From Optimal Glycemic Control to CVD Protection

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Relationship between cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM)

- CVD is a major cause of morbidity and mortality in diabetic patients
  - Patients with diabetes are 2–4 times more likely to develop CVD than those without diabetes[1]
  - The National Cholesterol Education Program (NCEP) identifies diabetes as a coronary heart disease risk equivalent[4]
- The negative CV impact of T2DM may be due to a constellation of pathogenic processes[5-8]
  - Accelerated atherosclerosis[5]
  - Abnormalities in inflammatory pathways[6]
  - Abnormalities in endothelial,[6-8] myocardial,[8] and platelet function[6]

1. American Diabetes Association. Diabetes statistics. Available at: http://www.diabetes.org/diabetes-basics/diabetes-statistics/. Accessed January 4, 2012; 2. Duckworth W et al. *N Engl J Med*. 2009;360:129-139; 3. Morrish NJ et al. *Diabetologia*. 2001;44(suppl 2):S14-S21; 4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497; 5. Wagenknecht LE et al. *Arterioscler Thromb Vasc Biol*. 2003;23:1035-1041; 6. Nathanson D et al. *Mol Cell Endocrinol*. 2009;297:112-12; 7. Avogaro A et al. *Diabetes Care*. 2011;34(suppl 2):S285-S290; 7; 8. Xu J, Zou MH. *Circulation*. 2009;120:1266-1286.

CVD as a major cause of morbidity and mortality in diabetic patients

- CVD accounts for approximately 50% to 60% of deaths in patients with T2DM[1]
- As many as 80% of patients with T2DM will develop and possibly die from macrovascular disease[2]
- Heart disease and stroke are the top causes of death and disability in diabetes[3]
- Myocardial infarction (MI) and stroke cause 75% of all deaths in patients with diabetes[4]

1. Duckworth W et al. *N Engl J Med.* 2009;360:129-139; 2. Buse JB et al. *Circulation*. 2007;115:114-126; 3. American Heart Association. Cardiovascular disease & diabetes. http://www.heart.org/HEARTORG/Conditions/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp. Updated September 8, 2010. Accessed November 18, 2011; 4. Ban K et al. *Am J Hypertens*. 2009;3:245-259; 5. Gregg EW et al. *Ann Intern Med*. 2007;147:149-155.

Diabetes as a CHD risk equivalent

The NCEP identifies diabetes as a CHD risk equivalent based on 3 lines of evidence

- The absolute risk for first major coronary events for T2DM patients approximates that for recurrent events in nondiabetic persons with CHD
- T2DM patients have an increased mortality rate with an MI
- Survival is much worse once T2DM patients develop CHD than it is for CHD patients without diabetes

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106:3143-3421.

Meta-analysis: improved glucose= reduction in macrovascular events

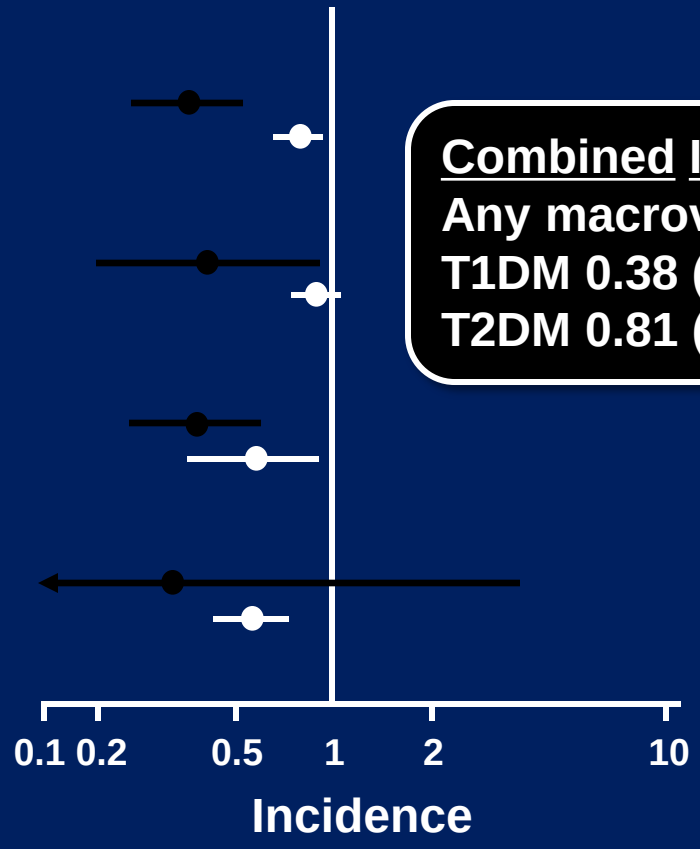
Meta-analysis of randomized clinical trials: conventional vs intensive interventions

Macrovascular
T1DM (8 randomized studies)
T2DM (6 randomized studies)

Cardiovascular
T1DM (8 randomized studies)
T2DM (6 randomized studies)

Peripheral vascular
T1DM (8 randomized studies)
T2DM (6 randomized studies)

Cerebrovascular
T1DM (8 randomized studies)
T2DM (6 randomized studies)



Combined Incidence
Any macrovascular event
T1DM 0.38 (95% CI, 0.26–0.56)
T2DM 0.81 (95% CI, 0.73–0.91)

T1DM N = 1800
T2DM N = 4472

Stettler C et al. *Am Heart J.* 2006;152:27–38.

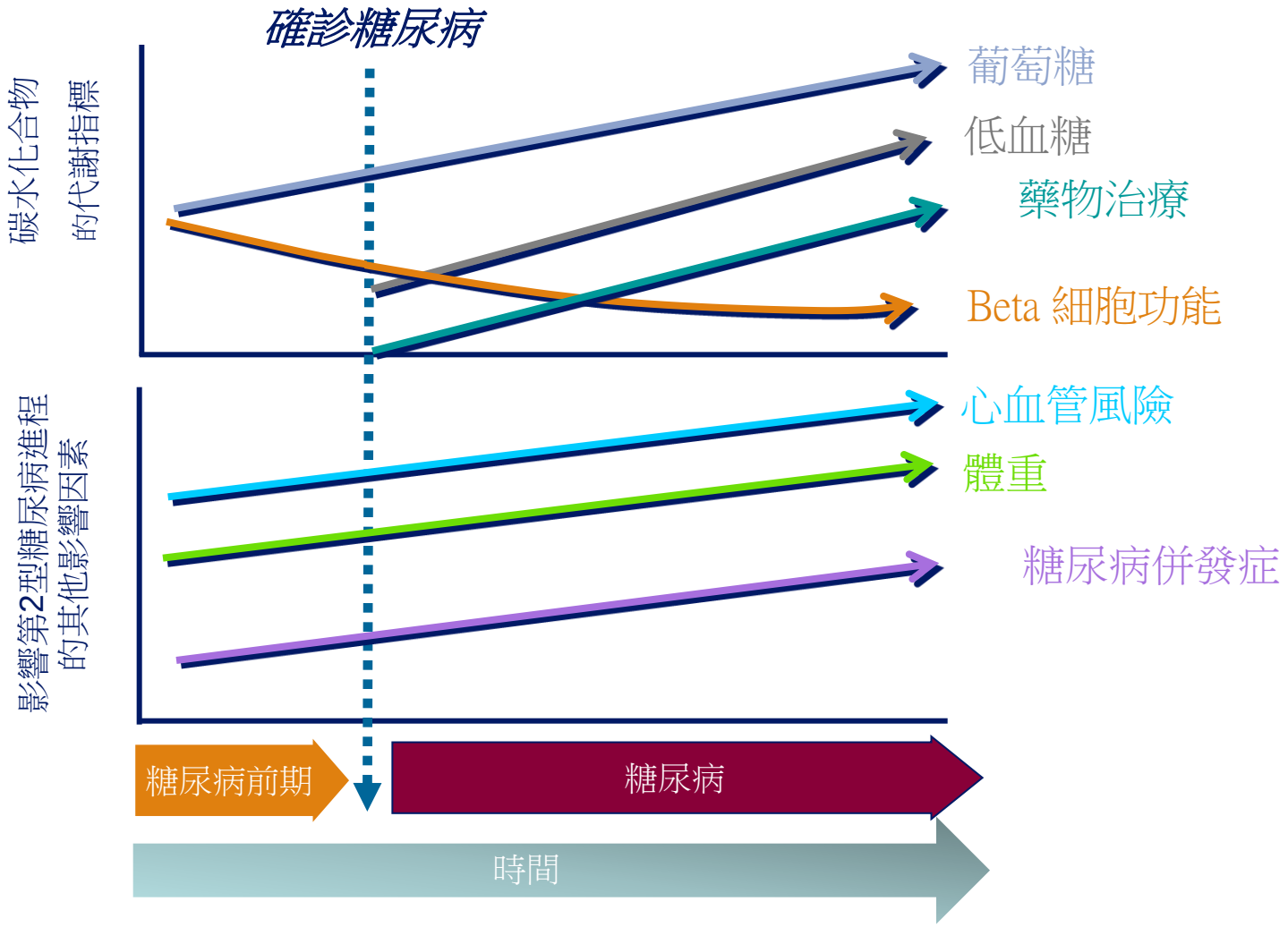
Association of glycemic control and reductions in CV morbidity and mortality: conflicting evidence

- There is conflicting evidence that achievement of glycemic control with antidiabetic therapy is associated with reductions in CV morbidity and mortality[1-7]
- Several randomized long-term studies (UKPDS, ACCORD, ADVANCE, VADT) failed to show a reduction in overall CV events with traditional diabetes therapy aimed at intensively lowering HbA1c[1-4]
- However, long-term follow-up of the UKPDS demonstrated a significant 15% to 33% reduction in MI within the intensive glycemic treatment group[5]
- Recent meta-analyses suggest that intensive glucose lowering does not significantly affect all-cause or CV mortality but may be associated with reductions in the risk of nonfatal MI[6,7]

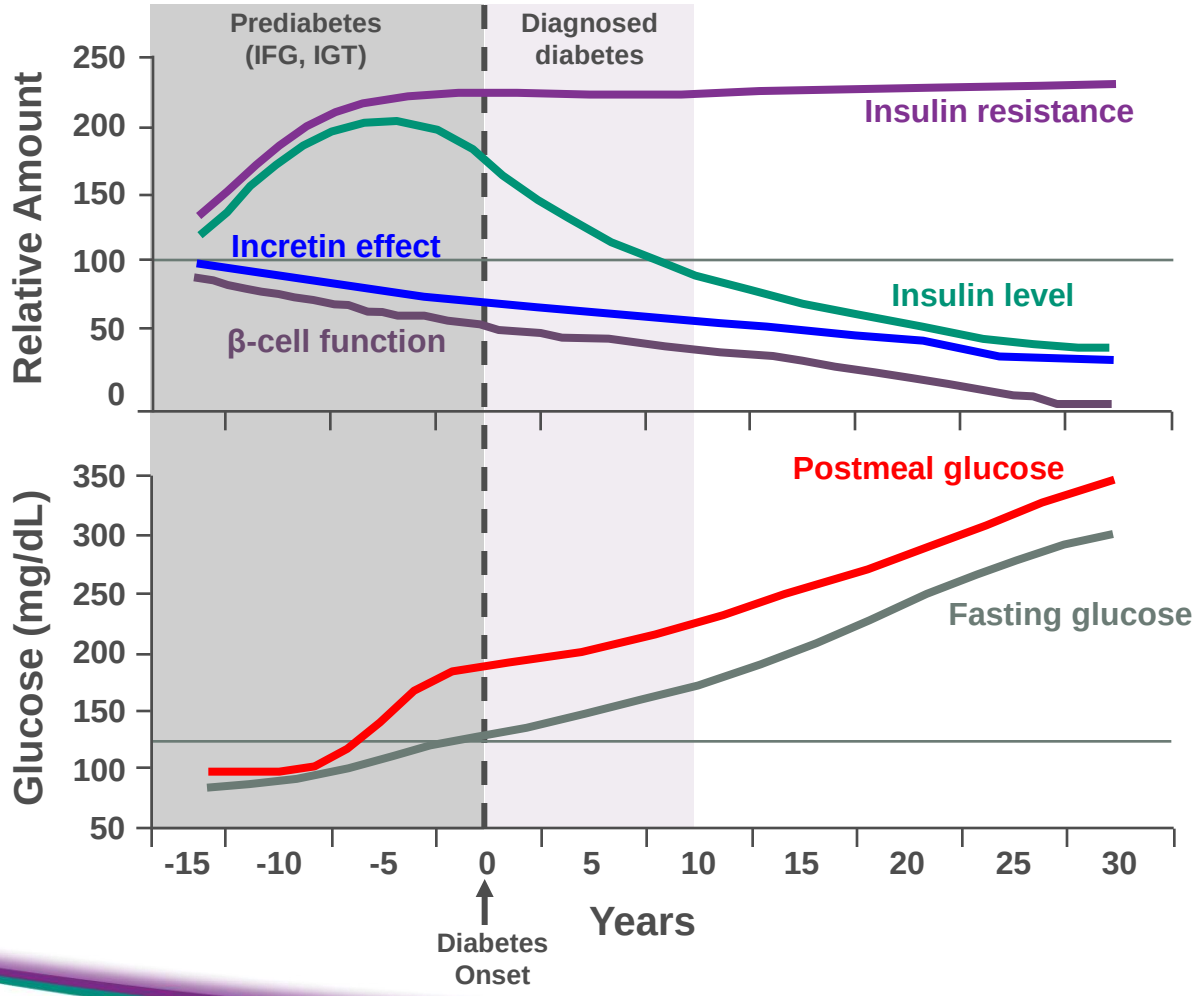
1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853; 2. The ACCORD Study Group. *N Engl J Med*. 2011;364:818-828; 3. The ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572; 4. Duckworth W et al. *N Engl J Med*. 2009;360:129-139; 5. Holman RR et al. *N Engl J Med*. 2008;359:1577-1589; 6. Boussageon R et al. *BMJ*. 2011;343:d4169; 7. Hemmingsen B et al. *BMJ*. 2011;343:d6898.

CVD Protection is result from optimal glycemic control or efficacy of antidiabetic agent?

第2型糖尿病的進程使患者面臨多方面的挑戰



Pathophysiology and Progression of Type 2 Diabetes



- In early stages, as insulin resistance rises, there is a compensatory increase in insulin secretion and glucose levels remain normal
- As β-cell dysfunction worsens, insulin secretion falls, IGT and hyperglycemia become apparent, and overt type 2 diabetes develops
- Glucose levels, both pre- and postprandially, increase steadily as the individual progresses from normoglycemia to IGT and, finally, type 2 diabetes

IFG=impaired fasting glucose;
IGT=impaired glucose tolerance.
Representative depiction of time course and function.

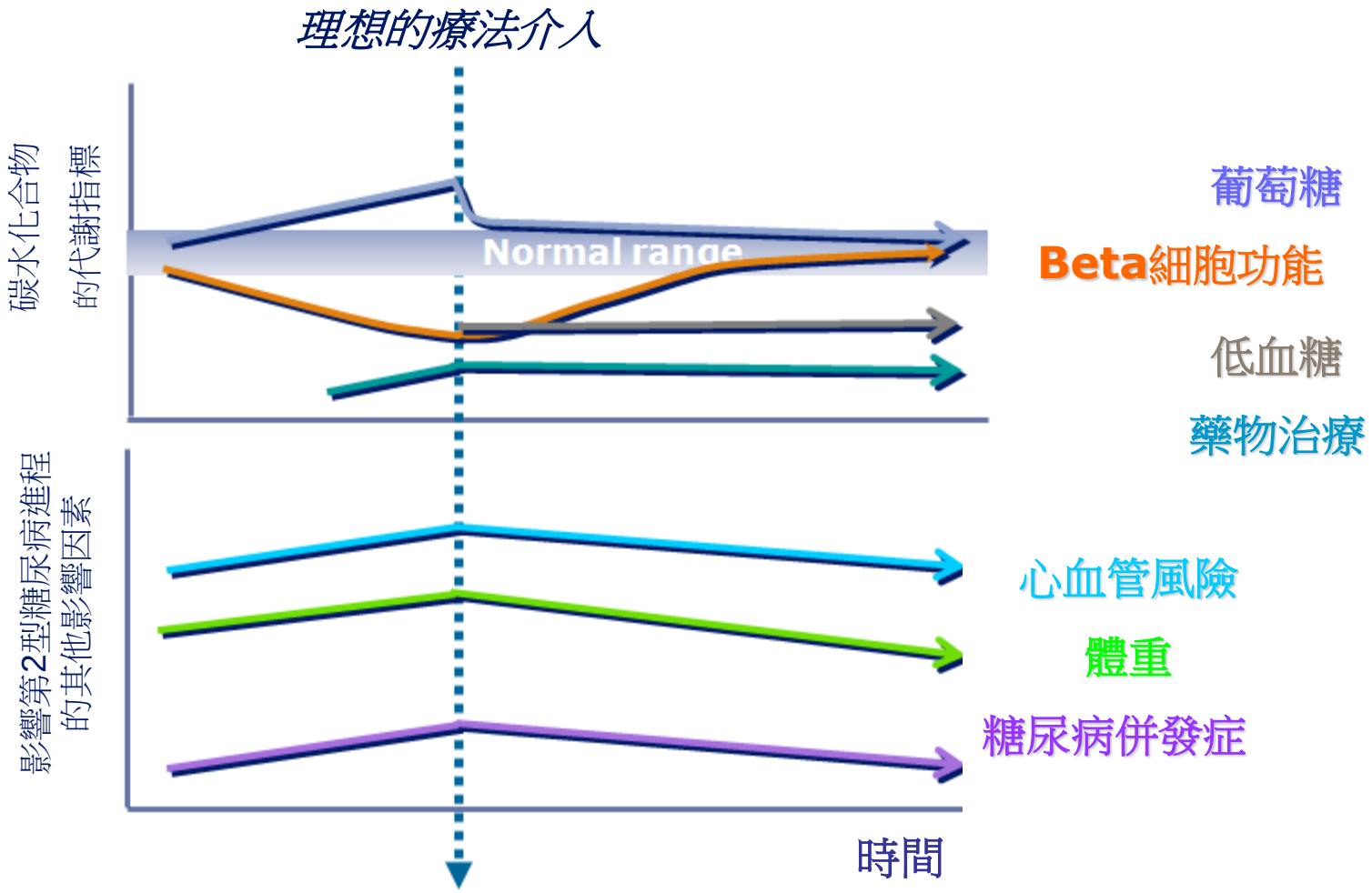
Working Together

Bristol-Myers Squibb AstraZeneca

MAR2015-ONGL-TW-13057 (28/Mar/2013)
KO-SL-TW130407-1304

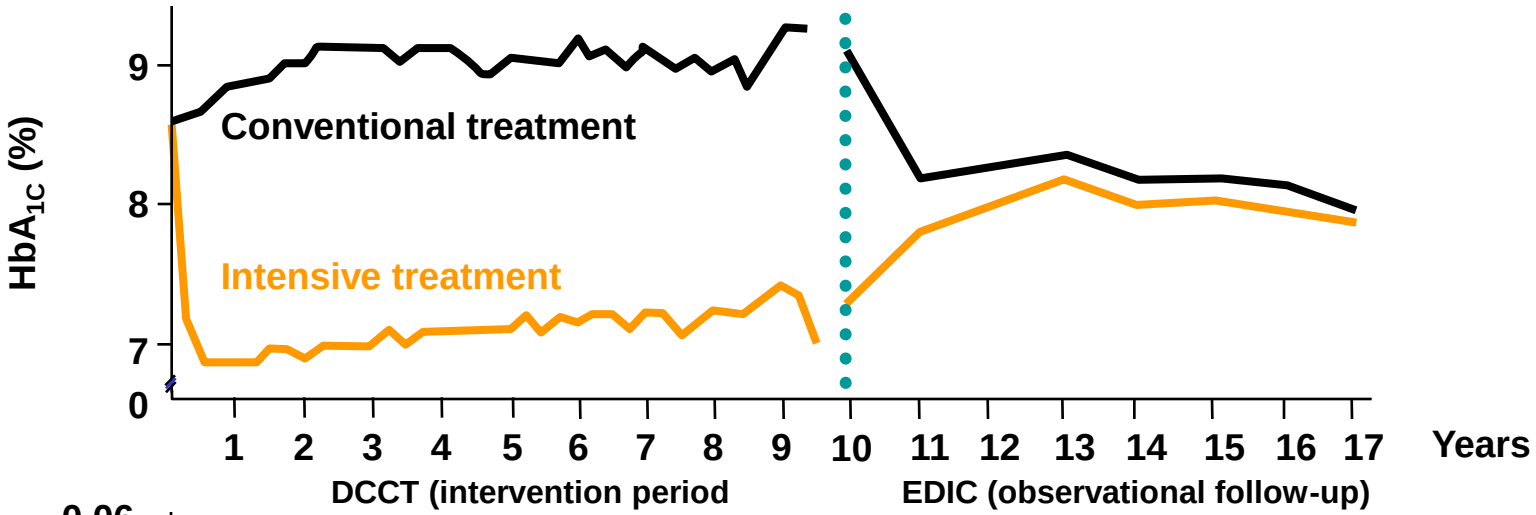
Kendall DM et al. Am J Med. 2009;122(6A):S37-S50.

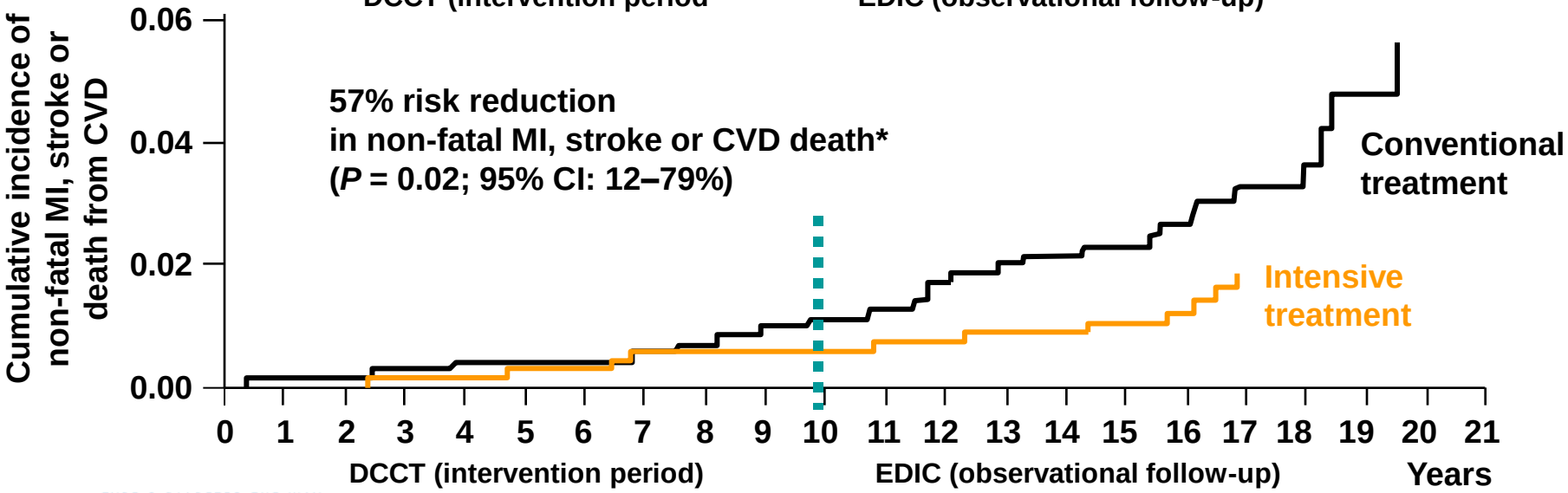
理想的治療需要克服疾病進程的主要問題



Legacy effect

DCCT/EDIC: glycaemic control reduces the risk of non-fatal MI, stroke or death from CVD in type 1 diabetes





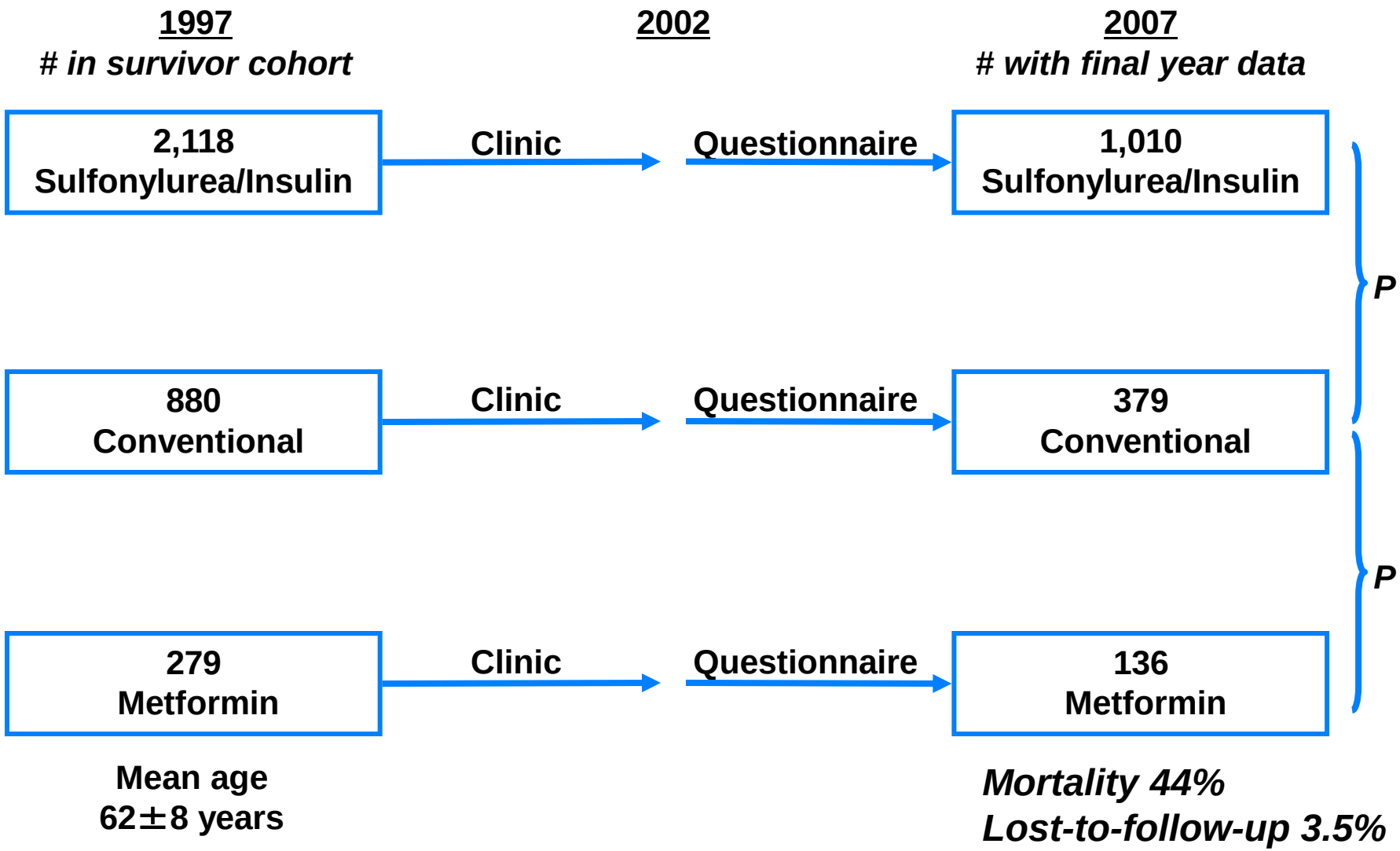
TYPE 2 DIABETES-THE WAY FORWARD

DCCT. *N Engl J Med* 1993; 329:977–986.
DCCT/EDIC. *N Engl J Med* 2005; 353:2643–2653.

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013

UKPDS: 30 year follow-up

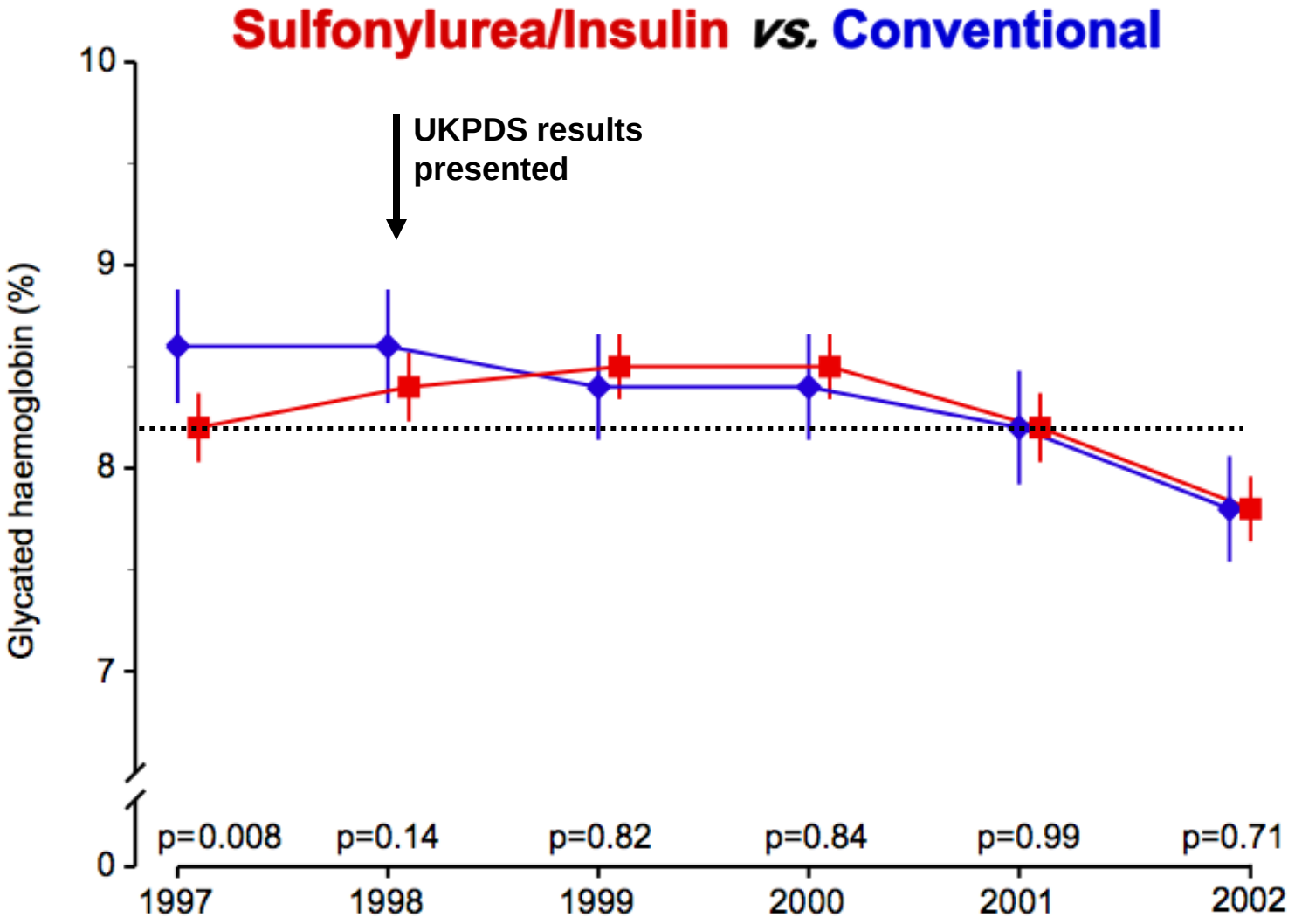
Post-Trial Monitoring: Patients



TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 359:1577-1589, 2008

Post-Trial Changes in HbA_{1c}



TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 359:1577-1589, 2008

Legacy Effect of Earlier Glucose Control-SU/insulin

After median 8.5 years post-trial follow-up

Aggregate Endpoints		1997	2007
Any diabetes related endpoints	RRR: P:	12% 0.029	9% 0.040
Microvascular disease	RRR: P:	25% 0.0099	24% 0.001
Myocardial infarction	RRR: P:	16% 0.052	15% 0.014
Diabetes related death	RRR: P:	10% 0.34	17% 0.01
Death from any cause	RRR: P:	6% 0.44	13% 0.007

RRR = Relative Risk Reduction

TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 359:1577-1589, 2008

Legacy Effect of Earlier Glucose Control-Metformin

After median 8.5 years post-trial follow-up

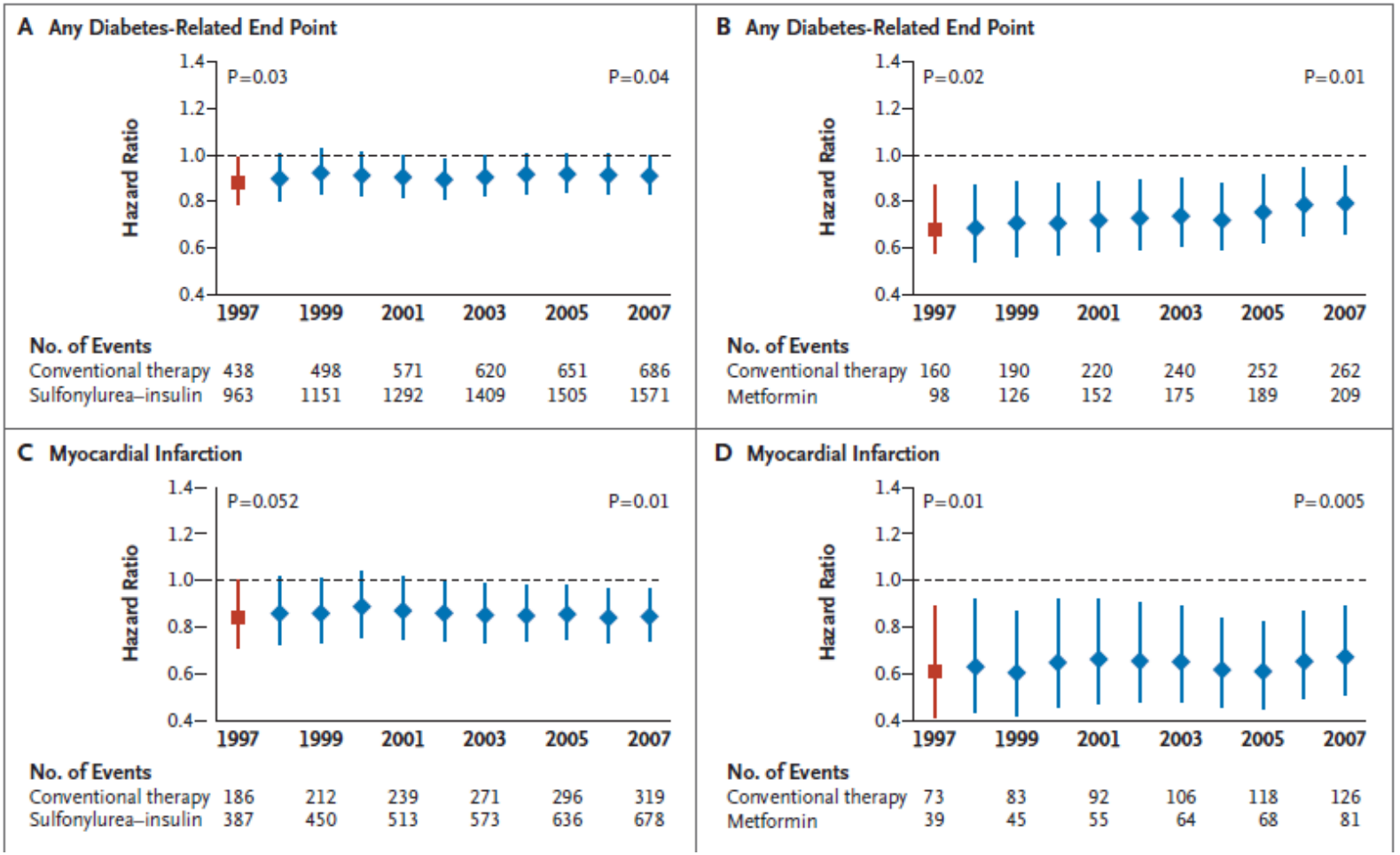
Aggregate Endpoints		1997	2007
Any diabetes related endpoints	RRR: P:	32% 0.002	21% 0.01
Microvascular disease	RRR: P:	29% 0.19	16% 0.31
Myocardial infarction	RRR: P:	39% 0.001	33% 0.005
Diabetes related death	RRR: P:	42% 0.017	30% 0.01
Death from any cause	RRR: P:	36% 0.011	27% 0.002

RRR = Relative Risk Reduction

TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 359:1577-1589, 2008

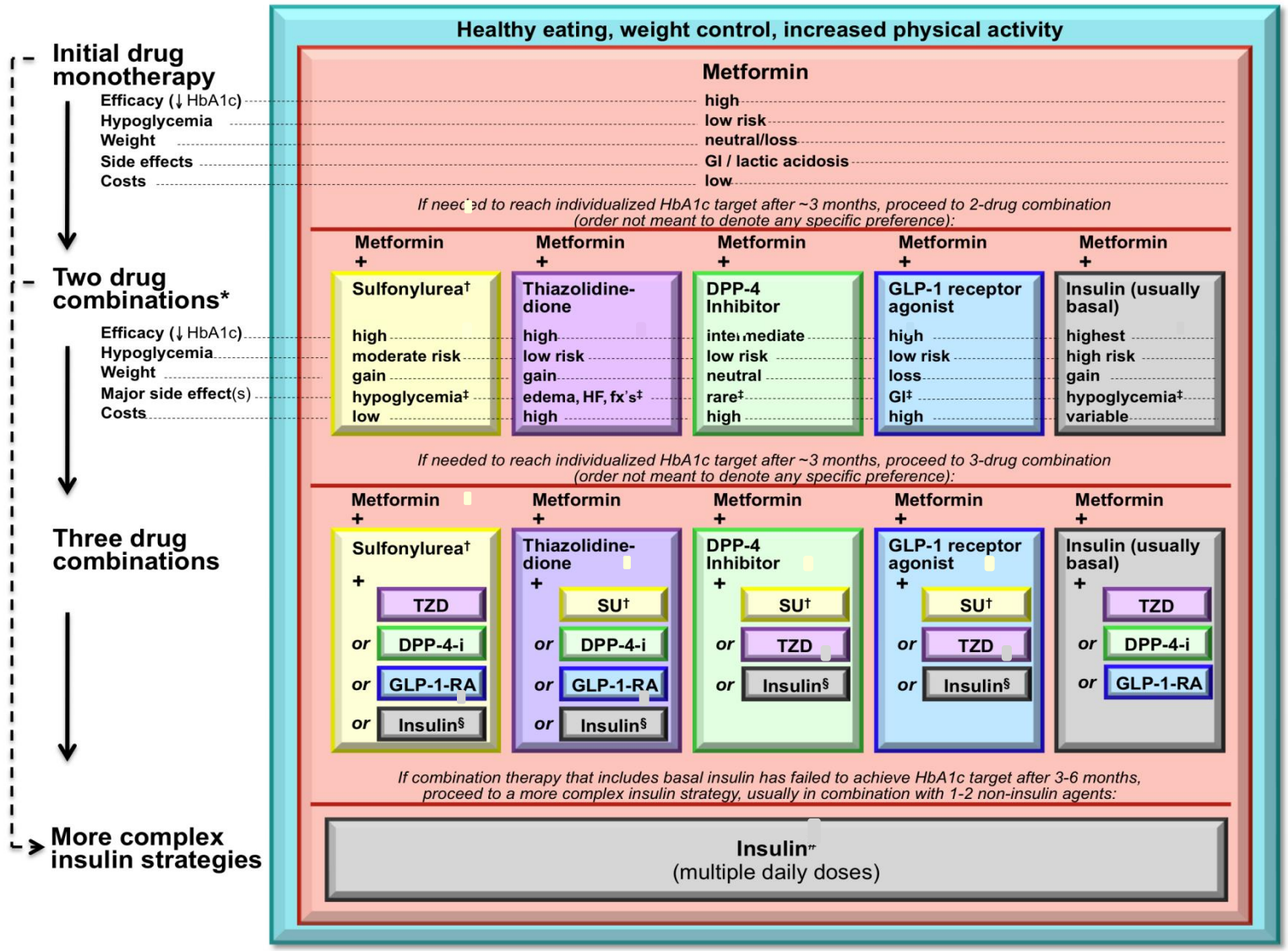
Metformin seems to provide greater benefits vs. SU + insulin



TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 359:1577-1589, 2008

New ADA/EASD position statement



T2DM Anti-hyperglycemic Therapy: General Recommendations
Diabetes Care, Diabetologia. 19 April 2012

Glycaemic control and prevention of CV events: Differences between ACCORD, ADVANCE and VADT

	ACCORD (n=10,251)	ADVANCE (n=11,140)	VADT (n=1,791)
Median baseline HbA_{1c} (%)	8.1	7.2	9.4
HbA_{1C} goals (%) (I vs S)	<6.0 vs 7.0–7.9	≤6.5 vs "based on local guidelines"	<6.0 (action if >6.5) vs planned separation of 1.5
Median duration of follow-up (years)	3.5 (terminated early)	5	5.6
Achieved median HbA_{1C} (%) (I vs S)	6.4 vs 7.5	6.3 vs 7.0	6.9 vs 8.5
Primary outcome	Non-fatal MI, non-fatal stroke, CVD death	Microvascular plus macrovascular (non-fatal MI, non-fatal stroke, CVD death) outcomes	Non-fatal MI, non-fatal stroke, CVD death, hospitalisation for heart failure, revascularisation
HR for primary outcome (95% CI)	0.90 (0.78–1.04)	0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06)	0.88 (0.74–1.05)
HR for mortality findings (95% CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)

I: Intensive glycaemic control
S: Standard glycaemic control

TYPE 2 DIABETES-THE WAY FORWARD

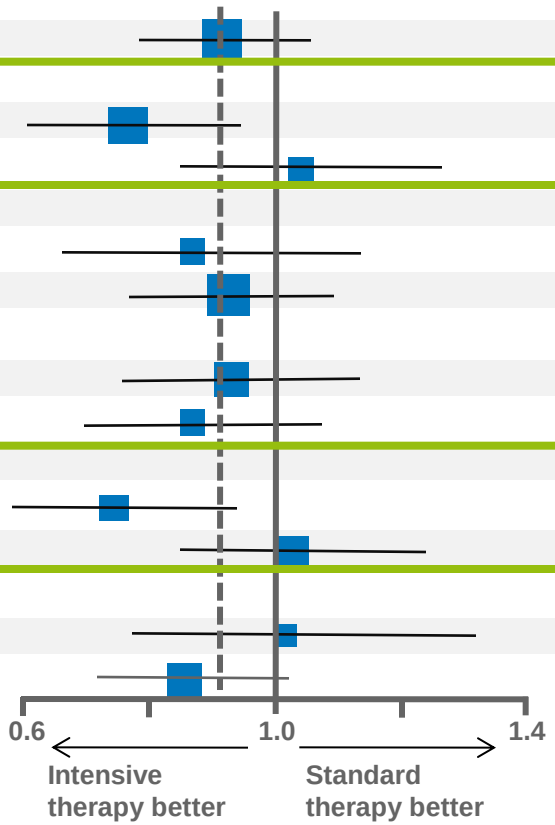
Adapted from: Skyler JS, et al. Diabetes Care. 2009;32:187-92

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013

ACCORD
Subgroup analysis primary endpoints

Primary outcome

Subgroup	No. of subjects	No. of events	*P* value
Total	10,251	723	
Previous cardiovascular event			0.04
No	6,643	330	
Yes	3,608	393	
Sex			0.74
Female	3,952	212	
Male	6,299	511	
Age at baseline			0.65
<65 yr	6,779	383	
>65 yr	3,472	340	
Glycated haemoglobin at baseline			0.03
<8.0%	4,868	284	
>8.0%	5,360	438	
Race			0.29
Non-white	3,647	222	
White	6,604	501	



- **Better outcomes were observed in subjects with no previous history of CV disease receiving intensive therapy**

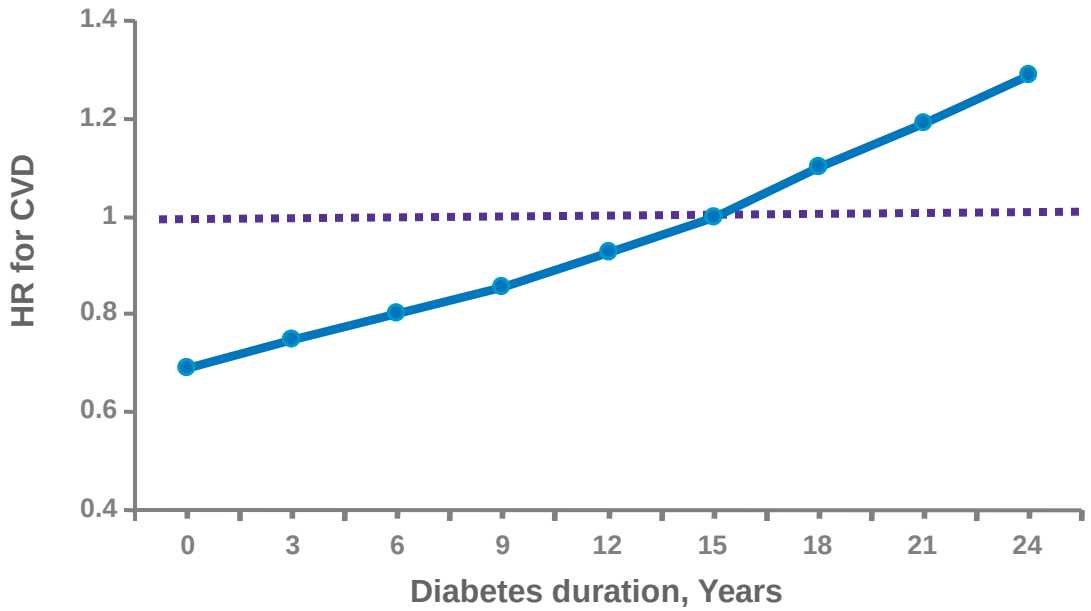
Median diabetes duration at baseline = 10 years

TYPE 2 DIABETES-THE WAY FORWARD

ACCORD Study Group. N Engl. J Med 2008;358:2545-59.

VADT
Subgroup analysis primary endpoints*

Duration of type 2 diabetes and risk of CVD with intensive therapy[1,2]



- **Hazard ratios for CVD owing to IGC was found to vary as a function of disease duration[2,3]**
  - Much reduced in patients with shorter diabetes duration
  - Reduction becomes smaller with longer disease duration, to actually worsen in individuals with long-standing diabetes

CVD: cardiovascular disease; IGC: intensive glucose control

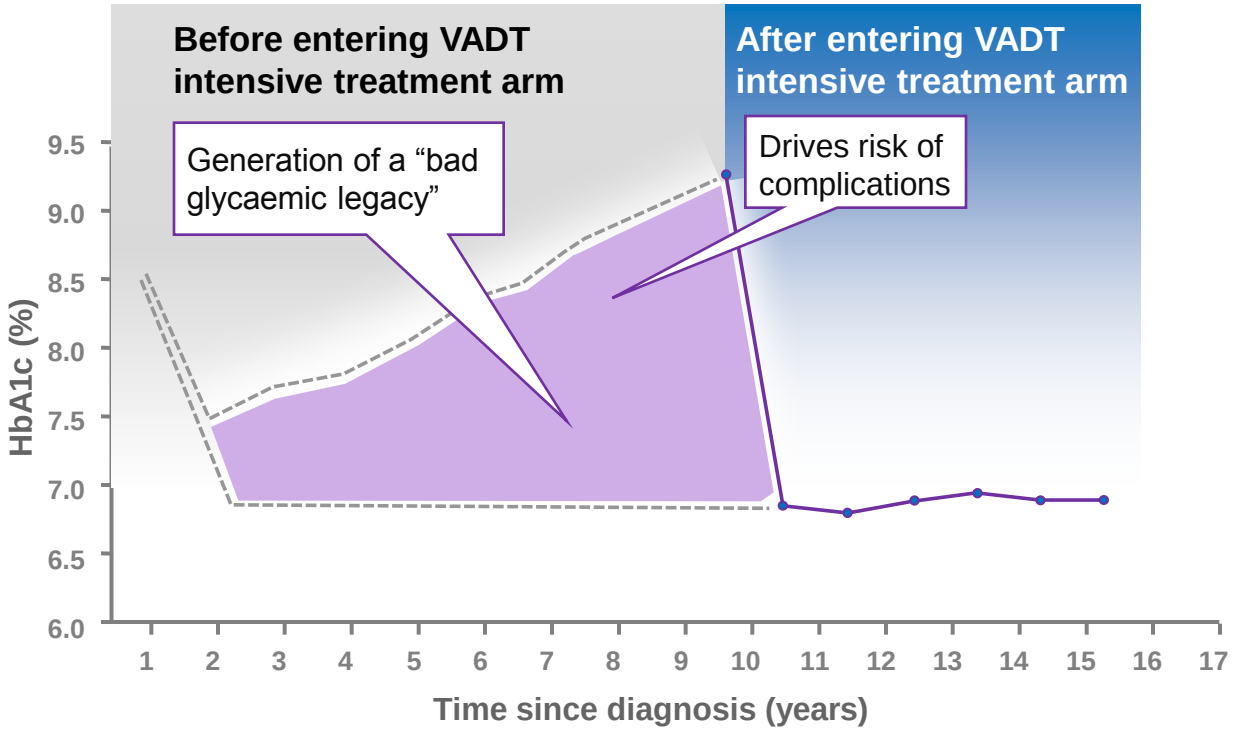
Mean diabetes duration at baseline = 11.5 years

TYPE 2 DIABETES-THE WAY FORWARD

1. Duckworth W, ADA Scientific Sessions, Symposia. Available at: http://webcasts.prous.com/netadmin/webcast_viewer/Preview.aspx?type=0&lid=3853. Accessed: 5 Oct, 2009. 2. Duckworth W, et al. N Engl J Med. 2009;360:129-39. 3. Del Prato S. Diabetologia. 2009;52:1219-26.

VADT
Time course of glycaemic control: “bad glycaemic legacy”

Hypothetical representation of the natural history of diabetes patients recruited in VADT



The upper dotted line represents the time course of HbA_{1c} estimated on the basis of the average glucose profile described by the UKPDS. The lower dotted line represents the ideal time course of glycaemic control. The solid line represents the time course of HbA_{1c} in the VADT.

Mean diabetes duration at baseline = 11.5 years

TYPE 2 DIABETES-THE WAY FORWARD

Del Prato S. Diabetologia. 2009;52:1219-26.

Which HbA_{1c} target?

9–8% → **7%**

Beneficial effect on micro- and macrovascular complications (DCCT-EDIC, UKPDS)[1-3]

→ **6.5%**

CV benefits if:

- Primary prevention (ACCORD)[4]
- HbA_{1c} <8% (ACCORD)[4]
- Diabetes duration <15 yrs (VADT)[5]

Excess mortality if:

- HbA_{1c} ≥8.5% at baseline
- Previous CV history
- Cardiac neuropathy (ACCORD)[4]

An individual tailored strategy: risk-benefit[7,8]
Avoid weight gain and hypoglycaemia
Lifestyle changes

Conclusions – Target HbA_{1c} of 6.5% if:

- Baseline HbA_{1c} <8%
- Diabetes duration <15 years
- Primary prevention
- No cardiac neuropathy
- Long life expectancy, no severe comorbidities, or if this goal may be attained easily

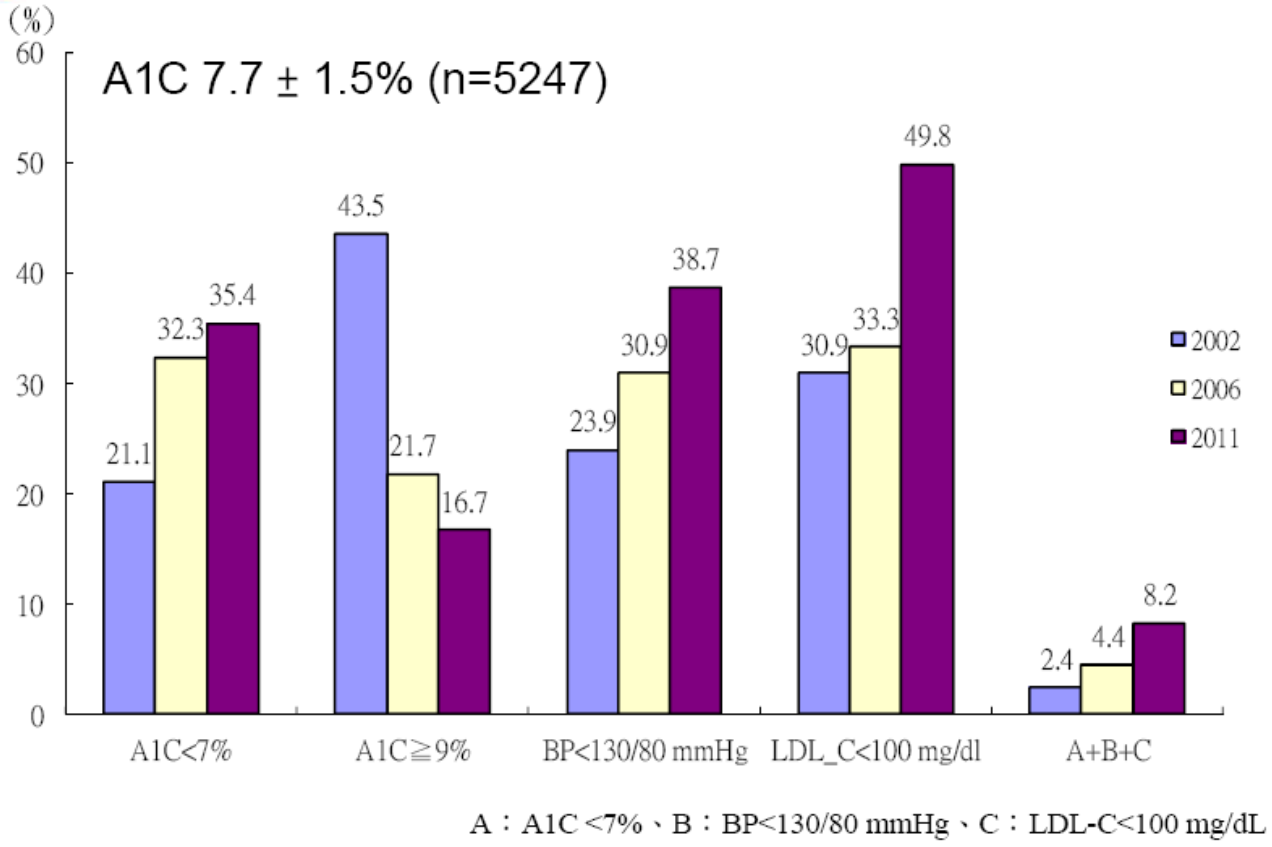
TYPE 2 DIABETES-THE WAY FORWARD

1. White NH, et al. Arch Ophthalmol. 2008;126:1707-15. 2. Nathan DM, et al. N Engl J Med. 2005;353:2643-53. 3. Holman RR. N Engl J Med. 2008;359:1577-89. 4. ACCORD Group. N Engl J Med. 2008;358:2545-59. 5. Duckworth W. ADA 68th Scientific Sessions. Symposia held on 8th June 2008. San Francisco, USA. 6. ADVANCE Group. N Engl J Med. 2008;358:2560-72. 7. Del Prato S. Diabetologia. 2009;52:1219-26. 8. Skyler JS, et al. Diabetes Care. 2009;32:187-92.

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013

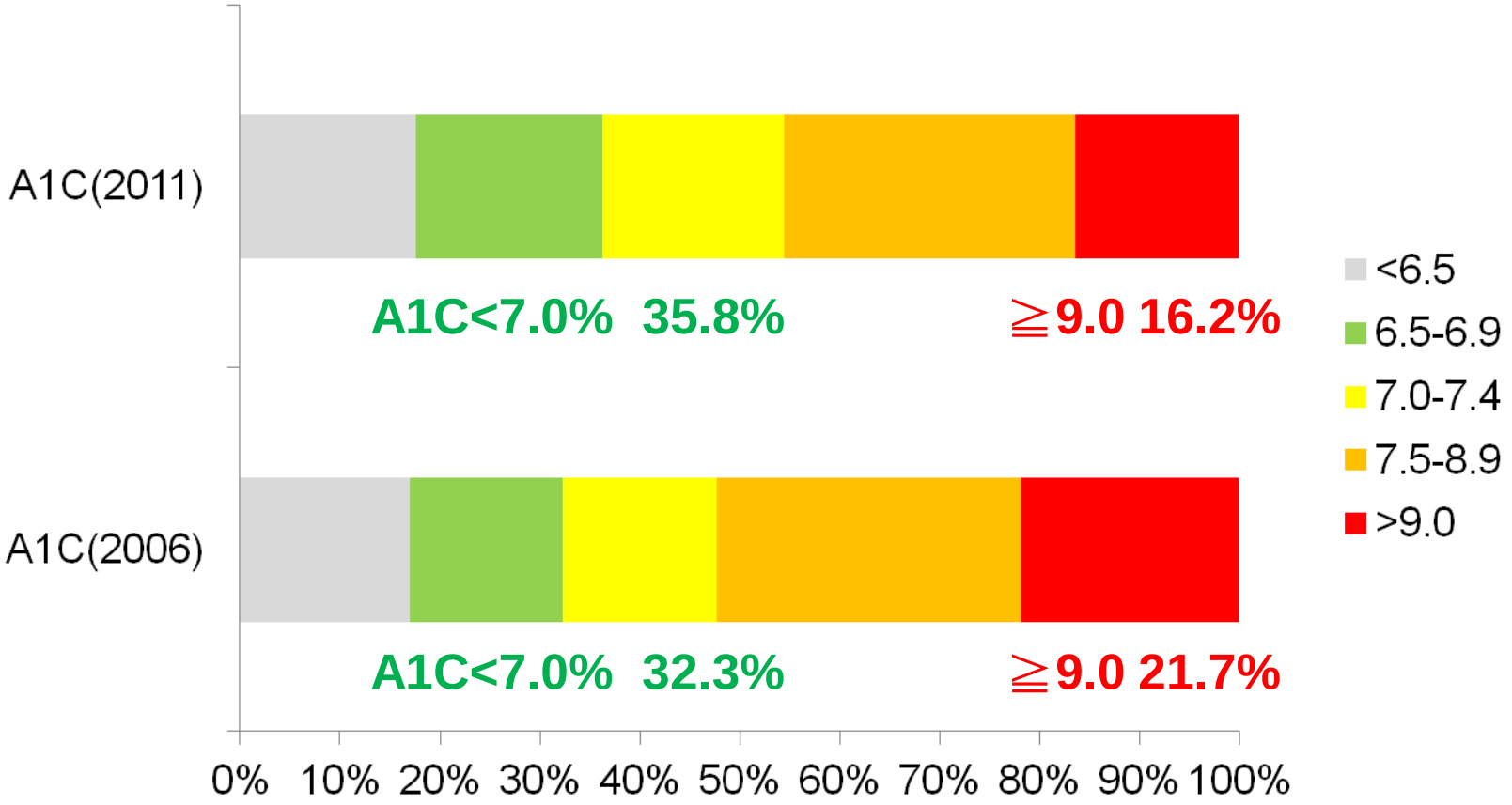
Unmet medical needs

Nearly 2/3 of all T2DM Patients remain uncontrolled on their current therapy



資料來源:健康局委託糖尿病衛教學會針對糖尿病健康促進機構抽樣調查
2006年 114家 7150人　2011年 145家 4296 人

Despite increasing levels of glycaemic control, there is still much room for improvement

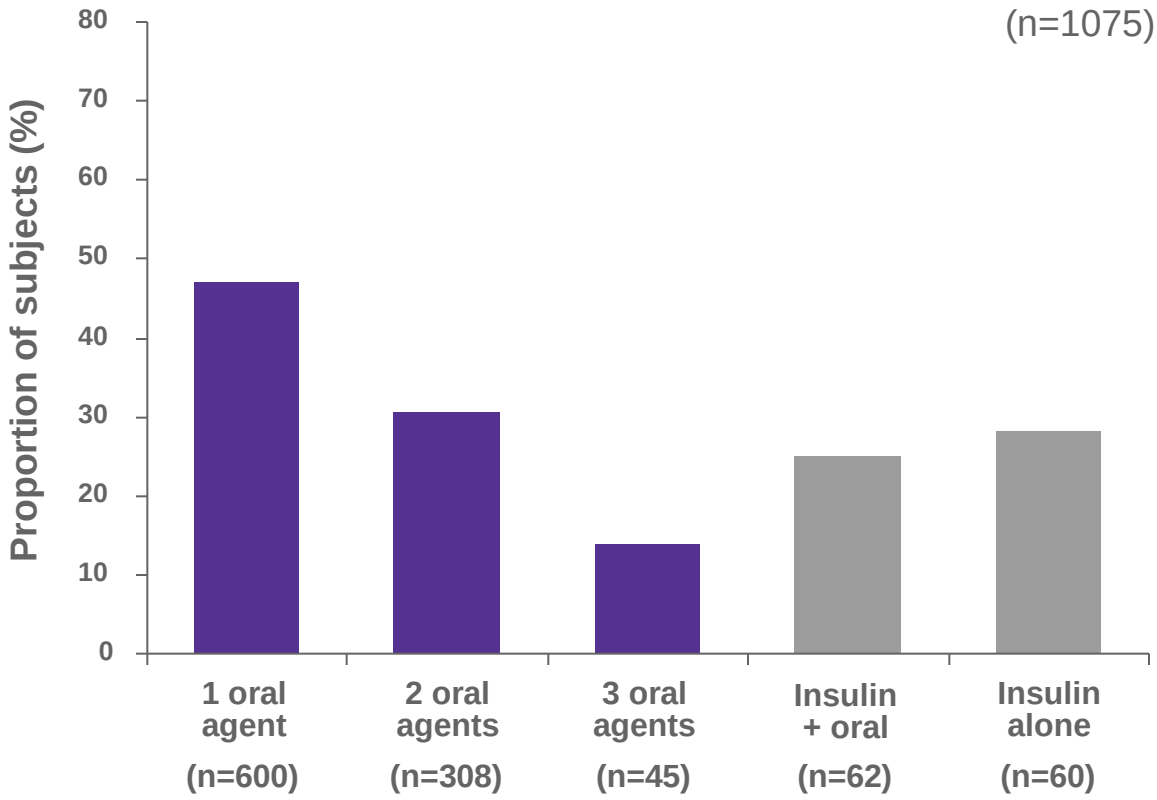


TYPE 2 DIABETES-THE WAY FORWARD

資料來源:健康局委託糖尿病衛教學會針對糖尿病健康促進機構抽樣調查
2006年 114家 7150人　2011年 145家 4296 人

Oral glucose-lowering therapies and achieving glycaemic control

Proportion of subjects with optimal glycaemic control (6 months after diagnosis)*



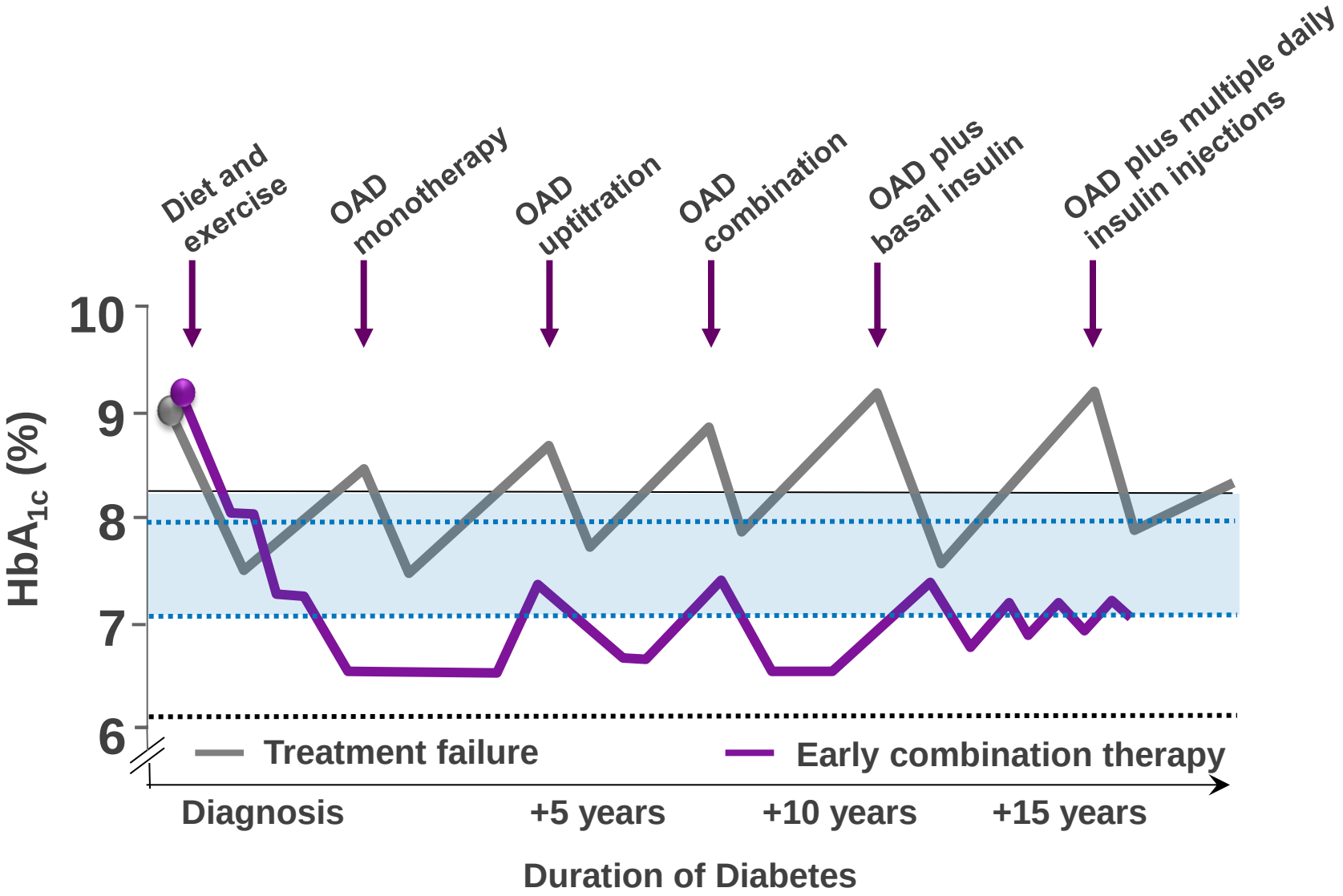
*Defined as the proportion of patients who had glycosylated haemoglobin <7% during the 6 months after the initial documentation of diabetes during the index data. **Adjusted odds ratio (95% CI)

TYPE 2 DIABETES-THE WAY FORWARD

Willey CJ, et al. Am J Manag Care. 2006;12:435-40.

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013

Due to efficacy/side effect tradeoffs, physician tend to delay adding treatment



TYPE 2 DIABETES-THE WAY FORWARD

Del Prato S, et al. Int J Clin Pract. 2005,59:1345-55

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013

FAQ:

積極的血糖控制對於第二型糖尿病患者是如此的重要，為何還有相當多的患者無法達到治療目標？

TYPE 2 DIABETES-THE WAY FORWARD

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013)).

National Estimates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, According to Therapeutic Category, 2007–2009.*

Table 2. National Estimates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, According to Therapeutic Category, 2007–2009.*

Therapeutic Category	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
	no.	*% (95% CI)*	%
Hematologic agents	42,104	42.3 (35.5–49.0)	44.6
Endocrine agents	22,726	22.8 (16.7–28.9)	42.1
Cardiovascular agents	9,800	9.8 (7.1–12.5)	42.3
Central nervous system agents	9,621	9.7 (7.6–11.8)	32.2
Antiinfective agents	3,759	3.8 (2.6–4.9)	17.4
Antineoplastic agents	2,882†	2.9 (0.9–4.9)†	51.0
Other agents	3,211	3.2 (2.6–3.8)	15.0
Medications not stated or not known	957	1.0 (0.5–1.5)	20.6
Medications in more than one therapeutic category	4,568†	4.6 (2.7–6.5)	41.2

* Estimates were based on data from the NEISS–CADES project. The proportion of emergency department visits resulting in hospitalization is the ratio of hospitalizations to total emergency department visits for adverse drug events involving the specified therapeutic category.

† The coefficient of variation was greater than 30%.

TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 2011; 365: 2002-12

National Estimates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, According to Therapeutic Category, 2007–2009.

	Annual National Estimate of Hospitalizations	Proportion of Emergency Department Visits Resulting in Hospitalization
	% (95% CI)	*%*
Endocrine agents		
Hypoglycemia with loss of consciousness or seizure	26.0 (13.5–38.4)	57.5
Hypoglycemia with altered mental status or other neurologic sequelae	40.7 (31.8–49.5)	42.4
Hypoglycemia with cardiovascular sequelae	8.3 (6.1–10.4)	49.6
Hypoglycemia with weakness, dyspnea, or respiratory distress	5.7 (3.0–8.5)	47.5
Hypoglycemia with other or unspecified sequelae	14.0 (6.2–21.8)	37.3

TYPE 2 DIABETES-THE WAY FORWARD

N Engl J Med 2011; 365: 2002-12

Hypoglycemia will affect patients' quality of life and is under detection

- Few patients report hypoglycaemia to their doctor[1]

A Diabetes UK survey of 1,954 type 2 diabetes patients and their experiences of hypoglycaemia[2]

Frequency

Half had experienced at least one hypo during a 2-week period

Quality of life

Over half thought mild-to-moderate hypos affect their quality of life

Time off work

1 in 10 reported having to take at least one day off work during the last year as a result of a mild or moderate hypo

Daily activities

Approximately a third said that mild-to-moderate hypos affect their ability to carry out day-to-day tasks, **including:** housework, social activities, sports activities, sleep

Anxiety

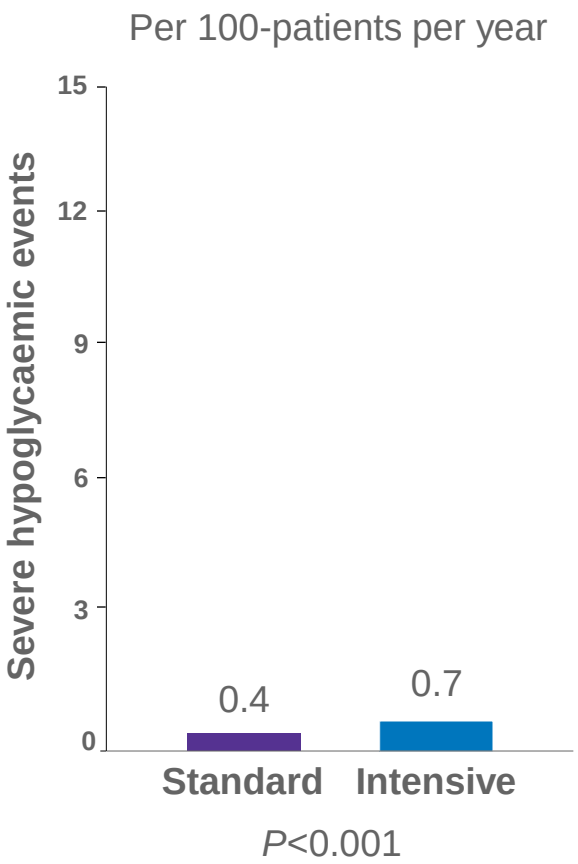
Nearly half said they worry about having a mild-to-moderate hypo and that their emotional wellbeing is affected

TYPE 2 DIABETES-THE WAY FORWARD

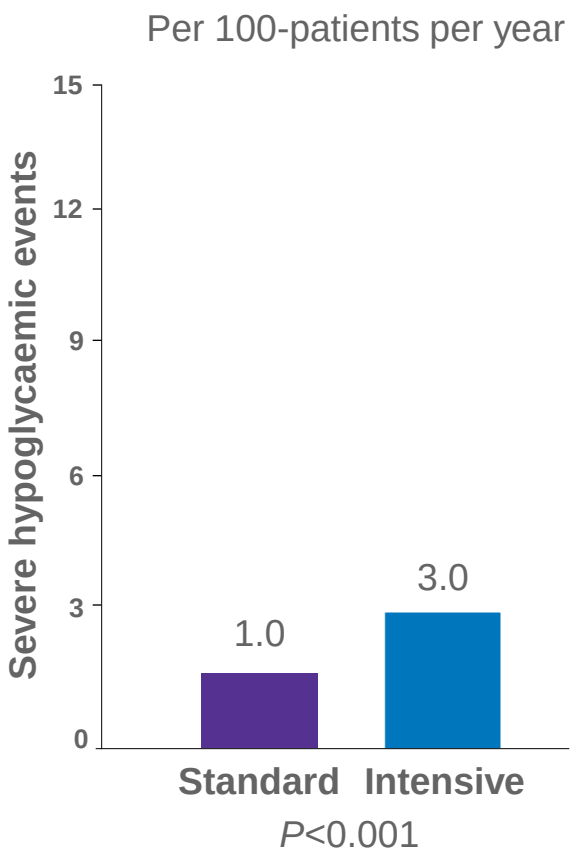
1. Amiel SA et al. Diabet Med. 2008;25:245–254.
2. Diabetes UK. Survey reveals hidden incidence of 'hypos' among people with type 2 diabetes. October 2009.

Increased incidence of severe hypoglycaemic events with intensive therapy in ADVANCE, ACCORD and VADT

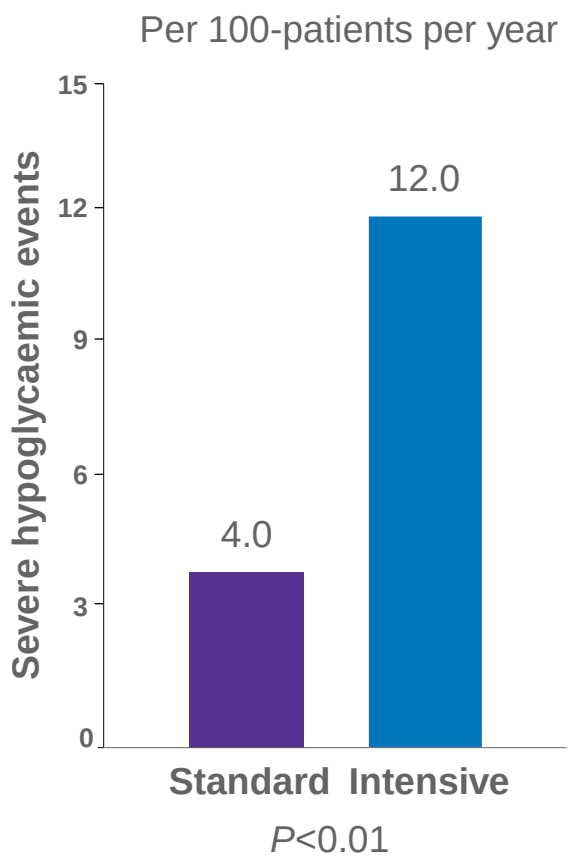
ADVANCE[1]



ACCORD[2]



VADT[3]



- **Intensive glucose lowering contributes to an increased risk of hypoglycaemia by 2- to 3-fold, particularly at later stages of type 2 diabetes**

TYPE 2 DIABETES-THE WAY FORWARD

1. ADVANCE Collaborative Group. N Engl J Med. 2008;358:2545-59. 2. ACCORD Study Group. N Engl J Med. 2008;358:2545-59. 3. Duckworth W (VADT). N Engl J Med. 2009;360:129-39.

ON-SL-TW130406-1304
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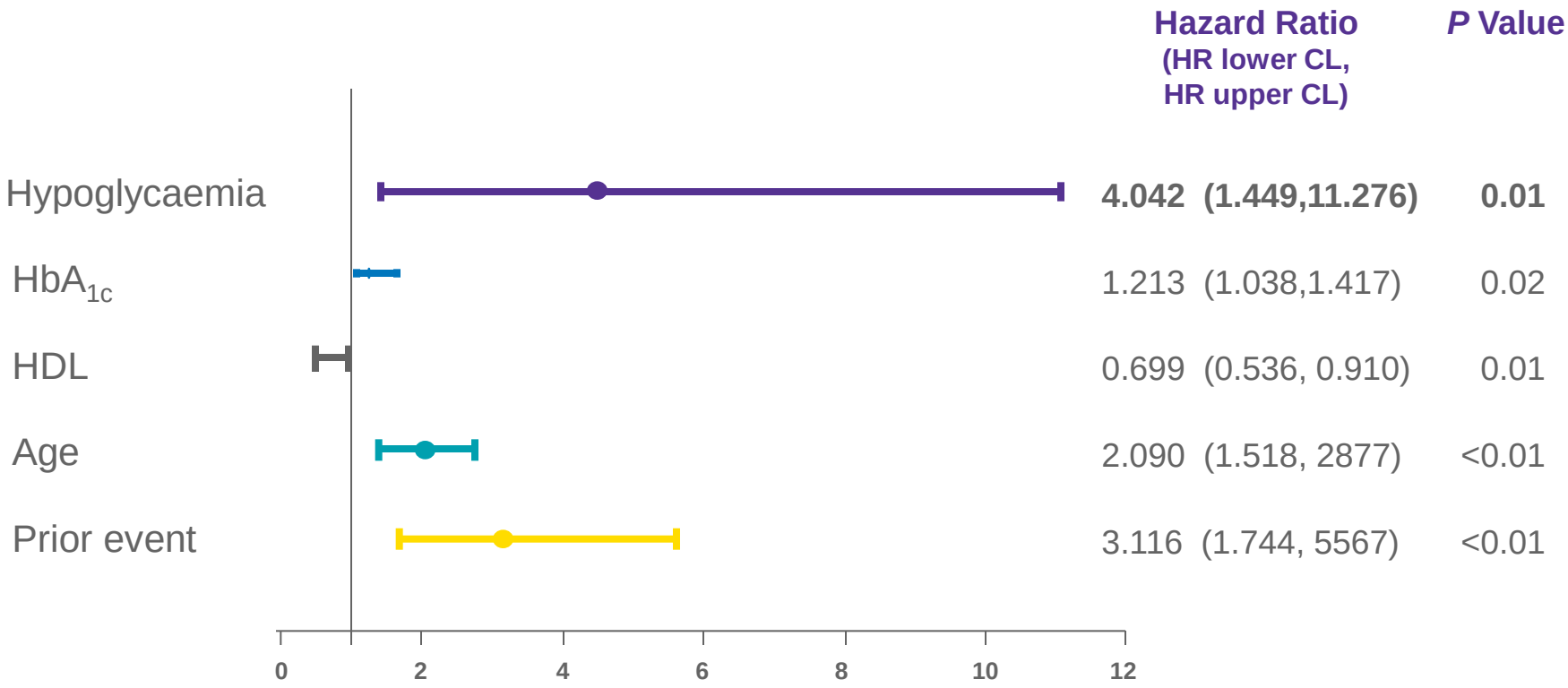
Hypoglycaemia – a major predictor of cardiovascular death in the VADT study



TYPE 2 DIABETES-THE WAY FORWARD

Duckworth W.(VADT): results. 2008. Available from http://webcasts.prous.com/netadmin/webcast_viewer/Preview.aspx?type=0&lid=3853, Accessed: 20 Oct 2009.

Hypoglycemia may increase the risk of morbidity and mortality in T2DM patients

Adjusted hazard ratio for primary and secondary clinical outcomes, ADVANCE patients who developed severe hypoglycemia vs those who didn't

End point	Severe hypoglycemia, n=231 (%)	No severe hypoglycemia, n=10 909 (%)	HR (95% CI)
Major macrovascular event*	15.9	10.2	3.53 (2.41–5.17)
Major microvascular event*	11.5	10.1	2.19 (1.40–3.45)
All-cause mortality	19.5	9.0	3.27 (2.29–4.65)
Cardiovascular mortality	9.5	4.8	3.79 (2.36–6.08)
Noncardiovascular mortality	10	4.3	2.80 (1.64–4.79)

TYPE 2 DIABETES-THE WAY FORWARD

Zoungas S. et al. N Engl J Med 2010; 363(15): 1410-8

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with SUs and metformin

Diabetologia (2006) 49: 930–936
DOI 10.1007/s00125-006-0176-9

ARTICLE

J. M. M. Evans · S. A. Ogston ·
A. Emslie-Smith · A. D. Morris

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin

Received: 27 September 2005 / Accepted: 25 November 2005 / Published online: 9 March 2006

Abstract *Aims/hypothesis:* The aim of this study was to evaluate the risk of adverse cardiovascular outcomes in patients with type 2 diabetes newly treated with sulfonylureas and metformin. *Subjects and methods:* The Diabetes Audit and Research in Tayside Scotland (DARTS) diabetes information system and the Medicines Monitoring Unit (MEMO) dispensed prescribing database for the population of Tayside, Scotland (400,000 people) were employed. Patients newly prescribed with oral hypoglycaemic agents between 1994 and 2001 were classified into five study cohorts according to the treatment received: metformin only, sulfonylureas only, sulfonylureas added to metformin, metformin added to sulfonylureas, and both drugs simultaneously. In Cox regression analyses, we estimated relative risks for all-cause mortality, cardiovascular mortality and cardiovascular hospital admission for patients in the five study cohorts, with metformin monotherapy as the reference group. *Results:* Of the 5,730 study patients, 1,000 died during a maximum of 8 years follow-up. Patients in the sulfonylureas only cohort had increased risks of mortality and cardiovascular mortality, with unadjusted relative risks of 3.12 (95% CI 2.54–3.84) and 3.71 (95% CI 2.64–5.22), respectively. After adjusting for differences between groups (age, sex, duration of diabetes, blood pressure, cholesterol, HbA_{1c}, smoking, previous hospital admission, treatment with cardiovascular medication), these relative risks were 1.43 (95% CI 1.15–1.77) and 1.70 (95% CI 1.18–2.45), respectively. Patients in the combination cohorts had significantly increased risks of cardiovascular hospital admission, as well as increased risks of mortality and cardiovascular mortality. *Conclusions/interpretation:* In this cohort study of patients newly treated with oral hypoglycaemic agents, those treated with sulfonylureas only, or combinations of sulfonylureas and metformin, were at higher risk of adverse cardiovascular outcomes than those treated with metformin alone.

Keywords Cardiovascular risk · Metformin · Sulfonylureas

Abbreviations DARTS: Diabetes Audit and Research in Tayside Scotland · MEMO: Medicines Monitoring Unit · UGDP: University Group Diabetes Program · UKPDS: United Kingdom Prospective Diabetes Study · NHS: National Health Service · OHA: oral hypoglycaemic agent · ICD-9/10: International Classification of Diseases, 9th and 10th revisions · AIIRA: angiotensin II receptor antagonist

Introduction

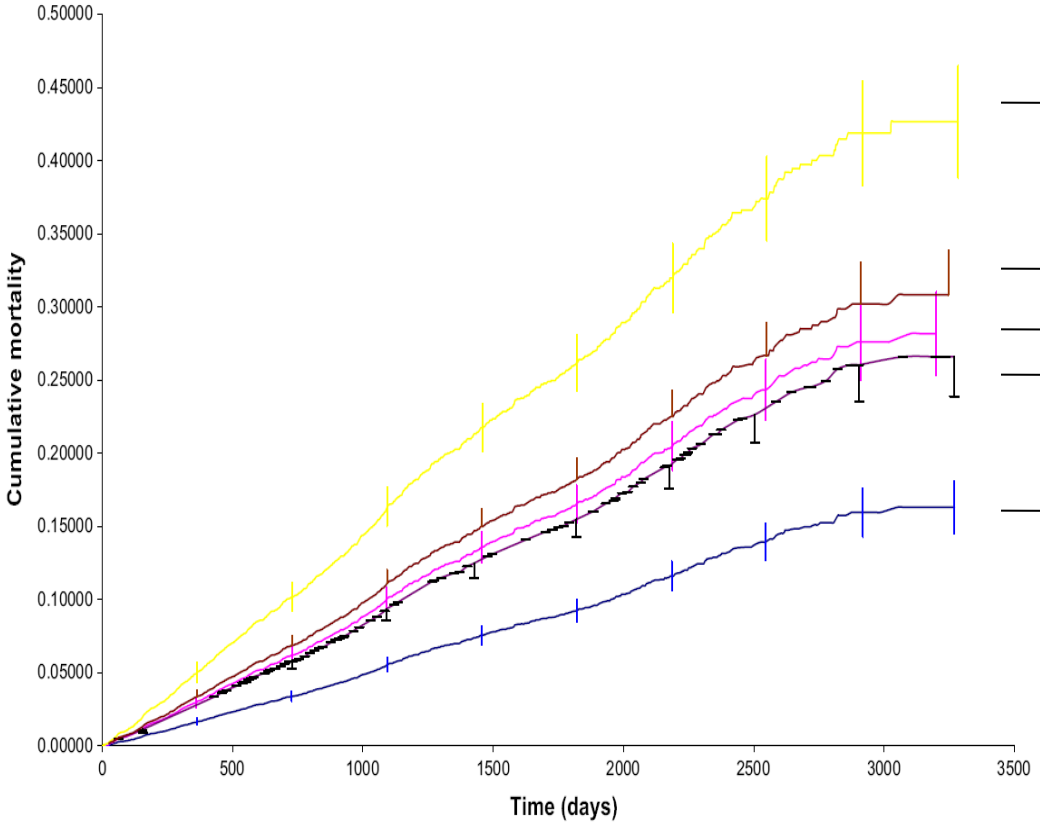
TYPE 2 DIABETES-THE WAY FORWARD

J.M.M. Evan. et al. Diabetologia 2006; 49: 930-936

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with SUs and metformin

DARTS: Cumulative Mortality Rates in 5 Study Cohorts

Fig. 1 Cumulative mortality rates (with standard errors at yearly intervals) in five study cohorts: 1. Metformin monotherapy: patients treated with metformin only (*blue line*). 2. Sulfonylureas monotherapy: patients treated with sulfonylureas only (*yellow line*). 3. Combination 1: patients treated with metformin with sulfonylureas added later (*pink line*). 4. Combination 2: patients treated with sulfonylureas with metformin added later (*brown line*). 5. Both: treatment with both sulfonylureas and metformin on the same day (*purple line*)



→ SU only

→ 先SU後Metformin

→ 先metformin後SU

→ SU & Metformin一起

→ Metformin only

TYPE 2 DIABETES-THE WAY FORWARD

J.M.M. Evan. et al. Diabetologia 2006; 49: 930-936

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with SUs and metformin

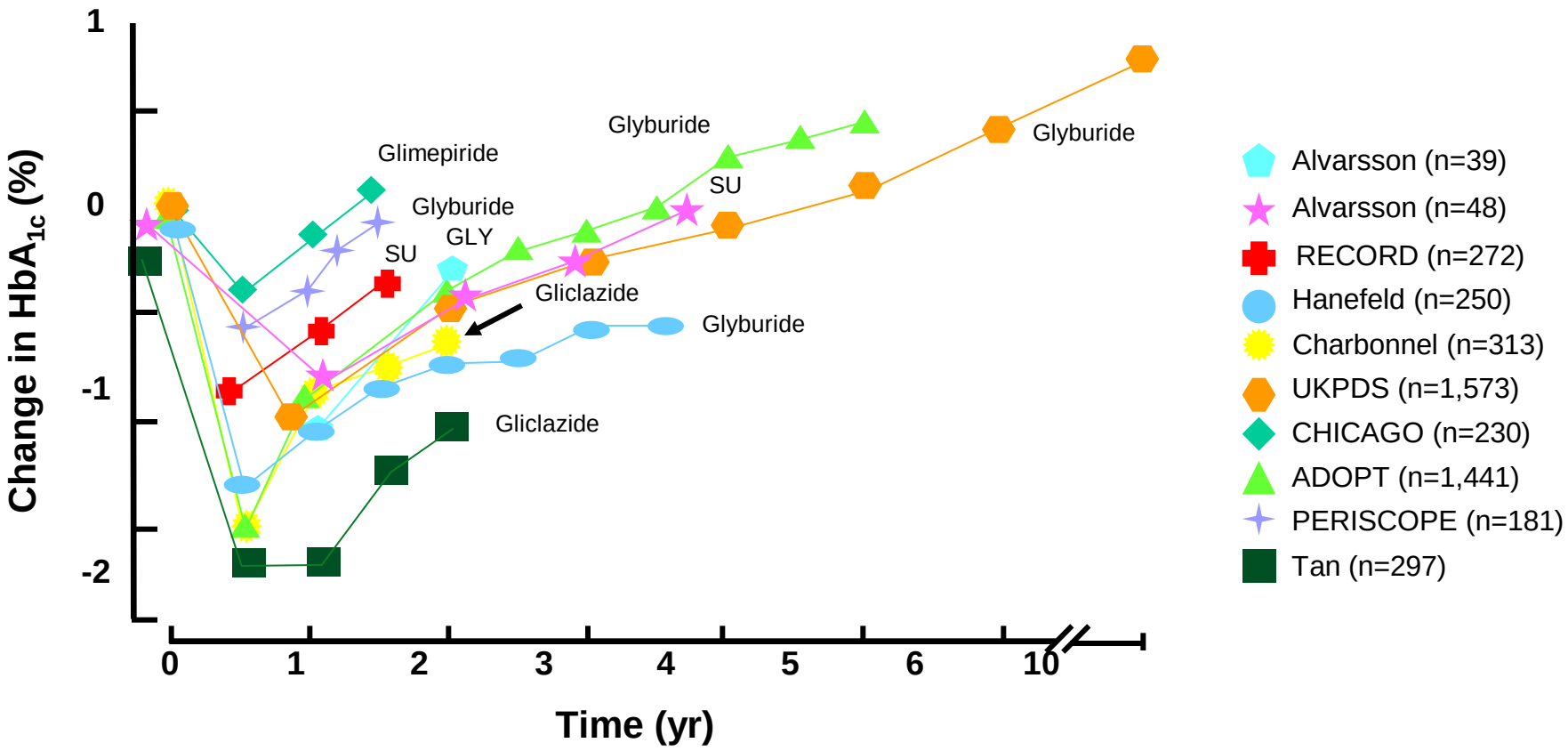
Conclusion

- **In this cohort study of patients newly treated with oral hypoglycaemic agents, those treated with sulfonylureas only, or combinations of sulfonylureas and metformin, were at higher risk of adverse cardiovascular outcomes than those treated with metformin alone.**

TYPE 2 DIABETES-THE WAY FORWARD

J.M.M. Evan. et al. Diabetologia 2006; 49: 930-936

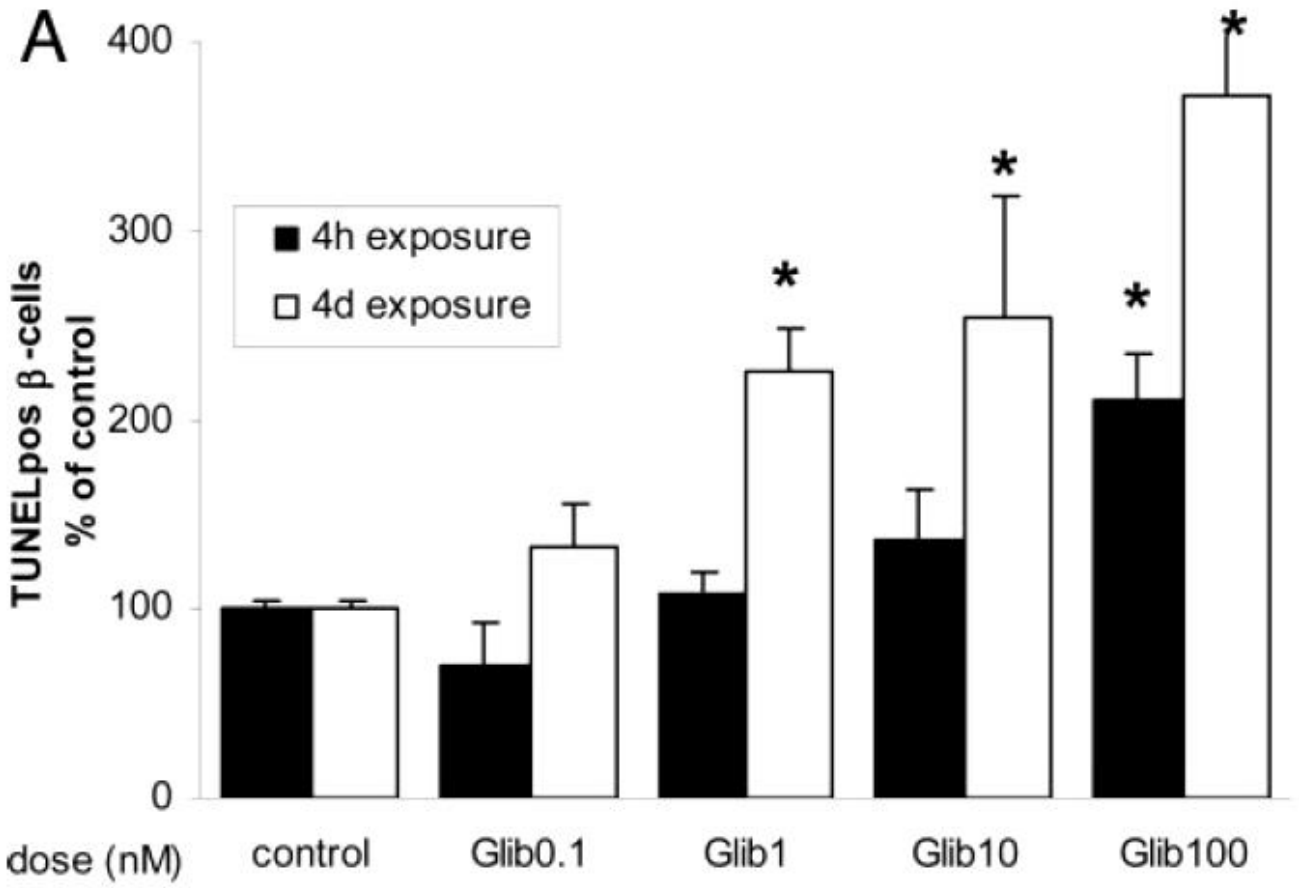
Sulfonylureas - Long-Term Efficacy



TYPE 2 DIABETES-THE WAY FORWARD

The American Journal of Medicine (2010) 123; S38-S48

SU induced β-cell Apoptosis in Human Pancreatic Islets



Maedler et al.J Clin Endocrinol Metab 2005;90;501-6

Check list for choosing medication

Checklist for chosing Medications

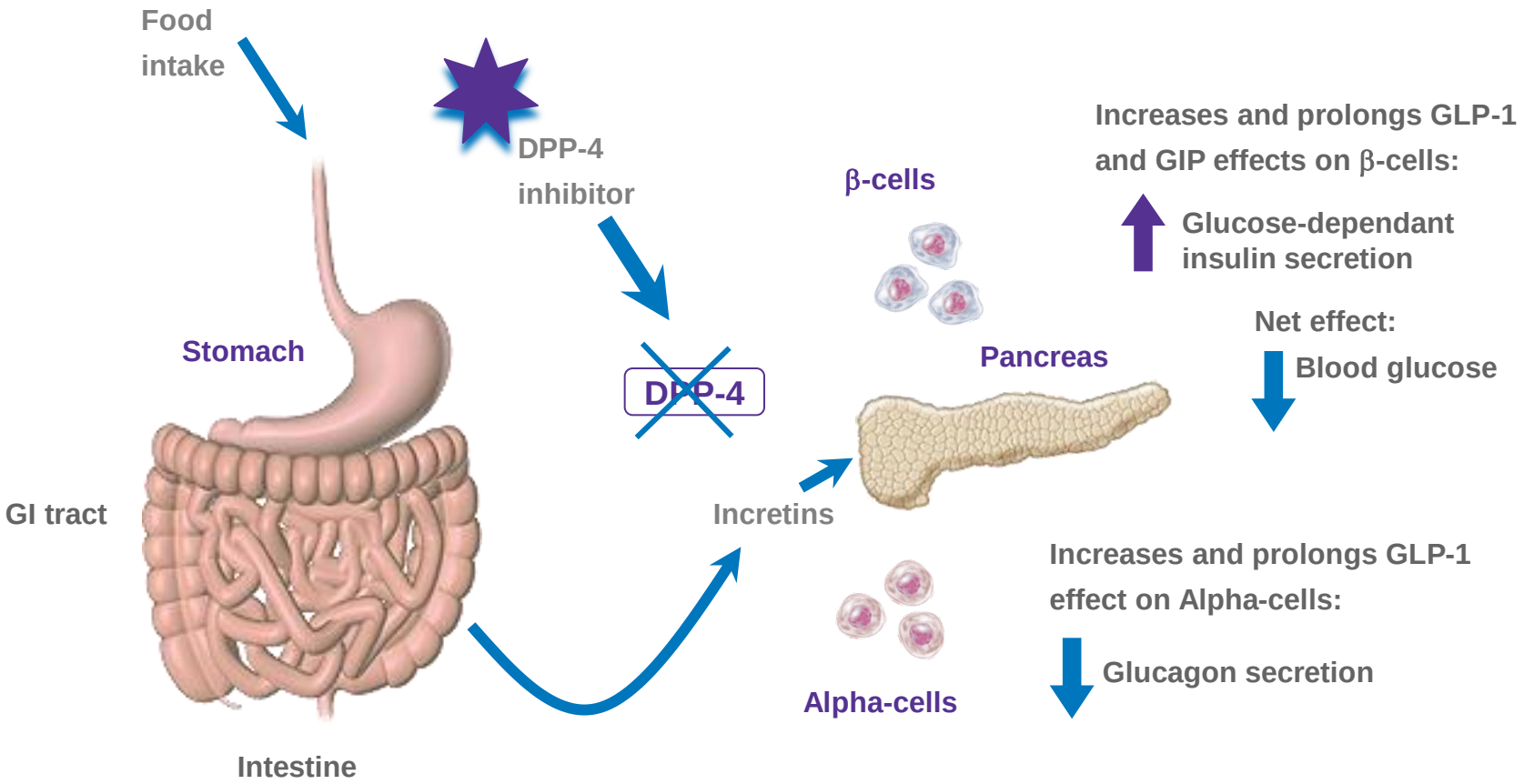
- ☑ Hypoglycemia
- ☑ Weight Gain
- ☑ Sustained Control

TYPE 2 DIABETES-THE WAY FORWARD

Role of the incretins

ON-SL-TW130406-1304
MAR2015-ONGL-TW-13056 (28/Mar/2013)).

DPP-4 inhibitors enhance incretins activity

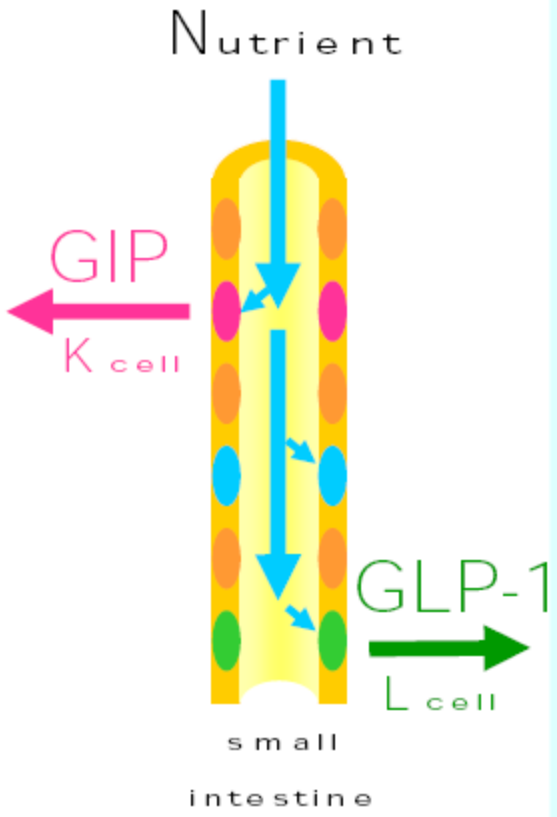


TYPE 2 DIABETES-THE WAY FORWARD

Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with Sus and metformin

ON-SL-TW130406-1304
MAR2015-ONCL-TW-13056 (28/Mar/2013

Divergent biological effects of Incretins, GLP-1 and GIP



Islet

β cell mass ↑
β cell death ↓
(demonstrated in animal)

Glucose dependant insulin secretion

Glucagon stimulation at hyperglycemia ?

Fat tissue

Obesity

Bone

Bone formation ↑

Islet

β cell mass ↑
β cell death ↓
(demonstrated in animal)

Glucose dependant
- Insulin secretion
- Glucagon suppression

Stomach

Gastric empty ↓

Brain

Appetite ↓

Vascular and nerve

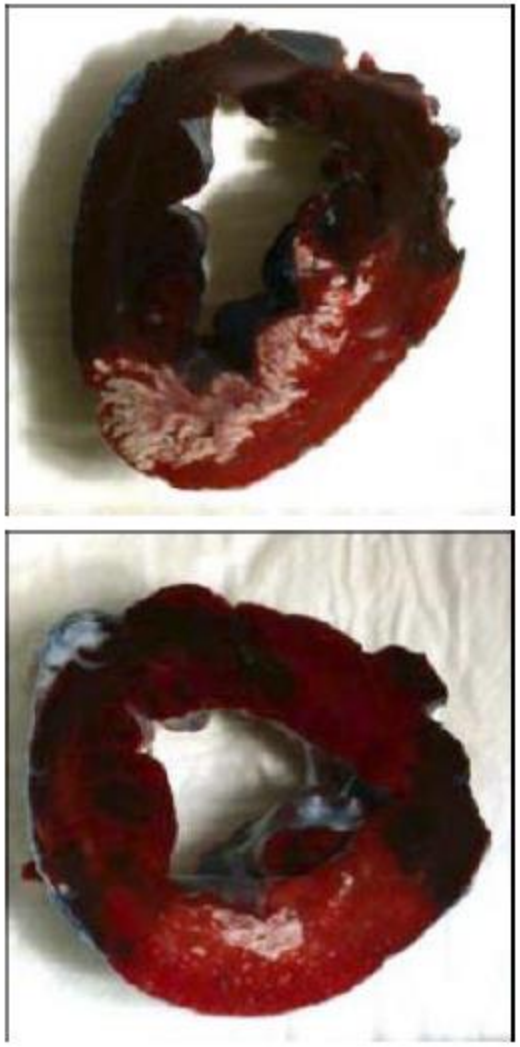
Function ↑

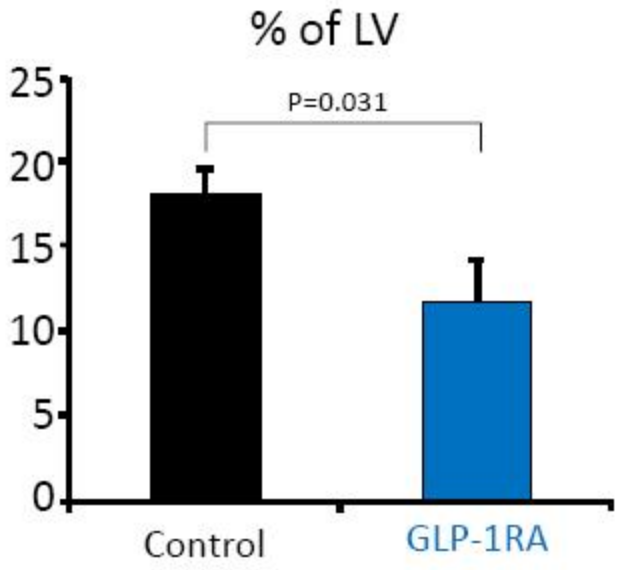
Favorable for the improvement of Type 2 DM

GLP-1 receptor activation exerts cardioprotective effects: The myocardial infarction pig model

Control

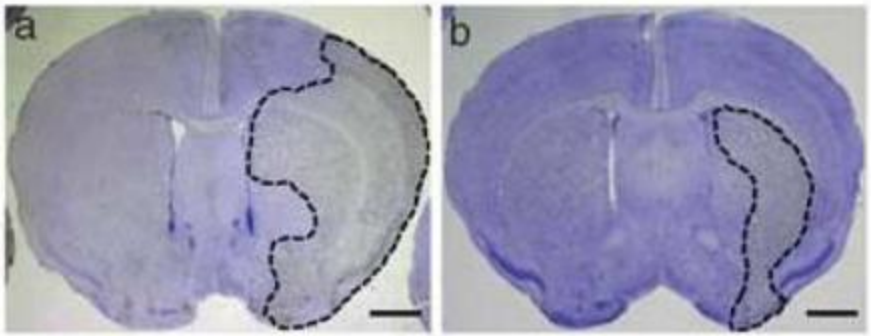
GLP-1RA



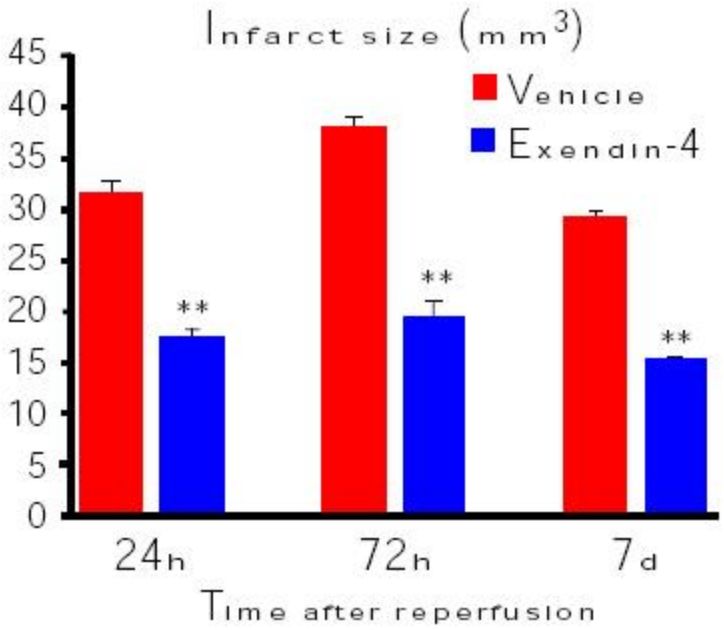


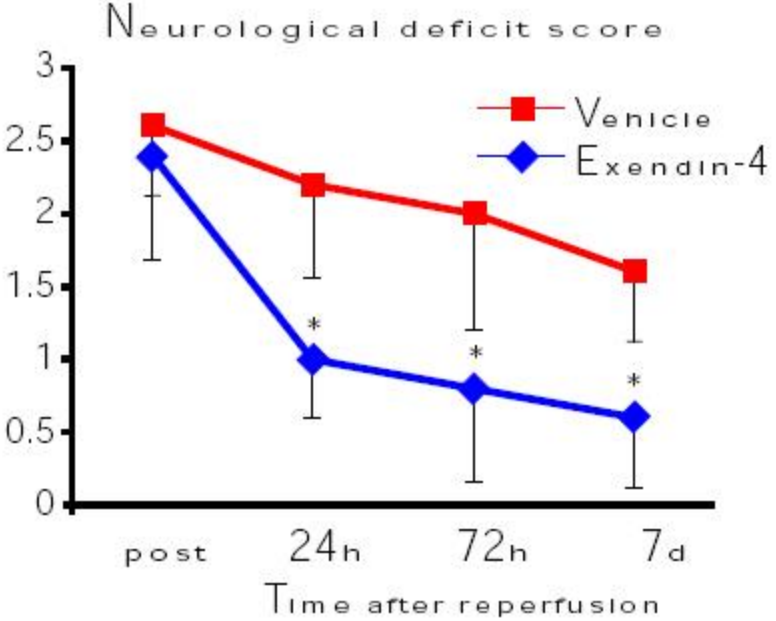
Timmers L, et.al. JACC 2009

GLP-1 receptor activation exerts neuroprotective effects: transient focal cerebral ischemia model (mouse)



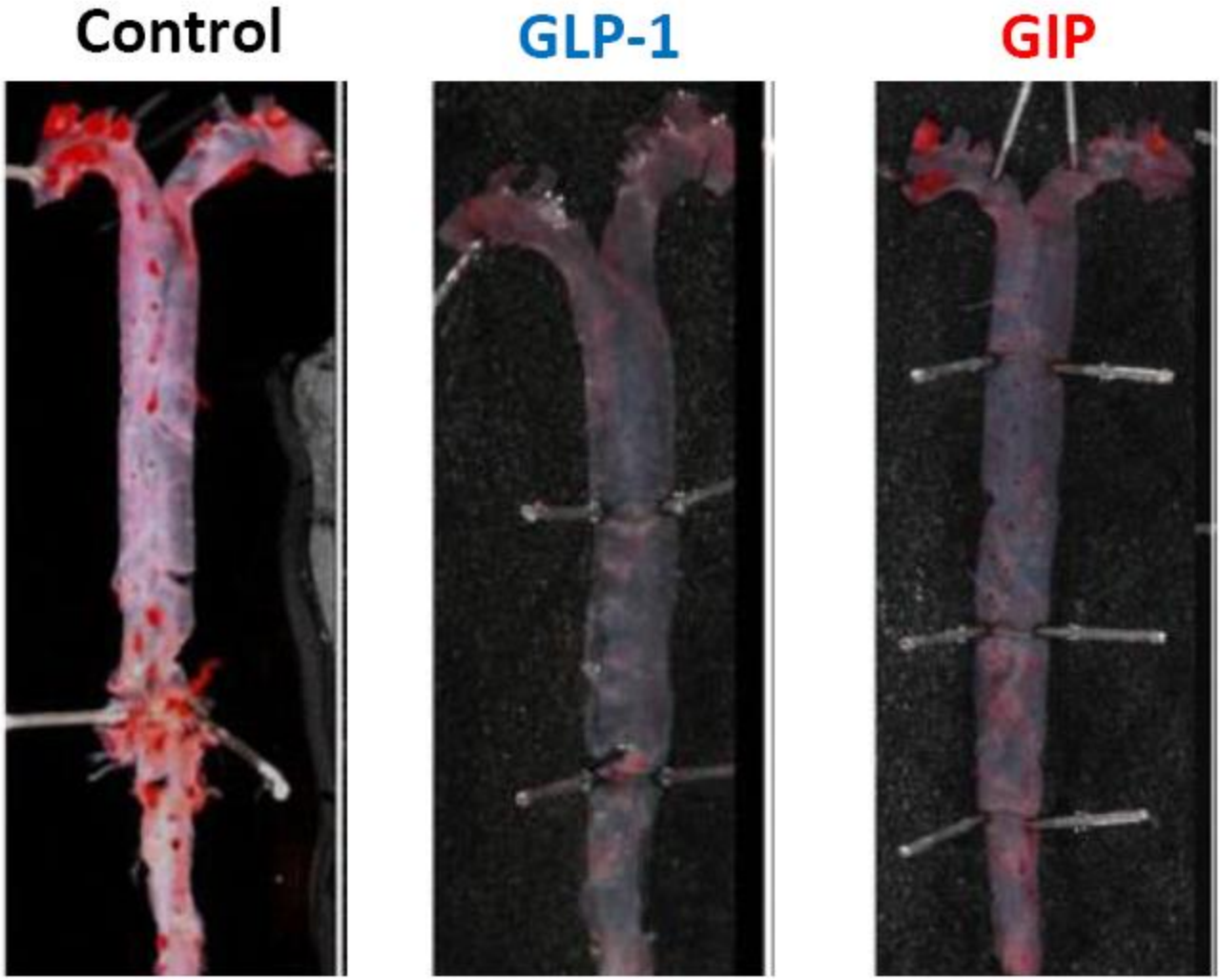
Vehicle Exendin-4





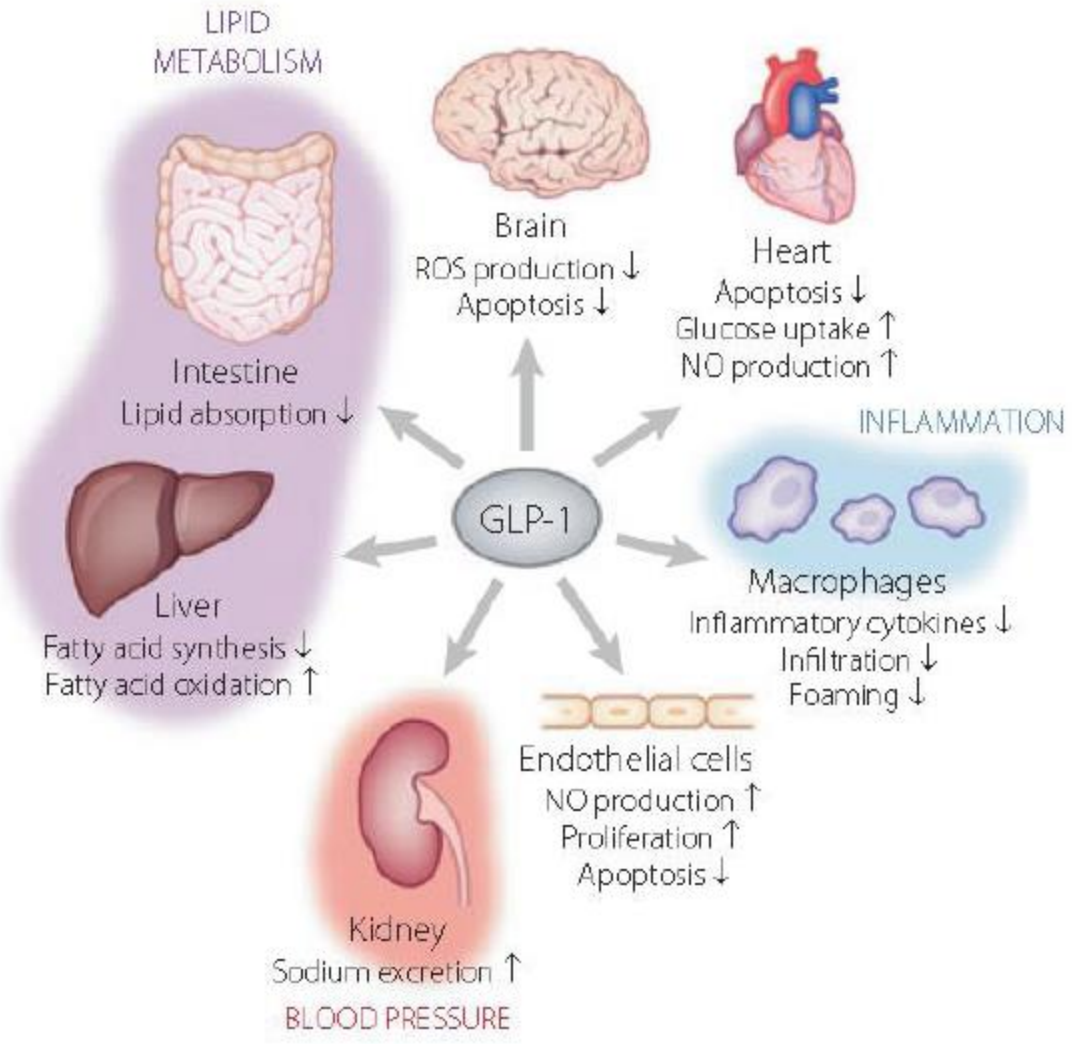
Teramoto S, et.al. *J Cereb Blood Flow Metab.* 2011

Infusion of GLP-1 or GIP prevents development of atherosclerotic lesions in apoE knockout



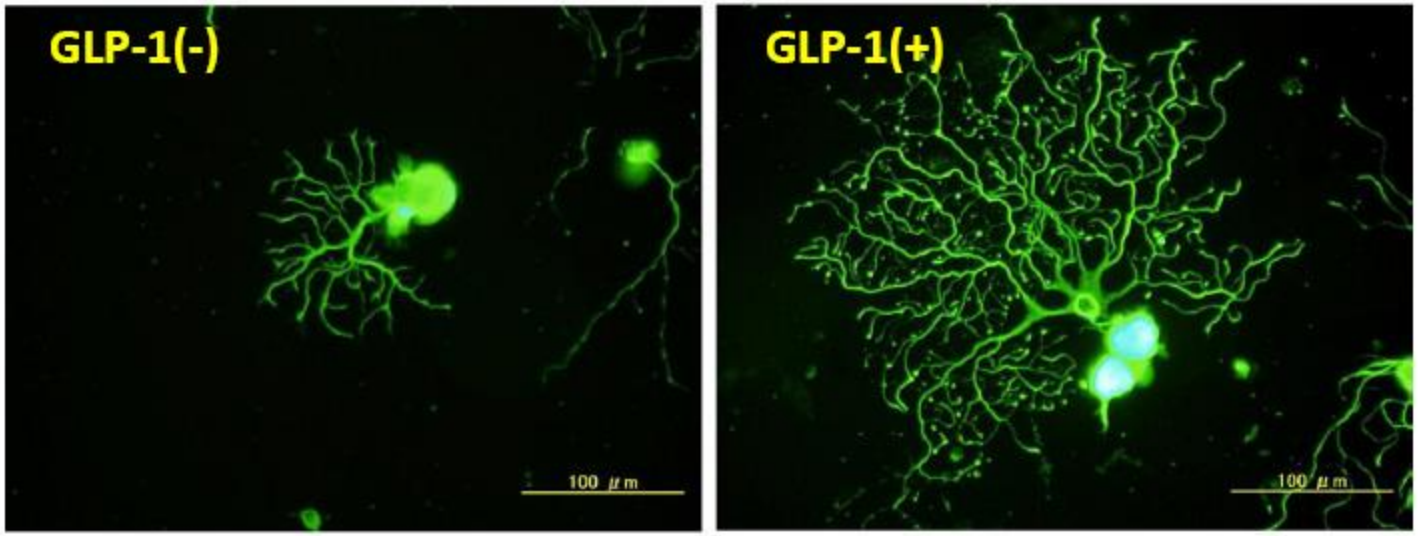
Nagashima M Hirano T et al., *Diabetologia* 2011

Underlying mechanisms for GLP-1's beneficial effects for cardiovascular complications



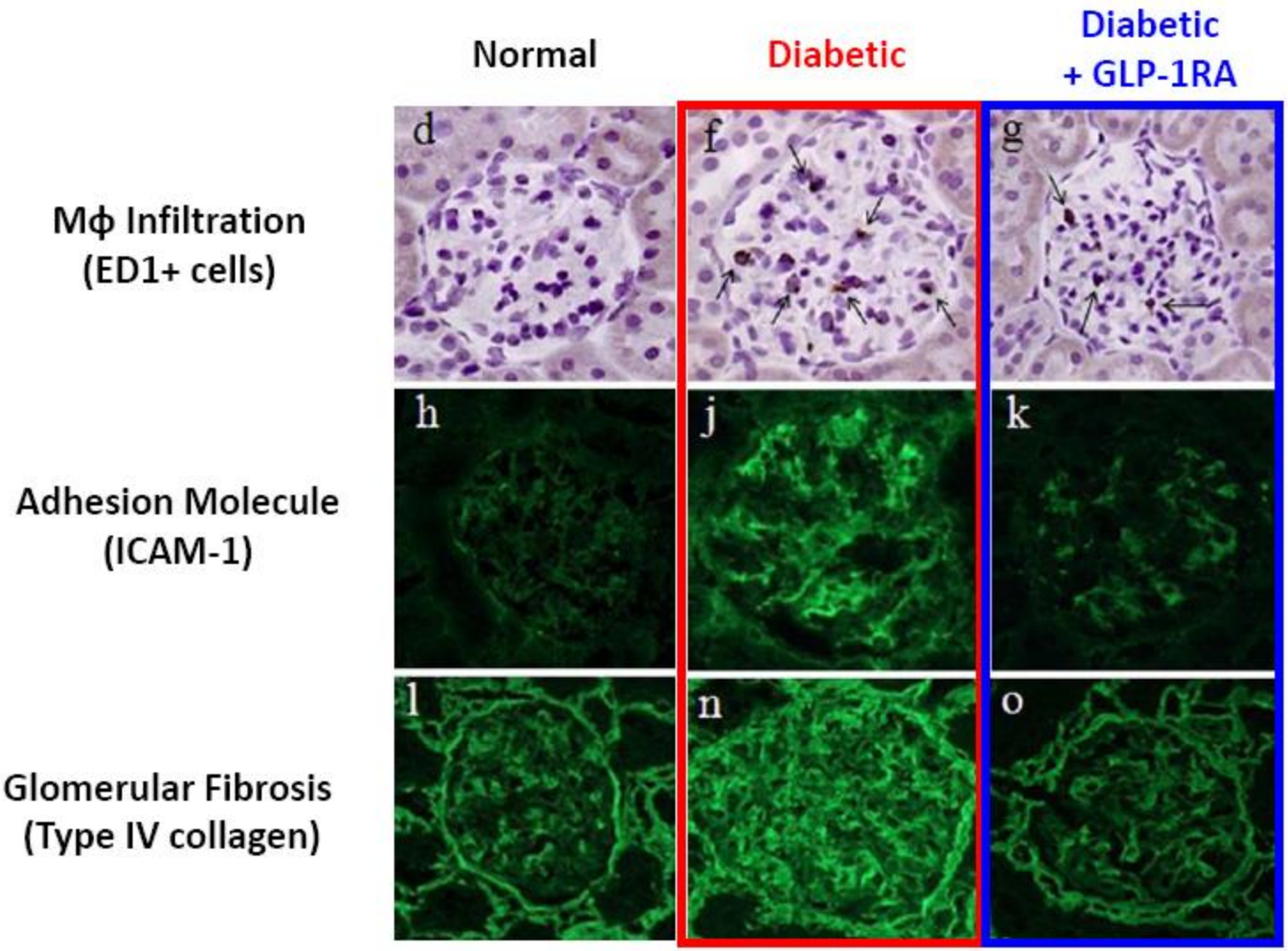
Seino Y, Yabe D, *JDI 2013*

GLP-1 promotes neurite outgrowth from the rat dorsal root ganglion



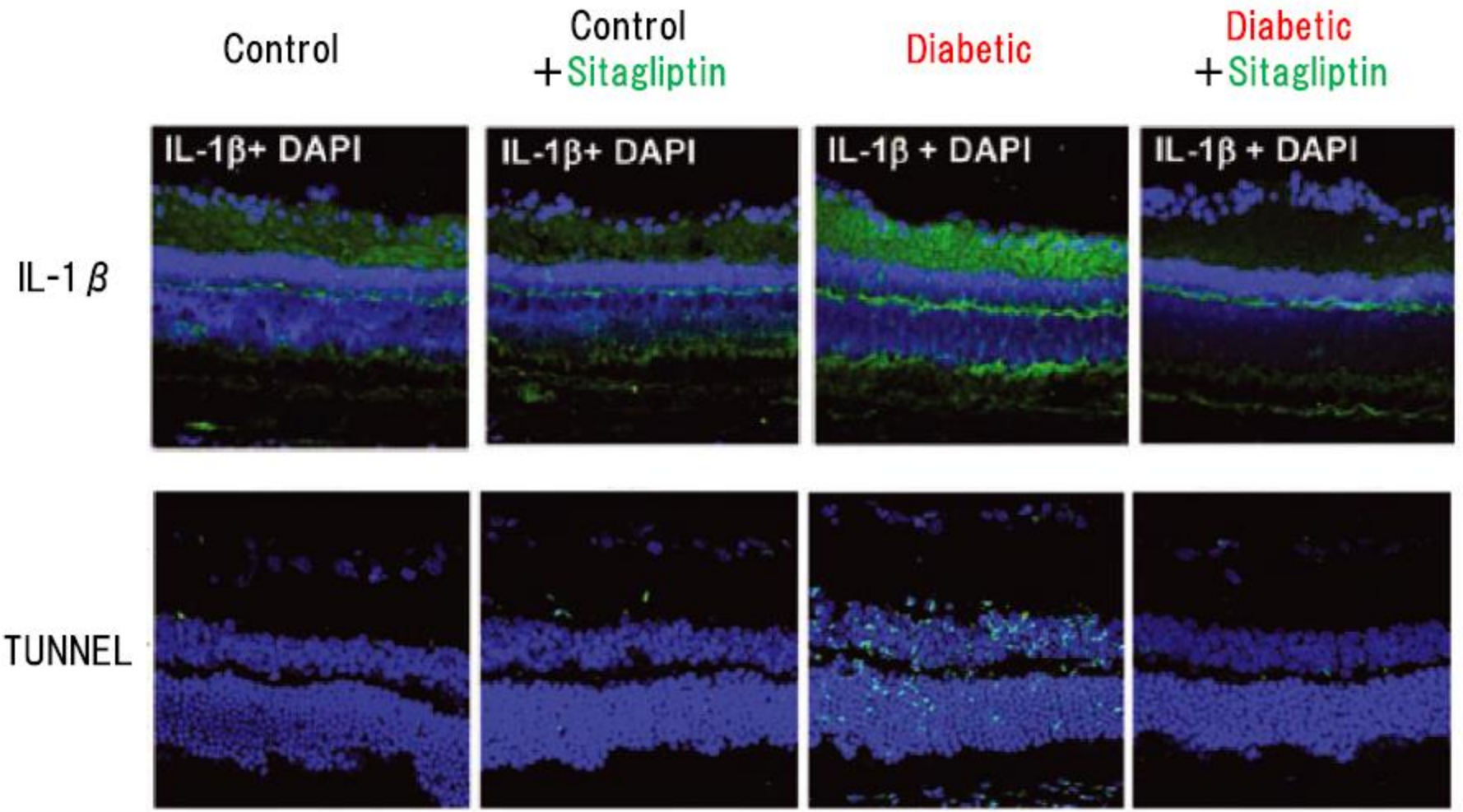
Himeno T, et al *Diabetes* 2011

GLP-1 prevents kidney lesions in STZ-induced diabetic rats



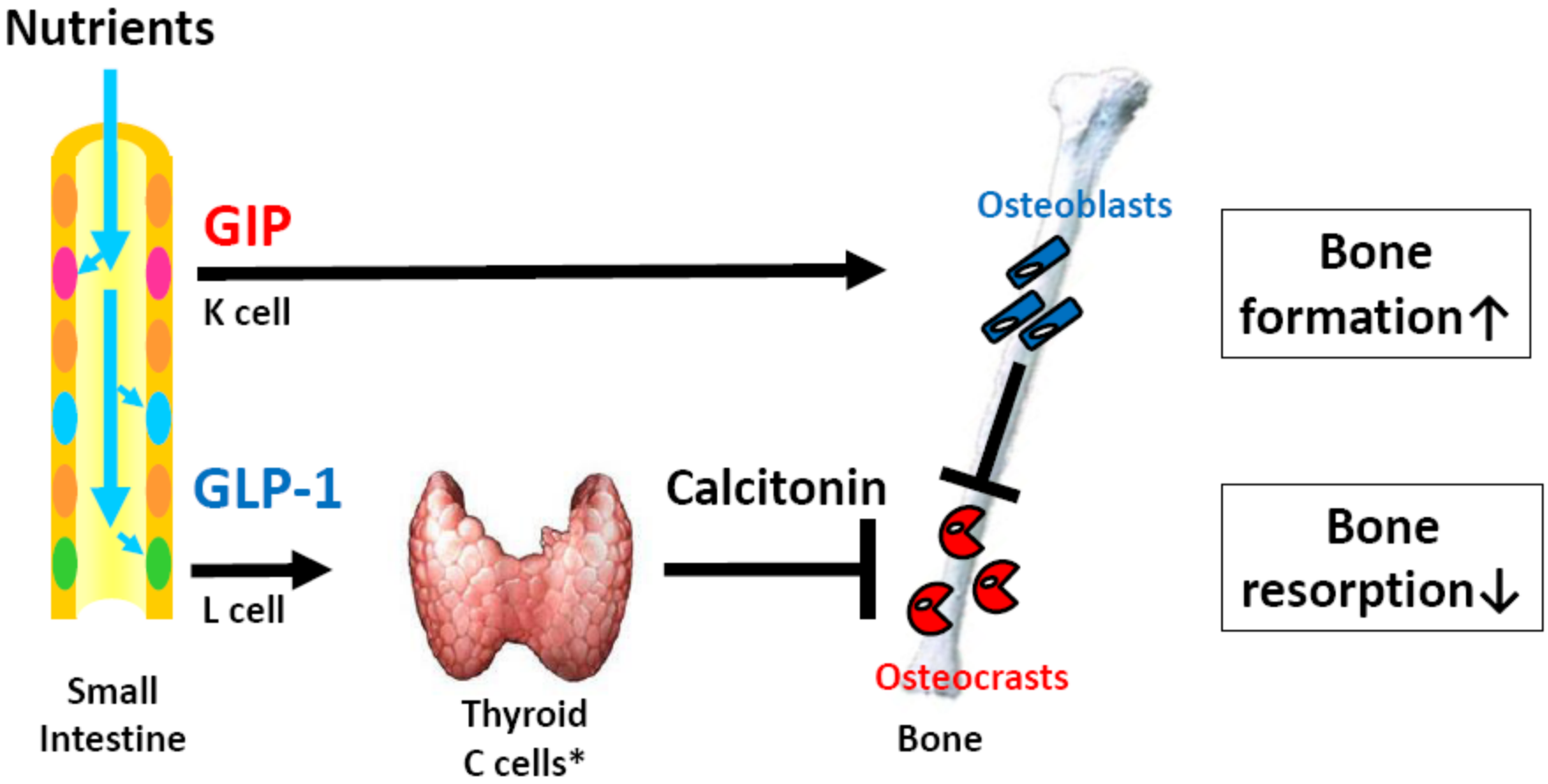
Kodera R, Makino H, et.al. *Diabetologia* 2011

DPP-4 inhibitor prevents inflammation and apoptosis in the retina of STZ-induced diabetic rats



Concalves A. et.al, DOM, 2012

Regulation of bone metabolism by GIP and GLP-1

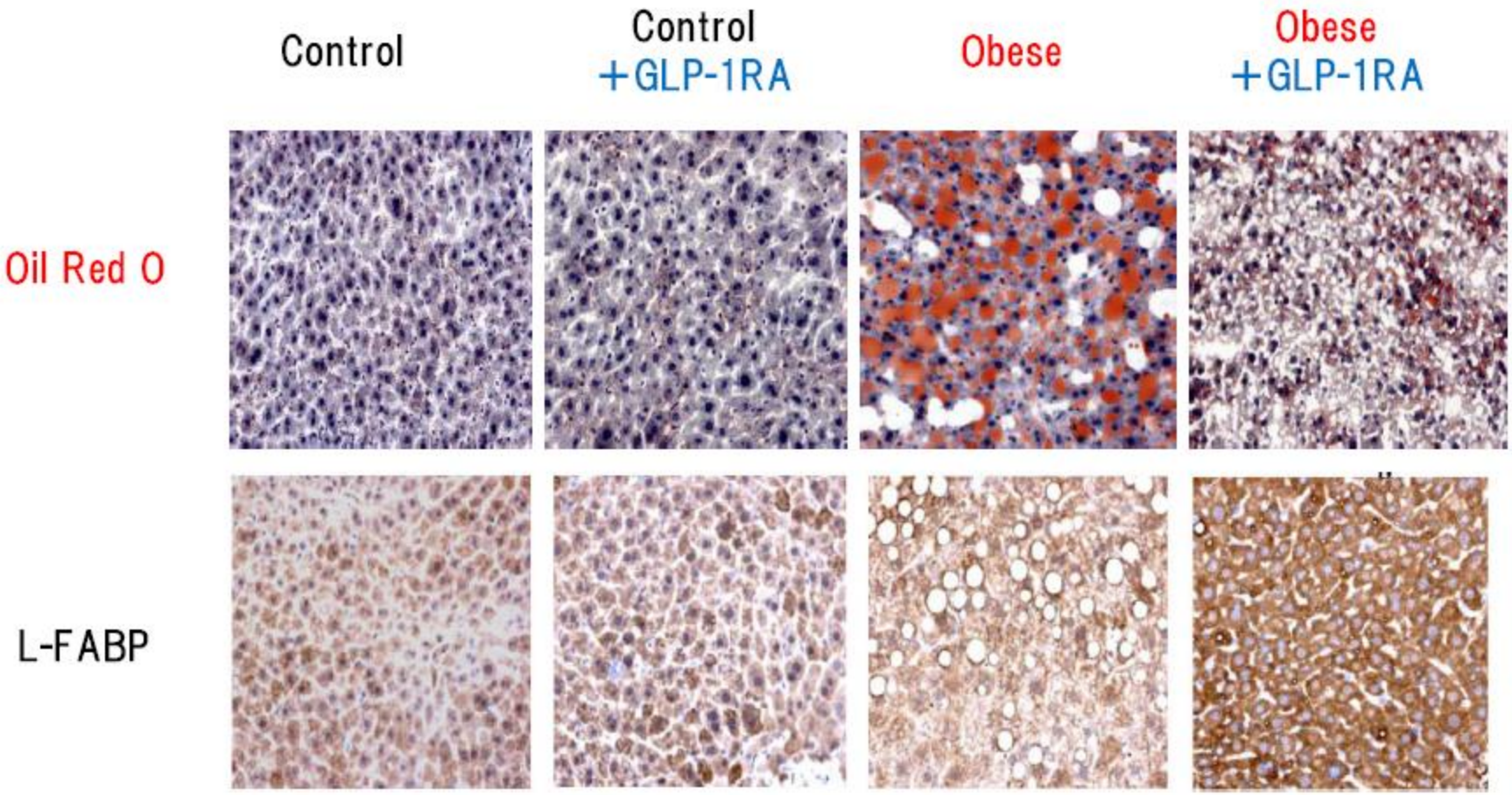


* Low expression of GLP-1R in human

Tsukiyama K,Yamada Y, Seino Y Mol Endocrinol 2006

Yamada C, Seino Y, Inagaki N et al Endocrinology, 2008

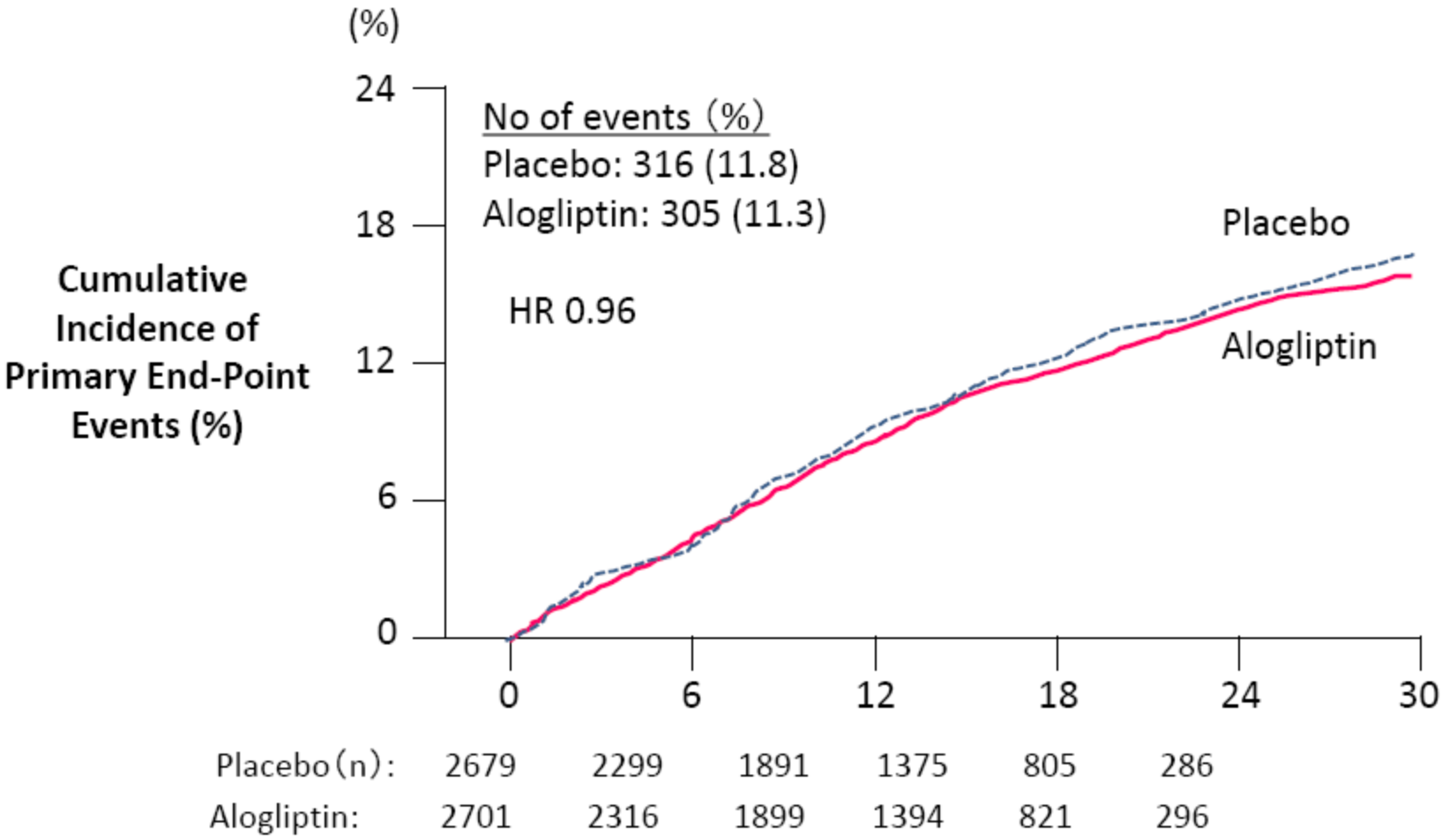
GLP-1 receptor activation ameliorates fatty liver in obese rats



GLP-1 ameliorates fatty liver by controlling expression of genes involved in fatty acid metabolism

Mellis. J.E. et.al, AJP Gasteroenterology 2012

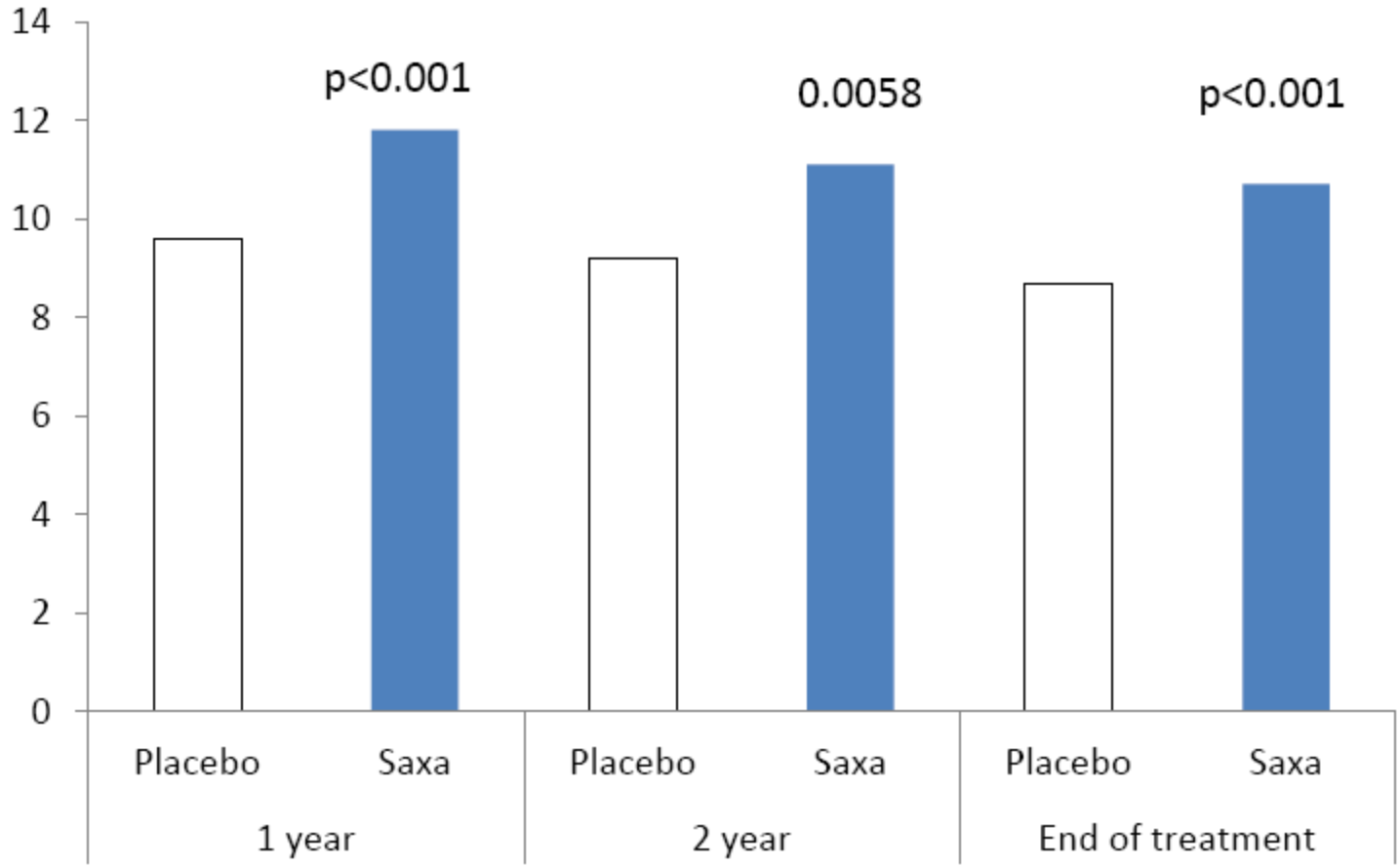
No improvement by alogliptin in cardiovascular outcomes in type 2 diabetic patients with acute coronary syndrome (EXAMINE)



Most patients were on aspirin, statin and ACEI/ARB

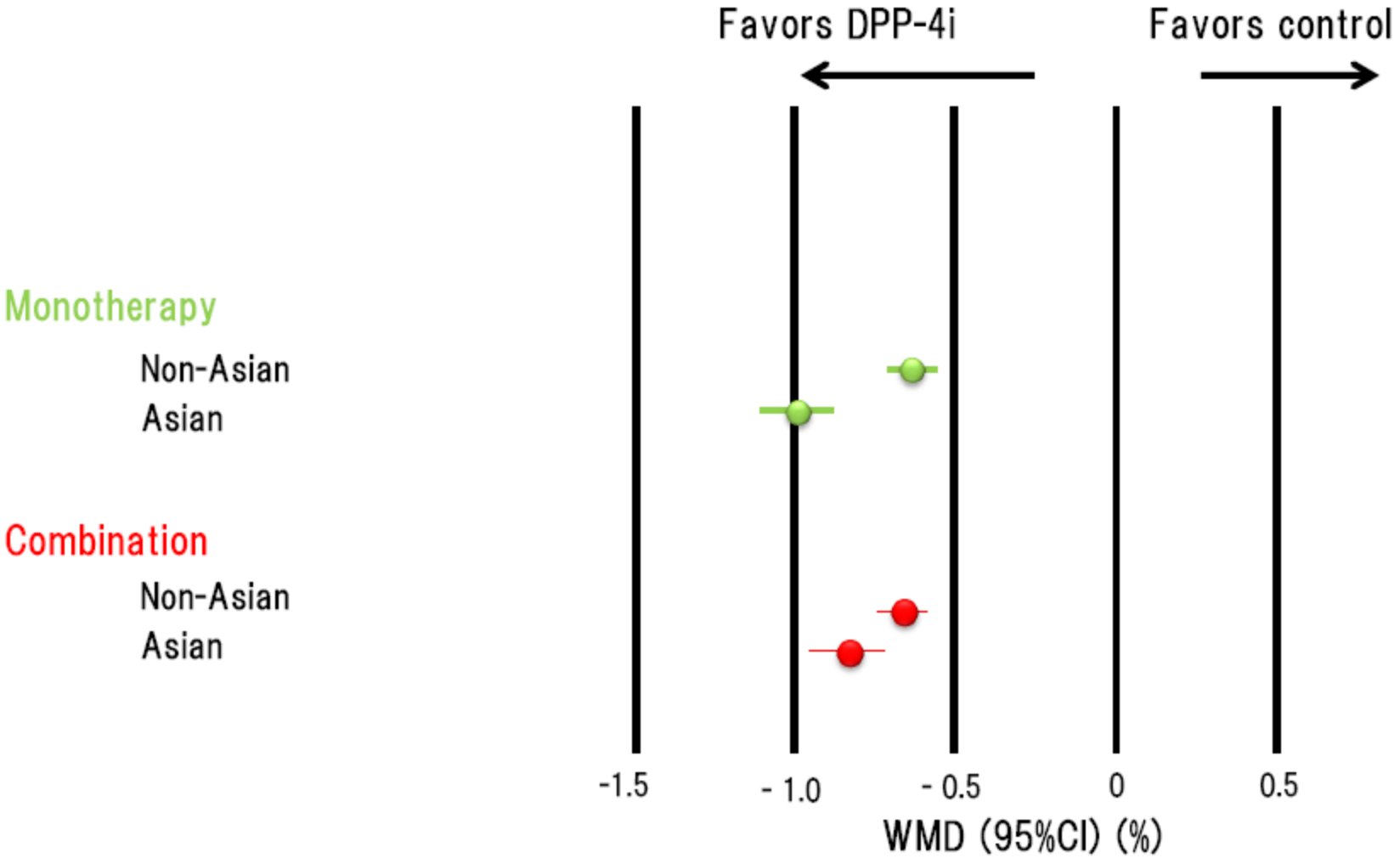
White WB et al NEJM, 2013.

Improvement of microalbuminuria in type 2 diabetic patients with a history of, or at high risk for CVD (SAVOR TIMI 53)



Scirica BM et al NEJM, 2013.

Efficacy of DPP-4 inhibitors (Meta analysis):
Comparison between Asian and non-Asian type 2 diabetes



DPP-4i demonstrates greater HbA1c lowering in Asian type 2 diabetes

Kim YG, Cho YM et al., Diabetologia 2013

Meal sequence and postprandial glucose (model)

①

Preload dietary fibers that reduce glucose absorption

②

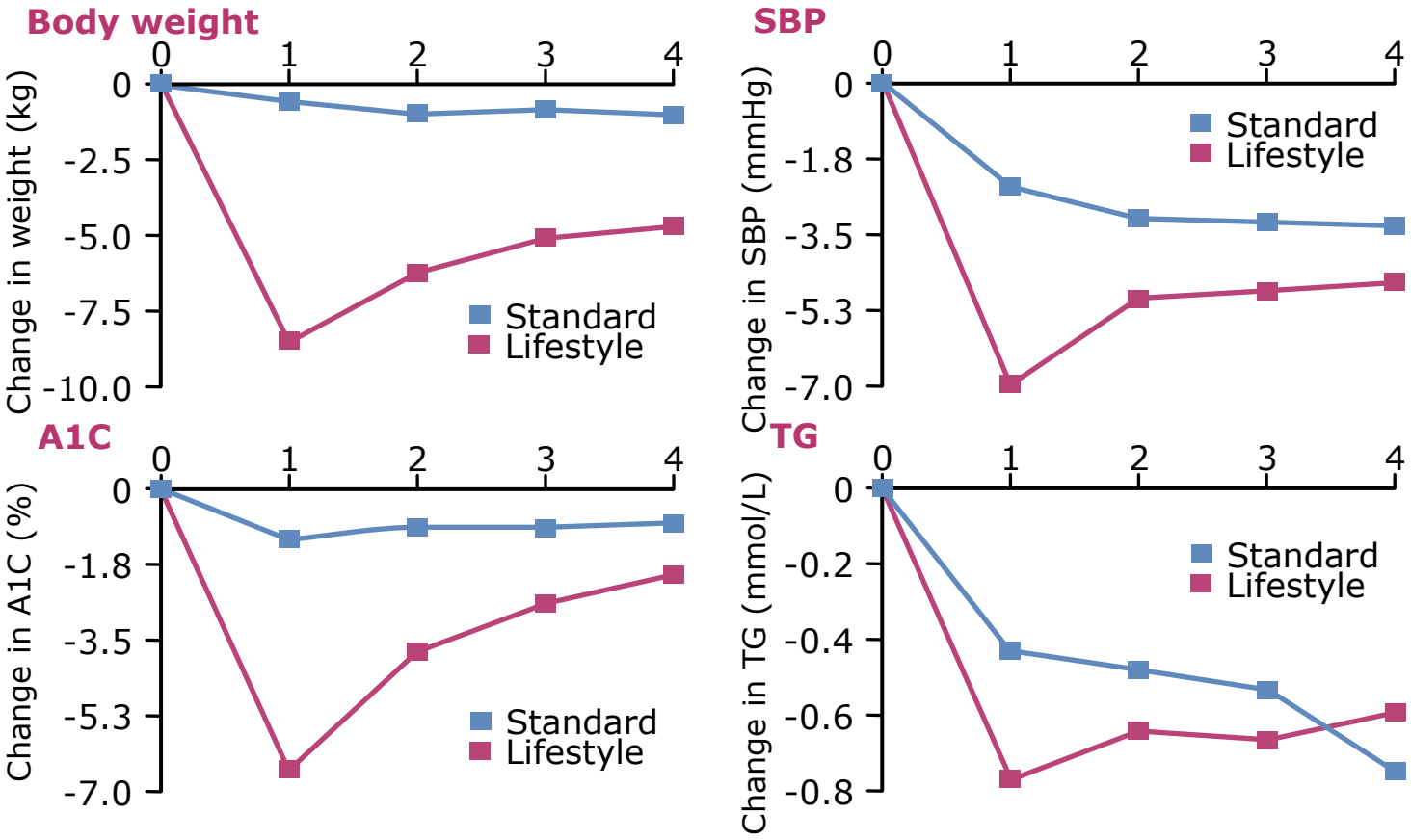
Enhance GLP-1 secretion by protein and fat

Ready to ingest carbohydrates

③

Reduce postprandial glucose levels

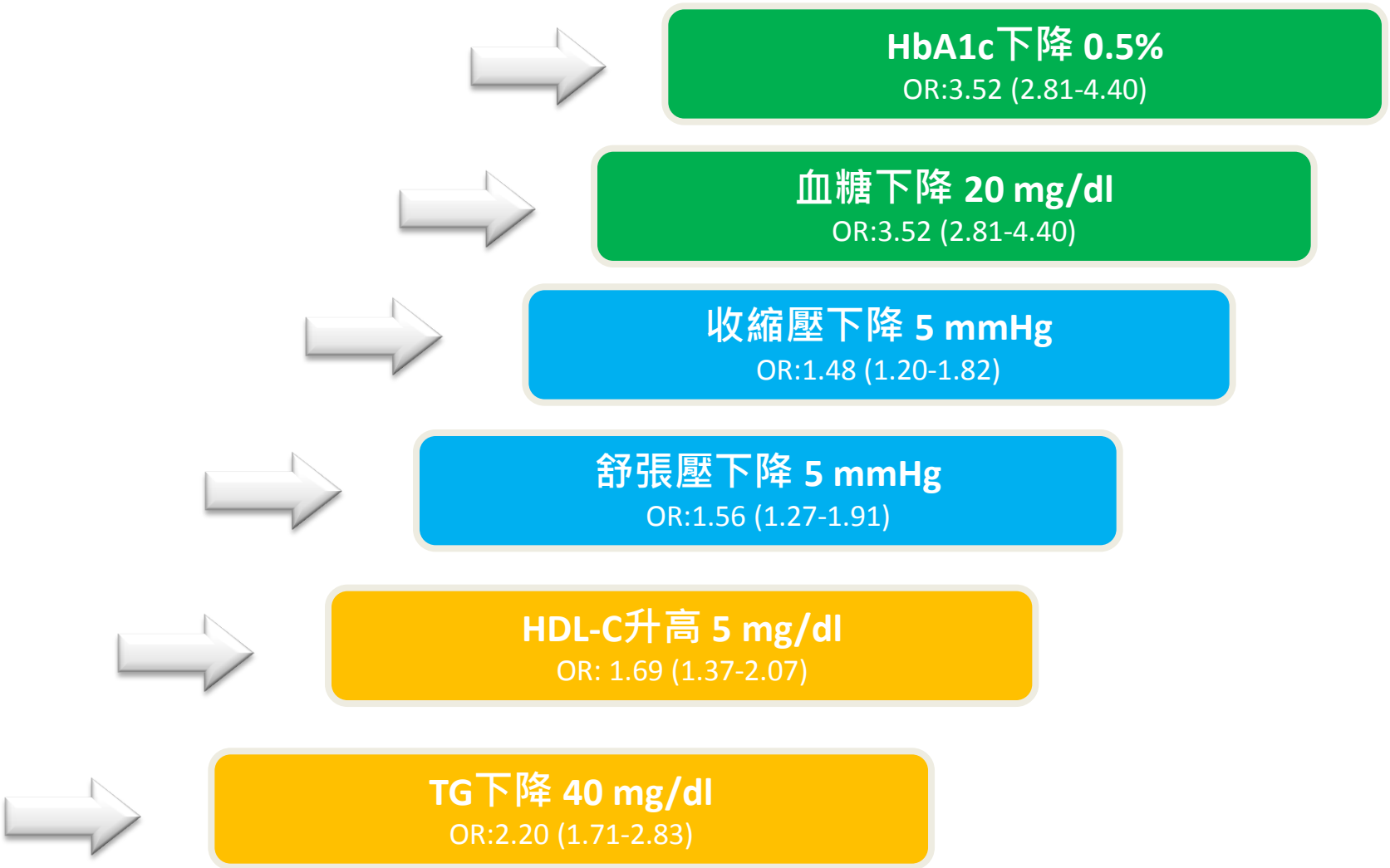
Look AHEAD: 1- and 4-year results



Weight loss: –6.15% vs. –0.88% (p<0.001)
A1C, Fitness, SBP, HDL-C better in intensive lifestyle group

Wing RR *et al. Arch Intern Med* 2010;170(17):1566–75

與體重不變的患者相比，減少體重5-10%的患者



WING RR,et al,Diabetes Care,2011; 34:1481–1486

CVD Protection is result from

optimal glycemic control

or

efficacy of antidiabetic agent?

Thank you!!