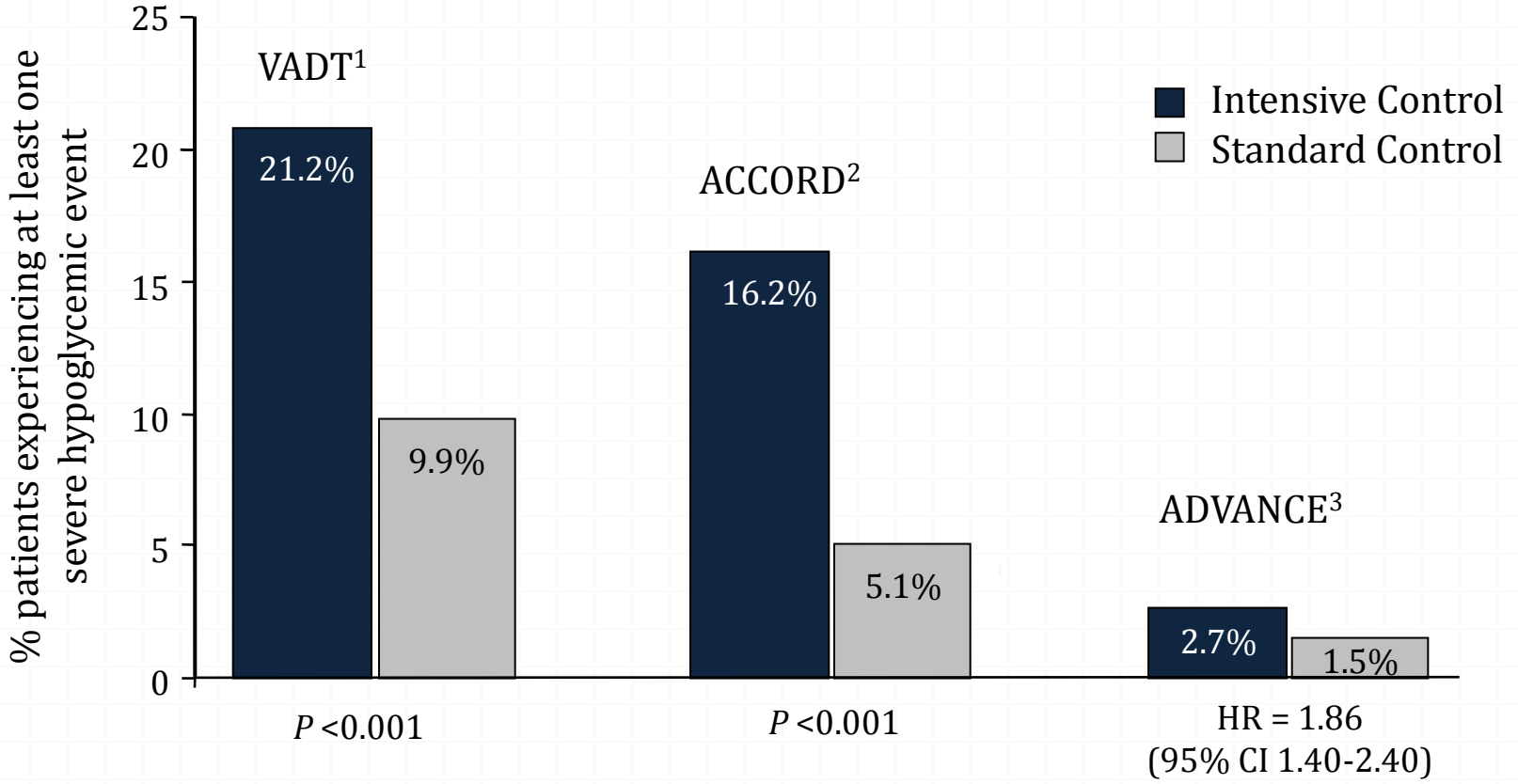
Scirica BM, et al. *N Engl J Med.* 2013; doi: 10.1056/NEJMoa1307684.

Prespecified Safety

	Saxagliptin (n=8,280)	Placebo (n=8,212)	
Thrombocytopenia	0.7%	0.8%	0.36
Lymphocytopenia	0.6%	0.5%	0.40
Severe infection	7.1%	7.0%	0.78
Opportunistic infection	0.3%	0.4%	0.06
Hypersensitivity reactions	1.1%	1.1%	0.82
Bone fracture	2.9%	2.9%	1.00
Skin reaction	2.8%	2.8%	0.81
Renal abnormality*	2.2%	2.0%	0.46
Cancer	3.9%	4.4%	0.15
Any liver abnormality†	0.7%	0.8%	0.28

Adjudicated renal events were similar between saxagliptin and placebo (doubling of creatinine, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL [2.2 vs 2.0%; P=0.46]).

HbA_{1c}: Low but not too low



1. Duckworth W, et al. N Engl J Med.2009;360:129–139; 2. Riddle MC. Circulation. 2010; 122:844-846.
3. ADVANCE Study Group. N Engl J Med. 2008;358(24):2560-72.

We need to have a full review of this accident