

I GLP1R-agonisti: dopo la metformina

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Diapositiva preparata da RICCARDO C. BONADONNA e ceduta alla Società Italiana di Diabetologia.
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Riccardo C. Bonadonna dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

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Consulente: Nessuno

Dipendente: Nessuno

Altro: Nessuno

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Benefici dei “nuovi” farmaci per il diabete di tipo 2

	DPP4-I	GLP1R-A	GLT2-I
Riduzione HbA1c a 3-6 mesi	++	+++	++
Riduzione HbA1c a 1-2 anni	++	+++	++
Riduzione HbA1c oltre 2 anni	++	+++	++
Riduzione peso corporeo	-	+++	++
Riduzione pressione arteriosa	-	+	++

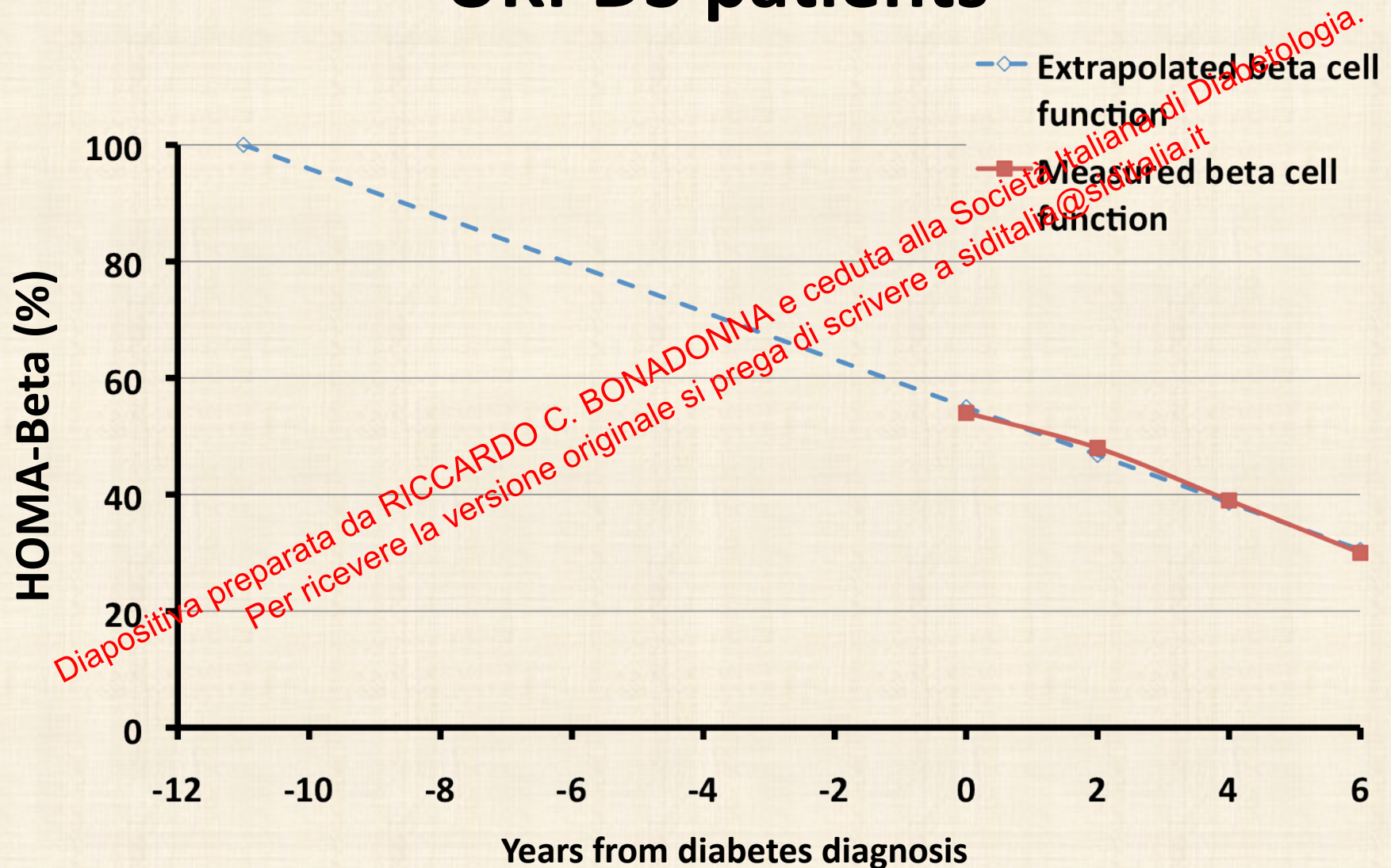
Effetti collaterali e rischi dei “nuovi” farmaci per il diabete di tipo 2

	DPP4-I	GLP1R-A	SGLT2-I
Interazioni con altri farmaci	-	-	-
Ipoglicemie	-	-	-
Aumento di peso	-	-	-
Pancreatiti	+/-	+/-	-
Fratture	-	-	-/+ ^a
Scompenso cardiaco	-/+ ^b	-	-
Disturbi gastro-intestinali	-	++	-/+
Infezioni genitali	-	-	+

^aSegnalato per canagliflozin ^bSegnalato per saxagliptin (trend per alogliptin)

Da: AMD-SID Standard italiani per la cura del diabete mellito 2016

Invololution of beta cell function in the UKPDS patients



UKPDS Group; Diabetes 1995

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



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

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

**EITHER/
OR**

GLP-1 RA
with proven
CVD benefit¹

SGLT2i with
proven CVD
benefit¹,
if eGFR
adequate²

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 insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

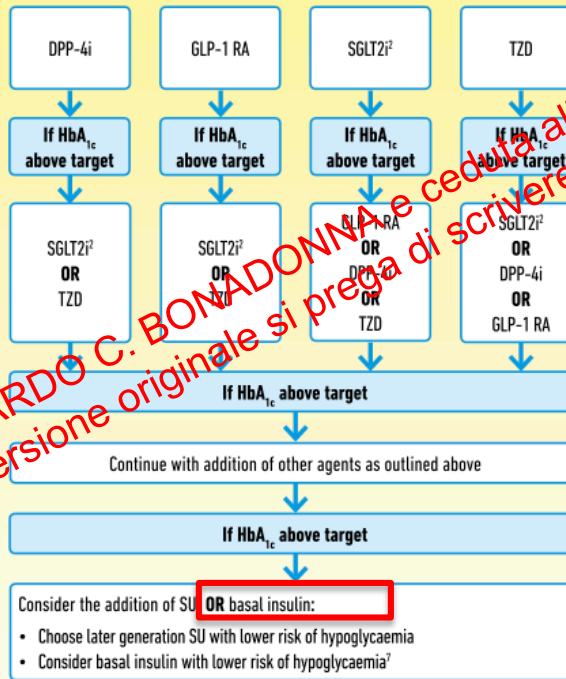
OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate³ add GLP-1 RA with proven CVD benefit¹

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 benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

**EITHER/
OR**

GLP-1 RA with good efficacy for weight loss⁸

SGLT2i

If HbA_{1c} above target

SGLT2i

GLP-1 RA with good efficacy for weight loss⁸

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

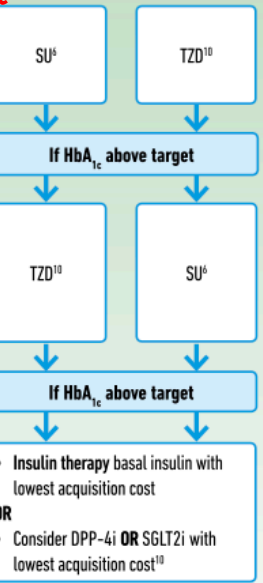
PREFERABLY

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:

- SU⁶ • TZD⁵ • Basal insulin

COST IS A MAJOR ISSUE⁹⁻¹⁰

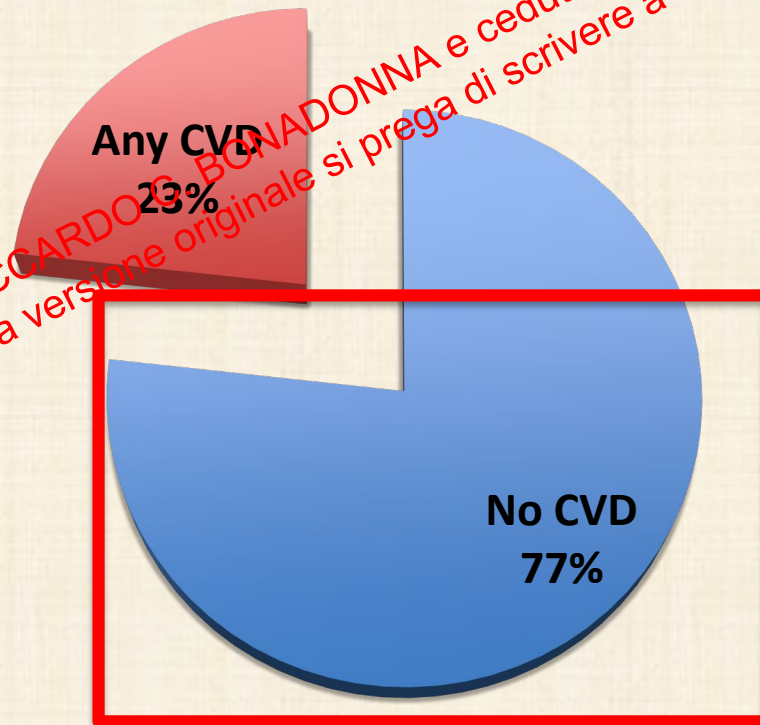


- Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
- Be aware that SGLT2i vary by region and individual agent with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

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

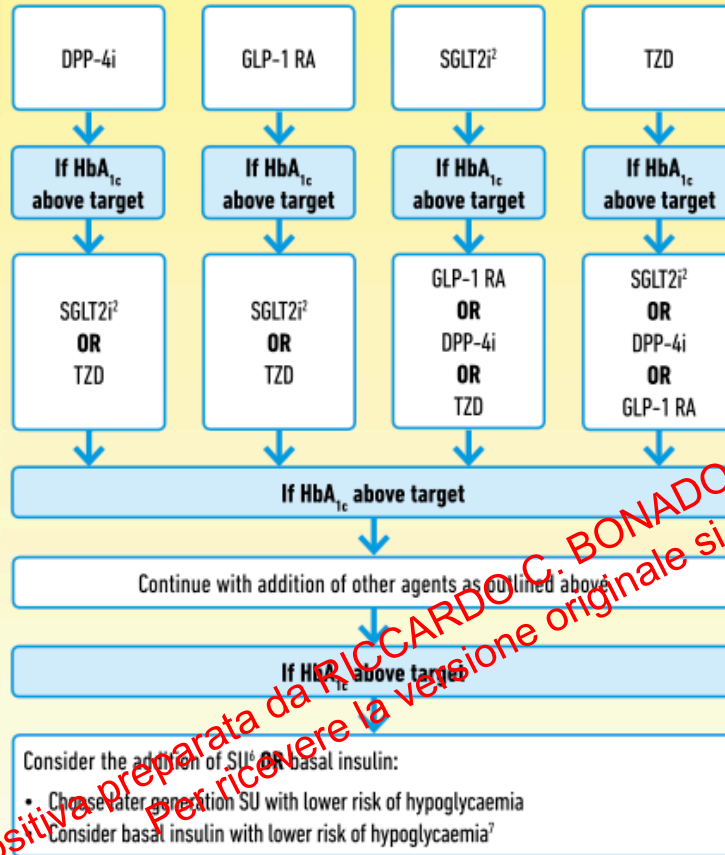
The RIACE Study: 15993 consecutive patients with diabetes from 19 Outpatient Diabetes Clinics in Italy, years 2007-2008

Prevalence of any CVD
in patients attending Outpatient Diabetes Clinics

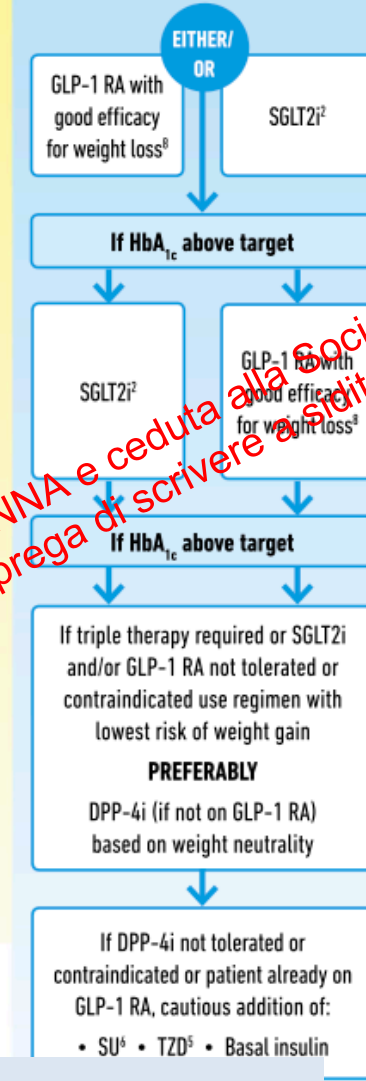


WITHOUT ESTABLISHED ASCVD OR CKD

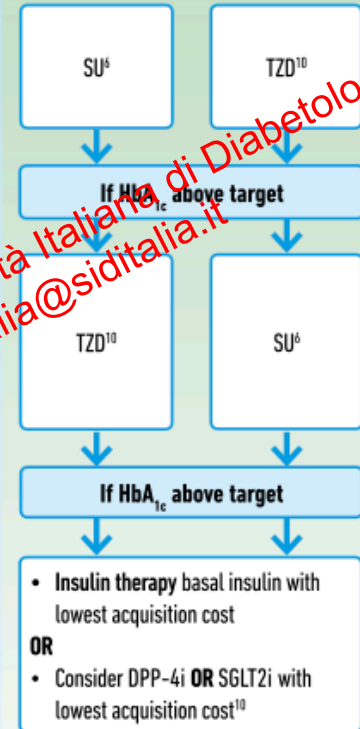
COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



COST IS A MAJOR ISSUE⁹⁻¹⁰



- Low dose may be better tolerated though less well studied for CVD effects
- Choose later generation SU with lower risk of hypoglycaemia
- Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- If no specific comorbidities (i.e. no established CVD, low risk)

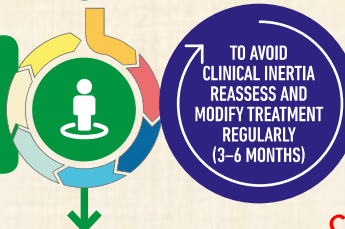
PARADIGM:
TREAT TO TARGET

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



In those **WITHOUT** established ASCVD OR CKD

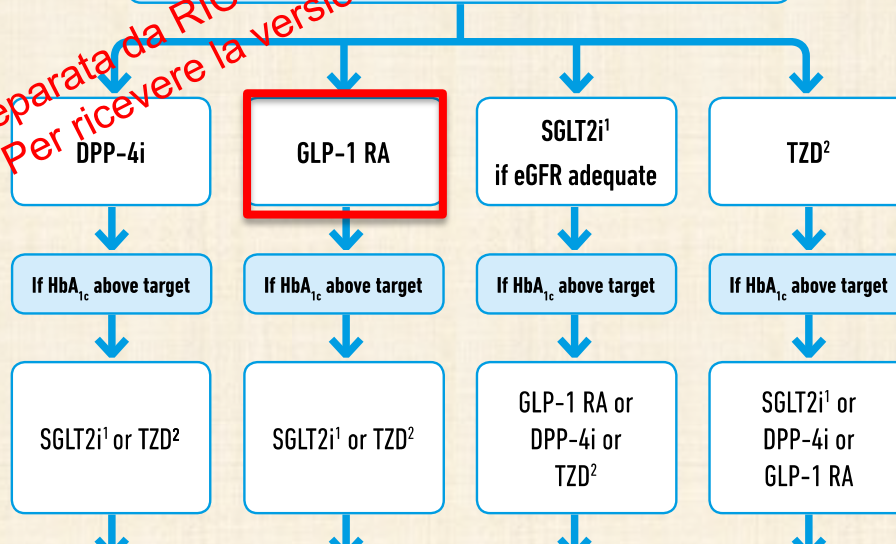
Use principles in Figure 1



Identify patient groups at highest risk of hypoglycaemia and set and/or adjust HbA_{1c} target to minimise risk of hypoglycaemia

First-line therapy is metformin
If HbA_{1c} is ≥ 17 mmol/mol (1.5%) above individualised HbA_{1c} target consider early combination therapy

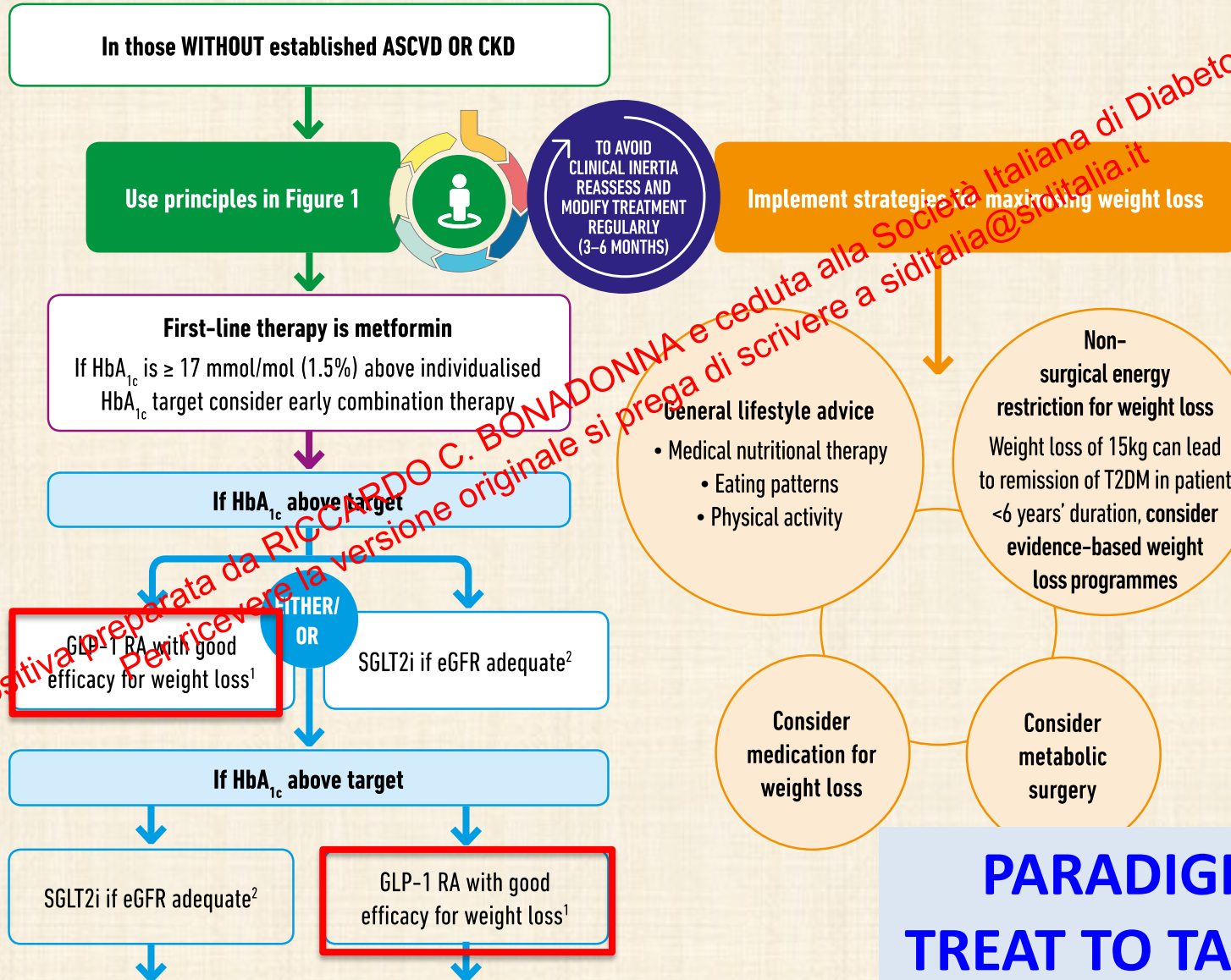
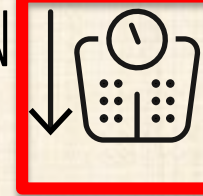
If HbA_{1c} above target



**PARADIGM:
TREAT TO TARGET**

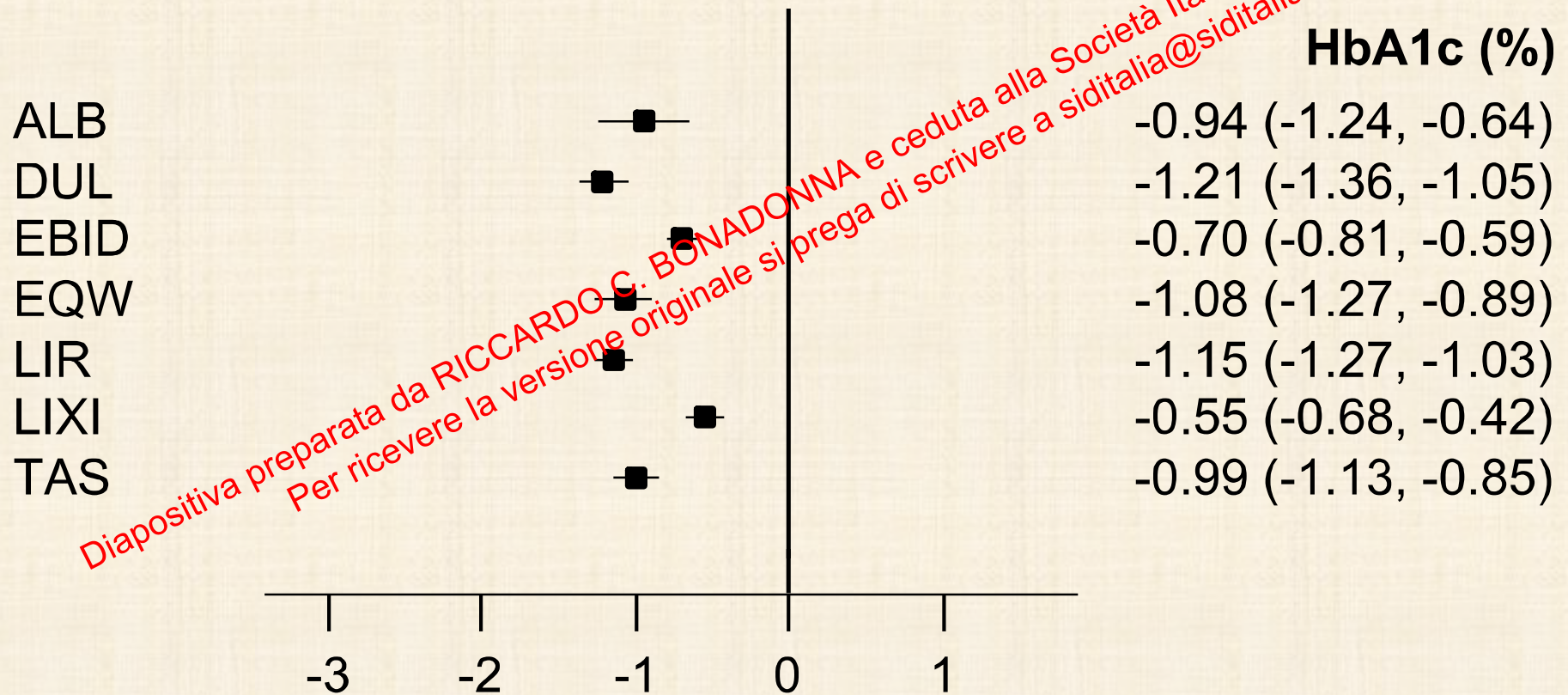
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CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

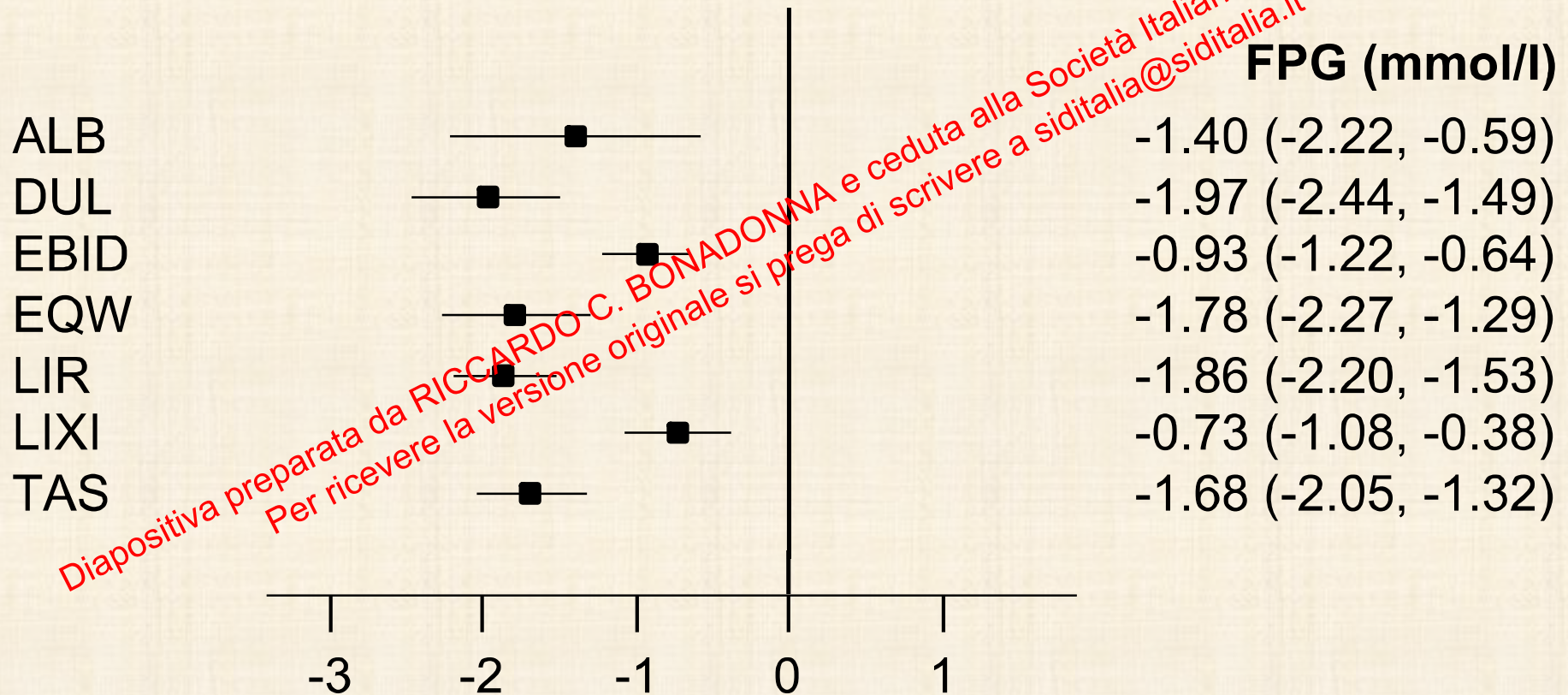


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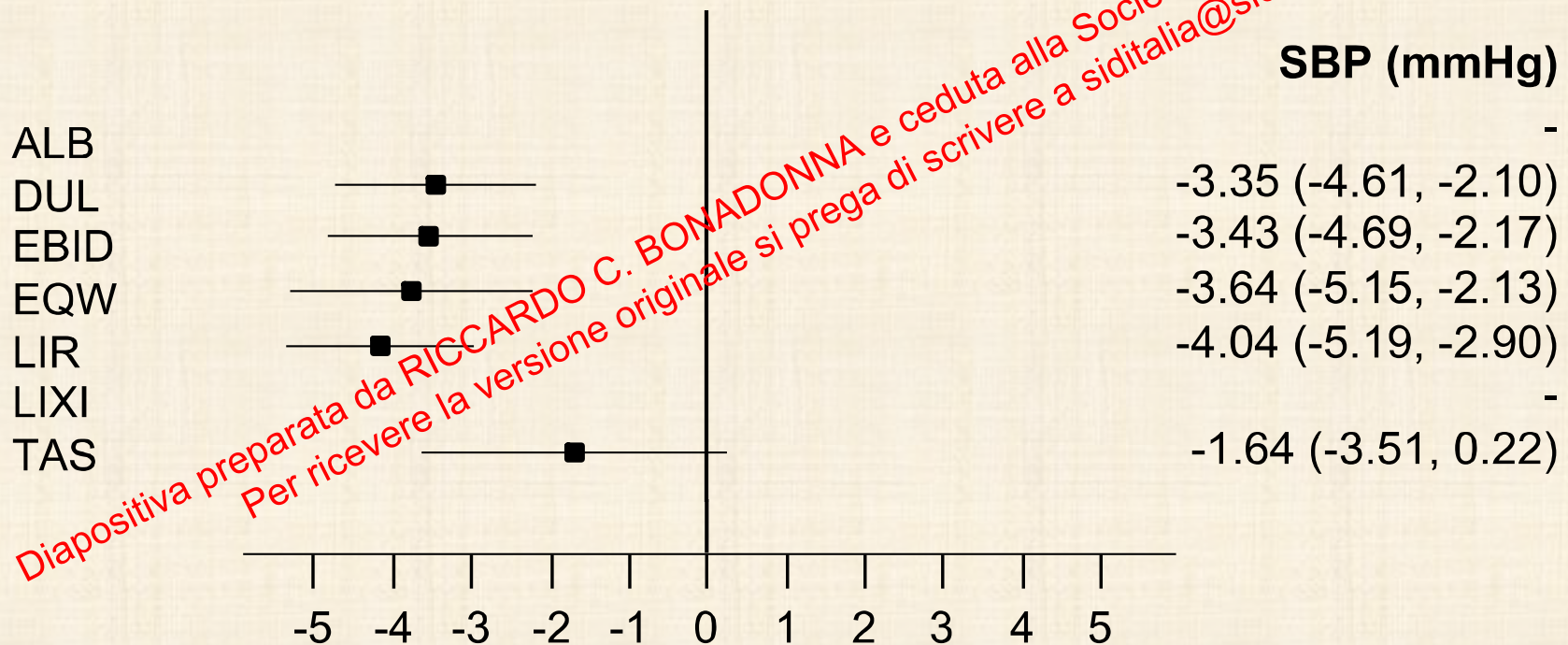
Differences of HbA_{1c} estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



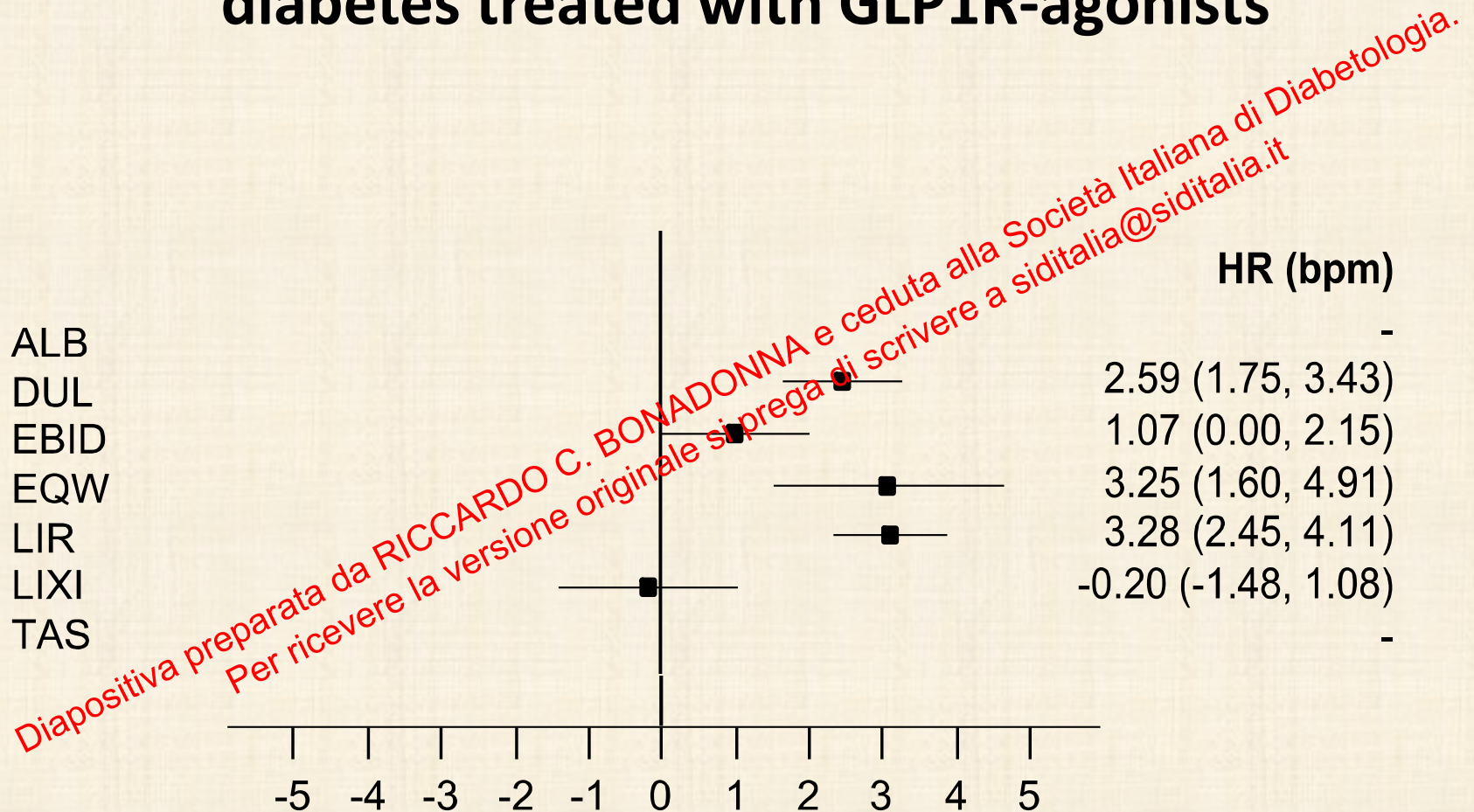
Differences of FPG estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



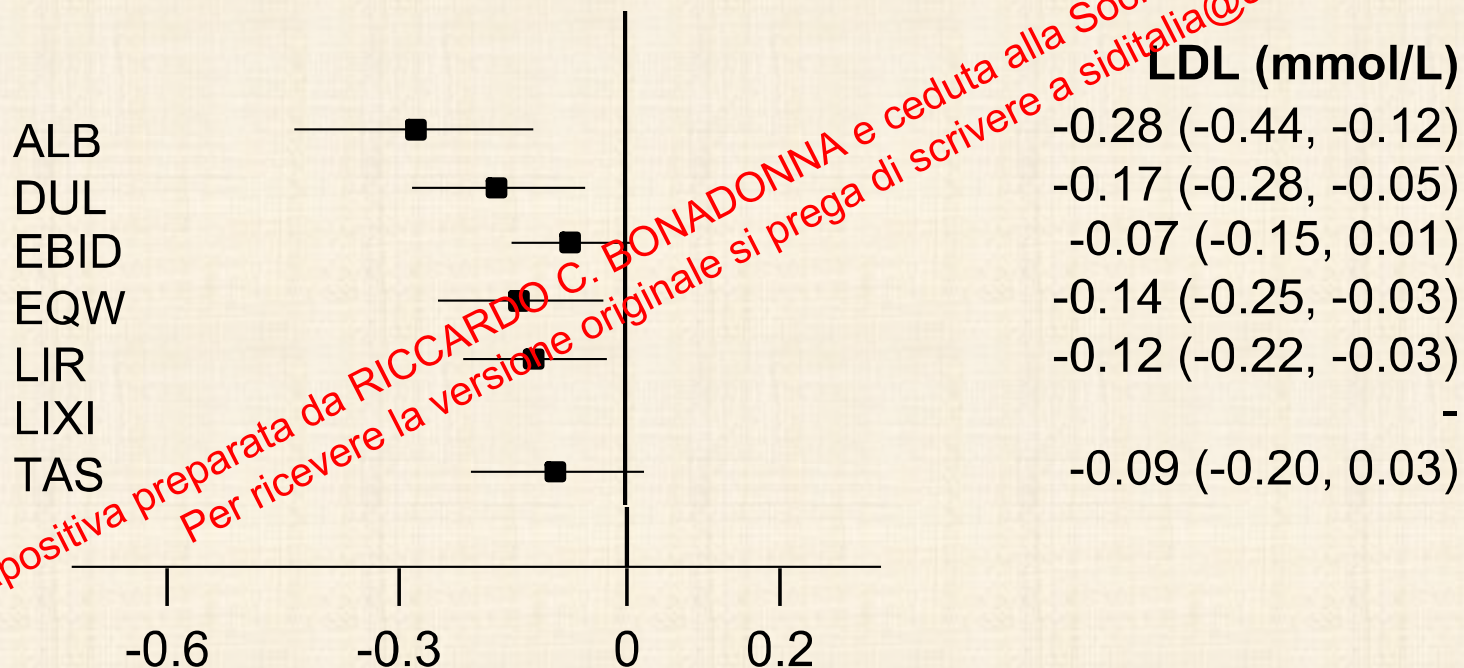
Differences of systolic blood pressure estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists.



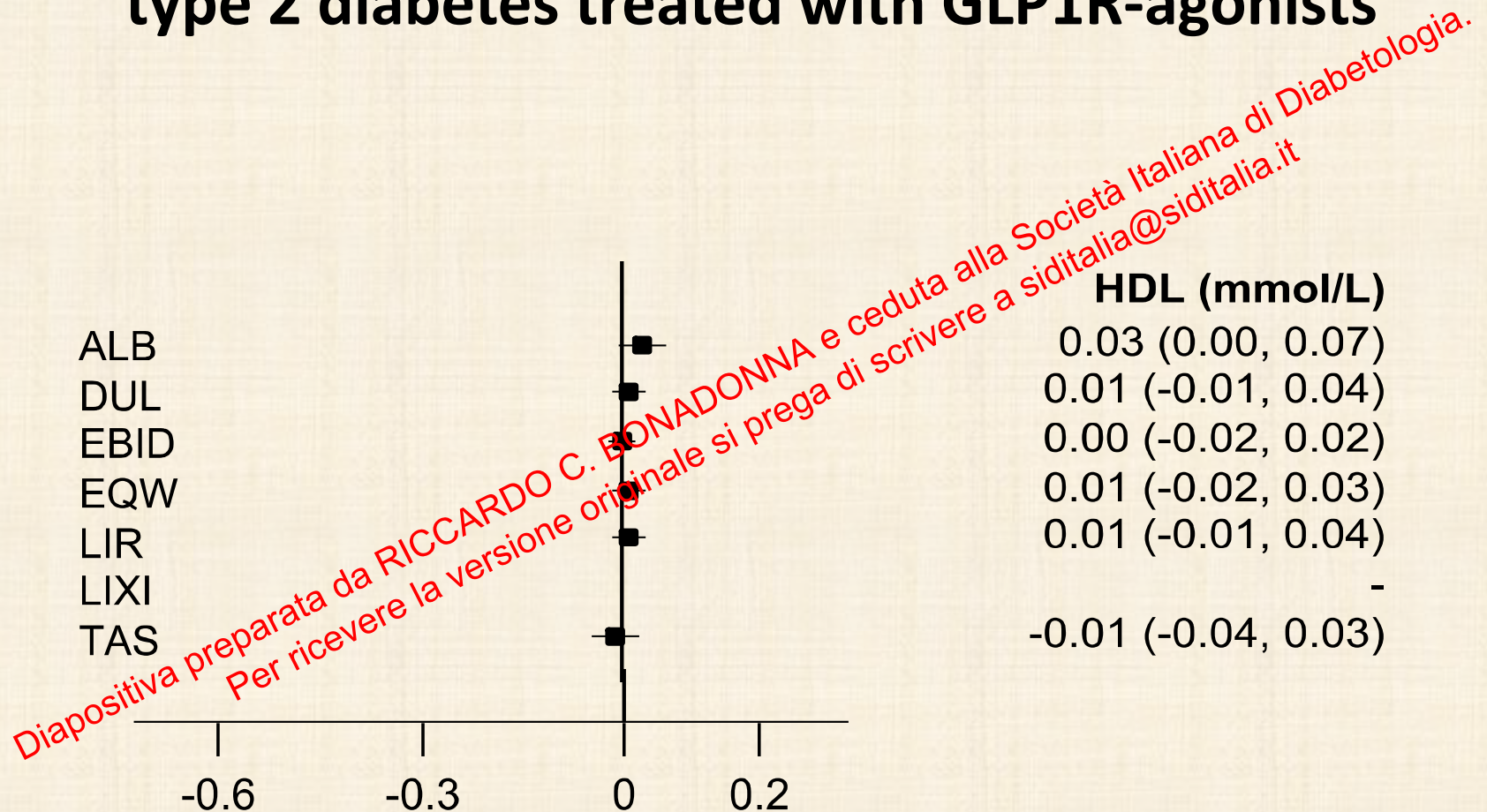
Differences of heart rate estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



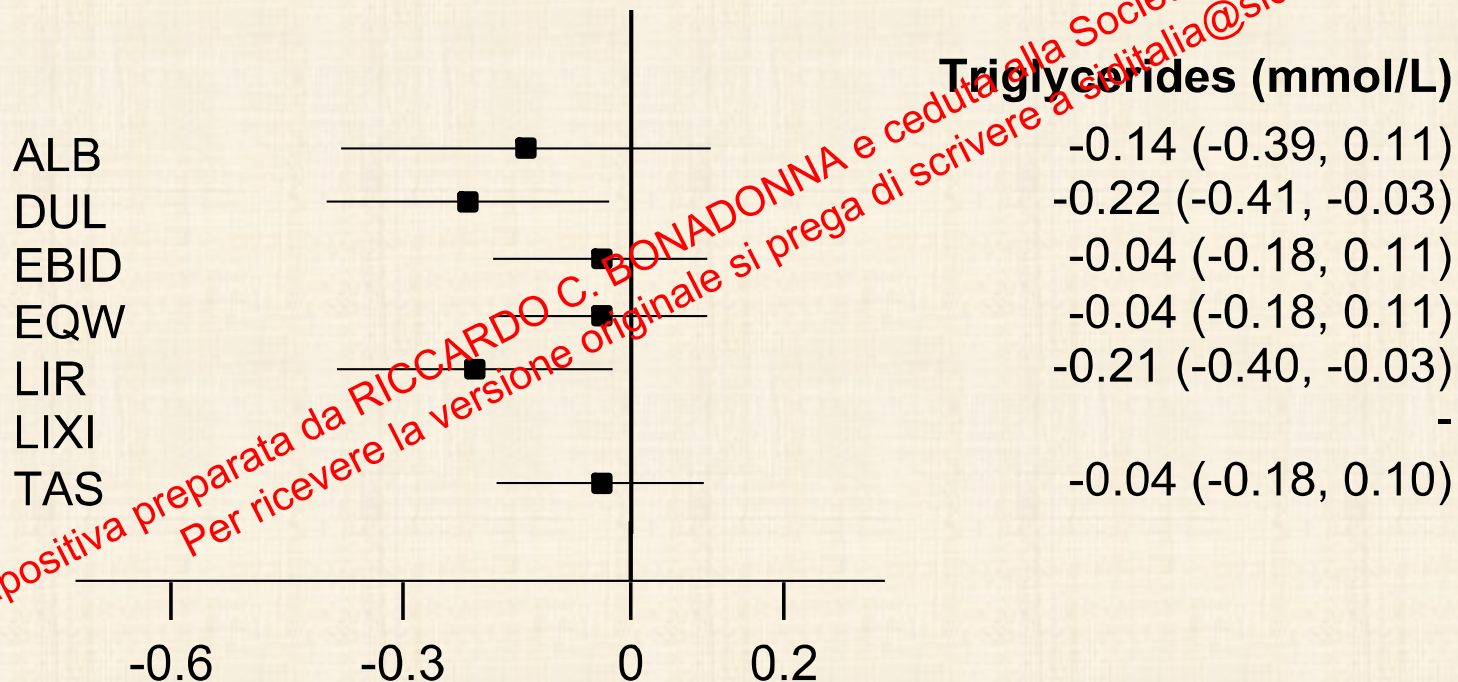
Differences of LDL-cholesterol estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



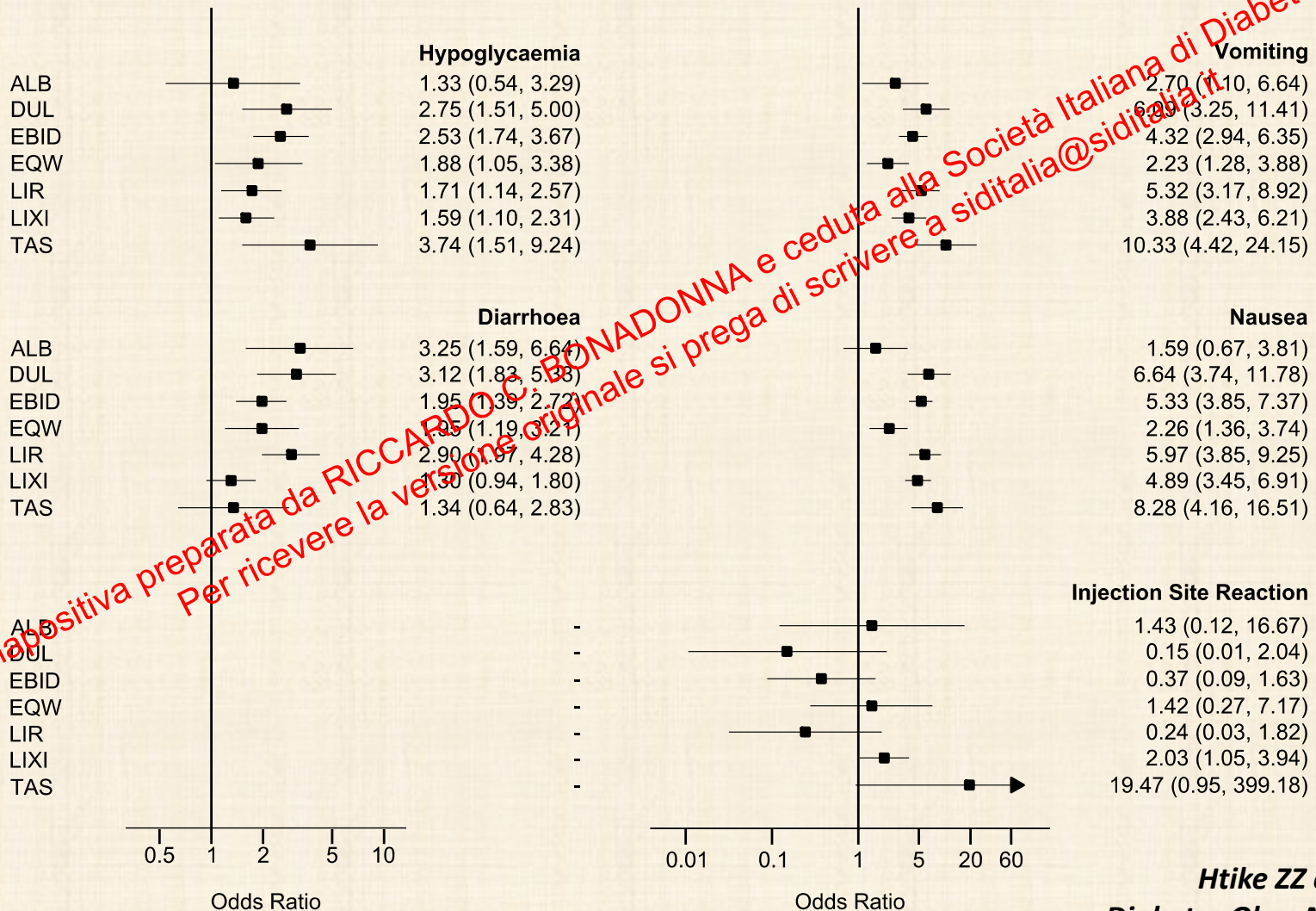
Differences of HDL-cholesterol estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



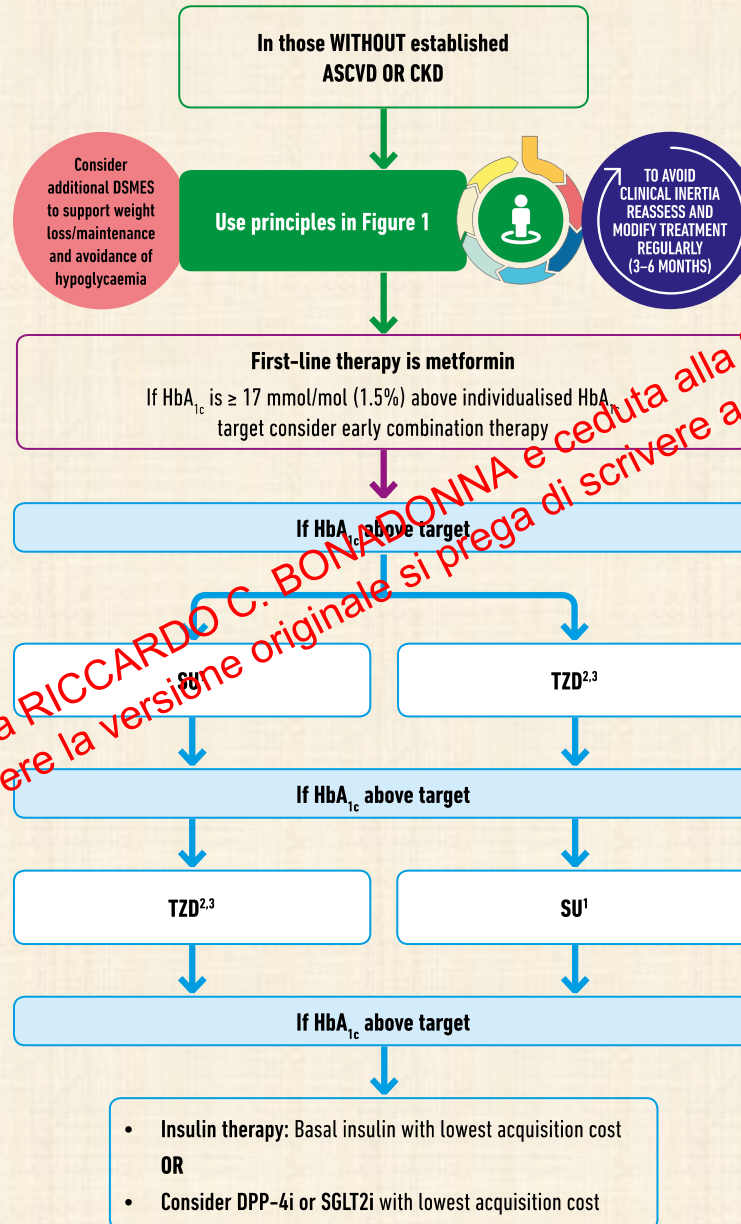
Differences of triglycerides estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



Differences of safety outcomes estimated with network meta-analysis vs placebo in patients with type 2 diabetes treated with GLP1R-agonists



CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

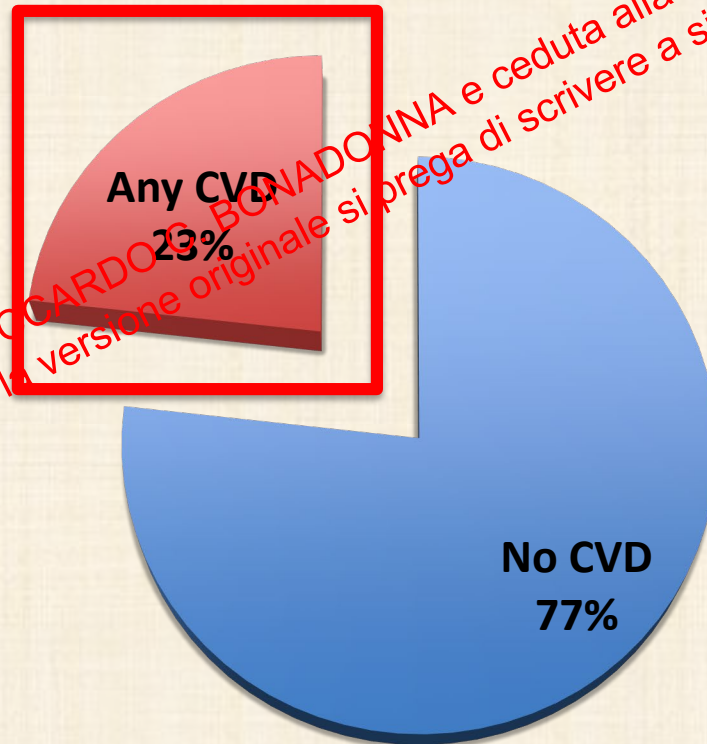


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**PARADIGM:
TREAT TO TARGET**

The RIACE Study: 15993 consecutive patients with diabetes from 19 Outpatient Diabetes Clinics in Italy, years 2007-2008

Prevalence of any CVD
in patients attending Outpatient Diabetes Clinics



Pharmacologic glucose-lowering therapy in type 2 diabetes: after the first step



ESTABLISHED ASCVD OR CKD

????????????????

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CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use principles in Figure 1

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

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit¹ (See below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit¹ (See below)

OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3 month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates



HF or CKD predominates



EITHER/
OR

GLP-1 RA with proven
CVD benefit¹

SGLT2i with proven
CVD benefit¹, if
eGFR adequate²

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD
progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less
than adequate² add GLP-1 RA with proven CVD benefit^{1,4}

**PARADIGM:
TREAT TO BENEFIT**

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Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., Ph.D., Hertz C. Gerstein, M.D., Lars V. Køber, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D., for the ELIXA Investigators*

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Restrepo, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lohnygina, Ph.D., John B. Buse, M.D., Ph.D., Juliana C. Chan, M.D., Jasmine Choi, M.S., Stephanie M. Gustavson, Ph.D., Nayyar Iqbal, M.D., Aldo P. Maggioni, M.D., Steven P. Marso, M.D., Peter Öhman, M.D., Ph.D., Neha J. Pagidipati, M.D., M.P.H., Neil Poulter, F.Med.Sci., Ambady Ramachandran, M.D., Bernard Zinman, M.D., and Adrian F. Hernandez, M.D., M.H.Sc., for the EXSCEL Study Group*

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Adrian F Hernandez, Jennifer B Green, Salim Janmohamed, Ralph B D'Agostino Sr, Christopher B Granger, Nigel P Jones, Lawrence A Leiter, Anne E Rosenberg, Kristina N Sigmon, Matthew C Somerville, Karl M Thorpe, John J V McMurray, Stefano Del Prato, for the Harmony Outcomes committees and investigators*

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Hertz C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogossova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators*

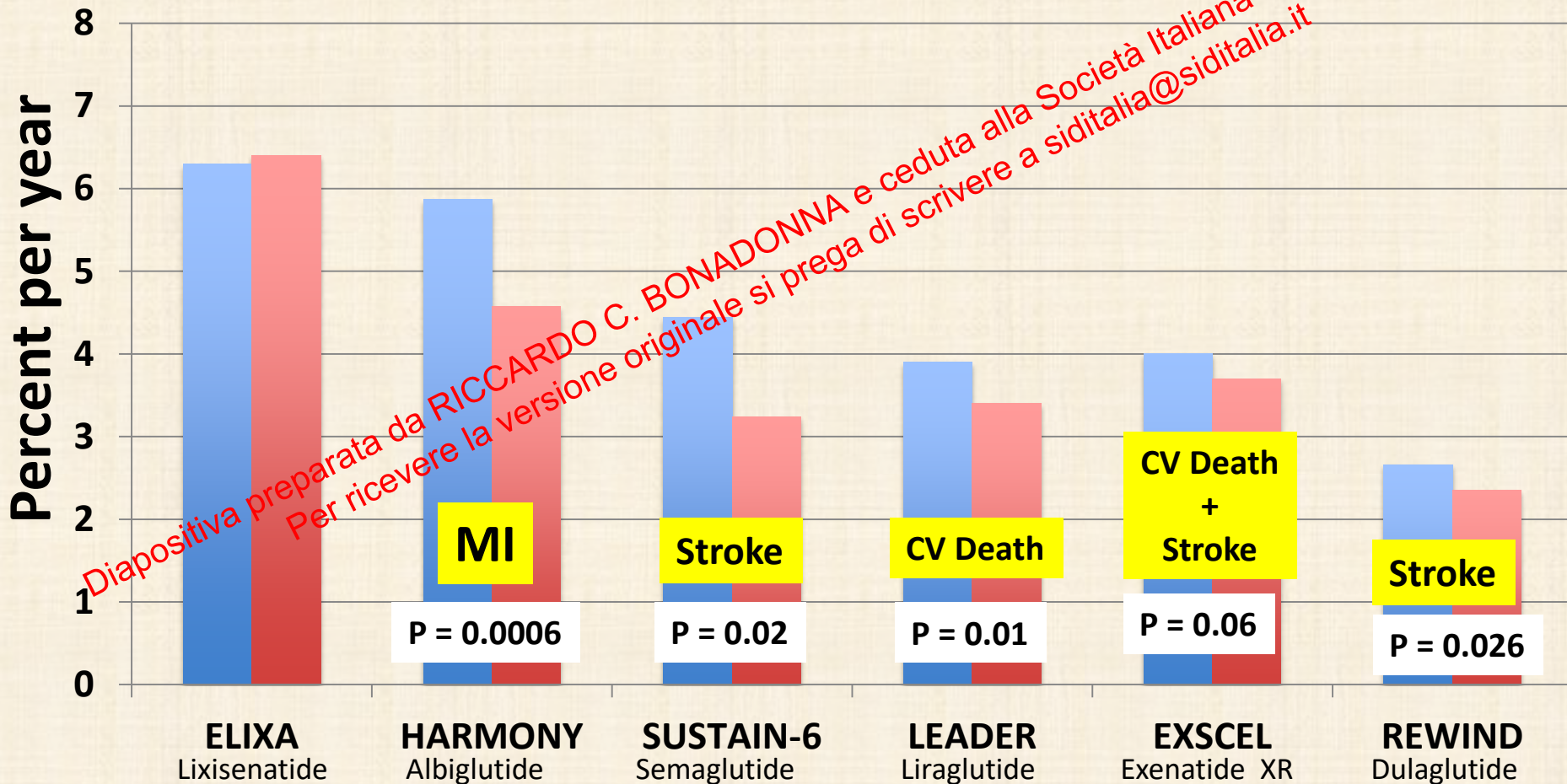
Focus on:

- **3-point MACE: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke**
- **All cause death rate**
- **Hospitalization for heart failure**
- **(Composite renal outcome: substantial fall of eGFR, initiation of renal replacement therapy, death from renal disease)**

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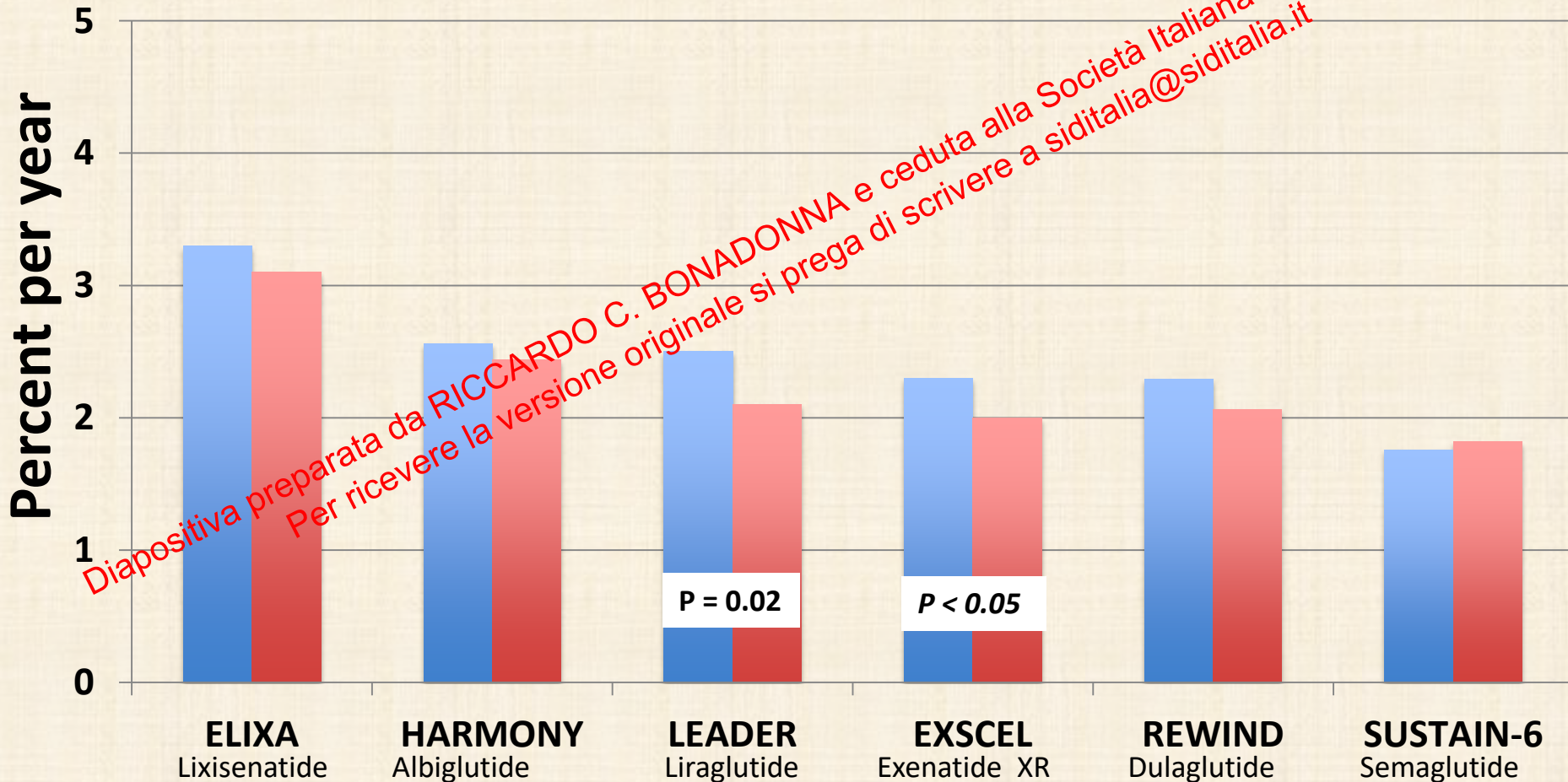
Incidence of MACE in the CVOTs with GLP1-RA

■ Placebo ■ GLP1-RA



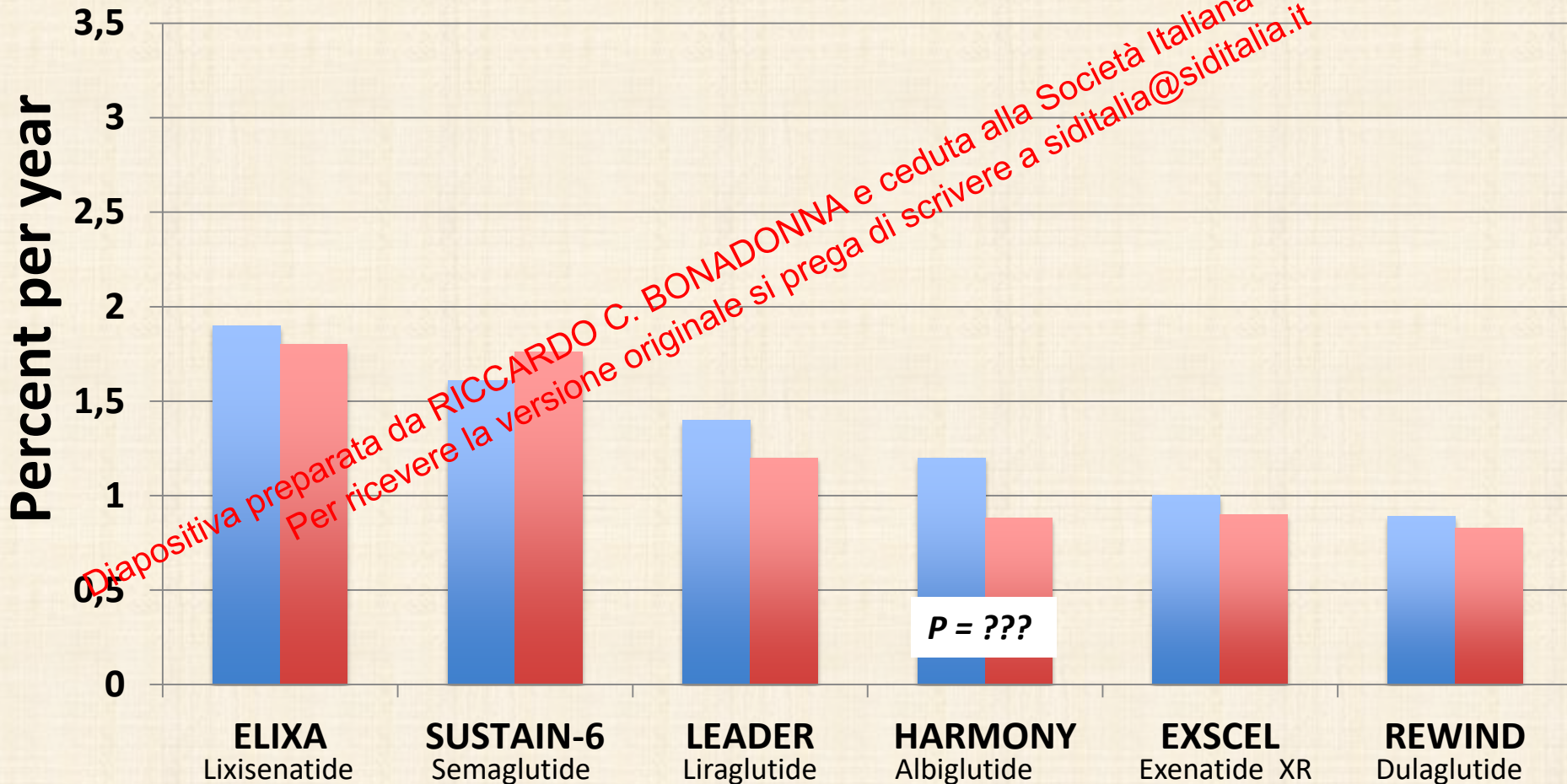
All cause death rate in the CVOTs with GLP1-RA

■ Placebo ■ GLP1-RA

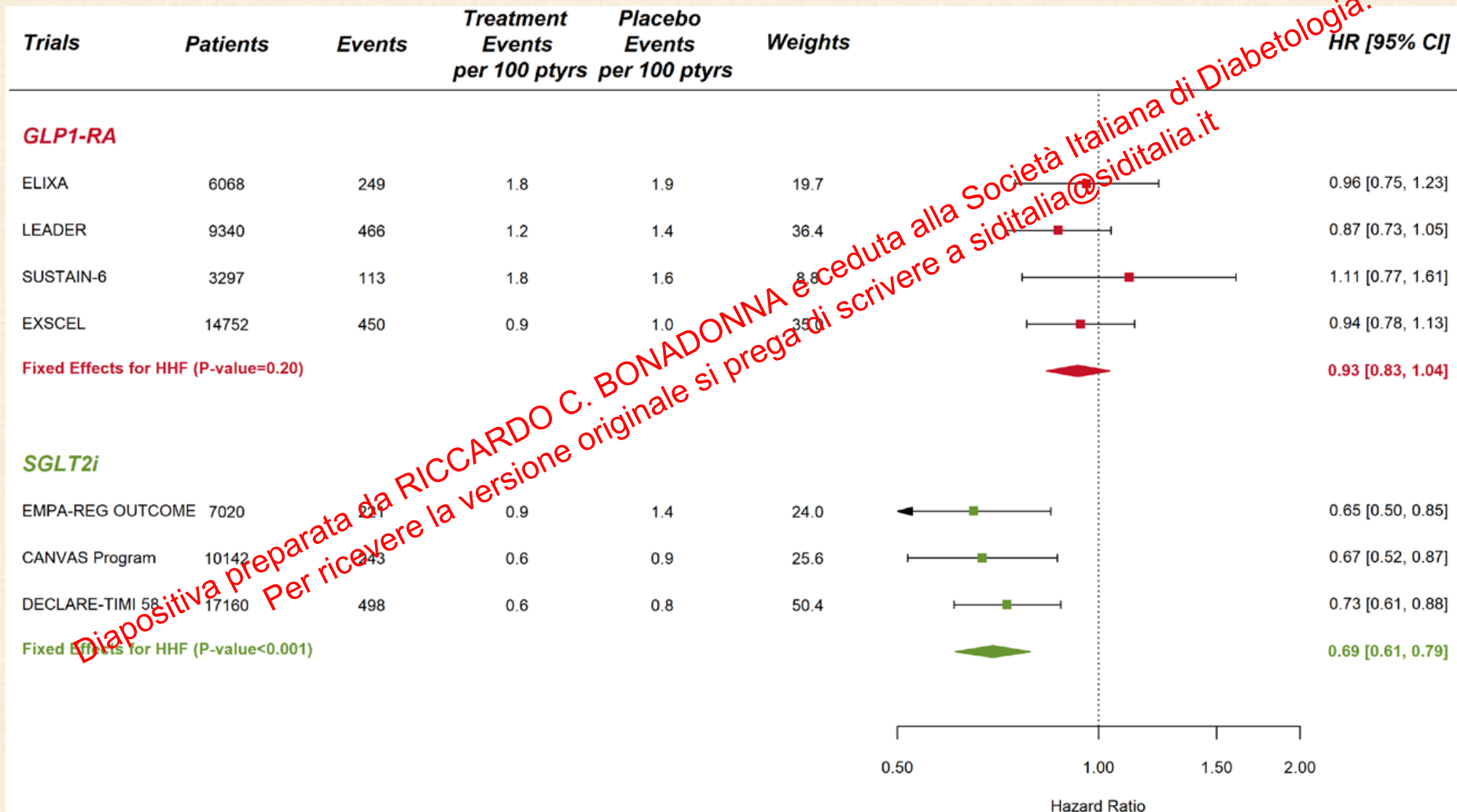


Hospitalization for heart failure in the CVOTs with GLP1-RA

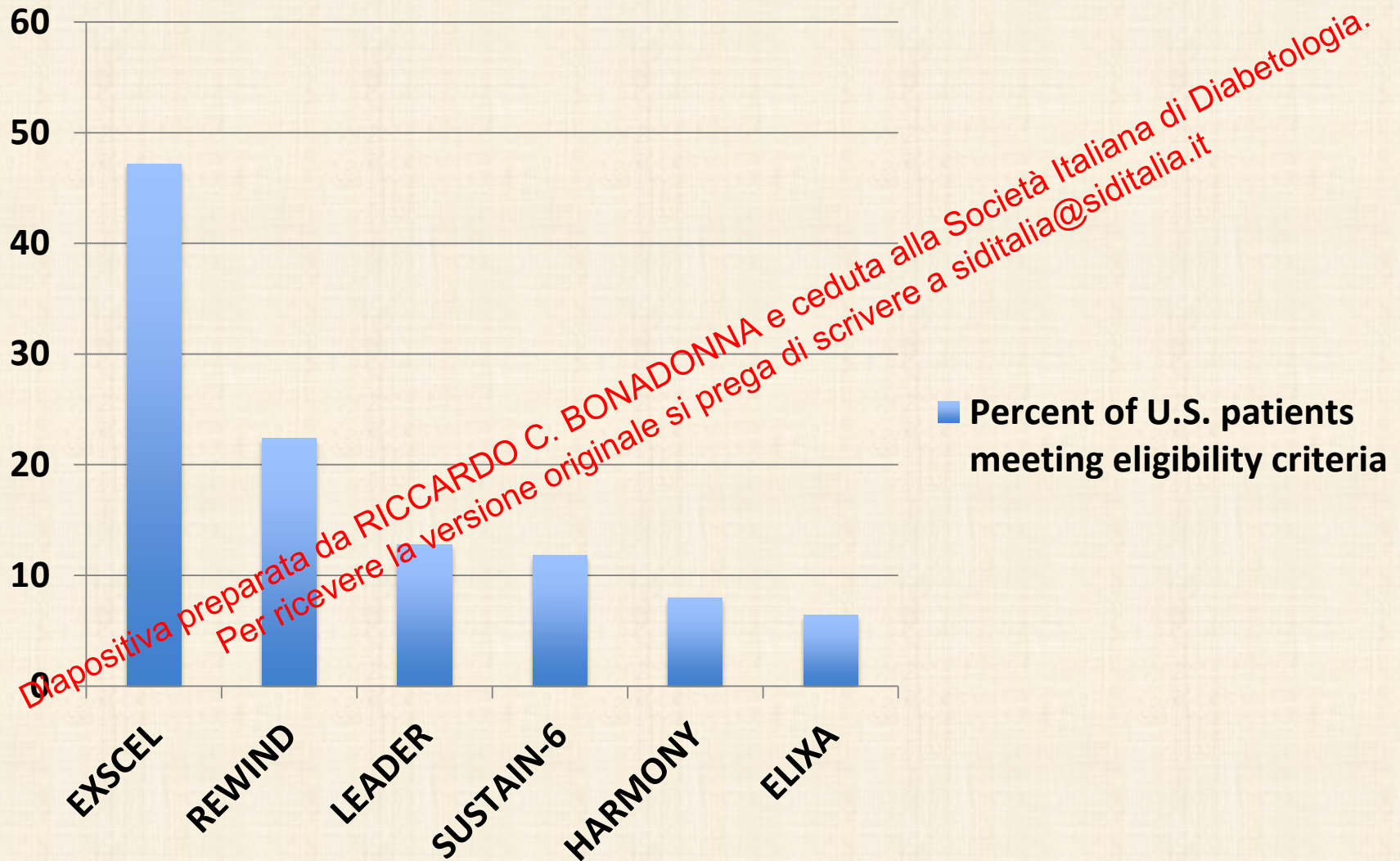
■ Placebo ■ GLP1-RA



Meta-analysis of GLP1-RA and SGLT2-I trials on hospitalization for heart failure (HHF)



Percentages of adults with T2DM in U.S.A. who would meet inclusion criteria for CVOT of GLP1-R agonists



Differences among GLP1R-A trials that may have influenced outcomes

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND
Agent	Lixisenatide	Liraglutide	Semaglutide	Exenatide XR	Alogliptine	Dulaglutide
Dose strategy	Increased if tolerated	Forced increase	Forced increase	Single dose	Clinical titration	Single dose
Baseline HbA1c (%)	7.7	8.7	8.7	8.1	8.7	7.35
Established CVD (%)	100	81	83	73	100	31.5
First MACE (n)	805	1302	254	1744	766	1257
Follow-up duration (yrs)	2.1	3.8	2.1	3.2	1.6	5.4

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Differences Among Agents That May Have Influenced Outcomes

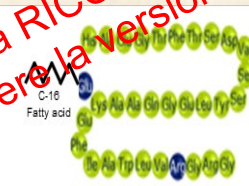
Drug	Lixisenatide od	Liraglutide od	Semaglutide qw	Exenatide XR qw	Albiglutide qw
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%)
In vivo EC ₅₀ nmol/kg)*	0.02	0.5	NA	0.01	1.4
t _{1/2}	2–4 h	11.6–13 h	7 days	2 weeks	~ 5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg

Albiglutide has high human GLP-1 homology, long t_{1/2} and lowest glycaemic potency

Lixisenatide



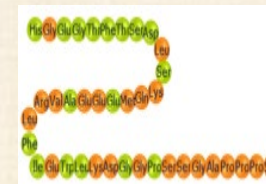
Liraglutide



Semaglutide



Exenatide



Albiglutide



*Dose producing 50% maximal glucose AUC following OGTT in db/db mice (data on file). Exenatide EC₅₀ values from exenatide not exenatide XR. Other data from Clin Pharmacokin 2018 (in press)

Green circles within molecular depictions represent amino acids homologous to human GLP-1
AUC, area under curve; t_{1/2}, terminal half-life; OGTT, oral glucose tolerance test

**HARMONY-Outcomes
EASD 2018**

Number of patients to treat to benefit (NNTB) in RCTs of patients with T2DM

TRIAL	OUTCOME	NNTB (patient-years)
UKPDS	Any diabetes related event	196
HOPE-Diabetes (ramipril)	MACE	97
EMPA-REG OUTCOME	MACE	154
LEADER	MACE	200
SUSTAIN-6	MACE	83
EXSCEL	MACE	(333)
HARMONY	MACE	77
REWIND	MACE	323

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Number of patients to treat to benefit (NNTB) in RCTs of patients with T2DM

TRIAL	OUTCOME	NNTB (patient-years)
UKPDS-FU (SU or Insulin)	DEATH	286
UKPDS-FU (metformin)	DEATH	139
HOPE-Diabetes (ramipril)	DEATH	137
EMPA-REG OUTCOME	DEATH	110
LEADER	DEATH	200
SUSTAIN-6	DEATH	∞
EXSCEL	DEATH	310
HARMONY	DEATH	∞
REWIND	DEATH	435

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Meta-analysis of GLP1-RA and SGLT2-I trials on composite renal outcome

A

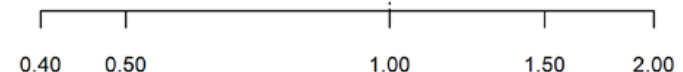
Trials Patients Events Treatment n/N Placebo n/N Weights HR [95% CI]

GLP1-RA

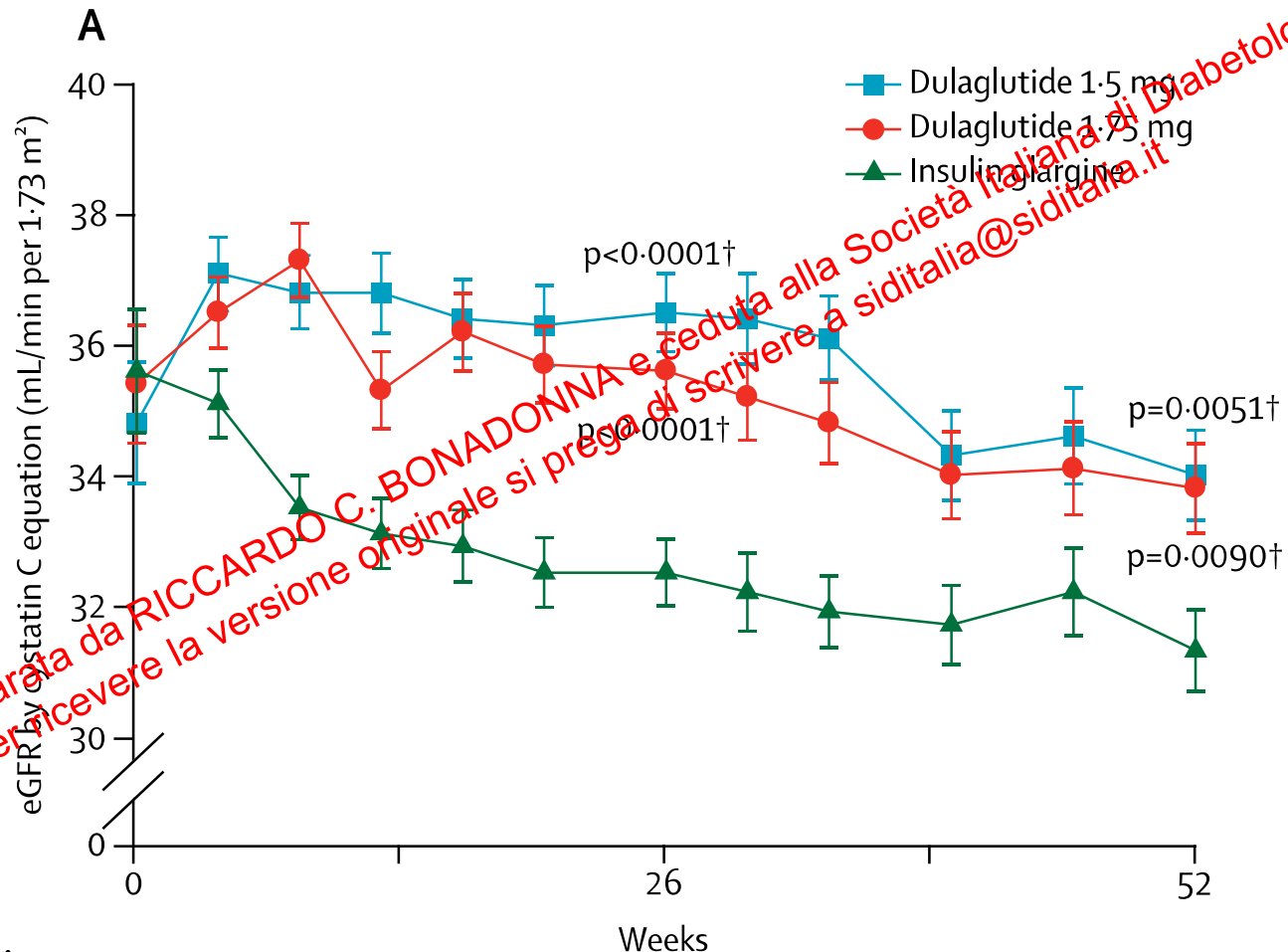
ELIXA	5286	375	203/2639	172/2647	20.0	0.84 [0.68, 1.02]
LEADER	9340	605	268/4668	337/4672	32.2	0.78 [0.67, 0.92]
SUSTAIN-6	3297	162	62/1648	100/1649	7.1	0.64 [0.46, 0.88]
EXSCEL	14752	773	366/6256	407/6222	46.7	0.88 [0.76, 1.01]
Fixed Effects for GLP1-RA (P-value<0.001)						0.82 [0.75, 0.89]

SGLT2i

EMPA-REG OUTCOME	6185	913	525/4124	388/2061	24.9	0.61 [0.53, 0.70]
CANVAS Program	10442	847	NA	NA	25.0	0.57 [0.50, 0.66]
DECLARE-TIMI 56	17160	1675	678/8582	997/8578	50.1	0.66 [0.60, 0.73]
Fixed Effects for SGLT2i (P-value<0.001)						0.62 [0.58, 0.67]



Dulaglutide preserves GFR in patients with type 2 diabetes and moderate-to-severe chronic kidney disease: the AWARD-7 trial



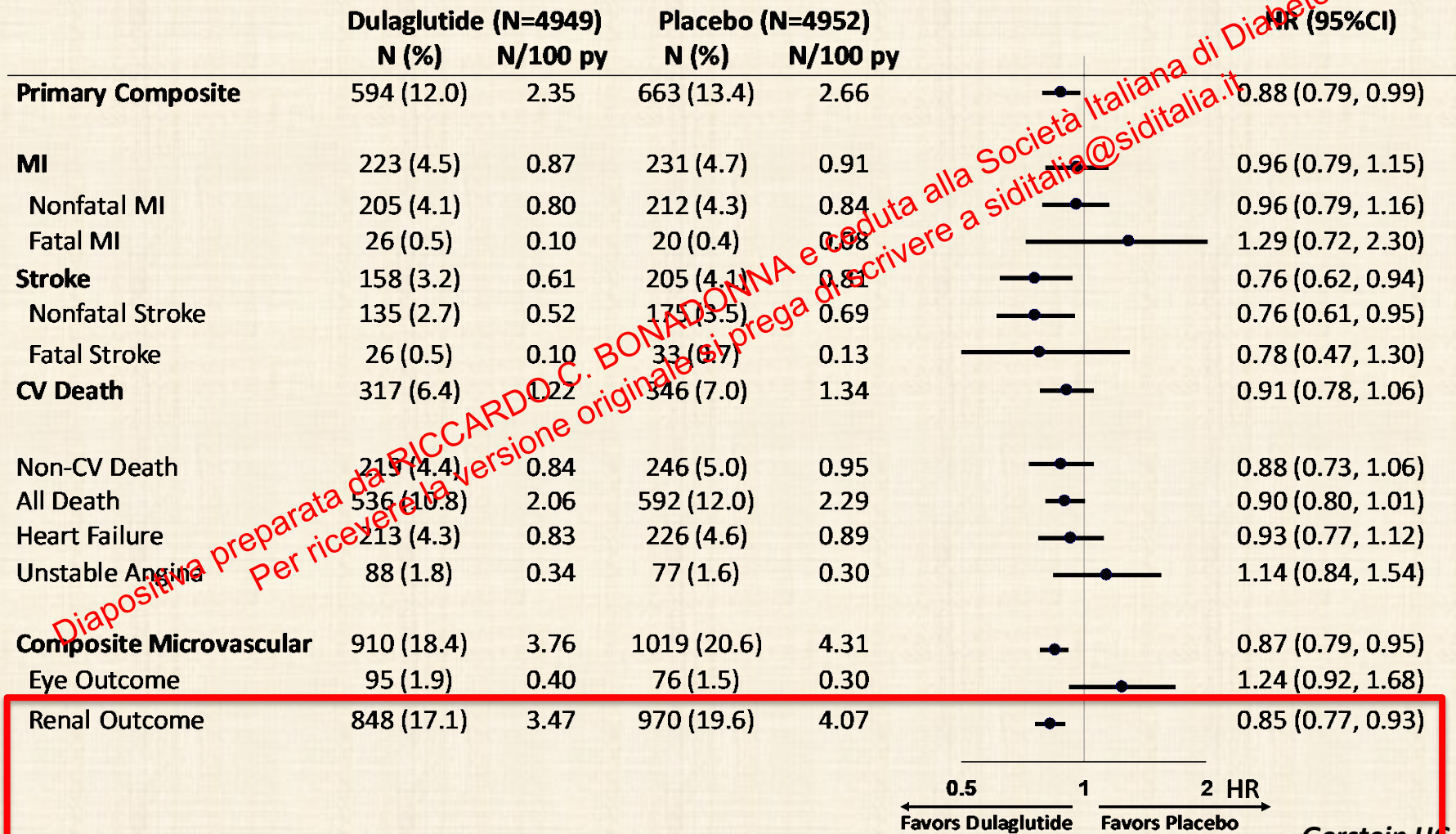
Number of patients

Dulaglutide 1.5 mg	192
Dulaglutide 0.75 mg	190
Insulin glargine	194

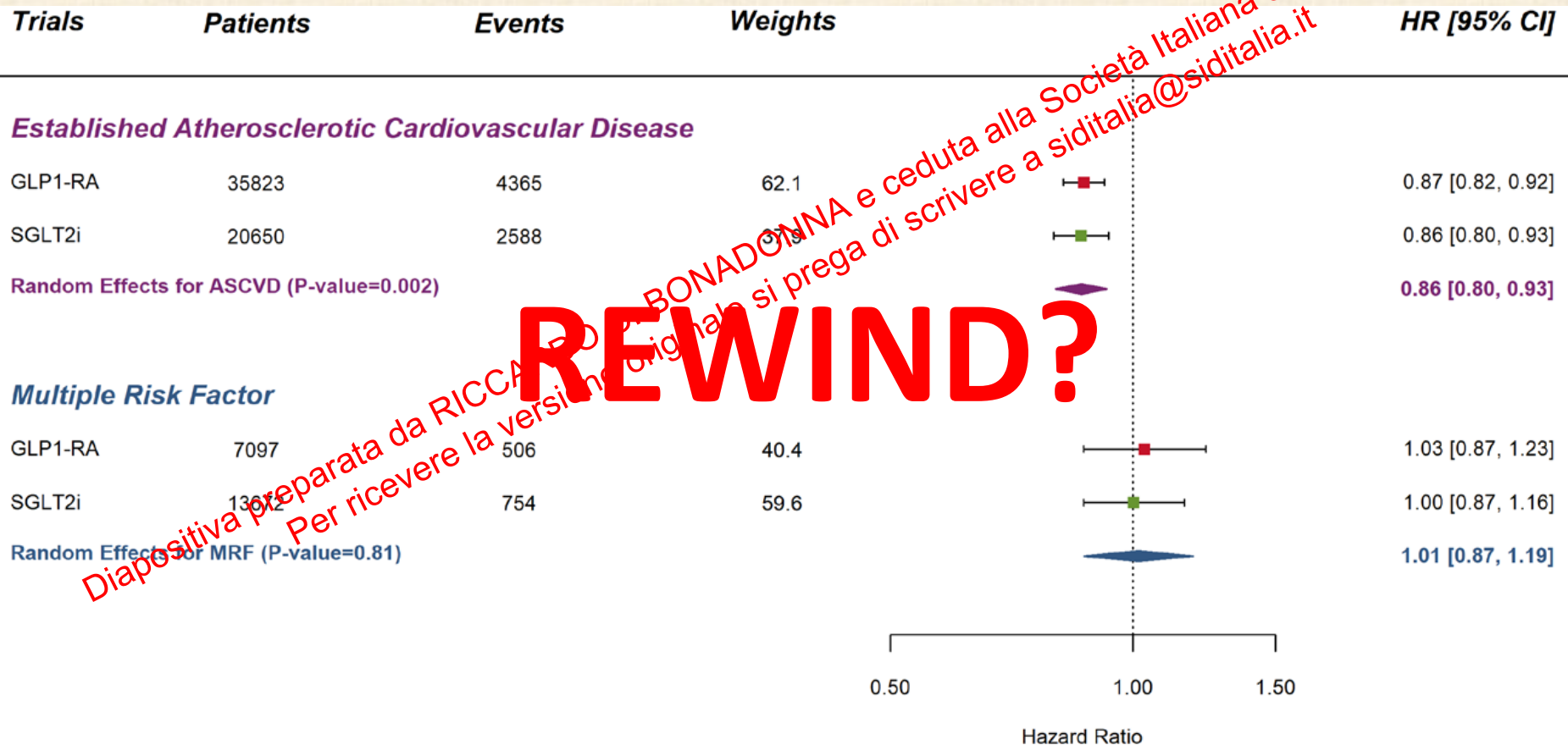
163
167
174

157	Tuttle KR et al.;
160	Lancet Diabetes
164	Endocrinol 2018

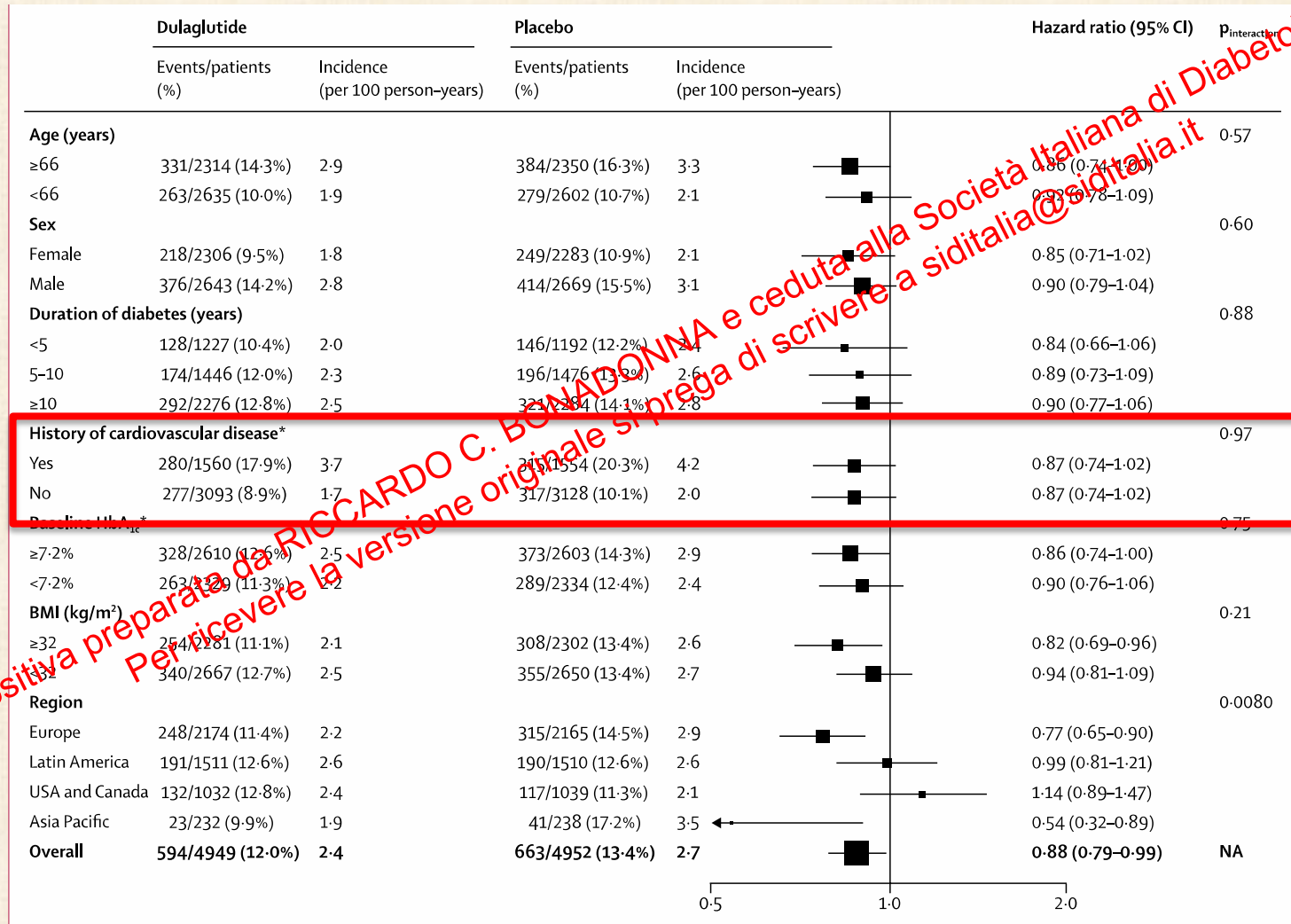
REWIND: summary of primary and secondary outcomes



Meta-analysis of GLP1-RA and SGLT2-I trials on the MACE endpoint stratified by the presence of atherosclerotic cardiovascular disease (ASCVD)



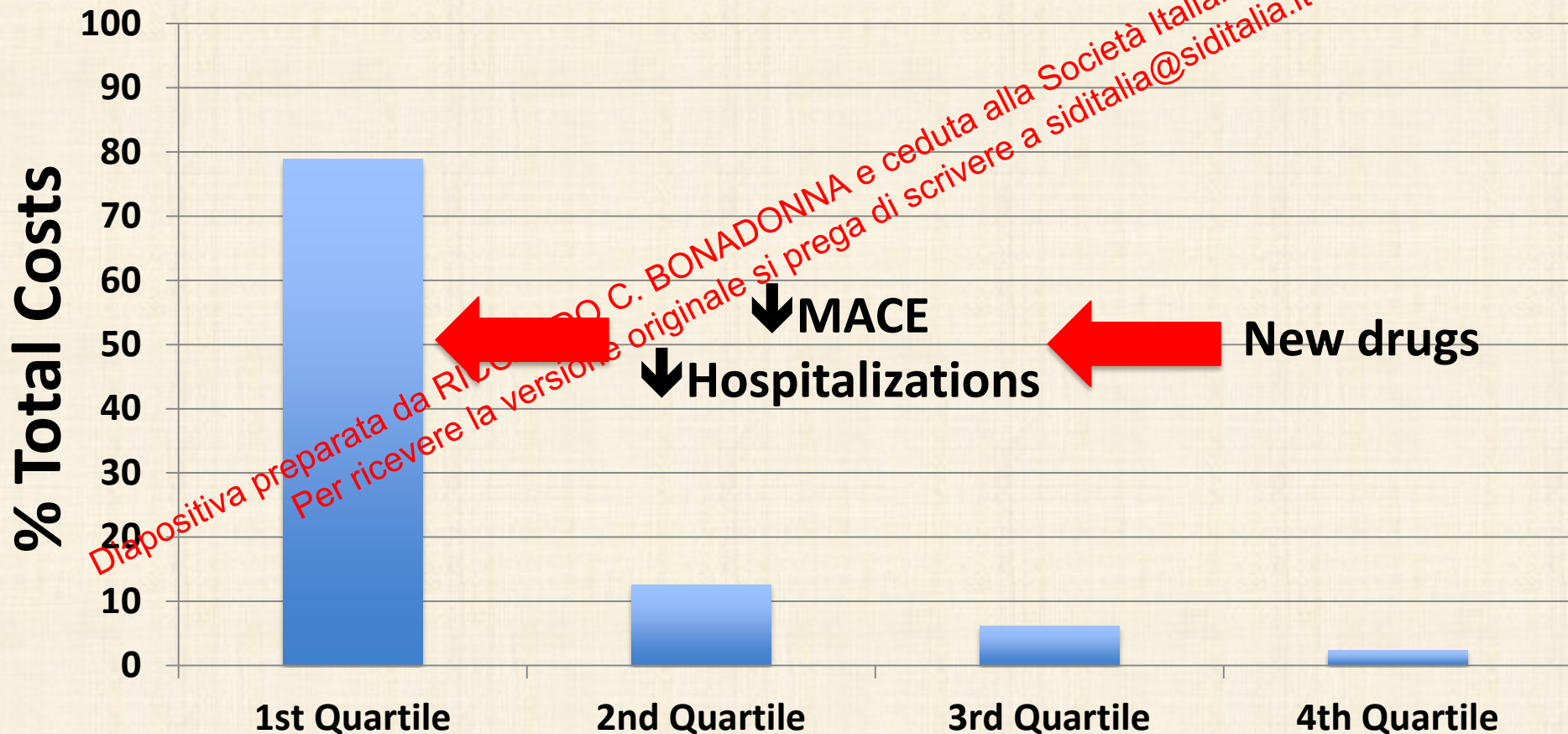
REWIND: subgroup analysis for the primary cardiovascular outcome



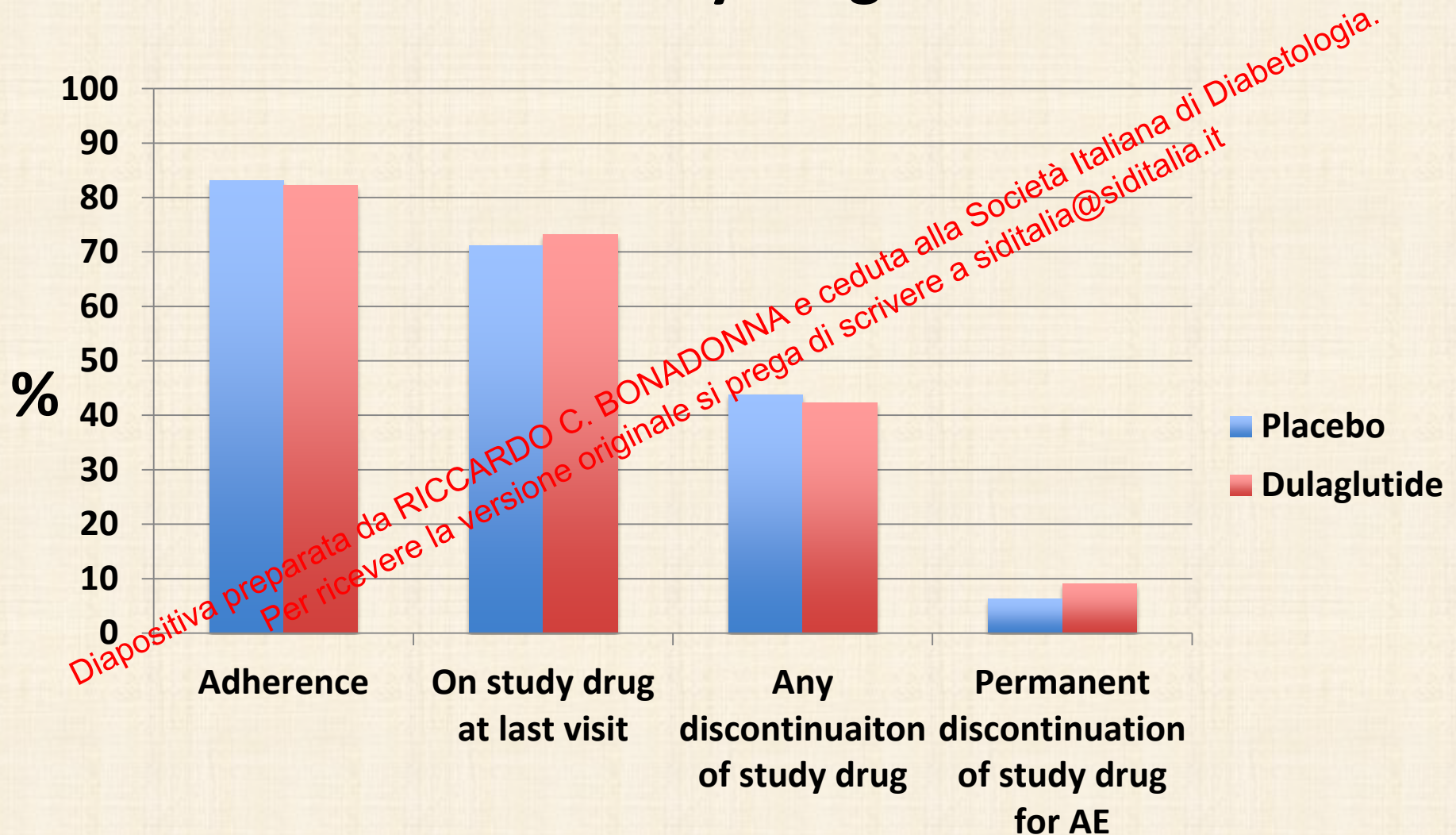
Region Emilia Romagna, year 2014

Distribution of health care costs for diabetes per diabetic patient quartiles (n=256372, total costs: 701 M€ per year)

Percent of Total Costs



REWIND: adherence to and discontinuation of study drug



Prices of yearly therapy with glucose lowering agents per T2DM patient

€ per year

Price (€ per year)



■ Price (€ per year)

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Considerazioni conclusive

- **Nei pazienti con diabete di tipo 2, i GLP1R-agonisti:**
 - Hanno ottima efficacia sul controllo glico-metabolico, con facilità d'uso (specie i composti a iniezione settimanale) con buona aderenza da parte dei pazienti
 - Sono ottimi agenti per la protezione dal rischio cardiovascolare in prevenzione secondaria
 - Sono un'eccellente opzione per l'intensificazione della terapia anti-diabete in aggiunta a metformina
 - Sono gravati da effetti collaterali gastrointestinali che ne causano l'interruzione in una relativamente piccola percentuale di pazienti
 - Sono la classe di farmaci anti-diabete con il costo più alto

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Grazie per l'attenzione

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