Le nuove linee guida ADA/EASD: quale posizione per gli inibitori di DPPIV

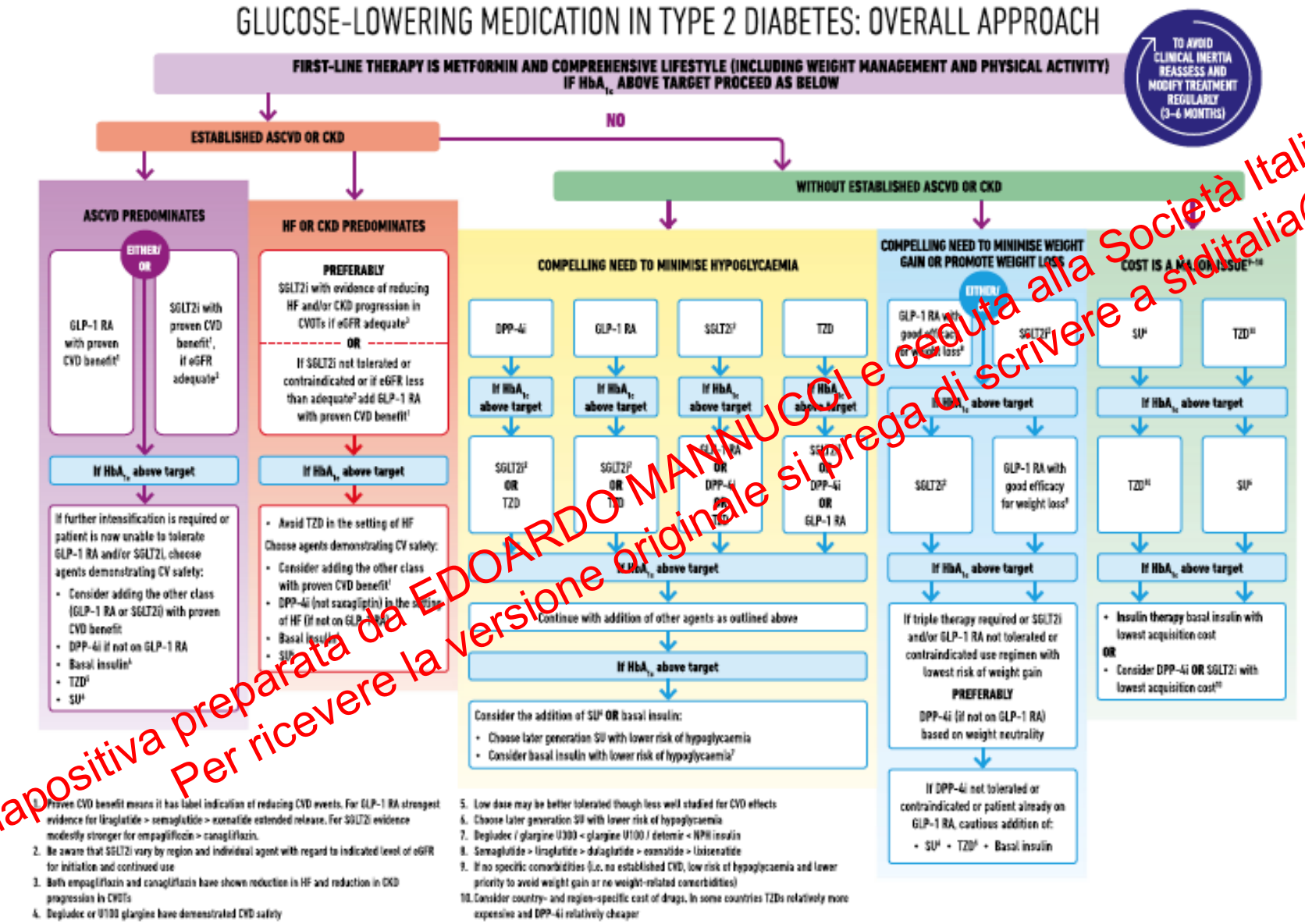
Edoardo Mannucci

Roma, 23 novembre 2019

Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto:
compensi per consulenze da ***AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Mundipharma*** e ***Novo Nordisk***
compensi per relazioni a corsi/convegni da ***Abbott*** e ***Eli Lilly***
compensi da agenzie in simposi sponsorizzati da ***Abbott, Allergan, AstraZeneca, Boehringer Ingelheim, Bruno, Eli Lilly, Menarini, Merck, Mundipharma, Novo Nordisk, Sanofi*** e ***Takeda***

La struttura diretta da E. Mannucci ha ricevuto:
finanziamenti per attività di ricerca e/o educative da ***AstraZeneca, Bayer, Boehringer Ingelheim, Molteni*** e ***Novo Nordisk***
compensi per trial clinici da:
AstraZeneca, Eli Lilly, Genentech, Janssen, Novartis e ***Novo Nordisk.***



1. 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.
2. Be aware that SGLT2i 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 and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

ADA-EASD Consensus Statement, 2018

Standard italiani per la cura del diabete mellito

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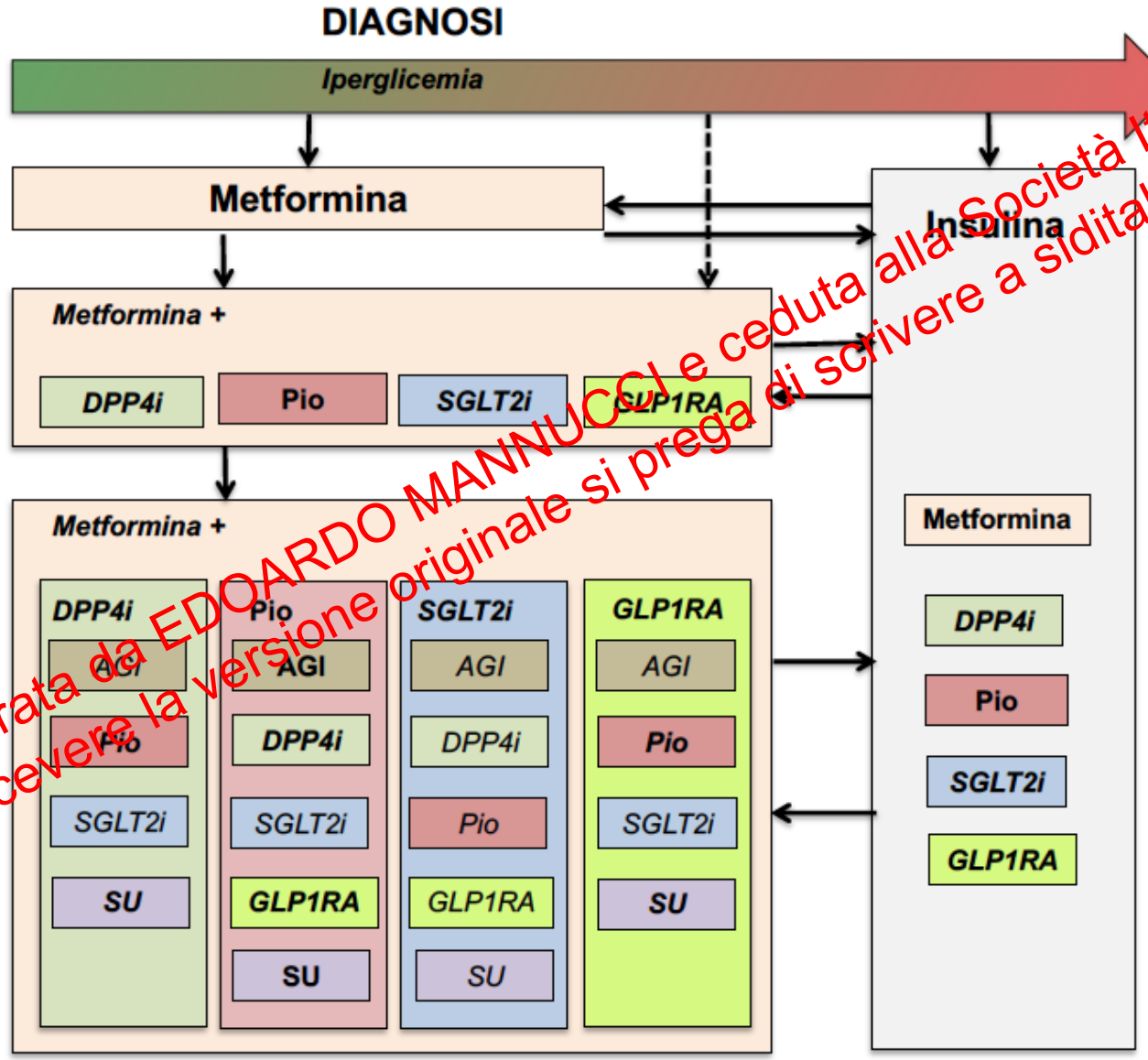

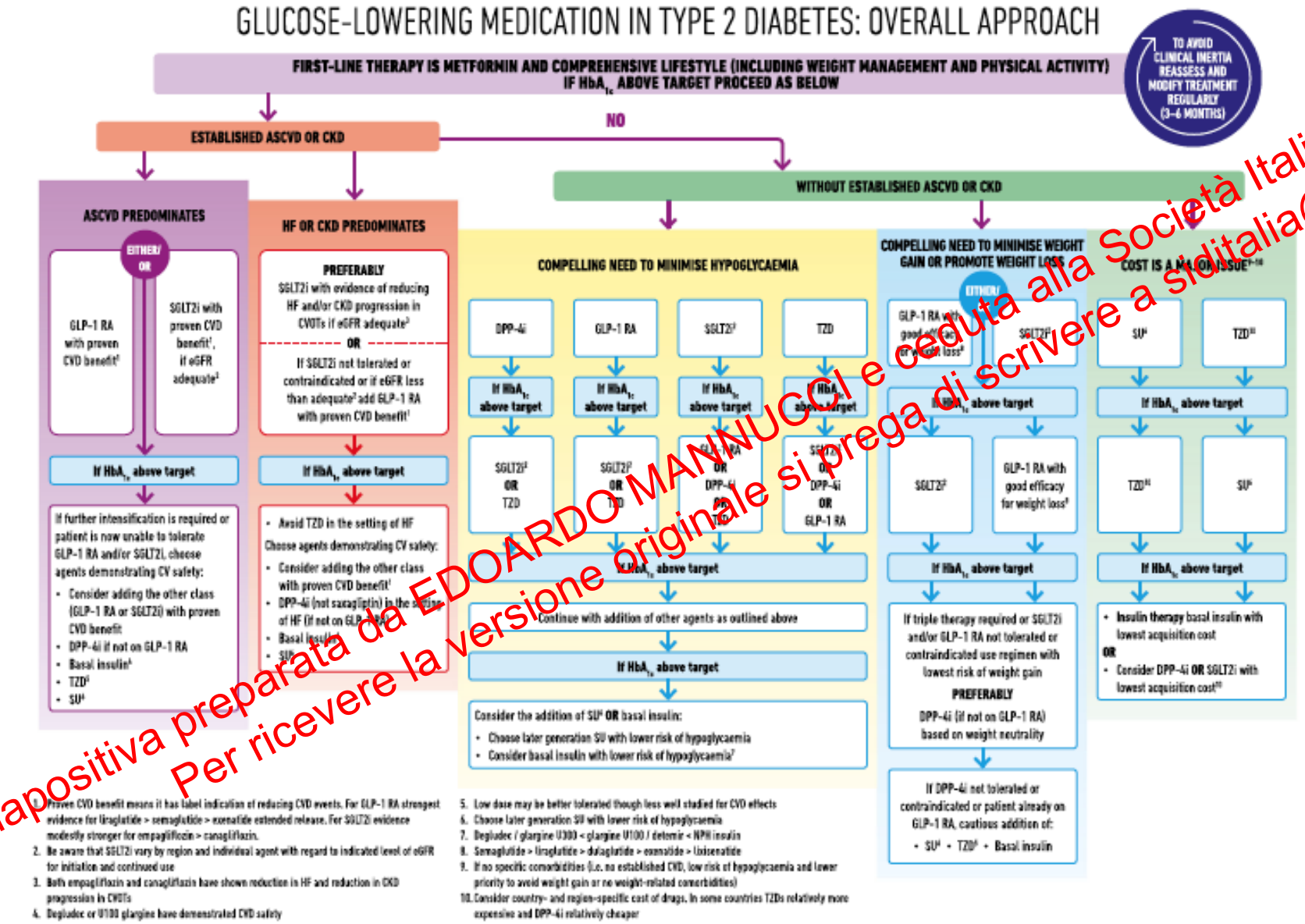

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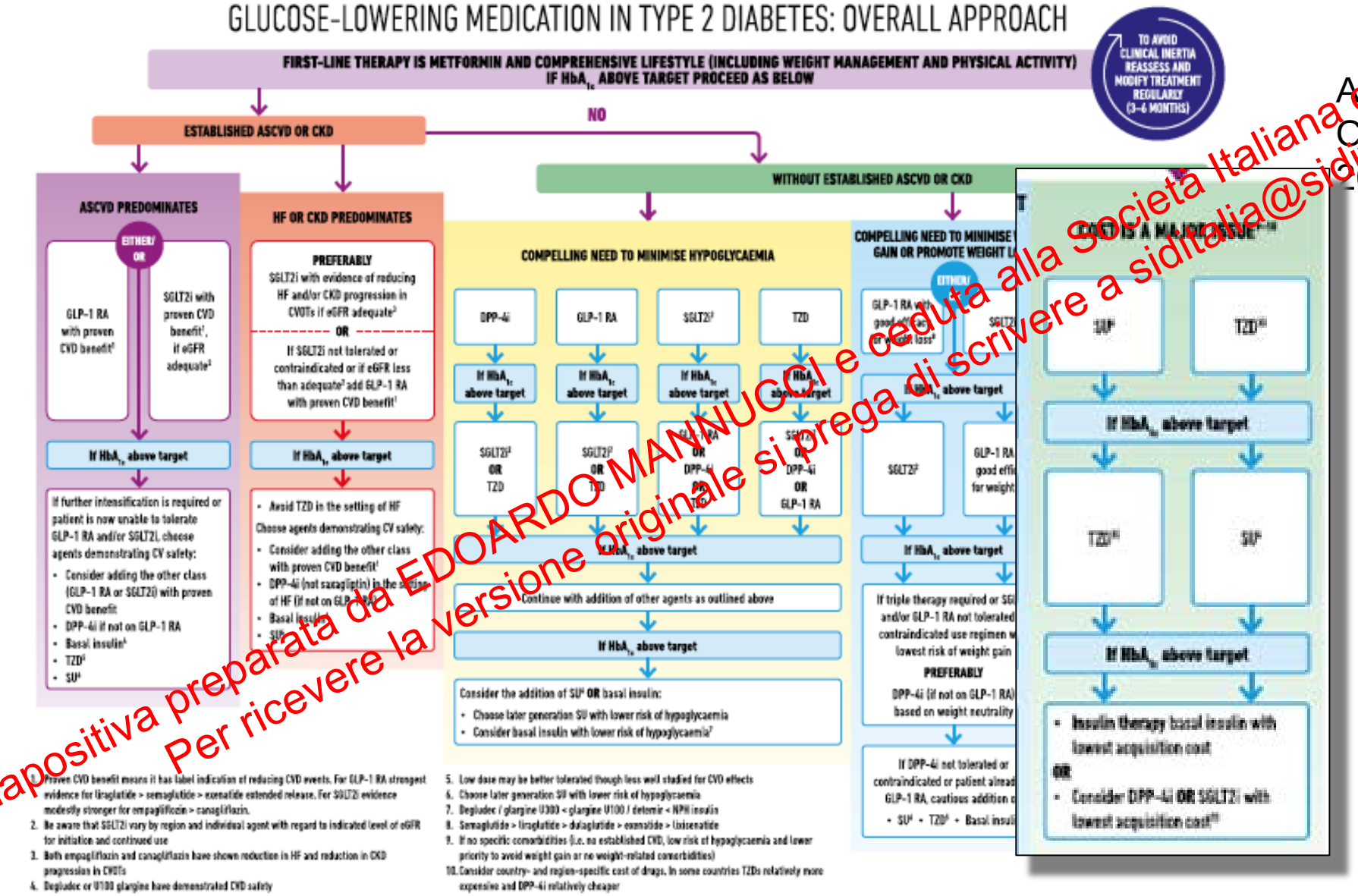

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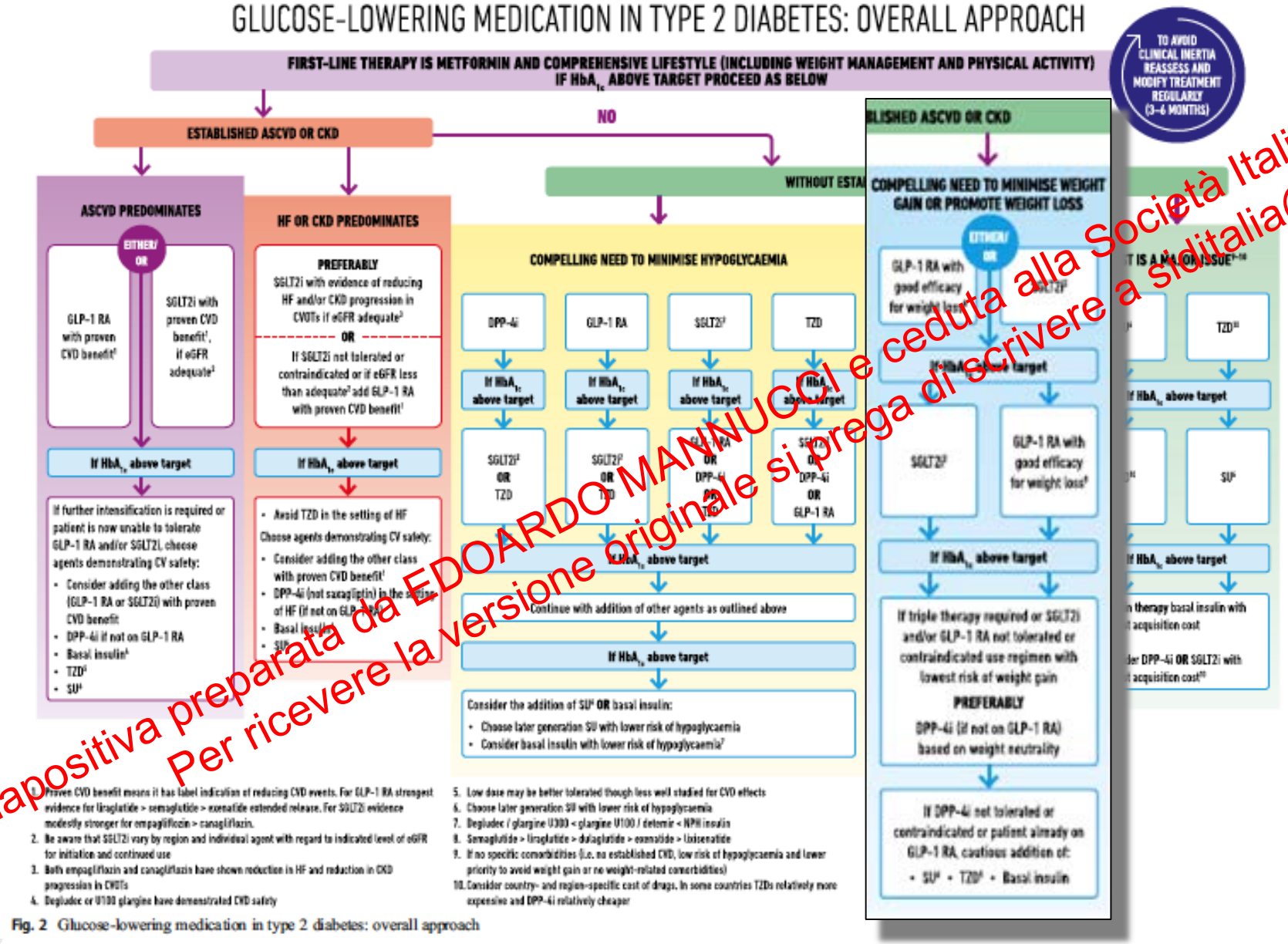

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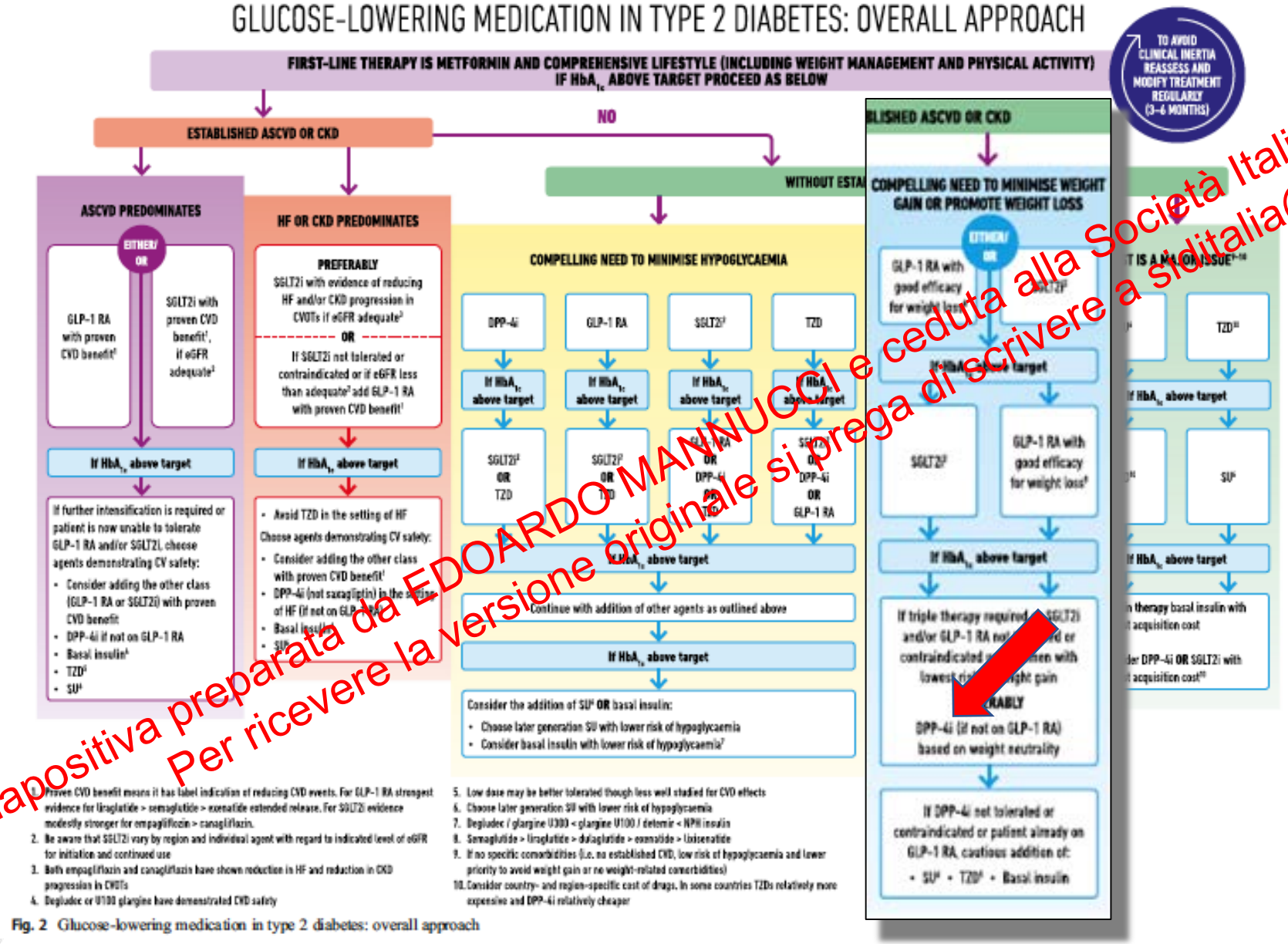

Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

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Nei pazienti obesi, si devono preferire, ove possibile, i farmaci che non determinano aumento di peso, ovvero, oltre alla metformina, agonisti del GLP-1, inibitori DPP4 e inibitori SGLT2. ***I B***

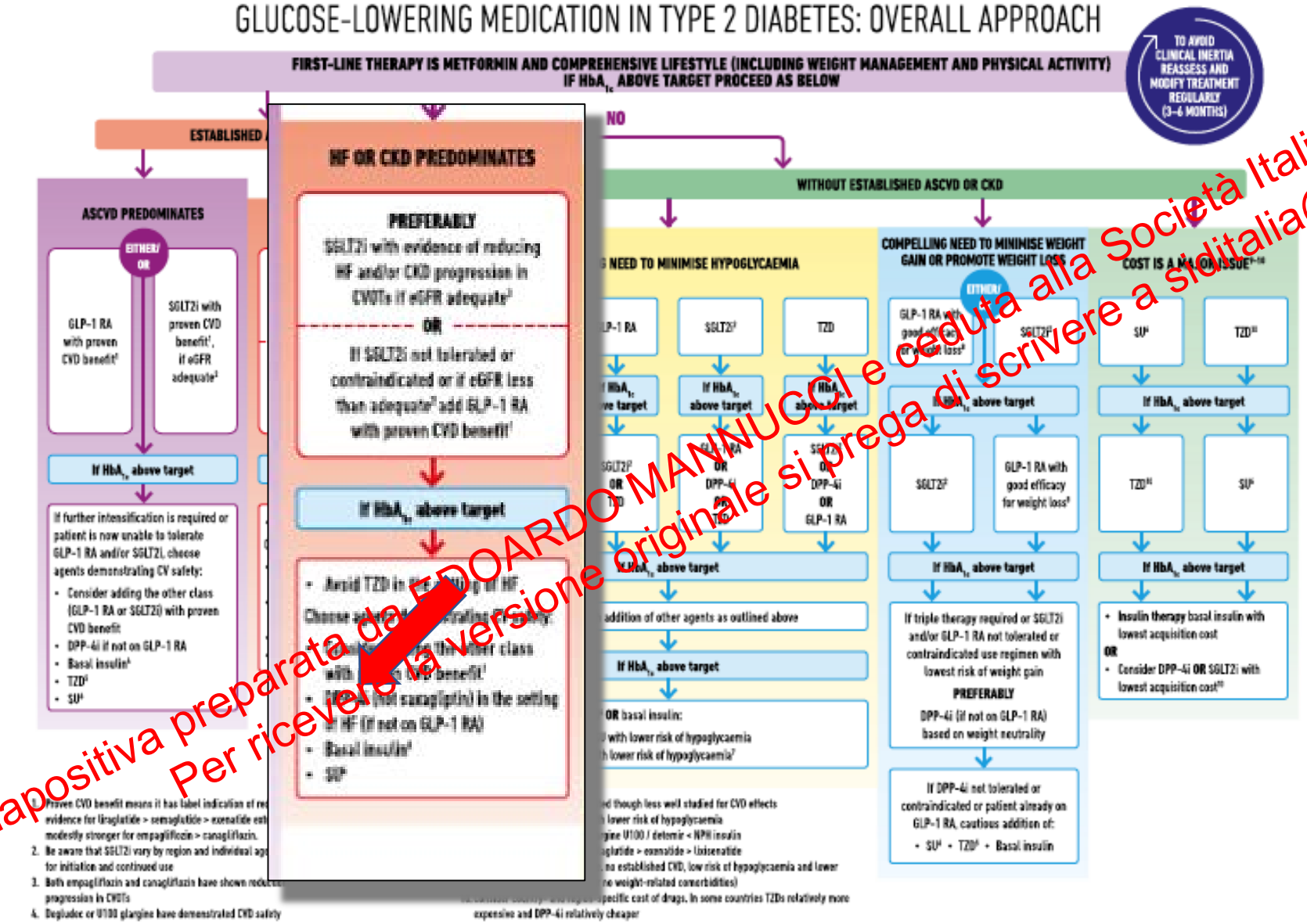


Fig. 2 Glucose-lowering medication in type 2 diabetes: overall approach

ADA-EASD Consensus Statement, 2018

eGFR, albuminuria and risk of eGFR decline

Results of a prospective observational study

Table 1—Frequency of decliners (eGFRcr-cys loss ≥3.3 %/year)

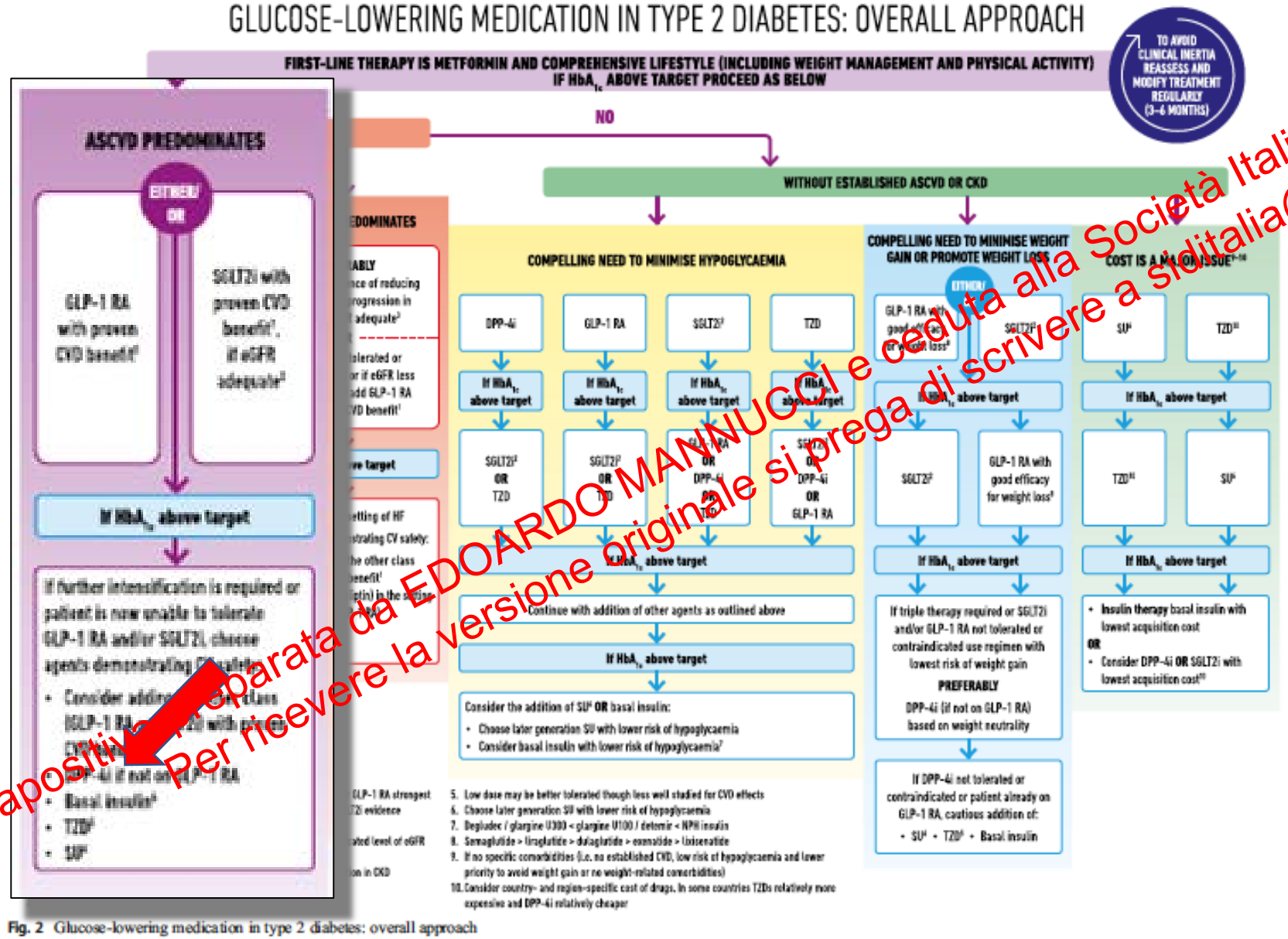
eGFRcr-cys (mL/min)	NA	MA
≥90	505 (7)	329 (24)
60–89	72 (18)	106 (40)
30–59	19 (21)	78 (48)
Total	595 (10)	513 (32)

Data are *n* (%). Observed during 4–10 years of follow-up in the study group included in the 2nd Joslin Study on Natural History of Early Renal Decline in T1D according to CKD stages and presence of NA and MA at entry into the follow-up (A.S.K., unpublished data).

Krolewski AS. *Diabetes Care* 38: 954-62, 2015

Farmaci per il diabete di tipo 2 e insufficienza renale

eGFR fino a (ml/min*1.73 m^2)	90	80	70	60	50	40	30	20	10	Dialisi
Metformina										
Acarbosio[a]										
Gliptine										
Sitagliptin										
Vildagliptin										
Saxagliptin[b]										
Linagliptin										
Alogliptin										
GLP1 agonisti										
Exenatide										
Exenatide LAR										
Liraglutide										
Lixisenatide										
Dulaglutide										
Sulfaniluree										
Glibenclamide										
Gliclazide										
Glimepiride										
Repaglinide										
Pioglitazone										
Gliflozine										
Dapagliflozin										
Empagliflozin[c]										
Canagliflozin[c]										



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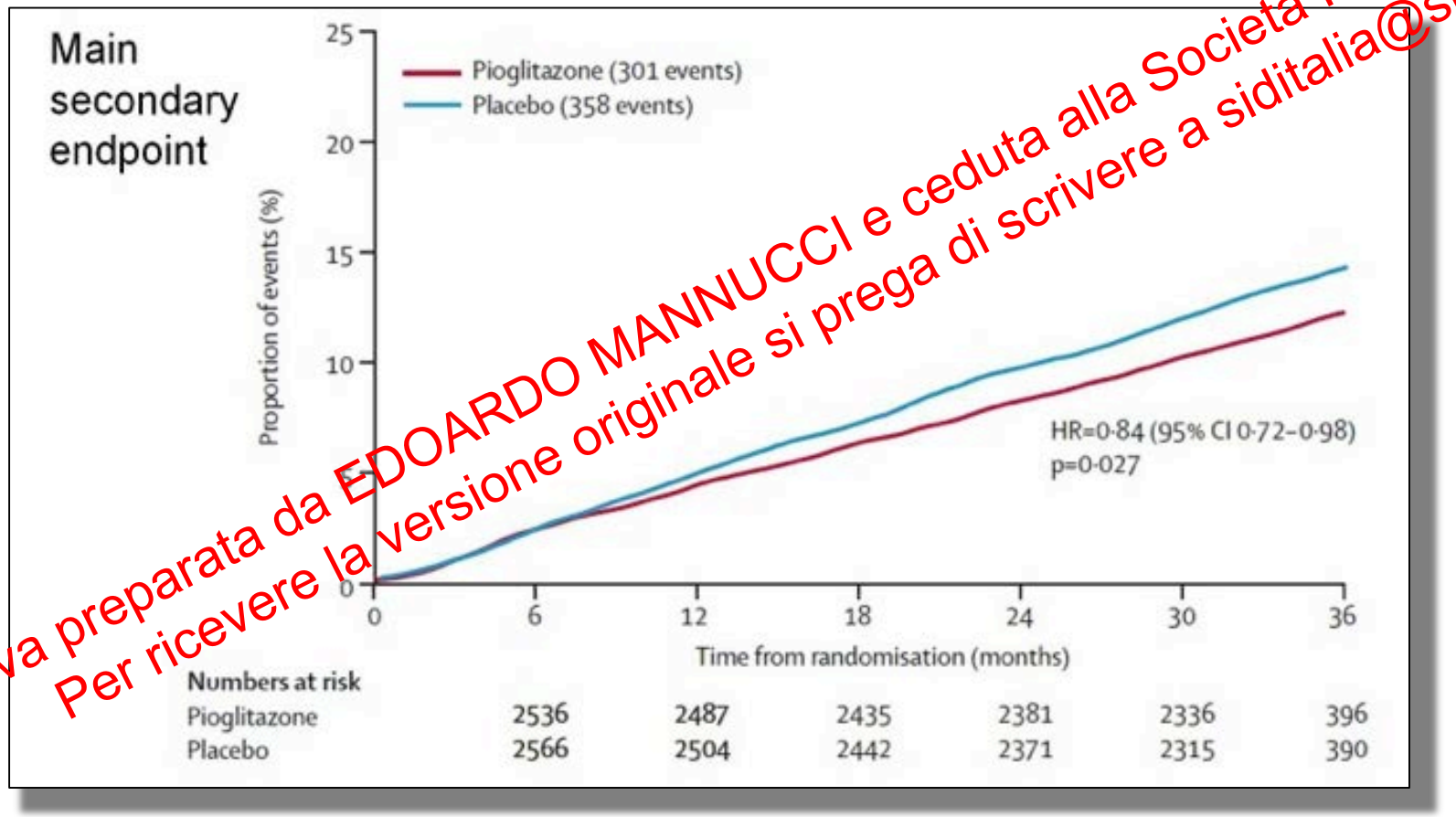
Nei pazienti con pregressi eventi cardiovascolari maggiori SGLT-2 inibitori, GLP-1 agonisti a lunga durata d'azione e pioglitazone devono essere considerati farmaci di prima scelta, salvo controindicazioni. ***II A***

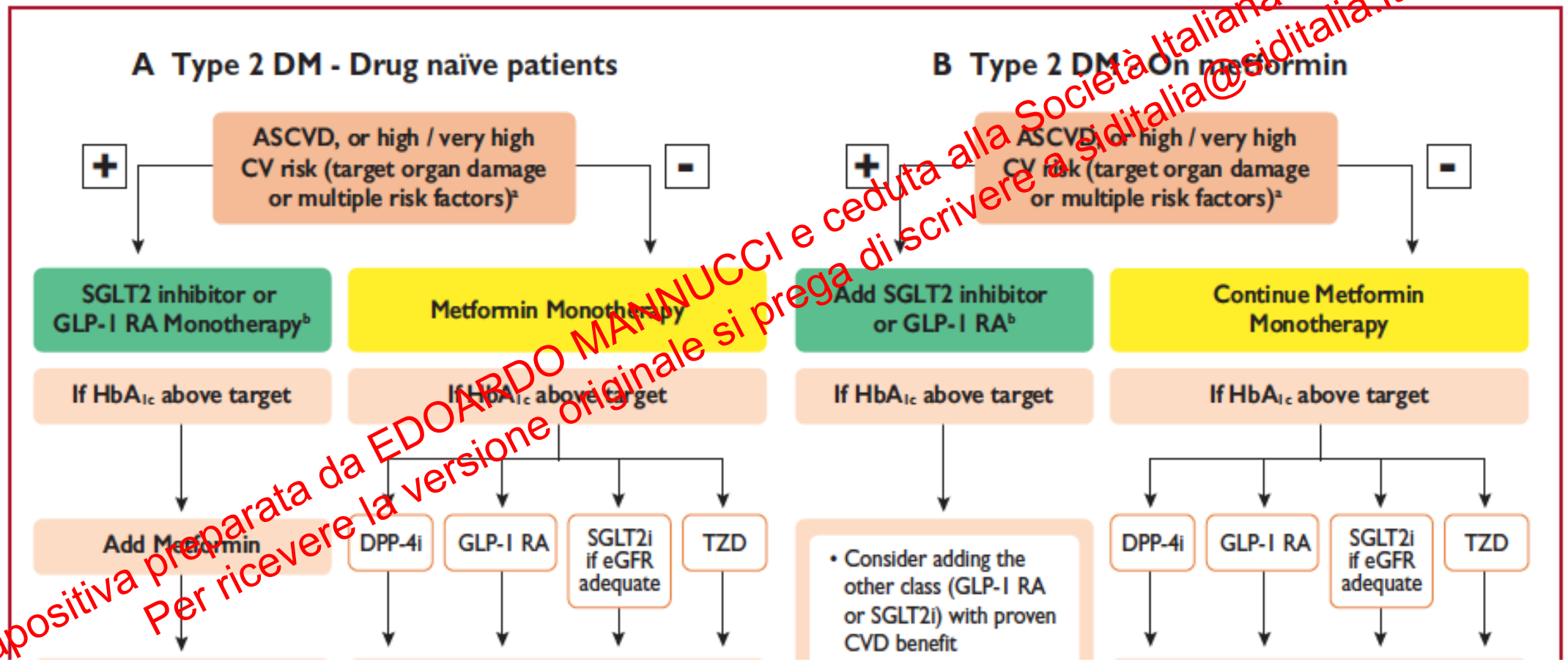
Pioglitazone: effect on major cardiovascular events

Results of the PROACTIVE trial



Dormandy J et al. *Lancet* 366: 1279-89, 2005

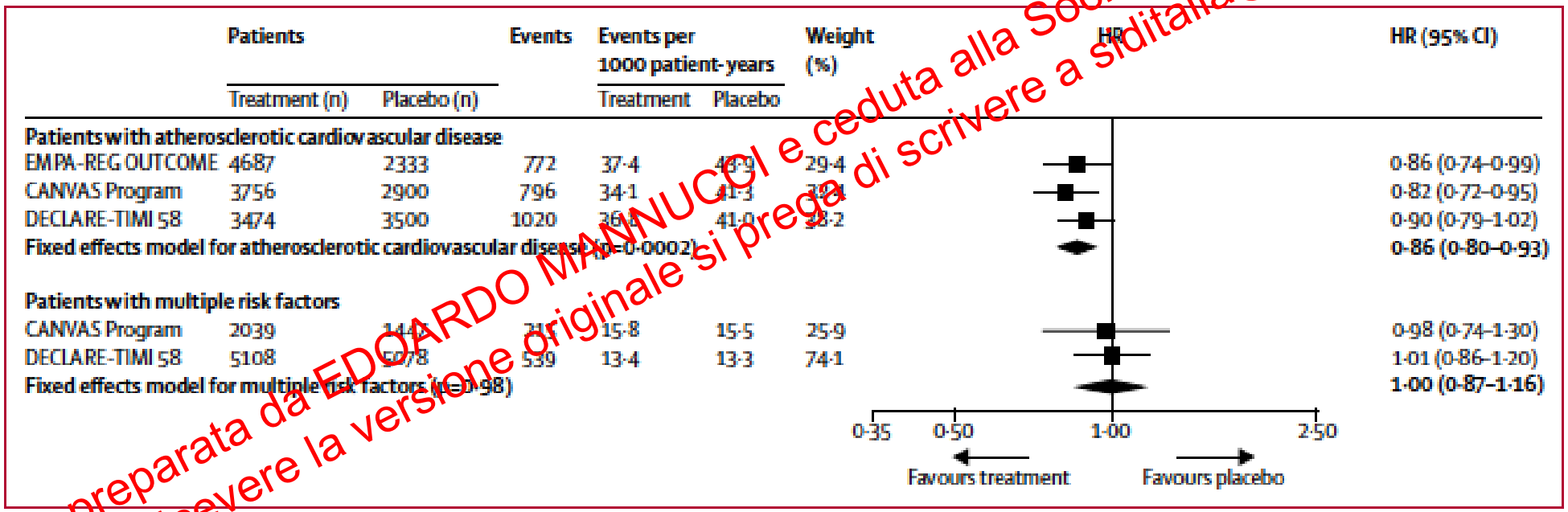
ESC-EASD Guidelines on type 2 diabetes, 2019



Cosentino F et al. *Eur Heart J* 2019

SGLT-2i: effects on MACE

A meta-analysis of CVOTs



	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·1		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·1	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (I^2=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039	1445	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

0·35 0·50 1·00 2·50

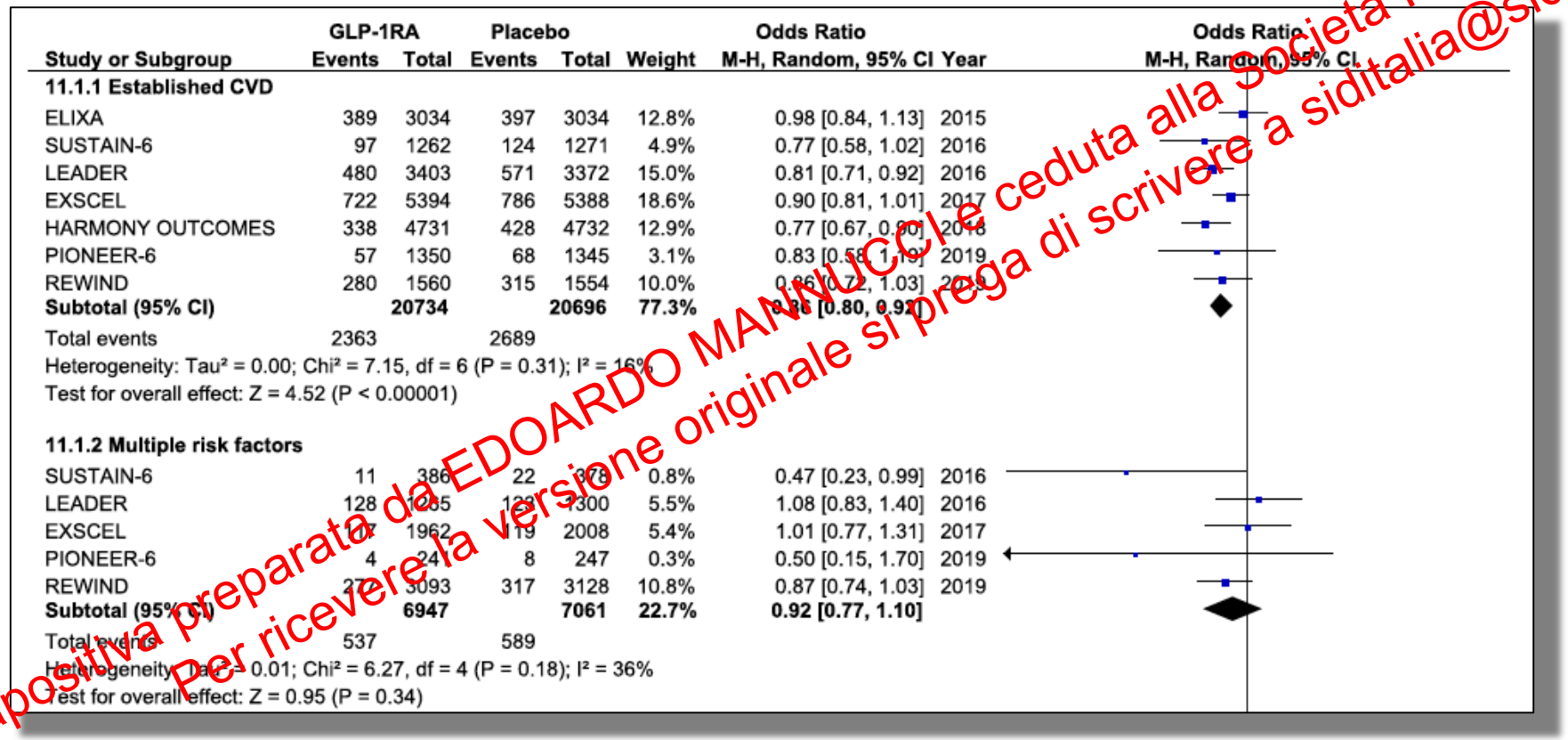
Favours treatment Favours placebo

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Zelniker TA et al. *Lancet* 393: 31–39, 2019

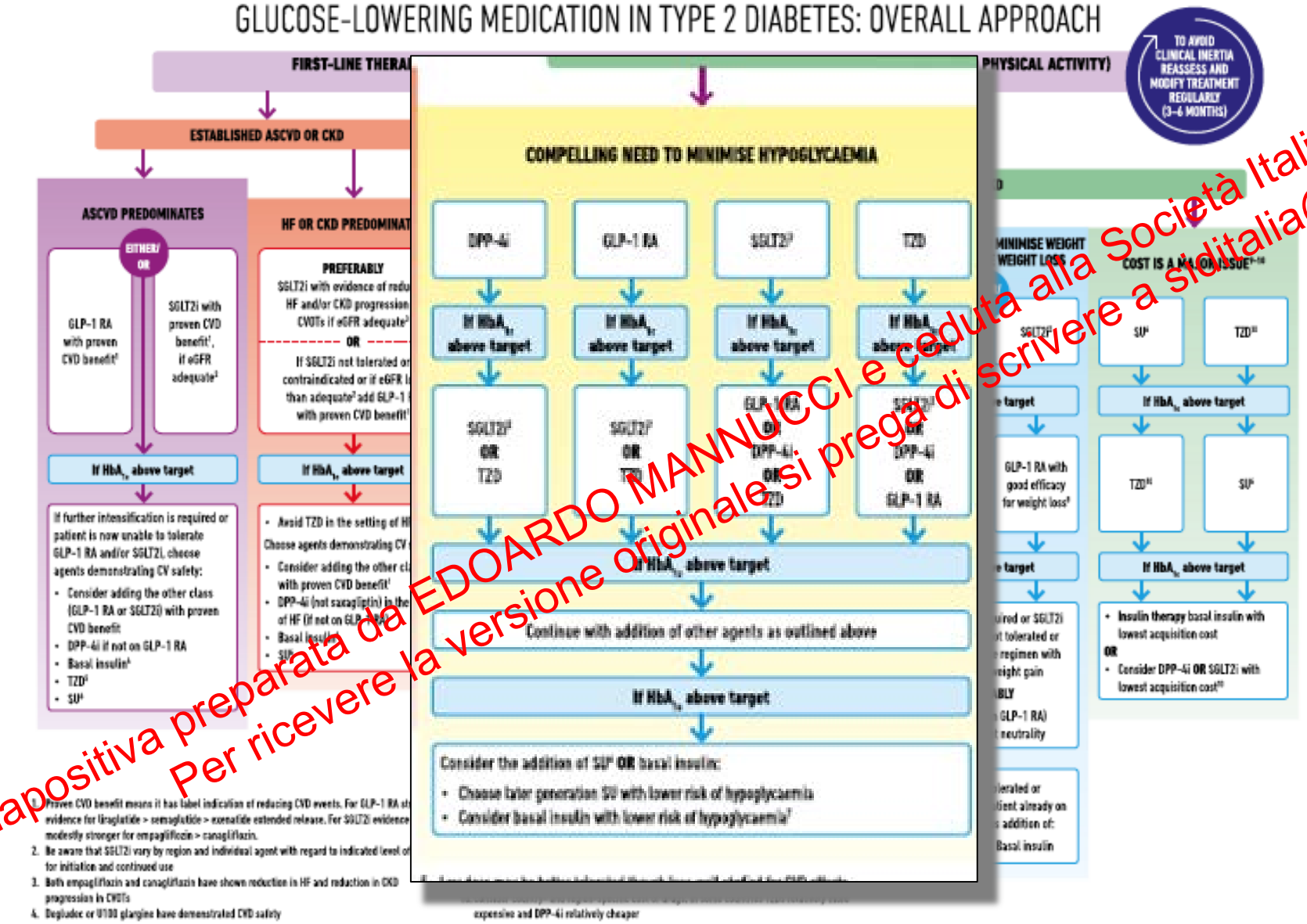
GLP-1 RA: effects on MACE

A meta-analysis of RCTs with CV endpoint



Study or Subgroup	GLP-1RA Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
11.1.1 Established CVD							
ELIXA	389	3034	397	3034	12.8%	0.98 [0.84, 1.13]	2015
SUSTAIN-6	97	1262	124	1271	4.9%	0.77 [0.58, 1.02]	2016
LEADER	480	3403	571	3372	15.0%	0.81 [0.71, 0.92]	2016
EXSCEL	722	5394	786	5388	18.6%	0.90 [0.81, 1.01]	2017
HARMONY OUTCOMES	338	4731	428	4732	12.9%	0.77 [0.67, 0.90]	2018
PIONEER-6	57	1350	68	1345	3.1%	0.83 [0.58, 1.19]	2019
REWIND	280	1560	315	1554	10.0%	0.86 [0.72, 1.03]	2019
Subtotal (95% CI)		**20734**		**20696**	**77.3%**	**0.86 [0.80, 0.92]**	
Total events	2363		2689				
Heterogeneity: Tau² = 0.00; Chi² = 7.15, df = 6 (P = 0.31); I² = 16%							
Test for overall effect: Z = 4.52 (P < 0.00001)							
11.1.2 Multiple risk factors							
SUSTAIN-6	11	386	22	378	0.8%	0.47 [0.23, 0.99]	2016
LEADER	128	1265	121	1300	5.5%	1.08 [0.83, 1.40]	2016
EXSCEL	107	1962	119	2008	5.4%	1.01 [0.77, 1.31]	2017
PIONEER-6	4	241	8	247	0.3%	0.50 [0.15, 1.70]	2019
REWIND	277	3093	317	3128	10.8%	0.87 [0.74, 1.03]	2019
Subtotal (95% CI)		**6947**		**7061**	**22.7%**	**0.92 [0.77, 1.10]**	
Total events	537		589				
Heterogeneity: Tau² = 0.01; Chi² = 6.27, df = 4 (P = 0.18); I² = 36%							
Test for overall effect: Z = 0.95 (P = 0.34)							

Mannucci E et al. *Diabetes Obes Metab* 2019



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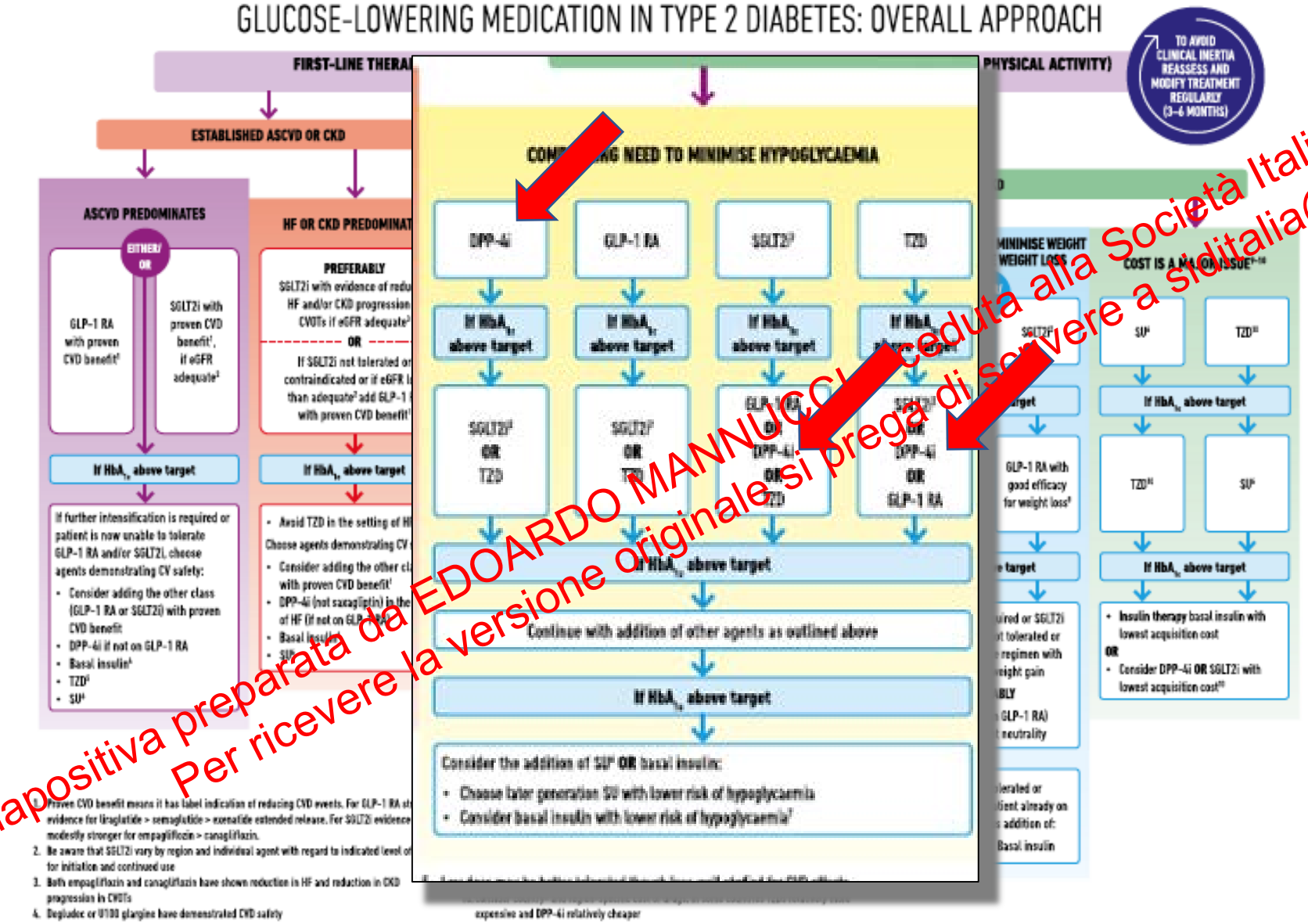

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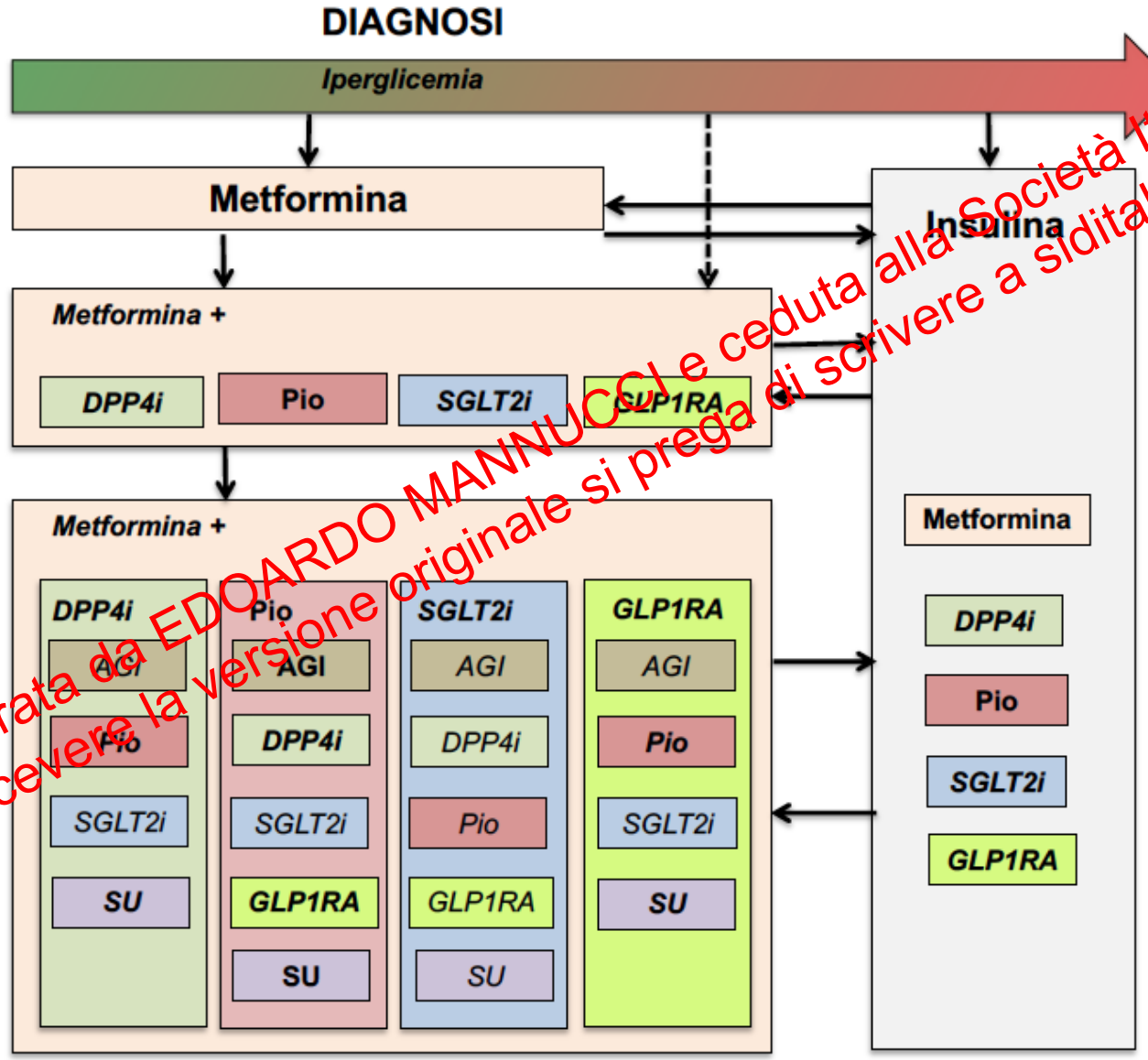


Use of DPP4 inhibitors in type 2 diabetes

DPP4 inhibtors should be used in patients in whom:

1. They have optimal safety
2. They have optimal efficacy
3. They are well tolerated

Saxagliptin: effect on hospitalization for heart failure

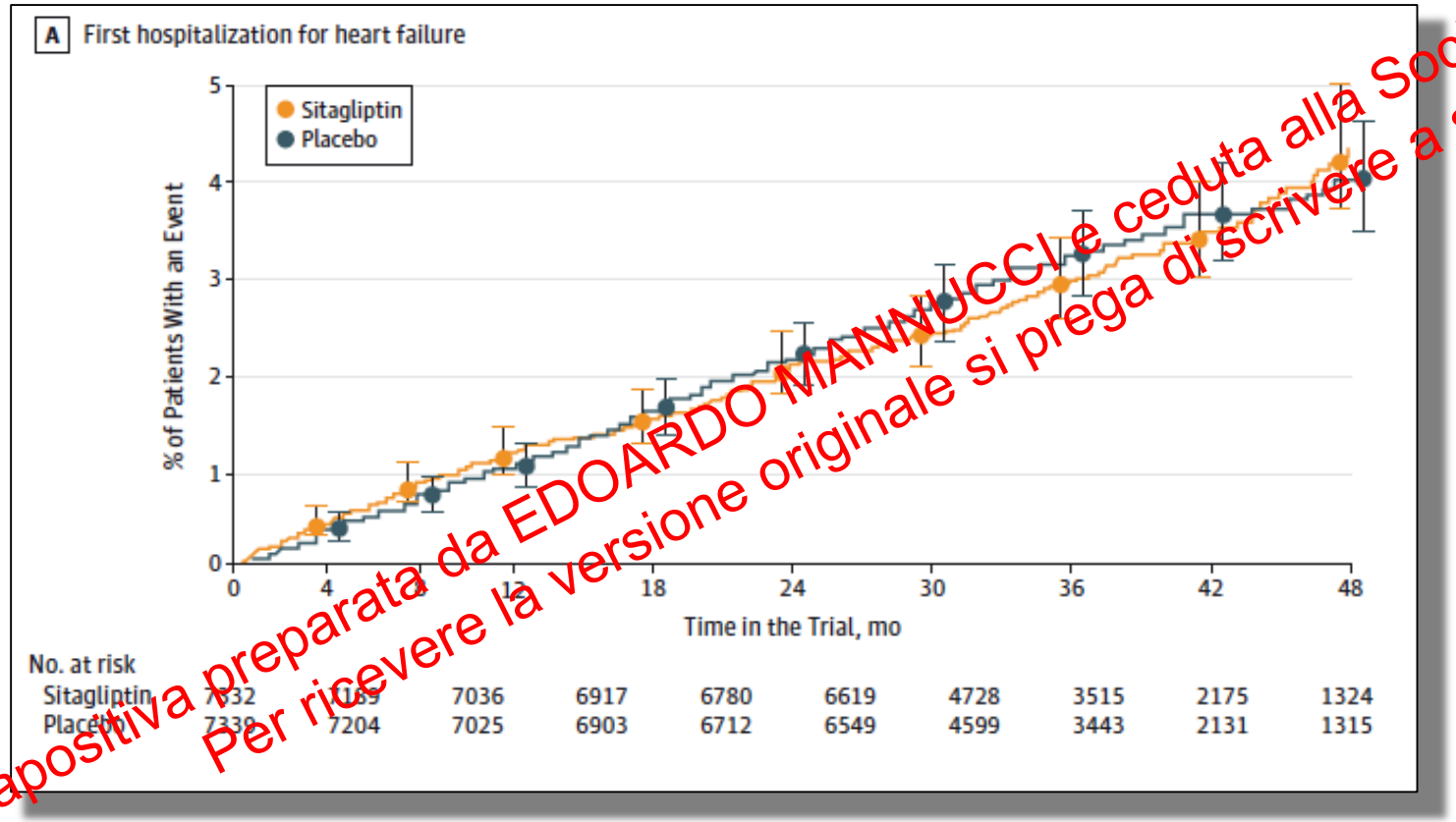
Results of the SAVOR-TIMI trial

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.3)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	[illegible]	[illegible]	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18

Scirica BM et al. *N Engl J Med* 369:1317-26, 2013

Sitagliptin: effect on hospitalization for heart failure

Results of the TECOS trial



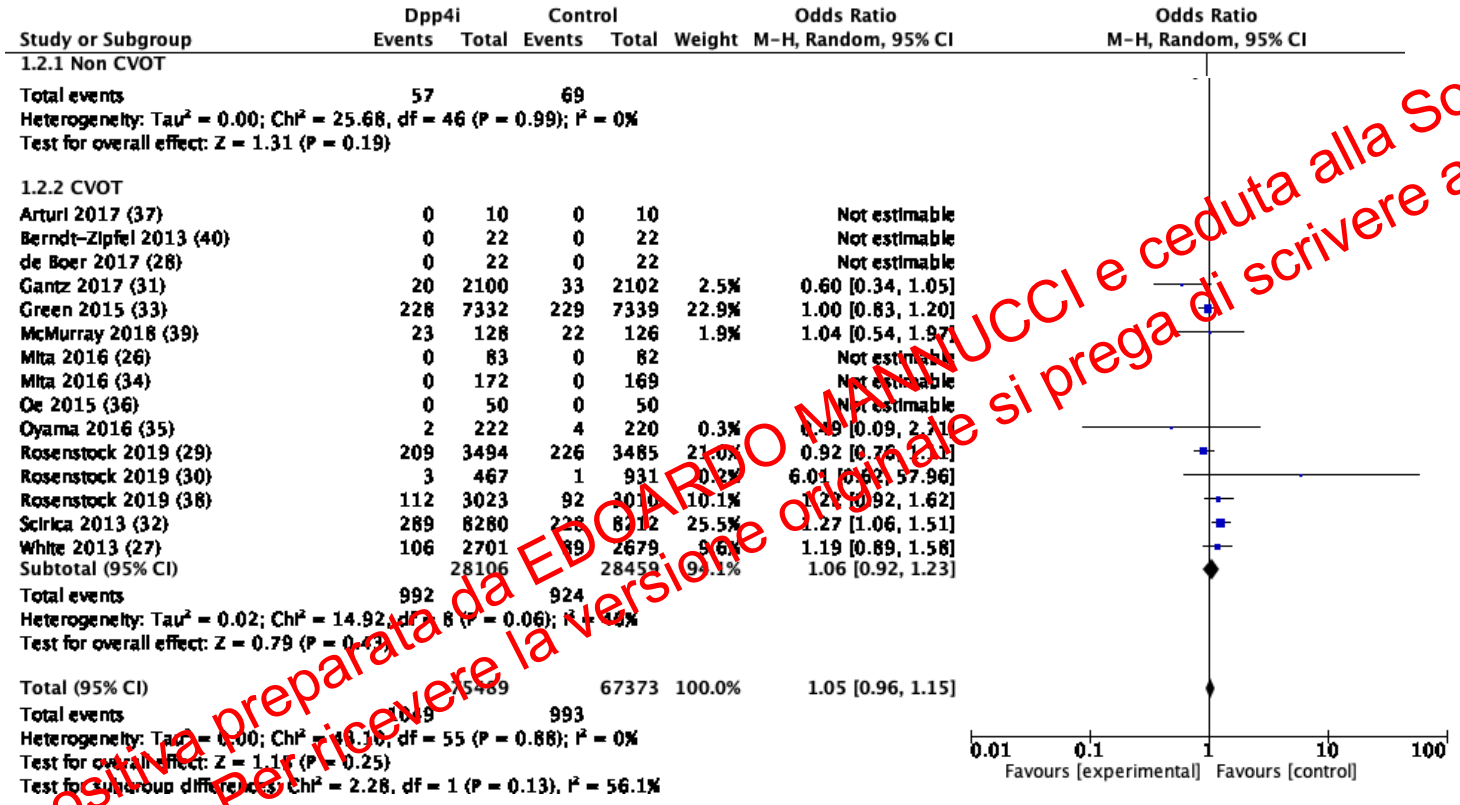
Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

14,671 T2DM patients with prior CVD,
sitagliptin vs placebo 1:1.
Follow-up: 3 y

McGuire DK et al. *JAMA Cardiol* 1:126-135, 2016

DPP4 inhibitors and heart failure

Metanalysis of RCTs: trial sequential analysis



Dicembrini I et al. *Manuscript in preparation*

Risk of pancreatitis with DPP4i

Observational data

	Unadjusted odds ratio (95% CI; p value)	Adjusted odds ratio (95% CI; p value)
Incretin use*	0·97 (0·69–1·36); p=0·8644	0·98 (0·69–1·38); p=0·8958
Previous disorders or treatments (in the past 5 years)		
Gallstones	4·18 (3·55–4·92); p<0·0001	3·87 (3·27–4·58); p<0·0001
Pancreatic or billiary cancer	1·99 (1·16–3·43); p=0·0132	1·23 (0·69–2·22); p=0·4870
Chronic or acute pancreatitis	3·56 (2·49–5·09); p<0·0001	1·83 (1·24–2·71); p=0·0024
Alcohol misuse	2·01 (1·06–3·82); p=0·0338	1·57 (0·81–3·06); p=0·184
Hypertriglyceridaemia	1·17 (0·93–1·48); p=0·1806	1·06 (0·82–1·35); p=0·6733
Obesity	1·55 (1·18–2·04); p=0·0017	1·32 (0·99–1·75); p=0·0553
Cardiovascular disease	1·23 (1·09–1·39); p=0·0006	1·12 (0·99–1·27); p=0·0745
Other antidiabetic drug use		
Metformin use	1·08 (0·98–1·18); p=0·1242	1·09 (0·98–1·21); p=0·1283
Glibenclamide use	1·08 (0·94–1·24); p=0·2707	1·01 (0·87–1·18); p=0·8941

*One case and one control received more than one incretin.

Table 2: Matched odds ratio of acute pancreatitis associated with exposure to incretins in the 6 months before index date

Retrospective case-control study.

Population-based study in Piedmont, Italy

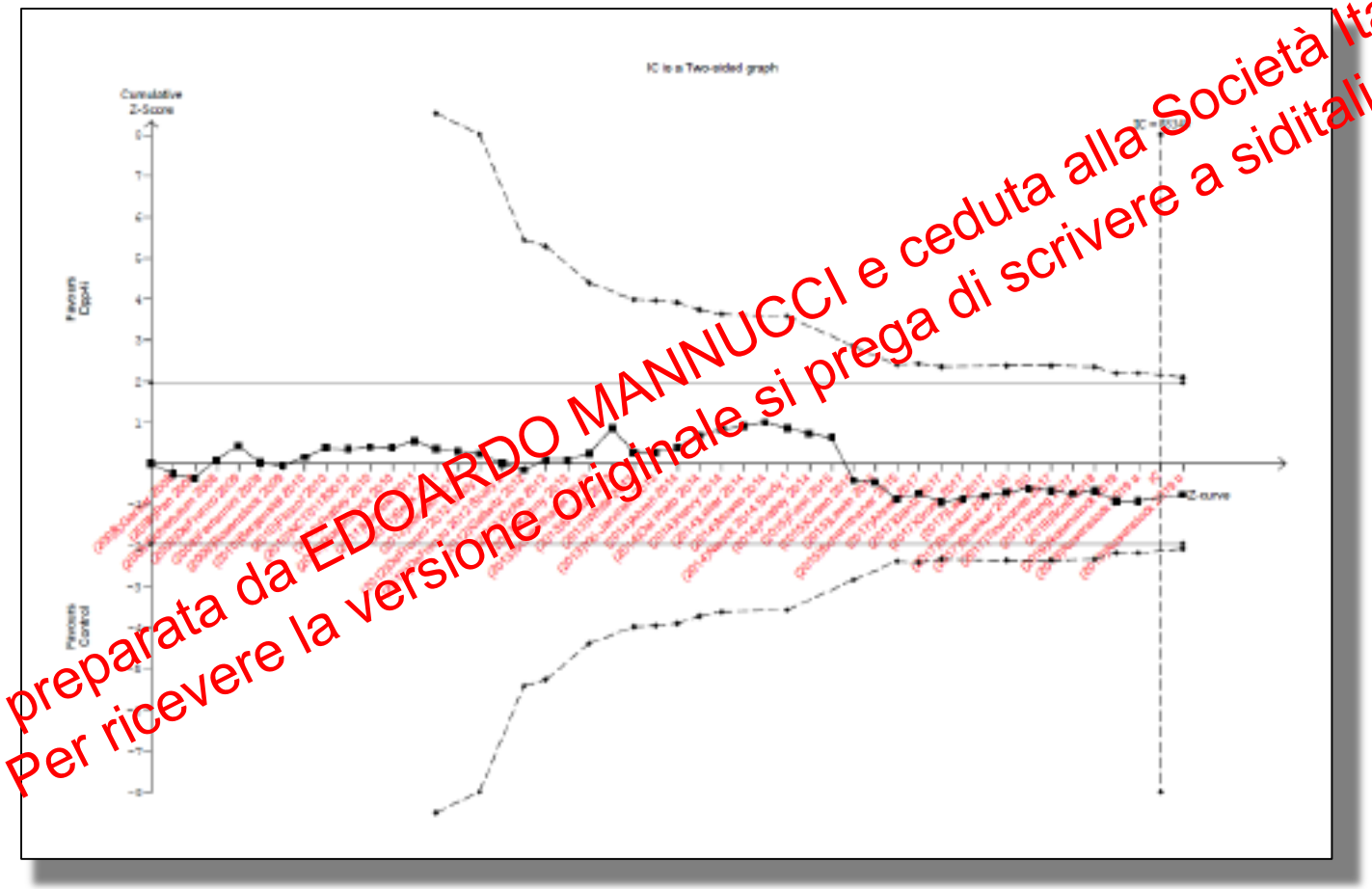
Cohort of 282,429 patients receiving drug treatment for diabetes in the years 2008-2012

Identification of incident pancreatitis through hospital discharge records

Giorda C, et al. *Lancet Diabetes Endocrinol* 2:111-115, 2014.

DPP4 inhibitors and pancreatitis

Metanalysis of RCTs: trial sequential analysis



Dicembrini I et al. *submitted*

Contraindications to drugs for type 2 diabetes

Table 1 Comorbidities as absolute or relative contraindication to the use of drugs for type 2 diabetes

	Met	SU/glin	AGI	TZD	GLP-1RA	DPP-4i	Ins
Renal failure	++	++−	−−	−	+−	−−	−−
Heart failure	++−	++−	−−	++	−−	−−	−−
Myocardial ischemia	−−	++−	−−	−−	−−	−−	−−
Liver cirrhosis	++	++	−−	++	+−	+−	−−
Hepatitis/NAFLD	−−	+−−	−−	−−	−−	−−	−−
Osteoporosis	−−	+−−	+−−	++	−−	−−	++−
Dementia/MCI	−−	+−−	−−	−−	−−	−−	+−
Bowel disease	+−−	−−	++	−−	+−−	−−	−−
Pancreatitis	−−	−−	−−	−−	++	+−	−−
Respiratory insufficiency	++	−−	−−	−−	−−	−−	−−

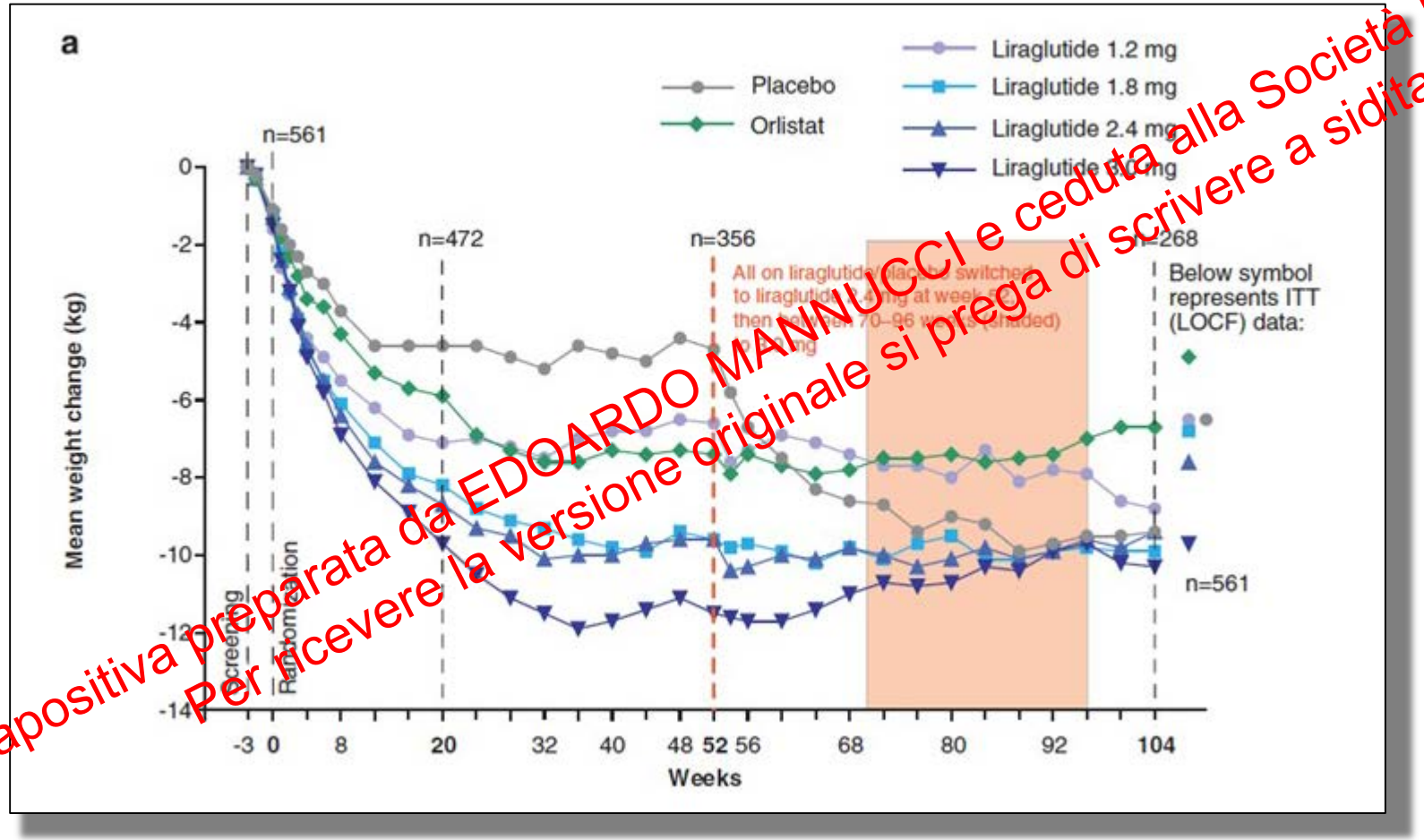
++ = absolute contraindication; ++− = absolute/relative contraindication; +−− = relative contraindication; +− = relative contraindication; −− = no contraindication

AGI alpha-glucosidase inhibitor, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *Ins* insulin, *MCI* mild cognitive impairment, *Met* metformin, *NAFLD* nonalcoholic fatty liver disease, *SU/glin* sulfonylureas or glinides, *TZD* thiazolidinediones

Paolisso G, Monami M, Marfella R, Rizzo MR, Mannucci E. *Adv Ther* 29:218-33, 2012.

DPP4 inhibitors and pancreatitis

Metanalysis of RCTs



Astrup A et al. *Int J Obes*, 38:1-11, 2011

Predictors of response to DPP4 inhibitors

Retrospective observational study on patients initiating DPP4i. Follow-up: 12 months

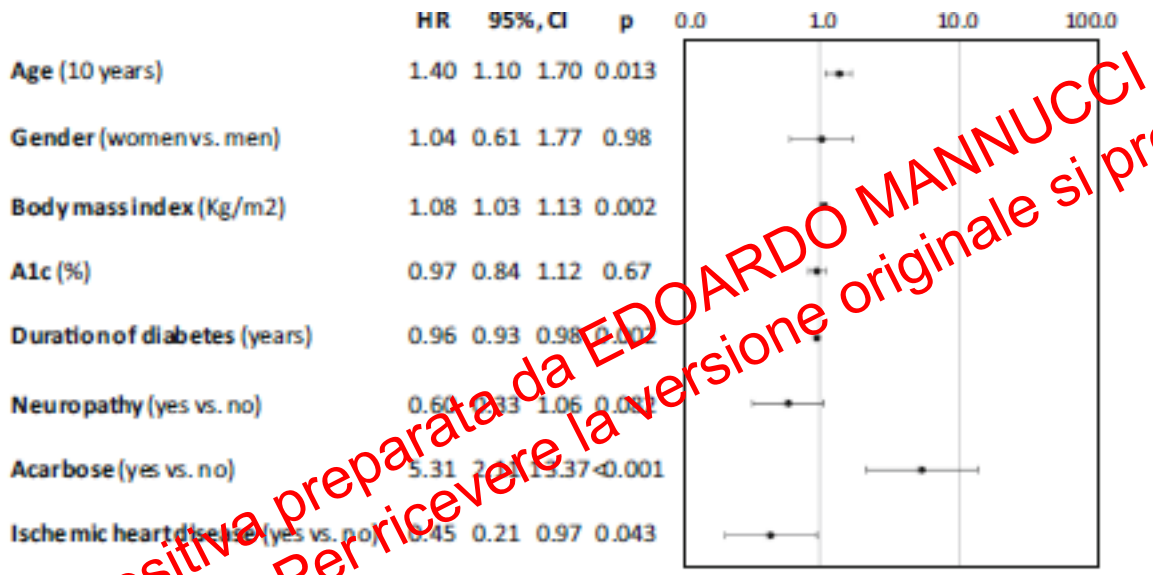
Variable	*Total (n = 13,525)*	*Responders (n = 1,708)*	*Nonresponders (n = 11,817)*	P *value*
Age (years)	62.3 (12.2)	62.9 (12.0)	62.2 (12.2)	0.04
HbA1c (%)	8.8 (1.5)	8.2 (1.3)	8.9 (1.5)	< 0.001
SBP (mm Hg)	134.7 (15.3)	134.3 (15.0)	134.8 (15.3)	0.3
DBP (mm Hg)	77.5 (9.6)	76.9 (9.6)	77.6 (9.6)	0.004
TC (mmol/L)	4.3 (1.1)	4.2 (1.0)	4.3 (1.1)	< 0.001
HDL (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.2

Mamza J et al. *Diabetes Technol Ther* 18:85-92, 2016.

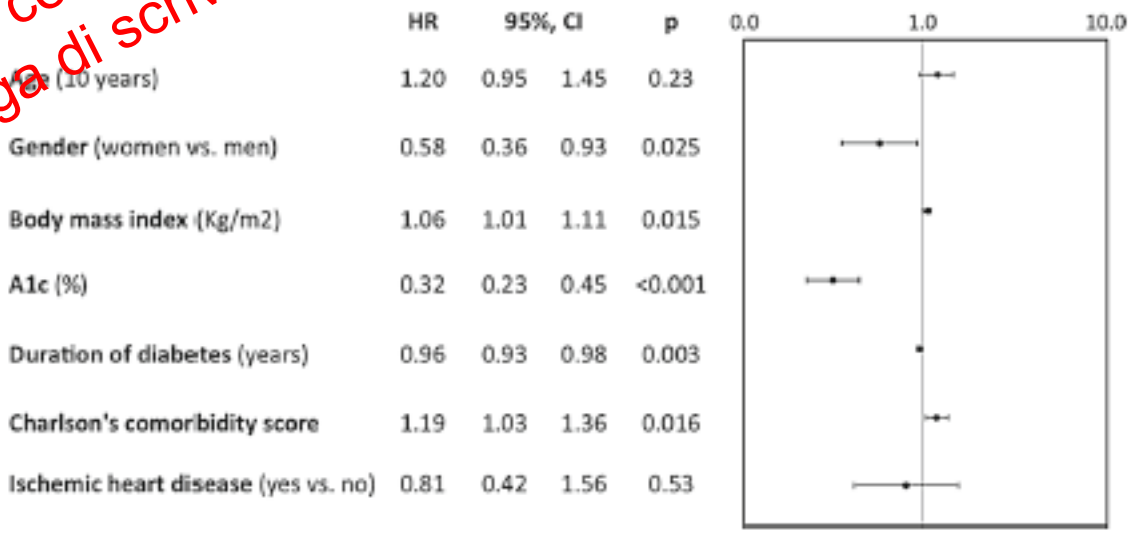
Predictors of response to basal insulin and DPP4 inhibitors

Retrospective observational study on patients failing to dual oral therapy and initiating either insulin or DPP4i. Follow-up: 36 months

Basal insulin (N=501)



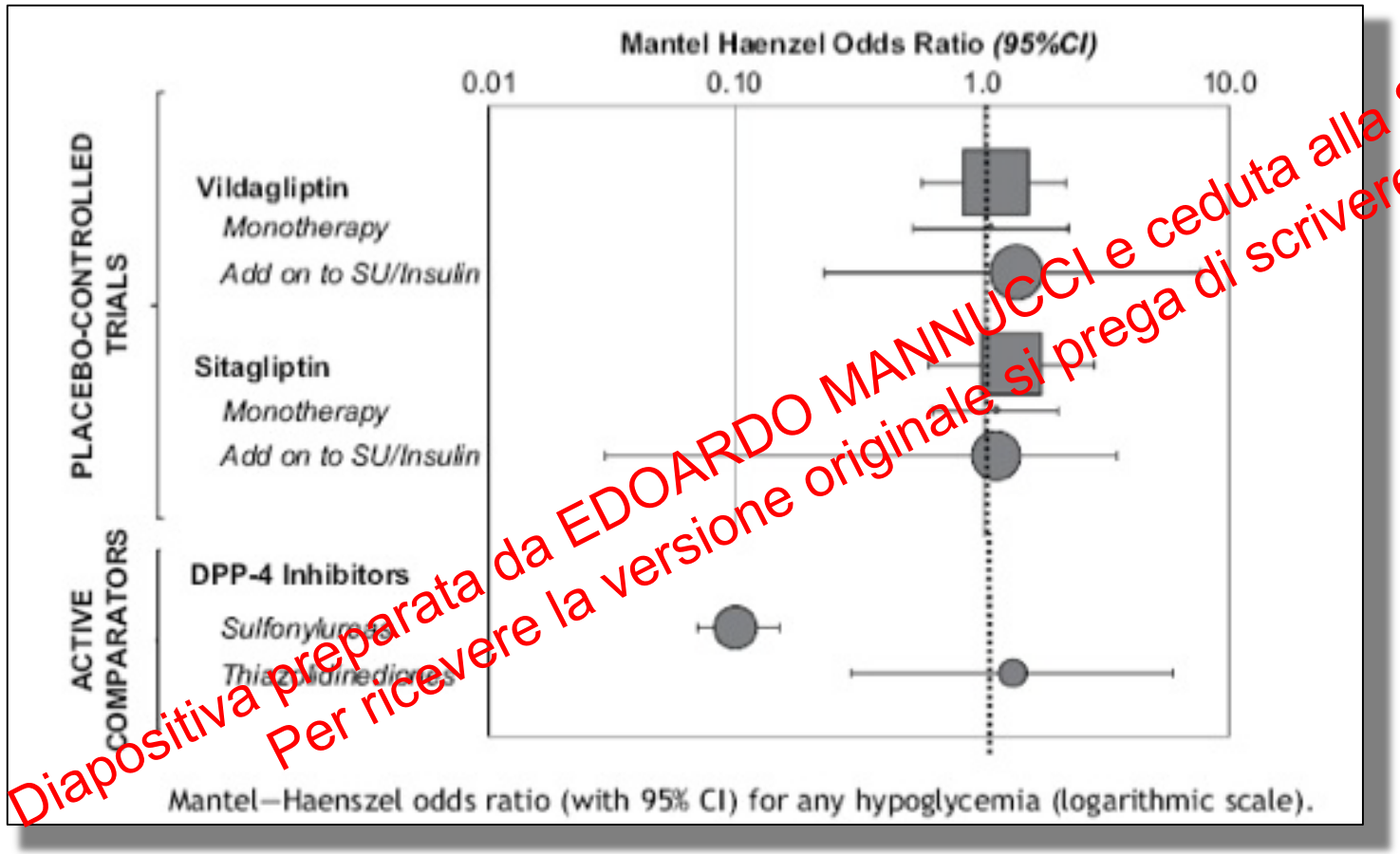
DPP4 inhibitor (N=501)



Monami M, Ragghianti B, Zannoni S, Vitale V, Nreu B, Mannucci E. *Acta Diabetol* 53:35-40, 2016.

DPP4 inhibitors and hypoglycemia

Meta-analysis of available RCTs



Mantel–Haenszel odds ratio (with 95% CI) for any hypoglycemia (logarithmic scale).

Available RCTs vs any comparator, duration 24 wk or longer, patients with T2DM.

N=41 RCTs

Monami M, Iacomelli I, Marchionni N, Mannucci E. *Nutr Metab Cardiovasc Dis*, 20:224-35, 2010

Predictors of response to DPP4 inhibitors

Retrospective observational study on patients initiating DPP4i. Follow-up: 12 months

Variable	*Total (n = 13,525)*	*Responders (n = 1,708)*	*Nonresponders (n = 11,817)*	P *value*
Age (years)	62.3 (12.3)	62.9 (12.0)	62.2 (12.2)	0.04
HbA1c (%)	8.8 (1.5)	8.2 (1.3)	8.9 (1.5)	< 0.001
SBP (mm Hg)	134.7 (15.3)	134.3 (15.0)	134.8 (15.3)	0.3
DBP (mm Hg)	77.5 (9.6)	76.9 (9.6)	77.6 (9.6)	0.004
TC (mmol/L)	4.3 (1.1)	4.2 (1.0)	4.3 (1.1)	< 0.001
HDL (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.2

Mamza J et al. *Diabetes Technol Ther* 18:85-92, 2016.