ASSOCIAZIONE MEDICI DIABETOLOGI 1974

XVIII CONGRESSO NAZIONALE
25|28 MAGGIO 2011

Rossano Calabro
Complesso Nausicaa - Itaca
c.da Zolfara, 1
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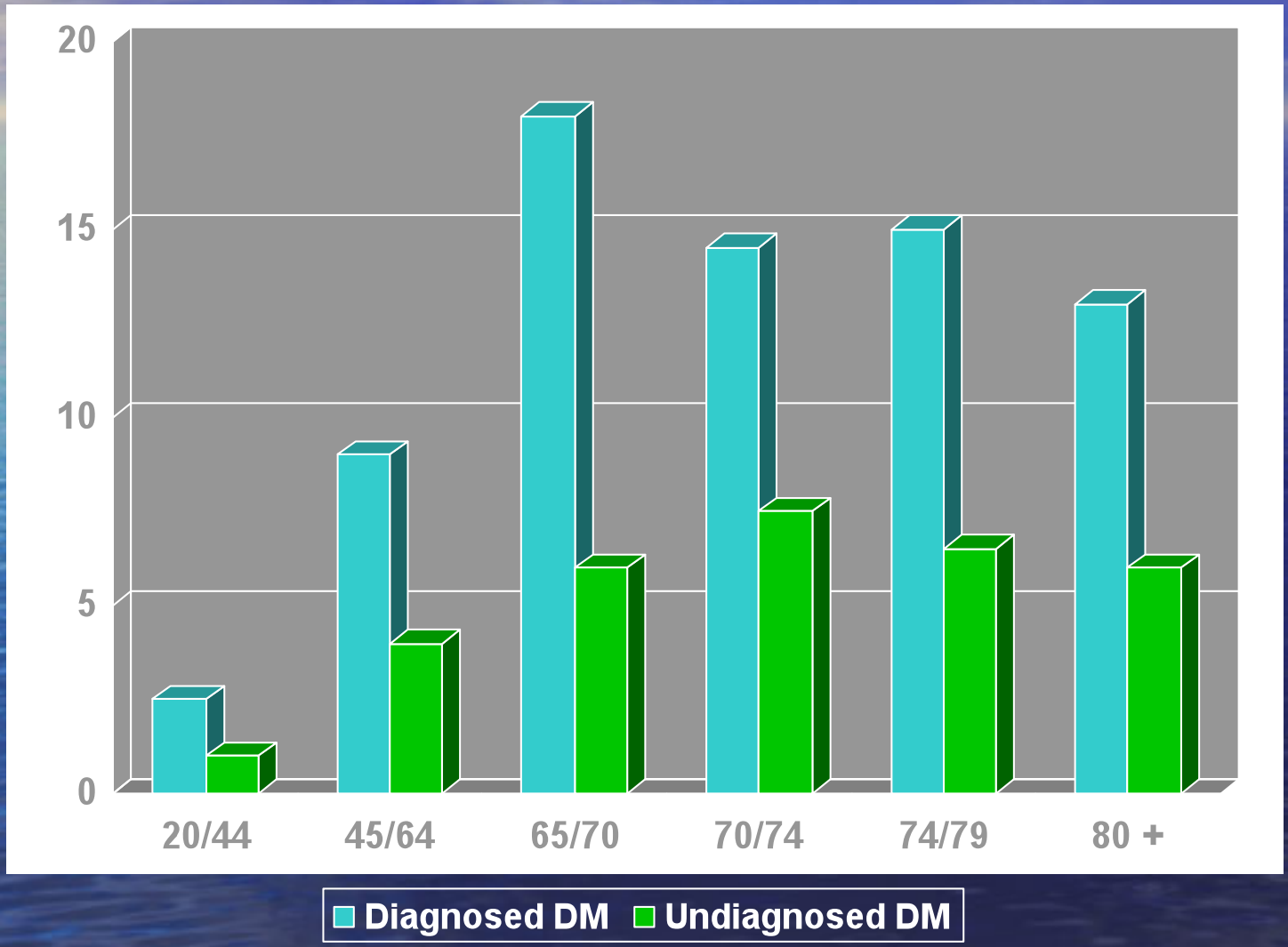
Efficacia e tollerabilita' della Vildagliptin in un gruppo di pazienti anziani affetti da DM T2

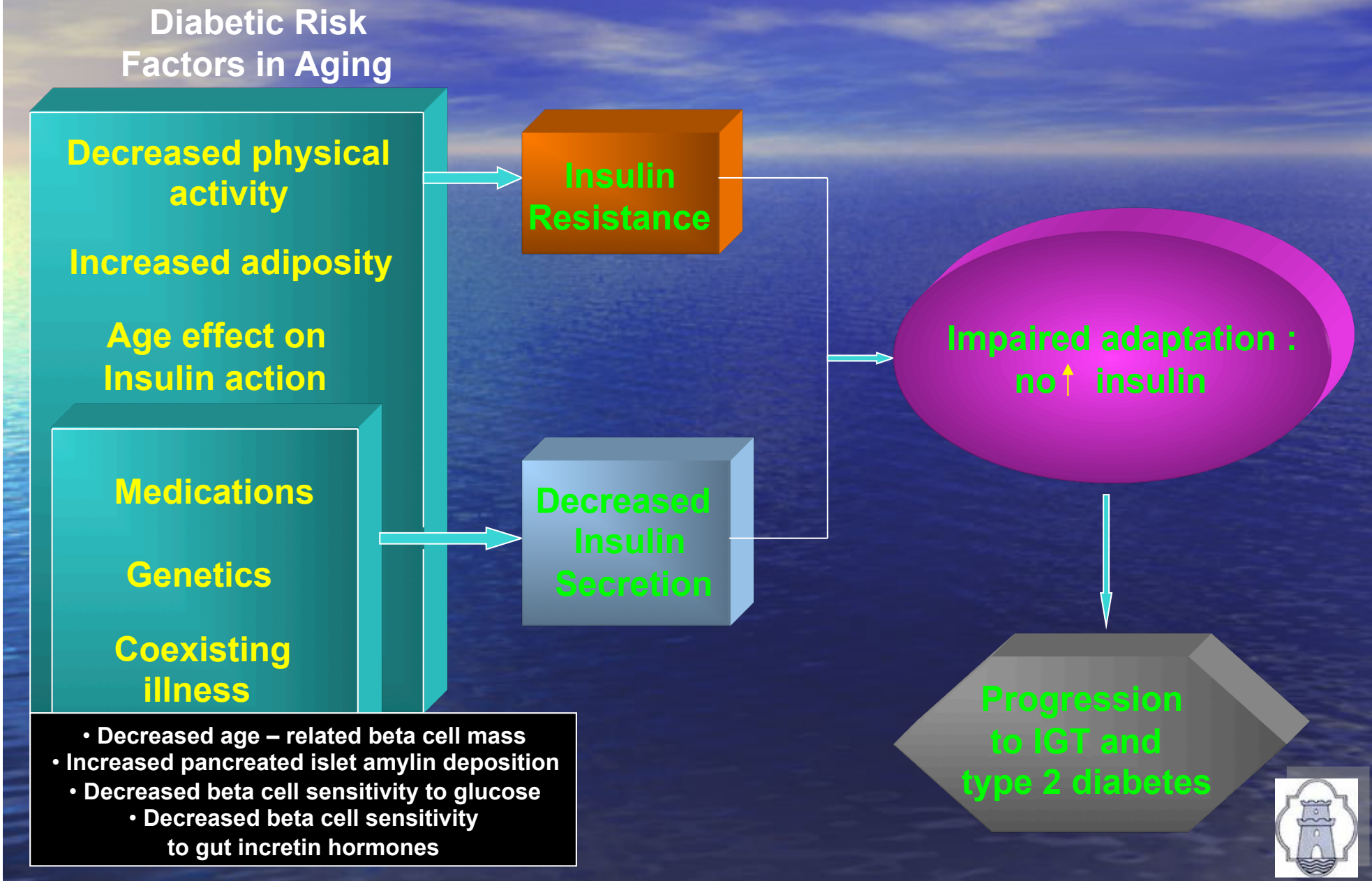
Dr. A. Maioli Castriota Scanderbech
S.O.D. di Diabetologia

Prevalence of Diagnosed & Undiagnosed Diabetes by Age , NHANES 1999 - 2002



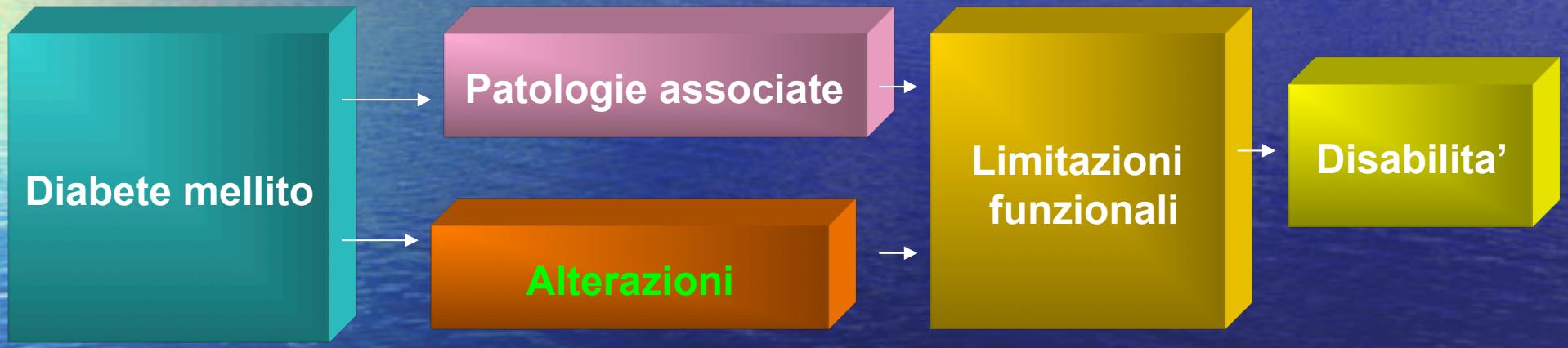
E. Selvin et al . Diabetes Care 29 : 2415 – 2419 ; 2006

Model for age – related hyperglycemia



Il diabete mellito come fattore di rischio di disabilita' nel soggetto anziano

Cardiopatia ischemica , scompenso cardiaco, arteriopatia degli arti inferiori , ipertensione , obesita' , artrosi .



- acuita' visiva
- sensibilita' periferica
- forza muscolare
- declino cognitivo

- velocita' di marcia
- equilibrio
- alzarsi

Therapeutic Regimens

DRUGS:

glimepiride

repaglinide

metformin

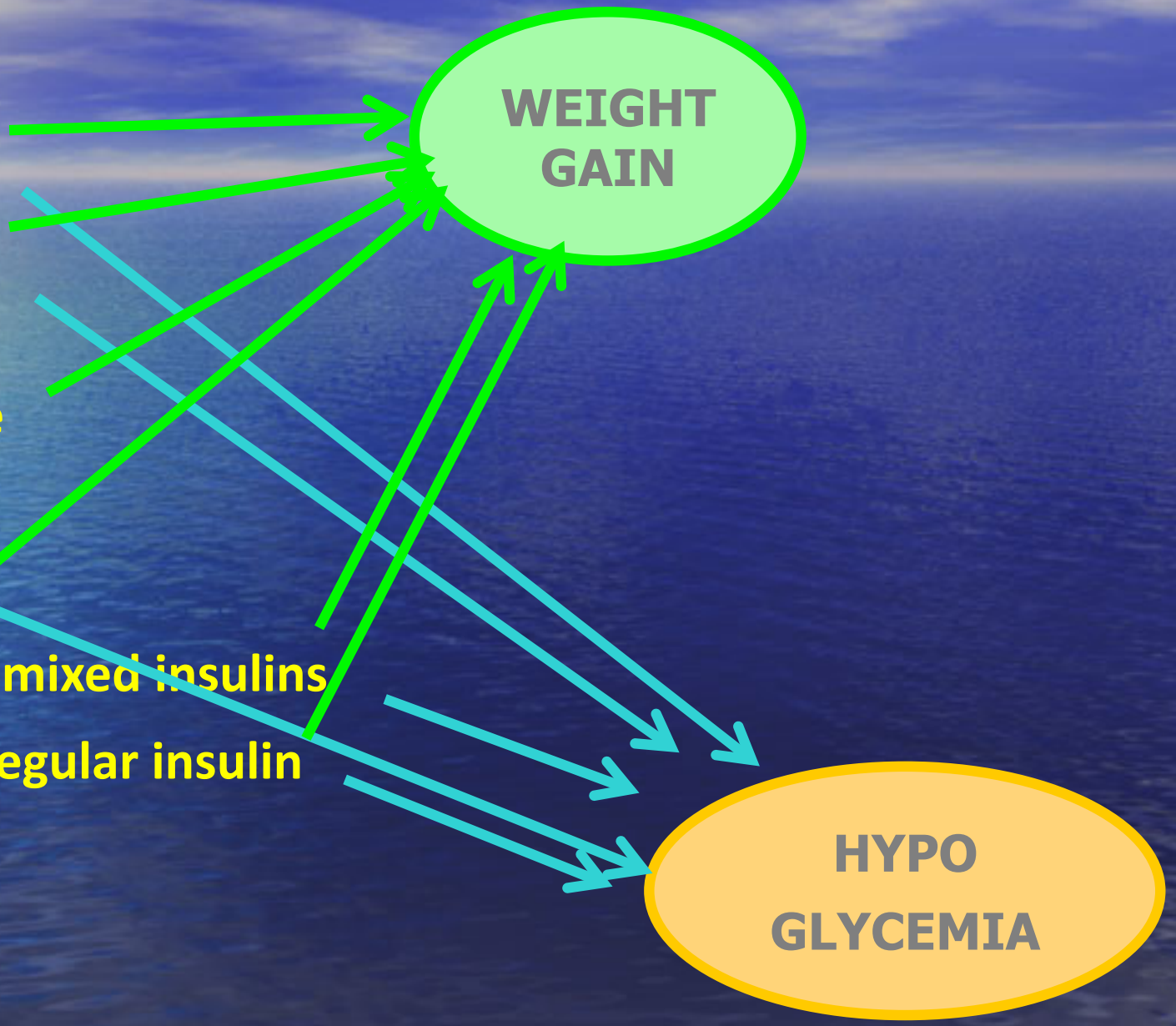
rosiglitazone

acarbose

glargine,

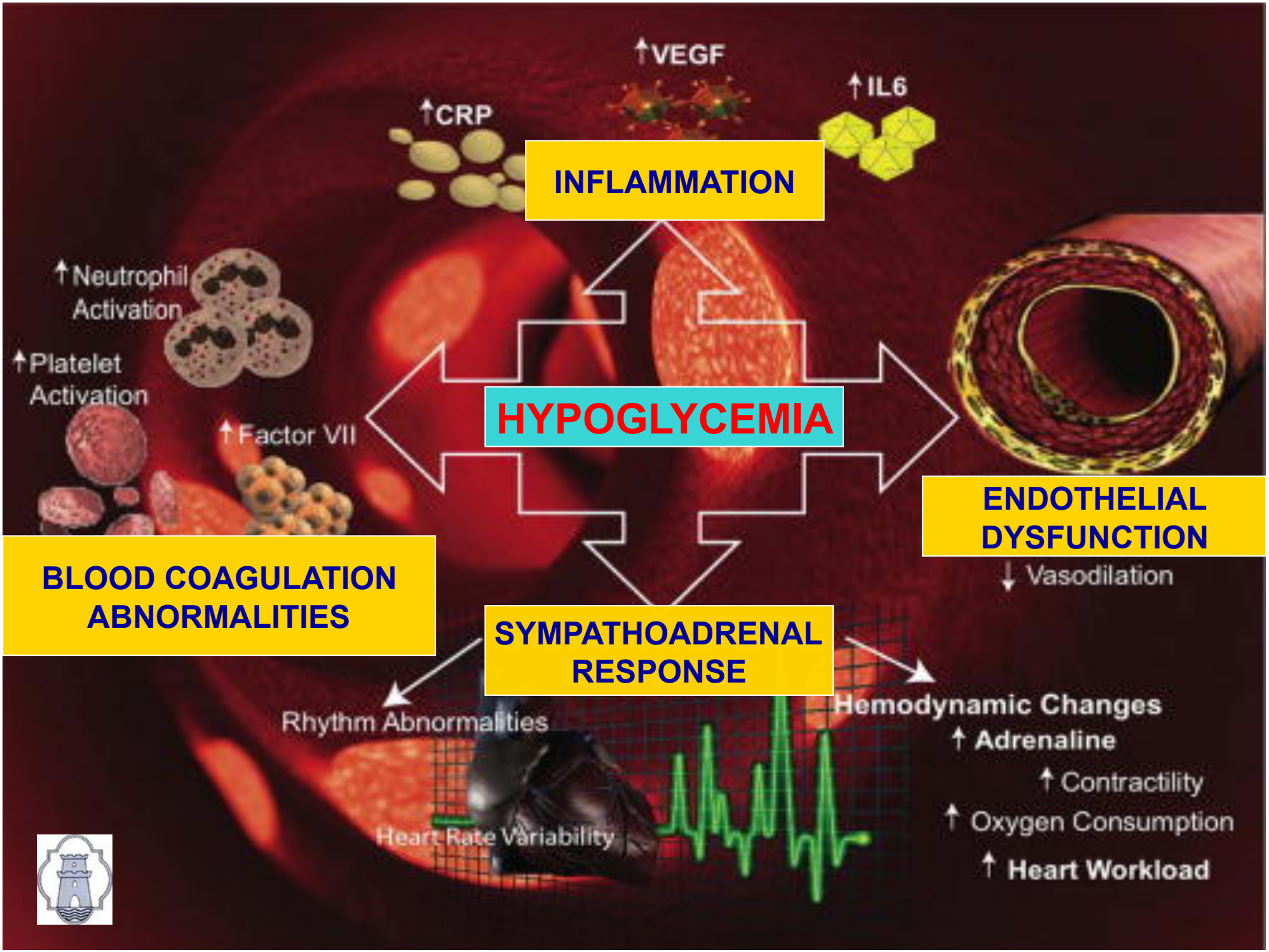
NPH and premixed insulins

Aspart and regular insulin



Fattori che predispongono i pazienti anziani diabetici alla ipoglicemia

- Scorretto o inadeguato apporto alimentare
- Compromissione dello stato cognitivo
- Politerapia e scarsa adesione agli schemi terapeutici
- Difficolta' a correggere precocemente le ipoglicemie
- Insufficienza epatica / renale
- Comorbilita' che masherano o confondono i sintomi (demenza , depressione , disturbi del sonno etc.)


↑VEGF
↑IL6
↑CRP
INFLAMMATION
↑Neutrophil Activation
↑Platelet Activation
↑Factor VII
HYPOGLYCEMIA
ENDOTHELIAL DYSFUNCTION
↓Vasodilation
BLOOD COAGULATION ABNORMALITIES
SYMPATHOADRENAL RESPONSE
Rhythm Abnormalities
Heart Rate Variability
Hemodynamic Changes
↑ Adrenaline
↑ Contractility
↑ Oxygen Consumption
↑ Heart Workload

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

Rachel A. Whitmer , Andrew J. Karter , Kristine Yaffe , Charkes P. Quesenberry , Joseph V. Selby .

JAMA 2009; (15) : 1565 - 1572

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 (1.64-2.81)	1.86 (1.42-2.43)	1.80 (1.37-2.36)
3 or more	43	2.60 (1.78-3.79)	2.10 (1.48-2.73)	1.94 (1.42-2.64)

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.
[a] Analyses combined using Cox proportional hazard models.
[b] The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.
[c] Adjustment made using a comorbidity composite scale.

Conclusion : Among older patients with type 2 diabetes , a hystory of severe hypoglycemic episodes was associated with a greater risk of dementia . Whether minor hypoglycemic episodes increase risk of dementa .

Older Patients Need Individualized Care

American Diabetes Association recommends less aggressive target goals for older patients with advanced complications, comorbid illness, cognitive, or functional impairment

FBG 140 mg/dL (vs 90-130 mg/dL)
Postprandial 200-220 mg/dL (vs <180mg/dL)

American Geriatric Society (AGS) recommends less stringent A1c if life expectancy less than 5 yrs

A1c 8%
BP140/80

but

A1c 7% reasonable, if relatively healthy and good functional status

Mechanism of Action of Incretin

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Pancreas

Beta cells

Alpha cells

Glucose dependent ↑ Insulin (GLP-1and GIP)

↑ Glucose uptake by peripheral tissue

↓ Blood glucose in fasting and postprandial states

Glucose-dependent ↓ Glucagon (GLP-1)

↓ Hepatic glucose production

(DPP-4 inhibitor) *Vildagliptin* *Sitagliptin* *Saxagliptin*

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Pleiotropic Actions of GLP-1

Pancreas

- ↑ Insulin synthesis and secretion
- ↑ Expression of β-cell genes
- ↑ β-cell proliferation/neogenesis
- ↓ β-cell apoptosis
- ↓ Glucagon secretion

Nervous System

- ↓ Appetite
- ↑ Satiety
- ↑ Neuronal cell proliferation/neogenesis
- ↑ Neuronal cell survival

Stomach and Intestine

- ↓ Gastric emptying
- ↓ Bowel motility

Cardiovascular System

- ↑ Arterial blood pressure and heart rate
- ↑ Post-ischemic myocardial function
- ↑ Endothelial relaxation

Liver

- ↑ Glucose uptake
- ↓ Glucose production

Fat/Muscle

- ↑ Glucose uptake
- ↑ Lipogenesis
- ↑ Glycogen synthesis

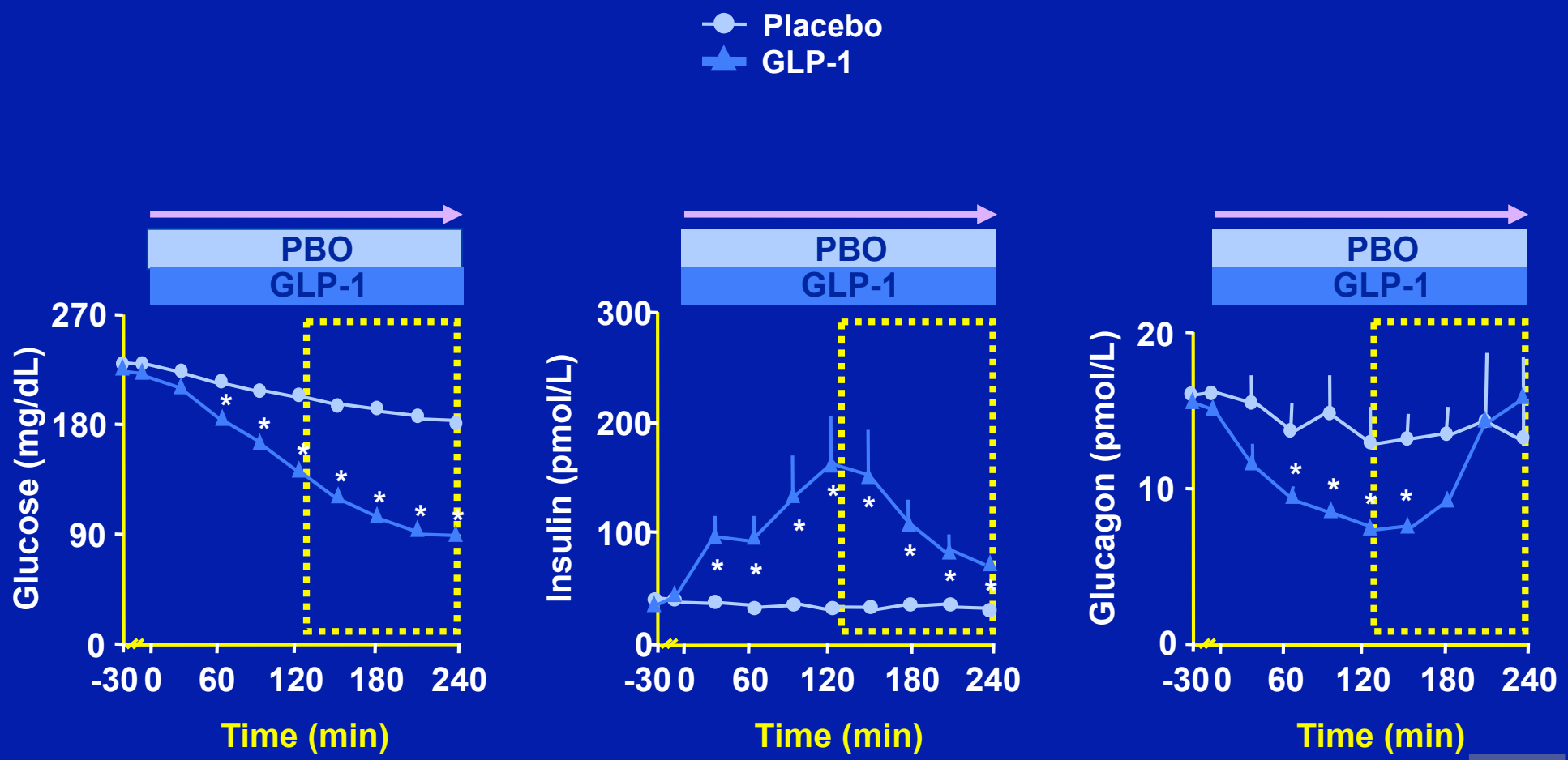
Endocrine System

- ↑ CRH-ACTH-cortisol axis
- ↑ GnRH-LH axis

Lungs

- ↑ Surfactant production
- ↑ Arterial vasorelaxation

GLP-1 Effects Are Glucose Dependent in Type 2 Diabetes



N = 10; Mean (SE); *$P<0.05$
Data from Nauck MA, et al. *Diabetologia*. 1993;36:741-744

Summary of Clinical Data

Efficacy and tolerability of **vildagliptin** monotherapy in drug – naive patients with type 2 diabetes .
Pi – Sunyer FX et al. Diabetes Res Clin Pract 2007 ; **76** : 132 - 138

Effects of **vildagliptin** on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin .
Bosi E. et al . Diabetes Care 2007 ; **30** : 890 - 895

Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy : a randomized , placebo – controlled study .
Garber AJ et al . Diabetes Obes Metab 2007 ; **9** : 166 - 174

Effects of **vildagliptin** on glucose control in patients with type 2 diabetes Inadequately controlled with a sulphonylurea .
Garber AJ. et al Diabetes Obes Metab 2008 ; **10** : 1047 - 1056

Addition of **vildagliptin** to insulin improves glycaemic control in type 2 diabetes.
Fonseca V. et al Diabetologia 2007 ; 50 : 1148 - 1155

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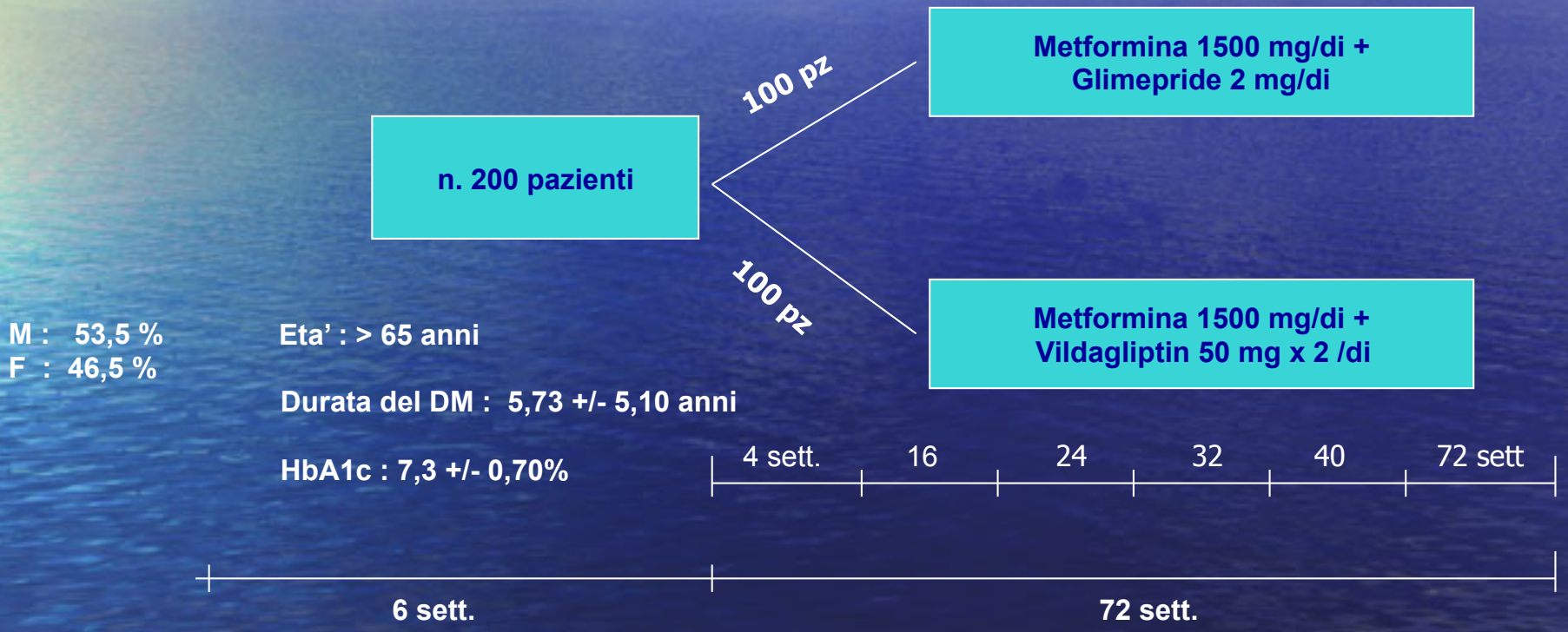
Efficacia e tollerabilita' della **Vildagliptin** in un gruppo di pazienti anziani affetti da DM T2

Lo scopo dello studio e' stato quello di valutare la efficacia e la sicurezza della Vildagliptin vs Glimepride in pazienti anziani affetti da DM T2 in controllo inadeguato con Metformina

Disegno dello studio



M : 53,5 %
F : 46,5 %

Eta' : > 65 anni

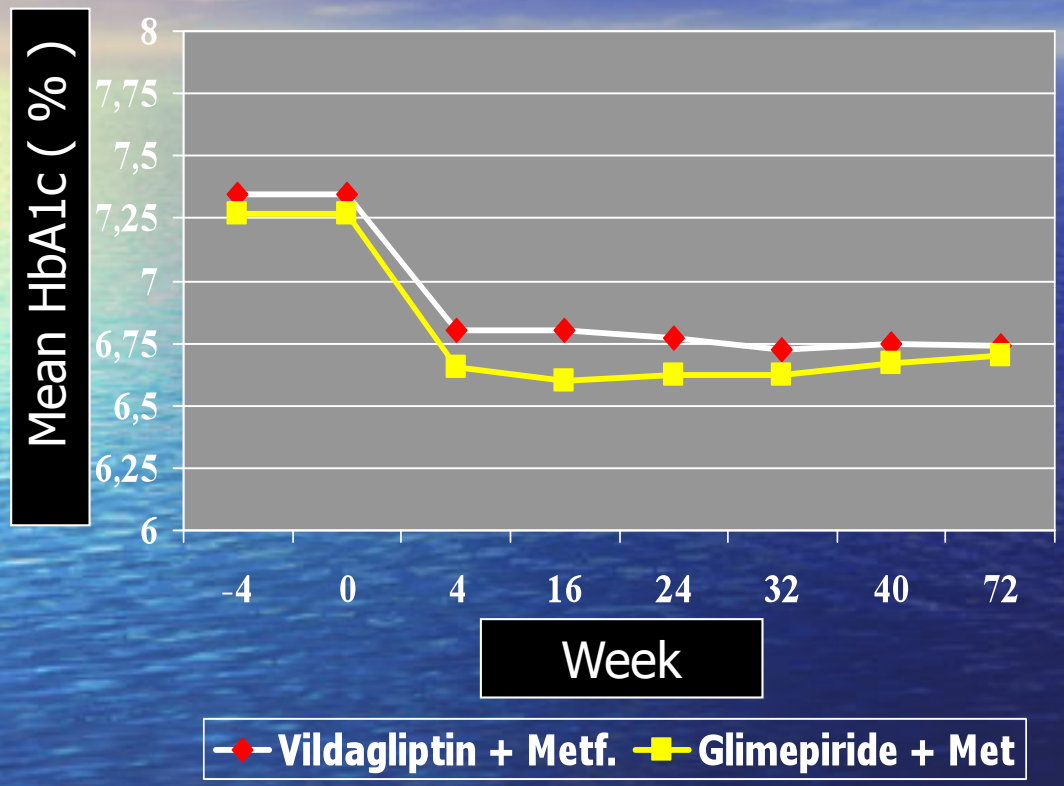
Durata del DM : 5,73 +/- 5,10 anni

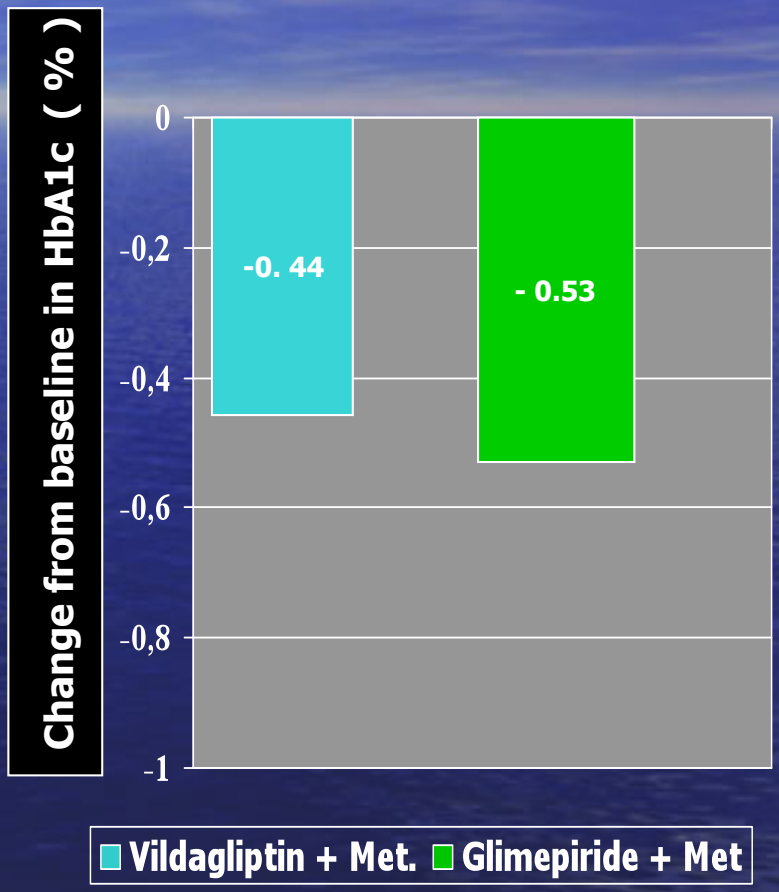
HbA1c : 7,3 +/- 0,70%

Caratteristiche della popolazione studiata

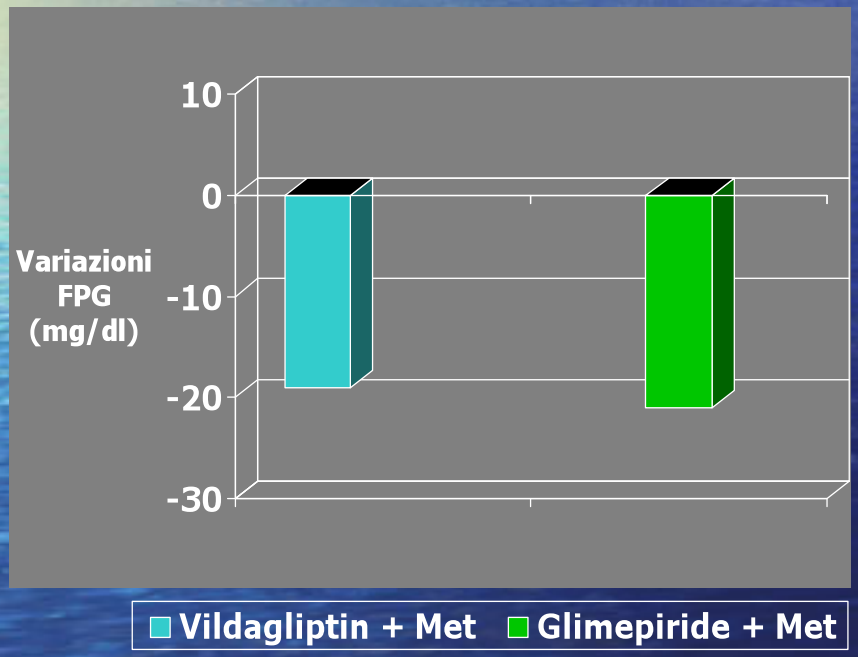
Parametri	Metformina +Glimepiride Gruppo A (n 100)	Metformina + Vildagliptin Gruppo B (n 100)
Anni	> 65 anni	> 65 anni
Maschi n %	53 %	54 %
Femmine n %	47 %	46 %
BMI kg/m2	31.80 +/- 5.27	31.69 +/- 5.25
Durata del Diabete (anni)	5.71 +/- 5.18	5.75 +/- 5.03
HbA1c %	7.31 +/- 0.70	7.30 +/- 0.70
FPG mg/dl	165 +/- 41	165 +/- 40
GFR : 60 – 90 ml/ min /1,73 m2	45 %	43 %
GFR : 30 – 60 ml/ min / 1,73 m2	4.5 %	5 %
Ipertensione arteriosa	65 %	69 %

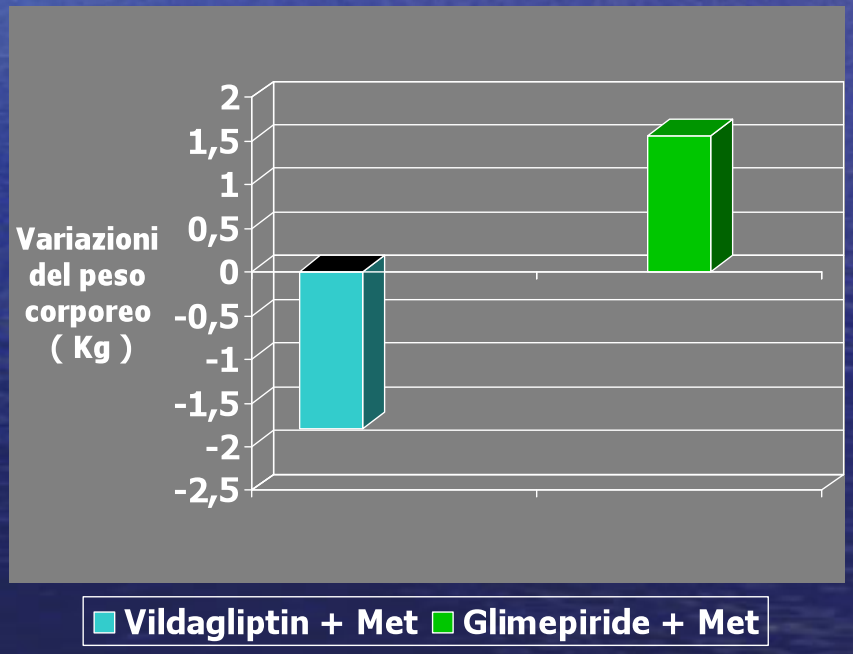
Variazione della HbA1c durante il follow - up



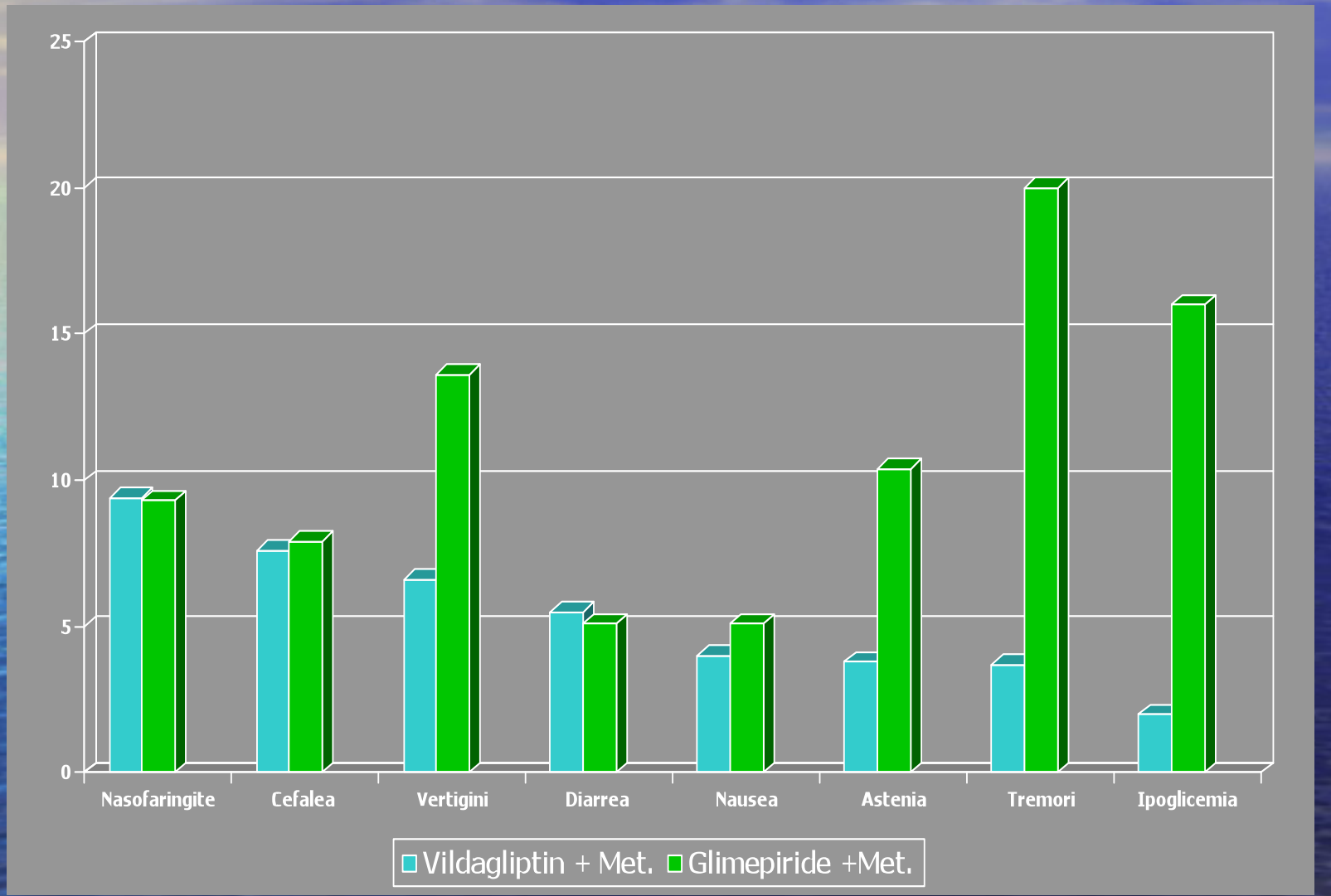


Variazioni della **FPG** e di **Peso Corporeo** al termine del follow – up





Gli effetti collaterali



CONCLUSIONI

La Vildagliptin (50 mg x 2/di) ha mostrato una non inferiorita' rispetto alla Glimepiride (2 mg/di) in termini di efficacia terapeutica accompagnandosi per di piu' ad una minore incidenza di episodi ipoglicemici e non determinando un incremento di peso . La Vildagliptin rappresenta un valido approccio terapeutico in pazienti affetti da DM T2 non ben controllati con la sola Metformina e specie in quei pazienti anziani particolarmente suscettibili alla ipoglicemia .

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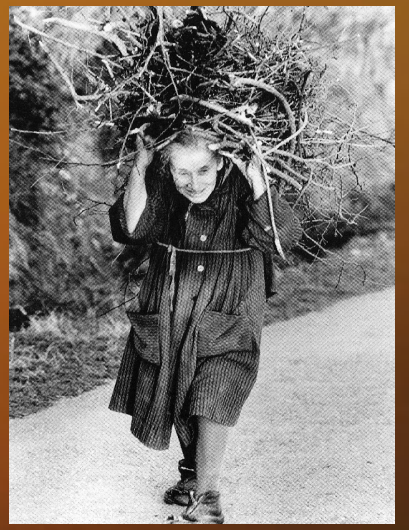
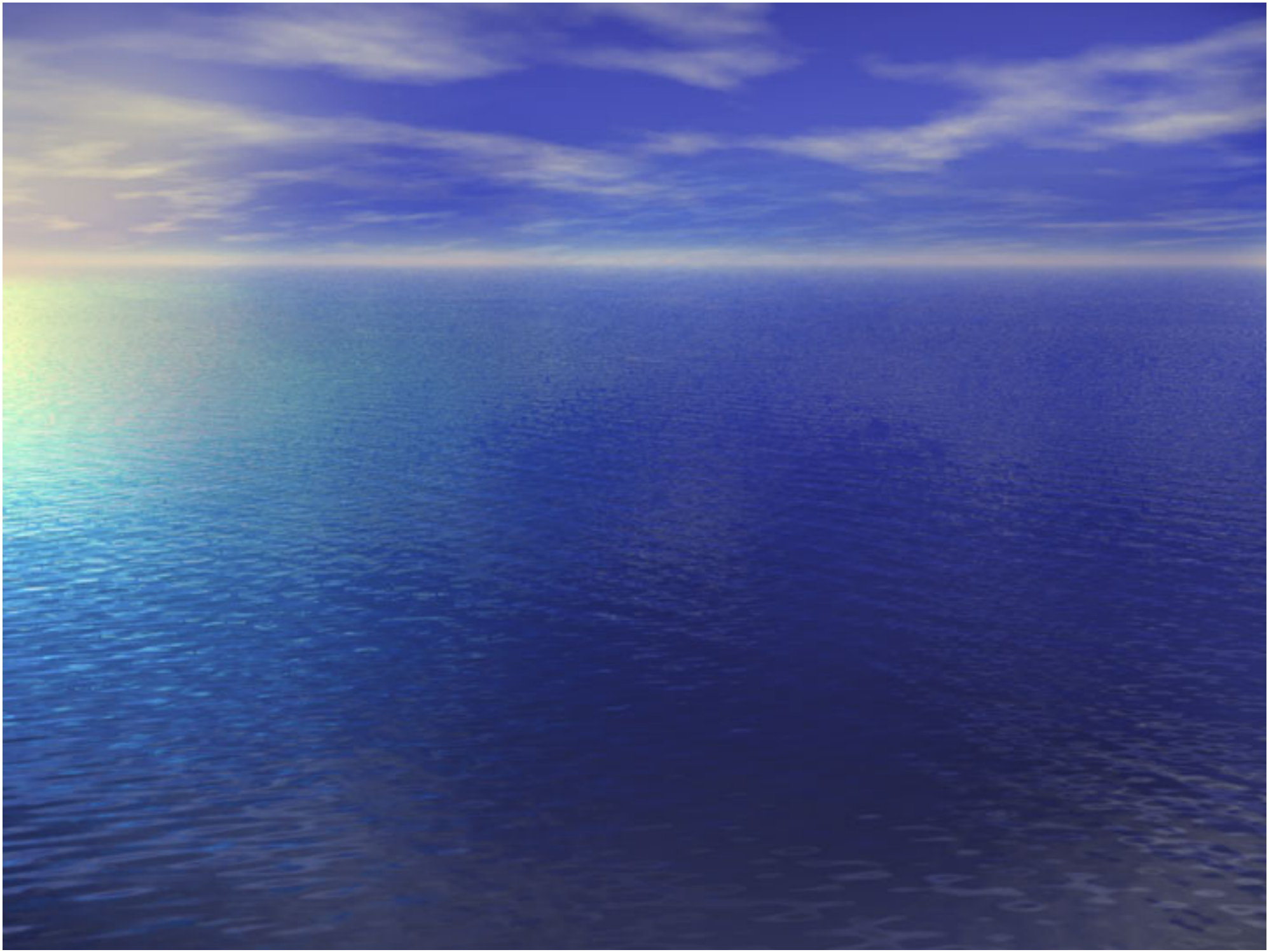
Il Diabete Mellito nell'anziano

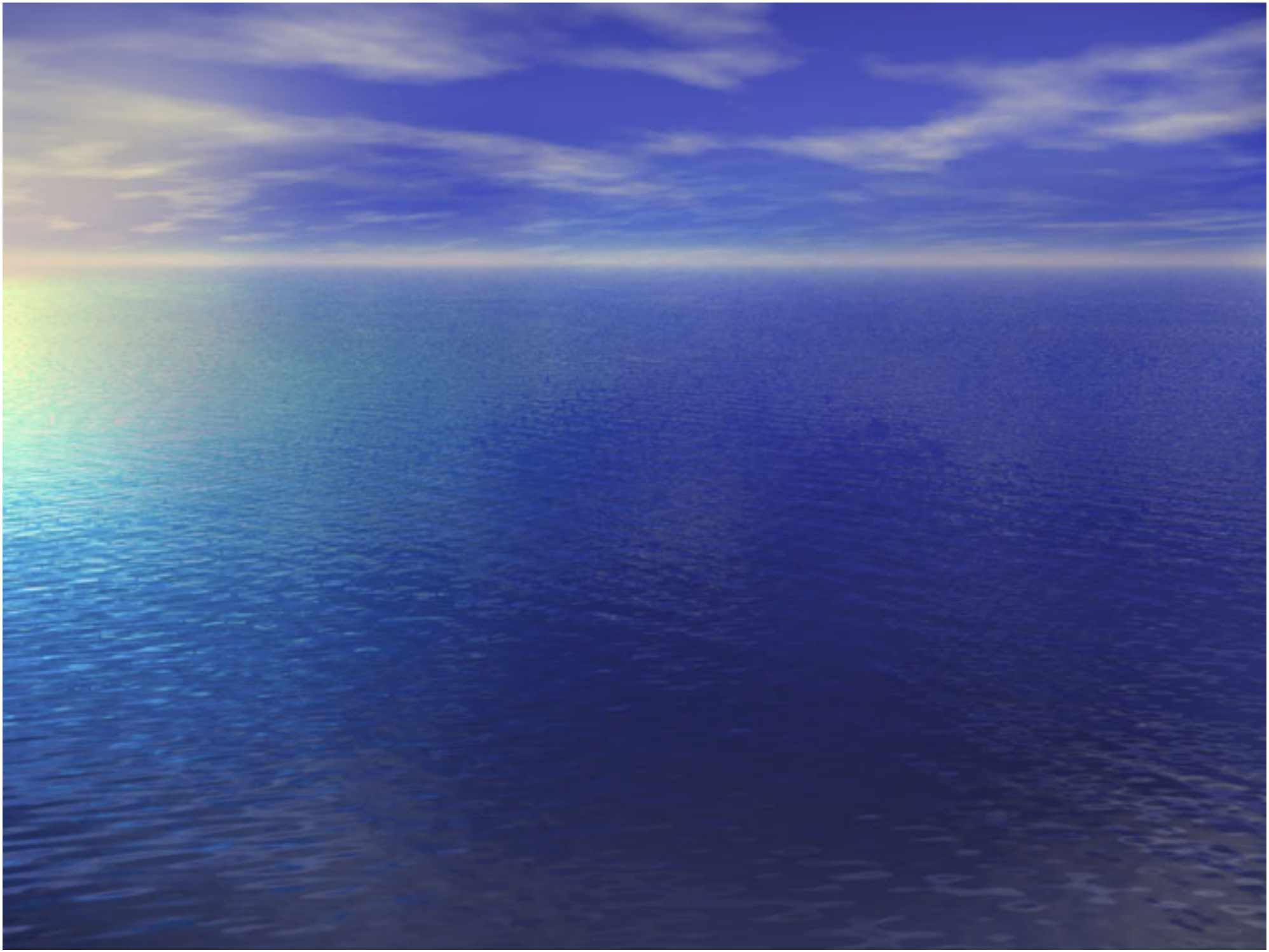
John Glenn
(REUTERS)

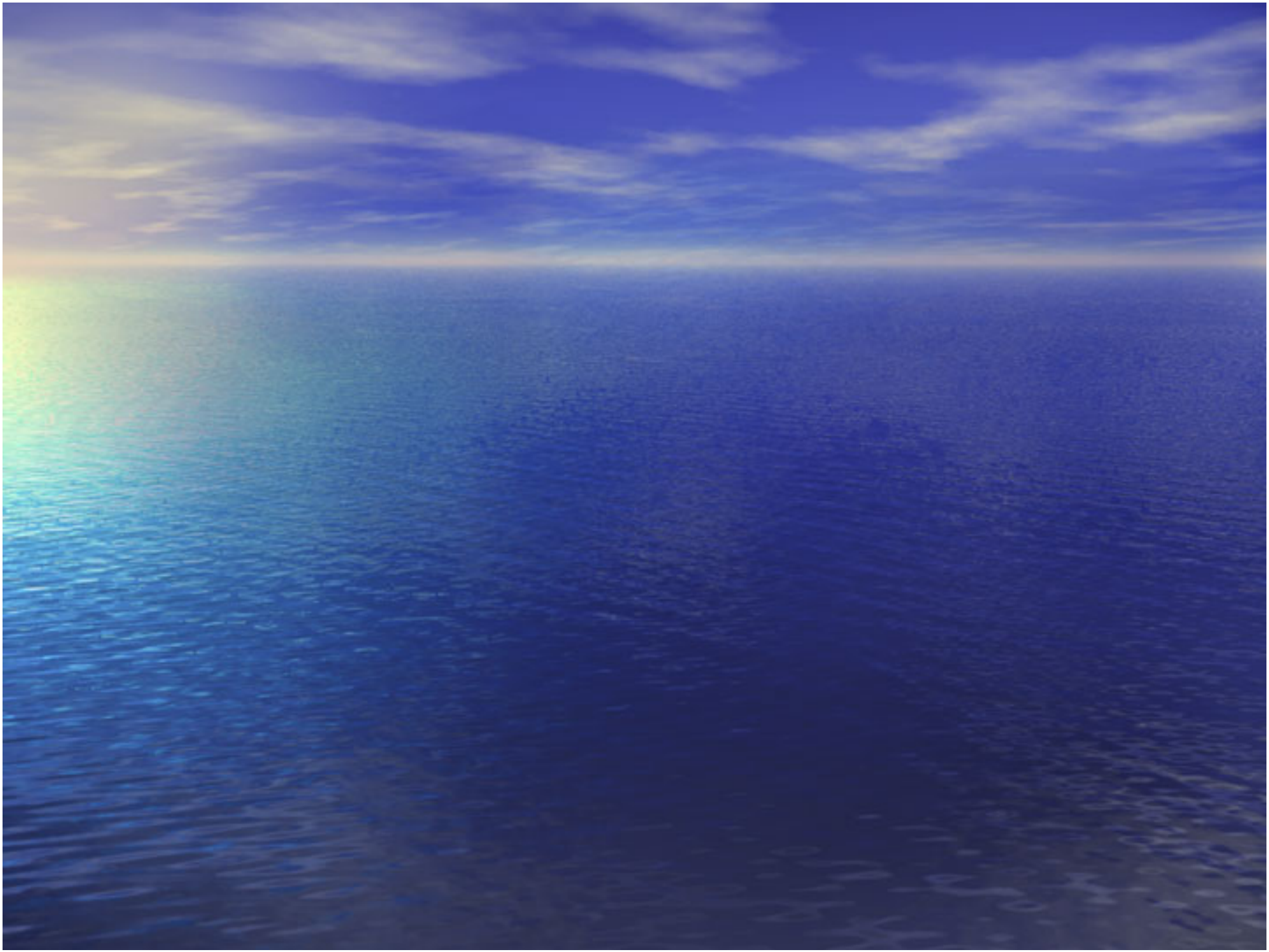


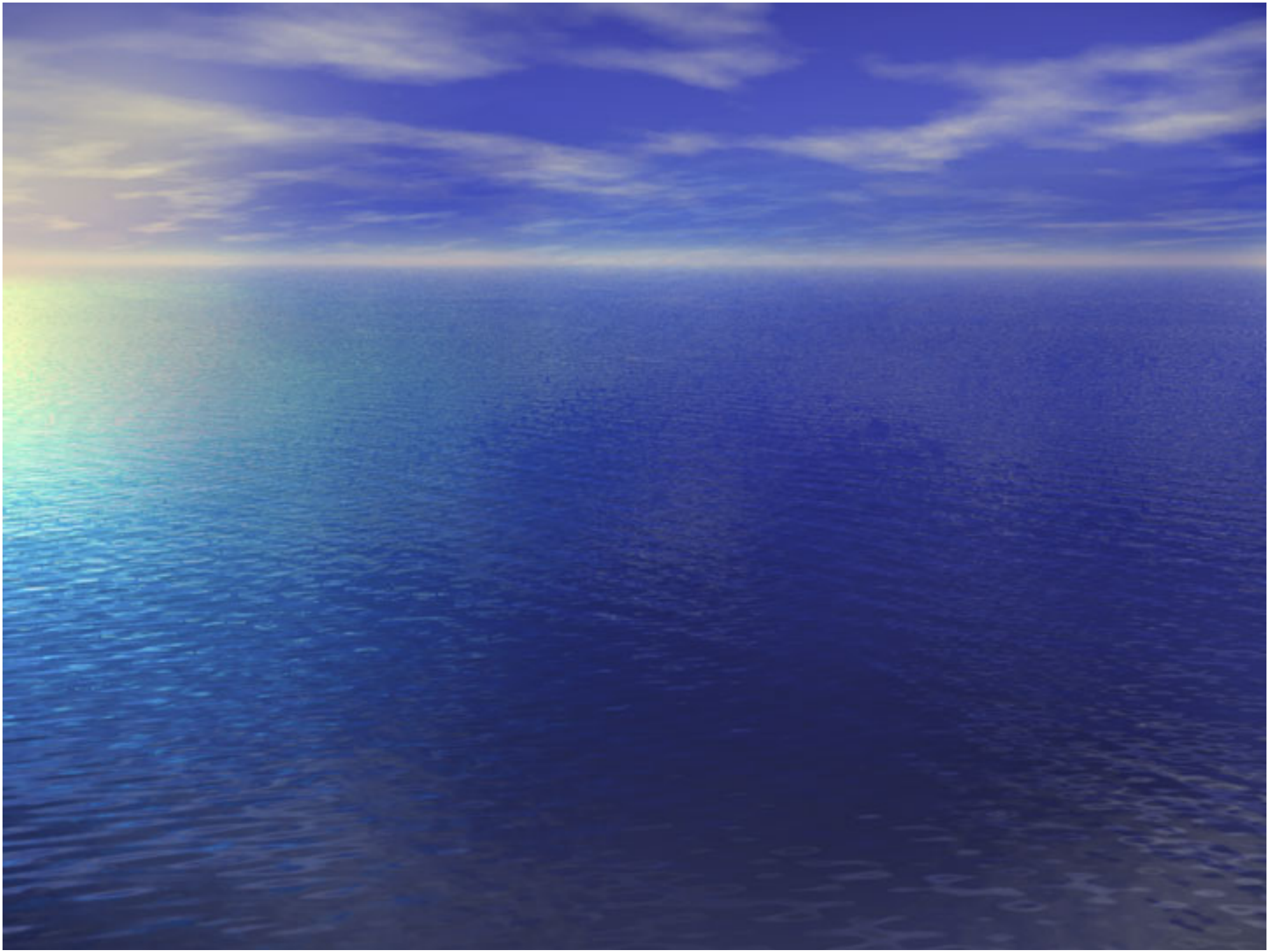
Grazie per l'attenzione !

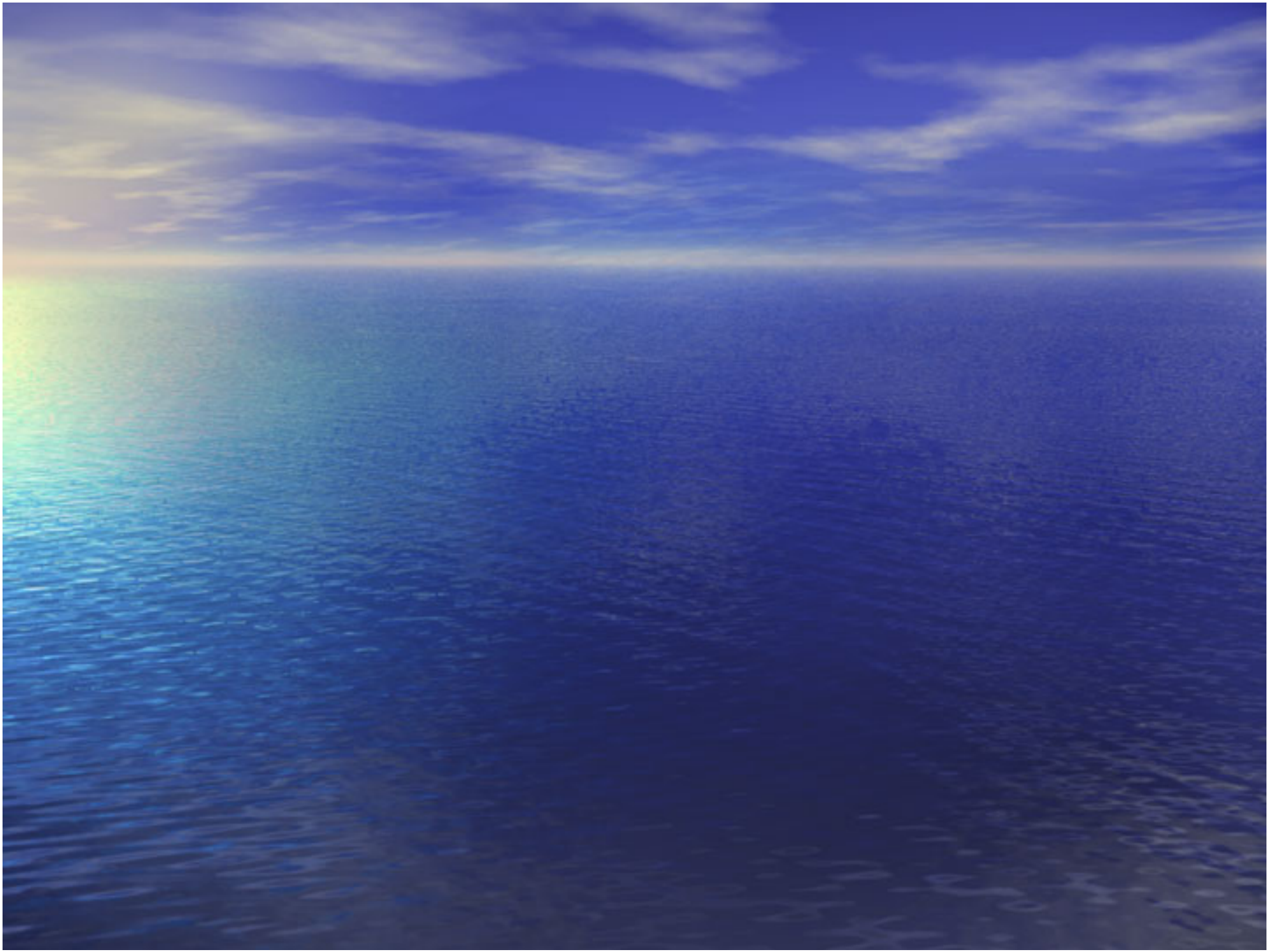
antonio.maioli@ospedalesancarlo.it











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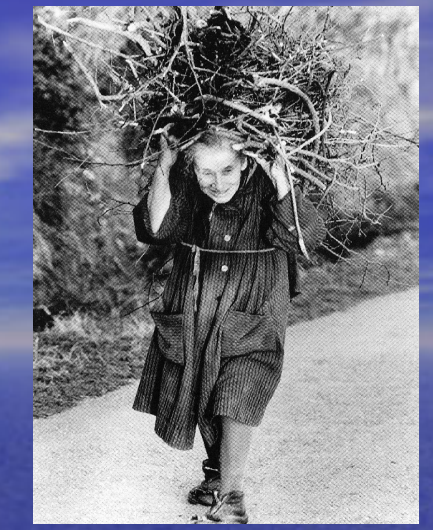
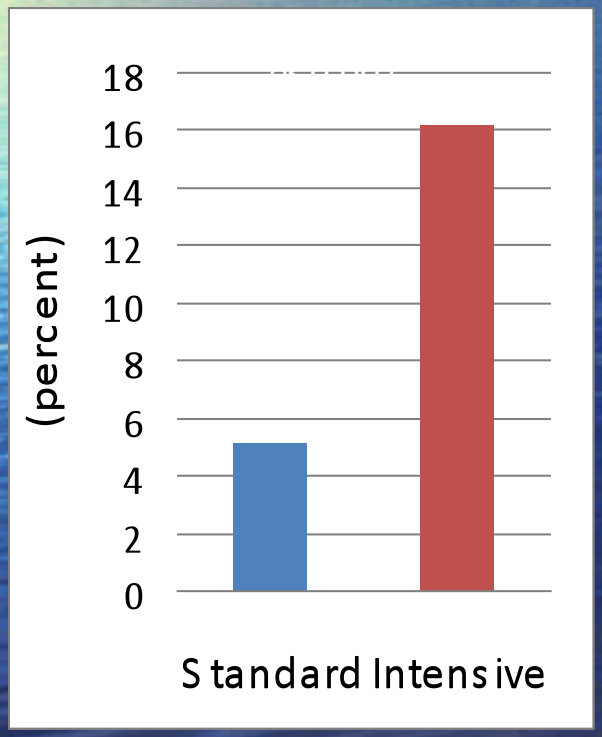


Efficacia e tollerabilita' della Vildagliptin in un gruppo di pazienti anziani affetti da DM T2

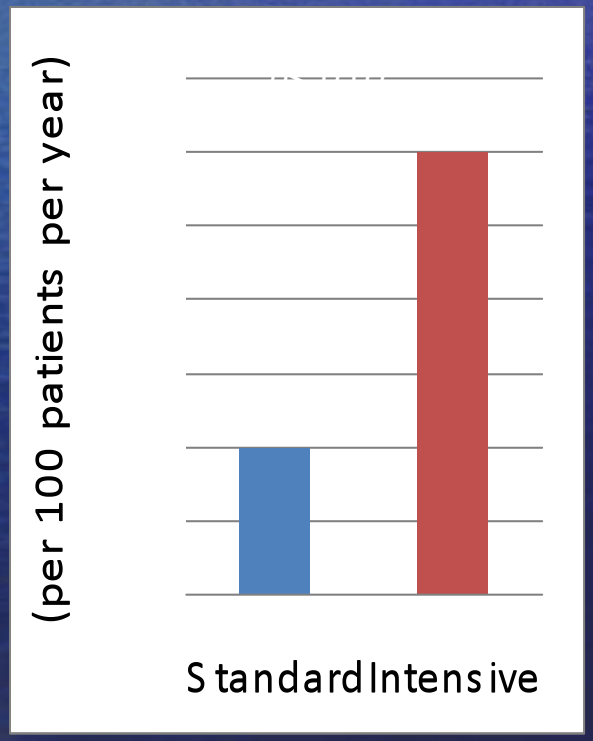
Dr. Antonio Maioli Castriota Scanderbech
S.O.D. Azienda Ospedaliera San Carlo - POTENZA

Severe hypoglycemic events in ACCORD, ADVANCE and VADT

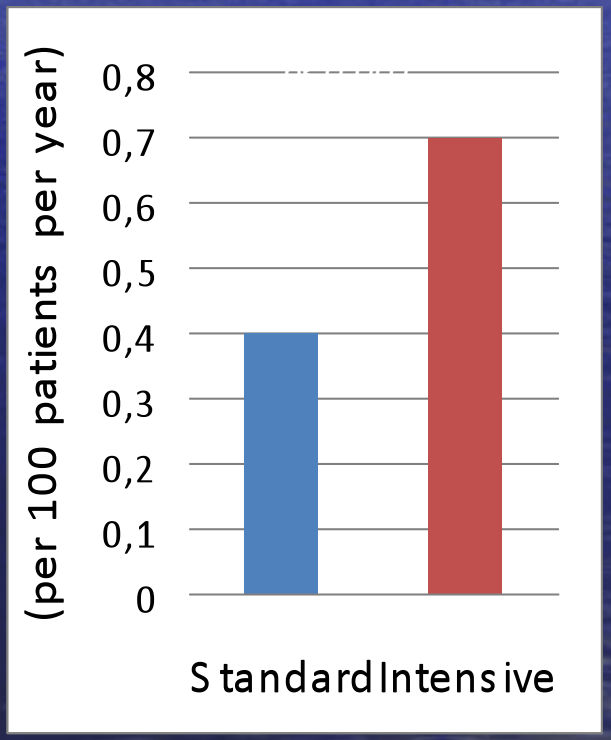
ACCORD



VADT

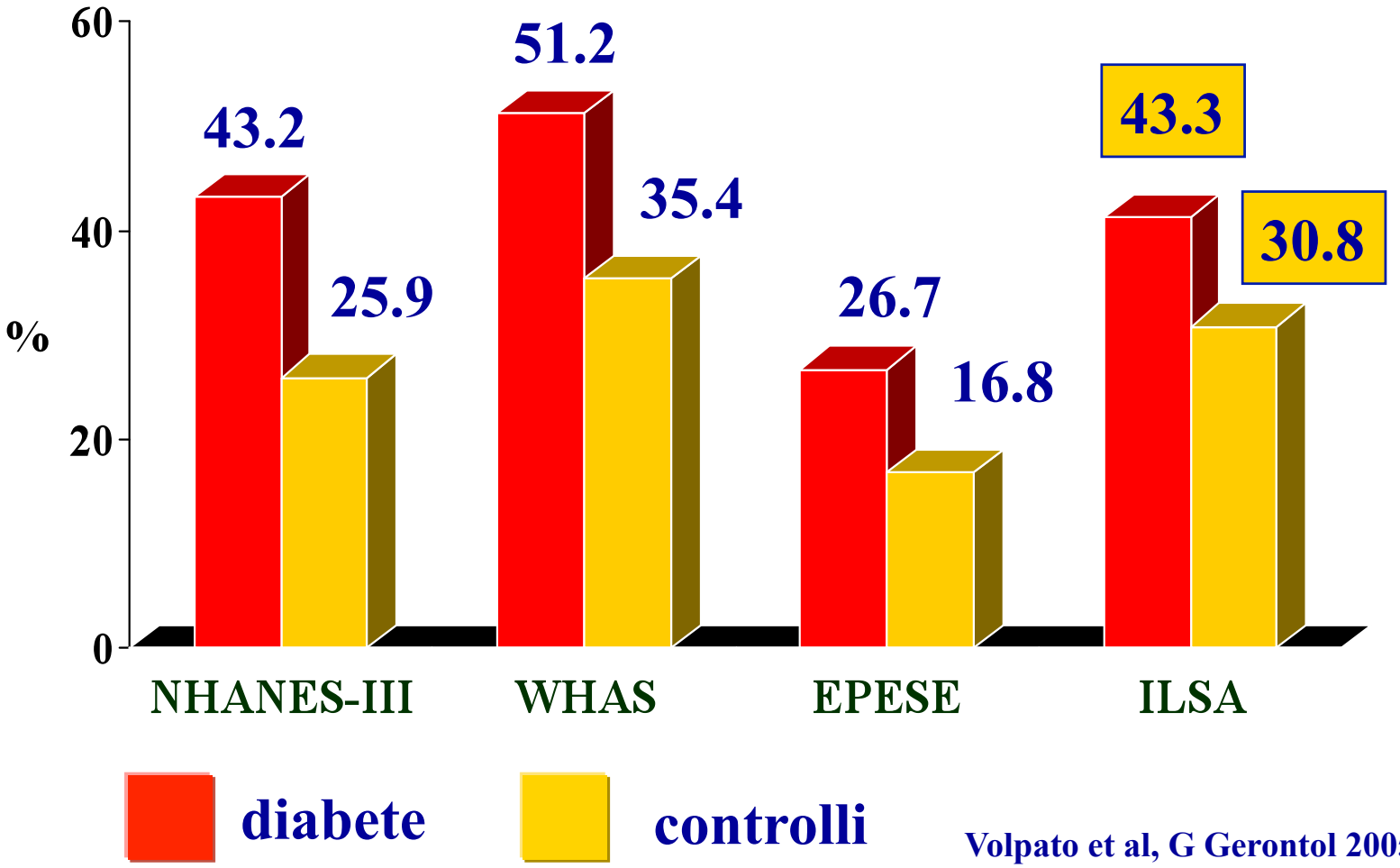


ADVANCE



[1]W. Duckworth et *NEJM* 2009;359:156; [2]The ACCORD Study Group *NEJM* 2008;358:2545;
[3]The ADVANCE Collaborative Group *NEJM* 2008,358:2560

Diabete mellito e disabilità fisica in studi epidemiologici

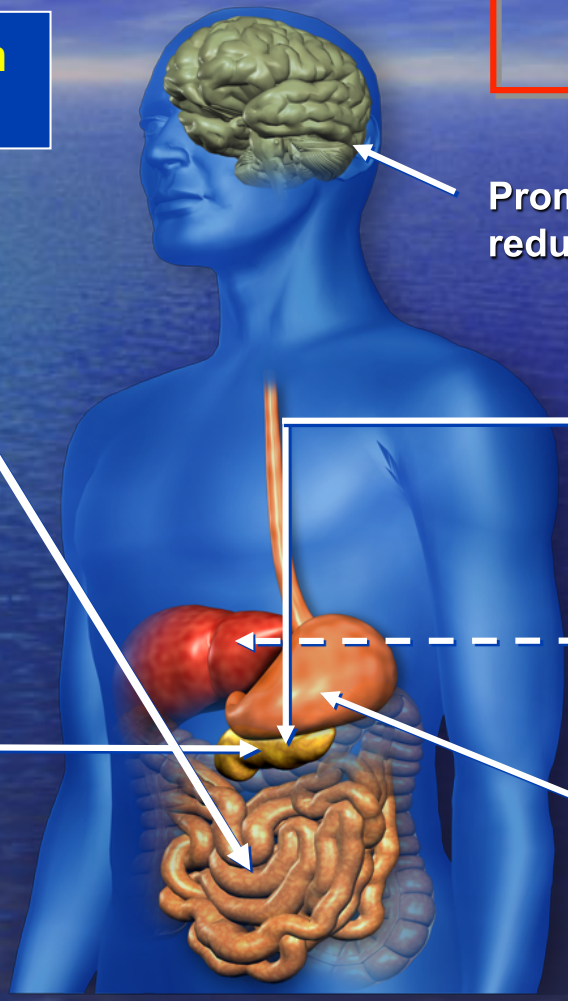


Volpato et al, G Gerontol 2005; 53:120-6

GLP-1 Modulates Numerous Functions in Humans

Long Term effects in Animals
↑ Cell mass
Maintains Cell function
Reduces cell apoptosis

GLP-1: Secreted upon the ingestion of food



Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

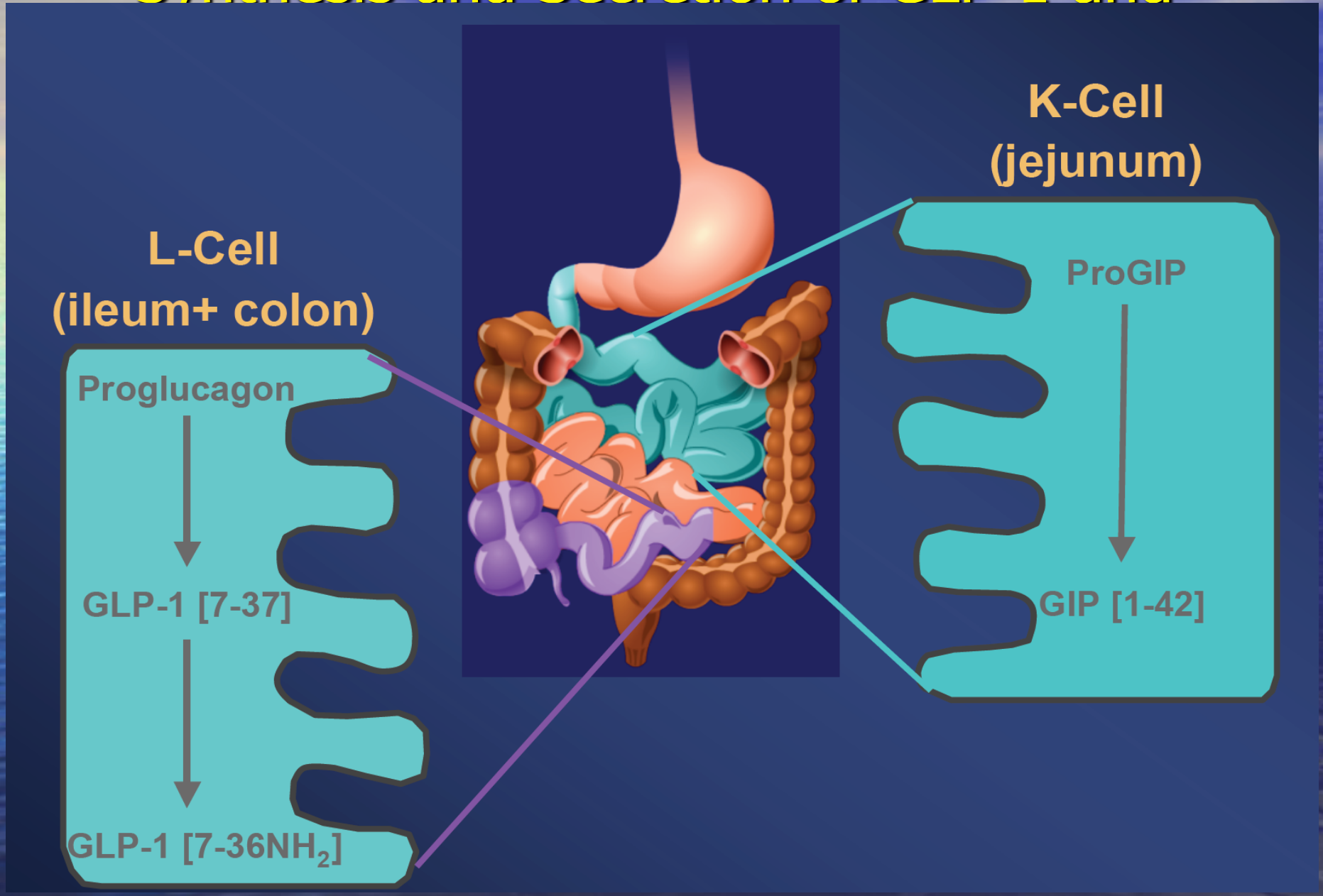
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

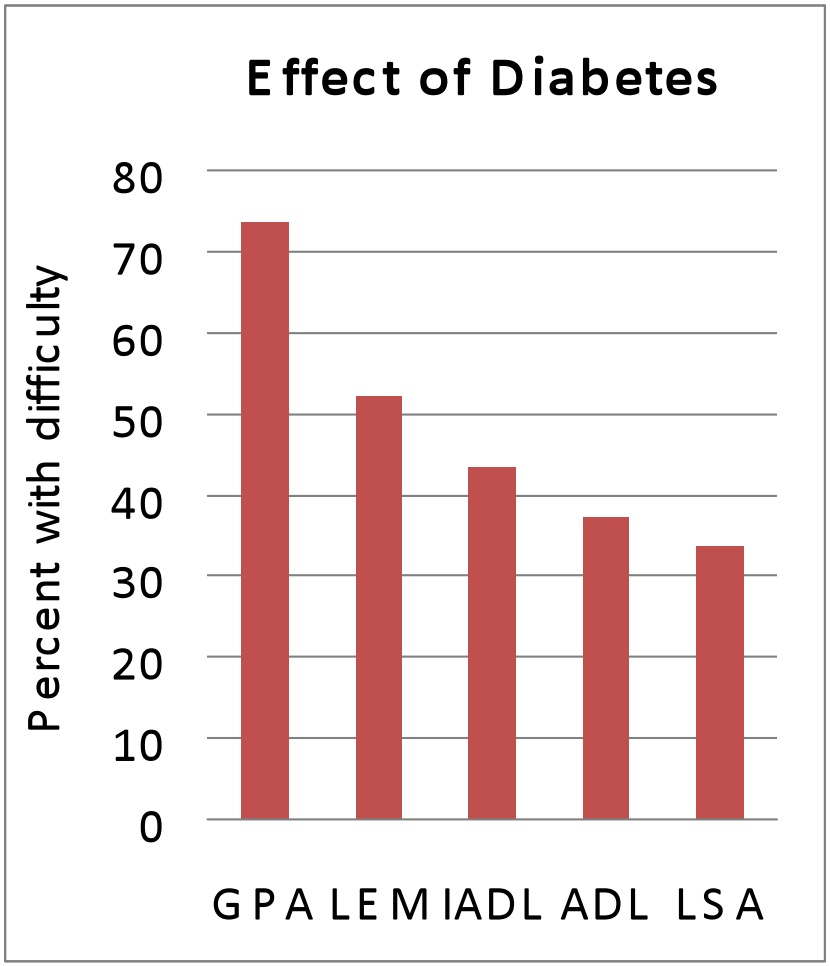
Data from Flint A, et al. *J Clin Invest*. 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553; Data from Drucker DJ. *Diabetes*. 1998;47:159-169

Synthesis and Secretion of GLP-1 and



NHANES 1999-2006 - Diabetes, Comorbidities, A1c and Functional Disability in Older Adults

Kalyani RR et al. ***Diabetes Care*** Publish Ahead of Print, published online February 25, 2010



Comorbidities and A1c

	Contribution to excess OR (%)
LEM	85
LSA	85
GPA	79
IADL	72
ADL	59

GPA: General Physical Activity; **LEM**: Lower Extremity Mobility; **IADL**: Instrumental Activity of Daily Life; **ADL**: Activity of Daily Life; **LSA**: Leisure and Social Activity

	UKPDS	ADVANCE	ACCORD	VADT
Participants (N.)	3,867	11,140	10,251	1,791
HbA_{1C} at baseline (%)	7.1	7.2	8.1	9.4
Diabetes duration (yrs)	Newly diagnosed	8	10	11.5
History of CVD (%)	7.5	32.0	35.0	40.0
Follow-up (median, yrs)	10.0	5.0	3.5†	5.6
HbA_{1C} at study end Intensive vs. Conv. (%)	7.0 vs. 7.9* (median values)	6.3 vs. 7.0*	6.4 vs. 7.5*	6.9 vs. 8.5*
Death from any cause (%)	17.9 vs. 18.7	8.9 vs. 9.6	5.0 vs. 4.0*	11.4 vs 11.0
Death from CV event (%)	10.1 vs. 11.1	4.5 vs. 5.2	2.6 vs. 1.8*	2.1 vs. 1.7
Nonfatal MI (%)	0.7 vs. 0.9	2.7 vs. 2.8	3.6 vs. 4.6*	6.1 vs. 6.3
Major hypoglycemia (%)	3.7 vs. 0.2*	2.7 vs. 1.5*	16.2 vs. 5.1*	21.2 vs. 9.9*
Weight gain (kg)	5.5 vs. 2.7*	0.0 vs. -1.0*	3.5 vs. 0.4*	7.8 vs. 3.4*

† terminated early