Oltre gli antidiabetici: le terapia cardioprotettive nel diabetico con scompenso cardiaco

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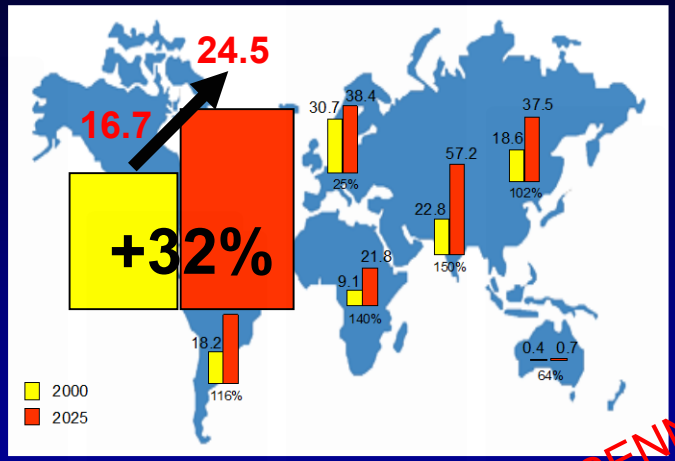
Michele Senni
Direttore
UOC Cardiologia

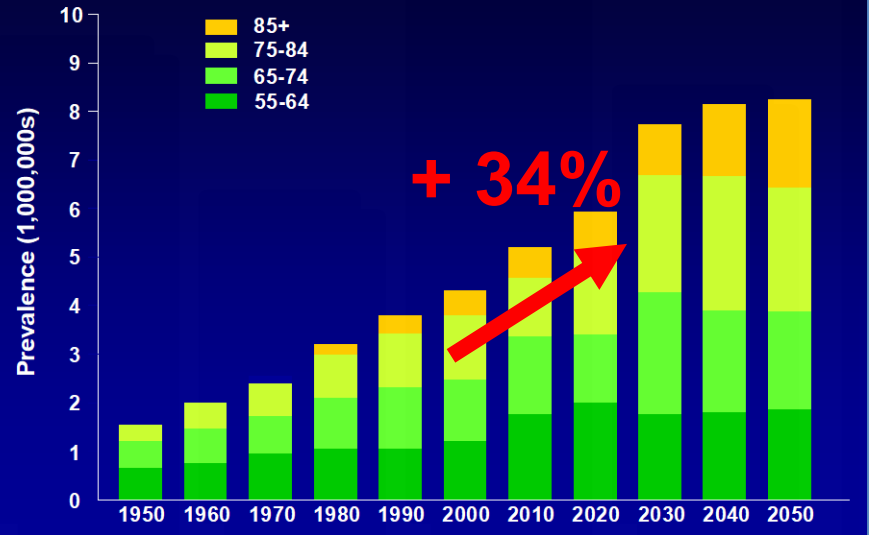
Temporal trends in Prevalence of Diabetes and Heart Failure

The global burden of diabetes (2000-2025)



	World	Developed	Developing
2000	154 m	55 m	99 m
2025	300 m	72 m	228 m

Past, Present and Estimated Prevalence of Heart Failure (USA 1950-2050)



Bristow MR, Lowes B Textbook of CV medicine, 7th ed 2004

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The diabetes and heart failure intersection

Incidence and Prevalence of HF in diabetes

Incidence and Prevalence of diabetes in HF

Therapeutic implications

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The diabetes and heart failure intersection

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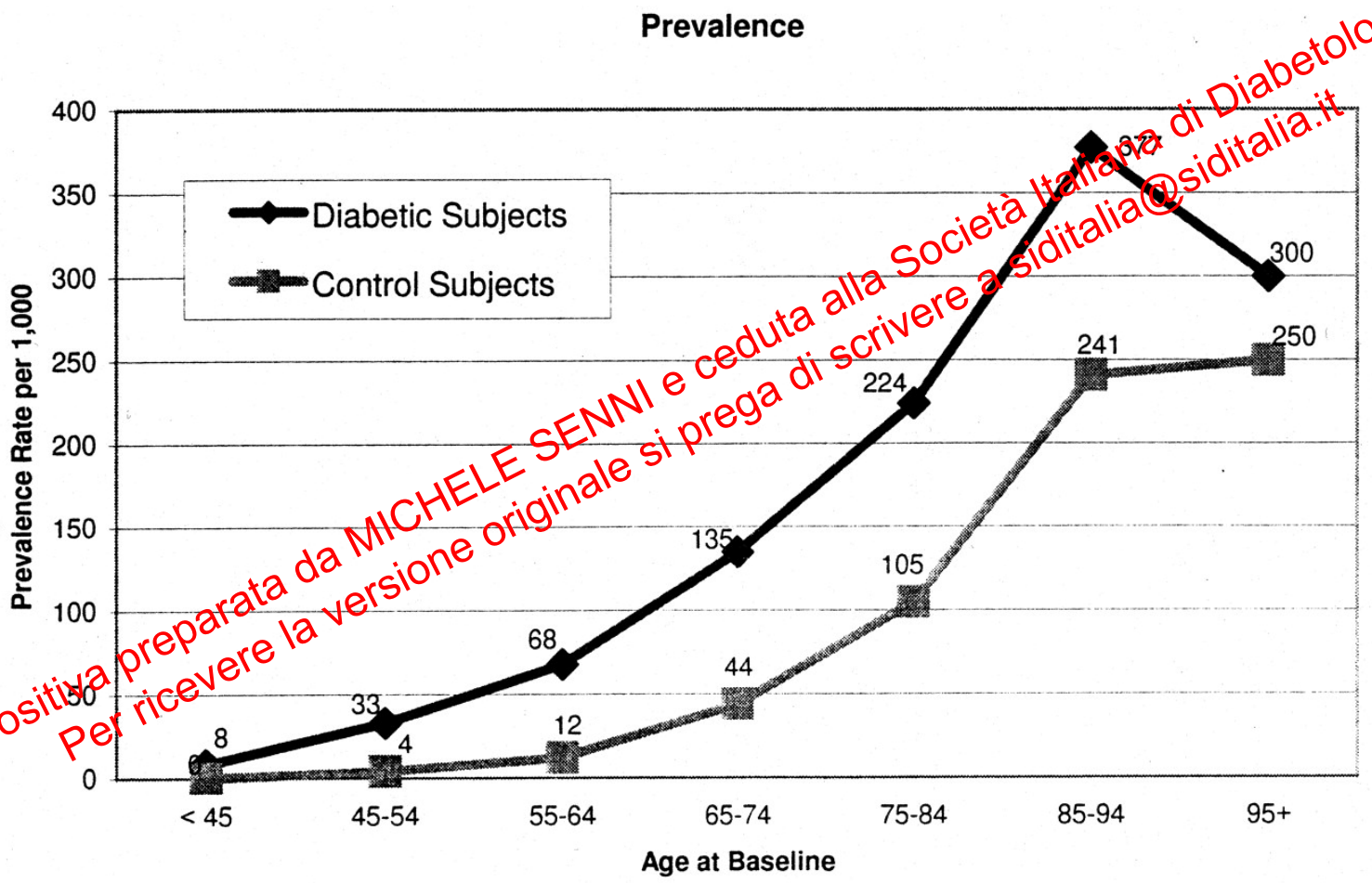
Prevalence of HF per 1,000 people.



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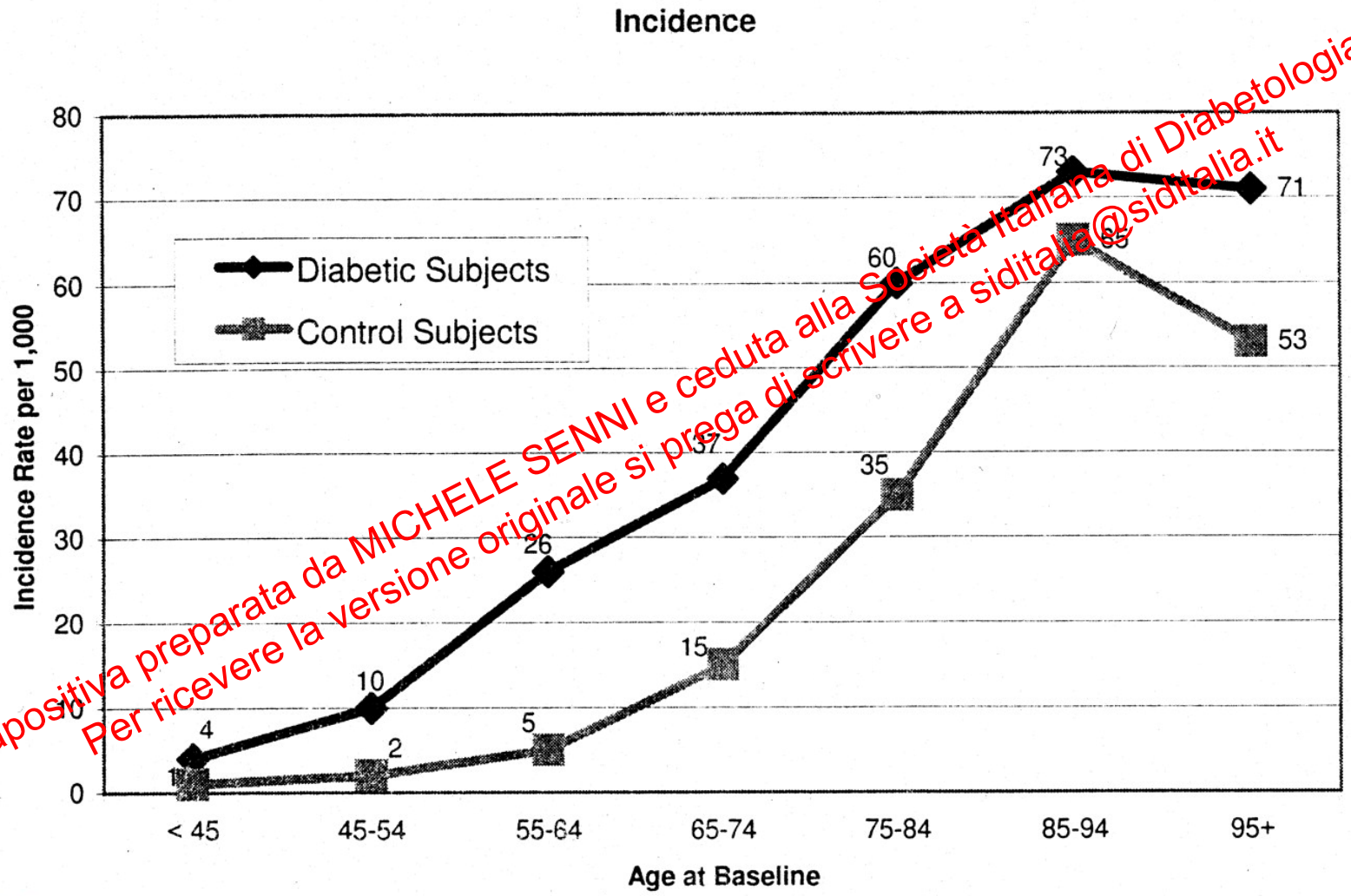
Gregory A. Nichols et al. Dia Care 2001;24:1614-1619

Prevalence of HF RCTs of 2 antidiabetic drugs

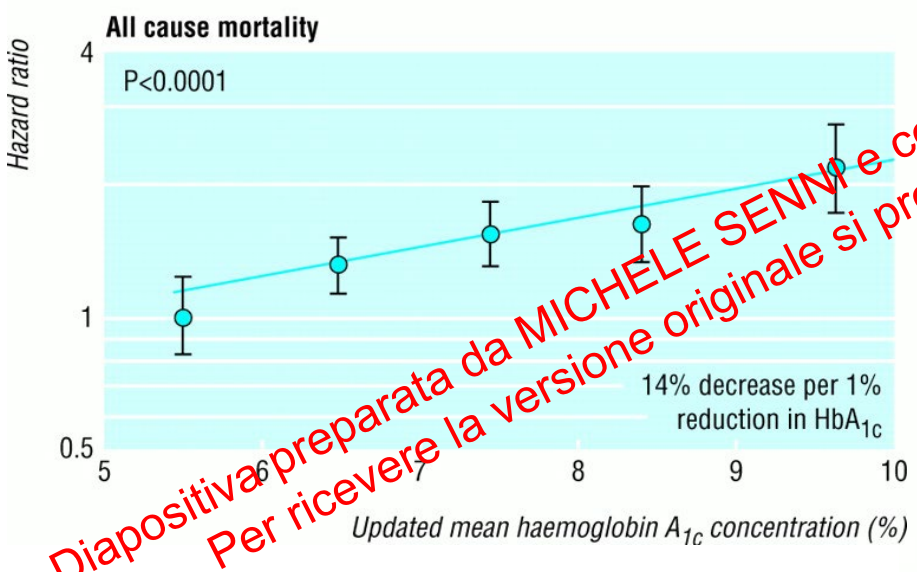
Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS 33[11]	NR (severe concurrent illness excluded)
ADVANCE[12,13]	NR
ACCORD[14]	4.3%
VADT[15]	NR
DPP4 inhibitor trials	
SAVOR-TIMI 53[16,17]	13%
TECOS[18]	18%
EXAMINE[19]	28%
SGLT2 inhibitor trials	
EMPA-REG OUTCOME[20]	10%
CANVAS[21]	14–15%
GLP-1 receptor agonist trials	
LEADER[22]	14%
ELIXA[23]	22%
EXSCEL[24]	16%

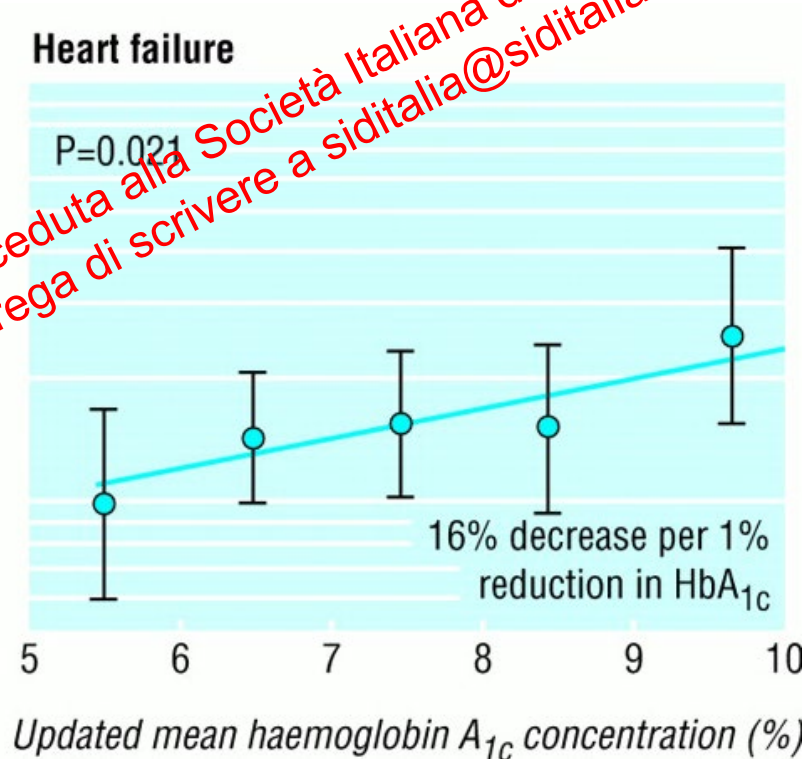
Annual incidence rates of HF per 1,000 people.



Gregory A. Nichols et al. Dia Care 2001;24:1614-1619

Association between mean haemoglobin A1c concentration and all cause mortality and heart failure.





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Irene M Stratton et al. BMJ 2000;321:405-412

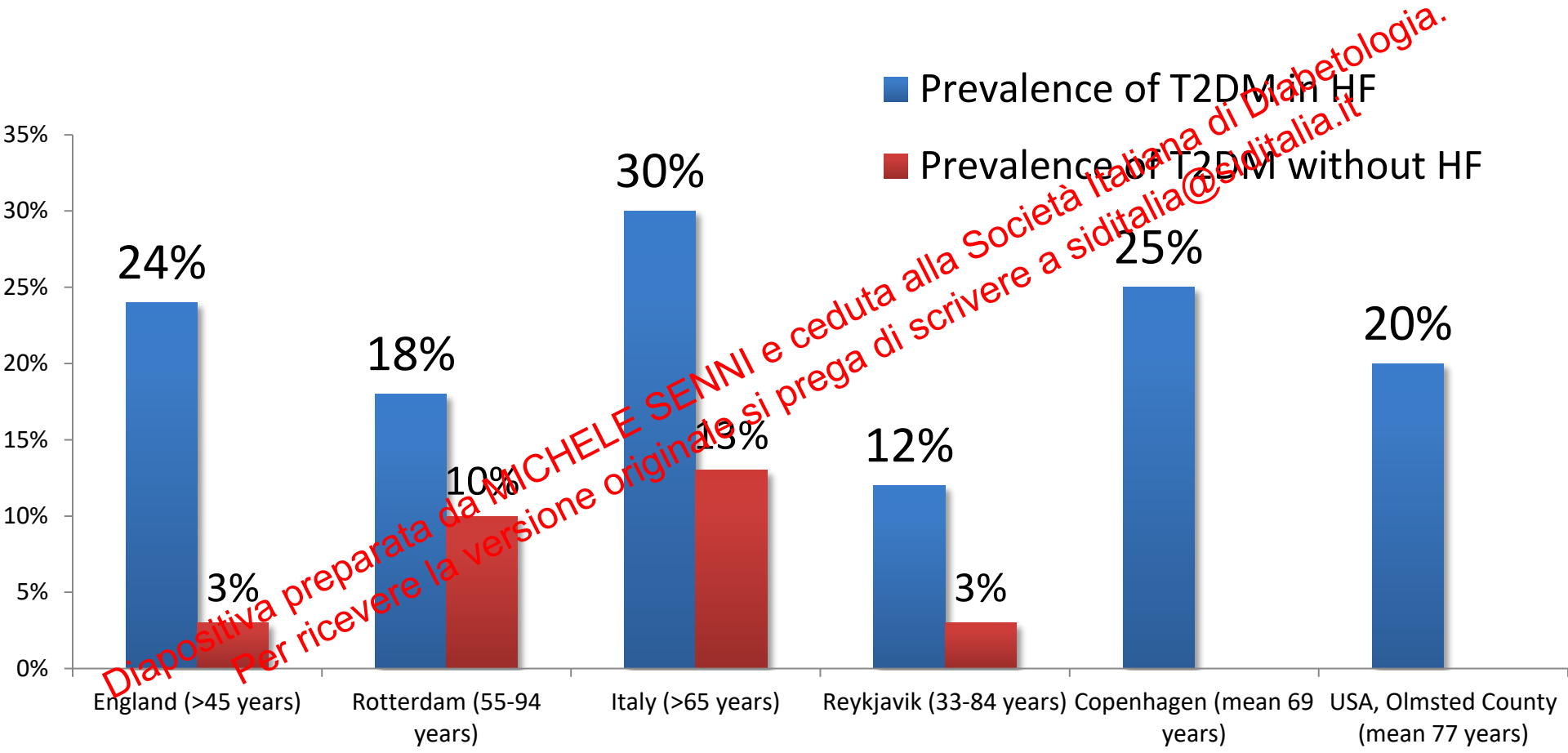
The diabetes and heart failure intersection

Incidence and Prevalence of HF in diabetes

Incidence and Prevalence of diabetes in HF

Higher prevalence of diabetes in heart failure

Population-based data



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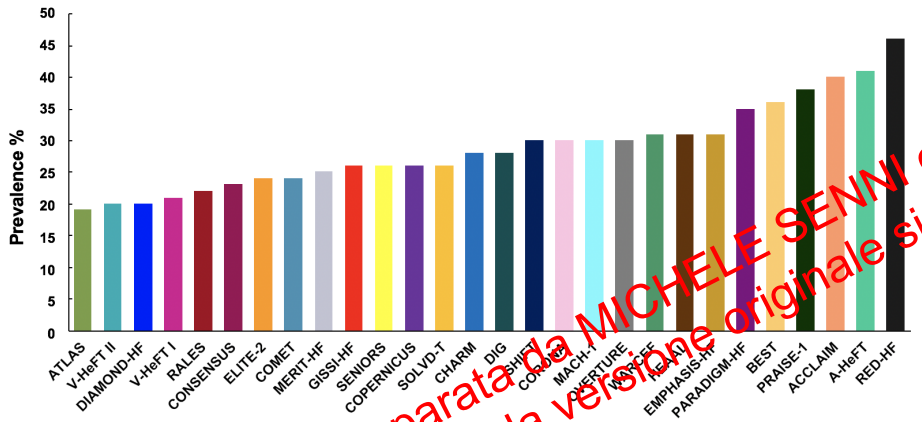
Seferović PM et al. Eur J Heart Fail. 2018

Prevalence of DM in RCTs of HF

HFrEF: Prevalence of diabetes



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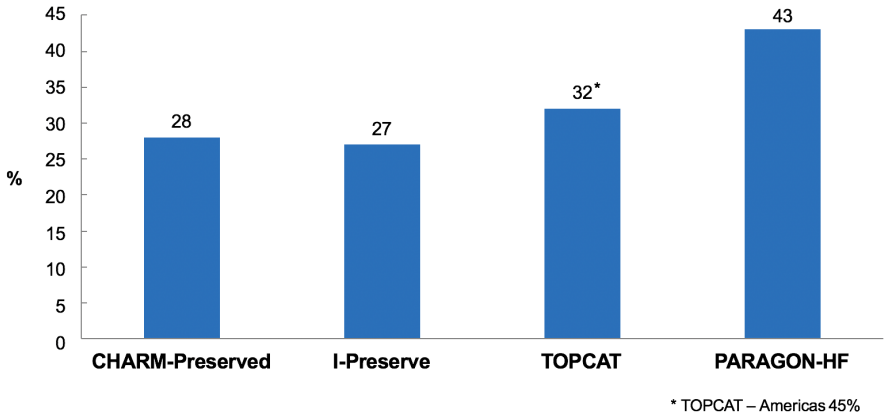
HFpEF: Prevalence of diabetes



* TOPCAT – Americas 45%

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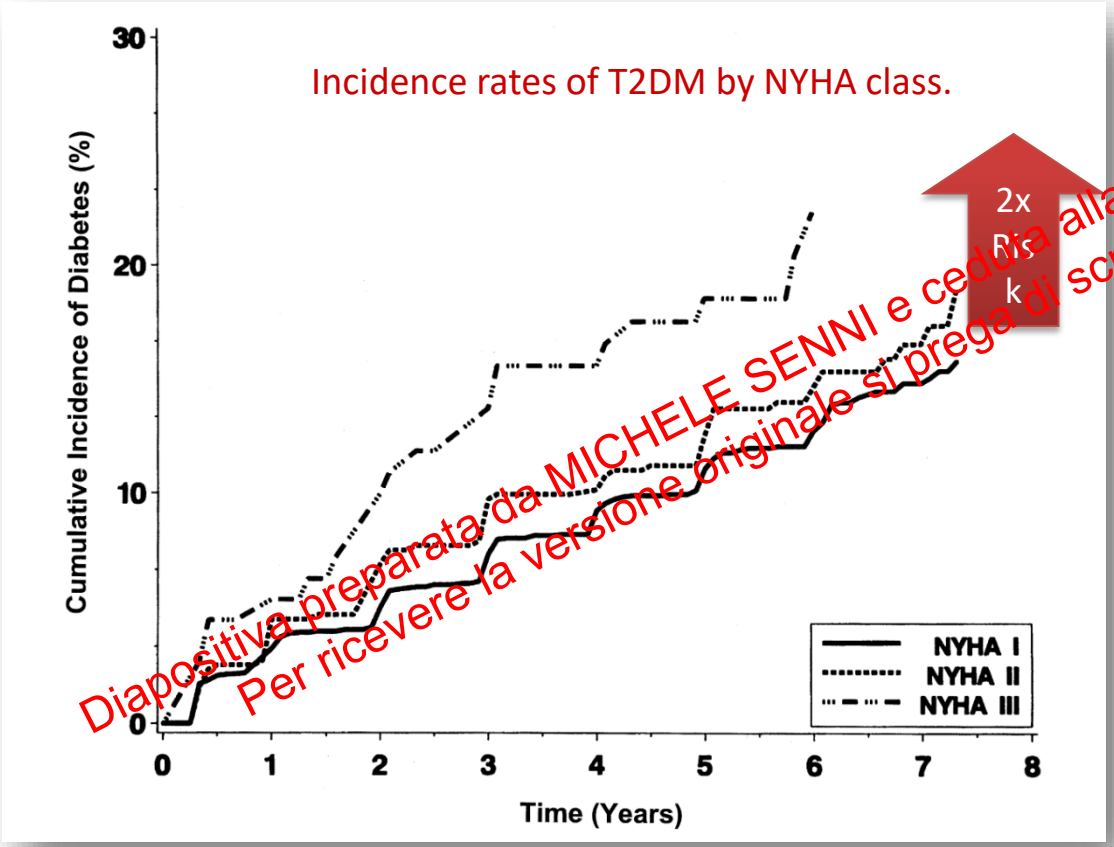
More severe HF is associated with a higher incidence of T2DM

- Observational study, n= 2,6216 patients without T2DM at baseline, follow-up: 7.7 years -



Comparison of curves (log-rank test):

- class III vs. class I (P=0.02);
- class II vs. class I (P=0.26).

Comparison of HR for T2DM:

- class III vs. class I:
  1.7 (95% CI 1.1 - 2.6).

Tenenbaum A et al. Am J Med 2003

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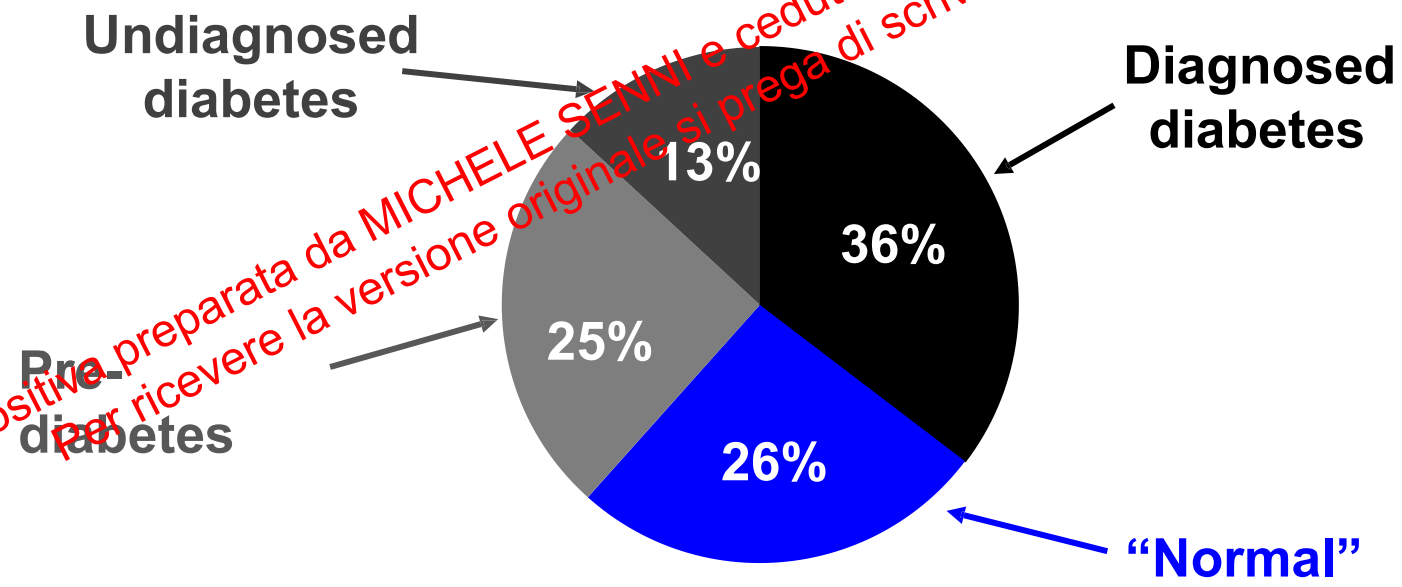
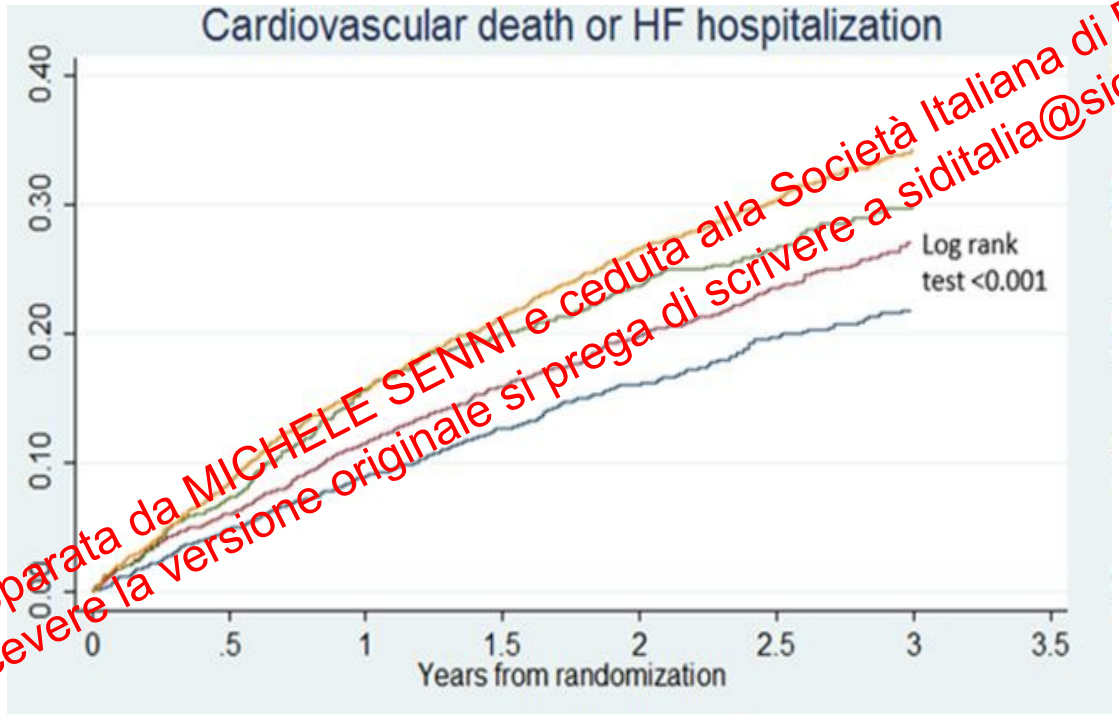
PARADIGM-HF: Dys-glycaemia in heart failure

8274 patients with HF-REF randomized in PARADIGM-HF. Diabetes = investigator reported diagnosis. Undiagnosed diabetes = no diagnosis of diabetes and HbA1c ≥ 6.5%. Pre-diabetes = no diabetes and HbA1c 6.0- <6.5%
(caveat: single HbA1c measurement)



Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction

Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial



Kristensen et al. Circulation Heart Fail 2016

Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction

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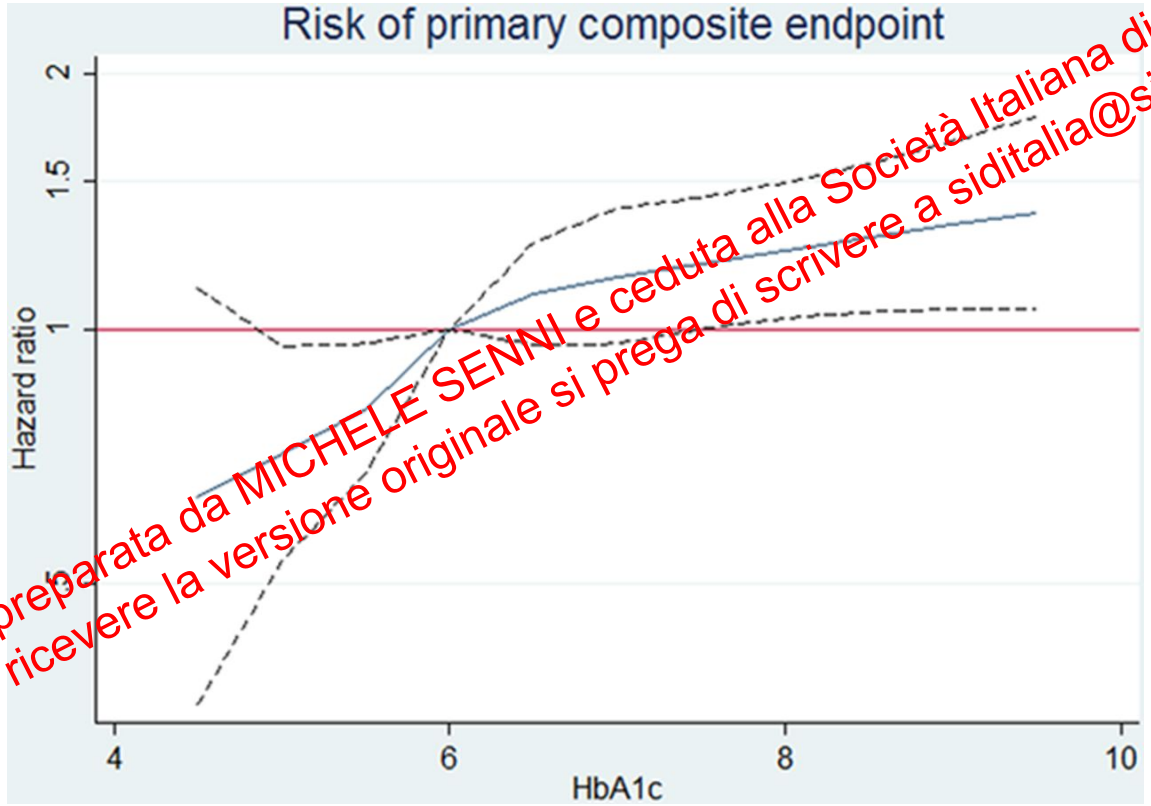

Kristensen et al. Circulation Heart Fail 2016

Comorbidity Burden & Prognosis (ClinicalTrials.gov Identifier: NCT02946476)

Impact of Comorbidities in HFpEF and HFrEF:

Interaction analysis and Population Attributable Fraction

- 2,442 HF patients,
- mean age 77±10,
- 65% male
- HFrEF 42%; HFpEF 58%

Similar prevalence non-cardiac comorbidities

Variable	HFrEF	HFpEF	
Diabetes mellitus	1.8¥ (1.3-3.3)	1.4¥ (1.4-2.4)	
Hyp			
Peri			
Cere			
Chronic Renal Failure	2.3¥ (1.1-3.2)	1.6 § (1.3-2.1)	0.0
Anemia	1.9¥ (1.2-3.0)	1.9 ¥ (1.4-2.6)	0.9
Chronic Pulmonary Disease	1.3§ (1.2-1.8)	1.4 § (1.1-1.8)	0.6
Obesity	0.6 (0.4-0.9)	0.6 (0.4-0.8)	0.8
Dementia	2.8* (1.2-6.9)	0.6 (0.9-4.8)	0.1
Liver Disease	1.3 (0.7-2.6)	0.8 (0.4-1.6)	0.3
Cancer	1.3 (0.9-3.7)	1.2 * (0.7-2.1)	0.8
Rheumatologic Disorders	1.1 (0.8-2.9)	1.3 (0.7-2.3)	0.8
Peptic Ulcer	1.9 (0.7-5.0)	1.3 (0.6-2.8)	0.4
	1.3 (0.6-2.6)	0.6 (0.2-1.5)	0.1

Noncardiac comorbidities		Crude HR (95% CI)	Adjusted HR (95% CI)	PAF exp, % (95% CI)	PAF pop, % (95% CI)
All-cause mortality					
Chronic obstructive pulmonary disease	Overall	1.7 (1.3-2.1)	1.6 (1.3-1.9)	39 (18-60)	12 (6-17)
	HFpEF	1.7 (1.3-2.3)	1.4 (1.1-1.8)	40 (16-64)	13 (4-21)
	HFrEF	1.7 (1.2-2.3)	1.3 (1.2-1.8)	45 (34-86)	12 (3-21)
Anemia	Overall	2 (1.6-2.5)	1.9 (1.5-2.4)	59 (33-85)	18 (13-22)
	HFpEF	1.6 (1.2-2.1)	1.9 (1.4-2.6)	42 (11-72)	16 (2-24)
	HFrEF	2.7 (2-3.8)	1.9 (1.2-2.5)	80 (41-98)	23 (14-30)
					2)
					0)
	HFrEF	2.4 (1.7-3.3)	1.9 (1.7-2.3)	35 (12-56)	26 (11-42)
Diabetes mellitus	Overall	1.3 (1.1-1.6)	1.4 (1.2-1.7)	39 (18-60)	18 (12-23)
	HFpEF	1.3 (1.1-1.6)	1.6 (1.4-2.4)	32 (7-57)	15 (5-25)
	HFrEF	1.7 (1.3-2.3)	1.8 (1.3-2.2)	40 (14-86)	22 (11-33)
Peripheral vascular disease	Overall	1.3 (1.1-1.7)	1.1 (0.9-1.5)	-	-
	HFpEF	1.1 (0.9-1.5)	1.2 (1.1-1.9)	-	-
	HFrEF	1.7 (1.3-2.5)	1.3 (1.1-1.8)	-	-

DM is one of the most disabling comorbidities complicating HF

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Iorio A, Senni M, … Eur J Heart Fail 2018

The diabetes and heart failure intersection

Incidence and Prevalence of HF in diabetes

Incidence and Prevalence of diabetes in HF

Therapeutic implications

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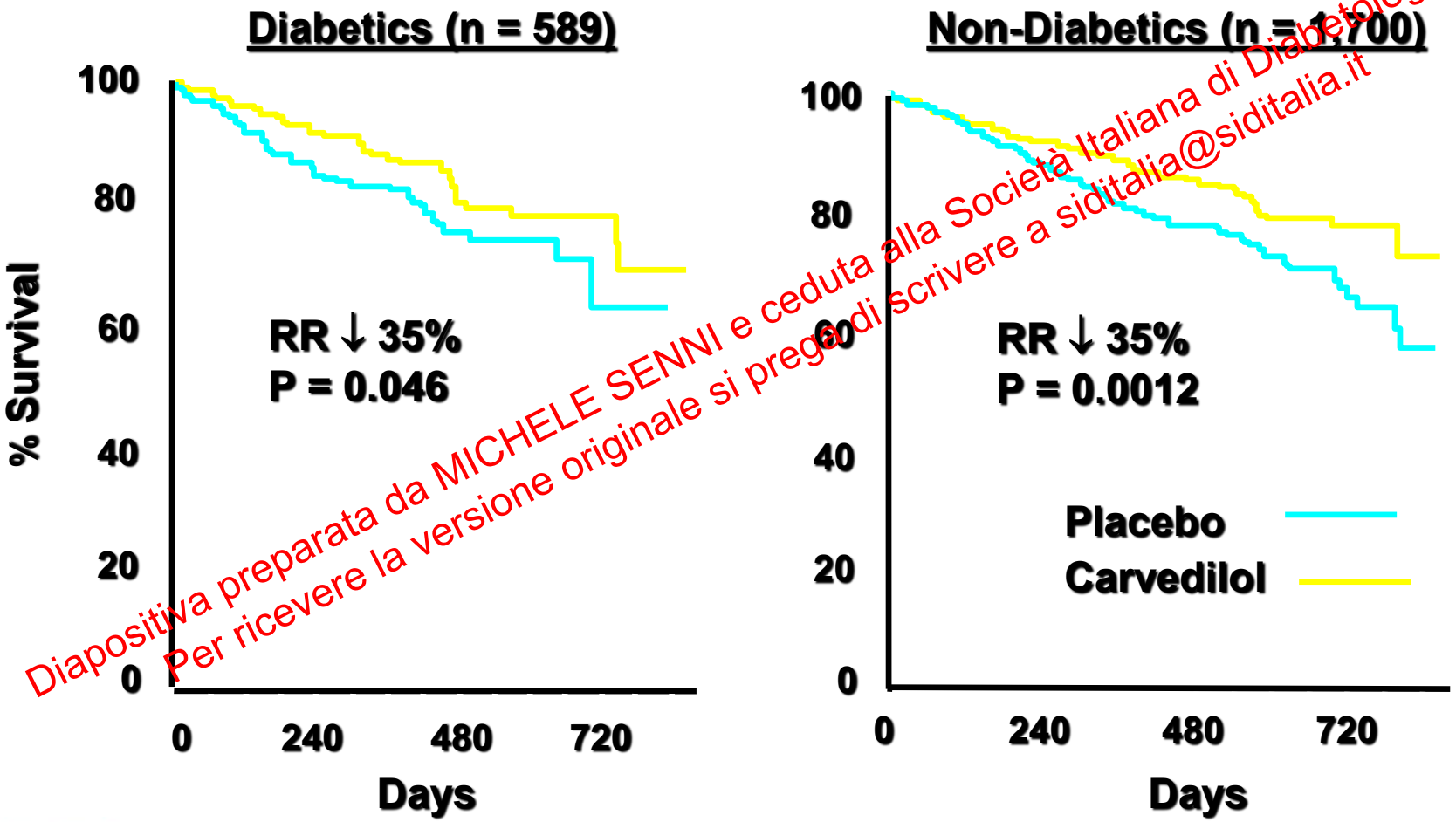
RANDOMIZED CLINICAL TRIALS in HEART FAILURE (1986-2018)

	HF (including diabetes)	HF and diabetes
• VASODILATORS :	**V-HeFT I, PROFILE, FIRST**	--
• ACE INHIBITORS :	**V-HeFT II, CONSENSUS, SAVE, SOLVD TREAT/PREV, NETWORK, ATLAS**	--
• AII R ANTAGONISTS:	**ELITE, RESOLVD, ELITE II, VAL-HeFT**	--
• Ca ANTAGONISTS :	**PRAISE, V-HeFT III, MACH-1**	--
• DIGITALIS :	**CAPTOPRIL-DIGOXIN MRG, CADS, RADIANCE, DIG**	--
• INOTROPES :	**PROMISE, VEST, PRIME II**	--
• AMIODARONE :	**GESICA, CHF-STAT**	--
• BETA-BLOCKERS :	**XAMOTEROL, MDC, CIBIS I, CIBIS II, ANZ, US CARVEDILOL, MERIT, BEST COPERNICUS, CAPRICORN**	--
• ARNI :	**PARADIGM**	--

COPERNICUS
Effect of Carvedilol on All-Cause Mortality



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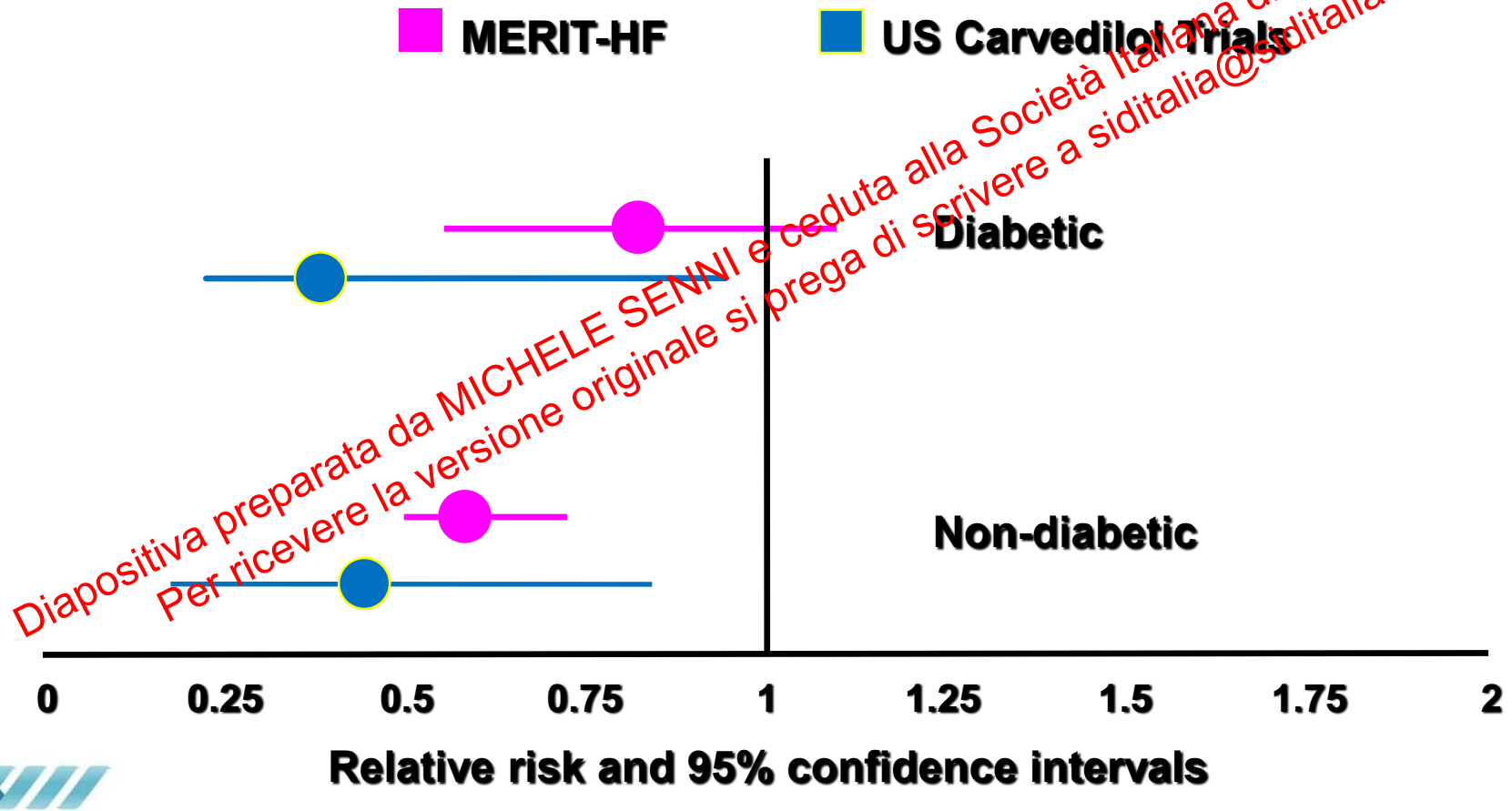
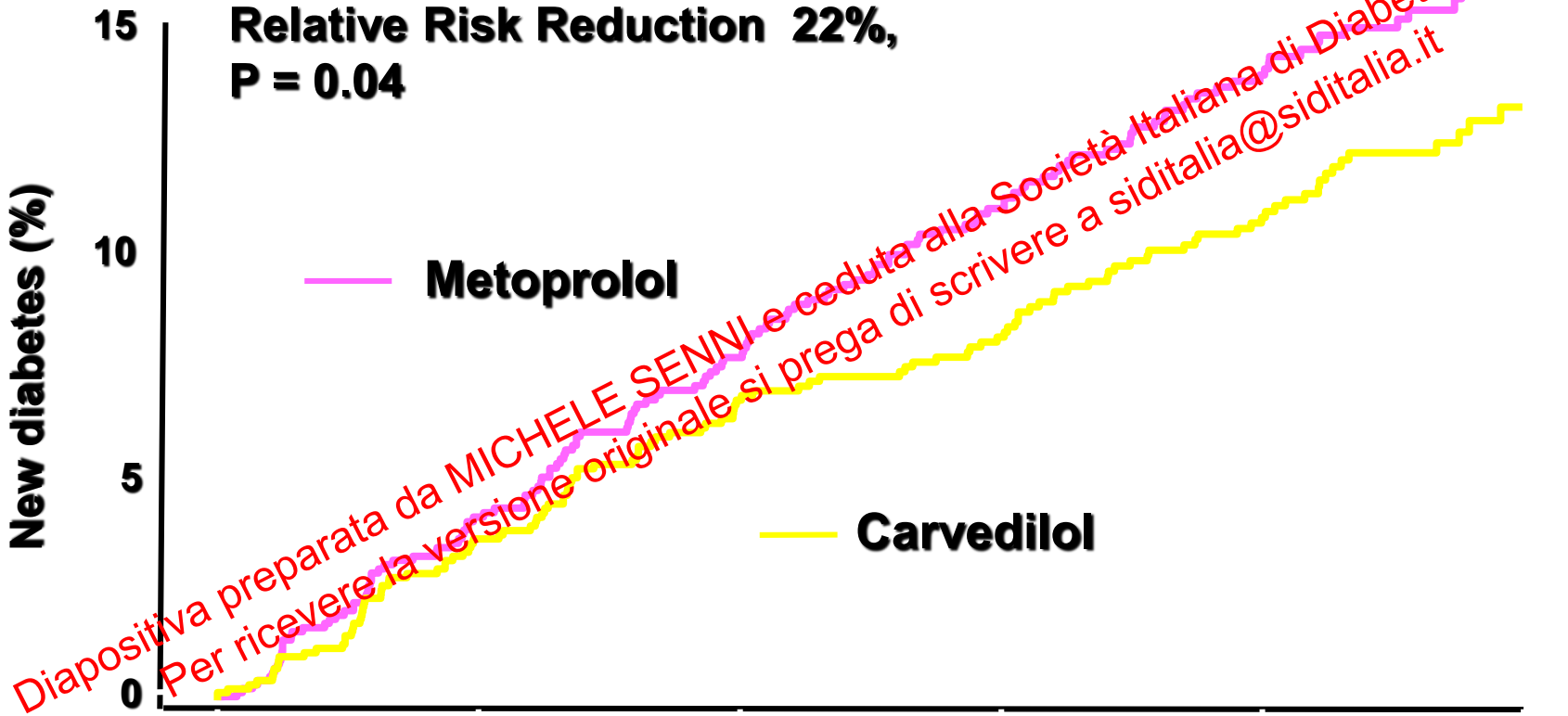
I. Circulation 2001

Effect of β-blockade on All-cause Mortality by Diabetic status



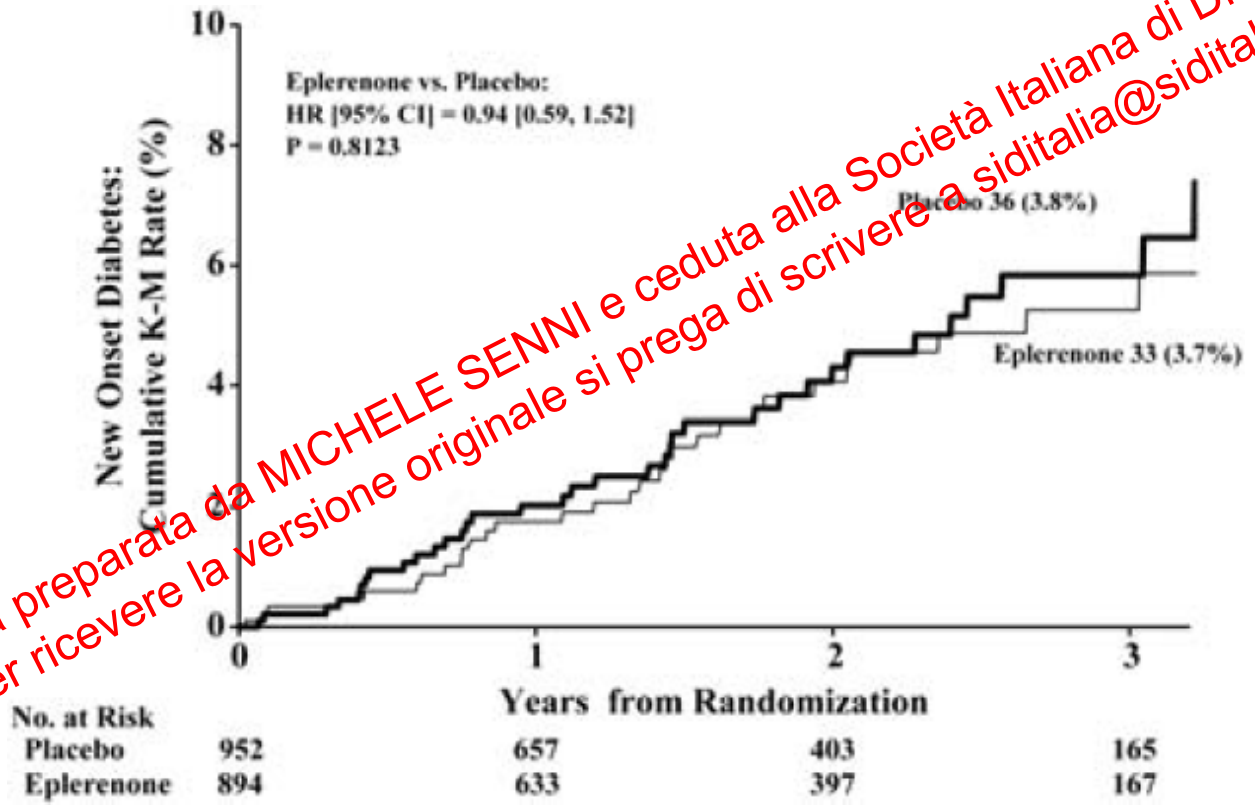
COMET
New onset of diabetes



Number at risk						
Metoprolol	1,147	991	879	764	626	221
Carvedilol	1,151	1,014	908	827	705	254

Top Pedersen et al Heart 2007

EMPHASIS-HF
Eplerenone and new-onset diabetes



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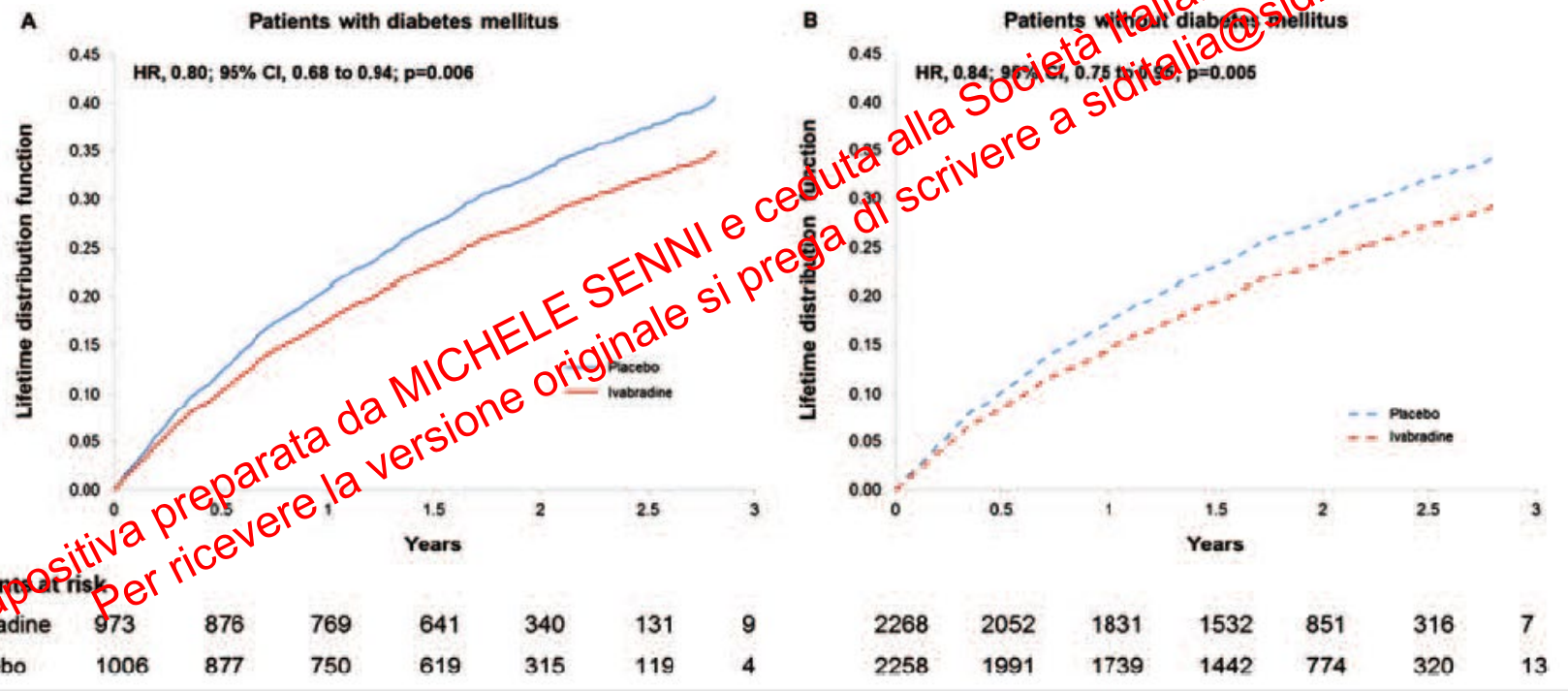
Preiss et al. European Journal of Heart Failure, 2014

Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial

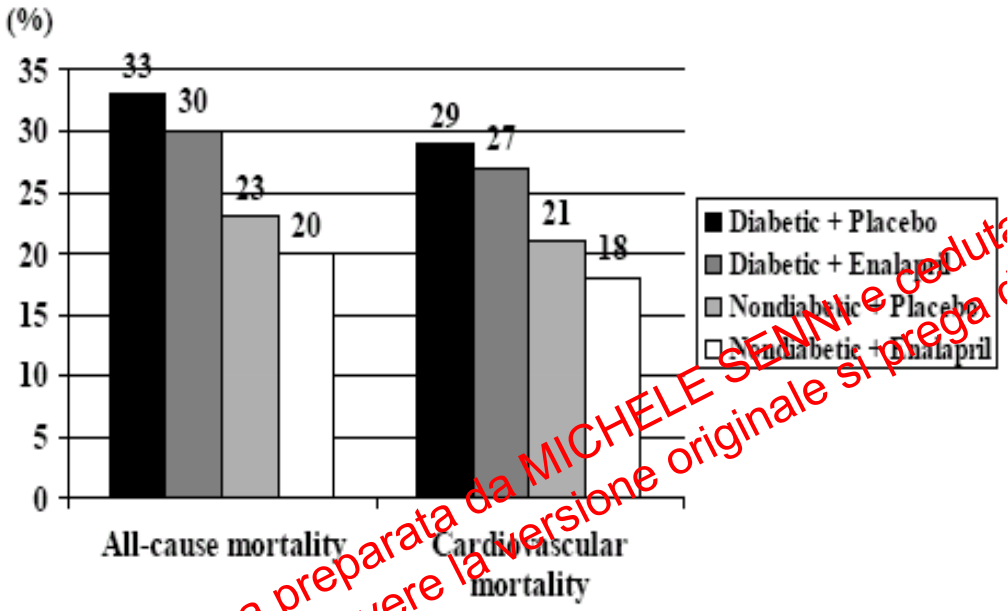
Michel Komajda[1]*, Luigi Tavazzi[2], Bernard G. Francq[3], Michael Böhm[4], Jeffrey S. Borer[5], Ian Ford[3], and Karl Swedberg[6], on behalf of the SHIFT Investigators

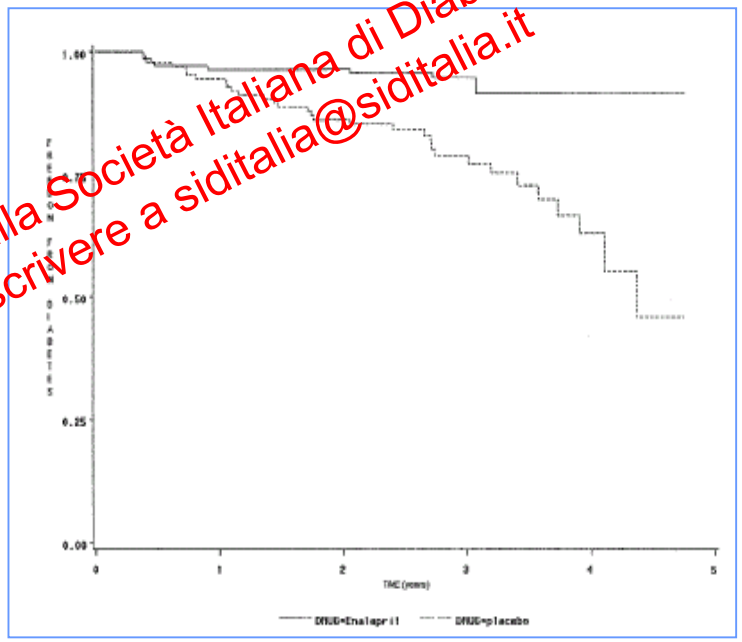


L.IT.MA.O2.2017.2189

Eur J Heart Fail 2015

SOLVD study : pazienti diabetici





Vermes et al. Circulation 2003; 107: 1291-1296

Efficacy of Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in the Management of Left Ventricular Systolic Dysfunction According to Race, Gender, and Diabetic Status

A Meta-Analysis of Major Clinical Trials

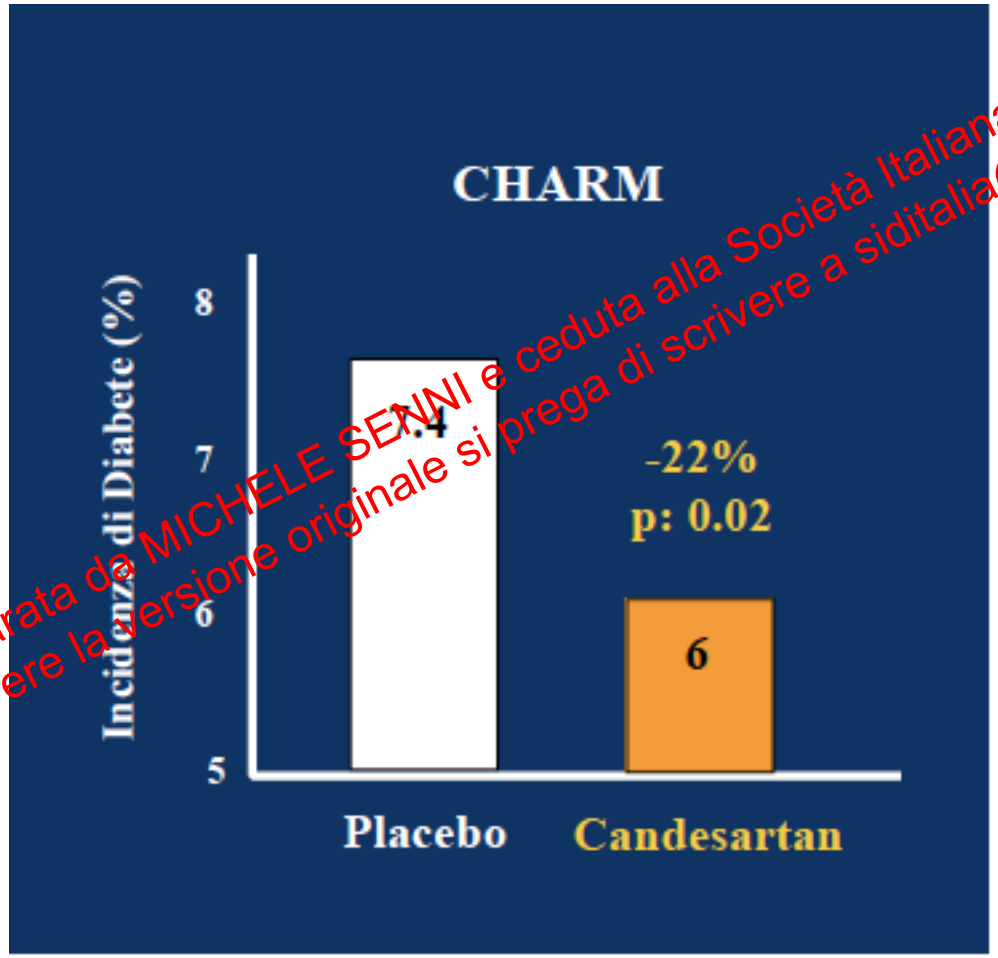
Table 4. Effect of ACE Inhibitors on Mortality From Heart Failure in Diabetic and Nondiabetic Patients

Study Name	Total N	Nondiabetic N	Diabetic N	RR Analysis: RR, Nondiabetic (95% CI)	RR, Diabetic (95% CI)	RRR (95% CI)
CONSENSUS	253	197	56	0.64 (0.46–0.88)	1.06 (0.65–1.74)	1.67 (0.93–3.01)
SAVE	2,231	1,739	492	0.82 (0.68–0.99)	0.89 (0.68–1.16)	1.09 (0.79–1.50)
SMILE	1,556	1,253	303	0.79 (0.54–1.15)	0.44 (0.22–0.87)	0.56 (0.25–1.22)
SOLVD-Prevention	4,228	3,581	647	0.97 (0.83–1.15)	0.75 (0.55–1.02)	0.77 (0.54–1.09)
SOLVD-Treatment	2,569	1,906	663	0.84 (0.74–0.95)	1.01 (0.85–1.21)	1.21 (0.97–1.50)
TRACE	1,749	1,512	237	0.85 (0.74–0.97)	0.73 (0.57–0.94)	0.87 (0.65–1.15)
Random effects pooled estimate		10,188	2,398	0.85 (0.78–0.92)	0.84 (0.70–1.00)	1.00 (0.80–1.25)

Abbreviations as in Table 2. Trial acronyms as in Abbreviation Box.

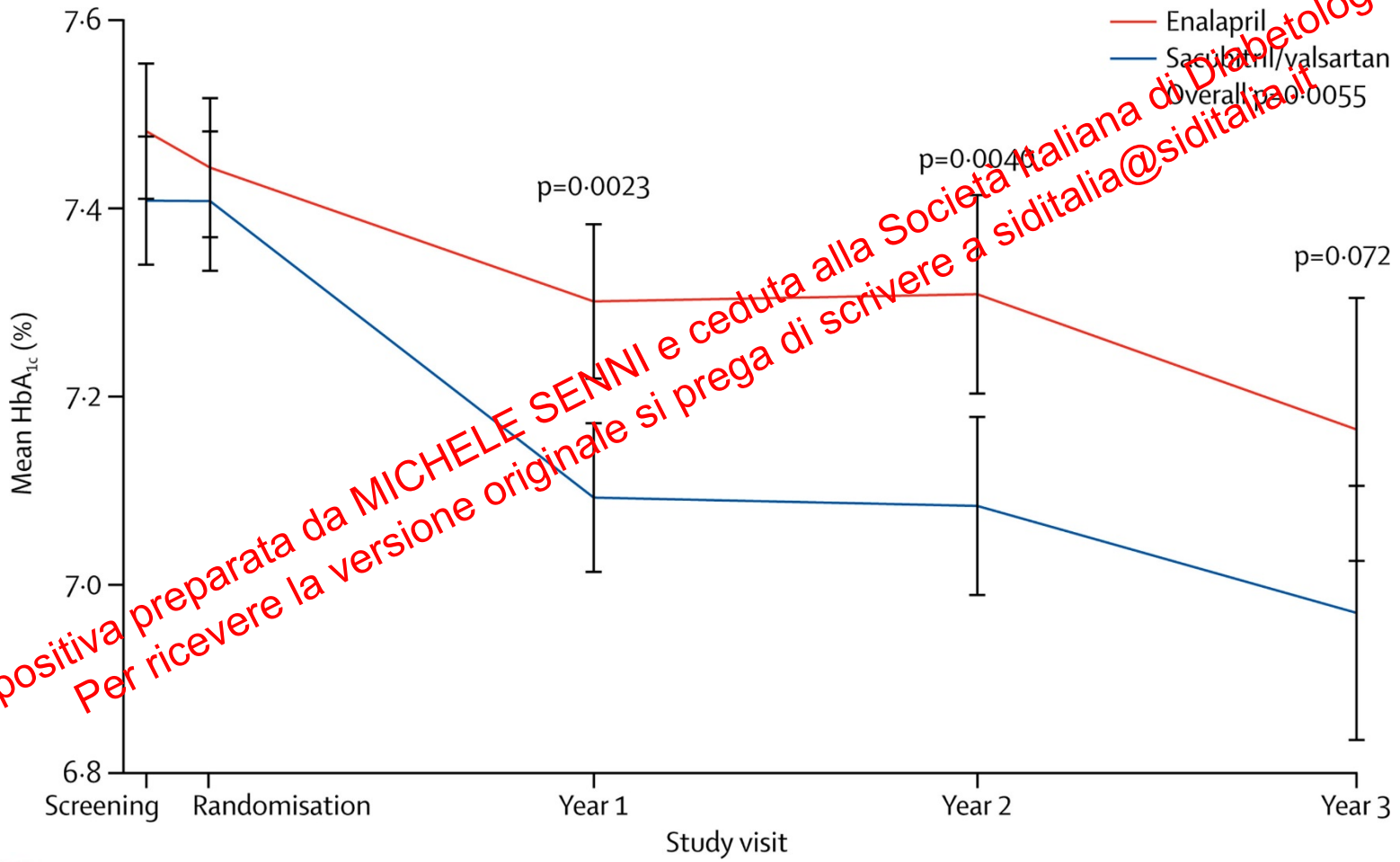
Shekelle et al: Journal of the American College of Cardiology Vol. 41, No. 9, 2003

CHARM
Candesartan and new onset of diabetes



Yusuf S et al, Circulation 2005;112:48

PARADIGM-HF
Changes in mean HbA1c in



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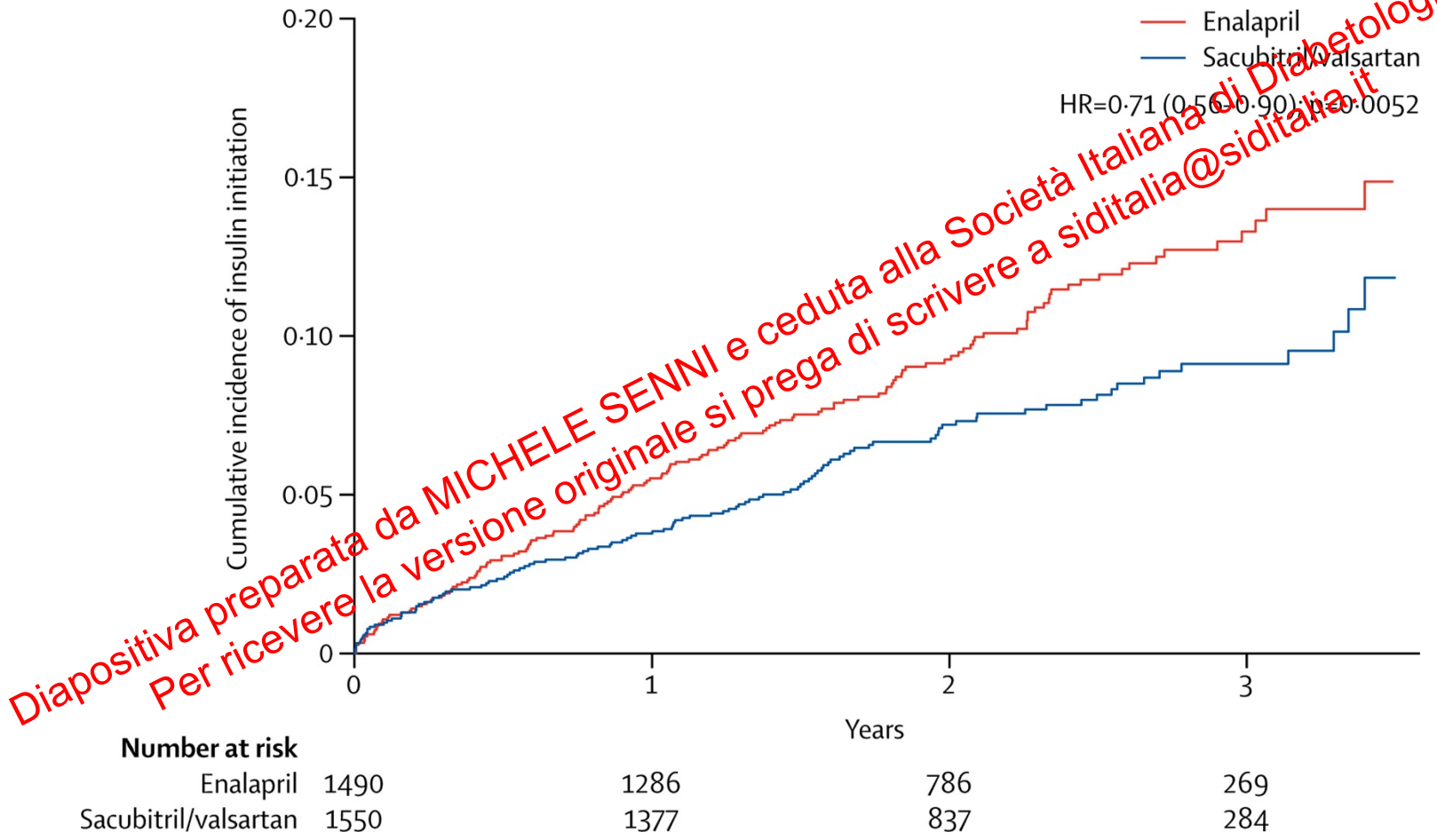
Seferovic JP et al. The Lancet Diabetes & Endocrinology 2017

Kaplan-Meier curves of time to insulin initiation



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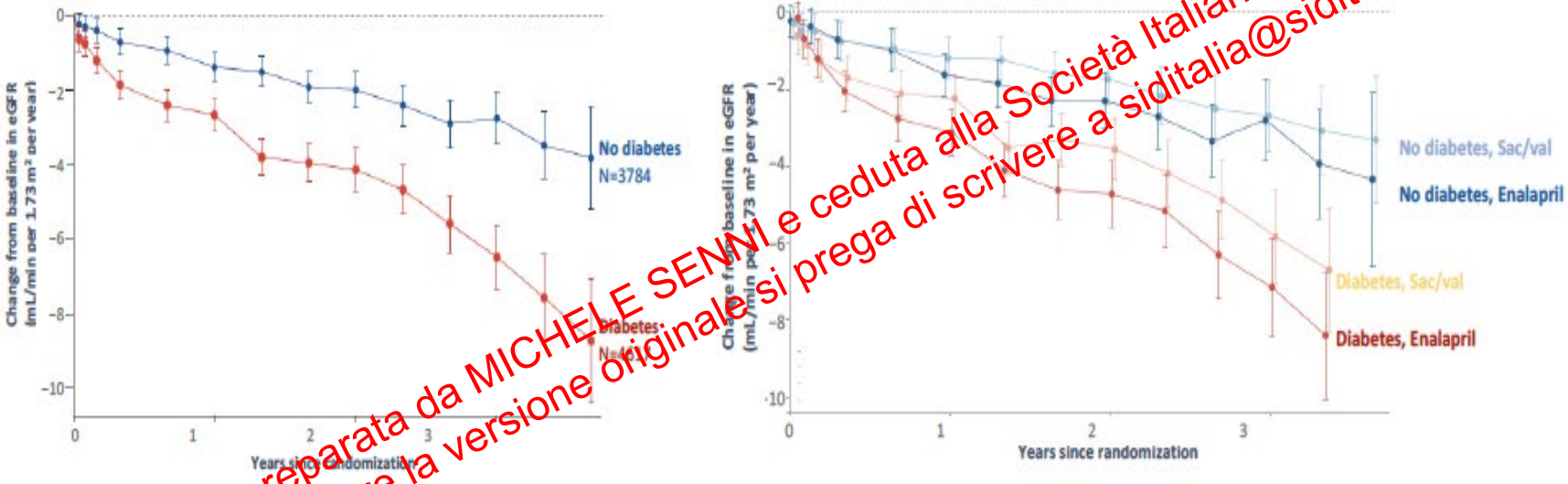
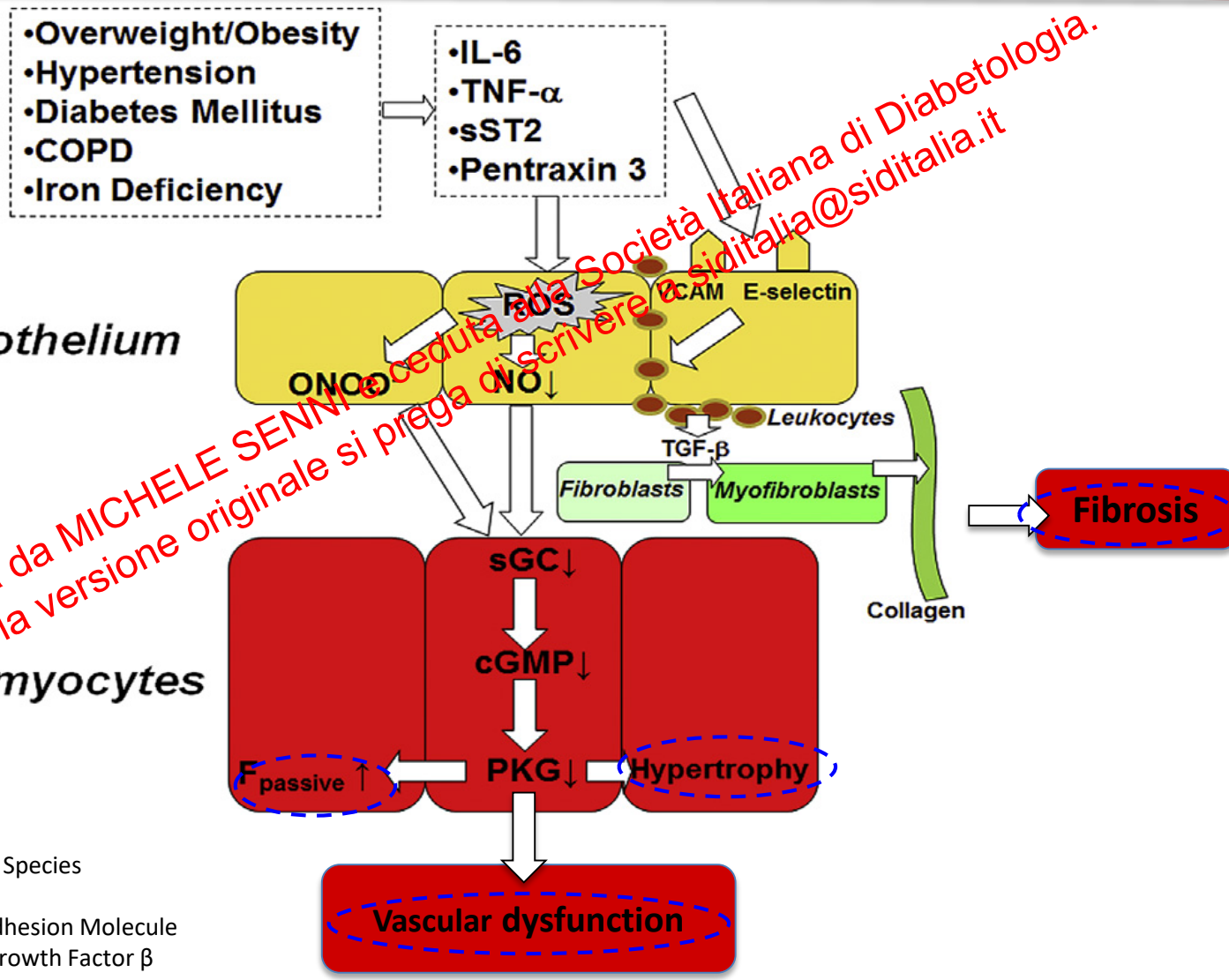
Seferovic JP et al. The Lancet Diabetes & Endocrinology 2017

PARADIGM-HF
HFrEF, Diabetes and worsening renal function



Packer M et al. The Lancet Diabetes & Endocrinology 2018

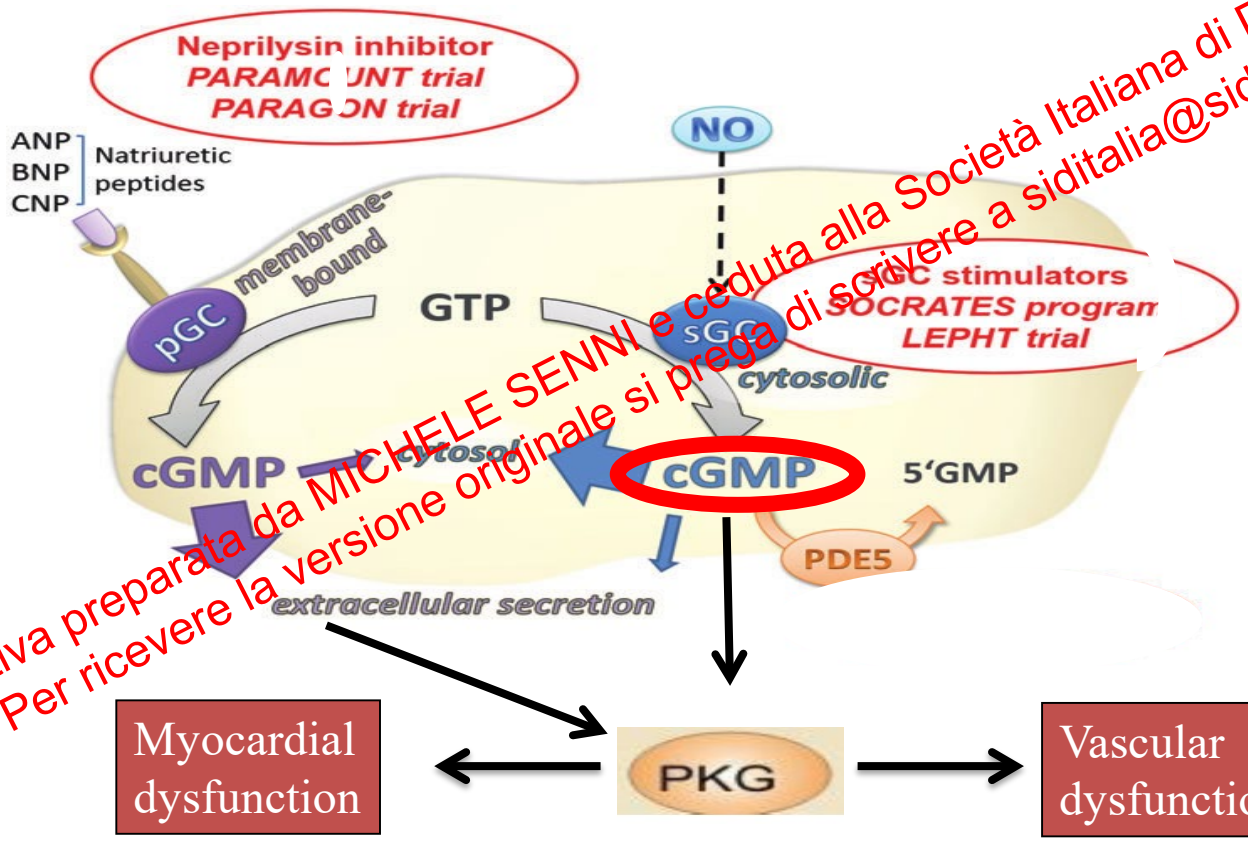
Myocardial-Vascular Dysfunction and Remodeling



*Reactive Oxygen Species
**Peroxynitrite
**Vascular Cell Adhesion Molecule
***Trasforming Growth Factor β

Modified from: Paulus and Tschoepe, JACC 2013

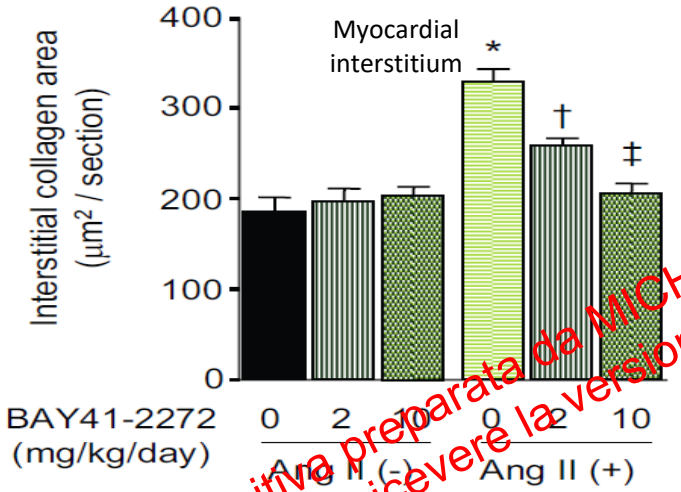
NO/cGMP pathway

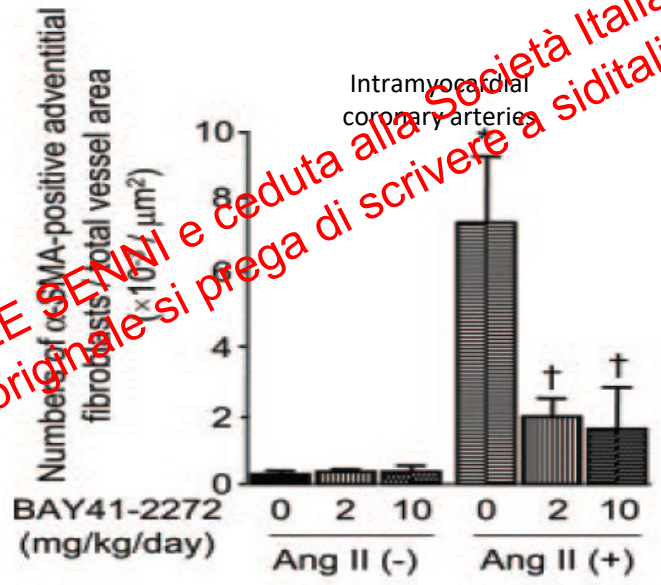


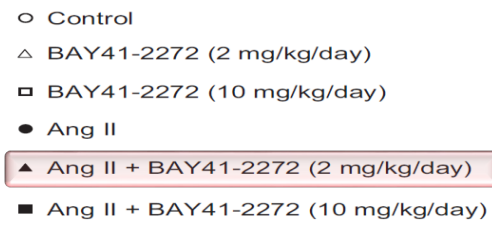
Senni M et al. Eur Heart J 2014

sGCs Produce Pressure-independent Reduction of Left Ventricular & Vascular Fibrosis

Rat model of hypertension induced by infusion of Ang II





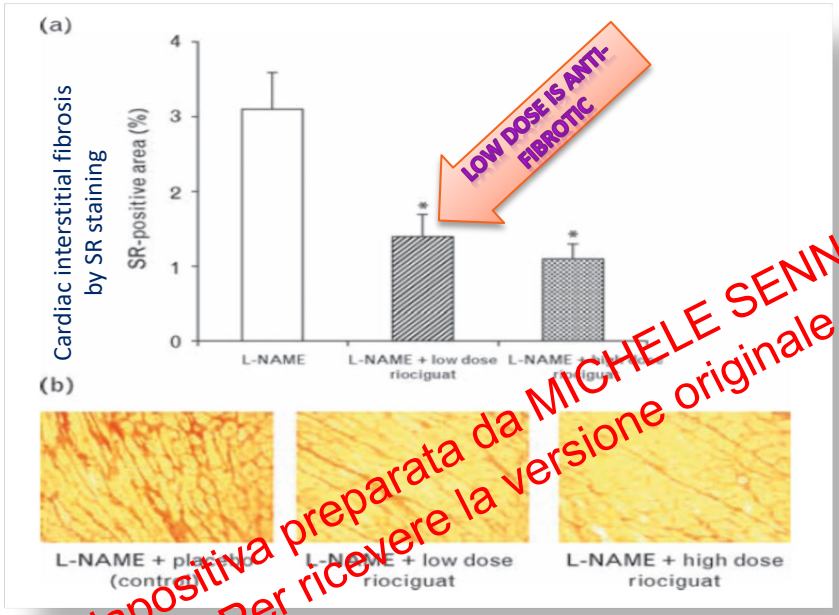


*P<0.05, **P<0.01 vs. control without Ang II and BAY, †P<0.05, ‡P<0.01, vs. Ang II without BAY (one-way ANOVA followed by Scheffe's test); mean+SEM.

Masuyama et al., Hypertension. 2006 Nov;48(5):972-8

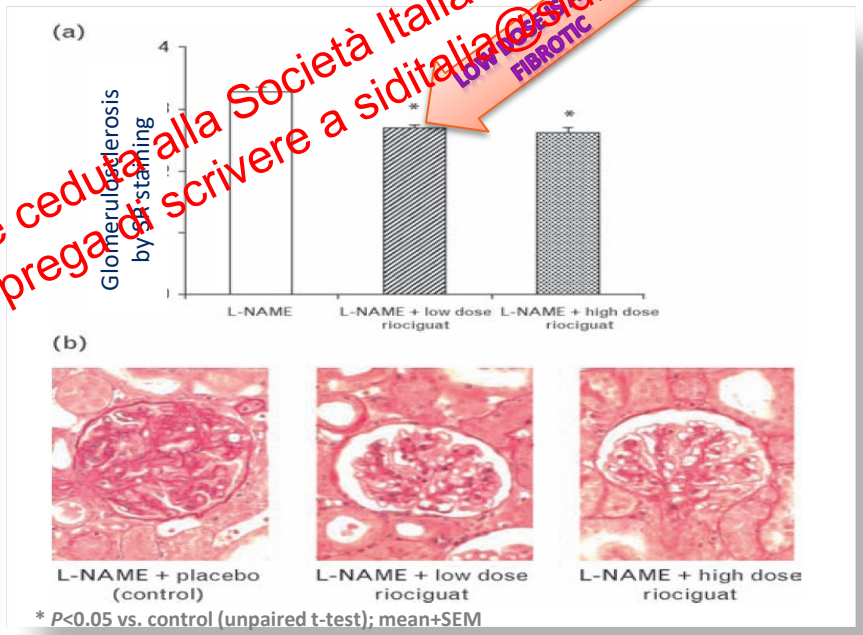
Reduction of cardiac & renal fibrosis – important co-morbidity in heart failure

sGC stimulator riociguat



Riociguat was administered per os by gavage once daily (3 and 10 mg/kg per day)

Renin-transgenic rats + L-NAME treatment



Sharkovska et al. J Hypertens. 2010 Aug;28(8):1666-75

Sac/vals mechanisms of action in HFpEF

Substrates

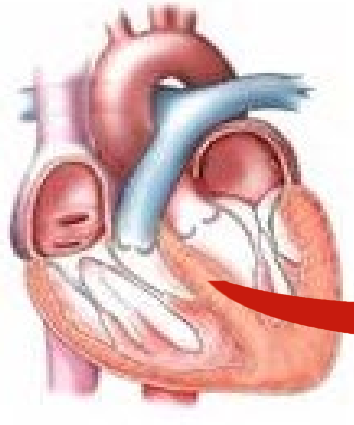
Multiorgan beneficial effect

Myocardium action

NPs
ADM
CGRP
BK

ET-1
ALD
AT I-II

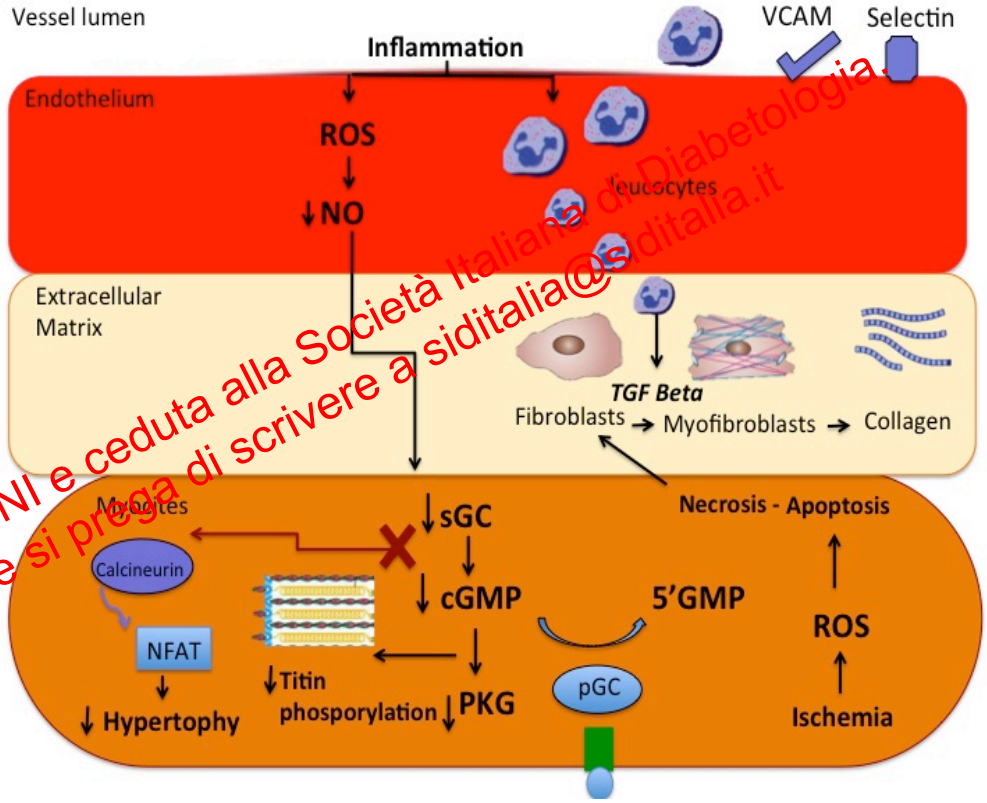
Inhibited by RAAS inhibitors



↓ Myocyte hypetrophy
↓ LV stiffness
↓ Fibroblast proliferation

↑ Fibroblast proliferation
↑ Diuresis and natriureis

↑ Endothelial dysfunction
↑ Fibroblast proliferation
↑ Arterial stiffness



Neprilysin inhibition → NPs

↓ **Volume overload**

↓ **LVEDP rest/effort**

↓ **HF signs and symptoms**

Improvement of arterial ventricular coupling

Gori M, D'Elia E, Senni M. Int J Cardiol 2018

Conclusions

Heart failure: Why does diabetes matter?

In both HFrEF and HFpEF

- **Higher mortality rate**
- **Higher hospitalization rate**
- **Worse renal function**
- **More left ventricular “diastolic dysfunction”**
- **Abnormal myocardial metabolism**

Conclusions

Treatment of HF in diabetes: Key points

- **Response to most evidence-based treatments similar in those with and without diabetes - ACE inhibitors/ARBs, beta-blockers, ivabradine, MRAs.**
- **In patients with diabetes in PARADIGM-HF, sacubitril/valsartan:**
  - **lowered HbA1c**
  - **delayed the time of insulin initiation**
  - **reduced the worsening renal function**