

Le complicanze cardiologiche nel paziente diabetico



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Diabetes and CV diseases

- Ischemic heart disease
- Asymptomatic LV Dysfunction
- Heart Failure
 - Heart Failure reduced Ejection Fraction
 - Heart Failure preserved Ejection Fraction

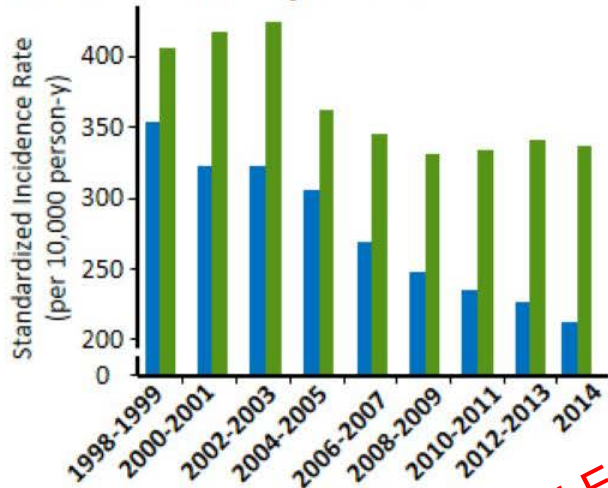
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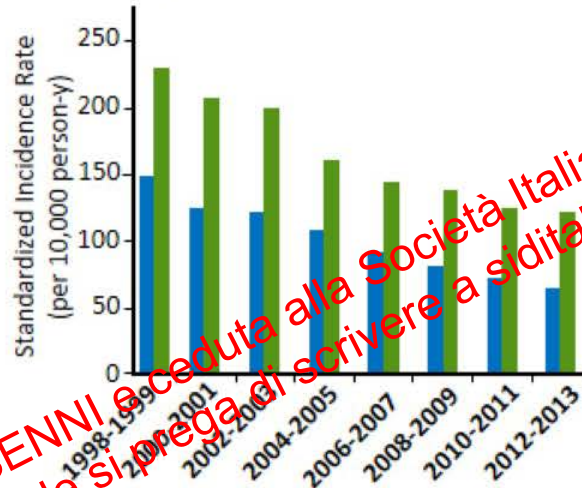
Diapositiva preparata da MICHELE SENNI e ceduta alla Società Italiana di Diabetologia.
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Mortality and CV diseases in T1D and T2D

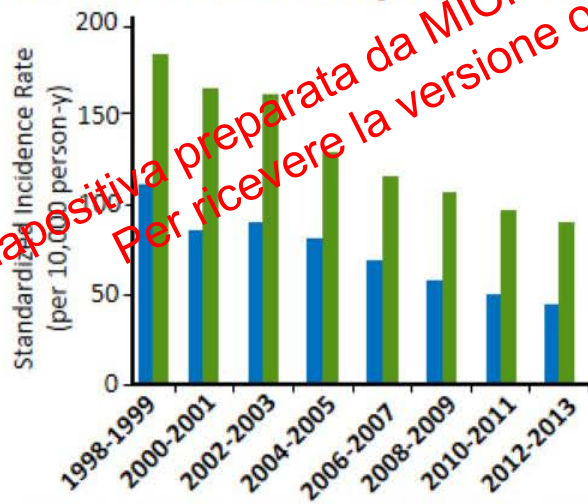
Death From Any Cause



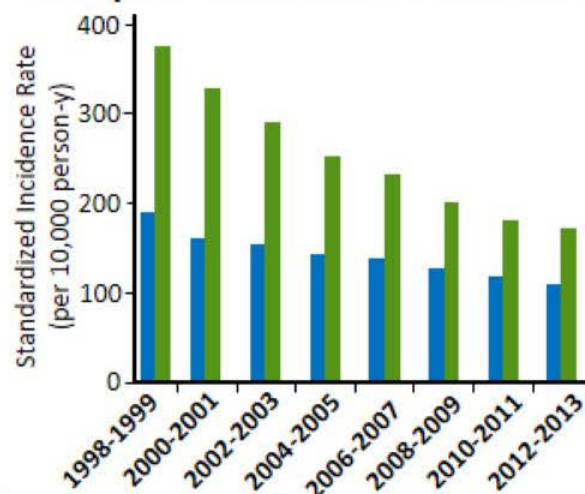
Death From CV Disease



Death From Coronary Heart Disease



Hospitalization for CV Disease



■ Patients with T2D
■ Matched controls

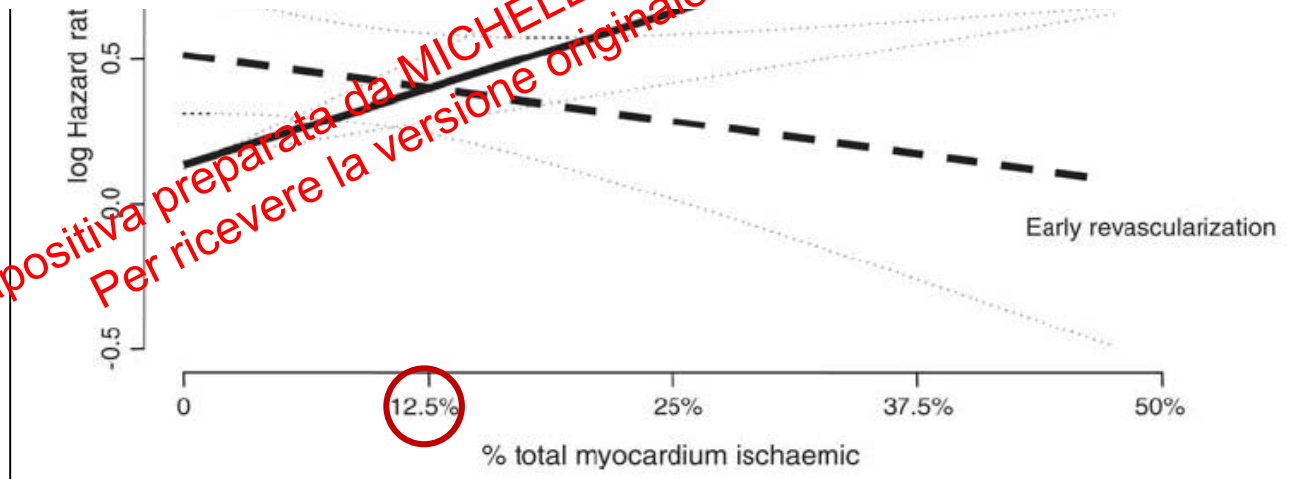


Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy

European Heart Journal (2011) 32, 1012–1024
doi:10.1093/eurheartj/ehq500



Stress-rest myocardial scintigraphy >10% LV ischemia



2014 ESC/EACTS Guidelines on myocardial revascularization

Indications for diagnostic testing in patients with suspected CAD and stable symptoms

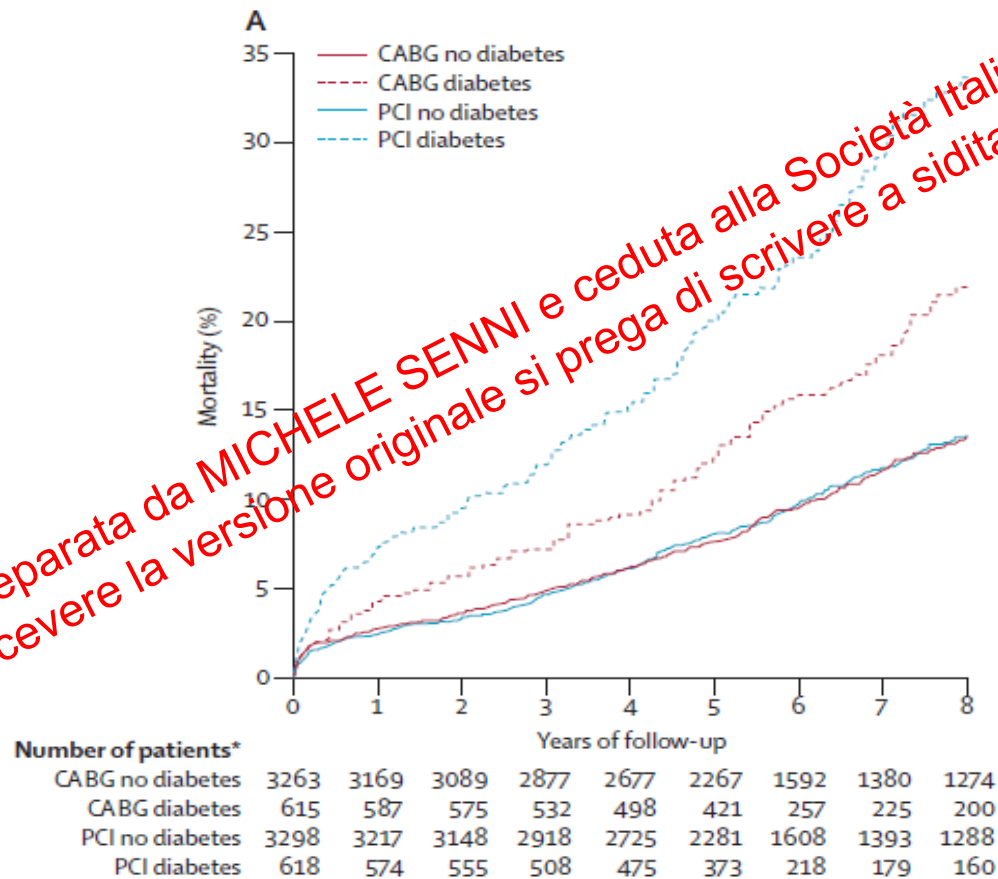
	Asymptomatic ^a		Symptomatic ^b /Silent ischemia					
			Probability of significant disease ^b					
			Low (<15%)		Intermediate (15–85%)		High (>85%)	
	Class ^c	Level ^d	Class ^c	Level ^d	Class ^c	Level ^d	Class ^c	Level ^d
Anatomical detection of CAD								
Invasive angiography	III	A	III	A	IIb	A	I	A
CT angiography ^{f,g}	IIb	B	III	C	IIa	A	III	B
Functional test								
Stress echo	III	A	III	A	I	A	III	A
Nuclear imaging	III	A	III	A	I	A	III	A
Stress MRI	III	B	III	C	I	A	III	B
PET perfusion	III	B	III	C	I	A	III	B
Combined or hybrid imaging test								
	III	C	III	C	IIa	B	III	B

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Coronary revascularization of patients with diabetes

Recommendations	Class ^a	Level ^b
Optimal medical treatment should be considered as preferred treatment in patients with stable CAD and DM unless there are large areas of ischaemia or significant left main or proximal LAD lesions.	IIa	B
CABG is recommended in patients with DM and multivessel or complex (SYNTAX Score >22) CAD to improve survival free from major cardiovascular events.	I	A
PCI for symptom control may be considered as an alternative to CABG in patients with DM and less complex multivessel CAD (SYNTAX score ≤22) in need of revascularization.	IIb	B
Primary PCI is recommended over fibrinolysis in DM patients presenting with STEMI if performed within recommended time limits.	I	B

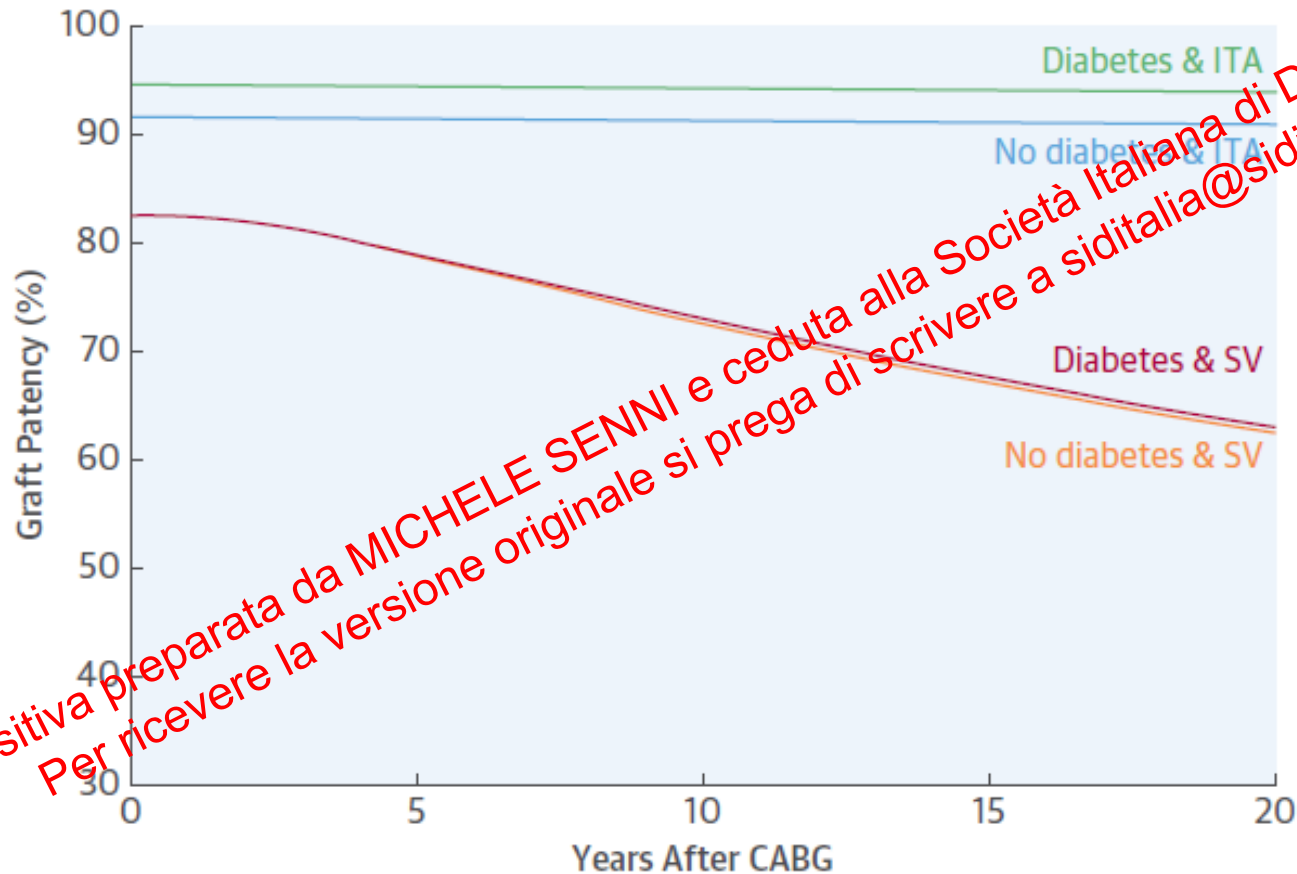
Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials



Hlatky MA et al. Lancet 2009.



Influence of Diabetes on Long-Term Coronary Artery Bypass Graft Patency



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PCI Versus CABG in Patients With Type 1 Diabetes and Multivessel Disease

Thomas Nyström, MD, PhD,^{a,b} Ulrik Sartipy, MD, PhD,^{c,d} Stefan Franzén, PhD,^e Björn Eliasson, MD, PhD,^e Soffia Gudbjörnsdottir, MD, PhD,^e Mervete Miftaraj, MSc,^e Bo Lagerqvist, MD, PhD,^f Ann-Marie Svensson, PhD,^e Martin J. Holzmann, MD, PhD^{g,h}

	CABG	PCI	Standardized Difference
Patients	683 (27)	1,863 (73)	N/A
Time period of revascularization			
1995–2000	441 (58)	324 (42)	N/A
2001–2006	197 (21)	741 (79)	N/A
2007–2013	45 (5)	798 (95)	N/A
Age, yrs	57.2 ± 10.0	61.1 ± 10.5	0.378
Female	36.6	41.1	0.093
HbA _{1c} , mmol/mol	68.8 ± 14.6	67.3 ± 13.4	0.11
Diabetes duration, yrs	29.6 ± 16.0	31.6 ± 16.8	0.123
Macroalbuminuria	24.1	22.4	0.040
Microalbuminuria	25.6	26.5	0.065
GFR, ml/min/1.73 m ²	70 ± 23	67 ± 29	0.094
Current smoker	15.0	14.5	0.016
BMI, kg/m ²	26.0 ± 3.9	26.4 ± 4.3	0.087
Systolic BP, mm Hg	142 ± 19	139 ± 18	0.141
Diastolic BP, mm Hg	75 ± 9	73 ± 10	0.152
Triglycerides, mg/dl	133 ± 80	133 ± 97	0.033
HDL cholesterol, mg/dl	58 ± 23	58 ± 19	0.038
LDL cholesterol, mg/dl	104 ± 39	108 ± 39	0.163
MI			0.602
Acute MI, within 14 days	13.6	36.7	
Previous MI	54.3	47.6	

	CABG	PCI	Standardized Difference
Comorbidities			
Previous stroke	4.6	9.6	0.111
Previous heart failure	16.3	19.5	0.086
Atrial fibrillation	7.0	6.0	0.043
COPD	2.9	3.3	0.023
Peripheral arterial disease	4.4	4.5	0.003
End-stage renal disease	3.2	7.0	0.179
Active cancer	1.5	3.9	0.149
Psychiatric disease	1.3	2.7	0.101
Education			0.126
<10 yrs	37.2	33.1	
10–12 yrs	42.5	44.8	
>12 yrs	17.0	16.7	
Income (Swedish krona)			0.289
Quartile 1	31	23	
Quartile 2	29	24	
Quartile 3	23	26	
Quartile 4	17	28	
Birth region			0.076
Nordic countries	90.8	88.5	
Other	9.2	11.5	

JACC 2017



Diabetes and CV diseases

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Heart Failure reduced Ejection Fraction



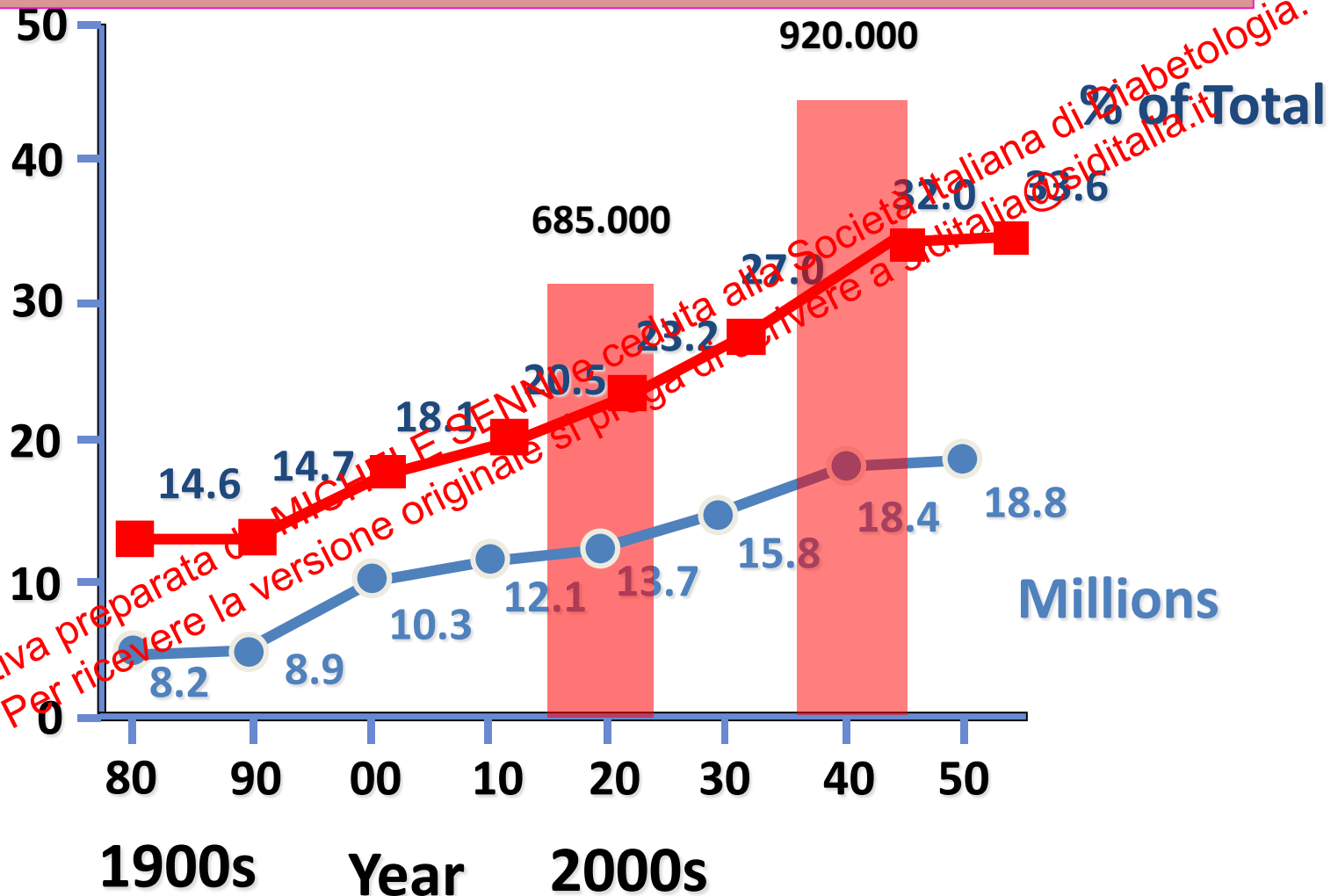
Heart Failure preserved Ejection Fraction

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Italian Population ≥65 Years

HF Prevalence = 5%

HF Prevalence in T2D ≈ 40% (270 mila nel 2020 e 370 mila nel 2040)



Data from: Italian Census Bureau (ISTAT)



Clinical Characteristics* of Patients with HF

Preserved and Reduced LV Function

	Preserved EF	Reduced EF
Age, ys	74	70
Women, %	63	38
Hypertension, %	74	65
CAD, %	46	58
AF, %	25	23
DM, %	38	40

*Weighted average

Borlaugh B & Redfield M, Circ 2011



How can we decrease the Prevalence of CHF?



Incidence



CHF survival

**Population
Demographics**

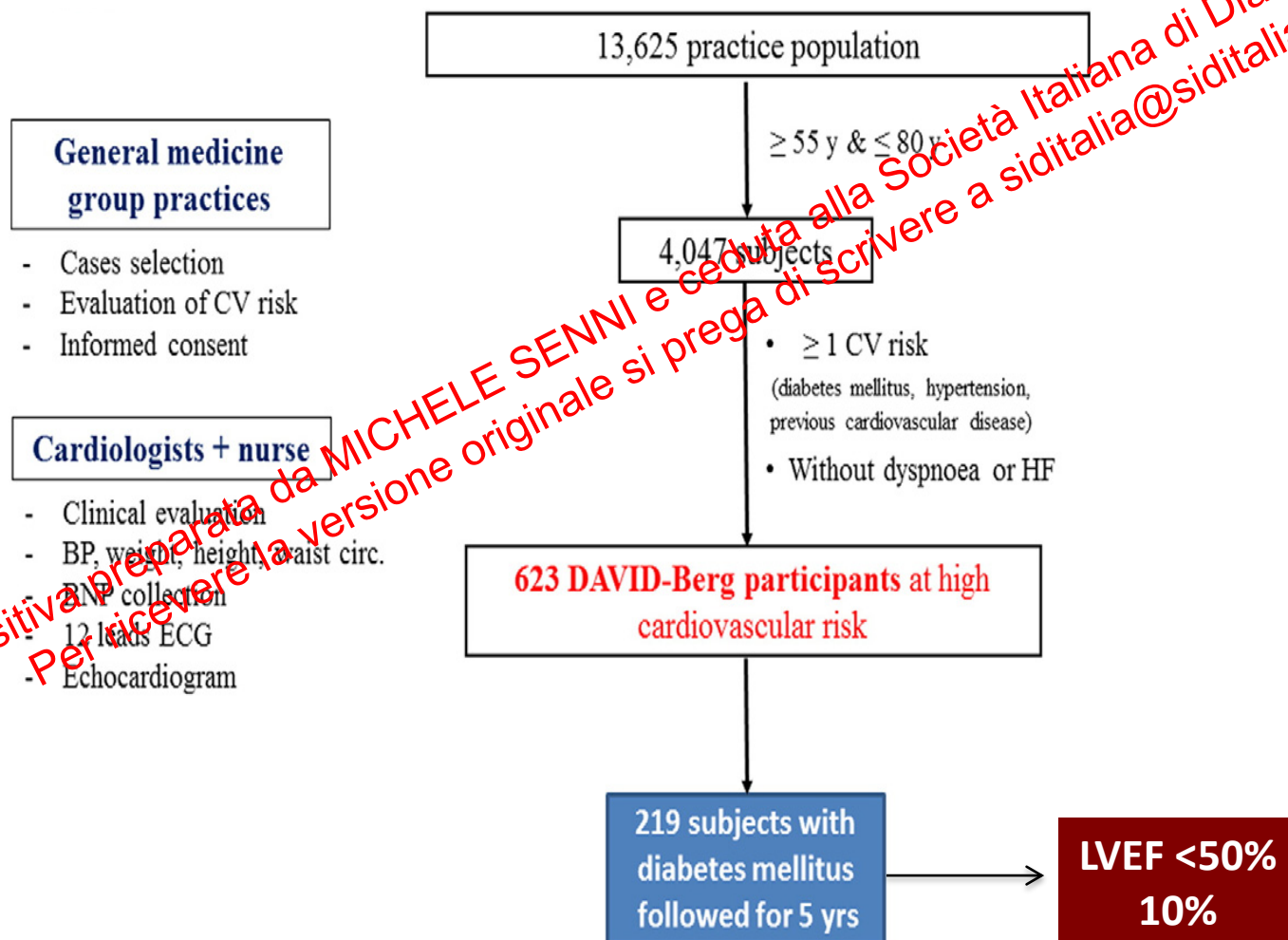
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Prevalence of ALVD in Population ($\approx EF \leq 40\%$)

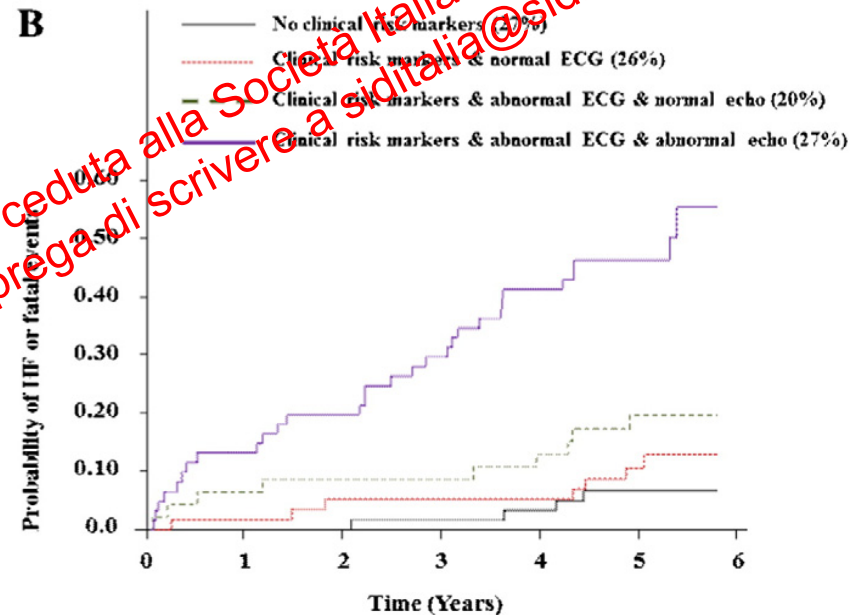
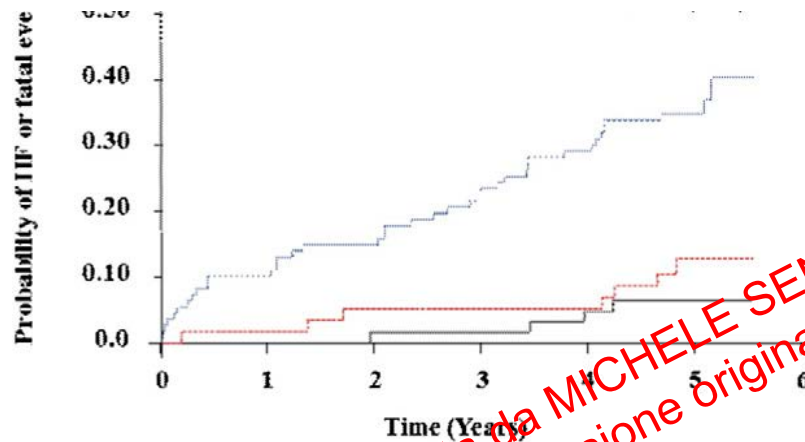
	%	Years
McDonagh T et al	1.4	25-74
Mosterd A et al	2.2	>55
Devereux R et al	2.1	45-74
Davies MK et al	0.9	>45
Gottdiener JS et al	2.4	>65
PAVD	1.2	>45

Strategy to identify subjects with diabetes mellitus more suitable for selective echocardiographic screening: The DAVID-Berg study

Mauro Gori ^{a,1}, Paolo Canova ^{a,1}, Alice Calabrese ^{a,1}, Giovanni Cioffi ^{b,1}, Roberto Trevisan ^{c,1}, Renata De Maria ^{d,1}, Aurelia Grosu ^{a,1}, Attilio Iacovoni ^{a,1}, Alessandra Fontana ^{a,1}, Paola Ferrari ^{a,1}, Stephen J. Greene ^e, Mihai Gheorghiade ^{f,1}, Gianfranco Parati ^{g,1}, Antonello Gavazzi ^{h,1}, Michele Senni ^{a,*,1}



Risk stratification with clinical variables - ECG abnormalities and adding echocardiographic data



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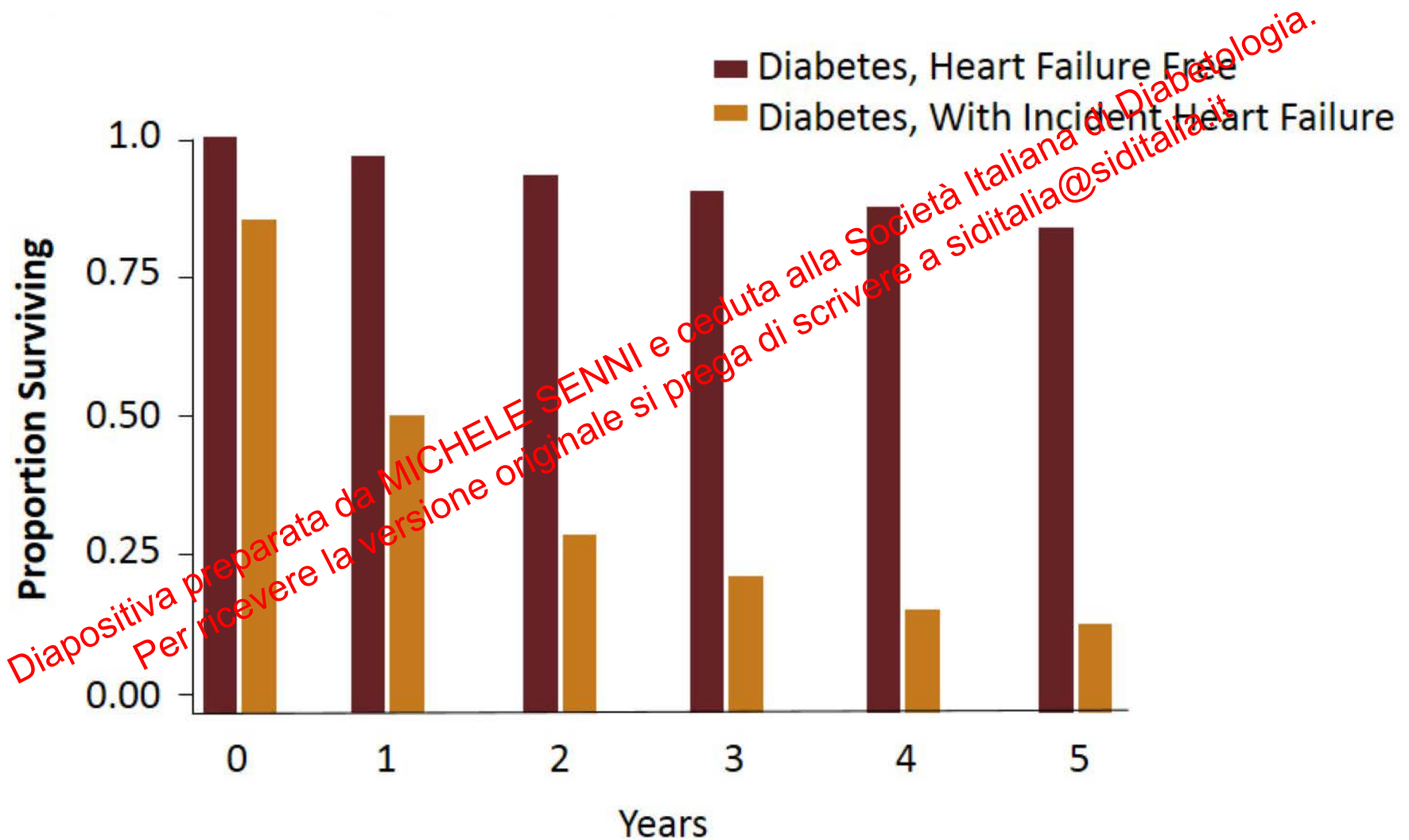
Heart Failure reduced Ejection Fraction



Heart Failure preserved Ejection Fraction

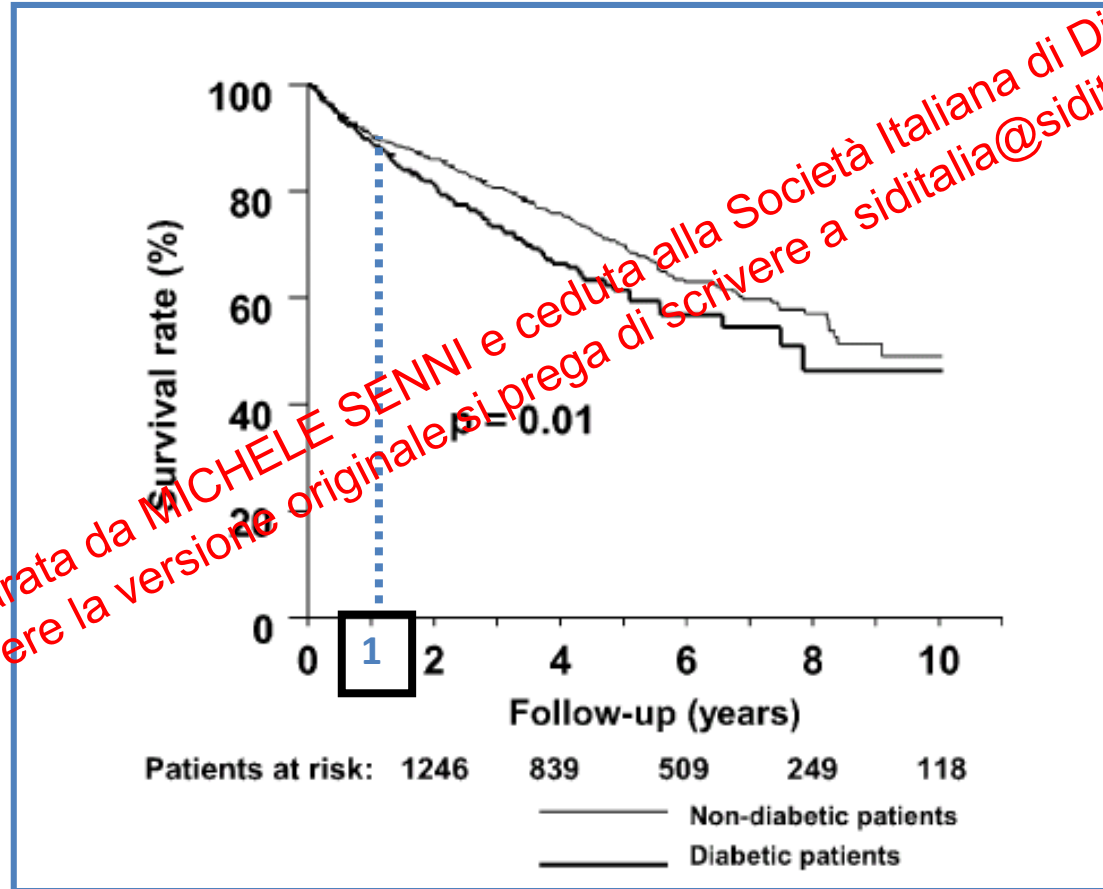
Diapositiva preparata da MICHELE SENNI e ceduta alla Società Italiana di Diabetologia.
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Diabetes with and without HF



Impact of diabetes mellitus on long-term survival in patients with congestive heart failure

Pascal de Groote^a, Nicolas Lamblin^a, Frédéric Mouquet^a, David Plichon^a,
Eugène McFadden^b, Eric Van Belle^a, Christophe Bauters^{a,*}



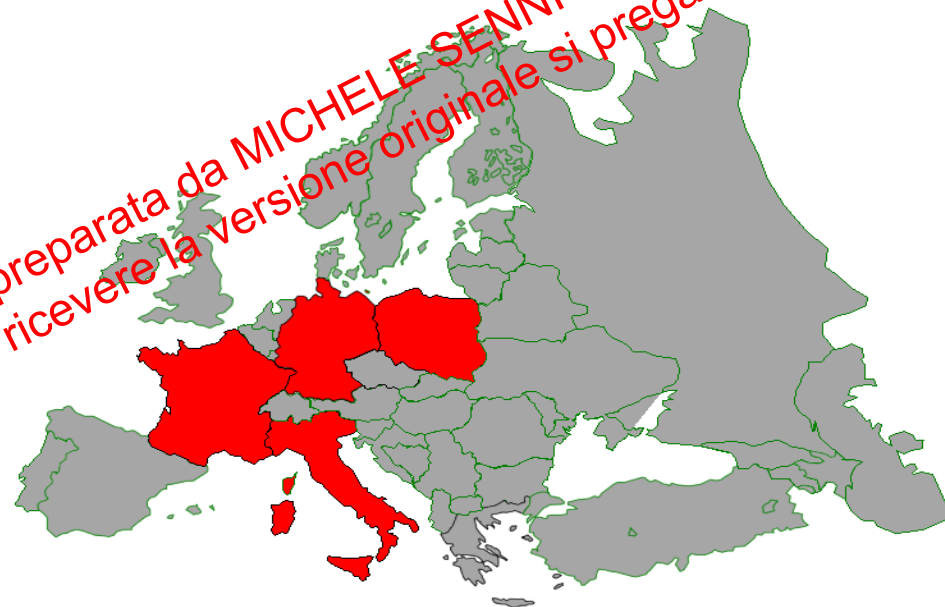


Int J Cardiol 2013;163:206-11, doi:10.1016/J.ijcard.2011.10.071

Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score[☆]

Michele Senni^{a,*}, Piervirgilio Parrella^a, Renata De Maria^b, Ciro Cottini^a, Michael Böhm^c, Piotr Ponikowski^d, Gerasimos Filippatos^e, Christophe Tribouilloy^f, Andrea Di Lenarda^g, Fabrizio Oliva^h, Giovanni Pulignanoⁱ, Mariantonietta Cicoira^j, Savina Nodari^k, Maurizio Porcu^l, Gianni Cioffi^m, Domenico Gabrielliⁿ, Oberdan Parodi^b, Paolo Ferrazzi^o, Antonello Gavazzi^o
and on behalf of the 3 C-HF Study Investigators

Cohort Study: 6.274 consecutive HF patients 5 European Countries



24 Centers

- Italy
- France
- Germany
- Greece
- Poland

Diapositiva preparata da MICHELE SENNI e ceduta alla Società Italiana di Diabetologia.
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Senni M et al. *Int J Cardiol* 2013;163:206-11.

Dichotomized logistic regression model and corresponding points for the additive version of the 3C-HF score (<http://www.3chf.org>).

Demographic

Variable	Odds ratio	95% confidence interval	P value ^a	Points (additive score)
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Age (per 10 years ≥ 40)	1.03	1.0–1.2	<0.0001	1
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Cardiac variables

NYHA class III–IV vs I–II	4.09	3.3–5.4	<0.0001	13
LVEF $<20\%$ vs $\geq 20\%$	3.77	1.5–4.1	<0.0001	11
No RAS inhibitors	2.01	1.6–2.5	<0.0001	8
Severe valve heart disease	2.02	1.6–2.4	<0.0001	7
Atrial fibrillation	1.58	1.2–1.8	<0.0001	7
No beta blocker	1.45	1.2–1.7	0.0003	4

Comorbid conditions

Chronic kidney dysfunction	1.79	1.5–2.1	<0.0001	6
Diabetes with target organ damage	1.62	1.4–1.8	<0.0001	6
Anemia	1.47	1.2–1.8	0.0011	4
Hypertension	0.78	0.6–0.9	0.0040	–4

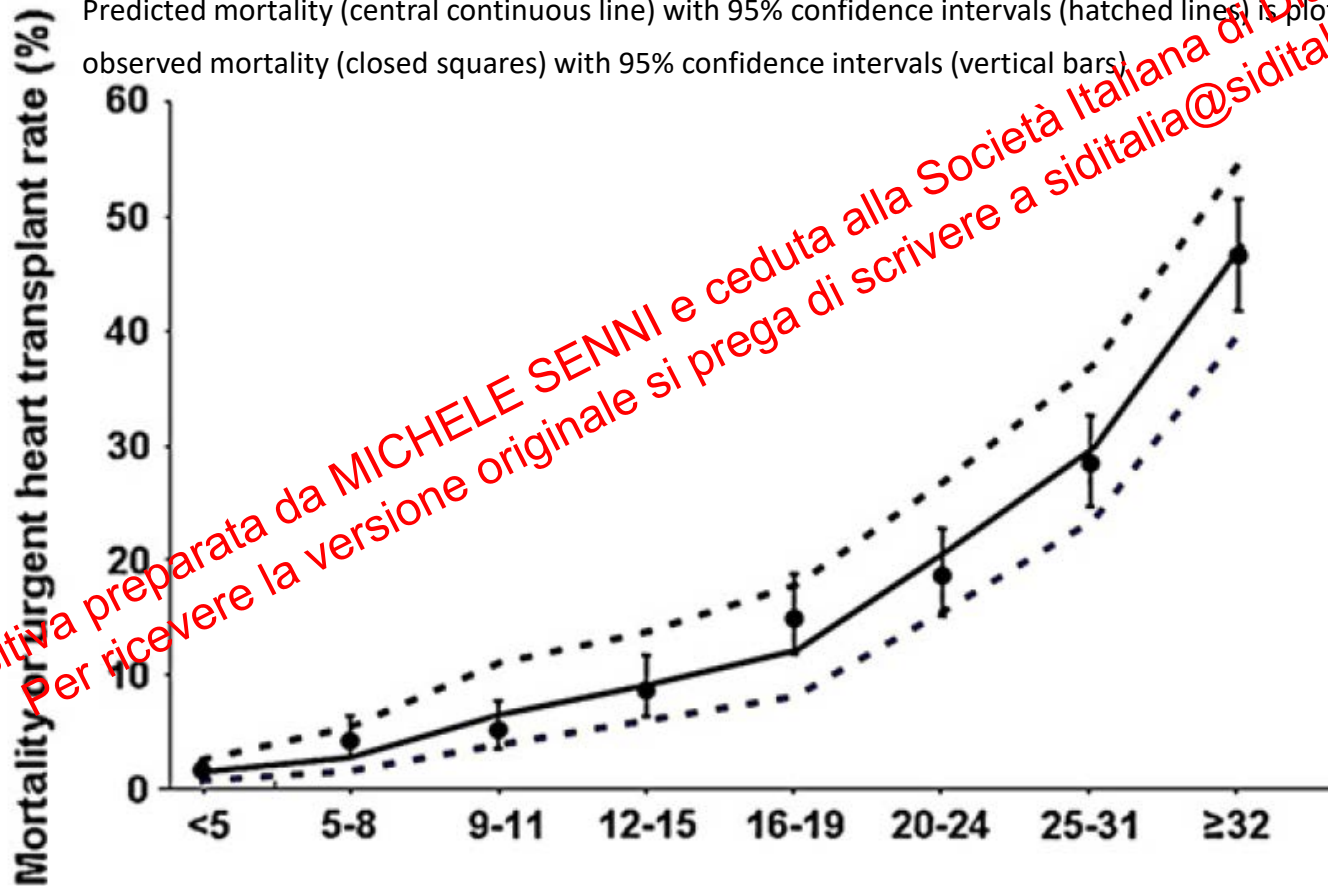




Total population AUC = 0.82

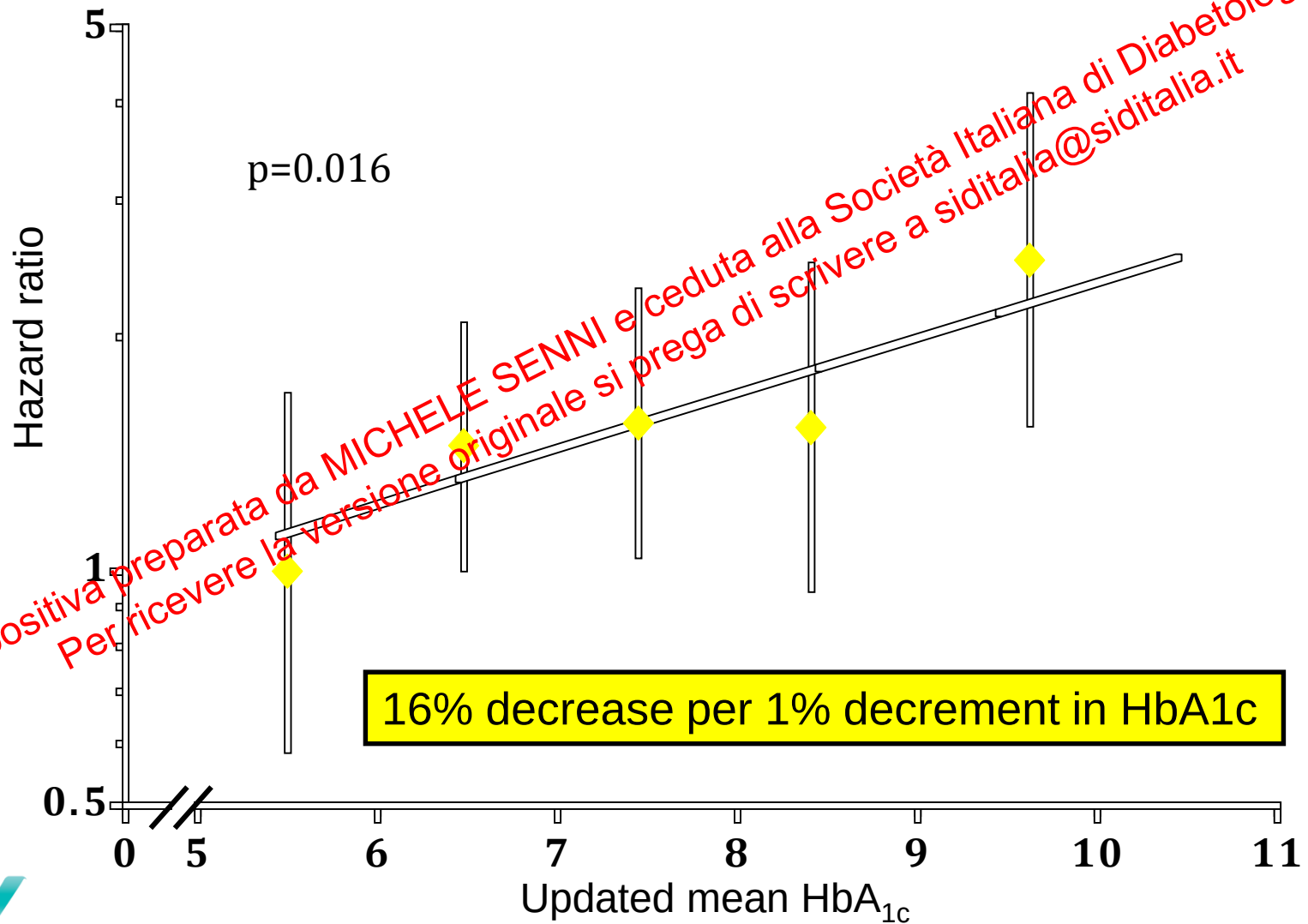
Event rates for the study end-point (all-cause death or urgent heart transplant) in the derivation (n = 2012) and validation (n = 4049) cohorts) by deciles of 3C-HF score.

Predicted mortality (central continuous line) with 95% confidence intervals (hatched lines) is plotted against observed mortality (closed squares) with 95% confidence intervals (vertical bars).



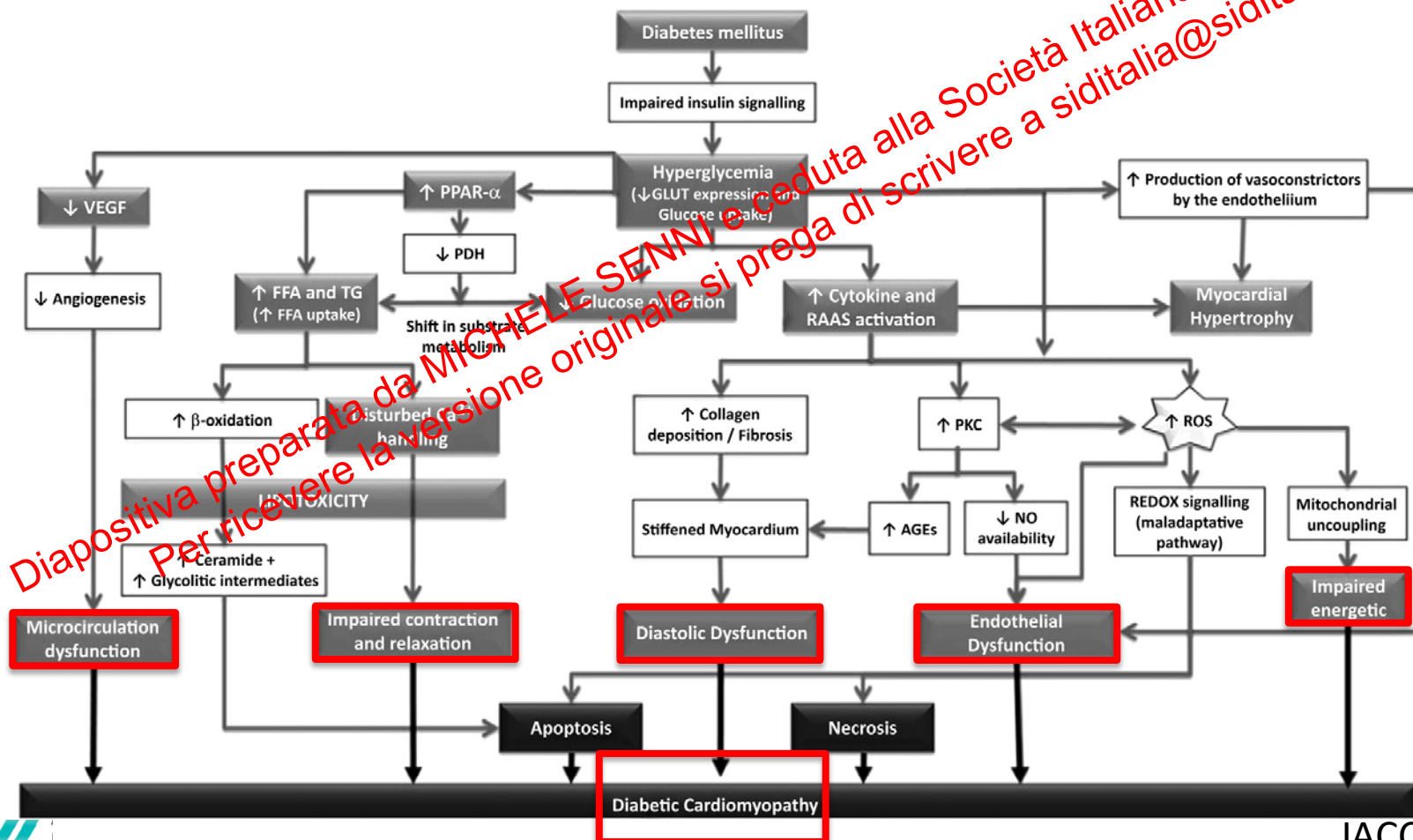
HEART FAILURE and HbA1c

UKPDS 35. BMJ 2000; 321: 405-12



Impact of Diabetes on Epidemiology, Treatment, and Outcomes of Patients With Heart Failure

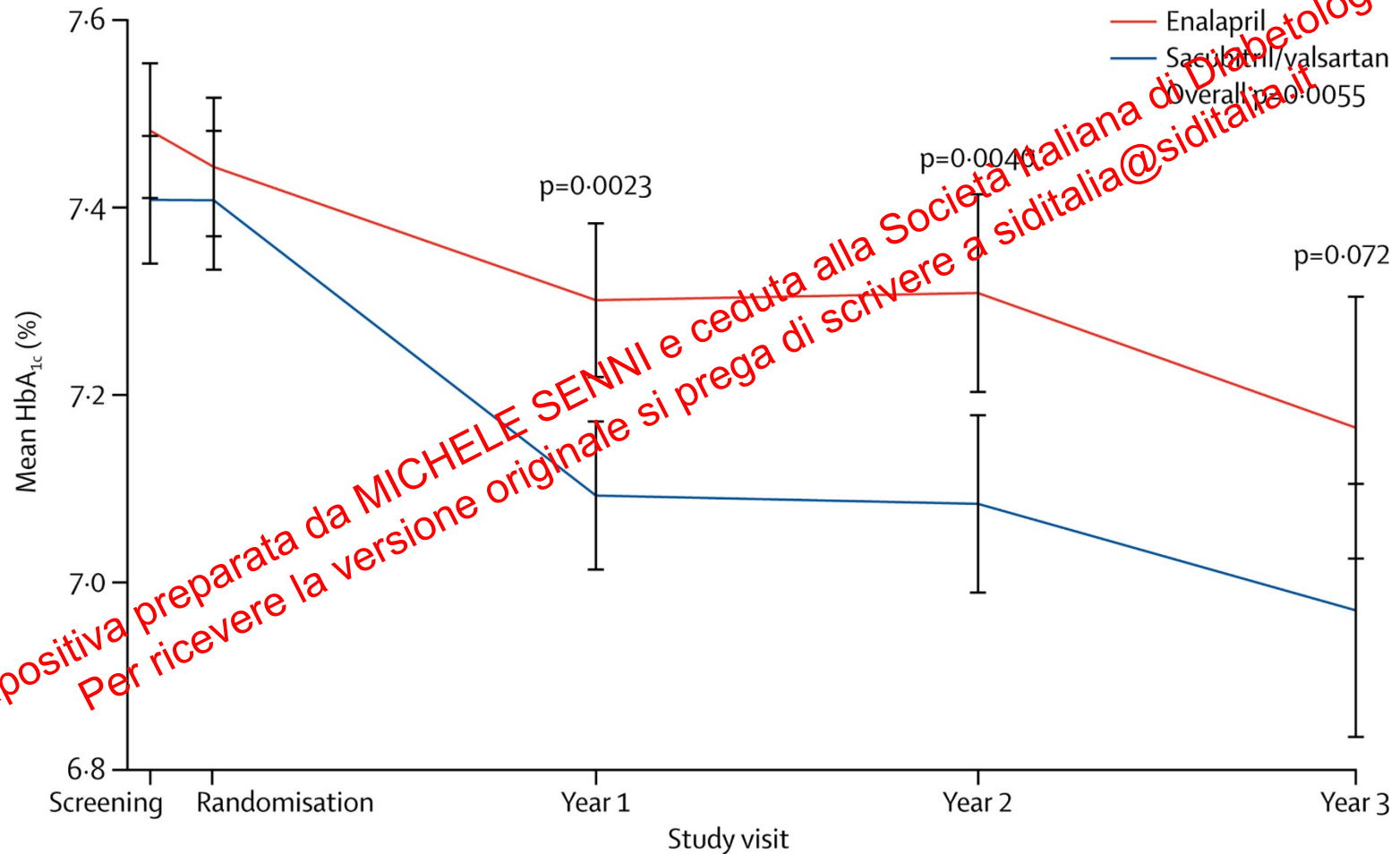
Alessandra Dei Cas, MD, PhD,* Sadiya S. Khan, MD,† Javed Butler, MD, MPH,‡ Robert J. Mentz, MD,§ Robert O. Bonow, MD, MS,|| Angelo Avogaro, MD, PhD,¶ Diethelm Tschoepe, MD,# Wolfram Doehner, MD, PhD,** Stephen J. Greene, MD,|| Michele Senni, MD,†† Mihai Gheorghiade, MD,|| Gregg C. Fonarow, MD,‡‡



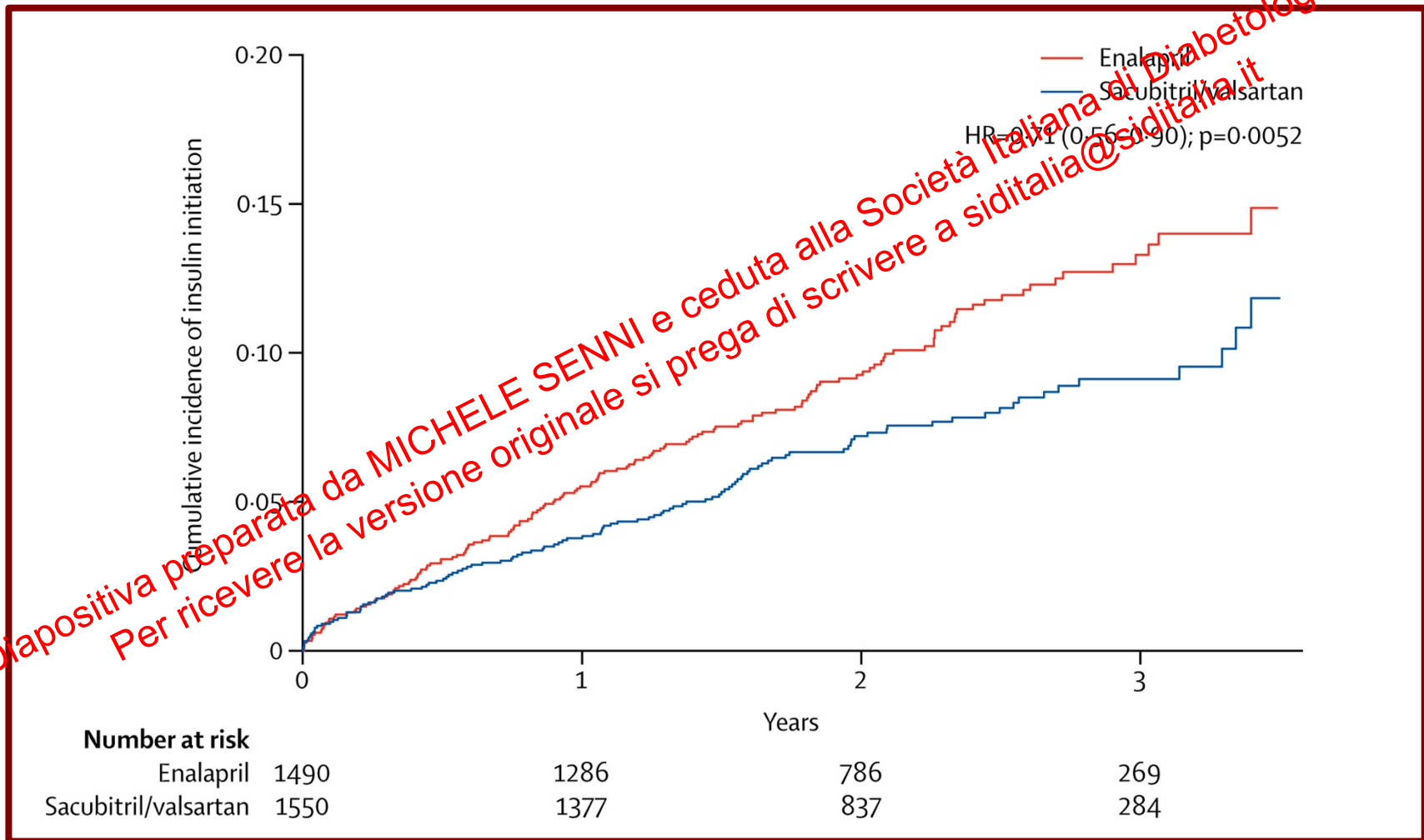
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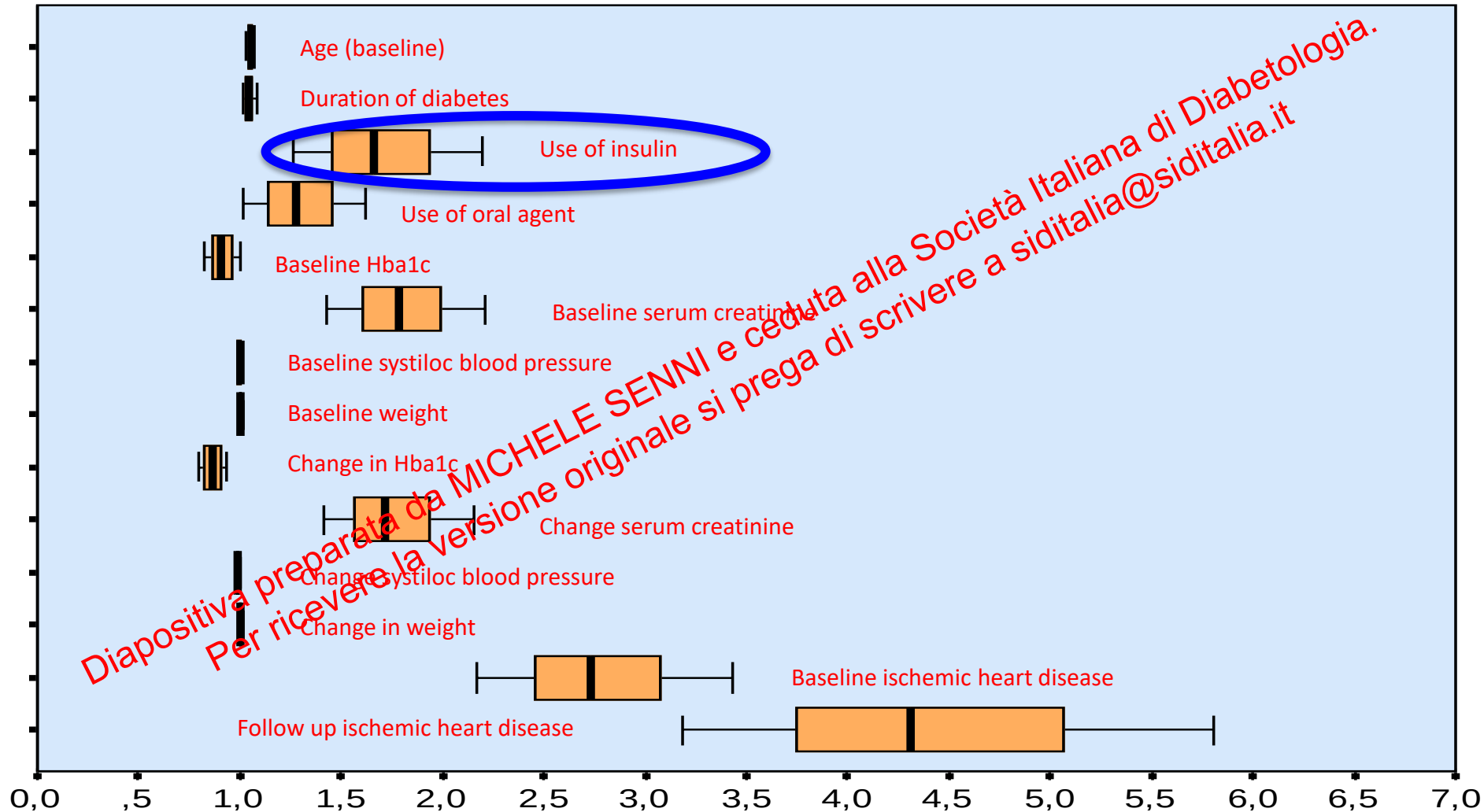
Glycaemic control with sac/vals in diabetic patients



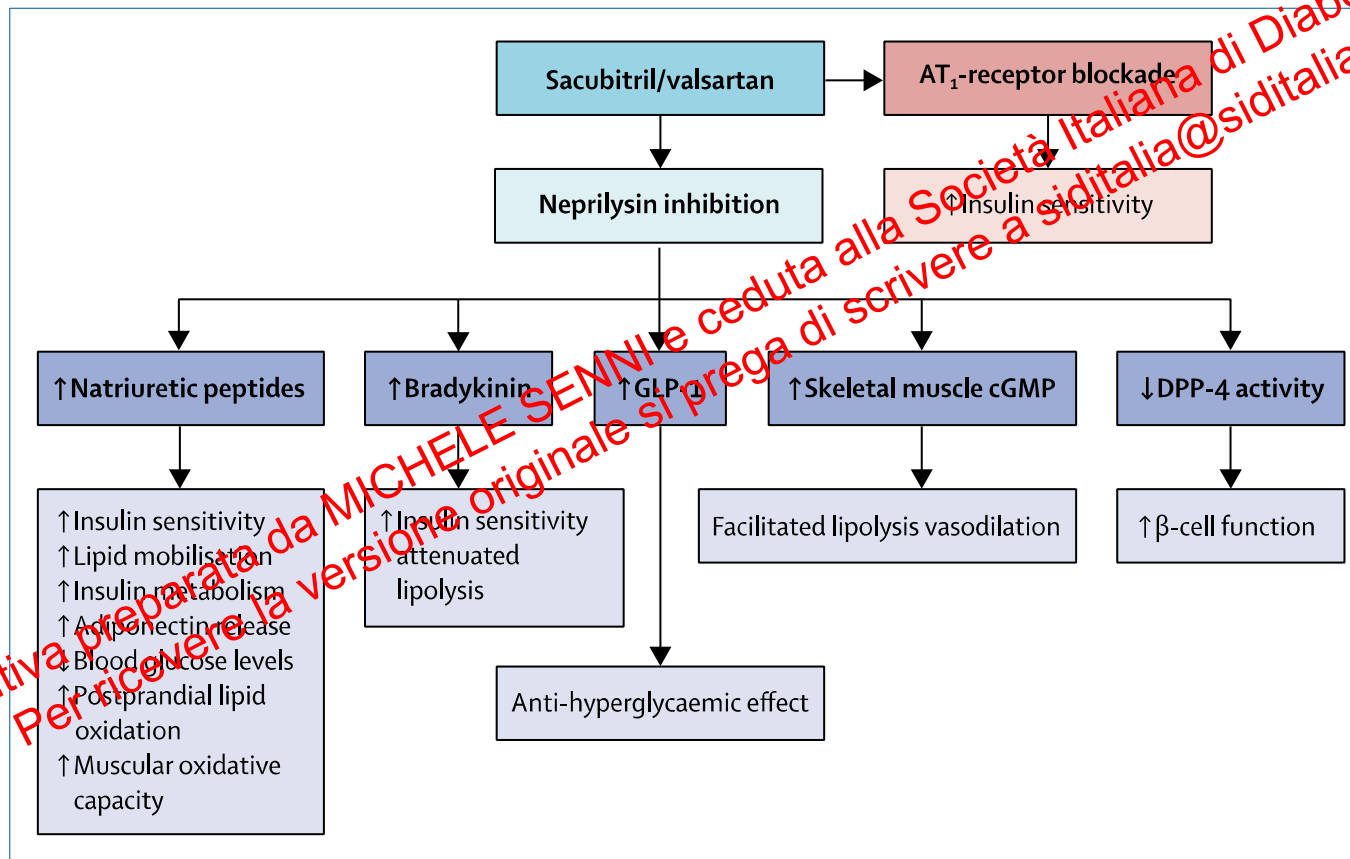
Time to insulin initiation in diabetic patient



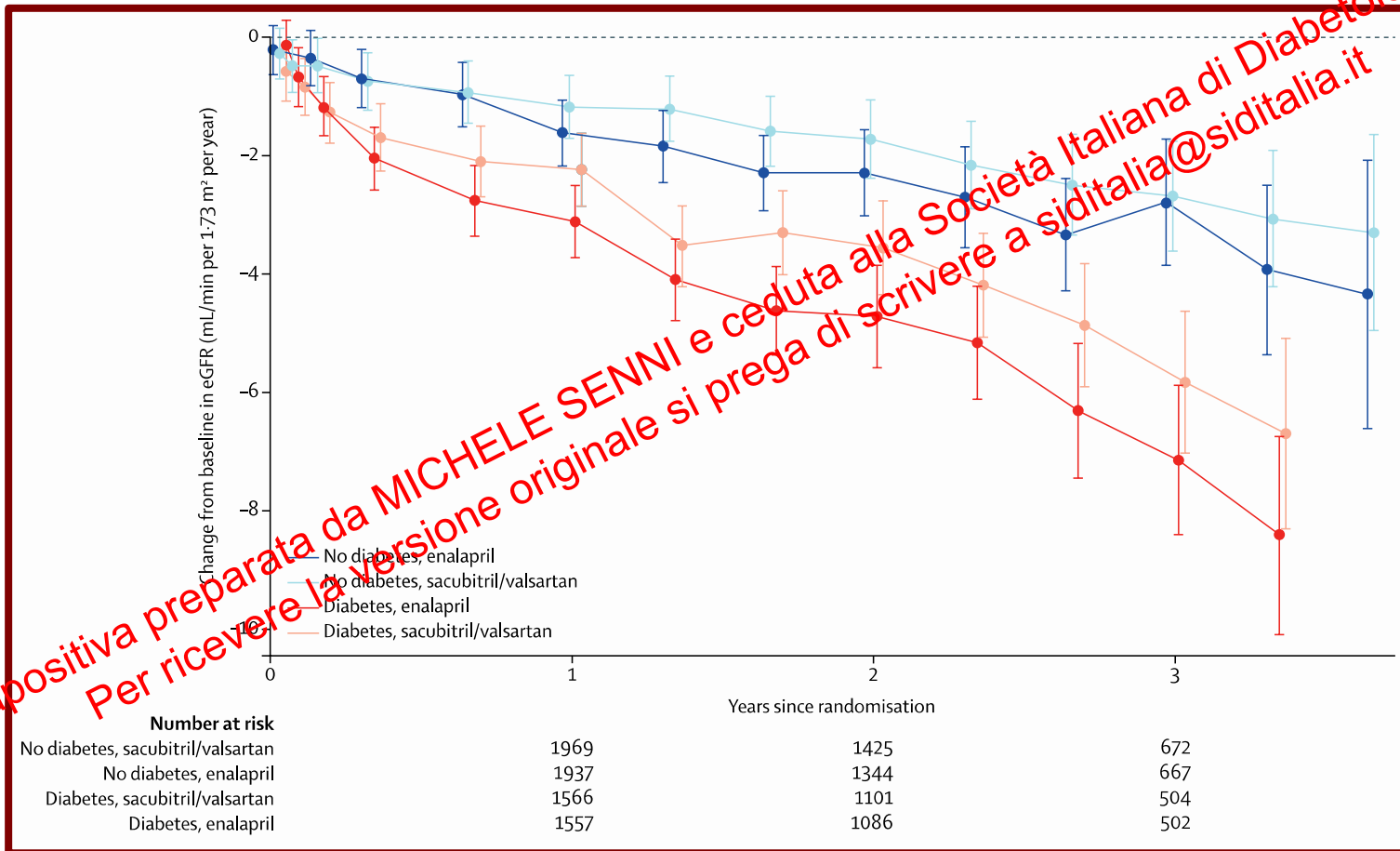
Insulin use and prognosis



Proposed mechanisms by which dual inhibition of renin-angiotensin system and neprilysin might lead to improved glycaemic control



Effect of sac/vals on renal function in patients with type 2 diabetes



Diabetes and CV diseases

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Comorbidity Burden & Prognosis

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

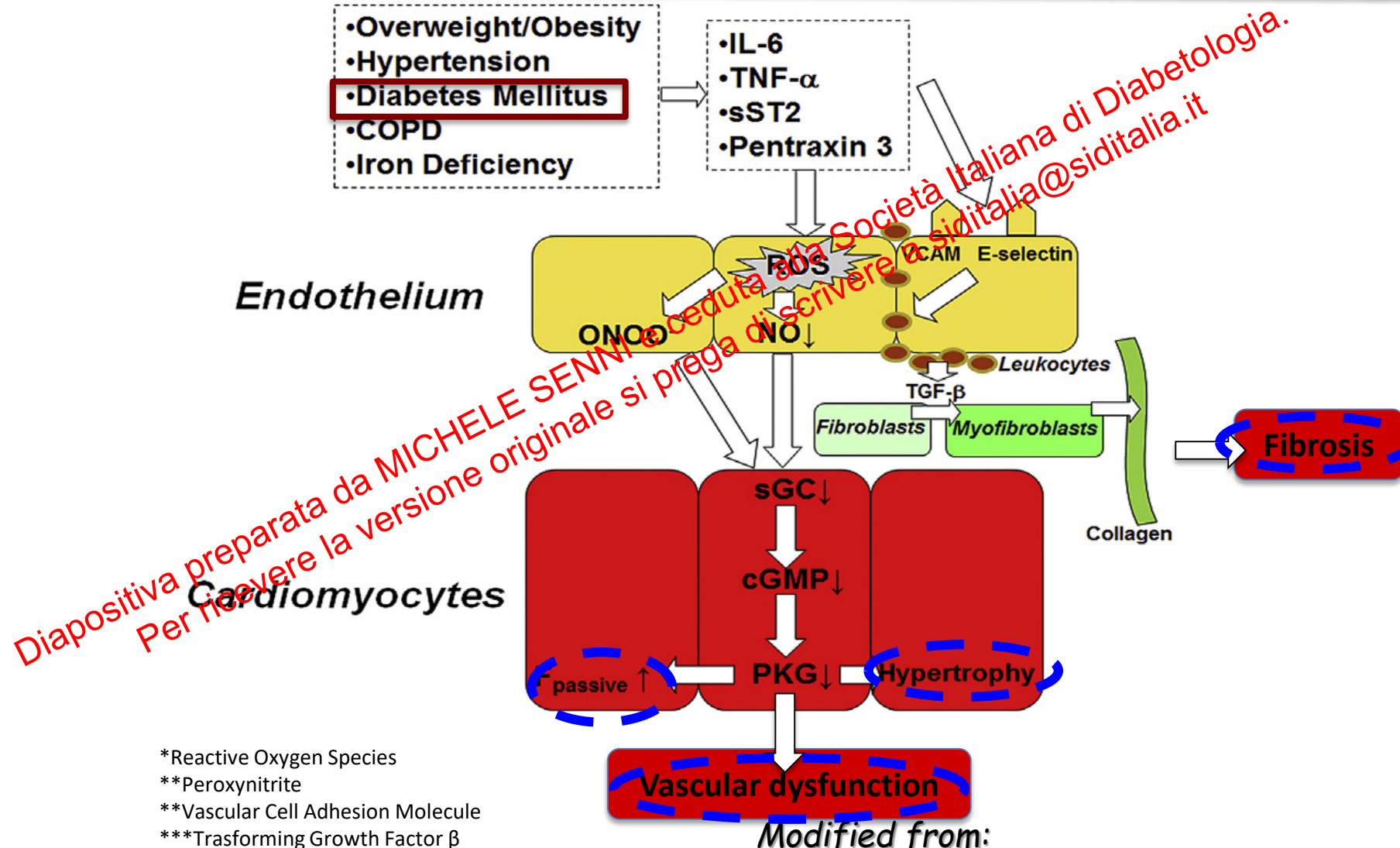
Variable	HFrEF	HFpEF
Diabetes mellitus	1.8% (1.3-3.3)	1.4% (1.1-2.4)
Hypertension	0.5 (0.7-0.93)	0.5 (0.5-1.6)
Peripheral Artery Disease	1.9% (1.2-3.4)	1.2% (0.1-1.6)
Cerebrovascular Disease	1.0 (0.7-1.6)	1.3 (0.5-1.1)
Chronic Renal Failure	2.3% (1.1-3.2)	1.6% (1.3-2.1)
Anemia		
Chronic Pulmonary disease		
Obesity		
Dementia		
Liver Disease		
Cancer		
Rheumatologic Disorders	1.1 (0.8-2.9)	1.3 (0.7-2.3)
Peptic Ulcer	1.9 (0.7-5.0)	1.3 (0.6-2.8)
Psychiatric Disorders	1.3 (0.6-2.6)	0.6 (0.2-1.5)

No variables had significant impact indicating no significant difference in impact between the 2 EF

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)	1.4 (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)
Chronic kidney disease	Overall	1.9 (1.5-2.3)	1.7 (1.3-2.0)	30 (14-42)	21 (9-32)
	HFpEF	1.6 (1.2-2.1)	1.6 (1.3-2.1)	28 (4-42)	18 (6-30)
	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)	-	-

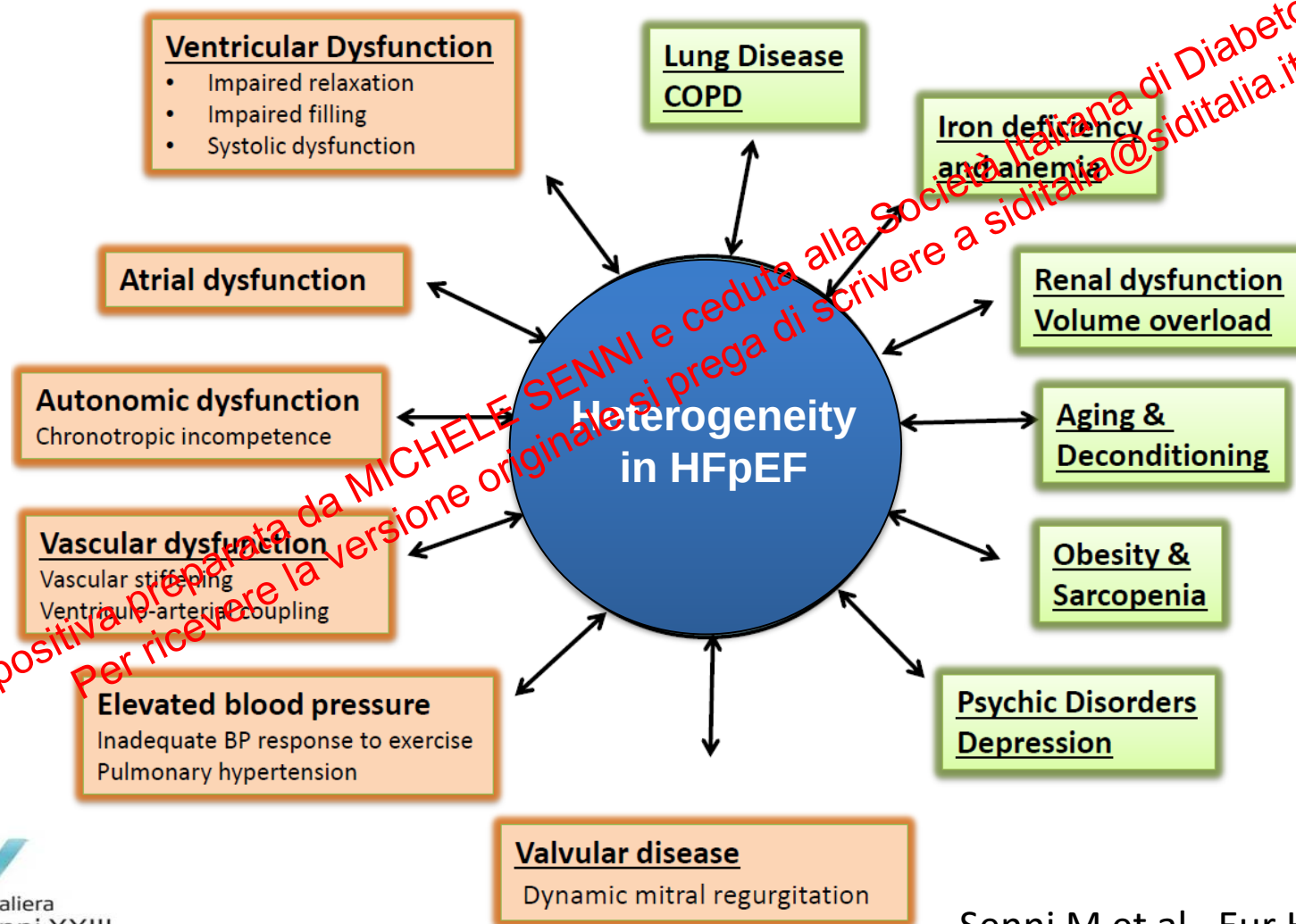


Myocardial-Vascular Dysfunction and Remodeling



Modified from:
Paulus and Tschoepe, JACC 2013

HFpEF: Pathophysiology



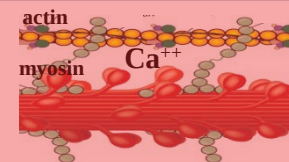
CARDIAC FACTORS

SYSTOLIC
DYSFUNCTION

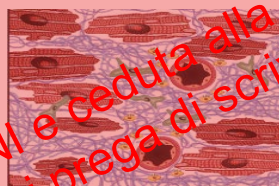
PULMONARY
HYPERTENSION

RIGHT VENTRICULAR
DYSFUNCTION

CHRONOTROPIC
INCOMPETENCE



DIASTOLIC
DYSFUNCTION



VASCULAR
STIFFNESS

ABDOMINAL
MECHANISMS

EXTRA-CARDIAC FACTORS

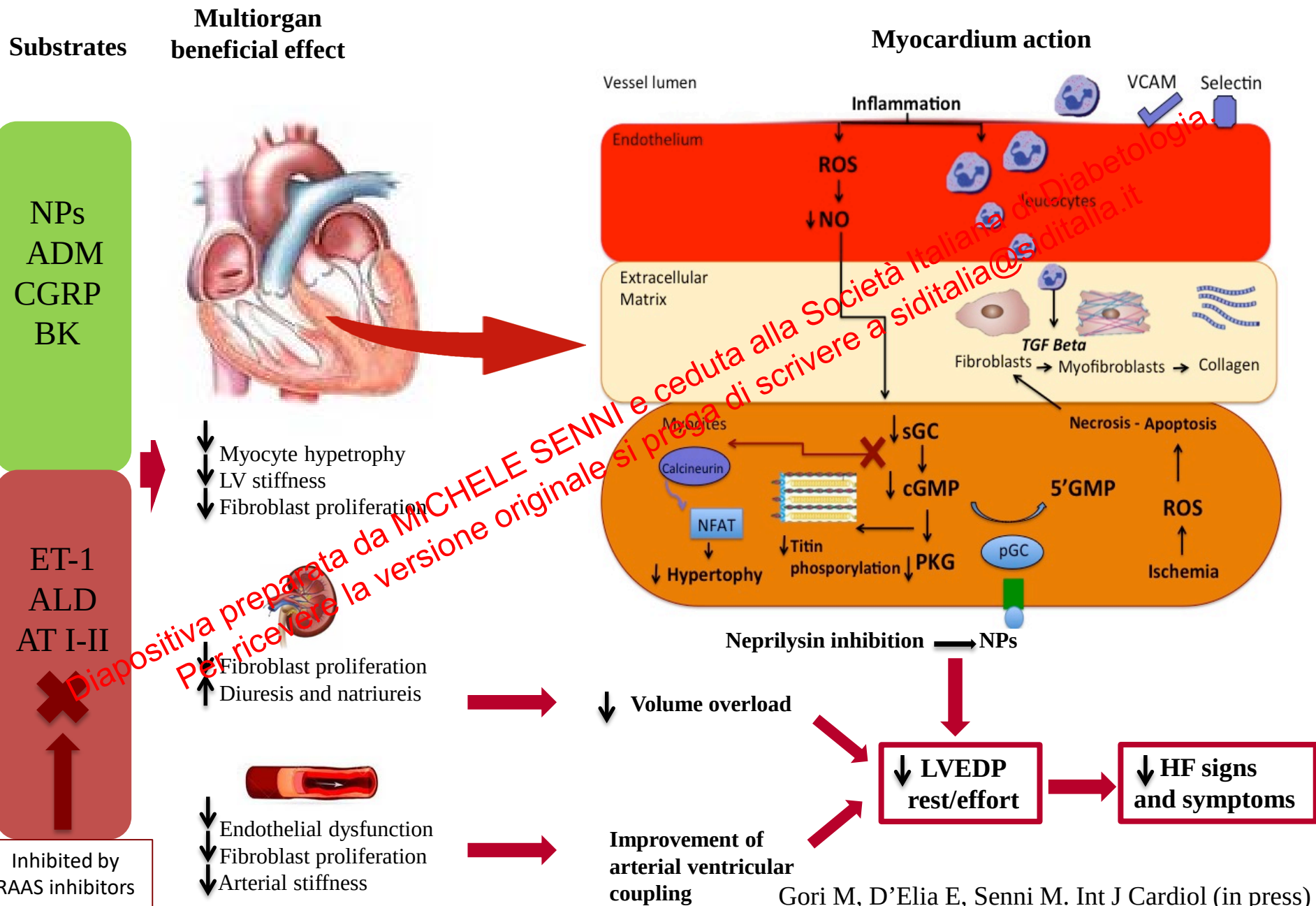
↑LVEDP

→ ↑NPs

- REST &/or
- EXERCISE



Potential Sacubitril/valsartan mechanisms of action in HFpEF patients



HFpEF: Therapy 2018

NYHA I	NYHA II	NYHA III	NYHA IV
?			
		?	
		?	
		?	
		?	
		?	
		Diuretics ?	

RANDOMIZED CLINICAL TRIALS in HEART FAILURE (1986-20018)

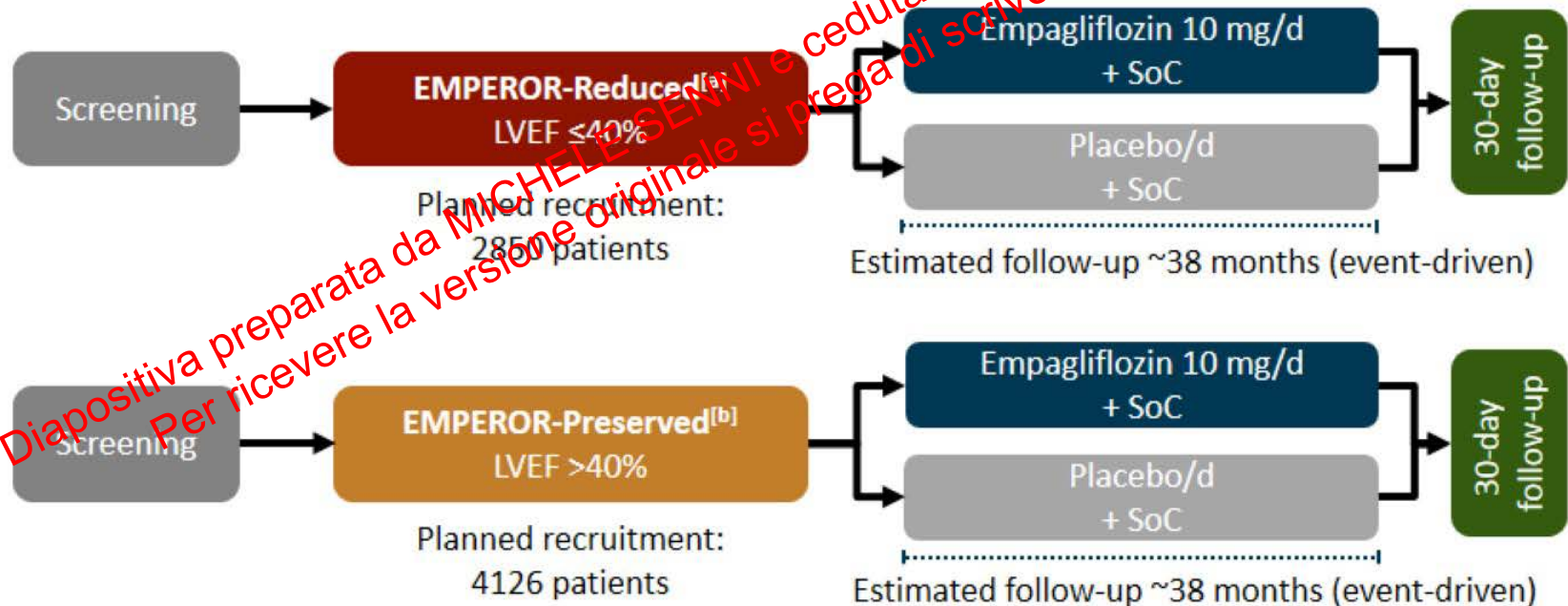
HF (including diabetes)

HF and diabetes

- | | | |
|------------------------------|--|----|
| • <u>VASODILATORS</u> : | V-HeFT I, PROFILE, FIRST | -- |
| • <u>ACE INHIBITORS</u> : | V-HeFT II, CONSENSUS, SAVE,
SOLVD TREAT/PREV,
NETWORK, ATLAS | |
| • <u>ALL R ANTAGONISTS</u> : | ELITE, RESOLVD, ELITE II, VAL-HeFT | -- |
| • <u>Ca ANTAGONISTS</u> : | PRAISE, V-HeFT III, MACH-1 | -- |
| • <u>DIGITALIS</u> : | CAPTOPRIL-DIGOXIN MRG, CADS,
RADIANCE, DIG | -- |
| • <u>INOTROPES</u> : | PROMISE, VEST, PRIME II | -- |
| • <u>AMIODARONE</u> : | GESICA, CHF-STAT | -- |
| • <u>BETA-BLOCKERS</u> : | XAMOTEROL, MDC, CIBIS I, CIBIS II,
ANZ, US CARVEDILOL, MERIT, BEST
COPERNICUS, CAPRICORN | -- |

EMPEROR-Reduced and EMPEROR-Preserved HF Outcome Trials

- Phase 3 randomized double-blind placebo-controlled studies
- Aim: To investigate the safety and efficacy of empagliflozin vs placebo on top of guideline-directed medical therapy in patients with HFrEF or HFpEF
- Population: T2D and non-T2D, aged ≥ 18 years, chronic HF (NYHA II-IV)

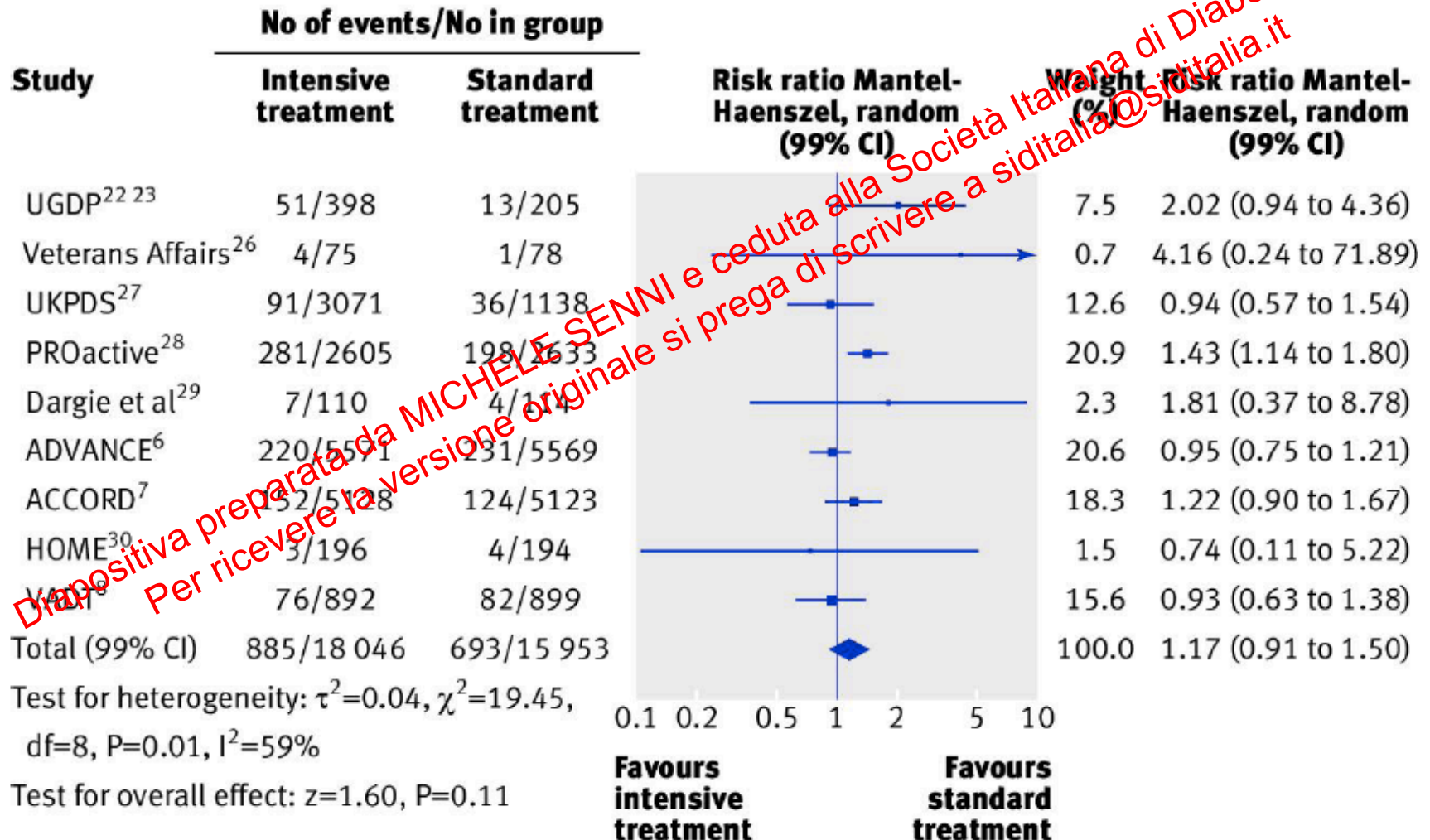


Diapositiva preparata da MICHELE SENNI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



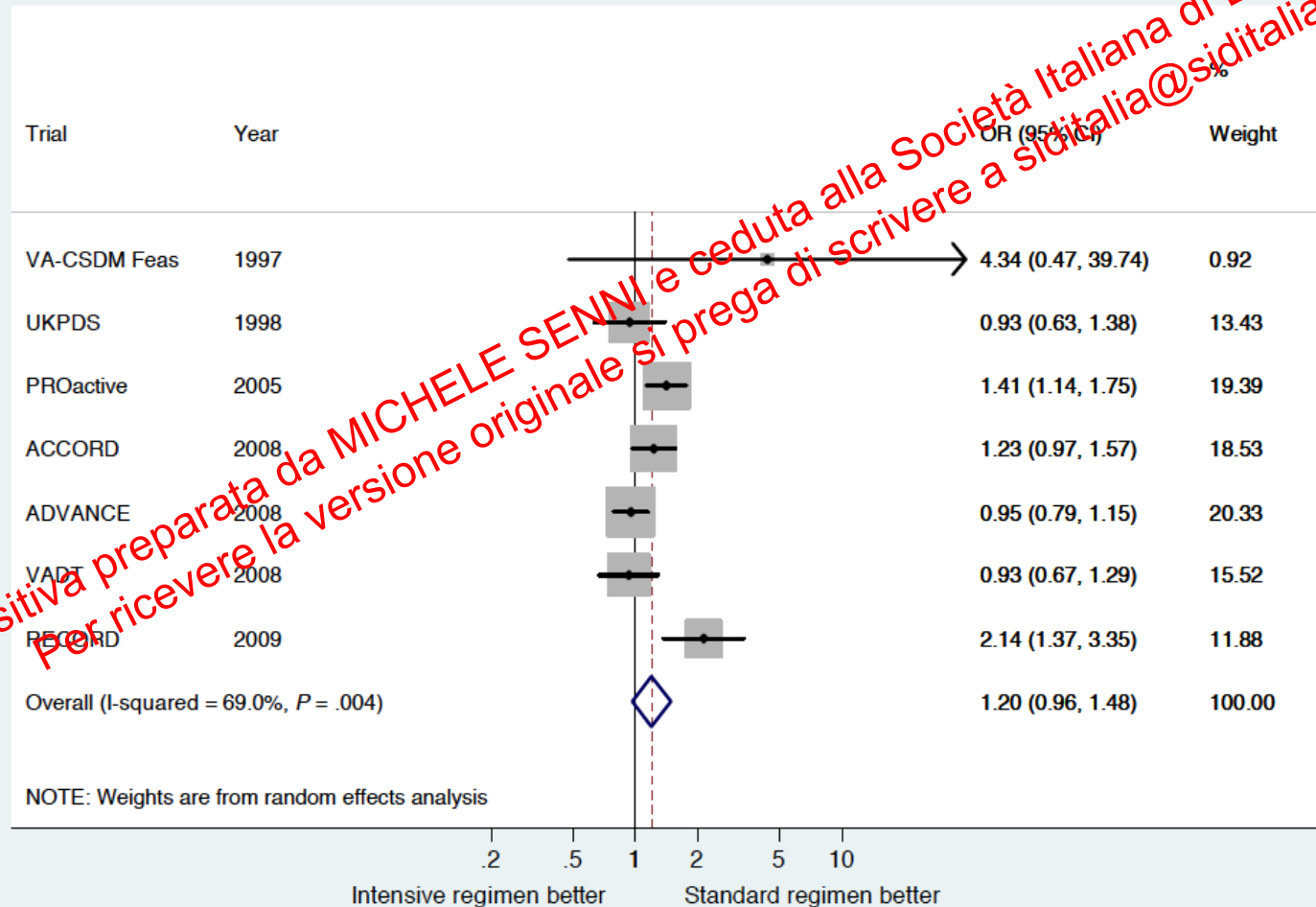
Forest plot for congestive heart failure

BMJ 2011;343:d4169 doi: 10.113



Probability of HF-related events with intensive glucose-lowering versus standard treatment

Am Heart J 2011;162:938-948



Diapositiva preparata da MICHELE SENNI e ceduta alla Societa Italiana di Diabetologia.
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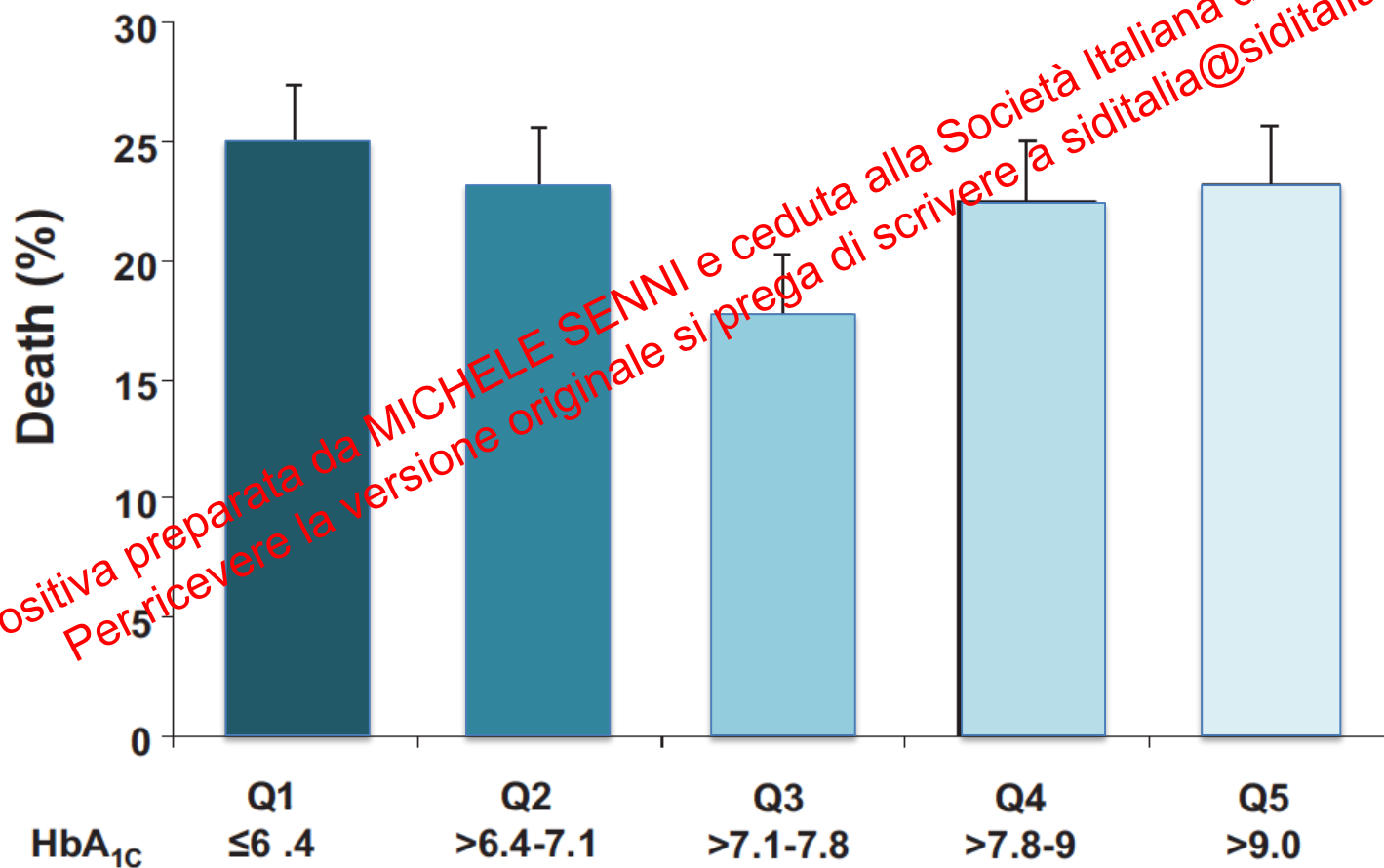
Why hasn't intensive glucose control decreased HF?

- Wrong hypothesis
- Wrong trials
- Wrong patients
- Wrong intervention...

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Proportion of patients with HF who died at 2-year follow-up by quintiles of HbA1c

J Am Coll Cardiol 2009;54:422–428



Empagliflozin in T2D patients with and without HF – EMPA-REG Outcome Trial

	Empagliflozin		Placebo		HR (95% CI)
	<i>n</i> with event/ <i>n</i>	%	<i>n</i> with event/ <i>n</i>	%	
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.73 (0.50–1.04)
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)

