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CATANIA 4 NOVEMBRE 2019

Cross-talk rene-cuore: effetti dello scompenso cardiaco sulla funzione renale

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Università di Genova

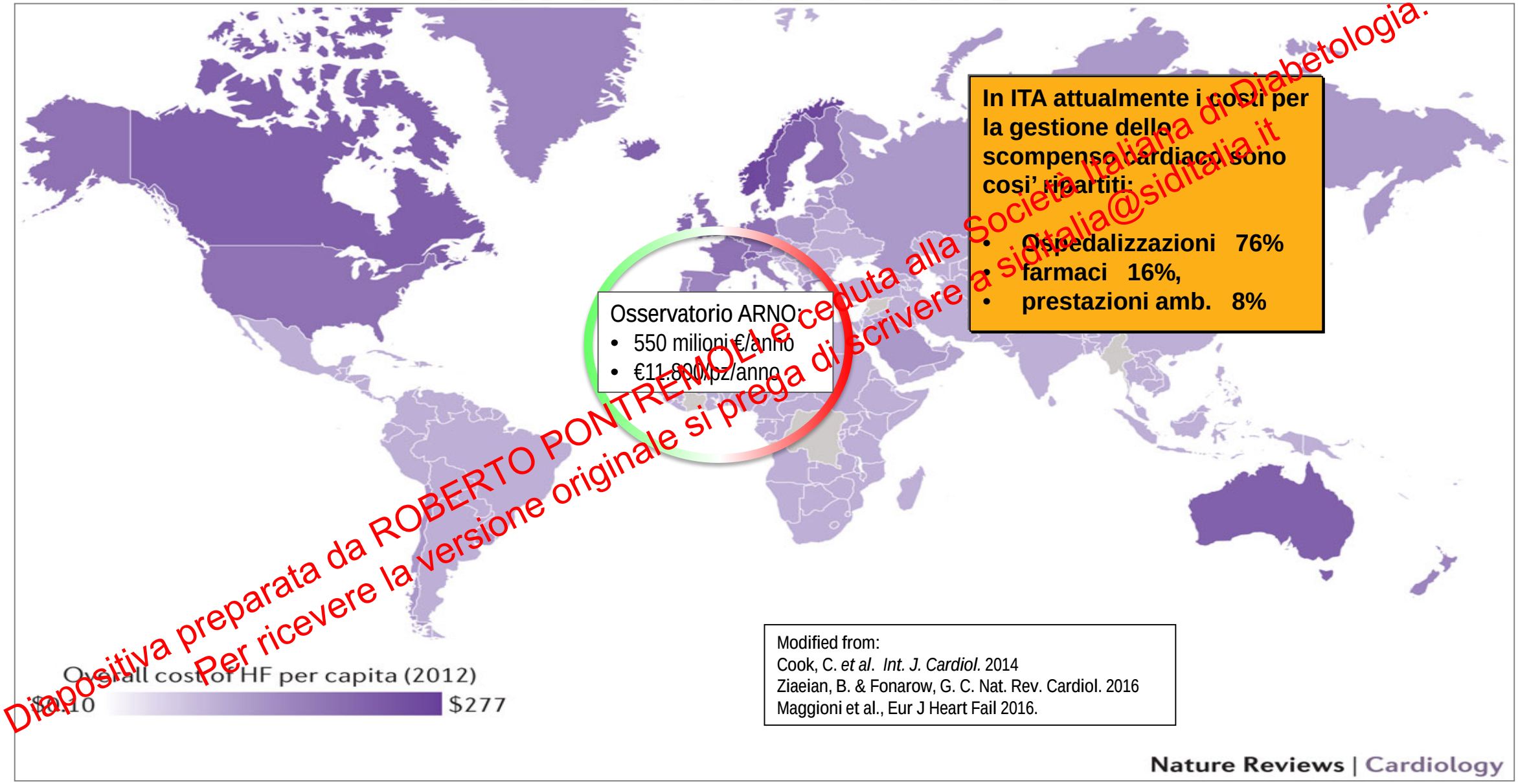
Il sottoscritto Roberto PONTREMOLI

dichiara

l’esistenza negli ultimi due anni di rapporti di natura finanziaria e lavorativa con le seguenti imprese commerciali operanti in ambito sanitario

- **Novartis**
- **Astrazeneca**
- **Menarini**
- **Lilly**
- **Boehringer Ingelheim**
- **MSD**
- **Alfasigma**

Cost of Heart Failure



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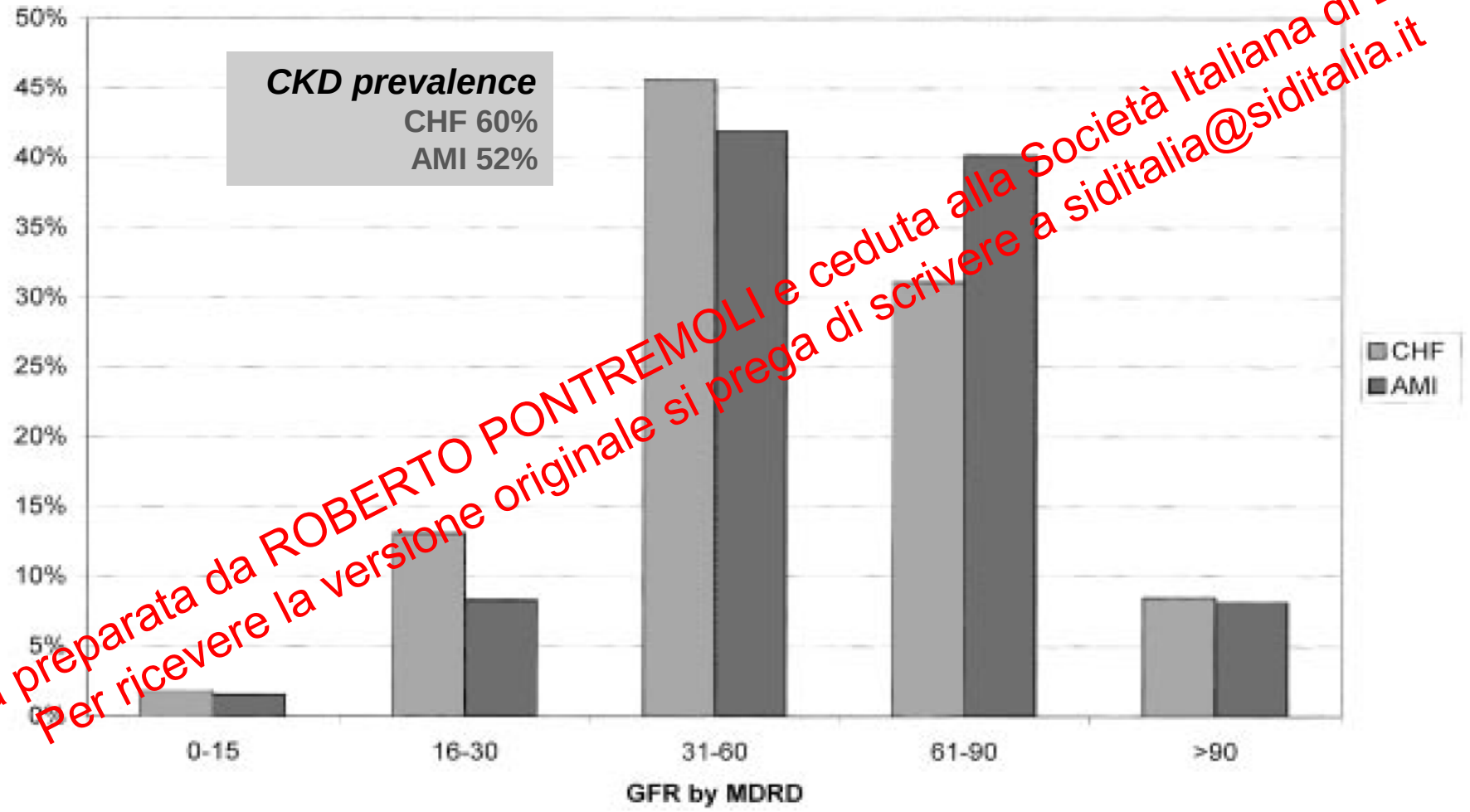
- *Problem dimension*
- *Pathophysiology*
- *Renal prognostic value*
- *Data from CVOTs in T2D*

CKD is highly prevalent in patients with CHF

Data from a real-life Community Hospital Cohort (Medicare)



J Am Soc Nephrol 15: 1912–1919, 2004

CKD is highly prevalent in patients with CHF

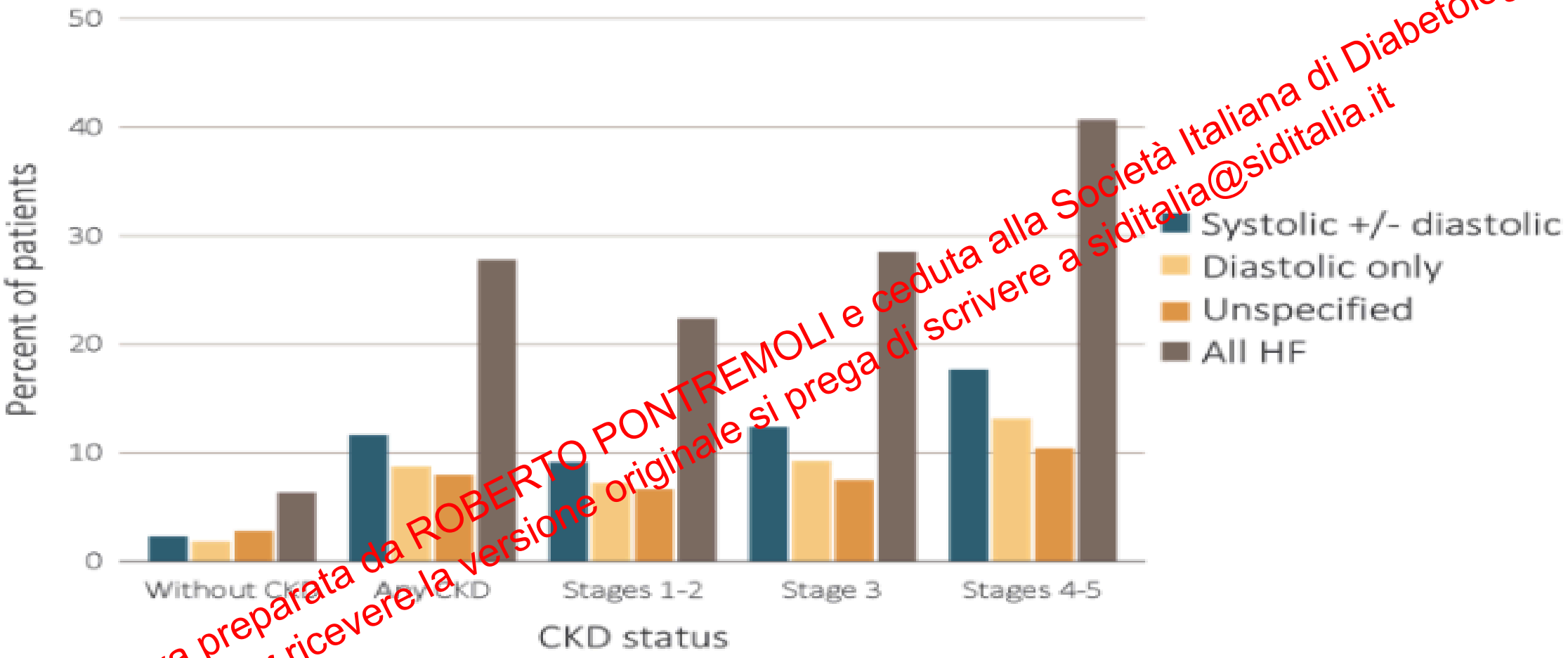
European Heart Failure Pilot Study

	HFrEF (LVEF <40%)	HFpEF (LVEF ≥40%)	P-value
Chronic kidney disease	541 (41)	383 (39)	0.381
Anaemia	349 (26)	306 (30)	0.130
Diabetes	470 (36)	343 (28)	0.191
COPD	205 (16)	173 (14)	0.101
Stroke	166 (11)	129 (10)	0.892
Sleep apnoea	69 (4)	49 (4)	0.578
Hypothyroidism	152 (10)	96 (8)	0.062
Hyperthyroidism	54 (4)	32 (3)	

3226 patients with CHF (ESC)
71% at least 1 comorbidity

European Journal of Heart Failure (2014)

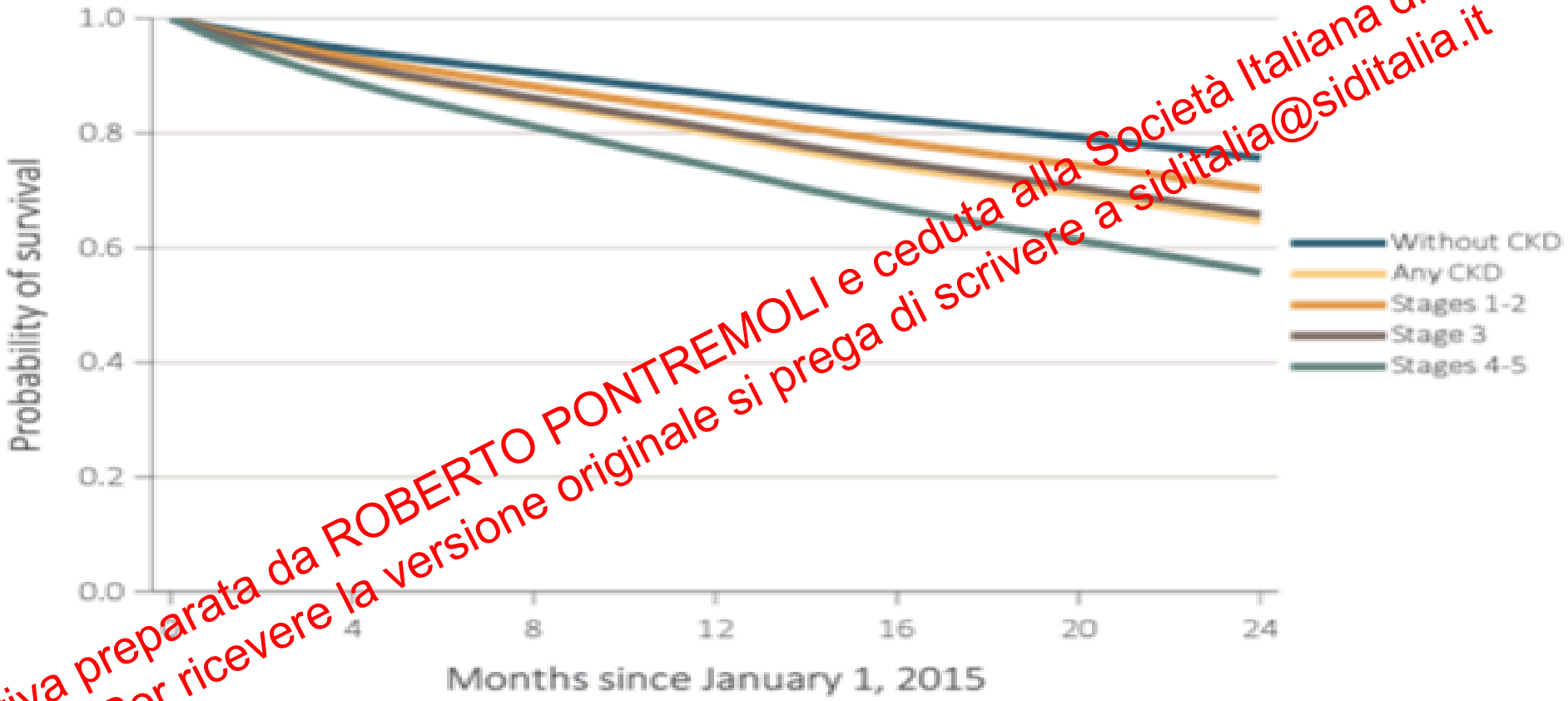
Heart failure in patients with or without CKD



Data Source: Special analyses, Medicare 5% sample. Patients aged 66 and older, alive, without end-stage renal disease, and residing in the United States on 12/31/2016 with fee-for-service coverage for the entire calendar year. Abbreviation: CKD, chronic kidney disease.

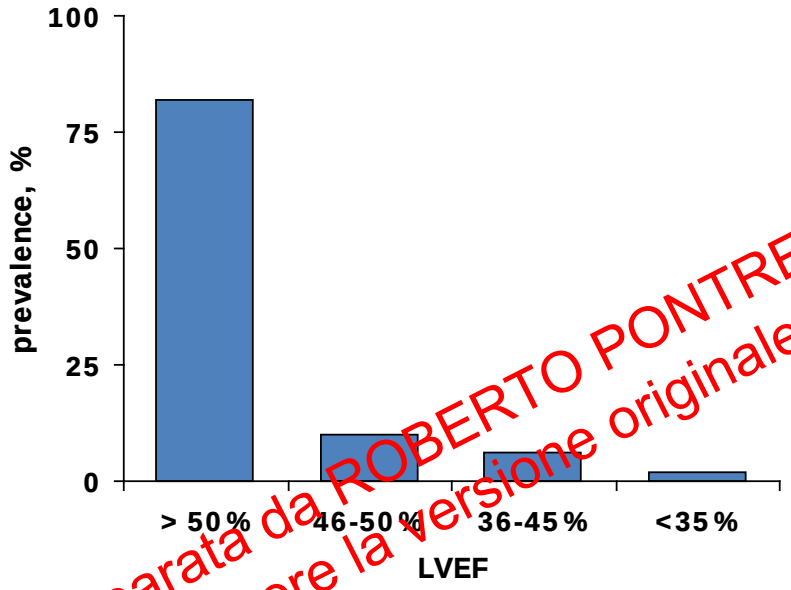
Survival of patients with heart failure by CKD status

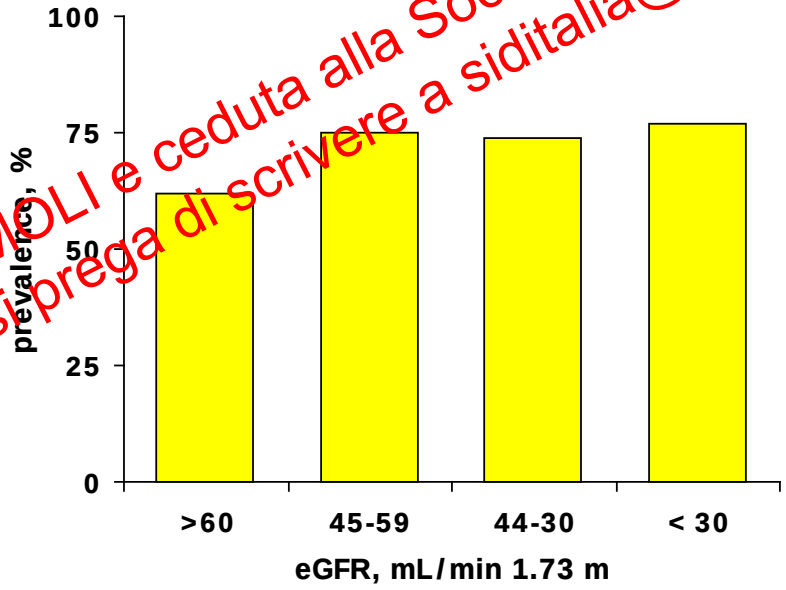
adjusted for age and sex



Data Source: Special analyses, Medicare 5% sample. Patients aged 66 and older, alive, without end-stage renal disease, and residing in the United States on 12/31/2014, with fee-for-service coverage for the entire calendar year. Abbreviation: CKD, chronic kidney disease.

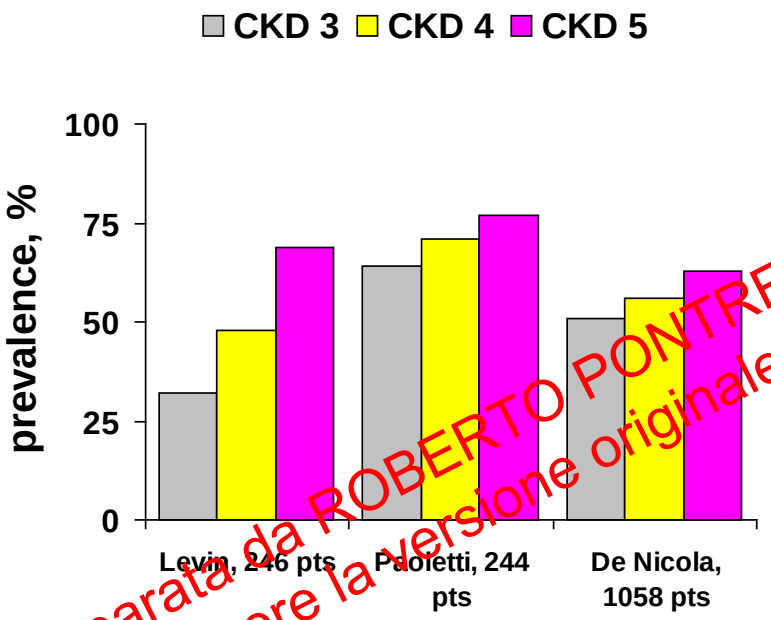
Prevalence of systolic and diastolic dysfunction in the CRIC Study cohort



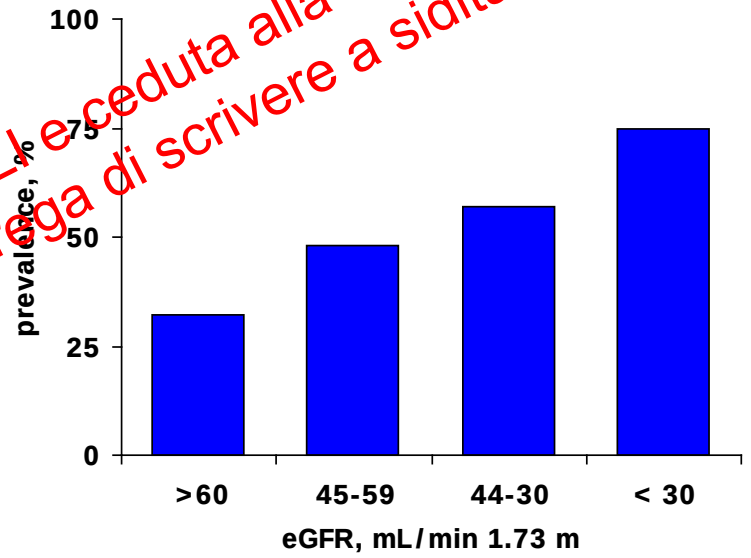


Park M, JASN 2012

Prevalence of left ventricular hypertrophy in non dialysis CKD patients



data from: Levin A et al., AJKD 1999
Paoletti E et al., AJKD 2005
DeNicola L et al., KI 2006



Park M, JASN 2012

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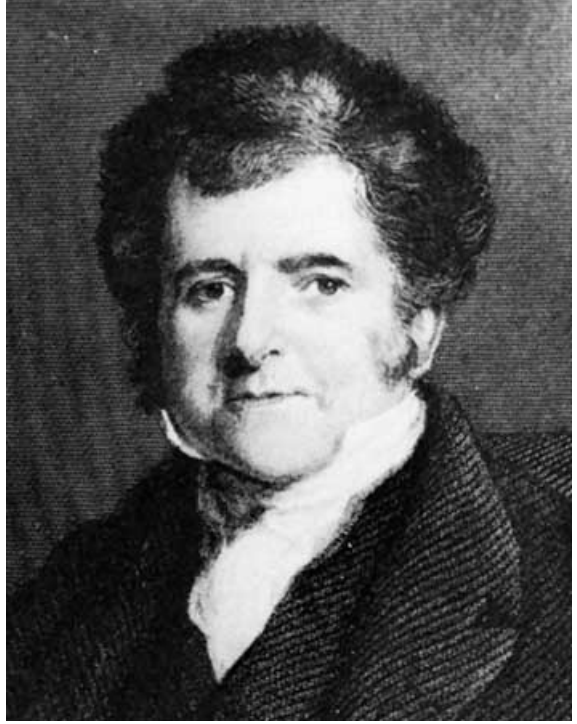
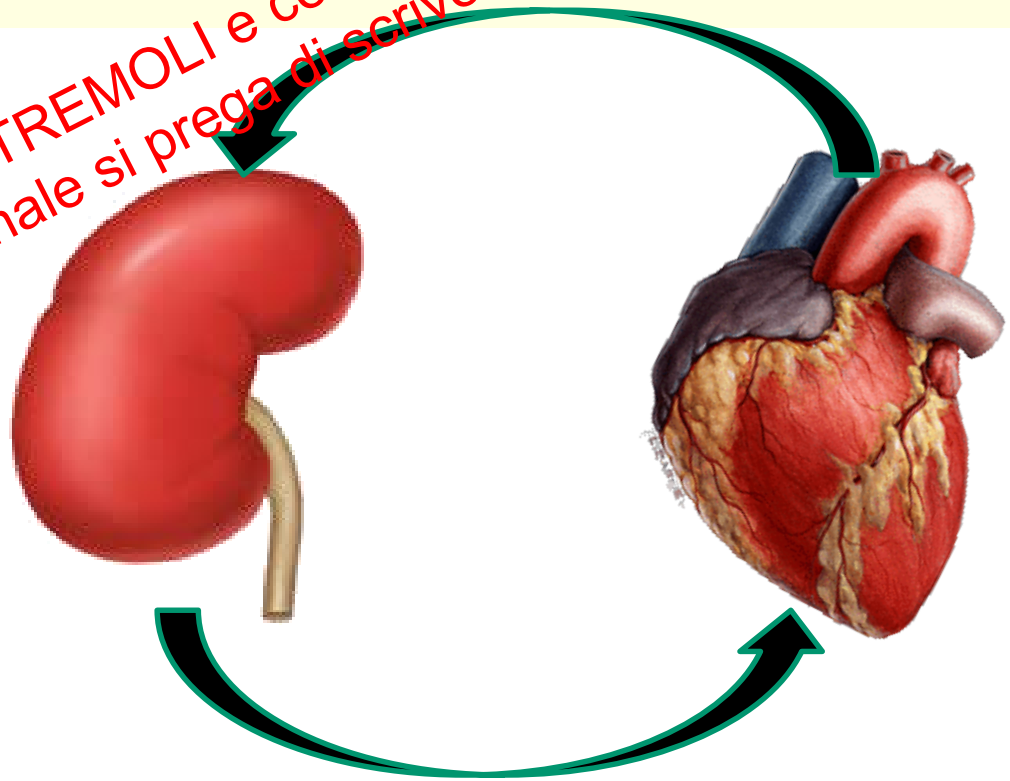
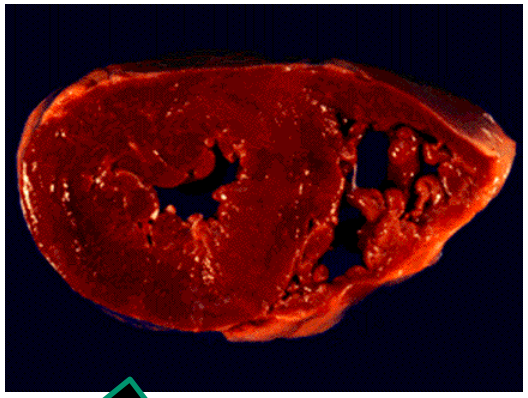


Richard Bright

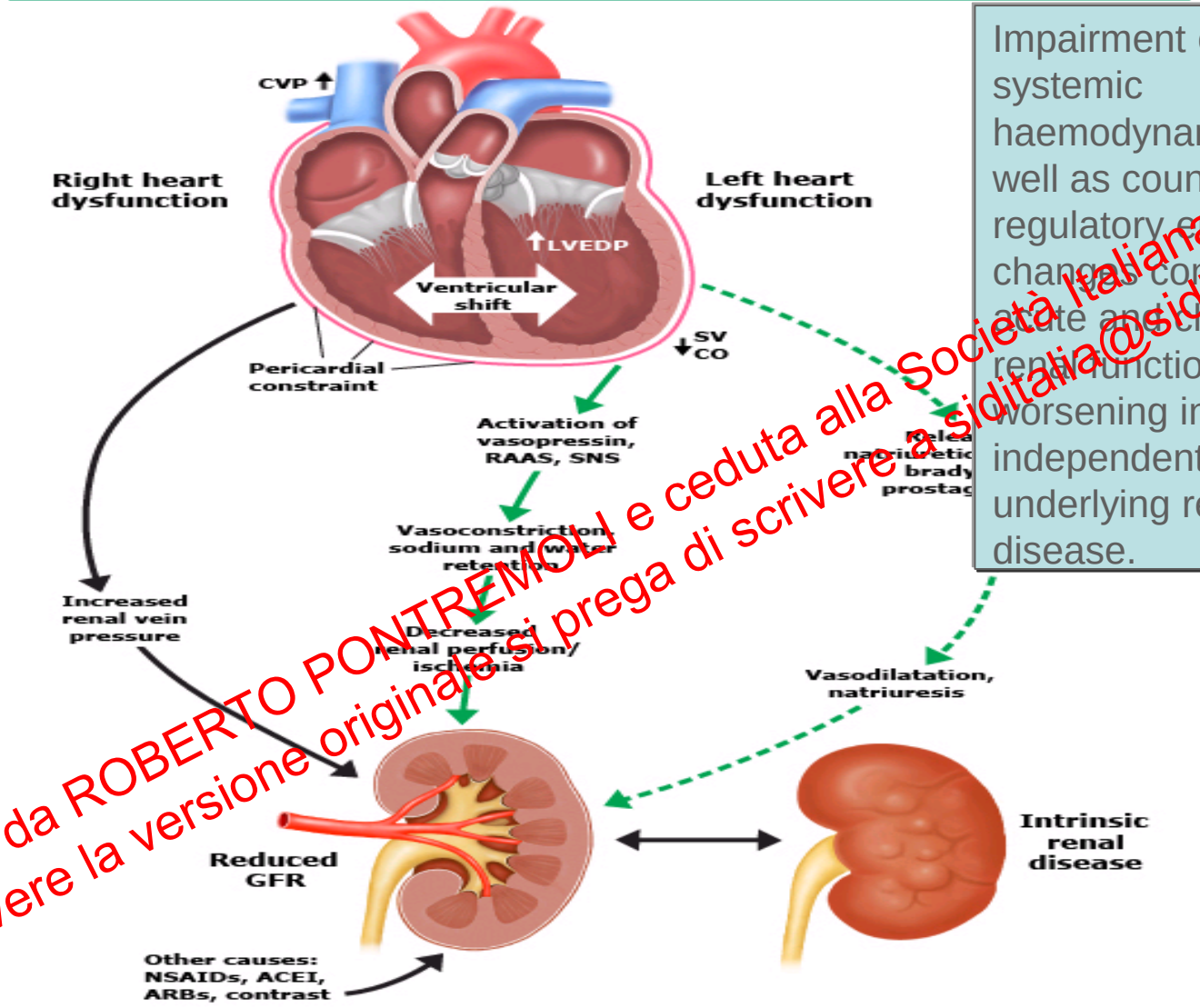
Cases and observations, illustrative of renal disease accompanied with the secretion of albuminous urine.
Guy's Hospital Reports, 1836, 1: 338-379.



"… the obvious structural changes in the heart [in patients with shrunken kidneys] have consisted chiefly of hypertrophy with or without valve disease; and, what is most striking, out of 52 cases of hypertrophy, no valvular disease whatsoever could be detected in 34"



Pathophysiology of cardiorenal syndrome



Impairment of systemic haemodynamics as well as counter-regulatory endocrine changes contribute to acute and chronic renal function worsening in CKD, independent of any underlying renal disease.

ACEI: angiotensin converting enzyme inhbitor; ARBs: angiotensin II receptor blockers; CO: cardiac output; CVP: central venous pressure; LVEDP: left ventricular end-diastolic pressure; ETs: endothelins; NO: nitric oxide; NP: natriuretic peptides; NSAIDs: nonsteroidal antiinflammatory drugs; RAAS: renal angiotenin aldosterone system; SNS: sympathetic nervous system; SV: stroke volume.

UpToDate

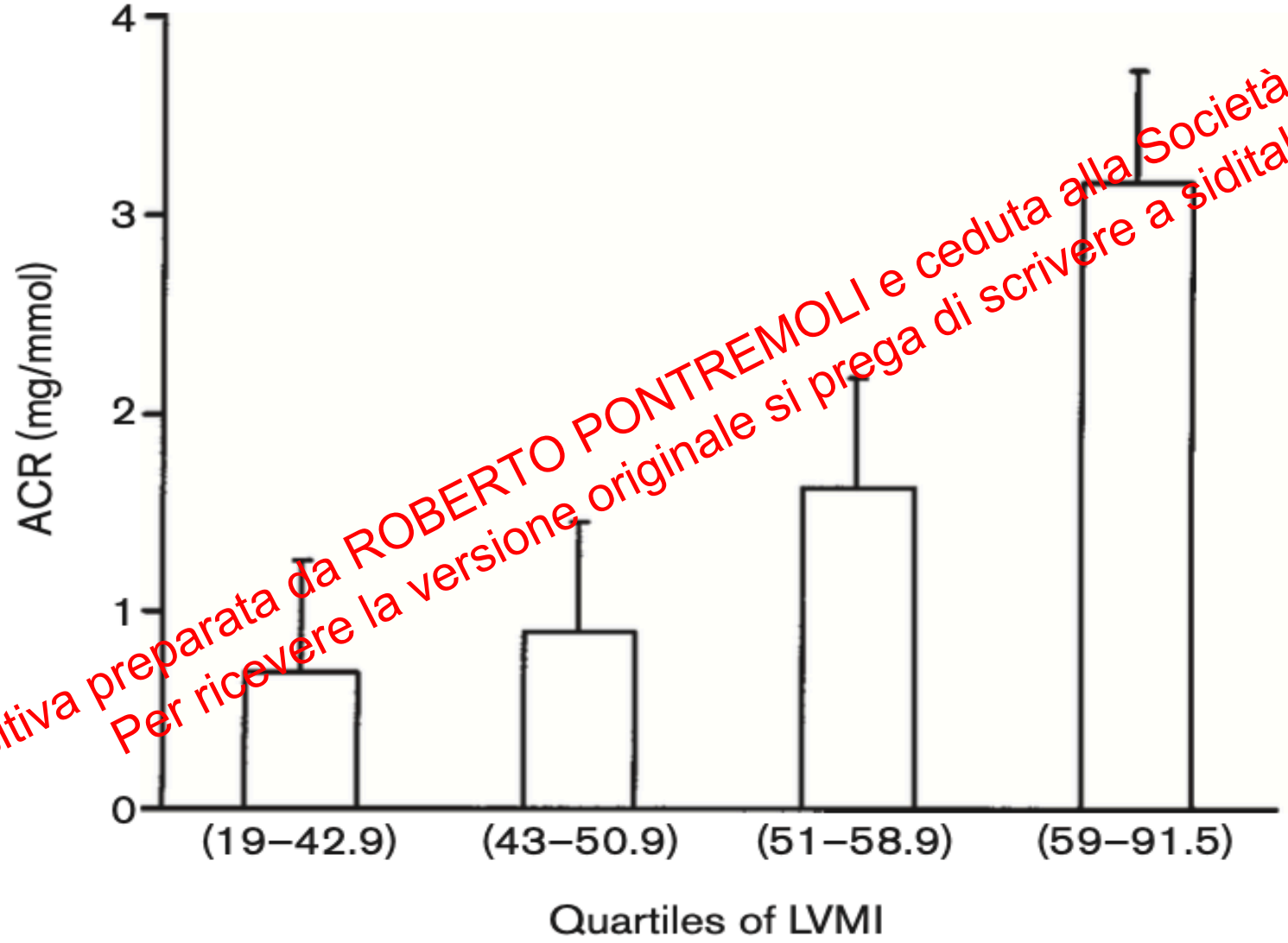
Hormones and Hemodynamics in Heart Failure

Robert W. Schrier, M.D.,
and William T. Abraham, M.D.

The New England Journal of Medicine August 19, 1999

Left ventricular geometry and function in patients with essential hypertension and microalbuminuria

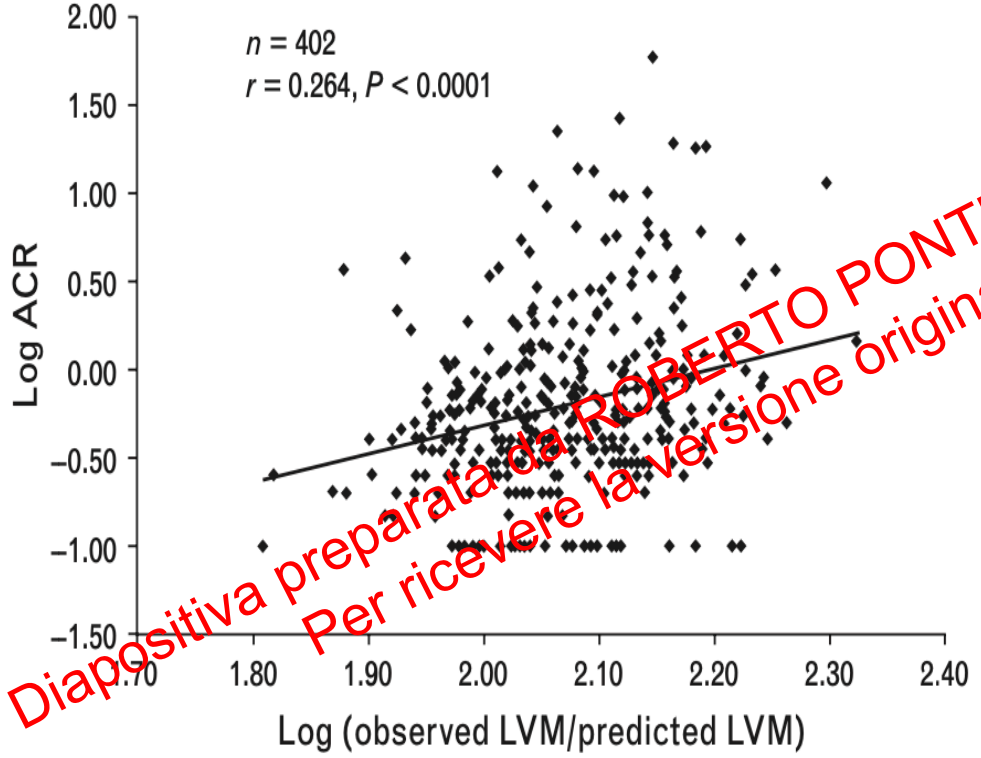
Roberto Pontremoli[a], Maura Ravera[a], Gian Paolo Bezante[a], Francesca Viazzi[a], Clizia Nicolella[a], Valeria Berruti[a], Giovanna Leoncini[a], Massimo Del Sette[b], Claudio Brunelli[a], Cinzia Tomolillo[a] and Giacomo Deferrari[a]

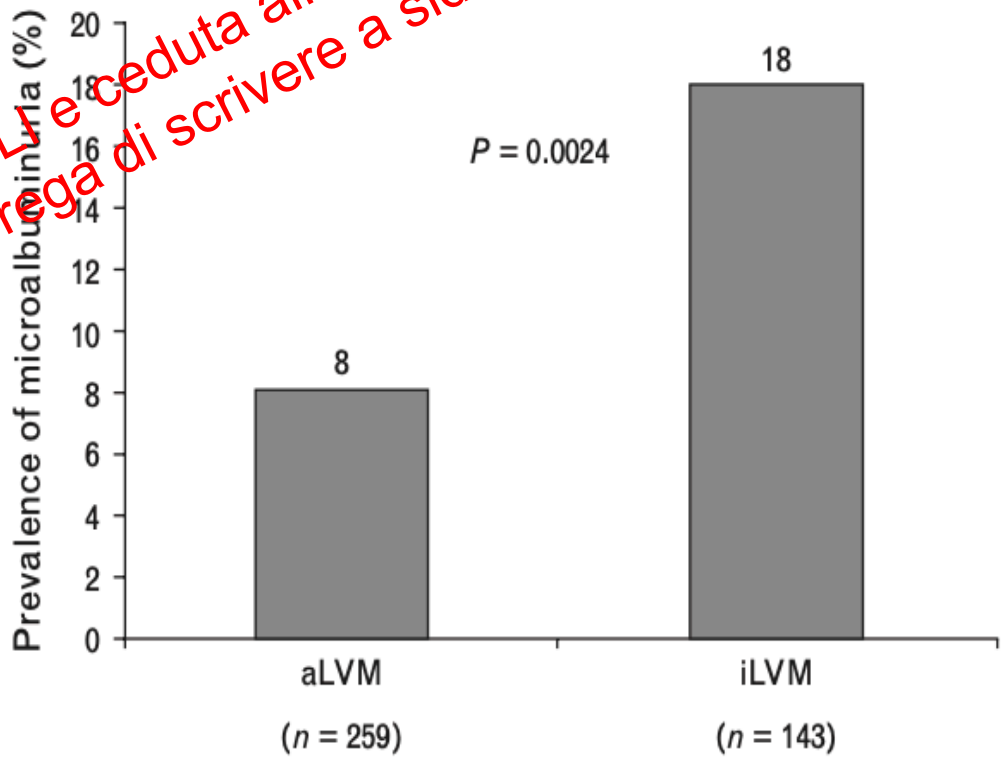


Journal of Hypertension 1999

Inappropriate left ventricular mass is associated with microalbuminuria independently of left ventricular hypertrophy in primary hypertension

Elena Ratto, Giovanna Leoncini, Francesca Viazzi, Gian Paolo Bezante, Valeria Falqui, Angelica Parodi, Novella Conti, Cinzia Tomolillo, Giacomo Deferrari and Roberto Pontremoli

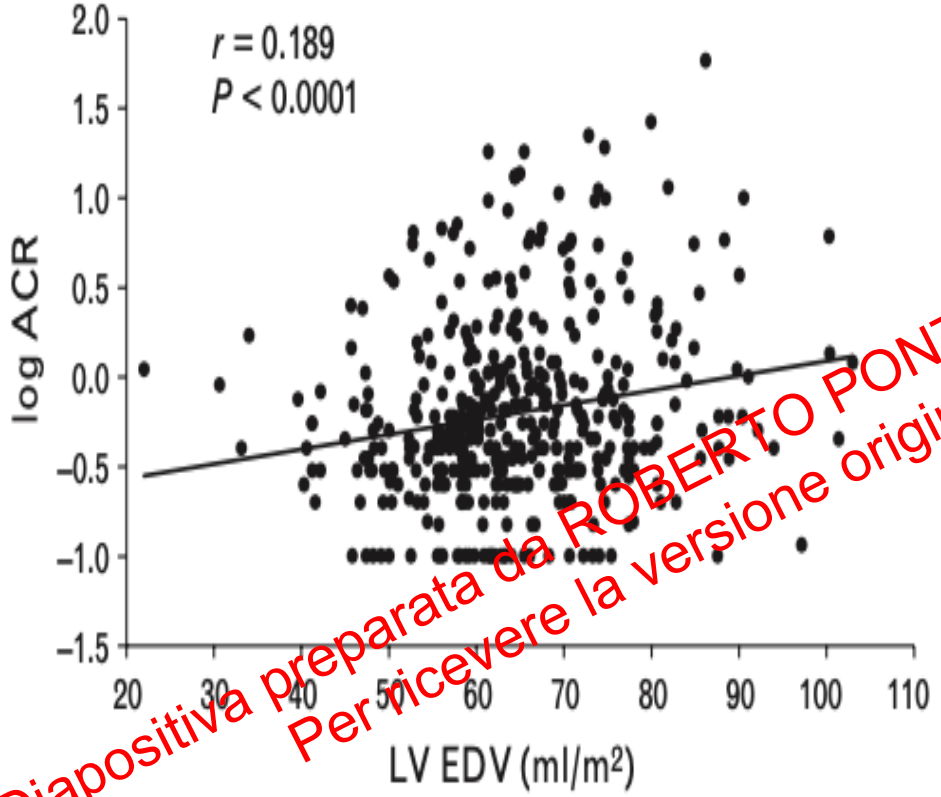


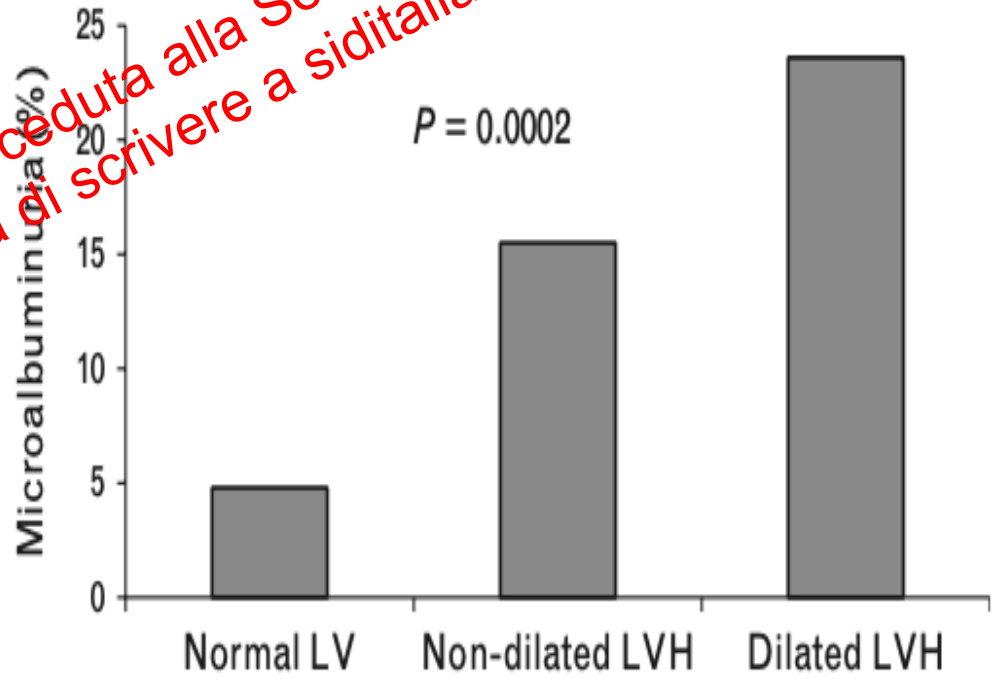


Journal of Hypertension 2008

Left ventricular dilatation and subclinical renal damage in primary hypertension

Elena Ratto, Francesca Viazzi, Barbara Bonino, Annalisa Gonnella, Debora Garneri, Emanuele L. Parodi, Gian Paolo Bezante, Lorenzo E. Derchi, Giovanna Leoncini, and Roberto Pontremoli



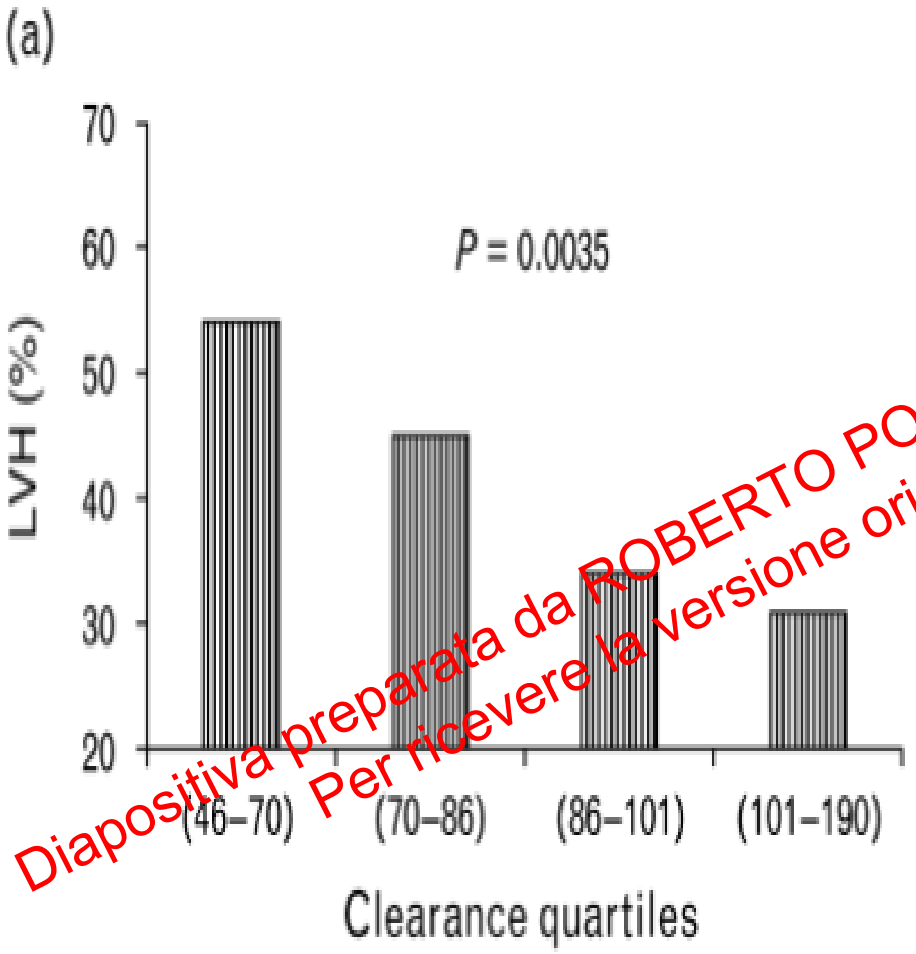


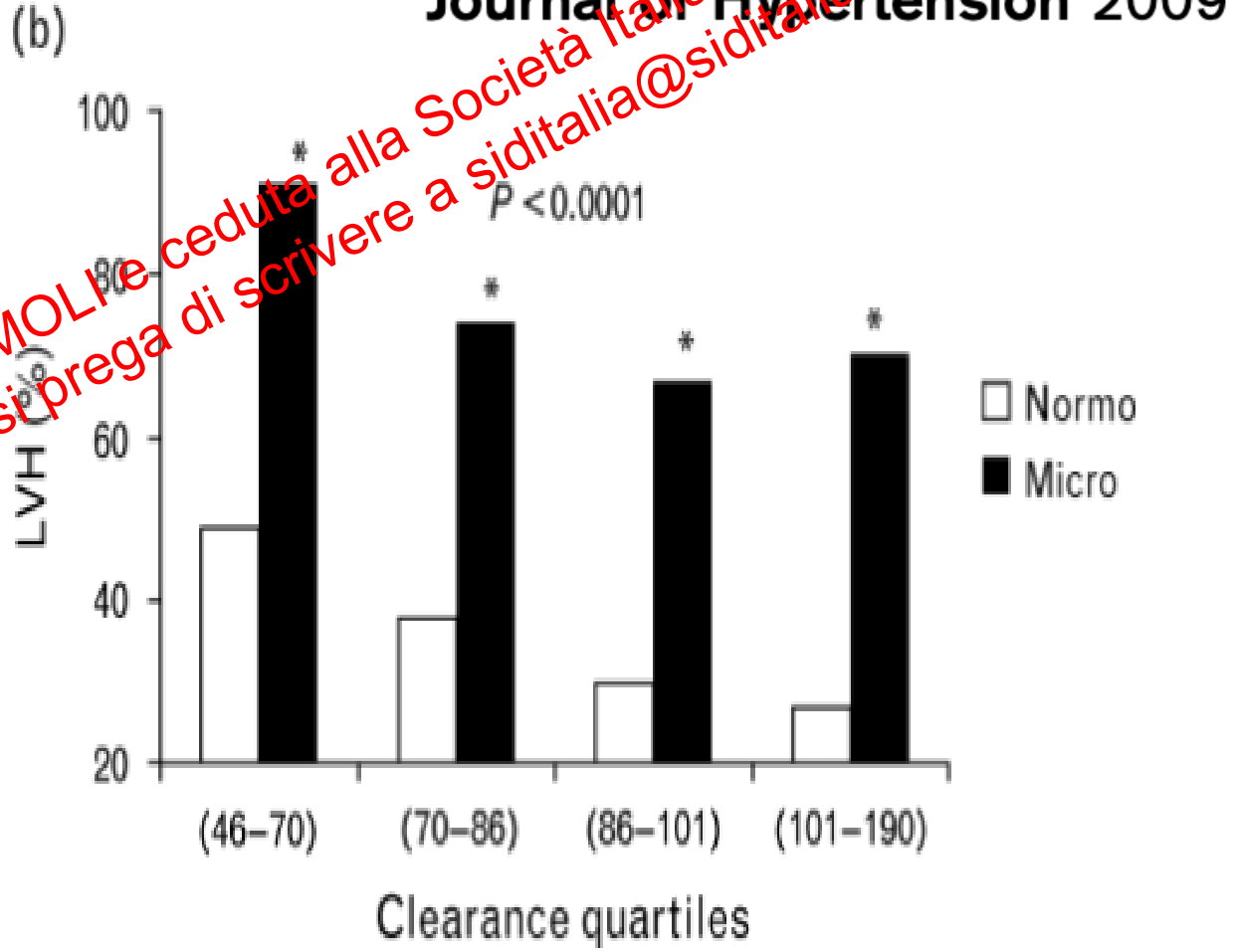
Journal of Hypertension 2015

Renal and cardiac abnormalities in primary hypertension

Giovanna Leoncini, Francesca Viazzi, Novella Conti, Elena Baratto, Cinzia Tomolillo, Gian Paolo Bezante, Giacomo Deferrari and Roberto Pontremoli

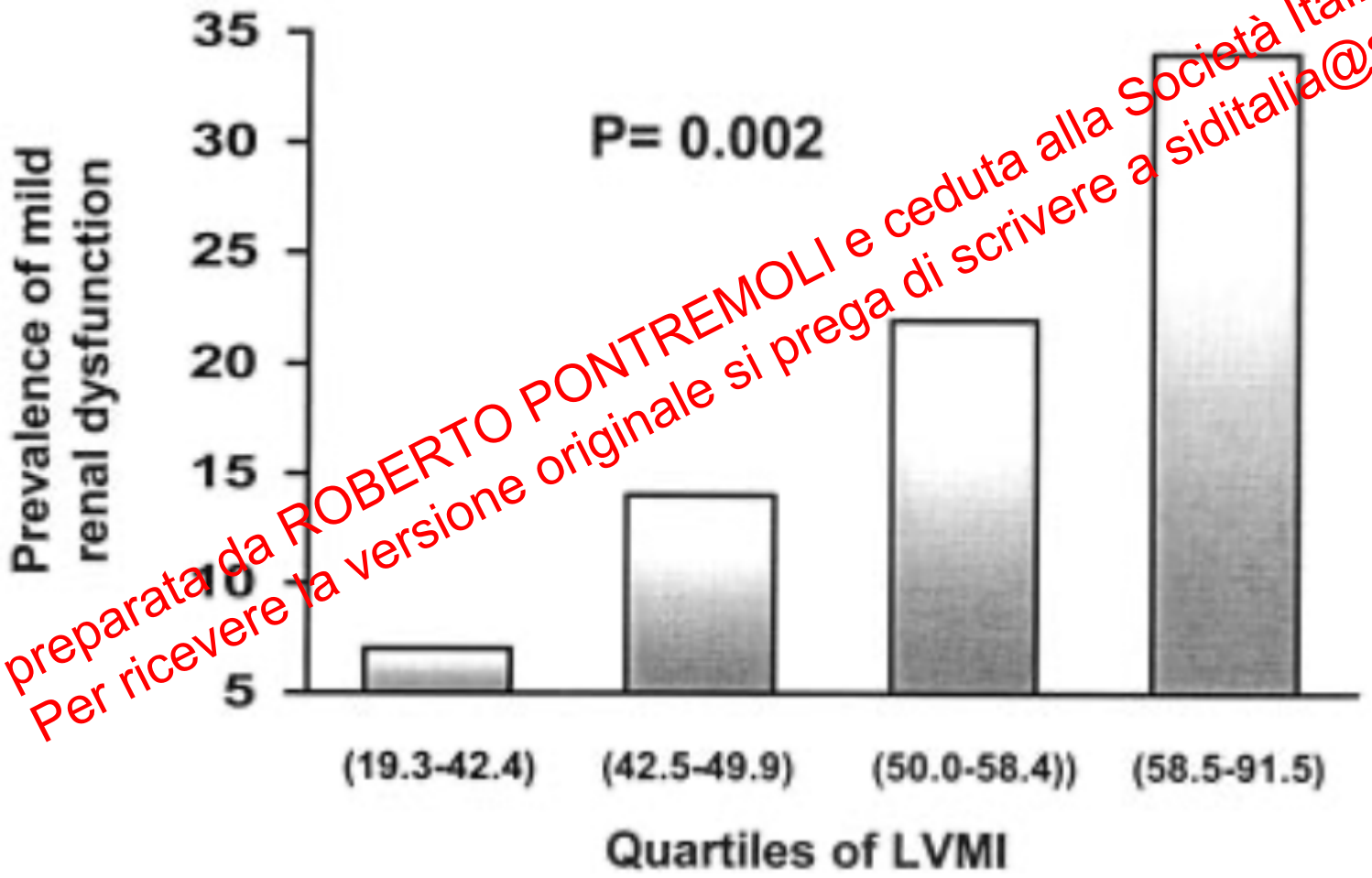
Journal of Hypertension 2009





Mild Renal Dysfunction and Subclinical Cardiovascular Damage in Primary Hypertension

Giovanna Leoncini, Francesca Viazzi, Denise Parodi, Simone Vettoretti, Elena Ratto, Maura Ravera, Cinzia Tomolillo, Massimo Del Sette, Gian Paolo Bezante, Giacomo Deferrari, Roberto Pontremoli



Hypertension. 2003;42:14-18

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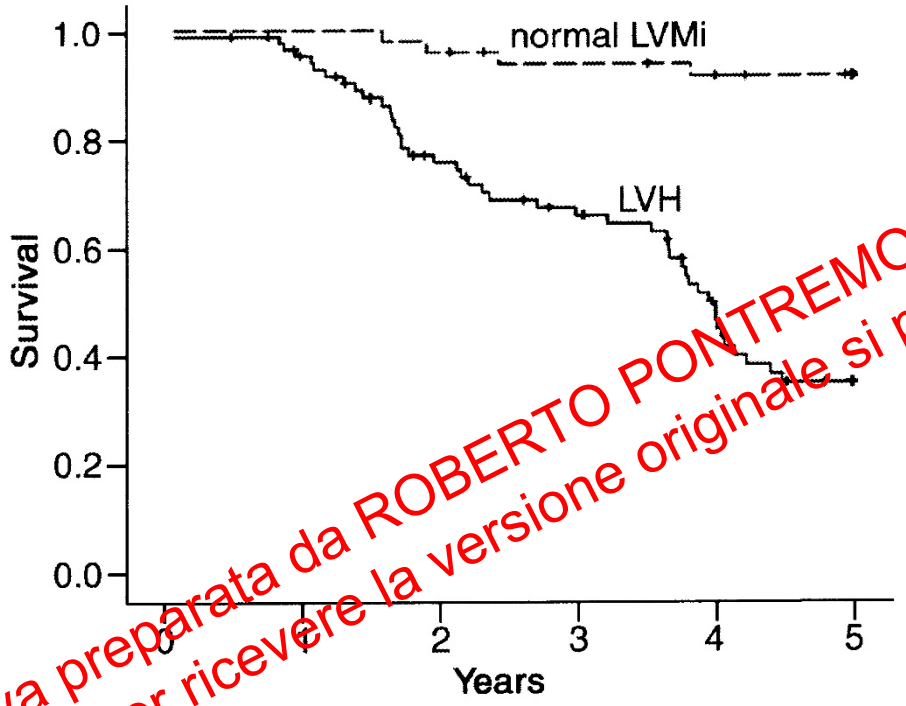
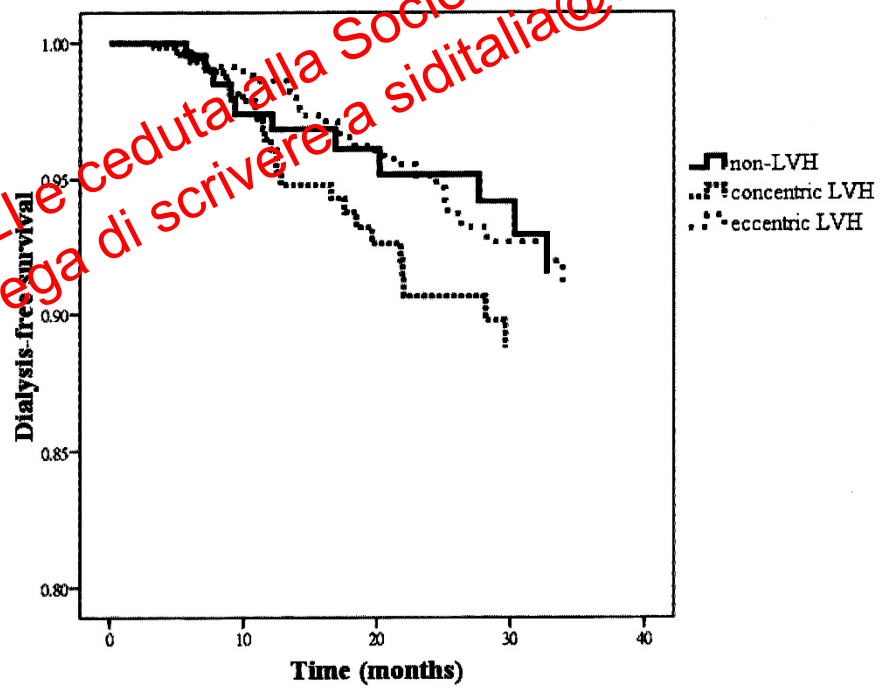
LVH and progression to dialysis in CKD patients

144 stage 3-4 CKD patients



Paoletti E, NDT 2010

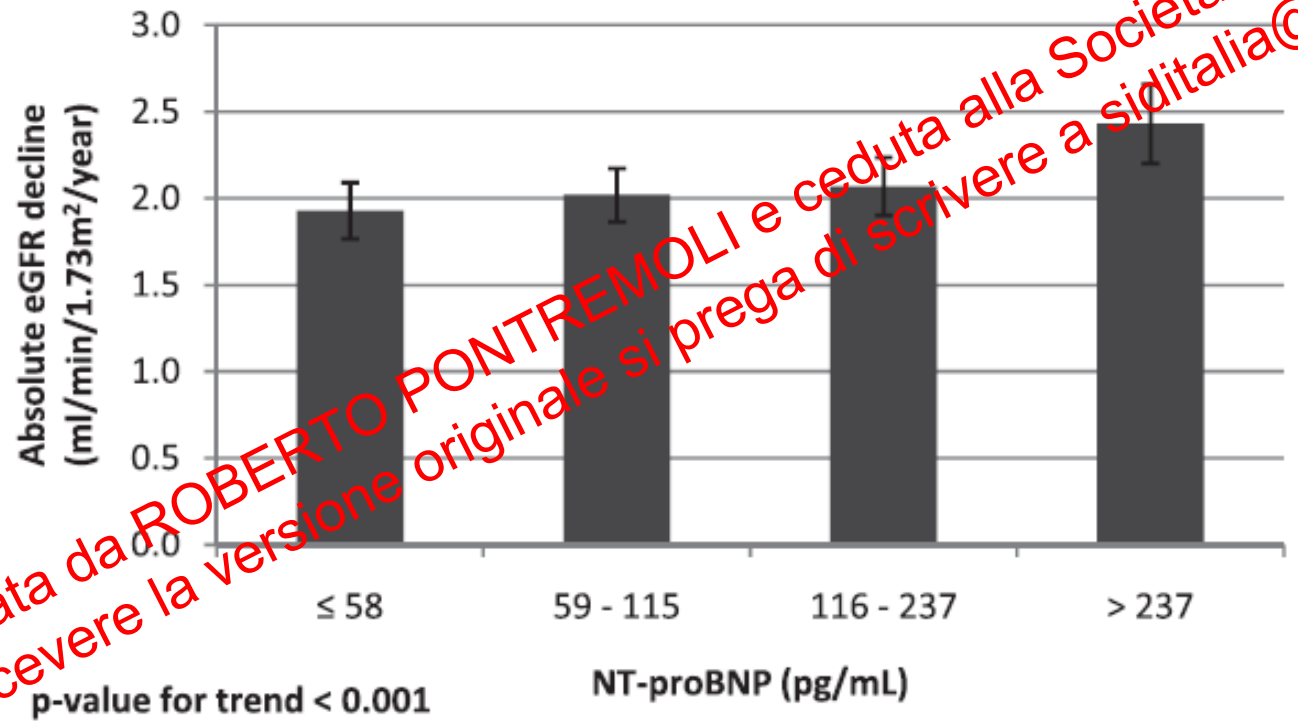
415 stage 3-5 CKD patients



Chen SC, CJASN 2011

NT-ProBNP and Troponin T and Risk of Rapid Kidney Function Decline and Incident CKD in Elderly Adults

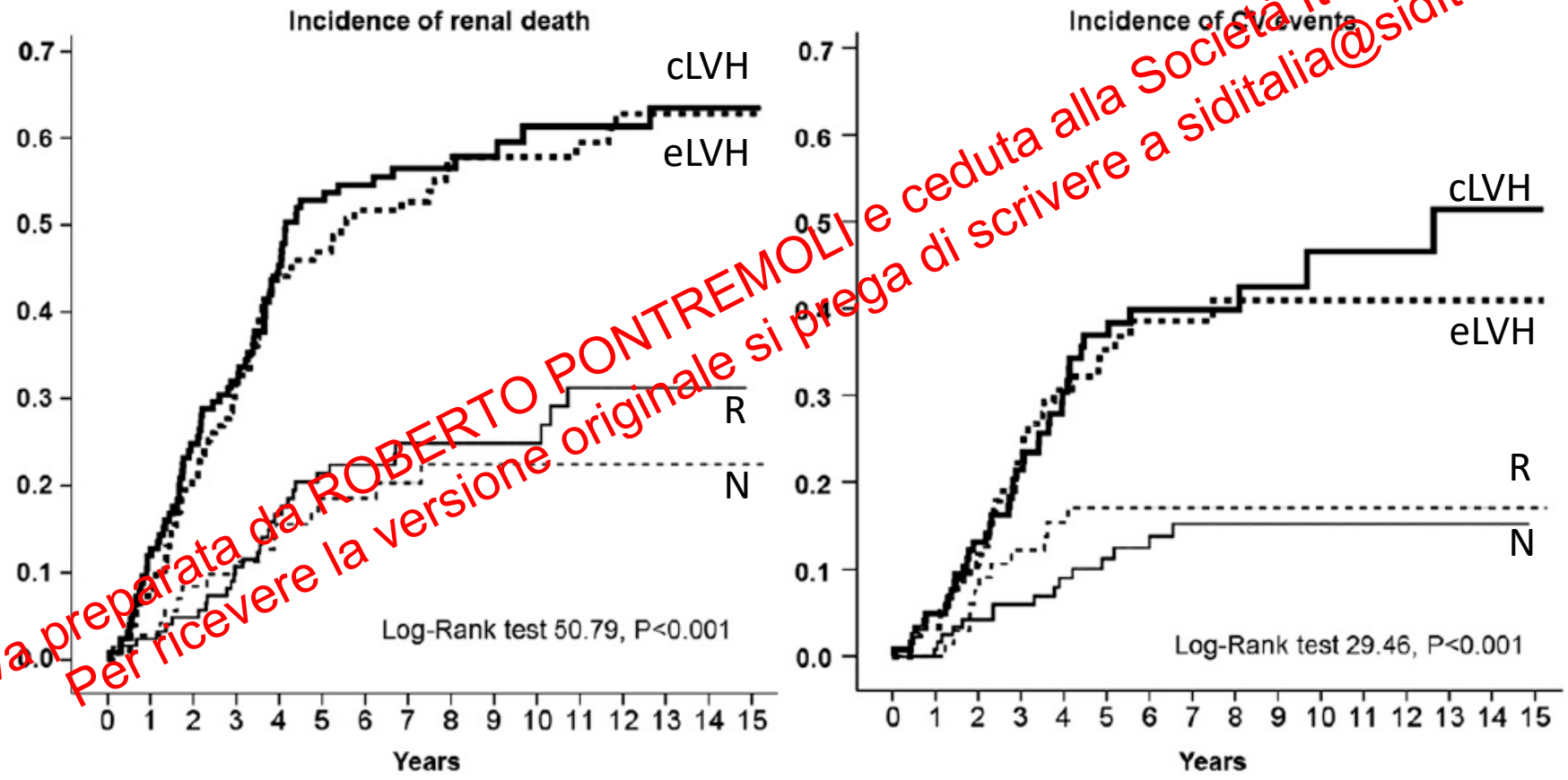
Nisha Bansal, Ronit Katz,* Lorien Dalrymple,† Ian de Boer,* Christopher DeFilippi,‡ Bryan Kestenbaum,* Meyeon Park,§ Mark Sarnak,‖ Stephen Seliger,¶ and Michael Shlipak**††‡‡§§*



CJASN 2015; 10: 205–214

Associations of Left Ventricular Hypertrophy and Geometry with Adverse Outcomes in Patients with CKD and Hypertension

Ernesto Paoletti, Luca De Nicola,† Francis B. Gabbai,‡ Paolo Chiodini,§ Maura Ravera,* Laura Pieracci,* Sonia Marre,* Paolo Cassottana,‖ Sergio Lucà,¶ Simone Vettoretti,** Silvio Borrelli,† Giuseppe Conte,† and Roberto Minutolo†*



CJASN 2016; 11: 271-279

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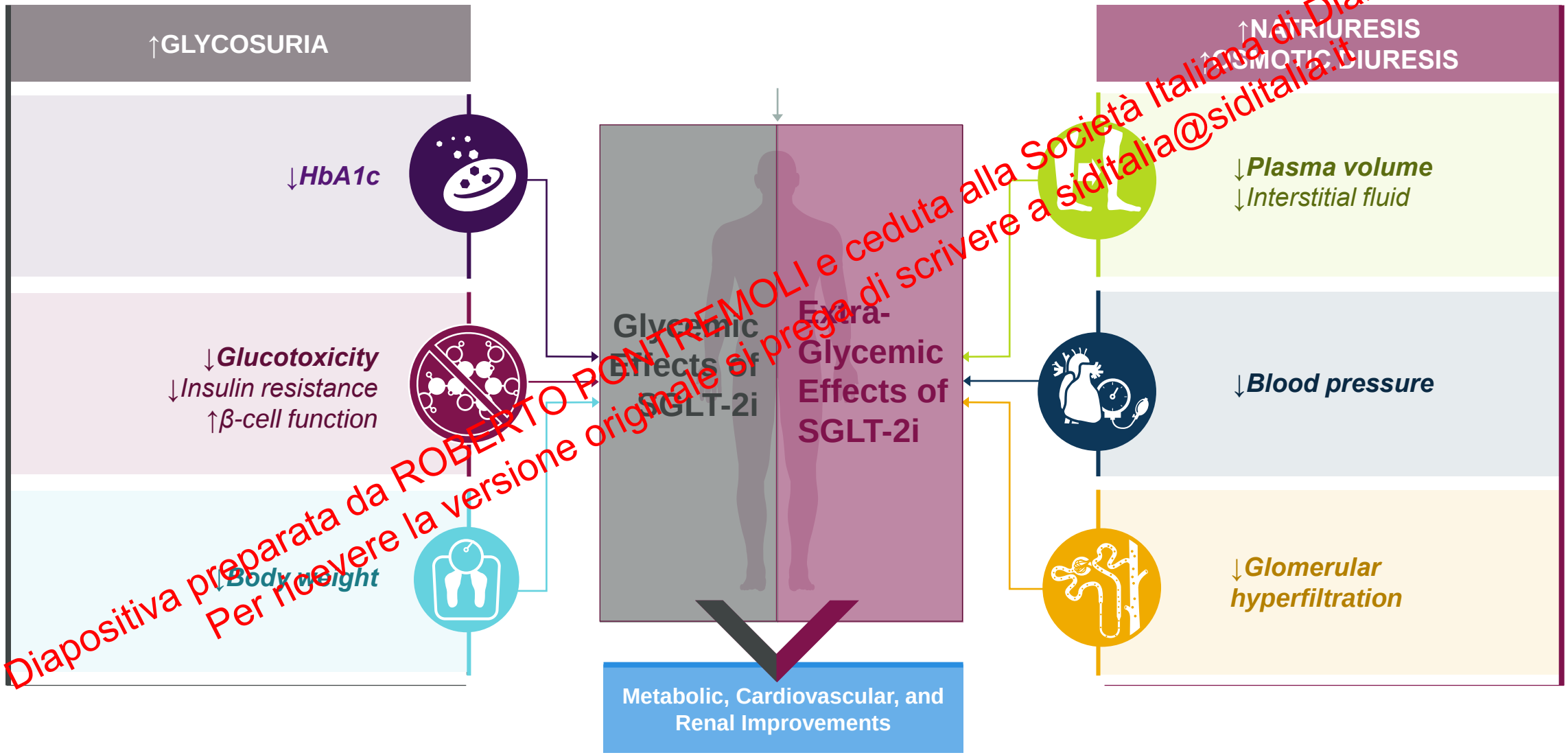
Key Physiological Effects of SGLT-2 Inhibition



HbA1C=hemoglobin A1C; SGLT-2=sodium-glucose co-transporter 2; SGLT-2i=sodium-glucose co-transporter 2 inhibitor.

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. van Baar MJB, et al. *Diabetes Care*. 2018;41(8):1543-1556. 3. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

Potential Effects by Which SGLT-2 Inhibition Improves Heart Failure Outcomes

SGLT-2 INHIBITION

Reduce Preload/Afterload[1,2]
↓Plasma volume
↓Vascular resistance

Improved Myocardial[2] **Energetics**
↓ Reliance on fatty acids
↑Ketone body formation
↓Cardiac NHE1

Cardiac Remodeling[1,2]
↓Inflammation/fibrosis
↓Cardiac wall stress

CLINICAL EFFECTS

BP Reduction[1]

Improved Cardiac Contractility
↓LV mass[3,4]
↑Diastolic function[2]

Protection Against Myocardial Injury/ Heart Failure[1,2]

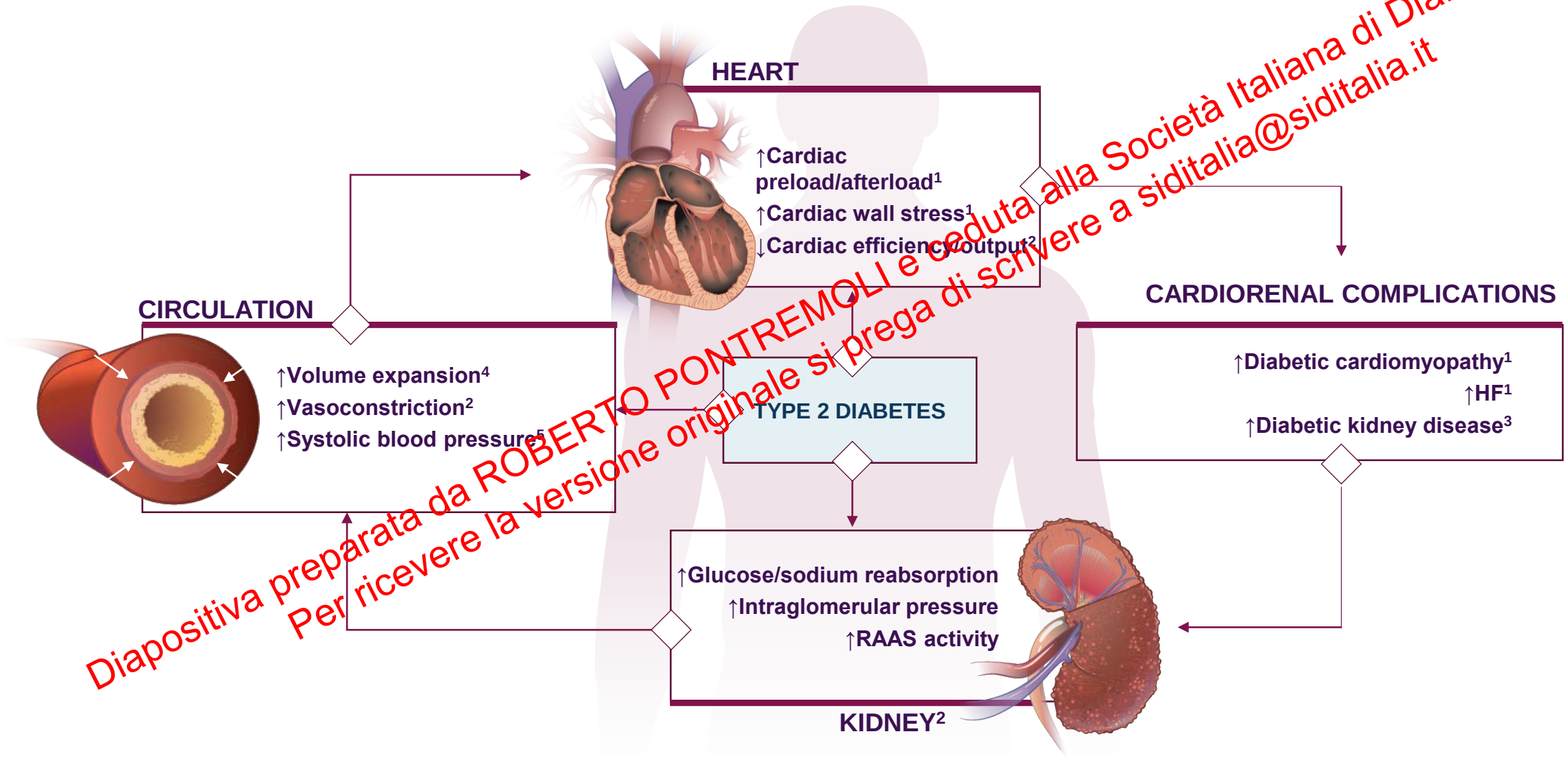
Improved Cardiac Function Reduced Heart Failure[1,2]

LV=left ventricular; NHE1=sodium-hydrogen exchanger 1.

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Verma S, et al. *Diabetes Care*. 2016;39(12):e212-e213. 4. Verma S. Presented at: American Heart Association Scientific Sessions; Nov. 10-12, 2018; Chicago.

Bidirectional, Pathophysiological Interaction Between Kidney and Heart in Type 2 Diabetes

Back to Summary Slide



1. Muralidaran Y, et al. *J Diabetes Metab.* 2015, 6:10. 2. Sattar N, et al. *Diabetologia*. 2016;59(7):1333-1339. 3. Wanner C, *Am J Cardiol*. 2017;120(1S):S59-S67. 4. Sattar N, et al. *Circulation*. 2018;138:7–9. 5. Mazidi M, et al. *J Am Heart Assoc*. 2017;6(6):e004007.

SGLT-2 Inhibition Improves Hemodynamic Parameters in Patients With Type 2 Diabetes Leading to Cardiorenal Protection

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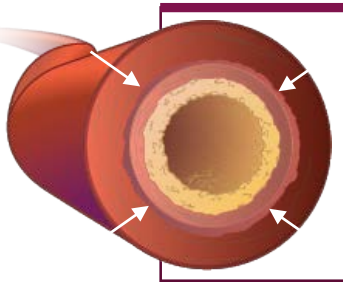
HEART[2]

↓Cardiac preload/afterload
↓Cardiac wall stress
↑Cardiac efficiency/output

CIRCULATION[1,2]



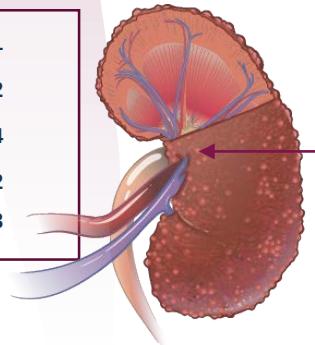
↓Plasma volume
↓Arterial stiffness
↓Systolic blood pressure
↑Hematocrit

SGLT-2 INHIBITION

Glycosuria[2]
Diuresis[3]
Natriuresis[2,3]

KIDNEY

↓Glucose/sodium reabsorption[1]
↓Intraglomerular pressure[2]
↓Intrarenal RAAS activity[4]
↓Hyperfiltration[2]
↓Inflammation/hypoxia[3]



CARDIORENAL PROTECTION[2,3]

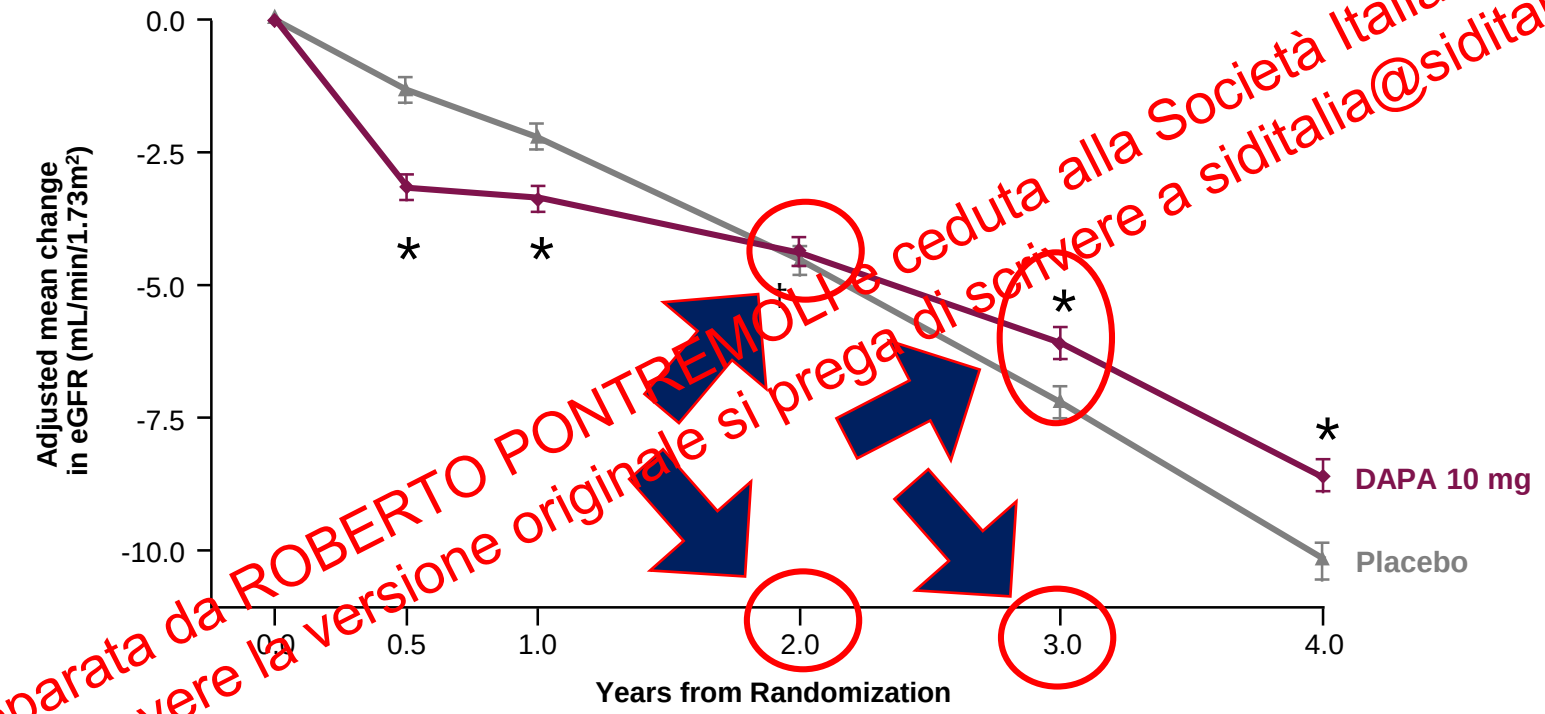
↑Cardiac function
↑Renal function

IMPROVED CLINICAL OUTCOMES[3,5]

↓CV outcomes
↓HF hospitalization
Stabilization of eGFR
↓Albuminuria

1. Sattar N et al. *Diabetologia*. 2016;59(7):1333-1339. 2. Verma S et al. *JAMA Cardiol*. 2017;2(9):939-940. 3. Scheen RJ. *Circ Res*. 2018;122:1439-1459. 4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 5. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

Change in eGFR Over Time

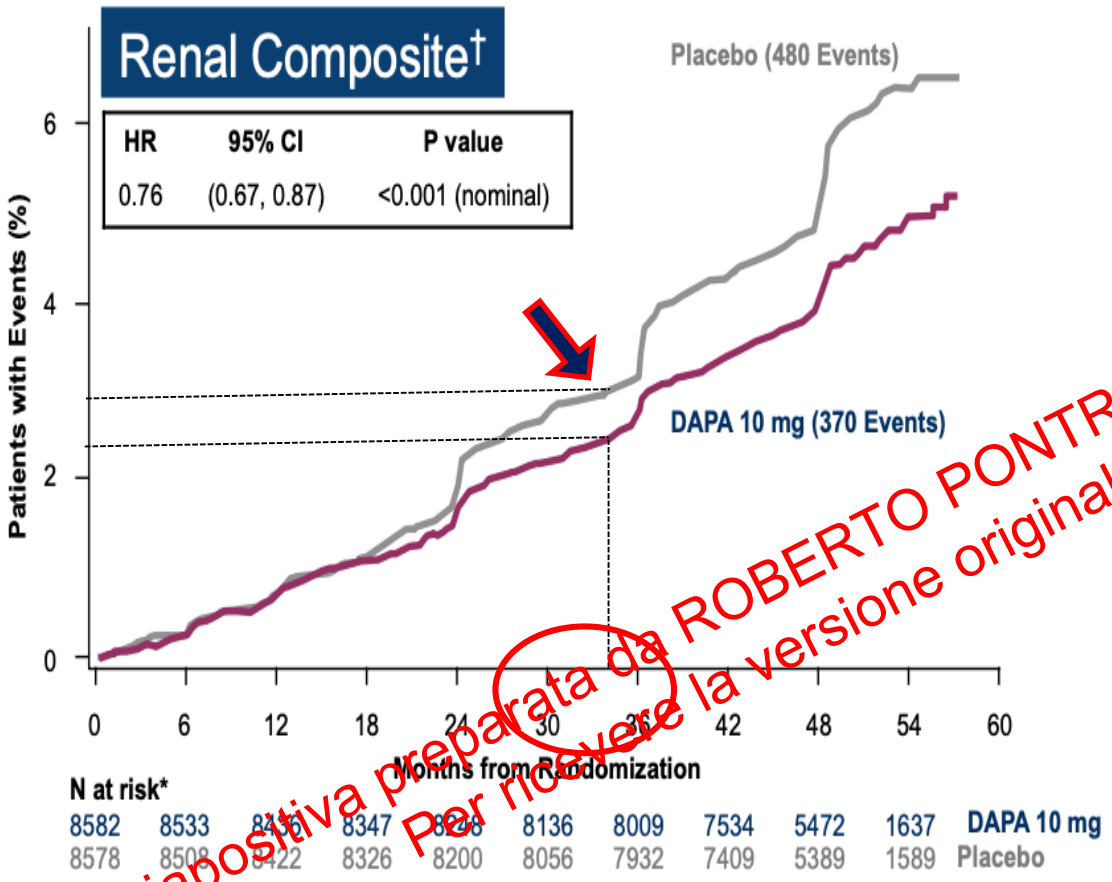


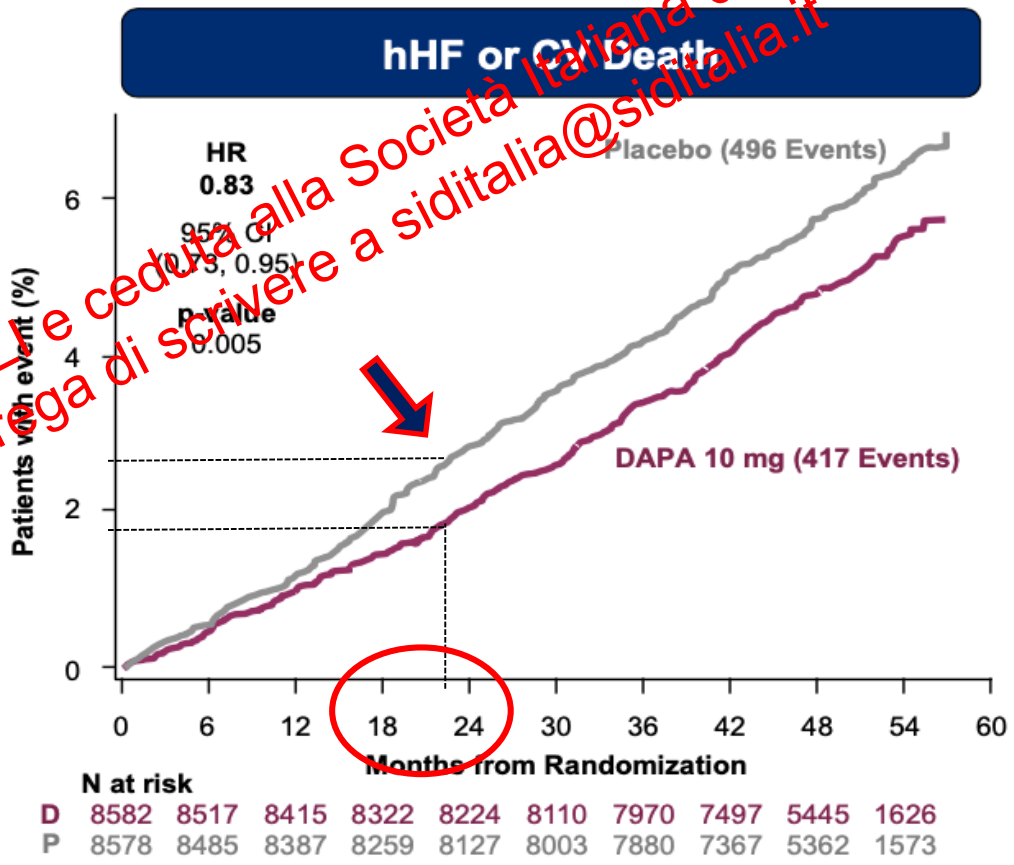
No. at risk

DAPA 10 mg	8581	8273	7978	7513	7098	6050
Placebo	8578	8223	7884	7316	6800	5770

Mosenzon O et al, *Lancet Diabetes Endocrinol*. 2019.

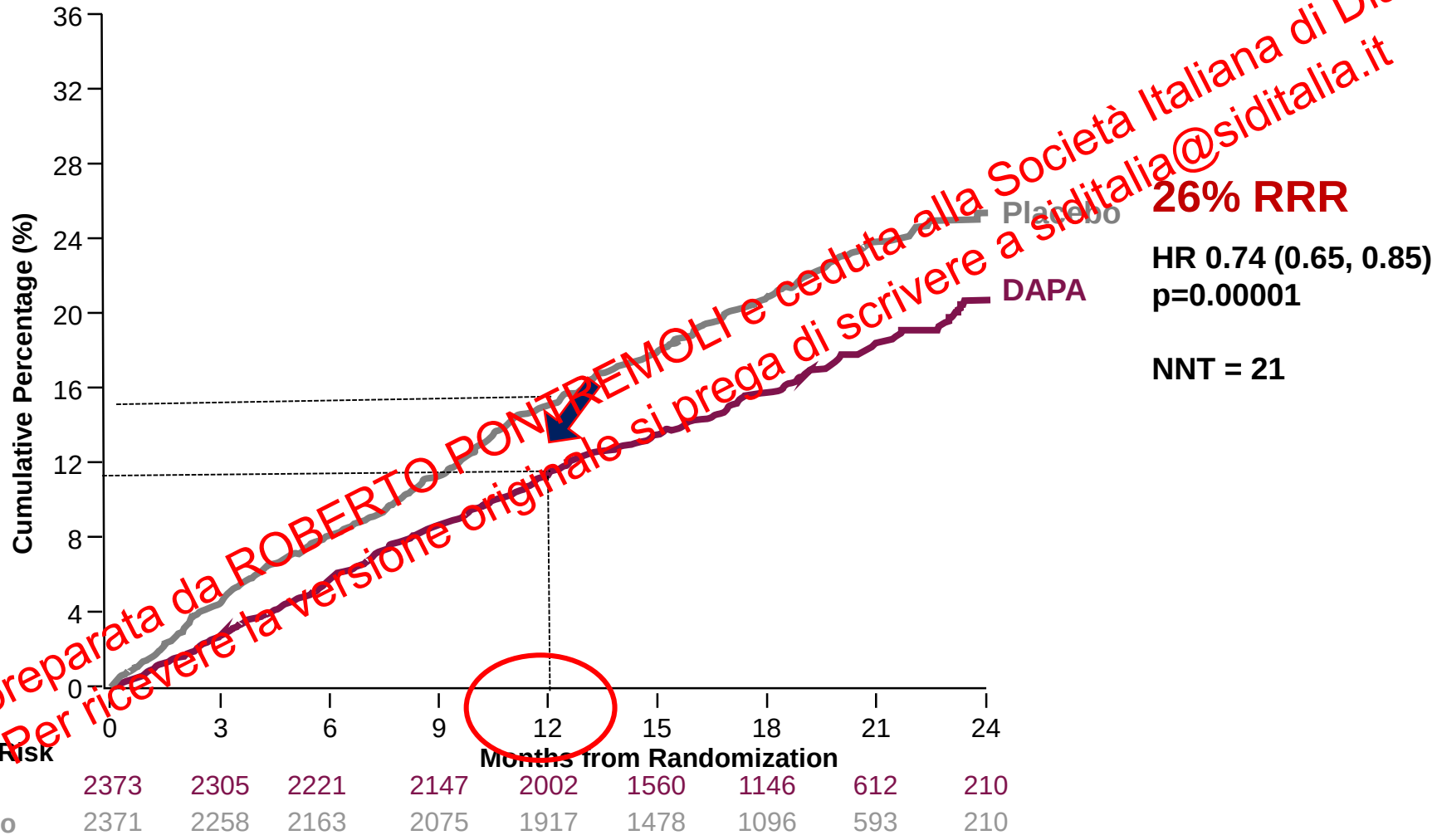
DECLARE-TIMI 58: Composite of hHF or CV death





Wiviott SD, et al. N Engl J Med 2018

Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1]



DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

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Take Home

- *Heart Failure and CKD often coexist and aggravate each other*
- *Heart Failure has a negative prognostic impact on renal outcome*
- *Results from CVOTs with SGLT2is support a role for HF improvement in renal protection*