Gestione del rischio globale del

# diabetico di tipo 2:

## *un ruolo per i DPP4?*



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

Cristina Bianchi, MD, PhD

U.O. Malattie Metaboliche e Diabetologia

Azienda Ospedaliero-Universitaria Pisana

*Milano, 9 Novembre 2019*

# *Dichiarazione Conflitto d'Interessi*

La sottoscritta Dott.ssa Cristina Bianchi

DICHIARA

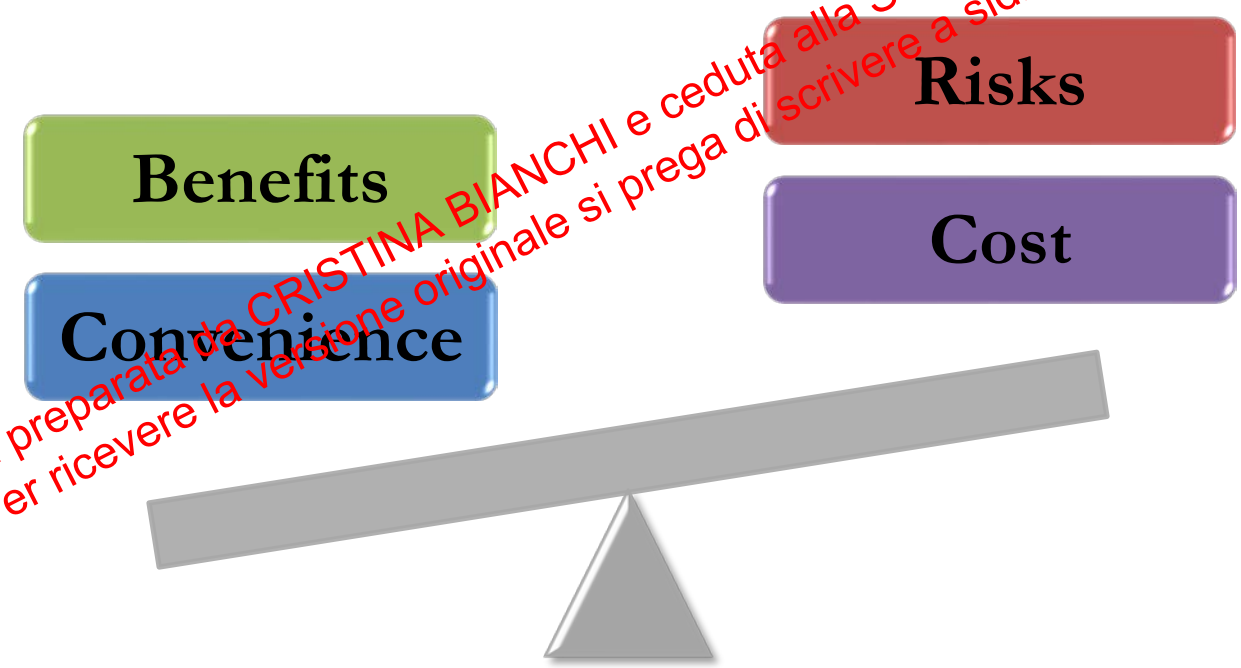
di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Roche Diagnostics



Cristina Bianchi, MD PhD

# Balancing risks and benefits



# Evaluating the benefits…

**Hard outcomes**

- Mortality benefit
- Morbidity benefit

**Surrogate outcomes**
(clinically rilevant?)

- HbA1c
- Body weight
- Lipid profile
- Cardiovascular risk factors

# DPP-4 inhibitors and MACE

| | EXAMINE | SAVOR/TIMI | TECOS | CARMELINA |
|---|---|---|---|---|
| Drug | Alogliptin | Saxagliptin | Sitagliptin | Linagliptin |
| Completion | 2013 | 2013 | 2015 | 2018 |
| Subjects, n | 5,380 | 16,492 | 14,671 | 6,980 |
| Study, years | 1.5 | 2.1 | 3.0 | 2.2 |
| DD, years | 7.3 | 10.3 | 11.6 | 14.7 |
| HbA1c, % | 8.0 | 8.0 | 7.2 | 7.9 |
| CVD, % | 100 | 79 | 74 | 90 |
| MACE drug vs placebo<br>HR (95%CI) | 11.3% vs 11.8%<br>0.95<br>(0.81-1.13) | 7.4% vs 7.4%<br>1.00<br>(0.90-1.12) | 11.4% vs 11.6%<br>0.99<br>(0.89-1.09) | 12.4% vs 12.1%<br>1.04<br>(0.90-1.19) |
| Meta-analysis | 10.0% vs 10.1%; 0.99 (0.93-1.06) | | | |



Alfayez OM et al., Canadian Journal of Diabetes, 43: 538-545, 2019

# DPP-4 inhibitors and HF

| | EXAMINE | SAVOR/TIMI | TECOS | CARMELINA |
|---|---|---|---|---|
| **Drug** | Alogliptin | Saxagliptin | Sitagliptin | Linagliptin |
| **Completion** | 2013 | 2013 | 2015 | 2018 |
| **Subjects, n** | 5,380 | 16,492 | 14,671 | 6,980 |
| **Study, years** | 1.5 | 2.1 | 3.0 | 2.2 |
| **DD, years** | 7.3 | 10.3 | 11.6 | 14.7 |
| **HbA1c, %** | 8.0 | 8.0 | 7.2 | 7.9 |
| **HF, %** | 28 | 13 | 18 | 27 |
| **hHF drug vs placebo HR (95%CI)** | 3.1% vs 2.9%<br>1.19<br>(0.90-1.58) | 3.5% vs 2.8%<br>**1.27**<br>(1.06-1.51) | 3.1% vs 3.1%<br>1.00<br>(0.83-1.20) | 6.0% vs 6.5%<br>0.92<br>(0.76-1.11) |
| **Meta-analysis*** | 3.8% vs 3.6%; 1.05 (0.87-1.28) | | | |



Alfayez OM et al., Canadian Journal of Diabetes, 43: 538-545, 2019

# Summary of CVOTs with DPP4 inhibitors

| | SAVOR-TIMI 53[1] | EXAMINE[2] | TECOS[3] | CARMELINA®[5] | CAROLINA®[4] |
|---|---|---|---|---|---|
| **Intervention** | Saxagliptin/ placebo | Alogliptin/ placebo | Sitagliptin/ placebo | Linagliptin/ placebo | Linagliptin/ glimepiride |
| **Main inclusion criteria** | History of or multiple risk factors for CVD | ACS within 15–90 days before randomisation | CVD | High risk of CV events (e.g. albuminuria, prior CVD) | ≥ 2 specified traditional CV risk factors or manifest CVD |
| **No. of patients** | 16,492 | 5380 | 14,671 | 8300 | 6042 |
| **Primary outcome** | 3P-MACE | 3P-MACE | 4P-MACE | 4P-MACE | 4P-MACE |
| **Median follow-up** | 2.1 years | 1.5 years | 3.0 years | 2.2 years | 6.3 years |
| **Mean age** | 65 years | 61 years | 65 years | 66 years | 64 years |
| **Diabetes duration** | 10.3 years | 7.2 years | 11.6 years | 15 years | 6.3 years |
| **$HbA_{1c}$** | 8.0% | 8.0% | 7.2% | 8.0% | 7.2% |
| **Main Results** | HR 1.00 (95% CI 0.89–1.12) | HR 0.96 (upper boundary of the one-sided repeated CI, 1.16) | HR 0.98 (95% CI, 0.89–1.08) | HR 1.02 (95% CI 0.89-1.17) | HR 0.98 (95% CI 0.84-1.14) |

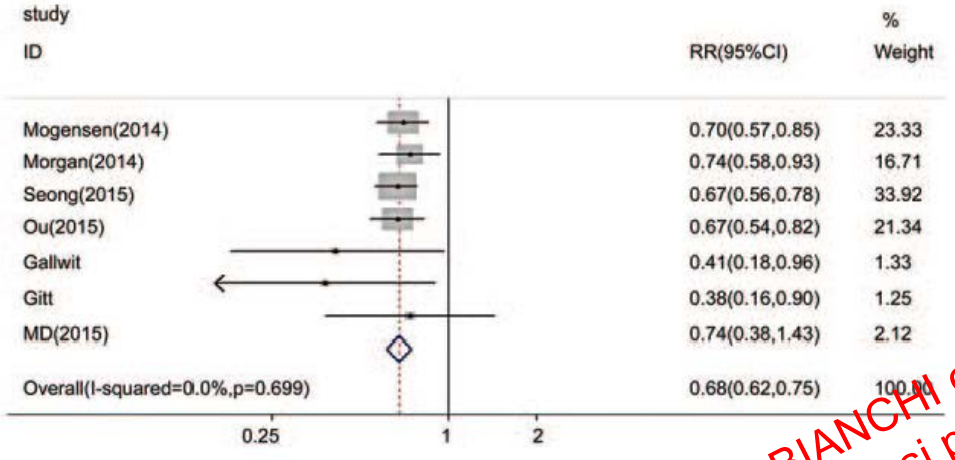


*Ongoing.

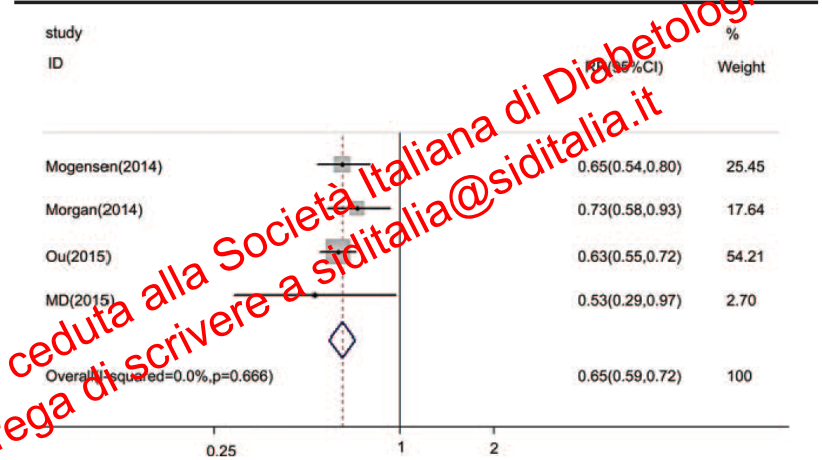
1. Scirica et al. N Engl J Med 2013;369:1317–26. 2. White et al. N Engl J Med 2013;369:1327–35. 3. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501352. 4. Marx et al. Diabetes Vasc Dis Res 2015;12:164–74. 5. NCT01897532. 6. Scirica et al. Am Heart J 2011;162:818–25.e6. 7. Data on file (BI trial no. 1218.22 trial protocol). 8. NCT01243424.

# Sulphonylurea compared to DPP-4 inhibitors: mortality and cardiovascular morbidity

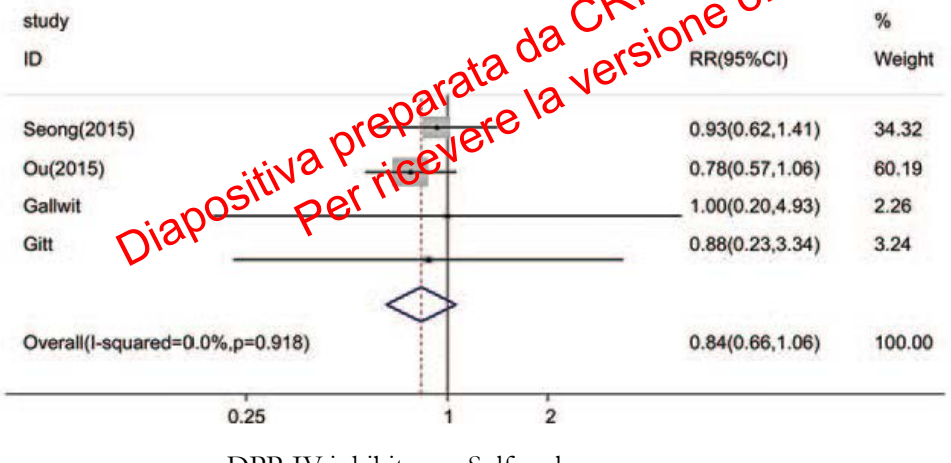
*Non-fatal CV events*



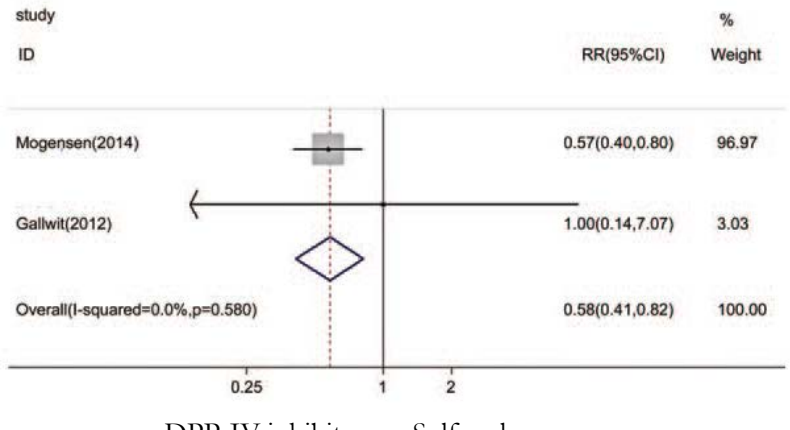

*CV mortality*




*Fatal CV events*




*All-cause mortality*

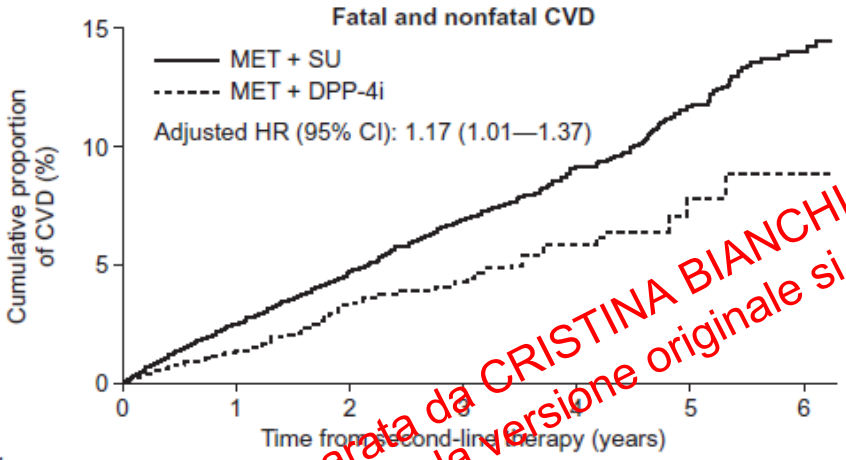





Wang F. Medicine 2017; 96:36

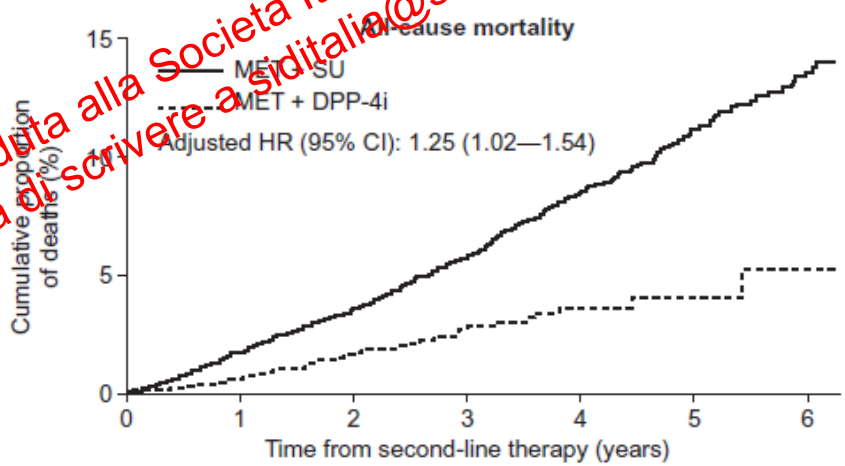
# Sulphonylurea compared to DPP-4 inhibitors: mortality and cardiovascular morbidity

52,760 patients; 77% started metformin + SU and 23% metformin + DPP-4i




*n* at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MET + SU, 40,736 | 19,384 | 9391 | 4781 | 2312 | 1116 | 442 |
| MET + DPP-4i, 12,024 | 4729 | 1878 | 795 | 338 | 128 | 24 |



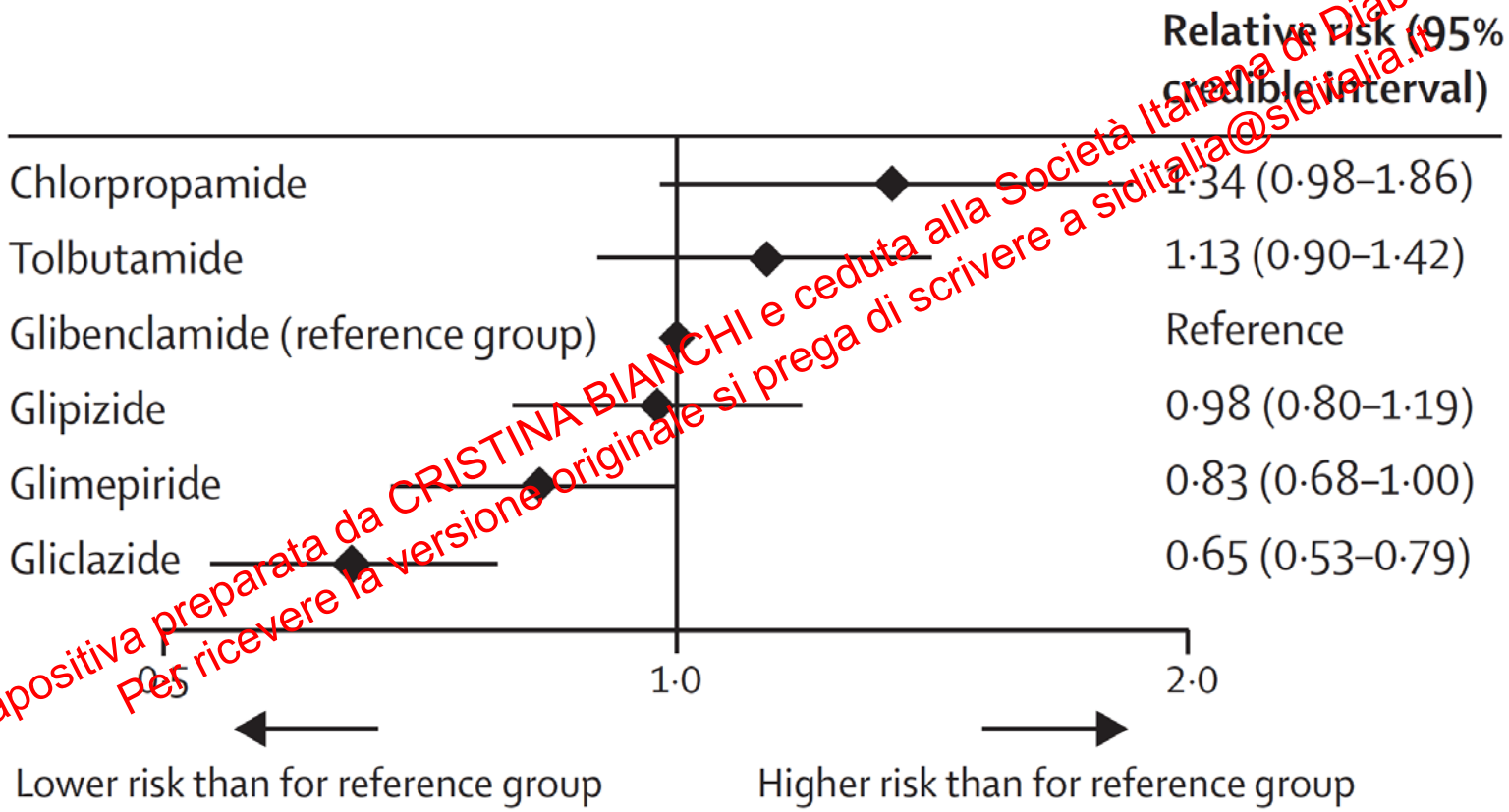

*n* at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MET + SU, 40,736 | 19,605 | 9656 | 4954 | 2407 | 1172 | 447 |
| MET + DPP-4i, 12,024 | 4767 | 1924 | 817 | 345 | 132 | 27 |



Eriksson JW. Diabetes Res Clin Pract 2016;117:39-47

# Mortality Risk among Sulfonylureas



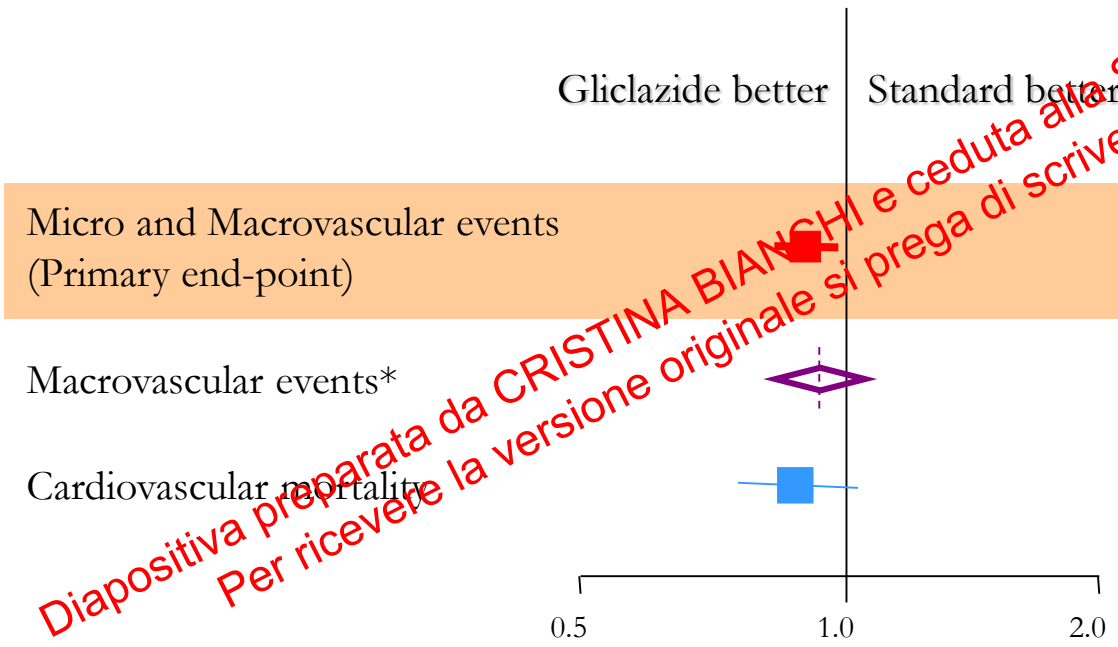



Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 18 studies.

Simpson SH et al Lancet Diabetes Endocrinol 2015;3:43–51

# Intensive blood glucose control with gliclazide and vascular outcomes

*The ADVANCE study*




| | Relative risk | p |
|---|---|---|
| Micro and Macrovascular events (Primary end-point) | -10% | 0.013 |
| Macrovascular events* | -6% | 0.32 |
| Cardiovascular mortality | -12% | 0.12 |

* Non-fatal stroke, Non-fatal IM, CV mortality

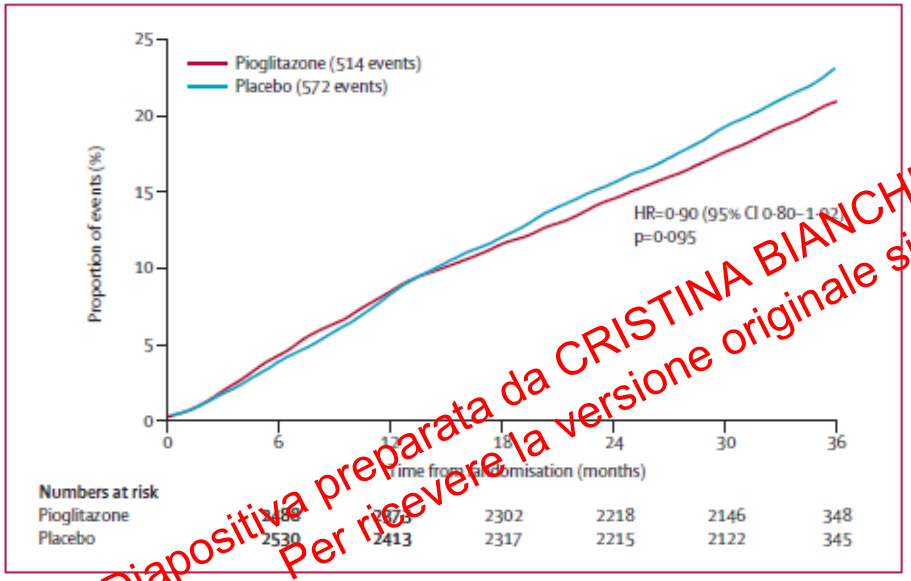


The ADVANCE Collaborative Group. N Engl J Med 2008; 358: 2560-2572

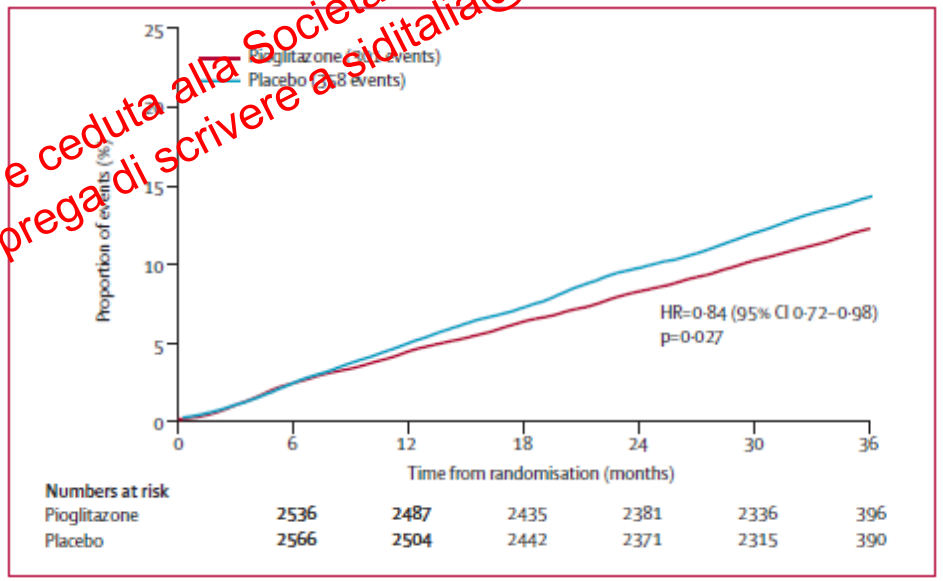
# Pioglitazone and secondary prevention of CV events in patients with type 2 diabetes

## *- The PROactive Study -*

*Primary endpoint**




*Secondary endpoint***






*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

**Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

Dormandy JA. Lancet 2005; 366: 1279–89

# GLP-1 Ras and MACE

| | ELIXA | LEADER | SUSTAIN-6 | EXSCEL | HARMONY | REWIND | PIONNER-6 |
|---|---|---|---|---|---|---|---|
| **Drug tested** | Lixisentide | Liraglutide | Semaglutide | Exenatide OW | Albiglutide | Dulaglutide | Semaglutide |
| **Dose** | 20 µg/day | 1.8 mg/day | 0.5-1 mg/wk | 2 mg/wk | 30-50mg/wk | 1.5 mg/wk | 14 mg/day (oral) |
| **N** | 6068 | 9340 | 3297 | 14752 | 9463 | 9901 | 3183 |
| **Women** | 31% | 36% | 39% | 38% | 31% | 46% | 32% |
| **Age** | 60 years | 64 years | 65 years | 62 years | 64 years | 66 years | 66 years |
| **BMI** | 30 Kg/m$^2$ | 33 Kg/m$^2$ | 31 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ |
| **HbA1c** | 7.7% | 8.7% | 8.7% | 8.0% | 8.7% | 7.3% | 8.2% |
| **Prior CVD** | 100% | 81% | 59% | 73% | 100% | 31% | 85% |
| **Follow-up** | 2.1 years | 3.8 years | 2.1 years | 3.2 years | 1.6 years | 5.4 years | 1.3 years |
| **MACE drug vs placebo HR (95%CI)** | 1.02 (0.89-1.17) | **0.87** (0.78-0.97) | **0.74** (0.58-0.95) | 0.91 (0.83-1.00) | **0.78** (0.68-0.90) | **0·88** (0·79–0·99) | 0.79 (0.57-1.11) |
| **Meta-analysis** | **0.88** (0.82-0.94) | | | | | | |



Kristensen SL. Lancet Diabetes Endocrinol 2019

# SGLT-2 inhibitors and MACE

| | EMPA-REG | CANVAS | DECLARE | CREDENCE |
|---|---|---|---|---|
| **Drug** | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin |
| **Completion** | 2015 | 2017 | 2018 | 2019 |
| **Subjects, n** | 7,020 | 10,142 | 17,160 | 4,401 |
| **Study, years** | 3.1 | 2.4 | 4.2 | 2.6 |
| **DD, years** | -- | 13.5 | 11.0 | 15.8 |
| **HbA1c, %** | 8.1 | 8.2 | 8.3 | 8.3 |
| **CVD, %** | 100 | 65.6 | 40.6 | 50.5 |
| **MACE drug vs placebo HR (95%CI)** | 37.4% vs 43.9%<br>**0.86**<br>(0.74-0.99) | 26.9% vs 31.5%<br>**0.86**<br>(0.75-0.97) | 22.6% vs 24.2%<br>0.93<br>(0.84-1.03) | 38.7% vs 48.7%<br>**0.80**<br>(0.67-0.95) |
| **Meta-analysis*** | **0.89** (0.83-0.96) | | | |



* Excluding CREDENCE

Bell D et al. Diabetes Obes Metab, 21: 1277-1290, 2019, updated

# SGLT-2 inhibitors and Heart failure

| | EMPA-REG | CANVAS | DECLARE | CREDENCE |
|---|---|---|---|---|
| **Drug** | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin |
| **Completion** | 2015 | 2017 | 2018 | 2019 |
| **Subjects, n** | 7,020 | 10,142 | 17,160 | 4,401 |
| **Study, years** | 3.1 | 2.4 | 4.2 | 2.6 |
| **DD, years** | -- | 13.5 | 11.0 | 15.8 |
| **HbA1c, %** | 8.1 | 8.2 | 8.3 | 8.3 |
| **HF, %** | 10.1 | 14.4 | 10 | 14.8 |
| **hHF drug vs placebo HR (95%CI)** | 9.4% vs 14.5%<br>**0.65**<br>(0.50-0.85) | 5.5% vs 8.7%<br>**0.67**<br>(0.52-0.87) | 6.2% vs 8.5%<br>**0.73**<br>(0.61-0.88) | 15.7% vs 25.3%<br>**0.61**<br>(0.47-0.80) |
| **Meta-analysis*** | **0.69** (0.61-0.79) | | | |



* Excluding CREDENCE

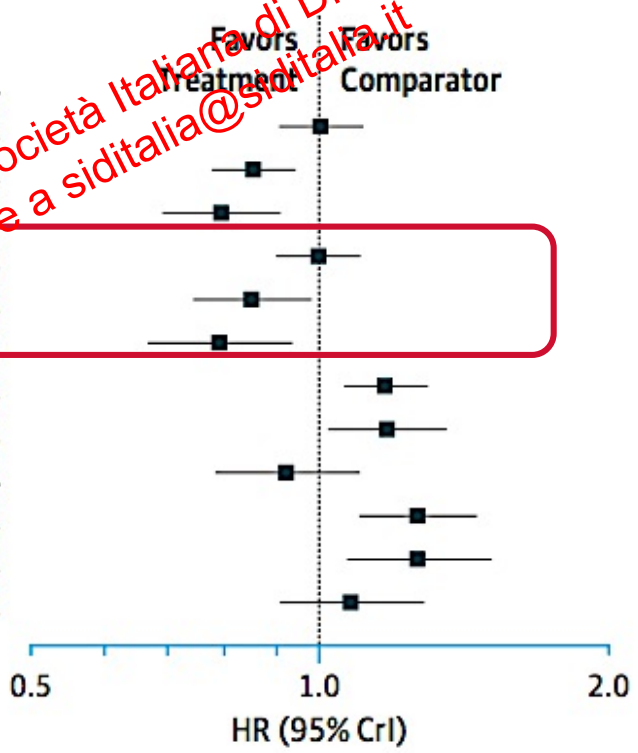
Bell D et al. Diabetes Obes Metab, 21: 1277-1290, 2019, updated

# Use of SGLT2-i, GLP1-RA, and DPP4-i and all cause mortality in patients with type 2 diabetes

236 trials randomizing 176,310 participants: **CV mortality, 56 trials**

| Treatment | Comparator | Absolute RD (95% CrI), % | HR (95% CrI) |
|---|---|---|---|
| DPP-4 inhibitor | vs Control | 0.0 (-0.3 to 0.4) | 1.00 (0.91 to 1.11) |
| GLP-1 agonist | | -0.5 (-0.8 to -0.1) | 0.85 (0.77 to 0.94) |
| SGLT-2 inhibitor | | -0.8 (-1.1 to -0.3) | 0.79 (0.69 to 0.91) |
| Control | vs DPP-4 inhibitor | 0.0 (-0.3 to 0.3) | 1.00 (0.90 to 1.10) |
| GLP-1 agonist | | -0.5 (-0.8 to -0.1) | 0.85 (0.74 to 0.98) |
| SGLT-2 inhibitor | | -0.7 (-1.1 to -0.2) | 0.79 (0.66 to 0.94) |
| Control | vs GLP-1 agonist | 0.5 (0.2 to 0.9) | 1.17 (1.06 to 1.30) |
| DPP-4 inhibitor | | 0.5 (0.1 to 1.0) | 1.18 (1.02 to 1.36) |
| SGLT-2 inhibitor | | -0.2 (-0.7 to 0.3) | 0.93 (0.78 to 1.10) |
| Control | vs SGLT-2 inhibitor | 0.8 (0.3 to 1.3) | 1.27 (1.10 to 1.46) |
| DPP-4 inhibitor | | 0.8 (0.2 to 1.5) | 1.27 (1.07 to 1.51) |
| GLP-1 agonist | | 0.2 (-0.3 to 0.8) | 1.08 (0.91 to 1.29) |

| Treatment | No. of Trials | No. With Events (%) | Total No. of Patients |
|---|---|---|---|
| Control | 50 | 1833 (3.6) | 50869 |
| DPP-4 inhibitor | 27 | 763 (3.1) | 24519 |
| GLP-1 agonist | 19 | 704 (3.0) | 23554 |
| SGLT-2 inhibitor | 19 | 468 (2.5) | 18407 |





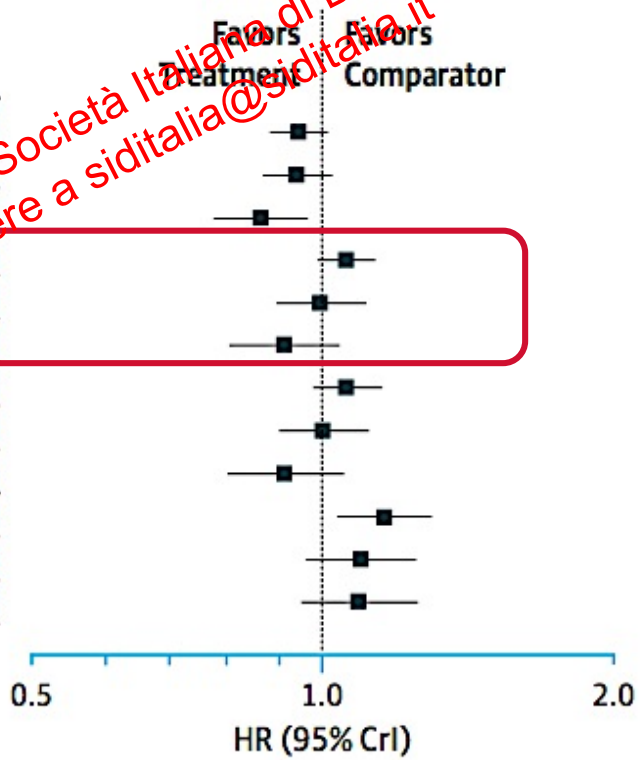

Zheng SL. JAMA 2018, 319: 1580-1591

# Use of SGLT2-i, GLP1-RA, and DPP4-i and myocardial infarction in patients with type 2 diabetes

236 trials randomizing 176,310 participants: **all myocardial infarction, 97 trials**

| Treatment | Comparator | Absolute RD (95% CrI), % | HR (95% CrI) |
|---|---|---|---|
| DPP-4 inhibitor | vs Control | -0.2 (-0.5 to 0.0) | 0.94 (0.88 to 1.01) |
| GLP-1 agonist | | -0.2 (-0.5 to 0.1) | 0.94 (0.87 to 1.02) |
| SGLT-2 inhibitor | | -0.6 (-0.9 to -0.1) | 0.86 (0.77 to 0.97) |
| Control | vs DPP-4 inhibitor | 0.1 (0.0 to 0.3) | 1.06 (0.99 to 1.13) |
| GLP-1 agonist | | 0.0 (-0.2 to 0.2) | 1.00 (0.90 to 1.11) |
| SGLT-2 inhibitor | | -0.2 (-0.4 to 0.1) | 0.91 (0.80 to 1.04) |
| Control | vs GLP-1 agonist | 0.3 (-0.1 to 0.6) | 1.06 (0.98 to 1.15) |
| DPP-4 inhibitor | | 0.0 (-0.4 to 0.3) | 1.00 (0.90 to 1.12) |
| SGLT-2 inhibitor | | -0.3 (-0.9 to 0.2) | 0.92 (0.80 to 1.05) |
| Control | vs SGLT-2 inhibitor | 0.4 (0.1 to 0.8) | 1.16 (1.04 to 1.30) |
| DPP-4 inhibitor | | 0.3 (-0.1 to 0.6) | 1.10 (0.96 to 1.25) |
| GLP-1 agonist | | 0.2 (-0.1 to 0.6) | 1.09 (0.95 to 1.25) |

| Treatment | No. of Trials | No. With Events (%) | Total No. of Patients |
|---|---|---|---|
| Control | 87 | 2133 (4.0) | 53099 |
| DPP-4 inhibitor | 50 | 616 (2.2) | 27462 |
| GLP-1 agonist | 30 | 1140 (4.3) | 26400 |
| SGLT-2 inhibitor | 32 | 505 (2.5) | 19958 |





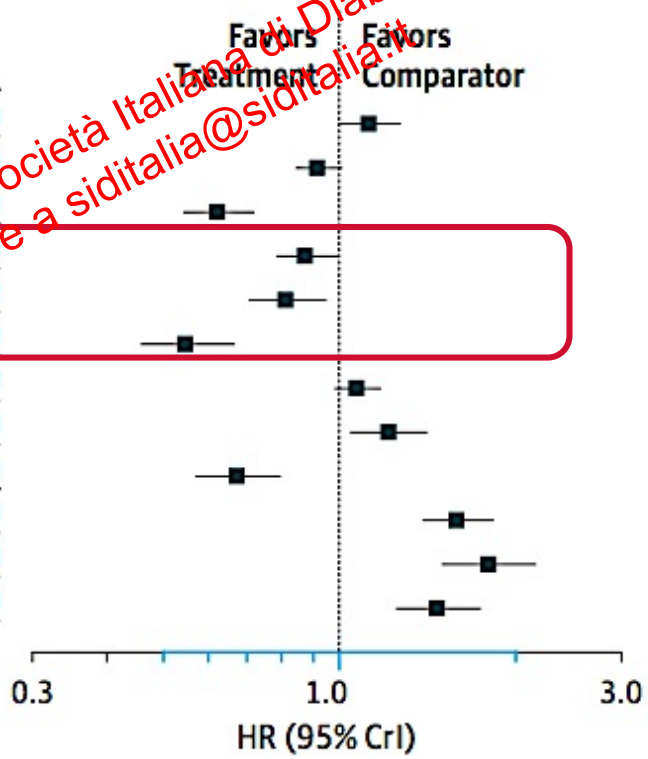

Zheng SL. JAMA 2018, 319: 1580-1591

# Use of SGLT2-i, GLP1-RA, and DPP4-i and heart failure in patients with type 2 diabetes

236 trials randomizing 176,310 participants: heart failure, 58 trials

| Treatment | Comparator | Absolute RD (95% CrI), % | HR (95% CrI) |
|---|---|---|---|
| DPP-4 inhibitor | vs Control | 0.4 (0.0 to 0.8) | 1.13 (1.00 to 1.28) |
| GLP-1 agonist | | -0.2 (-0.5 to 0.1) | 0.93 (0.84 to 1.02) |
| SGLT-2 inhibitor | | -1.1 (-1.3 to -0.8) | 0.62 (0.54 to 0.72) |
| Control | vs DPP-4 inhibitor | -0.3 (-0.5 to 0.0) | 0.88 (0.78 to 1.00) |
| GLP-1 agonist | | -0.4 (-0.7 to -0.1) | 0.82 (0.70 to 0.95) |
| SGLT-2 inhibitor | | -1.1 (-1.3 to -0.8) | 0.55 (0.46 to 0.67) |
| Control | vs GLP-1 agonist | 0.2 (-0.1 to 0.5) | 1.08 (0.98 to 1.18) |
| DPP-4 inhibitor | | 0.6 (0.1 to 1.1) | 1.22 (1.05 to 1.42) |
| SGLT-2 inhibitor | | -0.9 (-1.2 to -0.5) | 0.67 (0.57 to 0.80) |
| Control | vs SGLT-2 inhibitor | 1.0 (0.6 to 1.4) | 1.60 (1.39 to 1.84) |
| DPP-4 inhibitor | | 1.3 (0.8 to 2.0) | 1.81 (1.50 to 2.18) |
| GLP-1 agonist | | 0.8 (0.4 to 1.3) | 1.48 (1.25 to 1.76) |

| Treatment | No. of Trials | No. With Events (%) | Total No. of Patients |
|---|---|---|---|
| Control | 55 | 1370 (2.8) | 48362 |
| DPP-4 inhibitor | 24 | 544 (2.4) | 22327 |
| GLP-1 agonist | 21 | 638 (2.7) | 23363 |
| SGLT-2 inhibitor | 19 | 266 (1.7) | 15989 |

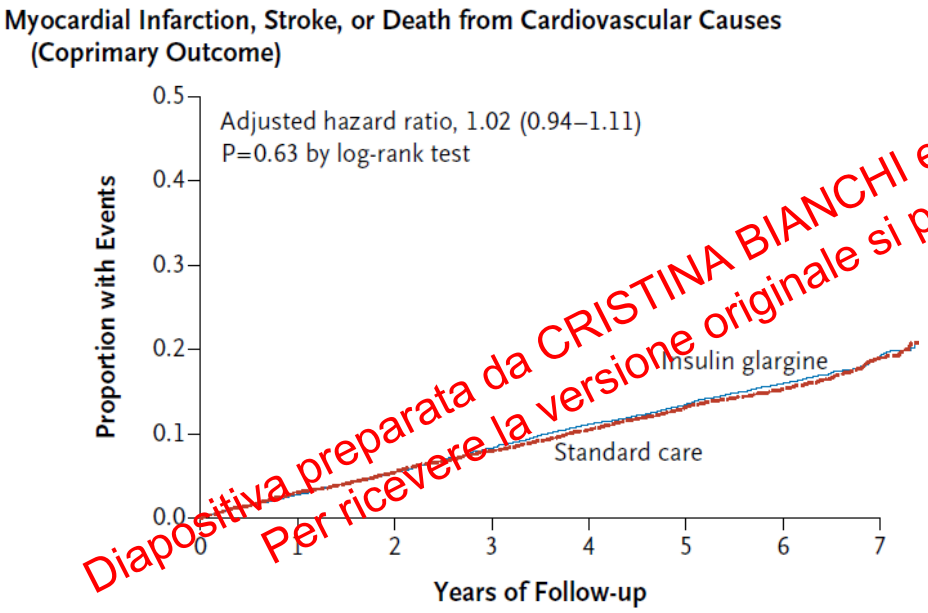




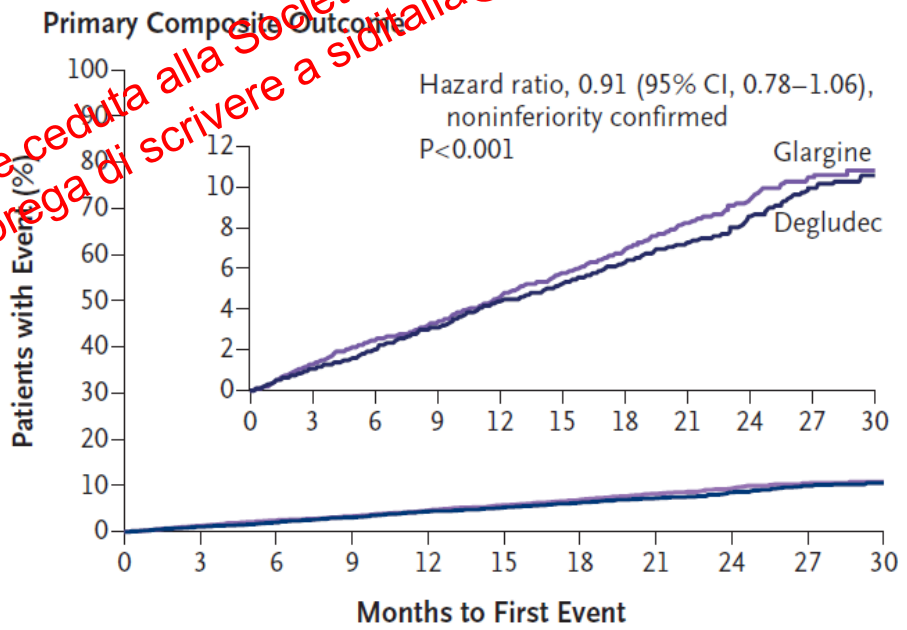

Zheng SL. JAMA 2018, 319: 1580-1591

# Basal Insulin and Cardiovascular outcomes

*ORIGIN Trial*




*DEVOTE Study*

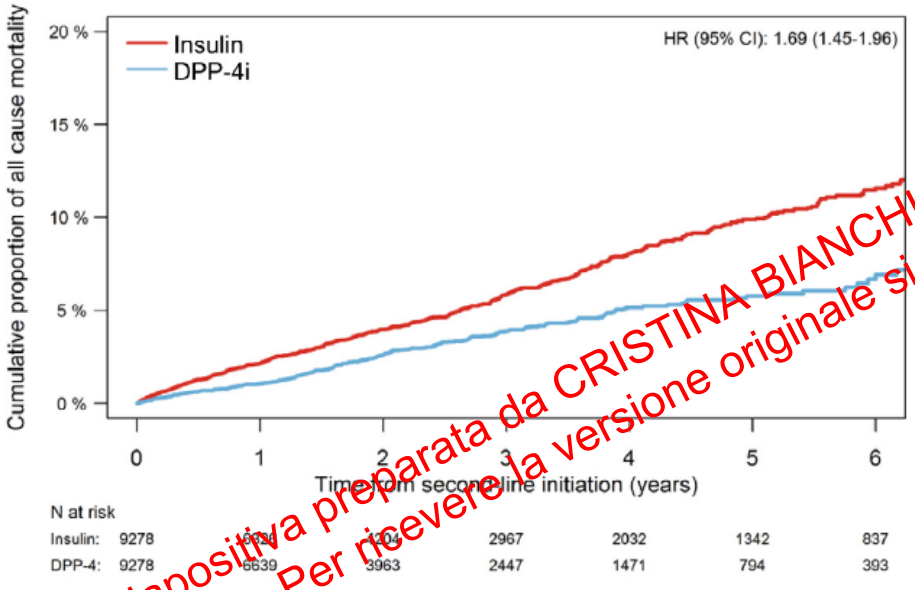


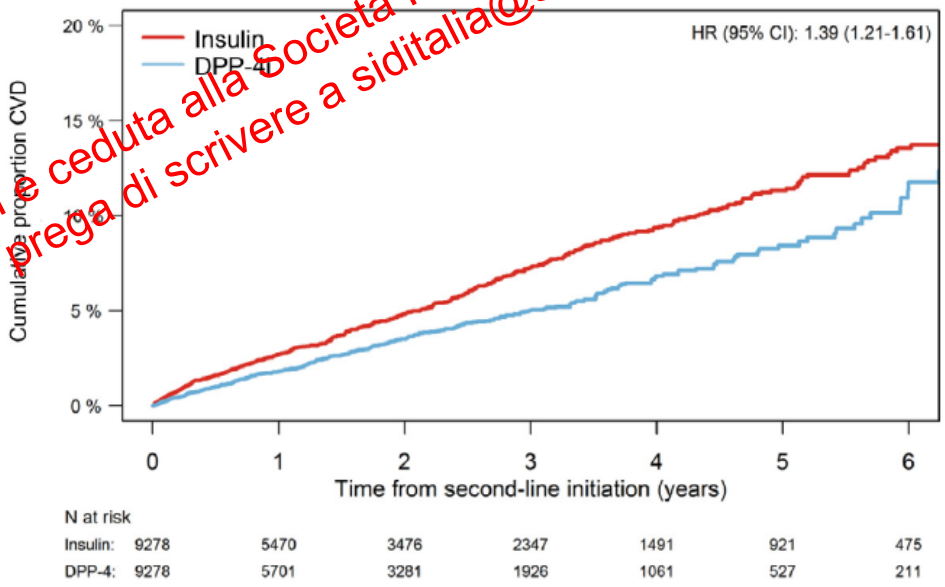



The ORIGIN Trial Investigators. N Engl J Med 2012;367(4):319-28; Marso SP. N Engl J Med 2017;377(8):723-732

# Insulin compared to DPP-4 inhibitors: mortality and cardiovascular morbidity

27,767 metformin-treated patients, 55.7% started insulin and 44.3% a DPP-4i





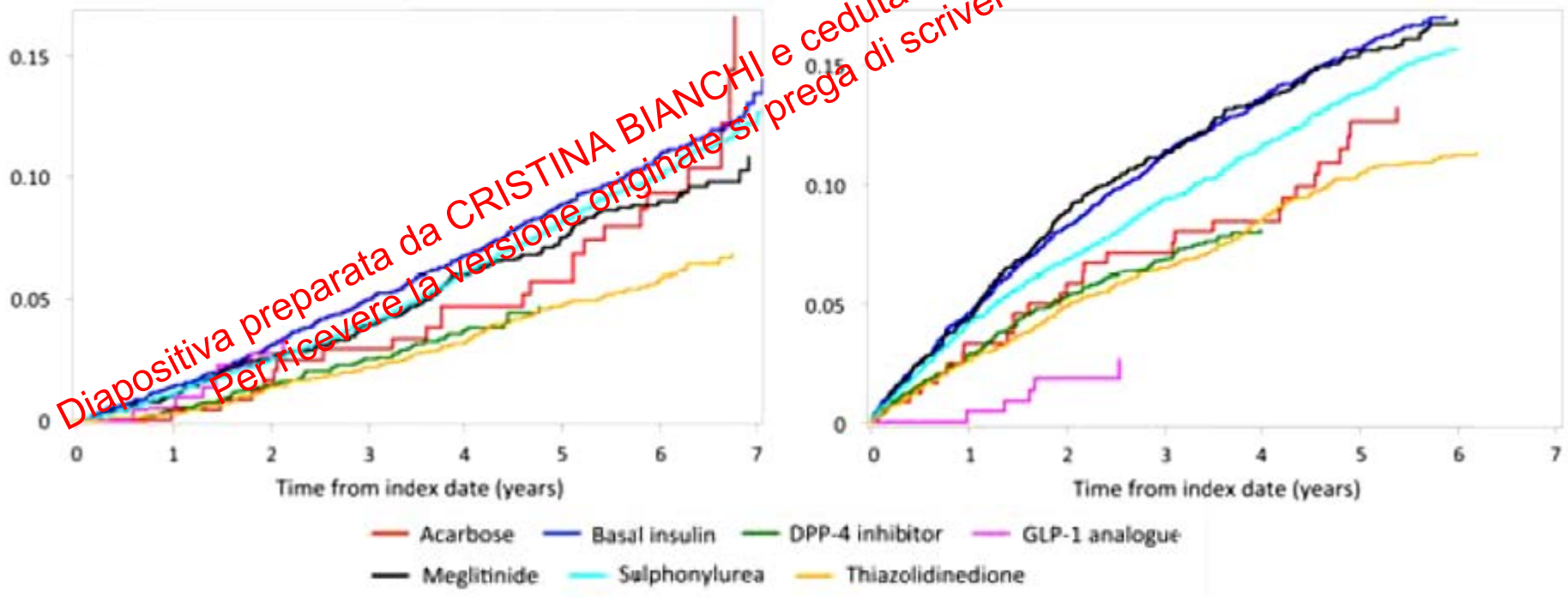

Nyström T. Diabetes Res Clin Pract 2017;123:199-208

# Cardiovascular safety of glucose-lowering agents as add-on to Metformin

20 422 patients included in the study, 43% started on second-line treatment with sulphonylurea (SU), 21% basal insulin, 12% thiazolidinedione (TZD), 11% meglitinide, 10% dipeptidyl peptidase-4 (DPP-4) inhibitor, 1% glucagon-like peptide-1 (GLP-1) receptor agonist and 1% acarbose

*All-cause mortality*

*Cardiovascular disease*






Ekström N. Diabetes Obes Metab 2016;18(10):990-8

# Association of second-line antidiabetic drugs with Cardiovascular events

Retrospective cohort study among 132 737 insured adults with type 2 diabetes who started therapy with a second-line antidiabetic drugs after taking either metformin

| | Composite Cardiovascular Outcome[b] | | Individual Cardiovascular Outcomes, HR (95% CI) | | | |
|---|---|---|---|---|---|---|
| ADM Class | No. of Events (%) | HR (95% CI) | Congestive Heart Failure | Stroke | Ischemic Heart Disease | Peripheral Artery Disease |
| DPP-4 inhibitors | 543 (1.9) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| GLP-1 receptor agonists | 104 (0.9) | 0.78 (0.63-0.96) | 0.65 (0.42-1.02) | 0.65 (0.44-0.97) | 0.91 (0.67-1.24) | 0.90 (0.42-1.95) |
| SGLT-2 inhibitors | 34 (0.6) | 0.81 (0.57-1.53) | 0.54 (0.24-1.22) | 0.56 (0.26-1.12) | 1.18 (0.74-1.87) | 1.11 (0.33-3.65) |
| TZDs | 132 (1.8) | 0.92 (0.76-1.11) | 0.93 (0.63-1.36) | 0.73 (0.51-1.05) | 0.95 (0.71-1.28) | 1.67 (0.94-2.97) |
| Basal insulin | 721 (4.4) | 2.03 (1.81-2.27) | 2.33 (1.90-2.87) | 1.77 (1.44-2.19) | 1.92 (1.59-2.32) | 2.92 (1.96-4.35) |
| SFUs | 1946 (3.1) | 1.36 (1.23-1.49) | 1.47 (1.23-1.75) | 1.28 (1.08-1.52) | 1.35 (1.16-1.57) | 1.65 (1.16-2.36) |

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio; SFUs, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2; TZDs, thiazolidinediones.

[a] All Cox proportional hazards models adjusted for patient baseline sociodemographic characteristics, hemoglobin $A_{1c}$, cardiovascular risk factors, diabetes complications including prior cardiovascular events, as well as prior use of metformin and cardiovascular medications included in Table 1. Models also adjusted for prescriber and health plan variables included in eTable 3 in the Supplement.

[b] Composite cardiovascular outcome included hospitalization for congestive heart failure, stroke, ischemic heart disease, or peripheral artery disease.



JAMA Netw Open. 2018;1(8):e186125

# SGLT-2 inhibitors and composite renal outcomes

| | EMPA-REG | CANVAS | DECLARE | CREDENCE |
|---|---|---|---|---|
| Drug | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin |
| Completion | 2015 | 2017 | 2018 | 2019 |
| Subjects, n | 7,020 | 10,142 | 17,160 | 4,401 |
| Study, years | 3.1 | 2.4 | 4.2 | 2.6 |
| DD, years | -- | 13.5 | 11.0 | 15.8 |
| HbA1c, % | 8.1 | 8.2 | 8.3 | 8.3 |
| eGFR <60, % | 25.5 | 20.1 | 7.4 | 58.9 |
| m/M, % | 28.7/11.0 | 22.6/7.6 | 23.9/6.9 | --/100 |
| CRO drug vs placebo HR (95%CI) | 1.7% vs 3.1%<br>**0.54**<br>(0.40-0.75) | ---% vs ---%<br>**0.60**<br>(0.47-0.77) | 4.3% vs 5.6%<br>**0.76**<br>(0.67-0.87) | 43.2% vs 61.2%<br>**0.60**<br>(0.47-0.77) |

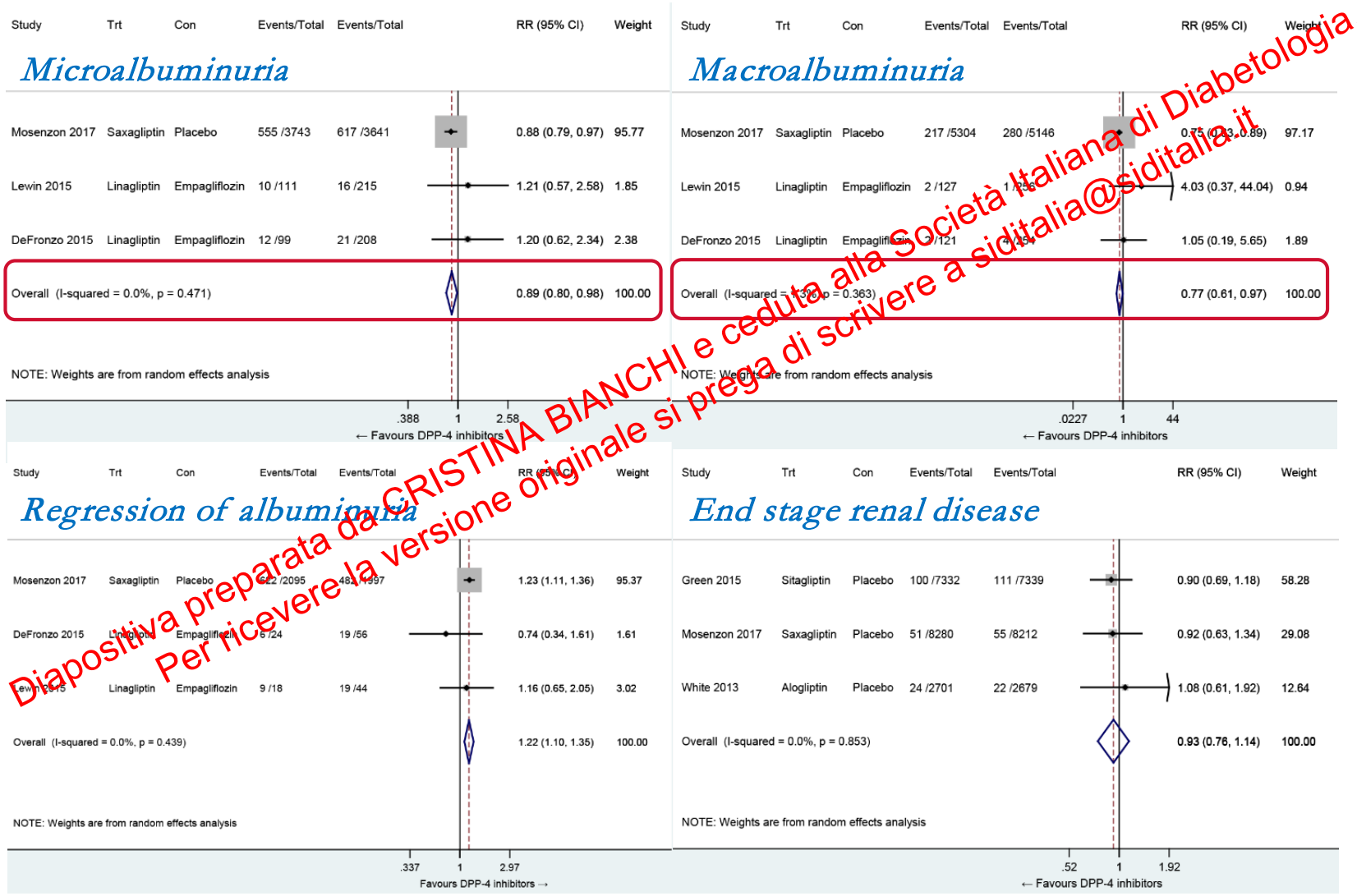
# GLP-1 Ras and composite kidney outcome (including macroalbuminuria)

| | ELIXA | LEADER | SUSTAIN-6 | EXSCEL | HARMONY | REWIND | PIONER-6 |
|---|---|---|---|---|---|---|---|
| **Drug tested** | Lixisentide | Liraglutide | Semaglutide | Exenatide OW | Albiglutide | Dulaglutide | Semaglutide |
| **Dose** | 20 µg/day | 1.8 mg/day | 0.5-1 mg/wk | 2 mg/wk | 30-50mg/wk | 1.5 mg/wk | 14 mg/day (oral) |
| **N** | 6068 | 9340 | 3297 | 14752 | 9463 | 9901 | 3183 |
| **Women** | 31% | 36% | 39% | 38% | 31% | 46% | 32% |
| **Age** | 60 years | 64 years | 65 years | 62 years | 64 years | 66 years | 66 years |
| **BMI** | 30 Kg/m$^2$ | 32 Kg/m$^2$ | 31 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ | 32 Kg/m$^2$ |
| **HbA1c** | 7.7% | 8.7% | 8.7% | 8.0% | 8.7% | 7.3% | 8.2% |
| **eGFR** | 78 | 80 | 80 | 77 | 79 | 75 | 74 |
| **Follow-up** | 2.1 years | 3.8 years | 2.1 years | 3.2 years | 1.6 years | 5.4 years | 1.3 years |
| **Meta-analysis** | **0·83** (0·78–0·89) | | | | | | |



Kristensen SL. Lancet Diabetes Endocrinol 2019

# Effects of DPP-4 Inhibitors on Renal Outcomes






Bae JH. Endocrinol Metab 2019;34:80-92

# Evaluating the benefits…

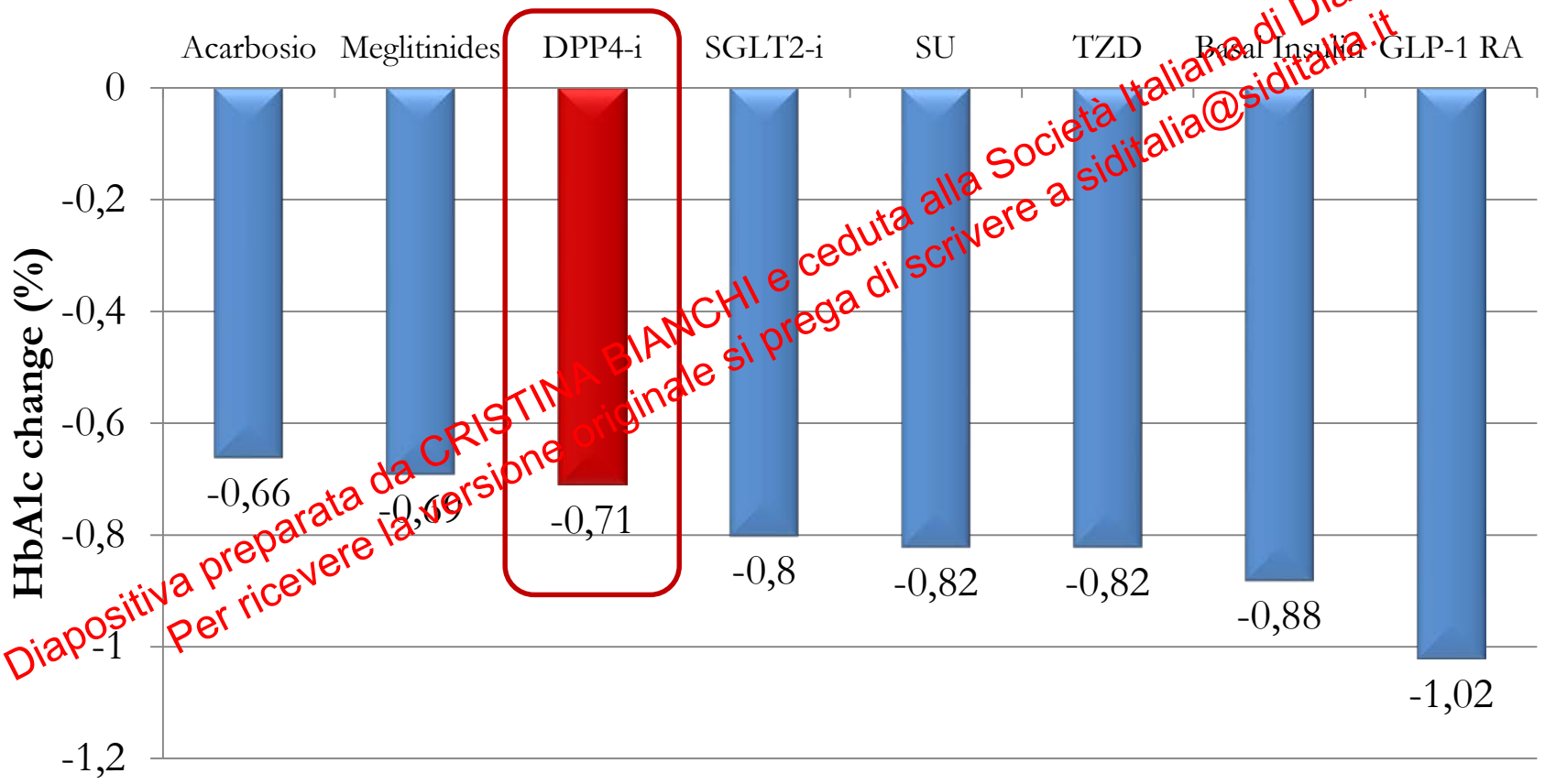
**Hard outcomes**

- Mortality benefit
- Morbidity benefit

**Surrogate outcomes**
(clinically rilevant?)

- HbA1c
- Body weight
- Lipid profile
- Cardiovascular risk factors

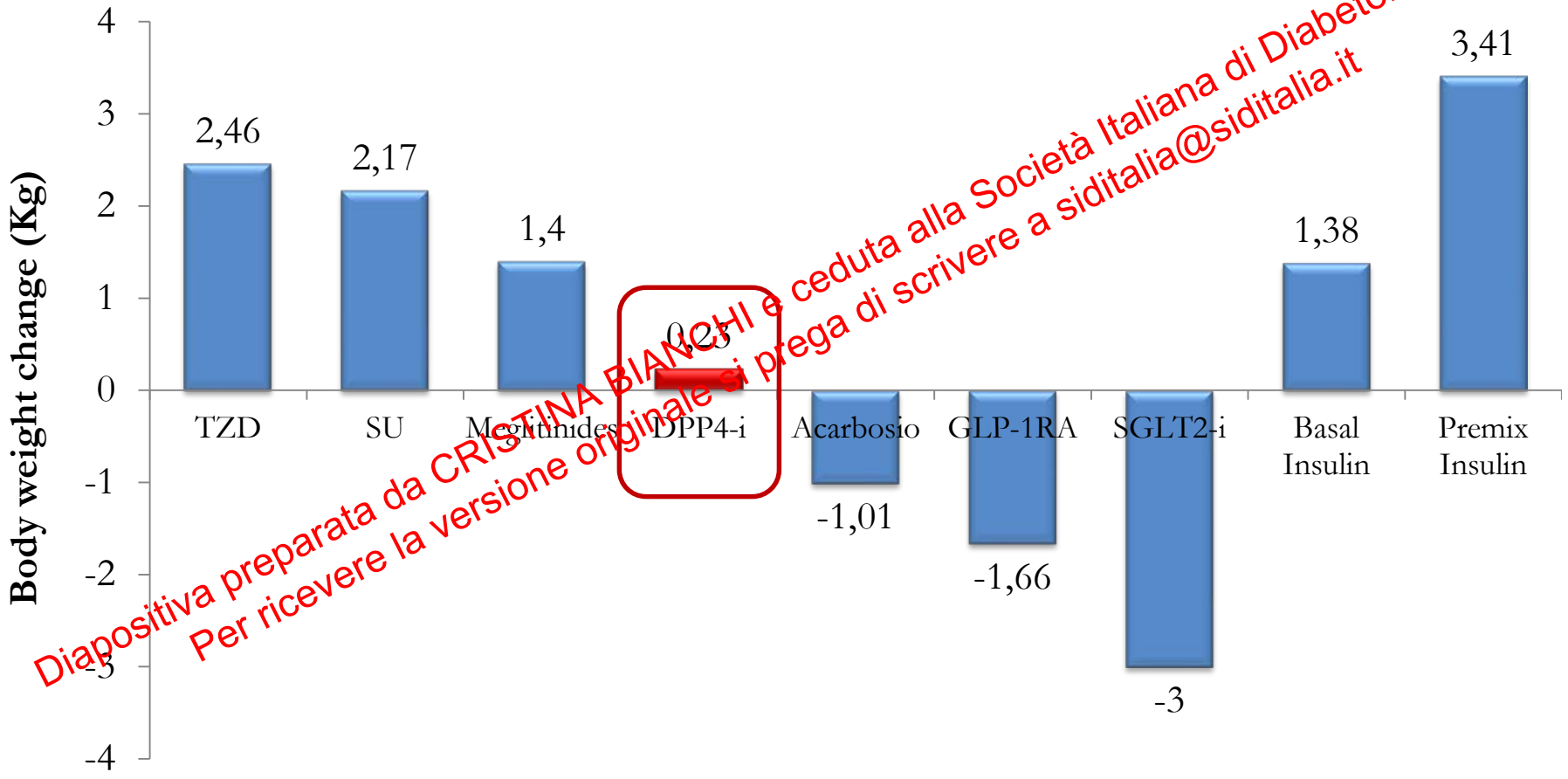
# Effect of antidiabetic agents added to metformin on glycaemic control






Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810–820
Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

# Effect of antidiabetic agents added to metformin on body weight






Liu S-C et al. Diabetes Obes and Metab 2012; 14: 810–820
Fujita Y et al. J Diabetes Investing 2014; 5: 265-275

# Diabetes drugs and surrogate endpoints

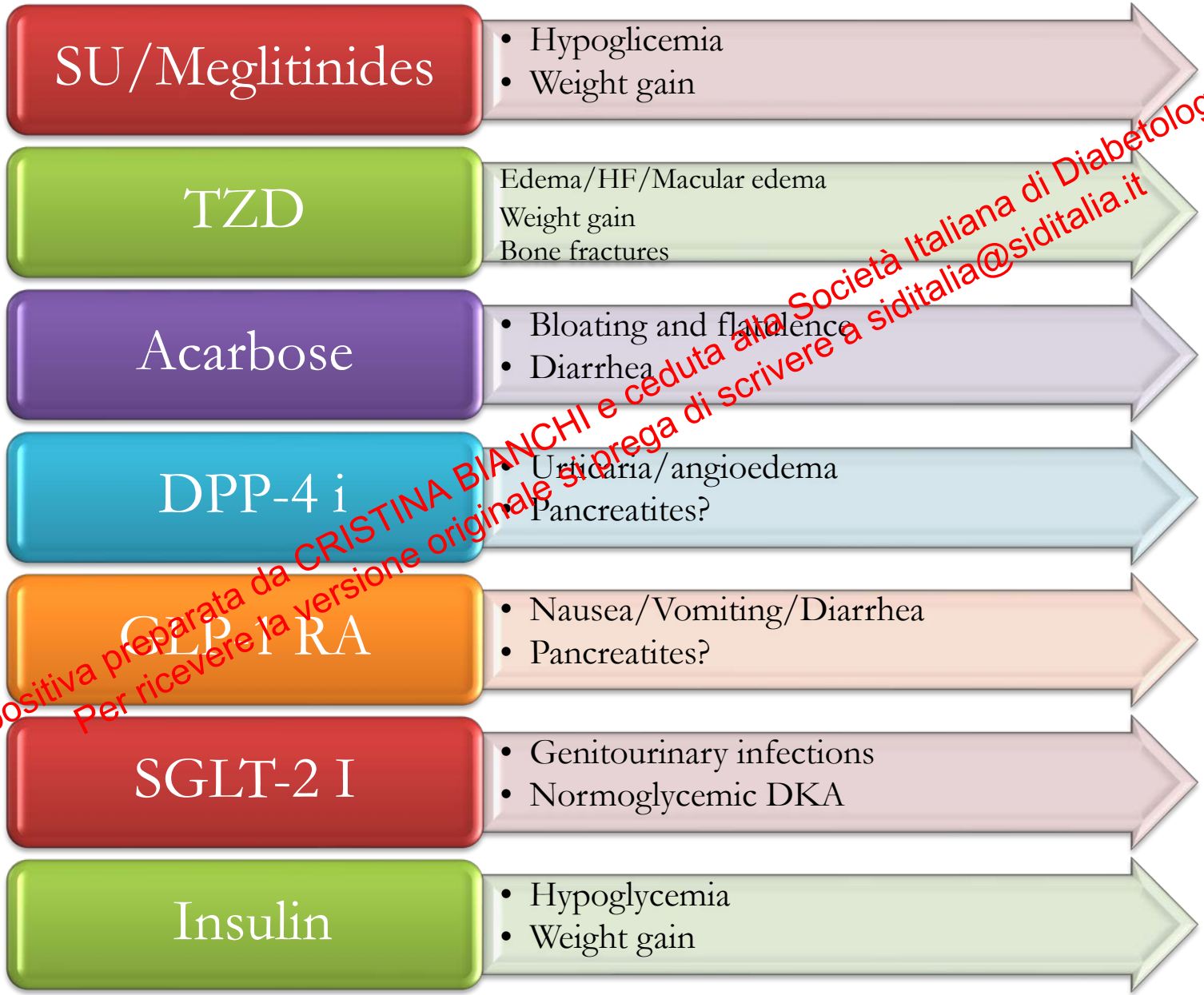
| Drug | Body Weight | Hypertension | Dyslipidemia |
|---|---|---|---|
| α-glucosidase inhibitors | Neutral | Improved | Neutral |
| DPP-4 inhibitors | Neutral | Neutral | Improved |
| GLP-1 agonists | Loss | Improved | Improved |
| Insulin | Gain | Neutral | Improved |
| Meglitinides | Gain | Neutral | Neutral |
| SGLT2 inhibitors | Loss | Improved | Neutral |
| Sulfonylureas | Gain | Neutral | Neutral |
| TZD | Gain | Improved | Improved |



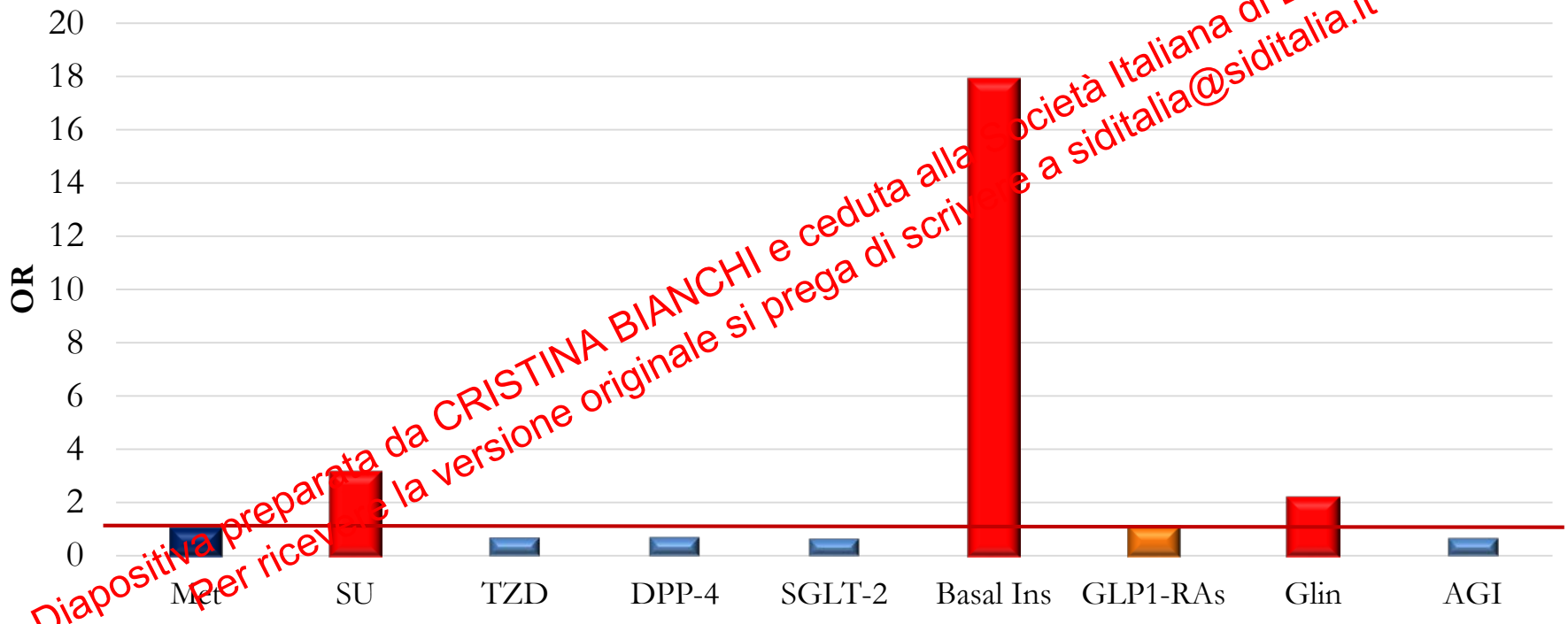
Basile JN. J Diabetes Complications 2013;27(3):280-286

# Evaluating the risks…

# Common and rare side effects of diabetes drugs



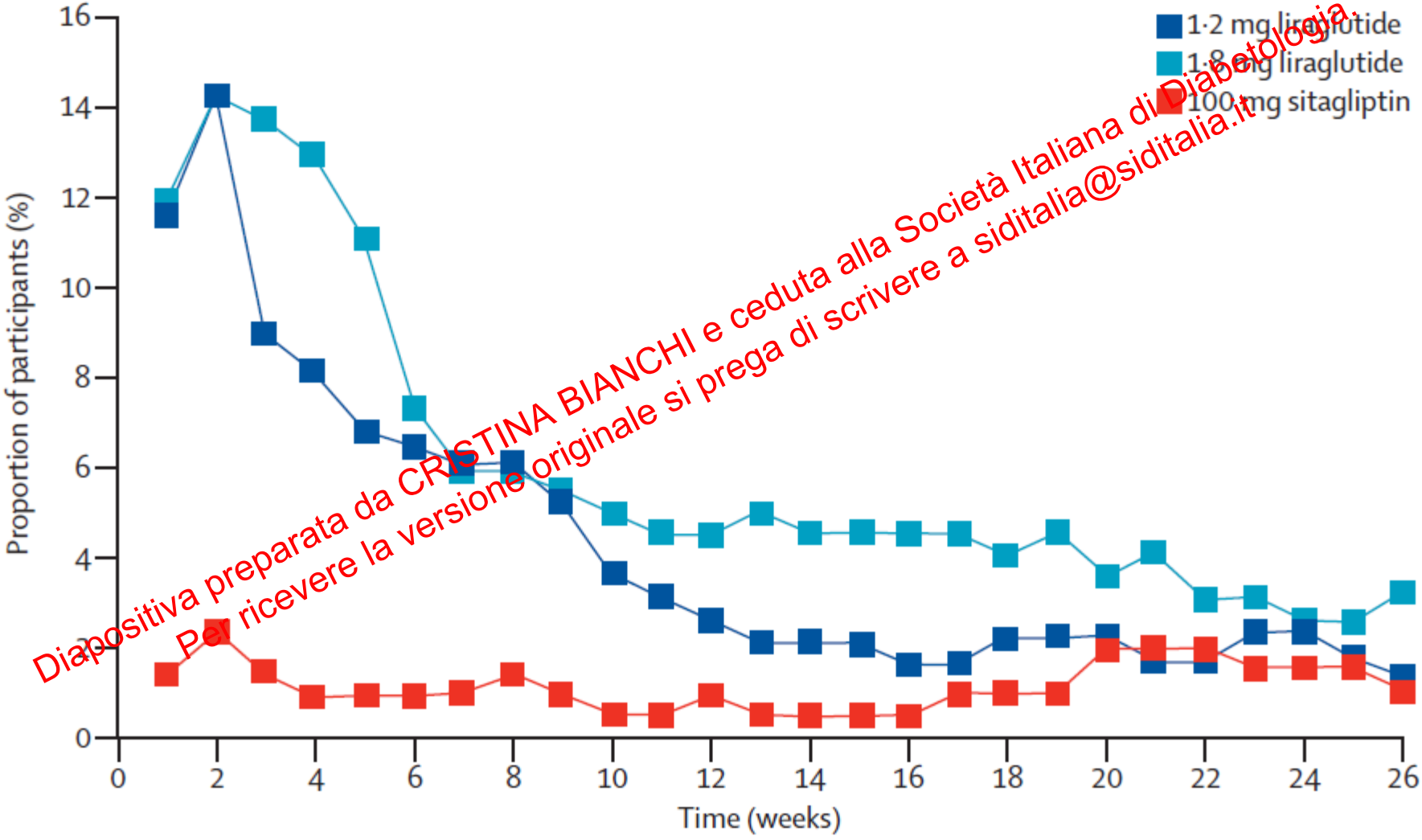
# Risk of hypoglycemia with antidiabetic agents in monotherapy






Adattato da Palmer C. JAMA 2016 ;316(3):313-24

# GLP-1 RA compared to DPP-4 inhibitors: nausea



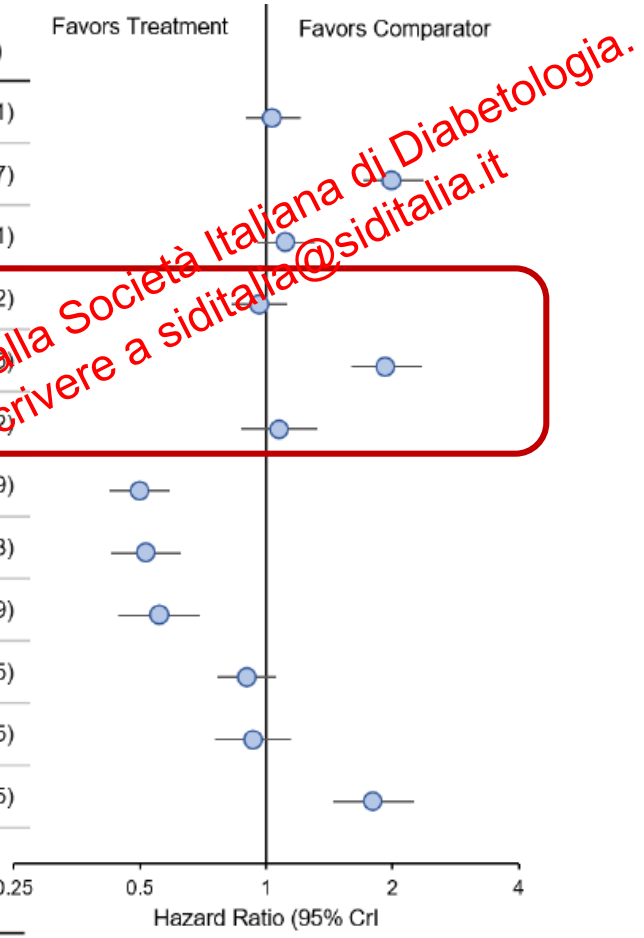



Pratley RE. Lancet 2010; 375: 1447–56

# Use of SGLT2-i, GLP1-RA, and DPP4-i and adverse events leading to withdrawal

| Treatment | Comparator | ARD (95% CI) | HR (95% CrI) |
|---|---|---|---|
| DPP-4 inhibitor | | +0.2% (-0.5% to +1.0%) | 1.04 (0.89-1.21) |
| GLP-1 agonist | vs Control | +4.7% (+3.3% to +6.5%) | 2.00 (1.70-2.37) |
| SGLT-2 inhibitor | | +0.5% (-0.2% to +1.5%) | 1.11 (0.95-1.31) |
| Control | | -0.1% (-0.6% to +0.4%) | 0.97 (0.83-1.12) |
| GLP-1 agonist | vs DPP-4 inhibitor | +3.1% (+2.0% to +4.5%) | 1.93 (1.59-2.36) |
| SGLT-2 inhibitor | | +0.2% (-0.4% to +1.1%) | 1.07 (0.87-1.32) |
| Control | | -3.5% (-4.1% to -2.9%) | 0.50 (0.42-0.59) |
| DPP-4 inhibitor | vs GLP-1 agonist | -3.4% (-4.0% to -2.6%) | 0.52 (0.43-0.63) |
| SGLT-2 inhibitor | | -3.0% (-4.0% to -2.2%) | 0.56 (0.44-0.69) |
| Control | | -0.7% (-1.7% to +0.4%) | 0.90 (0.76-1.05) |
| DPP-4 inhibitor | vs SGLT-2 inhibitor | -0.5% (-1.7% to +1.1%) | 0.93 (0.76-1.15) |
| GLP-1 agonist | | +5.8% (+3.2% to +9.0%) | 1.80 (1.44-2.25) |

186 trials; $I^2$ = 4%

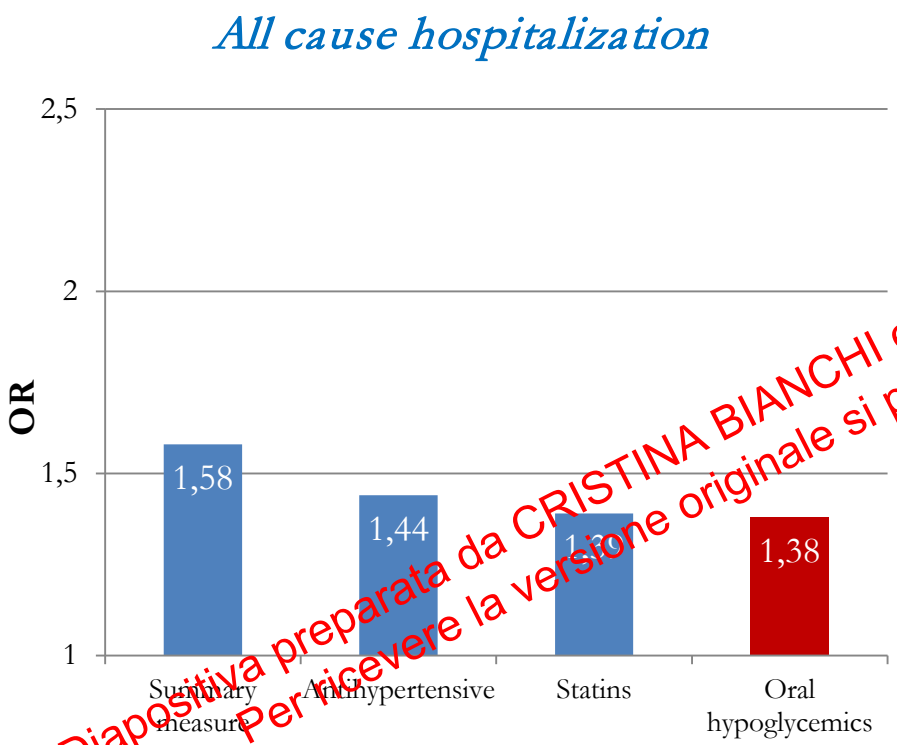


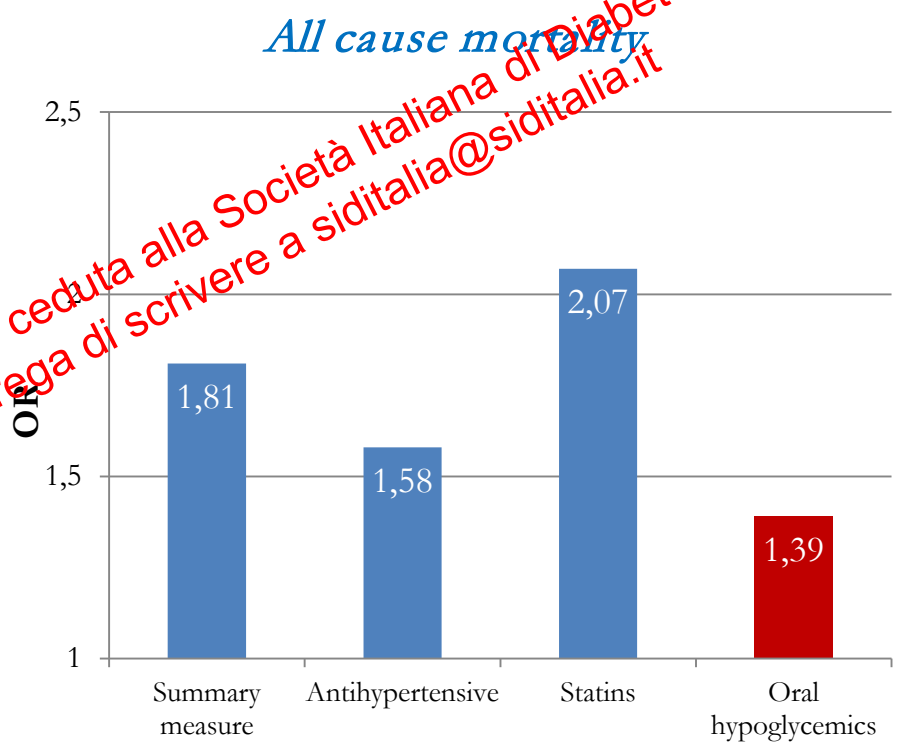

| Treatment | Number of trials | Events (%) | Total Patients |
|---|---|---|---|
| Control | 172 | 2112 (4.7) | 44,766 |
| DPP-4 inhibitor | 86 | 659 (3.4) | 19,620 |
| GLP-1 agonist | 60 | 2278 (7.1) | 32,094 |
| SGLT-2 inhibitor | 64 | 1584 (7.2) | 21,921 |



Zheng SL. JAMA 2018; 319: 1580-1591

# Medication nonadherence and risk of hospitalization or mortality among patients with diabetes mellitus





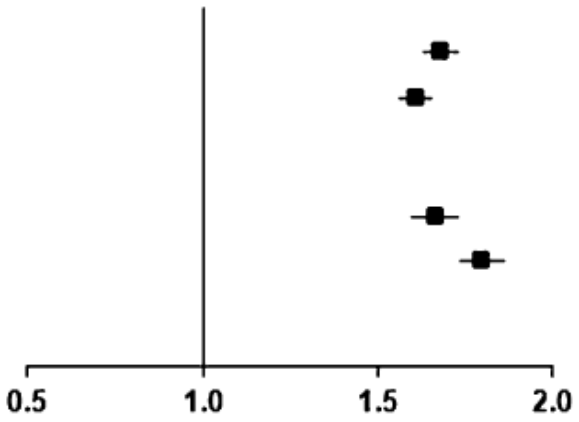

Ho PM. Arch Intern Med 2006;166(17):1836-41

# Long-Term Adherence

238372 patients (61399 DPP-4i, 134961 SU, 42012 TZD)

*Adherence*

| | AOR | CI | p-value |
|---|---|---|---|
| **1-Year Follow-Up** | | | |
| DPP-4i vs. SU | 1.678 | 1.631,1.727 | <0.001 |
| DPP-4i vs. TZD | 1.606 | 1.563,1.647 | <0.001 |
| **2-Year Follow-Up** | | | |
| DPP-4i vs. SU | 1.661 | 1.597,1.727 | <0.001 |
| DPP-4i vs. TZD | 1.795 | 1.730,1.859 | <0.001 |

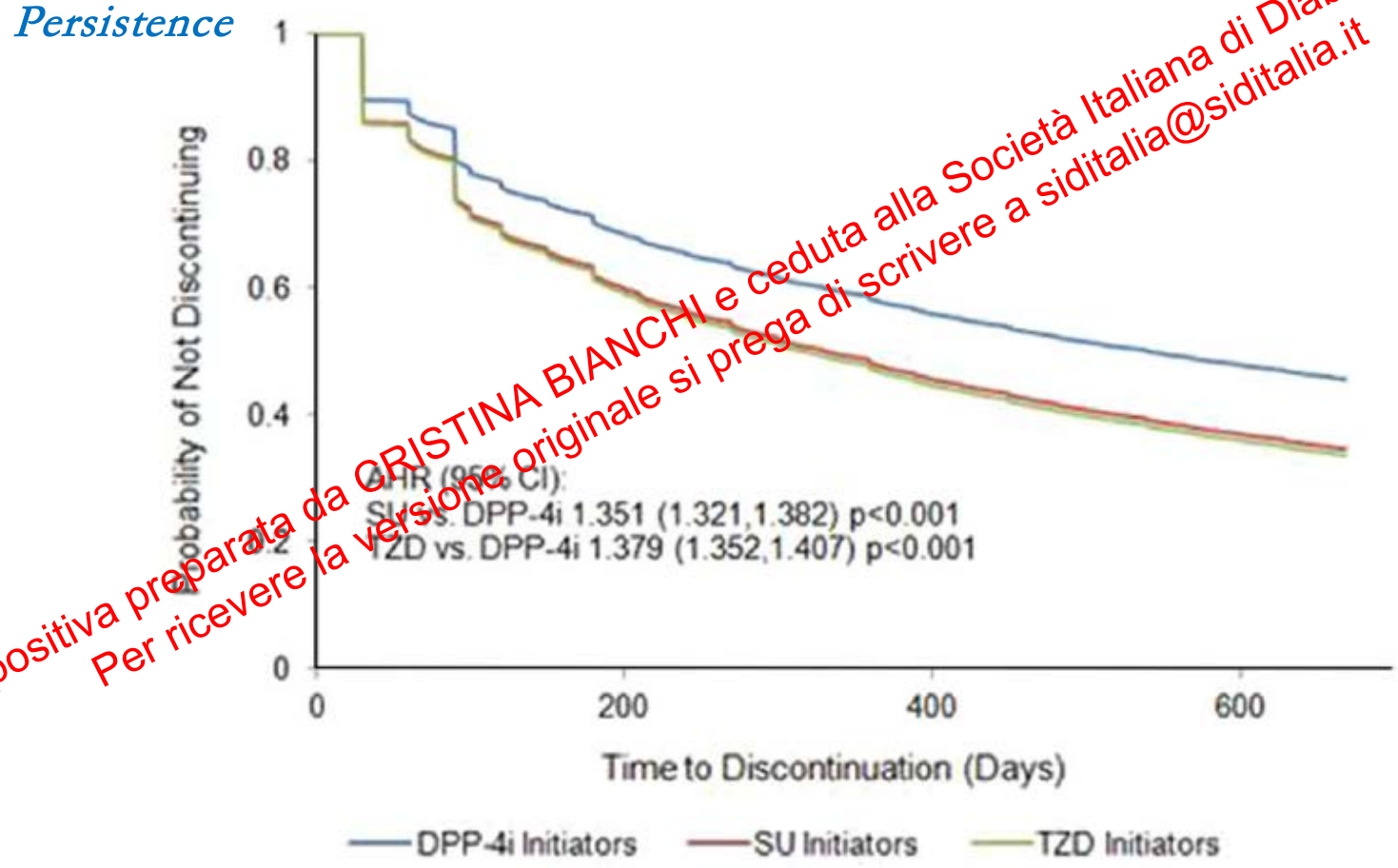





Far AM. Adv Ther 2014; 31:1287–1305

# Long-Term Persistence

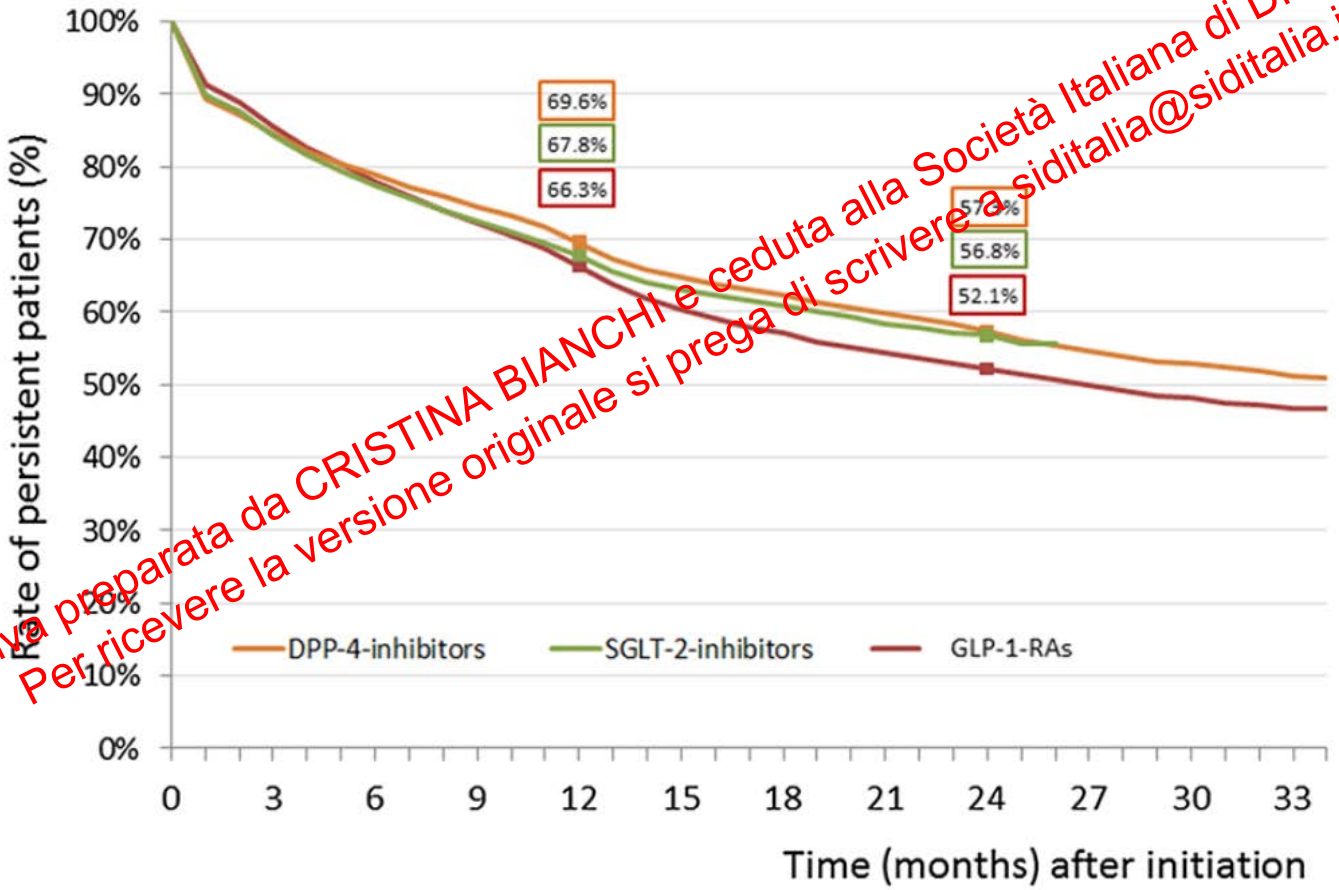
238372 patients (61399 DPP-4i, 134961 SU, 42012 TZD)






Far AM. Adv Ther 2014; 31:1287–1305

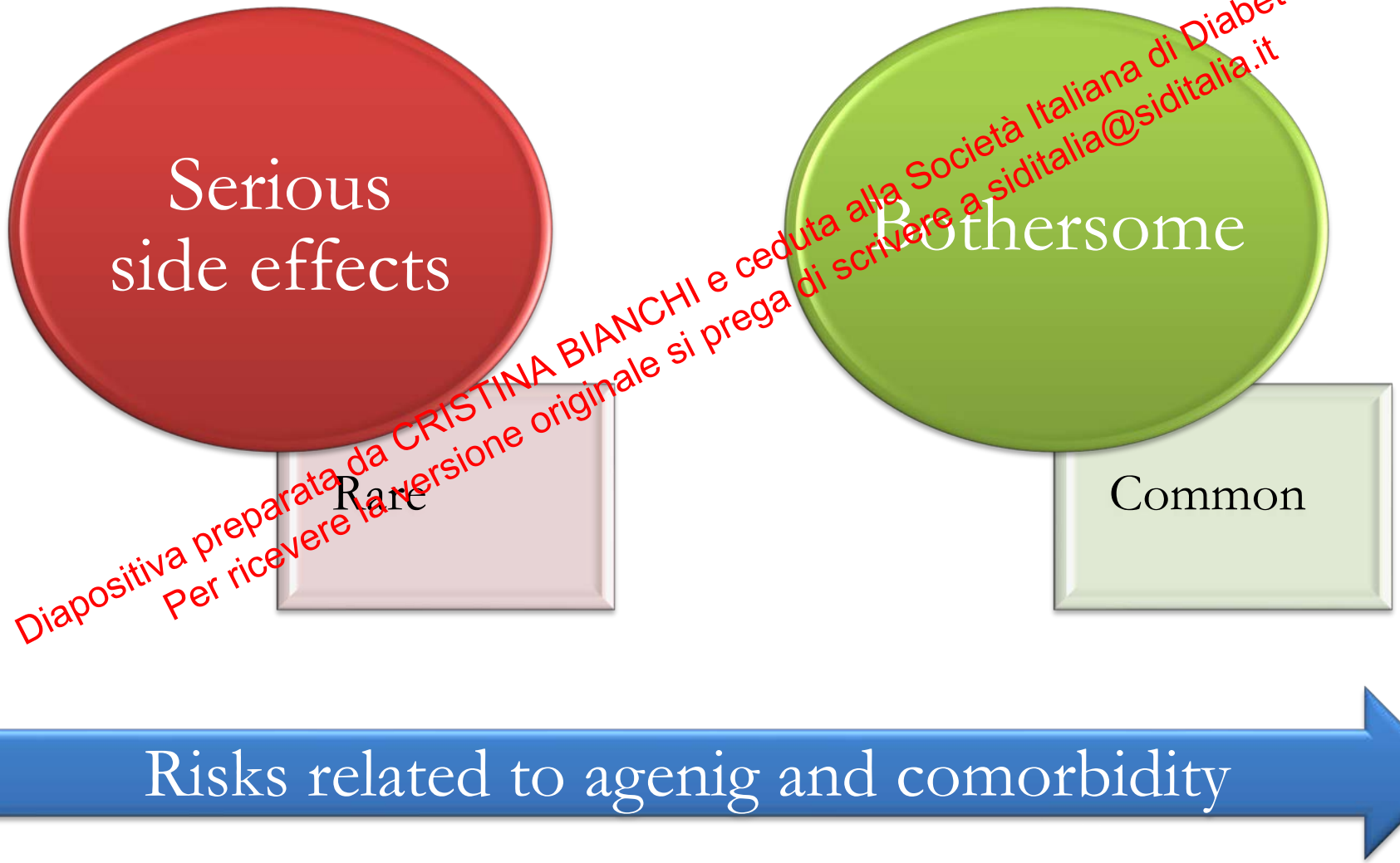
# Persistence to treatment with novel antidiabetic drugs



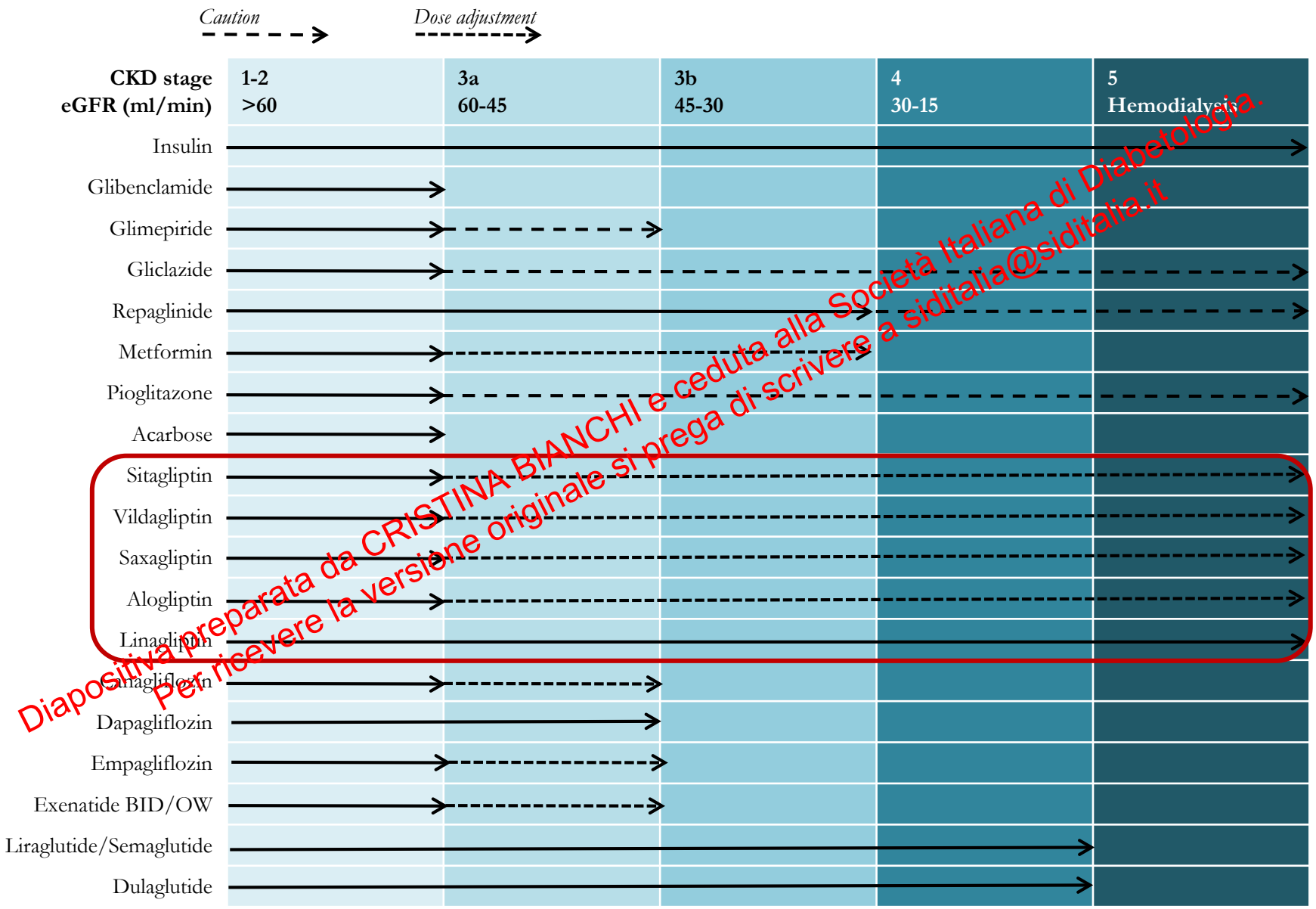



Jermendy G. Diabetes Ther 2018; 9:2133–2141

# Evaluating the risks…



# Anti-Diabetes Medications in CKD






Adapted from: Hahr and Molitch. Clin Diabetes Endocrinol 2015;1:2

# DPP4-inhibitors *vs.* conventional oral antidiabetics as add-on to metformin in elderly patients

## *The HYPOCRAS study*

1188 type 2 diabetes patients; mean age 71 years; baseline mean HbA1c 7.9%

| | DPP4-i $n=931$ | COAD $n=257$ | SU/Glinide | $P$ DPP4-i vs. COAD |
|---|---|---|---|---|
| % of patients with at least 1 episode of hypoglycemia | 6.4 | 20.1 | 26.0 | $<0.001^{*}$ |
| % of patients with at least 1 episode of severe hypoglycemia | 0.1 | 2.4 | 3.2 | $0.001^{**}$ |
| $HbA_{1c}$ (mean ± SD) | 6.9 ± 0.8 | 7.0 ± 0.7 | | $0.033^{\#}$ |
| Median | 6.8 | 6.9 | | |
| FPG (mg/dL) (mean ± SD) | 126 ± 28 | 129 ± 26 | | 0.034 |
| Median | 120 | 125 | | 120 |
| Successful bitherapy ($HbA_{1c}$ <7% without hypoglycemia) (MD[a]) | 59.7 (44) | 45.5 (12) | 41.4 (5) | $<0.001^{*}$ |
| % of patients who discontinued treatment | 1.6 | 6.6 | 6.8 | $<0.001^{*}$ |



Penfornis A. Diabetes Metab 2012;38(6):550-7

# DPP4-inhibitors *vs.* conventional oral antidiabetics as add-on to metformin in elderly patients

## *The HYPOCRAS study*

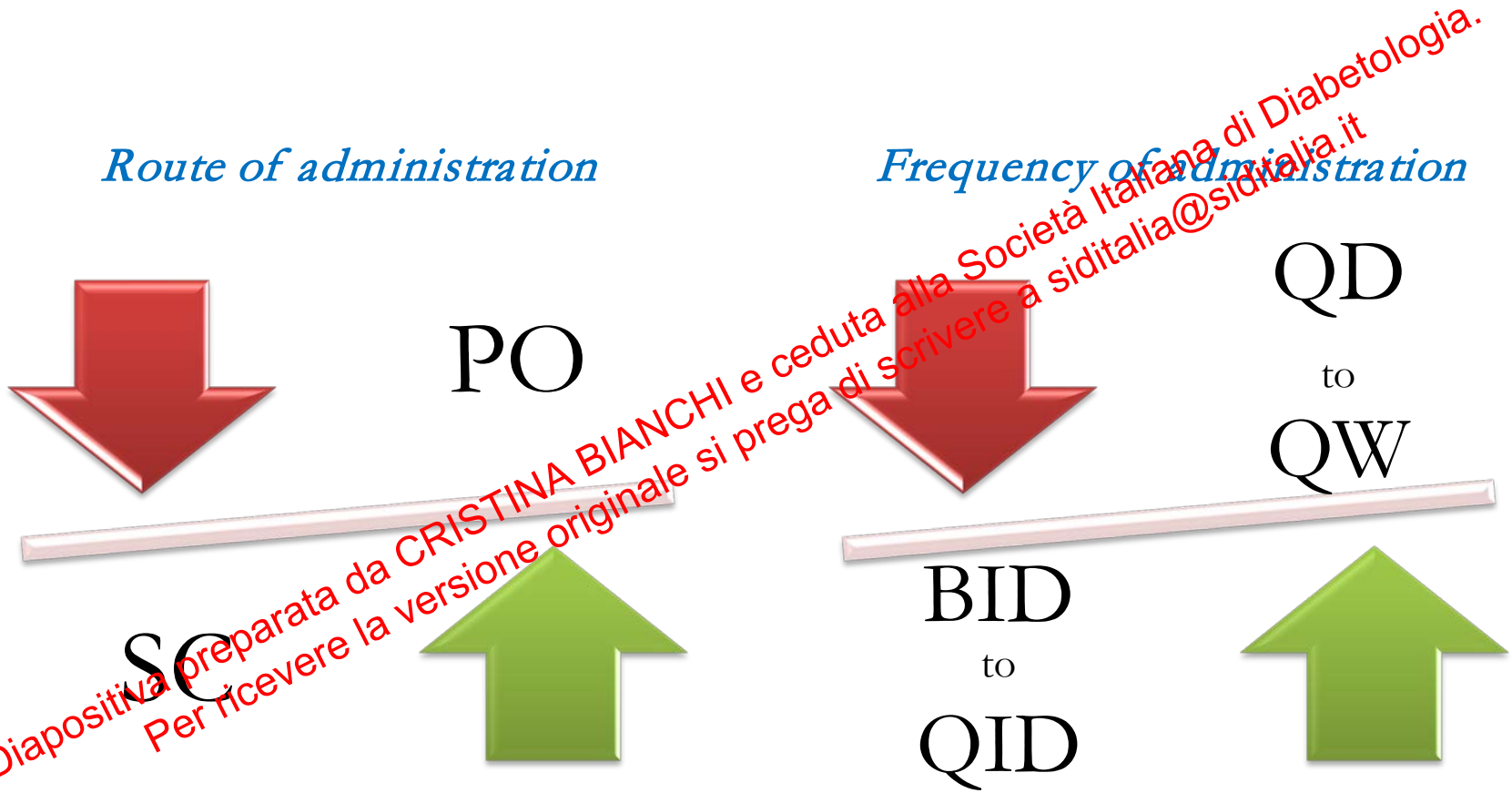


Reasons for choosing the second oral antidiabetic drug to be added on to metformin.

| Criterion cited as a reason for the choice | DPP4-i $n=931$ (%) | COAD $n=257$ (%) | Test *P*-value |
|---|---|---|---|
| Good personal experience with the class | 23.7 | 56.0 | $<0.001^*$ |
| Ease of use (no titration, low risk of interactions with other drugs) | 59.8 | 23.4 | $<0.001^*$ |
| Long-term use of the class | 6.7 | 45.1 | $<0.001^*$ |
| Obese patient for whom important to limit weight gain | 46.4 | 23.4 | $<0.001^*$ |
| Efficacy (target $HbA_{1c}$ reached) | 78.2 | 57.6 | $<0.001^*$ |
| Patient too old | 4.7 | 3.5 | $0.40^*$ |
| Patients with high cardiovascular risk and multiple co-medications | 31.5 | 17.9 | $<0.001^*$ |
| Vulnerable patients for whom important to avoid hypoglycemia | 30.7 | 15.6 | $<0.001^*$ |
| Intolerance or contraindications to other OADs | 6.6 | 8.6 | $0.264^*$ |
| To limit cost of therapy | 2.0 | 7.4 | $<0.001^*$ |
| To limit the number of tablets | 41.9 | 19.5 | $<0.001^*$ |

Penfornis A. Diabetes Metab 2012;38(6):550-7

# Convenience of administration



# Relevant interactions with antidiabetic medication in clinical routine (1)

| | Inhibitors | Inducers |
|---|---|---|
| **Sulfonylureas** | CYP29C9 inhibtor<br>• Clartromicin) ↑Glibenclamide +35%<br>• Fluconazole↑ Glimepiride 138% | CYP2C9 inducer<br>• Rifampin ↓gliclazide 70%<br>• Rifampin ↓ glimepiride 34%<br>• Rifampin ↓ glibenclamide 39% |
| **Repaglinide** | CYP inhibitor<br>• Claritromicin +40%<br>• Cyclosporin +144%<br>• Gemfibrozil +712% (Avoid)<br>• Itraconazole +41%<br>• Itraconazole+gemfibrozil +1839 (Avoid)<br>• Trimetohprim +61% | CYP inducer<br>• Rifampin -32-85% |
| **Pioglitazone** | CYP2C8 inhibitor<br>• Gemfibrozil +230%<br>• Trimethoprim +42% | CYP2C8 inducer<br>• Rifampin -54% |



Adapted from: https://hivclinic.ca/main/drugs_extra_files/Antihyperglycemic%20Agents%20Comparison%20Chart.pdf

# Relevant interactions with antidiabetic medication in clinical routine (2)

| DPP-4 Inhibitors | GLP-1 R. Agonists | SGLT2is |
|---|---|---|
| **Saxagliptin**<br>CYP3A4 inhibitor::<br>• Diltiazem 109%<br>• Ketoconazole 145%;<br>consider reducing dose of saxagliptin by 50% (to 2.5 mg daily)<br>CYP3A4 inducer: :<br>• Rifampin 76%<br><br>**Linagliptin**<br>No significant metabolic drug interactions<br>**Sitagliptin**<br>No significant metabolic interactions<br>**Alogliptin**<br>No metabolic drug interactions<br>**Vildagliptin**<br>No metabolic drug interactions | No known pharmacokinetic drug interactions | Metabolized in the liver by glucuronidation without involvement of CYP enzymes. With the exception of canagliflozin, which should be given in a higher daily dose when co-administered with UGT inducers such as rifampicin, phenytoin or ritonavir, and which might increase digoxin plasma levels |



Adapted from: https://hivclinic.ca/main/drugs_extra_files/Antihyperglycemic%20Agents%20Comparison%20Chart.pdf

# DPP-4 Inhibitors added to metformin

## *Summary*

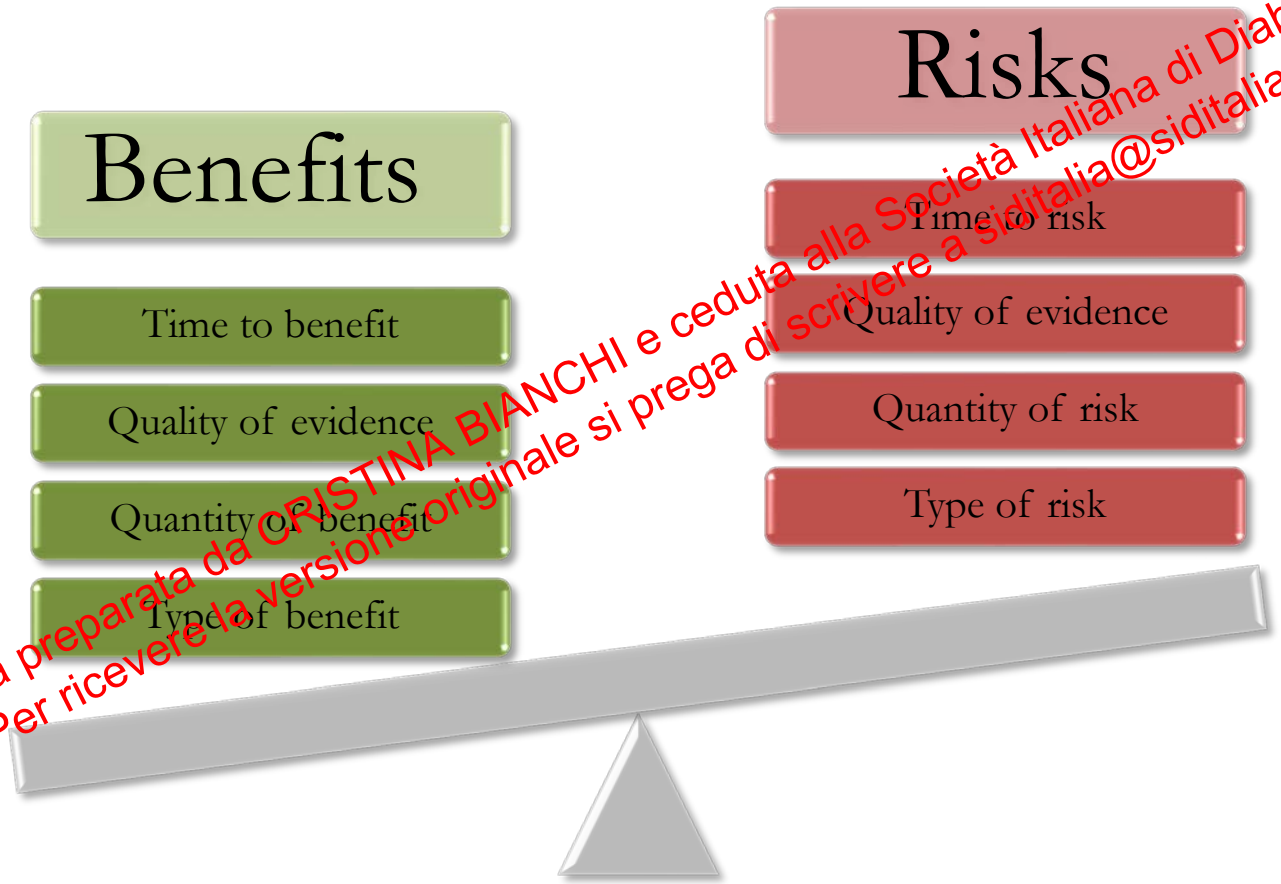
### Cons

- Not shown to reduce mortality and/or cardiovascular complications
- Less effective than GLP-1RA at lowering HbA1c
- ± expensive

### Pro

Reduce development or progression of albuminuria
Durable lowering effect on HbA1c
Low risk of hypoglycemia
Weight neutral
Well-tolerated
Ease of use (no titration, low risk of interaction with other drugs)
Safe in elderly
Safe in CKD

# Balancing risks and benefits



Nel momento della decisione,
la cosa migliore che puoi fare è la cosa giusta,
la seconda cosa migliore che puoi fare è la cosa sbagliata,
mentre la cosa peggiore che puoi fare è non fare nulla.

Theodore Roosevelt

unite for diabetes

# Grazie per l'attenzione!