L'insulinoterapia nel diabete con danno renale: quali novità?

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Ospedale Maggiore Policlinico

Conflitti di interesse

- Eli Lilly
- Novo Nordisk
- Astra Zeneca

Agenda

CKD e metabolismo del glucosio

Tipi di insulina e schemi terapeutici

Studi di efficacia e safety

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CKD e metabolismo del glucosio

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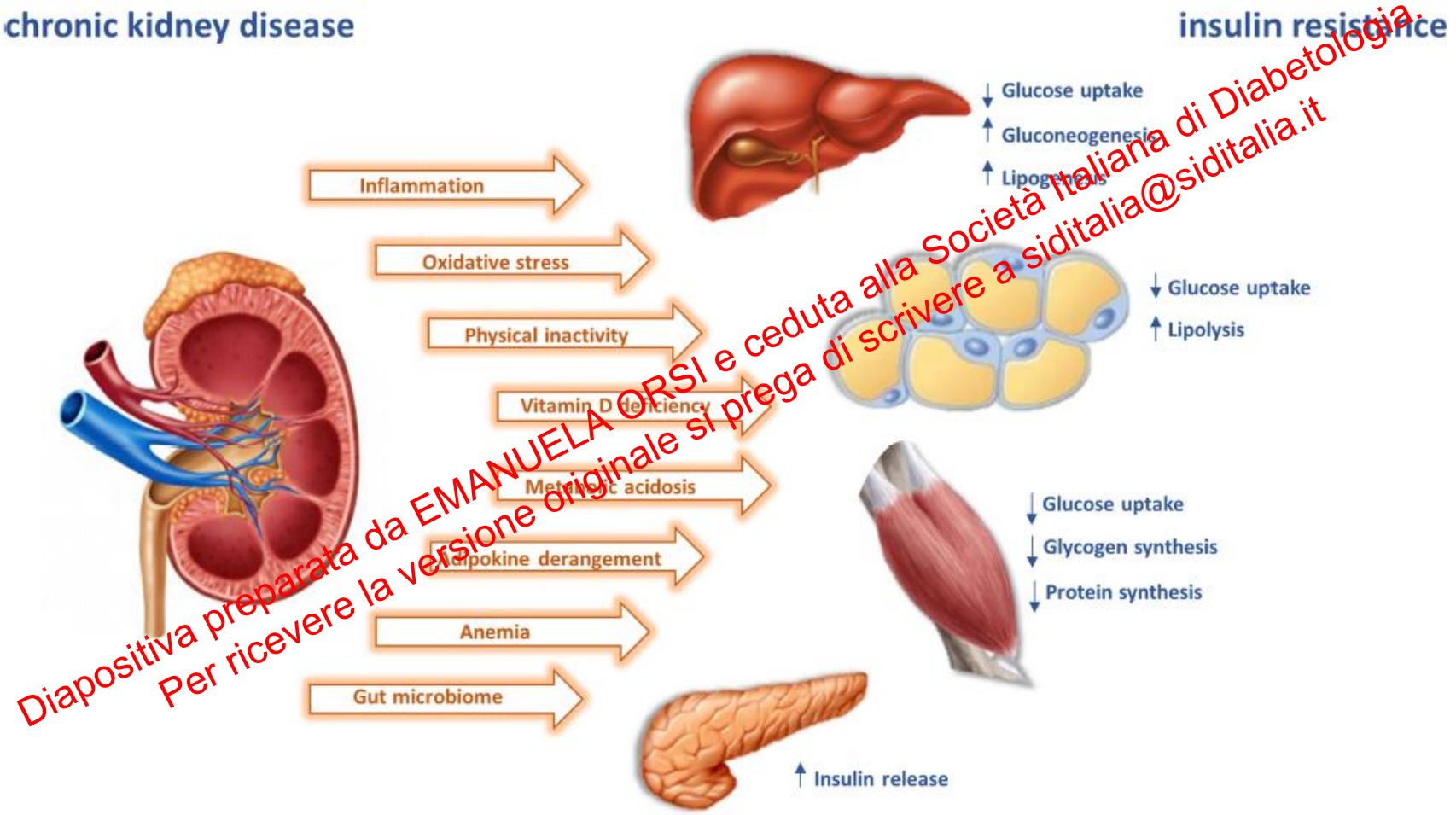
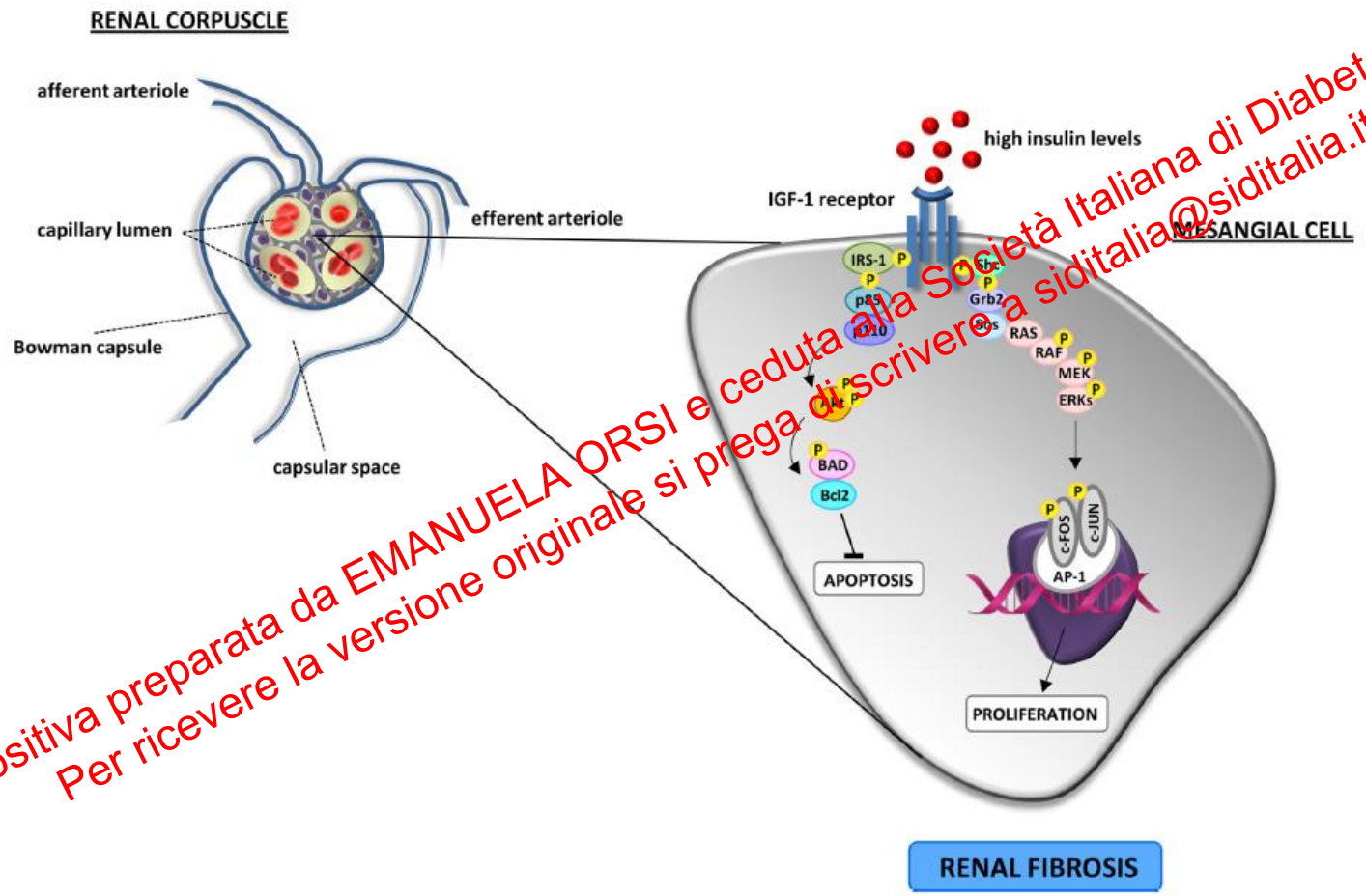
Insulin resistance in chronic kidney disease

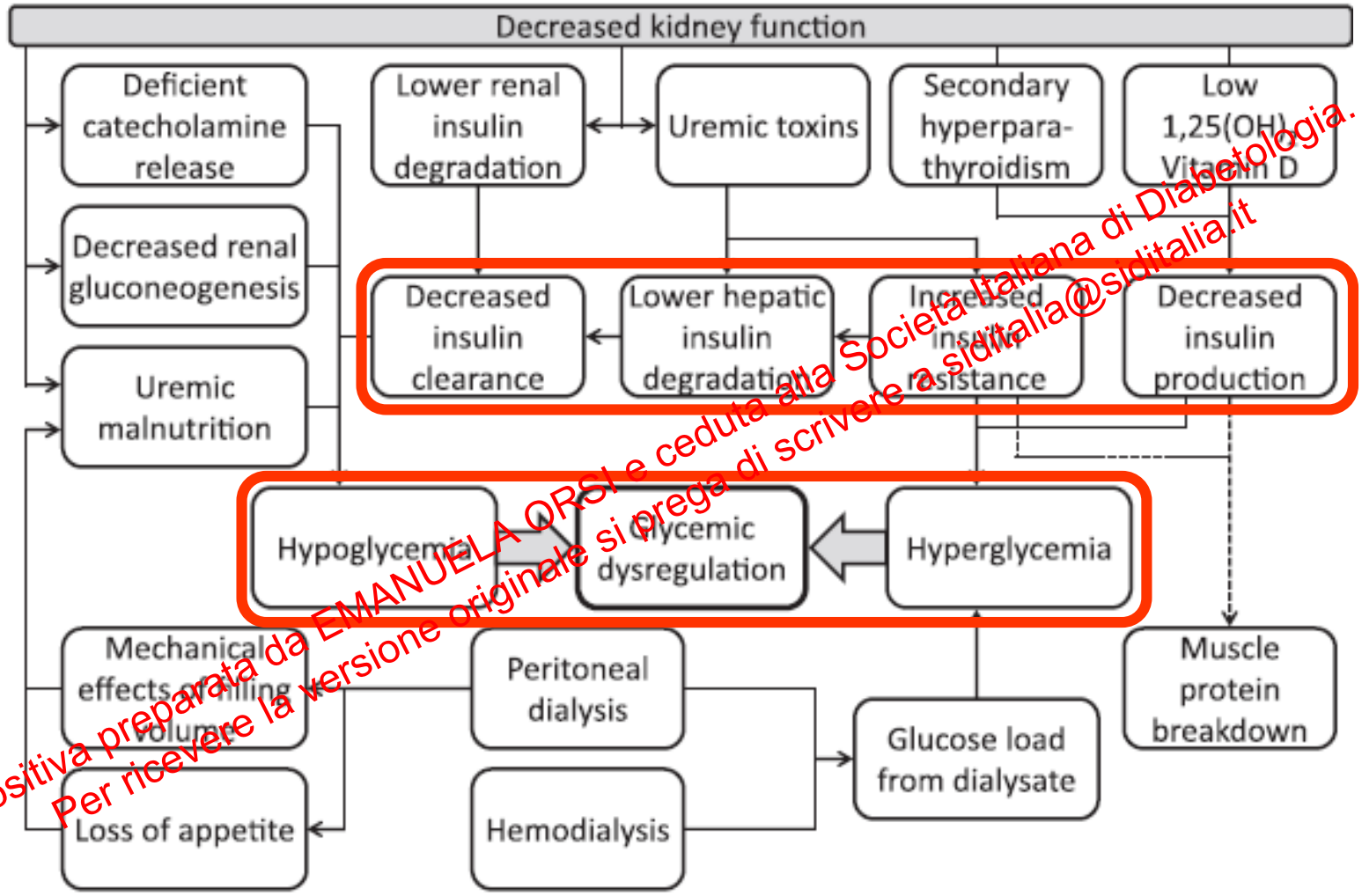


Spoto B et al, Am J Physiol Renal Physiol, 2016

Insulin resistance and kidney damage

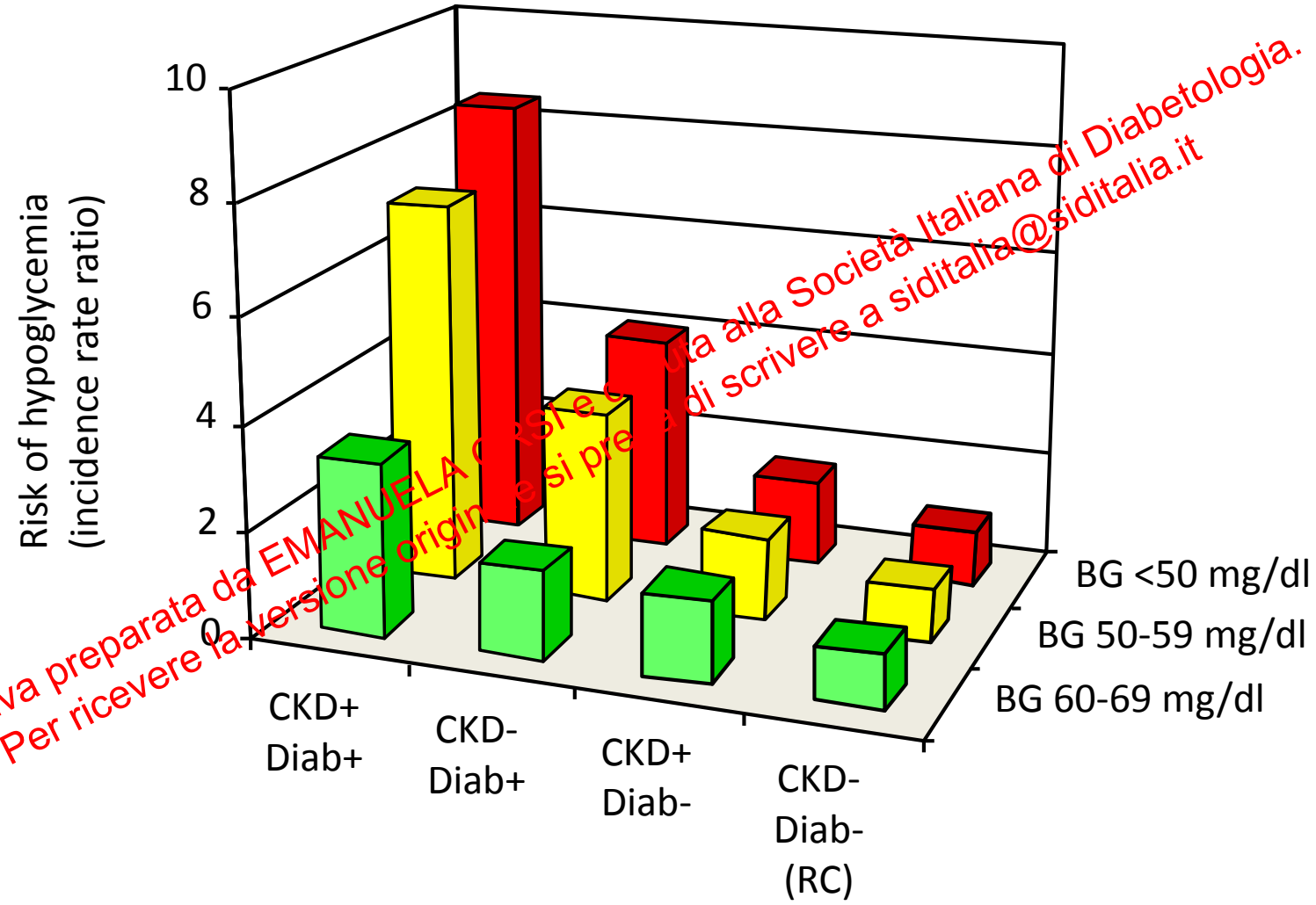


Spoto B et al, Am J Physiol Renal Physiol, 2016



Williams ME & Garg R, Am J Kidney Dis, 2014

Kidney dysfunction and risk of hypoglycemia



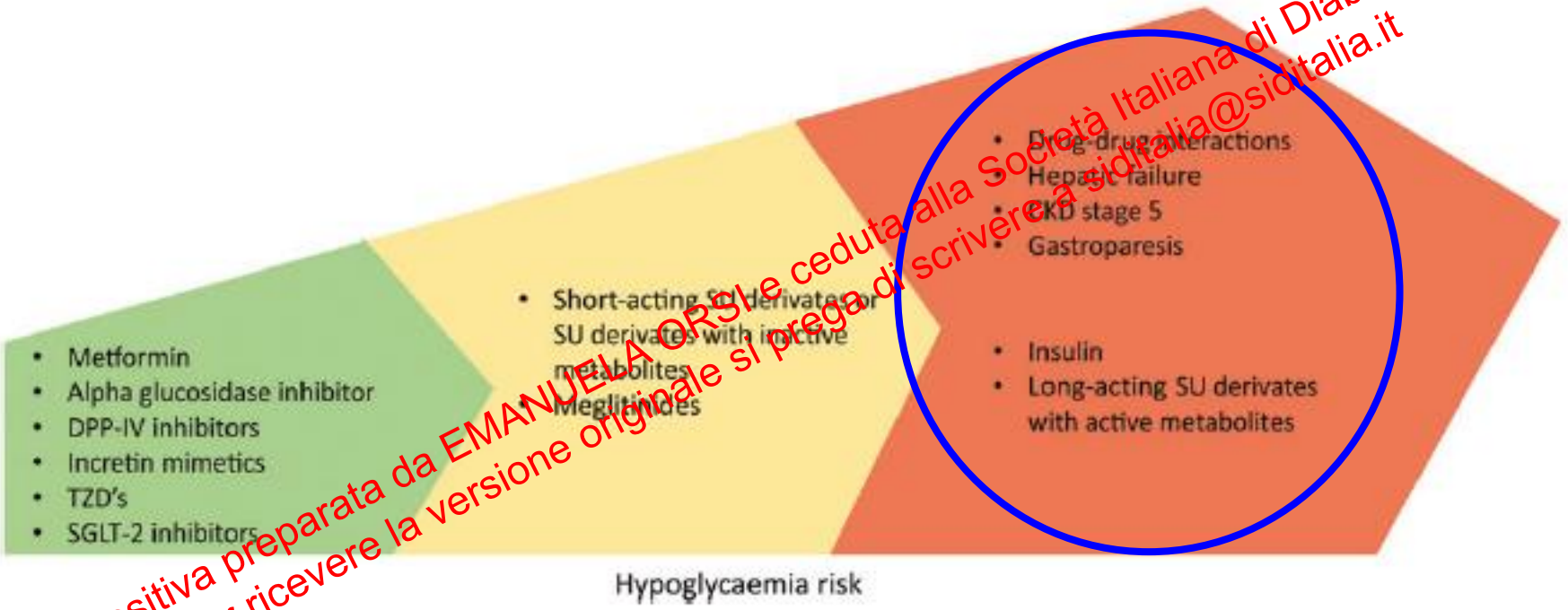
Moen MF et al. Clin J Am Soc Nephrol. 2009; 4:1121-1127

Kidney dysfunction and risk of hypoglycemia

- Decreased renal clearance of insulin
- Decreased hepatic clearance of insulin
- Impaired renal insulin degradation
- Increased insulin half-life due to conditions other than the above
- Decline in renal gluconeogenesis
- Deficient catecholamine release
- Other impacts of uremia on glucose homeostasis
- Diminished food intake due to anorexia, diabetic gastroparesis, etc.
- Protein-energy wasting (malnutrition-inflammation complex)
- Loss of body weight and fat mass
- Co-morbid conditions
- Hypoglycemia during hemodialysis treatments
- Effects of peritoneal dialysis on glucose metabolism
- Prescribed medications
- Imposed dietary restrictions
- Apparently low HbA_{1c} due to confounding by uremia or anemia

Kalantar-Zadeh K et al. J Ren Nutr. 2009; 19:33-37

Kidney dysfunction and risk of hypoglycemia



Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant . 2015; 30:ii1-ii142

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CKD e metabolismo del glucosio

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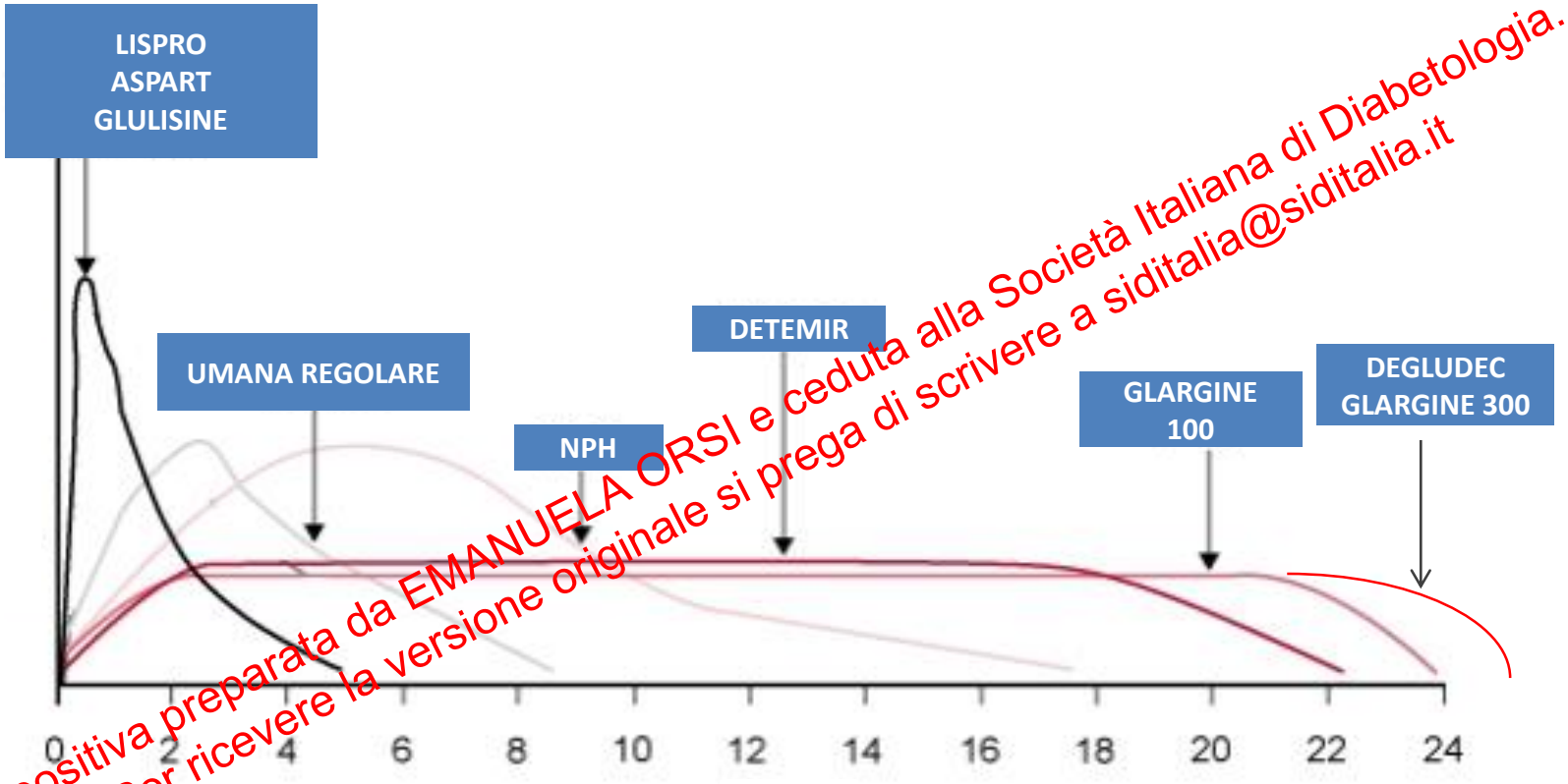
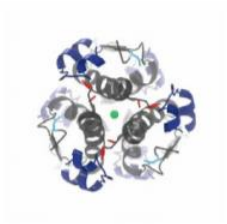
Insulin type	Insulin name	Onset of action	Peak effect	duration	kinetic	injection
Rapid action	regular	15-30’	2-4 h	6-8 h	Prandial Bolus	IV insulin infusion
Intermediate Action	NPH	1-2 h	4-8	12-18 h	basal	1-2/die
Rapid Action analogue	Lispro Aspart Glulisine	5-15’	1-2 h	4-6 h	Prandial Bolus	Can be taken after meal
Long acting analogue	Glargine100 Detemir Degludec Glargine 300	2 h	No peak	20-24 h 16-20 24 24	basal	1/die

Tipi di insulina



Ultra rapid insulin profiles: Faster Insulin Aspart (FIASP)

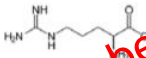


Insulin aspart

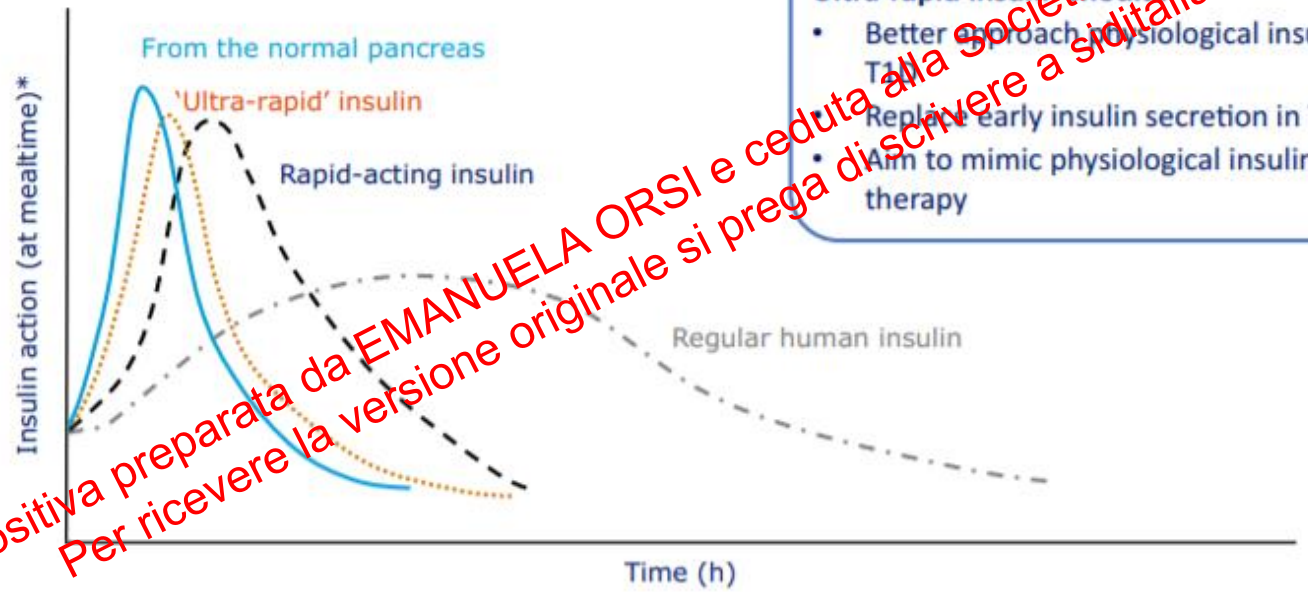
Niacinamide: absorption modifier

Vitamin B3

L-Arginine: added for stability



Naturally occurring amino acid



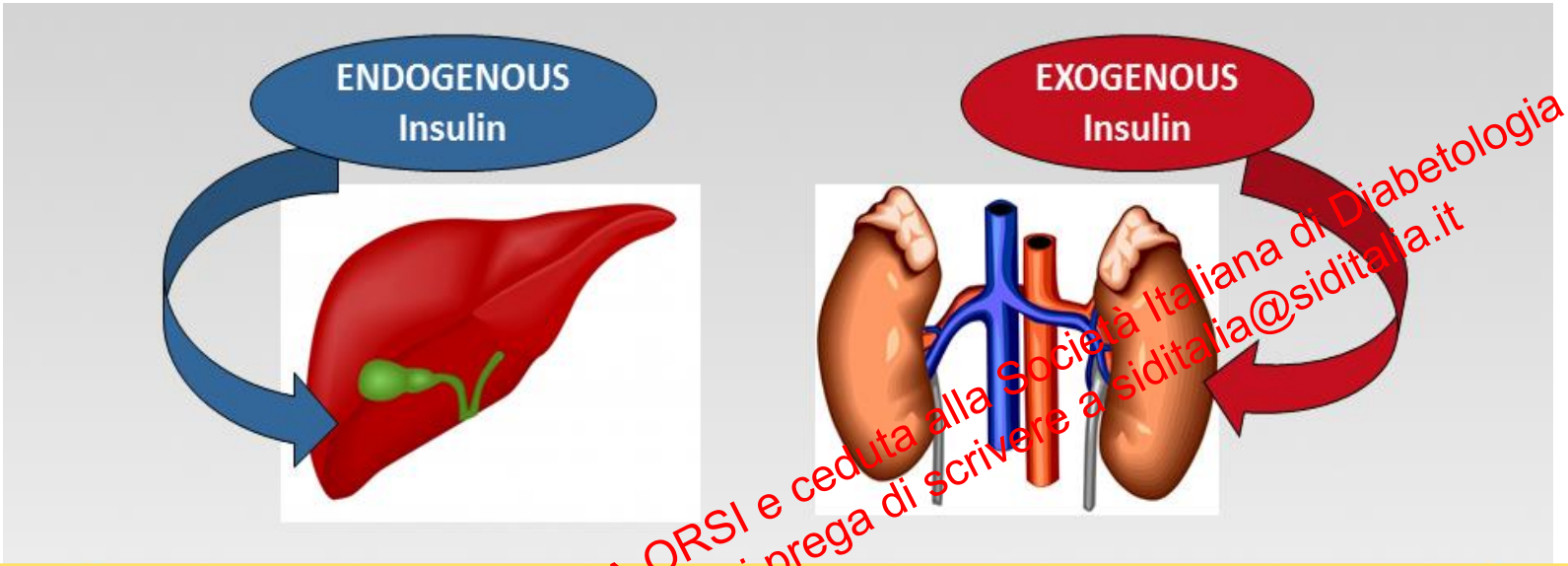
*Schematic representation

Ultra-rapid insulin should:

- Better approach physiological insulin secretion in T1D
- Replace early insulin secretion in T2D
- Aim to mimic physiological insulin profile for pump therapy

Evans M et al, Diabetes Ther, 2019

Human insulin



One third of exogenous insulin degradation is carried out by the kidney
Risk for hypoglycemia is higher in CKD due to reduced exogenous insulin catabolism

eGFR	Insulin dosage
10-50 ml/min	25% reduction
<10 ml/min	50% reduction

Freeman J, Postgraduate Medicine, 2019

Insulin	Action			Renal and hepatic dysfunction
	Start (min)	Peak (h)	Duration (h)	
Lyspro	<15	0.5-1	2-5	No influence
Aspart	<15	0.5-1	2-5	Usually no influence (renal) Reduced and variable absorption (hepatic)
Glulisine	<15	0.5-1	2-5	Usually no influence (renal) No data (hepatic)
Fiasp	5	0.4-1	2-5	Usually no influence (renal) absorption rate decreased and more variable (hepatic)

Insulin degludec (IDeg) concentrations at steady state and renal function

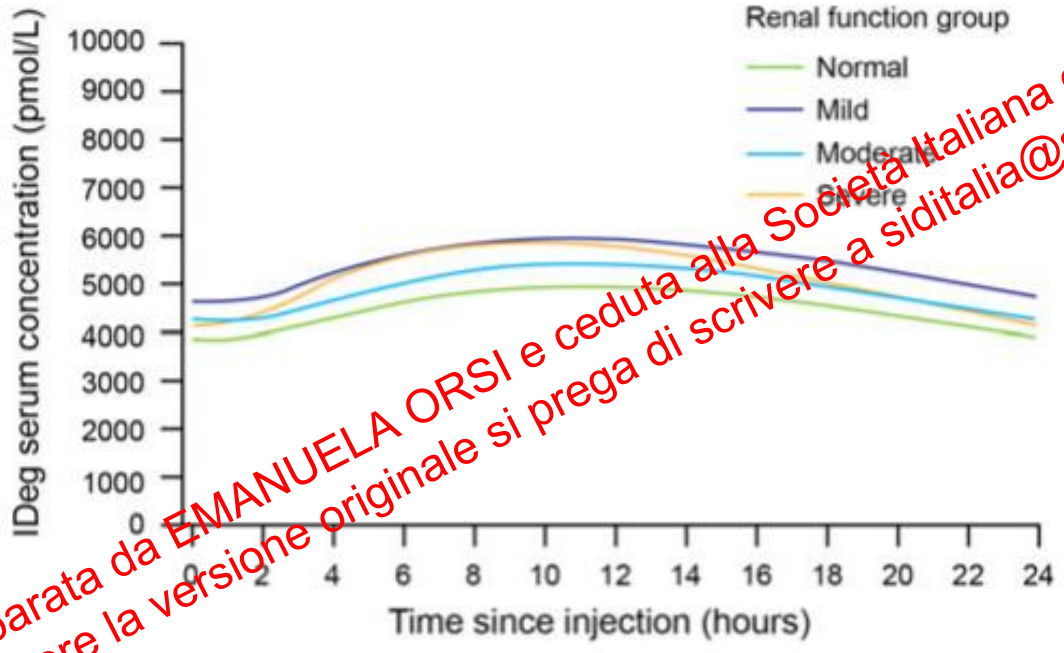
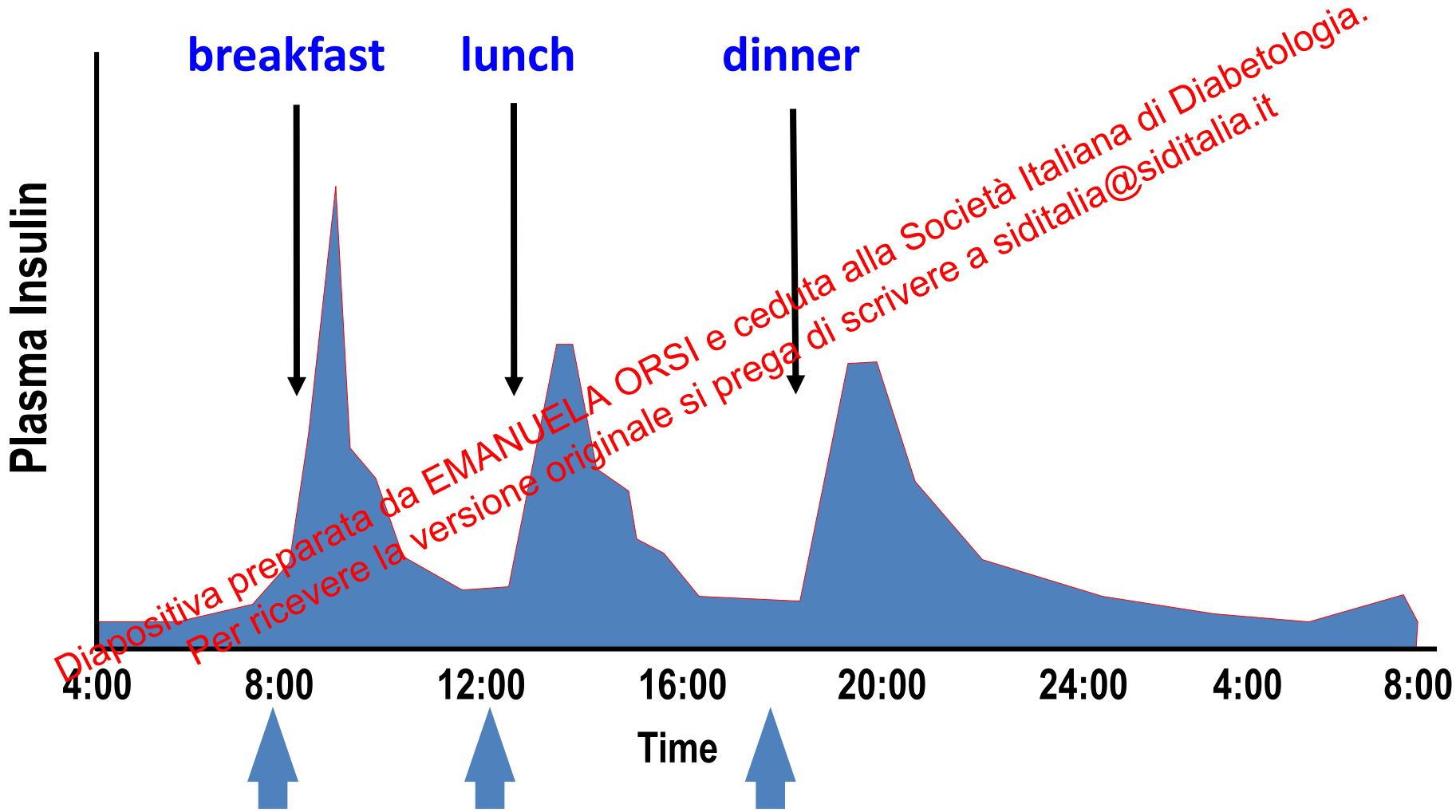
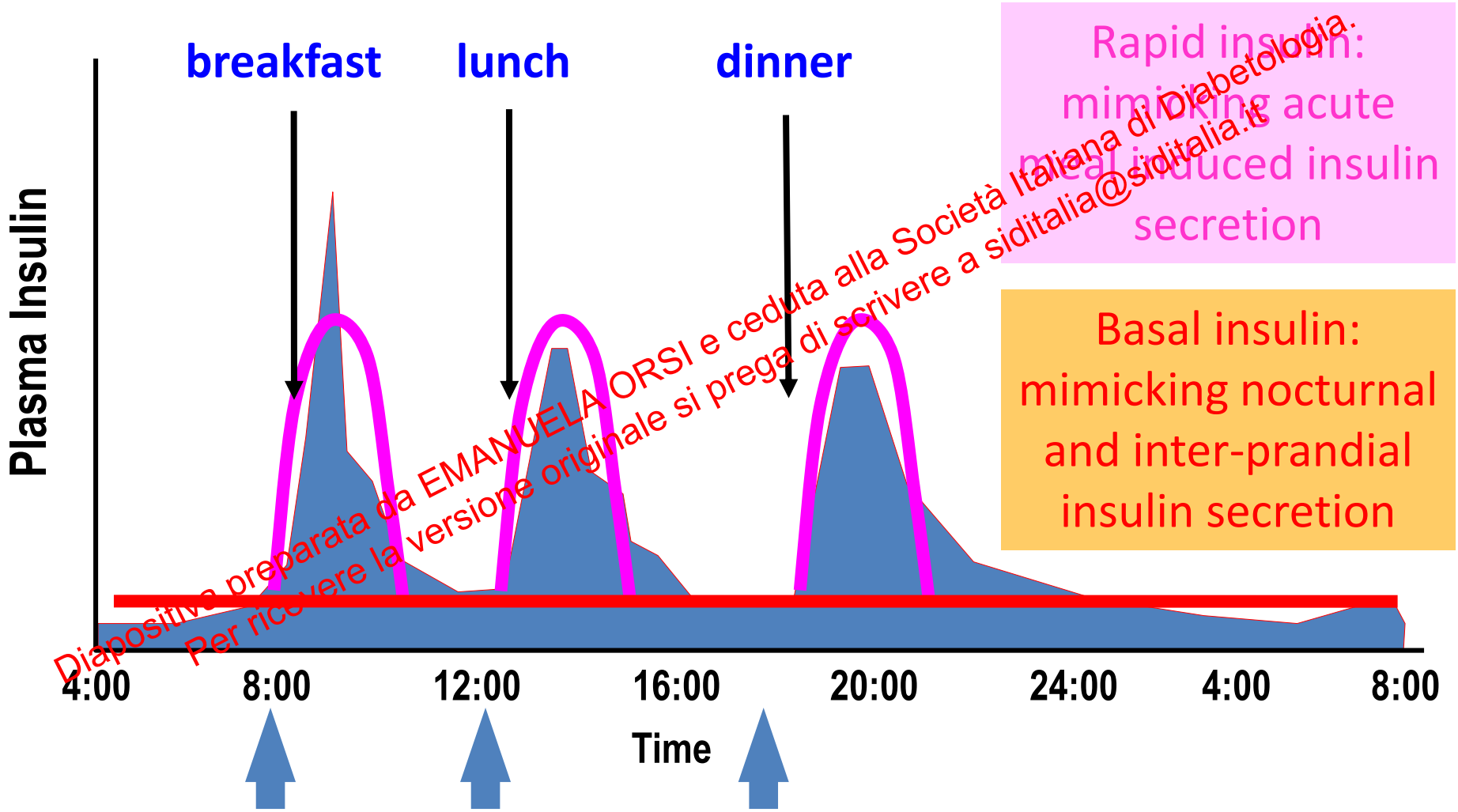


Fig. 3 Simulated mean insulin degludec (IDeg) concentrations at steady state (IDeg 0.4 U/kg subcutaneously)

Kiss I et al, Clin Pharmacokinet, 2014





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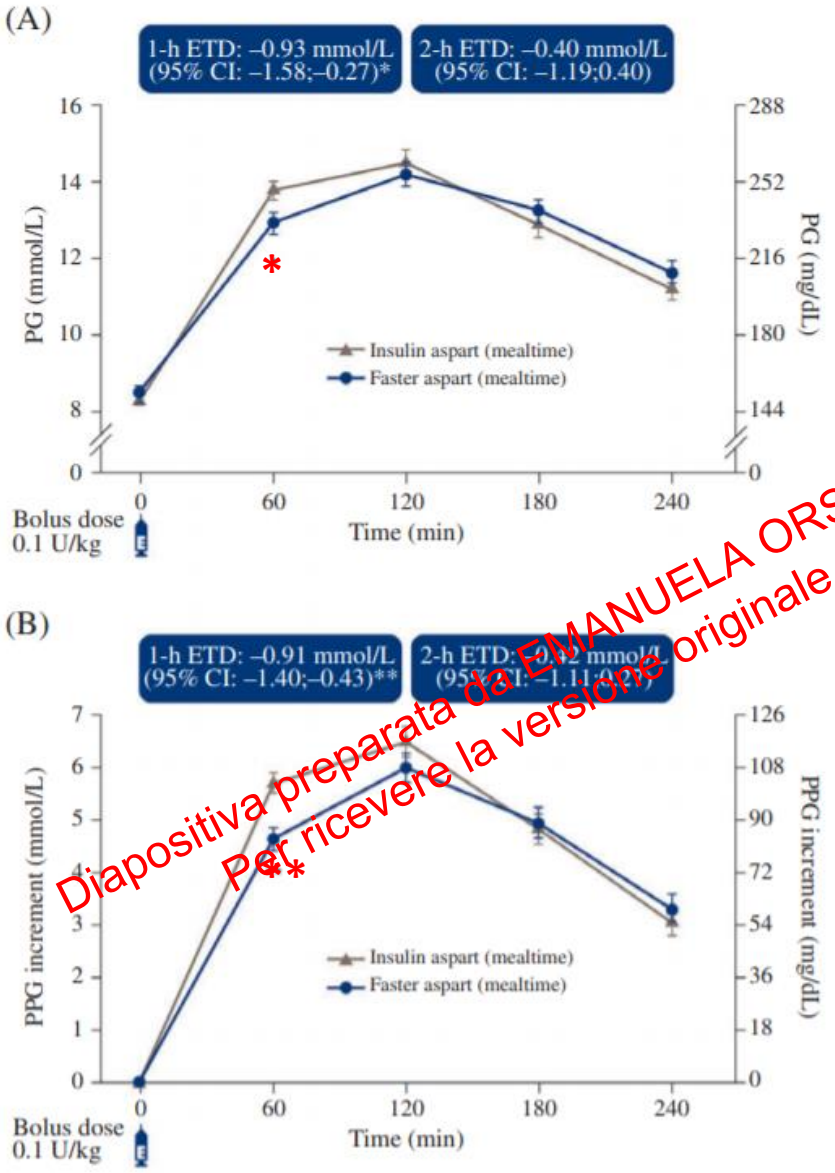
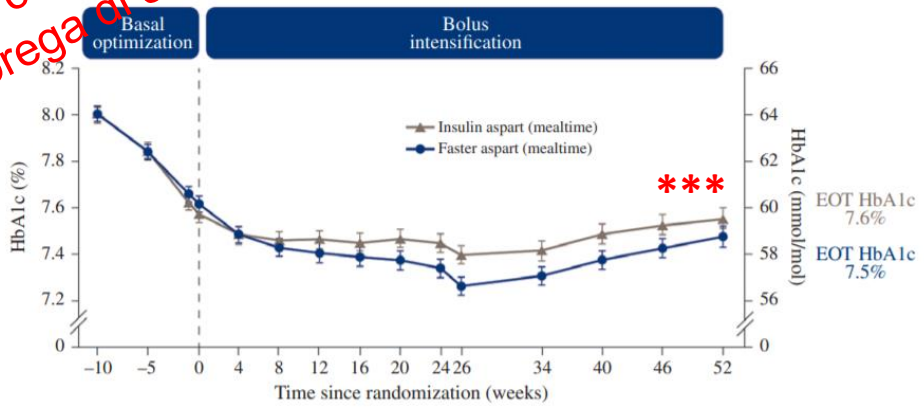
Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1)



* P = .0054
** P = .0002
*** P = .0424



Mathieu C et al, Diabetes Obes Metab, 2018

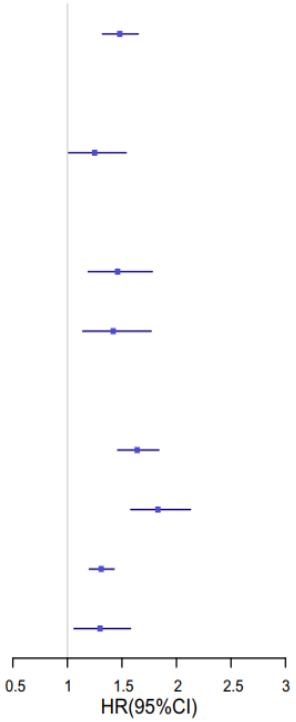
CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Chronic Kidney Disease, Basal Insulin Glargine, and Health Outcomes in People with Dysglycemia: The ORIGIN Study

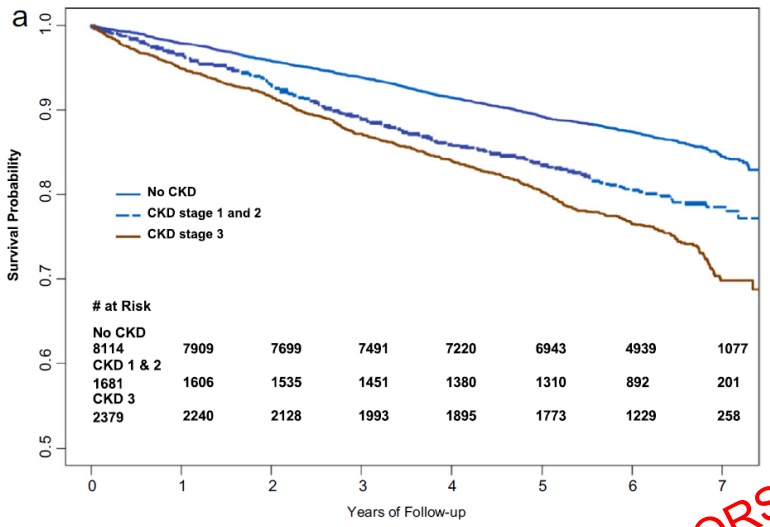
12.174 patients
8114 (67%) NON CKD
4060 (33%) CKD 1-3 stage

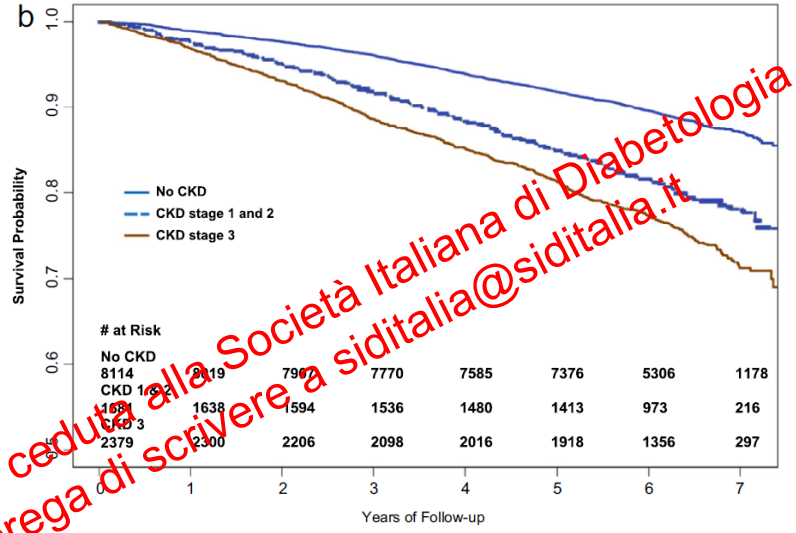
	CKD Rate (#events)	No CKD Rate (#events)	HR (95%CI)
Primary Outcome			
CV death, Non−fatal MI or Non−fatal Stroke	4.17(909)	2.99(1081)	1.48 (1.32−1.65)
Secondary Outcome			
Non−fatal MI	1.04(233)	0.73(351)	1.25 (1.01−1.54)
Stroke Any			
Stroke Non−fatal	1.29(290)	0.71(344)	1.46 (1.19−1.78)
Stroke	1.01(227)	0.61(295)	1.42 (1.14−1.77)
Death			
Any cause	4.03(925)	1.90(929)	1.64 (1.46−1.84)
Cardiovascular	2.55(586)	1.09(535)	1.83 (1.58−2.13)
Primary outcome plus revascularization or nonfatal HF	7.08(1405)	4.61(2007)	1.31 (1.20−1.43)
Major coronary disease event (Fatal/Non−fatal MI)	1.18(263)	0.79(380)	1.30 (1.06−1.58)

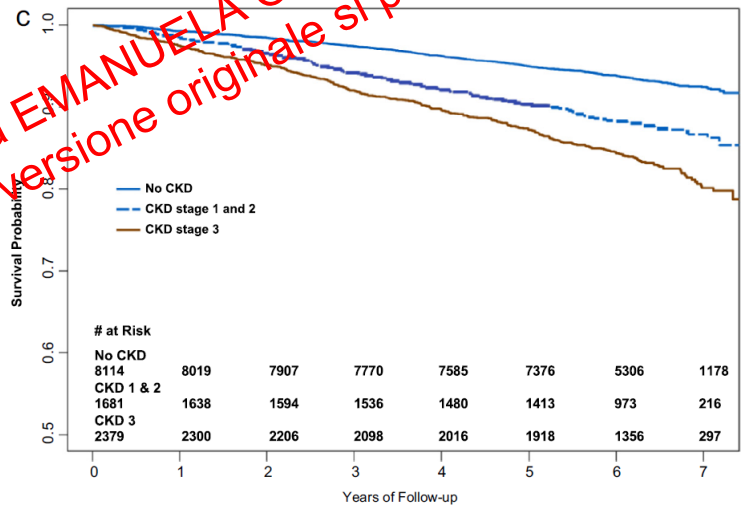


Papademetriou V et al, Am J Med, 2017

ORIGIN Study: primary oucome, all-cause mortality and CV mortality among participants without CKD, CKD stage 1 and 2, and CKD stage 3



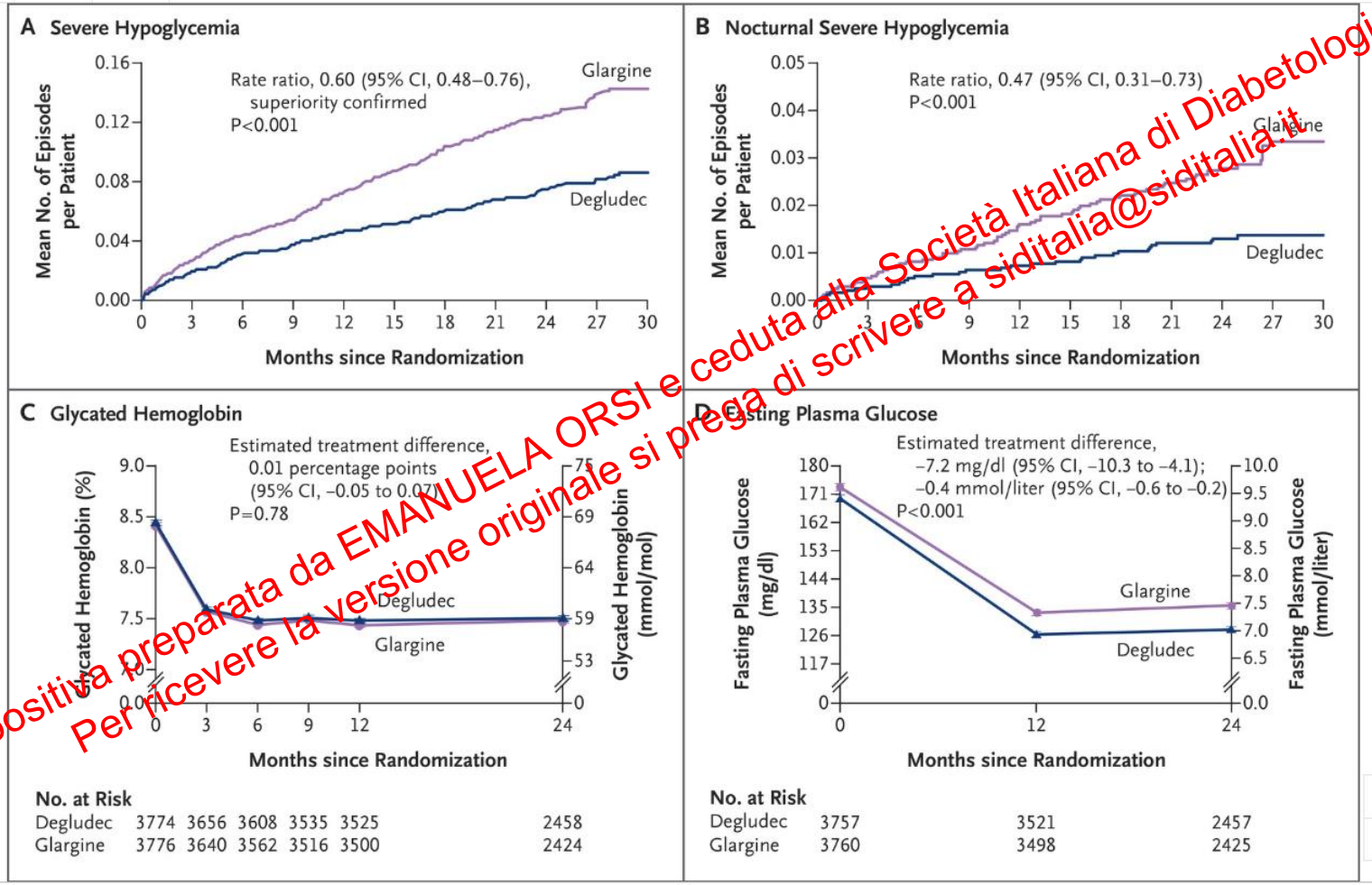




*** The composite end point were: nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes, and any of these events plus a revascularization procedure or hospitalization for heart failure.**

Papademetriou V et al, Am J Med, 2017

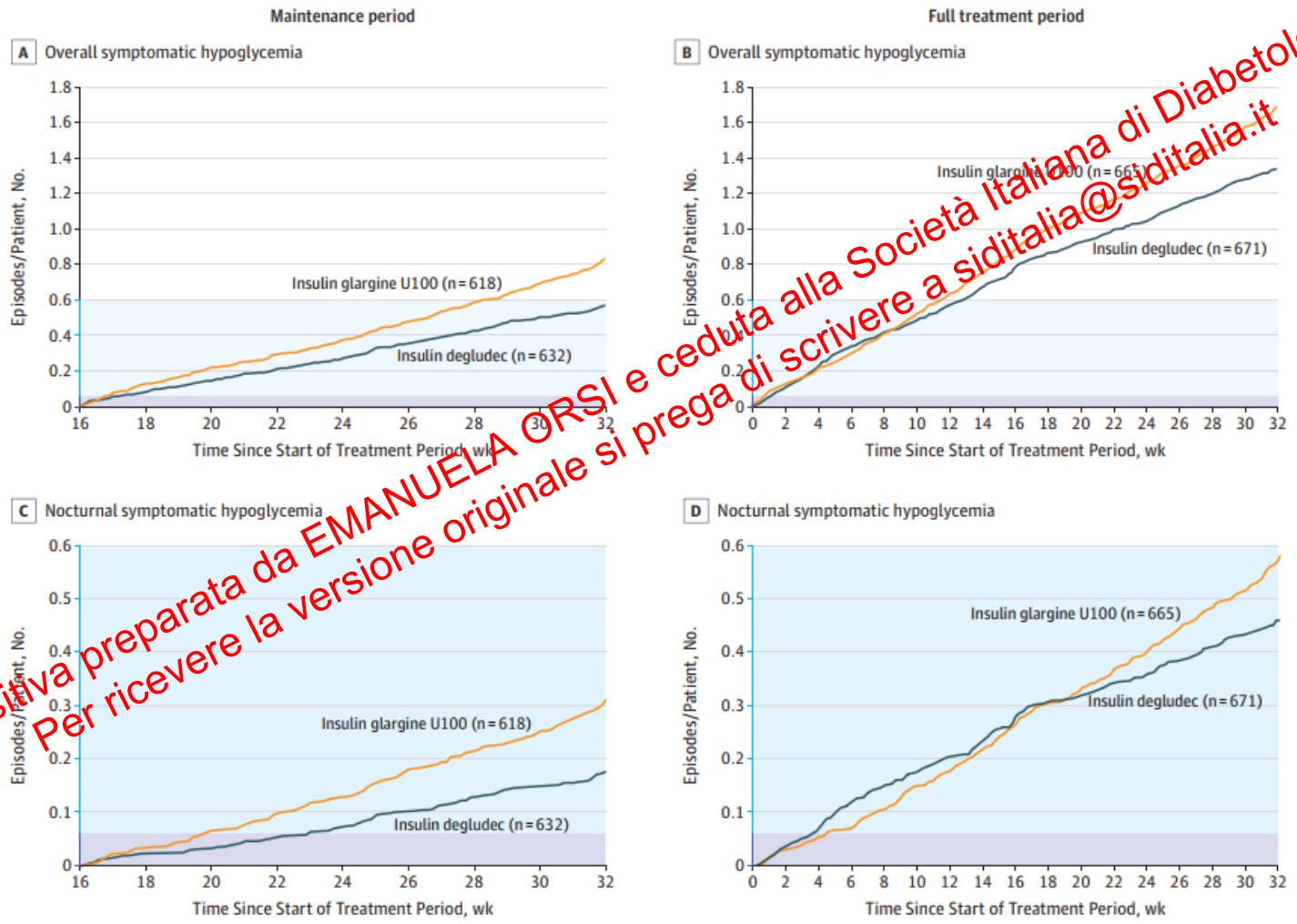
Degludec, Glargine 100 and hypoglycaemia: the DEVOTE Study



Marso S et al, NEJM, 2017

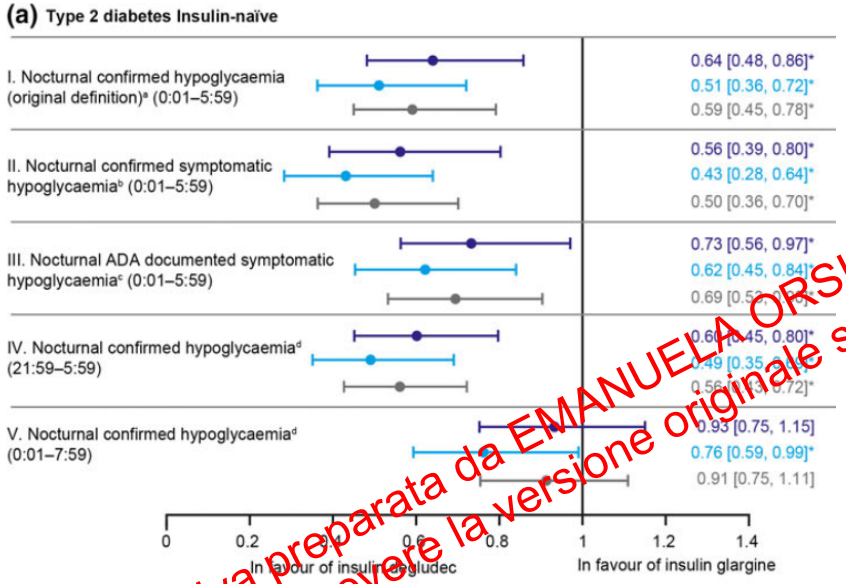
Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes

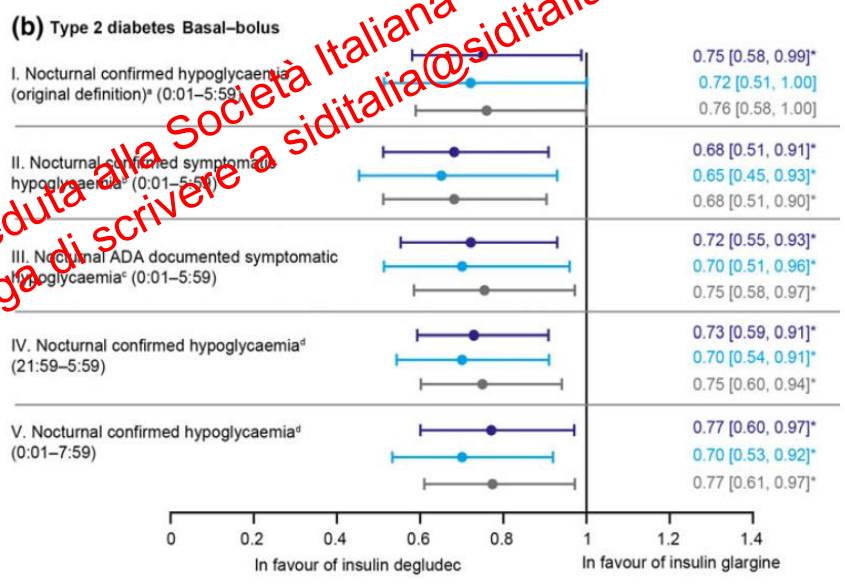
The SWITCH 2 Randomized Clinical Trial



Wysham C et al, JAMA, 2017

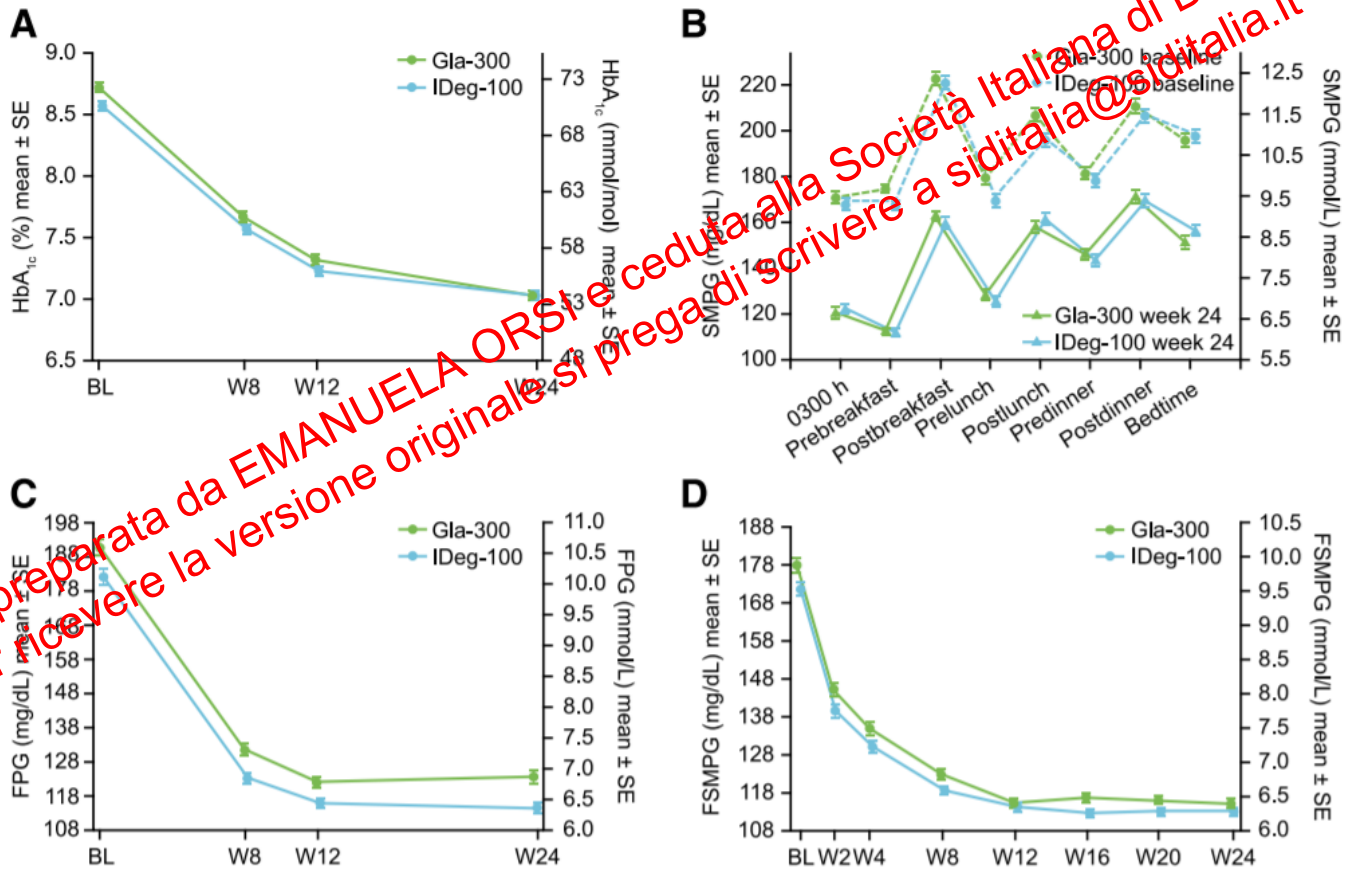
Nocturnal confirmed hypoglycaemia, using different definitions
Degludec vs Glargine 100





Heller S et al, Diabet Med, 2016

More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial

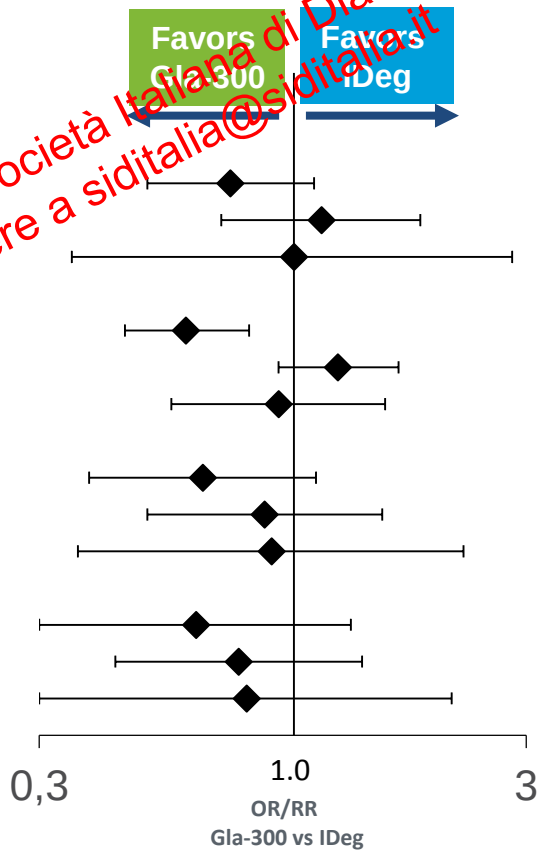


Rosenstock J et al, Diab Care, 2018

Hypoglycemia with Gla-300 versus IDeg over 24 weeks according to renal function

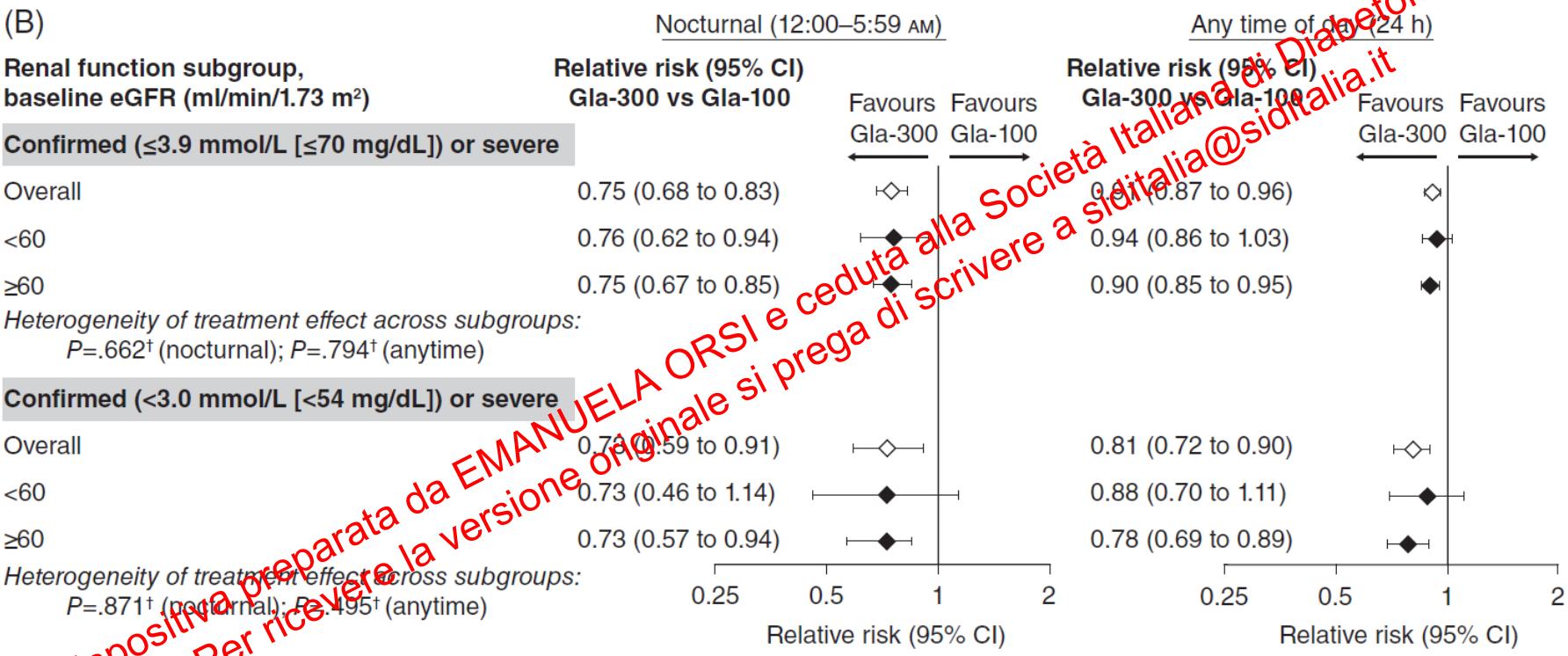
Baseline eGFR, mL/min/1.73 m²	OR/RR	95% CI
	Incidence of confirmed (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia	
≥90	0.74	0.50 to 1.10
60 to <90	1.14	0.71 to 1.82
<60	1.00	0.35 to 2.81
	Rate of confirmed (≤70 mg/dL [≤3.9 mmol/L]) hypoglycemia	
≥90	0.60	0.45 to 0.81
60 to <90	1.23	0.93 to 1.64
<60	0.93	0.56 to 1.54
	Incidence of confirmed (<54 mg/dL [<3.0 mmol/L]) hypoglycemia	
≥90	0.65	0.38 to 1.11
60 to <90	0.87	0.50 to 1.52
<60	0.90	0.36 to 2.23
	Rate of confirmed (<54 mg/dL [<3.0 mmol/L]) hypoglycemia	
≥90	0.63	0.30 to 1.31
60 to <90	0.77	0.43 to 1.38
<60	0.80	0.30 to 2.11

Rate ratios and CIs are based on an overdispersed Poisson regression model. Odds ratios and CIs are based on a logistic regression analysis.
CI, confidence interval; eGFR, estimated glomerular filtration rate; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec 100 U/mL; OR, odds ratio (for hypoglycemia incidence); RR, rate ratio (for hypoglycemia rates)



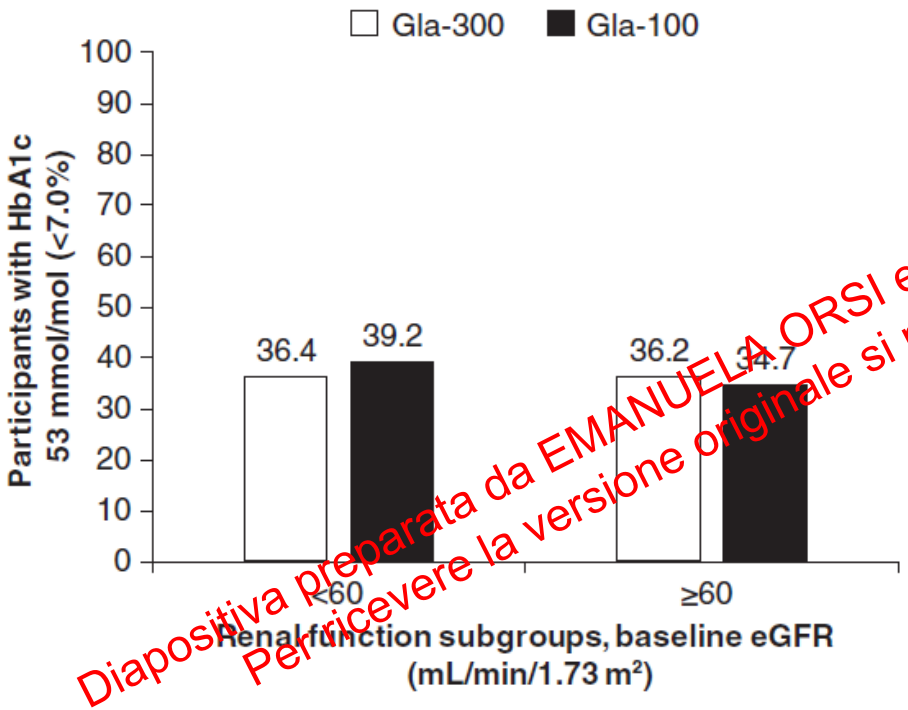
Rosenstock J et al, Diab Care, 2018

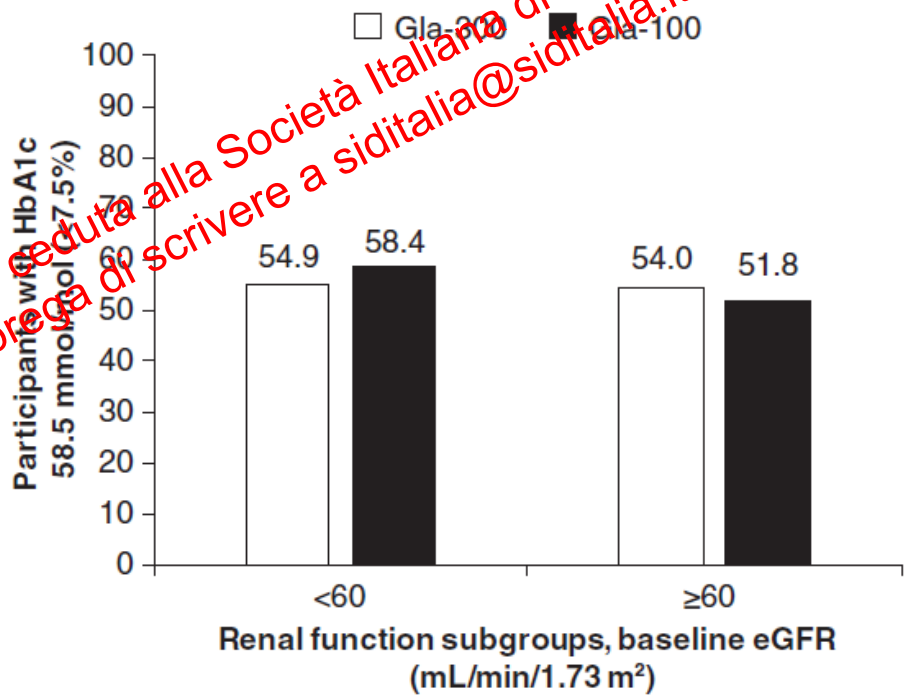
Gla 100 vs Gla 300: hypoglycemia



Escalada FG et al, Diabetes Obes Metab., 2018

Gla 100 vs Gla 300: glycometabolic control





Escalada FG et al, Diabetes Obes Metab., 2018

Insulin weekly

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Condition or disease	Intervention/treatment	Phase
Diabetes Mellitus, Type 2	Drug: **Insulin** 287 Drug: **Insulin** glargine U100	Phase 2

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	150 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Trial Comparing NNC0148-0287 C (**Insulin** 287) Versus **Insulin** Glargine U100, Both in Combination With Metformin, With or Without DPP4 Inhibitors and With or Without SGLT**2** Inhibitors, in Basal **Insulin** Treated Subjects With **Type 2 Diabetes** Mellitus
Actual Study Start Date :	May 9, 2019
Estimated Primary Completion Date :	December 19, 2019
Estimated Study Completion Date :	January 23, 2020

Grazie per l'attenzione