

Insulina e cuore; dalla fisiologia alla fisopatologia



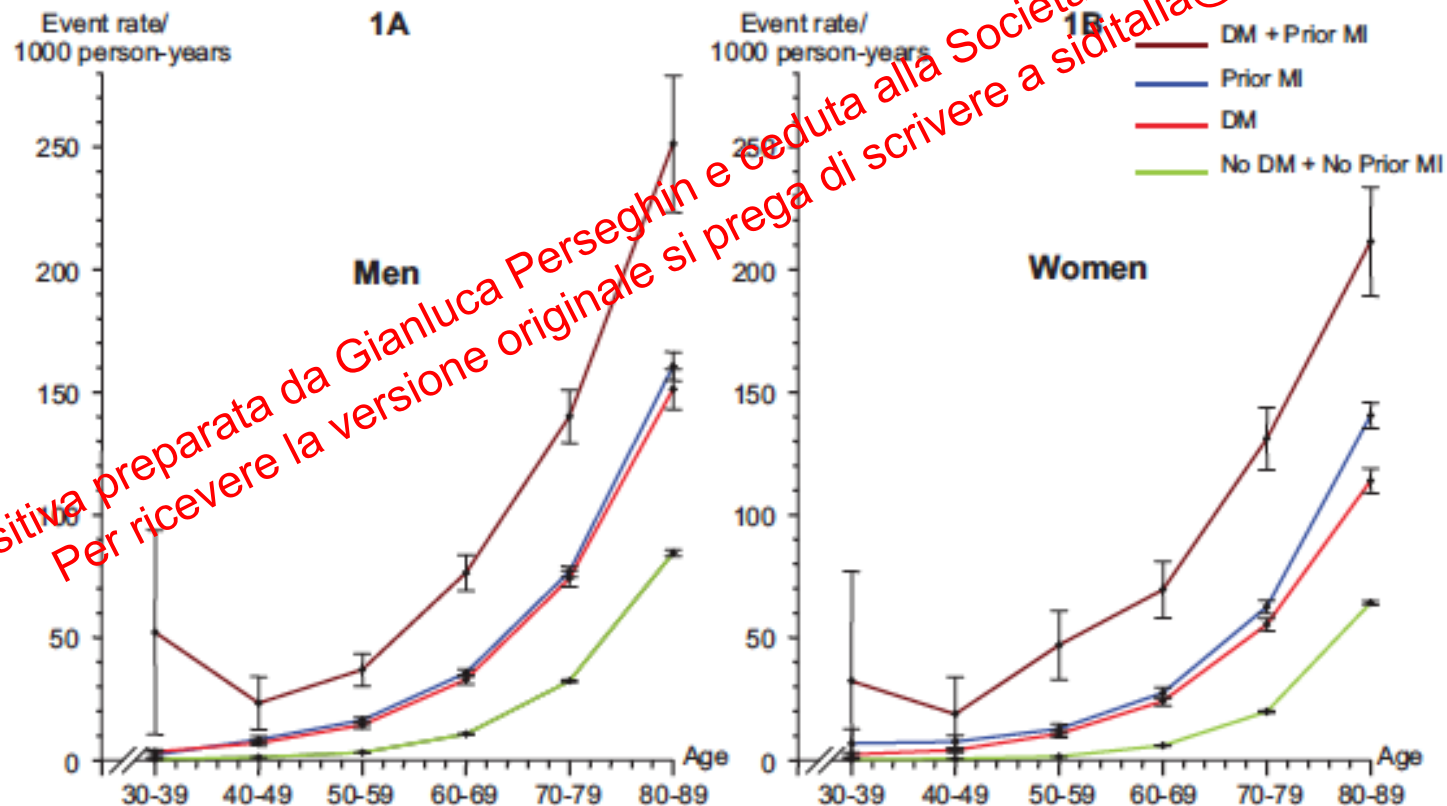
Gianluca Perseghin



Diabetes Patients Requiring Glucose-Lowering Therapy and Nondiabetics With a Prior Myocardial Infarction Carry the Same Cardiovascular Risk

A Population Study of 3.3 Million People

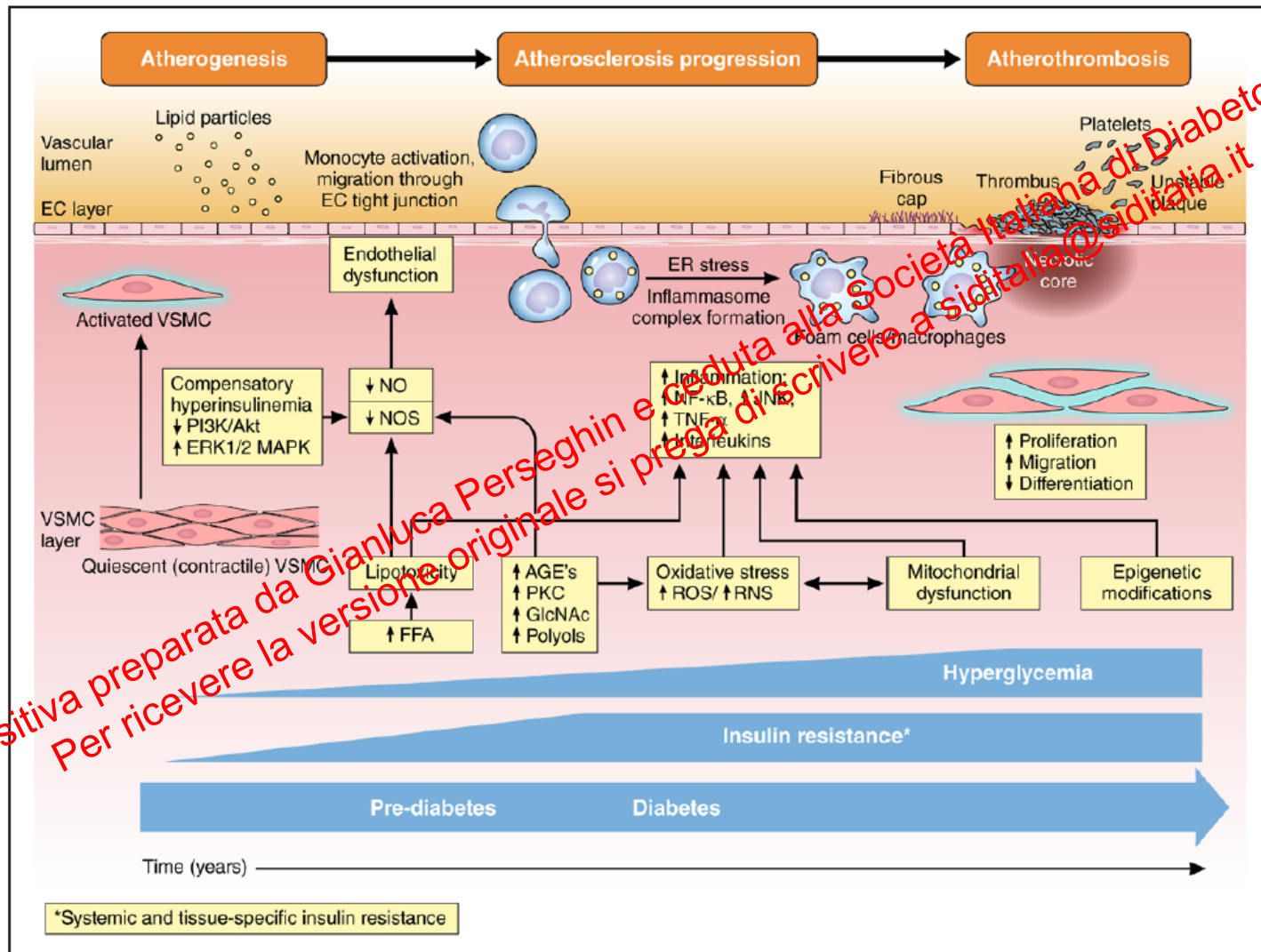
Tina Ken Schramm, MD; Gunnar H. Gislason, MD; Lars Køber, MD, DMSc; Søren Rasmussen, MSc, PhD; Jeppe N. Rasmussen, MD, PhD; Steen Z. Abildstrøm, MD, PhD; Morten Lock Hansen, MD; Fredrik Folke, MD; Pernille Buch, MD; Mette Madsen, MSc; Allan Vaag, MD, DMSc; Christian Torp-Pedersen, MD, DMSc



Schramm TK et al Circulation, 2008

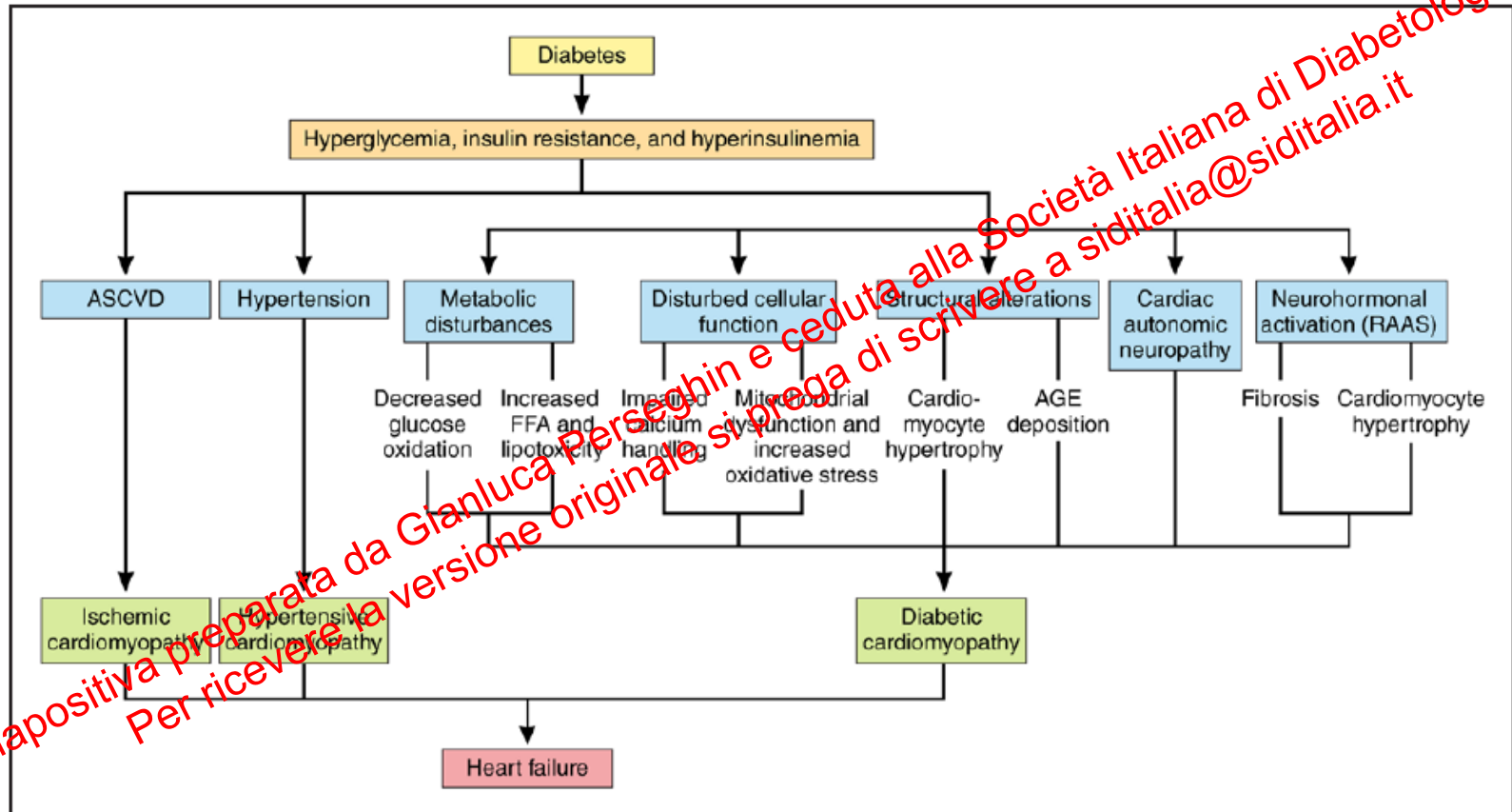
Cardiovascular disease in diabetes mellitus

Atherosclerosis



Cardiovascular disease in diabetes mellitus

Heart failure



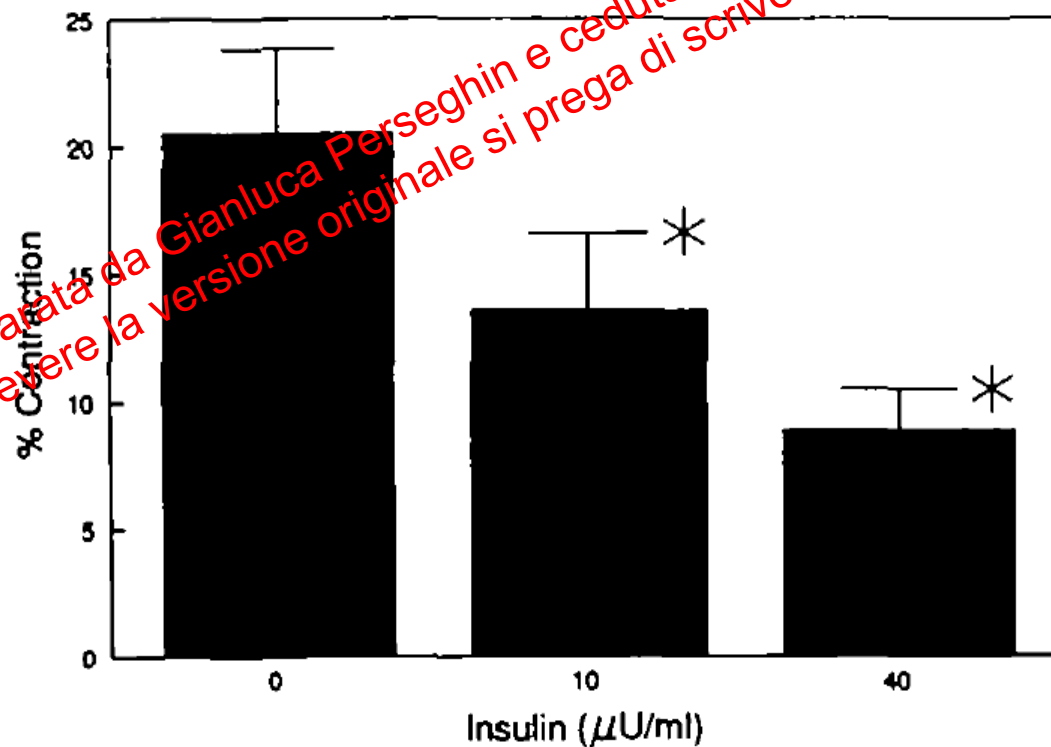
Acute vascular effects of Insulin

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Insulin Reduces Contraction and Intracellular Calcium Concentration in Vascular Smooth Muscle

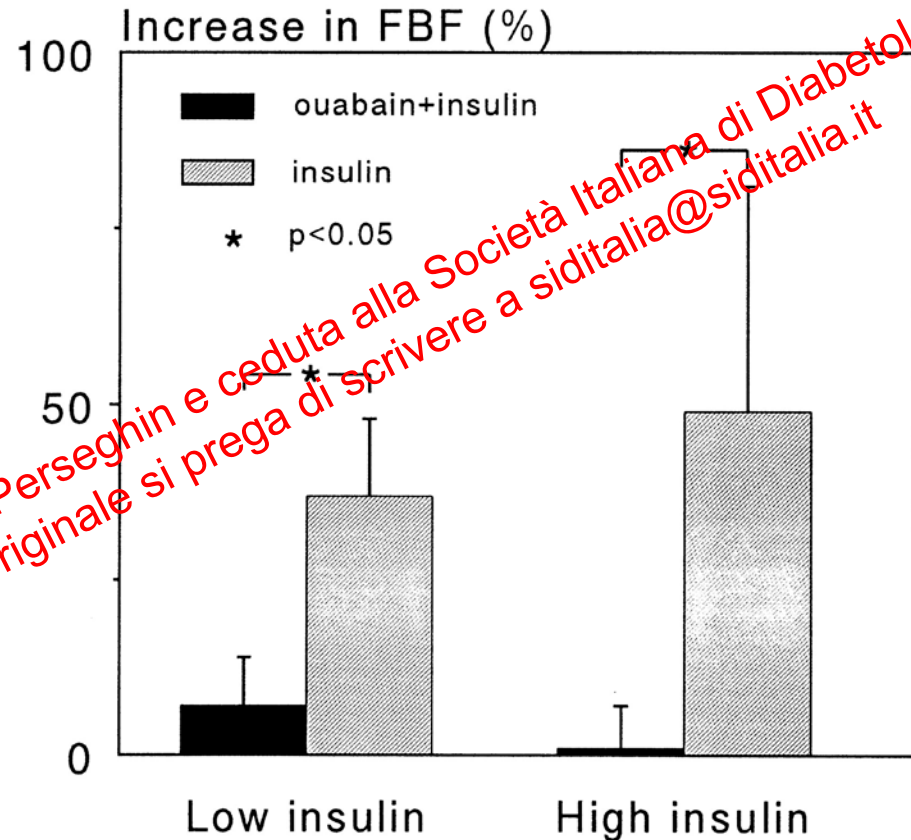
Andrew M. Kahn, Charles L. Seidel, Julius C. Allen, Roger G. O'Neil,
Harnath Shelat, Tom Song

738 **Hypertension** Vol 22, No 5 November 1995



Percent change in FBF after 90 minutes of low-dose ($430 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$) and high-dose ($860 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$) insulin infusions in control arm (insulin) and experimental arm (ouabain+insulin).

Na^+ , K^+ -ATPase
(mediated through endothelial
NO synthase)

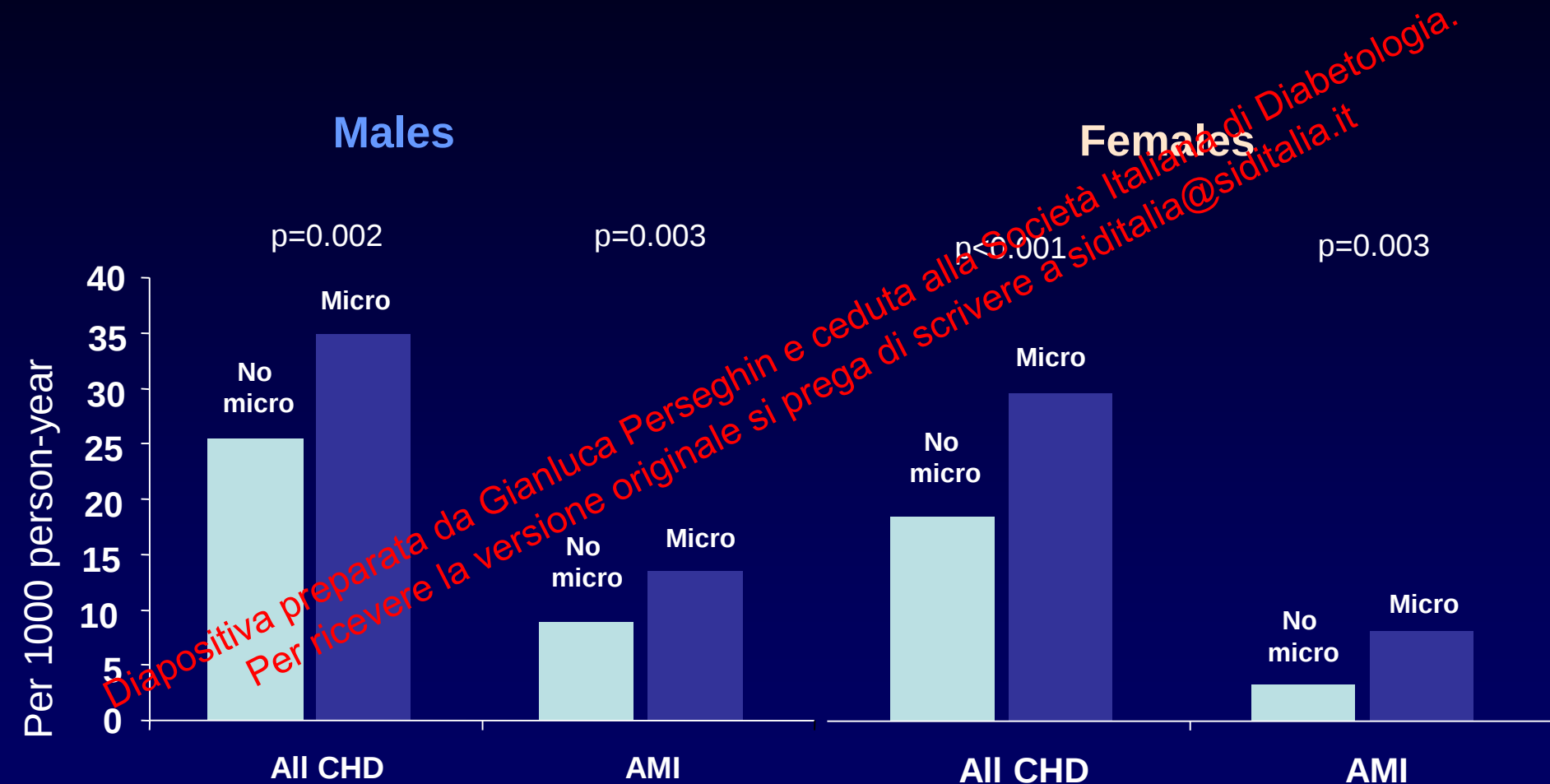


Tack CJ et al. Hypertension 1996;28:426-432

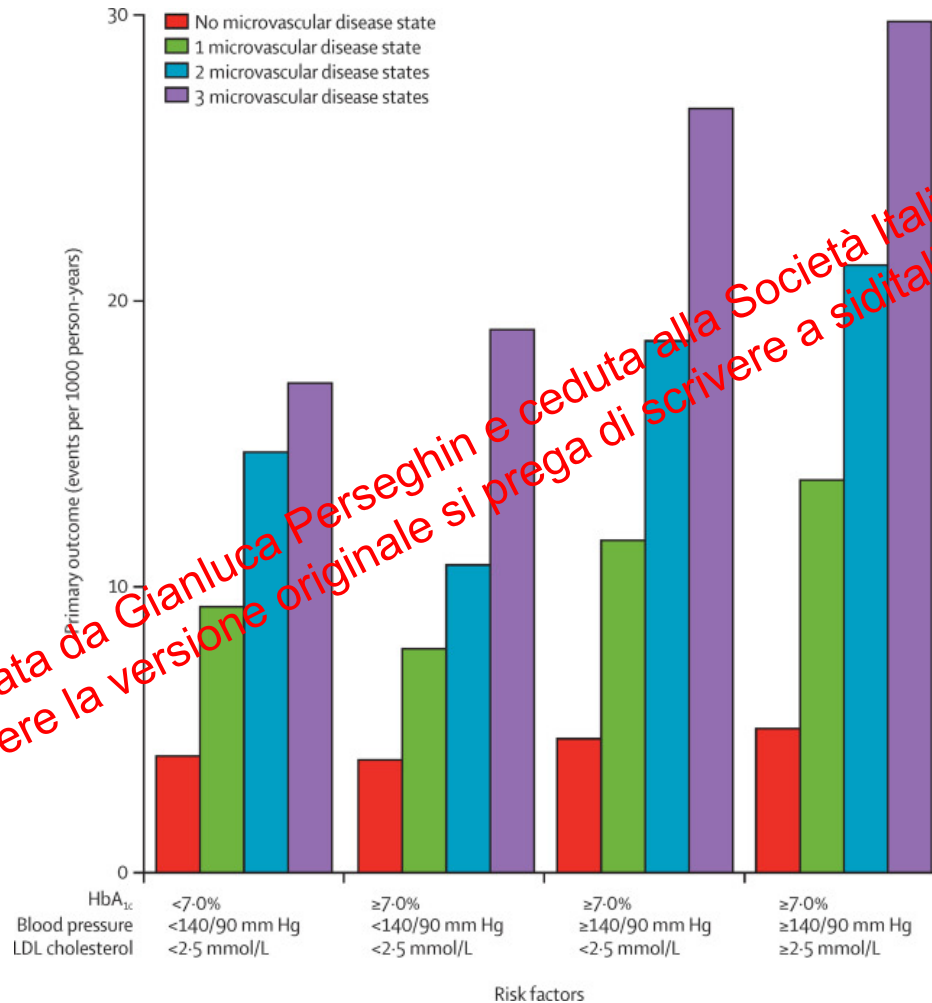
Altered microvasculature in pats with T2DM

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Incidence Rate of CHD Events: The role of microvascular complications



Adjusted event rates for the primary outcome by cumulative burden of microvascular disease and established risk factor goals



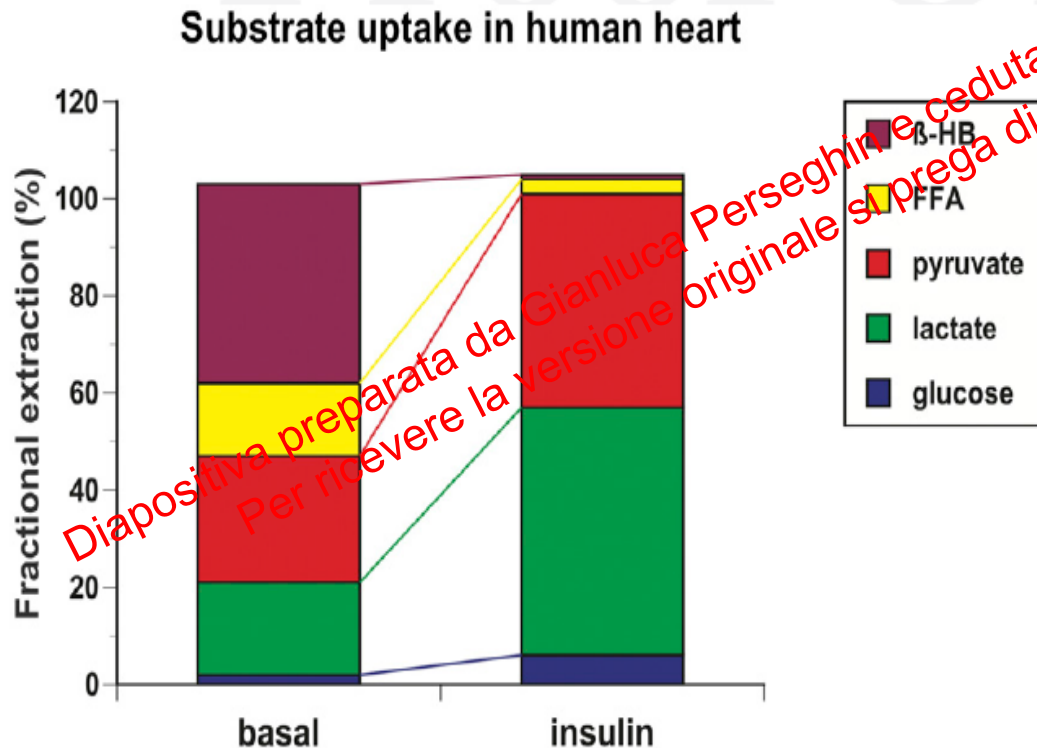
Acute metabolic effects of Insulin

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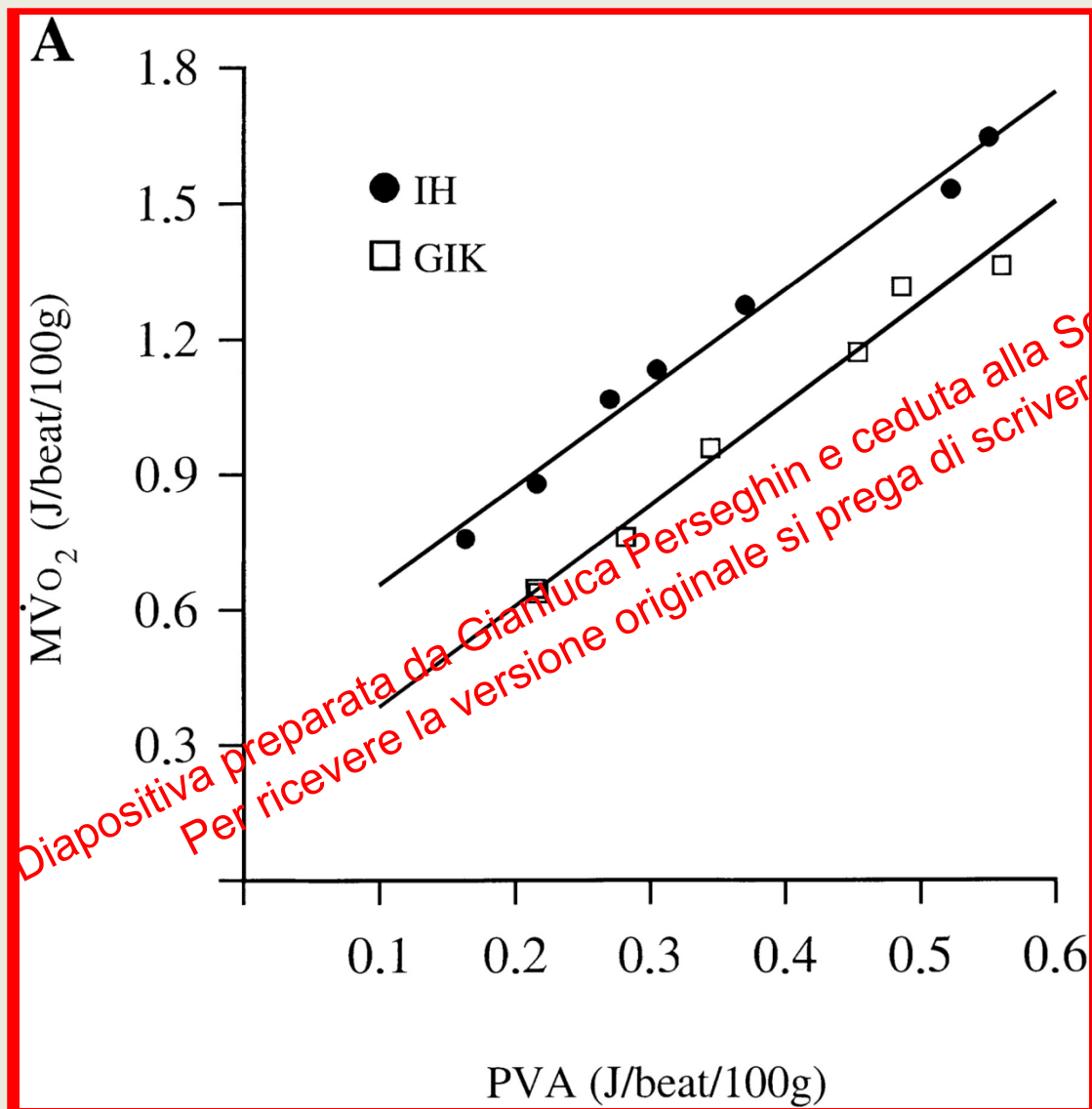
Cardiac energy metabolism

Ele Ferrannini,¹ Michael Mark,² and Eric Mayoux²

Diabetes Care 2016;39:1–7 | DOI: 10.2337/dc16-0330



Metabolic switch: why ?



GIK:

Glucose+insulin+K

IH:

Intralipid+heparin

PVA:

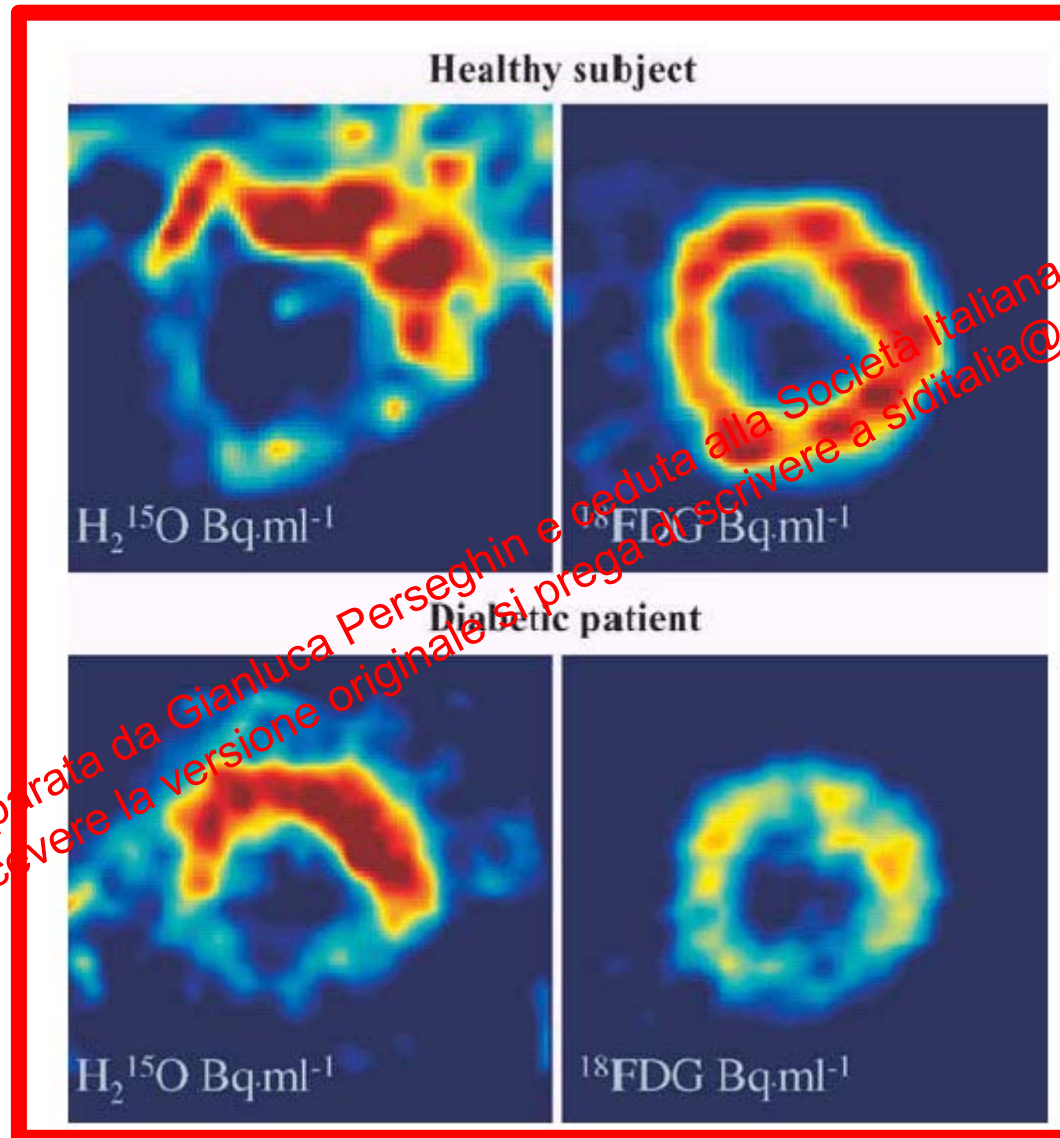
pressure-volume area
(Pig model)

Korvald C et al,
Am J Physiol 2000

Maladaptation of energy metabolism to insulin stimulation in pats with T2DM

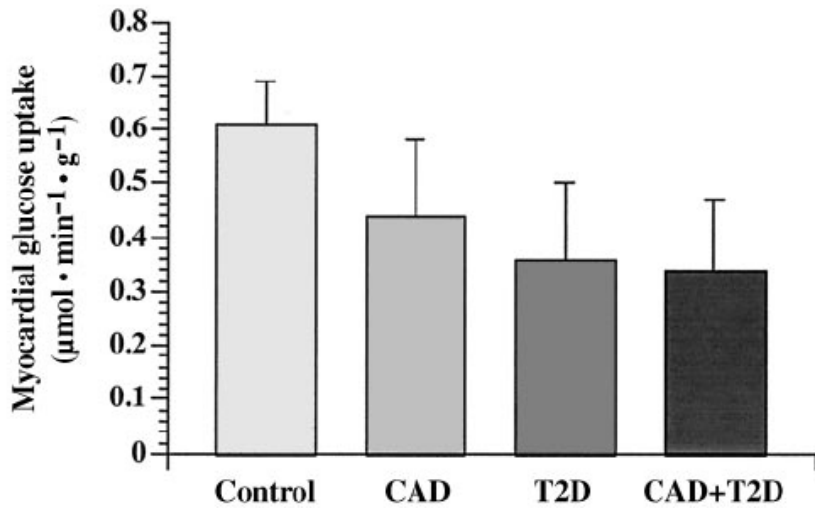
Diapositiva preparata da Gianluca Perseghin e ceduta alla Società Italiana di Diabetologia.
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Myocardial insulin resistance in T2DM

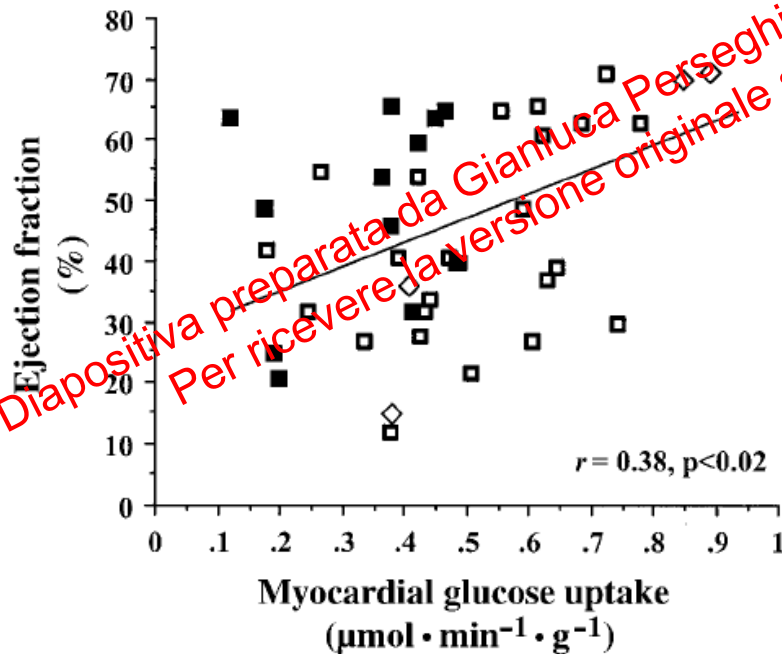


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Myocardial insulin resistance in T2DM



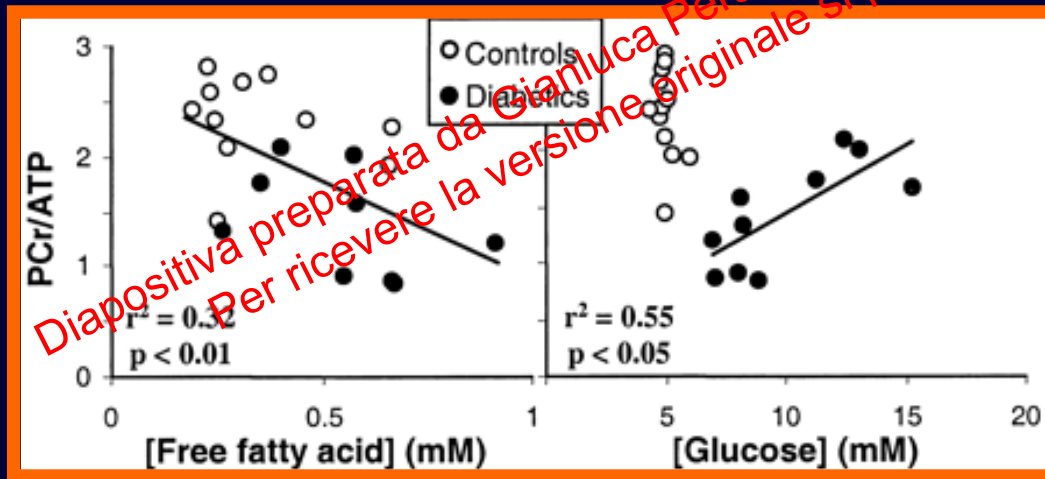
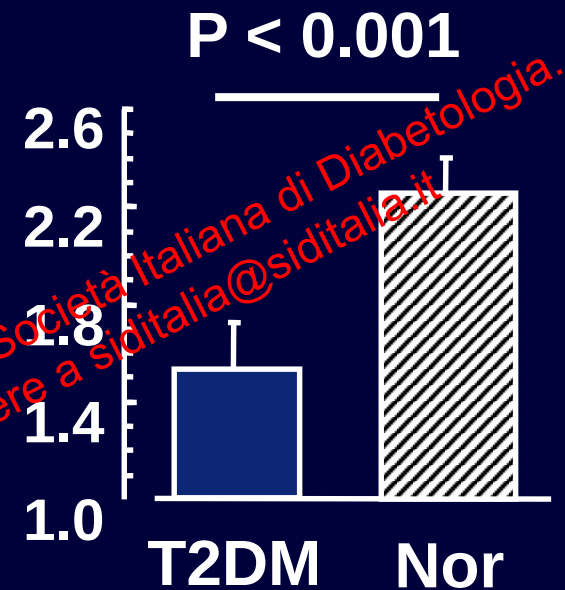
Baseline blood flow (^{15}O -water) and insulin-stimulated glucose uptake (^{18}F -fluoro-deoxyglucose) during clamps combined with PET



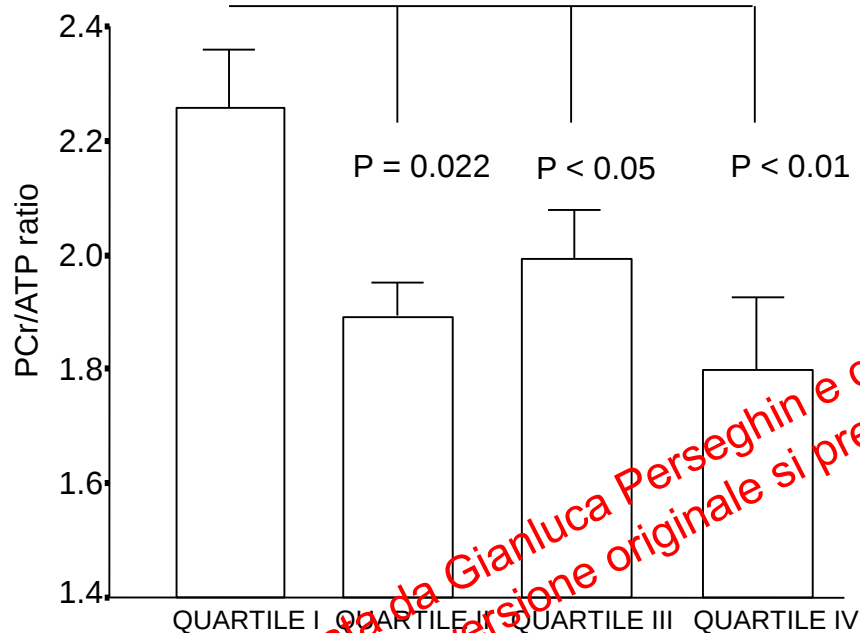
Iozzo P et al Diabetes, 2002

Cardiac energy metabolism in T2DM

PCr/ATP



Obesity: metabolic abnormalities in the absence of functional alterations



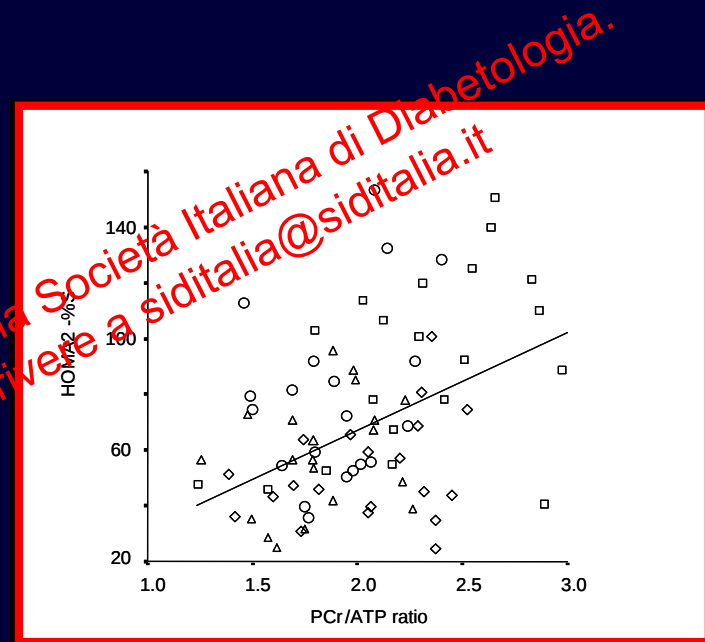
One-way ANOVA and Bonferroni post hoc

Quartile I: 18.5-23.2 kg/m²

II: 23.3-25.5 “

III: 25.5-29.0 “

IV: 30.0-35.3 “



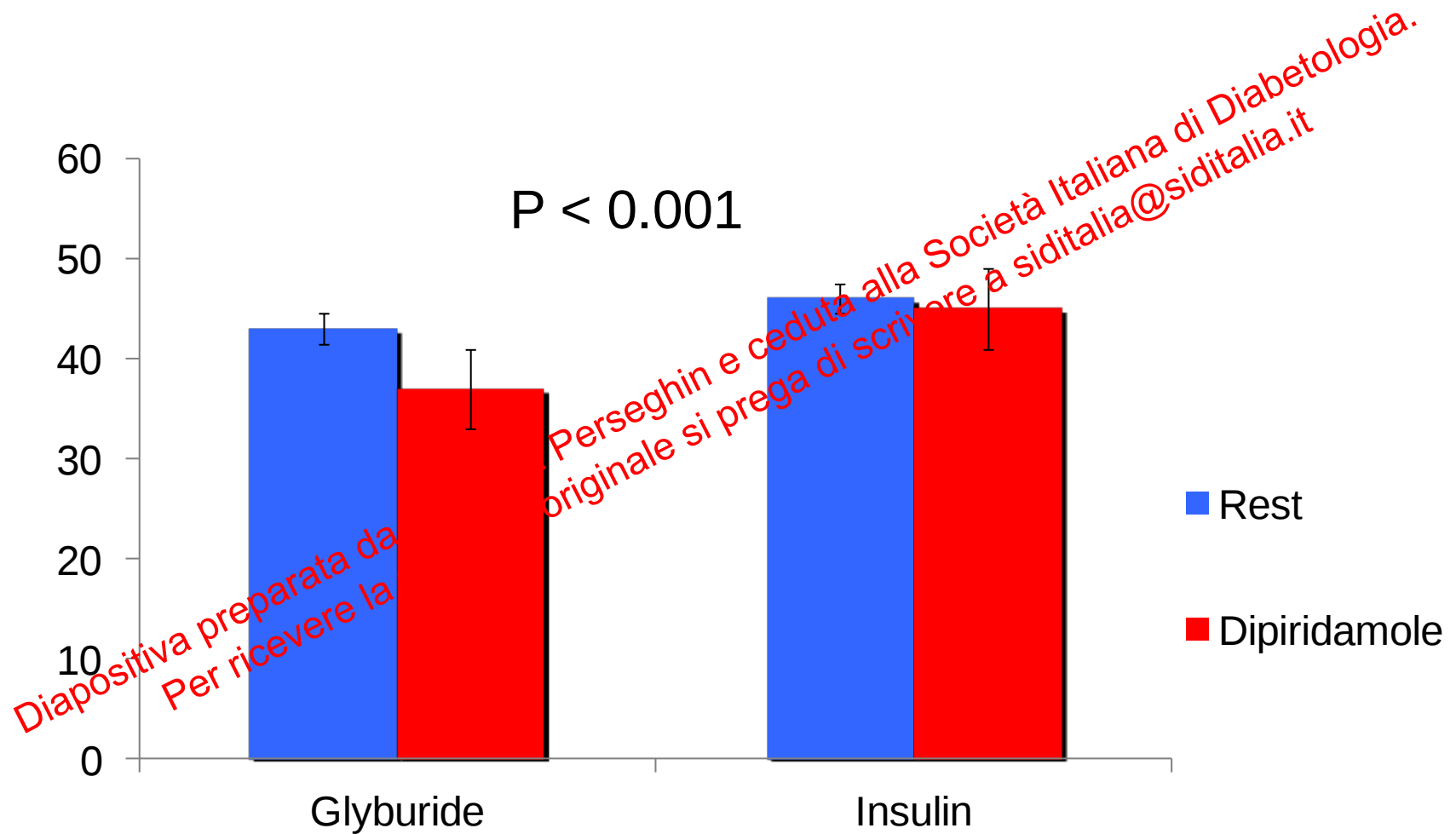
$r = 0.43$; $P < 0.001$

Perseghin G et al, *Diabetes Care* 2007

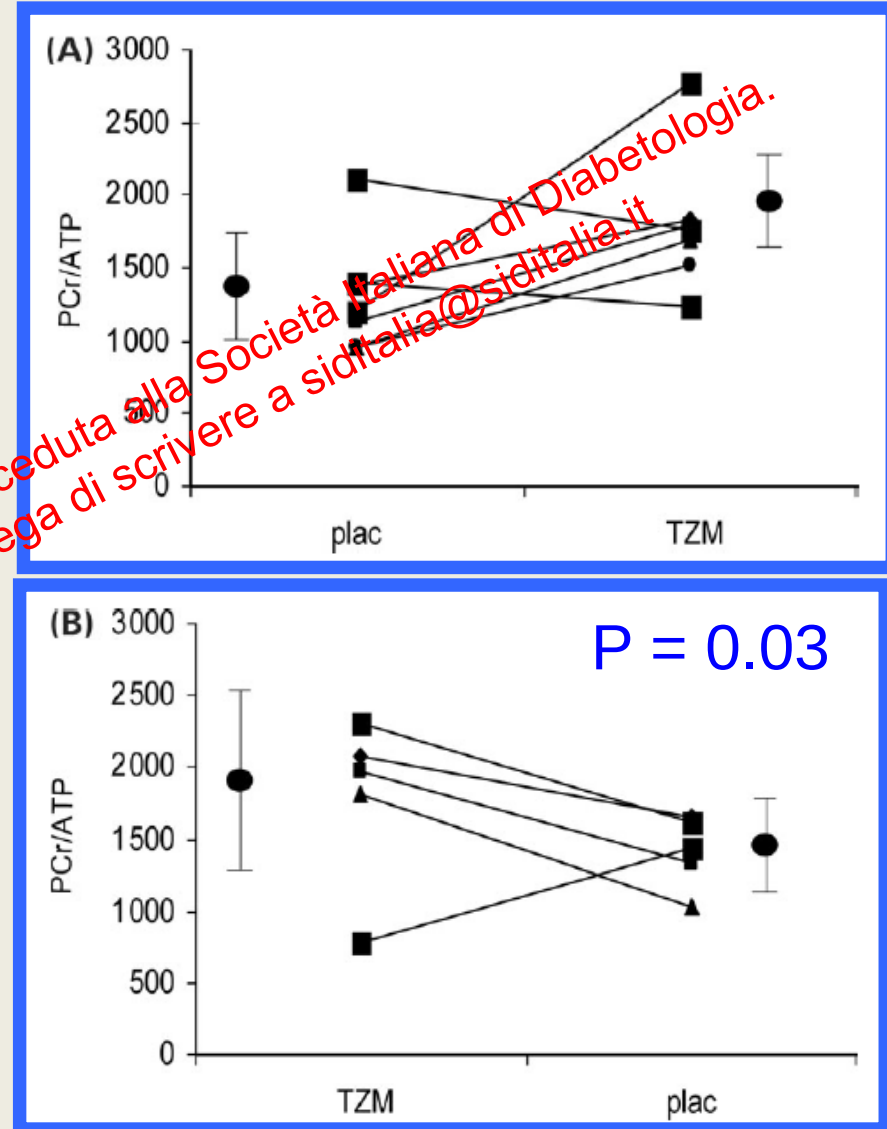
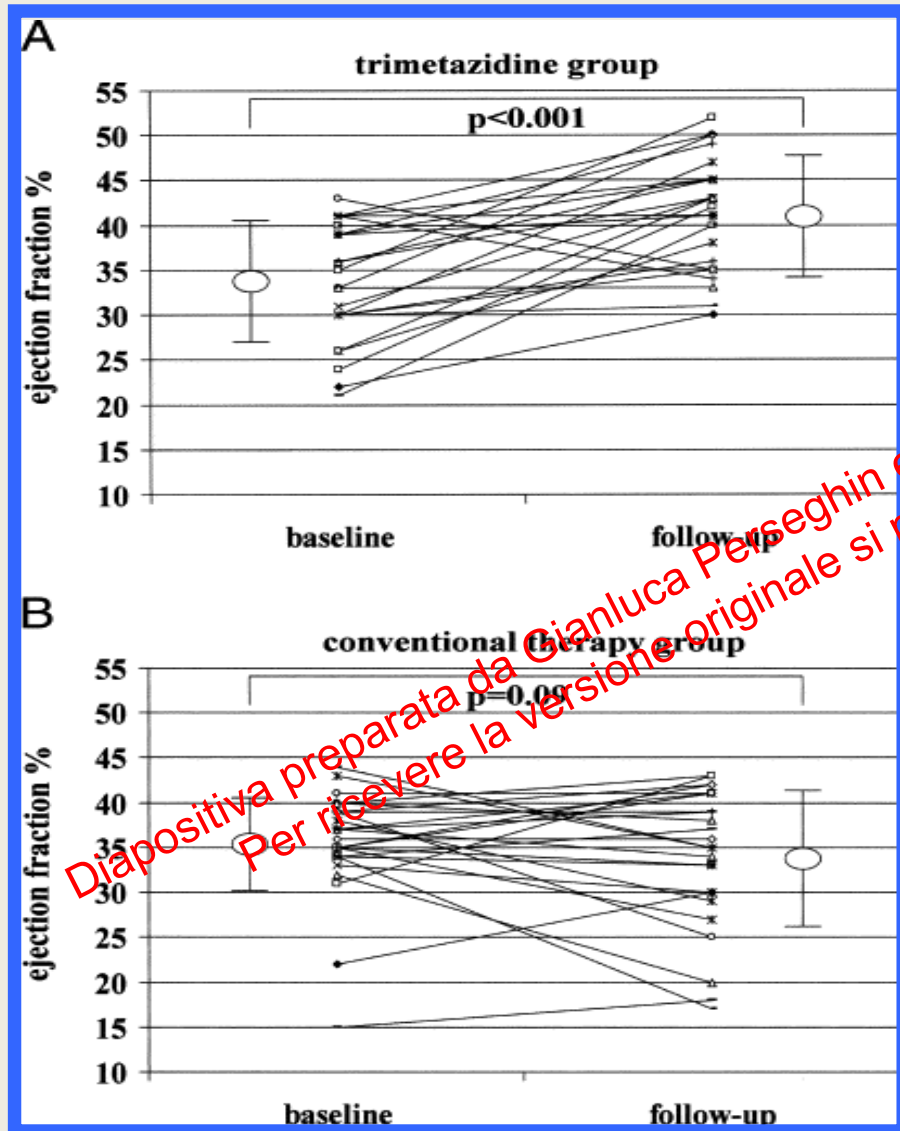
Direct and indirect beneficial effects of insulin

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Left ventricular ejection fraction in Type 2 patients with known CHD after 2-months period glibenclamide vs. insulin



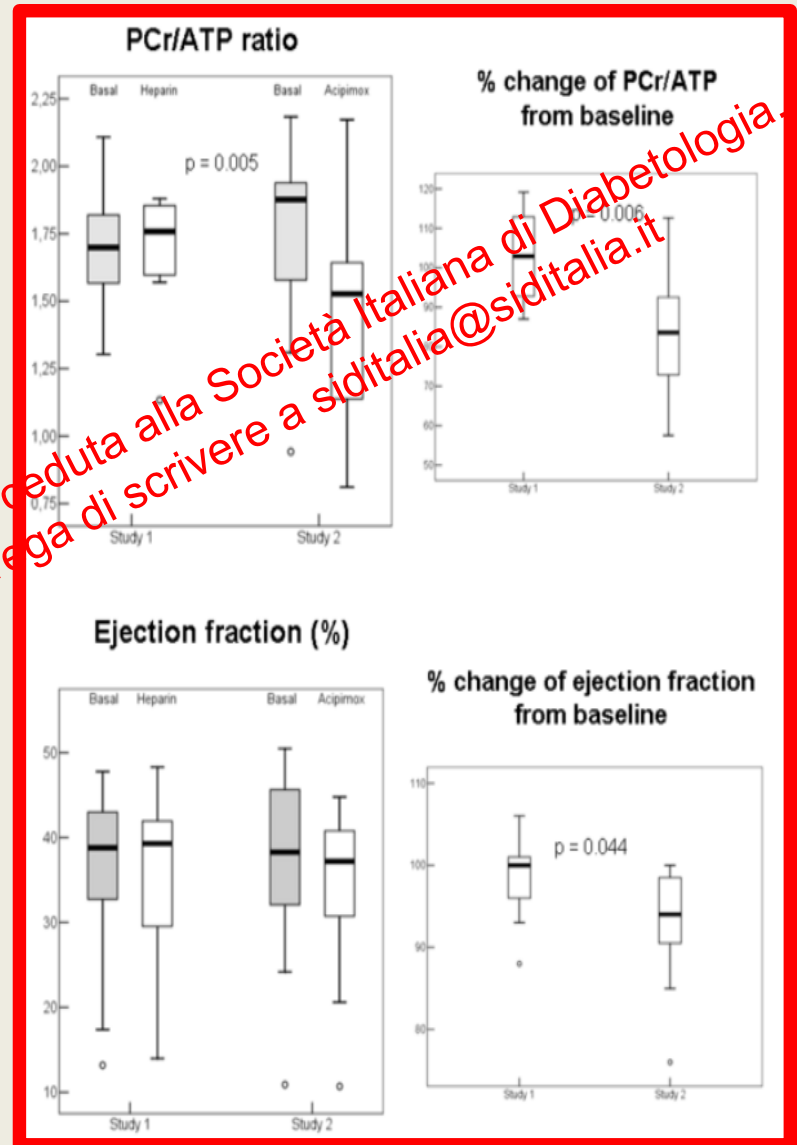
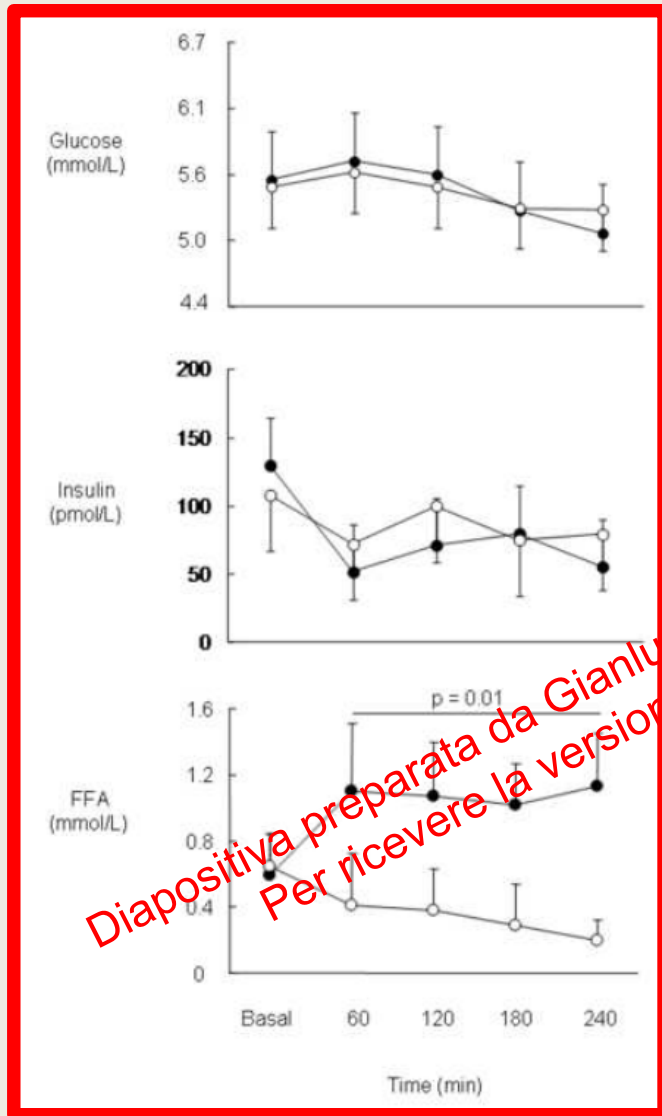
Metabolic therapy in cardiac failure: effects of Trimetazidine in the chronic setting (3 months)



..... with
caution

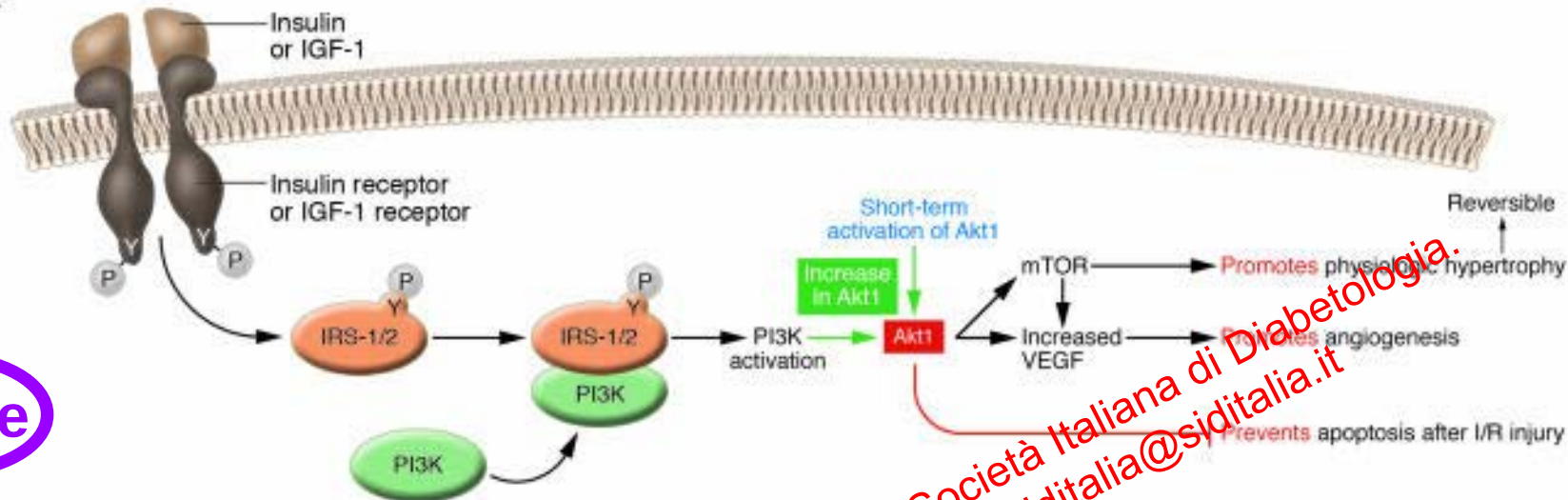
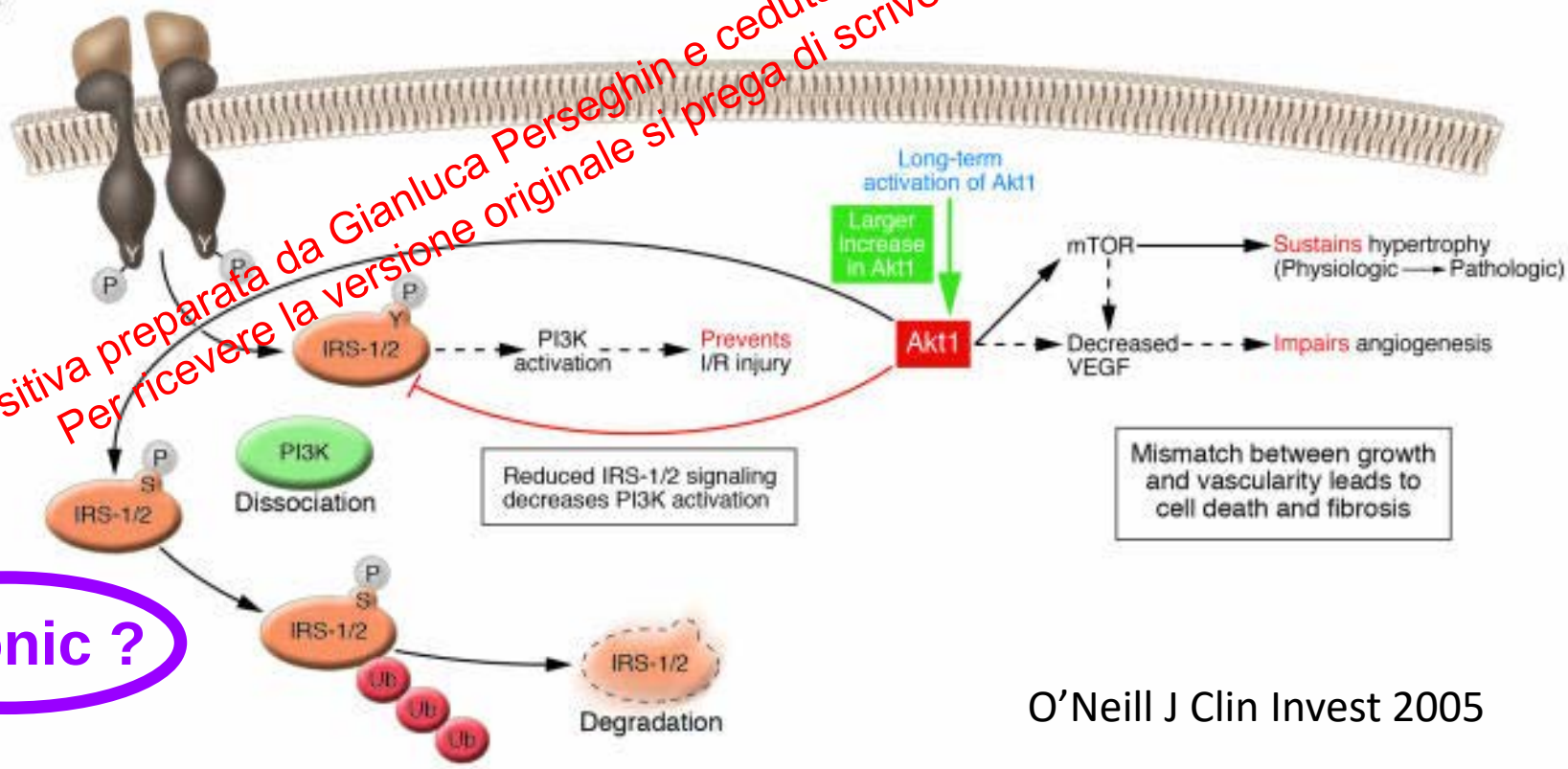
Diapositiva preparata da Gianluca Perseghini e ceduta alla Società Italiana di Diabetologia.
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Suppression of NEFA availability



Conclusioni

1. L'insulina induce acutamente benefici effetti diretti e indiretti emodinamici e metabolici sul miocardio
2. Il diabete, l'insulino-resistenza e la disfunzione endoteliale/microangiopatia associate contrastano e annullano questi effetti positivi dell'insulina
3. L'insulina costituisce un approccio terapeutico «safe» a patto da non indurre ipoglicemia e una contrazione eccessiva della disponibilità energetica

A**Acute****B****Chronic ?**

Summary

Diabetes, ATS and heart failure

Acute effects of insulin

Chronic effects of insulin

Controversies

ORIGIN

GLP1-RA and risk factors of ATS

Effects on LV function/reperfusion injury - animals

Effects on LV function/reperfusion injury - humans

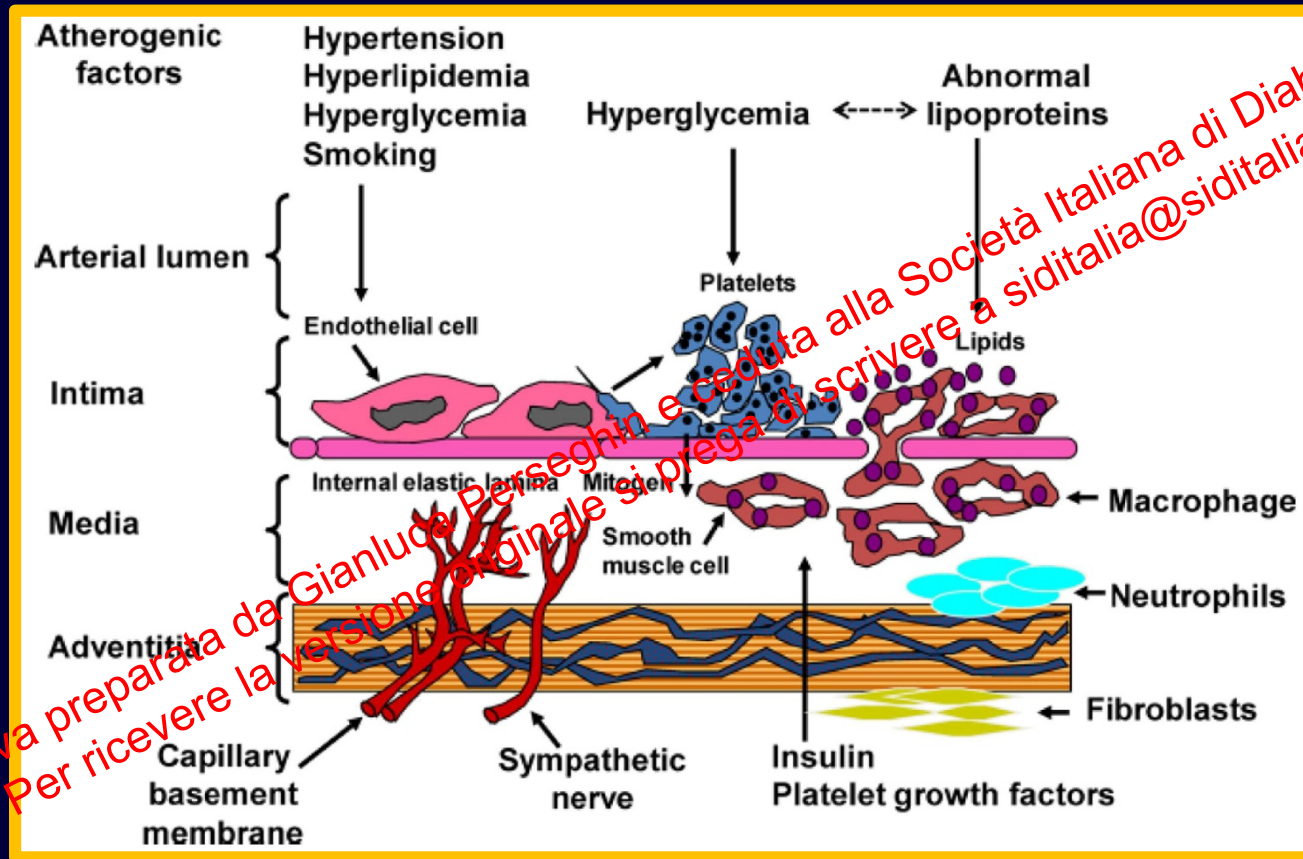
CV safety: meta-analysis and RCTs to come

Diapositiva preparata da Giulia Perseghin e ceduta alla Società Italiana di Diabetologia.
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Diabetes & atherosclerosis

Diapositiva preparata da Gianluca Perseghin e ceduta alla Società Italiana di Diabetologia.
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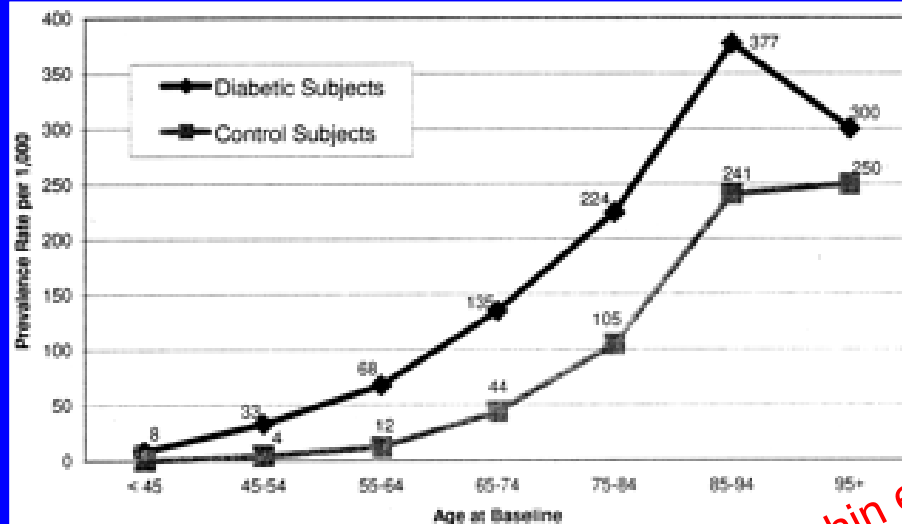
Diabetes & atherosclerosis



Diabetes & heart failure

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Diabetes and heart failure

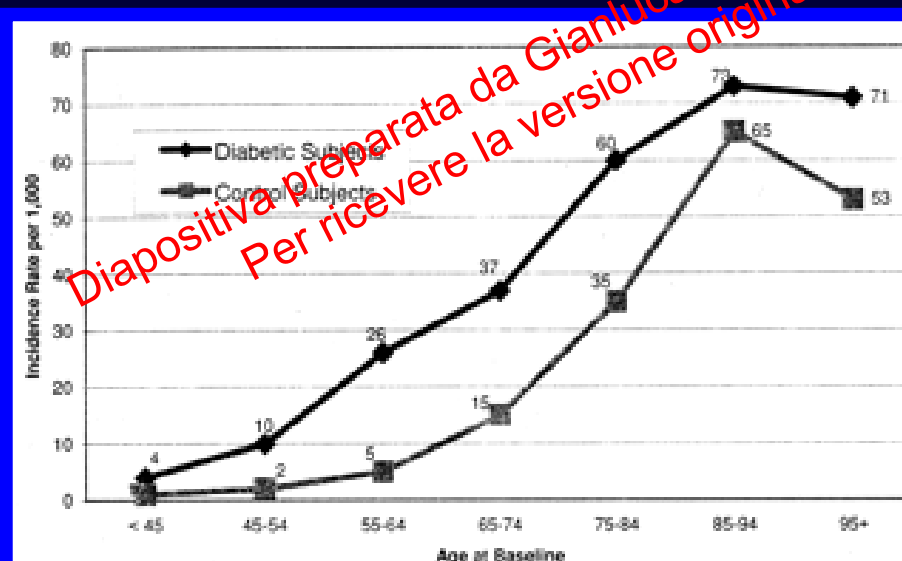


Prevalence

9,591 T2DM individuals

vs.
9,591 non diabetic subjects

12.0% vs. 4.5%



Annual Incidence

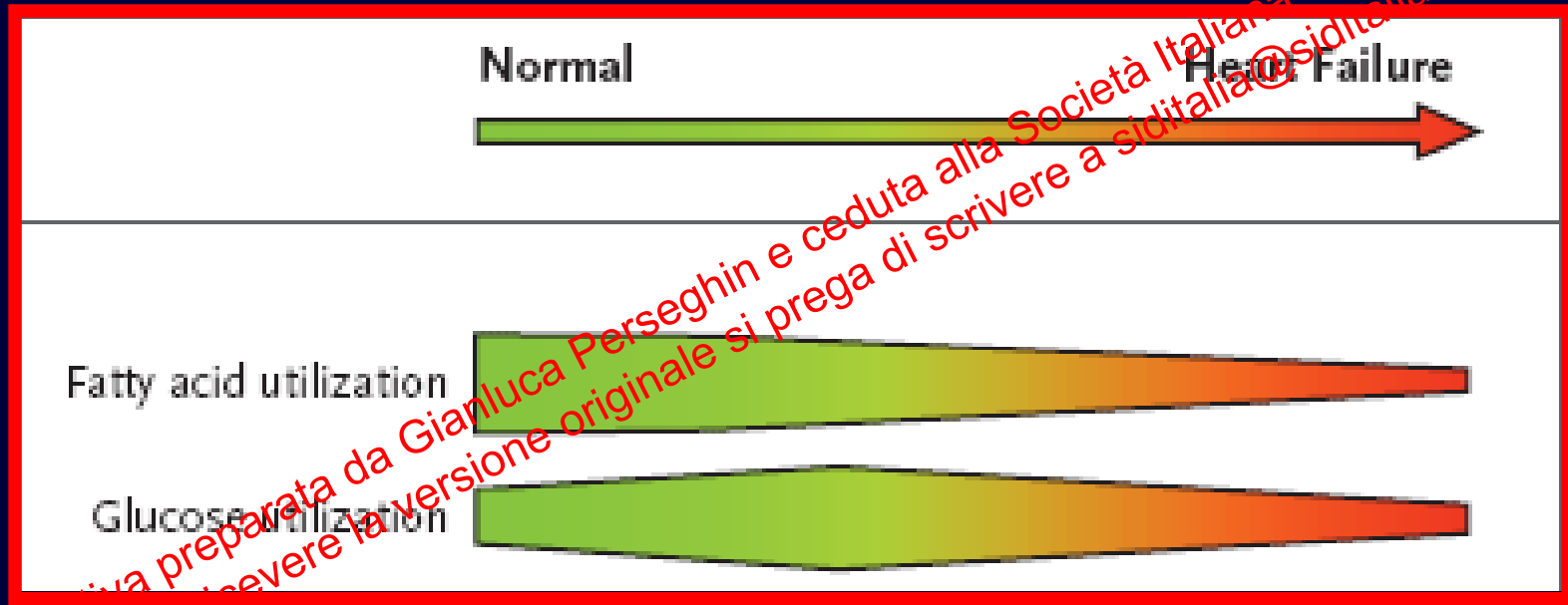
follow-up: 30 months

7.7% vs. 3.4%

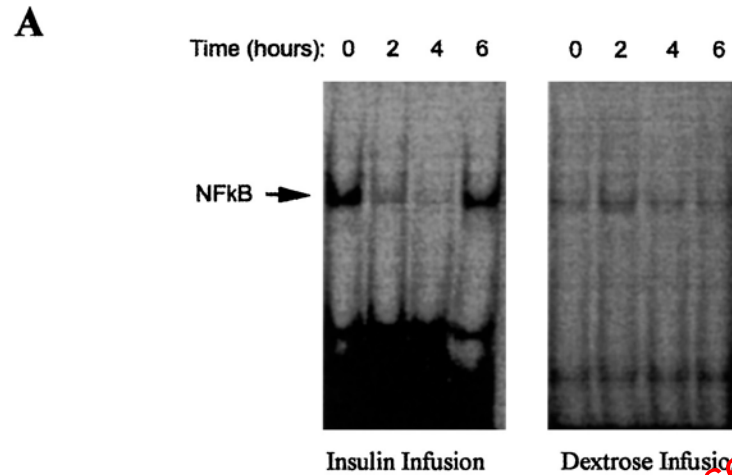
Nichols GA Diabetes Care, 2001

Cardiac metabolic adaptation in heart failure

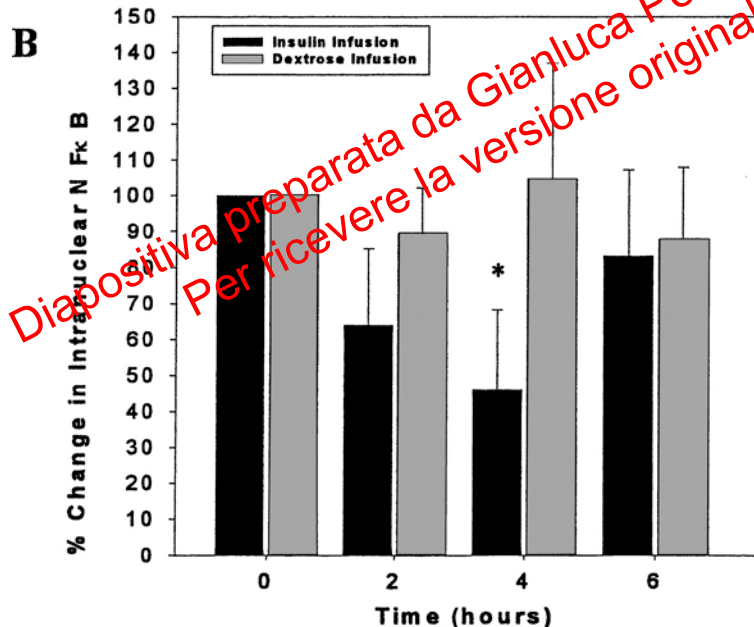
Metabolic switch in heart failure



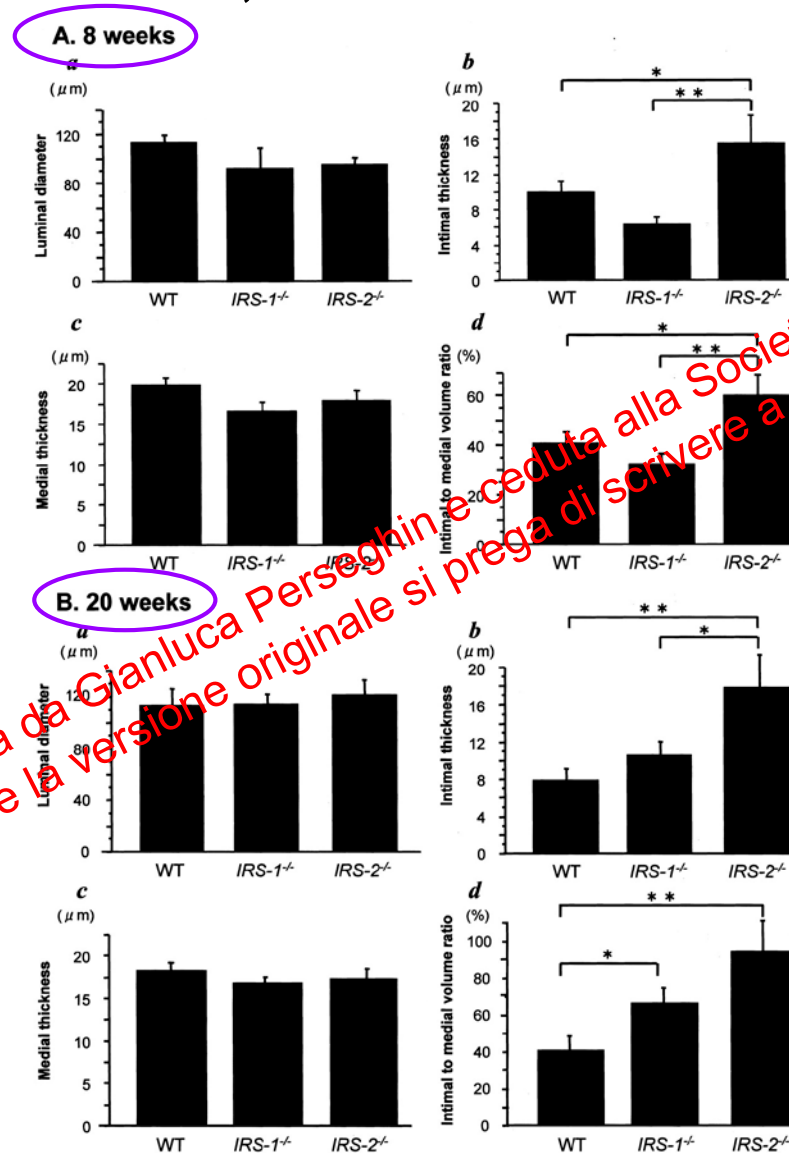
Gel shift assay showing the relative NFκB binding to the double-stranded oligonucleotide containing NFκB DNA binding site following insulin or dextrose infusion.



In vivo in human mononuclear cell

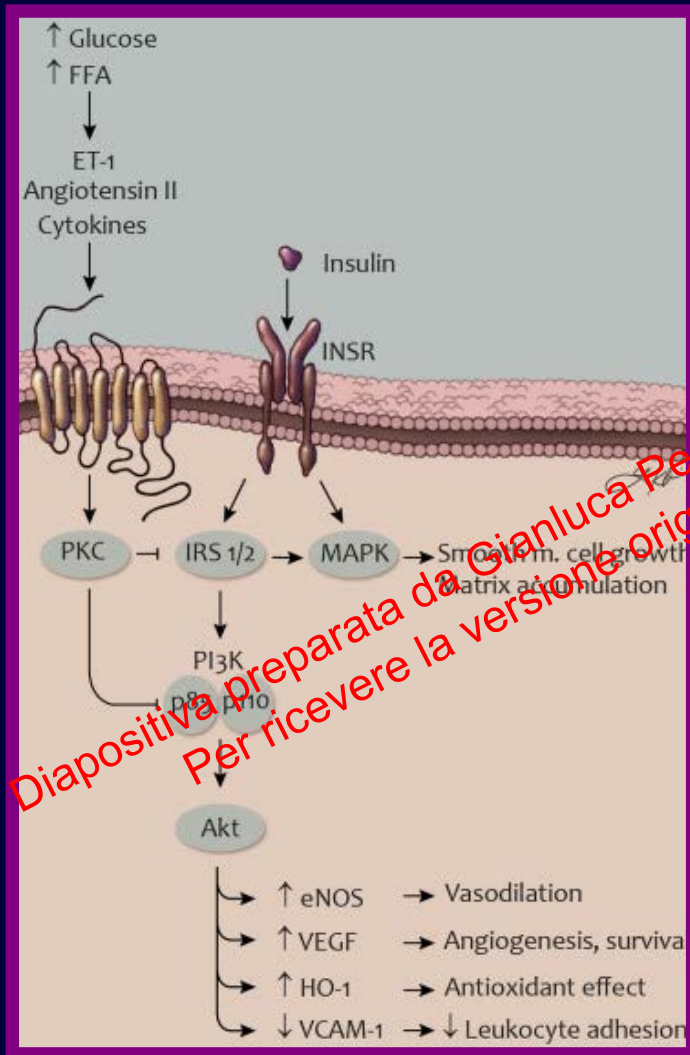


Morphometric analysis of vessels from wild-type (WT), IRS-1^{-/-}, and IRS-2^{-/-} mice.



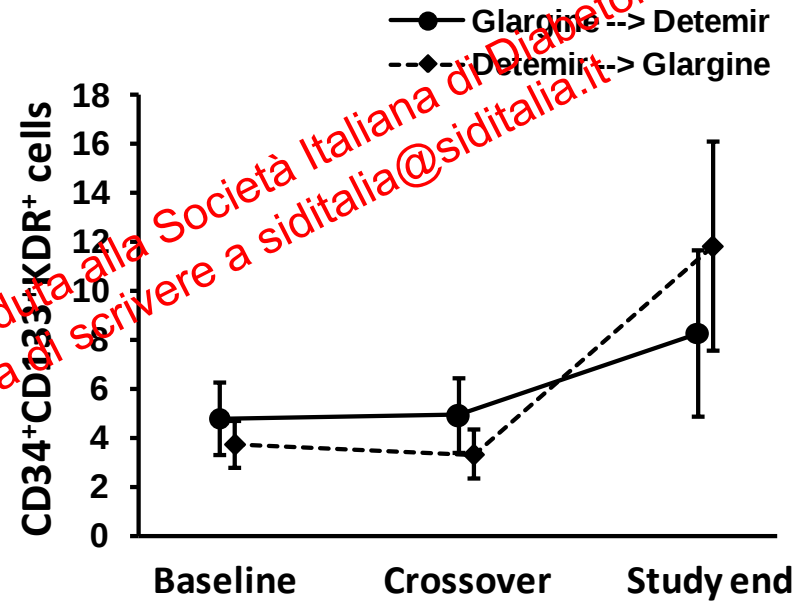
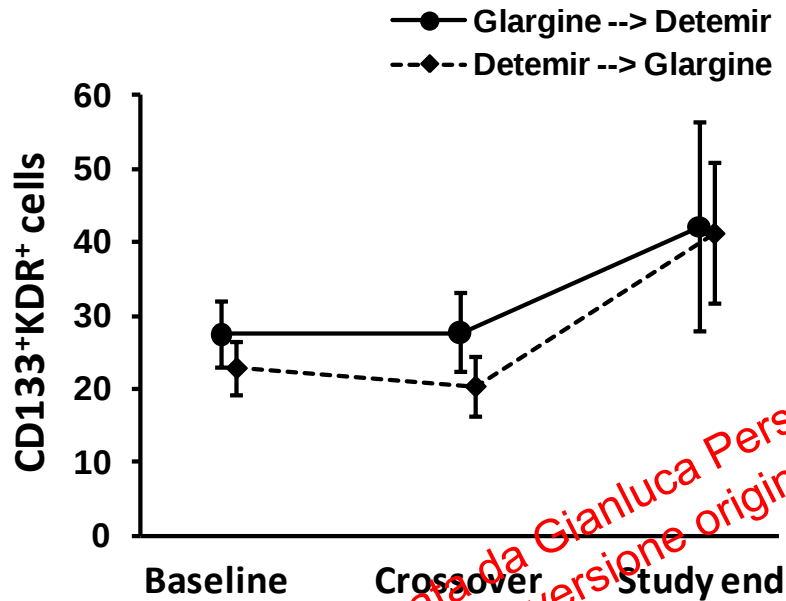
Acute effects of insulin

Mechanistic rationale



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Basal Insulin - Endothelial regeneration

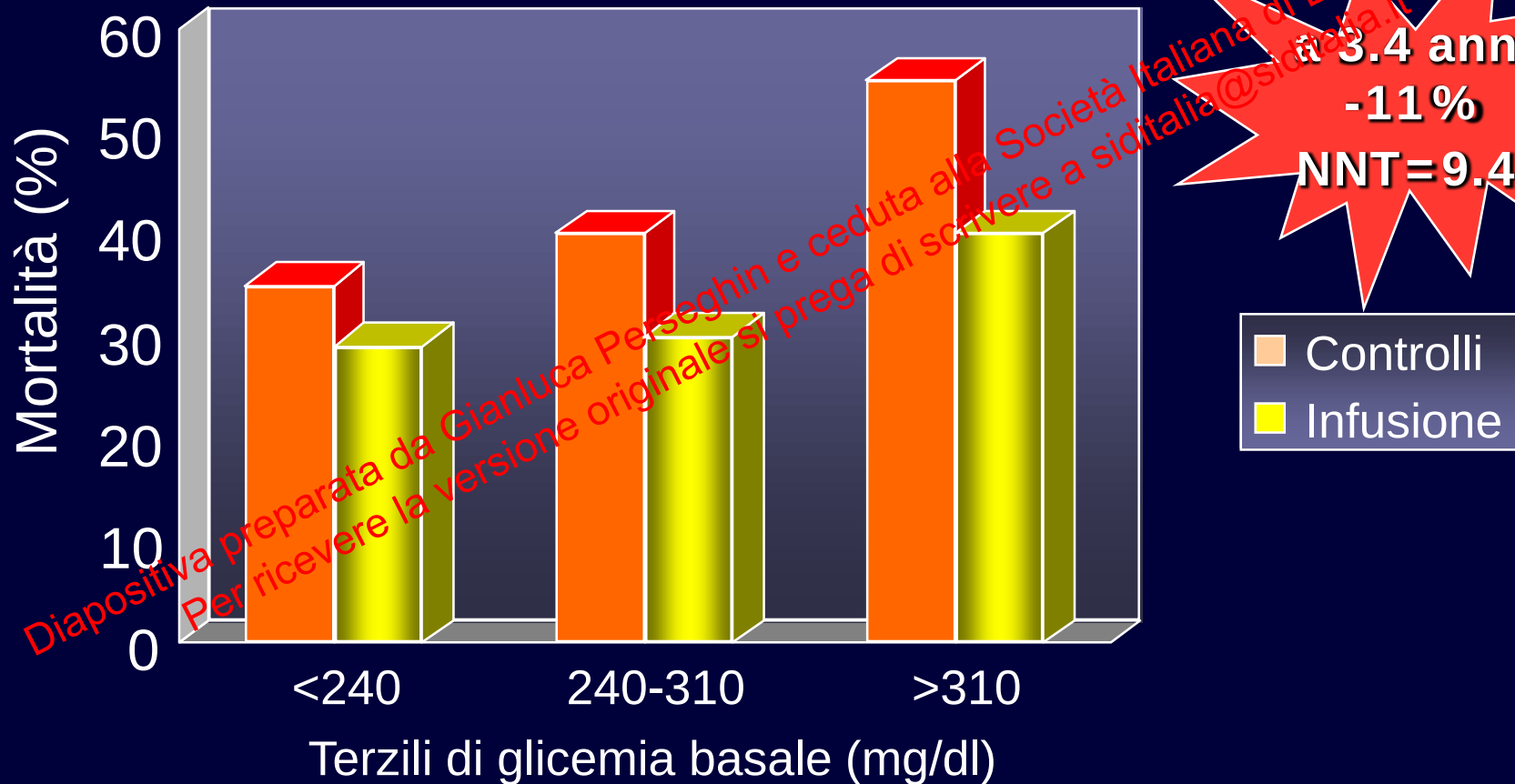


Controversies

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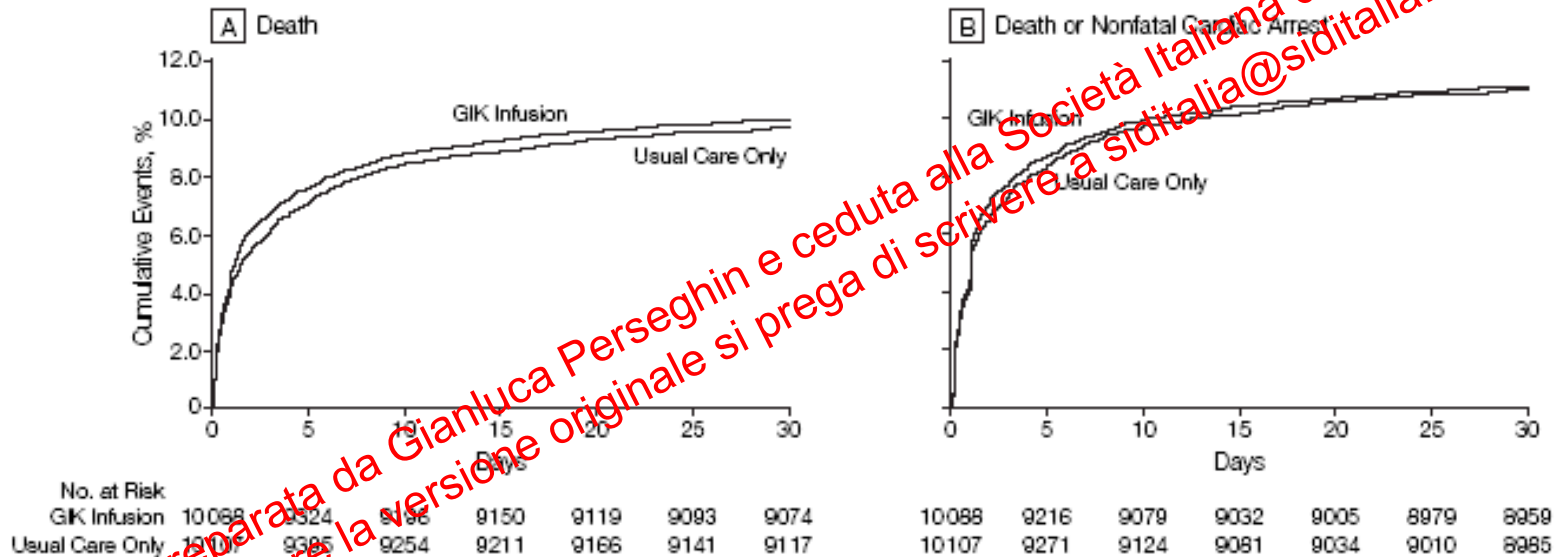
DIGAMI: mortalità a lungo termine e glicemia basale (at admission)

age, previous heart failure, and severity of the diabetic disease at admission



ECLA STUDY

Figure 2. Cumulative Hazard Rates of Death and Death/Nonfatal Cardiac Arrest Within 30 Days



For death, hazard ratio (HR), 1.03 (95% confidence interval [CI], 0.95-1.13); $P = .45$. For death or nonfatal cardiac arrest, HR, 1.01 (95% CI, 0.93-1.10); $P = .73$. GIK indicates glucose-insulin-potassium.

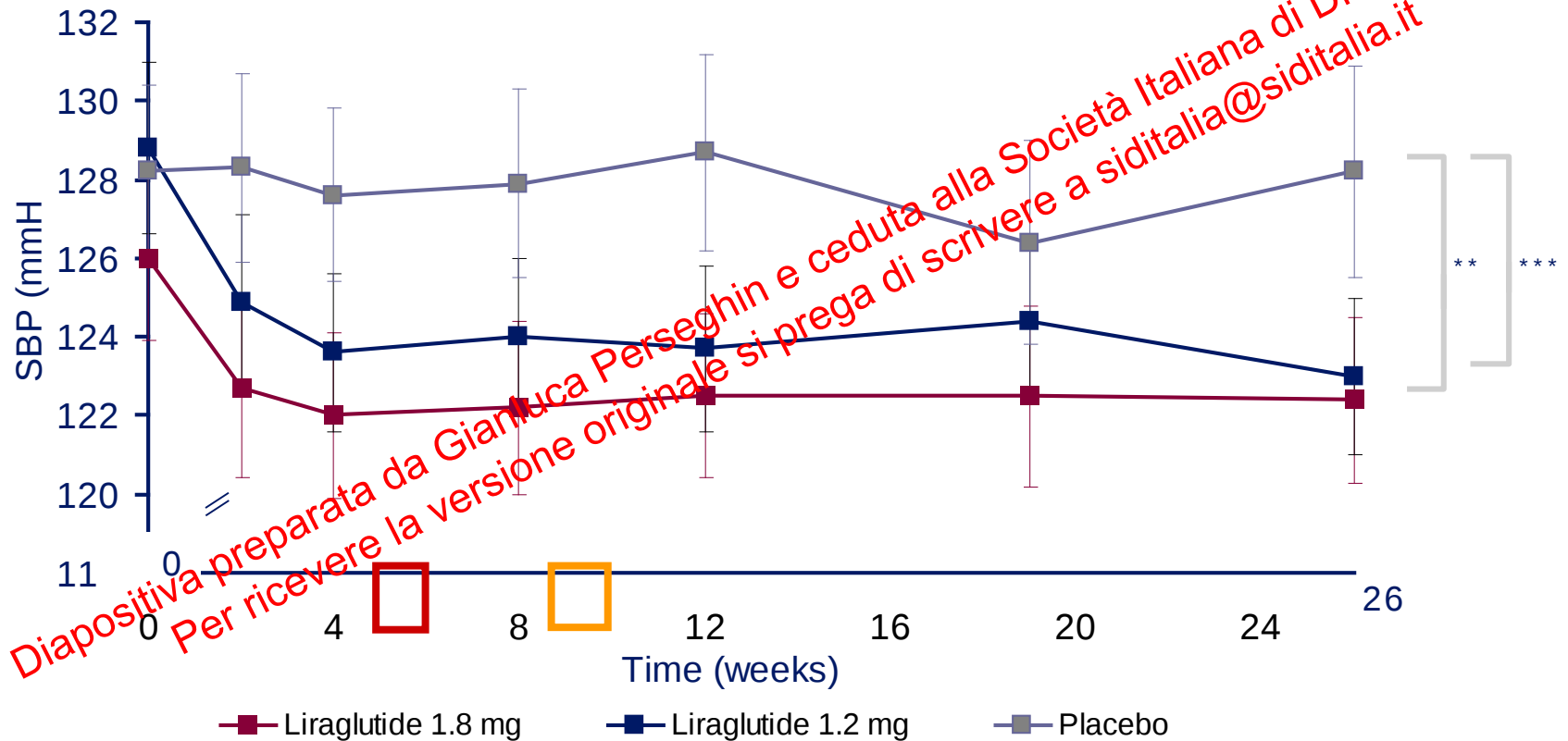
Cardiovascular effects of GLP1-RA

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Blood Pressure

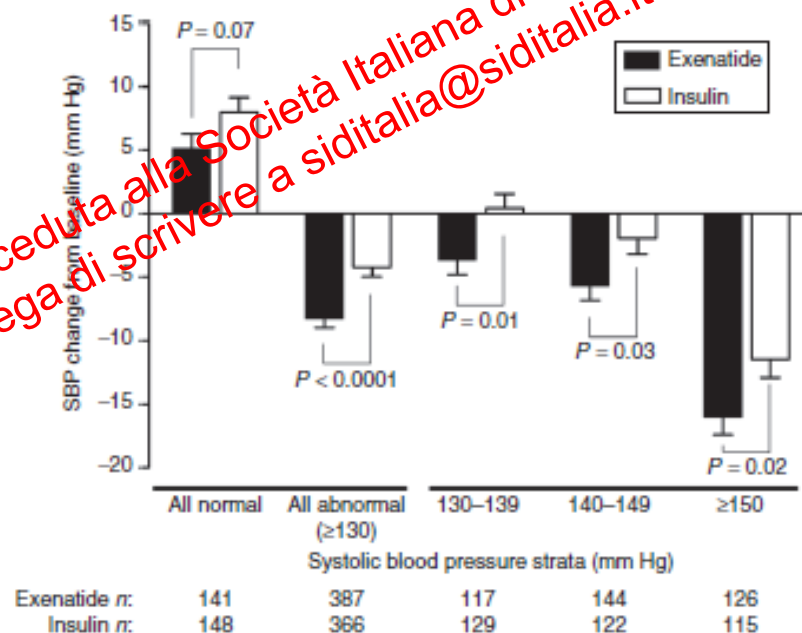
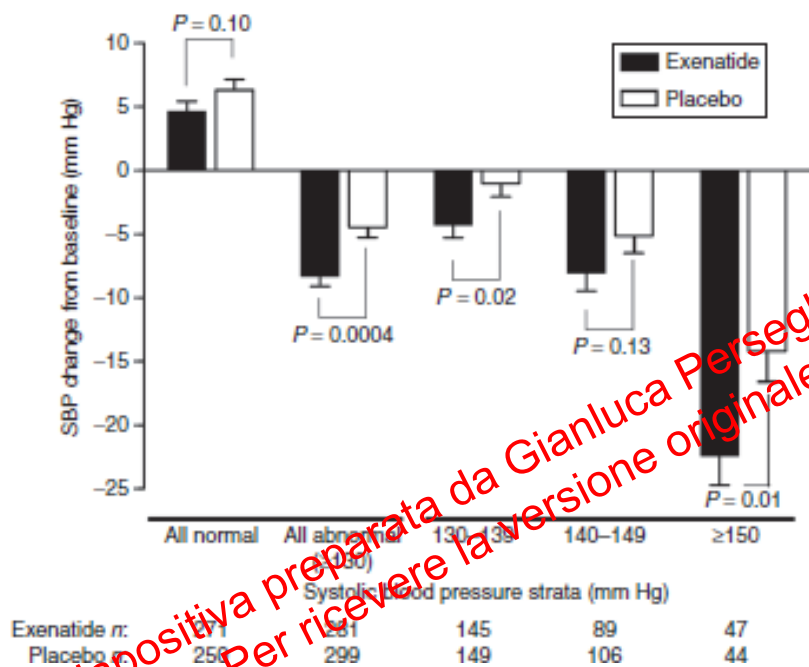
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Liraglutide and blood pressure



settimane riduzione pressione arteriosa
settimane riduzione peso corporeo

Exenatide and blood pressure



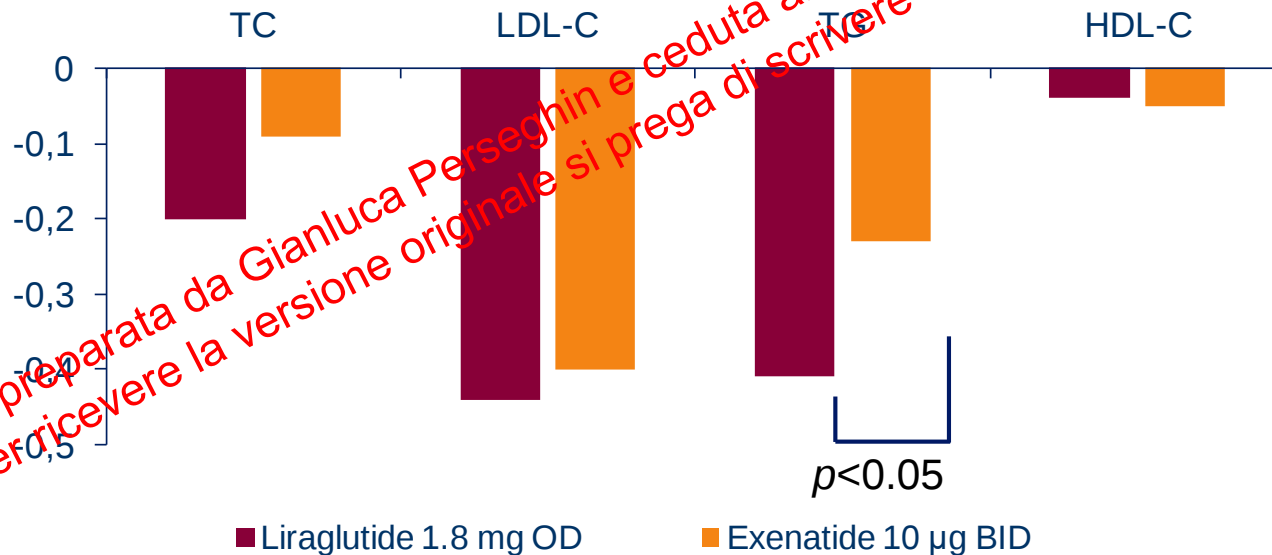
Lipids

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Liraglutide improves lipid profiles in patients with type 2 diabetes

LEAD-6

Change from baseline
(mmol/L)



BID, twice daily; OD, once daily

Buse *et al.* Lancet 2009 374:39-47.

Buse *et al.* Lancet 2009 374:39-47

**Il compenso glicemico ottenuto non è soddisfacente
(HbA1c 7.5%, obiettivo < 7%)**

**Cosa associereste alla metformina a basso
dosaggio e alla basale ?**

- 1. lascerei la terapia immutata**
- 2. introdurrei Sitagliptin 100 mg die**
- 3. introdurrei Sitagliptin 50 mg die**
- 4. introdurrei GLP1-RA**

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Dobbiamo modificare la terapia anti-iperglicemica del Sig Mario?

Viene impostata la seguente terapia

metformina 500 x 2 die

glargine 18UI alle 22

liraglutide 1.2 mcg 1 somm die

atorvastatina 80 mg dopo cena

clopidogrel 75 mg die

carvedilolo 6,25 x 2 die

amlodipina 5 mg die alla sera

ramipril 5 mg al mattino

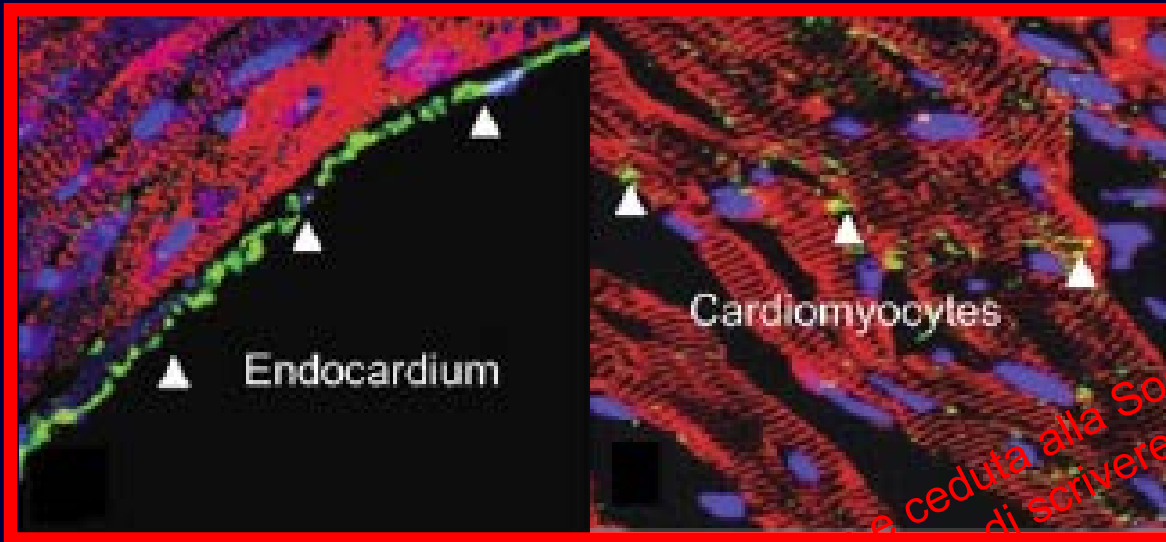
ramipril + idroclorotiazide 5/25 alla sera

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A direct cardiovascular role of GLP1-RA ?

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A role for GLP1R agonism ?



GLP-1 receptors have been demonstrated in cardiac myocytes

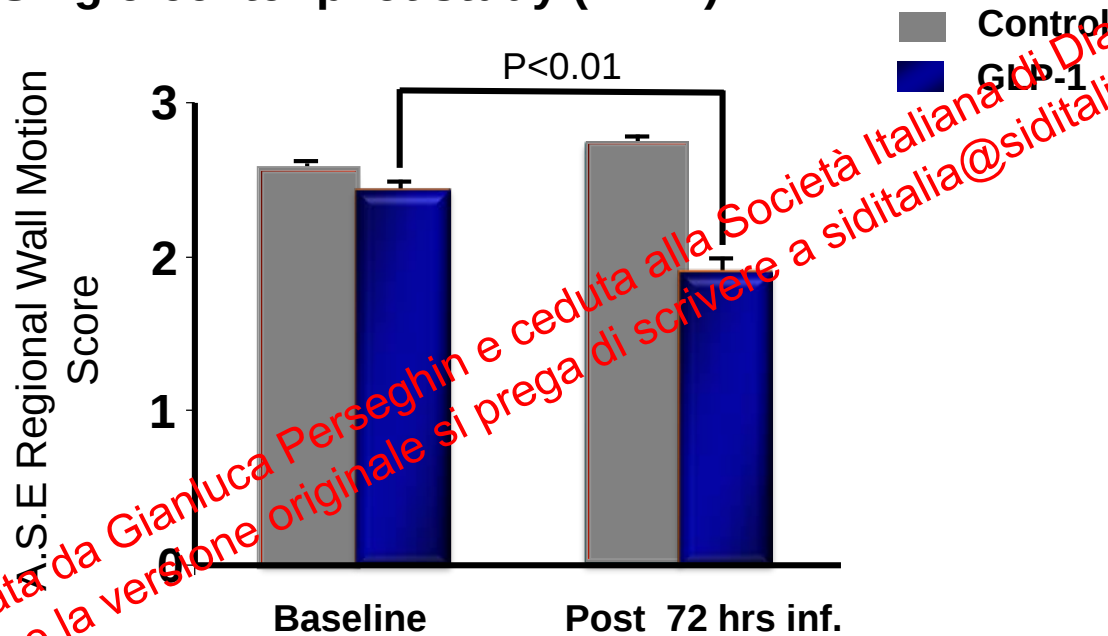
Yamamoto H et al Clin Invest
2002

Data in animal models

- GLP-1 may enhance recovery of LV function after transient coronary artery occlusion in an isolated rat heart model
- Beneficial outcomes were reported in the dog model of pacing-induced dilated cardiomyopathy

Effetti dell'infusione di GLP-1 sul “Ventricular Wall Motion” in soggetti con IM

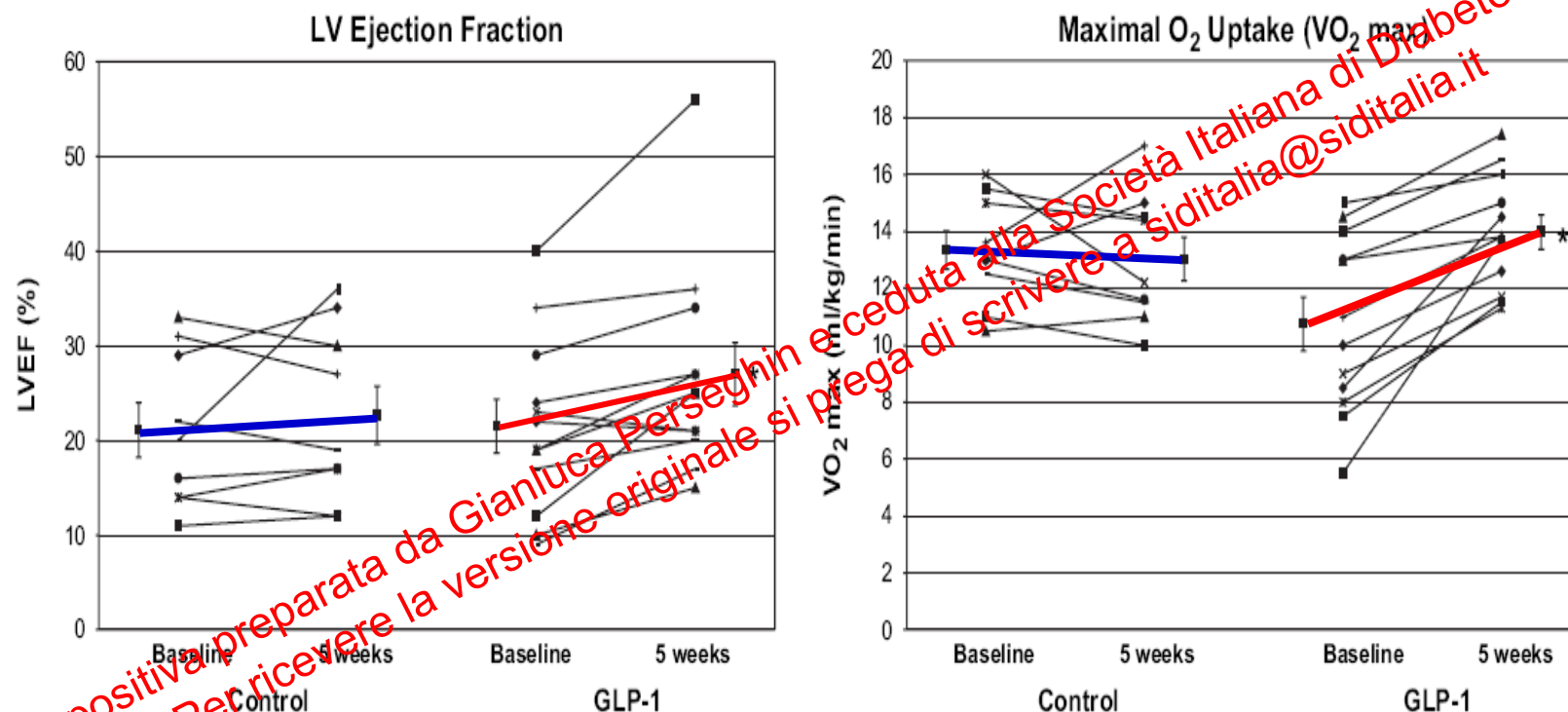
Single-center pilot study (N=21)



Mean $\pm$ SEM; Control Group, N=10; GLP-1 Group, N=11 (Patients with acute myocardial infarction (AMI) and LVEF <40% after successful primary angioplasty. LVEF = Left ventricular ejection function.

Post IV GLP-1 = post 72-hour intravenous GLP-1 infusion.

Effetto di 5 settimane di infusione di GLP-1 sulla frazione di eiezione ventricolare e lo stato funzionale in pazienti con scompenso cardiaco



Changes in left ventricular ejection fraction, and maximum myocardial ventilation oxygen consumption after 5 weeks of GLP-1 infusion (n=12) versus control (n=9) in subjects

Final infarct size and short-term duration of ischemia

Exenatide i.v 15 min before procedure and for 6 hours

290

Circ Cardiovasc Interv

April 2012

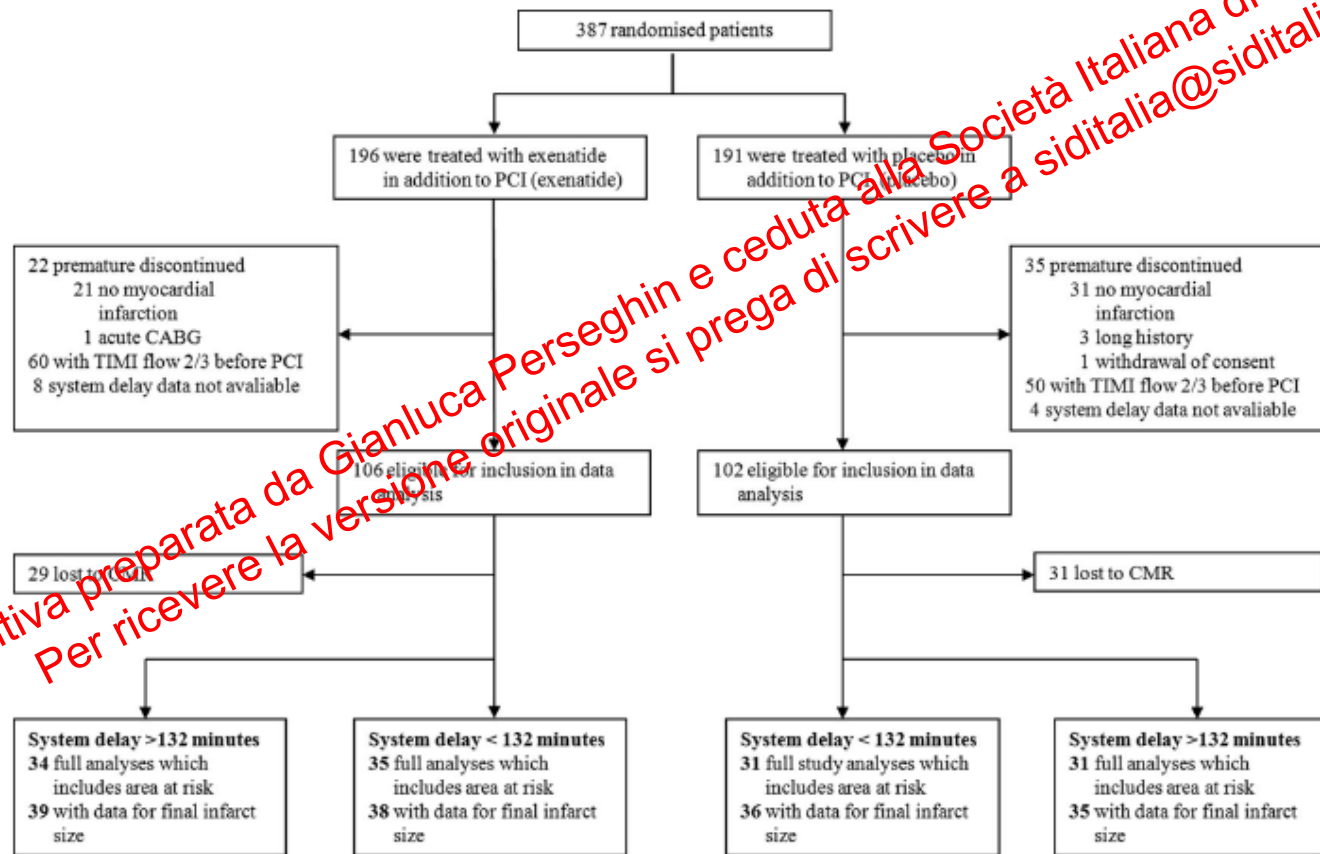


Figure 1. Trial profile. CABG indicates coronary artery bypass graft operation; CMR, cardiac magnetic resonance; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

Final infarct size and short-term duration of ischemia

Exenatide i.v 15 min before procedure and for 6 hours

Table 2. Outcomes Evaluated With Cardiac Magnetic Resonance

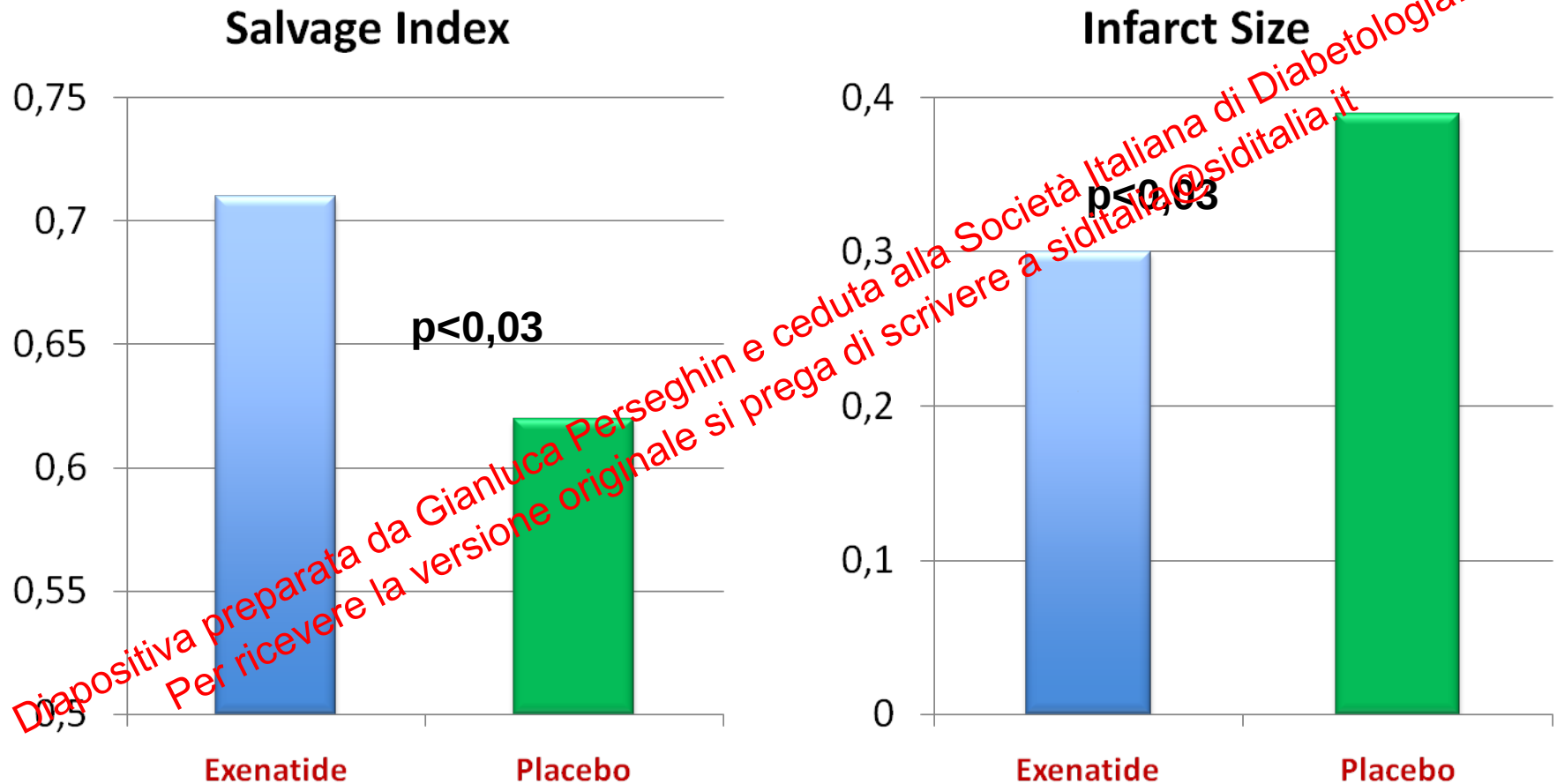
	n	Exenatide	n	Placebo	P value
● System delay less than or equal to median (≤ 132 min)*					
Final infarct size, g	38	9 (4–13)	36	15 (8–24)	0.008
Final infarct size, %LV	38	8 (4–12)	31	11 (7–17)	0.015
Area at risk, %LV	35	30 (23–38)	31	32 (27–40)	0.25
Myocardial salvage index	35	0.75 (0.60–0.83)	31	0.66 (0.59–0.76)	0.012
LV mass, g	38	111 (98–138)	36	127 (113–154)	0.08
LVEF, 3 mo, %	38	56 (41–65)	36	57 (49–63)	0.62
● System delay greater than median (>132 min)*					
Final infarct size, g	39	15 (11–24)	35	15 (10–22)	0.49
Final infarct size, %LV	39	12 (9–20)	35	12 (8–15)	0.46
Area at risk, %LV	34	34 (29–46)	31	30 (25–36)	0.05
Myocardial salvage index	34	0.67 (0.57–0.72)	31	0.68 (0.53–0.73)	0.84
LV mass, g	39	126 (107–144)	35	128 (98–152)	0.99
LVEF, 3 mo, %	39	53 (47–60)	35	55 (48–62)	0.41

LV indicates left ventricle; LVEF, left ventricular ejection fraction.

Data are presented as median (interquartile range).

*For interaction of system delay less than or equal to median with exenatide treatment, $P=0.018$ for final infarct size (%LV) and $P=0.021$ for myocardial salvage index.

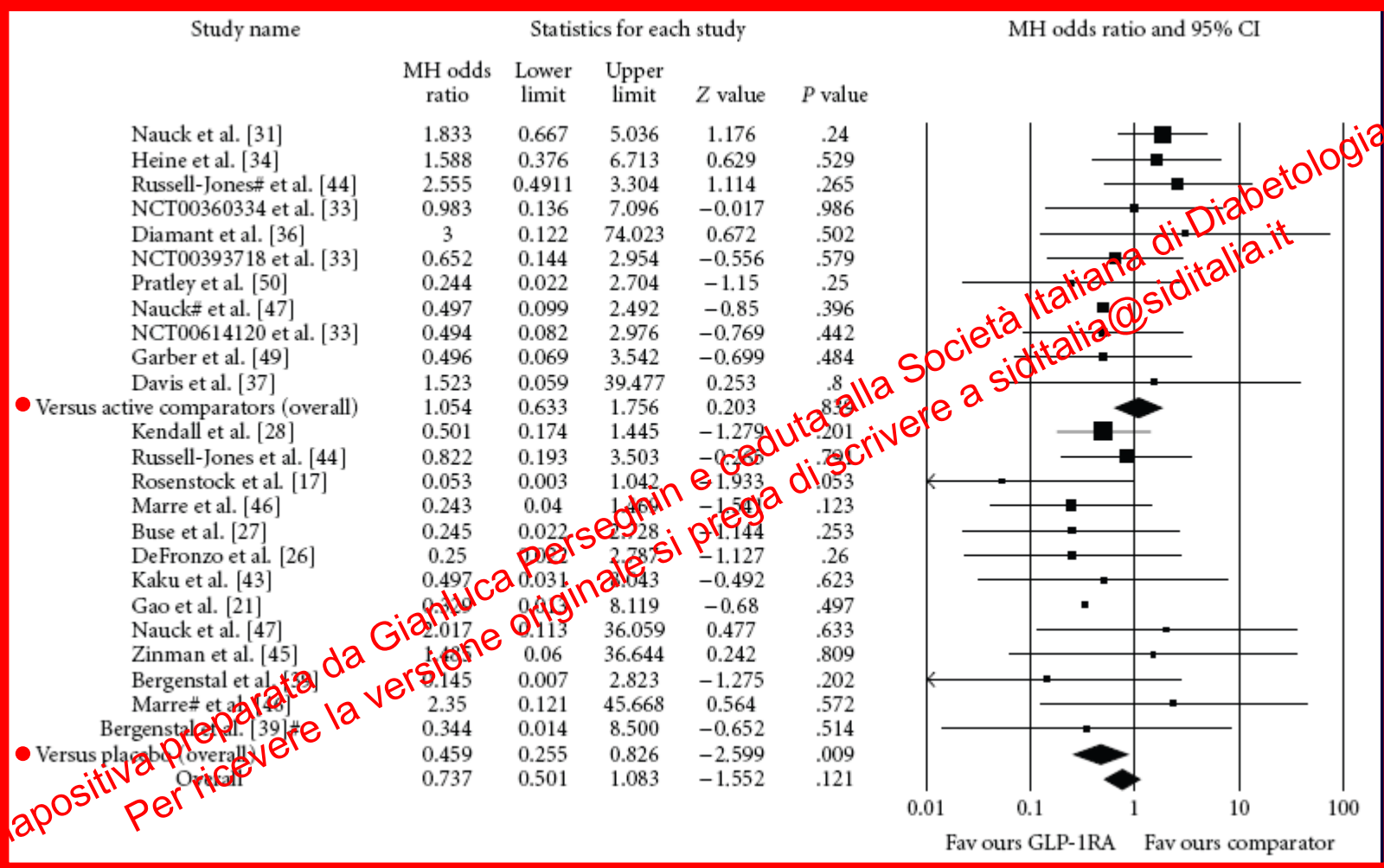
Salvage Index and Final Infarct Size in ST-segment elevation myocardial infarction treated by ballon angioplasty and exenatide or placebo infusion



Cardiovascular safety

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Meta-analisi a 12 settimane



Trials with at least 1 reported MACE
(63 studies)

Ongoing Trials: what to be expected

Table 1

Ongoing clinical trials evaluating treatment strategies for patients with diabetes mellitus

Title	Estimated Study Completion Date	Design	Intervention	Patients (N)	Primary Endpoints
ORIGIN ²⁹	April 2012	2 × 2 factorial design	Randomized clinical trial comparing 1 daily injection of insulin glargine vs dose titrated to achieve FPG ≤5.3 mmol/L (95 mg/dL), or standard glycemic care; and either omega-3 acid ethyl esters 90 (1 g consisting of EPA 465 mg and DHA 375 mg) or identical placebo	12,612 from 40 international centers	CV morbidity/mortality, major vascular events, all-cause mortality, [†] or resuscitated cardiac arrest
LEADER ³⁰	January 2016	Phase 3 clinical trial	Randomized clinical trial comparing max. dose of 1.8 mg liraglutide, injected SC once daily, administered in addition to subject's standard treatment, vs placebo	8,754	CV death, nonfatal MI, or nonfatal stroke; expanded composite CV outcome [‡]
SAVOR-TIMI 53 ³²	June 2015	Randomized, double-blind, placebo-controlled phase 4 trial	Saxagliptin 5 mg or 2.5 mg once daily vs placebo in patients with type 2 diabetes	12,000	CV death, nonfatal MI or nonfatal ischemic stroke; hospitalization for heart failure, unstable angina pectoris, or coronary revascularization
GENERATION ³⁴	October 2011	Randomized, double-blind, active control, multicenter phase 3b/4 study	Saxagliptin 5 mg oral tablet once daily vs glimepiride 1, 2, 3, 4 or 6 mg oral encapsulated tablet once daily	698	Proportion of patients reaching HbA _{1c} target <7% without hypoglycemia over 52-wk treatment period
TECOS ³⁵	December 2014	Randomized, placebo-controlled, phase 3 study	Sitagliptin phosphate (100-mg tablet once daily for patients with normal or mildly impaired renal function as defined by eGFR or 50-mg tablet once daily for patients with moderately impaired renal function as defined by eGFR vs placebo	14,000	CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization
EXSCEL ³¹	March 2017	Randomized, placebo-controlled, phase 3 clinical trial	Exenatide 2 mg SC injection, administered once weekly, vs placebo	9,500	All-cause mortality, time to first confirmed CV event, hospitalization for ACS or heart failure
TOSCA IT ³⁶	December 2017	Randomized, placebo-controlled, phase 4 trial	Metformin 2,000 mg + pioglitazone 15–45 mg or active comparator of metformin 2,000 mg + glibenclamide 5–15 mg or metformin 2,000 mg + gliclazide 30–120 mg or metformin 2,000 mg + glimepiride 2–6 mg	5,172	All-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, unplanned coronary revascularization

Elixa

2014

Lixisenatide in prevenzione secondaria

Rewind

2019

Dulaglutide

Il Sig Mario torna al controllo dopo 3 mesi

Esame Obiettivo

- PA: 140/85 mmHg; FC 78 bpm
- Peso: 83 Kg (- 4 kg), altezza 173 cm, BMI: 27.7 Kg/m²
- Circonferenza vita 105 cm

Esami ematochimici & strumentali

- FPG: 115 mg/dL e HbA1c: 6.8 %
- Creatinina stabile

- Colesterolo tot 201 mg/dL, HDL-col 46 mg/dL, trig 158 mg/L, LDL-col 123 mg/dL

CONCLUSION

How to achieve normoglycemia in T2DM patients ?

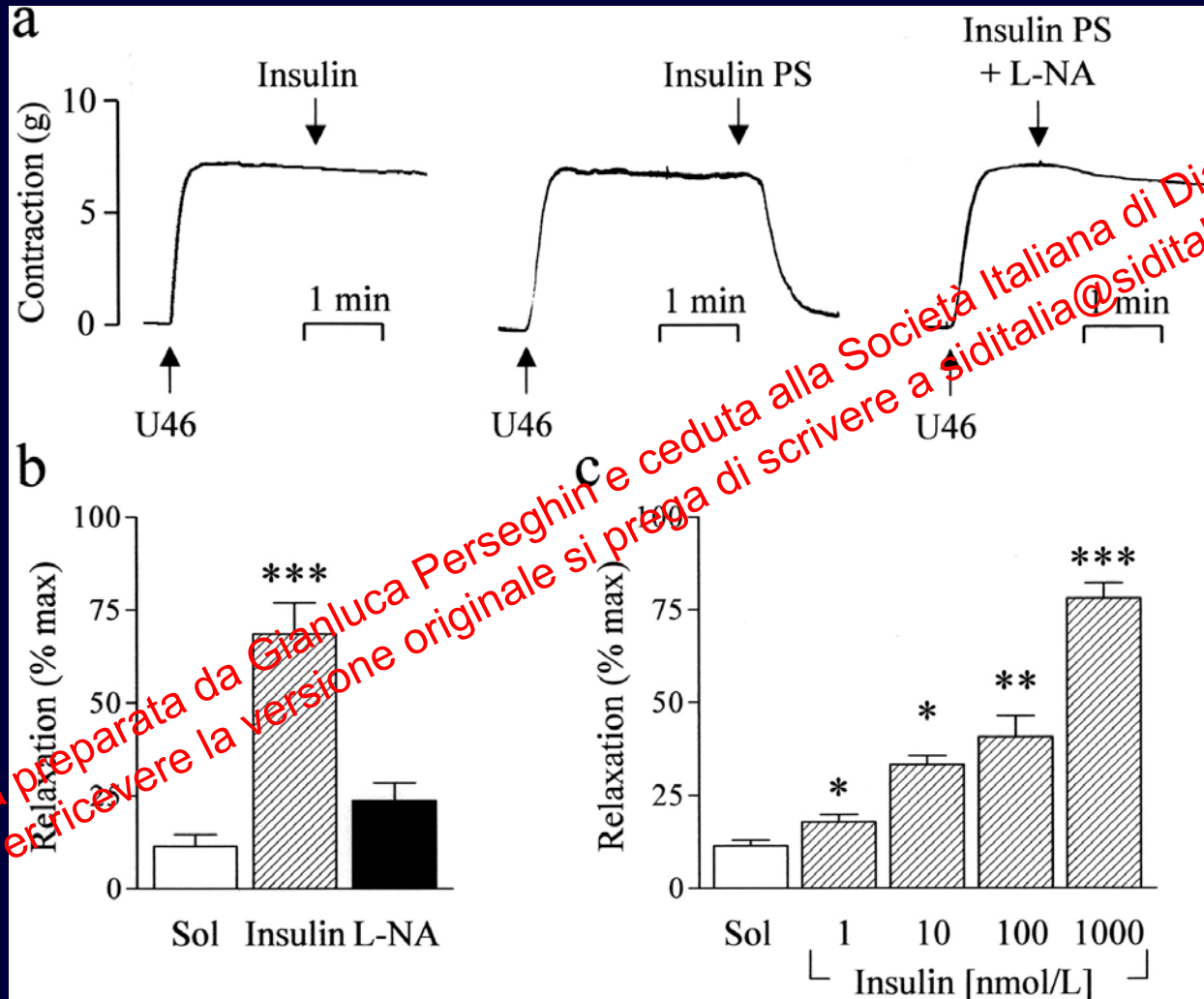
Pioglitazone Metformin SU GLP-1 RA Gliptins Insulin



Reduced perfusion
Diastolic Dysfunction
Systolic Dysfunction
EKG alterations
Angina
CHF

Diapositiva preparata da Gianluca Perseghin e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a diditalia@siditalia.it

Insulin elicits the release of vasoactive concentration of ATP and adenosine from human platelets via NO mechanism

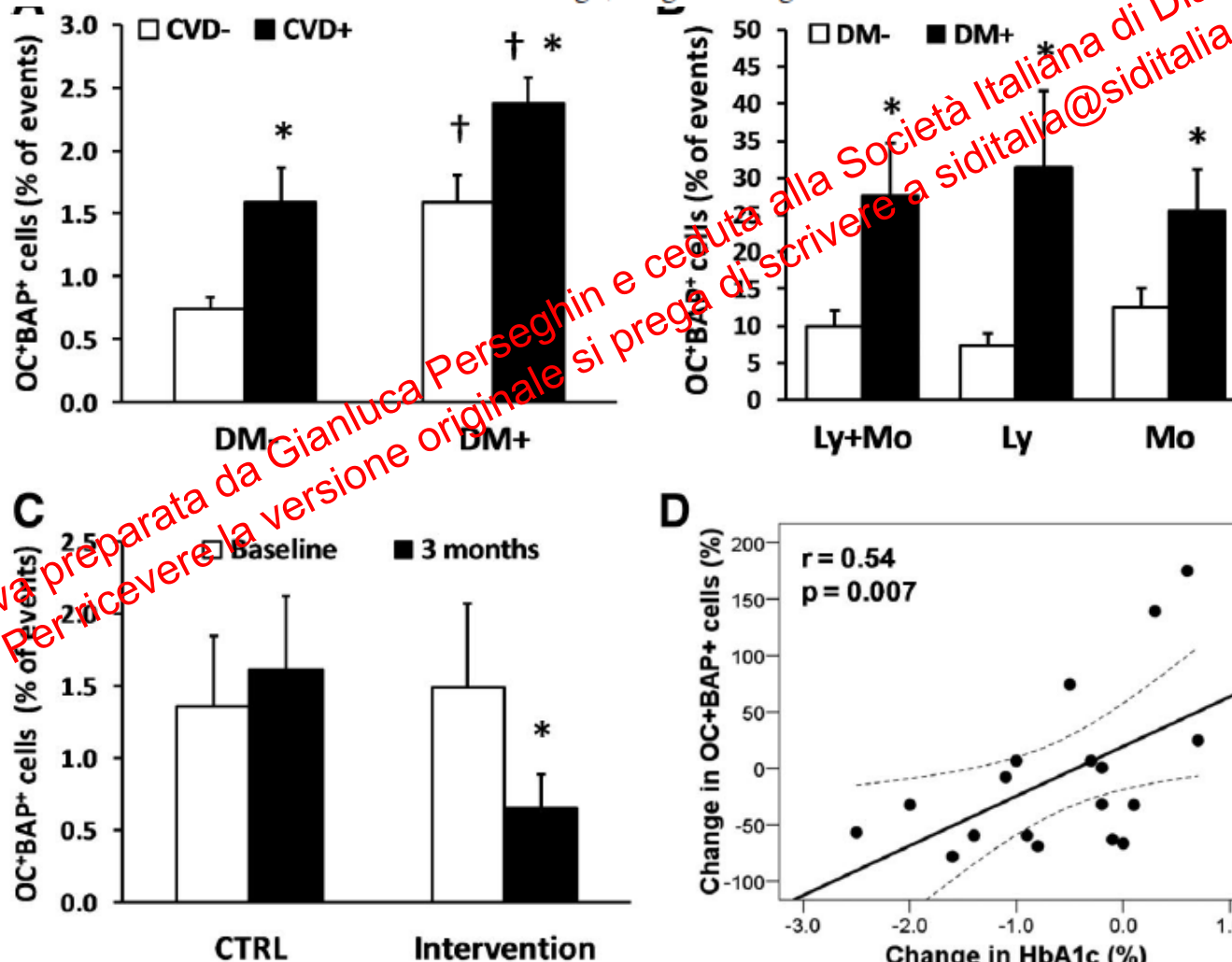


Randriamboavonjy V et al. J Exp Med 2004;199:347-356

Widespread Increase in Myeloid Calcifying Cells Contributes to Ectopic Vascular Calcification in Type 2 Diabetes

(*Circ Res.* 2011;108:1112-1121.)

Gian Paolo Fadini, Mattia Albiero, Lisa Menegazzo, Elisa Boscaro, Saula Vigili de Kreutzenberg, Carlo Agostini, Anna Cabrelle, Gianni Binotto, Marcello Rattazzi, Elisa Bertacco, Roberta Bertorelle, Lorena Biasini, Monica Mion, Mario Plebani, Giulio Ceolotto, Annalisa Angelini, Chiara Castellani, Mirko Menegolo, Franco Grego, Stefanie Dimmeler, Florian Seeger, Andreas Zeiher, Antonio Tiengo, Angelo Avogaro



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Rates of Death and Composite of Death or Heart Failure at 3 Days

Table 4. Rates of Death and Composite of Death or Heart Failure at 3 Days

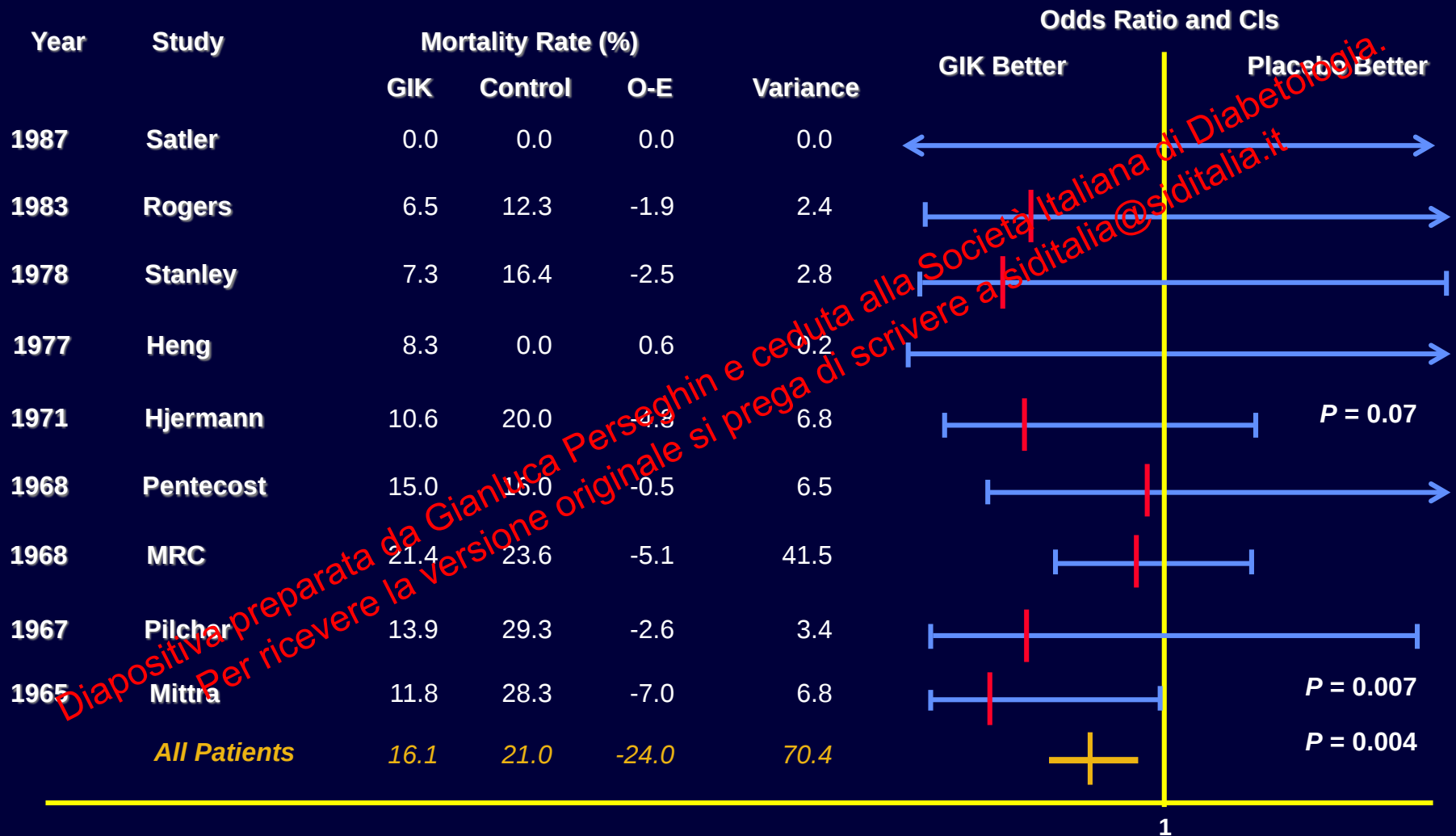
	Total No. of Patients	Allocated to GIK Group, %	Death at 3 Days			Death or Heart Failure at 3 Days		
			Event Rate in Combined GIK and Control Groups, %	AHR (95% CI) ^a	Adjusted P Value for Trend	Event Rate in Combined GIK and Control Groups, %	AHR (95% CI) ^a	Adjusted P Value for Trend
Glucose, mg/dL								
<126	9410	41	1.9	1 [Reference]	<.001	8.9	1 [Reference]	<.001
126-<144	3263	45	2.3	1.09 (0.82-1.44)		10.9	1.18 (1.02-1.35)	
≥144	9124	62	5.3	2.47 (2.04-2.98)		17.8	1.88 (1.69-2.08)	
Potassium, mEq/L								
<4	7157	39	3.1	1 [Reference]	.001	12.0	1 [Reference]	.001
4-<5	13 233	55	3.0	0.93 (0.79-1.11)		12.5	1.01 (0.92-1.11)	
≥5	1390	69	8.0	2.52 (1.59-2.56)		20.5	1.42 (1.22-1.65)	
Fluid balance								
Negative	3208	31	2.9	1 [Reference]	<.001	14.0	1 [Reference]	.09
Neutral	2793	44	4.3	1.14 (0.76-1.70)		13.1	0.79 (0.65-0.94)	
Positive	16 204	55	6.3	2.42 (1.79-3.27)		15.5	1.03 (0.90-1.18)	

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; GIK, glucose-insulin-potassium.

SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; potassium to mmol/L, multiply by 1.0.

^aAdjusted for age, sex, history of diabetes, GIK allocation, infarction location (eg, anterior wall vs other), reperfusion therapy (yes or no), and time from symptom onset to randomization. Each model for glucose, potassium, and fluid balance status also was adjusted for the other 2 covariates (eg, models for glucose strata also were adjusted for potassium and fluid status).

Overview of GIK Therapy for Acute MI: A 30year Perspective



GIK = glucose-insulin-potassium; MI = myocardial infarction; CI = confidence interval.
Fath-Ordoubadi F, Beatt KJ. *Circulation*. 1997;96:1152-1156. Reprinted with permission
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