G META OPEN FORUM
AL CUORE DEL DIABETE

Roma, 11 – 12 marxo 2022

CARDIOLOGO E DIABETOLOGO

IL DIABETE VISTO DAL CARDIOLOGO

Pasquale Perrone Filardi
Università Federico II di Napoli

DISPROF PASQUALE PERRONE FILARDI
DISCLOSURE

SPEAKER/CONSULTANCY
HONORARIA

ALEXION
AMARIN
AMGEN
ASTELLAS
ASTRAZENECA
AURORA BIOFARMA
BAYER
BMS PFIZER
BOEHRINGER INGELHEIM
BRUNO FARMACEUTICI
DAIICHI
DOC GENERICI
ELI LILLY
ERREKAPPA
MERCK SERONO
MENARINI
NOVARTIS
NOVONORDISK
PIAM
SANOFI
TAKEDA
VIFOR

THE CARDIO-NEFRO-METABOLIC CONTINUUM

HF, CKD, and T2D Are Often Comorbid

2 - 3% IN ITALIA
>1.000.000 PAZIENTI

HF

2017 Global Prevalence[1]
~64M

HF and **CKD** vicious circle: one causes/worsens the other[2]

CKD

2017 Global Prevalence[3]
~843M

7% IN ITALIA
>4.000.000 PAZIENTI

24% of patients with T2D have HF as their first complication[4]

Diabetes

2019 Global Prevalence[5]
~463M

58% of patients with T2D will develop CKD[6]

3,8 % IN ITALIA
>3.300.000 PAZIENTI

CKD = chronic kidney disease; HF = heart failure; M = million; T2D = type 2 diabetes.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Ronco C et al. *J Am Coll Cardiol.* 2008;52:1527-1539; 3. Jager KJ et al. *Nephrol Dial Transplant.* 2019;34:1803-1805; 4.Birkeland KI et al. *Diabetes Obes Metab.* 2020:22:1607-1618; 5. IDF Diabetes Atlas, 9th edition. www.diabetesatlas.org. Accessed September 1, 2021; 6. Parving HH et al. *Kidney Int.* 2006;69:2057-2063.

CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries

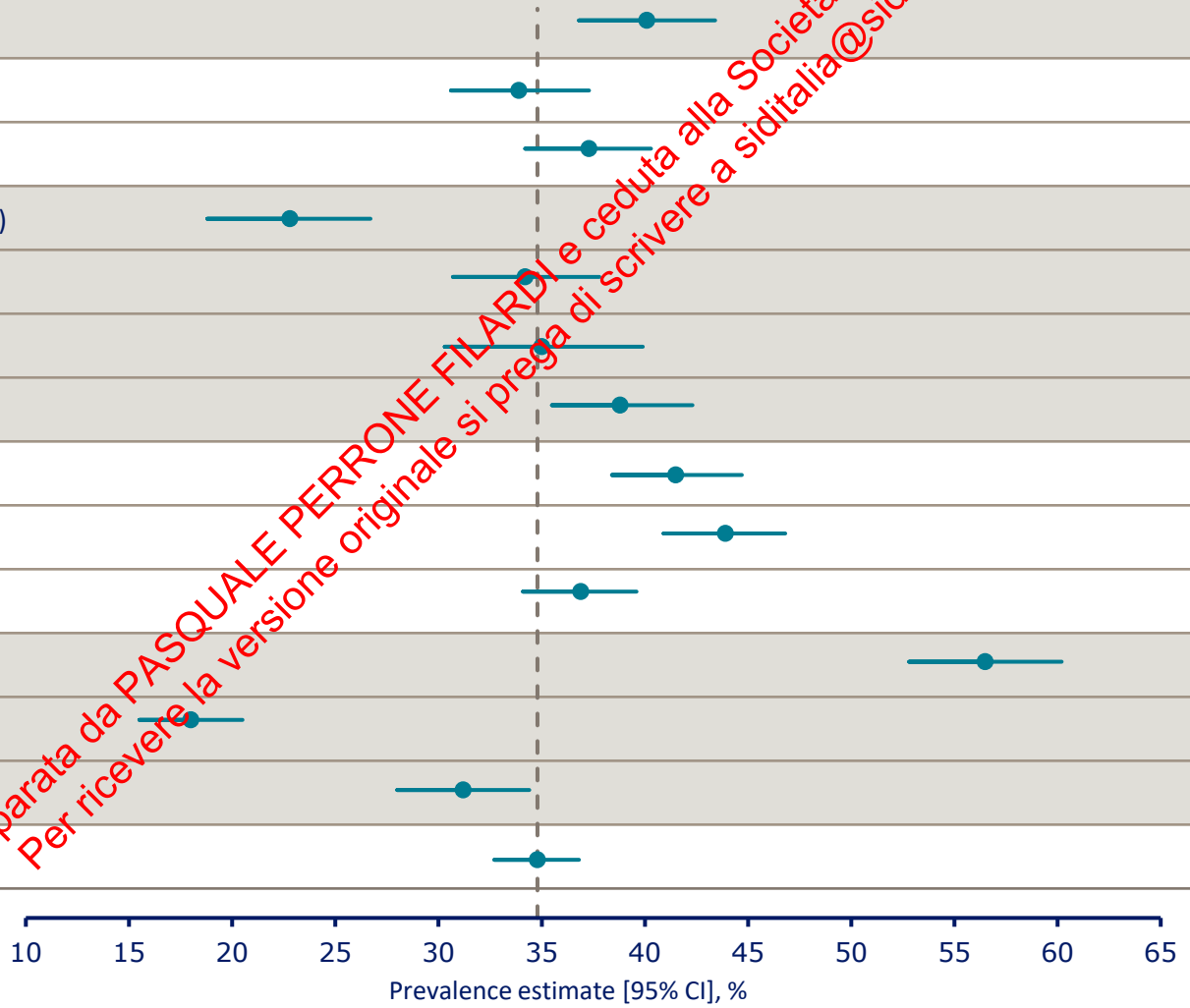
Ofri Mosenzon, Abdullah Alguwaihes, Jose Luis Arenas Leon, Fahri Bayram, Patrice Darmon, Timothy M.E. Davis, Guillermo Dieuzeide, Kirsten T. Eriksen, Tianpei Hong, Margit S. Kaltoft, Csaba Lengyel, Nicolai A. Rhee, Giuseppina T. Russo, Shinichiro Shirabe, Katerina Urbancova, Sergio Vencio, on behalf of the CAPTURE study investigators

Trial numbers: NCT03786406; NCT03811288

Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

Weighted CVD prevalence in people with T2D across the 13 countries

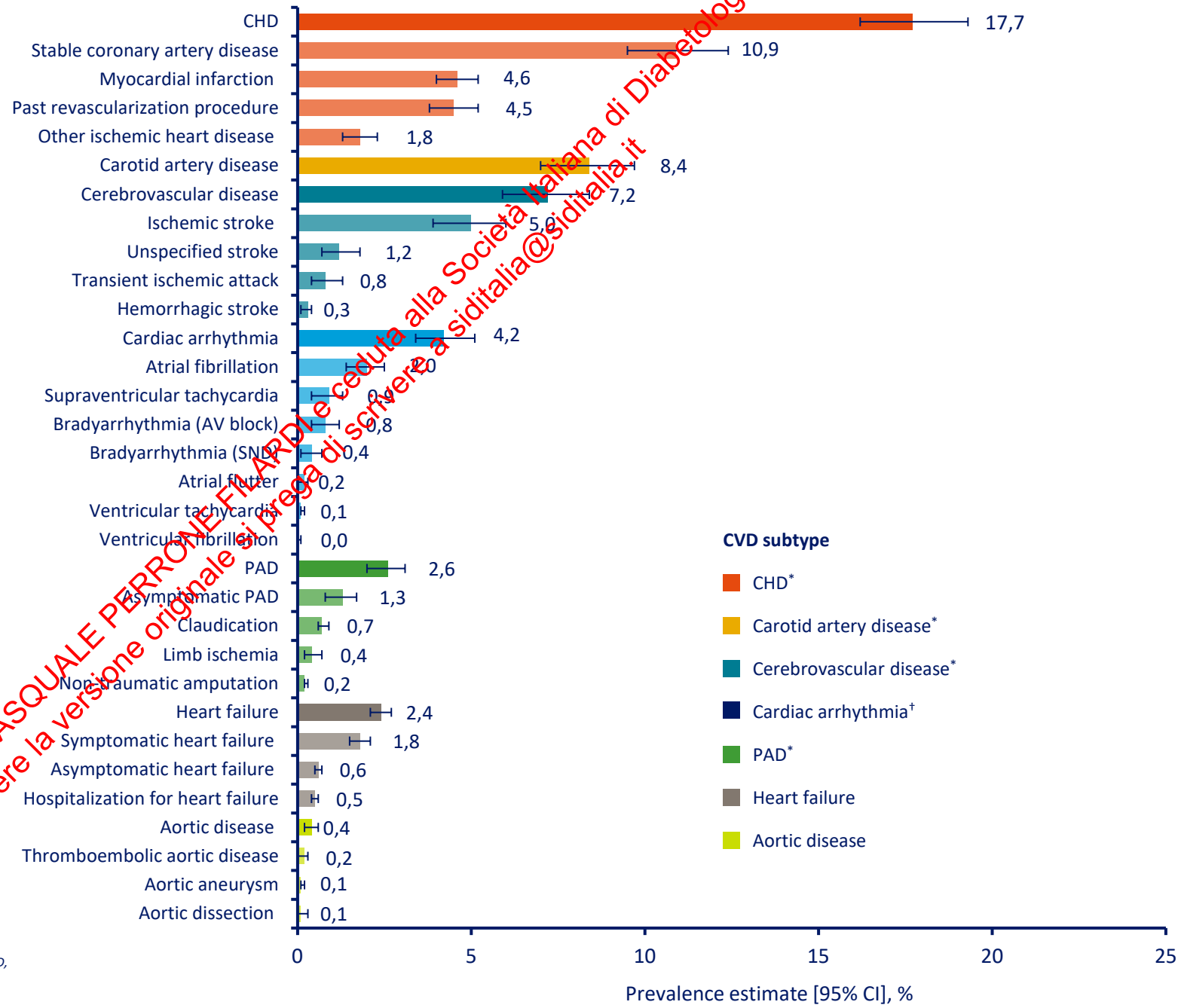
Region	Country (number of participants; estimated diabetes population size)	n	Prevalence estimate [95% CI], %
Australasia	**Australia** (824; 1,133,000)	332	40.1 [36.8; 43.4]
East Asia	**China** (805; 114,394,800)	273	33.9 [30.6; 37.3]
	Japan (800; 7,234,200)	298	37.3 [34.2; 40.3]
Europe	**Czech Republic** (400; 767,800)	91	22.8 [18.8; 26.7]
	France (659; 3,276,400)	220	34.2 [30.7; 37.8]
	Hungary (400; 706,800)	140	35.0 [30.3; 39.9]
	Italy (816; 3,402,300)	317	38.8 [35.5; 42.3]
Latin America	**Argentina** (834; 1,757,500)	347	41.5 [38.4; 44.7]
	Brazil (912; 12,465,800)	400	43.9 [40.9; 46.8]
	Mexico (820; 12,030,100)	302	36.9 [34.1; 39.6]
Middle East	**Israel** (869; 415,800)	454	56.5 [52.8; 60.2]
	KSA (883; 3,852,000)	158	18.0 [15.5; 20.5]
	Turkey (801; 6,694,400)	250	31.2 [28.0; 34.4]
Overall	**Overall** (9,823; 168,130,900)	3,582	34.8 [32.7; 36.8]



Adapted from Figure 1
CI, confidence interval; CVD, cardiovascular disease; KSA, Kingdom of Saudi Arabia; n, number of participants with CVD; T2D, type 2 diabetes

Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

Overall weighted CVD prevalence in people with T2D by CVD subtype and diagnosis



Adapted from Figure 2
**Categorized as ASCVD. †Included conduction abnormalities*
ASCVD, atherosclerotic CVD; AV, atrioventricular; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; PAD, peripheral artery disease; SND, sinus node dysfunction; T2D, type 2 diabetes

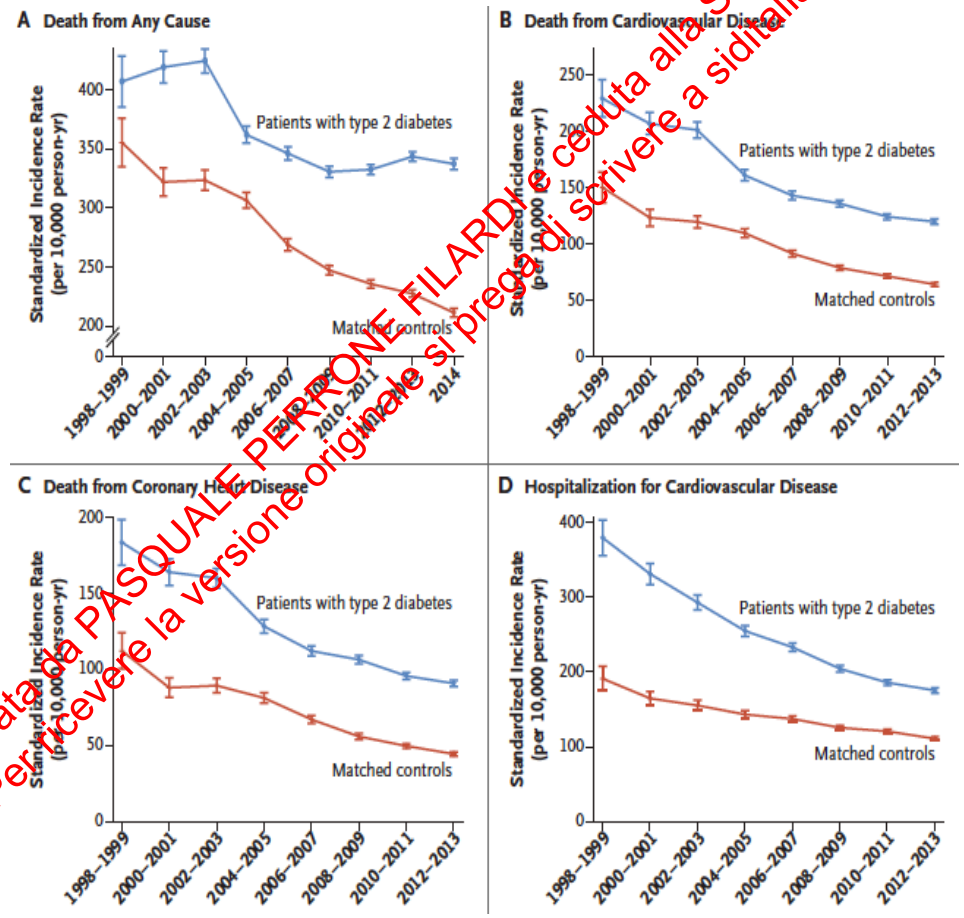
Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2017 VOL. 376 NO. 15

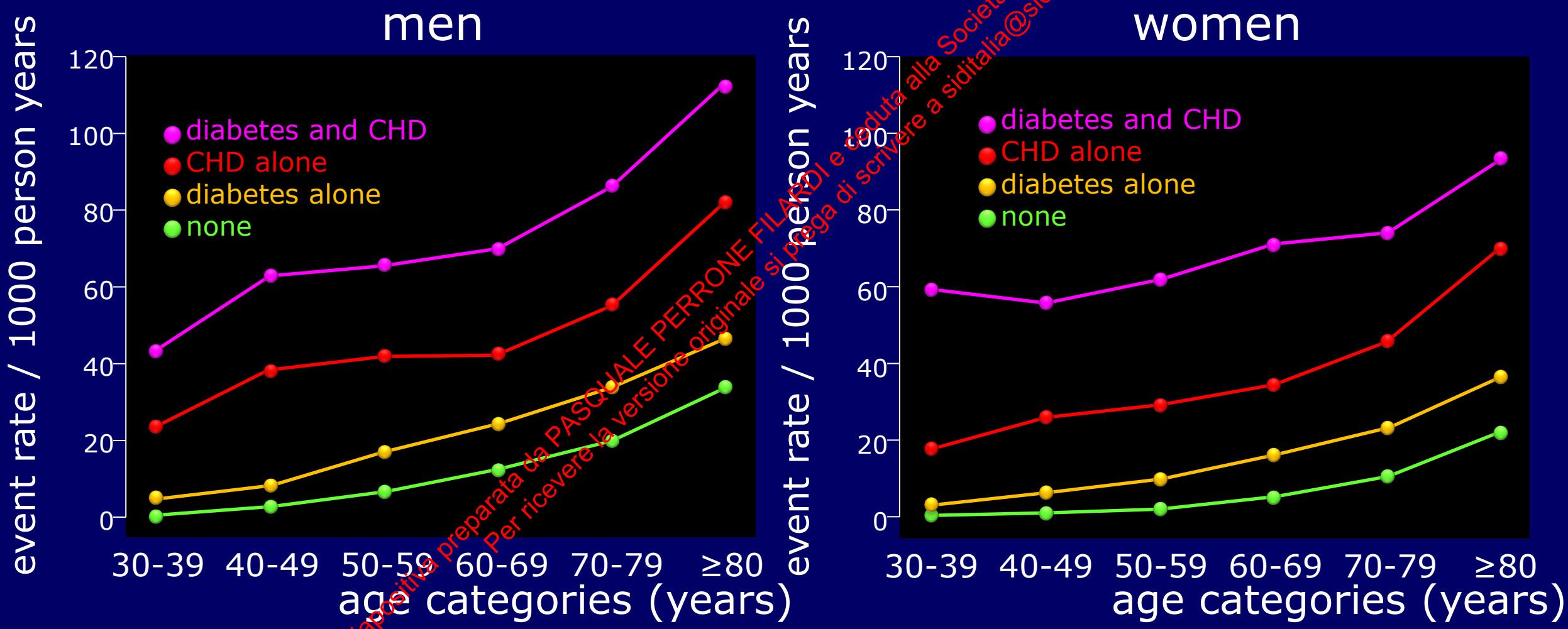
Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.



Coronary heart disease rates stratified by sex and age in four cohorts by history of DM or CHD

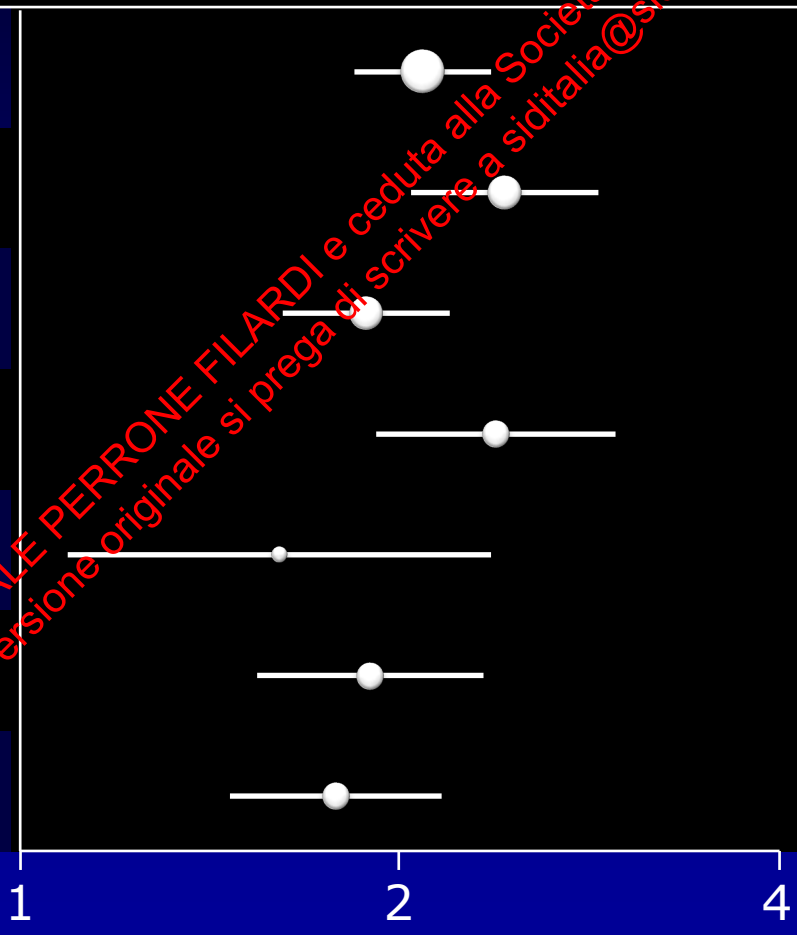
N=1,586,061 active KPNC members, ages 30 to 90 years



Rana JS et al.: J Gen Internal Med 31:387, 2016

vascular outcomes in patients with diabetes mellitus

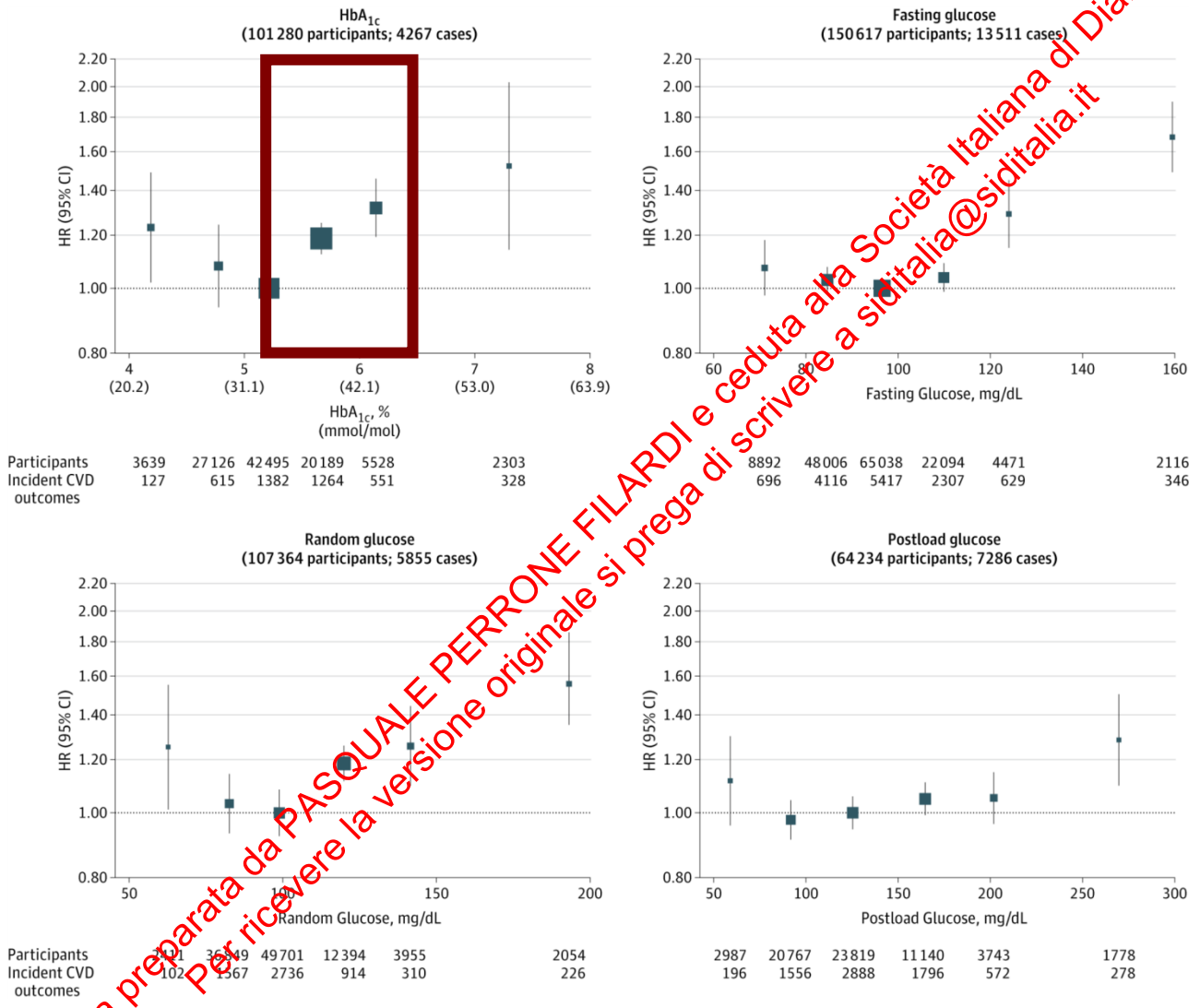
	cases	Hazard Ratio (95% CI)
coronary heart disease	26,505	2.00 (1.83 – 2.19)
coronary death	11,556	2.31 (2.05 – 2.60)
non-fatal myocardial inf.	14,741	1.82 (1.64 – 2.03)
ischemic stroke	3,799	2.27 (1.95 – 2.65)
haemorrhagic stroke	1,183	1.56 (1.19 – 2.05)
unclassified stroke	4,973	1.84 (1.59 – 2.13)
other vascular deaths	3,826	1.73 (1.51 – 1.98)



Based on 530 083 participants. Adjusted for age, smoking status, body-mass index, systolic blood pressure and, where appropriate, stratified by sex and trial arm

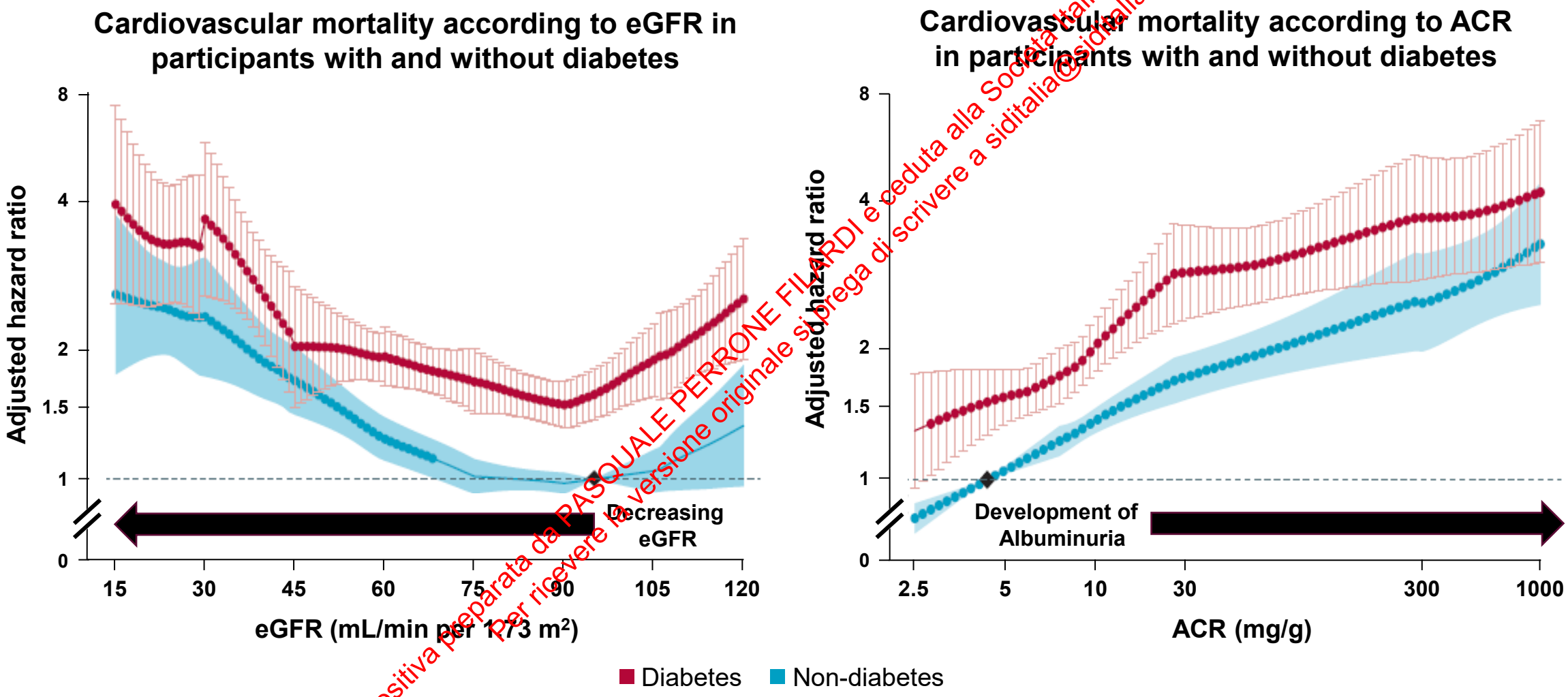
The Emerging Risk Factors Collaboration: Lancet 375:2215, 2010 doi: 10.1016/S0140-6736(10)60484-9.

Glycated Hemoglobin Measurement and Prediction of Cardiovascular Disease



JAMA. 2014;311(12):1225-1233. doi:10.1001/jama.2014.1873

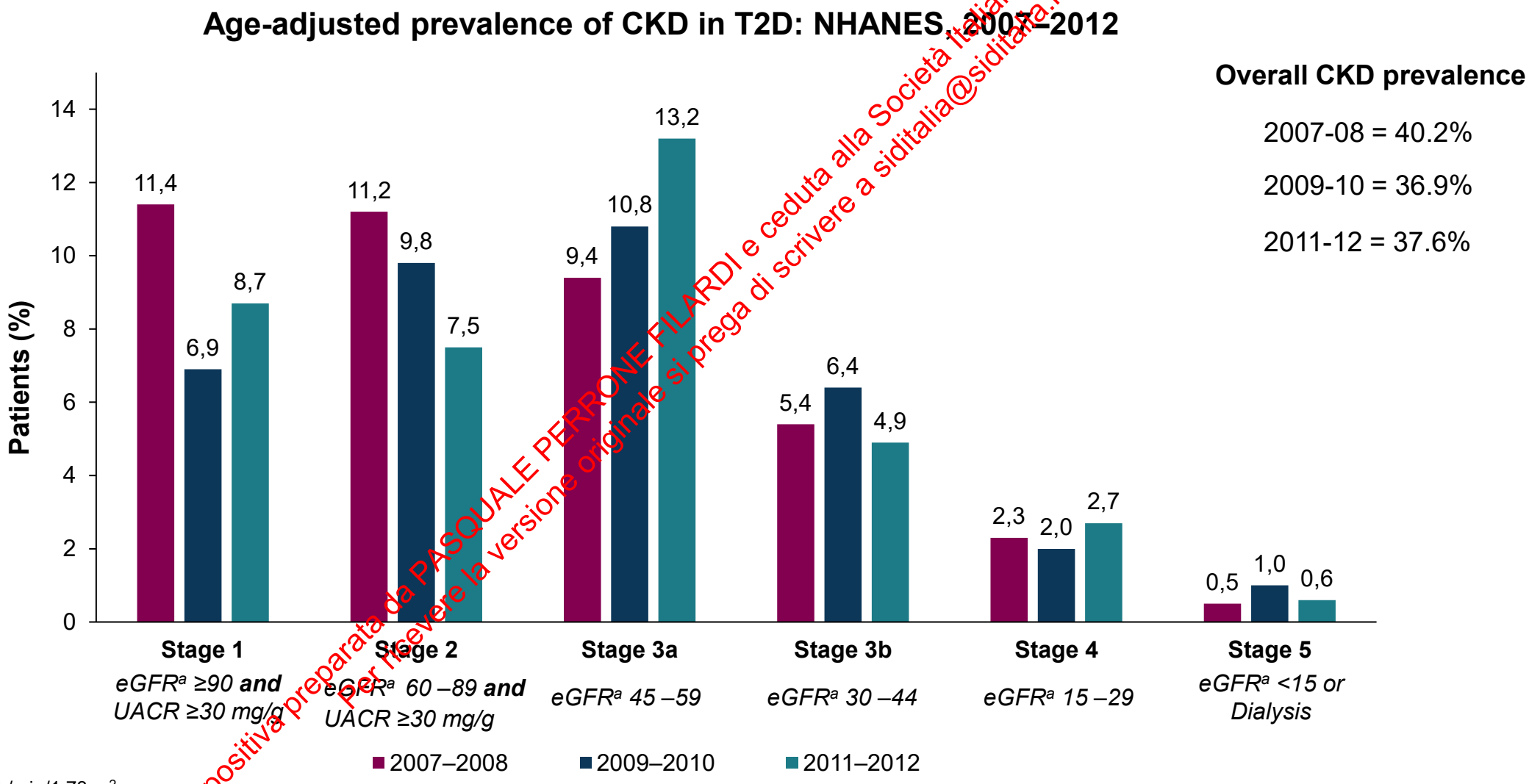
In the presence of T2D, lower eGFR and higher albuminuria independently predict higher CV mortality



ACR = albumin:creatinine ratio; CV = cardiovascular; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Fox C et al. *Lancet.* 2012;380:1662-1674.

The prevalence of CKD in patients with T2D remains high



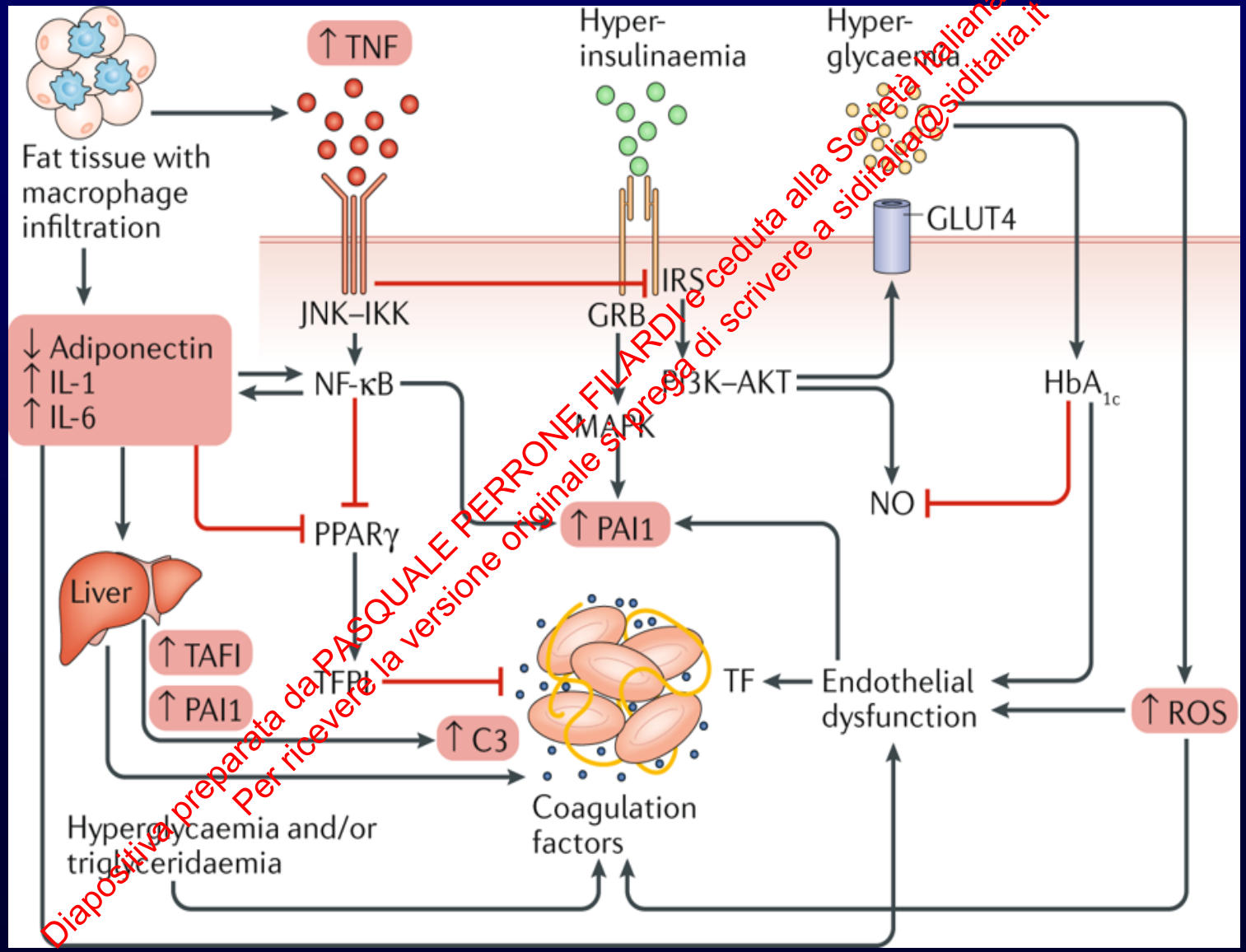
[a] eGFR units are mL/min/1.73 m^2.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio; T2D = type 2 diabetes.

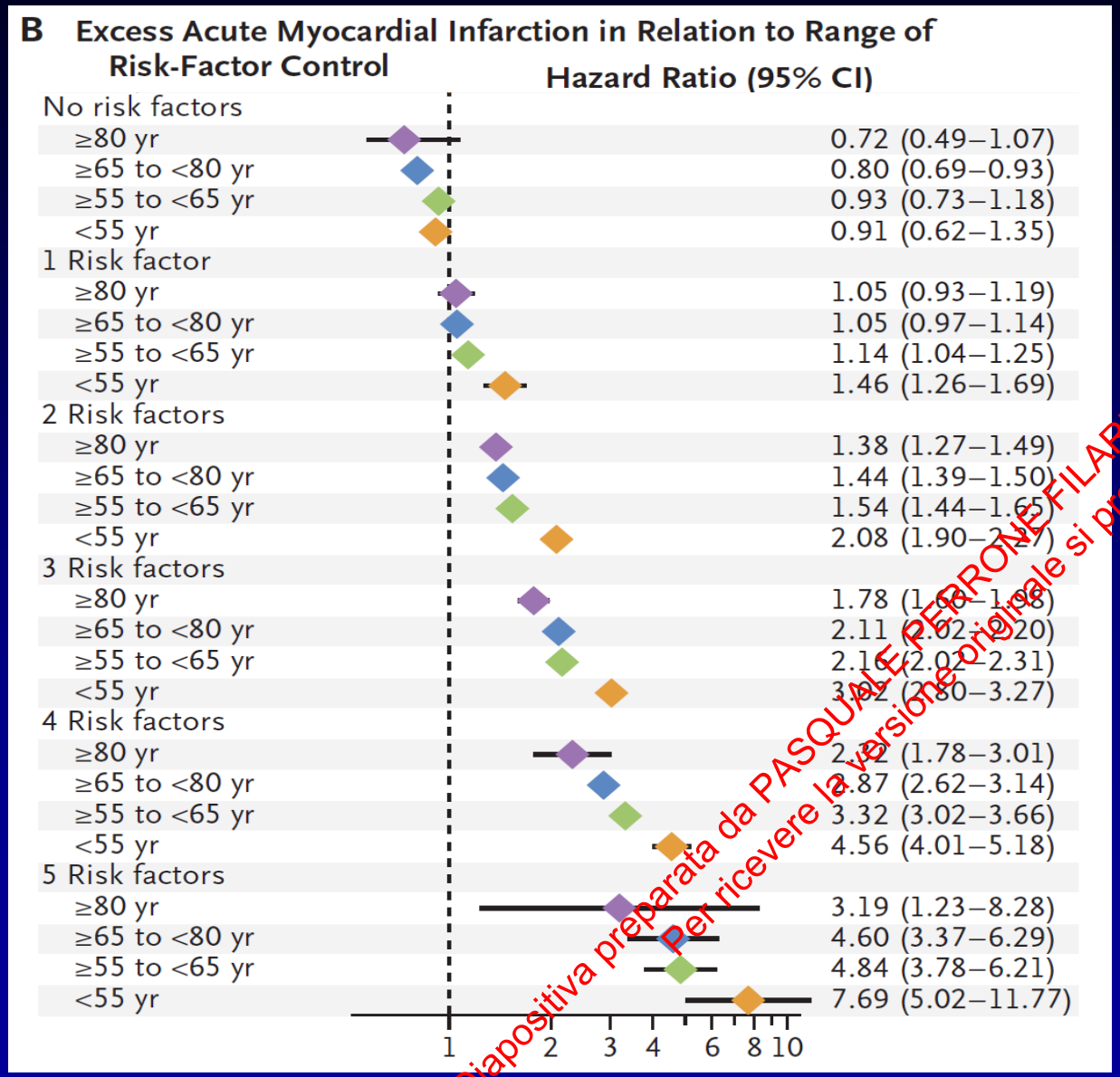
Wu B et al. Article and supplementary tables. *BMJ Open Diabetes Res Care.* 2016. https://dx.doi.org/10.1136/bmjdrc-2015-000154. Accessed February 22, 2019.

PREVENTION OF ATHEROTROMBOTIC EVENTS IN PATIENTS WITH DIABETES MELLITUS

Patti et al. Nat Rev Cardiol 2018

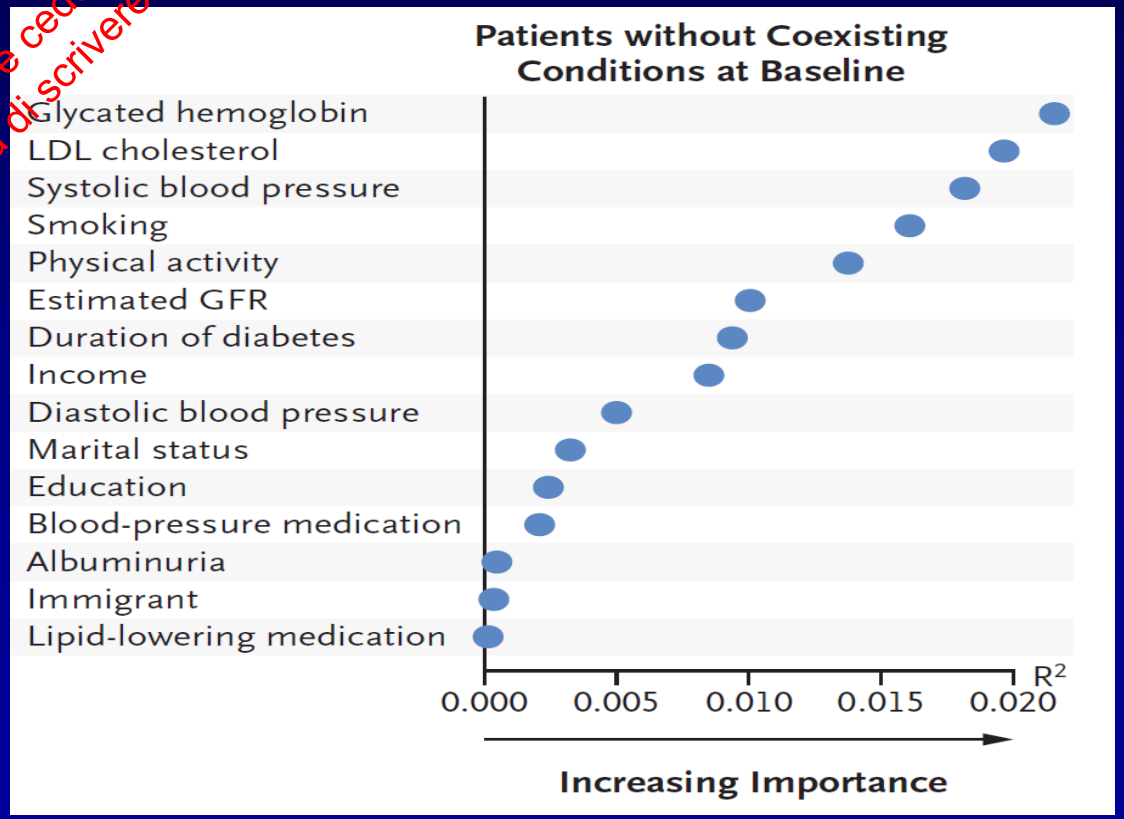


excess acute MI in diabetes



risk factors:

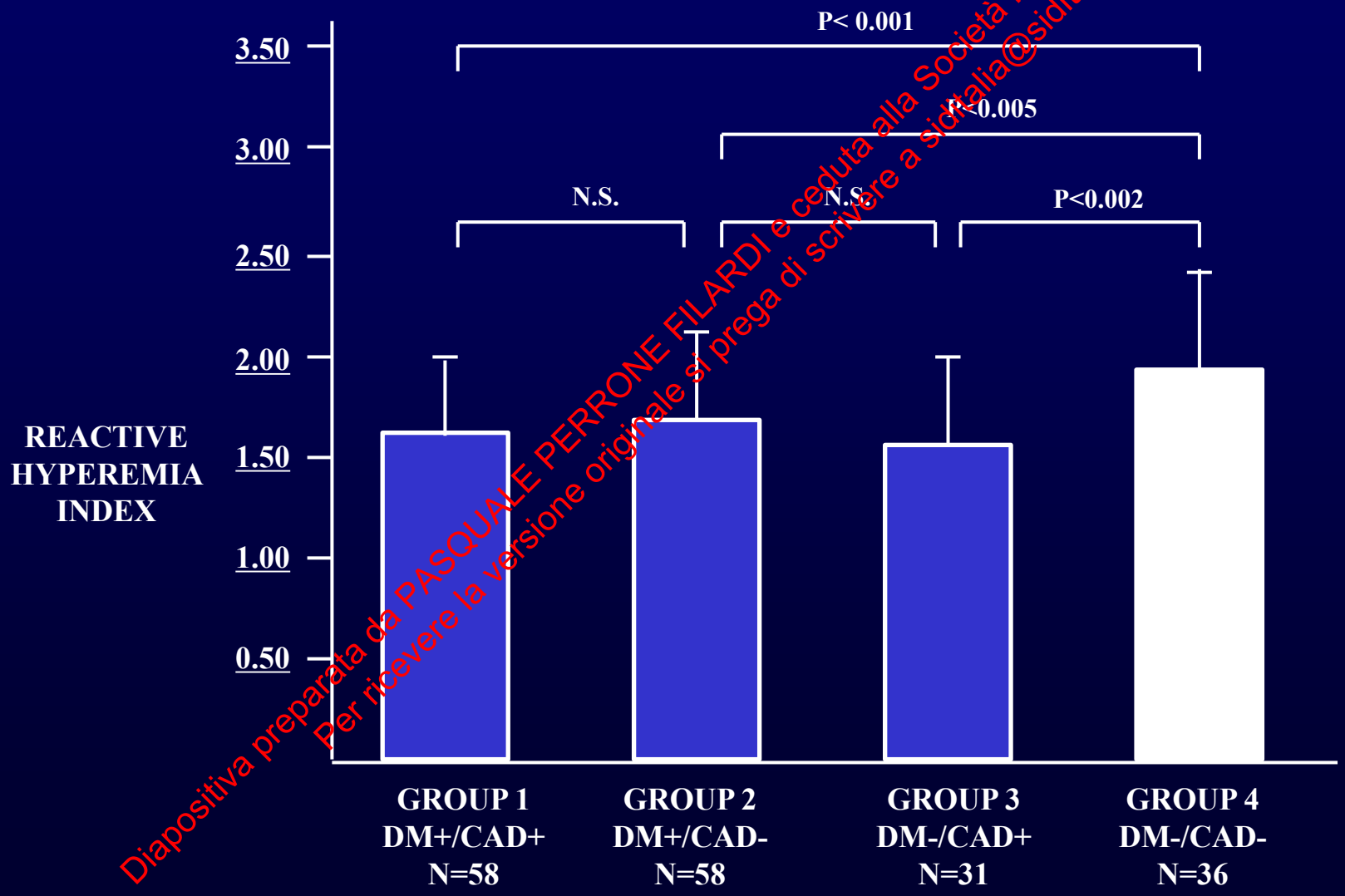
1. HbA1c
2. LDL
3. ACR
4. smoking
5. BP



Rawshani A et al.: NEJM 379:633, 2018

ENDOTHELIAL FUNCTION IN DIABETIC AND NON DIABETIC PATIENTS WITH AND WITHOUT CAD

Gargiulo et al. Int J Cardiol 2011



Effects of type 2 diabetes mellitus on coronary microvascular function and myocardial perfusion in patients without obstructive coronary artery disease

Marciano et al. Eur J Nucl Med & Mol Imaging 2012

Endothelial-dependent Flow reserve

Endothelial-independent Flow reserve

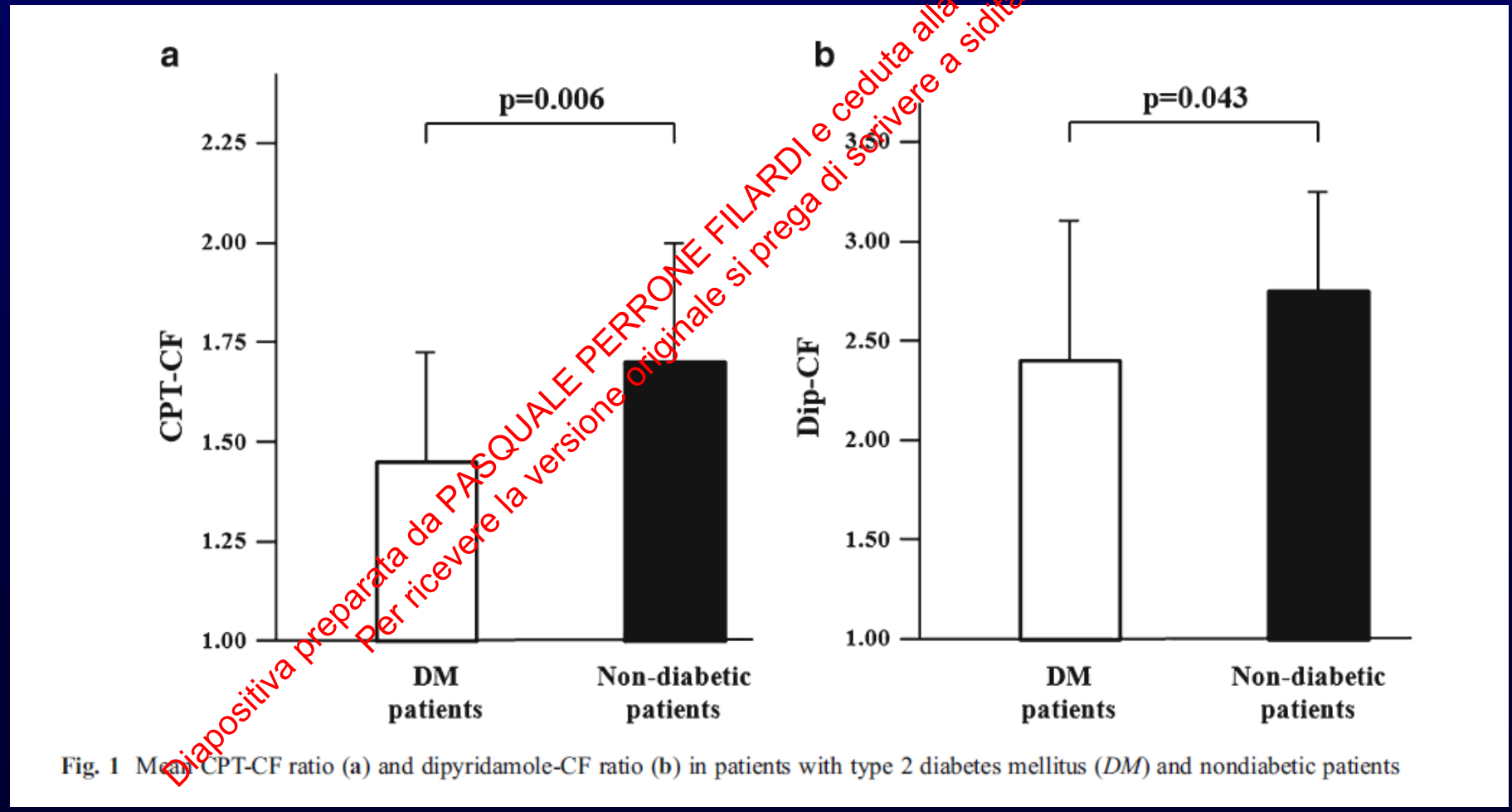
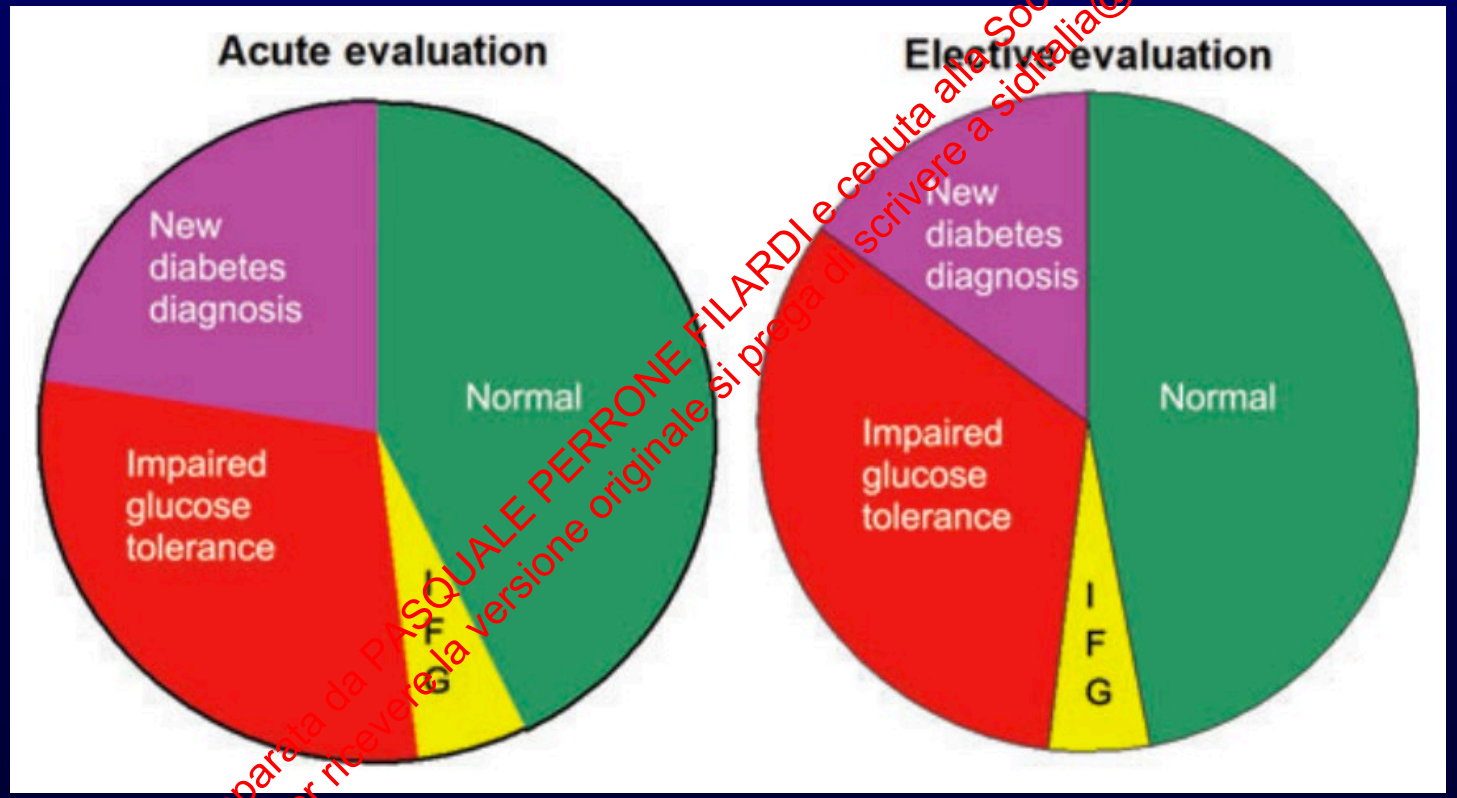


Fig. 1 Mean CPT-CF ratio (a) and dipyridamole-CF ratio (b) in patients with type 2 diabetes mellitus (*DM*) and nondiabetic patients

Prevalenza dei disturbi del metabolismo glucidico nei pazienti sottoposti a rivascolarizzazione coronarica



Bartnik et al. EHJ 2004

DOMANDA

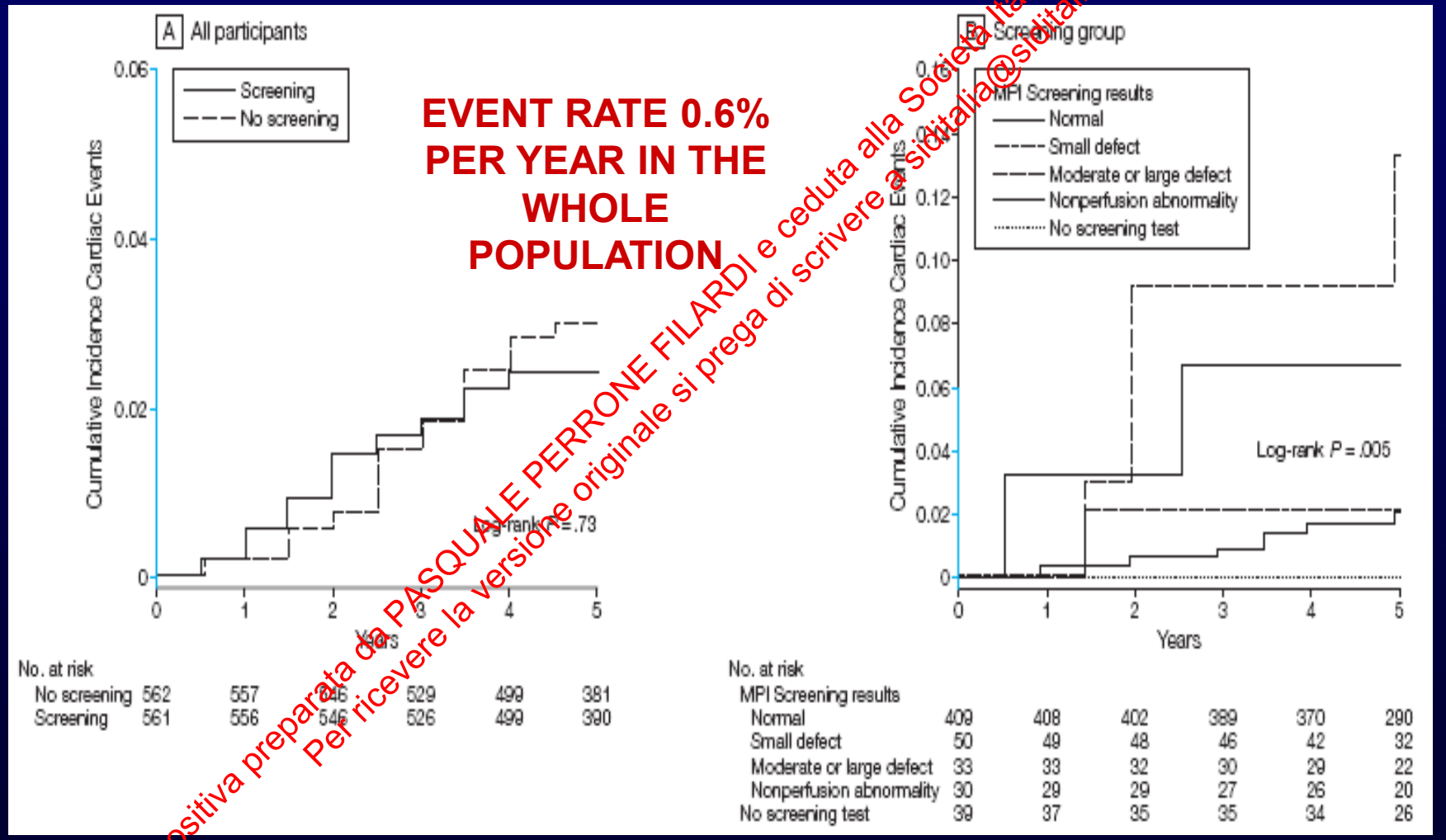
Lo screening di ischemia silente nel paziente diabetico senza precedenti eventi è sempre raccomandato

- VERO
- FALSO

IMPACT OF SCREENING FOR ASYMPTOMATIC ISCHEMIA IN DIABETIC PATIENTS WITHOUT KNOWN CAD

The *DIAD* Trial. *JAMA. 2009;301:1547*

EVENT RATE 0.6% PER YEAR IN THE WHOLE POPULATION



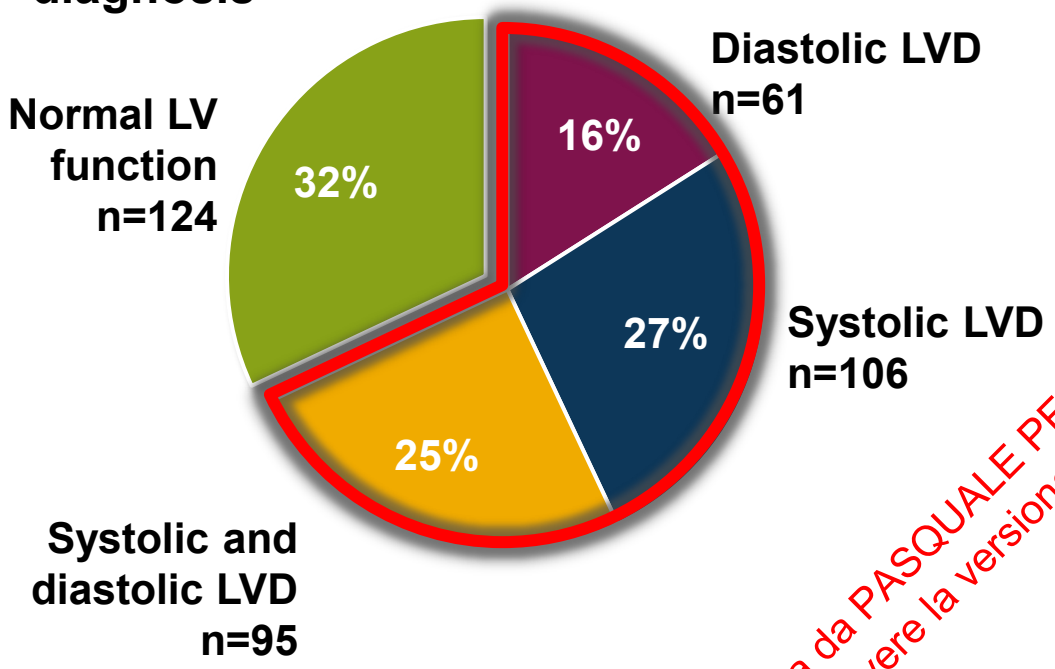
ESC recommendations for CV risk assessment in asymptomatic patients with diabetes

Recommendations	Class[a]	Level[b]
Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction high risk of future CVD.[27,38] ACR	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CV resting ECG	I	C
Assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier in asymptomatic patients with DM.[60–62] plaque @ US	IIa	B
CAC score with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic patients with DM at moderate risk.[c] [63] CAC score	IIb	B
CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with DM for screening of CAD.[47,48,64,65,67–70] CTCA or functional imaging	IIb	B
ABI may be considered as a risk modifier in CV risk assessment.[76] ABI	IIb	B
Detection of atherosclerotic plaque of carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with DM at moderate or high risk CV.[c] [75,77] plaque @ CT/NMR	IIb	B
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended.[62,73,78] NO IMT	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification.[27,] NO biomarkers	III	B
Risk scores developed for the general population are not recommende NO risk scores for non-diabetic	III	C

Eur Heart J 41:255, 2020 doi: 10.1093/eurheartj/ehz486

Left ventricular dysfunction is an early complication in T2D

68% of patients with T2D had evidence of LV dysfunction[1] 5 years (median) after T2D diagnosis



Patients had no evidence of inducible ischemia by stress testing at baseline[1]

Two distinct phenotypes of diabetes-related cardiomyopathy exist[2]

HFpEF[2] (earliest)	HFrEF[2]
▪ Cardiomyocyte hypertrophy ▪ Cardiomyocyte fibrosis ▪ Increased cardiomyocyte stiffness	▪ Cardiomyocyte apoptosis ▪ Cardiomyocyte necrosis ▪ Decreased cardiomyocyte shortening

This suggests the earliest defect in the diabetic heart is that of diastolic dysfunction not atherothrombosis[2]

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVD = LV dysfunction; T2D = type 2 diabetes.

1. Faden G et al. *Diabetes Res Clin Res.* 2013;101:309-316; 2. Seferović PM et al. *Eur Heart J*. 2015;36:1718-1727..

Outcomes in Patients with Type 2 Diabetes and 5 in-range RFs.

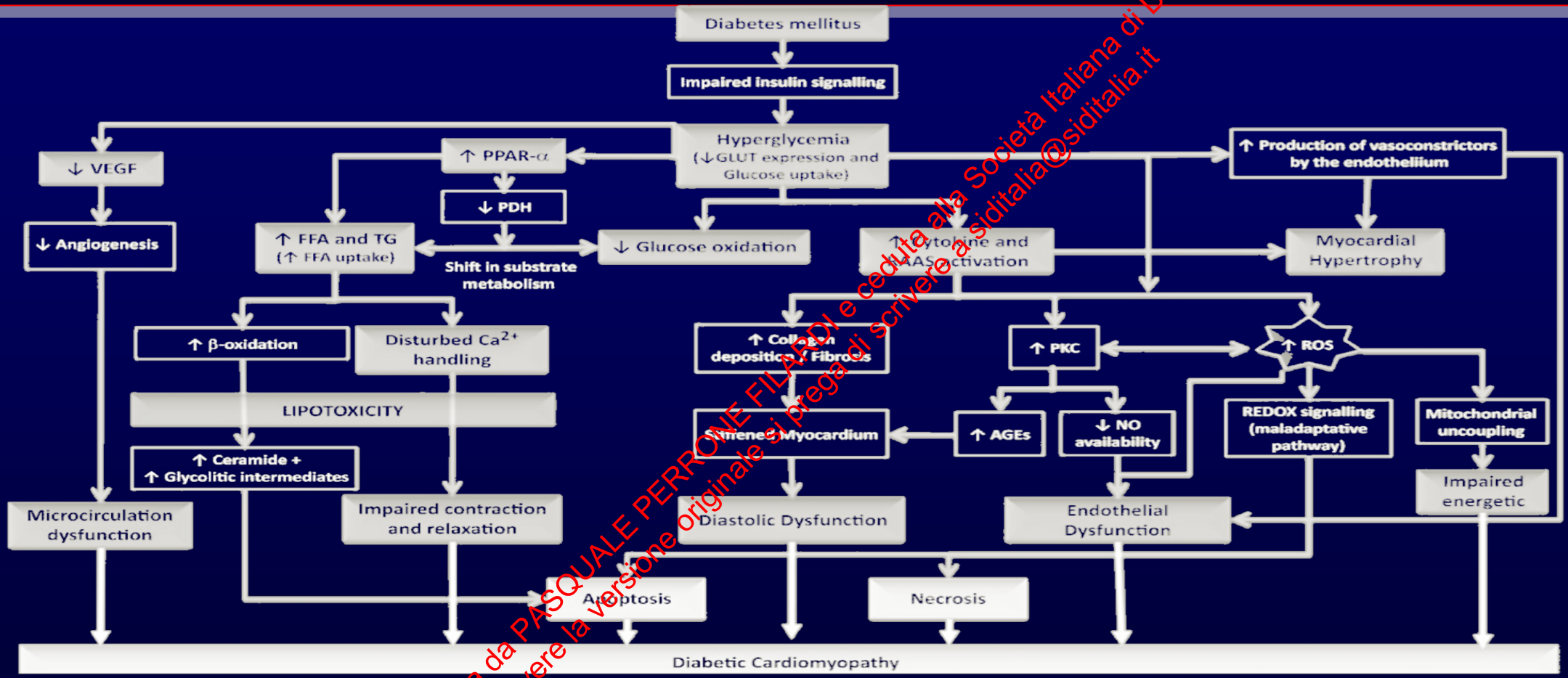
	HR	95% CI
All cause mortality	1,06	1,00-1,12
Acute MI	0,84	0,75-0,93
Stroke	0,95	0,84-1,07
Heart failure	1,45	1,34-1,57

RISK FACTORS
HbA1c, BP, LDL, SMOKING, ALBUMINURIA

Rawshani A. et al. NEJM 2018; 379:663-644

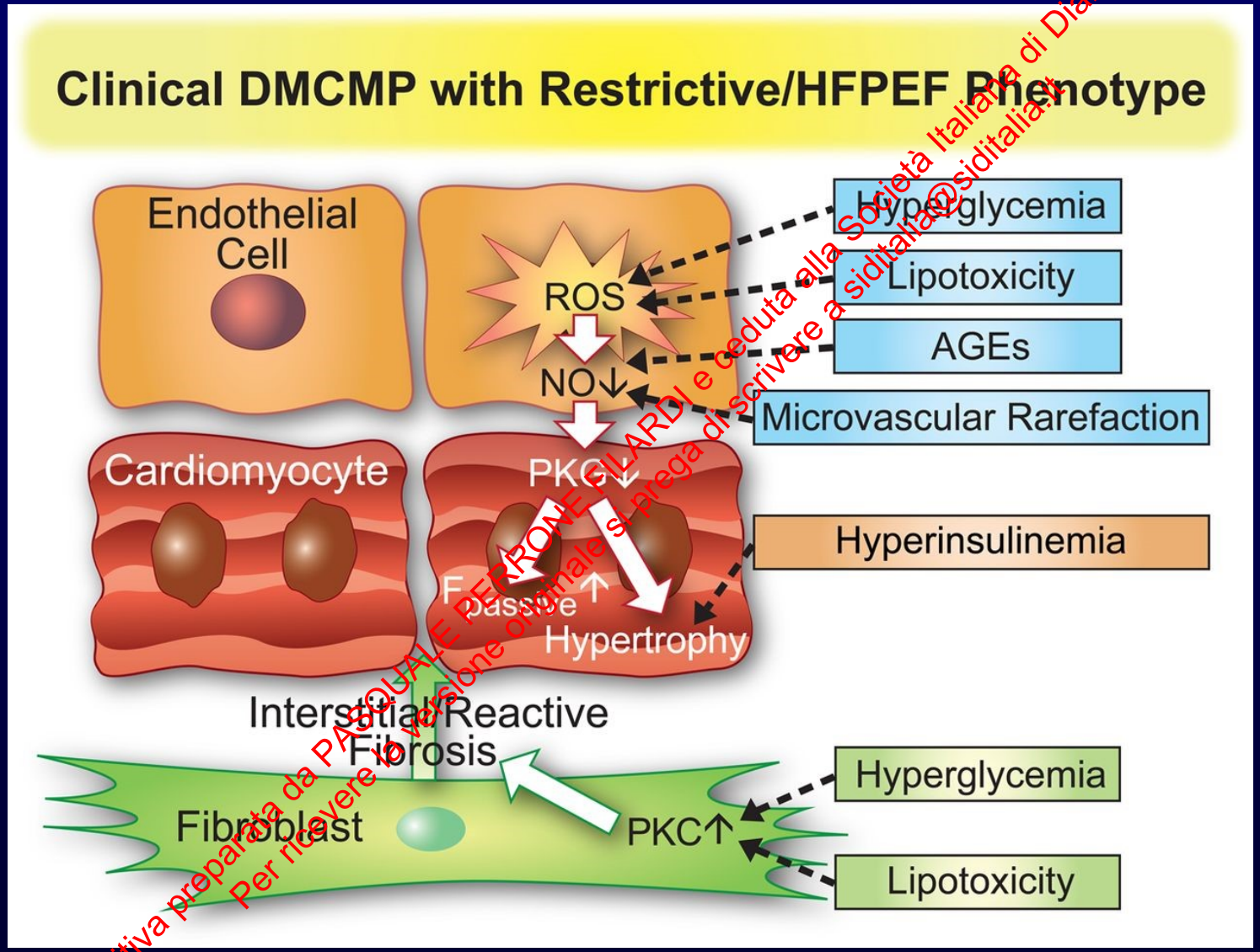
Pathophysiologic Abnormalities in Diabetes and Heart Failure

Dei Cas A, et al. JACC Heart Failure 2015



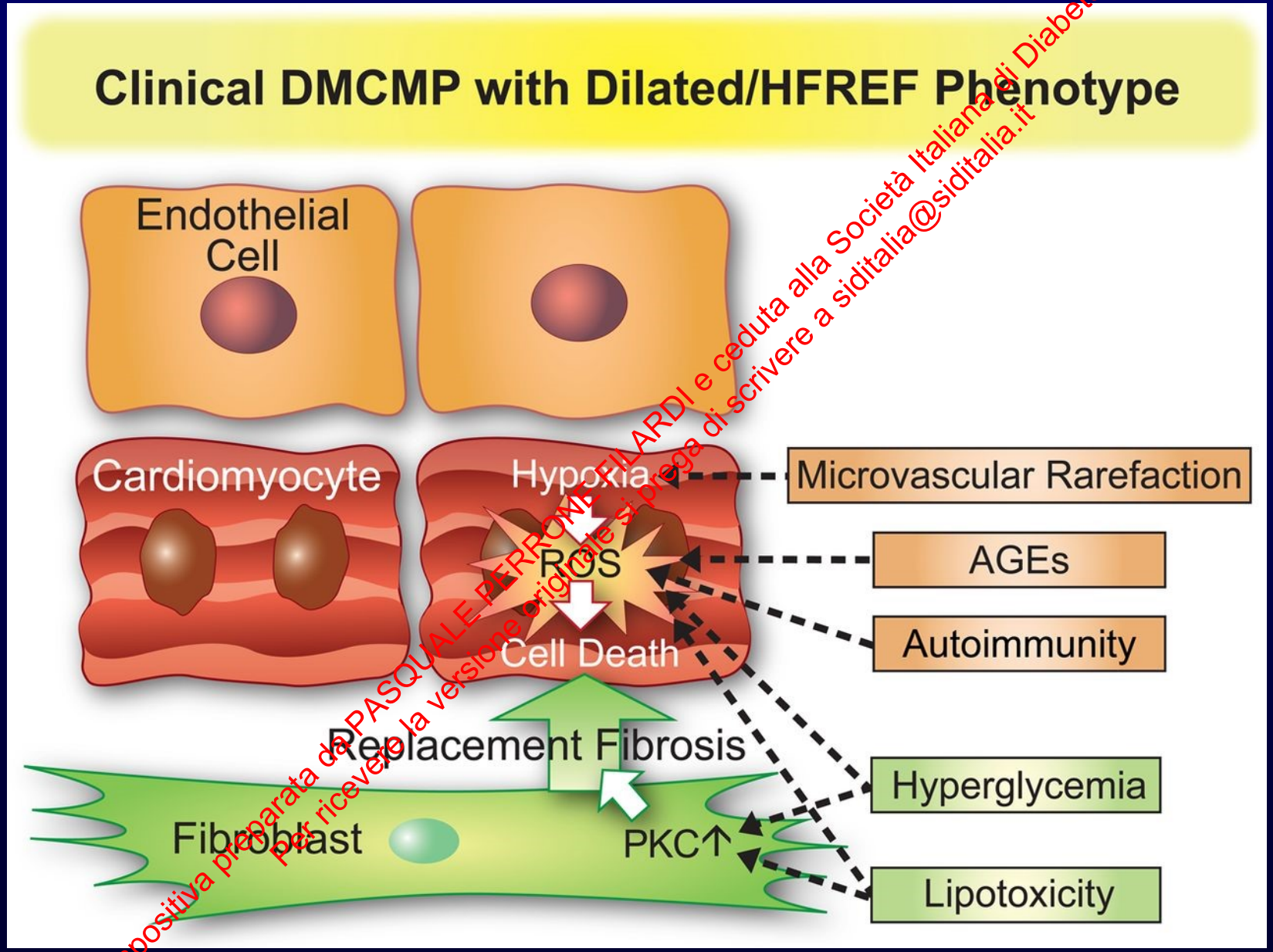
Multiple pathophysiologic mechanisms are activated and modulated by the presence of diabetes mellitus, resulting in abnormalities in the myocardial substrate unique to patients with diabetes mellitus and heart failure. Adapted with permission from Falcao-Pires I, Leite-Moreira AF. Heart Fail Rev 2012;17:325–44. AGE = advanced glycation end product; FFA = free fatty acid; GLUT = glucose transporter facilitators; PDH = pyruvate dehydrogenase; PKC = protein kinase C; PPAR = peroxisome proliferator-activated receptor; RAAS = renin-angiotensin-aldosterone system; REDOX = oxidation and reduction; ROS = reactive oxygen species; TG = triglyceride; VGEF = vascular endothelial growth factor.

DM-related pathophysiological mechanisms in DMCMP with restrictive/HFpEF phenotype



Seferovic, Eur Heart J. 2015;36(27)

DM-related pathophysiological mechanisms in DMCPM with dilated/HFrEF phenotype



Seferovic, Eur Heart J. 2015;36(27)

Relative impact of DM-related pathophysiological mechanisms

Table I **Relative importance of DM-related pathophysiological mechanisms for development of diabetes mellitus-related cardiomyopathy with restrictive/ heart failure with preserved left ventricular ejection fraction or dilated/ heart failure with reduced ejection fraction phenotypes**

	DMCMP with restrictive/HFPEF phenotype	DMCMP with dilated/HFREF phenotype
Hyperglycaemia	+++	+
Lipotoxicity	+++	+
AGEs deposition	+++	+++
Microvascular rarefaction	+++	+++
Autoimmunity	−	+++
Insulin resistance/ Hyperinsulinaemia	+++	−

DM, diabetes mellitus; DMCMP, diabetic cardiomyopathy; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; AGEs, advanced glycation end-products.

Seferovic, Eur Heart J. 2015;36(27)

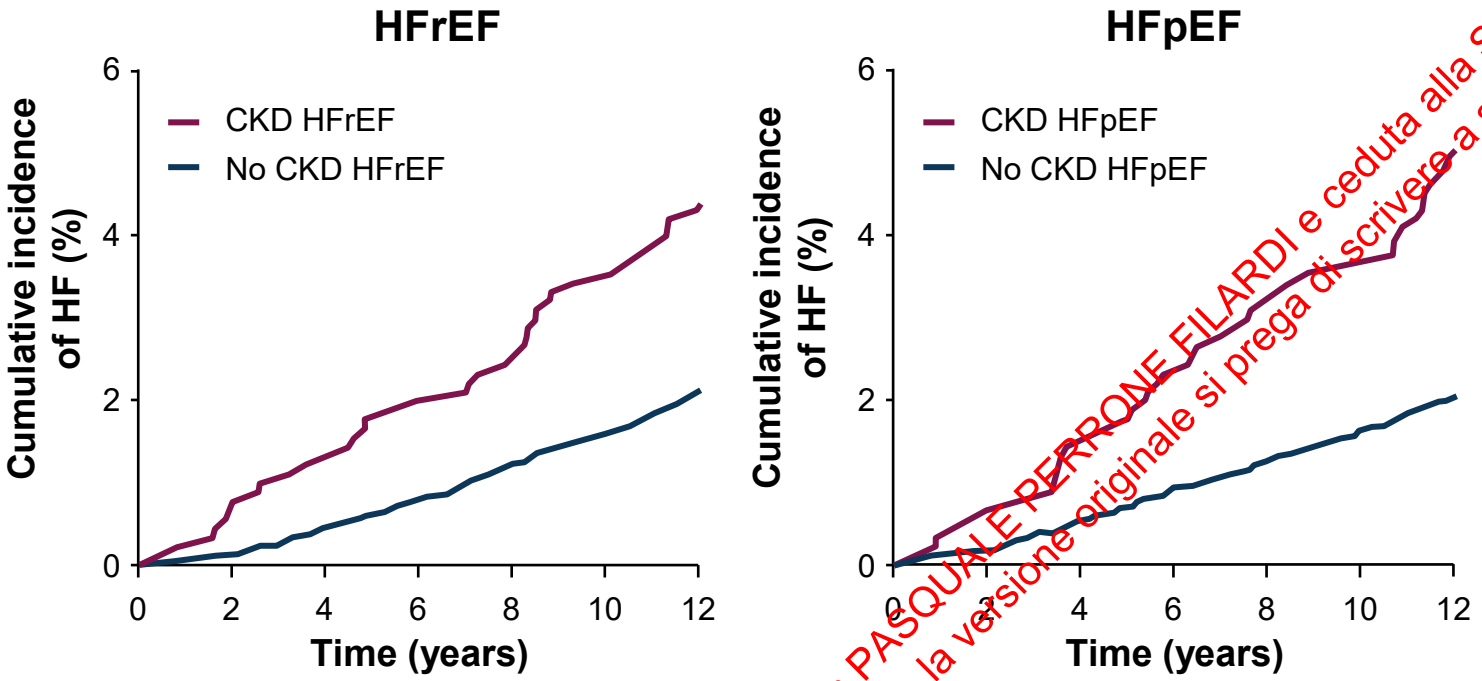
DOMANDA

LO SCOMPENSO CARDIACO DEL PAZIENTE DIABETICO È SEMPRE DOVUTO A SOTTOSTANTE CARDIOPATIA ISCHEMICA O IPERTENSIONE

- VERO
- FALSO

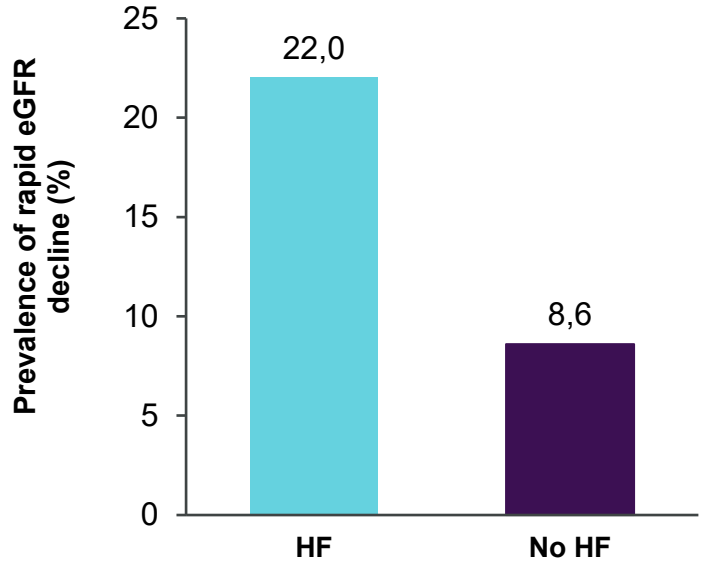
CKD and HF are interconnected: CKD is associated with increased risk of HF and conversely HF is associated with risk of eGFR decline

Incidences of HF are higher in those with CKD than those without[1]



CKD is associated with incident HF

HF is associated with rapid decline in eGFR[2,a]



HF is associated with the risk of kidney function decline

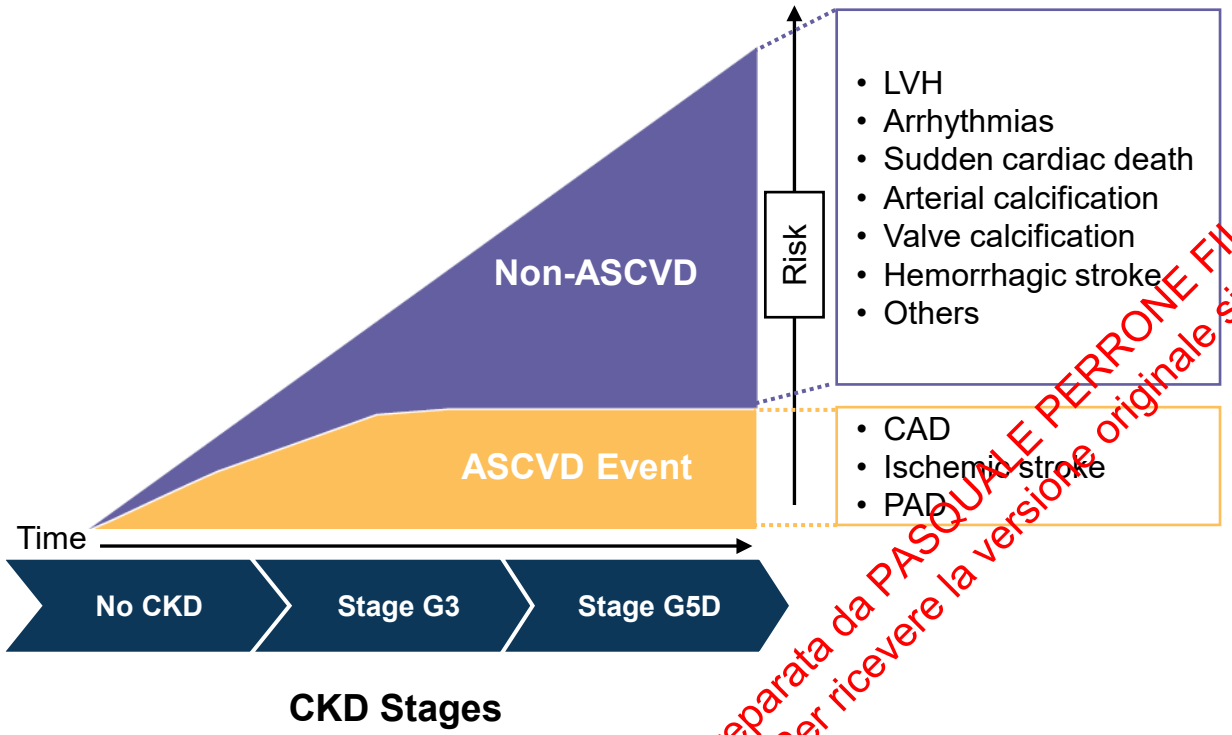
[a]Rapid rate of eGFR decline was defined as slopes steeper than −5 mL/min/1.73 m^2/year.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

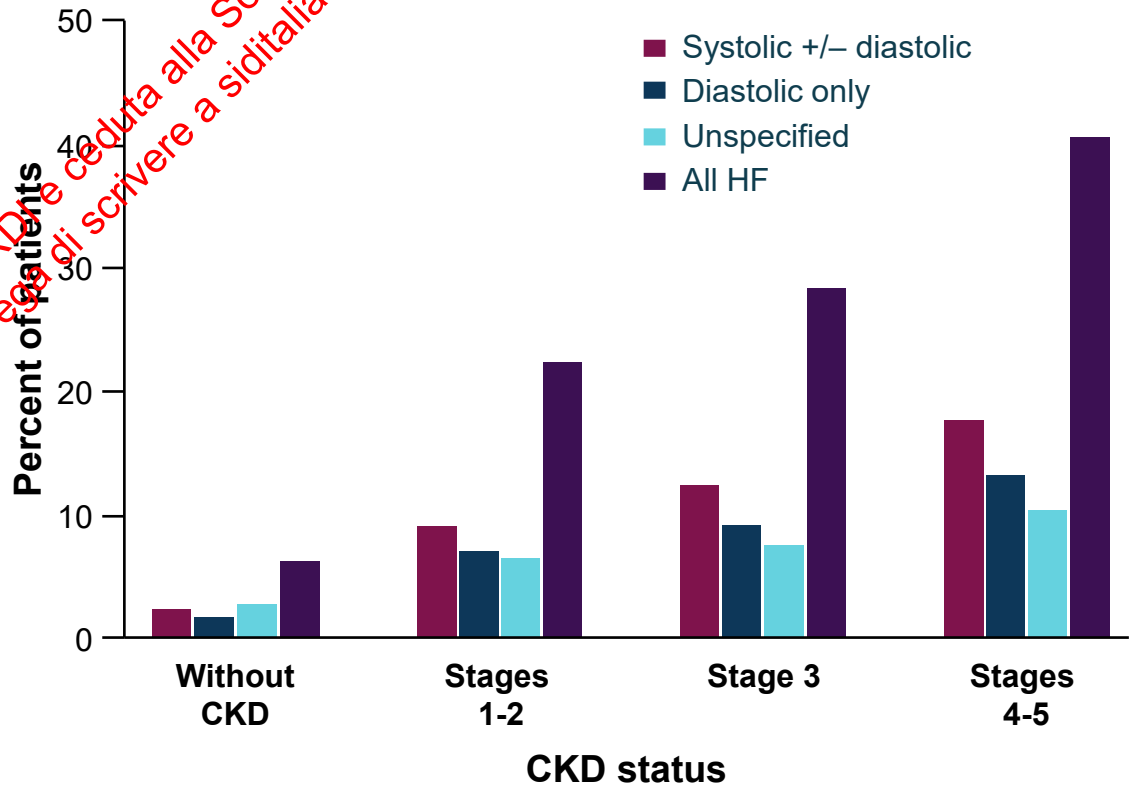
1. Nayor M et al. *Eur J Heart Fail.* 2017;19:615–623; 2. George LK et al. *Circ Heart Fail.* 2017;10:e003825.

The Burden of Non-Atherosclerotic Disease, Including Heart Failure, Predominates as CKD Progresses

Change in Non-ASCVD Risk, Continues to Increase During CKD Progression[1]



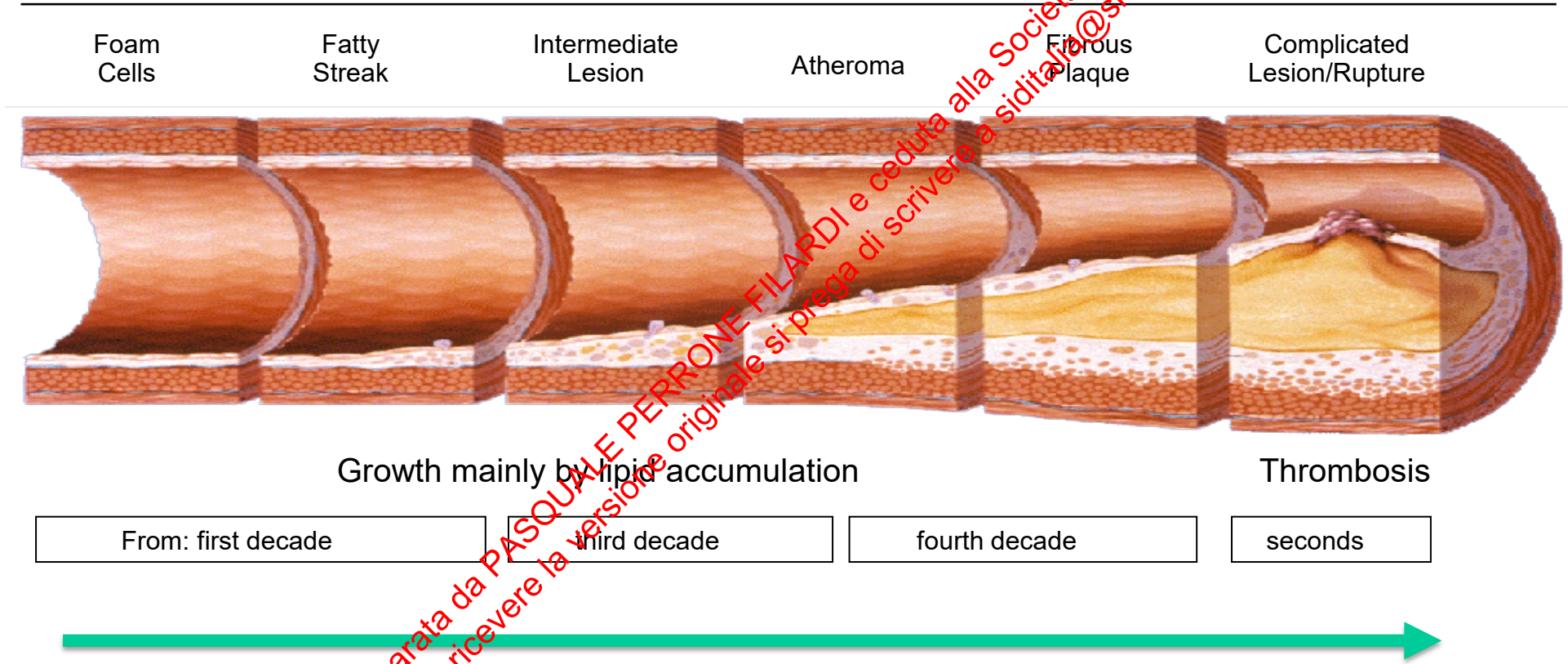
Prevalence of HF In Patients at Different Stages of CKD[2]



ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CKD = chronic kidney disease; HF = heart failure; LVH = left ventricular hypertrophy; PAD = peripheral artery disease.

1. Wanner C et al. *Lancet.* 2016;388:276–284; 2. USRDS 2018 ADR: Chapter 4. https://usrds.org/2018/view/v1_04.aspx. Accessed March 2020.

THE CONTINUUM OF ISCHEMIC CARDIOVASCULAR DISEASE



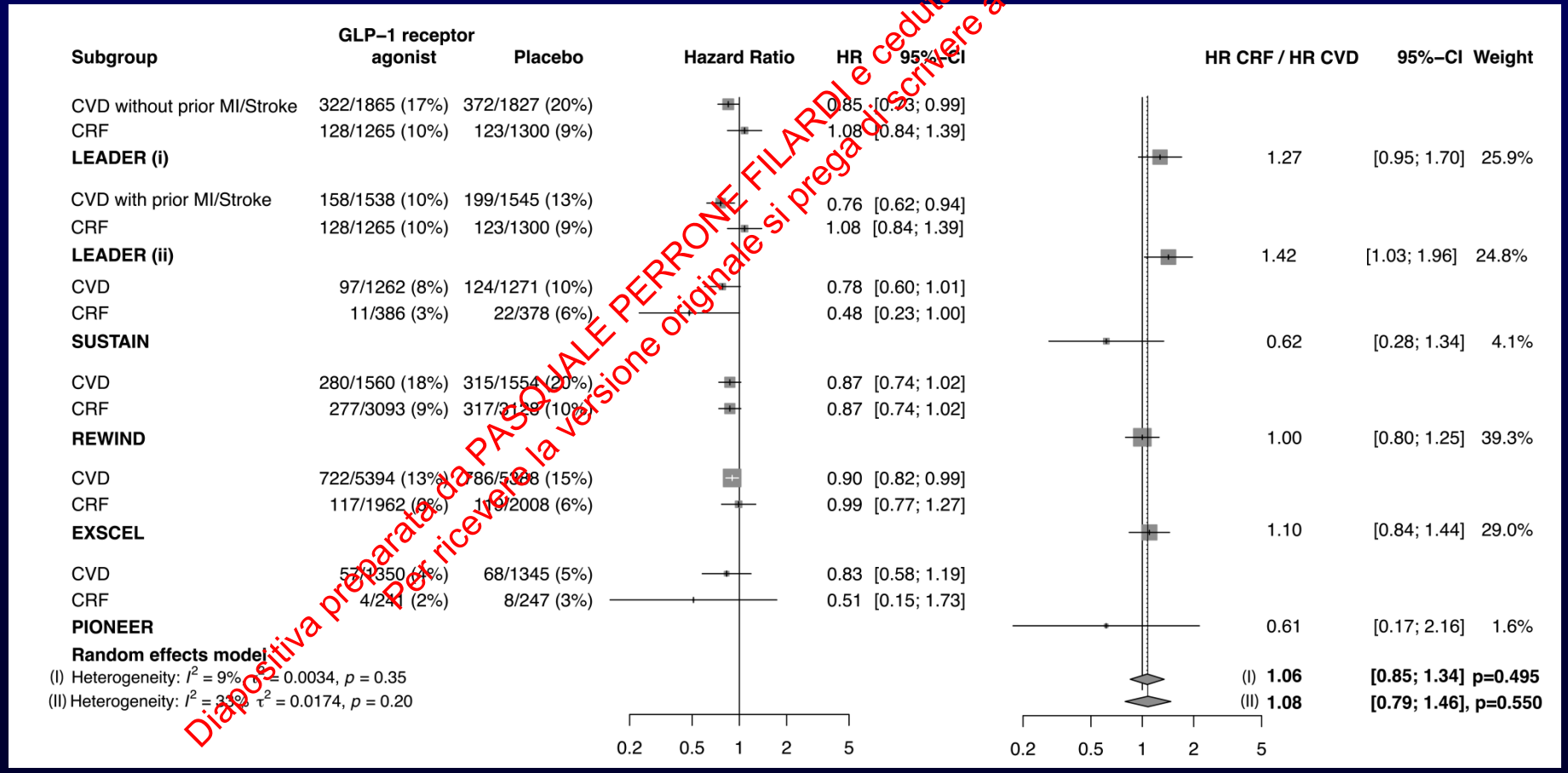
FROM RISK FACTORS TO ESTABLISHED CV DISEASE TO SECONDARY PREVENTION

Adapted from Stary HC et al. Circulation 1995

Effects of GLP1 receptor agonists on CV events in patients with type 2 diabetes mellitus with or without established CV disease: a meta-analysis of randomized controlled trials

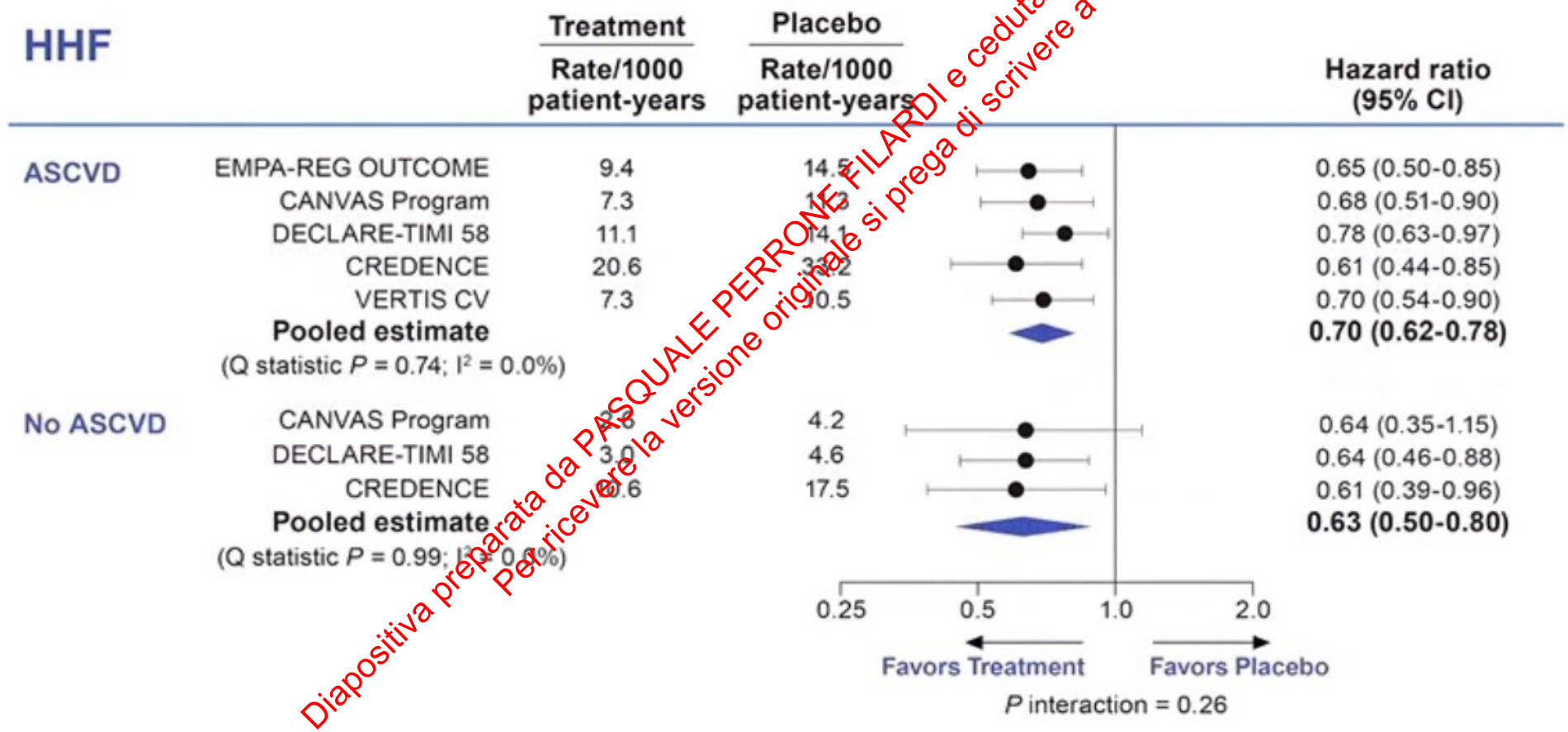
Marsico & Paolillo, Perrone Filardi. Eur Heart Journal 2020

Interaction analysis for the three-point MACE between pts with established CV disease and CV risk factors only



Effects of SGLT2i on first hospitalization for heart failure

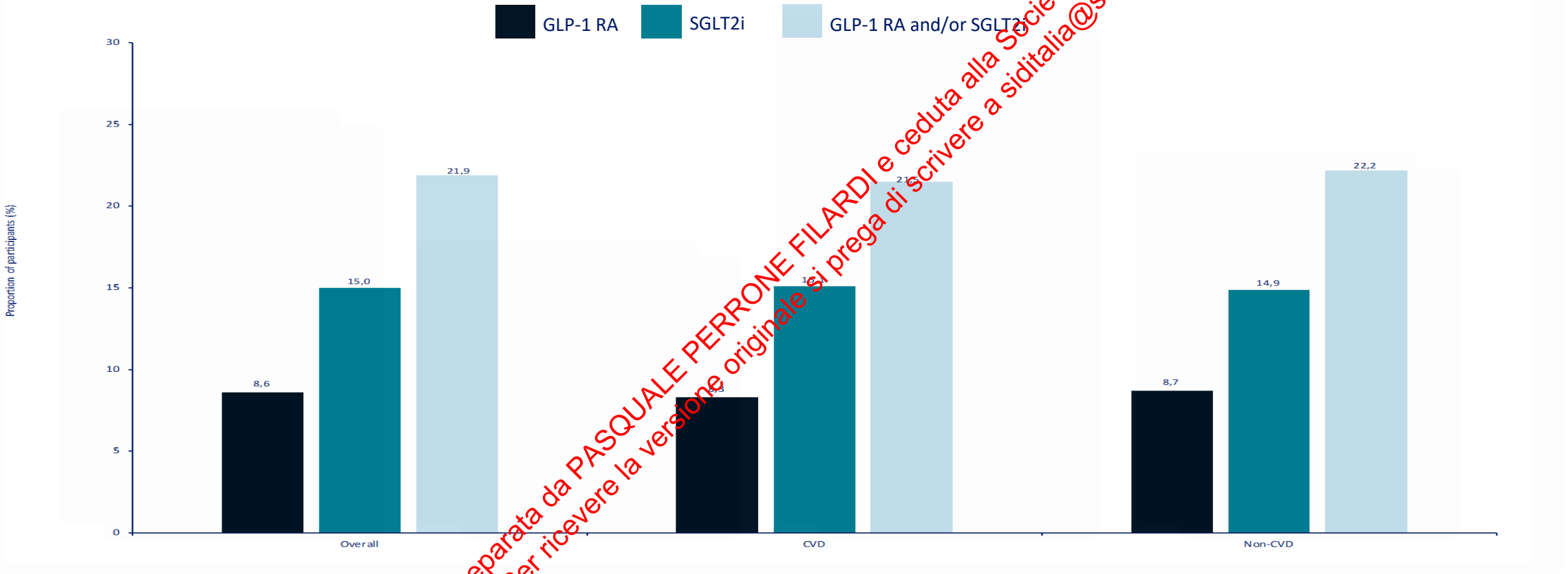
Time to first HHF – subgroup analysis by ASCVD



McGuire DK, et al. JAMA Cardiol 2020. doi:19.1001/jamacardio.2020.511.

ASCVD, atherosclerotic cardiovascular disease.

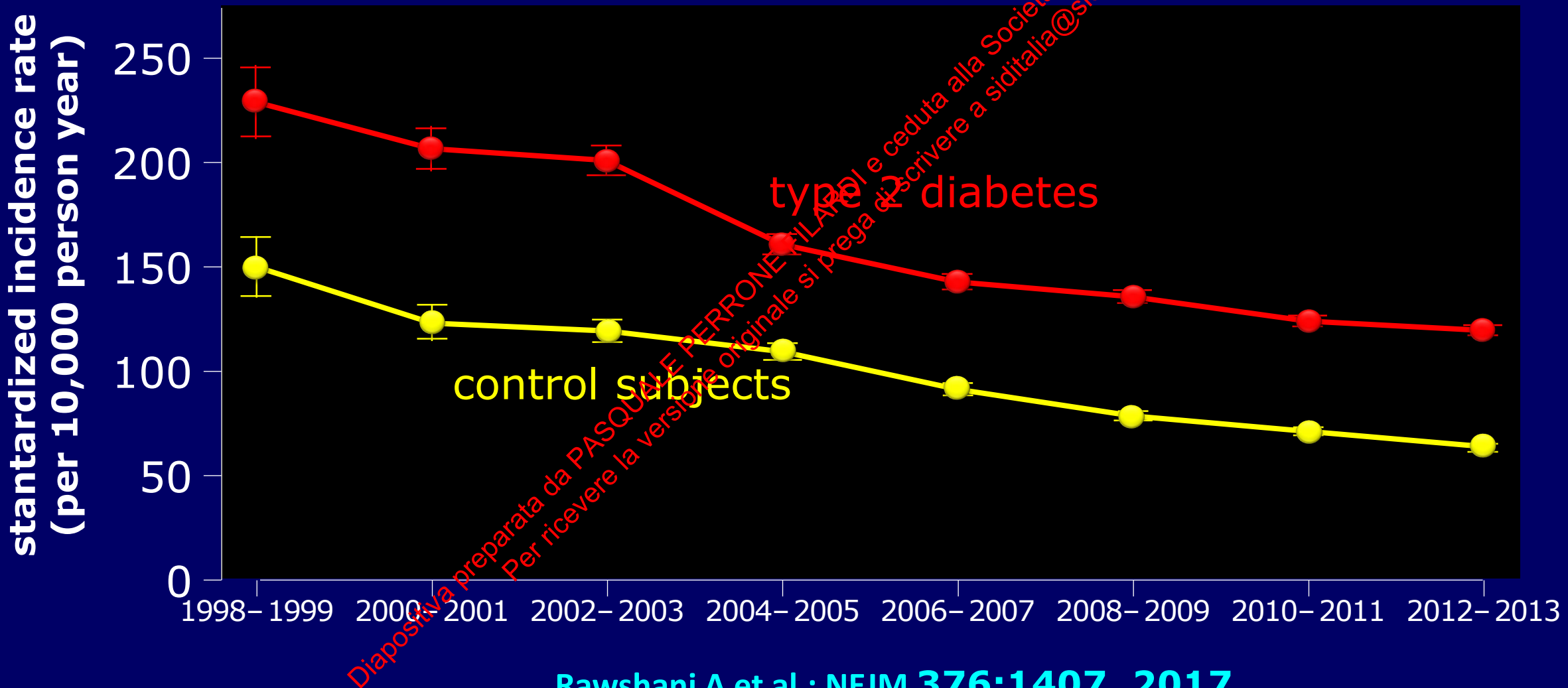
Use of GLAs with demonstrated CV benefit



Adapted from Figure 3b
Data are % and were not weighted. Data are presented for the CAPTARE study sample overall and stratified by CVD status. GLAs with demonstrated CV benefit were defined per 2020 American Diabetes Association guidelines as GLP-1 RAs: dulaglutide, liraglutide and semaglutide; and SGLT2is: canagliflozin, dapagliflozin and empagliflozin
CV, cardiovascular; CVD, cardiovascular disease; GLAs, glucose-lowering agents; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i sodium-glucose co-transporter-2 inhibitor

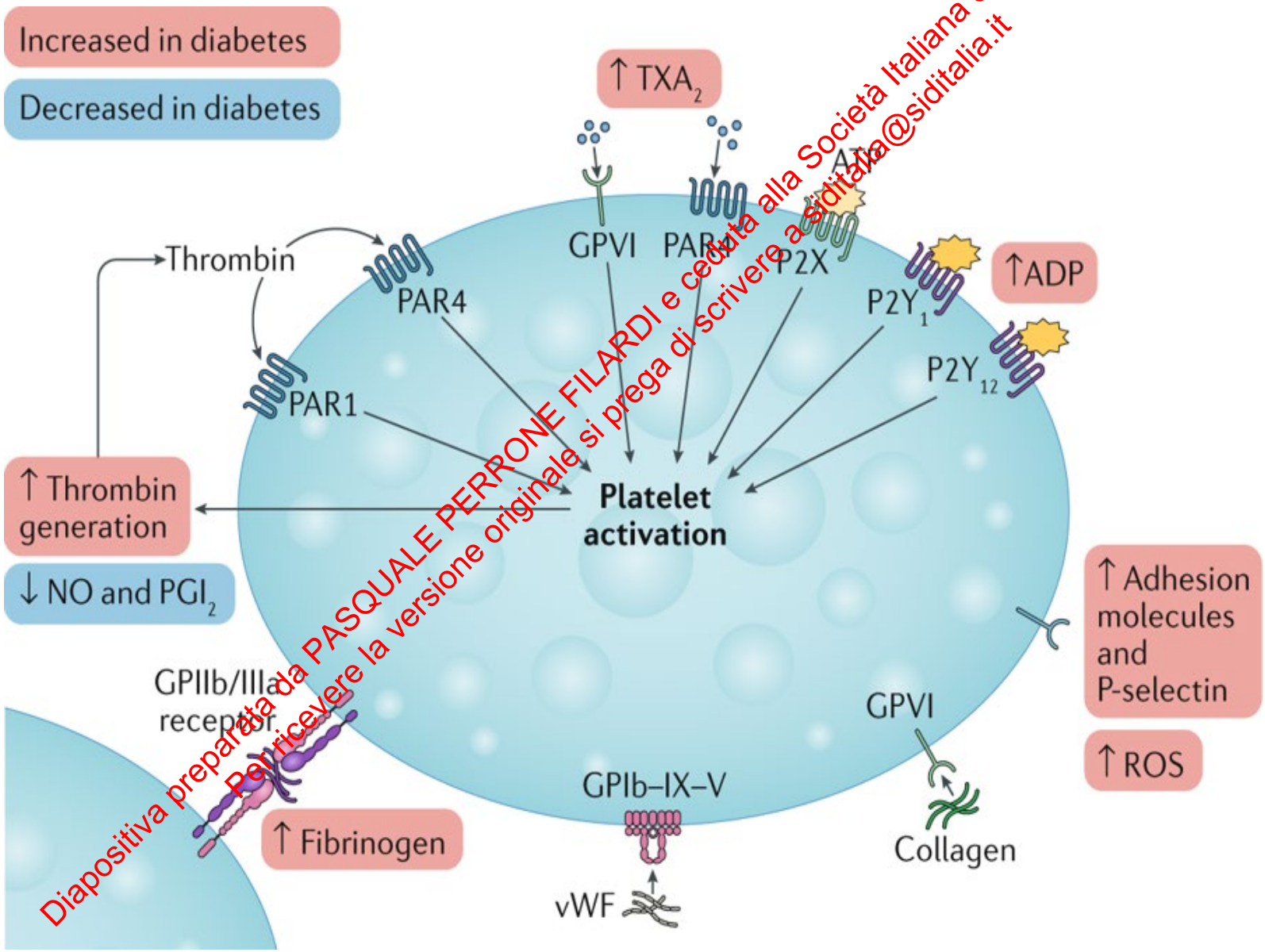
Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

cardiovascular death in type 2 diabetes
risk reduction during last 15 years

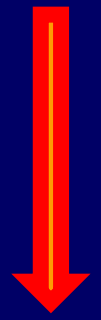


Rawshani A et al.: NEJM **376:1407, 2017**

Patti et al. Nat Rev Cardiol 2018



CARDIOVASCULAR CONSEQUENCES OF TYPE 2 DIABETES MELLITUS



ISCHEMIC EVENTS (MACE)

- CV death
- Stroke
- MI

HEART FAILURE

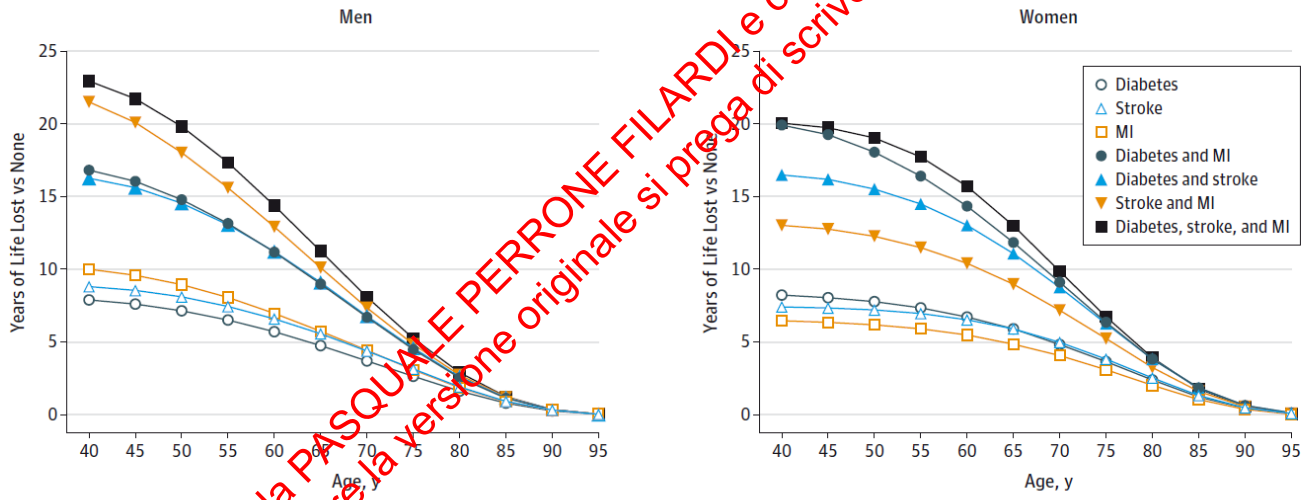
- CV death (due to HF)
- HF HOSPITALIZATION

Original Investigation

Association of Cardiometabolic Multimorbidity With Mortality

The Emerging Risk Factors Collaboration

Figure 3. Modeling of Years of Life Lost by Disease Status of Participants at Baseline Compared With Those Free of Diabetes, Stroke, and Myocardial Infarction (MI)

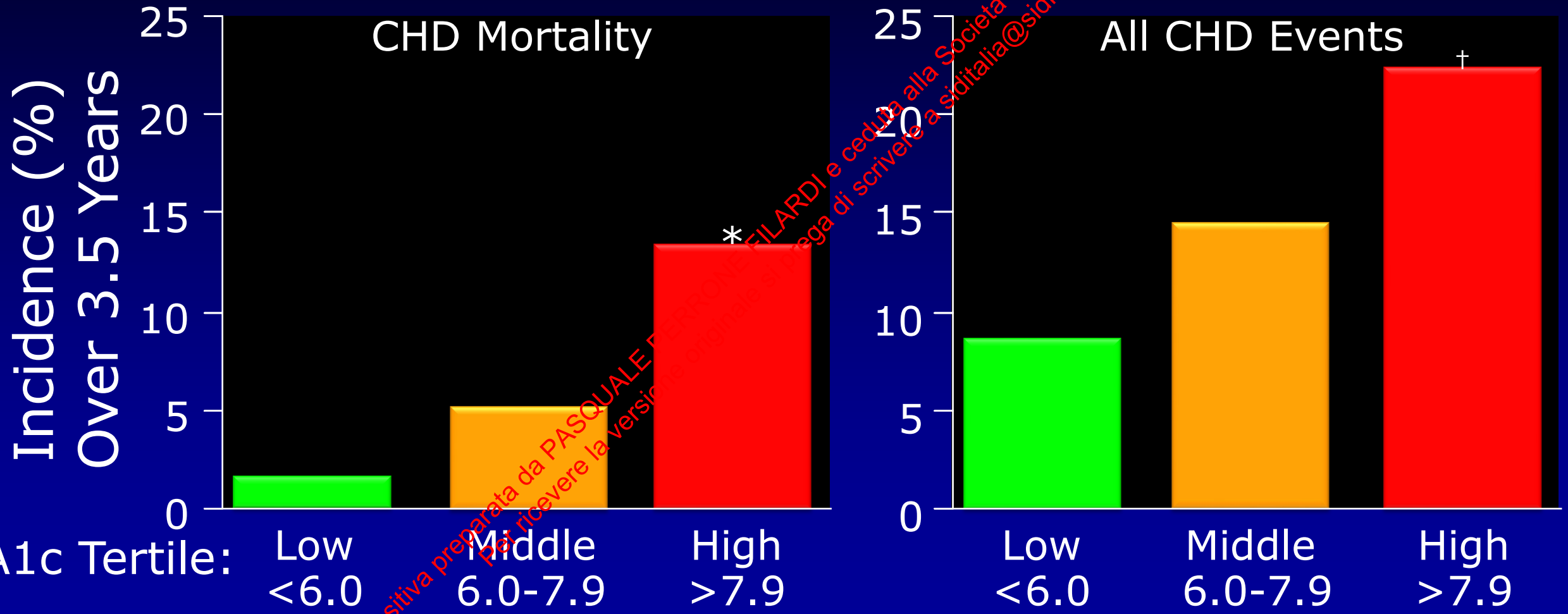


The estimates of cumulative survival from 40 years of age onward among the 8 baseline disease groups were calculated by applying hazard ratios (specific to age at risk and sex) for all-cause mortality associated with baseline disease status to US cause-specific death rates at the age of 40 years or older.

JAMA. 2015;314(1):52-60

A1c Predicts CV Risk

prospective study of 229 Finnish type 2 diabetic patients without previous vascular disease



A1c = glycosylated hemoglobin; CHD = coronary heart disease. *$P<0.01$ vs lowest tertile; †$P<0.05$ vs lowest tertile.

Kuusisto J et al. Diabetes 43:960, 1994

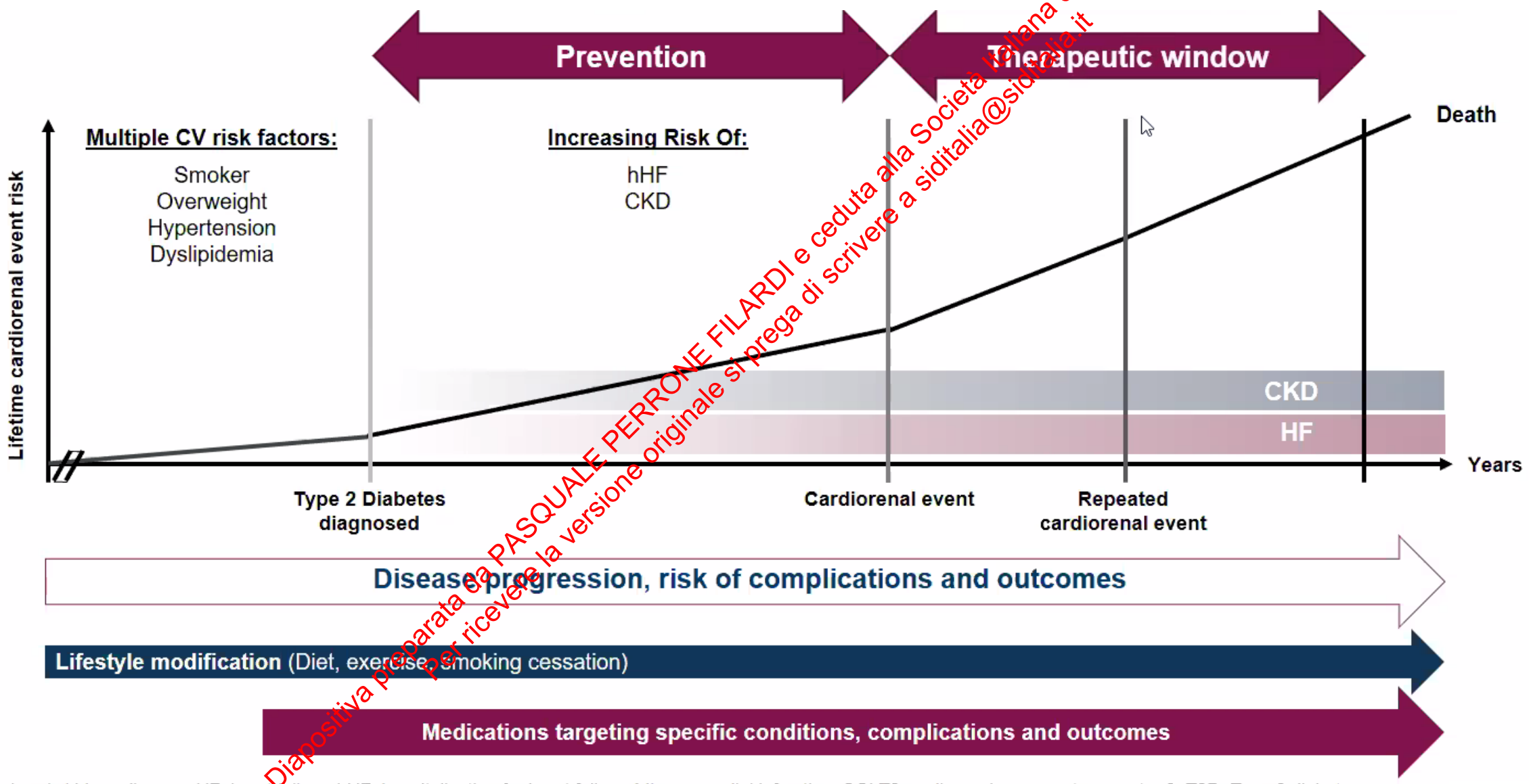
Outcomes in Patients with Type 2 Diabetes and 5 in-range RFs.

	HR	95% CI
All cause mortality	1,06	1,00-1,12
Acute MI	0,84	0,75-0,93
Stroke	0,95	0,84-1,07
Heart failure	1,45	1,34-1,57

RISK FACTORS
HbA1c, BP, LDL, SMOKING, ALBUMINURIA

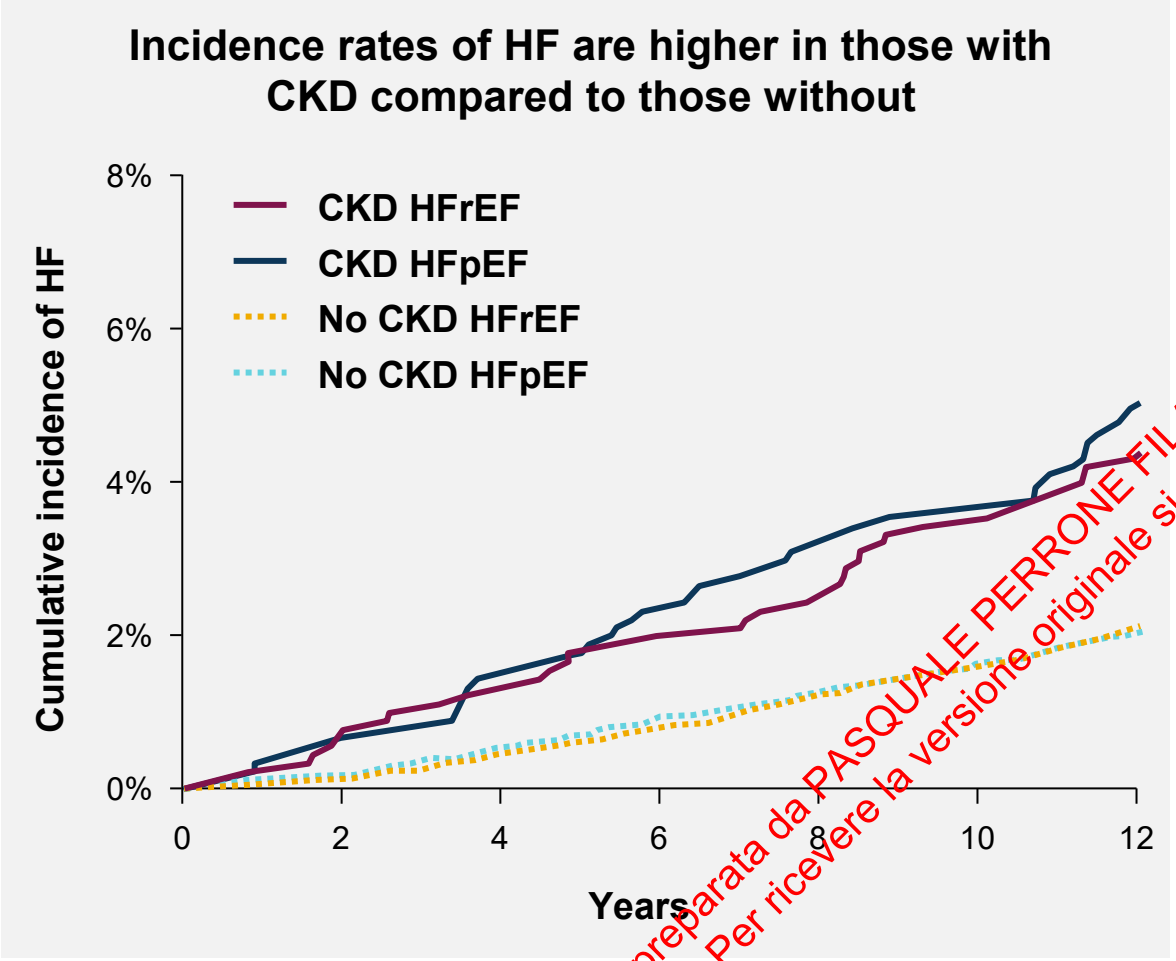
Rawshani A. et al. NEJM 2018; 379:663-644

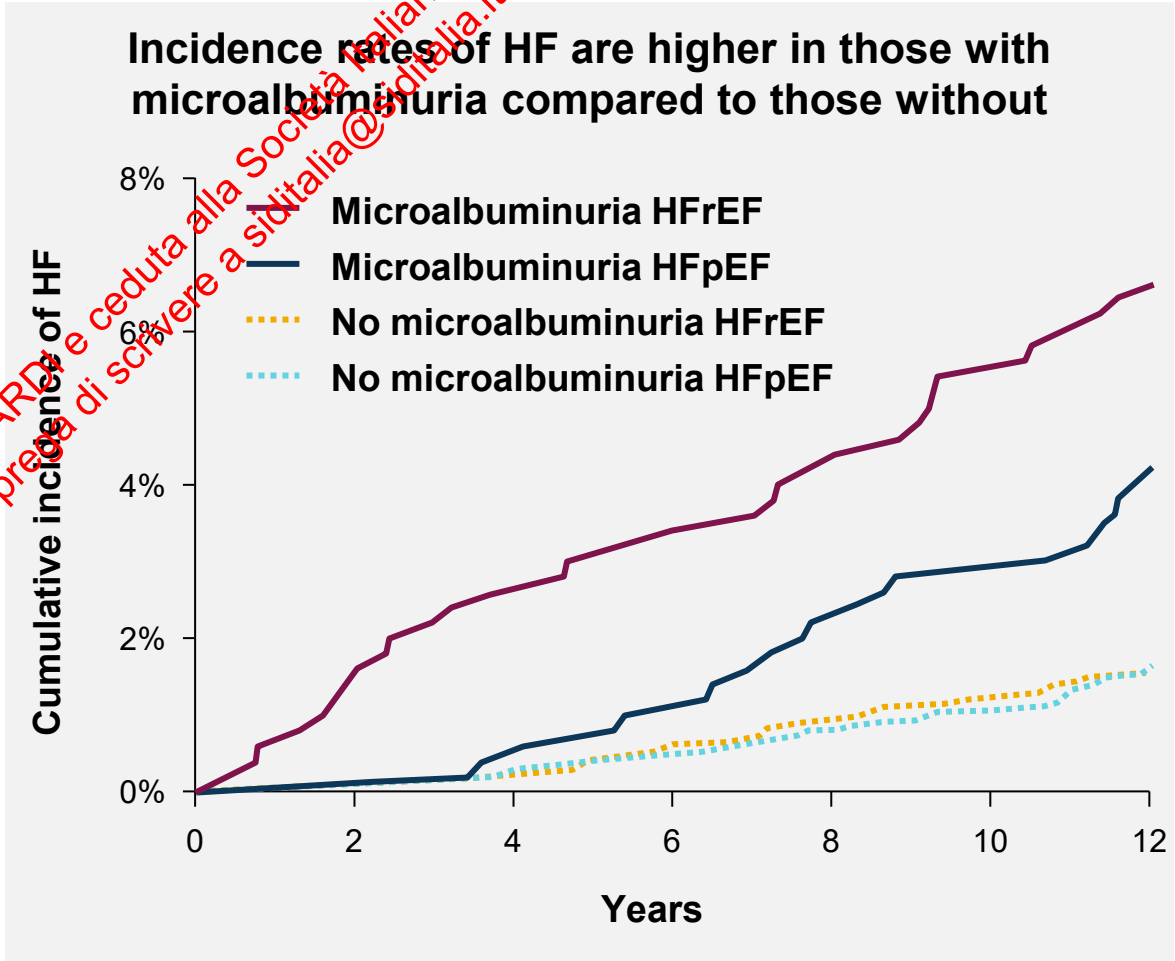
These data demonstrate the potential of SGLT2 inhibitors with regards to HF prevention and treatment



CKD, chronic kidney disease; HF, heart failure; hHF, hospitalisation for heart failure; MI, myocardial infarction; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes; adapted from Giorgino F, et al., Diabetes Obes Metab 2020

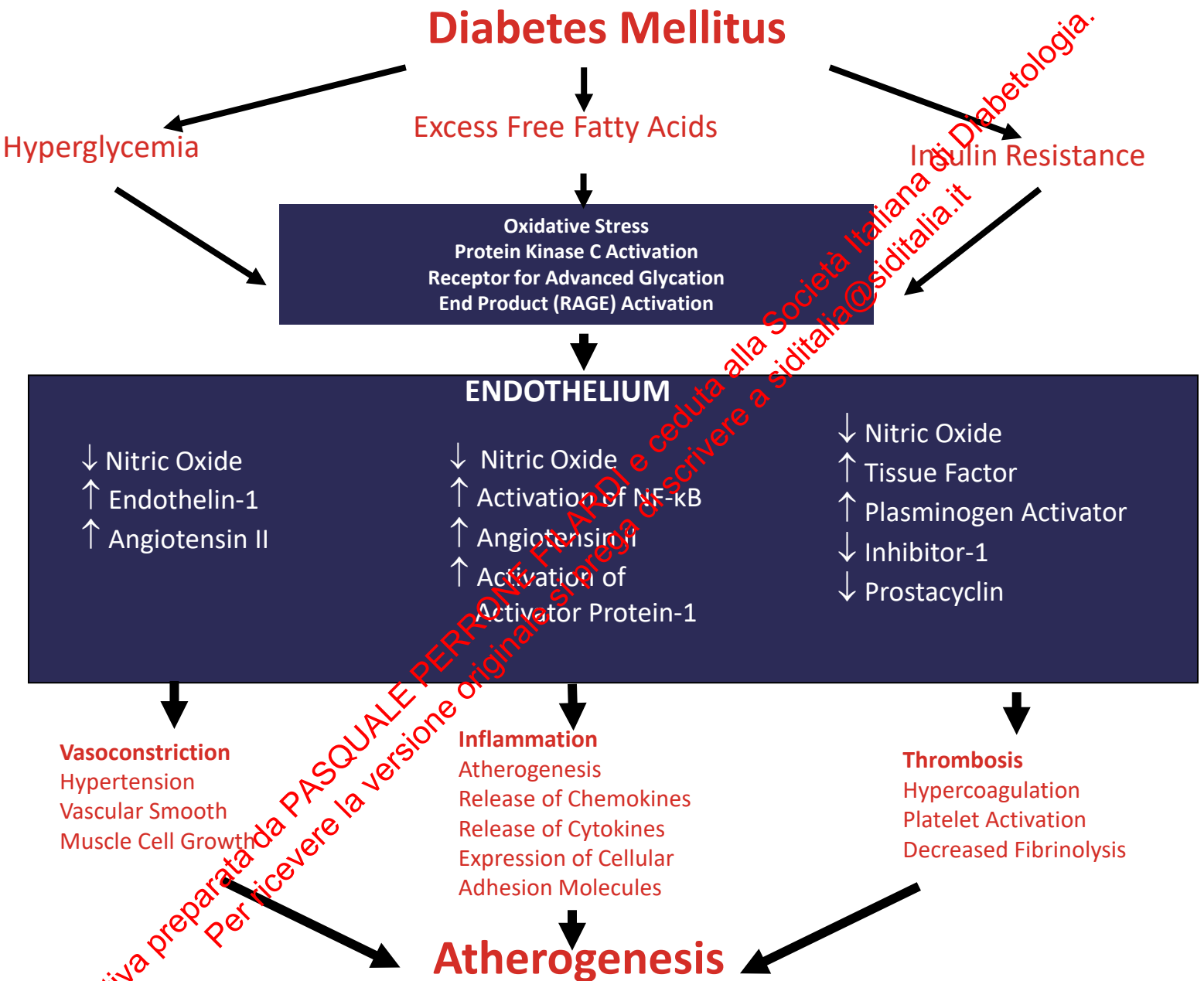
Declining renal function is associated with incident HF





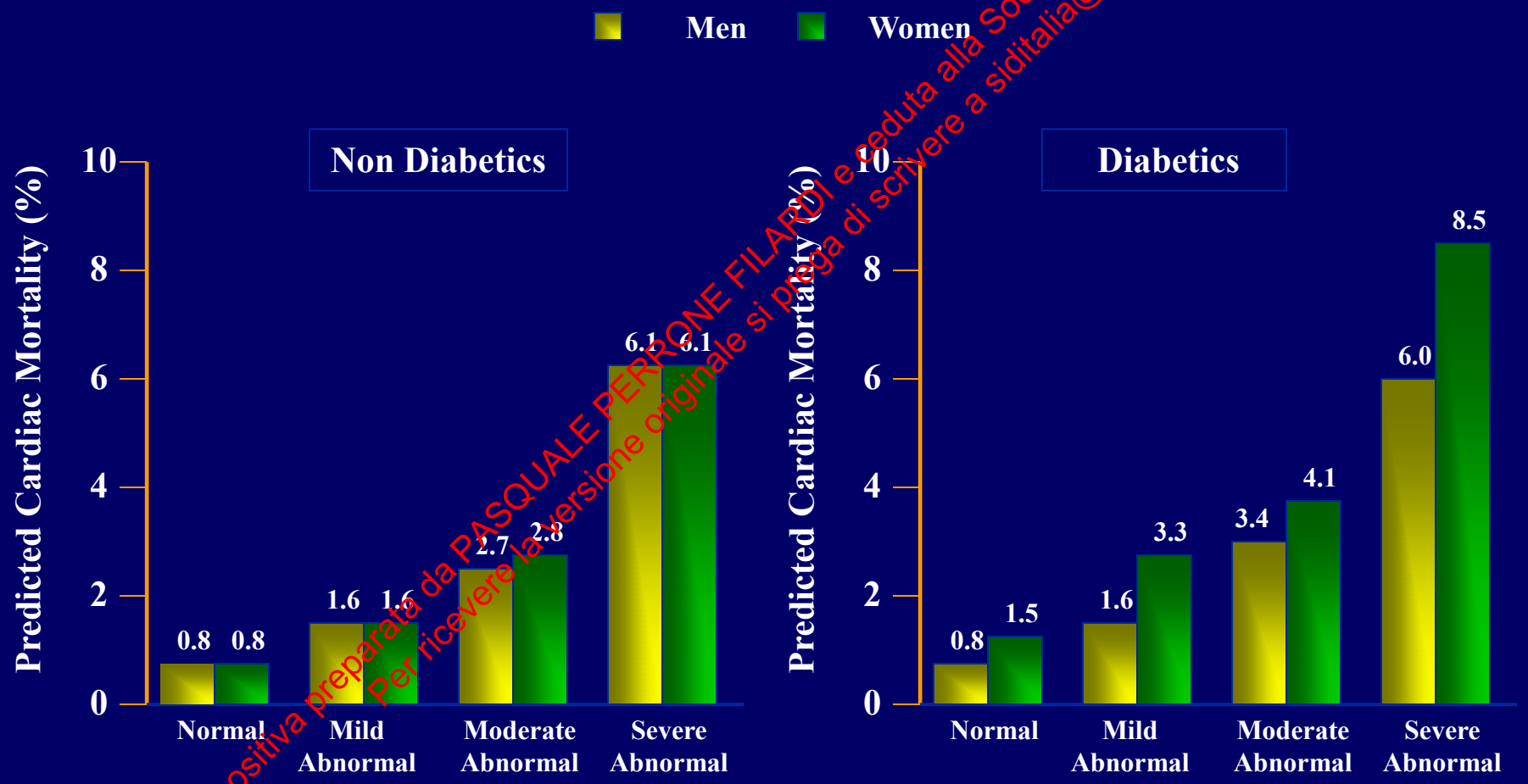
CKD = chronic kidney disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Nayor M et al. *Eur J Heart Fail.* 2017;19:615-623.

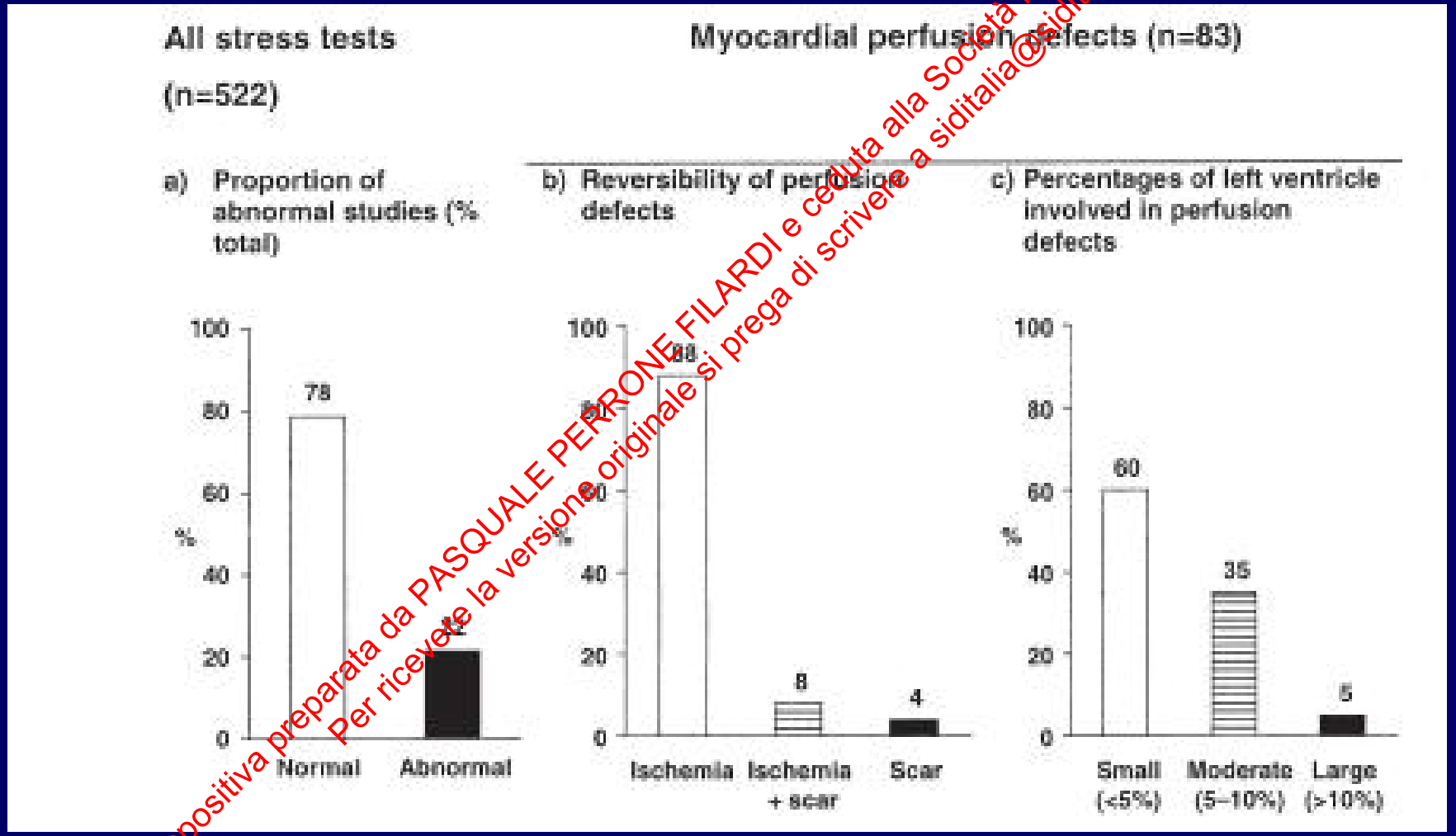


Prognostic Value of Adenosine SPECT in Diabetic and Non-Diabetic Women and Men

Berman et al., *JACC* 2003 (modified)



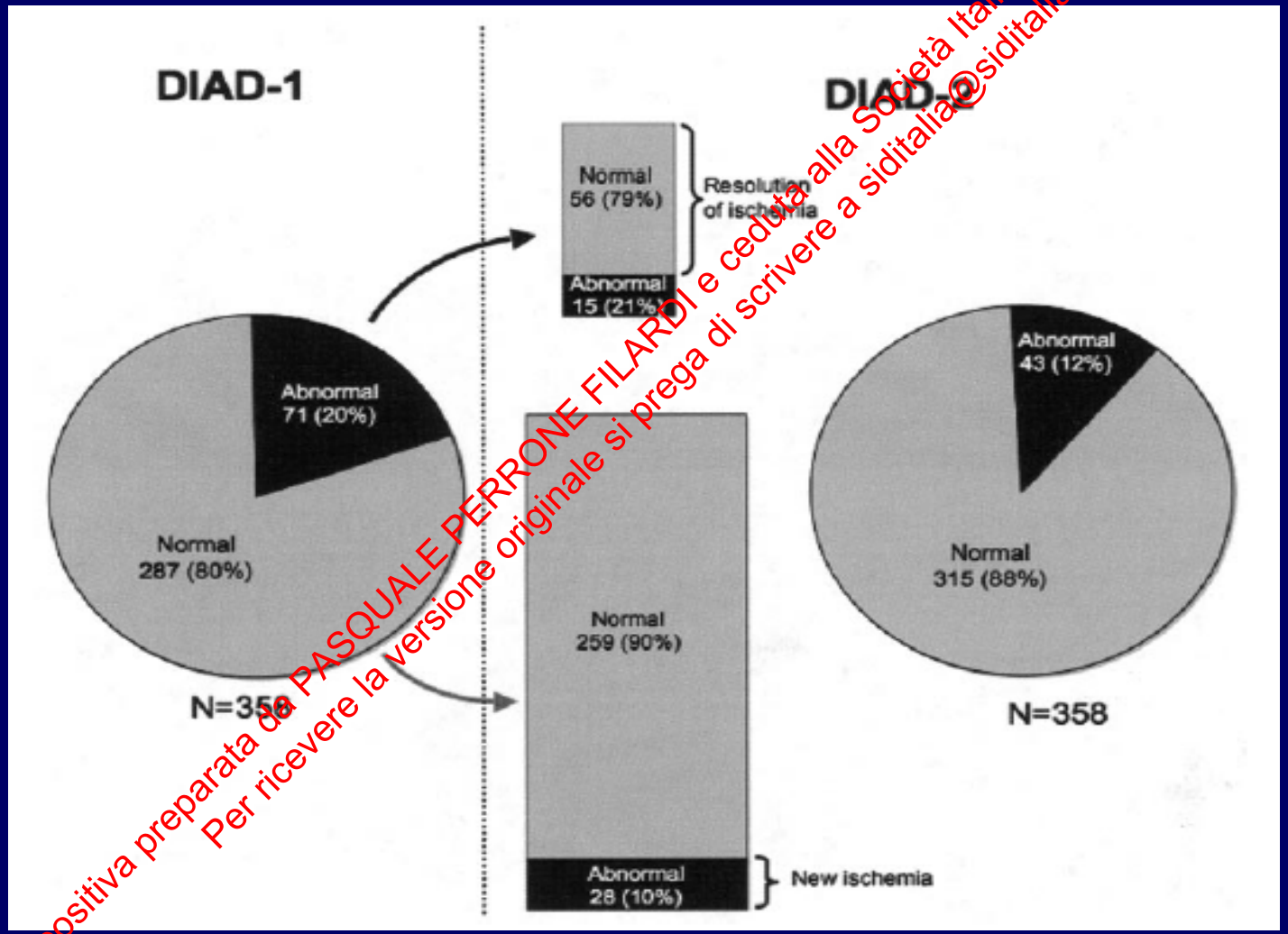
Prevalence of abnormal SPECT in asymptomatic diabetic patients without evidence of coronary artery disease



Wackers et al. Diabetes Care 2004

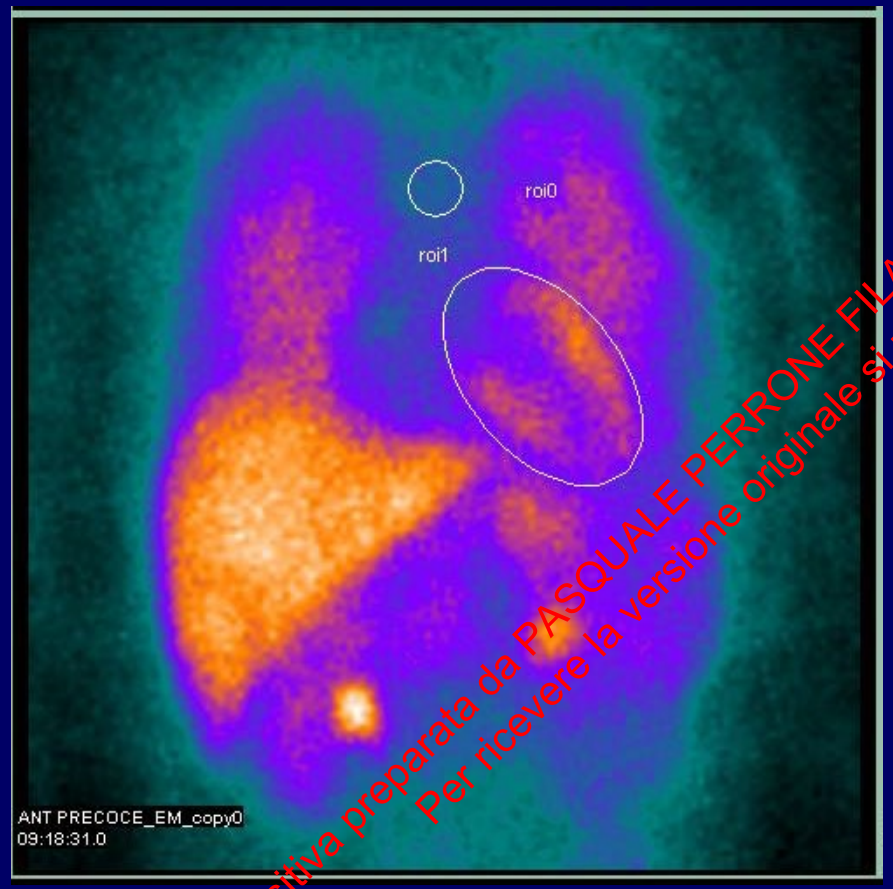
CHANGES AFTER 3-YEARS FOLLOW-UP OF MYOCARDIAL ISCHEMIA IN ASYMPTOMATIC DIABETICS SCREENED BY MPI

Wackers et al. for the *DIAD* Investigators. ***Diabetes Care 2007;30:2892***

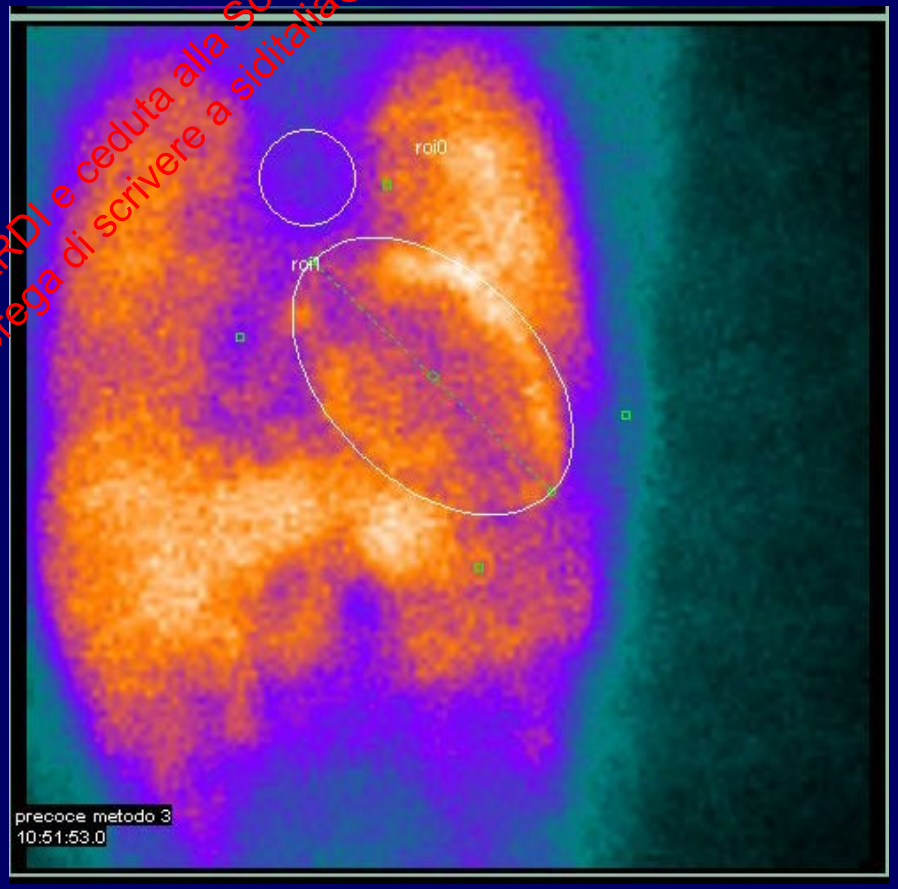


^{123}IMIBG BEFORE AND AFTER BETA BLOCKER THERAPY IN HF

Baseline



after 6 months beta blocker



Late Heart /Mediastinum ratio, studio della massima captazione cardiaca: 1.22 → 1.74

Cardiovascular and Metabolic Risk
ORIGINAL ARTICLE

Impact of Diabetes Mellitus on Cardiac Sympathetic Innervation in Patients With Heart Failure

A ^{123}I meta-iodobenzylguanidine (^{123}IMIBG) scintigraphic study

75 patient
with moderate to severe systolic HF (mean LVEF 31±7%)

37 patient
with systolic HF and DM

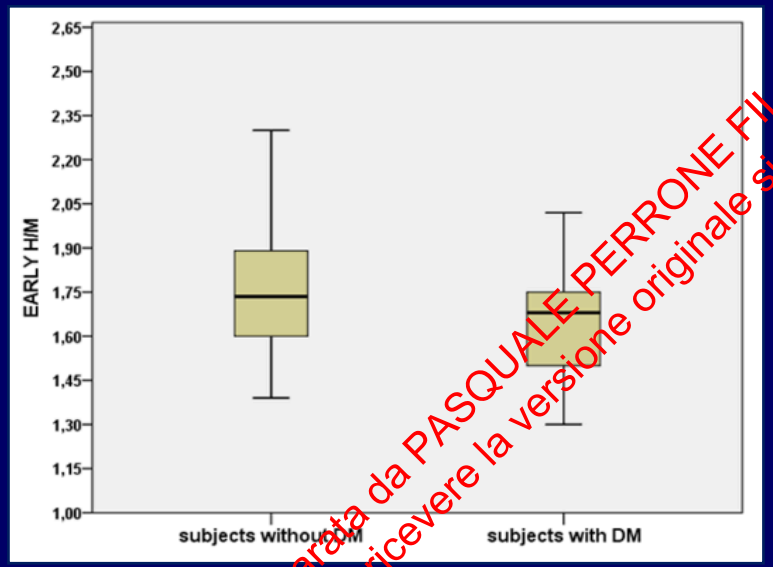
38 patient
with systolic HF and no DM

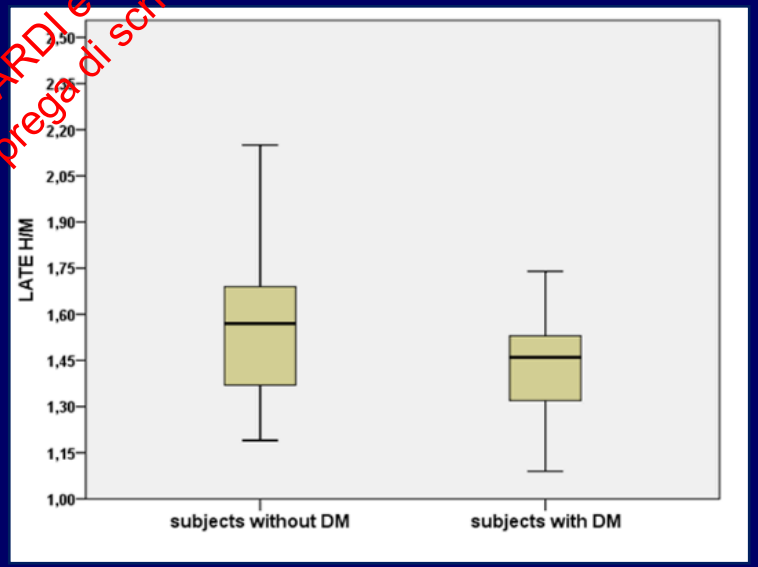
+ 14 DM patient
with normal left ventricular function

Paolillo et al. Diabetes Care 2013

I^{123} MIBG in the two groups of diabetic and non diabetic subjects

I^{123} MIBG parameter*	All	Subject with DM†	Subject without DM	*p value*
Early H/M ‡ ratio	1.70±0.22	1.65±0.21	1.75±0.21	0.05
Late H/M ‡ ratio	1.52±0.24	1.46±0.22	1.58±0.24	0.025
Washout rate	35.66±22.07	37.83±22.3	33.9±21.91	0.448





Paolillo et al. Diabetes Care 2013

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Summary

Background Although statin therapy reduces the risk of occlusive vascular events in people with diabetes mellitus, there is uncertainty about the effects on particular outcomes and whether such effects depend on the type of diabetes, lipid profile, or other factors. We undertook a prospective meta-analysis to help resolve these uncertainties.

Methods We analysed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of a further 71 370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings During a mean follow-up of 4·3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01; p=0·02), which was similar to the 13% reduction in those without diabetes (0·87, 0·82–0·92; p<0·0001). This finding reflected a significant reduction in vascular mortality (0·87, 0·76–1·00; p=0·008) and no effect on non-vascular mortality (0·97, 0·82–1·16; p=0·7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72–0·86; p<0·0001), which was similar to the effect observed in those without diabetes (0·79, 0·76–0·82; p<0·0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69–0·87; p<0·0001), coronary revascularisation (0·75, 0·64–0·88; p<0·0001), and stroke (0·79, 0·67–0·93; p=0·0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.

Interpretation Statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.

Lancet 2008; 371: 117–25

See Comment page 94

*Collaborators listed at end of paper

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ctt@ctsu.ox.ac.uk

or

National Health and Medical Research Council (NHMRC) Clinical Trial Centre, Mallett Street Campus M02, University of Sydney, NSW 2006, Australia
ctt@ctc.usyd.edu.au

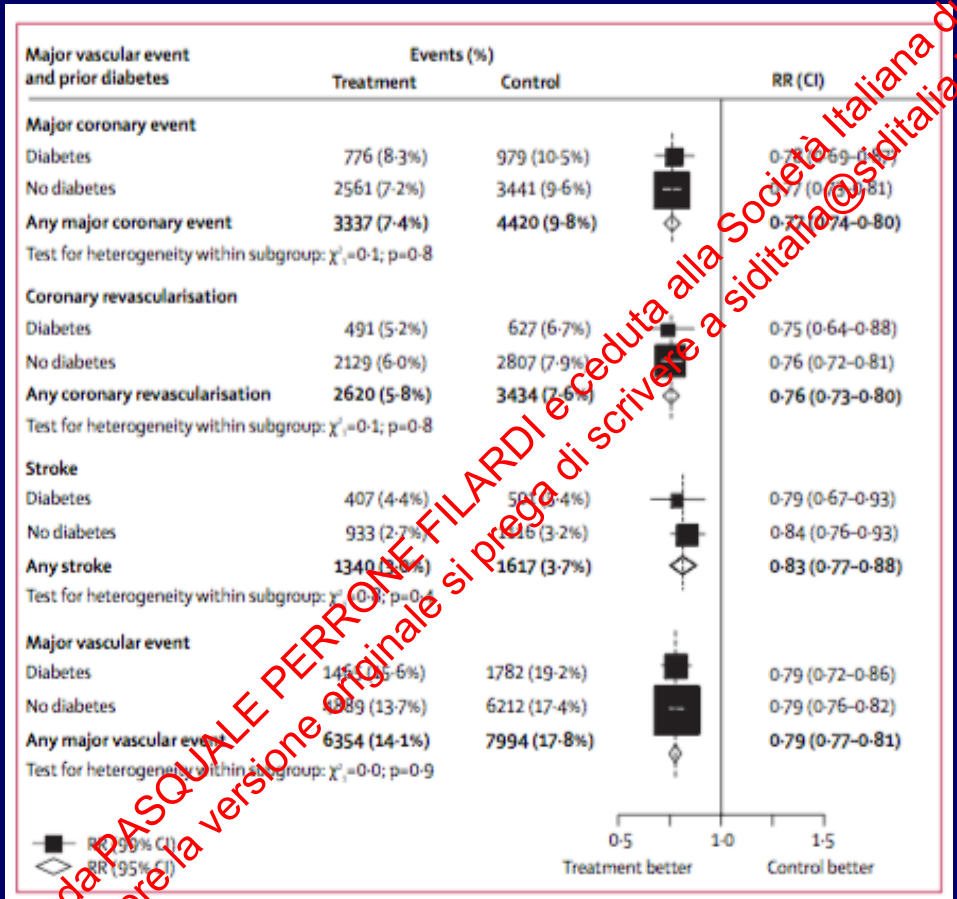


Figure 2: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes

Symbols and conventions as in figure 1.

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association

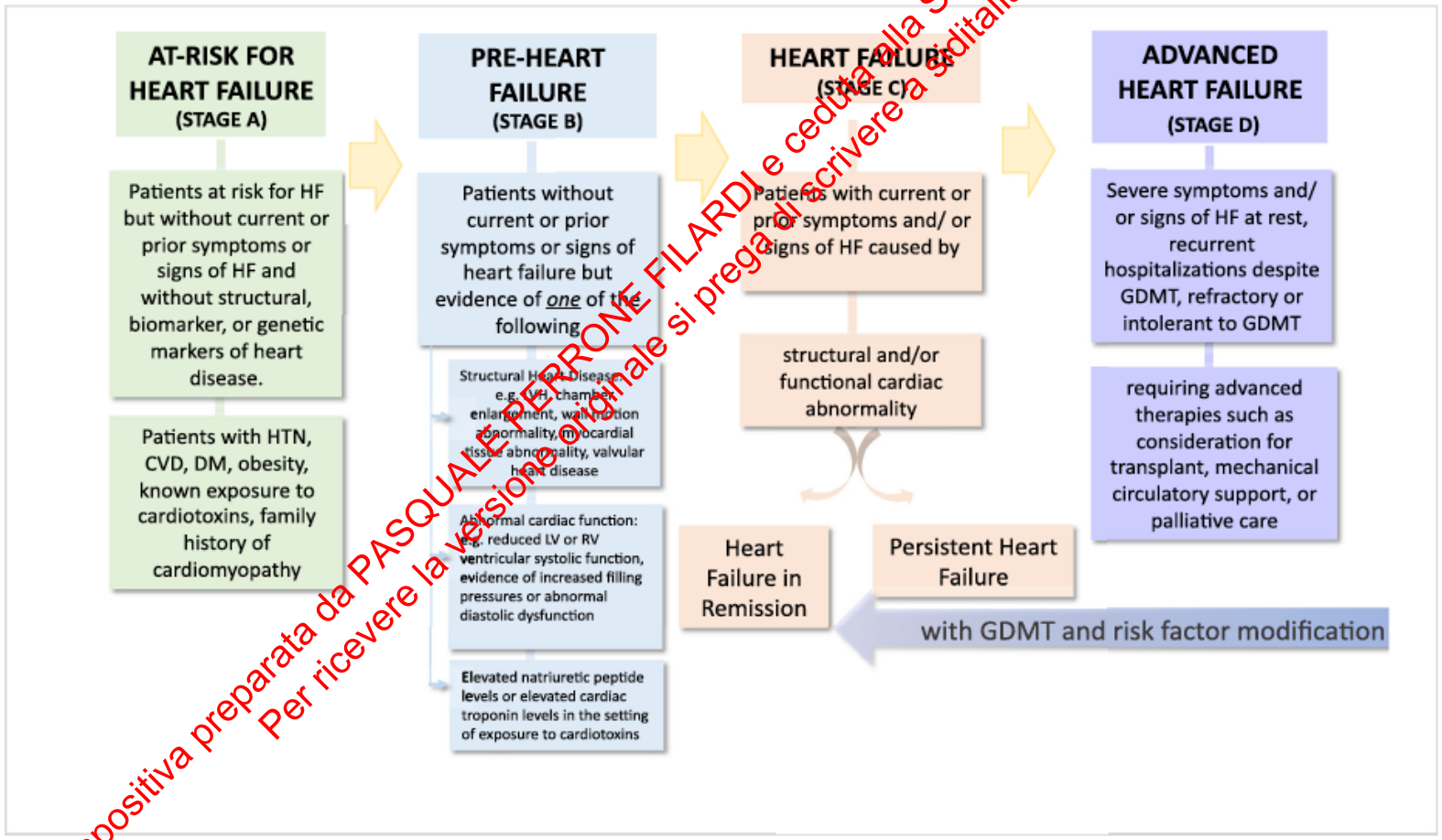
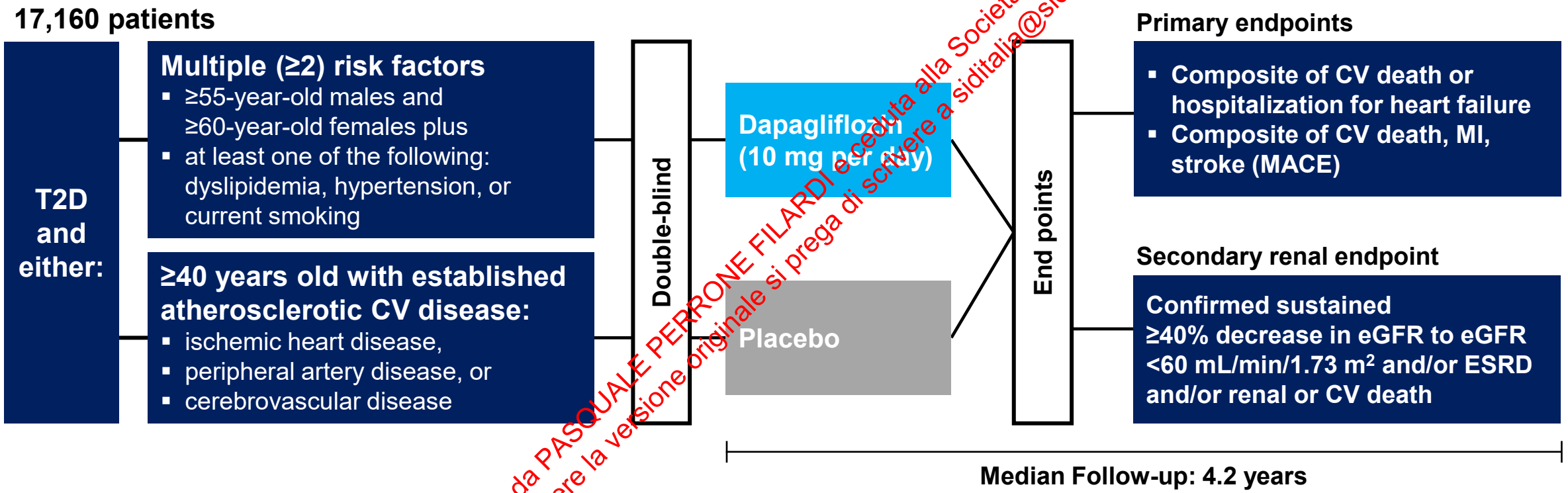


Figure 2. Stages in the development and progression of HF. CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension;

DECLARE evaluated CV and renal outcome in a large population of T2D patients with atherosclerotic CV disease and multiple cardiovascular risk factors[1-3]



- The mean eGFR[a] was 85.2 mL/min/1.73 m², including 7% of patients with eGFR <60 mL/min/1.73 m²

[a] eGFR calcolato con MDRD formula.

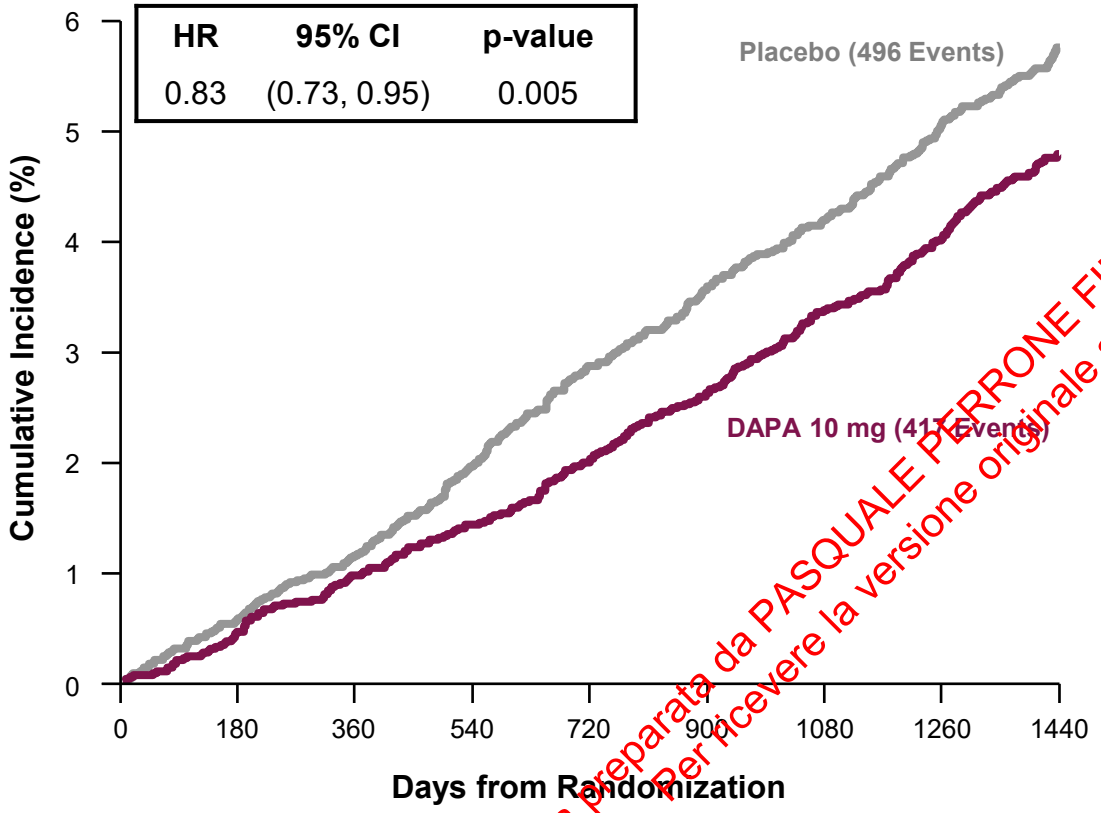
ASCVD = malattia CV aterosclerotica; CV = cardiovascolare; eGFR = velocità di filtrazione glomerulare stimata; ESRD = malattia renale terminale; MACE = maggiori eventi avversi cardiovascolari (morte CV, infarto miocardico non fatale, stroke ischemico non fatale); MI = infarto miocardico; T2D = diabete tipo 2.

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. *N Engl J Med*. 2019;380:347-357.

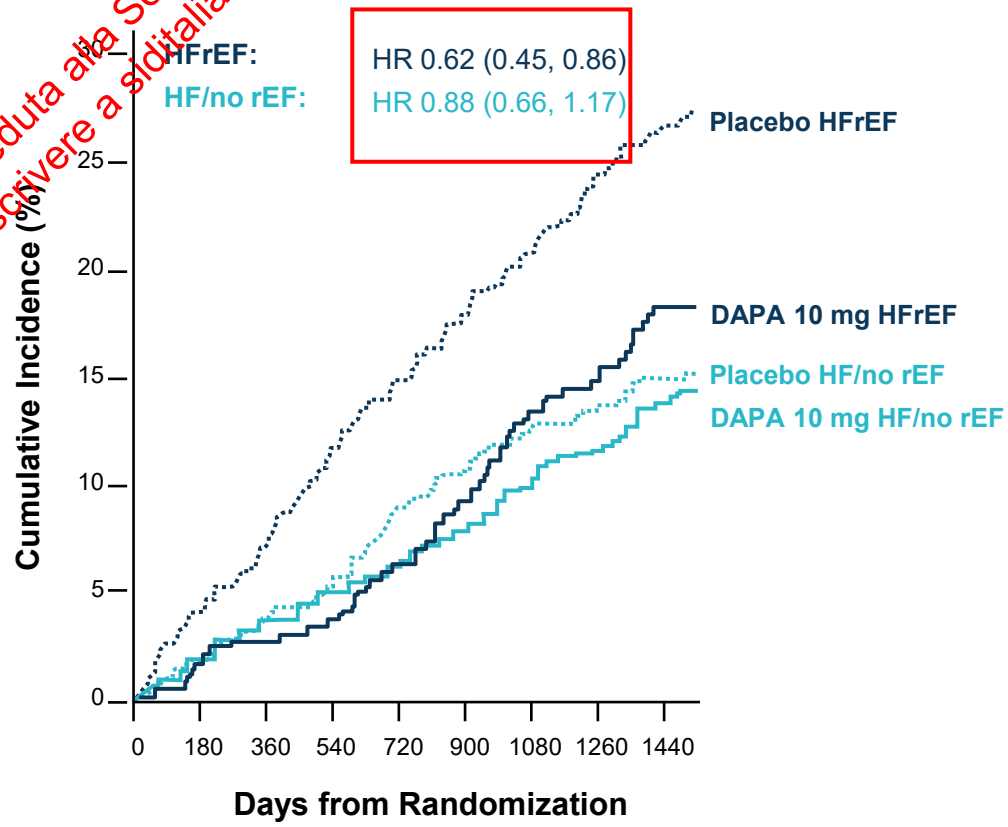
In DECLARE, Dapagliflozin Significantly Reduced hHF/CV Death in T2D Patients With Broad CV Risk and in the Subgroup of Patients With HFrEF

10% of patients in DECLARE had prior HF, 3.9% had HFrEF

Primary endpoint- hHF/CV death[1,a]



Subgroup analysis- hHF/CV death by history of HFrEF[2]

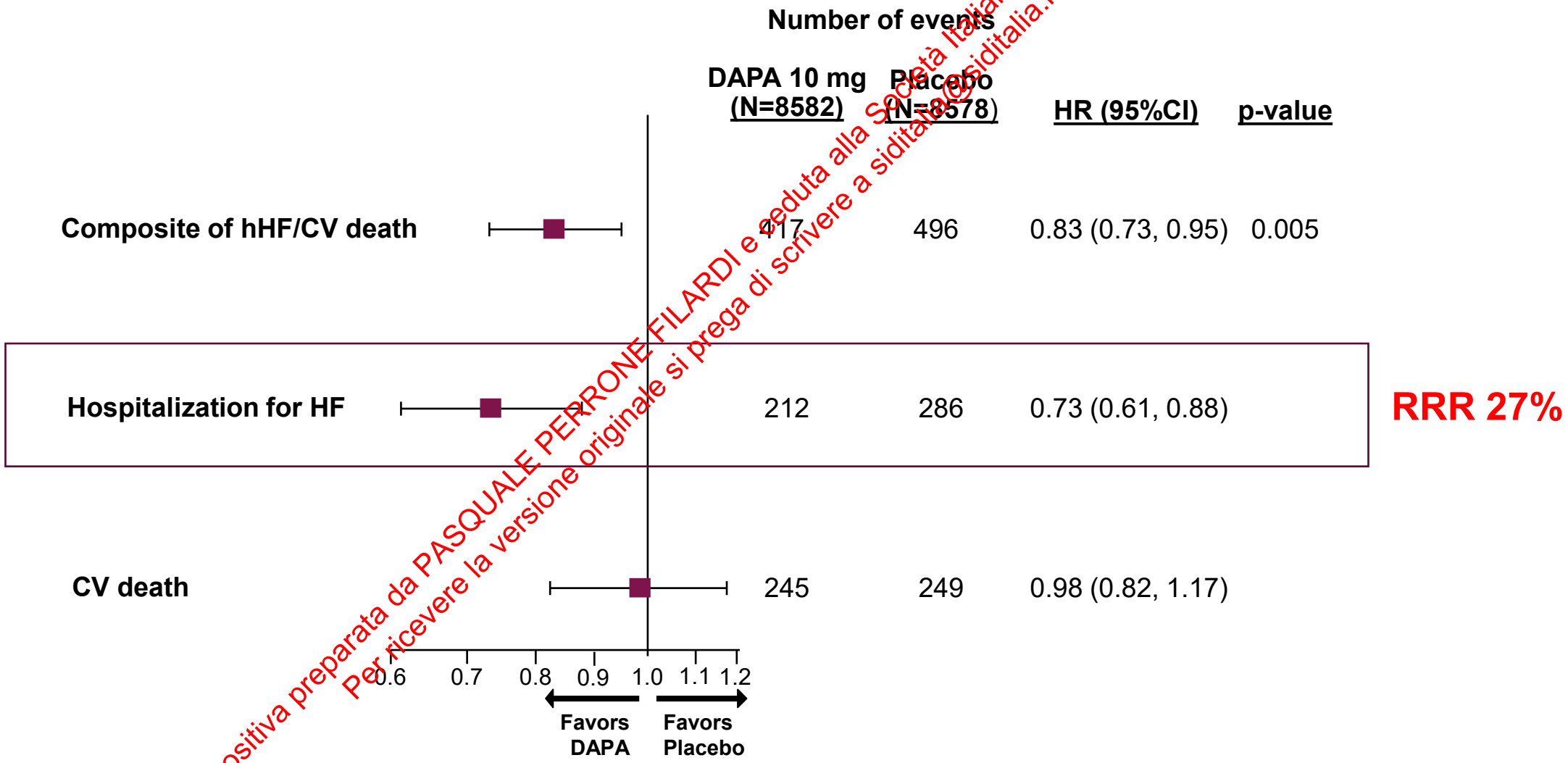


[a]2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; HR = hazard ratio; rEF = reduced ejection fraction; T2D = type 2 diabetes.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Kato ET et al. *Circulation.* 2019;139:2528-2536.

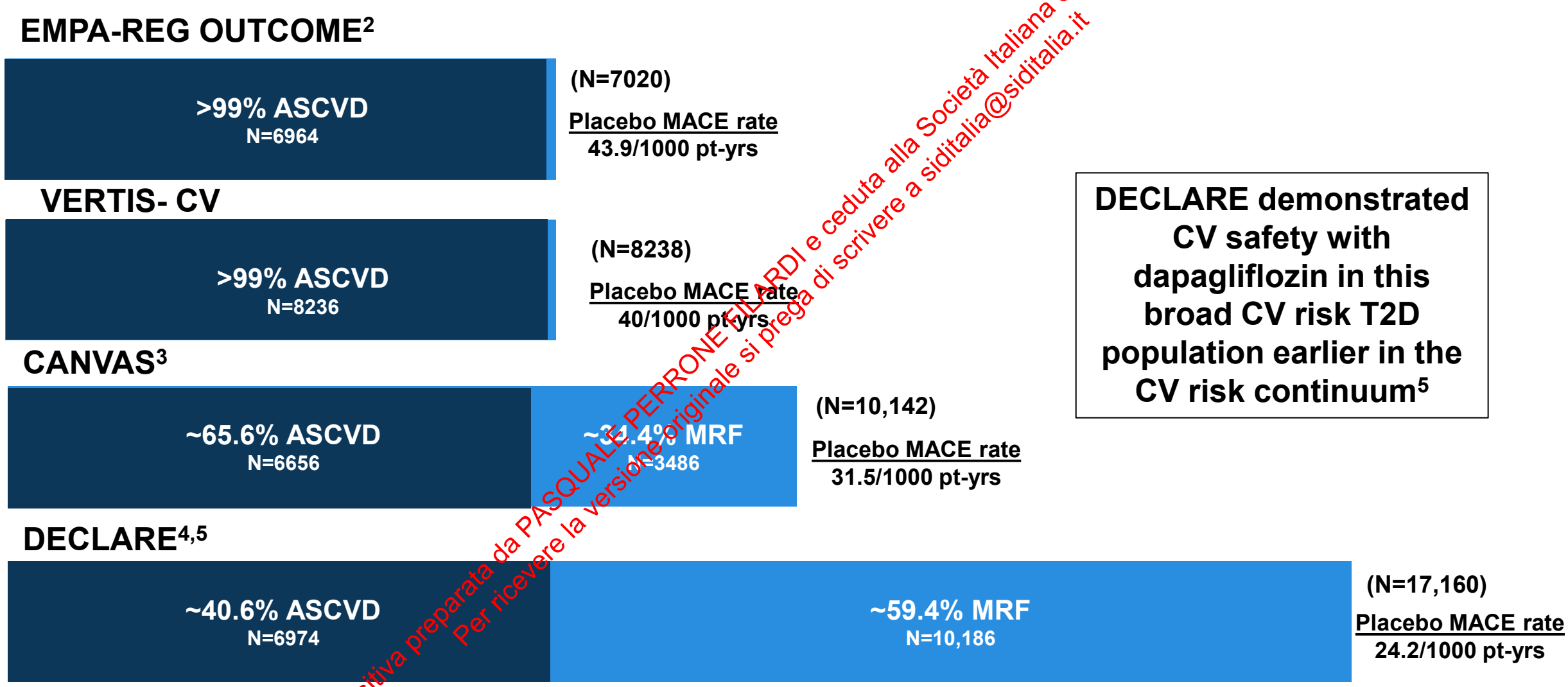
Primary Endpoint: Composite of hHF or CV death and the Individual Components



Two-sided p-value is shown for the primary efficacy composite outcome of CV death or hHF.
CV, cardiovascular; DAPA, dapagliflozin; HF, heart failure; hHF, hospitalization for heart failure.
Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

DECLARE has the largest T2D primary prevention population among the SGLT2i CVOTs

In the T2D patient population, most patients do not have established CV disease[1]



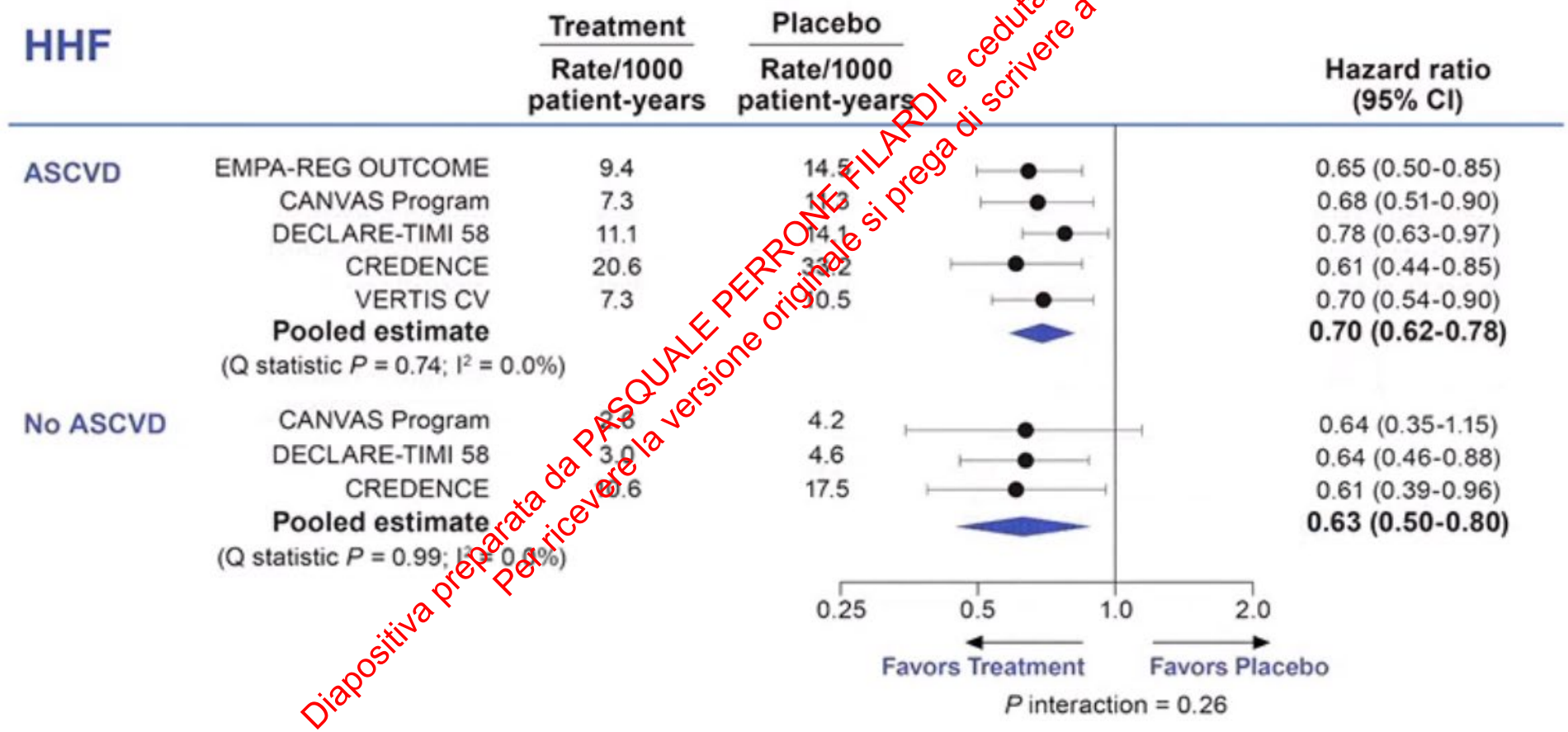
DECLARE demonstrated CV safety with dapagliflozin in this broad CV risk T2D population earlier in the CV risk continuum[5]

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVOT = cardiovascular outcome trial; MACE = major adverse cardiovascular event; MRF = multiple risk factors; SGLT2 = sodium glucose cotransporter 2; T2D = type 2 diabetes.

1. Einarson TR et al. *Cardiovasc Diabetol.* 2018:17:83; 2. Zinman B et al. Article and online supplement. *N Engl J Med.* 2015;373:2117–2128; 3. Neal B et al. *N Engl J Med.* 2017;377:644–657; 4. Raz I et al. *Diabetes Obes Metab.* 2018;20:1102-1110; 5. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357.

Effects of SGLT2i on first hospitalization for heart failure

Time to first HHF – subgroup analysis by ASCVD



McGuire DK, et al. JAMA Cardiol 2020. doi:19.1001/jamacardio.2020.511.

ASCVD, atherosclerotic cardiovascular disease.

DAPA-HF was the first SGLT2 inhibitor outcomes trial in patients with HFrEF with and without T2D

DAPAHF

Treatment for patients with HFrEF **with and without T2D** to improve CV outcomes and reduce mortality[1]

N=4744

1:1 randomization

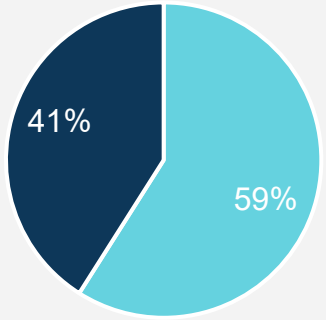
Dapagliflozin 10 mg and standard of care therapy

Placebo and standard of care therapy

Median follow-up time: 18 months

Patients with and without T2D

eGFR[3]

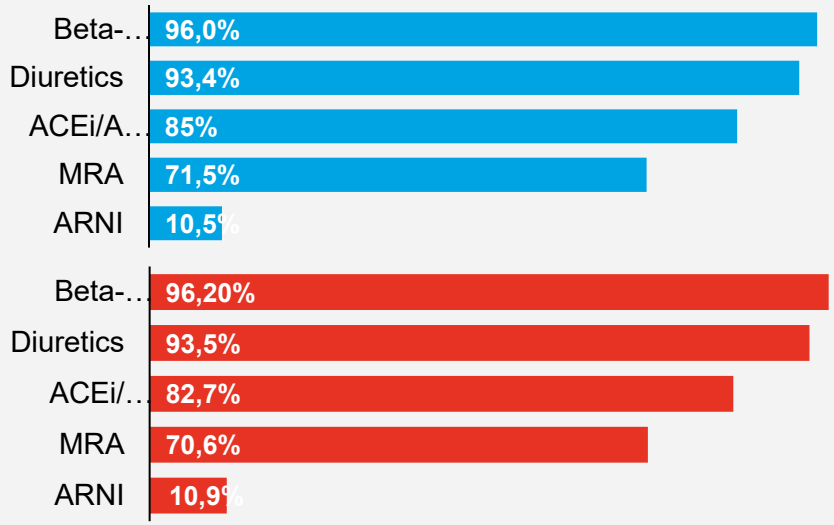


Baseline eGFR category
- ≥60 mL/min/1.73m²
- <60 mL/min/1.73m²

Key inclusion criteria

- Adults with or without T2D with HFrEF (LVEF ≤40%)
- NYHA class II-IV
- elevated NT-proBNP,
- eGFR ≥30 mL/min/1.73 m2
- Stable SoC HFrEF treatment

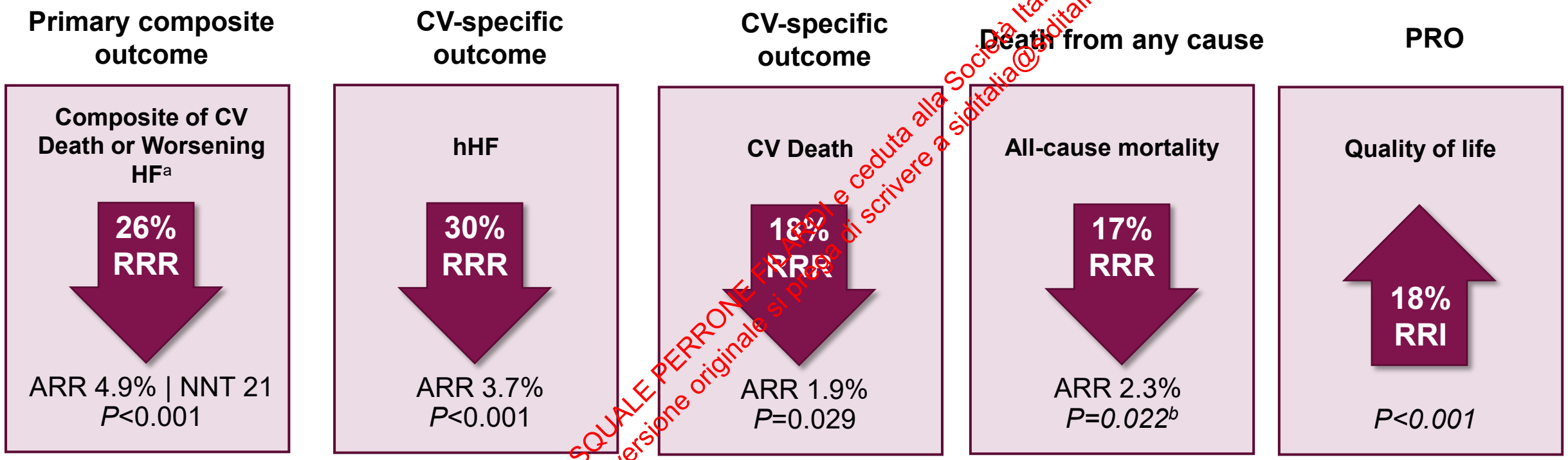
HF Therapy



ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes; UAC = urinary albumin:creatinine ratio.

McMurray JJV et al. Circulation. 2020;141:100-111

DAPA-HF was the first SGLT2 inhibitor outcomes trial in patients with HFrEF with and without T2D

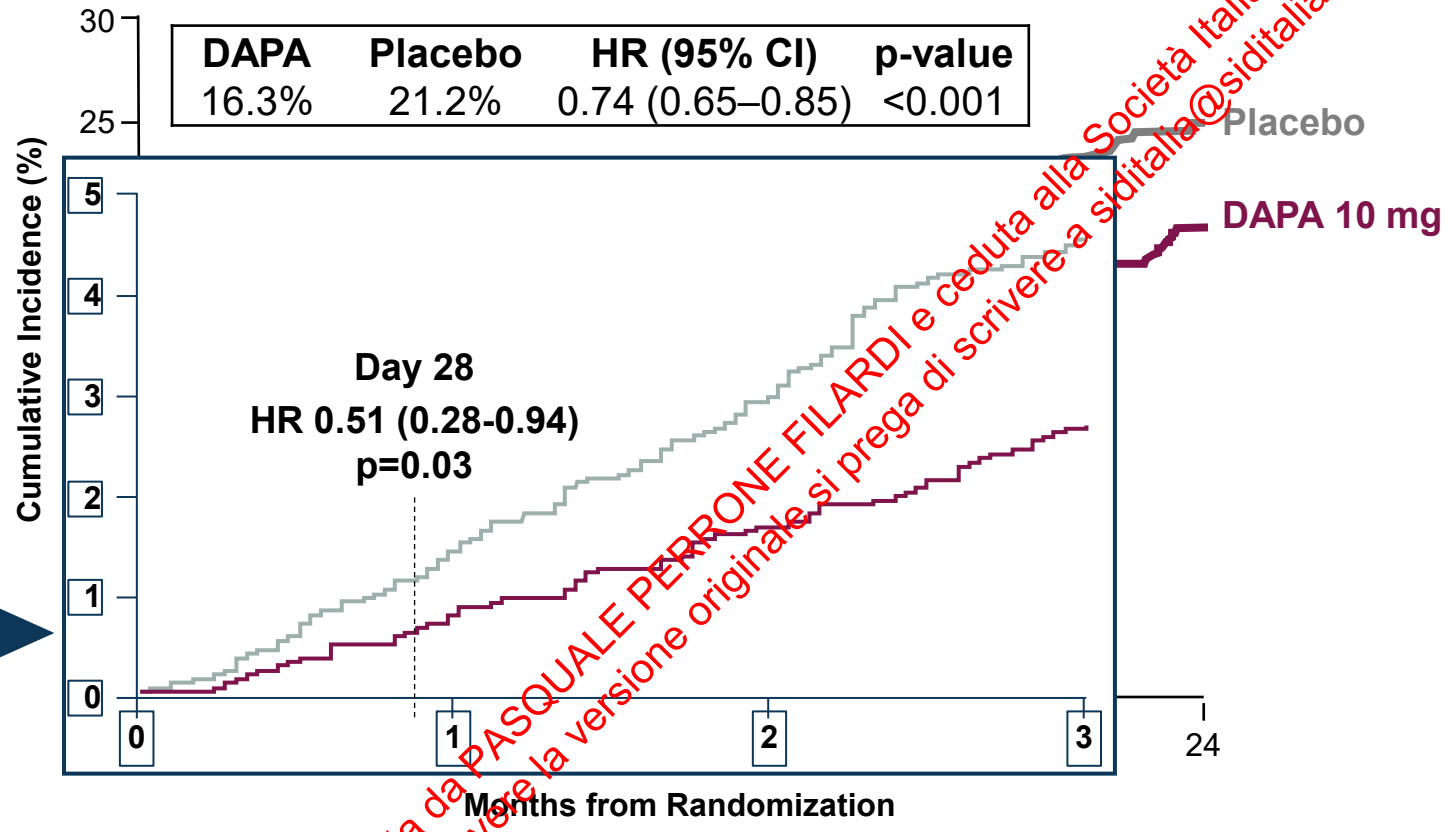


ARR = absolute risk reduction; CV = cardiovascular; hHF = hospitalization for heart failure; PRO = patient reported outcome; RRR = relative risk reduction; RRI = relative risk increase; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes.

a. Worsening HF includes hHF or urgent HF visit. b. Nominal p value

McMurray JJV et al. Circulation. 2020;141:100-111

Dapagliflozin Significantly Reduced the Relative Risk of CV Death or Worsening HF[a] on Top of Standard of Care by 26%[1]



Primary endpoint was statistically significant as early as Day 28[2]

26% RRR

4.9% ARR

NNT=21

Number at Risk

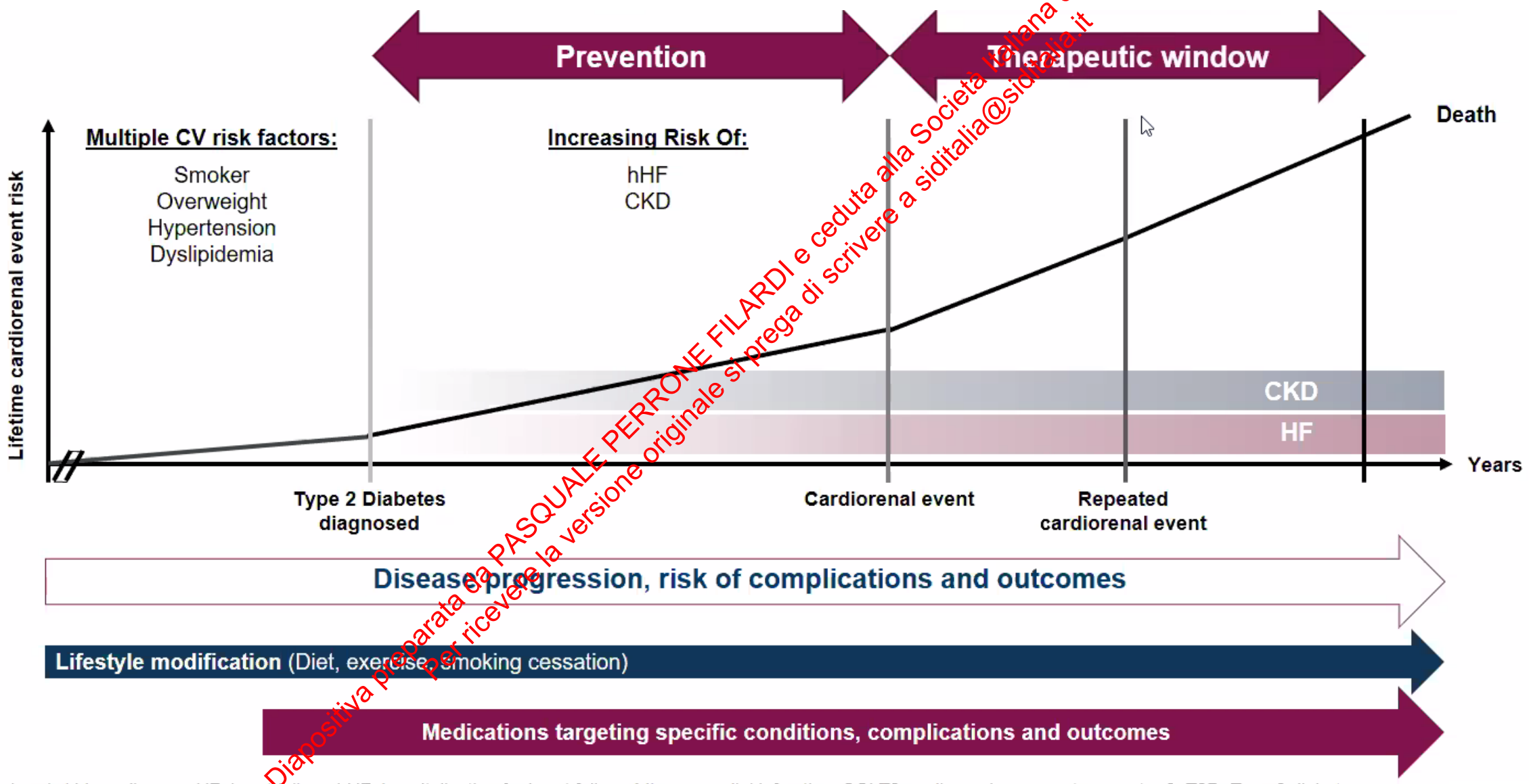
DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

[a]Worsening HF includes hHF or urgent HF visit.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

These data demonstrate the potential of SGLT2 inhibitors with regards to HF prevention and treatment



CKD, chronic kidney disease; HF, heart failure; hHF, hospitalisation for heart failure; MI, myocardial infarction; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes; adapted from Giorgino F, et al., Diabetes Obes Metab 2020

DECLARE-TIMI 58 ENROLLED PATIENTS WITH PREDOMINANTLY PRESERVED KIDNEY FUNCTION

DECLARE TIMI-58

Early intervention in patients with T2D to prevent cardiorenal complications[1]

N=17,160

1:1 randomization

- Dapagliflozin 10 mg
- Placebo

Median follow-up time: 4.2 years

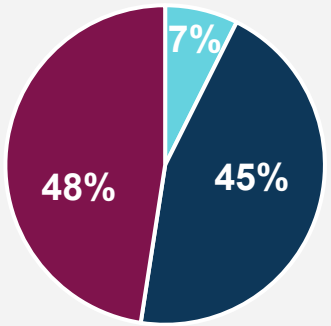
Patients with T2D

- eCVD 40.6% n=6974
- MRF 59.4% n=10,186

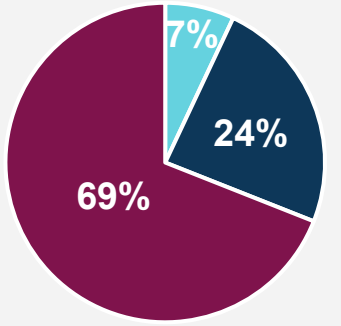
Key inclusion criteria

- T2D
- Age ≥40 years
- CVD or multiple risk factors for CVD
- HbA_{1c} ≥6.5% but <12.0%
- CrCl of ≥60 mL/min

eGFR[2]



UACR[3,a]

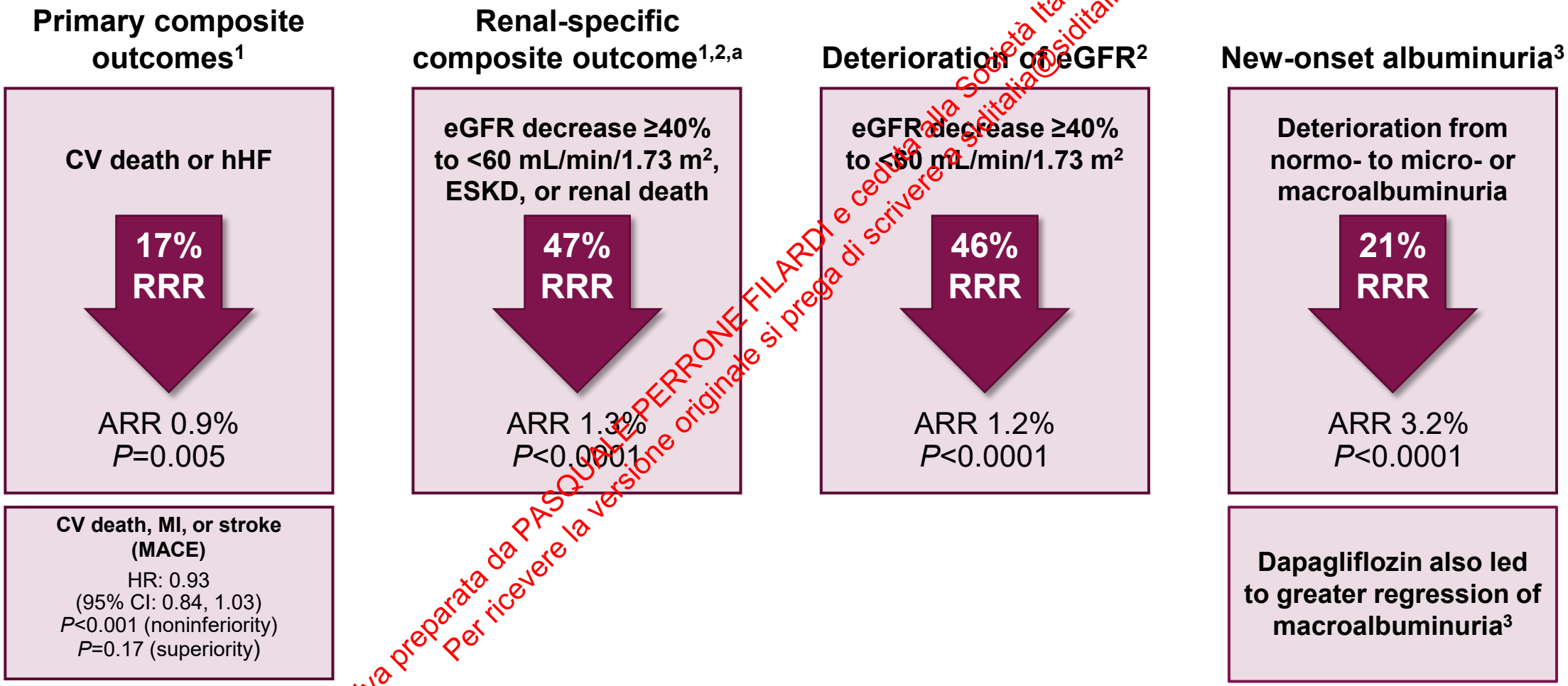


[a]Baseline UACR information was available for 98% of the total study population.

CrCl = creatinine clearance; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; eCVD = established cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; MRF = multiple risk factors; PAD = peripheral arterial disease; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357; 2. Mosenzon O et al. *Lancet Diabetes Endocrinol.* 2019;7:606-617; 3. Mosenzon O et al. *Diabetes Care.* 2021:dc210076.

In DECLARE-TIMI 58, dapagliflozin reduced the composite of hHF / CV death and slowed kidney disease progression in T2D patients with predominantly preserved kidney function



[a]Prespecified exploratory outcome.

ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; RRR = relative risk reduction; T2D = Type 2 diabetes.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Mosenzon O et al. *Lancet Diabetes Endocrinol*. 2019;7:606-617; 3. Mosenzon O et al. *Diabetes Care*. 2021:dc210076.

DAPA-CKD was the first and only SGLT2 inhibitor kidney outcomes trial in patients with CKD with and without T2D

DAPACKD

First treatment for patients with CKD **with and without T2D** to improve cardiorenal outcomes and reduce mortality[1]

N=4304

1:1 randomization

Dapagliflozin 10 mg and standard of care therapy

Placebo and standard of care therapy

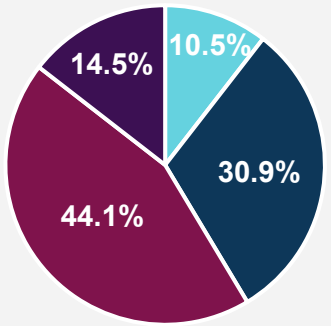
Median follow-up time: 2.4 years

Patients with and without T2D

Key inclusion criteria

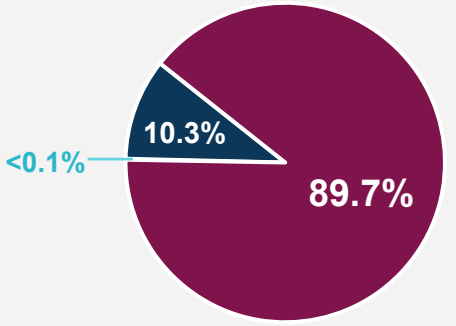
- Adults with or without T2D with eGFR of 25–75mL/min/1.73 m^2
- UACR of 200–5000 mg/g
- On a stable dose of an ACEi/ARB for at least 4 weeks, unless documented as unable to take ACEi/ARBs

eGFR[3]



Baseline eGFR category
- ≥60 mL/min/1.73m²
- 45 to <60 mL/min/1.73m²
- 30 to <45 mL/min/1.73m²
- <30 mL/min/1.73m²

UACR[3]

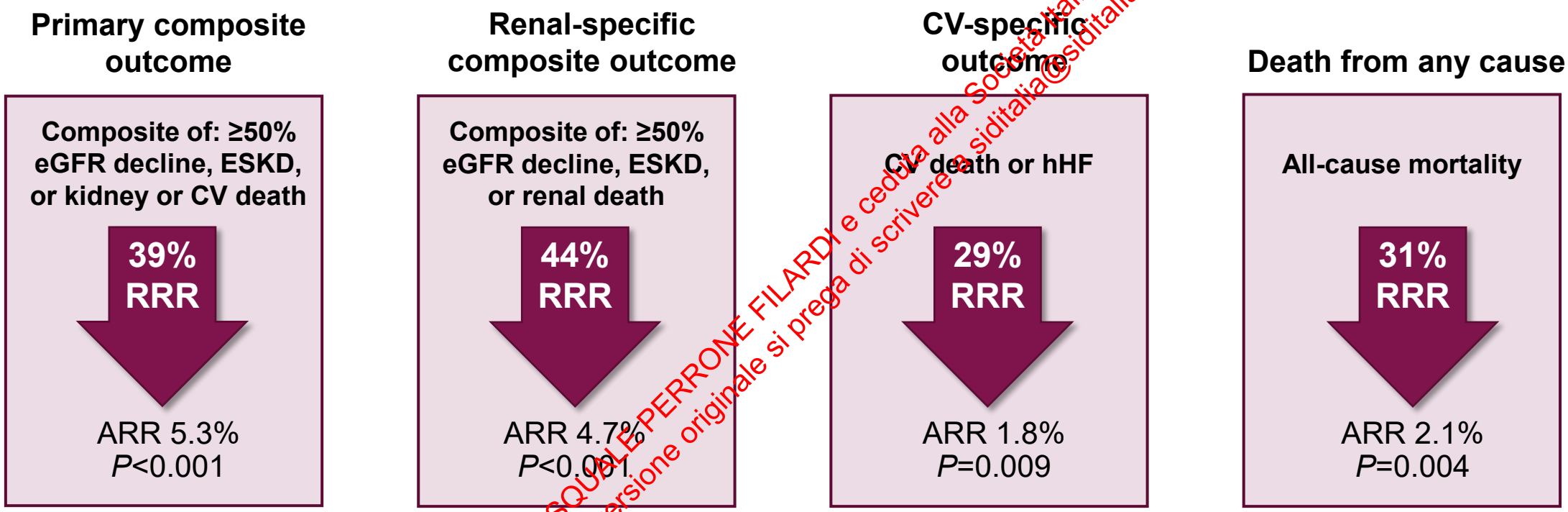


Baseline UACR category
- <30 mg/g
- 30 to ≤300 mg/g
- >300 mg/g

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes; UAC = urinary albumin:creatinine ratio.

1. Heerspink HJL et al. *N Engl J Med*. 2020:383:1436-1446; 2. Wheeler DC et al. *Nephrol Dial Transplant.* 2020;35:1700-1711.

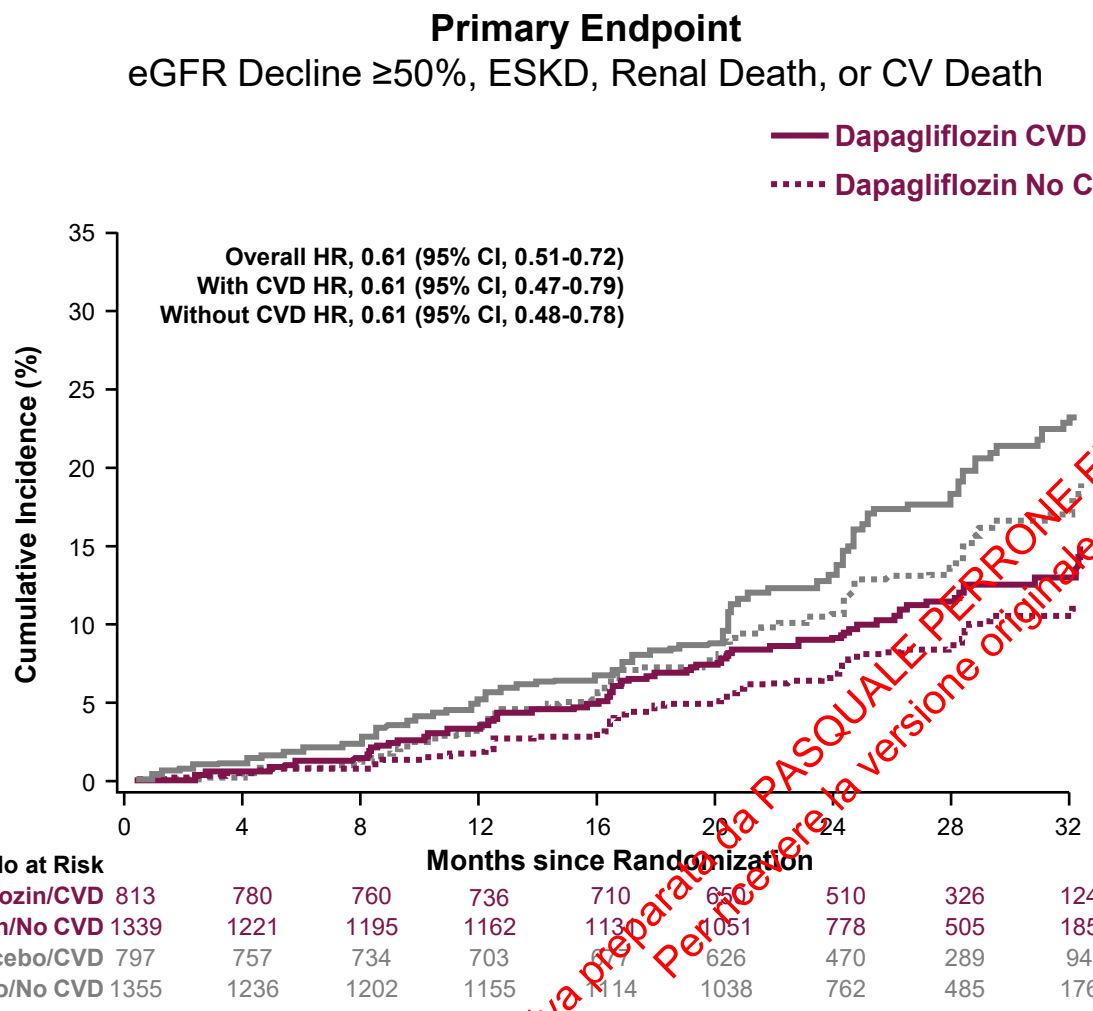
Dapagliflozin is the first and only SGLT2 inhibitor for patients with CKD, with and without T2D, to improve cardiorenal outcomes and reduce mortality

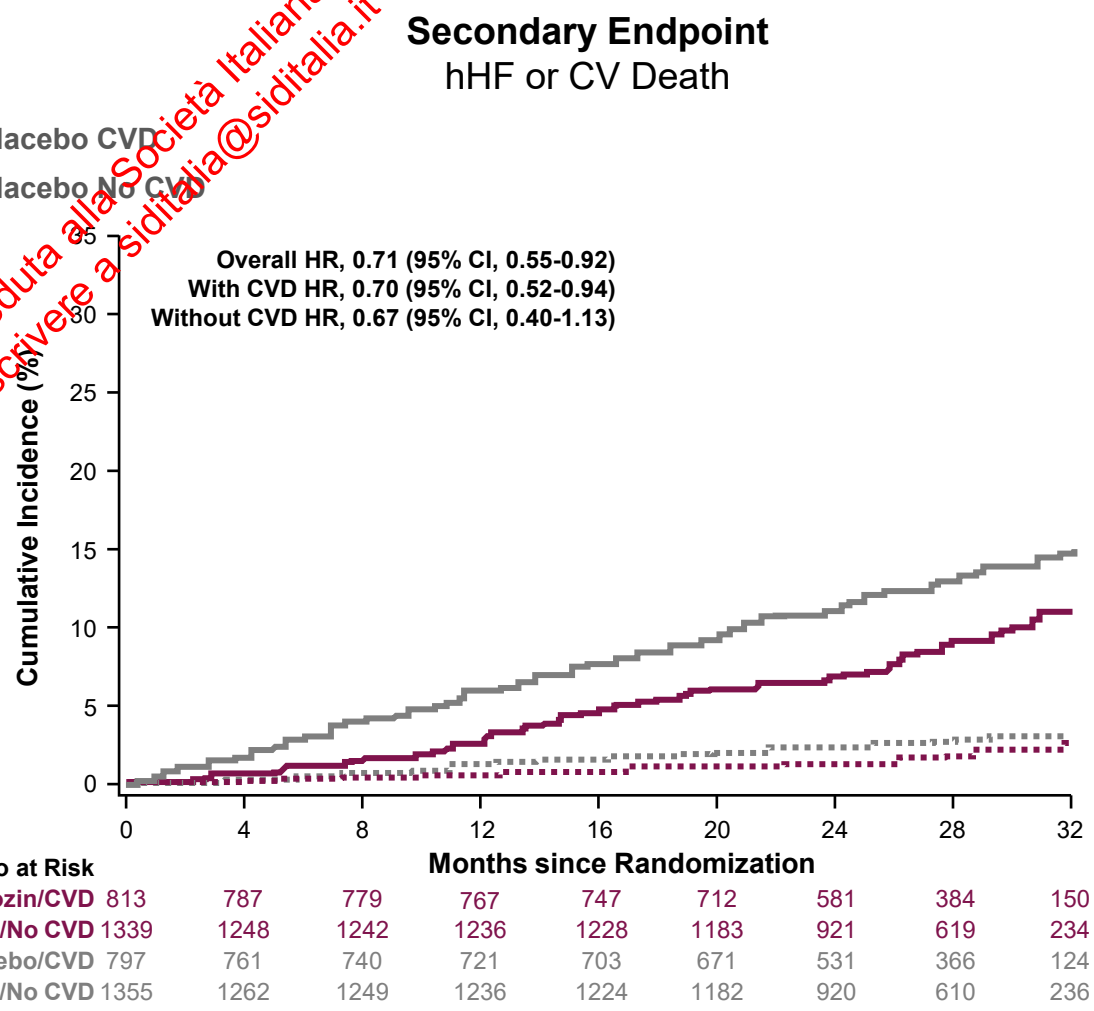


ARR = absolute risk reduction; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF, hospitalization for heart failure; RRR = relative risk reduction; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes.

Heerspink HJL et al. *N Engl J Med.* 2020;383:1436-1446.

Outcomes by Baseline CVD





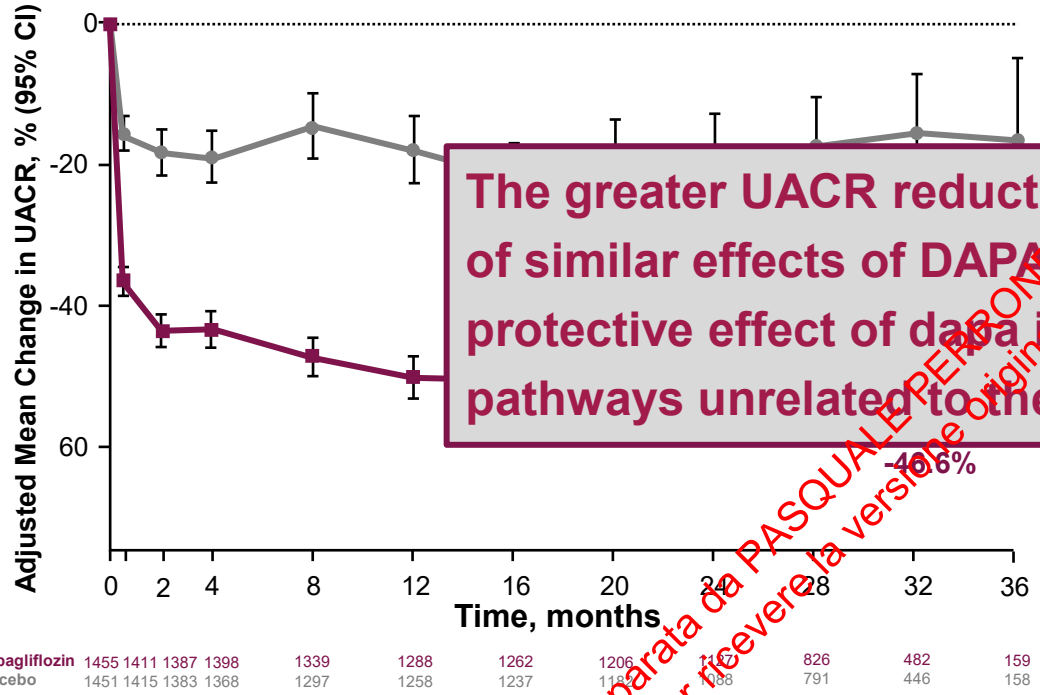
CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio.

 McMurray JJV et al. *Circulation*. 2021;143:438–448.

DAPA-CKD:
Antialbuminuric efficacy

Patients with T2D

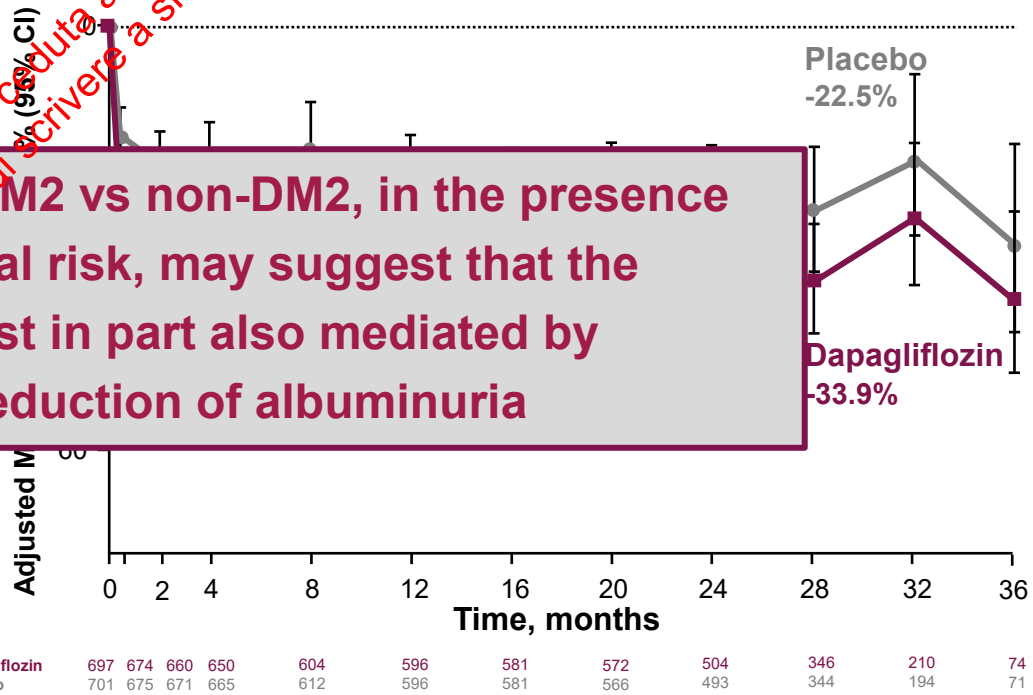
35.1% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI 30.6, 39.4; p<0.001)



Median (IQR) baseline UACR, mg/g
Dapagliflozin: 1025 (473–2111)
Placebo: 1005 (493–2017)

Patients without T2D

14.8% mean reduction in UACR (dapagliflozin vs. placebo)
(95% CI 5.9, 22.9; p=0.001)

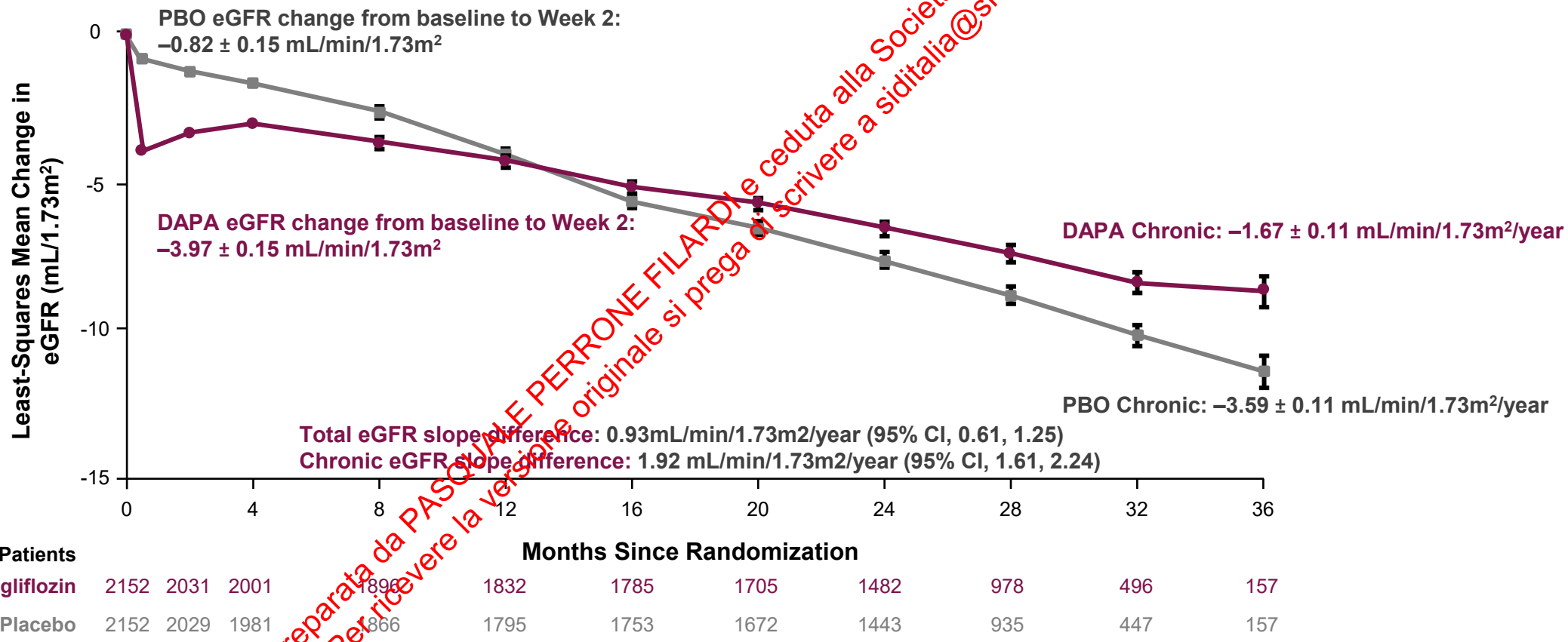


Median (IQR) baseline UACR, mg/g
Dapagliflozin: 870 (472–1554)
Placebo: 842 (459–1555)

The greater UACR reduction in DM2 vs non-DM2, in the presence of similar effects of DAPA on renal risk, may suggest that the protective effect of dapa is at least in part also mediated by pathways unrelated to the sole reduction of albuminuria

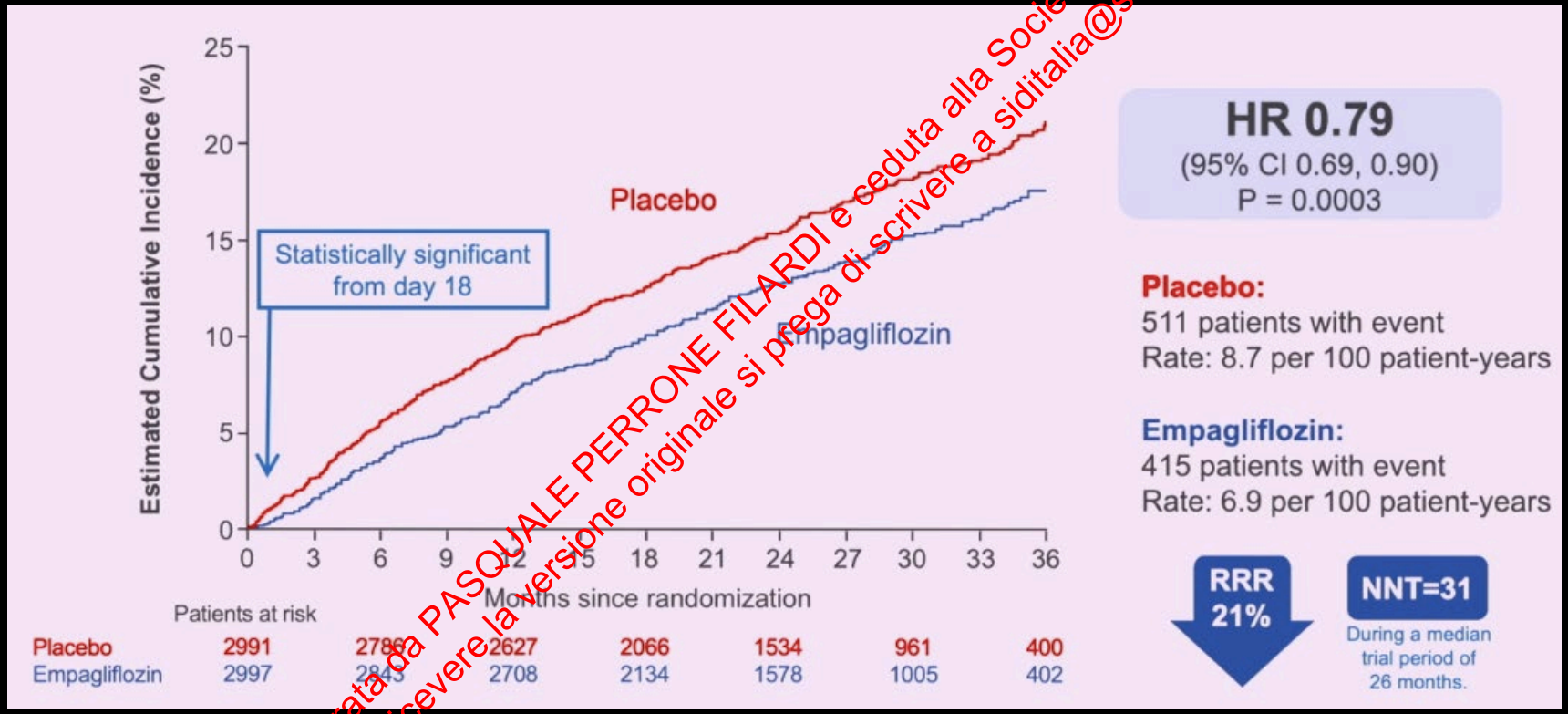
Jongs N et al. Lancet DE, 4 Oct 2021

Initial eGFR drop associates with better eGFR preservation in the long term



. Heerspink H et al. N Engl J Med. 2020

EMPEROR Preserved: Primary Endpoint



Anker et al. NEJM 2021

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01536-x

Check for updates

OPEN

The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial

Michael E. Nassif[1,2], Sheryl L. Windsor[1], Barry A. Borlaug[3], Dalane W. Kitzman[4], Sanjiv J. Shah[5], Fengming Tang[1], Yevgeniy Khariton[1,2], Ali O. Malik[1,2], Taiyeb Khumri[1], Guillermo Umpierrez[6], Sumant Lamba[7], Kavita Sharma[8], Sadiya S. Khan[5], Lokesh Chandra[9], Robert A. Gordon[10], John J. Ryan[11], Sunit-Preet Chaudhry[12], Susan M. Joseph[13], Chen H. Chow[14], Manreet K. Kanwar[15], Michael Pursley[16], Elias S. Siraj[17], Gregory D. Lewis[18], Barry S. Clemson[19], Michael Fong[20] and Mikhail N. Kosiborod[1,2,21,22] ✉

Inclusion Criteria

- HF with NYHA class II-IV symptoms (with or without T2D)
- Left Ventricular Ejection Fraction ≥ 45%
- NTproBNP ≥ 225 pg/mL (or BNP ≥ 75 pg/mL)*
- Requirement for diuretic therapy
- At least one of the following
  - Recent HF hospitalization or urgent HF visit requiring IV diuretic
  - Elevated filling pressures by right or left heart catheterization
  - Structural heart disease by echocardiography

*in patients with Atrial Fibrillation, NTproBNP ≥ 450 pg/mL or BNP ≥ 100 pg/mL

PRESERVED-HF
Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with PRESERVED Ejection Fraction Heart Failure

Primary Endpoint

- KCCQ clinical summary score (KCCQ-CS) at 12 weeks
  - Includes symptoms and physical limitations

Secondary Endpoints

- Six-minute walking distance
- Proportion of patients with clinically meaningful change in KCCQ (responder analysis)
- KCCQ Overall Summary Score at 12 weeks
- NTproBNP and BNP
- HbA1c, weight and SBP

PRESERVED-HF
Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with PRESERVED Ejection Fraction Heart Failure

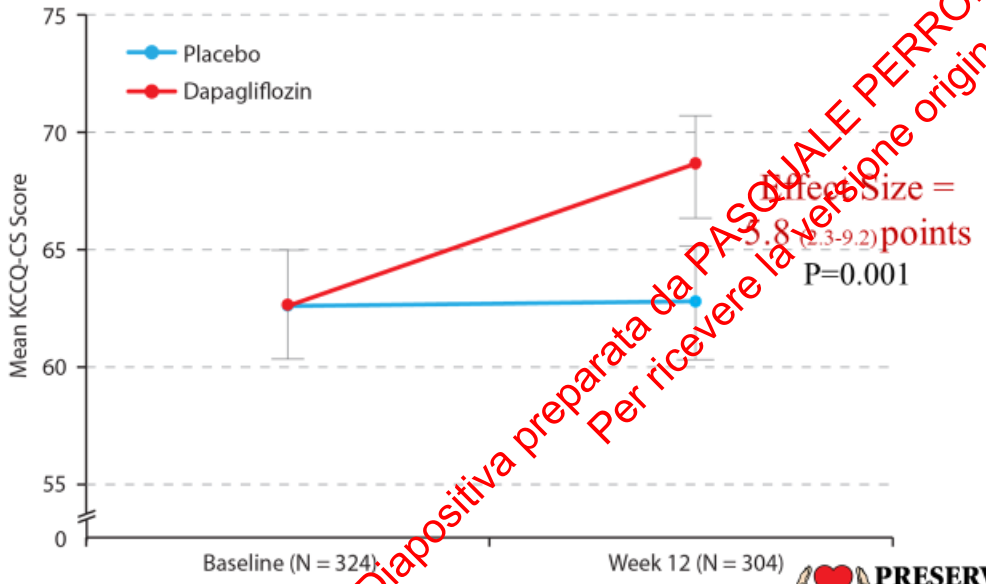
Baseline Characteristics

Baseline Characteristics	Dapagliflozin (n = 162)	Placebo (n = 162)	P-Value
Demographics			
Age (years)	69 (64, 77)	71 (63, 78)	0.44
Women	92 (57%)	92 (57%)	1.00
White	108 (67%)	109 (69%)	0.91
African American	50 (31%)	47 (30%)	
Medical History			
Duration of Heart Failure (years)	3.0 (1.1, 6.5)	3.2 (1.0, 6.6)	0.20
Prior Hospitalization for Heart Failure	98 (61%)	83 (51%)	0.09
Ejection Fraction (%)	60 (55, 65)	60 (54, 65)	0.89
Ischemic Heart Disease	32 (20%)	31 (19%)	0.89
Type 2 Diabetes	90 (56%)	91 (56%)	0.91
Atrial Fibrillation	82 (51%)	89 (55%)	0.44
ICD	7 (4%)	9 (6%)	0.61

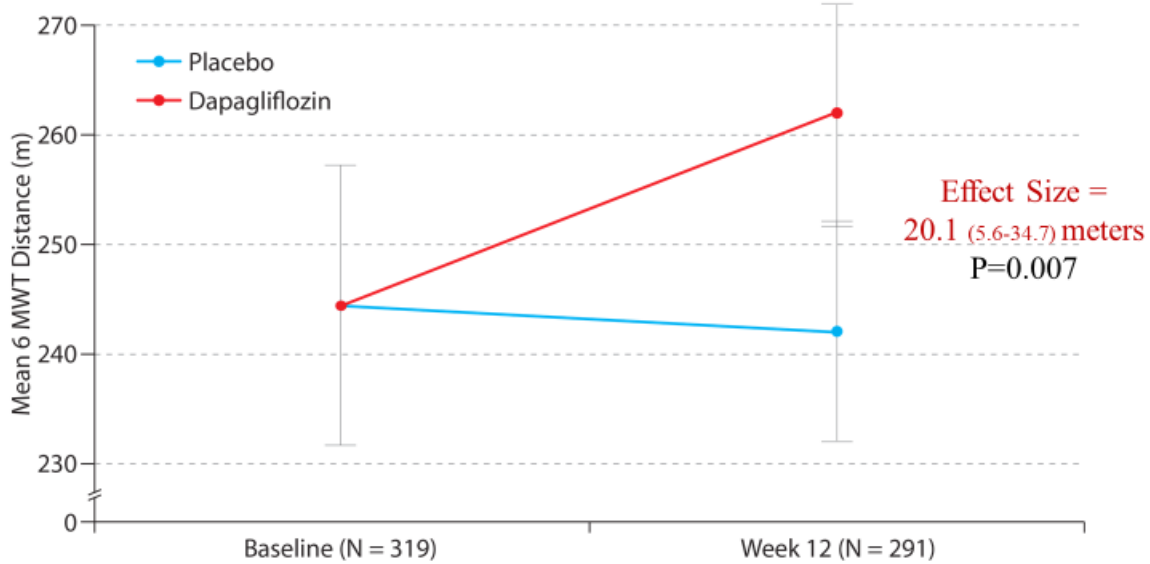
Baseline Characteristics

Baseline Characteristics	Dapagliflozin (n = 162)	Placebo (n = 162)	P-Value
Physical Exam			
Body Mass Index (median, IQR)	35 (30 – 42)	35 (30 – 40)	0.50
Heart Rate	70 (61, 77)	68 (62, 75)	0.28
Systolic Blood Pressure	134 (120, 152)	132 (118, 148)	0.14
Baseline Laboratory Studies			
NTproBNP (pg/mL)	641 (373, 1210)	710 (329, 1449)	0.83
eGFR (mL/min)	56 (42, 69)	54 (41, 68)	0.99
Hemoglobin A1c (%)	6.0 (5.6, 7.3)	6.2 (5.6, 7.1)	0.67
Functional Measures			
NYHA Class II	96 (59%)	90 (56%)	0.50
NYHA Class III-IV	65 (40%)	72 (44%)	
KCCQ-OS	63.2 ± 20.4	62.3 ± 20.6	0.68
KCCQ-CS	63.4 ± 19.7	61.8 ± 20.3	0.47
6-Minute Walk (m), Median (IQR)	244 (165, 329)	244 (154, 317)	0.65

KCCQ Clinical Summary Score



6 Minute Walk Test

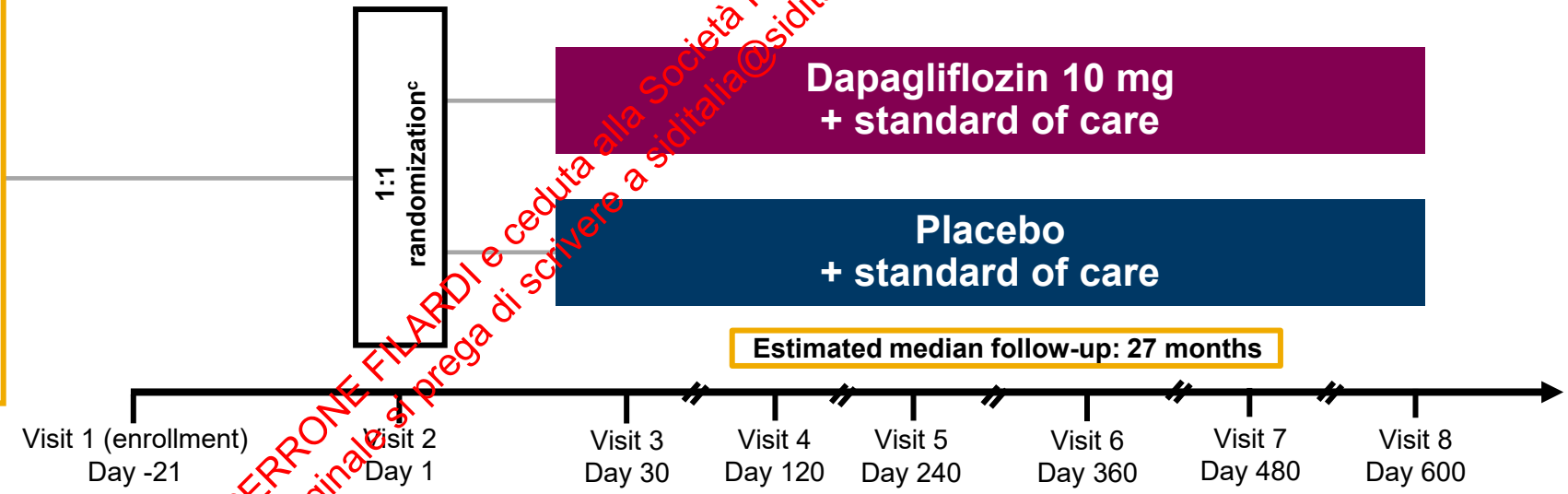


DELIVER

Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure[1]

6263 Patients

- ≥40 years of age with or without T2D
- LVEF >40% and evidence of structural heart disease[a] within 12 months
- Symptomatic NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- Elevated NT-proBNP levels
- eGFR[b] ≥25 mL/min/1.73 m^2
- Ambulatory or hospitalized off IV HF therapy for ≥24 hours



Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or HF events (hHF or urgent HF visit) assessed in dual primary analyses
  - Full patient population
  - Patients with LVEF <60%

Secondary Endpoints

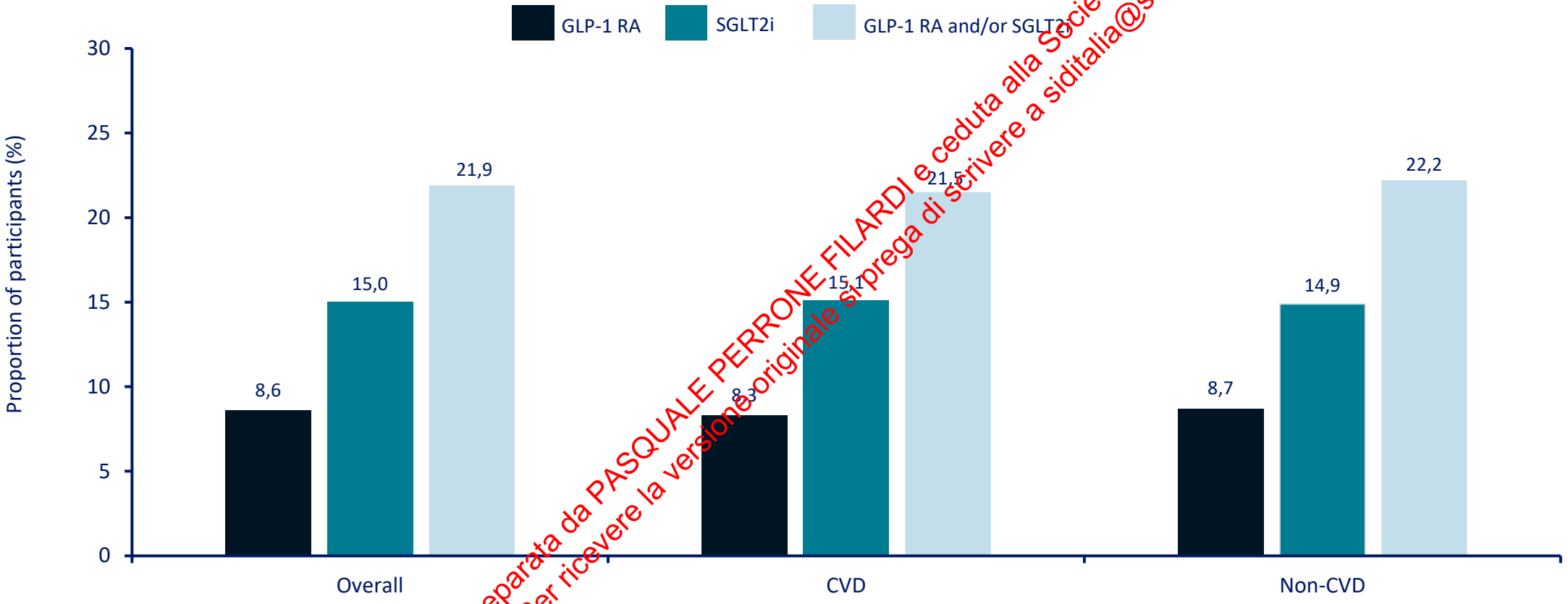
- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

Estimated Completion: January 2022[2]

[a]LV hypertrophy or LA enlargement; [b]Based on Chronic Kidney Disease-Epidemiology Collaboration Equation; [c]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment).

1. Solomon SD et al. *Eur J Heart Fail.* 2021;23:1217-1225; 2. Study NCT03619213. ClinicalTrials.gov website.

Use of GLAs with demonstrated CV benefit

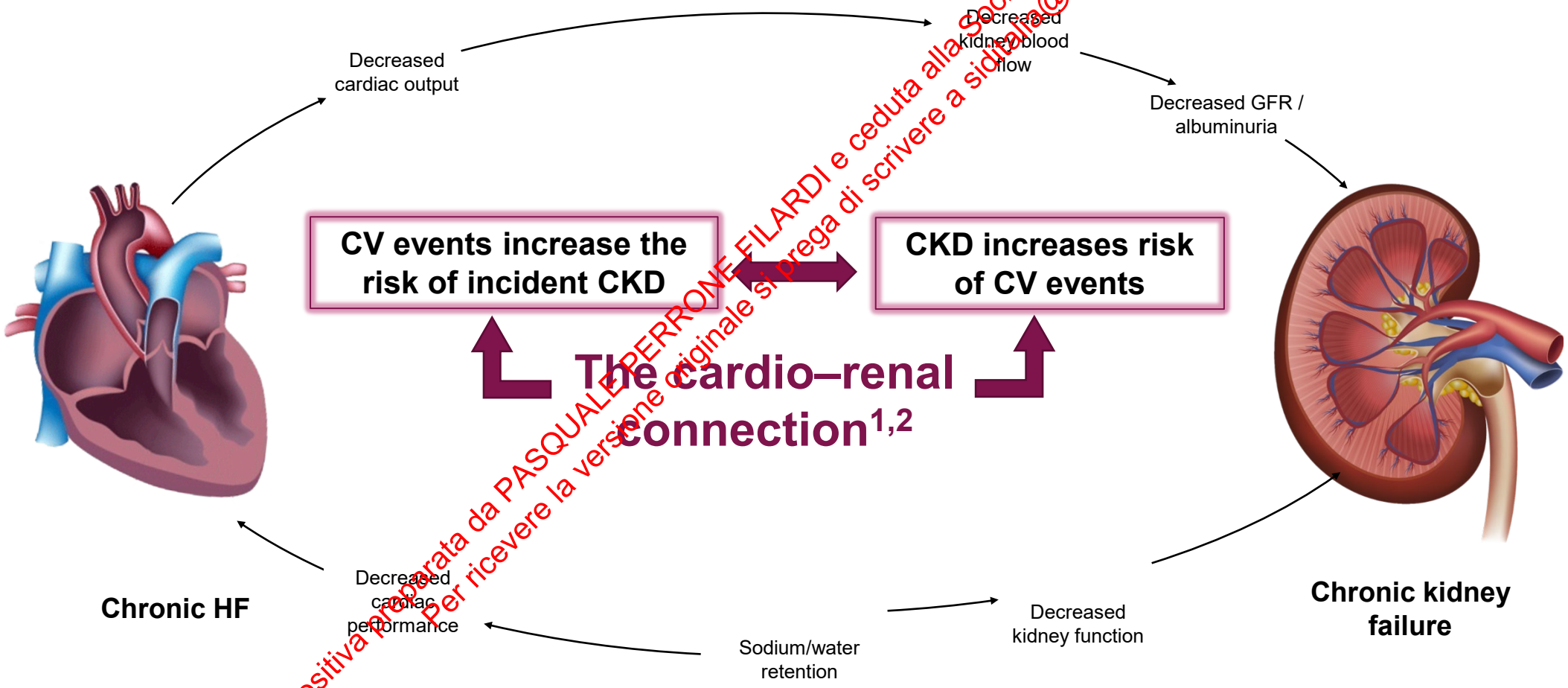


Adapted from Figure 3b
Data are % and were not weighted. Data are presented for the CAPTURE study sample overall and stratified by CVD status. GLAs with demonstrated CV benefit were defined per 2020 American Diabetes Association guidelines as GLP-1 RAs: dulaglutide, liraglutide and semaglutide; and SGLT2is: canagliflozin, dapagliflozin and empagliflozin
CV, cardiovascular; CVD, cardiovascular disease; GLAs, glucose-lowering agents; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i sodium-glucose co-transporter-2 inhibitor

Mosenzon et al. Cardiovasc Diabetol 2021;20:154.

HF and CKD – the Cardio-Renal Syndrome

There is a close and specific association between cardiac and kidney physiology



CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GFR = glomerular filtration rate; HF = heart failure.

1. Damman K et al. *J Am Coll Cardiol.* 2014;63:853–871; 2. Metra M et al. *Eur Heart J.* 2012;33:2135–2143.

NCT02993614

CVD-REAL

CVD-REAL 2[1]

OVERVIEW

CVD-REAL is a multinational, observational cohort study in patients with T2D evaluating the comparative effectiveness of initiating treatment with a SGLT2 inhibitor versus another glucose-lowering drug.

CVD-REAL 2 reports the comparison in terms of a broad range of CV outcomes.

PATIENTS

470,128

STATUS

Completed

PRIMARY ENDPOINT

- All-cause mortality

SECONDARY ENDPOINTS

- hHF
- Composite of all-cause mortality or hHF
- MI
- Stroke

STUDY DESIGN

Population

- Age ≥18 years
- New user receiving or dispensed prescription of SGLT2 inhibitor medication or other glucose-lowering drug, oral as well as injectable, including FDC products containing these medication groups
- T2D diagnosis
- >1 year data history in the database

CVD-REAL 2 includes Australia, Canada, Israel, Japan, Singapore, and South Korea

PATIENT FLOW CHART FOR ALL COUNTRIES/DATABASES COMBINED

FDC, fixed-dose combination; hHF, hospitalization for heart failure; MI, myocardial infarction; oGLD, other glucose-lowering drug; SGLT2, sodium–glucose co-transporter 2 (

1. Kosiborod M, et al. *J Am Coll Cardiol* 2018;71:2628–2639

NCT02993614

CVD-REAL

CVD-REAL 2[1]

STATUS

Completed

OVERVIEW

CVD-REAL is a multinational, observational cohort study in patients with T2D evaluating the comparative effectiveness of initiating treatment with a SGLT2 inhibitor versus another glucose-lowering drug. CVD-REAL 2 reports the comparison in terms of a broad range of CV outcomes.

PATIENTS

470,128

BASELINE CHARACTERISTICS

Characteristic	SGLT2 inhibitor (n=235,064)	Other GLD (n=235,064)	Standardized difference (%)
Age, years (SD)	56.7 (12.0)	56.7 (12.9)	0.4
Female sex	105,843 (45.0)	106,863 (45.5)	0.9
CV history	59,222 (26.8)	56,576 (25.6)	2.7
MI	7624 (3.4)	7479 (3.4)	0.4
Unstable angina	12,480 (5.6)	12,235 (5.5)	0.5
Heart failure	15,151 (6.8)	14,741 (6.7)	0.7
Atrial fibrillation	6026 (2.7)	5843 (2.6)	0.5
Stroke	20,983 (9.5)	20,153 (9.1)	1.3
Peripheral arterial disease	2446 (1.1)	2384 (1.1)	0.3
Microvascular disease	116,370 (52.6)	114,630 (51.8)	1.6
Chronic kidney disease	4211 (1.9)	4021 (1.8)	0.6
Frailty (yes)[a]	14,758 (6.7)	14,912 (6.7)	0.3
Baseline glucose-lowering therapies			
Metformin	173,783 (73.9)	175,266 (74.6)	1.7
Sulfonylurea	121,209 (51.6)	119,466 (50.8)	1.5
DPP-4 inhibitor	130,674 (55.6)	128,096 (54.5)	2.2
Thiazolidinediones	30,503 (13.0)	29,573 (12.6)	1.2
GLP-1 receptor agonist	6163 (2.6)	6022 (2.6)	0.4
Insulin	46,486 (19.8)	44,480 (18.9)	2.2

Characteristic	SGLT2 inhibitor (n=235,064)	Other GLD (n=235,064)	Standardized difference (%)
Cardiovascular therapies			
Antihypertensive therapy	147,166 (62.6)	145,014 (61.7)	1.9
Loop diuretics	16,451 (7.0)	16,100 (6.8)	0.6
Low-ceiling diuretics	17,608 (7.5)	17,173 (7.3)	0.7
ACE inhibitor	20,199 (8.6)	20,062 (8.5)	0.2
ARBs	109,620 (46.6)	109,347 (46.5)	0.2
Statin therapy	153,694 (65.4)	153,466 (65.3)	0.2
Beta blockers	44,786 (19.1)	43,947 (18.7)	0.9
Aldosterone antagonists	6719 (2.9)	6548 (2.8)	0.4
Index year			
2013	741 (1.5)	660 (1.3)	1.4
2014	31,639 (14.0)	32,009 (14.2)	0.5
2015	71,405 (32.3)	71,485 (32.3)	0.1
2016	116,940 (52.8)	115,997 (52.4)	0.9
2017	14,339 (27.0)	14,913 (28.1)	2.4

Data are n (%) unless otherwise indicated

[a]Frailty, hospitalized for >3 consecutive days in the last year

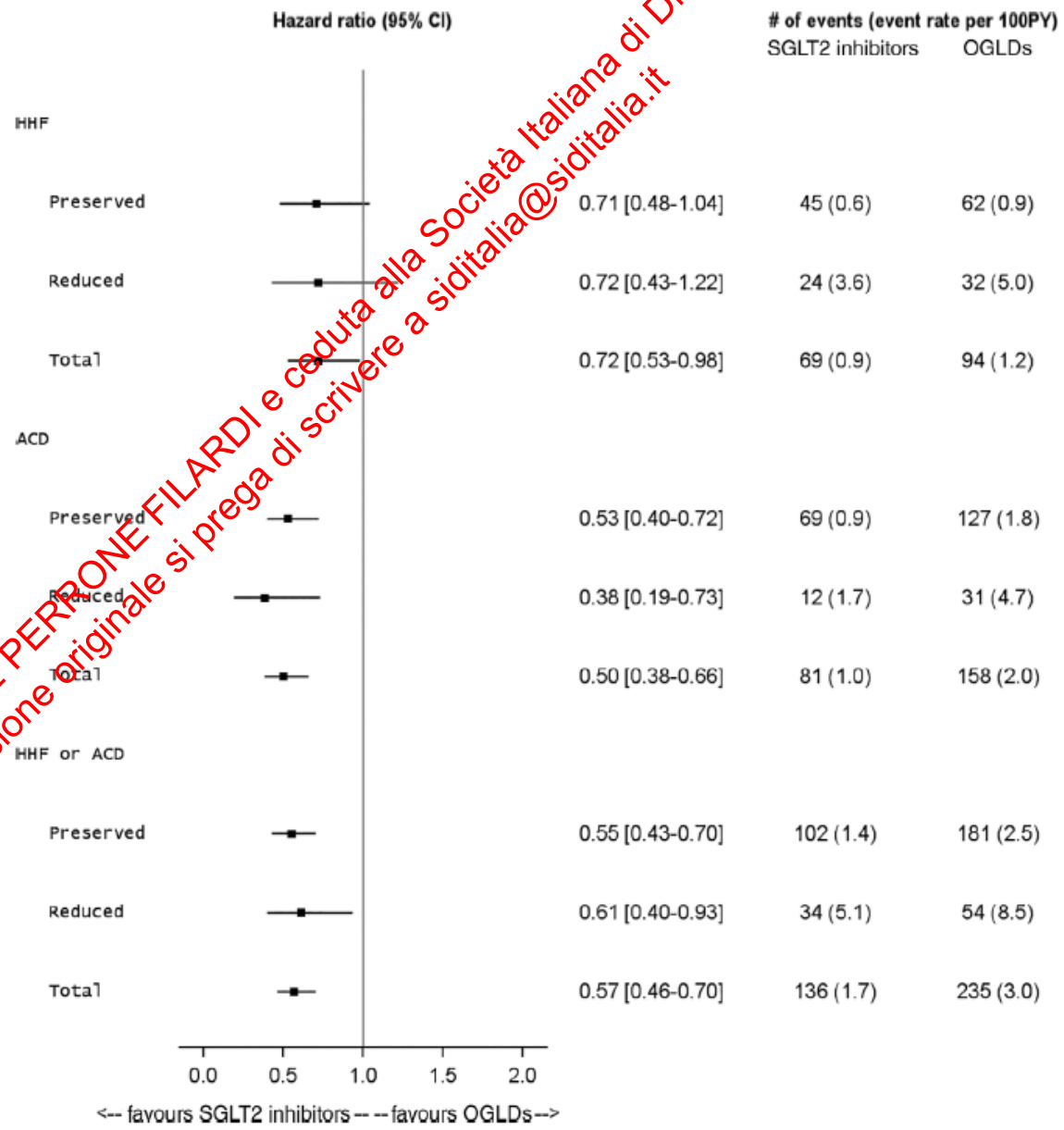
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLD, glucose-lowering drug; GLP-1, glucagon-like peptide-1; HF, heart failure; MI, myocardial infarction; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

1. Kosiborod M, et al. *J Am Coll Cardiol* 2018;71:2628–2639

BRIEF REPORT

WILEY

Association of sodium-glucose cotransporter-2 inhibitors with outcomes in type 2 diabetes with reduced and preserved left ventricular ejection fraction: Analysis from the CVD-REAL 2 study



DOI: 10.1111/dom.14356

Baseline Medical History by Baseline CVD History in DAPA-CKD patients

	Baseline cardiovascular disease, n (%) (n= 1610, 38%))		No baseline cardiovascular disease, n (%) (n=2694)	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
	n = 813	n = 797	n = 1339	n = 1355
Any atherosclerotic cardiovascular disease	663 (81.5)	666 (83.6)	-	-
Hypertension	803 (98.8)	788 (98.9)	1262 (94.2)	1268 (93.6)
Heart failure	235 (28.9)	233 (29.2)	-	-
Atrial fibrillation or flutter	115 (14.1)	112 (14.1)	-	-
Angina	201 (24.7)	204 (25.6)	-	-
Myocardial infarction	185 (22.8)	207 (26.0)	-	-
Coronary artery bypass grafting	74 (9.1)	102 (12.8)	-	-
Percutaneous coronary intervention	145 (17.8)	149 (18.7)	-	-
Stroke	144 (17.7)	154 (19.3)	-	-
Transient ischemic attack	41 (5.0)	38 (4.8)	-	-
Peripheral artery disease	154 (18.9)	171 (21.5)	-	-
Amputation	59 (7.3)	50 (6.3)	36 (2.7)	36 (2.7)
Type 2 diabetes	640 (78.7)	641 (80.4)	815 (60.9)	810 (59.8)

CVD = cardiovascular disease.

McMurray JJV et al. *Circulation*. 2021;143:438–448.

Dapagliflozin Addresses the Cardiorenal Burden Across the Spectrum of Patients With and Without T2D[1-4]

	DAPA-HF	DECLARE-TIMI 58	DAPA-CKD
Patient Population	**N = 4744** **HFrEF** **eGFR ≥30 mL/min/1.73 m²**	**N = 17,160** **ASCVD or Multiple CV Risk Factors** **eGFR ≥60 mL/min/1.73 m²**	**N = 4304** **CKD** **eGFR ≥25 to ≤75 mL/min/1.73 m²**
Glycemic Status	**With (45%) or Without (55%) T2D**	**With T2D**	**With (68%) or Without (32%) T2D**
Mean eGFR	**66 mL/min/1.73 m²**	**85.2 mL/min/1.73 m²**	**43 mL/min/1.73 m²**
Primary Endpoint	**CV death or worsening HF[a]** 0.74 (0.65, 0.85) p<0.001	**hHF or CV death** 0.83 (0.73, 0.95) p=0.005	**≥50% eGFR Decline, ESKD, or Renal or CV Death** 0.61 (0.51-0.72) p=0.000000028
Summary	**Confirming dapagliflozin as the new standard of care for patients with HFrEF with and without T2D[5]**	**Largest, broadest SGLT2 inhibitor CVOT in patients with T2D**	**FIRST and ONLY SGLT2 inhibitor renal outcomes trial in patients with CKD with and without T2D**

[a]Worsening HF includes hHF or urgent HF visit.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVOT = cardiovascular outcomes trial; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

1. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008; 2. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357; 3. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020; 4. Heerspink HJL et al. Online ahead of print. *N Engl J Med*. 2020; 5. Vaduganathan M et al. *Lancet*. 2020;396:121-128.

The new era of nephroprotection: SGLT2-I

2015

EMPA-REG OUTCOME®

Secondary renal endpoint:
- incident or worsening nephropathy

2017

CANVAS Program

Secondary renal endpoints:
- Progression of albuminuria
- ≥40% decrease eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal causes

2018

CREDENCE

Primary composite renal outcome in DKD:
- ESKD, doubling of serum creatinine, or death from renal causes

Secondary composite renal endpoint
- Decrease of ≥40% eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal causes

DECLARE TIMI-58

2019

Secondary composite renal outcome:
- ≥50% sustained decline in eGFR, ESRD or renal death
- **DM and non-DM HF**

DAPAHF

2020

EMPEROR-Reduced

Secondary renal outcome:
- Mean slope of change in eGFR
- **DM and non-DM HF**

Primary composite renal outcome:
- ≥50% sustained decline in eGFR, ESRD or renal death
- **DM and non-DM CKD**

DAPACKD

2021

VERTIS CV

Pre-specified exploratory renal outcome:
- Sustained 40% reduction from baseline in eGFR, dialysis or transplant, renal death

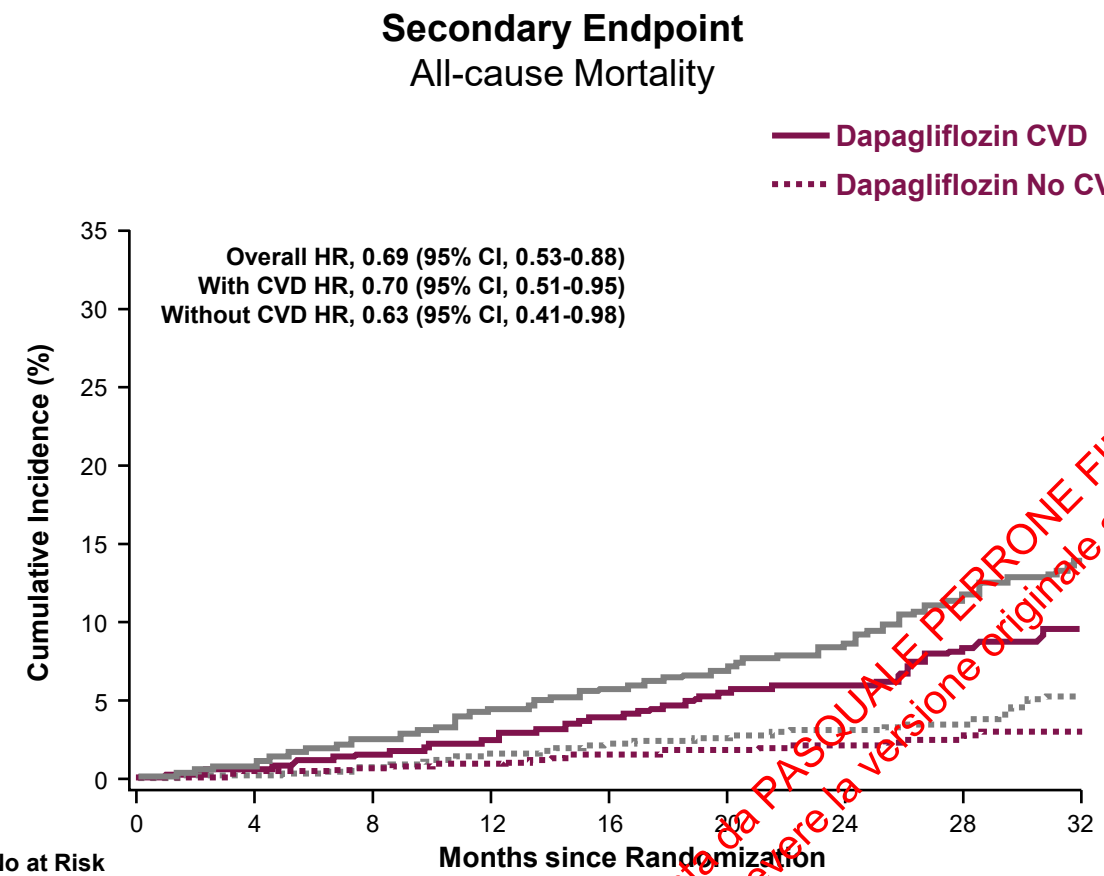
Secondary renal outcome:
- rate of decline in the eGFR during doubleblind
- treatment

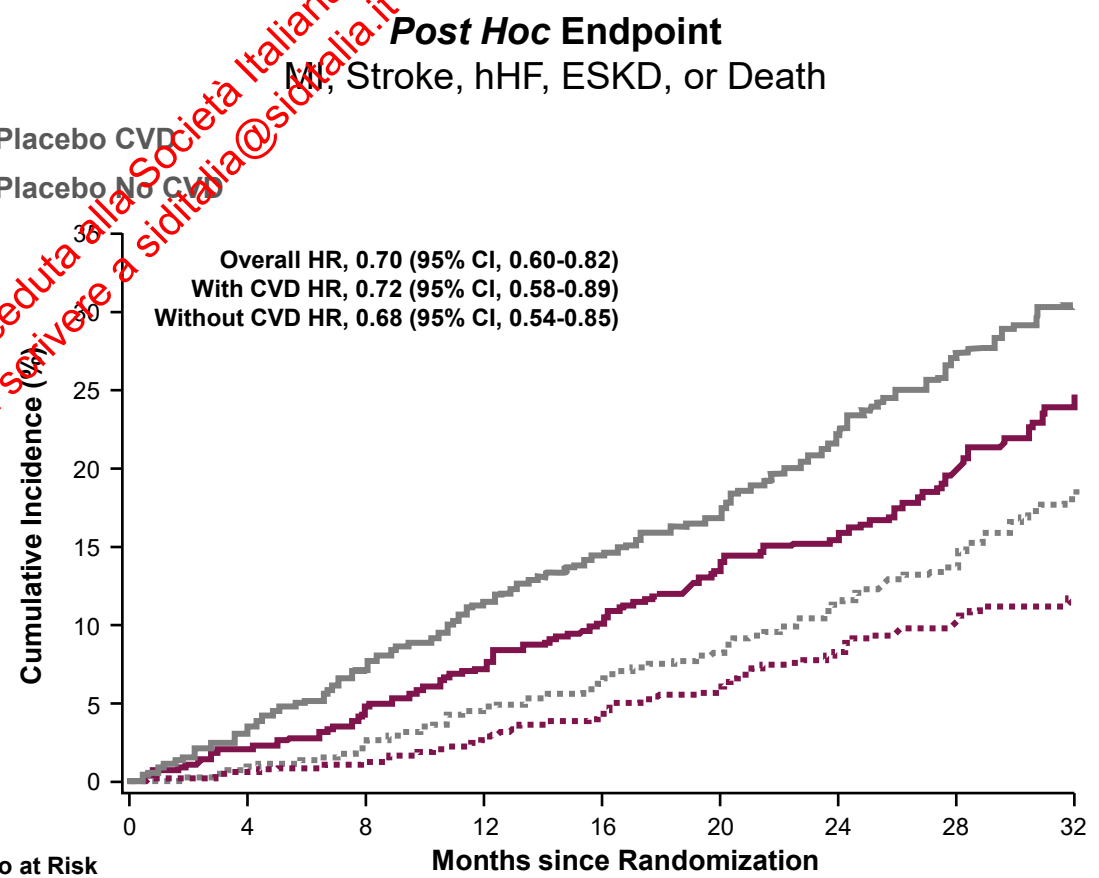
EMPEROR-Preserved Trial

Dapa RCTs investigate most of CVRM population

2018	2019	2020
Secondary composite renal endpoint • Decrease of ≥40% eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal causes	**Secondary composite renal outcome:** • ≥50% sustained decline in eGFR, ESRD or renal death • DM and non-DM HF	**Primary composite renal outcome:** • ≥50% sustained decline in eGFR, ESRD or renal death • DM and non-DM CKD
DECLARE TIMI-58	DAPAHF	DAPACKD
17,160 patients T2D (6.5% ≤ HbA1c <12%), ≥55 yrs (men) or ≥60 yrs (women) with ≥1 CV risk factor OR ≥40 yrs with ECVD (ACEi or ARB 81%)	**4,744 patients** with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less (ACEi or ARB 83%)	**4,304 patients** DM and non-DM CKD, eGFR 25-75, UACR 200–5000, under stable maximum tolerated dose of ACEi or ARB for ≥4 weeks

Outcomes by Baseline CVD



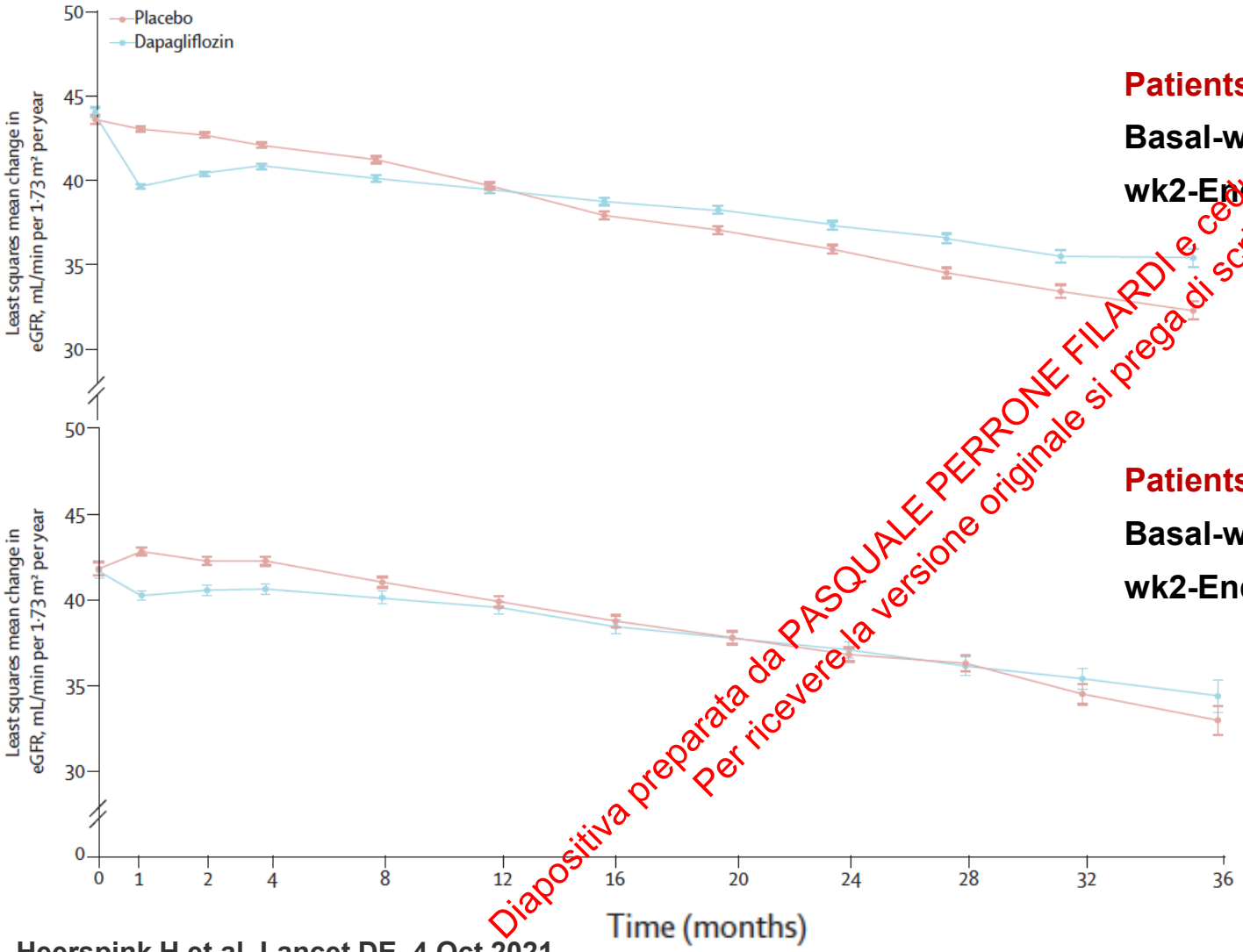


CV = cardiovascular; CVD = cardiovascular disease; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction.

81 McMurray JJV et al. *Circulation*. 2021;143:438–448.

Mechanism(s) of SGLT2-I Nephroprotection

Initial eGFR drop associates with better eGFR preservation in the long term



Patients with DM2

Basal-wk2 eGFR decline vs placebo: **2·61** mL/min

wk2-End Difference in chronic eGFR slope vs placebo: **2·26** mL/min

Patients without DM2

Basal-wk2 eGFR decline vs placebo: **2·01** mL/min

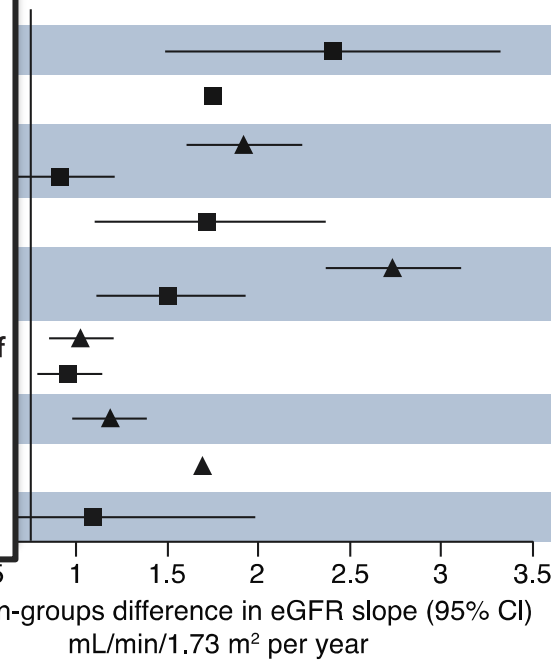
wk2-End Difference in chronic eGFR slope vs placebo: **1·29** mL/min

Heerspink H et al. Lancet DE, 4 Oct 2021

Initial eGFR drop associates with better eGFR preservation in the long term

Randomized clinical trial	SGLT2 inhibitor	Mean baseline eGFR	Mean absolute eGFR dip in the SGLT2 inhibitor group	Time from baseline to eGFR dip	Maximum follow-up duration
EMPEROR-Reduced (no CKD[a])	Empagliflozin				
DAPA-HF[b]	Dapagliflozin				
DAPA-CKD	Dapagliflozin				
EMPEROR-Reduced (total)	Empagliflozin				
CREDENCE	Canagliflozin				
VERTIS CV	Ertugliflozin				
CANVAS and CANVAS-R	Canagliflozin				
EMPA-REG OUTCOME[b]	Empagliflozin				
EMPEROR-Reduced (CKD[a])	Empagliflozin				

■ Slope calculated from baseline eGFR
▲ Slope calculated from the eGFR dip



Acute fall in glomerular filtration rate with renin–angiotensin system inhibition: a biomeasure of therapeutic success?

Matthew R. Weir[1]

Glomerular filtration rate (GFR) acutely declines with the introduction of renin–angiotensin system inhibition. This response is functional, not anatomical, and varies with volume status. The reduction in GFR with renin–angiotensin system inhibition may serve as a biomeasure of future therapeutic benefit.

Kidney International (2011) **80,** 235–237. doi:10.1038/ki.2011.132

Parker Gregg et al. cJASN 2021

Cardiovascular Studies with Dapagliflozin in HFrEF, HFpEF and Acute MI

DAPACARE

	HFrEF[1]	HFrEF[2]	HFpEF[3]	HFpEF[4]	Acute HF[5]	Acute MI[6]
	DAPAHF	DETERMINE REDUCED	DELIVER	DETERMINE PRESERVED	DAPA ACT HF - TIMI 68	DAPAMI
Enrollment	**N=4744**	**N=313**	**N~6100**	**N=504**	**N~2400**	**N~6400**
Primary endpoints	**Composite of CV death, hHF, or urgent HF visit**	**KCCQ-TSS KCCQ-PLS 6MWD**	**Composite of CV death, hHF, or urgent HF visit**	**KCCQ-TSS KCCQ-PLS 6MWD**	**Composite of CV death or worsening HF**	**Composite of CV death or hHF**
Glycemic status	With or Without T2D	With or Without T2D	With or Without T2D	With or Without T2D	With or Without T2D	Without Diabetes
Estimated completion	Completed	2020	2021	2020	2022	2023

Data from clinicaltrials.gov website obtained July 24, 2020.

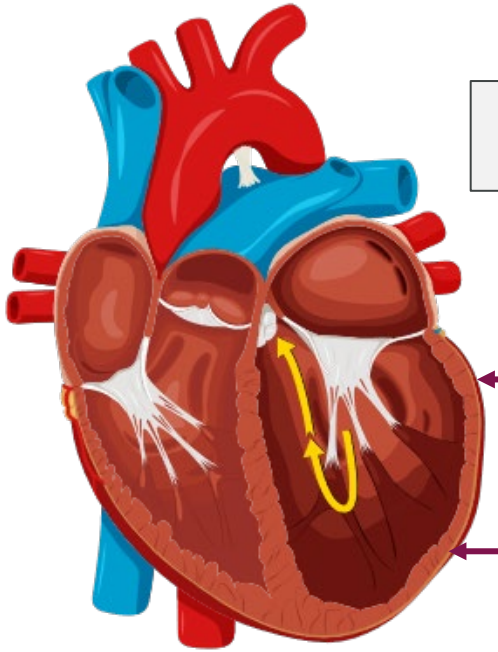
6-MWD = 6-minute walking distance; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; KCCQ-PLS = Kansas City Cardiomyopathy Questionnaire Physical Limitation Score; KCCQ –TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MI = myocardial infarction; T2D = type 2 diabetes.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Study NCT03877237. ClinicalTrials.gov website; 3. Study NCT03619213. ClinicalTrials.gov website; 4. Study NCT03877224. ClinicalTrials.gov website; 5. Study NCT04363697. ClinicalTrials.gov website; 6. Study NCT04564742. ClinicalTrials.gov website.

Differences in HF Pathophysiology[1-3]

HFrEF

LV contraction is reduced resulting in inadequate cardiac output.



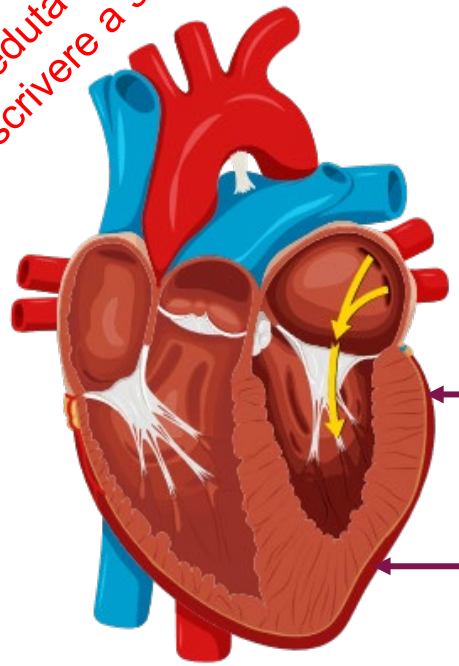
~2/3 of cases are due to CAD

- **LVEF ≤40%**
- **LV dilation**

- **Abnormal contractility**
- **LV remodeling**

HFpEF

LV filling is reduced so that, even though LVEF is normal, cardiac output is reduced.



Substantial pathophysiologic heterogeneity

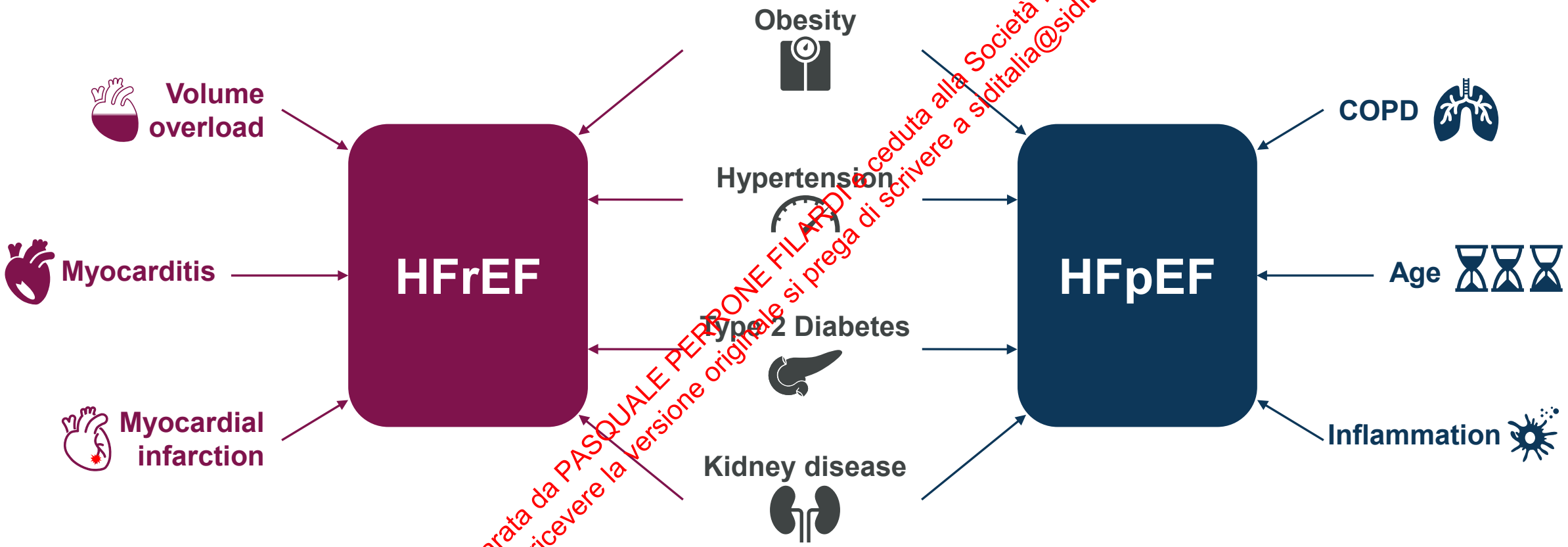
- **Normal LVEF (≥50%)**
- **No LV dilation**

- **Stiff, thickened walls**
- **Normal contractility**
- **Concentric LV hypertrophy**

CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction.

1. Bloom MW et al. *Nat Rev Dis Primers*. 2017;3:17058; 2. Borlaug BA. *Nat Rev Cardiol*. 2014;11:507-515; 3. Redfield MM. *N Engl J Med*. 2016;375:1868-1877.

HFrEF and HFpEF Share Many Comorbidities and Risk Factors, While Others Differ



COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

 Simmonds SJ et al. *Cells*. 2020;9:242.

HFpEF Is a Systemic Syndrome

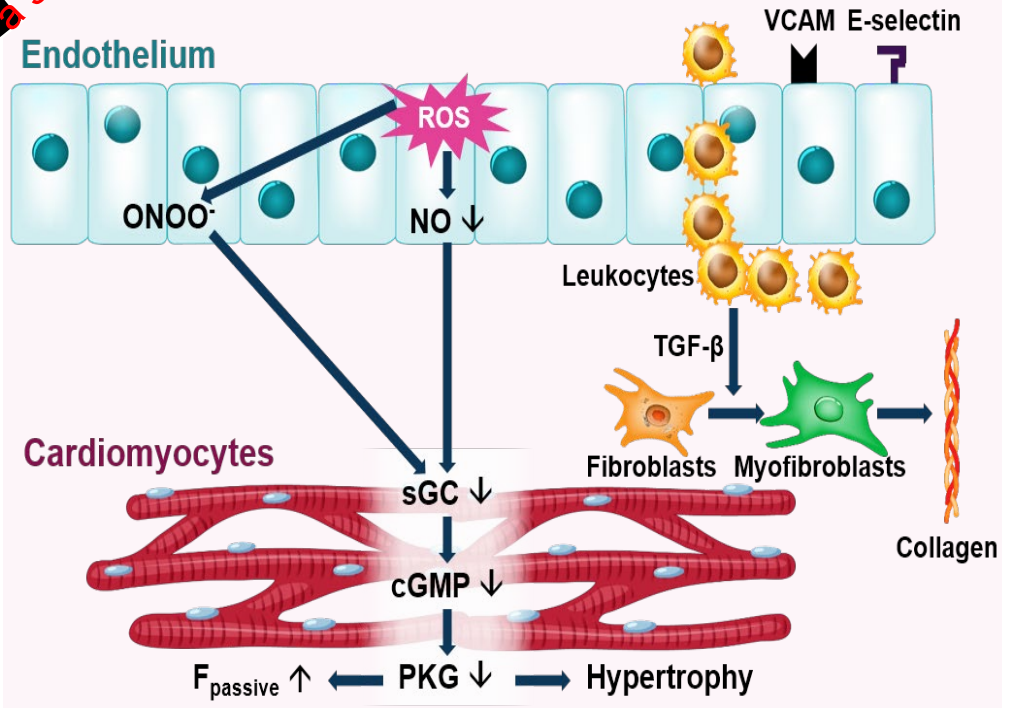
Comorbidities induce systemic inflammation

- Obesity
- Hypertension
- Type 2 Diabetes
- Renal Insufficiency

Multi-organ involvement leads to diverse HFpEF phenotypes

- Myocardial remodeling
- Pulmonary hypertension
- Renal sodium retention
- Deficient skeletal muscle O_2 extraction during exercise

Endothelium-Cardiomyocyte Signaling

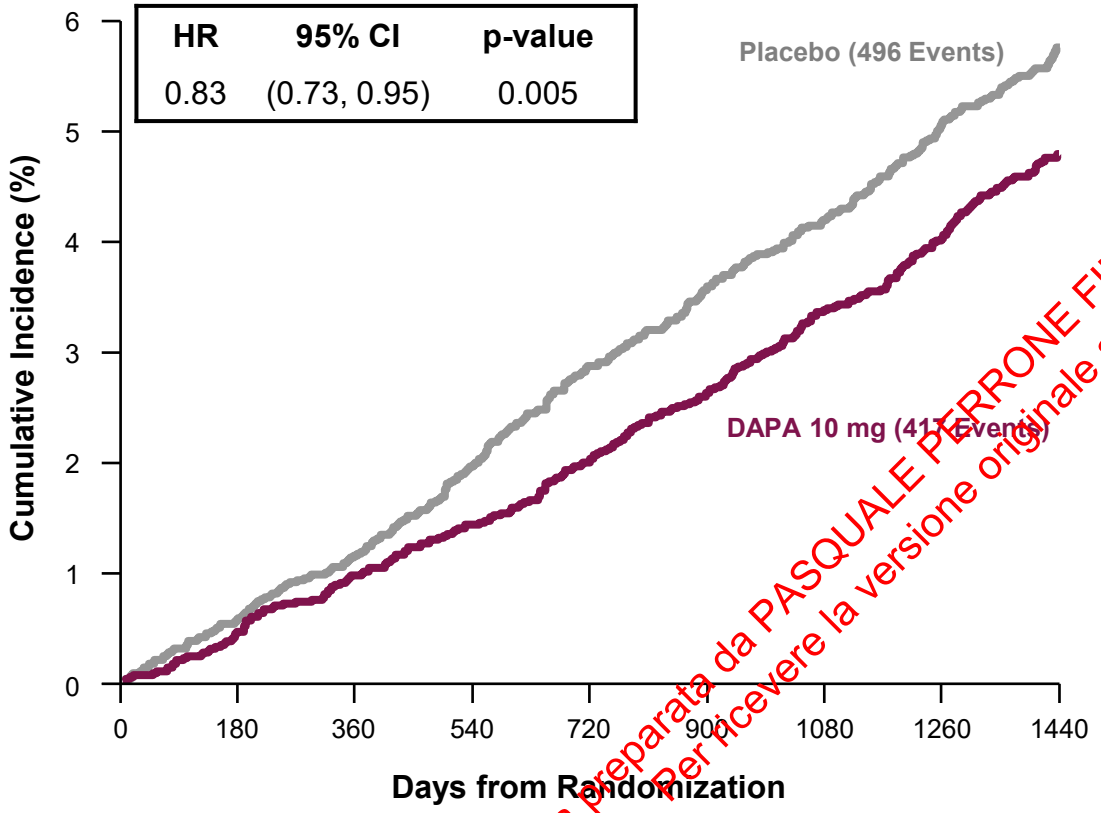


cGMP = cyclic guanosine monophosphate; $F_{passive}$ = passive force; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; NO = nitric oxide; O_2 = oxygen; $ONOO^-$ = peroxynitrite; PKG = protein kinase G; ROS = reactive oxygen species; sGC = soluble guanylate cyclase; TGF-β = transforming growth factor β; VCAM = vascular cell adhesion molecule.

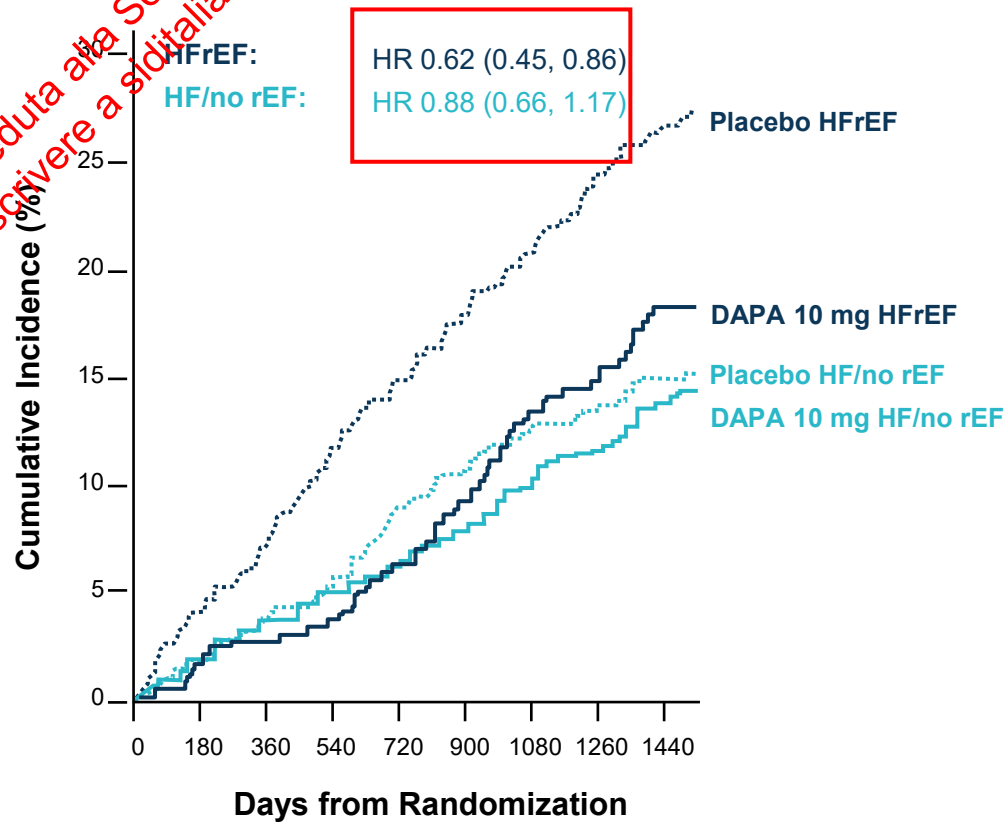
 Adapted from Shah SJ et al. *Circulation*. 2016;134:73-90.

In DECLARE, Dapagliflozin Significantly Reduced hHF/CV Death in T2D Patients With Broad CV Risk and in the Subgroup of Patients With HFrEF

Primary endpoint- hHF/CV death[1,a]



Subgroup analysis- hHF/CV death by history of HFrEF[2]



[a]2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; HR = hazard ratio; rEF = reduced ejection fraction; T2D = type 2 diabetes.

1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. Kato ET et al. *Circulation.* 2019;139:2528-2536.

“In the DECLARE-TIMI 58 trial, baseline heart failure (HF) status was collected from all patients, and EF was collected when available. HF with reduced EF (HFrEF) was defined as EF <45%”

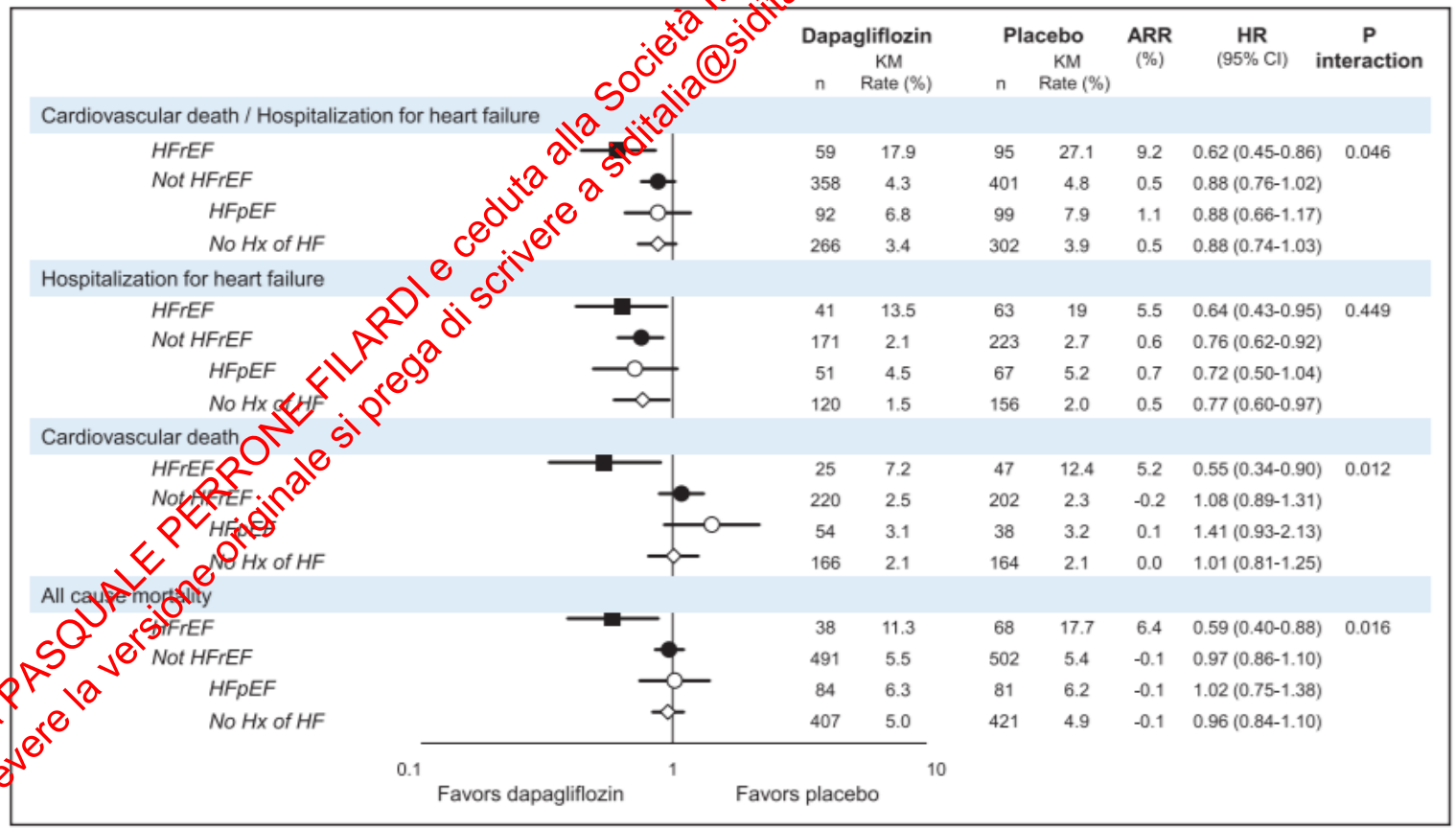
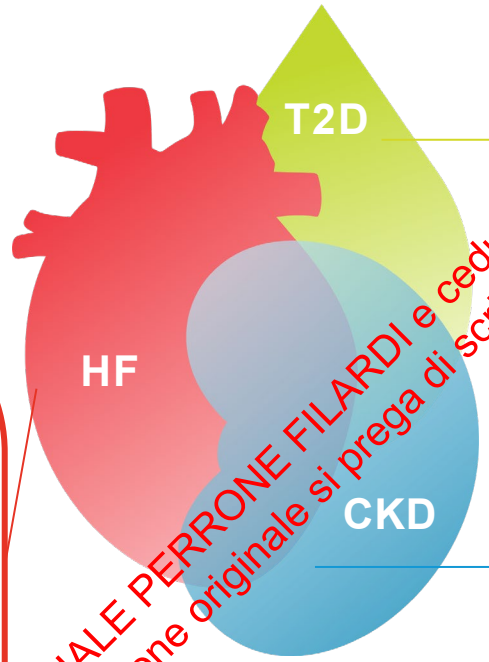


Figure 1. Cardiovascular outcomes by heart failure (HF) category.
There were 671 patients with HF with reduced ejection fraction (HFrEF) defined as left ventricular ejection fraction (EF) <45% (318 in the dapagliflozin group and 353 in the placebo group) and 16489 patients without HFrEF (8264 in the dapagliflozin group and 8225 in the placebo group). There were 1316 patients with HF without known reduced EF defined as a history (hx) of HF without left ventricular EF <45% (662 in the dapagliflozin group and 654 in the placebo group). There were 15173 patients without a history of HF and without left ventricular EF <45% (7602 in the dapagliflozin group and 7571 in the placebo group). *P* for interaction refers to an interaction between HFrEF and not HFrEF. Open circles and open diamonds are subsets of closed circles. ARR indicates absolute risk reduction; HR, hazard ratio; and KM, Kaplan–Meier.

Circulation. 2019;139:2528–2536. DOI: 10.1161/CIRCULATIONAHA.119.040130

Dapagliflozin offers patients protection from serious cardio and renal outcomes associated with these three interrelated diseases[1]



DAPA-HF

- *4744 pazienti con HFrEF con o senza T2D*
- 26% ↓ morte CV/peggioramento HF
- 30% ↓ hHF
- 25% ↓ morte CV/hHF
- 17% ↓ morte da tutte le cause

DECLARE

- *17160 pazienti con T2D e ASCVD o MRF*
- 17% ↓ morte CV/hHF
- 27% ↓ hHF
- 47% ↓ declino sostenuto ≥40% di eGFR, ESKD, morte renale

DAPA-CKD

- *4304 pazienti con CKD con o senza T2D*
- 39% ↓ declino sostenuto ≥50% di eGFR, ESKD, morte renale/morte CV
- 44% ↓ declino sostenuto ≥50% di eGFR, ESKD, morte renale
- 29% ↓ morte CV/hHF
- 31% ↓ morte da tutte le cause

Indicated for symptomatic HFrEF or CKD in adults, with and without T2D[1]

CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; T2D, Type 2 diabetes

1. AstraZeneca AB. Dapagliflozin EU Summary of Product Characteristics 2021. Available at: https://ec.europa.eu/health/documents/community-register/2021/20210805152483/anx_152483_en.pdf (Accessed August 2021); 2. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446

Dapagliflozin nel continuum CARDIO-RENALE-METABOLICO

DAPACARE

T2D[1]	HFrEF[2]	CKD[3]
DECLARE TIMI-58	DAPA HF	DAPACKD
Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes	**Dapagliflozin in Patients with HF and Reduced Ejection Fraction**	**Dapagliflozin in Patients with Chronic Kidney Disease**
Hospitalization for HF ↓ 27% RRR HR 0.73 (0.61-0.88)	**Hospitalization for HF** ↓ 30% RRR HR 0.70 (0.59-0.83)	
Hospitalization for HF or CV death ↓ 17% RRR HR 0.83 (0.73-0.95)	**CV death** ↓ 18% RRR HR 0.82 (0.69-0.98)	**Hospitalization for HF or CV death** ↓ 29% RRR HR 0.71 (0.55–0.92)
Composite of ≥40% decrease in eGFR to <60 mL/min/1.73 m², ESRD, or renal death ↓ 47% RRR HR 53 (0.43-0.66)	**Composite of ≥50% sustained decrease in eGFR, ESRD, or renal death** ↓ 29% RRR HR 0.71 (0.44-1.16)	**Composite of ≥50% sustained decrease in eGFR, ESRD, or renal death** ↓ 44% RRR HR 0.56 (0.45-0.68)
All Cause Mortality ↓ 7% RRR HR 0.93 (0.82-1.04)	**All Cause Mortality** ↓ 17% RRR HR 0.83 (0.71-0.97)	**All Cause Mortality** ↓ 31% RRR HR 0.69 (0.53–0.88)

CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal dsease

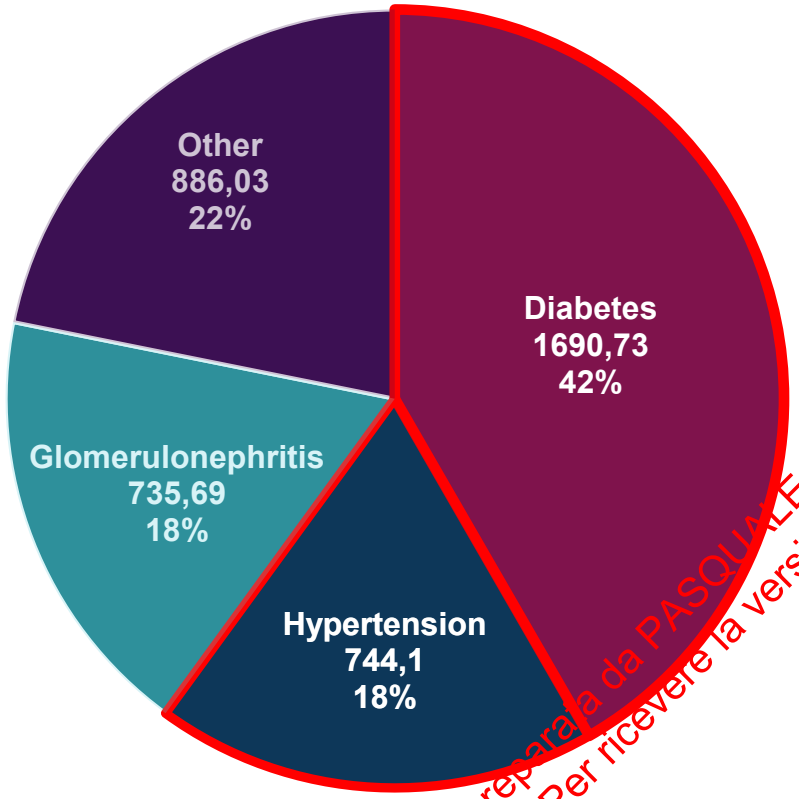
1. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357; 2. McMurray JJV et al. N Engl J Med. 2019;381(21):1995-2008; 3. Heerspink HJL et al. N Engl J Med. 2020;383(15):1436-1446

DAPACARE

- **Unici nel continuum cardiorenale.** SGLT2 classe che più di ogni altra agisce sulle due principali comorbidità del diabete, HF e CKD.
- **Tripla indicazione.** Differenziazione intraclasse di Dapagliflozin, il suo notevole vantaggio in termini di possibili indicazioni prescrittive.
- **Previene il rischio di ospedalizzazione e morte (CV e per tutte le cause) e migliora la qualità di vita dei pazienti con HFrEF.** Dapagliflozin migliora alcuni tra i più importanti outcome del trattamento dello scompenso
- **L'esigenza di diagnosi e gestione precoce della CKD.** L'elevata mortalità che si associa ad una patologia silente, sulla quale Dapagliflozin è l'unico ad avere indicazione.
- **Nessuna necessità di modifica della posologia in base a condizioni del paziente.** La semplicità di utilizzo di Dapagliflozin, che è l'unico ad avere un filtrato di partenza di 25 ml/min anche nel paziente con T2D.

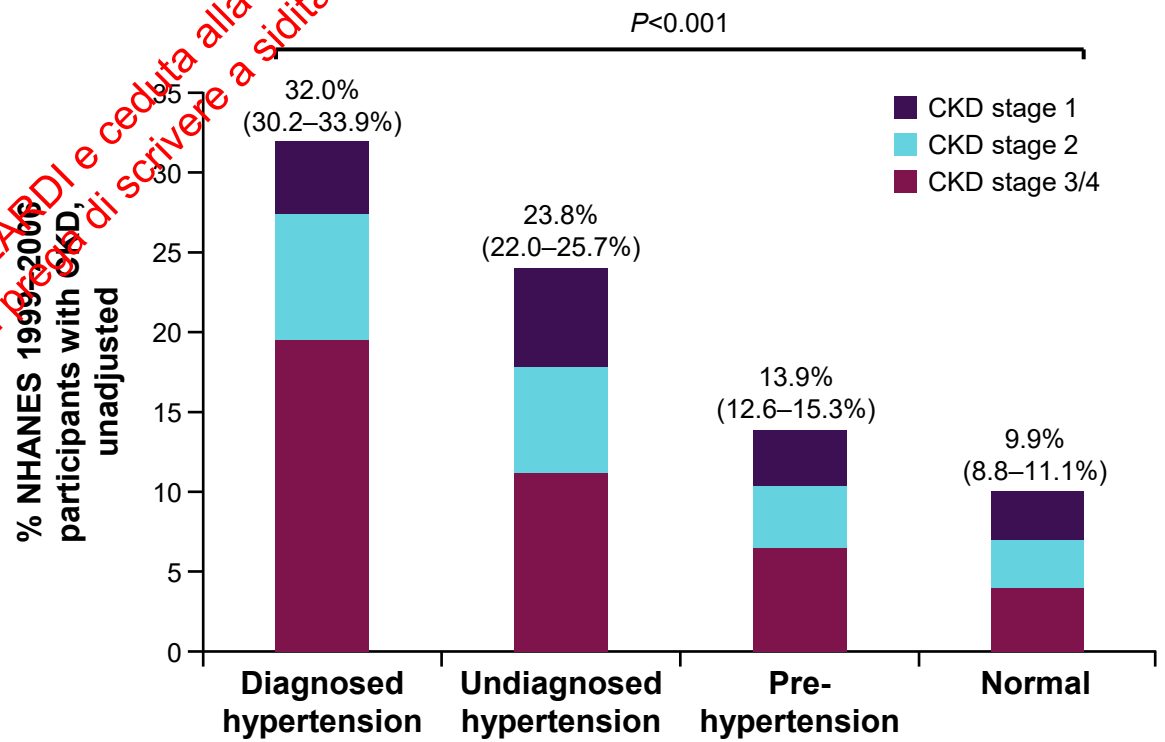
Diabetes and hypertension are the most significant causes of CKD and CKD prevalence increases with diabetes duration and hypertension status

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016[1]



Diabetes and hypertension cause approximately 60% of CKD cases

Prevalence of CKD according to hypertension status[2]



CKD = chronic kidney disease; NHANES = National Health and Nutrition Examination Survey.

1. Xie Y et al. *Kidney Int.* 2018;94:567-581; 2. Crews DC et al. *Hypertension.* 2010;55:1102-1109.