Misure di intervento farmacologico per la prevenzione primaria e secondaria degli eventi cardiovascolari nei pazienti con diabete tipo 2

FRANCESCO GIORGINO, M.D., PH.D.
PROFESSOR OF ENDOCRINOLOGY

DEPARTMENT OF EMERGENCY AND ORGAN TRANSPLANTATION
SECTION OF INTERNAL MEDICINE, ENDOCRINOLOGY,
ANDROLOGY AND METABOLIC DISEASES

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Il Prof Francesco Giorgino dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

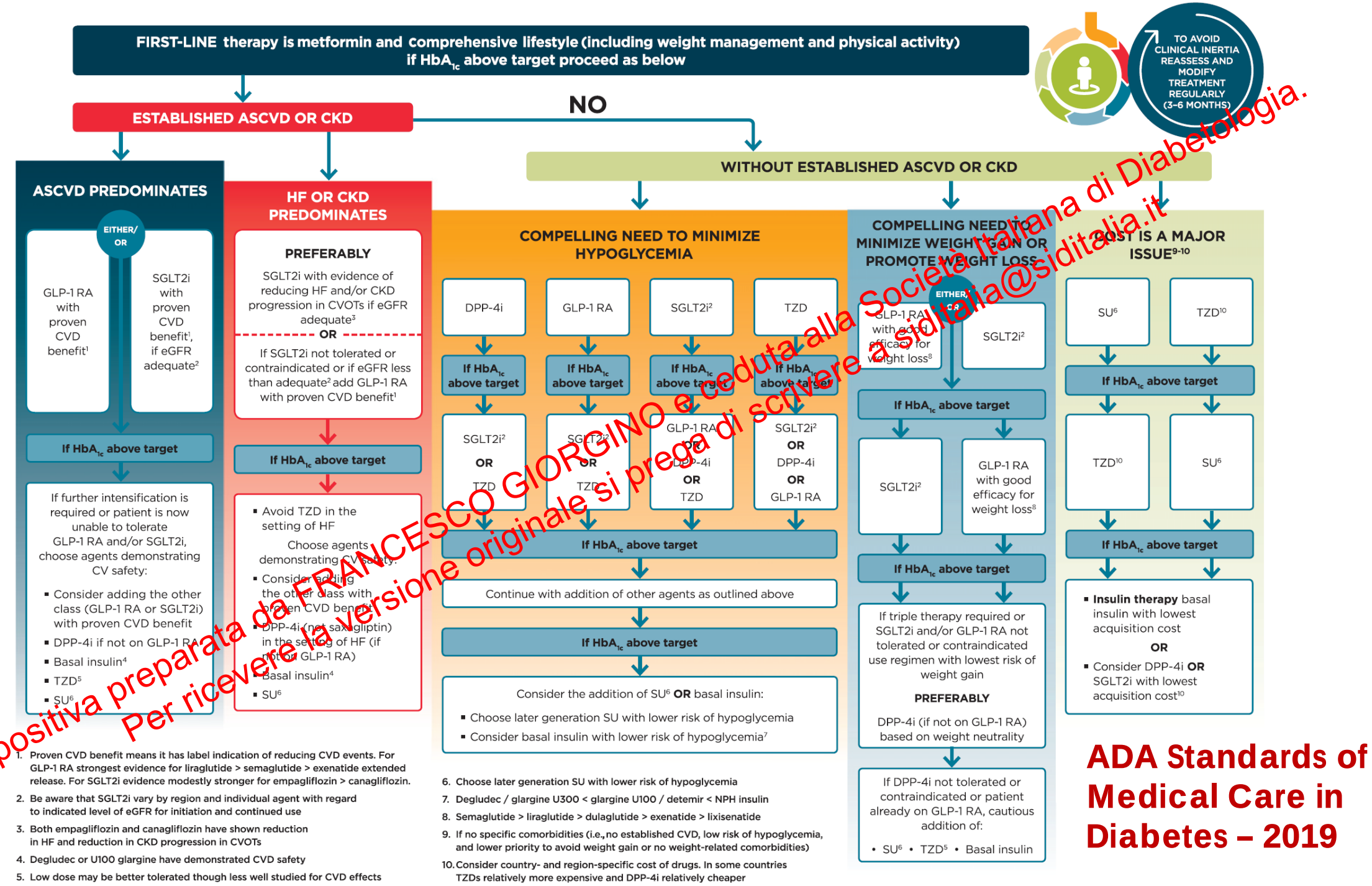
AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, Sanofi, NovoNordisk, Ipsen, Roche Diagnostics, Bayer, Lifescan, BMS, MSD, Novartis, Takeda, Sigma-Tau, Menarini Bruno Framaceutici

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Control of CV Risk Factors in Diabetes

Risk Factor	General Target	More Aggressive Target	Treatment	Drugs to be Used in Special Patients' Populations
HbA1c (%)	<7.0	<6.5% young, long life expectancy, short-duration T2D, well-controlled T2D, no CVD, no hypoglycemia	Lifestyle intervention Metformin, SU/glinide, pioglitazone, insulin, GLP-1 RA, DPP-4 I, SGLT2-I, acarbose	SGLT2-I in patients with CVD (empagliflozin, canagliflozin), HF (?) GLP-1 RA in patients with CVD (liraglutide)
Blood pressure (mmHg)	<140/90	<130/80 high risk of stroke/CVD high risk of nephropathy (?) high risk of retinopathy (?)	DASH dietary pattern ACE-I, ARB, thiazide-like diuretics, or dihydropyridine CCB	2-drug approach if >160/100 ACE-I or ARB in patients with micro/macro-albuminuria
LDL-C Triglyceride HDL-C (mg/dL)	<100 <150 >40/50	<70 / high intensity statin very high CV risk (?) evidence of CVD	Lifestyle intervention Statins PCSK9 I	Simvastatin + ezetimibe in patients post-ACS Statin + fenofibrate in patients with triglyceride >204, HDL-C <34
Platelet aggregation	No	Yes in: >50 yrs + 1 RF (?) evidence of CVD	ASA (clopidorel)	ASA + ticagrelor in patients with previous MI (?)

ASA, acetylsalicylic acid; ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; ACS, acute coronary syndrome; CCB, calcium channel blocker; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MI, myocardial infarction; PCSK9-I, PCSK9 inhibitor; RF, risk factor; SGLT2-I, SGLT2 inhibitor; T2D, type 2 diabetes.



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 hypoglycemia
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 hypoglycemia, 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

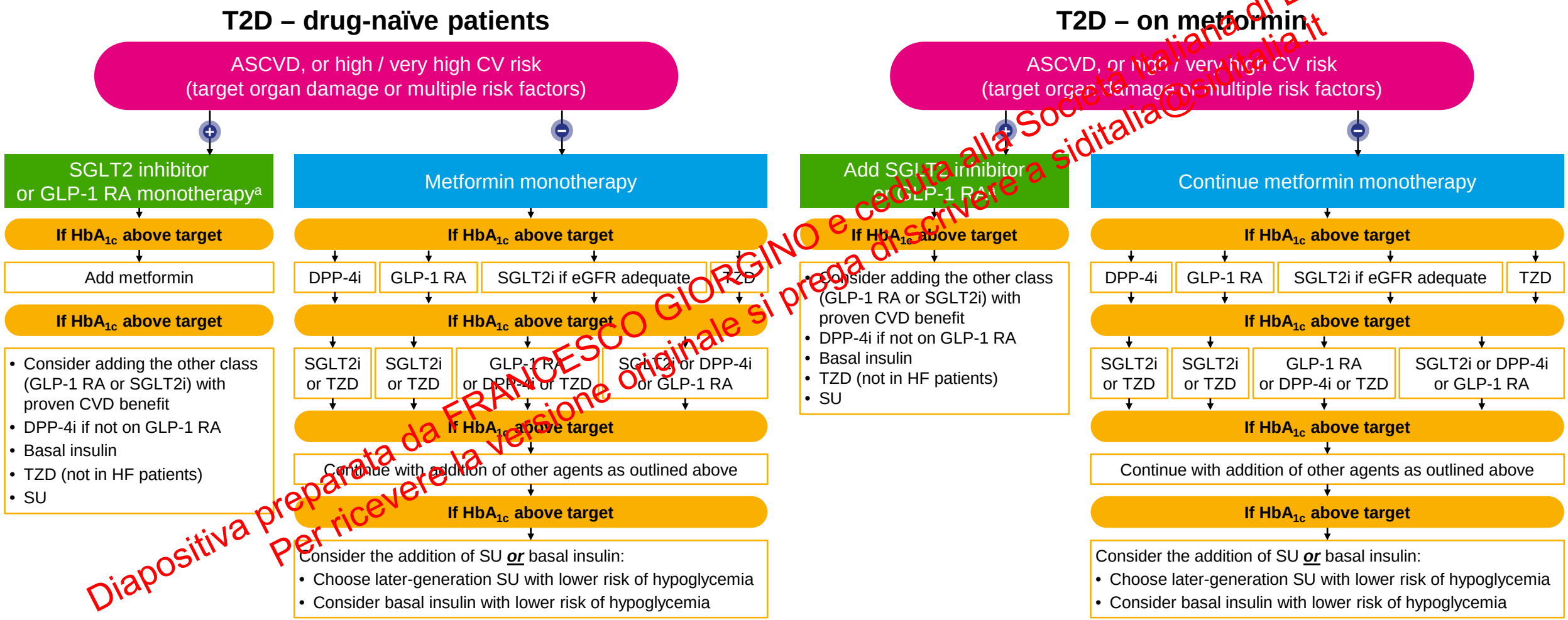
ADA Standards of Medical Care in Diabetes – 2019

This patient's CV risk according to ESC:

Very high risk	Patients with diabetes and established CVD **Or** other target organ damage[a] **Or** three or more major risk factors[b] **Or** early onset T1D of long duration (>20 years)
High risk	Patients with diabetes duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1D aged <35 years or T2D aged <50 years) with DM duration <10 years without other risk factors

[a]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy; [b]Age, hypertension, dyslipidemia, smoking, obesity
CV, cardiovascular; CVD, cardiovascular disease; T1D, Type 1 diabetes; T2D, Type 2 diabetes
Cosentino F, et al. Eur Heart J 2019;ehz 486:1–69

The 2019 ESC/EASD guidelines on diabetes, prediabetes, and CVD highlight the importance of managing CV risk



[a]Use drugs with proven CV benefit

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SU, sulfonylurea; T2D, Type 2 diabetes; TZD, thiazolidinedione

Cosentino F, et al. *Eur Heart J* 2019;0:1–69

2019 ADA Recommendations for Statin and Combination Treatment in People with Diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite r dose, consider adding additional LDL-lo ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥ dose, consider add ezetimibe or PCSK9 inhibitor)

‡Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL-cholesterol >100 mg/dL (2.6 mmol/L), high e, smoking, y disease, and family history ASCVD.

‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors.

*In addition to lifestyle therapy.

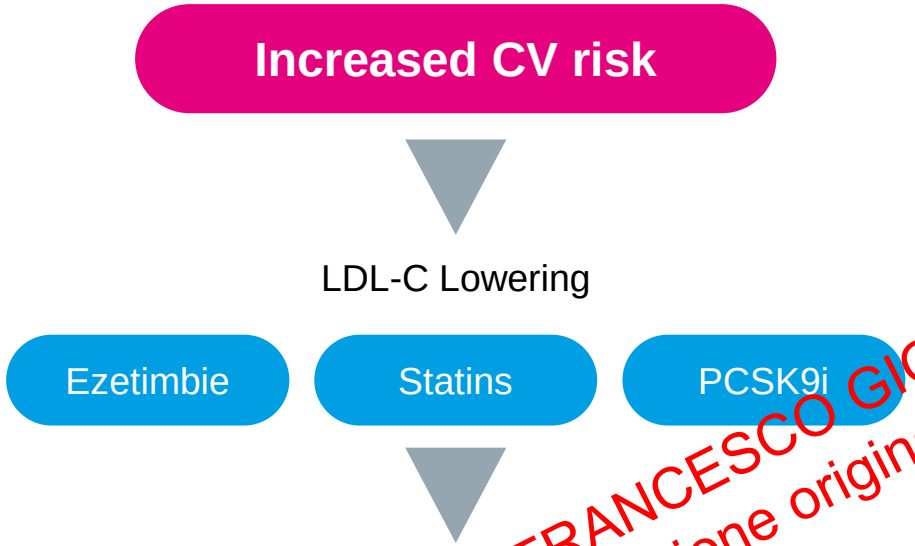
^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.

#Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction.

Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Therapeutic options for the management of dyslipidemia and HF in patients with high CV risk and HF

Available therapies for dyslipidemia management[1]



Elevated Triglycerides

- Icosapent ethyl
- ? Future agents

Decreased HDL-C

- No evidence-based treatment
- Stress lifestyle modification / address other risk factors

Increased Lipoprotein (a)

- ? Future targeted therapies
- Consider antiplatelet Rx

ESC recommendations for the management of dyslipidemia with lipid-lowering drugs[2]

Treatment		
Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient and the recommended LDL-C (or non-HDL-C) target levels.	I	A
If the target LDL-C is not reached, combination therapy with ezetimibe is recommend.	I	B
In patients at very high CV, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended.	I	A
Lifestyle intervention (with a focus on weight reduction, and decreased consumption of fast-absorbed carbohydrate and alcohol) and fibrates should be considered in patients with low HDL-C and high triglyceride levels.	IIa	B
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
Statins should be considered in patients with T1DM at high CV risk, irrespective of the baseline LDL-C level.	IIa	A
Statins may be considered in asymptomatic patients with T1D beyond the age of 30 years.	IIb	C
Statins are not recommended in women in childbearing potential.	III	A

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with implantable defibrillator; CV, cardiovascular; DM, diabetes mellitus; ESC, European Society of Cardiology; GLP-1 glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LDL-C, low-density lipoprotein cholesterol MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes mellitus

1. Berman AH, and Blankstein R. *Current Cardiology Reports* 2019 [ePub ahead of print]; 2 Cosentino F, et al. *Eur Heart J* 2019 [Epub ahead of print]

2019 ESC/EASD guidelines for the use of aspirin for the primary prevention of CV events in diabetes patients

Recommendations for the use of antiplatelet therapy in primary prevention in patients with diabetes

Recommendations	Class [a]	Level [b]
In patients with DM at high/very high risk,[c] aspirin (75-100 mg/day) may be considered in primary prevention in the absence of clear contraindications. [d] [231]	IIb	A
In patients with DM at moderate CV risk,[c] aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding. [232,235]	IIa	A

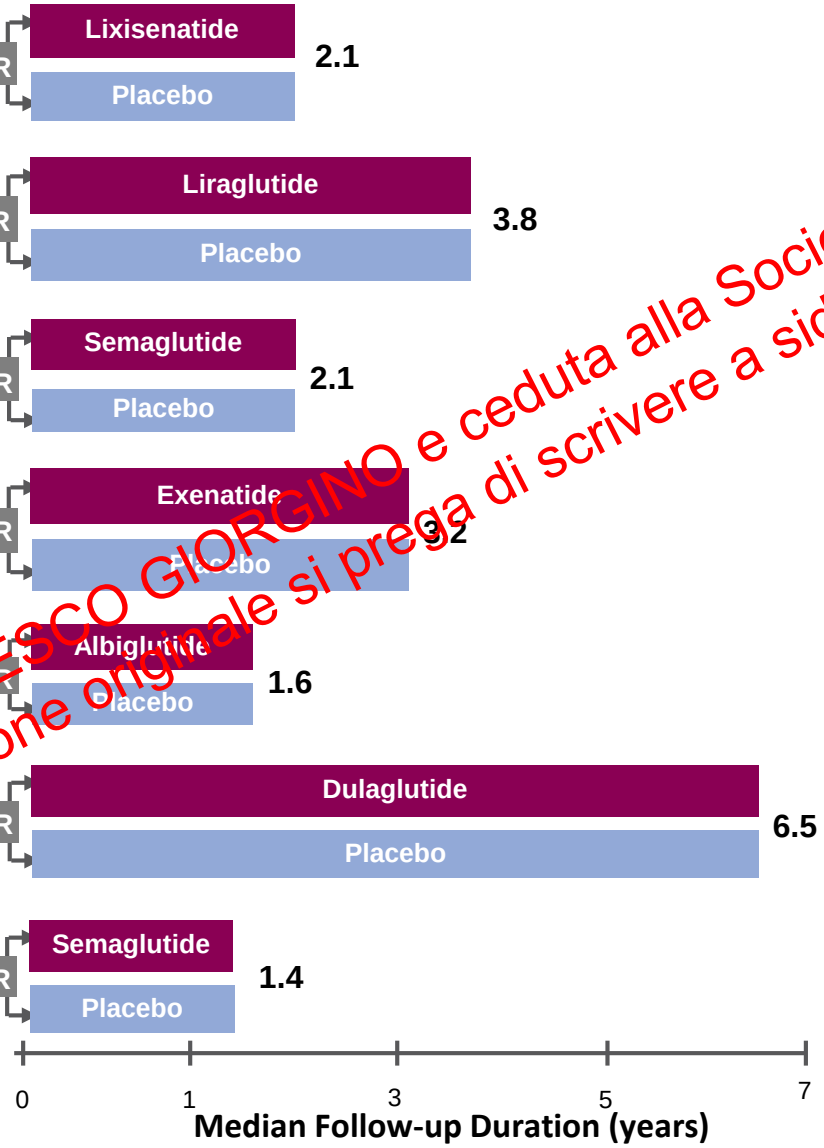
2019 ESC/EASD guidelines for the use of APT in post-ACS patients with diabetes

Recommendations	Class[a]	Level[b]
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in patients with DM.	I	A
Treatment with a $P2Y_{12}$ receptor blocker ticagrelor prasugrel is recommended in patients with DM and ACS for 1 year with aspirin, and in those who undergo PCI or CABG.	I	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving DAPT or oral anticoagulant monotherapy who are at high risk of gastrointestinal bleeding.	I	A
Clopidogrel is recommended as an alternative anti-platelet therapy in case of aspirin intolerance.	I	B
Prolongation of DAPT beyond 12 months should be considered, for up to 3 years, in patients with DM who have tolerated DAPT without major bleeding complications.	IIa	A
The addition of a second antithrombotic drug on top of aspirin for long-term secondary prevention should be considered in patients without high bleeding risk.[c]	IIa	A

[a]Class of recommendation; [b]Level of evidence; [c]Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2
ACS, acute coronary syndrome; APT, anti-platelet therapy; CABG, coronary artery bypass graft; DAPT, dual anti-platelet therapy; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; PCI. Percutaneous coronary intervention
Consentino F, et al. *Eur Heart J* 2019;00:1–69

Completed GLP-1 RA CVOTs

	Key inclusion criteria	HbA_{1C} (%)	Median follow-up duration (y)	Drug exposure time (y)	Primary End point
ELIXA (1) N=6068	ACS within 180 days ≥30y	5.5-11.0	Lixisenatide 2.1 / Placebo	1.9 / 2.0	MACE-4 (non-inferiority)
LEADER® (2) N=9340	≥50y with CVD/renal dysfunction/HF, or ≥60y with CV RFs	≥7.0	Liraglutide 3.8 / Placebo	3.5 / 3.5	MACE-3 (non-inferiority for safety/ superiority for efficacy)
SUSTAIN-6 (3) N=3297	≥50y with CVD, or ≥60y with subclinical CVD	≥7.0	Semaglutide 2.1 / Placebo	1.8 / 1.9	MACE-3 (non-inferiority)
EXSCEL (4) N=14752	Established CVD as well as primary prevention (70/30 split), ≥18y	6.5-10.0	Exenatide 3.2 / Placebo	2.4 / 2.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
HARMONY (5) N=9463	≥40y with established CVD	≥7.0	Albiglutide 1.6 / Placebo	1.4 / 1.3	MACE-3 (non-inferiority for safety/ superiority for efficacy)
REWIND (6,7) N=9901	≥50y with established clinical vascular disease, ≥55y with subclinical vascular disease, or ≥60y with ≥2 CV RFs	≤9.5	Dulaglutide 6.5 / Placebo	5.3 / 5.4	MACE-3 (superiority for efficacy)
PIONEER 6 (8) N=3183	≥50y with CVD, or ≥60y with CV RFs	≥7.0	Semaglutide 1.4 / Placebo	NR / NR	MACE-3 (non-inferiority for safety)



ACS, acute coronary syndrome; CV, cardiovascular; CVD, CV disease; CVOTs, cardiovascular outcomes trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; HF, heart failure; MACE, major adverse CV events; NR, not reported; R, randomisation; RFs, risk factors; y, years.

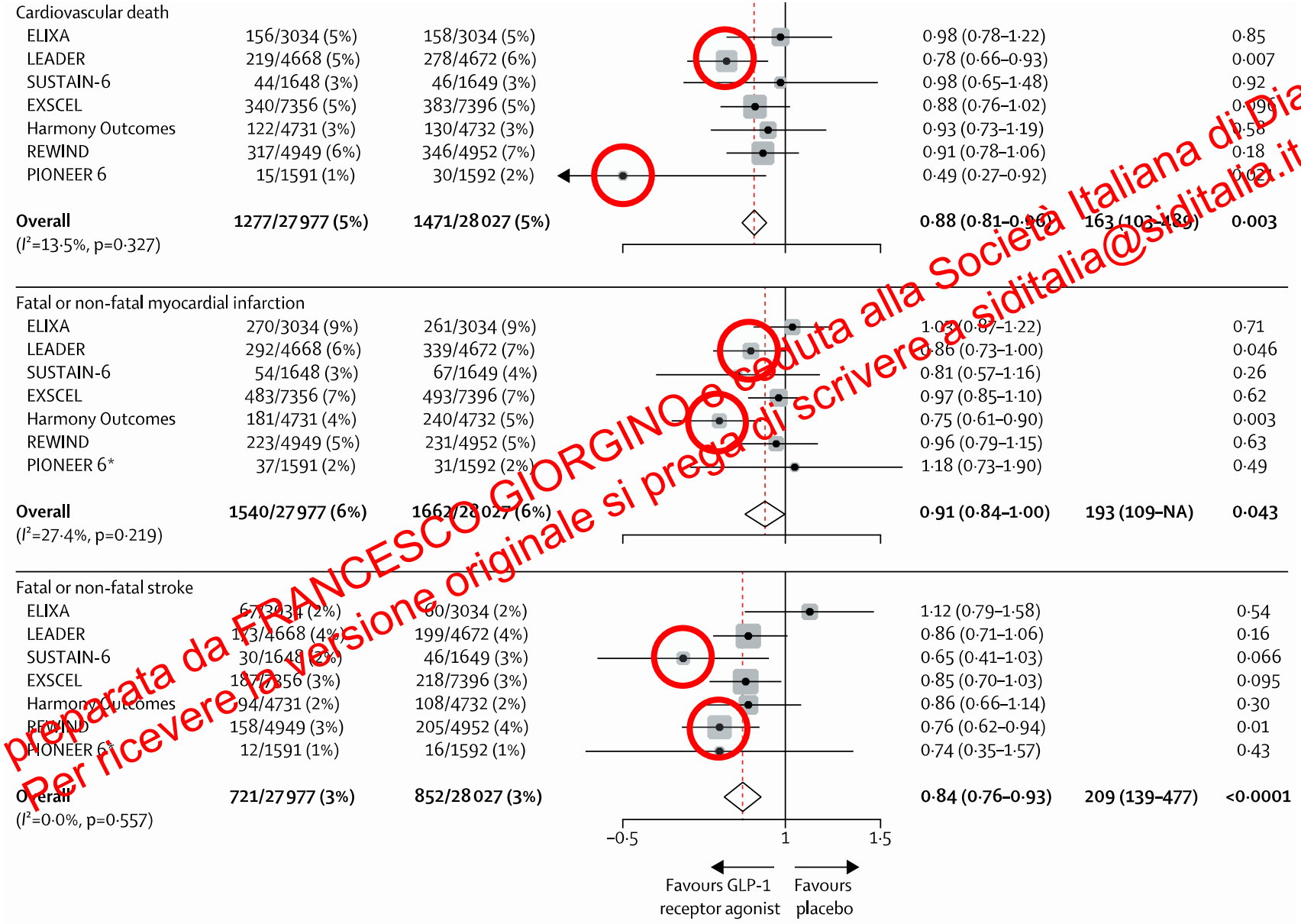
[1]Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
[2]Marso SP, et al. *N Engl J Med* 2016;375:311–322
[3]Marso SP, et al. *N Engl J Med* 2016;375:1834–1844
[4]Holman RR, et al., *N Engl J Med* 2017;377:1228–1239
[5]Hernandez AF, et al. *Lancet* 2018;392(10157):1519–1529
[6]Gerstein HC, et al. *Diabetes Obes Metab* 2018;20:42–49
[7]https://clinicaltrials.gov/ct2/show/NCT01394952
[8]Husain M, et al *N Eng J Med* 2019

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11) p=0.17	**Main Outcomes**
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74–1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	

Pfeffer, M.A. *et al.* (2015) *N. Engl. J. Med.* 373, 2247–2257; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 311–322; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 1834–1844; Holman, R.R. *et al.* (2017) *N. Engl. J. Med.* 377, 1228–1239; Hernandez, A.F. *et al.* (2018) *Lancet* 392, 1519–1529; Gerstein, H.C. *et al.* (2019) *Lancet* DOI: 10.1016/S0140-6736(19)31149-3; Husain, M. *et al.* (2019) *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1901118.

Caruso I et al., *Trends Endocrinol Metab* 2019

Individual Components of the Primary Endpoint in GLP-1RA CVOTs



Kristensen S, et al, Lancet 2019

All-Cause Mortality and Hospitalization for Heart Failure in GLP-1RA CVOT

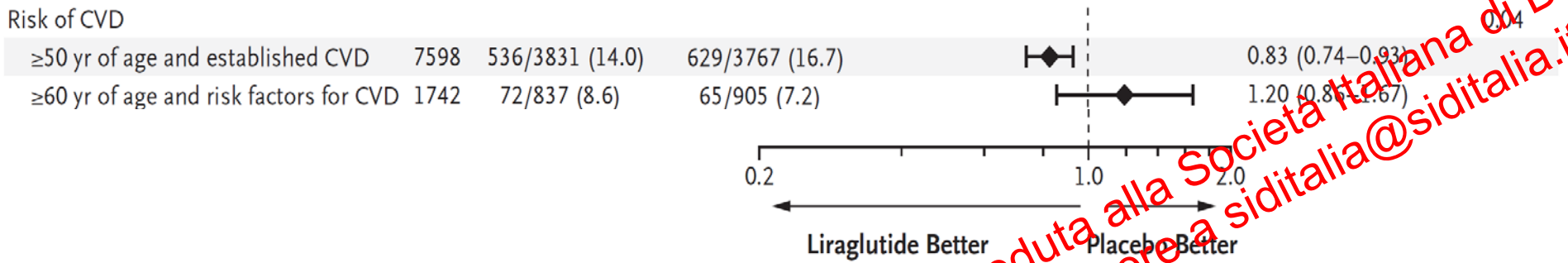
	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall (I^2=16·5%, p=0·304)	**1916/27977 (7%)**	**2246/28027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	78/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	11/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27977 (3%)**	**1016/28027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**

Kristensen S, et al, Lancet 2019

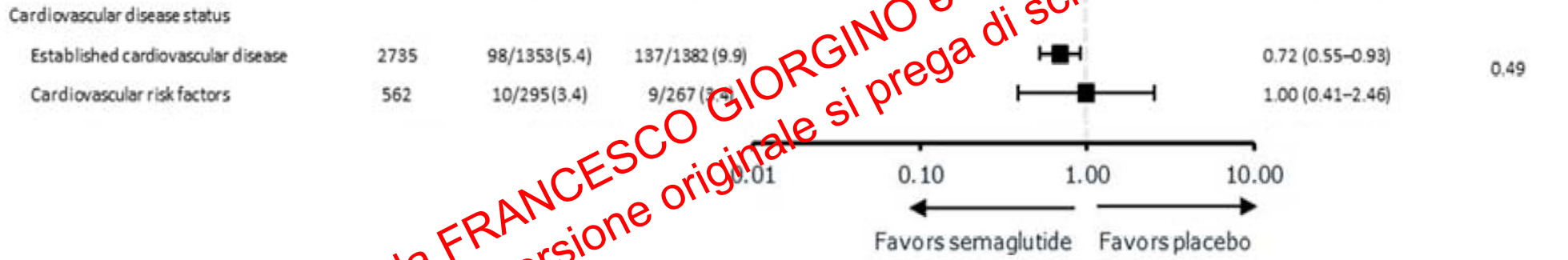
	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY	REWIND	PIONEER 6	
Diabetes duration (years)	9.3	12.8	13.9	12	14.1	10	14.9	**Baseline Risk Level**
Baseline HbA1c (%)	7.6	8.7	8.7	8.0	8.7	7.3	8.2	
Baseline BMI (kg/m²)	30.1	32.5	32.8	31.7	32.3	32.3	32.3	
History of CVD (%)	100	81.3	83	73.1	100	31.4	84.6	
Hypertension (%)	76.3	90	92.8	90.3	86.4	93.2	95.3	
eGFR <60 (%)	23.2	21.7	28.5	21.7	22.6	22.2	27	
Mortality rate (events/100 patient-yr)	3.1; 3.3	2.1; 2.5	1.8; 1.7	2.0; 2.3	2.4; 2.5	2.1; 2.3	1.1; 2.2	
MACE rate (events/100 patient-yr)	6.4; 6.3	3.4; 3.9	3.2; 4.4	3.7; 4.0	4.6; 5.9	2.4; 2.7	2.9; 3.7	
MACE HR	1.02 [95% CI 0.89–1.17])	**0.87 [95% CI 0.78–0.97] p=0.01**	**0.74 [95% CI 0.58–0.95] p=0.02**	0.91 [95% CI 0.83–1.00] p=0.06	**0.78 [95% CI 0.68–0.90] p=0.0006**	**0.88 [95% CI 0.79–0.99] p=0.026**	0.79 [95% CI 0.57-1.11] p=0.17	**Main Outcomes**
All-cause mortality HR	0.94 [95% CI 0.78–1.13]	0.85 [95% CI 0.74–0.97]	1.05 [95% CI 0.74 –1.50]	0.86 [95% CI 0.77–0.97]	0.95 [95% CI 0.79–1.16]	0.90 [95% CI 0.80–1.01]	0.51 [95% CI 0.31-0.84)	

Pfeffer, M.A. *et al.* (2015) *N. Engl. J. Med.* 373, 2247–2257; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 311–322; Marso, S.P. *et al.* (2016) *N. Engl. J. Med.* 375, 1834–1844; Holman, R.R. *et al.* (2017) *N. Engl. J. Med.* 377, 1228–1239; Hernandez, A.F. *et al.* (2018) *Lancet* 392, 1519–1529; Gerstein, H.C. *et al.* (2019) *Lancet* DOI: 10.1016/S0140-6736(19)31149-3; Husain, M. *et al.* (2019) *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1901118.

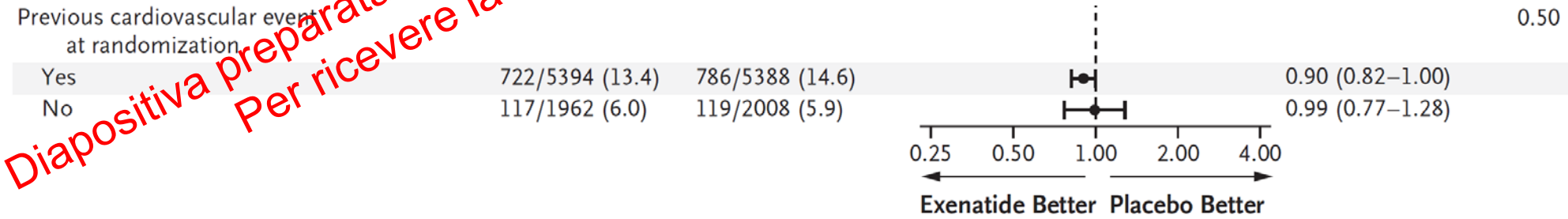
Primary Outcome in LEADER, SUSTAIN-6 and EXSCEL According to CVD – Subgroup Analysis



LEADER



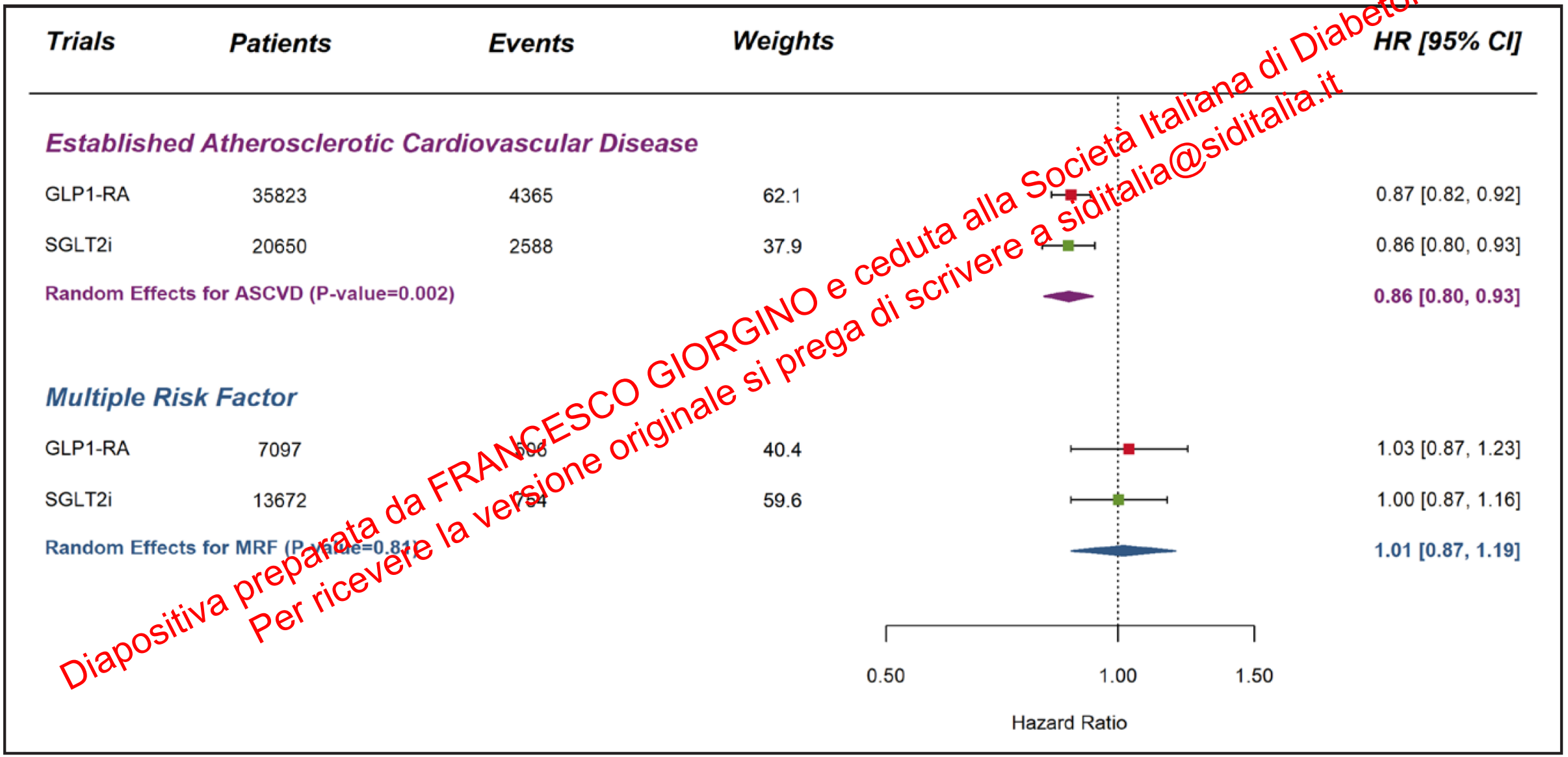
SUSTAIN-6



EXSCEL

Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med* 2017;377:1228–1239.

Meta-analysis of GLP-1RA and SGLT2i Trials on the Composite of MI, Stroke, and CV Death by the Presence of ASCVD

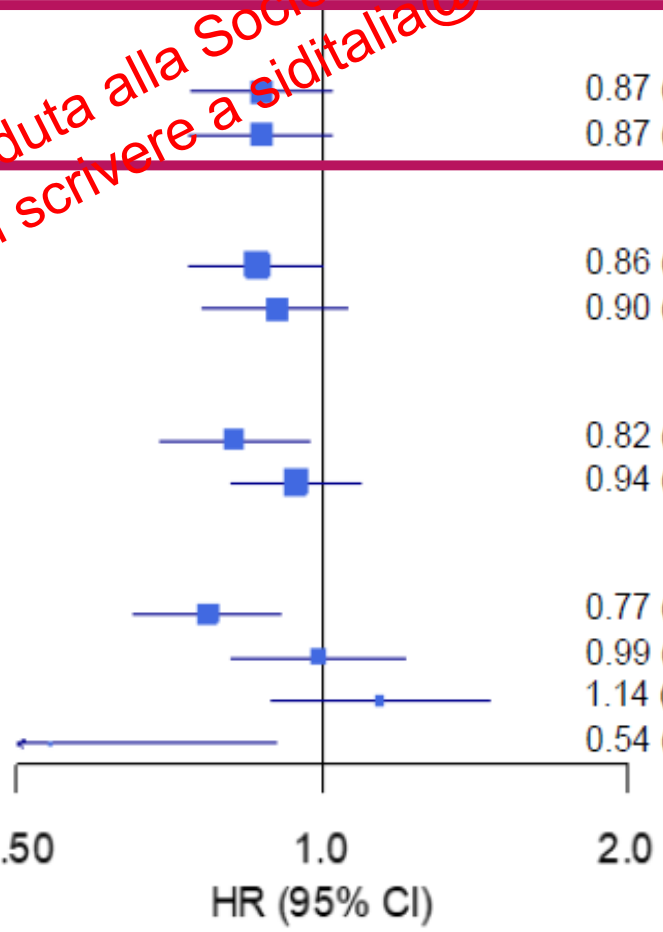


Zelniker TA, et al, Circulation 2019

REWIND
Dulaglutide CV Outcomes Trial

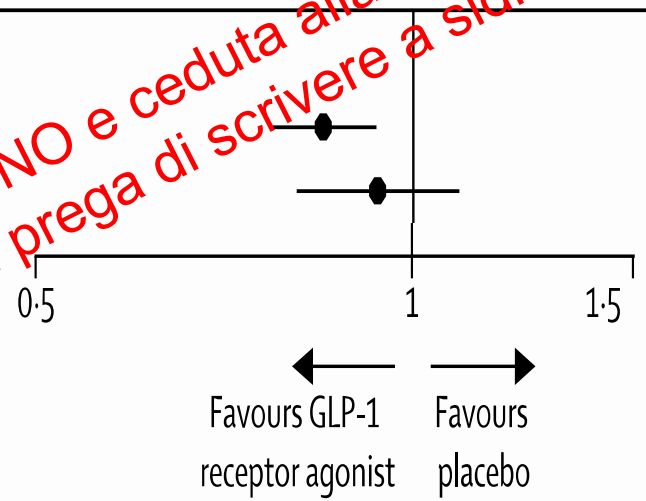
CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	
< 7.2%	263 /2329 (11.3)	2.2	289 /2324 (12.4)	2.4	0.90 (0.76-1.06)	0.746
BMI (kg/m^2)						
≥ 32	254 /2281 (11.1)	2.1	368 /2302 (13.4)	2.6	0.82 (0.69-0.96)	
< 32	340 /2667 (12.7)	2.5	355 /2650 (13.4)	2.7	0.94 (0.81-1.09)	0.214
Region						
Europe	248 /1174 (11.4)	2.2	315 /2165 (14.5)	2.9	0.77 (0.65-0.90)	
Latin America	191 /1514 (12.6)	2.6	190 /1510 (12.6)	2.6	0.99 (0.81-1.21)	
USA/Canada	131 /1032 (12.8)	2.4	117 /1039 (11.3)	2.1	1.14 (0.89-1.47)	
Asia Pacific	23 / 232 (9.9)	1.9	41 / 238 (17.2)	3.5	0.54 (0.32-0.89)	0.008



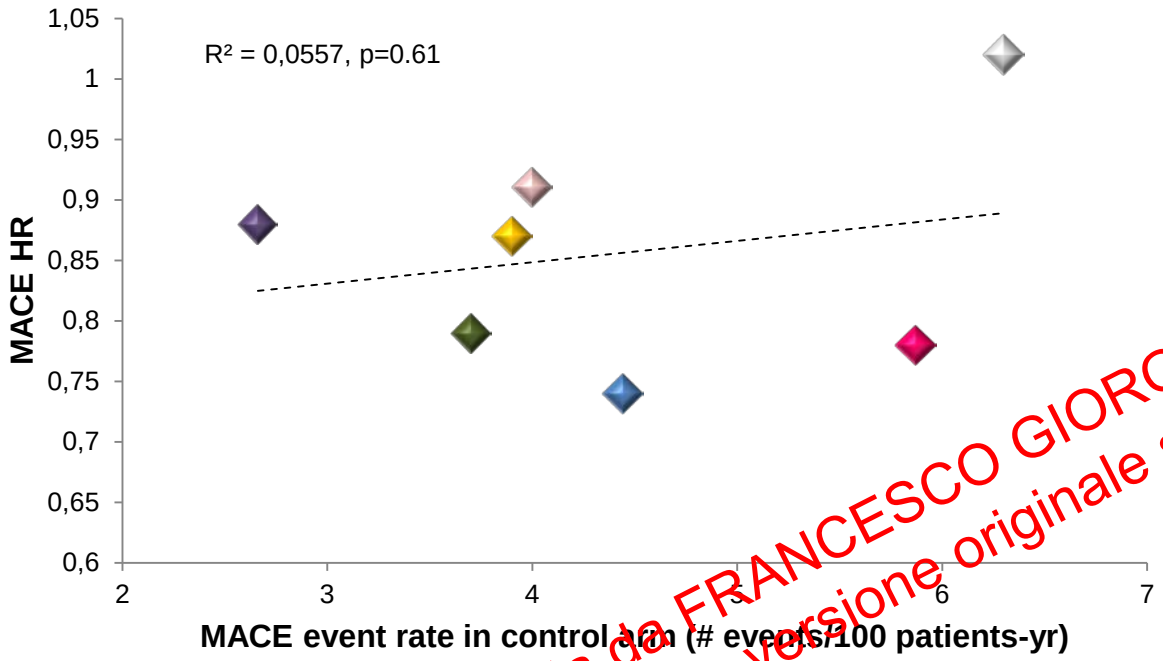
Meta-analysis of GLP-1RA Trials on the Composite of MI, Stroke, and CV Death by the Presence of ASCVD

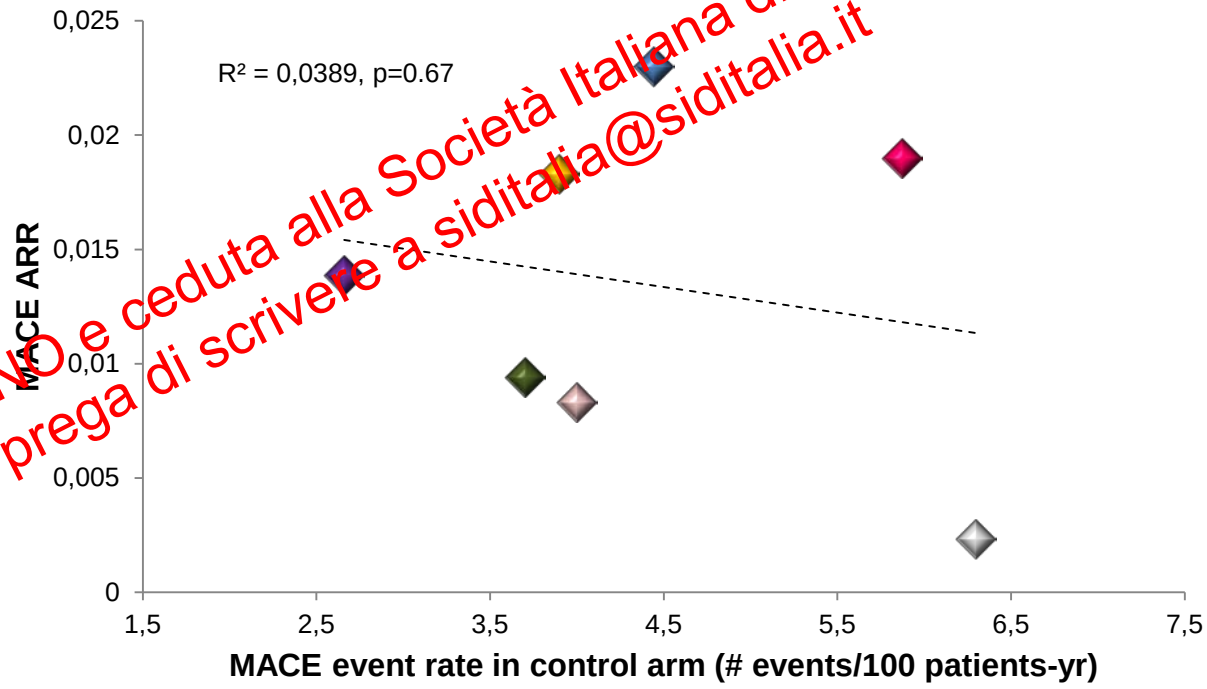
	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·22
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·79–0·94)	
No	480/6428 (7%)	518/6555 (8%)	0·95 (0·83–1·08)	



Kristensen S, et al, Lancet 2019

Correlation between CV Risk Level of Exposed Population and MACE ARR and HR



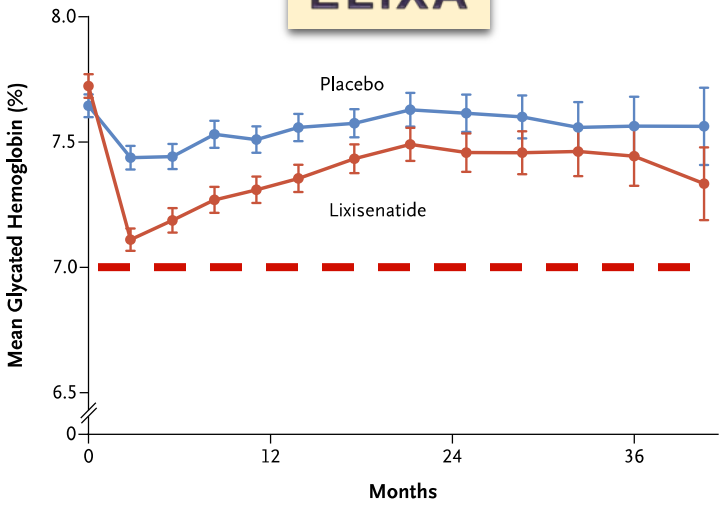


ELIXA LEADER SUSTAIN-6 EXSCEL HARMONY REWIND PIONEER 6

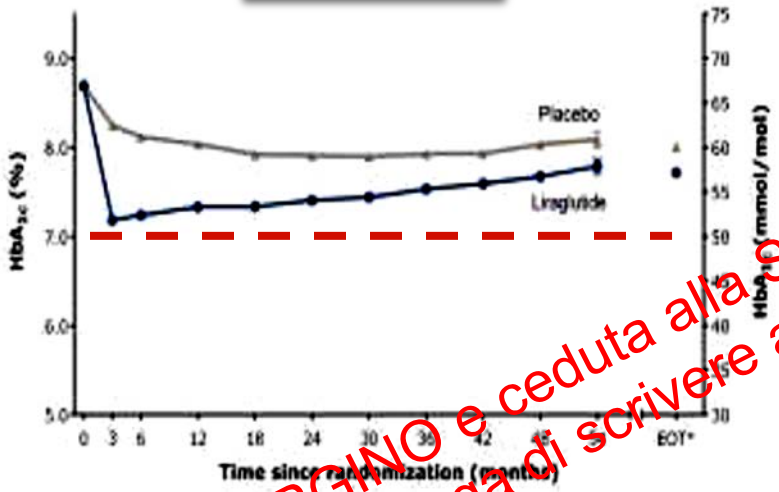
Caruso I et al., *Trends Endocrinol Metab* 2019

Change in HbA1c from Baseline throughout the Trial

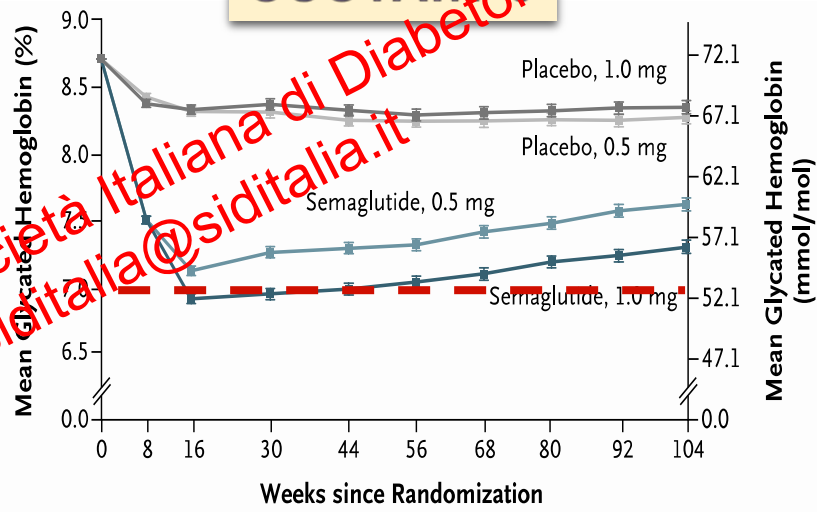
ELIXA



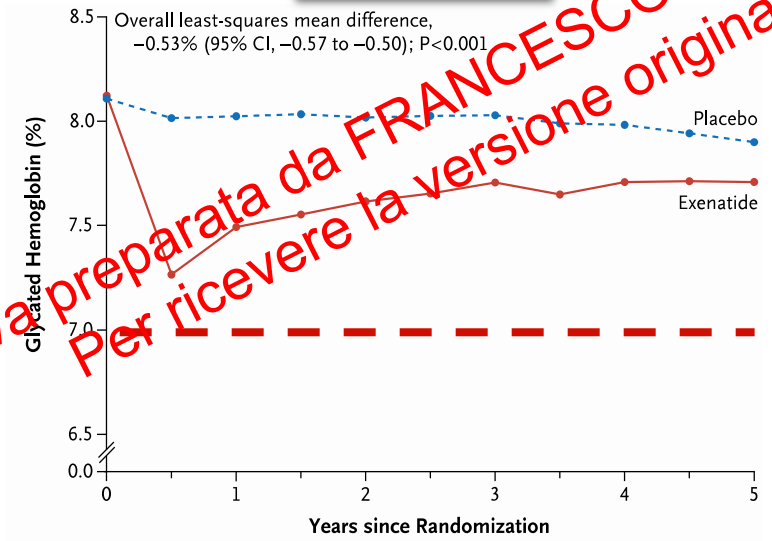
LEADER



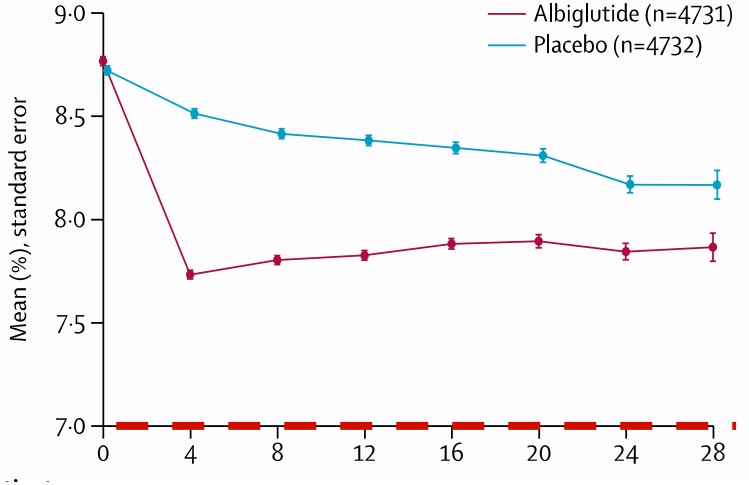
SUSTAIN-6



EXSCEL

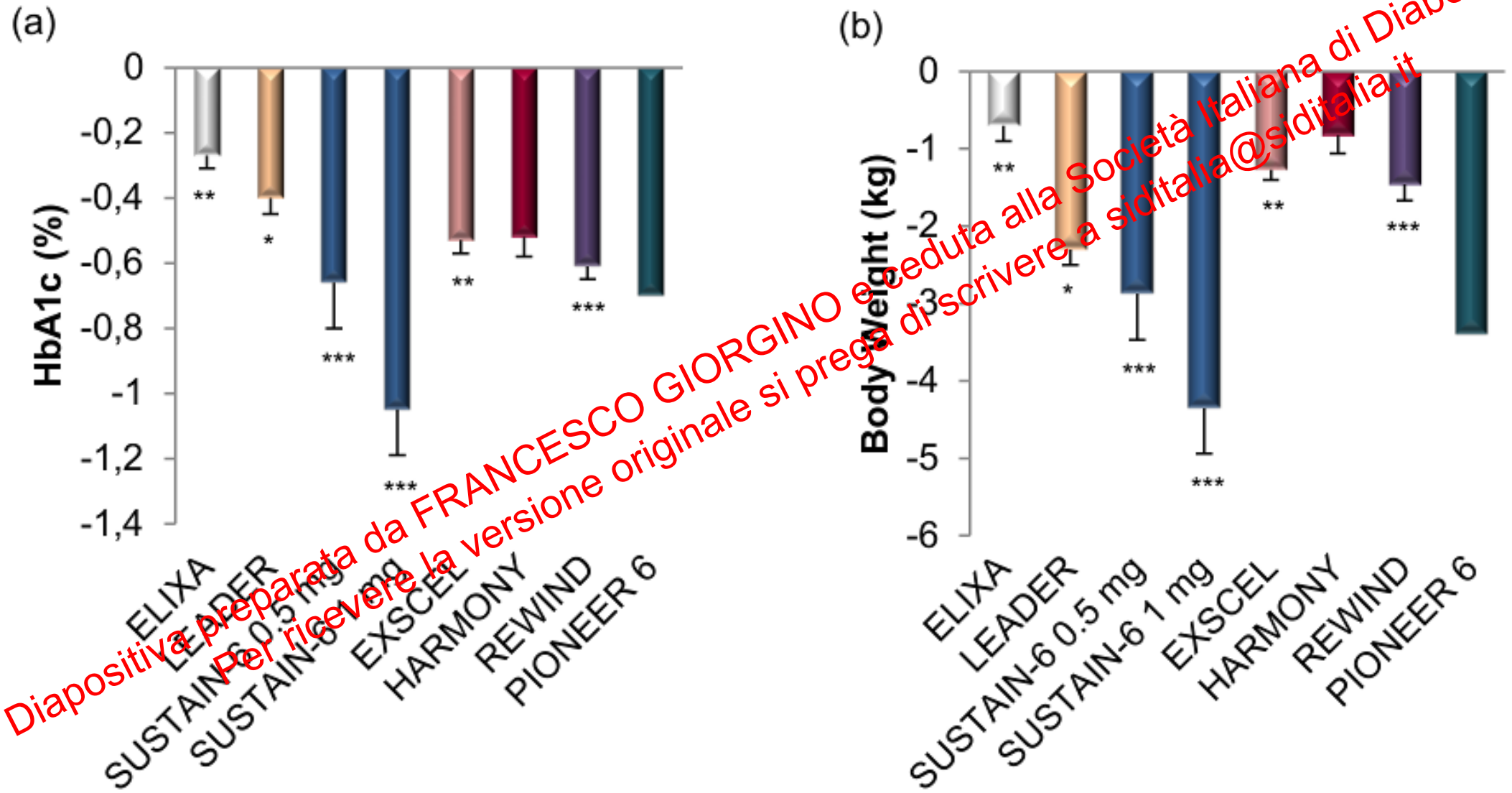


HARMONY



Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med* 2017;377:1228-1239; Hernandez A et al., *Lancet* 2018 Oct 1; pii: S0140-6736(18)32261-X.

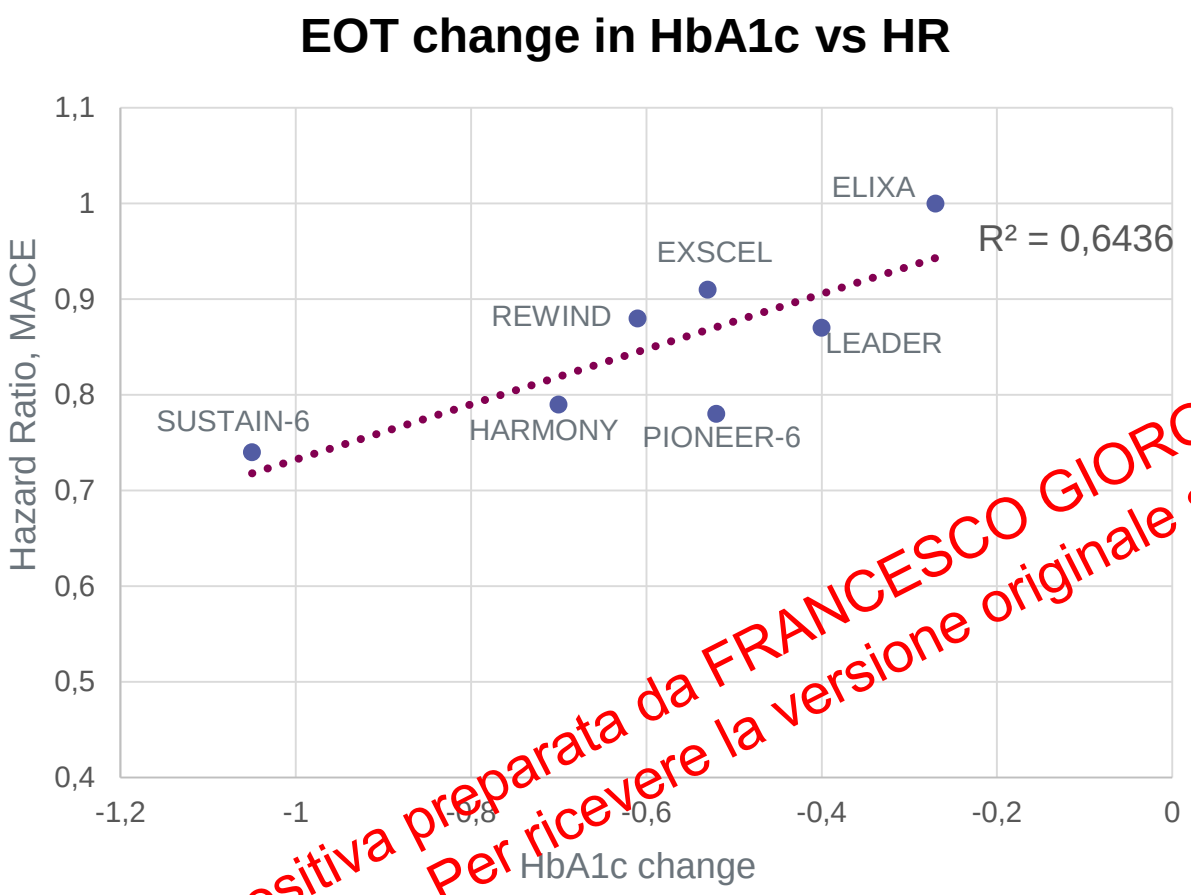
GLP-1 RA vs Usual Care: Changes in Factors Potentially Affecting CV Risk

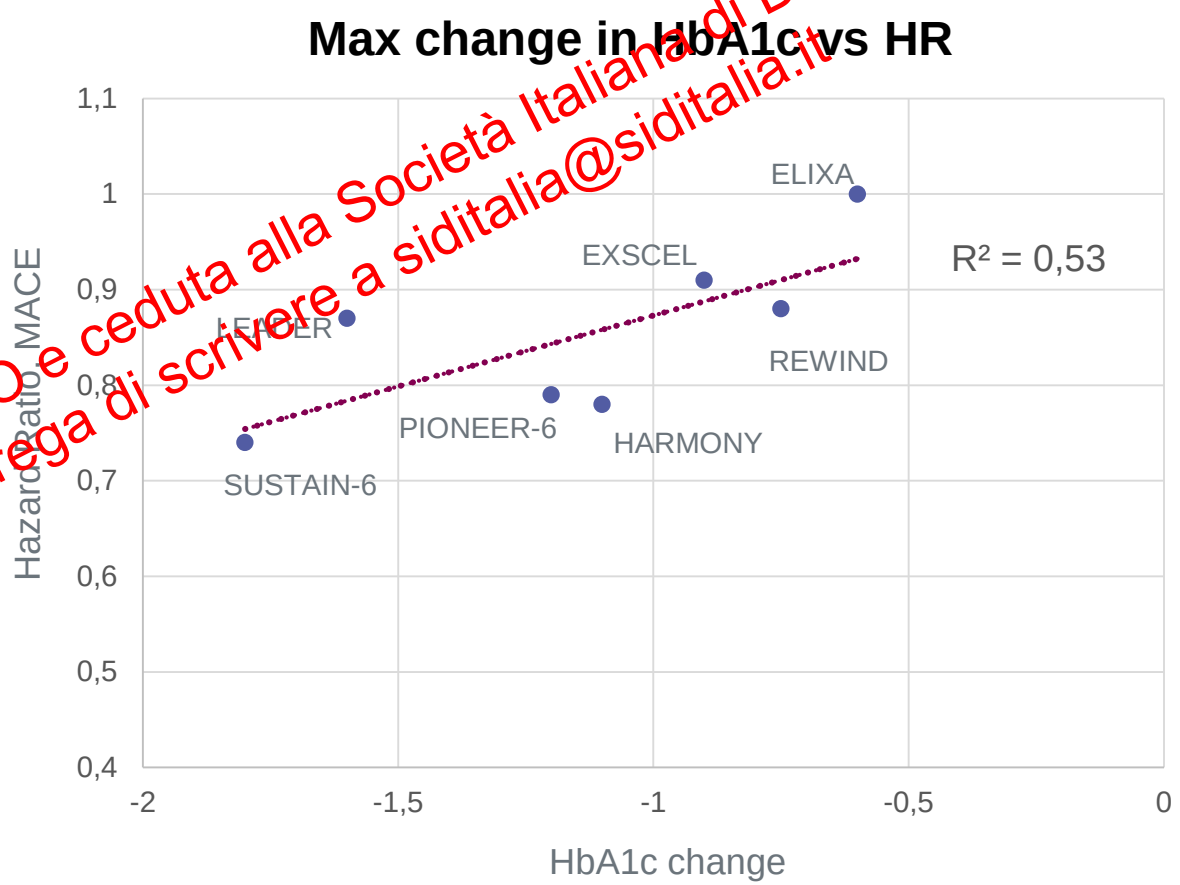


*p<0.05; **p<0.01;***p<0.001

Caruso I et al., *Trends Endocrinol Metab* 2019;30(9):578-589

Does Glycemia Matter?

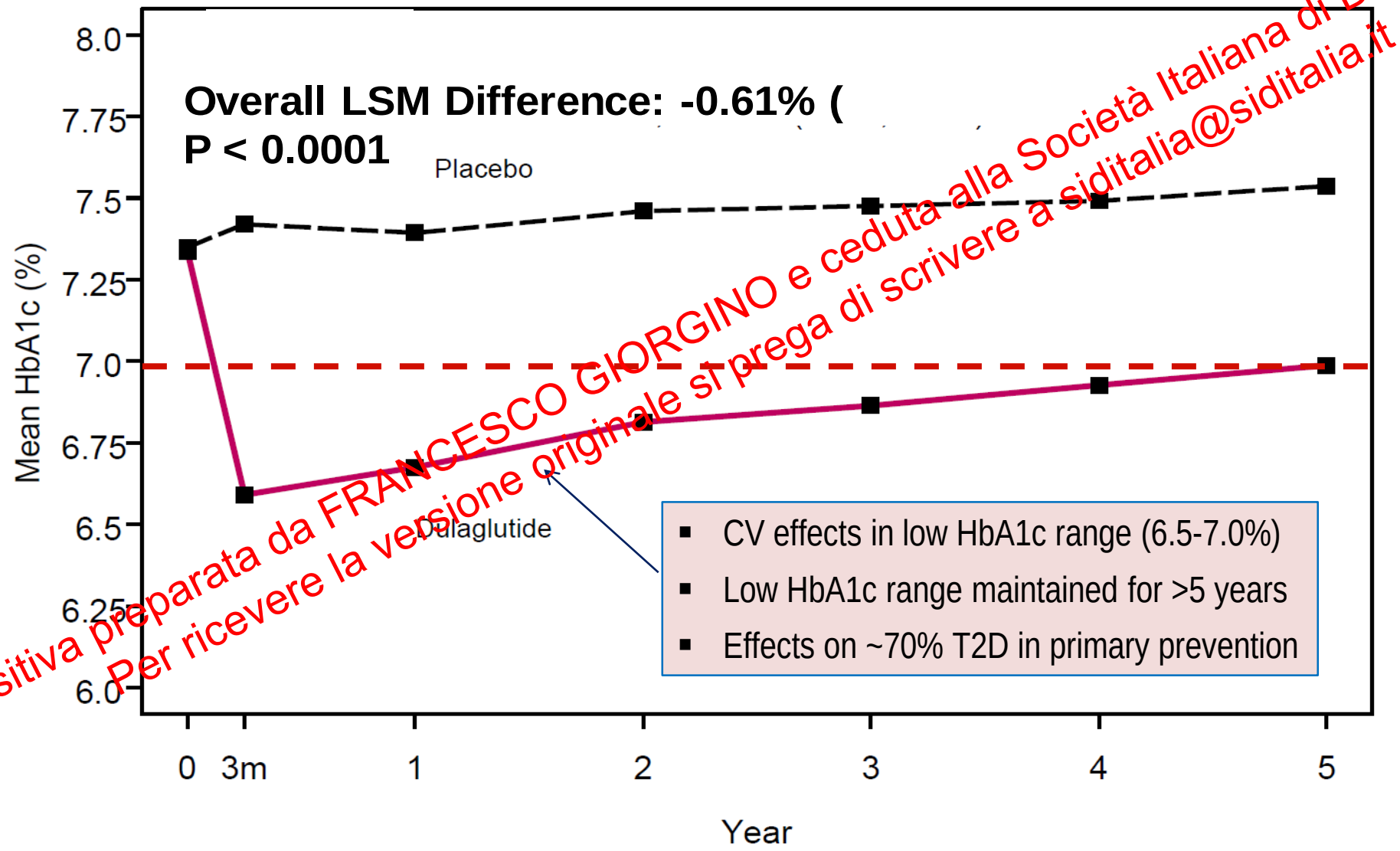




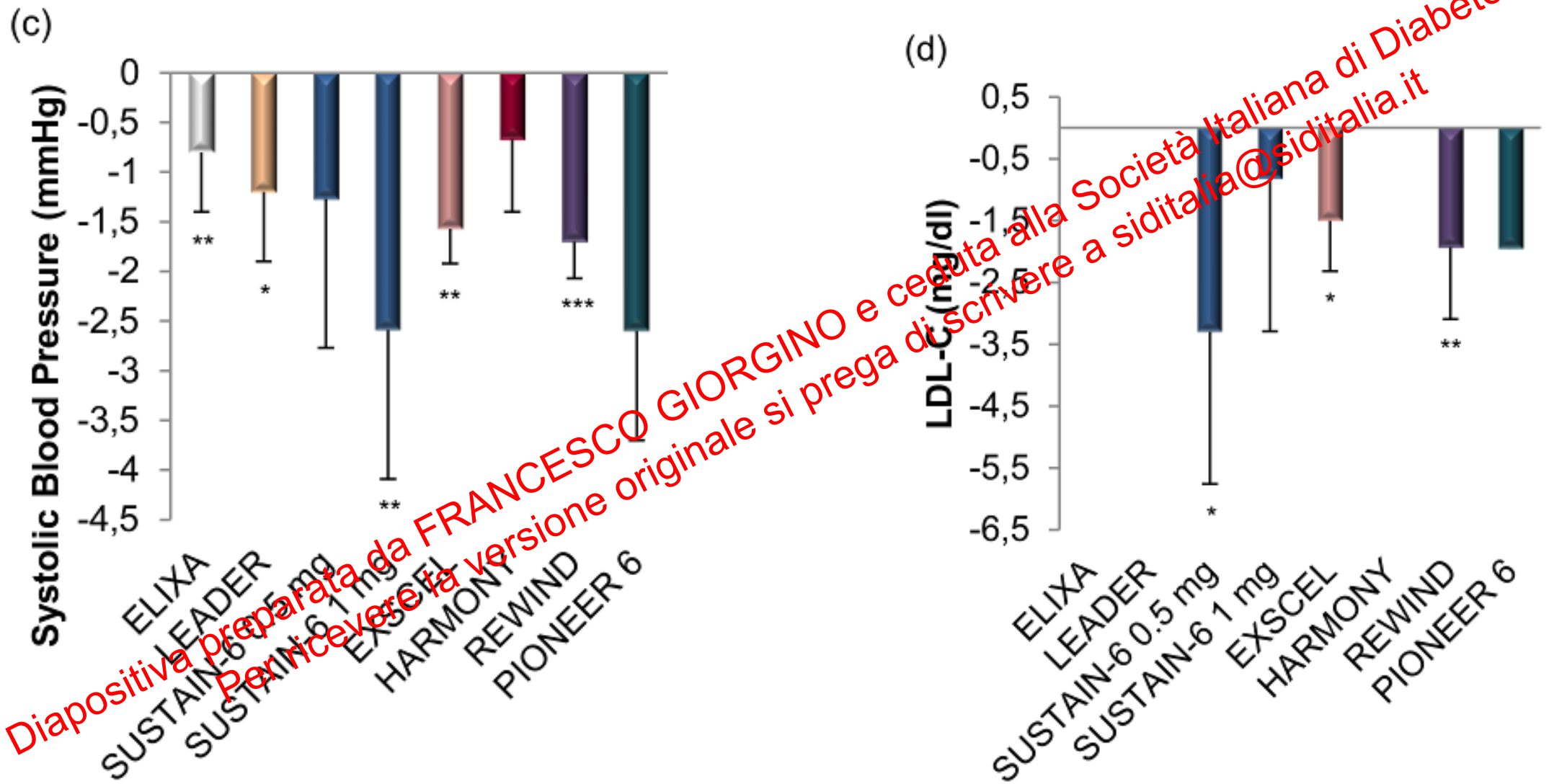
REWIND
Dulaglutide CV Outcomes Trial

Dulaglutide's Effect on HbA1c

Gerstein, H.C. *et al. Lancet* (2019) .1016/S0140-6736(19)31149-3



GLP-1 RA vs Usual Care: Changes in Factors Potentially Affecting CV Risk

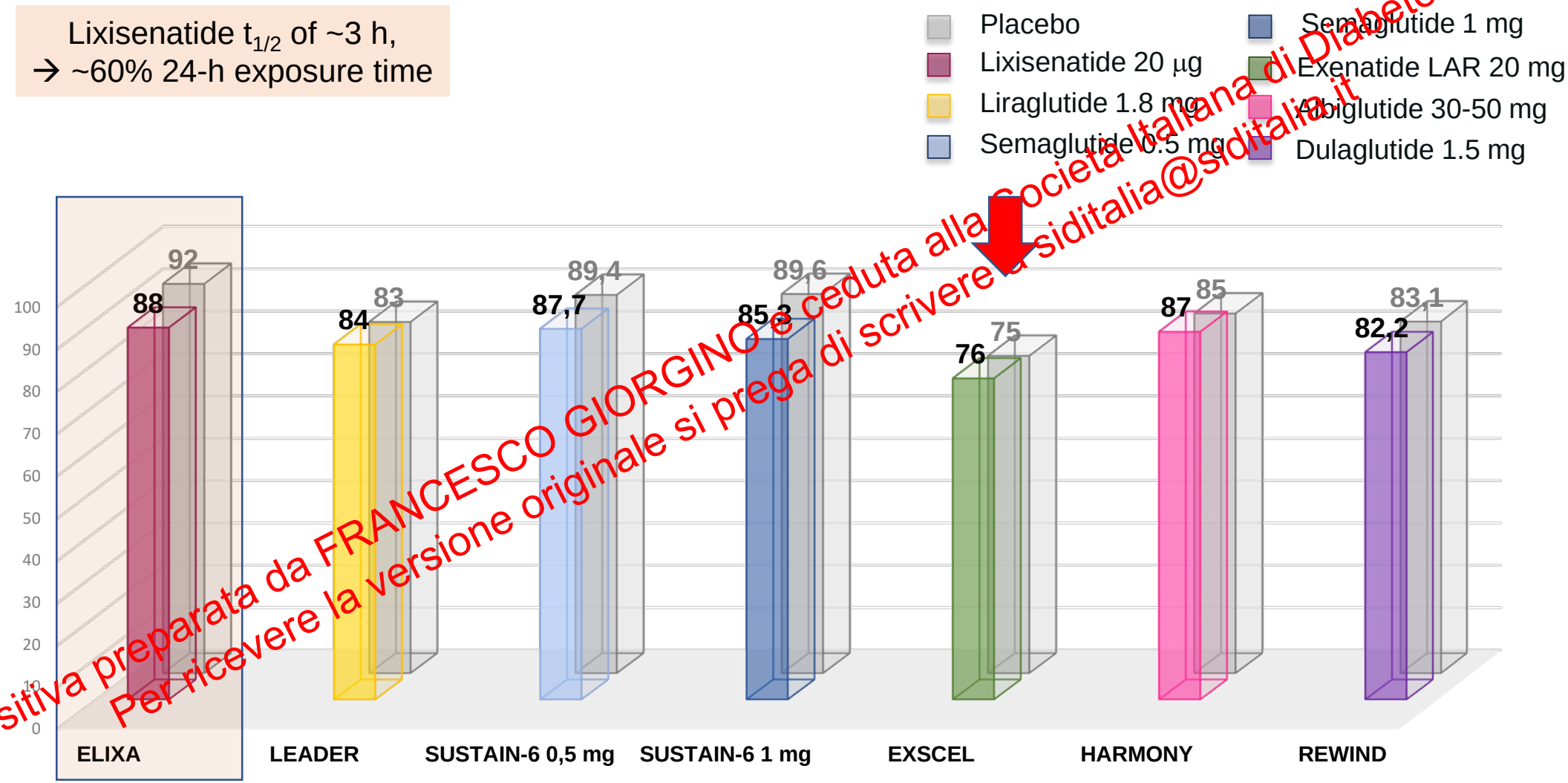


*p<0.05; **p<0.01;***p<0.001

Caruso I et al., *Trends Endocrinol Metab* 2019;30(9):578-589

Mean Percentage of Time That Participants Received the Trial Regimen

Lixisenatide $t_{1/2}$ of ~3 h,
→ ~60% 24-h exposure time

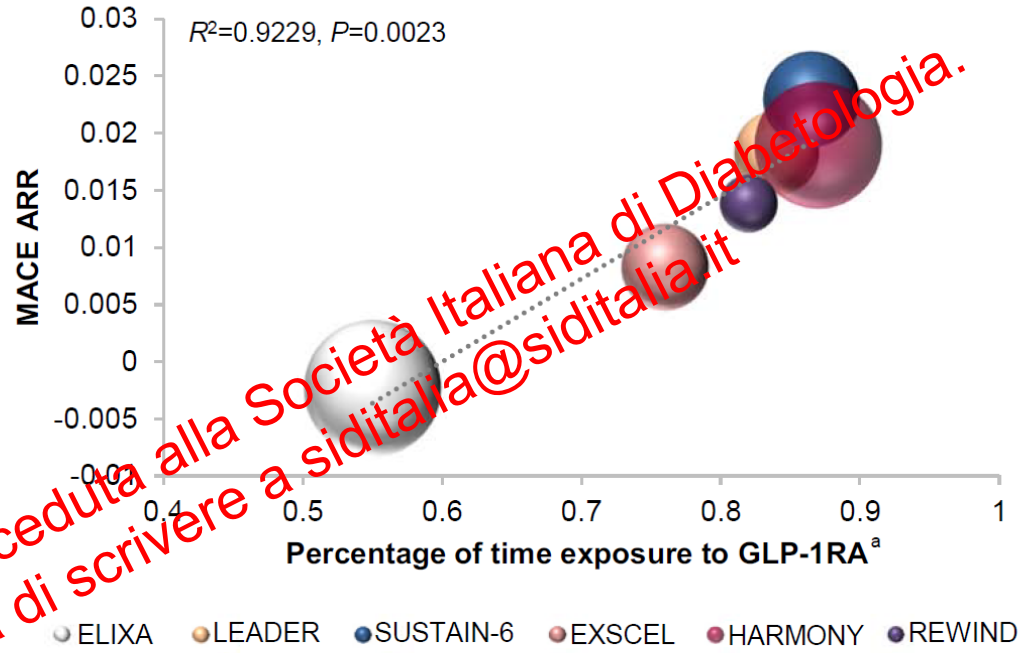


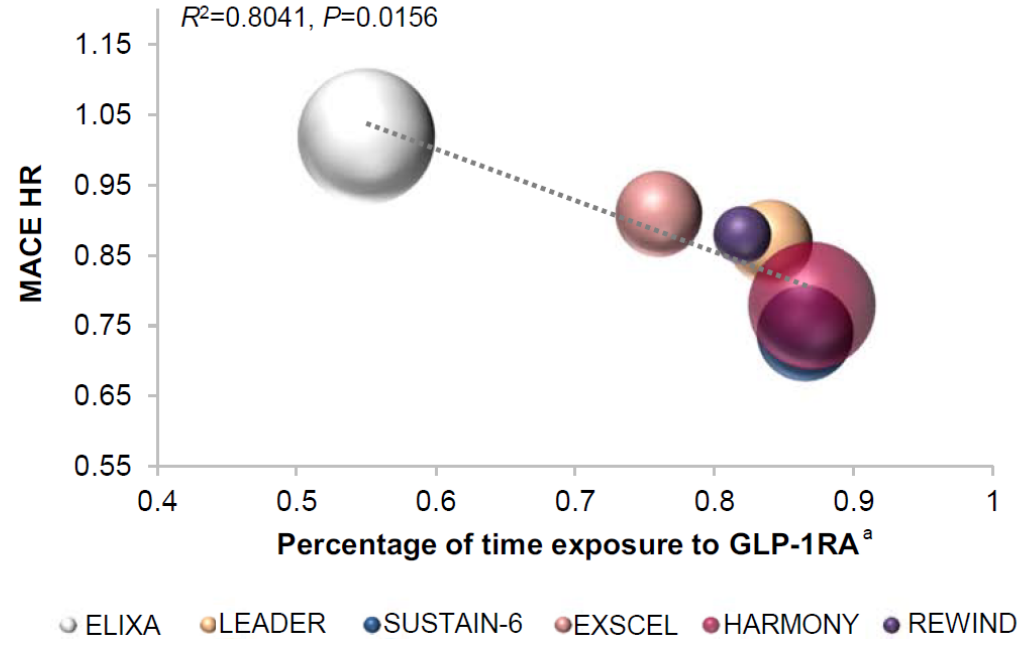
H, hours; LAR, long-acting release; $t_{½}$, elimination half-life.

Adapted from: Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247–2257; Marso SP, et al. *N Engl J Med*. 2016;375:311–22; Marso SP, et al. *N Engl J Med*. 2016 375:1834–1844; Holman RR, et al. *N Engl J Med*. 2017;377:1228–1239; Hernandez AF, et al. *Lancet*. 2018;392(10157):1519–1529; Gerstein HC, et al. *Lancet*. 2019 Jun 7. pii: S0140-6736(19)31149-3.

Correlation between Percentage of Time Exposure to Study Drug and MACE ARR and HR

- **Time of exposure to the investigational GLP-1 RA is positively correlated with the MACE ARR and, accordingly, negatively correlated with the MACE HR.**
  (Actual exposure to lixisenatide in ELIXA is estimated to be approximately 56%)
- **Baseline CV risk level does not seem to be related to changes in CV outcomes.**
  (Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])



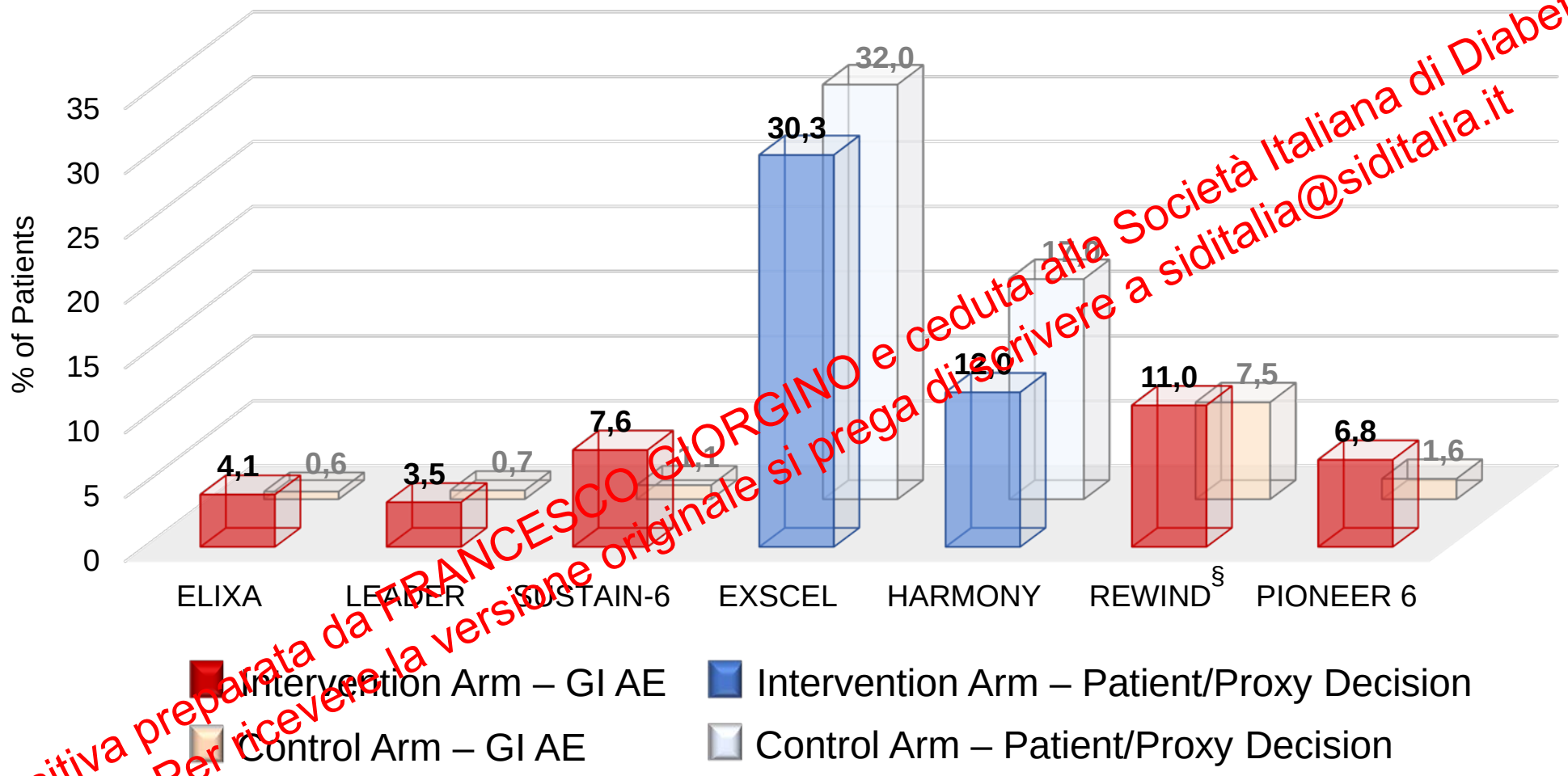


[a] The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes and REWIND, and as mean in LEADER, SUSTAIN–6 and EXSCEL

ARR, absolute risk reduction; CV; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event.

Caruso I et al., *Trends Endocrinol Metab* 2019

Main Reason for Investigational Product Discontinuation



§% of premature discontinuation due to AE, mostly GI

Pfeffer MA et al., *N Engl J Med* 2015; Marso SP, et al., *N Engl J Med* 2016; Marso SP, et al., *N Engl J Med* 2016; Holman RR et al., *N Engl J Med* 2017; Hernandez AF et al., *Lancet* 2018; Gerstein HC et al., *Lancet* 2019; Husain M et al., *N Engl J Med* 2019.

GLP-1 RA and cardiovascular benefit: conclusions

1. It is unclear whether the CV risk level of the exposed T2D population influenced the benefit. CV benefit was not seen in ELIXA (ACS patients) but was evident in HARMONY (100% with CVD). CV benefit was seen in the lower-risk patients of REWIND, suggesting that it may extend beyond secondary prevention.

2. Comparing GLP-1 RA vs usual care, differences in HbA_{1c} were similar in EXSCEL, LEADER and HARMONY and greater in SUSTAIN-6; differences in weight were highest in SUSTAIN-6 and lowest in HARMONY; less hypoglycaemia was seen only in LEADER and HARMONY. It is unclear whether these factors play a prominent role in the observed results.

3. Exendin-4-based and GLP-1-based agonists have yielded different results on MACE in the CVOTs. However, as of today, they seem to not differ qualitatively in their direct positive effects on cardiovascular cells and tissues, and the hypothesis of a «class effect» cannot be excluded.

4. The time of drug exposure during the trial appears to be the most important factor for CV benefit. CV benefit was observed only with long-acting GLP-1 RA producing 24-h coverage. High adherence and persistence to GLP-1 RA treatment (resulting from frequent follow-up and/or ease of drug administration) are important to gain in CV protection.

ACS, acute coronary syndrome; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes mellitus.

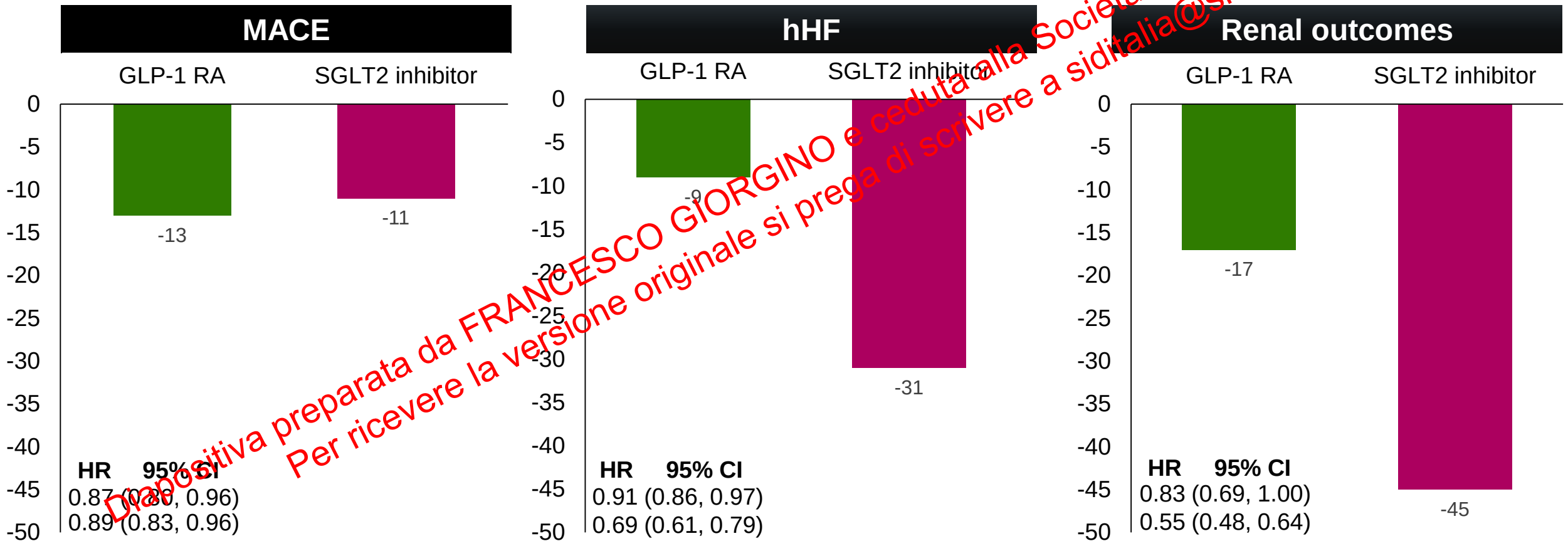
CV Outcome Studies with Intensive Glucose Lowering and SGLT-2i

Study	N	Follow-up (yr)	Age (yr)	Diabetes duration (yr)	CVD history (%)	HbA_{1c} (%) difference between arms	Primary endpoint	Primary endpoint HR (95% CI)	All-cause mortality HR (95% CI)
ACCORD	10,251	3.5	62	10	35	1.1	MACE	0.90 (0.78-1.04)	1.22 (1.01-1.46)
ADVANCE	11,140	5.0	66	8	32	0.8	MACE	0.94 (0.84-1.06)	0.93 (0.83-1.06)
VADT	1,791	5.6	60	12	40	1.5	MACE + HF, vascular surgery, new, ischemic amputation	0.88 (0.74-1.05)	1.07 (0.81-1.42)
UKPDS	3,867	10	54	0	2	0.9	MI	0.84 (0.71-1.00)	0.94 (0.80-1.10)
EMPA-REG	7,020	3.1	63	>10 (57%)	100	~0.4	MACE	**0.86 (0.74-0.99)**	**0.68 (0.57-0.82)**
CANVAS	10,142	3.6	63	13	66	0.6	MACE	**0.86 (0.75-0.97)**	0.87 (0.74-1.01)
DECLARE	17,160	4.2	64	10-11	41	0.42	MACE CV death + hHF	0.93 (0.84-1.03) **0.83 (0.73-0.95)**	0.93 (0.82-1.04)

CVD, cardiovascular disease; HR, hazard ratio, CI, confidence intervals; MACE, CV-death + non-fatal MI or stroke; MI, myocardial infarction; HF, heart failure.
Adapted from Giorgino F et al., *Diabetes Care* 39 Suppl 2:S187-95, 2016. Zinman B, et al. *N Engl J Med* 2015;373:2217–2128; Neal B, et al., *N Engl J Med*. 2017;377:644-657; Wiviott SD et al., *N Engl J Med* 2018, Nov 10.

The CVOTs have given us clear evidence that SGLT2 inhibitors and GLP-1 RAs provide significant relative risk reductions on top of standard of care

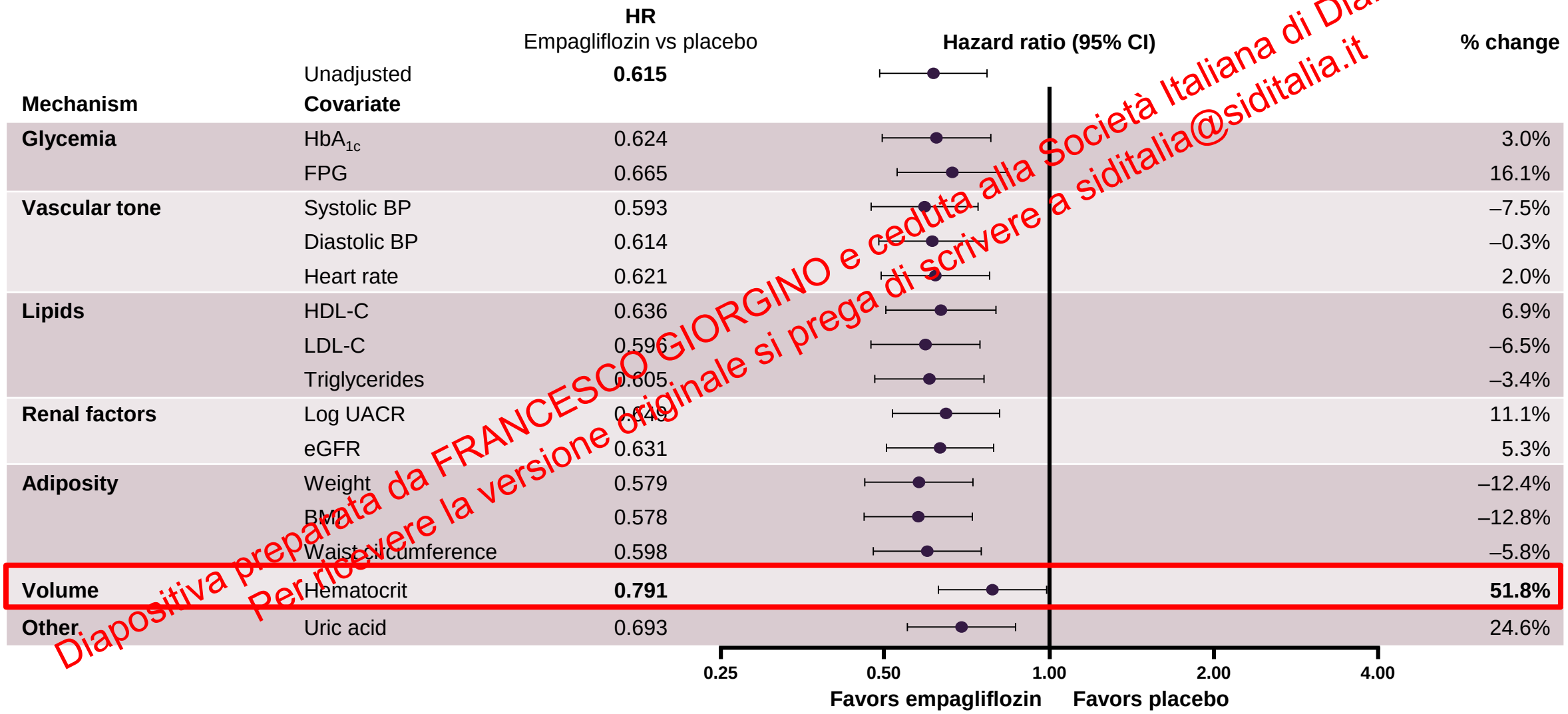
Data from meta-analyses of all CVOTs show that both SGLT2 inhibitors and GLP1-RAs provide significant cardiovascular and renal benefits[1,2]



CI, confidence interval; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; hHF, hospitalized heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2, sodium–glucose co-transporter 2

1. Giugliano D, et al. *Diabetes Obes Metab* 2019;Epub ahead of print; 2. Zelniker TA, et al. *Lancet* 2019;393:31–39

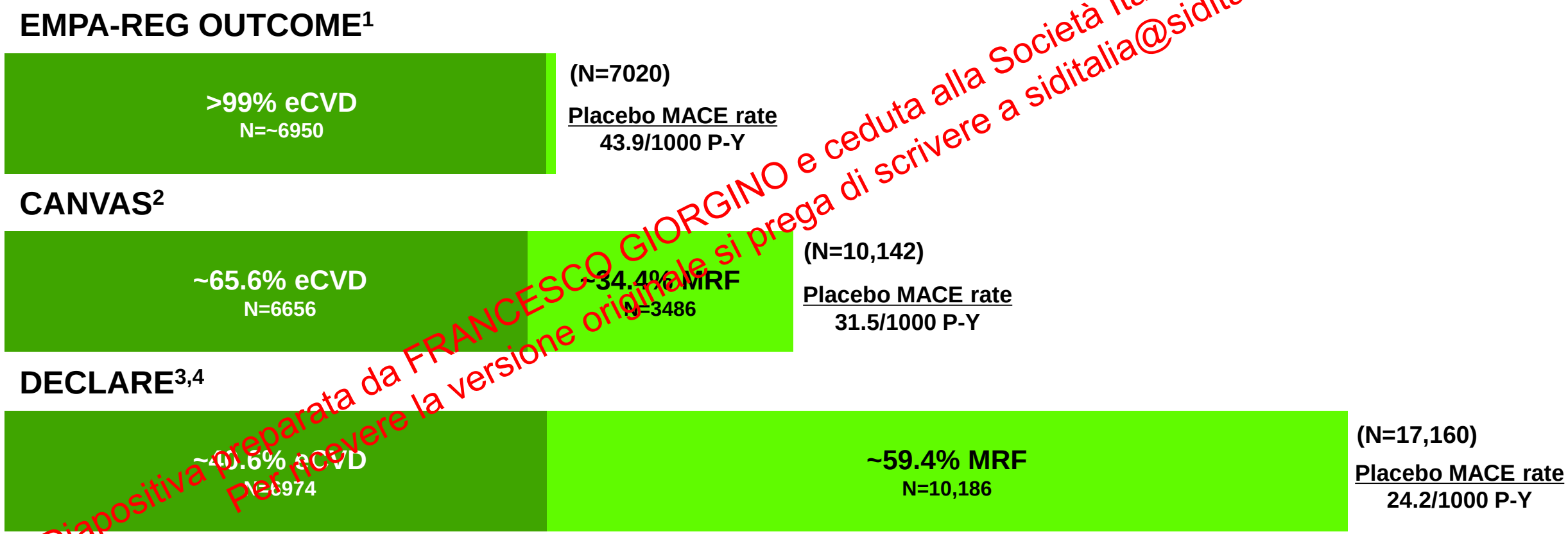
The effect of empagliflozin on CV mortality is more likely to be due to extraglycemic factors than glycemic control



BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; eFGR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; UACR, urine albumin:creatinine ratio

Inzucchi S, et al. *Diabetes Care* 2018;41:356–363

Proportion of T2D Patients without Established CVD in CVOTs with SGLT2i

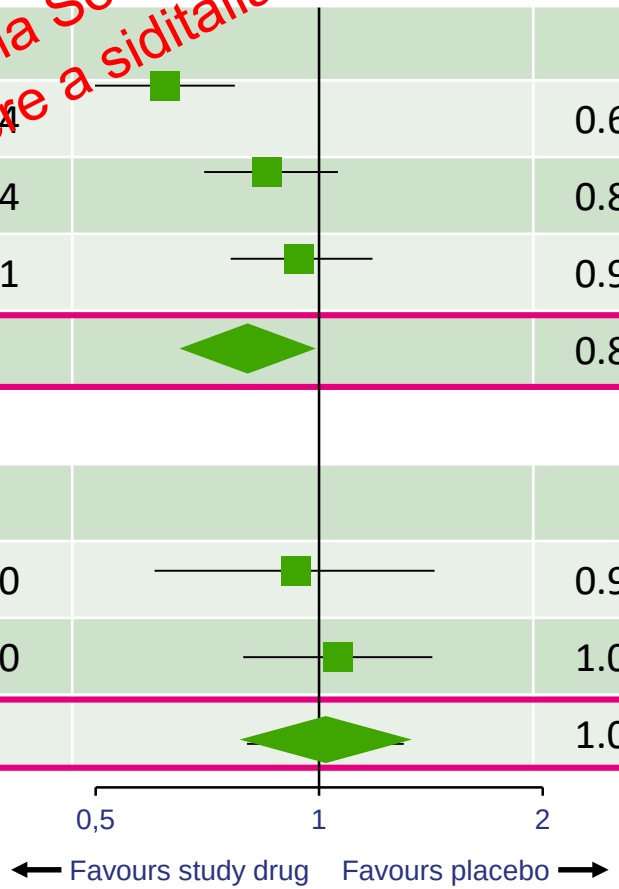


CV, cardiovascular; CVOT, cardiovascular outcomes trial; eCVD, established cardiovascular disease; MACE, major adverse cardiovascular events; MRF, multiple risk factors; P-Y, patient-years; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

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. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 4. Wiviott SD, et al. *N Engl J Med* 2019;380:347–357

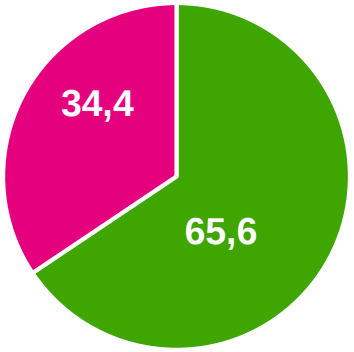
Placebo event rate for CV death in SGLT2i trials

	Patients	Events	Events per 1000 patient years		Weight (%)	Hazard Ratio (95% CI)
			Treatment	Placebo		
Patients with ASCVD						
EMPA-REG OUTCOME	020	309	12.4	20.2	32.4	0.62 (0.49–0.77)
CANVAS Program	6656	362	14.8	16.8	34.4	0.85 (0.70–1.06)
DECLARE-TIMI 58	6974	315	10.9	11.6	32.1	0.94 (0.76–1.18)
Fixed effects model for ASCVD (P=0.0005)						0.80 (0.71–0.91)
Patients with multiple risk factors						
CANVAS Program	3486	91	6.5	6.2	39.0	0.93 (0.60–1.43)
DECLARE-TIMI 58	10186	178	4.4	4.1	61.0	1.06 (0.79–1.42)
Fixed effects model for multiple risk factors (P=0.89)						1.02 (0.80–1.30)

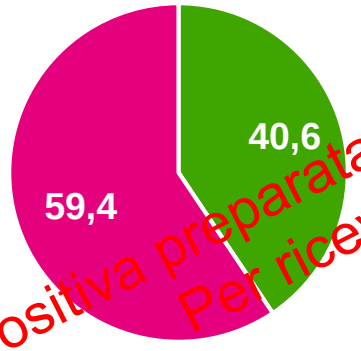


SGLT2 inhibitor trials with MRF populations without eCVD

CANVAS population[1]



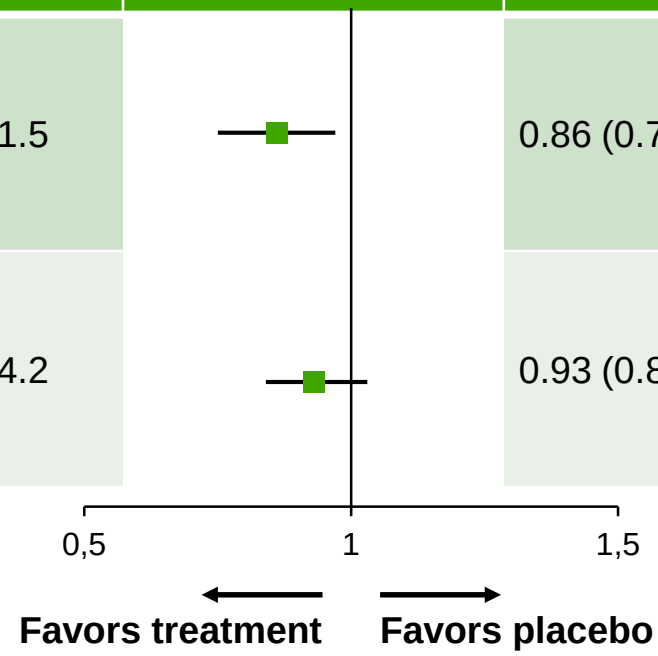
DECLARE-TIMI 58 population[2,3]



■ eCVD ■ MRF

Effect of canagliflozin and dapagliflozin on the risk of MACE in CANVAS and DECLARE-TIMI 58 overall trial populations[4]

Trial	Treatment events per 1000 P-Y	Placebo events per 1000 P-Y	HR (95% CI)
CANVAS program	26.9	31.5	0.86 (0.75, 0.97)
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84, 1.03)



CI, confidence interval; CVOT, cardiovascular outcomes trial; df, degrees of freedom; FE, fixed-effects; HR, hazard ratio; MACE, major adverse cardiovascular events; P-Y, person-years; SGLT2i, sodium–glucose co-transporter 2 inhibitor

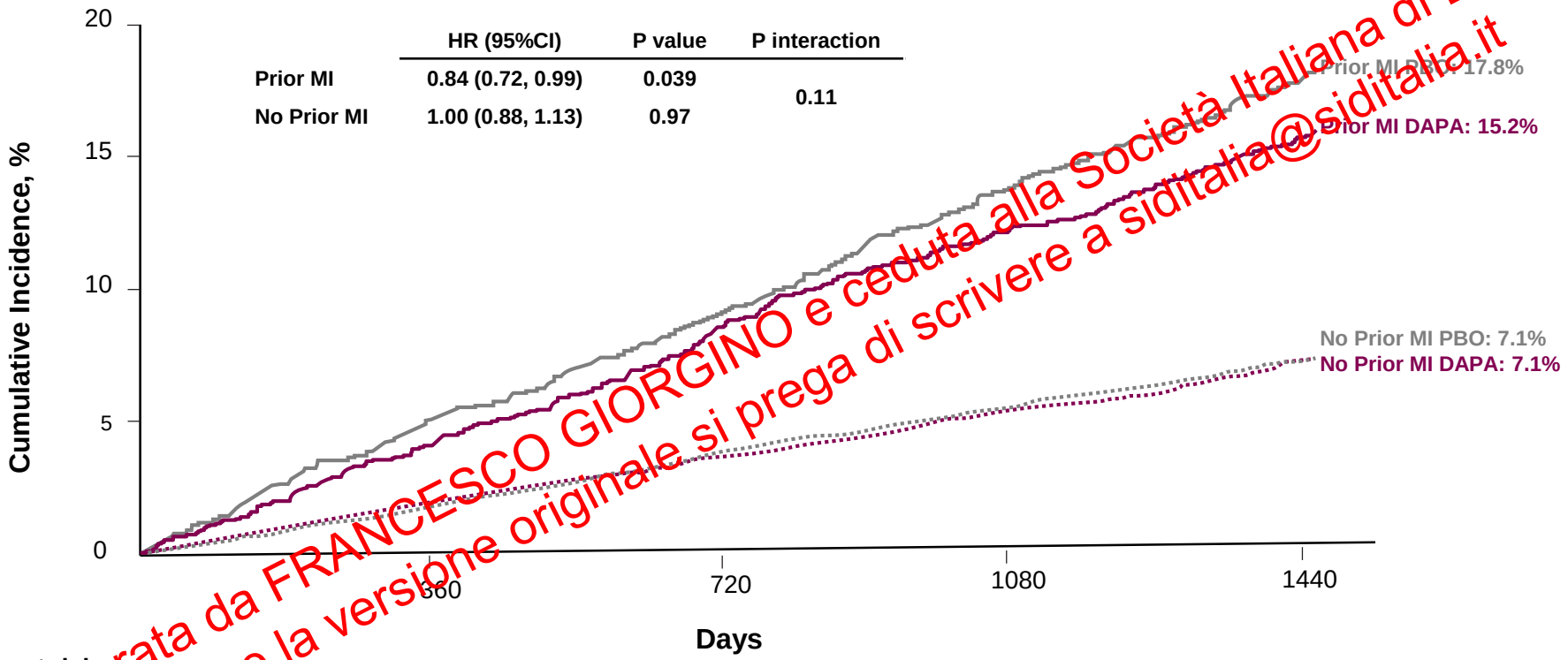
1. Neal B, et al. *N Engl J Med* 2017;377:644–657; 2. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 3. Wiviott SD, et al. *N Engl J Med* 2019;380:347–357; 4. Zelniker TA, et al. *Lancet* 2019;393:31–39

Meta-Analysis of GLP-1 RA and SGLT2 inhibitor trials on MACE Stratified by the presence of ASCVD

Trials	N	Events	HR (95% CI)
Established Atherosclerotic Cardiovascular Disease			
GLP-1	35823	4365	0.87 (0.82, 0.92)
SGLT2i	20650	2588	0.86 (0.80, 0.93)
Random effects for ASCVD (P=0.002)			0.86 (0.80, 0.93)
Multiple Risk Factors			
GLP-1	7097	506	1.03 (0.87, 1.23)
SGLT2i	13672	754	1.00 (0.87, 1.16)
Random effects for MRF (P=0.81)			1.01 (0.87, 1.19)

P-value for subgroup differences: 0.028.
Established ASCVD: GLP-1RA: Q-statistic=10.89, P=0.028; I^2=63.3%; SGLT2i: Q-statistic=0.94, P=0.63; I^2= 0%; Total: Q-statistic=11.85, P=0.11; MRF: GLP-1 RA: Q statistic=0.24, P=0.89; I2=0%; SGLT2i: Q-statistic=0.033, P=0.86; I^2=0%; Total: Q-statistic=0.34, *P*=0.99.
Adapted from Zelniker TA et al. Circulation. 2019 Feb 21. doi: 10.1161/CIRCULATIONAHA.118.038868

MACE Outcomes in Patients with Prior MI:
DECLARE Prior MI Subgroup Analysis



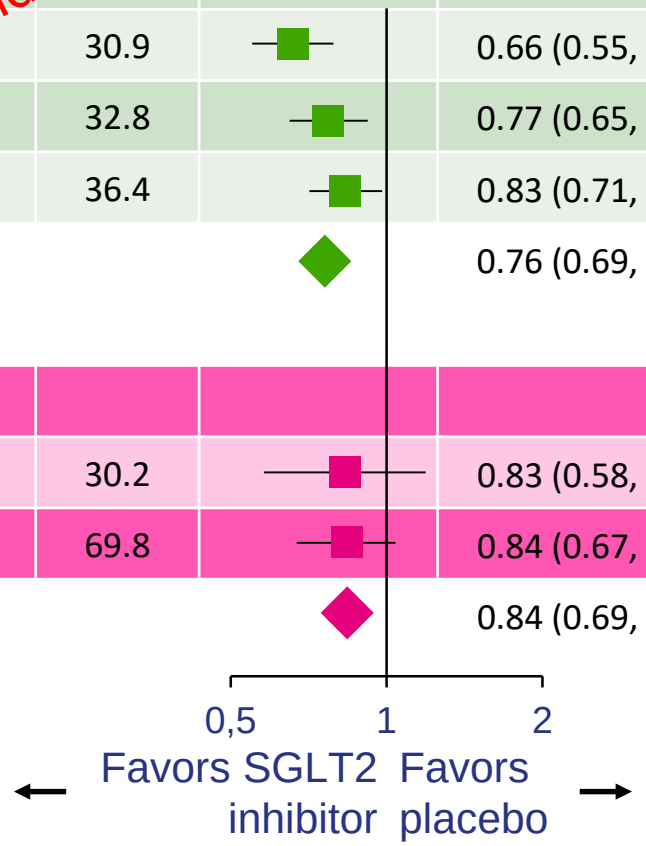
No. at risk

Prior MI-PBO	1807	1698	1607	1498	989
Prior MI-DAPA	1777	1687	1591	1504	1011
No Prior MI-PBO	6771	6583	6362	6151	4169
No Prior MI-DAPA	6805	6616	6426	6204	4214

Prior MI was a pre-specified subgroup of interest in DECLARE TIMI-58
CV = cardiovascular; DAPA = dapagliflozin; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; NNT = number needed to treat; No. = number; PBO = placebo.
Furtado RHM et al. Online ahead of print. *Circulation*. 2019. Accessed March 18, 2019.

CV death/hHF benefit according to the presence or absence of ASCVD

	Patients		Events	Events per 1,000 patient years		Weight (%)	Hazard Ratio (95% CI)
	Treatment n/N	Placebo n/N		Treatment	Placebo		
Patients with ASCVD							
EMPA-REG OUTCOME	4,687/7,020	2,333/7,020	463	19.7	30.1	30.9	0.66 (0.55, 0.79)
CANVAS Program	3,756/6,656	2,900/6,656	524	21.0	27.4	32.8	0.77 (0.65, 0.92)
DECLARE-TIMI 58	3,474/6,974	3,500/6,974	397	19.9	23.9	36.4	0.83 (0.71, 0.98)
Fixed effects model for ASCVD (*P*<0.0001)							0.76 (0.69, 0.84)
Patients with multiple risk factors							
CANVAS Program	2,039/3,486	1,447/3,486	128	8.9	9.8	30.2	0.83 (0.58, 1.19)
DECLARE-TIMI 58	5,108/10,186	5,078/10,186	316	7.0	8.4	69.8	0.84 (0.67, 1.04)
Fixed effects model for multiple risk factors (*P*=0.0634)							0.84 (0.69, 1.01)



Zelniker TA et al., Lancet 2018

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; hHF, hospitalization for heart failure; SGLT2, sodium–glucose co-transporter 2

Definition of Heart Failure Classifications:
DECLARE HF Subgroup Analysis

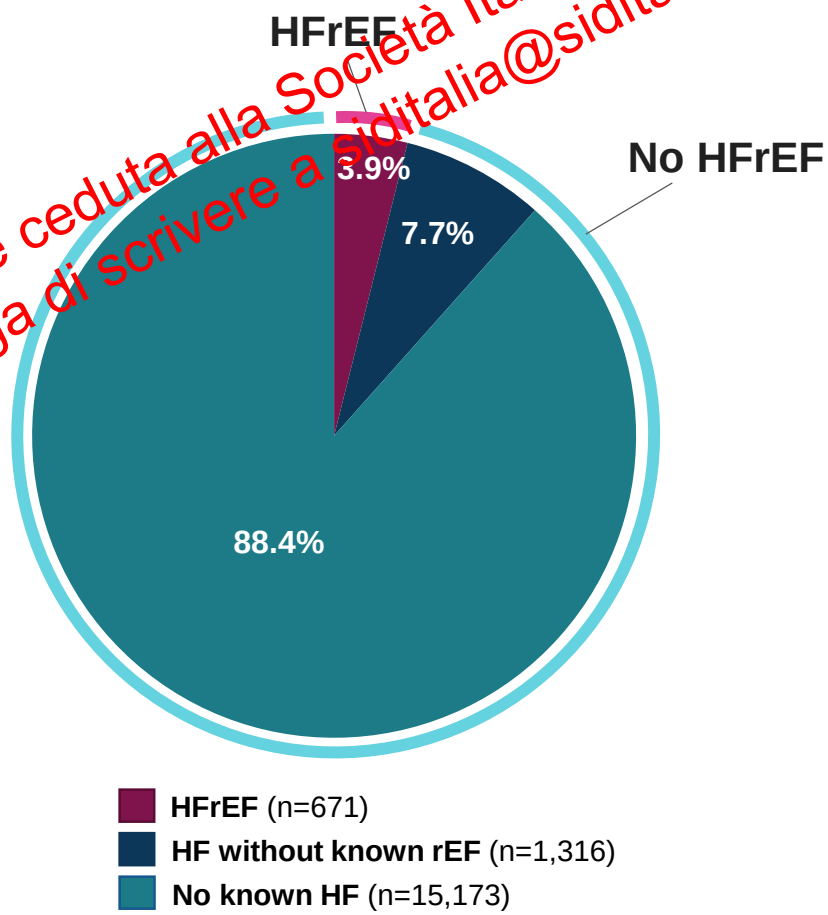
HFrEF

- Documented EF <45% or severe/moderate left ventricular systolic dysfunction

No HFrEF

- HF without known reduced EF
  - History of HF and EF ≥45%
  - History of HF and no documented EF
- No history of HF
  - EF ≥45%
  - No documented EF

DECLARE Patient Population

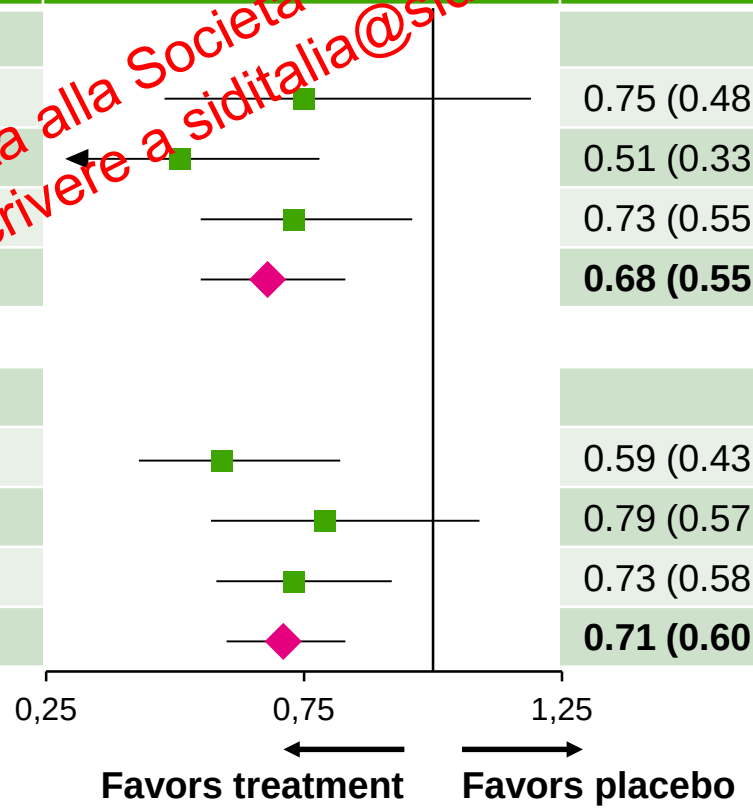


EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced EF; rEF = reduced EF.

Kato ET et al. Online ahead of print. *Circulation.* 2019. Accessed March 18, 2019.

SGLT2 inhibitors prevent hHF in patients with and without pre-existing HF

hHF	Events	Treatment events per 1000 P-Y	Placebo events per 1000 P-Y	HR (95% CI)
History of HF				
EMPA-REG OUTCOME	78	40.7	52.4	0.75 (0.48, 1.19)
CANVAS program	N/A	14.1	28.1	0.51 (0.33, 0.78)
DECLARE-TIMI 58	202	27.7	37.2	0.73 (0.55, 0.96)
FE model for history of HF (*P*=0.0002)				**0.68 (0.55, 0.83)**
No history of HF				
EMPA-REG OUTCOME	143	6.4	10.8	0.59 (0.43, 0.82)
CANVAS program	N/A	4.3	5.7	0.79 (0.57, 1.09)
DECLARE-TIMI 58	296	4.0	5.6	0.73 (0.58, 0.92)
FE model for no history of HF (*P*≤0.0001)				**0.71 (0.60, 0.83)**



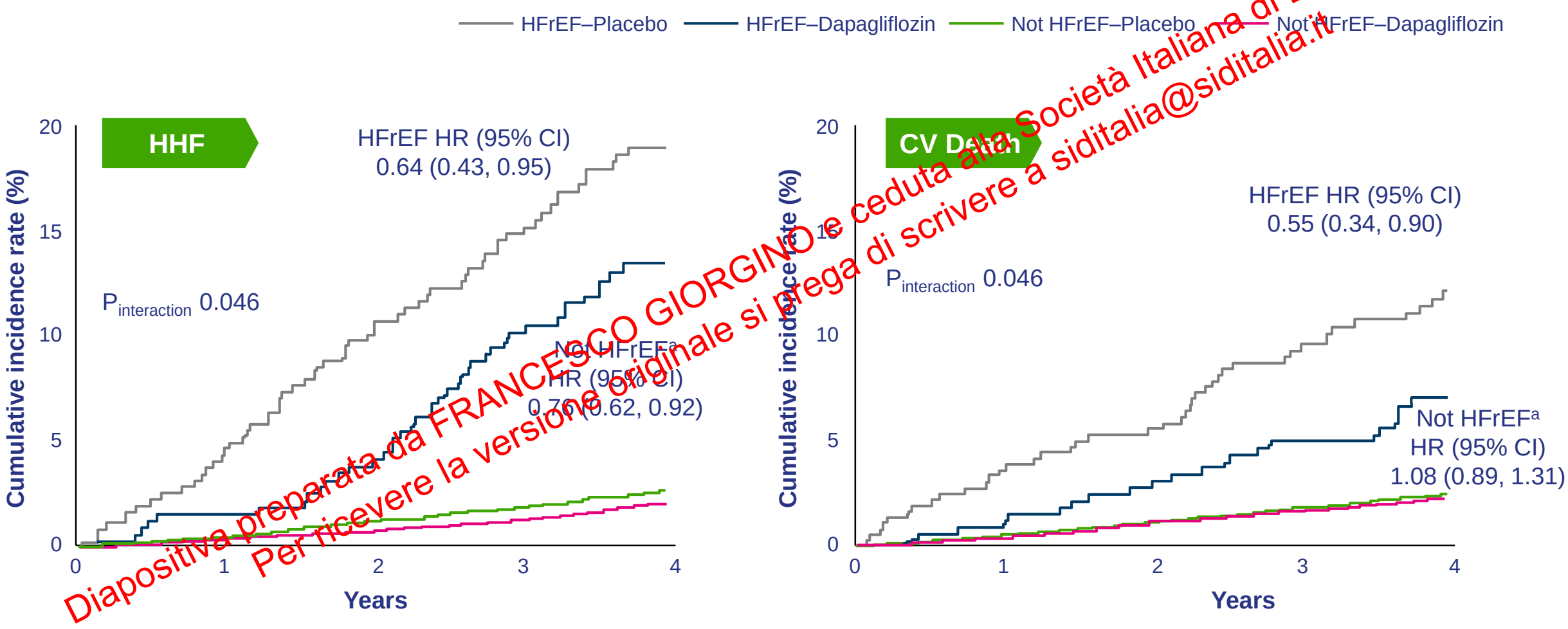
Heterogeneity between studies:
HF: Q=2.14, *P*=0.34, I^2=6.6
No HF: Q=1.73, *P*=0.42, I^2=0.0

Test for subgroup differences *P*=0.76

CI, confidence interval; CVOT, cardiovascular outcomes trial; FE, fixed-effects; HF, heart failure; hHF, hospitalized heart failure; HR, hazard ratio; P-Y, patient-years; SGLT2i, sodium–glucose co-transporter 2 inhibitor

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

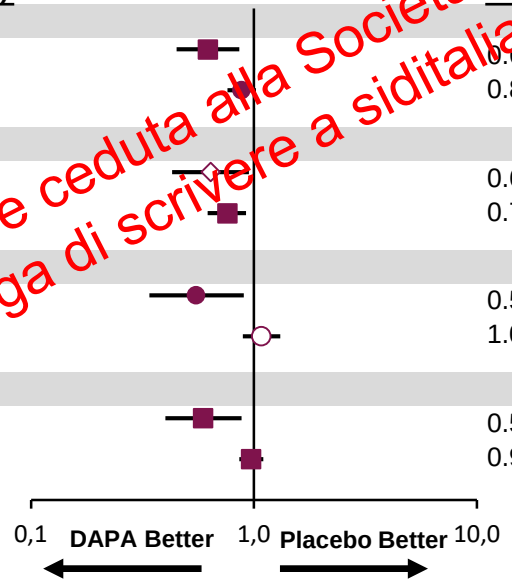
DECLARE-TIMI 58: Dapagliflozin reduced hHF/ CV death to a greater extent in people with a history of HFrEF



hHF/CV, hospitalization for heart failure/cardiovascular; HFrEF, heart failure with reduced éjection fraction.
a, Not HFrEF is a combination of no HF and HF without known reduced EF.
Adapted from Kato ET et al. Circulation. 2019;139:2528-2536.

Outcomes by Heart Failure Category:
DECLARE HF Subgroup Analysis

	DAPA		PBO				
	n/N	KM rate (%)	n/N	KM rate, %	ARR (%)	HR (95% CI)	P interaction
hHF/CV Death							
HFrEF	59/318	17.9	95/353	27.1	9.2	0.62 (0.45-0.86)	0.046
Not HFrEF	358/8264	4.3	401/8225	4.8	0.5	0.88 (0.76-1.02)	
hHF							
HFrEF	41/318	13.5	63/353	19.0	5.5	0.64 (0.43-0.95)	0.449
Not HFrEF	171/8264	2.1	223/8225	2.7	0.6	0.76 (0.62-0.92)	
CV death							
HFrEF	25/318	7.2	47/353	12.4	5.2	0.55 (0.34-0.90)	0.012
Not HFrEF	220/8264	2.5	202/8225	2.3	-0.2	1.08 (0.89-1.31)	
All cause mortality							
HFrEF	38/318	11.3	68/353	17.7	6.4	0.59 (0.40-0.88)	0.016
Not HFrEF	491/8264	5.5	502/8225	5.4	-0.1	0.97 (0.86-1.10)	



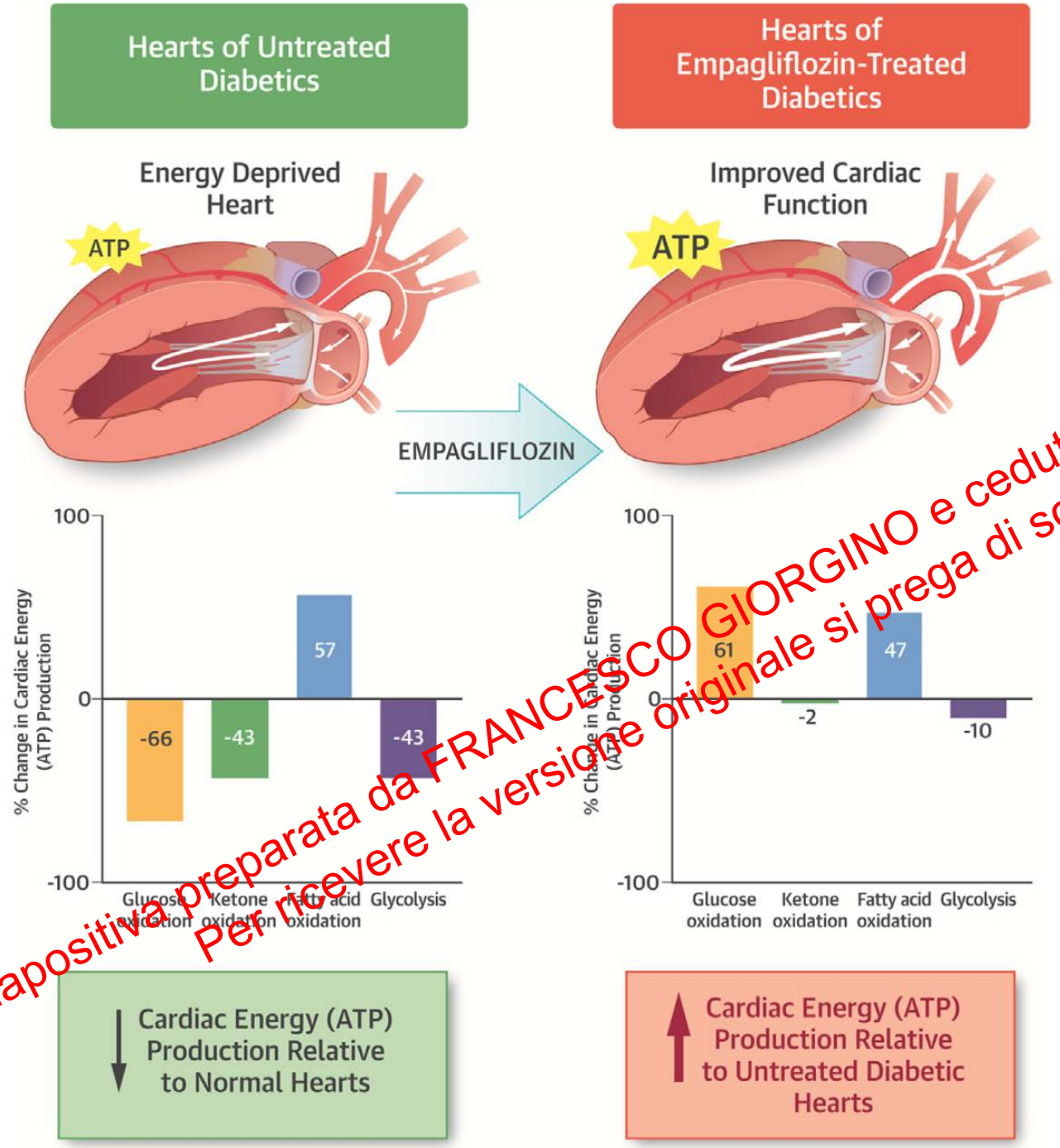
DECLARE HF Subgroup Analysis: HF Classifications

DECLARE HF Subgroup Analysis: Baseline Characteristics

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced EF; hHF = hospitalization for heart failure; HR = hazard ratio; PBO = placebo.

Kato ET et al. Online ahead of print. *Circulation*. 2019. Accessed March 18, 2019.

Empagliflozin Increases Cardiac Energy Production in Diabetes



Verma, S. et al.
J Am Coll Cardiol Basic Trans Science
2018;3(5):575–87.

SGLT2i and cardiovascular benefit: conclusions

1. In general, the results from CVOTs with SGLT2 inhibitors show that patients at higher CVD risk (i.e., those with established CVD or prior MI) obtain greater benefits on MACE from SGLT2 therapy than those at lower risk.
2. The results of DECLARE-TIMI 58 suggest that this benefit may be greater in patients with established CVD, specifically in those with recent prior MI. The lack of effect on MACE as primary endpoint in DECLARE may be due to the lower CV risk of this trial population.
3. By contrast, the benefit on hHF is apparently independent of HF at baseline, or possibly also the presence or absence of established CVD. This was a consistent finding in all three CVOTs (although in CANVAS a greater benefit was more apparent in patients with previous HF).
4. Patients with HFrEF in DECLARE show greater benefits for HF outcomes.

ESC/EASD 2019 recommendations for the use of anti-hyperglycemic agents in T2D patients with or at risk of HF

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended.	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 ml/min/1.73m^2 .	IIa	C
GLP1-RA$_S$ (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.	IIb	A
The DPP4 inhibitors sitagliptin and linaglip tin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.	IIb	B
Insulin may be considered in patients with advanced systolic HFrEF.	IIb	C
Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk oh HF (or with previous HF).	III	A
The DPP4 inhibitors saxaglip tin is associated with an increased risk of HF hospitalization, and is not recommended for DM treatment in patients at risk of HF (or with previous HF).	III	B

DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

Consentino F, et al. *Eur Heart J* 2019;00:1–69