New Insights on the Use of Acarbose for T2DM Management

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What is Different with 2017 ?

2017

Pharmacologic Therapy For T2DM

Start with Monotherapy unless:

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

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

Monotherapy Metformin **Lifestyle Management**

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

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

Dual Therapy Metformin + **Lifestyle Management**

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

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

New: "For patients with ASCVD, add a second agent with evidence of cardiovascular risk reduction after consideration of drug-specific and patient factors"

2018

Pharmacologic Therapy For T2DM

A1C is less than 9%, **consider Monotherapy.**

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

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

Monotherapy Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

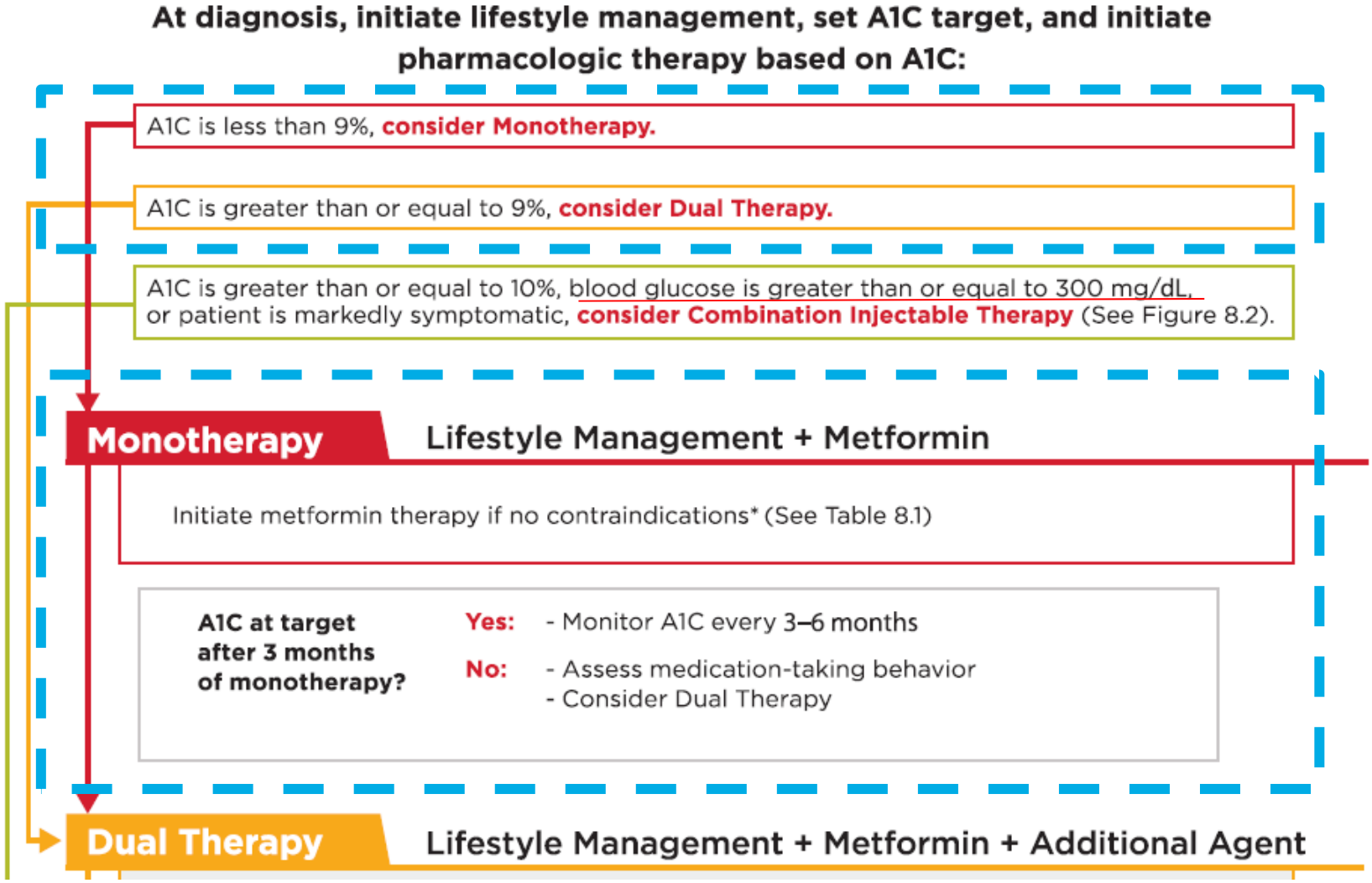
No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

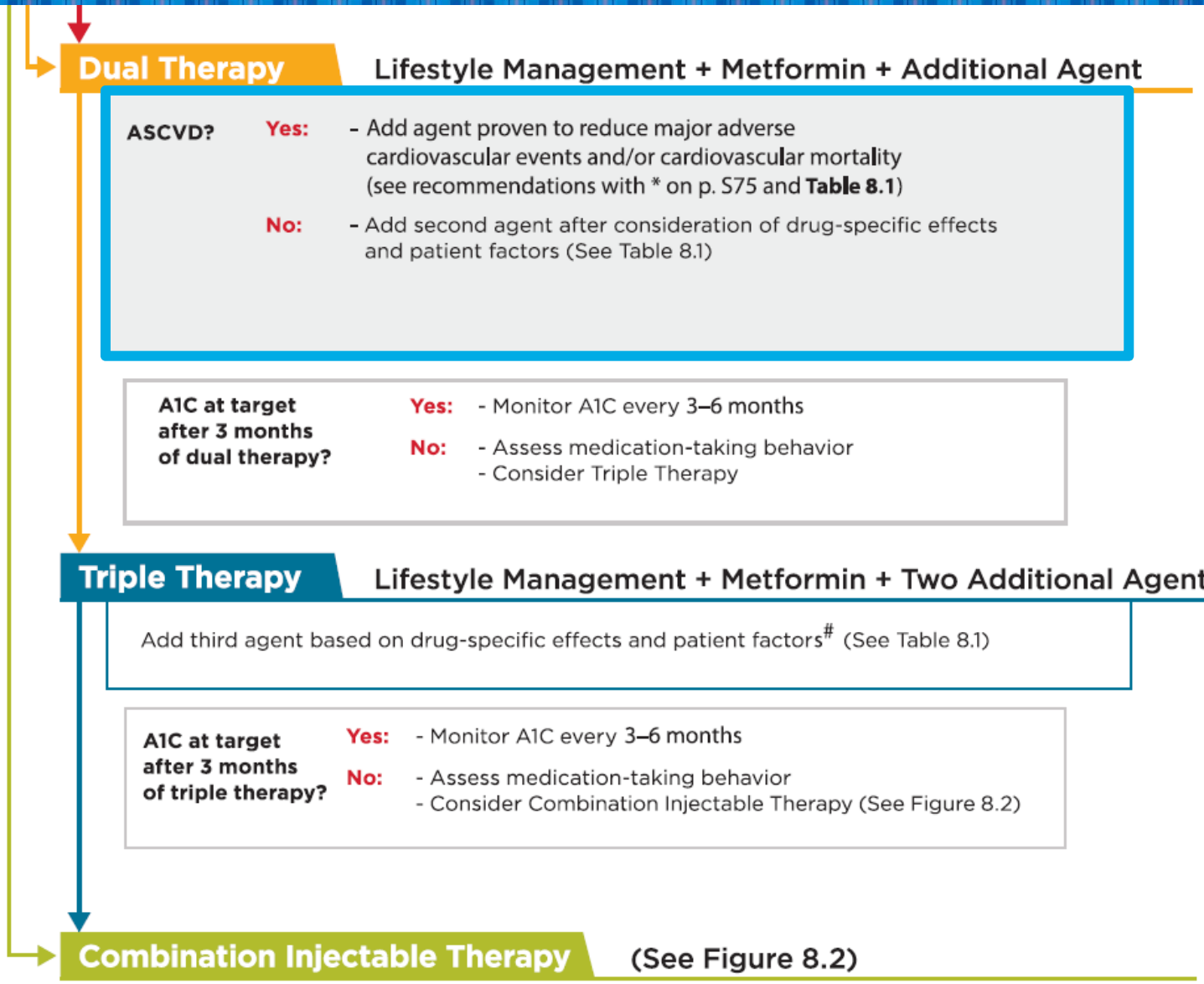
No: - Assess medication-taking behavior
- Consider Triple Therapy

2018 ADA Guideline



Diabetes Care 2018;41(Suppl. 1):S73 – S85

Antihyperglycemic Therapy in Adults for T2DM



Diabetes Care 2018;41(Suppl. 1):S73 – S85

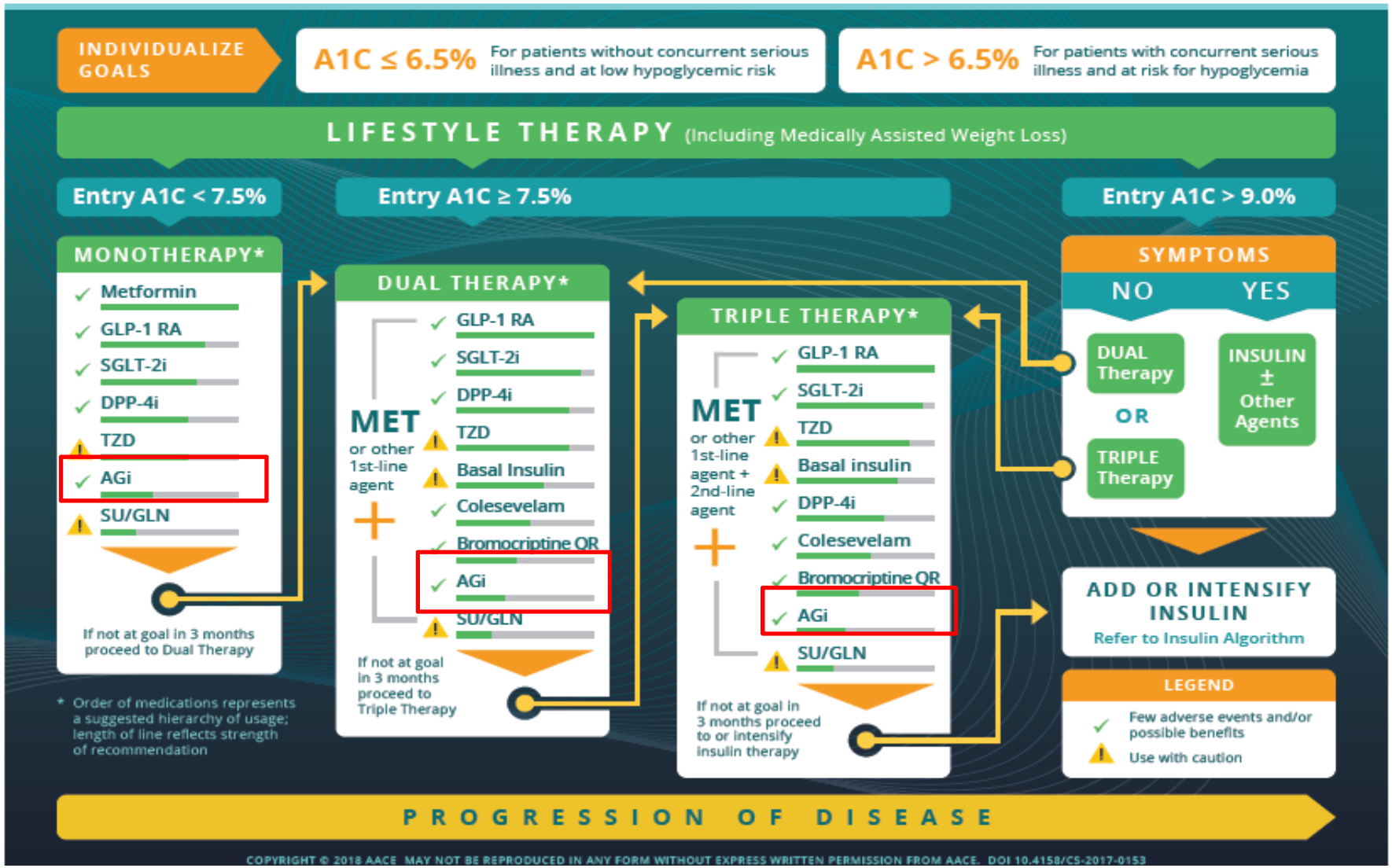
Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of CKD	Dosing/Use Considerations	
Metformin	High	NO	Neutral	Potential Benefit	Neutral	Low	Oral	Neutral	Contraindicated with eGFR<30	GI Side Effect Common (Diarrhea、Nausea) Potential B12 Deficiency
SGLT2 inhibitors	Intermediate	NO	Loss	Benefit : Canagliflozin Empagliflozin	Benefit : Canagliflozin Empagliflozin	High	Oral	Benefit : Canagliflozin Empagliflozin	Canagliflozin : Not Recommend with eGFR<45 Dapagliflozin : Not Recommend with eGFR<60 ; Contraindicated with eGFR<30 Empagliflozin : Contraindicated with eGFR<30	FDA Black Box : Risk of Amputation(Canagliflozin) Risk of Bone Fractures(Canagliflozin) DKA Risk(all, rare in T2DM) Genitourinary Infection Risk of Volume Depletion, Hypotention Raise LDL
GLP-1 RAs	High	NO	Loss	Neutral : Lixisenatide ; Exenatide ER Benefit : Liraglutide	Neutral	High	SQ	Benefit : Liraglutide	Exenatide : Not Indicated with eGFR<30 Lixisenatide : Caution with eGFR<30 Increase Risk of Side Effects in Patients with Renal Imparement	FDA Black Box : Risk of Thyroid C-cell Tumors(Liraglutide、Albiglutide、Dulaglutide、Exenatide ER) GI Side Effect Common(Nausea、Vomiting、Diarrhea) Injention site reactions ?Acute Pancretitis Risk
DPP-4 inhibitors	Intermediate	NO	Neutral	Neutral	Potential Risk : Saxaglipitin Aloglipitin	High	Oral	Neutral	Renal Dose Adjustment Required ; Can be Used in Renal Imparement	Potential Risk of Acute Pancretitis Joint Pain
TZD	High	NO	Gain	Potential Benefit : Pioglitazone	Increase Risk	Low	Oral	Neutral	No Dose Adjustment Required ; Generally not Recommended in Renal Imparement Due to Fluid Retention	FDA Black Box : CHF(Pioglitazone、rosiglitazone) Fluid Retention(Edema、CHF) Benefit in NASH Risk of Bone Fractures Bladder Cancer(Pioglitazone) Raise LDL(Rosiglitazone)
SU (2nd Generation)	High	YES	Gain	Neutral	Neutral	Low	Oral	Neutral	Gluburide : not Recommended ; Glipizide & Glimepiride Initiate Conservatively to Avoid Hypoglycemia	FDA Special Warning on Increased Risk of CV Motarlity(Studies from Older SU : Tolbutamide)
Insulin Huan	Highest	YES	Gain	Neutral	Neutral	Low	SQ	Neutral	Lower Insulin Doses Required with a Decrease in eGFR ; Titrate per Clinical Respose	Injection Site Reactions Higher Risk of Hypoglycemia woth Human Insulin (NPH or Premixed Formulations) vs. Analogs
Insulin Analogs						High	SQ			

Diabetes Care 2018;41(Suppl. 1):S73 – S85

2018 AACE/ACE Comprehensive T2DM Management Algorithm

Glycemic Control Algorithm



118 2018 AACE/ACE T2D Management, *Endocr Pract.* 2018;24(No. 1)

2018 AACE/ACE Comprehensive T2DM Management Algorithm

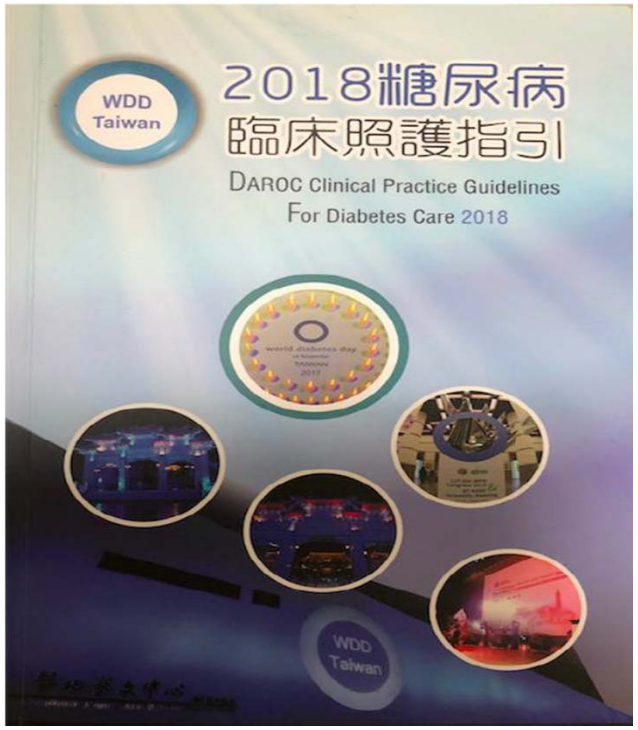
Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2I	DPP-4I	AGI	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC / ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits
Likelihood of adverse effects
Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

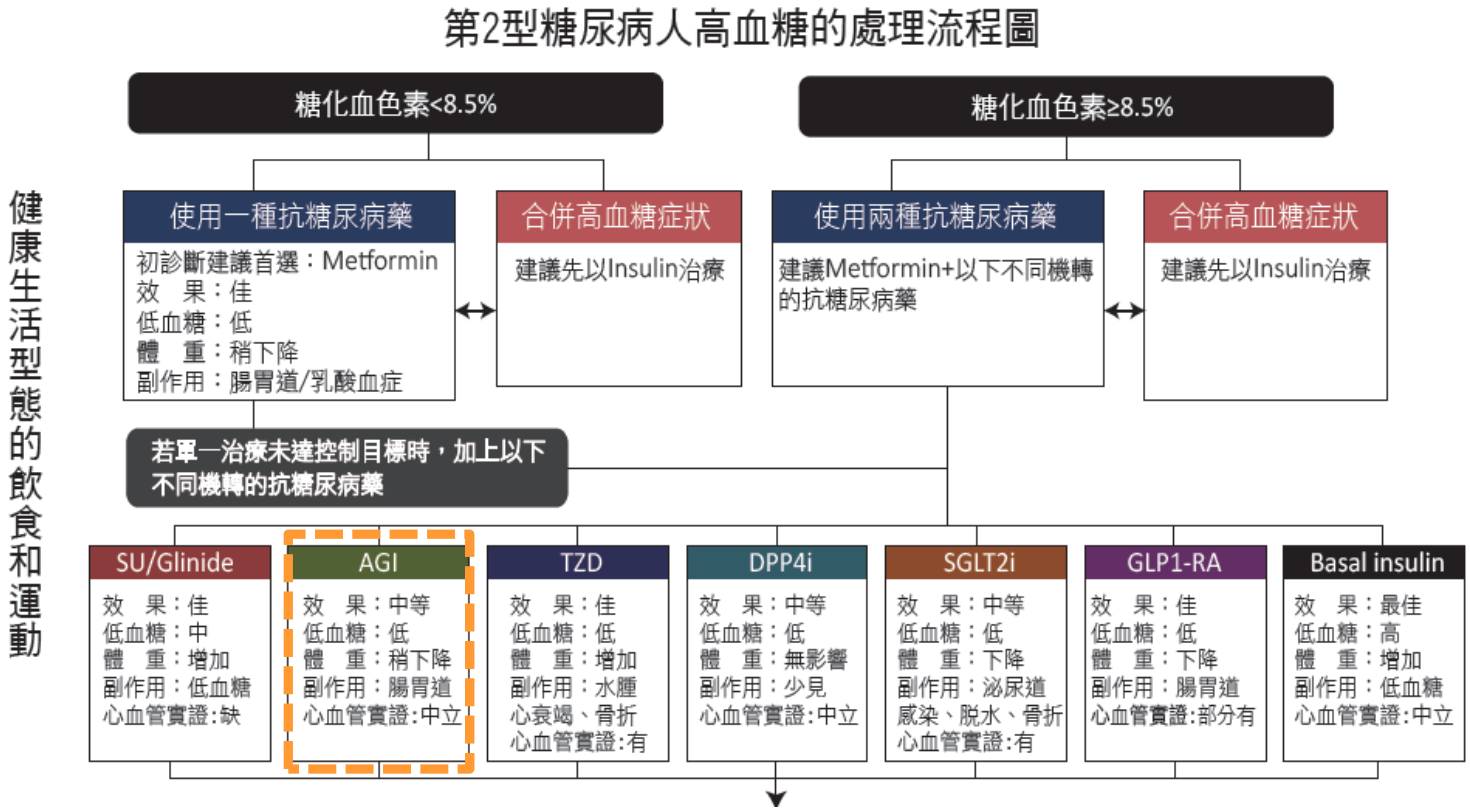
I20 2018 AACE/ACE T2D Management, *Endocr Pract.* 2018;24(No. 1)



2018 中華民國糖尿病學會
糖尿病臨床照護指引

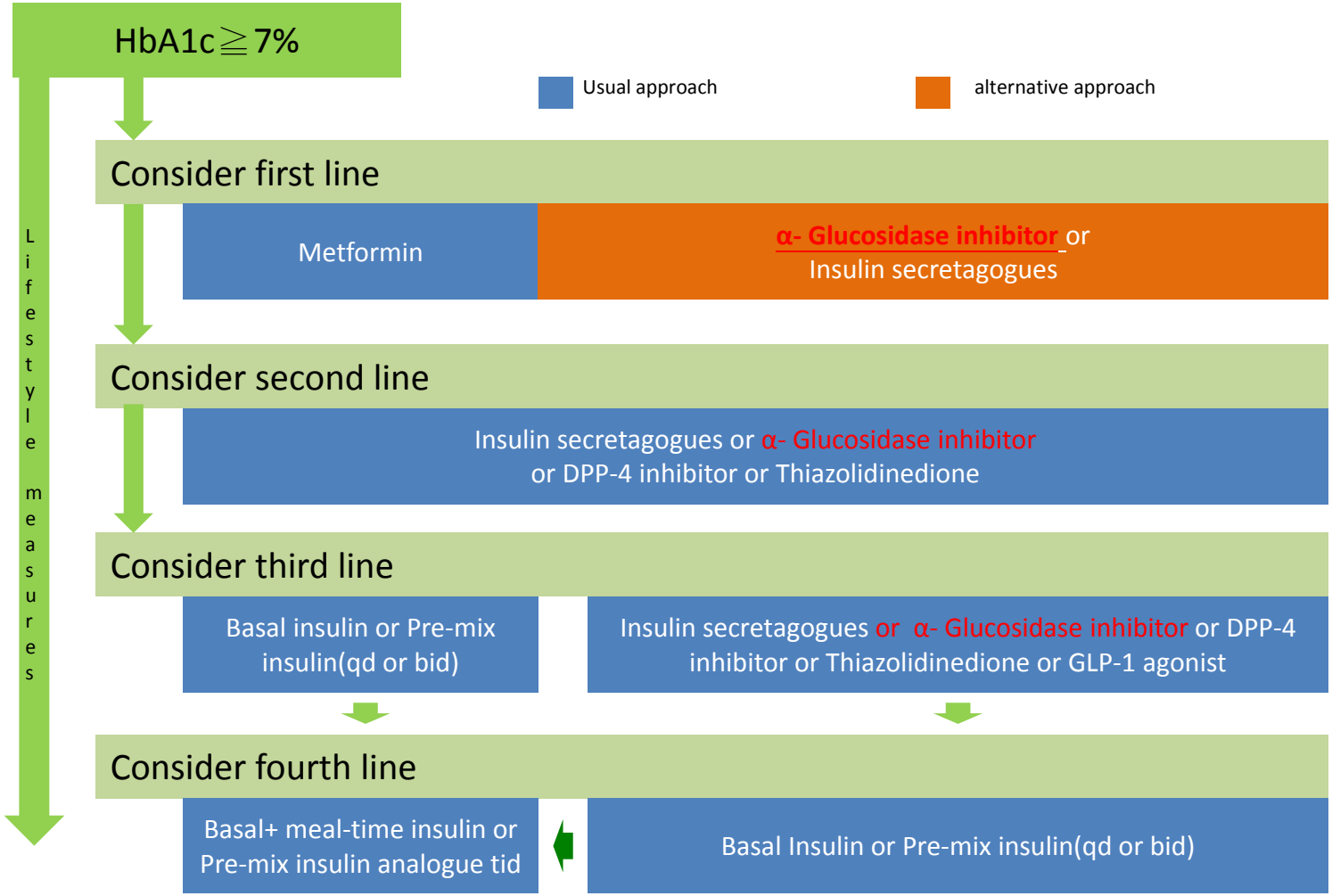
TZD is also Recognized as Evidenced-Based Choice in Reducing CV Events for Patients with T2DM[TDA18]

- In “2018糖尿病臨床照護指引”, TZD has been identified as one of 2nd line choice after metformin for T2DM pharmacological treatment.



TDA18. 2018 糖尿病臨床照護指引

Treatment Algorithm for T2DM in Updated Chinese Guideline



Ref: Chin J Diabetes Mellitus 2014;6(7):447-498. (In Chinese)
中華糖尿病雜誌

MARCH Study

(**M**etformin and **Glucobay** in **C**hinese as the initial **H**ypoglycemic Treatment)

Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial

Wenying Yang, Jie Liu, Zhongyan Shan, Haoming Tian, Zhiguang Zhou, Qiuhe Ji, Jianping Weng, Weiping Jia, Juming Lu, Jing Liu, Yuan Xu, Zhaojun Yang, Wei Chen

Lancet Diabetes Endocrinol 2014; 2: 46–55

Published Online October 18, 2013

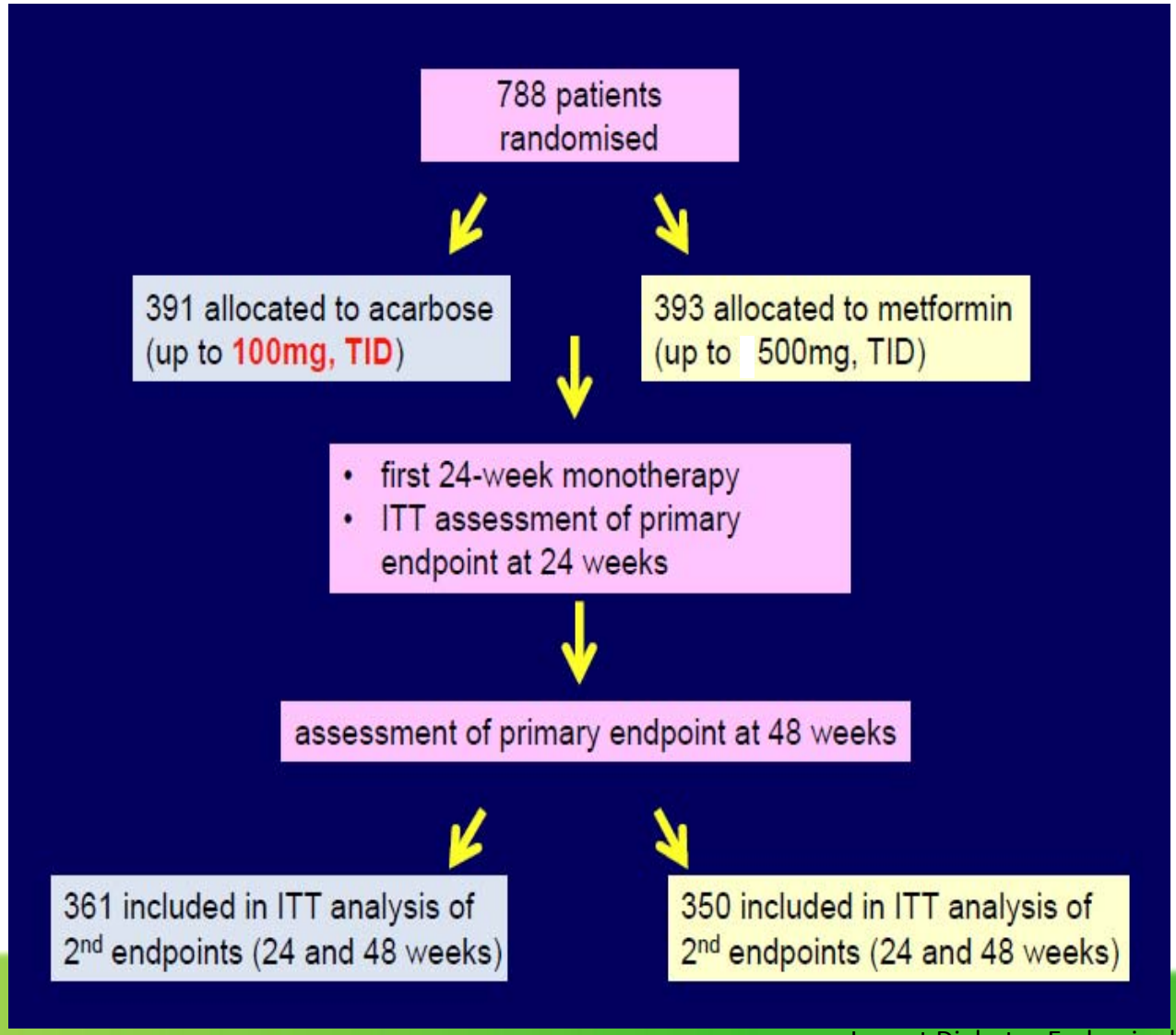
http://dx.doi.org/10.1016/S2213-8587(13)70021-4

Summary

Background Metformin is the only first-line oral hypoglycaemic drug for type 2 diabetes recommended by international guidelines with proven efficacy, safety, and cost-effectiveness. However, little information exists about its use in Asian populations. We aimed to ascertain the effectiveness of the α-glucosidase inhibitor acarbose, extensively adopted in China, compared with metformin as the alternative initial therapy for newly diagnosed type 2 diabetes.

- 48-week, randomised, open-label, non-inferiority trial, patients who were newly diagnosed with type 2 diabetes, with a mean **HbA1c of 7.5%,** were enrolled from 11 sites in China

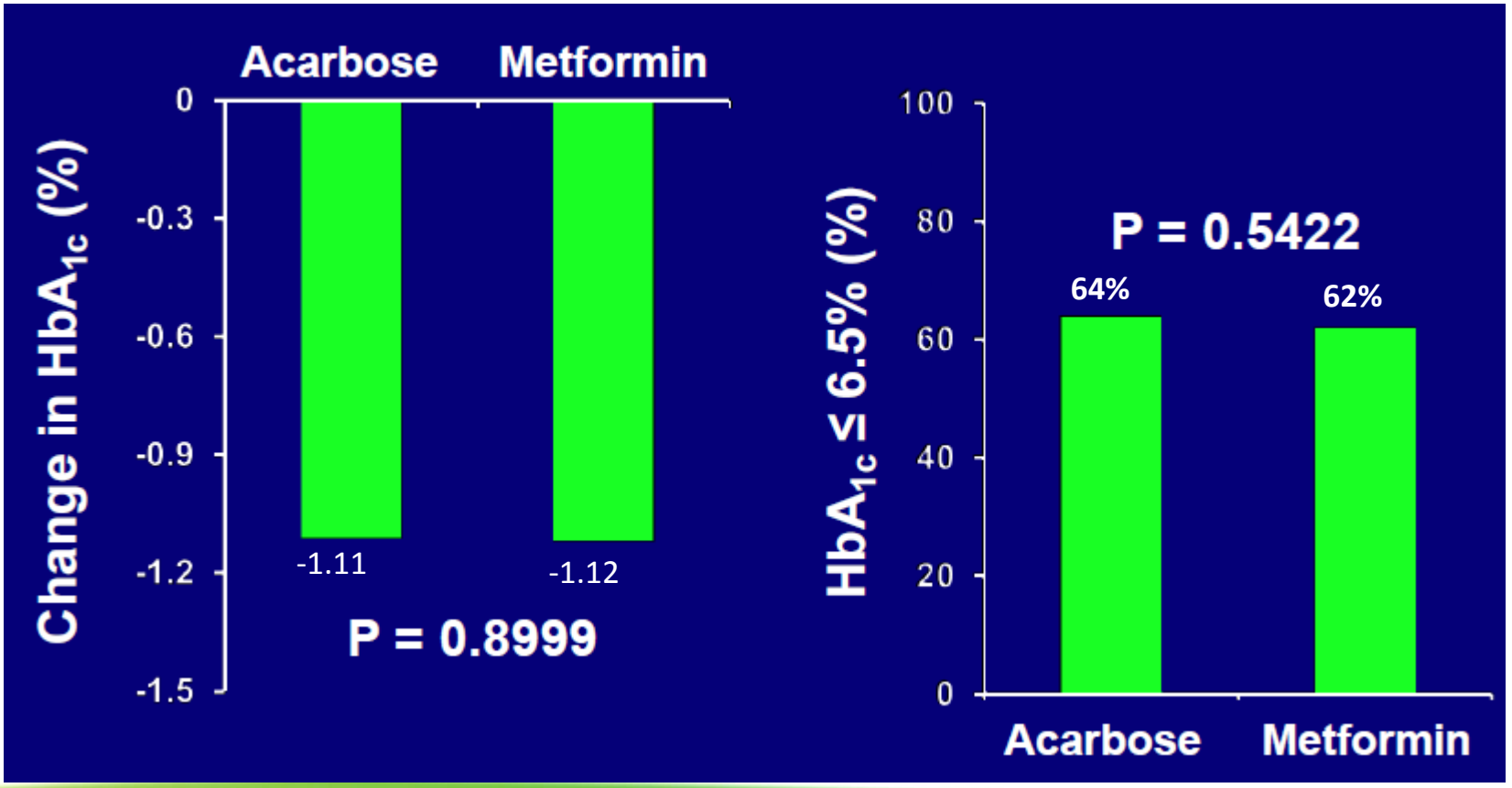
Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial



Lancet Diabetes Endocrinol 2014; 2: 46–55

At 48 Weeks, No Significant Difference in Change from Baseline HbA1c Between Acarbose and Metformin

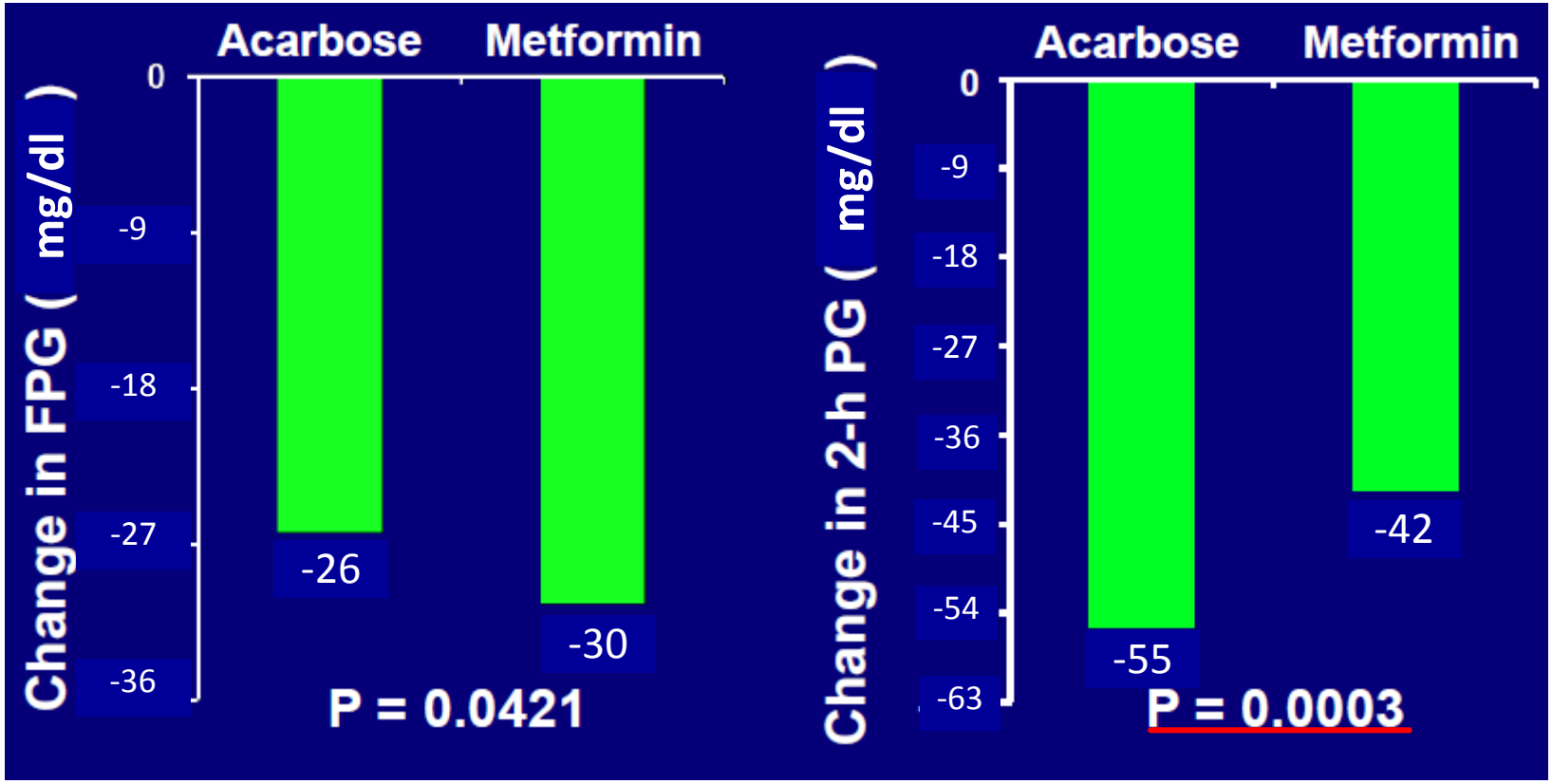
Mean baseline HbA1c 7.5%



Lancet Diabetes Endocrinol 2014; 2: 46–55

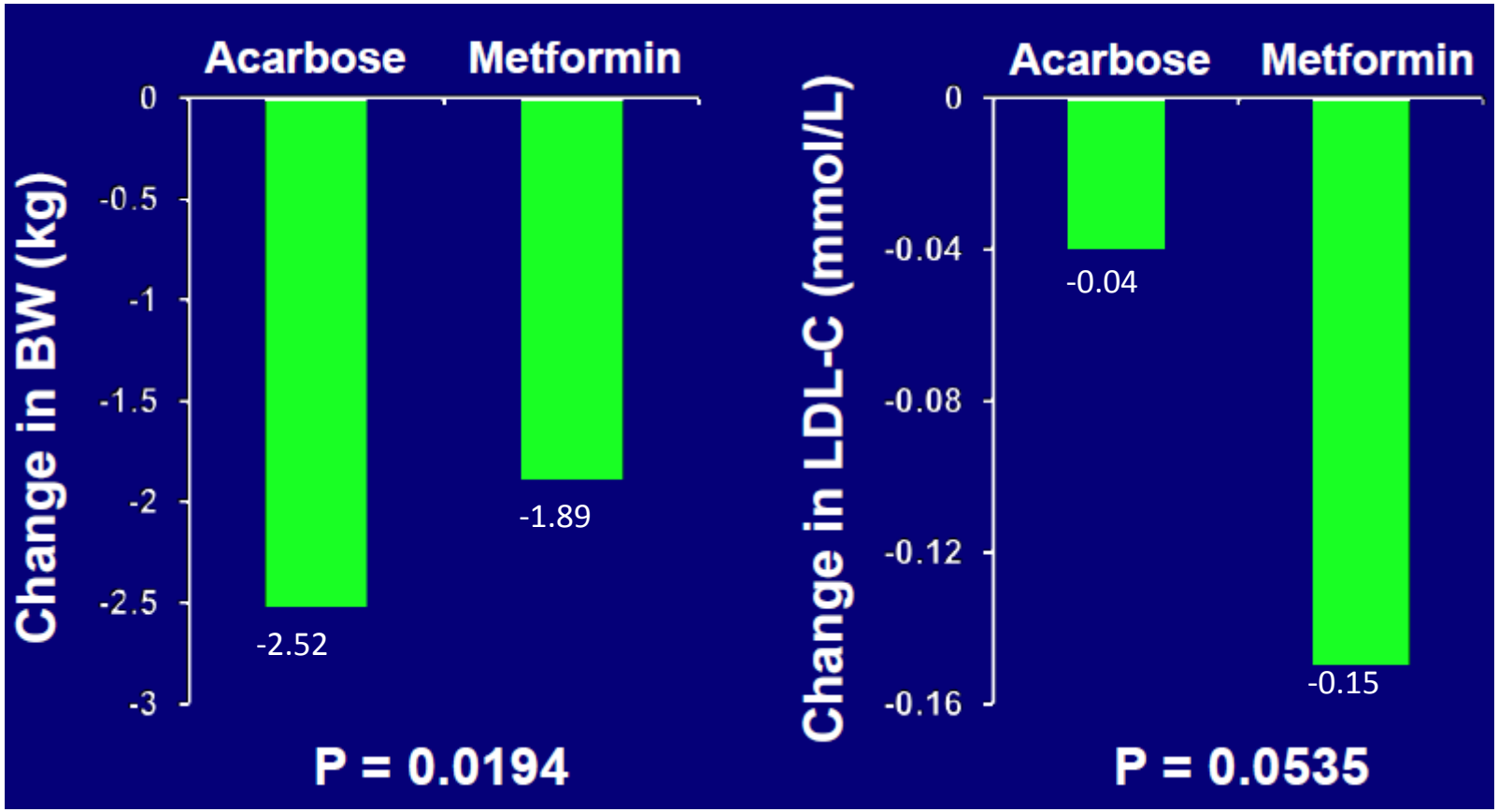
Reduction in 2-h Postprandial Glucose was Greater in Patients Taking Acarbose than Taking Metformin

Mean baseline HbA1c 7.5%



Lancet Diabetes Endocrinol 2014; 2: 46–55

At 48 Weeks, Patients Taking Acarbose Had Lost More Weight Than Metformin



Lancet Diabetes Endocrinol 2014; 2: 46–55

Start Low, Go Slow Strategy Reduce GI Side Effect

	Acarbose (n=371)	Metformin (n=366)
Serious adverse events		
All	6 (2%)	7 (2%)
Nervous system disorders	1	2
Injury, poisoning, and procedural complications	0	4
Respiratory, thoracic, and mediastinal disorders	0	1
Infections and infestations	1	0
General disorders and administration site conditions	1	0
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	2	0
Surgical and medical procedures	1	0
Adverse events*		
Gastrointestinal disorders	100 (27%)	107 (29%)
Infections and infestations	107 (29%)	97 (27%)
Metabolism and nutrition disorders	47 (13%)	46 (13%)
Nervous system disorders	34 (9%)	37 (10%)
Musculoskeletal and connective tissue disorders	9 (2%)	19 (5%)
Treatment-related adverse events*†		
Gastrointestinal disorders	64 (17%)	56 (15%)
Hypoglycaemic events‡		
All	2 (1%)	4 (1%)
Possibly related	1	4
Definitely related	1	0

Data are n (%) and are based on the safety analysis set (all patients randomly assigned to treatment groups with documented safety data). Hypoglycaemic events were reported separately and not included as adverse events. *Reported by more than 5% of either group. †Treatment-related adverse events were those judged to be "possibly related", "probably related", or "definitely related". ‡All hypoglycaemic episodes were reported in patients receiving monotherapy only.

Table 3: Adverse events and hypoglycaemic events in each treatment group, by system organ class

Glucobay 必須在用餐前，
以少量液體，整顆吞服，或用餐時與前數口食物一起咬碎吞下[3]

Ref: Lancet Diabetes Endocrinol 2014; 2: 46–55

Conclusion of MARCH Trial

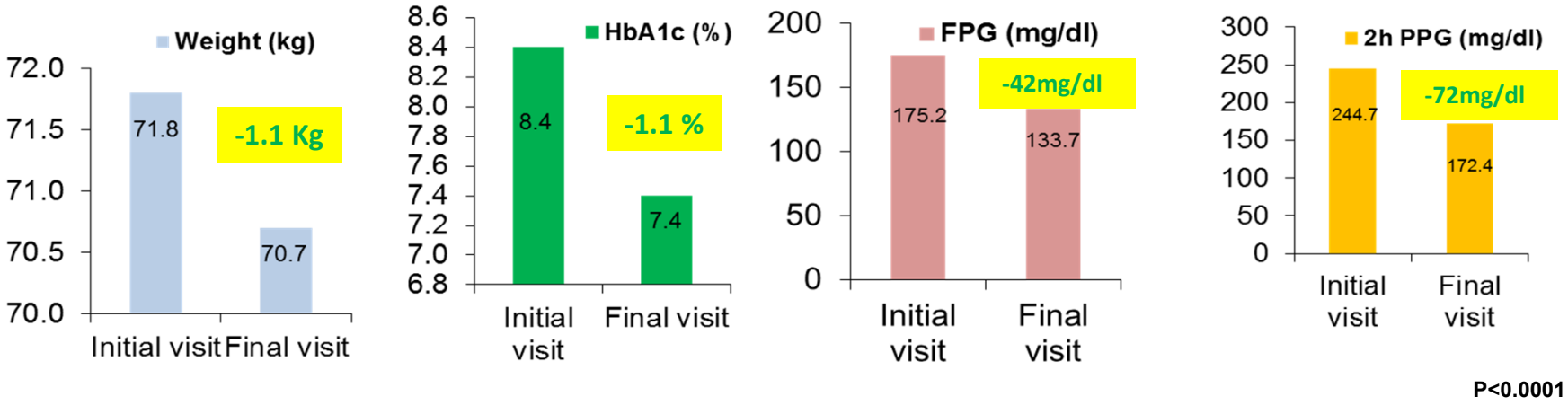
In Chinese patients newly diagnosed with T2DM:

- Glucobay (100mg tid) is non-inferior to Metformin in terms of A1c control
- Glucobay is superior to metformin with respect to **weight control** and **change in insulin sensitivity**
- While patients with **exaggerated postprandial excursion** can be treated with an **α-glucosidase inhibitor as an alternative therapy** before cardiovascular benefits of Glucobay are validated and confirmed in ongoing studies

Lancet Diabetes Endocrinol 2014; 2: 46–55

Real Practice Data with Glucobay from Eight Asian Countries

Observational study in **China**, **Middle-East, Indonesia, Morocco, Pakistan, Philippines, Poland and Taiwan**
14,574 patients with type 2 diabetes (74.1% previously treated with glucose-lowering agent); Final visit = **11.3 weeks** (mean)



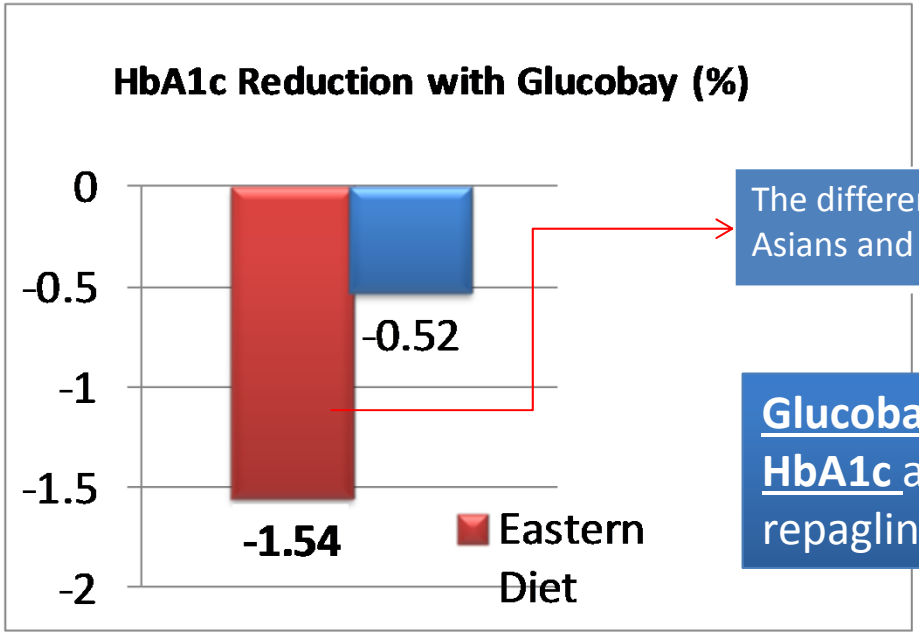
P<0.0001

Conclusion: Glucobay therapy was efficacious and well tolerated in daily life in patients with T2D

Li C et al. *Diabetes Res Clin Pract* 2011;92:57-64

Recent Meta-Analysis Shows More HbA1c Reduction in Eastern Diet Populations

Systematic Meta-analysis of 46 studies



The difference in HbA1c reduction with Glucobay therapy between Asians and Western population is as high as 1.02% ($P < 0.00001$)

Glucobay monotherapy had a similar ability to reduce HbA1c as sulfonylureas, metformin, and nateglinide/ repaglinide, regardless of diet type

Qibo Zhu, et al. Clin Ther. 2013;35:880–899

Mr. Kuo

69 years of age

BMI 27.1 kg/m^2

Hypertension

Fatty liver
CKD

Light to moderate
diet and exercise

DM duration
>15 years

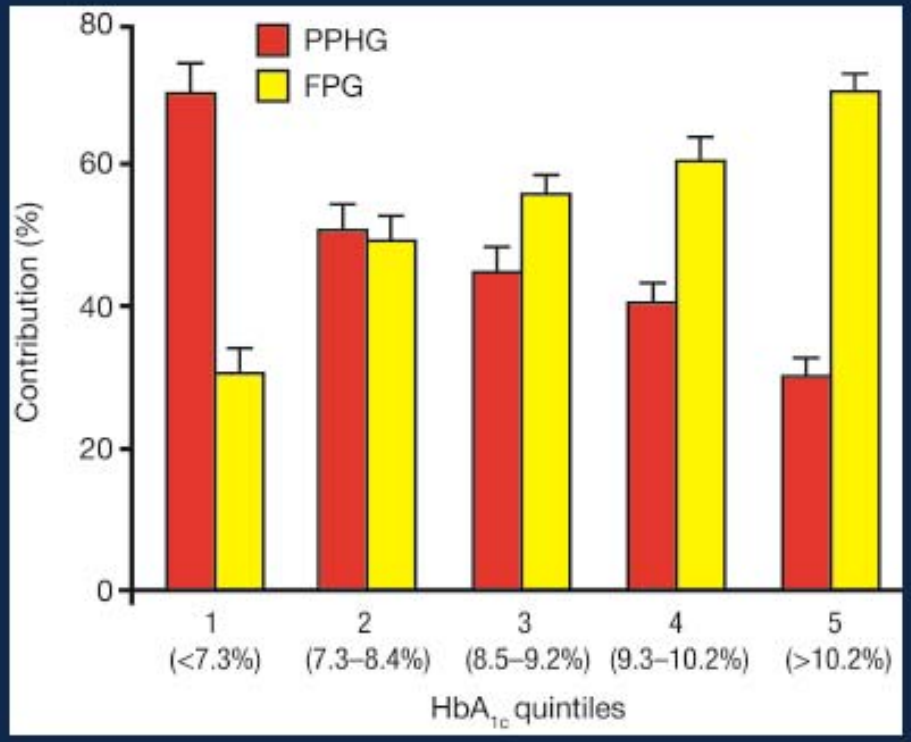
Glimipiride + Metformin
(Amaryl M) 2/500
1# bid

HbA1c 7.4%
Creatinine:1.7mg/dl
eGFR=29
SMBG (AC)-80+
SMBG (Pc)- 200-300+

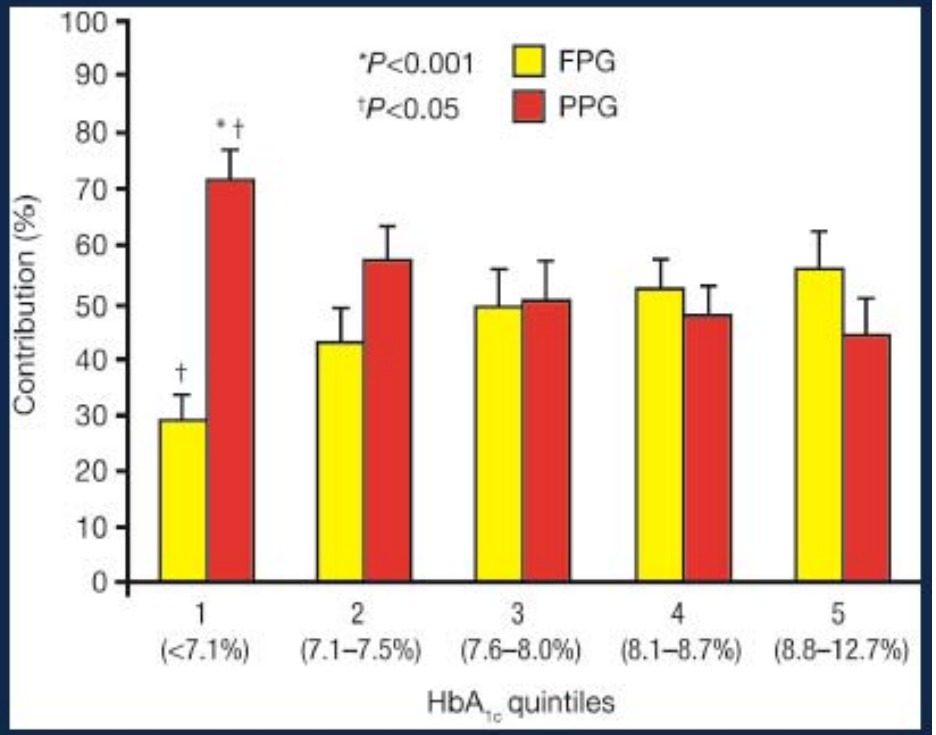
PPG contributes to HbA_{1c}

Different Greatly between Caucasians and Asian Type 2 Diabetes

Western T2D patients
(n=290)[1]



Asian T2D patients
(n=121)[2]



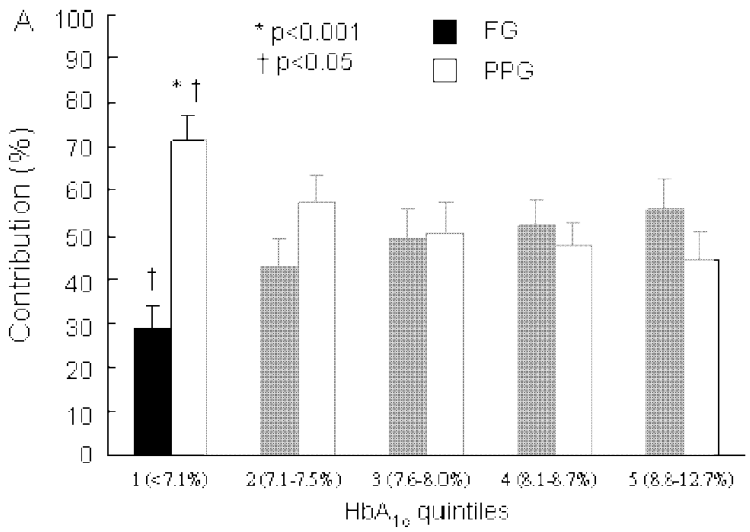
[1]Monnier L, et al. Diabetes Care 2003;26:881-5;

[2]Wang JS, et al. Diabetes Metab Res Rev 2011;27:79–84

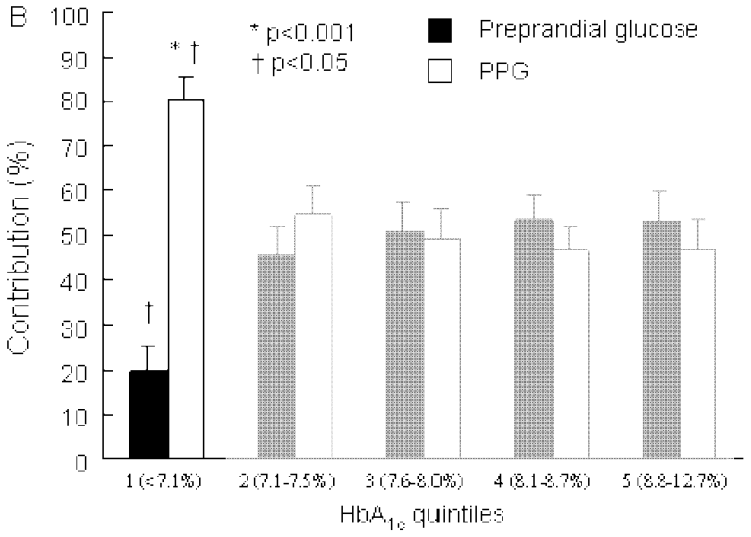
PPG has a dominant contribution to overall and 4-h postprandial hyperglycemia in the lowest HbA_{1c}

- The **relative contribution** of **PPG** to **24-h** and **4-h** hyperglycemia was significantly **higher** than that of **FG** in the lowest quintile of HbA1c ($p < 0.001$) in **Asian** T2DM patients.

Relative contributions of PPG to 24-h hyperglycemia



Relative contributions of PPG to 4-h hyperglycemia after meals

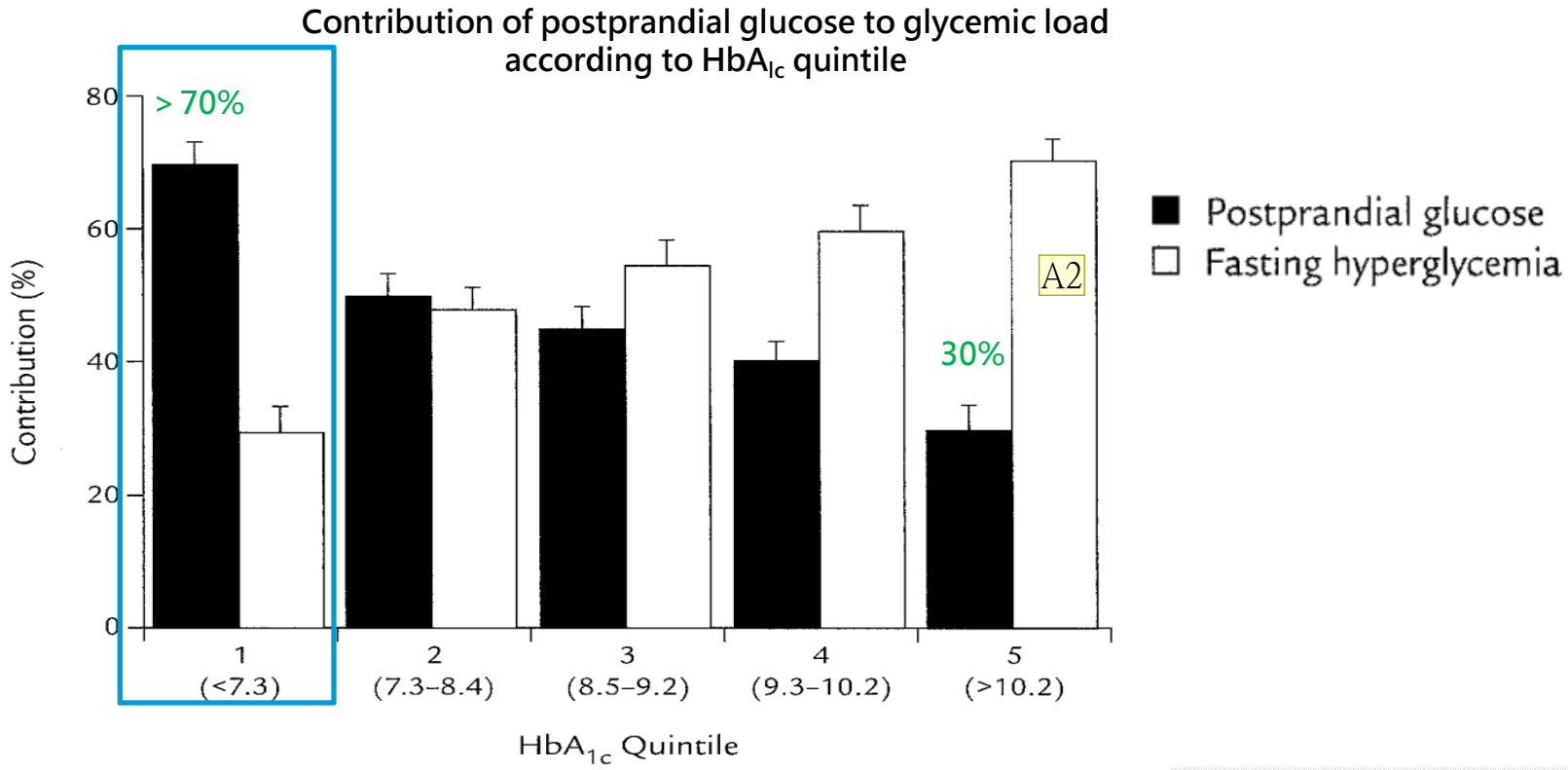


PPG = postprandial glucose; HbA_{1c} = hemoglobin A_{1c}

Diabetes Metab Res Rev 2011; 27: 79–84.

PPG is a predominant contributor to overall hyperglycemia in subjects with HbA_{1c} < 7.3%

- **PPG** could be a **clinically relevant guide** to glycemic control in the management of individuals with T2DM



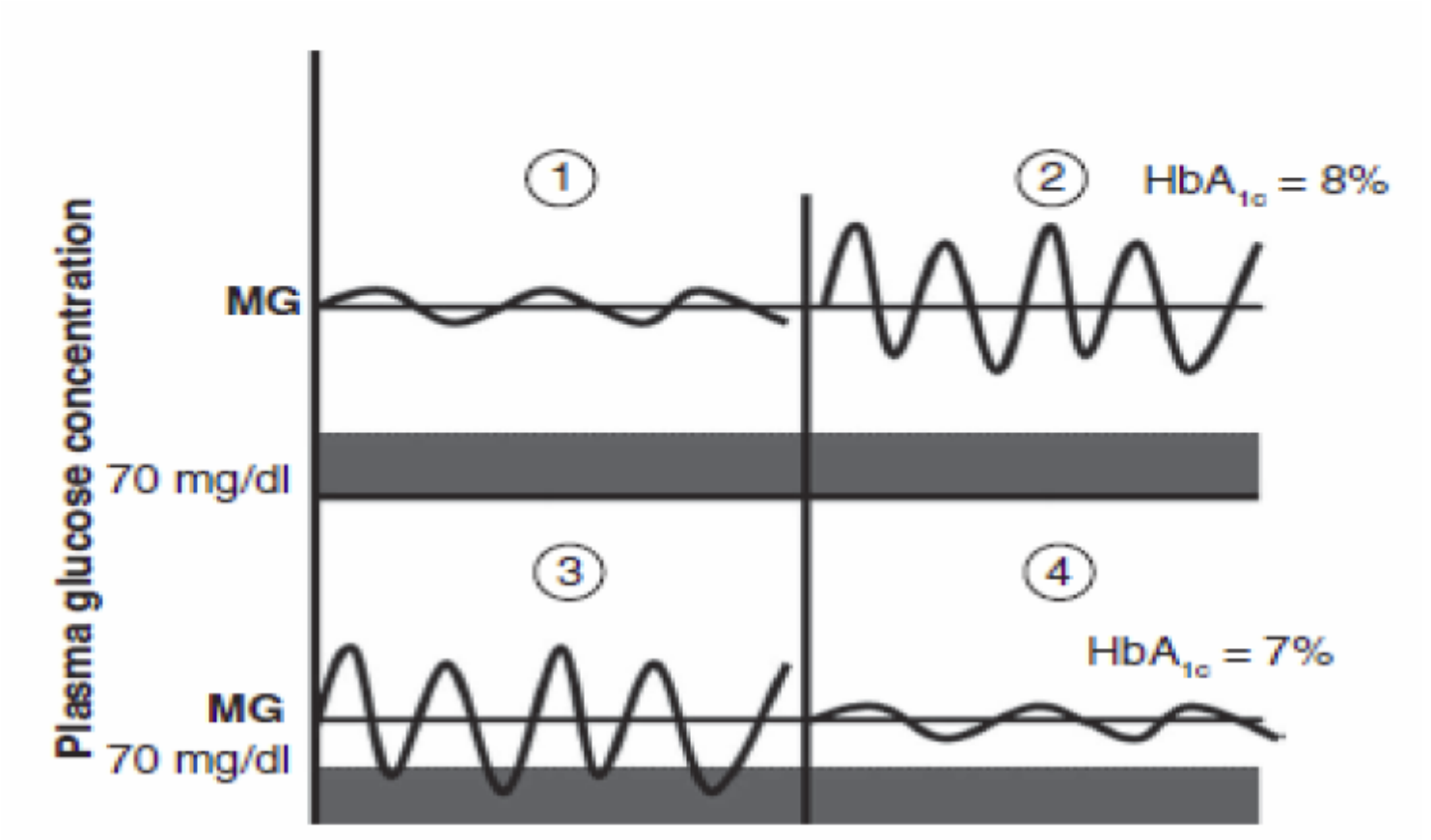
T2DN = type 2 diabetes mellitus; PPG = postprandial glucose; HbA_{1c} = hemoglobin A_{1c}

Clin Ther. 2005;27 Suppl B:S42-56.

A2

file:
Postprandial glucose regulation new data and new implications
page s44
Figure1
ASUS, 2018/3/9

An illustration of four clinical situations of four theoretical patients with different levels



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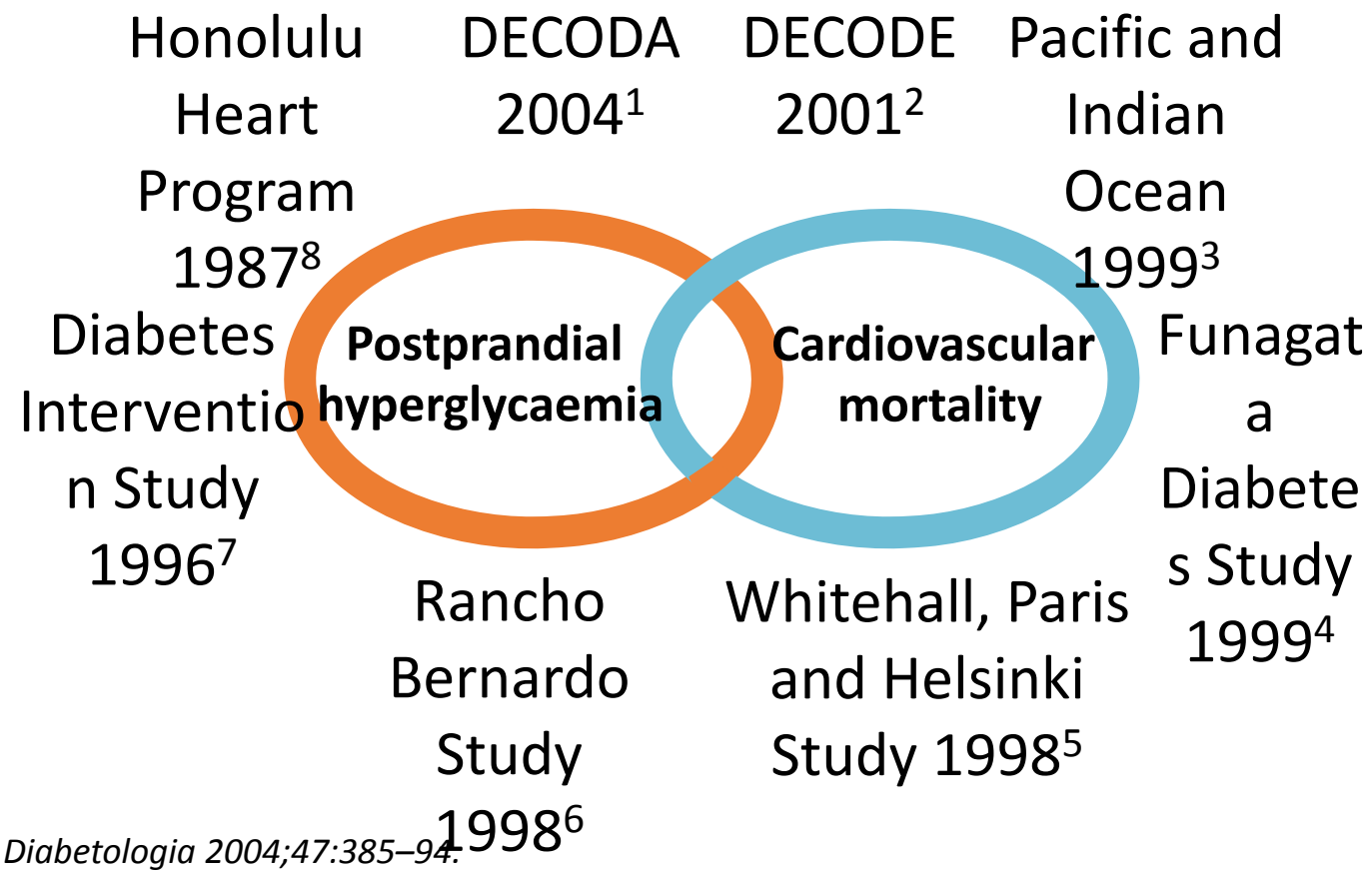
Diabetes and Metabolism 41(2015)6S9-6S15

Post-challenge Hyperglycaemia and CHD Mortality



1. *Nakagami T, et al. Diabetologia 2004;47:385–94.*
2. *DECODE. Diabetes Care 2003;26:688–96.*
3. *Shaw J, et al. Diabetologia 1999;42:1050–54.*
4. *Tominaga M, et al. Diabetes Care 1999;22;920–24.*
5. *Balkau B, et al. Diabetes Care 1998;21:360–67.*
6. *Barrett-Connor E, et al. Diabetes Care 1998;21:1236–39.*
7. *Hanefeld M, et al. Diabetologia 1996;39:1577–83.*
8. *Donahue R. Diabetes 1987;36:689–92.*

DECODA: Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Asia

DECODE: Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Europe

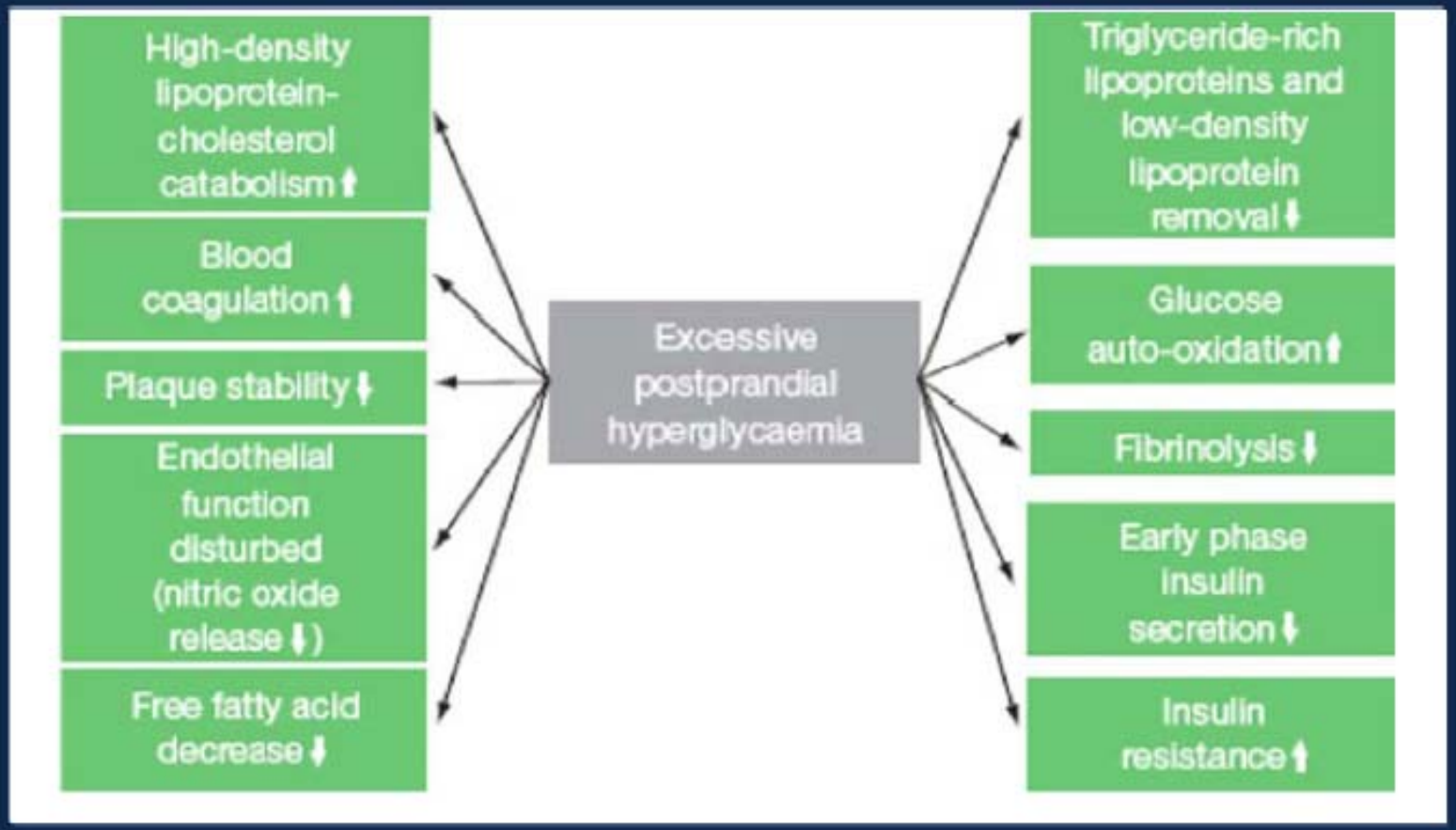
Postprandial Blood Glucose Predicts Cardiovascular Events and All-Cause Mortality in Type 2 Diabetes in a 14-Year Follow-Up

Lessons from the San Luigi Gonzaga Diabetes Study

- Consecutive type 2 diabetic patients (n = 505) followed up by diabetes clinic from baseline (1995) .
- Measurement : All-cause mortality and the first cardiovascular events occurring
- Glycemic control parameters :
  - FPG
  - 2 h PPG after breakfast
  - 2 h PPG after lunch
  - Blood glucose before dinner
  - A1C
  - 14-year follow-up
- Result : In type 2 diabetes, both PPG and A1C predict cardiovascular events and all-cause mortality in a long-term follow-up

Cavalot F, et,al, Diabetes care 2011 ; 34:2237–2243

Mechanisms by which PPHG could increase CVD risk



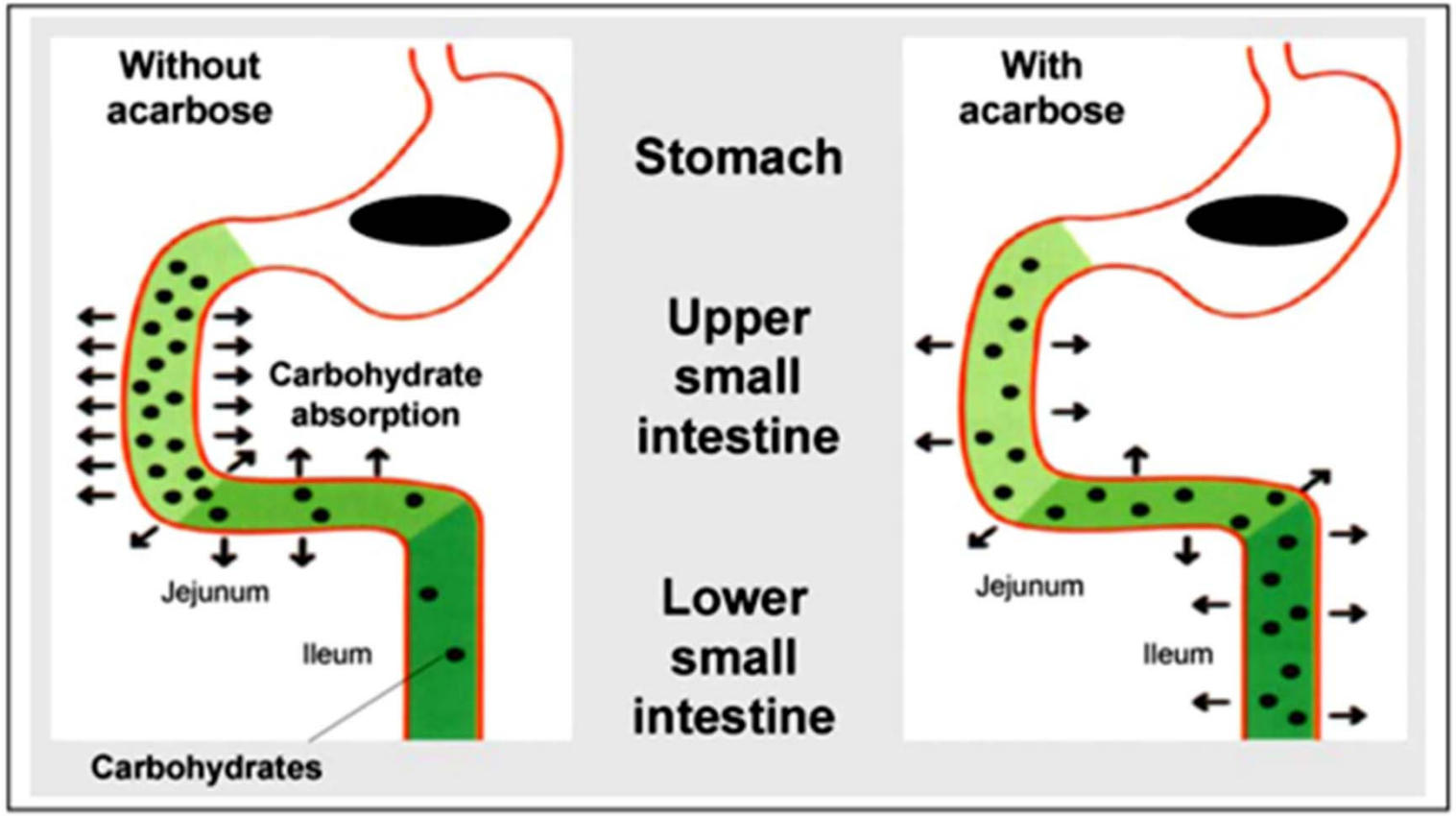
- PPG management is central to the achievement of long-term glycaemic control and an essential part of CVD prevention in IGT and type 2 diabetes.

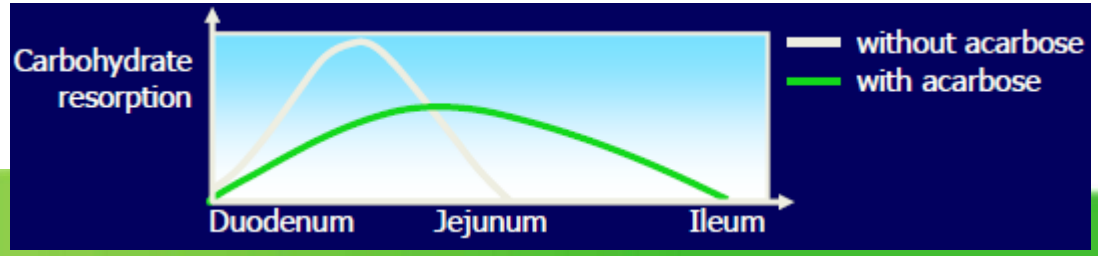
Sheu WHH, et,al, Diabetes Res Clin Pract 2011

Commonly used antidiabetic agents

	Mode of Action	Side Effects
Metformin	**↓FPG: ↓PPG, insulin sens.**	**G.I.**
SU's	**↓FPG: ↓PPG insulin secret.**	**Weight gain, hypos**
Meglitinides	**↓PPG: insulin secret.**	**Weight gain, hypos**
TZD's	**↓FPG ↓PPG : insulin sens.**	**Weight gain, edema, heart failure, bone fractures**
AGI's	**↓PPG: delay GI absorp.**	**G.I.**
GLP-I agonists	**↓PPG: insulin secret.** **delay gastric emptying** **suppress glucagon**	**Nausea/vomiting** **Pancreatitis?** **Thyroid tumors?** **Renal toxicity?**
DPP-4 inhibitors	**↓PPG ↓FPG : insulin secret.** **Suppress glucagon**	**URI** **UTI** **Pancreatitis**
Insulin	**↓FPG/ ↓PPG**	**Weight gain, hypos**

Alpha-Glucosidase Inhibitors
Mode of Action





Standl E, Schnell O. Diab Vasc Dis Res 9: 163-169, 2012

Mr. Kuo

69 years of age

BMI 27.1 kg/m^2

Hypertension

Fatty liver
CKD

Light to moderate
diet and exercise

DM duration
>15 years

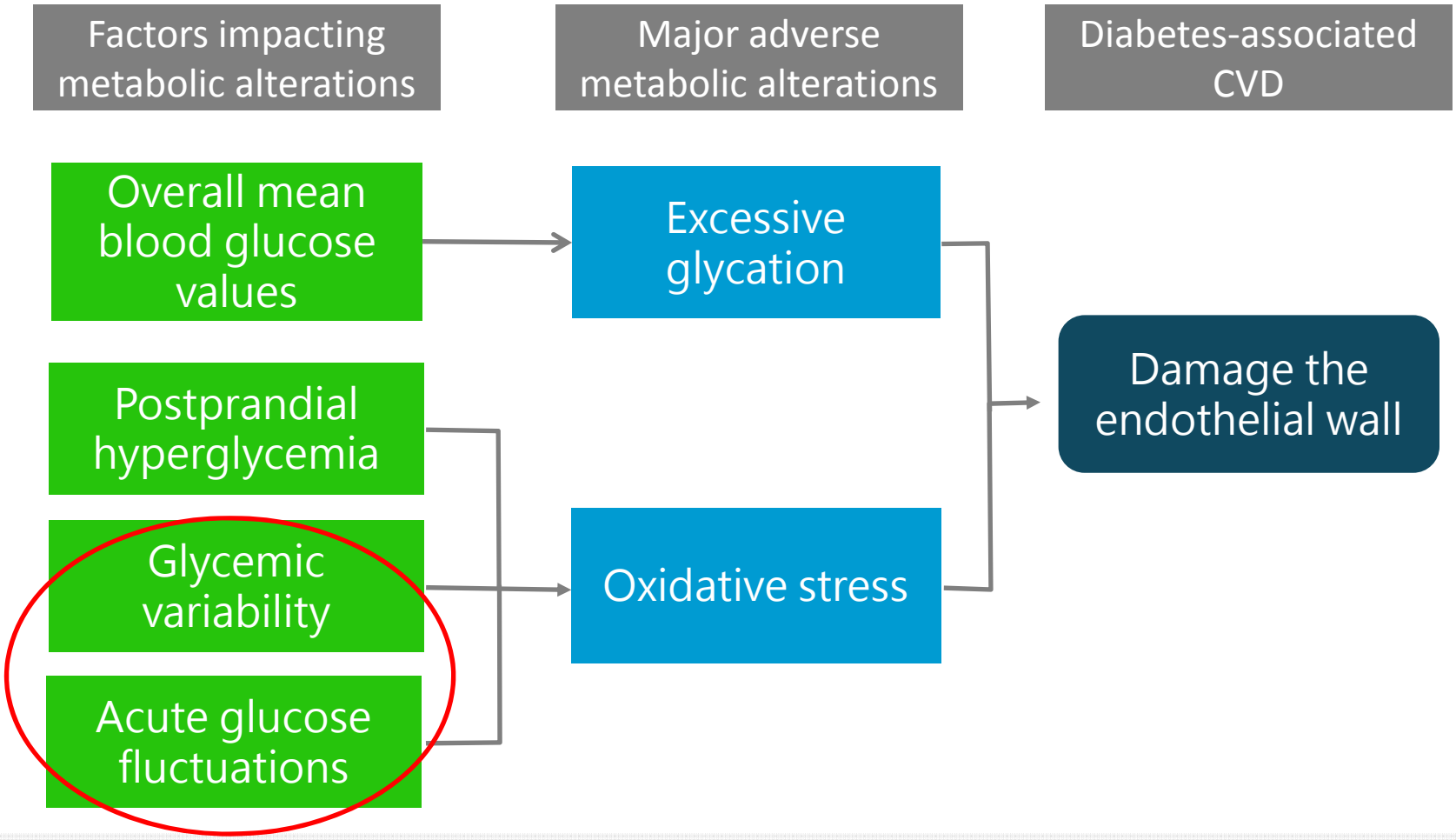
Glimipiride + Metformin
(Amaryl M) 2/500
1# bid-→
Diamicron MR 1# bid ac
Actos 1# qd
Glucobay 100mg 1# tidac

HbA1c =7.4→ 6.9%
Creatinine:1.7→1.54mg/dl
eGFR=29→35
SMBG (AC)-80+
SMBG (Pc)- 200-300→160+

The Implication of MAGE

Diabetes-associated cardiovascular disease

A10



CVD = cardiovascular disease

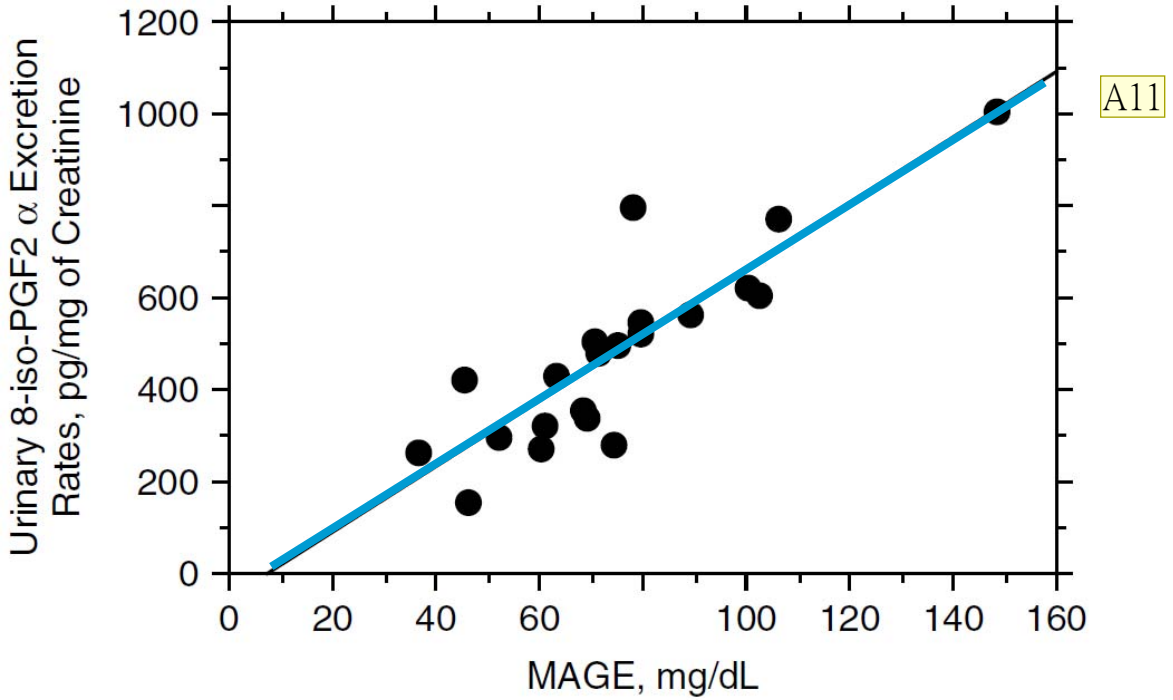
Diabetes Metab Res Rev 2009; 25: 393–402.

A10

file:
Integrating glycaemic variability in the glycemic disorders of T2DM
page 395
The role of postprandial hyperglycaemic variability in oxidative stress 黃底字
ASUS, 2018/3/20

Glucose fluctuation has strong correlation with oxidative stress activation

Linear correlation between 24-hour urinary excretion rates of 8-iso PGF2α and MAGE



- Urinary excretion rates of 8-iso $PGF_{2\alpha}$ have the strongest correlation was found with MAGE.

MAGE = mean amplitude of glycemic excursion;
8-iso $PGF_{2\alpha}$ = 8-iso-prostaglandin $F_{2\alpha}$

Diabetes Care. 201235:2076-2082. ; JAMA. 2006 ;295:1681-1687.

A11

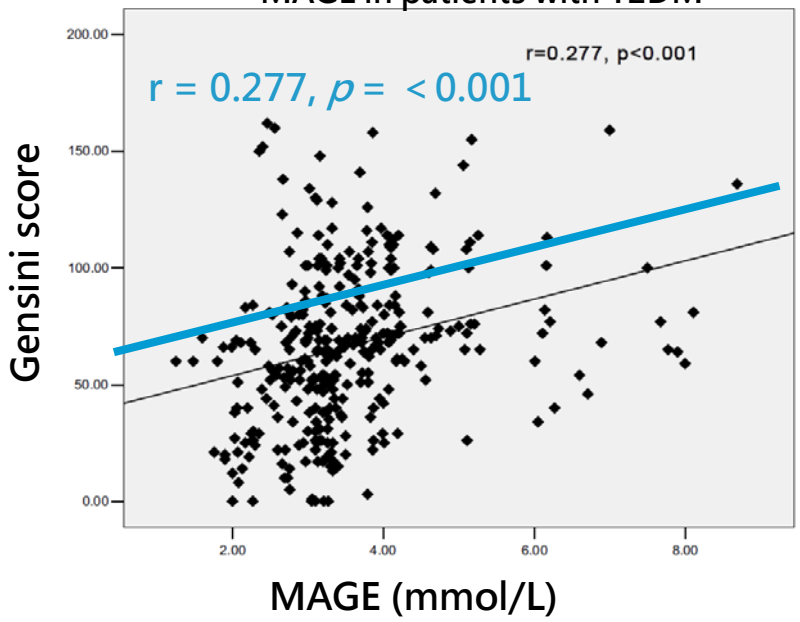
file:
Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia
page 4 Figure2
ASUS, 2018/3/20

Glucose excursions is associated with CAD in T2DM

- **Gensini score** correlated **positively** with the level of **MAGE**
- **MAGE** is an independent **risk factor** for the severity of **CAD**

Simple linear correlation of Gensini score and MAGE in patients with T2DM

A13



Multivate analysis of determinations of Gensini score

A14

Independent variables	Unstandardized coefficients		Standardized coefficients β	t	p value
	B	SE			
Constant	-55.587	14.441		-3.849	0
Age	1.004	0.181	0.270	5.533	0.000
MAGE	7.010	1.466	0.237	4.783	0.000
hs-CRP	0.468	0.148	0.159	3.164	0.002
HbA_{1c}	2.641	1.145	0.114	2.306	0.022
Adjusted multiple R^2	0.191				0

- **Gensini score** assesses the severity of **CAD**: it grades narrowing of the lumen of the coronary artery

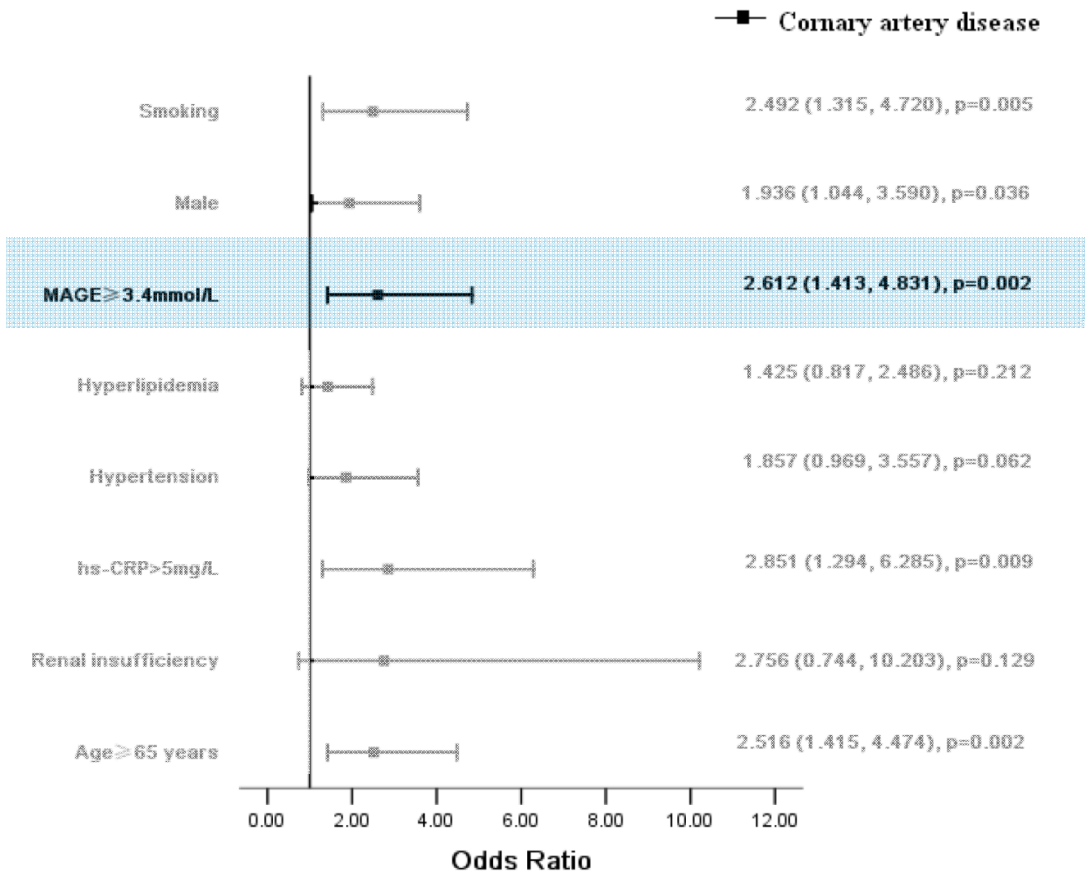
T2DM = type 2 diabetes mellitus; MAGE = mean amplitude of glycemic excursion;
CAD = coronary artery disease

Cardiovasc Diabetol. 2011;10:19.

A13 file:
Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes.
page5 Figure 2紅框
ASUS, 2018/3/20

A14 ASUS 2018/3/20
file:
Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes.
page6 Table 2
ASUS, 2018/3/20

MAGE ≥ 3.4 mmol/L is an independent predictor for the presence of CAD



A15

Multivariate analysis for independent determinants of CAD

CAD = coronary artery disease

Cardiovasc Diabetol. 2011;10:19.

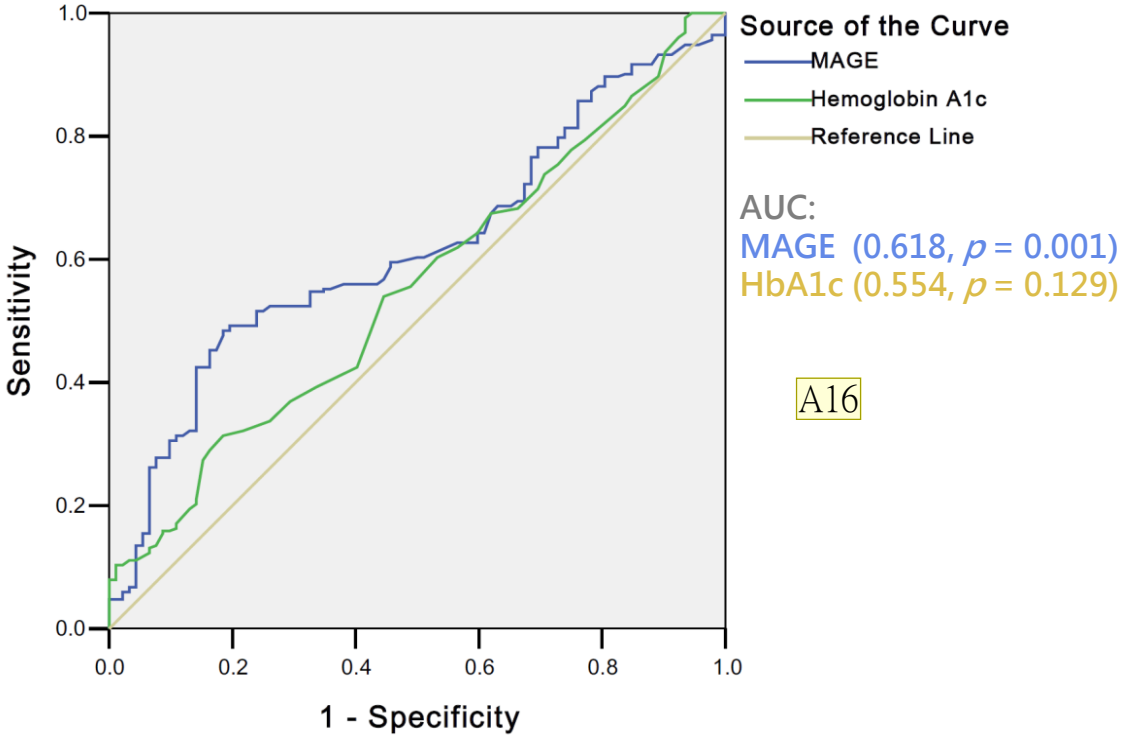
A15

file:
Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes.
page6 Figure3
ASUS, 2018/3/20

Glucose excursion contribute to generation of atherosclerosis

- **Glucose excursion** is an important **contributing factor** in the **severity** of **CAD**, which is independent of the average level of blood glucose.

Receiver-operating characteristic (ROC) curve for MAGE and HbA_{1c} in predicting CAD



CAD = coronary artery disease

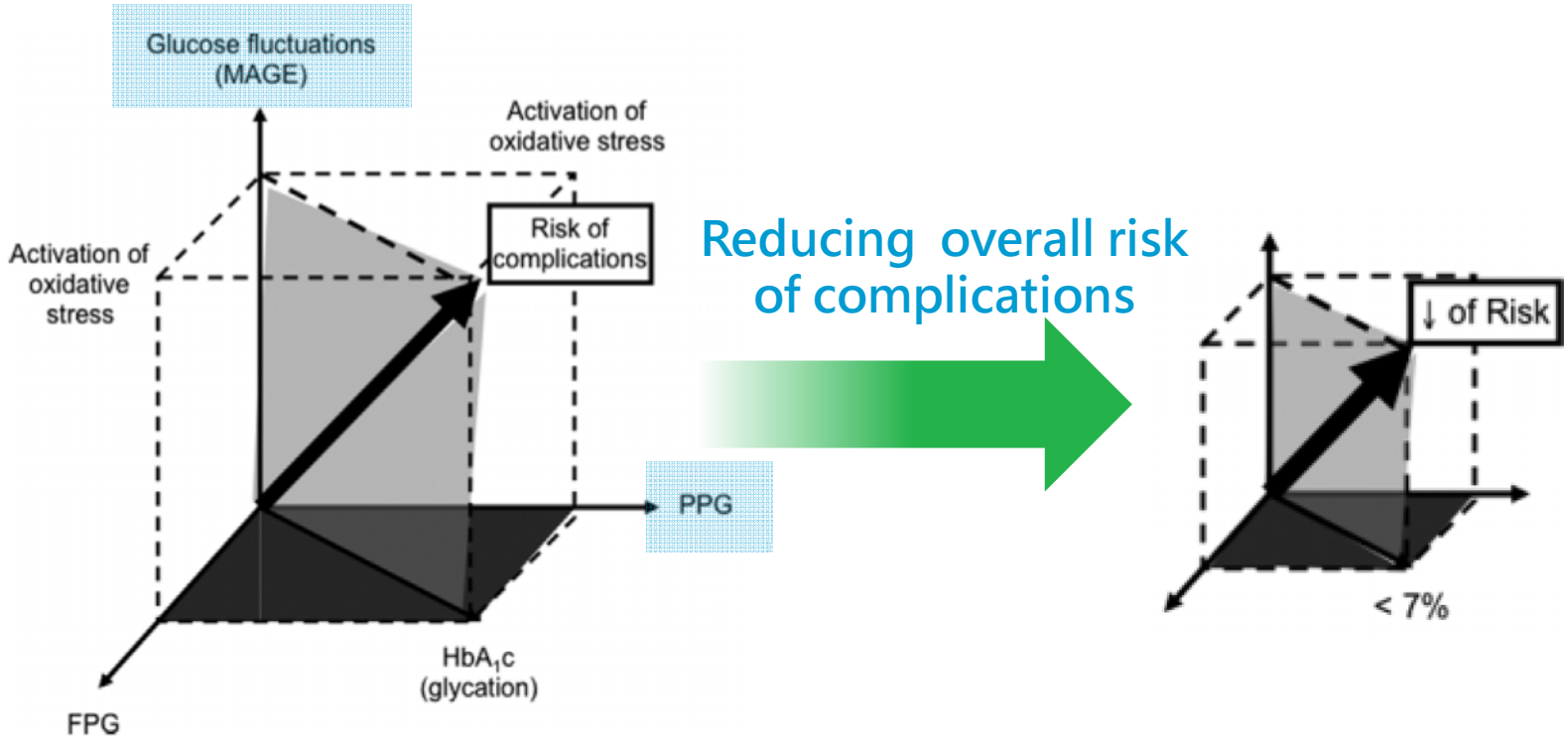
Cardiovasc Diabetol. 2011;10:19.

A16

file:
Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes.
Page 7 Figure4
ASUS, 2018/3/14

Treatment strategy: From the glucose triad to the glucose tetrad

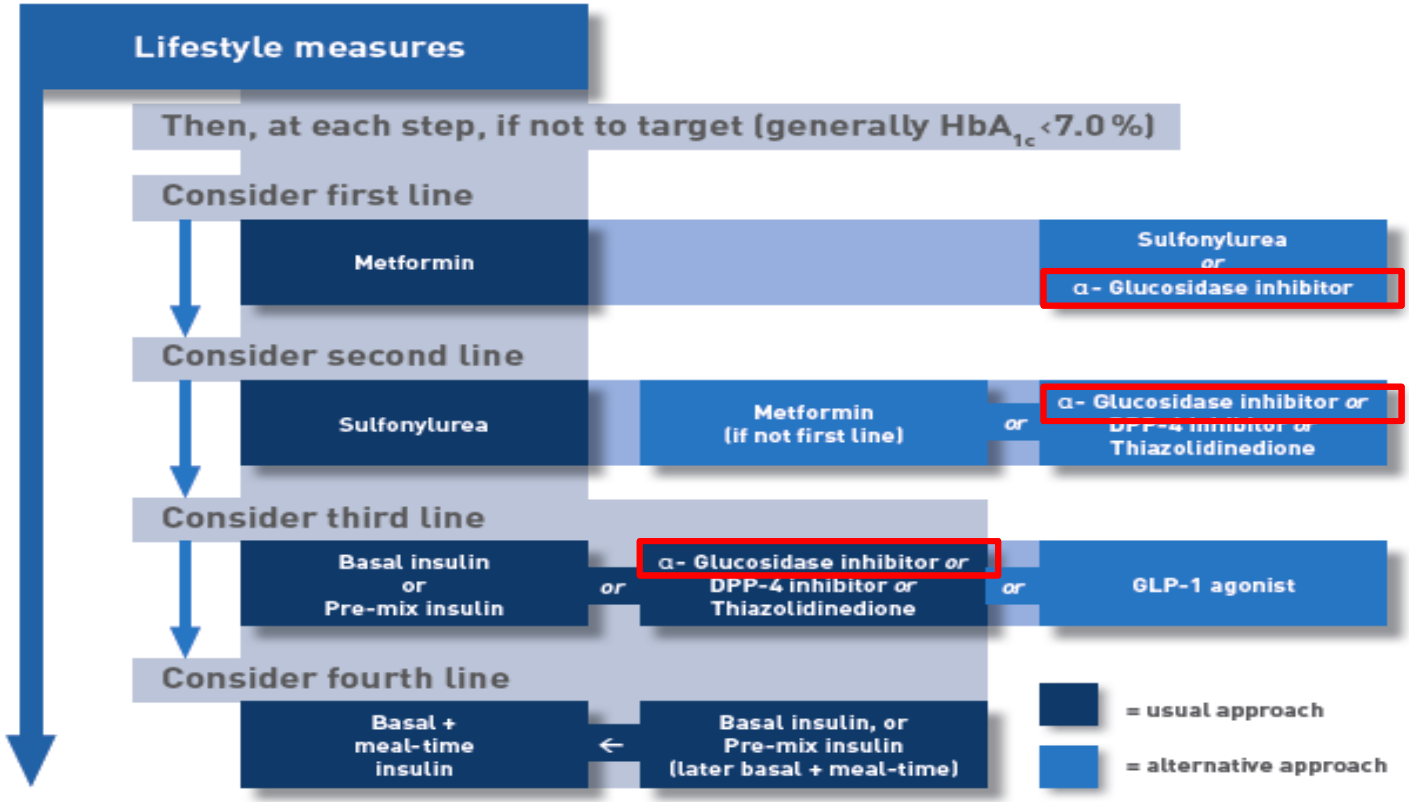
- The "glucose tetrad" takes the concept of the glucose triad a step further and introduces glucose fluctuations (i.e. MAGE index) into the strategy



FPG = fasting plasma glucose; PPG = postprandial glucose
MAGE = mean amplitude of glycemic excursion

Diabetes Care. 201235(10):2076-82.

2012 IDF Diabetes Treatment Algorithm



Source:2012 IDF treatment algorithum

IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care -2017

Initial pharmacologic treatment

5.1 Monotherapy

Previous versions of some guidelines considered the patient's phenotype to decide the first drug. In general, for overweight patients with T2D, metformin was the best option, whereas for lean patients, particularly Far East Asians, SU or AGI was preferred.

Now all the guidelines recommend metformin as the first choice for initiating pharmacologic treatment in people with T2D. Titration from 500 to 2000 mg per day, administration with or after meals and use of extended-release (XR) preparations can maximize tolerance. Metformin dose should be reduced to 1000 mg per day when renal function is in stage 3A and contraindicated when renal function is in stage 3B or above (Table 3 and Section 8.2.2).

In the event of definitive metformin intolerance or when it is contraindicated, there are discrepancies on which is the best choice to replace it. Some guidelines consider that any GLD with approved indication as monotherapy can be used and the choice would depend on the profile of the drug (efficacy, safety and local cost-effectiveness) and the preference of the patient (compliance, quality of life and affordability). This may be cumbersome at the primary care level considering the limited time to make decisions, and therefore some guidelines specify the best options. SU, AGI or DPP4 inhibitor is the first option, but one guideline (AACE) considers that weight loss is a main consideration and therefore GLP-1 receptor agonists or SGLT2 inhibitors should be the first options. Side effects must be considered, particularly hypoglycemia with SU, and therefore glibenclamide/glyburide is not recommended as it is associated with the greatest risk for hypoglycemia. When starting an SU, the patient must learn how to prevent, recognize and treat hypoglycemia.

Recommendations: Monotherapy

- Metformin is the preferred choice to start monotherapy and the PCP should make efforts to maximize tolerance by titrating the dose from 500 to 2000 mg per day, prescribe it with or after meals and use XR preparations, if necessary.
- When metformin is not tolerated, other GLDs can be used, preferably SU (except glibenclamide/glyburide), AGI or DPP4 inhibitor.

- **Metformin is the preferred choice to start monotherapy and the PCP should make efforts to maximize tolerance by titrating the dose from 500 to 2000 mg per day, prescribe it with or after meals and use XR preparations, if necessary.**
- **When metformin is not tolerated, other GLDs can be used, preferably SU (except (libenclamide/glyburide), AGI or DPP4 inhibitor.**

IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care -2017

Add-on therapy

6.1 Dual therapy

When monotherapy with metformin (or its replacement) is not sufficiently effective to reach the HbA1c target, or it fails afterwards, a second GLD is recommended by all guidelines.

The considerations for the choice of the second drug are the same as for initial combination. Therefore, the best choices of add-on to metformin are SUs (except glibenclamide/glyburide), DPP4 inhibitors or SGLT2 inhibitors. Both DPP4 inhibitors and GLP1 receptor agonists have been reported to be more effective in Asian than in white Europid patients in several meta-analyses. AGI is also a preferred choice to add to metformin in Asian patients. Gastrointestinal side effects may be potentiated when combining an AGI with metformin, but less severe if combined with XR metformin. A GLP1 receptor agonist may also be considered if there is a concern about an insufficient rate of weight loss.

The patient should not remain longer than 3 to 6 months with an HbA1c above target before adding a second GLD.

Table 3(next page) describes the main risks and benefits of the common GLDs.

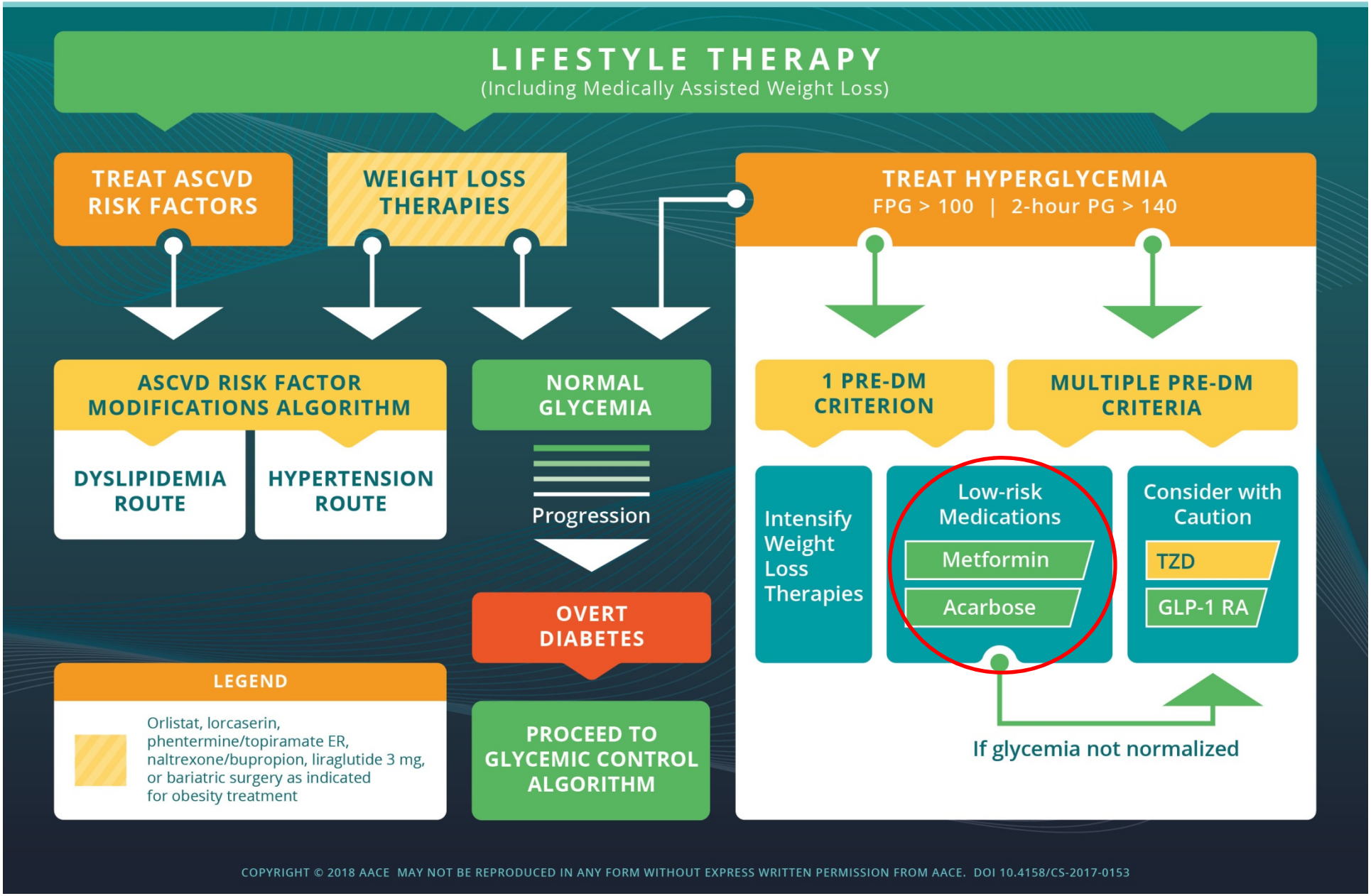
Recommendations: Dual therapy

- A second GLD should be added if monotherapy with metformin (or its replacement) is not sufficiently effective to reach the HbA1c target or fails afterwards.
- The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP4 inhibitor or a SGLT2 inhibitor. An AGI can be used as well. GLP1 receptor agonist can be used if weight loss is a priority and the drug is affordable.
- The PCP may consider patient's profile (age, body weight, complications and duration of disease) when choosing the best GLD to add.

- **The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP4 inhibitor or a SGLT2 inhibitor. An AGI can be used as well. GLP1 receptor agonist can be used if weight loss is a priority and the drug is affordable.**

Prediabetes Algorithm

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



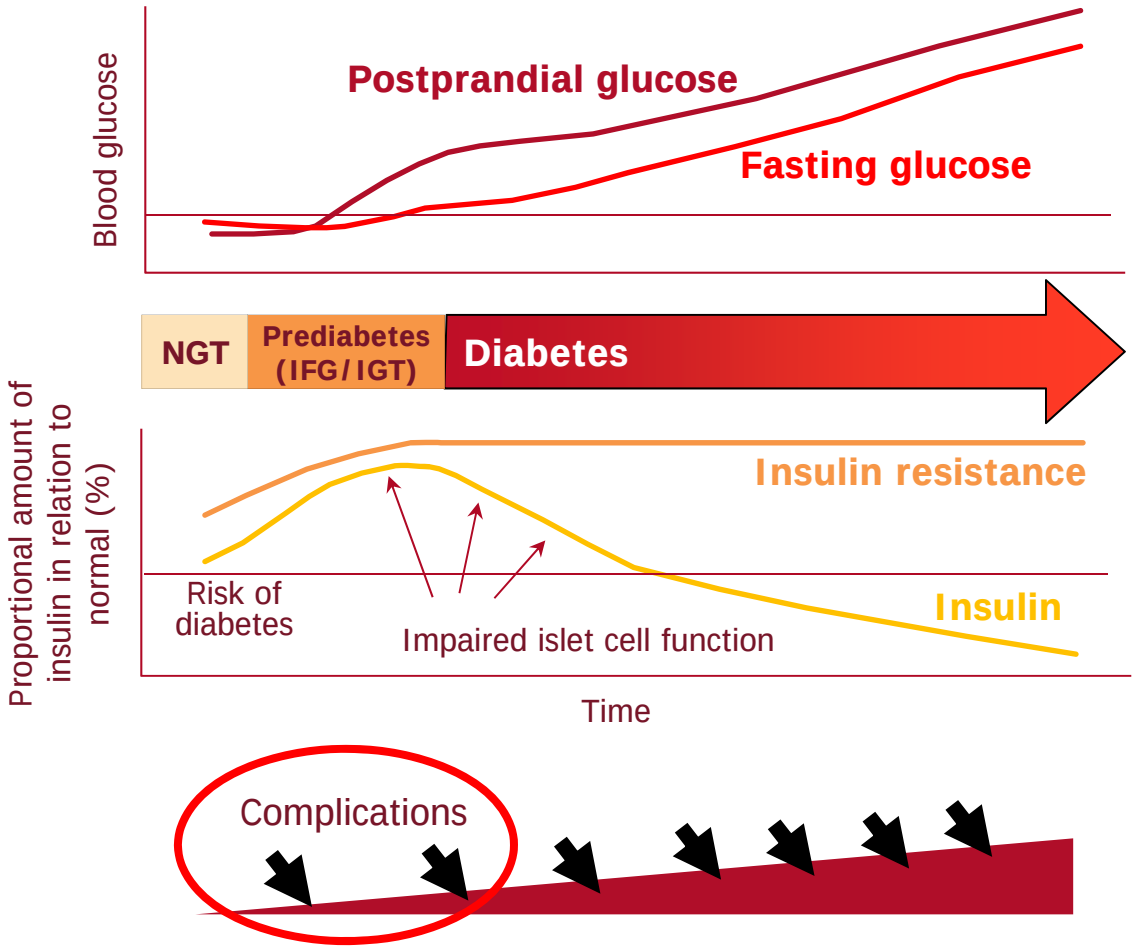
 DOI 10.4158/CS-2017-0153

What is the Impact of Uncontrolled Diabetes?

- A high percentage of patients develop microvascular 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.

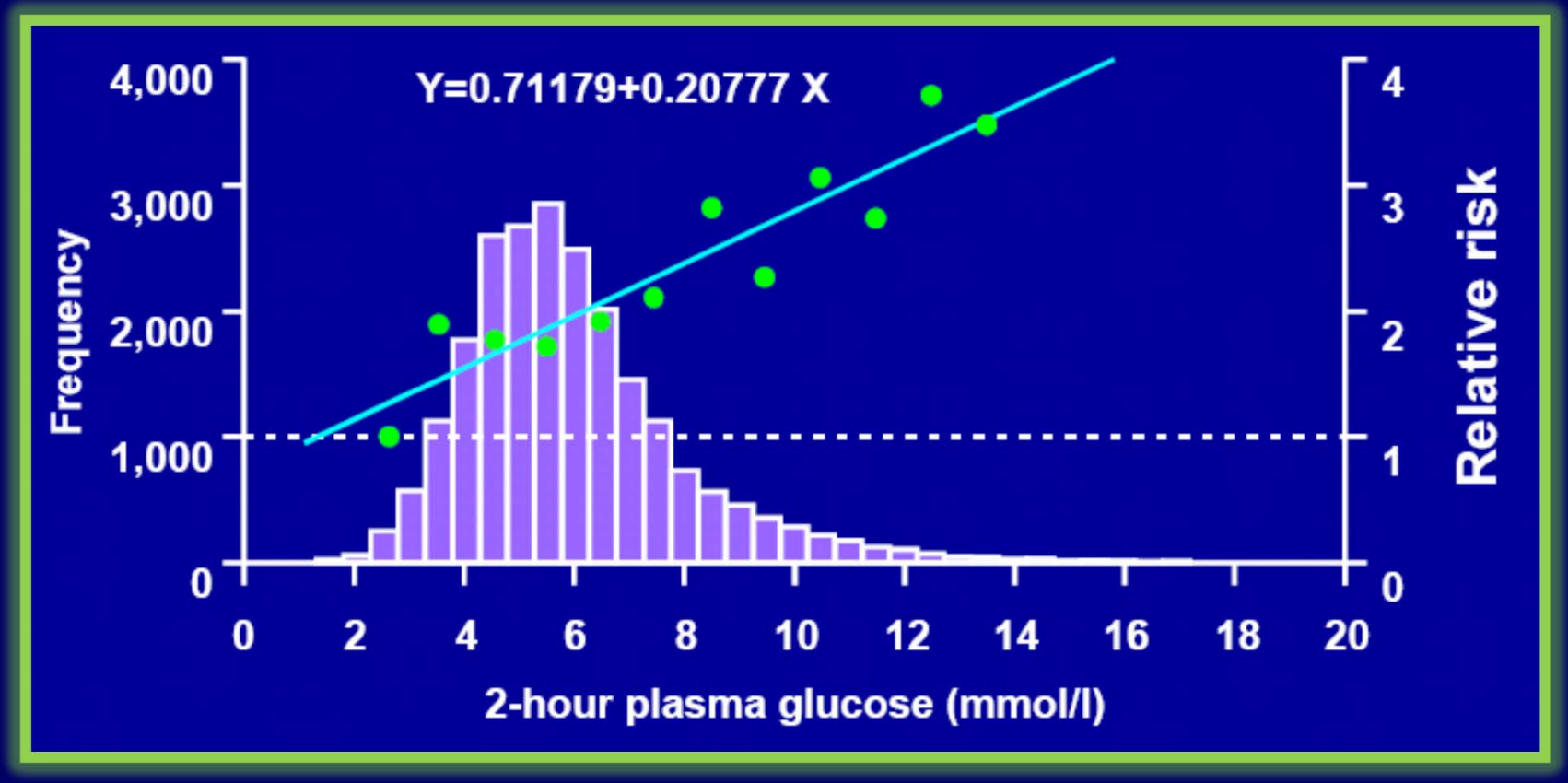
Duration of diabetes vs. beta-cell function



IFG=impaired fasting glucose; IGT=impaired glucose tolerance; NGT=normal glucose tolerance. Adopted from International Diabetes Center. Adopted from Type 2 Diabetes BASICS. Minneapolis, Minn: International Diabetes Center; 2000

Prediabetes increases the risk for cardiovascular events and death

Relative risk of death is linear by 2h-PG – DECODE study



DECODE study group. *Lancet* 1999

Retinopathy

	Pre Diabetes	**Diabetes Mellitus**
AusDiab (Australia Diabetes, Obesity and Lifestyle Study)	6.7%	<10% in <5 years >50% in 20 years
DPP	7.9%	

Diabetes Care 2007 30(10):2708-2715

Nephropathy

Microalbuminuria

	Normoglycemia	IFG	Undiagnosed DM	Diagnosed DM
NHANES 1999-2006	6%	10%	29%	29%

Macroalbuminuria

	Normoglycemia	IFG	Undiagnosed DM	Diagnosed DM
NHANES 1999-2006	0.6%	1.1%	3.3%	7.7%

Lancet 2012;379(9833):2279-2290

Neuropathy

	Pre Diabetes	Diabetes
Chronic Painful DSPN (distal symmetric sensorimotor polyneuropathy)	25 % 11-25% peripheral neuropathy 13-26% neuropathic pain	13-26%

Handbook Clinical Neurology,2014

The Diabetes Burden

- 9.7% of all adults in China – about 110 million people currently live with diabetes[1]
- Without urgent action to reduce lifestyle risk factors like unhealthy diet and lack of physical activity, that number is expected to increase to 150 million with diabetes by 2040 with major health, social and economic consequences
- Even more startling is the fact that almost half of all adults in China – close to 500 million people – have prediabetes[2]

1. *Yang WY et al. N Engl J Med. 2010;362:1090-1101.*
2. *Xu Y et al. JAMA 2013;310:948-959*

ACE (Acarbose Cardiovascular Evaluation) Trial: Background and Objectives

- The association between PPHG and increased risk of CVD has been demonstrated in large-scale studies in European1,2 and Asian3,4 cohorts
- In STOP-NIDDM, Glucobay reduced the risk of a first cardiovascular event in individuals with IGT5
- ACE will investigate whether Glucobay therapy can
  - Reduce the risk of a further cardiovascular event in patients with established CVD and IGT (secondary CVD prevention)
  - Prevent or delay transition to T2DM (primary diabetes prevention)
- ACE is the largest study of Glucobay to determine if glucose lowering treatment in the earliest stage of hyperglycaemia improves CVD prognosis

CVD, cardiovascular disease; IGT, impaired glucose tolerance; PPHG, postprandial hyperglycaemia; T2DM, type 2 diabetes mellitus.
STOP-NIDDM, Study TO Prevent Non-Insulin Dependent Diabetes Mellitus.

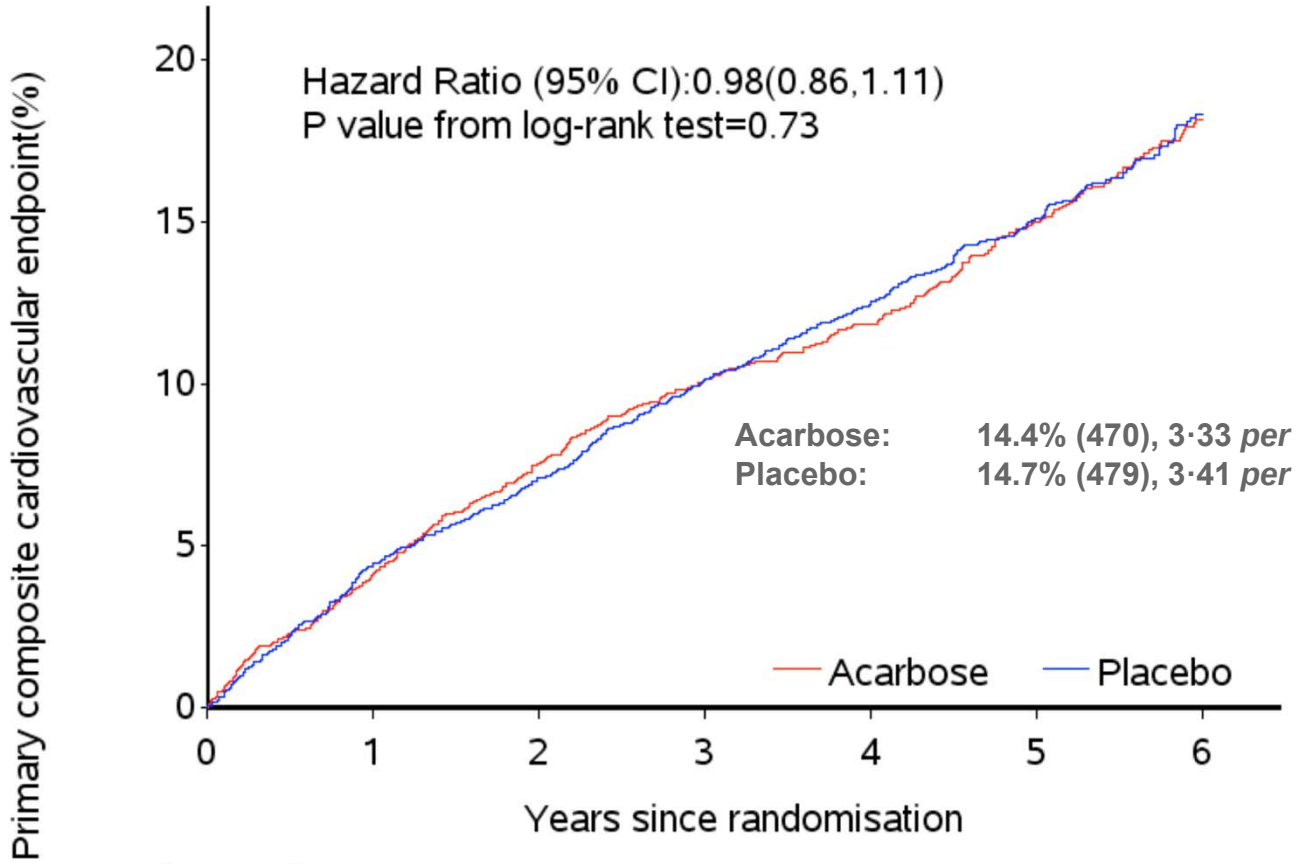
1. DECODE. Diabetes Care 2003;26:688–96.
2. Bartnik M, et al. Eur Heart J 2004;25:1880–90.
3. Nakagami T. Diabetologia 2004;47:385–94.
4. Hu DY, et al. Eur Heart J 2006;27:2573–9.
5. Chiasson JL, et al. JAMA 2003;290:486–94.

ACE(Acarbose Cardiovascular Evaluation) trial: Major Inclusion and Exclusion Criteria

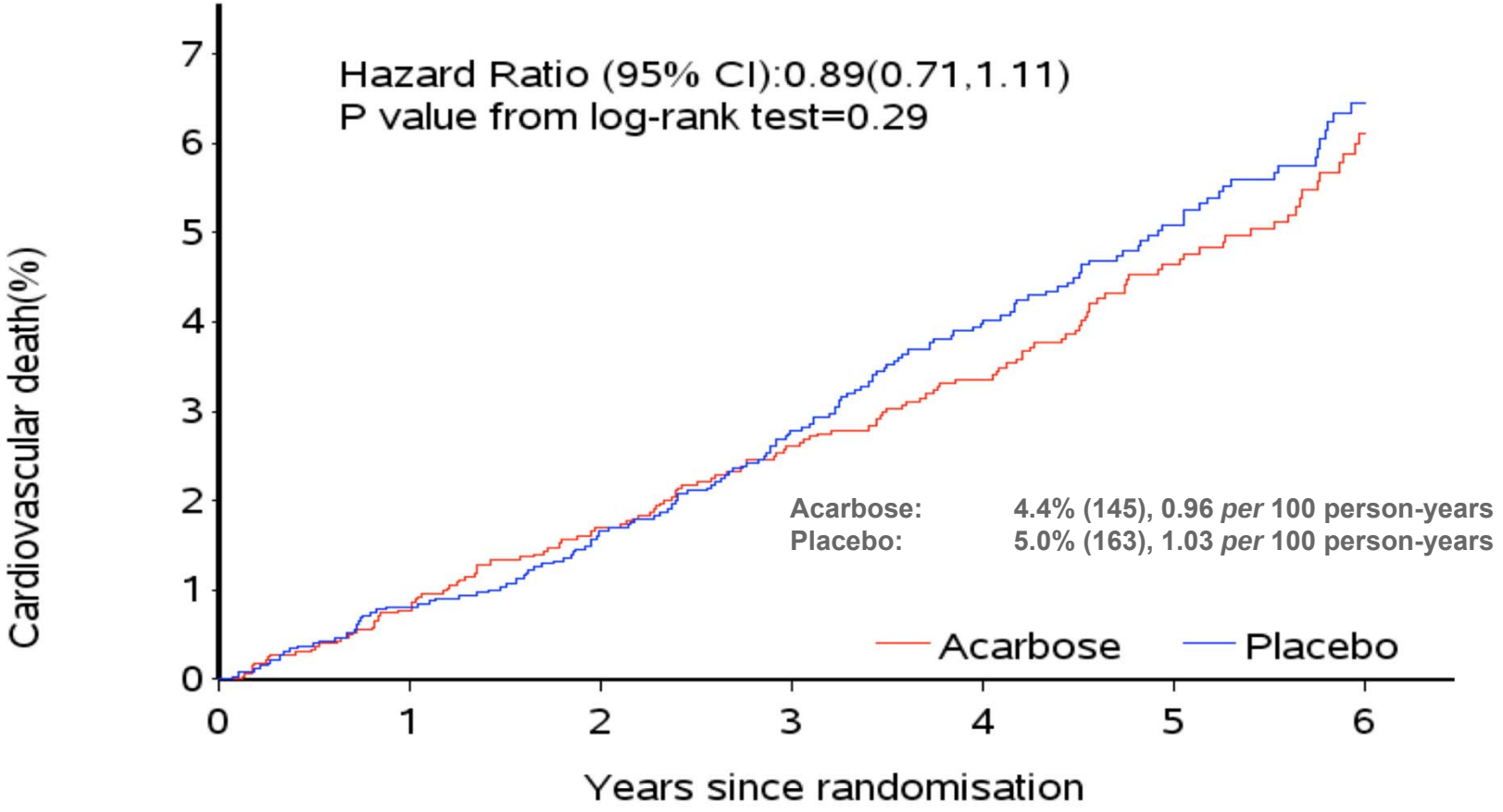
Inclusion criteria	Exclusion criteria
Male or female, aged ≥50 years	History of diabetes (except gestational diabetes)
Established CVD • Prior MI • Prior unstable angina • Current stable angina	MI, unstable angina, stroke or TIA within prior 3 months
IGT • Single OGTT: 2h PG 7.8–11.0 mmol/L and FPG <7.0 mmol/L	Planned or anticipated coronary, cerebrovascular or peripheral arterial revascularisation or other major surgical intervention
Optimised CVD drug therapy	NYHA class III or IV heart failure
≥80% adherent to single-blind placebo study medication during the run-in period	Severe hepatic disease
Written informed consent	Severe renal impairment (eGFR<30mL/min/1.73m^2)
	Known intolerance of α-glucosidase inhibitors or gastrointestinal problems

Primary	• **Composite of cardiovascular death, non-fatal MI, or non-fatal stroke**

Five-point Primary Outcome (ITT analysis)



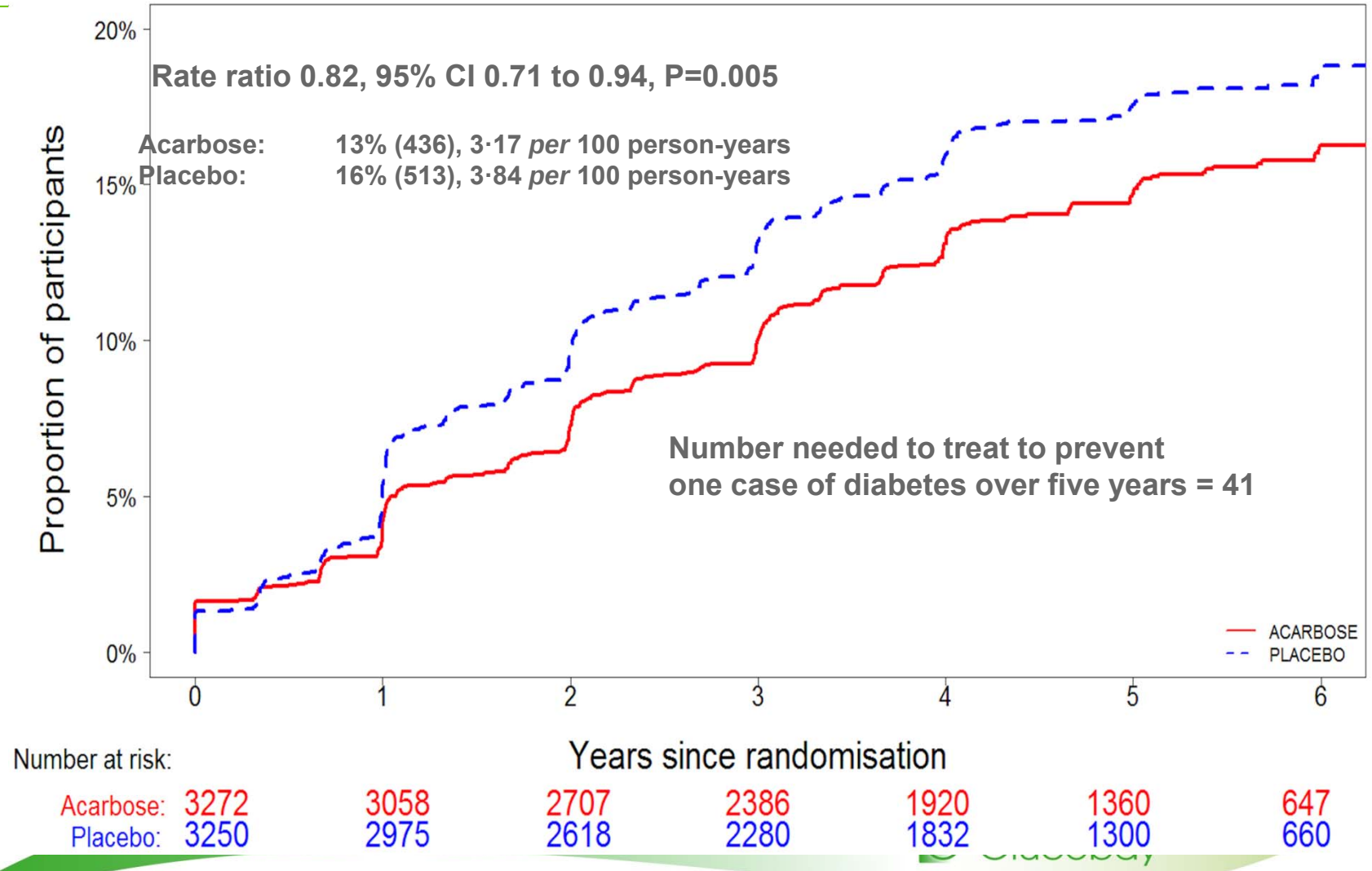
Cardiovascular Death



Number at risk:

Acarbose:3272	3190	2923	2666	2234	1623	791
Placebo:3250	3156	2912	2644	2202	1604	809

New-onset Diabetes



Summary

PPG

- A dominant contribution to hyperglycemia in patients with HbA_{1c} < 7.3%
- Predict CV events and all-cause mortality in T2DM

MAGE

- Glucose fluctuation (measured by MAGE)
- Association with PPG and oxidative stress activation
- A predictor for CAD

Acar-bose

- Not only reduce PPG and MAGE but also improve oxidative stress and the inflammatory profiles in patients with T2DM[1,2]
- Reduces the risk of new-onset diabetes in Chinese patients with IGT and CHD[3]
- Better ability to reduce HbA_{1c} levels in patients consuming an Eastern diet than a Western diet[4]

IGT = impaired glucose tolerance; CHD = coronary heart disease; T2DM = type 2 diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; PPG = postprandial glucose; CAD = coronary artery disease

1. Int J Endocrinol. 2015;2015:903524. **2.** Biomed Rep. 2016;5:461-466. **3.** Lancet Diabetes Endocrinol. 2017;5:877-886 **4.** Clin Ther. 2013 ;35:880-899.