Dapagliflozin is being evaluated for benefits in heart failure and CKD in 3 additional outcome studies in the AZ DapaCare Program

- **DapaCare involves nearly 30,000 patients across RCTs and is supported by a large real-world cohort**
- **DapaCare includes a spectrum of patients, including those with varying stages of CV and renal disease, with and without T2D. It will continue to advance our understanding of the CV and renal effects of dapagliflozin**

DAPA-HF
HFrEF Outcome Trial

Population	Symptomatic HFrEF (n ~4,500)
Treatment	Dapagliflozin 10 mg vs placebo on top of standard of care
Endpoint	Composite of CV death, hHF or urgent HF visit

DELIVER
HFpEF Outcome Trial

Population	Symptomatic HFpEF (n ~4,700)
Treatment	Dapagliflozin 10 mg vs placebo on top of standard of care
Endpoint	Composite of CV death, hHF or urgent HF visit

DAPA-CKD
CKD Outcome Trial

Population	CKD (n ~4,000)
Treatment	Dapagliflozin 10 mg vs placebo on top of standard of care
Endpoint	Composite of ≥50% sustained decline in eGFR, or reaching ESRD or CV death or renal death

Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

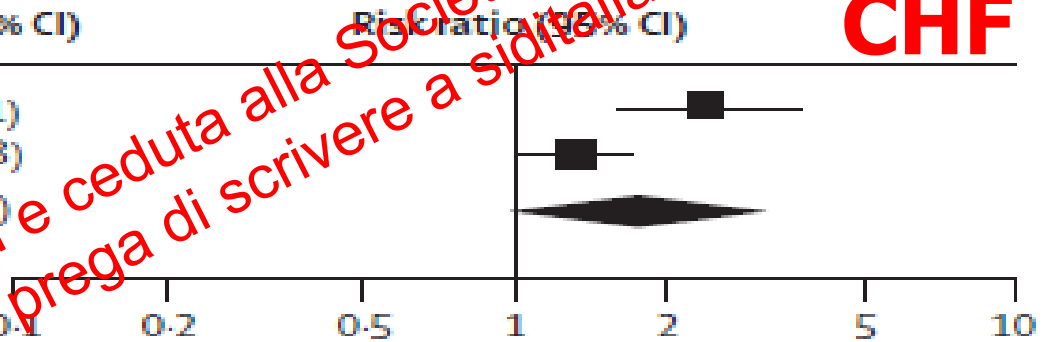
Rodrigo M Lago, Premranjan P Singh, Richard W Nesto

Lancet 2007; 370: 1129–36

CHF

A	Weight	Risk ratio (95% CI)
Rosiglitazone trials	46·2%	2·41 (1·61, 3·61)
Pioglitazone trials	53·8%	1·32 (1·04, 1·68)
Total	100·0%	1·74 (0·97, 3·14)

Test for heterogeneity: χ^2=61·27, df=1 (p=0·01), I^2=84·1%
Test for overall effect: Z=1·85 (p=0·07)



CV DEATH

B	Weight	Risk ratio (95% CI)
Rosiglitazone trials	79·2%	1·01 (0·70, 1·45)
Pioglitazone trials	20·8%	1·01 (0·49, 2·06)
Total	100·0%	1·01 (0·73, 1·40)

Test for heterogeneity: χ^2=1·15, df= (p=0·89), I^2=0%
Test for overall effect: Z=0·05 (p=0·96)

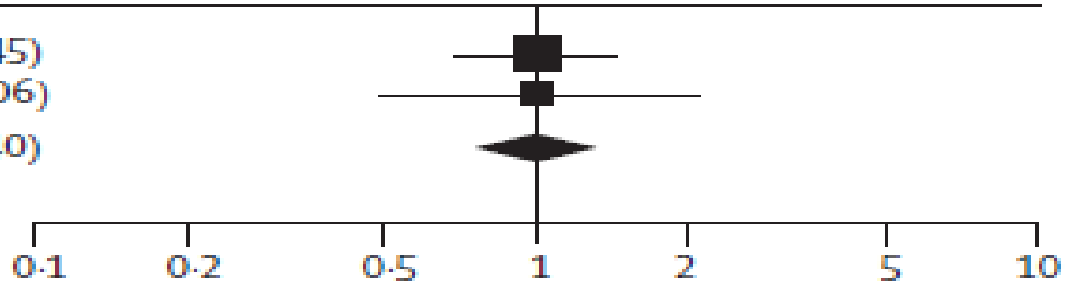


Figure 4: **Comparison of risk of congestive heart failure (A) and cardiovascular death (B) for rosiglitazone and pioglitazone**

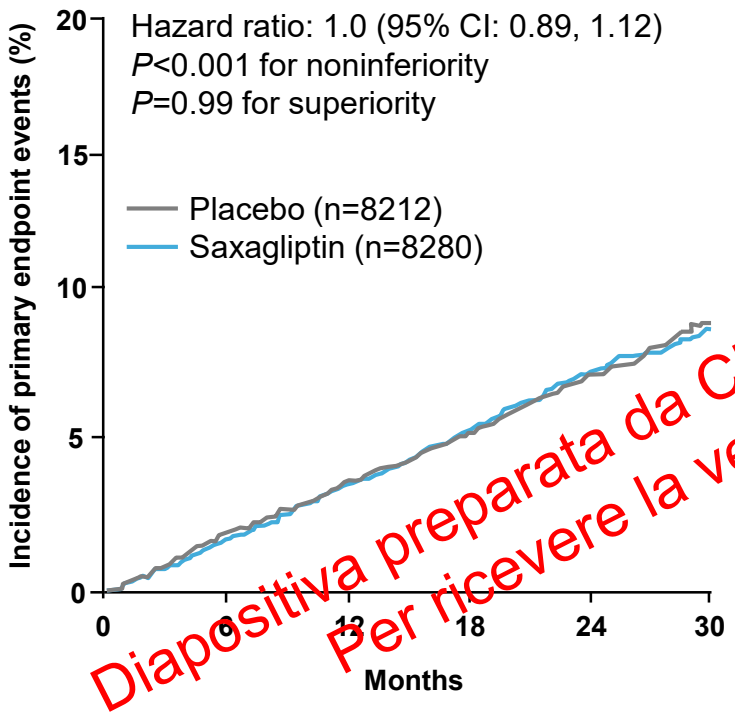
Farmaci antidiabetici e scompenso cardiaco

1. I farmaci (alcuni) aumentano il rischio di scompenso
2. I farmaci sono neutrali
3. I farmaci riducono il rischio di scompenso nei diabetici con cardiopatia strutturale
4. I farmaci riducono il rischio di scompenso nei diabetici in generale
5. I farmaci (alcuni) sono efficaci nel trattamento dello scompenso anche nei non diabetici

DPP-4 inhibitors were largely CV neutral on MACE

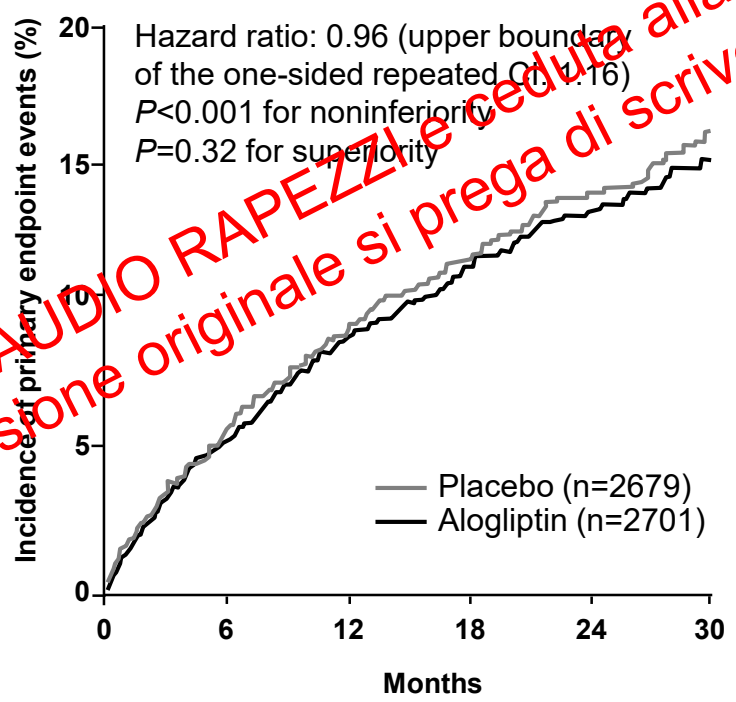
Saxagliptin (SAVOR trial)[1]

Primary endpoint: Composite of CV death, myocardial infarction, or ischemic stroke



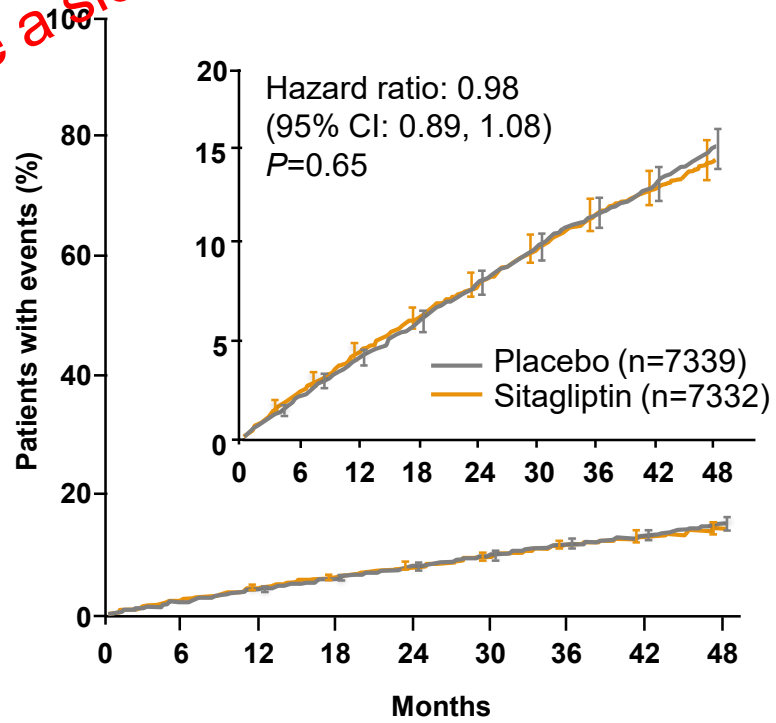
Alogliptin (EXAMINE trial)[2]

Primary endpoint: Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke



Sitagliptin (TECOS trial)[3]

Primary endpoint: Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina



CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Adapted from Scirica B, et al. *N Engl J Med* 2013;369:1317–1326; 2. Adapted from White W, et al. *N Engl J Med* 2013;369:1327−1335;
3. Adapted from Green JB, et al. *N Engl J Med* 2015;373:232–242

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

N ENGL J MED 369;14 NEJM.ORG OCTOBER 3, 2013

CONCLUSIONS

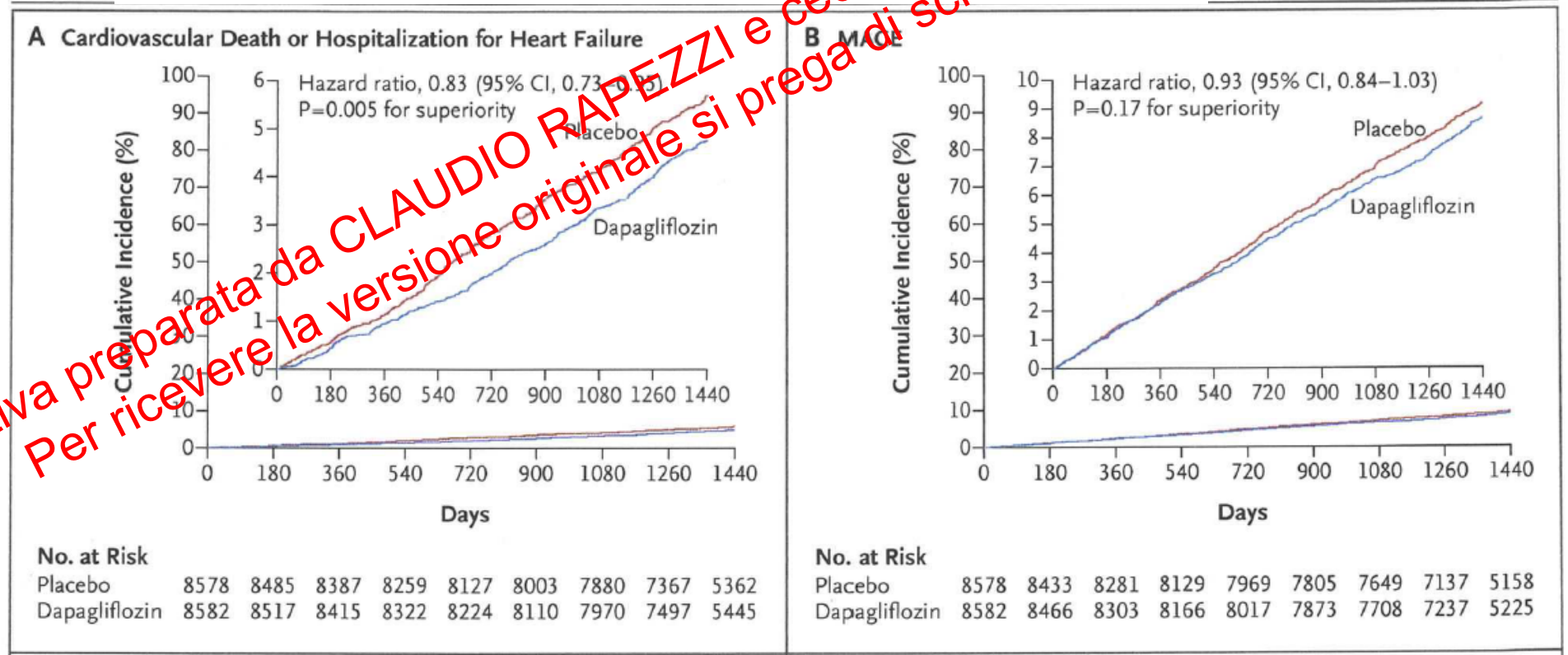
DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*



Hf and Diabetes

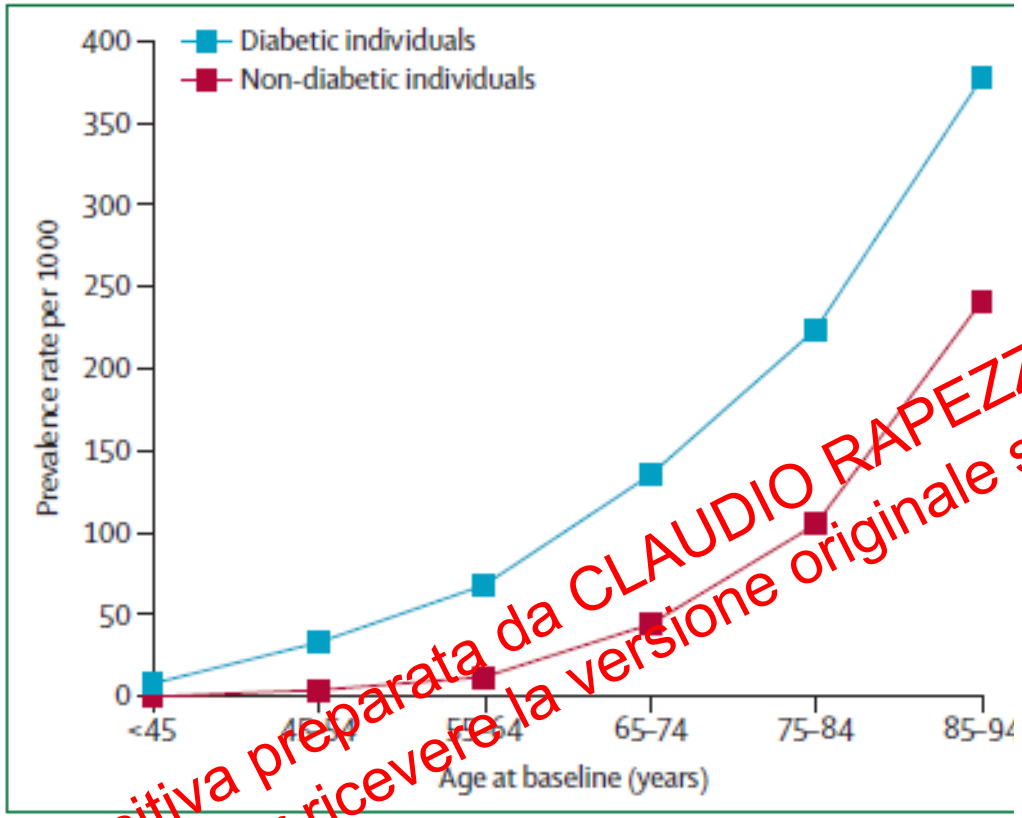


Figure 1: Age-associated prevalence of heart failure in diabetic and non-diabetic individuals

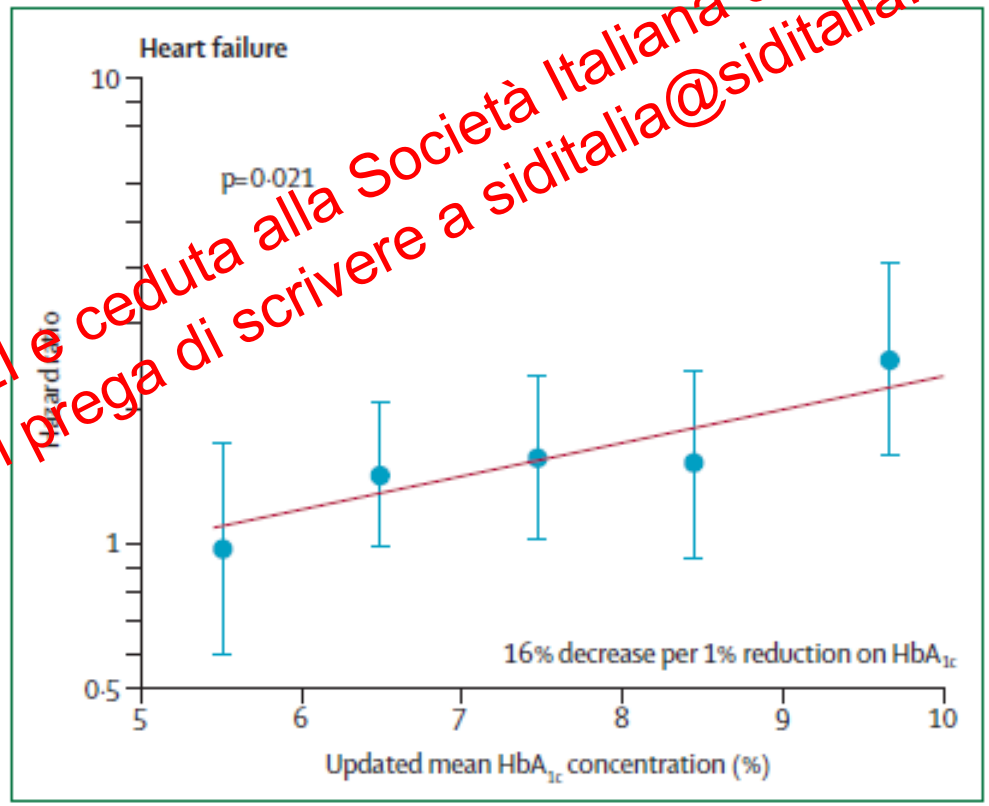


Figure 2: Hazard ratios (HRs), with 95% CIs as floating absolute risks, as an estimate of association between category of updated mean haemoglobin A_{1c} (HbA_{1c}) concentration and heart failure

Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy **Intensive vs less intensive**

Richard E Gilbert, Henry Krum

Lancet 2015; 385: 2107–17

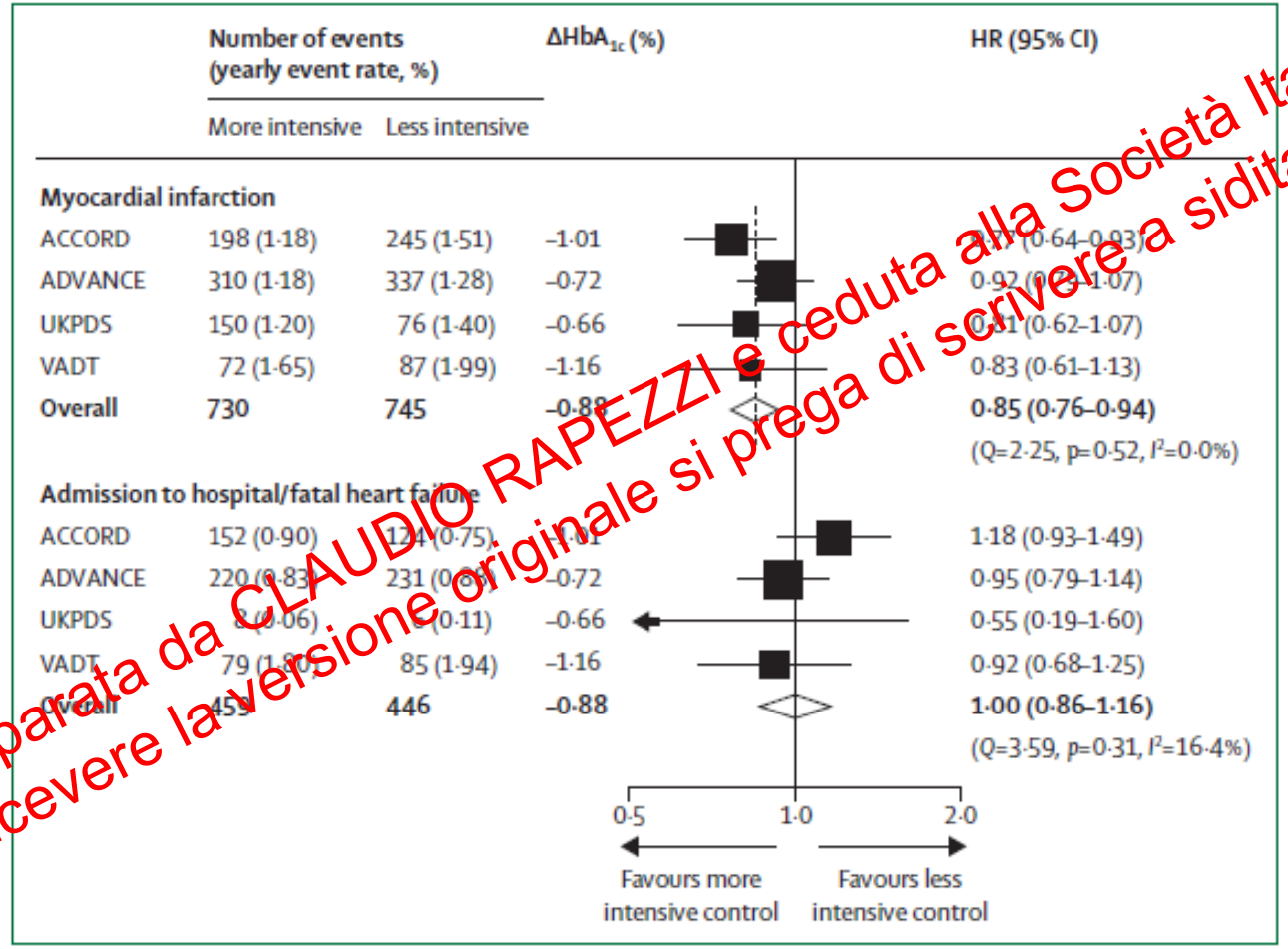
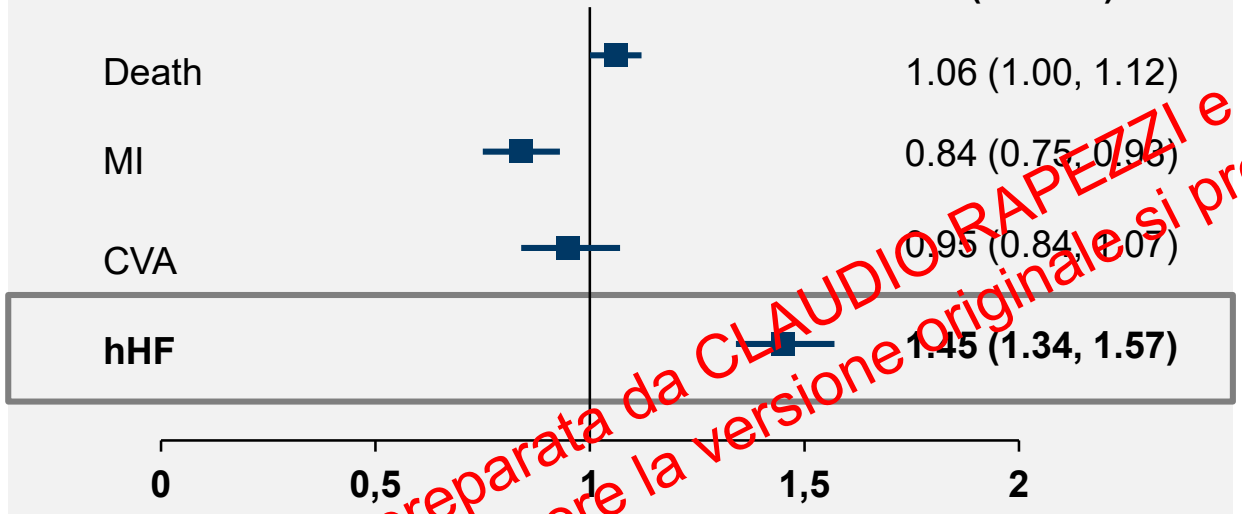


Figure 3: Effects in trials of more versus less intensive glycaemic control on myocardial infarction (fatal or non-fatal) and heart failure resulting in admission to hospital or death

Despite control of known CV risk factors, patients with T2D remain at elevated risk of developing HF

Risk of event in patients with T2D with no other risk factors out of range compared to patients without diabetes



- In this analysis the risk of hHF in patients with T2D (n=371,174) was compared to those without T2D (n=1,355,870)
- The following risk factors were either not present or within guideline range: systolic and diastolic BP, LDL-C, albuminuria and tobacco use
- A substantial risk for hHF remained among patients who had all the variables within target range

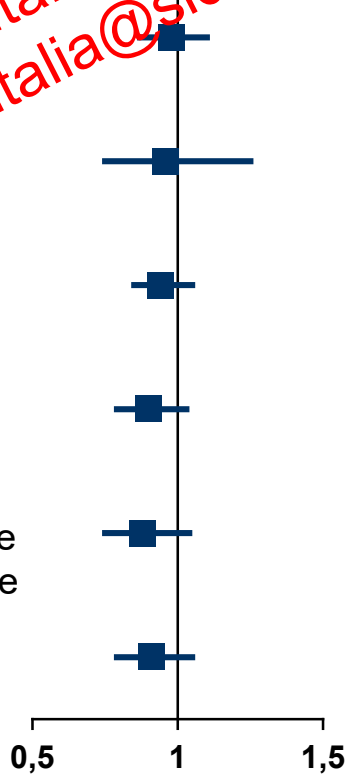
On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent

BP, blood pressure; CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; hHF, hospitalisation for HF; HR, hazard ratio; LDL-C, low density–lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes.

Rawshani A, et al. *N Engl J Med.* 2018;379:633-644.

‘Older’ glucose-lowering agents have not definitively shown positive effects on major CV events …

Trial	Outcome	HR (95% CI)
ACE (N=6522)[1] **Acarbose versus placebo + CV prevention therapy**	5P-MACE: CV death, NF-MI, NF-stroke, hUA, hHF	0.98 (0.86, 1.11)
TOSCA.IT (N=3,028)[2] **PIO versus SU as add-on to MET**	All-cause death, NF-MI, silent MI, NF-stroke, urgent coronary revascularization	0.96 (0.74, 1.26)
ADVANCE (N=11,140)[3] **HbA_{1c} ≤6.5% versus HbA_{1c} >6.5% (gliclazide + any other agent)**	3P-MACE: CV death, NF-MI, NF-stroke	0.94 (0.84, 1.06)
ACCORD (N=10,251)[4] **HbA_{1c} <6.0% versus HbA_{1c} 7.0–7.9% (MET, SU, TZD, insulin)**	3P-MACE: CV death, NF-MI, NF-stroke	0.90 (0.78, 1.04)
VADT (N=1791)[5] **HbA_{1c} –1.5% versus the standard group (MET or GLIM, ROSI, insulin)**	7P-MACE: CV death, MI, stroke, HF, surgery for vascular disease, inoperable CHD, amputation for ischemic gangrene	0.88 (0.74, 1.05)
DEVOTE (N=7367)[6] **IGlar versus IDeg**	3P-MACE: CV death, NF-MI, NF-stroke	0.91 (0.78, 1.06)



SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

MACE

Lancet 2019; 393: 31–39

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri S Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	20·4	0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·5	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039	1447	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)**

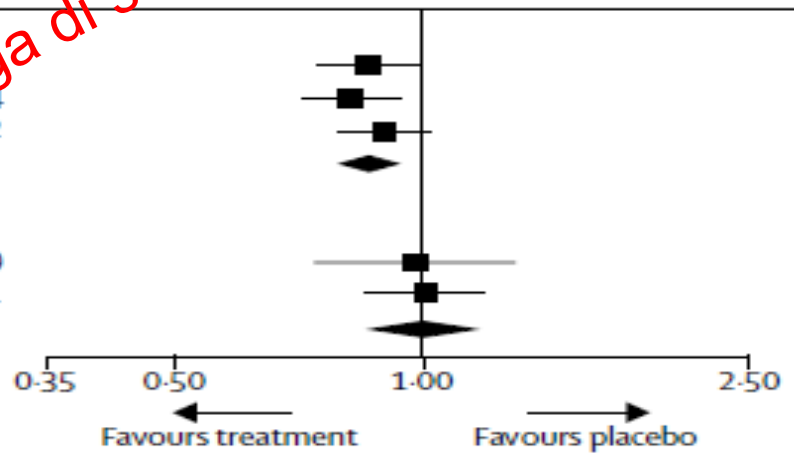


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

CHF

Lancet 2019; 393: 31–39

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eli V Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

	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	463	19·7	30·1	36·4		0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·4	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	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)**

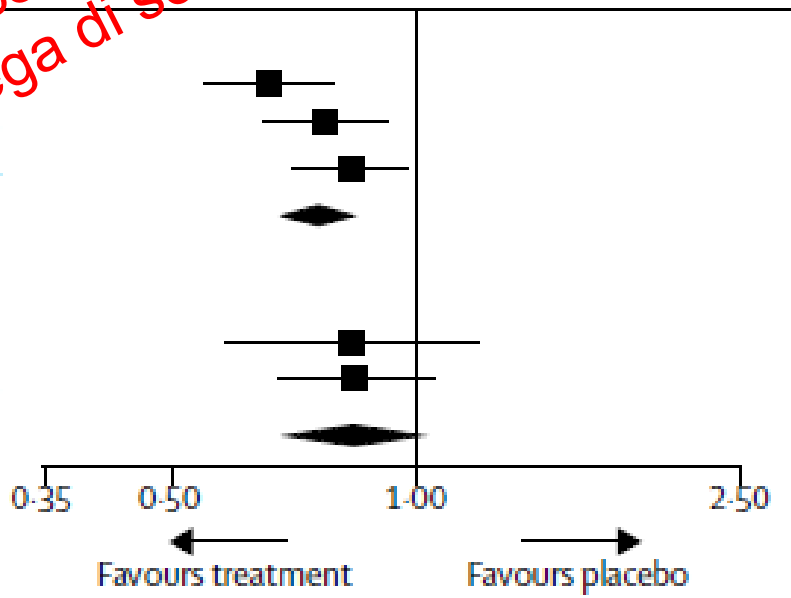


Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

CHF

Lancet 2019; 394: 121–130

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·6	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	33·4	66·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4997	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	6730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

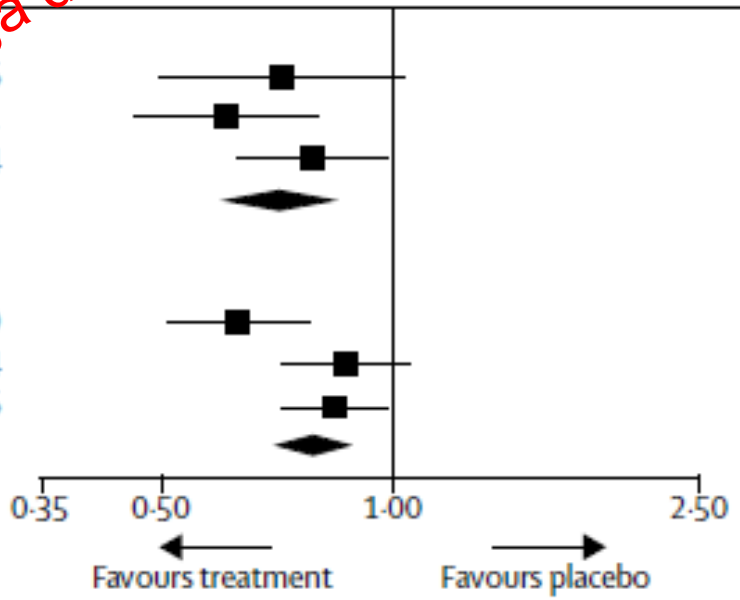


Figure 3: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**

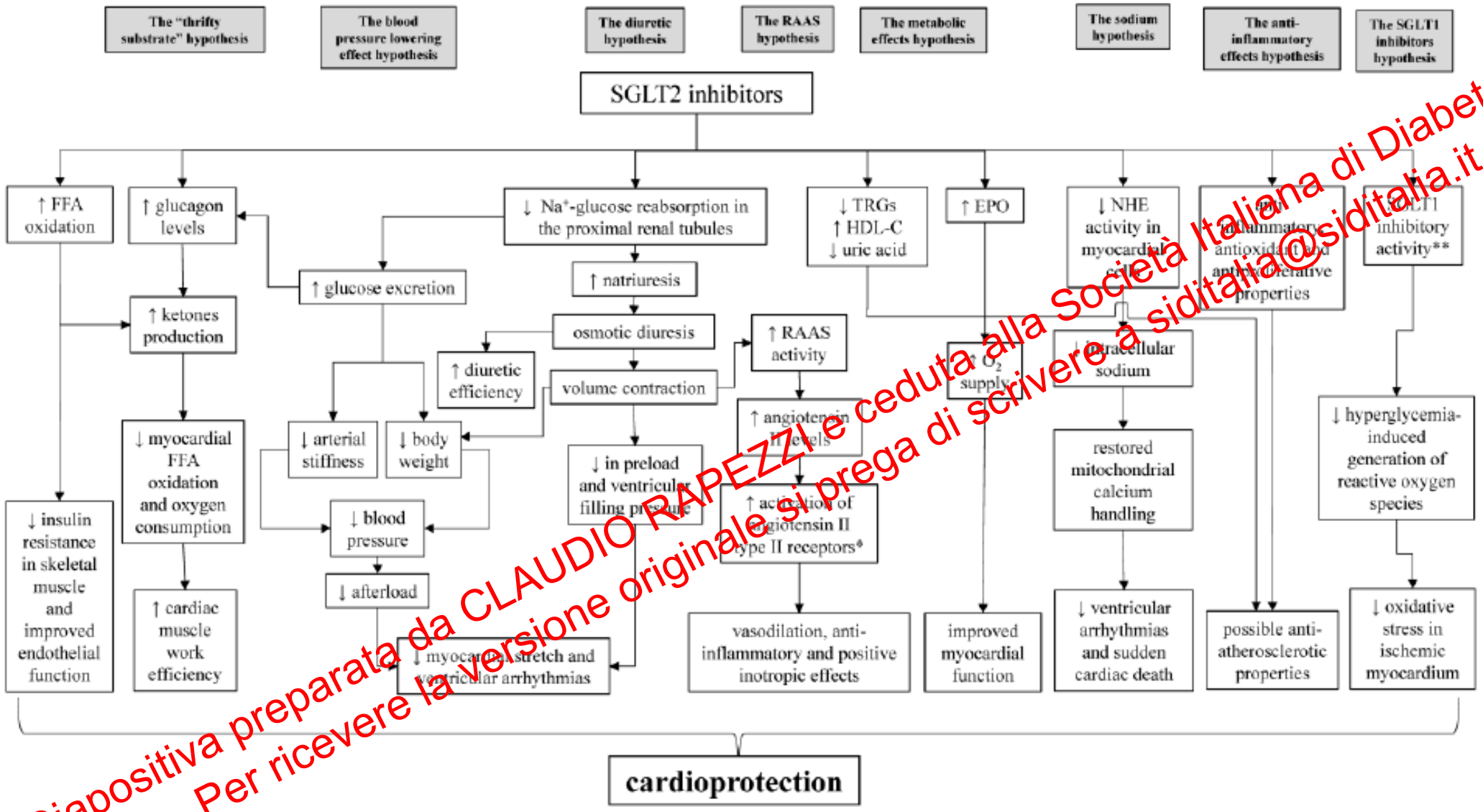
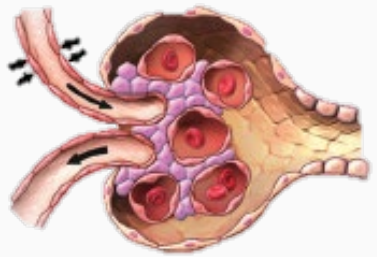


Figure 1. Suggested hypotheses for the cardioprotective effects of SGLT2 inhibitors.

There are a number of putative mechanisms to explain cardiorenal protection with SGLT2 inhibitors

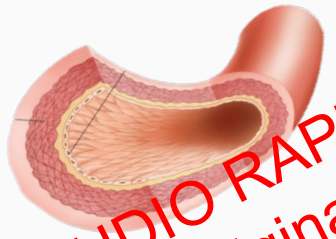
SGLT2i

KIDNEY



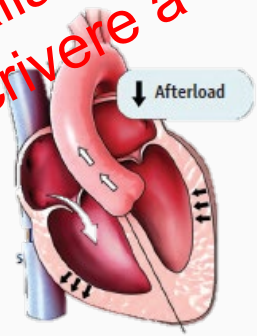
SGLT2i causes afferent arteriolar constriction, decreasing intraglomerular pressure[1]

CIRCULATION

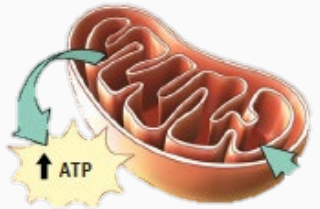


↓ Intravascular/ECF volume leads to ↑ haematocrit and ↓ systolic blood pressure[1,2]

HEART



Reduction in preload, afterload and LV wall stress improve filling conditions[1,2]



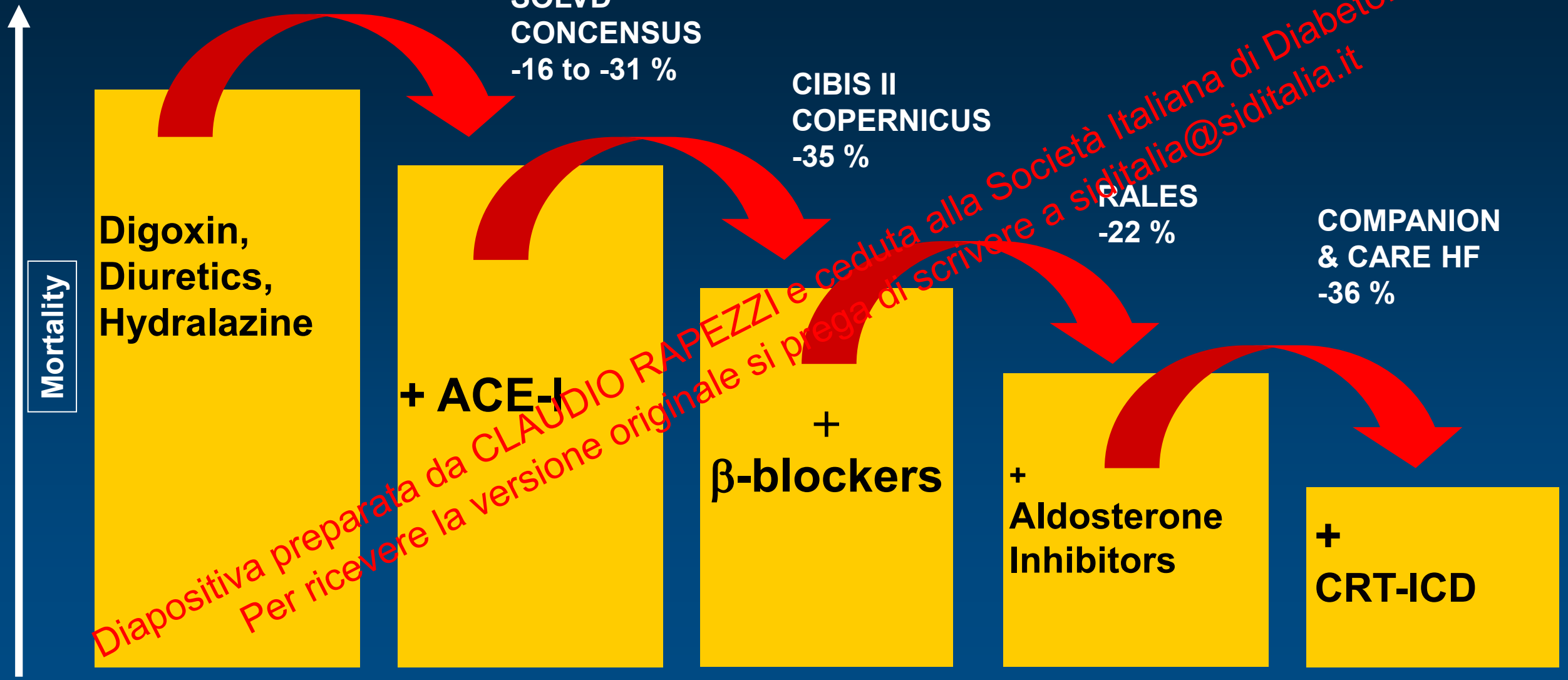
Improvement of myocardial energetics[1]

Improved renal function[2]

ECF, extracellular fluid; LV, left ventricular; SGLT2, sodium-glucose cotransporter 2.

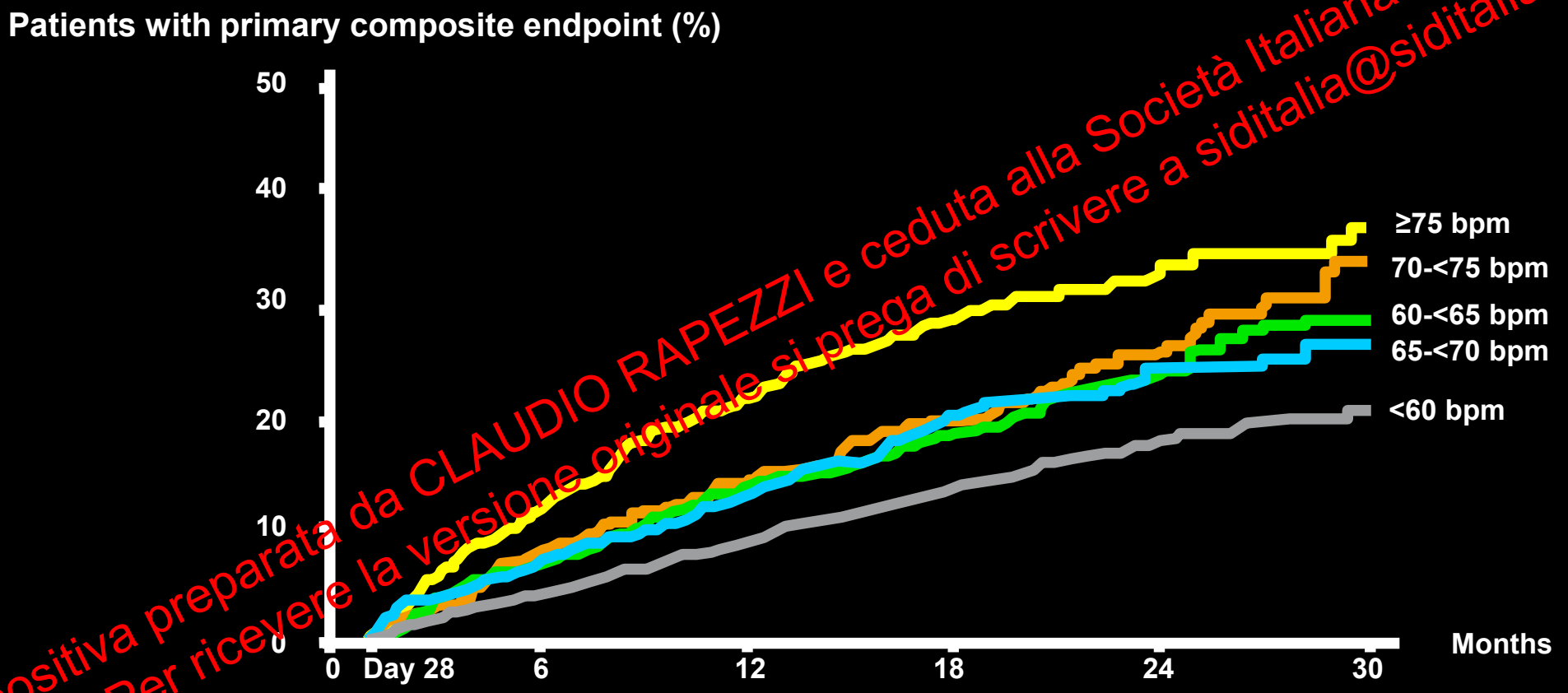
1. Verma S, et al. *JAMA Cardiol.* 2017;2:939-940. **2.** Sattar N, et al. *Diabetologia.* 2016;59:1333-1339.

HF TREATMENT PROGRESS



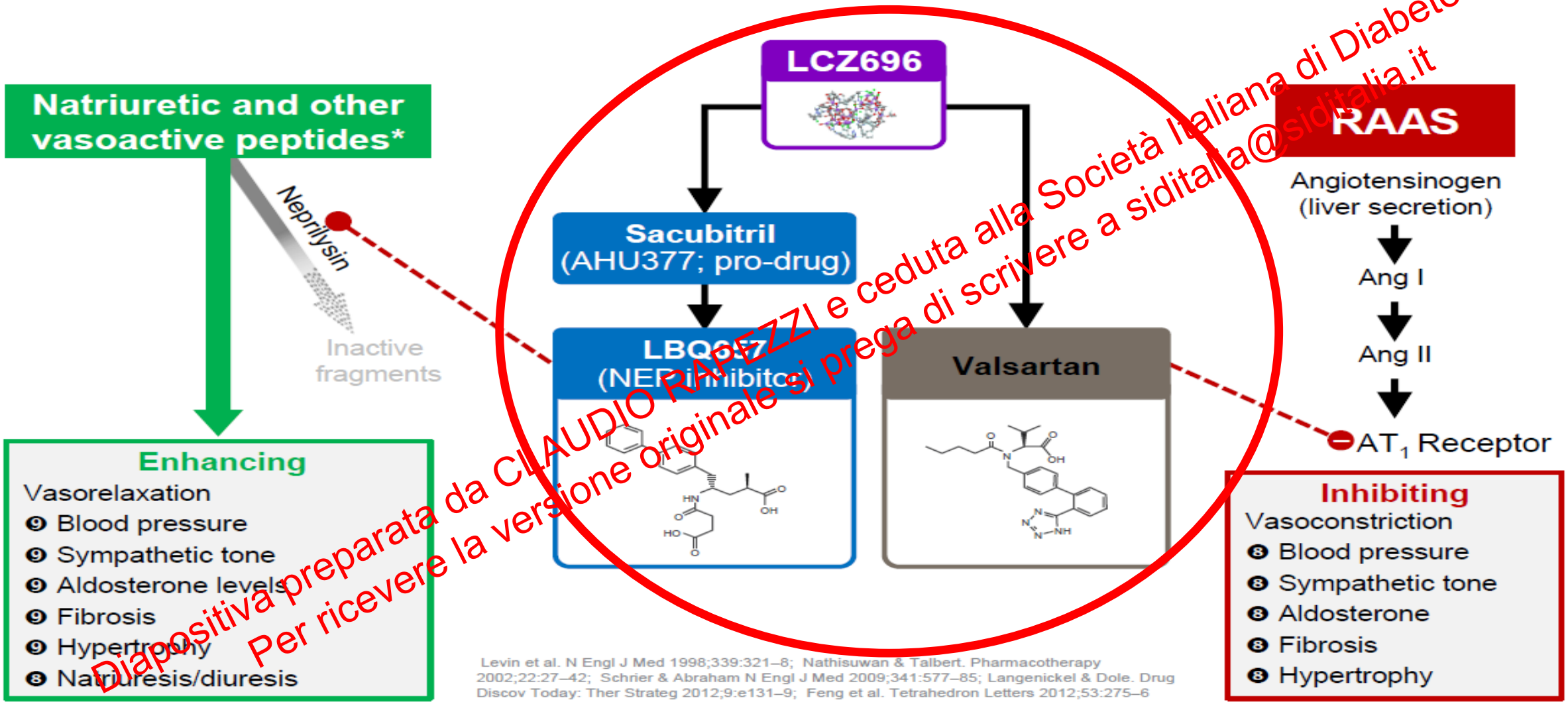
Ellenbogen KA, J Am Coll Cardiol 2005; 46: 2199-203

Primary composite endpoint according to HR achieved at day 28*



*Data exclude patients reaching primary composite endpoint in the first 28 days

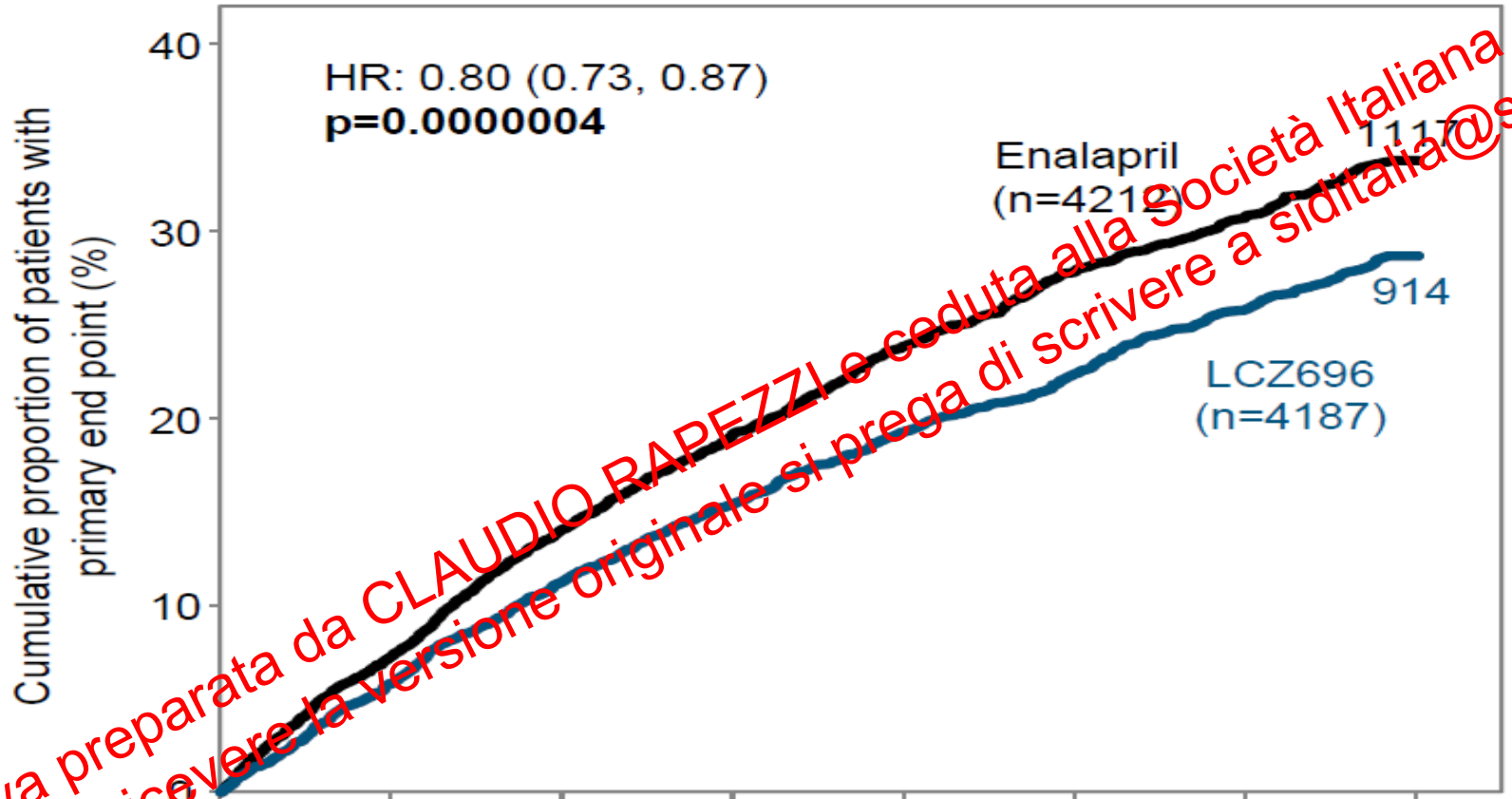
LCZ696 simultaneously inhibits NEP (via LBQ657) and blocks the angiotensin AT1 receptor (via valsartan)



Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Schrier & Abraham N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9; Feng et al. Tetrahedron Letters 2012;53:275–6

PARADIGM-HF: primary outcome

Death from CV causes or first hospitalisation

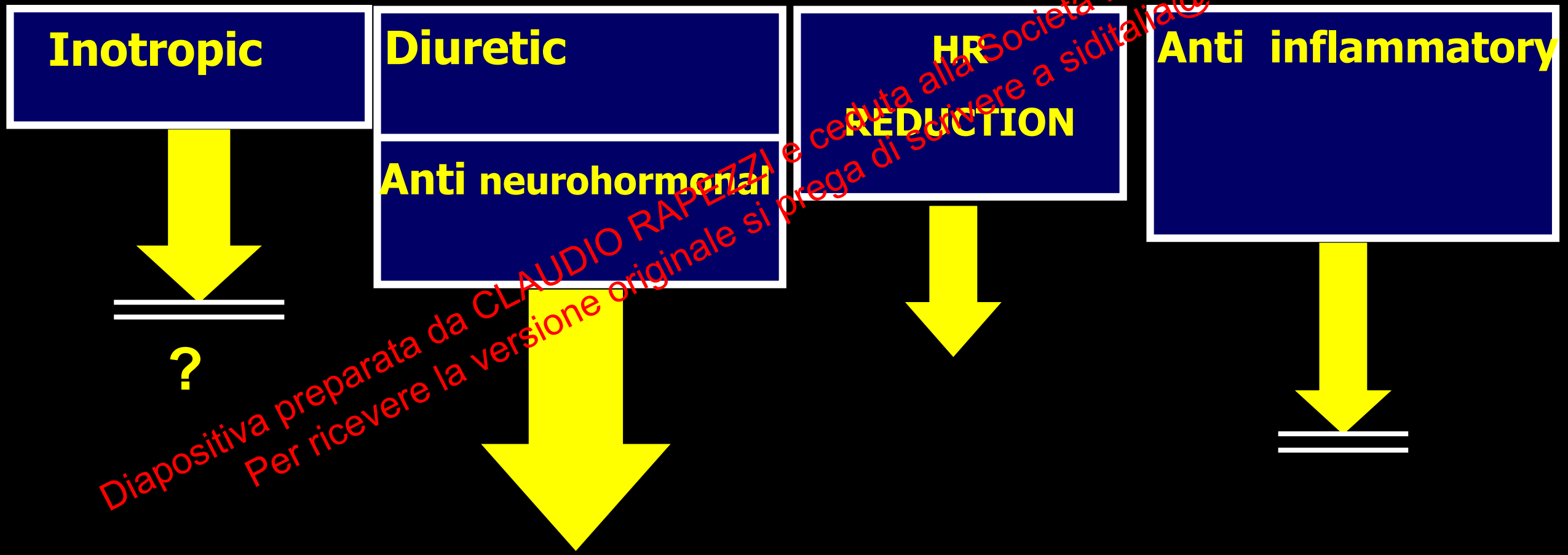


At risk

Enalapril:	4212	3883	3579	2922	2123	1488	853	236
LCZ696:	4187	3922	3663	3018	2257	1544	896	249

McMurray, Packer et al. N Engl J Med 2014; 371(11):993-1004

Recent Strategies in Heart Failure Therapy



Recent Strategies in Heart Failure Therapy

Hormonal substitution

CRT

Mitra Clip

Telemonitoring

?

Farmaci antidiabetici e scompenso cardiaco

1. I farmaci (alcuni) aumentano il rischio di scompenso
2. I farmaci sono neutrali
3. I farmaci riducono il rischio di scompenso nei diabetici con cardiopatia strutturale
4. I farmaci riducono il rischio di scompenso nei diabetici in generale
5. I farmaci (alcuni) sono efficaci nel trattamento dello scompenso anche nei non diabetici

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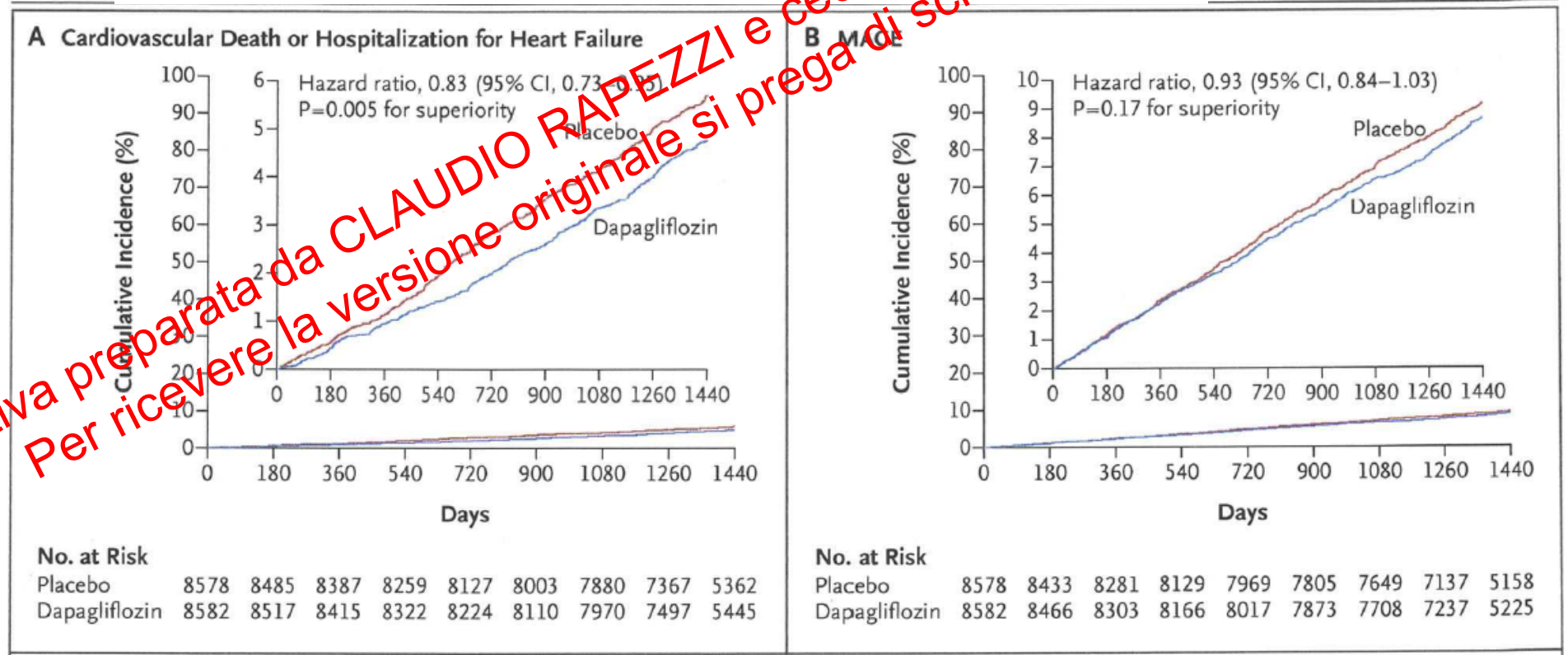
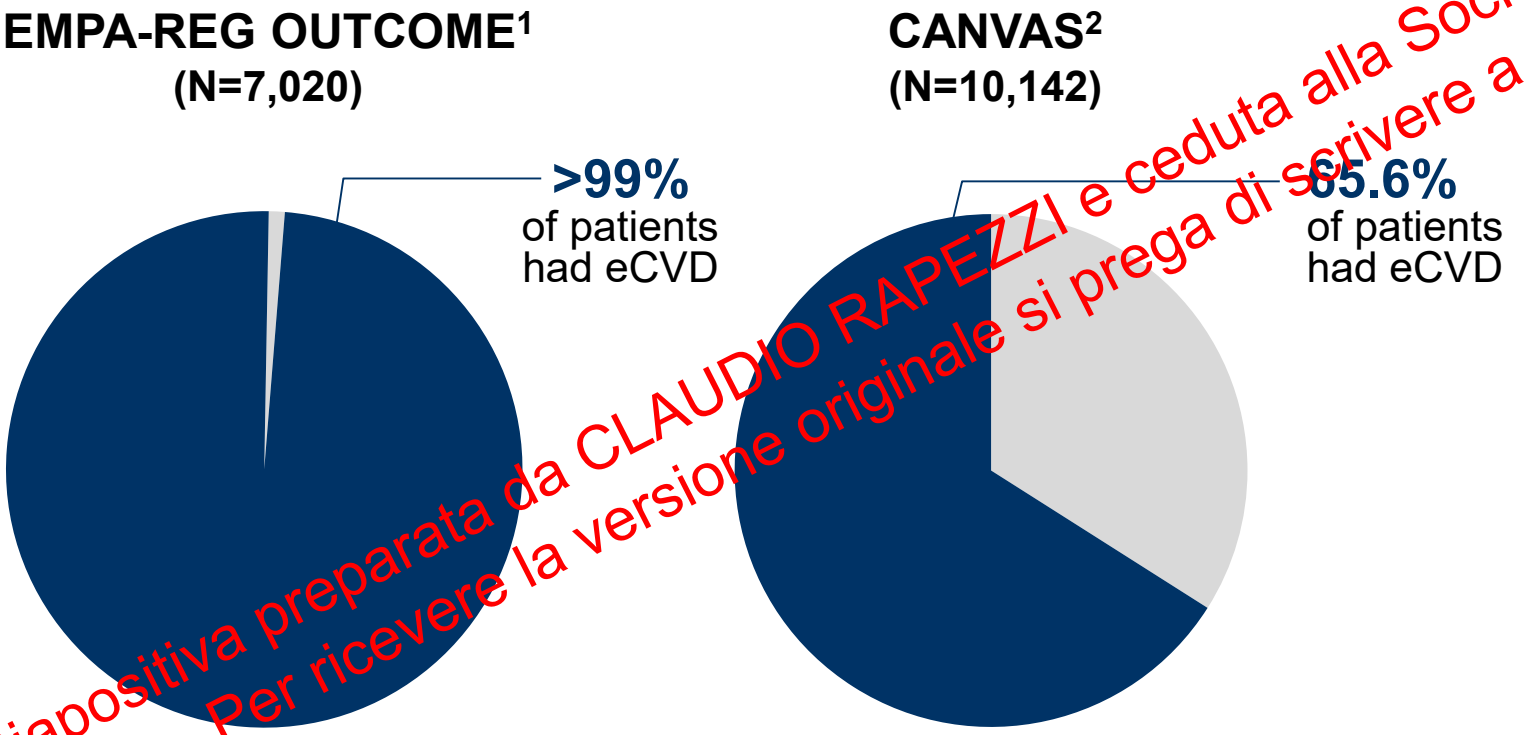
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*



While EMPA-REG and CANVAS suggest CV and renal risk can be reduced, these results were seen in T2D patients who predominantly (>65%) had established CV disease



>99% of T2D patients in the EMPA-REG OUTCOME trial and 65.6% of the T2D patients in the CANVAS trials already had established CV disease i.e. had a previous CV event (MI, stroke) or documented atherosclerosis (coronary artery stenosis, peripheral arterial stenosis)[1,2]

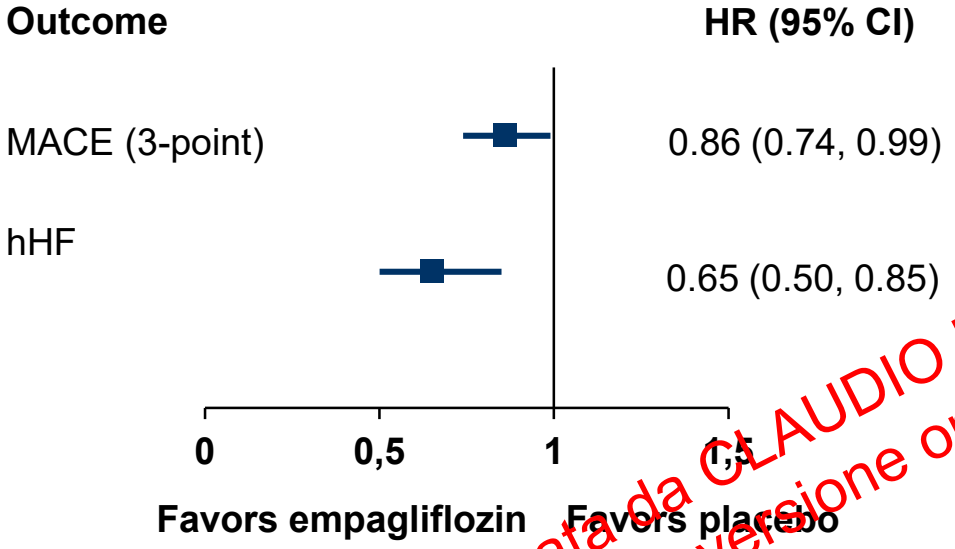
CV, cardiovascular; eCVD, established CV disease; MI, myocardial infarction; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

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

CV outcomes data for SGLT2 inhibitors are building

Two SGLT2 studies demonstrate a reduction in both MACE and heart failure endpoints

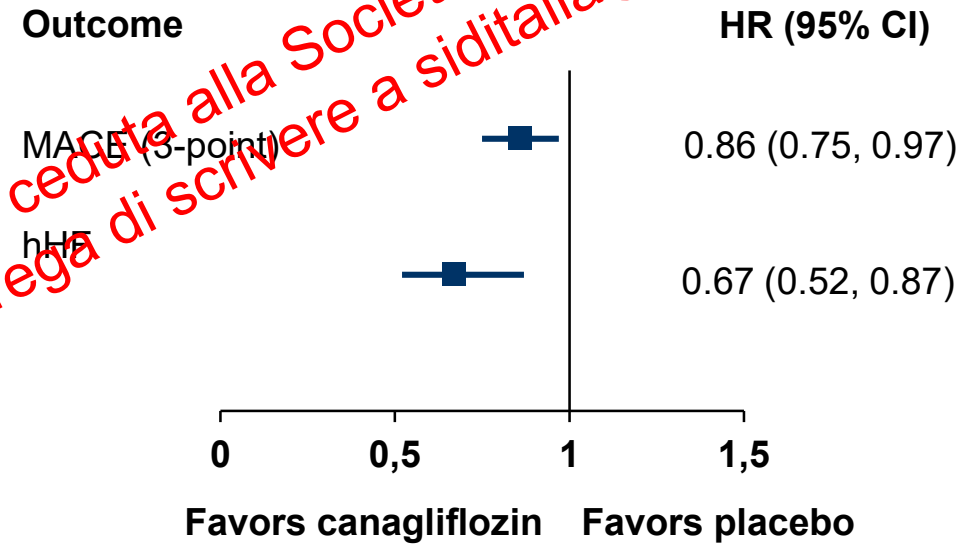
EMPA-REG OUTCOME



Demonstrated a significant reduction in CV events in patients receiving empagliflozin

Established CVD: 99%

CANVAS



Demonstrated a significant reduction in CV events in patients receiving canagliflozin

Established CVD: 66%

MACE, major adverse cardiovascular event (CV death, nonfatal MI and nonfatal stroke); MI, myocardial infarction; hHF hospitalization for heart failure.

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; Neal B, et al. *N Engl J Med* 2017 377:644-57

The majority of T2D patients in the DECLARE trial are in an earlier stage of the CV risk continuum and at lower CV risk

DECLARE included patients with T2D and either:

Multiple (≥2) risk factors
- ≥55-year-old males and ≥60 year-old females plus
- at least one of the following: dyslipidemia, hypertension or current smoking

≥40 years old with established atherosclerotic CV disease:
- ischemic heart disease,
- peripheral artery disease or
- cerebrovascular disease

Baseline Characteristics	Dapa (N=8,582)	Placebo (N=8,578)
Age, years, mean (SD)	63.9 (6.8)	64.0 (6.8)
BMI, kg/m^2, mean (SD)	32.1 (6.0)	32.0 (6.1)
HbA_{1c}, %, mean (SD)	8.3 (1.2)	8.3 (1.2)
eGFR, mean (SD)	85.4 (15.8)	85.1 (16.0)
Multiple risk factors, n (%)	**10,186 (59.4%)**	
Est CV disease, n (%)	**6,974 (40.6%)**	

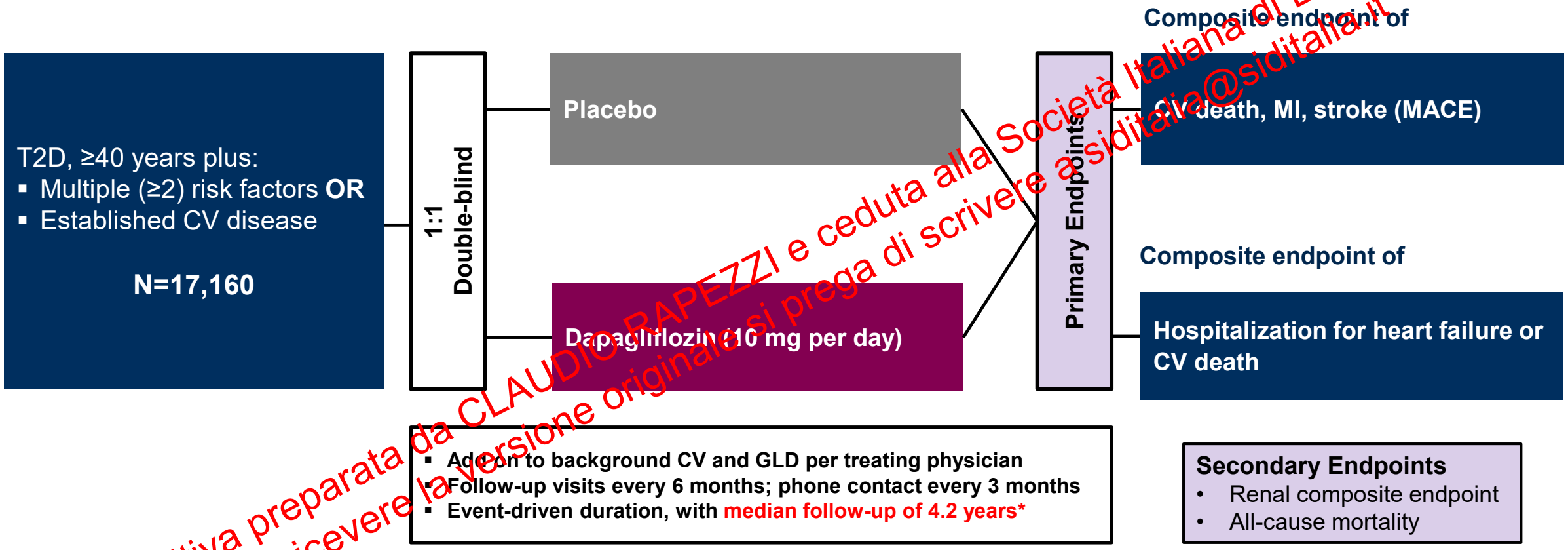
The patients in the DECLARE[1,2] trial had better baseline renal function than the EMPA-REG OUTCOME[3] or CANVAS[4] trials

	DECLARE	CANVAS	EMPA-REG
eGFR, mean (mL/min/1.73m^2)	**85.2**	76.5	74.1
Micro-/macro-albuminuria (%)	**30.2**	30.2	40.6

BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; SD, standard deviation; T2D, type 2 diabetes,

1. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 2. Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018; 3. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 4. Neal B, et al. *N Engl J Med* 2017;377:644–657

DECLARE-TIMI 58: Broad CV risk population & 2 clinically relevant and important CV primary endpoints in type 2 diabetes



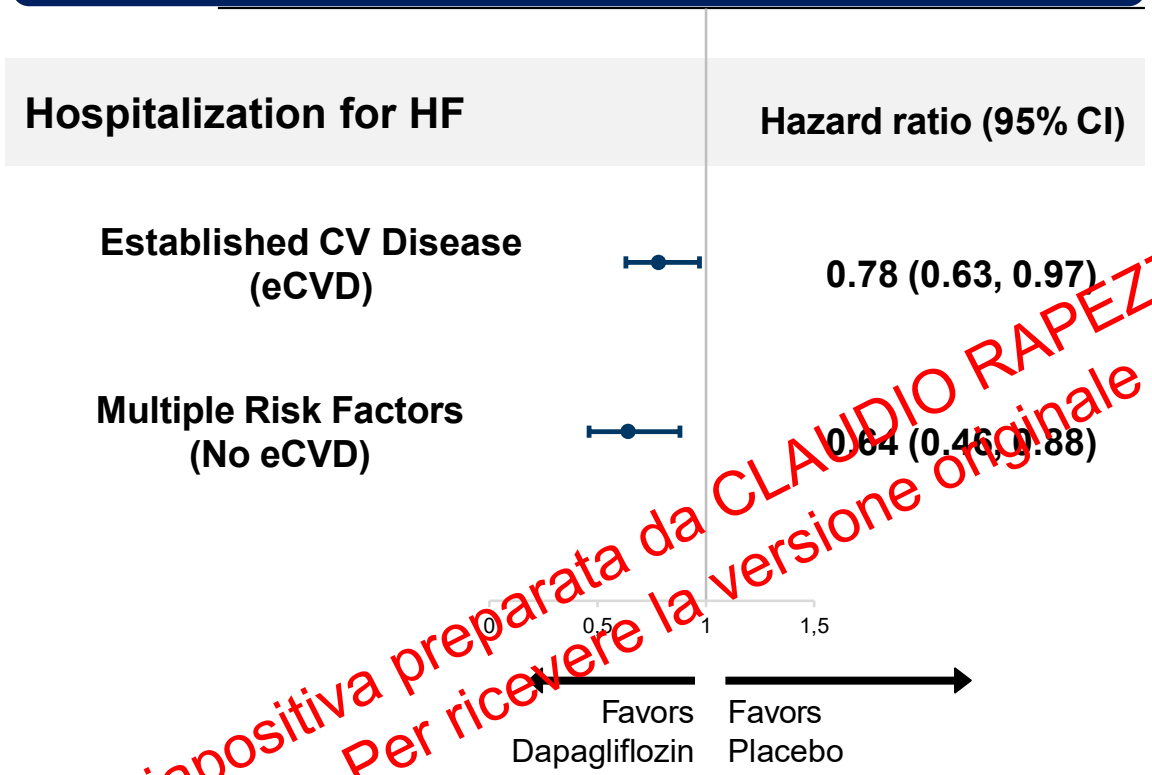
*median follow-up times: CANVAS – 2.4yrs; EMPA-REG OUTCOME – 3.1yrs

CV, cardiovascular; GLD, glucose-lowering drug; MACE, major adverse cardiac event; MI, myocardial infarction; T2D, type 2 diabetes

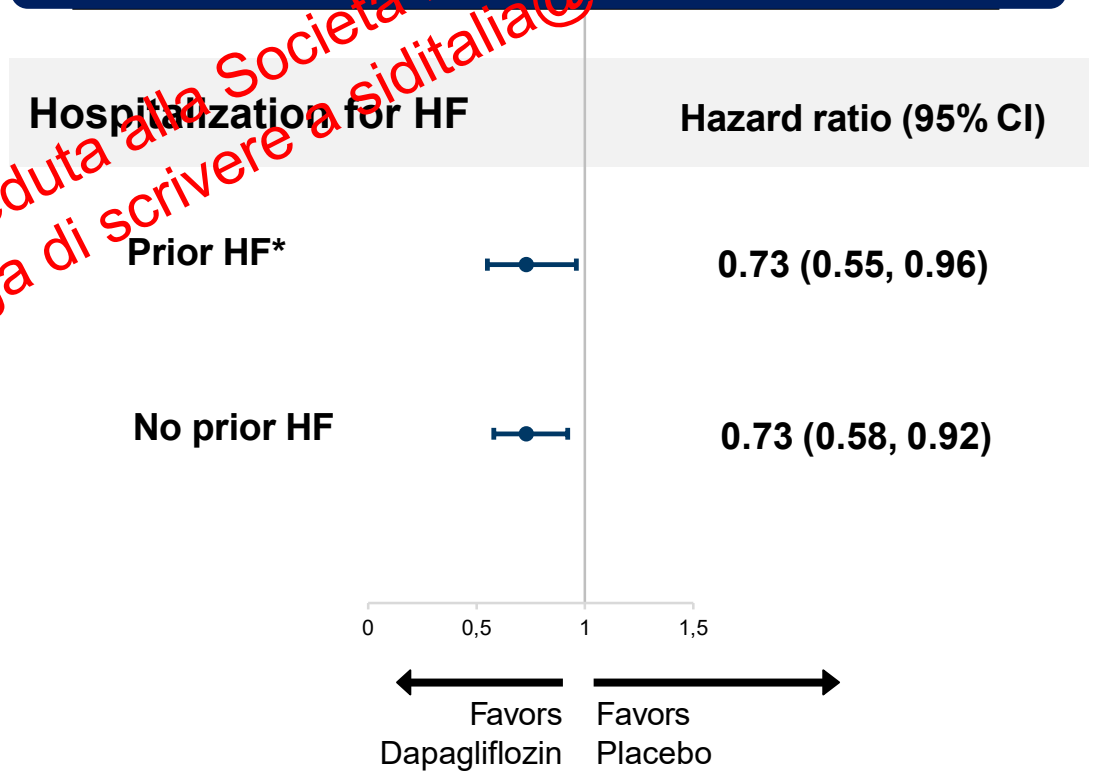
1. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 2. Wiviott SD, et al. *Am Heart J* 2018;200:83–89; 3. Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018; 4. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 5. Neal B, et al. *N Engl J Med* 2017;377:644–657

Dapagliflozin prevents hHF consistently across a broad range of T2D patients regardless of history of eCVD or HF

hHF by presence/absence of eCVD



hHF by presence/absence of previous HF



*10% of patients in DECLARE had prior HF

CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

Definition of Heart Failure Classifications: DECLARE HF Subgroup Analysis

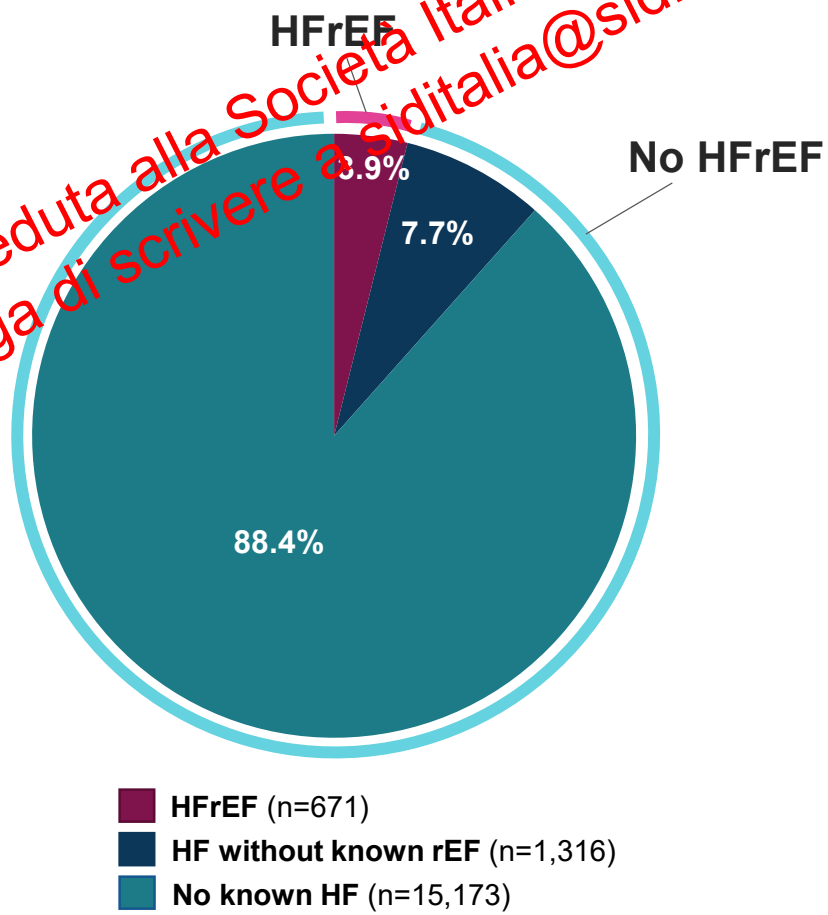
HFrEF

- 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

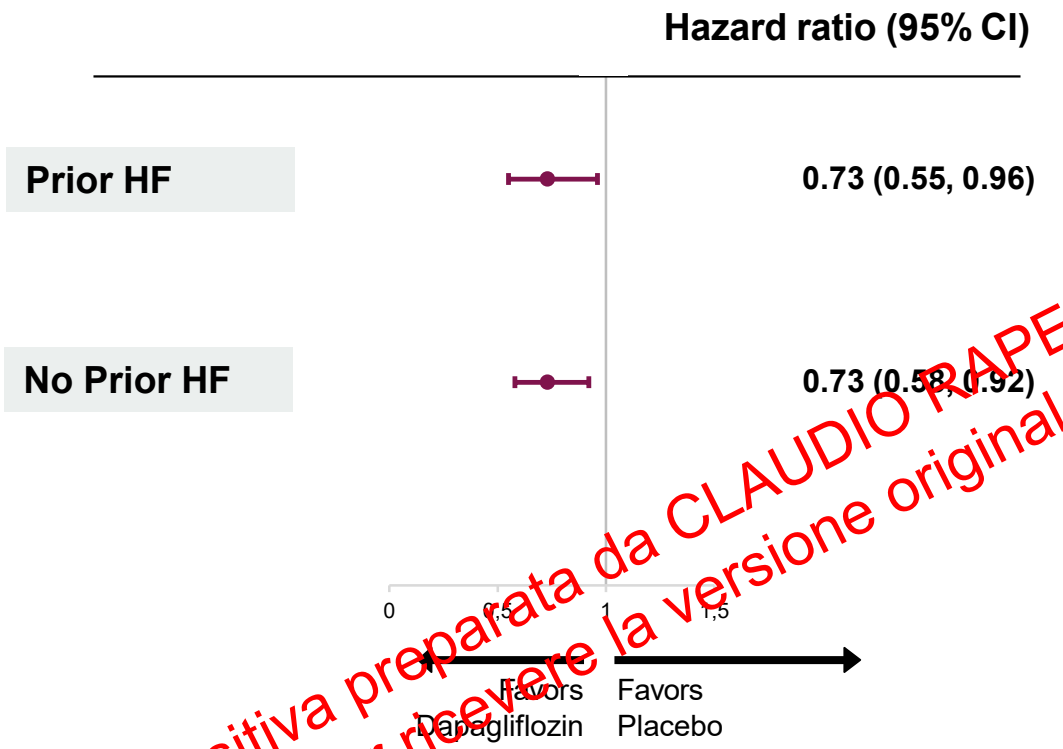


EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced EF; rEF = reduced EF.

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

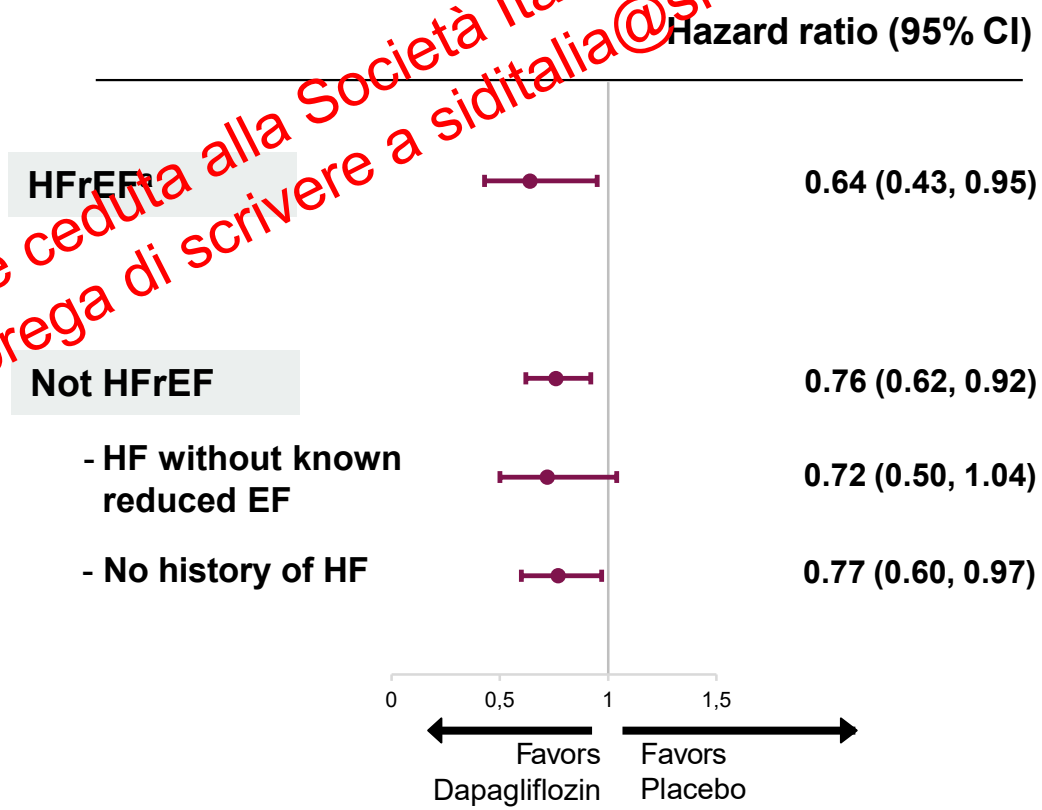
Dapagliflozin prevents hHF regardless of history of HF or ejection fraction in patients with T2D

hHF: history of HF[1]



10% of patients in DECLARE had prior HF

hHF: ejection fraction[2]

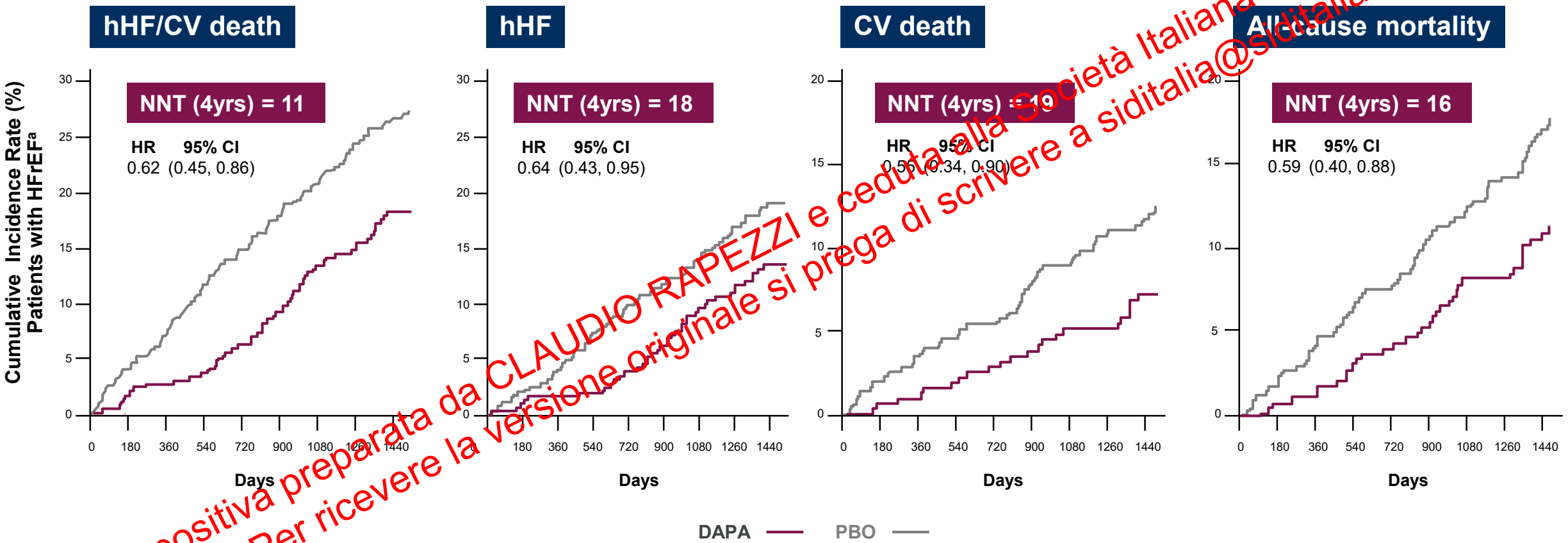


3.9% of patients in DECLARE had HFrEF[a]

[a]Defined as EF <45% or severe/moderate LV systolic dysfunction, with or without history of HF. CV = cardiovascular; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; LV = left ventricular.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Kato ET et al. Online ahead of print. *Circulation*. 2019.

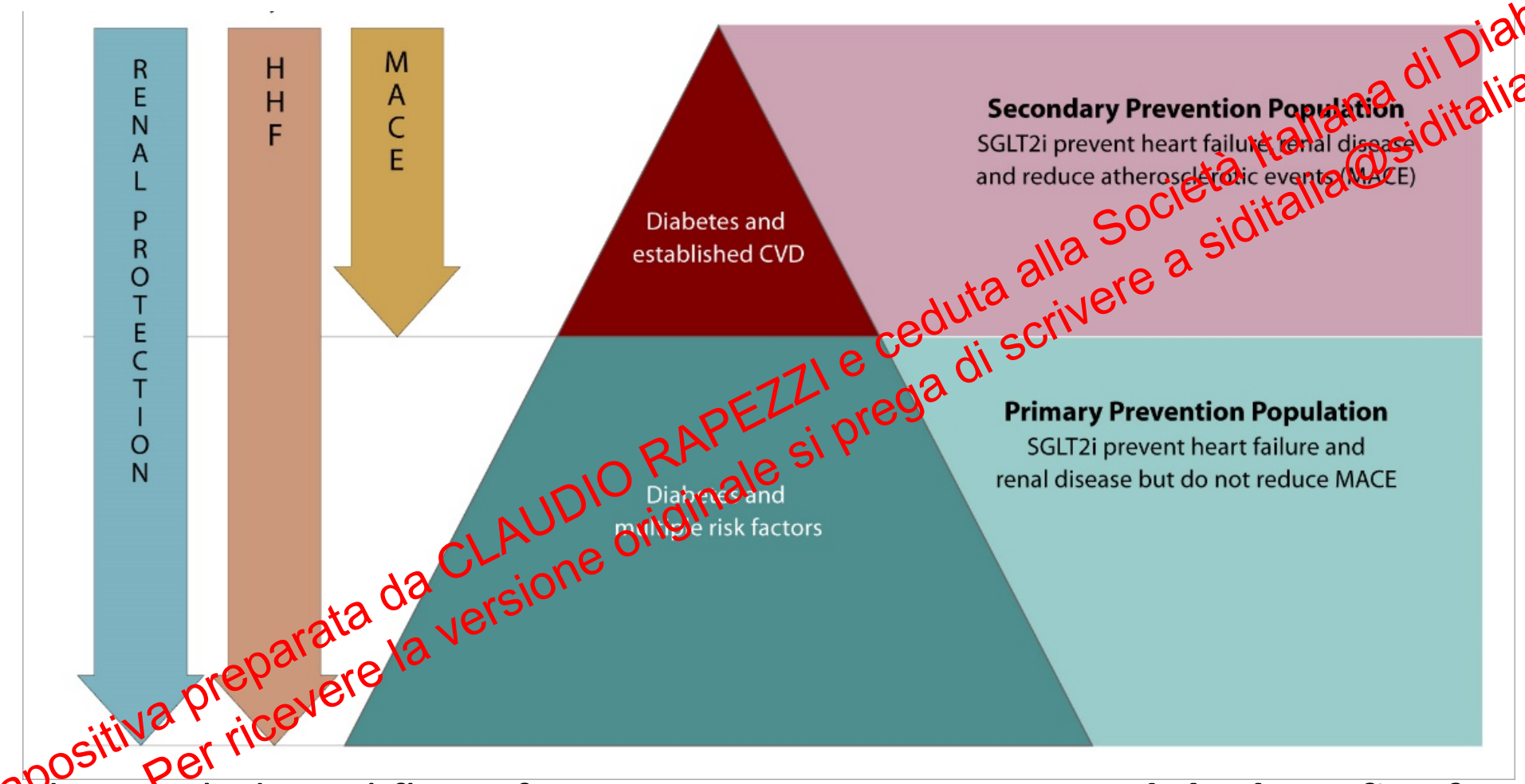
The CV benefits of dapagliflozin appear early in T2D patients with HFrEF[a]



[a]Defined as EF <45% or severe/moderate LV systolic dysfunction, with or without history of HF. CV = cardiovascular; DAPA = dapagliflozin; EF =ejection fraction; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; HR = hazard ratio; LV = left ventricular; NNT = number needed to treat; PBO = placebo; T2D = type 2 diabetes; yrs = years.

Kato ET et al. Online ahead of print. *Circulation.* 2019.

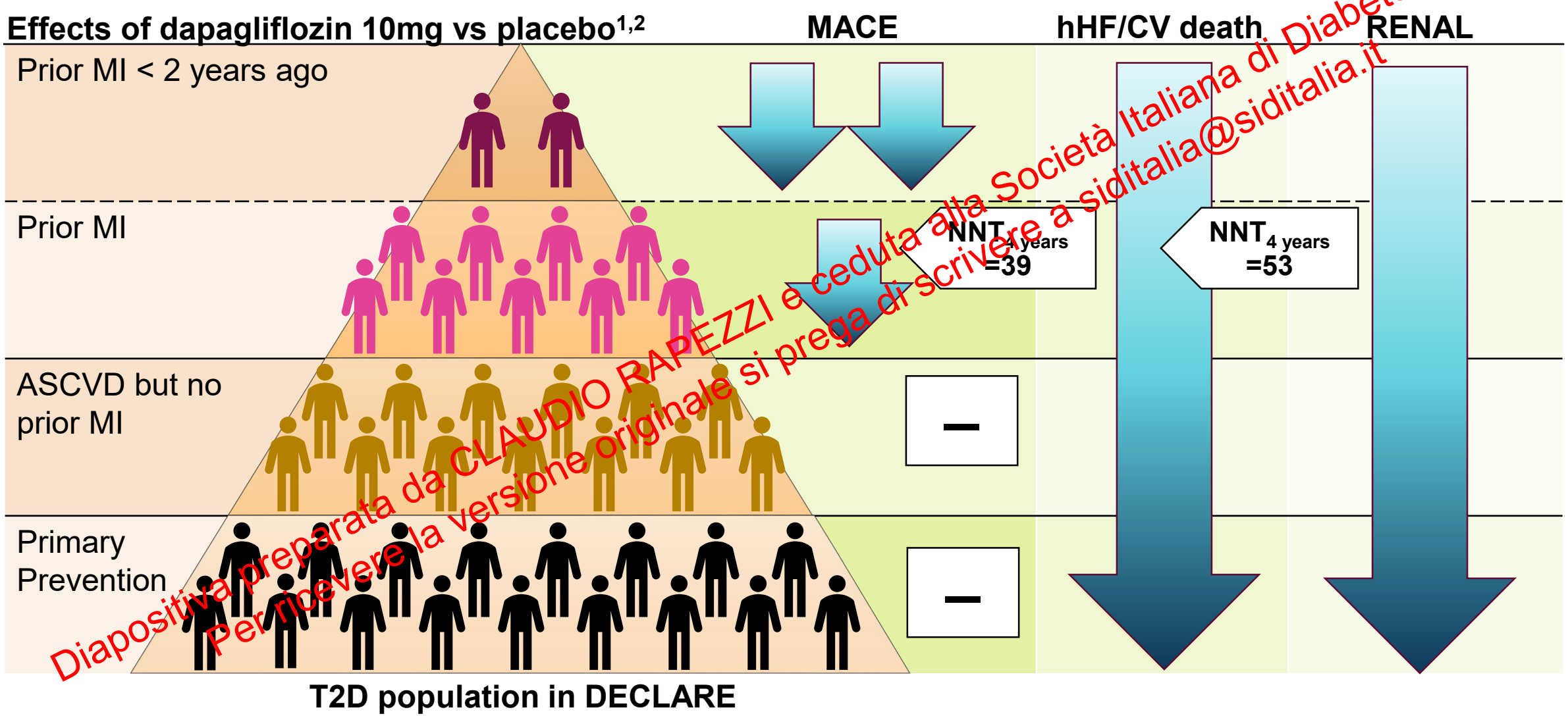
Pump, pipes, and filter: do SGLT2 inhibitors cover it all?



These data with dapagliflozin from **DECLARE- TIMI 58 extend the benefit of SGLT2i to a broader population of patients** for primary and secondary prevention

Verma S, Jüni P, Mazer CD, The Lancet 2018,

Pump, pipes and filter: dapagliflozin covers it all



ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; hHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction; NNT = number needed to treat; T2D = type 2 diabetes.

1. Verma S et al. Online ahead of print. *Circulation.* 2019; 2. Furtado RHM et al. Online ahead of print. *Circulation.* 2019.

Farmaci antidiabetici e scompenso cardiaco

1. I farmaci (alcuni) aumentano il rischio di scompenso
2. I farmaci sono neutrali
3. I farmaci riducono il rischio di scompenso nei diabetici con cardiopatia strutturale
4. I farmaci riducono il rischio di scompenso nei diabetici in generale
5. I farmaci (alcuni) sono efficaci nel trattamento dello scompenso anche nei non diabetici

Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists

Orly Vardeny, PharmD, MS,[a] Muthiah Vaduganathan, MD, MPH[b]

(J Am Coll Cardiol HF 2019;7:969–72)

CENTRAL ILLUSTRATION Stepwise Approach to Prescription of SGLT2 inhibitors by Cardiologists

Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target:

Switch non-metformin oral therapies (e.g. sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target:

Consider SGLT2i initiation

Drug Type

Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)

- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies

Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status

Pre-Initiation eGFR must be above:

- 60 mL/min/1.73 m^2 (dapagliflozin, ertugliflozin)
- 45 mL/min/1.73 m^2 (canagliflozin, empagliflozin)

Anticipatory Guidance

Consider diuretic dose reduction

Patient Counseling

- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care

Close communication with other providers, including PCPs and endocrinologists

Follow-up and Monitoring

- Serial assessment of renal function, body weights, blood pressure, and symptoms
- Dose uptitration guided by need for glycemic control
- Ensure adherence to SGLT2i, other therapies, and therapeutic lifestyle
- Multidisciplinary care team follow-up

Vardeny, O. et al. J Am Coll Cardiol HF. 2019;7(2):169–72.