Meta Open Forum

"Al CUORE del DIABETE"

Roma | 11.12 Marzo 2022

Aula Brasca, Policlinico Gemelli

PERCHÉ IL DIABETE AUMENTA IL RISCHIO CARDIOVASCOLARE

AGOSTINO CONSOLI

DMSI & CeSI-MeT Università d'Annunzio – CHIETI

ITALY

SID Società Italiana di Diabetologia

DISCLOSURES

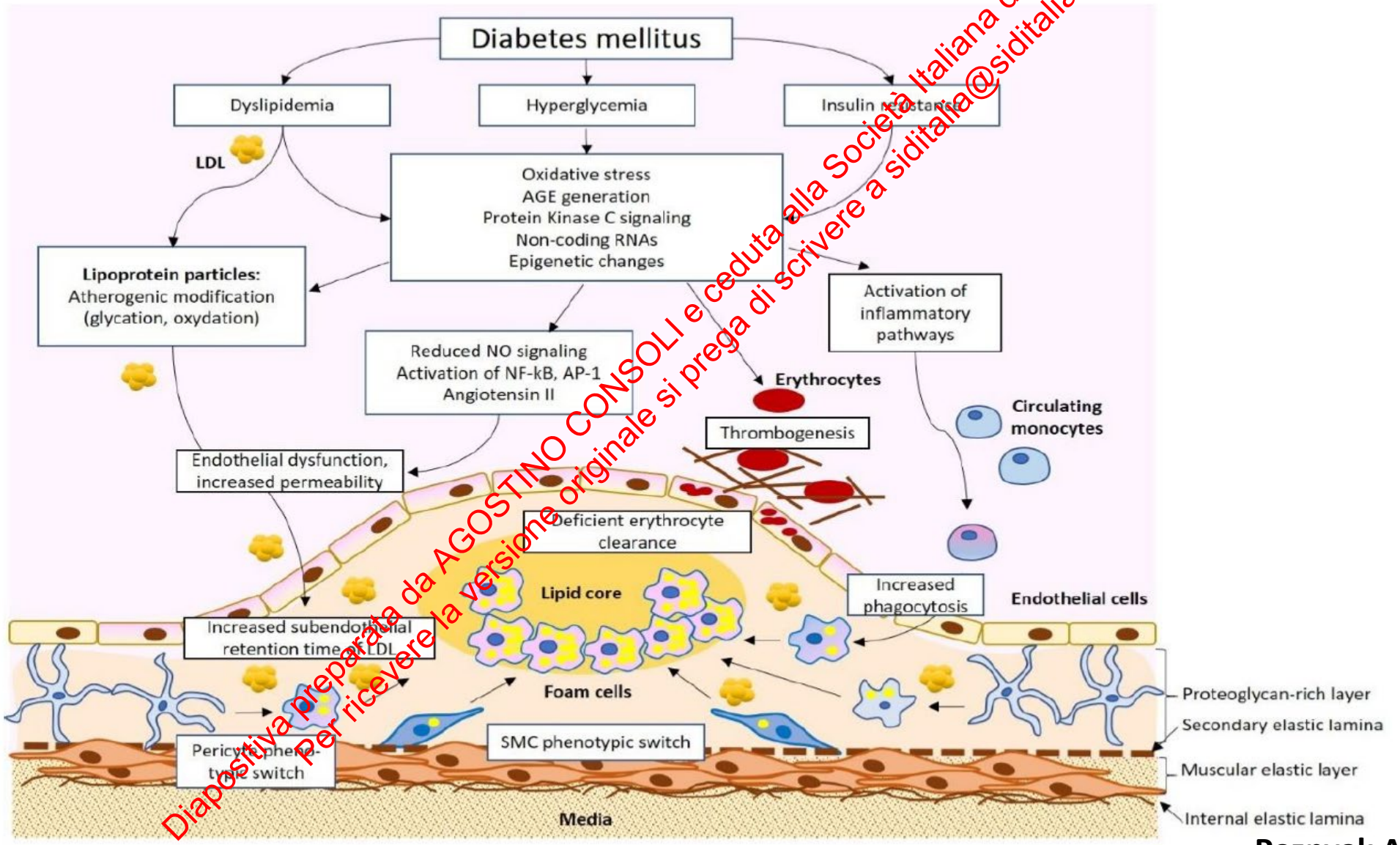
Bristol Mayer Squibb , Astra Zeneca, Boheringer Ingelhaim, Eli Lilly, Merck Sharp & Dhome , Novartis, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau, Takeda.
(Speaker)

Astra Zeneca, Bristol Mayer Squibb, Boheringer Ingelhaim, Eli Lilly, Janssen Farmaceutici, Merck Sharp & Dhome, Novo-Nordisk.
(Advisory Board)

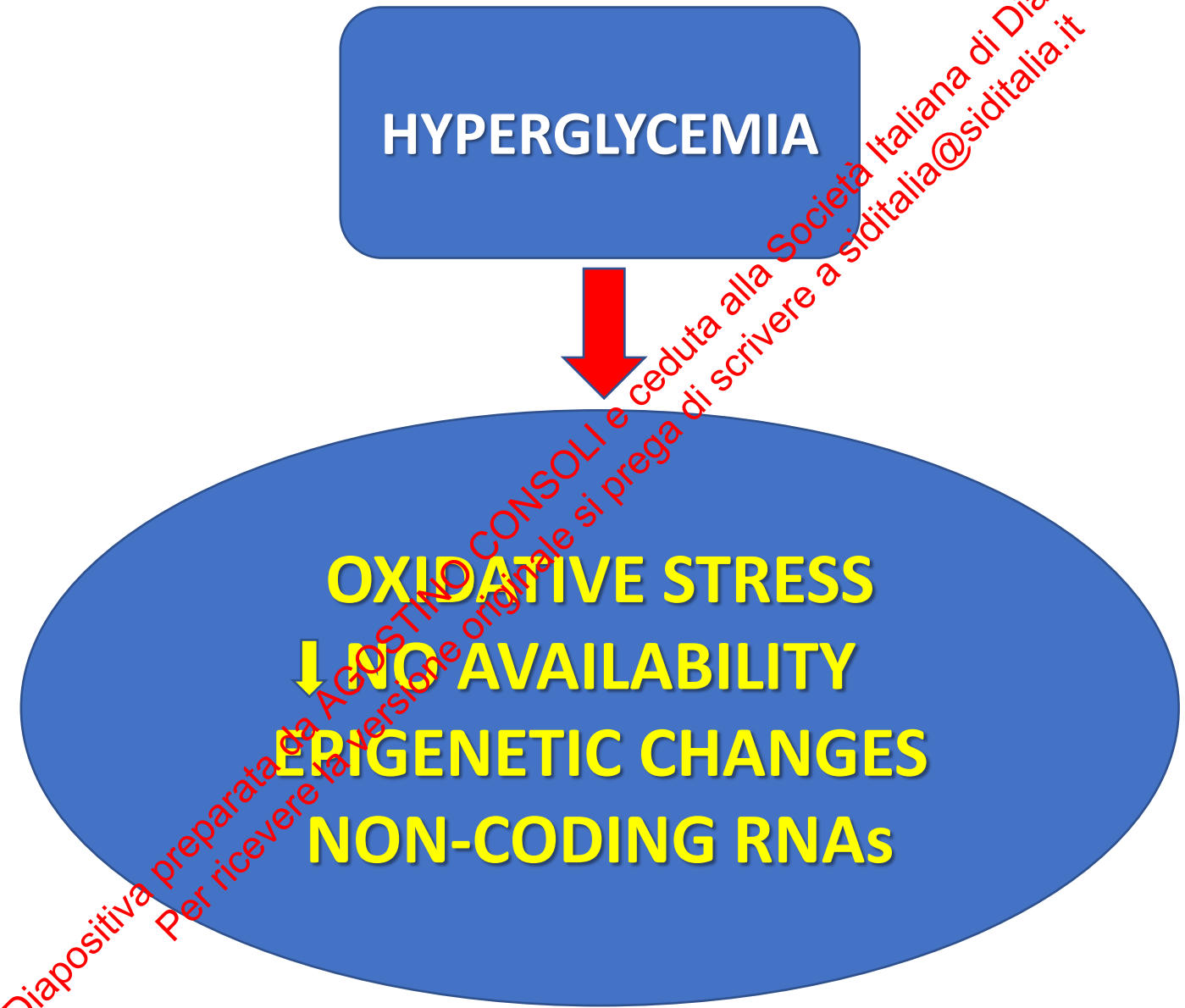
Astra Zeneca, Novo-Nordisk
(Consultant)

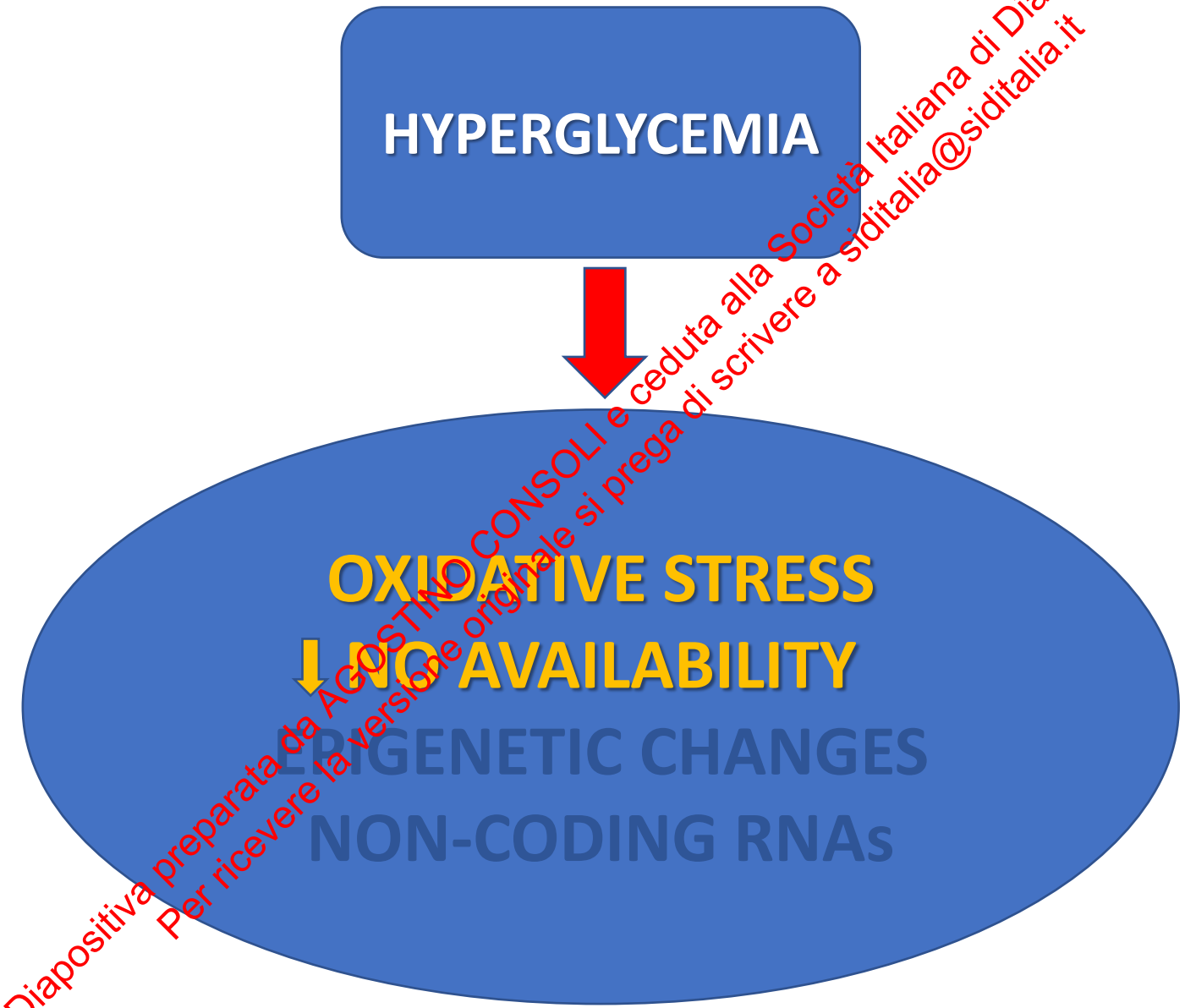
Eli Lilly, Novo-Nordisk
(Research Grant)

A *simplified* scheme of the pathophysiological connection between diabetes mellitus and atherosclerosis

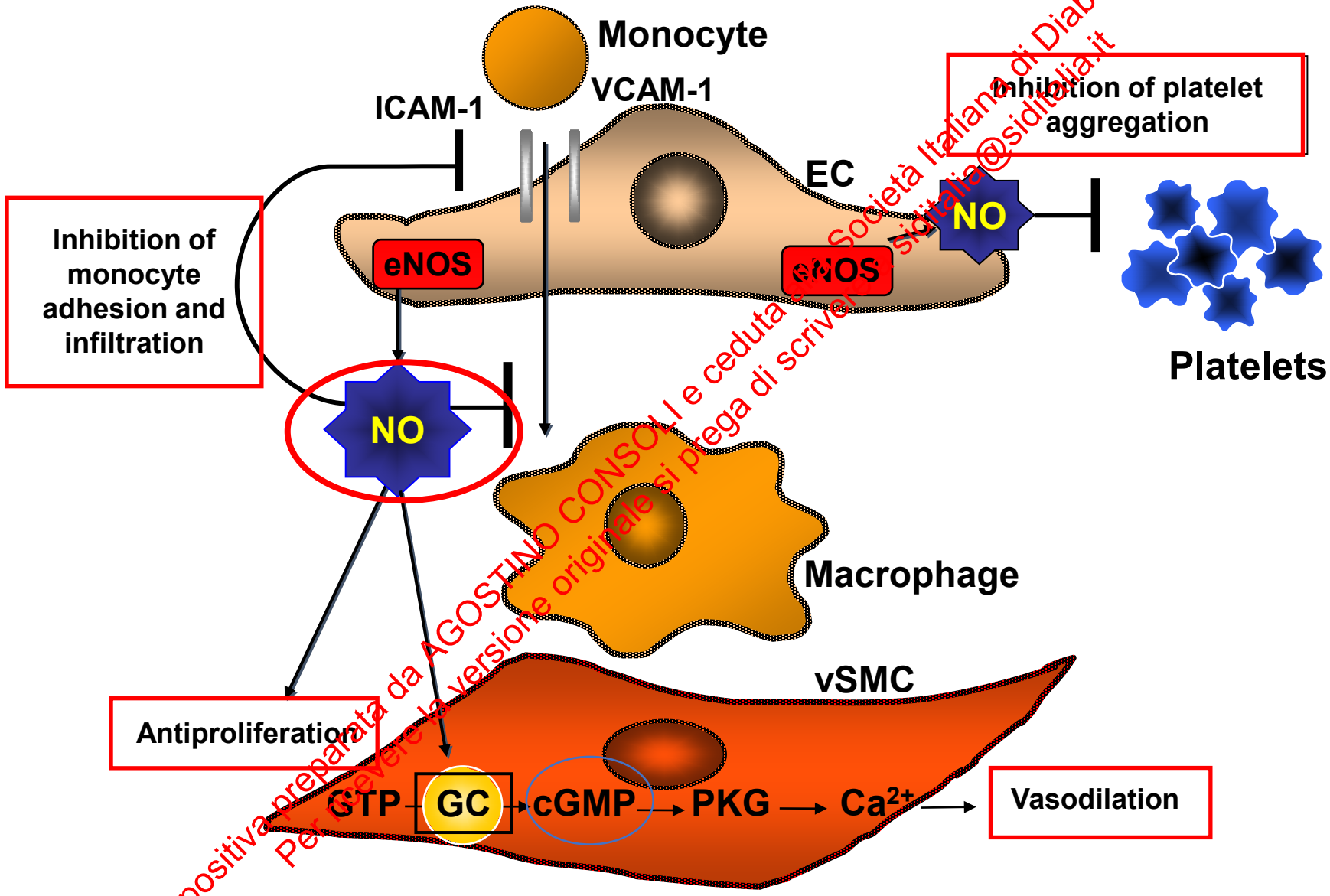


Poznyak A et al., 2020



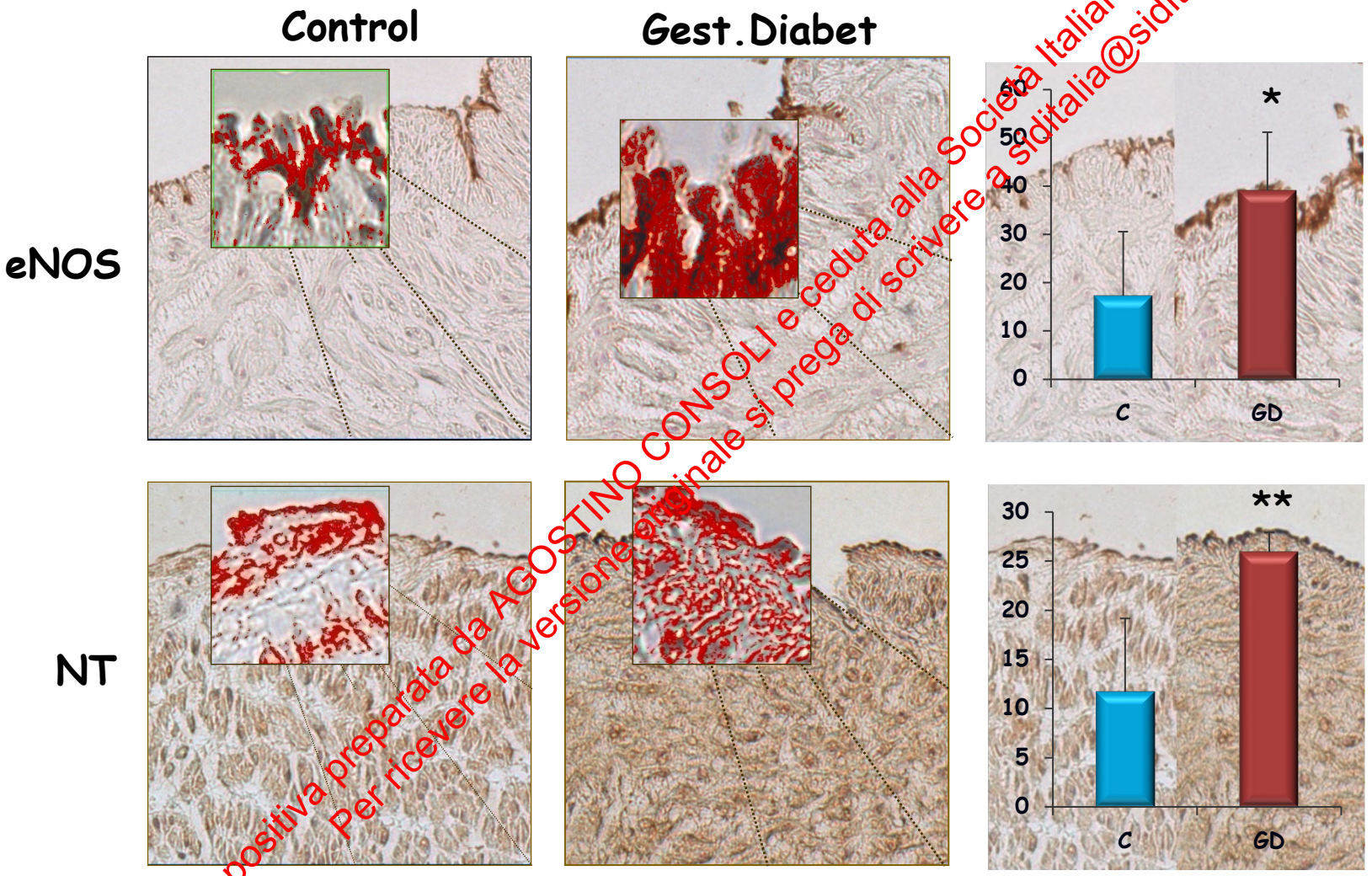


NORMAL ENDOTHELIAL FUNCTION



Pandolfi and De Filippis, Genes Nutr (2007) 2:195–208

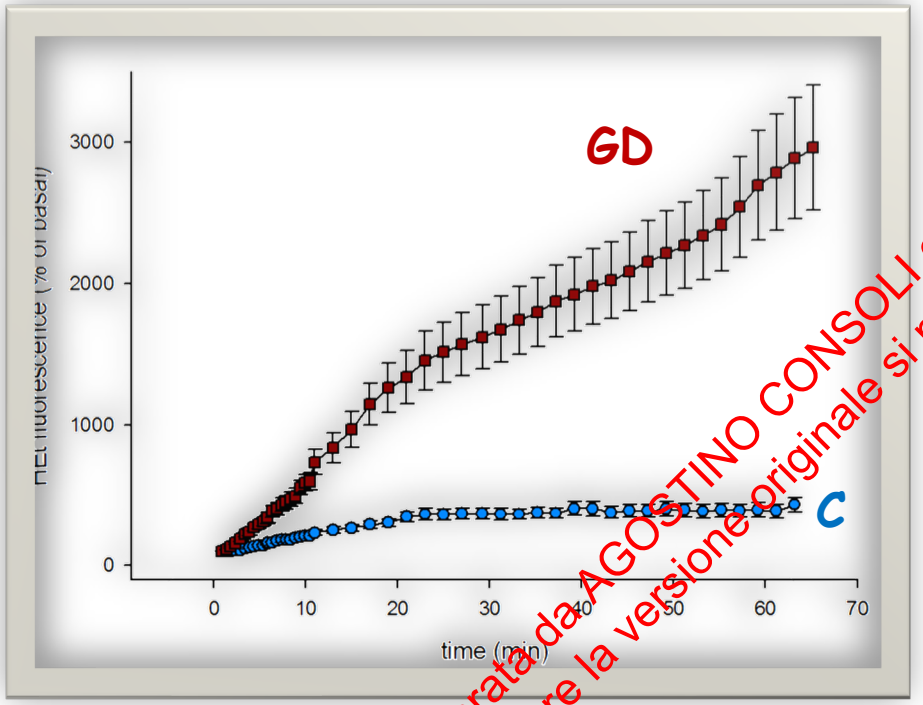
eNOS and Nitrotyrisine localization in the endothelial layer of vessels from umbilical cords obtained from women with Gestational Diabetes

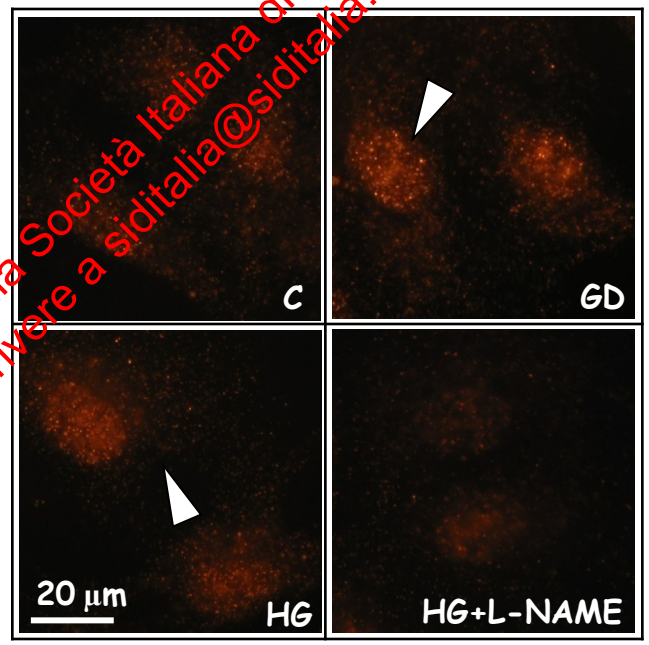


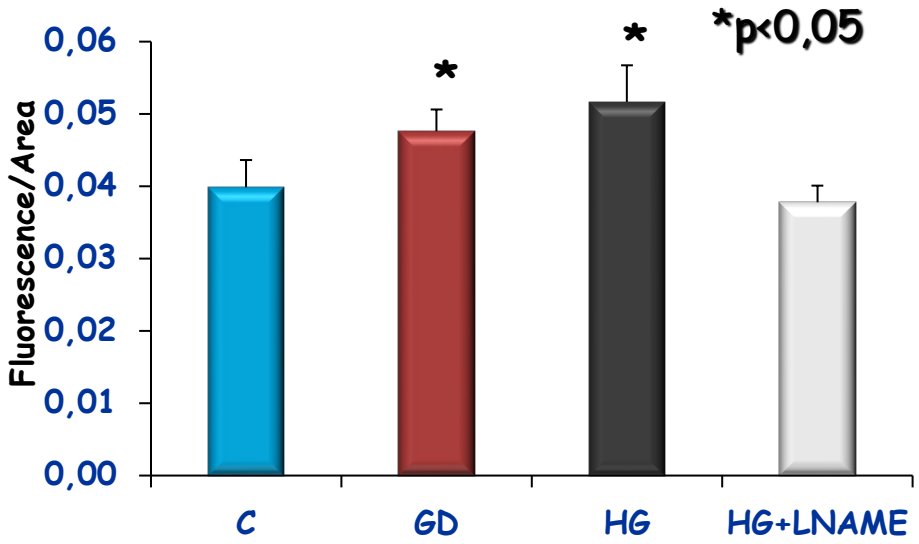
* p<0,01; **p<0,05 GD vs C

Di Fulvio et al., NMCD 2014

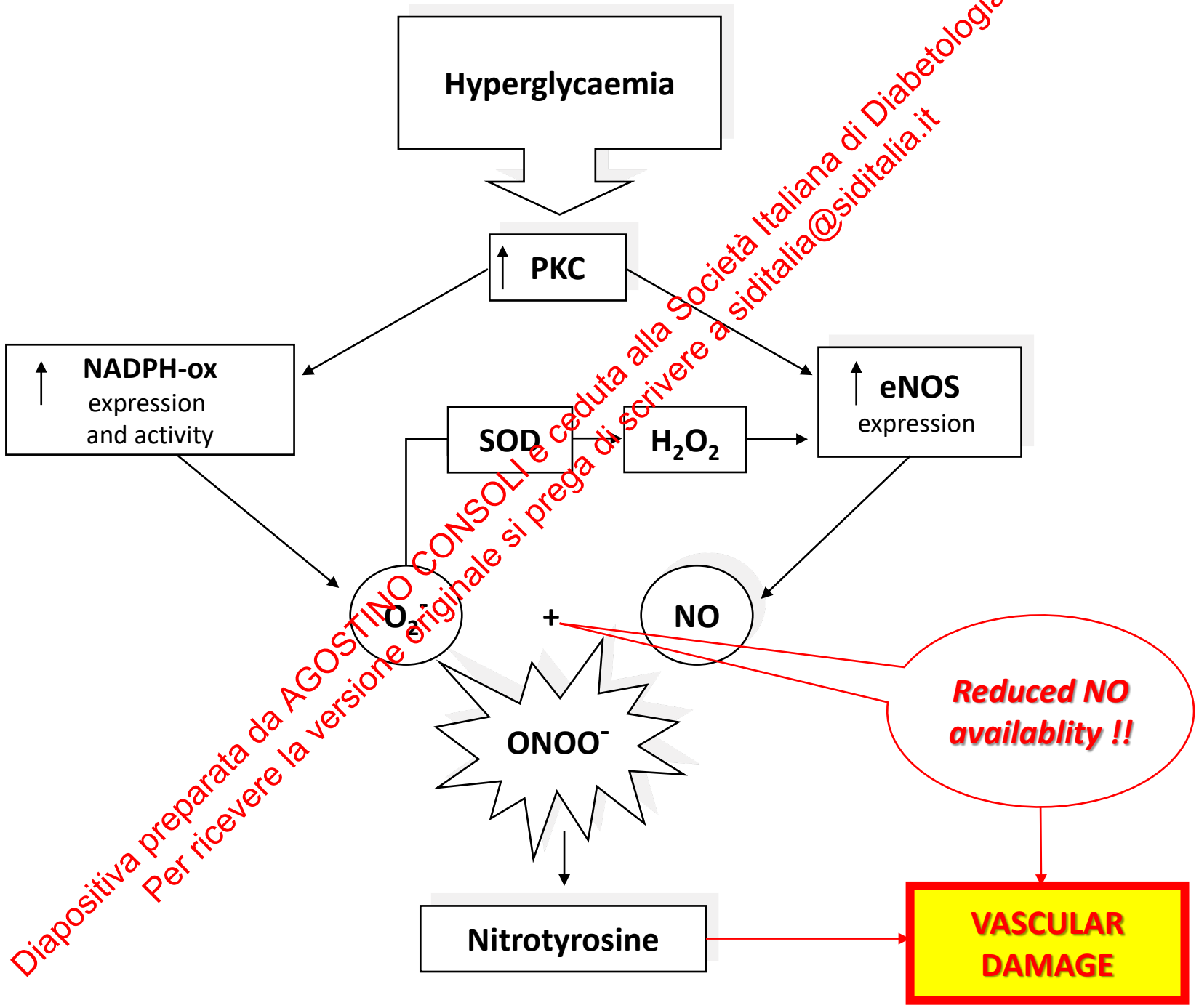
O_2^- production and nitrotyrosine immunofluorescence in HUVEC from umbilical cords obtained from women with Gestational Diabetes

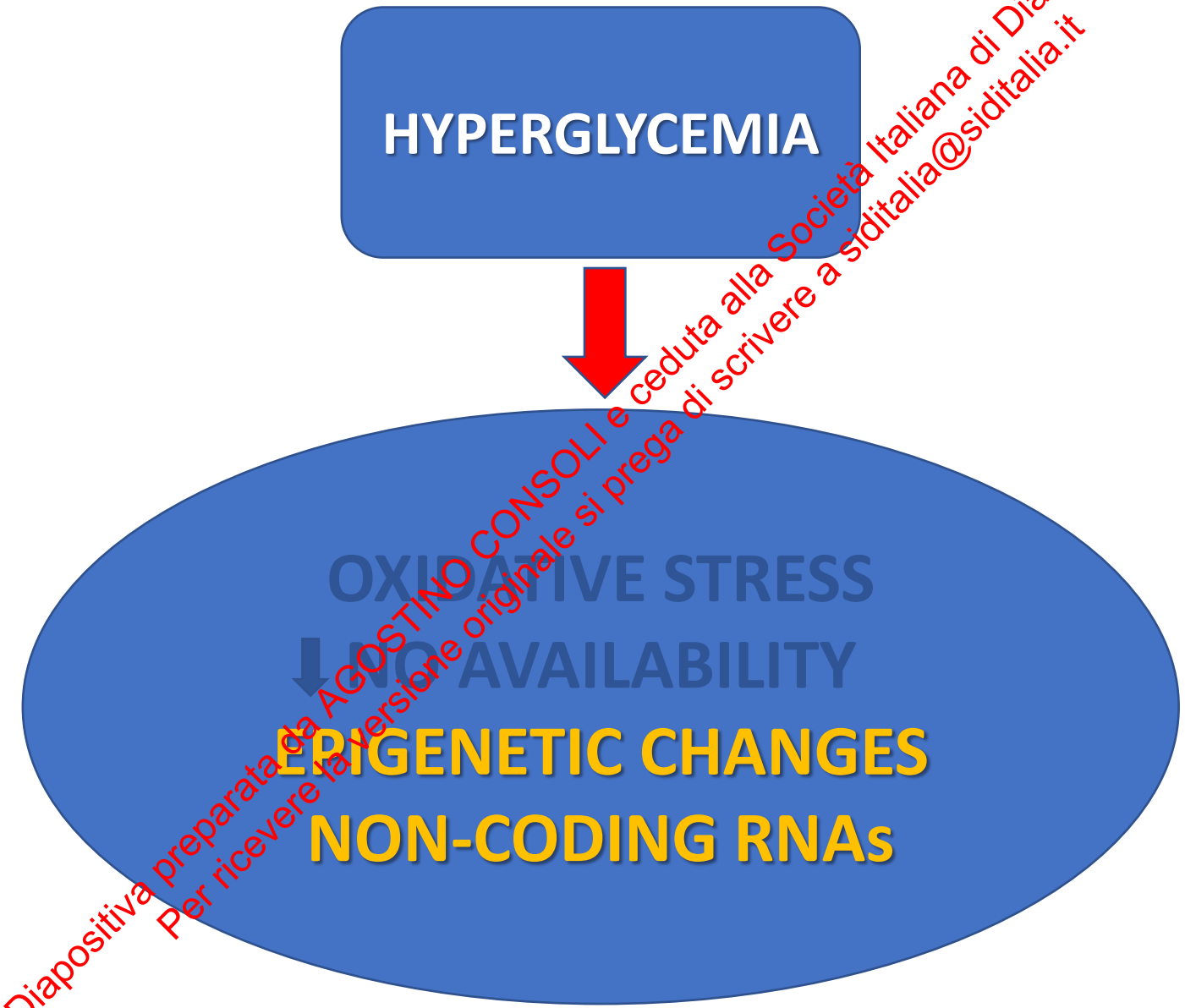


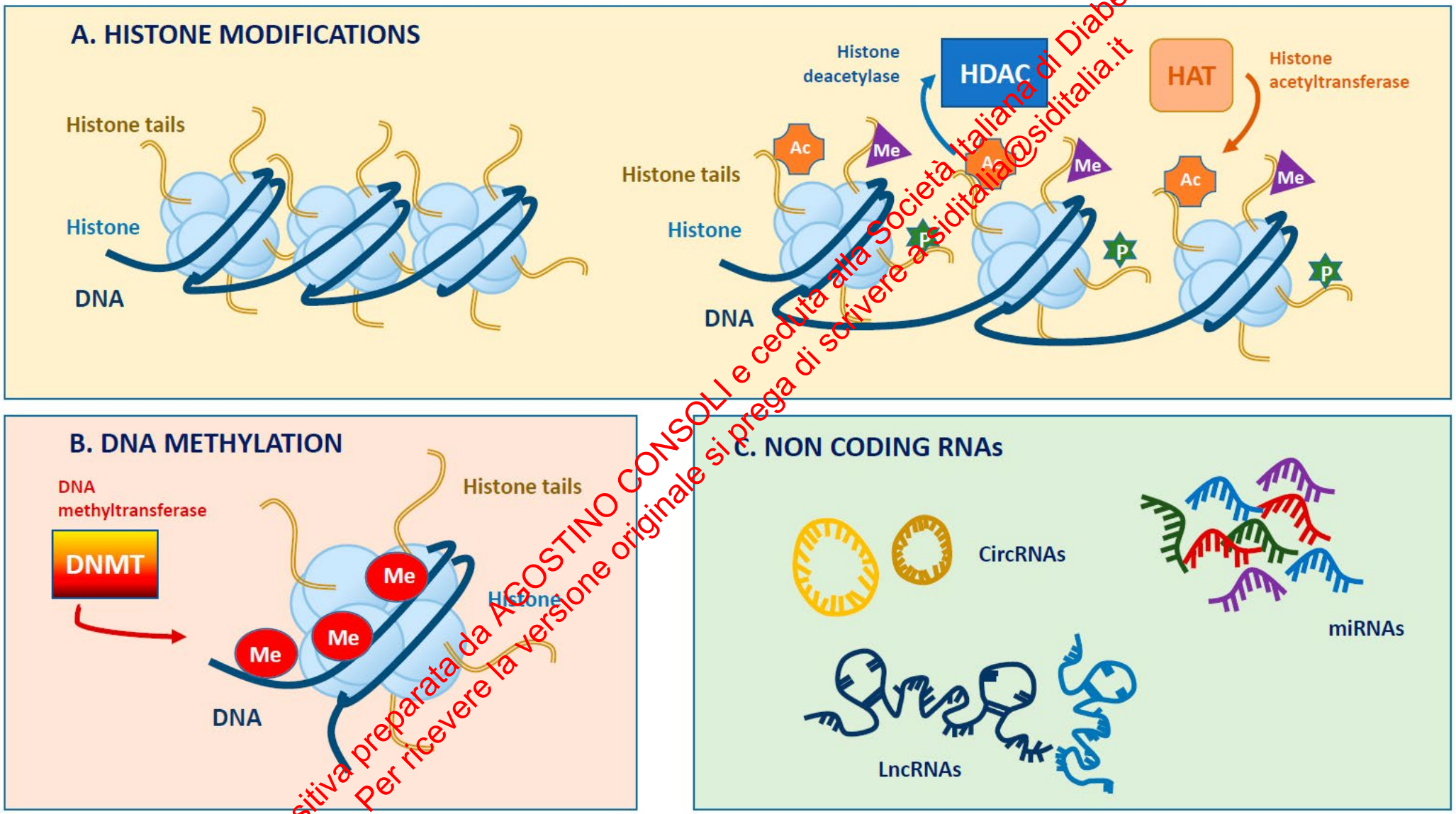




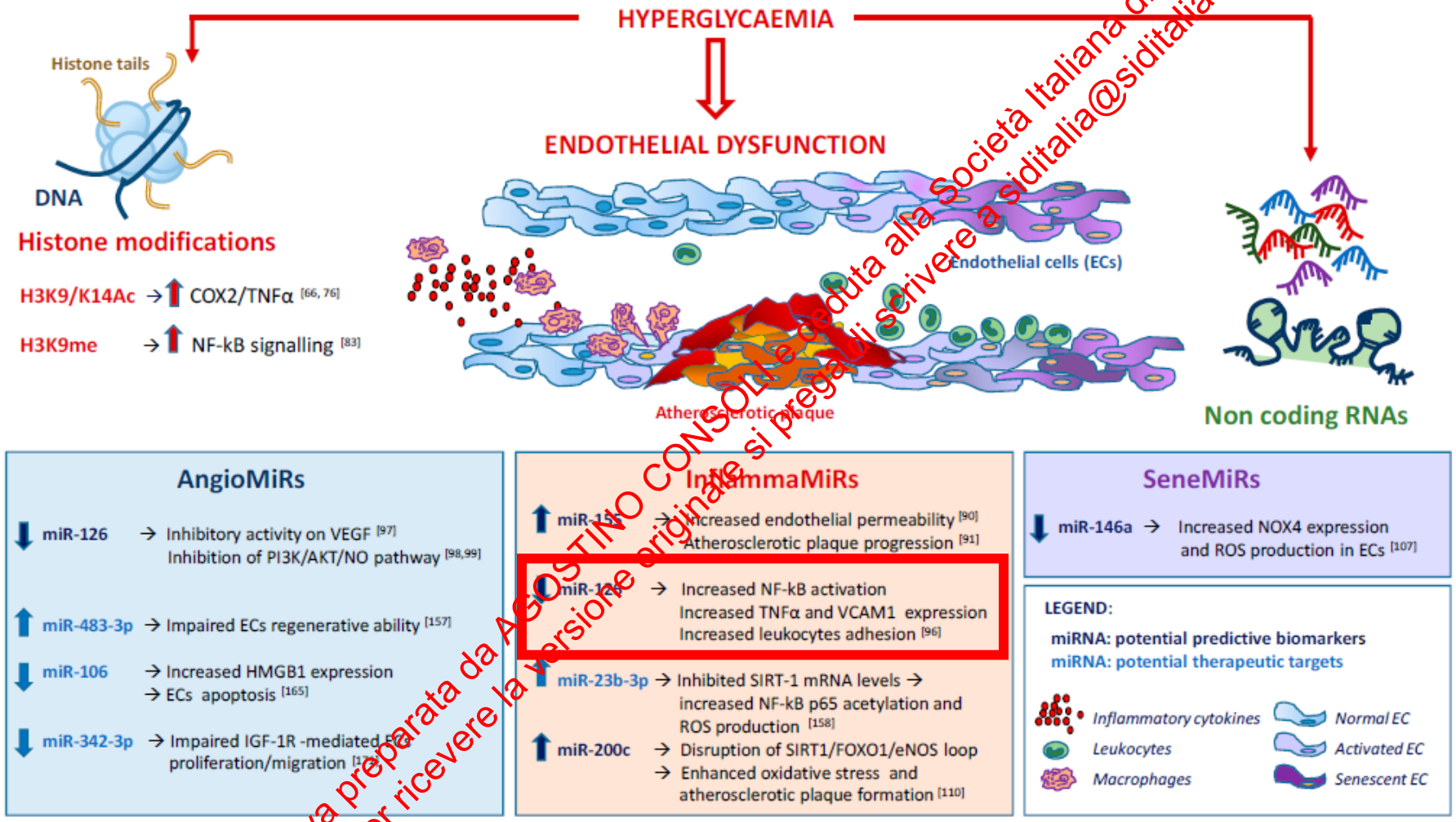
Di Fulvio et al., NMCD 2014







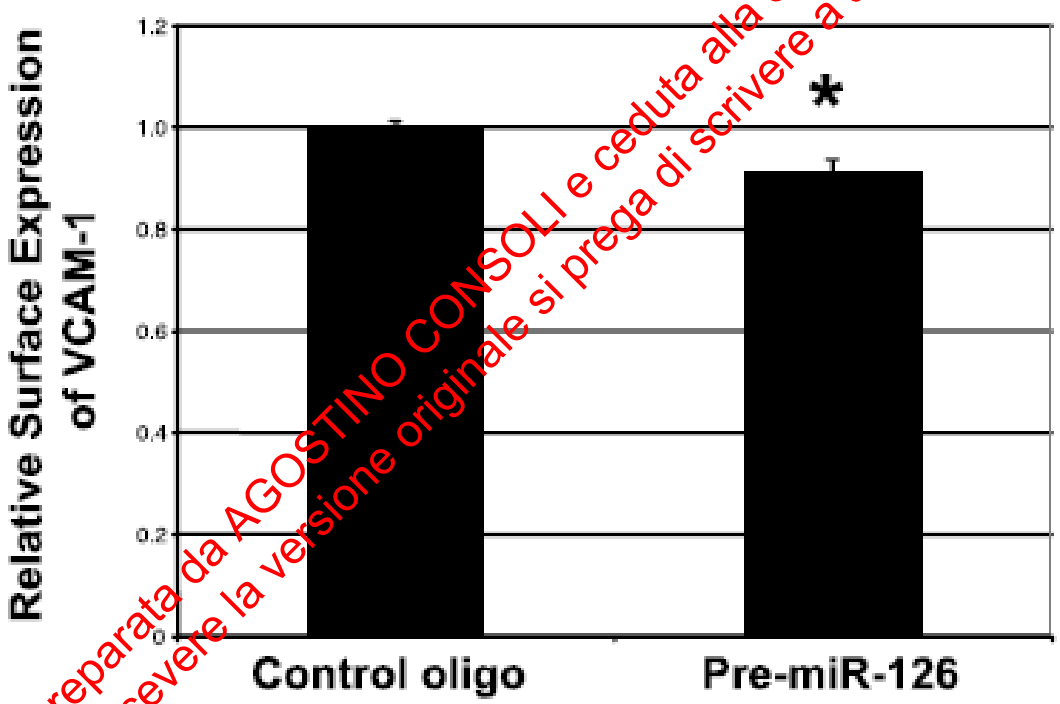
Coco C et al., Int J Mol Sci 2019



Coco C et al., Int J Mol Sci 2019

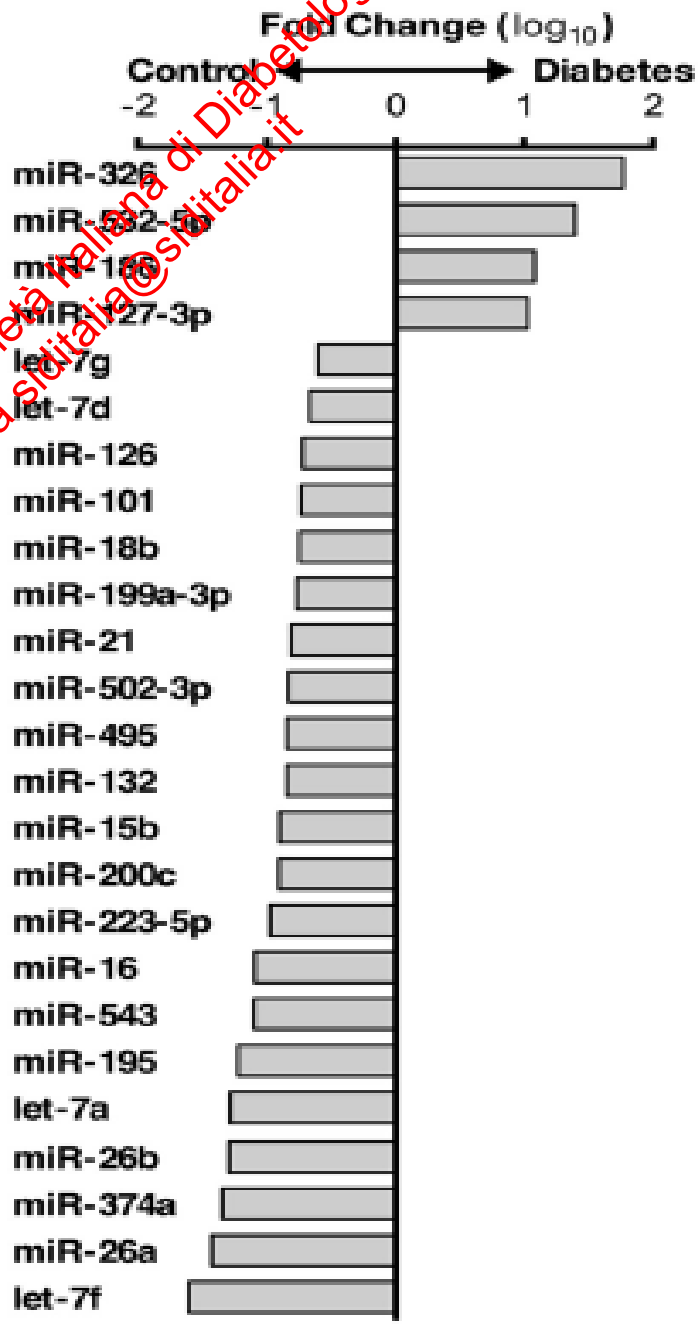
MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1

Tamia A. Harris*, Munekazu Yamakuchi†, Marcella Ferlito†, Joshua T. Mendell‡§¶, and Charles J. Lowenstein*†‖**



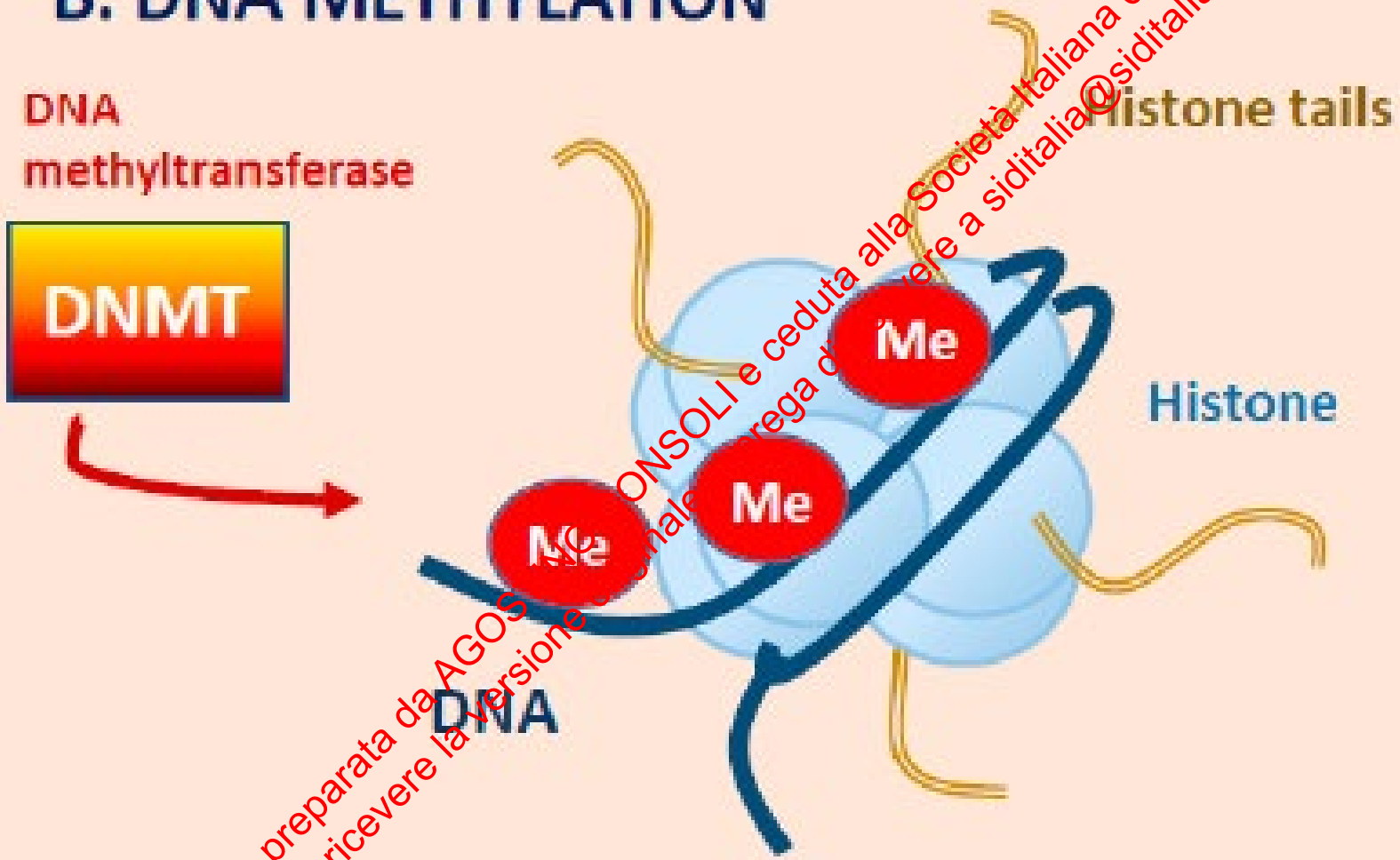
Harris TA et al, PNAS 2008

Circulating microRNA profile in diabetic patients

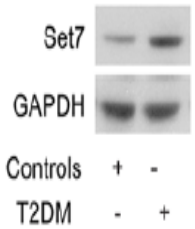


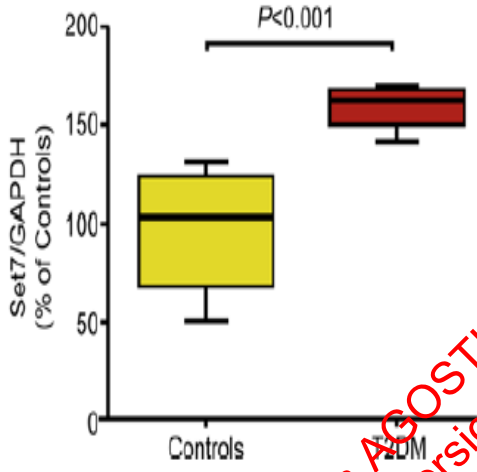
Santovito D et al, J Clin Endocrinol Metab 2014

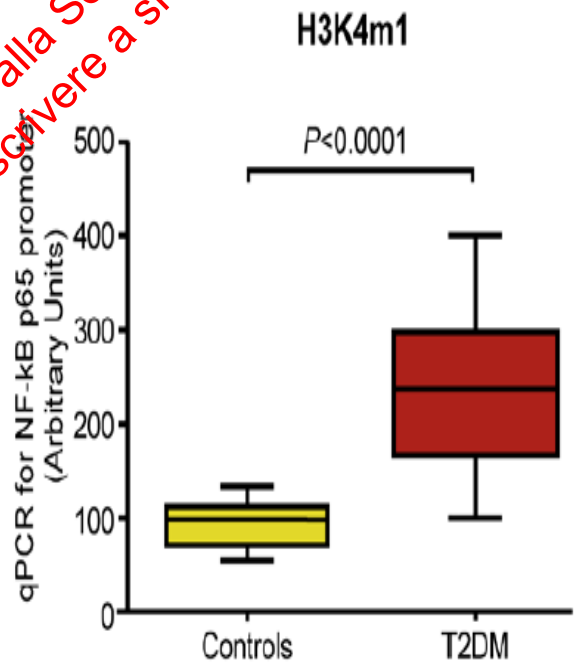
B. DNA METHYLATION



Methyltransferase Set7 expression and Histone H3K4 methylation in peripheral blood monocytes of Control and T2DM subjects

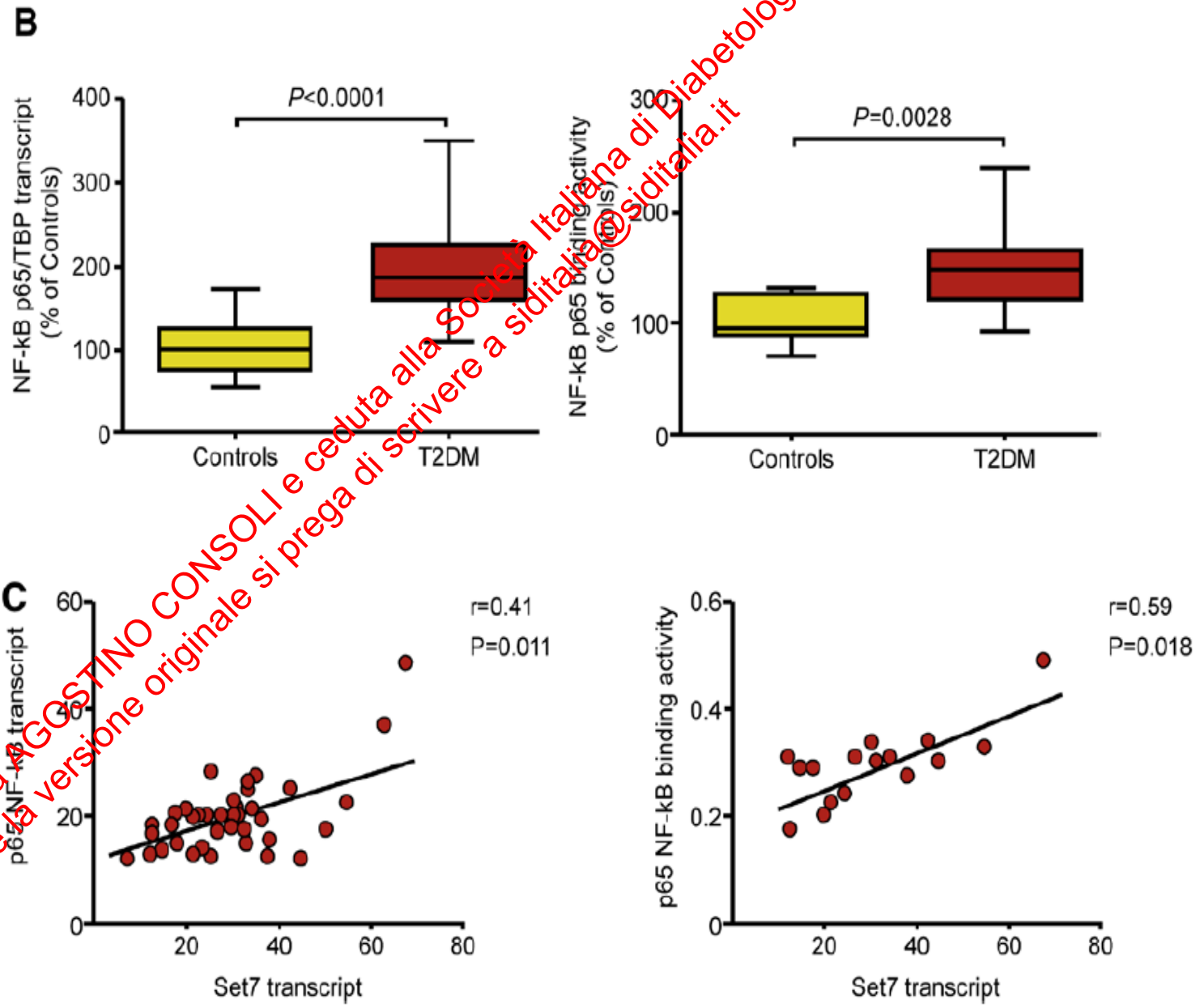






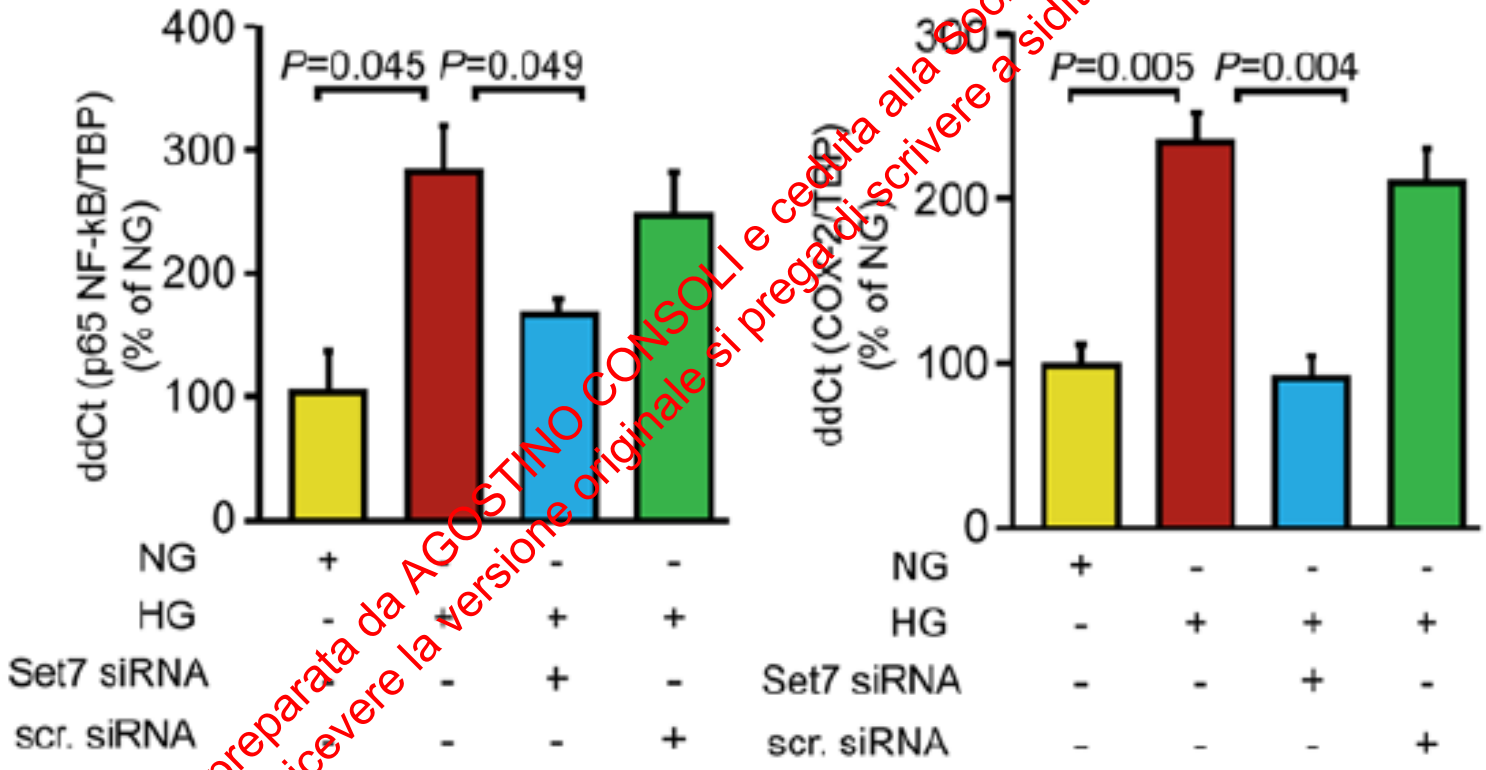
Paneni F et al, *Circ Cardiovasc Genet*. 2015

NF-kB transcript and activity are increased in T2DM subjects and correlate with methyltransferase Set7 transcript



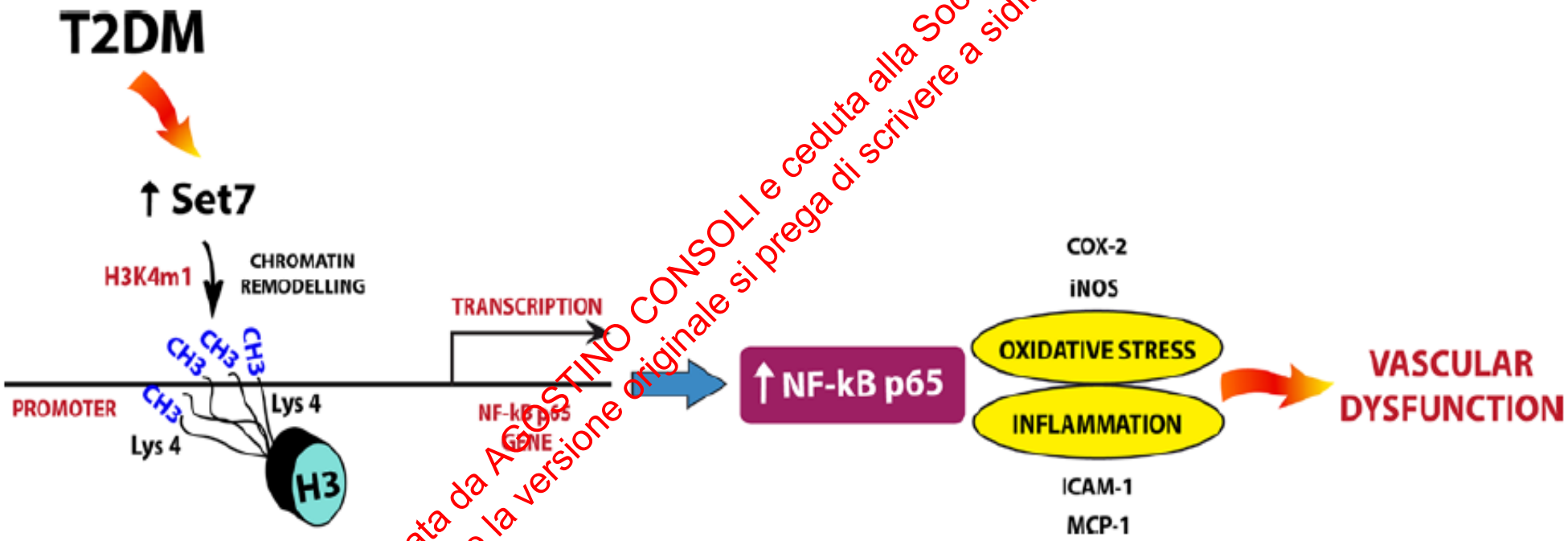
Paneni F et al, *Circ Cardiovasc Genet*. 2015

NF-kB and COX2 gene epression in HAEC exposed to high glucose concentrations in the presence or in the absence of Set7 silencing RNA



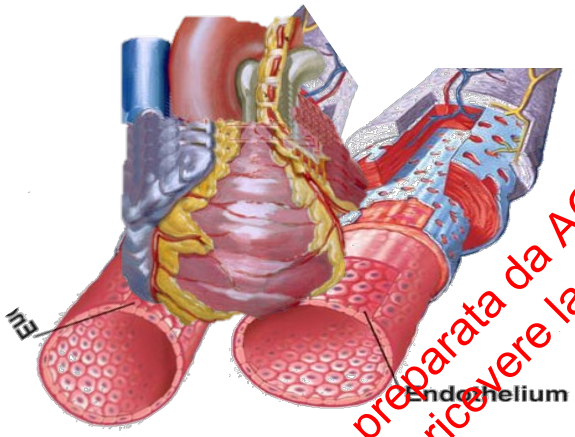
Paneni F et al, *Circ Cardiovasc Genet*. 2015

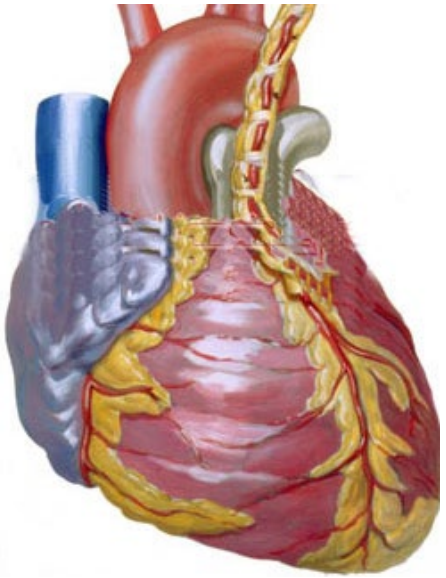
From T2DM to vascular dysfunction through epigenetic modifications



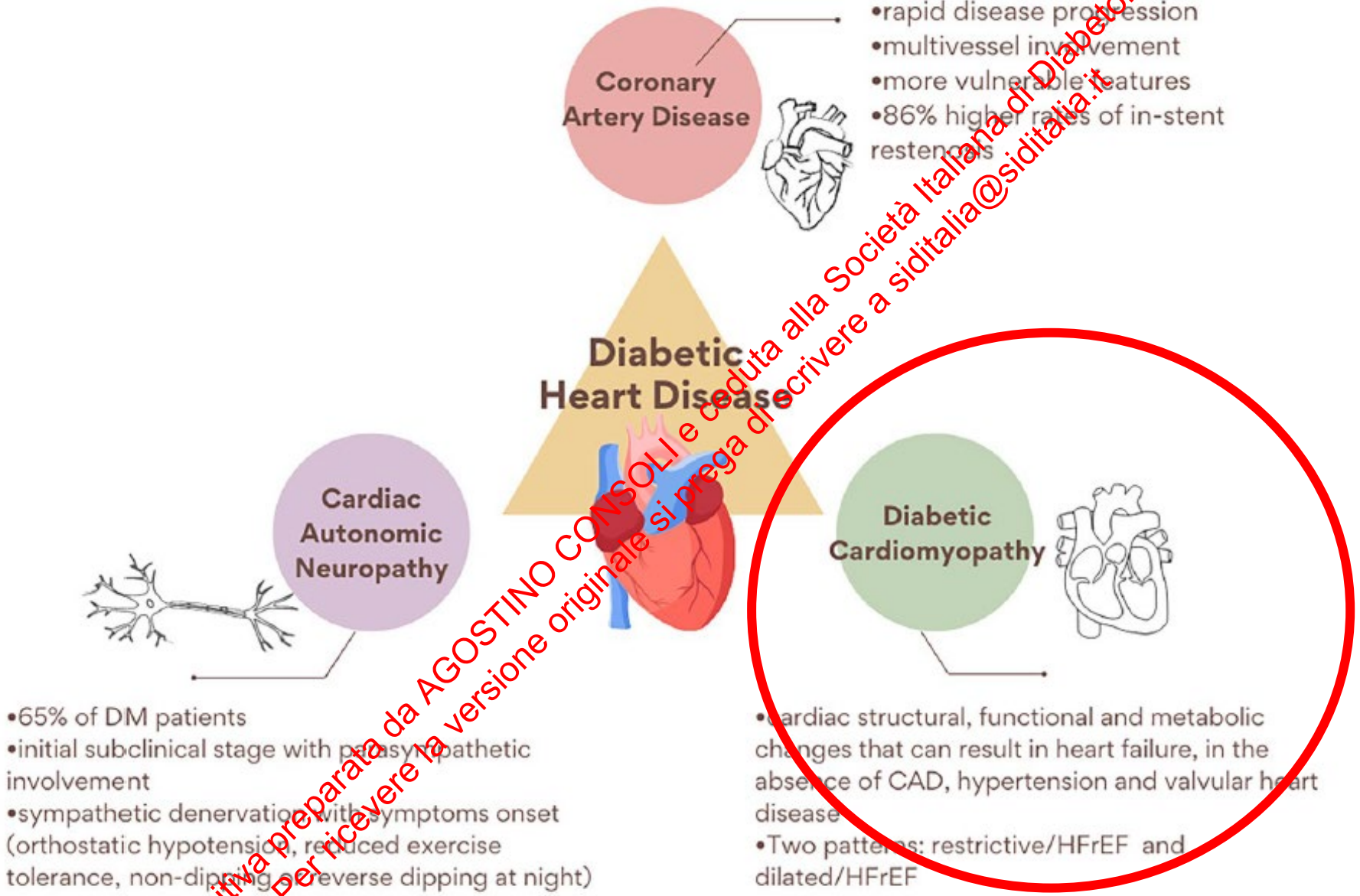
Paneni F et al, *Circ Cardiovasc Genet*. 2015

CARDIO VASCULAR RISK In T2DM

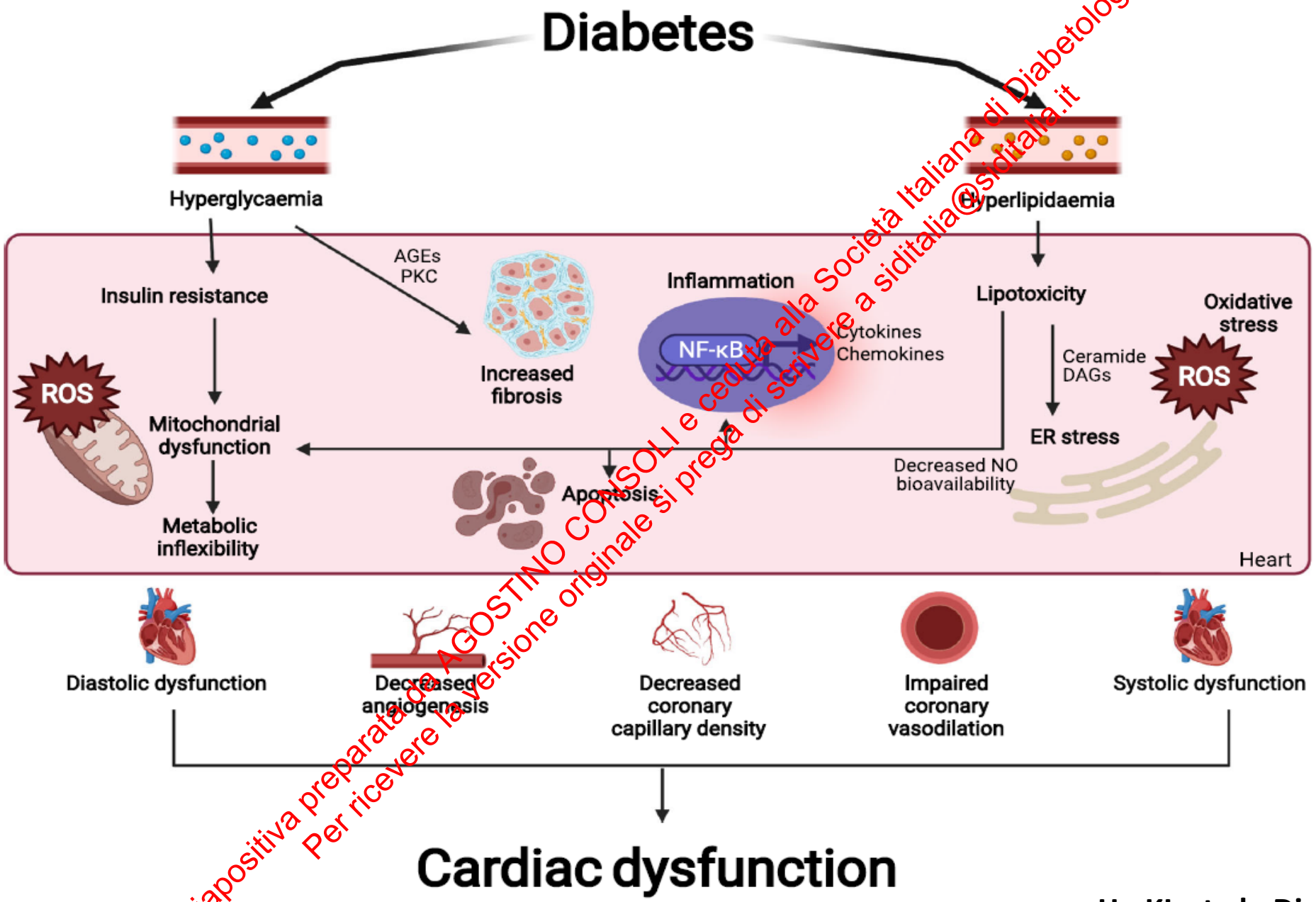




CARDIO VASCULAR RISK In T2DM



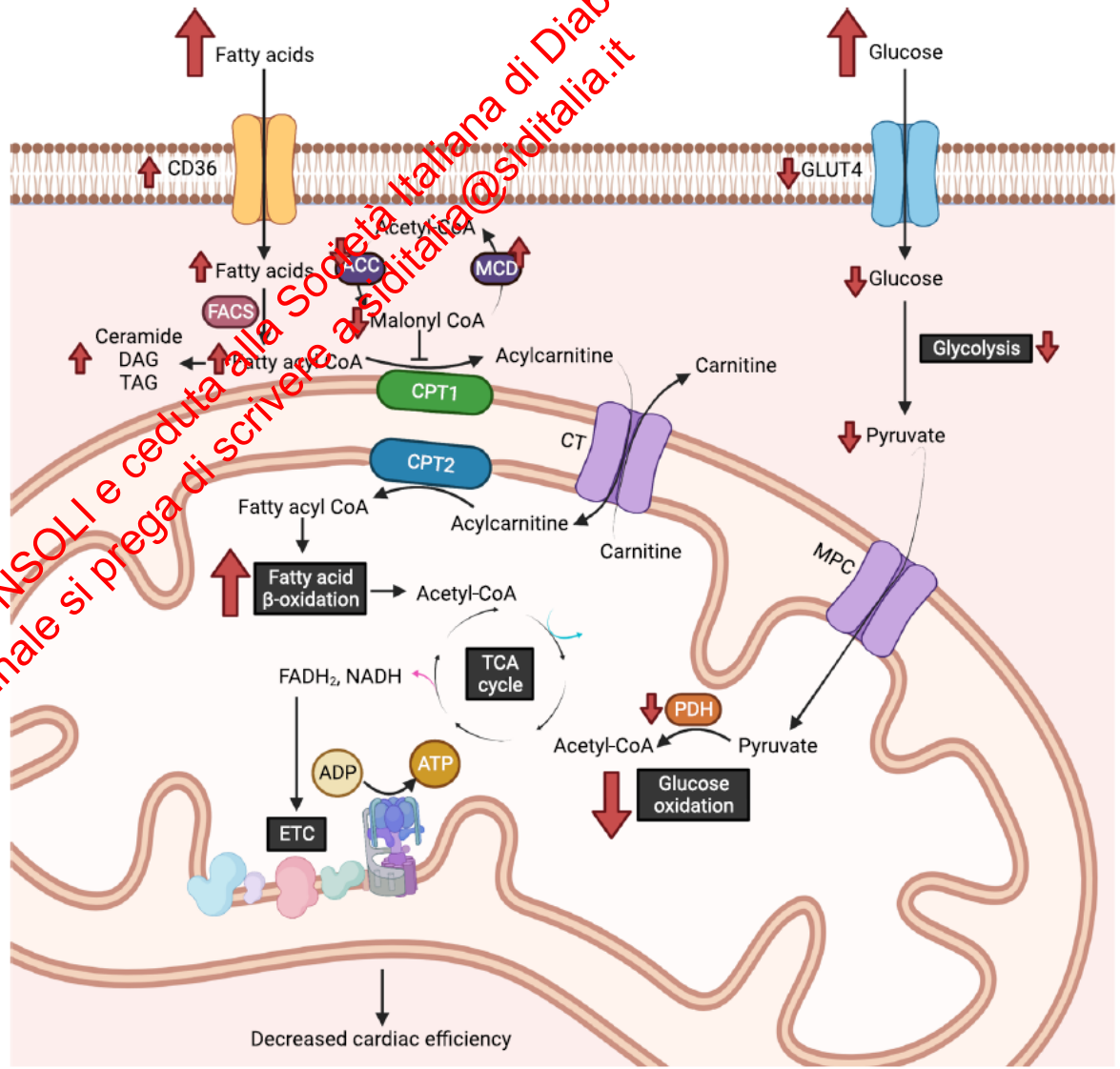
Prandi FR et al, Heart Fail Rev 2022



Ho KL et al., Diabetologia 2022

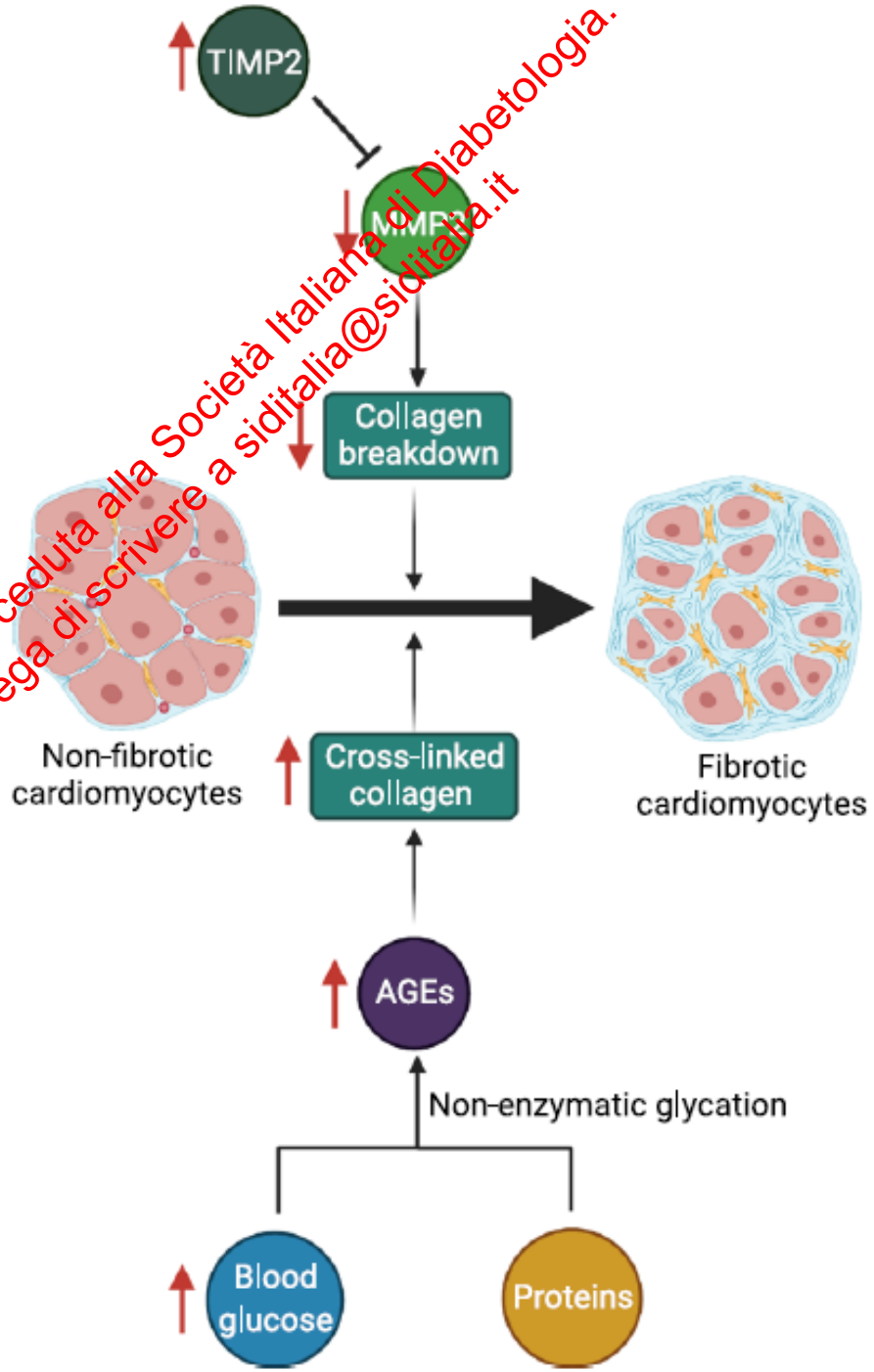
Cardiac energy metabolic changes in diabetes

- Increased myocardial fatty acid oxidation
- Decreased myocardial glucose uptake, glycolysis and glucose oxidation
- Decreased cardiac efficiency



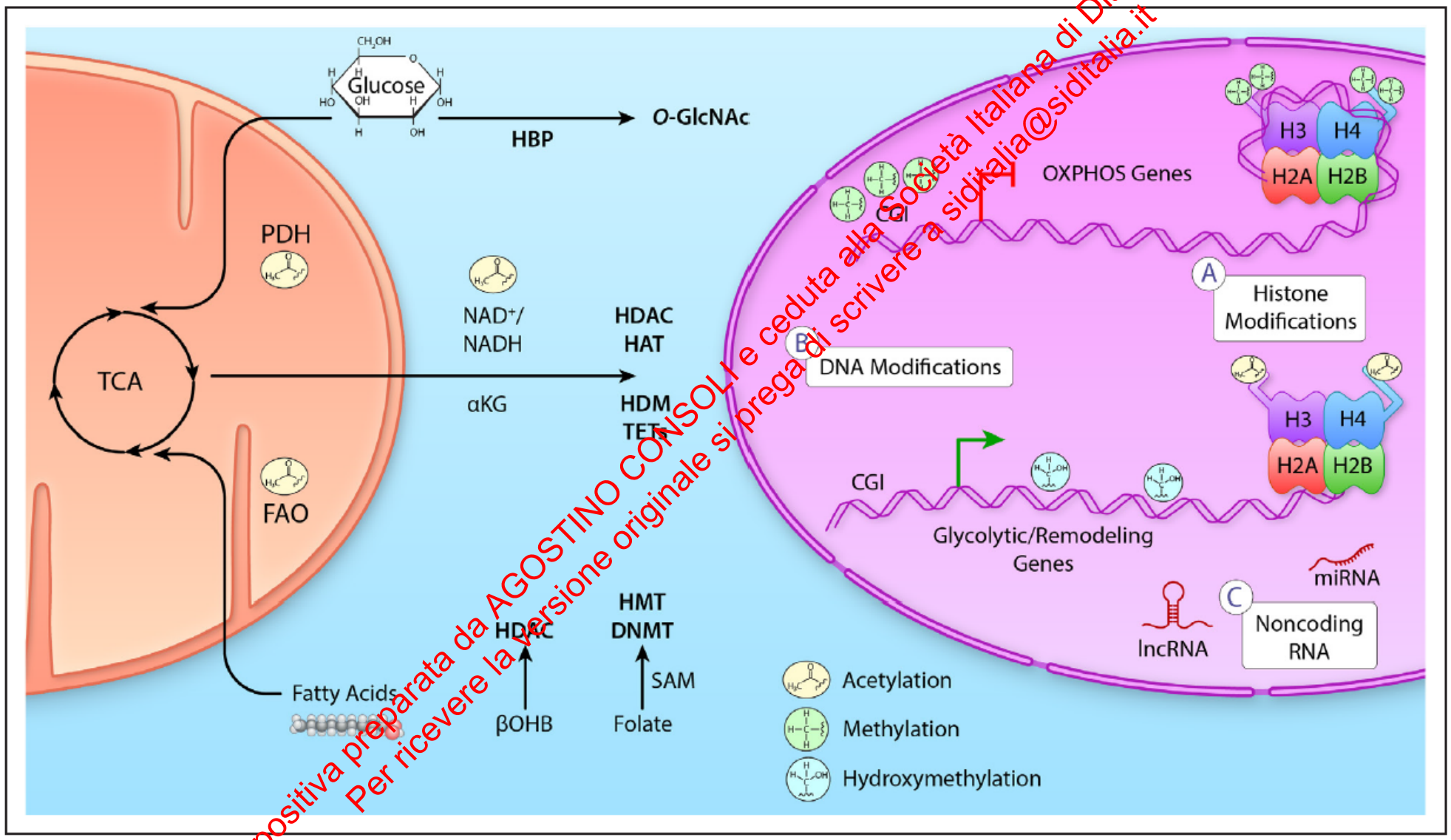
Ho KL et al., Diabetologia 2022

MECHANISMS FOR CARDIAC FIBROSIS IN DIABETES



Ho KL et al., Diabetologia 2022

Metabolic signaling to epigenetic transcriptional control in the failing heart



Lopaschuk GD et al., *Circulation Research.* 2021

Studies examining DNA methylation in DCM

Species	Genes	Methylation status	Reference
DCM patients	RASSF1A	Hypermethylation	Tao et al. (2019)
STZ-induced diabetic rats	LXRα	Demethylation	Cheng et al. (2011)
Type 2 diabetes patients	Keap1	Demethylation	Li et al. (2015)
STZ-induced diabetic rats	AT1b	Undermethylated	Bogdarina et al. (2007)
Type 2 diabetes patients	HIF3A	DNA methylation	Guo et al. (2021)
db/db mice	Histone H3	H3K9 and H3K23 acetylation H3K4 dimethylation	Gaikwad et al. (2010)
Diabetic rats	p21(Waf1/Cip1)	DNA methylation	Monkemann et al. (2002)
Type 2 diabetes patients and STZ-induced diabetic mice	JunD	Hypermethylation, Post-translational modification	Hussain et al. (2020)
STZ-induced diabetic mice	Sirt1 and DNMT3b	H3 acetylation and DNA Demethylation	Costantino et al. (2018)

Deng J et al. Frontiers in Cell and Developmental Biology 2021

miRNAs potentially involved in the pathogenesis of DCM.

Mechanism	miRNAs	Regulated genes	Species	Reference
Hypertrophy	↓miR-1	MEF2a/Gata4	HG-treated NRCMs and diabetic rats	Ikeda et al. (2009)
	↓miRNA-146a	DLST	HG-treated NRCMs	Heggermont et al. (2017)
	↓miR-133a	SCK1/IGF1R	STZ-induced diabetic mice	Feng et al. (2010)
	↓miR-150	p300	Diabetic rats	Duan et al. (2013)
	↑miR-200c	DUSP-1	HG and STZ-induced diabetic rats	Singh et al. (2017)
Fibrosis	↓miR-152-3p	Wnt1/β-catenin	HG-treated NRCMs	Xu et al. (2021)
	↑miR-26a/b-5p	GAS5	STZ-induced diabetes model	Zhu et al. (2021a)
	↓miR-29b-3p	circHIPK3	STZ-induced diabetes model	Wang et al. (2021)
	↓miR-223	NLRP3	HG-induced cardiomyocyte injury mode	Xu et al. (2020)
	↓miR-155	TGF-β1	STZ-induced diabetes model	Zhang et al. (2016)
	↓miR-21	DUSP8	HG-induced diabetes model	Liu et al. (2014a)
Apoptosis	↑miR-133a	caspase-3, caspase-8	Type 2 diabetic rats	Habibi et al. (2020)
	↑miR-181a-5p	JAK2/STAT3	Human cardiomyocytes	Tan et al. (2021)
	↑miR-146a	MAPK	H9C2 cells	Chu et al. (2021)
	↑miR-140-5p	HDAC4/Neat1	STZ-induced diabetic mice	Zou et al. (2019)
	↓miR-1	IGF1	Diabetic rats	Delfan et al. (2020)
	↓miR-675	VDAC1	STZ-induced diabetic rats	Li et al. (2016b)
Autophagy	↑miR-221-3p	GAS5	STZ-induced diabetic rats and HG treated H9C2	Chen and Zhang, (2021)
	↑miR-551b-5p	DCRF	STZ-induced diabetic rats	Feng et al. (2019)
	↑miR-34a	Bcl2 and Sirt1	HG treated H9C2	Zhu et al. (2019)
		-	STZ-induced diabetic mice and HG- induced cardiomyocytes	Ni et al. (2020)
Oxidative stress	↓miR-128	PIK3R1/Akt/mTOR	C57 BL/6 mice	Zhan et al. (2021)
	↓MiR-22	Sirt1	HFD and STZ-induced diabetic mice	Tang et al. (2018)
	↓miR-1 and ↓miR-499	RyR2	Diabetic rats	Yildirim et al. (2013)
	↓miR-150	P300	Diabetic rats	Duan et al. (2013)
Inflammation	↓miR-130	PPAR-γ	H9C2 cells	Chu et al. (2018)
	↑miR-150-5p	Smad7	HG- induced diabetes model	Che et al. (2020)
	↓miR146a	IL6, TNFα, IL-1β, MCP-1	Human cardiac microvascular endothelial cells and STZ-induced diabetes	Feng et al. (2017)
	↓miR-214-3p	KCNQ1	STZ-induced diabetes model and cardiomyocytes treated with HG	Yang et al. (2018)
	↓miR-675	VDAC1	STZ induced diabetic rats	Li et al. (2016b)

Deng J et al. Frontiers in Cell and Developmental Biology 2021

….However, our current insight is only a drop in the bucket regarding the role of extracellular ncRNAs in DCM

Further studies are needed to identify more ncRNAs involved and the underlying mechanism.

Then, the existing techniques could poorly label and trace the dynamic movement of extracellular ncRNAs, which limit further research in this field.

Moreover, large-scale and multi-center population studies are required for the identification of ncRNAs in body fluid as sensitive and specific biomarkers of DCM.

Last but not least, ongoing researches are expected to provide powerful tools for the routine clinical application of ncRNA-based therapy in DCM.

Yin Z & Chen C, J Cardiovasc Transl Res 2022

Abbiamo assistito ad un «cambio di paradigma» nel trattamento del DM2, con uno «shift» dal treat to target al treat to benefit. Ma in questo contesto, quanto conta, per proteggere il cuore della persona con diabete, raggiungere in sicurezza target ambiziosi di controllo glicemico ?

A. **MOLTISSIMO** (***e' necessario***)

B. **MOLTO** (***e' di fondamentale aiuto***)

C. **ABBASTANZA** (***puo' essere di aiuto***)

D. **RELATIVAMENTE POCO** (***la protezione e' legata quasi totalmente ad azioni dei farmaci innovativi indipendenti dalla glicemia***)