PROGRAMMA

I° CONVEGNO NAZIONALE CONGIUNTO SIN - SID

La Malattia Renale Diabetica (DKD): Presente e Futuro dell'Approccio Integrato Nefro-Diabetologico

TEAM WORK FOR WORK SUCCESS

RIMINI, 2 OTTOBRE 2019

Linee guida per il trattamento del paziente diabetico nefropatico: prospettive future

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Disclosures

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

- ✓ Partecipazioni a Congressi: Astra-Zeneca, Laboratori Guidotti, Sanofi-Aventis, Takeda;
- ✓ Relazioni/moderazioni/partecipazioni a board retribuite: Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, MundiPharma, Novartis, Novo Nordisk, Sigma-Tau, Takeda.

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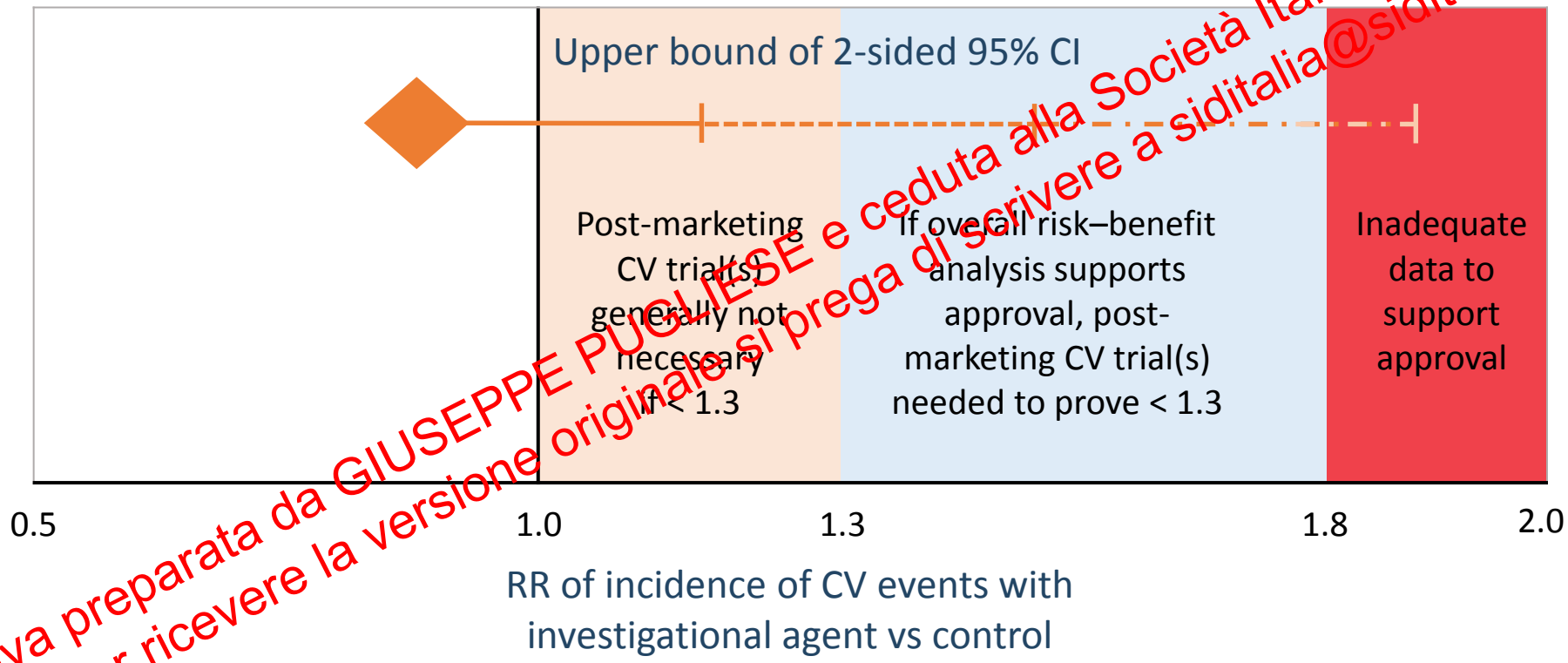
In fede

Giuseppe Pugliese

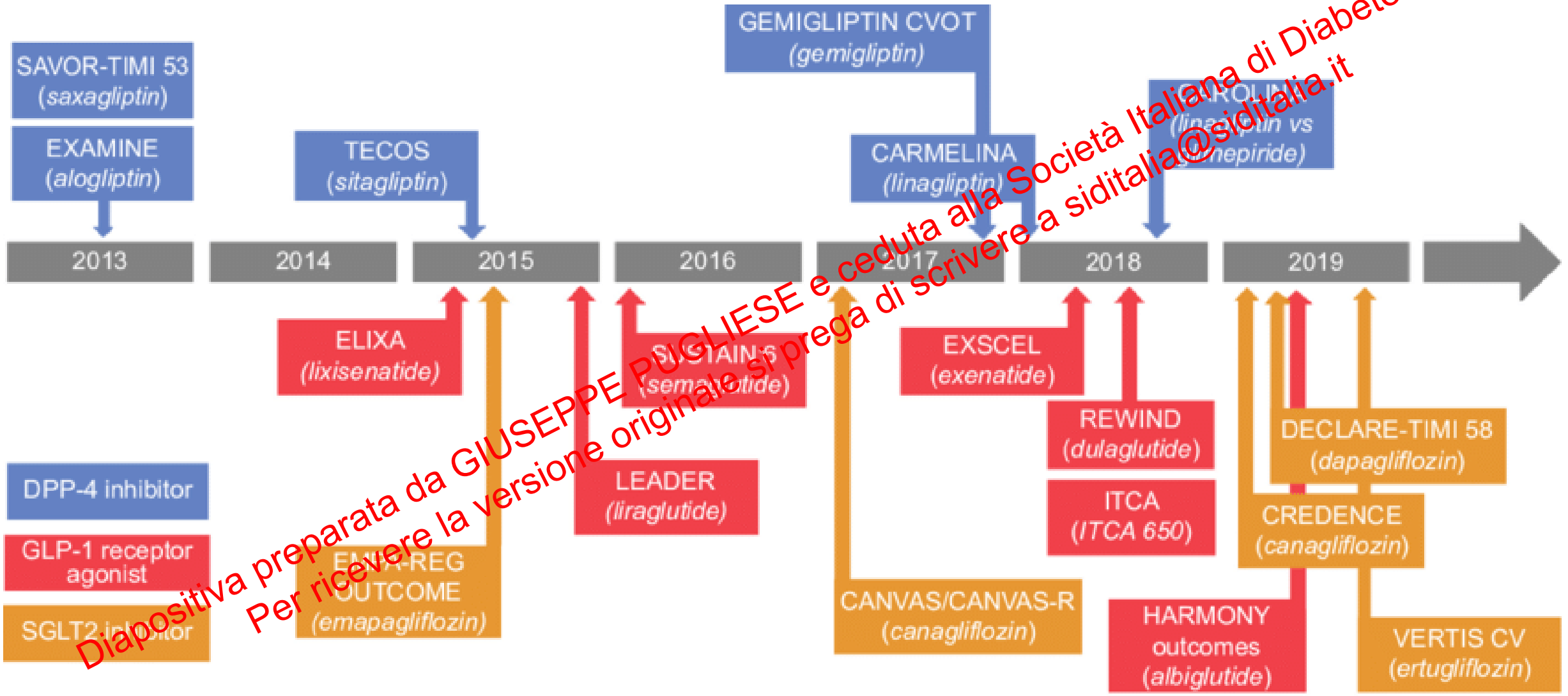
Cardiovascular Outcome Trials (CVOTs)

FDA guidance for cardiovascular outcome data: meta-analysis limits and outcome trial requirements



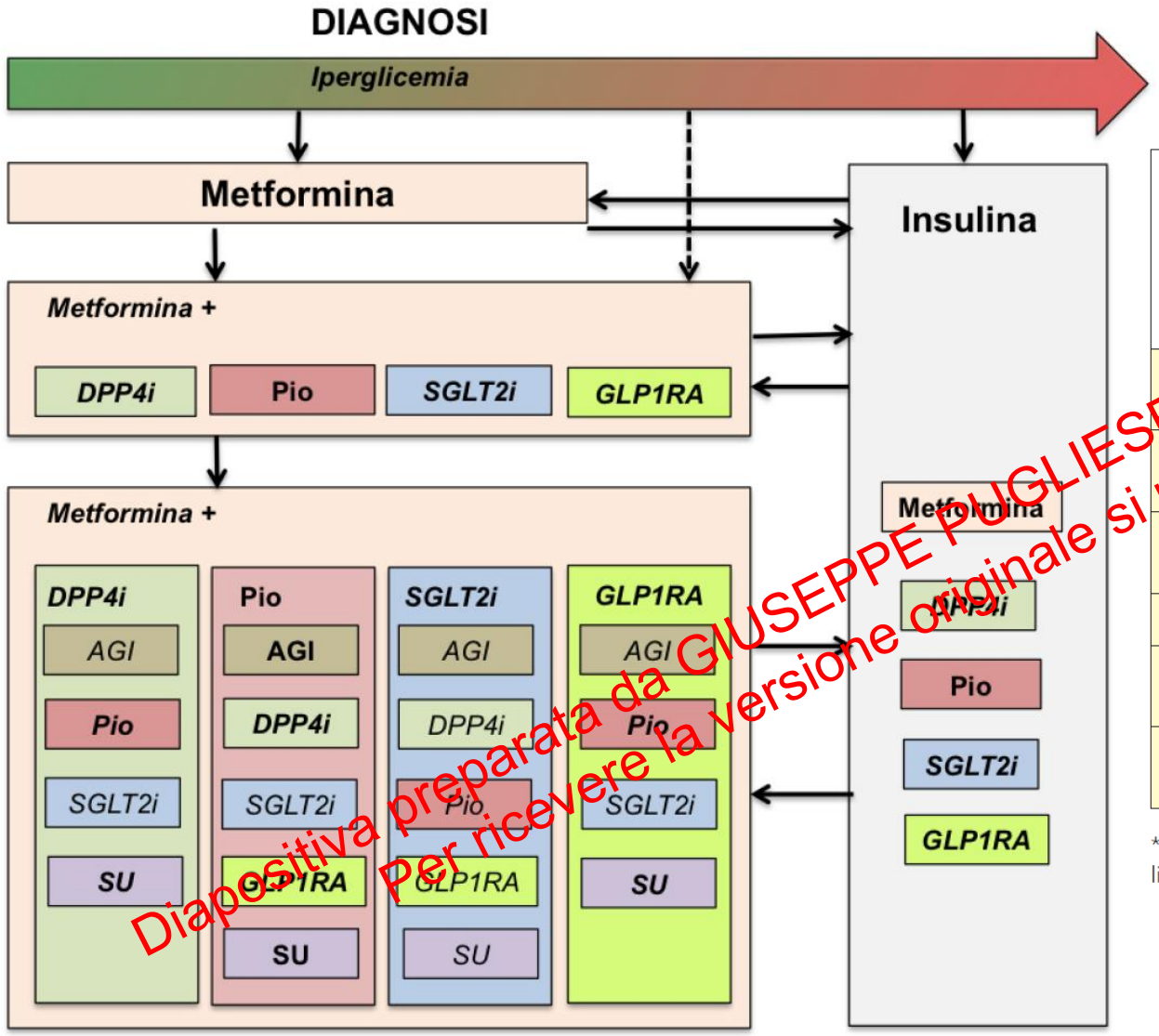
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Cardiovascular Outcome Trials (CVOTs)



Algorithm for anti-hyperglycemic therapy in adults with type 2 diabetes

Linee Guida Associazione Medici Diabetologi (AMD) e Società Italiana di Diabetologia (SID)



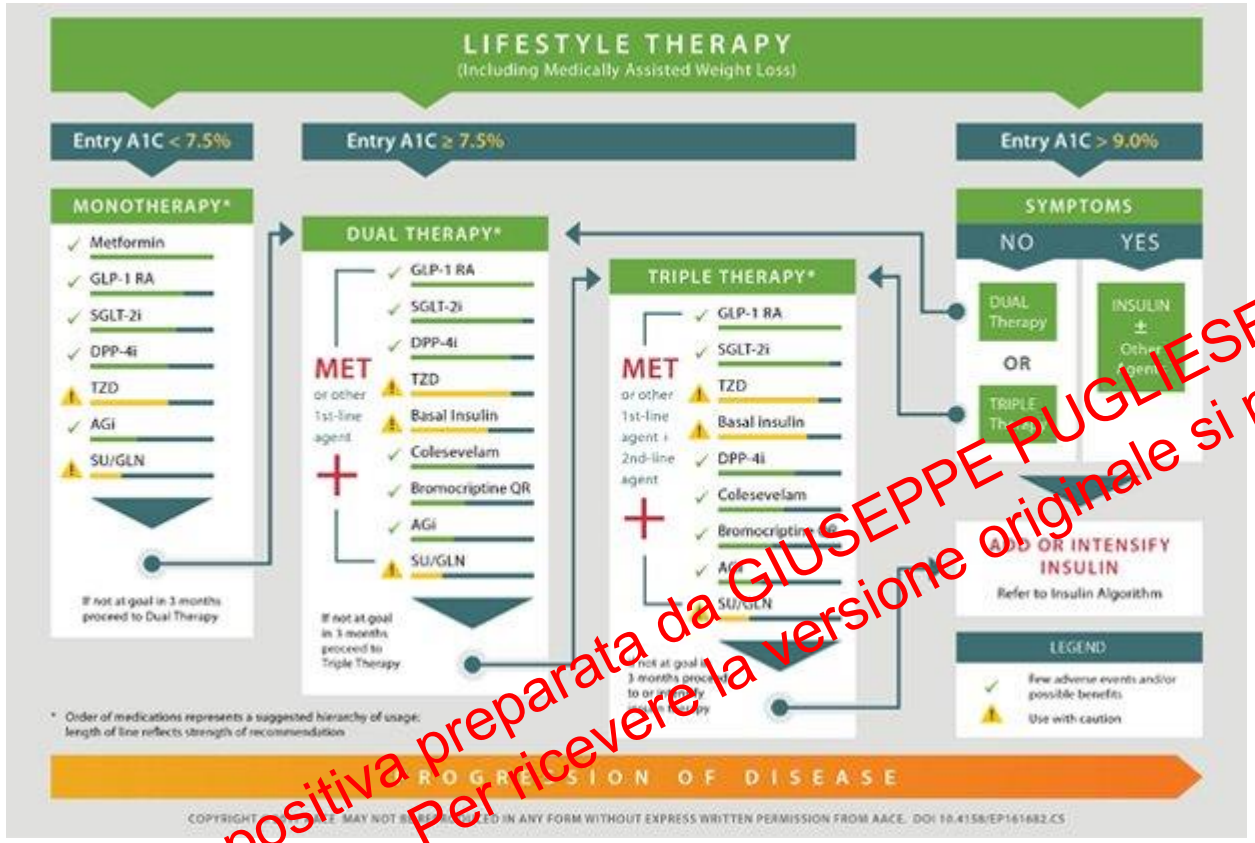
	Metformina	Acarbose	GLP1RA	Gliflozine	Gliptine	Pioglitazone	SU/glinidi	Insulina basale	Insulina ba-sal-bolus
Riduzione HbA1c a breve termine (3-4 mesi)	+++	+	+++	++	++	+	+++	+++	++++
Riduzione HbA1c a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione HbA1c a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione pressione arteriosa	+/-	-	+	++	-	+	-	-	-
Riduzione morbilità e mortalità cardiovascolare**	+/-	+/-	++[a]	+++[b]	-	++	-	-	-

* Derivata da studi di comparazione diretta con altri farmaci attivi. ** A parità di obiettivo glicemico perseguito. [a] Per liraglutide e semaglutide. [b] Per empagliflozin; per canagliflozin limitatamente alla morbilità. ND: dato non disponibile.

AMD-SID. Standard Italiani per la Cura del Diabete Mellito, 2018

Algorithm for anti-hyperglycemic therapy in adults with type 2 diabetes

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines



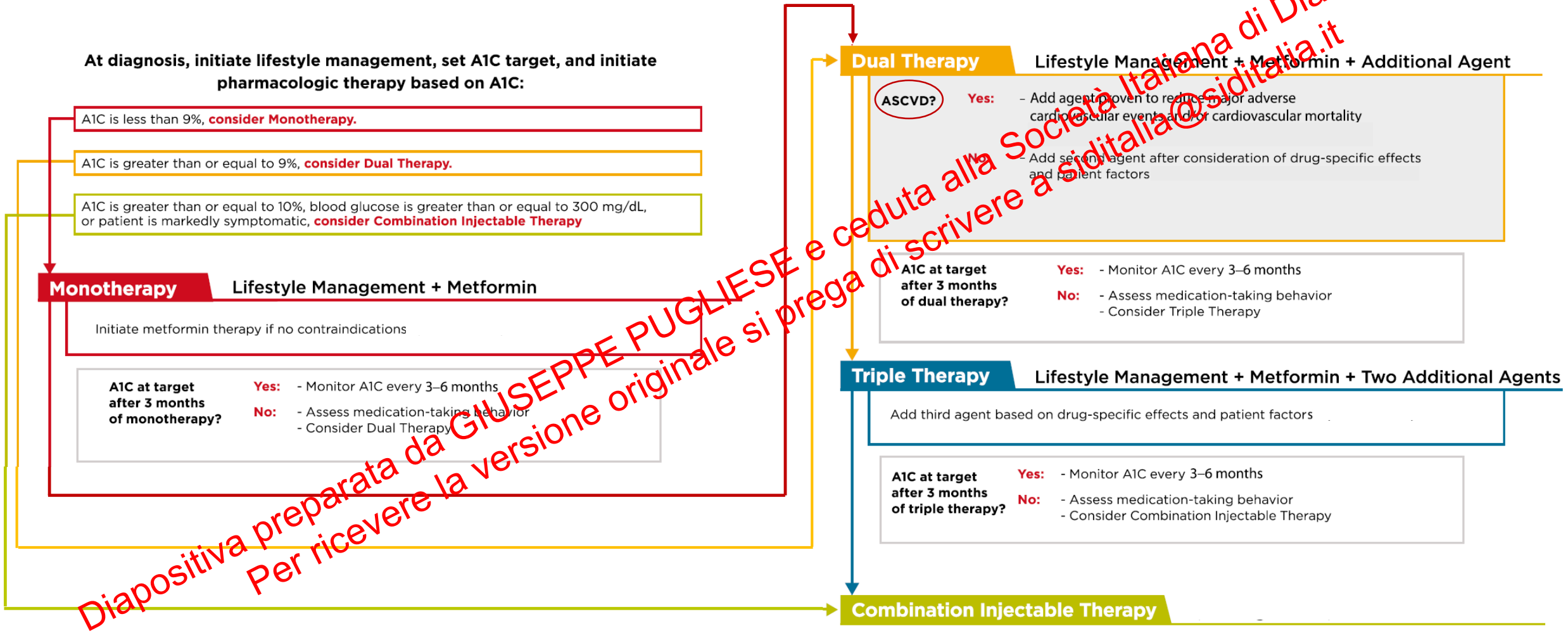
	MET	GLP-1 RA	SGLT-2i	TZD	AGi	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Neutral	Neutral	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contraindicated if eGFR < 30 mL/min/1.73 m²	Possible Benefit of Liraglutide	Not indicated for eGFR < 45 mL/min/1.73 m²; Genital Mycotic Infections; Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF CARDIAC* ASCVD	Neutral	Possible Benefit of Liraglutide; Possible CV Benefit	Possible Benefit of Empagliflozin; Possible CV Benefit	Possible Risk for Saxagliptin and Alogliptin; Neutral	Neutral	Moderate; May Reduce Stroke Risk	More CHF Risk; ?	Neutral	Benefit	Safe	More CHF Risk; Neutral	Neutral
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits · Use with caution · Likelihood of adverse effects · ? Uncertain effect · * FDA indication to prevent CVD death in diabetes plus prior CVD events

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm, 2019

Algorithm for anti-hyperglycemic therapy in adults with type 2 diabetes

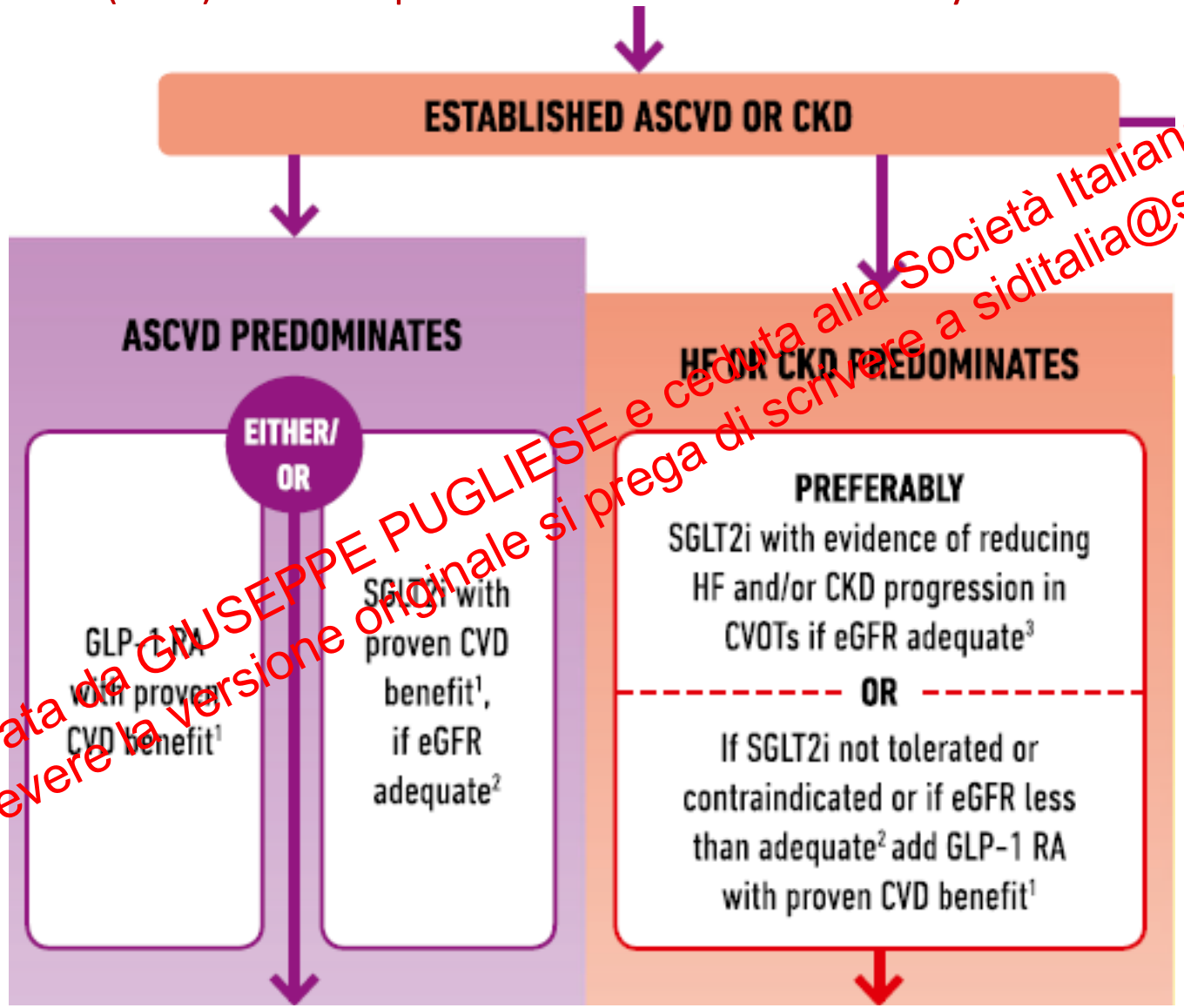
American Diabetes Association (ADA) Standard of Medical Care in Diabetes



American Diabetes Association. Diabetes Care. 2018;41(Suppl.1):S73-S85

Algorithm for anti-hyperglycemic therapy in adults with type 2 diabetes

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus Report



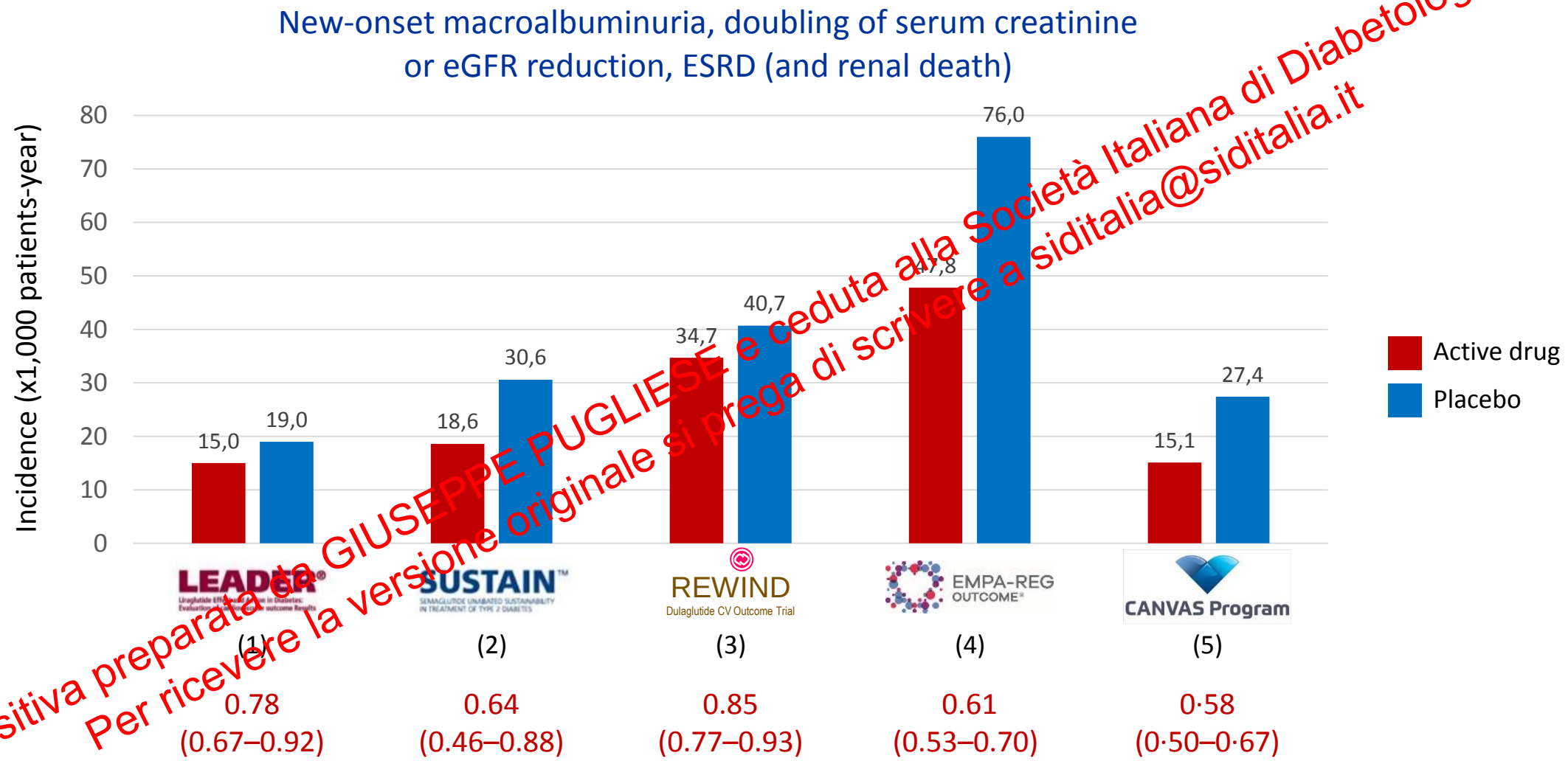
Davies MJ et al. Diabetologia. 2018;61:2461-2498

Renal protection with GLP-1 receptor agonists and SGLT2 inhibitors

	LEADER® (1)	REWIND (2)	EMPA-REG OUTCOME® (3)	CANVAS Program (4)	DECLARE (5)	CREDENCE (6)
Drug	Liraglutide	Dulaglutide	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
N	9,340	9,901	7,020	10,142	17,160	4,401
Follow-up (years)	3.8	5.4	3.1	2.4	4.2	2.6
Prevalence of any DKD (%)	47.6	48.9	52.2	42.1	34.4	100
Prevalence of ↓ eGFR (%)	23.1	22.8	25.9	19.8	7.4	60
Prevention of macroalbuminuria	0.74 (0.60–0.91)	0.77 (0.68–0.87)	0.95 (0.87–1.04)	0.80 (0.73-0.87)	0.77 (0.68–0.87)	NA
Progression of albuminuria	NA	NA	0.62 (0.54-0.72)	0.58 (0.50-0.68)	0.73 (0.67–0.79)	NA
Regression of albuminuria	NA	NA	1.61 (1.34-1.94)	1.70 (1.51-1.91)	1.41 (1.27–1.56)	NA
Doubling of serum creatinine	0.89 (0.67-1.19)	NA	0.56 (0.39–0.79)	0.50 (0.30–0.84)	NA	0.60 (0.48–0.76)
40% eGFR reduction	NA	0.70 (0.57–0.85)	NA	0·60 (0·47–0·78)	0.54 (0.43–0.67)	NA
ESRD/RRT	0.87 (0.61–1.24)	0.75 (0.39–1.44)	0.45 (0.21–0.97)	0.77 (0.30–1.97)	0.31 (0.13–0.79)	0.68 (0.54–0.86)
Death due to renal cause	1.59 (0.52–4.87)	NA	NA	NA	0.60 (0.22–1.65)	NA

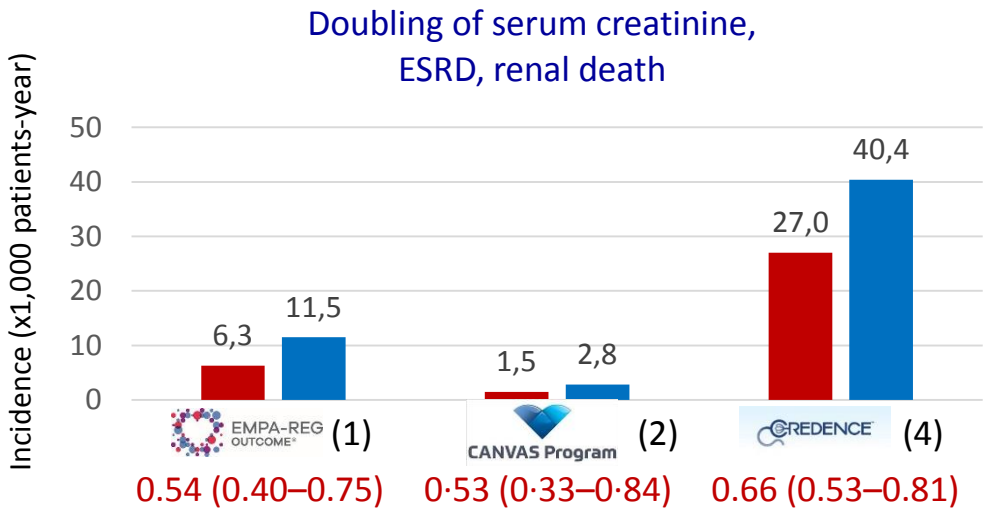
1. Marso SP et al. N Engl J Med. 2016;375;311-322; 2. Gerstein H et al. Lancet. 2019; June 10;
3. Wanner C et al. N Engl J Med. 2016;375:323-334; 4. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704;
5. Mosenzon O et al. Lancet Diabetes Endocrinol. 2019 June 9; 6. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

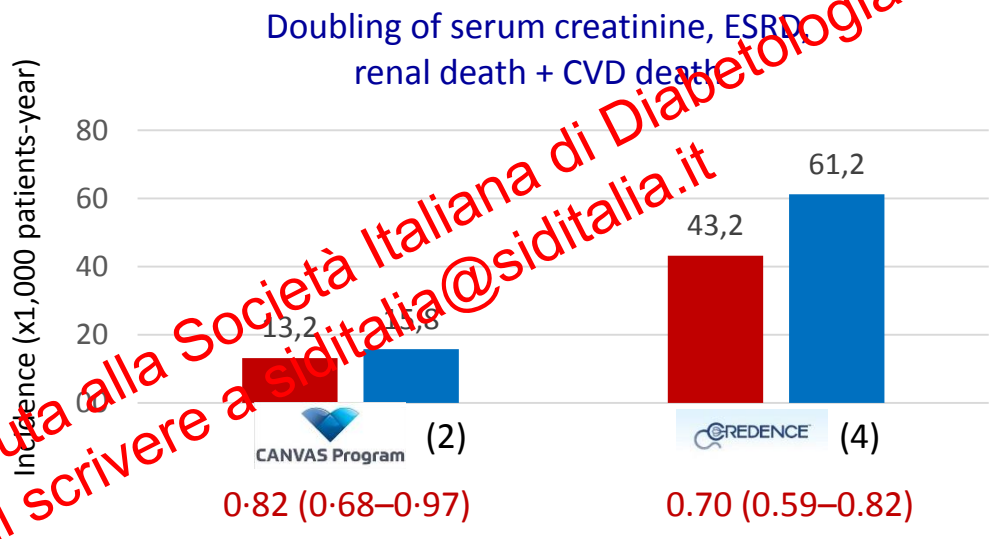
Renal protection with GLP-1 receptor agonists and SGLT2 inhibitors

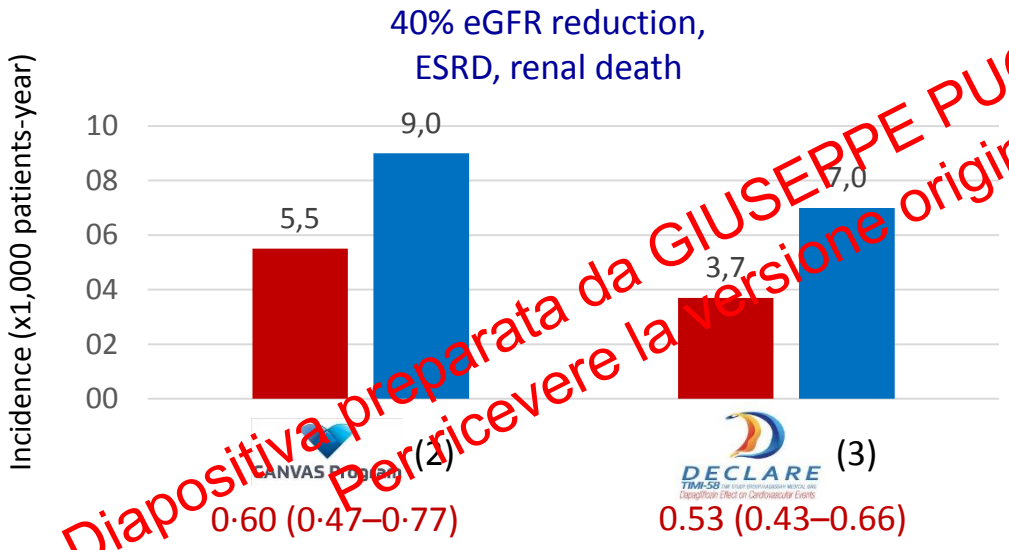


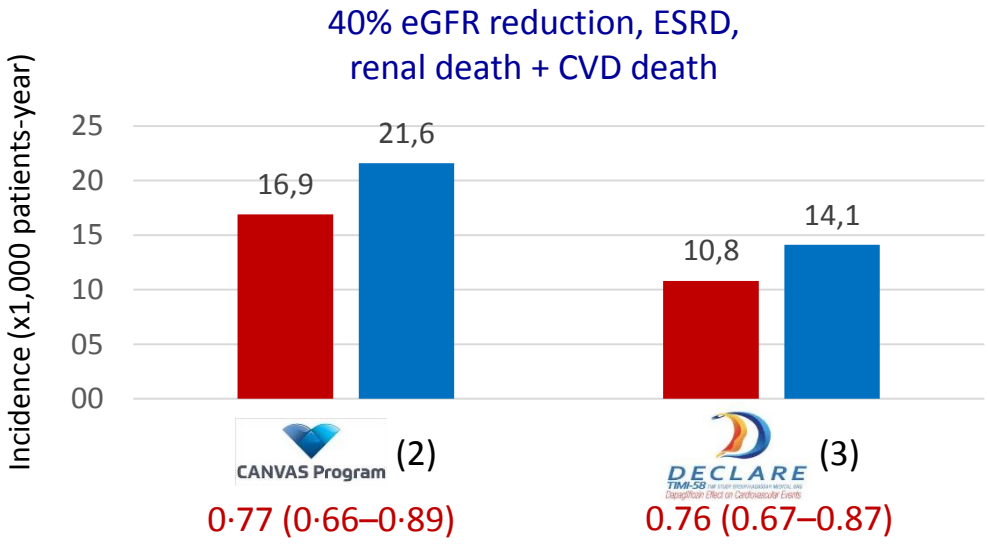
1. Marso SP et al. N Engl J Med. 2016;375;311-322
2. Marso SP et al. N Engl J Med. 2016;375:1834–1844
3. Gerstein H et al. Lancet. 2019; June 10
4. Wanner C et al. N Engl J Med. 2016;375:323-334
5. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704

Renal protection with SGLT2 inhibitors









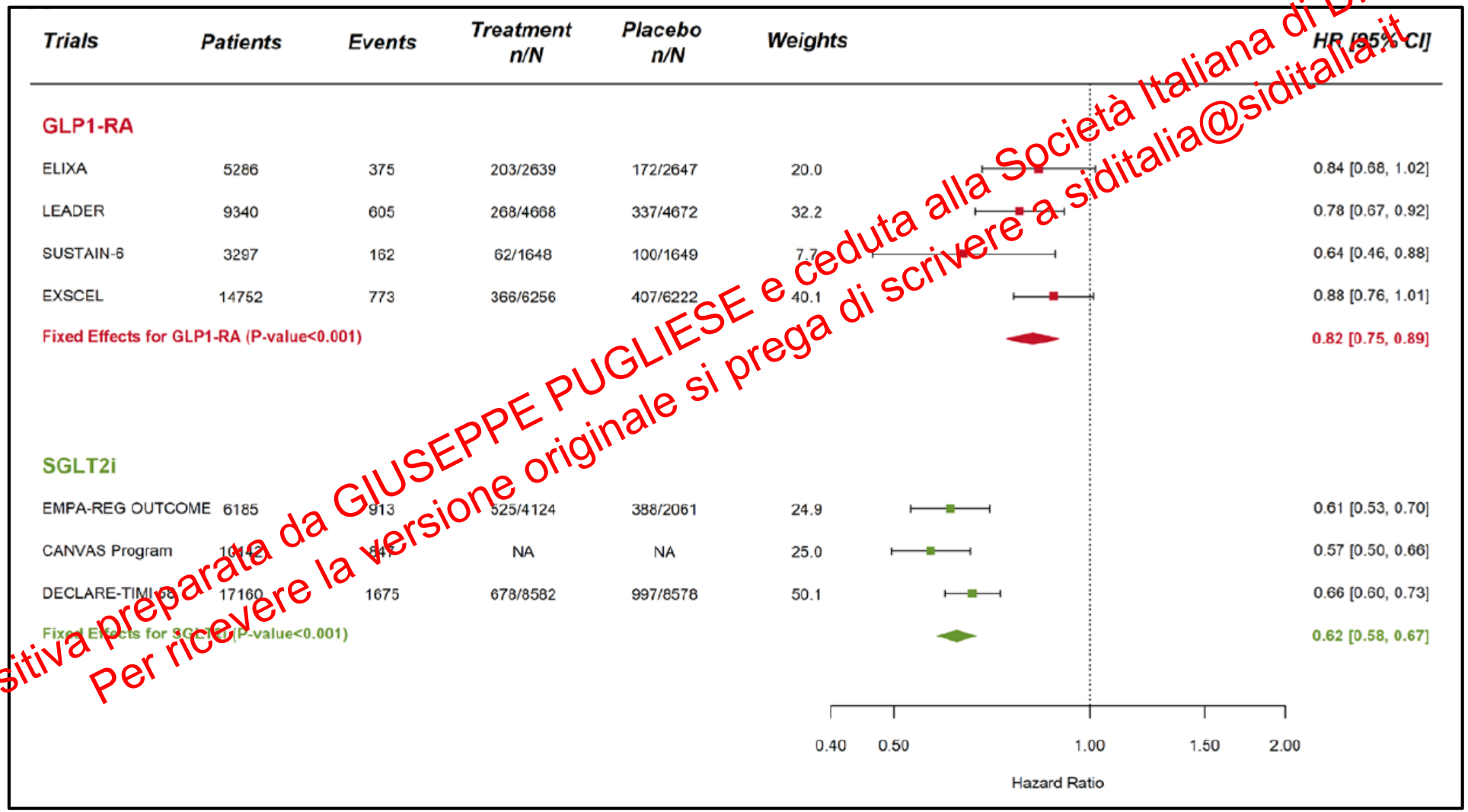
Active drug
Placebo

1. Wanner C et al. N Engl J Med. 2016;375:323-334
2. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357
4. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

Renal protection with GLP-1 receptor agonists versus SGLT2 inhibitors

Renal composite

(new-onset macroalbuminuria, sustained doubling of serum creatinine or eGFR decrease ≥40%, ESRD, or renal death)

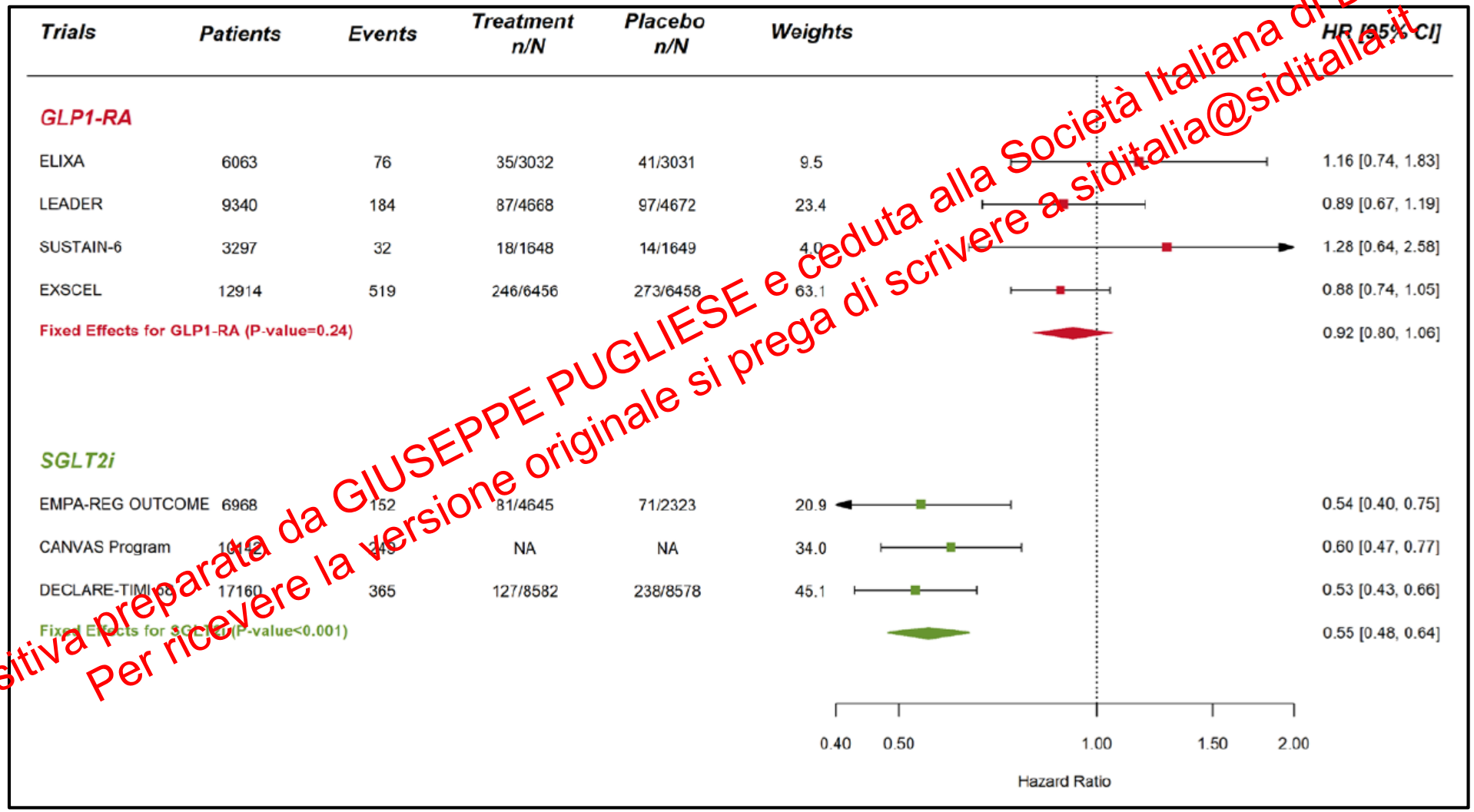


Zelniker TA et al. Circulation. 2019;139:2022-2031

Renal protection with GLP-1 receptor agonists versus SGLT2 inhibitors

Renal composite

(sustained doubling of serum creatinine or eGFR decrease ≥40%, ESRD, or renal death)



Zelniker TA et al. Circulation. 2019;139:2022-2031

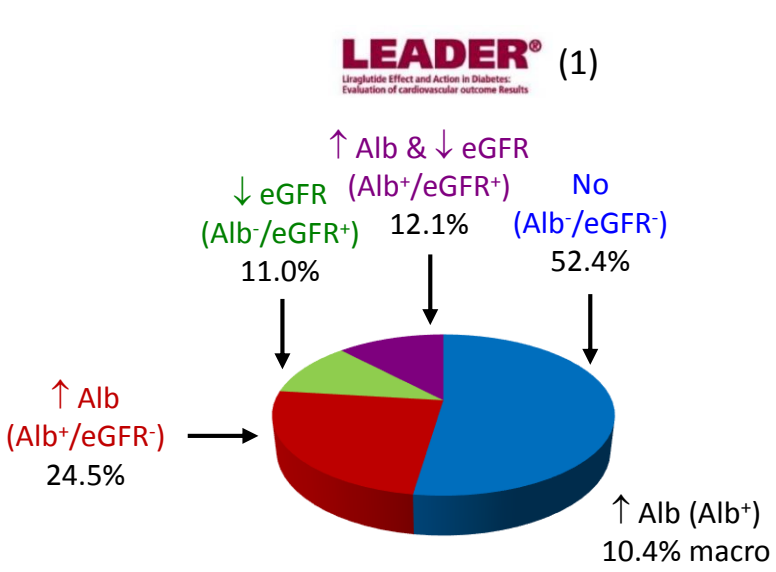
Guidelines for diabetic kidney disease (DKD): future perspectives

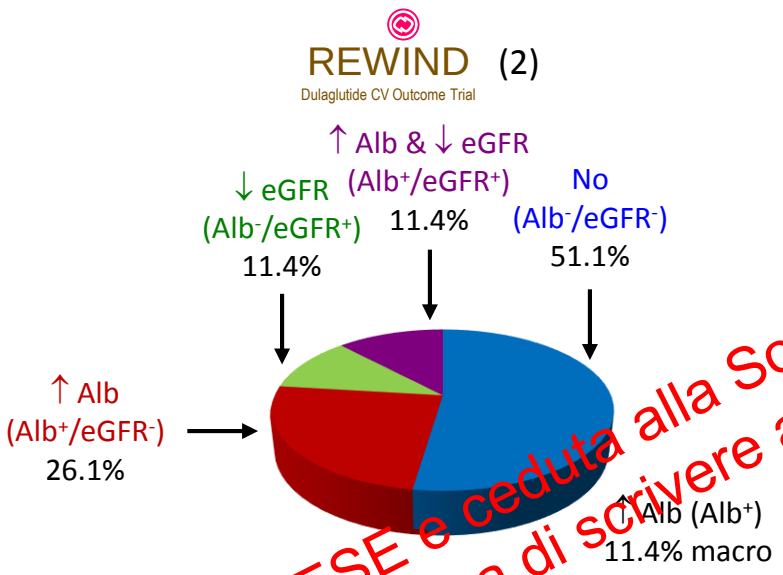
Lowering of eGFR threshold for SGLT2-i treatment → Threshold and dosage

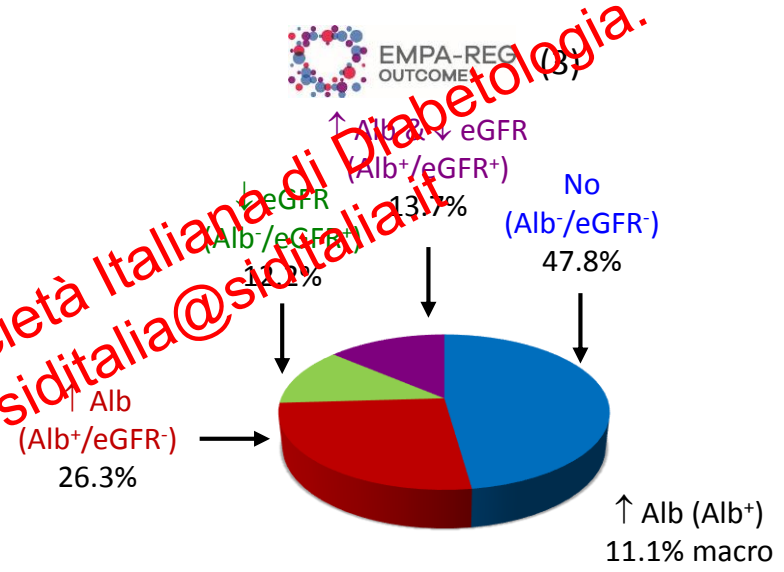
Use of agents with proven DKD benefit in primary prevention of DKD → Definition of high renal risk

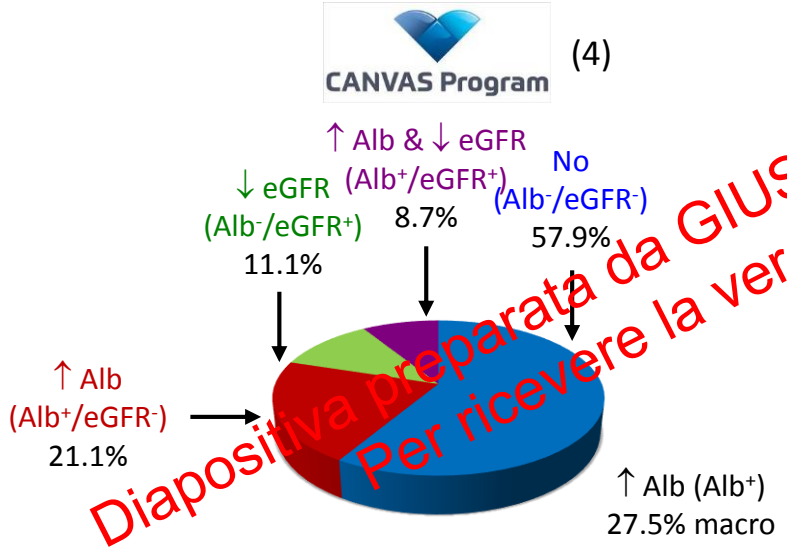
Use of agents with proven DKD benefit in patients with type 1 diabetes → Trials with renal endpoints

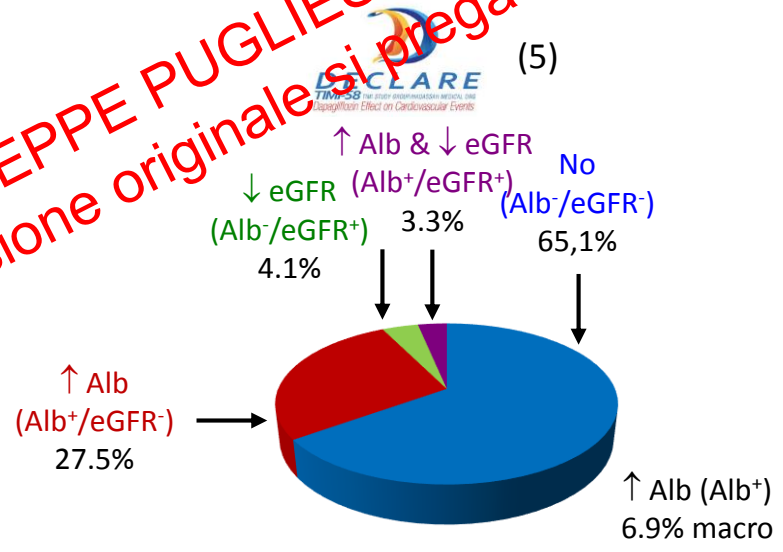
Baseline CKD in CVOT with GLP-1 receptor agonists and SGLT2 inhibitors

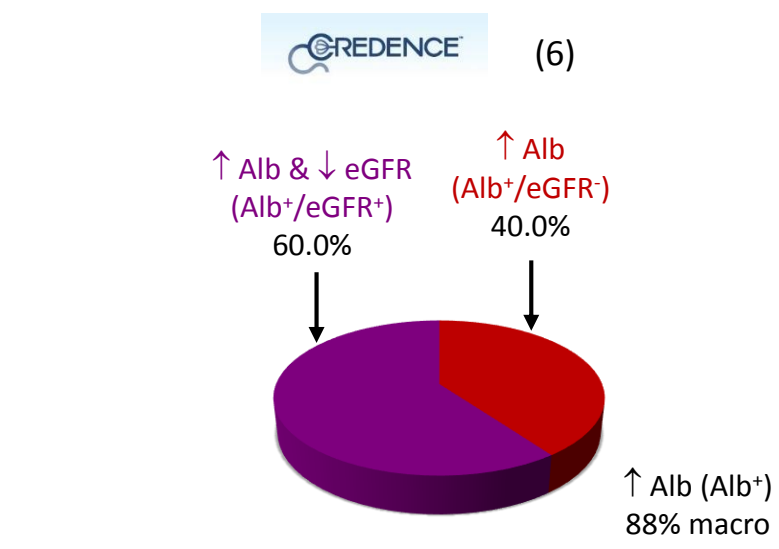










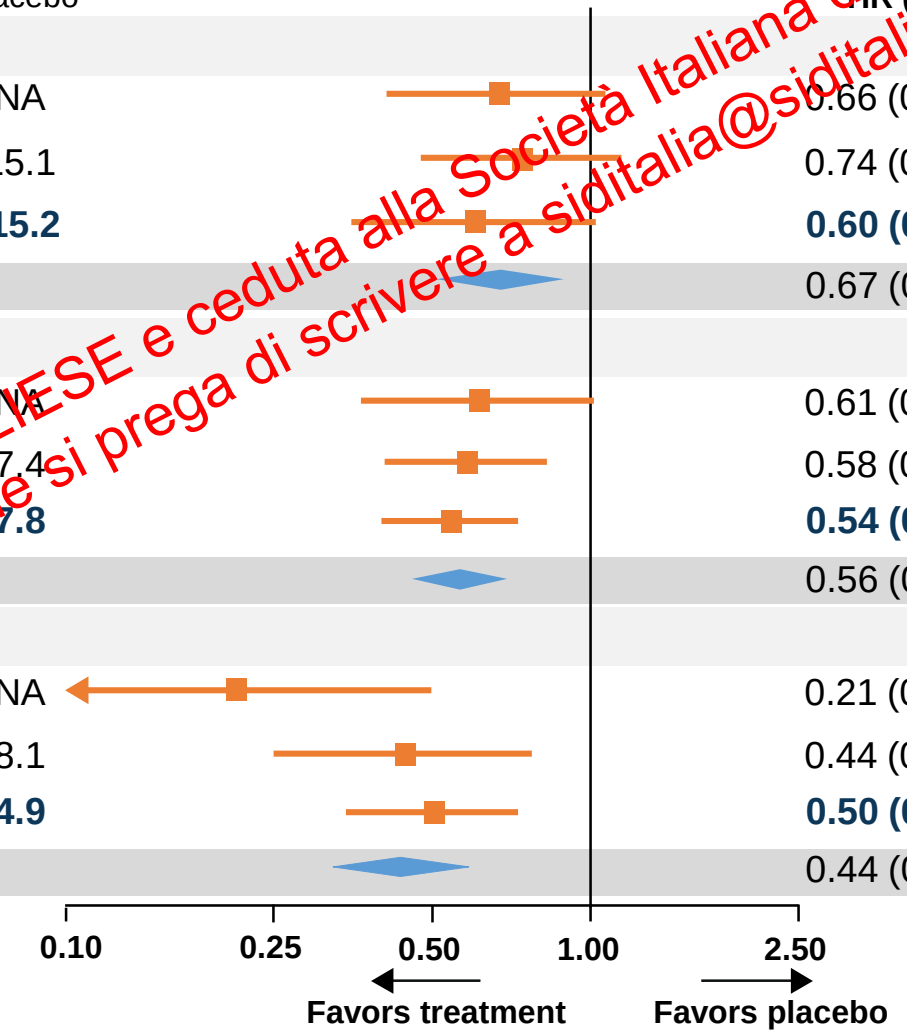


1. Marso SP et al. N Engl J Med. 2016;375;311-322; 2. Gerstein H et al. Lancet. 2019; June 10;
3. Wanner C et al. N Engl J Med. 2016;375:323-334; 4. Perkovic V et al. Lancet Diabetes Endocrinol. 2018;6:691–704;
5. Mosenzon O et al. Lancet Diabetes Endocrinol. 2019 June 9; 6. Perkovic V et al. N Engl J Med. 2019;80:2295-2306

Renal protection with SGLT2 inhibitors by eGFR

Renal composite (worsening eGFR, ESRD, or renal death)

	Events per 1000 patient-years: Treatment	Placebo	HR (95% CI)
eGFR <60 mL/min/m²			
EMPA-REG OUTCOME	NA	NA	0.66 (0.41, 1.07)
CANVAS Program	11.4	15.1	0.74 (0.48, 1.15)
DECLARE-TIMI 58	**8.9**	**15.2**	**0.60 (0.35, 1.02)**
FE model for eGFR <60 (p=0.0054)			0.67 (0.51, 0.89)
eGFR 60 to <90 mL/min/m²			
EMPA-REG OUTCOME	NA	NA	0.61 (0.37, 1.03)
CANVAS Program	4.6	7.4	0.58 (0.41, 0.84)
DECLARE-TIMI 58	**4.2**	**7.8**	**0.54 (0.40, 0.73)**
FE model for eGFR 60 to <90 (p<0.0001)			0.56 (0.46, 0.70)
eGFR ≥90 mL/min/m²			
EMPA-REG OUTCOME	NA	NA	0.21 (0.09, 0.53)
CANVAS Program	3.8	8.1	0.44 (0.25, 0.78)
DECLARE-TIMI 58	**2.5**	**4.9**	**0.50 (0.34, 0.73)**
FE model for eGFR ≥90 (p<0.0001)			0.44 (0.32, 0.59)

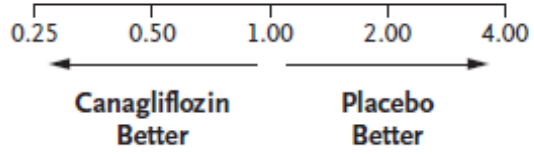


Zelniker TA et al. Lancet. 2019;393:31–39

Renal protection with SGLT2 inhibitors by renal function

CREDENCE

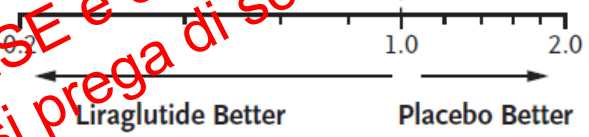
Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m^2	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m^2	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m^2	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.3	0.76 (0.55–1.04)	
>1000	176/1017	253/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m^2	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m^2	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m^2	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	



Perkovic V et al. N Engl J Med. 2019;80:2295-2306

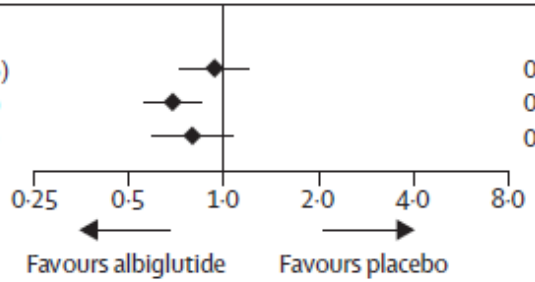
Cardiovascular protection with GLP-1 receptor agonists by eGFR

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m²	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m²	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m²	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m²	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	



LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (1)

	Number of patients	Albiglutide Events/patients (%)	Placebo Events/patients (%)	Hazard ratio	Hazard ratio (95% CI)	$p_{interaction}$
Baseline eGFR (mL/min per 1·73 m²)						0·186
<60	2222	116/1098 (10·6%)	128/1124 (11·4%)		0·93 (0·73–1·20)	
≥60 to <90	4417	144/2208 (6·5%)	206/2209 (9·3%)		0·69 (0·56–0·85)	
≥90	2824	78/1425 (5·5%)	94/1399 (6·7%)		0·79 (0·59–1·07)	

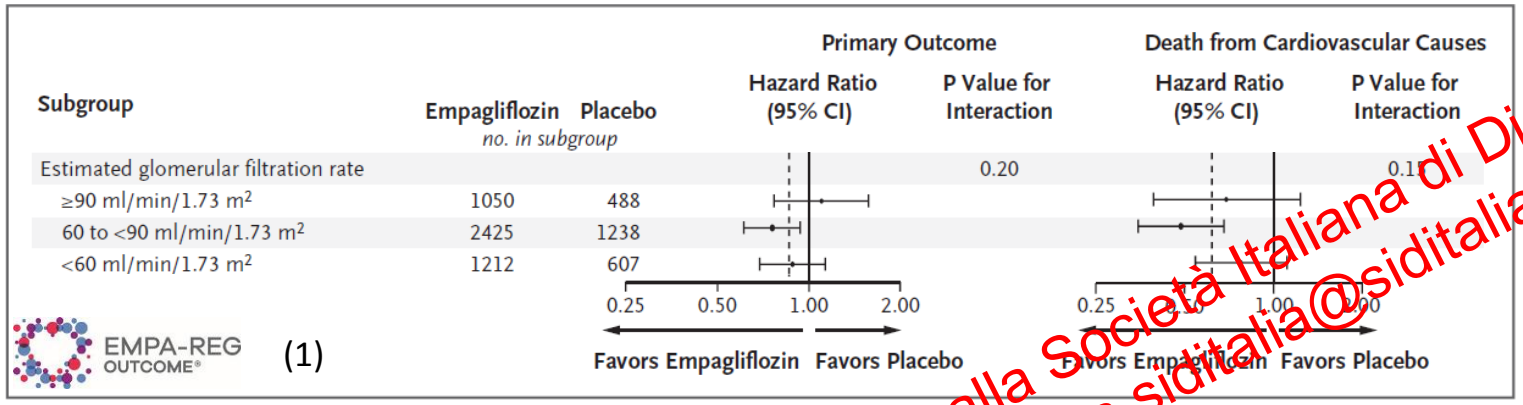


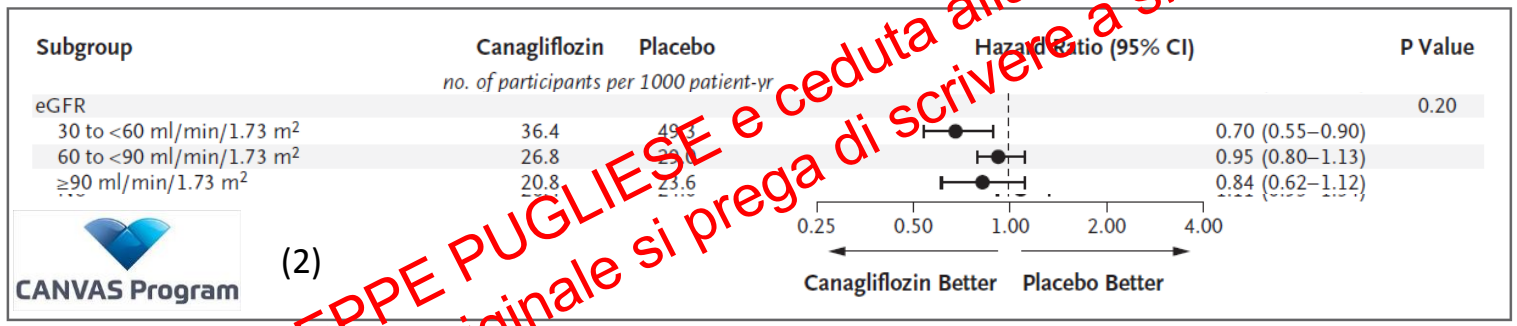
Harmony Outcomes (2)

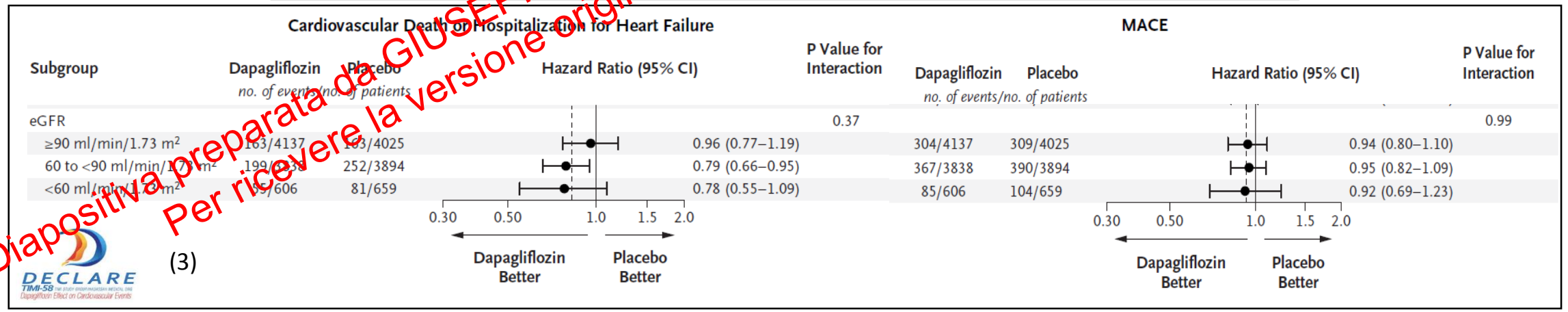
1. Marso SP et al. N Engl J Med. 2016;375;311-322

2. Hernandez HF et al. Lancet. 2018;392:1519–1529

Cardiovascular protection with SGLT2 inhibitors by eGFR





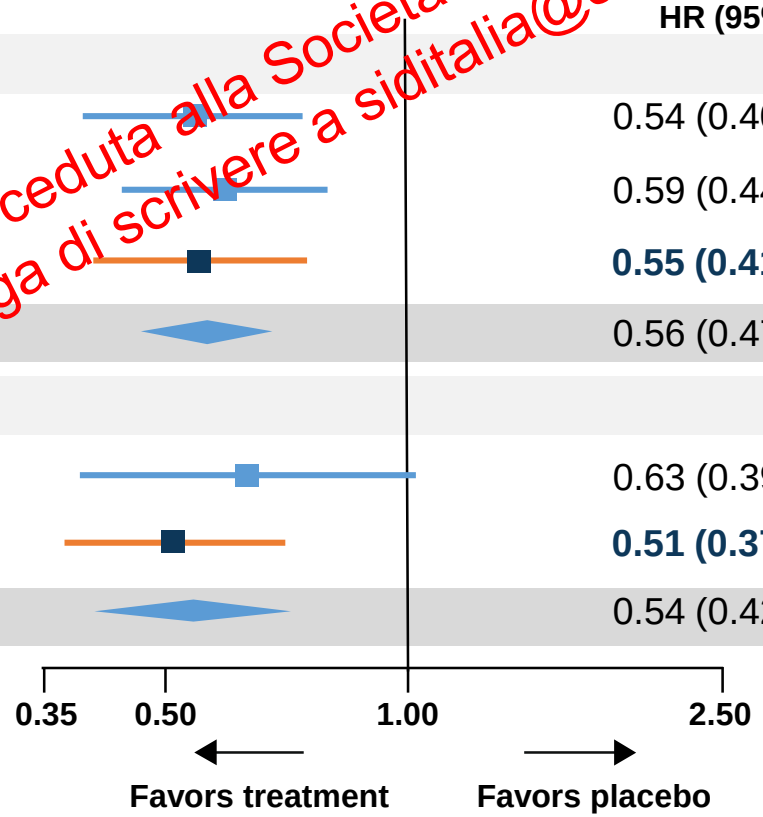


1. Zinman B et al. N Engl J Med. 2015; 373:2117-2128
2. Neal B et al. N Engl J Med. 2017;377:644-657
3. Wiviott SD et al. N Engl J Med. 2019;380:347-357

Renal protection with SGLT2 inhibitors by prior CVD

Renal composite (worsening eGFR, ESRD, or renal death)

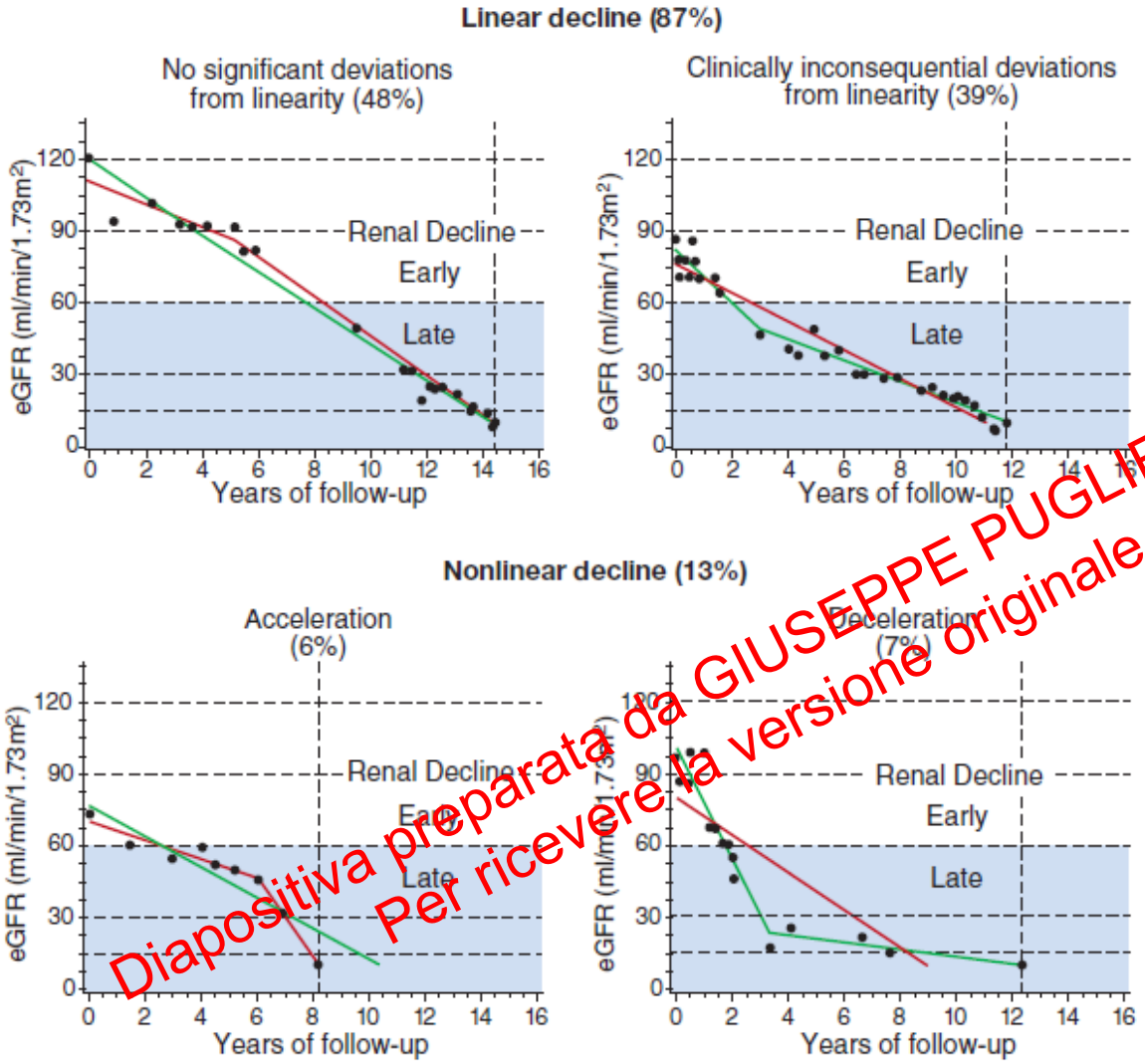
	Events per 1000 patient-years		
	Treatment	Placebo	HR (95% CI)
Patients with ASCVD			
EMPA-REG OUTCOME	6.3	11.5	0.54 (0.40, 0.75)
CANVAS Program	6.4	10.5	0.59 (0.44, 0.79)
DECLARE-TIMI 58	**4.7**	**8.6**	**0.55 (0.41, 0.75)**
FE model for ASCVD (p<0.0001)			0.56 (0.47, 0.67)
Patients with MRF			
CANVAS Program	4.1	6.6	0.63 (0.39, 1.02)
DECLARE-TIMI 58	**3.0**	**5.9**	**0.51 (0.37, 0.69)**
FE model for MRF (p<0.0001)			0.54 (0.42, 0.71)



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

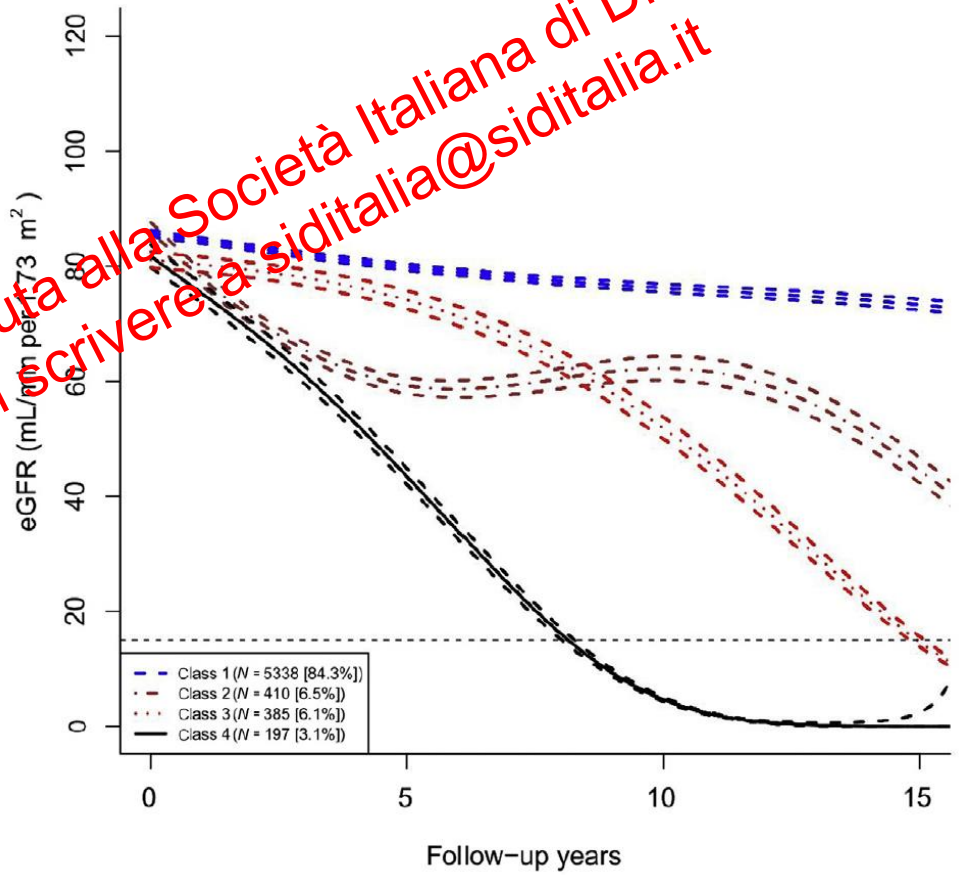
eGFR decline in type 1 and 2 diabetes

The Joslin Kidney Studies



Skupien J et al. Diabetes Care. 2016;39:2262–2269

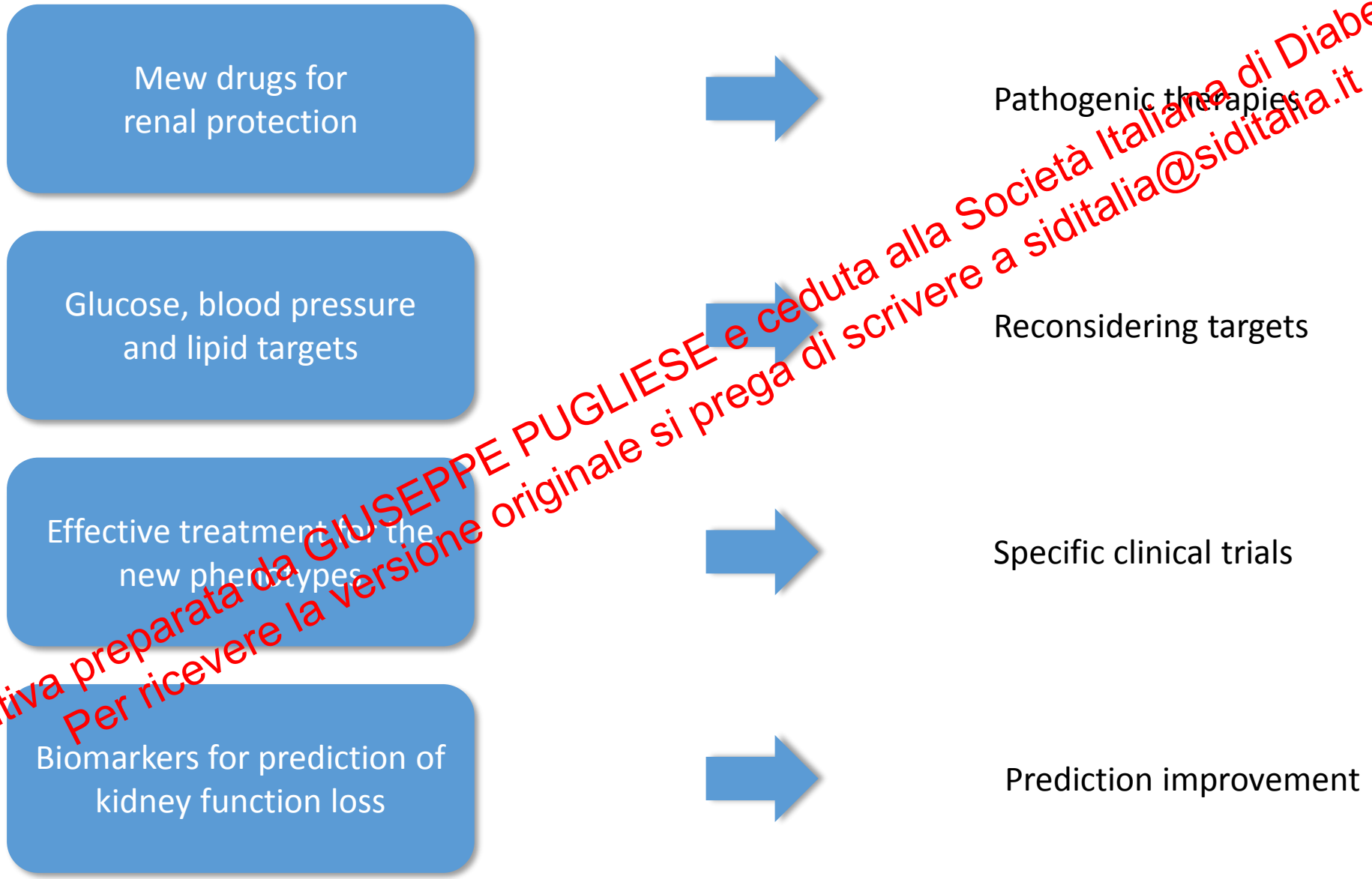
The Hong Kong Diabetes Register



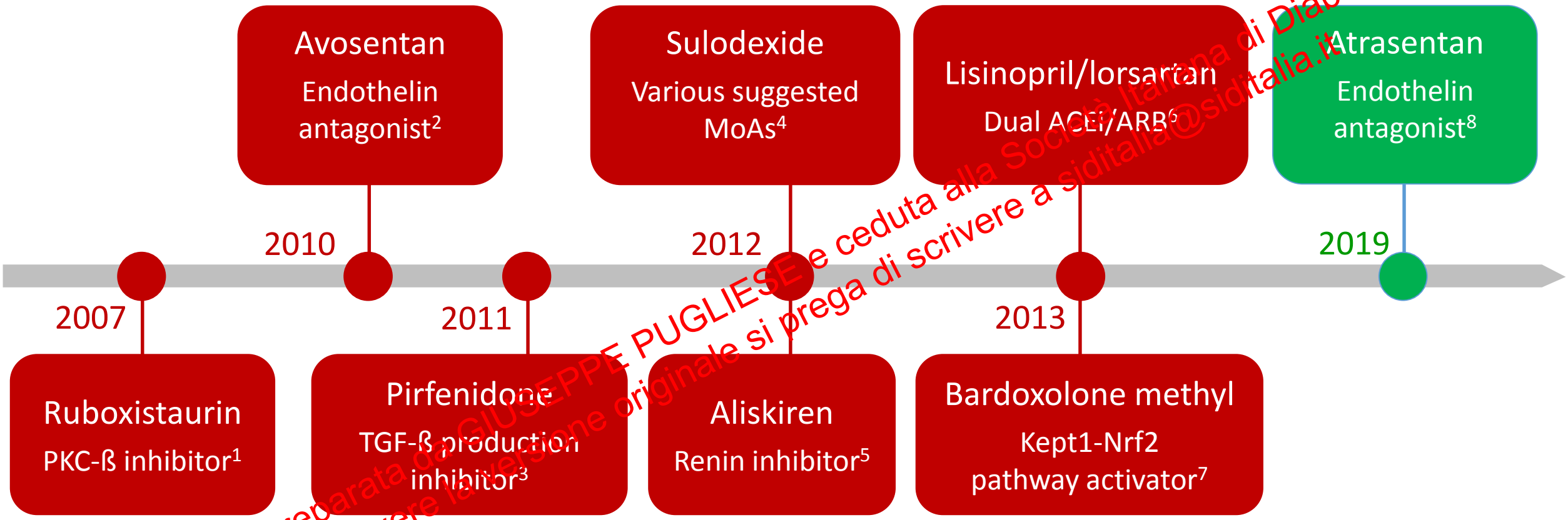
Class 1: slow eGFR decline; Class 2: curvilinear eGFR decline;
Class 3: progressive eGFR decline; Class 4: accelerated eGFR decline.

Jiang G et al. Kidney Int. 2019;95:178-187

Guidelines for diabetic kidney disease (DKD): future perspectives



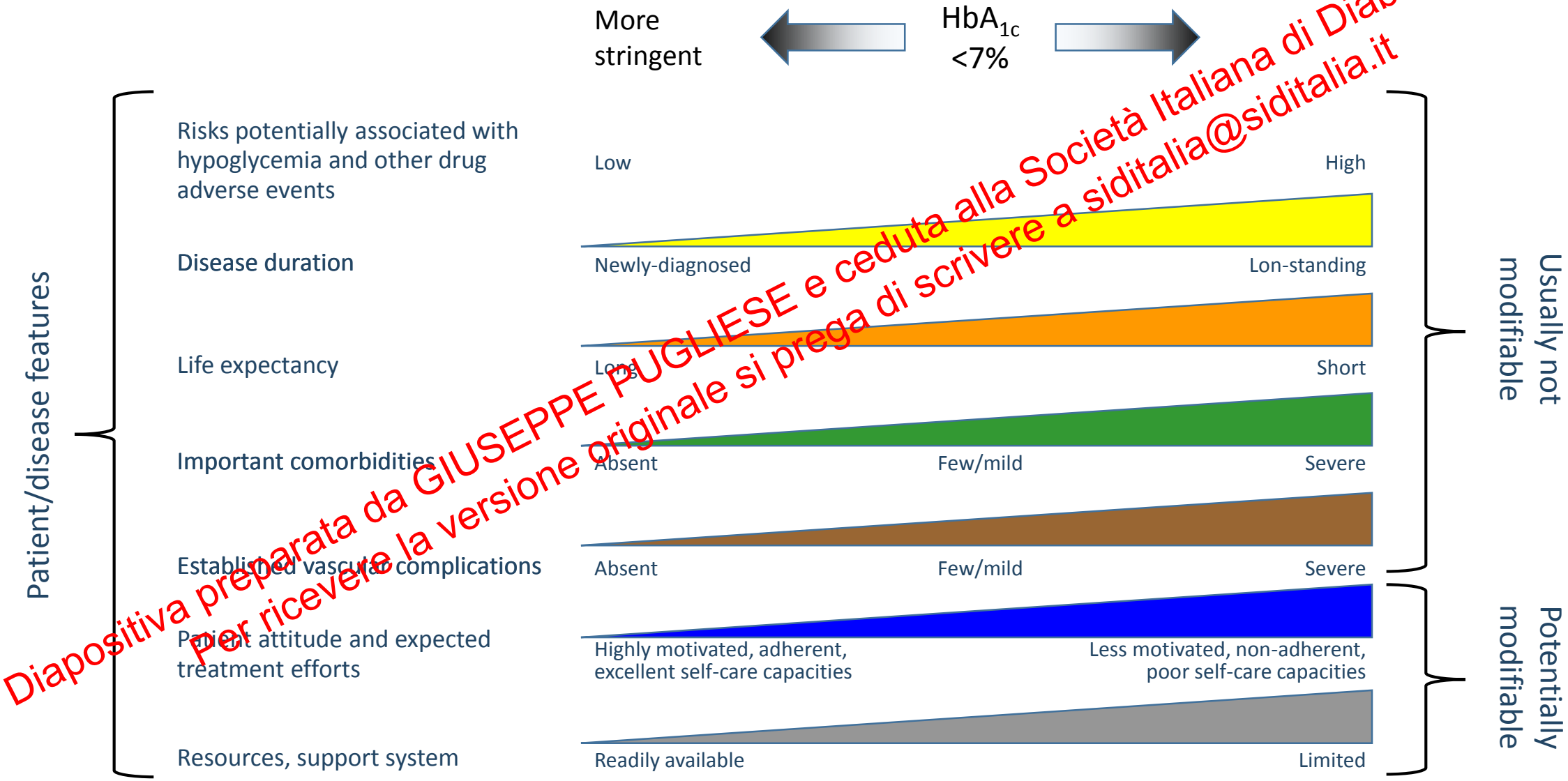
New «pathogenic» drugs for renal protection



1. Tuttle KR et al. Clin J Am Soc Nephrol. 2007;2:631-636
2. Mann JFE et al. J Am Soc Nephrol. 2010;21:527-535
3. Sharma K et al. J Am Soc Nephrol. 2011;22:1144-1151
4. Packham DK et al. J Am Soc Nephrol. 2012;23;123-130
5. Parving HH et al. N Engl J Med. 2012;367:2204-2213
6. Fried LF et al. N Engl J Med. 2013;369:1892-1903
7. de Zeeuw D et al. N Engl J Med. 2013;369:2492-2503
8. Heerspink HJL et al. Lancet. 2019;393:1937-1947

Glycemic targets in DKD

American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Position Statement



Inzucchi SE et al. Diabetes Care 2015;38:140–149

Intensive glycemic control and renal outcomes

Meta-analysis of 13 randomized clinical trials

	ACCORD	ADVANCE	UKPDS	VADT	Total
HbA_{1c}	-1.01	-0.72	-0.66	-1.16	-0.88
Major micro-vascular events	1.00/0.95	0.86	0.75	--	--
Renal events	1.05/1.02#	0.79*	--	0.62	--
1. Newly-diagnosed microalbuminuria	0.79/0.85	0.91	--	0.71	0.90 (0.85 - 0.96)
2. Newly-diagnosed macroalbuminuria	0.69/0.72	0.70	0.66	0.64	--
3. Doubling of serum creatinine	1.07/1.04	1.15	0.26	1.00	
4. ESRD or renal death	0.95/0.92	0.64	0.73	0.63	
5. Composite §	--	0.35	--	--	

* Newly-diagnosed or worsening nephropathy;

any 2, 3 or 4;

§ dialysis, transplant, renal death, serum creatinine >200 µmol/L, persistent doubling of serume creatinine

Boussageon R et al. BMJ 2011; 343:d4169

Blood pressure targets in DKD

	KDIGO 2012	JCN-8 2014	ACC/AHA 2017
Reduced eGFR without albuminuria	<140/90	<140/90	<130/80
Albuminuria with or without reduced eGFR	<130/80	<140/90	<130/80

Chang AR & Appel LJ. Clin Am Soc Nephrol. 2018;13:1572–1574

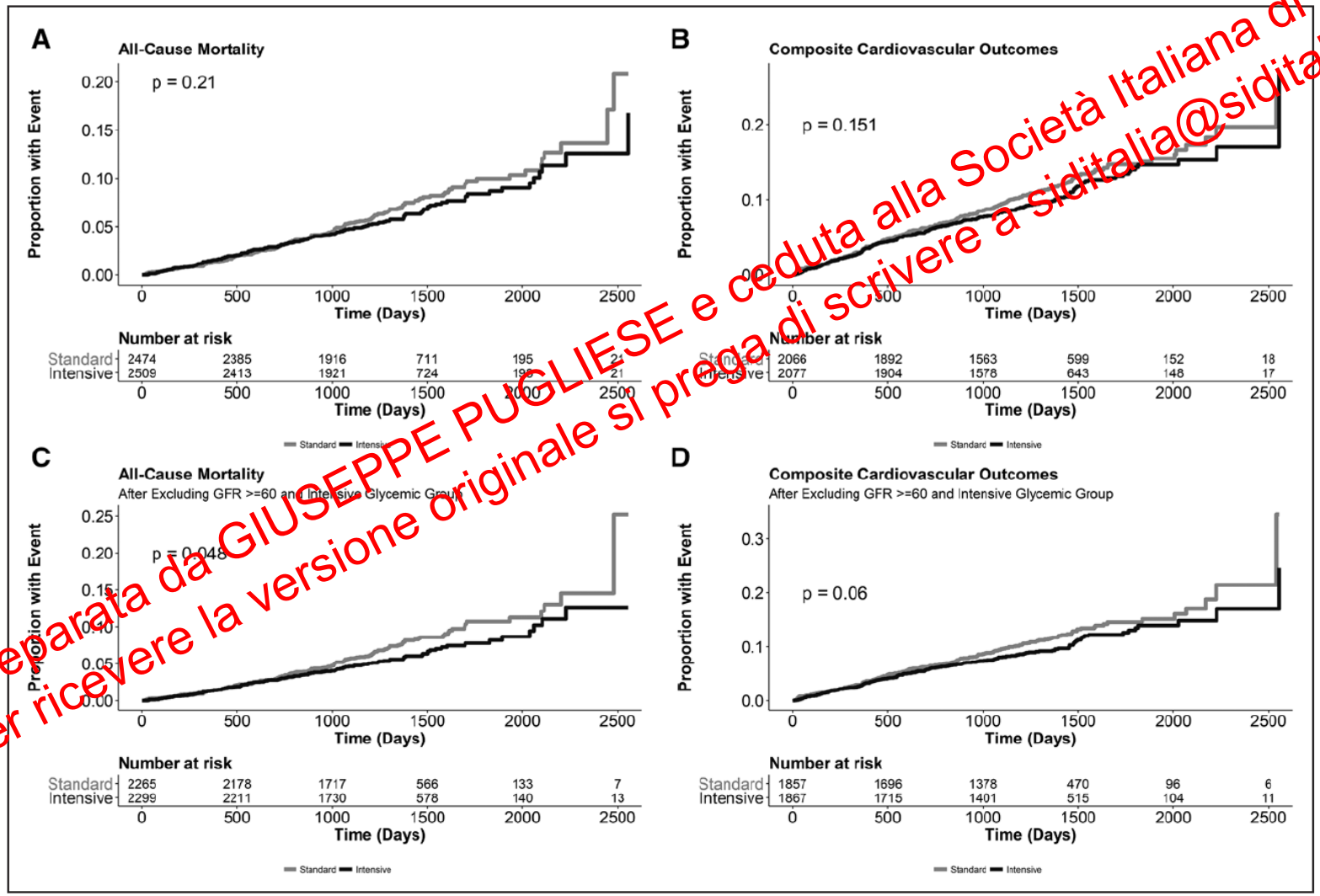
European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) Guidelines

Recommendations	Class[a]	Level[b]
Treatment targets		
Antihypertensive drug treatment is recommended for people with DM when office BP is >140/90 mmHg.[155,178–180]	I	A
It is recommended that patients with hypertension and DM are treated in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.[155,159,160,181–183]	I	A
It is recommended that target DBP is targeted to <80 mmHg, but not <70 mmHg.[160]	I	C
An on-treatment SBP of <130 mmHg may be considered in patients at particularly high risk of a cerebrovascular event, such as those with a history of stroke.[154–157,173]	IIb	C
Treatment and evaluation		
A RAAS blocker (ACEI or ARB) is recommended in the treatment of hypertension in patient with DM, particularly in the presence of microalbuminuria, albuminuria, proteinuria, or LV hypertrophy.[167–170]	I	A

Inzucchi SE et al. Diabetes Care 2015;38:140–149

Intensive blood pressure control and mortality and cardiovascular outcomes

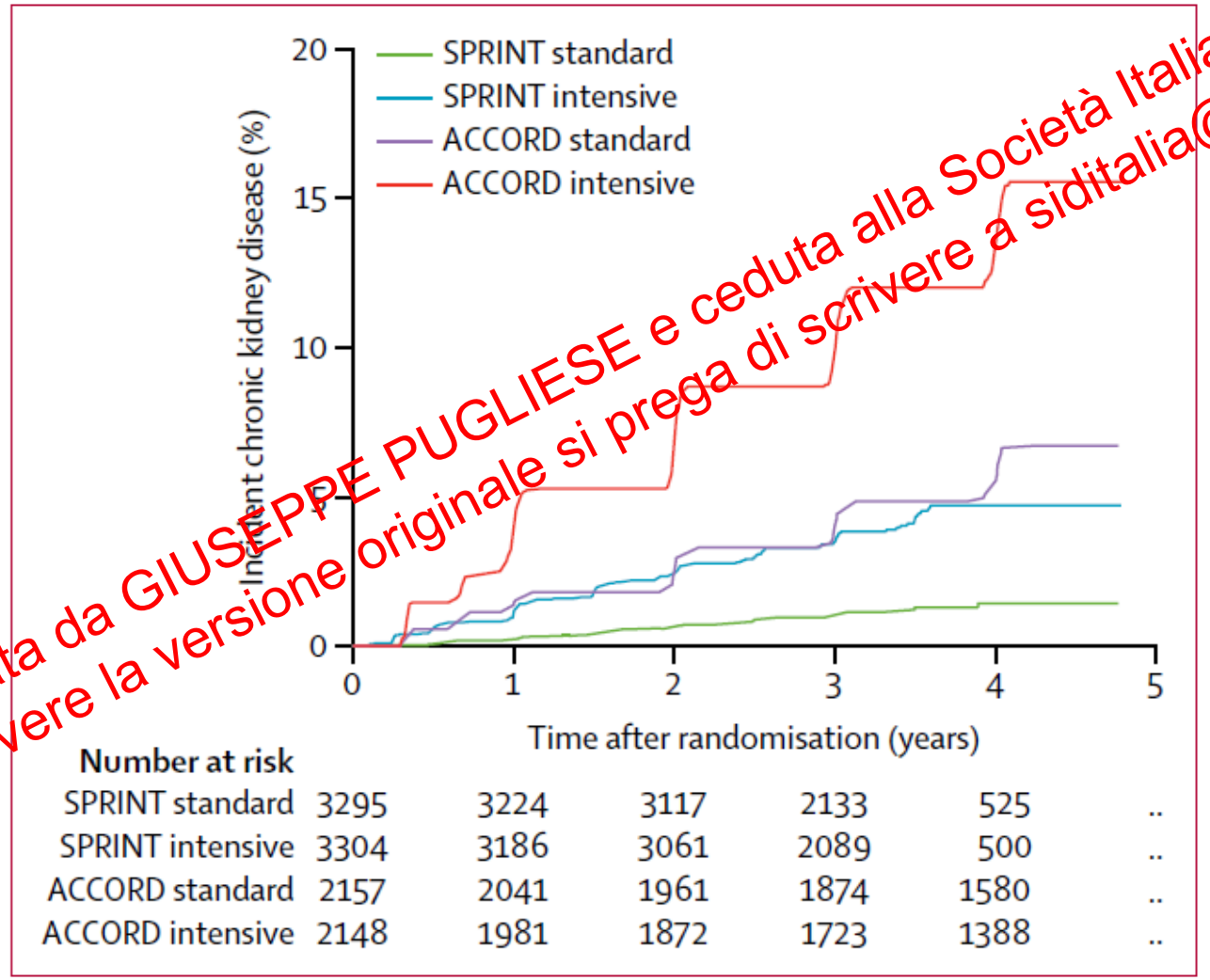
Pooled data analysis from the African American Study of Kidney Disease and Hypertension (AASK), Action to Control Cardiovascular Risk in Diabetes (ACCORD), Modification of Diet in Renal Disease (MDRD), and Systolic Blood Pressure Intervention Trial (SPRINT)



Aggarwal R et al. Hypertension. 2019;73:1275-1282

Intensive blood pressure control and incident chronic kidney disease

Secondary analysis from participants without chronic kidney disease at baseline from the Systolic Blood Pressure Intervention Trial (SPRINT, without diabetes) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD, with diabetes)



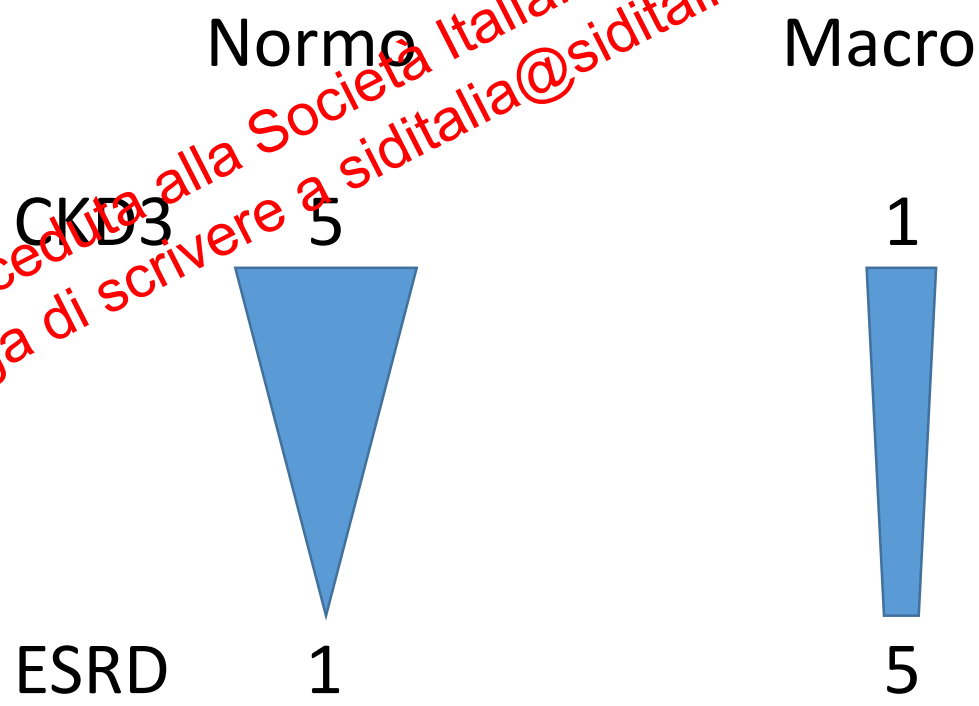
Number at risk						
SPRINT standard	3295	3224	3117	2133	525	..
SPRINT intensive	3304	3186	3061	2089	500	..
ACCORD standard	2157	2041	1961	1874	1580	..
ACCORD intensive	2148	1981	1872	1723	1388	..

Beddhu S et al. Lancet Diabetes Endocrinol. 2018;6:555–563

Progressive renal decline

The Joslin Kidney Studies

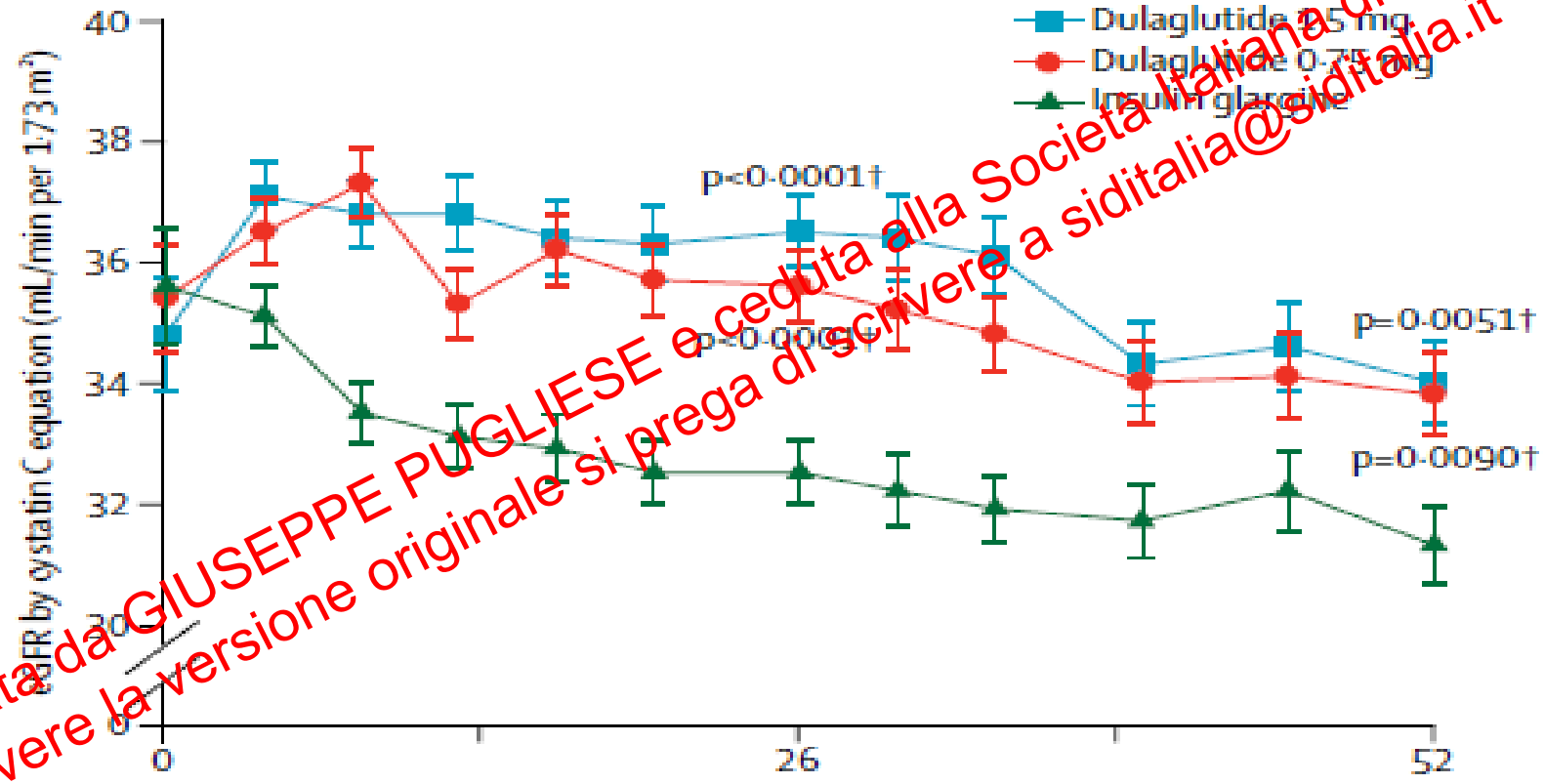
eGFR decline ml/min/year	Normo albuminuria % (n)	Micro albuminuria % (n)	Macro albuminuria % (n)	Total % (n)
T1D				
<2.9	91	78	49	81
3-4.9	6	11	16	8
5-9.9	2	7	19	7
≥10	1	4	16	4
Total	100 (932)	100 (525)	100 (275)	100 (1,732)
T2D				
<2.9	80	67	32	72
3-4.9	13	18	17	15
5-9.9	6	12	30	10
≥10	1	3	21	3
Total	100 (681)	100 (418)	100 (82)	100 (1,181)



Krolewski AS et al. Kidney Int. 2017;91:1300–1311

Renal protection with GLP-1 receptor agonists

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7)

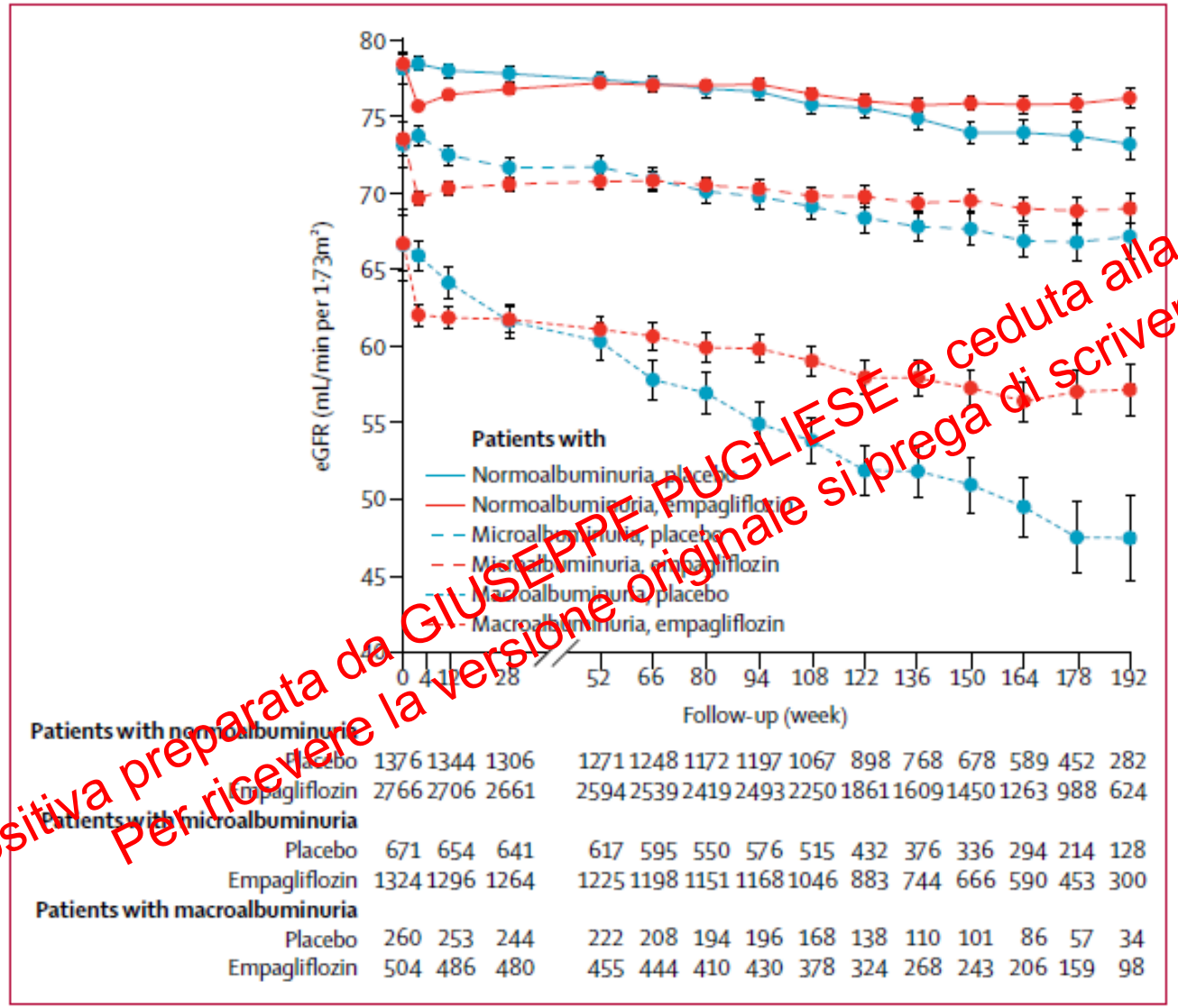


Number of patients			
Dulaglutide 1·5 mg	192	163	157
Dulaglutide 0·75 mg	190	167	160
Insulin glargine	194	174	164

Tuttle KR et al. Lancet Diabetes Endocrinol. 2018;6:605-617

Renal protection with SGLT2 inhibitors by albuminuria

EMPA-REG OUTCOME®



Patients with normoalbuminuria													
Placebo	1376	1344	1306	1271	1248	1172	1197	1067	898	768	678	589	452	282
Empagliflozin	2766	2706	2661	2594	2539	2419	2493	2250	1861	1609	1450	1263	988	624
Patients with microalbuminuria														
Placebo	671	654	641	617	595	550	576	515	432	376	336	294	214	128
Empagliflozin	1324	1296	1264	1225	1198	1151	1168	1046	883	744	666	590	453	300
Patients with macroalbuminuria														
Placebo	260	253	244	222	208	194	196	168	138	110	101	86	57	34
Empagliflozin	504	486	480	455	444	410	430	378	324	268	243	206	159	98

eGFR ≥60 ml/min/1.73 m² 3,332 (79.6%)
eGFR <60 ml/min/1.73 m² 849 (20.4%)

eGFR ≥60 ml/min/1.73 m² 1,396 (62.2%)
eGFR <60 ml/min/1.73 m² 849 (37.8%)

eGFR ≥60 ml/min/1.73 m² 431 (56.0%)
eGFR <60 ml/min/1.73 m² 338 (44.0%)

Cherney DZI et al. Lancet Diabetes Endocrinol. 2017;5:610–621

Trials with GLP-1 receptor agonists or SGLT2 inhibitors in DKD patients

CREDENCE

DAPACKD

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

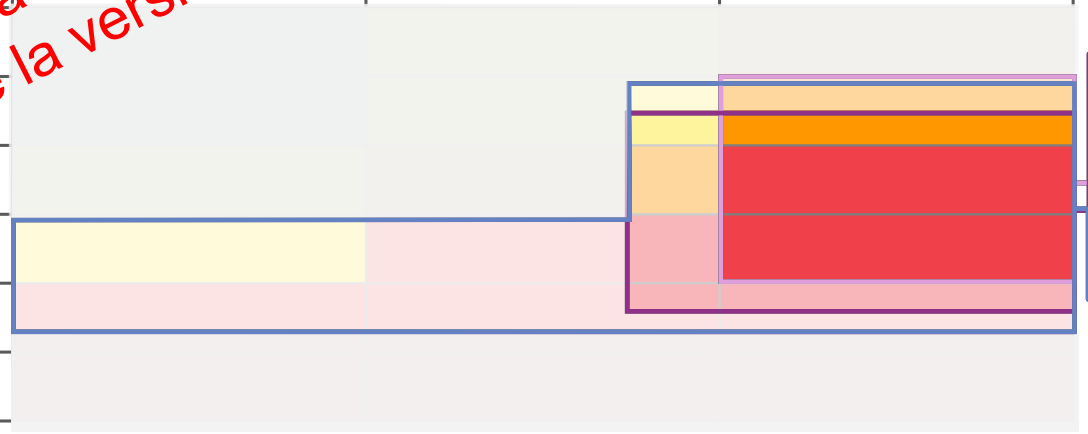
FLOW
semaglutide | renal outcomes trial

FLOW population
eGFR ≤75 to ≥50 ml/min/1.73 m^2
and UACR >300 to <5000 mg/g
eGFR <50 to ≥25 ml/min/1.73 m^2
and UACR >100 to <5000 mg/g

Low CKD risk | Moderately increased CKD risk | High CKD risk | Very high CKD risk

GFR category and range (ml/min/1.73 m^2)	
Stage 1	≥90
Stage 2	60–89
Stage 3a	45–59
Stage 3b	30–44
Stage 4	15–29
ESKD 5	<15

Albuminuria stage, description and range (mg/g)		
A1	A2	A3
No albuminuria	Microalbuminuria	Macroalbuminuria
<30	30–300	>300



CREDENCE population[1]
eGFR ≥30 to <90 ml/min/1.73 m^2
and UACR >300 mg/g

DAPA-CKD population[2]
eGFR >25 to <75 ml/min/1.73 m^2
and UACR >200 mg/g

EMPA-KIDNEY population[3]
eGFR ≥20 to <45 ml/min/1.73 m^2
eGFR ≥45 to <90 ml/min/1.73 m^2
and UACR ≥200 mg/g

eGFR slope versus albuminuria change as a surrogate enpoint in clinical trials

Hierarchy of End Points for Kidney Disease Progression for Phase 3 RCTs

End Point	Strength of Evidence
Kidney failure	Clinical outcome
Doubling of Scr (confirmed) (57% eGFR decline)	Valid surrogate end point
GFR decline > 40% (confirmed)	Valid surrogate end point
GFR slope reduction (mean) > 0.5-1.0 mL/min/1.73 m^2/y	
GFR decline > 30% (confirmed)	Reasonably likely surrogate end point in many trials and valid surrogate end point in some trials
UACR reduction (mean) > 30%	

Levey AS et al. Am J Kidney Dis. 2019 Aug 23

Biomarkers for DKD prediction

Study	Biomarker	Study design	Sample size	Study population	Length of follow-up (years)	Outcomes of interest	Adjustment for confounders
Many biomarkers, not as a panel							
Niewczas *et al.* [38]	Plasma TNFR1, TNFR2, IL-6, total TNFα, free TNFα, PAI-1, ICAM-1 and VCAM-1, CRP	Prospective	410	Type 2 diabetes	8–12	ESRD and mortality	Many risk factors
Fufaa *et al.* [43]	Urinary KIM-1, L-FABP, NAG, NGAL	Prospective	260	Pima Indians with type 2 diabetes	14	ESRD	Albuminuria and eGFR
Agarwal *et al.* [50]	17 Urine and 7 plasma	Prospective	67	Type 2 diabetes with CKD	2–6	eGFR decline, progression to ESRD and/or death	Albuminuria and eGFR
Combined biomarker panel							
Persson *et al.* [51]	TGF-β1 and BMP-7	Nested Randomized control trial	269	Type 2 diabetes with hypertension and microalbuminuria	2	Onset of diabetic nephropathy	Albuminuria and treatment allocation
Desai *et al.* [52]	Tnt and NT-pro-BNP	Nested Randomized control trial	995	Type 2 diabetes with baseline eGFR 20–60 mL/min/1.73 m^2	3.5	Incidence of ESRD and composite of death or ESRD	Many risk factors
Wong *et al.* [53]	Endothelial dysfunction, inflammation, growth factors and AGEs	Nested Randomized control trial	281	Type 2 diabetes ≥30 years of age	5	Renal hard end point	Albuminuria and eGFR
Verhave *et al.* [54]	7 Urinary cytokines	Prospective	83	Mostly type 2 diabetes (>97%)	2.1	Overt diabetic nephropathy	Proteinuria, initial MAP, number of BP medications
Pena *et al.* [55]	Panel of 13 serum/plasma biomarkers	Prospective	82	Type 2 diabetes	4	eGFR decline	Albuminuria, eGFR, smoking, sex, BP, oral diabetic medication

Pena MJ et al. Nephrol Dial Transplant. 2015;30:86–95

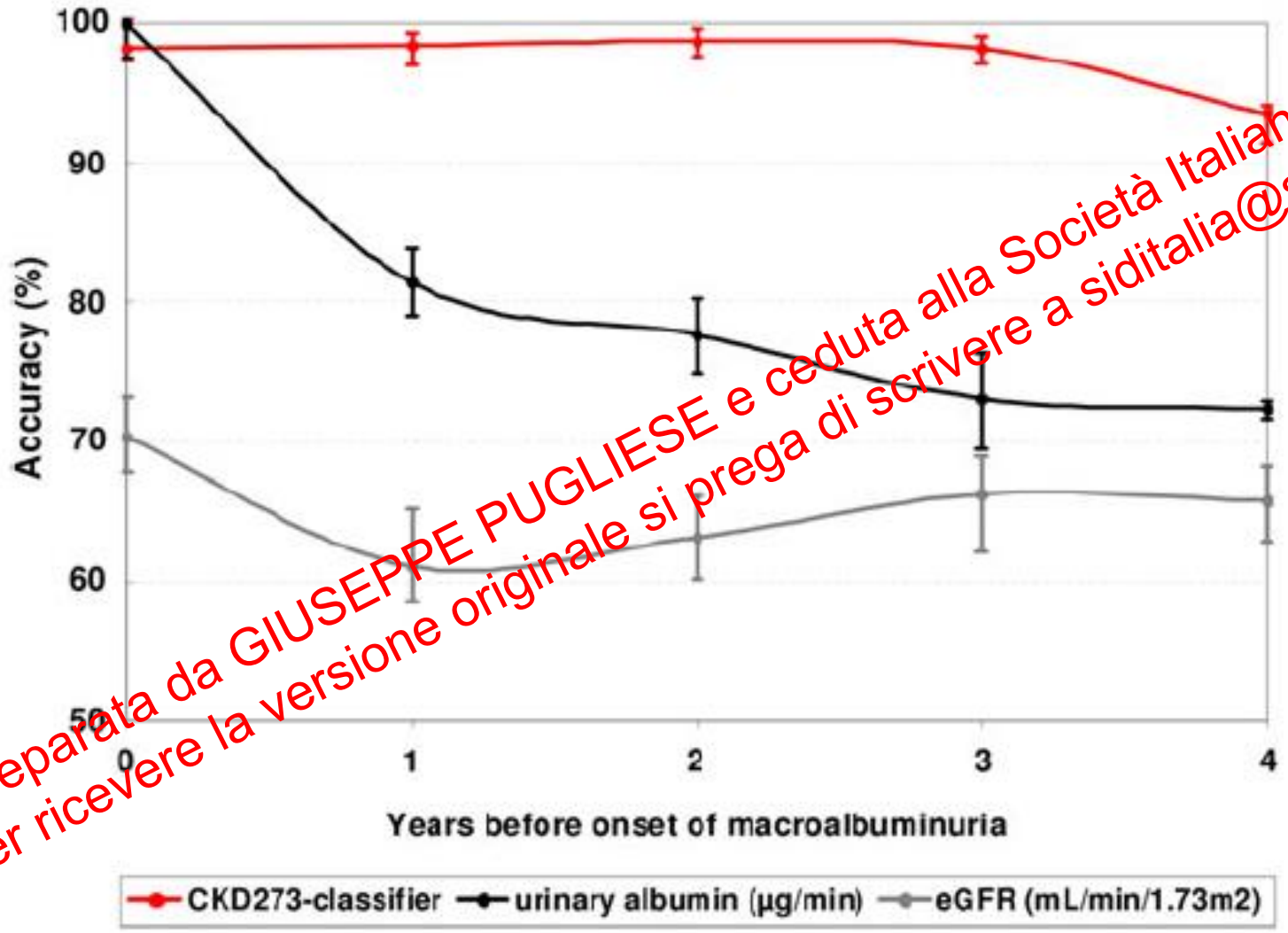
Biomarkers for DKD prediction

Study	Biomarker	Study design	Sample size	Study population	Length of follow-up (years)	Outcomes of interest	Adjustment for confounders
Urine							
Otu *et al.* [61]	Urine peptides	Prospective	62	Pima Indians with type 2 diabetes	10	Development of diabetic nephropathy	HbA1c
Zurbig *et al.* [63]	CKD273	Prospective	35	Type 1 and type 2 diabetes	10–15	Development of macroalbuminuria	Albuminuria
Roscioni *et al.* [68]	CKD273	Prospective	88	Type 2 diabetes	3	Progression of albuminuria stage	Albuminuria, eGFR, RAASi
Bhensdadia *et al.* [62]	Urine peptides	Randomized control trial	204	Type 2 diabetes from the VA Diabetes Trial	4	Renal function decline	Albuminuria, treatment, ACEi
Siwy *et al.* [37]	CKD273	Prospective	165	Type 2 diabetes	Unspecified	Discrimination of diabetic nephropathy	Albuminuria
Plasma							
Pena *et al.* [64]	Plasma peptides	Prospective	207	Type 2 diabetes and hypertension	4	Progression of albuminuria stage	Albuminuria, eGFR, RAASi

Study	Biomarker	Study design	Sample size	Study population	Length of follow-up (years)	Outcomes of interest	Adjustment for confounders
Zhang *et al.* [74]	Phytosphingosine, glycine, lysine, dihydrosphingosine, leucine	Cross-sectional	66	Healthy controls and type 2 diabetes	n/a	Discrimination of healthy controls from patients with type 2 diabetes with and without nephropathy	No
Han *et al.* [75]	35 Non-esterified and 52 esterified fatty acids (plasma)	Cross-sectional	150	Health controls and type 2 diabetes	n/a	Discriminate albuminuria stages	No
Hirayama *et al.* [76]	194 serum metabolites	Cross-sectional	156	Type 2 diabetes	n/a	Discriminate between overt diabetic nephropathy and without diabetic nephropathy	No
Sharma *et al.* [77]	19 Urine metabolites of mitochondrial metabolism	Cross-sectional	128	Health controls, type 1 and 2 diabetes	n/a	Differences in urine metabolome between health controls and diabetes mellitus + CKD cohorts	Age, race, sex, MAP, BMI, HBA1c, diabetes duration
Pena *et al.* [65]	Urine hexose, glutamine, tyrosine and plasma butenoylcarnitine and histidine	Prospective	90	Type 2 diabetes	3	Progression of albuminuria stage	Albuminuria, eGFR, RAASi
Niewczas *et al.* [78]	Plasma uraemic solutes and essential amino acids	Prospective	80	Type 2 diabetes	8–12	ESRD	Albuminuria, eGFR, HbA1c

Pena MJ et al. Nephrol Dial Transplant. 2015;30:86–95

Biomarkers for DKD prediction



Zurbig P et al. Diabetes. 2012;61:3304–3313

Conclusions

Results from studies on cardiorenal protection with new classes of anti-hyperglycemic drugs may prompt:

- ❖ lowering of eGFR threshold for SGLT2-i treatment;
- ❖ use of agents with proven DKD benefit in primary prevention of DKD;
- ❖ utilization of these drugs for renal protection also in patients with type 1 diabetes.

Future studies may provide evidence for:

- ❖ new «pathogenic» drugs for renal protection;
- ❖ reconsideration of treatment targets;
- ❖ effective treatment for the new DKD phenotypes;
- ❖ Biomarkers for improving DKD prediction beyond albuminuria and eGFR.