VIII Convegno Nazionale Fondazione AMD

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TRA INERZIA TERAPEUTICA E APPROPRIATEZZA PRESCRITTIVA: IL VALORE DEL DPP-IV INIBITORE

Il trattamento precoce del diabete di tipo II: lo stato dell'arte

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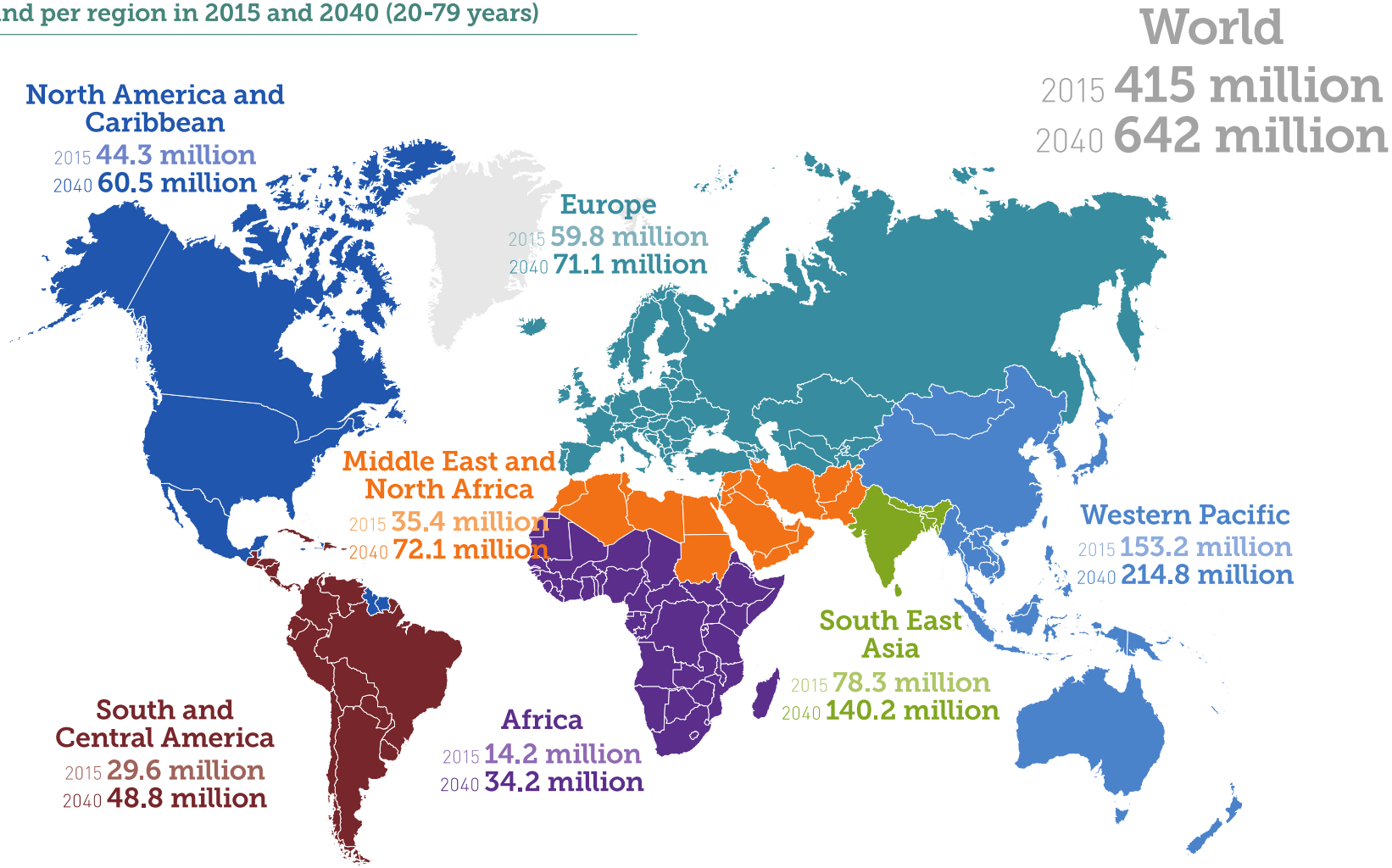
PALERMO, 17-19 NOVEMBRE 2016

Diabetes: A global emergency

International Diabetes Federation

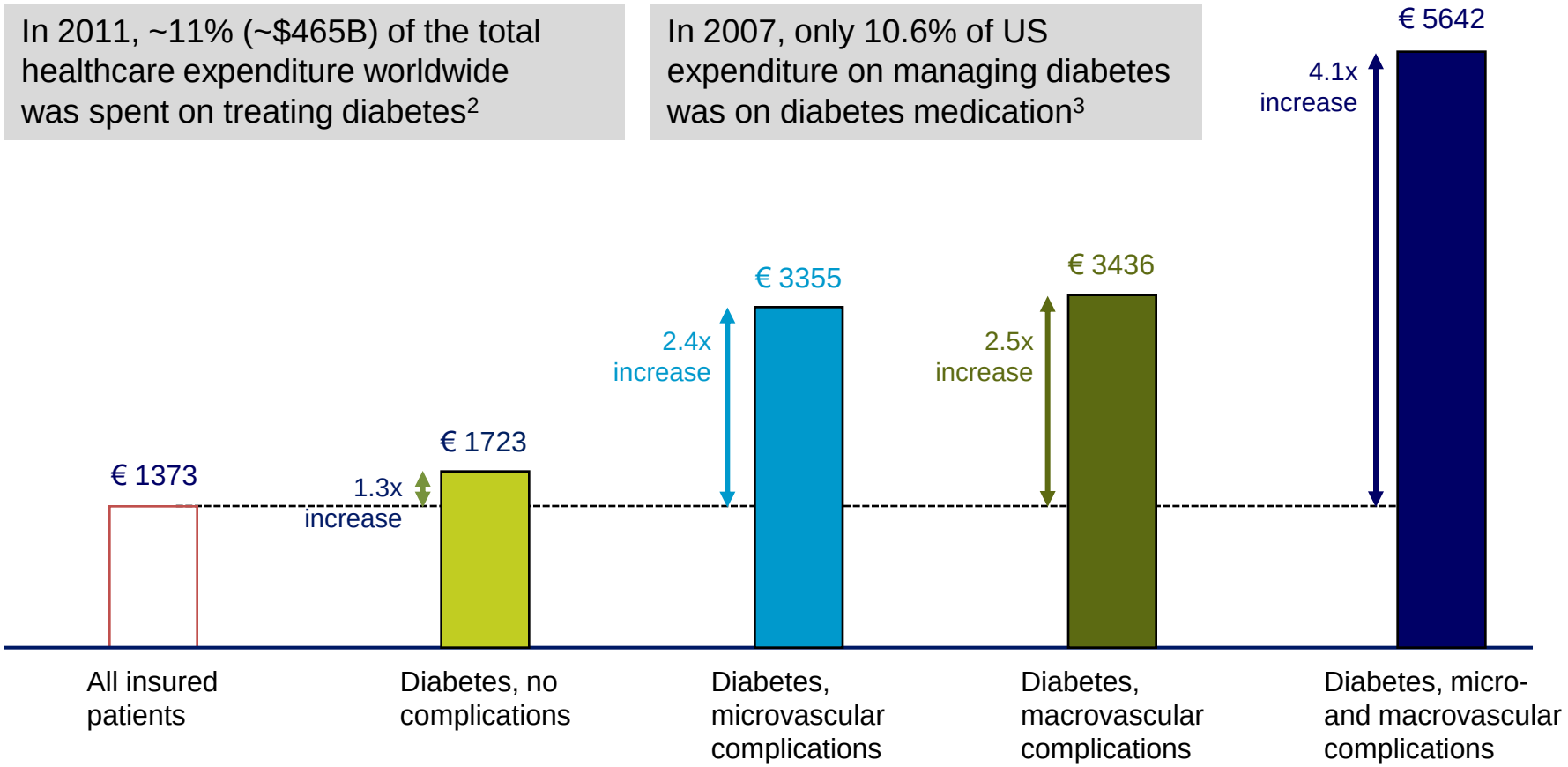
Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



Treating type 2 diabetes and its complications creates major economic burdens

In 2011, ~11% (~$465B) of the total healthcare expenditure worldwide was spent on treating diabetes[2]

In 2007, only 10.6% of US expenditure on managing diabetes was on diabetes medication[3]



Annual costs per patient[1]

Based on an exchange rate of 1 Euro = 1.4156 US dollars. Exchange rate as of 30 Oct 2011.

1. *Liebl et al. Dtsch Med Wschr 2001;126:585–89 (CODE-2 Study);*
2. *IDF Diabetes Atlas, 5th Edition. http://www.idf.org/diabetesatlas/5e/healthcare-expenditures. Accessed November 2013;*
3. *American Diabetes Association Diabetes Care 2008;31:596–615*

La terapia del diabete è «*treat to target*»

Standard italiani
per la cura del diabete mellito
2016

Questo testo è disponibile, in forma elettronica
riferimento: www.standarditaliani.it, raggiung

Data di rilascio: 20 giugno 2016

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diabete mellito 2016
Tutti i diritti riservati. Nessuna parte di questo documento può
scopo, senza l'autorizzazione esplicita di AMD e SID.

Si ricorda che è sempre responsabilità del medico curante, in base alle proprie esperienze e nel rispetto della normativa vigente e della deontologia professionale, determinare la cura migliore per il paziente. Per le indicazioni terapeutiche, la posologia, i modi di somministrazione e per le altre caratteristiche delle singole specialità medicinali citate, fare riferimento ai rispettivi riassunti delle caratteristiche di prodotto autorizzati. I medici sono invitati a contattare le rispettive

Partecipanti al progetto

Comitato di coordinamento:
Marco Giorgio Baroni
Riccardo Candido
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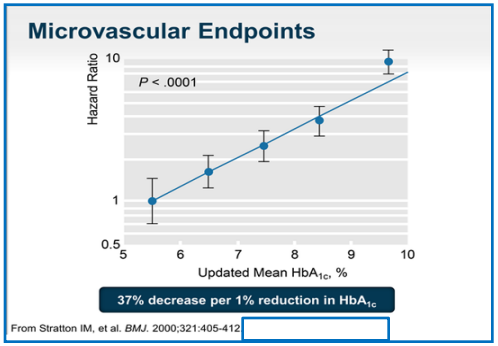
Maria Chantal Ponziani
Giuseppina Russo

UKPDS (33); The Lancet 1998



Reduction of Macrovascular Risk with HbA_{1c} Lowering Has Not Been Consistently Observed

Randomized Controlled Trials	Follow-up (median)	Microvascular Risk	Macrovascular Risk
DCCT[1]	6.5 years (mean)	↓	↔
UKPDS[2]	10 years	↓	↔
ADVANCE[3]	5 years	↓	↔
ACCORD[4,5]	3.7 years	↓	↔
VADT[6,7]	5.6 years	↔	↔
Observational Long-term Follow-up	**Follow-up (median)**	**Microvascular Risk**	**Macrovascular Risk**
DCCT/EDIC[8,9]	4 (micro) 11 (macro) years post-intervention	↓	↓
UKPDS[10]	10 years post-intervention	↓	↓
ADVANCE-ON[11]	9.9 years post-intervention	↔	↔
VADT[12]	9.8 years post-intervention	not reported	↓

Tabella 9. Obiettivi glicemici in diabetici adulti tipo 1 e 2

HbA_{1c} <53 mmol/mol (<7,0%)* (≤48 mmol/mol [≤6,5%] in singoli pazienti)
Glicemia a digiuno e preprandiale 70-130 mg/dl
Glicemia postprandiale§ <160 mg/dl

* Facendo riferimento ai valori di 20-42 mmol/mol (4,0-6,0%) della popolazione non diabetica, con il metodo utilizzato dal DCCT.

§ La misurazione della glicemia postprandiale deve essere effettuata tra 1 e 2 ore dopo l'inizio del pasto (IDF 2011).

2. OBIETTIVI GLICEMICI

RACCOMANDAZIONI

In tutte le persone con diabete le glicemie e l'HbA_{1c} vanno mantenute entro i livelli appropriati per la specifica condizione clinica al fine di ridurre il rischio di complicanze acute e croniche.
(Livello della prova I, Forza della raccomandazione A)

EARLY

Il trattamento dell'iperglicemia deve essere tempestivamente aggiornato quando il controllo è perduto e l'obiettivo di HbA_{1c} dovrebbe essere collocato sotto 53 mmol/mol (7,0%) (**Tabella 9**), valori che consentono di prevenire l'incidenza e la progressione delle complicanze microvascolari.
(Livello della prova I, Forza della raccomandazione B)

Un obiettivo di HbA_{1c} pari o inferiore a 53 mmol/mol (7,0%) è generalmente consigliabile per i soggetti adulti con diabete anche per prevenire l'incidenza e la progressione delle complicanze macrovascolari.
(Livello della prova III, Forza della raccomandazione B)

EARLY

Obiettivi glicemici più stringenti (HbA_{1c} ≤48 mmol/mol [≤6,5%]) dovrebbero essere perseguiti in pazienti di nuova diagnosi o con diabete di durata (<10 anni), senza precedenti di malattie cardiovascolari, abitualmente in discreto compenso glicemico e senza comorbilità che li rendano particolarmente fragili.
(Livello della prova III, Forza della raccomandazione C)

Obiettivi di compenso glicemico meno stringenti (HbA_{1c} ≤64 mmol
perseguiti in pazienti con diabete di lunga durata (>10 anni) sopra
cardiovascolari o una lunga storia di inadeguato compenso glicemic
Questo è particolarmente appropriato se la terapia consta di farma
(Livello della prova VI, Forza della raccomandazione B)

Nei pazienti in terapia intensiva si consiglia l'utilizzo di algoritr
insulinica in quanto facilitano il raggiungimento degli obiettivi glicer
(Livello della prova II, Forza della raccomandazione B)

Il rischio di ipoglicemie deve essere considerato nella valutazione c
paziente.
(Livelo della prova III, Forza della raccomandazione B)

Standard italiani
per la cura del diabete mellito
2016

Questo testo è disponibile, in forma elettronica e interattiva, presso il website di riferimento: www.standarditaliani.it, raggiungibile anche dai website di AMD e SID

Data di rilascio: 20 giugno 2016

© Associazione Medici Diabetologi (AMD) - Società Italiana di Diabetologia (SID) - *Standard italiani per la cura del diabete mellito 2016*
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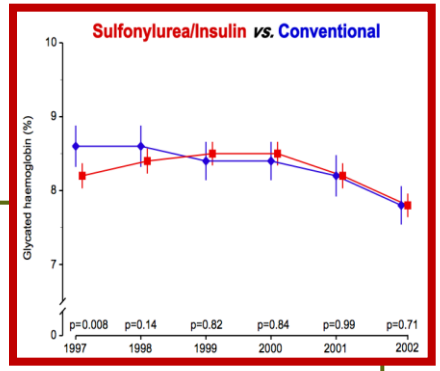
Ma i target vanno personalizzati… "early" è diverso da "late"

Good *early* glycaemic control matters:



UKPDS original results:
Intensive vs. conventional treatment

10-year post-trial follow-up
(non-interventional)

1977–1991
Randomisation

1997
(20 years)

2007
(30 years)

12%*

25%*

16%

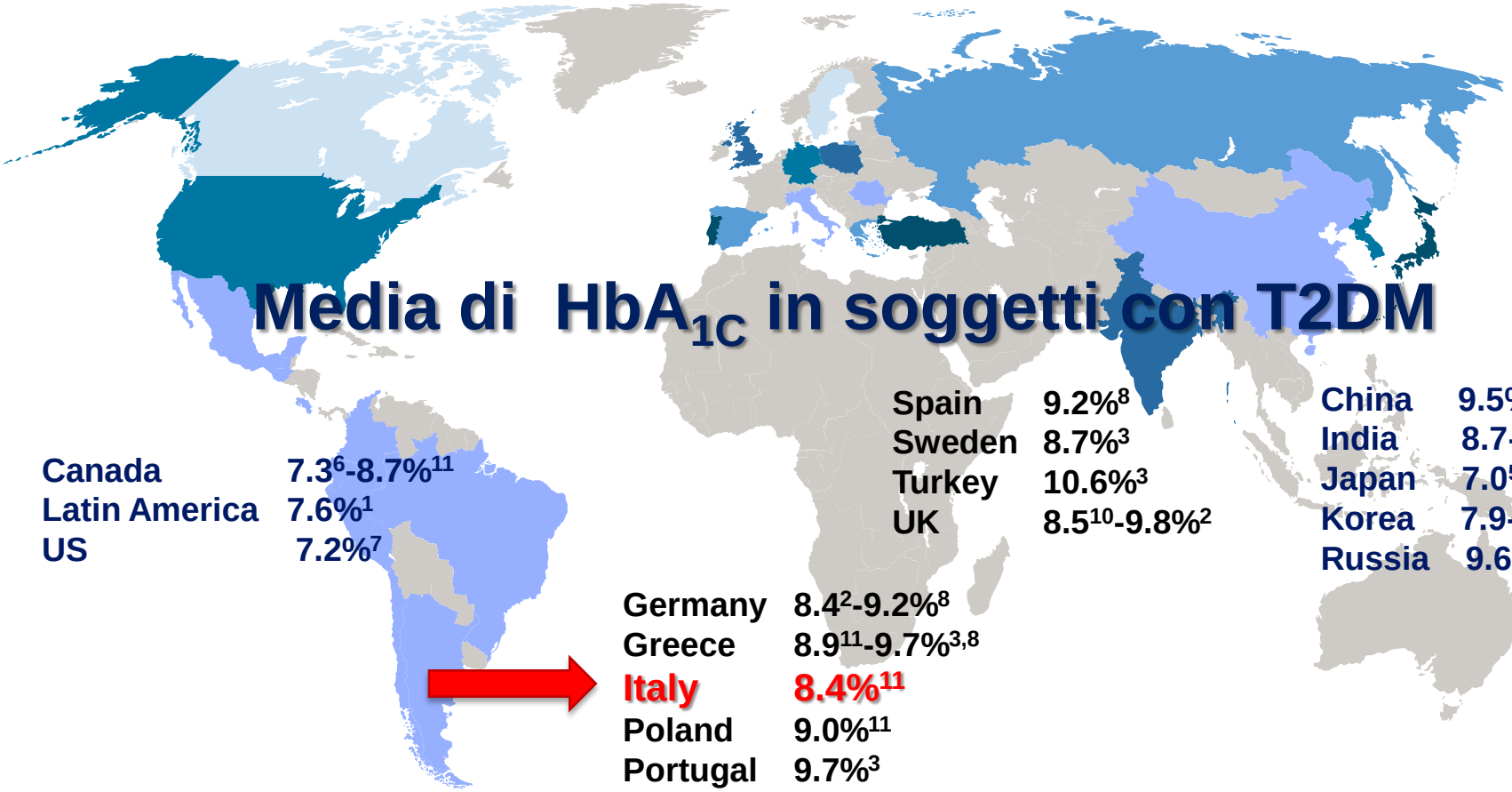
- Any diabetes-related endpoint
- Microvascular disease
- Myocardial infarction

In type 2 diabetes, improvements in glycaemic control reduce the risk of early and late complications

*$p<0.05$; intensive vs. conventional treatment

Adapted from Holman et al, N Engl J Med, 2008;359:1577–89
UKPDS Study Group, Lancet, 1998;352:837–53

Nessun paese raggiunge i target desiderati



Media di HbA_{1C} in soggetti con T2DM

Canada	7.3[6]-8.7%[11]
Latin America	7.6%[1]
US	7.2%[7]

Spain	9.2%[8]
Sweden	8.7%[3]
Turkey	10.6%[3]
UK	8.5[10]-9.8%[2]

China	9.5%[11]
India	8.7-9.6%[9,11]
Japan	7.0[5]-9.6%[11]
Korea	7.9-8.7%[4]
Russia	9.6%[11]

Germany	8.4[2]-9.2%[8]
Greece	8.9[11]-9.7%[3,8]
Italy	**8.4%[11]**
Poland	9.0%[11]
Portugal	9.7%[3]
Romania	9.9%[3]

1. *Lopez Stewart et al. Rev Panam Salud Publica 2007;22:12-20;*
2. *Kostev & Rathmann Primary Care Diabetes 2013;7:229-33;*
3. *Oguz et al. Curr Med Res Opin 2013;29:911-20;*
4. *Ko et al. Diab Med 2007;24:55-62;*
5. *Arai et al. Diab Res Clin Prac 2009;83:397-401;*
6. *Harris et al. Diabetes Res Clin Pract 2005;70:90-7;*
7. *Hoerger et.al. Diabetes Care 2008;31:81-6;*
8. *Liebl et al. Diab Ther 2012;3:e1-10;*
9. *Shah et al. Adv Ther 2009;26:325-35;*
10. *Blak et al. Diab Med 2012;29:e13-20;*
11. *Valensi et al. Int J Clin Pract 2008;62:1809-19*

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Sex Disparities in the Quality of Diabetes Care: Biological and Cultural Factors May Play a Different Role for Different Outcomes

A cross-sectional observational study from the AMD Annals initiative

Table 2—*Quality indicators of diabetes care according to sex*

	Quality indicators (%)		Crude OR (95% CI)	OR adjusted for case mix (age, diabetes duration, BMI) (95% CI)	OR adjusted for case mix and cluster (95% CI)	ICC
	M	F				
Process indicators						
HbA_{1c}	92.6	92.2	0.95 (0.93–0.97)	0.97 (0.94–1.00)	1.01 (0.98–1.05)	0.35
Favorable outcome indicators						
HbA_{1c} ≤7.0% (≤53 mmol/mol)	45.5	41.7	0.85 (0.84–0.87)	0.88 (0.87–0.89)	0.86 (0.85–0.87)	0.10
Indicators of treatment intensity/appropriateness						
No insulin despite HbA_{1c} >9.0% (>75 mmol/mol)	47.3	37.6	0.69 (0.64–0.74)	0.77 (0.74–0.81)	0.76 (0.73–0.80)	0.07
Overall quality of care						
Q score <15	7.2	8.5	1.34 (1.25–1.45)	1.15 (1.12–1.18)	1.17 (1.14–1.20)	0.11
Q score >25	38.0	34.2	0.73 (0.70–0.77)	0.89 (0.87–0.90)	0.89 (0.87–0.90)	0.14

Rossi C, Manicardi V et al., Diabetes Care 2013

Perchè non riusciamo a raggiungere i target?

1. *Complessità della cura*
2. *Inerzia terapeutica e scarsa aderenza*
3. *Complessità del paziente*
4. *Perché i target sono difficili da raggiungere e….*
5. *mantenere*

Perchè non riusciamo a raggiungere i target?

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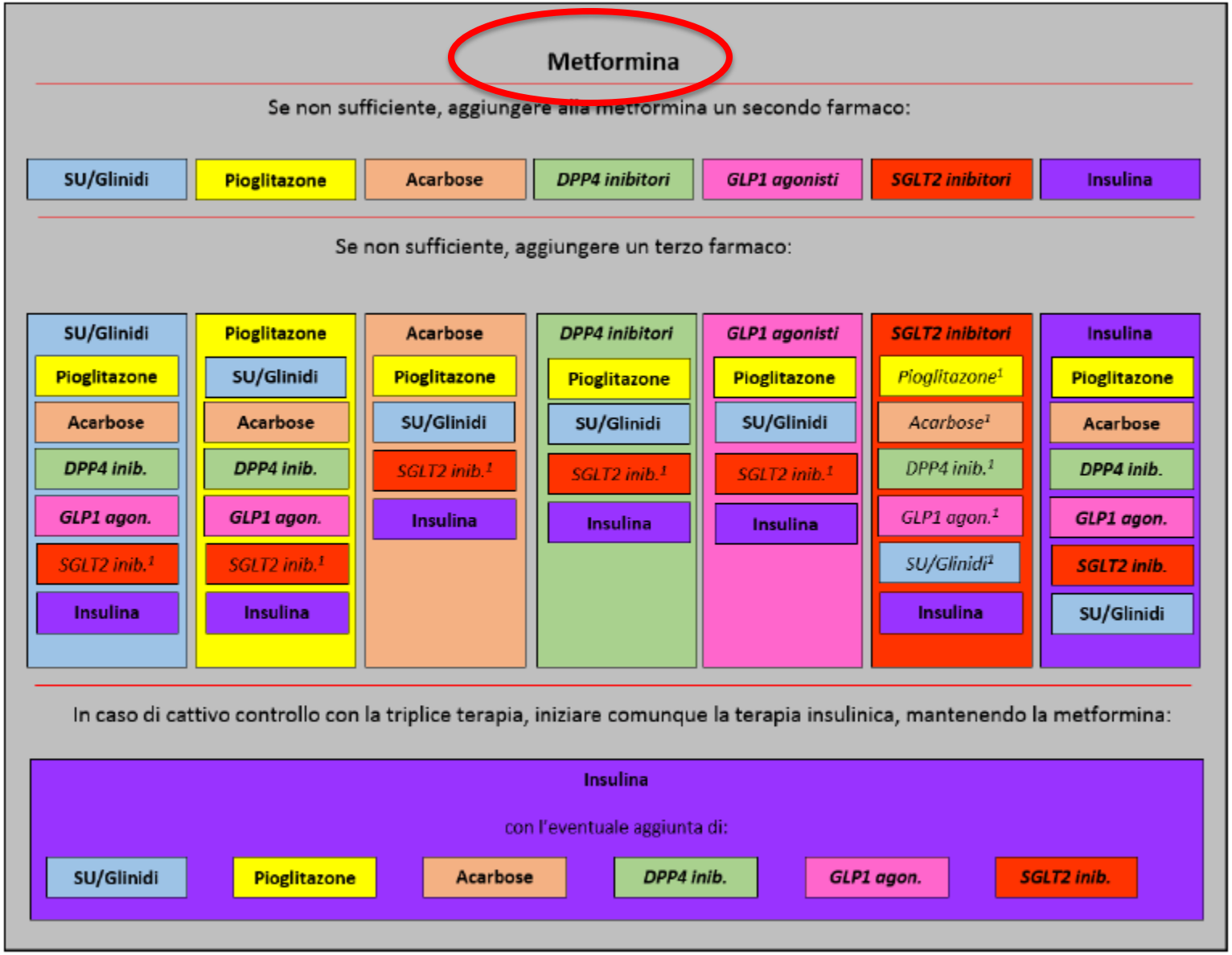
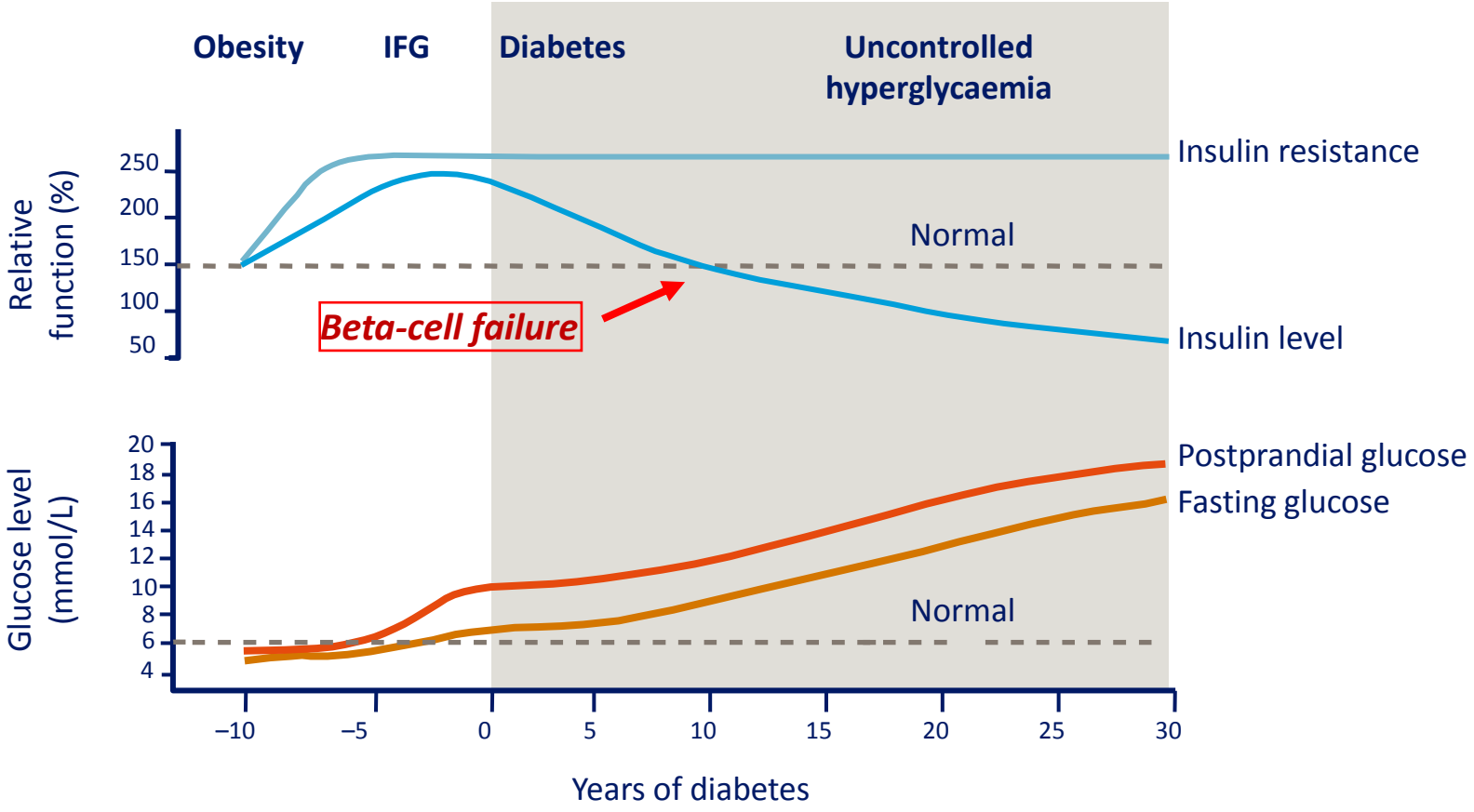
4. *Perché i target sono difficili da raggiungere e….*
5. *mantenere*

Figura 2. Schema generale della terapia farmacologica del diabete di tipo 2



Standard Italiani per la cura del diabete 2016

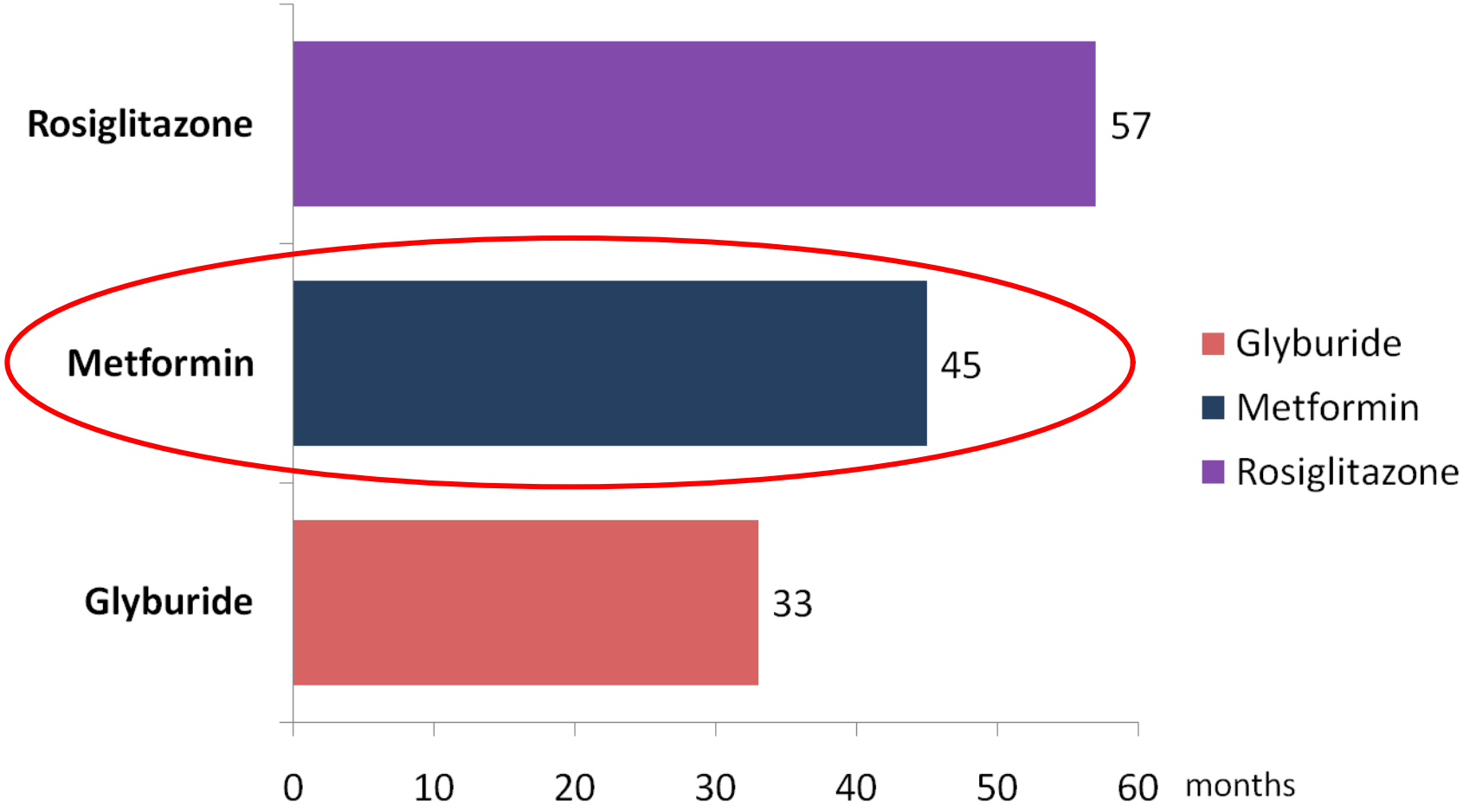
Disease progression: ADD-ON therapy becomes necessary in type 2 diabetes



IFG, impaired fasting glucose

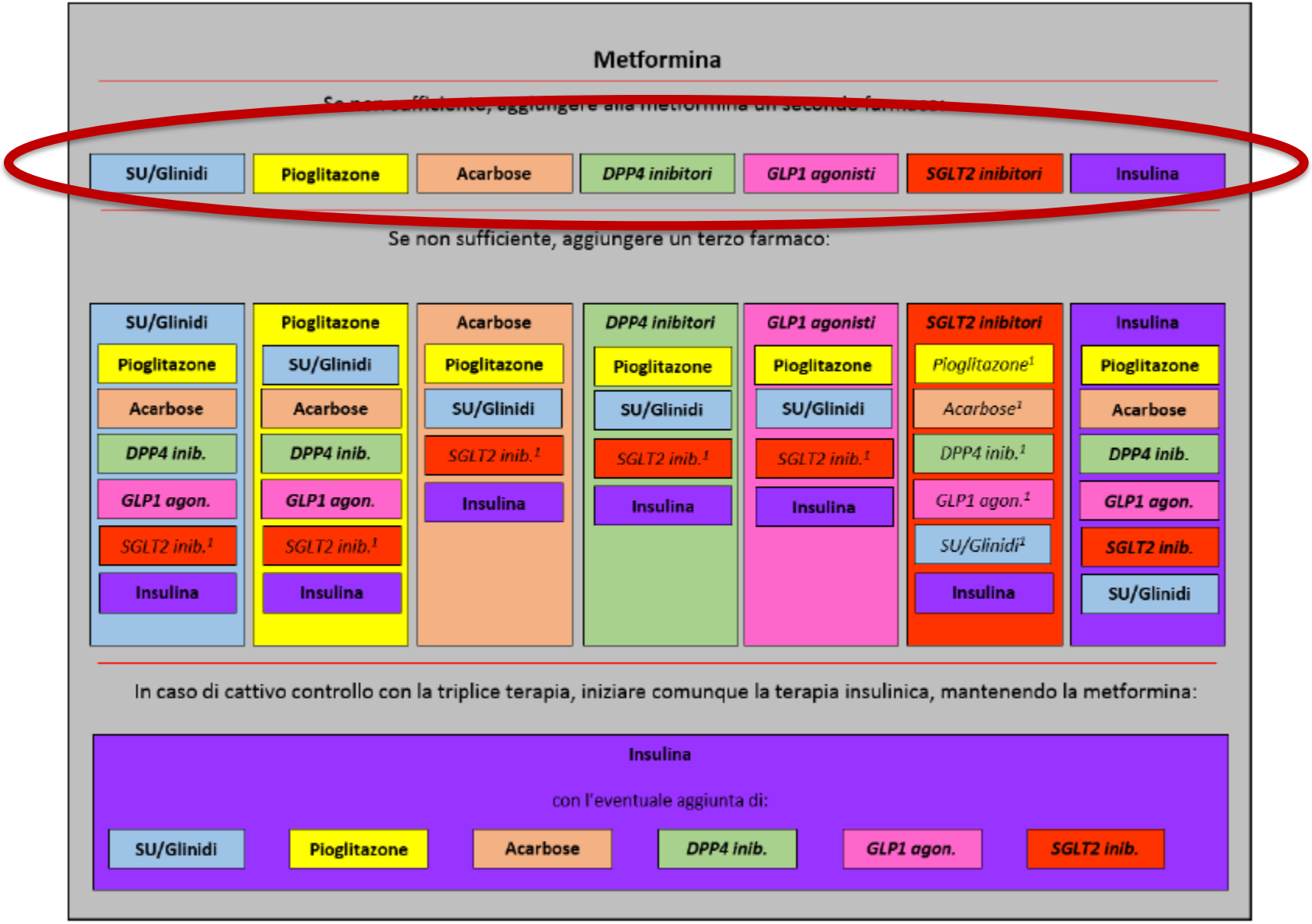
Adapted from Bergenstal *et al. Endocrinology.* Philadelphia, PA: WB Saunders Co; 2001:821–35

Durata del controllo glicemico: Tempo alla $HbA1_c$ > 7% (ADOPT)



Kahn SE et al. NEJM 2006; **355**: 2427–2443

Figura 2. Schema generale della terapia farmacologica del diabete di tipo 2



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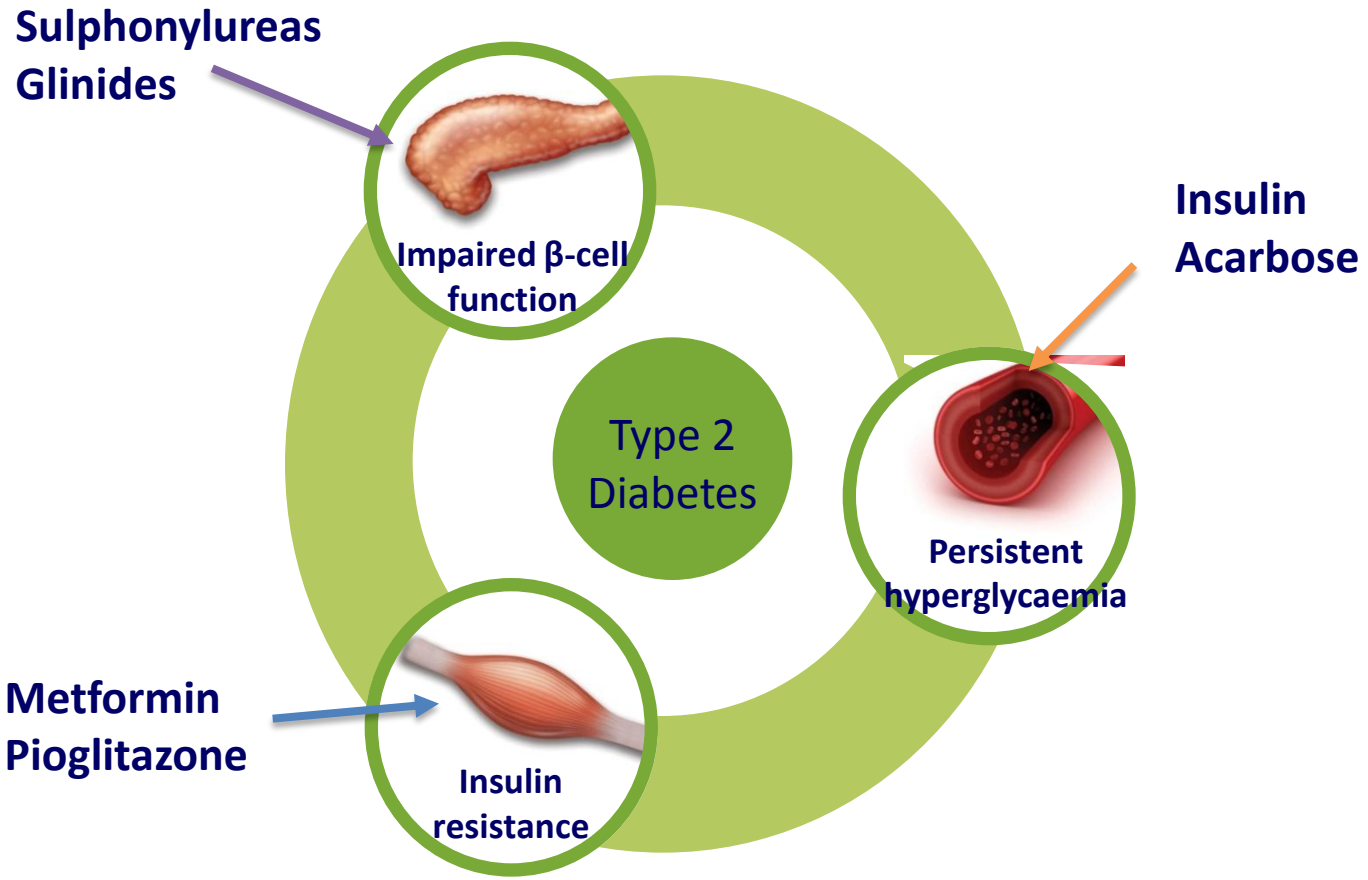
T2D is a dysregulation of glucose homeostasis characterized by persistent hyperglycaemia, impaired β-cell function and insulin resistance[1–3]

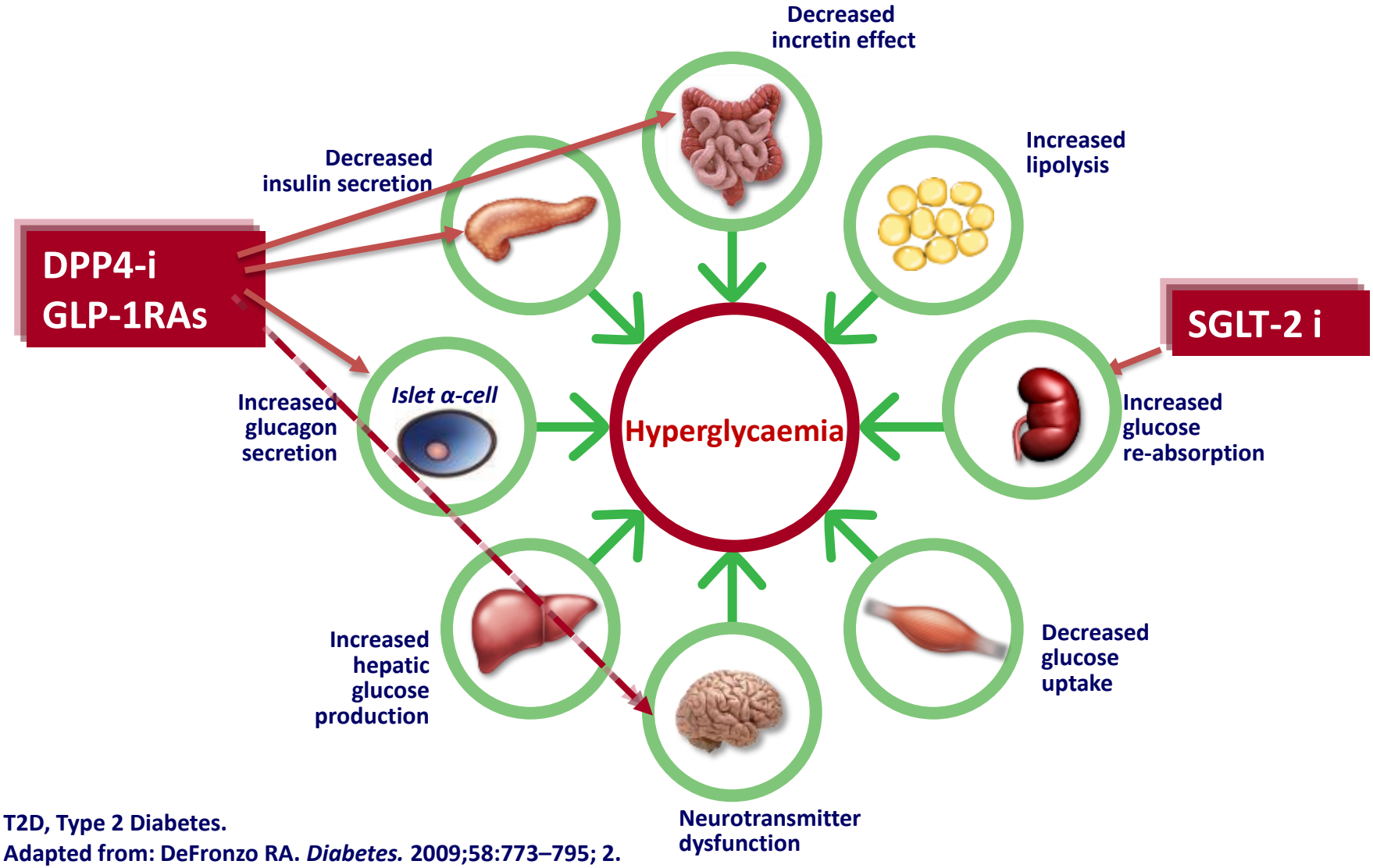


T2D, Type 2 Diabetes.

1. Adapted from: DeFronzo RA. *Diabetes*. 2009;58:773–795; 2. Adapted from: Poitout V, Robertson RP. *Endocrinology*. 2002;143:339–342;

3. Adapted from: Robertson RP, et al. *Diabetes*. 2003;52:581–587.

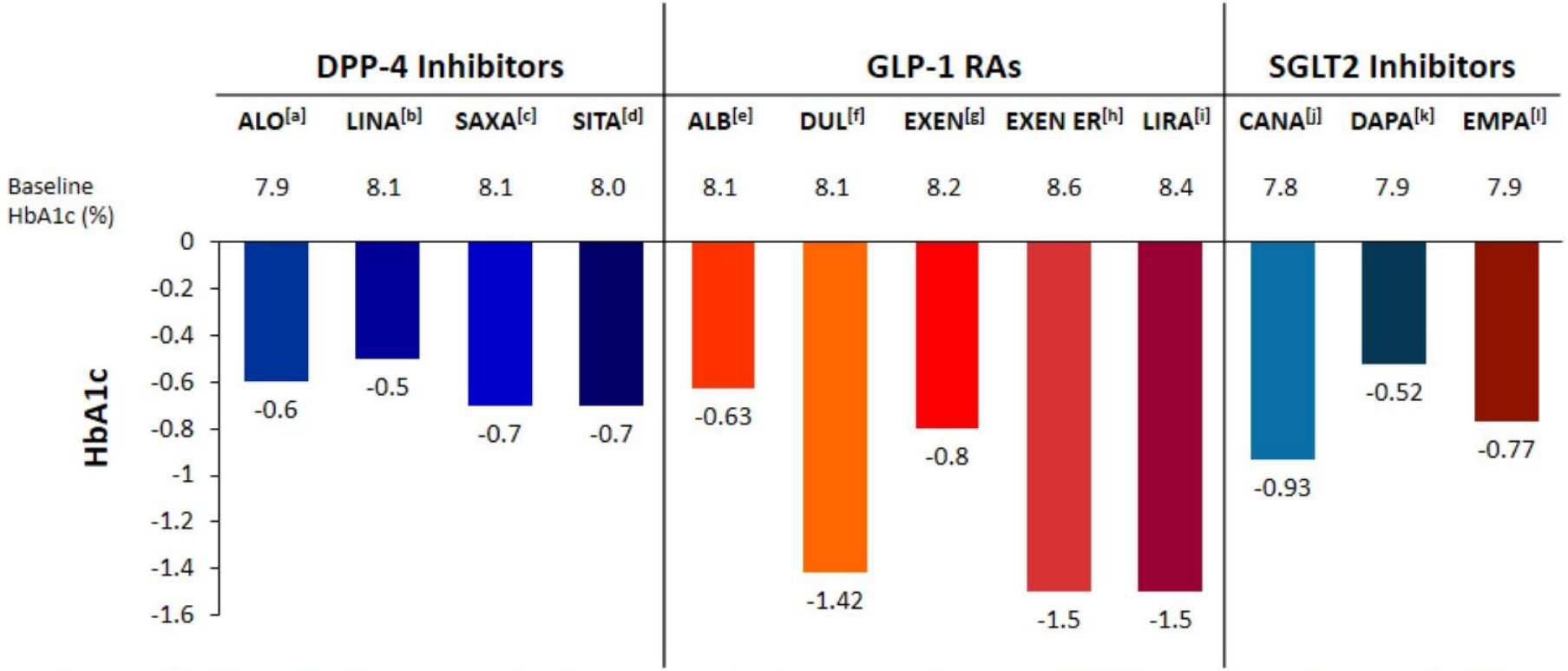
From the triumvirate to the *ominous octet*: a new paradigm for the treatment of T2D[1,2]



T2D, Type 2 Diabetes.
Adapted from: DeFronzo RA. *Diabetes.* 2009;58:773–795; 2.
Adapted from: Tahrani AA, et al. *Lancet*. 2011;378:182–197.

Comparison of Glycemic Reduction With Other Noninsulin Agents

DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin (Absolute Changes from Baseline; Not Head-to-Head Trials*)



*Data shown are for informational purposes only and not meant to be direct comparisons, as study designs and populations may be different.

a. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55; b. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74; c. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655; d. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643; e. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148; f. Dungan KM, et al. *Lancet*. 2014;384:1349-1357; g. DeFronzo RA, et al. *Diabetes Care*. 2005;28:1092-1100; h. Bergenstal RM, et al. *Lancet*. 2010;376:431-439; i. Pratley RE, et al. *Lancet*. 2010;375:1447-1456; j. Cefalu WT, et al. *Lancet*. 2013;382:941-950; k. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022; l. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659.

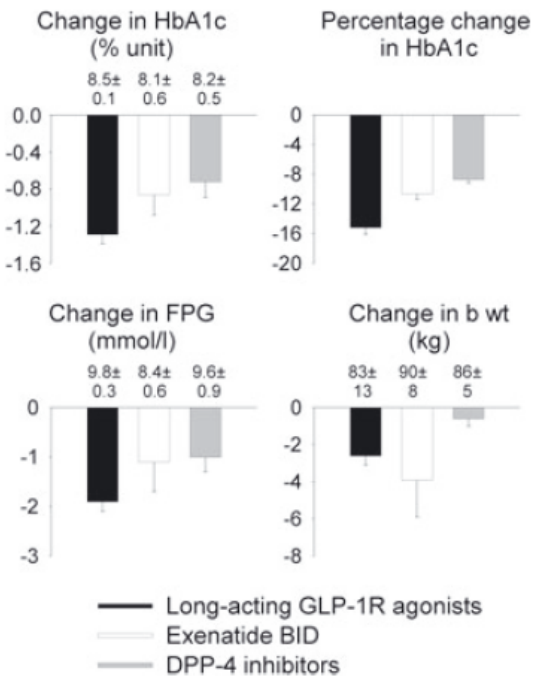
original article

Diabetes, Obesity and Metabolism 14: 762–767, 2012.
© 2012 Blackwell Publishing Ltd

Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes—a review and meta analysis

C. F. Deacon[1], E. Mannucci[2] & B. Ahrén[3]

[1]Department of Biomedical Sciences, Copenhagen University, Copenhagen, Denmark
[2]Diabetes Agency, Careggi Teaching Hospital, Florence, Italy
[3]Department of Clinical Sciences Lund, Lund University, Lund, Sweden



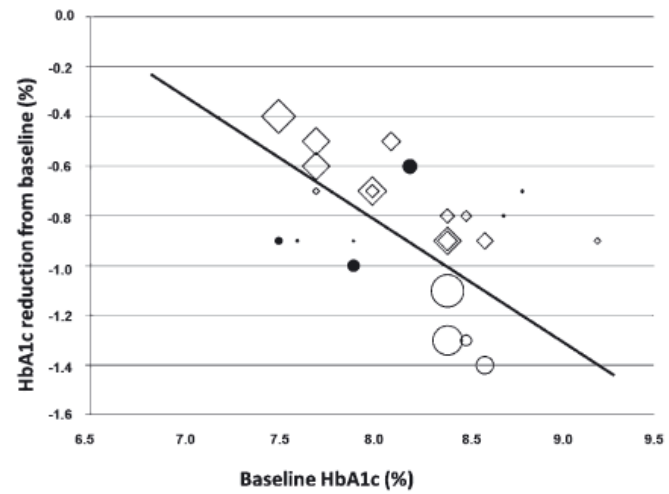


Figure 2. Relation between baseline HbA1c and change in HbA1c following 16–30 week treatment with incretin-based therapy as add-on to metformin in subjects with type 2 diabetes. Open circles show long-acting glucagon-like peptide-1 (GLP-1) receptor agonists, closed circles exenatide BID and squares dipeptidyl peptidase-4 (DPP-4) inhibitors. Trial size illustrated by size of symbol.

Perchè non riusciamo a raggiungere i target?

1. *Complessità della cura*
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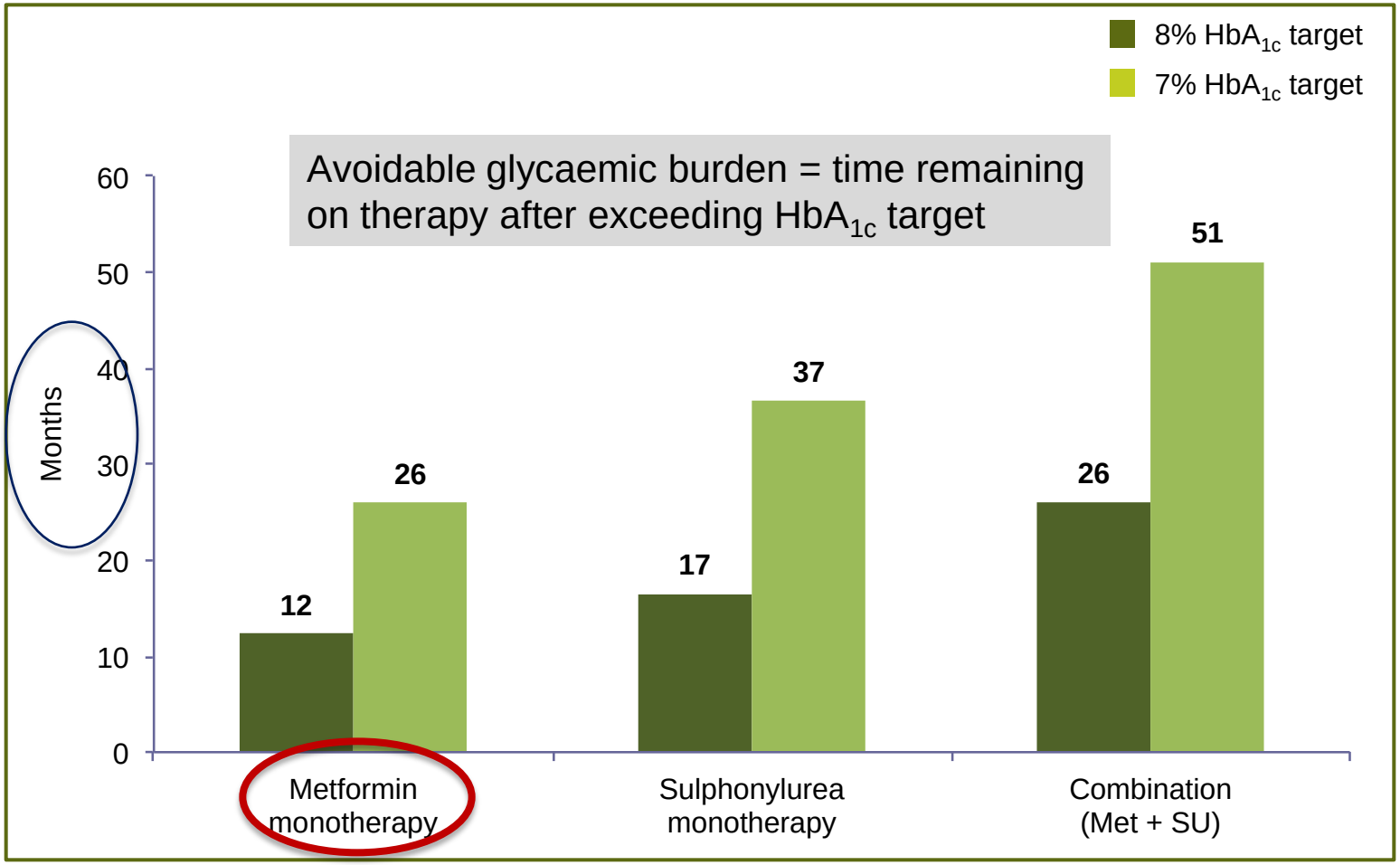
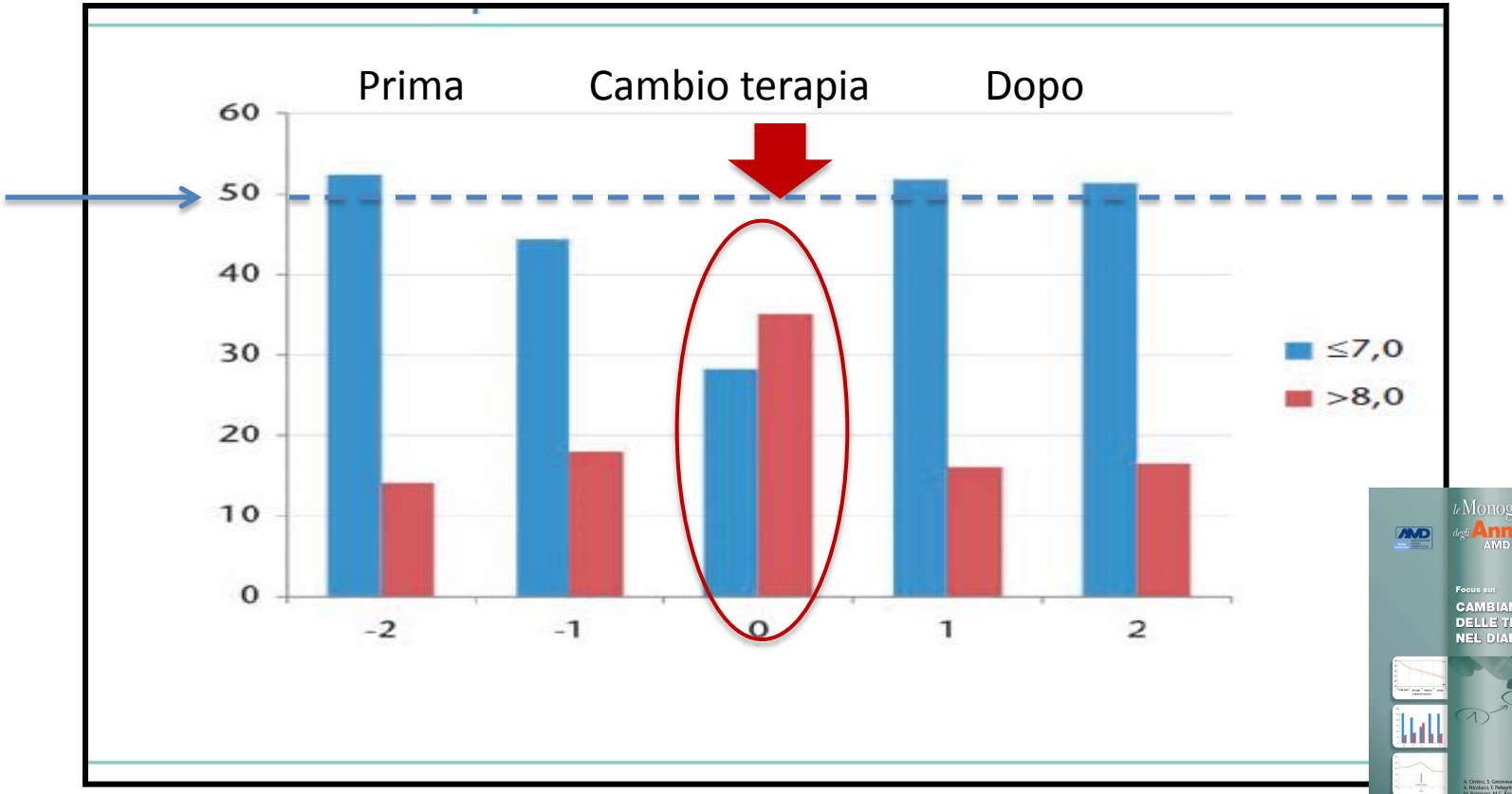
Intensification of glucose-lowering treatment is delayed despite OAD failure

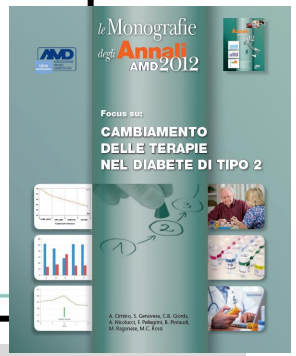


Met, metformin; OAD, oral antidiabetic drug; SU, sulphonylurea

Modified by Brown et al, Diabetes Care, 2004;75:1535–40 "The burden of treatment failure in type 2 diabetes"

Proporzione di pazienti in monoterapia con metformina con valori di HbA1c ≤ 7,0% o > 8,0% nel periodo compreso fra i due anni precedenti e i due anni successivi al cambio di terapia.



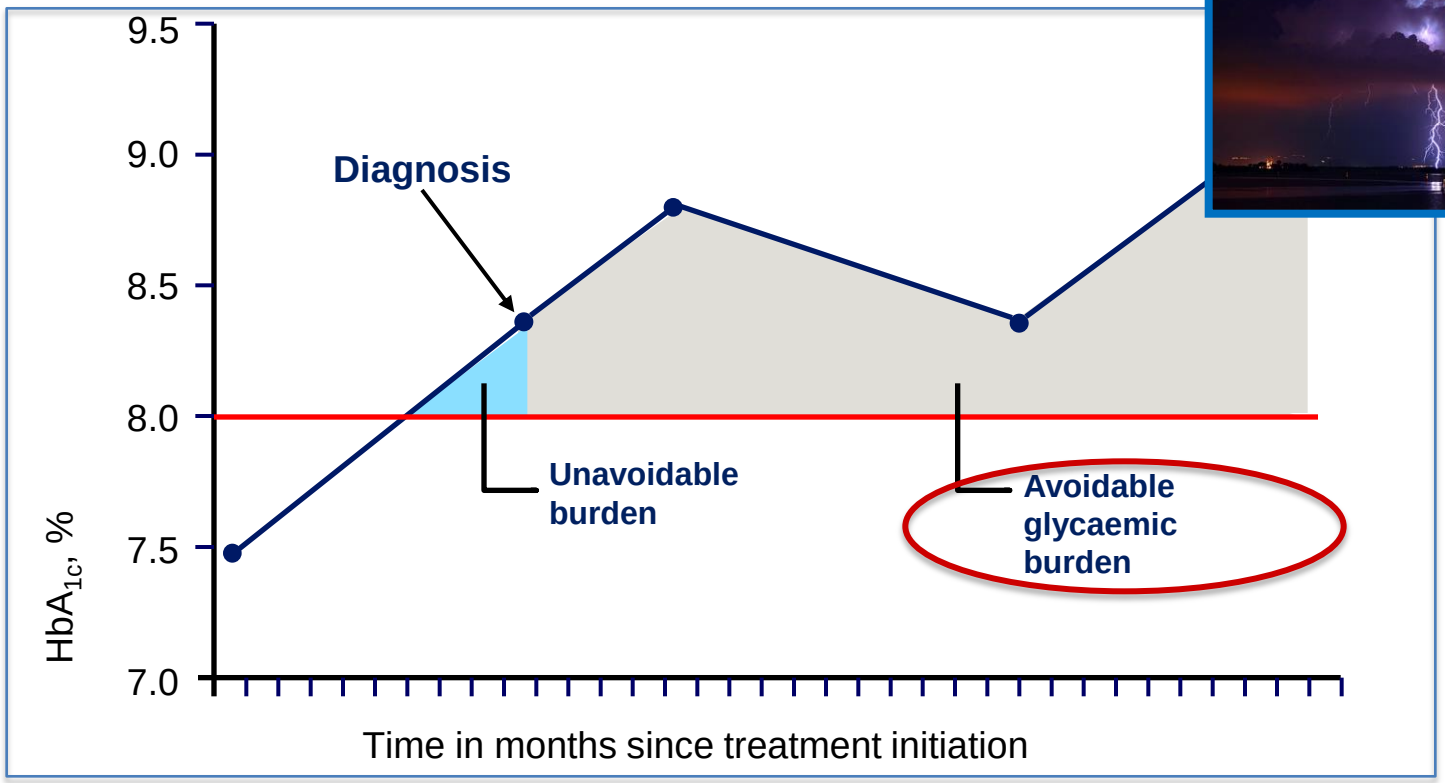


- **70% del campione al momento del cambio di terapia fuori target**
- **18,1% dei pazienti HbA1c > 8,0% un anno prima del cambio di terapia e 14% due anni prima**
- **Oltre 45% HbA1c > 7% nei due anni**

- **Dopo il cambio di terapia: 51% soggetti a target sia dopo un anno sia dopo due anni . Tuttavia, circa la metà del campione non raggiunge i target raccomandati e il 49% dei pazienti dopo due anni non sono a target**

Tutto questo comporta che vi sia un periodo più o meno lungo di *Glycaemic burden associated with* ***clinical inertia***

(mancata intensificazione della terapia nonostante una indeguata riposta)



Total burden = $\sum_{t=1}^{T} (G_1 - K)$, where t indicates the number of months elapsed since diagnosis or treatment initiation;

T = number of months elapsed when a successor treatment is initiated;

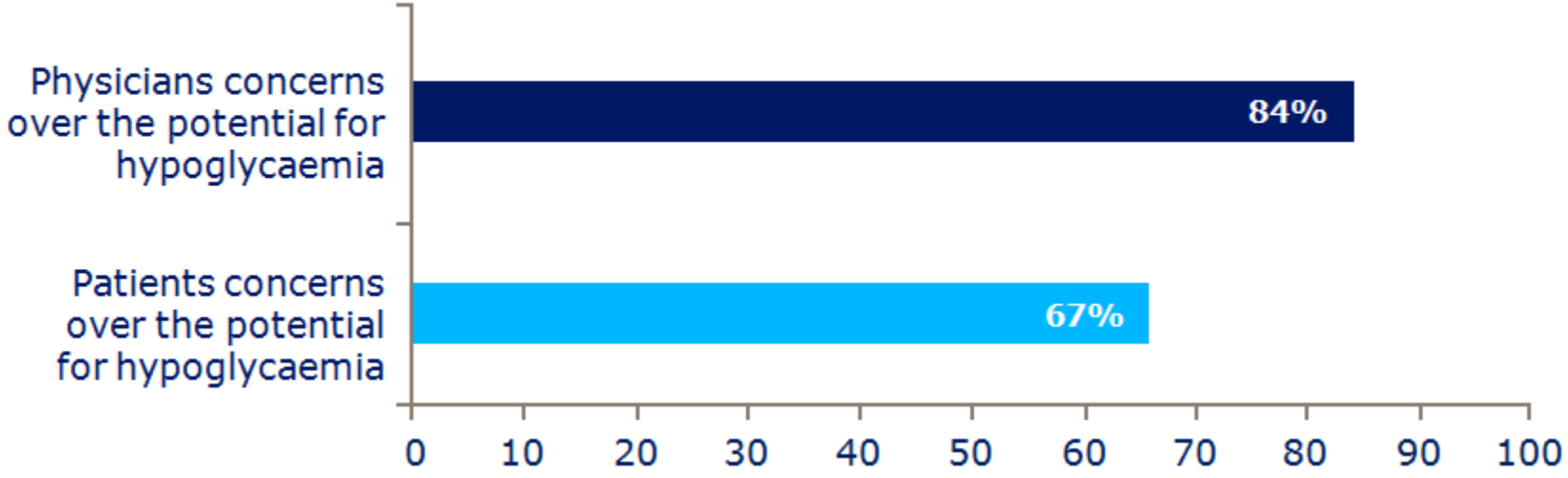
G = actual or interpolated value of HbA_{1c} in month t; and K is the base from which burden is calculated (in this example, K = 8.0).

Brown et al, Diabetes Care, 2004;27:1535–1540

IPERGLICEMIA
IPOGLICEMIA
SCILLA
CARIDDI

Hypoglycaemia is a barrier to effective glycaemic management

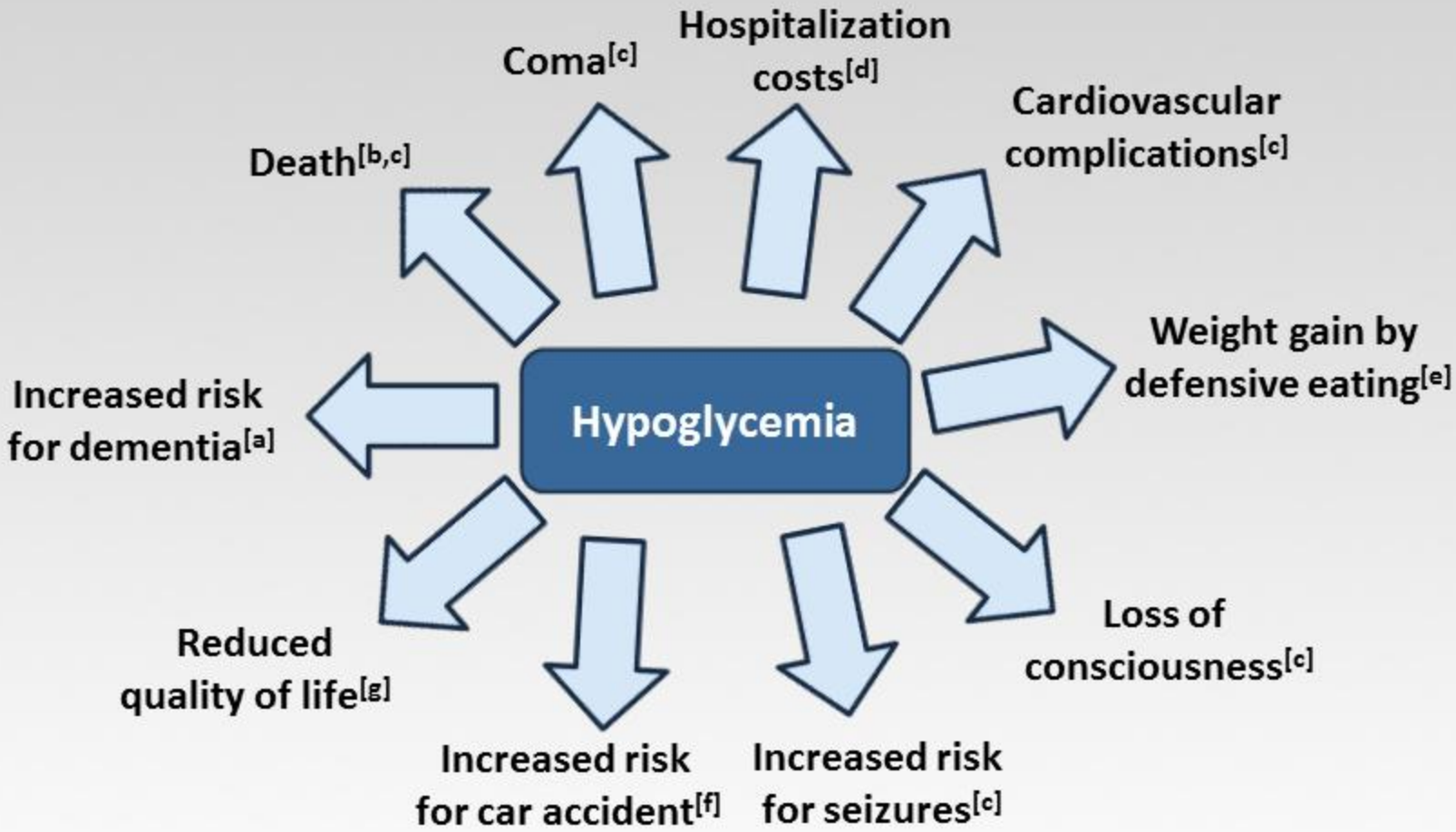
Results:



- **High levels of concern over hypoglycaemia**
- **60% of patients experienced a hypoglycaemic event in the past 12 months**
- **76% of patients said that hypoglycaemia is one of the most fearful parts of having diabetes**
- **74% of physicians would treat patients' diabetes more ambitiously if there was no concern over hypo events**

Peyrot et al. Diabetes Care 2010;33:240–5; Peyrot et al. Diabetes 2011;60(Suppl. 1):A225

The Consequences of Hypoglycemia



a. Whitmer RA, et al. *JAMA.* 2009;301(15):1565-1572; b. Bonds DE, et al. *BMJ.* 2010;340:b4909;
c. Barnett AH. *Curr Med Res Opin.* 2010;26(6):1333-1342; d. Jönsson L, et al. *Value Health.* 2006;9(3):193-198;
e.Foley JE, et al. *Vasc Health Risk Manag.* 2010;6:541-548; f. Begg IS, et al. *Can J Diabetes.* 2003;27:128-140;
g. McEwan P, et al. *Diabetes Obes Metab.* 2010;12(5):431-436.

Medscape EDUCATION

Appropriate treatment in elderly patients

RACCOMANDAZIONI

Il compenso glicemico e il trattamento ipoglicemizzante

Nei diabetici anziani gli obiettivi glicemici dovrebbero essere individualizzati. Gli obiettivi di emoglobina glicata potranno essere ambiziosi (<7%-7,5%; 53-58 mmol/mol) per pazienti autosufficienti, in condizioni generali buone e aspettativa di vita di almeno 8-10 anni.
(Livello della prova VI, Forza della raccomandazione B)

Negli anziani fragili (con complicanze, affetti da demenza, con pluri
rischio di ipoglicemia è alto e nei quali i rischi di un controllo glicemico
benefici attesi) è appropriato un obiettivo meno restrittivo (<8,0-8,5%; 64
(Livello della prova VI, Forza della raccomandazione B)

Gli obiettivi metabolici vanno perseguiti in sicurezza, evitando o cercand
il rischio di ipoglicemia. Non è raccomandato il perseguimento di una
<108 mg/dl e si sconsiglia di iniziare un trattamento ipoglicemizzante se
non è stabilmente >126 mg/dl.
(Livello della prova VI, Forza della raccomandazione B)

Se in un soggetto anziano è indicata una terapia con antidiabetici or
l'utilizzo di glibenclamide.
(Livello della prova IV, Forza della raccomandazione A)

La gliclazide è la sulfanilurea da preferire, in quanto associata a u
ipoglicemia.
(Livello della prova II, Forza della raccomandazione B)

In diabetici anziani la metformina è utilizzabile con cautela fino a un
ml/min^{-1}/1,73 m^{-2}, purché siano attentamente considerati i fattori di rischio di peggioramento
della funzione renale; al di sotto di tali valori non è opportuno l'uso di metformina.
(Livello della prova IV, Forza della raccomandazione B)

In diabetici anziani trattati con metformina il controllo
dovrebbe essere effettuato almeno una volta all'anno e
posologico.
(Livello della prova VI, Forza della raccomandazione B)

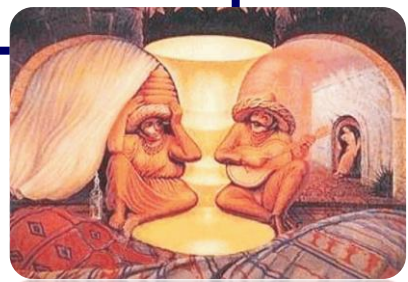
Nei diabetici anziani lo schema di automonitoraggio dovre
di autosufficienza e quindi alle singole capacità funzionali.
deve essere basato sugli obiettivi glicemici e di HbA_{1c} programmati, sulle reali possibilità di modificare la terapia e sul rischio di ipoglicemia.
(Livello della prova VI, Forza della raccomandazione B)

Gli inibitori della DPP-4

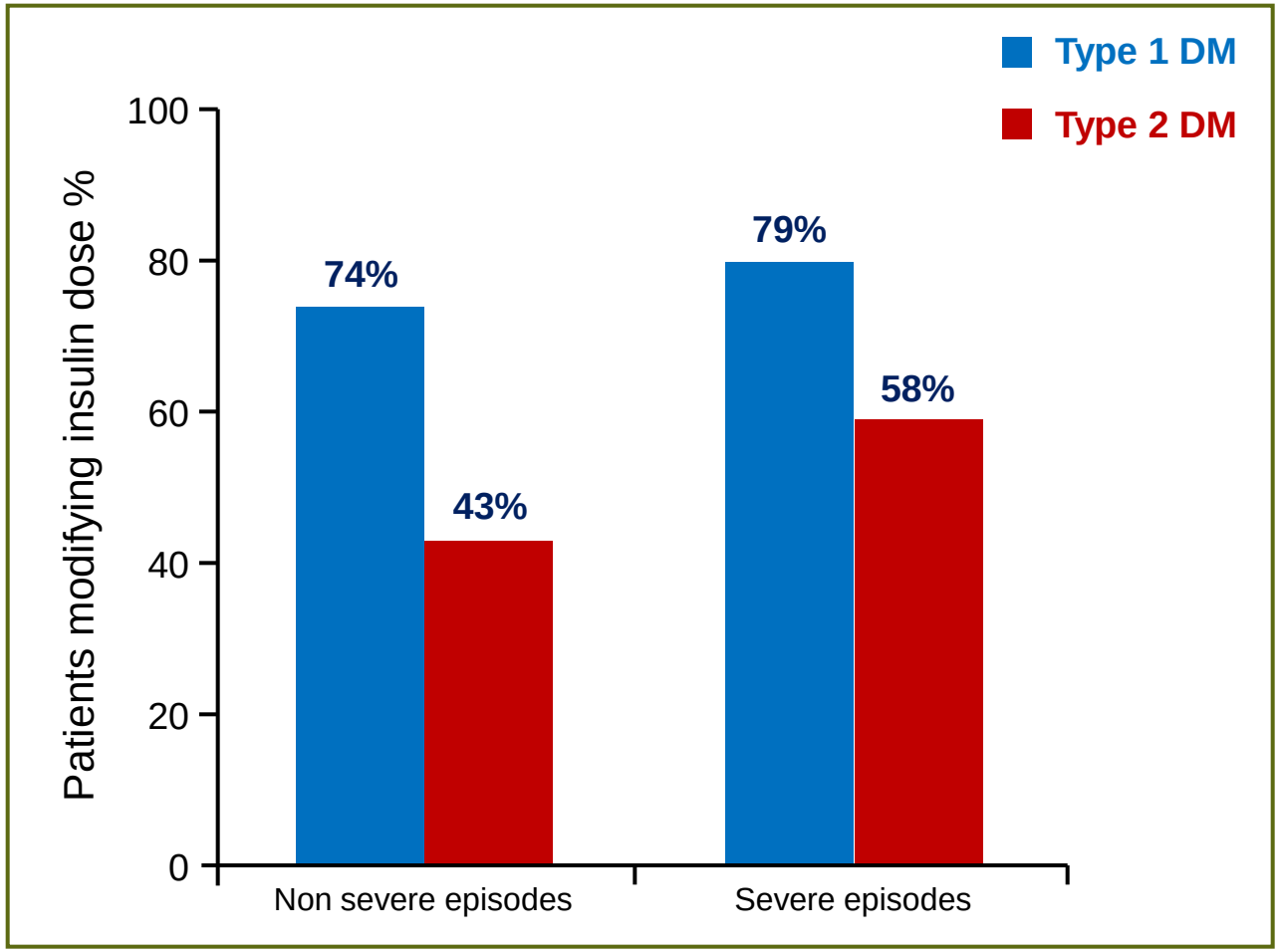
Al momento attuale, in Italia sono presenti in commercio ma, con differenti modalità prescrittive proposte da AIFA, sitagliptin, vildagliptin, saxagliptin e linagliptin, farmaci somministrabili per os.

I dati più recenti evidenziano una loro efficacia sul controllo glicometabolico leggermente inferiore rispetto agli altri ipoglicemizzanti orali (58). Tali farmaci agiscono prevalentemente riducendo la glicemia postprandiale, senza provocare ipoglicemia, sono neutri sul peso corporeo (58) ed è documentata la loro maggiore efficacia clinica nei pazienti anziani (59), presumibilmente per le peculiari caratteristiche fisiopatologiche del diabete di questi pazienti in cui sono maggiormente espressi il deficit secretivo di insulina e l'iperglucagonemia (60,61). Probabilmente sono i soli farmaci ipoglicemizzanti a poter vantare dei trial di intervento su pazienti di età superiore ai 65 e, nel caso del vildagliptin, anche in pazienti con più di 75 anni (62,63,64,65). I DDP-4 inibitori inoltre possono essere usati, a dosaggio ridotto, fino a gradi estremi di insufficienza renale (66,67,68,69,70). Per il linagliptin non è necessario alcun aggiustamento posologico (71). La compromissione renale, spesso presente nell'anziano diabetico, aumenta il rischio di ipoglicemia grave (72). Pertanto, anche per tale motivo la prescrizione di DPP4i risulta particolarmente sicura nella popolazione anziana.

Recenti metanalisi hanno dimostrato possibili effetti benefici sull'assetto lipidico (73), sul rischio cardiovascolare (74) e sulla incidenza di fratture (75). Oltre 4 anni di uso nella pratica clinica quotidiana hanno permesso di documentare un eccellente profilo di sicurezza, escludendo aumentato rischio di morte per tutte le cause, di neoplasie, di pancreatiti e di importanti seri eventi avversi (58). Tutte queste caratteristiche ne fanno una classe da considerare di prima linea nel trattamento del paziente diabetico anziano, in aggiunta o in alternativa alla metformina (76).



Fear of hypoglycaemia reduces patient adherence and may affect glycaemic control

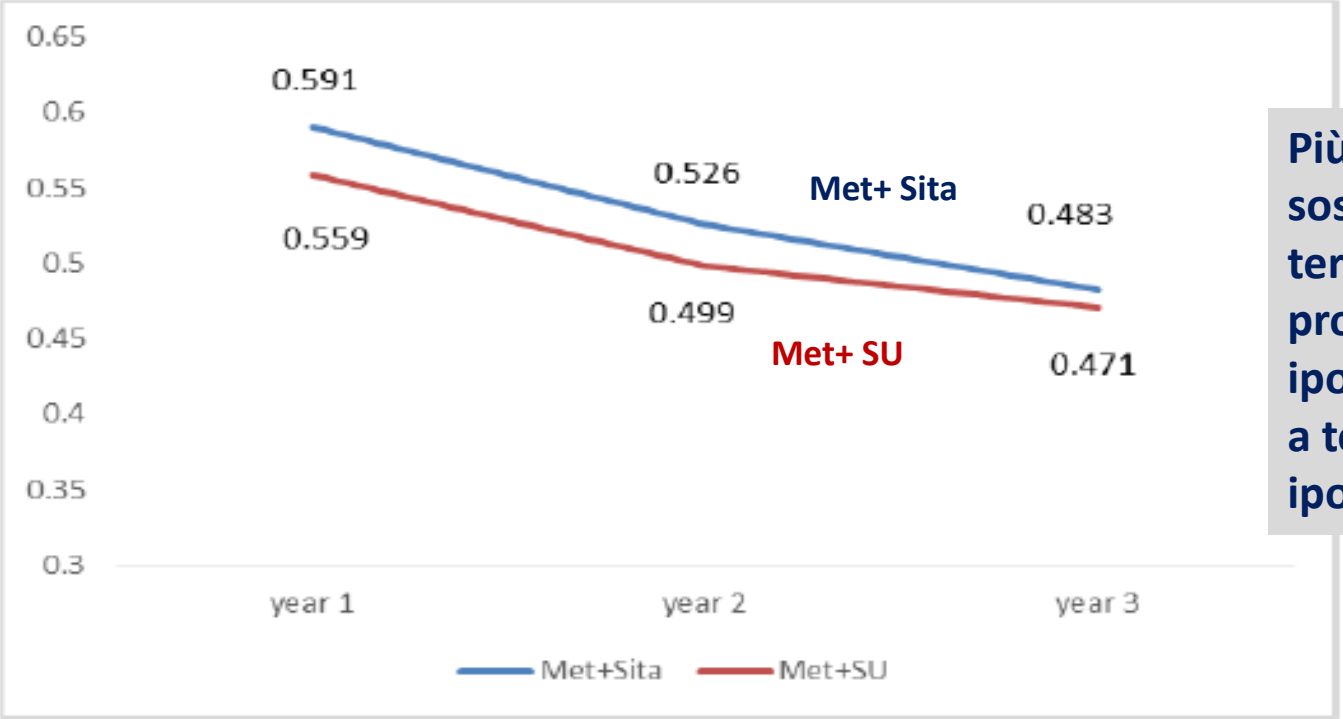


Total patient sample, n=335
Type 1 diabetes, n=202
Type 2 diabetes, n=133

Many patients decrease HYPOGLYCAEMIC TREATMENTS following a hypoglycaemic event.

Leiter et al, Can J Diabetes, 2005;29:186–92

Adherence, persistence, and treatment discontinuation with sitagliptin compared to sulfonylureas as add-ons to metformin: A retrospective cohort database study



Più bassa *rate* di sospensione con terapie che non provocano ipoglicemia rispetto a terapie a rischio di ipoglicemia

Proportions of: 1) days covered (PDC; *Panel A*) and 2) numbers of study participants with PDC ⩾ 80% (*Panel B*), over time in Model 1 (unadjusted). Sitagliptin + metformin (SITA + MET) group (*blue line*) compared to sulfonylurea (SU) + MET group (*burgundy line*).

SYSTEMATIC REVIEW

HYPOGLYCAEMIA WHEN ADDING SULPHONYLUREA TO METFORMIN: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Stig Ejdrup Andersen, Mikkel Christensen

Aims

The risk of hypoglycaemia may differ among sulphonylureas (SUs), but evidence from head-to-head comparisons is sparse. Performing a network meta-analysis to use indirect evidence from randomized controlled trials (RCTs), we compared the relative risk of hypoglycaemia with newer generation SUs when added to metformin.

Methods

A systematic review identified RCTs lasting 12–52 weeks and evaluating SUs added to inadequate metformin monotherapy (≥1000 mg/day) in type 2 diabetes. Adding RCTs investigating the active comparators from the identified SU trials, we established a coherent network. Hypoglycaemia of any severity was the primary end point.

Results

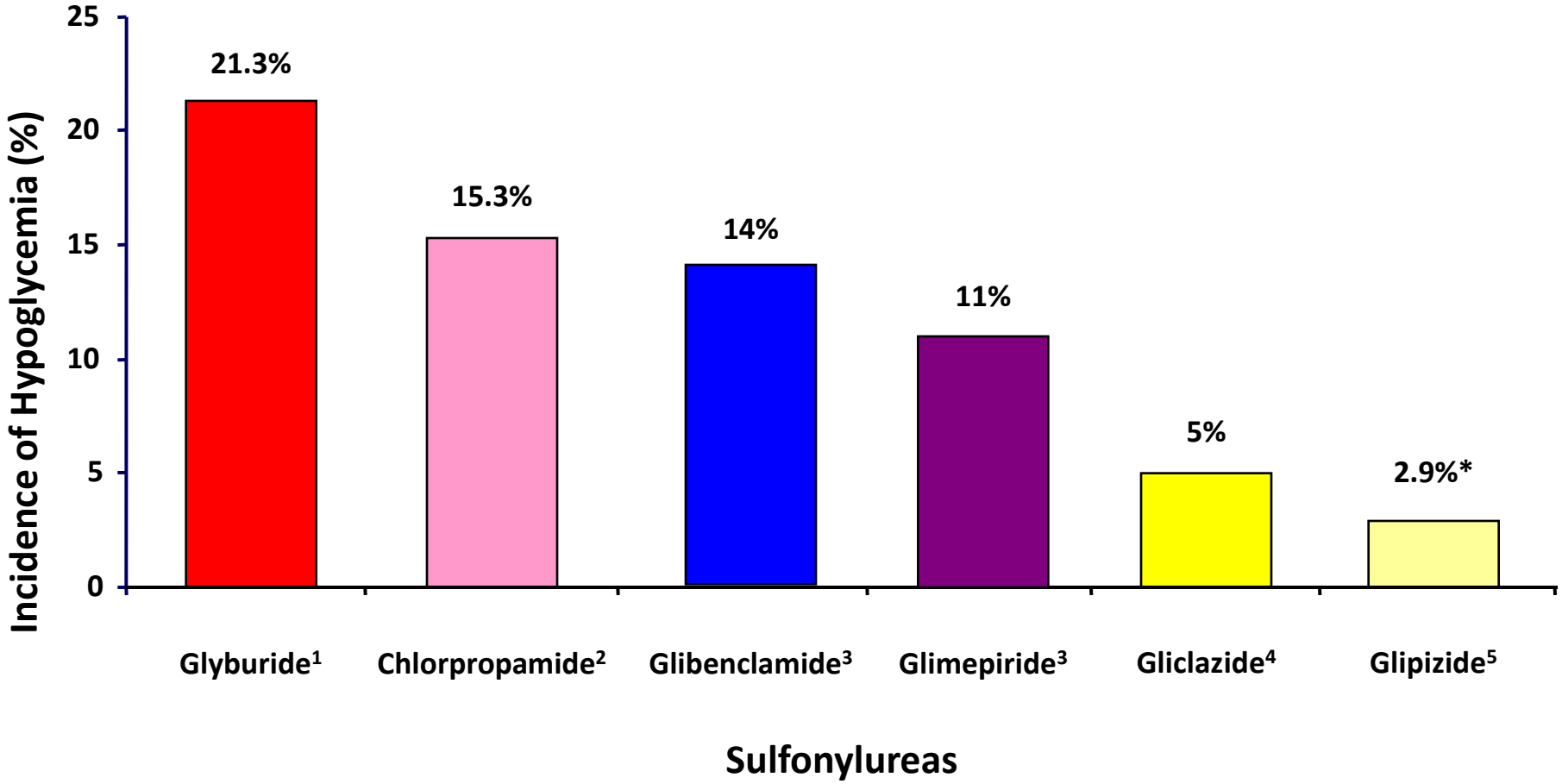
Thirteen trials of SUs and 14 of oral non-SU antihyperglycaemic agents (16 260 patients) were included. All reported hypoglycaemia only as adverse events. Producing comparable reductions in HbA_{1C} of −0.66 to −0.84% (−7 to −9 mmol/mol), the risk of hypoglycaemia was lowest with gliclazide compared to glipizide (OR 0.22, CrI: 0.05 to 0.96), glimepiride (OR 0.40, CrI: 0.13 to 1.27), and glibenclamide (OR 0.21, CrI: 0.03 to 1.48). A major limitation is varying definitions of hypoglycaemia across studies.

Conclusions

When added to metformin, gliclazide was associated with the lowest risk of hypoglycaemia between the newer generation SUs. Clinicians should consider the risk of hypoglycaemia agent-specific when selecting an SU agent.

Volume 82, Issue 5; November 2016; Pages 1291–1302

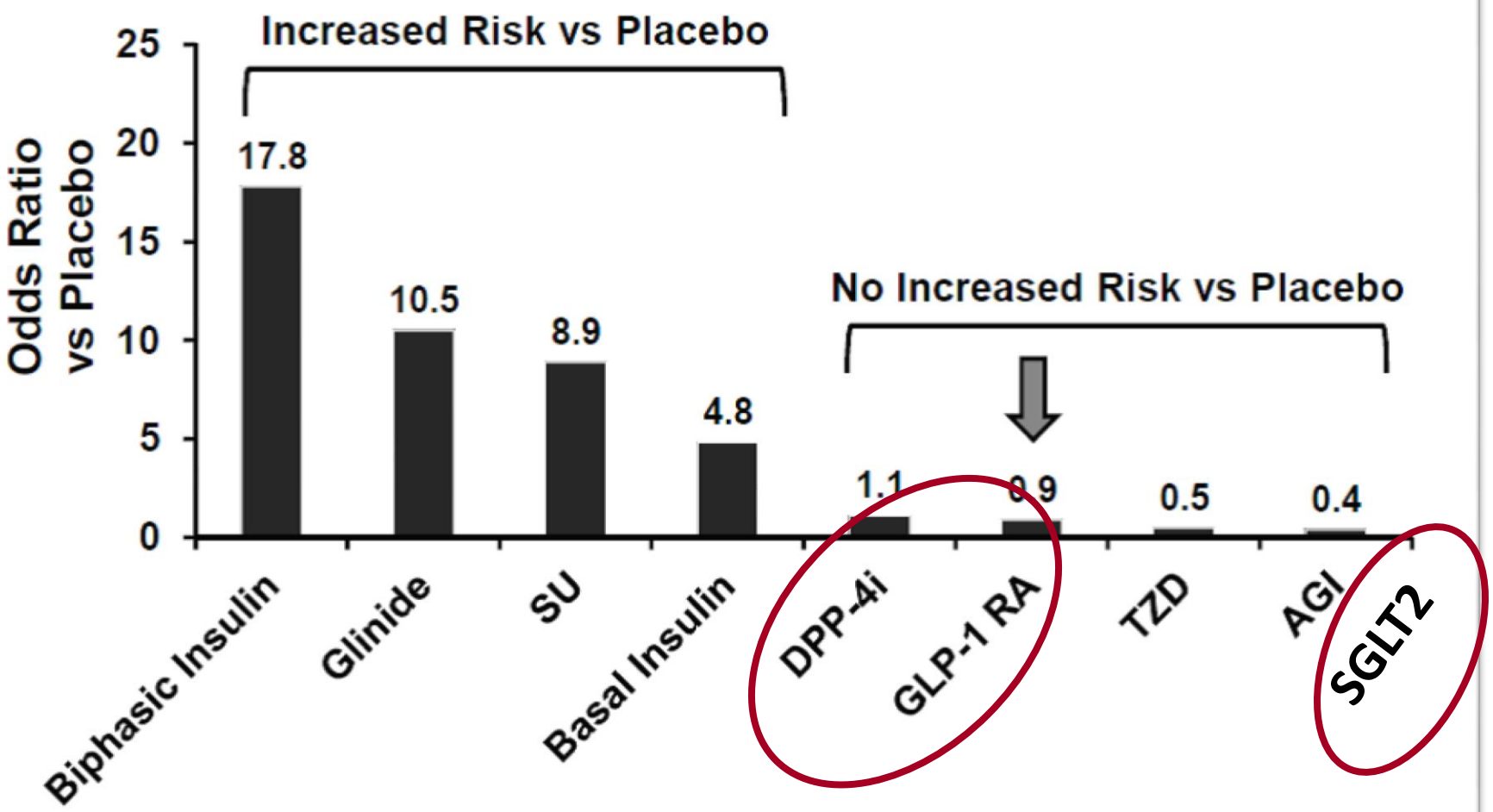
L'ipoglicemia è frequente con le sulfoniluree



- *Hypoglycemia: fingerstick blood glucose measurement ≤50 mg/dL (2.75 mmol/L)

- 1. Glucovance [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2004. 2. UKPDS Group. *Lancet* 1998; 352: 837–853. 3. Draeger KE, et al. *Horm Metab Res*. 1996; 28: 419–425. 4. McGavin JK, et al. *Drugs* 2002; 62; 1357–1364. 5. Metaglip [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2002

Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin: A Network Meta-Analysis[a]

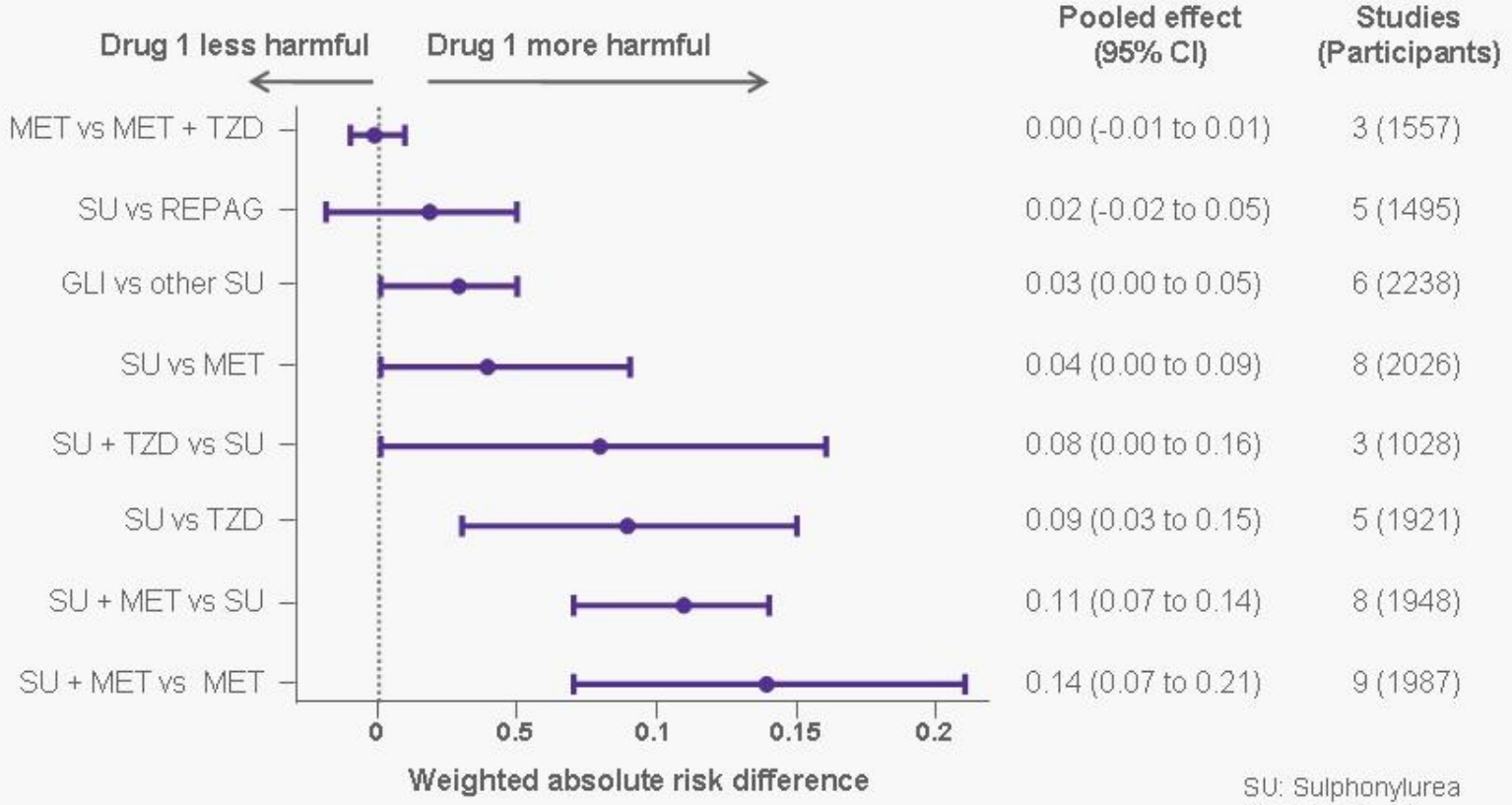


AGI, α-glucosidase inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.
[a] 39 randomized controlled trials.

Liu S, et al. *Diabetes Obes Metab.* 2012;14:810-820

Meta-analisi sull'incidenza di *ipoglicemia* con i diversi farmaci ipoglicemizzanti

Pooled hypoglycaemia results for randomised trials, by drug comparison



SU: Sulphonylurea
MET: Metformin
GLI: Glibenclamide
TZD: Thiazolidinedione

Bolen S Ann Int Med 2007; 147:386-99

Perchè non riusciamo a raggiungere i target?

1. *Complessità della cura*
2. *Inerzia terapeutica e scarsa aderenza*
3. ***Complessità del paziente***
4. *Perché i target sono difficili da raggiungere e….*
5. *mantenere*

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and
the European Association for the Study of Diabetes (EASD)

American Diabetes Association

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

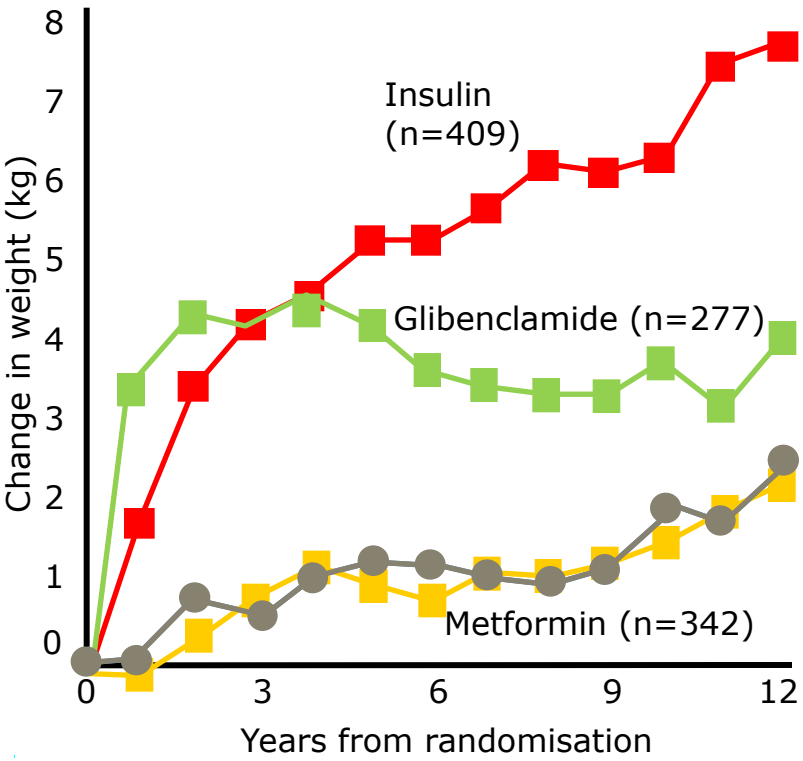
EASD

Appropriate hypoglycaemic treatment according to patient clinical characteristic and lifestyle

Glucose Control	Lifestyle/Frailty/ Hypoglycaemia	BMI / Waist	Co-morbidities	Long-term complications
•HbA1c •FBG •PPG •Durability	• Age • Sex • Ethnic group • Diabetes duration • Psychiatric disorders • Others	• Normal • Overweight/ Obesity • Sarcopeny	• Hypertension • Dyslipidemia • Osteoporosis • Cancer • NAFLD/ Liver • Respiratory diseases • Others	• CVD • DKD • Neuropathy • Retinopathy

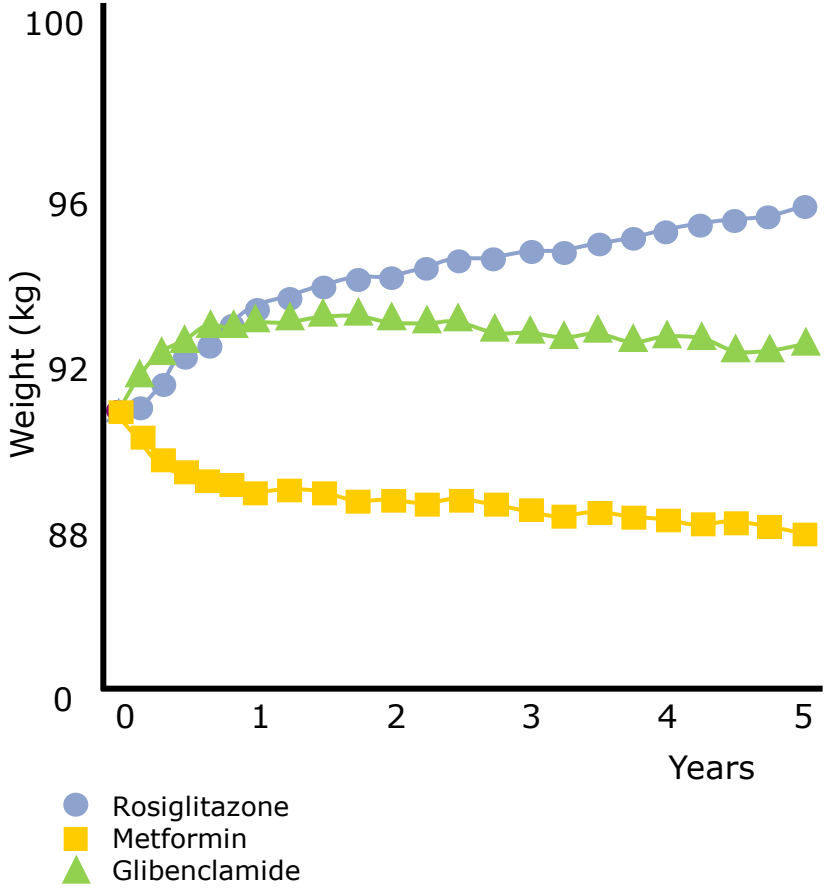
Most therapies result in weight gain over time

UKPDS: up to 8 kg in 12 years



- Conventional treatment (n=411); diet initially then sulphonylureas, insulin and/or metformin if FPG >15 mmol/L

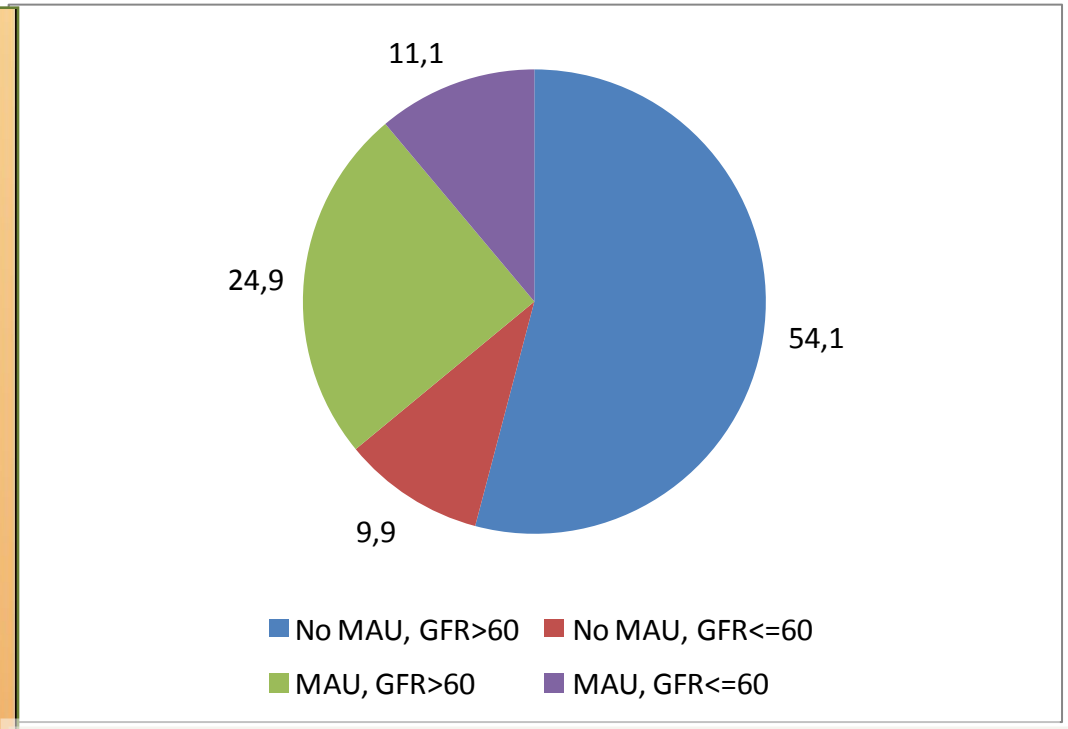
ADOPT: up to 4.8 kg in 5 years



Comparison of Innovative Antidiabetic Drugs

	TZD	DPP-4i	GLP-1 RA	SGLT2i
HbA1c-lowering (at about 8.0%)	+	+	+	+
HbA1c-lowering (at >9.0%)	++	+	++	++
Weight reduction			+	+
BP reduction	+		+	+
Oral intake	+	+		+
Side effects	+	?	+	+
ß-cell independent				+
Low risk for hypos	+	+	+	+
Can be used in CKD	+	+		

GFR and Micro/macroalbuminuria in T2DM subjects in the Annali AMD Initiative



I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.

De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile S, Russo G, Rossi MC, Nicolucci A, Guida P,Di Bartolo P,Pontremoli R and the AMD-Annals Study Group. Nephrol Dial Transplant (2015) 0: 1–8; doi: 10.1093/ndt/gfv101

	Mild CKD GFR 60-89 ml/min	Moderate CKD GFR 30-59 ml/min	Severe CKD GFR 15-29 ml/min	GFR <15 ml/min o dialysis
Sitagliptin	100 mg/die	50 mg/die	25mg/die	25mg/die
Vildagliptin	50 mg x2/die	50 mg/die	50 mg/die	50 mg/die
Saxagliptin	5 mg/die	2.5 mg/die	2.5 mg/die	2.5 mg/die
Linagliptin	5 mg/die	5 mg/die	5 mg/die	5 mg/die
Alogliptin	25 mg/die	12.5 mg/die	6.25 mg/die	6.25 mg/dl
Exe BID	yes	5 µg x2/die	no	no
Exe LAR	yes	no	no	no
Liraglutide	yes	yes	no	no
Lixisenatide	yes	caution	no	no
Canagliflozin	yes	no *	no	no
Dapagliflozin	yes	no	no	no
Empagliflozin	yes	no*	no	no

Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 759–766

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

Novel antidiabetic drugs and cardiovascular risk: *Primum non nocere*

R.C. Bonadonna [a,1], C. Borghi [b,1], A. Consoli [c,*,1], M. Volpe [d,e,1]

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Available online 27 May 2016

I più comuni effetti collaterali degli ipoglicemizzanti

Table 4
Comparative perspective of conventional drugs with phyto-drugs.

S. No	Anti-diabetic drug classes	Specific target (Via Mechanistic study)	Conventional Drugs	
			Drugs	Possible side effects
1.	Insulin Sensitizers	AMPK / GLUT4 mediated	*Metformin*	• Diarrhea • Nausea • Abdominal cramps • Vomiting, • Gastrointestinal tract disorder • Lactic acidosis • Vitamin B_{12} deficiency
		PPARγ mediated / modulated lipid metabolism	*TZDs*	• Cardiovascular risk • Excess production of VEGF • Congestive cardiac failure • Oedema • Myocardial infarction • Weight gain • Fluid retention
2.	Insulin Secretagogues	Modulating pancreatic β-cell function/ differentiation/ calcium influx	*Sulfonylureas/ Non-sulfonylureas*	• Hypoglycaemia • Weight gain • Abdominal pain • Hypersensitivity • Teratogenic • Increased risk of cardiovascular death

Pharmacological Research 113 (2016) 636–674

Contents lists available at ScienceDirect

Pharmacological Research

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

Review

Efficacy and risk profile of anti-diabetic therapies: Conventional vs traditional drugs—A mechanistic revisit to understand their mode of action

Prachi Gupta[a,1], Manju Bala[a,1], Sanjeev Gupta[a], Anita Dua[a], Rajesh Dabur[b], Elisha Injeti[c], Ashwani Mittal[a,*]

3.	Incretins	GLP-1 analogues DPP-4 inhibitors	*Exenatide* *Sitagliptin*	• Decreased gastric motility • Nausea • Increased risk of infection • Headache
4.	SGLT2 inhibitors	Modulating renal glucose reabsorption	*Gliflozin*	• Failed in clinical trials due to safety concern • Bladder and breast cancer • Reduces body weight • Gastrointestinal infection
5.	Alpha-glucosidase inhibitors	Modulating glucose absorption via intestinal tract	*Acarbose*	• Unpleasant side effects • Flatulence • Diarrhea • Pneumatosis cystoides • Intestinalis • Low efficacy in decreasing glycemia

European Heart Journal (2015) **36**, 2288–2296
doi:10.1093/eurheartj/ehv239

REVIEW

Clinical update

Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes

Ele Ferrannini[1]* and Ralph A. DeFronzo[2]

CVD Safety RCTs

Table 1 Cardiovascular outcome trials in type 2 diabetes

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4i	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin	Linagliptin
Comparator	Placebo	Placebo	Placebo	Sulfonylurea	Placebo
Number	16 500	5400	14 000	6000	8300
Results	Ref. 213	Ref. 215	ADA 2015	2018	2018
	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP-1RA	Liraglutide	Lixisenatide	Semaglutide	Exenatide LR	Dulaglutide
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Number	8754	6000	6000	9500	9600
Results	2018	ADA 2015	2016	2018	2018
	EMPA-REG	CANVAS	DECLARE	NCT01986881	
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	
Comparator	Placebo	Placebo	Placebo	Placebo	
Number	7300	7000	22 200	3900	
Results	2015	2017	2019	2020	

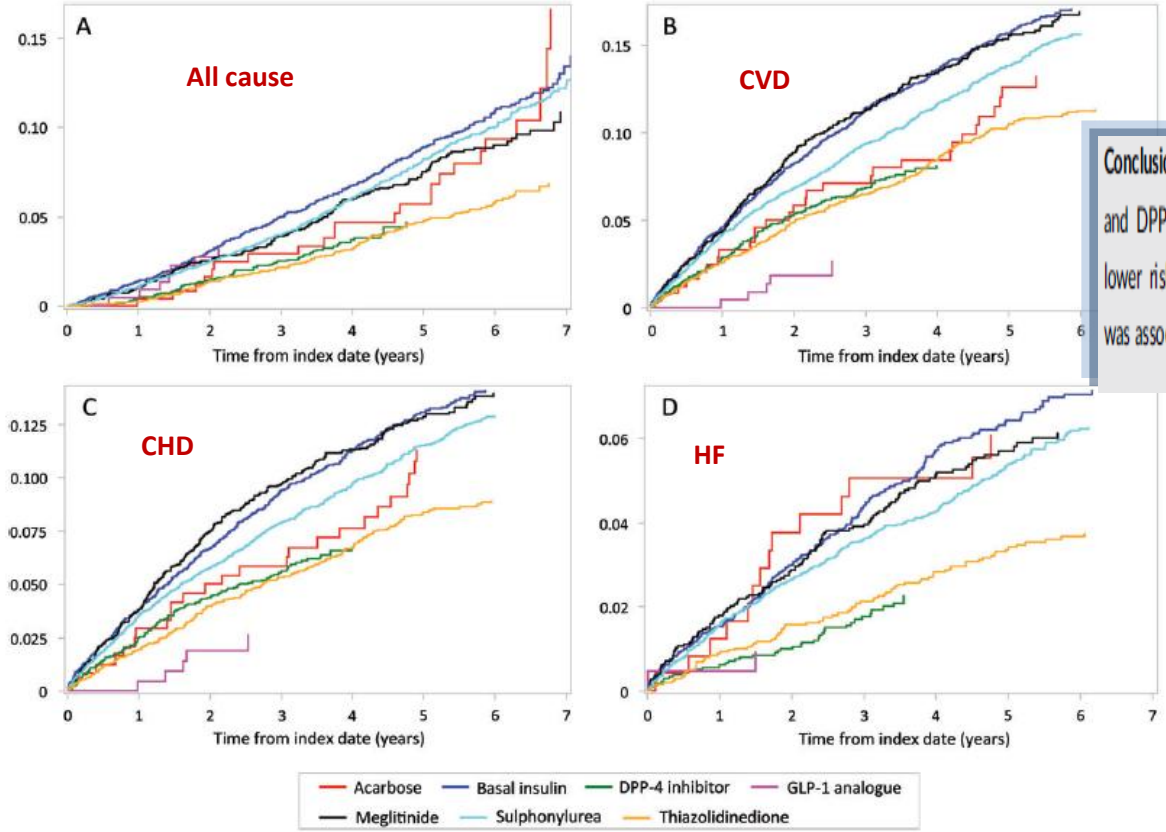
Received: 21 February 2016 | Revised: 26 May 2016 | Accepted: 4 June 2016
DOI 10.1111/dom.12704

WILEY

ORIGINAL ARTICLE

Cardiovascular safety of glucose-lowering agents as add-on medication to metformin treatment in type 2 diabetes: report from the Swedish National Diabetes Register

Nils Ekström MD, PhD[1,2] | Ann-Marie Svensson RN, PhD[3] | Mervete Miftaraj MSC[3] | Stefan Franzén PhD[3] | Björn Zethelius MD, PhD[4,5] | Björn Eliasson MD, PhD[1] | Soffia Gudbjörnsdottir MD, PhD[1,3]



Conclusions: This nationwide observational study showed that second-line treatment with TZD and DPP-4 inhibitor as add-on medication to metformin were associated with significantly lower risks of mortality and cardiovascular events compared with SU, whereas basal insulin was associated with a higher risk of mortality.

FIGURE 2 Crude cumulative incidence of all-cause mortality (A), cardiovascular disease (B), coronary heart disease (C) and congestive heart failure (D) by treatment group.

Effect of Hypoglycemic Agents on Ischemic Preconditioning in Patients With Type 2 Diabetes and Symptomatic Coronary Artery Disease

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Augusto Hiroshi Uchida, MD, PhD
Paulo Cury Rezende, MD
Eduardo Gomes Lima, MD
Cibele Larrosa Garzillo, MD, PhD
Desiderio Favarato, MD
Celia M.C. Strunz, MD, PhD
Myrthes Takiuti, RN, PhD
Priscyla Girardi, RN, PhD
Whady Hueb, MD, PhD
Roberto Kalil Filho, MD, PhD
José A.F. Ramires, MD, PhD

OBJECTIVE—To assess the effect of two hypoglycemic drugs on ischemic preconditioning (IPC) patients with type 2 diabetes and coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS—We performed a prospective study of 96 consecutive patients allocated into two groups: 42 to group repaglinide (R) and 54 to group vildagliptin (V). All patients underwent two consecutive exercise tests (E 1 without drugs. In phase 2, 1 day after ET1 and -2, 2 mg repaglinide thre vildagliptin twice daily was given orally to patients in the respective gro seventh day, 60 min after 6 mg repaglinide or 100 mg vildagliptin, all pa consecutive exercise tests (ET3 and ET4).

RESULTS—In phase 1, IPC was demonstrated by improvement in th segment depression and rate pressure product (RPP). All patients develo however, 83.3% of patients in group R experienced ischemia earlier in ET improvement in RPP, indicating the cessation of IPC ($P < 0.0001$). In g patients demonstrated IPC cessation, with 72% still having the protective

CONCLUSIONS—Repaglinide eliminated myocardial IPC, probably b channel. Vildagliptin did not damage this protective mechanism in a relevan type 2 diabetes and CAD, suggesting a good alternative treatment in this

Diabetes Care

Ischemic preconditioning (IPC) is recognized as a protective endogenous mechanism by which brief and recurrent episodes of myocardial ischemia may self-protect from prolonged ischemic injury and, thus, limit the size of myocardial infarction (1). This mechanism can reduce the severity of myocardial ischemia associated with coronary angioplasty, intermittent aortic cross-clamping during coronary artery bypass graft surgery, and exercise testing (2). Subjects with chronic ischemic heart disease frequently describe angina provoked by an initial exercise and realize that the pain is attenuated and even disappears if th the exercise. This p "warm-up" or "wal has been related to IP in a number of studi cise testing (3–8). Th underlying IPC are n and are undoubtedly triggers, mediators, in fectors. All steps appe ponents, such as ad receptors, the activation of K_{ATP} channel, and the ε-isoform of protein kinase C, as well as others, including the paradoxical protective role of oxygen radicals (9). The K_{ATP} channel opening in cardiac myocytes has consistently been observed to be important in contributing to protection from IPC (10).

Drugs that act by inhibiting K_{ATP} channels, such as some sulphonylureas, are related to loss of IPC (11–14). Tolbutamide and glibenclamide, drugs in the sulphonylurea family, promote additional binding to K_{ATP} channels with different molecular conformations in cardiac

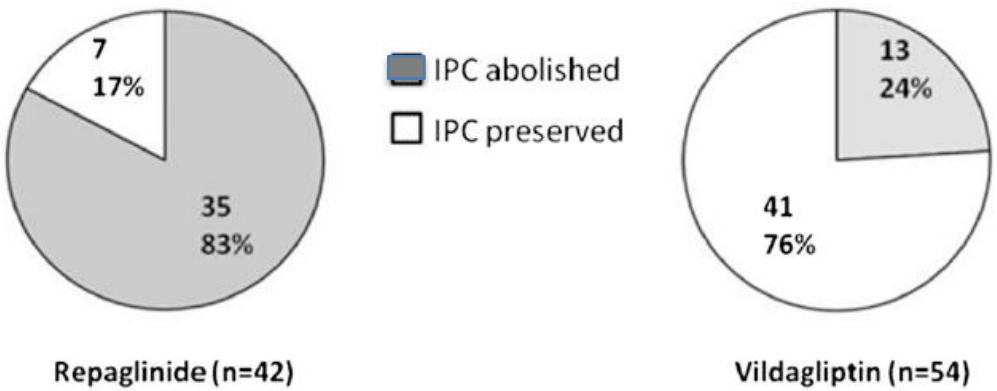

Figure 1—*Pie charts showing the number and percentage of patients with IPC abolished and preserved in the R and V groups.*

incretin system. By inhibiting DPP-4, V prolongs the half-lives of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide—intestinal hormones that support glucose homeostasis and insulin secretion (20). GLP-1 is rapidly degraded by the enzyme DPP-4, which is widely expressed in many tissues, including kidney, liver, lung, and the small intestine. DPP-4 inhibitors exert their antidiabetes actions largely through potentiation of GLP-1 receptor (GLP-1R)

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Diabetes Volume 65, September 2016 2795

Rui Liu,[1] Haitao Wang,[1,2] Baofeng Xu,[1,2] Wenliang Chen,[1,2,3] Ekaterina Turlova,[1,2] Nan Dong,[1] Christopher L.F. Sun,[1] Yangqingqin Lu,[1] Hanhui Fu,[1,2] Ranran Shi,[1,2] Andrew Barszczyk,[1] Dongzi Yang,[4] Tianru Jin,[1,5] Edoardo Mannucci,[6] Zhong-Ping Feng,[1] and Hong-Shuo Sun[1,2,3,5]

Cerebrovascular Safety of Sulfonylureas: The Role of K_{ATP} Channels in Neuroprotection and the Risk of Stroke in Patients With Type 2 Diabetes

Diabetes 2016;65:2795–2809 | DOI: 10.2337/db15-1737

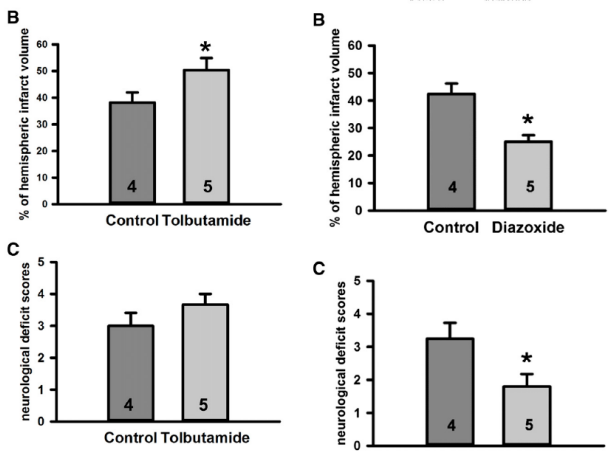
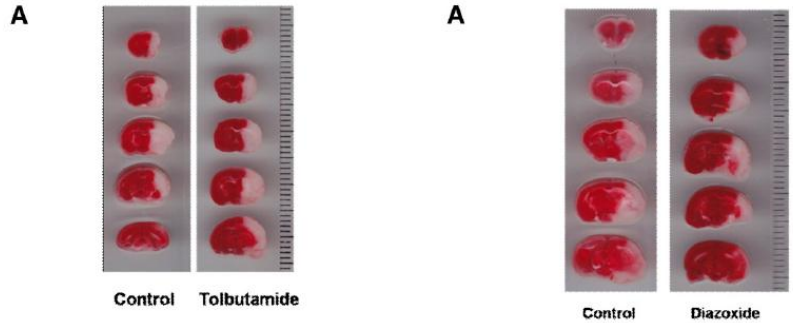


Figure 5—Effects of tolbutamide in increasing infarct volume in mouse pMCAO model. Tolbutamide (100 mg/kg in DMSO) or



Perchè non riusciamo a raggiungere i target?

1. *Complessità della cura*
2. *Inerzia terapeutica e scarsa aderenza*
3. *Complessità del paziente*
4. ***Perché i target sono difficili da raggiungere e….***
5. ***mantenere***

DIABETES RESEARCH AND CLINICAL PRACTICE 117 (2016) 100–103

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Diabetes Research and Clinical Practice

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

Treatment urgency: The importance of getting people with type 2 diabetes to target promptly

Anne-Marie Felton [a], *James LaSalle* [b], *Margaret McGill* [c,*],
on behalf of the Global Partnership for Effective Diabetes Management

[a] *Foundation of European Nurses in Diabetes, London, UK*
[b] *Medical Arts Research Collaborative, Excelsior Springs, MO, USA*
[c] *Diabetes Centre, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia*

Table 1 – Ten steps to get more type 2 diabetes patients to goal [17].

1. Aim for an appropriate individualized glycemic target, for example, HbA_{1c} 6.5–7% (48–53 mmol/mol) (fasting/preprandial plasma glucose 110–130 mg/dL [6.0–7.2 mmol/L] where assessment of HbA_{1c} is not possible) when safe and appropriate
2. Monitor HbA_{1c} every 3 months in addition to appropriate glucose self-monitoring
3. Appropriately manage all cardiovascular risk factors
4. Refer all newly diagnosed patients to a unit specializing in diabetes care where possible
5. Address the underlying pathophysiology of diabetes, including the treatment of β-cell dysfunction and insulin resistance
6. Treat to achieve appropriate target HbA_{1c} within 6 months of diagnosis
7. After 3 months, if patients are not at the desired target HbA_{1c}, consider combination therapy
8. Consider initiating combination therapy or insulin for patients with $HbA_{1c} \geqslant 9\%$ ($\geqslant$75 mmol/mol)
9. Use combinations of anti-hyperglycemic agents with complementary mechanisms of action
10. Implement a multidisciplinary team approach that encourages patient self-management, education and self-care, with shared responsibilities to achieve goals

La funzione β-cellulare è ridotta nel diabete di tipo 2

✓ **Uno studio miliare su reperti autoptici di pancreas ha infatti riportato una perdita del 40% della massa β-cellulare nei soggetti con ridotta tolleranza glucidica (IGT) e una perdita di oltre il 60% in quelli affetti da diabete (T2DM).**

Butler AE, et al., Diabetes 2003

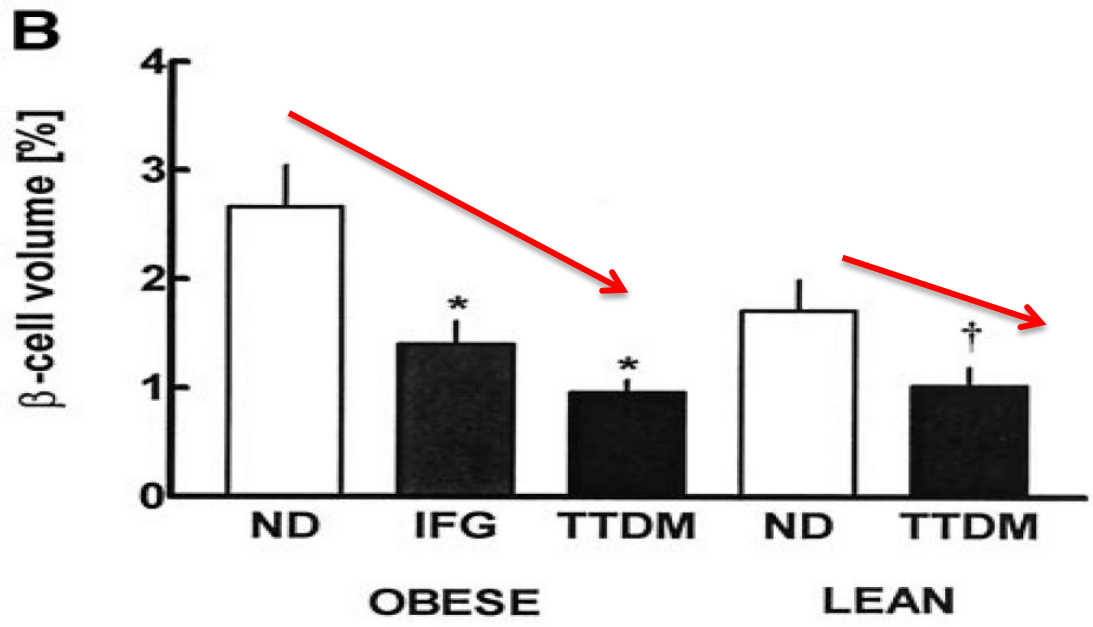
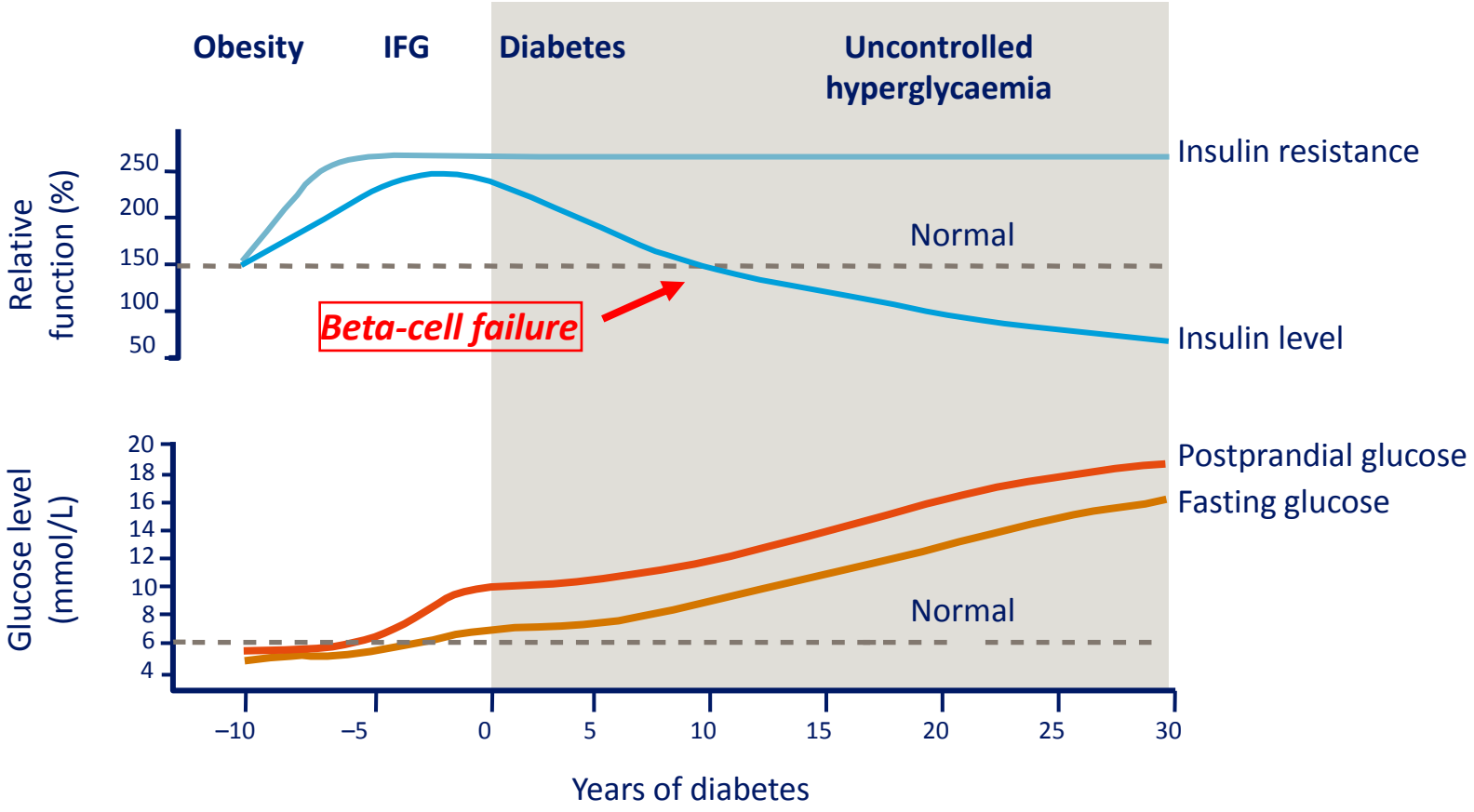


FIG. 2. The mean FPG concentration (*A*) and the mean relative β-cell volume (*B*) in obese (nondiabetic [ND], IFG, and diabetic subjects [TTDM]) and lean cases (nondiabetic and type 2 diabetic subjects).

Disease progression: ADD-ON therapy becomes necessary in type 2 diabetes



IFG, impaired fasting glucose

Adapted from Bergenstal *et al. Endocrinology.* Philadelphia, PA: WB Saunders Co; 2001:821–35

Meccanismi alla base della disfunzione beta cellulare nel DM2

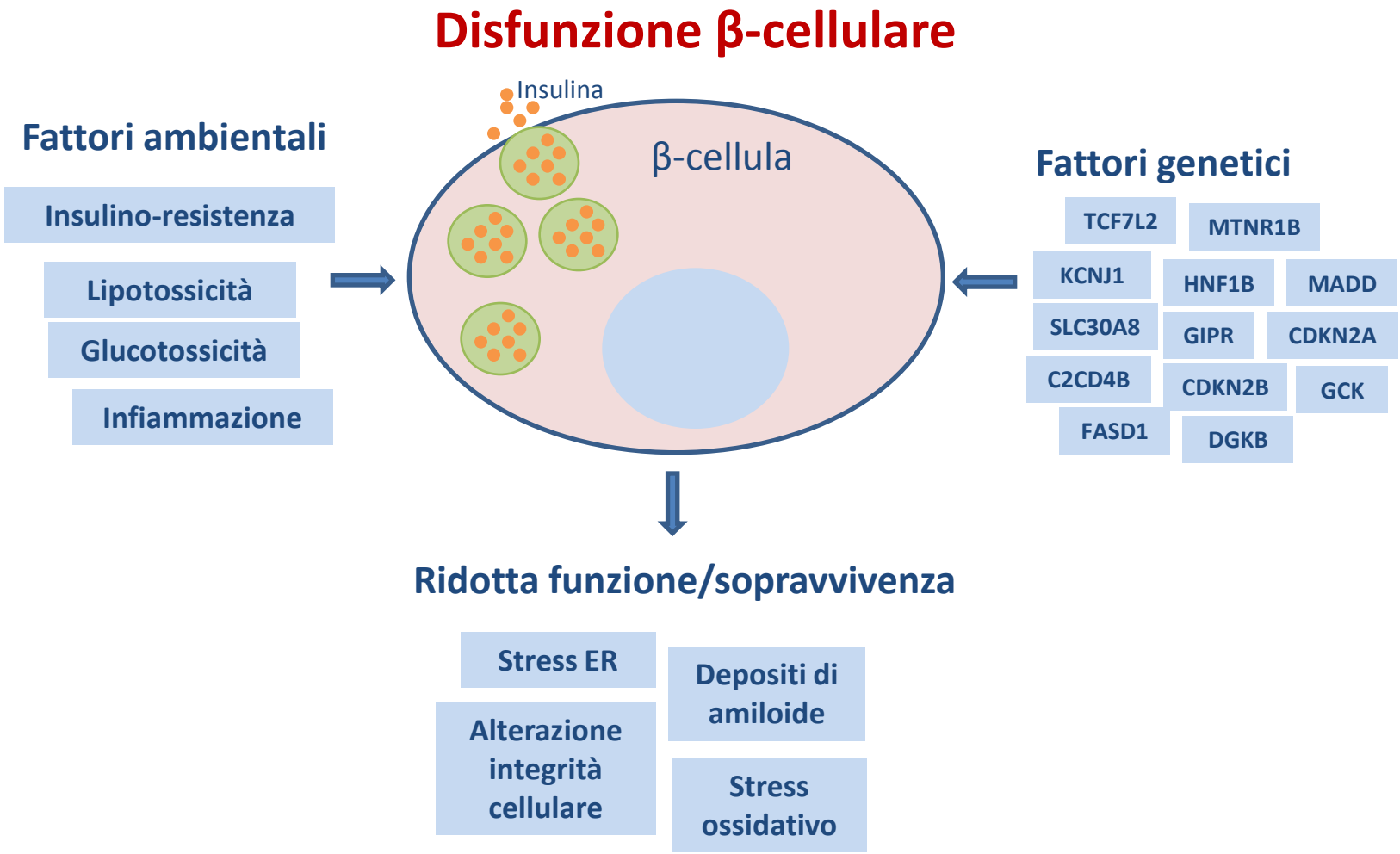
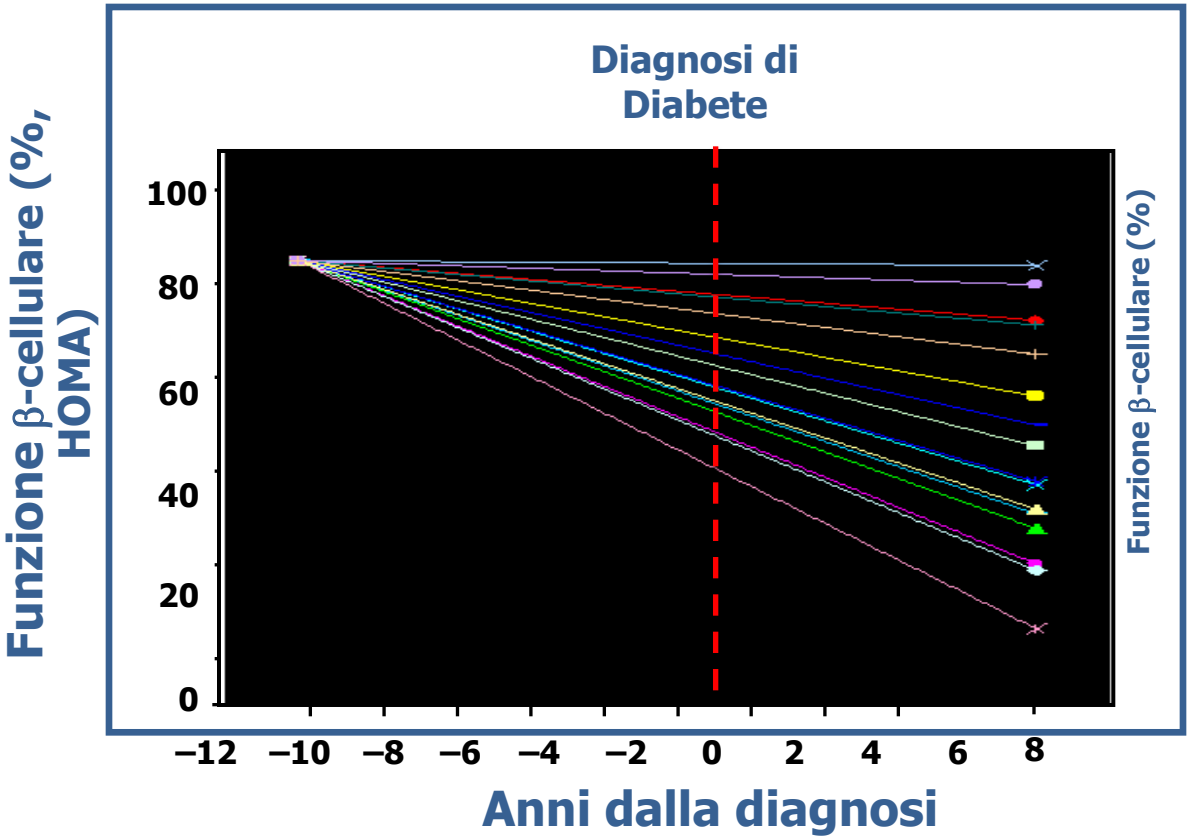


Figura 1 - Meccanismi alla base della disfunzione β-cellulare e risposta della β-cellula agli *stressors*.

La funzione β-cellulare si riduce nel tempo



✓La **VELOCITA' di PROGRESSIONE** del deficit beta cellulare è molto **variabile** e **potenzialmente influenzata** da diversi fattori genetici, clinici, metabolici, legati allo stile di vita e/o dalle diverse terapie ipoglicemizzanti.

✓**IDENTIFICARE** questi fattori è un passaggio necessario per migliorare gli *outcomes* delle attuali terapie sul diabete.

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Factors Associated with Beta-Cell Dysfunction in Type 2 Diabetes: The BETADECLINE Study

Giuseppina T. Russo[1]*, Carlo Bruno Giorda[2], Stefania Cercone[3], Antonio Nicolucci[4], Domenico Cucinotta[1], on behalf of BetaDecline Study Group[¶]

1 Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, 2 Metabolism and Diabetes Unit ASL TO5, Chieri, Italy, 3 MSD, Rome, Italy, 4 Department of Clinical Pharmacology and Epidemiology Fondazione Mario Negri Sud, S. Maria Imbaro, Italy

Abstract

Aims: Beta-cell dysfunction is an early event in the natural history of type 2 diabetes. However, its progression is variable and potentially influenced by several clinical factors. We report the baseline data of the BetaDecline study, an Italian prospective multicenter study on clinical predictors of beta-cell dysfunction in type 2 diabetes.

Materials and Methods: Clinical, lifestyle, and laboratory data, including circulating levels of inflammatory markers and non-esterified fatty acids, were collected in 507 type 2 diabetic outpatients on stable treatment with oral hypoglycemic drugs or diet for more than 1 year. Beta-cell dysfunction was evaluated by calculating the proinsulin/insulin ratio (P/I).

Results: At baseline, the subjects in the upper PI/I ratio quartile were more likely to be men and receiving secretagogue drugs; they also showed a borderline longer diabetes duration ($P = 0.06$) and higher serum levels of glycated hemoglobin (HbA_{1c}), fasting blood glucose, and triglycerides. An inverse trend across all PI/I quartiles was noted for BMI and serum levels of total cholesterol (T-C), LDL-C, HDL-C and C reactive protein (CRP), and with homeostatic model assessment (HOMA-B) and HOMA of insulin resistance (HOMA-IR) values ($P<0.05$ for all). At multivariate analysis, the risk of having a P/I ratio in the upper quartile was higher in the subjects on secretagogue drugs (odds ratio [OR] 4.2; 95% confidence interval [CI], 2.6–6.9) and in the males (OR 1.8; 95% CI, 1.1–2.9).

Conclusions: In the BetaDecline study population, baseline higher PI/I values, a marker of beta-cell dysfunction, were more frequent in men and in patients on secretagogues drugs. Follow-up of this cohort will allow the identification of clinical predictors of beta-cell failure in type 2 diabetic outpatients.

Citation: Russo GT, Giorda CB, Cercone S, Nicolucci A, Cucinotta D, et al. (2014) Factors Associated with Beta-Cell Dysfunction in Type 2 Diabetes: The BETADECLINE Study. PLoS ONE 9(10): e109702. doi:10.1371/journal.pone.0109702

Editor: Franco Folli, University of Texas Health Science Center at San Antonio, United States of America

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: This study was organized by AMD Foundation Rome, and was in part funded by Merck Sharp & Dohme Corp. The funds are used for the costs of laboratory and data monitoring. There is no one outside of the author SC who is employed or has relationships with Merck Sharp & Dohme. SC's contribution is in data analysis and interpretation. No additional funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: One of the authors is employed by a commercial company (MSD, Rome, Italy). This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

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¶ Membership of the BetaDecline Study Group is provided in the Acknowledgments.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide [1]. T2DM is sustained by insulin resistance and impaired insulin secretion. Impaired insulin secretion due to either beta-cell dysfunction and/or beta-cell loss is now recognized in the pathogenesis and progression of diabetes. The loss of beta-cell mass and the progressive decline in beta-cell function is an early feature of the natural history of diabetes and it is detectable prior to diagnosis [2]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that beta-cell function, as evaluated by the homeostatic model assessment (HOMA-B) index, was already decreased by 50% by the time of the diagnosis and that it continued to decline over the 6-year observation period, even with on-going hypoglycemic therapy [3].

The relative increase of α-cells mass, another typical defect on Langerhans islets of diabetic subjects, may even precede beta-cells loss, being already observed in normoglycaemic baboons with different degrees of obesity [4].

Beta-cell mass is influenced by a balance between proliferative and pro-apoptotic signals, which may be modulated by various growth factors, cytokines, and hormones, whose specific role in the rate of beta-cell decline remains unclear.

High levels of glucose and free fatty acids (gluco-and lipotoxicity), islet amyloid polypeptide deposition, and circulating inflammatory cytokines have been all implicated in beta-cell apoptosis [4–15] Thus, *in vitro* studies have demonstrated that

Current therapies according to quartiles of proinsulin/insulin (PI/I) ratio in total population and by gender.

	PI/I ratio quartiles				
Variables	I° ≤0.485	II° 0.486-0.80	III° 0.81-1.355	IV° >1.355	P
Diet alone (%)	8.1	3.9	7.4	2.4	-
Metformin (%)	84.7	85.0	83.6	83.1	-
SU (%)	29.0	26.0	37.7	47.6	<0.0001
Glinides (%)	10.5	11.8	15.6	26.6	<0.0001
Secretagog. (%)	37.9	37.0	53.3	71.0	<0.0001
TZDs (%)	8.9	9.4	13.1	8.1	-
Acarbose (%)	0.8	1.6	4.1	2.4	-
BP Drugs (%)	76.5	71.0	70.1	72.6	-
Lipid-drugs (%)	59.0	70.4	64.1	60.9	-
Aspirin (%)	39.8	47.2	44.7	58.5	0.03

Factors associated with beta-cell dysfunction at univariate and multivariate analyses

Male gender<	OR 1.8;	95% CI, 1.1-2.9
Secretagogues	OR 4.20;	95% CI, 2.55-6.91

Author's personal copy

Acta Diabetol
DOI 10.1007/s00592-016-0868-7

ORIGINAL ARTICLE

Incidence and correlated factors of beta cell failure in a 4-year follow-up of patients with type 2 diabetes: a longitudinal analysis of the BETADECLINE study

Carlo B. Giorda[1] · Giuseppina T. Russo[2] · Stefania Cercone[3] · Salvatore De Cosmo[4] · Antonio Nicolucci[5] · Domenico Cucinotta[2]

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Table 3 Multivariate Cox regression analysis of risk of initiating insulin therapy

Characteristics	HR	95 % CI	*p*
Hemoglobin A1c	1.46	1.24–1.71	<0.0001
Interleukin-6	1.06	1.03–1.10	<0.0001
HOMA-B (quartiles)			
IV	1.0	–	–
III	2.32	0.74–7.30	0.15
II	2.23	0.72–6.97	0.17
I	3.67	1.25–10.79	0.02
Therapy			
Metformin	1.0	–	–
Secretagogues	1.19	0.25–5.77	0.83
Metformin + secretagogues	4.32	1.88–9.95	0.001
Metformin + thiazolidinediones	1.73	0.35–8.42	0.50

Variables tested and not significant: age, diabetes duration, fasting plasma glucose, triglycerides, proinsulin, homeostatic model assessment-IR

The likelihood of initiating insulin therapy during 4 years of follow-up increased with longer diabetes duration and with higher baseline values for hemoglobin A1c, fasting plasma glucose, triglycerides, proinsulin, interleukin-6, HOMA-IR and lower values for HOMA-B. Our results show that commonly measured parameters as well as treatment with metformin plus a secretagogue may predict treatment failure in type 2 diabetes.

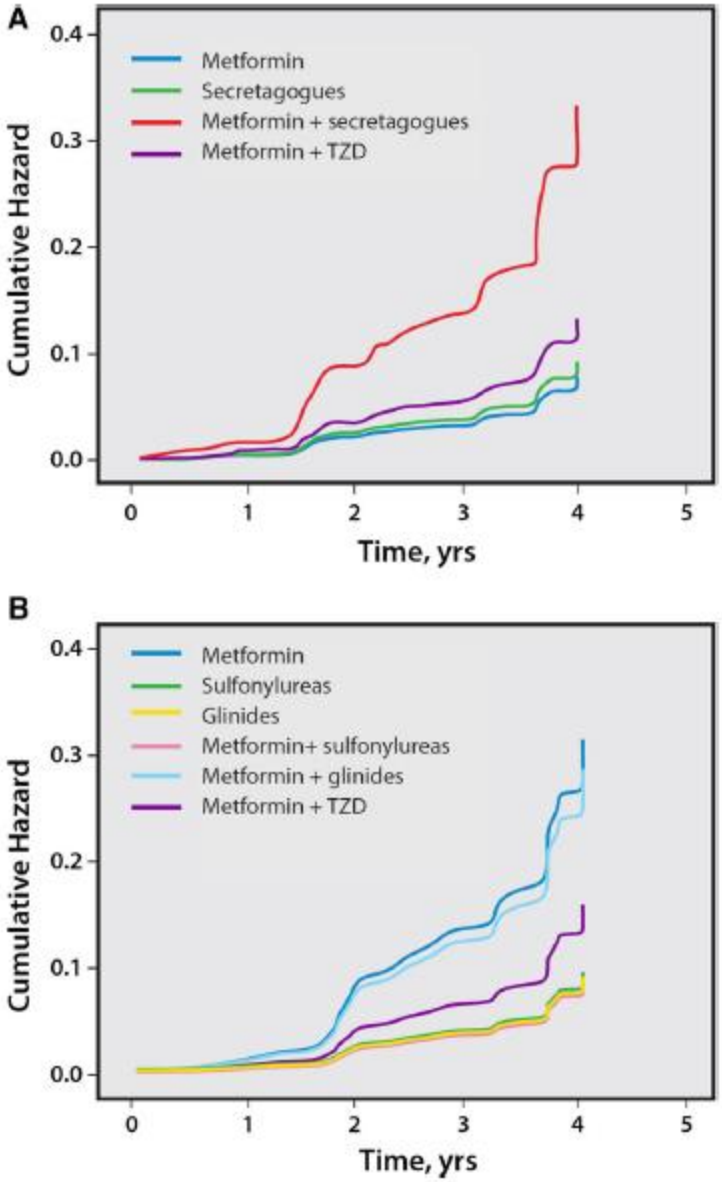


Fig. 1 Cumulative risk of insulin initiation according to diabetes therapeutic scheme at baseline (a), and considering individual type of secretagogues (sulfonylurea vs. glinides) (b). *Curves* adjusted for variables significantly associated with the initiation of insulin therapy at the multivariate Cox model (including HbA1c, IL-6, HOMA-B)

Ridotta massa beta cellulare in pazienti diabetici in trattamento con dieta, insulina o sulfaniluree

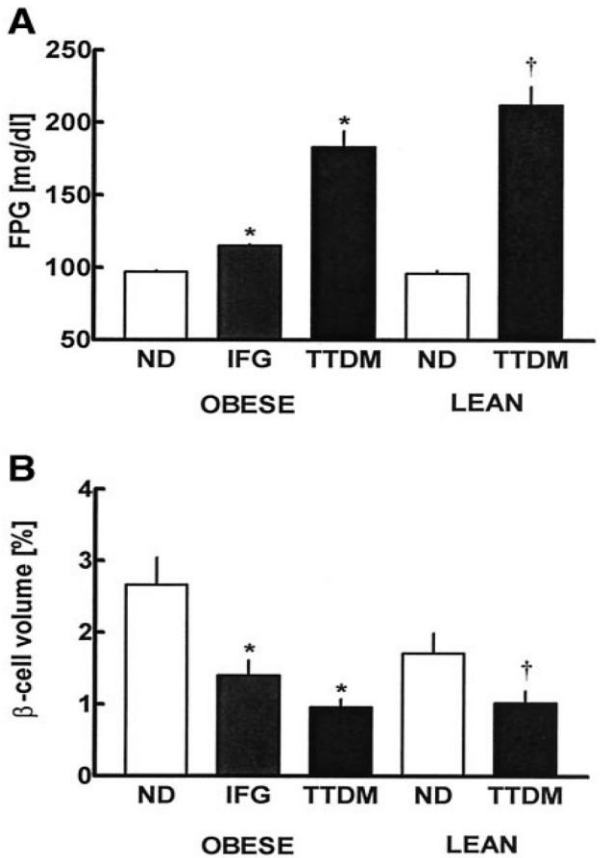


FIG. 2. The mean FPG concentration (*A*) and the mean relative β-cell volume (*B*) in obese (nondiabetic [ND], IFG, and diabetic subjects [TTDM]) and lean cases (nondiabetic and type 2 diabetic subjects).

relative β-cell volume irrespective of whether they were

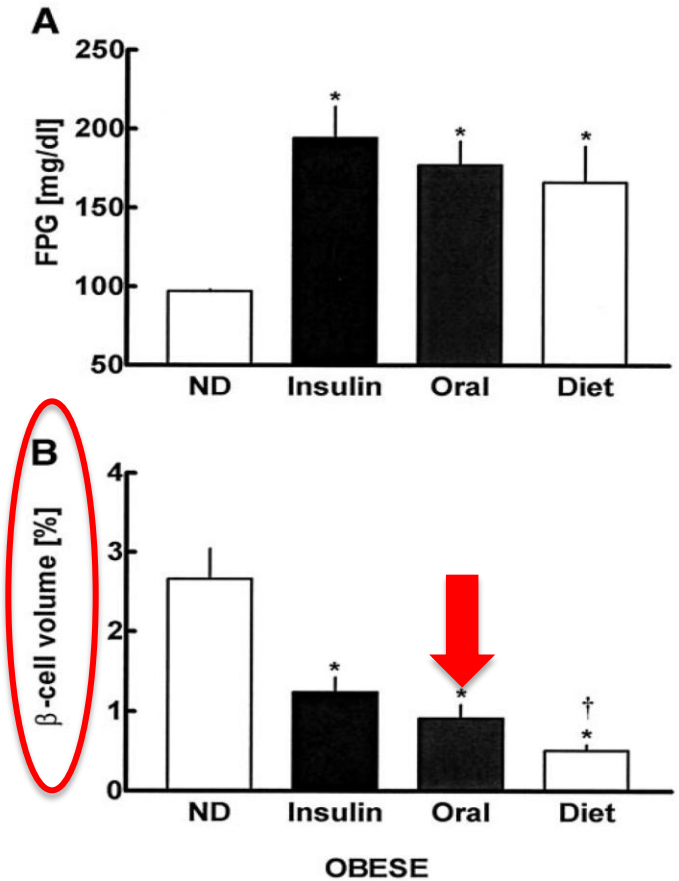


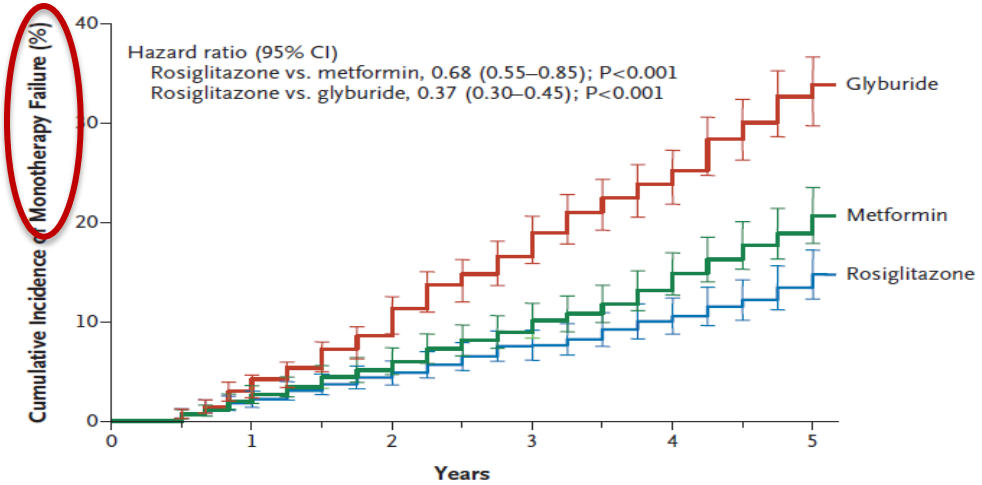
FIG. 3. The mean FPG concentration (*A*) and the relative β-cell volume (*B*) in the obese group of nondiabetic (ND) subjects or diabetic patients who were treated with insulin, sulfonylurea pills (Oral), or diet only.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Steven E. Kahn, M.B., Ch.B., Steven M. Haffner, M.D., Mark A. Heise, Ph.D., William H. Herman, M.D., M.P.H., Rury R. Holman, F.R.C.P., Nigel P. Jones, M.A., Barbara G. Kravitz, M.S., John M. Lachin, Sc.D., M. Colleen O'Neill, B.Sc., Bernard Zinman, M.D., F.R.C.P.C., and Giancarlo Viberti, M.D., F.R.C.P.,



No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years.

Treatment was considered to have failed if a patient had a confirmed or adjudicated level of fasting plasma glucose of more than 180 mg per deciliter. Risk reduction is listed for comparisons of pairwise groups from a baseline covariate-adjusted Cox proportional-hazards model. Gray's estimates of cumulative incidence adjusted for all deaths were smaller than Kaplan–Meier estimates of treatment failure: 10% in the rosiglitazone group, 15% in the metformin group, and 25% in the glyburide group. I bars indicate 95% CIs.

Effetti della monoterapia con metformina, sitagliptin e pioglitazone sui valori di PI/I Ratio

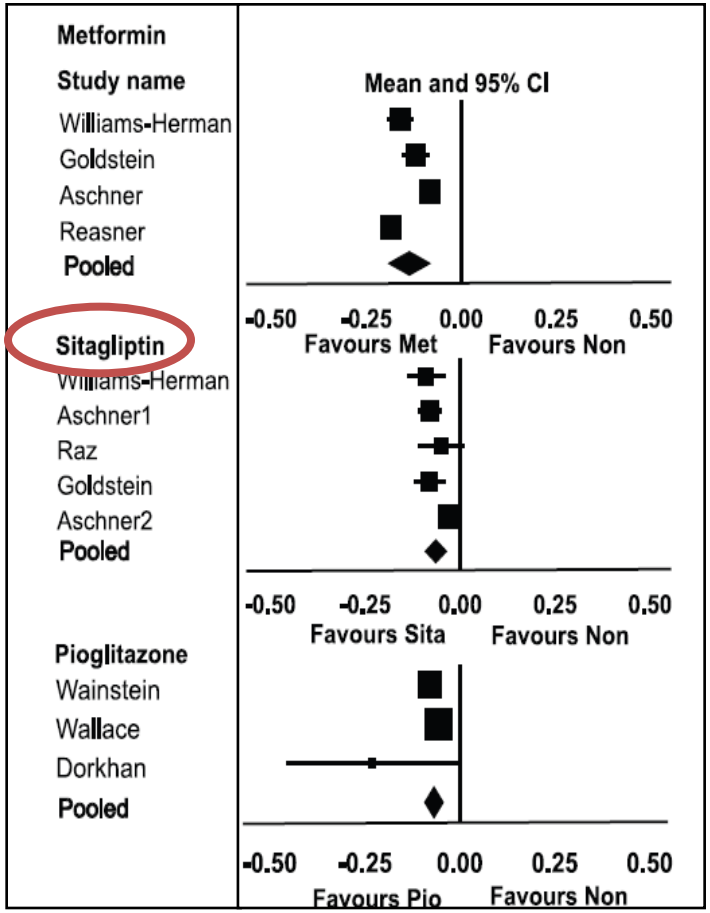
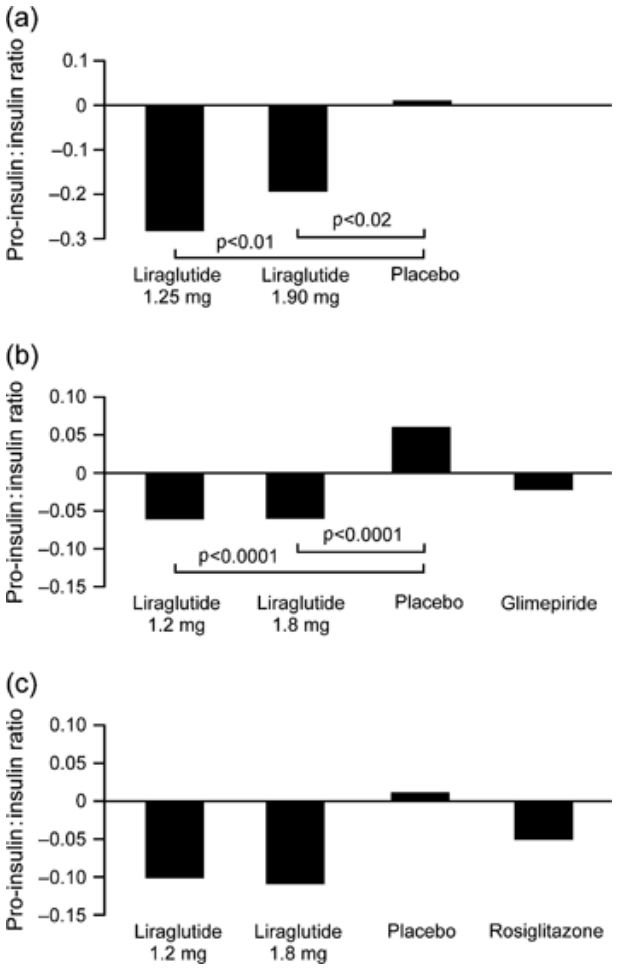


Figure 4. Meta-analyses for changes in the proinsulin/insulin ratio (PI/IR) for different monotherapies. Favours Non : favours no medication.
doi:10.1371/journal.pone.0076713.g004

J. Lu, PLOS ONE 2013

Effetti dei GLP-1 RAs sulle beta- cellule



Visboll T., Diabetes, Obesity and Metabolism 2009

GLP-1 stimola la rigenerazione β-cellulare e aumenta la massa cellulare nei modelli animali

↑ **Proliferazione β-cellulare**

↑ **Ipertrofia β-cellulare**

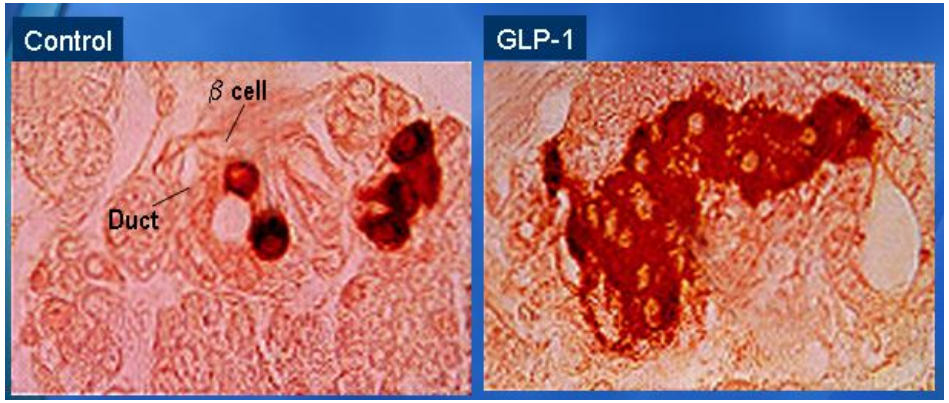
↓ **Apoptosi β-cellularc**

↑**Neogenesi β-cellulare**

↑ **Differenziazione β-cellulare**

β-cellula

GLP-1 increases b-cell mass in a genetic rat model of diabetes



- Increased pancreatic insulin stores and beta cell mass vs. control
- GLP-1 treatment led to a doubling of beta cell mass in 5 days.

Bulotta et al. J Mol Endocrinol 2002;29:347–360
Farilla et al. Endocrinology 2003;144:5149–5158

Tourrel C. et al. *Diabetes*. 2002; 51:1443–1452

Dipeptidyl Peptidase-4 Inhibitors Administered in Combination With Metformin Result in an Additive Increase in the Plasma Concentration of Active GLP-1

EM Migoya[1], R Bergeron[2], JL Miller[1], RNK Snyder[1], M Tanen[1], D Hilliard[1], B Weiss[1], P Larson[1], M Gutierrez[3], G Jiang[1], F Liu[1], KA Pryor[1], J Yao[1], L Zhu[1], JJ Holst[4], C Deacon[4], G Herman[1], N Thornberry[1], J Amatruda[1], D Williams-Herman[1], JA Wagner[1] and R SinhaRoy[1]

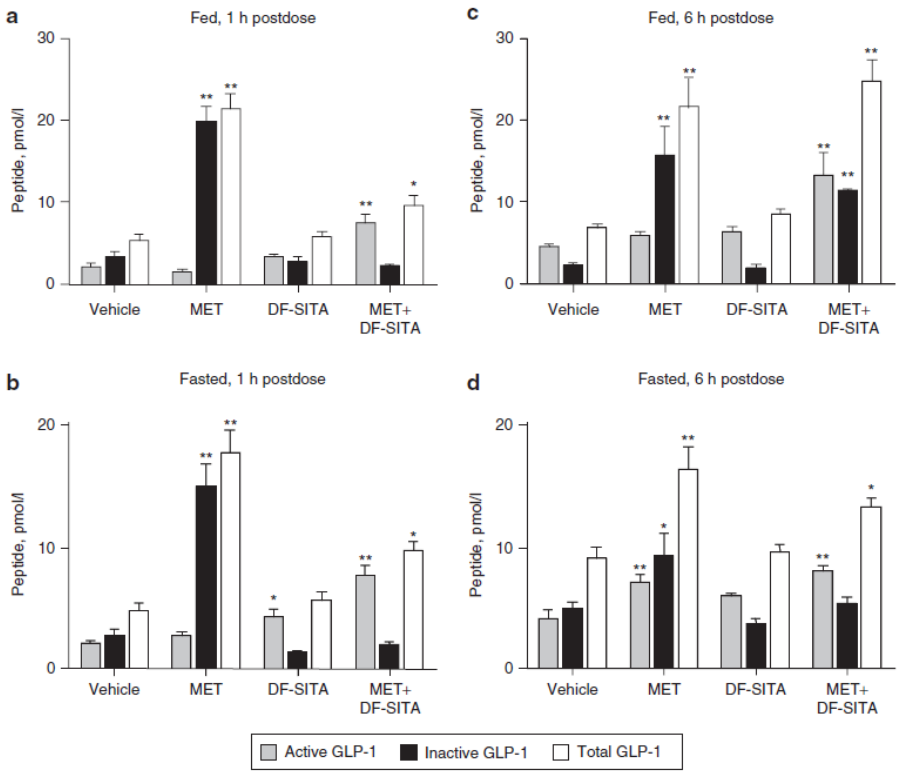
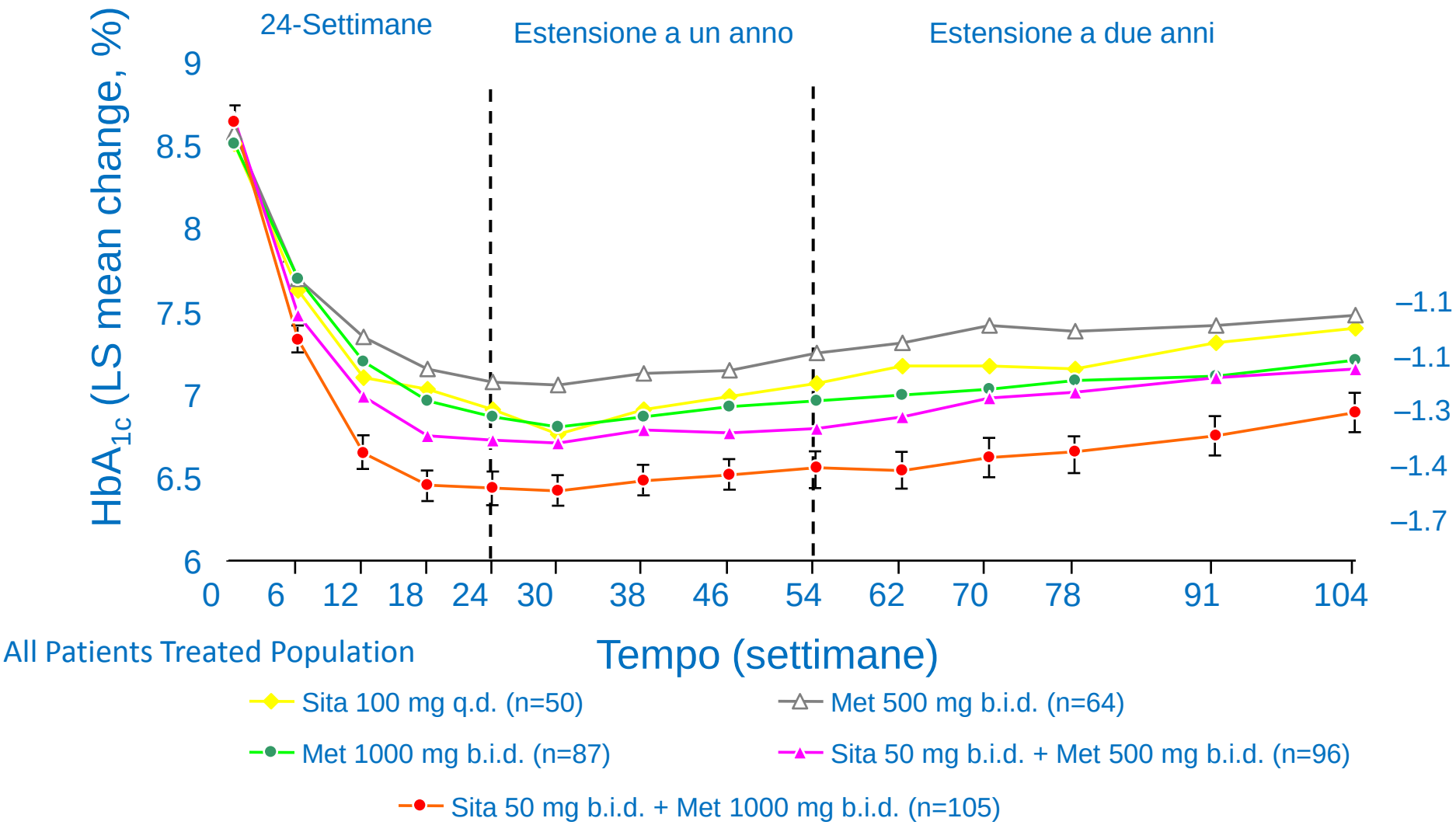


Figure 1 GLP-1 peptide concentrations in plasma in fed DIO mice (top panels) and fasted DIO mice (bottom panels). Active (gray bars), inactive (black bars), and total (white bars) GLP-1 concentrations determined in plasma samples obtained either (**a**, **b**) 1 h or (**c**, **d**) 6 h postdose. Values are reported in pmol/l, as mean values ± SE; $n = 7$ in each group. *$P < 0.05$, **$P < 0.01$ vs. respective vehicle group. DF-SITA, desfluorositagliptin; DIO, diet-induced obesity; GLP-1, glucagon-like peptide 1; MET, metformin; MET + DF-SITA, metformin + desfluorositagliptin (coadministration).

Durability di Sitagliptin e Metformina–Studio di combinazione iniziale



Williams Herman D. Diabetes Obes Metab. 2010; 12(5):442-51

Glucotossicità e funzione beta cellulare

Glucotossicità

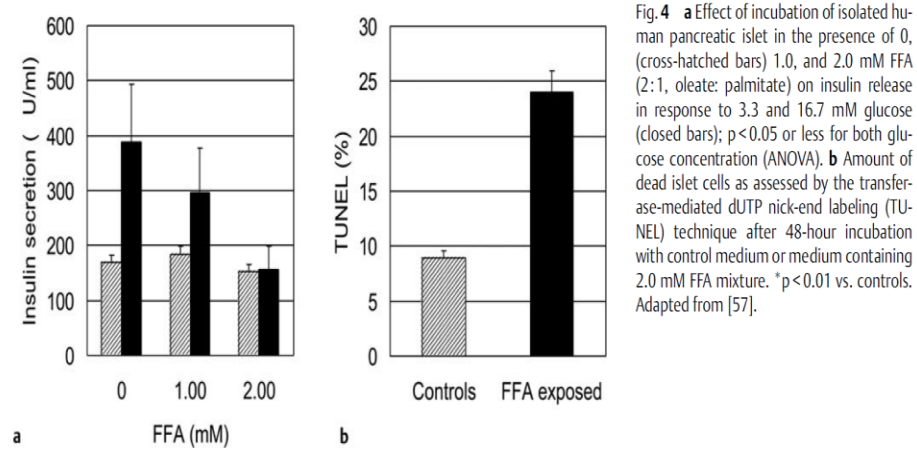
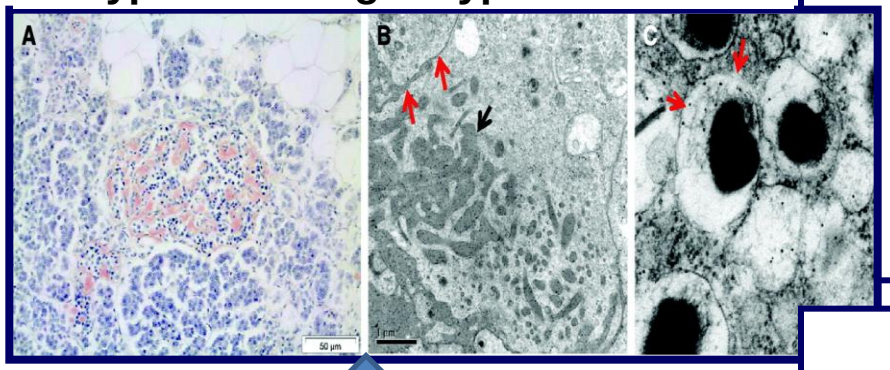


Fig. 4 **a** Effect of incubation of isolated human pancreatic islet in the presence of 0, (cross-hatched bars) 1.0, and 2.0 mM FFA (2:1, oleate: palmitate) on insulin release in response to 3.3 and 16.7 mM glucose (closed bars); $p<0.05$ or less for both glucose concentration (ANOVA). **b** Amount of dead islet cells as assessed by the transferase-mediated dUTP nick-end labeling (TUNEL) technique after 48-hour incubation with control medium or medium containing 2.0 mM FFA mixture. $^{*}p<0.01$ vs. controls. Adapted from [57].

Del Prato, Marchetti et al. *Hormon Metabol Res 2004*

Human pancreatic islet with extracellular amyloid deposits, a typical finding in type 2 diabetes.



Westermark P et al. *Physiol Rev* 2011

Depositi di amiloide

Lipotossicità

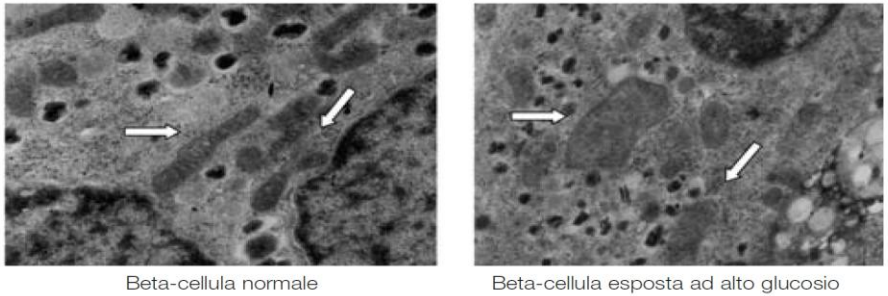


Figura 2 *A seguito dell'esposizione a elevate concentrazioni di glucosio, i mitocondri (frecce) delle beta-cellule mostrano varie alterazioni morfologiche, tra cui rigonfiamento e minore definizione delle creste e della matrice.*

Marchetti et al. *GIDM* 2009

Terapia insulinica intensiva e remissione diabete

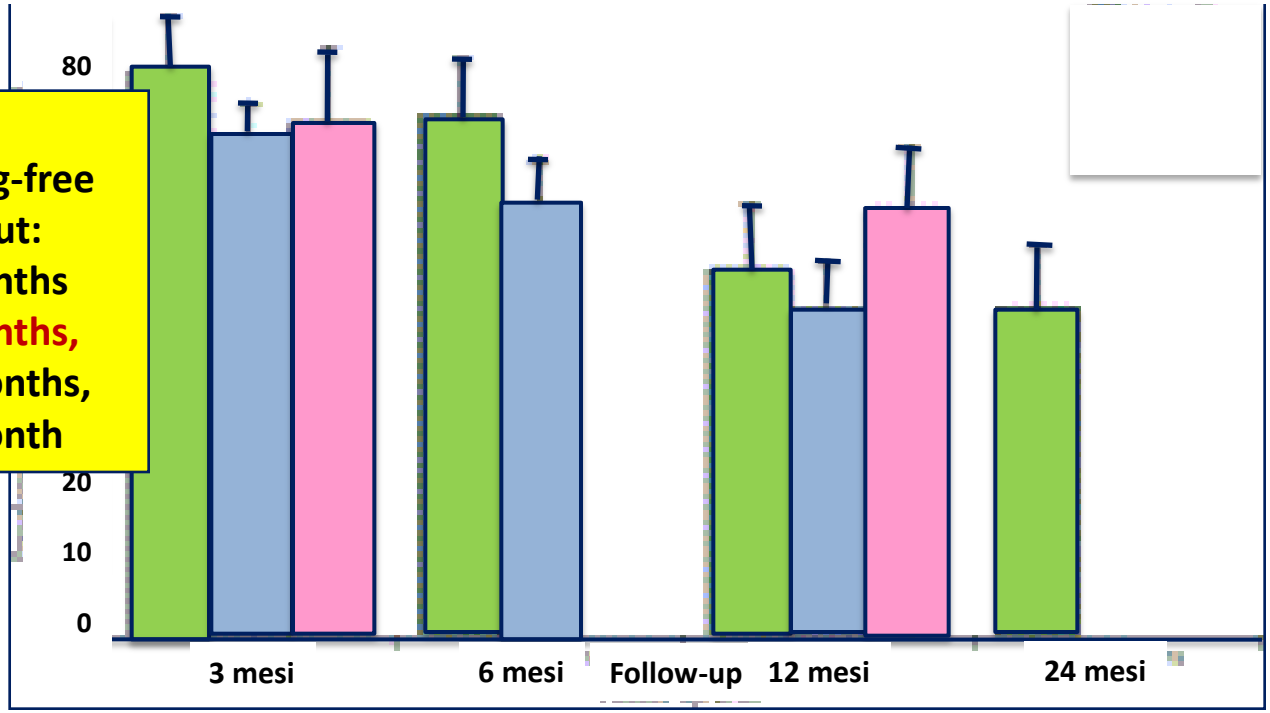
Short-term the *intensive insulin* therapy in type 2 diabetes mellitus: a systematic review and meta-analysis

Caroline Kaercher Kramerx, MD, Prof Bernard Zinman, MD, Dr Ravi Retnakaranx, MD

The Lancet Diabetes & Endocrinology , Volume 1 , Issue 1 , 28 – 34, 2013

CrossMark

the proportion of participants in drug-free remission was about:
- **66·2% after 3 months**
- **58·9% after 6 months,**
- **46·3% after 12 months,**
- **42·1% after 24 month**



Prevalence of participants in drug-free glycaemic remission during follow-up after short-term intensive insulin therapy, by study

Bars are 95% CIs.

Ma l'indicazione alla terapia insulinica non vi è solo quando la funzione delle beta cellule è al capolinea

MEDIA
SEZIONE DI FORMAZIONE PER L'AUTOVALUTAZIONE 1 MeDia 2014;14:1-71
GOVERNO CLINICO

Terapia insulinica nel diabete mellito di tipo 2: un viaggio non di sola andata

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Riassunto

Nell'ampio panorama di scelte terapeutiche oggi disponibili per il trattamento dei pazienti con diabete mellito di tipo 2, la terapia insulinica non rappresenta sempre l'ultima opzione utilizzabile dopo il fallimento delle altre terapie ipoglicemizzanti. Il suo utilizzo risulta infatti consigliabile o necessario in numerosi momenti della storia della malattia, anche solo temporaneamente.

Numerosi studi hanno stabilito, ad esempio, i benefici di una terapia insulinica intensiva negli stadi precoci del diabete di tipo 2, sia sulla funzione β-cellulare che sul mantenimento del compenso glicemico a lungo termine.

Allo stesso modo, dalla programmazione e gestione della gravidanza alla risoluzione degli scompensi glicemici conseguenti a traumi, ospedalizzazioni o malattie intercorrenti, l'utilizzo della terapia insulinica, da sola o in associazione ad altri farmaci ipoglicemizzanti, deve essere sempre considerata come una valida e talora momentanea "arma" a disposizione del paziente con diabete di tipo 2.

Figura 2. Flow-chart per la terapia del diabete mellito di tipo 2.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico [ref. 1])

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2 g/die

↓

	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti GI	Costo
Add on a metformina								
Sulfonilurea o repaglinide	1D	1D	Non indicato in IRC (3)	3C (2)	1B	1B	1A	Basso
Pioglitazione	1A	1D	Fratture	1A	1A	1E	1A	Medio
Acarbosio	1A	1D	Rari	2B	2B	3C	1C	Basso
Insulina basale	1D	1A	Rari	1B	1A	1B	1A	Medio

Most of CONSOLIDATE diabetes therapies have a high risk of hypoglycaemia and weight gain, but lower costs

Colori:

- effetto o parametro negativo o sconsigliato
- effetto o parametro parzialmente negativo o sconsigliato
- effetto o parametro positivo o probabilmente positivo
- il farmaco non ha effetti significativi sul parametro o viene dato un giudizio neutro

Figura 2. Flow-chart per la terapia del diabete mellito di tipo 2.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico [ref. 1])

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2 g/die

↓

NEW drugs have low hypoglycaemic risk, BW unchanged or lower , but they have higher costs

Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti GI	Costo
Gliptina	1A	1B	Rari	1A	1B	2B (2)	1A	Elevato
A.R. GLP-1	1A	1A	Non indicato in IRC	3B	1A	2B	1C	Elevato

Ease of use:Oral therapy (Gliptins, SGLT-2)/ Injectable (GLP-1RAS)
No tritation (sigle dosage all, according to renal function DPP4i)
Safety profile: good for all

Gliflozina	1A	1A	Infezioni GU	3C	2B	2B	1A	???

Colori:

- effetto o parametro negativo o sconsigliato
- effetto o parametro parzialmente negativo o sconsigliato
- effetto o parametro positivo o probabilmente positivo
- il farmaco non ha effetti significativi sul parametro o viene dato un giudizio neutro

BMJ Open Diabetes Research & Care

Early treatment revisions by addition or switch for type 2 diabetes: impact on glycemic control, diabetic complications, and healthcare costs

Phil Schwab,[1] Vishal Saundankar,[1] Jonathan Bouchard,[2] Neil Wintfeld,[2] Brandon Suehs,[1] Chad Moretz,[1] Elsie Allen,[2] Antonio DeLuzio[2]

Table 2 Patient characteristics for overall cohort, patients with early treatment revision (within 90 days of index), and patients with delayed treatment revision

	Overall		Early treatment revision		Delayed treatment revision		
	n=8463 (100.0%)		n=2673 (31.6%)		n=5790 (68.4%)		p Value
Age, mean (SD)	66.4	(10.8)	65.7	(11.2)	66.8	(10.6)	0.0001
Female, n (%)	4052	(47.9%)	1302	(48.7%)	2750	(47.5%)	0.3031
HbA1c at index, mean (SD)	10.2%	(1.2%)	10.4%	(1.4%)	10.1%	(1.1%)	<0.0001
DCI (preindex), mean (SD)	2.5	(2.0)	2.3	(1.9)	2.6	(2.1)	<0.0001
Office visits (preindex), mean (SD)	12.3	(10.3)	11.9	(10.6)	12.5	(10.2)	<0.0001
Insulin treatment (preindex), n (%)	2796	(33.0%)	567	(21.2%)	2229	(38.5%)	<0.0001
Multiple treatments (preindex), n (%)	3826	(45.2%)	749	(28.0%)	3077	(53.1%)	<0.0001

p Values reported for comparisons between early treatment revision and delayed treatment revision are from Wilcoxon rank-sum test for continuous variables, and χ^2 test for categorical variables.
DCI, Deyo-Charlson Comorbidity Index; HbA1c, glycosylated hemoglobin.

Table 3 Patterns of treatment revision for members on common oral antidiabetic medication regimens

Patterns of treatment revision	n	Per cent
All others	32	3.7
Baseline treatment=metformin (n=342)		
Addition		
Switch sulfonylurea	136	39.8
Add sulfonylurea	95	27.8
Add thiazolidinedione	27	7.9
Add basal insulin	26	7.6
Switch basal insulin	20	5.9
Switch thiazolidinedione	11	3.2
All others	27	7.8

BMJ Open Diabetes Research and Care 2016;**4**:e000099. doi:10.1136/bmjdrc-2015-000099

Periodo di osservazione 2004-2011

53.932 pazienti in monoterapia con metformina ha avuto un cambiamento di terapia

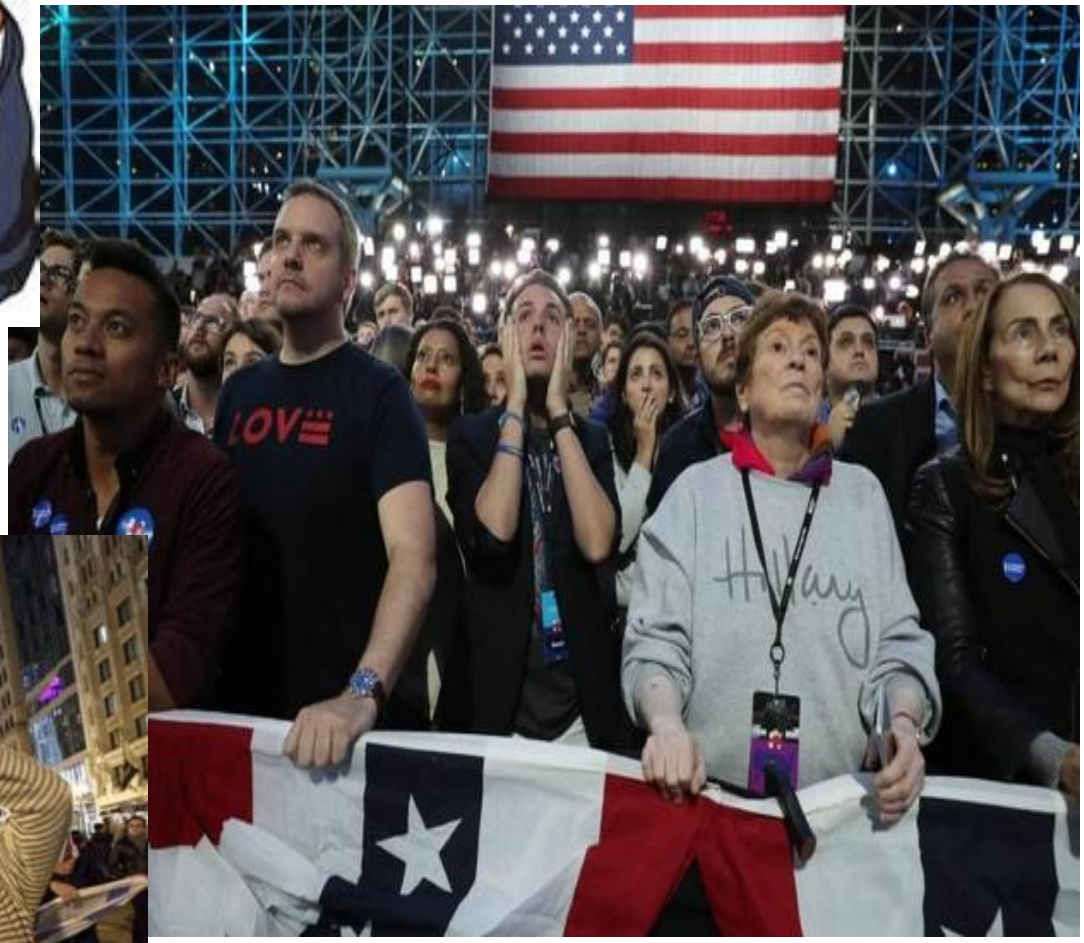
Caratteristiche	Media±ds o %
Età (anni)	58,1±11,0
Maschi (%)	55,9
Durata diabete (anni)	5,9±6,3
BMI (Kg/m²)	30,9±5,5
HbA1c (%)	7,8±1,4
HbA1c ≤7% (%)	28,3
HbA1c >8% (%)	35,0

Farmaci utilizzati nello switch dalla monoterapia con metformina

Classi di farmaci	Tutti (%)	HbA1c ≤7% (%)	HbA1c >7% (%)
Metformina	77,4	64,0	84,7
Sulfaniluree (SU)	59,7	56,5	63,6
Glinidi	14,9	18,8	11,9
Inibitori della DPP-IV (DPP-IV)	12,5	8,9	14,2
Glitazonici (TZD)	11,0	12,3	11,6
Insulina	8,9	5,3	7,9
Insuline rapide	5,8	3,8	4,8
Insuline lente	4,7	2,2	4,5
Acarbose	3,0	4,3	2,4
Analoghi del GLP-1 (GLP-1)	2,6	2,5	2,4
Insuline ad azione intermedia	0,5	0,3	0,5
Insuline premix	0,4	0,3	0,4

Combinazioni	Tutti (%)	HbA1c ≤7% (%)	HbA1c >7% (%)
Metformina+SU	43,7	38,2	48,6
SU	6,8	12,4	4,4
Metformina+SU+DPP-IV	6,5	4,2	7,7
Metformina+Glinidi	6,5	6,3	5,9
Metformina+TZD	6,2	5,4	7,3
Glinidi	5,3	10,0	2,8
Metformina+DPP-IV	5,2	3,7	5,9
Insulina	4,3	3,6	3,2
TZD	3,4	5,6	2,8
Metformina+Insulina	3,3	1,2	3,4
Metformina+Glinidi+GLP-1	2,1	1,9	2,1

Nobody voted for me…..



Thank you
It is time for better therapies…