

INQUADRAMENTO E STRATEGIE TERAPEUTICHE DELL'ANZIANO DIABETICO



IL RISCHIO DI IPOGLICEMIA

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Firenze, 23 Ottobre 2017



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Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Lilly
- Menarini
- Sanofi
- Medtronic

In fede, Francesca Porcellati

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American Diabetes Association Workgroup on Hypoglycemia (DEFINITION)

Diabetes Care, 2005

Hypoglycemia Plasma Glucose ≤ 70 mg/dl

FDA (Food and Drug Administration)

EMA (European Medicines Agency, 2013)

(Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, 2012)

ISPAD (International Society for Pediatric and Adolescent Diabetes)

(Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence, 2011)

SID-AMD

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International Hypoglycemia Study Group (DEFINITION)

Diabetes Care, 2017

Plasma Glucose ≤ 70 mg/dl : Glucose alert value

Glucose alert value (PG ≤ 70 mg/dl)

(Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy)

Clinically significant hypoglycemia (≤ 54 mg/dl)

(Sufficiently low to indicate serious, clinically important hypoglycemia)

Severe hypoglycemia (no specific glucose threshold)

(Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery)



HYPOGLYCEMIA IN DIABETES

....The average patient with T1DM suffers two episodes of moderate hypoglycemia/week, thousands of such episodes over a lifetime of diabetes and one episode of temporarily disabling hypoglycemia, often with seizure or coma, per year.

An estimated 2–4% of people with T1DM die from hypoglycemia.

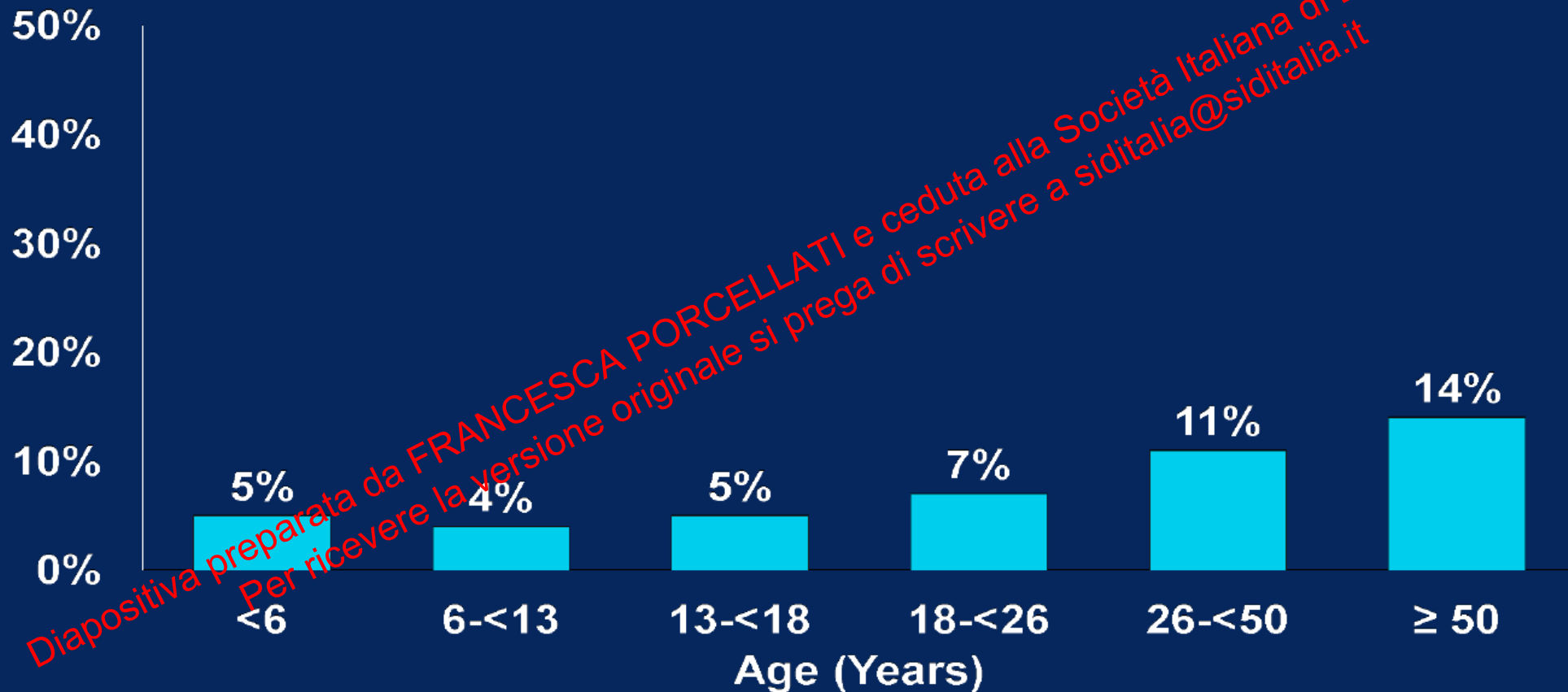
In T2 DM frequency of hypoglycemia increases with disease duration and hypoglycemic risk increases during intensified treatment

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12-month Frequency of Severe Hypoglycemia * According to Age

* 1 or more events: defined as seizure or loss of consciousness





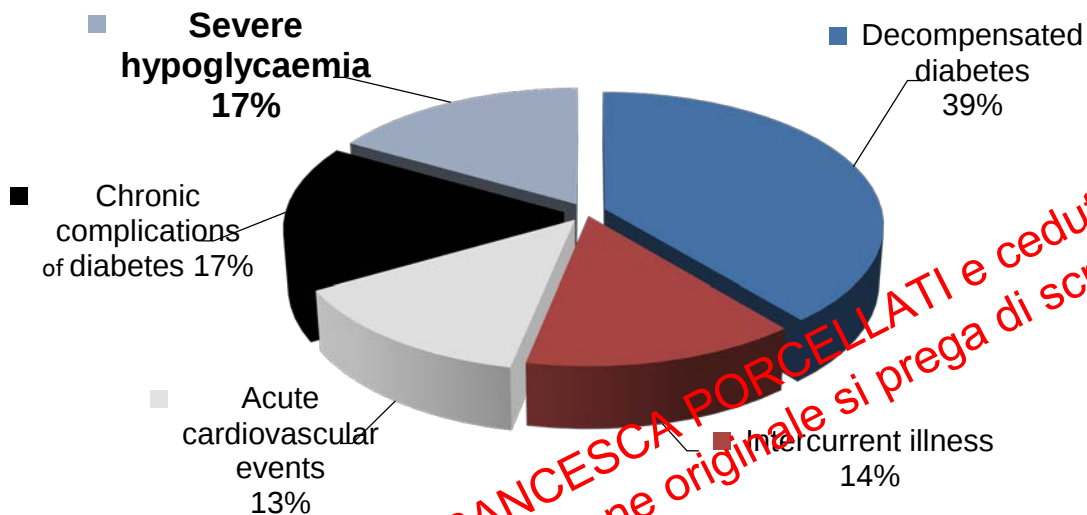
Incidence of Severe Hypoglycemia in Diabetes in Italy

	Population	N	Incidence (epis/100pt/y)	% of with ≥ 1 epis/y
Hypos-1 ¹	T2DM	2023	9	4.7
Hypos-1 ¹	T2DM ≥ 75 aa	381	15	6.0
Hysberg ²	T2DM ≥ 65 aa	1323	14.9	8.1
Hypos-1 ¹	T1DM	206	49	16.5

¹ Giorda CB et al. J Diabetes Metab 2014; ² Nicolucci A, et al, Acta Diabetol 2015;



Severe Hypoglycemia and Hospitalizations

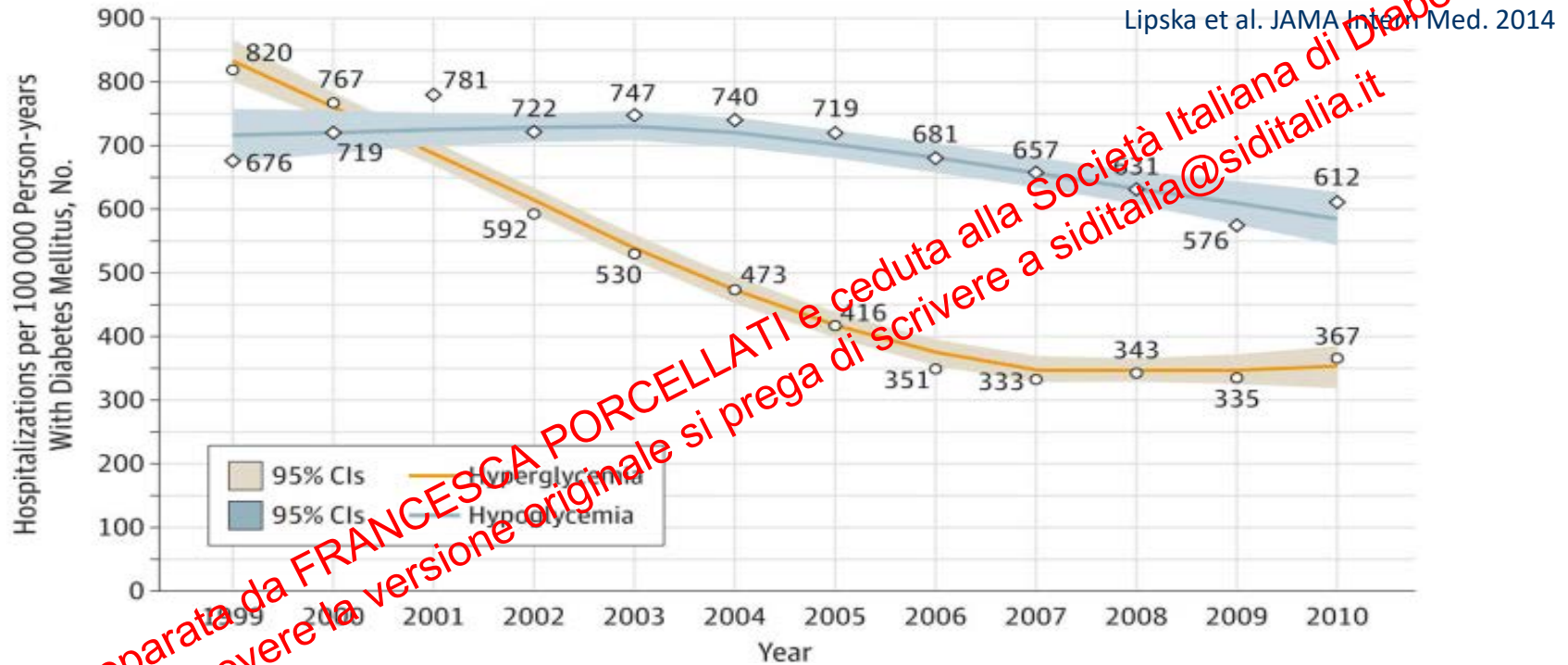


- Commonest OAD was glibenclamide
- 49% were demented
- 50% had renal impairment
- Average HbA_{1c} was < 6,5% (<48 mmol/mol)

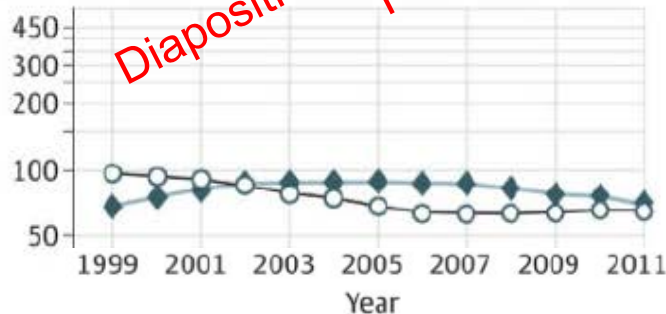
Severe hypoglycemia accounts for almost 20% of all hospitalizations for type 2 diabetes in the elderly



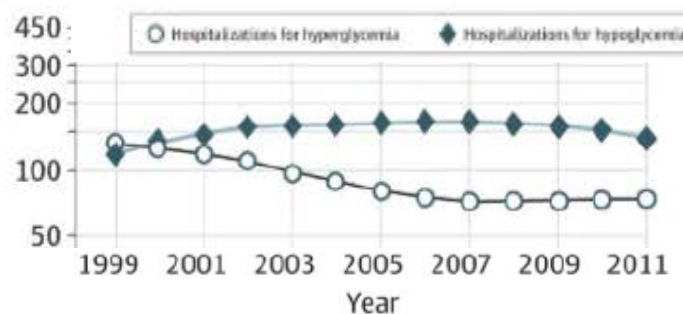
Rates of Estimated Hospital Admissions for Hyperglycemia and Hypoglycemia Among Medicare Beneficiaries with Diabetes Mellitus, 1999 to 2010



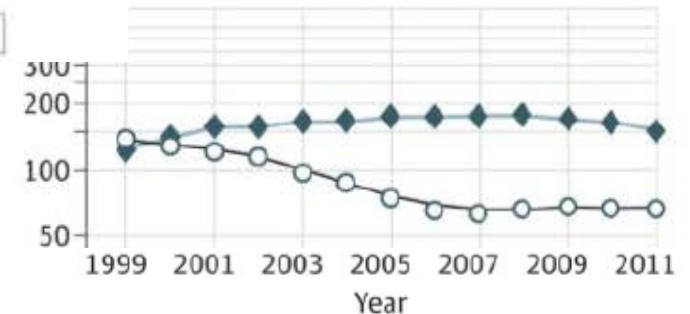
65-74 Years Old



75-84 Years Old



≥85 Years





Emergency Hospitalizations for Adverse Drug Events

Table 4. National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.*

Medication	Annual National Estimate of Hospitalizations (N = 99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
	no.	% (95% CI)	%
Most commonly implicated medications†			
Warfarin	33,171	33.3 (28.0–38.5)	46.2
Insulins	13,854	13.9 (9.8–18.0)	40.6
Oral antiplatelet agents	18,263‡	13.3 (7.5–19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1–13.3)	51.8
Opioid analgesics	4,778	4.8 (3.5–6.1)	32.4
Antibiotics	4,205	4.2 (2.9–5.5)	18.3
Digoxin	3,465	3.5 (1.9–5.0)	80.5
Antineoplastic agents	3,329‡	3.3 (0.9–5.8)‡	51.5
Antiadrenergic agents	2,899	2.9 (2.1–3.7)	35.7
Renin–angiotensin inhibitors	2,870	2.9 (1.7–4.1)	32.6
Sedative or hypnotic agents	2,469	2.5 (1.6–3.3)	35.2
Anticonvulsants	1,653	1.7 (0.9–2.4)	40.0
Diuretics	1,071‡	1.1 (0.4–1.8)‡	42.4



Hypoglycemia

CAUSES

- Iatrogenic hyperinsulinemia

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Therapeutic options in Type 1 Diabetes

Insulin (MDI or CSII)

Iatrogenic hyperinsulinemia

Therapeutic options in Type 2 Diabetes

Metformin; Sulphonylureas; Glinides; Insulin; Glitazones; Acarbose;

GLP-1 RAs, DPP 4 inhi., SGLT2-inhi.

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Hypoglycemia

CAUSES

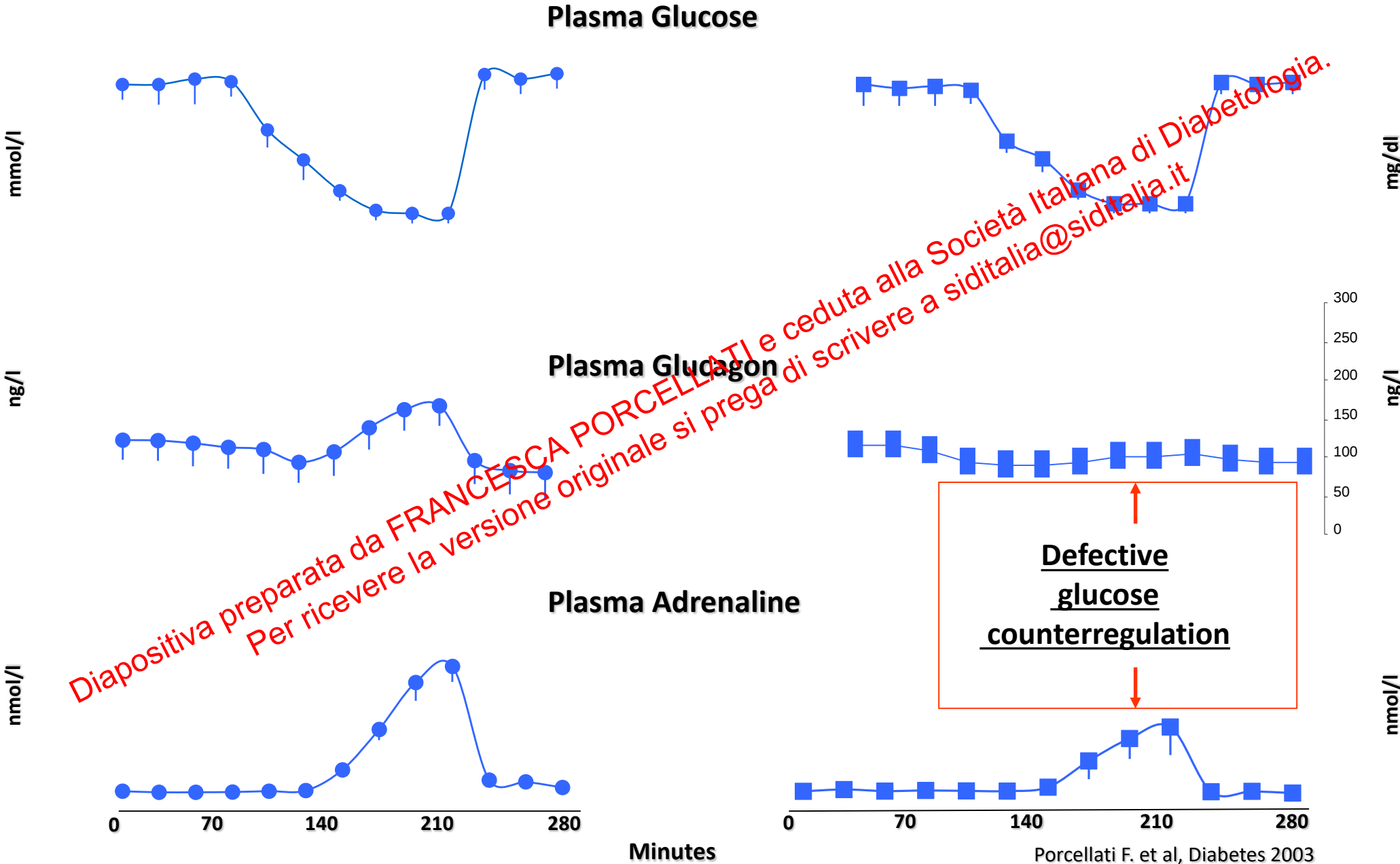
- Iatrogenic hyperinsulinemia
- Defective glucose counterregulation

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NON-DIABETIC SUBJECTS

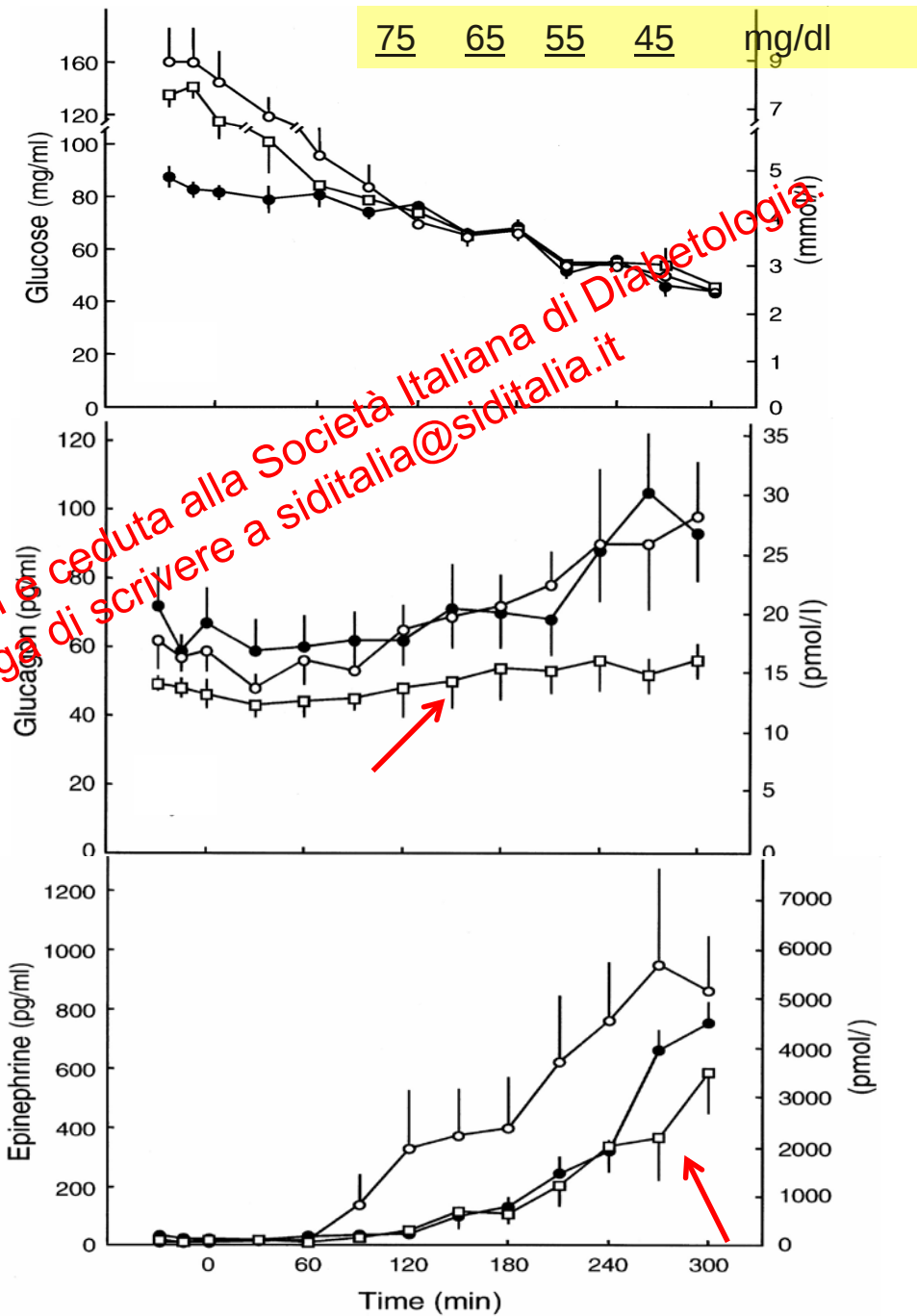
T1 DIABETIC SUBJECTS





- Nondiabetics;
- Type 2 DM-OHA;
- Type 2 DM-Insulin

	Non-diabetics	T2 OHA	T2 Insulin
Age (years)	50 ± 6	56 ± 6	57 ± 6
Female/male	8/7	4/3	3/3
BMI (kg/m ²)	30.2 ± 1.0	32.4 ± 2.7	34.0 ± 2.7
HbA1c (%)	5.6 ± 0.4	8.6 ± 1.1	7.9 ± 0.7
Years of OHA or insulin Rx	—	10 ± 5	5 ± 3
Fasting C-peptide (ng/ml)	2.3 ± 1.1	2.3 ± 1.1	1.1 ± 0.4†

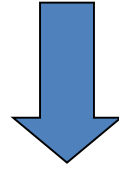




Recurrent Hypoglycemia



Defective
Glucose
Counterregulation



Hypoglycemia
unawareness

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Hypoglycemia-Associated Autonomic Failure (HAAF)



...recurrent hypoglycemia and

Hypoglycemia Unawareness:

“failure to recognize the warning symptoms of hypoglycemia at their physiological plasma glucose concentrations”



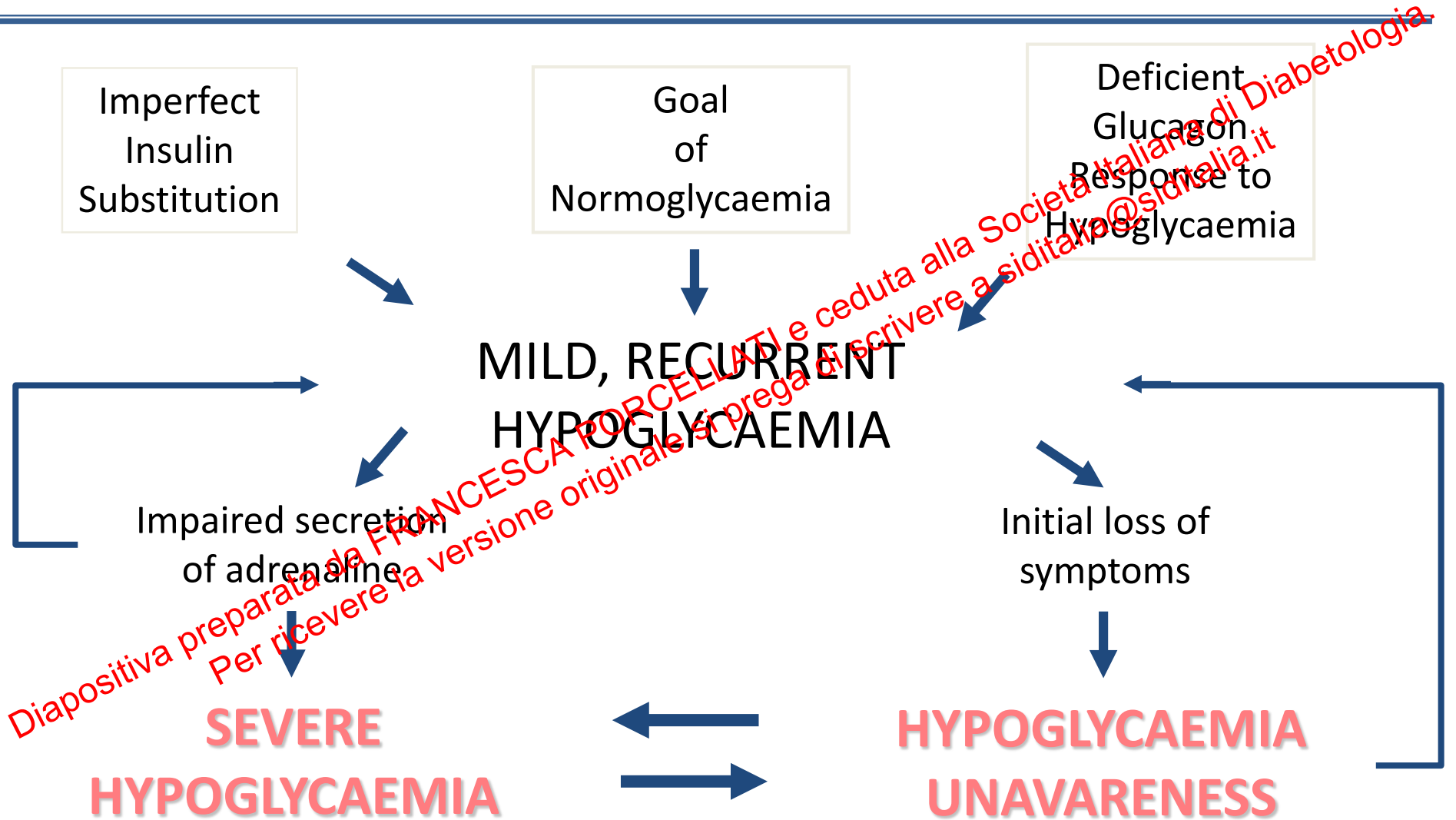
Absent / delayed correction of impending hypoglycemia

Risk for severe hypoglycemia

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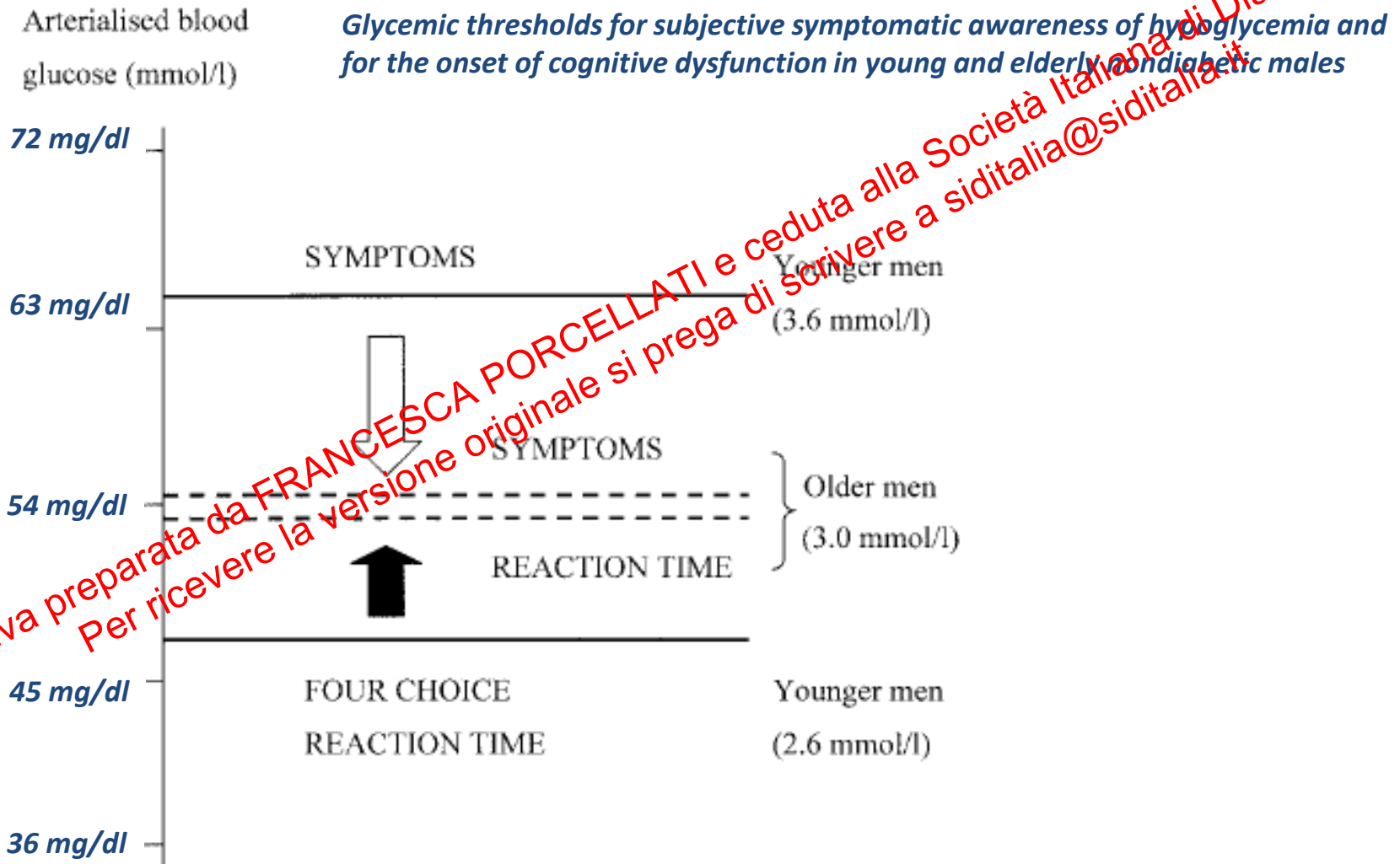


INSULIN TREATMENT in diabetes



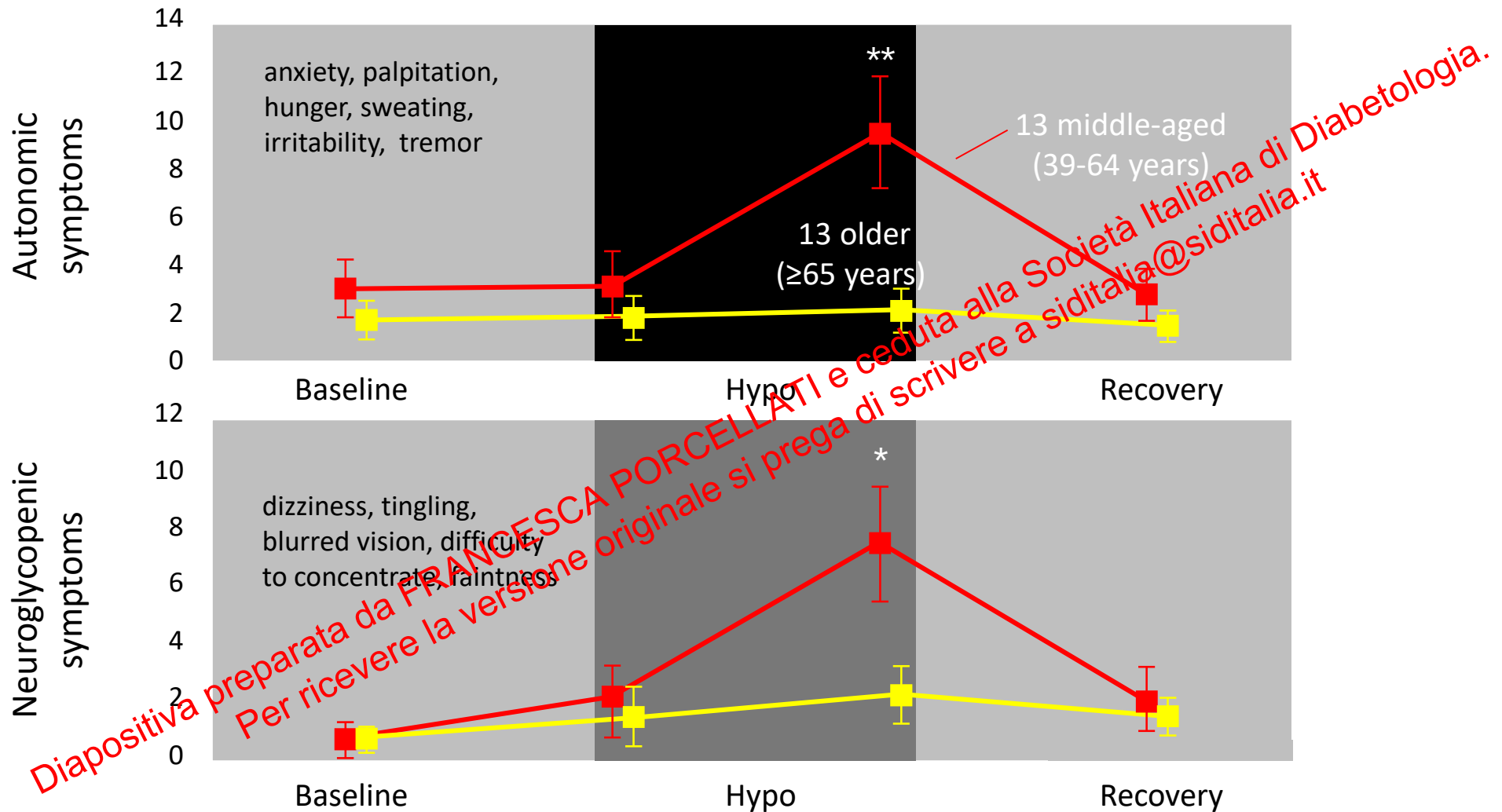


Symptoms and Cognitive Dysfunction Occur Almost Simultaneously in Older Individuals





Hypoglycemia Unawareness in Older Patients with T2 Diabetes



At the end of the hypoglycemic clamp, 7 of 13 middle aged patients, but only 1 of 13 older patients, correctly estimated their blood glucose level to be 3.3 mmol/l



Age-Related Symptoms of Hypoglycemia in people with Type 2 Diabetes

YOUNGER

Shaking

Drowsiness

Dizziness

Confusion

OLDER

Sweating

Anxiety

Dizziness

Weakness

Blurred vision

Poor coordination

AUTONOMIC

NEUROGLYCOPENIC

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Hypoglycemia in the Elderly

- Glycemic threshold for onset of symptoms is altered: lower blood glucose is required to initiate symptoms
- Symptomatic responses to hypoglycemia are modified
 - Symptom profile differs from young adults
 - Intensity of all symptoms is very low
- Symptoms may be misinterpreted as cerebrovascular disease (TIA), dementia or psychiatric disorder, or neurological disease
- Knowledge of symptoms is poor both in patients and relatives

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Factors Contributing to Hypoglycemia in Older Adults with Diabetes

- Stringent glycemic control
- Hypoglycemia unawareness
- Medications: insulin, sulfonylureas, glinides
- Number of medications
- Poor coordination between insulin administration and food delivery
- Chronic hepatic or renal dysfunction
- Intercurrent acute illnesses, sepsis
- Dementia
- Social isolation
- Frailty
- Alcohol
- Depression

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Consequences of Hypoglycemia

Cardiovascular events ^(1, 2)

Dementia ⁽³⁾

Reduced quality of life ^(4, 5)

Experiencing fractures ⁽⁶⁾

Fear against hypoglycemic therapy ⁽⁷⁾

Overall mortality ⁽⁸⁾

Increase in body weight (defensive eating) ⁽⁹⁾

Car accidents ⁽¹⁰⁾

Increased cost of the expenditure on diabetes ⁽¹¹⁾

1) Johnston SS. et al Diabetes Care 34:1164–1170, 2011.

3) Whitmer RA et al JAMA 301:1565–1572, 2009.

5) McCoy RG et al. Diabetes Care 35:1897–1901, 2012.

7) Laiteerapong N et al. Diabetes Care 34:1749–1753, 2011.

9) Foley JE et al. Vasc Health Risk Manag 6:541-548, 2010 .

11) Frier BM. Br J Diabetes Vasc Dis 11: (Suppl 1) S10-S12, 2011

2) Desouza CV. Et al. Diabetes Care 33:1389-94, 2010.

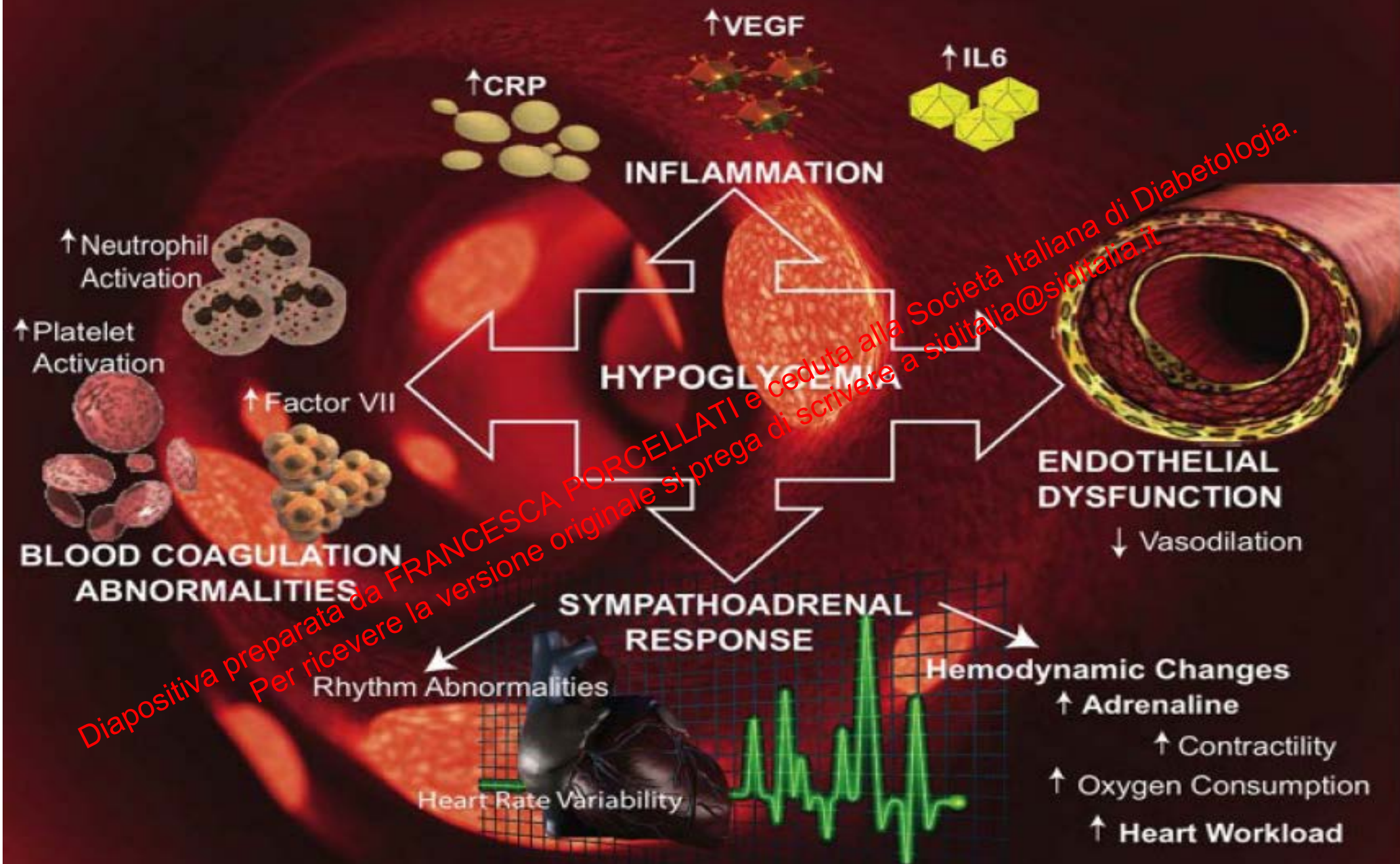
4) Green AJ et al. Diabetes Res Clin Pract 96:313–318, 20125)

6) Johnston SS et al. Diabetes Obes Metab 14: 634–643, 2012.

8) Leiter LA et al. Canadian Journal Diabetes 29:186–192, 2005.

10) Cox DJ et al. Diabetes Care, 29: 467-42006

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Association of Severe Hypoglycemia with the Risk of an Adverse Clinical Outcome or Death

Events	Severe Hypoglycemia (N=231) no. of patients with events (%)	No Severe Hypoglycemia (N=10,909) no. of patients with events (%)	Hazard Ratio (95% CI)
Major macrovascular events	33 (15.9)	1114 (10.2)	
Unadjusted model			4.05 (2.41–5.74)
Adjusted model			2.53 (2.41–2.65)
Major microvascular events	24 (11.5)	1107 (10.1)	
Unadjusted model			2.39 (1.60–3.59)
Adjusted model			2.19 (1.40–3.45)
Death from any cause	45 (19.5)	986 (9.0)	
Unadjusted model			4.86 (3.60–6.57)
Adjusted model			3.27 (2.29–4.65)

“Severe hypoglycemia was strongly associated with increased risks of a range of adverse clinical outcomes. It is possible that severe hypoglycemia contributes to adverse outcomes, but these analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events”

N Engl J Med 2010;363:14108.

Unadjusted model			2.97 (1.90–4.63)
Adjusted model			2.20 (1.31–3.72)
Diseases of the skin	6 (2.7)	146 (1.3)	
Unadjusted model			5.02 (2.20–11.40)
Adjusted model			4.73 (1.96–11.40)
Cancer	5 (2.2)	149 (1.4)	
Unadjusted model			3.44 (1.40–8.42)
Adjusted model			2.11 (0.65–6.82)

0.1 1.0 10.0

Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

Rachel A. Whitmer, PhD

Andrew J. Karter, PhD

Kristine Yaffe, MD

Charles P. Quesenberry Jr, PhD

Joseph V. Selby, MD

Cohort study from 1980-2007 of 16 667 patients; mean age of 65 years

Table 3. Hypoglycemia and Risk of Incident Dementia.

Table 3. Hypoglycemia and Risk of Incident Dementia^a

No. of Hypoglycemic Episodes ^b	No. of Dementia Cases	Hazard Ratio (95% Confidence Interval)		
		Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes	Additionally Adjusted for Comorbidities ^c	Additionally Adjusted for 7-Year Mean HbA _{1c} Level, Diabetes Treatment, and Years of Insulin Use
1 or more	250	1.68 (1.47-1.93)	1.48 (1.29-1.70)	1.44 (1.25-1.66)
1	150	1.45 (1.23-1.72)	1.29 (1.10-1.53)	1.26 (1.10-1.49)
2	57	2.15 (1.64-2.84)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
3 or more	43	2.60 (1.68-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.
^aAnalyses combined using Cox proportional hazard models.
^bThe 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.
^cAdjustment made using a comorbidity composite score.

Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes was associated with a greater risk of dementia.

we observed a 2.39% increase in absolute risk of dementia per year of follow-up for patients with history of hypoglycemia, compared with patients without a history. Although this 1-year

Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial

B. E. de Galan • S. Zoungas •

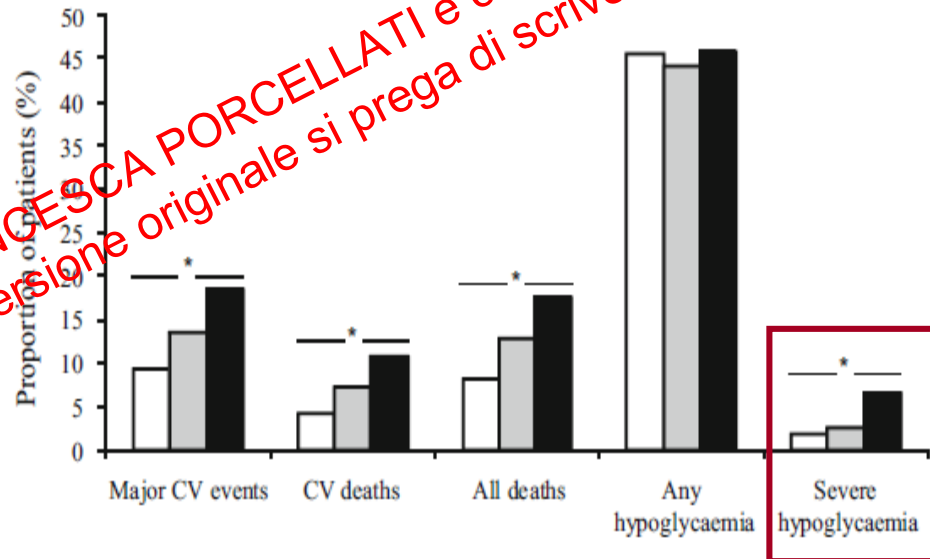


Fig. 1 Proportion of patients with clinical outcomes during follow-up according to cognitive function status at baseline. White bars, normal cognitive function; grey bars, mild cognitive dysfunction; black bars, severe cognitive dysfunction. CV, cardiovascular. * p for trend <0.0001



Current Approaches Available to Prevent Hypoglycemia in Diabetes

- Assess for level of functional dependency (frialty)
- Individualize blood glucose targets
- Assess the perception of hypoglycemia to exclude the presence of hypoglycemia unawareness

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Register Events and Assess the Perception of Hypoglycemia

IPO IPOGLICEMIA

21/10/2014 | 20/08/2014 | 19/03/2014 | 01/01/2014

IPOGLICEMIA GRAVE ☒ NO ☐ SI N° ipoglicemie da autocontrolli: 6

IPOGLICEMIA SINTOMATICA DIMOSTRATA: ☐ NO ☒ SI
N° Episodi per settimana: 4 Prevalentemente di: ☒ Giorno ☐ Notte ☐ Giorno e notte

IPOGLICEMIA ASINTOMATICA DIMOSTRATA: ☐ NO ☒ SI ☐ Parzialmente Sintomatica
N° Episodi per settimana: 3 Prevalentemente di: ☒ Giorno ☐ Notte ☐ Giorno e notte

QUESTIONARIO PER STABILIRE LA CAPACITÀ DI RICONOSCERE I SINTOMI DELL'IPOGLICEMIA

1. E' in grado di riconoscere l'ipoglicemia (la glicemia bassa)?
☐ Mai ☒ A volte ☐ Spesso/Sempre

2. Al di sotto di quale valore sente che la glicemia è bassa?
☐ Tra 70 e 55 mg/dl ☐ Tra 55 e 45 mg/dl ☒ Sotto 45 mg/dl

3. Si accorge dei sintomi quando la glicemia è bassa?
☒ NO ☐ SI

4. Durante l'ultimo anno, ha avuto episodi ipoglicemia di tale gravità da richiedere l'assistenza di un'altra persona o di iniezioni di glucagone o di personale di pronto intervento (118) o del pronto soccorso?
☒ NO ☐ SI

Capacità di riconoscere i sintomi dell'ipoglicemia: **ASSENTE**

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The Reversibility of Hypoglycemia Unawareness

Recommendations:

Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be *advised to raise their glycemic targets to strictly avoid further hypoglycemia* for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. (A)

ADA Standards of Medical Care in Diabetes — 2017 Diabetes Care 40:Suppl.1

Fanelli CG, et al. Diabetes 42:1683, 1993.

Fanelli CG, et al. Diabetologia 37:1265, 1994.

Cranston I, et al. Lancet 344:283, 1994.

Dagogo-Jack S, et al. Diabetes 43:1426, 1994.



Current Approaches Available to Prevent Hypoglycemia in Diabetes

- Assess for level of functional dependency (frialty)
- Individualize blood glucose targets
- Assess the perception of hypoglycemia to exclude the presence of hypoglycemia unawareness
- Glucose monitoring based on the complexity of regimen and the risk of hypoglycemia

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The Impact of Real-Time Continuous Glucose Monitoring in Patients 65 Years and Older

	Total sample (n = 285)	Current CGM users (n = 210)	CGM hopefuls (n = 75)	Univariate model	Adjusted model
Mild/moderate hypoglycemic episodes (yes/no)					
Moderate episodes (≥ 1), past 6 months	232 (81.4%)	164 (78.1%)	68 (90.7%)	OR = 2.73*	OR = 4.67**
BG reading < 70, with symptoms (≥ 1), in past month	137 (56.8%)	99 (57.9%)	38 (54.3%)	OR = 0.86	OR = 1.37
BG reading < 70, no symptoms (≥ 1), in past month	147 (60.7%)	103 (59.9%)	44 (62.9%)	OR = 1.13	OR = 1.31
Severe hypoglycemia-related events (yes/no)					
Episode requiring assistance (≥ 1), past 6 months	181 (63.5%)	121 (57.6%)	60 (80.0%)	OR = 2.92**	OR = 3.51**

	Current RT-CGM user	RT-CGM hopeful	Univariate model	Adjusted model
Episode requiring assistance (yes/no)			OR = 4.35***	OR = 5.53***
During the 6 months before starting, or seeking, RT-CGM	154 (73.3%)	56 (74.7%)		
Last 6 months	121 (57.6%)	60 (80.0%)		
Pre-post difference	-15.7%***	+5.3%		

CONCLUSIONS: These data suggest that RT-CGM use in seniors is associated with reductions in episodes of severe hypoglycemia and improved QOL.



Current Approaches Available to Prevent Hypoglycemia in Diabetes

- Assess for level of functional dependency (frialty)
- Individualize blood glucose targets
- Assess the perception of hypoglycemia to exclude the presence of hypoglycemia unawareness
- Glucose monitoring based on the complexity of regimen and the risk of hypoglycemia
- Use of insulin analogs and of glucose lowering agents with minimal hypoglycemic risk

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Hypoglycemia Hospitalization Frequency in Persons with T2 diabetes Mellitus: the French Health Insurance Database

1440 patients were exposed to vildagliptin and 10019 to insulin secretagogues.

Rates of HH and of all emergency calls were significantly lower with vildagliptin vs insulin secretagogues

	Vildagliptin N=1440	Sulfonylureas/Glinides N=10019	P-value
Person-years of exposure	581	4403	
N° of patients with hospitalization for hypoglycemia (%)	0 (0.0%)	59 (0.59%)	0.034
N° of hospitalization for hypoglycemia	0	60	
Adjusted rate of hospitalization for hypoglycemia/1.000 PY	0.0 (0.0; 0.0)	13.6 (10.4; 17.5)	0.0003
N° of patients with emergency calls (any cause)	60 (4.20%)	823 (8.21%)	<0.0001
N° of emergency calls	77	1035	
Adjusted rate of emergency calls/1.000 PY	132.6 (104.6; 165.6)	235.0 (220.9; 249.8)	<0.0001



Current Approaches Available to Prevent Hypoglycemia in Diabetes

- Assess for level of functional dependency (frialty)
- Individualize blood glucose targets
- Assess the perception of hypoglycemia to exclude the presence of hypoglycemia unawareness
- Glucose monitoring based on the complexity of regimen and the risk of hypoglycemia
- Use of insulin analogs and of glucose lowering agents with minimal hypoglycemic risk
- Provide education support to patients and care givers

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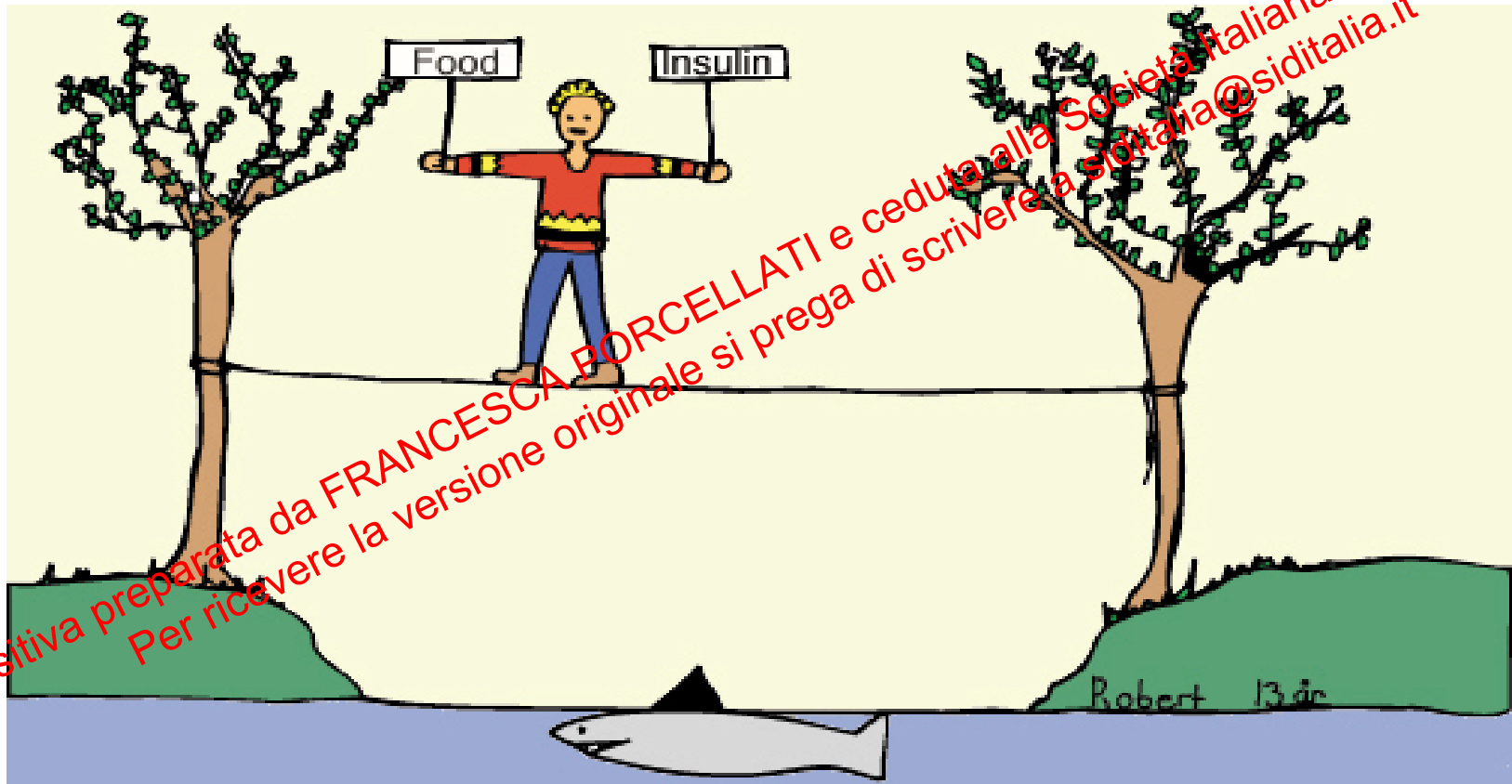


CONCLUSIONS

- Ageing *per se* modifies the counterregulatory and symptomatic responses to hypoglycemia
 - Effective self-treatment of hypoglycemia may be compromised
 - Little knowledge of the symptoms and treatment of hypoglycemia are reported
- Hypoglycemia in older people with diabetes is less recognized and under reported and this is of concern as in the elderly morbidity of hypoglycemia poses particular problems and the mortality may be unrecognized
- Efforts should focus to its prevention by:
 - recording events and individualize targets of cure
 - rationalizing use of drugs
 - educating the diabetes team, patients and care givers

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Hypoglycaemia is iatrogenic

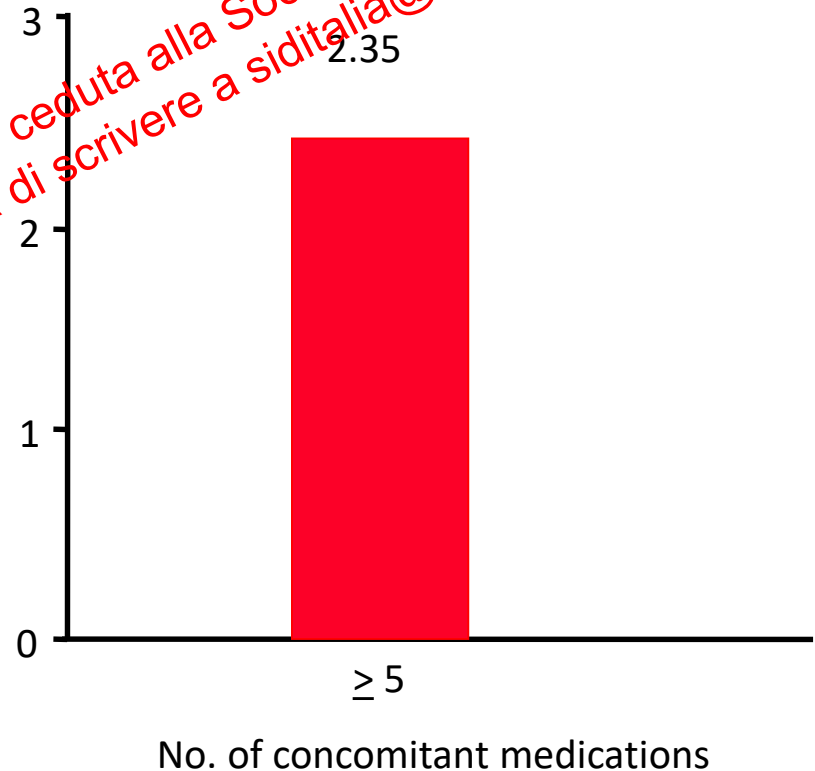
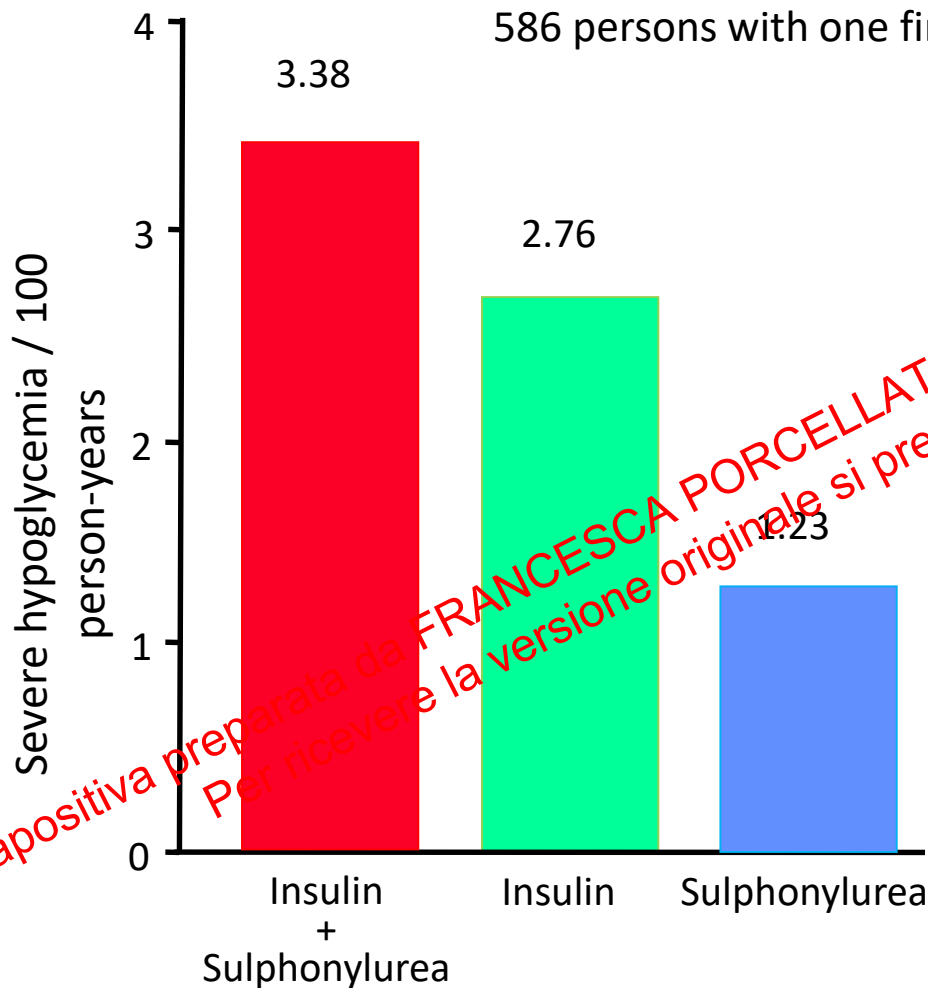


Diapositiva preparata da FRANCESCA PORCELLATI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Thank you for your attention



Severe Hypoglycemia in Type 2 Diabetes





Ospedalizzazioni per ipoglicemia grave: la nostra osservazione

Periodo dal 1° luglio 2005 al 30 giugno 2011 → 205 accessi in PS per ipoglicemia grave

Il 49.5% ha richiesto l'ospedalizzazione

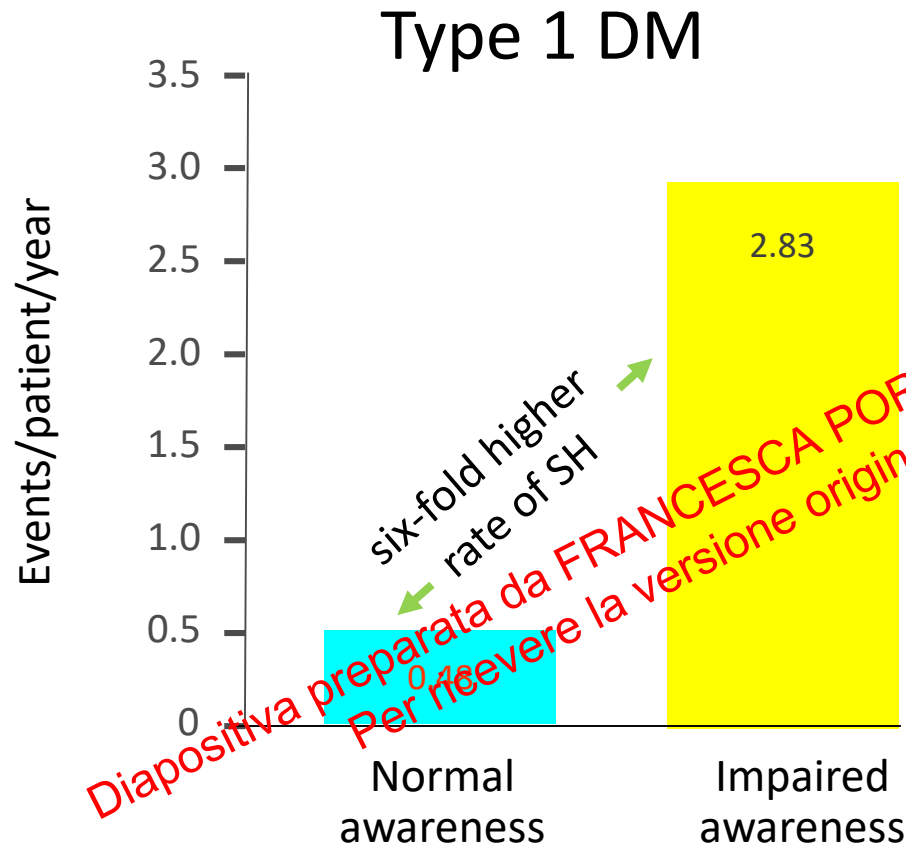
Il 57 % in terapia insulinica, il 43 % con ipoglicemizzanti orali; di questi ultimi, più della metà (62 %) era trattato con sulfoniluree

Genere (M/F)	16/18
Età (anni)	79 (3.8)
HbA1c (%)	6.2 (0.89)
Durata diabete (anni)	9.7 (11)
Creatinina (mg/dl)	1.68 (min 0.4; max 5.5)
eGFR (ml/min/1.73m ²)	45 (7)
Glicemia al momento del ricovero (mg/dl)	35 (12)

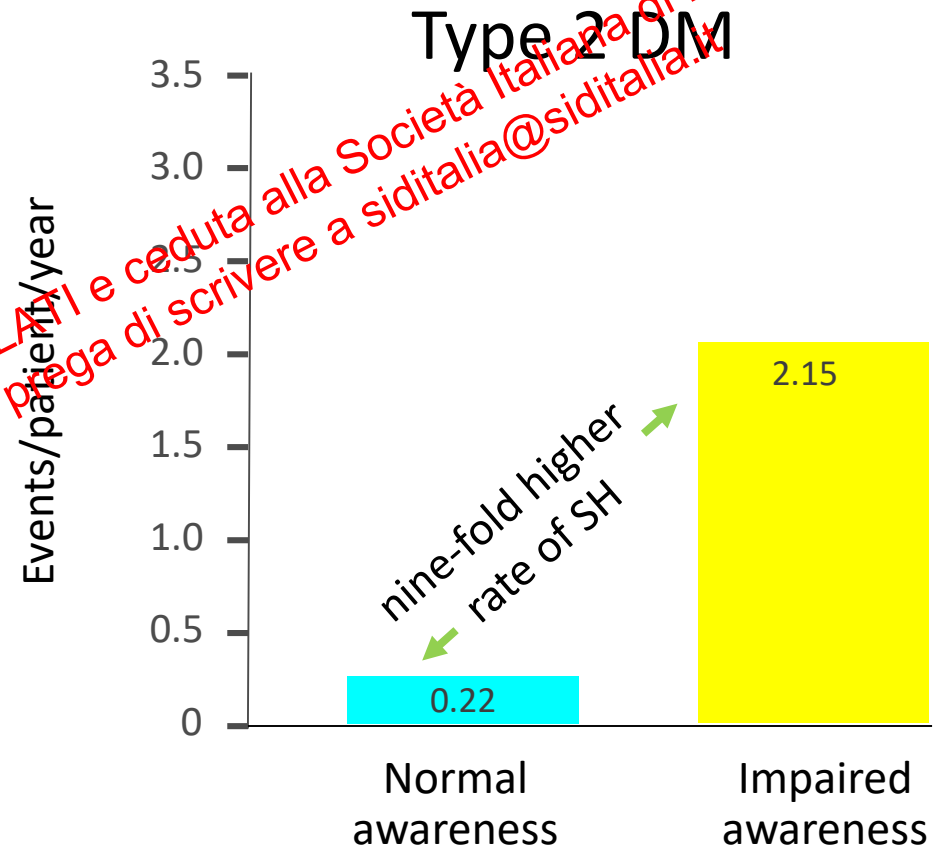
Dati espressi come media (SD) se non altrimenti specificato



Loss of Awareness Increases the Risk of Severe Hypoglycemia (SH)



Gold A.E. et al.
Diabetes Care 17:697-703, 1994



Henderson J.N. et al.
Diabetic Med 20:10161021,2003



Patients With Type 2 Diabetes and Dementia: the DIMORA Study

Patients with dementia and SH compared to those with dementia without SH

Characteristic	Hypoglycemia, n = 202	No Hypoglycemia, n = 981	P
Age, y	85 (7)	82 (8)	.007
Sex (men/women)	(65/137)	(261/720)	.57
BMI	24.8 (3.4)	24.3 (4.8)	.211
HbA1c, %	7.3 (1.0)	7.0 (1.2)	.008
ADL impairments	4.8 (0.7)	4.4 (1.3)	<.001
Length of stay, y	1.7 (3.0)	2.0 (7.7)	.006
Comorbidities	2.2 (1.0)	1.9 (1.2)	.002
AOD, n (%)	138 (70)	402 (43)	<.001
Insulin use, n (%)	54 (24)	336 (36)	.001
Insulin + AOD, n (%)	10 (6)	56 (6)	.995

Variables	Unadjusted OR (95% CI)	P	Model AOD [†] OR (95% CI)	P	Model Insulin [†] OR (95% CI)	P
Metformin	0.859 (0.565–1.306)	.480	0.678 (0.380–1.210)	.189		
Sulphonylurea	4.931 (3.186–7.630)	<.001	8.805 (4.260–18.201)	<.001		
Metformin + sulphonylurea	2.931 (1.796–4.782)	<.001	6.639 (3.273–14.710)	.001		
Glinides	0.458 (0.164–1.281)	.137	1.486 (0.401–5.508)	.554		
Insulin rapid	0.548 (0.355–0.848)	.007			0.333 (0.184–0.602)	<.001
Insulin intermediate*	1.306 (0.537–3.175)	.556			0.812 (0.211–3.123)	.762
Insulin long acting	0.414 (0.148–1.154)	.092			0.248 (0.070–0.882)	.031