# ottimizzazione della terapia nel paziente complesso

63° CONGRESSO NAZIONALE SIGG

TEAM DIABETE Gemelli

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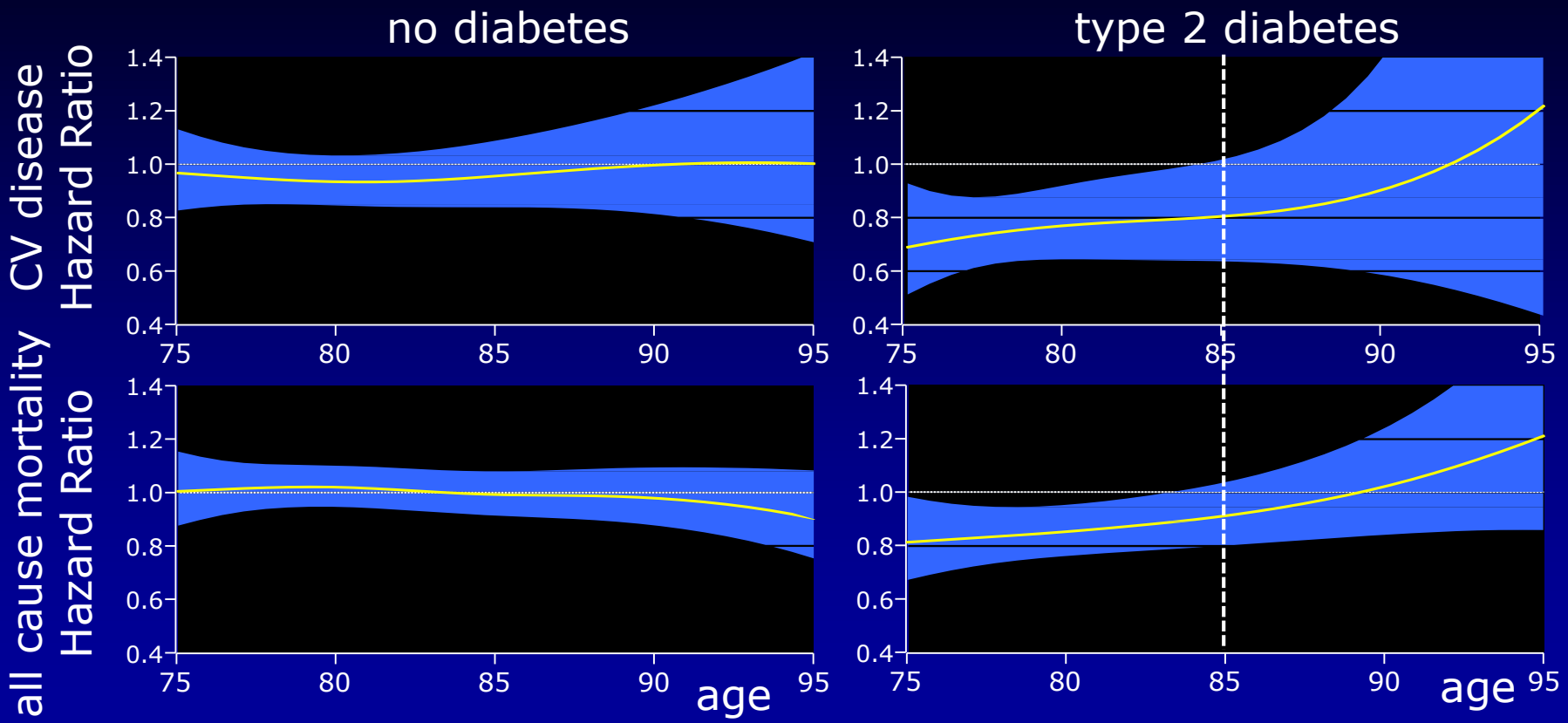
# 11. Older Adults: *Standards of Medical Care in Diabetes—2018*

*American Diabetes Association*

*Diabetes Care 2018;41(Suppl. 1):S119–S125 | https://doi.org/10.2337/dc18-S011*

| category | HbA1c target | statin |
|---|---|---|
| 1. healthy | < 7.5 | yes |
| 2. complex / intermediate healthy | < 8.0 | yes |
| 3. very complex / poor health | < 8.5 | consider |

# Statins for primary prevention in old adults




*Ramos R. et al.: BMJ 362:k3359, 2018 doi: 10.1136/bmj.k3359.*

# ADA/EASD

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)**
**IF $HbA_{1c}$ ABOVE TARGET PROCEED AS BELOW**

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

## ESTABLISHED ASCVD OR CKD

### ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

**If $HbA_{1c}$ 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[4]
- TZD[5]
- SU[6]

### HF OR CKD PREDOMINATES

**PREFERABLY**
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

**OR**

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

**If $HbA_{1c}$ above target**

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

## WITHOUT ESTABLISHED ASCVD OR CKD

### COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

| DPP-4i | GLP-1 RA | SGLT2i[2] | TZD |
|---|---|---|---|
| **If $HbA_{1c}$ above target** | **If $HbA_{1c}$ above target** | **If $HbA_{1c}$ above target** | **If $HbA_{1c}$ above target** |
| SGLT2i[2] **OR** TZD | SGLT2i[2] **OR** TZD | GLP-1 RA **OR** DPP-4i **OR** TZD | SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA |

**If $HbA_{1c}$ above target**

Continue with addition of other agents as outlined above

**If $HbA_{1c}$ above target**

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia[7]

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

EITHER/OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

**If $HbA_{1c}$ above target**

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

**If $HbA_{1c}$ 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[6]
- TZD[5]
- Basal insulin

### COST IS A MAJOR ISSUE[9-10]

- SU[6]
- TZD[10]

**If $HbA_{1c}$ above target**

- TZD[10]
- SU[6]

**If $HbA_{1c}$ above target**

- **Insulin therapy** basal insulin with lowest acquisition cost

**OR**

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

expensive and DPP-4i relatively cheaper

# Step 1: assess cardiovascular disease

## Presence of cardiovascular disease is compelling indication

### ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit[1]

or

SGLT2-i with proven CVD benefit[1-2] if eGFR adequate

if HbA1c above target

if further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit
- DPP4i if not on GLP-1 RA
- basal insulin[4]
- TZD[5]
- SU[6]

### HEART FAILURE (HF) PREDOMINATES

SGLT2-i with proven CVD benefit[2-3] if eGFR adequate

or

GLP-1 RA with proven CVD benefit[1]

if HbA1c above target

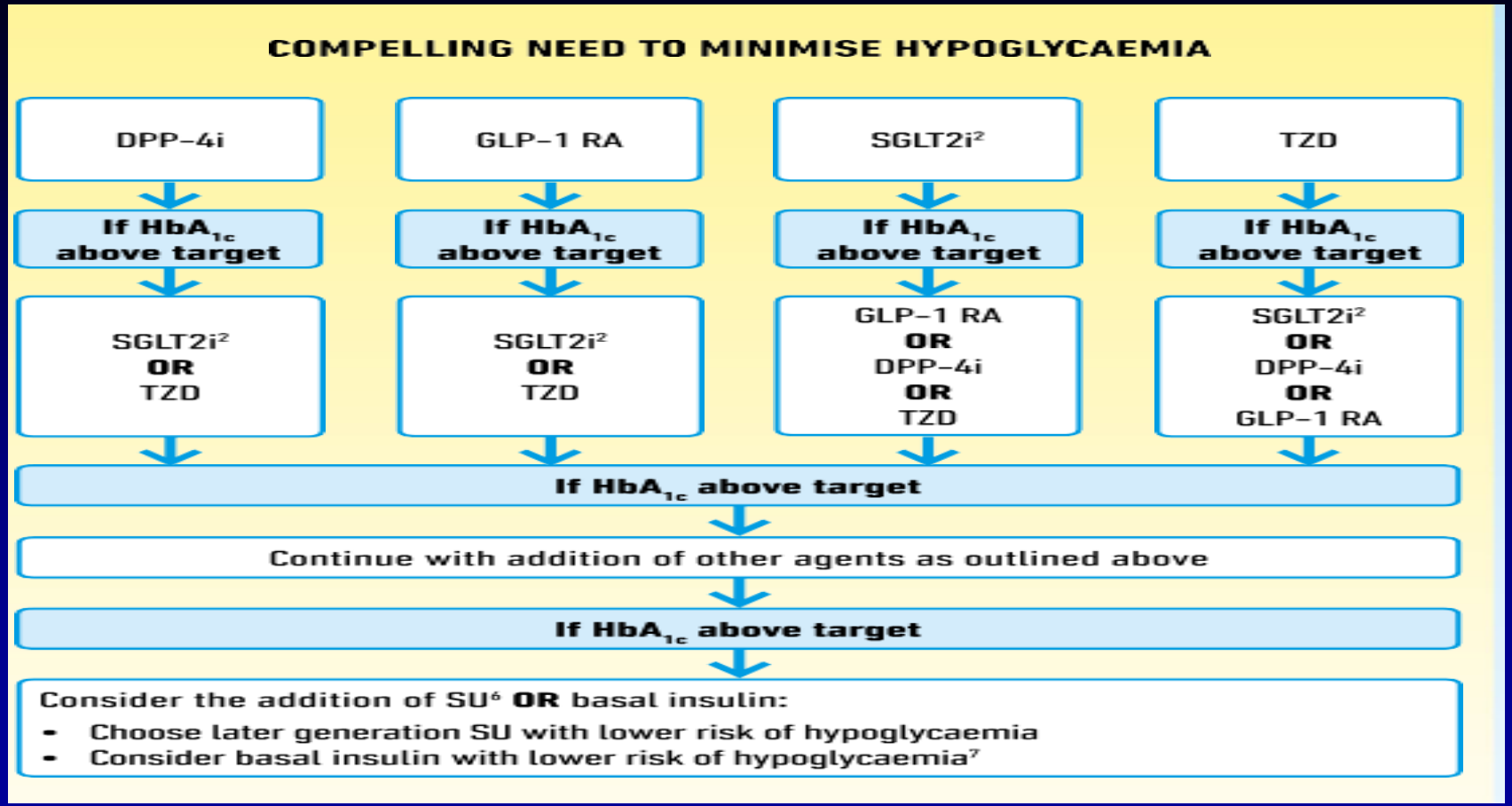
- Avoid TZD

Choose agents demonstrating CV safety:

- consider adding the other class with proven CVD benefit[1]
- DPP4i (not saxagliptin) if not on GLP-1 RA
- basal insulin[4]
- SU[6]

1. SGLT2-i = empagliflozin preferred, GLP-1 RA = liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events. 2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use. 3. Both empagliflozin and canagliflozin have shown reduction in HF in CVOT trial. 4. Degludec or U100 glargine have demonstrated CVD safety. 5. Low dose may be better though less well studied for CVD effect. 6. Choose later generation SU with lower risk of hypoglycaemia.

# ADA/EASD



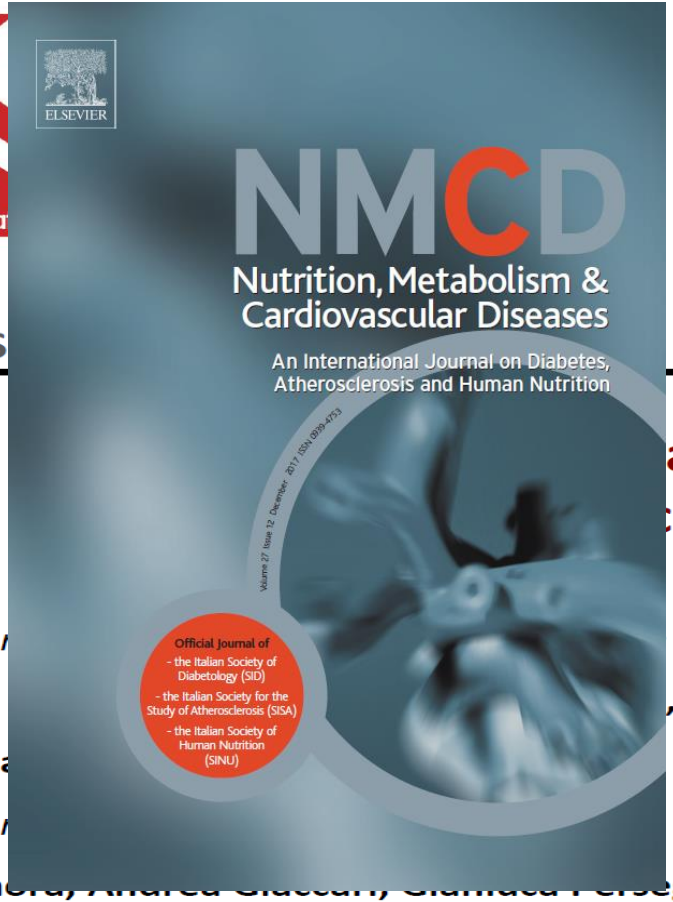

expensive and DPP-4i relatively cheaper

# Terapia farmacologica nell'anziano:

*Principali fattori da considerare:*

- rischio di ipoglicemia
- insufficienza renale
- pregresso ictus/IMA
- storia di scompenso cardiaco
- profilo glicemico
- riserva funzionale beta cellula
- **stato nutrizionale**
- **facilità di somministrazione**

# SIGG-SID per la terapia del diabete




SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

POS

**attamento dell'iperglicemia**
**con diabete tipo 2**

*Autori per* *Geriatria:*

**Raffaele** **, Stefania Maggi, Giuseppe Paolisso, Gianluigi Vendemia**

*Autori per*

**Enzo Bonora, Andrea Giaccari, Gianluca Perseghin, Francesco Purrello, Giorgio Sesti**

# obiettivi e terapia del diabete

obiettivo di glicata

↓

farmaco per il diabete

# obiettivi e terapia del diabete

farmaco per il diabete

NON a rischio di ipoglicemia

1ª scelta

- metformina
- SGLT-2i
- DPP-4i
- GLP-1 RA
- pioglitazone
- acarbosio

a rischio di ipoglicemia

2ª scelta

- SUs
- repaglinide
- insulina

obiettivo di glicata

HbA1c < 7%

se fragile

HbA1c 7.0 – 7.5 %

HbA1c 7.5 – 8.0 %

# Terapia farmacologica nell'anziano

| | rischio di IPO | uso in IRC | prev CVD | scomp card | fenotipo glic | riserva β-cell | stato nutr. | facilità somm. | fragile |
|---|---|---|---|---|---|---|---|---|---|
| Metformina | | | | | | | | | |
| SU e glinidi | | | | | | | | | |
| pioglitazone | | | | | | | | | |
| Gliptine | | | | | | | | | |
| GLP-1 RA | | | | | | | | | |
| Gliflozine | | | | | | | | | |
| Insulina bas | | | | | | | | | |

*Management of Diabetes in Older Adults*
*Sesti G. et al.: NMCD 28:206, 2018 doi: 10.1016/j.numecd.2017.11.007*

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| Metformina | NO | no<30 | SI | NO | digiuno | = | — | XR | |
| SU e glinidi | | | | | | | | | |
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| GLP-1 RA | | | | | | | | | |
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| Metformina | NO | no<30 | SI | NO | digiuno | = | — | XR | |
| SU e glinidi | SI | solo gliclazide | rischio | neutro | vari | SI | + | no | |
| pioglitazone | | | | | | | | | |
| Gliptine | | | | | | | | | |
| GLP-1 RA | | | | | | | | | |
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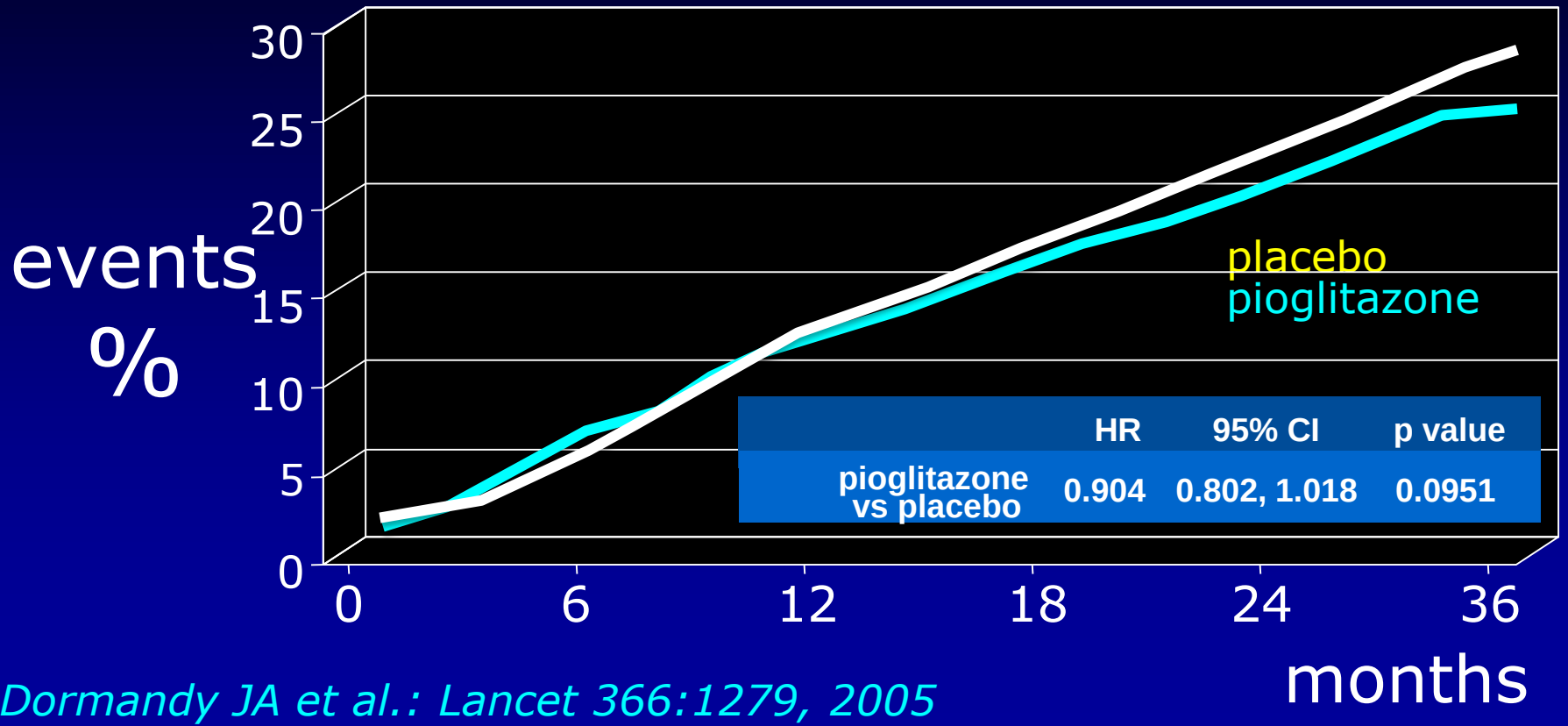
# PROACTIVE: primary outcome

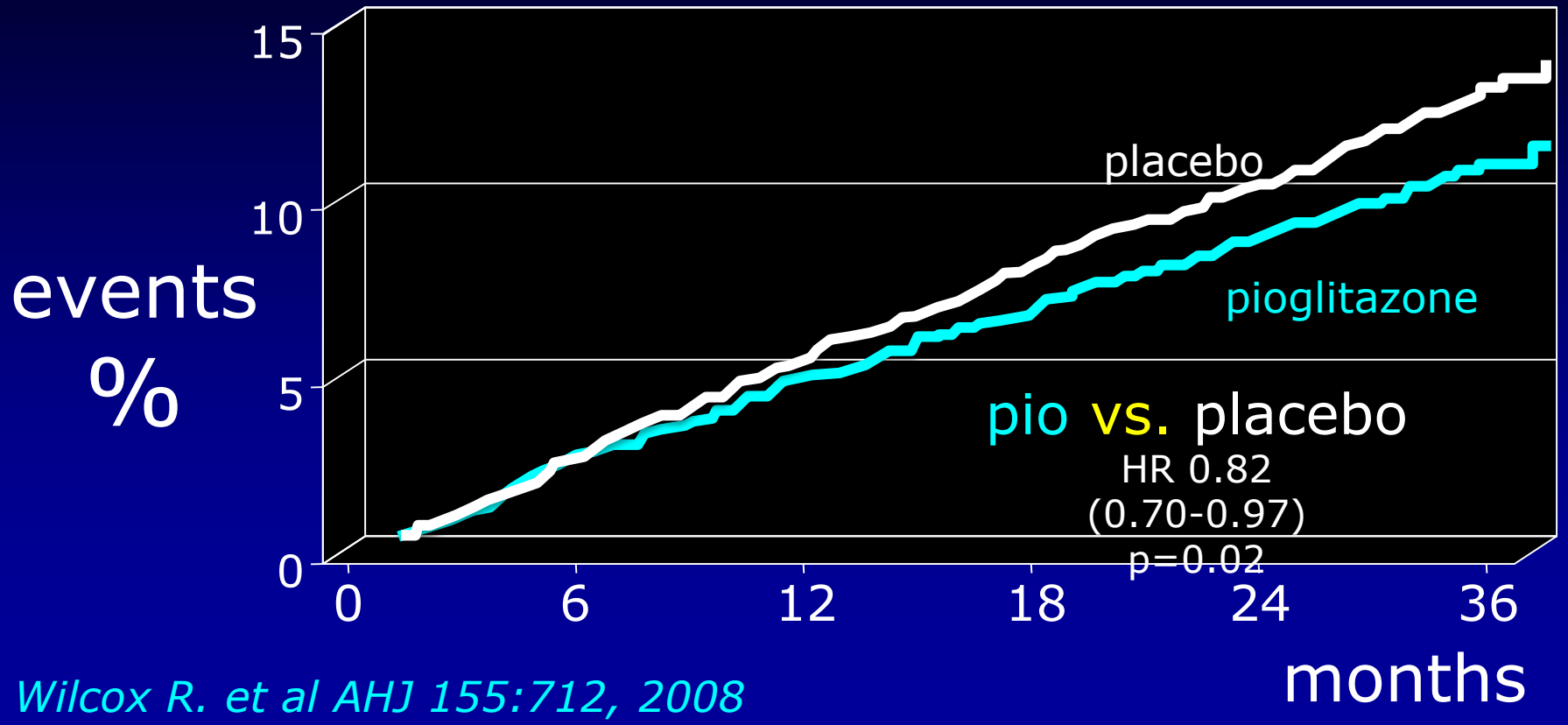



| | HR | 95% CI | p value |
|---|---|---|---|
| pioglitazone vs placebo | 0.904 | 0.802, 1.018 | 0.0951 |

*Dormandy JA et al.: Lancet 366:1279, 2005*

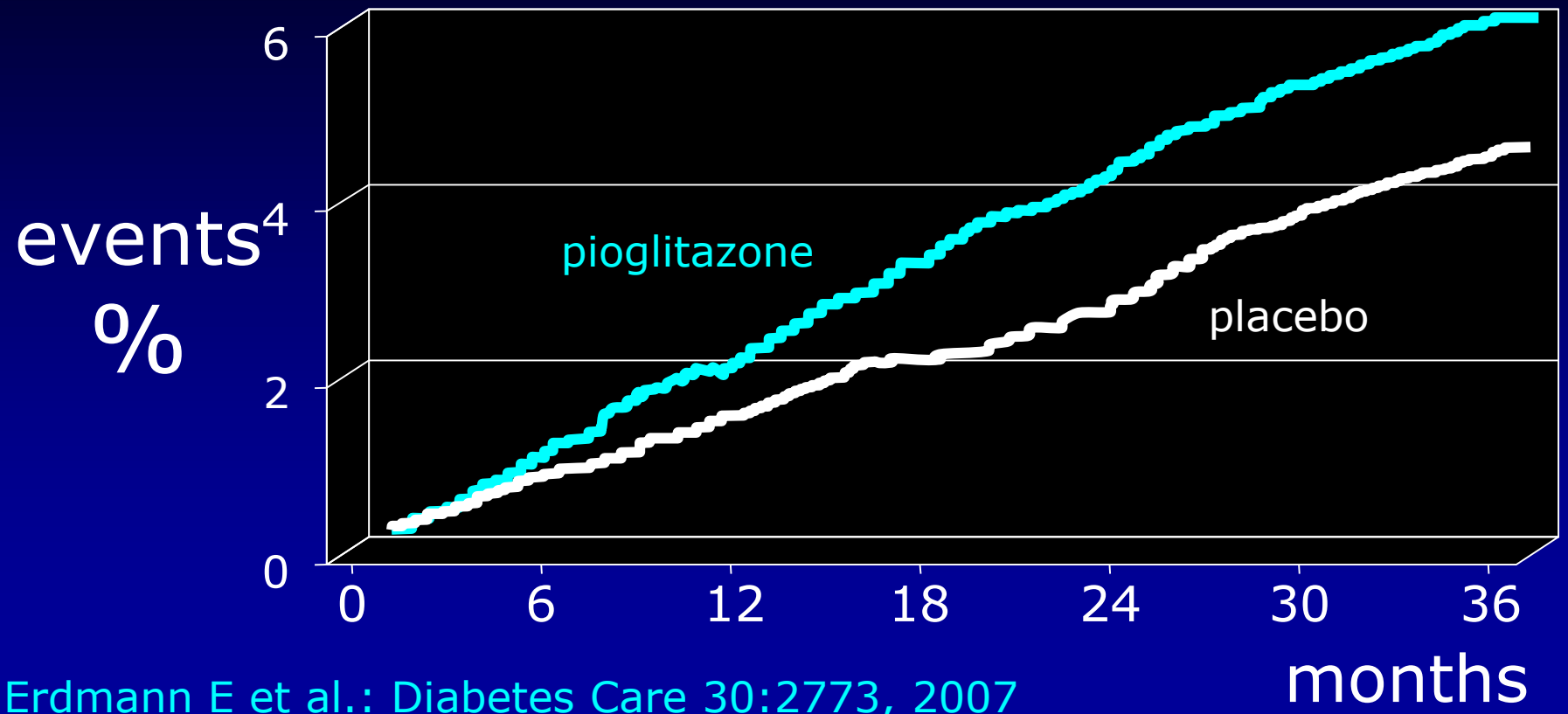
# PROACTIVE: MACE

## MI, stroke and CV mortality




*Wilcox R. et al AHJ 155:712, 2008*

# PROACTIVE: Heart failure risk




Erdmann E et al.: Diabetes Care 30:2773, 2007

# diabetes treatments and CV risk

## a cohort (469,688) study in primary care in UK

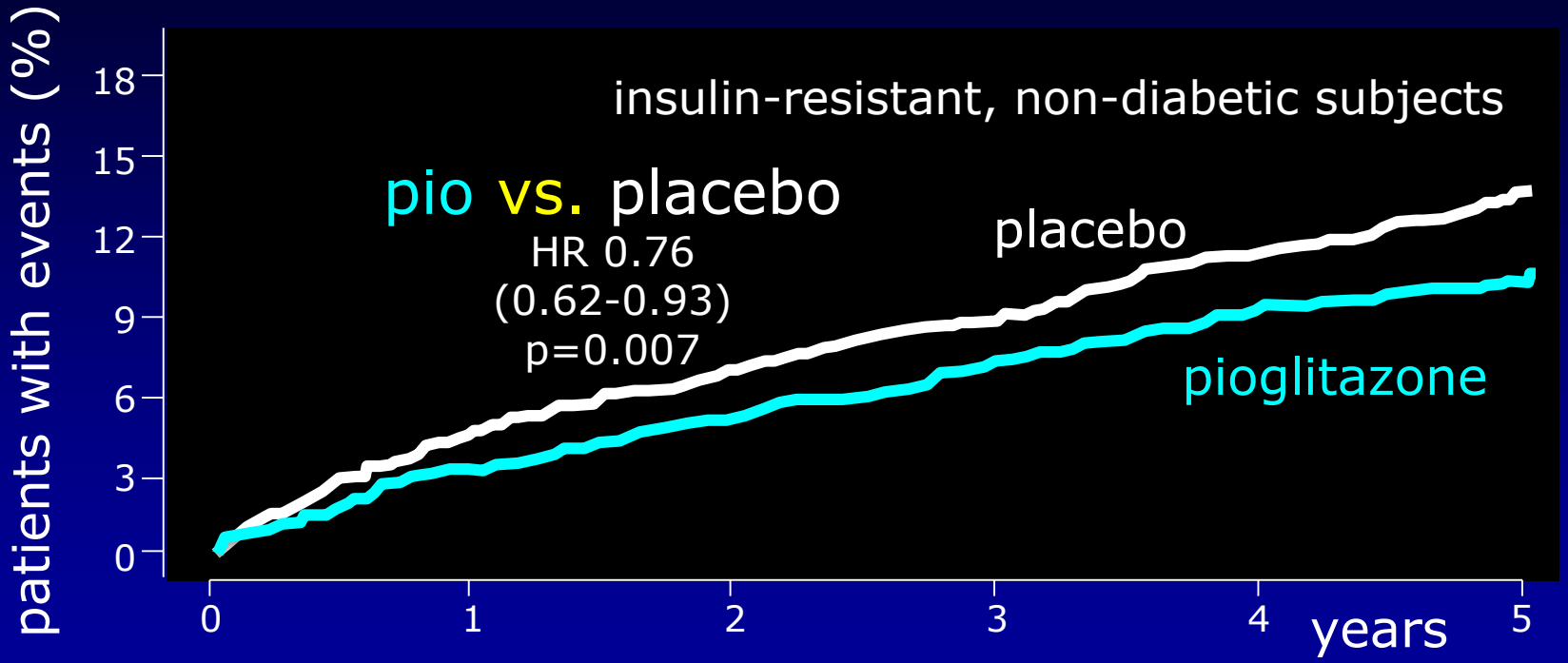
| | Heart Failure | CV disease | All cause mortality |
|---|---|---|---|
| **No treat.** | 1.00 | 1.00 | 1.00 |
| **Metformin** | 0.68 * (0.65 to 0.71) | 0.76 * (0.74 to 0.79 | 0.64 * (0.63 to 0.66 |
| **SUs** | 1.00 (0.94 to 1.07) | 1.00 (0.95 to 1.05) | 1.24 † (1.20 to 1.28) |
| **Insulin** | 1.26 † (1.10 to 1.44) | 1.22 † (1.08 to 1.37) | 1.64 † (1.55 to 1.74) |
| **Glitazones** | 0.50 * (0.26 to 0.97) | 0.79 (0.53 to 1.18) | 0.89 (0.67 to 1.18) |
| **Gliptins** | 0.87 (0.58 to 1.31) | 1.14 (0.85 to 1.54) | 1.20 (1.00 to 1.44) |

*Hippisley-Cox J et al.: BMJ 354:i3477, 2016*

# IRIS primary endpoint

(stroke or MI, fatal or non-fatal)

Insulin Resistance Intervention after Stroke




*Kernan WN et al. NEJM 374:1321, 2016*

The NEW ENGLAND JOURNAL of MEDICINE

# Terapia farmacologica nell'anziano

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| SU e glinidi | SI | solo gliclazide | rischio | neutro | vari | SI | + | no | |
| pioglitazone | NO | no<15 | SI | SI | digiuno | = | + | si | |
| Gliptine | | | | | | | | | |
| GLP-1 RA | | | | | | | | | |
| Gliflozine | | | | | | | | | |
| Insulina bas | | | | | | | | | |

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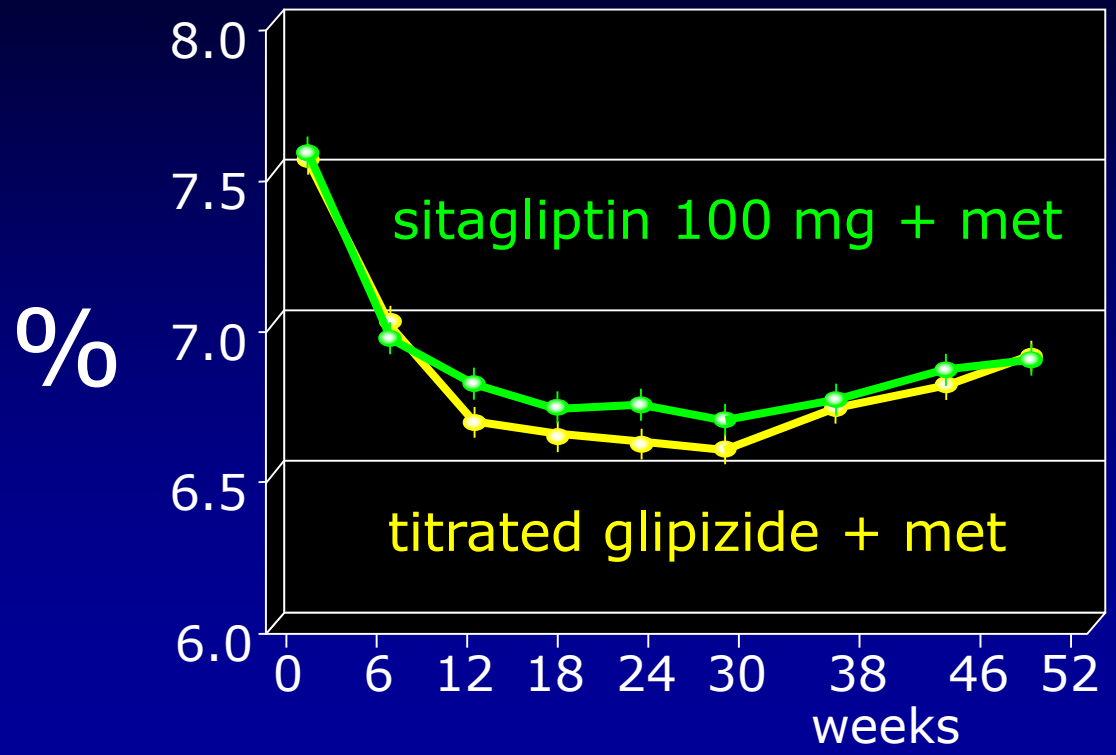
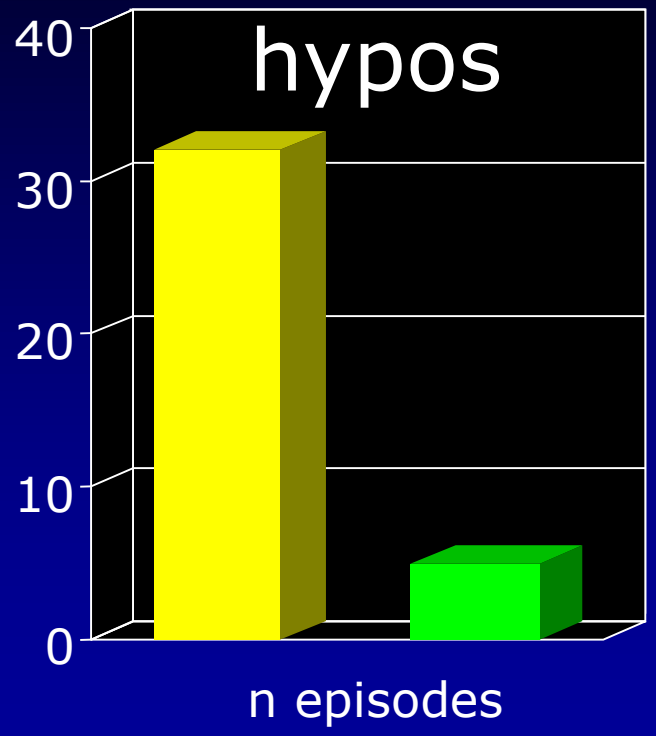
# gliptin vs. glipizide

## add-on to metformin

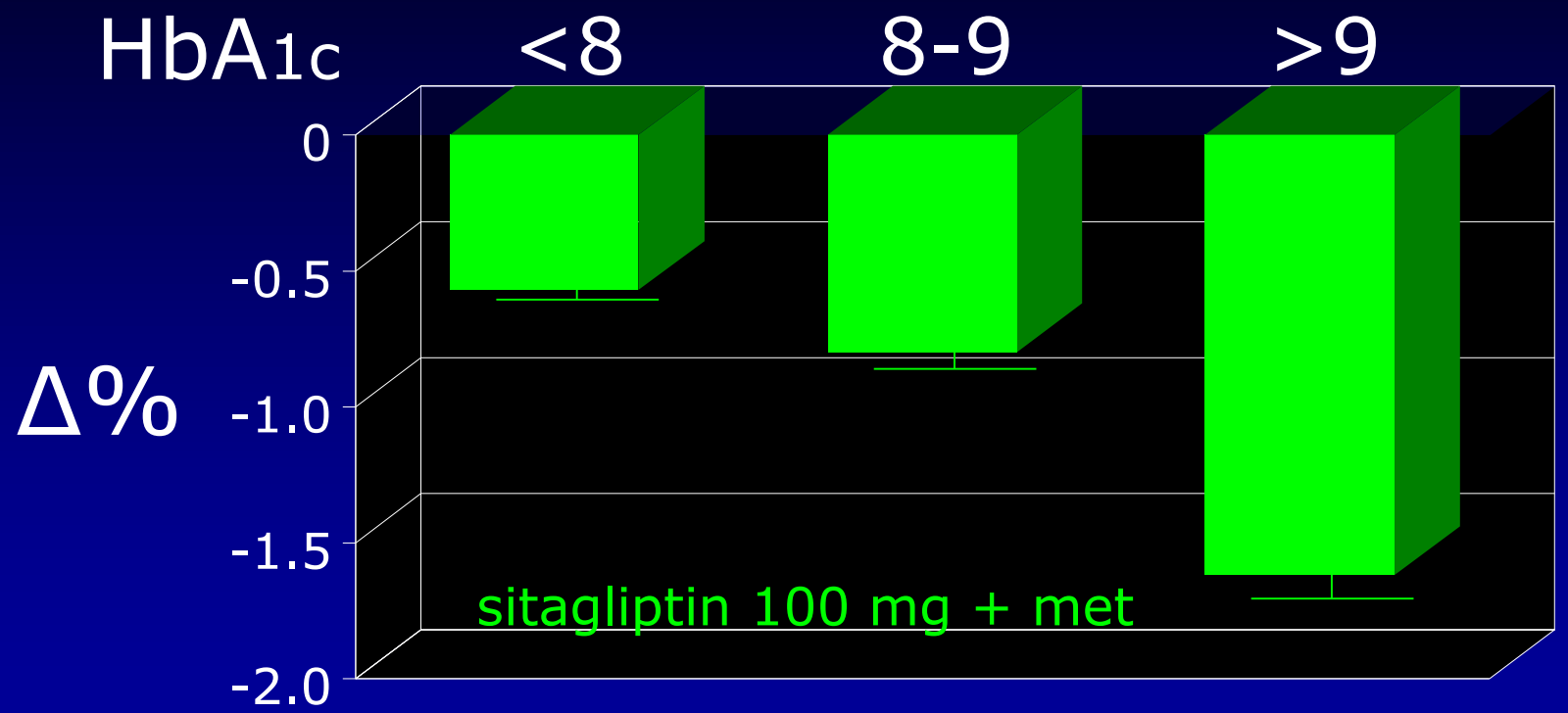



Nauck MA Diab Ob Metab 9:194, 2007

# gliptins: efficacy according to basal HbA1c

the higher is HbA1c, the higher is efficacy

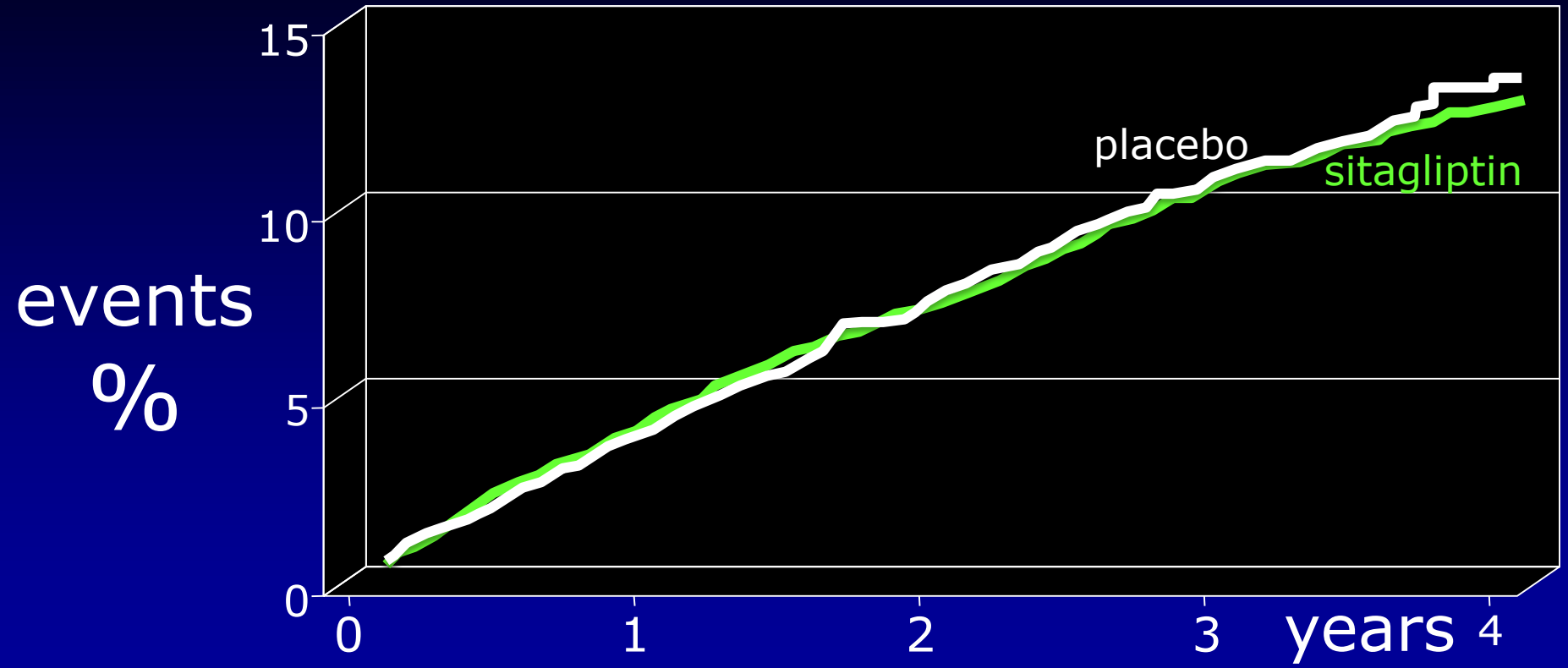



*Reductions are placebo-subtracted*

Nauck MA Diab Ob Metab 9:194, 2007

# TECOS: Primary CV Outcome

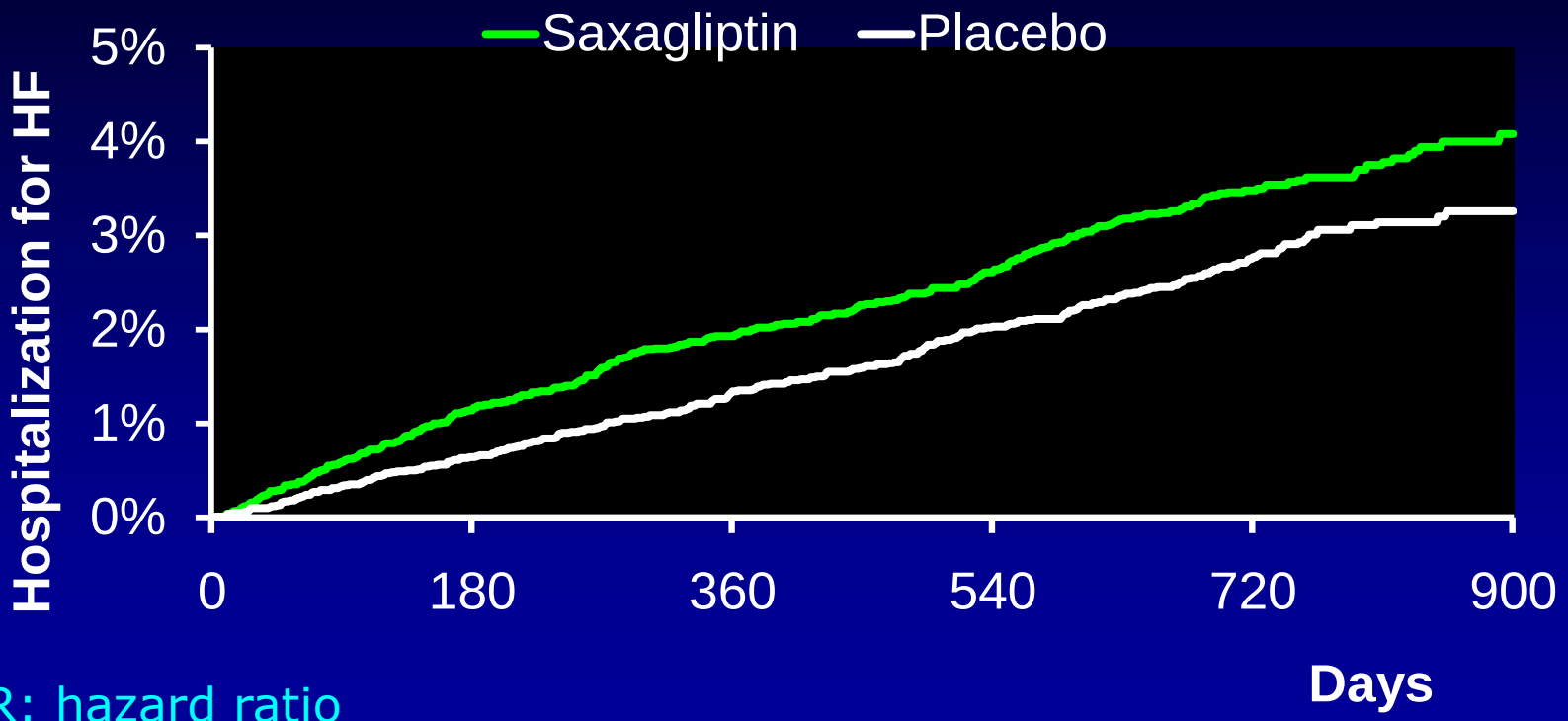
## PP Analysis for Non-inferiority




** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

*Green JB et al. NEJM 2015*

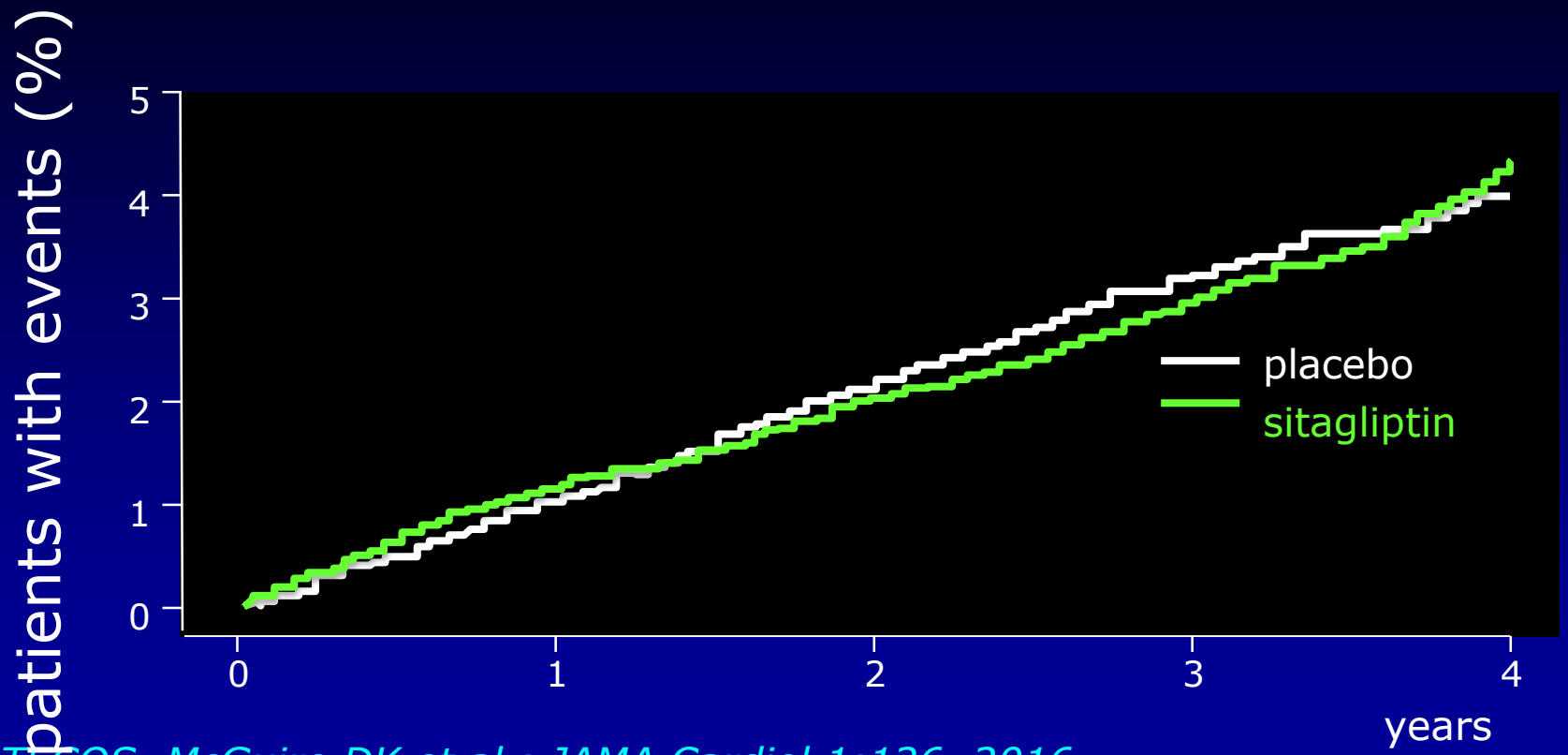
# SAVOR: Hospitalization for HF




HR: hazard ratio

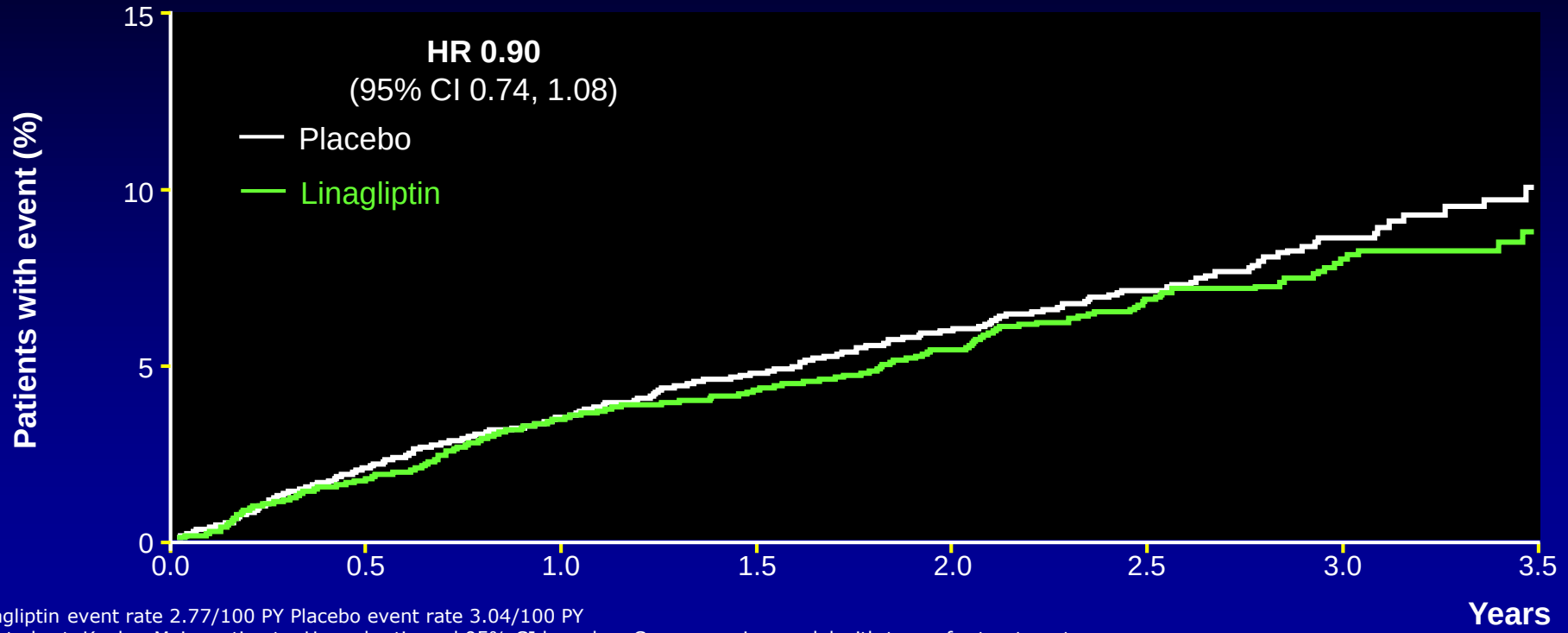
Scirica BM, et al. November 2013.

# TECOS: First hospitalization for HF



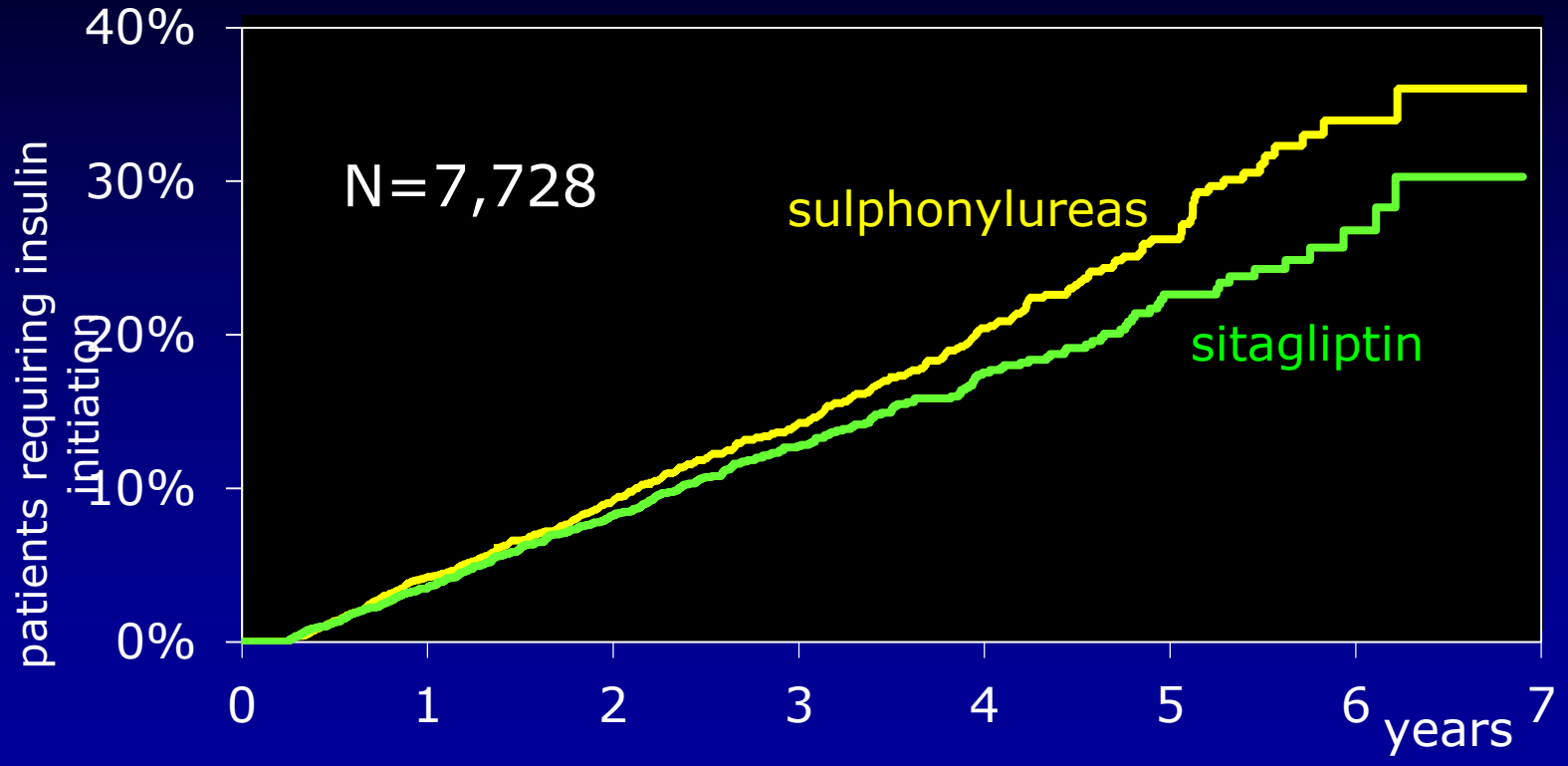

*TECOS, McGuire DK et al.: JAMA Cardiol 1:126, 2016*

# CARMELINA hHF




Linagliptin event rate 2.77/100 PY Placebo event rate 3.04/100 PY
Treated set, Kaplan-Meier estimate. Hazard ratio and 95% CI based on Cox regression model with terms for treatment group (p=0.2635), region (p=0.0012), history of heart failure (p≤0.0001); *Two-sided
hHF, hospitalization for heart failure
Rosenstock J *et al. JAMA* 2018; doi: 10.1001/jama.2018.18269

# gliptins: time to insulin initiation




*Valensi P et al. for The Odyssee Observational Study: Diabetes Metab 41:231, 2015*

# Terapia farmacologica nell'anziano

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|---|---|---|---|---|---|---|---|---|---|
| Metformina | NO | no<30 | SI | NO | digiuno | = | — | XR | |
| SU e glinidi | SI | solo gliclazide | rischio | neutro | vari | SI | + | no | |
| pioglitazone | NO | no<15 | SI | SI | digiuno | = | + | si | |
| Gliptine | NO | SI | NO | farmaci diversi | dig/pra | SI | = | si | |
| GLP-1 RA | | | | | | | | | |
| Gliflozine | | | | | | | | | |
| Insulina bas | | | | | | | | | |

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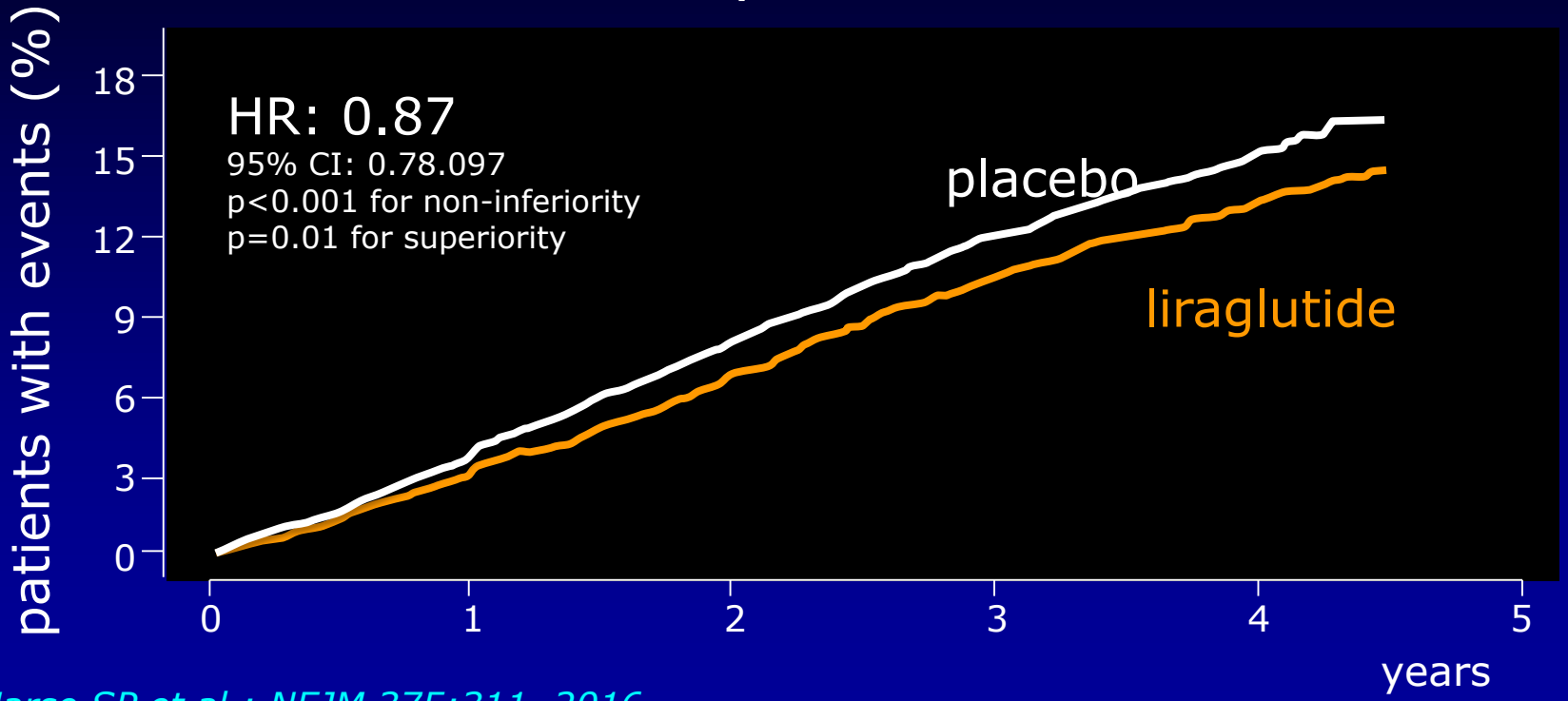
# short and long-acting GLP-1R agonists

| | Short-acting GLP-1 RA | Long-acting GLP-1 RA |
|---|---|---|
| FPG reduction | + | +++ |
| PPG reduction | +++ | ++ |
| HbA1c reduction | ++ | +++ |
| Body weight reduction | ++ | ++ |
| Gastric empting rate | +++ | + |
| fasting glucagon secr. | +/Neutral | ++ |
| GI effects | ++ | + |
| Compliance | + | ++ |

# LEADER: primary composite CV outcome

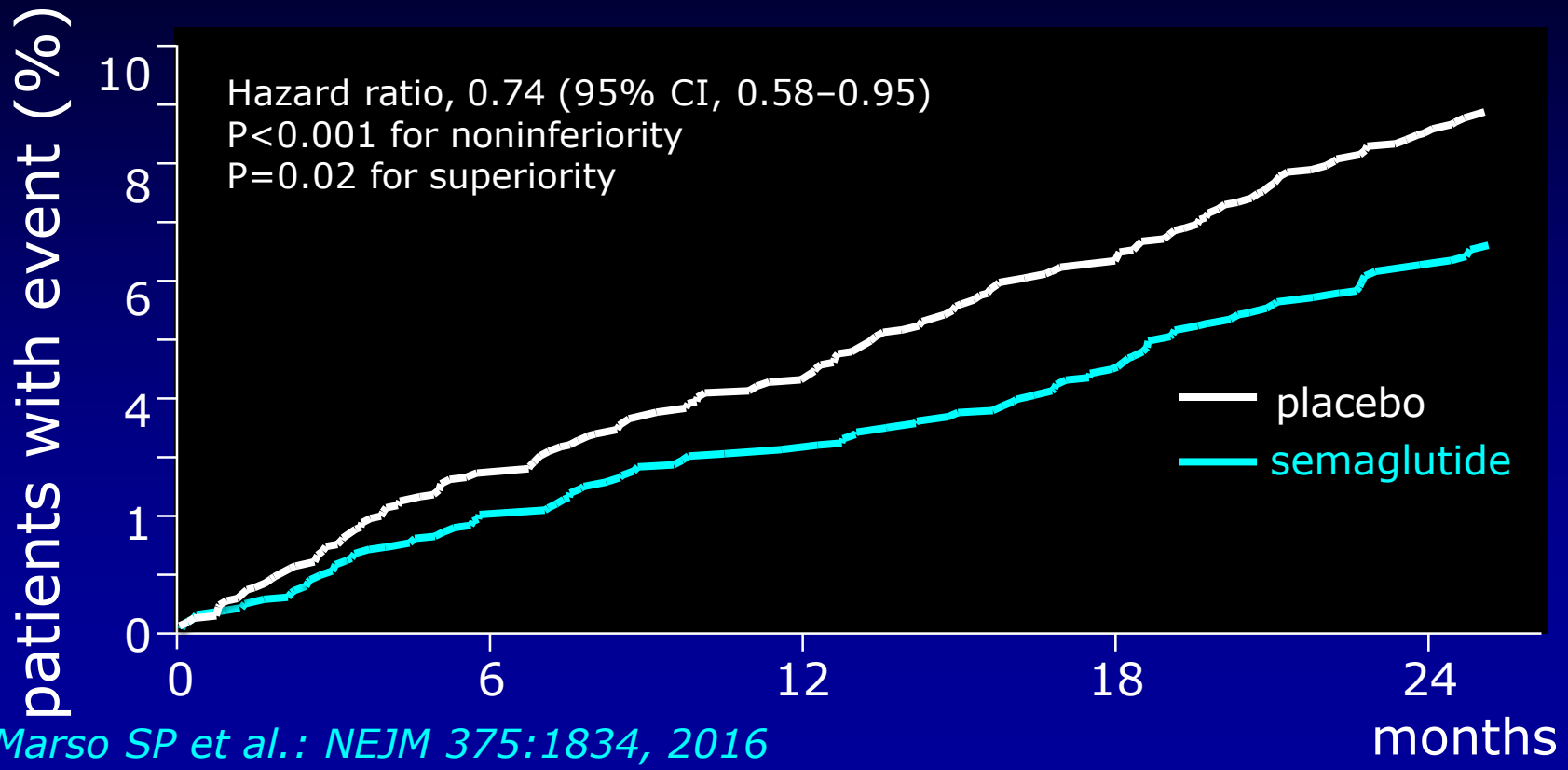
## MACE 3: CV death, non-fatal MI or stroke




*Marso SP et al.: NEJM 375:311, 2016*

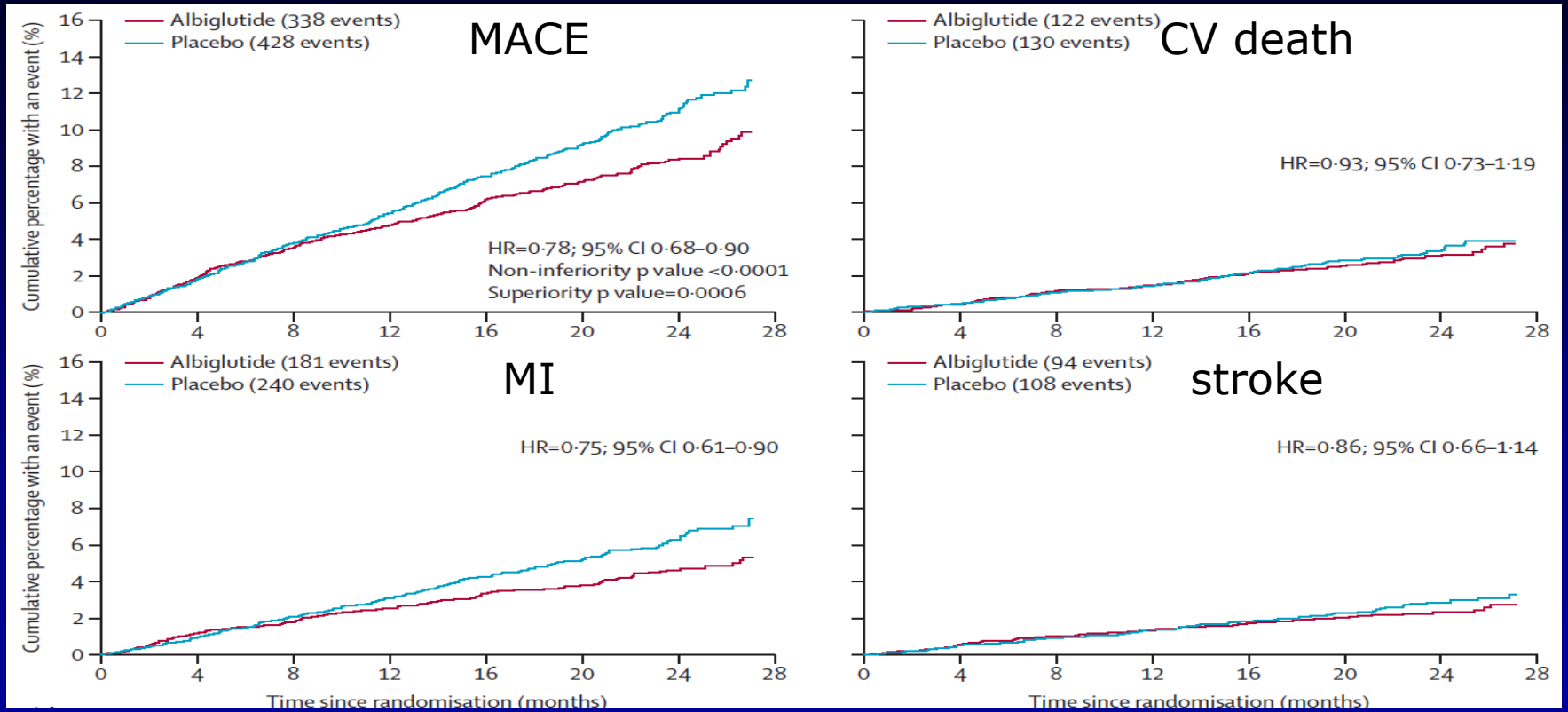
# SUSTAIN6: MACE (primary outcome)

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke




*Marso SP et al.: NEJM 375:1834, 2016*

# HARMONY OUTCOMES




Hernandez AF et al.: Lancet. 2018 Oct 1. doi: 10.1016/S0140-6736(18)32261-X

# REWIND press release

**[redacted]® (dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes**

November 5, 2018

**Only 31 percent of REWIND trial participants had established CV disease**

INDIANAPOLIS, Nov. 5, 2018 /PRNewswire/ -- [redacted] (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. [redacted] once-weekly [redacted] is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.

Experience the interactive Multichannel News Release here: https://www.multivu.com/players/English/8442751-lilly-trulicity-rewind-trial-type-2-diabetes/

The study included a majority of patients without established CV disease at baseline, a first for the GLP-1 receptor agonist class. REWIND assessed the risk of MACE in adults with type 2 diabetes with a wide range of CV risk. The study compared the effect of once-weekly [redacted] 1.5 mg to placebo when added to standard of care.

"The REWIND study was ambitious, assessing whether [redacted] could protect people with type 2 diabetes from experiencing an initial cardiovascular event, and prevent future events in those who have established cardiovascular disease," said Hertzel Gerstein, M.D., MSc, FRCPC, professor of medicine and deputy director of the Population Health Institute at McMaster University and Hamilton Health Sciences, and REWIND study chair. "The MACE reduction demonstrated by [redacted], across a broad range of people with type 2 diabetes, is compelling and we look forward to analyzing and reporting all of the data."

REWIND is distinct compared to other CV outcome trials due to the limited number of people with established CV disease who participated in the trial, allowing [redacted] CV effect to be measured in a broad population of people with type 2 diabetes. Importantly, REWIND had a median follow-up period of more than 5 years, the longest for a CV outcome trial in the GLP-1 receptor agonist class. In comparison, other CV outcome trials had more people with a higher baseline A1C and a greater percentage of patients who had established CV disease. Of the 9,901 REWIND participants, the mean baseline A1C was relatively lower at 7.3 percent, and only 31 percent had established CV disease.

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| Gliptine | NO | SI | NO | farmaci diversi | dig/pra | SI | = | si | |
| GLP-1 RA | NO | NO | farmaci diversi | NO | vario | SI | — | farmaci diversi | |
| Gliflozine | | | | | | | | | |
| Insulina bas | | | | | | | | | |

*Management of Diabetes in Older Adults*
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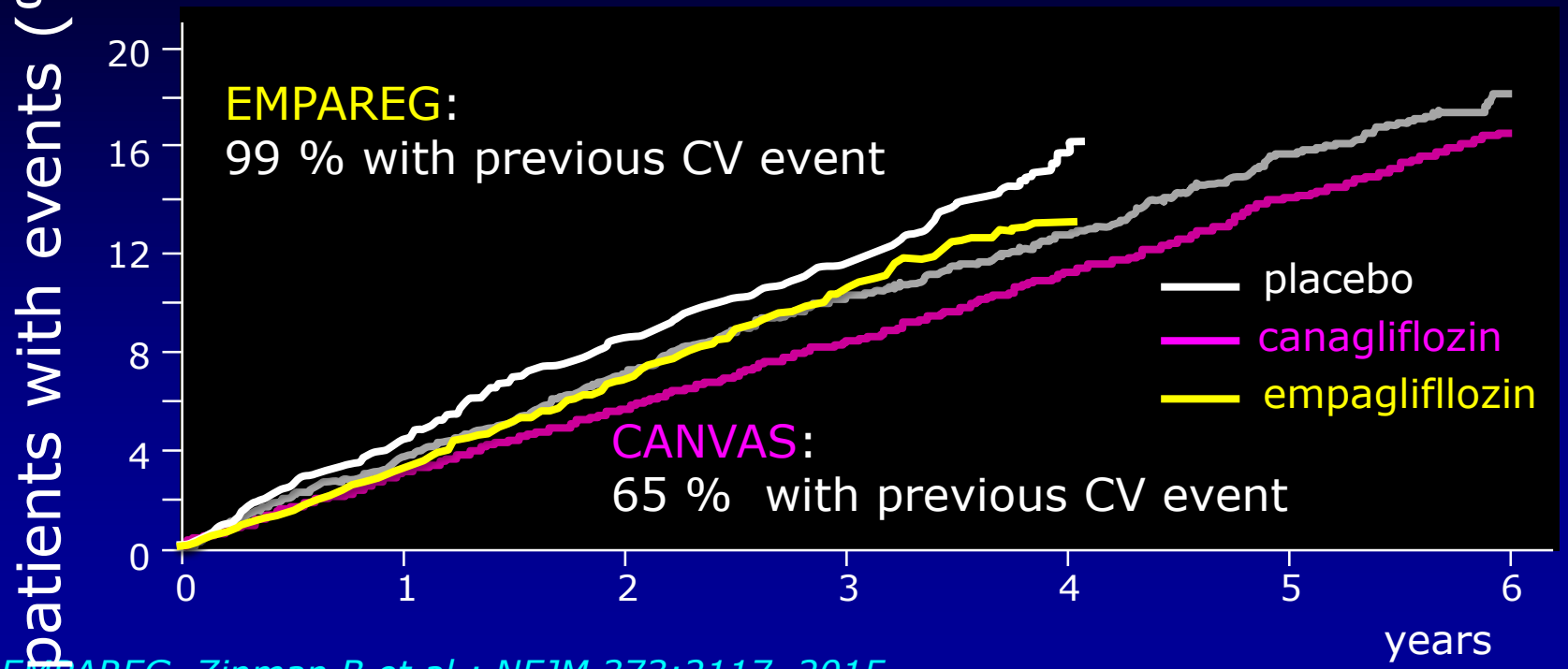
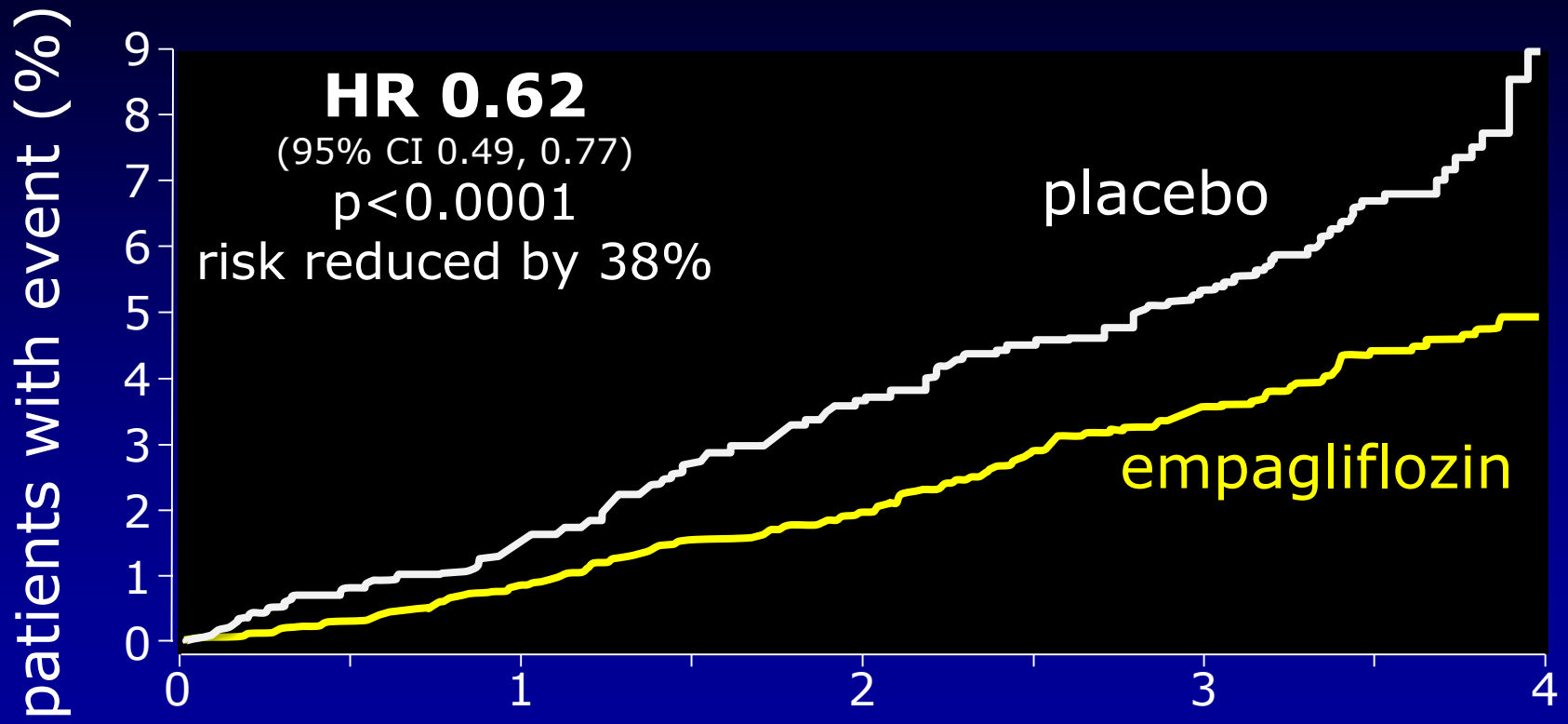
# CANVAS & EMPAREG

## MACE 3: CV death, non-fatal MI or stroke




*EMPAREG, Zinman B et al.: NEJM 373:2117, 2015*
*CANVAS, Neal B et al.: NEJM Jun 12, 2017*

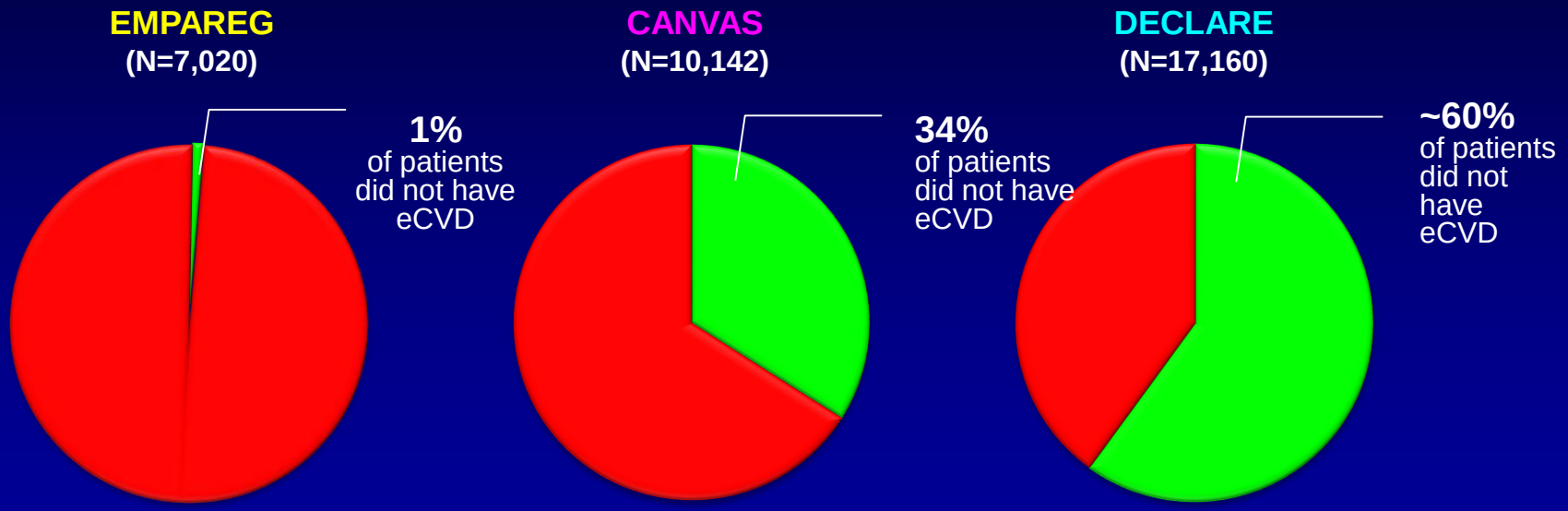
# EMPAREG: CV mortality




Zinman B et al.: NEJM 373:2117, 2015

# DECLARE has the broadest representation of the T2D patients with CV risk among the of the SGLT2i CV outcomes studies

**The proportion of patients with and without established CV disease varied across the three SGLT2 CV outcome studies**

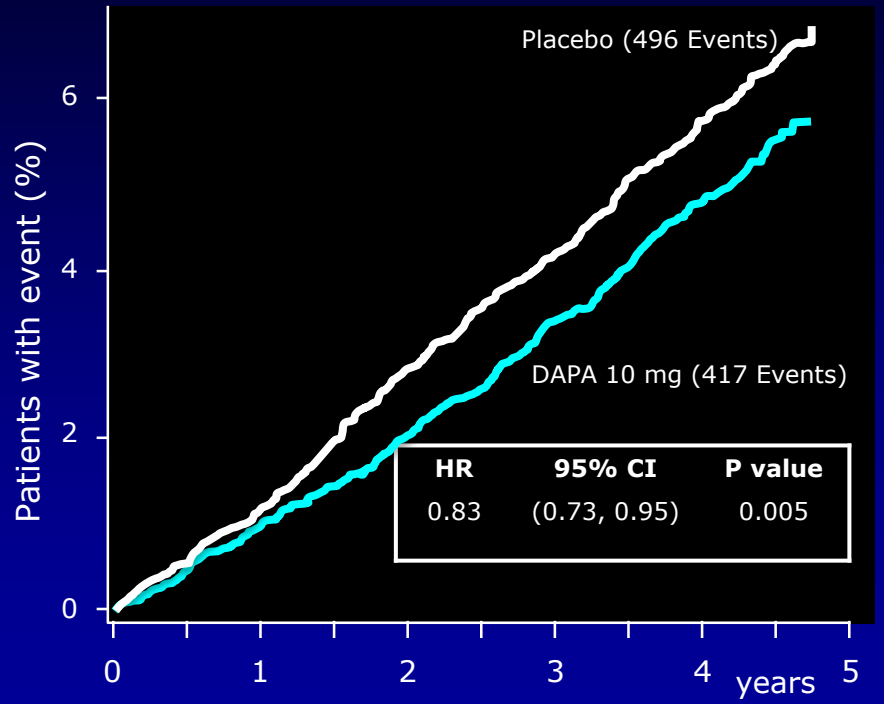



CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes; eCVD, established CV disease.

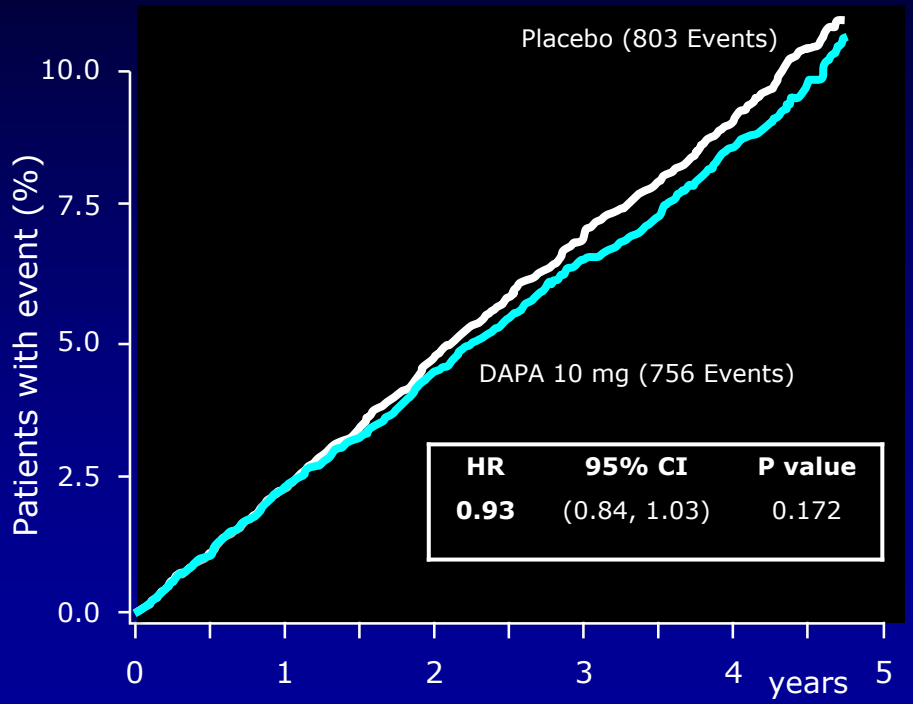
1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

# In this low CV risk population, dapagliflozin patients had a significant reduction of hHF/CV death and fewer MACE events compared to placebo

## hHF/CVD



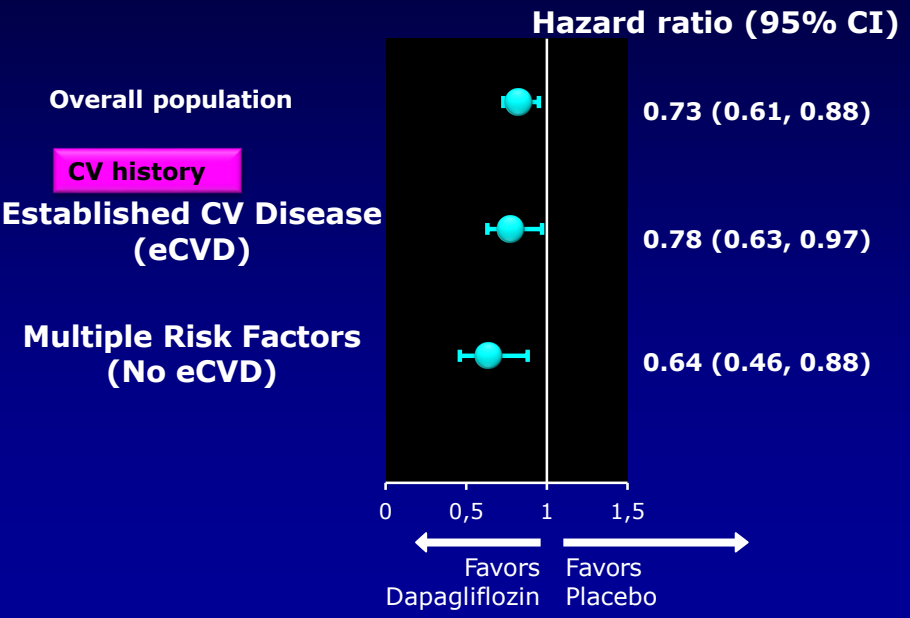

## MACE



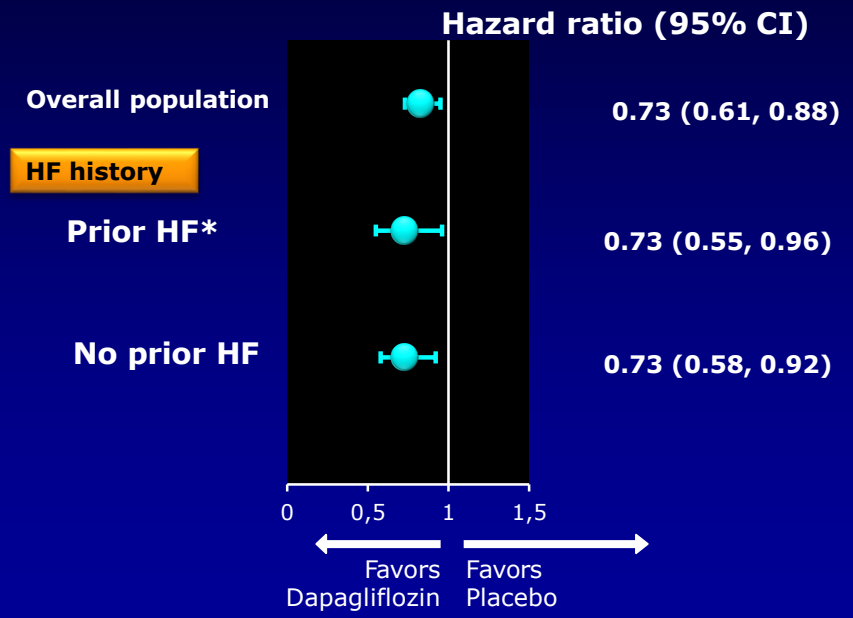

N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.
CV, cardiovascular; Dapa, dapagliflozin; hHF, hospitalization for heart failure; MACE, major adverse cardiac event
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

# Dapagliflozin prevents hHF consistently across a broad range of T2D patients regardless of history of eCVD or HF

## hHF per **CV** history




## hHF per **HF** history

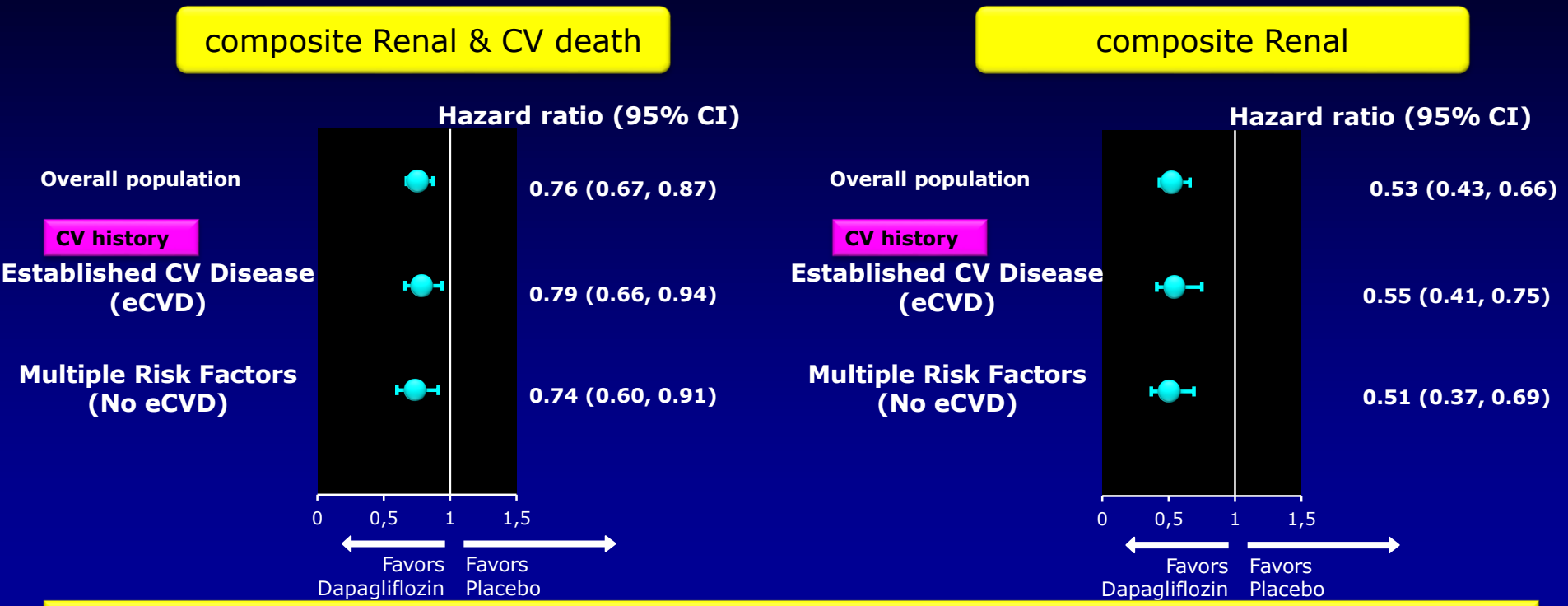



***10% of patients in DECLARE had prior HF**

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

# The renal protective effects of dapagliflozin were similar across baseline CV risk subgroup

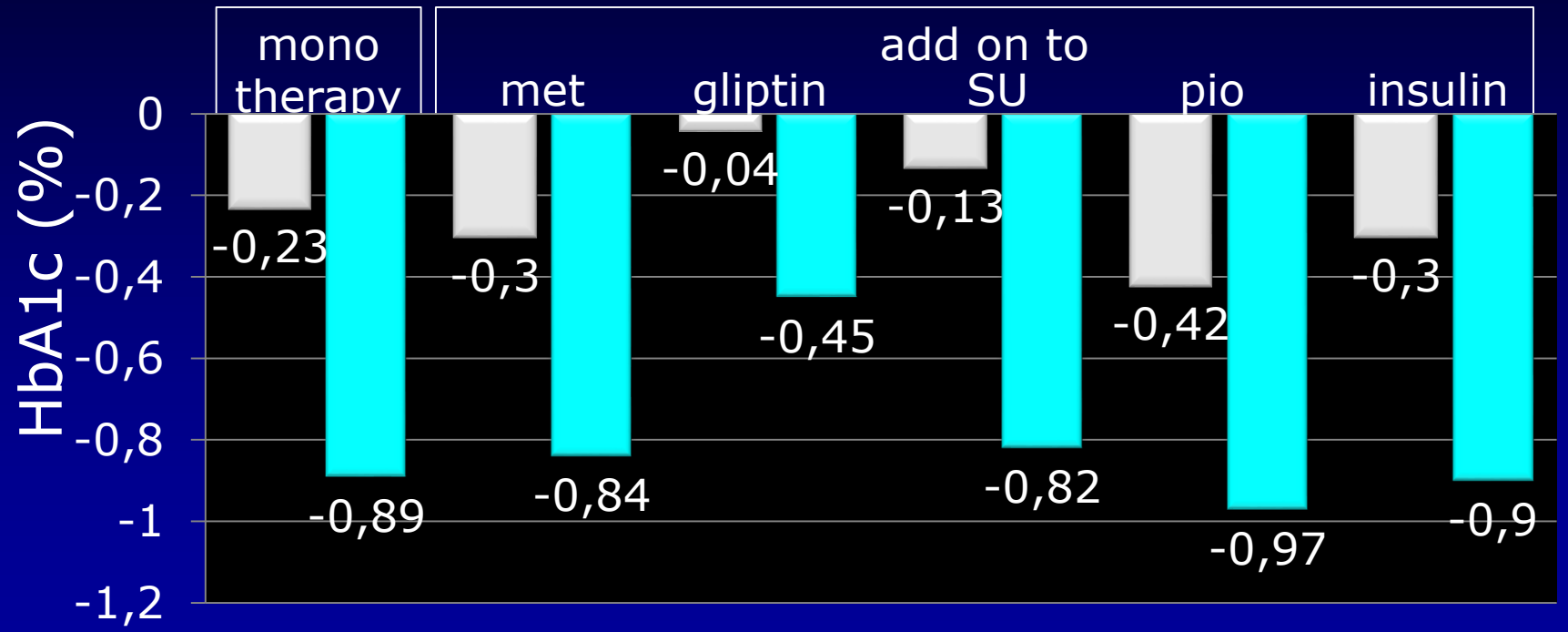



composite Renal: composite of ≥40% decrease in eGFRa to <60 mL/min/1.73 m2, ESRD, or renal death

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

# efficacy of gliflozins in various settings compared vs. placebo at 24 weeks




*1Ferrannini E, et al. Diabetes Care 2010;33:2217-24. 2Bailey CJ, et al. Lancet 2010;375:2223-33. 3Jabbour et al., Diabetes Care, pub online 15Jan2014 ; 4Strojek K, et al. Diabetes Obes Metab 2011;13:928-38. 5Rosenstock J, et al. 71st ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 0986-P. 6Wilding J, et al. Diabetes. 2010;59 (Suppl 1):A21-A22. Abstract 0078-OR*

# Terapia farmacologica nell'anziano

| | rischio di IPO | uso in IRC | prev CVD | scomp card | fenotipo glic | riserva β-cell | stato nutr. | facilità somm. | fragile |
|---|---|---|---|---|---|---|---|---|---|
| Metformina | NO | no<30 | SI | NO | digiuno | = | — | XR | |
| SU e glinidi | SI | solo gliclazide | rischio | neutro | vari | SI | + | no | |
| pioglitazone | NO | no<15 | SI | SI | digiuno | = | + | si | |
| Gliptine | NO | SI | NO | farmaci diversi | dig/pra | SI | = | si | |
| GLP-1 RA | NO | NO | farmaci diversi | NO | vario | SI | — | farmaci diversi | |
| Gliflozine | NO | NO | SI | previene ! | dig/pra | = | — | si | |
| Insulina bas | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
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| SU e glinidi | SI | solo gliclazide | rischio | neutro | vari | SI | + | no | |
| pioglitazone | NO | no<15 | SI | SI | digiuno | = | + | si | |
| Gliptine | NO | SI | NO | farmaci diversi | dig/pra | SI | = | si | |
| GLP-1 RA | NO | NO | farmaci diversi | NO | vario | SI | — | farmaci diversi | |
| Gliflozine | NO | NO | SI | previene ! | dig/pra | = | — | si | |
| Insulina bas | SI | SI | NO | NO | dig | prandiale | + | no | obbligato? |

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# take home messages

Migliorare qualità della VITA

Evitare i sintomi della iperglicemia

Evitare ipoglicemie

Prevenire il calo ponderale eccessivo

Evitare reazioni avverse

Prevenire complicanze vascolari

Prevenire rischio cardiovascolare

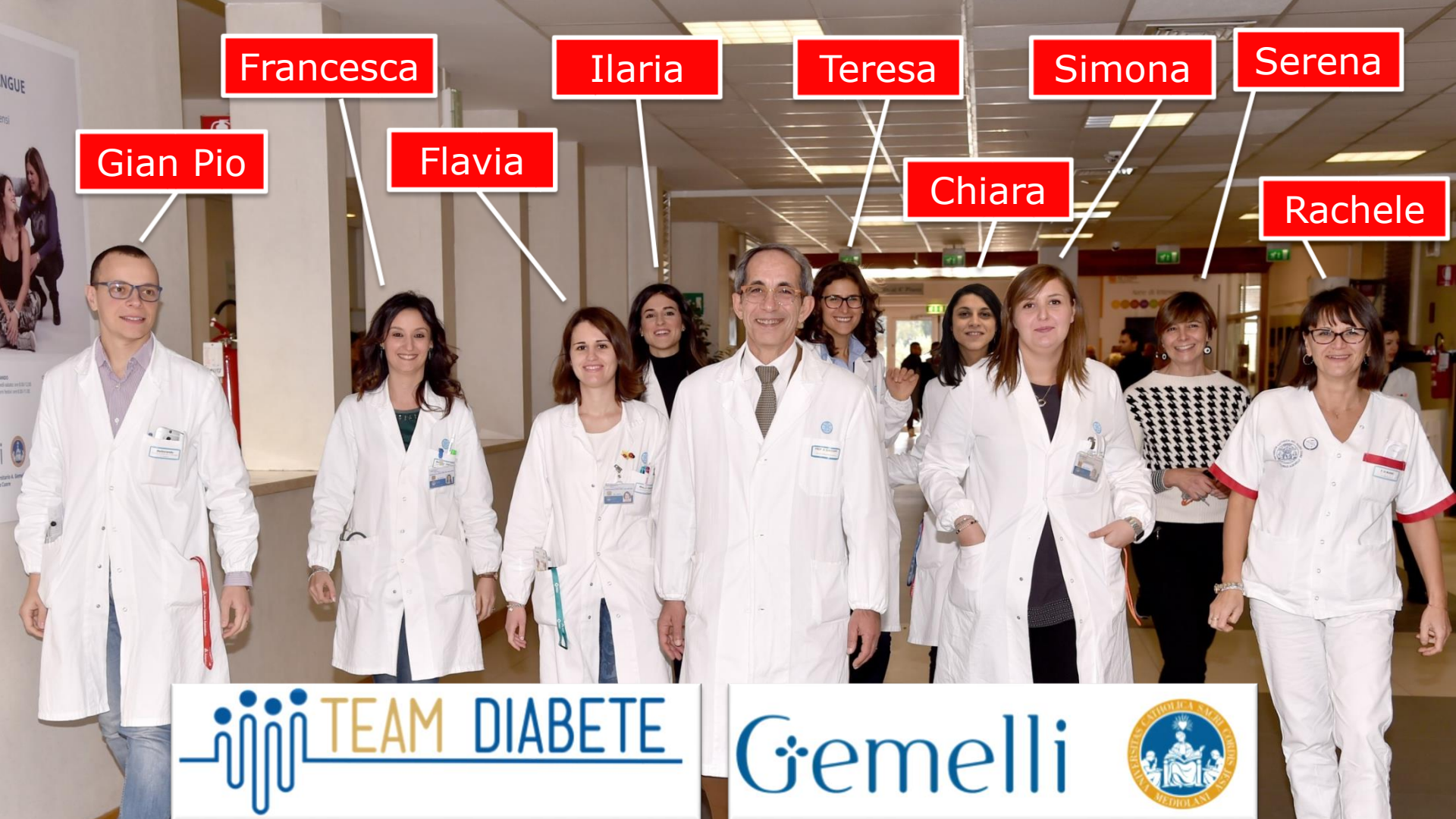
**obiettivi della personalizzazione della terapia nell' anziano diabetico**

conoscere il PAZIENTE

conoscere i FARMACI

Valutazione comprensiva BIOLOGICA-PSICOLOGICA-SOCIALE

Scelta del miglior rapporto rischio beneficio possibile


Gian Pio
Francesca
Flavia
Ilaria
Teresa
Chiara
Simona
Serena
Rachele
TEAM DIABETE
Gemelli