Insulina e Cuore: dalla Fisiologia alla Fisiopatologia

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SEZIONE DI MEDICINA INTERNA, ENDOCRINOLOGIA, ANDROLOGIA E MALATTIE METABOLICHE

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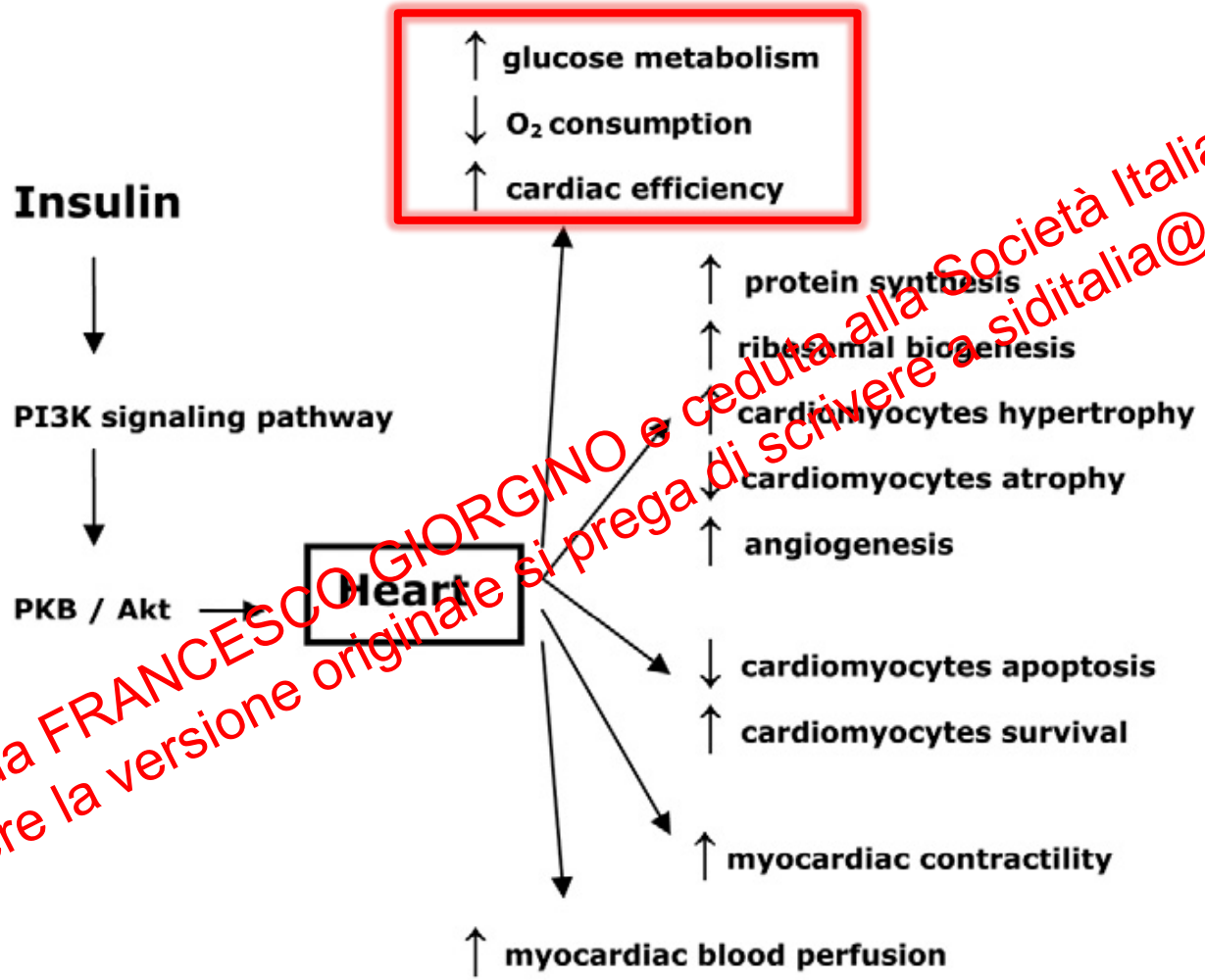
Disclosures

- Advisory Boards: AstraZeneca/BMS; Eli Lilly; Roche Diagnostics, Takeda
- Consultant: AstraZeneca/BMS; Boehringer Ingelheim; Lifescan; Merck Sharp & Dohme; Novo Nordisk; Sanofi
- Research Support: AstraZeneca/BMS; Eli Lilly; Lifescan; Sanofi; Takeda

I. Physiology

Cardiac Actions of Insulin



Iliadis et al., *Diabetes Res Clin Pract*, 2011

Heart Metabolism

- The heart consumes about 10% of whole body energy expenditure for cardiac contraction via:

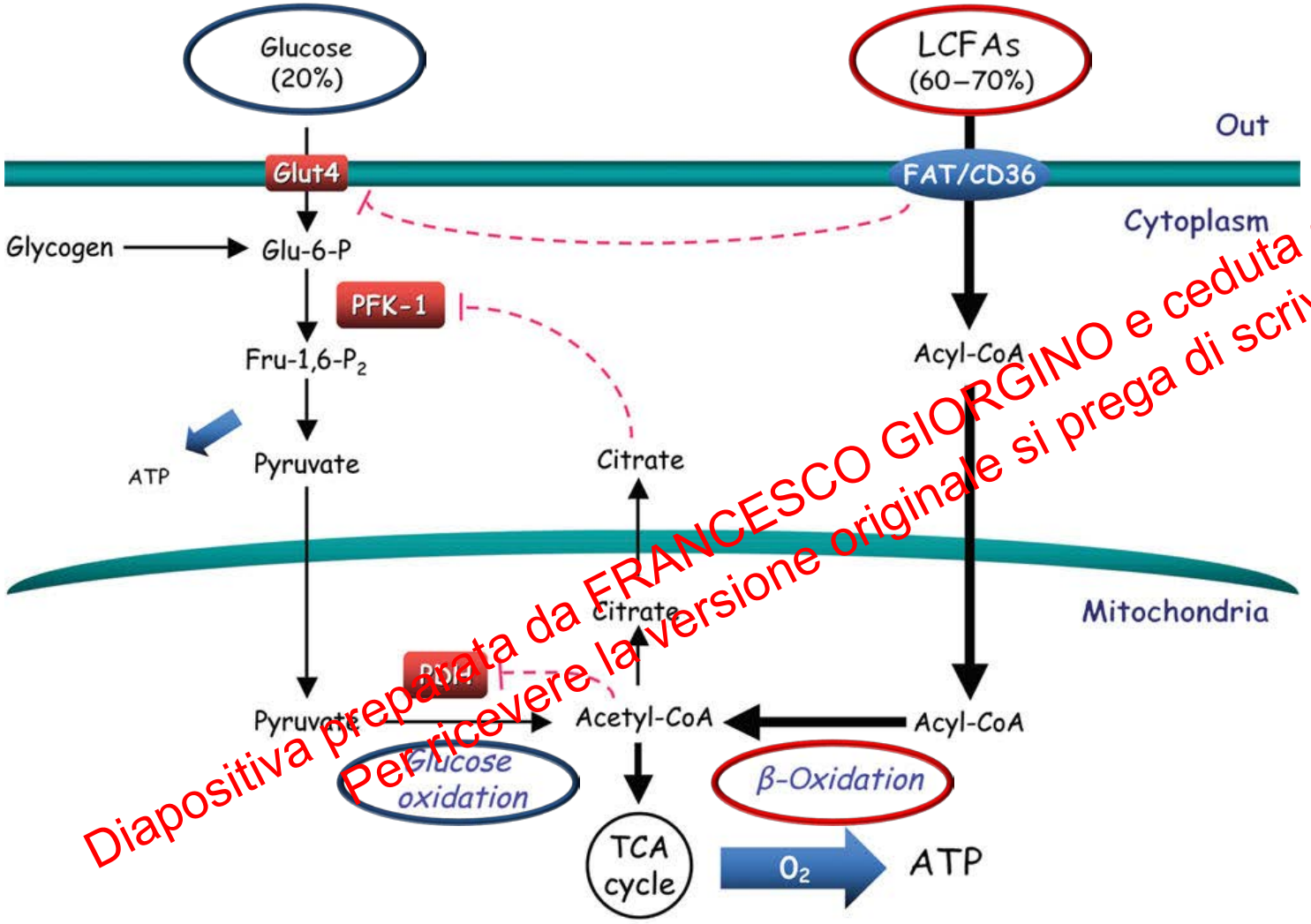
  (1) *the cellular uptake of free fatty acids and glucose*
  (2) the catabolism of these substrates by beta-oxidation and glycolysis
  (3) the entry of the intermediary metabolites in the Krebs cycle
  (4) the oxidative phosphorylation by the mitochondrial respiratory chain
  (Barsotti et al., 2009, Kolwicz et al., 2013).

- The principal mediator of energy transformation is adenosine triphosphate (ATP) and ATP levels are essential for the uninterrupted myocardial contraction/relaxation cycle.

- The human heart produces and consumes between 3.5 and 5 kg of ATP everyday to sustain pumping *(Onie et al., 2004)*. The way to generate this energy depends on the cardiac environment including coronary flow, blood substrate supply, hormones and nutritional status *(Lopaschuk et al., 2007; Stanley et al., 2005; Kodde et al., 2007; Ventura-Clapier et al., 2004)*.

Cardiac Metabolism under Physiological Conditions

I. During Fasting

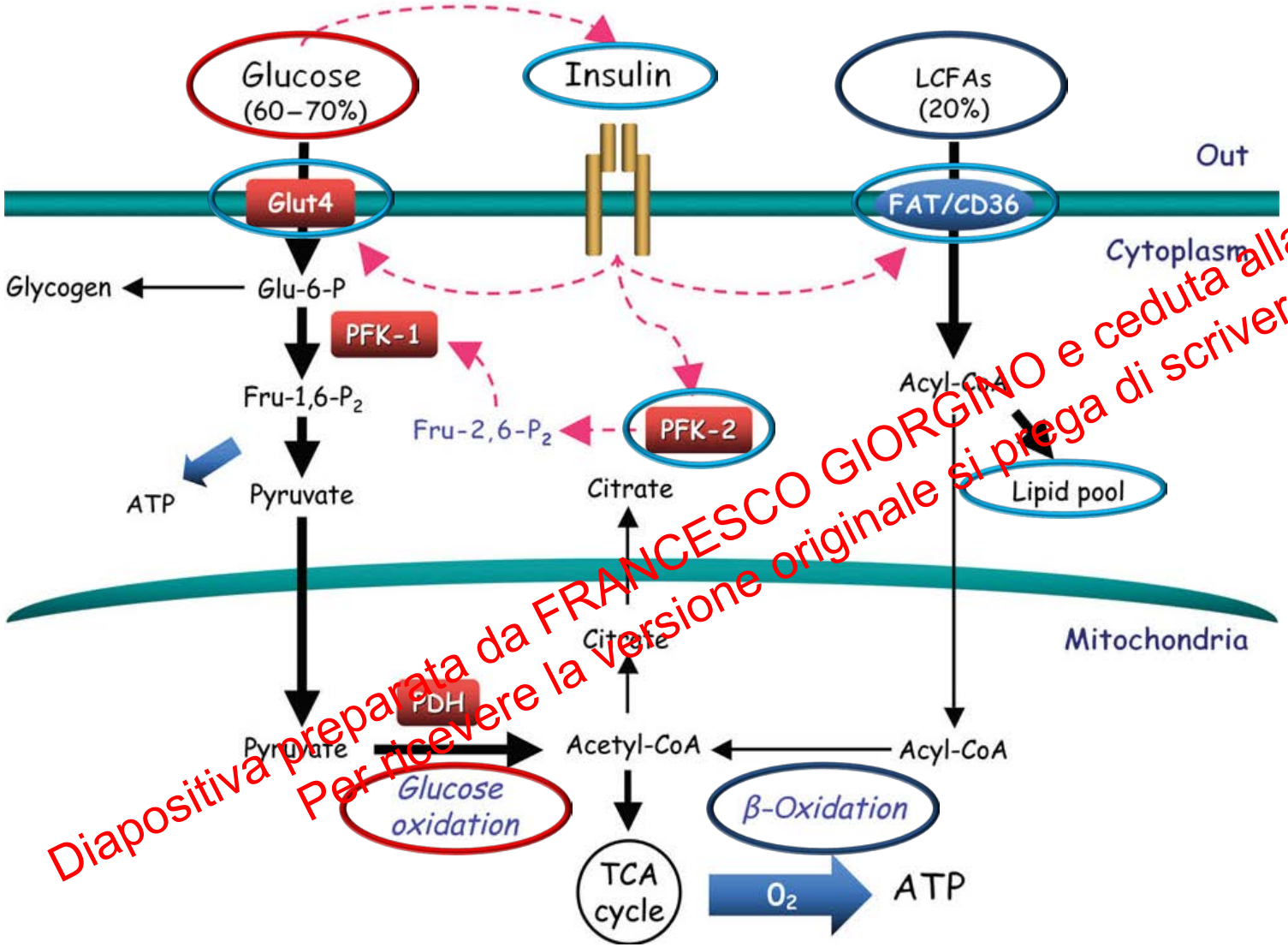


- The heart prefers to consume long chain fatty acids (LCFAs) – fatty acid breackdown gives more energy than glucose (e.g. oxidation of one molecule of palmitic acid produces 129 ATP, while one molecule of glucose produces only 36 ATP) *(Iliadis et al., 2011)*.
- Glucose uptake and metabolism are reduced by the increased fatty acid oxidation via the Randle cycle (red lines).
- **However, free fatty acid catabolism requires about 10% more oxygen to produce the same amount of ATP deriving from glucose breakdown** *(Lopaschuk et al., 2002)*.

Adapted from Bertrand et al., 2008

Cardiac Metabolism under Physiological Conditions

II. During Postprandial State

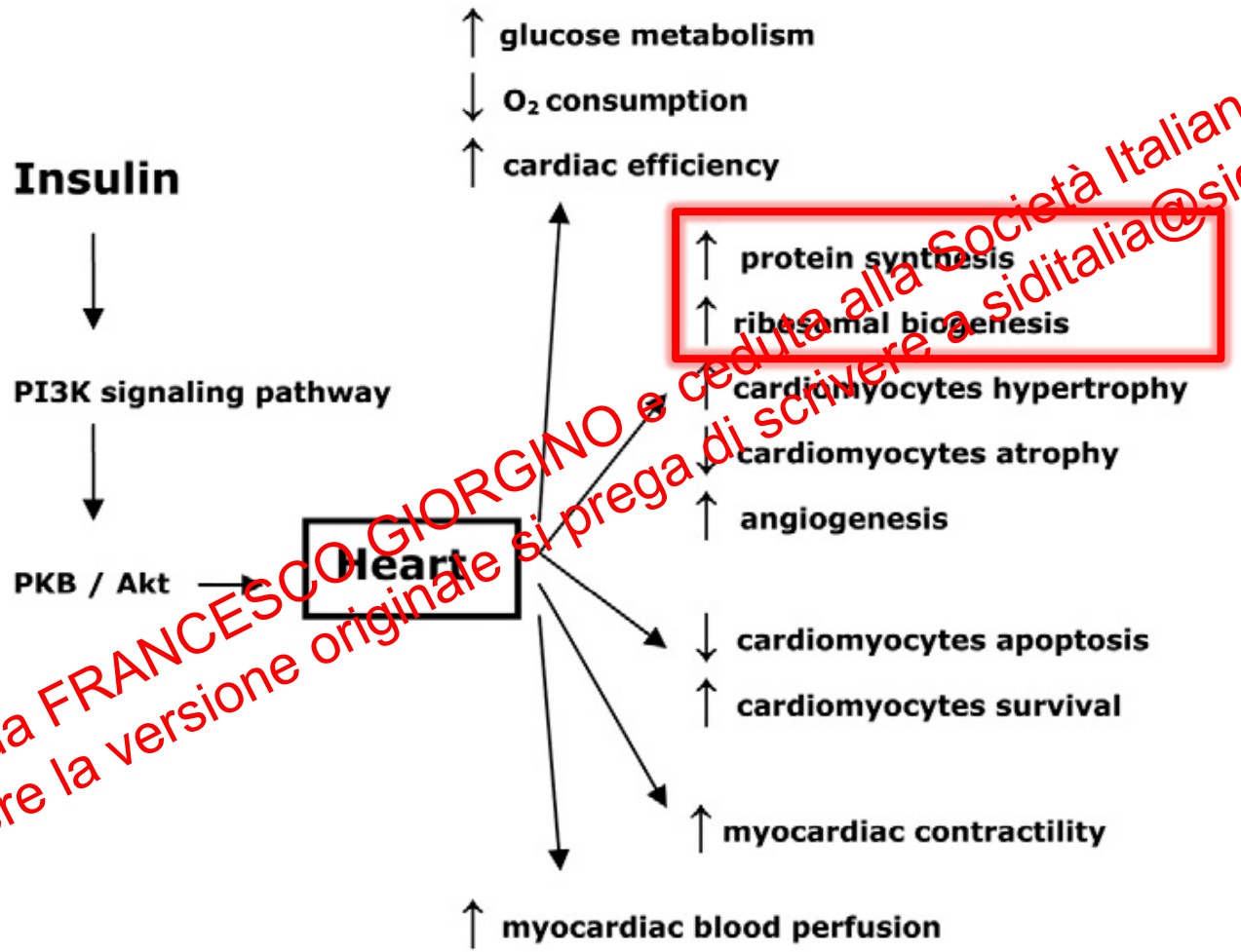


- Insulin secretion stimulates: GLUT4 translocation, 6-phosphofructo-2-kinase (PFK-2) activation, LCFAs uptake.

- In contrary to glucose, the resulting increase in intracellular LFCA concentration does not result in the increase in LCFA oxidation, but in the storage of this excess into the intracellular pool of lipids *(Dyck et al., 2001)*.

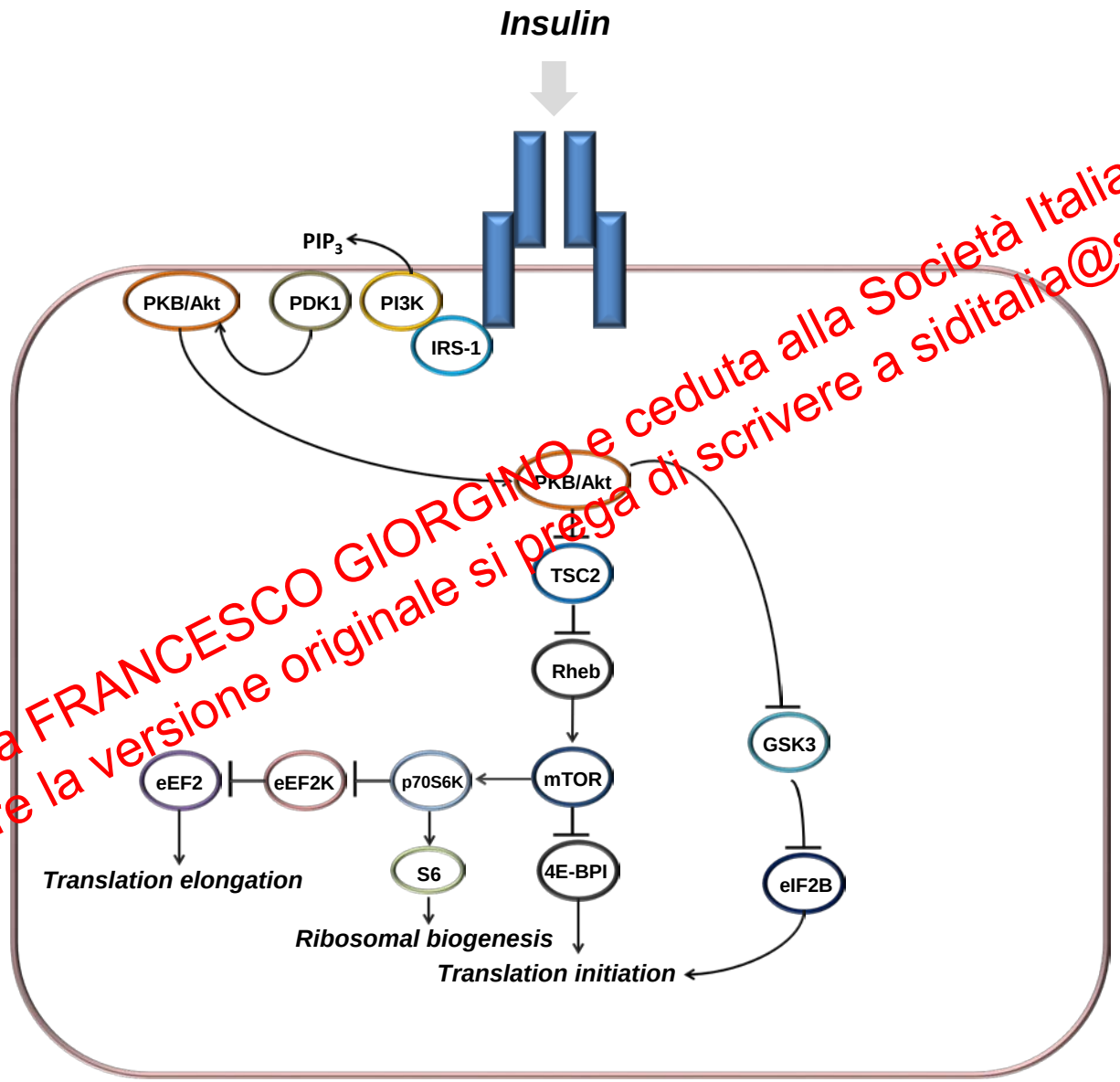
Adapted from Bertrand et al., 2008

Cardiac Actions of Insulin

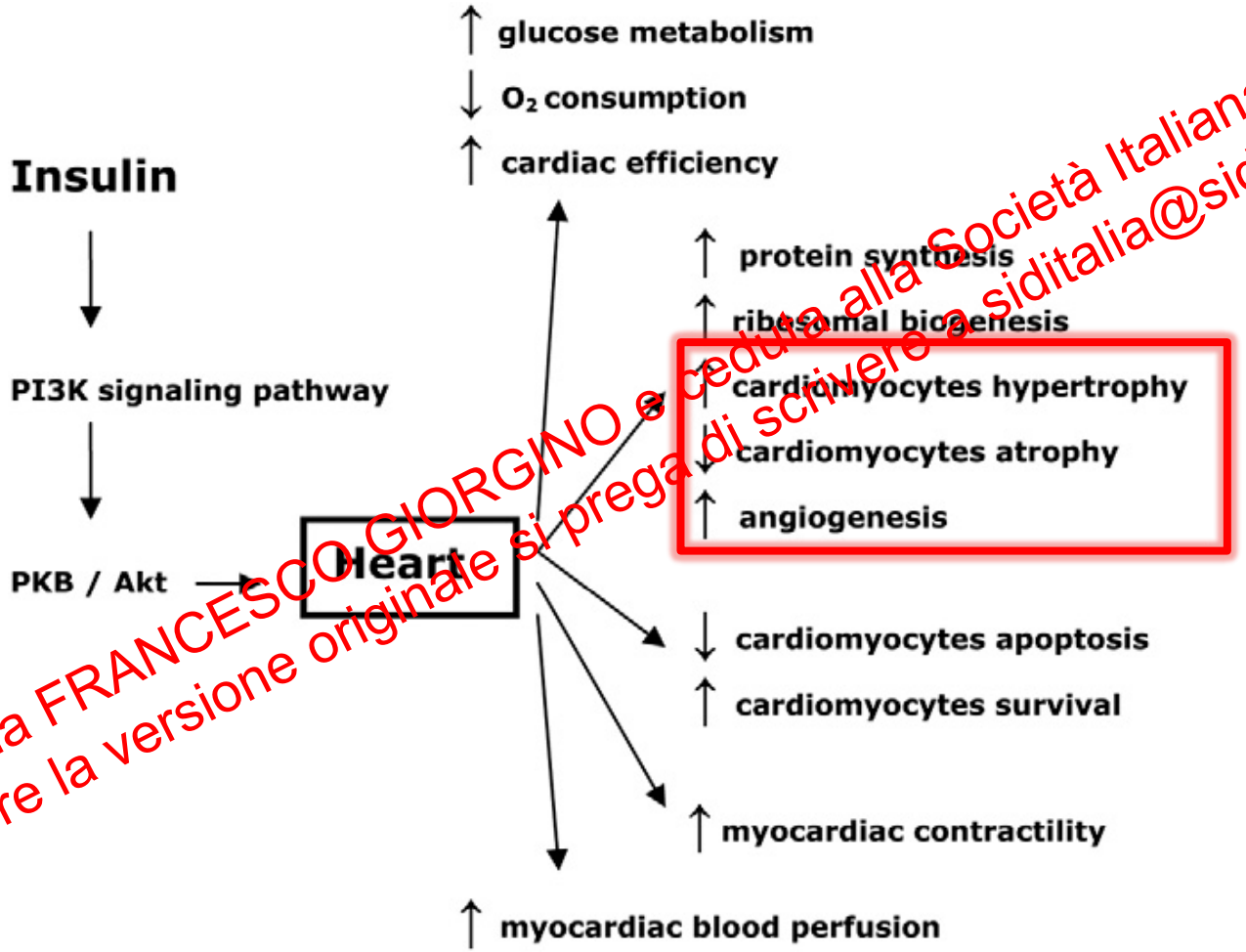


Iliadis et al., *Diabetes Res Clin Pract,* 2011

Regulation of Protein Synthesis by Insulin

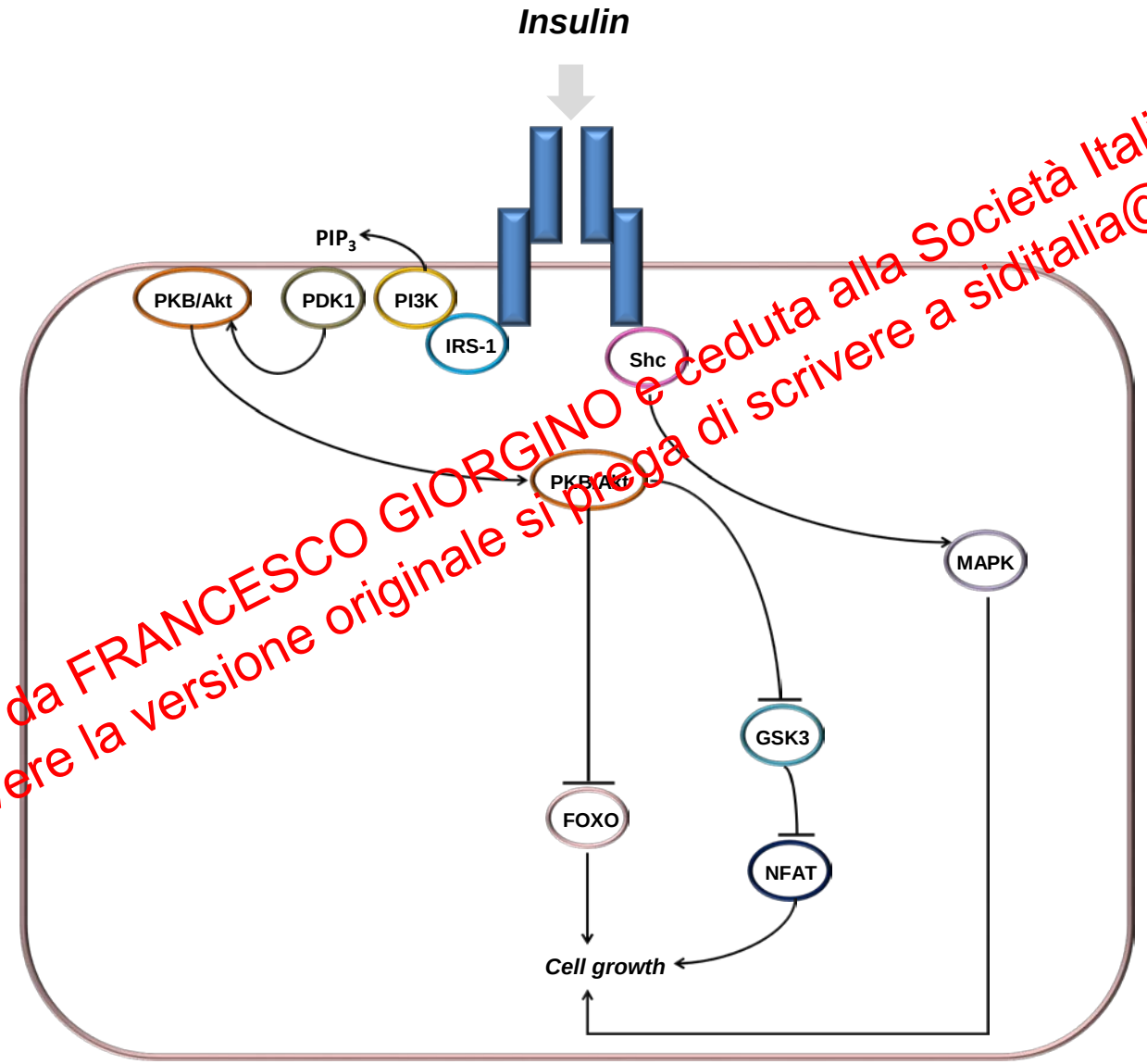


Cardiac Actions of Insulin



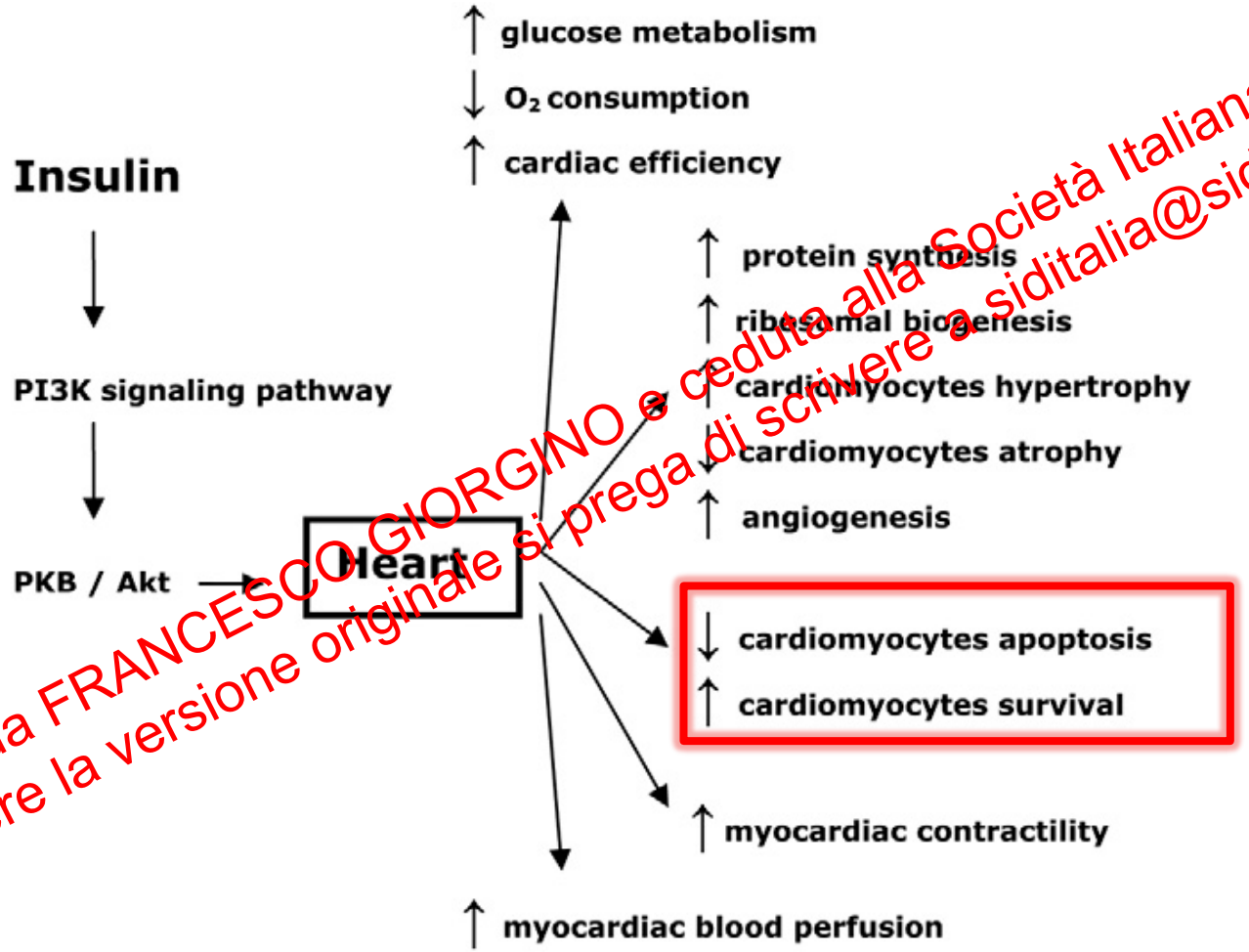
Iliadis et al., *Diabetes Res Clin Pract,* 2011

Insulin and Cardiomyocytes Hypertrophy, Atrophy and Angiogenesis



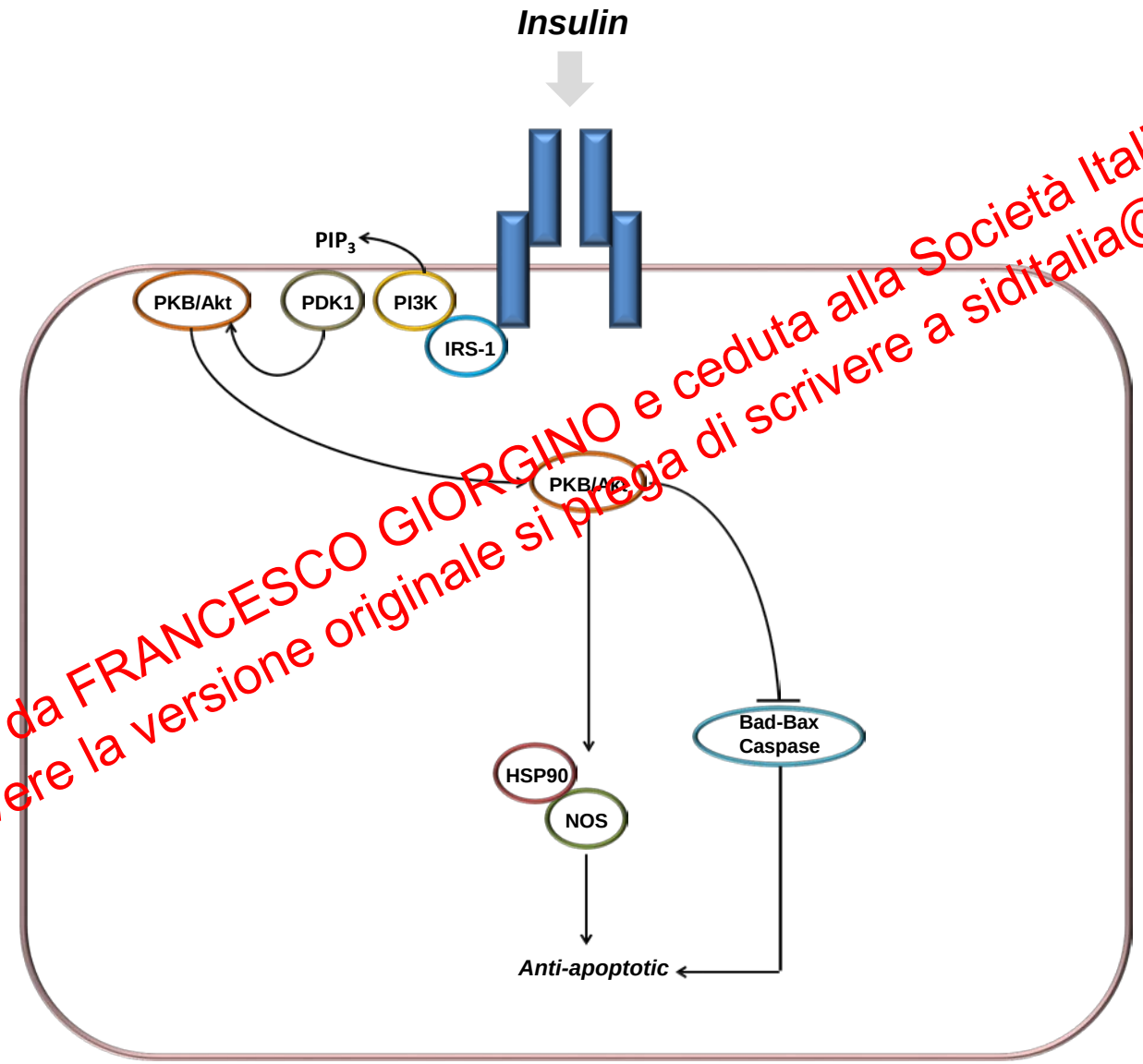
Cardiomyocyte hypertrophy alone might have detrimental effects. However insulin stimulates VEGF and thereby angiogenesis, restoring the imbalance between cardiac hypertrophy and blood perfusion *(Walsh et al., 2006; O'Neill et al., 2005)*.

Cardiac Actions of Insulin

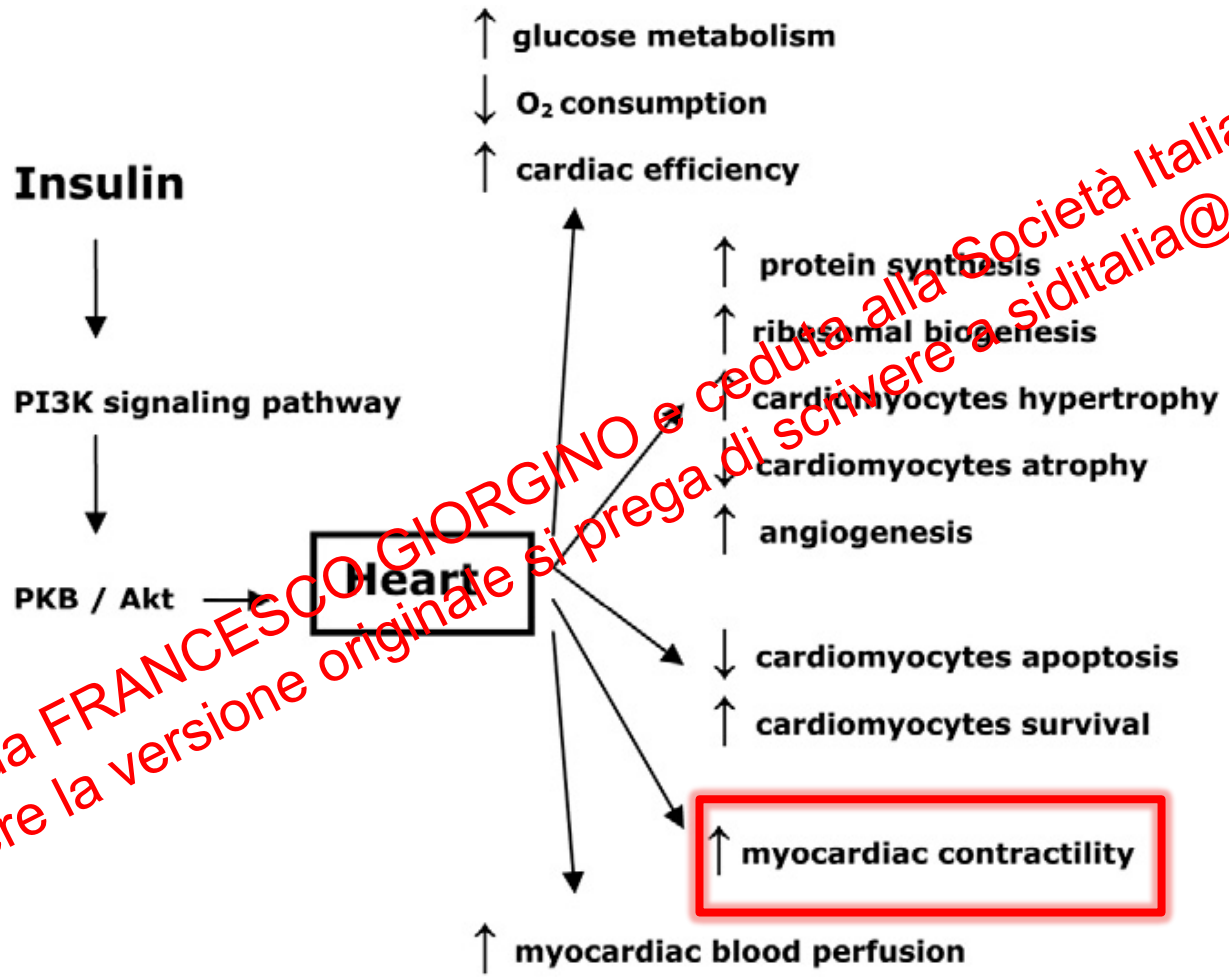


Iliadis et al., *Diabetes Res Clin Pract*, 2011

Insulin and Cardiomyocyte Apoptosis and Survival



Cardiac Actions of Insulin



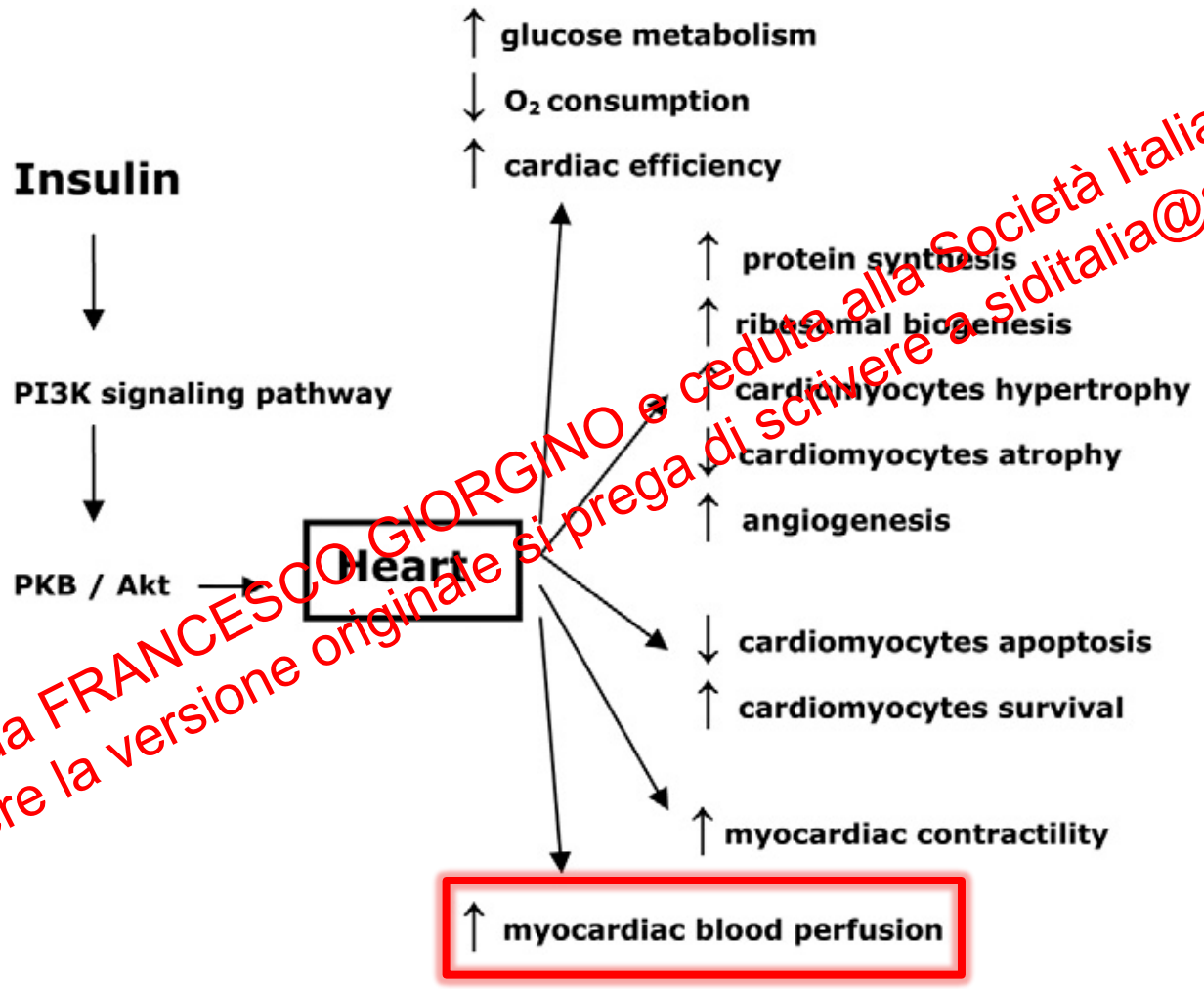
Iliadis et al., *Diabetes Res Clin Pract,* 2011

Insulin and Cardiac Contractility

Insulin augments myocardiac contractility by increasing:

- sarcoplasmic Ca^{2+} inflow via L channels *(Maier et al., 1999)* or reverse Na^{+}/Ca^{2+} exchanger *(von Lewinski et al., 2005)*;
- mRNA expression of both ryanodine receptor (RYR) and Ca^{2+} pump (SERCa2+-ATPase) of sarcoplasmic reticulum *(Teshima et al., 2000)*;
- cardiomyocyte contraction *(Iliadis et al., 2011)*.

Cardiac Actions of Insulin

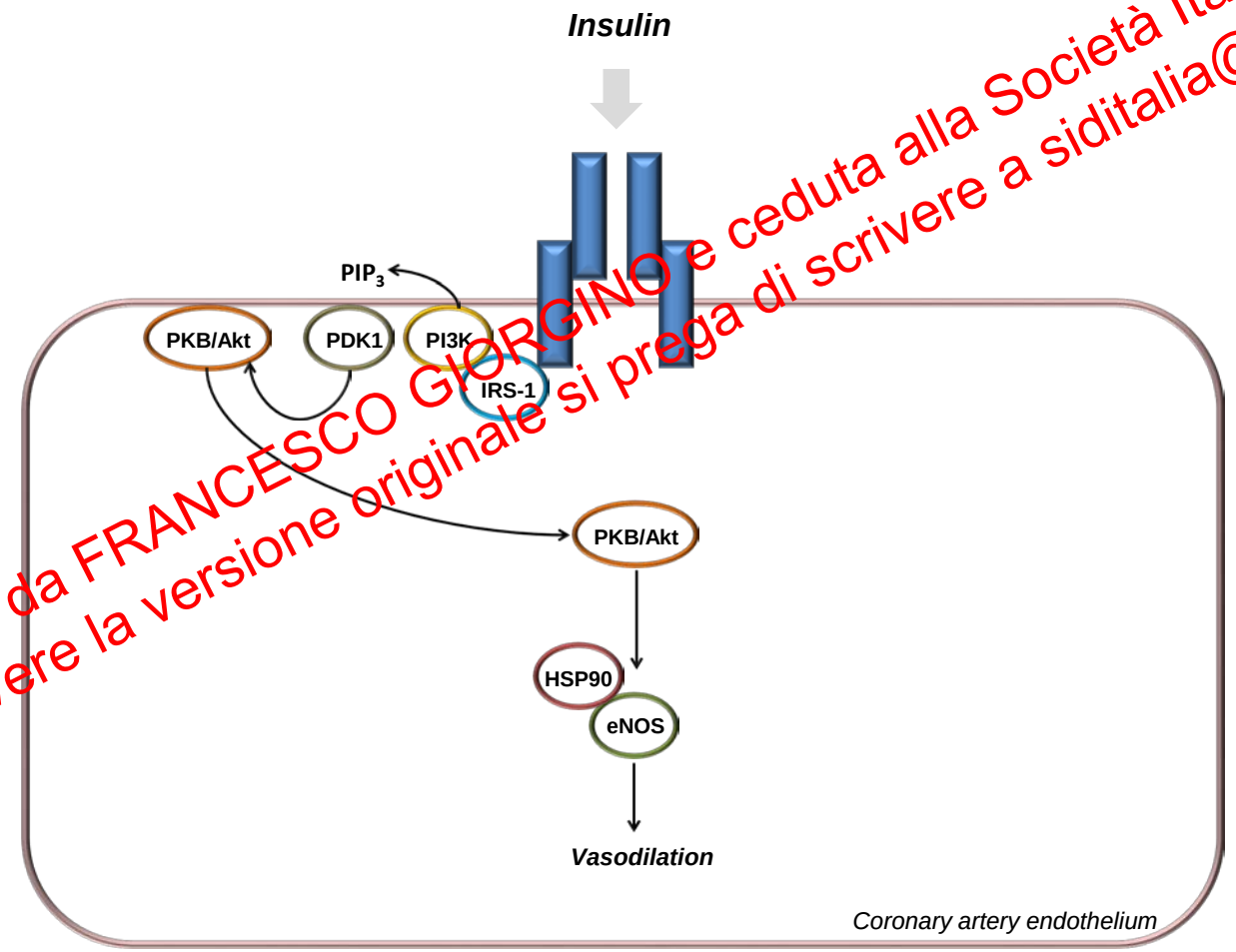


Iliadis et al., *Diabetes Res Clin Pract,* 2011

Insulin and Myocardial Blood Pressure

Insulin has important **vascular actions** that lead to:

- Vasodilation;
- Increased blood flow;
- Subsequent augmentation of glucose disposal in insulin-target tissues *(Bertrand et al., 2008)*.

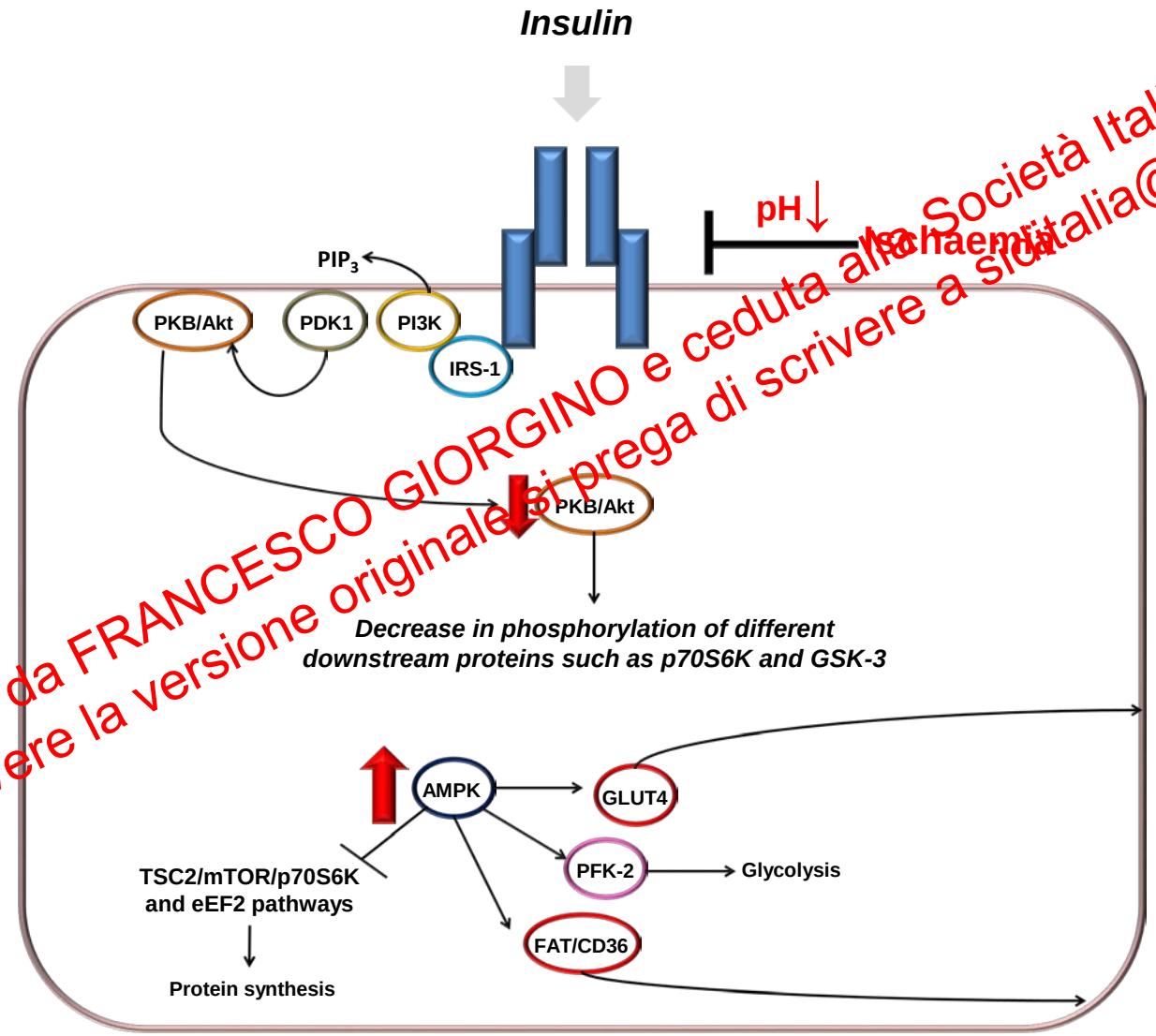


Produced nitric oxide (NO) is diffused to vascular smooth muscle cells (VSMCs), where it activates soluble guanylyl cyclase (sGC) and increases cGMP concentration, which causes VSMCs relaxation and vasodilation through Ca^{2+} decreases *(Sundell et al., 2003)*.

II. Pathophysiology

Insulin Action under Ischaemia

Insulin signaling and action are greatly altered under myocardial ischaemia *(Hue et al., 2002)*.

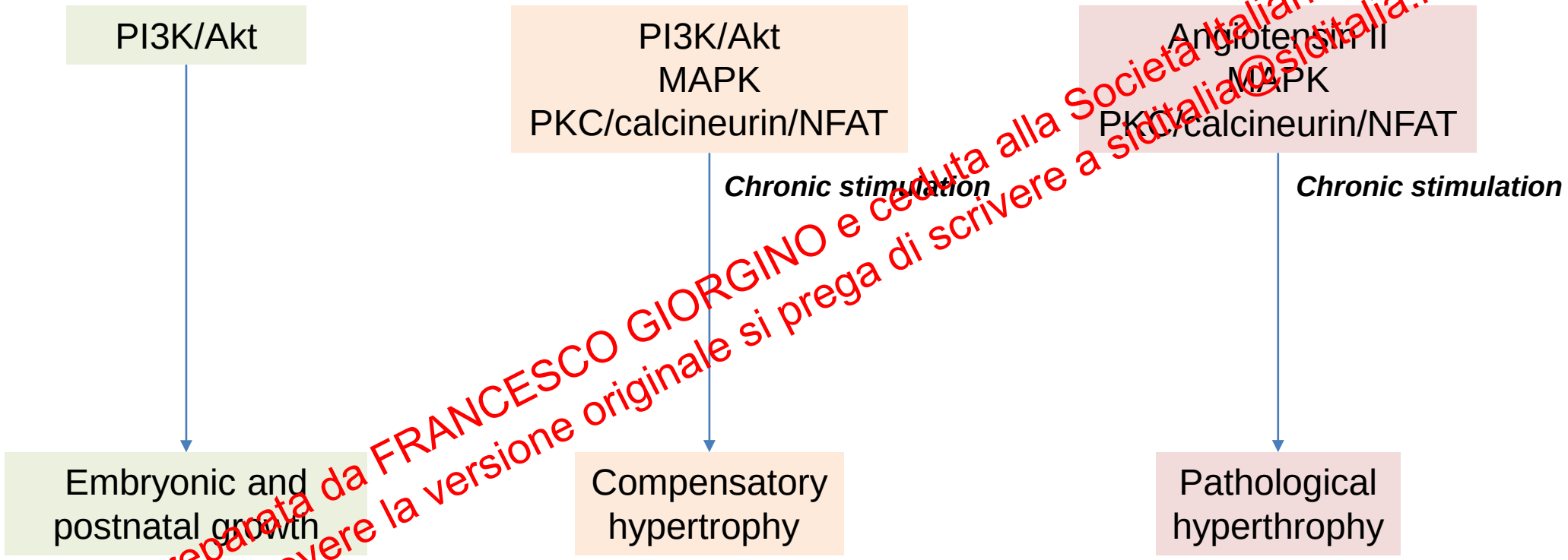


Beneficial Insulin Effects During Myocardial Ischaemia and Reperfusion

- Reduce fatty acid levels
- Increase glucose-derived ATP production
- Decrease ROS production
- Decrease O_2 consumption
- Increase the ATP production/O_2 consumption ratio
- Antagonize the detrimental effects of AMPK during reperfusion
- Activate cellular survival
- Protect from apoptosis
- Exert anti-inflammatory properties (↓NFκ, ↓MCP-1, ↓ICAM-1,↓CRP, ↑IκB)
- Exert anti-thrombotic properties (↓TF, ↓PAI-1)
- Increase blood flow in ischemic myocardial segments

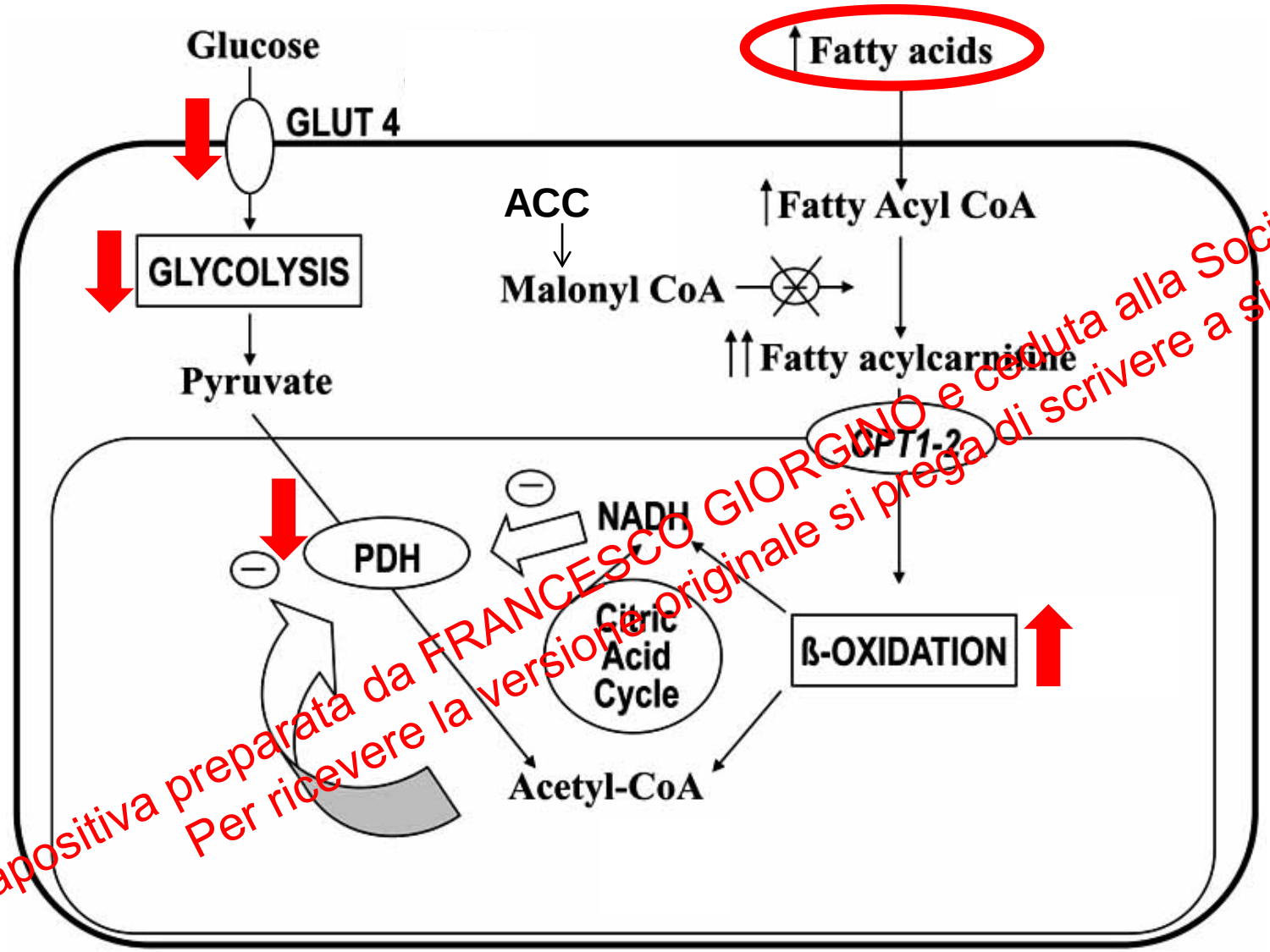
Iliadis et al., *Diabetes Res Clin Pract,* 2011

Insulin Signalling and Cardiac Hypertrophy



Heineke et al., 2006; McMullen et al., 2007; Proud et al., 2004; Samuelsson et al., 2006.

Diabetes-Induced Alterations in Cardiac Glucose and Fatty Acid Metabolism

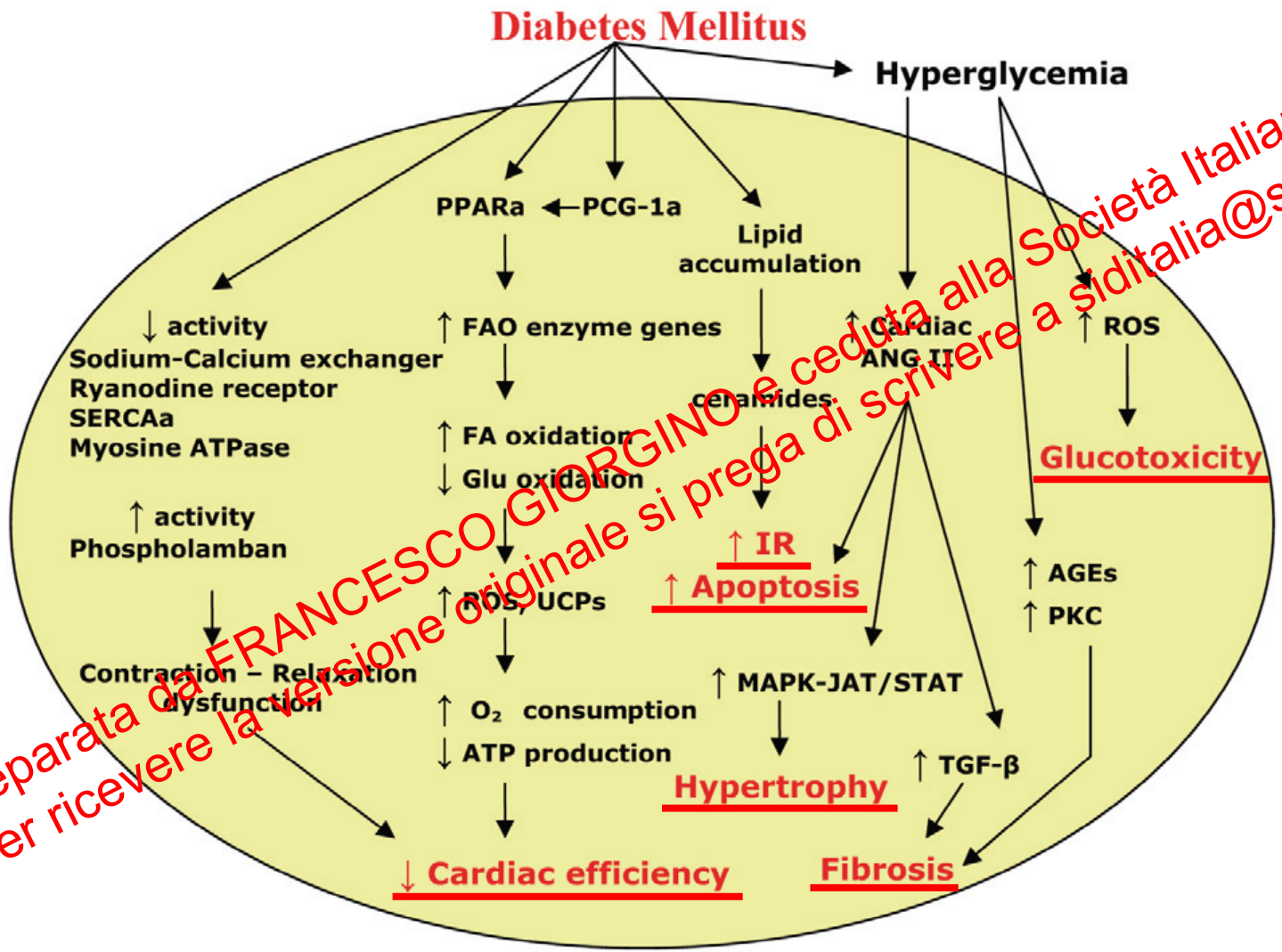


- Decreased glucose uptake and oxidation.
- Increased LCFA uptake and oxidation
- Increase in LCFA oxidation not sufficient to prevent lipid accumulation
- Myocardial lipid accumulation (especially ceramides)
  → insulin resistance

ACC: Acetyl-CoA carboxylase
CPT1-2:carnitine-palmitoyl-transferases

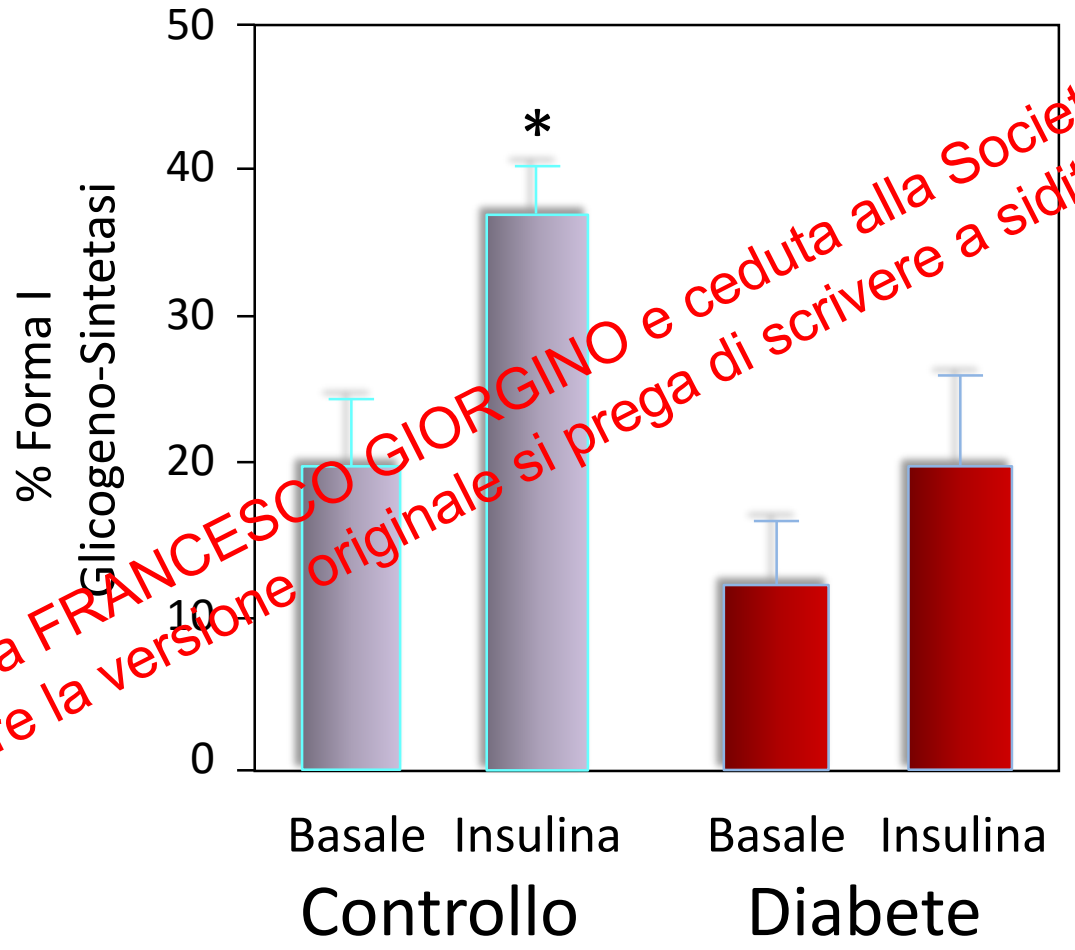
Bertrand et al., 2008; Barsotti et al., 2009; Iliadis et al., 2011

Proposed Mechanisms of Diabetic Cardiomyopathy



Iliadis et al., *Diabetes Res Clin Pract*, 2011

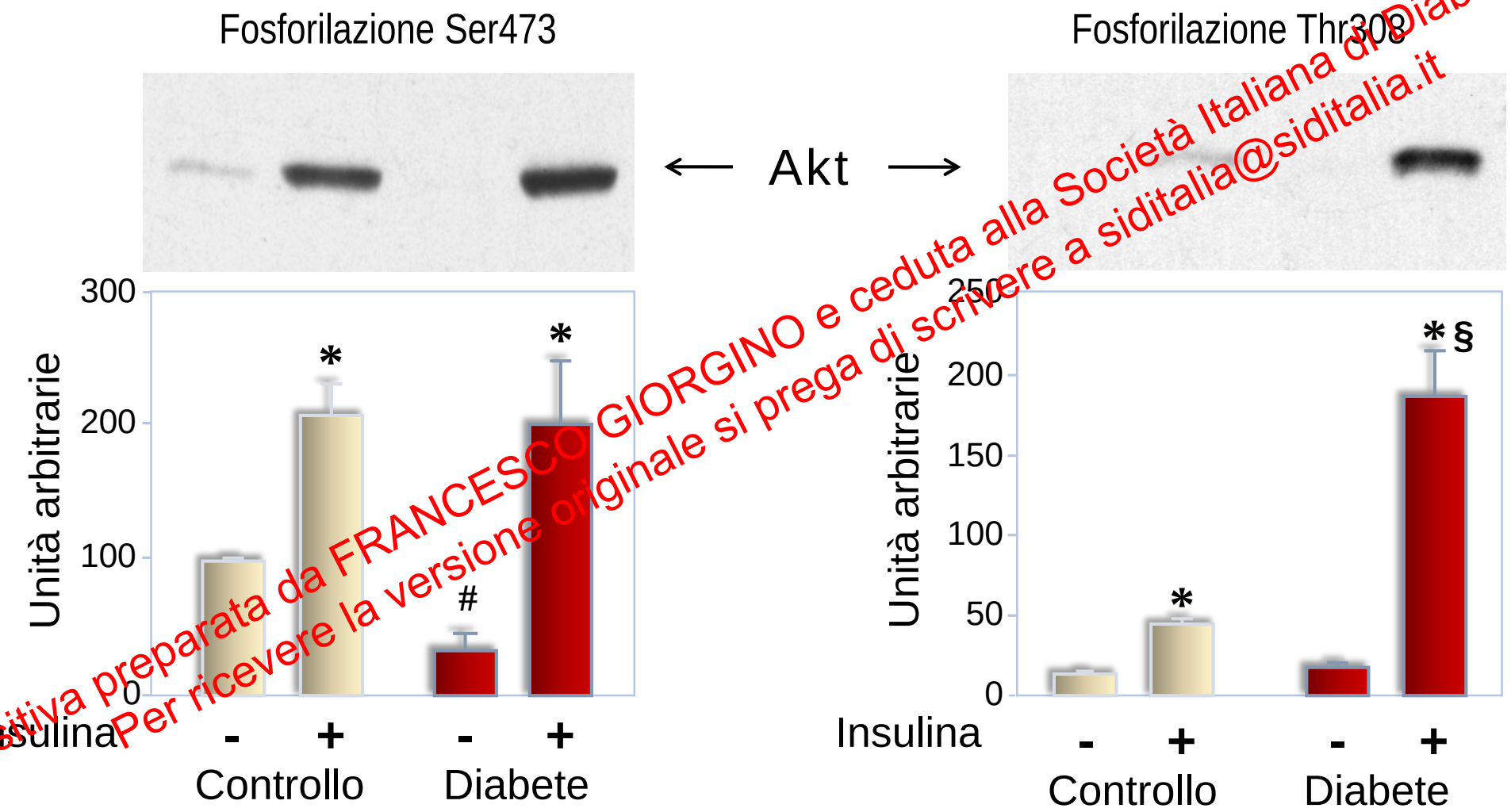
Effetti dell'Insulina sulla Sintesi di Glicogeno nel Miocardio di Ratti Diabetici



Attività della Glicogeno-Sintetasi

Wang PH et al., Endocrinology, 1999

Fosforilazione della Chinasi Akt nel Miocardio di Ratti Diabetici

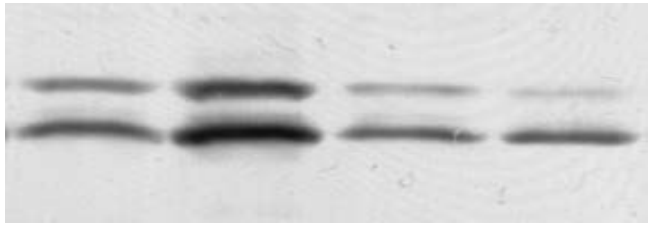


Laviola L. et al., *Diabetes*, 2001

Attività della Chinasi Akt nel Miocardio di Ratti Diabetici

In Vivo

Immunoblot anti-fosfo-GSK-3

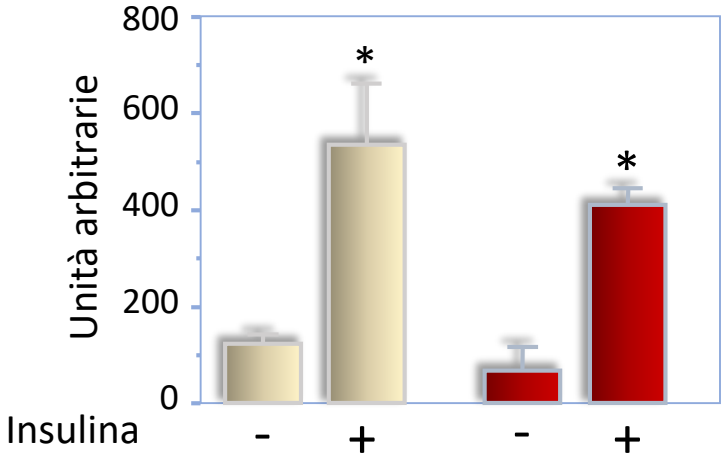


Insulina - + - +
Controllo Diabete

In Vitro

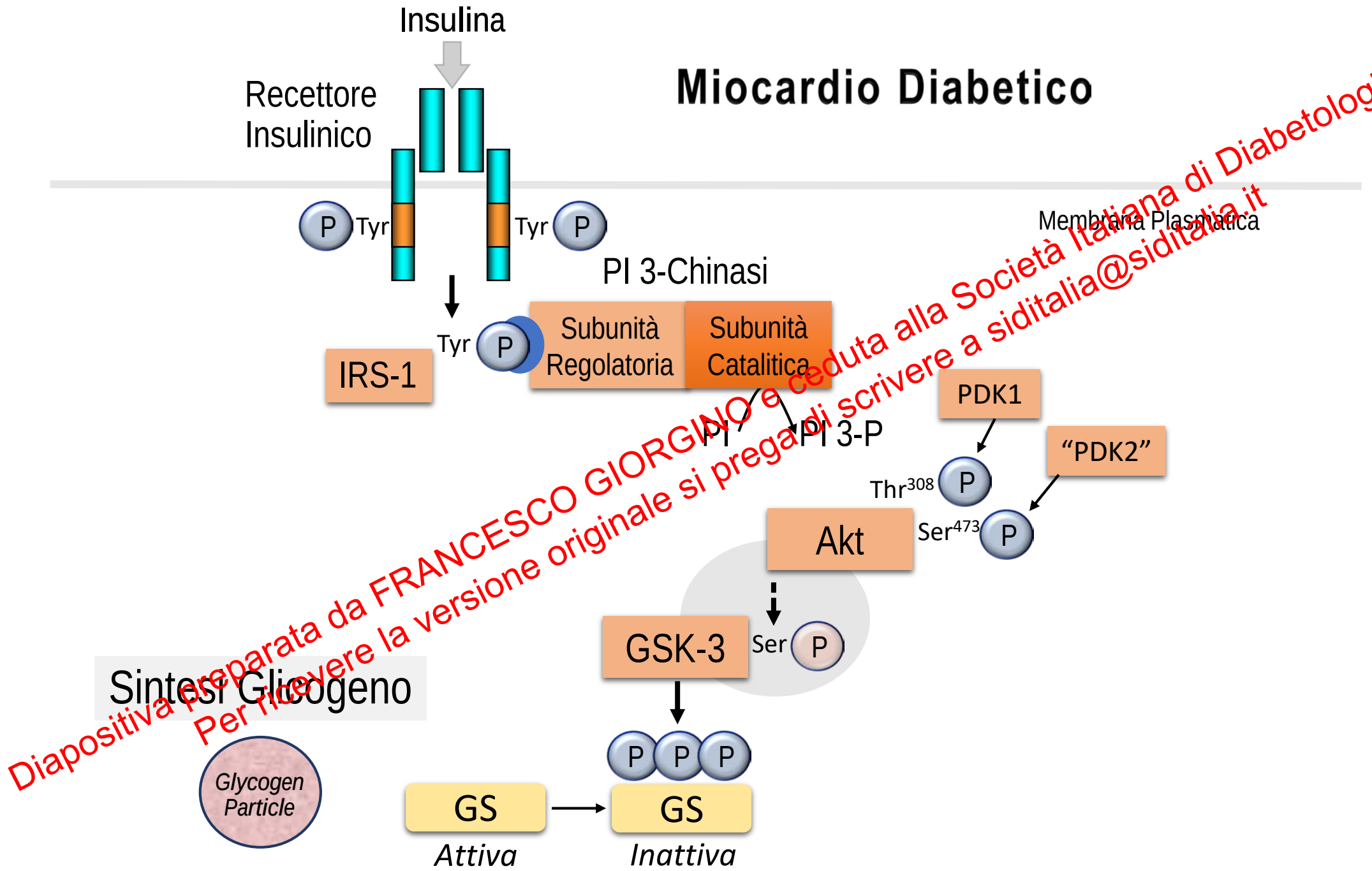
Immunoblot anti-fosfo-GSK-3

Insulina - + - +
Controllo Diabete

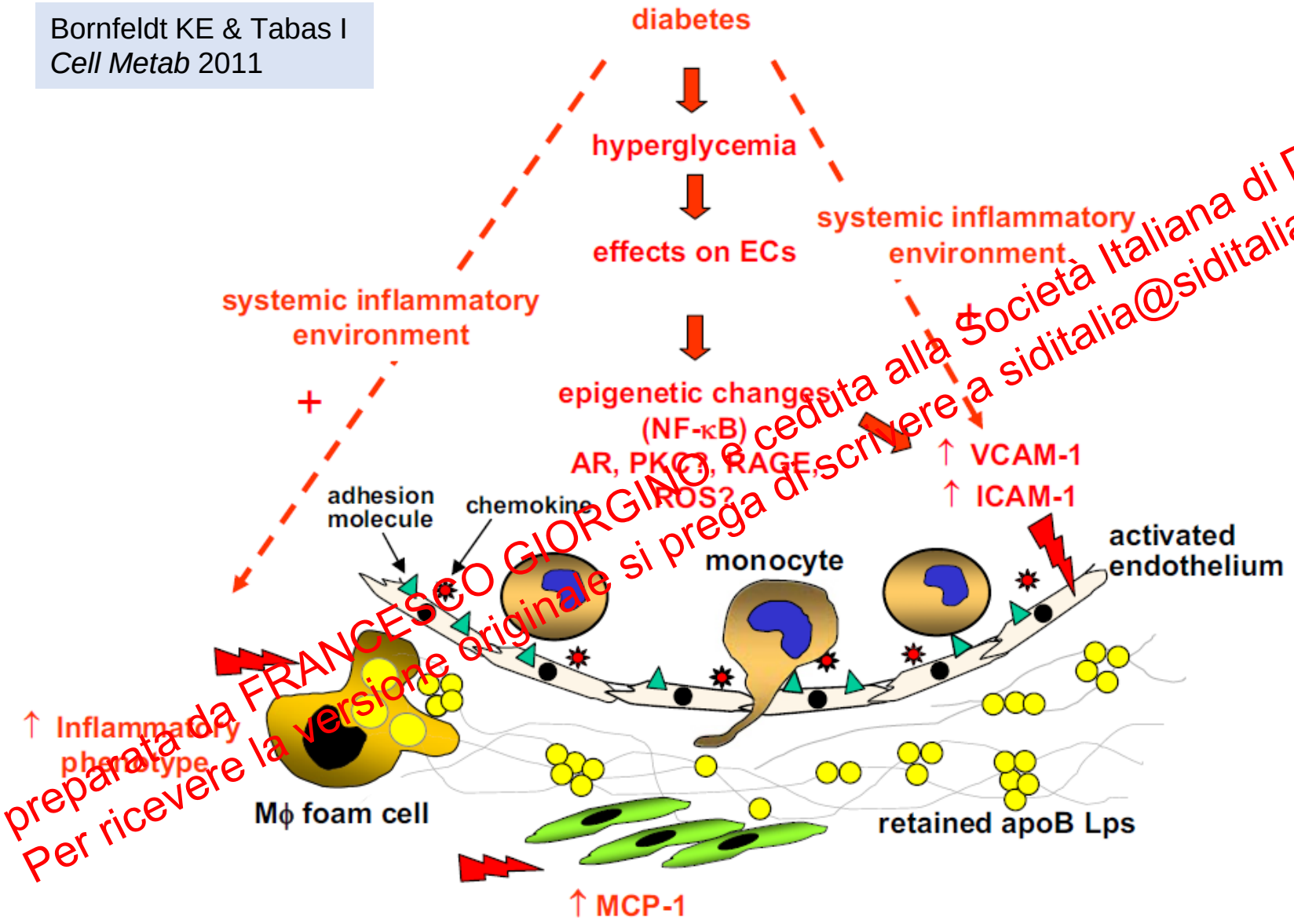


Laviola L. et al., *Diabetes*, 2001

Miocardio Diabetico

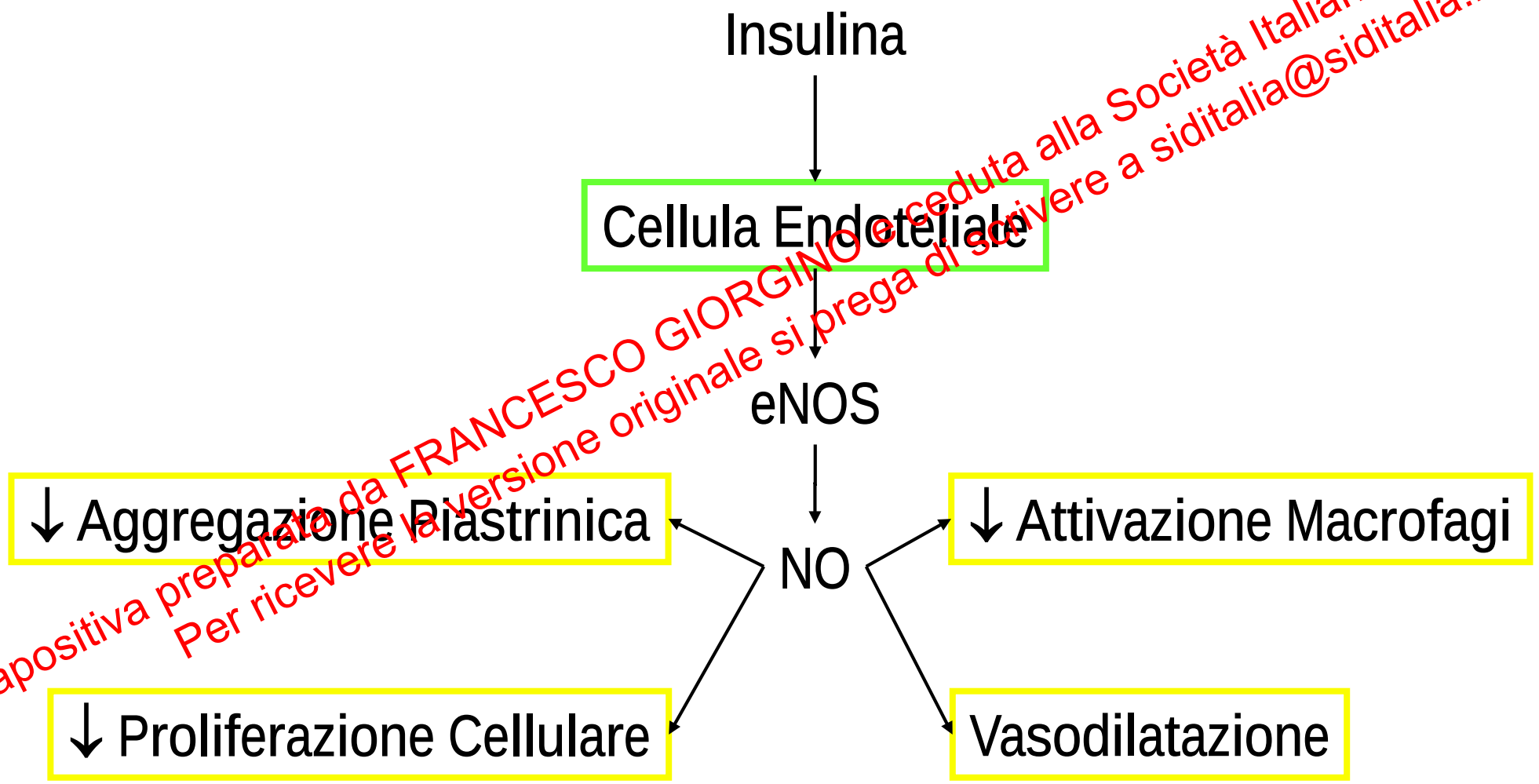


Bornfeldt KE & Tabas I
Cell Metab 2011

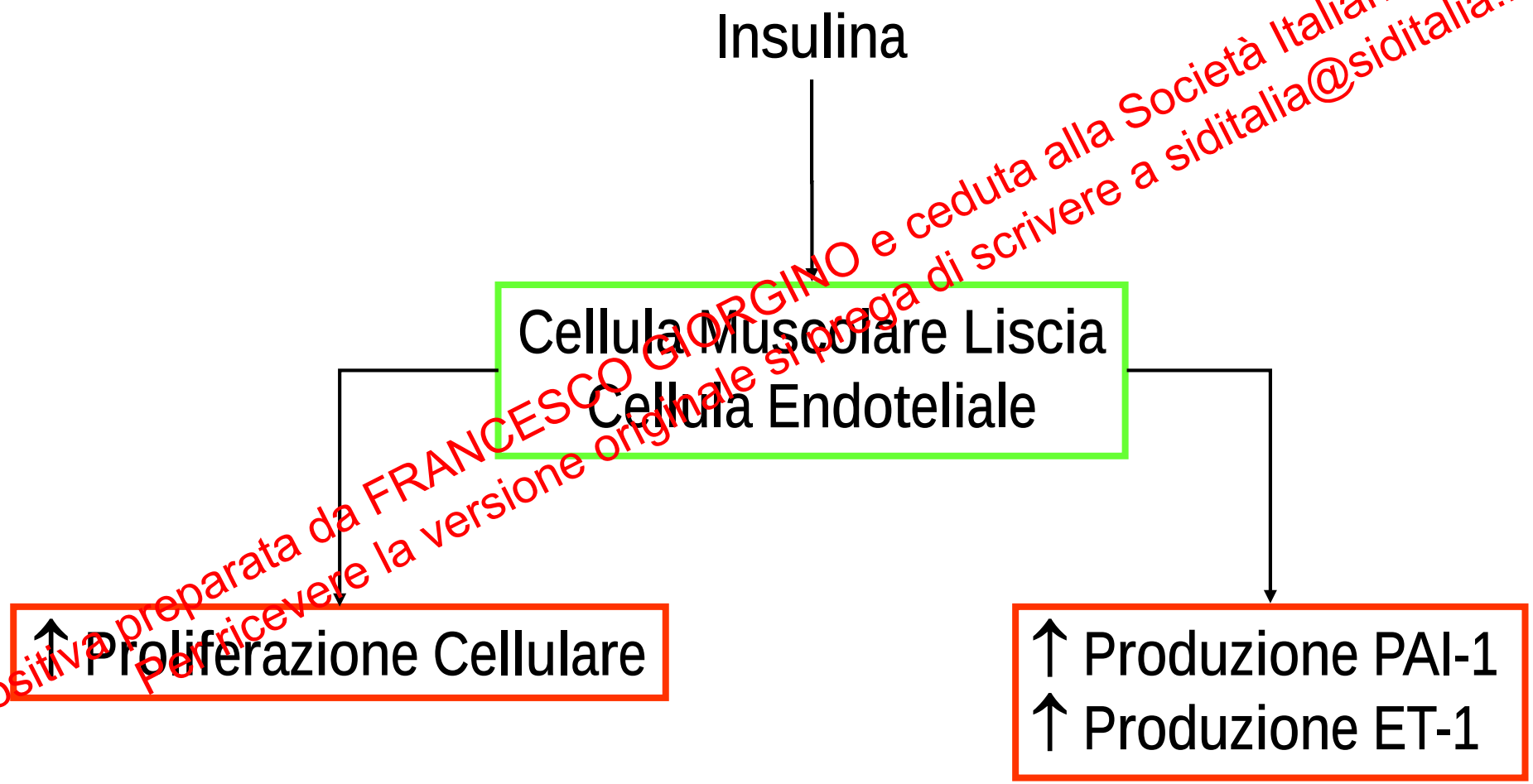


Early atherogenesis

Effetti dell'Insulina sul Sistema Vascolare
Protezione

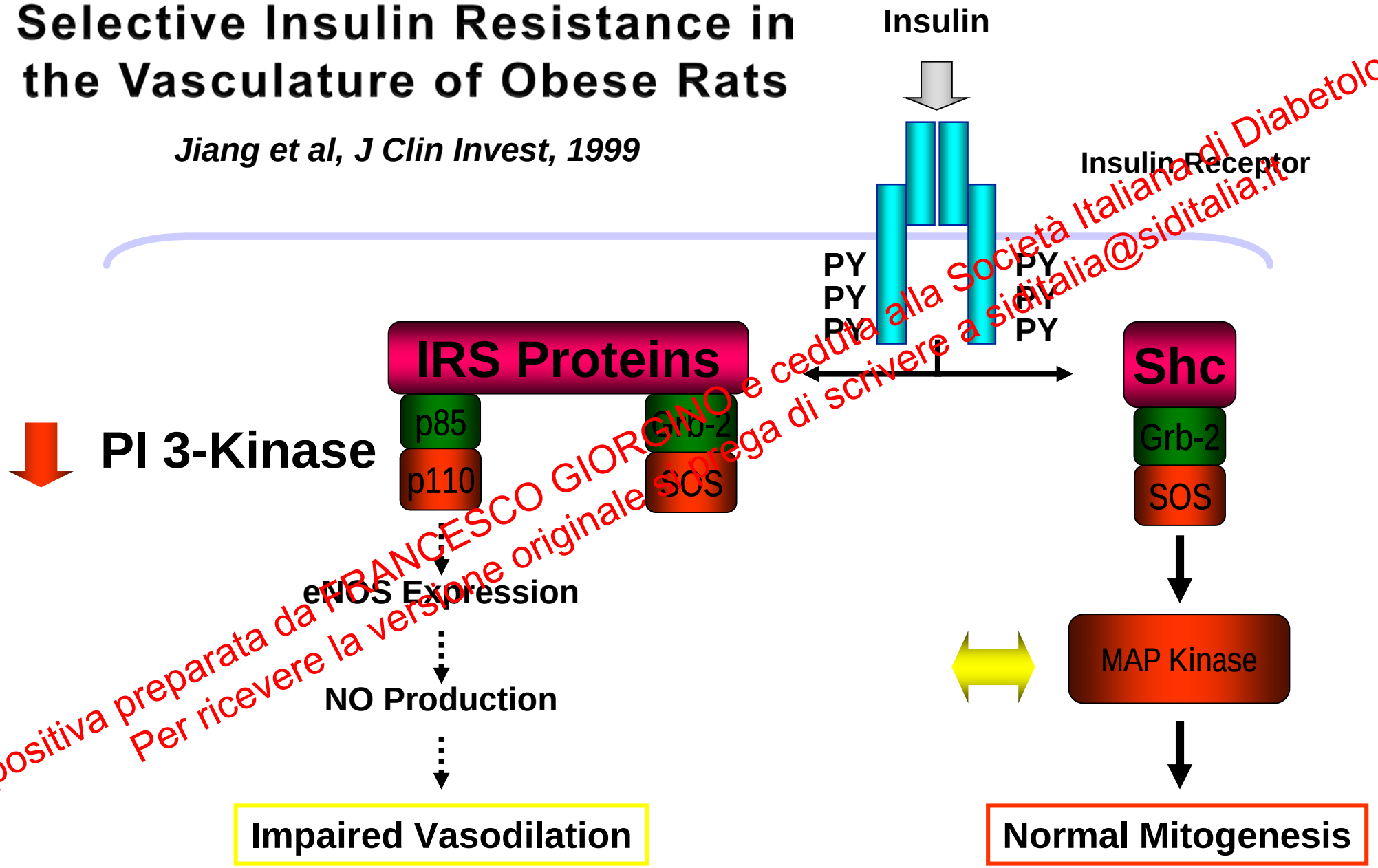


Effetti dell'Insulina sul Sistema Vascolare
Potenziale Danno

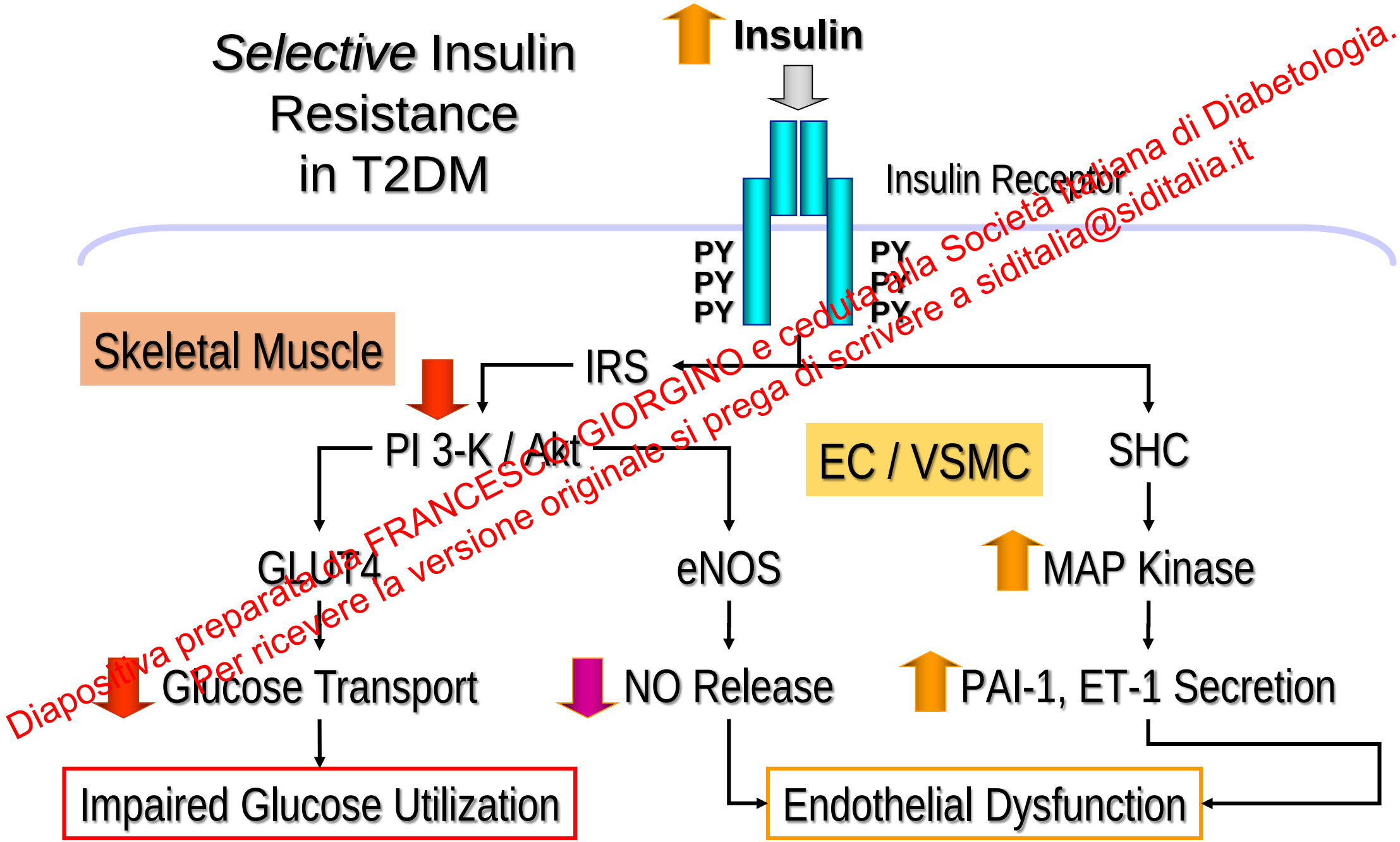


Selective Insulin Resistance in the Vasculature of Obese Rats

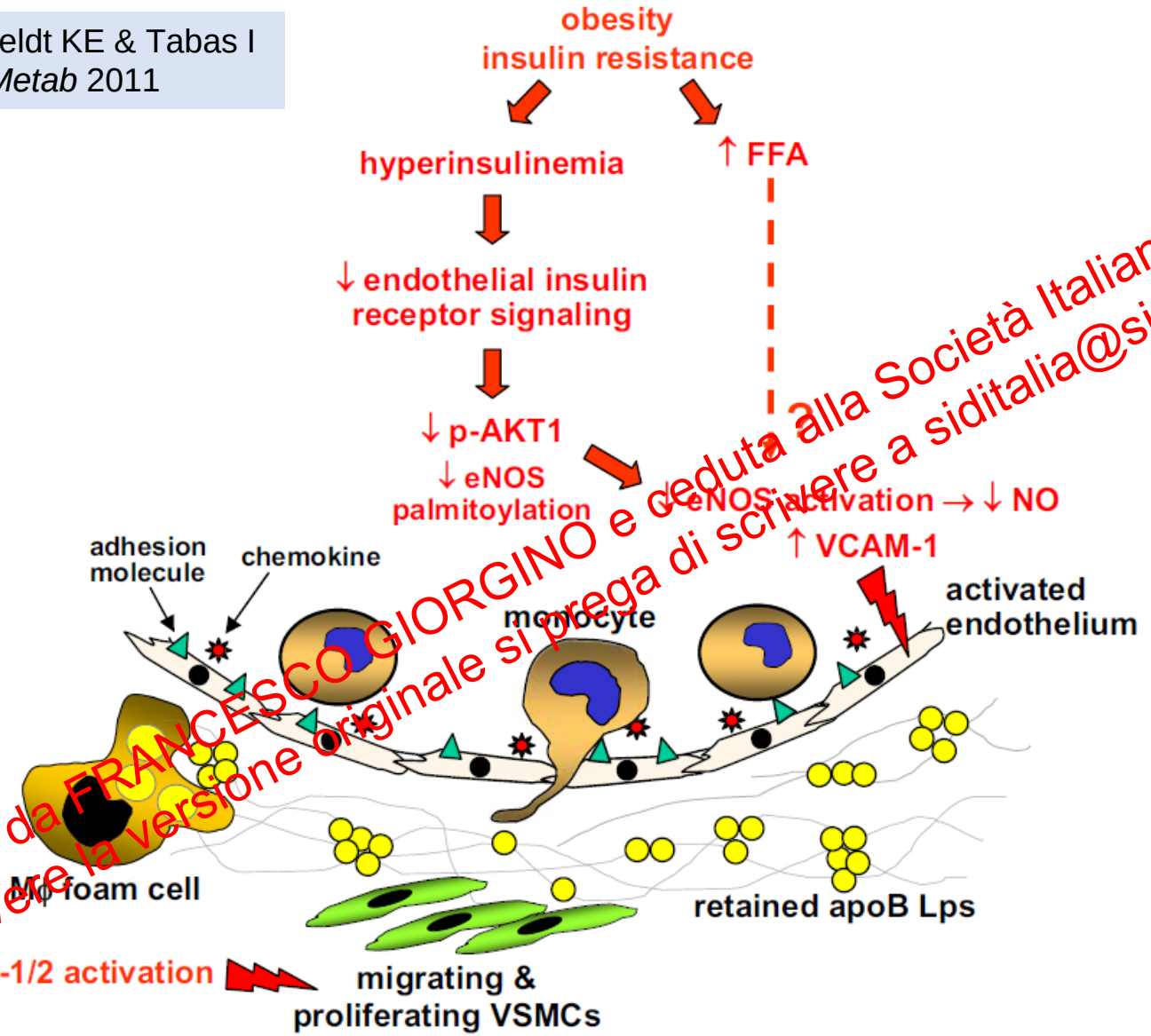
Jiang et al, J Clin Invest, 1999



Selective Insulin Resistance in T2DM

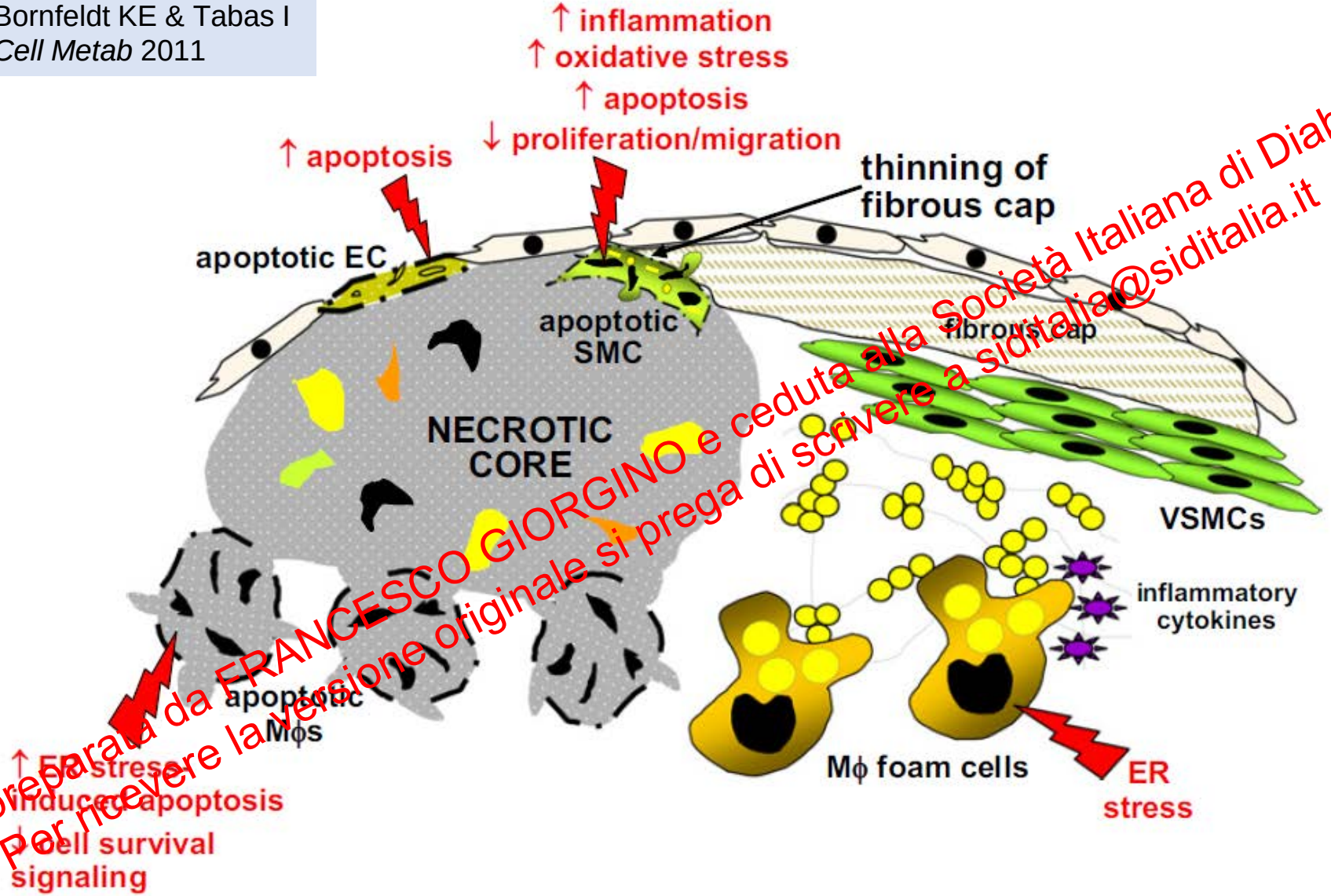


Bornfeldt KE & Tabas I
Cell Metab 2011



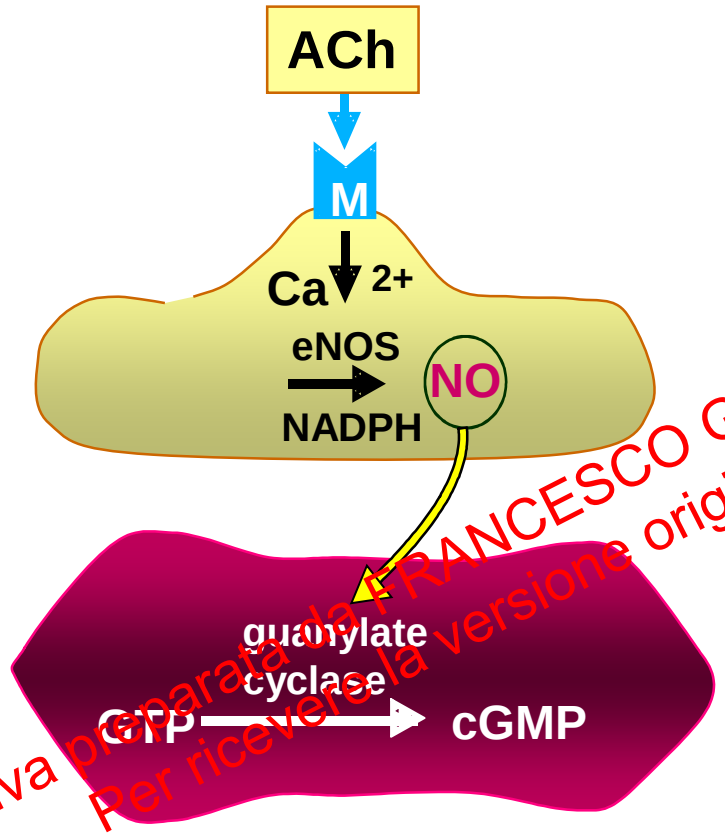
Early atherogenesis—Insulin resistance

Bornfeldt KE & Tabas I
Cell Metab 2011



Advanced plaque progression—Insulin resistance

Insulin and Endothelial Function
Implicatons for CVD Prevention in T2DM



Endothelial dysfunction predicts CV events

- Hypertensive patients: *Perticone F et al, Circulation 104: 191-196, 2001*
- CHD patients: *Heitzer T et al, Circulation 104: 2673-2678, 2001*

Insulin therapy improves endothelial function

- Vehkavaara S et al, *Arterioscler Thromb Vasc Biol 20: 545-550, 2000*
- Rask-Madsen C et al, *Diabetes 50: 2611, 2001*
- Gaenzer H et al, *Am J Cardiol 15: 431, 2002*
- Vehkavaara S et al, *Arterioscler Thromb Vasc Biol 24: 325-30, 2004*

Insulin and Atherosclerosis

- "Insulin resistance" can mean either defective insulin receptor signaling or overstimulation of insulin receptor pathways caused by hyperinsulinemia.
- Relative importance of insulin resistance vs. hyperglycemia.
- Systemic risk factors induced by these syndromes vs. direct processes acting at the level of the arterial wall.
- Early-to-mid-stage atherogenesis (subendothelial retention of apoB-containing lipoproteins; EC activation; recruitment of monocytes and other inflammatory cells; cholesterol loading of lesional cells; and VSMC migration to intima) distinct from advanced plaque progression (plaque necrosis and thinning of a collagenous "scar" overlying the lesion called the fibrous cap).

Insulin Receptor (IR) in Vascular Cells

EIRAKO mice (EC-specific IR ko, *apoE*$^{-/-}$ background)

- reduced levels of eNOS and endothelin-1 mRNA in ECs and aorta (Vicent et al., JCI 2003).
- increased atherosclerosis, decreased eNOS activity, increased VCAM-1 expression and leukocyte adhesion (Rask-Madsen et al., Cell Metab 2010).

Akt1$^{-/}$, *apoE*$^{-/-}$ mice

- increase in aortic atherosclerosis; very large coronary arterial lesions; increased lesional inflammatory cytokines and decreased p-S1176-eNOS (Fernandez-Hernando C et al., Cell Metab 2006).

IGF-I R masks the antiinflammatory capacity of insulin in VSMCs (Engberding N et al., ATVB 2009)

Insulin Receptor (IR) in Macrophages

Macrophage IR ko, *apoE*$^{-/-}$ background

- Protection from atherosclerosis (Tabas I et al., Circ Res 2010).

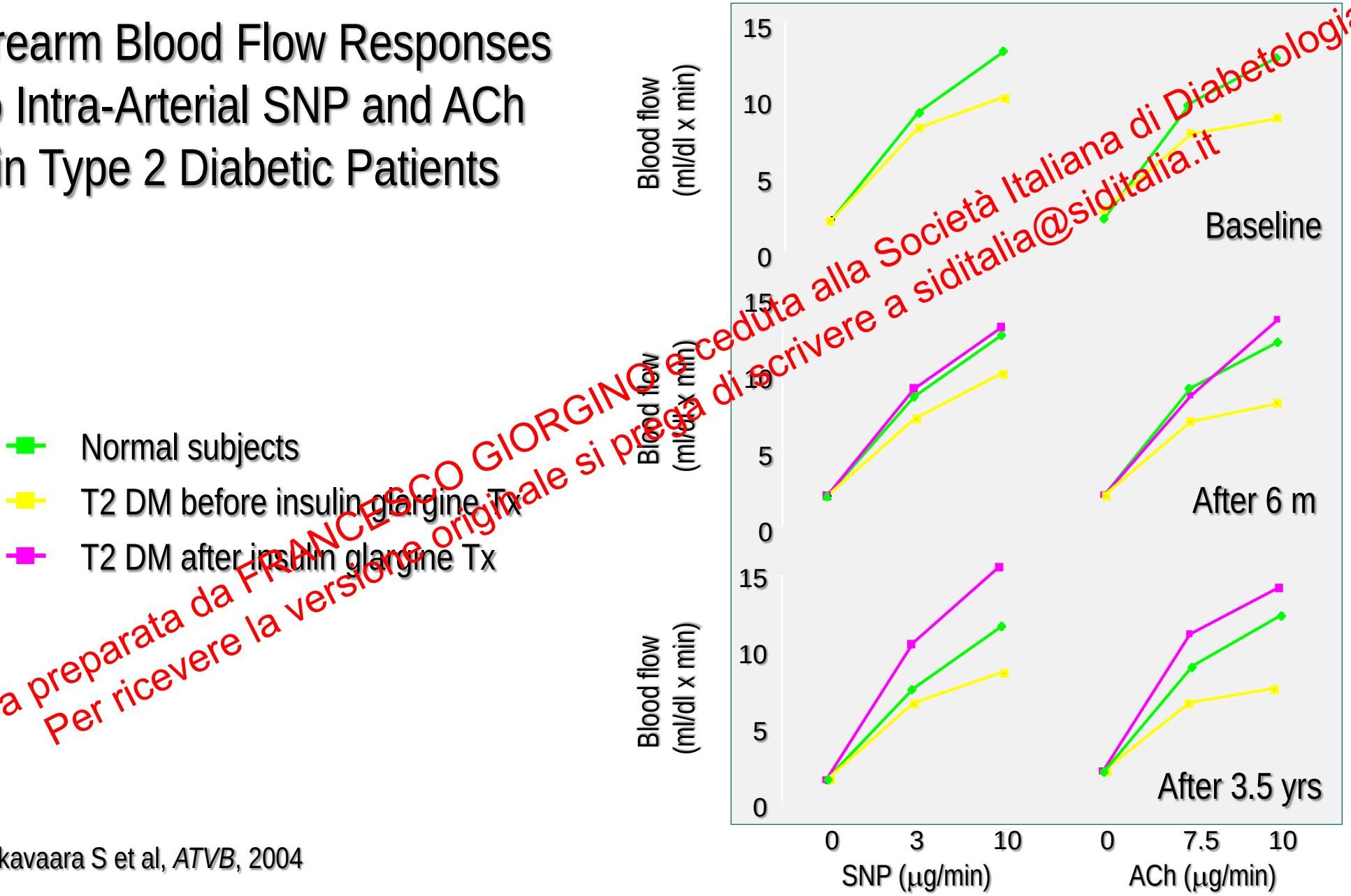
Macrophage IR or IRS-2 ko, *apoE*$^{-/-}$ background

- Protection from atherosclerosis (Baumgartl J et al., Cell Metab 2006).

IR KO bone marrow into C57BL6 *Ldlr*$^{-/-}$ mice fed Western diet

- Increased apoptosis of macrophages in advanced lesions
  → increased plaque necrosis and potential for rupture (Han S et al., Cell Metab 2006).

Forearm Blood Flow Responses to Intra-Arterial SNP and ACh in Type 2 Diabetic Patients



Vehkavaara S et al, *ATVB*, 2004