

New Treatments in Diabetes

HOW TO GET ORIENTED IN DIABETES TREATMENT: THE ITALIAN GUIDELINES

Cairo
November 21st
2014

Andrea Giaccari

Endocrine
Metabolic
Diseases

Policlinico
Gemelli

Rome
Italy



Gemelli

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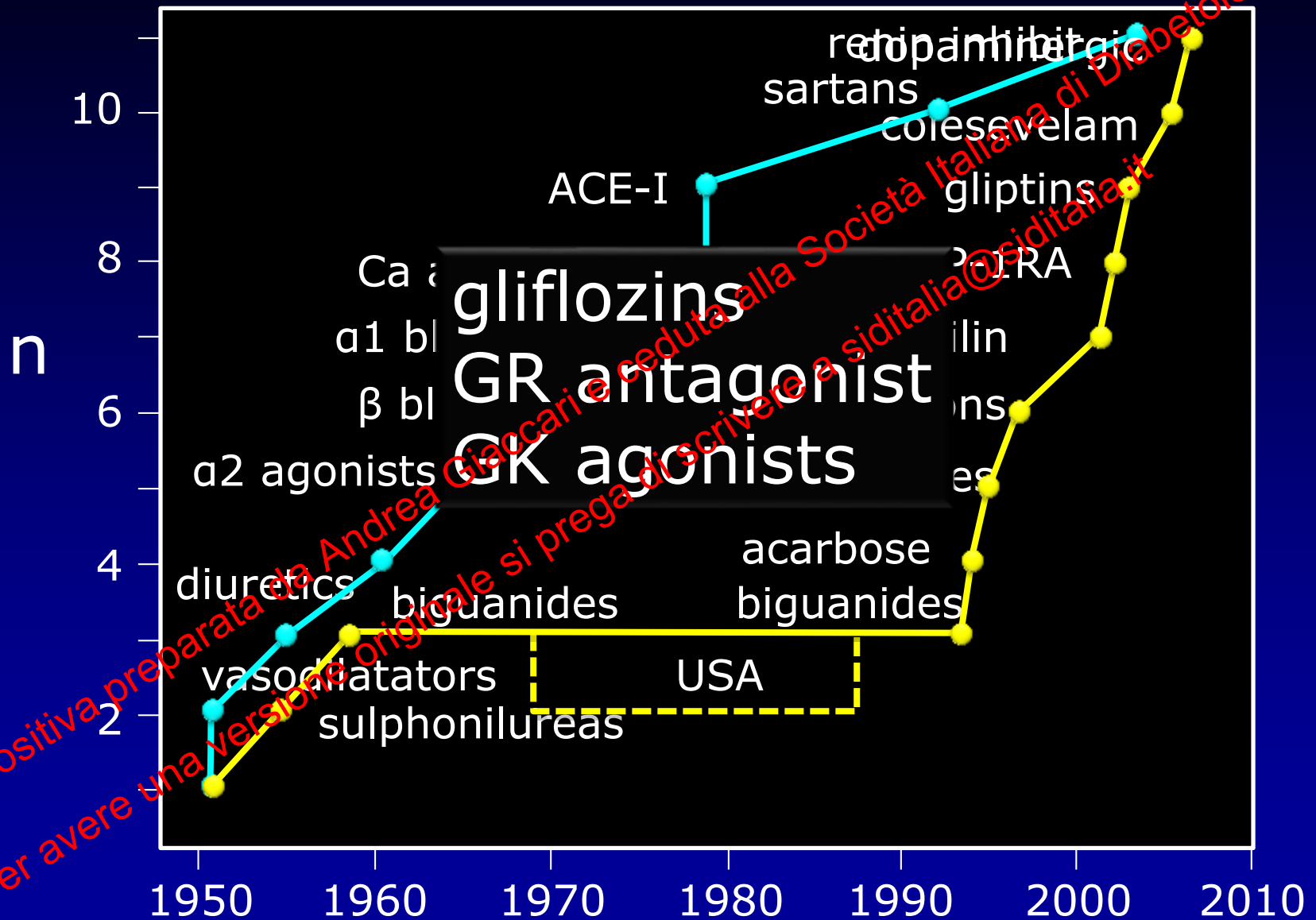
disclosure

During the last 2 years I received:

- consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, sanofi and Takeda.
- Research grants from GSK, Laboratori Guidotti, MSD (Merck), Novartis.

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classes of drugs for type 2 diabetes (USA)



Ralph DeFronzo's ominous octet

reduced
insulin
secretion

β -cell

reduced
incretin
effect

increased
lipolysis

Blood vessel

hyperglycemia

α -cell

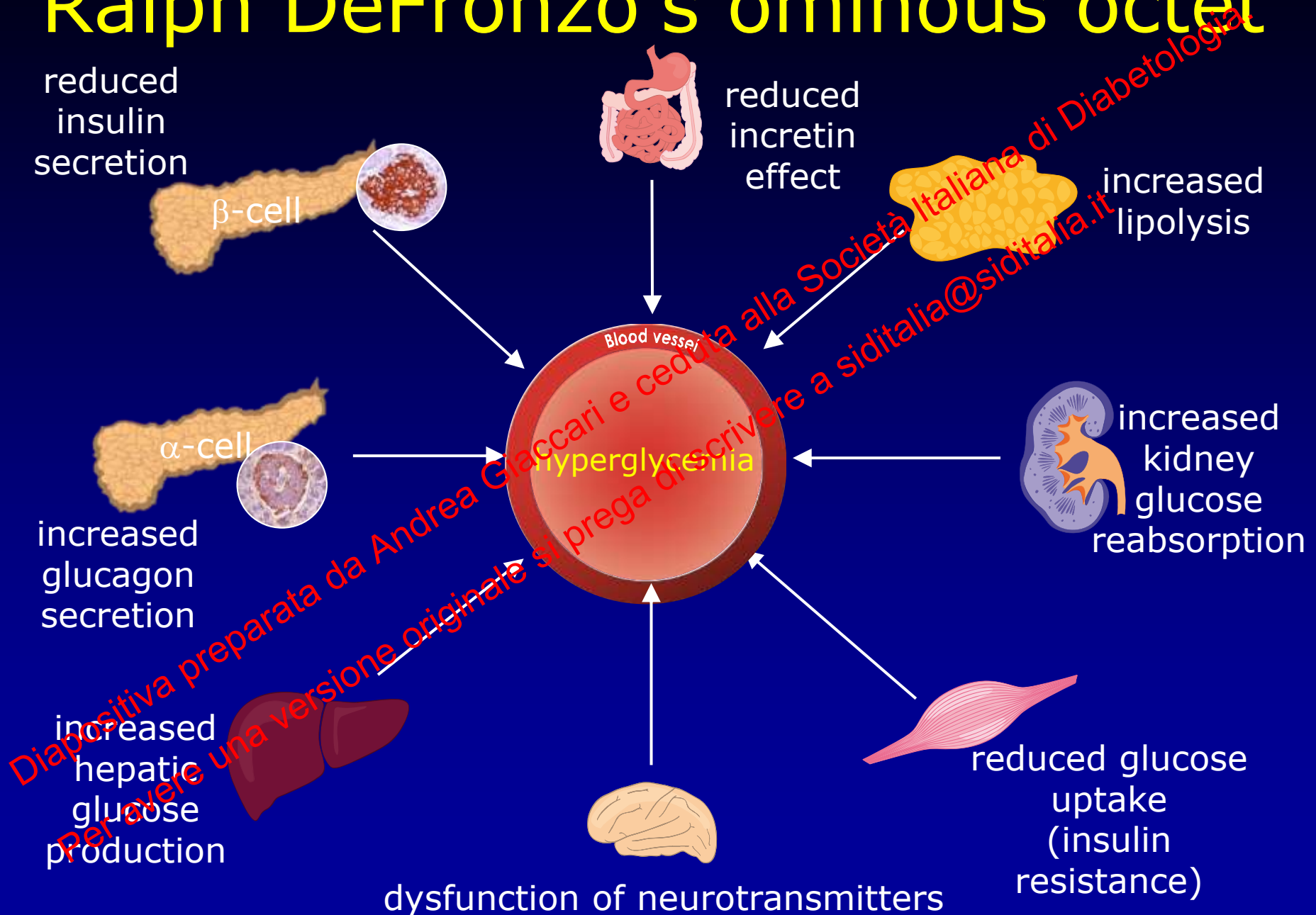
increased
glucagon
secretion

increased
kidney
glucose
reabsorption

increased
hepatic
glucose
production

reduced glucose
uptake
(insulin
resistance)

dysfunction of neurotransmitters



classes of medicines for type 2 diabetes

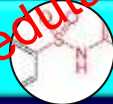
- Detemir
- Glargine
- Degludec
- NPH

INSULIN



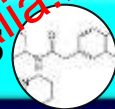
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Glipizide
- Glipizide

SULPHONYLUREAS



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINS



- Pioglitazone

TZDS



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS



need to personalize!

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Initial drug monotherapy

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs

Two drug combinations*

Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs

Three drug combinations

More complex insulin strategies

Healthy eating, weight control, increased physical activity

Metformin

high
low risk
neutral/loss
GI / lactic acidosis
low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea†	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin (usually basal)
high	high	intermediate	high	highest
moderate risk	low risk	low risk	low risk	high risk
gain	gain	neutral	loss	gain
hypoglycemia‡	edema, HF, fx†	rare‡	GI‡	hypoglycemia‡
low	high	high	high	variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

Metformin +	Metformin +	Metformin +	Metformin +	Metformin +
Sulfonylurea†	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin (usually basal)
+ TZD	+ SU†	+ SU†	+ SU†	+ TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or DPP-4-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§			

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

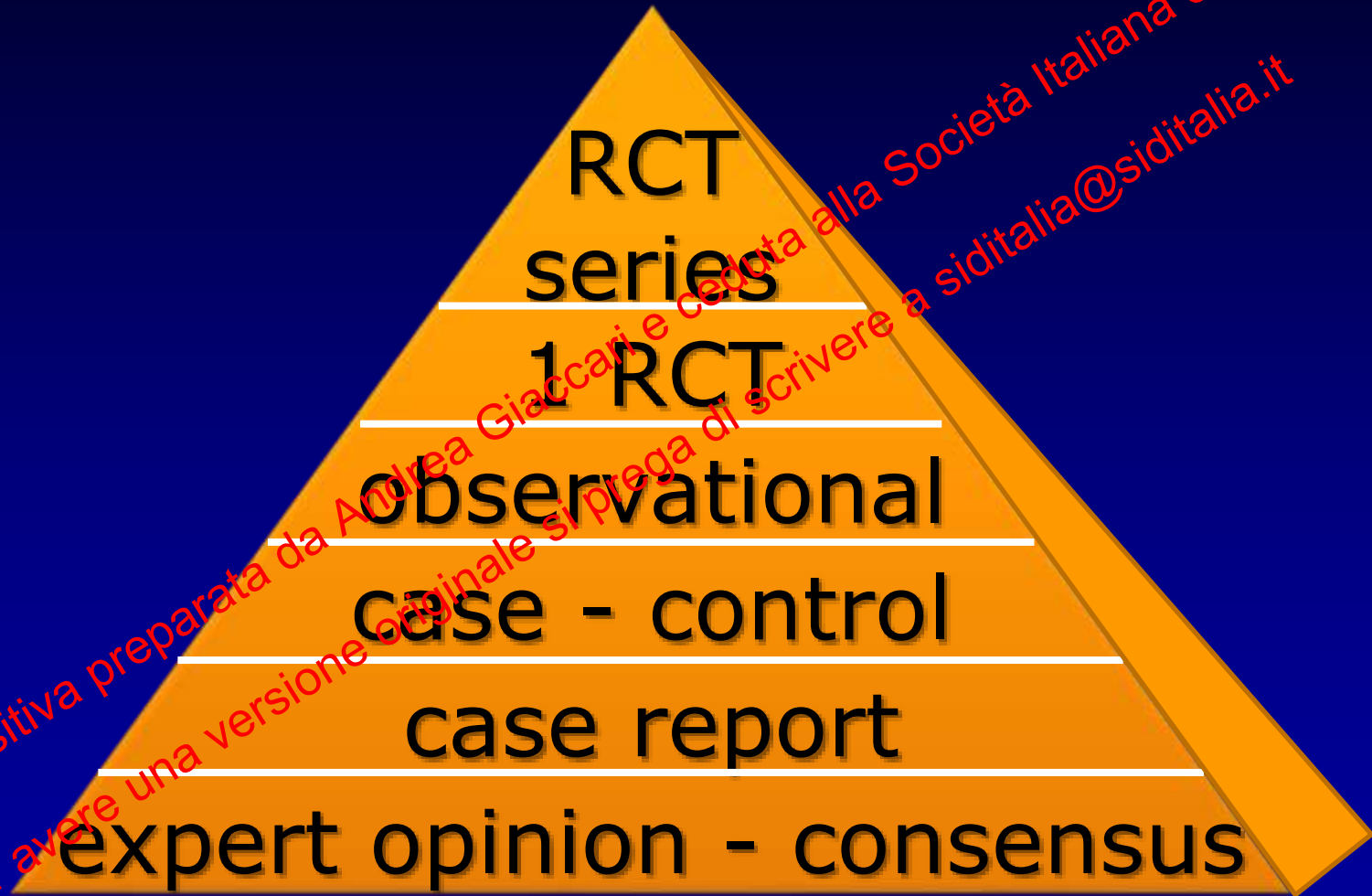
Insulin#
(multiple daily doses)

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	typical patient
Metformin	
Gliptin	
GLP-1 R.A.	
Sulphonylurea or Repaglinide	
Pioglitazone	
Acarbose	
Gliflozin	
Insulin (basal)	

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the pyramid of evidences



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the only evidence-based guideline

CLINICAL GUIDELINE



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.

For author affiliations, see end of text.

www.annals.org

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Description: The American College of Physicians developed this guideline to present the recommendations on the comparative effectiveness of diabetes medications.

Methods: This guideline is based on a systematic review of evaluating literature published from April 2010 that was identified in MEDLINE, EMBASE, and Controlled Trials. Searches for clinical outcomes, all-cause mortality, cardiovascular morbidity, neuropathy, and guideline grades the evidence. The American College of Physicians System.

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes

Recommendation 1:

- add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, *have failed*

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Methods: This guideline is based on a systematic evidence review evaluating literature published from April 2010 that was updated in December 2010. The review included Controlled Trials and Observational Studies. The clinical outcomes included all-cause mortality, cardiovascular morbidity, and quality of life. The guideline grades were based on the American College of Physicians (ACP) System.

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.

Recommendation 2:

- prescribe monotherapy with metformin for initial therapy to treat most patients with t2D

Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes

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Description: The American College of Physicians developed this guideline to present recommendations on the combination of oral diabetes medications.

Methods: This guideline evaluated literature published April 2010 that was identified in a search of the MEDLINE (December 2010), EMBASE, and Cochrane 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.

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Recommendation 3:

- add a second agent to metformin to treat patients with persistent hyperglycemia

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HOW TO PERSONALIZE TREATMENT OF TYPE 2 DIABETES

- glycemic phenotype and pathogenesis of hyperglycemia
- weight
- complications
- compliance

whatever the patient,
always start with
metformin!

- obesity
- «hepatic»

- second phase
- global

- kidney
- incretin deficiency

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4 Rules for metformin Rx

1. At least 2g daily
2. Run-in
3. For all patients with T2D
4. Attention to eGFR
 - a. Monitor if eGFR < 60 mL/min
 - b. Discontinue if eGFR < 30 mL/min
 - c. Discontinue (temp.) if procedures carry risk of acute renal failure (e.g. iodinated contrast media)

and then?

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T2D therapy: classes of drugs

- Detemir
- Glargine
- Degludec
- Lispro
- Aspart
- Glulisine
- NPH
- human

Insulins



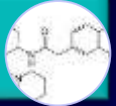
- Gliclazide
- Glibenclamide/
glyburide
- Glimepiride
- Tolbutamide
- Chlorpropamide
- Glipizide

SUs



- Nateglinide
- Repaglinide

Glinides



- Metformin

Biguanides



- Pioglitazone

TZDs



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

Gliptins



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

α Glucosidase inhibitors



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 inhibitors



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which combination?

- personal experience
- efficacy
- pathogenic therapy
- meta-analysis

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which combination?

- 5 classes of drugs:
 - sulphonylurea (and glinides)
 - pioglitazone
 - incretins (DPP-4i & GLP1-RA)
 - acarbose
 - insulin

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which combination?

- 5 classes of medicines:
- number of combinations: 5!

$$5 * 4 * 3 * 2 = 120$$

plus gliflozins $120 * 6 = 720$

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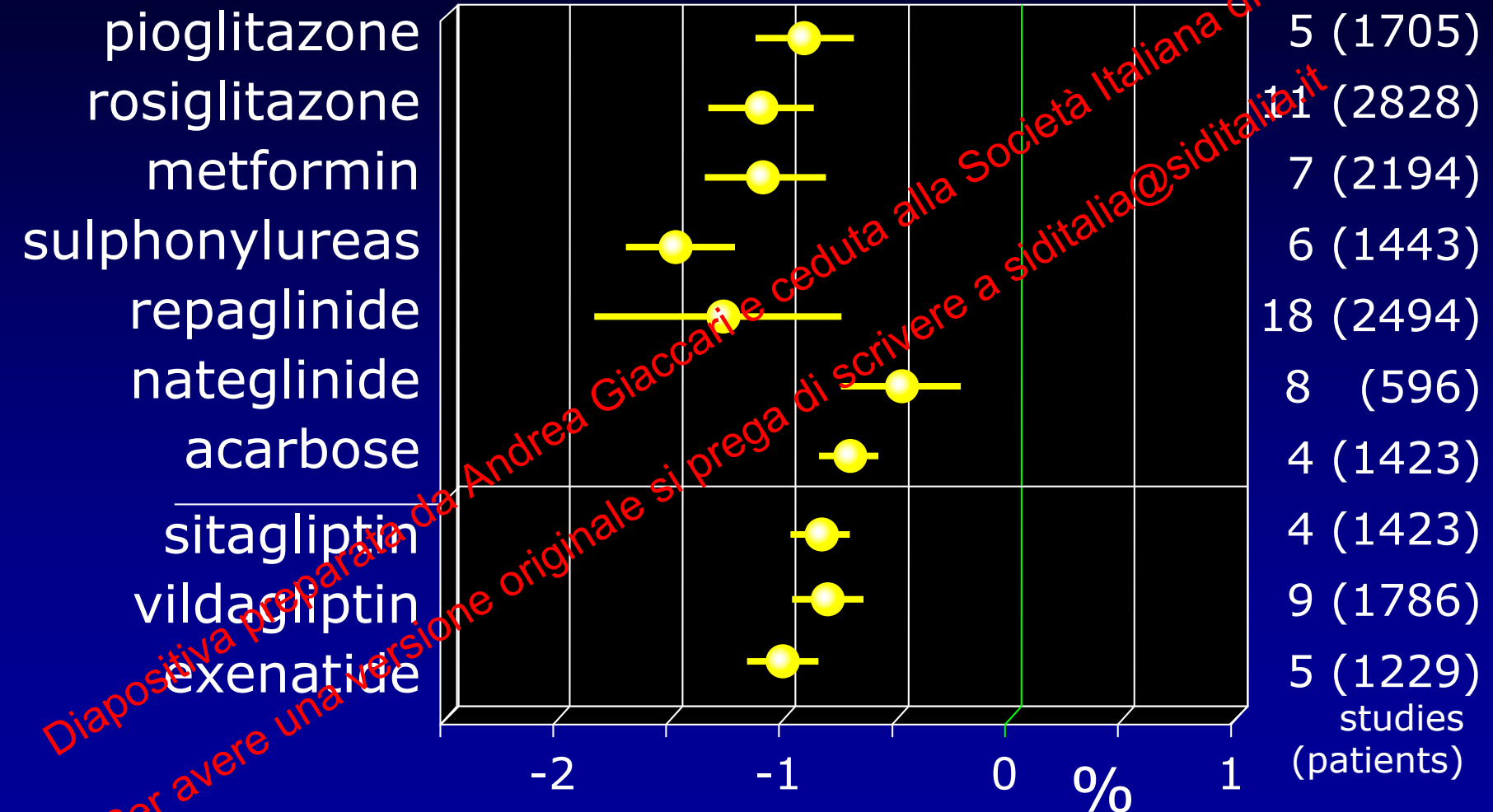
which combination?

- personal ~~experience~~
- efficacy

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effect on HbA1c vs. placebo

meta-analysis of drug studies



Bolen S. et al: Ann Intern Med 147:386, 2007

Amori RE et al: JAMA 298:194, 2007

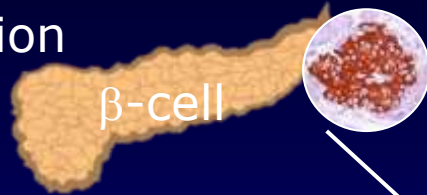
which combination?

- personal ~~experience~~
- ~~efficacy~~
- pathogenic therapy

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Ralph DeFronzo's ominous octet

reduced
insulin
secretion



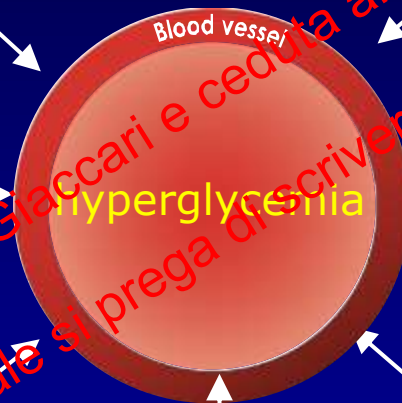
reduced
incretin
effect



increased
lipolysis



increased
glucagon
secretion

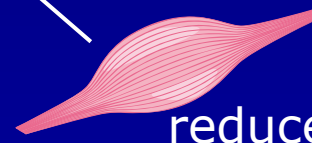


increased
kidney
glucose
reabsorption

increased
hepatic
glucose
production



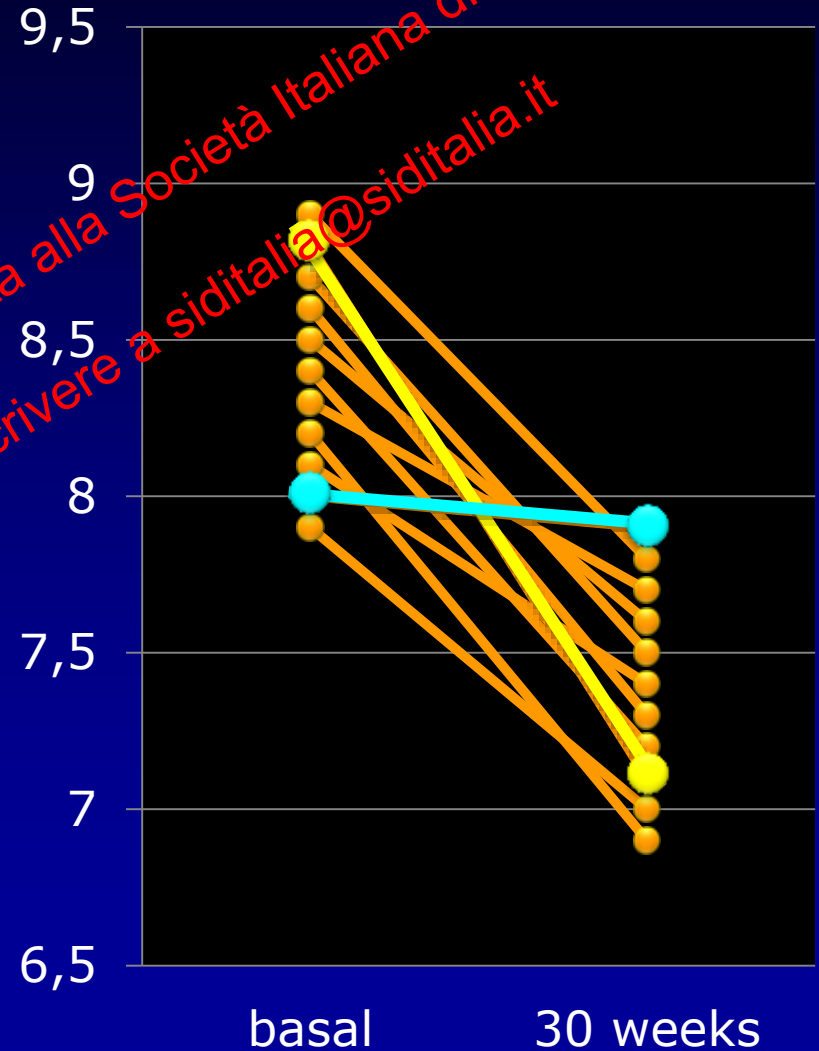
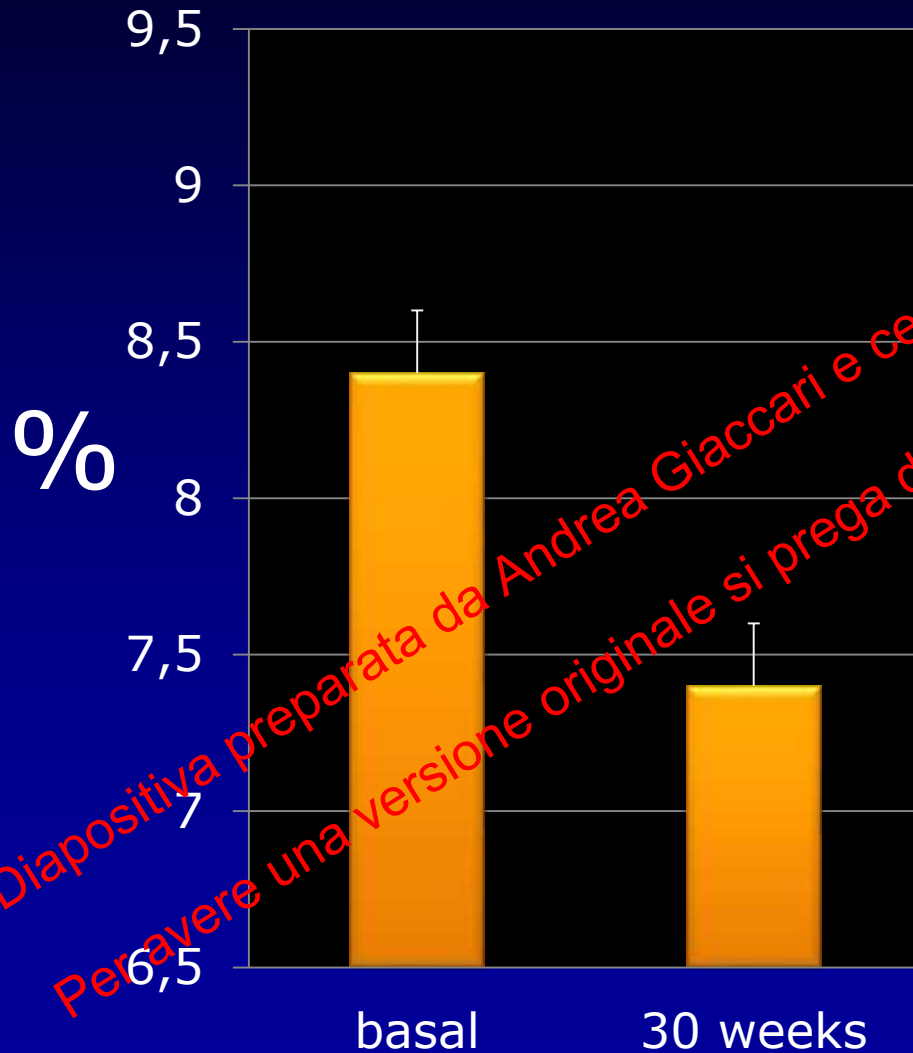
dysfunction of neurotransmitters



reduced glucose
uptake
(insulin
resistance)

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exenatide: add on metformin effect on HbA1c



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Evidence for personalized therapy

This drug should
be prescribed for
obese diabetic
patients

Does this mean
that it might not
be used in **lean**
patients?

**You had
better not
say that!**



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but then, which combination?

- personal experience
- efficacy
- pathogenic therapy
- meta-analysis

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rosiglitazone: the final meta-analysis for MI

RECORD

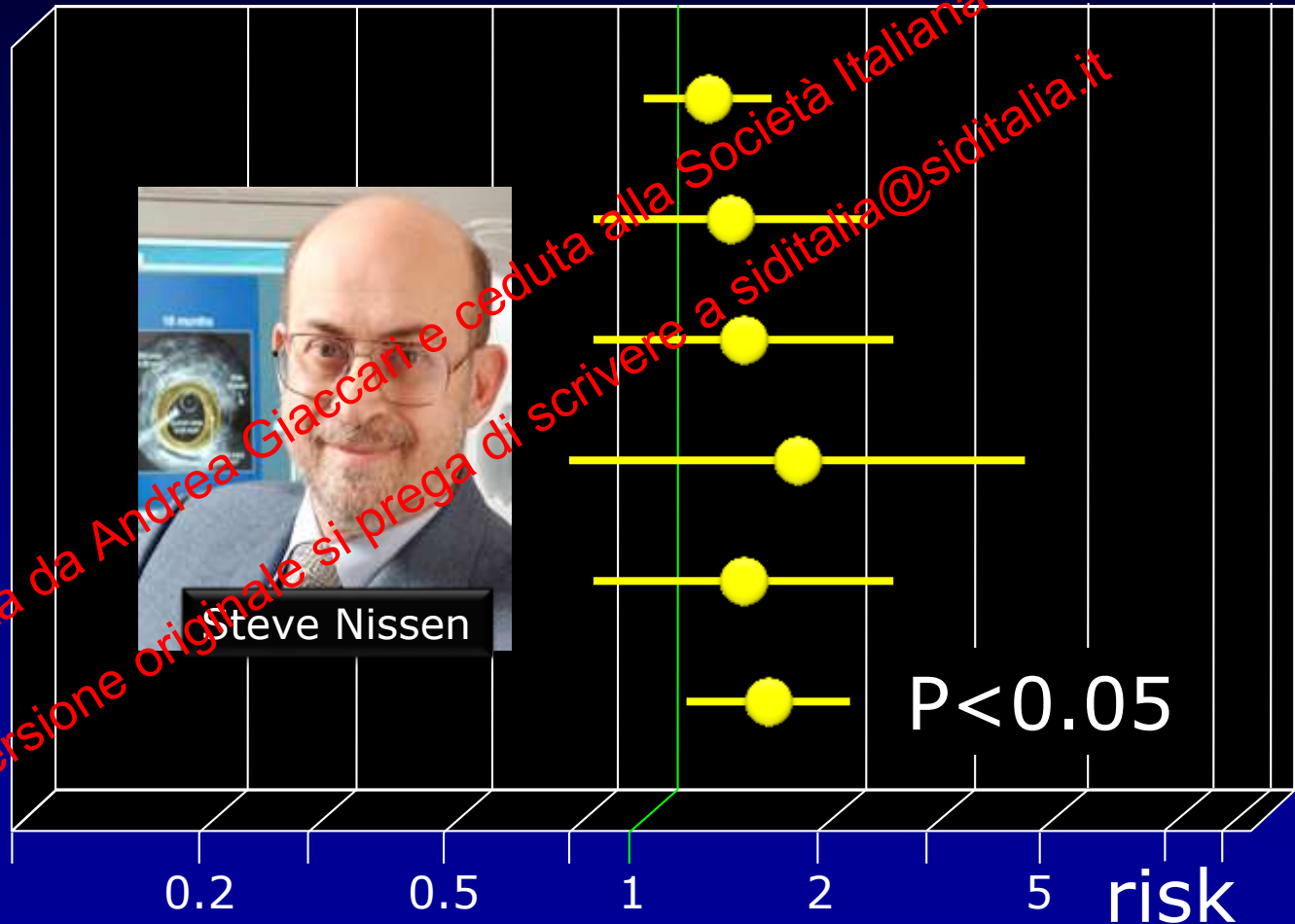
ADOPT

DREAM

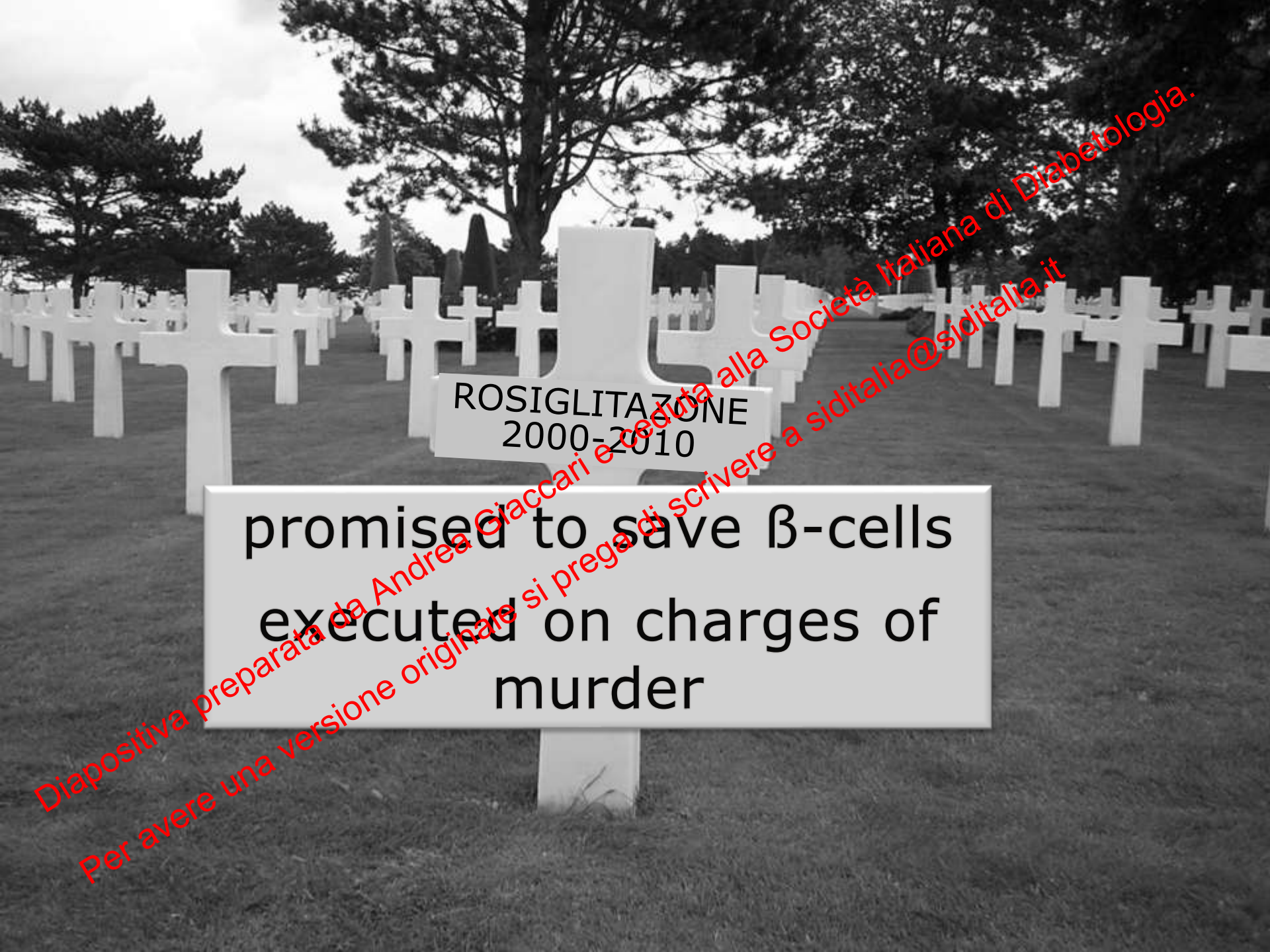
3 arms

2 arms

all



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ROSIGLITAZIONE
2000-2010

promised to save β -cells
executed on charges of
murder

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NEWS

FDA panel advises easing restrictions on rosiglitazone

Miriam E Tucker

Bethesda, Maryland

A joint Food and Drug Administration advisory panel has voted to ease the current stringent restriction on prescription of the antidiabetes drug rosiglitazone (marketed by GlaxoSmithKline as Avandia), despite lingering concerns about its cardiovascular safety.

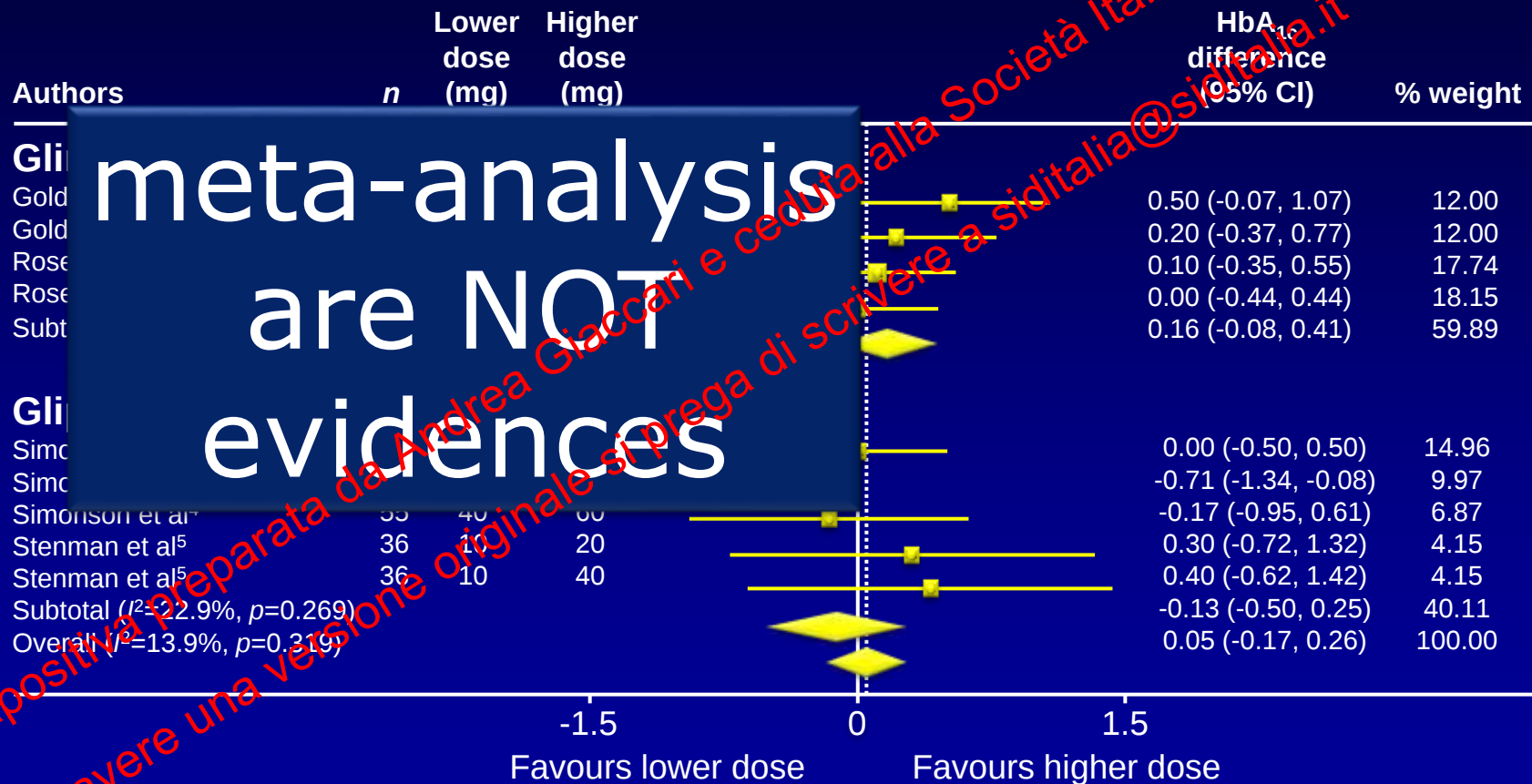
infarction, or stroke; cardiovascular death; myocardial infarction; stroke; and all causes of death—were significant.

Panel members said that they were somewhat reassured by the readjudication, but they also expressed concern that the trial's

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Higher doses of SUs do not reduce HbA1c more than lower doses

Meta-analysis of head-to-head studies (N=911)



Pooled mean difference in HbA_{1c} (high vs low dose): 0.05, 95% CI -0.17, 0.26

1. Hirst JA, et al. *Diabetologia* 2013;56:973-984.
2. Goldberg RB, et al. *Diabetes Care* 1996;19:849-856.
3. Rosenstock J, et al. *Diabetes Care* 1996;19:1194-1199.
4. Simonson DC, et al. *Diabetes Care* 1997;20:597-606.
5. Stenman S, et al. *Ann Intern Med* 1993;118:169-172

but then, which combination?

- personal ~~experience~~

- ~~efficacy~~

- pathog ~~evidence-based~~

- meta-~~a~~ **pros and cons
of each
treatment**

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Insulins



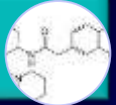
- Gliclazide
- Glibenclamide/
glyburide
- Glimepiride
- Tolbutamide
- Chlorpropamide
- Glipizide

SUs



- Nateglinide
- Repaglinide

Glinides



- Metformin

Biguanides



- Pioglitazone

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SGLT2 inhibitors



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classes of medicines for type 2 diabetes

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INSULIN



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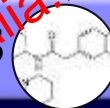
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GLINIDES



- Metformin

BIGUANIDES



- Acarbose
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ALPHA GLUCOSIDASES INHIBITORS



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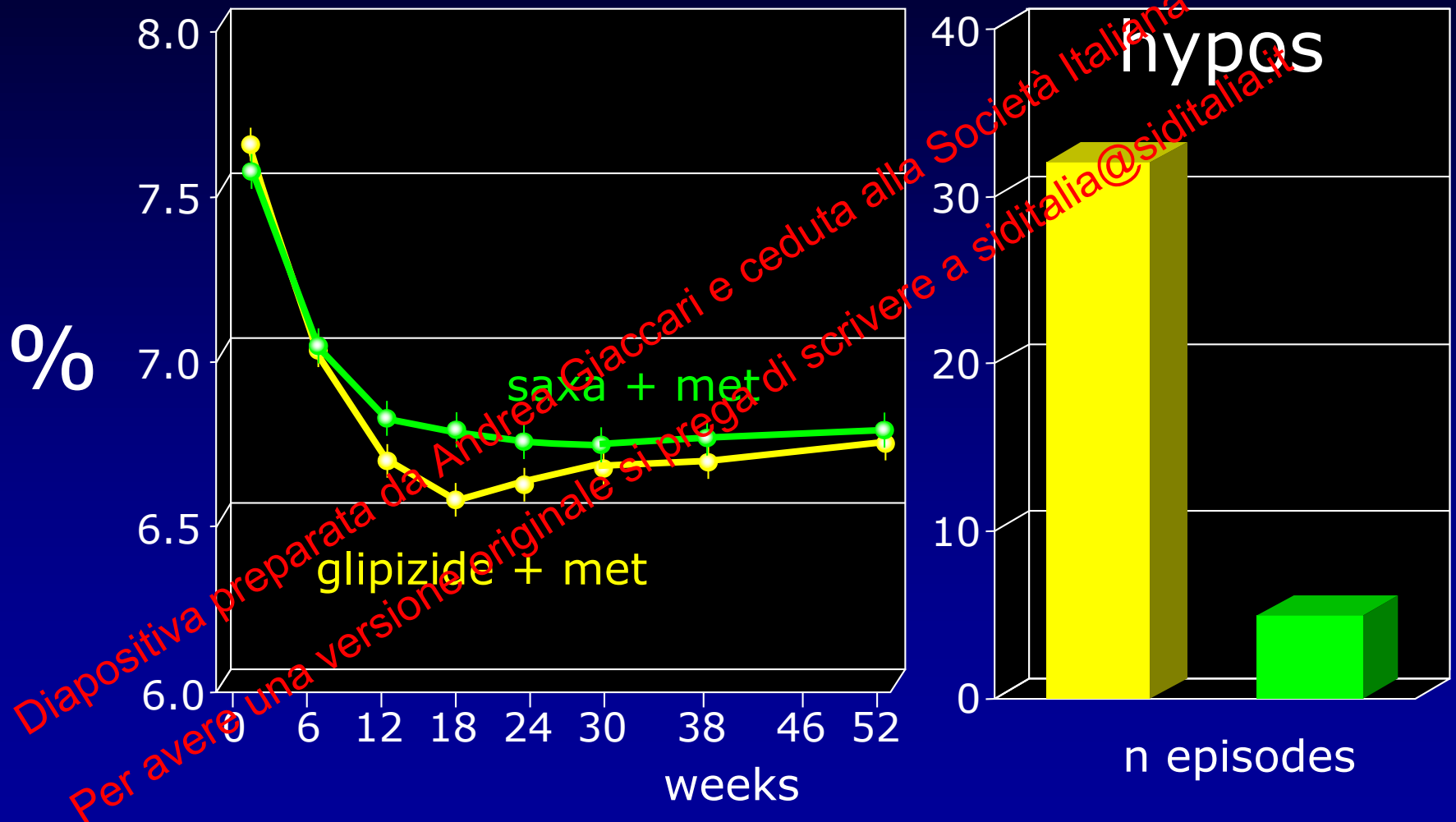
SGLT2 INHIBITORS



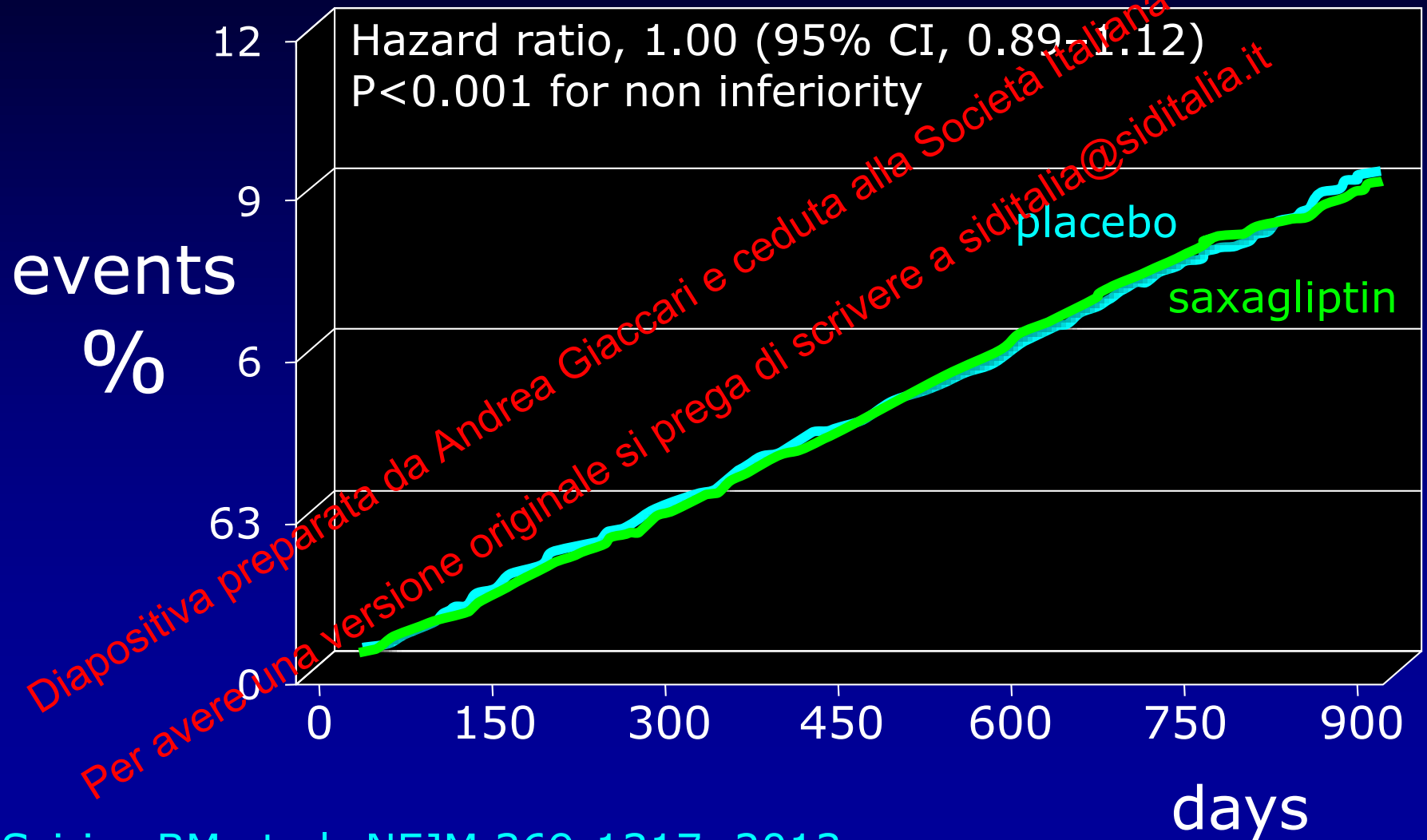
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gliptin vs. glipizide

add-on to metformin

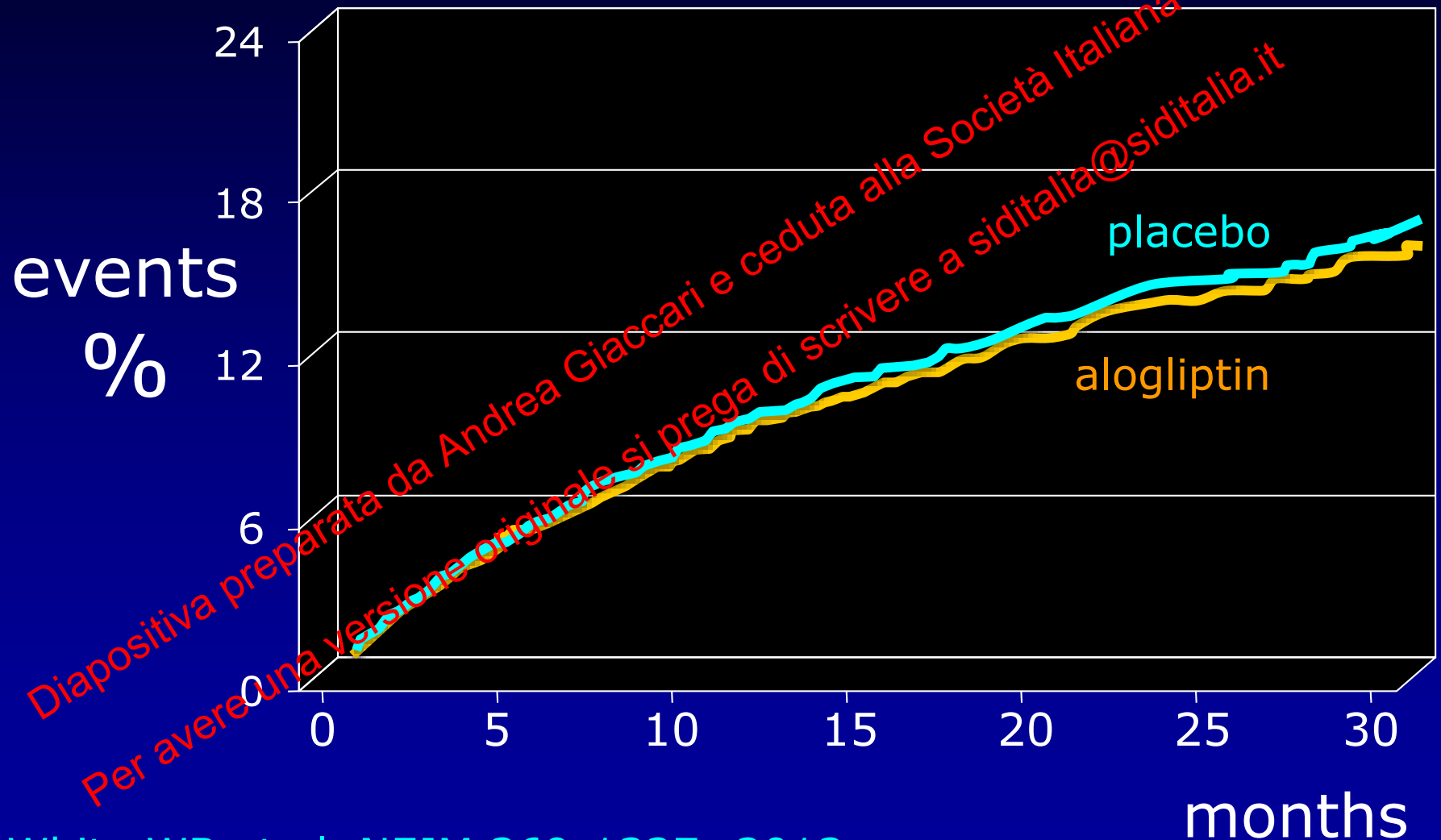


SAVOR-TIMI: MACE cumulative incidence



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EXAMINE: MACE cumulative incidence



White WB et al. NEJM 369:1327; 2013

gliptins: pros & cons

pros

- absence of hypoglycemia
- no weight increase (decrease)
- rare side effects
- no effects on CV risk factors
- no gastrointestinal side effects
- no titration

cons

cost

doubts

heart failure?

classes of medicines for type 2 diabetes

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INSULIN



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- Glipizide

SULPHONYLUREAS



- Pioglitazone

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- Alogliptin

GLIPTINS



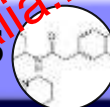
- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS



Diapositiva preparata da Andrea Giaccari e ceduta alla Societa Italiana di Diabetologia.
Per avere una versione originale si prega di scrivere a siditalia@siditalia.it

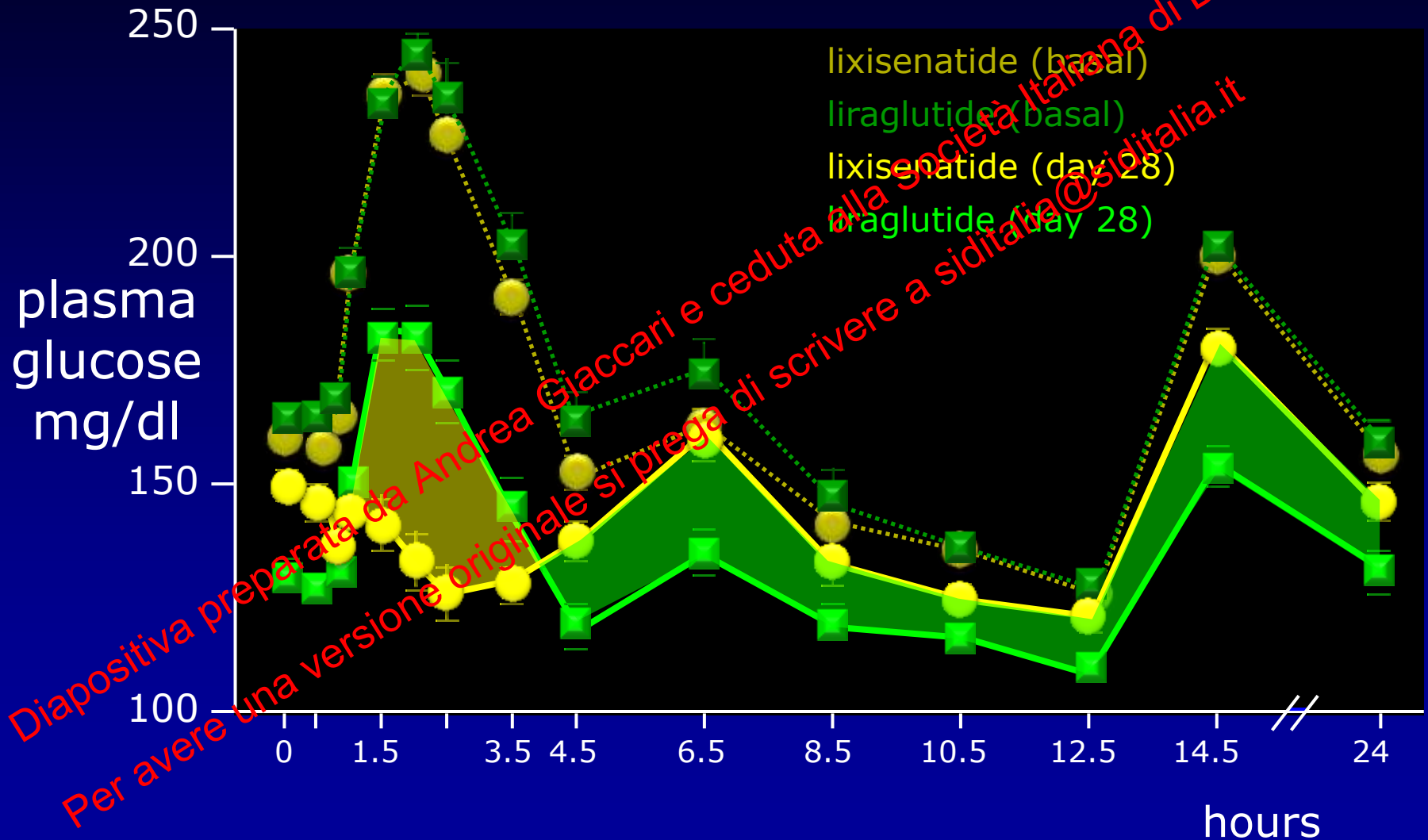
short and long-acting GLP-1R agonists

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

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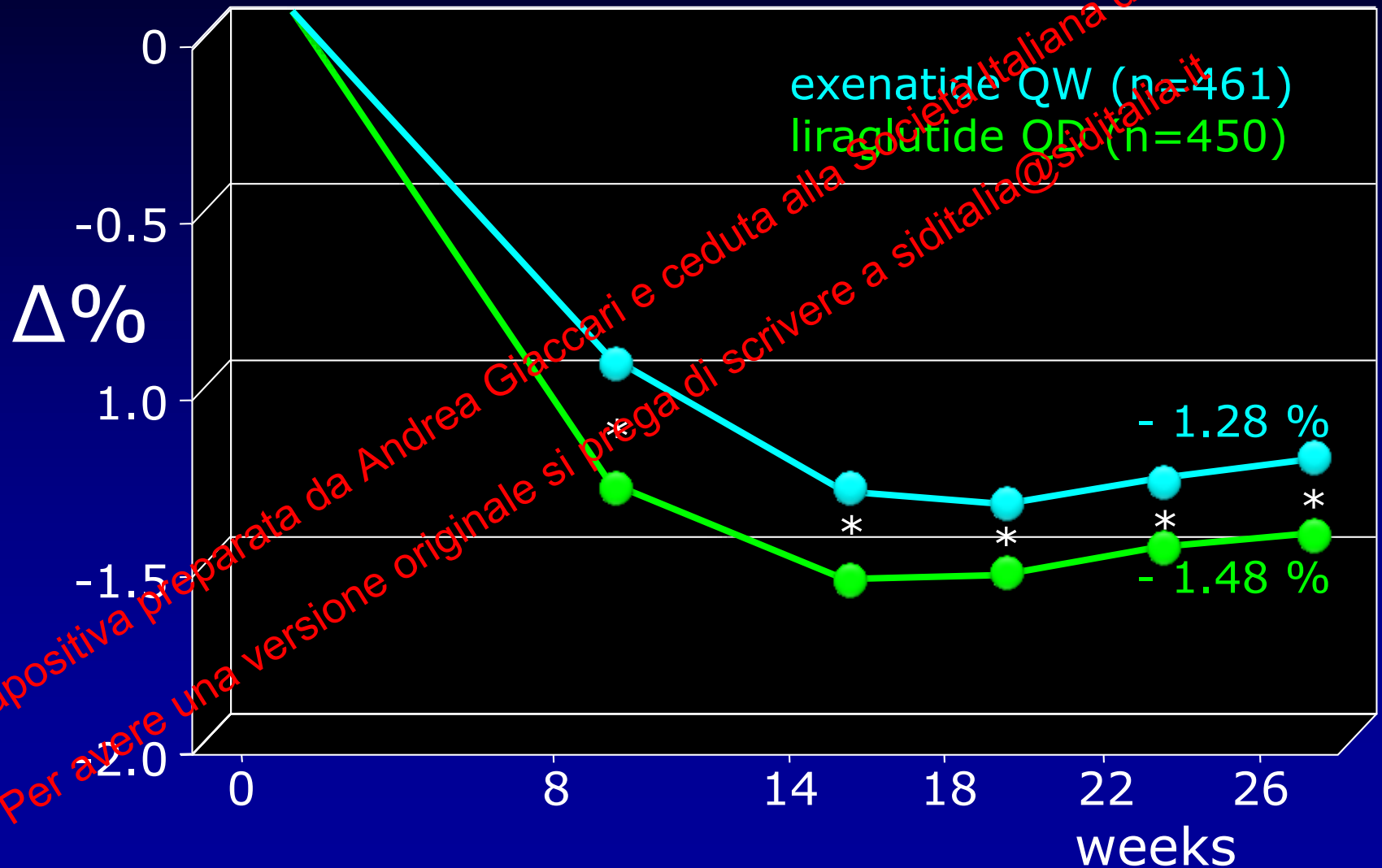
short and long-acting GLP-1 R As

24h plasma glucose profile



DURATION-6: change in HbA1c

a head to head comparison between Exe QW vs. Lira QD



DURATION-6: incidence of adverse events

a head to head comparison between Exe QW vs. Lira QD

	Exenatide QW (N = 461)		Liraglutide QD (N = 450)
Nausea	9.3	<<	20.7
Diarrhea	6.1	<<	13.1
Vomiting	3.7	<<	10.7
Dyspepsia	2.4	<	6.0
Headache	5.9	<	8.4
Nasopharyngitis	6.7	=	7.1
Injection site bump	10.4	>>>	1.1

Treatment-emergent Adverse Events with Incidence $\geq 5\%$
In Either Treatment Group

GLP1 R A: pros & cons

pros

- absence of hypoglycemia
- significant weight loss
- reduced CV risk factors
- easy titration

cons

- gastrointestinal side effects (some less)
- injections
- cost

doubts

- not indicated in CKD

classes of medicines for type 2 diabetes

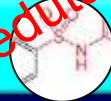
- Detemir
- Glargine
- Degludec
- NPH

INSULIN



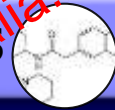
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULPHONYLUREAS



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINS



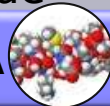
- Pioglitazone

TZDS



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS



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SU and repa: pros & cons

pros

rapid
cheap

cons

hypoglycemia!
rapid beta-cell failure
weight gain
increased CV risk
not indicated in CKD

doubts

myocardial infarction

classes of medicines for type 2 diabetes

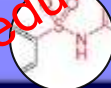
- Detemir
- Glargine
- Degludec
- NPH

INSULIN



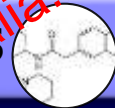
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULPHONYLUREAS



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINS



- Pioglitazone

TZDS



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

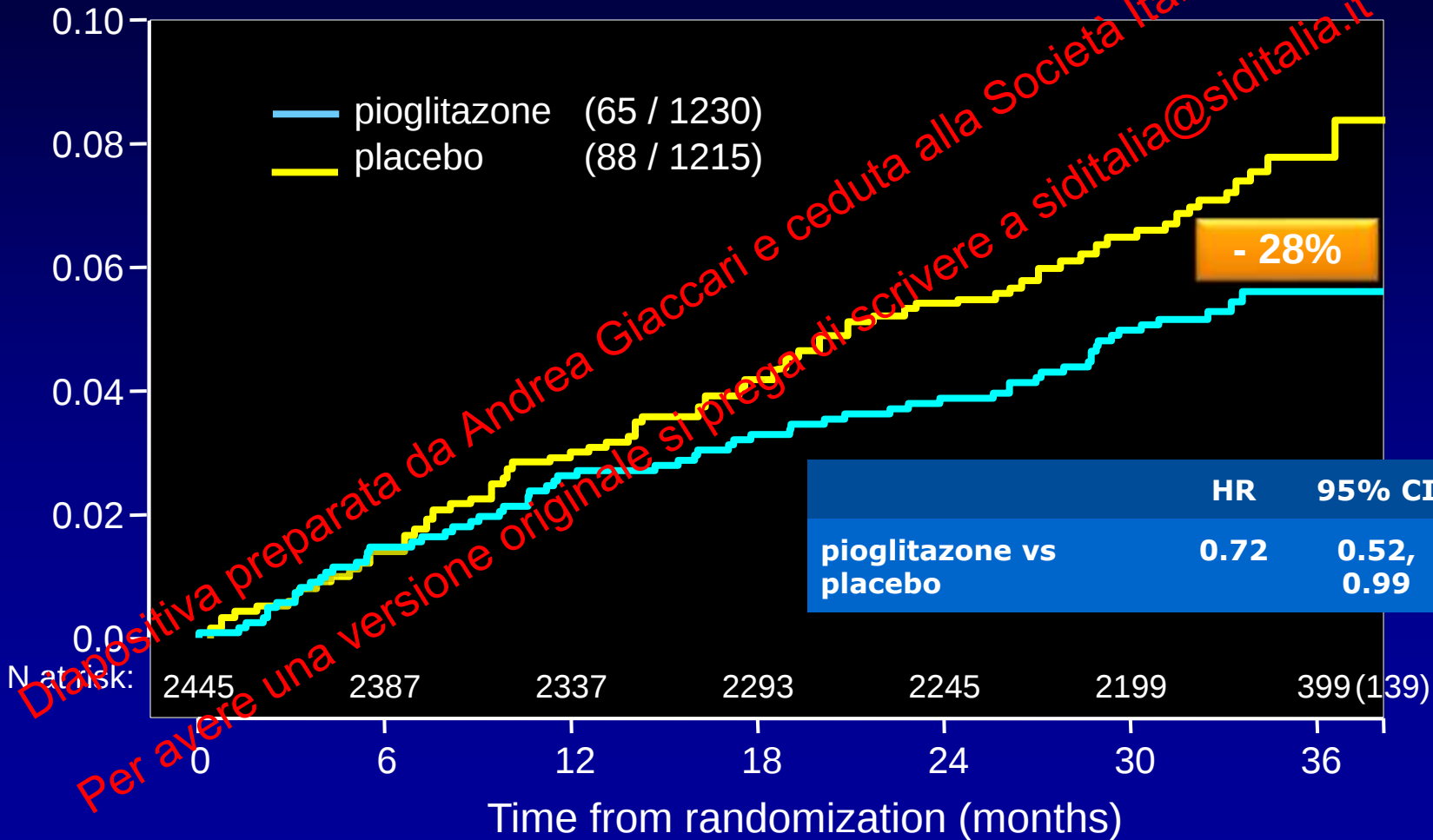
SGLT2 INHIBITORS



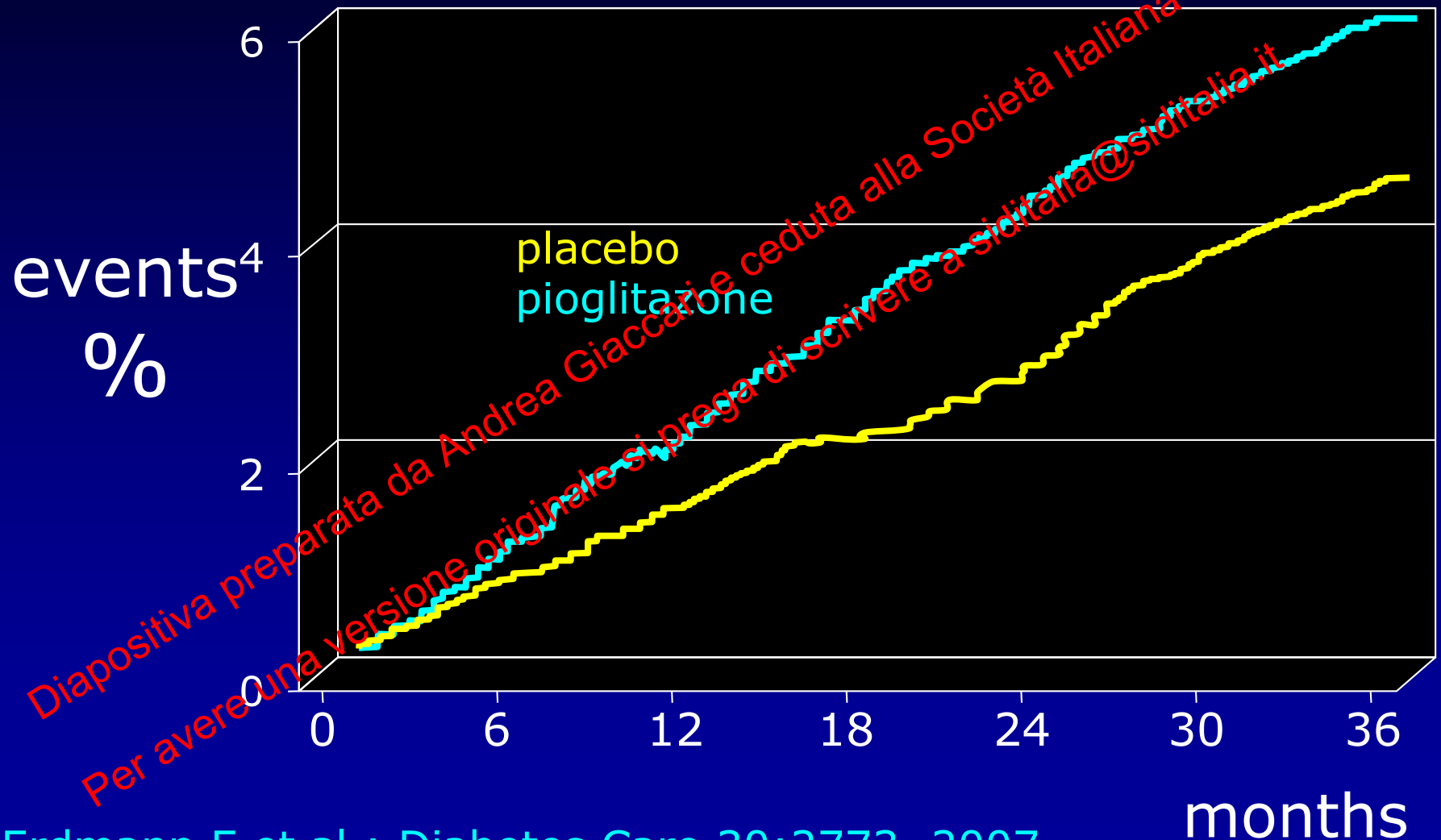
Diapositiva preparata da Andrea Giaccari e ceduta alla Societa Italiana di Diabetologia.
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PROACTIVE: fatal/non fatal MI (silent MI excluded)

Kaplan-Meier event rate



PROACTIVE: Heart failure risk



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

pioglitazone: pros & cons

pros

secondary CV prevention
no hypoglycemia
cheap

cons

slow action
heart failure and fluid retention
significant weight gain
fractures

doubts

beta-cell preservation?

classes of medicines for type 2 diabetes

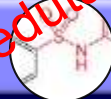
- Detemir
- Glargine
- Degludec
- NPH

INSULIN



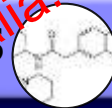
- Gliclazide
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- Glimepiride
- Gliquidone
- Glipizide

SULPHONYLUREAS



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINS



- Pioglitazone

TZDS



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS



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acarbose: pros & cons

pros

- not absorbed
- no hypoglycemia
- cheap

cons

- poor efficacy
- gastrointestinal side effects

doubts

- reduced CV risk?

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classes of medicines for type 2 diabetes

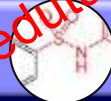
- Detemir
- Glargine
- Degludec
- NPH

INSULIN



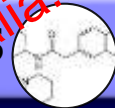
- Gliclazide
- Glibenclamide/glyburide
- Glimepiride
- Gliquidone
- Glipizide

SULPHONYLUREAS



- Nateglinide
- Repaglinide

GLINIDES



- Metformin

BIGUANIDES



- Sitagliptin
- Saxagliptin
- Vildagliptin
- Linagliptin
- Alogliptin

GLIPTINS



- Pioglitazone

TZDS



- Exenatide
- Exenatide LAR
- Liraglutide
- Lixisenatide

GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS



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basal insulin: pros & cons

pros

most effective

cons

hypoglycemia! (some less)

weight gain

injection

poor effect on post-prandial glucose

doubts

no

classes of medicines for type 2 diabetes

- Detemir
- Glargine
- Degludec
- NPH

INSULIN



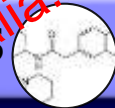
- Gliclazide
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SULPHONYLUREAS



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GLINIDES



- Metformin

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- Linagliptin
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GLIPTINS



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TZDS



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GLP-1 RA



- Acarbose
- Miglitol

ALPHA GLUCOSIDASES INHIBITORS



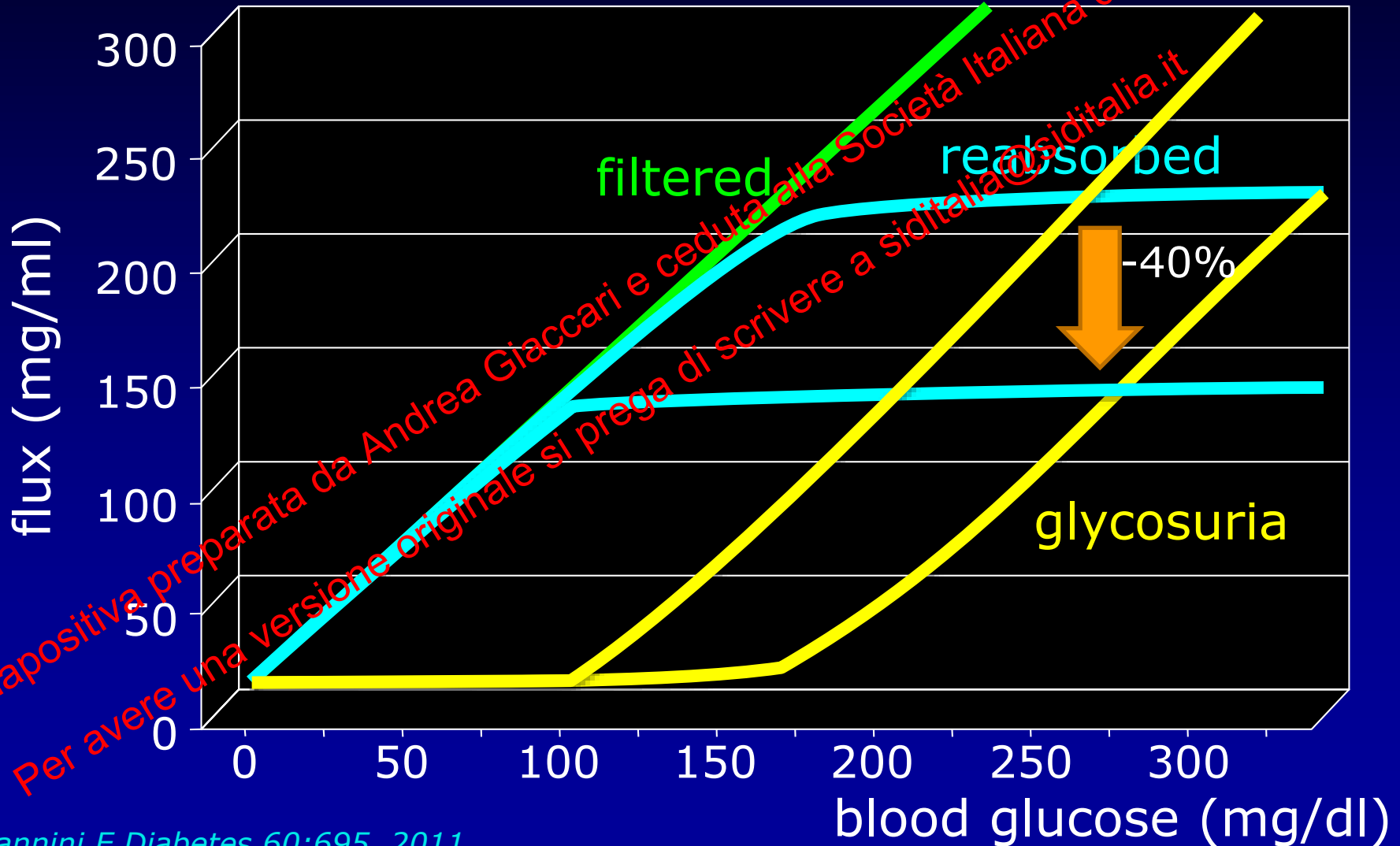
- Dapagliflozin
- Canagliflozin
- Empagliflozin

SGLT2 INHIBITORS

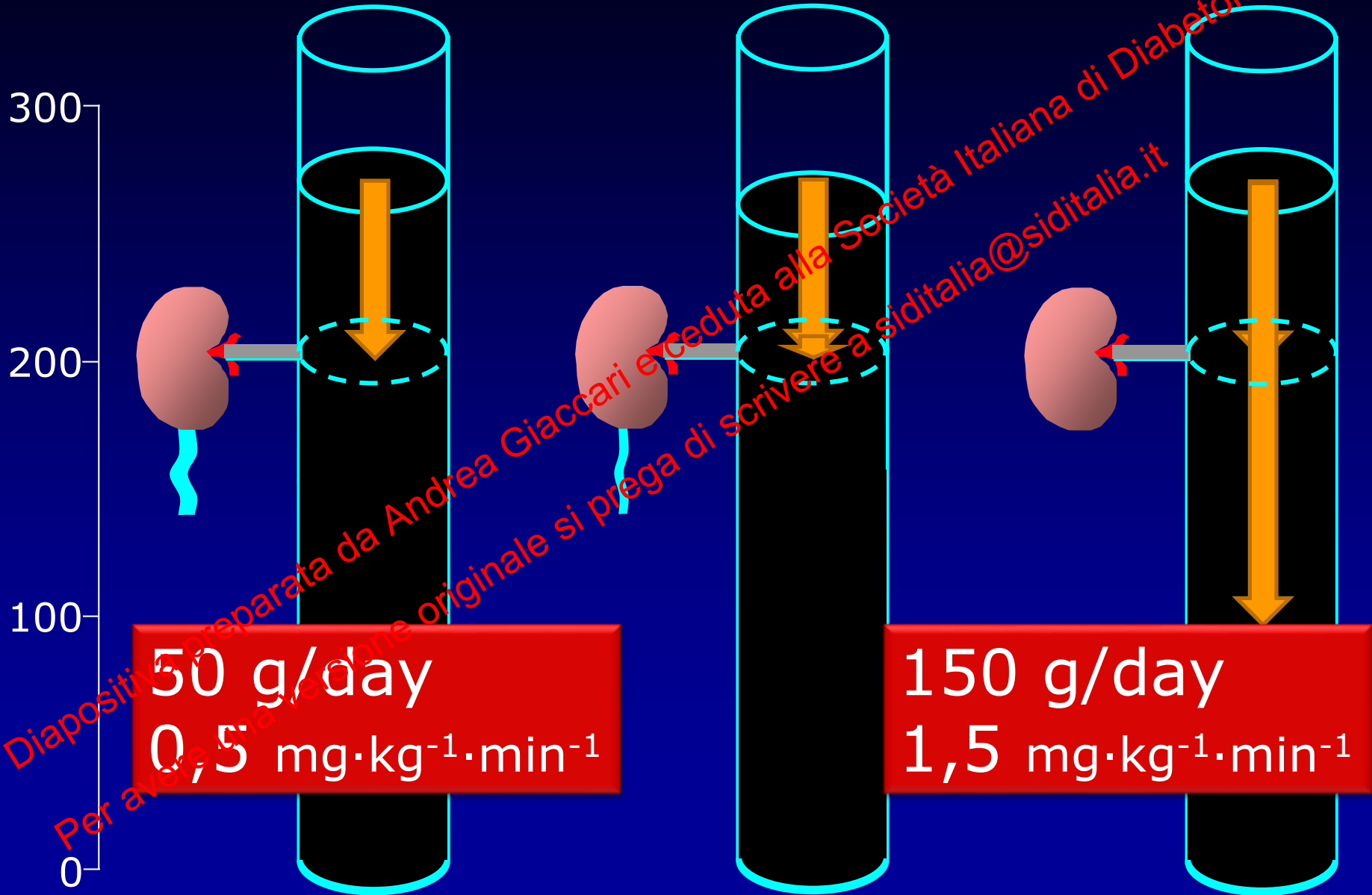


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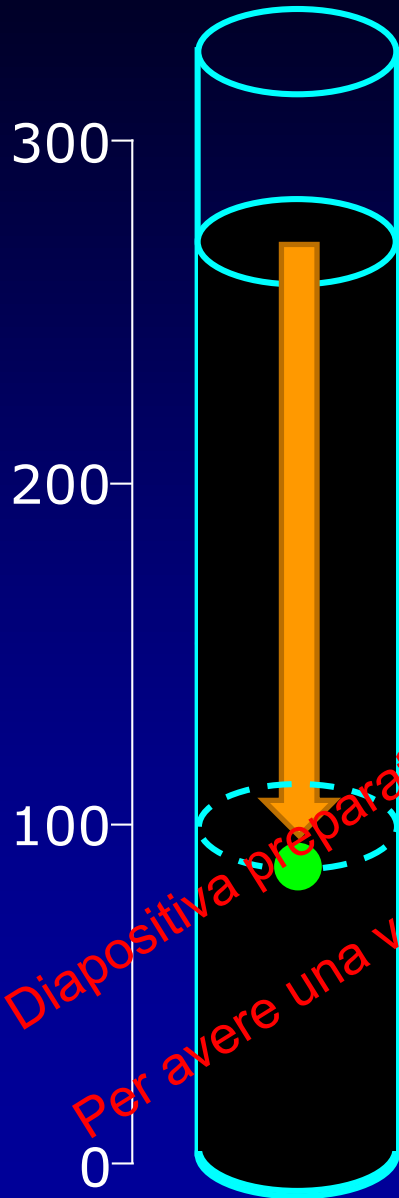
renal glucose flux



flux in glycosuria



flux in glycosuria



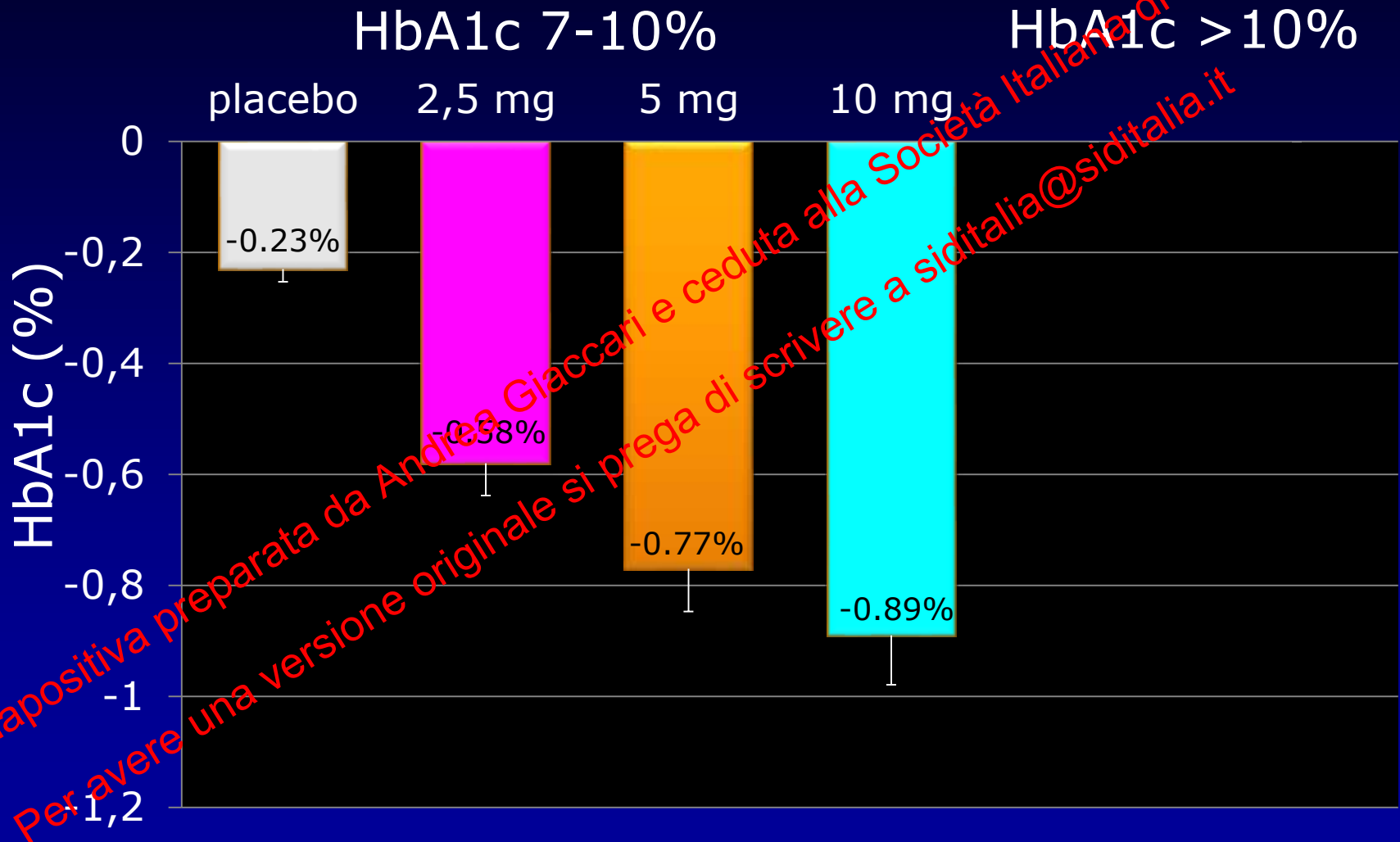
the amount of glucose lost
in the urine depends
exclusively from:

1. glycemia

2. renal function (eGFR)

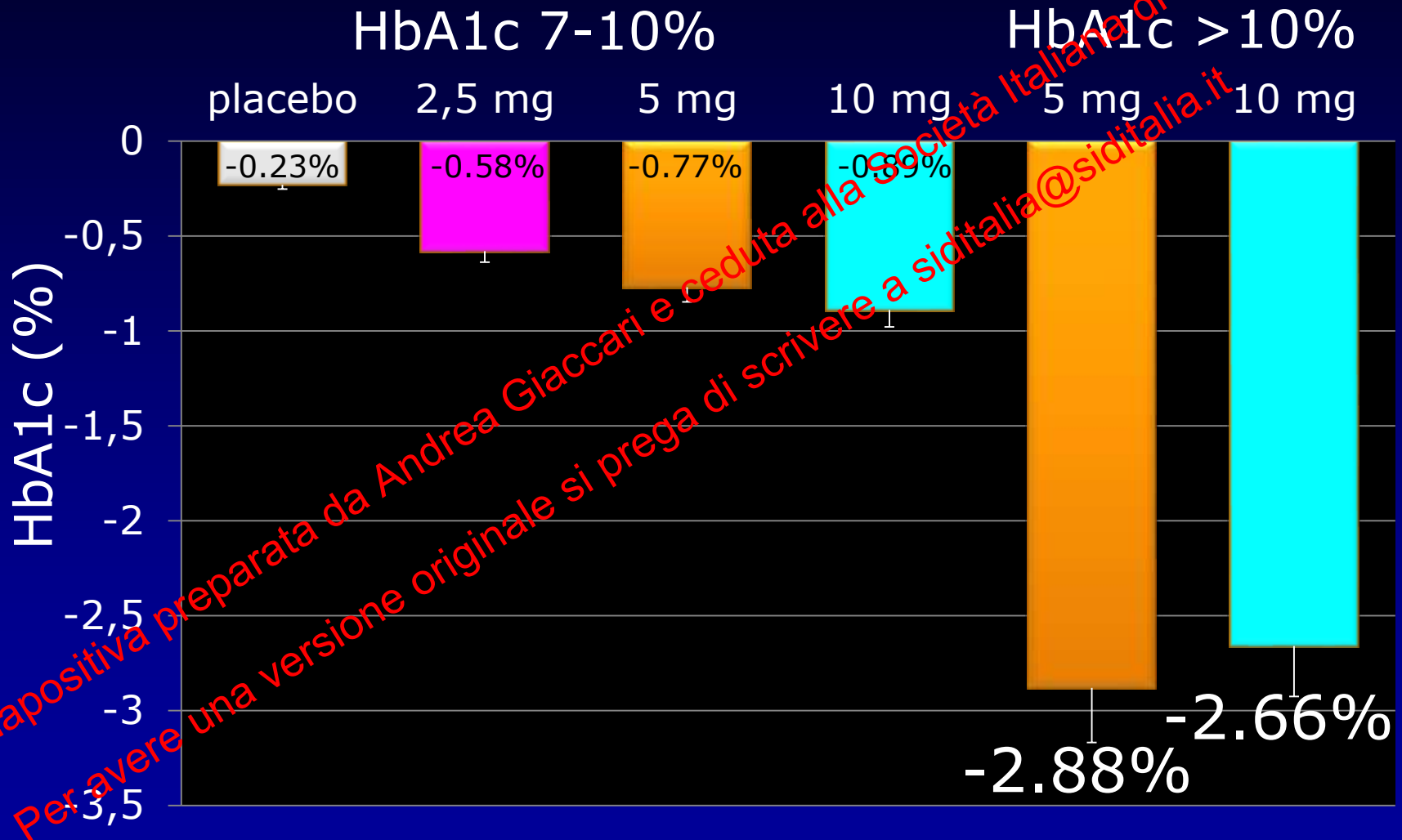
Diapositiva preparata da Andrea Giaccari e ceduta alla Società Italiana di Diabetologia.
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dose response: SGLT-2 monotherapy (drug-naïve patients)



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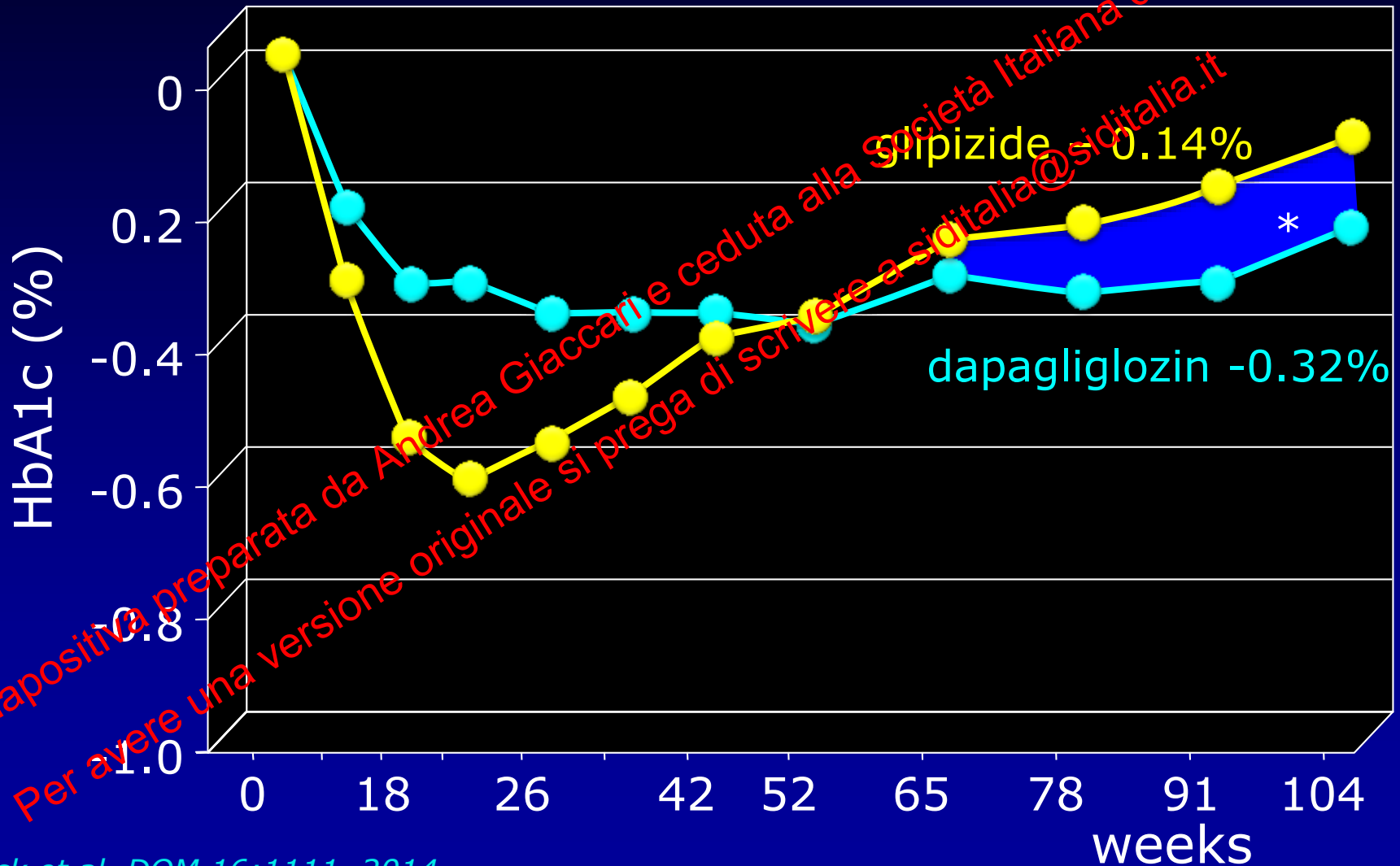
dose response: SGLT-2 monotherapy (drug-naïve patients)



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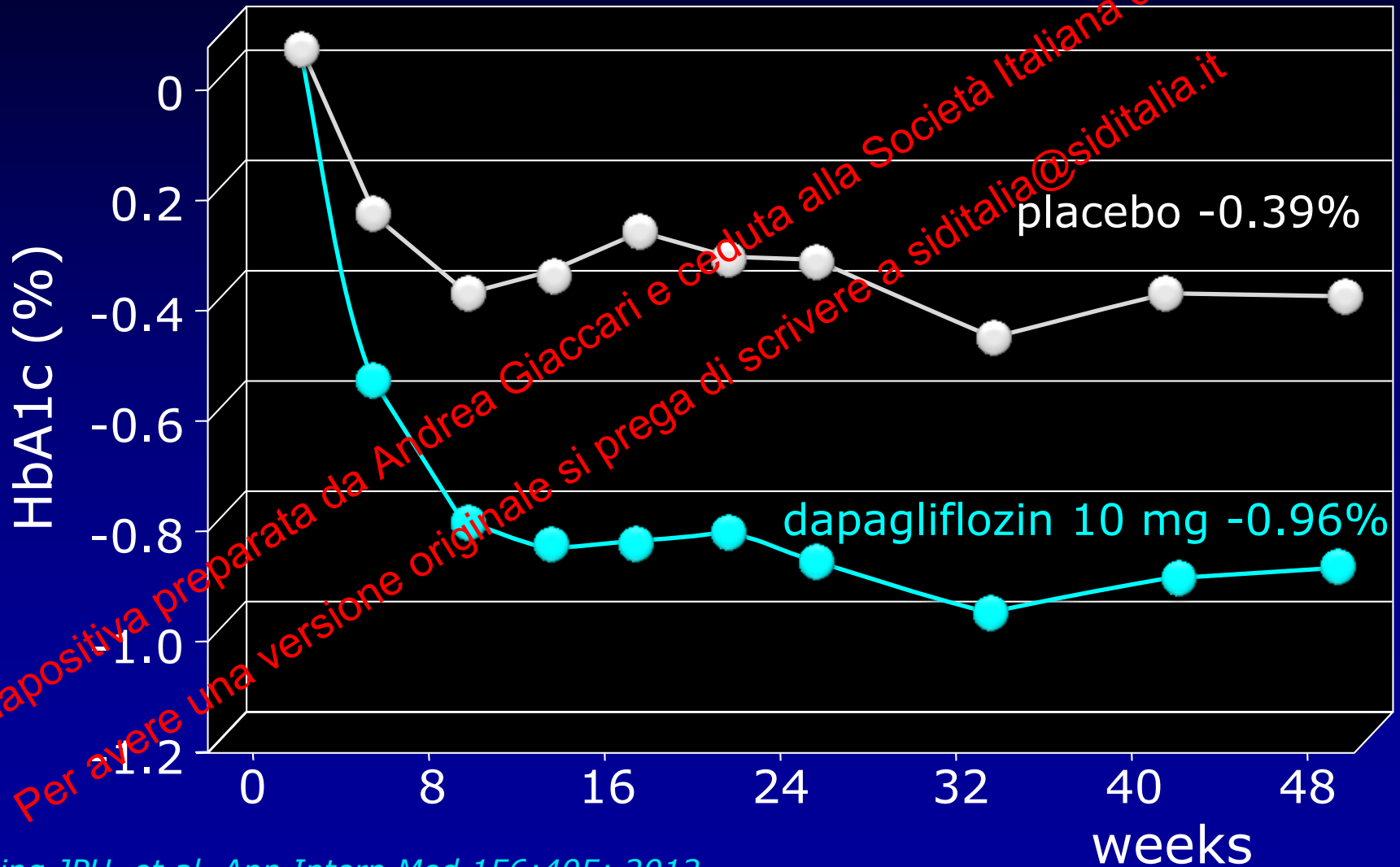
gliflozin vs. glipizide in add on to met.

(met ≥ 1.500 mg, dapa ≤ 10 mg, glipizide ≤ 20 mg)



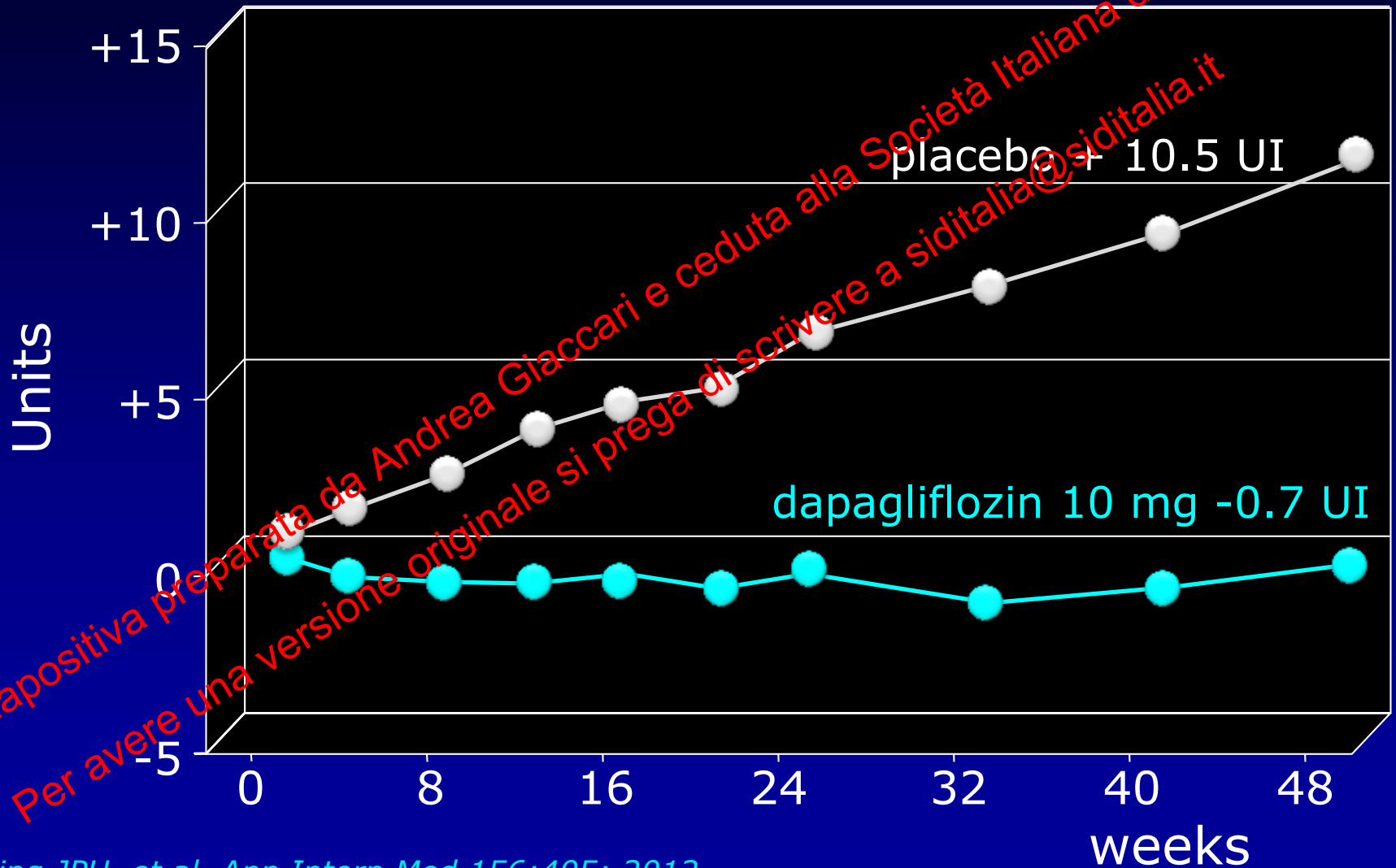
gliflozin as add on to insulin

HbA1c: dapagliflozin vs. placebo

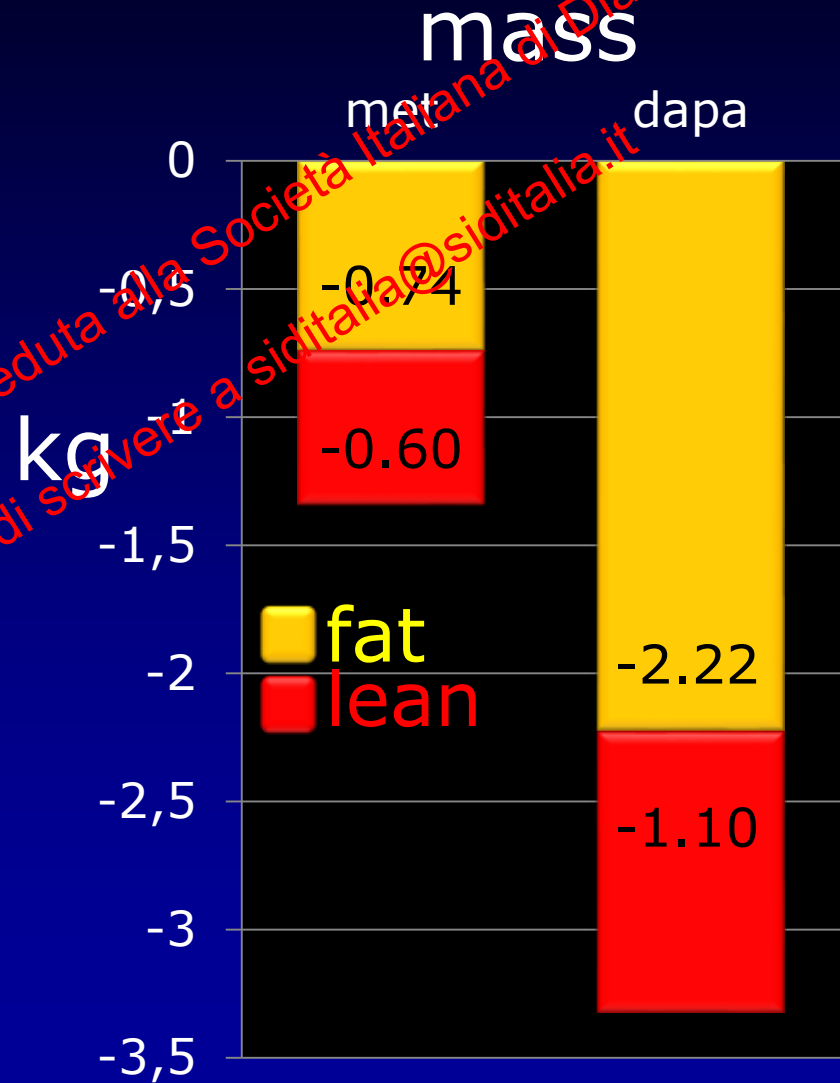


gliflozin as add on to insulin

Units of insulin: dapa vs. placebo

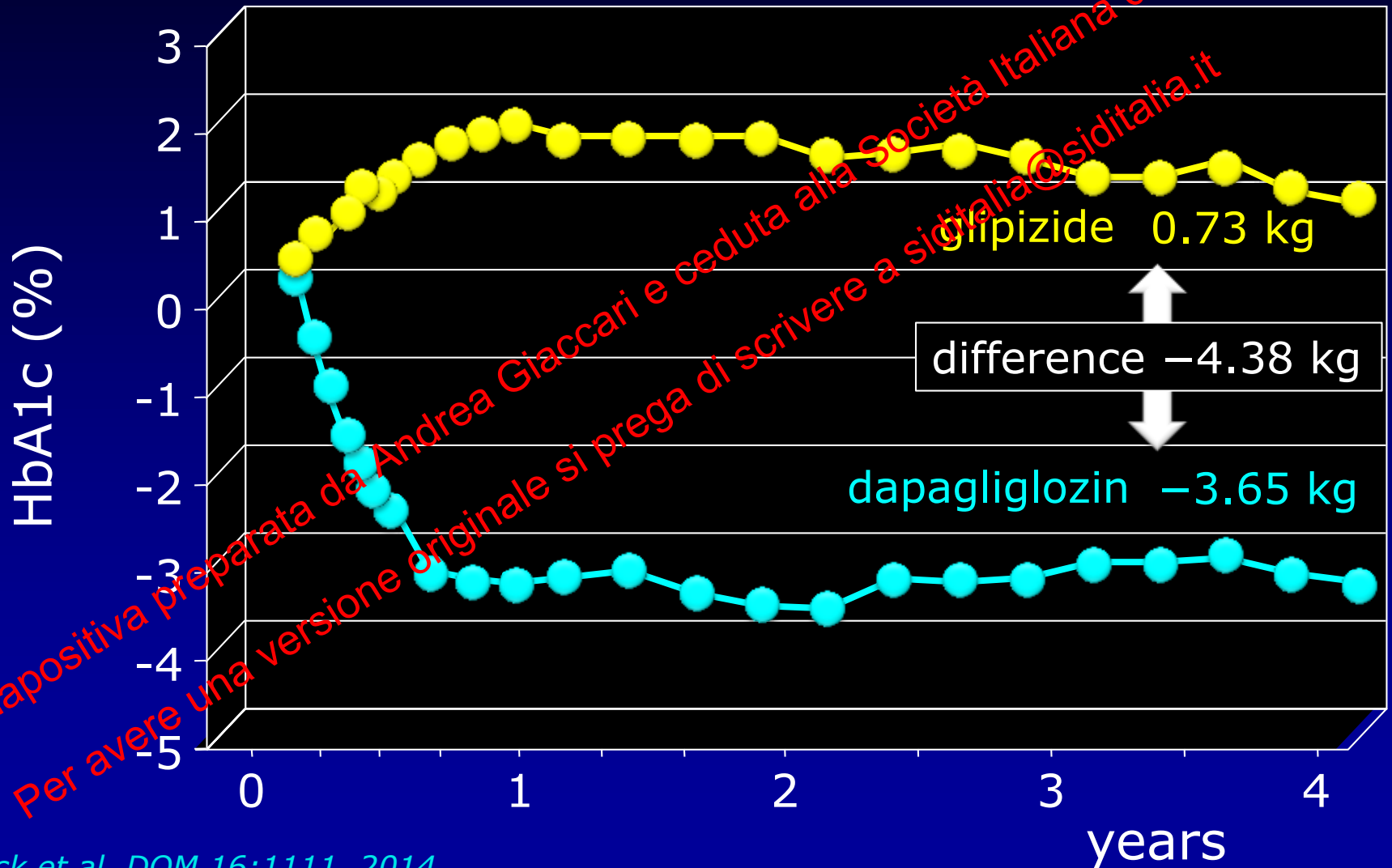


gliflozin: effect on weight



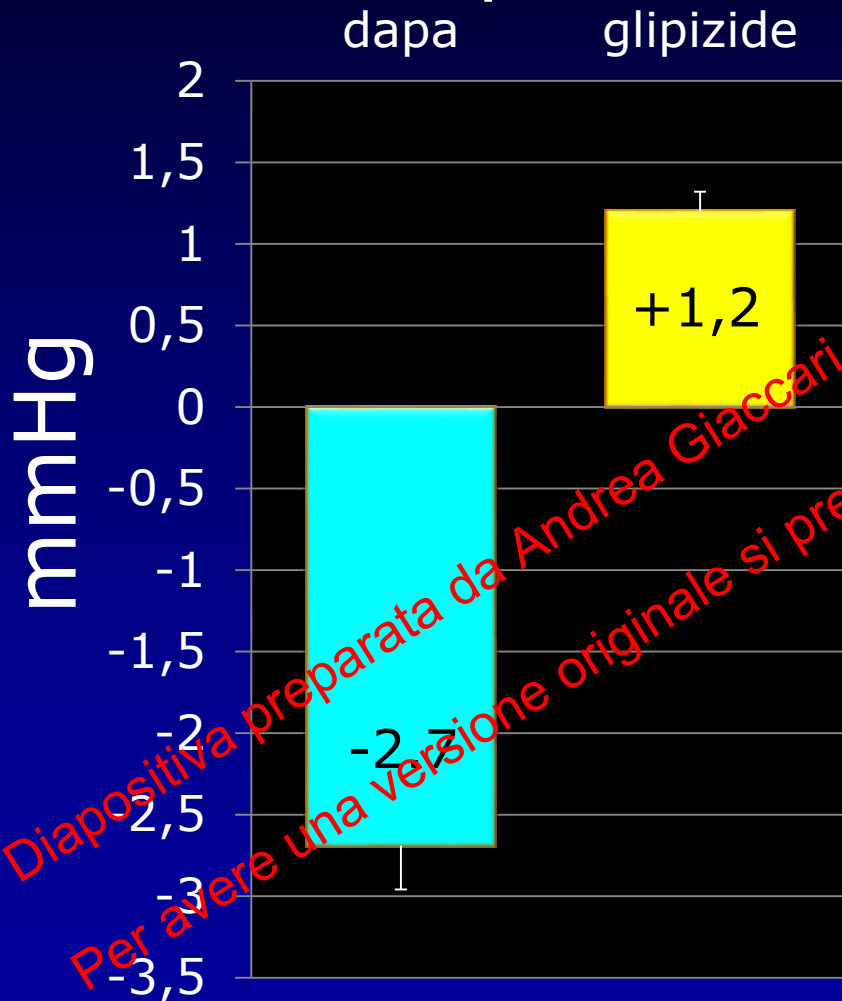
gliflozin vs. glipizide as add on to met

(met ≥ 1.500 mg, dapa ≤ 10 mg, glipizide ≤ 20 mg)

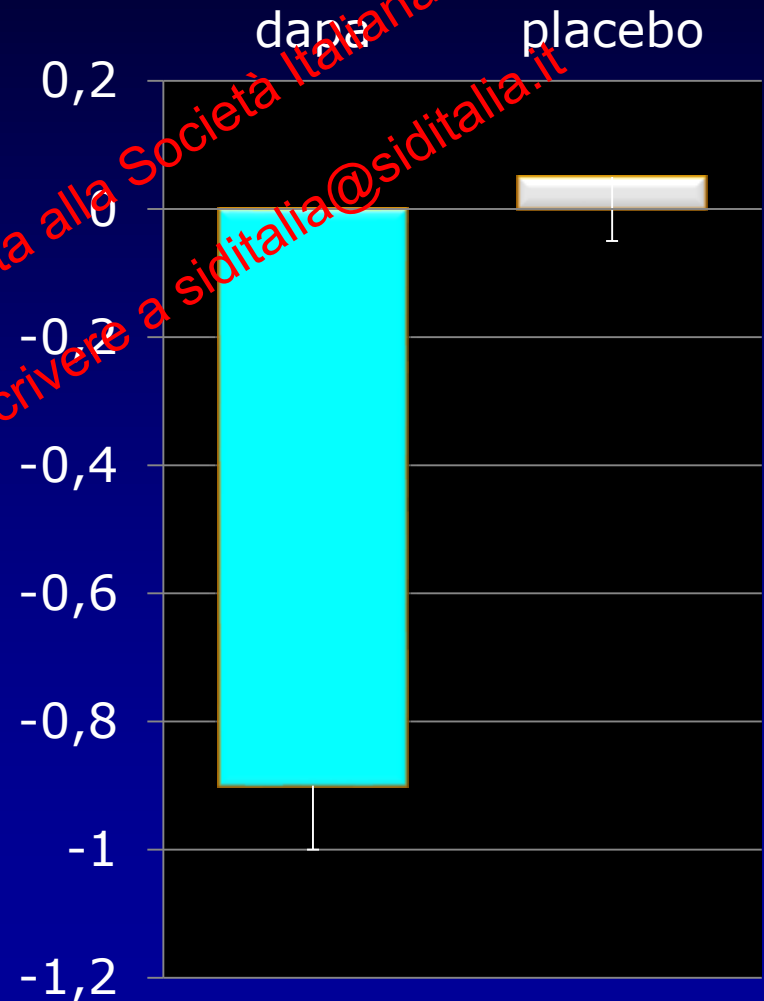


gliflozin: effect on BP and Uric Ac.

blood pressure



uric acid



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familiar renal glycosuria

genetic forms – clinic aspects

presentation	• glycosuria: 1-170 g die • completely asymptomatic
blood	• normal blood glucose • no hypoglycemia or hypovolemia
kidney / bladder	• no tubular dysfunction • normal histology and function
complications	• No increased incidence of – chronic kidney disease – diabetes – urinary tract infection

Diapositiva preparata da Andrea Gnocchi e ceduta alla Società Italiana di Diabetologia.
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gliflozins: pros & cons

pros

effective on all patients
no hypoglycemia
removes glucose toxicity
significant and persistent weight loss
reduces blood pressure

cons

not effective with low eGFR
GU infections

doubts

increased food intake?

	typical patient
Metformin	
Gliptin	
GLP-1 R.A.	
Sulphonylurea or Repaglinide	
Pioglitazone	
Acarbose	
Gliflozin	
Insulin (basal)	

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start with lifestyle improvement (unless severe hyperglycemia is present)

add (with appropriate run in) metformin, up to a dose of at least 2 g/day

add on to metformin	Hypos	weight	other effects	CVD	CV risk factors	Heart failure	G.I. effects	Cost
gliptin	1A	1B	Rare	1A	1B	2B ²	1A	elevated
GLP-1 R. A.	1A	1A	not indicated in CKD	3B	1A	2B	1C	elevated
SU or repaglinide	1D	1D	not indicated in CKD	3C	1B	1B	1A	low
pioglitazone	1A	1D	Fractures	1A	1A	1E	1A	medium
acarbose	1A	1C	Rare	2B	2B	3C	1C	low
gliflozin	1A	1A	G.U. infections	3C	2B	2B	1A	???
basal insulin	1D	1D	Rare	1B	1A	1B	1A	

1 to 5: grade of evidence

A to E: strength of recommendation

Take home messages

- There is no “one-size-fits-all” solution: treatment needs to be individualized
 - There is no strict evidence suggesting appropriateness of certain drugs for certain patients
- however*
- There are well demonstrated pros and cons for each drug
 - Our duty is to ponder each of them, and match our patients with the best therapy for each of them