NAPOLI, 17-20 maggio 2017

XXI CONGRESSO NAZIONALE AMD

Diabete ed Etnie

L'algoritmo farmacologico nelle varie etnie è sempre lo stesso?

Stefano Genovese

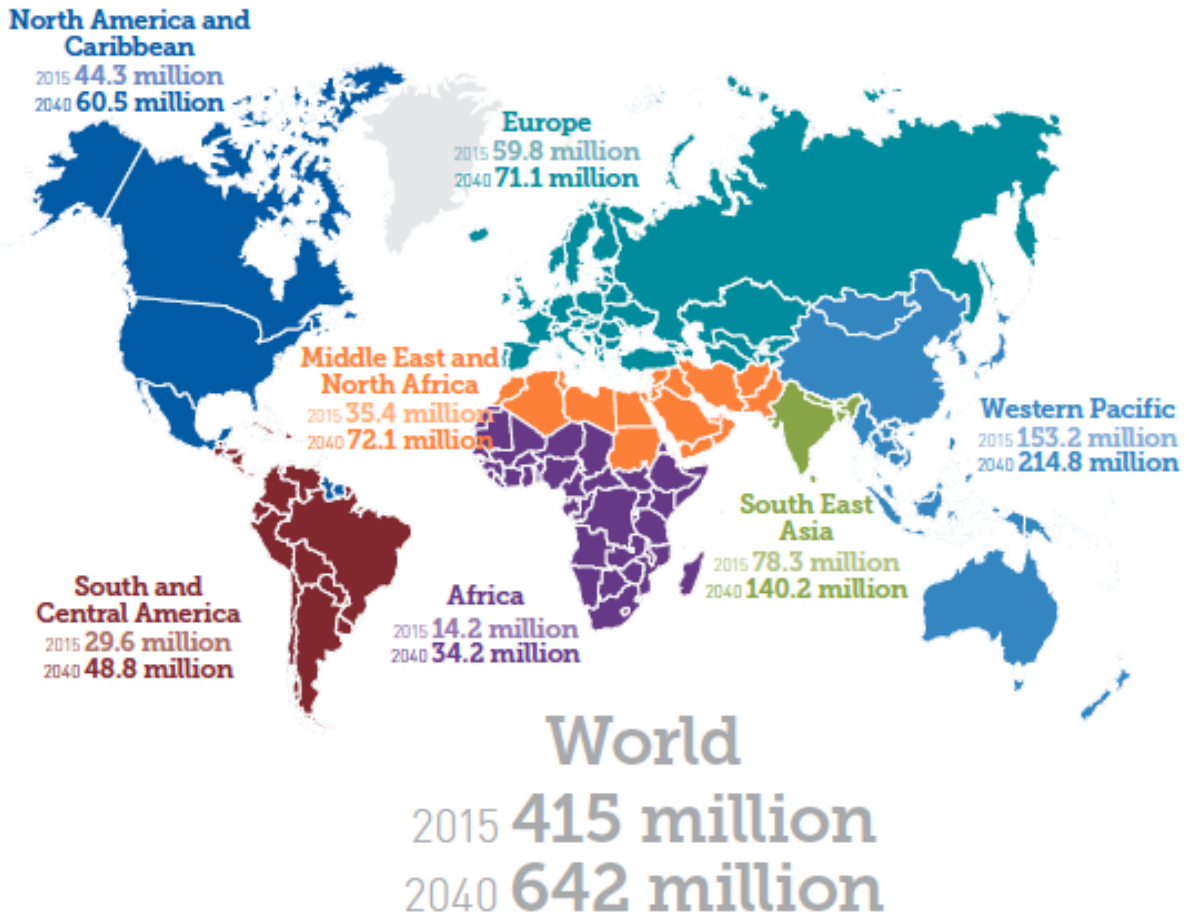
UO di Diabetologia, Endocrinologia e Malattie Metaboliche

IRCCS MultiMedica
Dipartimento Cardiovascolare e Metabolico

Disclosure Statement

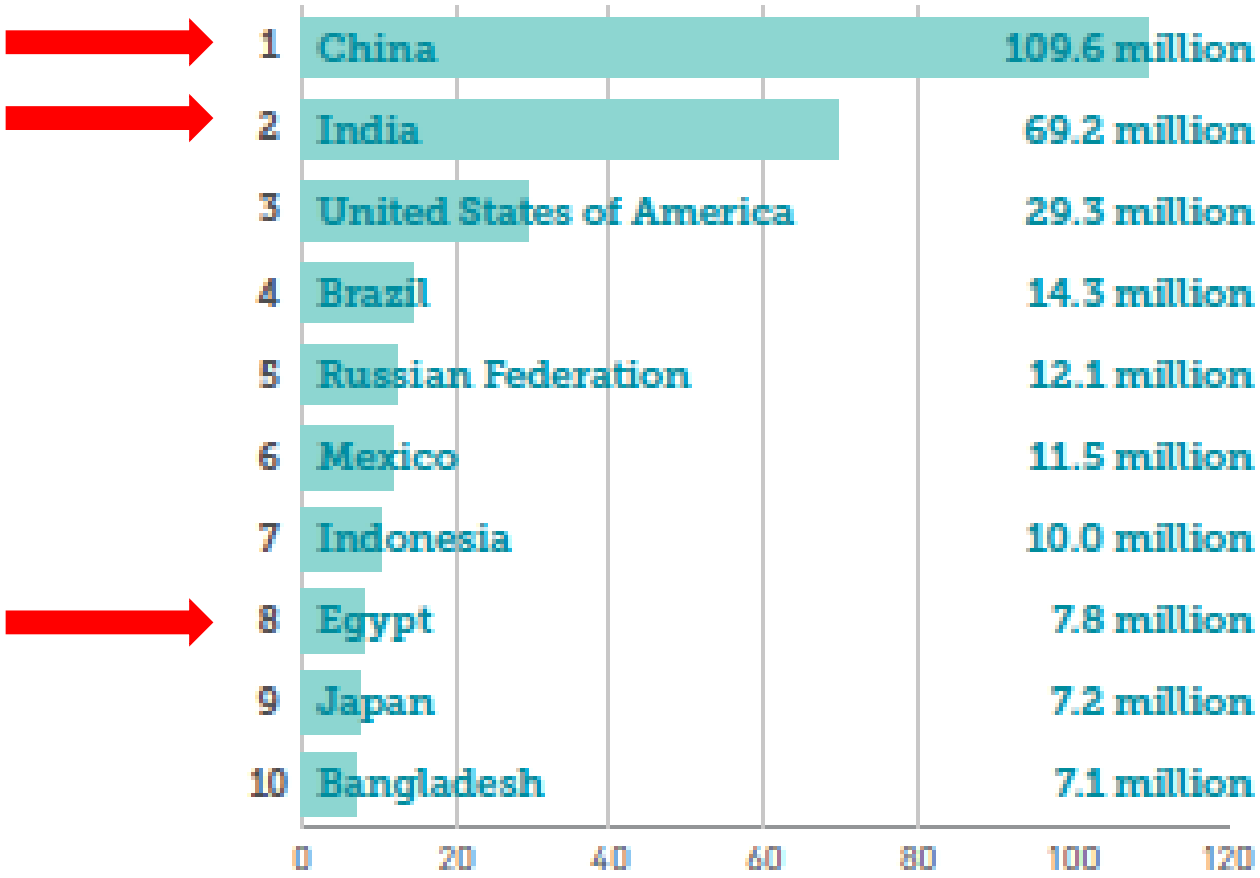
- Stefano Genovese has participated in clinical research, scientific advisory boards, served as a consultant or received honoraria for:
  - Abbott Diabetes Care
  - AstraZeneca
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - Bruno Farmaceutici
  - Eli Lilly
  - Janssen
  - Lifescan
  - Menarini
  - Merck Sharp & Dohme
  - Novartis
  - Novo Nordisk
  - Sanofi
  - Takeda

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



IDF Diabetes Atlas · Seventh Edition 2015

Top ten countries/territories for number of adults with diabetes



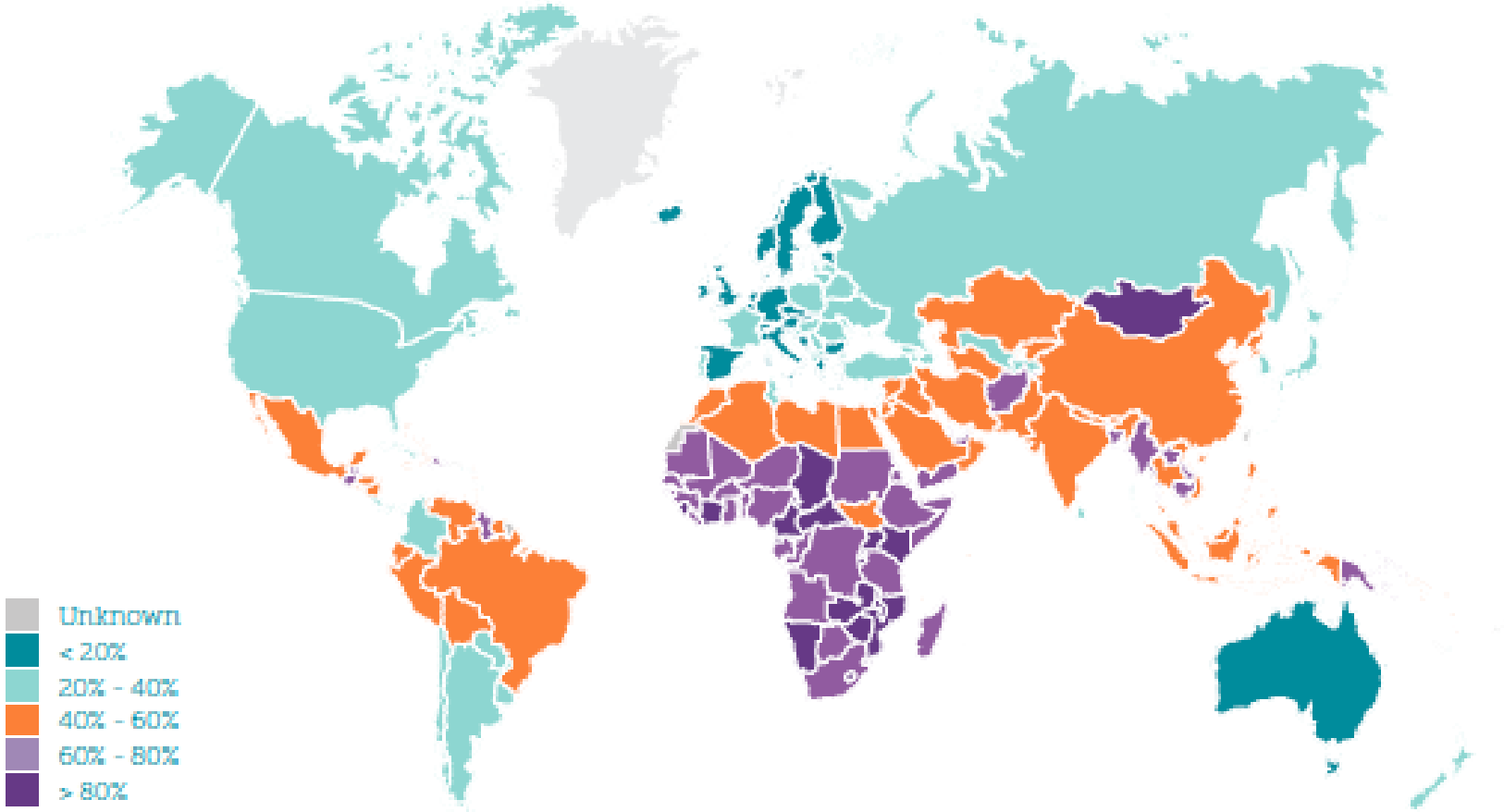
IDF Diabetes Atlas · Seventh Edition 2015

Proportion and number of people (20-79 years) living with diabetes who are undiagnosed, 2015

IDF region	Proportion undiagnosed	Number of undiagnosed people with diabetes
Africa	66.7%	9.5 million
Europe	39.3%	23.5 million
Middle East and North Africa	40.6%	14.4 million
North America and Caribbean	29.9%	13.3 million
South and Central America	39.0%	11.5 million
South-East Asia	52.1%	40.8 million
Western Pacific	52.1%	79.8 million
World	**46.5%**	**192.8 million**

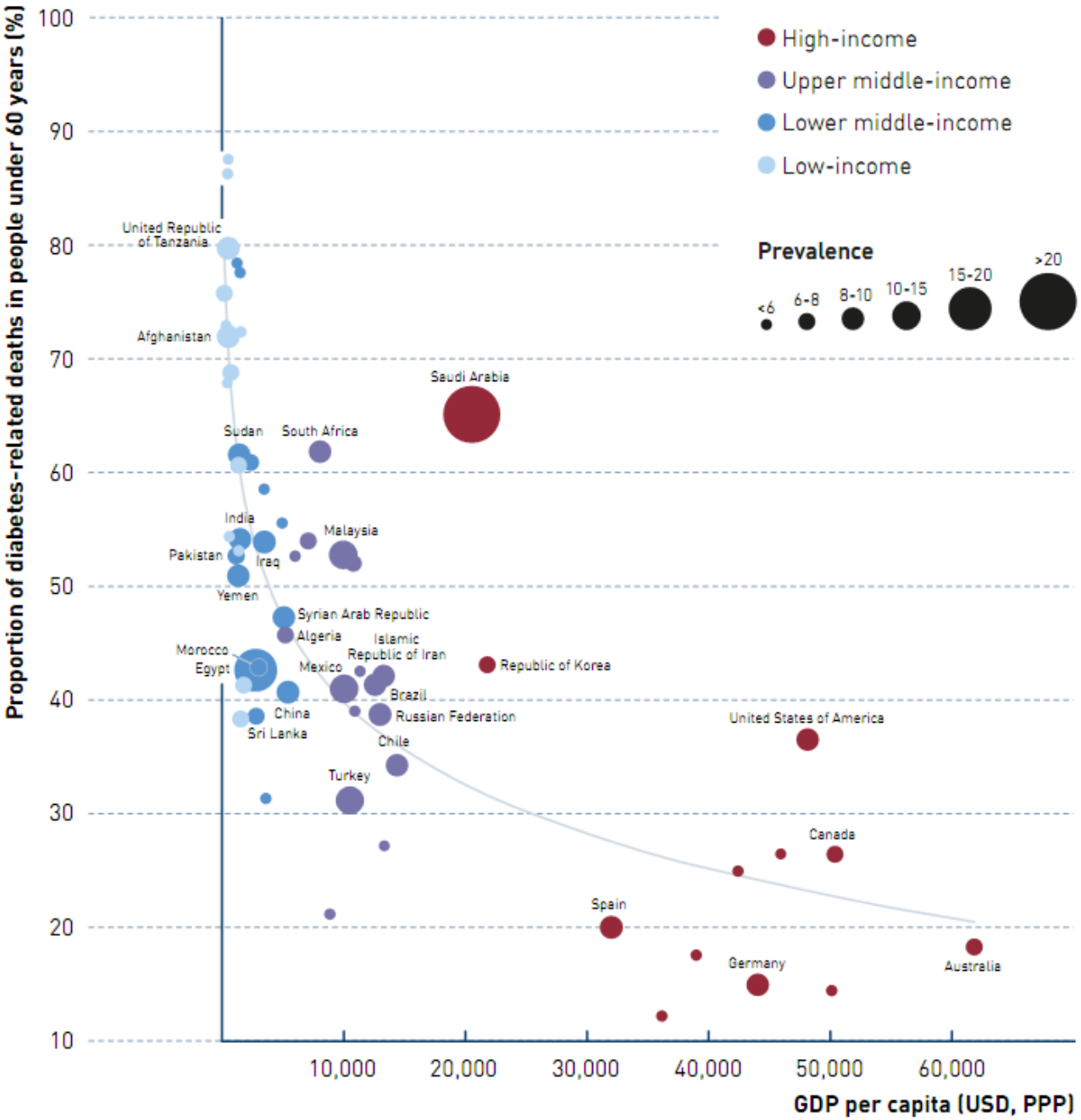
IDF Diabetes Atlas · Seventh Edition 2015

Proportion (%) of people who died from diabetes before the age of 60



IDF Diabetes Atlas · Seventh Edition 2015

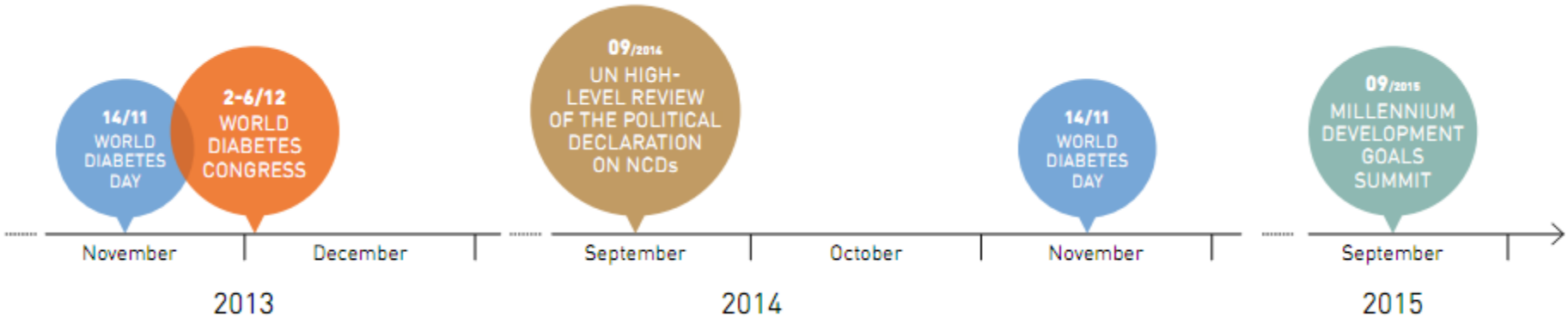
Figure 4.1 Deaths due to diabetes in people under 60 (%) by GDP per capita (USD, PPP), 2013*



* Only countries with adult populations greater than 10,000,000 were plotted.

Increasing development and **wealth** is **correlated** with **decreasing early mortality** due to diabetes

Diabetes is more than a health issue and requires **concerted policy action** across many sectors

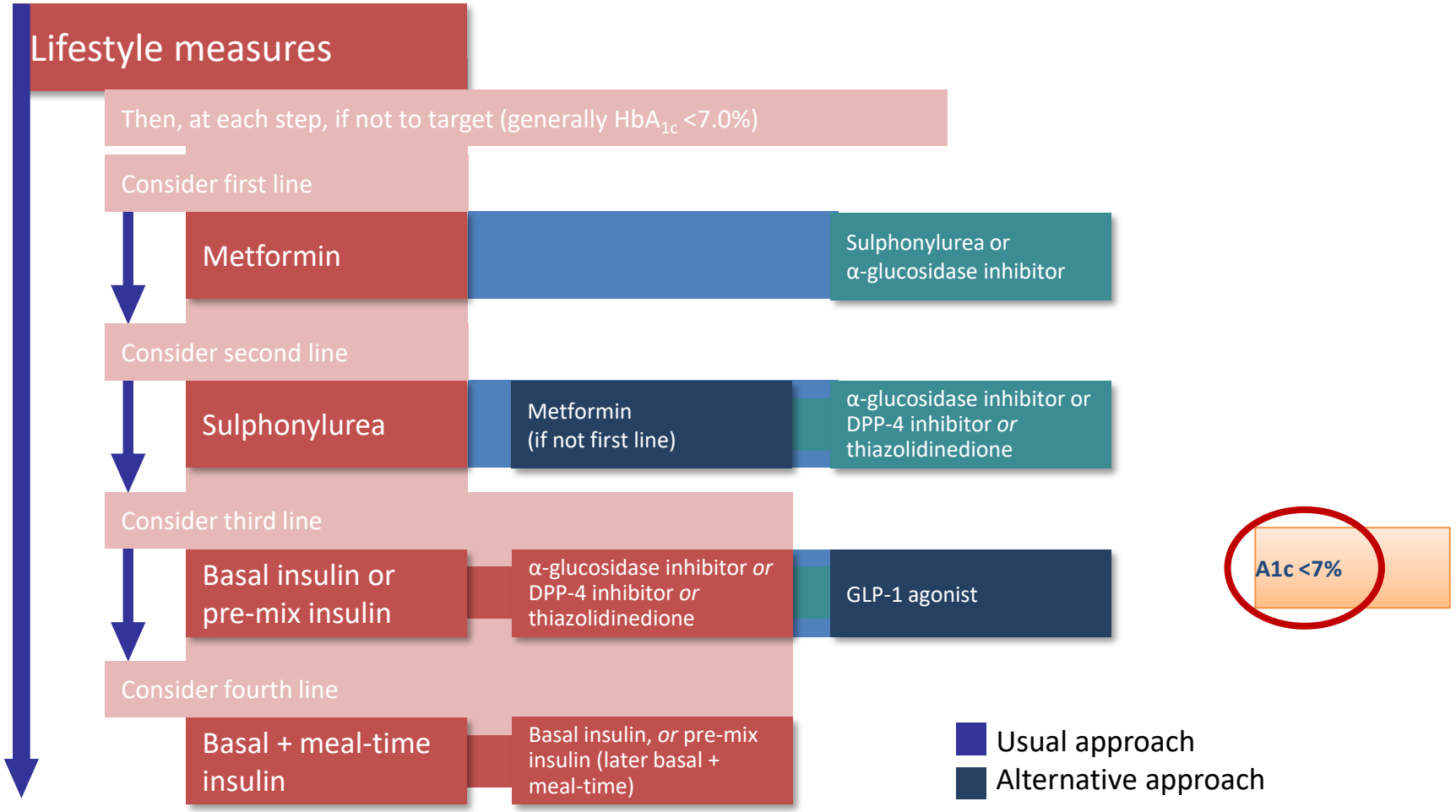


International Diabetes Federation


1 - DA DOVE VENGONO I MIGRANTI
Est.
Lett.
Federazione Russa
Cina 157
Lituania
Danimarca
Mare del Nord
Irlanda
Gran Bretagna
Paesi Bassi
Germania
Polonia
Bielorussia
90
Belgio
133 Ucraina
Rep. Ceca
Austria
Oceano Atlantico
Francia
Thörl-Maglern
70 Moldova
Chiasso
Brennero
Romania 625
Modane
Trieste
Malpensa
Serbia e Montenegro 69
Ventimiglia
Ancona
Mar Nero
Perú
Spagna
78 Macedonia
Fiumicino
Italia
Albania 402
Bari
71
Brindisi
Turchia
73
Ecuador
Grecia
Pantelleria
Le porte d'Italia
Paesi base del transito organizzato
Americhe
Europa orientale
Africa
Asia
Il numero dei migranti è espresso in migliaia
Lampedusa
Filippine 106
Algeria
63
Senegal
94
India 77
366
Tunisia
61
Sri Lanka
Marocco
Libia
77
Egitto

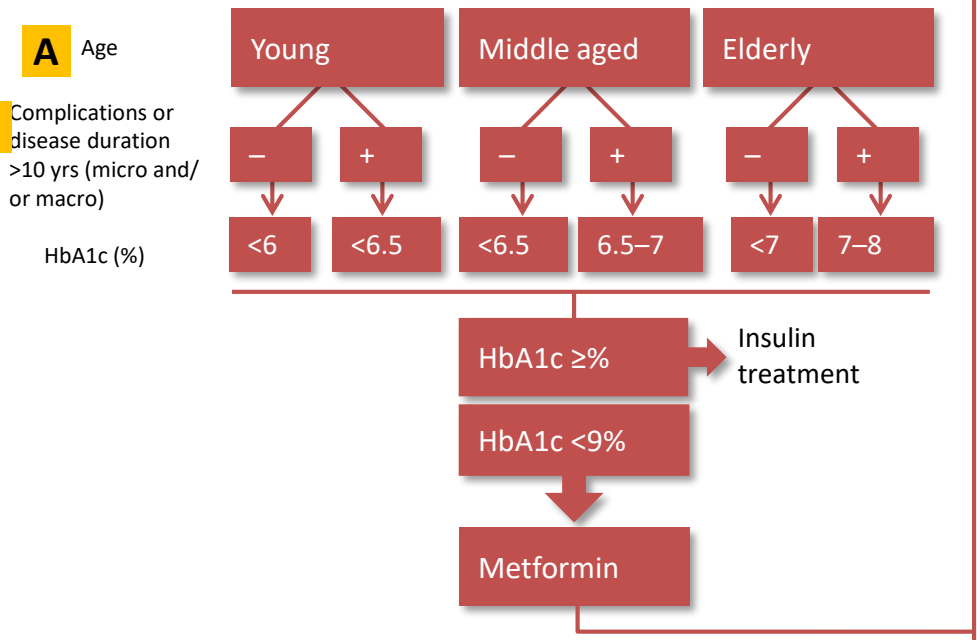
IDF 2010

IDF treatment algorithm for people with T2D



IDF Treatment Algorithm for People with Type 2 Diabetes. Available at: http://www.idf.org/treatment-algorithm-people-type-2-diabetes. Last accessed October 2015.

The A1c and ABCD of glycaemia management in T2D: a physician's personalised approach



B Physician should choose drug according to patient's risk of weight gain, hypoglycaemia **C** cardio-renal complications

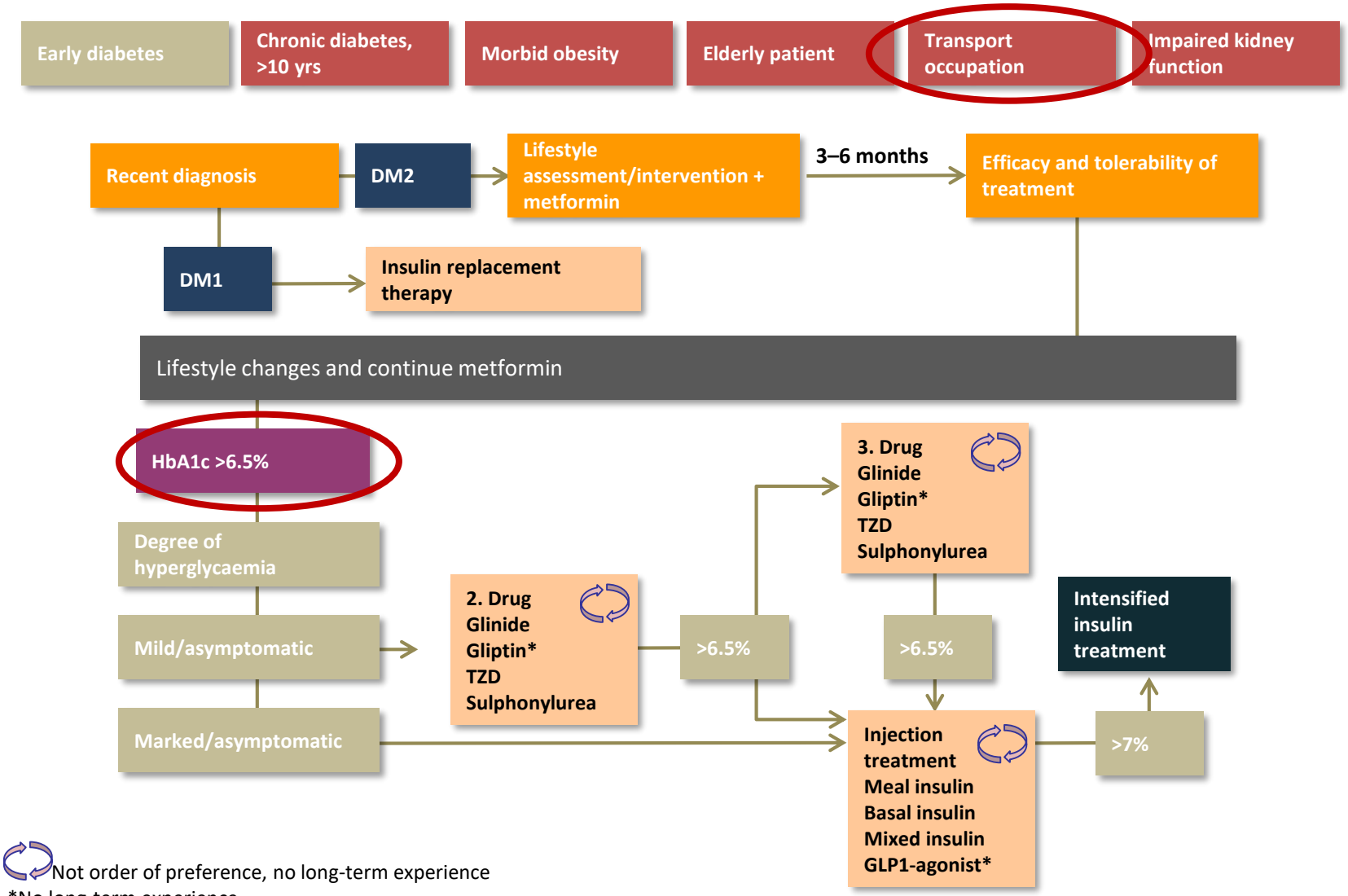
Class	Effect on body weight	Risk of hypoglycaemia	Cardio-renal complications: contraindications
Metformin	Weight loss	Negligible as monotherapy	Moderate renal failure; heart failure
GLP-1 analogues	Weight loss	Negligible as monotherapy	Severe renal failure
DPP-4 inhibitors	Neutral	Negligible as monotherapy	Severe renal failure
Glucosidase inhibitors	Neutral	Negligible as monotherapy	Severe renal failure
Thiazolidinediones	Weight gain	Negligible as monotherapy	Renal failure; heart failure (class III or IV)
Insulin analogues: Rapid-acting analogues Long-acting analogues	Weight gain (rapid-acting> long-acting)	High risk Minimal risk	
Sulphonylureas	Weight gain	Minimal to significant (depending on agent)	Moderate renal failure
Glinides	Weight gain	Minimal/moderate	

			At presentation				Add-on therapy to metformin	
			Mild hyperglycaemia		Severe hyperglycaemia			
Strategy	Glycaemic goal	Time frame to reach glycaemic goal	Definition	Type of intervention	Definition	Type of intervention	Principles in selecting interventions	Drugs excluded
ABCD	Individualised <6–8%	Individualised 3–12 months	A1c <9%	Lifestyle + metformin	A1c ≥9%	Insulin	Age; body weight; complications; diabetes duration	–

ABCD: age, body weight, complications and duration of disease

Pozzilli P et al. *Diabetes Metab Res Rev* 2010;26:239–244.

Diabetes treatment algorithm from the Diabetes Current Care Guideline. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society of Internal Medicine



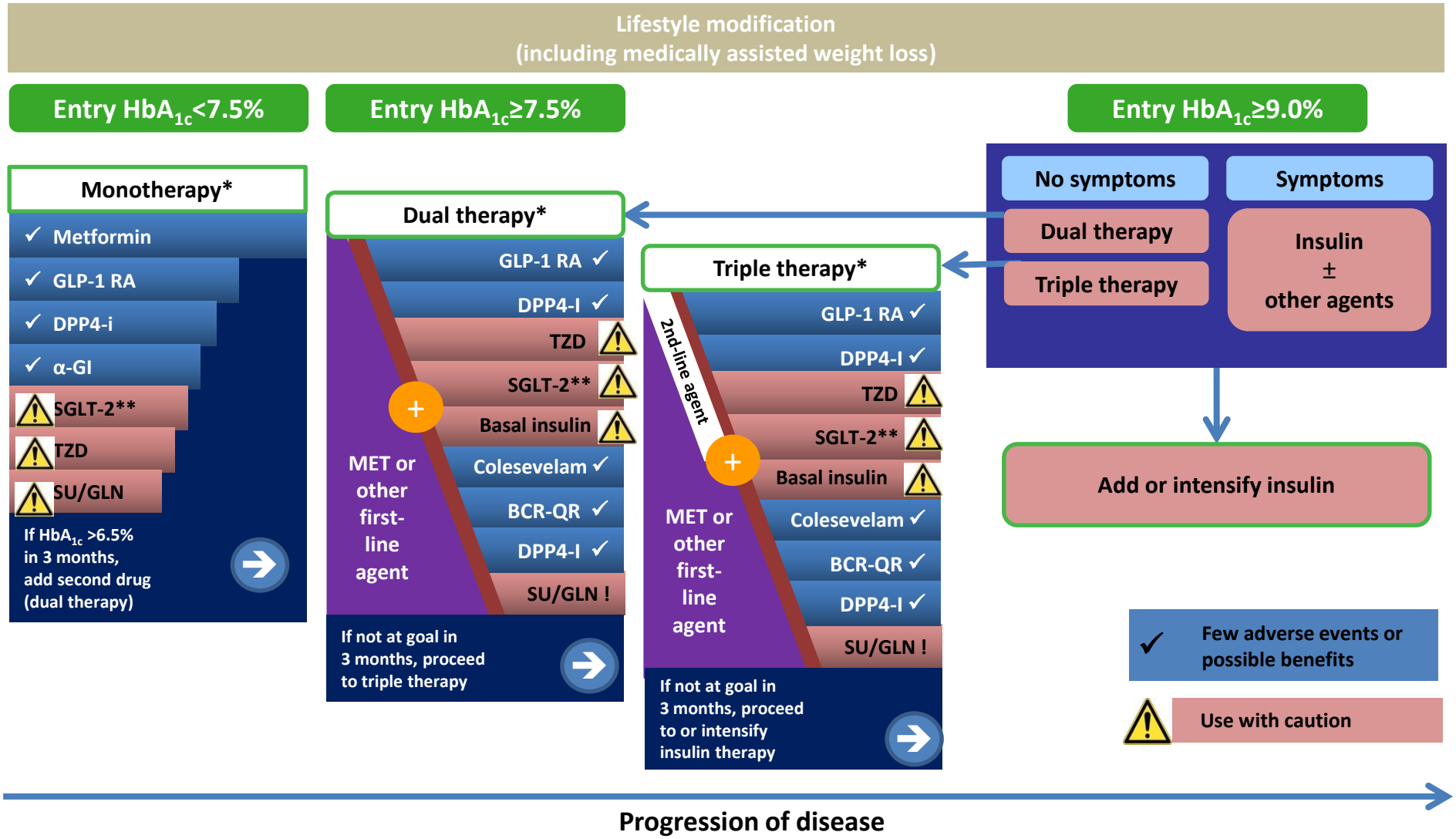
Not order of preference, no long-term experience

*No long-term experience

Glucose-lowering effect of differen

Available at: www.terveysportti.fi/xmedia/ccs/varhainen_diabetes_en.html. Last accessed October 2015.

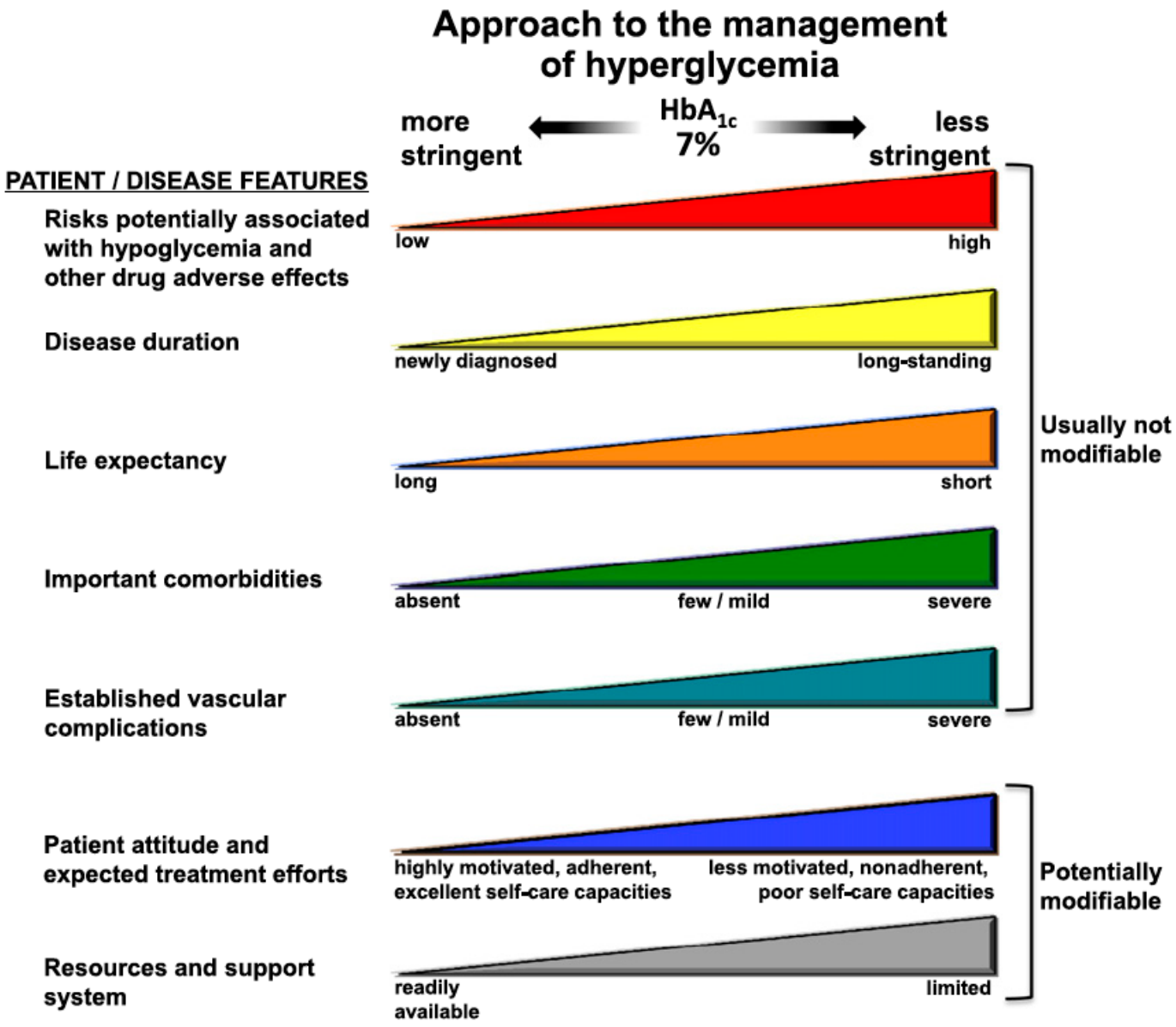
American Association of Clinical Endocrinologists (AACE) treatment guidelines



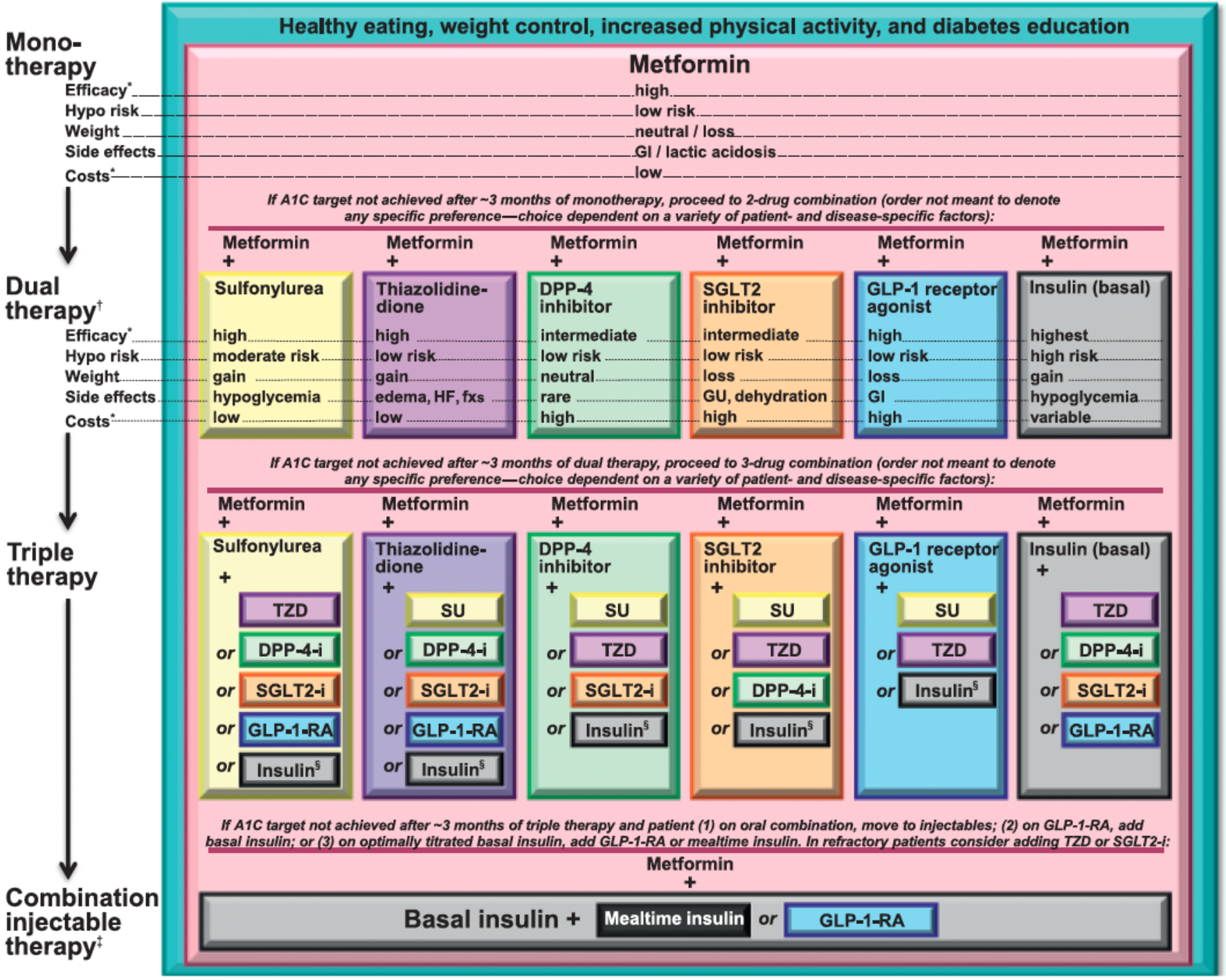
*Order of medications listed are a suggested hierarchy of usage

**Based on data from Phase 3 clinical trials.

Available at: https://www.aace.com/publications/algorithm Last accessed October 2015.



Inzucchi SE et al. *Diabetes Care* 2015; 38:140–149.


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy*
high
Hypo risk
low risk
Weight
neutral / loss
Side effects
GI / lactic acidosis
Costs*
low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy*: high
Hypo risk: moderate risk
Weight: gain
Side effects: hypoglycemia
Costs*: low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~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- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Attualità in
DIETETICA e NUTRIZIONE CLINICA
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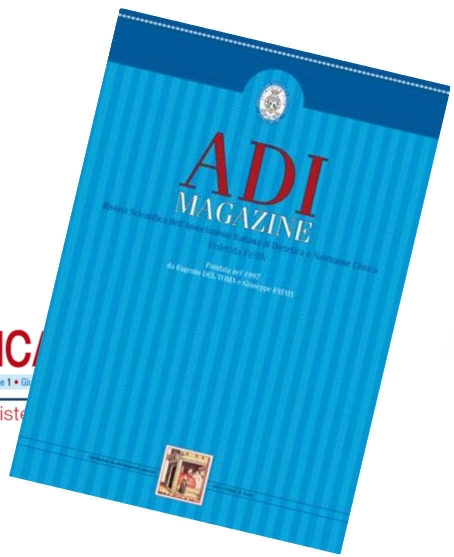
Orientamenti per le moderne dinamiche clinico-assist



CMI Clinical Management Issues

Editoriale

Diabete e Ramadan: necessità di un intervento culturalmente orientato

N. Visalli[1], S. Casucci[2], L. Cipolloni[3], M. Ciotola[4], A. Lai[5], G. Careddu[6], G. Fatati[7], L. Fontana[8], M. Altomare[8], S. Abbruzzese[8], S. Carletti[8], S. Leotta[8]

Diabetes and Ramadan: need for a cultural action

CMI 2014; 8(2): 3-9
http://dx.doi.org/10.7175/cmi.v8i2.921

[1] UOC Diabetologia e Dietologia – Ospedale S. Spirito – Roma
[2] Dipartimento Medicina Interna e Scienze endocrine e metaboliche – Università Perugia
[3] Sovrano Ordine Militare Cavalieri di Malta, CAD Palmiro Togliatti – Roma
[4] Centro Assistenza Diabetici CAD – Napoli
[5] Presidio Ospedaliero SS. Trinità Servizio di Diabetologia Cagliari
[6] SC Malattie Endocrine Nutrizione e Ricambio. Asl 3 – Genova
[7] UOC di Diabetologia, Dietologia e Nutrizione Clinica, Az. Osp. S. Maria Terni
[8] UOC Dietologia, Diabetologia e Malattie Metaboliche Osp. Sandro Pertini – Roma

INTRODUZIONE

La multietnia è una realtà in continua crescita. Le culture d'origine rivestono molta importanza nel condizionare le condotte, le richieste di cura e la disponibilità a determinate terapie. In Italia, il 33% dei cittadini non comunitari è di fede islamica, numero raddoppiato negli ultimi 10 anni [1].

Le differenze religiose/culturali hanno un ruolo importante nella gestione del diabete; il digiuno per i musulmani durante il Ramadan rappresenta un caso emblematico, vero e proprio banco di prova in termini terapeutici e alimentari per gli operatori sanitari [2-4].

RAMADAN: INQUADRAMENTO CULTURALE

Il mese di Ramadan è il nono del calendario islamico, è sacro all'Islàm perché è «il mese in cui fu rivelato il Corano come guida per gli uomini e prova chiara di retta direzione e salvezza» (Sura II, v. 185). Si tratta di un mese di purificazione, ricco di grazie, durante il quale, in una delle sue ultime notti dispari, la "notte del destino", le porte del cielo sono più dischiuse.

Il Corano stabilisce l'obbligo del digiuno (Sura II, v. 183) come atto basilare di culto per tutti i musulmani. Nella prova del digiuno è più importante il significato spirituale di quello materiale: l'uomo obbedisce a un ordine divino, impara a tenere sotto controllo i suoi desideri fisici e supera la sua natura umana. Si abitua alla moderazione: abbandonarsi senza freni anche a bisogni leciti, come il cibo e i rapporti sessuali, rende l'uomo schiavo di abitudini e voglie.

Nel digiuno, il ricco prova le ristrettezze che il povero ha quotidianamente e tutta la comunità vive una comunione di spirito che aumenta il senso di fratellanza, di pazienza e di disciplina fra i musulmani. Tutti i musulmani che abitano l'emisfero nord e quello sud hanno la possibilità, nel corso della loro esistenza, di digiunare in stagioni diverse, perché i mesi lunari sono alternativamente di 29 e 30 giorni e l'anno lunare in tutto è di 354 giorni, undici giorni in meno rispetto a quello solare. Il Ramadan cade così in diverse stagioni. In certi Paesi, durante l'inverno, le giornate sono corte e fredde e il digiuno di Ramadan è certamente meno impegnativo da rispettare che nella stagione estiva. In tutto questo, il credente intravede la saggezza, la giustizia e la misericordia di Dio. Il digiuno deve essere preceduto dalla pronuncia dell'intenzione (*niyyah*) (intenzione). Dopo la pronuncia dell'intenzione, si incomincia a digiunare, all'aurora.

Il pasto *iftar*, consumato al tramonto, rappresenta il momento della rottura del digiuno. È caratterizzato da 3 portate. La prima è

Corresponding author
Dott.ssa Laura Cipolloni
l.cipolloni@hotmail.it

Disclosure
Gli autori dichiarano di non avere conflitti di interesse di natura finanziaria in merito ai temi trattati nel presente articolo

GIDM
GIORNALE ITALIANO di DIABETOLOGIA e METABOLISMO

5 CAPILLARIZZAZIONI NAZIONALI

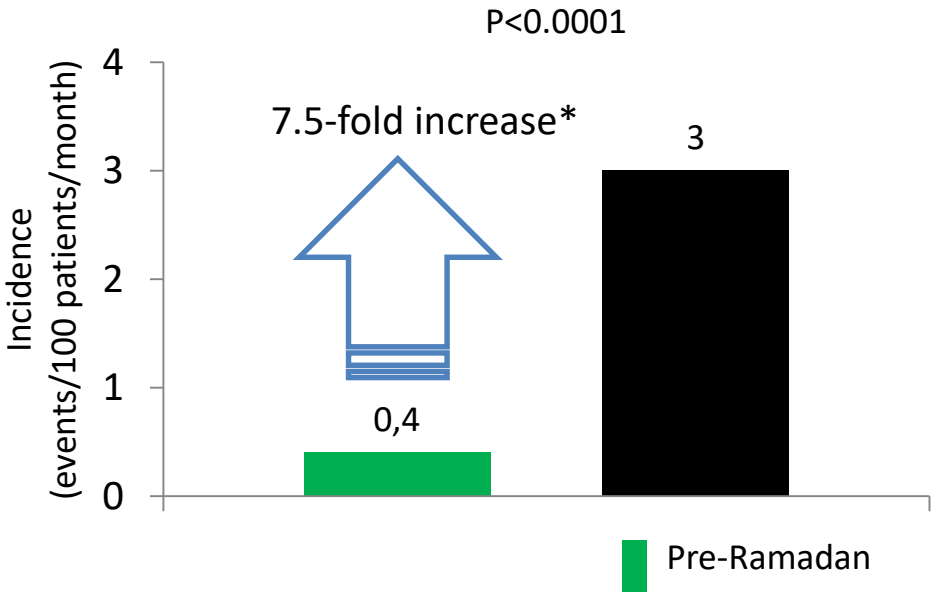
per il formazione di 150 medici

EPIDIAR study:

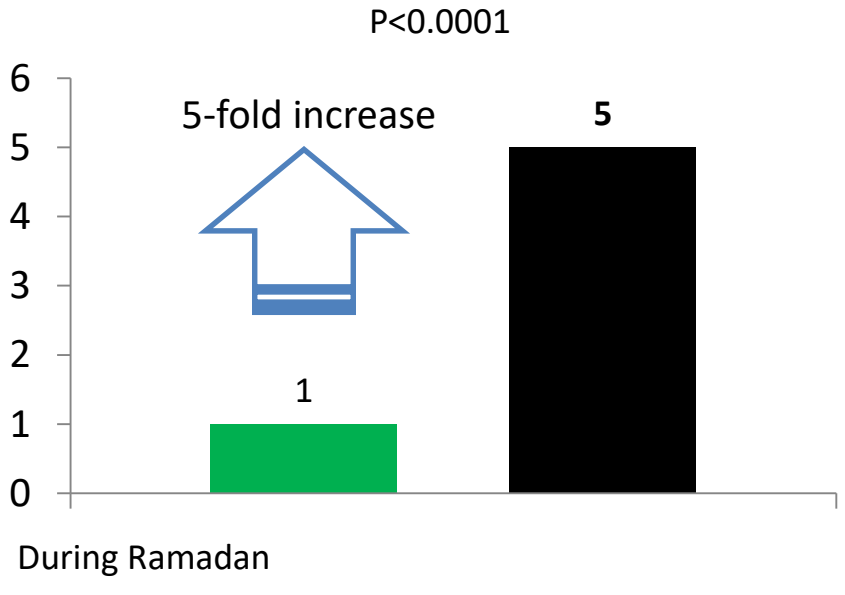
il Ramadan aumenta il rischio di episodi severi sia di ipoglicemia che di iperglicemia nel diabete 2

11,173 pazienti con diabete tipo 2
78.7% hanno scelto di digiunare almeno 15 giorni durante il mese Ramadan

Rischio aumentato di ipoglicemie durante il mese Ramadan



Rischio di iperglicemie aumentato durante il mese ramadan



Pre-Ramadan During Ramadan

†Events requiring hospitalization in overall population with T2DM; ‡compared with previous months
* There was a 7.5 fold difference of hypoglycaemia in overall population fasting during Ramadan. For patients who fasted for ≥ 15 days difference was, 6.7 fold
EPIDIAR = EPIdemiology of DIAbetes and Ramadan; T2DM = type 2 diabetes mellitus

[1]Salti I, et al. Diabetes Care 2004;27:2306–11;
[2]Al-Arouj M, et al. Diabetes Care 2010;33:1895–902

Ramadan Fasting: A Study of Changes in Glucose Profiles Among Patients With Diabetes Using Continuous Glucose Monitoring

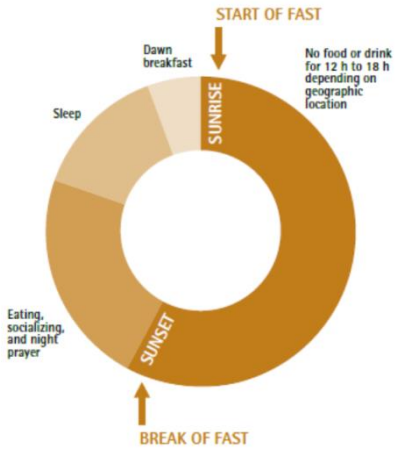
We have explored changes in glucose profiles of patients with type 2 diabetes in a prospective observational study using continuous glucose monitoring (CGM; Medtronic MiniMed CGMS Gold). This was performed for at least 3 consecutive days during Ramadan (2). Nonfasting CGM for the same length of time was obtained on each patient either before or after Ramadan. A mean CGM curve for all patients was obtained during and outside the Ramadan fasting period (3).

NADER LESSAN, MRCP, MD[1]
HAYDAR HASAN, MD[2]
MAHA T. BARAKAT, MRCP[1]

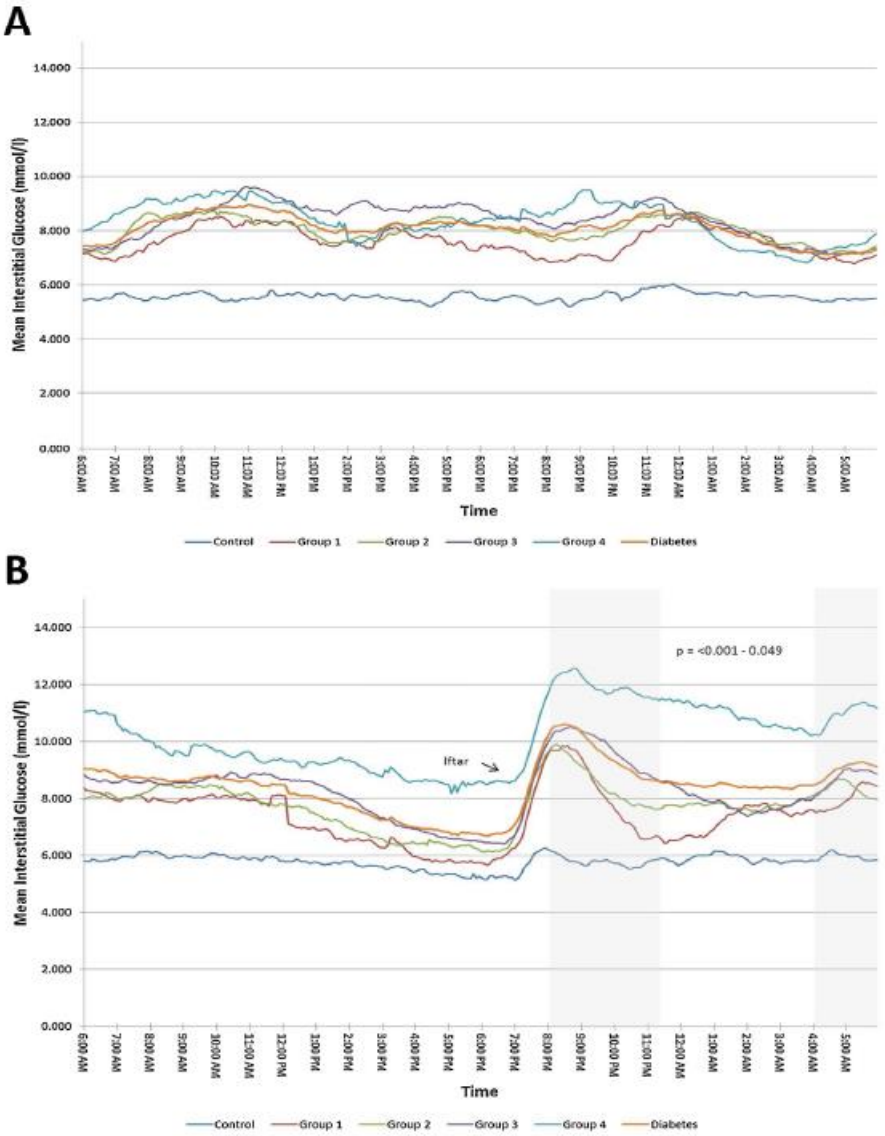
DIABETES CARE, VOLUME 35, MAY 2012

Grande variabilità
inter e intra individuale

correlata al momento della giornata, al tipo di alimenti introdotti, alle modifiche di terapia



CGMS in RAMADAN



Non Fasting

Fasting

International Diabetes Federation

DaR Diabetes & Ramadan International Alliance

Diabetes and Ramadan: Practical Guidelines

International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance

April 2016

Diabetes and Ramadan Practical Guidelines

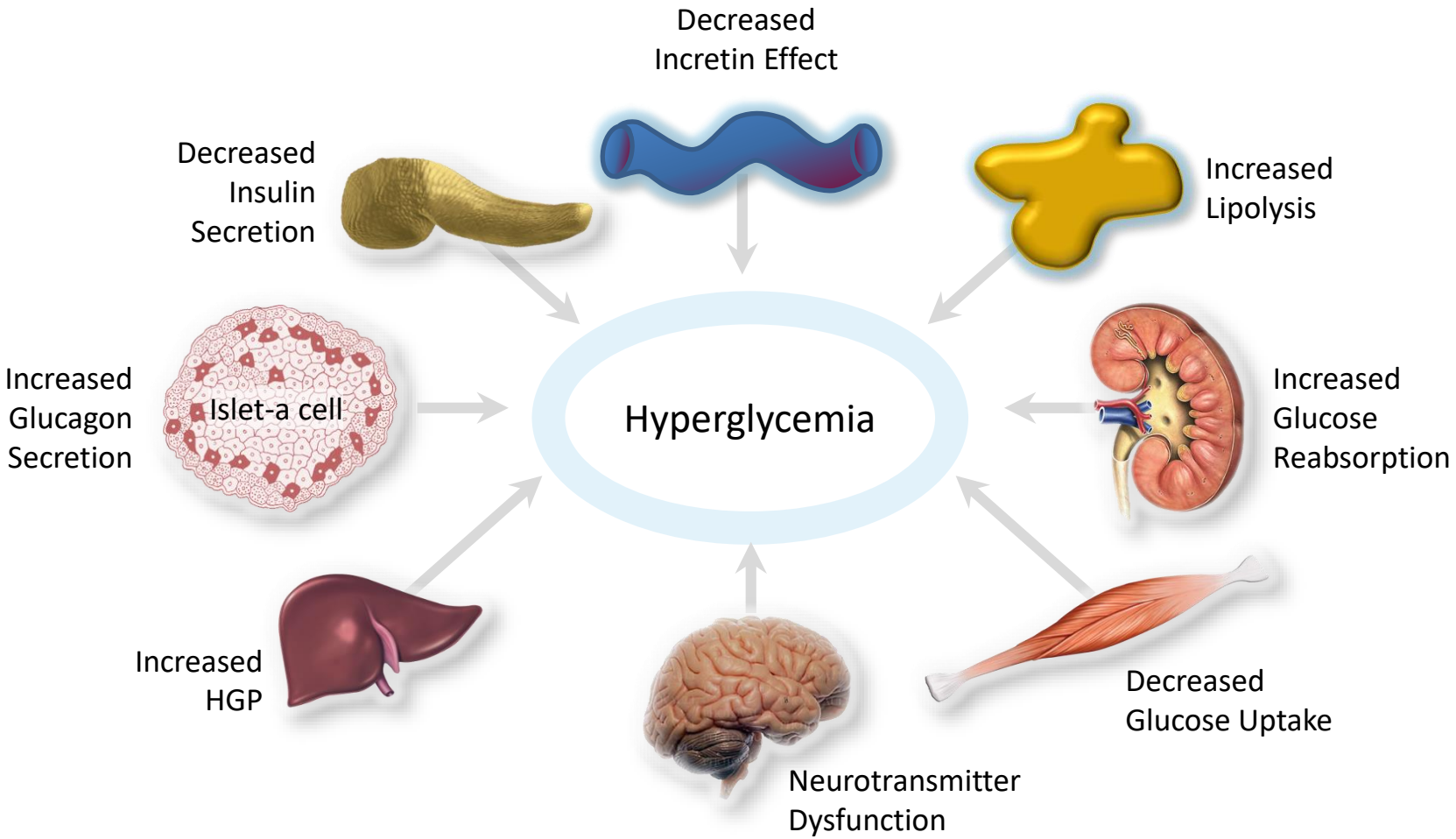
- Epidemiology of diabetes and Ramadan fasting
- Physiology of Ramadan
- Stratification of individuals with Diabetes before Ramadan
- Diabetes and Ramadan: a medico-religious perspective
- Pre-Ramadan education
- Ramadan Nutrition Plan (RNP) for patients with diabetes
- Management of diabetes during Ramadan
- Identifying and overcoming barriers to Guideline implementation
- Summary of the response of Egypt's Mofty to diabetes and Ramadan risk categories religious ruling (Arabic and English)

I farmaci

T2D treatment based upon pathophysiology

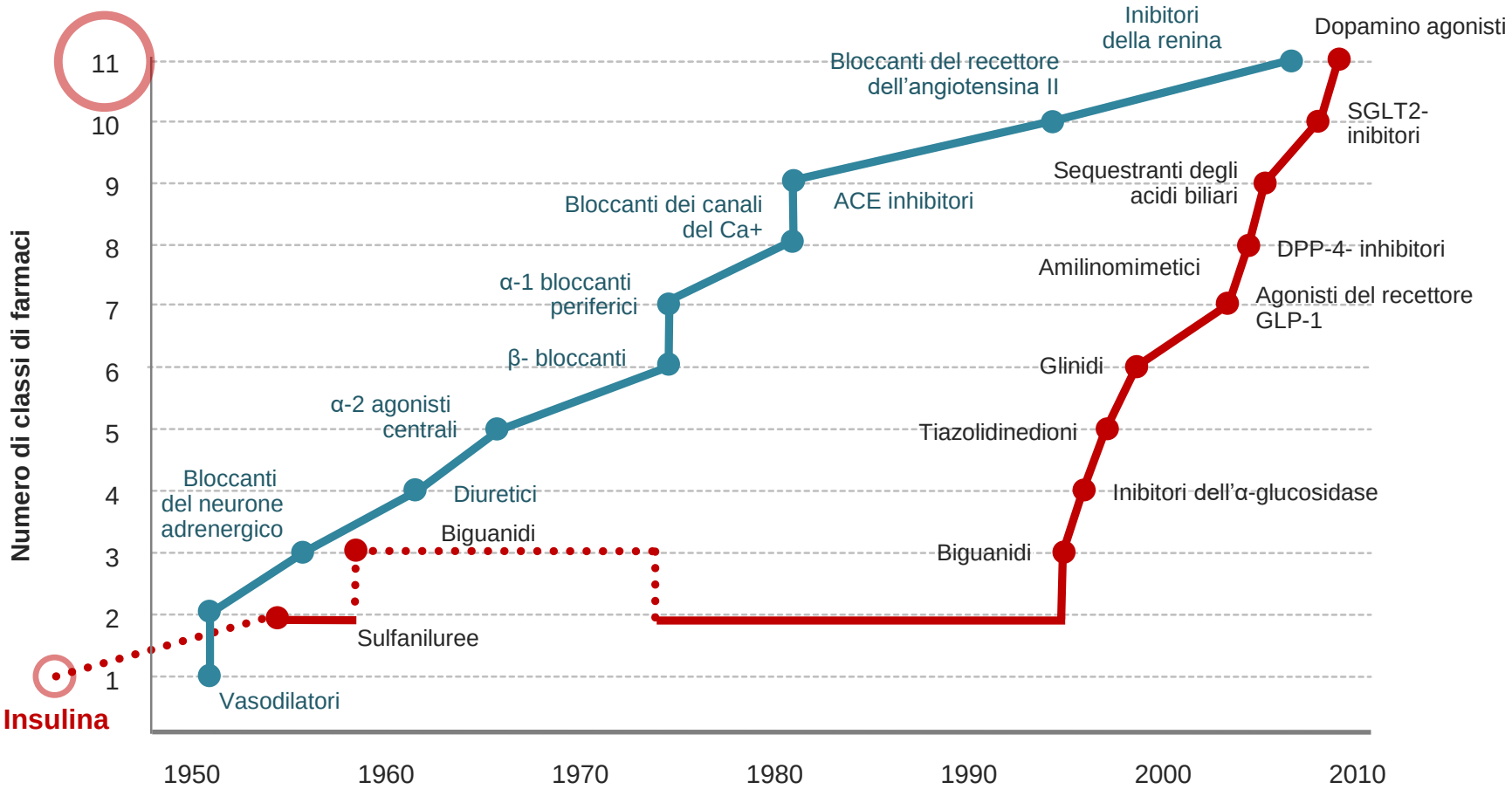
- Decrease insulin resistance (liver, skeletal muscle, adipose tissue)
- Re-establish an appropriate insulin secretion profile
  - Sufficient basal secretion
  - Appropriate post-prandial secretion (especially in the early
    phase after meal)
- Counteract lipotoxicity
- Decrease glucotoxicity

The pathophysiology of diabetes



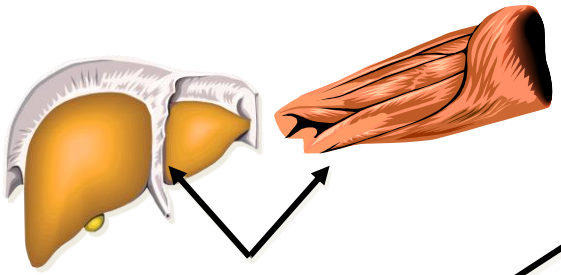
De Fronzo RA. Diabetes 2009;58:773-795

Ipertensione & diabete:
classi di farmaci negli USA nel corso degli ultimi 50 anni



Options for antidiabetic treatment

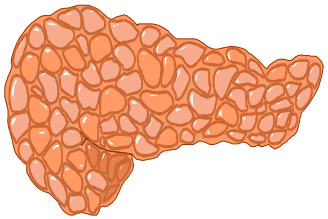
Insulin resistance



Metformin

Pioglitazone

Insulin secretion



Glucose independent

Sulphonylurea

Glinides

Exogenous insulin

Glucose dependent

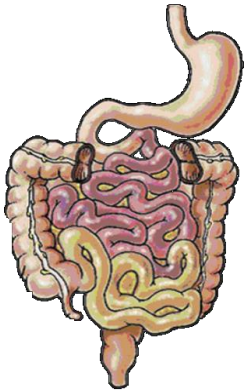
DPP-4 inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin

GLP-1 mimetics

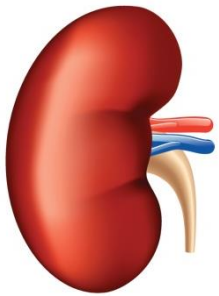
Exenatide, Liraglutide, Lixisenatide

Inhibition of glucose reabsorption



α-Glucosidase inhibitors

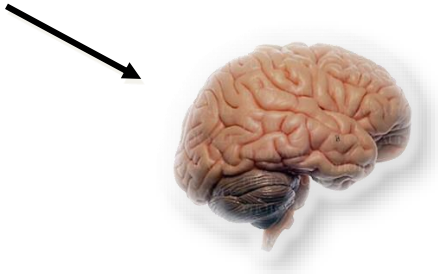
Acarbose, Miglitol, Voglibose



Inhibition of renal glucose reabsorption

SGLT2-Inhibitors

Dapagliflozin, Canagliflozin, Empagliflozin



The ideal drug

- Efficacy
- Safety
- Other Clinical Advantages
- No/Few Adverse Effects
- Reasonable Cost/Value

Ramadan

COMMENTARY

Recommendations for Management of Diabetes During Ramadan

Update 2010

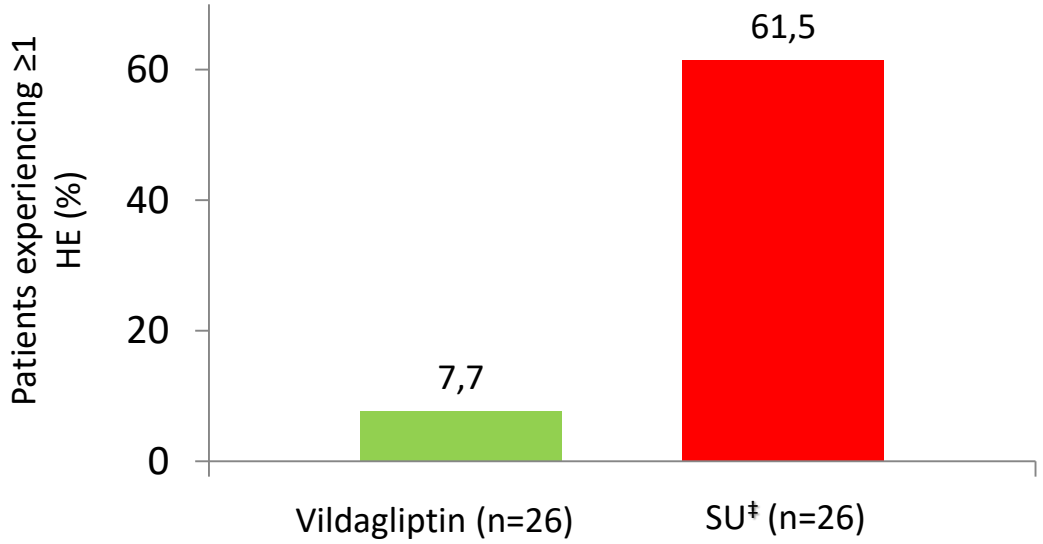
Monira Al-Arouj, MD[1]
Samir Assaad-Khalil, MD, PHD[2]
John Buse, MD, PHD[3]
Ibtihal Fahdil, MD, PHD[4]
Mohamed Fahmy, MD, PHD[5]
Sherif Hafez, MD, FACP[6]
Mohamed Hassanein, FRCP[7]
Mahmoud Ashraf Ibrahim,
David Kendall, MD[9]
Suhail Kishawi, MD[10]
Abdulrazzaq Al-Madani, M
Abdullah Ben Nakhi, MD[1]
Khaled Tayeb, MD[12]
Abraham Thomas, MD[13]

Table 3—*Recommended changes to treatment regimen in patients with type 2 diabetes who fast during Ramadan*

Before Ramadan	During Ramadan
Patients on diet and exercise control	Consider modifying the time and intensity of physical activity; ensure adequate fluid intake
Patients on oral hypoglycemic agents	Ensure adequate fluid intake
Biguanide, metformin 500 mg, three times daily	Metformin, 1,000 mg at the sunset meal, 500 mg at the predawn meal
TZDs, AGIs, or incretin-based therapies	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal; adjust the dose based on the glycemic control and the risk of hypoglycemia
Sulfonylureas twice a day	Use half the usual morning dose at the predawn meal and the usual dose at sunset meal
Patients on insulin	Ensure adequate fluid intake
Premixed or intermediate-acting insulin twice daily	Consider changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal

Episodi ipoglicemici in pazienti diabetici in Ramadan trattati con vildagliptin vs glicazide in add on a metformina

UK observational study in patients with T2DM fasting during Ramadan (baseline HbA1c >8.5%) treated with metformin in addition to the DPP4 inhibitor, vildagliptin or gliclazide



Between groups difference –53.8% (95% CI: –74.9 to –26.3); P<0.001

*Total number of HEs was 24 with gliclazide and 2 with vildagliptin, one severe HE with gliclazide & none with vildagliptin

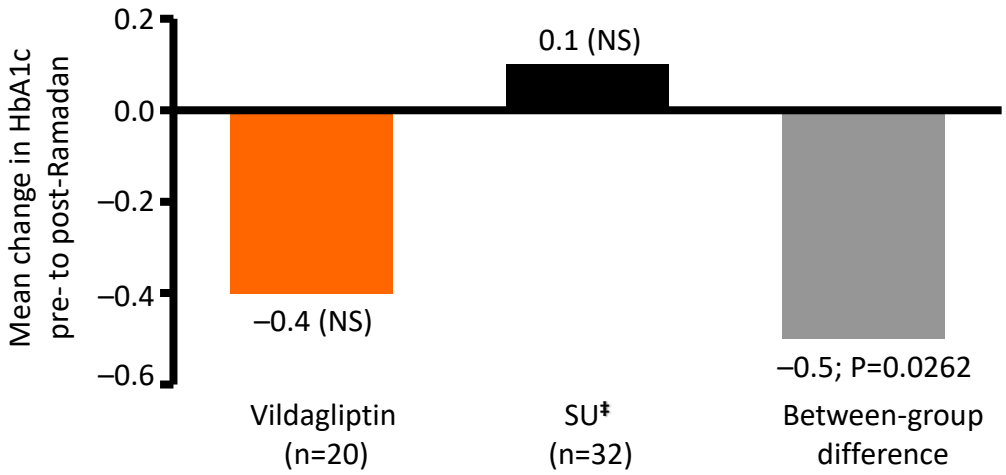
‡ SU = Sulfonylurea (gliclazide)

HE = hypoglycaemic event; T2DM = type 2 diabetes mellitus; CI = confidence interval; SU = sulphonylurea; DPP4 = dipeptidyl peptidase 4
Hypoglycaemic events defined as plasma glucose measurement <3.5 mmol/L with or without symptoms .*Hypoglycaemia was the only adverse event monitored

Devendra D et al. Int J Clin Pract 2009;63:1446–50

VECTOR study: variazioni HbA1c in pazienti diabetici in Ramadan trattati con vildagliptin vs glicazide in add on a metformina

HbA1c reduction for vildagliptin vs. gliclazide pre- to post Ramadan; between-group difference –0.5% (P=0.0262)



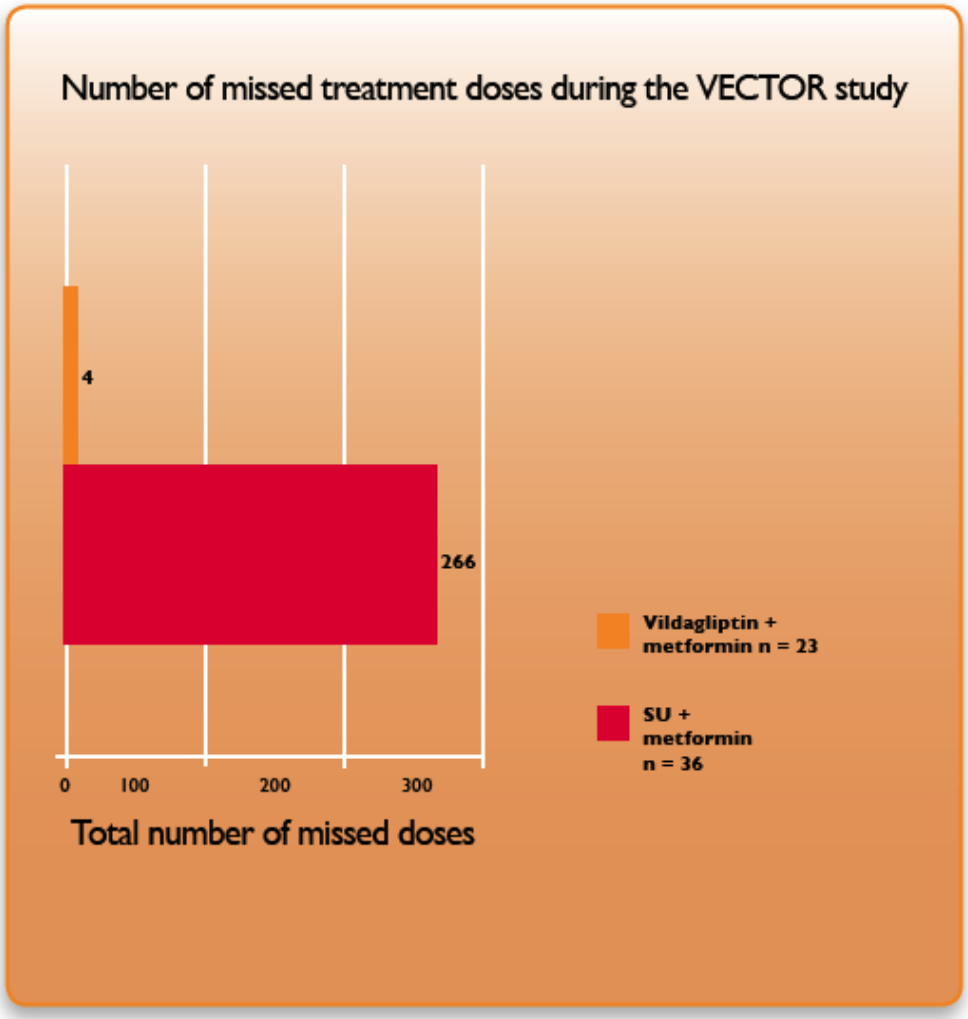
- **Mean number of missed doses was lower with vildagliptin (mean between-group difference –7.4; P=0.0204)**
- Body weight remained unchanged in both groups

Prospective observational study of up to 16 weeks duration in 72 fasting Muslim patients with T2DM observed in UK clinical practice, receiving vildagliptin or SU as an add-on treatment to metformin; per protocol set with pre- and post Ramadan HbA1c assessments, HbA1c; safety set, AEs and SAEs.

‡ SU = Sulfonylurea (gliclazide); VECTOR= Vildagliptin Experience Compared To gliclazide Observed during Ramadan; AE = adverse event; SAE = severe adverse event; NS = non-significant difference pre- to post Ramadan

Hassanein M et al. Curr Med Res Opin 2011;27:1367–74

VECTOR Study:
Aderenza alla terapia nei due gruppi



- **The mean number of missed doses was markedly lower with Vildagliptin than with gliclazide** (0.2 vs 7.6; between-group difference −7.4 doses; p = 0.0204)

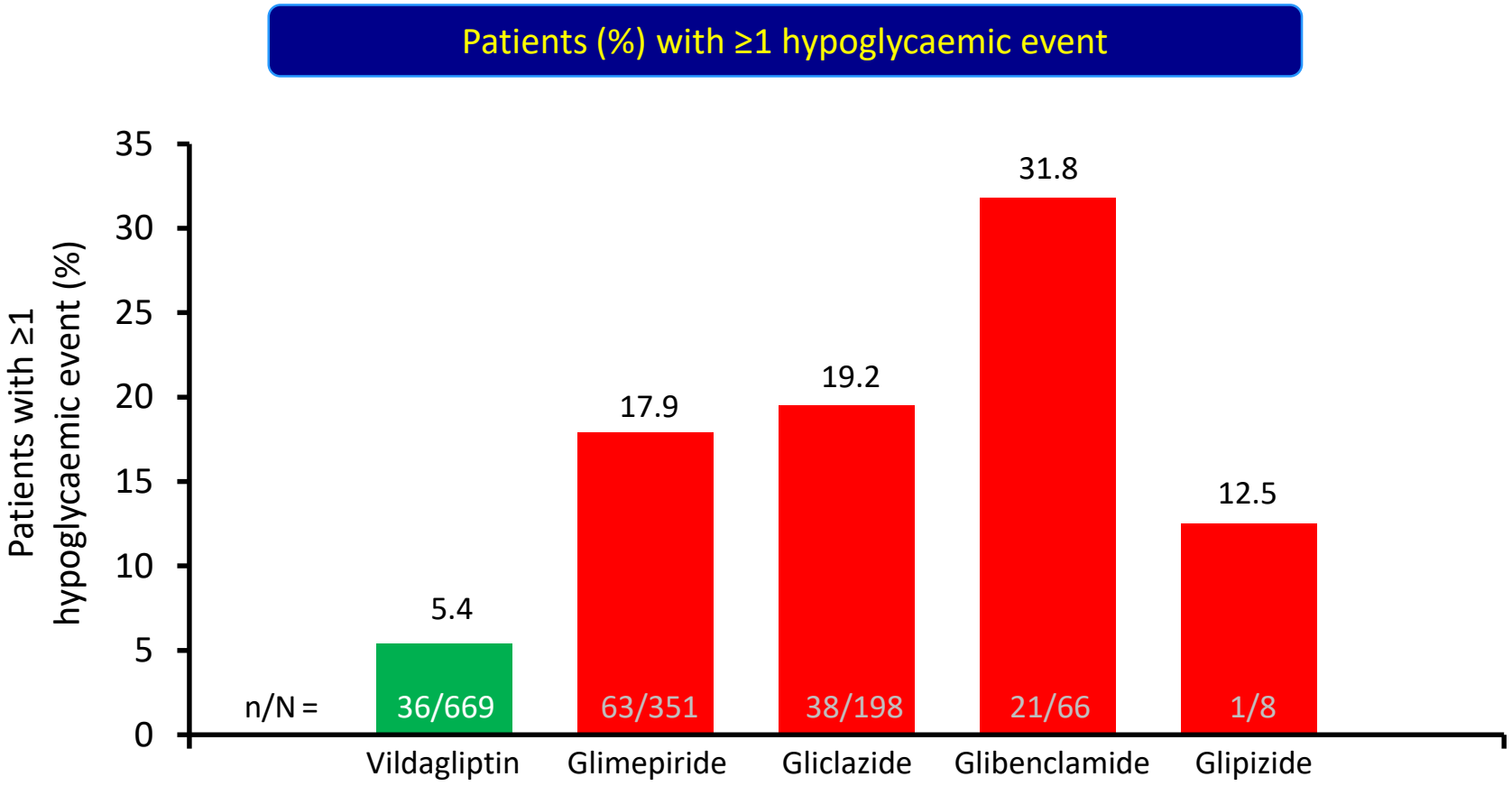
- On average, patients had 7 fold more missed doses with gliclazide than Vildagliptin

- Only 1 patient in the Vildagliptin group missed at least one dose, compared with 10 patients in the SU group

- There were a total of 4 missed doses in the Vildagliptin arm versus 266 in the SU arm

Hassanein M et al. Curr Med Res Opin 2011;27(7):1367-74

VIRTUE:
i risultati migliori sulle ipoglicemie per vildagliptin sono indipendenti dalle sulfoniluree impiegate



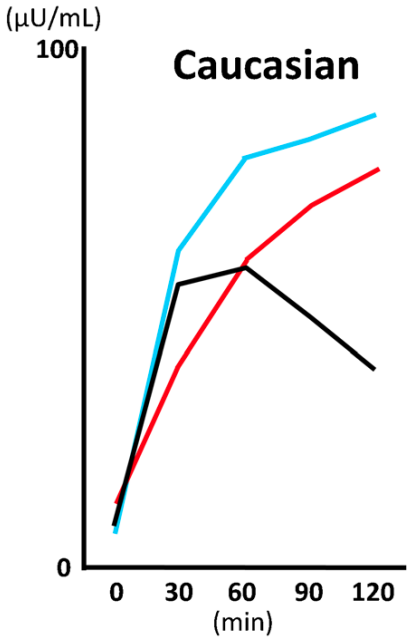
Post hoc descriptive analysis.
Safety set. SU = sulphonylurea

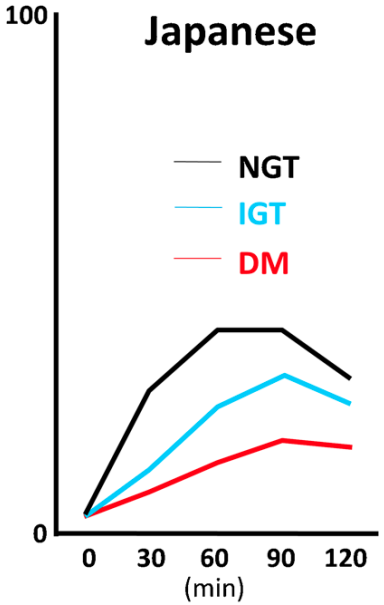
Al-Arouj M. et al, International Journal of Clinical Practice 2013

Estremo Oriente

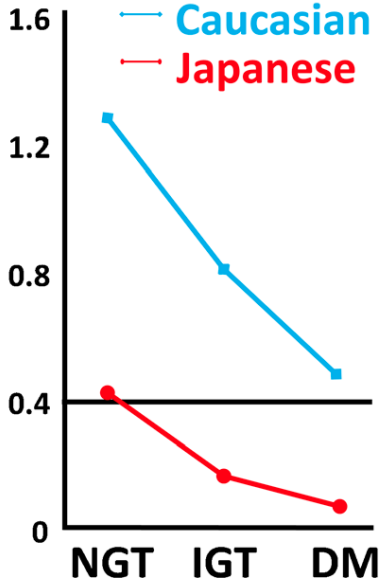
β Cell Dysfunction Versus Insulin Resistance in the Pathogenesis of Type 2 Diabetes in East Asians

Insulin response to oral glucose tolerance



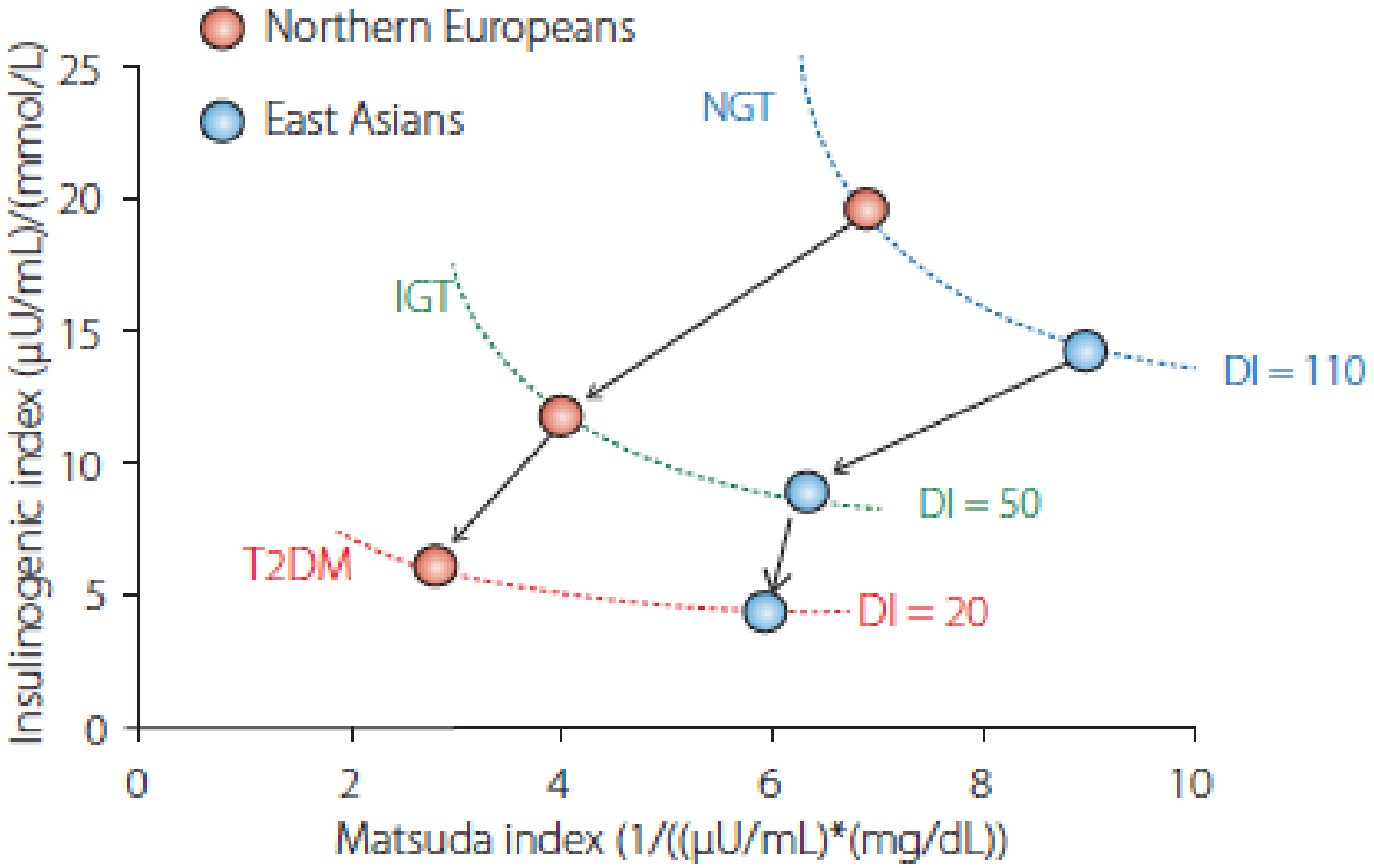


Insulinogenic Index and HOMA- IR



Yabe D et al. Curr Diab Rep (2015) 15: 36

A comparison of insulin secretion and insulin sensitivity between East Asians and Northern Europeans



Young Min Cho J Diabetes Invest 2015; 6: 495–507

Allele frequency of genetic variants associated with incretin biology in Europe and East Asia

Gene	Reported effects in incretin biology	Representative genetic variants	Risk allele frequency in Europeans	Risk allele frequency in East Asians
GIPR	Incretin effect, postprandial glucose and BMI	rs10423928	0.18[23]	0.18[89]
GLP-1R	β-cell response to GLP-1	s6923761	0.36†	0.02†
TCF7L2	GIPR and GLP-1R expression in β-cells, treatment response to linagliptin	rs7903146	0.27[28]	0.03[28]
KCNQ1	Glucose-stimulated GIP and GLP-1 secretion	rs2283228*	0.59[27]	0.92[27]
WFR1	GLP-1 induced insulin secretion	rs6446482*	0.56[90]	0.95[91]
CTRB1/2	Response to GLP-1 and DPP-4 inhibitors	rs7202877	0.89[31]	0.78†

*These particular variants have not been identified to be associated with the reported function of the gene. †Allele frequencies reported in the International HapMap Project site (http://hapmap.ncbi.nlm.nih.gov).

Young Min Cho J Diabetes Invest 2015; 6: 495–507

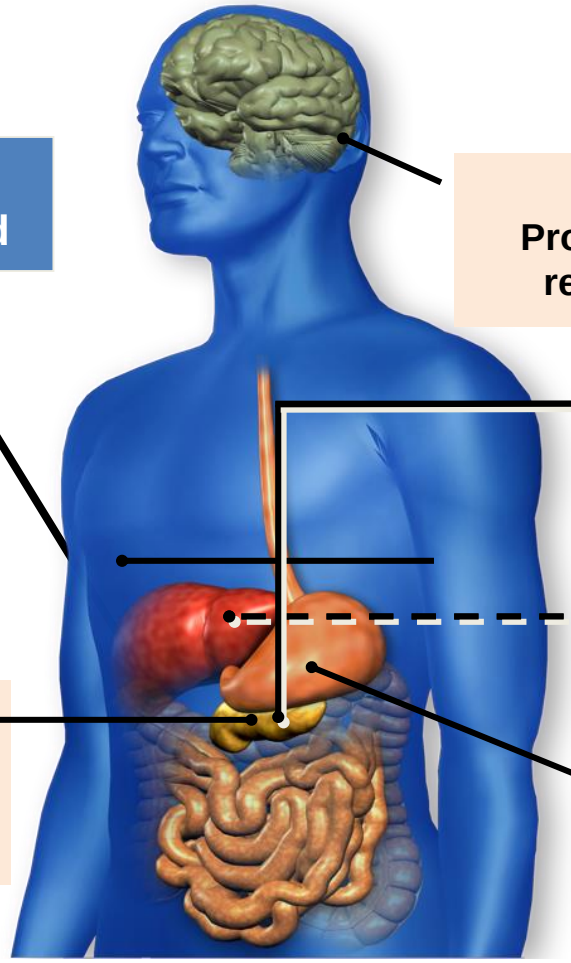
Comparisons of postprandial circulating glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide concentrations according to glucose tolerance statuses in East Asians

Population and reference	Comparison group	Types of nutrients	GLP-1	GIP	DPP-4
Japanese, Lee *et al.*[37]	T2DM (n = 21), IGT (n = 7), NGT (n = 12)	Mixed meal, 480 kcal (carbohydrate:protein:fat = 2.8:1:1)	No difference in iAUC (intact)	No difference in iAUC (intact*)	No difference in plasma concentrations
		Oral glucose (75 g)	No difference in iAUC (intact)	No difference in iAUC (intact*)	
Japanese, Yabe *et al.*[38]	T2DM (n = 18), non-T2DM (n = 17)	Mixed meal, 480 kcal (carbohydrate:protein:fat = 2.8:1:1)	No difference in iAUC (both total and intact)	No difference in iAUC (both total and intact)	N/A
		Oral glucose (75 g)	No difference in iAUC (both total and intact)	No difference in iAUC (both total and intact)	
Koreans, Han *et al.*[36]	T2DM (n = 20), non-T2DM (n = 20)	Mixed meal, 556 kcal (carbohydrate 87 g protein 15 g, and fat 18 g)	No difference in iAUC (intact)	No difference in iAUC (total)	DPP-4 activity was increased in T2DM.
Koreans, Oh *et al.*[39]	T2DM (n = 16), NGT (n = 14)	Oral glucose (75 g)	No difference in iAUC (total)	No difference in iAUC (total)	N/A

The designation total or intact in parenthesis denotes total or intact hormones. *It was uncertain whether the ELISA kit used in the study measured intact or total glucose-dependent insulinotropic polypeptide (GIP). However, the authors assumed that the values should be intact GIP levels. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curves; IGT, impaired glucose tolerance; N/A, not available; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus.

Young Min Cho J Diabetes Invest 2015; 6: 495–507

GLP-1 effects in humans: understanding the natural role of incretins



GLP-1 secreted upon the ingestion of food

5. Brain:
Promotes satiety and reduces appetite[4,5]

2. α-cell:
Suppresses postprandial glucagon secretion[1]

3. Liver:
reduces hepatic glucose output[2]

1. β-cell:
Enhances glucose-dependent insulin secretion in the pancreas[1]

4. Stomach:
slows the rate of gastric emptying[3]

GLP-1=glucagon-like peptide-1

1. Nauck MA, et al. *Diabetologia* 1993;36:741–744;
2. 2. Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422;
3. 3. Nauck MA, et al. *Diabetologia* 1996;39:1546–1553;
4. Flint A, et al. *J Clin Invest* 1998;101:515–520; 5. Zander et al. *Lancet* 2002;359:824–830

Summary of the meta-analyses comparing the efficacy of incretin-based therapy in Asians and non-Asians

Types of therapies and reference/clinical end-points	Asian-dominant studies	Non-Asian-dominant studies	Difference and/or statistical significance
DPP-4 inhibitors[60]			
HbA1c-lowering from baseline (%)	−0.92 (−1.03 to −0.82)	−0.65 (−0.69 to −0.60)	−0.26 (−0.36 to −0.17), $P < 0.001$
RR of achieving HbA1c <7.0%	3.4 (2.6 to 4.7)	1.9 (1.8 to 2.0)	$P < 0.05$
GLP-1 receptor agonists[62]			
HbA1c-lowering from baseline (%)	−1.16 (−1.48 to −0.85)	−0.83 (−0.97 to −0.70)	−0.32 (−0.64 to −0.01), $P < 0.05$
RR of achieving HbA1c <7.0%	5.7 (3.8 to 8.7)	2.8 (2.4 to 3.3)	$P = 0.082$

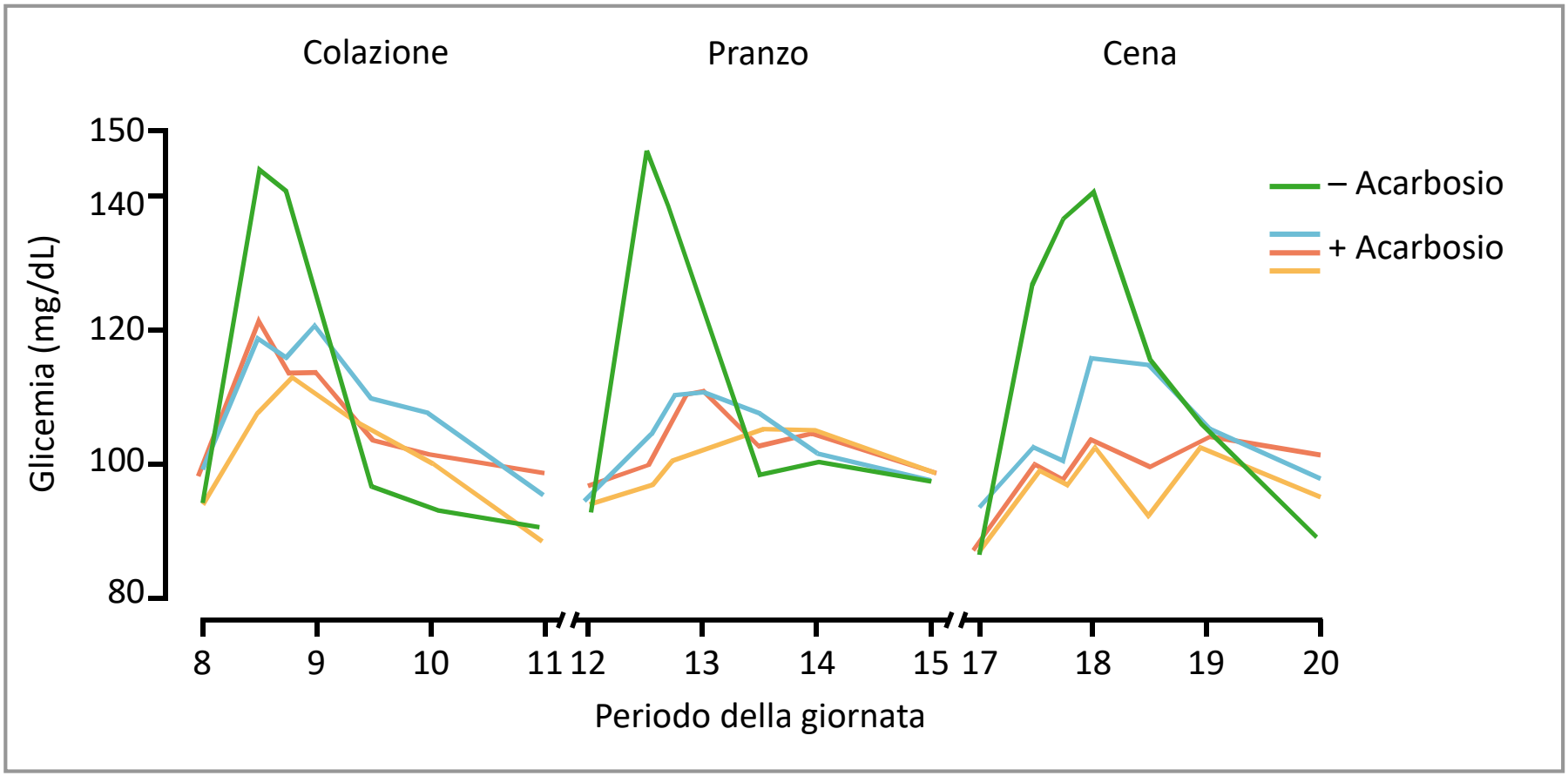
Numbers in parenthesis denote 95% confidence intervals. If the proportion of Asian participants was ≥50% in a study, it was classified as an Asian-dominant study. Otherwise, it was classified as a non-Asian-dominant study. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; RR, relative risk.

Young Min Cho J Diabetes Invest 2015; 6: 495–507

Changes in dietary pattern in East Asian countries and United States of America

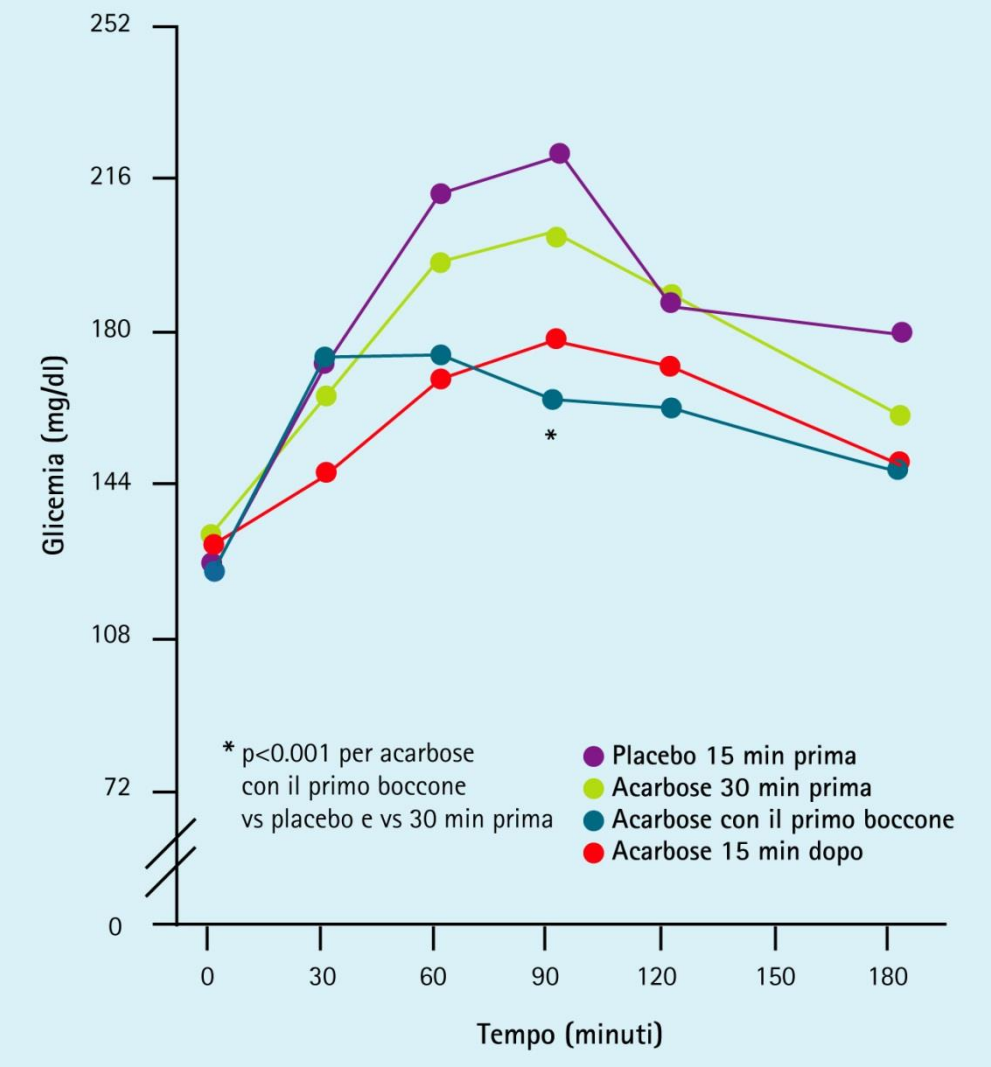
Japan	Year of survey	1950	1960	1970	1980	1990	2000	2005	2010
	Total energy intake (kcal)	2098	2096	2210	2219	2026	1948	1904	1849
	Protein (%)	13.0	13.3	14.0	14.2	15.5	16.0	16.2	14.6
	Fat (%)	7.7	10.4	18.9	22.6	25.3	26.5	25.1	26.1
	Carbohydrate (%)	79.7	76.1	66.6	55.7	56.7	54.6	56.1	55.7
China	Year of survey	1952	1962	1970	1982	1992	2000	2004	2009
	Total energy intake (kcal)	2056	1697	1978	2518	2328	M2146/F1941	M2064/F1807	M1943/F1969
	Protein (%)	9.3	9.7	9.6	10.6	11.7	M24.0/F23.7	M24.6/F24.4	M25.5/F24.4
	Fat (%)	7.6	5.5	7.4	17.5	22.5	M26.3/F26.4	M26.9/F26.4	M27.8/F29.2
	Carbohydrate (%)	83.0	84.8	82.9	71.8	65.8	M58.9/F58.7	M57.8/F58.3	M56.2/F54.9
Korea	Year of survey			1969	1979	1989	2000	2005	2010
	Total energy intake (kcal)			2105	2098	1871	1863	1826	1691
	Protein (%)			12.5	13.3	16.1	16.4	16.6	14.7
	Fat (%)			7.2	11.2	13.4	19.7	21.3	20.0
	Carbohydrate (%)			80.4	75.3	69.1	63.9	62.1	65.1
United States of America	Year of survey	1950	1960	1970	1980	1990	2000	2005	2010
	Total energy intake (kcal)	3200	3100	3300	3500	3800	4200	4100	4000
	Protein (%)	11.8	11.9	11.9	12.7	12.4	11.8	12.0	12.0
	Fat (%)	39.1	40.1	40.1	41.7	39.6	40.9	42.6	42.8
	Carbohydrate (%)	52.0	50.1	48.6	46.6	49.3	48.1	47.6	47.4

Acarbosio riduce l'iperglicemia post-prandiale ritardando l'assorbimento intestinale del glucosio



Bischoff, H. Clin Invest Med 1995;18:303–11.

Effetto del tempo di somministrazione di acarbosio sulla glicemia postprandiale



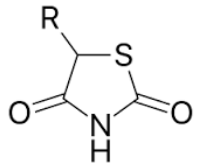
Profili glicemici in relazione ai diversi tempi di assunzione di acarbose o placebo rispetto ad un pasto standard. La significatività statistica si riferisce alla AUC (area sotto la curva).

L'assunzione di acarbosio deve avvenire all'inizio del pasto. L'assunzione 30' prima del pasto comporta una riduzione dell'efficacia del 50%.

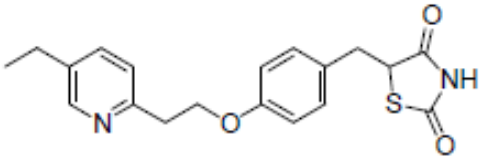
Rosak C et al Diabetic Medicine 12: 979-984, 1995

Thiazolidinediones (TZD)

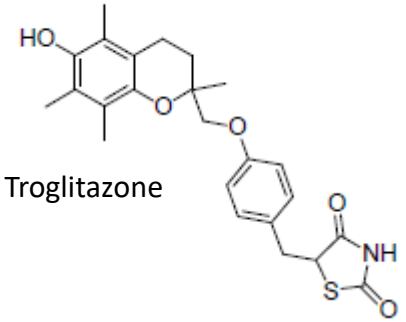
- ✓ Class of drugs for type 2 diabetes mellitus treatment
- ✓ They act primarily by increasing insulin sensitivity (insulin-sensitizing drugs)
- ✓ Synthetic small molecule activators of peroxisome proliferator-actived receptor ϒ (PPAR-ϒ) that contain a thiazole-2,4-dione (thiazolidinedione, TZD) functional group



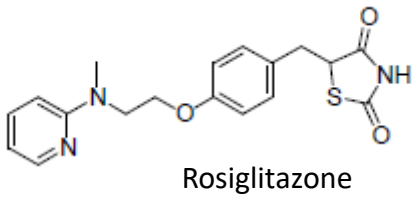
Thiazolidinedione



Pioglitazone



Troglitazone



Rosiglitazone

Terapeutic mechanisms of TZD in diabetes type 2

PPAR-ϒ-dependent mechanism

TZD binds and activates the canonical target PPAR-ϒ

Effects on transcriptional regulation of genes involved in lipid and glucose metabolism

PPAR-ϒ-independent mechanism

TZD interacts with non-PPAR-ϒ targets:

- Family of mitochondrial iron-sulfur proteins, the NEET family (CISD1-2)

Effects on mitochondrial function/energetic metabolism

- Complex of mitochondrial Pyruvate Carrier (Mpc1-2)

(Wright et al., Mol endocrinol 2014)

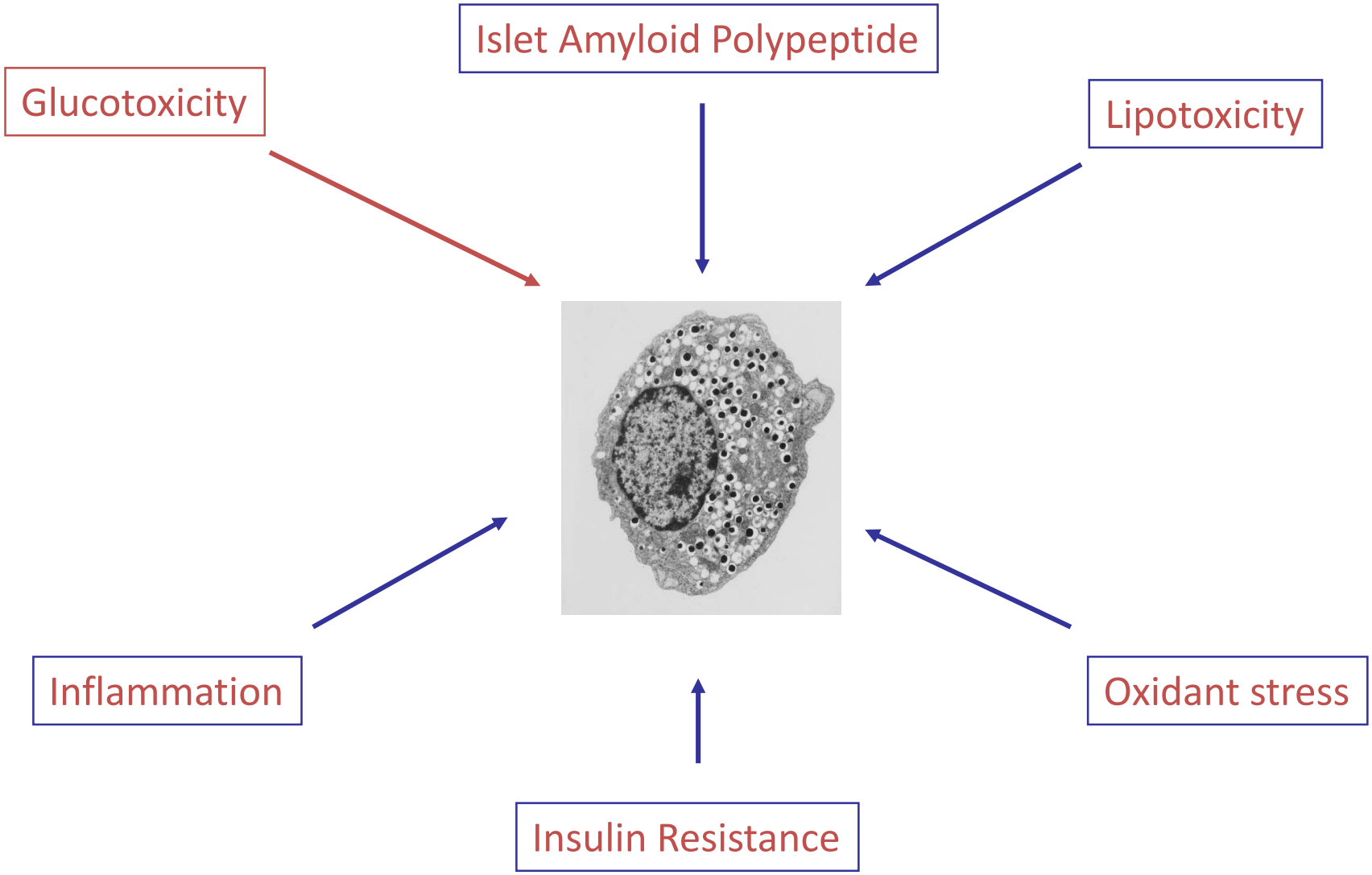
Theapeutic effects of TDZ-induced activation of PPAR-ϒ

TZD –induced activation of PPAR-ϒ in type 2 diabetic patients results in:

- ✓ decrease in the levels of circulating free fatty acids and increase in lipid storage in adipocytes
- ✓ increase in insulin sensitivity of adipocytes, muscle and liver
- ✓ decrease in insulin resistance
- ✓ enhacement in insulin signaling cascade

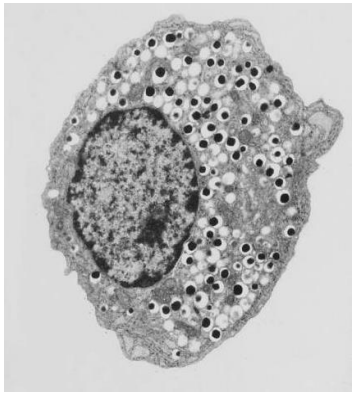
Soccio et al., Cell Metab. 2014

Insults to the Beta-Cell



E. Bonora, NMCD 2008; 18: 74-83

Protecting the Beta-Cell from Insults



Islet Amyloid Polypeptide

Glitazones

Glucotoxicity

Lifestyle
Acarbose
Metformin
SU & Glinides
Glitazones
Incretin system drugs
Insulin

Lipotoxicity

Lifestyle
Metformin
Orlistat
Glitazones

Inflammation

Lifestyle
Metformin
Glitazones
RAS inhibitors
Statins

Insulin Resistance

Lifestyle
Metformin
Glitazones

Oxidant stress

Lifestyle
Metformin
Glitazones
RAS inhibitors
Statins

E. Bonora, NMCD 2008; 18: 74-83

Effect of Pioglitazone Versus Metformin on Cardiovascular Risk Markers in Type 2 Diabetes

Table 2 Laboratory efficacy and safety variables with pioglitazone versus metformin

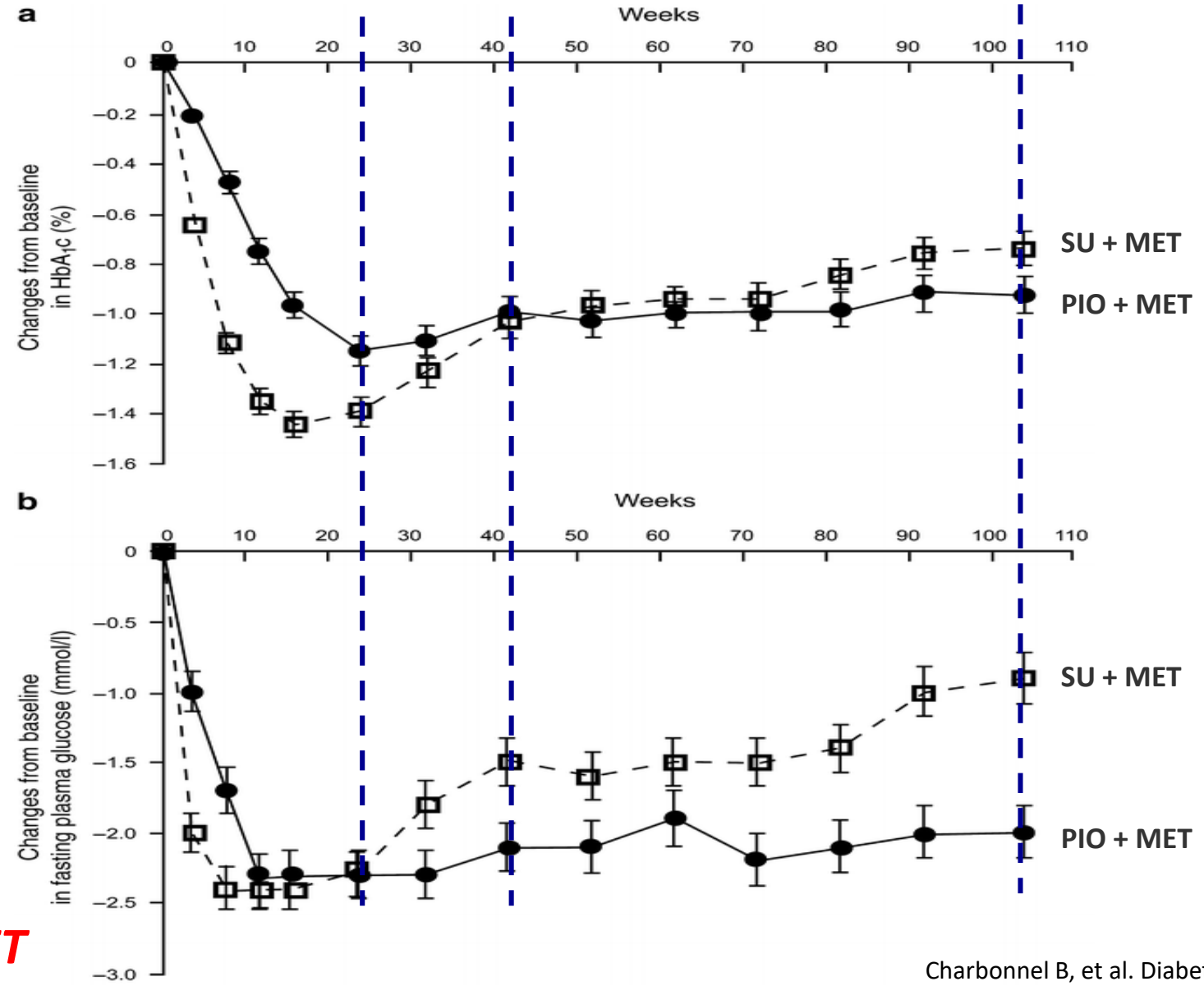
Parameter	Pioglitazone Baseline	Pioglitazone Week 16	Metformin Baseline	Metformin Week 16	*P* value
Number of patients	24	24	26	26	–
Markers of inflammatory response					
CRP (mg/L)	1.8 (1.1–4.7)	1.4 (0.5–2.5)*	2.0 (1.1–2.9)	1.8 (0.8–3.7)	0.04
P-selectin (μg/mL)	56.9 (26.7–140)	52.2 (29.3–126.8)	41.3 (31.2–68.1)	47.5 (29.2–74.1)	0.73
E-selectin (μg/mL)	70.2 (52.6–81.5)	57.8 (53.7–83.8)**	65.1 (59.1–79.9)	68.5 (62.9–78.3)	0.01
ICAM-1 (μg/mL)	292 (233–322)	269 (241–312)	251 (230–296)	252 (215–309)	0.87
CD40L (pg/mL)	1.6 (0.5–2.9)	2.0 (0.4–3.6)	1.3 (0.8–2.5)	1.4 (0.8–2.4)	0.98
Markers of platelet activation and thrombogenesis					
TXB2 (pg/mg creatinine)	146 (82–221)	121 (87–198)	123 (85–304)	159 (106–191)	0.61
TF (pg/mL)	113 (102–131)	139 (113–172)	141 (100–189)	145 (111–223)	0.23
PAI-1 (ng/mL)	55.1 (21.0–82.4)	35.8 (23.8–66.1)	32.7 (24.3–81.7)	39.5 (31.7–46.2)	0.69
Markers of oxidative stress					
Nitrotyrosine (nM)	6.7±1.5	6.6±1.6	6.5±1.4	6.3±1.0	0.82

Genovese S et al. Adv Ther 2013; 30 (2) 190-202

Glucose parameters					
FPG (mg/dL)	153±40	126±25***	144±47	135±48*	0.01
HbA_{1c} (%)	6.9±0.9	6.5±0.8**	6.7±0.7	6.5±0.7*	0.36
Insulin (mU/L)	8.3 (6.7–14.7)	6.3 (4.7–9.2)***	10.0 (5.3–12.8)	8.1 (5.6–10.6)	0.014
HOMA index	3.2 (2.1–5.4)	2.0 (1.3–2.9)***	3.2 (2.0–4.1)	2.3 (2.1–3.3)	0.015
Lipid parameters					
Total cholesterol (mg/dL)	212±24	222±35**	215±35	212±35	0.05
HDL-C (mg/dL)	41±10	45±11*	40±9	42±9***	0.19
LDL-C (mg/dL)	141±26	148±34	147±29	142±27	0.07
VLDL-C (mg/dL)	22.8 (18.2–33.5)	23.8 (16.0–32.2)	24.3 (17.4–36.4)	26.4 (17.8–37.2)	0.94
FFA (mmol/L)	0.4 (0.3–0.5)	0.4 (0.2–0.5)	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.07
Triglycerides (mg/dL)	114 (91–168)	119 (80–161)	122 (87–182)	132 (89–186)	0.94
Safety parameters					
Hemoglobin (g/dL)	14.4±1.1	14.1±1.0	14.6±1.0	14.4±1.1	0.58
WBCs (10^9/L)	6.2±1.5	5.9±1.4**	6.5±1.9	6.3±1.7	0.60
Neutrophils (%)	51.4±8.0	50.2±7.2	53.5±7.8	53.7±9.3	0.72
ALT (U/L)	26.5 (20.5–33.0)	19.0 (17.0–23.5)***	28.0 (23.0–48.0)	27.5 (23.0–46.0)	<0.0001
AST (U/L)	20.0 (18.0–23.0)	18.5 (15.0–22.0)*	20.0 (17.0–24.0)	21.0 (16.0–26.0)	0.003
γGT (U/L)	28.0 (21.0–36.5)	19.5 (14.0–26.5)***	35.5 (24.0–40.0)	32.0 (23.0–40.0)	<0.0001

Genovese S et al. Adv Ther 2013; 30 (2) 190-202

Long-term efficacy (104 wks) of pioglitazone + metformin *versus* gliclazide + metformin



QUARTET

Charbonnel B, et al. Diabetologia 2005

The ideal/personalized drug

- Efficacy
- Safety
- Other Clinical Advantages
- No/Few Adverse Effects
- Reasonable Cost/Value