Lo scompenso cardiaco nel paziente con diabete: quale ruolo nocivo per l'iperglicemia?

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Il /la dr./sa Alessandra Dei Cas dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

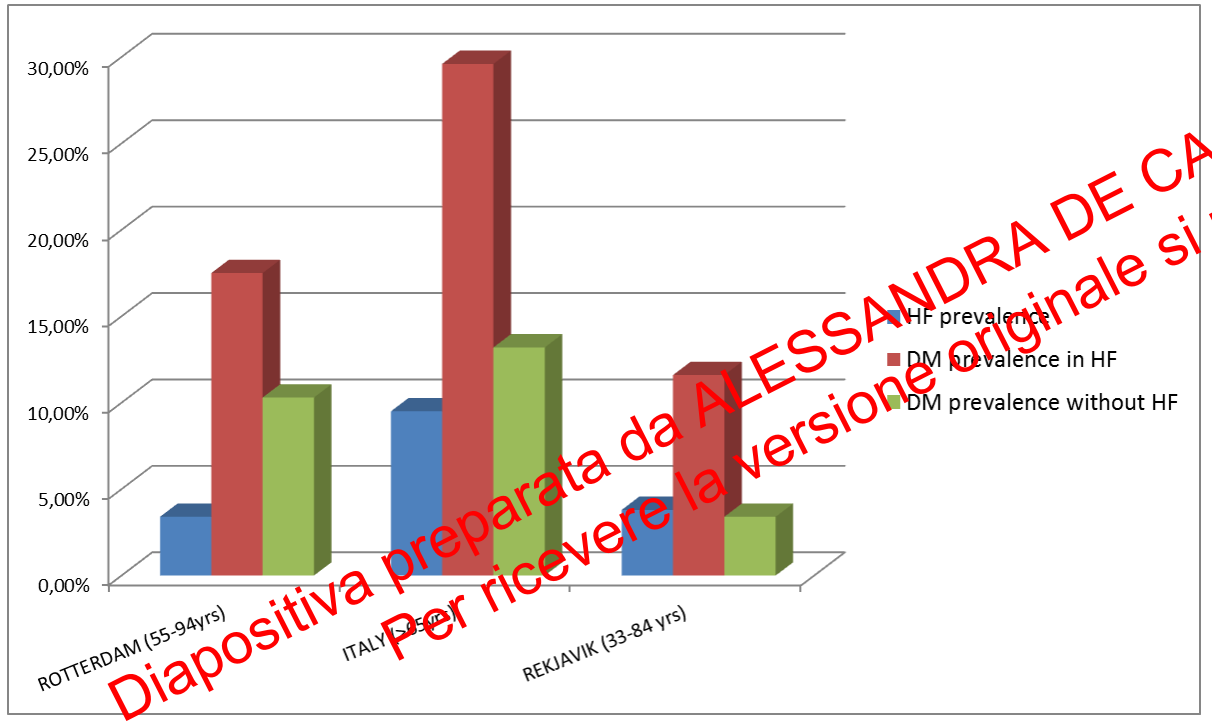
- ✓ MSD
- ✓ Eli Lilly
- ✓ Boehringher
- ✓ Doc generici
- ✓ Servier
- ✓ Bruno farmaceutici

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

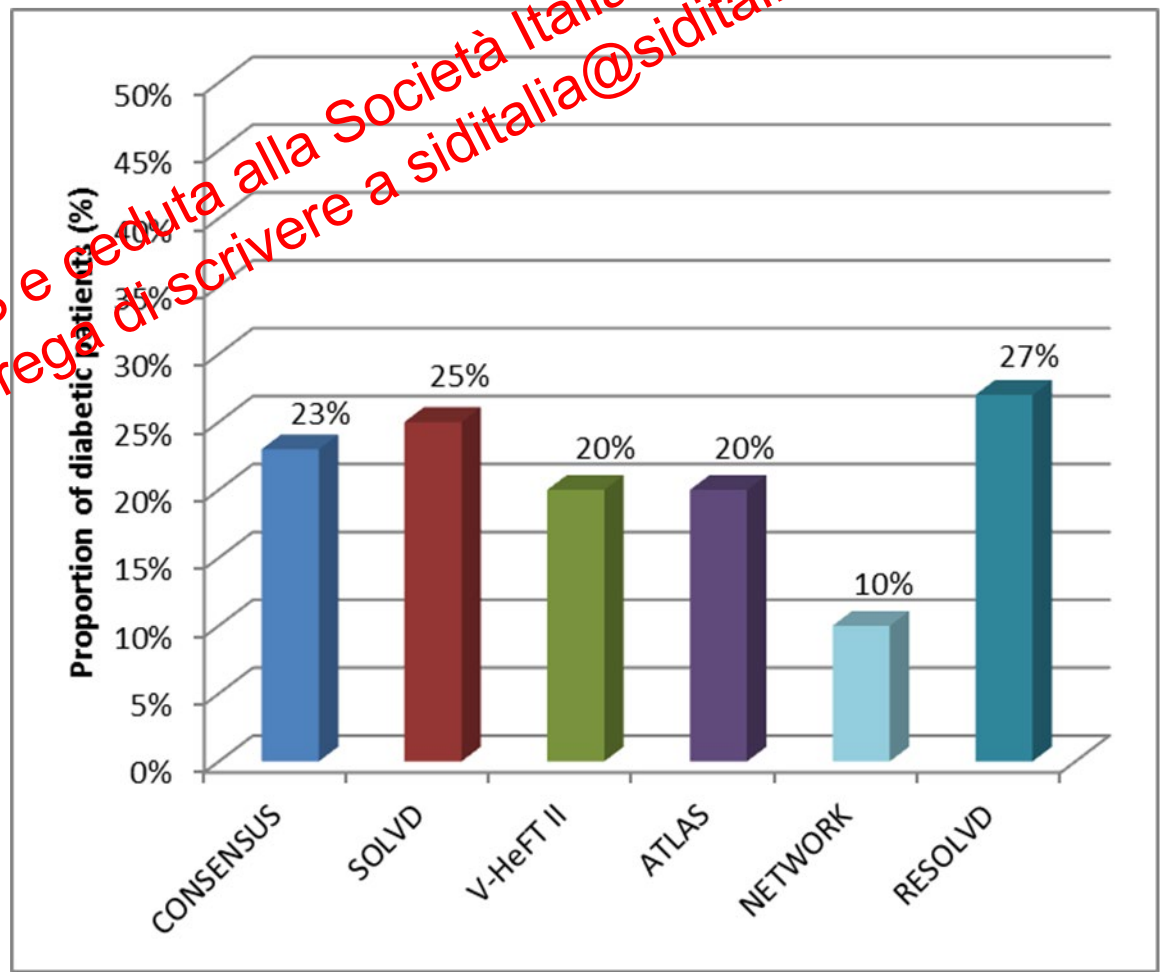
Heart Failure and Diabetes

- Epidemiology
- Pathophysiology
- Response to treatments

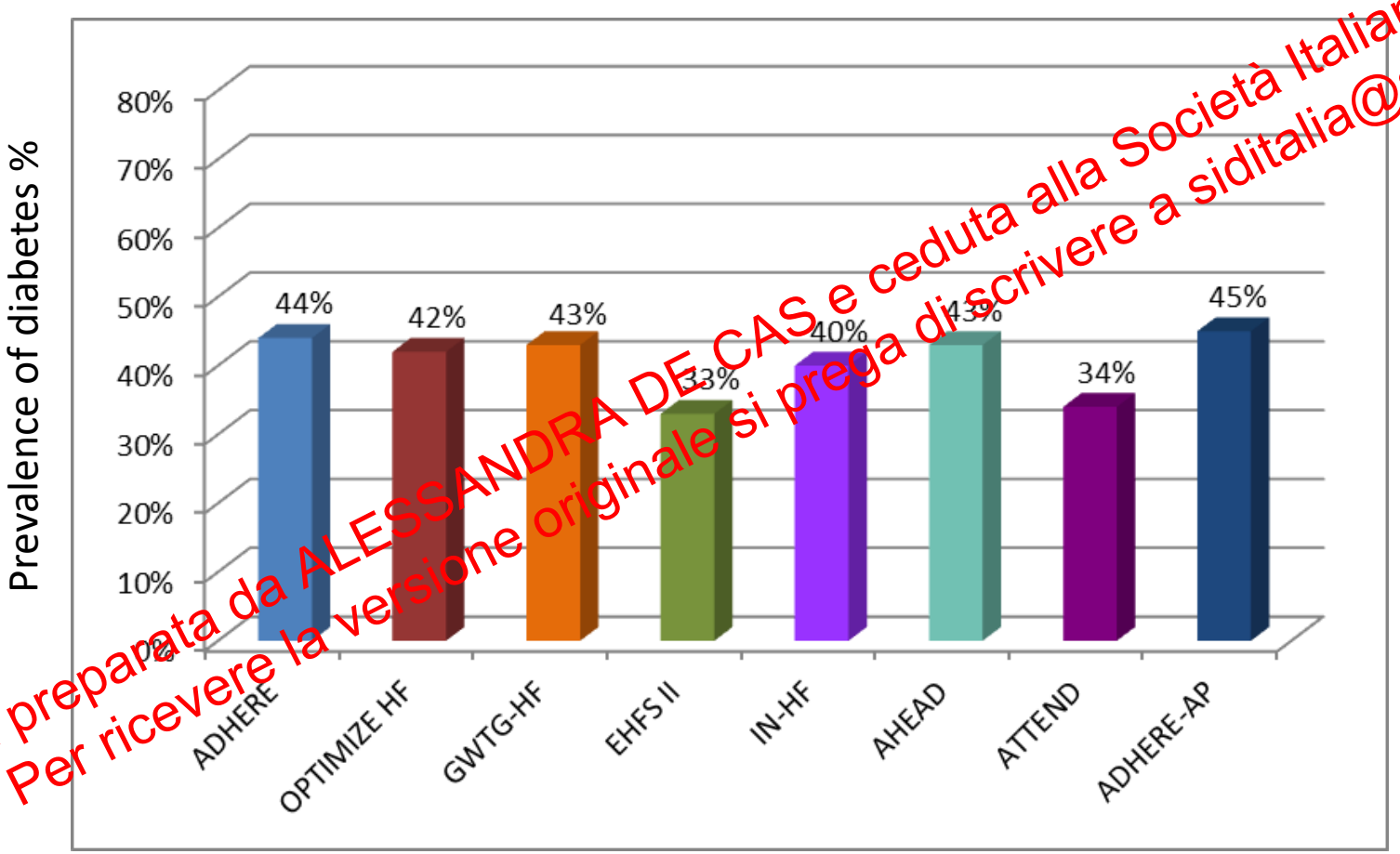
Prevalence of DM in the general population with and without HF



Prevalence of DM in patients with HF in representative registries

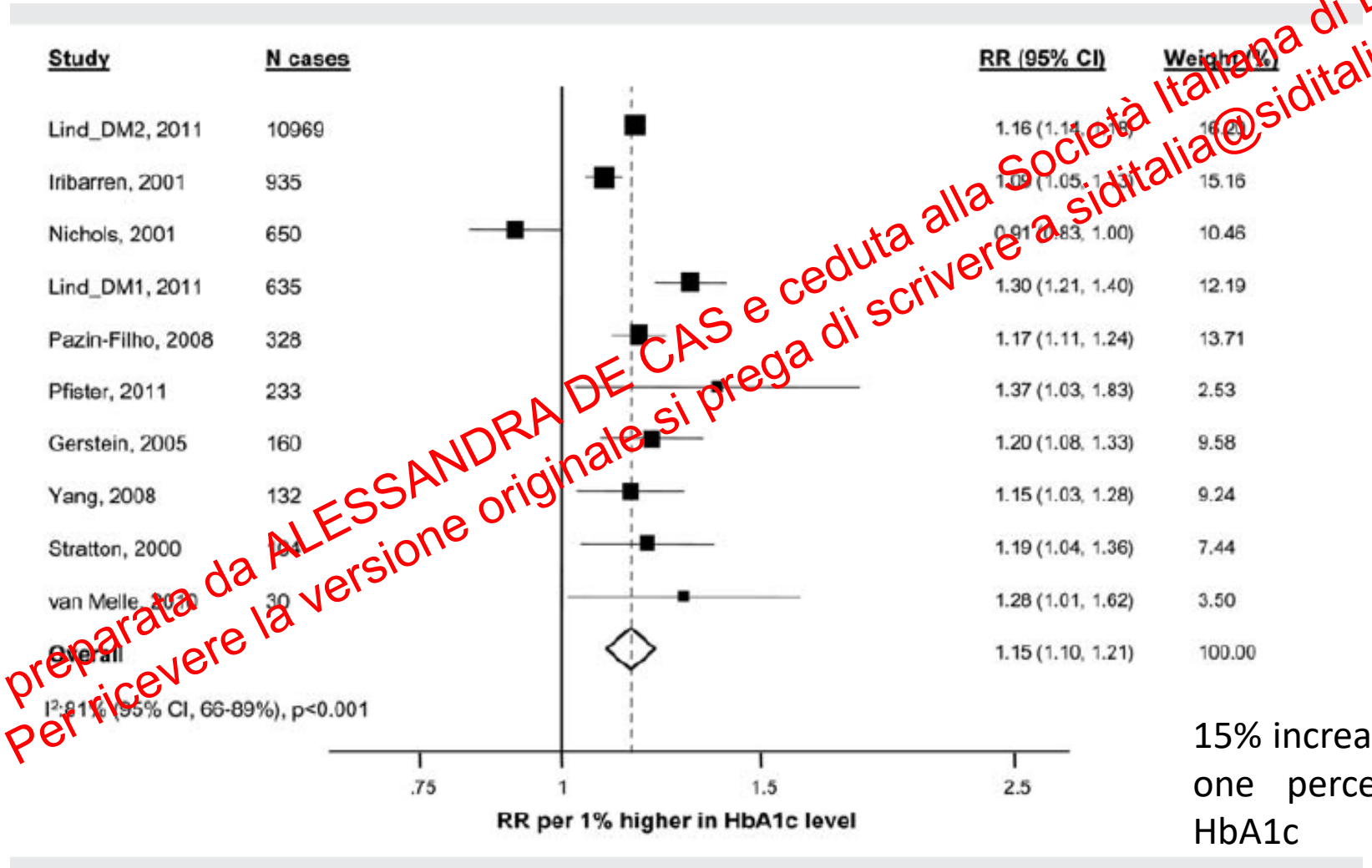


Prevalence of DM in patients hospitalized for worsening HF in Representative HHF Registries



Modified from Ambrosy et al JACC 2014

Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis



15% increase in risk of CHF each one percentage point higher HbA1c

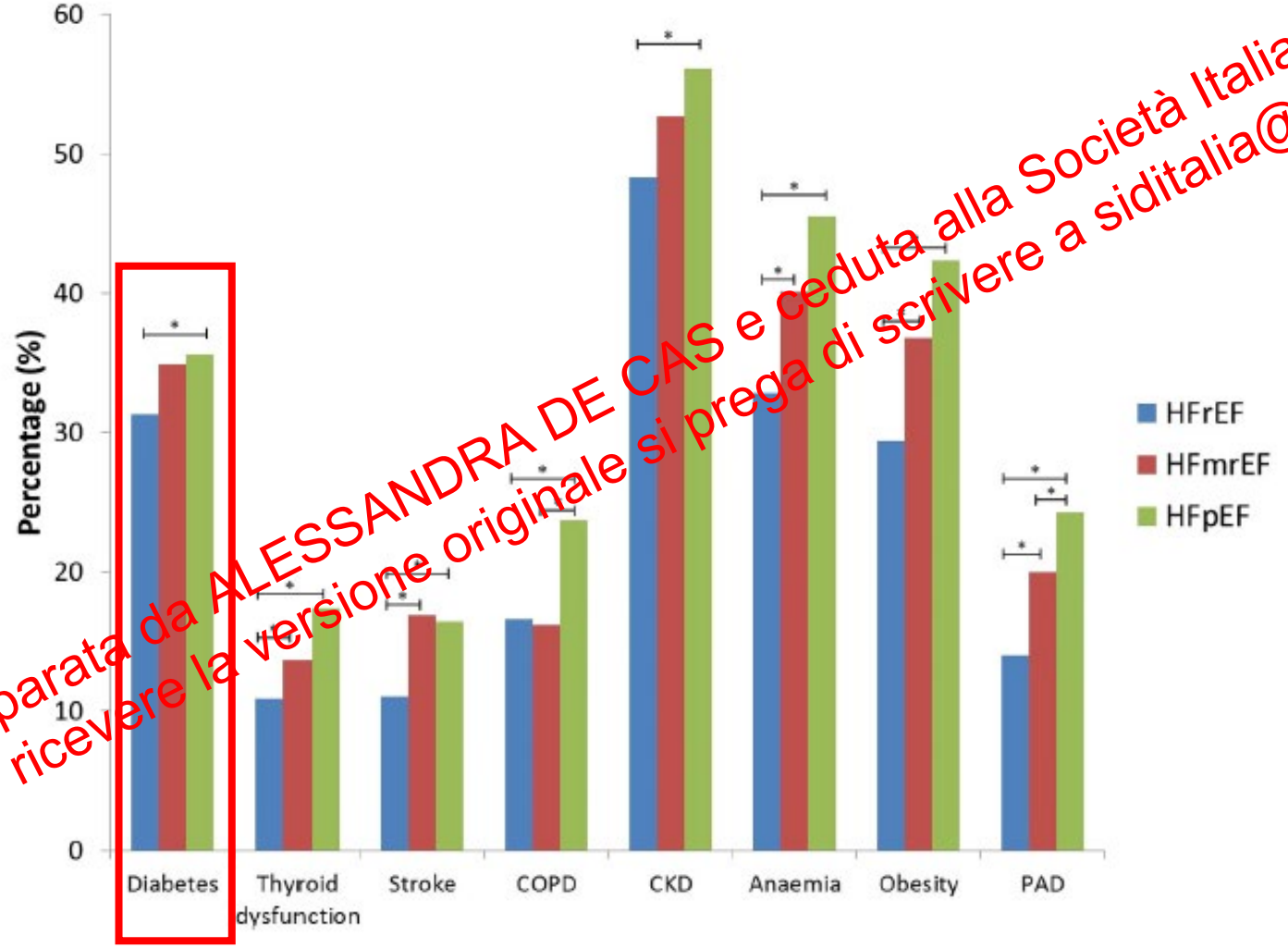
European Journal of Heart Failure (2013) 15, 185–193

Terminology of heart failure based on ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Ponikowski, Voors et al. European Journal of Heart Failure (2016)

Prevalence of non-cardiac comorbidities in heart failure groups BIOSTAT-CHF

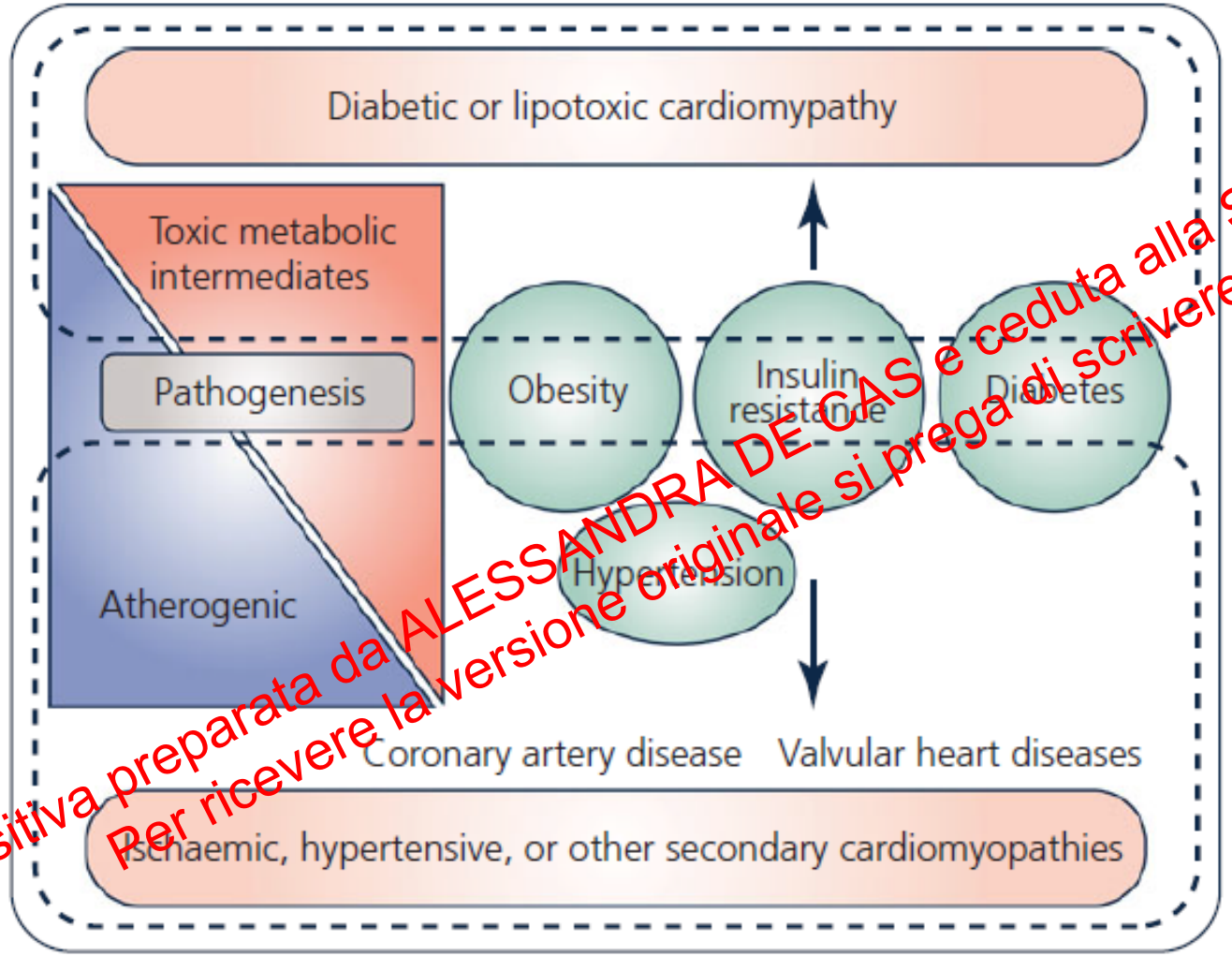


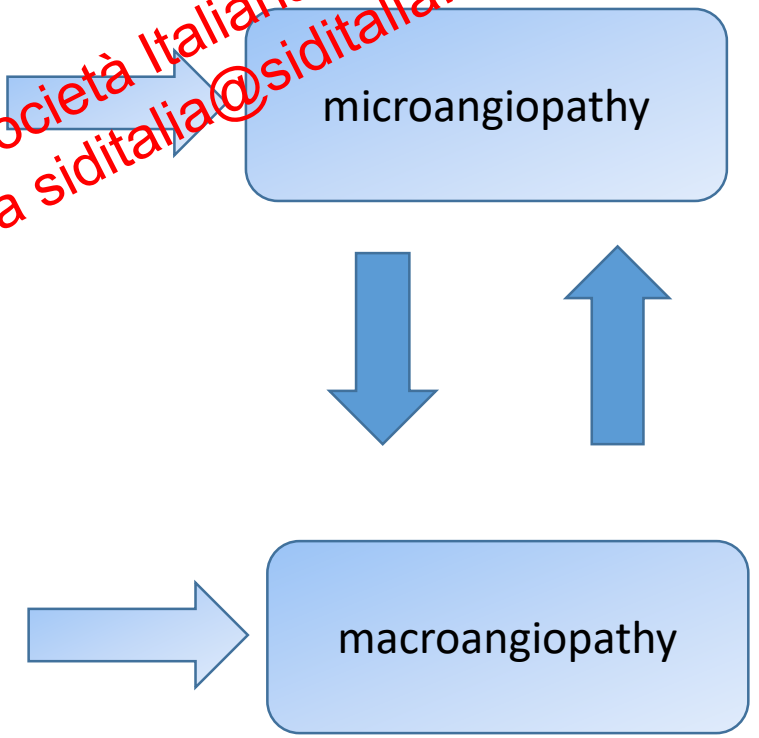
International Journal of Cardiology 271 (2018) 132–139

Heart Failure and Diabetes: a distinct entity

- Pathophysiology: role of hyperglycemia in driving HF phenotype
- Response to treatments

HF in diabetes





Modified from J Physiol 0.0 (2019) pp 1–17

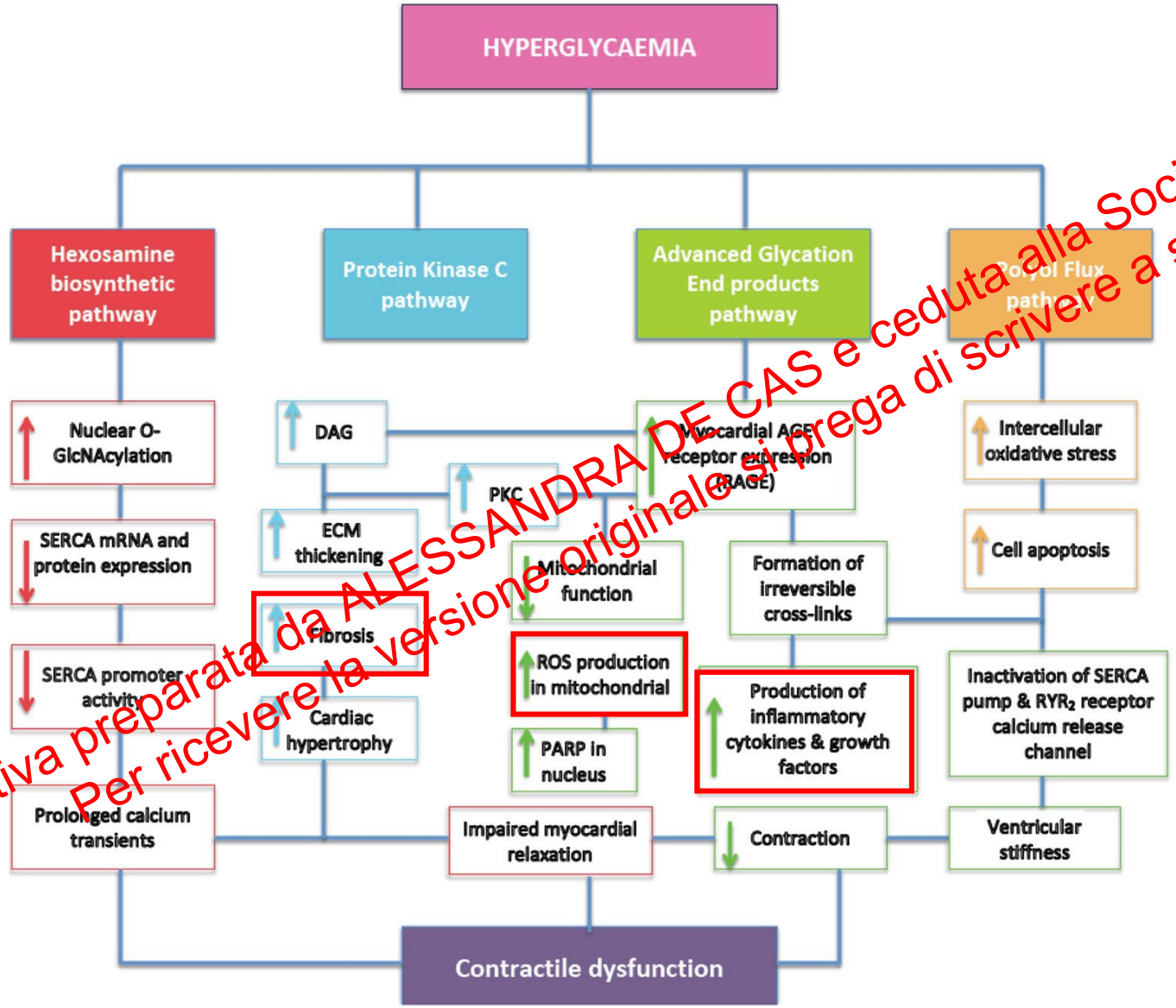
Relative importance of DM-related pathophysiological mechanisms for development of HFpEF vs HFrEF phenotypes

	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.

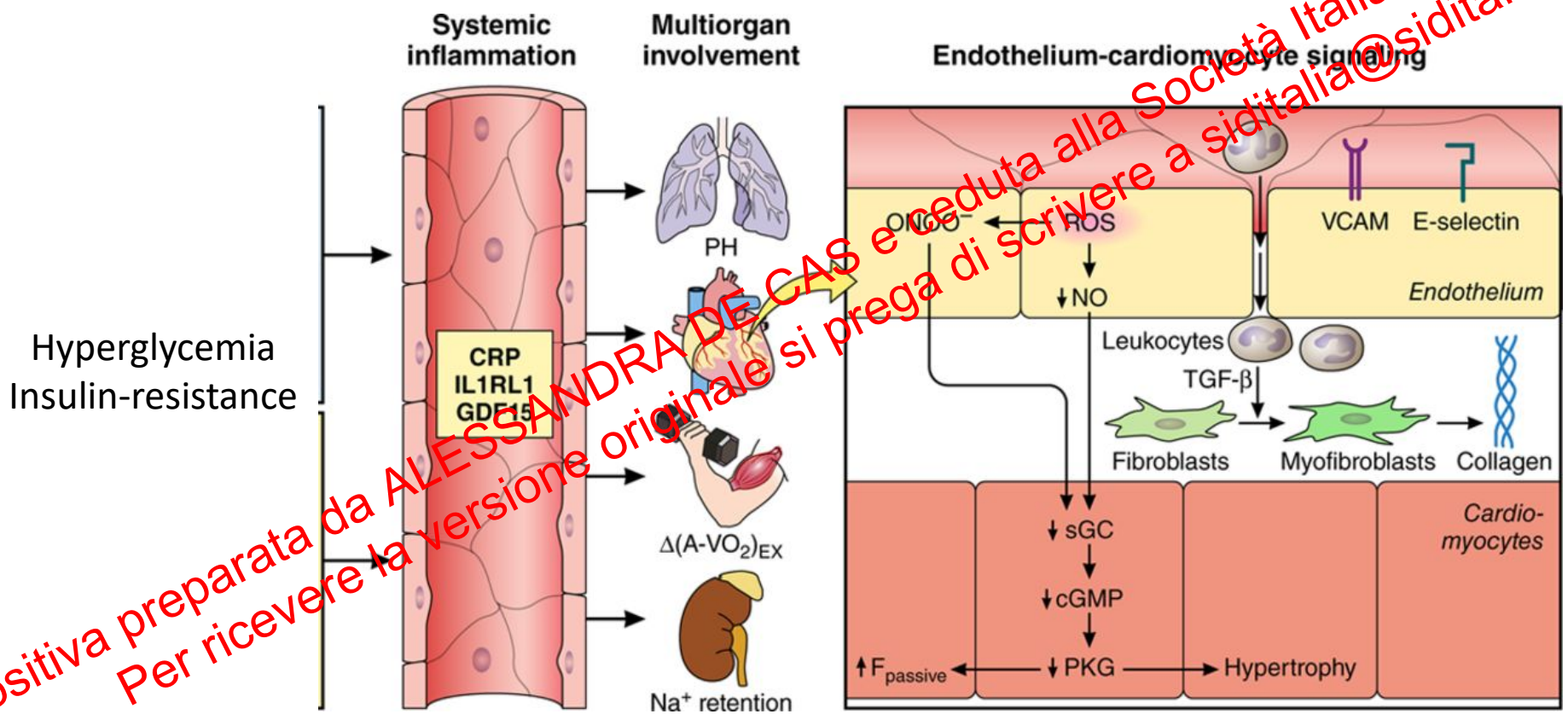
European Heart Journal (2015) 36, 1718–1727

A schematic flow chart representation highlighting the role of hyperglycemia in DCM



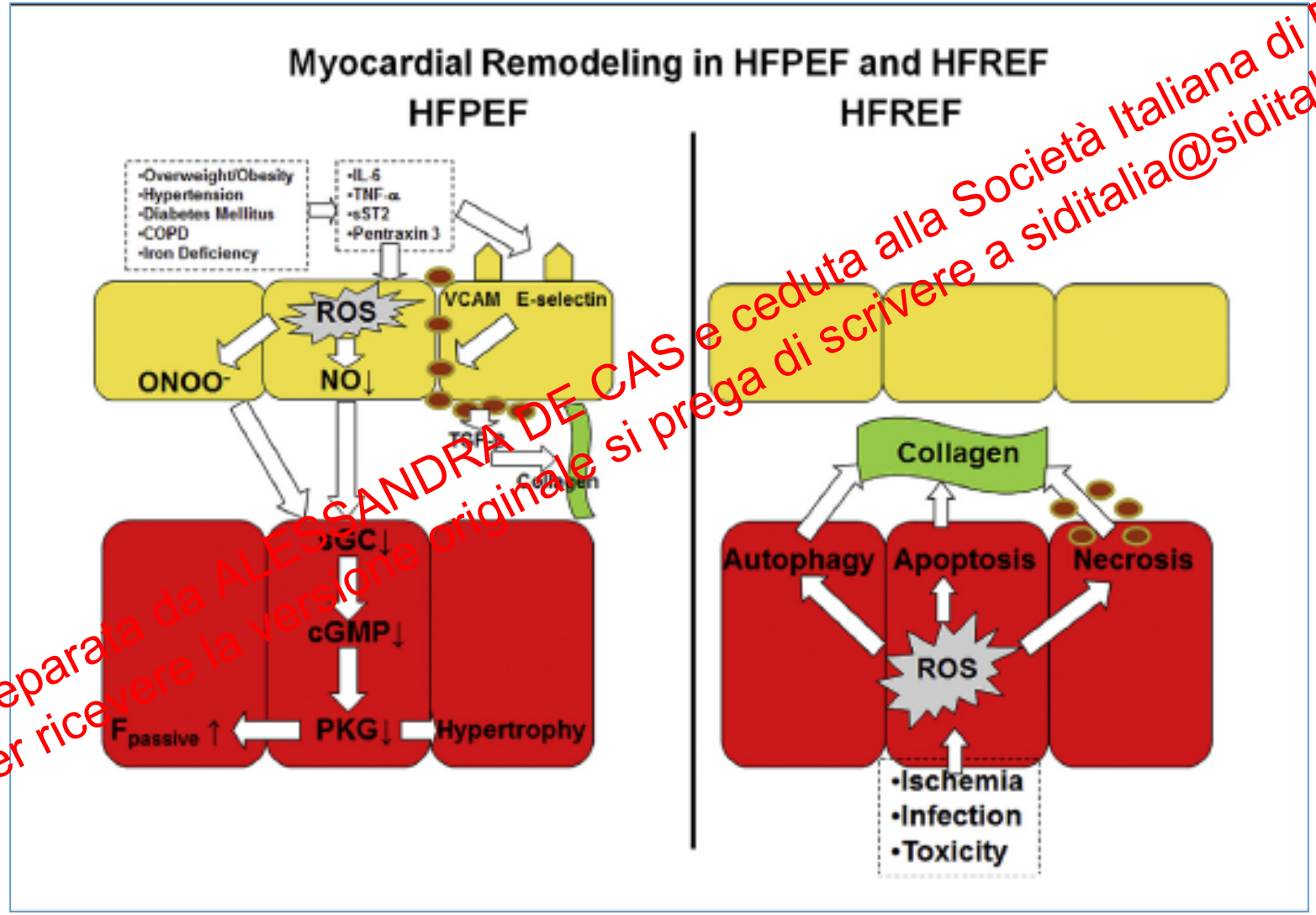
Heart Fail Rev (2018) 23:37–54

Systemic and myocardial signaling in HFpEF



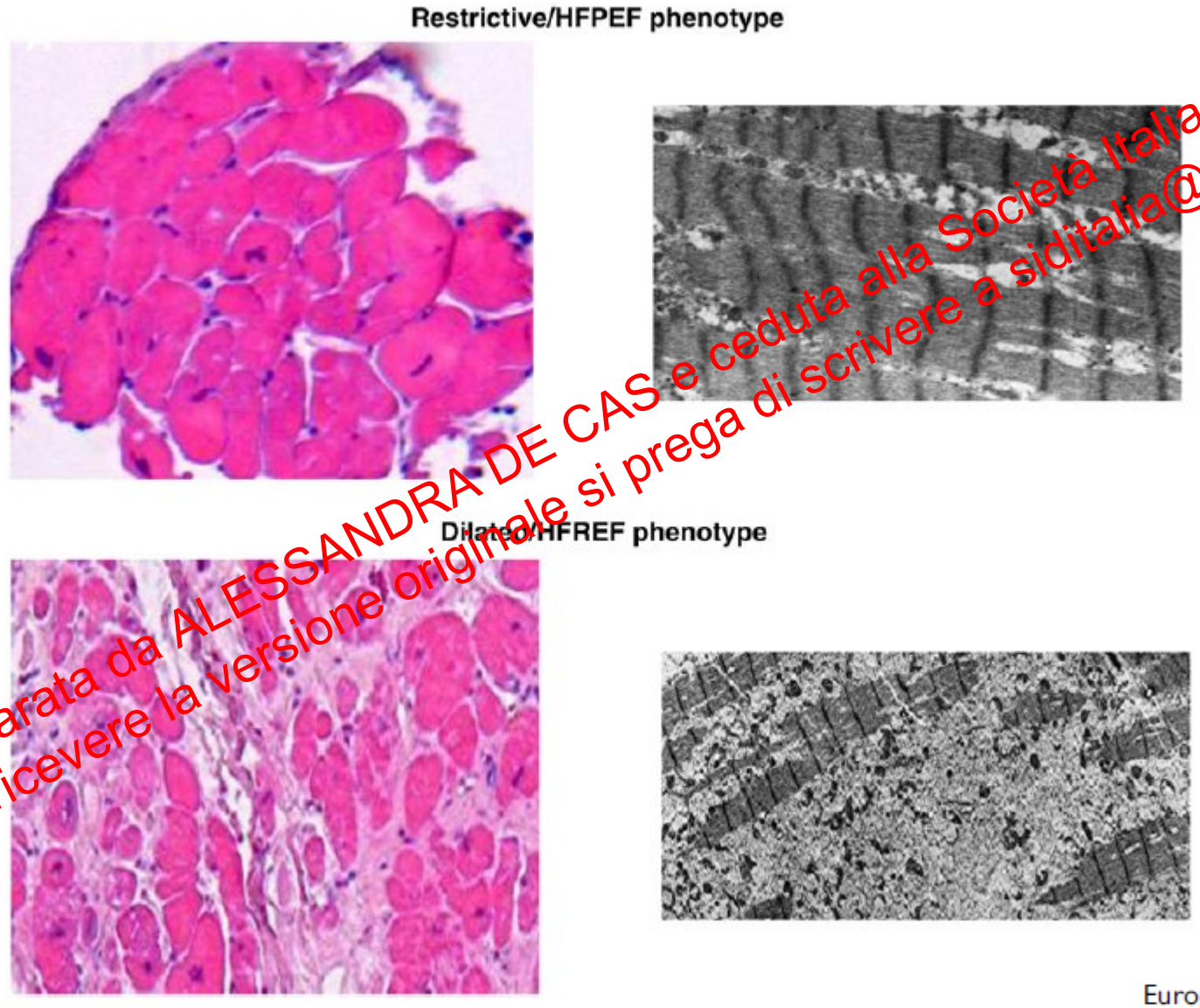
Sanjiv J. Shah et al. Circulation. 2016;134:73-90

Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation



J Am Coll Cardiol 2013;62:263–71

Myocardial structure in HFpEF and HFrEF phenotypes

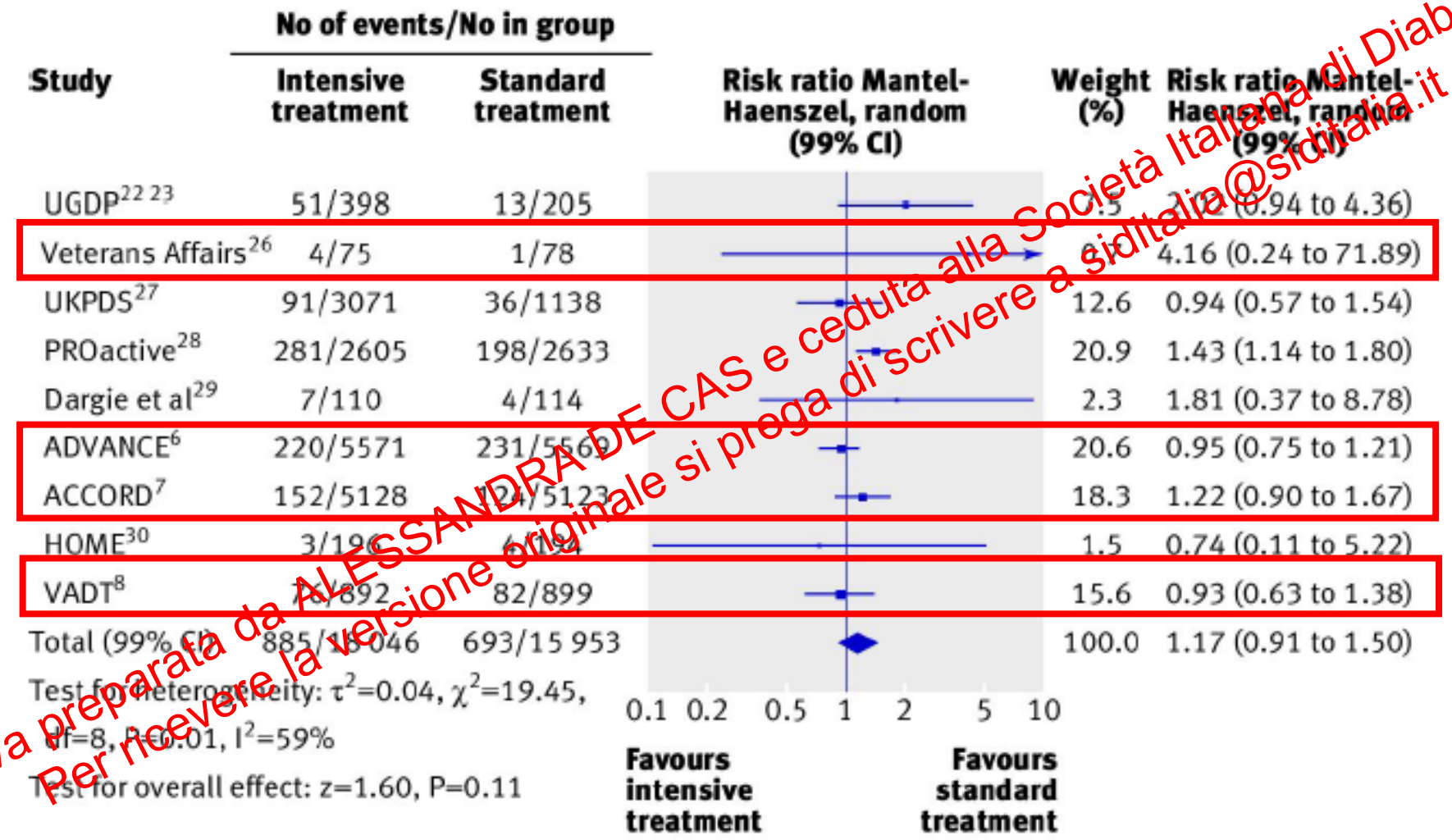


European Heart Journal (2015) **36**, 1718–1727

Heart Failure and Diabetes: a distinct entity

- Pathophysiology
- Response to treatments

Risk of HF in seminal diabetic trials



Study	No of events/No in group: Intensive treatment	No of events/No in group: Standard treatment	Weight (%)	Risk ratio Mantel-Haenszel, random (99% CI)
UGDP[22 23]	51/398	13/205	1.5	2.02 (0.94 to 4.36)
Veterans Affairs[26]	4/75	1/78	0.7	4.16 (0.24 to 71.89)
UKPDS[27]	91/3071	36/1138	12.6	0.94 (0.57 to 1.54)
PROactive[28]	281/2605	198/2633	20.9	1.43 (1.14 to 1.80)
Dargie et al[29]	7/110	4/114	2.3	1.81 (0.37 to 8.78)
ADVANCE[6]	220/5571	231/5569	20.6	0.95 (0.75 to 1.21)
ACCORD[7]	152/5128	124/5123	18.3	1.22 (0.90 to 1.67)
HOME[30]	3/196	4/194	1.5	0.74 (0.11 to 5.22)
VADT[8]	74/892	82/899	15.6	0.93 (0.63 to 1.38)
Total (99% CI)	885/18 046	693/15 953	100.0	1.17 (0.91 to 1.50)

Test for heterogeneity: $\tau^2=0.04$, $\chi^2=19.45$, df=8, P=0.01, $I^2=59\%$

Test for overall effect: z=1.60, P=0.11

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Table 8 Heart failure outcomes in published large cardiovascular outcome trials in patients with type 2 diabetes mellitus

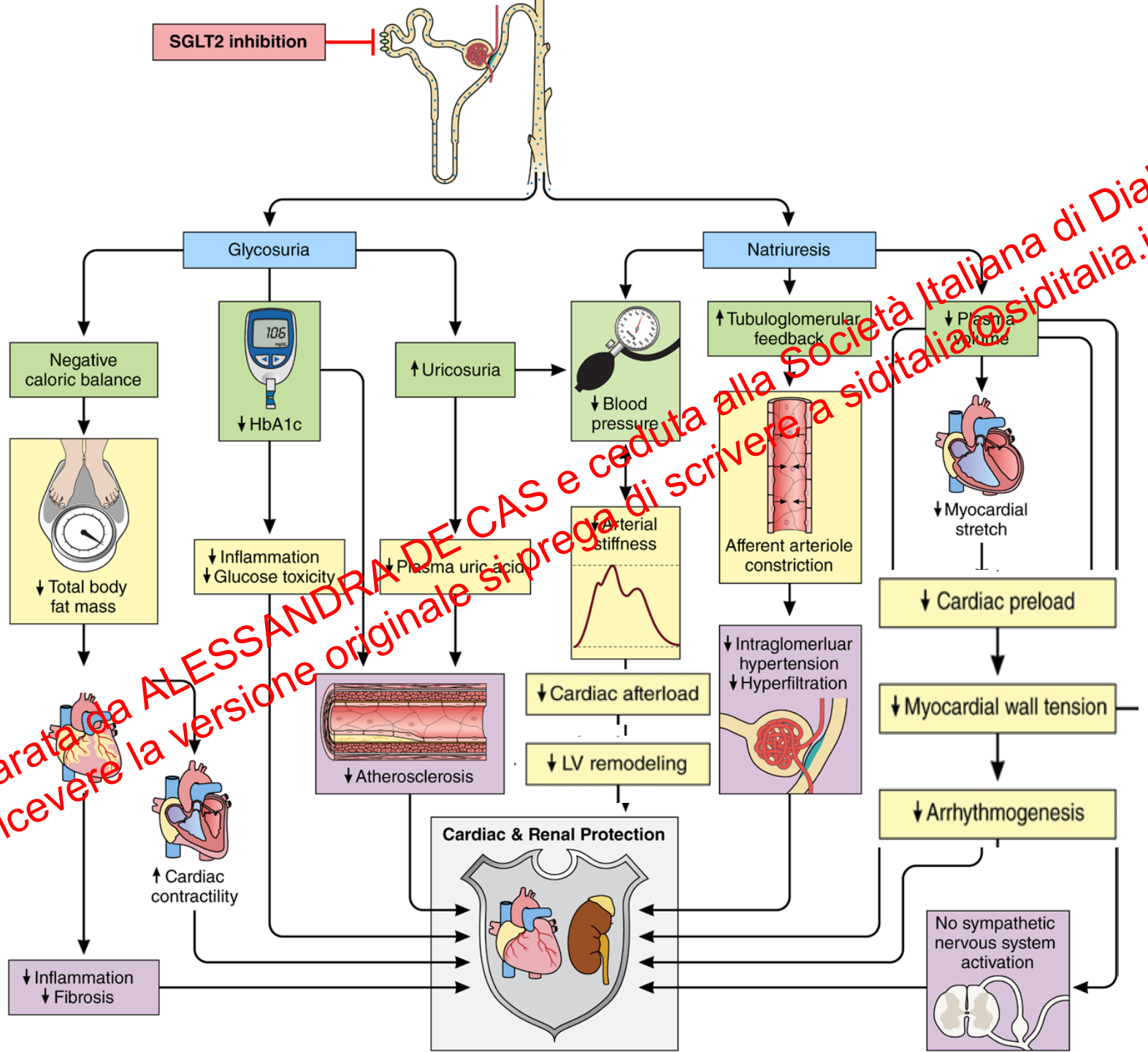
Study	Antidiabetic drug	Comparator	Results
DPP4 inhibitors			
SAVOR-TIMI 53[16,17]	Saxagliptin	Placebo	Increase in HF hospitalization
EXAMINE[19,184]	Alogliptin	Placebo	No statistically significant increase in HF hospitalization
TECOS[18,185]	Sitagliptin	Placebo	No effect on HF hospitalization
GLP-1 receptor agonists			
ELIXA[23]	Lixisenatide	Placebo	No effect on HF hospitalization
LEADER[22]	Liraglutide	Placebo	No effect on HF hospitalization
SUSTAIN-6[186]	Semaglutide	Placebo	No effect on HF hospitalization
EXSCEL[24]	Exenatide	Placebo	No effect on HF hospitalization

European Journal of Heart Failure (2018) **20**, 853–872

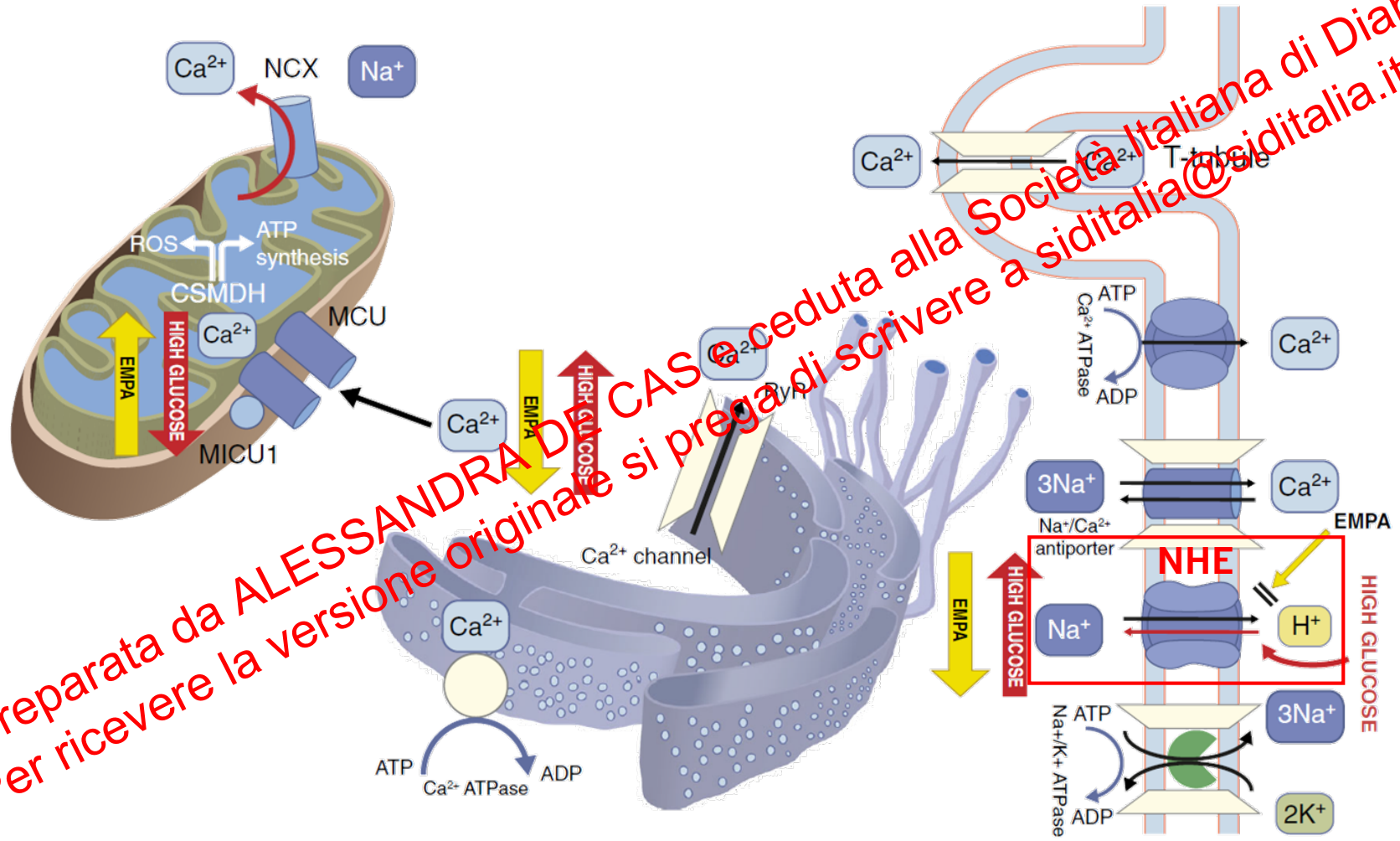
CVOTs and SGLT2i

Outcome	EMPAREG	CANVAS	DECLARE
3-point MACE	**HR= 0.86**	**HR= 0.86**	HR=0.53
CV death	**HR=0.62**	HR=0.87	HR=0.98
(Non) –fatal MI	HR= 0.87	HR=0.85	HR 0.89
(Non)-fatal stroke	HR=1.24	HR=0.90	HR= 1.01
All-cause death	**HR=0.68**	HR=0.87	HR=0.93
Hospitalisation for HF	**HR= 0.65**	**HR=0.67**	**HR=0.73**

N Engl J Med. 2015 Nov 26;373(22):2117-28.
N Engl J Med. 2017 Aug 17;377(7):644-657
N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389



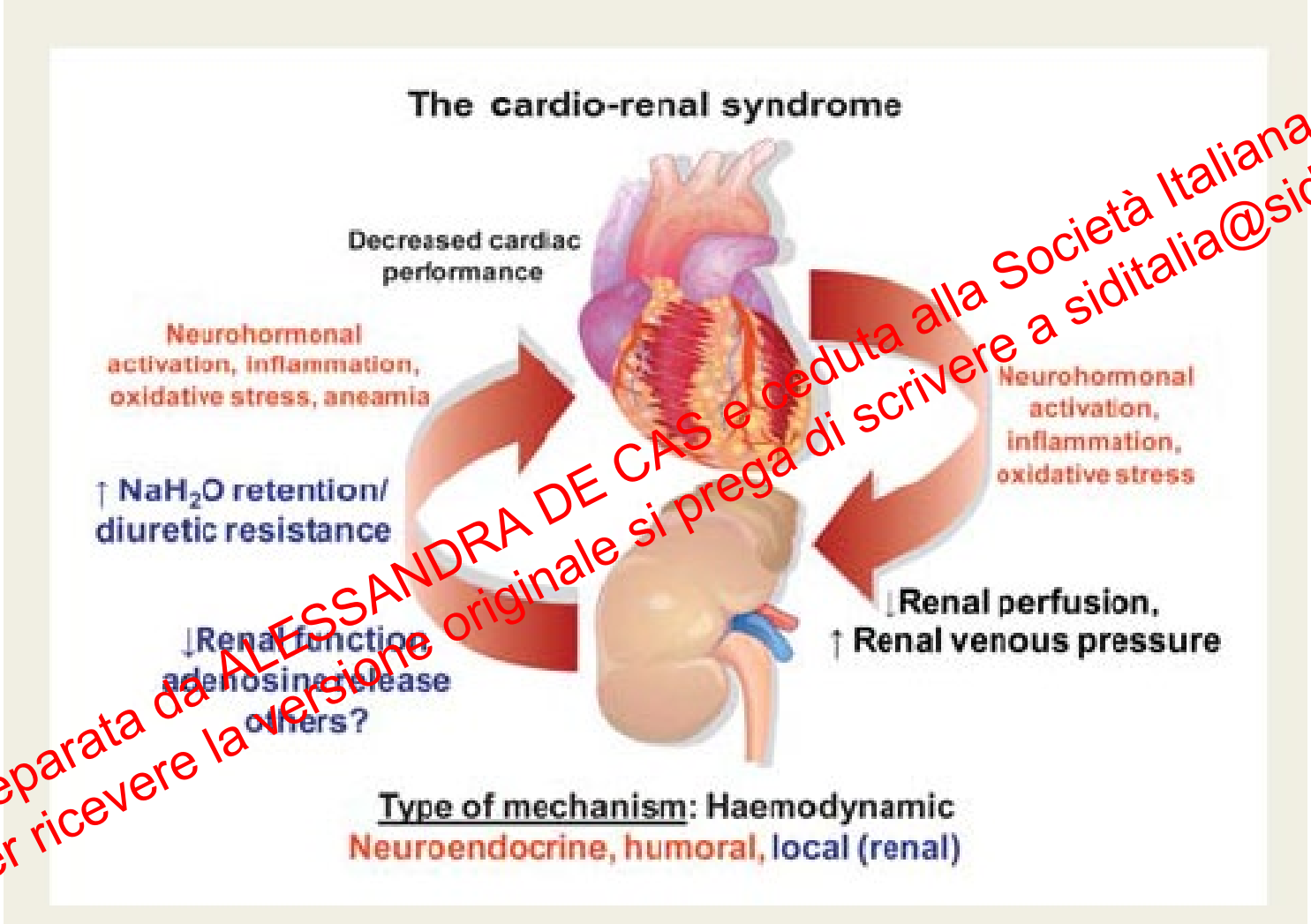
Empagliflozin blocca lo scambiatore Na^+/H^+ (NHE)



Vettor R, et al. Diabetologia. 2017 Jan 11.

Baartscheer A et al. Diabetologia. 2016 Oct 17

Sindrome cardio-renale



European Heart Journal (2012) **33**, 2135–2143
doi:10.1093/eurheartj/ehs205

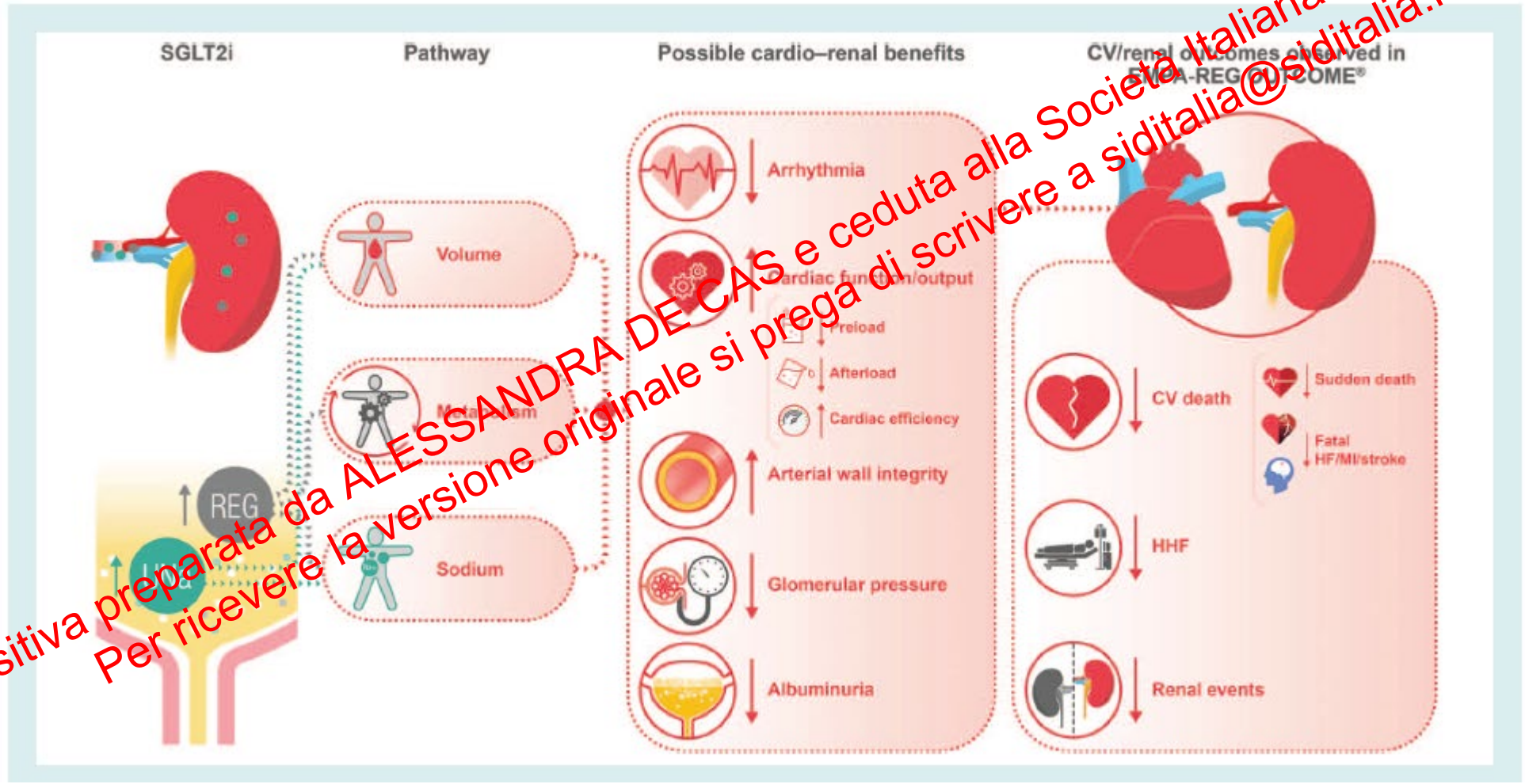
Relative risk of HF in 3490 patients with DM by quartile of albuminuria

ACR (mg/mmol) quartiles RR (95%CI)

	1st	2nd	3rd	4th	
Variable	<0.22	0.22 - 0.57	0.58 - 1.62	>1.62	P for trend
MI, Stroke & CV death	1	0.85 (0.63 – 1.14)	1.11 (0.86 – 1.43)	1.89 (1.52 – 2.63)	<0.001
All cause mortality	1	0.86 (0.58 – 1.28)	1.41 (1.01 – 1.95)	2.38 (1.80 – 3.20)	<0.001
CHF	1	0.72 (0.32 – 1.63)	1.83 (0.98 – 3.43)	3.65 (2.06 – 6.46)	<0.001

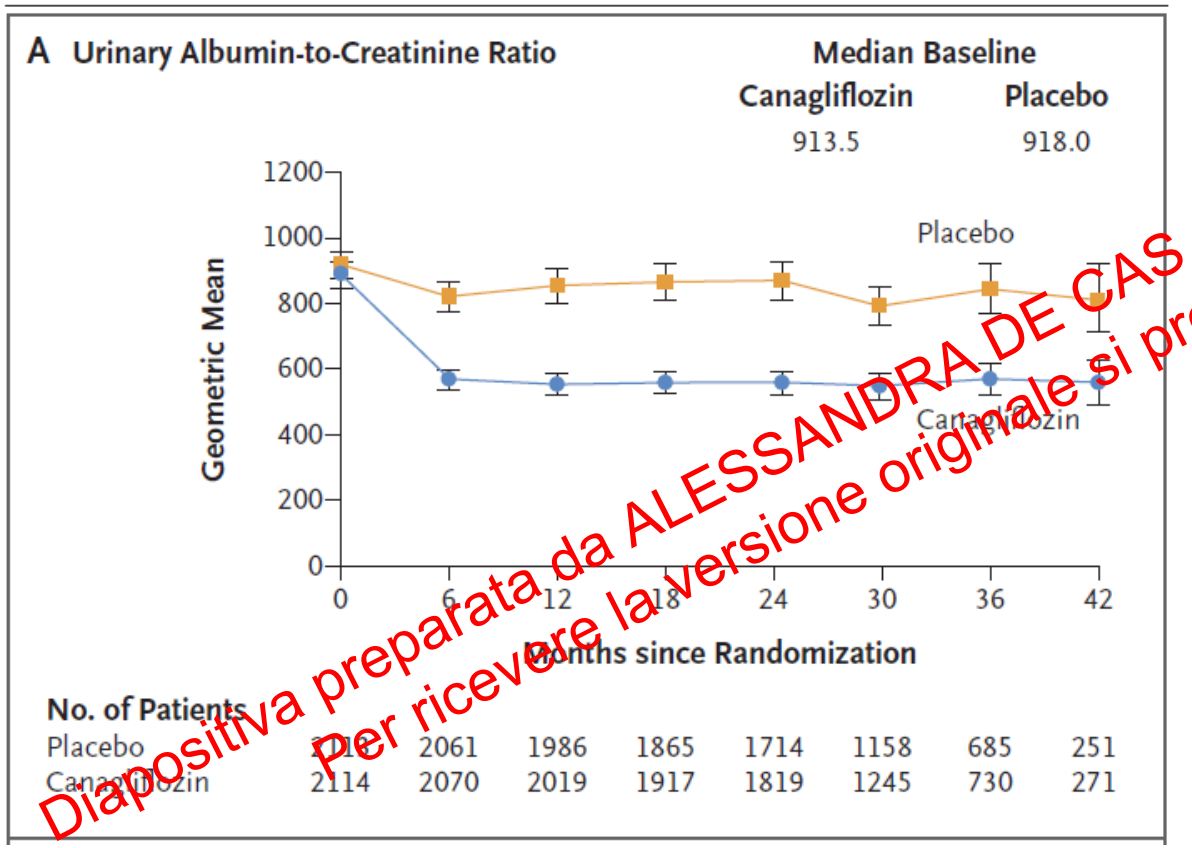
Gerstein et al JAMA 2001

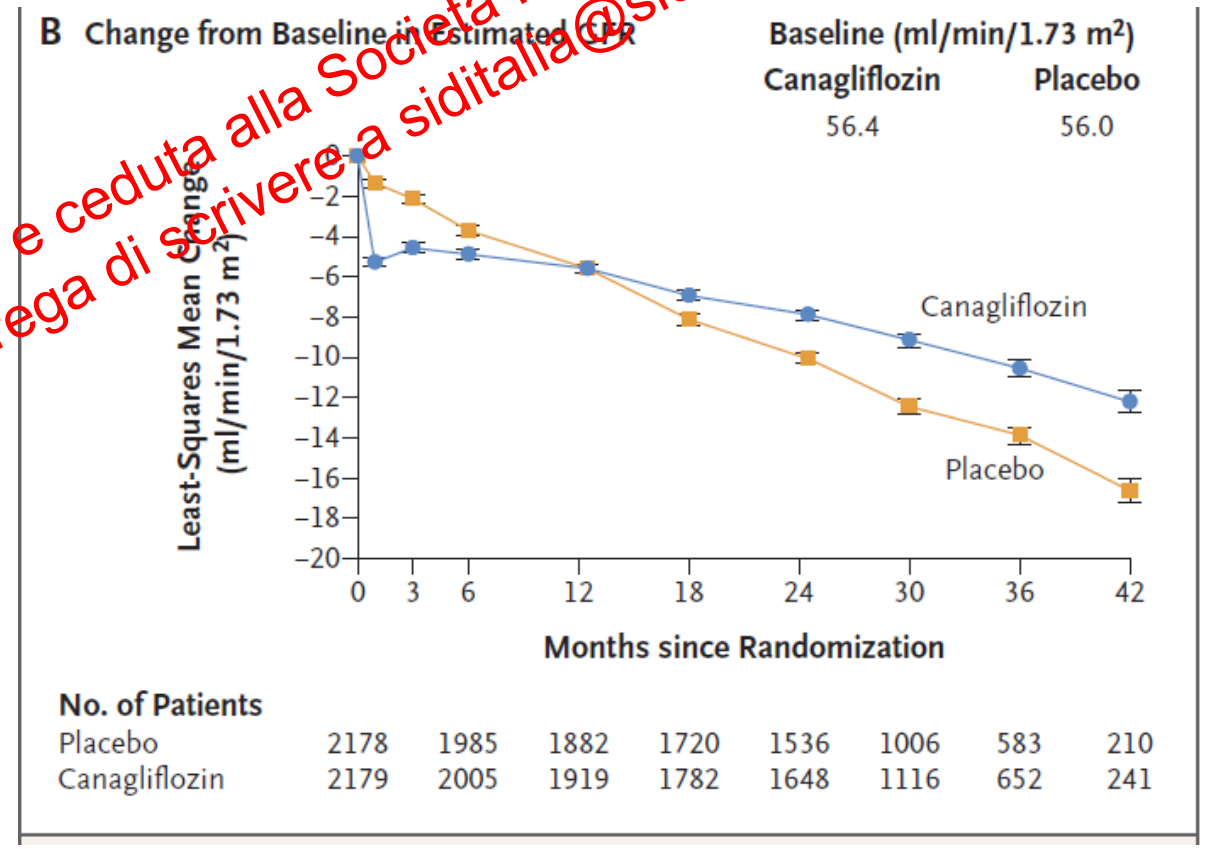
Potential pathways linking SGLT2i with cardio-renal benefits



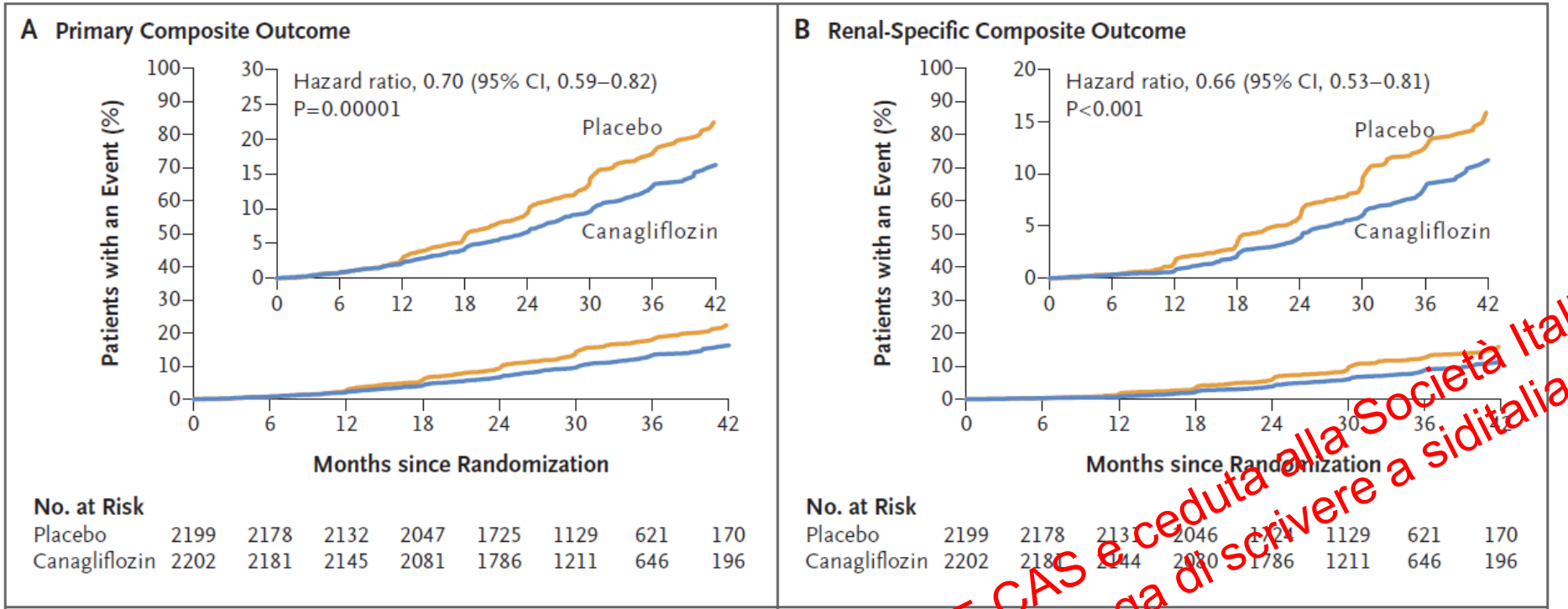
European Journal of Heart Failure (2017) 19, 1390–1400

Effects on albuminuria and eGFR (CREDENCE study)





N Engl J Med 2019;380:2295-306.



composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

N Engl J Med 2019;380:2295-306.

Conclusions

- ✓ The large current and projected increase in HF in DM makes this entity an important health problem
- ✓ The presence of diabetes (hyperglycemia) mainly drives a HpEF phenotype
- ✓ SGLT-2i, beyond glucose control, show benefits in HHF
- ✓ Future studies are needed to elucidate underlying mechanisms

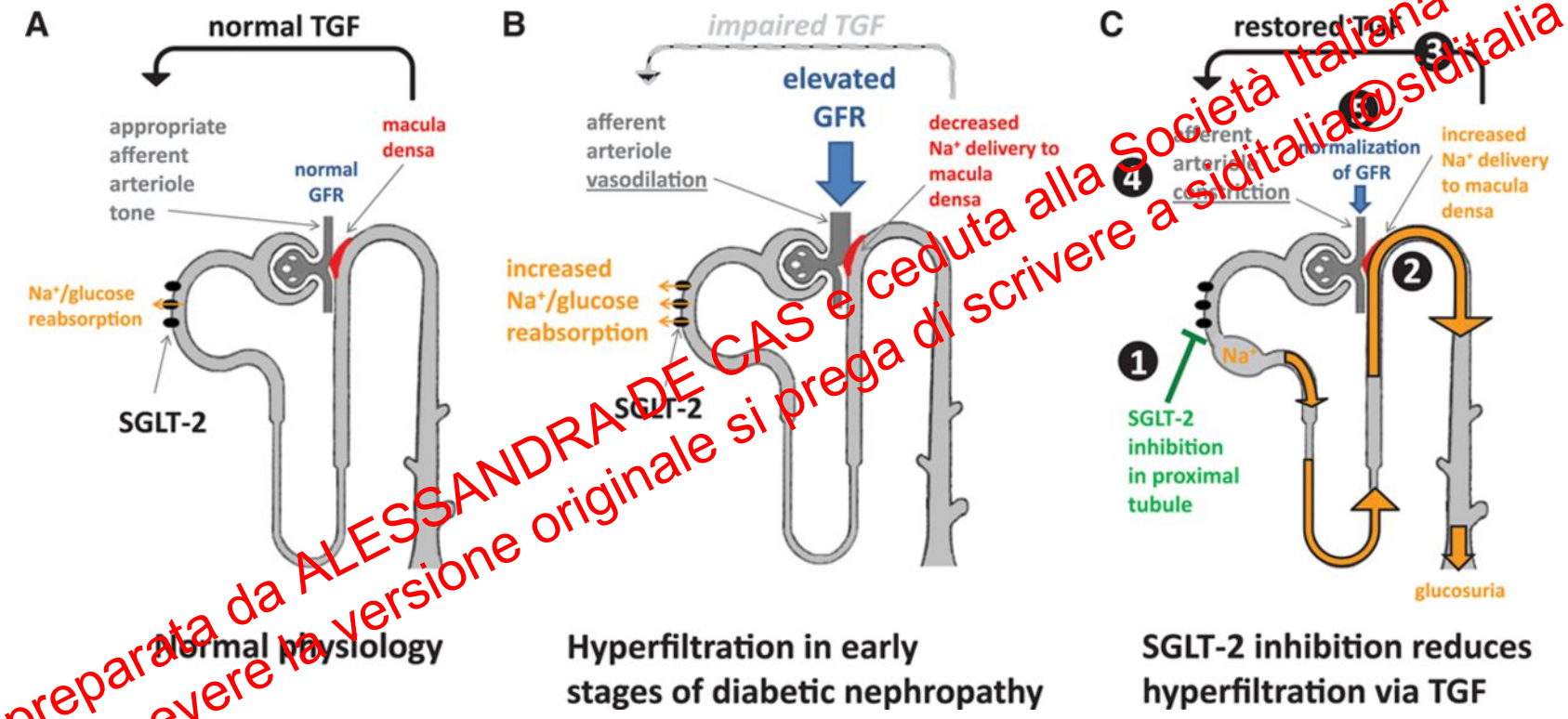
Selected ongoing randomized clinical trials of SGLT2 inhibitors in patients with HFpEF

Clinical trial	Brief description of the trial
PRESERVED-HF (NCT03030235)	Dapagliflozin Effect on Symptoms and Biomarkers in patients HFpEF • Study population: HFpEF with T2DM or pre-diabetes. • Estimated enrolment: *n*=320. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: baseline to week 6 and 12) as a measure of treatment impact on HF.
EMPEROR-Preserved (NCT03057951)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction • Study population: HFpEF, with and without T2DM. • Estimated enrolment: *n*=4126. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).

European Journal of Heart Failure (2018) 20, 853–872

Possible mechanism for dapagliflozin nephroprotection

Postulated tubulo glomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT) 2 inhibition.

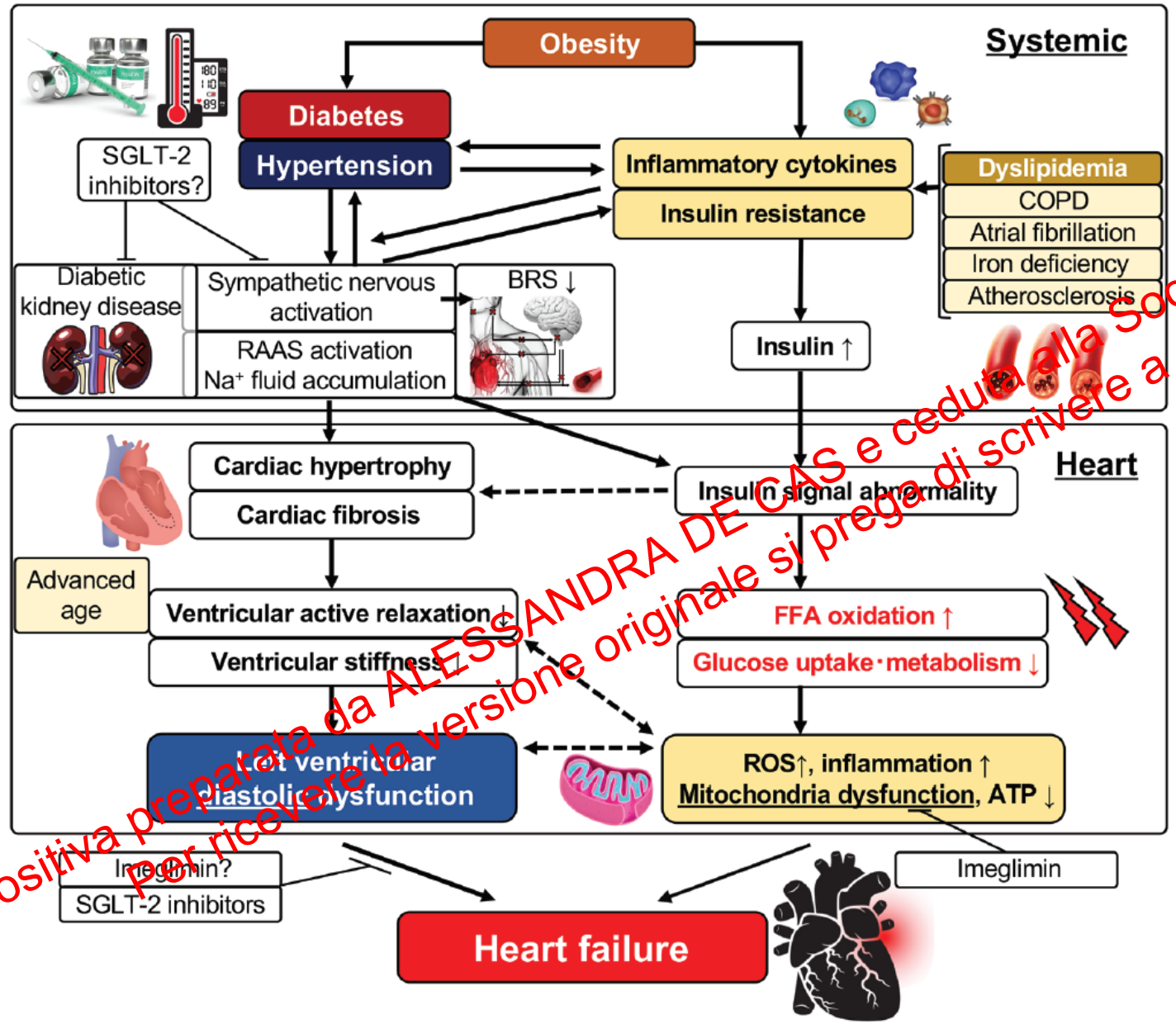


Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

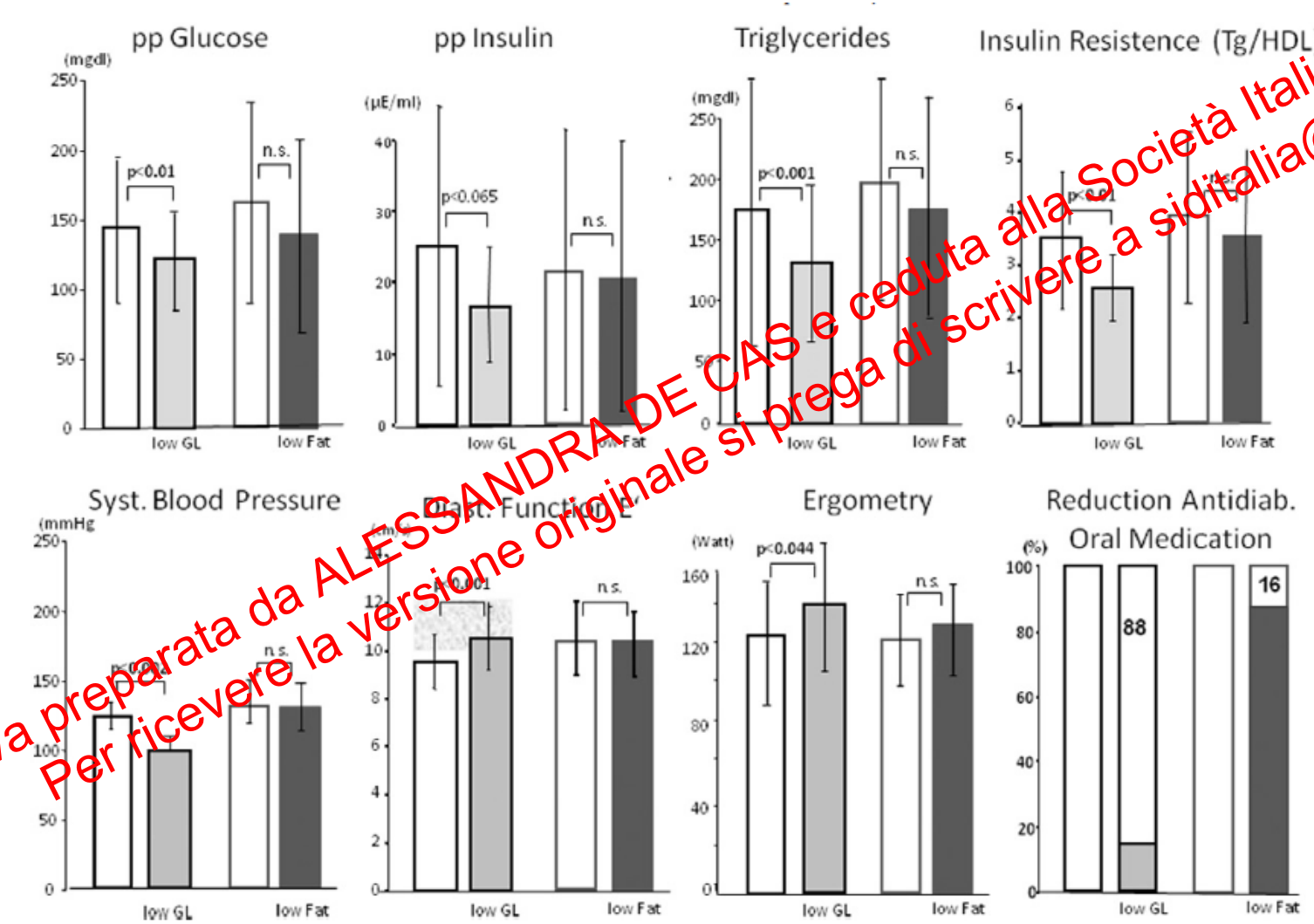
SGLT-2 inhibition reduces hyperfiltration via TGF

Cherney D Z et al. Circulation. 2014;129:587-597



J Clin Med Res. 2018;10(11):799-805

Reduced glycemic load ameliorate LV diastolic dysfunction independeltly of weight reduction in obese type-2-diabetics



three weeks of moderate aerobic exercise + a low glycemic load (low GL)

vs

three weeks of moderate aerobic exercise + isocaloric food (1800 kcal) with high carbohydrate (50%)/low-fat composition

International Journal of Cardiology 234 (2017) 7–15

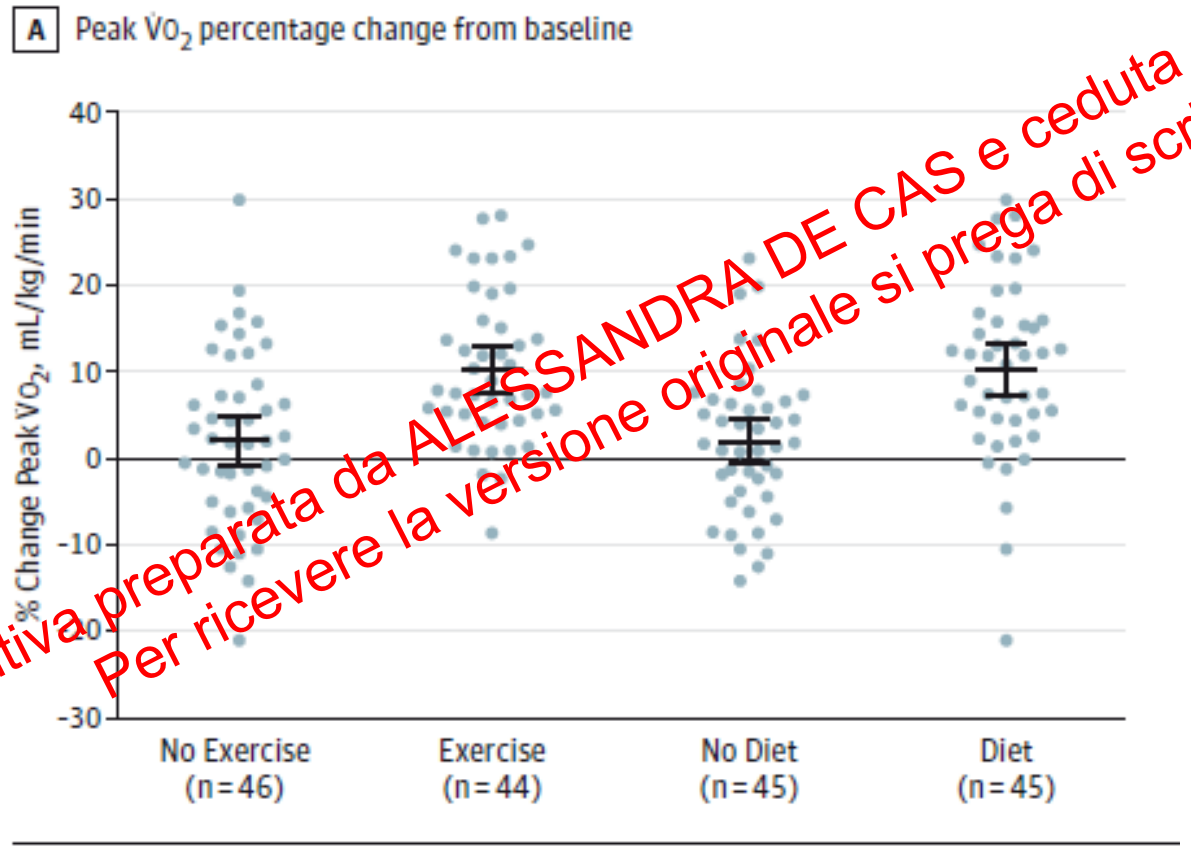
COMORBIDITY	BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION	HEART FAILURE SPECIFICS
Chronic obstructive pulmonary disease	Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects	More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF)
	Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function	Higher mortality risk in HFpEF
Anemia	Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines	More prevalent in HFpEF
	Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate	Similar increased risk for mortality in both groups
Diabetes	Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease	More prevalent in HFpEF
	Incident and worsening diabetes mellitus via sympathetic and RAAS activation	Similar increased risk for mortality in both groups
Renal dysfunction	Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation	Similar prevalence in both groups
	Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure	Similar increased risk for mortality in both groups
Sleep-disordered breathing	Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion	Similar prevalence in both groups
	Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system	Unknown mortality differential associated with HFpEF vs. HFrEF
Obesity	Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus	More prevalent in HFpEF
	Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies	Obesity paradox; potential for a U-shaped association with mortality

Mentz, R.J. (

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 21, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.08.036

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction A Randomized Clinical Trial



Twenty weeks of diet, exercise, or both;

-7Kg diet group

- 3 Kg exercise group

JAMA. 2016;315(1):36-46.

Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure

Result for primary end point, showing a significant decrease in E/e’ 6 months after administration of dapagliflozin

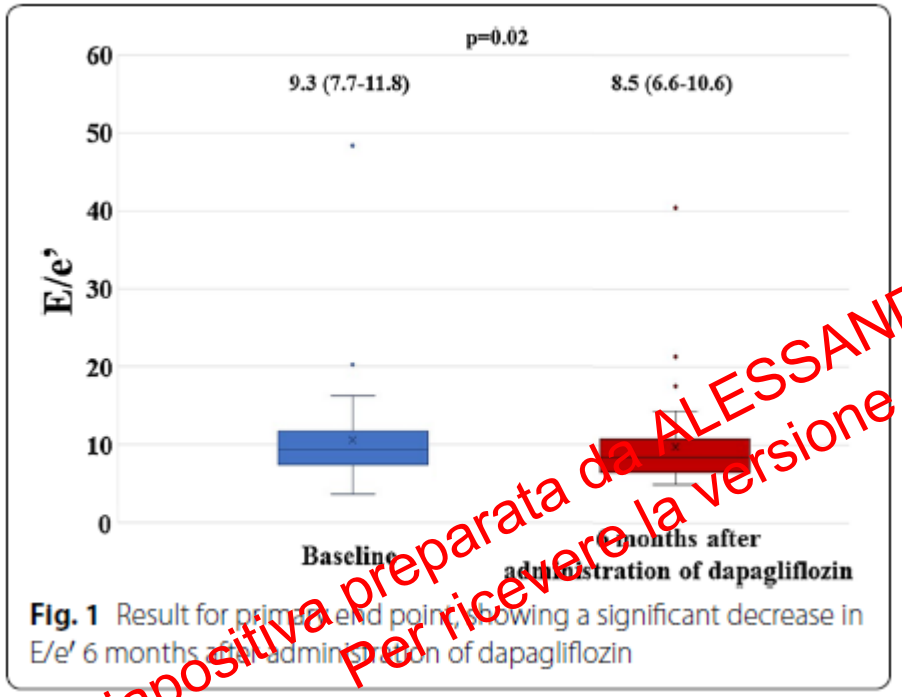
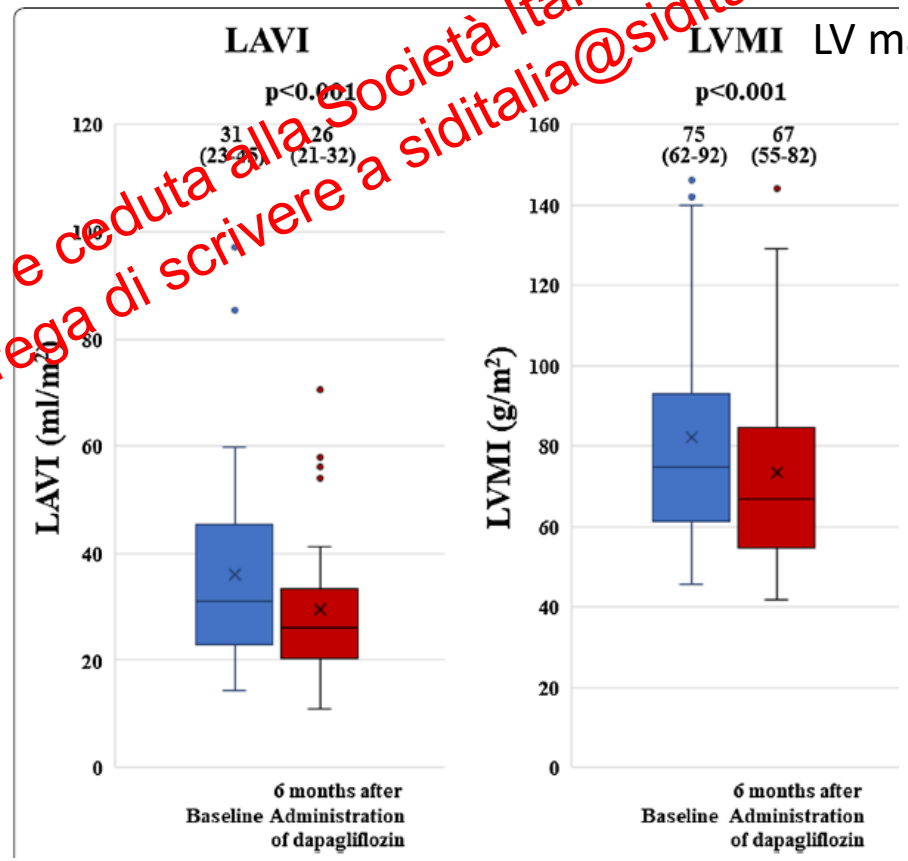


Fig. 1 Result for primary end point, showing a significant decrease in E/e’ 6 months after administration of dapagliflozin

Results for secondary end points show a significant decrease in LAVI and LVMI significant decreased 6 months after administration of dapagliflozin

left atrial volume index

LV mass index



Soga et al. Cardiovasc Diabetol (2018) 17:132

Phenotype-specific HFpEF treatment strategy using a matrix of predisposition phenotypes and clinical presentation phenotypes.

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes				
	Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Sanjiv J. Shah et al. Circulation. 2016;134:73-90

Differential Effects of Risk Factors on HFpEF vs HFrEF in Multivariable Analysis in 28,820 participants from 4 community-based cohorts

	HFpEF	HFrEF	
	sHR* (95% CI)	sHR* (95% CI)	*P* for equality
Age, per 10 y	1.91 (1.78–2.06)	1.69 (1.59–1.80)	0.02
Male sex	0.91 (0.79–1.05)	1.87 (1.63–2.16)	<0.0001
Systolic BP, per 20 mm Hg	1.13 (1.05–1.21)	1.20 (1.12–1.28)	0.24
Body mass index, per 4 kg/m^2	1.28 (1.22–1.36)	1.18 (1.11–1.25)	0.05
Antihypertensive treatment	1.41 (1.21–1.65)	1.33 (1.14–1.54)	0.59
Diabetes mellitus	1.42 (1.17–1.72)	1.58 (1.32–1.90)	0.44
Current smoker	1.04 (0.85–1.28)	1.44 (1.21–1.72)	0.02
Previous myocardial infarction	1.30 (1.02–1.67)	2.70 (2.25–3.24)	<0.0001
Left ventricular hypertrophy	1.16 (0.84–1.60)	2.08 (1.60–2.69)	0.009
Left bundle branch block	1.30 (0.81–2.09)	3.65 (2.62–5.09)	0.0008

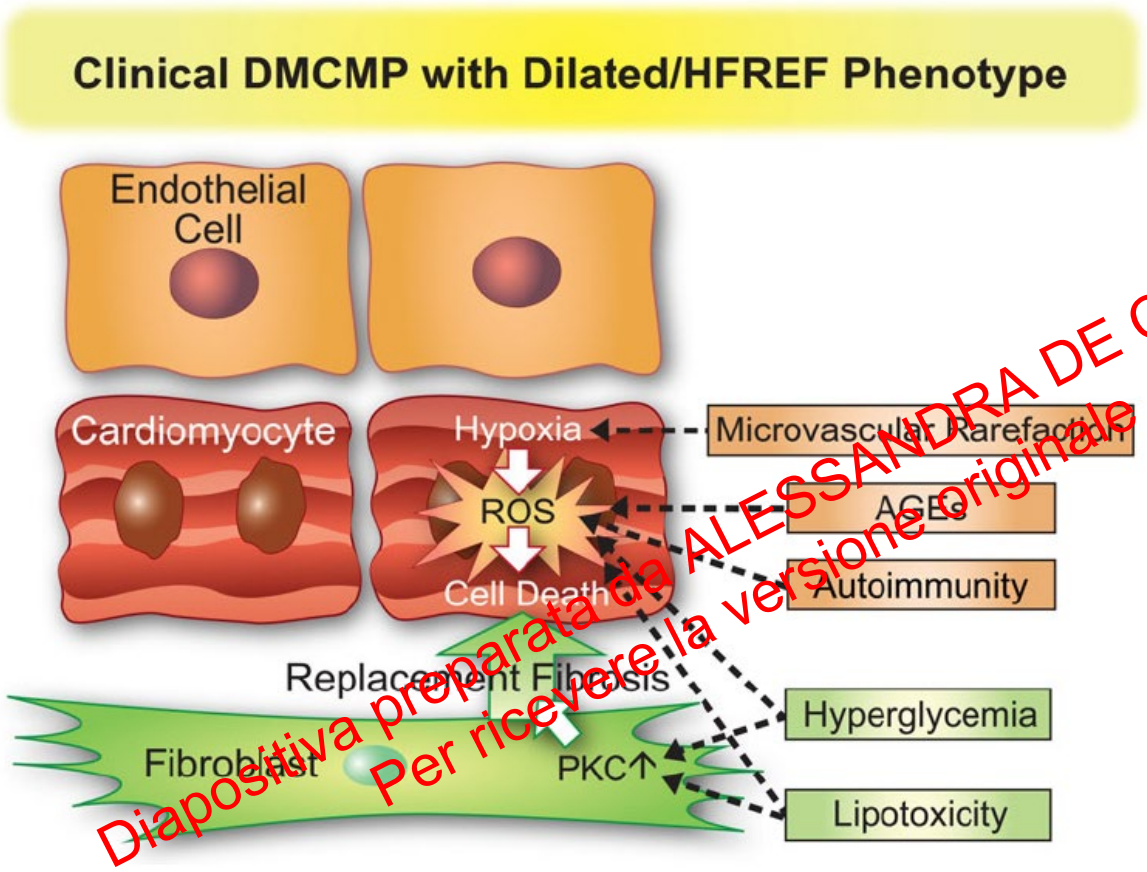
Bold face indicates significant *P* value using a Bonferroni-corrected threshold of 0.005 for number of variables tested. BP indicates blood pressure; CI, confidence interval; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; and sHR, subdistribution hazard ratio.

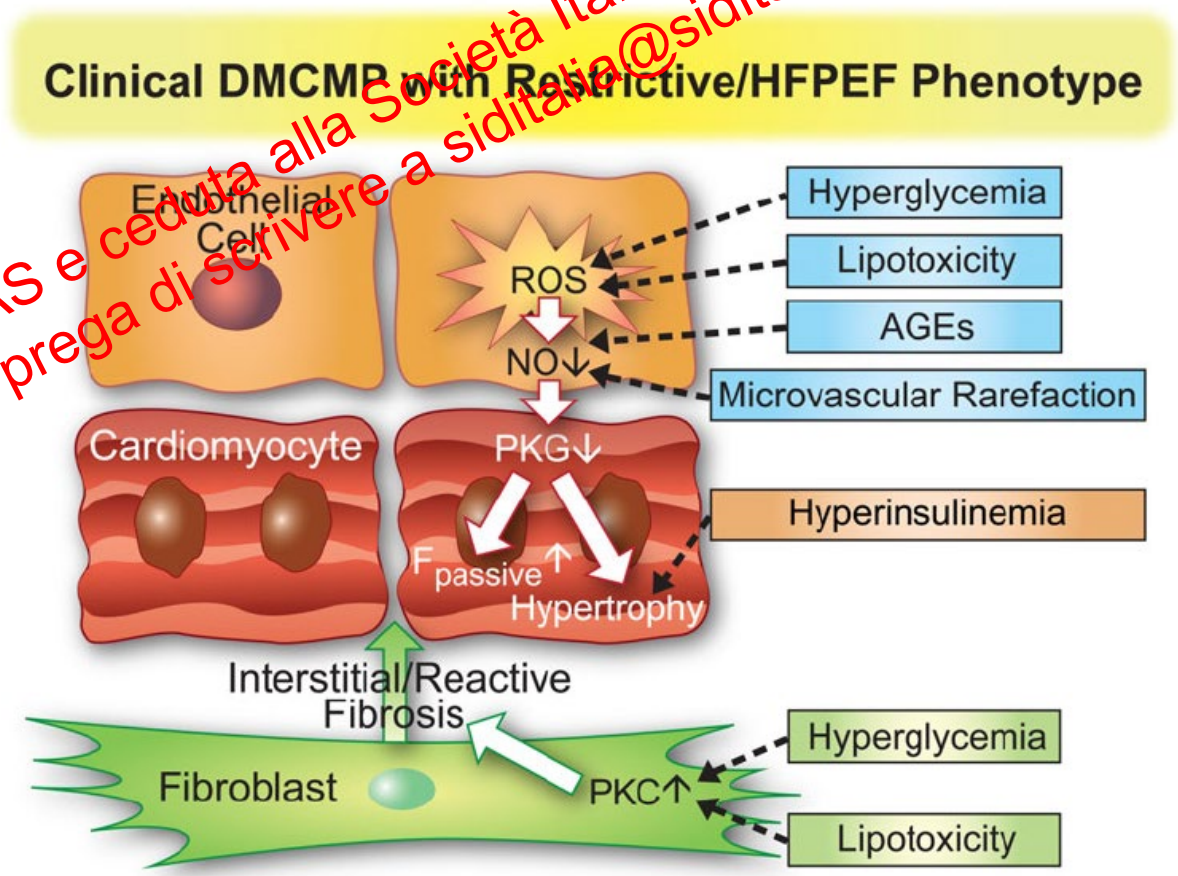
*Hazard ratio is for the presence versus absence of dichotomous predictors, and per increase in continuous predictors as specified in the table with all covariates shown in the model simultaneously.

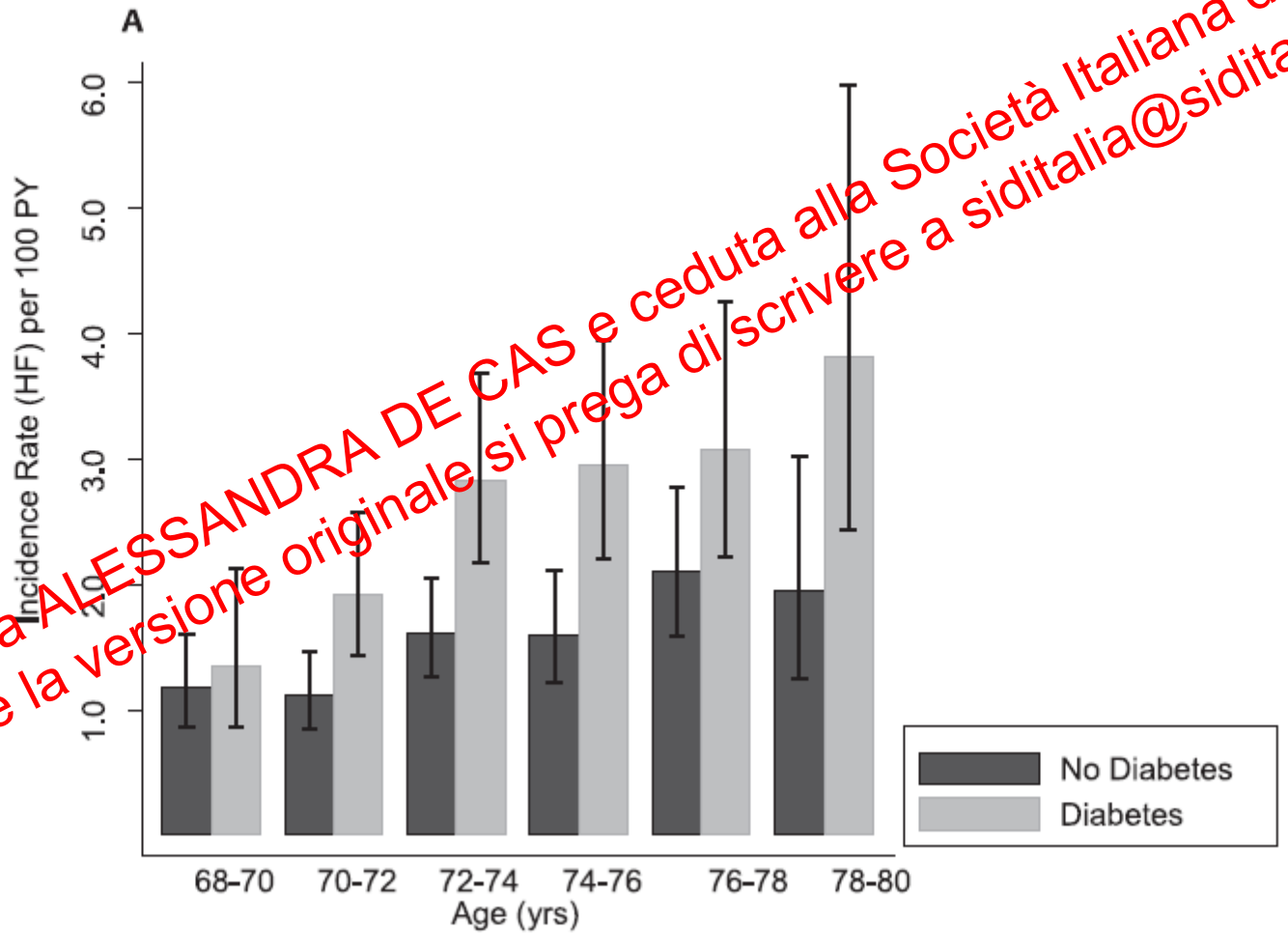
Circ Heart Fail. 2016;9:e003116

Cellular, subcellular, and interstitial differences between HFpEF and HFrEF

	HFpEF	HFrEF
Cardiomyocyte diameter	↑	↓
Myofibrillar density	↑	↓
Passive cardiomyocyte resting tension	↑↑	↑
Cardiomyocyte calcium sensitivity	↑↑	↑
Abnormal phosphorylation of sarcomeric proteins	↑↑	↑
Titin isoform N2BA/N2B ratio	↓	↑
Myocardial protein kinase G activity	↓	↑
Myocardial oxidative stress	↑	↔
Myocardial cyclic guanosine monophosphate concentration	↓	↑
Myocardial pro-B-type natriuretic peptide-108 expression	↔/↑	↑↑
Mysial collagen volume fraction	↑	↓
Perivascular collagen volume fraction	↑	↑↑
Scar-related collagen volume fraction	↑	↑↑
Endomyocardial MMP-1:TIMP-1 ratio	↔	↑↑
Myocardial advanced glycation end products in diabetic HF	↑	↑↑







Associations of cardiac and non-cardiac co-morbidities with heart failure

Co-morbidity	Risk factor for HF	Negative effect on LV structure/ function	Worsening of HF outcomes
Hypertension	+++	+++	HFpEF (+++) HFrEF (−/+)
Myocardial infarction	+++	+++	+++
Atrial fibrillation	+++	+++	+++
Chronic obstructive pulmonary disease	++	++	++
Anaemia/iron deficiency	++	++	++
Diabetes	++	++	++
Renal dysfunction	+++	++	++
Sleep-disordered breathing	+	++	++
Obesity	++	++	+/−
Depression	+	+	++

+++: definite; ++: probable; +: possible; +/− doubtful.
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

European Journal of Heart Failure (2016) 18, 744–758

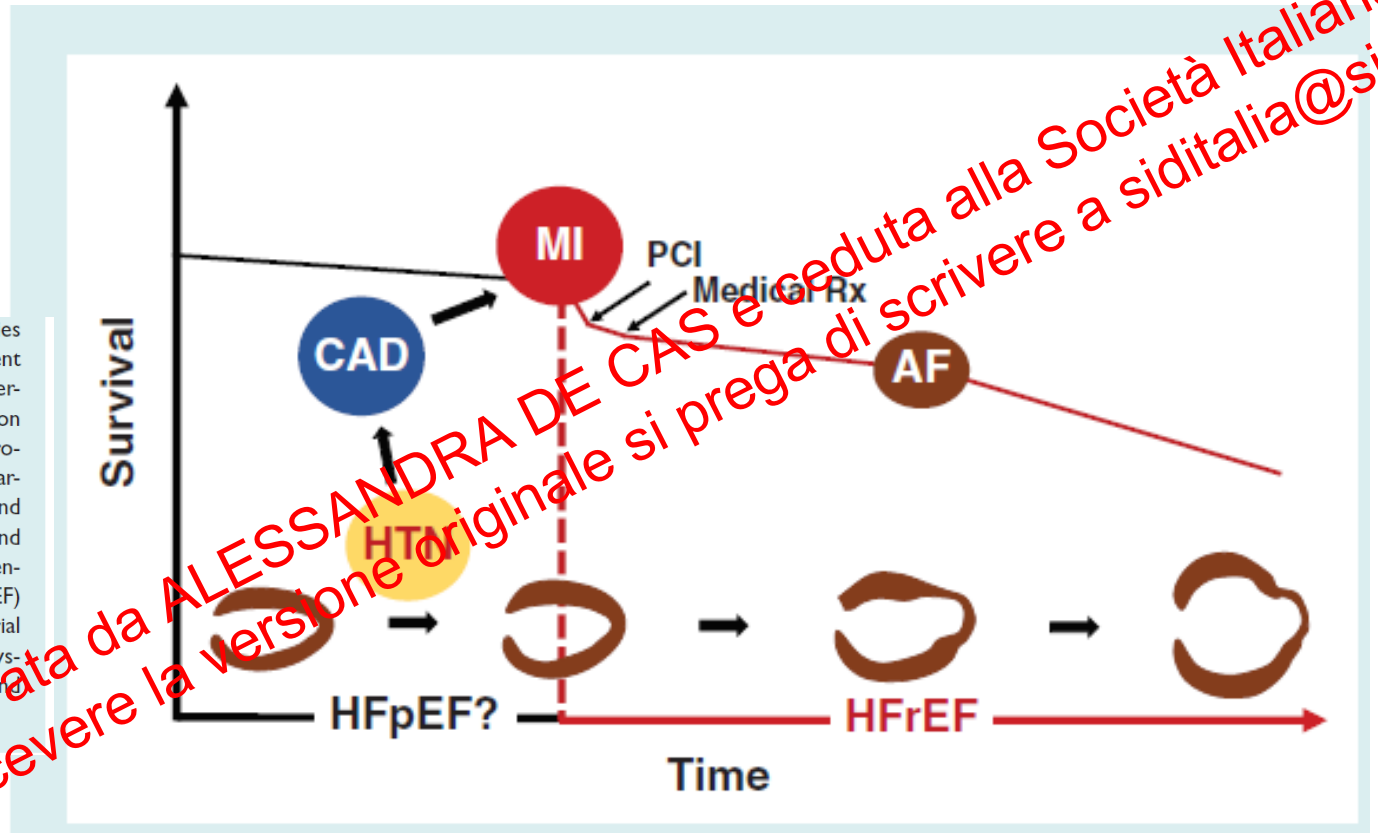
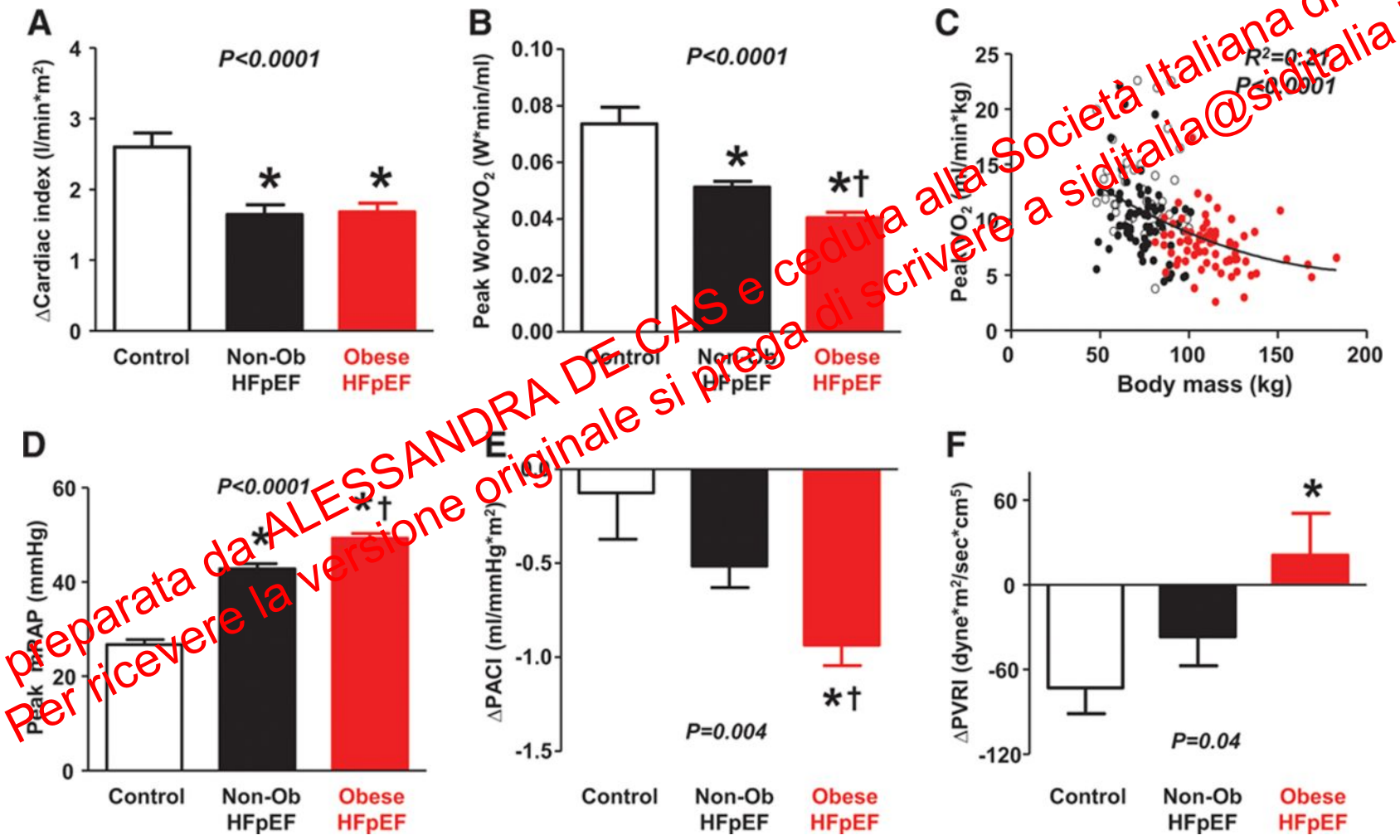


Figure 1 Example of the complex influence of co-morbidities on the pathogenesis and outcome of heart failure (HF). A patient with hypertension (HTN) develops left ventricular (LV) hypertrophy, which is a risk factor for HF with preserved ejection fraction (HFpEF). However, as HTN is also a risk factor for coronary artery disease (CAD), the patient suffers an acute myocardial infarction (MI). Following MI, primary angioplasty (PCI) and medical treatment (Medical Rx) limit myocardial damage and favourably influence prognosis. Nevertheless, eventually, eccentric LV remodelling and HF with reduced ejection fraction (HFrEF) develop. Patient prognosis is further impaired by incident atrial fibrillation (AF), which often appears in the setting of LV dysfunction and, in turn, adversely affects LV structure, function and prognosis.

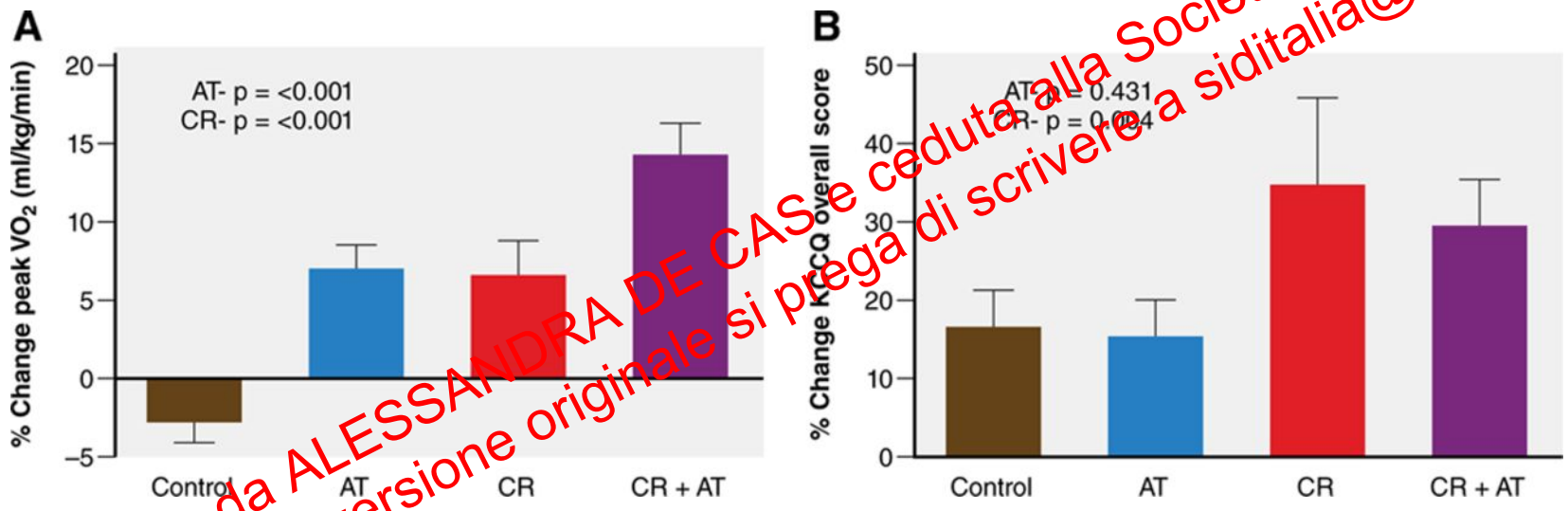
European Journal of Heart Failure (2016) 18, 744–758

Exercise capacity and hemodynamic reserve is reduced in obese heart failure with preserved ejection fraction (HFpEF).



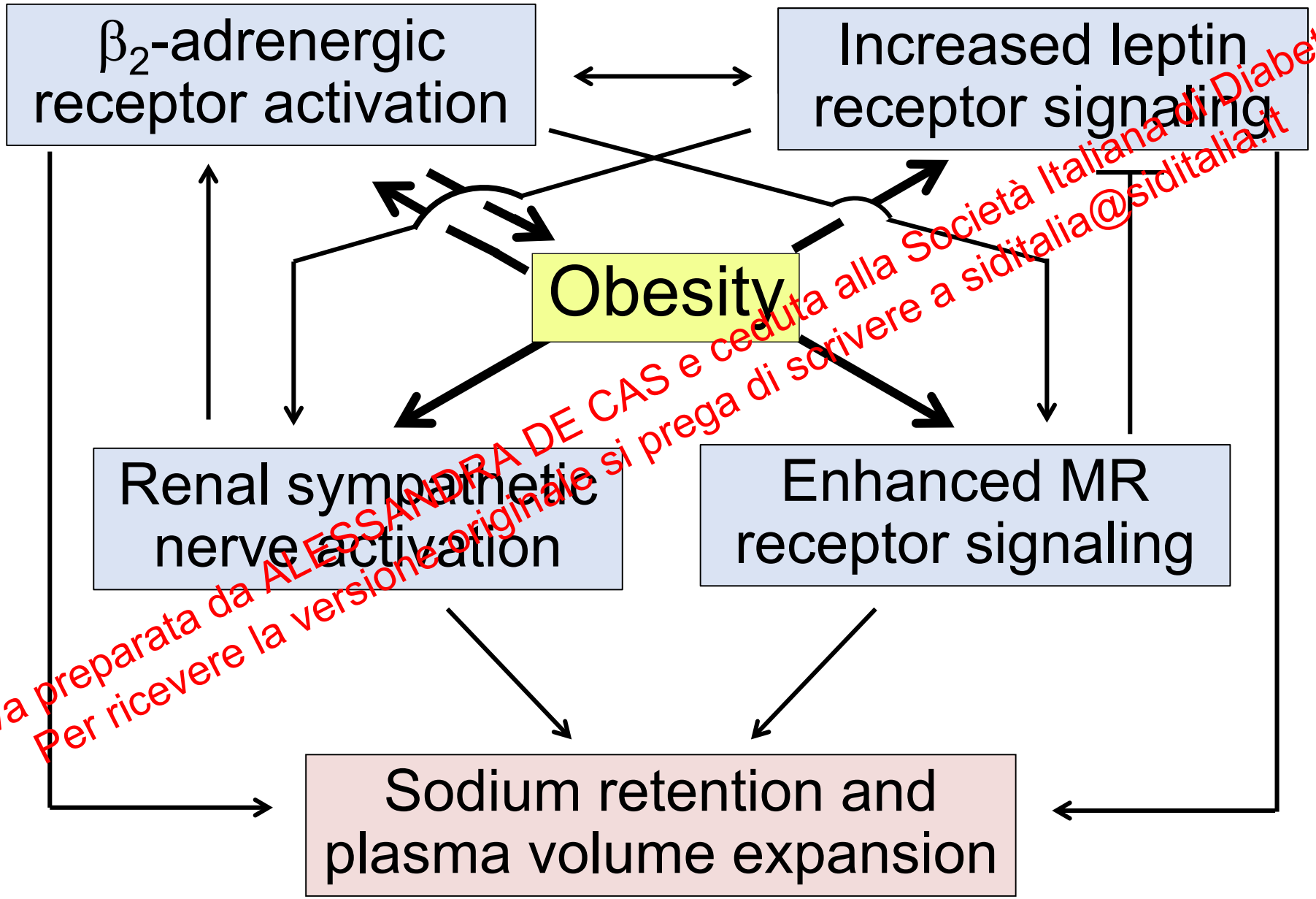
Masaru Obokata et al. Circulation. 2017;136:6-19

Effects of a 20-week caloric restriction diet on exercise capacity and quality of life in HFpEF.



AT aerobic exercise training;
CR, caloric restriction diet.

Sanjiv J. Shah et al. Circulation. 2016;134:73-90

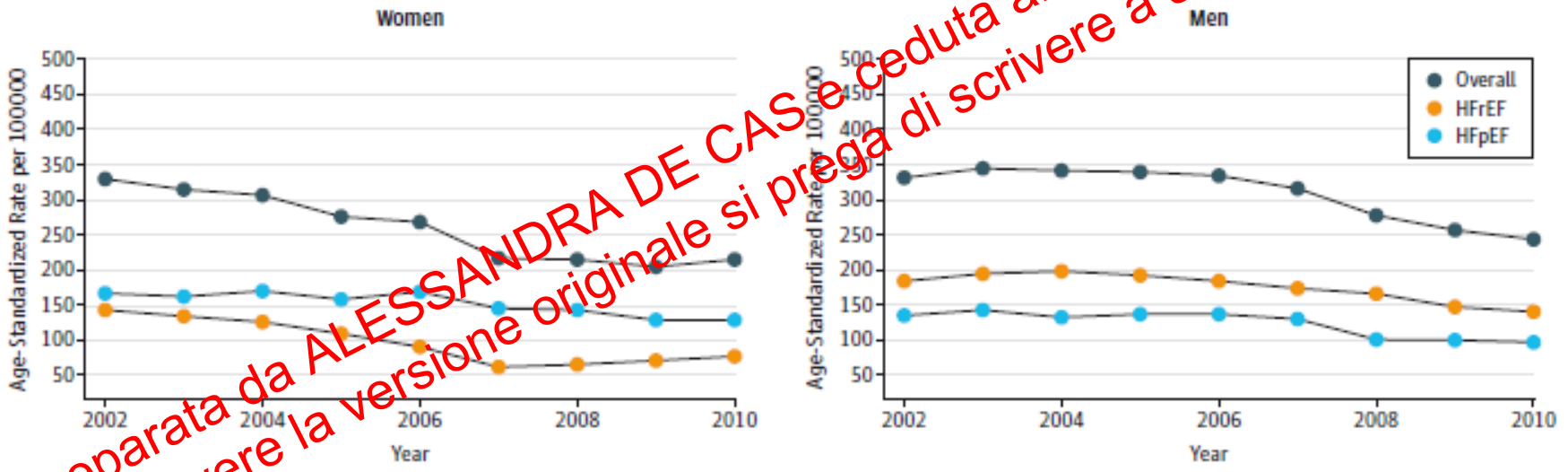


Original Investigation

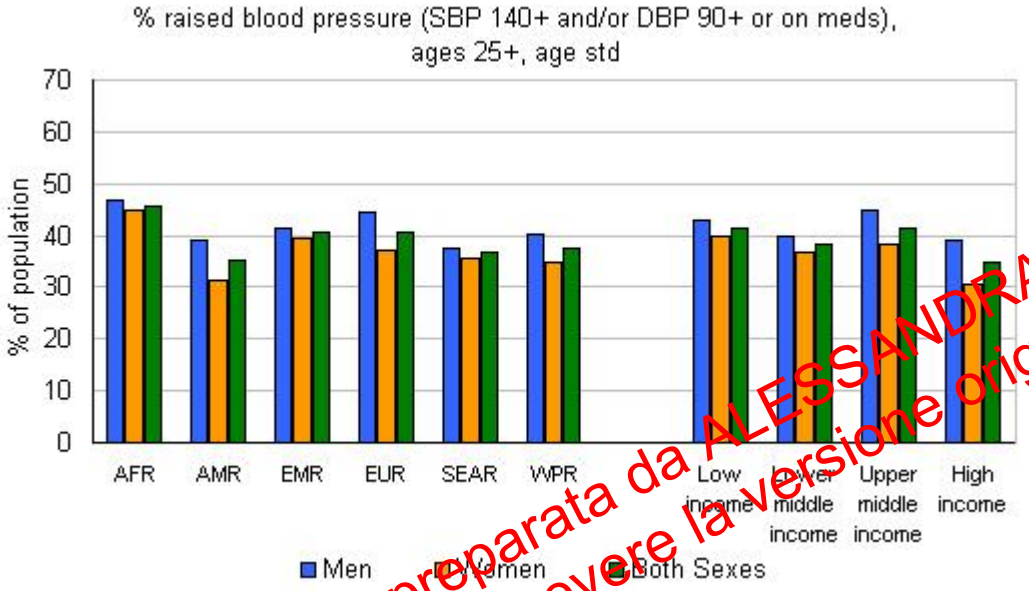
A Contemporary Appraisal of the Heart Failure Epidemic in Olmsted County, Minnesota, 2000 to 2010

Yariv Gerber, PhD; Susan A. Weston, MS; Margaret M. Redfield, MD; Alanna M. Chamberlain, PhD; Sheila M. Manemann, MPH; Ruoxiang Jiang, BS; Jill M. Killian, BS; Véronique L. Roger, MD, MPH

Figure 1. Temporal Trends in Heart Failure Incidence Rates Overall and by Reduced or Preserved Ejection Fraction Among Women and Men in Olmsted County, Minnesota, 2000 to 2010



JAMA Intern Med. 2015;175(6):996-1004. doi:10.1001/jamainternmed.2015.0924
Published online April 20, 2015.

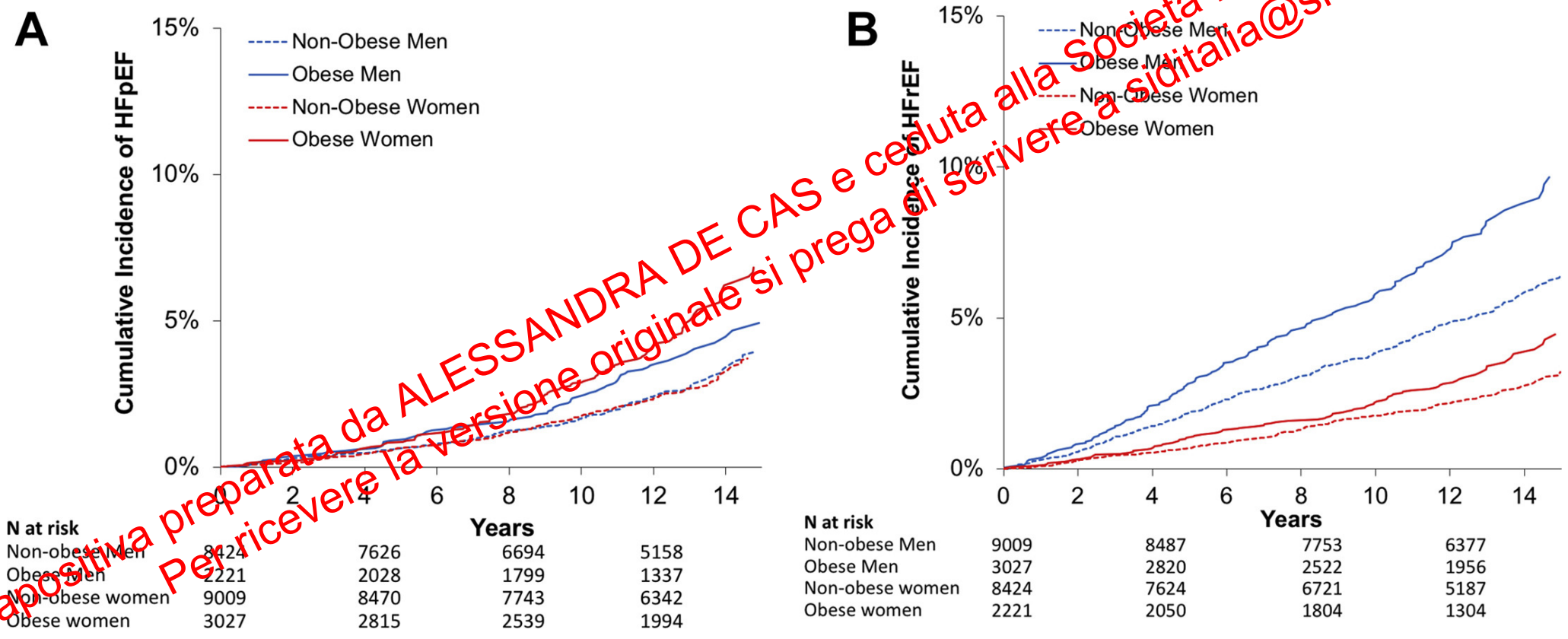


WHO 2019 data

Rank	IDF region	Age-adjusted comparative diabetes prevalence	Raw diabetes prevalence
			2017
1	North America and Caribbean	11.0% (9.2-12.5%)	13.0% (10.8-14.5%)
2	Middle East and North Africa	10.8% (7.5-14.2%)	9.6% (6.7–12.7%)
3	South-East Asia	10.1% (7.9-12.8%)	8.5% (6.5–10.7%)
4	Western Pacific	8.6% (7.6-11.0%)	9.5% (8.4–12.0%)
5	South and Central America	7.6% (6.3-9.5%)	8.0% (6.7–9.8%)
6	Europe	6.8% (5.4-9.9%)	8.8% (7.0–12.0%)
7	Africa	4.4% (2.9-7.8%)	3.3% (2.1–6.0%)

IDF regions ranked by prevalence (%) of diabetes (20-79 years) per region 2017

Type 2 diabetes and hypertension coprevalent or correlated?



JACC: Heart Failure Volume 6, Issue 8, August 2018, Pages 701-709

Type 2 diabetes and hypertension coprevalent or correlated?

	CANVAS (n=10,142)	EMPAREG (n=5700)	DECLARE	CARMELINA	HARMONY		
History of hypertension — no. (%)	9125 (90.0)	4446 (94.9)	(81.3% on ARBS or ACEi	91.2	87%		
History of heart failure — no. (%)		10.5	852 (9.9) 872 (10.2)	26.4	20%		
Cardiovascular death or hospitalization for heart failure rate/1000 patient-yr			14.7		2·92		
Hospitalization for heart failure		14.5	8.5	3.04			
Death from any cause		28.6	16,4	4.80	2·56		

Table 3 Prevalence of type 2 diabetes mellitus in selected trials of heart failure

Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM-HF[31]	35%
SHIFT[32]	30%
EchoCRT[33]	41%
HF-ACTION[34]	32%
SENIORS[35]	26%
SOLVD[36]	15%
MERIT-HF[37]	25%
CHARM-Added[38]	29%
DIG-REF[39]	28%
Trials of HFpEF	
I-Preserve[40]	27%
PEP-CHF[41]	21%
DIG-PEF[42]	29%
CHARM-Preserved[43]	28%
TOPCAT[44]	33%
Trials of acute HF	
EVEREST[45]	39%
TRUE-AHF[46]	39%
ASCEND-HF[47]	42.6%
RELAX-AHF-2[48]	47%

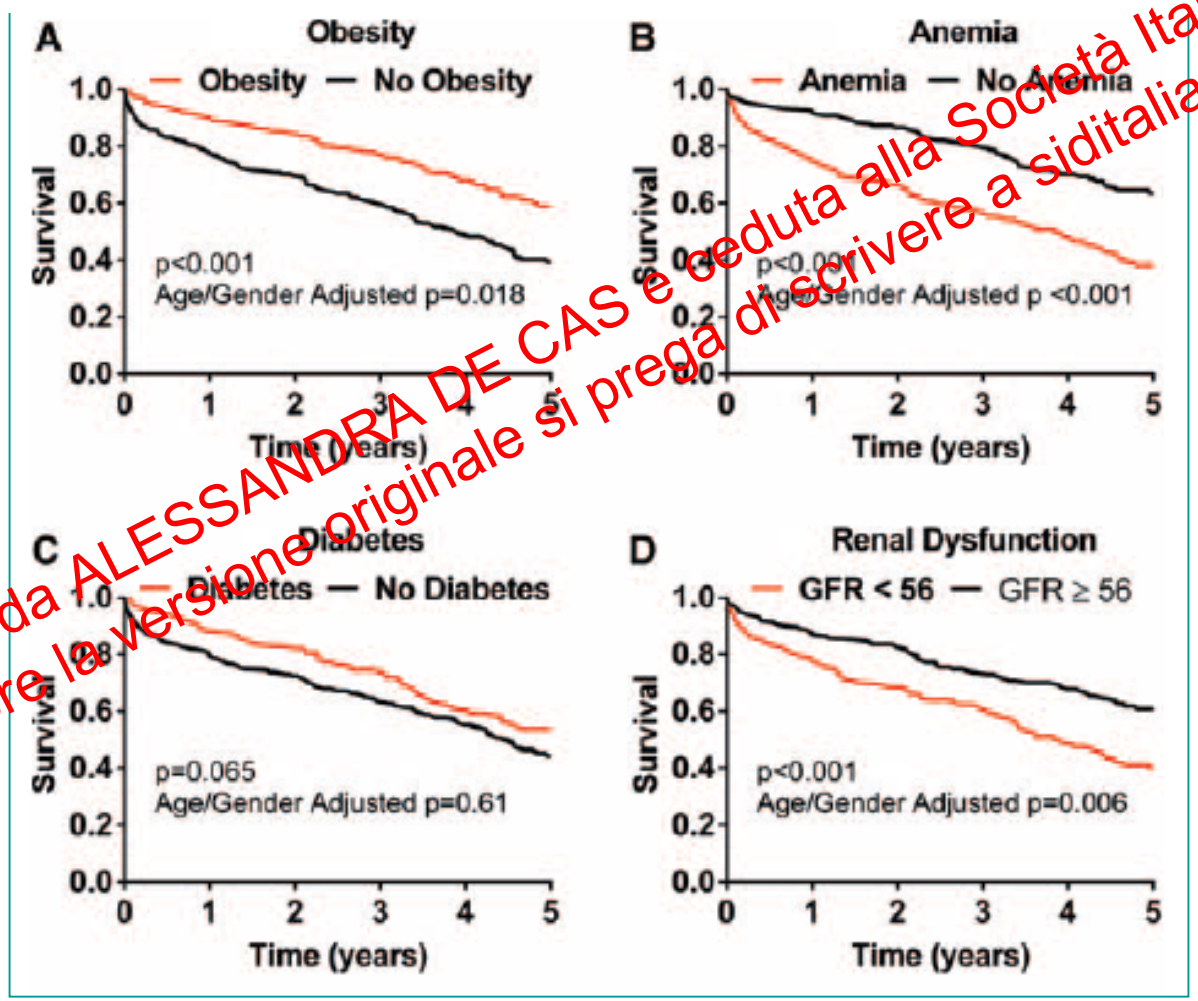
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

Large outcome trials and registries all revealed HFpEF patients to be of advanced age and predominantly women and to have multiple comorbidities such as overweight/ obesity (84%),15 arterial hypertension (60%–80%),16 type 2 diabetes mellitus (20%–45%),16 renal insufficiency, and sleep apnea.

Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure With Preserved Ejection Fraction

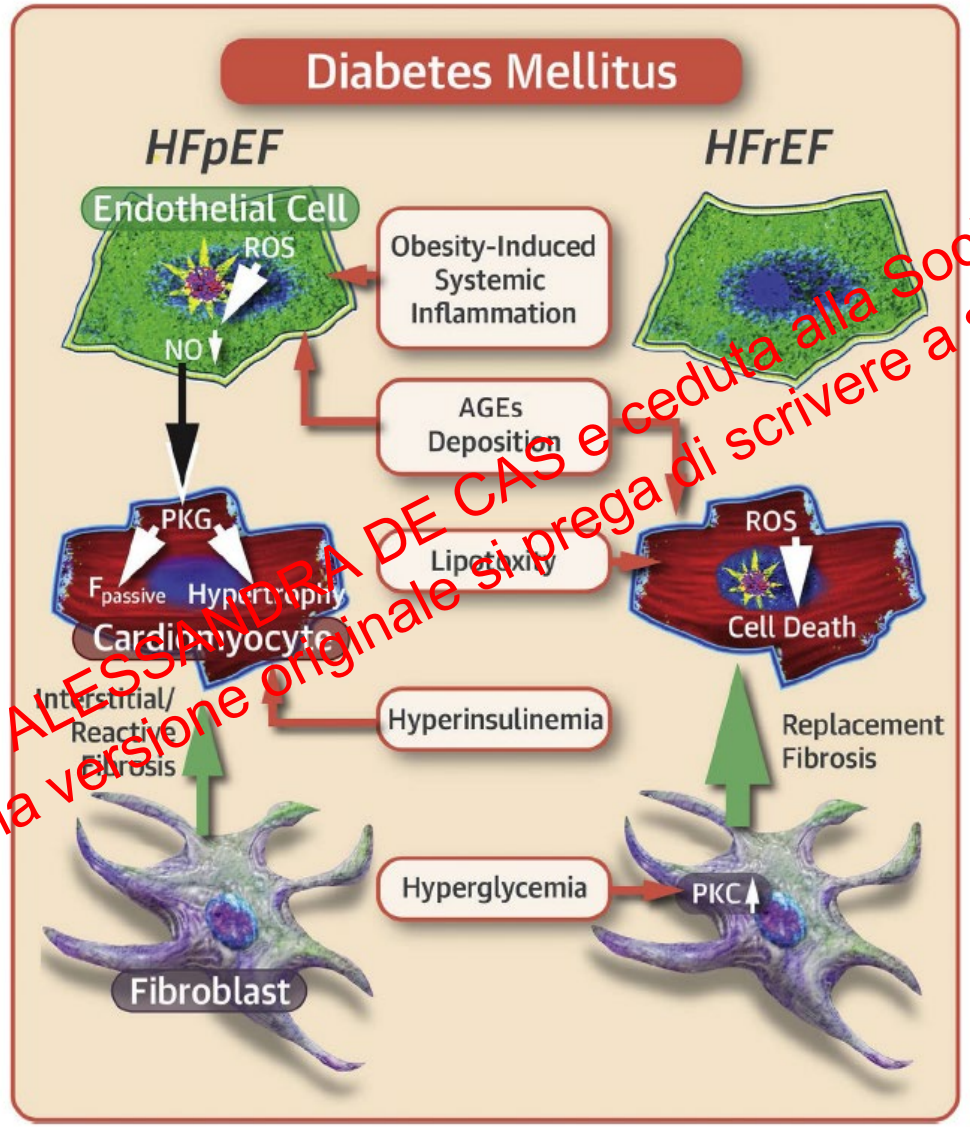
A Community-Based Study

Selma F. Mohammed, MBBS; Barry A. Borlaug, MD; Véronique L. Roger, MD, MPH; Sultan A. Mirzoyev; Richard J. Rodeheffer, MD; Julio A. Chirinos, MD; Margaret M. Redfield, MD



Circ Heart Fail . 2012 November ; 5(6): 710–719

Distinct cell-type myocardial injury in HFpEF and HFrEF



Paulus, W.J. et al. J Am Coll Cardiol HF. 2018;6(1):1-7.

European Heart Journal (2016) **37**, 463–465
doi:10.1093/eurheartj/ehv561

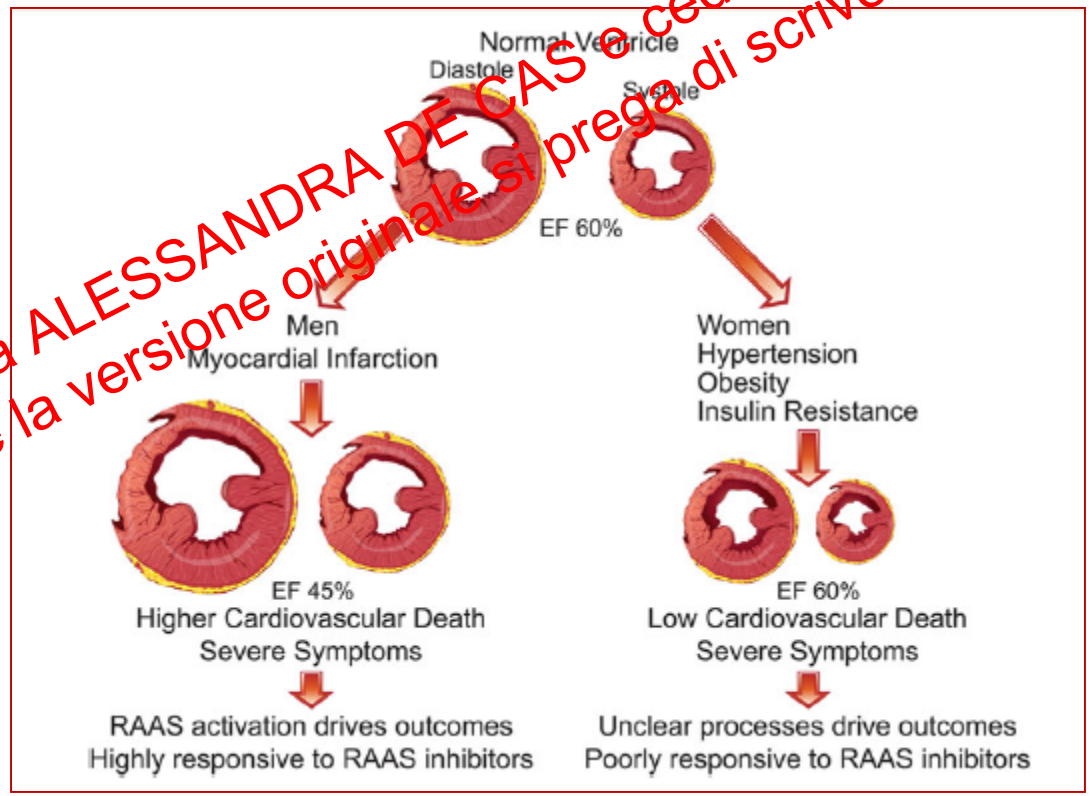
EDITORIAL

Defining HFpEF: where do we draw the line?

Barry A. Borlaug*

The Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic Rochester, MN, USA

Online publish-ahead-of-print 3 November 2015

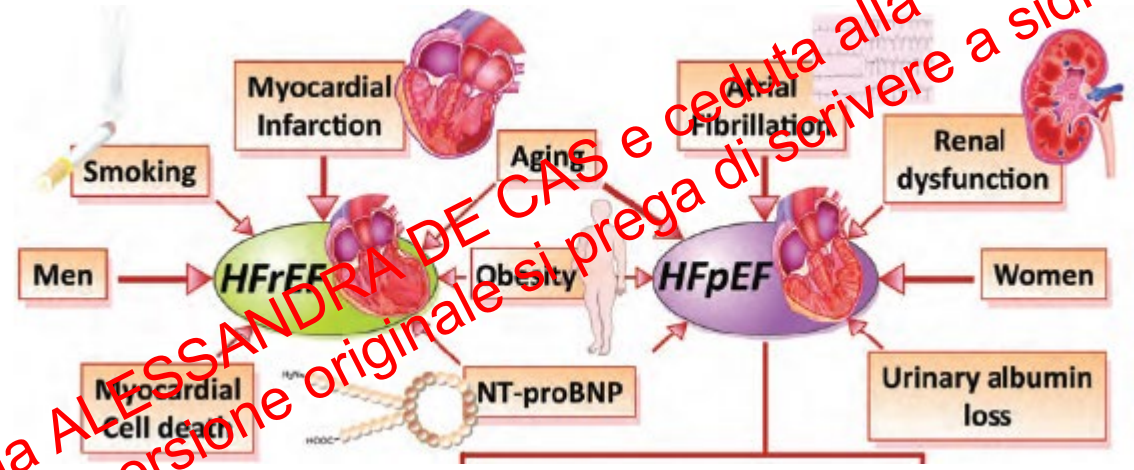


European Heart Journal (2013) **34**, 1393–1395
doi:10.1093/eurheartj/eht117

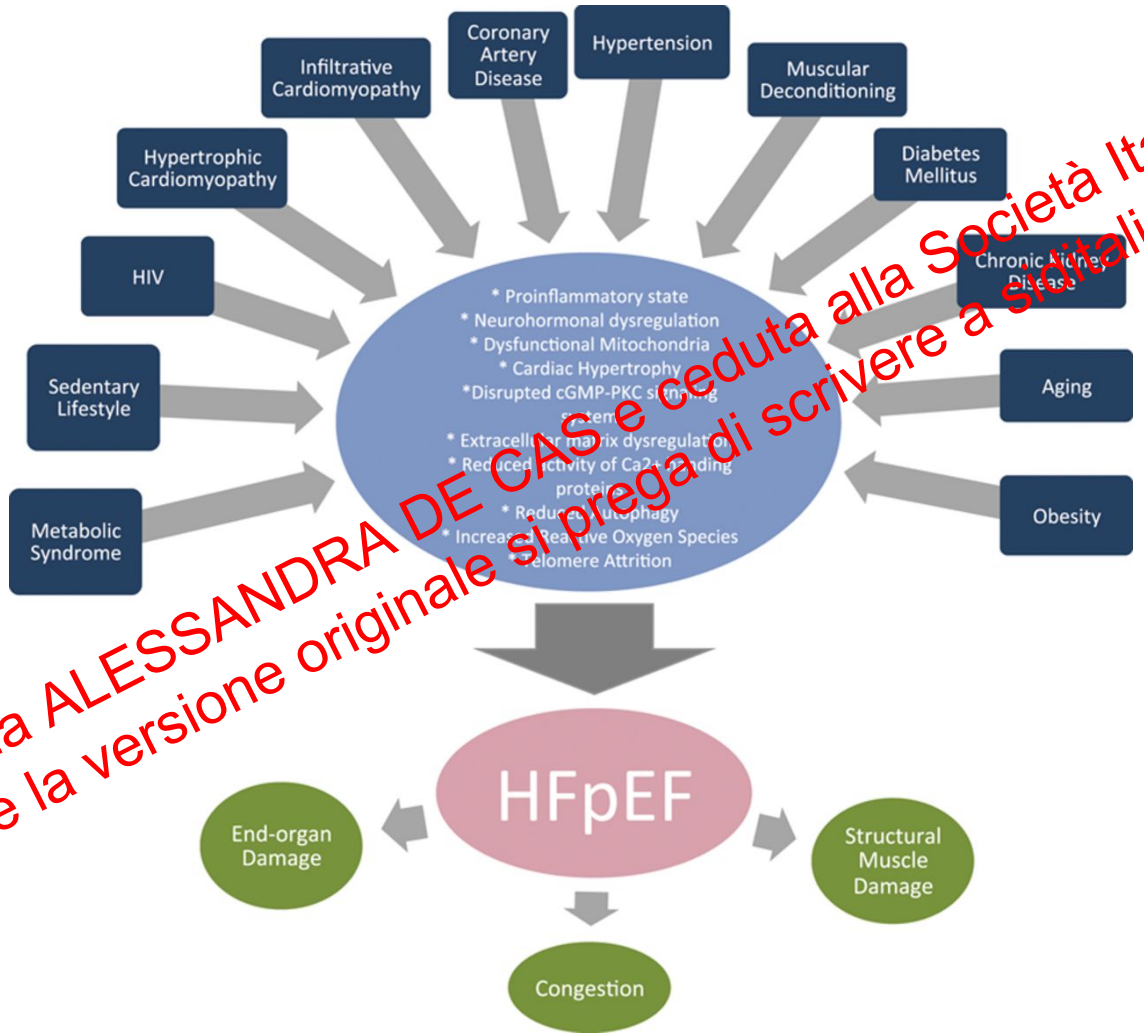
EDITORIAL

Heart failure with preserved and reduced ejection fraction: different risk profiles for different diseases

Barry A. Borlaug*



Variable pathophysiological mechanisms for heart failure with preserved ejection fraction (HFpEF).



Javed Butler et al. Circ Heart Fail. 2016;9:e003358

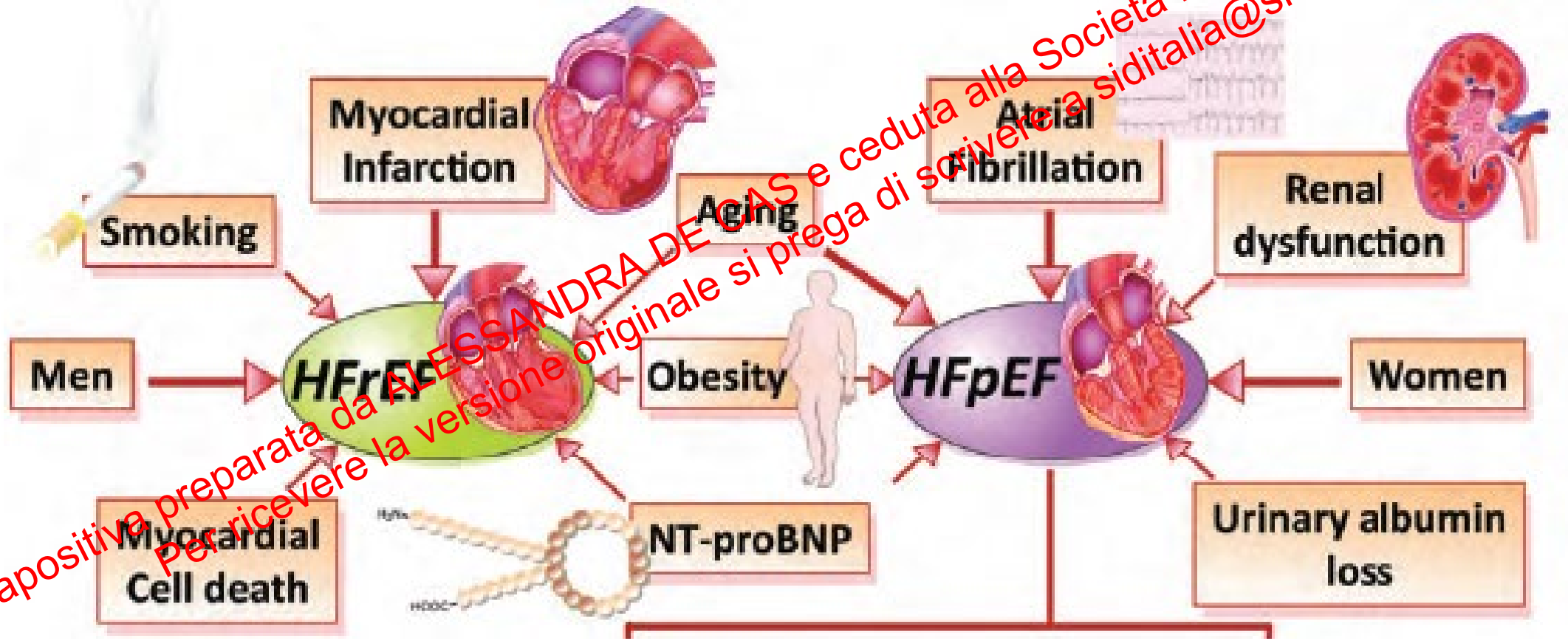
Incidence and epidemiology of new onset heart failure with preserved *vs.* reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND (n=8592)

	Adjusted for age and sex		Mutually adjusted[a]		HFrEF	HFpEF	P^{b}_{cr}
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	HR (95% CI)	
Age (per 10 years)	–	–	1.81 (1.47–2.24)	<0.001	1.61 (1.24–2.09)	2.63 (1.93–3.30)	0.018
Males	–	–	1.48 (1.03–2.13)	0.035	2.45 (1.49–3.99)	0.56 (0.31–1.01)	<0.001
Obesity	1.93 (1.37–2.73)	<0.001	1.62 (1.10–2.37)	0.014	–	–	0.750
Heart rate (per 5 b.p.m.)	1.05 (0.98–1.13)	0.155					
Hypertension	1.99 (1.37–2.89)	<0.001	1.17 (0.77–1.77)	0.458	–	–	0.288
Myocardial infarction	3.45 (2.38–4.99)	<0.001	2.27 (1.54–3.34)	<0.001	2.77 (1.73–4.43)	1.25 (0.64–2.45)	0.058
Smoking or quit smoking <1 year	1.31 (0.96–1.79)	0.087	1.24 (0.87–1.77)	0.228	1.51 (0.96–2.36)	0.80 (0.46–1.41)	0.086
Atrial fibrillation	2.64 (1.23–5.66)	0.013	1.10 (0.55–2.19)	0.787	0.42 (0.19–0.93)	3.79 (1.64–8.77)	<0.001
Diabetes mellitus	2.41 (1.51–3.85)	<0.001	1.66 (0.99–2.78)	0.056	–	–	0.794
Hypercholesterolaemia (mmol/L)	1.65 (1.21–2.26)	0.002	1.34 (0.95–1.88)	0.096	–	–	0.713
Log Creatinine (per doubling)	1.00 (0.84–1.20)	0.973					
eGFR >60 mL/min/kg	1.07 (0.66–1.74)	0.782					
Log Cystatine C (per doubling)	1.43 (1.23–1.68)	<0.001	1.08 (0.94–1.24)	0.295	0.98 (0.86–1.11)	1.45 (1.03–2.04)	0.033
Log UAE (per doubling)	1.35 (1.22–1.50)	<0.001	1.01 (0.91–1.14)	0.798	0.96 (0.84–1.09)	1.21 (0.98–1.48)	0.061
Log hs-C-reactive protein (per doubling)	1.41 (1.17–1.70)	<0.001	1.14 (0.92–1.41)	0.228	–	–	0.230
Log NT-proBNP (per doubling)	2.11 (1.79–2.49)	<0.001	1.68 (1.39–2.04)	<0.001	1.85 (1.42–2.41)	1.35 (1.06–1.72)	0.082
Log hs-TnT (per doubling)	1.67 (1.51–1.86)	<0.001	1.33 (1.17–1.52)	<0.001	1.38 (1.18–1.60)	1.10 (0.90–1.36)	0.091

European Heart Journal 2013;34:1424-31

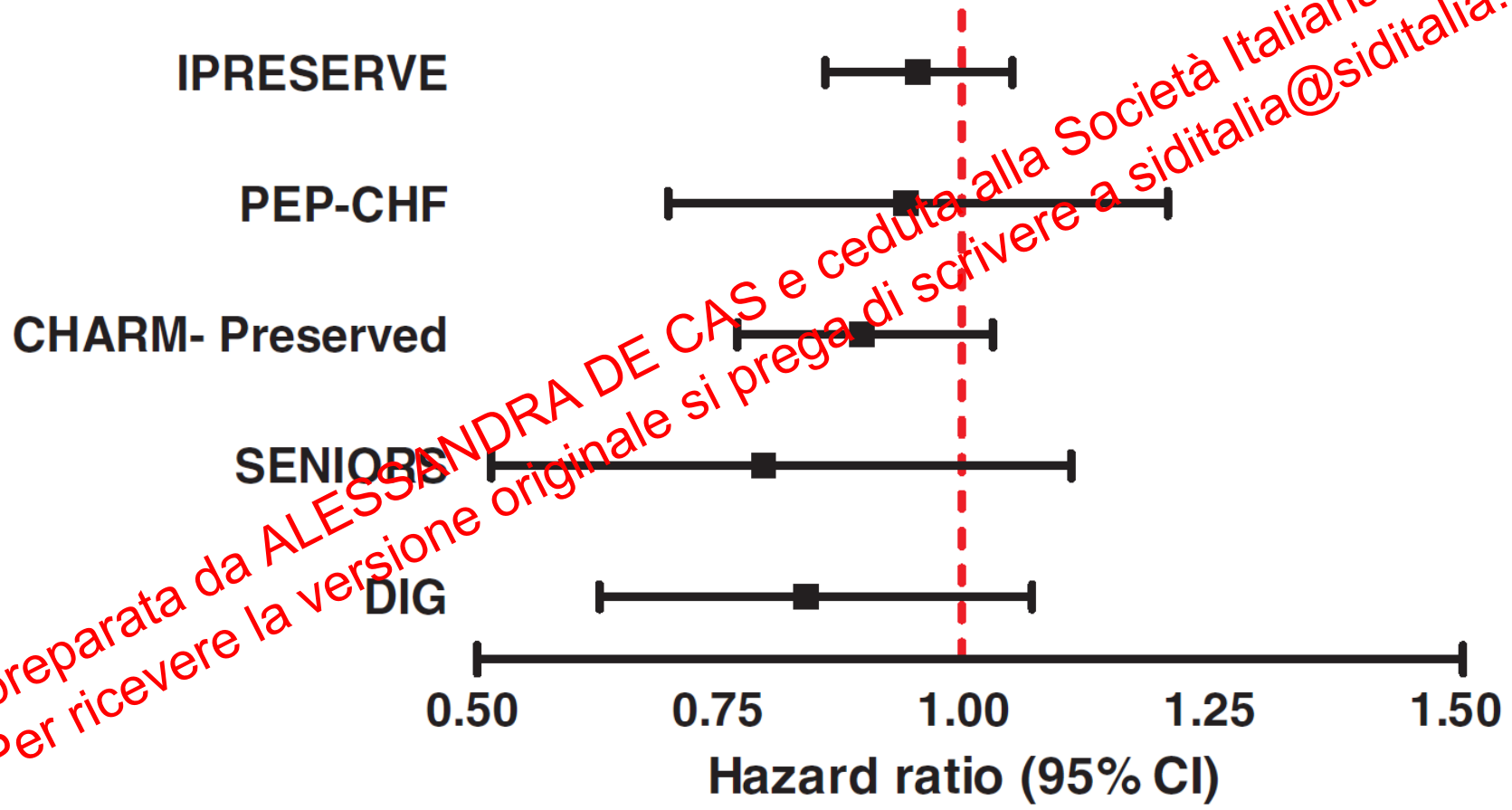
Incidence and epidemiology of new onset heart failure with preserved *vs.* reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND

	Adjusted for age and sex		Mutually adjusted[a]		HFrEF	HFpEF	P^{b}_{cr}
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	HR (95% CI)	



European Heart Journal 2013;34:1424-31

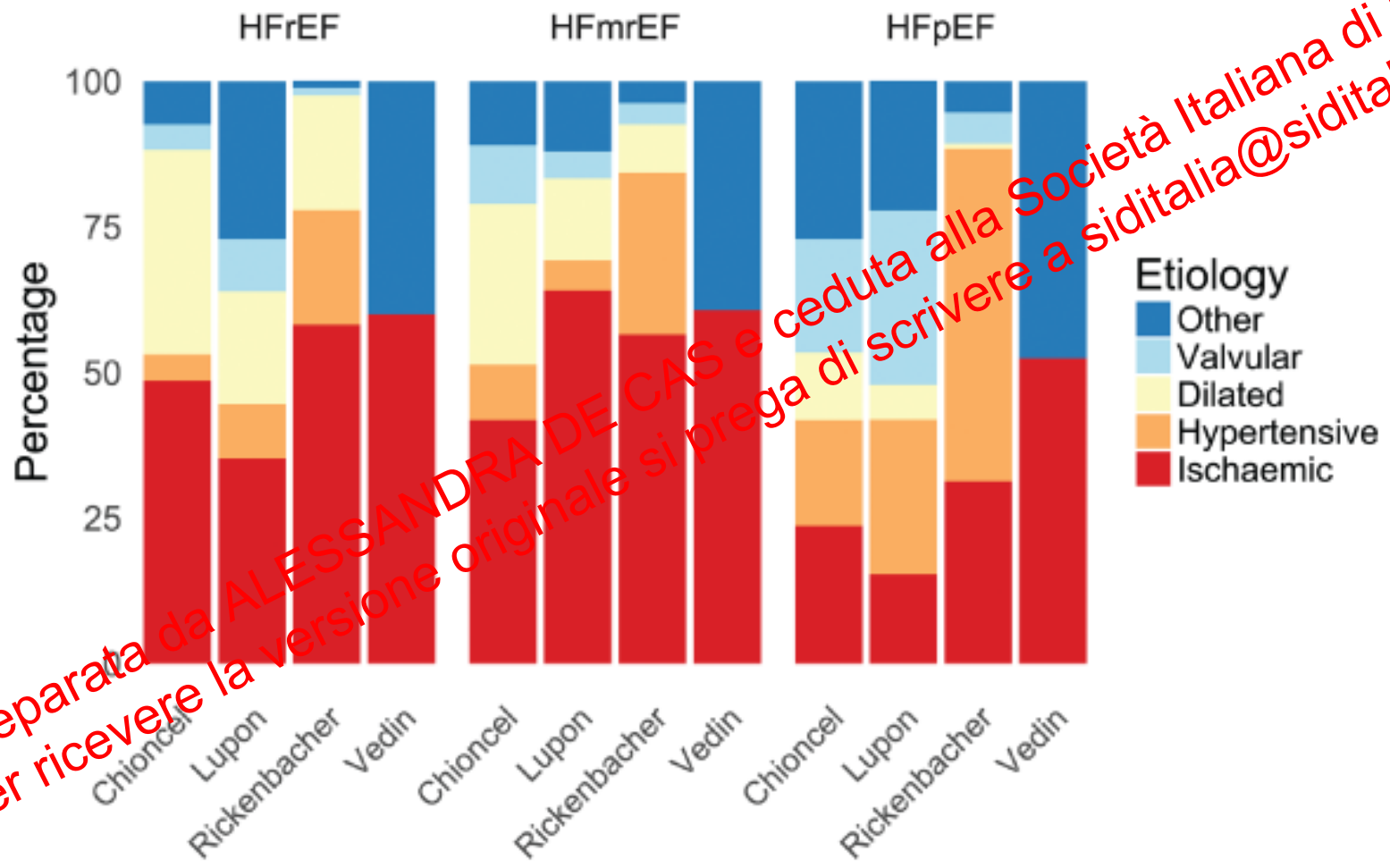
Large trials in HFpEF – no benefit



CI=confidence interval

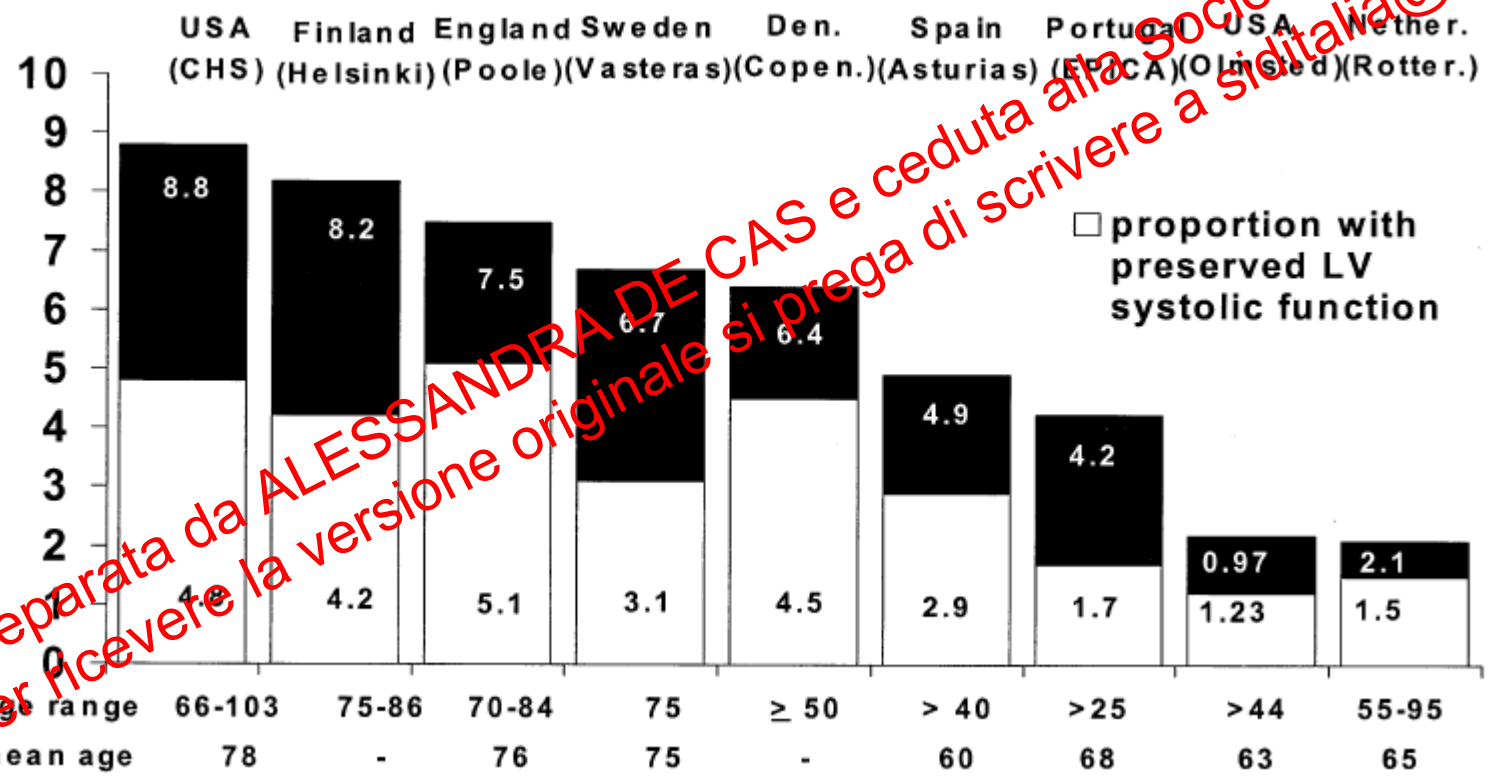
Redfield MM, et al. Circ Heart Fail 2012;5;653–9

Hypertensive and ischaemic aetiologies for heart failure with reduced (HFrEF), mid-range (HFmrEF), and preserved ejection fraction (HFpEF) in recent studies.



Nauta et al European Journal of Heart Failure; 2017;19:1569-1573

Prevalence of HF in cross-sectional, population-based, echocardiographic studies



JACC Vol. 43, No. 3,2004:317–27

Original Investigation

A Contemporary Appraisal of the Heart Failure Epidemic in Olmsted County, Minnesota, 2000 to 2010

Yariv Gerber, PhD; Susan A. Weston, MS; Margaret M. Redfield, MD; Alanna M. Chamberlain, PhD; Sheila M. Manemann, MPH; Ruoxiang Jiang, BS; Jill M. Killian, BS; Véronique L. Roger, MD, MPH

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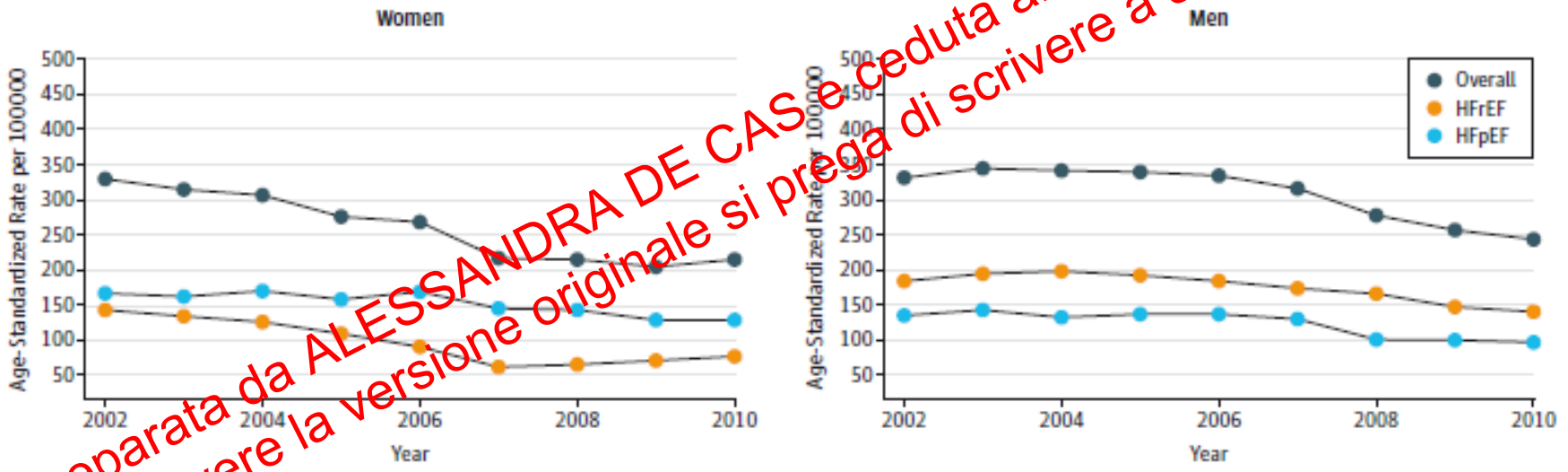

JAMA Intern Med. 2015;175(6):996-1004. doi:10.1001/jamainternmed.2015.0924
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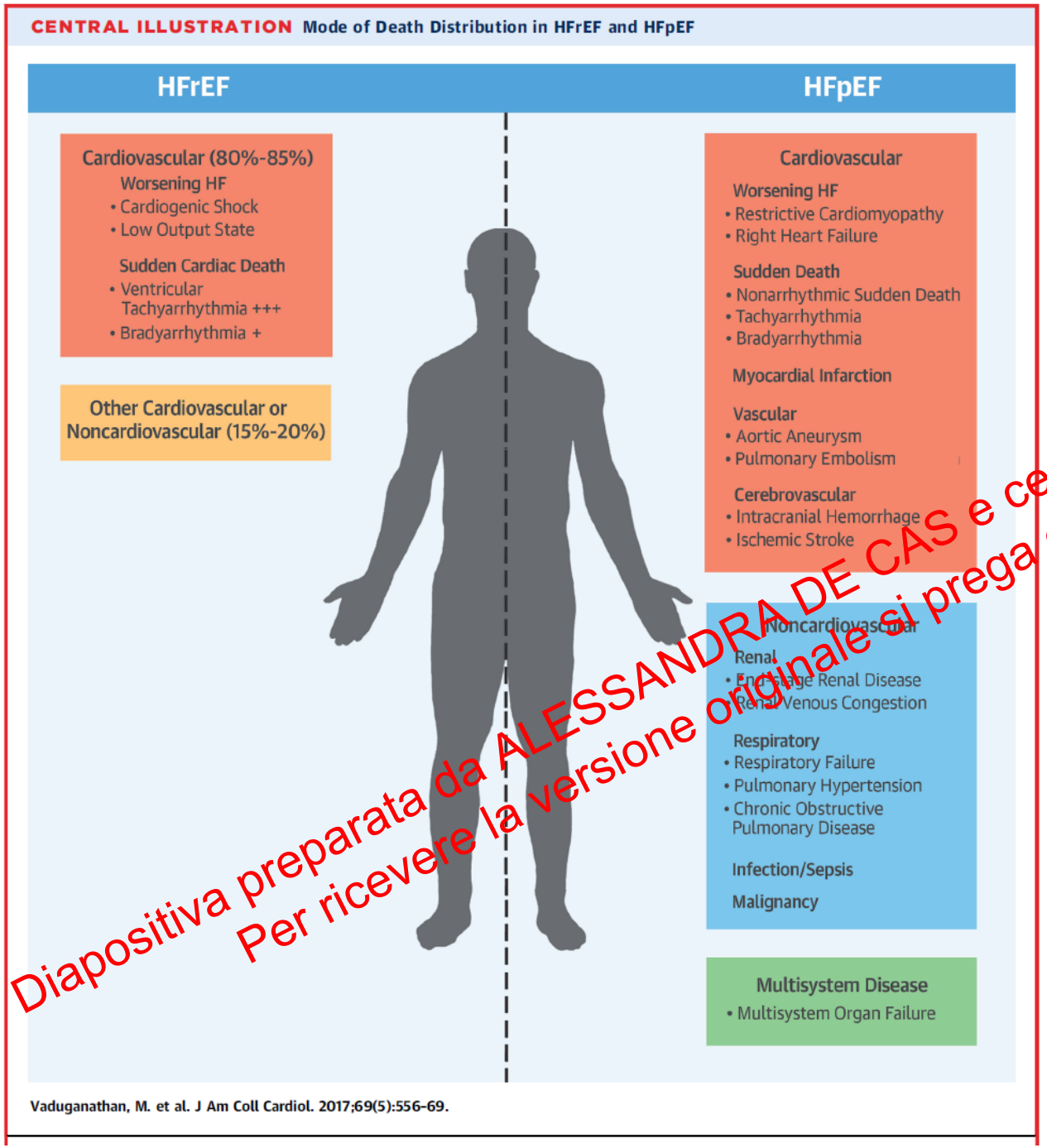


Vaduganathan, M. et al. J Am Coll Cardiol. 2017;69(5):556–69.

European Heart Journal (2012) **33**, 1750–1757
doi:10.1093/eurheartj/ehr254

The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

Received 18 March 2011; revised 30 May 2011; accepted 4 July 2011; online publish-ahead-of-print 6 August 2011

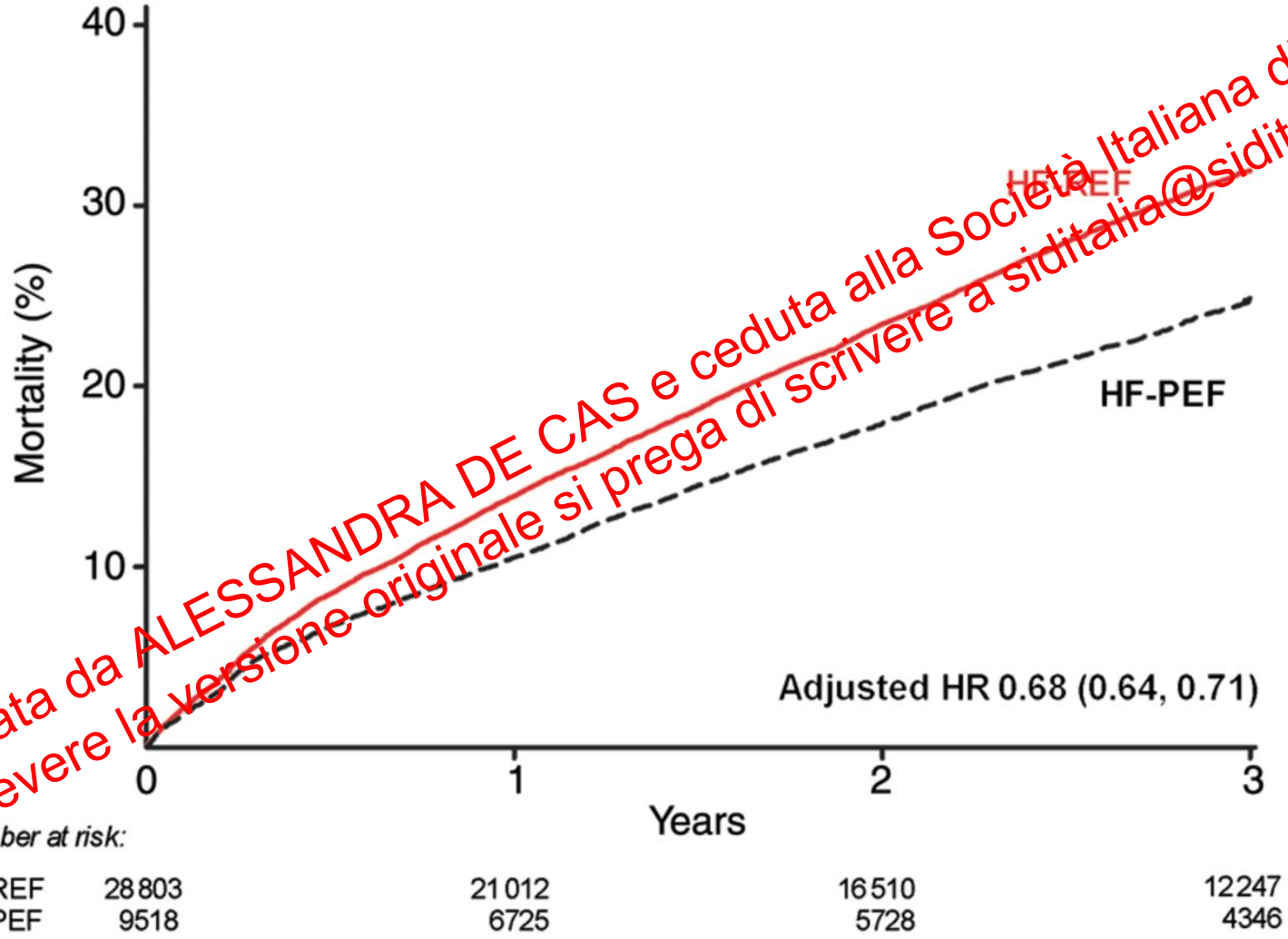
See page 1718 for the editorial comment on this article (doi:10.1093/eurheartj/ehr339)

Aims A substantial proportion of patients with heart failure have preserved left ventricular ejection fraction (HF-PEF). Previous studies have reported mixed results whether survival is similar to those patients with heart failure and reduced EF (HF-REF).

Methods and results We compared survival in patients with HF-PEF with that in patients with HF-REF in a meta-analysis using individual patient data. Preserved EF was defined as an EF ≥ 50%. The 31 studies included 41 972 patients: 10 347 with HF-PEF and 31 625 with HF-REF. Compared with patients with HF-REF, those with HF-PEF were older (mean age 71 vs. 66 years), were more often women (50 vs. 28%), and have a history of hypertension (51 vs. 41%). Ischaemic aetiology was less common (43 vs. 59%) in patients with HF-PEF. There were 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in those with HF-PEF and 141 (95% CI: 138, 144) deaths per 1000 patient-years in those with HF-REF. Patients with HF-PEF had lower mortality than those with HF-REF (adjusted for age, gender, aetiology, and history of hypertension, diabetes, and atrial fibrillation); hazard ratio 0.68 (95% CI: 0.64, 0.71). The risk of death did not increase notably until EF fell below 40%.

Conclusion Patients with HF-PEF have a lower risk of death than patients with HF-REF, and this difference is seen regardless of age, gender, and aetiology of HF. However, absolute mortality is still high in patients with HF-PEF highlighting the need for a treatment to improve prognosis.

Mortality for patients with HF-PEF (heart failure with preserved left ventricular ejection fraction) and HF-REF (heart failure with low left ventricular ejection fraction), adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.



Mortality data adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.

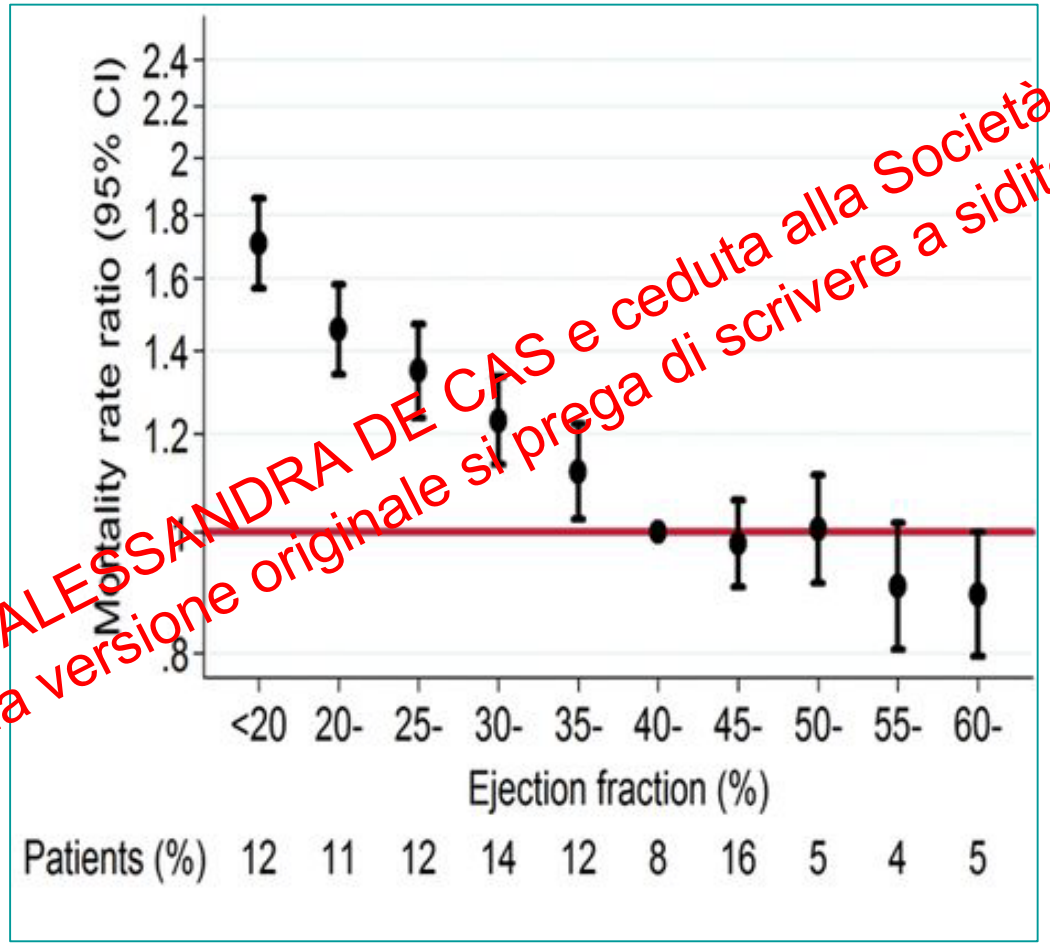
Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) Eur Heart J 2012;33:1750-1757

Cox's proportional adjusted hazards ratios for all-cause death and cardiovascular death

Variable	Death from any cause Hazard ratio (95% CI)	Cardiovascular death Hazard ratio (95% CI)
HF-PEF	0.66 (0.64, 0.71)	0.55 (0.49, 0.61)
Male gender	1.23 (1.18, 1.28)	1.23 (1.14, 1.33)
Age (years)	1.04 (1.04, 1.04)	1.03 (1.03, 1.04)
Ischaemic aetiology	1.07 (1.02, 1.12)	1.11 (1.03, 1.19)
Hypertension	0.93 (0.89, 0.97)	0.94 (0.88, 1.00)
Diabetes	1.41 (1.35, 1.47)	1.51 (1.41, 1.62)
Atrial fibrillation	1.10 (1.05, 1.16)	1.28 (1.16, 1.41)

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) Eur Heart J 2012;33:1750-1757

Mortality rate ratios (and 95% CIs) for each LVEF category



Pocock S J et al. Eur Heart J 2013;34:1404-1413

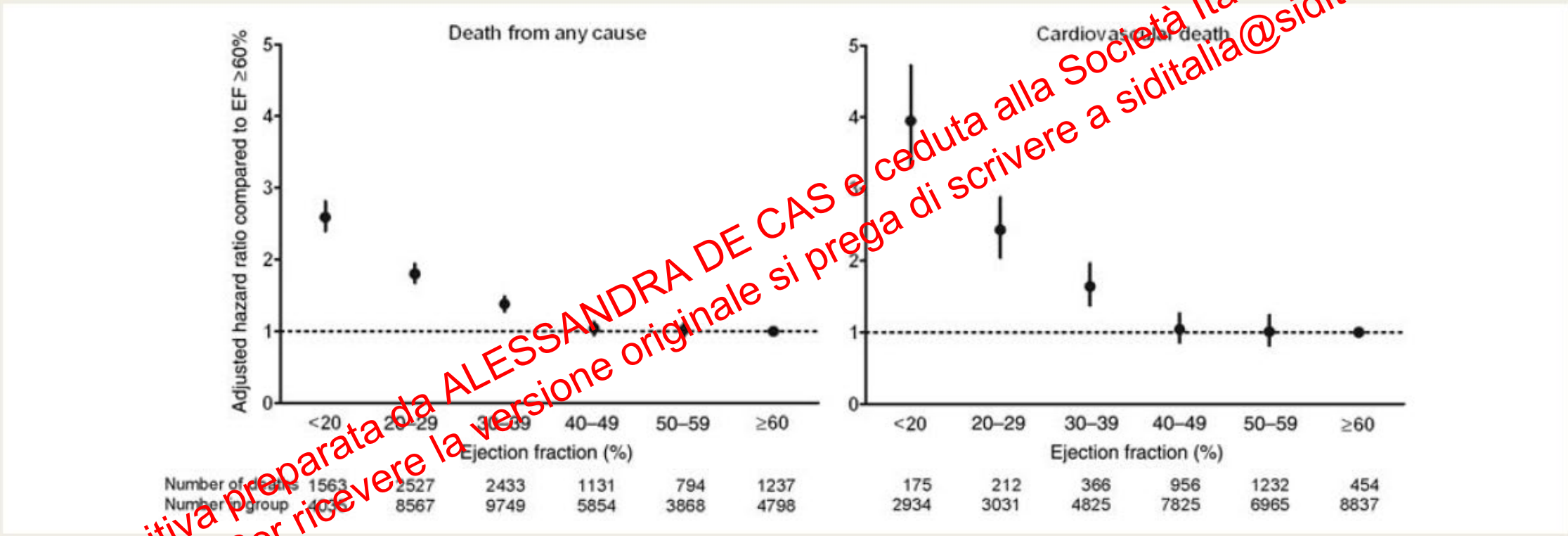
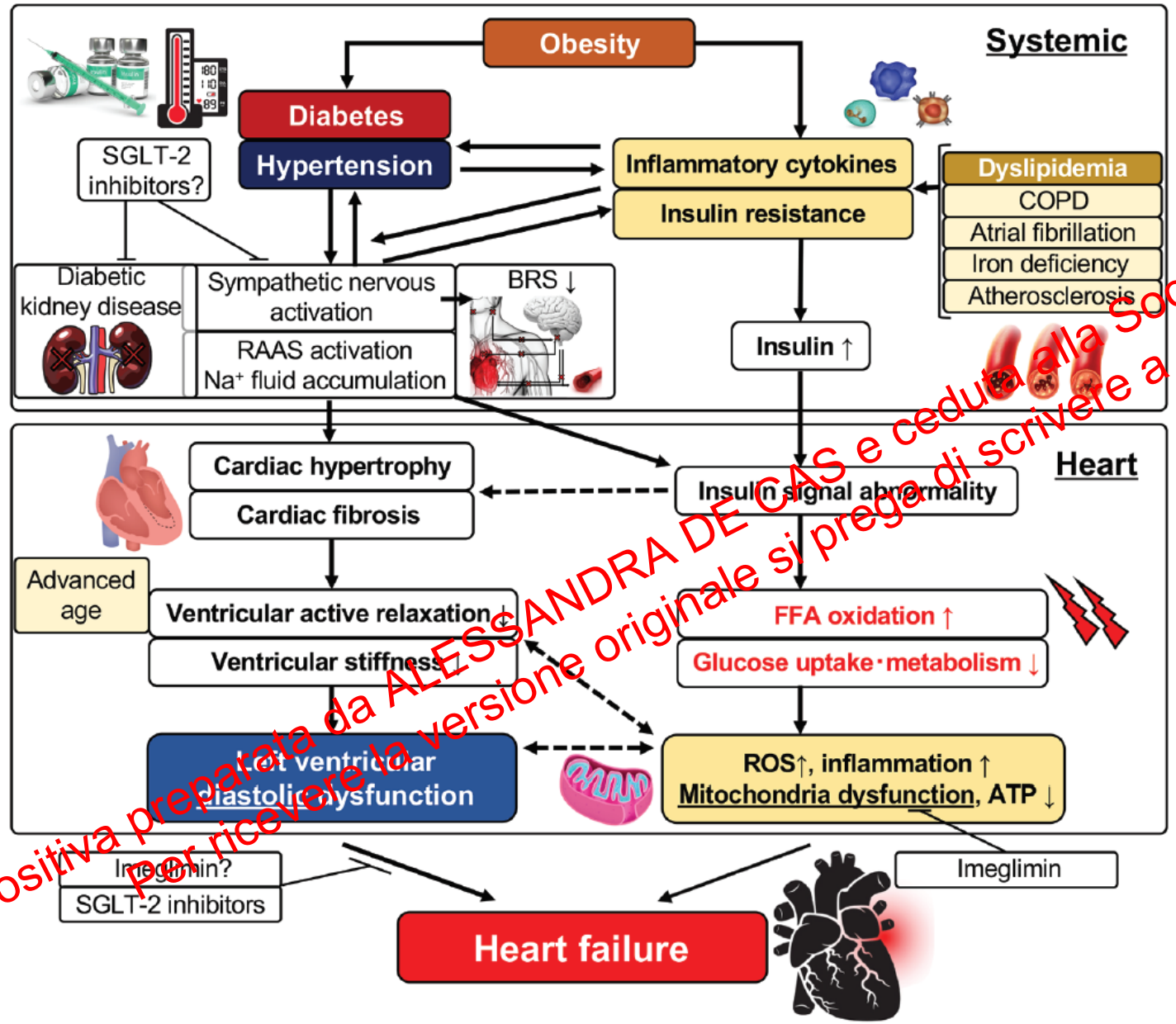


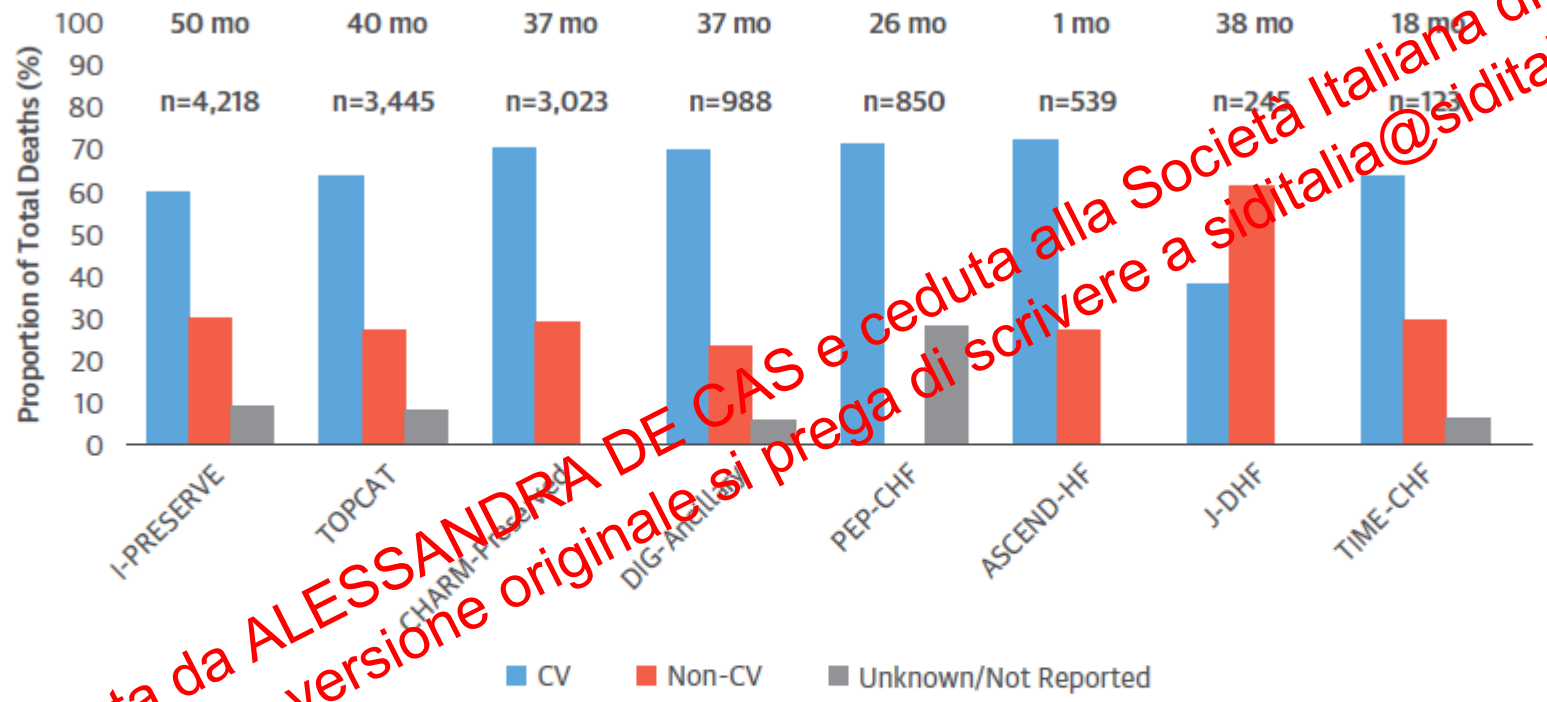
Figure 3 Adjusted hazard ratios comparing death from any cause and cardiovascular death by groups of left ventricular ejection fraction (with LVEF ≥ 60% as the reference group).



J Clin Med Res. 2018;10(11):799-805

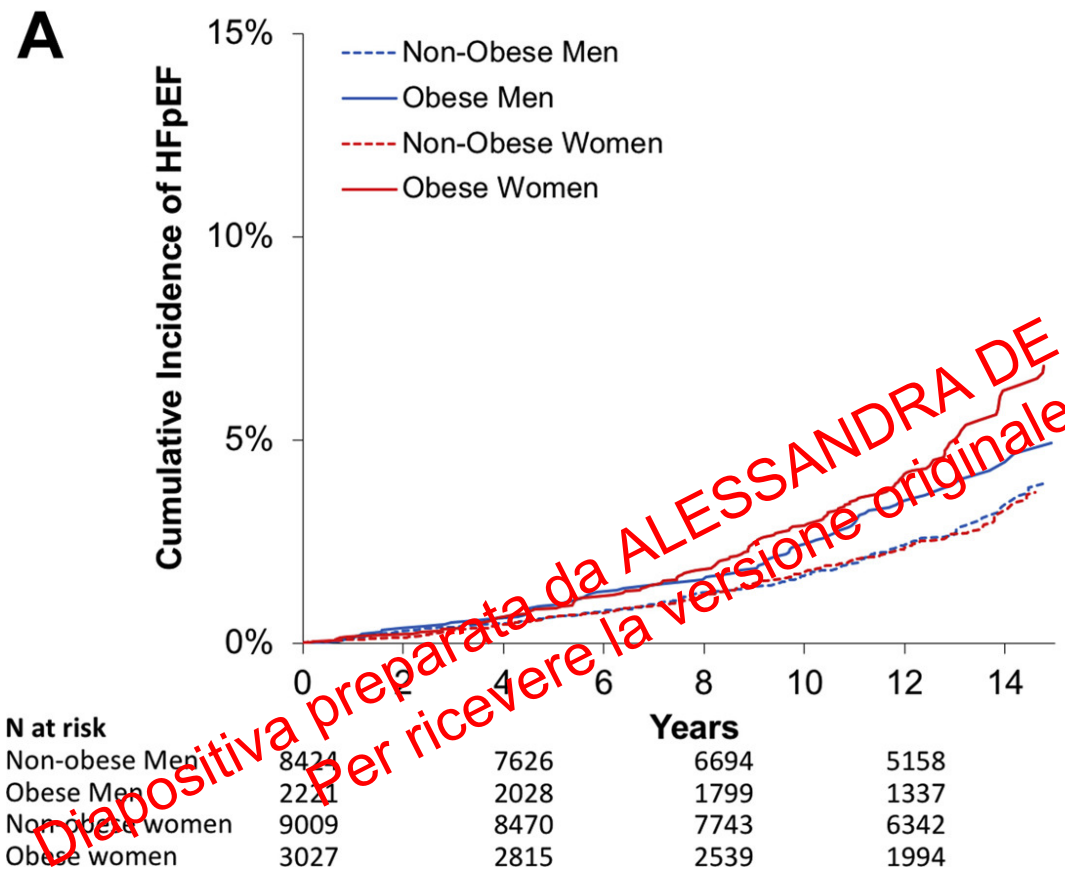
Alteration	Underlying mechanisms	Effects	Structural features	Functional features
↑ FFA concentration	↑ FFA uptake ↓ GLUT4 and glucose uptake ↑ PPARα activation	↑ FFA oxidation ↓ Glucose oxidation	Normal LV size, wall thickness, and mass	Diastolic dysfunction
	Accumulation of TG and DAG	Cardiolipotoxicity		
↑ Mitochondrial dysfunction	Alteration of mitochondrial protein	↓ ATP production	Normal LV size, wall thickness, and mass	Diastolic dysfunction
	↓ Mitochondrial oxidative capacity	↓ Mitochondrial energetic metabolism		
↓ Ca^{2+} homeostasis	↓ Release of Ca^{2+} from the SR ↓ SERCA activity by oxidative stress ↓ Myofilament Ca^{2+} sensitivity	↓ Cardiac contractility	Substructural changes in myocytes	Diastolic dysfunction
↑ PKC activation	↓ NO availability	↑ Endothelial dysfunction	Myocellular hypertrophy and fibrosis	Diastolic dysfunction and normal or slightly decreased EF
	↑ ET-1 production Stimulates CTGF expression	↑ Cell permeability ↑ Cardiac fibrosis		
↑ AGE formation	Cross-link formation between AGEs and proteins	Fibrosis ↑ Myocardial stiffness ↓ Myocardial relaxation	Myocellular hypertrophy and fibrosis Slightly increased LV mass, wall thickness, or size	Diastolic dysfunction and normal or slightly decreased EF
	AGE/RAGE binding stimulates ↑ TGFβ production ↑ ROS production	Oxidative stress Inflammation		
↑ Activation of RAS	↑ Production of AngII	↑ Myocyte apoptosis ↑ Interstitial fibrosis Oxidative stress Inflammation	Myocellular hypertrophy and fibrosis	Increase in LV mass, wall thickness, or size

FIGURE 2 Proportion of CV vs. Non-CV Deaths in RCTs of HFpEF

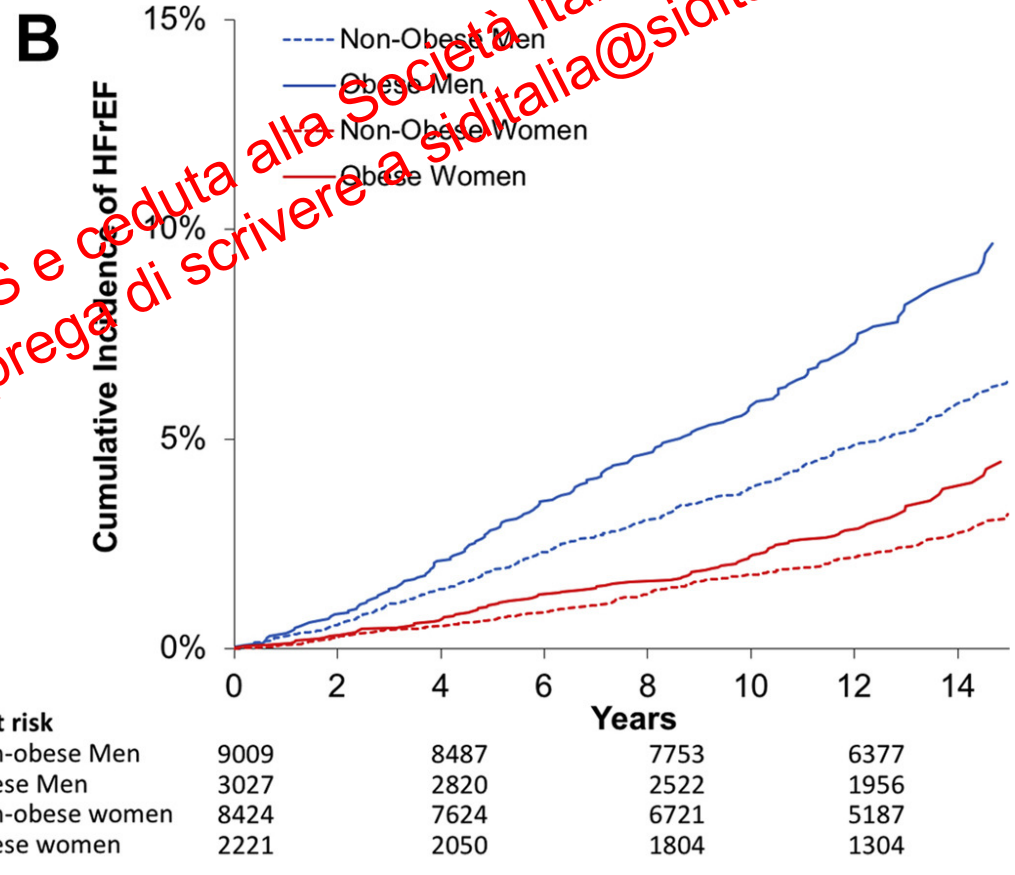


The average duration of follow-up and total number of HFpEF patients enrolled in each trial are provided. ASCEND-HF = Acute Studies of Nesiritide in Decompensated Heart Failure; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CV = cardiovascular; DIG = Digitalis Investigation Group; HFpEF = heart failure with preserved ejection fraction; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; J-DHF = Japanese Diastolic Heart Failure; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; RCT = randomized controlled study; TIME-CHF = Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

Cumulative Incidence of HF Subtypes Among Obese and Nonobese Men and Women in 22,681 participants from 4 community-based cohorts



N at risk				
Non-obese Men	8424	7626	6694	5158
Obese Men	2221	2028	1799	1337
Non-obese women	9009	8470	7743	6342
Obese women	3027	2815	2539	1994



N at risk				
Non-obese Men	9009	8487	7753	6377
Obese Men	3027	2820	2522	1956
Non-obese women	8424	7624	6721	5187
Obese women	2221	2050	1804	1304

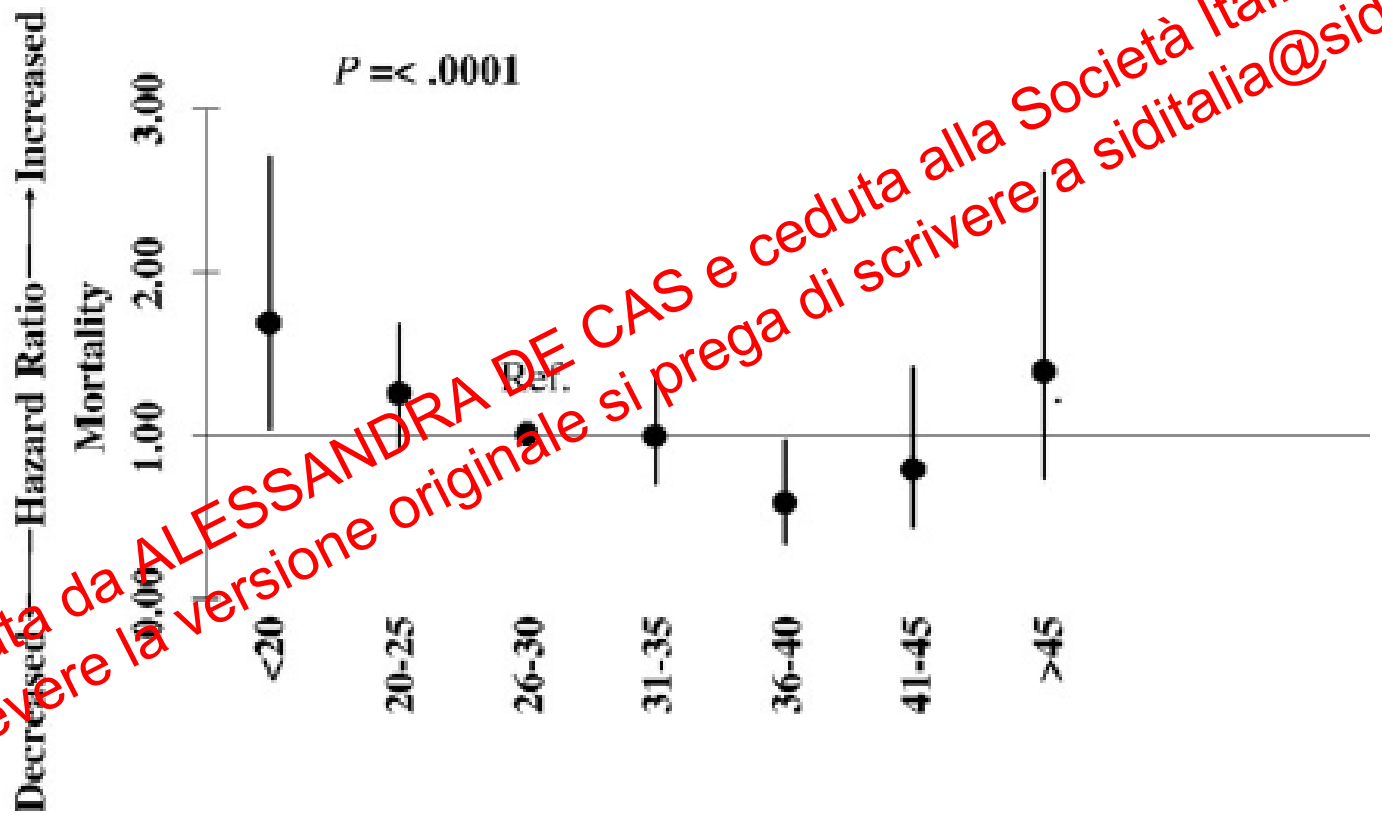
J Am Coll Cardiol HF 2018

Association of obesity-related traits with HF subtypes

Predictor	Outcome	Multivariable-Adjusted HR (95% CI)	p Value
BMI	Incident HFpEF	1.34* (1.24-1.45)	<0.0001
	Incident HFrEF	1.18 (1.10-1.27)	<0.0001
WC	Incident HFpEF	1.32 (1.22-1.44)	<0.0001
	Incident HFrEF	1.19 (1.10-1.29)	<0.0001
WHR	Incident HFpEF	1.19 (1.10-1.29)	<0.0001
	Incident HFrEF	1.14 (1.06-1.22)	0.001
HOMA-IR	Incident HFpEF	1.20* (1.05-1.37)	0.006
	Incident HFrEF	0.99 (0.88-1.11)	0.81
TG/HDL ratio	Incident HFpEF	1.06 (0.96-1.17)	0.27
	Incident HFrEF	1.13 (1.04-1.23)	0.003
Fasting glucose	Incident HFpEF	1.15 (1.08-1.23)	<0.0001
	Incident HFrEF	1.07 (0.99-1.16)	0.08
SBP	Incident HFpEF	1.20 (1.11-1.20)	<0.0001
	Incident HFrEF	1.19 (1.11-1.27)	<0.0001

J Am Coll Cardiol HF 2018

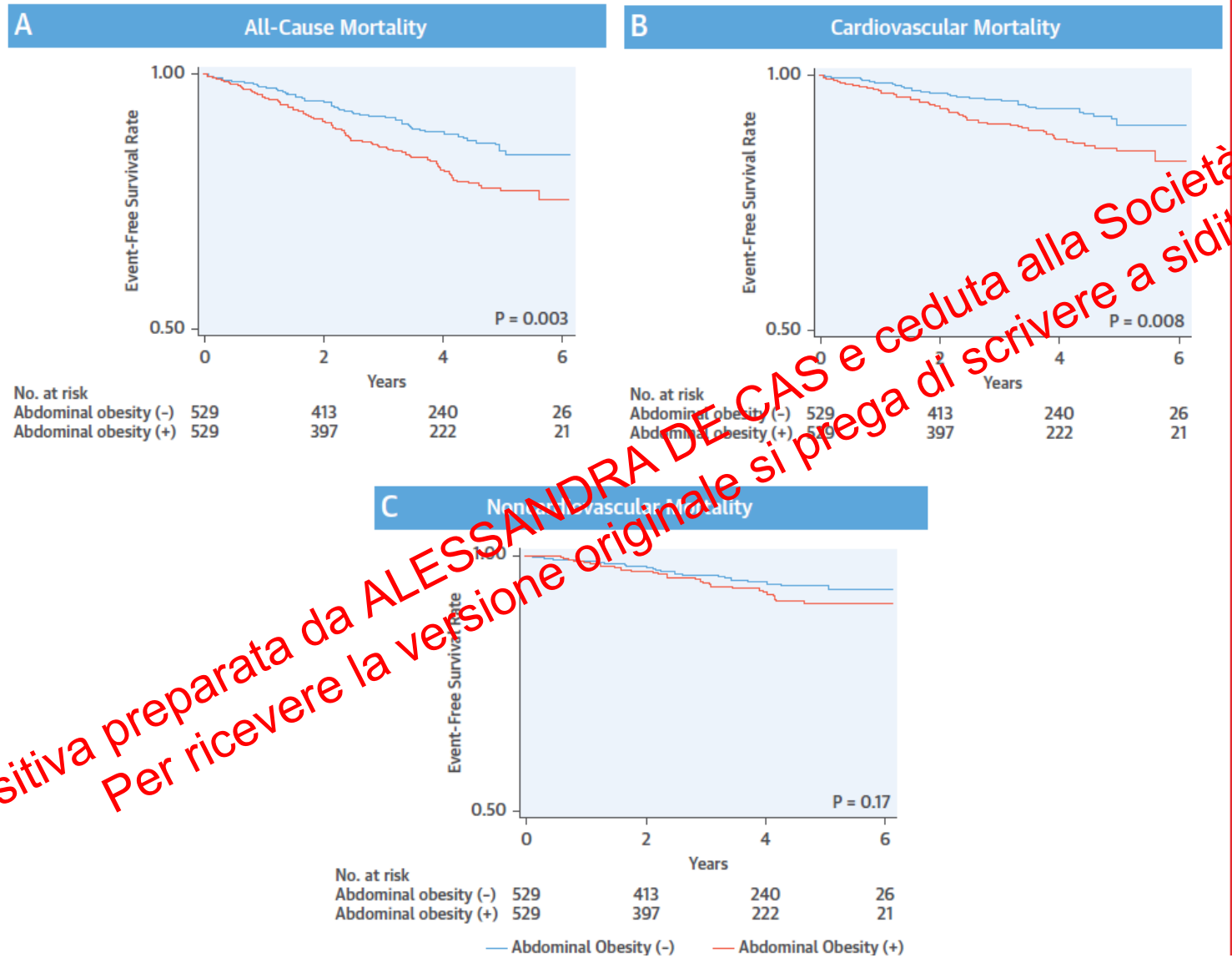
Hazard ratios for mortality by BMI in 1,236 patients with a HFpEF: A U-shape relationship persists between BMI and mortality



after adjustment for age, history, labs, medications and echocardiographic findings

Am Heart J 2010;159:75-80

Abdominal Obesity Is Associated With an Increased Risk of All-Cause Mortality in Patients With HFpEF



J Am Coll Cardiol 2017;70:2739–49

Predictors of Physical Function in obese patients with HFpEF

	Peak Vo_2, ml/kg per min		6-Min Walk Distance, m		Leg Press Power, W	
	Partial R^2	p Value	Partial R^2	p Value	Partial R^2	p Value
Age	0.140	<0.001	0.156	<0.001	0.053	0.021
Sex	0.355	<0.001	0.093	<0.001	0.293	<0.001
Race	0.086	0.001	0.005	0.43	0.015	0.23
Intra-abdominal fat	0.358	0.003	0.200	<0.001	-	-
Abdominal SCF	0.077	<0.001	0.182	<0.001	0.075	0.006
Epicardial fat	0.034	0.046	0.033	0.048	-	-

*Age, sex, race forced into model; thigh intermuscular fat did not reach significance for peak Vo_2 or 6-min walk distance.

Vo_2 = oxygen consumption; other abbreviations as in Table 5.

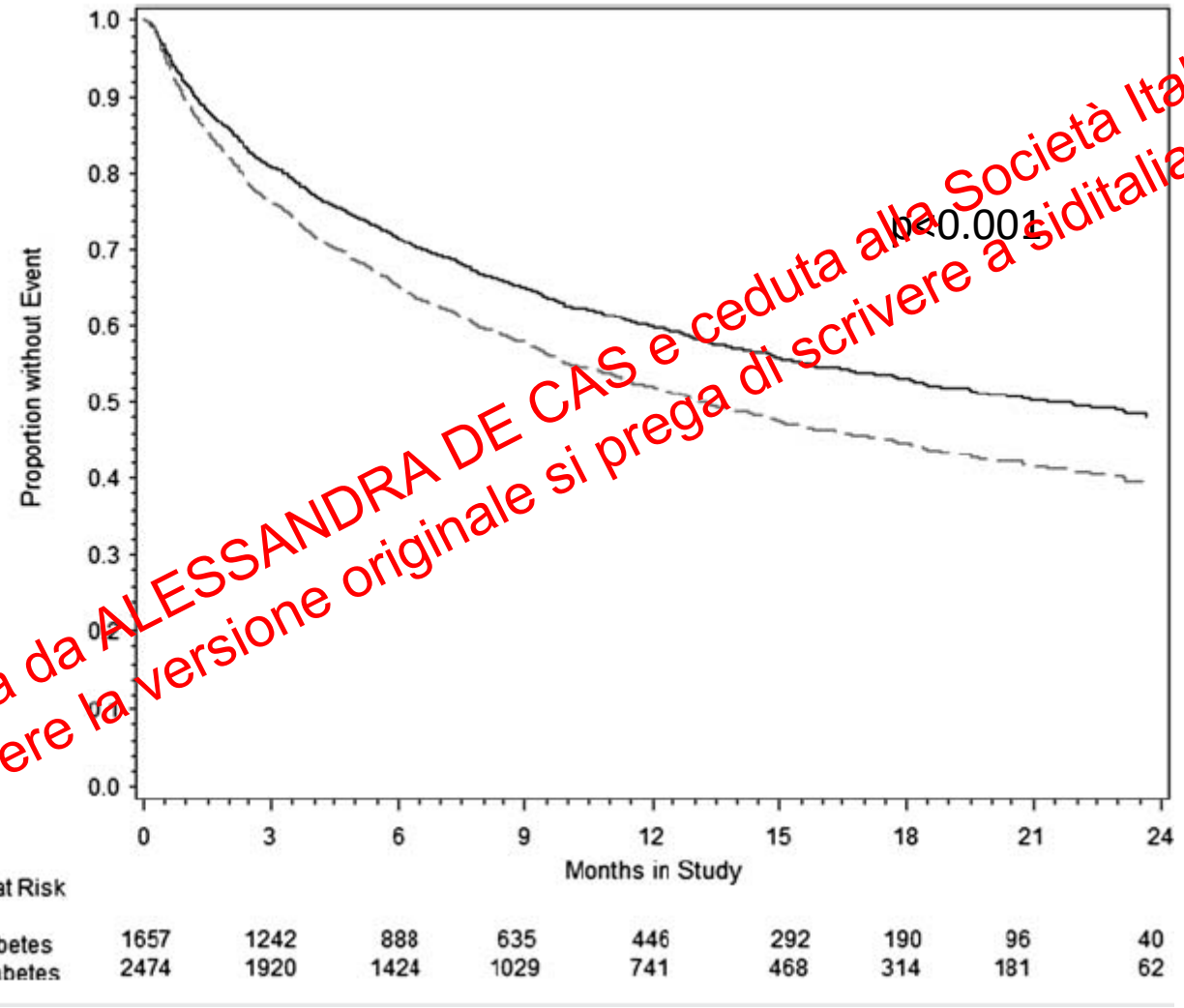
N=100

JACC Heart Fail. 2018;6(8):640-649

Heart Failure and Diabetes: a distinct entity

- Pathophysiology : role of comorbidities leading to a distinct phenotype
- Prognosis
- Response to treatments

Rates of age-adjusted CV mortality or HF re-hospitalisation in patients with and without DM in the EVEREST trial

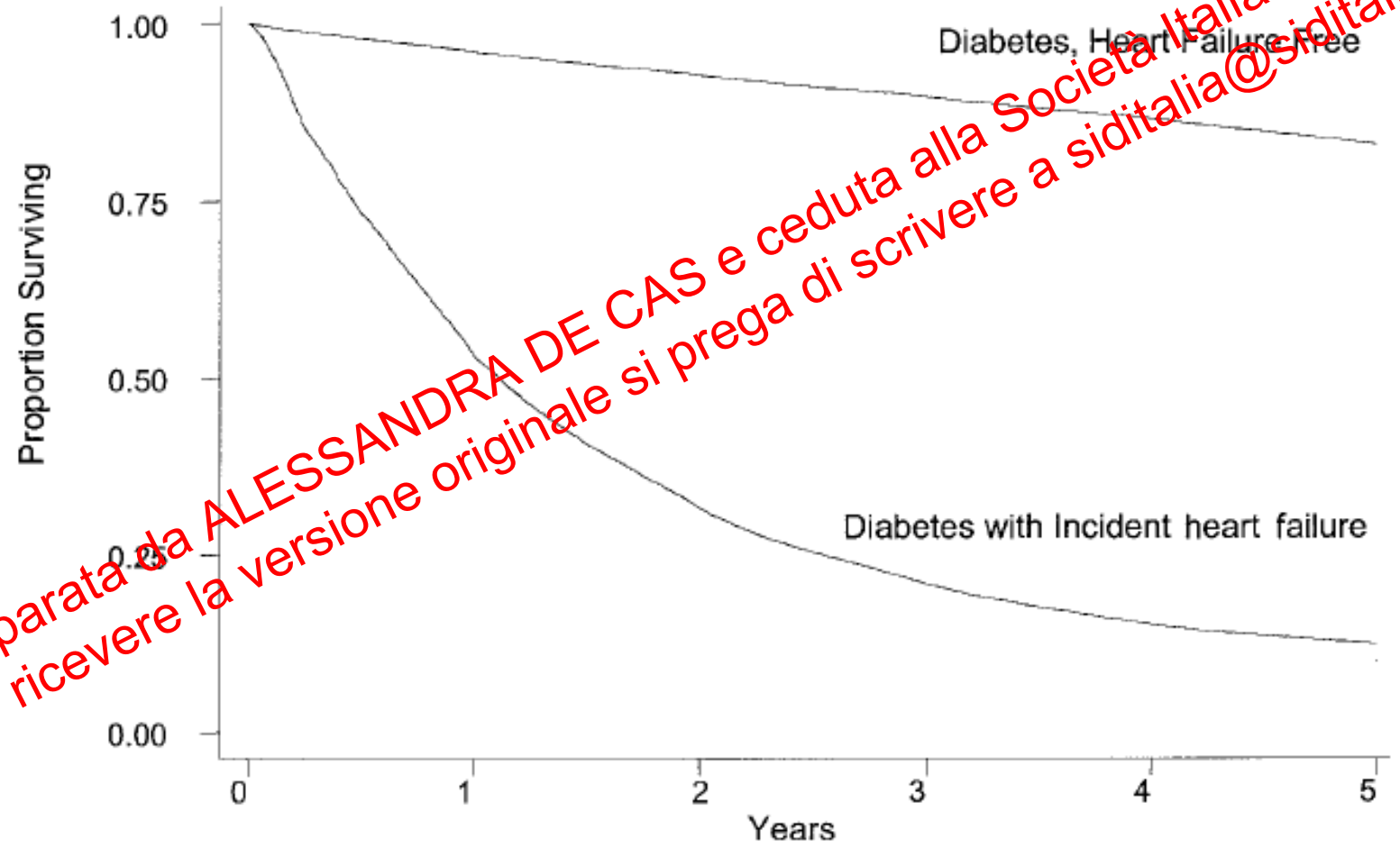


no-diabetes

diabetes

Sarma S et al. European Journal of Heart Failure 2013

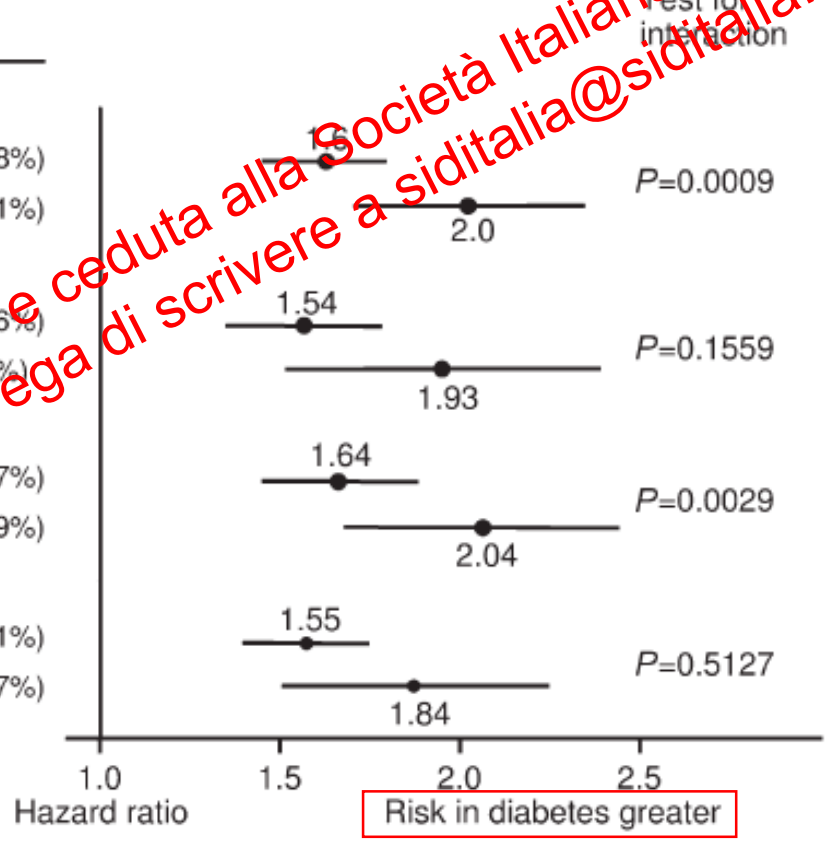
Five-year Kaplan-Meier survival estimates for 115,803 adults age > 65 yrs with DM by incidence HF status



Bertoni G et al Diabetes Care 2004

Risk of different outcomes associated with DM in the CHARM programme

		Diabetes	No diabetes
CV death or hospitalization due to HF	Low EF	657/1306 (50.3%)	1104/3270 (33.8%)
	Preserved EF	308/857 (35.9%)	391/2166 (18.1%)
CV death	Low EF	413/1306 (31.6%)	707/3270 (21.6%)
	Preserved EF	140/857 (16.3%)	200/2166 (9.2%)
Hospitalization due to HF	Low EF	449/1306 (34.4%)	709/3270 (21.7%)
	Preserved EF	238/857 (27.8%)	279/2166 (12.9%)
All-cause mortality	Low EF	496/1306 (38.0%)	854/3270 (26.1%)
	Preserved EF	185/857 (21.6%)	296/2166 (13.7%)



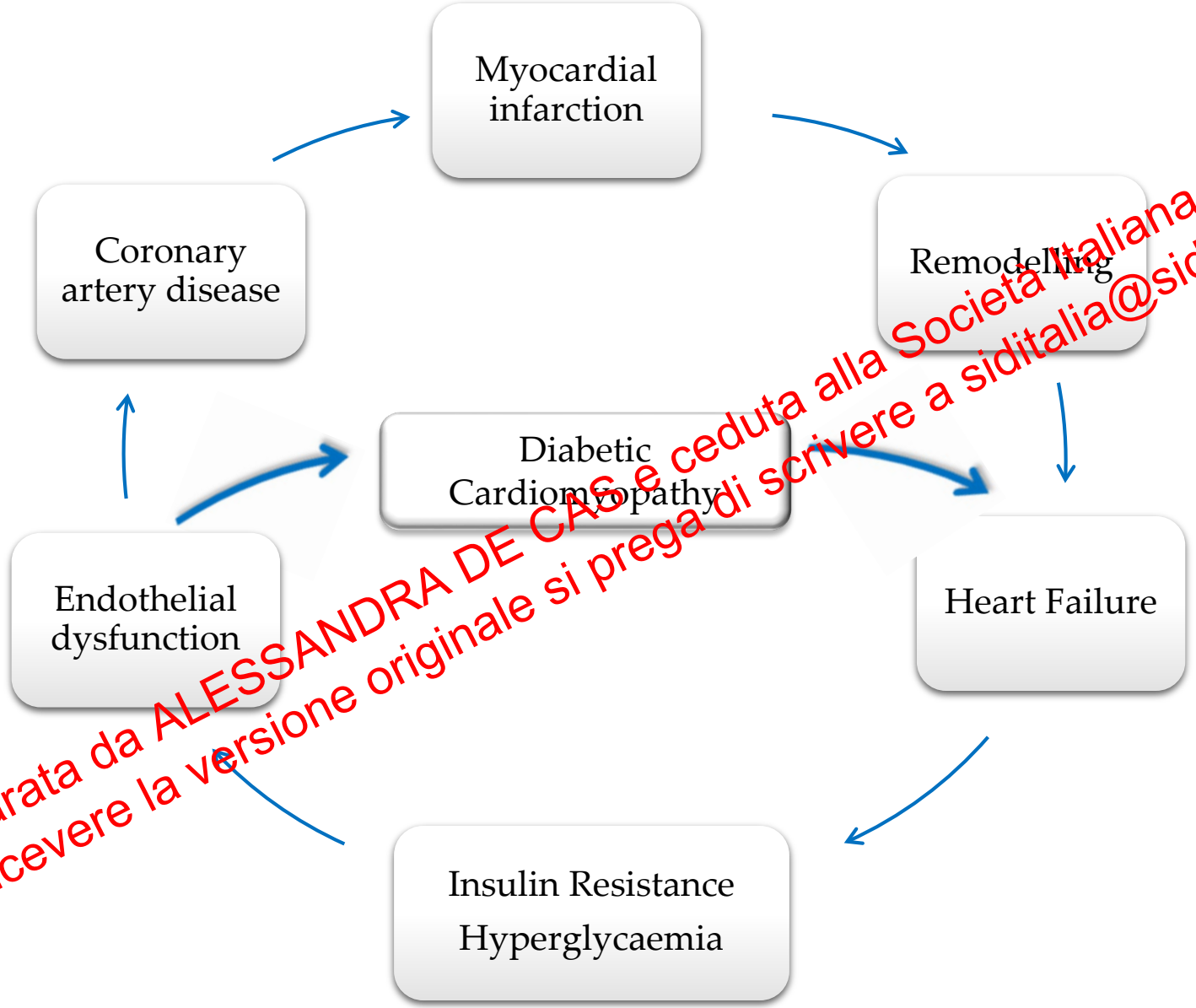
*HR are adjusted for 32 covariates

MacDodnald M et al. European Heart Journal 2008

Weighted means of HRs in Denmark, Norway and Sweden for new users of dapagliflozin vs new DDP-4i (PS 1:3 matched for age, gender, frailty, comorbidity and treatment)

	Dapagliflozin N=10,227		DPP-4i N=30,681		Weighted average estimates N=40,908		
	No. events	Events/100 PYR	No. events	Events/100 PYR	Hazard ratio	95% CI	p-value
MACE	177	1.86	693	2.34	0.79	(0.67-0.94)	0.006
Nonfatal myocardial infarction	87	0.91	304	1.02	0.91	(0.72-1.16)	0.445
Nonfatal stroke	69	0.72	270	0.90	0.79	(0.61-1.03)	0.086
Cardiovascular mortality	38	0.40	160	0.53	0.76	(0.53-1.08)	0.122
HHF	95	0.99	467	1.57	0.62	(0.50-0.77)	<0.001
MACE +	202	2.12	779	2.63	0.81	(0.69-0.94)	0.007
Unstable angina	37	0.39	107	0.36	1.09	(0.75-1.59)	0.655
MACE ++	285	3.01	1164	3.96	0.75	(0.66-0.86)	<0.001
All-cause mortality	120	1.03	644	1.75	0.44	(0.33-0.60)	<0.001
Atrial fibrillation	140	1.47	469	1.58	0.92	(0.76-1.12)	0.414
Severe hypoglycemia	91	0.95	300	1.01	0.94	(0.74-1.19)	0.618

Lancet Diabetes Endocrinol. 2017;5(9):709-717



Dei Cas A et a. Curr Prob Cardiol in press

Diabetic cardiomyopathy pathophysiological mechanisms "metabolic hypothesis"

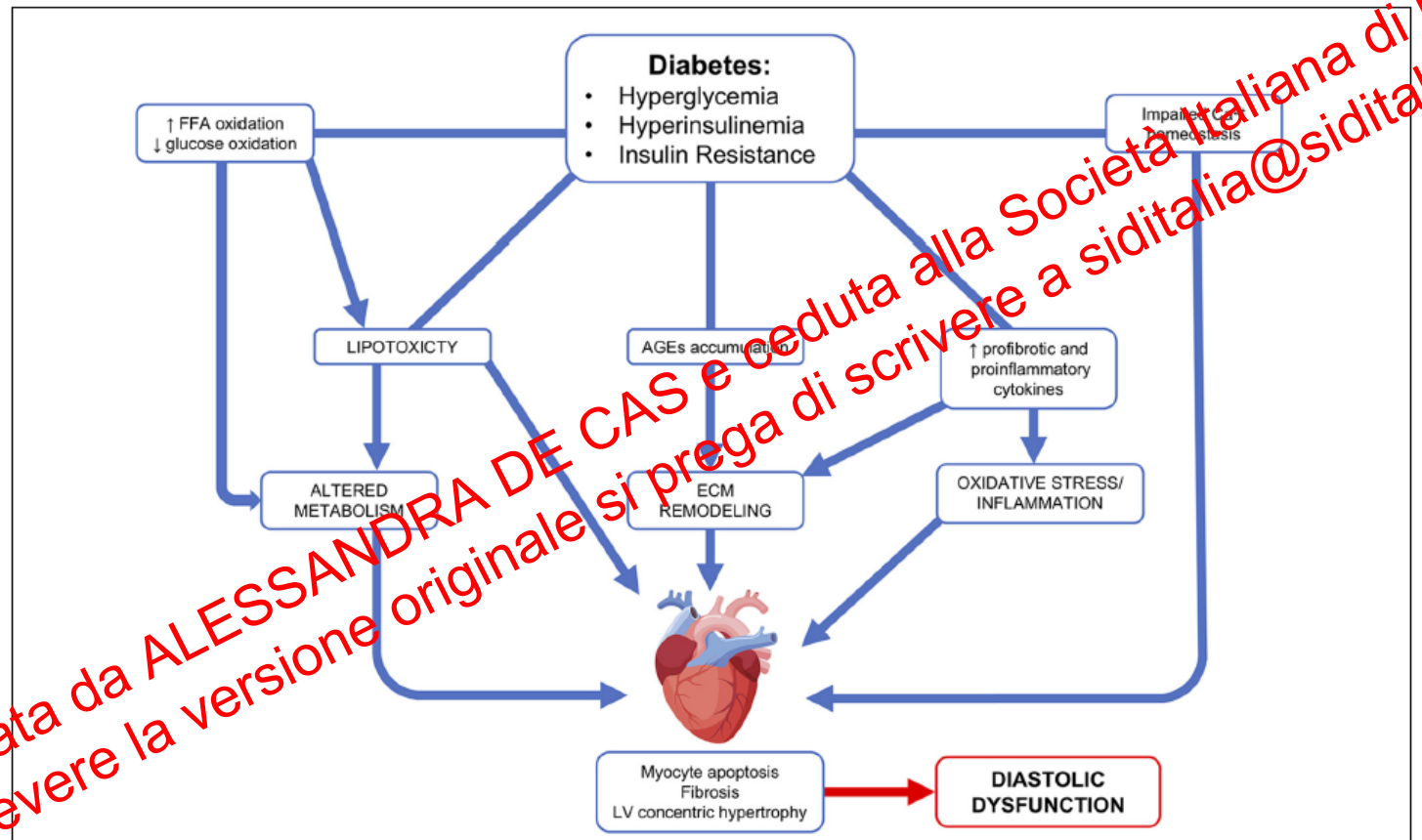
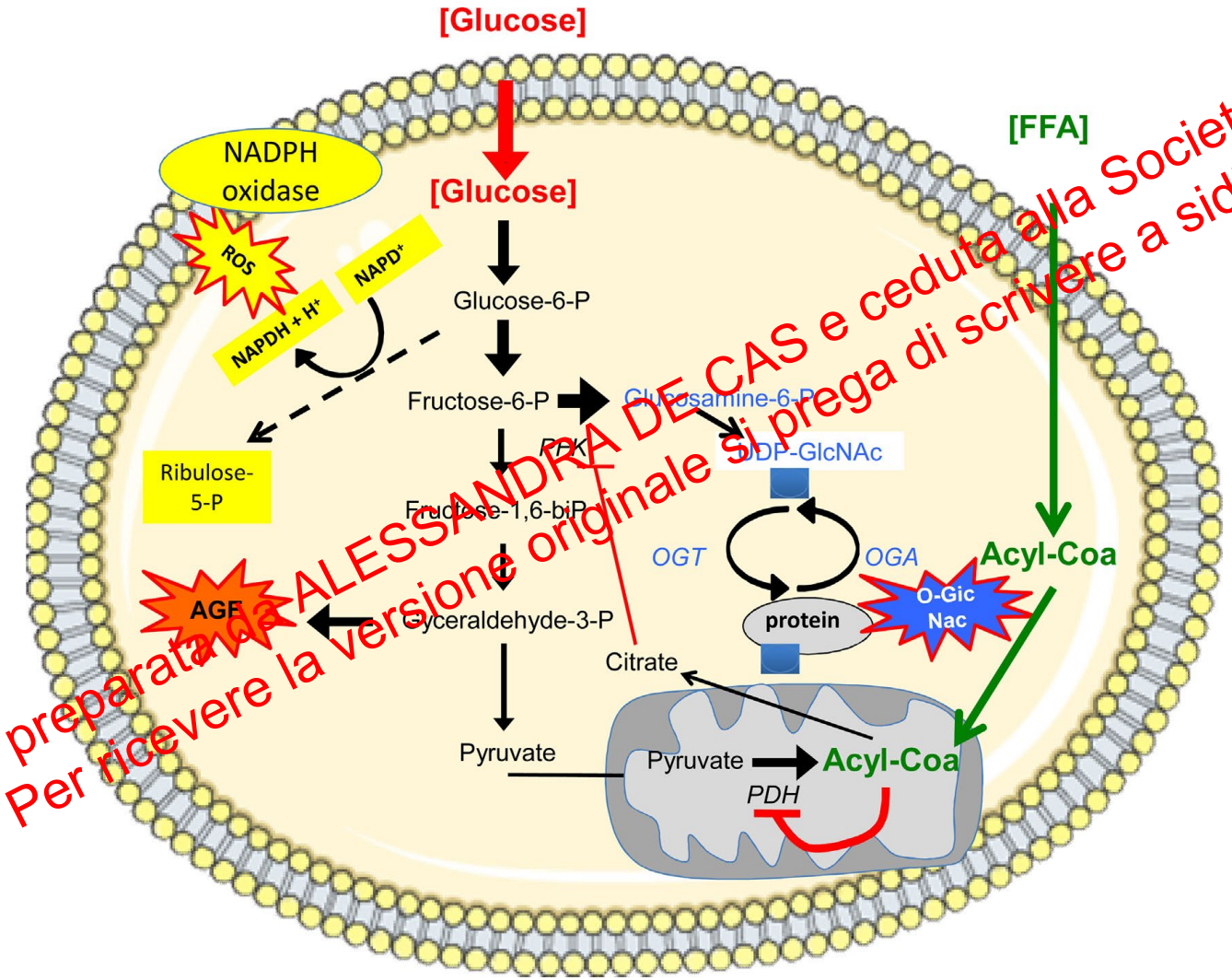


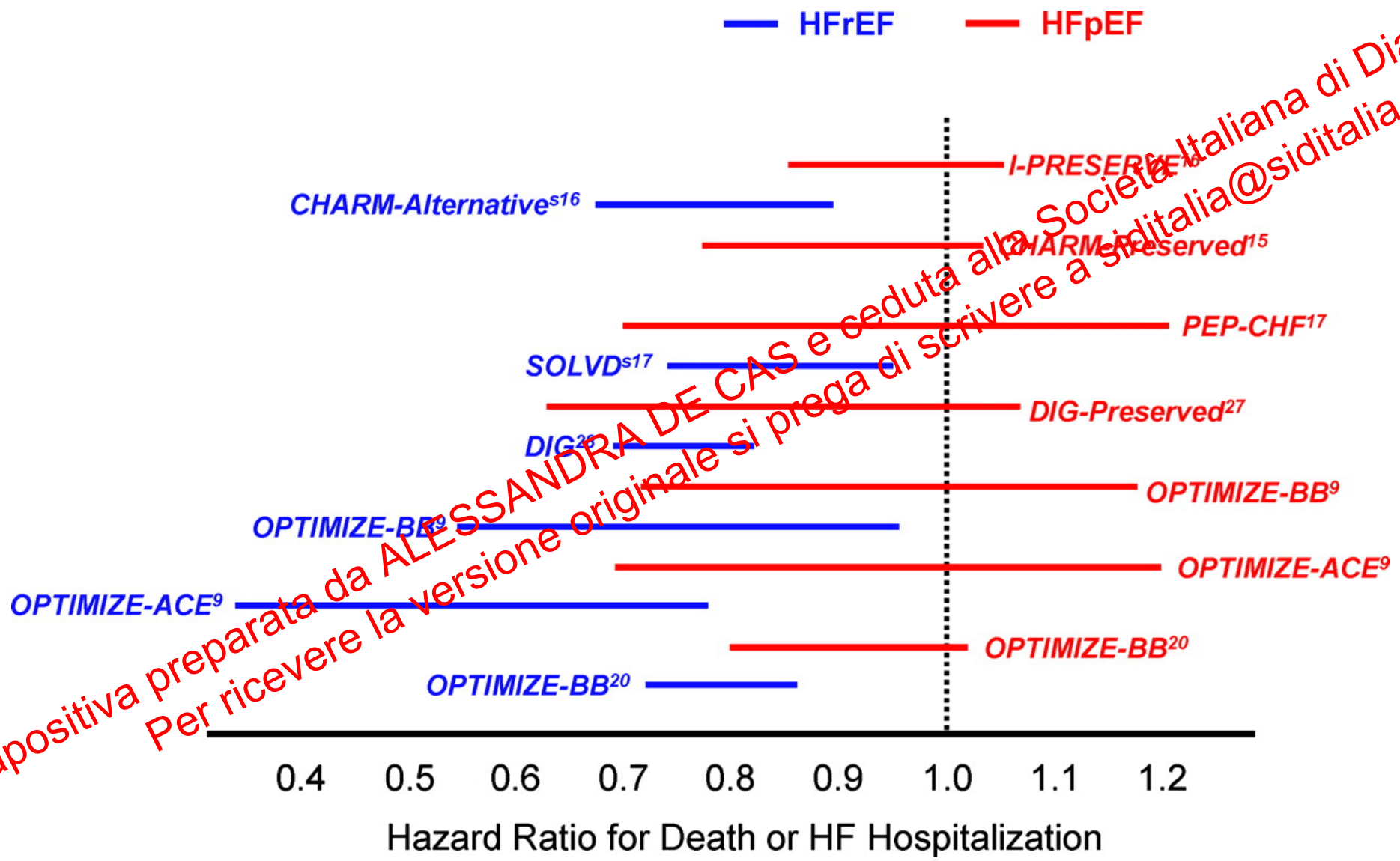
FIGURE 1 | Diabetic cardiomyopathy pathophysiological mechanisms. Hyperglycemia, hyperinsulinemia, and insulin resistance lead to an increase in free fatty acid (FFA) oxidation, profibrotic and proinflammatory cytokines, as well as an accumulation of advanced glycation end products (AGEs). These abnormalities lead to altered metabolism, extracellular remodeling, oxidative stress, and inflammation. Ultimately, this leads to cardiac effects, such as myocyte apoptosis, fibrosis, and LV concentric hypertrophy.

Diabetic hearts display metabolic inflexibility, characterized by a decreased ability to utilize glucose as an energy substrate.

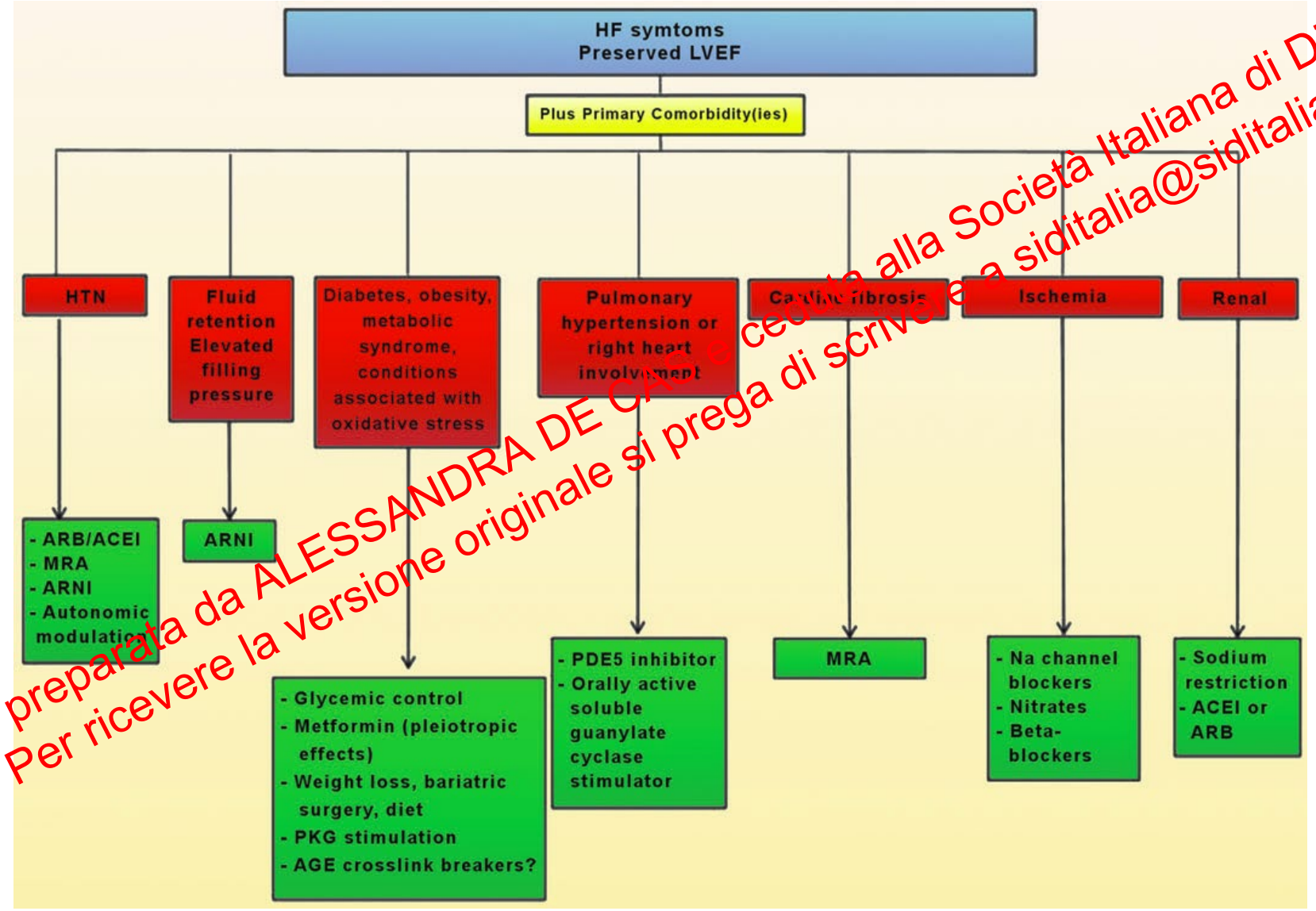


M. Joubert et al. /Diabetes & Metabolism 45 (2019) 238–247

Differential response to treatment in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

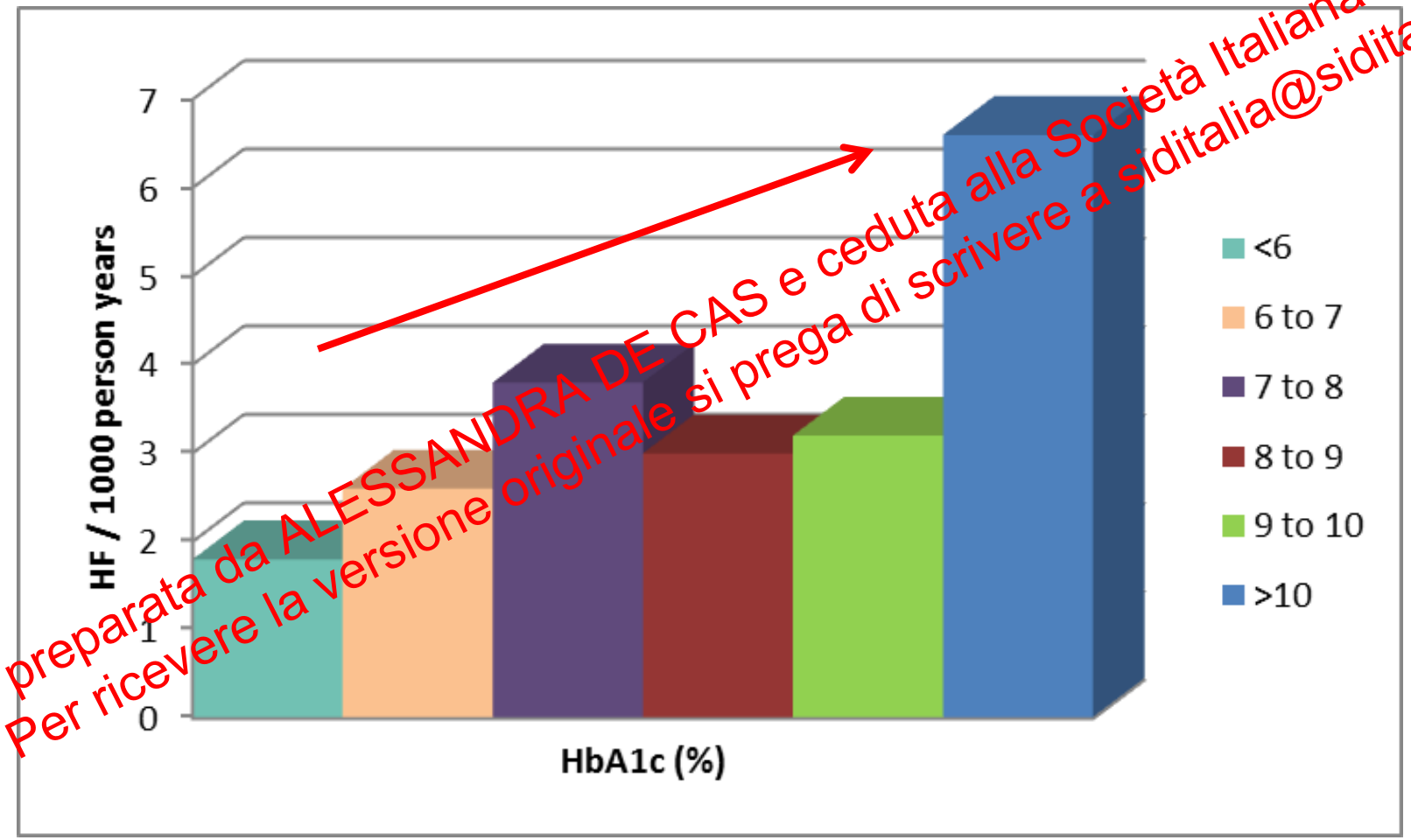


Potential approach for matching key HFpEF phenotypes with therapeutic interventions.



Senni et al. Eur Heart J. 2014;35(40):2797-815

Glycemic control and incident HF in newly diagnosed Type 2 DM patients in the UKPDS



Stratton IM et al. MBJ 2000