
# Algoritmi di terapia personalizzata (AMD)

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ARS LIGURIA
AGENZIA REGIONALE SANITARIA

Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- BAYER
- STRODER

In fede
*Alberto De Micheli*

# Il «tormentone» della terapia personalizzata

# Il controllo della glicemia: dati epidemiologici vs. intervento terapeutico

## Analisi epidemiologica: UKPDS

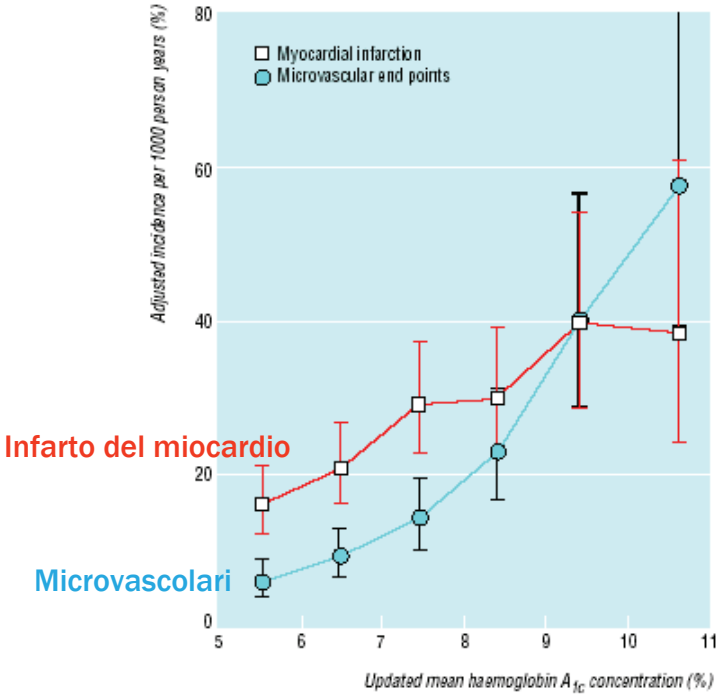
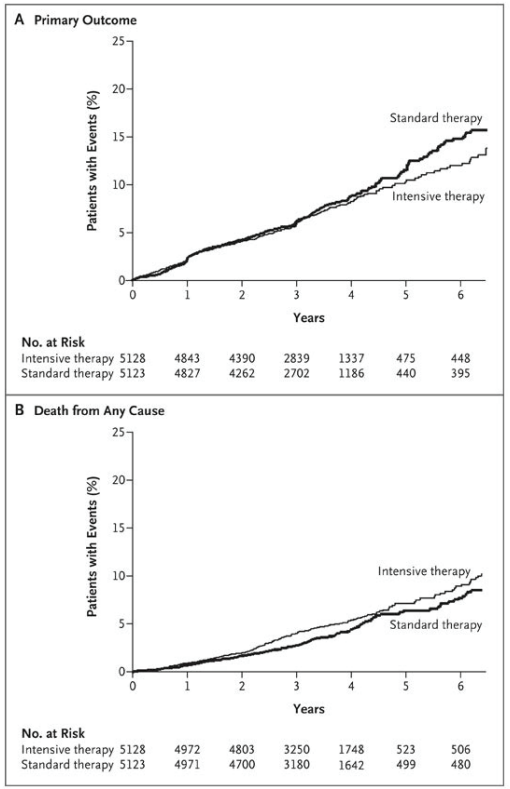



Fig 2 Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin $A_{1c}$ concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

*UKPDS 35, Stratton IM, BMJ 2000; 321:405-12*

## Intervento: ACCORD




**Outcome primario**

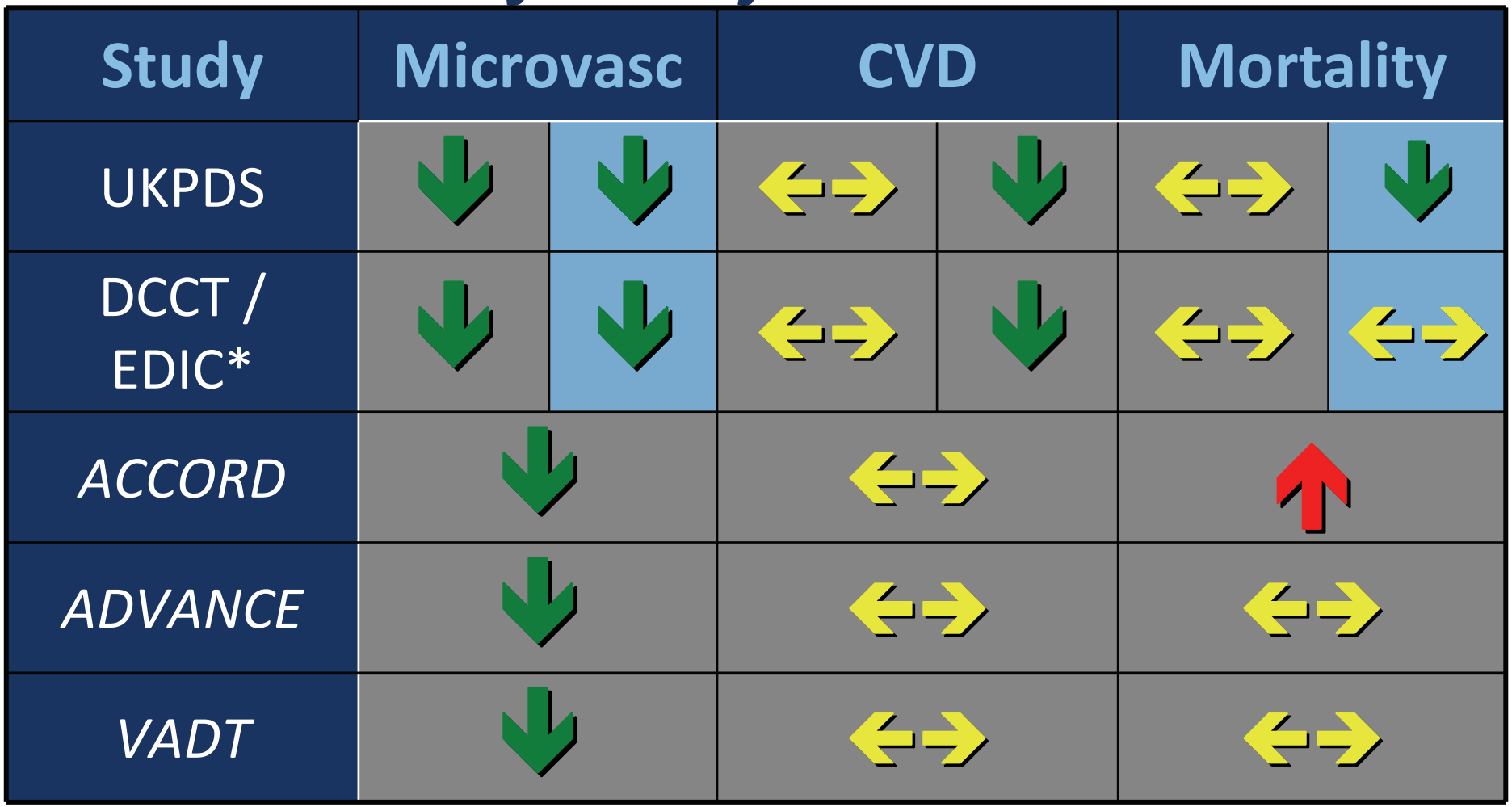
**2.11 vs. 2.29% /anno**
**HR 0.90; 95% CI, 0.78 to 1.04;**
**P = 0.16**

**Mortalità per ogni causa**

**1.41 vs 1.14 %/ anno**
**HR 1.22; 95% CI, 1.01 to 1.46**
**P = 0.04**

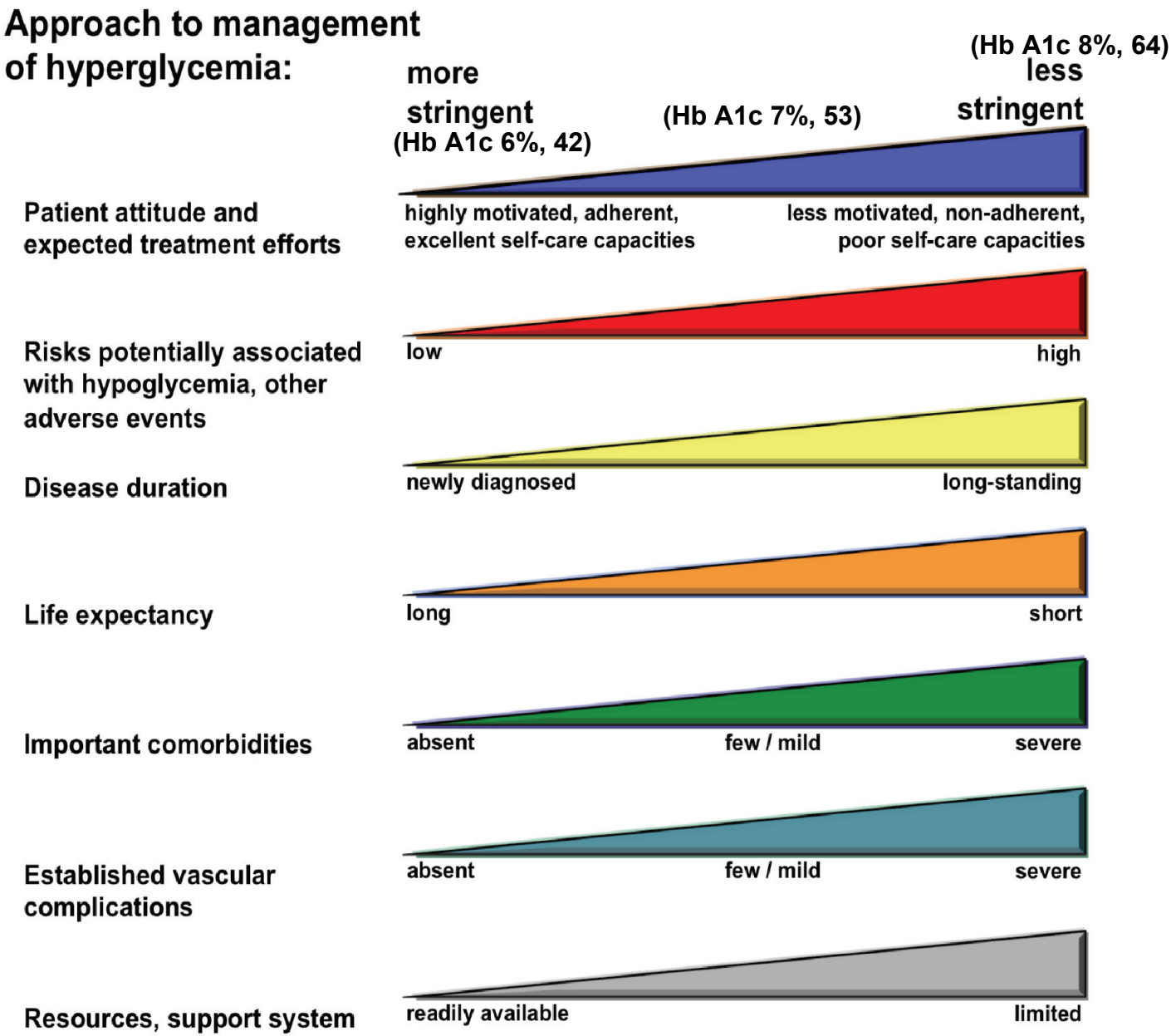
*The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-59*

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




*Kendall DM, Bergenstal RM. © International Diabetes Center 2009*

*UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854.*
*Holman RR et al. N Engl J Med. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.*
*Nathan DM et al. N Engl J Med. 2005;353:2643. Gerstein HC et al. N Engl J Med. 2008;358:2545.*
*Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. N Engl J Med 2009;361:1024)*




*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*

*(Adapted with permission from: Ismail-Beigi F, et al. Ann Intern Med 2011;154:554)*

CLINICAL GUIDELINE

ACP Clinical Practice®
American College of Physicians
GUIDELINES

Stile di vita

Metformina

Secondo farmaco

# Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians

**Amir Qaseem, MD, PhD, MHA; Linda L. Humphrey, MD, MPH; Donna E. Sweet, MD; Melissa Starkey, PhD; and Paul Shekelle, MD, PhD, for the Clinical Guidelines Committee of the American College of Physicians***

**Description:** The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the comparative effectiveness and safety of type 2 diabetes medications.

**Methods:** This guideline is based on a systematic evidence review evaluating literature published on this topic from 1966 through April 2010 that was identified by using MEDLINE (updated through December 2010), EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline included all-cause mortality, cardiovascular morbidity and mortality, cerebrovascular morbidity, neuropathy, nephropathy, and retinopathy. This guideline grades the evidence and recommendations by using the American College of Physicians clinical practice guidelines grading system.

**Recommendation 1:** ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).

**Recommendation 2:** ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).

**Recommendation 3:** ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).

*Ann Intern Med.* 2012;156:218-231. www.annals.org
For author affiliations, see end of text.

***Qaseem A Ann Intern Med. 2012; 156: 218- 231***

# Personalizzazione della terapia

**Step 1**

1. stile di vita
2. **acarbose**
3. **metformina**
4. **sulfoniluree**
5. **glinidi**
6. **glitazoni**
7. **inibitori DPP-IV**
8. GLP-1
9. insulina

**Step 2**

**6 x 7 = 42**

**Step 3**

**6 x 7 x 6 = 252**

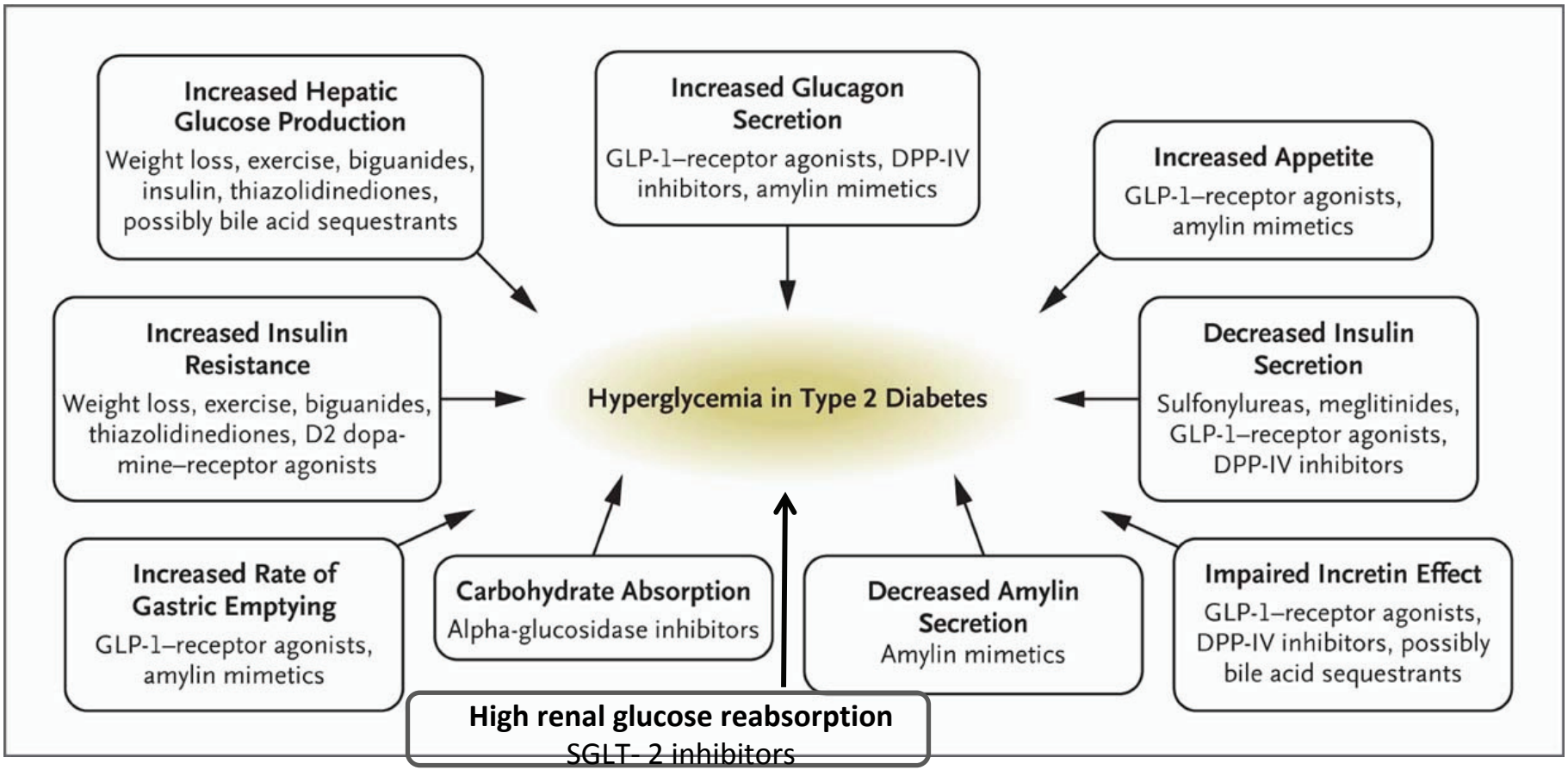
**Step 4**

**6 x 7 x 6 x 5 = 1260**

- **inibitori SGLT-2**
- **diverse opzioni (SU, gliptine, insuline…)**
- **diversi dosaggi**

***Marco Gallo 2012***

# Terapia del diabete tipo 2 basata sulle alterazioni fisiopatologiche




*Ismail-Beigi F. N Engl J Med 2012;366:1319-1327*

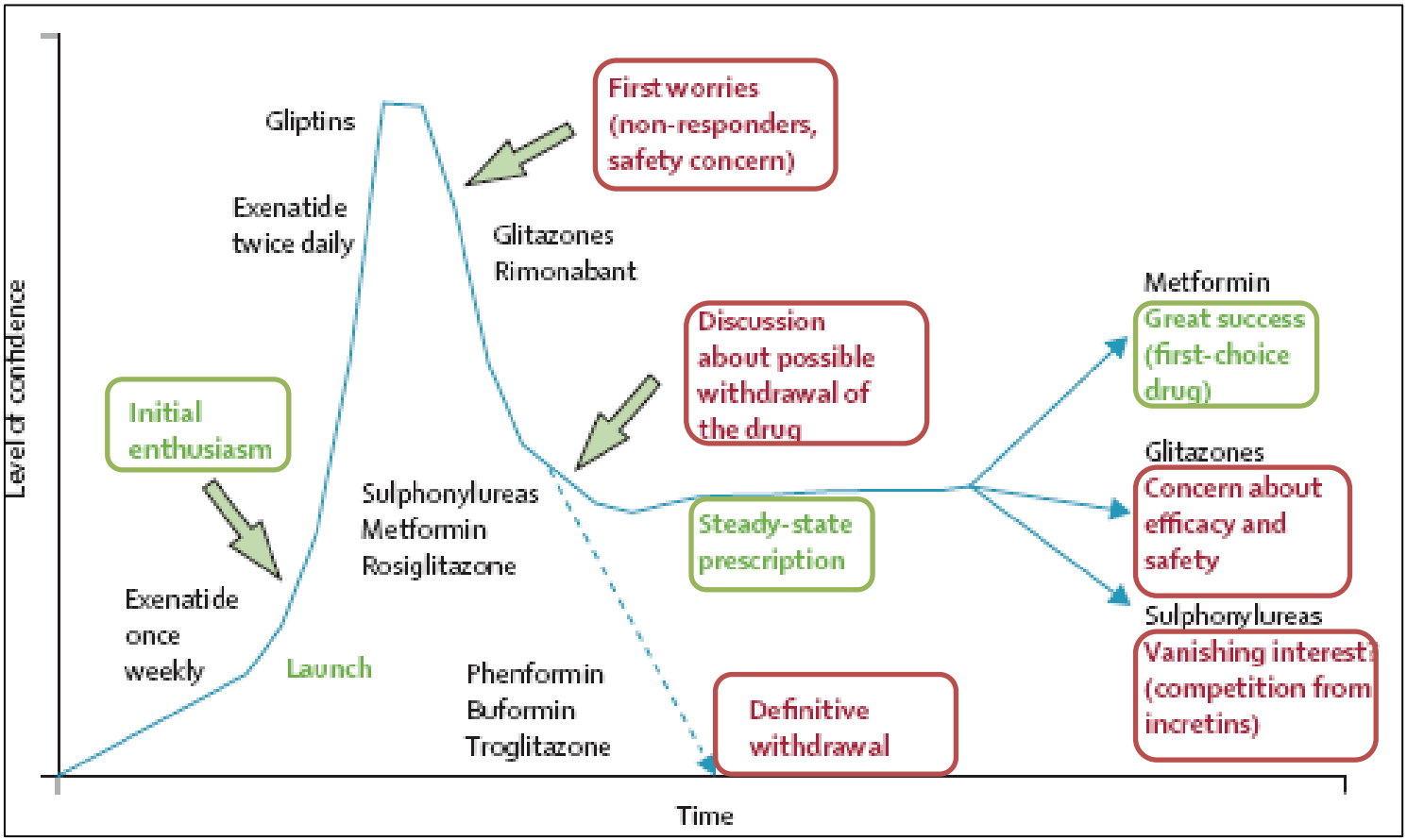
The NEW ENGLAND JOURNAL of MEDICINE

# Diabetes Medication Comparison Table: Benefits and Risks

| | Metformin | DPP4 Inhibitor | Sulfonylurea | Glinide | TZD's | Colesevelam | Alpha-glucosidase inhibitor | GLP-1 Agonist | Insulin | Pramlintide | Cycloset |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Benefits** | | | | | | | | | | | |
| 1. Postprandial Glucose Lowering (PPG) | Mild | Moderate (Mod.) | | | Mild | | Mod. | Moderate to severe | | | Mod. |
| 2. Fasting Glucose Lowering (FPG) | Mod. | Mild | Mod. | Mild | Mod. | Mild | Neutral | Mild | Mod. to severe | Mild | Neutral |
| 3. Reduces Nonalcoholic fatty liver disease | Mild | Neutral | | | Mod. | Neutral | | Mild | Neutral | | Neutral |
| **Risks** | | | | | | | | | | | |
| 4. Hypoglycemia | Neutral | | Mod. | Mild | Neutral | | | | Mod. to severe | Neutral | Mild |
| 5. Gastrointestinal Symptoms | Moderate | Neutral | | | Moderate | | | | Neutral | Mod. | Mod. To severe |
| 6. Risk of use with renal insufficiency | Severe | Reduce Dosage | Mod. | Neutral | Mild | Neutral | | Moderate | | Unk. | Mild-Mod. |
| 7. Contraindicated in liver failure or predisposition to lactic acidosis | Severe | Neutral | Moderate | | | Neutral | | | | | Mild |
| 8. Heart failure/ Edema | Use with caution in CHF | Neutral | | | Mild/Mod. (Contra-indicated in class 3,4 CHF) | Neutral | | | Neutral unless with TZD | Neutral | Neutral |
| 9. Weight gain | Benefit | Benefit | Mild | | Mod. | Neutral | Neutral | Benefit | Mild to Mod. | Benefit | Neutral |
| 10. Fractures | Neutral | | | | Mod. | Neutral | | | | | Neutral |
| 11. Drug-Drug interactions | Neutral | | Mod. | | Neutral | | | | | | Mod. |

*This chart has been adapted from a 2009 AACE Guidelines chart.* ***http://www.diabetesincontrol.com/articles/features/11666***

# Hypothetical timeline of most important oral antidiabetic drugs




*Ds Scheen AJ Lancet 2008; 372: 1197- 8, modificata*


LA PERSONALIZZAZIONE DELLA TERAPIA NEL DIABETE DI TIPO 2 - Windows Internet Explorer
http://www.aemmedi.it/algoritmi/
Search the web (Babylon)
File Modifica Visualizza Preferiti Strumenti ?
LA PERSONALIZZAZIONE DELLA TERAPIA NEL DIABE...
Pagina Strumenti
1974
ASSOCIAZIONE MEDICI DIABETOLOGI
www.aemmedi.it
LA PERSONALIZZAZIONE DELLA TERAPIA NEL DIABETE DI TIPO 2
Versione italiana
PERSONALISATION OF THERAPY IN TYPE 2 DIABETES
L'algoritmo AMD 2011
start
AMD
3 Microsoft Offi...
Linee-guida e Ra...
ARRIVATI: 5 mes...
LA PERSONALIZZ...
LA PERSONALIZZ...
IT
19.13

# Fondamenti

- Fenotipizzare i pazienti
- Personalizzare gli obiettivi
- Valutare le glicemie circadiane
- Scegliere i farmaci in successione razionale sulla base:
  - del fenotipo
  - dei profili glicemici in SMBG
- Interattività

# La fenotipizzazione

- ✓ Età
- ✓ Complicanze macro
- ✓ Obiettivi Hb A1c
- ✓ BMI
- ✓ Hb A1c
- ✓ Rischio di ipoglicemia
- ✓ Funzionalità renale
- ✓ SMBG

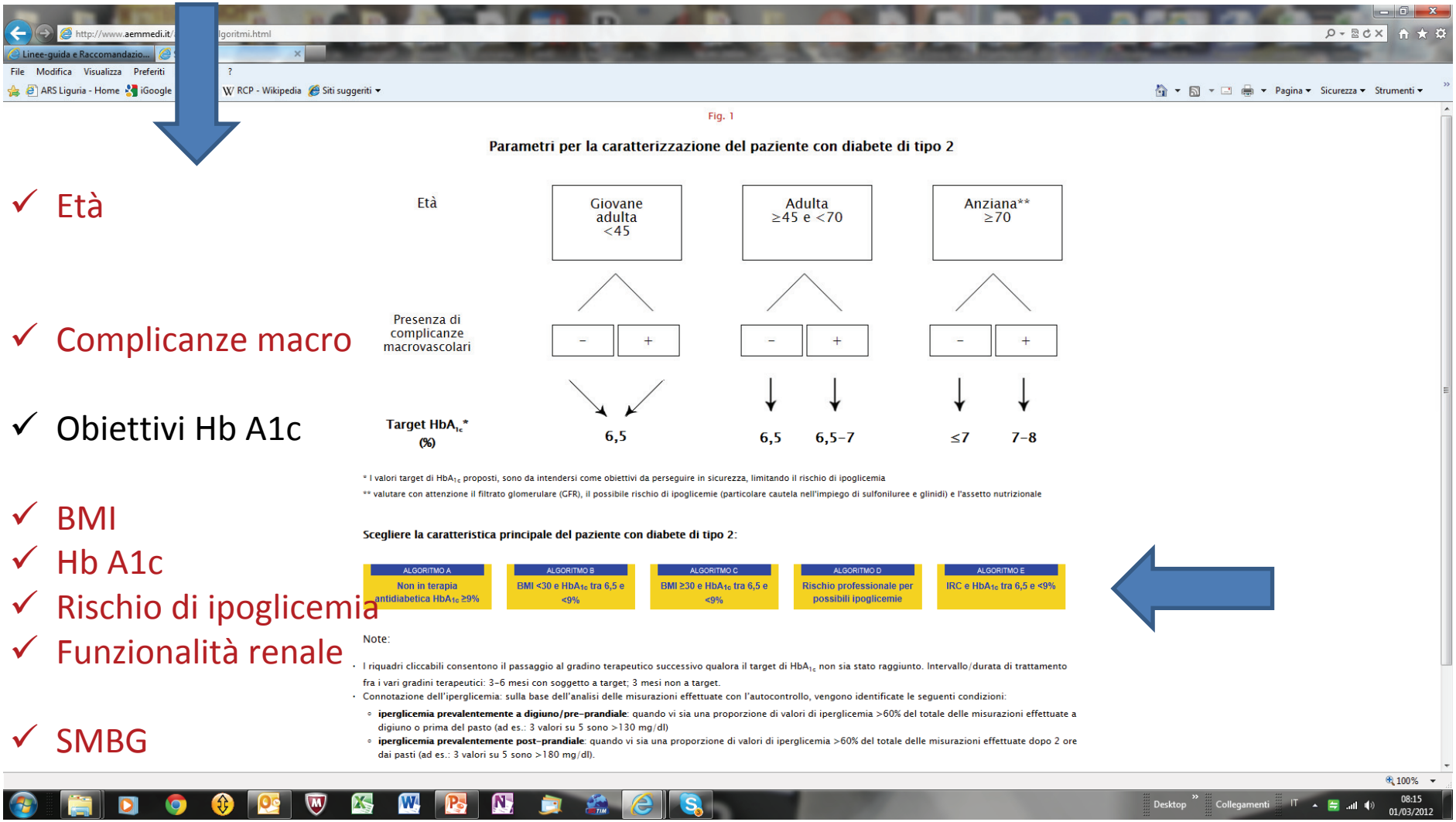


Fig. 1

**Parametri per la caratterizzazione del paziente con diabete di tipo 2**

| | | | |
|---|---|---|---|
| Età | Giovane adulta <45 | Adulta ≥45 e <70 | Anziana** ≥70 |
| Presenza di complicanze macrovascolari | – / + | – / + | – / + |
| Target $HbA_{1c}$* (%) | 6,5 | 6,5 | 6,5–7 | ≤7 | 7–8 |

* I valori target di $HbA_{1c}$ proposti, sono da intendersi come obiettivi da perseguire in sicurezza, limitando il rischio di ipoglicemia

** valutare con attenzione il filtrato glomerulare (GFR), il possibile rischio di ipoglicemie (particolare cautela nell'impiego di sulfoniluree e glinidi) e l'assetto nutrizionale

**Scegliere la caratteristica principale del paziente con diabete di tipo 2:**

| ALGORITMO A | ALGORITMO B | ALGORITMO C | ALGORITMO D | ALGORITMO E |
|---|---|---|---|---|
| Non in terapia antidiabetica $HbA_{1c}$ ≥9% | BMI <30 e $HbA_{1c}$ tra 6,5 e <9% | BMI ≥30 e $HbA_{1c}$ tra 6,5 e <9% | Rischio professionale per possibili ipoglicemie | IRC e $HbA_{1c}$ tra 6,5 e <9% |

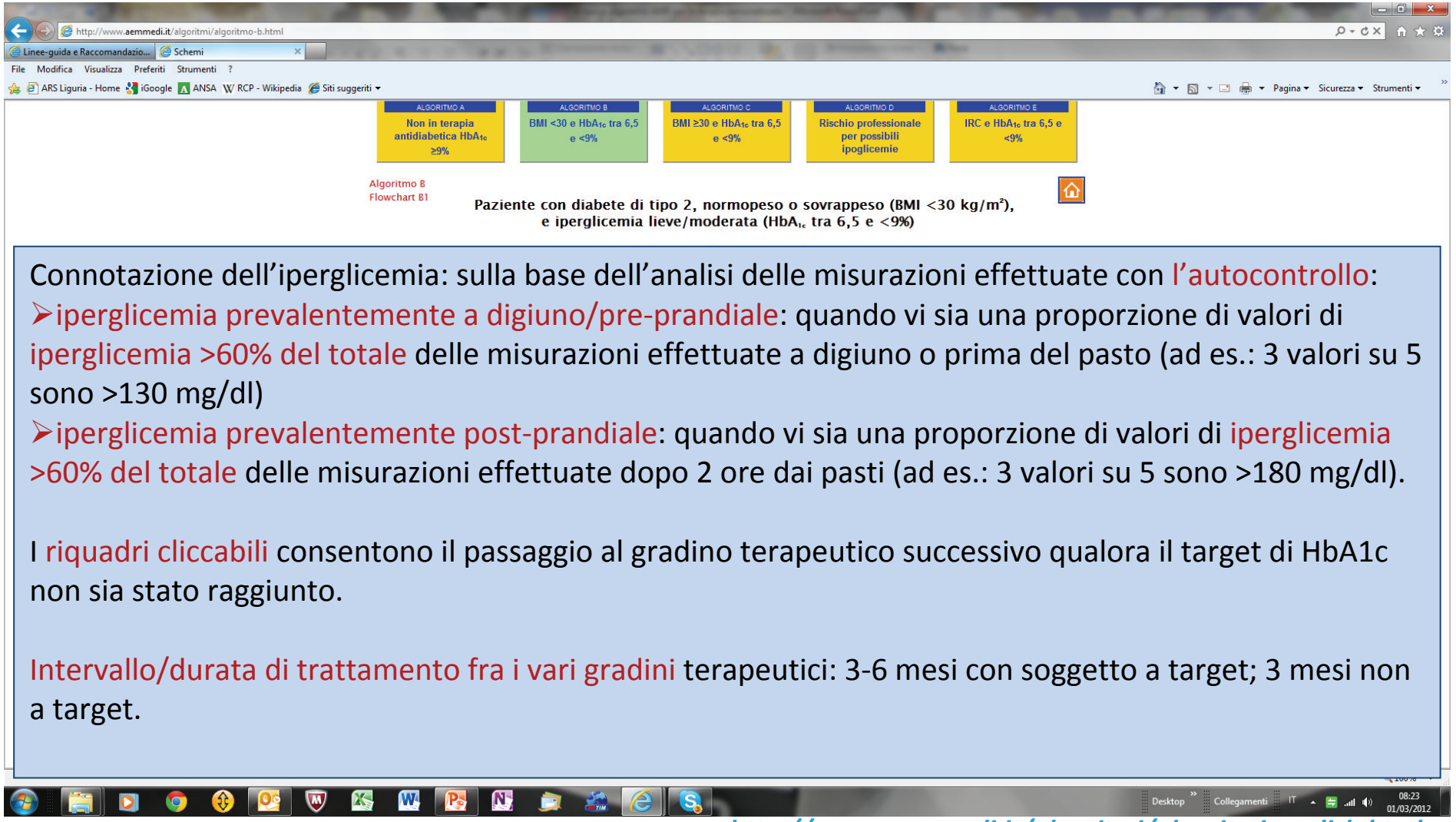
Note:

- I riquadri cliccabili consentono il passaggio al gradino terapeutico successivo qualora il target di $HbA_{1c}$ non sia stato raggiunto. Intervallo/durata di trattamento fra i vari gradini terapeutici: 3–6 mesi con soggetto a target; 3 mesi non a target.
- Connotazione dell'iperglicemia: sulla base dell'analisi delle misurazioni effettuate con l'autocontrollo, vengono identificate le seguenti condizioni:
  - **iperglicemia prevalentemente a digiuno/pre–prandiale**: quando vi sia una proporzione di valori di iperglicemia >60% del totale delle misurazioni effettuate a digiuno o prima del pasto (ad es.: 3 valori su 5 sono >130 mg/dl)
  - **iperglicemia prevalentemente post–prandiale**: quando vi sia una proporzione di valori di iperglicemia >60% del totale delle misurazioni effettuate dopo 2 ore dai pasti (ad es.: 3 valori su 5 sono >180 mg/dl).

***http://www.aemmedi.it/algoritmi/algoritmi-english.html***

***Ceriello A DIABETES TECHNOLOGY & THERAPEUTICS 2012; 14 : Jan 4 [Epub ahead of print]***

# Glicemia a digiuno e post- prandiale




Connotazione dell'iperglicemia: sulla base dell'analisi delle misurazioni effettuate con l'autocontrollo:

- iperglicemia prevalentemente a digiuno/pre-prandiale: quando vi sia una proporzione di valori di iperglicemia >60% del totale delle misurazioni effettuate a digiuno o prima del pasto (ad es.: 3 valori su 5 sono >130 mg/dl)
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I riquadri cliccabili consentono il passaggio al gradino terapeutico successivo qualora il target di HbA1c non sia stato raggiunto.

Intervallo/durata di trattamento fra i vari gradini terapeutici: 3-6 mesi con soggetto a target; 3 mesi non a target.

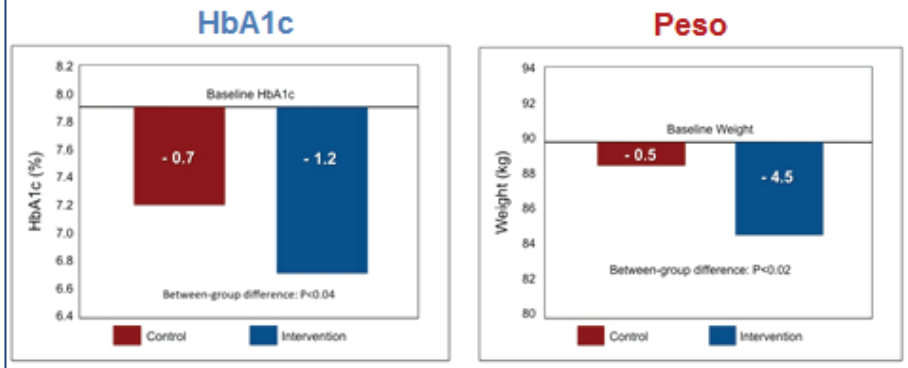
*http://www.aemmedi.it/algoritmi/algoritmi-english.html*

*Ceriello A DIABETES TECHNOLOGY & THERAPEUTICS 2012; 14 : Jan 4 [Epub ahead of print]*

# La valorizzazione dell'autocontrollo glicemico nel diabete tipo 2

## Studio ROSES : riduzione di Hb A1c e peso corporeo

**Risultati a 6 mesi: *(ITT)***

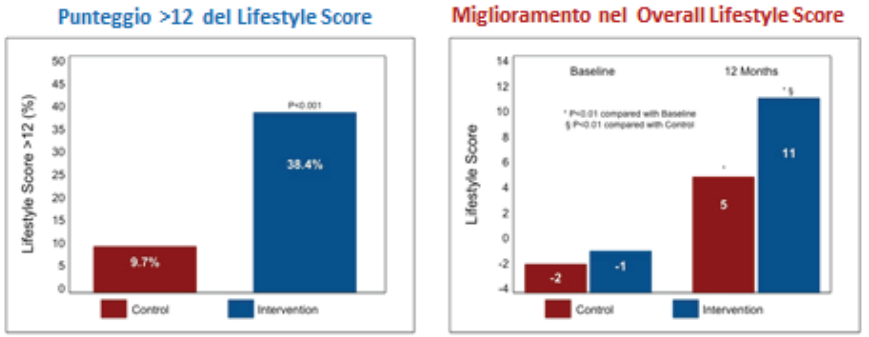



*Franciosi M Diabet. Med. 2011; 28, 789– 796*

marzo 2012 Master Glucoteam 2012 177

## Benefici del SMBG all'esordio del diabete: il St Carlos Study

**Stile di vita: risultati a 12 mesi**




- I provedimenti educativi e le decisioni terapeutiche basati su SMBG strutturato sono efficaci
- Medici e pazienti sono incoraggiati ad ottimizzare gli interventi sullo stile di vita e la terapia

*Duran A, Journal of Diabetes 2010; 2: 203–211*

marzo 2012 Master Glucoteam 2012 180


# L'algoritmo AMD 2012
# Perché un aggiornamento?

# Perché un aggiornamento?

- Variazioni di indicazioni terapeutiche
- Introduzione in commercio di nuovi farmaci
- Nuove linee guida
- Nuove consensus internazionali

*The American Journal of Medicine (2011) 124, S54–S61*

THE AMERICAN JOURNAL of MEDICINE®

# Incretin-Based Therapies in Complex Patients: Practical Implications and Opportunities for Maximizing Clinical Outcomes: A Discussion with Dr. Vivian A. Fonseca

**Vivian A. Fonseca, MD**

original article

*Diabetes, Obesity and Metabolism* 13: 947–954, 2011.


# Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial

V. Lukashevich[1], A. Schweizer[2], Q. Shao[1], P.-H. Groop[3,4] & W. Kothny[1]

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[2] *Novartis Pharma AG, Basel, Switzerland*
[3] *Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland*
[4] *Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki of Helsinki, Finland*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 April 2012
EMA/CHMP/257385/2012
Press Office

**Press release**

## European Medicines Agency recommends authorisation of novel treatment for type 2 diabetes

SGLT2 transporter protein inhibitor improves glycaemic control in adult patients with type 2 diabetes mellitus

**Annals of Internal Medicine** | ORIGINAL RESEARCH

## Long-Term Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Receiving High Doses of Insulin

### A Randomized Trial

John P.H. Wilding, DM; Vincent Woo, MD; Norman G. Soler, MD, PhD; Andrea Pahor, MD; Jennifer Sugg, MS; Katja Rohwedder, MD; and Shamik Parikh, MD, for the Dapagliflozin 006 Study Group*

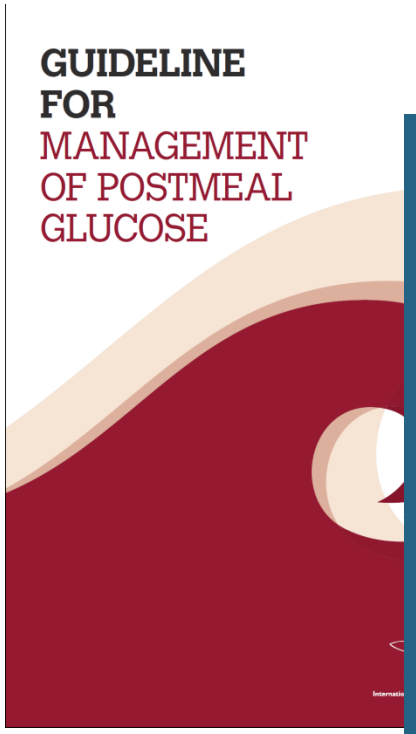
***20 April 2012, EMA/CHMP/257385/2012,Press Office, www.ema.europa.eu***

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

## Effects of Dapagliflozin, a Sodium-Glucose Cotransporter-2 Inhibitor, on Hemoglobin A1c, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy

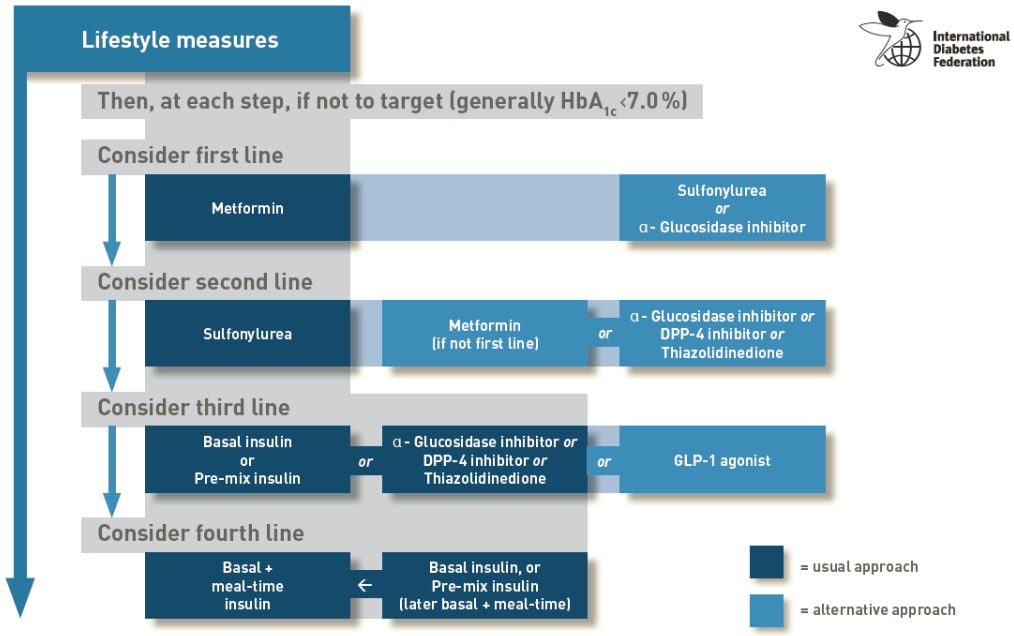
JULIO ROSENSTOCK, MD[1]
MARISA VICO, MD[2]
LI WEI, PHD[3]
AFSHIN SALSALI, MD[4]
JAMES F. LIST, MA, MD, PHD[4]

Diabetes Care Publish Ahead of Print, published online March 23, 2012




**2011 Guideline for Management of PostMeal Glucose in Diabetes**

## IDF Treatment Algorithm for People with Type 2 Diabetes



Diabetologia
DOI 10.1007/s00125-012-2534-0

POSITION STATEMENT

# Management of hyperglycaemia 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)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews

Received: 24 February 2012 / Accepted: 24 February 2012


Reviews/Consensus Reports/ADA Statements
POSITION STATEMENT

# 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)

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**Diabetes Care Publish Ahead of Print, published online April 19, 2012**

# Le novità dell'algoritmo 2012


# Obiettivi glicemici

# Algoritmo 2012 obiettivi glicemici

## Obiettivi glicemici

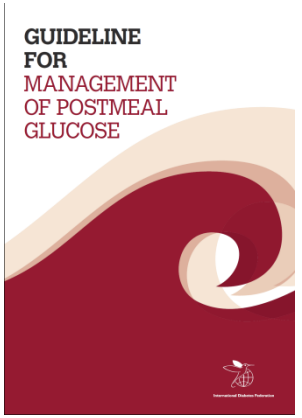
- Glicemia a digiuno e pre-prandiale: 70- 115 mg/dl (3,9-6,4 mmol/l).
- Glicemia post-prandiale: 160 mg/dl (8,9 mmol/l).

## Connotazione dell'iperglicemia

- **Iperglicemia prevalentemente a digiuno:**
  quando vi sia una proporzione di valori di iperglicemia misurati a digiuno in automonitoraggio, >60% sul totale delle misurazioni effettuate(ad es.: 3 su 5 valori sono >115 mg/dl) (6,4 mmol/l).
- **Iperglicemia prevalentemente post-prandiale:**
  quando vi sia una proporzione di valori di glicemia misurati a 1-2 ore dal pasto in automonitoraggio (secondo l'indicazione IDF) >60% sul totale delle misurazioni effettuate (ad es.: 3 su 5 sono >160 mg/dl) (8,9 mmol/l).

***http://www.aemmedi.it/algoritmi_it_2012/***

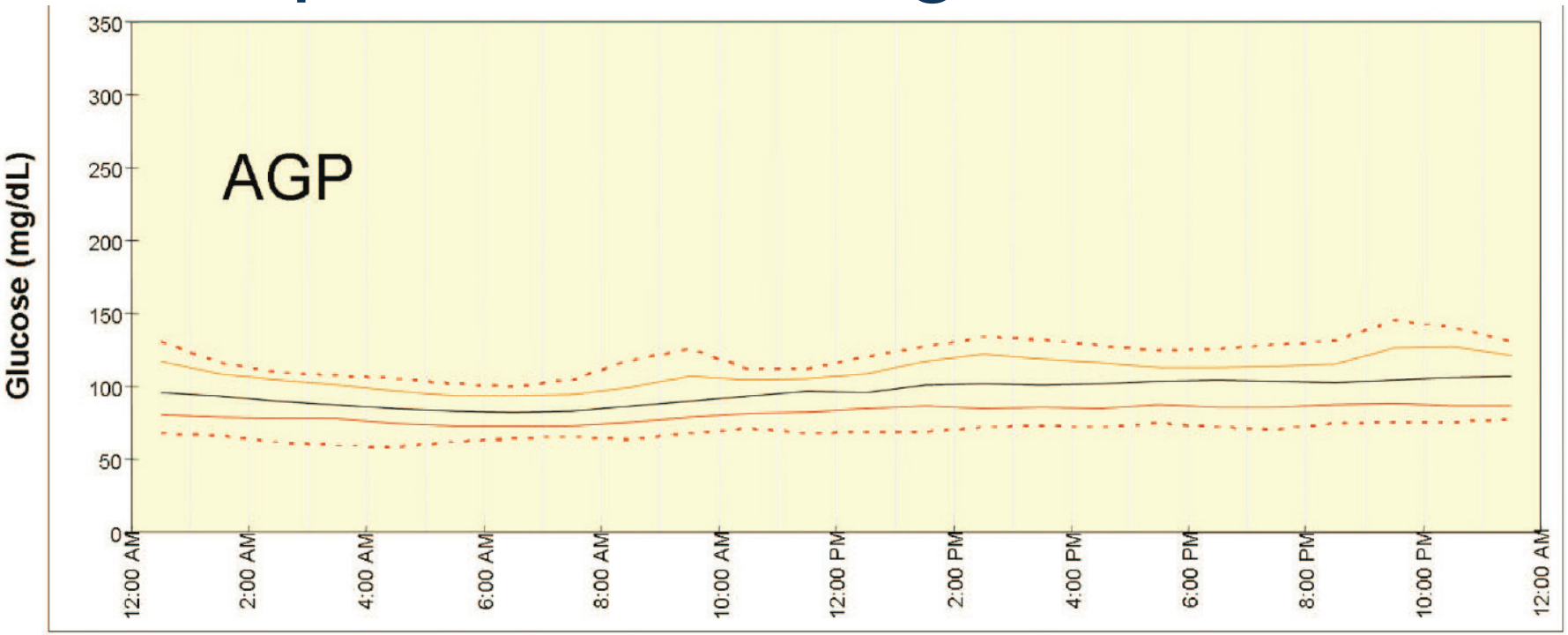
# IDF Guideline 2011




- Postmeal plasma glucose levels
  - seldom rise above 7.8 mmol/l (140 mg/dl) in people with normal glucose tolerance
  - typically return to basal levels two to three hours after food ingestion. [Level 1++]
- For reasons of safety, the IDF sets a glycaemic target slightly above the normal levels and for postmeal glucose this target is 9.0 mmol/l (160 mg/dl).

*http://www.idf.org/2011-guideline-management-postmeal-glucose-diabetes*

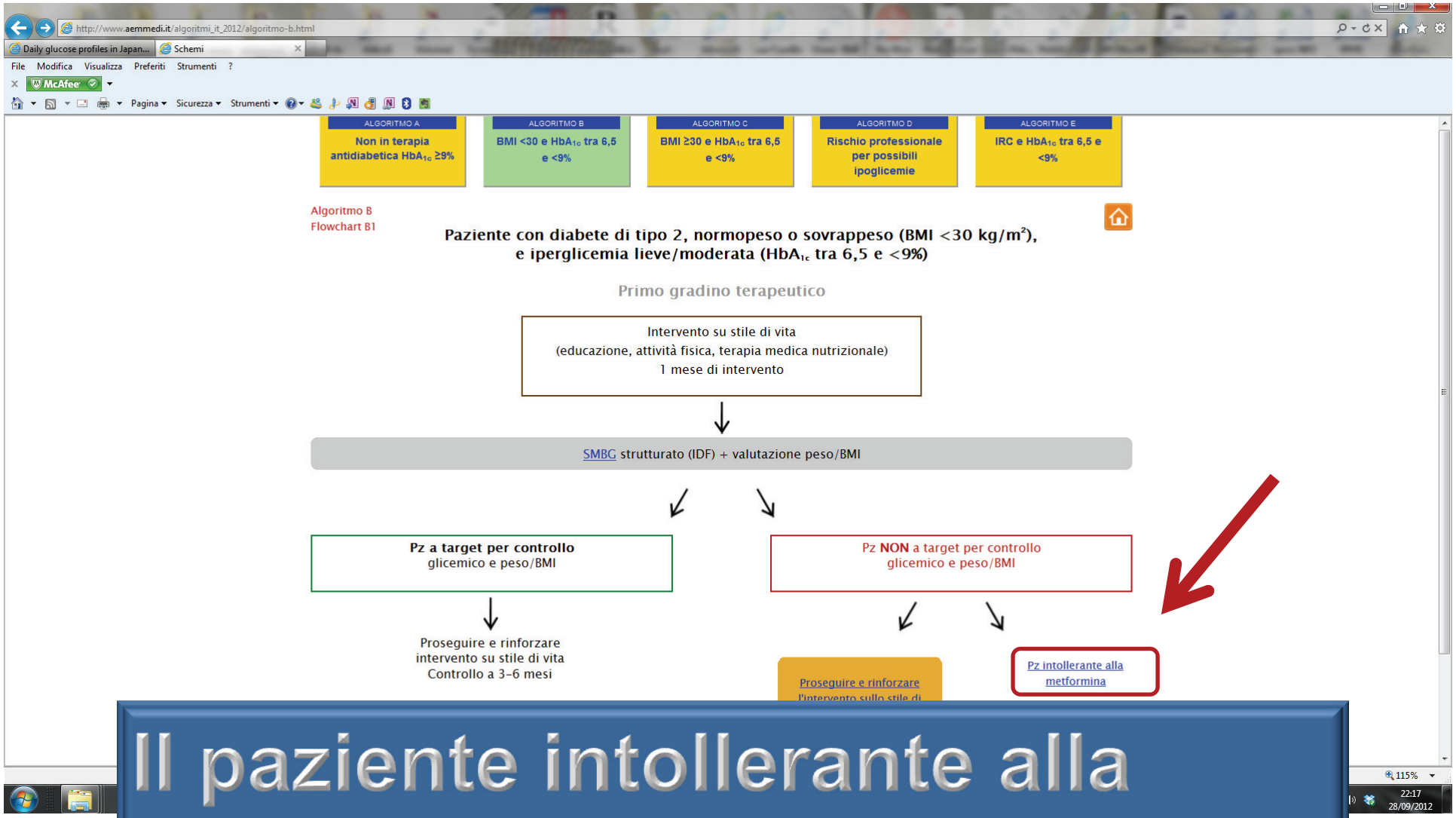
# Profilo glicemico ambulatoriale di pazienti normoglicemici




| N | Targets (mg/dL) | <70 | 70-140 | >140 | MEAN | SD | MAX | MIN | Total AUC | Hourly |
|---|---|---|---|---|---|---|---|---|---|---|
| 3628 | | 11.8% | 84.7% | 3.4% | 95.3 | 22.6 | 189.0 | 30.0 | 2296 mg-24hr/dL | 96 mg-hr/dL |
| | HbA1c | Percentile | 10th | 25th | 50th | 75th | 90th | IQR | Waking | Sleeping |
| | 5.20% | | 68.7 | 81.7 | 95.7 | 109.8 | 121.2 | 28.1 | 107 mg-hr/dL | 83 mg-hr/dL |

All values are expressed in mg/dL except where indicated.

*Mazze RS Diabetes Technol Ther 2008; 10: 149- 59*




# Il paziente intollerante alla metformina

# Metformina: controindicazioni ed intolleranza

## Controindicazioni

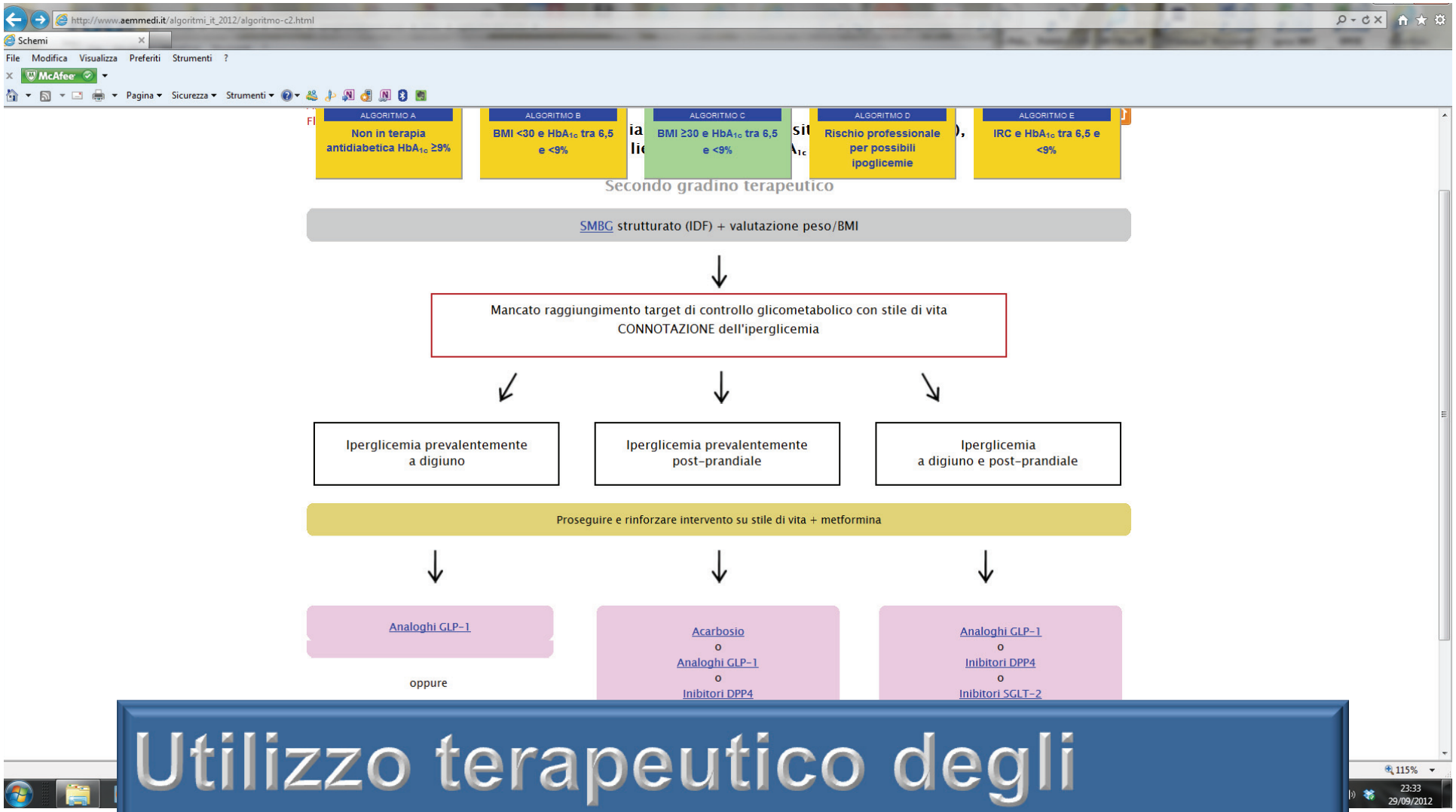
- Ipersensibilità
- Insufficienza renale
- Insufficienza epatica
- Alcoolismo
- Infezioni
- Disidratazione
- Shock

## Effetti collaterali

**Molto comuni: 1/ 10 pazienti**

- Nausea
- Vomito
- Diarrea
- Algie addominali
- Inappetenza

***http://www.medicines.org.uk/emc/medicine/1043***




# Utilizzo terapeutico degli inibitori del SGLT-2

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 April 2012
EMA/CHMP/257385/2012
Press Office

**Press release**

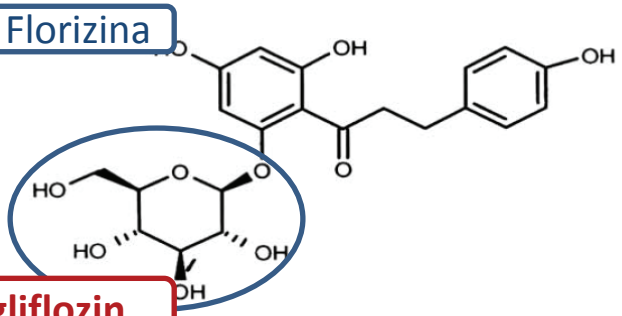
# European Medicines Agency recommends authorisation of novel treatment for type 2 diabetes

SGLT2 transporter protein inhibitor improves glycaemic control in adult patients with type 2 diabetes mellitus

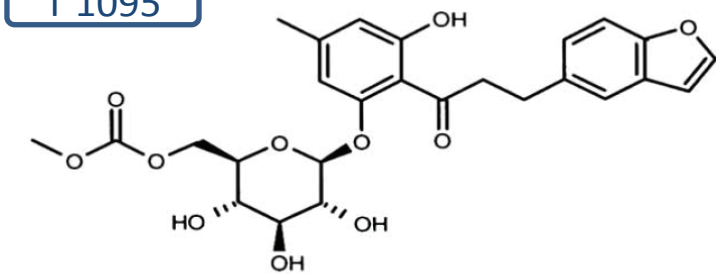
***20 April 2012, EMA/CHMP/257385/2012,Press Office, www.ema.europa.eu***

# Strutture chimiche degli inibitori di SGLT 2

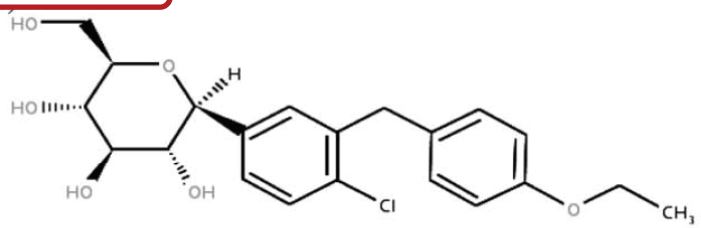
Florizina



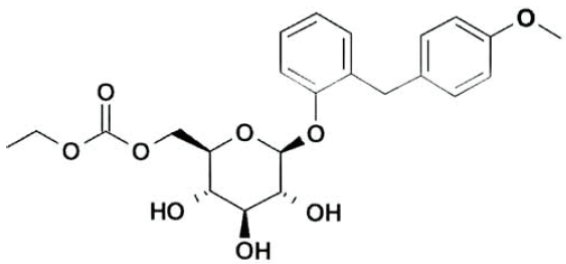
T 1095



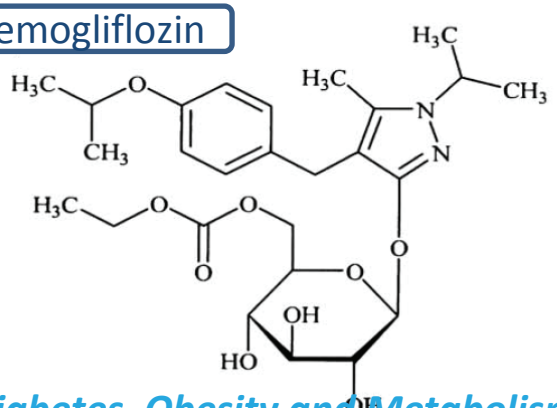
**Dapagliflozin**



Sergliflozin

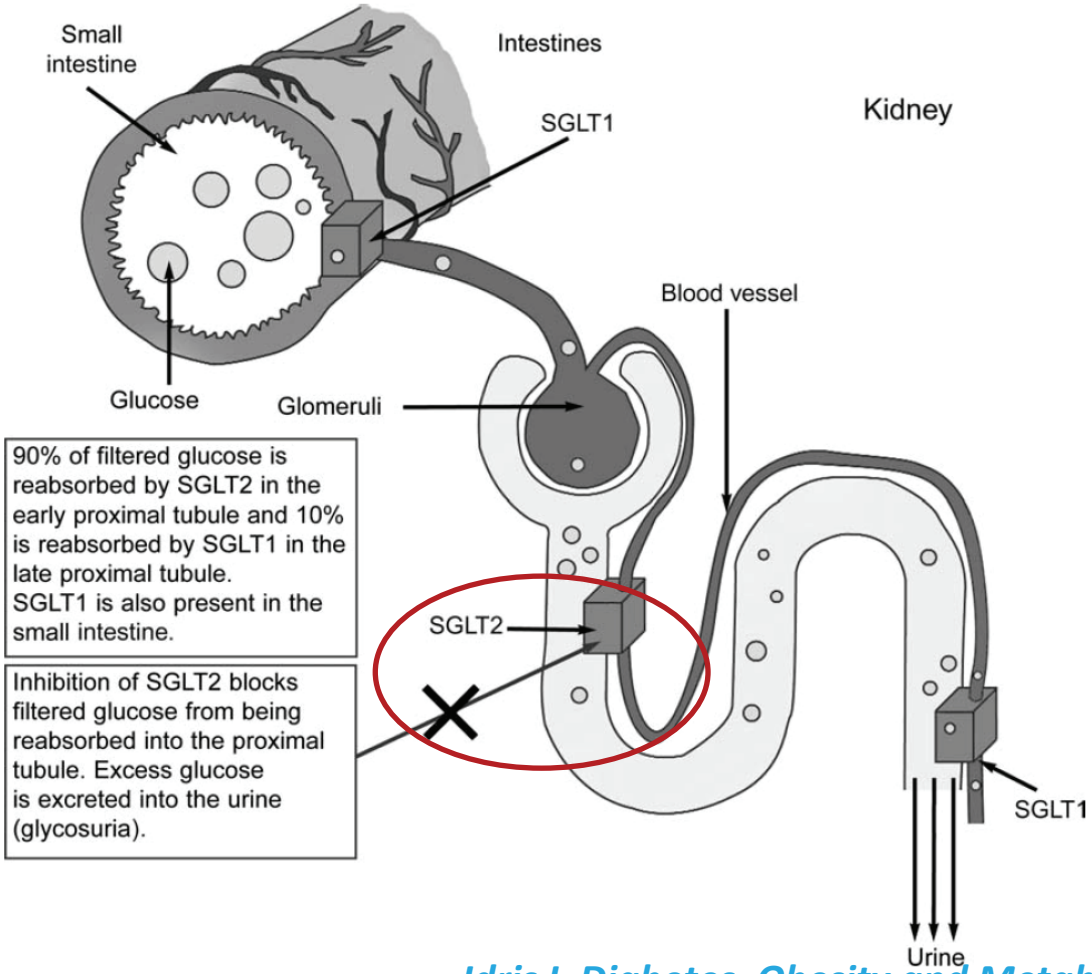


Remogliflozin



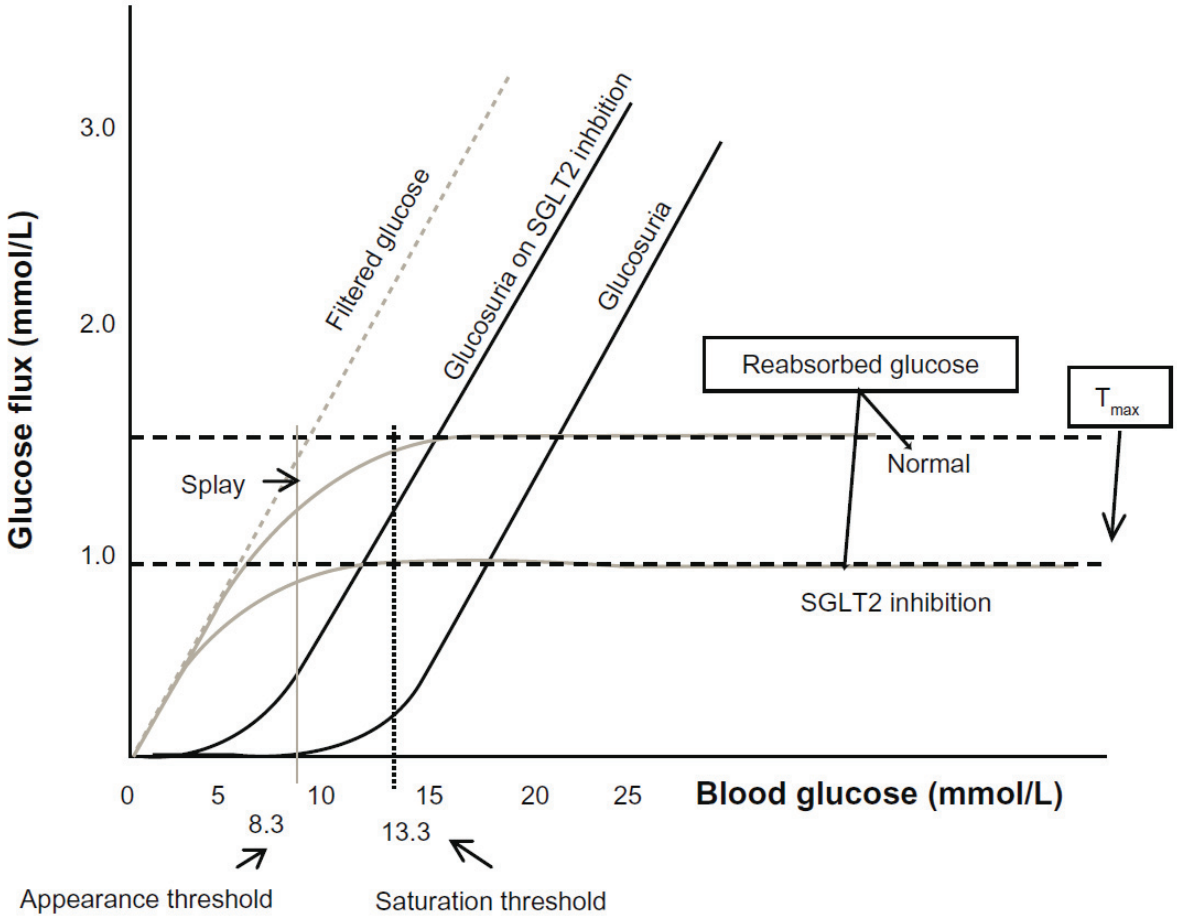
*Idris I, Diabetes, Obesity and Metabolism 2009; 11: 79–88*

# Meccanismo d'azione degli inibitori di SGLT 2 (sodium–glucose co-transporter)




*Idris I, Diabetes, Obesity and Metabolism 2009; 11: 79–88*

# Variazione del flusso urinario di glucosio dopo inibizione di SGLT- 2




*Nair S J Clin Endocrinol Metab. 2010; 95: 34– 42*

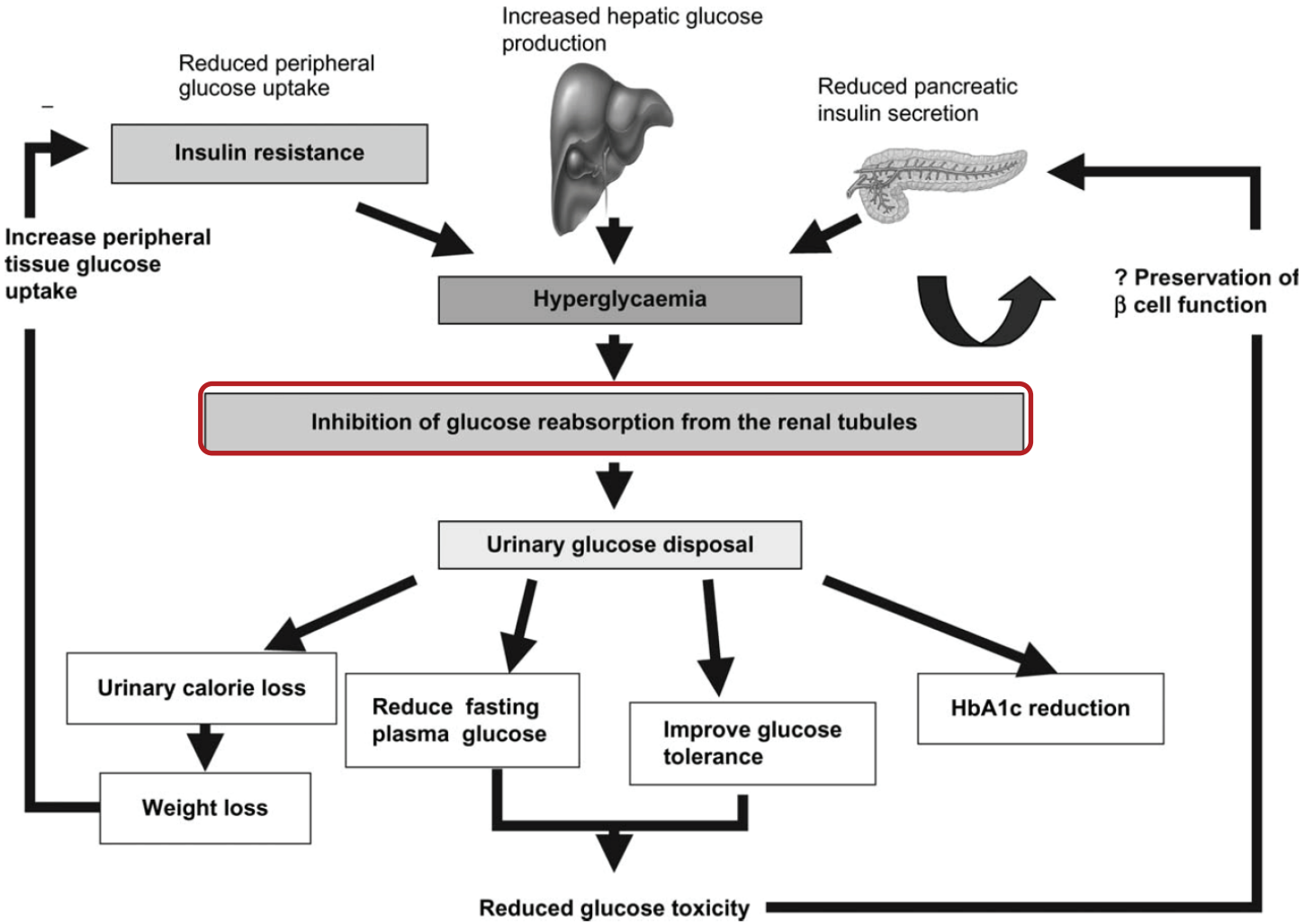
*Kim Y Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2012:5 313–327*

# Razionale per l'utilizzo terapeutico degli inibitori del SGLT- 2

- Nei soggetti diabetici tipo 2 e 1 $Tm_G$ è aumentato del 20- 40%
- Nelle cellule tubulari renali dei diabetici in cultura sono aumentate rispetto ai non diabetici l'espressione di SGLT- 2, la sua concentrazione e la sua capacità di trasporto di glucosio *(difetto intrinseco o adattamento?)*
- Nel ratto pancreatectomizzato al 90% la resistenza periferica ed epatica all'insulina ed il difetto beta cellulare acquisito sono totalmente ripristinati dalla florizina
- La glicosuria cronica non è dannosa: la glicosuria renale familiare è una malattia benigna

***Ferrannini E, Diabetes 2011; 60: 695- 6***

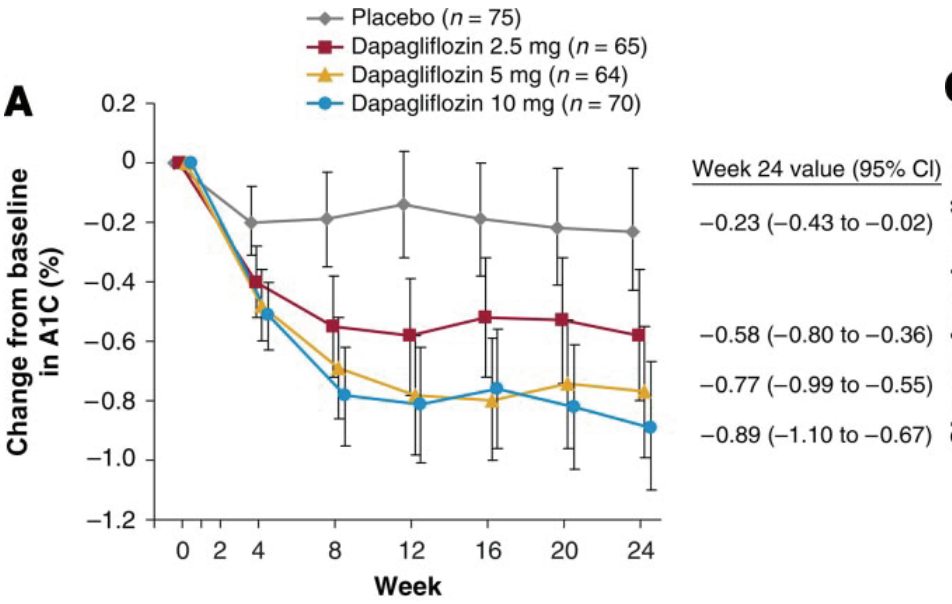
# Rappresentazione schematica degli effetti clinici degli inibitori di SGLT- 2




*Idris I, Diabetes, Obesity and Metabolism 2009; 11: 79–88*

# Efficacia di dapagliflozin in monoterapia

## Hb A1c




**HbA1c dopo 24 settimane:**

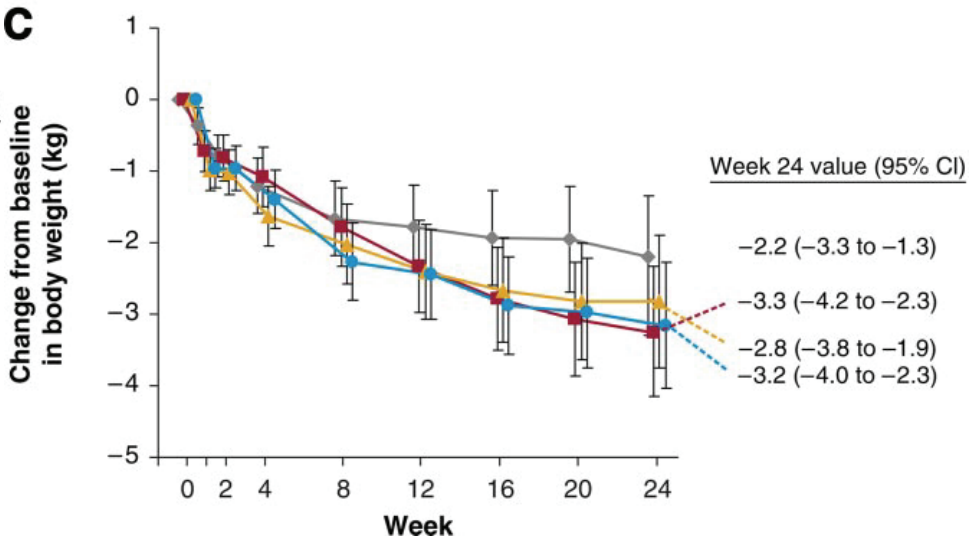
**–0·23% ( –0·43 a –0·02) placebo**

**–0·58% (–0·80 a –0.36, p=0·0005) dapagliflozin 2·5 mg**

**–0·77% (–0·99 a –0·55, p<0·0005) dapagliflozin 5 mg**

**–0·89% (–1·10 a –0·67, p<0·0001)dapagliflozin 10 mg**

## Peso corporeo




**Peso corporeo dopo 24 settimane:**

**–2·2 (–3·3 a –1·3) placebo**

**–3·3 (–4·2 a –2·3) dapagliflozin 2·5 mg**

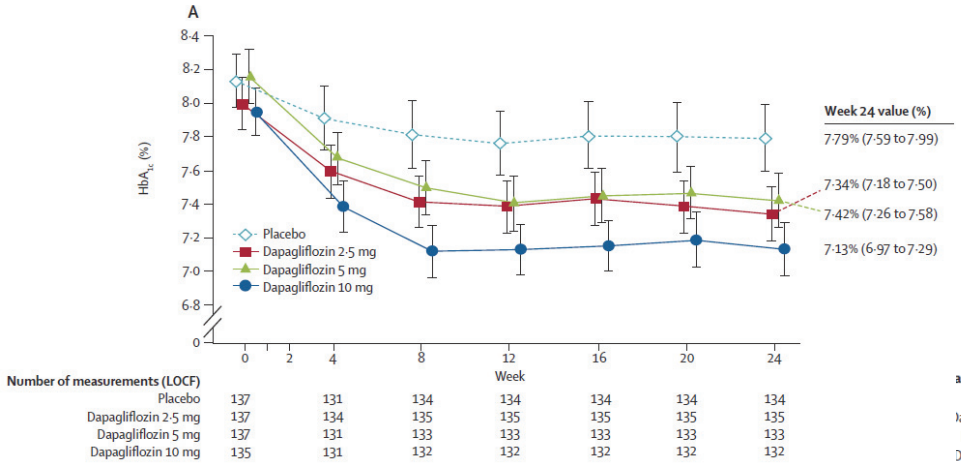
**–2·8 (–3·8 a –1·9) dapagliflozin 5 mg**

**–3·2 (–4·0 a –2·3) dapagliflozin 10 mg**

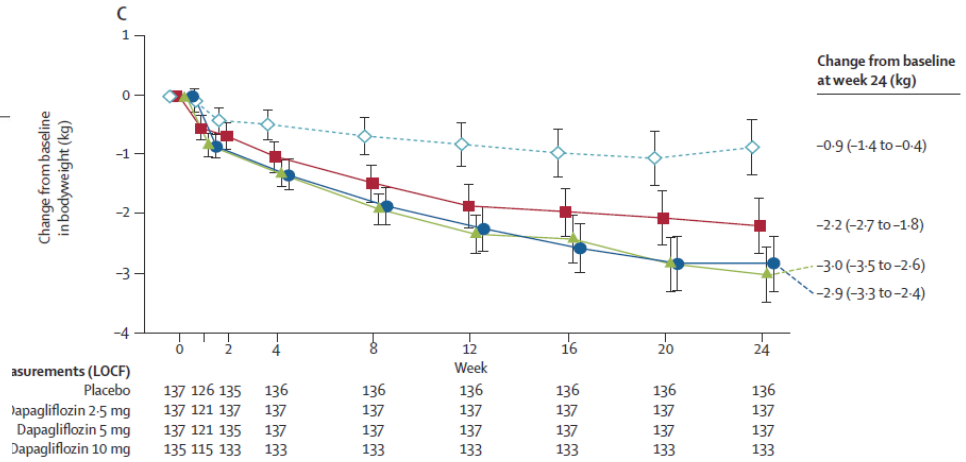
***Ferrannini E Diabetes Care 2010; 33:2217–2224***

# Efficacia di dapagliflozin aggiunto a metformina

## Hb A1c




## Peso corporeo




**HbA1c dopo 24 settimane:**

**–0·30% (–0·44 a –0·16) placebo**
**–0·67% (–0·81 a –0·53, p=0·0002) dapagliflozin 2·5 mg**
**–0·70% (–0·85 a –0·56, p<0·0001) dapagliflozin 5 mg**
**–0·84% (–0·98 a –0·70, p<0·0001) dapagliflozin 10 mg**

**Peso corporeo dopo 24 settimane:**

**–0·9 (–1·4 a –0·4) placebo**
**–2·2 (–2·7 a –1·8) dapagliflozin 2·5 mg**
**–3·0 (–3·5 a –2·6) dapagliflozin 5 mg**
**–2·9 (–3·3 a –2·4) dapagliflozin 10 mg**

***Bailey C, Lancet 2010; 375: 2223–33***

# Prove sul possibile impatto clinico del dapagliflozin

| Misure di outcome | Prove | Implicazioni |
|---|---|---|
| Orientate alla malattia | **Riduzione** di:<br>Hb a1c<br>glicemia a digiuno<br>glicemia post prandiale<br>Studi di **associazione** con farmaci diversi<br>**Meccanismo nuovo** | **Perdita di peso** senza ipoglicemia ( sicurezza)<br><br>Più accettabile di terapie parenterali<br><br>?? |
| Orientate al paziente | Mancano studi a lungo termine<br><br>Possibili eventi avversi ( ca vescica, mammella) discussi (FDA vs. EMA) | Non chiare al momento.<br><br>Infezioni fungine genitali<br>Infezioni delle vie urinarie ( possibile limite all'uso) |
| Implicazioni economiche | Non disponibili | Sconosciute al momento |

*Chao EC Core Evidence 2012; 7: 21–28*


# Algoritmi terapeutici nell'insufficienza renale cronica

# I problemi

- Dati  insufficienti o discordanti in letteratura sull'uso dei farmaci in IRC
- Classificazione disomogenea dell'IRC nelle schede tecniche dei farmaci
- Differenti indicazioni in schede tecniche nazionali ed internazionali
- Aggiornamento delle schede tecniche alla letteratura più recente talora carente
- Opinioni e indicazioni discordanti in linee guida e consensus

# Metformina

- Secondo la scheda tecnica italiana il farmaco non deve essere utilizzato in presenza di insufficienza renale con livelli di creatinina sierica
  - >1,53 mg/dl negli uomini
  - >1,25 mg/dl nelle donne
- Le attuali linee-guida del National Institute for Health and Clinical Excellence (NICE) raccomandano :
  - rivedere il dosaggio della metformina qualora il tasso stimato di filtrazione glomerulare (eGFR) sia <45 ml/min/1,73 $m^2$,
  - di interromperla nei pazienti in cui l'eGFR risulti <30 ml/min/1,73 $m^2$.

***http://www.aemmedi.it/algoritmi_it_2012/algoritmo-e.html***

# HR per malattie cv acidosi/ infezioni gravi, mortalità per ogni causa in pazienti con diversi gradi di IRC

| | 30≤ eGFR <45 | | | 45≤ eGFR <60 | | | eGFR ≥60 | | | All patients | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N (% of total) | Events (% of total) | HR (95 % CI) | N (% of total) | Events (% of total) | HR (95 % CI) | N (% of total) | Events (% of total) | HR (95 % CI) | N | Events |
| Any CVD | | | | | | | | | | | |
| Metformin | 670 (35.4) | 210 (30.7) | 1.00 (0.83 to 1.19) | 3839 (57.7) | 849 (51.2) | 0.94 (0.84 to 1.05) | 27 083 (67.3) | 3698 (63.4) | 0.98 (0.92 to 1.05) | 31 628 | 4774 |
| Insulin | 1180 (62.3) | 474 (69.2) | 1.30 (1.02 to 1.64)* | 3201 (48.1) | 930 (56.1) | 1.24 (1.09 to 1.42)** | 16 718 (41.5) | 2853 (48.9) | 1.19 (1.11 to 1.27)*** | 21 503 | 4476 |
| Other OHA | 702 (37.1) | 241 (35.2) | 1.03 (0.85 to 1.26) | 2450 (36.8) | 608 (36.7) | 1.05 (0.93 to 1.18) | 13 552 (33.7) | 2065 (35.4) | 1.03 (0.97 to 1.09) | 16 817 | 2965 |
| Total in group | 1894 | 685 | | 6655 | 1657 | | 40 239 | 5829 | | | |
| Any acidosis/serious infection | | | | | | | | | | | |
| Metformin | 692 (33.9) | 143 (28.4) | 0.98 (0.79 to 1.21) | 4000 (57.5) | 557 (49.4) | 0.85 (0.74 to 0.97)* | 27 618 (67.3) | 2444 (60.6) | 0.91 (0.84 to 0.98)* | 32 345 | 3155 |
| Insulin | 1302 (63.7) | 366 (72.6) | 1.34 (1.02 to 1.76)* | 3406 (48.9) | 652 (57.9) | 1.07 (0.91 to 1.26) | 17 152 (41.8) | 2057 (51) | 1.22 (1.12 to 1.32)*** | 22 310 | 3260 |
| Other OHA | 738 (36.1) | 166 (32.9) | † | 2555 (36.7) | 379 (33.6) | 0.87 (0.75 to 1.00) | 13 852 (33.7) | 1375 (34.1) | 1.02 (0.95 to 1.09) | 17 265 | 1960 |
| Total in group | 2044 | 504 | | 6960 | 1127 | | 41 048 | 4034 | | | |
| All-cause mortality | | | | | | | | | | | |
| Metformin | 715 (33.3) | 179 (27) | 1.02 (0.84 to 1.24) | 4079 (56.8) | 558 (46.5) | 0.87 (0.77 to 0.99)* | 28 015 (67.1) | 2120 (56.9) | 0.87 (0.81 to 0.94)*** | 32 848 | 2873 |
| Insulin | 1386 (64.6) | 468 (70.5) | 1.16 (0.91 to 1.47) | 3550 (49.5) | 701 (58.4) | 1.12 (0.95 to 1.31) | 17 565 (42.1) | 1921 (51.5) | 1.29 (1.19 to 1.41)*** | 23 000 | 3328 |
| Other OHA | 766 (35.7) | 222 (33.4) | 0.97 (0.79 to 1.19) | 2626 (36.6) | 429 (35.7) | 0.97 (0.84 to 1.11) | 14 049 (33.6) | 1375 (36.9) | 1.10 (1.02 to 1.19)* | 17 578 | 2087 |
| Total in group | 2146 | 664 | | 7177 | 1201 | | 41 756 | 3729 | | | |

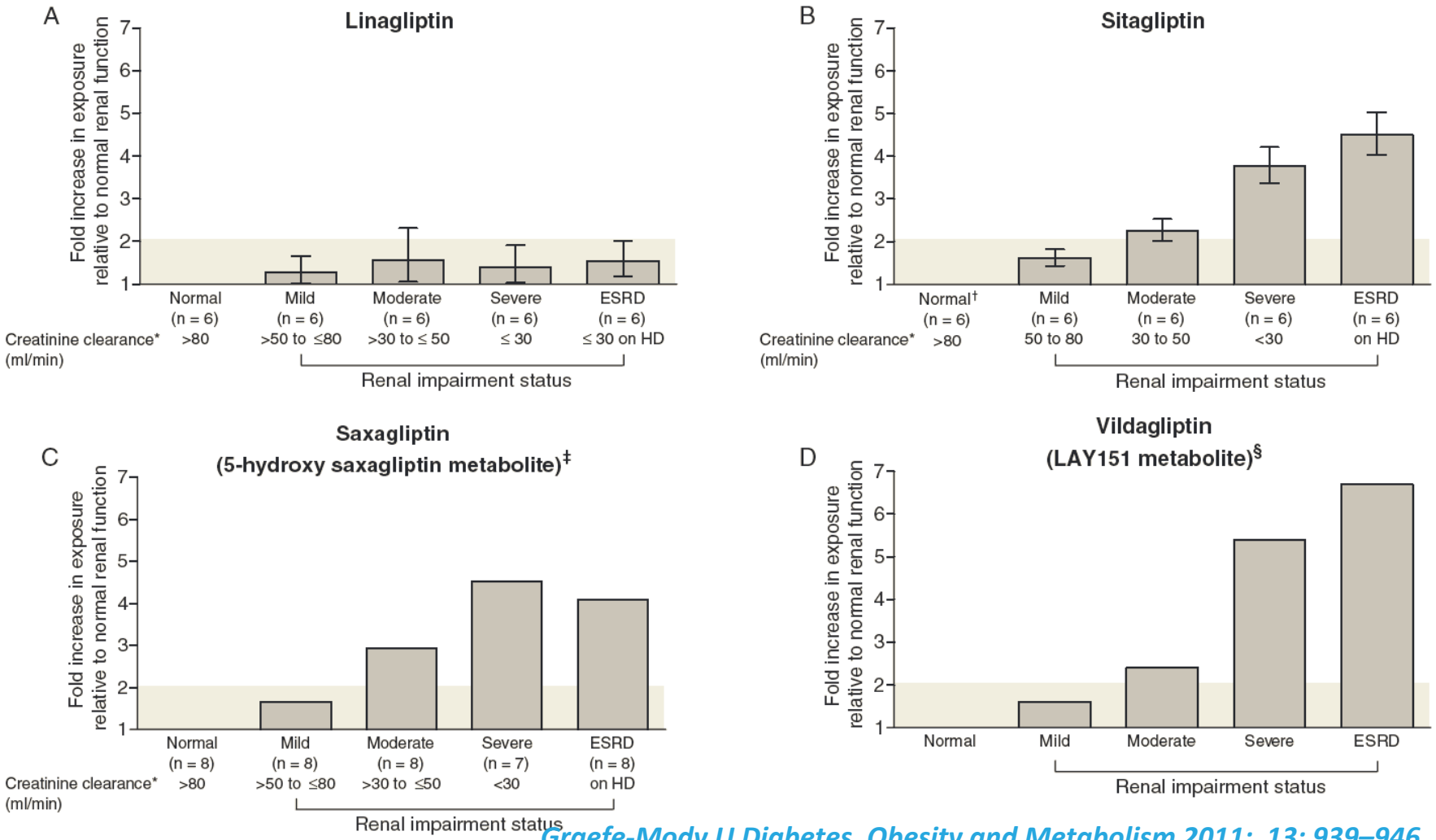
*Ekström N, BMJ Open 2012;2:e001076*

# Indicazioni recenti

- Pharmacokinetic studies of metformin suggest that metformin doses should be reduced by one third in patients with eGFRs of <45 mL/min/1.73 m2.
- Metformin is likely to be tolerated at eGFRs of <30 mL/min/1.73 m2, particularly in patients with stable chronic kidney disease with no other significant liver or respiratory failure.
- However, more detailed pharmacokinetic investigation of metformin elimination in renal patients is required before current dosing guidelines can be modified.
- Furthermore, plasma concentrations are not available in routine clinical practice

*Rocha A, J Nephrol. 2012: 0. doi: 10.5301/jn.5000166. [Epub ahead of print]*

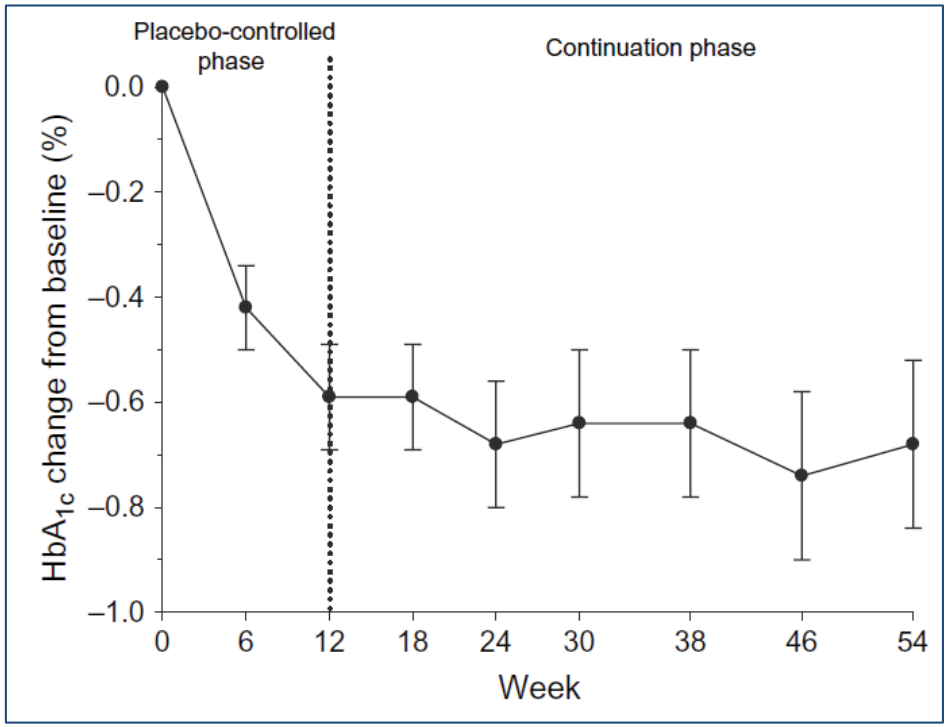
# Studi sulla farmacocinetica delle gliptine in diversi gradi di insufficienza renale




*Graefe-Mody U Diabetes, Obesity and Metabolism 2011; 13: 939–946*

# Tollerabilità ed efficacia del sitagliptin nell'IRC

## Efficacia

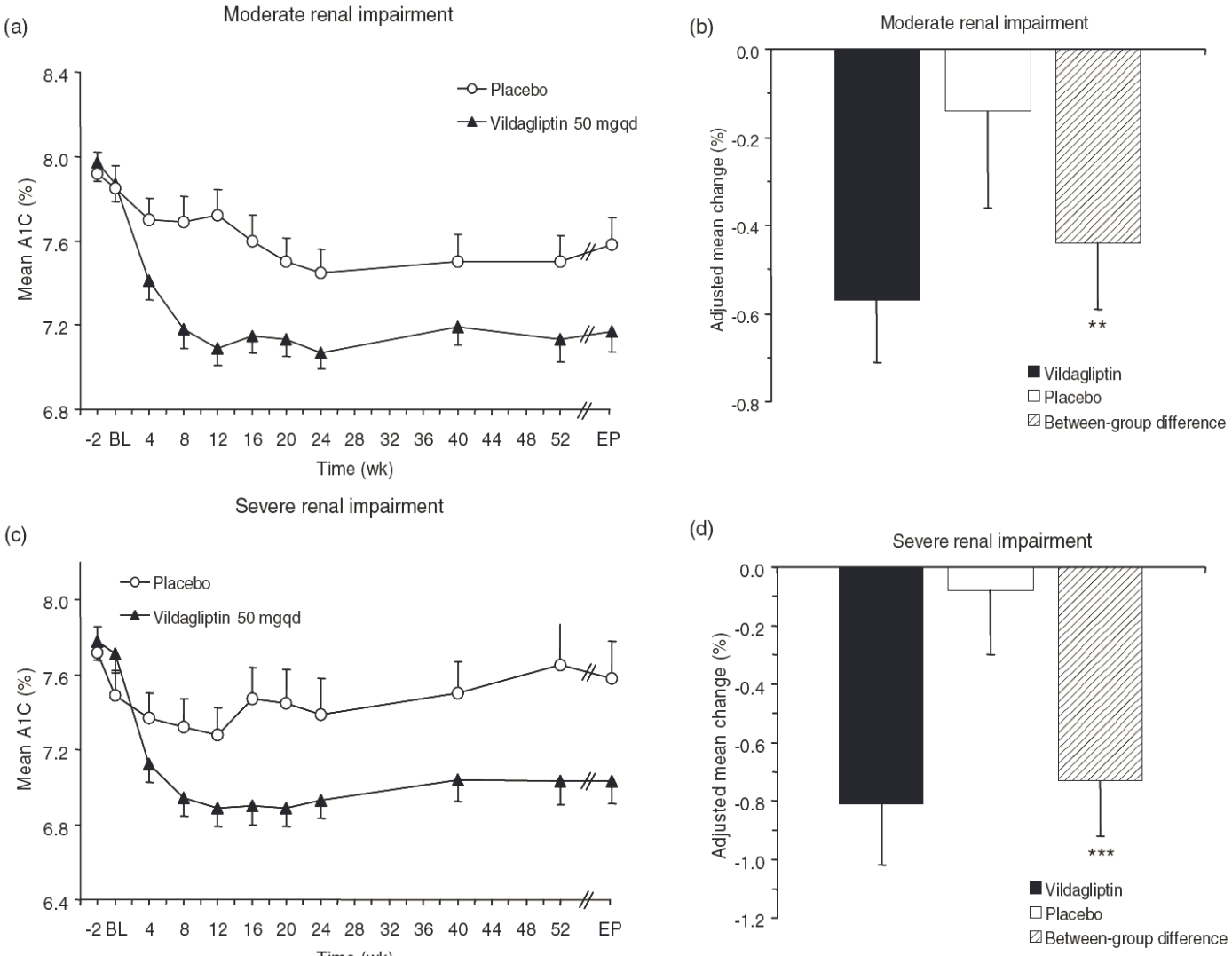



## Eventi avversi

| | Sitagliptin (n = 65), n (%) | Placebo/glipizide* (n = 26), n (%) |
|---|---|---|
| One or more clinical adverse experiences (AEs) | 52 (80.0) | 22 (84.6) |
| Drug-related clinical AEs† | 8 (12.3) | 5 (19.2) |
| Serious clinical AEs | 20 (30.8) | 10 (38.5) |
| Drug-related serious clinical AEs† | 1 (1.5) | 0 |
| Died, n (%) | 5 (7.7) | 1 (3.8) |
| Discontinuations | | |
| Because of clinical AEs | 4 (6.2) | 2 (7.7) |
| Because of drug-related clinical AEs | 1 (1.5) | 0 |
| Because of serious clinical AEs | 4 (6.2) | 2 (7.7) |
| Because of drug-related serious clinical AEs | 1 (1.5) | 0 |

*Chan JCN Diabetes, Obesity and Metabolism 2008; 10: 545–555*

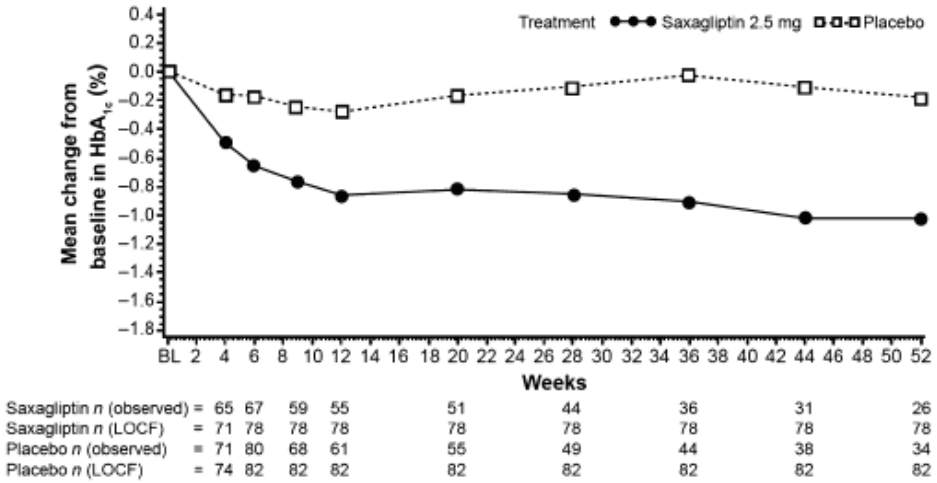
# Tollerabilità ed efficacia del vildagliptin nell'IRC




*Kothny W Diabetes Obes Metab. 2012 Jun 12. doi: 10.1111/j.1463-1326.2012.01634.x. [Epub ahead of print]*

# Tollerabilità ed efficacia del saxagliptin nell'insufficienza renale cronica

## Efficacia

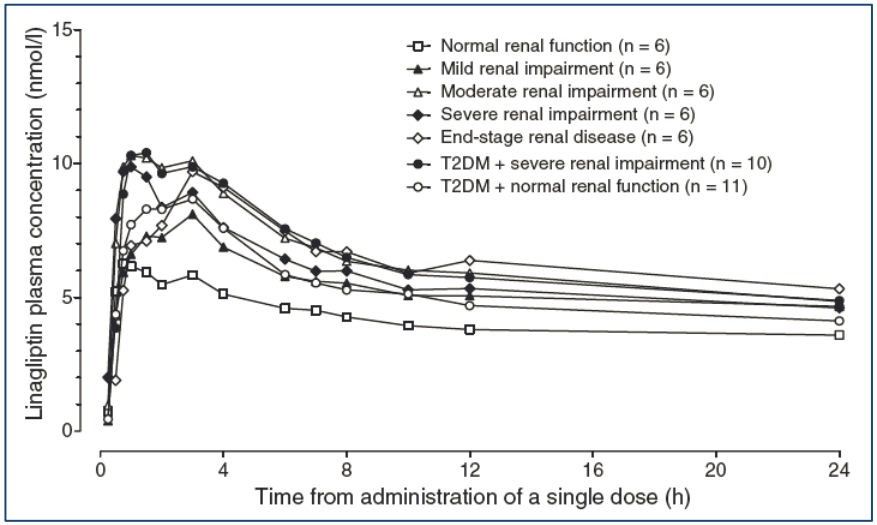


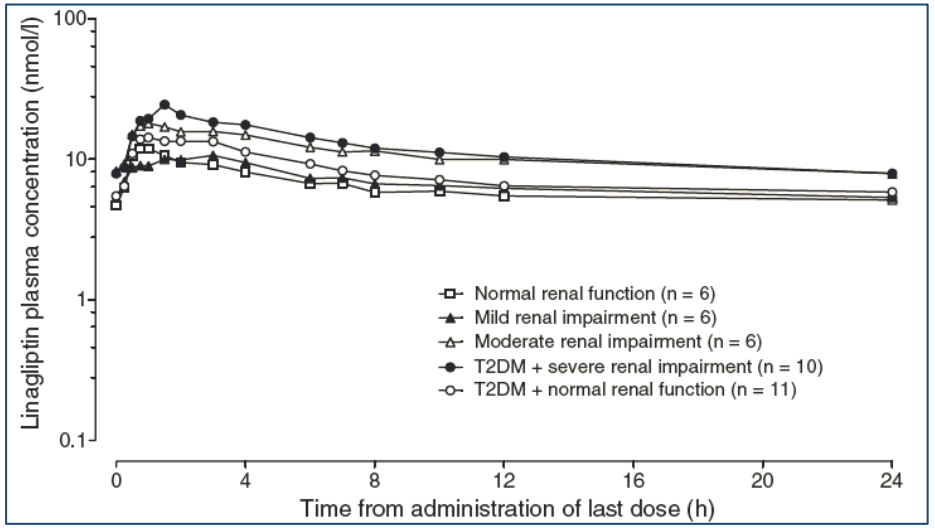

## Eventi avversi

| | | |
|---|---|---|
| **AEs*** | | |
| Patients reporting ≥ 1 AE | 64 (75.3) | 60 (70.6) |
| Patients reporting ≥ 1 serious AE | 23 (27.1) | 24 (28.2) |
| Discontinuation of study medication owing to AE | 10 (11.8) | 7 (8.2) |
| Discontinuation of study medication owing to serious AE | 6 (7.1) | 6 (7.1) |
| Death | 3 (3.5) | 4 (4.7) |
| **Most common AEs (≥ 5% in either treatment group)†** | | |
| Urinary tract infection | 6 (7.1) | 3 (3.5) |
| Anaemia | 5 (5.9) | 7 (8.2) |
| Hypertension | 5 (5.9) | 5 (5.9) |
| Dyspnoea | 5 (5.9) | 0 |
| Peripheral oedema | 3 (3.5) | 6 (7.1) |
| **Reported hypoglycaemic event‡** | 24 (28.2) | 25 (29.4) |
| Moderate baseline renal impairment | 14/48 (29.2) | 16/42 (38.1) |
| Severe baseline renal impairment | 6/18 (33.3) | 4/23 (17.4) |
| ESRD at baseline | 4/19 (21.1) | 5/20 (25.0) |
| **Confirmed hypoglycaemic event‡** | 8 (9.4) | 4 (4.7) |
| Moderate baseline renal impairment | 5/48 (10.4) | 3/42 (7.1) |
| Severe baseline renal impairment | 1/18 (5.6) | 0/23 |
| ESRD at baseline | 2/19 (10.5) | 1/20 (5.0) |

*Nowicki M, Int J Clin Pract, 2011; 65: 1230–1239*

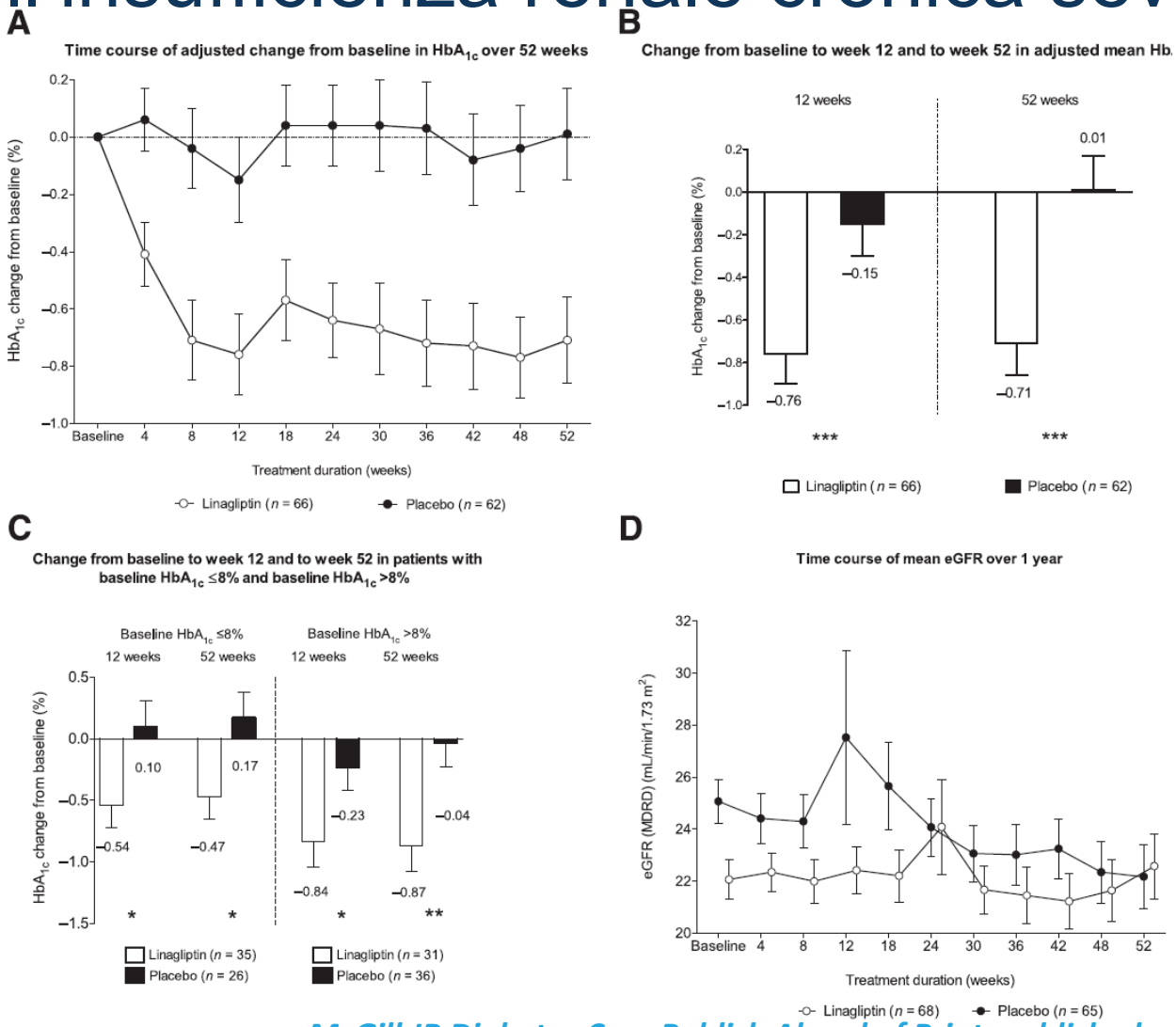
# Effetto dell'insufficienza renale sulla farmacocinetica del linagliptin



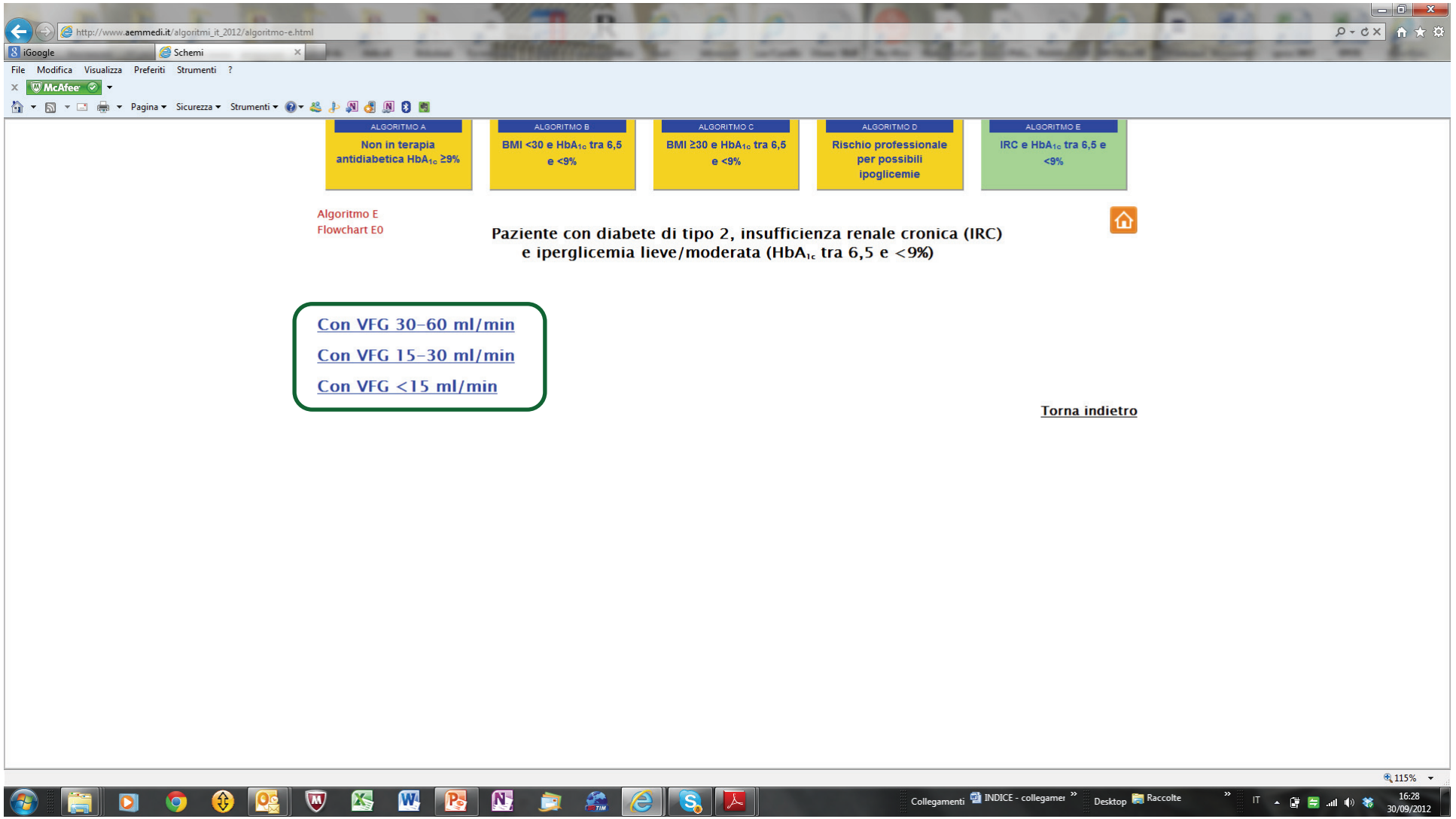




***Graefe-Mody U Diabetes, Obesity and Metabolism 2011; 13: 939–946***

# Tollerabilità ed efficacia del linagliptin nell'insufficienza renale cronica severa




*McGill JB Diabetes Care Publish Ahead of Print, published online October 1, 2012*

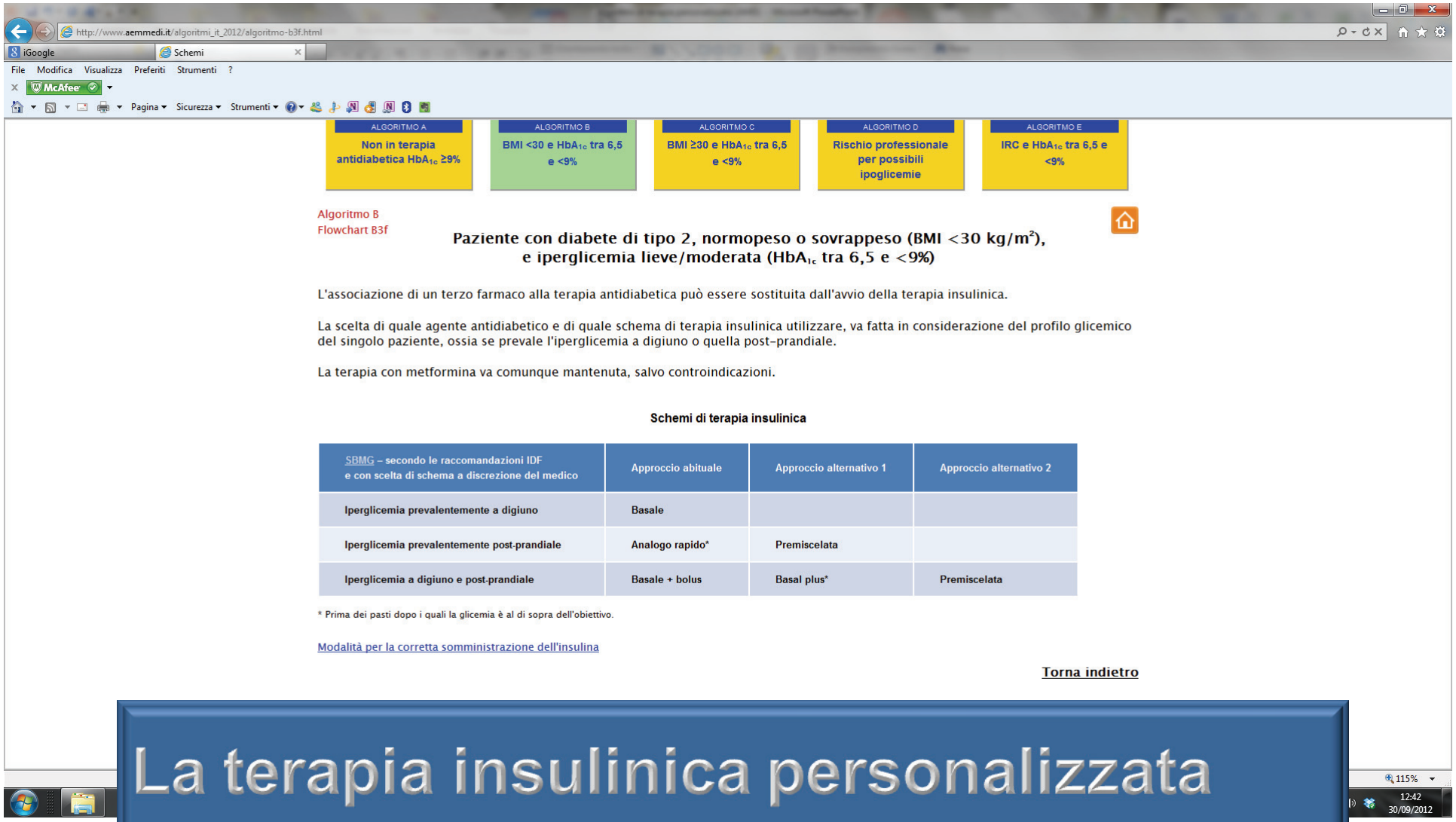

http://www.aemmedi.it/algoritmi_it_2012/algoritmo-e.html
iGoogle
Schemi
File Modifica Visualizza Preferiti Strumenti ?
McAfee
Pagina Sicurezza Strumenti
ALGORITMO A
Non in terapia antidiabetica HbA1c ≥9%
ALGORITMO B
BMI <30 e HbA1c tra 6,5 e <9%
ALGORITMO C
BMI ≥30 e HbA1c tra 6,5 e <9%
ALGORITMO D
Rischio professionale per possibili ipoglicemie
ALGORITMO E
IRC e HbA1c tra 6,5 e <9%
Algoritmo E
Flowchart E0
Paziente con diabete di tipo 2, insufficienza renale cronica (IRC) e iperglicemia lieve/moderata (HbA1c tra 6,5 e <9%)
Con VFG 30–60 ml/min
Con VFG 15–30 ml/min
Con VFG <15 ml/min
Torna indietro
115%
Collegamenti
INDICE - collegamer
Desktop
Raccolte
IT
16:28
30/09/2012

# Tabella sinottica per l'uso della terapia antidiabetica non insulinica nell'insufficienza renale

| Farmaco | IR lieve (VFG 60-89 ml/ min) | IR moderata (VFG 30-59 ml/min) | IR grave (VFG 15-29 ml/min) | Dialisi o VFG < 15 ml/ min |
|---|---|---|---|---|
| **Metformina** | Dose normale | Dose ridotta, monitoraggio | no | no |
| **Glibenclamide** | Dose ridotta, monitoraggio | Dose ridotta ,monitoraggio | no | no |
| **Gliclazide** | Dose normale | Dose ridotta , monitoraggio | no | no |
| **Repaglinide** | Dose normale | Attenzione alla titolazione | no | no |
| **Pioglitazone*** | Dose normale | Dose normale | Dose normale | no |
| **Acarbose** | Dose normale | Dose normale | no | no |
| **Sitagliptin** | Dose normale | 50 mg uid | 25 mg uid | 25 mg uid |
| **Vildagliptin** | Dose normale | 50 mg uid | 50 mg uid | no |
| **Saxagliptin** | Dose normale | 2.5 mg uid | 2.5 mg uid | no |
| **Linagliptin**** | Dose normale | Dose normale | Dose normale | Dose normale |
| **Exenatide** | Dose normale | 5 µg (10 µg con cautela) | no | no |
| **Liraglutide** | Dose normale | No (scarsa esperienza) | No (nessuna esperienza) | no |
| **Insulina** | Dose normale | Possibile riduzione fabbisogno | Possibile riduzione fabbisogno | Possibile riduzione fabbisogno |

* Può causare ritenzione idrica che può esacerbare o precipitare una insufficienza cardiaca.
** Al momento non disponibile in Italia.

***http://www.aemmedi.it/algoritmi_it_2012/algoritmo-e.html***




# La terapia insulinica personalizzata nella secondary failure

# Schemi di terapia insulinica

- **La scelta di quale agente antidiabetico e di quale schema di terapia insulinica utilizzare, va fatta in considerazione del profilo glicemico del singolo paziente, ossia se prevale l'iperglicemia a digiuno o quella post-prandiale.**

| SBMG | Approccio abituale | Approccio alternativo 1 | Approccio alternativo 2 |
|---|---|---|---|
| Iperglicemia prevalentemente a digiuno | Basale | | |
| Iperglicemia prevalentemente post-prandiale | Analogo rapido* | Premiscelata | |
| Iperglicemia a digiuno e post-prandiale | Basale + bolus | Basal plus* | Premiscelata |

* Prima dei pasti dopo i quali la glicemia è al di sopra dell'obiettivo.



http://www.aemmedi.it/algoritmi_it_2012/

# Indicazioni di linee guida e consensus

| Guidelines | Recommendations | | | |
|---|---|---|---|---|
| | Glycaemic target | Analogues vs human | Insulin initiation | Insulin intensification |
| ADA/EASD (52) | <7.0% (but with consideration to patient factors including life expectancy, risk of hypoglycaemia, and the presence of CVD) | No clear preference stated | Intermediate- or long-acting basal insulin | Sequential addition of rapid-acting insulin at mealtimes |
| IDF (53) | <6.5% | Insulin analogues preferred due to lower risk of hypoglycaemia | Long-acting or NPH insulin, or twice-daily premix insulin (biphasic insulin) particularly with higher HbA1c | Multiple daily injections (meal-time and basal insulin) where blood glucose control is sub-optimal on other regimens, or meal-time flexibility is desired |
| AACE (54) | <6.5% (but allowances for individualisation of therapy according to comorbidity, duration of diabetes, history of hypoglycaemia, hypoglycaemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications) | Insulin analogues recommended in all instances due to lower risk of hypoglycaemia | Basal, premix, or basal bolus | No clear recommendation |
| NICE (56, 57) | <7.5% | Human insulin unless patient experiences significant hypoglycaemia, is unable to use the device needed to inject NPH insulin or requires 3rd party assistance and use of analogue insulin would reduce number of injections | Intermediate acting insulin (NPH) with consideration of premix once- or twice-daily if HbA1c ≥9.0% | From basal to twice-daily premix or basal-bolus regimen; or from twice daily premix to basal-bolus regimen |
| CDA (55) | ≤7.0% with scope to tailor targets according to patient factors (e.g. patient's age, prognosis, level of glycaemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycaemia). ≤6.5% may be considered in some patients to further decrease risk of nephropathy | No clear preference stated | Intermediate or long-acting basal insulin | Intensive insulin therapy (basal-bolus) |

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; IDF, International Diabetes Federation; AACE, American Association of Clinical Endocrinologists; NICE, National Institute of Clinical Excellence; CDA, Canadian Diabetes Association; NPH, neutral protamine Hagedorn.

*Vaag A European Journal of Endocrinology 2012; 166: 159– 170*

# Gli Standard di cura


**Quando si avvia la terapia insulinica:**

- Utilizzare un'insulina basale come detemir, glargine, umana NPH o lispro protamina

*oppure*

- Utilizzare un analogo rapido ai pasti

*oppure*

- Utilizzare direttamente uno schema basal-bolus

*oppure*

- In presenza di gravi ed evidenti problemi di compliance, utilizzare una doppia somministrazione di insulina premiscelata (bifasica), tentando comunque di educare il paziente verso uno schema basal-bolus.

***AMD, SID Standard italiani per la cura del diabete mellito 2009-2010***
***http://www.infodiabetes.it/standard_di_cura/2010_linee_guida.pdf; http://www.siditalia.it/documenti/2010_linee_guida.pdf***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Joanne F. Keenan, B.A., Sanjoy Paul, Ph.D., and Jonathan C. Levy, M.D., F.R.C.P., for the 4-T Study Group*

Holman RR N Engl J Med 2007; 357: 1716-1730
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Jonathan C. Levy, M.D., F.R.C.P., Julie L. Darbyshire, M.A., M.Sc., Joanne F. Keenan, B.A., and Sanjoy K. Paul, Ph.D., for the 4-T Study Group*

Holman RR N Engl J Med 2009;361:1736-47.

# Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial

*Reinhard G Bretzel*, Ulrike Nuber, Wolfgang Landgraf, David R Owens, Clare Bradley, Thomas Linn**

## Dose titration algorithm and monitoring

**Insulin glargine**

*Titration monitoring*

Starting dose: 10 U per day. Direct investigator contact. Additional calls to adjust insulin

*Insulin dose titration algorithm*

Starting dose: 10 U per day. If self-monitored fasting blood glucose for 2 consecutive days with no severe hypoglycaemia is:

- >8·9 mmol/L: add 8 U per day
- >7·8–≤8·9 mmol/L: add 6 U per day
- >6·7–≤7·8 mmol/L: add 4 U per day
- >5·5–≤6·7 mmol/L: add 2 U per day
- ≤5·5 mmol/L: no further titration

**Insulin lispro**

*Titration monitoring*

Starting dose: 4 U per day. Direct investigator contact. Additional calls to adjust insulin dose if haemoglobin $A_{1c}$ >7%

*Insulin dose titration algorithm*

Preprandial blood glucose:

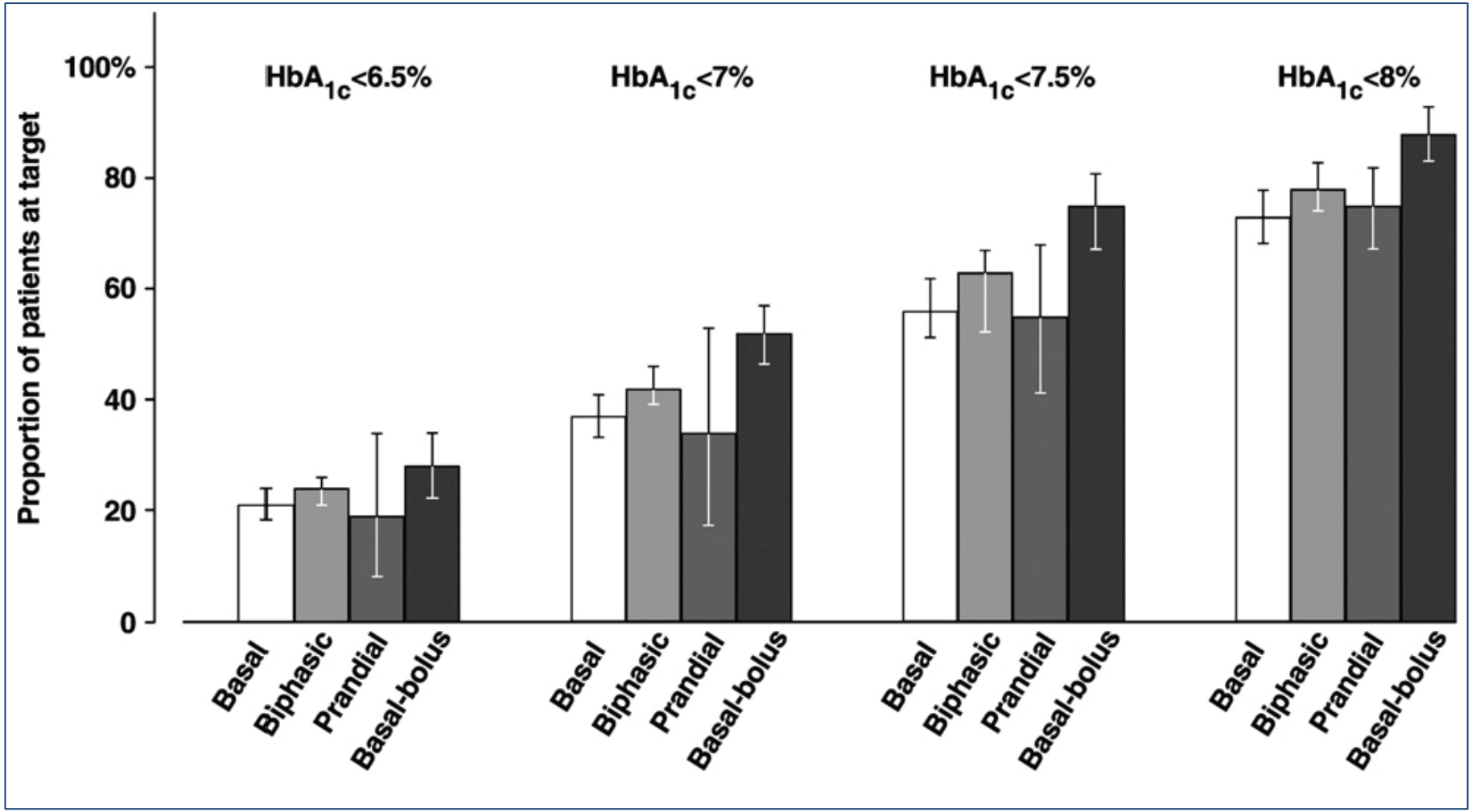
- >11·1 mmol/L: add 3 U before main meal
- >8·3–≤11·1 mmol/L: add 2 U before main meal
- >5·5–≤8·3 mmol/L: add 1 U before main meal
- <5·5 mmol/L: no further titration

Postprandial blood glucose:

- >10·3 mmol/L: add 2 U before main meal
- >7·5–≤10·3 mmol/L: add 1 U before main meal
- ≤7·5 mmol/L: no further titration

***Bretzel RG , Lancet 2008; 371: 1073–84***

# Percentuale di pazienti che raggiungono diversi obiettivi glicemici con diversi regimi insulinici




*Giugliano D Journal of Diabetes and Its Complications 2011; 25: 275– 281*

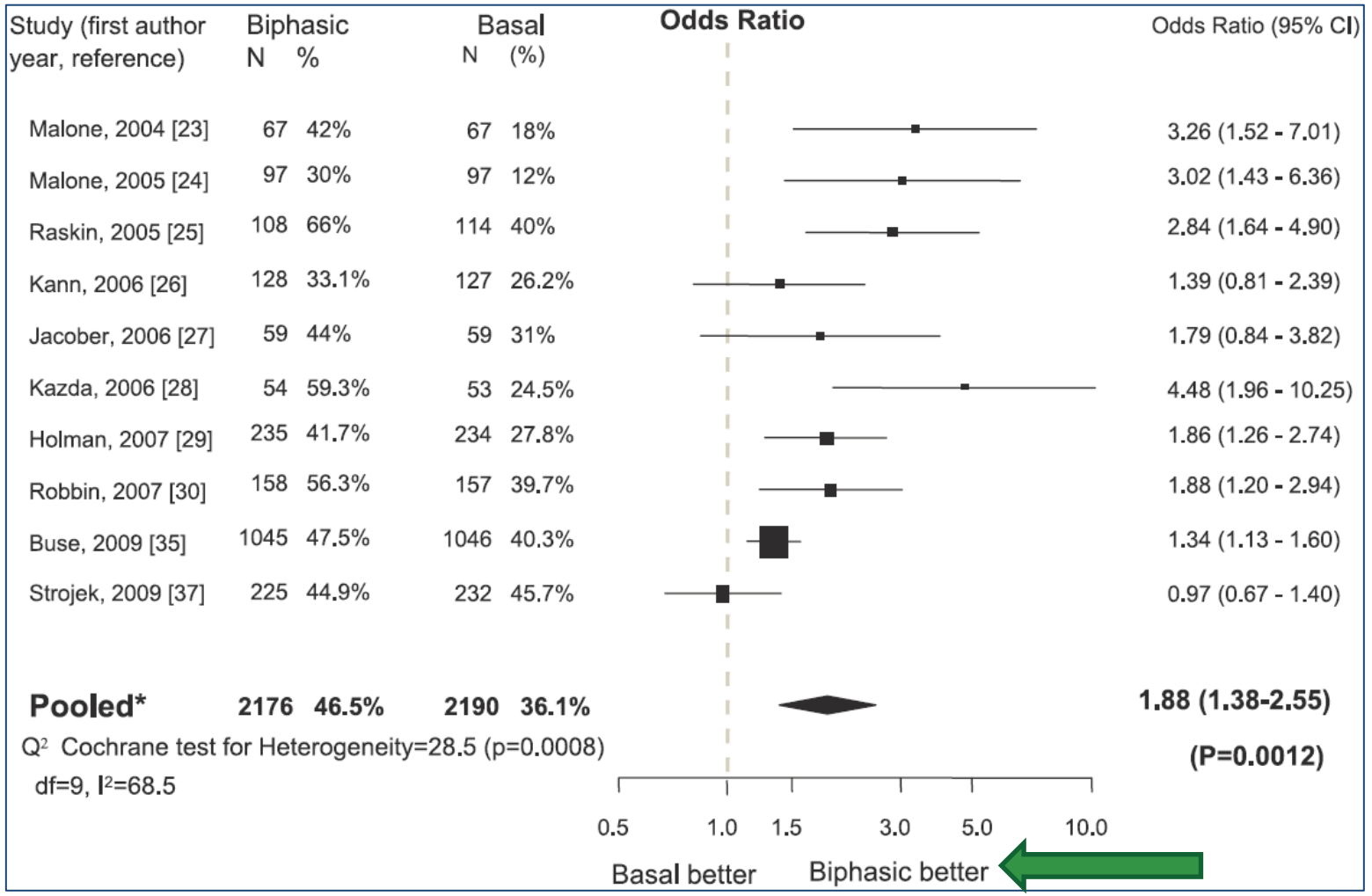
# Efficacy of Insulin Analogs in Achieving the Hemoglobin $A_{1c}$ Target of <7% in Type 2 Diabetes

## Meta-analysis of randomized controlled trials

DARIO GIUGLIANO, MD, PHD[1]
MARIA IDA MAIORINO, MD[1]
GIUSEPPE BELLASTELLA, MD[1]
PAOLO CHIODINI, MD[2]
ANTONIO CERIELLO, MD[3]
KATHERINE ESPOSITO, MD, PHD[1]

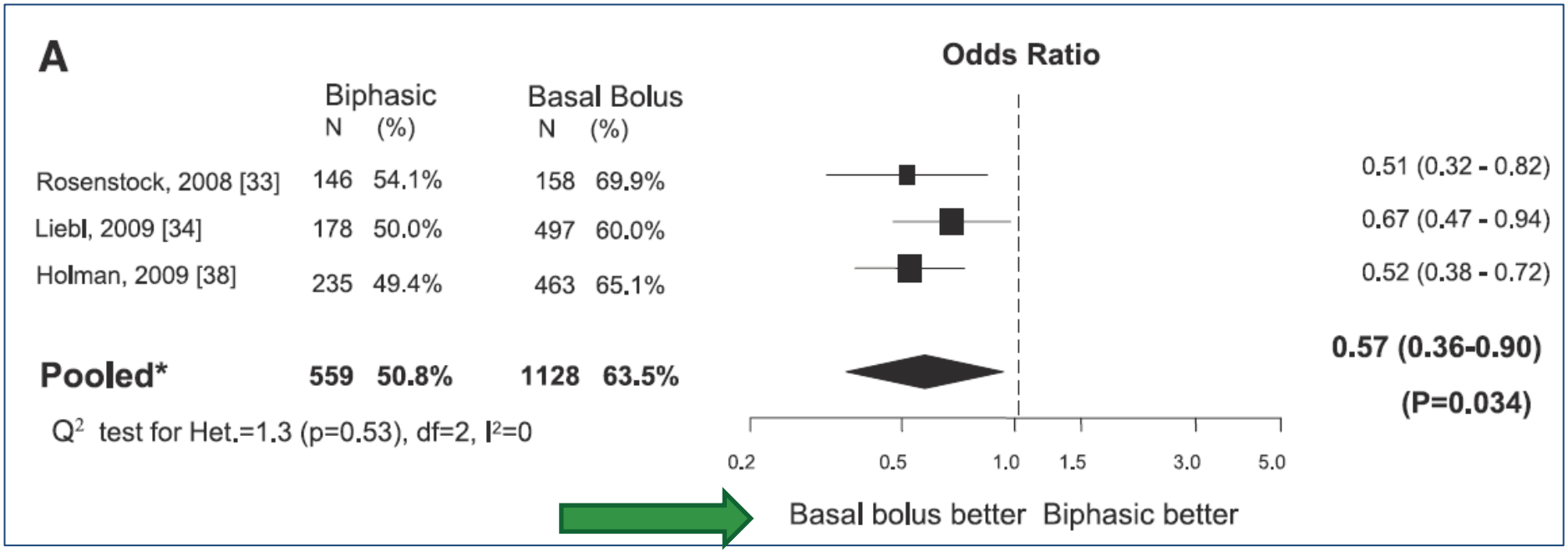
*Diabetes Care* 34:510–517, 2011

# Proporzione di pazienti con Hb A1c <7%: bifasica vs. basale



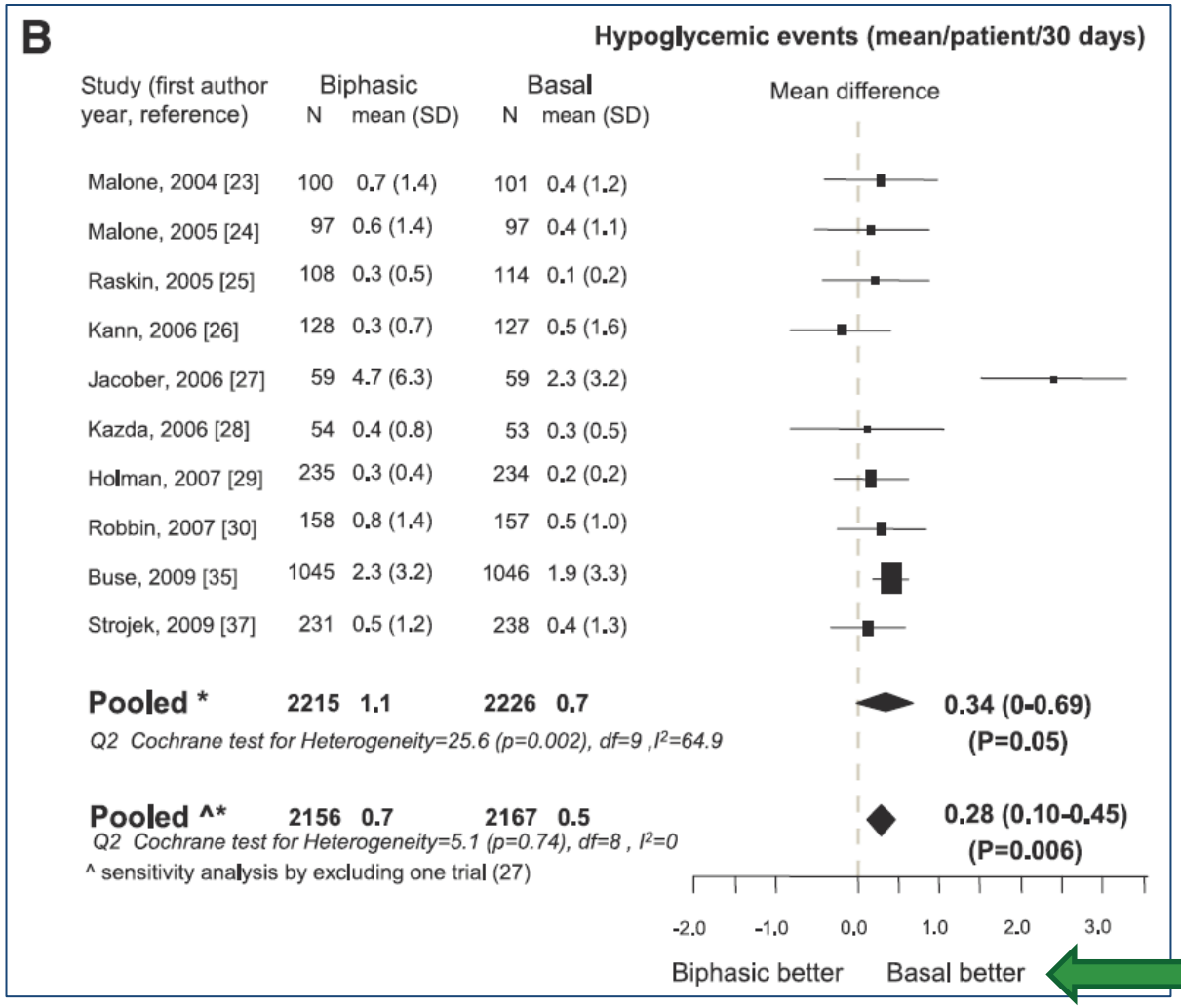

*Giugliano D Diabetes Care 2011; 34:510–517*

# Proporzione di pazienti con Hb A1c <7%: bifasica vs. basal bolus



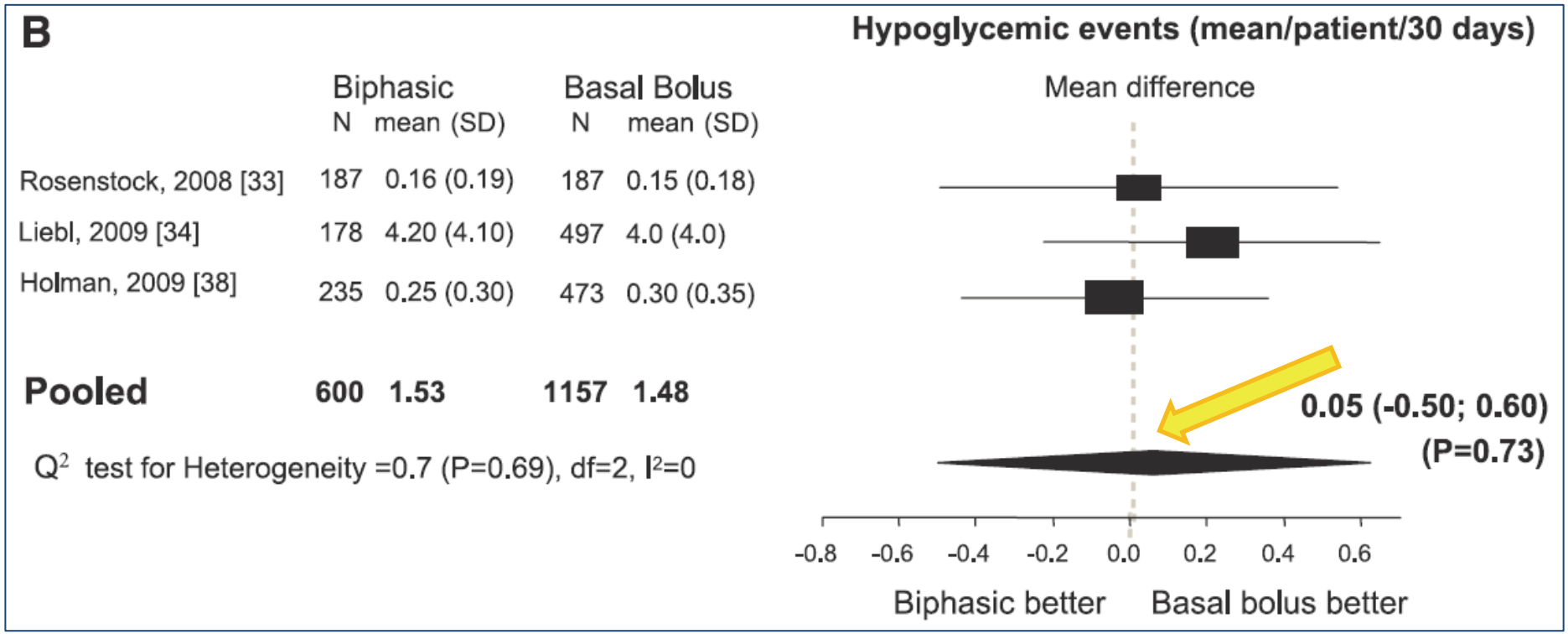

*Giugliano D Diabetes Care 2011; 34:510–517*

# Variazione dell'incidenza di ipoglicemia: bifasica vs. basale



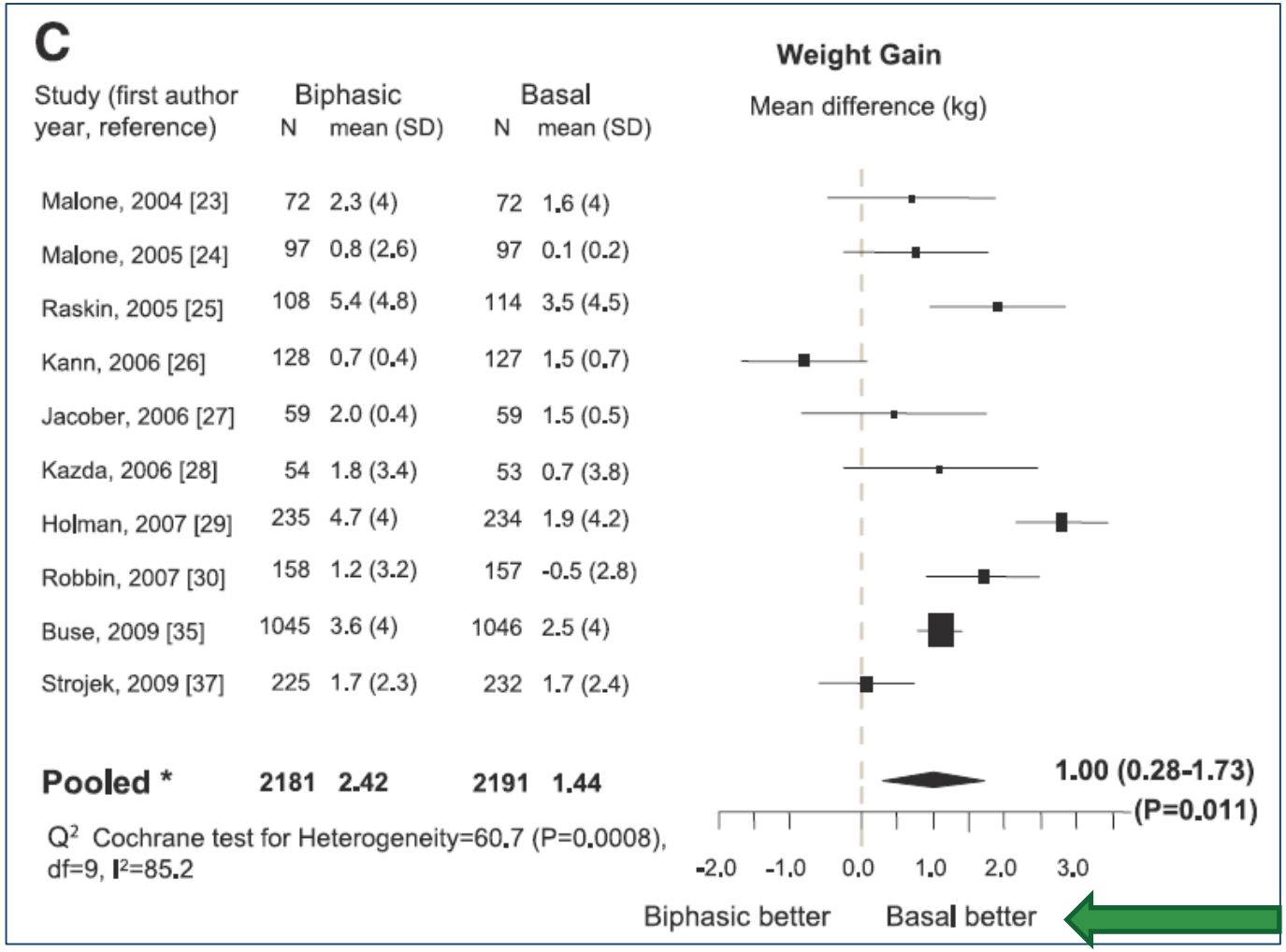

*Giugliano D Diabetes Care 2011; 34:510–517*

# Variazione dell'incidenza di ipoglicemia: bifasica vs. basal bolus



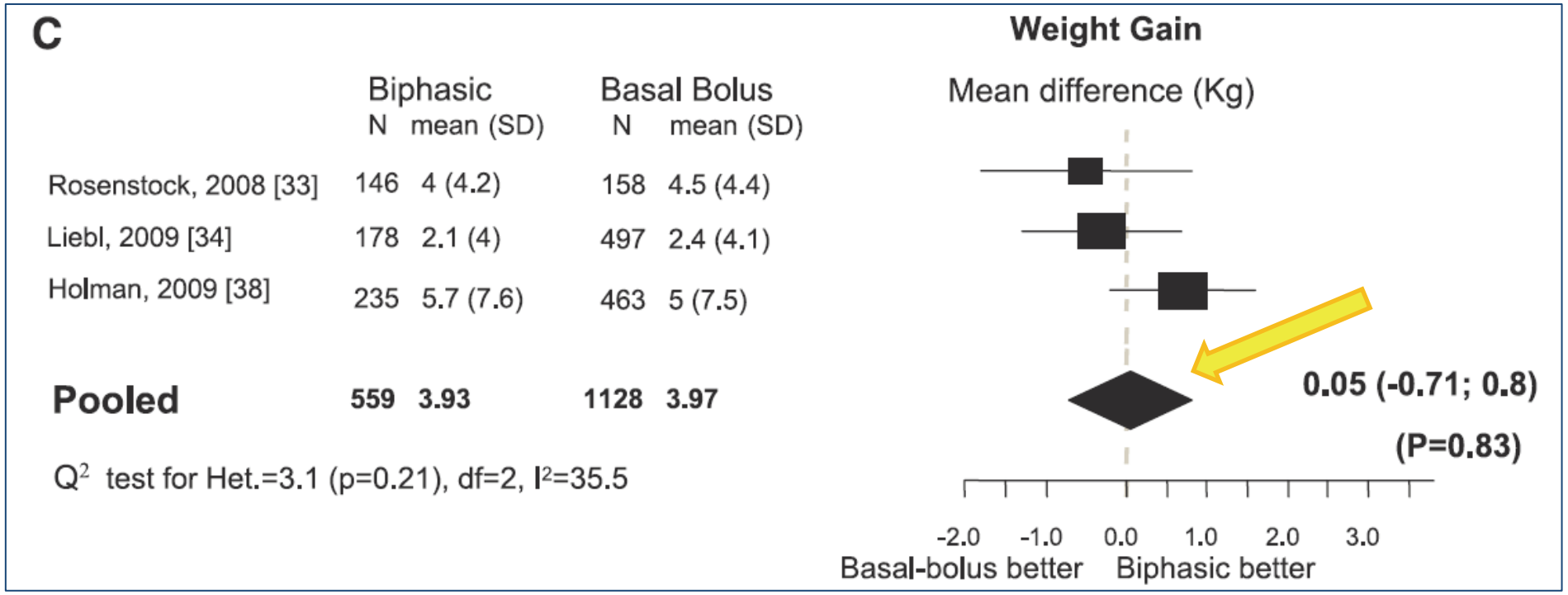

*Giugliano D Diabetes Care 2011; 34:510–517*

# Variazione nel peso: bifasica vs. basale




*Giugliano D Diabetes Care 2011; 34:510–517*

# Variazione nel peso: bifasica vs. basal bolus




*Giugliano D Diabetes Care 2011; 34:510–517*

# Conclusioni 2

- La terapia con analogo bifasico o prandiale può essere efficace ma espone a maggiori rischi di ipoglicemia, senza vantaggi significativi rispetto all'analogo lento
- La terapia con analogo rapido ottiene un maggior controllo dell'iperglicemia post prandiale con maggiori ipoglicemie
- La terapia con analogo lento è efficace ed è la più gradita dai pazienti

Diabetologia (2012) 55:2853–2855
DOI 10.1007/s00125-012-2642-x

LETTER

# To what extent is the new position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) 'personalised'?

**A. Ceriello · M. Gallo · S. Gentile · C. B. Giorda · A. De Micheli · on behalf of Associazione Medici Diabetologi (AMD)**

**Un po' di polemica scientifica**

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- The document appears to fail in its purpose, by focusing—as do all guidelines available to date—on a lengthy though highly detailed list of the possible therapeutic choices.
- An effective way of overcoming this problem would be to use an online interactive resource, as recently proposed with the algorithms relating to tailoring drug therapy for patients with type 2 diabetes issued by the Finnish Medical Society
- This computerised system allows people to quickly find subjects of interest according to their own particular clinical features, as well as to follow easy, step-by-step suggestions for additional therapeutic pathways.

*Ceriello A et al, Diabetologia 2012; 55:2853–2855*

Diabetologia (2012) 55:2856–2857
DOI 10.1007/s00125-012-2669-z

LETTER

**ADA/EASD position statement of the treatment of type 2 diabetes: Reply to Rodbard HW and Jellinger PS [letter], Scheen AJ [letter] and Ceriello A, Gallo M, Gentile S et al [letter]**

D. R. Matthews · S. E. Inzucchi · for the Position Statement Writing Group

- *Our position statement is not, and was not designed to be, an algorithm. The rationale for this is that we felt that expressing 'strong preferences' would not be correct, and think that the authors' belief that specific prescriptive approach( es) are highly advantageous may be misplaced. Such robust views meld poorly with the concept of a patient centred approach.*
- *We have been careful to avoid any dogmatic therapeutic propositions… Indeed, we are trying to encourage the process of decision-making on a flexible basis, individualising patient-centred care on criteria other than those simply obtained from a laboratory—without denying the profound importance of such measures.*
- *We entirely agree that there can be many ways to help with clinical decision-making—and that computers can be of particular help in analysing complexities and guiding the physician in other ways.*

*Matthews DR et al, Diabetologia 2012; 55:2856–2857*

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- In the 2012 ADA/EASD position statement [1], moreover, the importance of controlling postprandial hyperglycaemia remains largely undervalued, despite being a key contributory factor to achievement of the HbA1c goal
- It is very surprising that the ADA/EASD position statement neglects this aspect, particularly if we consider that the main defect in Asian patients is loss of the first phase of insulin secretion, rather than insulin resistance [5], which is why drugs like α-glucosidase inhibitors are among the first therapeutic choices in these patients. This is even more surprising given that there are Asian populations in North America and Europe [6].

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- *We are aware, of course, of the International Diabetes Federation (IDF) guidelines on postmeal glucose [ which state that 'uncertainties remain about a causal association between postmeal plasma glucose and complications and additional research is needed to clarify our understanding in this area. Logic and clinical judgment remain critical components of diabetes care and implementation of any guideline recommendations'.*

*Ceriello A et al, Diabetologia 2012; 55:2853–2855*

*Matthews DR et al, Diabetologia 2012; 55:2856–2857*

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- Finally, within the context of 'customising' therapy, it is questionable that initiation of insulin therapy must be carried out exclusively with basal insulin, not including the possibility of using insulin that deals with postprandial hyperglycaemia

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- *Short-acting insulin usually needs more injections than basal insulin therapy, but we would not wish to argue for the primacy of one approach above another.*

*Ceriello A et al, Diabetologia 2012; 55:2853–2855*

*Matthews DR et al, Diabetologia 2012; 55:2856–2857*

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- In the ADA/EASD position statement, self-monitoring of blood glucose (SMBG), is also completely overlooked unless insulin therapy starts the best compromise between efficacy, safety and therapeutic adherence.
- To achieve this goal, AMD has developed tailored therapeutic algorithms for some of the most common type 2 diabetes phenotypes.
- In our opinion, this innovative approach, tailored to the real-world situation may facilitate more timely and appropriate treatment changes, counteracting clinical inertia

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- *Enthusiasm for self-monitoring glucose may not be wrong, but the costs can also be high.*
- *Only when therapeutic decisions (or lifestyle decisions) flow directly from these data can there be full justification for undertaking this. In practice many patients on oral agents are finger-pricking frequently for no clearly justifiable outcome.*
- *One agent will be good for one patient, another for the next.*
- *An individual's motivation may or may not be improved by finger-prick glucose monitoring. He or she might, for example, prefer not to have sore fingers and be able play the cello unimpaired*

*Ceriello A et al, Diabetologia 2012; 55:2853–2855*

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- In our opinion, compared with the recent ADA/EASD position statement, the algorithm proposed by AMD offers suggestions that are more detailed and closer to the everyday decision-making processes carried out by every physician facing an individual patient with specific characteristics, and having to make therapeutic choices the most effective for that particular patient, or rather, for that individual person suffering from diabetes.

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- *The skill of the physician cannot be codified into any rigid or mathematical formula.*
- *We need to use all our international collegiate combined medical knowledge, skill and wisdom if we are to serve our patients beyond the mathematics of greater-than and less-than signs and the self imposed statistical fundamentalism that implies that we cannot decide anything beyond the constraints of a p value.*

*Ceriello A et al, Diabetologia 2012; 55:2853–2855*

*Matthews DR et al, Diabetologia 2012; 55:2856–2857*


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1974
Grazie per l'attenzione