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# **Dopo la metformina (pro e contro rispetto agli altri farmaci)**

Diapositiva preparata da GABRIELE PERRIELLO e presentata alla Società Italiana di Diabetologia.  
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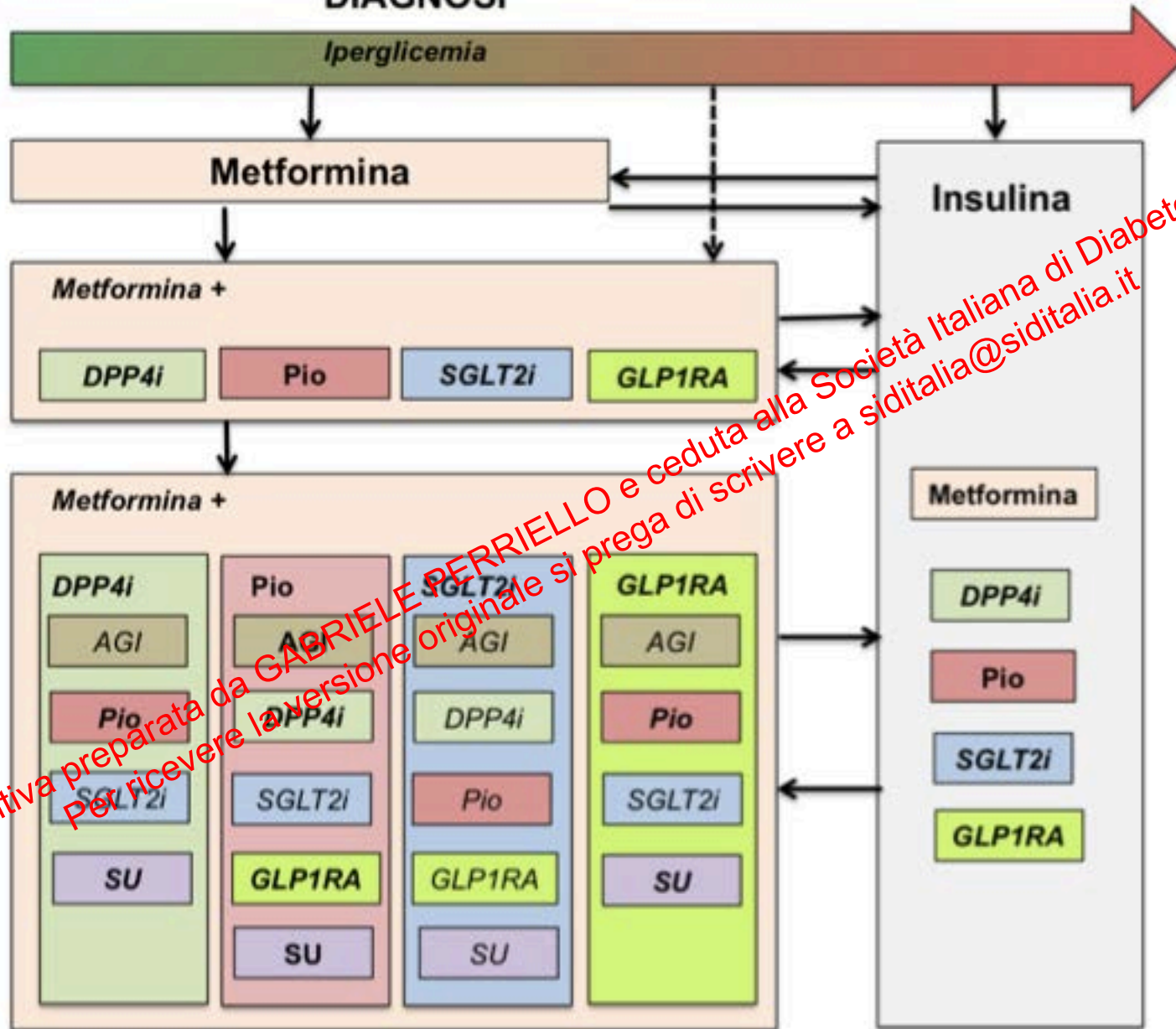
23 novembre 2019

Il sottoscritto dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

*Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

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# DIAGNOSI



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**FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)**  
If HbA<sub>1c</sub> above target proceed as below



## ESTABLISHED ASCVD OR CKD

### ASCVD PREDOMINATES

**GLP-1 RA with proven CVD benefit<sup>1</sup>** **OR** **SGLT2i with proven CVD benefit<sup>2</sup>, if eGFR adequate<sup>3</sup>**

If HbA<sub>1c</sub> above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin<sup>4</sup>
- TZD<sup>5</sup>
- SU<sup>6</sup>

### HF OR CKD PREDOMINATES

#### PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate<sup>3</sup>  
**OR**  
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate<sup>3</sup> add GLP-1 RA with proven CVD benefit<sup>1</sup>

If HbA<sub>1c</sub> above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin<sup>4</sup>
- TZD<sup>5</sup>
- SU<sup>6</sup>

NO

## WITHOUT ESTABLISHED ASCVD OR CKD

### COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i<sup>7</sup>

TZD

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

SGLT2i<sup>7</sup>

OR

TZD

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

GLP-1 RA

OR

DPP-4i

OR

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

Continue with addition of other agents as outlined above

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

Consider the addition of SU<sup>6</sup> OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia<sup>7</sup>

### COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss<sup>8</sup>

SGLT2i<sup>7</sup>

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

SGLT2i<sup>7</sup>

GLP-1 RA with good efficacy for weight loss<sup>8</sup>

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:  
• SU<sup>6</sup> • TZD<sup>5</sup> • Basal insulin

### COST IS A MAJOR ISSUE<sup>9-10</sup>

SU<sup>6</sup>

TZD<sup>5</sup>

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

TZD<sup>5</sup>

SU<sup>6</sup>

If HbA<sub>1c</sub> above target

If HbA<sub>1c</sub> above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider DPP-4i OR

SGLT2i with lowest acquisition cost<sup>9</sup>

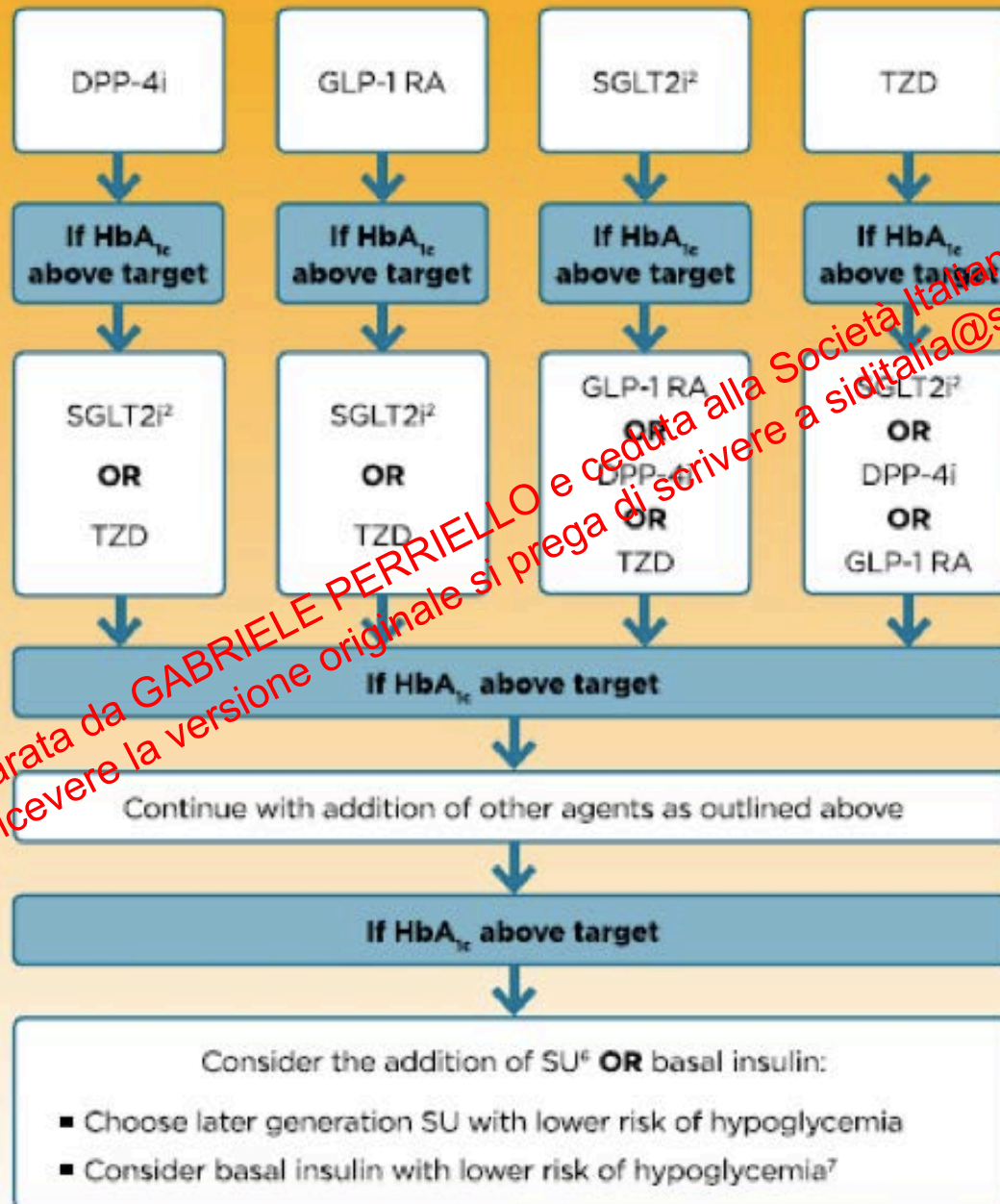
- Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
- Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
- Degludec or U100 glargine have demonstrated CVD safety
- Low dose may be better tolerated though less well studied for CVD effects

- Choose later generation SU with lower risk of hypoglycemia
- Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
- Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Pharmacologic Approaches to Glycemic Treatment:  
*Standards of Medical Care in Diabetes - 2019. Diabetes Care* 2019; 42 (Suppl. 1): S90-S102



## COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



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# Recommendations of the Israel National Diabetes Council

## Lifestyle Modification, Teamwork and Patient Empowerment

**Target HbA1c**

SET HbA1c TARGET according to patient characteristics and glucose-lowering agents

**A1c < 6.5%**

Lifestyle intervention + metformin \*eGFR > 30 ml/min/BSA

If HbA1c not at target after 3-6 months add:

**A1c > 7.5%**

Consider combination therapy

**A1c > 9%**

and/or symptomatic consider (short term) insulin

**A1c < 7%**

BMI < 30  
DPP-4i or SGLT-2i  
GLP-1RA

30 < BMI < 35  
SGLT-2i or GLP-1RA  
DPP-4i

BMI ≥ 35  
GLP-1RA  
SGLT-2i  
Bariatric Surgery

When cost is a major limiting factor less preferable GLAs to consider:  
TZD, AGI, insulin, glinide, sulfonylurea

If HbA1c not at target after 3-6 months add/replace:

**A1c < 7% (LR<sup>+</sup>)**

**A1c < 8% (HR<sup>+</sup>)**

Combination therapy according to patient characteristics

|                    |         |   |         |   |         |   |          |
|--------------------|---------|---|---------|---|---------|---|----------|
| Obese              | GLP-1RA | + | SGLT-2i | + | TZD     |   |          |
| A1c > 9%/FPG > 180 | Insulin | + | GLP-1RA | + | DPP-4i  |   |          |
| Established CVD    | SGLT-2i | + | GLP-1RA | / | Insulin |   |          |
| Elderly            | DPP-4i  | + | AGI     | + | TZD     | / | AGI      |
| Economic issues    | SU      | / | Insulin | / | Insulin | / | SGLT-2i* |
| Renal Failure      | DPP-4i  | / | Glinide | / | Insulin | / | GLP-1RA* |

If HbA1c not at target after 6-12 months add/replace:

\* eGFR > 45 ml/min/BSA

\* eGFR > 30 ml/min/BSA

**A1c < 7% (LR<sup>+</sup>)**

**A1c < 8% (HR<sup>+</sup>)**

MDI vs. Insulin Pump/Metabolic surgery +/- MET, SGLT-2i, GLP-1RA

| Dual Therapy <sup>†</sup><br><small>According to<br/>ADA/EASD position statement</small> | Sulfonylurea         | Thiazolidine-<br>dione | DPP-4<br>Inhibitor   | SGLT-2<br>Inhibitor  | GLP-1 receptor<br>agonist | Insulin (basal)                         |
|------------------------------------------------------------------------------------------|----------------------|------------------------|----------------------|----------------------|---------------------------|-----------------------------------------|
| Efficacy*                                                                                | high                 | high                   | intermediate         | intermediate         | high                      | highest                                 |
| Hypo risk                                                                                | moderate risk        | low risk               | low risk             | low risk             | low risk                  | high risk                               |
| Weight                                                                                   | gain                 | gain                   | neutral              | loss                 | loss                      | gain                                    |
| Side effects                                                                             | hypoglycemia         | edema, HF, fxs         | rare                 | GU, dehydration      | GI<br>high                | hypoglycemia                            |
| Costs*                                                                                   | low                  | low                    | high                 | high                 | high                      | variable                                |
| Efficacy/<br>Durability                                                                  | ↑                    | ↑↑                     | ↑                    | ↑↑                   | ↑↑                        | ↑↑                                      |
| Hypo                                                                                     | ↑                    | ↓                      | ↓                    | ↓                    | ↓                         | ↑                                       |
| Weight                                                                                   | ↑                    | ↑↑                     | ↔                    | ↓                    | ↓↓                        | ↑                                       |
| Other<br>Side Effects                                                                    | ↔                    | ↑↑                     | ↓                    | ↑                    | ↑                         | ↔                                       |
| Cost                                                                                     | ↓                    | ↓*                     | ↑                    | ↑                    | ↑                         | ↓↑**                                    |
| CV Safety                                                                                | not available        | ↑                      | ↑                    | ↑↑                   | ↑↑                        | ↑                                       |
| Recommendation                                                                           | 3 <sup>rd</sup> line | 3 <sup>rd</sup> line   | 2 <sup>nd</sup> line | 2 <sup>nd</sup> line | 2 <sup>nd</sup> line      | 1 <sup>st</sup> or 3 <sup>rd</sup> line |

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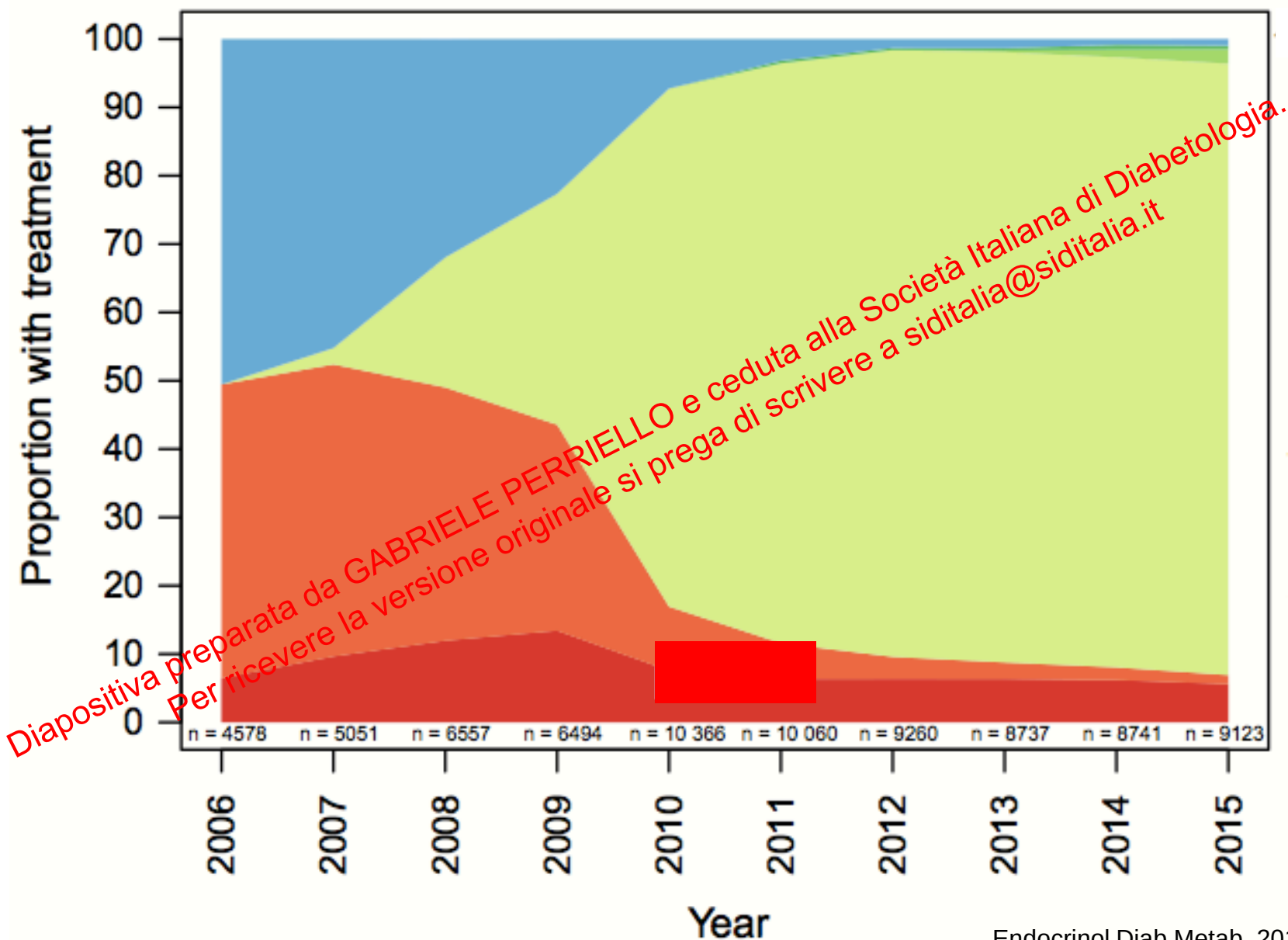


| Dual Therapy <sup>†</sup><br><small>According to<br/>ADA/EASD position statement</small> | DPP-4<br>Inhibitor   | SGLT-2<br>Inhibitor  | GLP-1 receptor<br>agonist |
|------------------------------------------------------------------------------------------|----------------------|----------------------|---------------------------|
| Efficacy*                                                                                | intermediate         | intermediate         | high                      |
| Hypo risk                                                                                | low risk             | low risk             | low risk                  |
| Weight                                                                                   | neutral              | loss                 | loss                      |
| Side effects                                                                             | rare                 | GU, dehydration      | GI                        |
| Costs*                                                                                   | high                 | high                 | high                      |
| Efficacy/<br>Durability                                                                  | ↑                    | ↑                    | ↑↑                        |
| Hypo                                                                                     | ↓                    | ↓                    | ↓                         |
| Weight                                                                                   | ↔                    | ↓                    | ↓↓                        |
| Other<br>Side Effects                                                                    | ↓                    | ↑                    | ↑                         |
| Cost                                                                                     | ↑                    | ↑                    | ↑                         |
| CV Safety                                                                                | ↑                    | ↑↑                   | ↑↑                        |
| Recommendation                                                                           | 2 <sup>nd</sup> line | 2 <sup>nd</sup> line | 2 <sup>nd</sup> line      |

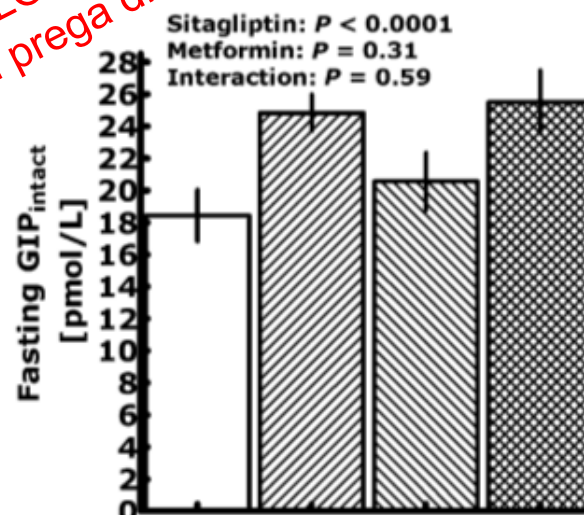
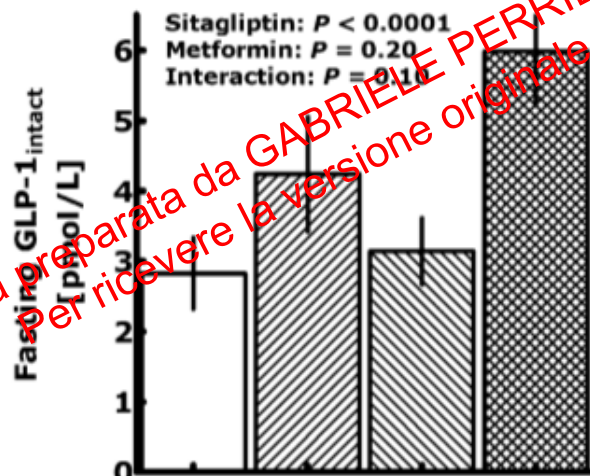
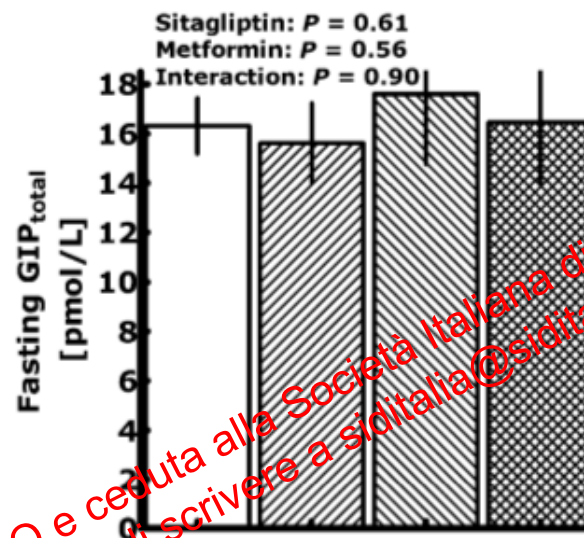
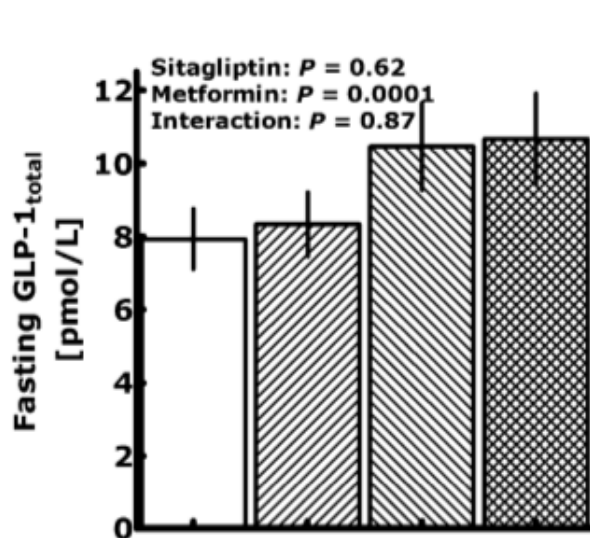
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■ Insulin 
 ■ SU 
 ■ DPP4 
 ■ SGLT2 
 ■ GLP1 
 ■ Other



# Synergistic effect of association sitagliptin/metformin on active GLP-1 production/secretion



Placebo  
Sitagliptin  
Metformin  
Sitagliptin + Metformin

Placebo  
Sitagliptin  
Metformin  
Sitagliptin + Metformin

# Glycemic effect of various agents as add-on therapy to metformin

| <i>Drug</i>             | <i>Decrease in A1c (%) when used as add-on therapy to metformin</i> |
|-------------------------|---------------------------------------------------------------------|
| <i>DPP4 inhibitors</i>  | -0.5-0.8                                                            |
| <i>SGLT2 inhibitors</i> | -0.5-0.9                                                            |
| <i>TZDs</i>             | -1.0-1.2                                                            |
| <i>GLP-1 Ras</i>        | -0.9-1.5                                                            |
| <i>Sulfonylureas</i>    | -0.5-1.3                                                            |

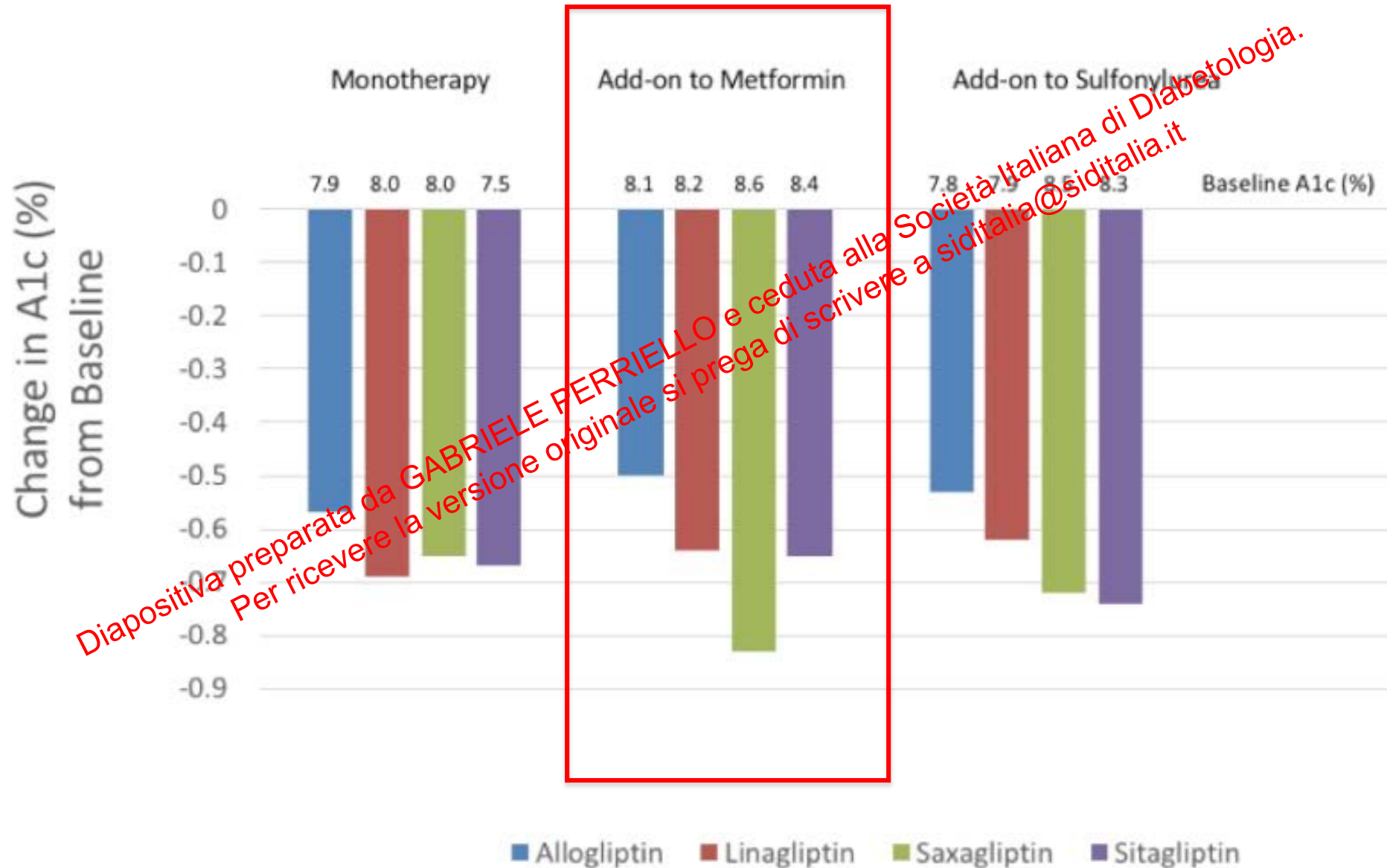
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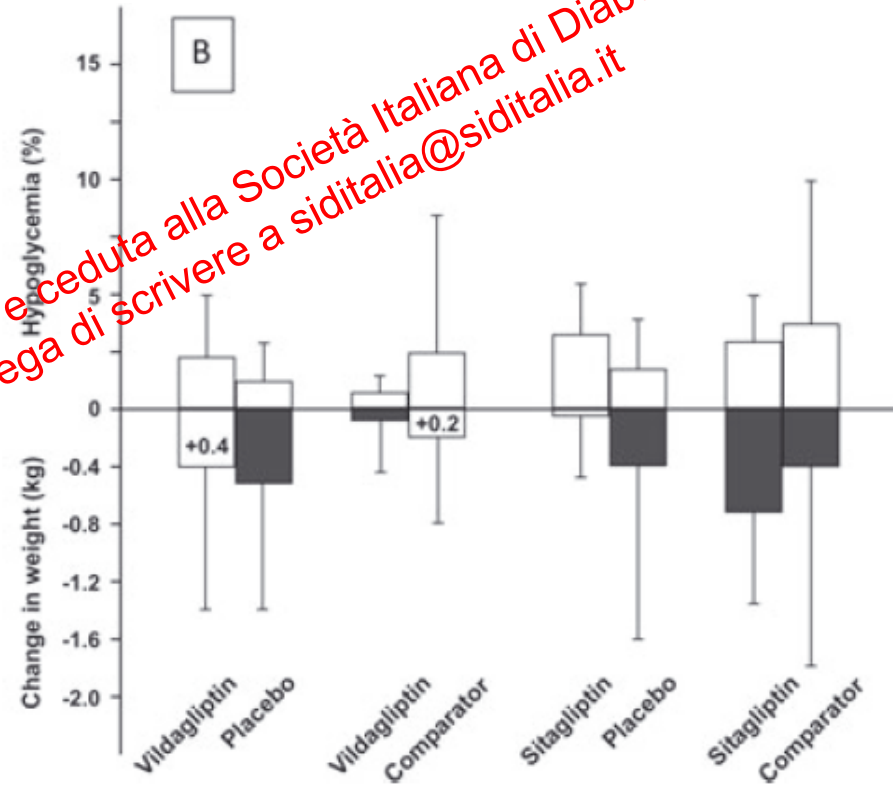
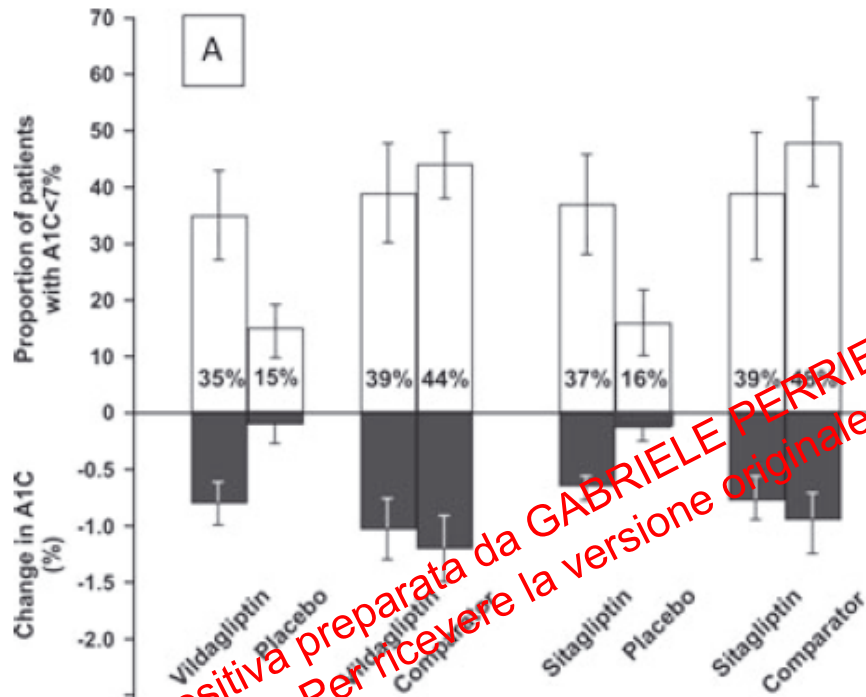
|                  | Fasting Glucose | Post-meal glucose |
|------------------|-----------------|-------------------|
| Metformin        | ↓↓              | ↓                 |
| GLP-1 RA         | ↓ To ↓↓         | ↓↓ To ↓↓↓         |
| SGLT-2I          | ↓↓              | ↓                 |
| DPP-4I           | ↓               | ↓↓                |
| TZD              | ↓↓              | ↓                 |
| AGI              | ↓               | ↓↓                |
| Colesevalem      | ↓               | ↓                 |
| BCR-QR           | -               | ↓                 |
| SFU              | ↓↓              | ↓↓                |
| Glinide          | ↓               | ↓↓                |
| Basal Insulin    | ↓↓ To ↓↓↓       | -                 |
| Prandial Insulin | -               | ↓↓ To ↓↓↓         |
| Pramlintide      | ↓               | ↓↓ To ↓↓↓         |

# Glucose Control With DPP-4 Inhibitors

Placebo-Adjusted Change in A1c (%) from Baseline  
(Not Head-to-Head Trials)

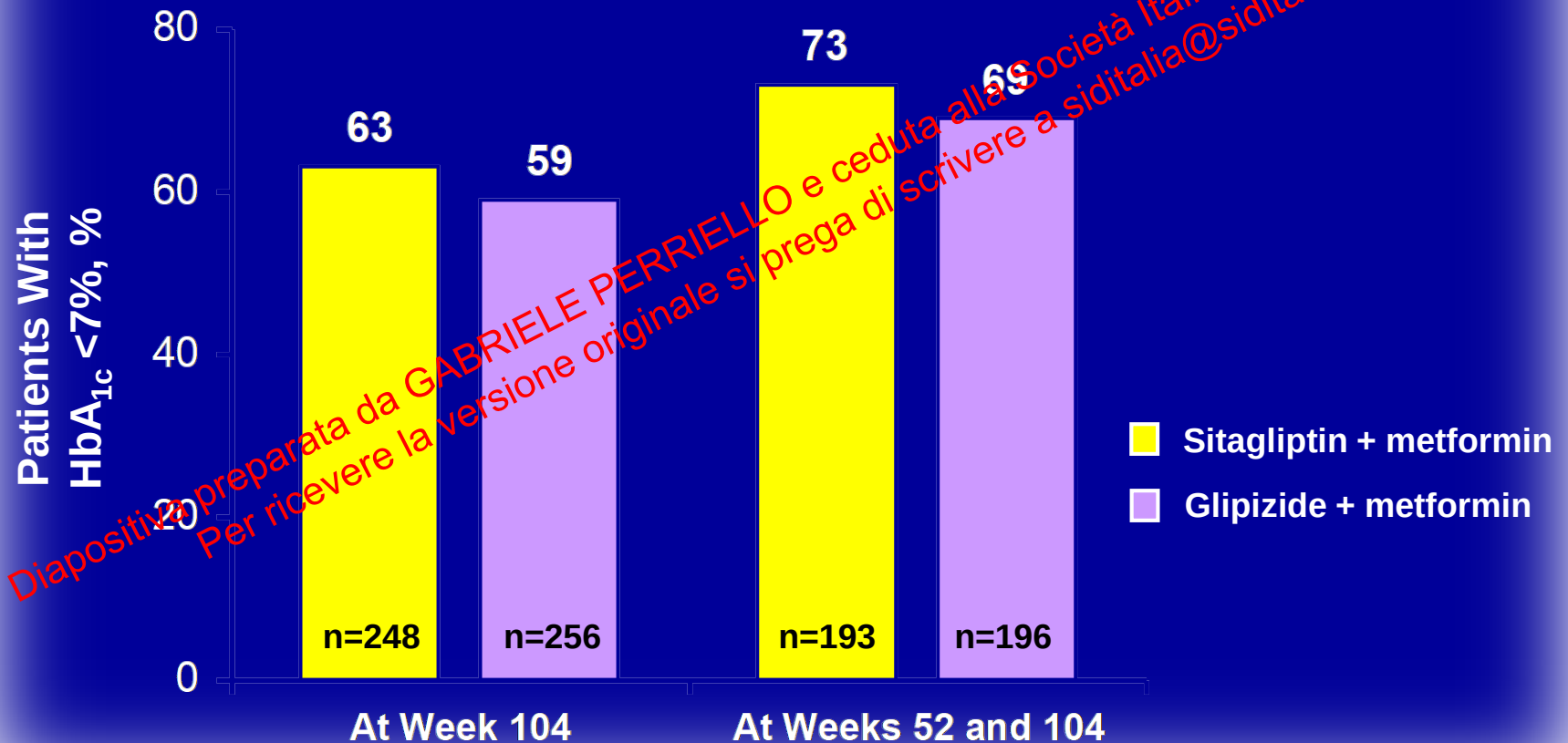


# Proportion of patients with Hba1c <7%, hypoglycemia and change in weight



# Similar Proportions of Patients Receiving Sitagliptin or Glipizide Achieved HbA<sub>1c</sub> Levels <7.0 % at 104 Weeks

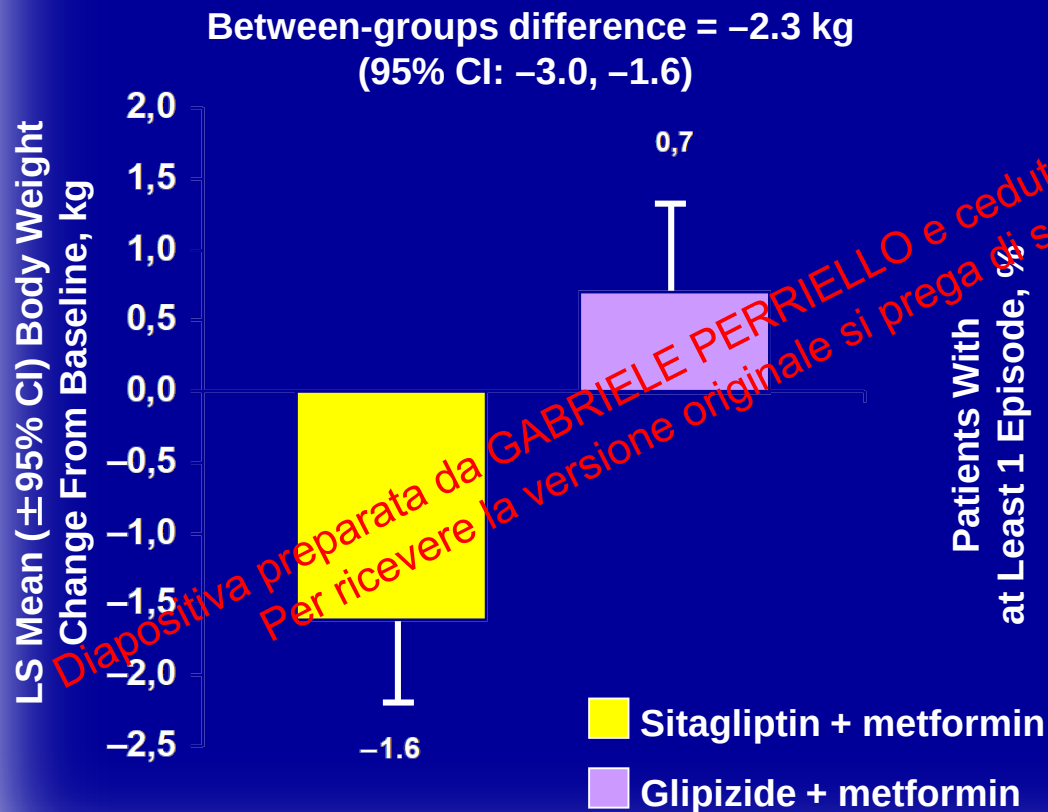
2-Year Per-Protocol Population  
(Patients Inadequately Controlled on Metformin)



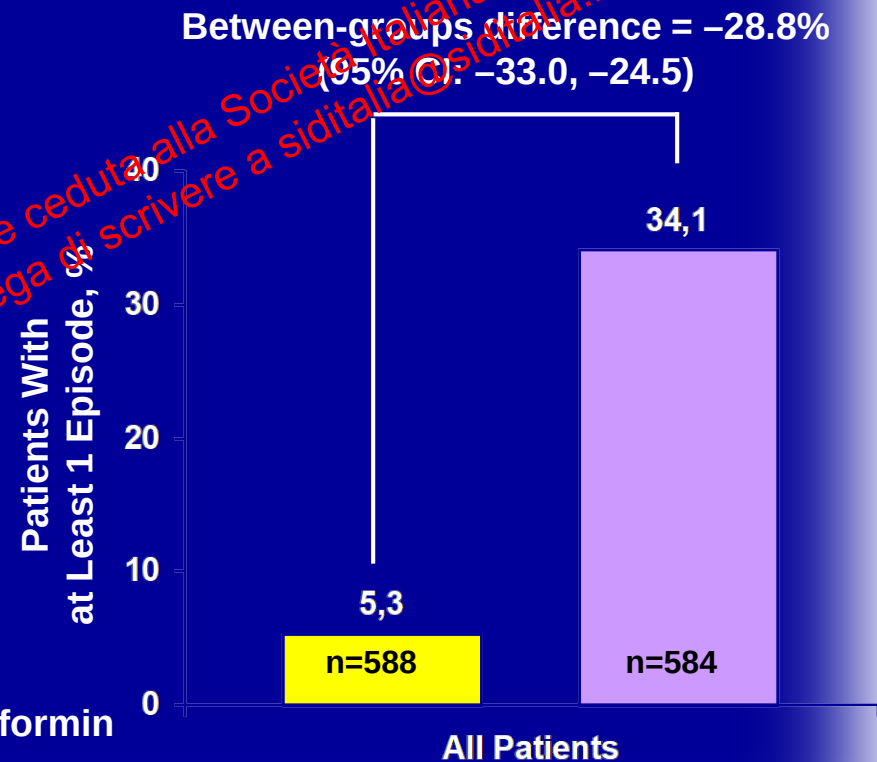


# Sitagliptin vs Glipizide: Weight Change and Incidence of Hypoglycemia

Body weight at week 104



Hypoglycemia over 104 weeks



# Weighted mean difference in change in HbA<sub>1c</sub> (%) from baseline

## Combined with metformin: DPP-4 inhibitor v sulfonylurea

|                                 |              |      |              |      |     |                       |
|---------------------------------|--------------|------|--------------|------|-----|-----------------------|
| Seck 2010 <sup>37</sup>         | -0.33 (1.00) | 576  | -0.35 (1.10) | 559  | 11  | 0.02 (-0.20 to 0.14)  |
| Arechavaleta 2011 <sup>25</sup> | -0.46 (0.92) | 509  | -0.52 (0.86) | 509  | 13  | 0.06 (-0.05 to 0.17)  |
| Study 020 phase B <sup>45</sup> | -0.73 (1.00) | 198  | -0.69 (0.90) | 107  | 3   | -0.04 (-0.26 to 0.18) |
| Filozof 2010 <sup>27</sup>      | -0.80 (1.12) | 503  | -0.83 (1.11) | 490  | 8   | 0.03 (-0.11 to 0.17)  |
| Matthews 2010 <sup>38</sup>     | -0.03 (0.78) | 1518 | -0.13 (0.77) | 1476 | 51  | 0.10 (0.04 to 0.16)   |
| Goke 2010 <sup>33</sup>         | -0.57 (0.80) | 423  | -0.66 (0.80) | 423  | 14  | 0.09 (-0.02 to 0.20)  |
| Subtotal (95% CI)               |              | 3727 |              | 3564 | 100 | 0.07 (0.03 to 0.11)   |
| with prediction interval        |              |      |              |      |     | (0.02 to 0.13)        |

Test for heterogeneity:  $\tau^2=0.00$ ,  $\chi^2=3.15$ ,  $df=5$ ,  $P=0.68$ ,  $I^2=0\%$

Test for overall effect:  $z=3.68$ ,  $P<0.001$

## Combined with metformin: DPP-4 inhibitor v pioglitazone

|                              |              |     |              |     |     |                       |
|------------------------------|--------------|-----|--------------|-----|-----|-----------------------|
| Bergental 2010 <sup>30</sup> | -0.90 (1.31) | 166 | -1.20 (1.31) | 165 | 22  | 0.30 (0.02 to 0.58)   |
| Handayani 2010 <sup>42</sup> | -0.57 (0.53) | 86  | -0.56 (0.47) | 60  | 39  | -0.01 (-0.19 to 0.17) |
| Bolli 2009 <sup>39</sup>     | -0.58 (1.20) | 293 | -0.64 (1.00) | 277 | 39  | 0.06 (-0.12 to 0.24)  |
| Subtotal (95% CI)            |              | 519 |              | 502 | 100 | 0.09 (-0.07 to 0.24)  |
| with prediction interval     |              |     |              |     |     | (-1.40 to 1.57)       |

Test for heterogeneity:  $\tau^2=0.01$ ,  $\chi^2=3.33$ ,  $df=2$ ,  $P=0.19$ ,  $I^2=40\%$

Test for overall effect:  $z=1.08$ ,  $P=0.28$

# Weighted mean difference in change in body weight (kg) from baseline

## Combined with metformin: DPP-4 inhibitor v sulfonylurea

|                                 |              |      |             |      |
|---------------------------------|--------------|------|-------------|------|
| Seck 2010 <sup>37</sup>         | -1.6 (5.27)  | 253  | 0.7 (5.36)  | 261  |
| Arechavaleta 2011 <sup>25</sup> | -0.8 (3.3)   | 465  | 1.2 (3.29)  | 461  |
| Matthews 2010 <sup>38</sup>     | -0.26 (4.32) | 1539 | 1.19 (4.29) | 1520 |
| Goke 2010 <sup>33</sup>         | -1.1 (3.5)   | 424  | 1.1 (3.51)  | 426  |
| Subtotal (95% CI)               |              | 2681 |             | 2668 |

with prediction interval

Test for heterogeneity:  $\tau^2=0.12$ ,  $\chi^2=9.80$ ,  $df=3$ ,  $P=0.02$ ,  $I^2=69\%$

Test for overall effect:  $z=8.80$ ,  $P<0.001$



|     |                        |
|-----|------------------------|
| 24  | -2.30 (-3.22 to -1.38) |
| 28  | -2.00 (-2.42 to -1.58) |
| 32  | -1.45 (-1.76 to -1.14) |
| 26  | -2.20 (-2.67 to -1.73) |
| 100 | -1.92 (-2.34 to -1.49) |
|     | (-3.70 to -0.14)       |

## Combined with metformin: DPP-4 inhibitor v pioglitazone

|                              |              |     |             |     |
|------------------------------|--------------|-----|-------------|-----|
| Bolli 2009 <sup>39</sup>     | 0.21 (3.25)  | 293 | 2.61 (4.16) | 277 |
| Bergental 2010 <sup>30</sup> | -0.81 (4.27) | 166 | 2.8 (3.93)  | 165 |
| Subtotal (95% CI)            |              | 459 |             | 442 |

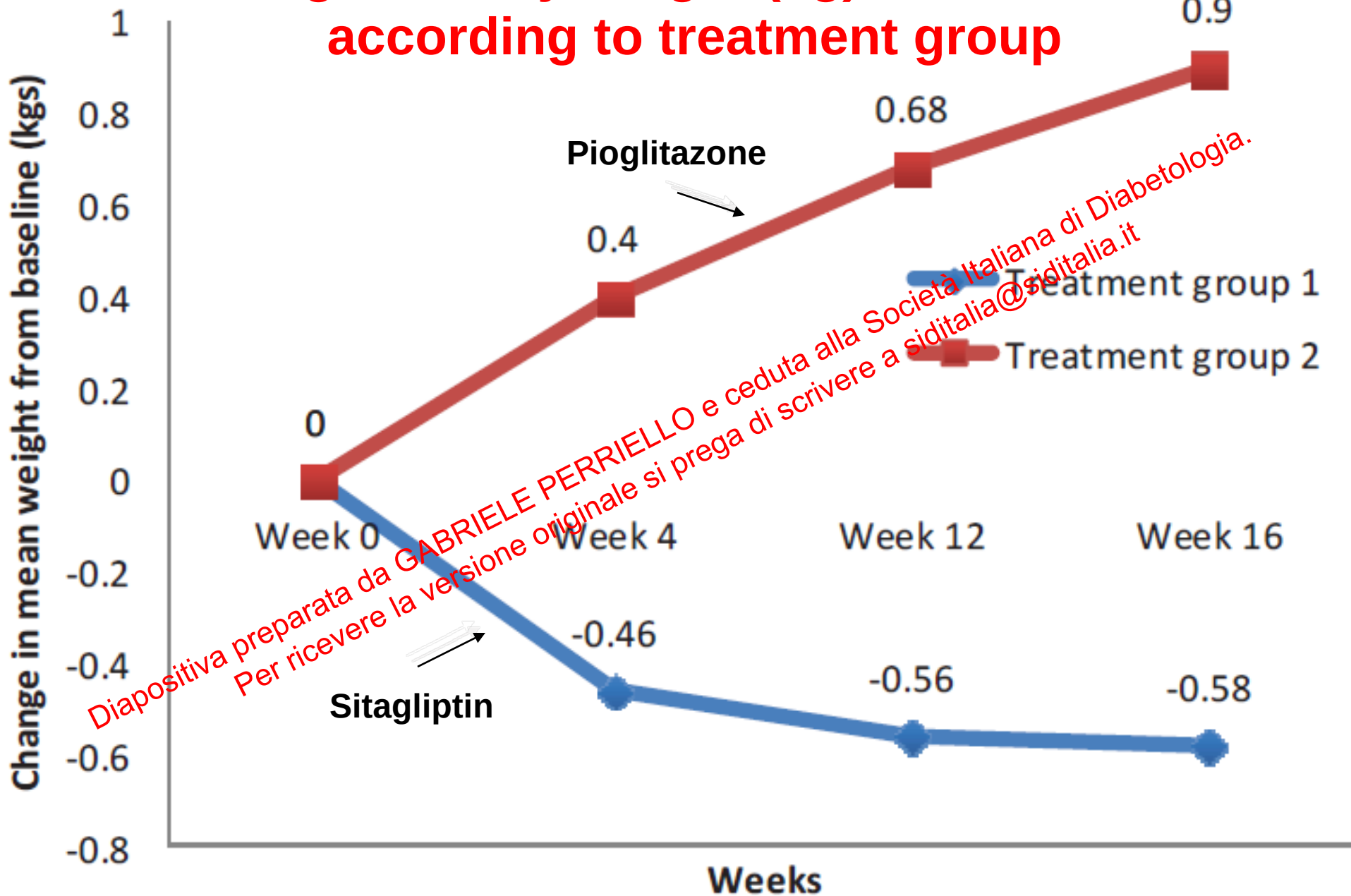
Test for heterogeneity:  $\tau^2=0.57$ ,  $\chi^2=4.77$ ,  $df=1$ ,  $P=0.03$ ,  $I^2=79\%$

Test for overall effect:  $z=4.94$ ,  $P<0.001$



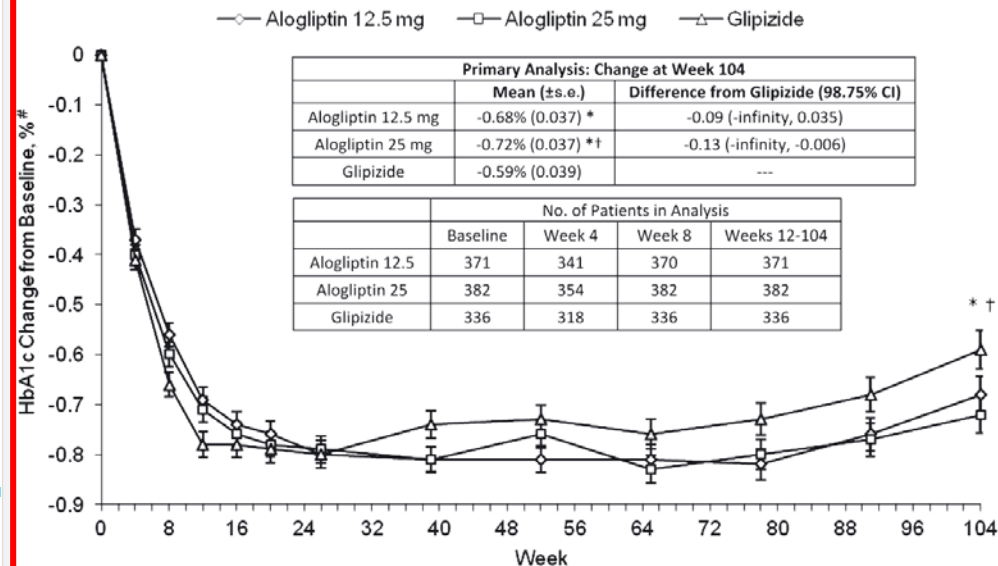
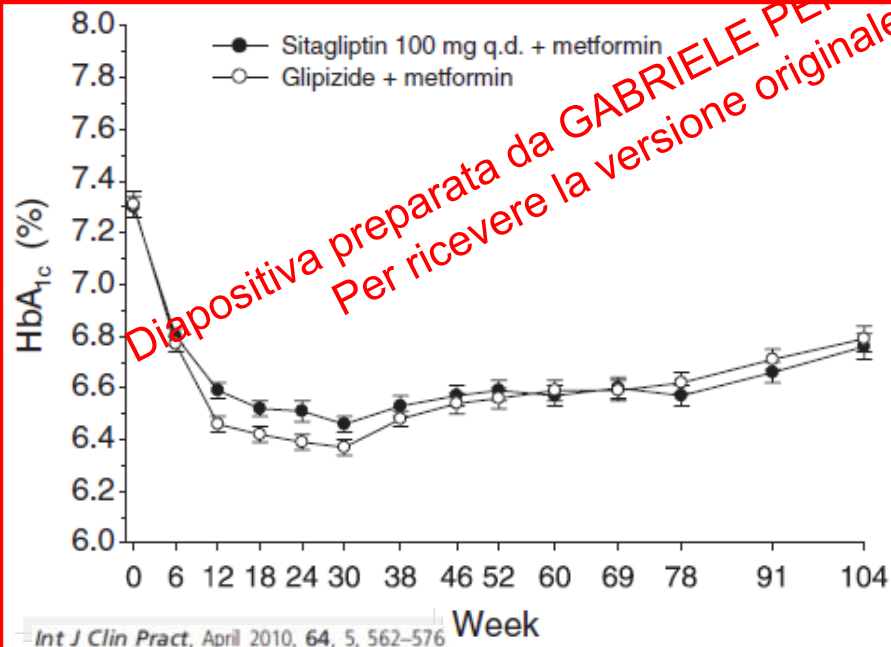
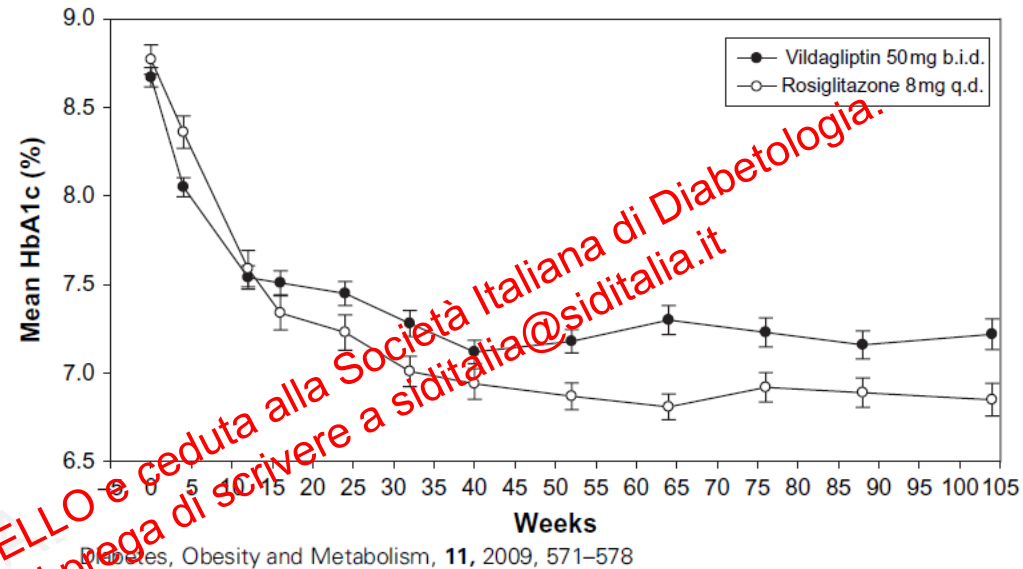
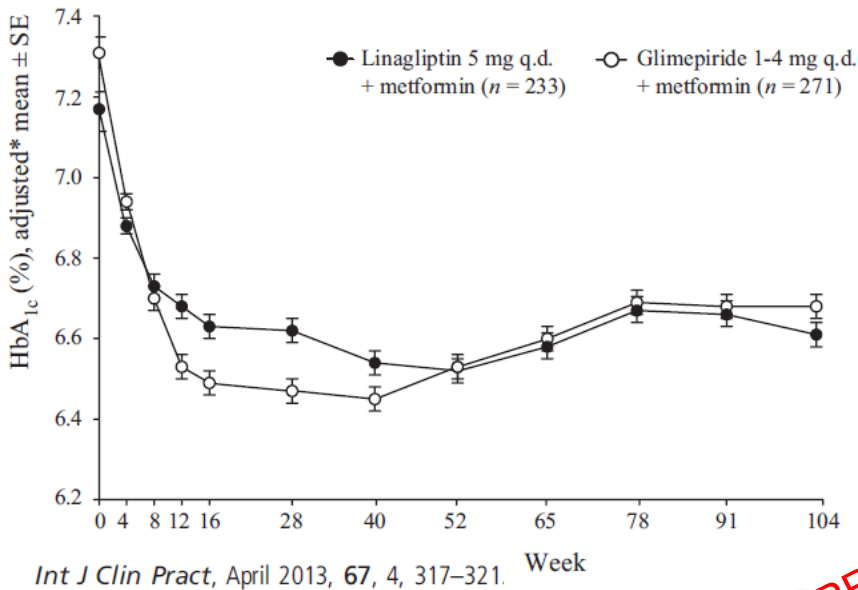
|     |                        |
|-----|------------------------|
| 54  | -2.40 (-3.02 to -1.78) |
| 46  | -3.60 (-4.48 to -2.72) |
| 100 | -2.96 (-4.13 to -1.78) |

# Change in body weight (kg) from baseline according to treatment group





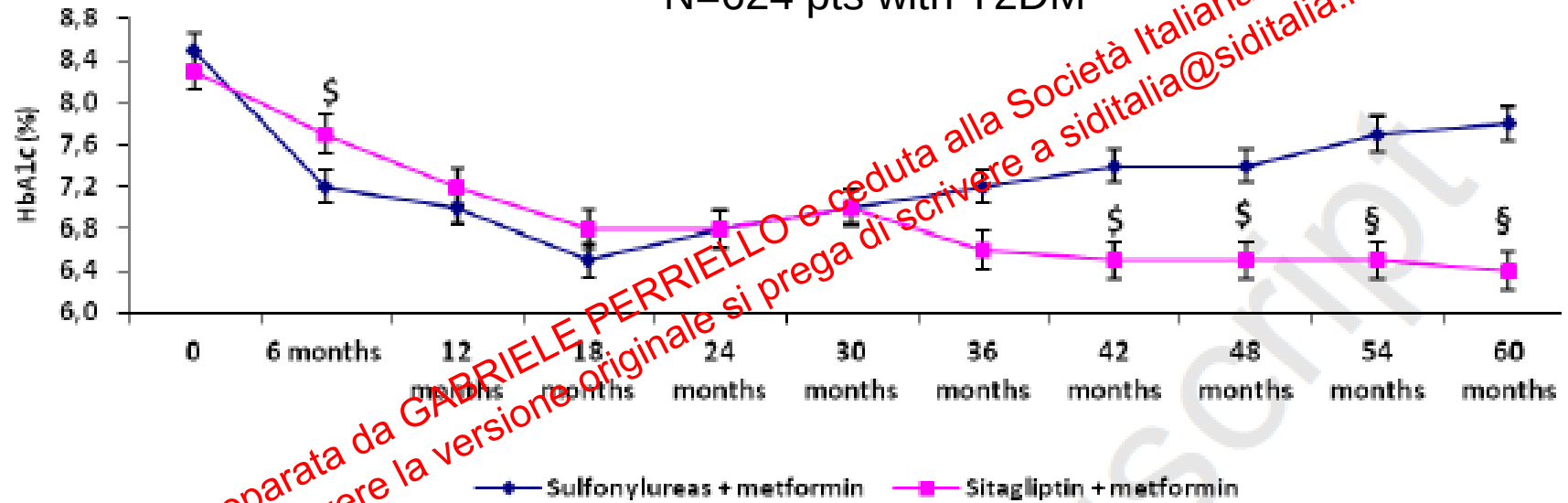
# Durability of Efficacy of DPP-4 Inhibitors



*Diabetes, Obesity and Metabolism* 2014.

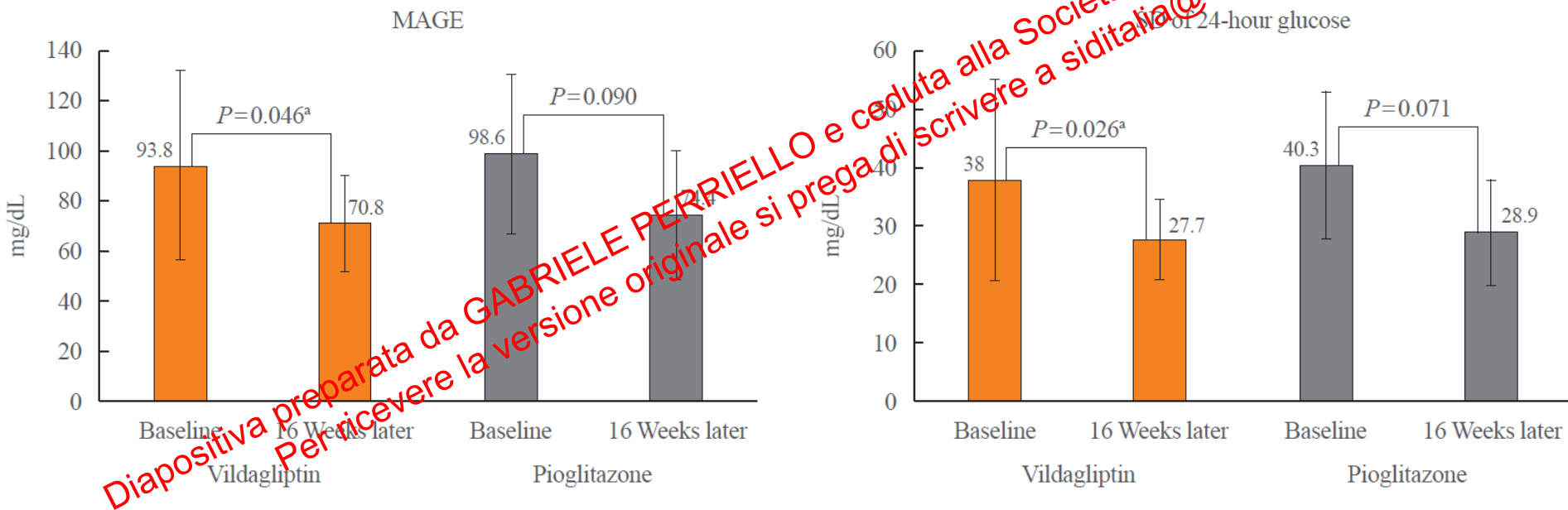
# Hypoglycemic efficacy of DPP4-I over 5 years

N=624 pts with T2DM



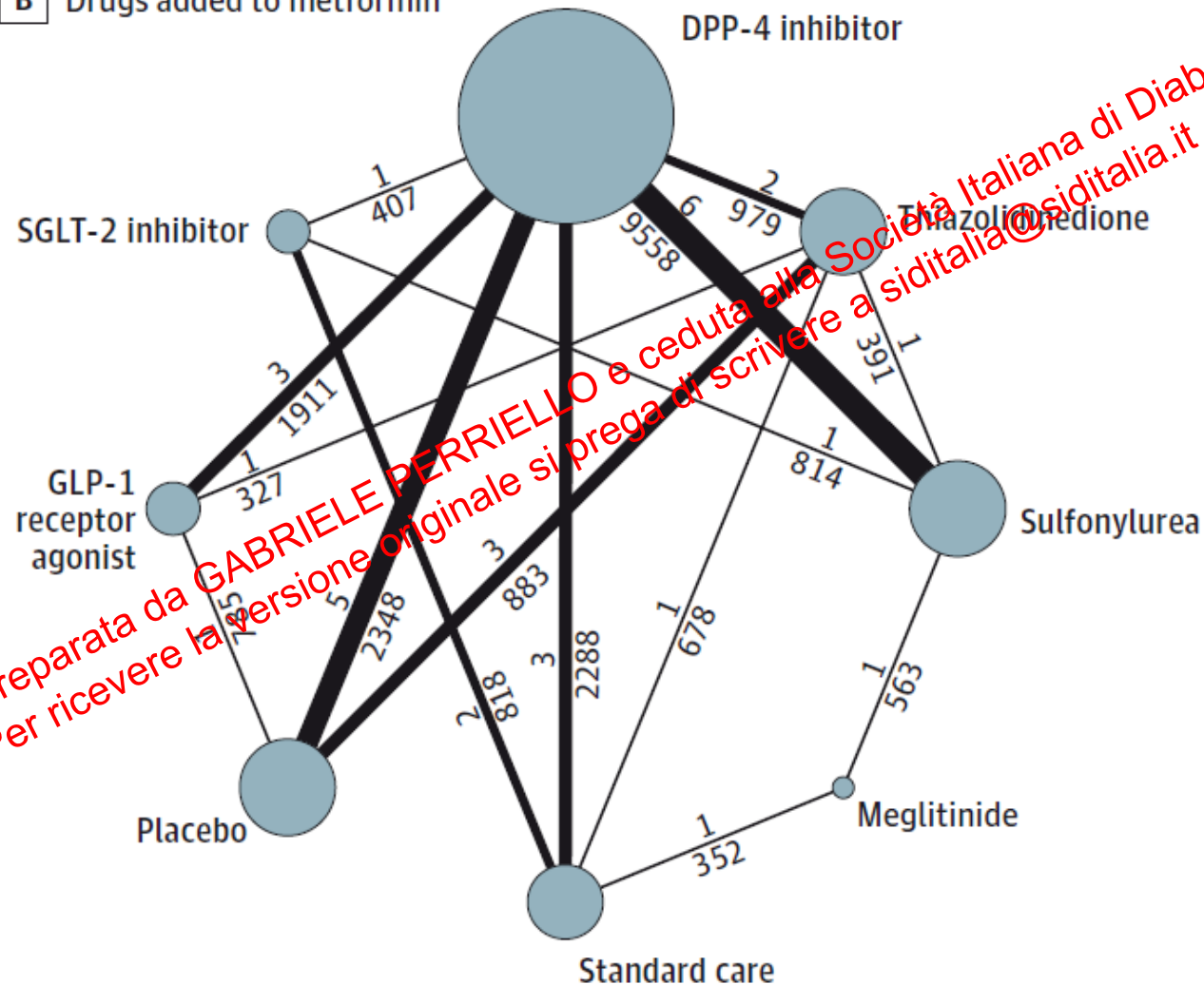
\$ p < 0.05 vs competitor; \$ p < 0.01 vs competitor

# Effects of DPP4-i on glucose variability in patients with T2DM



# Network Meta-Analysis (NMA) for indirect comparisons between OHAs in T2DM

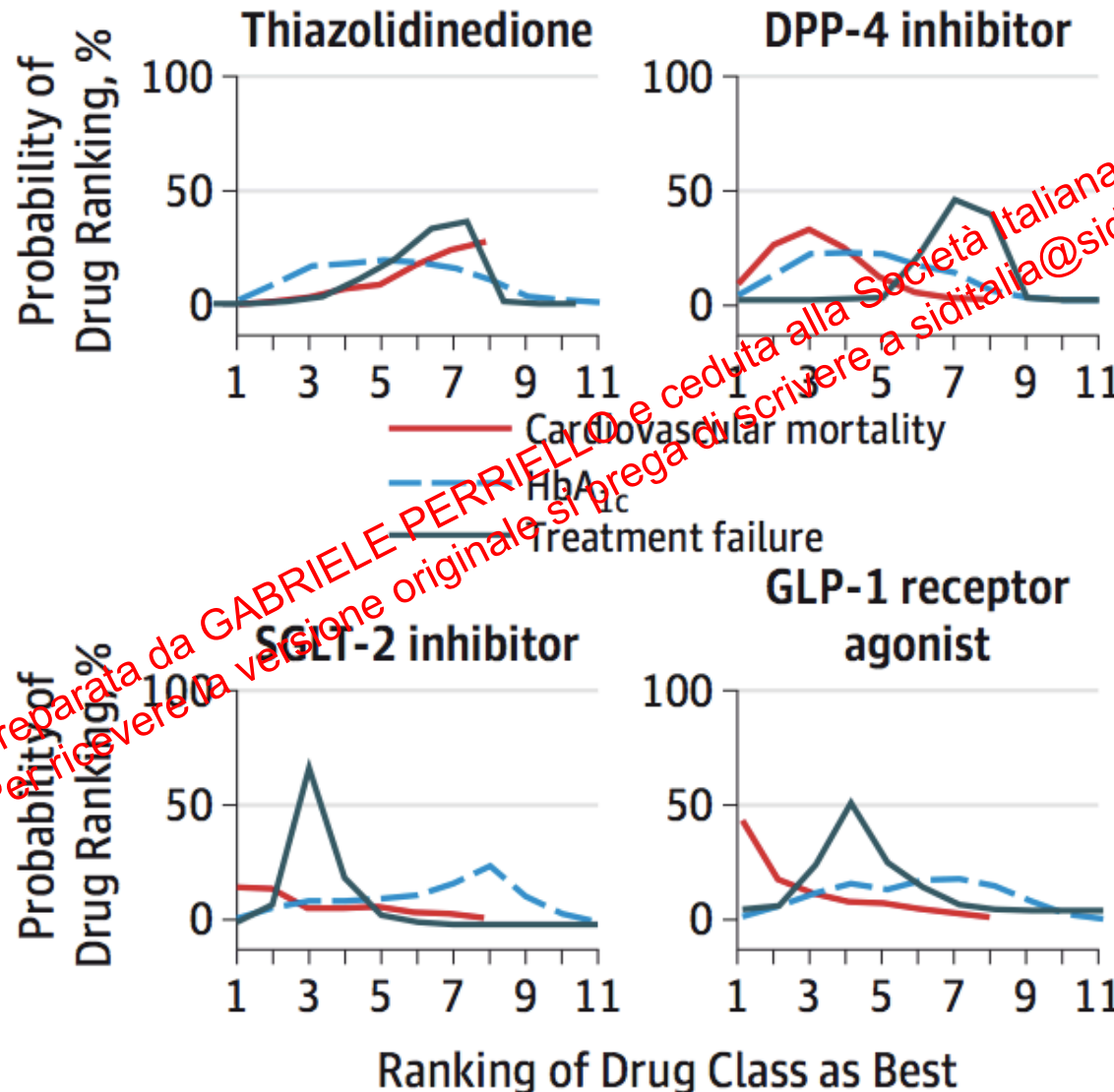
**B** Drugs added to metformin



26 Trials (20 690 patients); 286 157 Patient-months follow-up

# Efficacy rankings for add-on to metformin of different OHA classes in Type 2 Diabetes

26 RCT trials; n= 20690 patients

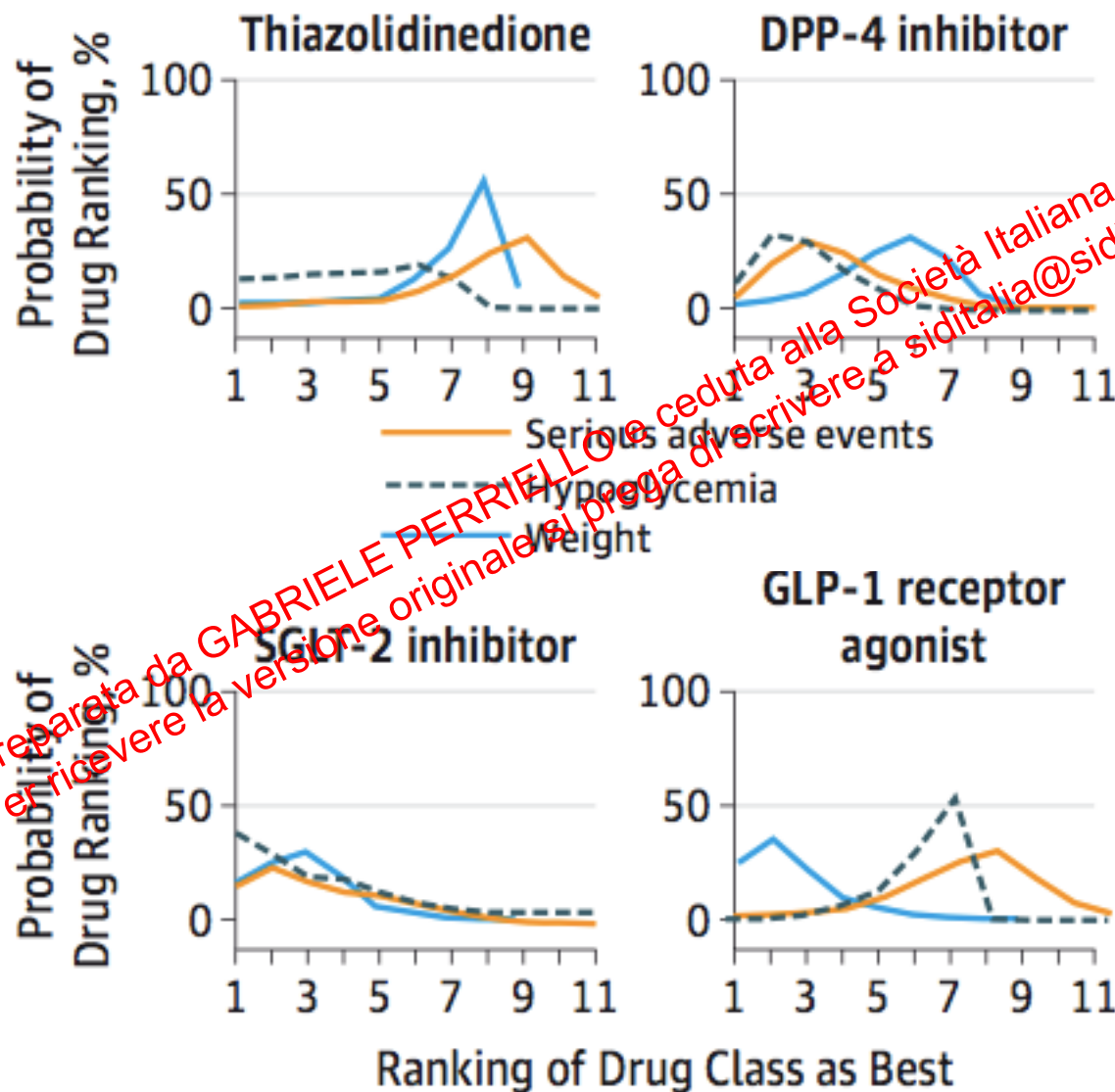


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# Adverse event rankings for add-on to metformin of different OHA classes in Type 2 Diabetes

26 RCT trials; n= 20690 patients



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# DPP-4 Inhibitors vs GLP-1 receptor agonists

| Properties/Effects                    | DPP-4 Inhibitors                                      | GLP-1 Analogues                                                 |
|---------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------|
| ↑ Glucose-dependent insulin secretion | Yes                                                   | Yes                                                             |
| ↓ Glucagon secretion                  | Yes                                                   | Yes                                                             |
| Effect on incretins                   | Endogenous incretins enhanced to physiological levels | Endogenous GLP-1: Possible Immune response (antibody formation) |
| Effect on body weight                 | Weight neutral                                        | Body weight decreased                                           |
| Inhibition of gastric emptying        | Marginal                                              | Yes                                                             |
| Hypoglycaemia                         | No                                                    | No                                                              |
| Side Effects                          | No nausea, vomiting                                   | Reported nausea, vomiting                                       |
| Administration                        | Oral                                                  | Subcutaneous                                                    |

## DIAGNOSIS OF TYPE 2 DIABETES IN OLDER ADULTS

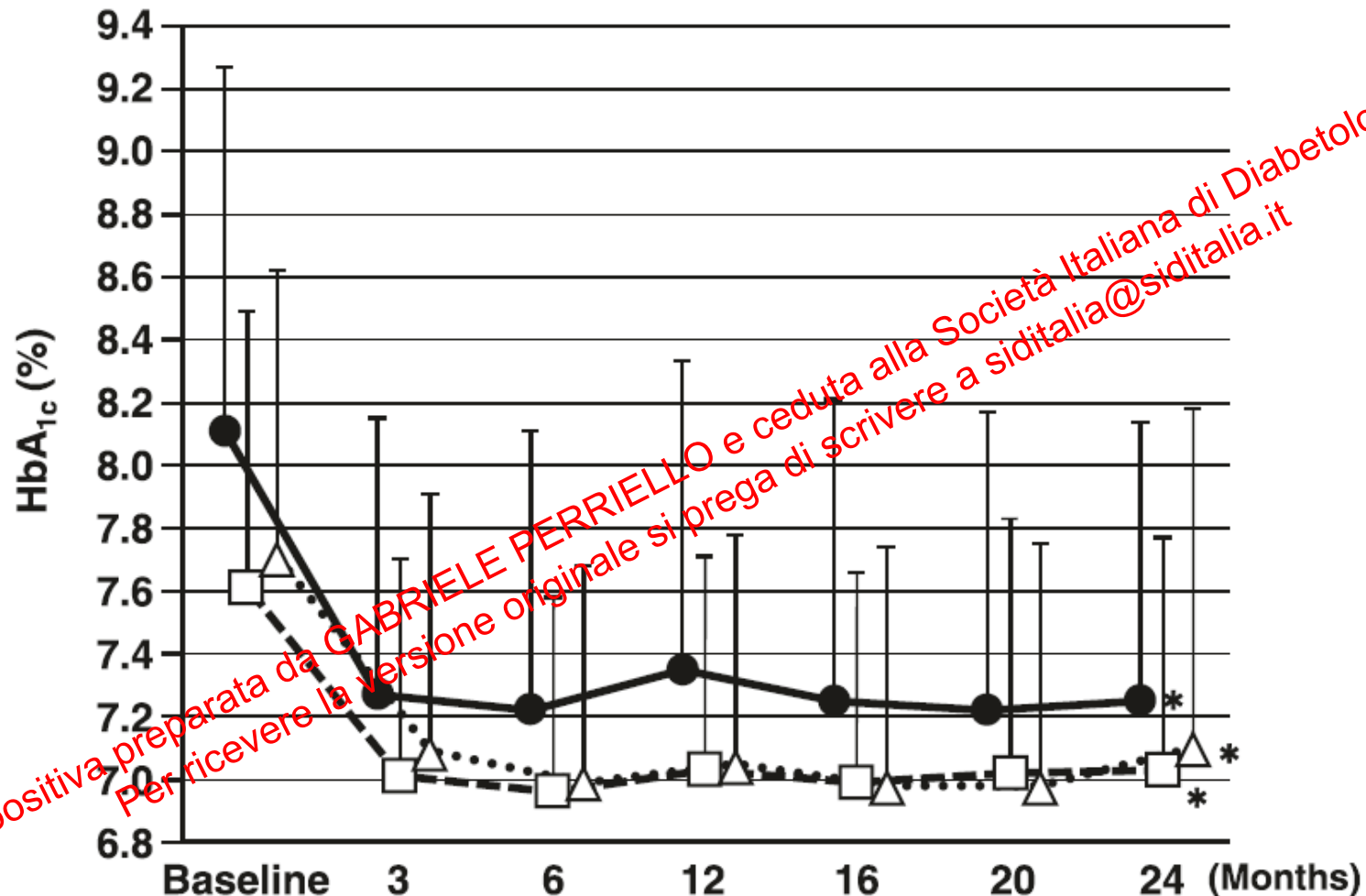


Personalized antihyperglycemic therapy  
according to patient characteristics



| Class/drug       | Risk of Hypoglycemia | Notes                                                                                                   | Contraindications, major side effects and warnings                                                                                                                                                                                                     |
|------------------|----------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DPP-4 inhibitors | No                   | <ul style="list-style-type: none"><li>- No interactions</li><li>- No HF risk with sitagliptin</li></ul> | <ul style="list-style-type: none"><li>- Increased level of hepatic enzymes (linagliptin)</li><li>- Potential risk of pancreatitis (saxagliptin)</li><li>- Potential slight increased risk for heart failure with saxagliptin and alogliptin;</li></ul> |

# Two-year assessment of the efficacy of sitagliptin in elderly patients with type 2 diabetes



—●— <65 years (n=405)  
- -□- - 65-74 years (n=276)  
...△... ≥75 years (n=119)

\* : p<0.05 (ANOVA vs. baseline)

# Why prefer DPP4-i in add-on to metformin

- Synergistic effects on GLP-1 activity
- As effective as all other OHAs
- Greater effects on PPG vs SGLT2i/TZD
- Long-term efficacy
- No hypos & weight neutral (vs SU/TZD)
- Cardiovascular safety (neutral)
- Better tolerability/compliance vs GLP1-Ras
- First choice (sitagliptin) in elderly patients

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**Grazie per la  
vostra attenzione**

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